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SCIENTIFIC

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CHAPTER

ONE

INTRODUCTION

1.1 Overview

The *SZMAP* product uses a semi-continuum solvation theory, to analyze and understand if presence of water in the binding site has a stabilizing or destabilizing effect on a protein-ligand complex.

1.2 Applications

The **SZMAP** distribution comprises 2 applications:

SZMAP

The **SZMAP** program is an application for analyzing sites on the surface of a protein and/or ligand using an explicit probe molecule, usually water, and producing 3D grids of estimated thermodynamic properties. **SZMAP** can also evaluate solvent thermodynamics rapidly at specified coordinates.

GamePlan

The **GamePlan** tool identifies interesting coordinates near a ligand or in a protein binding site, runs *SZMAP*, and analyzes the results, comparing ligand properties to the binding site environment, generating a set of hypotheses for ligand modification and identifying sites where water either stabilizes or destabilizes the complex.

1.3 Utility Programs

The following utility programs are also included in this distribution:

- *SzmapGrid*: This program displays information about grids within an OE binary file (*.oeb*) and can split out a particular grid into a separate file. It also displays property tags in `-at_coords` results.
- *GridComp*: This program performs various mathematical operations on a grid or pair of grids to facilitate grid comparisons.
- *SzmapReport*: This program produces *.pdf* files containing 2D renderings of *SZMAP* results using the **OEDepict** and **Grapheme** technology.

1.4 A Word About Pronunciation

Like a number of *OpenEye* product names, *SZMAP* (solvent-zap-map) contains the letter pair *sz* which sounds similar to *sh*. It is pronounced *'shmăp*.

CHAPTER

TWO

SPRUCE BEFORE SZMAP

2.1 Overview

The SPRUCE program for preparing structures into input ready for *SZMAP* or *GamePlan*. The input can be in PDB, MMCIF, or any fileformat that includes residue information (e.g. OEB). The ligand will be autodetected, but can also be specified on the command line if multiple potential ligands are present.

See more:

SPRUCE

CHAPTER

THREE

SZMAP

3.1 Overview

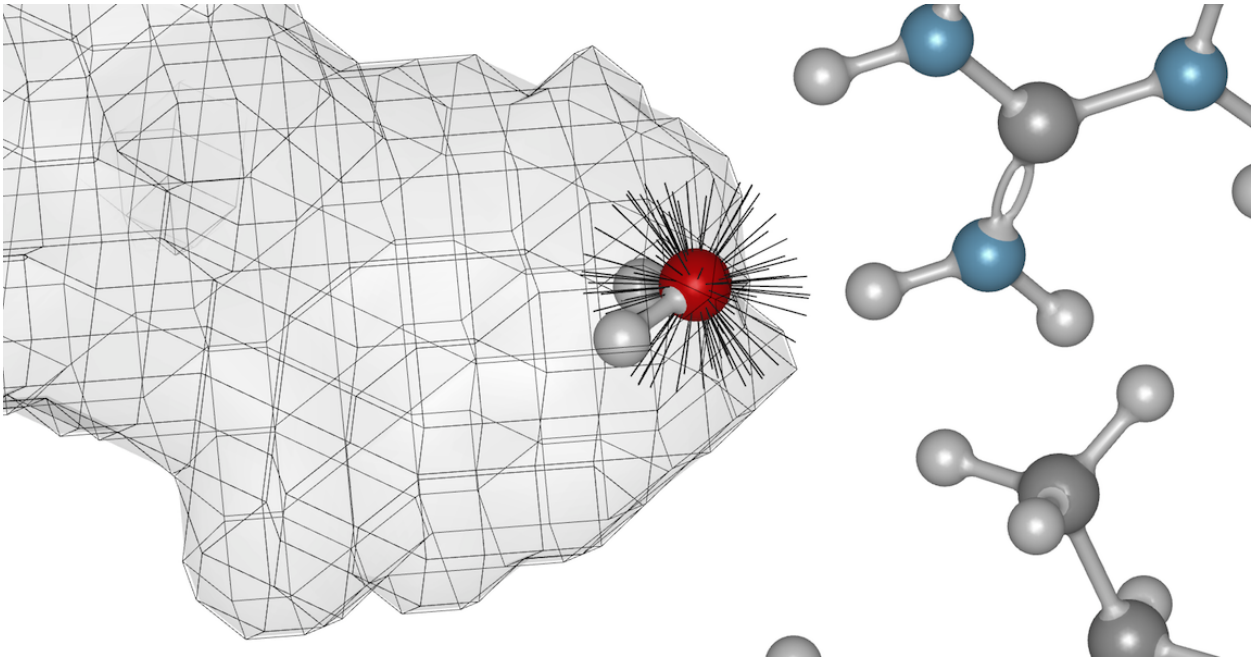


Fig. 1: **Semi-continuum Solvation**

The **SZMAP** application analyzes sites near the surface of a protein or ligand using semi-continuum solvation theory, which combines a single explicit probe water with Poisson-Boltzmann continuum theory. By sampling various probe water orientations as it interacts with continuum solvent and with protein and ligand molecules, **SZMAP** can estimate thermodynamic properties useful in understanding the solvent role in ligand binding. One of the advantages of this semi-continuum approach is that **SZMAP** can place the probe anywhere one wishes to analyze, even locations that molecular dynamics simulations may not be able to sample adequately. The *Technical Details* section of chapter *Technical Details* describes how these values are computed.

The most important question **SZMAP** can address is whether displacing water in a given region of a binding site is likely to increase or decrease binding affinity. A related question is what to replace a water with once the decision has been made to displace it. And finally, there is the question of whether water sites can be made to contribute to binding affinity *without* being displaced.

The analysis section of the *SZMAP Workflow* goes through how to determine whether a site is a good candidate for solvent replacement by looking at *apo*, complex and stabilization results. It also touches on questions of what to

replace water with by looking at difference free energies, probe water orientations and *GamePlan* results.

In addition to being run directly, **SZMAP** is called indirectly by *GamePlan*. The **SZMAP** results are analyzed to produce hypotheses for ways to optimize the ligand, showing specific substituent geometries based on water energetics.

3.2 SZMAP Input and Output

SZMAP takes molecule files as input—usually molecules representing a protein and a corresponding ligand—and generates an OEBinary file as output. The molecular input is assumed to have explicit hydrogens and partial charges. Making sure the input molecules are properly prepared is *essential* in order to obtain useful results and we recommend using OEDesignUnit generated with SPRUCE for this. See the *SZMAP Workflow* chapter for more information on preparing molecules.

> **Note**
>
> When using OEDesignUnits, note that they potentially include both solvent and a bound ligand, depending on the structure. There are two flags that are crucial to keep in mind, `-excludeDUsolvent` and `-excludeDUligand`, to control whether those two components should be part of the calculation or not.

When **SZMAP** reads input molecules, it checks for missing hydrogens and missing partial charges and will halt if the protein input does not appear to be complete; for ligands AM1BCC charges and Zap9 radii are assigned if partial charges are not pre-assigned. When the ligand(s) are already split out from the protein, MolCharge may be used to add partial different partial charges to the ligands. The option `-warn_if_missing_hydrogens` can be used to prevent halting, but before using it you should analyze the problem to see if it is due to an error in the input or something else, such as a disagreement with OEChem as to the proper bond order or charge state for your molecule. Mistakes in encoding alternate conformation codes can, for example, lead to very long and very short bonds, with the short ones interpreted as double bonds. And aromatic or double bonds that are not flat enough can cause OEChem to interpret them as single bonds.

> **Warning**
>
> If *SZMAP* is given an input *.pdb* file which still contains the usual occupancy and B-factor, rather than radii and partial charges, any energies it generates will be meaningless.

SZMAP output contains the input molecules along with either one or more computed grids or with computed values attached to individual atoms. The output file can be opened in *VIDA* where the results will be displayed in the context of the input molecules. See the *SZMAP Workflow* and the chapters describing the *WaterColor VIDA Extension*, the *Water Orientation VIDA Extension* and the *Color By Atom Properties* for step-by-step information on visualizing the results.

Calculations done at specific coordinates produce a tab-delimited table listing the results, which can be processed by *Excel* or other programs.

The output file can also be interpreted by the utility programs *SzmapGrid*, *GridComp* and *SzmapReport*. Although *VIDA* is the best tool for analyzing **SZMAP** results, *SzmapGrid* can be used to write out grid data in other formats.

3.3 Example Commands

3.3.1 Grid Calculations

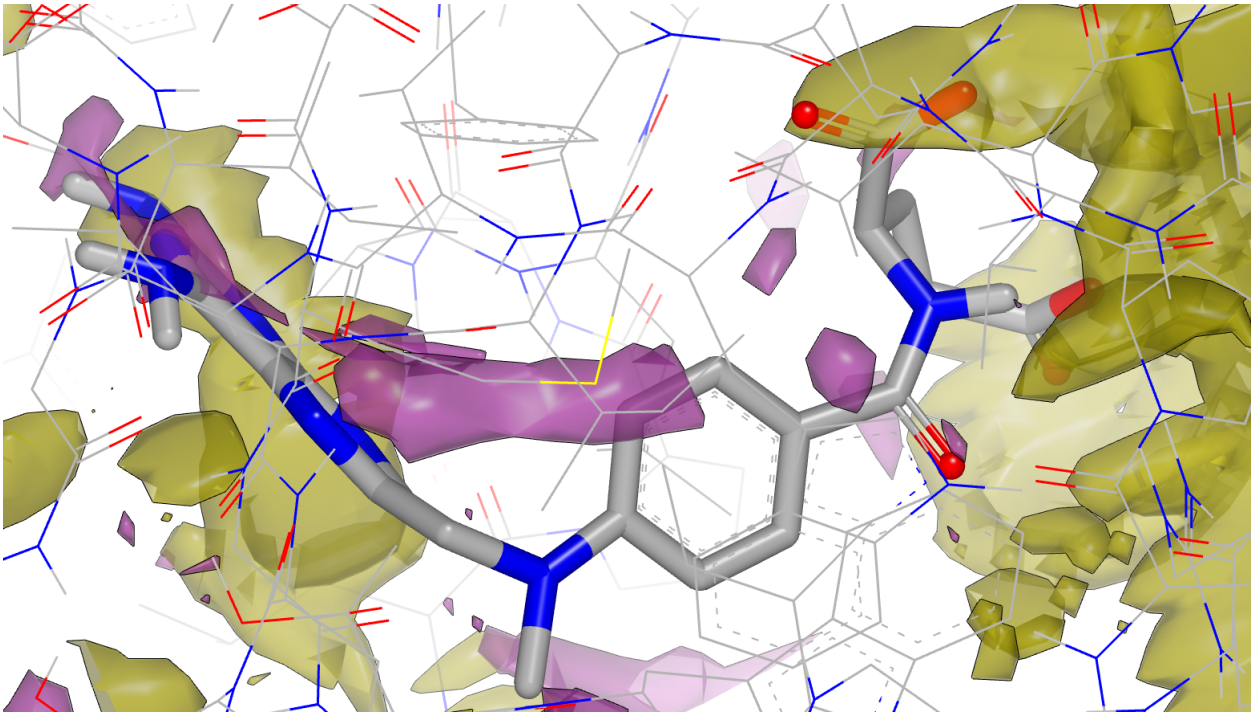


Fig. 2: **apo Neutral Difference Free Energy Grid**

If a ligand is provided, either bound in the OEDesignUnit or separately on the command line, and no other selection criterion are specified, **SZMAP** will perform grid calculations centered around the ligand. If not using a design unit as input and the structure has multiple binding sites, it is usually appropriate to focus on only one of these by making sure only one molecule is in the input ligand file. Other ways to define the calculation area include a bounding box, the region around a particular protein residue or small molecule, even the entire surface of the protein. Beware, surface

calculations generate a *very* large number of points and take a correspondingly long time to compute. It is usually best to focus the computation on a smaller region.

```
> szmap -mpi_np 4 -stbl -prefix 1dds_stbl -p 1DDS_AB__DU__MTX_A-201.oedu

or

> szmap -mpi_np 4 -stbl -prefix 1dds_stbl -p 1DDS_AB__DU__MTX_A-201_target.oeb.gz -l␣
↪1DDS_AB__DU__MTX_A-201_ligand.oeb.gz
```

Because there are often a great many points to be tested in a grid calculation, the MPI multiprocessing options `-mpi_np <num>` and `-mpi_hostfile <file>` can be used to speed calculations by running **SZMAP** on multiple cores or multiple networked computers.

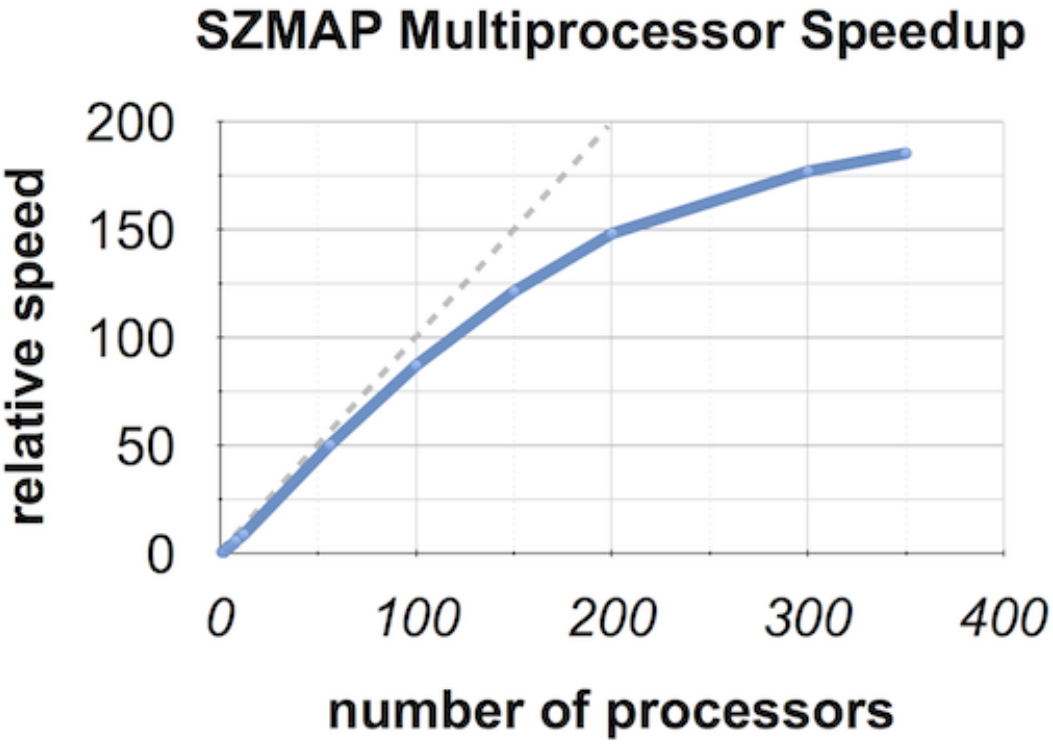


Fig. 3: **Speed vs Processors**

The figure *Speed vs Processors* is from a stabilization grid calculation run across a wide range of processor numbers. The dashed line is the diagonal for reference. With 8 processors, **SZMAP** runs over 6 times faster, and with 200 processors, about 150 times faster.

By default, grid output consists of four types:

- **neutral difference free energy**, a hydrophilic/hydrophobic polarity scale described below,
- **van der Waals energy**, an energy term not included in the neutral difference free energy,

- **order**, the fractional loss of rotational entropy due to electrostatics, indicating how much energy can be liberated by displacing water at this site,
- **mask**, an accurate solvent accessible surface—the region where the calculations were performed and the probe did not clash.

Neutral difference free energies compare the water probe with an uncharged or neutral water probe, a water where all the atoms have a partial charge of 0.0. The uncharged probe is a proxy for a hydrophobic group of the same size and shape as the standard probe water and these difference energies map out variations in the hydrophobic/hydrophilic nature of the binding site. High affinity ligands put nonpolar groups where these energies are positive and polar groups where these energies are negative, mimicking the donor-acceptor pattern of the solvent in the *apo* pocket.

Neutral difference free energies do not capture variations in van der Waals energies, which subtract out in the difference calculation. Van der Waals results are provided separately and complement the information in the neutral difference free energies.

Many additional grids are produced when the option `-results_set` `max` is specified. The most useful of these extra grids are probably *psolv* and *wsolv*—protein and water desolvation, respectively. They are always penalties (> 0.0 kcal/mol) and reveal the extent to which burying a charge costs energy, which needs to be compensated for by a complementary charge.

For most grid calculations, the `-stabilization` option is recommended. This causes *complex, ligand* and *apo* calculations all to be performed (although ligand calculations are by default restricted to solvent regions from the complex). Stabilization free energy values—computed as *(complex + bulk) - (apo + ligand)* where bulk-solvent is defined as 0.0—show how water energies are affected by binding. Negative stabilization free energies are regions that are stabilized by binding, or looked at another way, regions that stabilize binding. The simplest thing to do with them is leave them as they are, since they increase affinity. They *can* be displaced without destroying affinity, however, but only if they are displaced with a group that makes similar beneficial interactions. Positive stabilization free energies indicate regions where water is destabilized on binding. These waters lower affinity and are relatively easy to displace productively. Note that positive stabilization free energies can be found in regions where the neutral difference free energies in the complex are negative, and vice-versa. These two types of energies are not always correlated.

When comparing a series of ligands, all docked into the same binding site, the *apo* calculations can be done once separately by dropping the `-stabilization` option and specifying `-apo_grids`. Then these *apo* grids can be used in stabilization calculations for a series of ligands with the `-use_apo_from` option. If the ligands are all concatenated into one file, the `-split_lig` option will split each one out and perform the *complex* and *ligand* and *stabilization* calculations one-by-one.

```
> szmap -apo_grids -prefix 1dds_apo -p 1DDS_AB__DU__MTX_A-201.oedu -l 1dds_lig_series.
↪oeb.gz

> szmap -mpi_hostfile myhosts.txt -stbl -use_apo_from 1dds_apo.oeb.gz -split_lig  \
        -prefix 1dds_stbl -p 1DDS_AB__DU__MTX_A-201.oedu -l 1dds_lig_series.oeb.gz

or

> szmap -apo_grids -prefix 1dds_apo -p 1DDS_AB__DU__MTX_A-201_target.oeb.gz -l 1dds_lig_
↪series.oeb.gz

> szmap -mpi_hostfile myhosts.txt -stbl -use_apo_from 1dds_apo.oeb.gz -split_lig  \
        -prefix 1dds_stbl -p 1DDS_AB__DU__MTX_A-201_target.oeb.gz -l 1dds_lig_series.oeb.
↪gz
```

Note

The line above with a '\' as the very last character indicates that the command was too long to fit on one line and

continues on the following line.

Most grids are masked to show only regions where the minimum *Coulombic interaction + vdw energy* is at or below `-mask_cutoff` (0.0 kcal/mol by default); anything above this is considered a *CLASH*. The *mask_grid* represents this solvent-accessible region. Somewhat surprisingly, errors in coordinates of atoms in a structure, even small errors, occasionally lead to clashes being indicated in areas where a crystallographic water is observed. Typically, there will be an adjacent region where the probe water does not clash.

Grid results can be processed with the utility *GridComp* to break-out the region of the *apo* grid that has been displaced by the ligand.

```
> grid_comp -op lig_disp -i 4std_stbl.oeb.gz -o 4std_stbl_disp.oeb.gz
```

The volume of water displaced by the ligand plus the volume of water in the complex equals the volume of water in the full *apo* pocket. Displacement grids are useful in identifying, for example, precisely which waters are displaced by each of a series of substituents.

3.3.2 "At Coords" Calculations

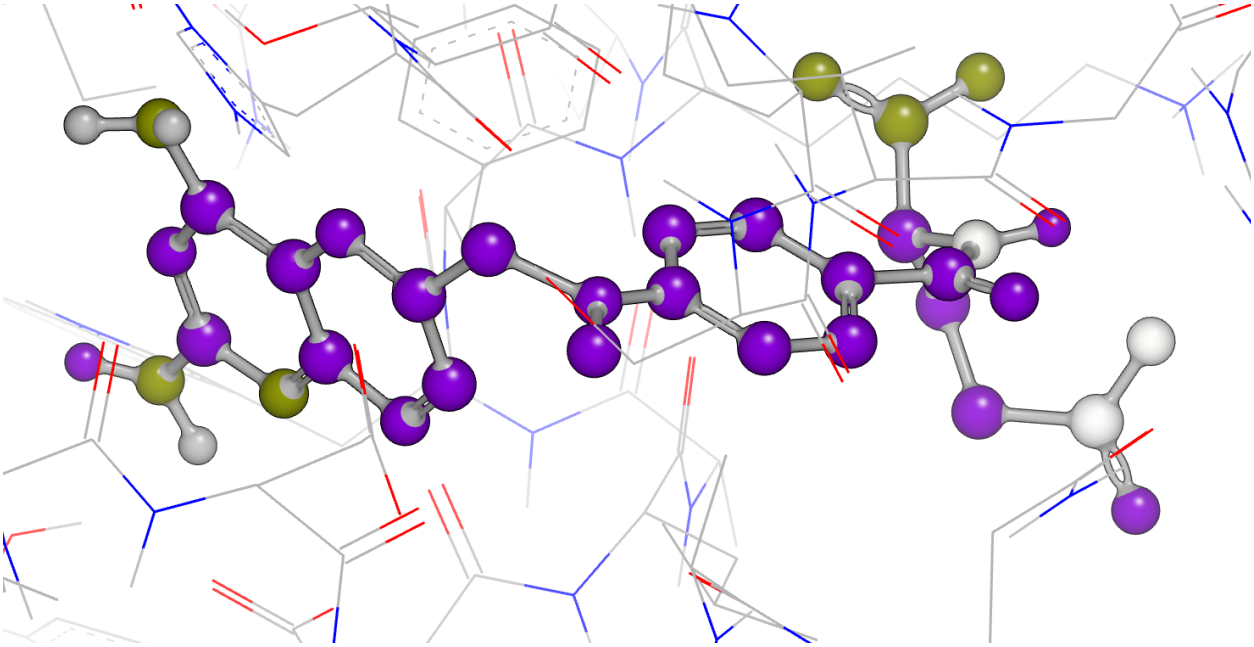


Fig. 4: **apo Neutral Difference Free Energy at Ligand Coordinates**

When the `-at_coords` option is used, no grid is produced. Instead calculations are done only at the coordinates of any atoms in the coordinates file and written out attached to those atoms for use by *SzmapReport*, the *Water Orientation VIDA Extension* and the *Color By Atom Properties*. A tab-delimited table of these results is written to a text file, which can easily be loaded into a spreadsheet program for further analysis. "At coords" calculations produce many different results values at each point (see the *Appendix 2: SZMAP Atom Properties*), but the four types of results enumerated in the grid section above are the most useful.

```
> szmap -prefix 1dds_coords -p 1DDS_AB__DU__MTX_A-201.oedu -at_coords 1dds_lig.oeb.gz -
↪excludeDUligand
```

(continues on next page)

(continued from previous page)

```
> szmap -prefix 1dds_coords -p 1DDS_AB__DU__MTX_A-201_target.oeb.gz -at_coords 1dds_lig.
↪oeb.gz
```

SZMAP *-at_coords* calculations are much faster than grid calculations because they operate over a much more limited set of points. Keep in mind that a region where there is a large gradient in a property will be undersampled if the coordinates there are widely spaced. Points labeled "CLASH" have *Coulombic interaction + vdw energy* greater than the *-mask_cutoff* (analogously to how the *mask_grid* is determined for a grid calculation). The "CLASH" label can be displayed in *VIDA* using the generic label function under the *Aa+* button in the style panel.

If coordinates are taken from the ligand, as above, then stabilization calculations are not possible. But coordinates at other locations, such as crystallographic waters, can be used to rapidly produce stabilization results.

```
> szmap -stbl -at_coords 1dds_waters.oeb.gz -prefix 1dds_xtal_waters \
        -p 1DDS_AB__DU__MTX_A-201.oedu
> szmap -stbl -at_coords 1dds_waters.oeb.gz -prefix 1dds_xtal_waters \
        -p 1DDS_AB__DU__MTX_A-201_target.oeb.gz -l 1DDS_AB__DU__MTX_A-201_ligand.oeb.gz
```

GamePlan runs **SZMAP** at specific coordinates around the binding site and up-to two single bonds away from the ligand, analyzing the results to provide insight into ways to optimize the ligand.

3.3.3 Probe Orientation Data

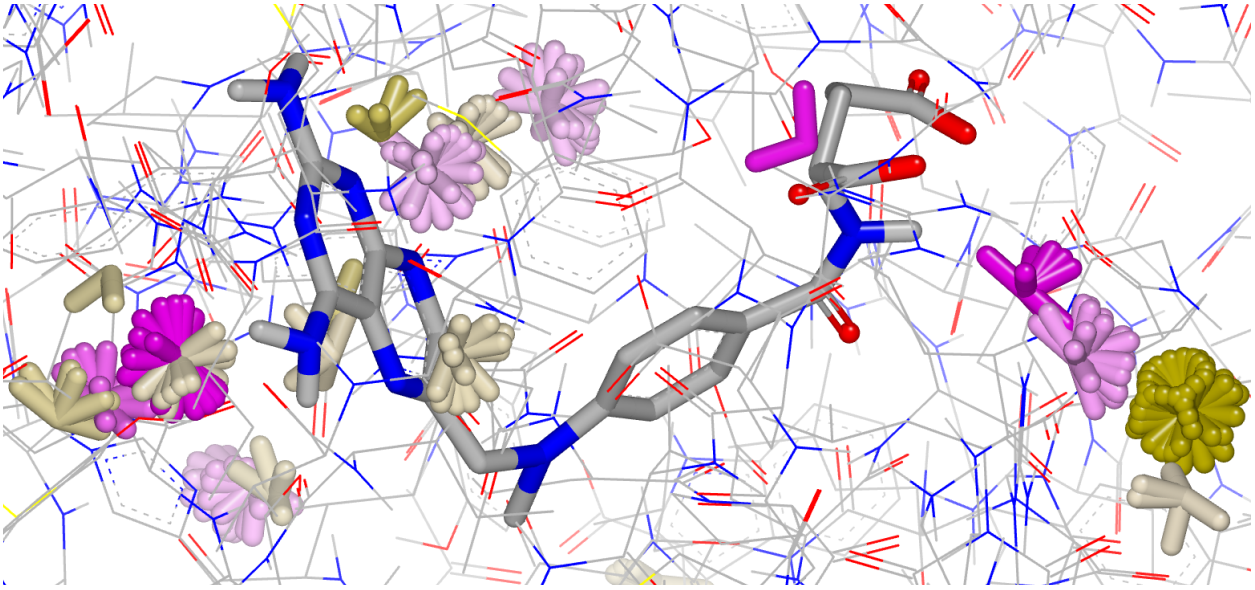


Fig. 5: **Probe Water Orientations**

In both types of **SZMAP** results, grids and "at coords", information is stored about the energies and probabilities of the probe for each point. This information can be processed by the *Water Orientation VIDA Extension* to identify regions of local energy minima and maxima and to display probe order or disorder. The probe geometry at dominant sites in the region where water is displaced can be compared to that of the ligand. High affinity ligands mimic both the difference free energy pattern and the specific geometry of the displaced water. This more "molecular" display is often easier to understand than continuous grids of data and it contains structural information that complements the numerical energy values.

3.4 Command Line Help

A description of the command line interface can be obtained by executing **SZMAP** with the *–help* option.

```
> szmap --help
```

will generate the following output:

```
Help functions:
  szmap --help simple      : Get a list of simple parameters
  szmap --help all         : Get a complete list of parameters
  szmap --help defaults    : List the defaults for all parameters
  szmap --help <parameter> : Get detailed help on a parameter
  szmap --help html        : Create an html help file for this program
  szmap --help versions    : List the toolkits and versions used in the application
```

3.5 Required Parameters

-target <filename>

-protein <filename>

-p <filename>

[keyless parameter 1]

The format must be one that retains partial charges: OEBinary, Tripos .mol2, or DelPhi flavor PDB (where there is radii in the occupancy field and charge in the B-factor field).

The file format of the input file is automatically determined from the file extension. The extensions *.oeb*, *.oeb.gz* can be OEBinary; *.oedu for OEDesignUnit; *.mol2* for Tripos Mol2 files; *.pdb* for PDB format files.

File type	Extension
OEDesignUnit	.oedu
OEBinary	.oeb .oeb.gz
PDB(DelPhi)	.pdb .ent .pdb.gz .ent.gz
MOL2	.mol2 .mol2.gz

Warning

By default, charges and radii are expected to be in this file and the results will be meaningless if they are missing. The program SPRUCE is provided to prepare the biomolecular structure including assigning charges and radii.

Atoms from waters, metals, ligands, co-factors, modified proteins and nucleic acids will be included in the calculation, except when using an OEDesignUnit, in which case only the protein and nucleic acid content will be used. *VIDA* can be used to create a new molecule where the protein is split from these.

3.6 Optional Parameters

3.6.1 Input File Options

-ligand <filename>

-l <filename>

[keyless parameter 2]

If an OEDesignUnit was used as input for the protein, and it contained a ligand the ligand from this will be used unless otherwise specified.

The format can be one that retains partial charges: OEBinary, Tripos .mol2, or DelPhi flavor PDB (where there is radii in the occupancy field and charge in the B-factor field).

> **Note**
>
> If no charges are present on the read molecule, AM1BCC charges and Zap9 radii are assigned to the molecule.

-warn_if_missing_hydrogens

If specified, missing hydrogens will not terminate the program, but will instead generate a warning message. Otherwise, missing hydrogens on the ligand or on more than 10 percent of the protein heavy atoms will cause **szmap** to fail.

-split_lig

Separate ligand file into individual molecules and run each individually.

3.6.2 Output File Options

-prefix <prefix>

Prefix used to name output files. Using `-prefix FOO` will create results in an OEBinary file named `FOO.oeb.gz` (see *-output_mol*). The table produced with *-at_coords* will be written to `FOO.txt` (see *-table*). Additionally, a parameter file named `FOO.param` (see *-param*) and a log file named `FOO.log` (see *-log*).

[Default=szmap]

-output_mol <filename>

-o <filename>

[keyless parameter 3]

OEBinary output file (*.oeb* or *.oeb.gz*), with calculated results attached to a copy of the input *-protein* and any *-ligand*.

If not specified, *-prefix* will be used to name the output.

-table <filename>

A tab-delimited table of results from *-at_coords* calculations is written to this file. If specified, this will override the filename created from *-prefix*. Specify `-table -` to send to *standard-output*.

-std_box <filename>

Write *standard* (complex) grid bounding box to output 'box molecule' coordinate file.

File type	Extension
OEBinary	.oeb .oeb.gz
MacroModel	.mmod .mmod.gz
MDL	.mdl .mdl.gz
MOL2	.mol2 .mol2.gz
MOPAC	.mopac .mopac.gz
PDB	.pdb .ent .pdb.gz .ent.gz
SDF	.sdf .mol .sdf.gz .mol.gz
XMol xyz	.xyz .xyz.gz

To facilitate visualization, box corners are represented by nitrogen atoms and bonds define the box edges in formats that support bonds. Use *-box_mol* to select based on this file.

-lig_box <filename>

Write *ligand* grid bounding box to output 'box molecule' coordinate file.

File type	Extension
OEBinary	.oeb .oeb.gz
MacroModel	.mmod .mmod.gz
MDL	.mdl .mdl.gz
MOL2	.mol2 .mol2.gz
MOPAC	.mopac .mopac.gz
PDB	.pdb .ent .pdb.gz .ent.gz
SDF	.sdf .mol .sdf.gz .mol.gz
XMol xyz	.xyz .xyz.gz

To facilitate visualization, box corners are represented by nitrogen atoms and bonds define the box edges in formats that support bonds. Use *-box_mol* to select based on this file.

-apo_box <filename>

Write *apo* grid bounding box to output 'box molecule' coordinate file.

File type	Extension
OEBinary	.oeb .oeb.gz
MacroModel	.mmod .mmod.gz
MDL	.mdl .mdl.gz
MOL2	.mol2 .mol2.gz
MOPAC	.mopac .mopac.gz
PDB	.pdb .ent .pdb.gz .ent.gz
SDF	.sdf .mol .sdf.gz .mol.gz
XMol xyz	.xyz .xyz.gz

To facilitate visualization, box corners are represented by nitrogen atoms and bonds define the box edges in formats that support bonds. Use *-box_mol* to select based on this file.

3.6.3 Selection Options

If the input is an OEDesignUnit, then the following flags can be used to exclude pieces from the structure before the calculation

-excludeDUsolvent

Excludes structural waters from the input design unit

-excludeDUligand

Excludes the bound ligand from the input design unit

If a *-ligand* is provided but none of the selection method's options are specified, points are selected around the ligand when grids are generated, even for *apo* grids (see *-distance_cutoff*).

-at_coords <filename>

-coords <filename>

Perform calculations just at the coordinates of atoms in any molecules in the file. Write those molecules, with the (masked) results attached to the atoms, to the output file.

File type	Extension
OEBinary	.oeb .oeb.gz
MacroModel	.mmod .mmod.gz
MDL	.mdl .mdl.gz
MOL2	.mol2 .mol2.gz
MOPAC	.mopac .mopac.gz
PDB	.pdb .ent .pdb.gz .ent.gz
SDF	.sdf .mol .sdf.gz .mol.gz
XMol xyz	.xyz .xyz.gz

Text formats such as `.xyz` are easily modified in a text editor to specify an arbitrary set of coordinates.

The tags that will be used when assigning values to atoms are listed in *Appendix 2: SZMAP Atom Properties*.

A tab-delimited table of calculation results is printed to a text file (see *-table*). In the abbreviated column heading, `n_` stands for neutral and `v_` stands for vacuum. A mask value of 0 indicates that the *intvdw* value is above *-mask_cutoff* and this row of data should not be used.

-residue_number <number>

-res <number>

Select grid points around the selected residue (see *-distance_cutoff*).

-residue_chain <letter>

-chain <letter>

Protein chain used with *-residue_number*. Case sensitive. Underscore ('_') stands for blank.

[Default='_']

-residue_insert <letter>

-inscode <letter>

Protein insertion code used with *-residue_number*. Case sensitive. Underscore ('_') stands for blank.

[Default='_']

-like_std <filename>

Select points in the same bounding box as the *standard* (complex) grids from the specified OEBinary (*.oeb* or *.oeb.gz*) file.

-like_lig <filename>

Select points in the same bounding box as the *ligand* grids from the specified OEBinary (*.oeb* or *.oeb.gz*) file.

-like_apo <filename>

Select points in the same bounding box as the *apo* grids from the specified OEBinary (*.oeb* or *.oeb.gz*) file.

-like_box <filename>

Select points in the same bounding box as the *box_mol* in the specified OEBinary (*.oeb* or *.oeb.gz*) file.

-around_mol <filename>

-around <filename>

Select points enclosing the atoms in the specified file (using *-distance_cutoff* to define how much extra space beyond the atoms is include).

File type	Extension
OEBinary	.oeb .oeb.gz
MacroModel	.mmod .mmod.gz
MDL	.mdl .mdl.gz
MOL2	.mol2 .mol2.gz
MOPAC	.mopac .mopac.gz
PDB	.pdb .ent .pdb.gz .ent.gz
SDF	.sdf .mol .sdf.gz .mol.gz
XMol xyz	.xyz .xyz.gz

Text formats such as `.xyz` are easily modified in a text editor to adjust the region of interest.

-box_mol <filename>

Select points in bounding box defined by atoms in the input 'box molecule' file (without a *-distance_cutoff*).

File type	Extension
OEBinary	.oeb .oeb.gz
MacroModel	.mmod .mmod.gz
MDL	.mdl .mdl.gz
MOL2	.mol2 .mol2.gz
MOPAC	.mopac .mopac.gz
PDB	.pdb .ent .pdb.gz .ent.gz
SDF	.sdf .mol .sdf.gz .mol.gz
XMol xyz	.xyz .xyz.gz

Text formats such as `.xyz` are easily modified in a text editor to adjust the region of interest.

-bounding_box <xmin> <ymin> <zmin> <xmax> <ymax> <zmax>

-bbox <xmin> <ymin> <zmin> <xmax> <ymax> <zmax>

Select points in the bounding box defined by minimum and maximum coordinate values.

-surface_points

-surf

Select grid points over the entire surface of the input molecule(s).

> **Warning**
>
> This usually results in very long run times.

-distance_cutoff <number>

-dcutoff <number>

Maximum distance from atoms of selected points, a margin around the focus region.

[Default=4.0 Å]

-value_cutoff <number>

-vcutoff <number>

Minimum *FRED* surface shape score value for selected points.

[Default=0.05]

-restrict_calc <level>

Control which points are used for calculations. Restricting calculations makes **szmap** run faster but make the that portion of the results less useful. In particular, restricting *apo* calculations may not be worth the speed increase because it prevents you from being able to analyze the full *apo* pocket.

Level	Meaning
none	Calculate full grids
ligand	Restrict ligand calc to region from complex
apo	Restrict apo calc to region from complex
both	Restrict ligand & apo to region from complex

[Default=ligand]

3.6.4 Grid/Coord Options

If a grid or coord request option is not specified, all *apo* results will be generated, and if a ligand is supplied, all *std* (complex) results as well.

-results_set <type>

-properties <type>

-grids <type>

Defines which sets of properties are included in grid or coordinate results.

Type	Output
min	Only the standard (complex) results; minimal grid output;
full coord	output
default	Both standard and *apo* results, if possible; minimal
grid output;	full coord output
max	Both standard and *apo* results, if possible; Full grid
and coord	output

min or *default* used for a grid calculation produces the following properties:

- *neut_diff_free_energy_grid* (or the corresponding *lig* or *apo* grid)
- *vdw_grid*
- *order_grid*
- *mask_grid*

See *Appendix 1: SZMAP Grids* for lists of properties.

[Default=default]

-stabilization

-stbl

Generate *(complex - (ligand + apo-pocket))* values that show where water is stabilized or destabilized upon ligand binding. This requires extra calculations with the ligand alone.

-mask_cutoff <number>

Points where the minimum interaction + van der Waals energy above this cutoff will be set to 0.0 in the output grids.

[Default=0.0 kcal/mol]

-grid_spacing <number>

-space <number>

Distance between grid points. We recommend this value be above 0.25 Å. **szmap** creates a grid by first building a temporary grid around the protein and/or ligand molecules that contains values of a function describing the space near the molecular surface. This temporary grid has the same grid spacing as the final grid, so using a very fine grid spacing can generate enormous temporary grids that fill memory.

[Default=0.5 Å]

-standard_grids

-std_grids

-cplx_grids

-std_coords

Generate all *standard* (holo-complex) grids or coords. The actual grids or coord data will depend on *-results_set*.

-lig_grids

-lig_coords

Generate all *ligand* grids or coords. The actual grids or coord data will depend on *-results_set*.

The *std* and/or *apo* grids will still be generated as usual even if this option is specified.

-apo_grids

-apo_coords

Generate all *apo* grids or coords. The actual grids or coord data will depend on *-results_set*.

-point_grid

Generate the grid of test points where the calculation is done (1 = test, 0 otherwise). If a ligand is provided, values are for the protein/ligand complex.

-lig_point_grid

Generate the grid of test points where the calculation is done (1 = test, 0 otherwise). Values are for the ligand without the protein.

-apo_point_grid

Generate the grid of test points where the calculation is done (1 = test, 0 otherwise). If a ligand is provided, values are for the protein without the ligand.

3.6.5 Calculation Options

-num_orientations <number>

-rot <number>

Number of probe-molecule orientations to sample at each grid point. If this number is set to 24, 60, 216, 360, or 648 then the set of rotations will be symmetric. Otherwise, they will be random and may have lopsided gaps in coverage. For most purposes, 60 is the minimum required for reliable energy calculations and 360 generates robust results.

[Default=60]

-dielectric_model <type>

-model <type>

Type of surface defining the boundary between *-inner_dielectric* and *-outer_dielectric* values.

Type	Meaning
gaussian	Dielectric value changes smoothly over a distance of approximately 2 Å.
molecular surface	Dielectric changes abruptly at molecular surface

[Default=gaussian]

-inner_dielectric <number>

-eps_in <number>

Dielectric value used inside the protein and ligand atom surface (see *-dielectric_model*).

[Default=1.0]

-outer_dielectric <number>

-eps_out <number>

Dielectric value used outside the protein and ligand atom surface (see *-dielectric_model*). This is the dielectric of bulk solvent.

[Default=80.0]

-salt_conc <number>

-salt <number>

Salt concentration in Poisson Boltzmann calculation (units: moles/liter).

[Default=0.05 M]

-zap_spacing <number>

Distance between grid points within the ZAP calculation. To avoid excessive memory requirements and ensure stability during the PB calculation, it is usually best for ZAP spacing to be greater than 0.25 Å.

[Default=0.5 Å]

-boundary_spacing <number>

-boundary <number>

Extra buffer outside the extents of the selection molecule.

[Default=4.0 Å]

-boundary_radius <number>

Size of probe for boundary calculation.

[Default=1.4 Å]

-water_charge <type>

Which charges are used on the probe water: *scaled* or *am1bcc*. *Scaled* means scale AM1BCC charges to match the water dipole.

[Default=scaled]

-vdw_scale <number>

Scale for van der Waals between probe atoms and other atoms.

[Default=1.0]

-use_apo_from <filename>

Use the *apo* grids in the *.oeb* results file from a previous **szmap** run rather than calculating them. This can speed up calculations for a series of ligands docked to a single ligand.

This option is also useful when the *apo* protein and the *complex* adopt slightly different states. For example, a key amino acid may have an ionized sidechain in the *apo* protein and a neutral sidechain in the *complex*.

3.6.6 MPI Options

These options control how MPI is used. Unless one of these options is specified, **szmap** will run in single processor mode.

-mpi_np <number>

Run **szmap** calculations in MPI multiprocessor mode using the specified number of processors. If an MPI hostfile is not specified with the -mpi_hostfile option all processor will be launched on the local machine.

-mpi_hostfile <filename>

Run **szmap** calculations in MPI multihost mode using the specified MPI hostfile. If an MPI hostfile is not specified all processes will be run on the local machine. The hostfile format is a text file with each line specifying a machine and the number of processes to launch on it.

The following example hostfile specified 3 hosts that can run up to 4, 2 and 5 processes respectively.

```
host1.mydomain.com slots=4
host2.mydomain.com slots=2
host3.mydomain.com slots=5
```

This example hostfile would typically be used with -mpi_np 11 to make use of all the processors (4+2+5=11).

Note that multiprocessor is only supported on the local machine under Windows, and in homogeneous environments for other architectures (i.e., machines with the same operating system environment).

3.6.7 Other Options

-param <filename>

Defines the control parameter file. This file can contain a collection of parameters which can be used instead of writing each parameter to the command-line. In addition, the parameter file written by any **szmap** run (see *-prefix*) can be used with the *-param* flag in subsequent **szmap** runs. Any command given explicitly on the command line will supersede any command found in a file specified with the *-param* flag.

-logfile <filename>

-log <filename>

If specified, this will override the filename created from *-prefix*. Specify "-log - " (dash) to send to *standard-output*.

-progress <style>

How to display progress information:

Style	Output
none	no progress shown
dots	print a period (.) for every point tested
percent	print percentage complete every 10 points
log	print percentage to log file

[Default=percent]

-verbose

-v

Print additional information to log during calculations.

CHAPTER

FOUR

GAMEPLAN

4.1 Overview

The **GamePlan** application analyzes a protein and a bound or docked ligand to determine points where solvent information may be interesting, runs *SZMAP* at these points, and then processes the results, formulating various hypotheses for ligand modification and identifying sites where water is stabilizing or destabilizing.

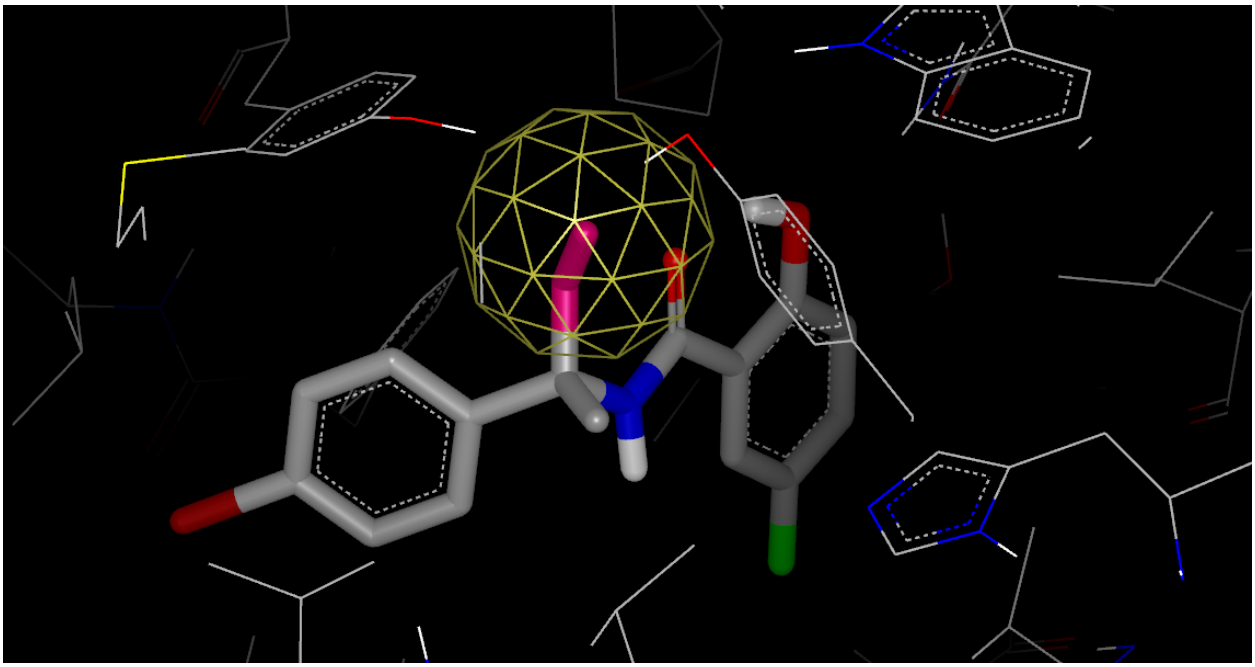


Fig. 1: **Gameplan Hypothesis**

4.2 Example Commands

4.2.1 Running Gameplan

The usual workflow starts with preparing the protein and ligand by adding hydrogens and assigning partial charges. See the *SZMAP Workflow* for a thorough discussion of preparation.

Next, run **GamePlan** and view the results in VIDA using the *WaterColor VIDA Extension* to configure the annotations. On average, a **GamePlan** calculation will take 4 to 8 minutes on Linux using four 2.8GHz processors, for example.

```
> gameplan -szmap_mpi_np 4 -prefix 2xdl_gameplan -p 2XDL_AB__DU__2DL_A-1225.oedu

or

> gameplan -szmap_mpi_np 4 -prefix 2xdl_gameplan -p 2XDL_AB__DU__2DL_A-1225_target.oeb.
↪gz -l 2XDL_AB__DU__2DL_A-1225_ligand.oeb.gz

> vida 2xdl_gameplan.oeb.gz
```

In *Gameplan Hypothesis*, the bonds in hot-pink represent an idea about how to modify the ligand to add a two-atom hydrogen-bond acceptor group that could interact favorably with nearby tyrosine residues. The yellow ball indicates that water makes a strong polar interaction at this site in the *apo*-protein.

When **GamePlan** reads input molecules, it checks for missing hydrogens and missing partial charges and will halt if the input does not appear to be complete. The option `-warn_if_missing_hydrogens` can be used to prevent halting, but before using it you should analyze the problem to see if it is due to an error in the input or even a disagreement with OEChem as to the proper bond order and charge state for your molecule. Mistakes in encoding alternate conformation codes can, for example, lead to very long and very short bonds, with the short ones interpreted as double bonds. And aromatic or double bonds that are not flat enough can cause OEChem to think they are single bonds. See *Protein and Ligand preparation for SZMAP and GamePlan* for discussion of preparation and how to resolve such pathologies using SPRUCE.

By default, **GamePlan** hypotheses respect the hybridization of aromatic atoms in the input ligand. Specifying the option `-sp3_aromatic` will permit **GamePlan** to explore the effect of a change of hybridization of aromatic atoms. Note that only the local hybridization at the attachment site is altered, often leading to odd-looking geometry. But the point is to generate fresh ideas for how you might modify your ligand.

4.2.2 Gameplan Results

Open the results in **VIDA**, highlight any part of the output in the List window, and run the *WaterColor VIDA Extension* to configure the annotation and focus the view to the region around the ligand. See the last section of chapter *WaterColor VIDA Extension* for a step-by-step guide to doing this.

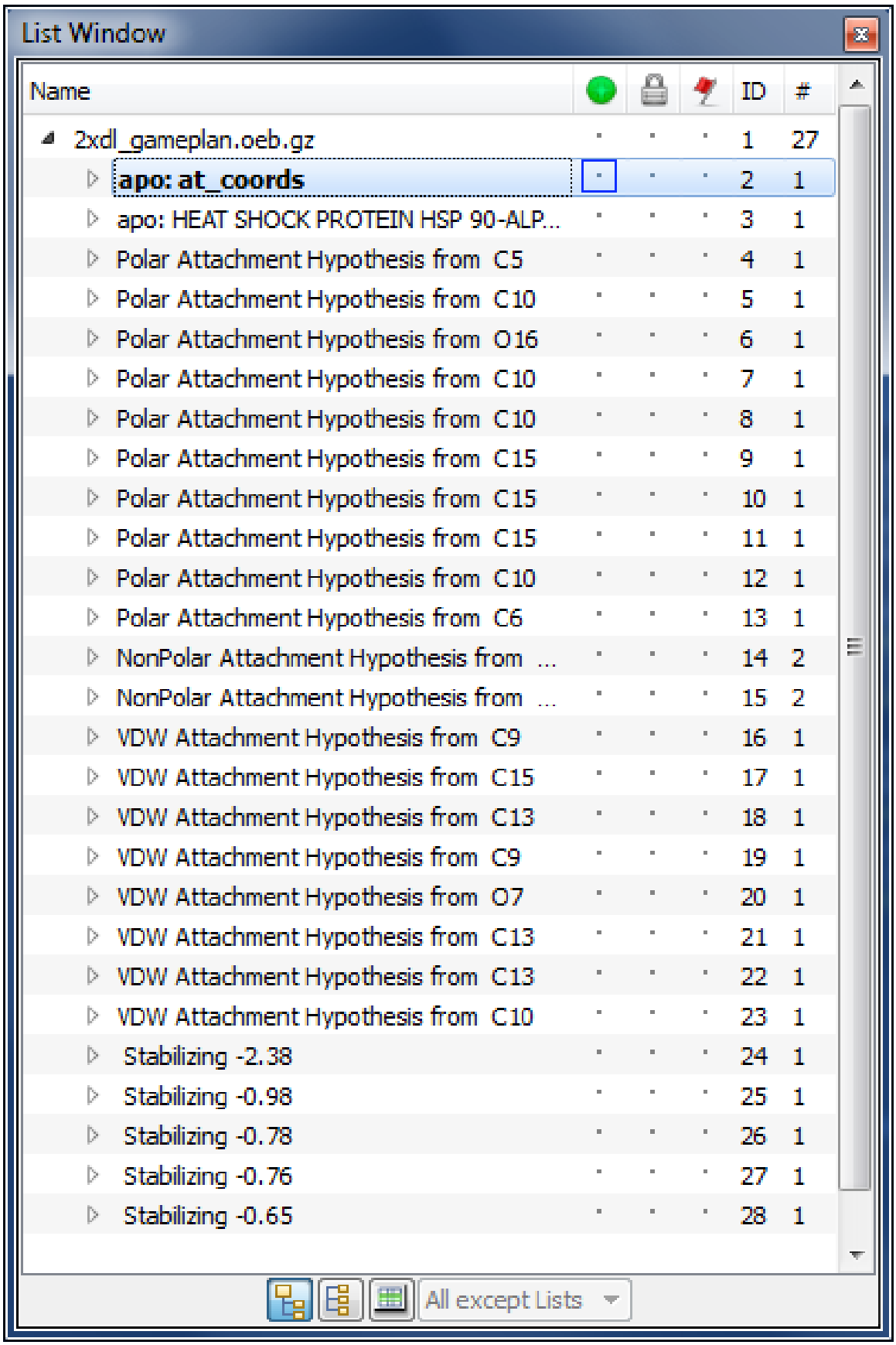


Fig. 2: **Gameplan List Window**

GamePlan results are organized into three main sections (see figure *Gameplan List Window*):

1. An analysis of how well the ligand compares to the solvent in the binding site with colored annotation around atoms that indicates the type of site (figure *Ligand Compared to apo Binding Site*). The protein is also included here for context.
2. A series of hypotheses for substituents that could be added to the ligand. Each attachment is modeled using dummy atoms that show up in hot-pink in *VIDA*, with annotation that indicates the type of site: polar, non-polar and van der Waals (see figures *Hypothesis for a Polar Substituent* and *Hypothesis for a Nonpolar/VDW Substituent*).
3. A (possibly empty) section showing stabilizing and destabilizing water sites (figure *Stabilizing Site*).

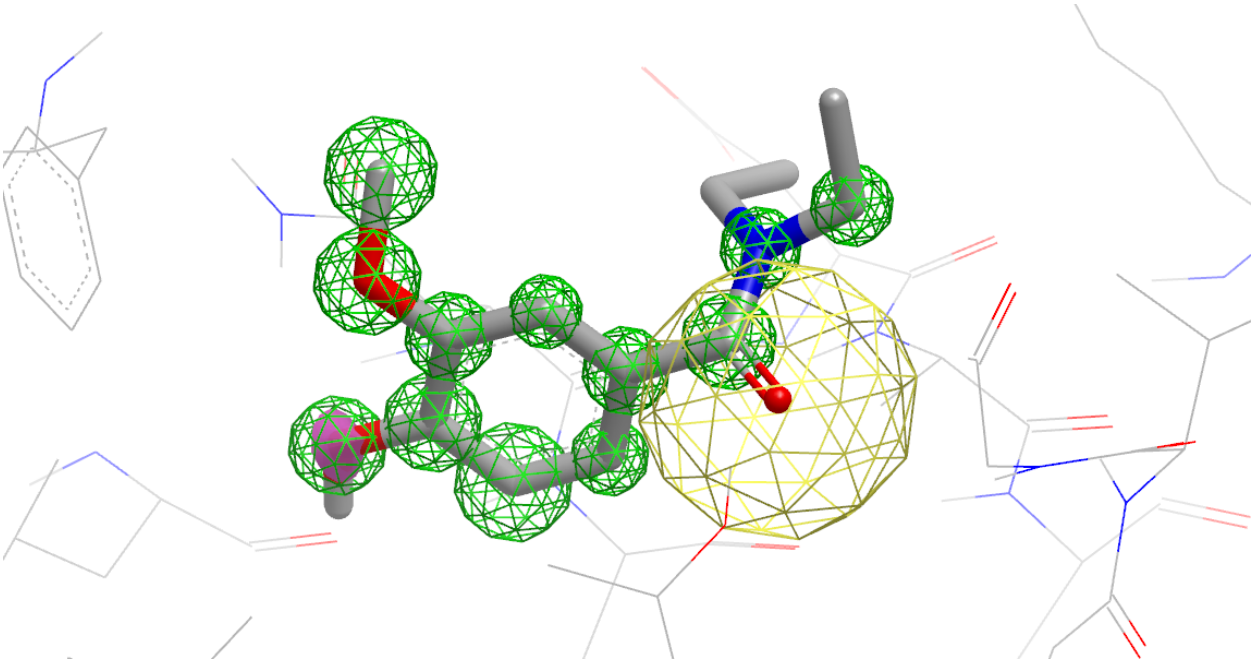


Fig. 3: **Ligand Compared to apo Binding Site**

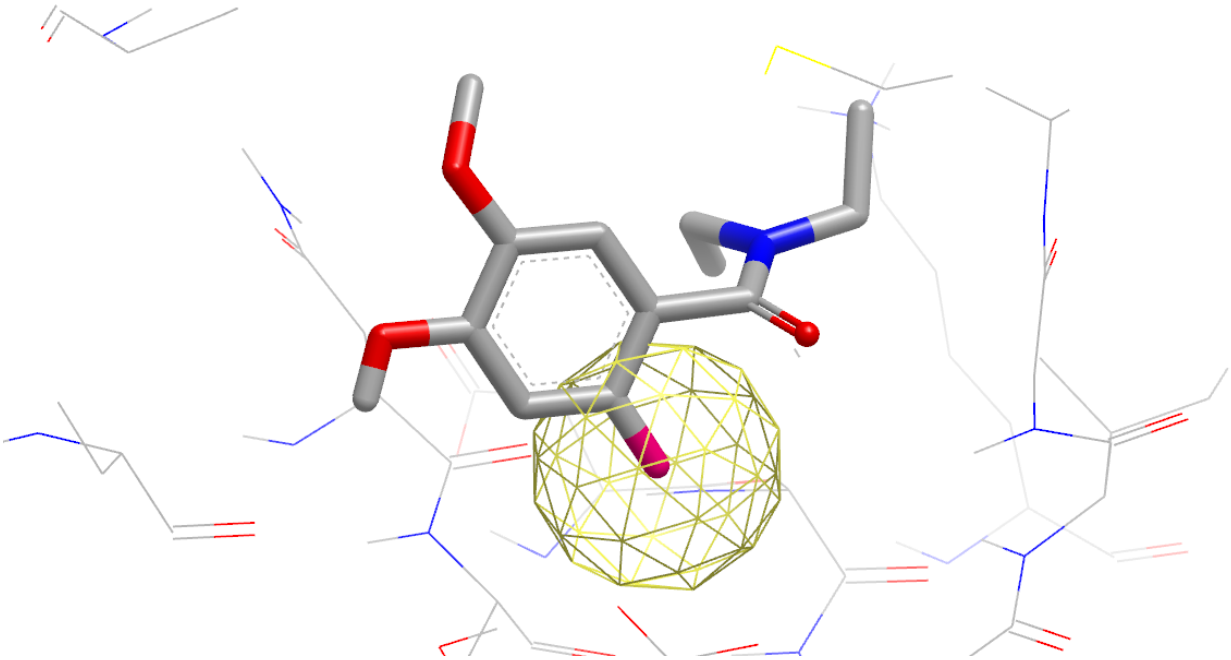


Fig. 4: **Hypothesis for a Polar Substituent**

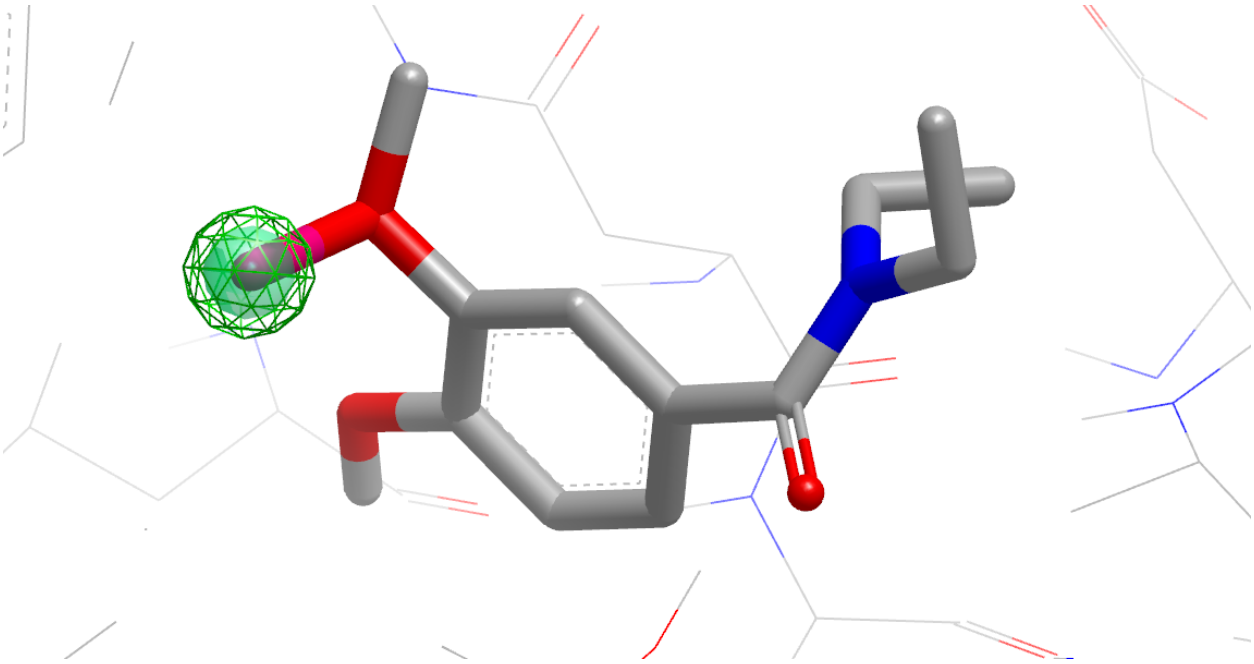


Fig. 5: **Hypothesis for a Nonpolar/VDW Substituent**

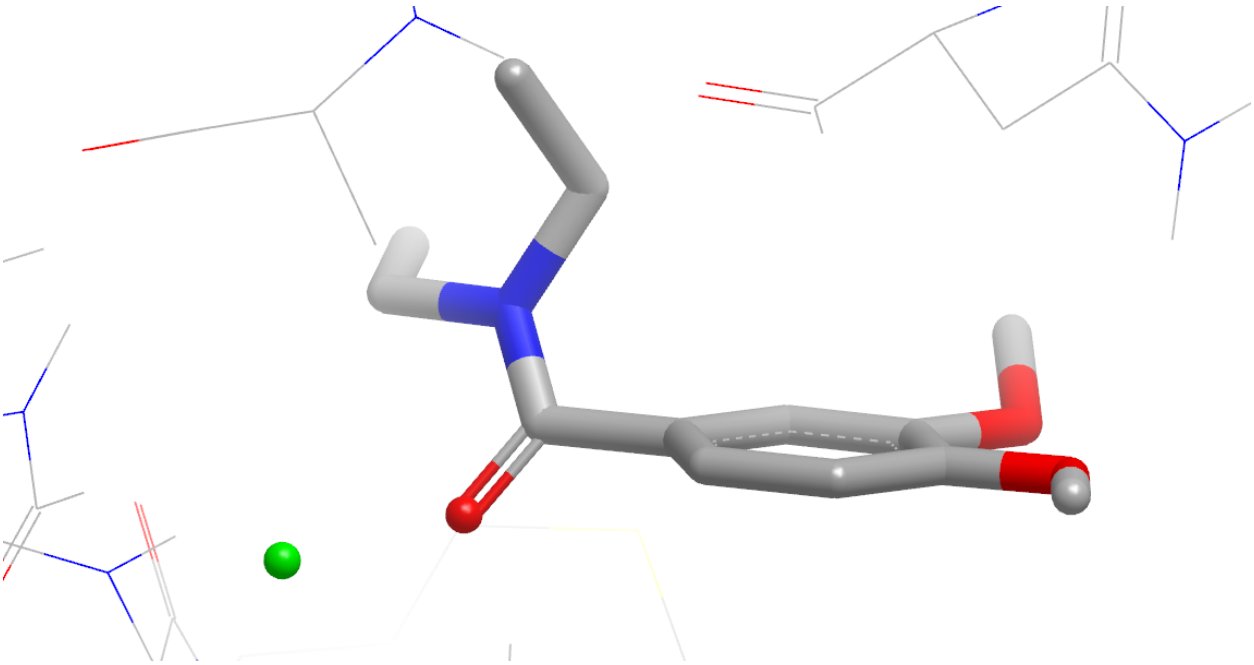


Fig. 6: **Stabilizing Site**

Annotations are:

- **Yellow mesh sphere:** polar site; the size of the sphere indicates the magnitude of the polar interaction.
- **Green mesh sphere:** van der Waals site; the size of the sphere indicates the magnitude of the VDW interaction.
- **Green translucent sphere:** non-polar site.
- **Purple top:** mismatch site, where the ligand polarity does not match that of the solvent.
- **Small green and red spheres:** stabilizing and destabilizing points, respectively.

Based on your results, you may want to modify your ligand to make it more compatible with the *apo* pocket solvent electrostatics, add a substituent based on the suggested hypotheses, displace a destabilizing water or carefully replace a stabilizing water, mimicking the interactions of the water.

4.3 Command Line Help

A description of the command line interface can be obtained by executing **Gameplan** with the *–help* option.

```
> gameplan --help
```

will generate the following output:

```
Help functions:
  gameplan --help simple      : Get a list of simple parameters
  gameplan --help all         : Get a complete list of parameters
  gameplan --help defaults    : List the defaults for all parameters
  gameplan --help <parameter> : Get detailed help on a parameter
  gameplan --help html        : Create an html help file for this program
  gameplan --help versions    : List the toolkits and versions used in the application
```

4.4 Required Parameters

-target <filename>
-protein <filename>
-p <filename>

[keyless parameter 1]

The format must be one that retains partial charges: OEBinary, Tripos .mol2, or DelPhi flavor PDB (where there is radii in the occupancy field and charge in the B-factor field).

The file format of the input file is automatically determined from the file extension. The extensions *.oeb*, *.oeb.gz* can be OEBinary; *.oedu for OEDesignUnit; *.mol2* for Tripos Mol2 files; *.pdb* for PDB format files.

File type	Extension
OEDesignUnit	.oedu
OEBinary	.oeb .oeb.gz
PDB(DelPhi)	.pdb .ent .pdb.gz .ent.gz
MOL2	.mol2 .mol2.gz

Warning

By default, charges and radii are expected to be in this file and the results will be meaningless if they are missing. The program SPRUCE is provided to prepare the biomolecular structure including assigning charges and radii.

4.5 Optional Parameters

4.5.1 Input Options

-ligand <filename>
-l <filename>

[keyless parameter 2]

If an OEDesignUnit was used as input for the protein, and it contained a ligand the ligand from this will be used unless otherwise specified.

The format can be one that retains partial charges: OEBinary, Tripos .mol2, or DelPhi flavor PDB (where there is radii in the occupancy field and charge in the B-factor field).

Note

If no charges are present on the read molecule, AM1BCC charges and Zap9 radii are assigned to the molecule.

4.5.2 Output Options

-prefix <prefix>

Prefix used to name output files. Using `-prefix FOO` will create results in an OEBinary file named `FOO.oeb.gz` (see *-output*). Additionally, a parameter file named `FOO.param` (see *-param*) and a log file named `FOO.log` (see *-log*).

[Default=gameplan]

-output <filename>

-o <filename>

[keyless parameter 3]

OEBinary output file (*.oeb* or *.oeb.gz*), containing calculated results.

If not specified, *-prefix* will be used to name the output.

4.5.3 Parameters

-merge <number>

[Default=0.35 Å]

Distance cutoff for merging two sample points.

-sp3_aromatic <bool>

-sp3aromatic <bool>

Sample sp3 hybridization at each aromatic ligand atom.

[Default=false]

-stabilization <bool>

-stbl <bool>

Search for regions where water is stabilized or destabilized by in the protein/ligand complex.

[Default=true]

-clean <bool>

Remove temporary files written by *SZMAP* during this run of gameplan.

[Default=true]

-light_background

-light_bkg

If specified, annotation colors will be adjusted to better match a white background. By default, they are chosen to match a dark background.

-warn_if_missing_hydrogens

If specified, missing hydrogens will not terminate the program, but will instead generate a warning message. Otherwise, missing hydrogens on the ligand or on more than 10 percent of the protein heavy atoms will cause *gameplan* to fail.

-num_orientations <number>

-rot <number>

Number of orientations for the SZMAP probe.

[Default=60]

4.5.4 MPI Options

-szmap_mpi_np <number>

Run *GamePlan* calculations in MPI multiprocessor mode using the specified number of processors. If an MPI hostfile is not specified with the -mpi_hostfile option all processor will be launched on the local machine.

-szmap_mpi_hostfile <filename>

Run *GamePlan* calculations in MPI multihost mode using the specified MPI hostfile. If an MPI hostfile is not specified all processes will be run on the local machine. The hostfile format is a text file with each line specifying a machine and the number of processes to launch on it.

The following example hostfile specified 3 hosts that can run up to 4, 2 and 5 processes respectively.

```
host1.mydomain.com slots=4
host2.mydomain.com slots=2
host3.mydomain.com slots=5
```

This example hostfile would typically be used with -szmap_mpi_np 11 to make use of all the processors (4+2+5=11).

Note that multiprocessor is only supported on the local machine under Windows, and in homogeneous environments for other architectures (i.e., machines with the same operating system environment).

4.5.5 Other Options

-param <filename>

Defines the control parameter file. This file can contain a collection of parameters which can be used instead of writing each parameter to the command-line. In addition, the parameter file written by any gameplan run (see *-prefix*) can be used with the *-param* flag in subsequent gameplan runs. Any command given explicitly on the command line will supersede any command found in a file specified with the *-param* flag.

-logfile <filename>

-log <filename>

If specified, this will override the filename created from *-prefix*. Specify `-log -` to send to *standard-output*.

-progress <style>

How to display *SZMAP* progress information:

Style	Output
none	no progress shown
dots	print a period (.) for every point tested
percent	print percentage complete every 10 points
log	print percentage to log file

[Default=dots]

-verbose

-v

Print additional information to log during calculations.

CHAPTER

FIVE

UTILITIES

5.1 SzmapGrid

5.1.1 Overview

The **szmap_grid** utility reads an OEBinary (*.oeb* or *.oeb.gz*) file generated by *SZMAP* and displays information about the grids within. If atom property tags from a *SZMAP* `-at_coords` calculation are found, it will list the all property names.

5.1.2 Example Commands

```
> szmap_grid 4std_stbl.oeb.gz

szmap-meta-data attached to molecule 1, 'complex: PROTEIN (SCYTALONE DEHYDRATASE) +␣
↪residue 'BFS''.
'mask_grid' dimensions: 38 29 33
'neut_diff_free_energy_grid' dimensions: 38 29 33
'vdw_grid' dimensions: 38 29 33
'order_grid' dimensions: 38 29 33

szmap-meta-data attached to molecule 2, 'ligand: residue 'BFS''.
'lig_mask_grid' dimensions: 38 29 33
'neut_diff_lig_free_energy_grid' dimensions: 38 29 33
'lig_vdw_grid' dimensions: 38 29 33
'lig_order_grid' dimensions: 38 29 33

szmap-meta-data attached to molecule 3, 'apo: PROTEIN (SCYTALONE DEHYDRATASE)'.
'apo_mask_grid' dimensions: 38 29 33
'neut_diff_apo_free_energy_grid' dimensions: 38 29 33
'apo_vdw_grid' dimensions: 38 29 33
'apo_order_grid' dimensions: 38 29 33

szmap-meta-data attached to molecule 4, 'stabilization'.
'stbl_mask_grid' dimensions: 38 29 33
'neut_diff_stbl_free_energy_grid' dimensions: 38 29 33
'stbl_vdw_grid' dimensions: 38 29 33
'stbl_order_grid' dimensions: 38 29 33

Input appears to be the results file from a SZMAP grid calculation.
SZMAP grids but no -at_coords property tags in input file.
```

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```
> szmap_grid 2w3a_coords.oeb.gz

szmap-meta-data attached to molecule 1, 'apo: TOP'.
atom property tags: szmap_mask, szmap_neut_diff_free_energy, szmap_neut_diff_enthalpy,
szmap_neut_diff_entropy, szmap_vdw, szmap_order, szmap_vac_diff_free_energy,
szmap_vac_diff_enthalpy, szmap_vac_diff_entropy, szmap_free_energy, szmap_enthalpy,
szmap_entropy, szmap_neutral_free_energy, szmap_neutral_enthalpy,
szmap_neutral_entropy, szmap_interaction, szmap_psolv, szmap_wsolv, szmap_intvdw,
szmap_probe_burial, szmap_clash

szmap-meta-data attached to molecule 2, 'apo: DIHYDROFOLATE REDUCTASE+ion+cofact'.

Input appears to be the results file from a SZMAP -at_coords calculation.
SZMAP -at_coords property tags but no grids in input file.
```

szmap_grid can also split a given grid out into a separate grid file. The output grid can be in OEBinary, Grasp, CCP4, or ascii format. Since *PyMOL* can read Grasp *.phi* maps, they provide a way to transfer grids from *SZMAP* to *PyMOL*.

```
> szmap_grid 4std_stbl.oeb.gz neut_diff_apo_free_energy_grid 4std_nddG.phi
```

The options `-output_all_format` and `-prefix` will generate a separate grid file for all grids in the *SZMAP* results.

```
> szmap_grid -output_all_format .phi -prefix 4std 4std_stbl.oeb.gz
```

If the **szmap_grid** option `-at_coords` is used, the specified grid's values will be interpolated at the coordinates of any atoms in the input coordinates file and written out attached to those atoms in a file defined by *-mol* for use by other tools. A tab-delimited table of these results is written to *standard-output*.

```
> szmap_grid -at_coords coords.sdf -mol out.oeb szmap.oeb.gz vdw_grid >table.txt
```

Note

A direct calculation at these coordinates using *SZMAP* will be superior to these interpolated values.

Meta-data

SZMAP attaches meta-data to molecules in the results file that documents run conditions. This data is displayed when the **szmap_grid** option *-verbose* is used.

```
szmap-meta-data attached to molecule 1, 'complex: PROTEIN (SCYTALONE DEHYDRATASE) +␣
↪residue 'BFS''.

points: grid
system: complex
prot-title: PROTEIN (SCYTALONE DEHYDRATASE)
prot-num-atoms: 2680
prot-num-bonds: 2720
lig-title: residue 'BFS'
lig-num-atoms: 33
lig-num-bonds: 34
dielectric-model: gaussian
eps-outer: 80
```

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```
eps-inner: 1
salt-conc: 0.05M
probe-type: water
orientations: 60
rotation-matrices: symmetrical
mask-cutoff: 0
mask: calculation=1.01
mask: bulk solvent=0.99
mask: clash=0
grid-spacing: 0.5A
zap-spacing: 0.5A
zap-iters: 5
run-date: Jan 23 2013
run-time: 10:48:03
version: 20130123
release: 1.1.1
arch: redhat-RHEL5-x64
platform: redhat-RHEL5-g++4.1-x64
licensee: Initech
site: Austin
```

The meta-data includes the version and release of *SZMAP* used to generate the results. Early releases used a different format, `version: 110` for version 1.1.0.

5.1.3 Command Line Help

A description of the command line interface can be obtained by executing **SzmapGrid** with the *–help* option.

```
> szmap_grid --help
```

will generate the following output:

```
Help functions:
  szmap_grid --help simple      : Get a list of simple parameters
  szmap_grid --help all         : Get a complete list of parameters
  szmap_grid --help defaults    : List the defaults for all parameters
  szmap_grid --help <parameter> : Get detailed help on a parameter
  szmap_grid --help html        : Create an html help file for this program
  szmap_grid --help versions    : List the toolkits and versions used in the application
```

5.1.4 Required Parameters

-input_mol <filename>

-i <filename>

[keyless parameter 1]

OEBinary input file (*.oeb* or *.oeb.gz*), with calculated grids attached to copy input molecule(s).

5.1.5 Optional Parameters

Grid Options

-grid <name>

-g <name>

[keyless parameter 2]

Grid to extract or display information about. Name must be one of the grid names listed in *Appendix 1: SZMAP Grids*.

If not specified, information will be displayed about all grids.

-output_grid <filename>

-o <filename>

[keyless parameter 3]

The file format of the output grid file is automatically determined from the file extension.

File type	Extension
OE grid	.grd .grd.gz
Grasp grid	.phi .phi.gz
Ascii grid	.agd .agd.gz
CCP4 map	.map .map.gz .ccp .ccp.gz
.ccp4 .ccp4.gz	

Use *-output_all_format* instead to write all grids into separate files.

-output_all_format <format>

-all <format>

Write out every grid to individual files in the specified format. Used in conjunction with *-prefix*.

File type	Format
OE grid	.grd .grd.gz
Grasp grid	.phi .phi.gz
Ascii grid	.agd .agd.gz
CCP4 map	.map .map.gz .ccp .ccp.gz
.ccp4 .ccp4.gz	

-prefix <text>

Filename prefix for grid files written when *-output_all_format* is specified. Can include file path in addition to the beginning portion of the filename.

[Default=szmap_grid]

-slice

Print grid values to *standard-output* as a series of 2D tabular slices.

-std_box <filename>

Write *standard* (complex) grid bounding box to output 'box molecule' coordinate file.

File type	Extension
SDF	.sdf .mol .sdf.gz .mol.gz
MOL2	.mol2 .mol2.gz
PDB	.pdb .ent .pdb.gz .ent.gz
MacroModel	.mmod .mmod.gz
OEBinary	.oeb .oeb.gz

To facilitate visualization, box corners are represented by nitrogen atoms and bonds define the box edges.

-lig_box <filename>

Write *ligand* grid bounding box to output 'box molecule' coordinate file.

File type	Extension
SDF	.sdf .mol .sdf.gz .mol.gz
MOL2	.mol2 .mol2.gz
PDB	.pdb .ent .pdb.gz .ent.gz
MacroModel	.mmod .mmod.gz
OEBinary	.oeb .oeb.gz

To facilitate visualization, box corners are represented by nitrogen atoms and bonds define the box edges.

-apo_box <filename>

Write *apo* grid bounding box to output 'box molecule' coordinate file.

File type	Extension
SDF	.sdf .mol .sdf.gz .mol.gz
MOL2	.mol2 .mol2.gz
PDB	.pdb .ent .pdb.gz .ent.gz
MacroModel	.mmod .mmod.gz
OEBinary	.oeb .oeb.gz

To facilitate visualization, box corners are represented by nitrogen atoms and bonds define the box edges.

-box_mol <filename>

Write *box_mol* bounding box to output 'box molecule' coordinate file, if a *box_mol* is found in the input *.oeb* file.

File type	Extension
SDF	.sdf .mol .sdf.gz .mol.gz
MOL2	.mol2 .mol2.gz
PDB	.pdb .ent .pdb.gz .ent.gz
MacroModel	.mmod .mmod.gz
OEBinary	.oeb .oeb.gz

To facilitate visualization, box corners are represented by nitrogen atoms and bonds define the box edges.

Interpolation Options

-at_coords <filename>

-coords <filename>

Interpolate the values of the selected grid (and the corresponding mask grid) at the coordinates of atoms in any molecules in the file. Write those molecules, with the (masked) results attached to the atoms, to the output file.

File type	Extension
SDF	.sdf .mol .sdf.gz .mol.gz
MOL2	.mol2 .mol2.gz
PDB	.pdb .ent .pdb.gz .ent.gz
MacroModel	.mmod .mmod.gz
OEBinary	.oeb .oeb.gz

One of the following tags will be used when assigning values to atoms (without any apo_ or lig_):

- *szmap_mask*
- *szmap_neut_diff_free_energy*
- *szmap_neut_diff_enthalpy*
- *szmap_neut_diff_entropy*
- *szmap_vac_diff_free_energy*
- *szmap_vac_diff_enthalpy*
- *szmap_vac_diff_entropy*
- *szmap_free_energy*
- *szmap_enthalpy*
- *szmap_entropy*
- *szmap_neutral_free_energy*
- *szmap_neutral_enthalpy*
- *szmap_neutral_entropy*
- *szmap_interaction*
- *szmap_psolv*
- *szmap_wsolv*
- *szmap_vdw*
- *szmap_intvdw*
- *szmap_probe_burial*

-output_mol <filename>

-mol <filename>

OEBinary output file (*.oeb* or *.oeb.gz*), with interpolated grid values attached to *-at_coords* molecule's atoms.

[Default=szmap_grid_interp.oeb.gz]

-no_table

Do not print a tab-delimited table of interpolated grid values to *standard-output* when *-at_coords* is the selection.

-mask_cutoff <number>

Points where interpolated mask values are less than or equal to this cutoff will have values attached to atoms set to 0.0. The default value tries to account for the edges of the masked area where interpolation can generate distorted results.

[Default=0.8]

Other Options

-verbose

-v

Print additional grid details (and *SZMAP* meta-data) to *standard-output*.

5.2 GridComp

5.2.1 Overview

The **GridComp** utility reads grids, from an OEBinary file (*.oeb* or *.oeb.gz*) generated by *SZMAP*, or from an individual grid file, and performs an operation, usually producing a grid file containing the results. It is designed to make it easy to compare grids and produce new types of grids by combining others. It handles grids with different shapes or that do not completely overlap and will interpolate if the grid points are not aligned.

GridComp can compute the sum, difference, average and other mathematical transformations of grids. The operations *set_above*, *set_below*, *mask*, and *not_mask* are used to truncate grids.

The operations *total* and *integrate* are the only ones that do not require an output grid. They write summary statistics describing a grid to standard output.

The operations *lig_disp* and *prot_disp* take a *SZMAP* results OEBinary file and produce another OEBinary file containing additional results for the region in the *apo* pocket displaced by the ligand when the complex if formed or the region around the ligand displaced by the protein in the complex, respectively.

The operations *mask_all* and *stabilization* also processes an OEBinary file to produce another.

5.2.2 Example Commands

A common operation is to append data to *SZMAP* output for the region in the *apo* protein where the ligand displaces solvent in the complex:

```
> grid_comp -op lig_disp -i 4std_stbl.oeb.gz -o 4std_stbl_disp.oeb.gz
```

SZMAP output contains masks that can be used, for example, to define the region that the *integrate* operation sums over:

```
> grid_comp integrate my.oeb.gz     free_energy_grid same mask_grid > int.txt
> grid_comp integrate my.oeb.gz apo_free_energy_grid same mask_grid >>int.txt
> grid_comp integrate my.oeb.gz lig_free_energy_grid same mask_grid >>int.txt
```

In the example above, the complex *mask_grid* is used for all integrations so that the results can be combined to yield a solvent correction to *ZAP bind*: (*complex* + *bulk*) - (*apo* + *ligand*), where *bulk* = 0.0. The free energy grids used, which are not the same as the *difference* free energy grids, are only available if **SZMAP** is run with the option `-results_set max`. Usually, the grid *file* and the grid *name* are specified in pairs. The keyword `same` used in the example above refers to the same file as the energy grid, *my.oeb.gz*, and is just used for convenience.

The following command creates a mask file defining regions where the van der Waals energy in the complex is less than or equal to -2 kcal/mol (*low.grd.gz*) and applies the mask to the complex neutral difference free energy grid to produce the file *nddG.grd.gz* containing a subset of that grid:

```
> grid_comp -leq -2.0 make_mask my.oeb.gz vdw_grid same point_grid low.grd.gz
> grid_comp mask my.oeb.gz neut_diff_free_energy_grid low.grd.gz na nddG.grd.gz
```

The keyword na stands for not-applicable and is a convenience used to skip the grid_name field (which is not needed because the file *low.grd.gz* contains only one grid), allowing all the parameters to be specified without having to sprinkle the command line with a large number of -flags.

5.2.3 Command Line Help

A description of the command line interface can be obtained by executing **GridComp** with the *–help* option.

```
> grid_comp --help
```

will generate the following output:

```
Help functions:
  grid_comp --help simple      : Get a list of simple parameters
  grid_comp --help all         : Get a complete list of parameters
  grid_comp --help defaults    : List the defaults for all parameters
  grid_comp --help <parameter> : Get detailed help on a parameter
  grid_comp --help html        : Create an html help file for this program
  grid_comp --help versions    : List the toolkits and versions used in the application
```

5.2.4 Required Parameters

-operation <value>

-op <value>

[keyless parameter 1]

Operation to be performed on grid(s). The *scale* operation scales by *-scale*. Operations *set_above* and *set_below* use cutoff values of *-cutoff* and set values to *-new_value*. The *total* and *integrate* operations treat *-input_file2* / *-grid2* as a mask (mask values above *-masked_point_cutoff* are summed) and write the result to standard output. If an optional third (point) grid is supplied for *total* and *integrate*, the second grid is treated as an energy grid and the mask is built on-the-fly.

Value	Type	Operation
sum	binary	Sum of the two grid values
diff	binary	Difference of the two grid values
min	binary	Minimum of the two grid values
max	binary	Maximum of the two grid values
avg	binary	Average of the two grid values
mul	binary	Multiply the two grid values
total	binary	Display total of values within mask
integrate	binary	Display integral of values within mask
make_mask	binary	Build a mask from value and point grids
mask	binary	Keep values only in masked regions
not_mask	binary	Keep values only outside of masked regions
lig_disp	binary	Add apo data displaced in complex by ligand
prot_disp	binary	Add lig data displaced in complex by protein
scale	unary	Multiply values by scale factor
offset	unary	Add an offset to each grid value
set_above	unary	Modify values that are above cutoff
set_below	unary	Modify values that are below cutoff
largest	unary	Grid subset within the largest contour
stabilization	unary	Calculate stabilization grids
mask_all	unary	Build and apply a mask to all grids

Binary operations require two grids and unary operations require only one. The *lig_disp*, *prot_disp*, *mask_all*, and *stabilization* operations work on the entire set of grids in the *.oeb* input file and do not take a grid name. They do, however, require the output file to be an *.oeb* file.

The operations *total* and *integrate* send numerical results to *standard-out* but can also optionally write an output grid if a mask is calculated on-the-fly.

The operation *largest* makes contour surfaces based on `-cutoff` and suppresses values outside of the largest contour region.

-input_file1 <filename>

-in1 <filename>

-i <filename>

[keyless parameter 2]

Grid file to operate on. If an OEBinary file is used, `-grid1` must be specified. The file format of the grid file is automatically determined from the file extension.

File type	Extension
OEBinary	.oeb .oeb.gz (requires `-grid1`)
OE grid	.grd .grd.gz
Grasp grid	.phi .phi.gz
Ascii grid	.agd .agd.gz
CCP4 map	.map .map.gz .ccp .ccp.gz
.ccp4 .ccp4.gz	

5.2.5 Optional Parameters

Grid Options

-grid1 <name>

[keyless parameter 3]

Grid in OEBinary input_file1 to operate on.

Name must be one of the grid names listed in *Appendix 1: SZMAP Grids*.

A value of *na* is used with keyless options when the grid is in a separate grid file and not attached to an OEBinary file.

-input_file2 <filename>

-in2 <filename>

[keyless parameter 4]

Grid file to operate on. If an OEBinary file is used, *-grid2* must be specified. The file format of the grid file is automatically determined from the file extension.

File type	Extension
OEBinary	.oeb .oeb.gz (requires *-grid2*)
OE grid	.grd .grd.gz
Grasp grid	.phi .phi.gz
Ascii grid	.agd .agd.gz
CCP4 map	.map .map.gz .ccp .ccp.gz
.ccp4 .ccp4.gz	

A value of *same* is used to refer to the same file as *-input_file1*.

A value of *na* is used with keyless options when *-input_file2* is not required.

-grid2 <name>

[keyless parameter 5]

Grid in OEBinary input_file2 to operate on.

Name must be one of the grid names listed in *Appendix 1: SZMAP Grids*.

A value of *na* is used with keyless options when the grid is not an OEBinary file or the grid will not be used.

-input_file3 <filename>

-in3 <filename>

Grid file to operate on. Contains the (point) grid required when *-leq_mask* or *-geq_mask* is used with operation `total` or `integrate` to create the mask on the fly.

If an OEBinary file is used, *-grid3* must be specified. The file format of the grid file is automatically determined from the file extension.

File type	Extension
OEBinary	.oeb .oeb.gz (requires *-grid3*)
OE grid	.grd .grd.gz
Grasp grid	.phi .phi.gz
Ascii grid	.agd .agd.gz
CCP4 map	.map .map.gz .ccp .ccp.gz
.ccp4 .ccp4.gz	

A value of *same* is used to refer to the same file as *-input_file2*.

A value of *na* is used with keyless options when *-input_file3* is not required.

-grid3 <name>

Grid in OEBinary input_file3 to operate on.

Name must be one of the grid names listed in *Appendix 1: SZMAP Grids*.

A value of *na* is used with keyless options when the grid is not an OEBinary file or the grid will not be used.

-output_grid <filename>

-o <filename>

[keyless parameter 6]

Not used with the operations: *total* and *integrate*.

The file format of the output grid file is automatically determined from the file extension.

File type	Extension
OE grid	.grd .grd.gz
Grasp grid	.phi .phi.gz
Ascii grid	.agd .agd.gz
CCP4 map	.map .map.gz .ccp .ccp.gz
.ccp4 .ccp4.gz	

For `remask` operation, the file must be in OEBinary format (with extension .oeb or .oeb.gz).

Parameter Options

-leq_mask <number>

-leq <number>

When generating a mask for the operations `total` and `integrate`, values in grid2 equal to or less than this are counted as in the mask if the value of the corresponding point in grid3 is > *-masked_point_cutoff*. Grid2 is often the `intvdw_grid` and grid3 is often `point_grid`.

When used with the operation `make_mask`, values of grid1 equal to or less than this are counted in the mask if the value of the corresponding point in grid2 is > *-masked_point_cutoff*.

When used with the operation `mask_all`, values of *intvdw_grid*, *apo_intvdw_grid* and *lig_intvdw_grid* equal to or less than this are counted in the mask if the value of the corresponding point in *point_grid*, *apo_point_grid* or *lig_point_grid* is greater than *-masked_point_cutoff*.

-geq_mask <number>

-geq <number>

When generating a mask for the operations `total` and `integrate`, values in grid2 equal to or greater than this are counted as in the mask if the value of the corresponding point in grid3 is > *-masked_point_cutoff*. Grid2 is often the `intvdw_grid` and grid3 is often `point_grid`.

When used with the operation `make_mask`, values of grid1 equal to or greater than this are counted in the mask if the value of the corresponding point in grid2 is > *-masked_point_cutoff*.

When used with the operation `mask_all`, values of *intvdw_grid*, *apo_intvdw_grid* and *lig_intvdw_grid* equal to or greater than this are counted in the mask if the value of the corresponding point in *point_grid*, *apo_point_grid* or *lig_point_grid* is greater than *-masked_point_cutoff*.

-cutoff <number>

Cutoff value for *set_above*, *set_below*, and *largest* operations.

[Default=0.0]

-masked_point_cutoff <number>

Cutoff value for the mask. Mask values greater than this are selected. The (strict) default selects both calculation (1.01) and solvent (0.99) points.

[Default=0.98]

-new_value <number>

-to <number>

Value assigned to values beyond the cutoff with the *set_above* and *set_below* operations.

[Default=0.0]

-by <number>

-scale <number>

Amount grid values are multiplied by with the *scale* operator or amount added to grid values with the *offset* operator.

[Default=1.0]

-default_value <number>

-default <number>

Value assigned to points where grids do not overlap and assigned to unselected points during *mask* and *mask_all* operations.

[Default=0.0]

-int_method <value>

-method <value>

Method used when performing the integrate operation.

Value	Meaning
voxel	Sum masked values and scale by grid voxel/water volume
average	Average masked values and scale by excluded/water volume
grow	Grow edge values into the excluded volume and average

[Default=voxel]

-mask_vdw

Override behavior of `mask_all` operation to use *vdw_grid* rather than *intvdw_grid*, etc.

Other Options

-verbose

-v

Print additional grid details to *standard-error*.

5.3 SzmapReport

5.3.1 Overview

The **szmap_report** utility reads an OEBinary file (*.oeb* or *.oeb.gz*) generated by using the `-at_coords` flag with *SZMAP* and produces a *.pdf* file containing one or more 2-dimensional renderings of the results. The calculated values for a given property are shown as colored patches around each coordinate position. (You can also visualize these properties in 3D using *Color By Atom Properties*). Atoms at coordinates with no calculated property, because the probe clashed when placed there, are grayed out.

> **Note**
>
> Versions of *SZMAP* prior to 1.1.0 attach only a limited number of properties to atoms. To display *vdw* or *order*, for example, you may need to rerun calculations with the latest *SZMAP* version.

If a concatenated series of molecules are used as input to `szmap -at_coords`, **szmap_report** will produce a figure for each molecule. You can control the formatting to either place the output for each molecule on a separate page, or align the output for different molecules on the same page.

By default option *-surface* is *true*, meaning a 2D surface boundary for the molecule is shown with different line types depending on how loose or tight the binding site is around each atom. Boundary styles are: simple black lines for close contacts, lines with short radial lines indicate a small gap, and outward reaching fingers indicate a cavity, a place with enough space to place a water or other atoms. Thin gray lines indicate a solvent exposed region.

If hydrogens are in the output, they are usually suppressed from the display. If you want to display data calculated at hydrogen positions, use *-keep_hydrogens*, but because surfaces are rendered only for heavy atoms, *-surface* must also set to false.

The output is rendered by OpenEye's **OEDepict** and **Grapheme** toolkits (additional licenses not required). See figure *SZMAP report output*.



Fig. 1: **SZMAP report output**

5.3.2 Example Commands

```
prompt> szmap_report 4std_lig_coords.oeb.gz 4std_lig_coords.pdf
```

This executes **SzmapReport** with the default parameters. The file *4std_lig_coords.oeb.gz* containing **SZMAP** - *at_coords* results is used as input, and the output is written to the file *4std_lig_coords.pdf*,

5.3.3 Command Line Help

A description of the command line interface can be obtained by executing **SzmapReport** with the `--help` option.

```
> szmap_report --help
```

will generate the following output:

```
Help functions:
  szmap_report --help simple      : Get a list of simple parameters
  szmap_report --help all         : Get a complete list of parameters
  szmap_report --help defaults    : List the defaults for all parameters
  szmap_report --help <parameter> : Get detailed help on a parameter
  szmap_report --help html        : Create an html help file for this program
  szmap_report --help versions    : List the toolkits and versions used in the␣
↪application
```

5.3.4 Required Parameters

-input <filename>

-i <filename>

[keyless parameter 1]

OEBinary input file (*.oeb* or *.oeb.gz*), with results calculated at specified coordinates.

5.3.5 Optional Parameters

-output <filename>

-o <filename>

[keyless parameter 2]

Output .pdf file containing one or more 2D renderings.

[Default=szmap_report.pdf]

-tagname <prop>

-t <prop>

[keyless parameter 3]

Atom property used to generate color patches around each atom:

Prop must be one of the property names listed in *Appendix 2: SZMAP Atom Properties*. The list of tags for a given results file can be displayed by *SzmapGrid*.

The *szmap_neut_diff_free_energy* property is one of the most useful. It describes the hydrophilicity/hydrophobicity at each coordinate.

If no tag is specified, an array of properties will be displayed for each input molecule.

Molecule Display Options

-aromstyle <style>

-astl <style>

Aromatic ring display style: *Kekule, Circle, Dash*.

[Default=Kekule]

-atomcolor <color>

-acolor <color>

Atom coloring style: *WhiteCPK, BlackCPK, WhiteMonochrome, BlackMonochrome, cow, cob, bow, wob*.

Style	Meaning
cow	(color on white) same as WhiteCPK
cob	(color on black) same as BlackCPK
bow	(black on white) same as WhiteMonochrome
wob	(white on black) same as BlackMonochrome

[Default=WhiteCPK]

-atomstereostyle <style>

-atomsstl <style>

Atom stereo display style: *Hidden, AtomStereo, StandardStyle, FancyStyle*. Combined expressions: Created by combining primitive tokens with "|".

[Default=AtomStereo|FancyStyle]

-bondcolor <color>

-bcolor <color>

Bond coloring style: *ByElement, Monochrome*.

[Default=ByElement]

-bondstereostyle <style>

-bondsstl <style>

Bond stereo display style: *Hidden, BondStereo, CIPBondStereo*. Combined expressions: Created by combining primitive tokens with "|".

[Default=BondStereo]

General Options

-title <text>

Title for each page.

[Default="SZMAP Report"]

-pagesize <size>

-size <size>

Output file page size: *US_Letter, A4*.

[Default=US_Letter]

-rows <number>

Number of rows on a page [1-10].

-cols <number>

Number of columns on a page [1-10].

-resolution <level>

Quality of color maps representing properties. The level will influence the size of the output—*high* produces output several times larger than *medium* produces.

Level	Meaning
low	chunky (grain size: 5 x 5)
medium	smooth (grain size: 2 x 2)
high	very smooth (grain size: 1 x 1)

[Default=medium]

-separate

Output separate pages for each at_coords molecule. The default is to concatenate output. Use *-rows* and *-cols* to adjust the formatting.

-legend <bool>

Show property legend.

[Default=true]

-surface <bool>

Show 2D molecular surface outline.

[Default=true]

-keep_hydrogens

Show all the explicit hydrogens in depictions. Requires *-surface* to be set to false.

[Default=false]

-tag_set <set>

Tag set used when no explicit tag is specified. The set 'v1' is provided for backwards compatibility with *SZMAP* version 1 results.

Set	Meaning
min	szmap_neut_diff_free_energy, szmap_vdw, szmap_order
max	szmap_neut_diff_free_energy, szmap_neut_diff_entropy,
szmap_interaction,	szmap_vdw, szmap_psolv, szmap_wsolv
v1	szmap_neut_diff_free_energy, szmap_probe_burial

[Default=min]

Other Options

-verbose

-v

Print status information to *standard-error*.

CHAPTER

SIX

VIDA EXTENSIONS

6.1 Introduction

There are three *VIDA* extensions for working with *SZMAP* output:

1. The *Water Orientation VIDA Extension* identifies key waters and analyzes their energies and orientational constraints.
2. The *WaterColor VIDA Extension* changes the display styles of *SZMAP* grids and *GamePlan* annotation to facilitate analysis.
3. The *Color By Atom Properties* colors molecules based on properties calculated at atomic coordinates.

6.2 Installing VIDA Extensions

See the *VIDA* manual (http://www.eyesopen.com/documentation/) for a complete description of how to use the program, including installation of the extensions that are included in the *SZMAP* distribution. This section will give a brief description of how to install the extensions.

The *VIDA* extensions are located in

```
{SZMAP Version Examples}/vida_extensions/{vida-version}/
```

The extensions are organized by VIDA version number:

- **4.2.1** - the *WaterColor VIDA Extension* v1.7.7, the *Color By Atom Properties* v1.3.0 and the *Water Orientation VIDA Extension* v1.1.2. These extensions can be used with *VIDA* versions 4.2.1 or higher.

You can check your version of *VIDA* using the *Help* >> *About...* menu.

Note

If you already have previous versions of any *SZMAP* extensions installed in *VIDA's Extensions* menu, go to the *Edit >> Extensions...* menu and unsubscribe using the *Manage Subscriptions...* button or, if one or more *SZMAP* extension has been installed separately, uninstall by clicking the red "X". Then restart *VIDA*.

If you have not already installed *SZMAP*, do so before installing the extensions.

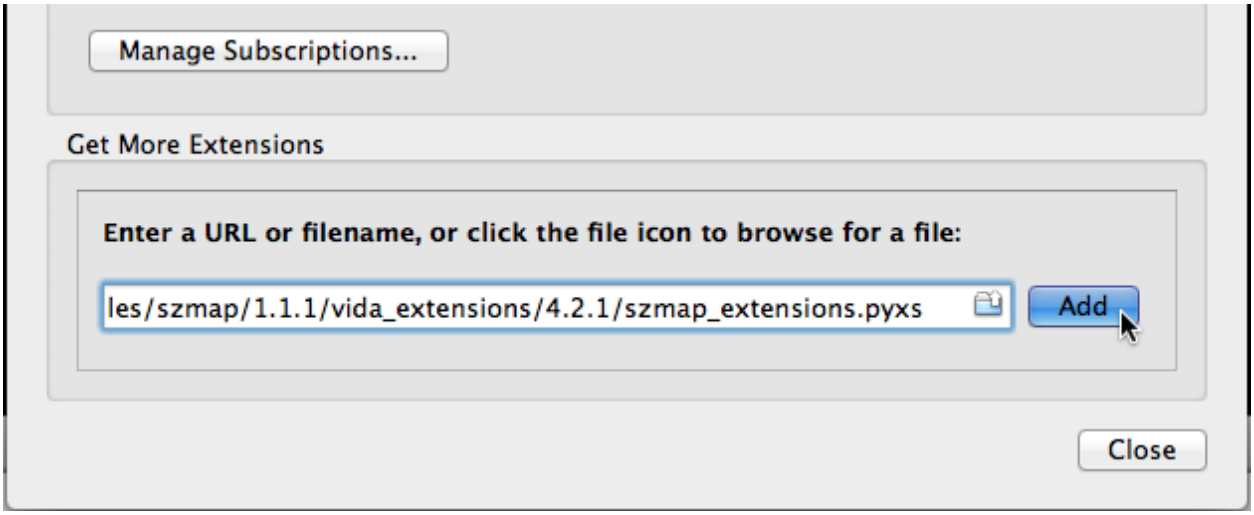


Fig. 1: **Add the Subscription**

To install the *SZMAP* extensions: open *VIDA* and select the *Edit >> Extensions...* menu item, then click on the small folder icon in the *Get More Extensions* section at the bottom of the window. Browse to the `{SZMAP Version Examples}/vida_extensions/{vida-version}/` directory/folder, and open the file called `szmap_extensions.pyxs` that packages the extensions. Then click *Add* to subscribe to the extensions. Each extension will show up in the upper part of the window and be added to the *Extensions* menu.

Note

By mistake, *SZMAP* 1.0.0 installed the extensions in a location without a *SZMAP* version number in the directory path and these old extensions could be confused with the current versions of the extensions. Make sure you load extensions from the path shown above, where `{szmap-version}` is 2026.1.0 and `{vida-version}` corresponds to the version of VIDA you are using or earlier.

You should now be able to select the *SZMAP* extensions in the *Extensions* menu. You will need to select *WaterColor VIDA Extension* each time you open *SZMAP* or *GamePlan* results in *VIDA*, but the other extensions only need to be selected when the control panel is not visible.

6.3 WaterColor VIDA Extension

The *WaterColor* extension is used to set-up *SZMAP* and *GamePlan* output in *VIDA*.

For *SZMAP* grids, it alters the contour surface display properties. It sets up a standard color scheme for grids, sets some grids to solid surfaces while leaving others wire-mesh, sets up any difference grids to show both positive (yellow) and negative (purple) contours, and sets the contour levels to "reasonable" default values. Feel free to change any of the

properties afterwards. It also restricts the display of protein atoms to just those that surround the ligand and turns on the display of both the protein and the ligand. And protein molecular surface is added to the protein, but not displayed by default.

For *GamePlan* results, the extension makes the annotation visible. It also restricts the protein and ligand display and generates a molecular surface as described for grids.

This extension is not required to analyze `-at_coords` results but if engaged, will set the protein and ligand display as above, along with the molecular surface.

See *Installing VIDA Extensions* for information on installing this extension.

6.3.1 Viewing Results Grids

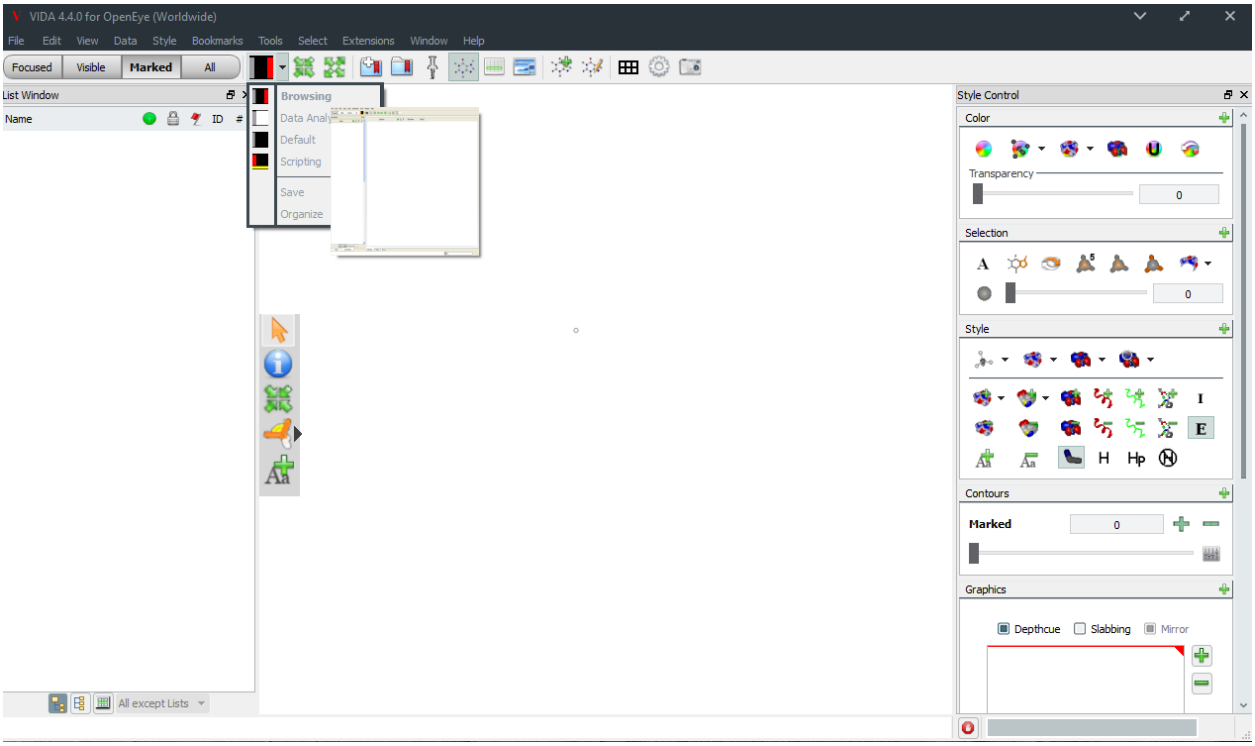


Fig. 2: **Browse View**

- **Step 1**

  Open *VIDA* and make sure the 3D viewer, the *list* panel and the *style* panel are available. If not, select the *Browsing* view (figure *Browse View*) to setup your display. You can move the *list* and *style* panels to as needed—here, we have stacked them on top of one another to save space.

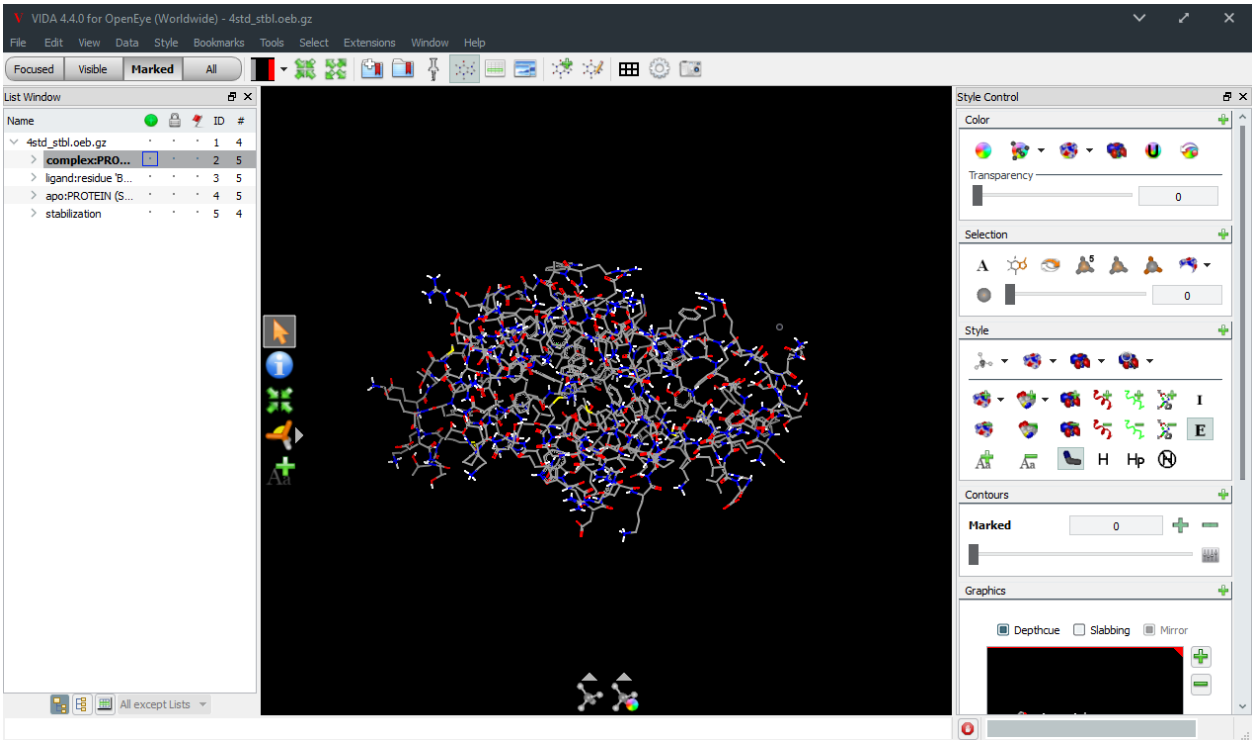


Fig. 3: **List Panel**

- **Step 2**

  Select *File >> Open* and choose the *.oeb.gz* or *.oeb* file containing your *SZMAP* grid results. The file should show up in the *List Panel* and the structure should show in the 3D viewer.

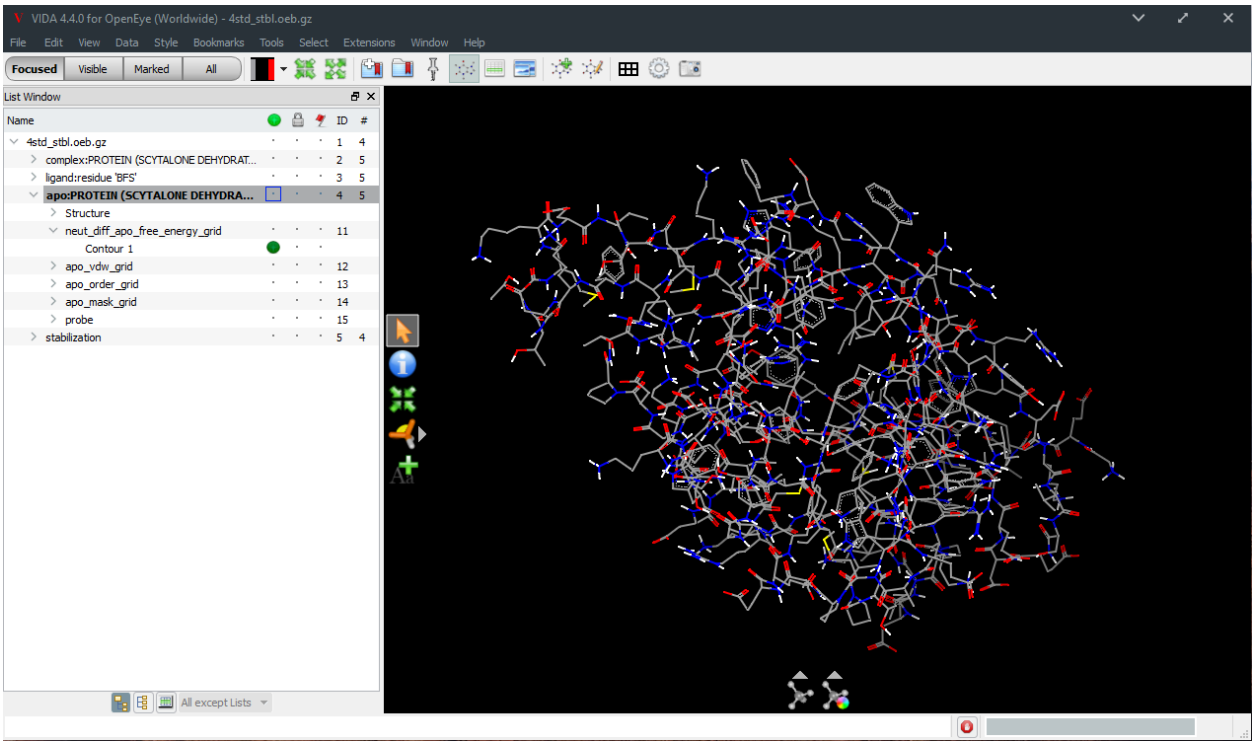


Fig. 4: **Showing Grids**

Click on the > triangle beside the molecule name to show the contents and expand the list panel to show the full contents (figure *Showing Grids*).

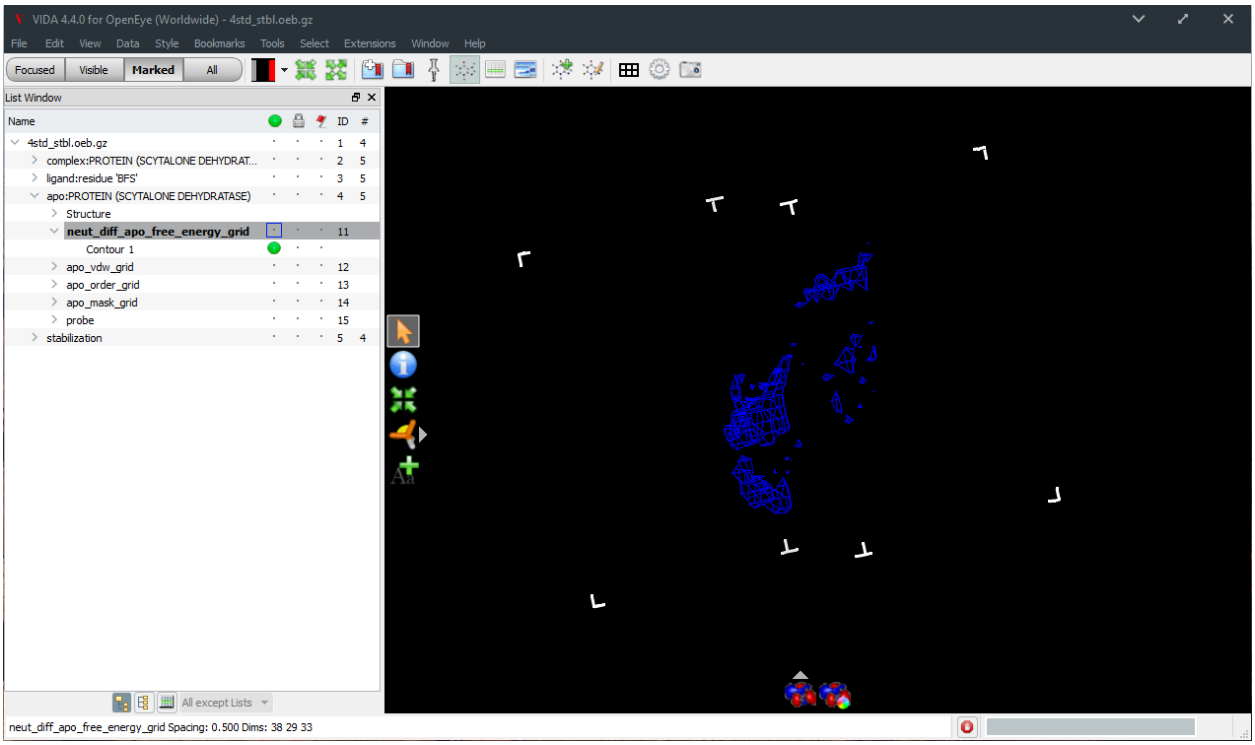


Fig. 5: **Select Grid**

- **Step 3**

  Clicking on the grid name will show that grid (figure *Select Grid*) but the molecule is now deselected and just the grid contour is shown.



Fig. 6: **Isolevel**

You may have to change the contour level slider in the style panel to see the contour (figure *Isolevel*).

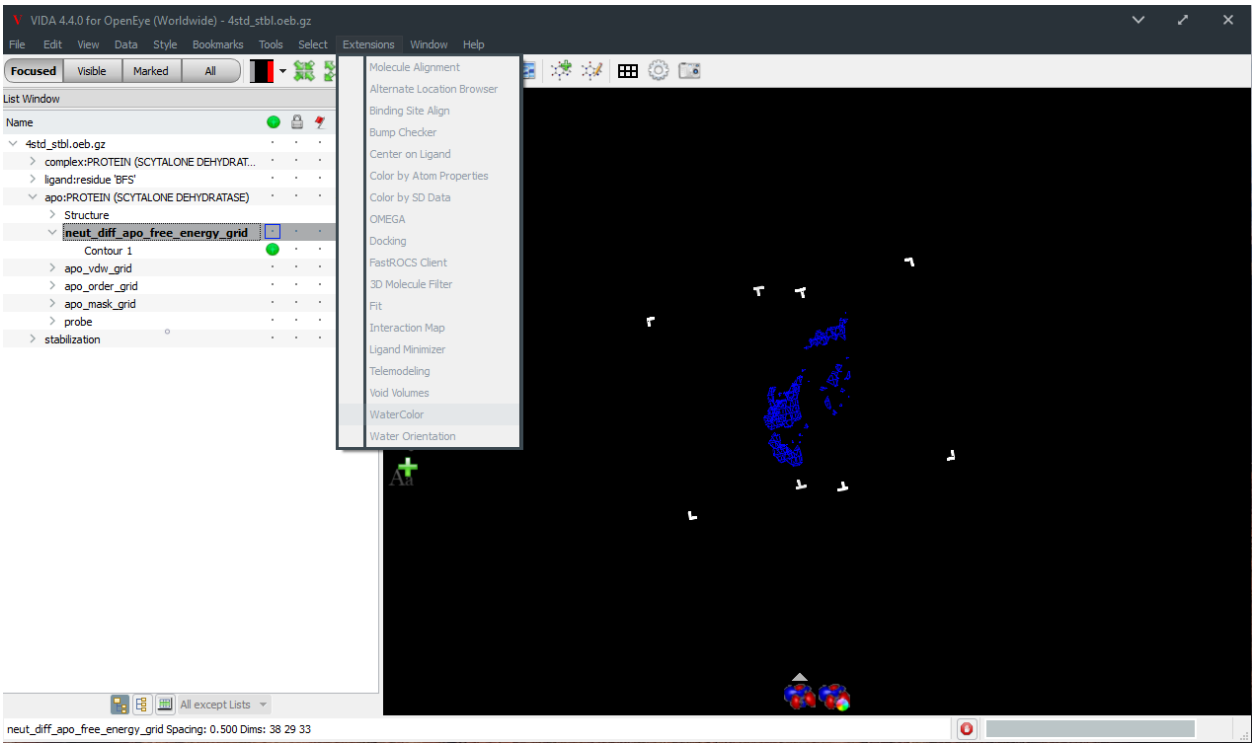


Fig. 7: **WaterColor Extension**

- **Step 4**

  Run the *WaterColor* extension (figure *WaterColor Extension*), to set the contour levels to better starting values and also change the colors and rendering styles so that the various grids are easily distinguish. These settings can be modified using the style panel. It also hides all protein atoms that are not near to the binding site. Finally, it generates a molecular surface associated with the protein that shows the boundary of the binding site. This surface can be selected and displayed in the same way as a grid.

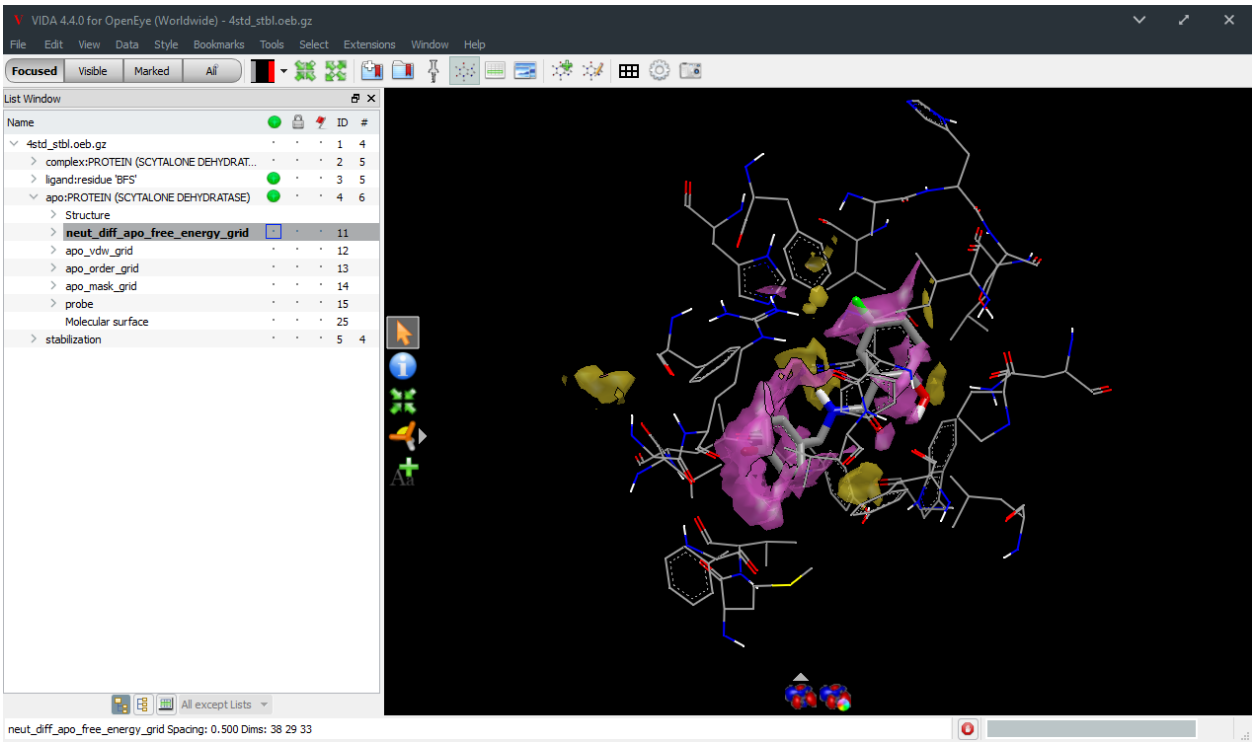


Fig. 8: **Molecule and Grid**

- **Step 5**

  After *WaterColor* runs, the ligand and protein should have a green dot in the visibility column. If it is not visible, click on the *neut_diff_apo_free_energy* list item to show that grid in the context of the input molecules (figure *Molecule and Grid*).

- **Step 6**

  The scene can be scaled (or zoomed) by holding down the Middle mouse button by itself, the Left and Right mouse buttons together, or by using the mouse wheel. The scene can also be scaled using the W and S keys on the keyboard.



Fig. 9: **Center**



Fig. 10: **Select**

You may also need to recenter by clicking on the center button to the left of the 3D viewer (figure *Center*).

Click on the lightning bolt to get out of centering mode and back to selection mode (figure *Select*).

You can pan by holding down the shift key as you drag the mouse.

If you need to adjust the clipping planes, use the + and - buttons in the Graphics style panel (figure *Clipping*).

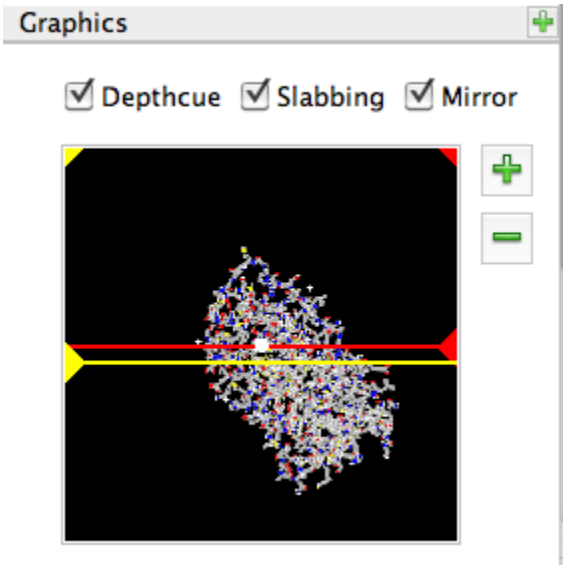


Fig. 11: **Clipping**

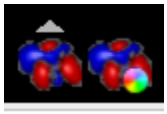


Fig. 12: **Surface Style**

- **Step 7**

  You can change the color of the grid and switch between wireframe lines, solid surface, and point clouds (select the ^ button above the surface icon at the bottom of the 3D display figure *Surface Style*; points have jitter added).

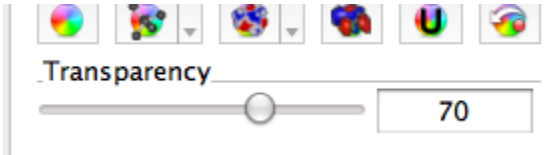


Fig. 13: **Transparency**

When using a solid surface, it can be useful to set the surface transparency in the style menu to, say, 70% (figure *Transparency*).

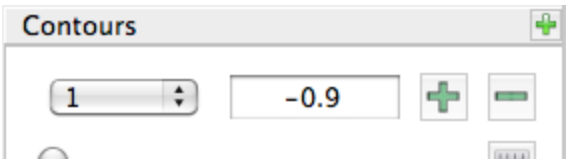


Fig. 14: **Adding Contours**

You can increase the number of contours for a given grid with the + button in the contour style panel (figure *Adding Contours*).

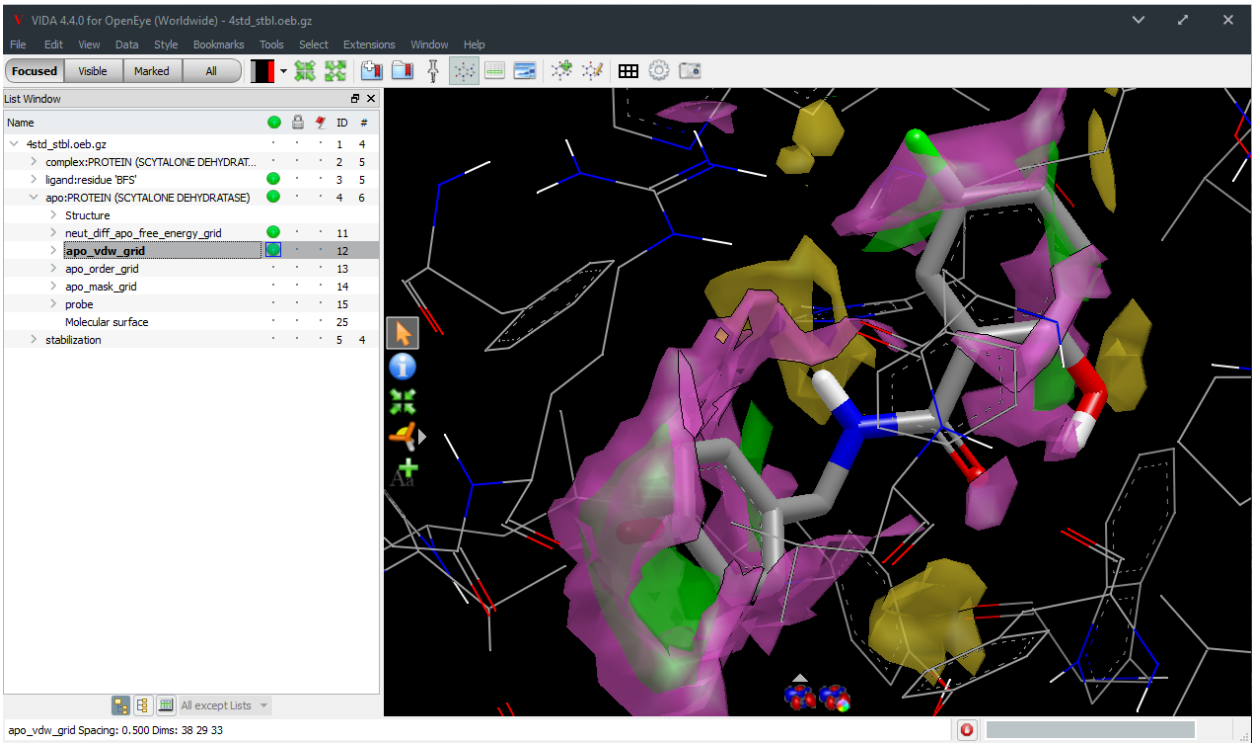


Fig. 15: **Multiple Grids**

- **Step 8**

  Overlapping contours from different grids requires that you select all the grids in the list panel (figure *Multiple Grids*). This can be a little counter-intuitive; play with multiple selections until you get the hang of it.

> **Hint**
>
> Only select one grid at a time if you are trying to change the color or style or transparency to a value different from other grids.

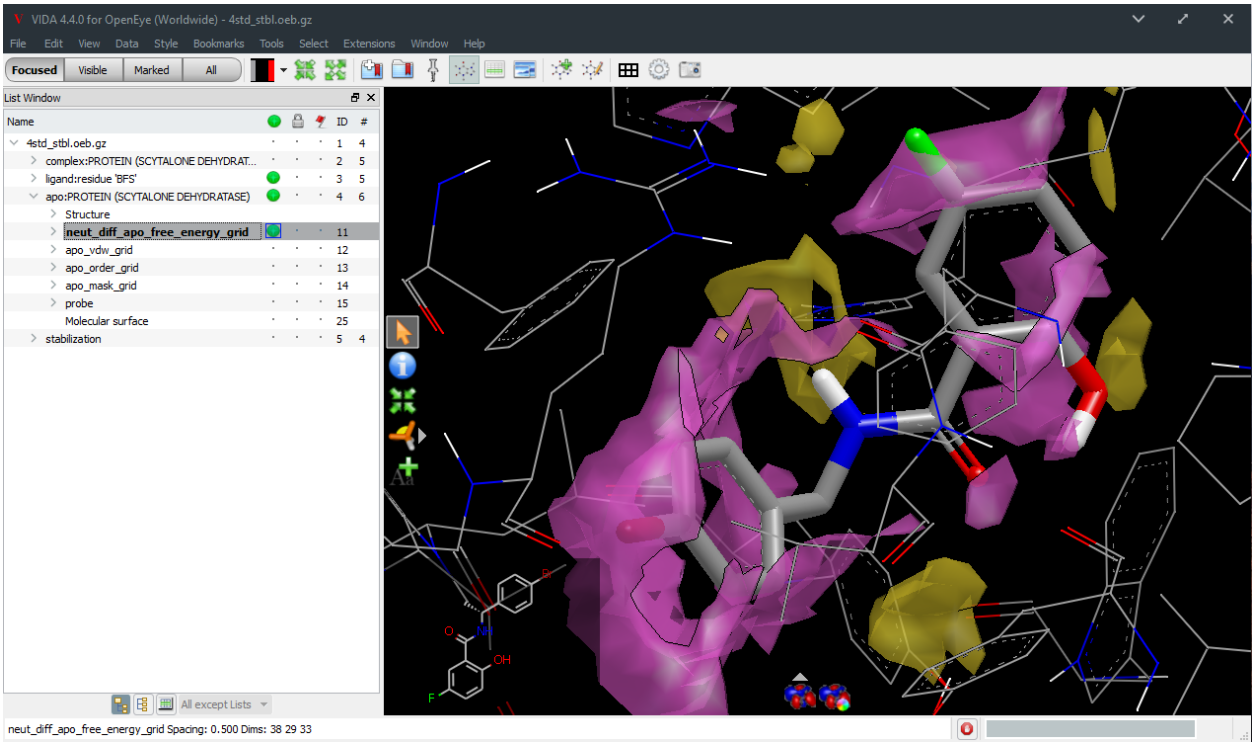


Fig. 16: **Difference Grid**

- **Step 9**

  Difference grids represent the difference between standard water and uncharged water, a proxy for hydrophobic atoms in the ligand. The *WaterColor* extension configures them as a pair of contours: negative in yellow representing areas where standard water has lower values—for ΔG and ΔH standard water is more favorable here—and positive in purple representing areas where uncharged water has lower values (figure *Difference Grid*). The hydrophobic/hydrophilic pattern within a site is matched by high-affinity ligands.

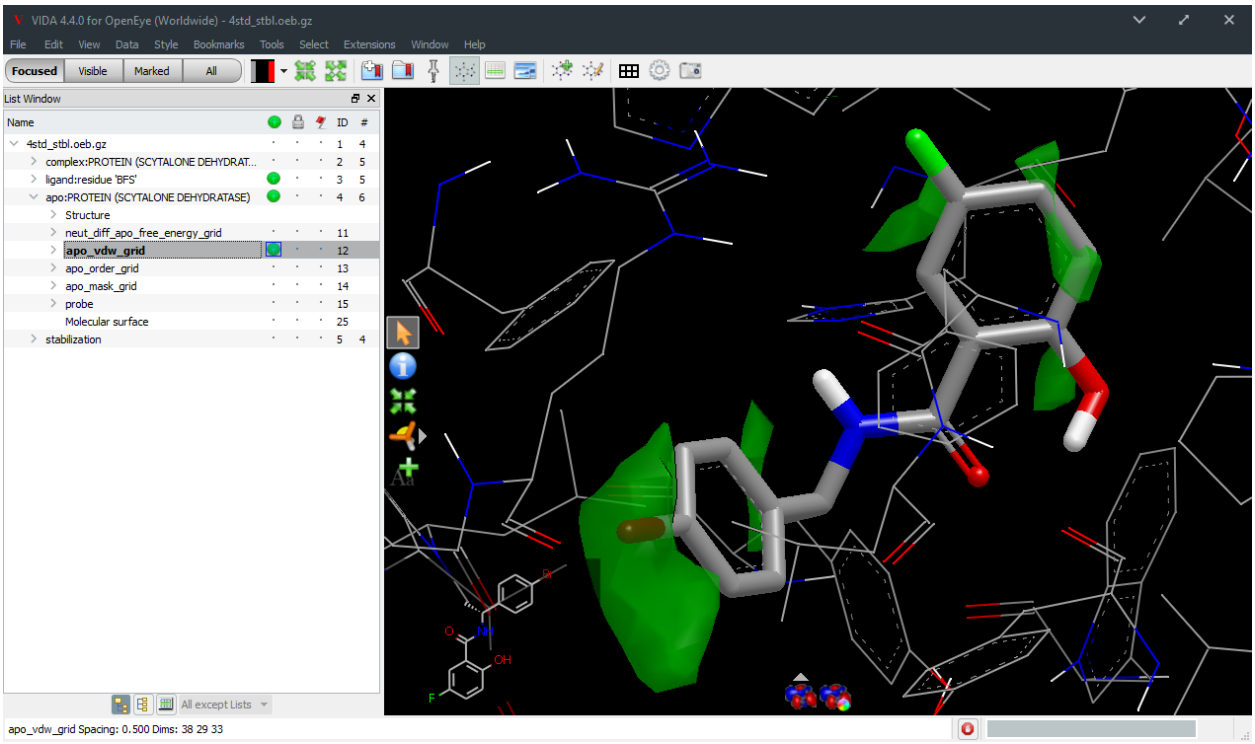


Fig. 17: **VDW Grid**

Van der Waals grids show a component of the energy that is not a part of the difference free energy (because it subtracts out). The default VDW (green) contours are -2 kcal/mol, containing the lowest 5% (approx.) of the negative VDW waters (figure *VDW Grid*). Low VDW regions are found in regions with weak polar interactions. Conversely, regions with strong polar interactions have positive VDW energy. The balance between Coulombic interactions and VDW interactions defines the masked, or nonclashing, region.

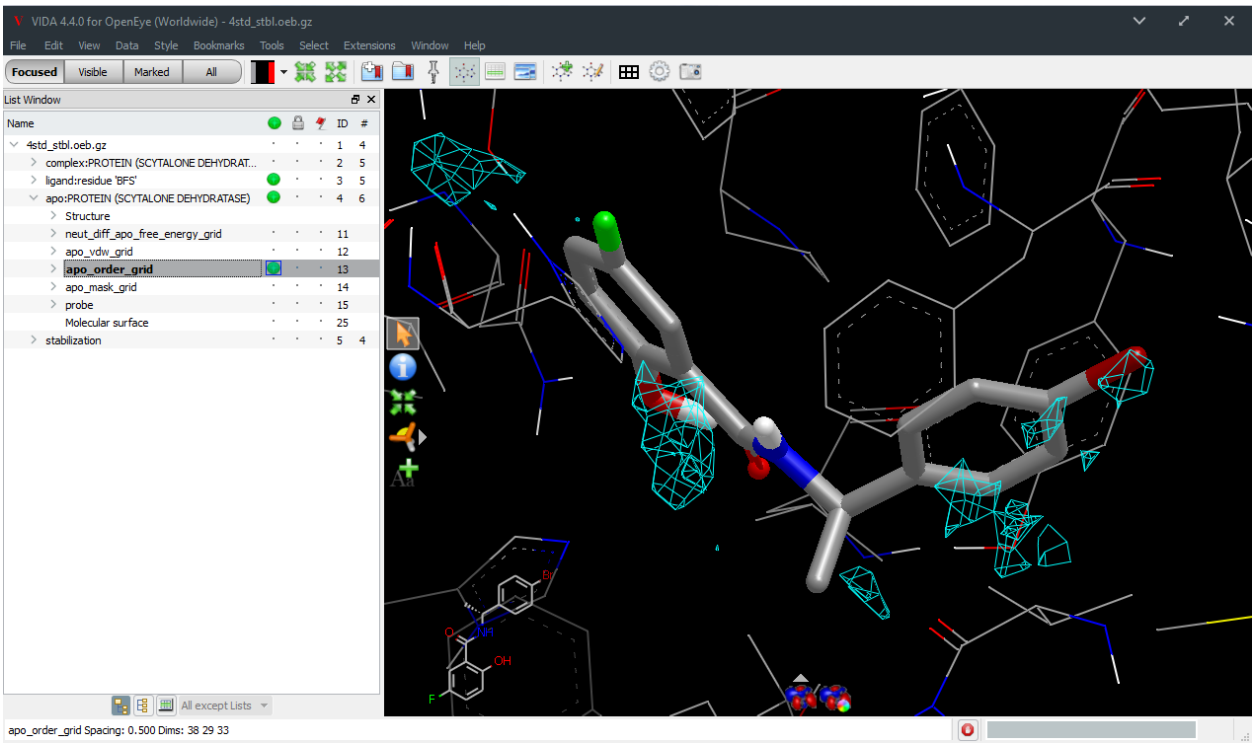


Fig. 18: **Order Grid**

Order grids (light blue mesh) show the fraction of water entropy lost due to electrostatic interactions (figure *Order Grid*). A value of 1.0 means the site is highly ordered and displacing water from there will liberate almost all this rotational entropy (approximately 2.4 kcal/mol). A value of 0.0 means the water orientation is completely degenerate and displacing it will not liberate any rotational entropy. The energy gained by displacing water is primarily entropic, enthalpy mainly serves as a filter that discriminates between different ligands.

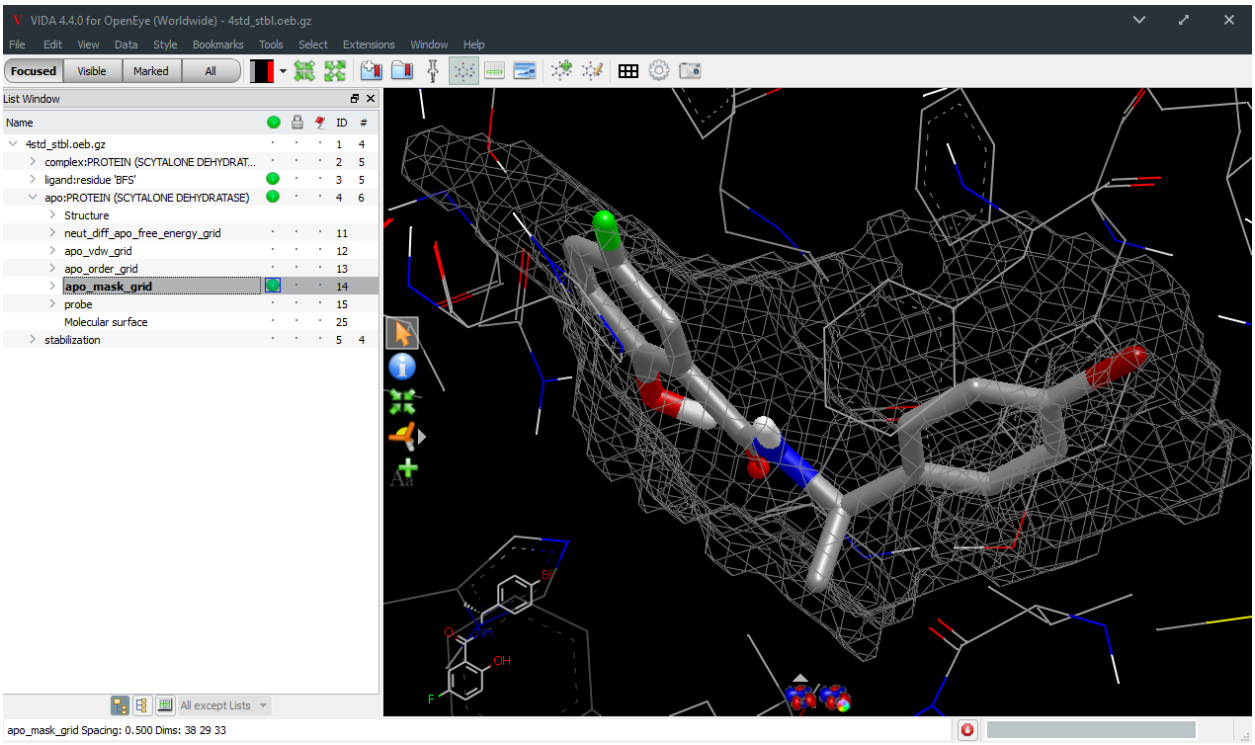


Fig. 19: **Mask Grid**

Mask grids (gray mesh) are an accurate description of the *solvent accessible surface*, calculated as regions where the minimum *Coulombic interaction + VDW* energy is below a threshold (figure *Mask Grid*). Examining the mask grid clarifies where water fits and where it clashes. The displaced region of the *apo* pocket contains the volume of the *apo* mask minus that of the complex mask. To speed up ligand calculations during a stabilization run, the ligand analysis is limited to the region within the complex mask, by default. In "at_coords" calculations, points that are not in the mask are labeled "CLASH".

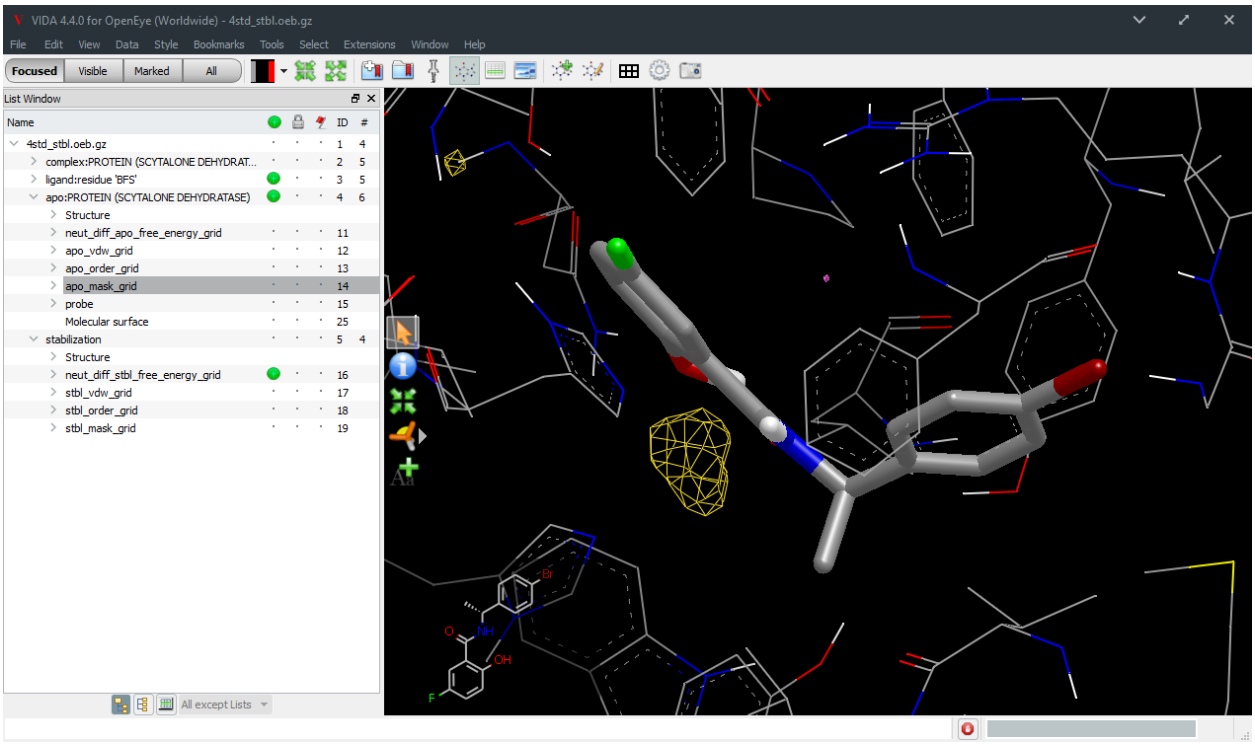


Fig. 20: **Stabilization Grid**

Stabilization grids are special kinds of difference grids (*complex - apo - ligand*), showing how water is stabilized or destabilized upon binding (figure *Stabilization Grid*). They provide information about the possible effects of modifying the ligand.

If you have calculated *displacement* grids—with *apo* data in regions where water has been displaced—these will be found at the end of the list of items in the results. Examining them can clarify how far a ligand's reach extends.

Other grids can be produced but these capture the main elements required to understand solvation.

- **Step 10**
  Explore!

6.3.2 Viewing Gameplan Results

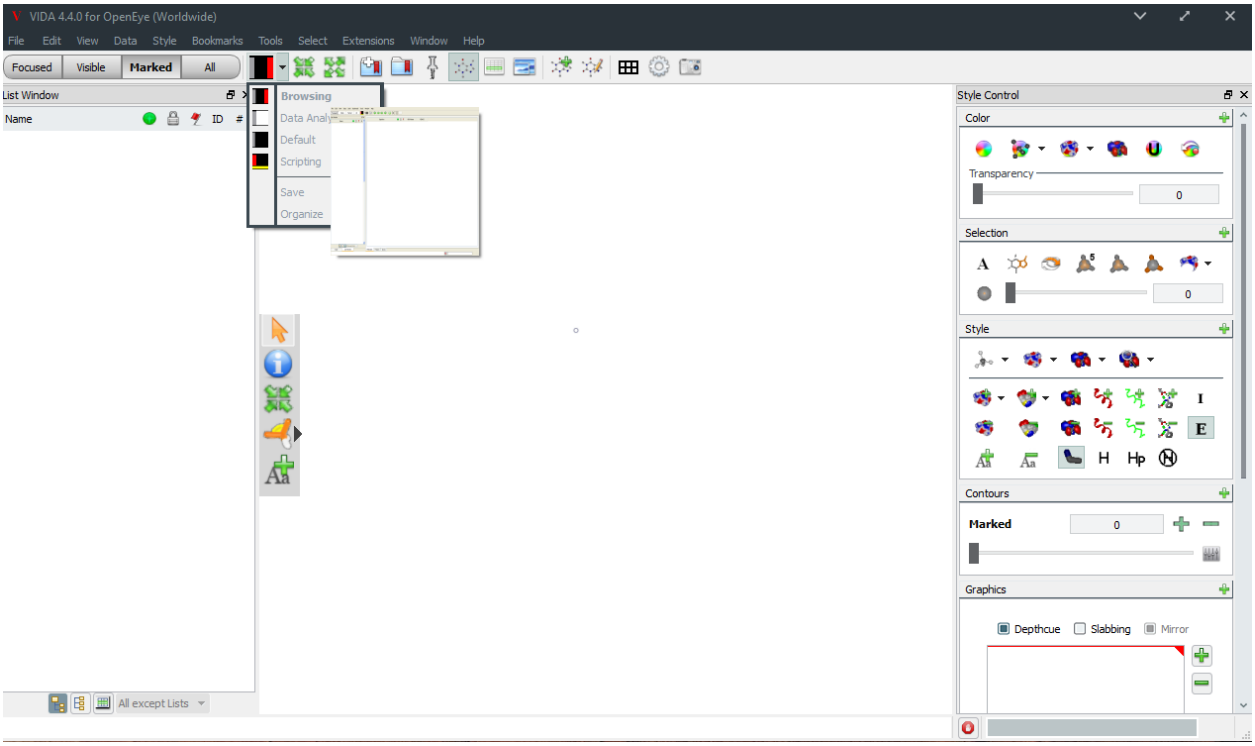


Fig. 21: **Browse View**

- **Step 1**
  Open *VIDA* and make sure the 3D viewer, the list panel and the style panel are available. If not, select the *Browsing* view (figure *Browse View*) to setup your display.

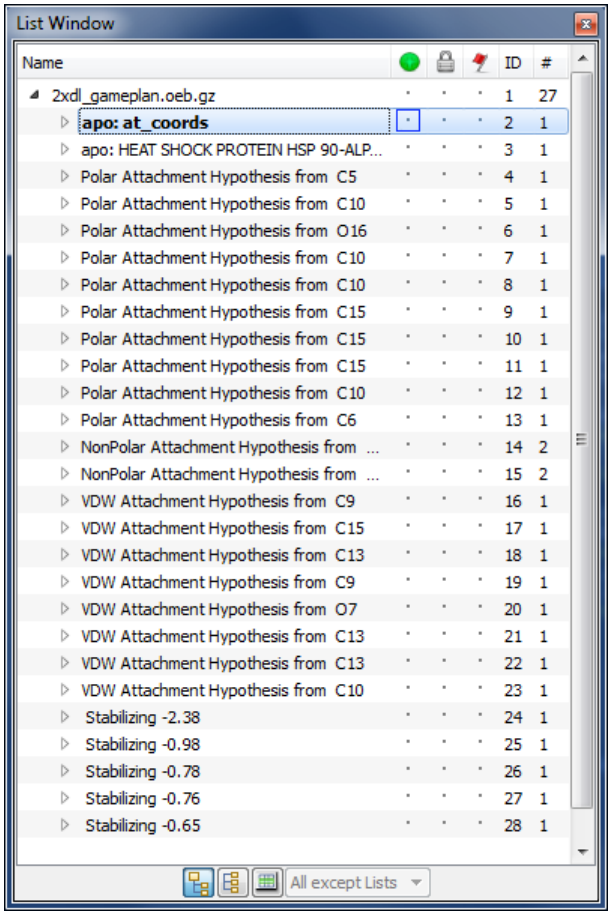


Fig. 22: **Gameplan List Window**

- **Step 2**

  Select *File* >> *Open* and choose the *.oeb.gz* or *.oeb* file containing your *GamePlan* results. The file should show up in the list panel (figure *Gameplan List Window*; the blue bar identifies the active entry) and the ligand structure should show in the 3D viewer.

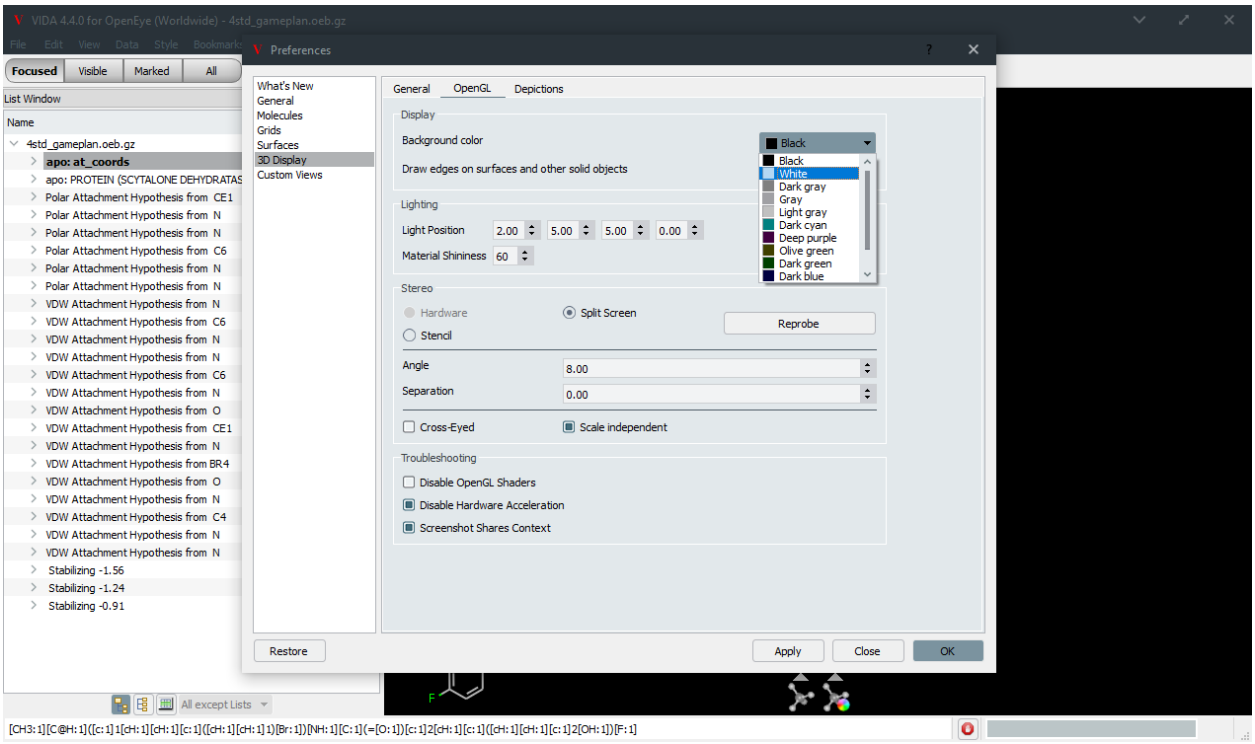


Fig. 23: **Changing Background**

Note

The figures shown here have a white background which is recommended for presentations and publications. You can change the background color in *VIDA* by bringing up the *Edit >> Preferences* window (*Vida >> Preferences* on Mac OS X), selecting *3D Display* and then clicking on the *OpenGL* tab (figure *Changing Background*).

- **Step 3**

  Run the *WaterColor* extension to activate the display of annotation explaining the various ligand modification hypotheses. It also adds a surface that shows the boundary of the binding site, and hides all protein atoms that are not near to the binding site. These settings can be modified using the style panel.

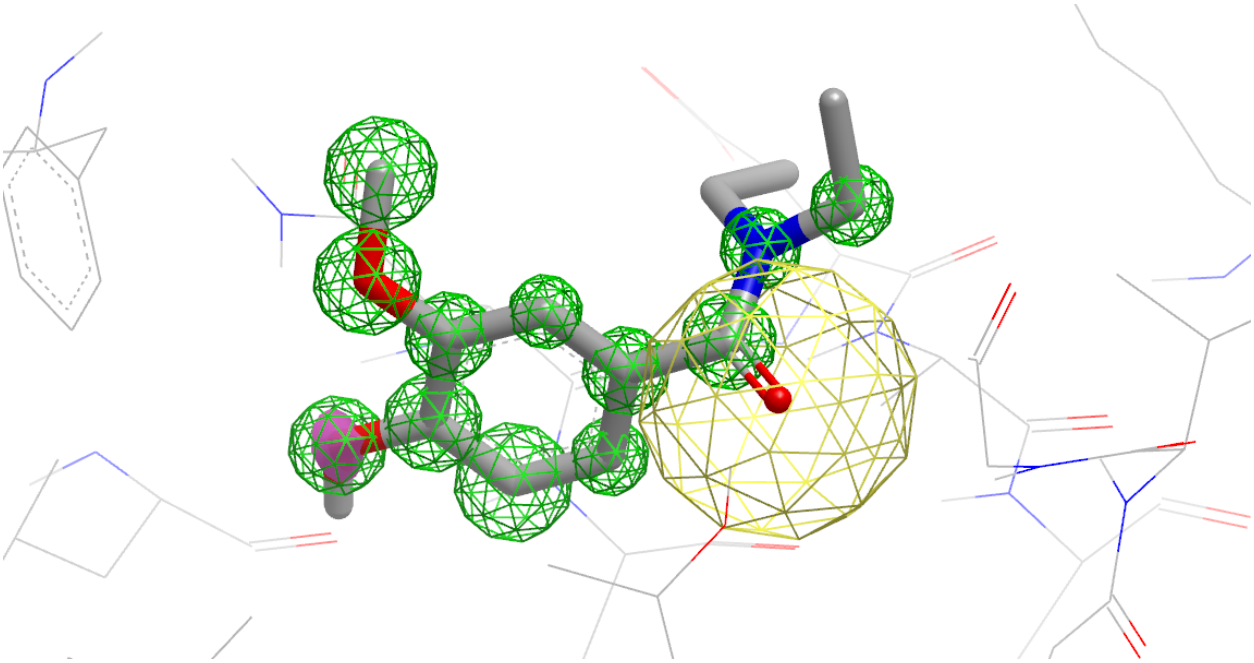


Fig. 24: **Ligand Compared to apo Binding Site**

- **Step 4**

  The first entry analyzes how the ligand (figure *Ligand Compared to apo Binding Site*) Yellow mesh spheres show polar sites, green mesh spheres are van der Waals sites, translucent green spheres are non-polar sites, and purple diamonds indicate a mismatch, where the ligand is either much more or much less polar than the binding site. See chapter *GamePlan* for a complete description of the annotation symbols.

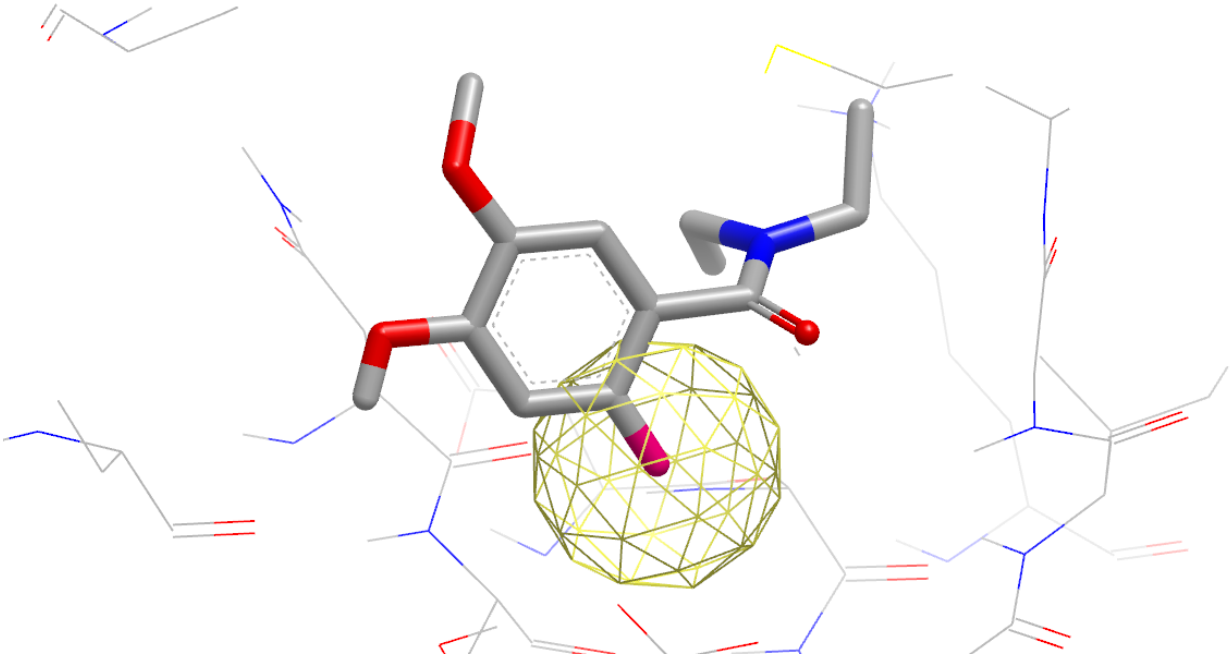


Fig. 25: **Hypothesis for a Polar Substituent**

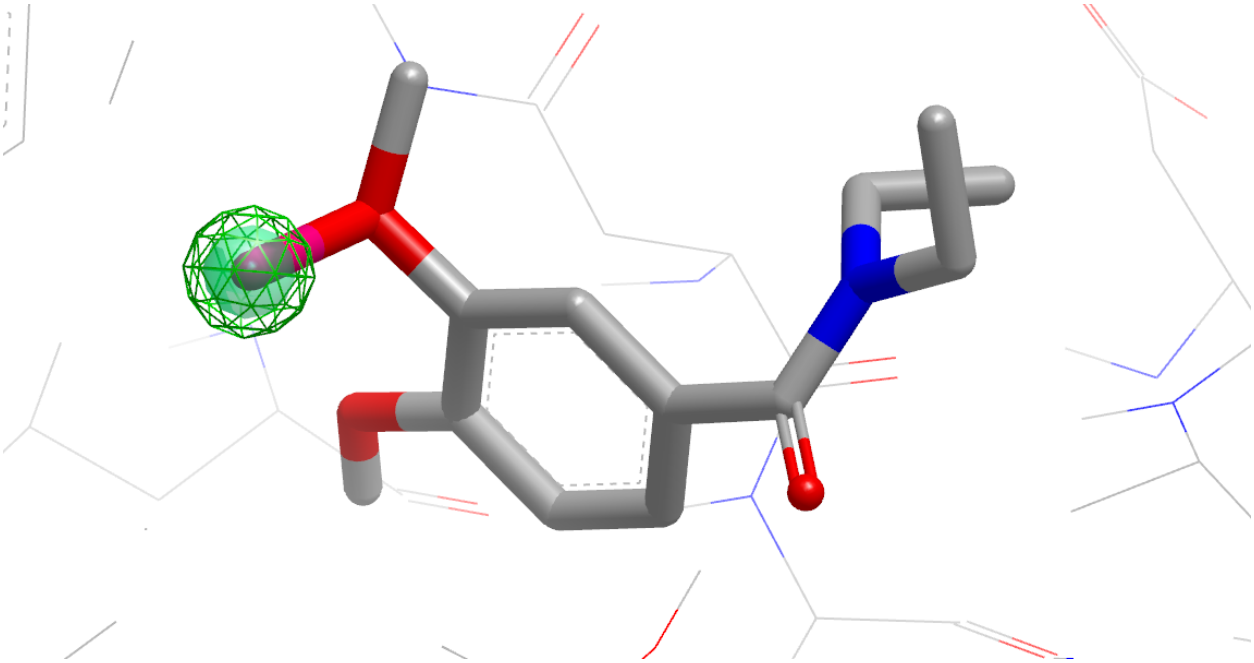


Fig. 26: **Hypothesis for a Nonpolar/VDW Substituent**

- **Step 5**

  Next comes the *apo*-protein, then a series of hypotheses for ligand modification.

  Scarlet colored bonds indicate a proposed modification to the ligand. Gameplan tries to explore a wide range of possible ways to improve the ligand, and has an option that permits the hybridization to differ from that in the original ligand. See the `-sample_hybridization` option in chapter *GamePlan* for details.

  Using the arrow keys to step between the different hypotheses, you will see yellow cages around atoms where water makes good polar interactions (figure *Hypothesis for a Polar Substituent*), green cages around atoms where water has good van der Waals energy, and translucent green balls around atoms where a fluorine or methyl group may be a good fit (figure *Hypothesis for a Nonpolar/VDW Substituent*).

  The same substituent may show up with different conformations or under different categories.

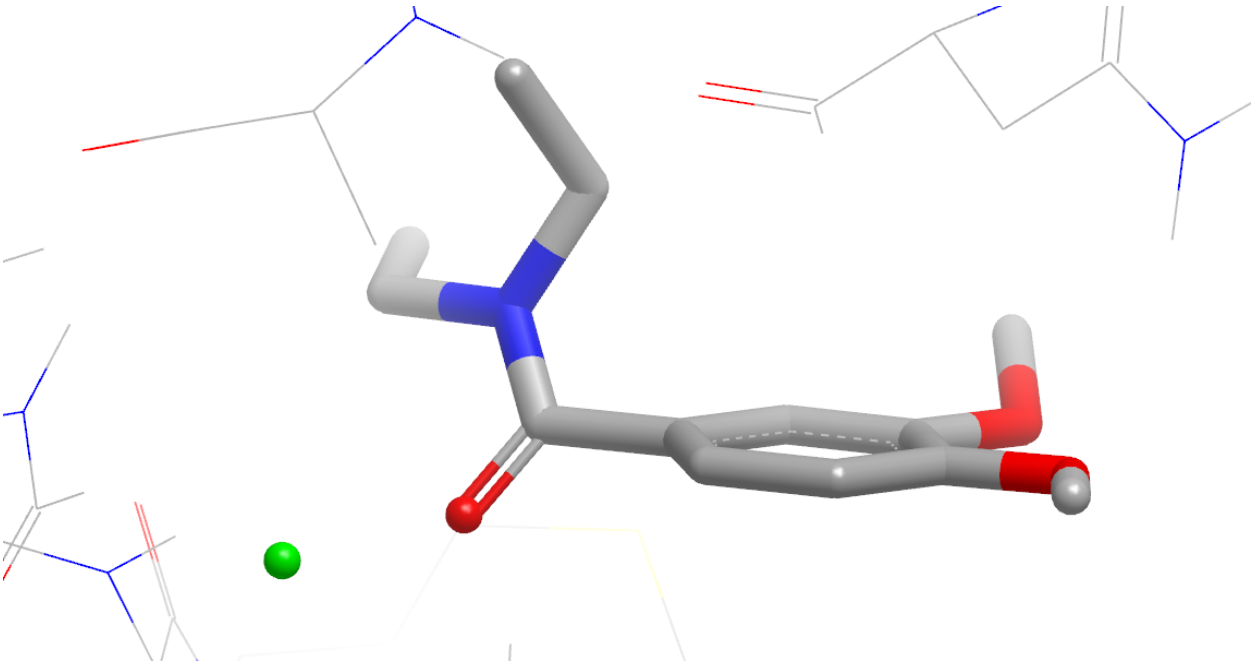


Fig. 27: **Stabilizing Site**

- **Step 6**

  Finally points where water is stabilizing (green) or destabilizing (red) the complex are enumerated (figure *Stabilizing Site*). Destabilizing points may be good candidates for displacement, while stabilizing points can be left in place. But if a stabilizing site contains highly ordered water in the complex, careful replacement of this water with a substituent that makes the same number of interactions can liberate as much as 2 kcal/mol of rotational entropy.

6.4 Water Orientation VIDA Extension

6.4.1 Using

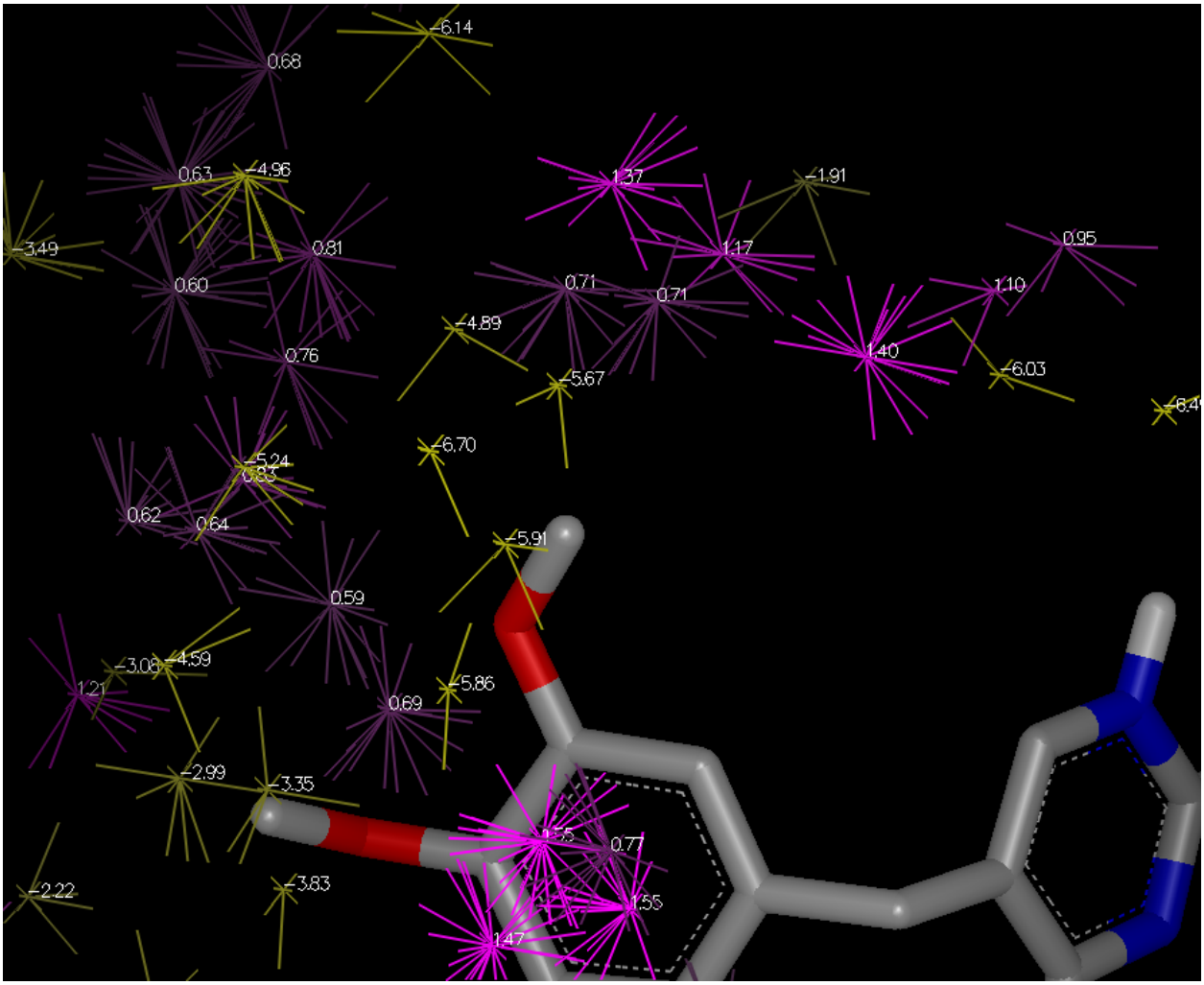


Fig. 28: **Water Orientations With Energy Coloring**

The *Water Orientation* extension provides a means of accessing the calculated properties of key water sites and orientations stored within an *SZMAP* results OEBinary file. The figure *Water Orientations With Energy Coloring* shows an example of the display, with dominant points colored and labeled by their *SZMAP* energy and the highest probability probe orientations indicated (yellow: negative energies, purple: positive energies).

See *Installing VIDA Extensions* for information on installing the extension.

To get started, load *SZMAP* results into *VIDA*—both grid calculations or `-at_coords` calculations will work. Highlight part of the results in the list window and run the *WaterColor VIDA Extension*. Then, if the *Water Orientation* panel is not already open, open it from the extensions menu. Select the set of orientation data you want to display with the *Apply to* pop-up in the panel and press the *Update* button. The *Water Orientation* extension will analyze the orientations and add a package of points and water orientations to *VIDA's* list window, colored by the selected color scheme, *by Energy* by default. Points and water orientations can be displayed or hidden independently.

The numbers by each point (energies or order parameters) always refer to all orientations collectively, not any partic-

ular orientation, even if only one orientation is visible for a point. The same is true of the color schemes, except for *by Probability* where each orientation is colored differently (although the order parameter numbers still refer to the ensemble).

Changing the filtering controls does not update the display until you press *Update* again. Pressing the *Duplicate* button makes a duplicate copy of the package of points and water orientations.

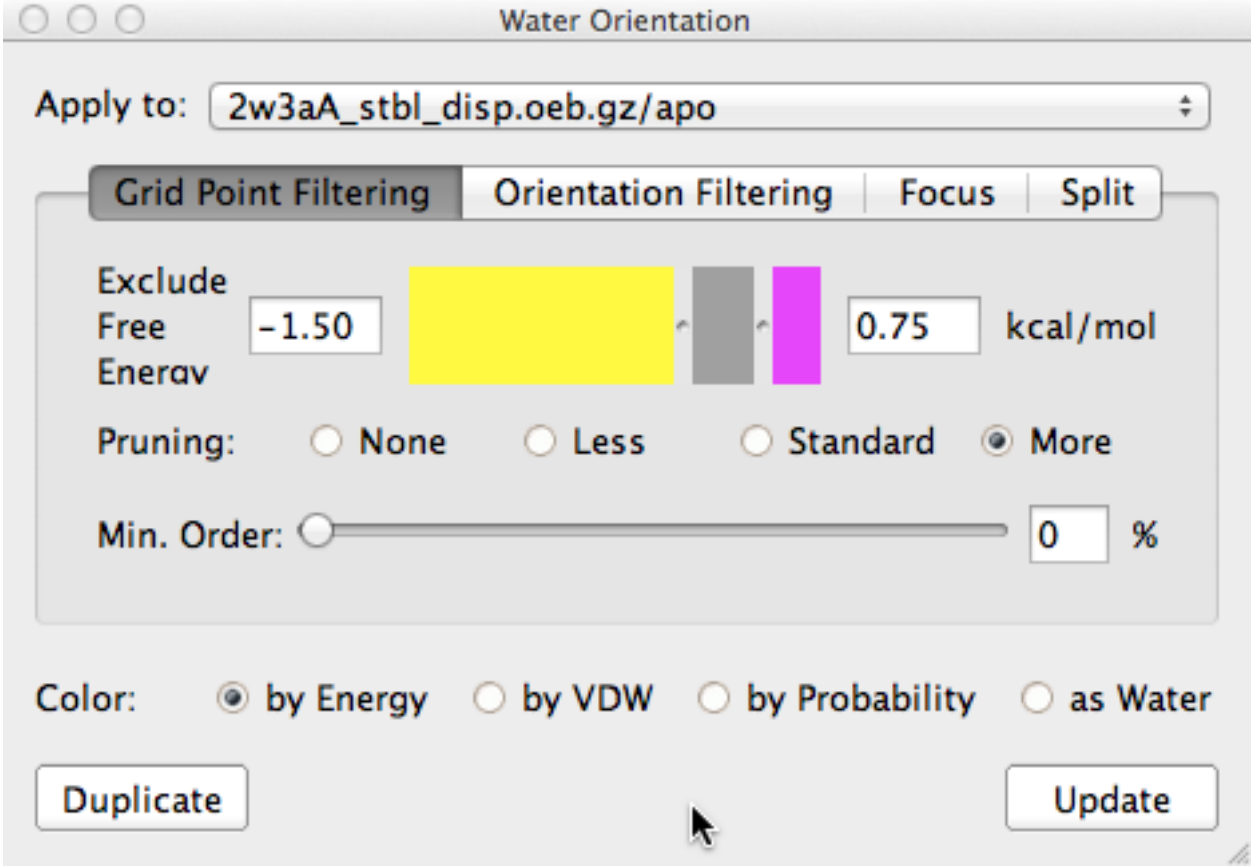


Fig. 29: **Grid Point Filtering Panel**

The *Grid Point Filtering Panel* controls which points are displayed. It is generally useful to show only the key points: those with the lowest or highest energies in each region. The range sliders select which energies are excluded from display—values between -0.5 and +0.5 kcal/mol are ignored by default. The range control is labeled with the type of energy used: *neutral difference free energy* for results from *SZMAP* 1.1.0 and later, *neutral difference enthalpy* for results from earlier versions of *SZMAP*. *Pruning* is an operation that picks points with the lowest or highest energies and then excludes nearby points where energies are closer to 0.0 kcal/mol. The *Min. Order* slider controls the display of degenerate points, locations where waters have little or no orientational preference. The default of 5% will only skip the most degenerate points.

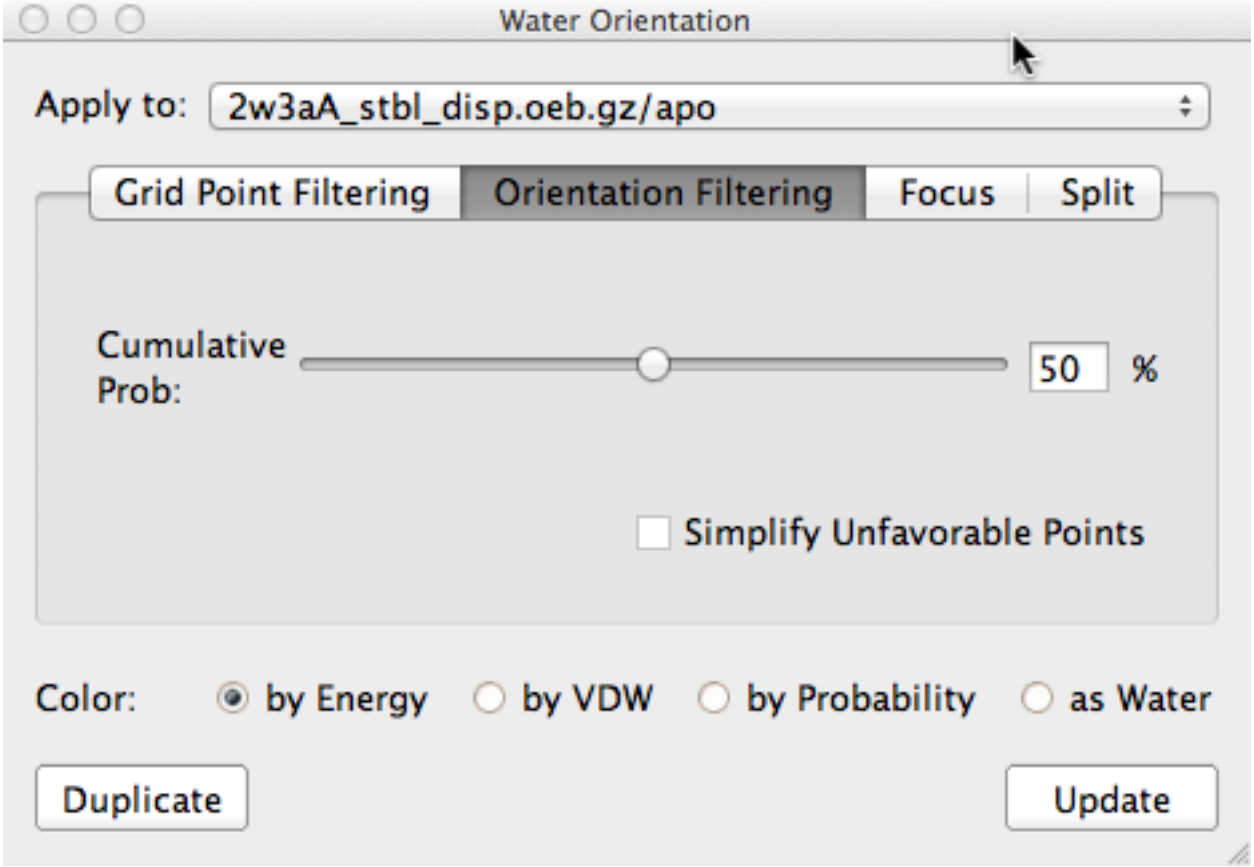


Fig. 30: **Orientation Filtering Panel**

The *Orientation Filtering Panel* controls the number of orientations displayed for each point shown. By default the most probable orientations are show for each point with favorable energies (< 0.0 kcal/mol), up-to a cumulative probability of 50%. Since points with unfavorable energies are mostly degenerate we usually simplify them, only showing the single most probable orientation. Occasionally, it is useful to show more unfavorable orientations by un-checking the *Simplify Unfavorable Points* check-box as was done to make the figure *Water Orientations With Energy Coloring*.

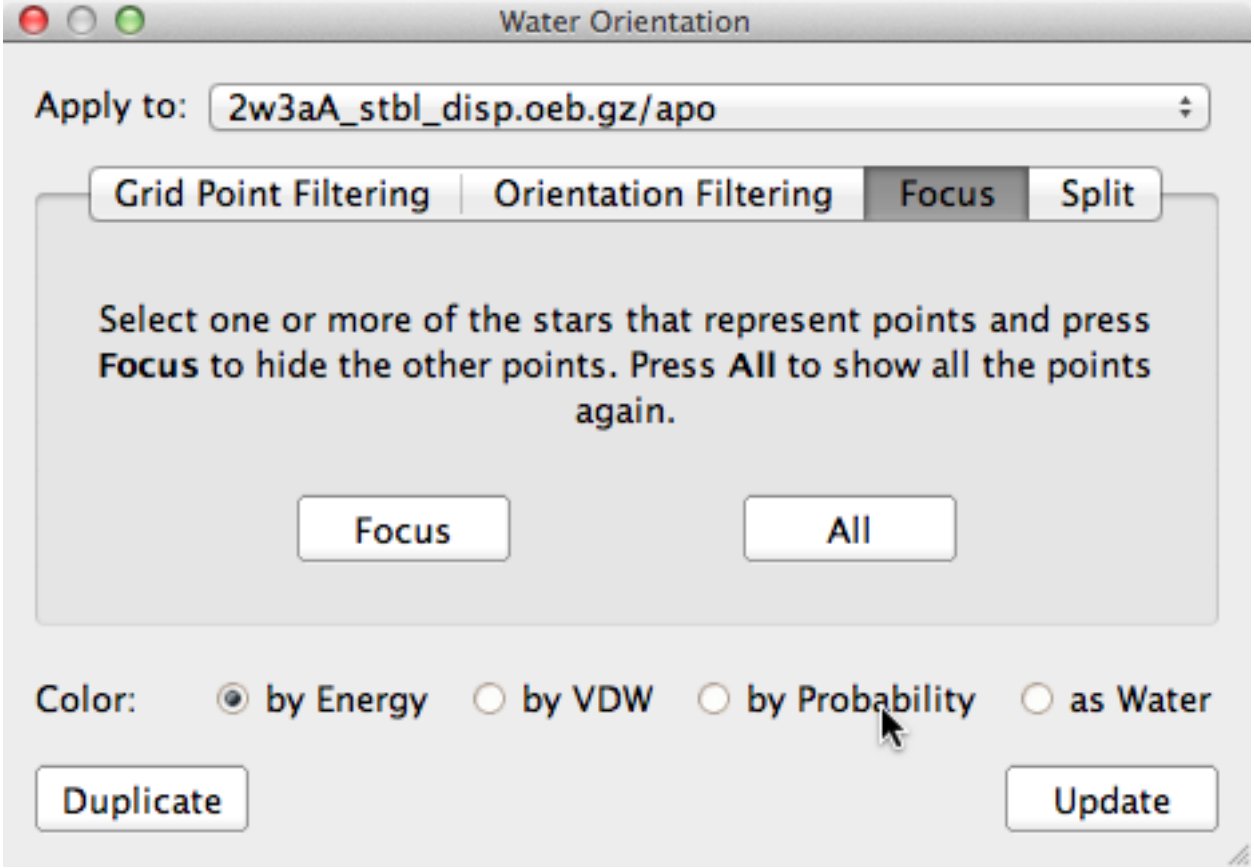


Fig. 31: **Focus Panel**

The *Focus Panel* allows you to select one or more points generated by the *Water Orientation* extension and, by pressing the *Focus* button, clear the display of all but the selected points. Pressing *all* shows all the points once again. To select a point, click on the cross at the center of each position (not the orientations) and to select multiple points, use shift-click. Turning off the display of the water orientations (the "probe" sub-section in the *VIDA* List window) can make it easier to click on the points.

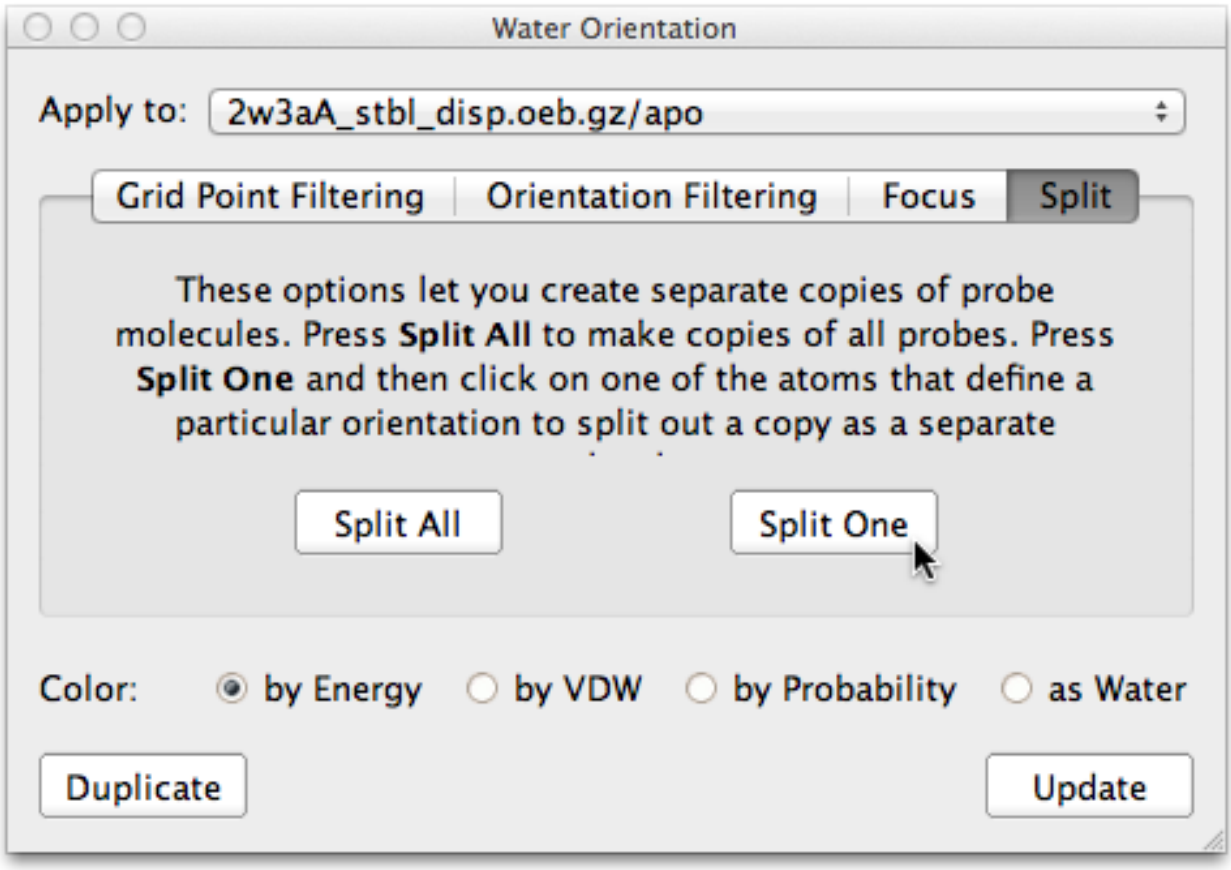


Fig. 32: **Split One**

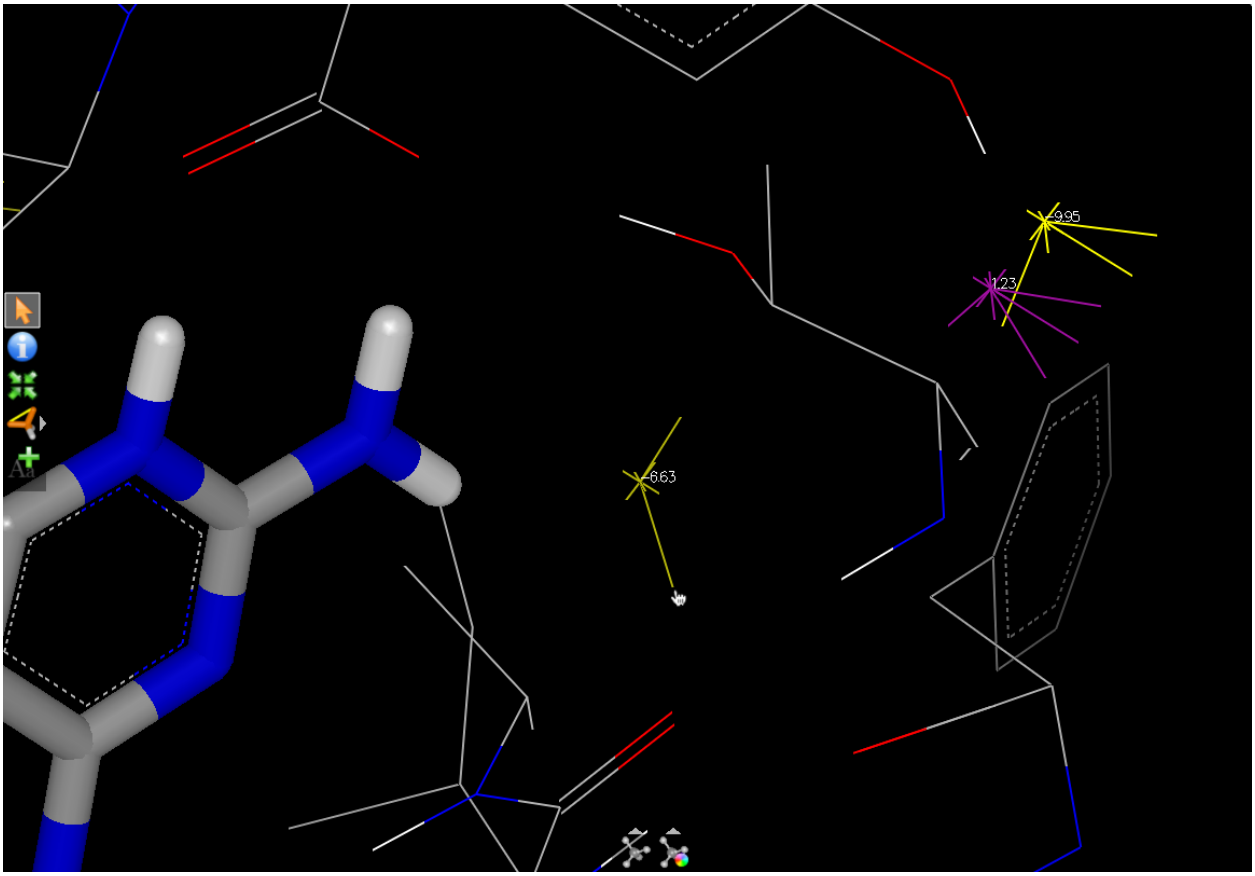


Fig. 33: **Click on Hydrogen**

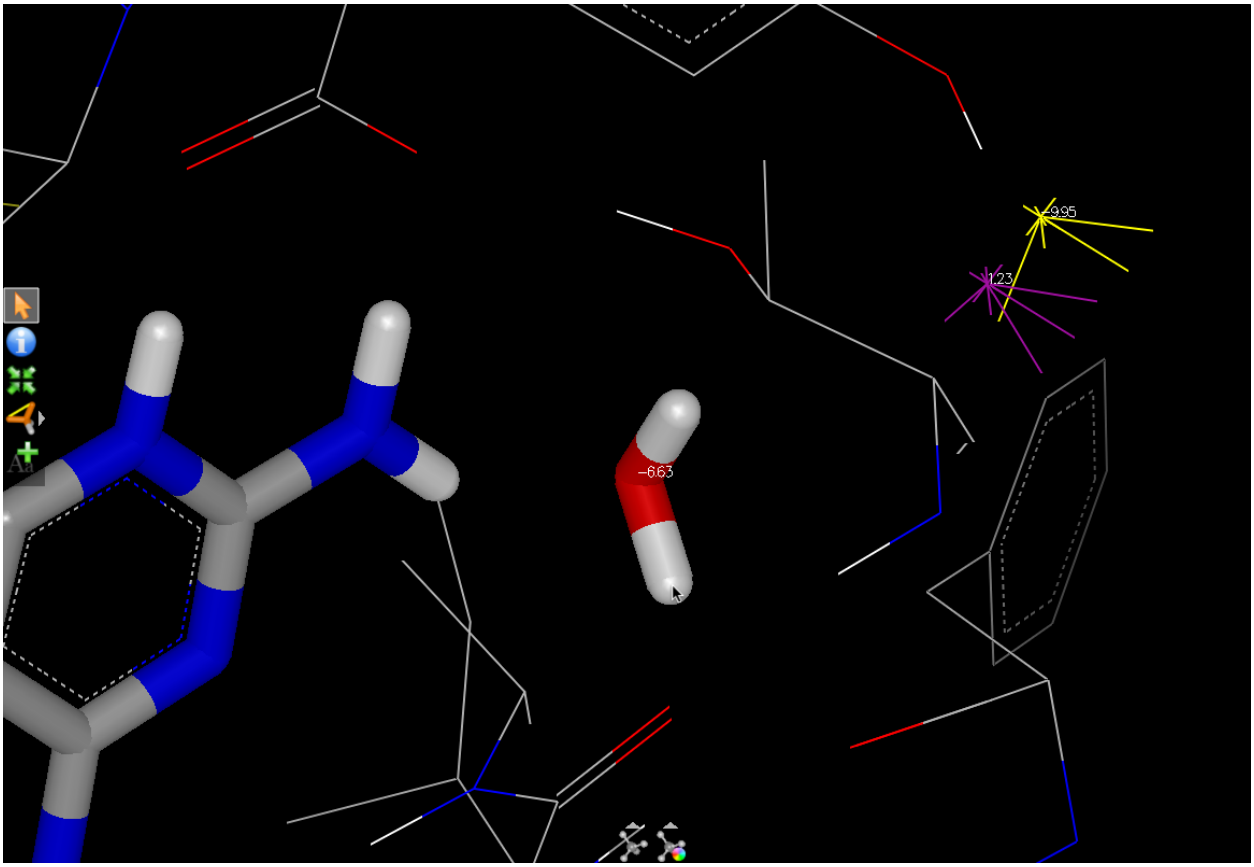


Fig. 34: **After Split**

The *Split Panel* provides a means of converting individual water orientations into a separate molecule (including *SZMAP* partial charges) which can be saved by *VIDA* and used in other calculations. For example, a particularly structured water can be split out and saved and then added to the protein as part of a *SZMAP* calculation. To use it, you press the *Split Orientation* button (figure *Split One*) and then click on one of the hydrogens in the orientation you want to split (figure *Click on Hydrogen*). The selected water orientation will be reproduced as an individual molecule (figure *After Split*) which can be written out to a file, if required.

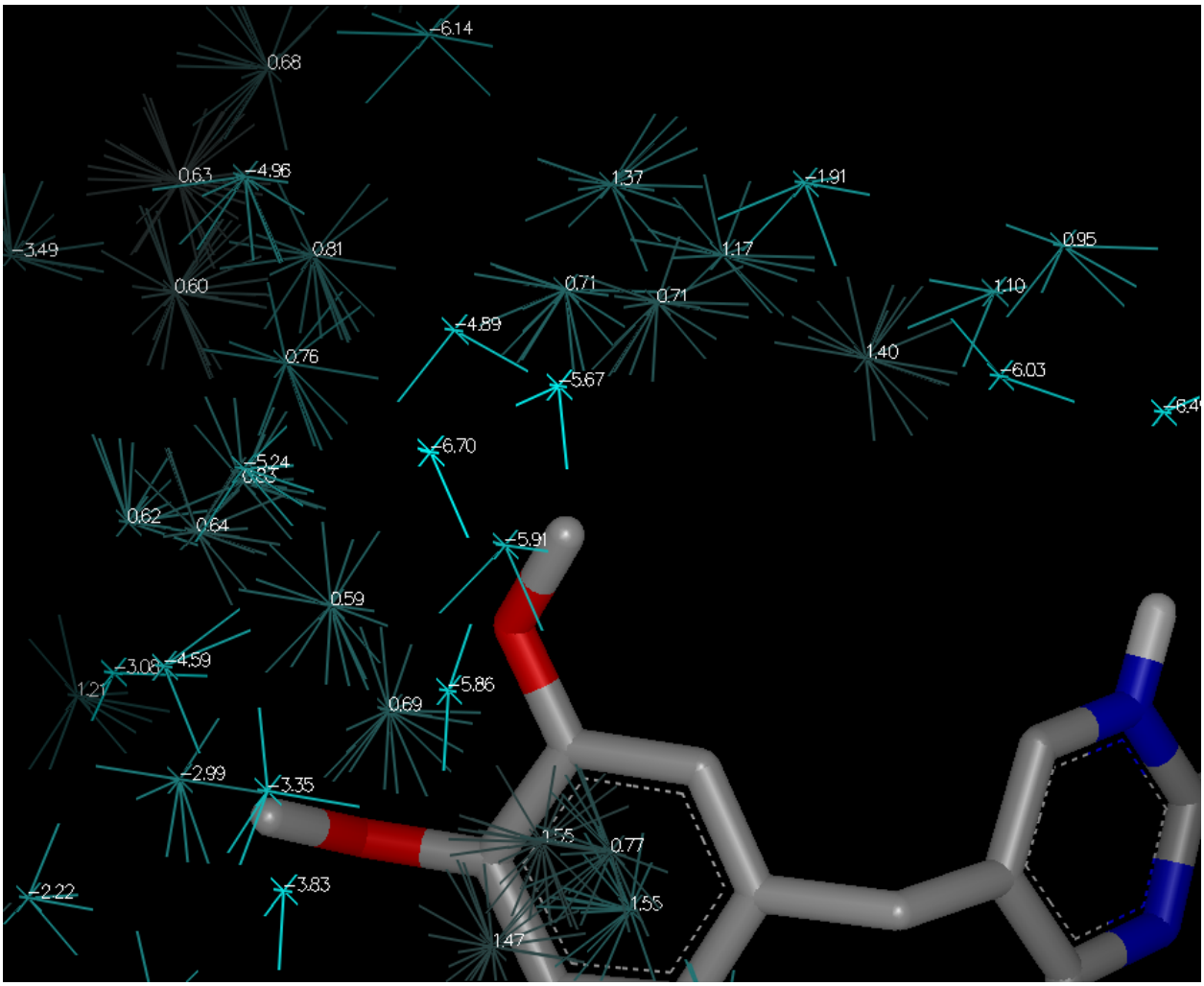


Fig. 35: **Order Coloring**

Changing the color-scheme results in an immediate update of the current display. Besides the *Energy Coloring* shown above, there are three other color-schemes. In figure *Order Coloring*, each point is colored light-blue with brighter colors indicating more ordered positions and darker colors indicating more degenerate positions. Order represents a transformation of the entropy term to normalize it between 0% and 100%, where a value of 0% represents a degenerate point where all orientations are equivalent and 100% is a completely ordered point.

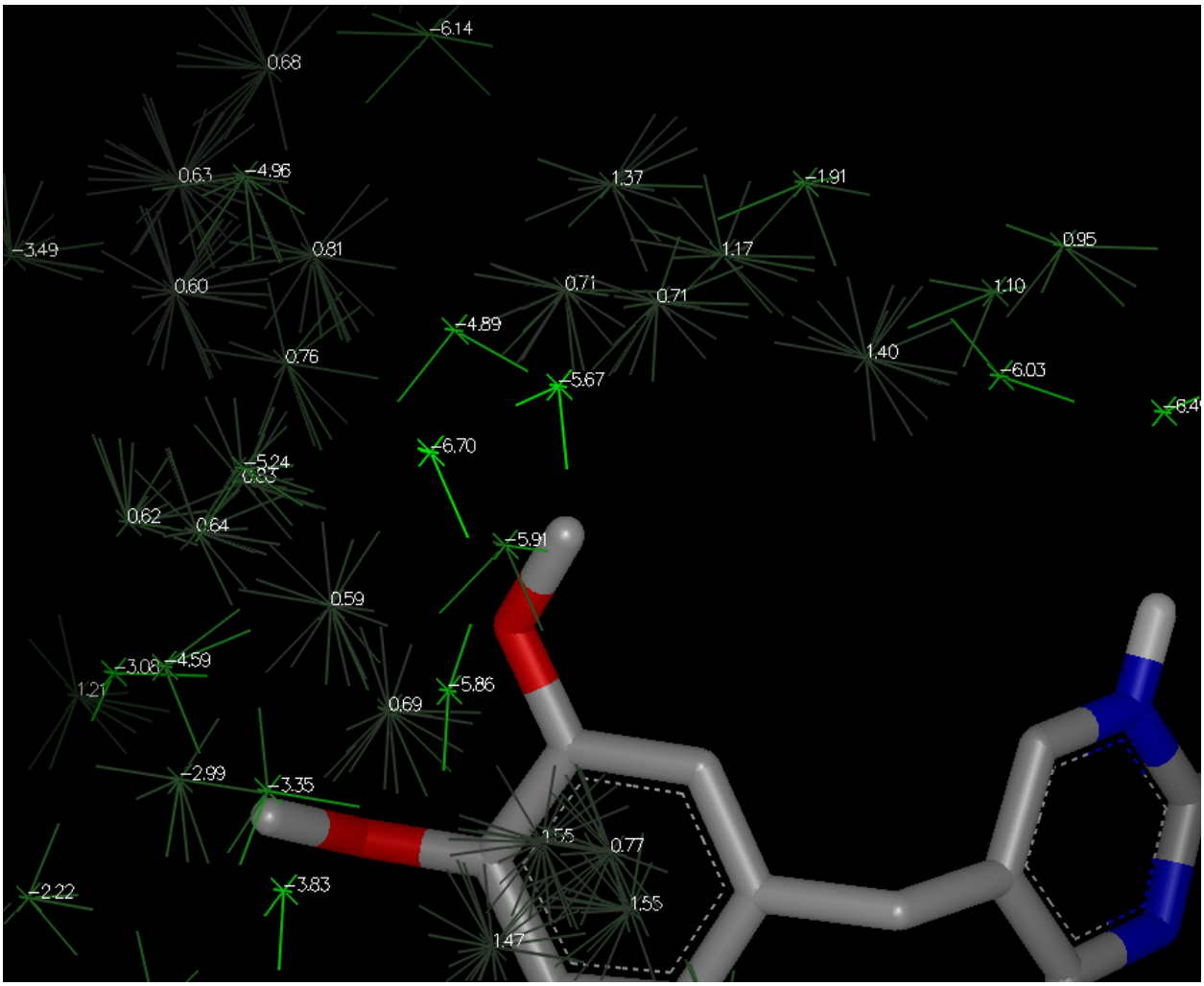


Fig. 36: **Probability Coloring**

In figure *Probability Coloring*, each orientation is colored green with brighter colors indicating more probable orientations. This color-scheme is the only one that will display multiple colors for different orientations a position, whereas energy and order colors are *ensemble* properties.

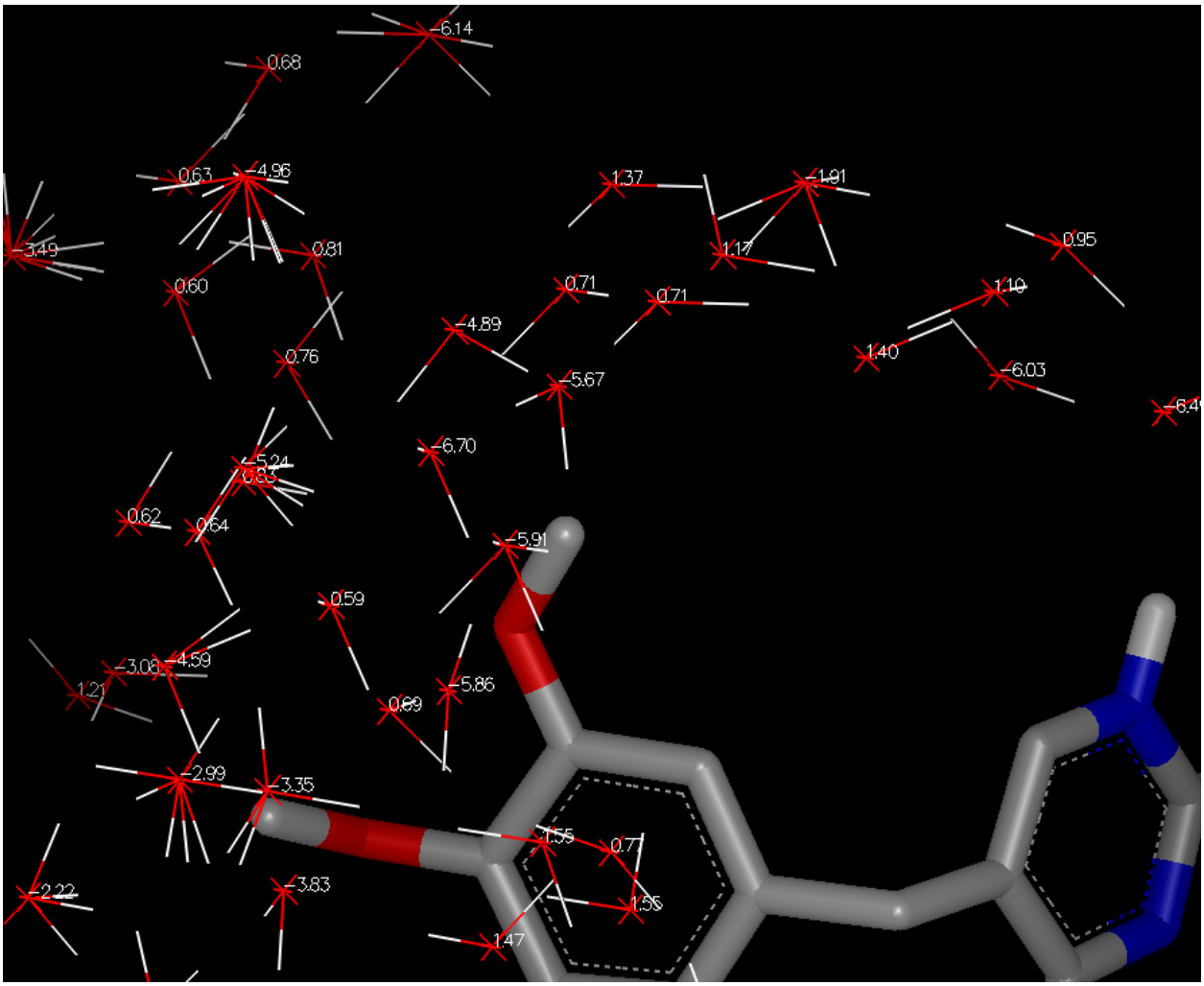


Fig. 37: **Water Coloring**

Finally, figure *Water Coloring* shows the color-scheme where probe orientations are colored according to the CPK colors for the corresponding atoms, red for oxygen and white for hydrogen.

6.4.2 Stick Display

As shown in the figures above, individual orientations are rendered as thin (wireframe) lines. Numerical energies and orientations are associated with the ensemble at each point and do not refer to any particular orientation.

For presentations, it is usually better to "fatten-up" these lines by changing the rendering style.

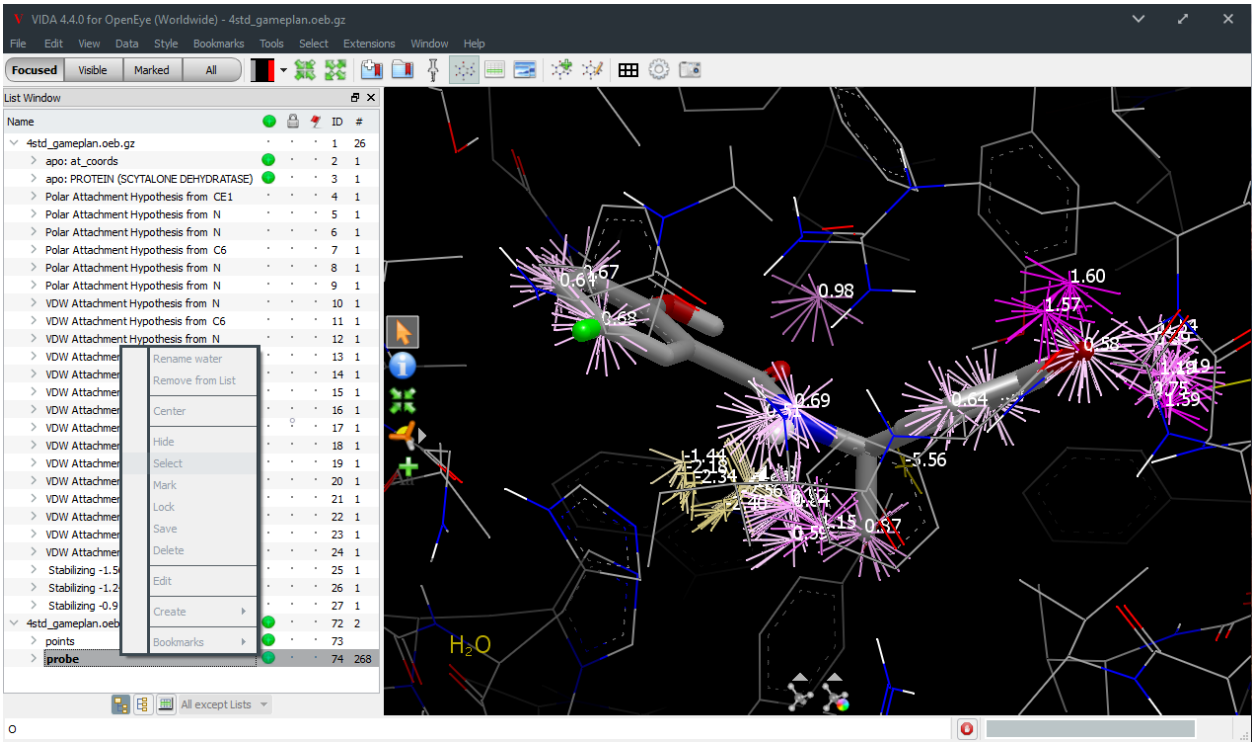


Fig. 38: **Selecting the Probes**

First, open up the orientation package in the list window and select the probes (figure *Selecting the Probes*).

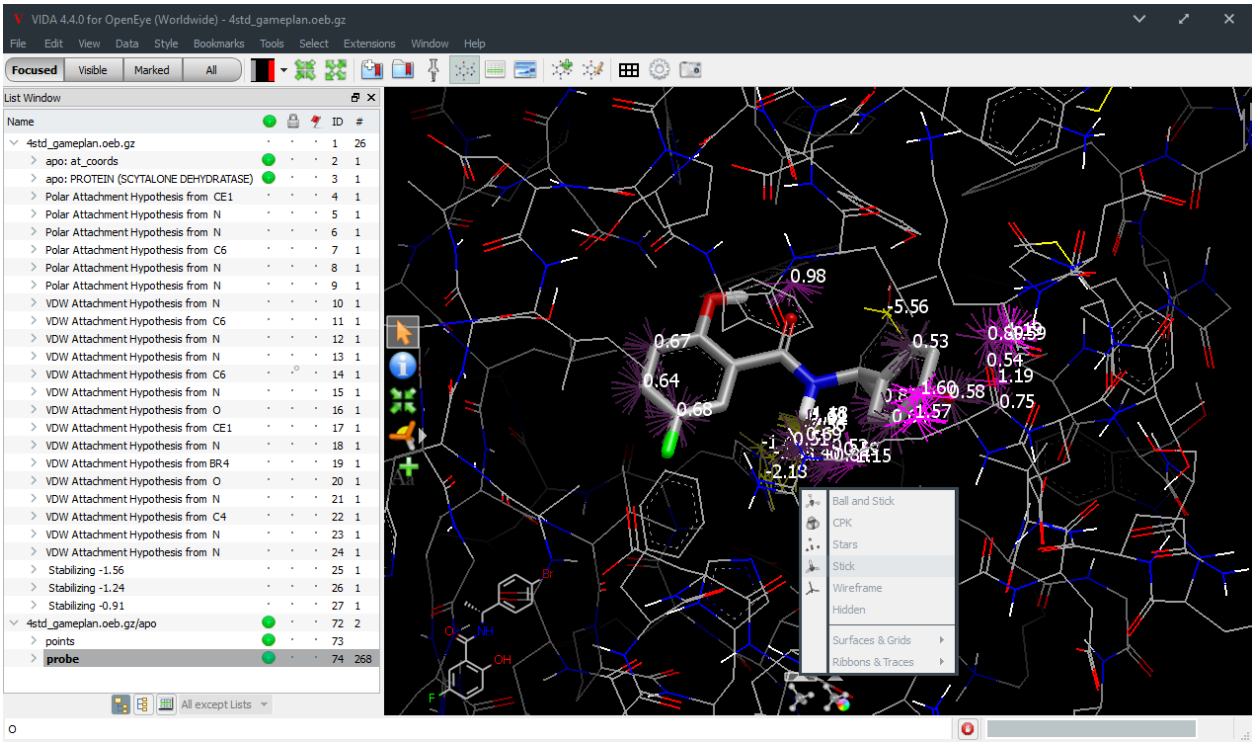


Fig. 39: **Render as Sticks**

Next, change the display style (figure *Render as Sticks*).

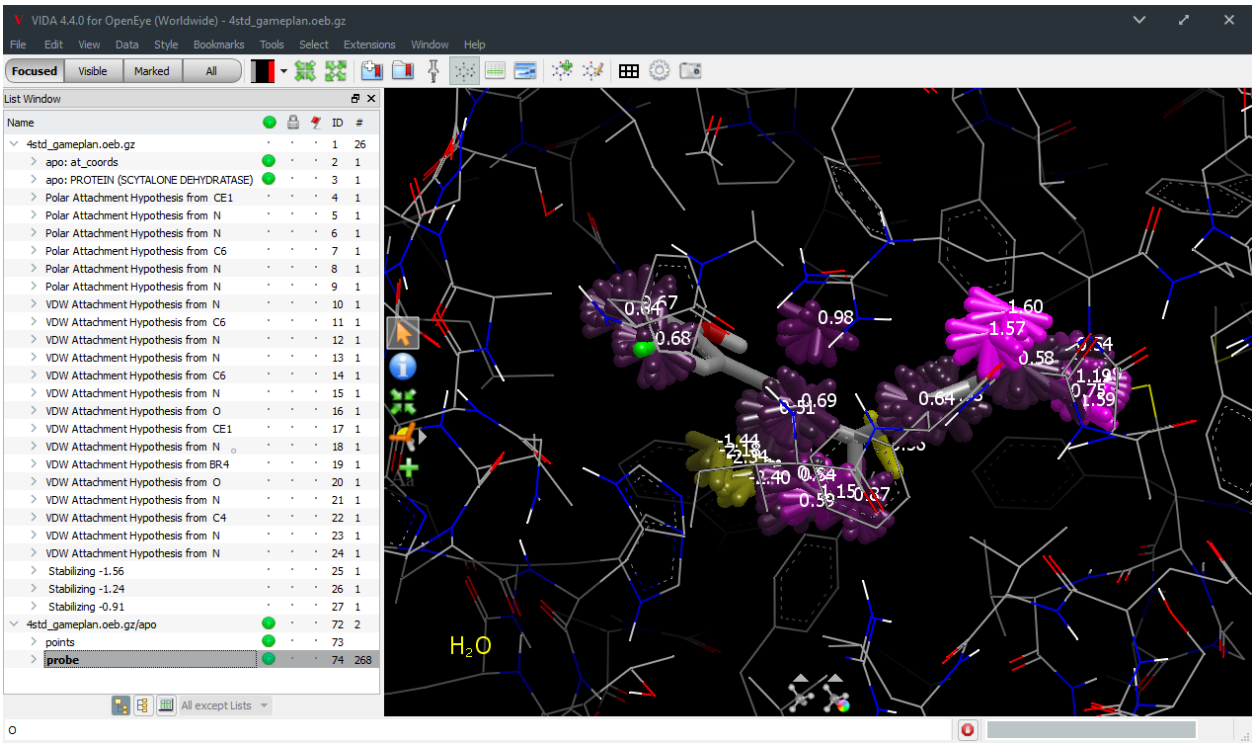


Fig. 40: **Stick Display**

Then, click on the background to unselect the probes (figure *Stick Display*).

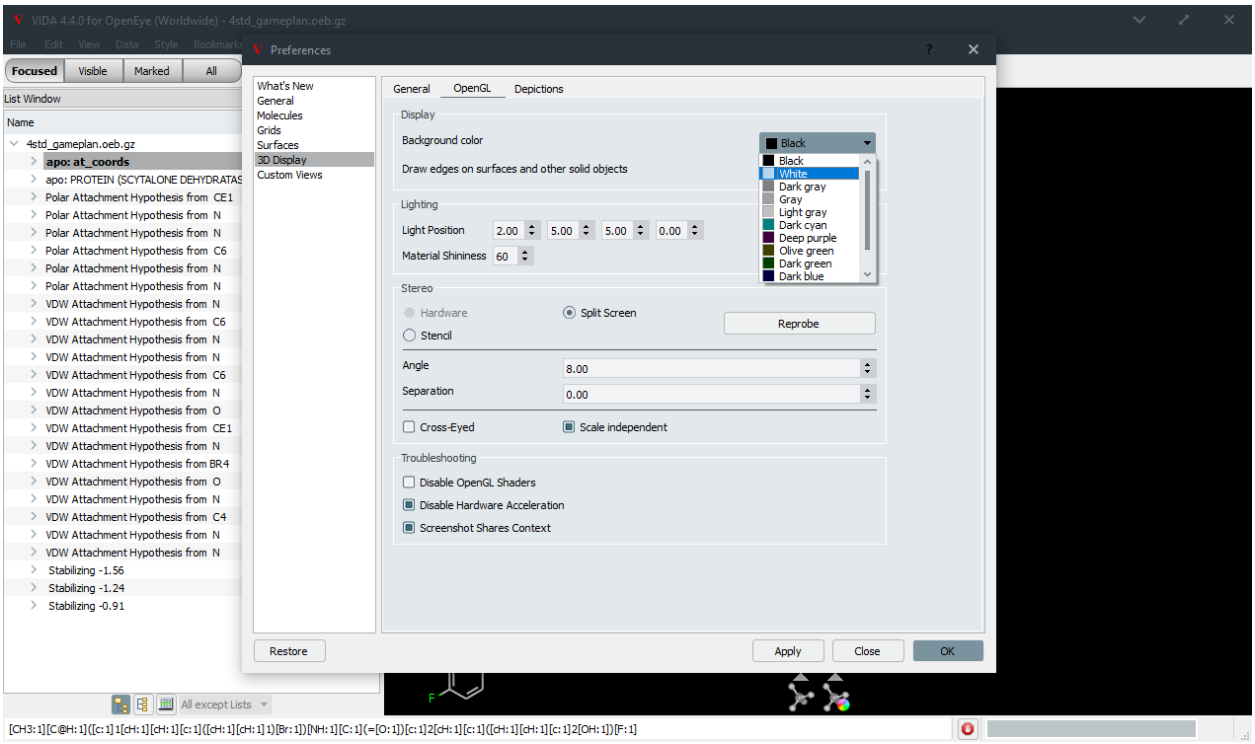


Fig. 41: **Changing Background**

For presentations and publications, a white background which is recommended. You can change the background color in *VIDA's* Preferences/3D Display/OpenGL window (figure *Changing Background*).

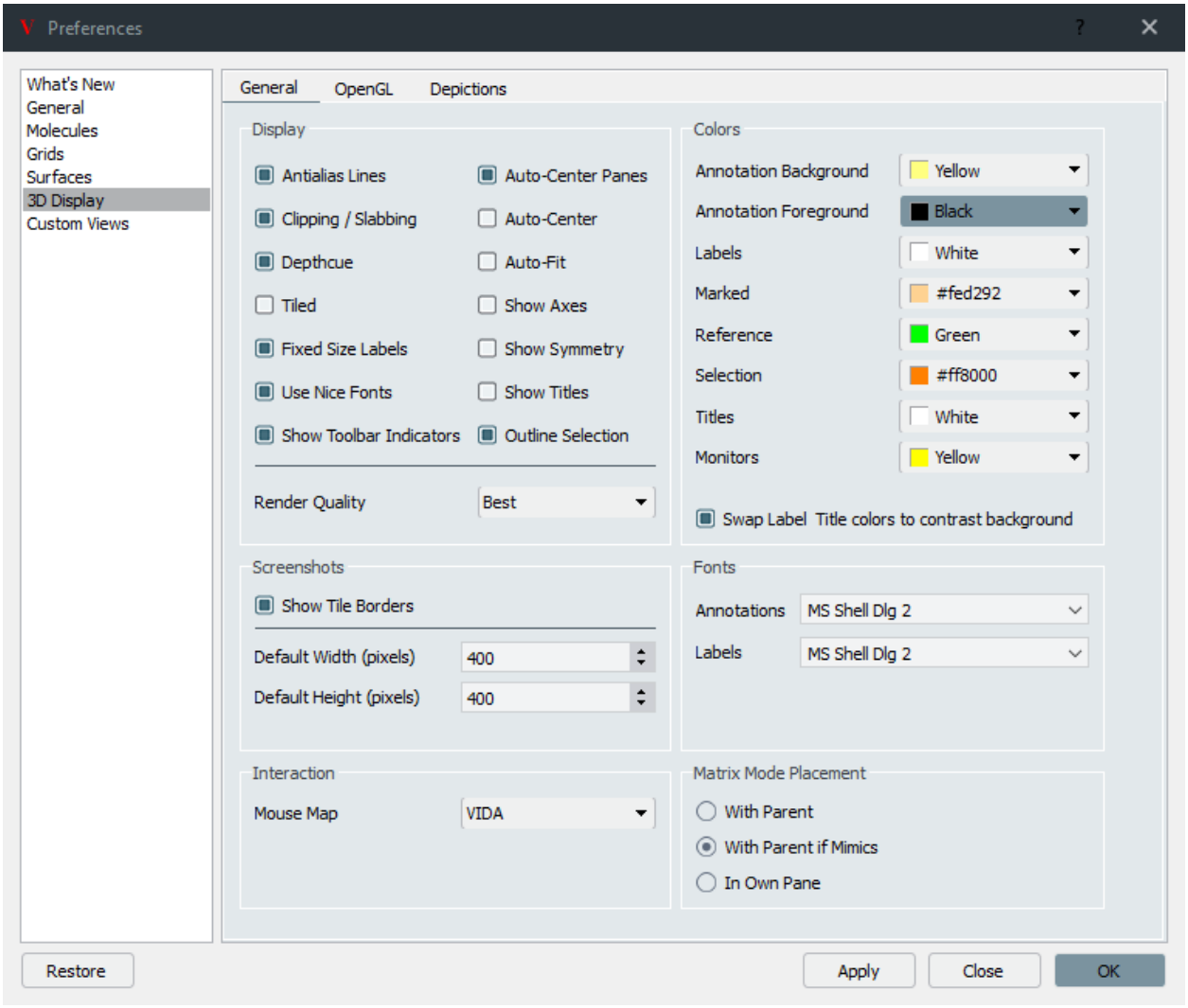


Fig. 42: **Changing Text Label Color**

You can also adjust the text label color by choosing *VIDA's File >> Preferences* menu (*Vida >> Preferences* on MacOS X) selecting *3D Display* and clicking on the *General* tab (figure *Changing Text Label Color*).

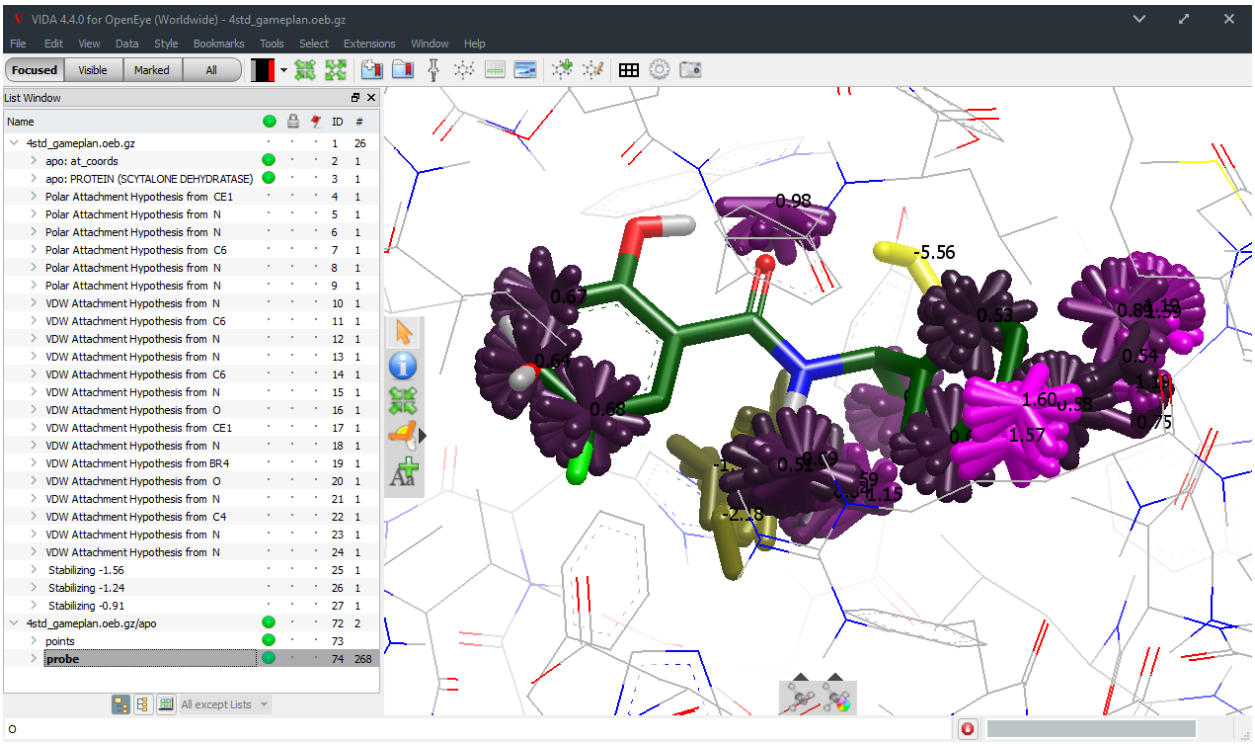


Fig. 43: **White Background**

The result (see figure *White Background*) is works well for presentations. But most versions of *VIDA* recolor carbon to green when the background color is white.

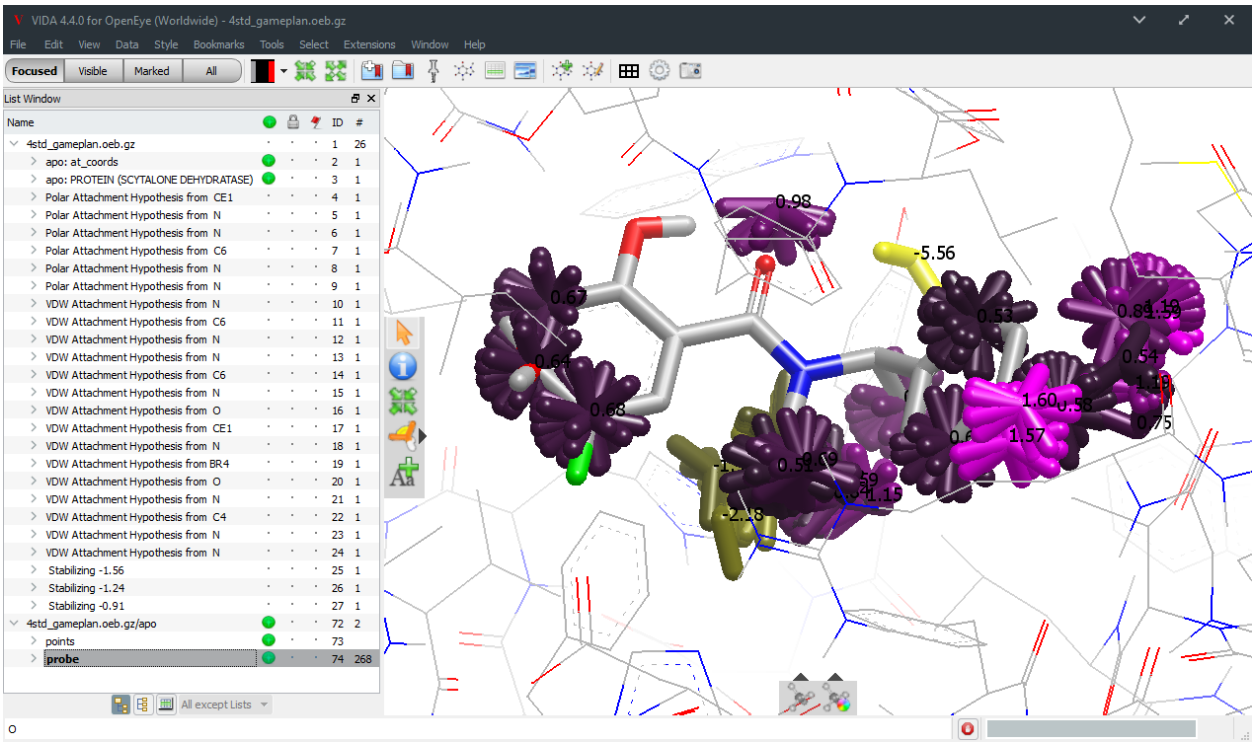


Fig. 44: **Gray Carbons**

If necessary, you can change atom colors as follows. Using *VIDA's Edit >> Select >> Query menu item*, selecting carbon either from the menu or by typing `C` (for aliphatic carbons) or `c` (for aromatic carbons) in the query box, and using the color pop-up at the bottom of the 3D window to change the carbon color to gray, will usually produce a more pleasing result (see figure *Gray Carbons*).

6.5 Color By Atom Properties

The *Color by Atom Properties* extension provides a method for displaying the results in an OEBinary file from a *SZMAP* calculation performed using the `-at_coords` option. You can also view properties using *SzmapReport*.

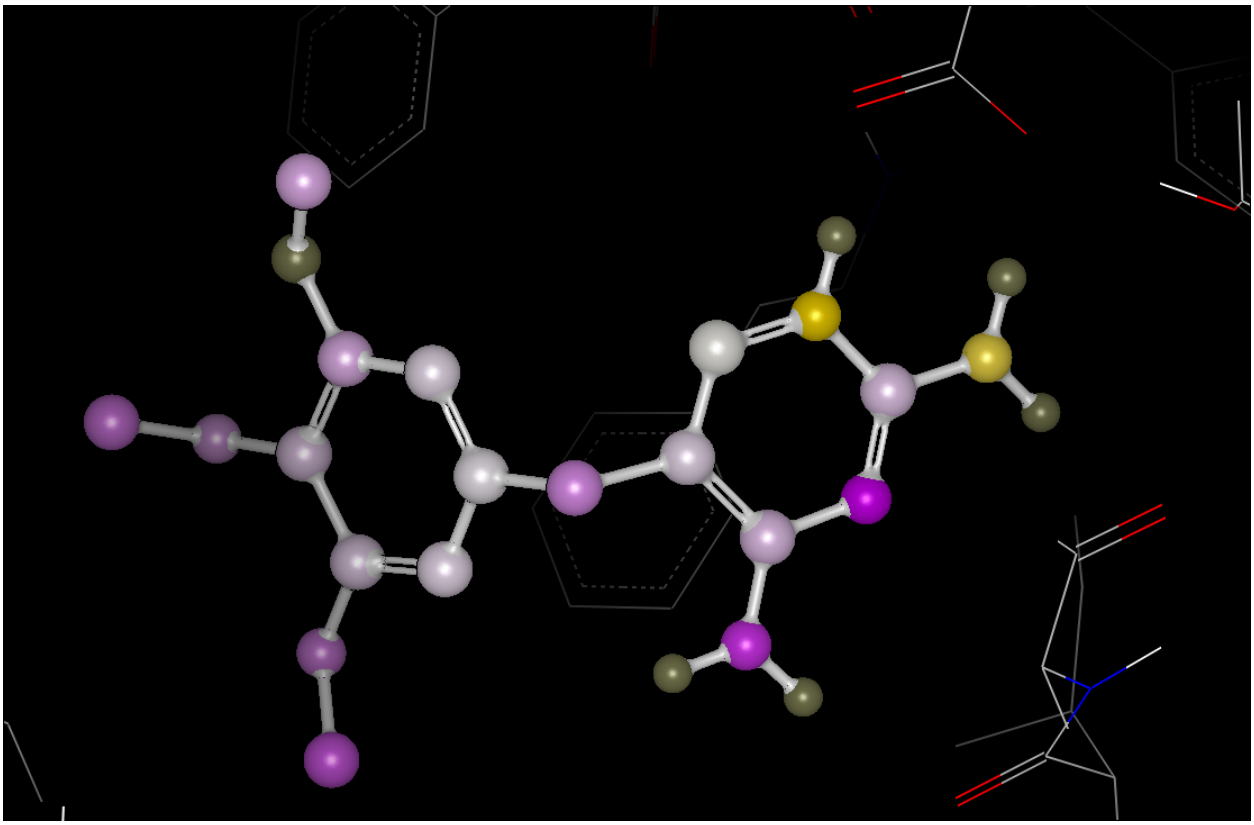


Fig. 45: **Color By Atom Properties**

SZMAP results generated with `-at_coords` contain the molecule specified by the `-at_coords` parameter with *SZMAP* results tagged as properties associated with each atom. While these property values can be displayed as atom labels using *VIDA's* generic property labeling function, the *Color by Atom Properties* extension makes it easy to survey these values by coloring the atoms of the active molecule based on a color gradient defined by selected *SZMAP* data as shown in figure *Color By Atom Properties*. Individual waters split out by the *Water Orientation VIDA Extension* are also tagged with properties that this extension can interpret.

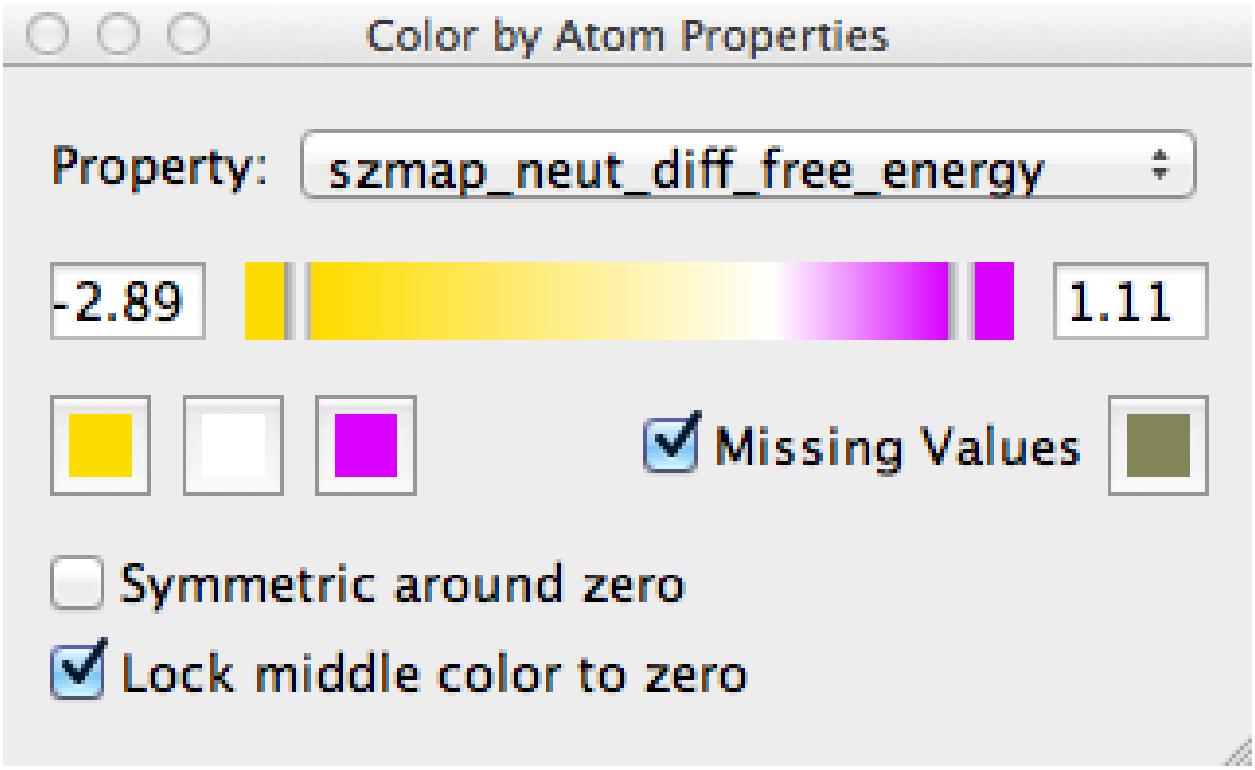


Fig. 46: **Color By Atom Properties Interface Panel**

See *Installing VIDA Extensions* for information on installing the extension.

Bring up the control panel by selecting the *Extensions >> Color by Atom Properties* pull-down menu. The extension will only color atoms when the control panel is open. The extension (see figure *Color By Atom Properties Interface Panel*) is composed of several elements:

- **Active molecule** is the *at_coords* entry selected in the *VIDA* list window: complex, ligand, *apo,* stabilization, etc.
- **Property** drop-down box to select the calculated *SZMAP* property to display. Any property in any open molecule will be listed, even if only some properties are associated with the selected molecule.
- **Range Sliders** (gray vertical bars in the color gradient) specify the range of values over which the three-color gradient will apply. Note atoms with values beyond the range selected will still be displayed, and will be colored by the respective high or low color.
- **Three Color Boxes** on the lower left set the low, middle, and high color values for the color gradient. Atoms containing values within the range selected by the *Min. Value* and *Max. Value* sliders are colored using a linear interpolation between these colors.
- **Missing Values** checkbox explicitly sets the color of atoms for which *SZMAP* values were not calculated. Checking this checkbox ensures that atoms determined to be masked out during the *SZMAP* calculations are colored a different color (specified by the color box on the lower right) to differentiate them from atoms that have a calculated value near zero. Missing values are found where the water probe *clashes*.
- **Symmetric around zero** checkbox enforces a symmetric range where the absolute value of the *Min. Value* and the *Max Value* are equal. Activating this checkbox ensures that the positive and negative color scales are equivalent, and also dictates that the color selected as the middle color in the gradient will represent a value of zero.

- **Lock middle color to zero** checkbox sets the color of atoms with values close to 0.0 to the middle color even if the negative and positive ranges are of different magnitudes.

CHAPTER

SEVEN

TUTORIALS

7.1 SZMAP Workflow

The sections represent a tutorial, going through a typical workflow and analysis of the PDB entry 4STD. Example input and output files and a list of commands for the following workflow are found in `{SZMAP Version Examples}/tutorial_files` Images are provided to guide the user when visualizing *SZMAP* results.

The workflow consists of three basic parts:

- Preparing molecules so that they can be used as input to *SZMAP* or *GamePlan*.
- Running *SZMAP* or *GamePlan*.
- Analyzing the results in *VIDA* with the help of the *SZMAP* extensions.

7.2 Protein and Ligand Preparation

In this section SPRUCE is used to prepare the proteins. You are free to use alternative methods to perform this and other "prep" tasks.

> **Note**
>
> If pre-prepared structures in *.oedu fileformat* from SPRUCE are available, these can directly be used as input and the rest of this page can be skipped. When using OEDesignUnits, note that they potentially include both solvent and a bound ligand, depending on the structure. There are two flags that are crucial to keep in mind, `-excludeDUsolvent` and `-excludeDUligand`, to control whether those two components should be part of the calculation or not.

Good protein and ligand preparation is vital before running *SZMAP* or *GamePlan*. This consists of building partial sidechains, capping chains breaks, adding hydrogens, and assigning partial charges, and atomic radii.

The commands below are shown in a form appropriate for Linux and macOS. When you install *SZMAP* on *Windows*, a pre-configured version of the DOS command prompt is constructed and can be used to run any *SZMAP* program or utility without any extra setup. This window can be found under the *Start* menu in *All Apps >> OpenEye-applications >> OpenEye-applications {version} Command line*.

First, examine your structure in *VIDA*. *VIDA* can read gzipped structure files as-is and has the *File >> Open Special >> From PDB* menu command to fetch structures from the Protein Data Bank directly.

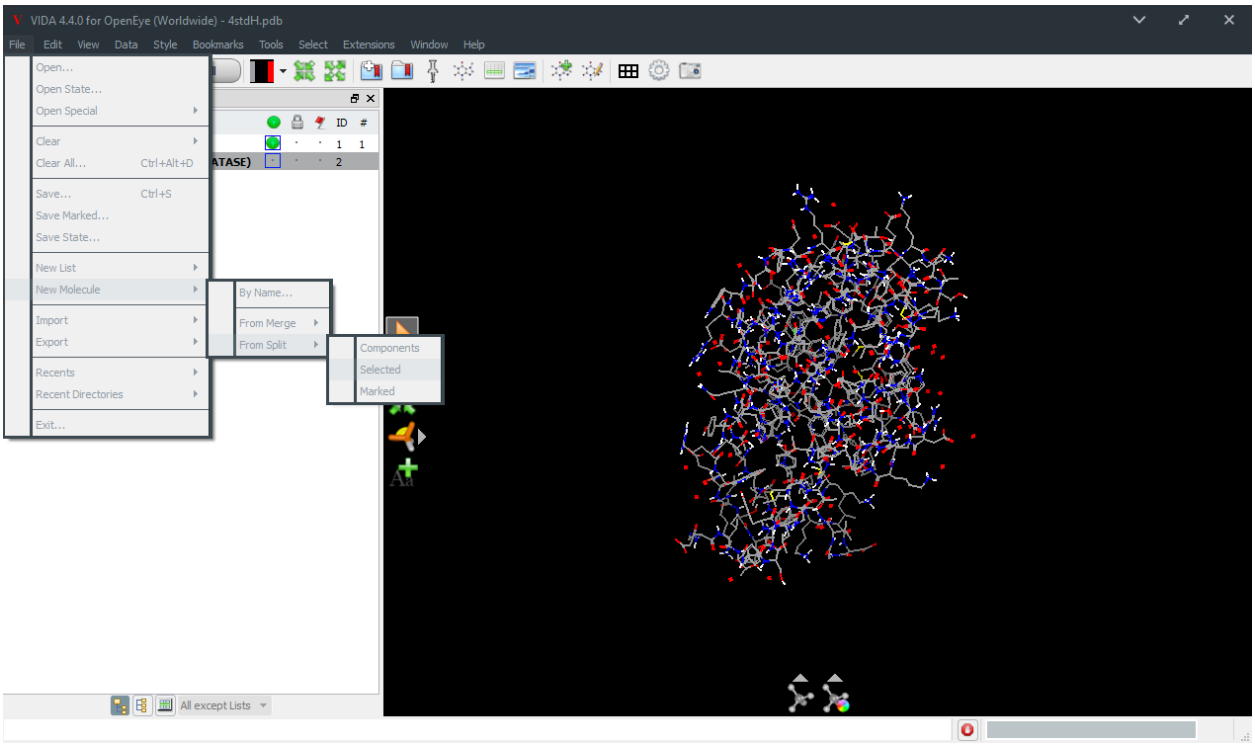


Fig. 1: **File >> New Molecule >> From Split >> Selected**

The structure for 4STD is a trimer with the ligand some distance from the protein/protein interface. If you wish to delete detergents or other extraneous molecules, select everything you want to keep and make sure they are *not* selected. Then go to the menu item and split out the piece desired. *File >> New Molecule >> From Split >> Selected*. Alternatively, you may prefer to edit your molecule by hand as follows. If your structure file is gzipped PDB file, unzip it. Edit it to delete extra subunits, detergent, or other extraneous molecules using whichever text editor you prefer. It is not necessary to remove the waters at this stage, they wil be split out later. It is also not necessary to prune the connection table—any references to deleted atoms will be ignored

Since *SZMAP* and *GamePlan* require explicit hydrogen atoms on the molecules and most PDB structures do not include the hydrogen atoms, the next steps produce a protein structure with all the hydrogen atoms explicitly represented. There are many ways to do this. Here, we will use SPRUCE, the application will automatically generate biologically relevant units from the asymmetric unit (if needed), enumerates alternate locations, builds partial sidechains, caps chain breaks, places and optimizes protons including tautomer searching for ligands and co-factors. The alterante location enumeration and biological unit generation, means the application can output multiple structures based on the input unit.

```
>  spruce -in 4std.pdb -prefix szmap_

szmap_4STD_A__DU__BFS_A-173.oedu
```

In this case the application wrote one structure into three files, the target/receptor structure, the automatically detected ligand, and a molecule containing the solvent. In these files the molecules have already had charges and radii assigned. If the ligand molecule is < 100 atoms, it will have AM1BCC charges assigned along with Zap9 radii, otherwise it will have MMFF charges assigned and Bondi radii. Protein molecules will have AmberFF94 charges assigned for any standard amino acid residue and AM1BCC for nonstandard residues. The function will fall back to assign the entire protein MMFF94 charges if there is a failure. Nucleic acids will have MMFF94 charges assigned. Water molecules are assigned SZMAP water parameters, described further in the The Szmap TK Standard Water Model chapter of the SZMAP toolkit.

7.3 Running SZMAP Stabilization Calculations

Assuming the input structures have been prepared as described above, *SZMAP* grids can be calculated for the region around the ligand as follows:

```
> szmap -mpi_np 4 -prefix 4std_stbl -stbl -p 4STD_ABC__DU__BFS_A-173.oedu -
↪excludeDUsolvent

or

> szmap -mpi_np 4 -prefix 4std_stbl -stbl -p 4STD_A__DU__BFS_A-173_target.oeb.gz -l 4STD_
↪A__DU__BFS_A-173_ligand.oeb.gz
```

Note

The option `-excludeDUsolvent` is needed to exclude structural waters from the stabilization calculation if the input is using a design unit.

Stabilization calculations can also be performed with a dataset of pre-posed non-native ligands, using the commands below.

```
> szmap -mpi_np 4 -prefix 4std_stbl -stbl -p 4STD_ABC__DU__BFS_A-173.oedu -
↪excludeDUsolvent -l posed_ligands.oeb
```

Calculations for *complex, apo,* and *ligand* grids will be done (requiring about 40 minutes for this example on Linux using four 2.8GHz processors) and then further processed to yield *(complex - apo - ligand)* stabilization grids, describing where water is stabilizing or destabilizing the binding reaction. The output consists of the calculated grids in an *.oeb.gz* file, along with a parameter file and a log file, all with names prefixed with "4std_stbl".

To run on only a single processor, drop the `-mpi_np #` option. More information on options can be found in chapter *SZMAP*.

Note

SZMAP (and *GamePlan*) will check for missing hydrogens and missing partial charges and halt if they are missing on the protein, but that will typically not be a problem if the input is an OEDesignUnit. It also shouldn't be a problem with the ligand read from an OEDesignUnit, however, if a ligand is passed with missing partial charges, they will be assigned AM1BCC charges and Zap9 radii. If reading from a PDB, sometimes, OEChem will have a different opinion about the charge or bond order than what you expect. For example, if your structure has significantly nonterminal geometry around an aromatic or double bond, OEChem may try to treat it as a single bond. The option `-warn_if_missing_hydrogens` will allow you to run *SZMAP* and *GamePlan* despite OEChem thinking there are hydrogens that are not explicitly in your structure. But you may also need to change the formal charge of a polar group before running pch, either in *VIDA's* builder or by modifying the structure file using a text editor.

7.4 Analyzing SZMAP Results

7.4.1 Determining the Ligand Displacement Region

The results can be processed with *GridComp* to break-out the region of the *apo* grid that has been displaced by the ligand.

```
> grid_comp -op lig_disp -i 4std_stbl.oeb.gz -o 4std_stbl_disp.oeb.gz
```

While not required, these displacement grids can be useful. For example, they can be used to identify precisely which waters are displaced by each of a series of substituents. They also make it easy to determine the volume of water displaced by the ligand.

7.4.2 Analyzing Grid Results

SZMAP grid results can be visualized in *VIDA* using the *WaterColor VIDA Extension* (sets grid styles for viewing—the link leads to information about the extension) and the *Water Orientation VIDA Extension* (shows water orientational preferences). If *VIDA* is in your command search path, the following command will open *VIDA* and load the file *4std_stbl_disp.oeb.gz*. *VIDA* can also be launched by clicking on the *VIDA* icon and the file can then be loaded using the *Open...* command in the *File* menu. You can also drag and drop molecule files onto a *VIDA* instance.

```
> vida 4std_stbl_disp.oeb.gz
```

Note

VIDA extensions need to be installed before they can be used. For instructions, see *Installing VIDA Extensions*.

The neutral difference *(water - uncharged)* grids map the polarity throughout the site and the stabilization grids describe the binding reaction *(complex - apo - ligand)*: they have negative energies where water enhances binding affinity and positive where it decreases binding affinity.

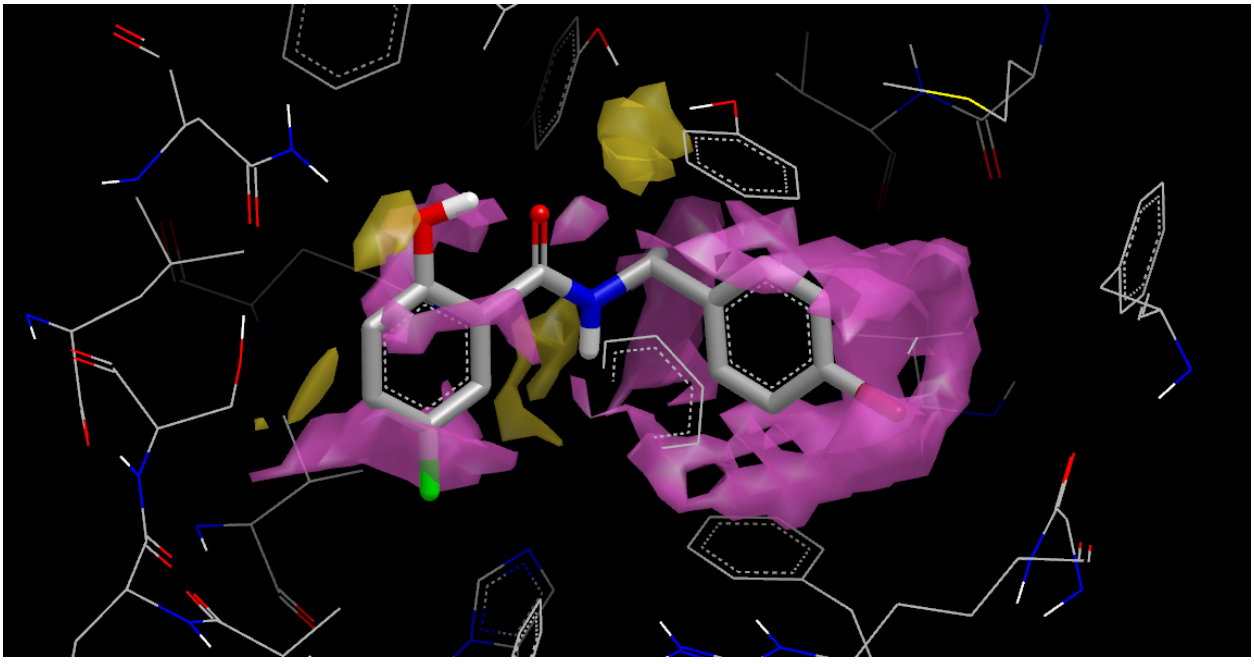


Fig. 2: **Displaced Neutral Difference Free Energy**

The figure *Displaced Neutral Difference Free Energy* was generated by selecting *4std_stbl_disp.oeb.gz* in *VIDA's* list window and running the *WaterColor VIDA Extension* to setup the contour levels and display styles, then opening the *lig_disp:apo:PROTEIN...* item in the list window and displaying the *neut_diff_apo_free_energy_grid*. You must run

WaterColor on each new *SZMAP* results file opened in *VIDA*. See chapter *WaterColor VIDA Extension* for more detailed instructions.

The figure *Displaced Neutral Difference Free Energy* shows that the ligand displaces regions with both negative (yellow) and positive (purple) neutral difference free energies. These energies represent a polarity scale: negative regions favor polar groups while positive regions favor non-polar groups. Note that the hydroxyl oxygen nicely substitutes for solvent that acts as an H-bond acceptor. The region in the upper center, on the other hand, contains solvent interacting with a pair of tyrosine hydroxyls that is displaced but not replaced with a similar group. This suggests placing a polar group into this site.

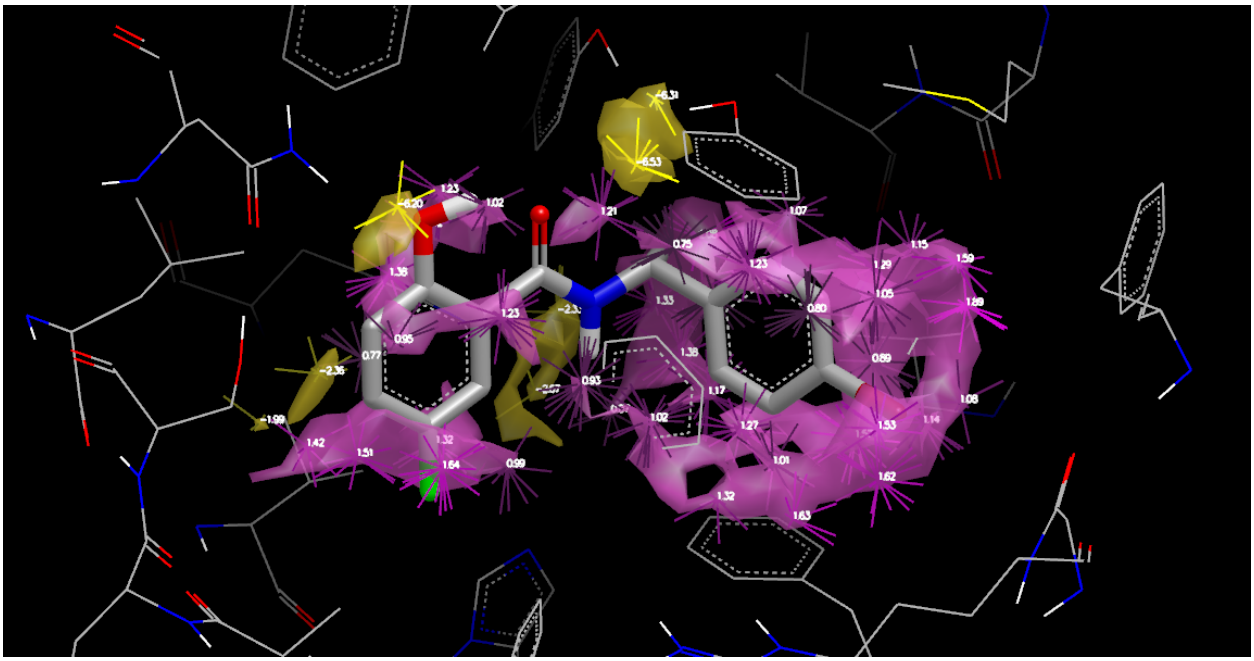


Fig. 3: **Orientations and Displaced Neutral Difference Free Energy**

The *Water Orientation VIDA Extension* will display the most probable water orientations for each point in the calculation, filtered to show only the dominant points (local minima and maxima). It makes it easy to determine where waters donate or accept H-bonds and where waters do not make any significant interactions. Open the control panel by selecting the *Extensions* >> *Water Orientation* menu in *VIDA* (it will remain open until you close it).

The figure *Orientations and Displaced Neutral Difference Free Energy* adds information indicating both the magnitude of the free energies and the geometry that must be taken into account in positioning a substituent. To generate the figure, set the `Apply to:` popup in the *Water Orientation VIDA Extension* to `4std_stbl_disp.oeb.gz/apo(lig_disp)`—the ligand displacement *apo* results—and press the *Update* button.

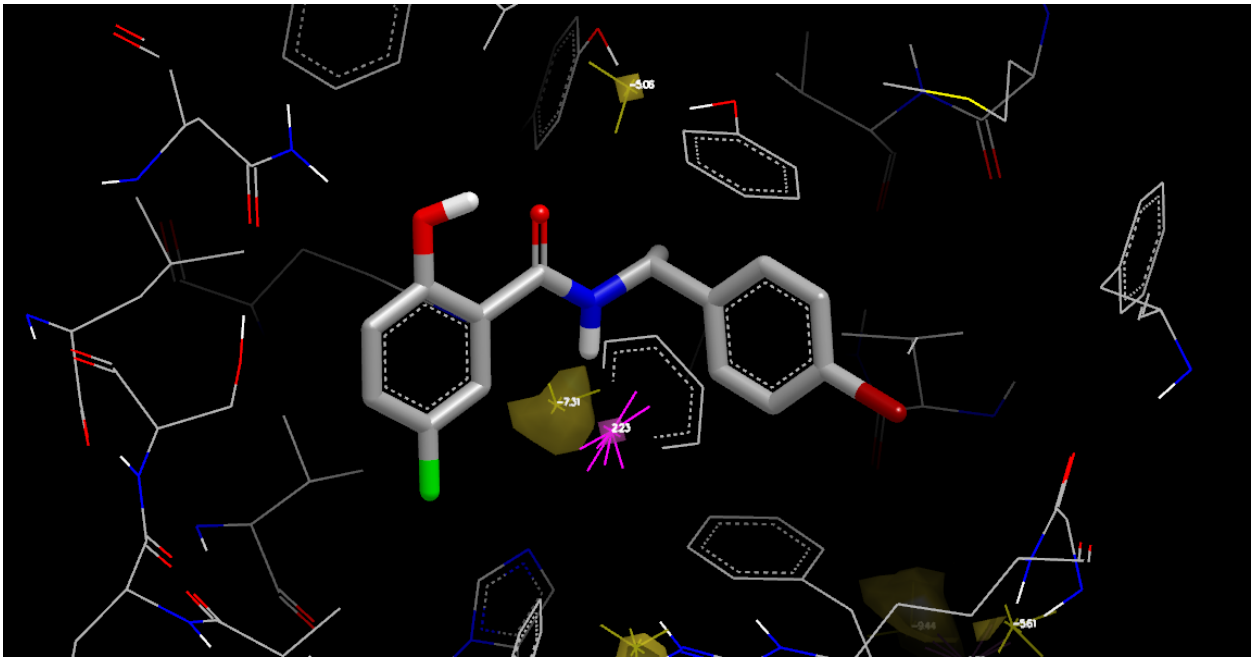


Fig. 4: **Complex Neutral Difference Free Energy**

The next stage is to examine the protein-ligand complex grid, illustrated in *Complex Neutral Difference Free Energy*. First, undisplay all grids from the *lig_disp:apo:PROTEIN...* entry in *VIDA's* list window, along with the *4std_stbl_disp.oeb.gz/apo(lig_disp)* entry from the previous orientation display. Next, open the *complex:PROTEIN...* section of *VIDAs* list window to reveal the set of grids calculated for the complex. Select and display the *neut_diff_free_energy_grid*. Finally, set the *Water Orientation VIDA Extension* to applied to `4std_stbl_disp.oeb.gz/complex` and press *Update*. The display shows two regions of negative free energy: a region at the bottom were solvent interacts with two histidines and the amide NH of the ligand, and a smaller region at the top, just beyond the displaced region, that interacts with the previously mentioned tyrosines, along with one region of positive free energy.

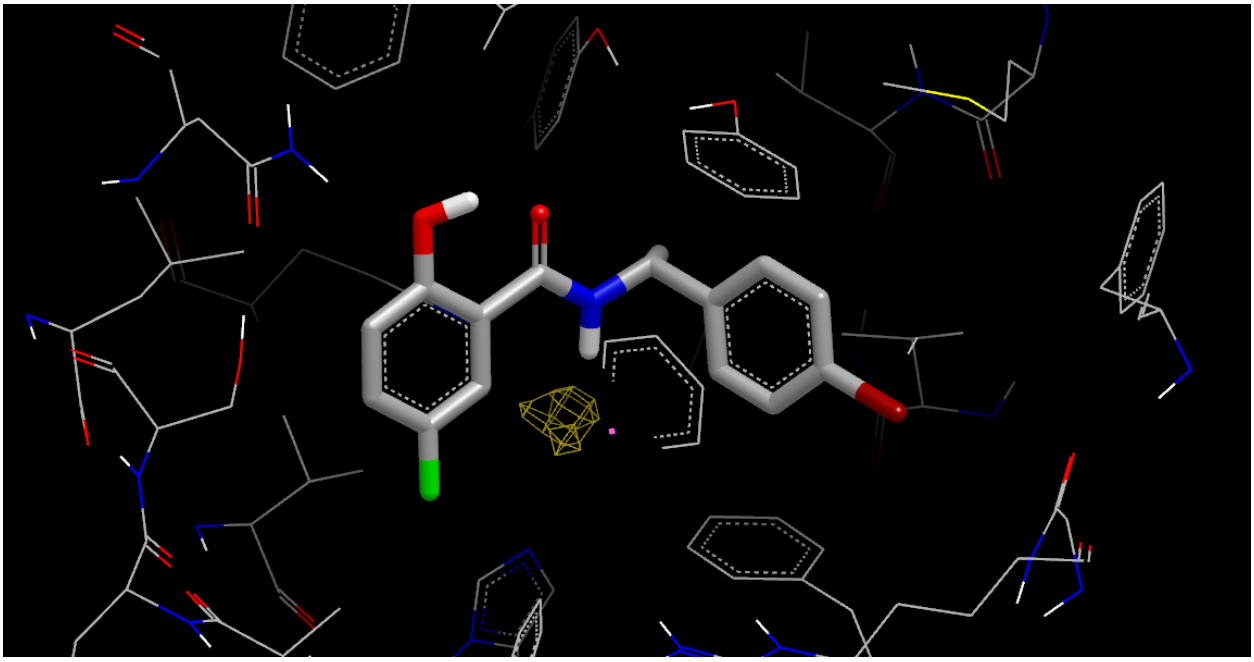


Fig. 5: **Stabilization Neutral Difference Free Energy**

Looking at the *Stabilization Neutral Difference Free Energy* (by undisplaying any other grids or orientations and then opening the *stabilization:PROTEIN...* item in the *VIDA* list window and displaying the *neut_diff_stbl_free_energy_grid*), it is clear that only the lower region is stabilizing the bound ligand, adding weight to the idea of displacing water in the upper region.

7.5 Running SZMAP at Coordinates

SZMAP can be run at arbitrary coordinates, for example the atom positions in the ligand. Because this calculation is performed only over the atom coordinates specified in `-at_coords <mol_file>` it will run very quickly, around 1 minute for this example. While not as informative as a full grid calculation, "at coords" calculations are a rapid way to survey a binding site (about 20 seconds on four 2.8GHz processors).

```
> szmap -mpi_np 4 -prefix 4std_lig_coords -at_coords 4std_lig.oeb.gz -p 4STD_ABC__DU__
↪BFS_A-173.oedu -excludeDUligand

or

> szmap -mpi_np 4 -prefix 4std_lig_coords -at_coords 4std_lig.oeb.gz -p 4STD_A__DU__BFS_
↪A-173_target.oeb.gz
```

The output for `-at_coords` calculations includes a text file containing tab-delimited tables of results and an *.oeb* file with *SZMAP* results as properties attached to the atoms used to define the coordinates.

> **Warning**
>
> If the at_coords positions overlap with atoms in the protein or design unit file, the coordinate will be skipped. The current clash definition is a near perfect atom overlaps (0.1A)

7.5.1 Analyzing Coordinate Results

If the calculations were done at specified coordinates (using the `-at_coords` parameter) the results can be visualized with the *Water Orientation VIDA Extension* or the *Color By Atom Properties* (which colors coordinates by calculated values). Open the file in *VIDA* using the command below or, if *VIDA* is already open, by using the *File >> Open* menu.

```
> vida 4std_lig_coords.oeb.gz
```

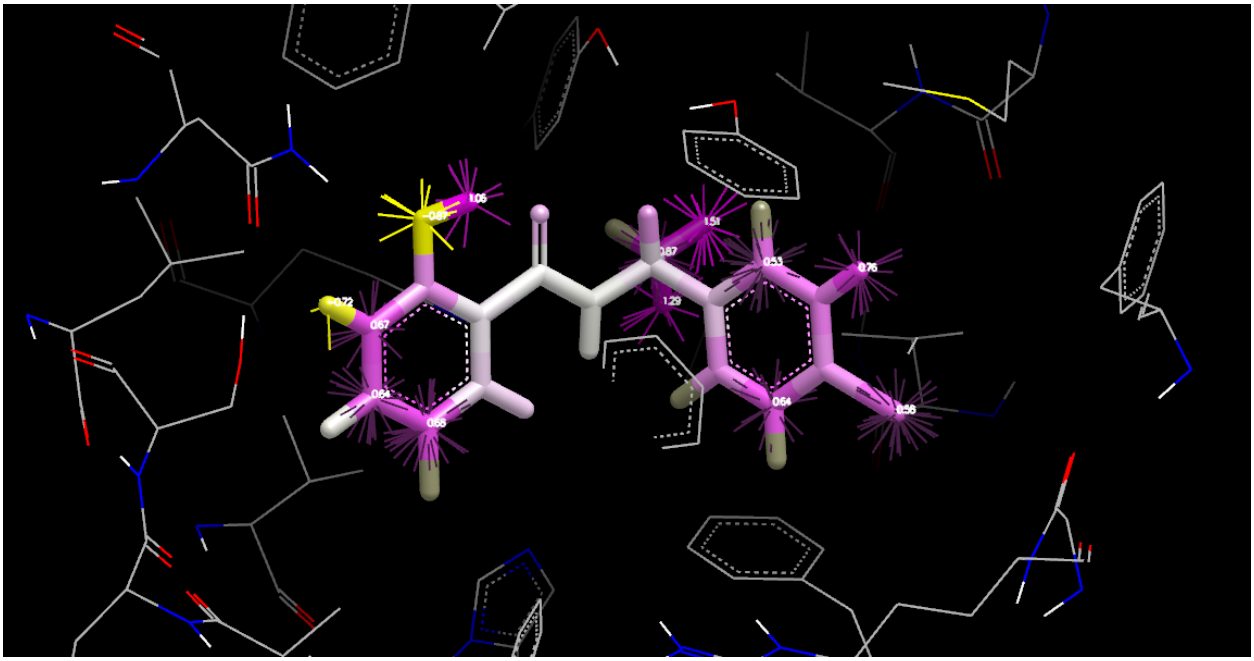


Fig. 6: **Apo Neutral Difference Free Energy at Ligand Coordinates**

The figure *Apo Neutral Difference Free Energy at Ligand Coordinates* shows results similar to the *Orientations and Displaced Neutral Difference Free Energy*. Calculating at the ligand coordinates is very quick but produces a coarse sampling and in regions where the gradient is large, can be somewhat misleading.

To generate this figure, the *Water Orientation VIDA Extension* panel was accessed to `Apply to: 4std_lig_coords.oeb.gz/apo` and the *Update* button was pressed. Next, the *apo: at_coords* entry in the list window was selected and the "H" button in the style panel was used to display all the ligand hydrogens. With the *apo: at_coords* entry still highlighted in the list window, the *Color By Atom Properties* was opened and the property *szmap_neut_diff_free_energy* was selected. Then, if this is the first time the panel has been used, the color tiles in the center-left were selected one-by-one and changed so that the left one was yellow, the center one was white, and the right one was purple (the standard *SZMAP* color scheme). The missing values color tile was also set to a dark gray color easily distinguished from the others. Finally, the options "Lock middle color to zero" and "Missing Values" were checked. The dark gray atoms along outer edges of the ligand are at positions where a water probe is slightly too large to fit without clashing, but it is worth noting that this can occasionally be alleviated with a shift of just a fraction of an Ångström.

7.5.2 Two-dimensional Coordinate Reports

In addition to the 3D graphics, you can also produce a printable *.pdf* report of `-at_coords` results with *SzmapReport*. The molecule is shown in 2D, colored by their numerical value of the *SZMAP* results. If multiple ligands were used for the coordinate calculations, *SzmapReport* will depict all of them for easy comparison.

```
> szmap_report 4std_lig_coords.oeb.gz 4std_lig_coords.pdf szmap_neut_diff_free_energy
```

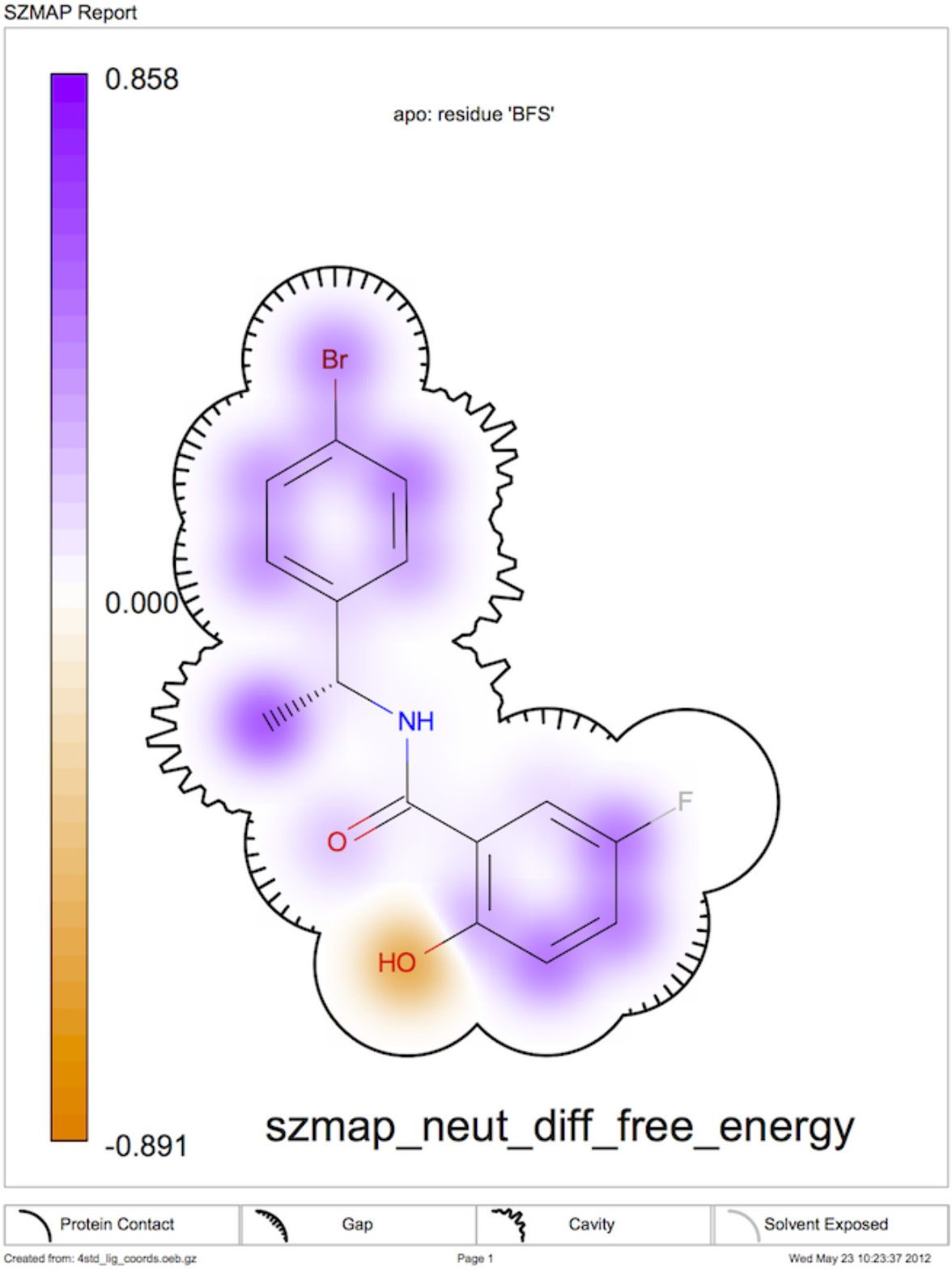


Fig. 7: **Neutral Difference Free Energy in 2D**

Figure *Neutral Difference Free Energy in 2D* shows a **SzmapReport** for the neutral difference free energy with a surface representing how tightly or loosely the ligand fits into the binding site. See chapter *SzmapReport* for more information on this surface representation. In this case, the phenolic ring is held tightly while the methyl group is adjacent to a cavity. The pocket around the fluorine is so tight that a probe water cannot fit there, indicated by the gray color of the fluorine atom.

7.5.3 Stabilization at Coordinates

While calculations at ligand atom coordinates cannot produce stabilization energies, calculations at coordinates other than the ligand *can*. They can also be very quick ways to explore properties of the complex, with the same caveat that they represent a coarse sampling.

In our example, the two crystallographic waters closest to the ligand are split from the original PDB file and used to calculate stabilization values at these coordinates. Although the splitting can also be done with *VIDA* or with a text editor, here we use the *egrep* command generally available on Linux, Mac OS X or Windows *cygwin*.

```
> egrep 'HOH A 187' 4std.pdb >  4std_selected_waters.pdb
> egrep 'HOH A 190' 4std.pdb >> 4std_selected_waters.pdb

> szmap -prefix 4std_wat_coords -at_coords 4std_selected_waters.pdb \
>       -mpi_np 4 -stbl -p 4STD_ABC__DU__BFS_A-173.oedu

or

> szmap -prefix 4std_wat_coords -at_coords 4std_selected_waters.pdb \
>       -mpi_np 4 -stbl -p 4STD_A__DU__BFS_A-173_target.oeb.gz
```

Tip

The line above with a '\' as the very last character indicates that the command was too long to fit on one line and continues on the following line.

7.5.4 Analyzing Coordinate Stabilization Results

```
> vida 4std_wat_coords.oeb.gz
```

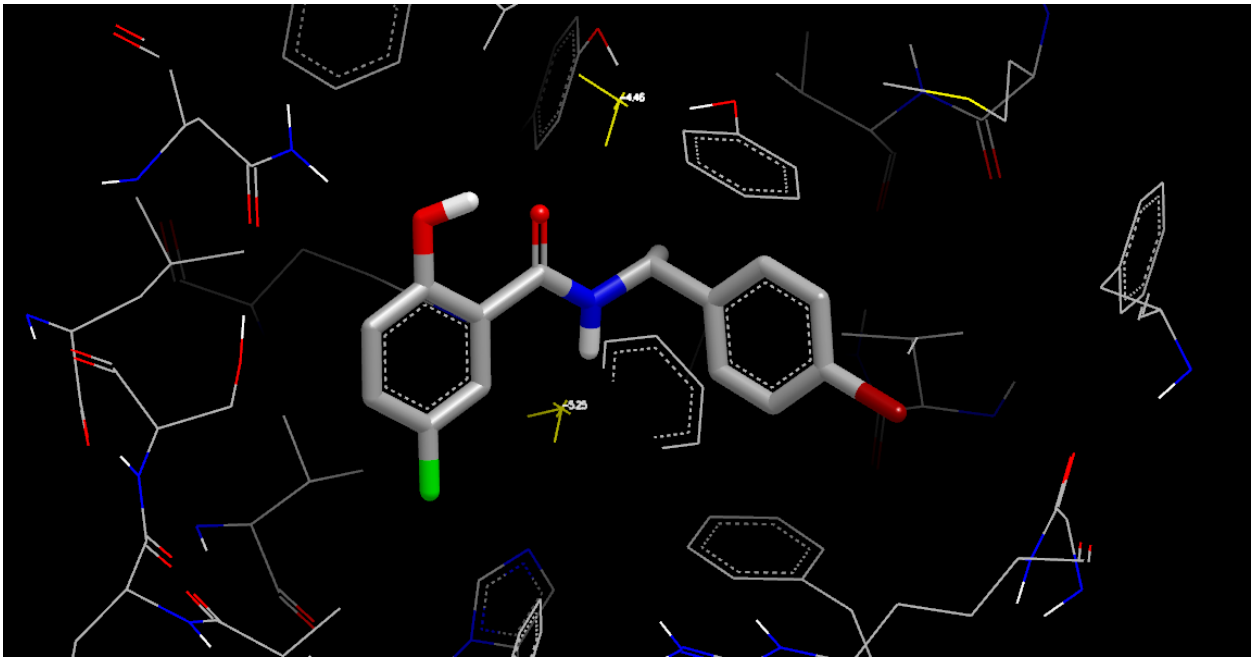


Fig. 8: **Complex Neutral Difference Free Energy at Water Coordinates**

The *Complex Neutral Difference Free Energy at Water Coordinates* (with orientations and energies from the *Water Orientation VIDA Extension*) shows results similar to the *Complex Neutral Difference Free Energy* but were produced much more quickly.

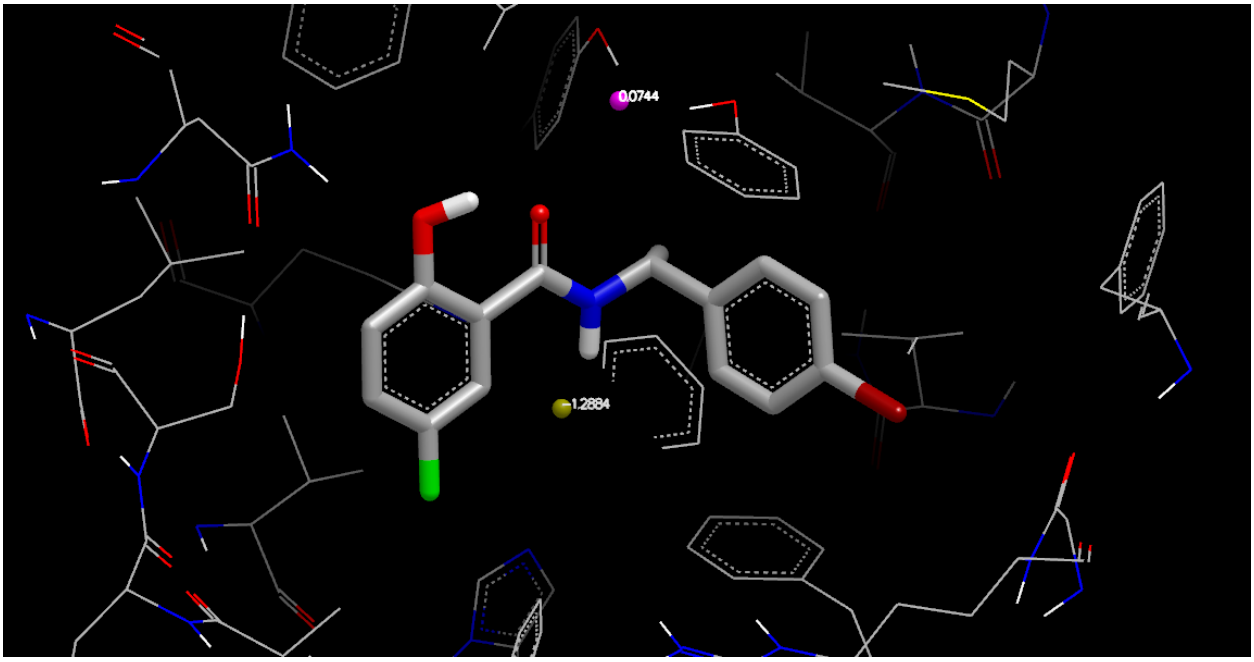


Fig. 9: **Stabilization Neutral Difference Free Energy at Water Coordinates**

In *Stabilization Neutral Difference Free Energy at Water Coordinates*, the *stabilization: at_coords* waters were highlighted in the list window and colored based on the property *szmap_neut_diff_stbl_free_energy* using *Color By Atom*

Properties. No orientation data is shown because orientation information is not produced by stabilization calculations, only complex, ligand, and *apo* calculations. But using *VIDA's* generic data labeling capabilities, the coordinates can be labeled by the neutral difference stabilization free energy values. This is a quick way to visualize energies from a stabilization grid calculation. Rather than using crystallographic waters in the calculation, the "at coords" positions can be waters from a previous grid calculation using the "Split" tool in the *Water Orientation VIDA Extension*, or generated by some other procedure.

7.6 Running Gameplan

The application *GamePlan* uses *SZMAP* to analyze ways to modify ligand chemistry based on water structure and energetics in the immediate environment of the ligand. By testing a limited number of coordinates based on the structure of the ligand and the binding site, *GamePlan* quickly generates: a description of how compatible the ligand is with the binding site, a series of hypotheses for ligand variants, and stabilizing or destabilizing waters.

Again, assuming the input protein and ligand structures have been prepared as described above, a *GamePlan* calculation can be performed as follows:

```
> gameplan -szmap_mpi_np 4 -prefix 4std_gameplan -p 4STD_ABC__DU__BFS_A-173.oedu

or

> gameplan -szmap_mpi_np 4 -prefix 4std_gameplan -p 4STD_A__DU__BFS_A-173_target.oeb.gz -
↪l 4STD_A__DU__BFS_A-173_ligand.oeb.gz
```

The protein and ligand in the OEDesignUnit are analyzed and the most informative sample points are identified. *SZMAP* is then run on those points, and the results are transformed into a set of potential ligand modifications. All of this takes about 4 minutes on four 2.8GHz processors and the output is placed in the file "4std_gameplan.oeb.gz", which can be analyzed in *VIDA* using the *WaterColor VIDA Extension*. The file "4std_gameplan.log" documents the results, including the energy values for each attachment hypothesis.

The command line option `-szmap_mpi_np #` controls how *GamePlan* runs *SZMAP* to compute the results. More information on options can be found in chapter *GamePlan*.

7.6.1 Analyzing Gameplan Results

Results from *GamePlan* contain ideas for ligand modifications and points where water is stabilizing or destabilizing the protein/ligand complex.

```
> vida 4std_gameplan.oeb.gz
```

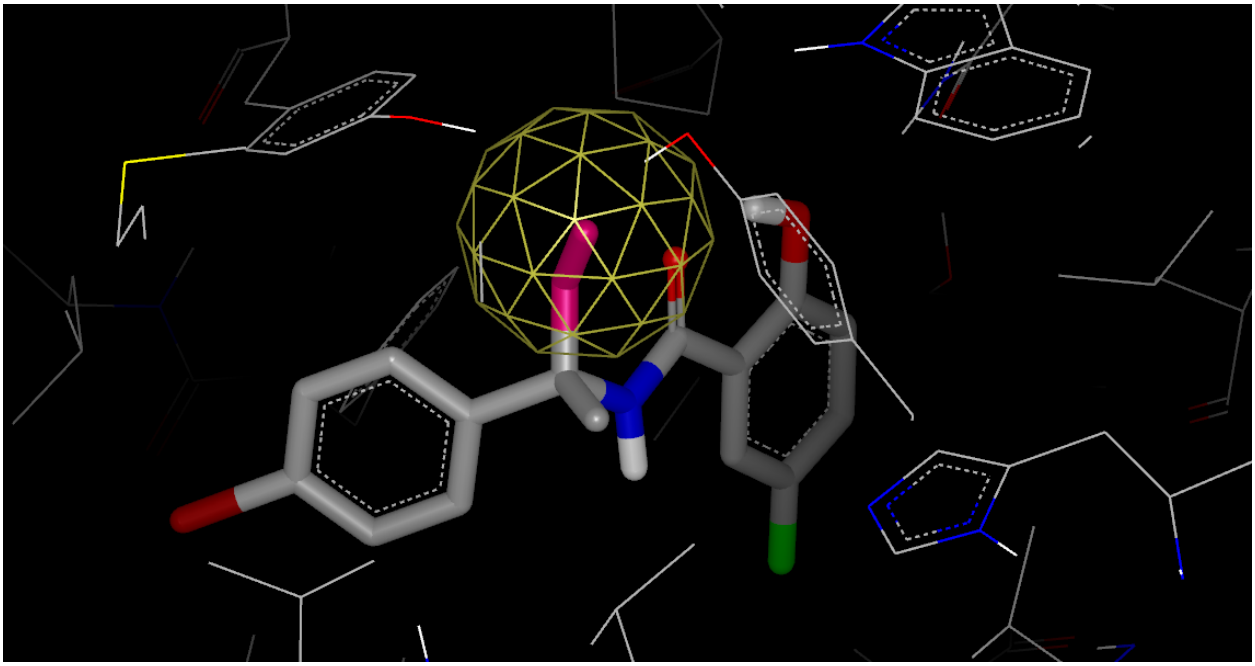


Fig. 10: **Gameplan Hypothesis for a Polar Attachment**

In *Gameplan Hypothesis for a Polar Attachment*, the *WaterColor VIDA Extension* has been used to configure the display of the *GamePlan* results by highlighting any part of the gameplan results in the list window and running *WaterColor VIDA Extension*. Using the up-arrow and down-arrow keys, you can browse through the different components of the results in the list window. Shown in pink is a suggestion for a site where a hydrogen-bond acceptor might interact favorably with nearby tyrosine residues. The yellow ball indicates that water makes a strong polar interaction at this site in the *apo*-protein. For a complete description, see chapter *GamePlan*.

CHAPTER

EIGHT

THEORY

8.1 Philosophy and Design

We all care about water. It is the one thing we always need to take into account and it's also the one thing we have most trouble modeling. A recent historical review of theories of water lists over thirty different models [Guillot-2002], none of which are comprehensive in their predictive abilities, *i.e.* are able to reproduce all of water's many properties. However, we really don't care about the thermal conductivity or viscosity of water, we just want to know how it interacts with solutes of interest, typically a drug molecule and a protein. Here, simple atomistic modeling of water ought to be adequate. And for very simple molecules, *e.g.* alkanes, mono-functional substituted alkanes, simple aromatics, all-atom simulations can appear to be capturing interactions between water and the solute quite well, for instance in predicting the transfer energy from vacuum to water. However, attempts to predict such energies on more complicated molecules are much less accurate and, what is worse, appear to be no better than a simplistic approach such as Poisson-Boltzmann (PB) [Nicholls-2008], [Nicholls-2009]. In PB we model water not atomistically but as a continuum, as a high dielectric that responds to the potential produced by the solute. PB cannot account for the van der Waals interactions between water and the solute other than by some simple area term and cannot account for discrete water effects, hydrogen-bonding patterns or correlation between waters. All it can do is to present an effective response, a long-time response if you will, of a material that macroscopically acts like water in its dielectric response. Yet PB continues to prove useful and predictive, presumably because the behavior it does model is the dominant behavior for interaction energetics and because many of the aspects of water claimed to be important either are not or cancel each other in some poorly understood manner. An example of this was discovered early in PB theory, namely that of the results for highly charged ions, where water structure was presumed to be absolutely necessary for prediction. Closer study illuminated two effects: electrostriction, causing water density to be higher near the ion, and dielectric saturation, *i.e.* the field of the ion so aligns water that it no longer responds linearly to that field. These two effects act to cancel each other—electrostriction increases the effective dielectric while saturation decreases it. As a consequence, PB is quite accurate for highly charged ions.

Despite the fact that all-atom simulations have proven quite poor at predicting the energies of anything but simple molecules (*e.g.* RMS error of $\sim 2\, kcal\, mol^{-1}$) they are routinely applied to the much more complicated task of active site modeling. It is natural to try such techniques because this is the area of interest for drug discovery and, to be fair, the solvation of simple amino acids is well understood. It is also felt that simulations must be more useful than PB for this task because active sites represent volumes where solvent behavior is, perhaps, much less likely to be like bulk, *i.e.* how can PB represent the behavior of water that must be more discrete than continuous? In answer to this, one first has to remember that there is no experimental proof that all-atom simulations work well in active sites either—other than the occasional paper claiming to predict binding affinities on a particular system(s) with particular properties, *i.e.* anecdotal science. However, because simulations allow one to present images of waters and water behavior it is the more compelling technology. We are all prone to capture by images. And, to be fair again, the results from simulation ought to make some qualitative sense, *e.g.* waters in enclosed areas will differ from bulk water in their behavior in expected ways. The questions before us are: what can PB tell us in both a faster and simpler way, and can this be captured quantitatively?

To consider these questions, we should first acknowledge the work of Barry Honig and his group during the early nineties on the hydrophobic effect [Sharp-1991a], [Sharp-1991b], [Nicholls-1991]. Honig is known, of course, for bringing PB to the field of molecular modeling with the program DelPhi and later, in a visual sense, with GRASP.

Barry once related a story concerning a review of one of his early grant applications which said that while Honig's work was clearly competent on the electrostatics of water the reviewer could not recommend funding because clearly Honig had never heard of the hydrophobic effect. The printable part of Barry's righteous anger over this remark was "one thing at a time," and around 1991 Anthony Nicholls, Kim Sharp and Barry started thinking about hydrophobicity and how we might account for it by something other than a simple area term, *e.g.* by multiplying the accessible area, that of the locus of points formed by the center of a sphere the size of water run over the VDW surface of a molecule. There were complicated area models for sure, *i.e.* ones where the area belonging to different atom types were accorded different energies [Eisenberg-1986], but these were already accounting for some of the electrostatic effects that PB included. Instead we concentrated on non-polar molecules in an attempt to partition out the electrostatics, the assumption being that the two components, *i.e.* the hydrophobic and the electrostatics, were relatively orthogonal. The principle puzzle that drove us at this time was the difference in this area term for small molecules and for the macroscopic. For instance, for small molecules the transfer energy of an alkane from hydrocarbon to water gave roughly $32\,cal\,Angstrom^{-2}mol^{-1}$ (unfavorable). This comes from the work of Hermann [Hermann-1972], where the increase in transfer energy from hydrocarbon to water is $0.88\,kcal\,mol^{-1}$ per methyl group added in going from ethane to decane. However, the surface tension at a water/ hydrocarbon interface works out to about $72\,cal\,Angstrom^{-2}mol^{-1}$ (unfavorable). Why was there an almost three fold difference in behavior between microscopic and macroscopic areas? We investigated many possibilities, detailed in our papers from that era, but the most fascinating was the concept of curvature. There was a formula from Tolman, a giant in the area of statistical mechanics, for the surface tension of small oil droplets [Tolman-1949]. This formula showed that as drops became smaller the surface tension should decrease. This made physical sense in that water at the boundary to such a highly curved surface would make more interactions with neighboring waters than when pressed against a flat surface, *i.e.* would be less perturbed by the hydrocarbon surface. Was there a way in which this formula could bridge the gap we were looking at between microscopic and macroscopic?

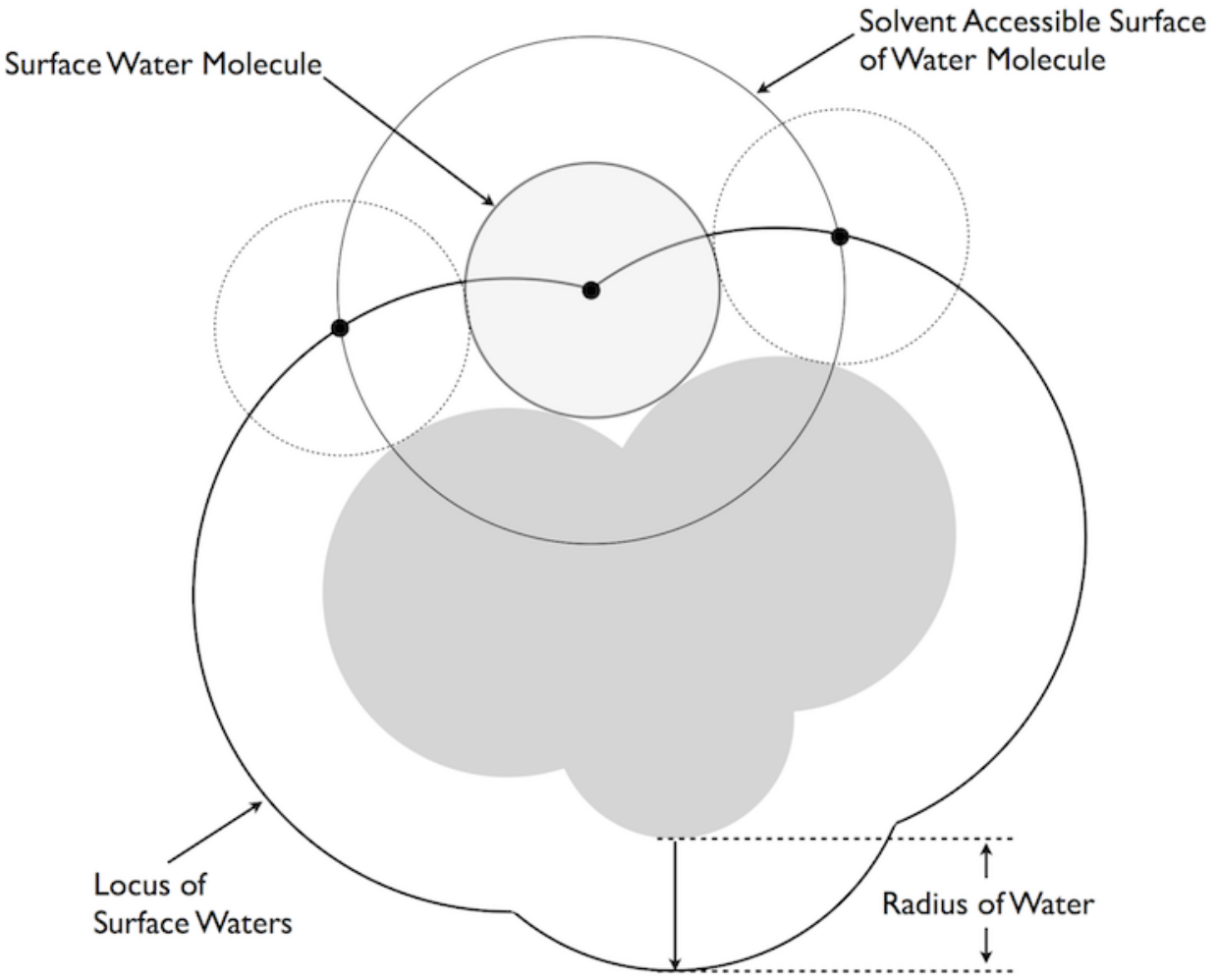


Fig. 1: **Curvature**
The basic curvature model of Nicholls and Honig [Nicholls-1991].

Unfortunately, Tolman's formula was only a signpost in that it included a parameter that should be of the order of molecular dimensions but with no clear indications as to what it should actually be. The seminal insight from our work was to associate this parameter with the diameter of water. If this association was made then Tolman's formula actually described the fractional change of the accessible area of a water molecule at the surface of the droplet, *i.e.* from 2π steradians at a flat surface to 4π in solution and 0π when isolated from other waters (figure *Curvature*). The neat thing about this translocation of ideas is that we could calculate a "Tolman"-like correction for any shaped surface, not just a spherical droplet. All we had to do was to put a sphere the size of water (radius 1.4 Ångströms) up to the surface of a molecule and calculate its loss of accessible area. If the surface was planar you lost exactly half its accessible area, if the surface was concave more area was lost and if it was convex less was lost. The idea was very simple: water likes being in contact with water and its own accessible area was a measure of how happy (energetically favorable) it was. As described in our *Science* paper [Sharp-1991b], this curvature correction became an integral part in our attempt to bridge the microscopic/macroscopic gap. What happened next is, perhaps, an illustration of another gap: that between the simulation world and the continuum world. What was really needed was someone well versed in the simulation world to test the predictions of this model—we had proposed a straight linear correspondence between the loss of area a water might experience and the energy penalty/hydrophobicity at that point in space. Simulations could have at least tested the form of this concept, for instance by simulating water around the surface of an uncharged macromolecule. However, not one simulation group stepped forward because, after all, this is a continuum theory and was seen as competition, at that time, to the simulation approach (and for grant money).

In the end, the majority use of the curvature concept was in graphics; it became a standard way in GRASP to illuminate the convex and concave parts of a protein or DNA. In fact, finding large regions of contiguous concavity proved a useful way to spot areas of functional utility for both. Lost was the concept of this as a quantitative measure of water's chemical potential.

Then, in 2006, I revisited the problem from a different angle. I'd heard some years ago at an ACS meeting that Alex Rashin, a Russian scientist who had worked with Barry on some of his earliest PB papers, had played around with placing a water, *i.e.* a molecular representation of water, around a solute and calculating the PB energy of such a water in an attempt to predict, not the total free energy of hydration, but the enthalpy and entropy. This seemed very ambitious and I am not sure if Alex published his results. Barry's opinion was that perhaps Alex believed a little too much in PB and was pushing the theory too far. However, by that time I was looking at our ability to predict the transfer of small molecules from vacuum to water and it was clear that there were persistent outliers the theory was only just capturing. For instance, tetrafluoromethane has a very unfavorable transfer energy of $+3.1\,kcal\,mol^{-1}$, yet PB wants to make this molecule almost soluble (predicts around $0.0\,kcal\,mol^{-1}$). Even if you turned off all the charges in this molecule and just assumed it was a waxy blob you would only get a prediction of about $+1\,kcal\,mol^{-1}$. PB just does not have the facility to correctly predict $+3.1\,kcal\,mol^{-1}$. Another example, in the opposite direction, is bromoform, *i.e.* a methane with three bromines attached. In this case the experimental result is $-1.98\,kcal\,mol^{-1}$ but PB predicts an unfavorable $+1\,kcal\,mol^{-1}$ transfer energy (essentially because there is little polarity in the molecule and it is big and bulky). Now, an all-atom simulationist would look at this and immediately recognize the problem: *van der Waals*. Fluorine has very small van der Waals interactions and bromine has large ones—using a single area term is bound to fail for these molecules. This may well be a part of the problem, however thinking back to the curvature model I could see another. Fluorinated compounds are often used by the electronic industry where the goal is to reduce the cross-talk between circuits; fluorinated materials have a lower dielectric and hence electrical signals propagate less through them. Similarly, the refractive index of fluorinated compounds is always lower than that of unfluorinated compounds. Bromine (and Iodine) force the dielectric in the other direction, both are more polarizable. Neither observation should be a surprise since VDW interactions themselves are the result of virtual polarization of electron clouds: fluorine is hard to polarize and hence has smaller VDW interactions. Could this effect be captured by PB? Traditionally we think of the solvent as the volume that polarizes in PB, not the solute, but there is nothing to stop us including a solute dielectric to represent its polarizability. This will affect the solvation energy and it does so in the right way, *i.e.* tetrafluoromethane is less soluble in a polarizable model, bromoform is more soluble. However, it also occurred to me that this will affect the hydrophobic effect as well. If the root of hydrophobicity is that water would rather interact with water than hydrocarbon then surely this will depend on how polarizable that 'hydrocarbon' might be. This was the concept I explored before and presented at CUP 8 in February, 2007 and forms, in many ways, the theoretical basis for *SZMAP*.

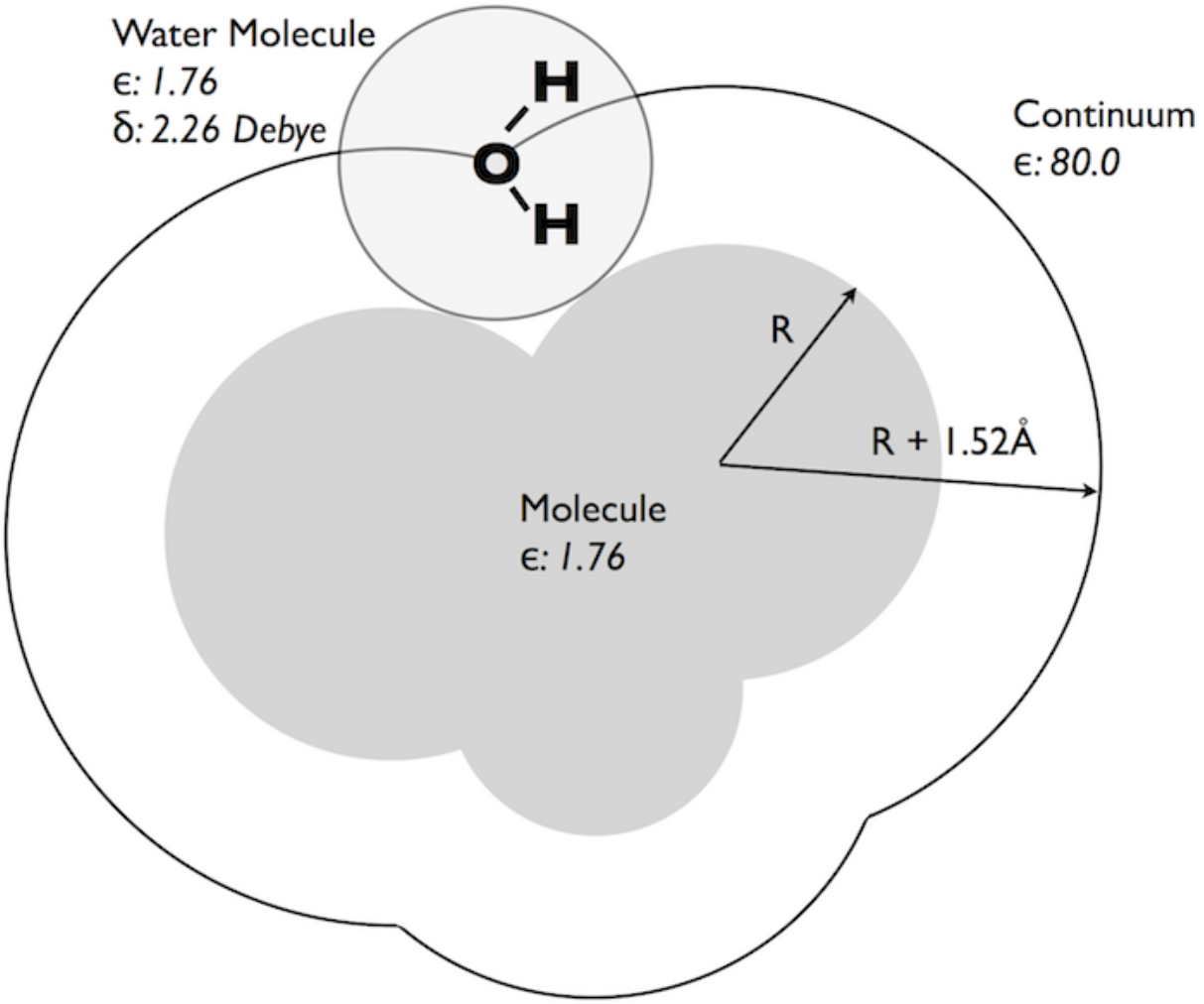


Fig. 2: **CUP8 Model**
Basic physical properties of the CUP8 model for dielectric hydrophobicity. **Note:** *SZMAP* currently uses a protein/probe dielectric of 1.0 and the probe water dipole is 1.86 Debye.

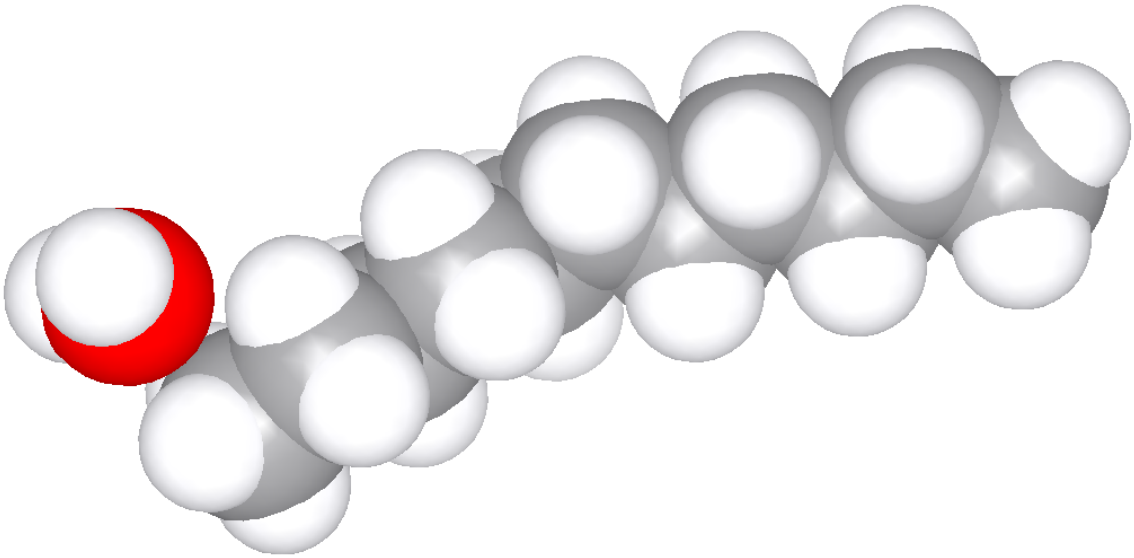


Fig. 3: **Water Probe**
Sampling of contact positions of water against a conformation of a large alkane.

The basic idea behind what I refer to as a *Dielectric Theory of Hydrophobicity* is illustrated in figures *CUP8 Model* and *Water Probe*. Essentially, one does a lot of PB calculations where the only charged molecule is a water molecule pressed up against a solute of interest. The solute 'desolvates' water, *i.e.* produces a small energetic penalty for water at the surface of a solute. Each such water has many orientations possible to it, some of which will be more desolvated than others, *e.g.* orientations that have protons closer to the solute. If you sample enough orientations then the Boltzmann average of those energies produces a 'partition function' for the water 'partitioning' from bulk to the surface of the solute. From the partition function you can derive any thermodynamic property you like, *e.g.* enthalpy or entropy, with one caveat. That caveat is that the energies that make up the partition function are themselves free energies—they are the energies of 'binding' a water molecule to the surface of a solute in a particular orientation. They are free energies because that is what PB calculates (essentially, the electrostatic energies in PB are derived from the reorganization of the dielectric, which is a work function, which therefore produces a free energy). As such, each term in the partition function is already a free energy and contains a component of enthalpy and entropy that we cannot separate out. However, we can produce a measure of entropy, *i.e.* the entropy due to the restriction of orientation of the water (because there are preferred directions of the water up against the solute). We just have to remember that this is not the total entropy of binding/hydrophobicity, because some of that is wrapped up in the PB (free) energy. Similarly, we can calculate an 'enthalpy', which is really the average free energy of binding because it is, in fact, the Boltzmann average of the free energy of binding. The free energies are real, the thermodynamic decomposition in *SZMAP* is incomplete.

What was surprising about the exercise described above is what happens if you use the basic physical properties of water in the model: Bondi radii, dielectrics derived from refractive indices, charges based on vacuum dipoles and typical estimates of water density, *i.e.* how many waters are likely to cover a solute (figure *CUP8 Model*). These basic values for water accurately reproduce the transfer of energy from vacuum to water, but surprisingly produce an energetic cost per square Ångström very close to what is seen experimentally, *e.g.* around $32\,cal\,Angstrom^{-2}mol^{-1}$. Furthermore, the flat surfaces of molecules like benzene gave higher than expected hydrophobicity, unless the higher polarizability of such was also included, in which case the value fell back into the same range as aliphatic molecules (figure *Oil-Water Transfer*). For an unparameterized model the result was surprisingly sensible. Furthermore, from vacuum-water surface tension you could predict the non-polar term for the vacuum-water transfer energy term to be right where one would expect, *i.e.* in the $6\,to\,10\,cal\,Angstrom^{-2}mol^{-1}$ range, except that this value would be dielectric dependent, *i.e.* lower for polarizable molecules and higher for the unpolarizable. This dependence empirically seems to remove

most of the observed variance from experiment seen in the halide containing molecules in the Rizzo set [Rizzo-2006] we have used for vacuum-water transfer energy prediction (figures *AM1BCC* and *AM1BCC+QM Corrected*).

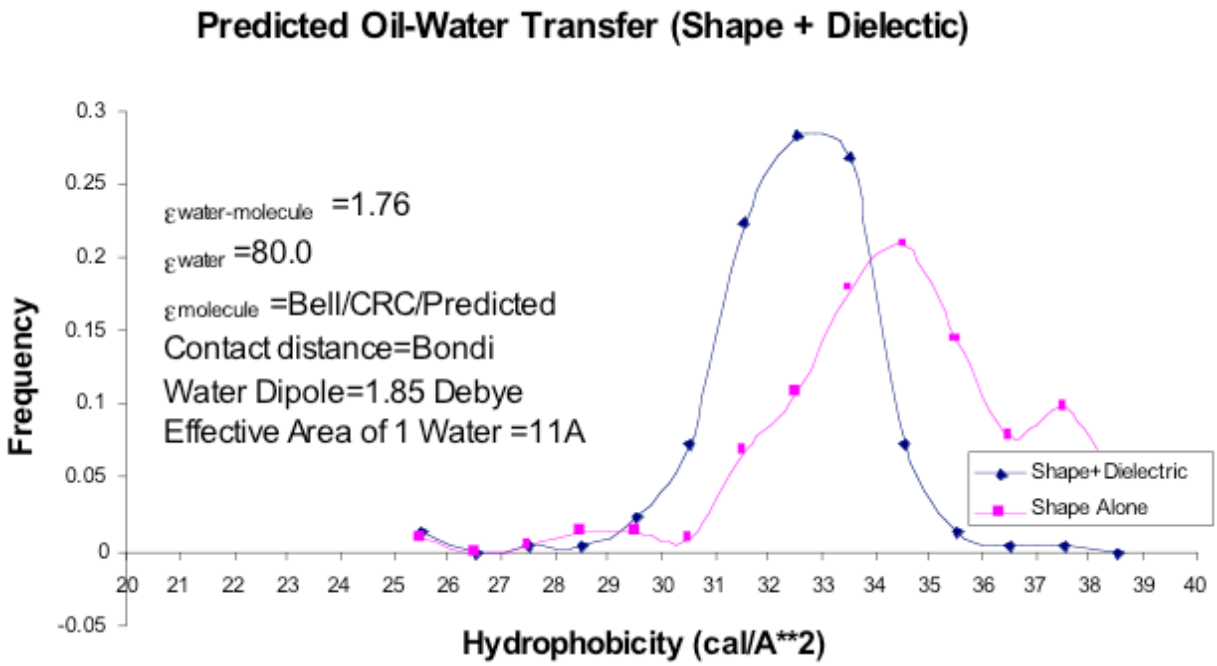


Fig. 4: **Oil-Water Transfer**
The results from the investigation of dielectric hydrophobicity. Using only shape, with no regard to the dielectric constant of the solute, gives the two peaked curve. Including the solute dielectric, which is normally greater than the electronic polarization of water (1.76 relative to vacuum), shifts the curve to smaller values and also brings flat, aromatic molecules into the same distribution as aliphatic molecules. **Note:** *SZMAP* currently uses a protein/probe dielectric of 1.0 and the probe water dipole is 1.86 Debye.

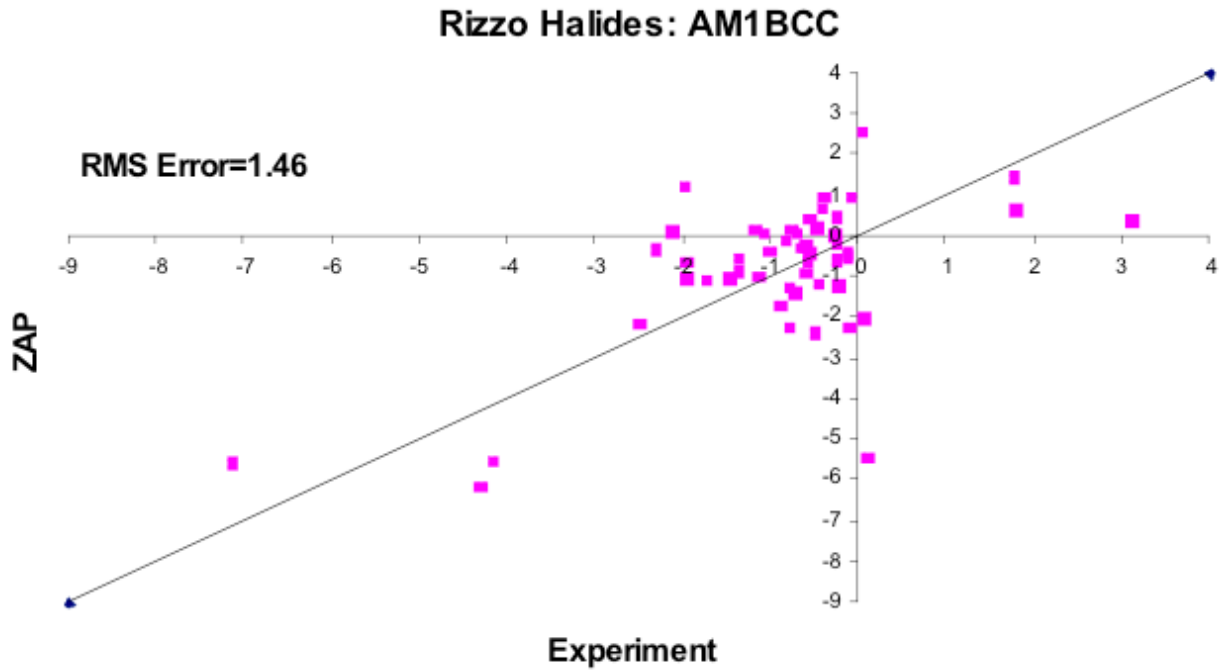


Fig. 5: **AM1BCC**
The subset of molecules from the Rizzo set containing F, Cl, Br or I, using AM1BCC charges with Bondi radii.

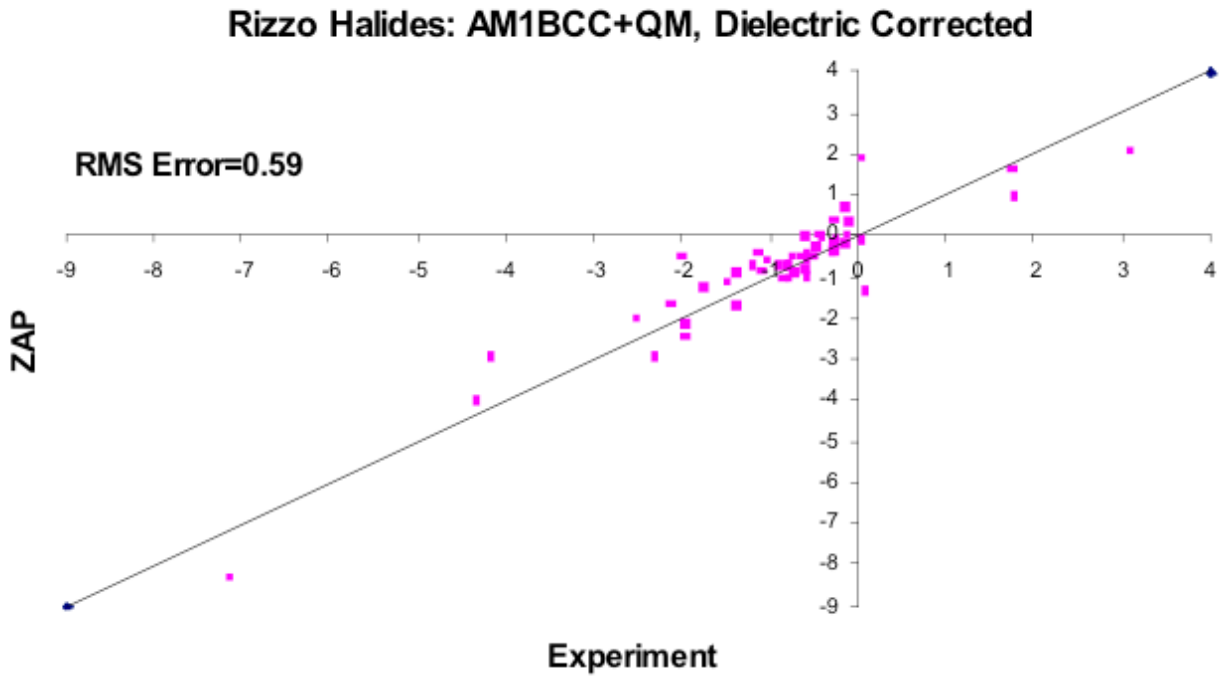


Fig. 6: **AM1BCC+QM Corrected**
The subset of molecules from the Rizzo set containing F, Cl, Br or I, using better quality charges (correcting the AM1BCC parameter for Iodine, for example) and the dielectric version of hydrophobicity outlined here.

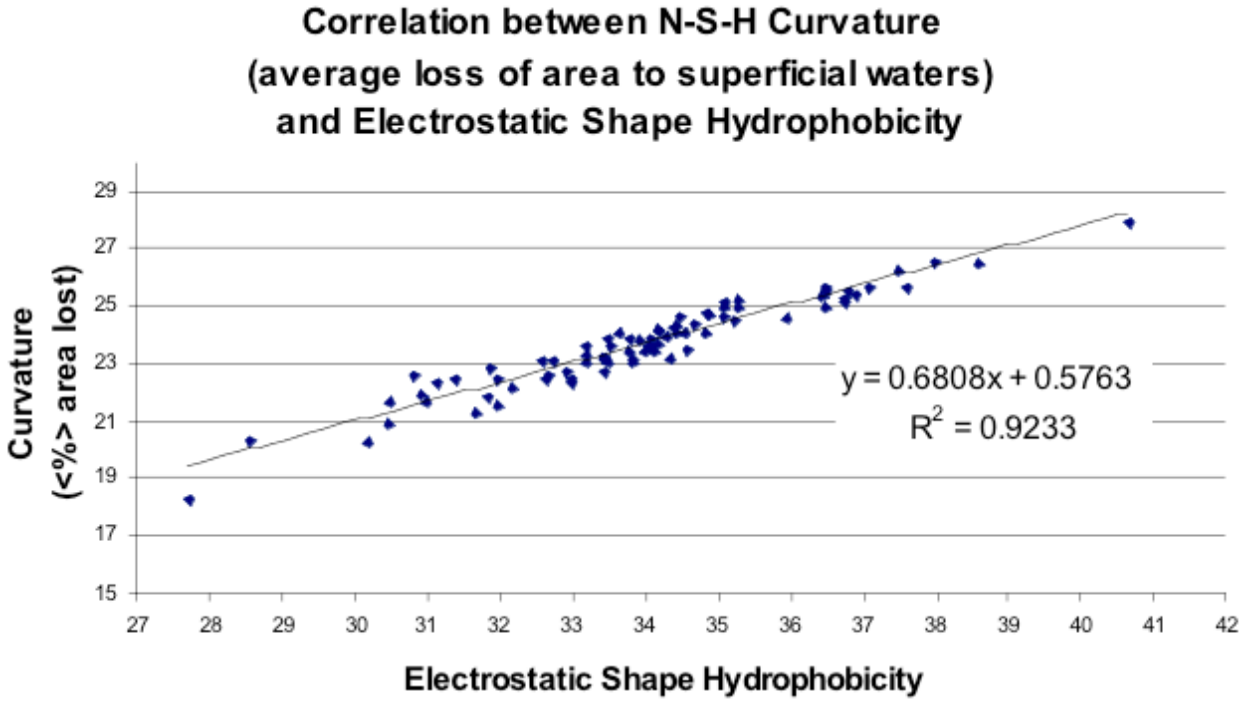


Fig. 7: **Hydrophobicity vs Curvature**
*Correlation between the net curvature of ~100 small molecules from the Rizzo set and the *SZMAP*-type energy function (molecules uncharged). Note that curvature here is represented as % of area lost, i.e. more area lost means more energy to place a water molecule in this position.**

Finally, how did this explicit enumeration of orientations and positions compare to the very simple Nicholls/Honig curvature model from 1991? Figure *Hydrophobicity vs Curvature* illustrates that there was a strong correspondence when both curvature and partition function were averaged over the entire surface of a subset of small molecules from the Rizzo set [Rizzo-2006]. More interesting was to look at the point by point comparison of the free energy approach and curvature. This is shown in figure *Curvature vs Hydrophobicity*. What this shows is that there is good correlation between the two models when the curvature is small, but that when the curvature is large, *i.e.* a water begins to be enclosed by the solute, this agreement breaks down, *i.e.* it takes more energy to bury a water than it does to merely make it sit on the surface of a convex solute. The reason this was good news is that the attempt to bridge the microscopic/macroscopic gap in 1991 had had to rely on other factors than just curvature because the effect was just not big enough. Here the results suggest why, *i.e.* that planar surfaces are more hydrophobic than the simple curvature model predicts. In fact, by constructing a planar surface from methyl groups the CUP8 procedure gets close to the macroscopic value ($62\, cal\ Angstrom^{-2} mol^{-1}$).

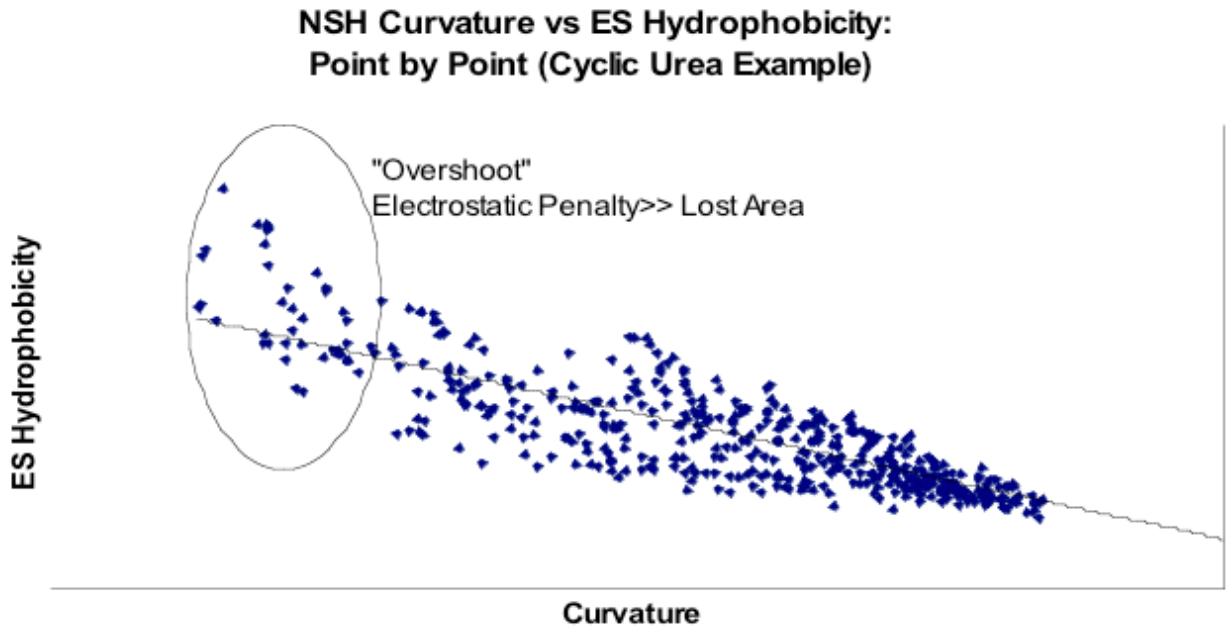


Fig. 8: **Curvature vs Hydrophobicity**
Correlation over the surface of a single molecule, a cyclic urea. Note that in this graph curvature is as traditionally defined, i.e. larger means more convex, i.e. less area occluded. Note, therefore that in regions of most negative curvature the non-polar term from ZAP increases above the trend line.

All of this leads to *SZMAP* because the next step in this work is to allow the solute to be charged, *i.e.* to introduce possibly compensating effects for a surface water due to the electrostatic field produced by the solute. For instance, the interactions between a water and a charged group will be favorable and will overcome the desolvation of the water, relative to the rest of the bulk solvent. And this is essentially what *SZMAP* attempts to estimate, *i.e.* it is the exact same procedure of estimating the binding energy of water over a set of orientations. In the initial version of *SZMAP* a discrete set of orientations are used, however there are ways in future versions for this to be made more comprehensive, with little loss in speed. The other change we introduce is to allow the sampling of water positions that do not make contact with the solute. The reason to do such was brought home to me during conversations with Eric Manas of GSK. He pointed out that the model should suggest water would begin to lose contact with other water before it actually touched the surface. In fact, based on close packing arguments the distance two surfaces would have to come before there was an effective surface-surface force due to dewetting would be $Diameter_{water} + \sqrt{3\,Diameter_{water}}$, *i.e.* about 6 Ångströms—close to that seen by simulations by the Berne group at Columbia [Huang-2003]. As such, *SZMAP* calculates a volume function, not a surface function such as the curvature function in GRASP. Of course, this may also mean that the concordance between experimental alkane-water hydrophobic energies and the CUP8 work was partly fortuitous, *i.e.* there would more formally be energetic contributions from positions further way from the surface.

The remaining difference in *SZMAP* is that we decided to take on the VDW interaction of water to the solute, namely by adding the VDW energy for each orientation of the water to the solute. We felt this was important for a couple of reasons. For one thing we know it will move the desolvation energy in the correct direction for polarizable atoms. We also can prevent anomalous interactions, *e.g.* close contacts between protons and charged groups that would be compensated for by VDW repulsion. Finally, in PBSA theory we have the choice of either using a buried area term (typically $25\,cal\,Angstrom^{-2}mol^{-1}$) or explicitly calculating the VDW interactions and using a much smaller area term (for instance $6\,cal\,Angstrom^{-2}mol^{-1}$ when using AM1BCC charges). As we are aiming at some verisimilitude with reality it seems a straightforward choice to explicitly include VDW. As a consequence, there should be a small residual area term that depends on the buried accessible area of the water.

A few words on how points are chosen. We use the shape scoring function in *FRED* to provide positions of water that are making some contact with the protein, removing points that VDW would clearly disallow [McGann-2003].

This provides a regular lattice of points on which the oxygen of water is positioned. The orientations are calculated for the protons about this center. One of the advantages of using PB technology for this process is that for each water orientation we get a potential field throughout the protein. This field can be used to calculate interactions with many different protein charge states. We have not implemented this at present, but it will be a feature in future versions of *SZMAP*.

At present the output from *SZMAP* consists of the thermodynamic quantities calculated at each grid point, *i.e.* the rotationally averaged free energy of a water in each position. The breakdown that we can do into entropic and enthalpic contributions is included, as are the classic curvature values. From our previous work we anticipate these volume functions will yield interesting and quantitative numbers, for instance the energy of displacing water, whether relative or absolute, and the prediction of 'condensed' water, *i.e.* what are typically, but incorrectly, referred to as crystallographic waters. Most such labeled waters are figments of crystallographer's desires to reduce their R factor, but some are real, *i.e.* some waters are undoubtedly bound substrates to the protein. It may also be possible to build chains of water from the preferred orientations and positions of single waters, although the thermodynamics and physics of this process are more dubious. We can also include more polarization physics, for instance by implementing the *EPIC* model of Jean-Francois Truchon [Truchon-2009]. At this point *SZMAP* is a tool, *an engine for discovery.*

Anthony Nicholls, Santa Fe, 2010.

8.2 Technical Details

8.2.1 Energy Calculations

Energy values are calculated at each grid point as follows. The energy for each probe water orientation *j* is the sum of the *ZAP* protein:water Coulombic interaction energy, the protein and water desolvation penalties and the van der Waals energy. For speed, the protein desolvation term is not computed for each orientation, but is instead computed once per grid point using a spherical united-atom representation of the probe water.

$$E_j = ZAP_{int}(P:W) + P^*_{desolv} + W_{desolv} + VDW \;\; \{j = 1 \cdots N_{orient}\}$$

The partition function *Q* is the usual sum:

$$Q = \sum_{j=1}^{N_{orient}} e^{-\frac{E_j}{kT}}$$

The probability of each orientation is then:

$$prob_j = \frac{e^{-\frac{E_j}{kT}}}{Q}$$

The probe water orientation entropy difference from continuum water is:

$$T\Delta S = (-kT \sum_{j=1}^{N_{orient}} prob_j \ln prob_j) - kT \ln N_{orient}$$

Likewise, the probe water free energy difference from continuum water is:

$$\Delta G = -(kT \ln Q - kT \ln N_{orient})$$

And of course, the enthalpy difference is the sum:

$$\Delta H = \Delta G + T\Delta S$$

The variance in estimated energies varies with the number of random probe orientations sampled. See figure *Variation in Energy Estimates*. At 50 random orientations per point, half of repeated free energy estimates are within about

$0.2\ kcal\ mol^{-1}$ of one another. This gives us a way to examine the balance between precision and calculation speed. Symmetrical probe orientations, the default in *SZMAP*, are completely reproducible and sample positions evenly. Sixty symmetrical orientations produce reliable energy estimates, but when more precision is required, 360 symmetrical orientations are recommended.

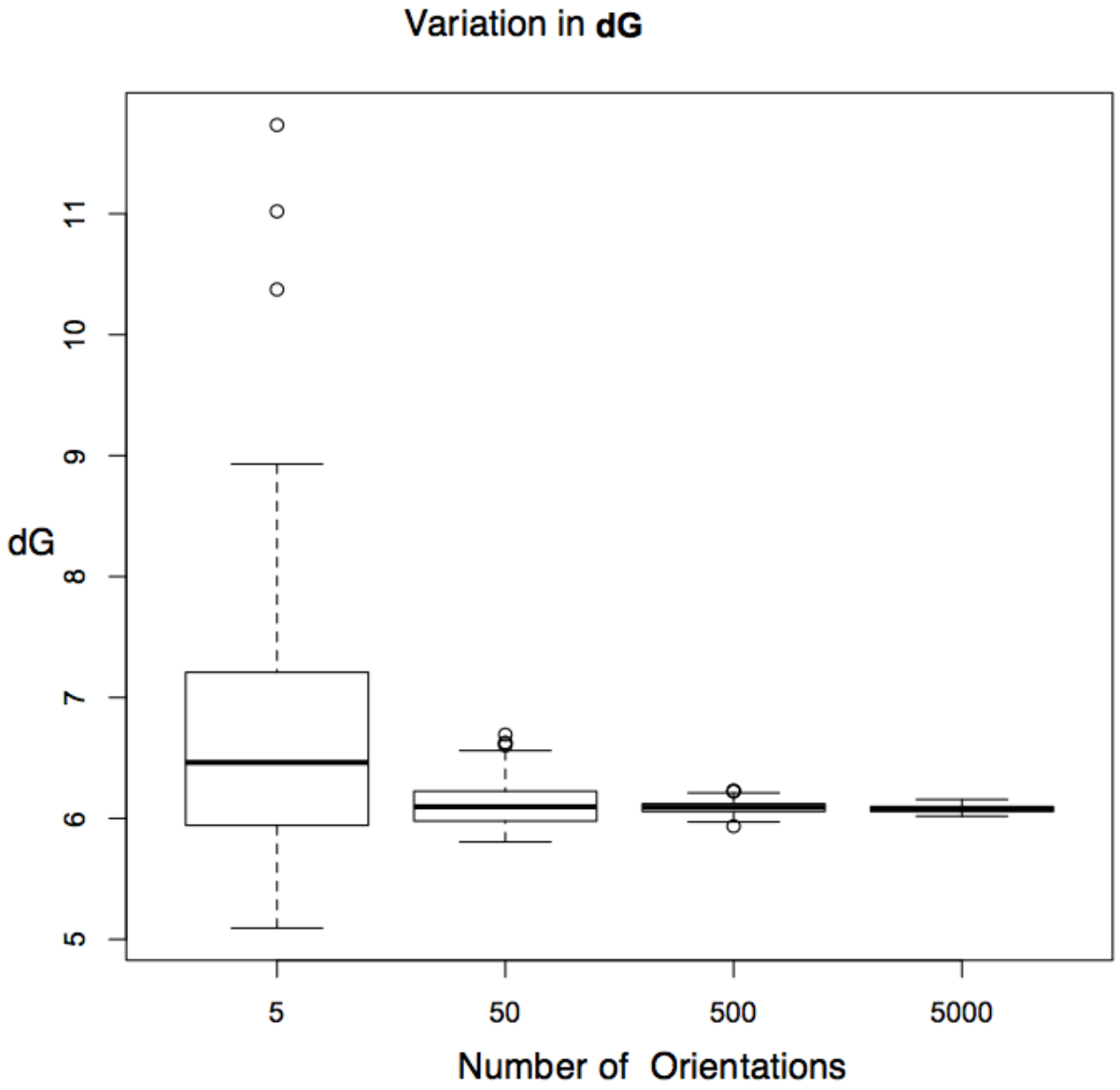


Fig. 9: **Variation in Energy Estimates**
Box plots for repeated calculations of free energy at a single point using random orientations. The mode is indicated with a heavy line, rectangles enclose 50% of data points and the whiskers enclose 90%.

The probe water *order* parameter represents the fractional loss of entropy due to electrostatics:

$$order = 1 - \frac{-\sum_{j=1}^{N_{orient}} prob_j^* \ln prob_j^*}{\ln N_{orient}}$$

where $prob_j^*$ is the probability for orientation *j* based on the electrostatic energy terms only, without the van der Waals term. Order calculated in this way is highly correlated with the neutral difference entropy.

8.2.2 Water Geometry, Radii, and Charges

PB calculations require you to know three things for each atom: the position, the charges and the radii. What should we use for water? The geometry for the probe water in *SZMAP* is the same as for *"TIP"* water: $r(OH) = 0.9572$ Å and $HOH\ angle = 104.52°$. Work for SAMPL meetings has shown that Bondi radii are a good starting point for PB calculations, although some atoms tend to need slight adjustments, for instance carbonyl oxygens always seem to want to be slightly bigger, nitrogens smaller. Water is an odd case as no other oxygen behaves chemically in the same way. So by the principle of maximum indifference we just use Bondi radii (H: 1.20 Å and O: 1.52 Å).

What charges should we use? Most force-field charges give water a dipole of between 2.4 and 3.0 Debye. This might seem odd because the actual, vacuum dipole of water is 1.86D. The force field community justify this because water is polarized in solution with estimates of its polarized dipole in the range of that used in force-fields. It is typical of this community—charges are over polarized to attempt to account for the lack of polarization in their models. AM1BCC, for instance, gives water a dipole of 2.24D, about 20% too large. This has consequences for the vacuum-water transfer energy—PB predicts an electrostatic component of transfer for AM1BCC charges and Bondi radii of $-9.95\,kcal\,mol^{-1}$. Add to that a typical "hydrophobic" term (yes, for water!) of about $+0.65\,kcal\,mol^{-1}$ (surface area of 107 $Angstrom^2$; $6\,cal\,Angstrom^{-2}mol^{-1}$) this gives us $-9.3\,kcal\,mol^{-1}$ prediction for vacuum-water. The only problem is that the experimental value is about $-6.3\,kcal\,mol^{-1}$. This is a huge % error for a simple model and would be very bad news for *SZMAP* since we want to estimate the energy of a water molecule burying itself into an active site. What happens if instead we use charges that reproduce the vacuum dipole? The electrostatic component becomes $-6.9\,kcal\,mol^{-1}$. Adding the ubiquitous surface term we get $-6.25\,kcal\,mol^{-1}$, *i.e.* just right. But what about polarization? Well, we are using protein charges that are also derived from vacuum potentials so in some ways this is not an inconsistent description. Overall, at this stage we feel it is more important to correctly calculate the desolvation of water. Therefore *SZMAP* uses point charges for hydrogen and oxygen of +0.327 and -0.654, respectively.

The next stage may be to use a simple polarization model presented at CUP7 that involved a real molecular dielectric (*i.e.* $\epsilon = 2$) and an increased radius for each atom. In this model water would have charges with a dipole of 2.48D in line with experimental estimates. Preliminary results from this model suggest that for many situations the binding energies of molecules is not dissimilar from unpolarized models. A further step will be to use the *EPIC* model developed by Jean-Francois Truchon at Merck-Frosst [Truchon-2009].

8.2.3 Uncharged Water, Difference Energies, Bubbles, and Stabilization

The values *SZMAP* calculates for ΔG, ΔH and $T\Delta S$ represent differences between the explicit probe water and the continuum water. In other words, a positive ΔG indicates that the continuum model over-estimates the cost of displacing water at that position. When trying to decide which modifications are most likely to increase binding affinity, we would prefer to compare the water probe to the ligand atom that displaces it, or at least a proxy for the ligand atom. In *SZMAP*, this proxy is the water probe without any of the energy terms that involve a charge on the water (leaving only $P_{desolv} + VDW$). Because these energy terms have already been determined, calculating the properties for this "uncharged" or "neutral" water requires no additional time, it's free. The difference in free energy between standard and uncharged water is negative where standard water is more favored and positive where the uncharged water, our hydrophobic group proxy, is more favored.

SZMAP can also calculate the difference between our probe and a vacuum bubble of the same size (defined as just the P_{desolv} term). Because protein desolvation is treated as constant over all probe orientations only the vacuum free energy and enthalpy differences are calculated, not the entropy differences.

Grids are *masked* such that regions where the sum of the van der Waals and interaction energies is greater than a cutoff (by default $0\,kcal\,mol^{-1}$) are set to zero. This is done so that grids are displayed only in regions where solvent atoms can physically fit.

As to how to interpret these difference grids, it should be beneficial for a hydrophobic ligand atom to overlap a region where the neutral free energy difference is positive because this involves displacing water that is less favorable than the neutral probe. Overlapping a region where the neutral free energy difference is negative, on the other hand, requires the overlapping group to be at least as polar as water and making a similar level of interactions.

Finally, *SZMAP* can calculate *stabilization* energies from the neutral difference values as a reaction energy

$$(holo\text{-}complex + bulk\text{-}solvent) - (apo\text{-}pocket + free\text{-}ligand)$$

where *bulk-solvent* is defined as $0\,kcal\,mol^{-1}$.

Negative free energy values indicate water is stabilized at that location in the complex, over and above the same location in the ligand and the *apo* pocket. Positive values are found where the water is destabilized in the complex. The stabilization or destabilization says nothing about the actual level of stability, so these energies need to be compared to others such as the *apo* or complex neutral difference free energy.

CHAPTER

NINE

RELEASE HISTORY

9.1 SZMAP 1.7.4

Minor internal improvements have been made.

9.1.1 Related Toolkit Information

9.2 Szmap TK 1.7.4

Minor internal improvements have been made.

9.3 SZMAP 1.7.3

Minor internal improvements have been made.

9.3.1 Related Toolkit Information

Szmap TK 1.7.3

Minor internal improvements have been made.

9.4 SZMAP 1.7.2

Minor internal improvements have been made.

9.4.1 Related Toolkit Information

Szmap TK 1.7.2

Minor internal improvements have been made.

9.5 SZMAP 1.7.1

Minor internal improvements have been made.

9.6 Szmap TK 1.7.1

Minor internal improvements have been made.

9.7 SZMAP 1.7.0

9.7.1 Minor bug fixes

- The application now properly validates output file formats.

9.8 Szmap TK 1.7.0

9.8.1 Documentation changes

- Examples have been updated to use design units as inputs.

9.9 SZMAP 1.6.7

9.9.1 Szmap TK 1.6.7

Minor internal improvements have been made.

9.10 SZMAP 1.6.6

Minor internal improvements have been made.

9.10.1 Szmap TK 1.6.6

Minor internal improvements have been made.

9.11 SZMAP 1.6.5

Fall 2022

Minor internal improvements have been made.

9.12 Szmap TK 1.6.5

Minor internal improvements have been made.

9.13 SZMAP 1.6.4

Spring 2022

- Minor internal improvements have been made.

9.14 Szmap TK 1.6.4

- Minor internal improvements have been made.

9.15 SZMAP 1.6.3

Fall 2021

- Minor internal improvements have been made.

9.16 Szmap TK 1.6.3

Fall 2021

- Minor internal improvements have been made.

9.17 SZMAP 1.6.2

July 2021

- `Spruce4Szmap` has been removed. We recommend using SPRUCE instead.

9.18 Szmap TK 1.6.2

July 2021

Minor internal improvements have been made.

9.19 SZMAP 1.6.1.0

Fall 2020

- Minor internal improvements have been made.

9.20 Szmap TK 1.6.1

Fall 2020

- Minor internal improvements have been made.

9.21 SZMAP 1.6.0

Spring 2020

- This version of **SZMAP** has been built using **OEToolkits 2020.0**.

9.21.1 Major bug fixes

- Using an OEDesignUnit as an input for stabilizing calculations now properly performs all 3 calculation stages.

9.21.2 Minor bug fixes

- **SzmapReport** warning messages have been cleaned up.

9.22 SZMAP 1.5.0

Nov 2019

- This version of **SZMAP** has been built using **OEToolkits 2019.Oct**. The previous version was built using **OEToolkits 2019.Apr**.

9.22.1 New features

- A New utility application, **Spruce4Szmap**, has been added to properly prepare a structure for use in **SZMAP** or **GamePlan**. **Spruce4Szmap** replaces the three previous utility applications, `Pch`, `MKHetDict` and `FixDupAtomNames`. With **Spruce4Szmap**, using external program `reduce` as part of structure preparation workflow is no longer necessary.
- The `-protein` parameter for both **SZMAP** or **GamePlan** now accepts an `OEDU` files, representing design units generated from **SPRUCE**.

9.22.2 Minor bug fixes

- **SZMAP** now generates an output box file if `-lig_box` or `-apo_box` is set. In addition, it performs the same calculations regardless of whether a box (Std, Apo or Lig) is output or not.
- **SZMAP** now gives a fatal error if no ligand is specified and `-stbl` is set to `true`.
- **SZMAP** now exits cleanly when an empty ligand or protein file is used as input in MPI mode.
- **SZMAP** now attaches *szmap-meta-data* to protein in an *at_coords* calculation.
- **SZMAP** now only performs *apo grid calc* when `-apo_grids` is set to `true`.
- **SzmapReport** no longer generates repeated images of stable waters.

9.23 SZMAP 1.4.1

May 2019

- This version of **SZMAP** has been built using **OEToolkits 2019.Apr**. The previous version was built using **OEToolkits 2018.Oct**.

9.23.1 Minor bug fixes

- Output ligand box are now properly written in a `.mol` or `.sdf` file.

9.24 SZMAP 1.4.0

November 2018

- This version of **SZMAP** has been built using **OEToolkits 2018.Oct**. The previous version was built using **OEToolkits 2013.Oct**.

9.24.1 Major bug fixes

- An issue related to running **GamePlan** in `MPI` mode has been fixed.

9.24.2 Minor bug fixes

- Finding the location of the **SZMAP** application in **GamePlan** is no longer platform-dependent.

9.25 SZMAP 1.3.0

August 2015

Update to *SZMAP* applications.

9.25.1 New Features

- A new *mkhetdict* option `-no_pka_adjustment` can be used to prevent deleting or renaming ligand hydrogens which cause *reduce* to generate too many hydrogens.

9.25.2 Bug Fixes

- Grids written out in `.ccp4` format now contain scaling information to make them comparable to other grid formats.
- *mkhetdict* verbose output now shows the correct input file name.

9.25.3 Other changes

- Now checking for legal ranges on *SZMAP* options: `-bounding_box -mask_cutoff -vdw_scale`

9.26 SZMAP 1.2.1

February 2015

Update to *SZMAP* applications.

9.26.1 Improvements

- The *Water Orientation VIDA Extension* now saves orientation probability data and ensemble energy, vdw and order data on probe molecules as SDData. When probes generated by this extension are written to an `.sdf` file, these values will be written as well.

9.26.2 Bug Fixes

- The *Water Orientation VIDA Extension* (version `1.1.2`) now displays the correct water orientations for results from *SZMAP* version 1.2.0.
- *GamePlan* no longer crashes when all stabilization test sites clash.
- *The pch applicatoin* no longer treats CYS residues bonded through the sidechain to a non-CYS as anionic.
- *The pch applicatoin* no longer duplicates nonstandard groups containing a metal (such as cofactors) and groups they are bonded to.
- The hydrogen charge on the standard water probe is now correctly listed as +0.327 not +0.237 in *Theory*.

9.27 SZMAP 1.2.0

July 2013

Update to *SZMAP* applications.

9.27.1 Improvements

- *Multiprocessor Support* : Calculations can be performed much faster with *SZMAP* and *GamePlan* by using multiple processor on a single machine and on different machines with the same operating system installed. Because of this and other improvements to the software, numerical results will differ slightly from those produced by previous versions and the set of points that are determined to be clashing may vary slightly. *SZMAP* is highly parallelizable—big calculations scale very well when run on large numbers of processors.
- *SzmapGrid* will now split out all *SZMAP* grids into separate files in one step when the options `-output_all_format` and `-prefix` are used.
- *SzmapReport* now supports a `-resolution` option to control the quality of the property maps.
- *GamePlan* now indicates the stabilization magnitude in the log.
- To streamline the *SZMAP* program, the following obscure command line options have been eliminated: `-only_protein`, `skip_modified`, `-protein_charge`, `-protein_hydrogen`, `-ligand_charge`, `-ligand_hydrogen`, `-charged_mol`, `-no_probe_data`, `-require_explicit`, `-add_neutral`, `-add_vacuum`, `-details`. There are more direct ways to perform each of the functions that they controlled. The simple help for options in each of the *SZMAP* applications and utilities has been streamlined.
- The *WaterColor VIDA Extension* has been updated so that it no longer changes the scale of *GamePlan* results in VIDA.
- The *Quick Start* chapter is now called the *SZMAP Workflow* and has been reorganized to improve clarity.

9.27.2 Bug Fixes

- When running from a directory with a space character somewhere in the path name, *GamePlan* is now able to find the corresponding version of *SZMAP*.
- The naming scheme for temporary files created by *GamePlan* has been changed to avoid a bug that interfered with reading *SZMAP* output under certain circumstances.
- The *Coulombic interaction+van der Waals* (intvdw) value produced by *SZMAP* is now the minimum of the values for each of the different orientations, the same value used to determine clashes.
- Single grid *SZMAP* calculations (for example using `-apo_grids`) no longer output all grid types by default.
- To improve consistency, clashes in stabilization results are now marked by the text "CLASH" in the atom property *szmap_stbl_clash* instead of *szmap_clash*.
- The options section in the *SZMAP* chapter has been modified to document additional file formats supported for some operations.
- The minimum legal setting for the *SZMAP* options `-inner_dielectric` and `-outer_dielectric` has been increased to 1.0. Lower values can lead to problems with ZAP calculations.
- The maximum legal setting for the *SZMAP* option `-zap_spacing` has been lowered to 1.0. Higher values can lead to problems with ZAP calculations.

9.27.3 Other changes

- This will be the last release to support SuSe 10.
- The *SZMAP* options `-point_grid`, `-lig_point_grid`, and `apo_point_grid` can no longer be used to setup the calculation without doing any actual calculations. This will be fixed in a future release.

9.28 SZMAP 1.1.1

January 2013

Bug fix to *SZMAP* applications, utilities and *VIDA* extensions.

9.28.1 Improvements

- The *Water Orientation* VIDA extension now identifies ligand or protein displacement entries by appending *(lig_disp)* or *(prot_disp)* to the name in the selection pop-up.

9.28.2 Bug Fixes

- A rare bug in how *szmap* decides which grid points will be analyzed has been fixed. This bug only affected *apo* pocket calculations where part of the ligand used to define the pocket extends away from the protein more than ~5 Å in the negative *x, y,* or *z* direction, causing some regions that should have been analyzed to be skipped, and other regions that should have been skipped to be analyzed.
- The metadata added to *szmap* output now includes the correct version number.
- The position of points tested for stabilization by *gameplan* no longer differ slightly between architectures.
- Running *gameplan* from a directory containing the word "gameplan" works properly now.
- The *grid_comp* utility now produces the appropriate subset of probe orientations when the operations *lig_disp* or *prot_disp* are used.
- The *Watercolor* VIDA extension no longer changes the modification hypothesis molecule to wireframe when the user has highlighted a hypothesis in the list window before running the extension.

9.29 SZMAP 1.1.0

August 2012

Major update to *SZMAP* applications, utilities and *VIDA* extensions.

9.29.1 Improvements

- The *Water Orientation* VIDA extension has been completely rewritten to be more capable and easier to use. *szmap* now generates orientation information tagged with the neutral difference free energy rather than the neutral difference enthalpy. The *Water Orientation* VIDA extension will recognize this difference between newer and older *szmap* results.
- A new command-line program, *gameplan*, identifies interesting coordinates near a ligand or in a protein binding site, runs *szmap* and analyzes the results, producing hypotheses of various ways the ligand might be improved based on the solvent environment.
- *szmap* can now use *apo* grids and coordinate output from previous runs with the `-use_apo_from <results.oeb.gz>` command line option. Combined with the new option `-split_lig`, a series of ligands all bound to the same protein can be easily analyzed with *szmap*.
- The default grid contour levels used in the *Watercolor* VIDA extension for most difference grids have been changed from -0.5/+0.5 kcal/mol to -1.5/+0.75 kcal/mol to emphasize regions with the largest energy differences. VDW grids are now contoured at -2.0 kcal/mol to emphasize good contacts.Colors are now generated taking into account whether the background is dark or light.
- By default, *szmap* grid calculations will now output van der Waals values and the degree to which the probe is ordered, but not the probe burial fraction. Use `-results_set max` to get the probe burial. At_coords calculations now produce max results by default in order to enable analysis and categorization of points.

- It is now a fatal error in *szmap* and *gameplan* for hydrogens to be missing from the ligand or from more than 10 percent protein heavy atoms. The option `-warn_if_missing_hydrogens` will cause a warning to be generated, but the calculation will proceed despite the missing atoms. Proteins may have missing atoms far from the active site due to mobile side-chains or loops without affecting the results significantly. Missing hydrogens on the ligand are more problematic. But the option to override the fatal error is provided so that special cases, where there is ambiguity about whether a hydrogen is missing or not, can be handled.
- By default, *szmap* now performs ligand calculations just in the regions available in the complex, speeding up -stabilization runs. A new option `-restrict_calc <level>` controls this behavior.
- The set of symmetrical probe orientations available to *szmap* users has been expanded to include sets with 216 and 648 orientations. Setting the number of orientations higher than a symmetrical set size but less than the next higher set, will take the symmetrical orientations and pad out the remainder with random orientations.
- *szmap* now clearly identifies different output categories in the results file: complex, ligand, apo, stabilization. It also now puts the molecule plus data package previously known as 'probe-orientation-data' under each of these sections, renaming it 'probe'.
- The *szmap* log information printed when -verbose and -details are specified has been modified to make it easier to parse and to include more information.
- *grid_comp* now supports five new operations: *lig_disp* and *prot_disp* append grids and orientation data for regions displaced in the complex by the ligand and the protein, respectively. *largest* returns a grid containing only the largest connected region of the source grid based on contours at a user specified level. *not_mask* returns data in regions that are *not* in the mask. *offset* adds a constant to each grid point. In addition, *grid_comp* now does a better job of describing the operations it performs.
- *pch* now produces output even if `-ligand_res <RES>` was specified but the given residue name was not located in the input molecule. It also now supports the options `-ligand_resnum <num>`, `-ligand_inscode <char>`, `-ligand_chain <char>`, and `-ligand_model <num>` allowing you to more specifically identify which residue is to be written to the ligand file.
- *pch* now supports the `-fix_elements` option which instructs the program to attempt to substitute elements that will work in *szmap* (such as Zn) for those where MMFF vdw parameters are not defined (such as Hg).
- *pch* now supports the `-nonsymmetrized_charges` option to generate AM1BCC partial charges where topologically equivalent atoms—think methyl protons—are not required to have the same charge. The default charge-symmetrized AM1BCC charges are recommended for any workflows down the road where the ligand conformation is subject to change.
- *pch* now writes out waters in the input if the `-output_waters <filename>` option is specified.
- *szmap_report* now supports the option `-tag_set <set>` to provide more control over the output when no tags are specified. The tag set `v1` provides backward compatibility with szmap 1.0 output.
- *szmap_report* now supports the option `-keep_hydrogens` to force the rendering of all explicit hydrogens.
- Version, release, platform, etc. information for *szmap* and related programs is now written to the display only when the -verbose flag is used or when the command is run without arguments. The status of your *SZMAP* license is now included along with the other information.
- On *Windows*, the installer now adds the OpenEye bin directory to the environment path to better support the use of alternative command shells.

9.29.2 Bug Fixes

- *SZMAP* vida_extensions and tutorial_files are now installed inside a version-specific sub-directory: openeye/examples/szmap/{szmap-version}/.
- A bug that caused *pch* to treat reduced cysteine residues (CYS) to be charged as if they were oxidized (CYX) has been fixed. De-protonated cysteines (CYM) were not affected.

- A bug that prevented *pch* from adding Amber charges to the C-term capping residue NME.
- The *Watercolor* VIDA extension has been modified so that it can be run multiple times successfully on a given set of *szmap* output.
- The length of the OH bond in *szmap* probe waters has been reduced by 0.001A so that the water probe geometry is identical to that of TIP models.
- *szmap* can now save molecules with the -charged_mol flag to *.oeb* and *.oeb.gz* files.
- A bug that prevented CLASH tags from showing up in *szmap* stabilization results for -at_coords calculations has been fixed.
- The minimum number of orientations in *szmap* is now 2. The previous version allowed 1 orientation but the calculations would fail. Note that runs with less than the default of 60 orientations are likely to give poor energies.
- Fixed a minor bug in the calculation of probe fractional buried surface area in *szmap*.
- *szmap_grid* generates a more complete report describing *SZMAP* data in the input.
- *szmap_report* provides clearer error messages when it does not find *SZMAP* data in the input and the -verbose flag now works properly. It also renders text at a larger, easier to read size.
- The manual has been updated to fix a large number of typographic errors and oversights.

9.30 SZMAP 1.0.0

June 2011

First product release of *SZMAP* application, utilities and *VIDA* extensions.

9.30.1 Features

- Calculates solvent energies on a grid and at user specified coordinates.
- Includes VIDA extensions to facilitate visualization of *szmap* results.
- Includes a Grapheme-based report writer that projects *SZMAP* values onto 2D images.
- Includes a tool to integrate grids to quantify *SZMAP* results.
- Includes a tool to add partial charges and radii to protein and ligand atoms preparation for running *szmap*.
- Includes tools to facilitate using *reduce* to add and optimize protons required for running *szmap*.
- Includes a tool to convert output grids to different formats and perform various mathematical operations on grids.

SZMAP Appendix

CHAPTER

TEN

APPENDIX 1: SZMAP GRIDS

Here is a list of all the grids that can be produced by *SZMAP*. By default, only a subset of these are written to the results file. The default output grids are in **bold**. *Bump* means the point failed a quick bump-check and *clash* means the intvdw > cutoff.

10.1 Protein + Ligand Complex

Grid Name (prot + lig complex)	Description
neut_diff_free_energy_grid	water - neutral probe free energy difference
neut_diff_enthalpy_grid	water - neutral probe enthalpy difference
neut_diff_entropy_grid	water - neutral probe entropy difference
vdw_grid	van der Waals energy
order_grid	fractional entropy loss from electrostatics
mask_grid	clash: 0, bulk solvent: 0.98, no clash: 1.01
point_grid	bump: 0, bulk solvent: 0.98, calc: 1.01
vac_diff_free_energy_grid	water - vacuum probe free energy difference
vac_diff_enthalpy_grid	water - vacuum probe enthalpy difference
free_energy_grid	free energy of probe water vs continuum
enthalpy_grid	enthalpy of probe water vs continuum
entropy_grid	entropy of probe water vs continuum
neutral_free_energy_grid	free energy of neutral probe vs continuum
neutral_enthalpy_grid	enthalpy of neutral probe vs continuum
neutral_entropy_grid	entropy of neutral probe vs continuum
interaction_grid	Poisson Boltzmann electrostatic interaction
psolv_grid	protein desolvation penalty
wsolv_grid	water probe desolvation penalty
intvdw_grid	interaction + van der Waals *(for masking)*
probe_burial_grid	fractional amount water probe is buried

10.2 Ligand Only

Grid Name (ligand only)	Description
neut_diff_lig_free_energy_grid	water - neutral probe free energy difference
neut_diff_lig_enthalpy_grid	water - neutral probe enthalpy difference
neut_diff_lig_entropy_grid	water - neutral probe entropy difference
lig_vdw_grid	van der Waals energy
lig_order_grid	fractional entropy loss from electrostatics
lig_mask_grid	clash: 0, bulk solvent: 0.98, no clash: 1.01
lig_point_grid	bump: 0, bulk solvent: 0.98, calc: 1.01
vac_diff_lig_free_energy_grid	water - vacuum probe free energy difference
vac_diff_lig_enthalpy_grid	water - vacuum probe enthalpy difference
lig_free_energy_grid	free energy of probe water vs continuum
lig_enthalpy_grid	enthalpy of probe water vs continuum
lig_entropy_grid	entropy of probe water vs continuum
neutral_lig_free_energy_grid	free energy of neutral probe vs continuum
neutral_lig_enthalpy_grid	enthalpy of neutral probe vs continuum
neutral_lig_entropy_grid	entropy of neutral probe vs continuum
lig_interaction_grid	Poisson Boltzmann electrostatic interaction
lig_psolv_grid	protein desolvation penalty
lig_wsolv_grid	probe desolvation penalty
lig_intvdw_grid	interaction + van der Waals *(for masking)*
lig_probe_burial_grid	fractional amount water probe is buried

10.3 Protein Only

Grid Name (protein only)	Description
neut_diff_apo_free_energy_grid	water - neutral probe free energy difference
neut_diff_apo_enthalpy_grid	water - neutral probe enthalpy difference
neut_diff_apo_entropy_grid	water - neutral probe entropy difference
apo_vdw_grid	van der Waals energy
apo_order_grid	fractional entropy loss from electrostatics
apo_mask_grid	clash: 0, bulk solvent: 0.98, no clash: 1.01
apo_point_grid	bump: 0, bulk solvent: 0.98, calc: 1.01
vac_diff_apo_free_energy_grid	water - vacuum probe free energy difference
vac_diff_apo_enthalpy_grid	water - vacuum probe enthalpy difference
apo_free_energy_grid	free energy of probe water vs continuum
apo_enthalpy_grid	enthalpy of probe water vs continuum
apo_entropy_grid	entropy of probe water vs continuum
neutral_apo_free_energy_grid	free energy of neutral probe vs continuum
neutral_apo_enthalpy_grid	enthalpy of neutral probe vs continuum
neutral_apo_entropy_grid	entropy of neutral probe vs continuum
apo_interaction_grid	Poisson Boltzmann electrostatic interaction
apo_psolv_grid	protein desolvation penalty
apo_wsolv_grid	probe desolvation penalty
apo_vdw_grid	van der Waals energy
apo_intvdw_grid	interaction + van der Waals *(for masking)*
apo_probe_burial_grid	fractional amount water probe is buried

10.4 (Complex - Protein - Ligand) Stabilization

Grid Name (cplx - prot - lig)	Description
neut_diff_stbl_free_energy_grid	neutral free energy difference stabilization
neut_diff_stbl_enthalpy_grid	neutral enthalpy difference stabilization
neut_diff_stbl_entropy_grid	neutral entropy difference stabilization
stbl_vdw_grid	van der Waals stabilization
stbl_order_grid	fractional entropy loss (ES) stabilization
stbl_mask_grid	clash: 0, bulk solvent: 0.98, no clash: 1.01
vac_diff_stbl_free_energy_grid	vacuum free energy difference stabilization
vac_diff_stbl_enthalpy_grid	vacuum enthalpy difference stabilization
stbl_free_energy_grid	probe water free energy stabilization
stbl_enthalpy_grid	probe water enthalpy stabilization
stbl_entropy_grid	probe water entropy stabilization
stbl_neutral_free_energy_grid	neutral probe free energy stabilization
stbl_neutral_enthalpy_grid	neutral probe enthalpy stabilization
stbl_neutral_entropy_grid	neutral probe entropy stabilization
stbl_interaction_grid	Electrostatic interaction stabilization
stbl_psolv_grid	protein desolvation penalty stabilization
stbl_wsolv_grid	water desolvation penalty stabilization
stbl_vdw_grid	van der Waals stabilization
stbl_intvdw_grid	interaction + van der Waals stabilization
stbl_probe_burial_grid	fractional probe burial stabilization

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APPENDIX 2: SZMAP ATOM PROPERTIES

SZMAP calculations at a list of coordinates attach one or more of the following properties to the atoms that specify the coordinates. Key properties are in **bold**.

11.1 Complex, Apo or Ligand

Property Name (cplx, lig, or apo)	Description
szmap_neut_diff_free_energy	water - neutral probe free energy difference
szmap_neut_diff_enthalpy	water - neutral probe enthalpy difference
szmap_neut_diff_entropy	water - neutral probe entropy difference
szmap_vdw	van der Waals energy
szmap_order	fractional entropy loss from electrostatics
szmap_clash	if point clashes, property = "CLASH"
szmap_mask	clashing: 0, nonclashing: 1
szmap_vac_diff_free_energy	water - vacuum probe free energy difference
szmap_vac_diff_enthalpy	water - vacuum probe enthalpy difference
szmap_vac_diff_entropy	water - vacuum probe entropy difference
szmap_free_energy	free energy of probe water vs continuum
szmap_enthalpy	enthalpy of probe water vs continuum
szmap_entropy	entropy of probe water vs continuum
szmap_neutral_free_energy	free energy of neutral probe vs continuum
szmap_neutral_enthalpy	enthalpy of neutral probe vs continuum
szmap_neutral_entropy	entropy of neutral probe vs continuum
szmap_interaction	Poisson Boltzmann electrostatic interaction
szmap_psolv	protein desolvation penalty
szmap_wsolv	water probe desolvation penalty
szmap_intvdw	interaction + van der Waals *(for masking)*
szmap_probe_burial	fractional amount water probe is buried

11.2 (Complex - Protein - Ligand) Stabilization

Property Name (cplx - prot - lig)	Description
szmap_neut_diff_stbl_free_energy	neutral free energy difference stabilization
szmap_neut_diff_stbl_enthalpy	neutral enthalpy difference stabilization
szmap_neut_diff_stbl_entropy	neutral entropy difference stabilization
szmap_stbl_vdw	van der Waals energy stabilization
szmap_stbl_order	fractional entropy loss (ES) stabilization
szmap_stbl_clash	if point clashes, property = “CLASH”
szmap_stbl_mask	clashing: 0, nonclashing: 1
szmap_vac_diff_stbl_free_energy	vacuum free energy difference stabilization
szmap_vac_diff_stbl_enthalpy	vacuum enthalpy difference stabilization
szmap_vac_diff_stbl_entropy	vacuum entropy difference stabilization
szmap_stbl_free_energy	probe water free energy stabilization
szmap_stbl_enthalpy	probe water enthalpy stabilization
szmap_stbl_entropy	probe water entropy stabilization
szmap_stbl_neutral_free_energy	neutral probe free energy stabilization
szmap_stbl_neutral_enthalpy	neutral probe enthalpy stabilization
szmap_stbl_neutral_entropy	neutral probe enthalpy stabilization
szmap_stbl_interaction	Poisson Boltzmann electrostatic interaction
szmap_stbl_psolv	protein desolvation stabilization
szmap_stbl_wsolv	water probe desolvation stabilization
szmap_stbl_intvdw	interaction + van der Waals stabilization
szmap_stbl_probe_burial	fractional probe burial stabilization

CHAPTER

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CITATION

Note

To cite SZMAP please use the following:

SZMAP 1.7.4.0. OpenEye, Cadence Molecular Sciences, Santa Fe, NM. http://www.eyesopen.com. (2013)

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Orion 2025.1. OpenEye, Cadence Molecular Sciences, Santa Fe, NM. http://www.eyesopen.com.
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15.2 Orion Floes

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```
OpenEye Large-Scale Floes 4.2.3. OpenEye, Cadence Molecular Sciences, Santa Fe, NM.␣
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```

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- Bioisostere TK
- OEChem TK
- OEDepict TK
- OEDocking TK
- OEFF TK
- Eon TK
- FastROCS TK
- Grapheme TK
- GraphSim TK
- Lexichem TK
- OEMedChem TK
- MolProp TK
- Omega TK
- Quacpac TK
- Shape TK
- Spicoli TK
- Spruce TK
- Szmap TK
- Szybki TK
- Zap TK
- AFITT Application
- BROOD Application
- OEDocking Application
- EON Application
- OMEGA Application
- PICTO Application
- pKa-Prospector Application
- QUACPAC Application

- ROCS Application
- SiteHopper Application
- SPRUCE Application
- SZMAP Application
- SZYBKI Application
- VIDA Application

You can use the version number of the individual Application or Toolkit. For example:

```
SZYBKI Application 2.8.0.1. OpenEye, Cadence Molecular Sciences, Santa Fe, NM. http://
↪www.eyesopen.com.

Szybki TK 2.8.0.1. OpenEye, Cadence Molecular Sciences, Santa Fe, NM. http://www.
↪eyesopen.com.
```

The first documentation pages give the product names and version numbers, as in https://docs.eyesopen.com/applications/szybki/index.html and https://docs.eyesopen.com/toolkits/python/szybkitk/index.html.

15.4 Publications for Bibliographies

Please also cite these publications if the corresponding product was used in your research.

15.4.1 Orion

Sørensen, J., Bannan, C.C., Calabrò, G., Jain, V., Ovanesyan, G., Smith, A., Zhang, S., Bayly, C.I., Darden, T.A., Geballe, M.T., LeBard, D.N., McGann, M., Moon, J.B., Muddana, H.S., Shewmaker, A., LaFon, J., Tolbert, R.W., Skillman, A.G., Nicholls, A. Orion® A Cloud-Native Molecular Design Platform. In *Computational Drug Discovery*. V. Poongavanam and V. Ramaswamy, Eds. Wiley-VCH, 2024; pp. 579–615. DOI: 10.1002/9783527840748.ch24

15.4.2 AFITT and FLYNN Applications

Wlodek, S.; Skillman, A.G.; Nicholls, A. Automated Ligand Placement and Refinement with a Combined Force Field and Shape Potential. *Acta Crystallogr., Sect. D: Struct. Biol.* **2006**, *62* (7), 741–749. DOI: 10.1107/s0907444906016076

15.4.3 OEDocking Application and Toolkit

Kelley, B.P.; Brown, S.P.; Warren, G.L.; Muchmore, S.W. POSIT: Flexible Shape-Guided Docking For Pose Prediction. *J. Chem. Inf. Model.* **2015**, *55* (8), 1771-1780. DOI: 10.1021/acs.jcim.5b00142

McGann, M. FRED Pose Prediction and Virtual Screening Accuracy. *J. Chem. Inf. Model.* **2011**, *51* (3), 578-596. DOI: 10.1021/ci100436p

McGann, M. FRED and HYBRID Docking Performance on Standardized Datasets. *J. Comput.-Aided Mol. Des.* **2012**, *26* (8), 897-906. DOI: 10.1007/s10822-012-9584-8

15.4.4 OMEGA Application and Toolkit

If you are using OMEGA in torsion driving mode, please cite the following two publications.

Hawkins, P.C.D.; Skillman, A.G.; Warren, G.L.; Ellingson, B.A.; Stahl, M.T. Conformer Generation with OMEGA: Algorithm and Validation Using High Quality Structures from the Protein Databank and the Cambridge Structural Database. *J. Chem. Inf. Model.* **2010**, *50* (4), 572-584. DOI: 10.1021/ci100031x

Hawkins, P.C.D. and Nicholls, A. Conformer Generation with OMEGA: Learning from the Data Set and the Analysis of Failures. *J. Chem. Inf. Model.* **2012**, *52* (11), 2919–2936. DOI: /10.1021/ci300314k

If you are using OMEGA in macrocyle mode, please cite the following.

Hawkins, P.C.D. and Wlodek, S. Decisions with Confidence: Application to the Conformation Sampling of Molecules in the Solid State. *J. Chem. Inf. Model.* **2020**, *60* (7), 3518–3533. DOI: /10.1021/acs.jcim.0c00358

15.4.5 ROCS Application

Hawkins, P.C.D.; Skillman, A.G.; Nicholls, A. Comparison of Shape-Matching and Docking as Virtual Screening Tools. *J. Med. Chem.* **2007**, *50* (1), 74-82. DOI: 10.1021/jm0603365

15.5 OpenEye MMDS Web Service

To cite use of the Macromolecular Data Service (MMDS) web service, please use the syntax:

```
Macromolecular Data Service <version-number>. OpenEye, Cadence Molecular Sciences, Santa␣
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```

For example:

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Macromolecular Data Service 1.1. OpenEye, Cadence Molecular Sciences, Santa Fe, NM.␣
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The MMDS version number appears on the web service's release notes.

CHAPTER

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angular-mocks	https://github.com/angular/angular.js	https://raw.githubusercontent.com/angular/angular.js/master/LICENSE
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angular-ui-grid	https://github.com/angular-ui/ui-grid	https://github.com/angular-ui/ui-grid
angular-ui-router	https://github.com/angular-ui/ui-router	https://github.com/angular-ui/ui-router/raw/master/LICENSE
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arpack	https://www.caam.rice.edu/software/ARPACK/	https://www.caam.rice.edu/software/ARPACK/
arrow	https://github.com/arrow-py/arrow	https://github.com/arrow-py/arrow?tab=Apache-2.0-1-ov-file#readme
ascii85	https://github.com/huandu/node-ascii85	https://github.com/huandu/node-ascii85/raw/master/LICENSE
ase	https://wiki.fysik.dtu.dk/ase/	https://wiki.fysik.dtu.dk/ase/development/licenseinfo.html#license-info
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babel	https://babel.pocoo.org/ OR https://github.com/python-babel/babel	https://github.com/python-babel/babel/blob/master/LICENSE OR https://babel.pocoo.org/en/latest/license.html#babel-license
Babel	https://github.com/python-babel/babel	https://github.com/python-babel/babel/blob/master/LICENSE
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beautifulsoup4	https://www.crummy.com/software/BeautifulSoup/	https://www.crummy.com/software/BeautifulSoup/

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blas	https://www.netlib.org/blas/	https://www.netlib.org/blas/#_licensing
bleach	https://github.com/mozilla/bleach	https://github.com/mozilla/bleach/blob/main/LICENSE
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boltons	https://github.com/mahmoud/boltons	https://github.com/mahmoud/boltons/blob/master/LICENSE
Boltz	https://boltz.bio	https://github.com/jwohlwend/boltz/blob/main/LICENSE
boost	https://www.boost.org/doc/libs/1_71_0/libs/python/doc/html/index.html	https://www.boost.org/LICENSE_1_0.txt
boost-cpp	https://www.boost.org/doc/libs/1_71_0/libs/python/doc/html/index.html	https://www.boost.org/LICENSE_1_0.txt
bootstrap-vue	https://github.com/bootstrap-vue/bootstrap-vue	https://github.com/bootstrap-vue/bootstrap-vue/raw/master/LICENSE
boto3	https://github.com/boto/boto3	https://github.com/boto/boto3/blob/develop/LICENSE
botocore	https://github.com/boto/botocore	https://github.com/boto/botocore/blob/develop/LICENSE.txt
Bottleneck	https://bottleneck.readthedocs.io/en/latest/index.html	https://bottleneck.readthedocs.io/en/latest/license.html
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brotli-python	http://python-hyper.org/projects/brotlipy/en/latest/	https://github.com/python-hyper/brotlicffi/blob/main/LICENSE
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brotlipy	https://github.com/python-hyper/brotlicffi	https://github.com/python-hyper/brotlicffi/blob/main/LICENSE

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Name of Project	Website	License URL
bson	http://github.com/py-bson/bson	https://github.com/py-bson/bson/blob/master/LICENSE_APACHE
bytefmt	https://code.cloudfoundry.org/bytefmt	https://github.com/cloudfoundry/bytefmt/blob/master/LICENSE
bzip2	https://www.bzip.org	https://spdx.org/licenses/bzip2-1.0.6.html
c-ares	https://github.com/c-ares/c-ares	https://github.com/c-ares/c-ares/blob/main/LICENSE.md
ca-certificates	https://github.com/conda-forge/ca-certificates-feedsto	https://wiki.mozilla.org/CA/Included_Certificates
cached-property	https://github.com/pydanny/cached-property	https://github.com/pydanny/cached-property/blob/master/LICENSE
cachetools	https://github.com/tkem/cachetools/	https://github.com/tkem/cachetools/blob/master/LICENSE
cairo	https://pycairo.readthedocs.io/en/latest/	https://github.com/pygobject/pycairo/blob/master/COPYING
canvas	https://github.com/Automattic/node-canvas	https://github.com/Automattic/node-canvas
cctbx	https://github.com/cctbx/cctbx_project	https://github.com/cctbx/cctbx_project/blob/master/cctbx/LICENSE_2_0.txt
celery	https://github.com/celery/celery	https://github.com/celery/celery/blob/master/LICENSE
Cerberus	https://docs.python-cerberus.org/en/stable/	https://docs.python-cerberus.org/en/stable/license.html
certifi	https://certifiio.readthedocs.io/en/latest/	https://wiki.mozilla.org/index.php?title=CA/IncludedCertificates&redirect=no

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Name of Project	Website	License URL
cffi	https://github.com/python-cffi	https://github.com/cffi/cffi/blob/master/COPYRIGHT
cftime	https://pypi.org/project/cftime/	https://github.com/Unidata/cftime/blob/master/LICENSE
chardet	https://github.com/chardet/chardet	https://github.com/chardet/chardet/blob/master/LICENSE
charset-normalizer	https://github.com/ousret/charset_normalizer	https://github.com/Ousret/charset_normalizer/blob/master/LICENSE
ChEMBL Structure Pipeline	https://github.com/chembl/ChEMBL_Structure_Pipeline/tree/master	https://github.com/chembl/ChEMBL_Structure_Pipeline/blob/master/LICENSE
choreographer	https://github.com/mazpie/choreographer	https://github.com/mazpie/choreographer/blob/main/LICENSE
chunkreader	https://github.com/jackc/chunkreader/v2	https://github.com/jackc/chunkreader/blob/master/LICENSE
click	https://palletsprojects.com/p/click/	https://github.com/pallets/click/blob/main/LICENSE.rst
click-completion	https://github.com/click-contrib/click-completion	https://github.com/click-contrib/click-completion/blob/master/LICENSE
click-didyoumean	https://github.com/click-contrib/click-didyoumean	https://github.com/click-contrib/click-didyoumean/blob/master/LICENSE
click-plugins	https://github.com/click-contrib/click-plugins	https://github.com/click-contrib/click-plugins/blob/master/LICENSE.txt

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Name of Project	Website	License URL
click-repl	https://github.com/untitaker/click-repl	https://github.com/click-contrib/click-repl/blob/master/LICENSE
cloudpickle	https://github.com/cloudpipe/cloudpickle	https://github.com/cloudpipe/cloudpickle/blob/master/LICENSE
cmake	https://cmake.org/	https://cmake.org/licensing/
colorama	https://github.com/tartley/colorama	https://github.com/tartley/colorama/blob/master/LICENSE.txt
comm	https://github.com/ipython/comm	https://github.com/ipython/comm/blob/master/LICENSE
compose	https://github.com/docker/compose	https://github.com/docker/compose/blob/v2/LICENSE
conda-content-trust	https://github.com/conda/conda-content-trust	https://github.com/conda/conda-content-trust/blob/main/LICENSE
conda-libmamba-solver	https://github.com/conda/conda-libmamba-solv	https://github.com/conda/conda-libmamba-solv blob/main/LICENSE
conda-pack	https://conda.github.io/conda-pack/	https://github.com/conda/conda-pack/blob/main/LICENSE.txt
conda-package-handling	https://github.com/conda/conda-package-handli	https://github.com/conda/conda-package-handli blob/main/LICENSE
conda-package-streaming	https://anaconda.org/conda-forge/conda-package-stream	https://github.com/conda/conda-package-stream blob/main/LICENSE
conda-token	https://anaconda.org/anaconda/conda-token	https://anaconda.org/anaconda/conda-token

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Name of Project	Website	License URL
conda_package_strear	https://github.com/conda/conda-package-streamtree/main/conda_package_streaming	https://github.com/conda/conda-package-streamtab=License-1-ov-file
confuse	https://github.com/beetbox/confuse	https://github.com/beetbox/confuse/blob/main/LICENSE
contourpy	https://github.com/contourpy/contourpy	https://github.com/contourpy/contourpy/blob/main/LICENSE
cpp-expected	https://github.com/TartanLlama/expected	https://github.com/TartanLlama/expected?tab=CC0-1.0-1-ov-file#readme
cpp-peglib	https://github.com/yhirose/cpp-peglib	https://github.com/yhirose/cpp-peglib/blob/master/LICENSE
cryptography	https://github.com/pyca/cryptography	https://github.com/pyca/cryptography/blob/main/LICENSE
cssselect2	https://github.com/Kozea/cssselect2/	https://github.com/Kozea/cssselect2/blob/master/LICENSE
cuda-bindings	https://nvidia.github.io/cuda-python/cuda-bindings/latest/install.html	https://github.com/NVIDIA/cuda-python/blob/main/cuda_bindings/LICENSE
cuda-pathfinder	https://nvidia.github.io/cuda-python/cuda-pathfinder/latest/	https://nvidia.github.io/cuda-python/cuda-pathfinder/latest/license.html
cudatoolkit	https://developer.nvidia.com/cuda-toolkit	https://docs.nvidia.com/cuda/eula/index.html
cuequivariance-ops-cu12	https://developer.nvidia.com/cuequivariance	https://github.com/NVIDIA/cuEquivariance/blob/main/LICENSES/LICENSE

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Name of Project	Website	License URL
cuequivariance-ops-torch-cu12	https://developer.nvidia.com/cuequivariance	https://github.com/NVIDIA/cuEquivariance/blob/main/LICENSES/LICENSE
cuequivariance-torch	https://docs.nvidia.com/cuda/cuequivariance/	https://github.com/NVIDIA/cuEquivariance/blob/main/LICENSES/LICENSE
cupy-cuda113	https://cupy.dev/	https://github.com/cupy/cupy/blob/main/LICENSE
cupy-cuda11x	https://cupy.dev/	https://github.com/cupy/cupy/?tab=MIT-1-ov-file#readme
curl	https://curl.se	https://curl.se/docs/copyright.html
cycler	https://github.com/matplotlib/cycler	https://github.com/matplotlib/cycler/blob/main/LICENSE
cyrus-sasl	https://github.com/cyrusimap/cyrus-sasl	https://github.com/cyrusimap/cyrus-sasl/blob/master/COPYING
Cython	https://cython.org	https://www.apache.org/licenses/LICENSE-2.0.html
d3	https://github.com/mbostock/d3	https://github.com/mbostock/d3/raw/master/LICENSE
dataclasses	https://github.com/ericvsmith/dataclasses	https://github.com/ericvsmith/dataclasses/blob/master/LICENSE.txt
ddsketch	http://github.com/datadog/sketches-py	https://github.com/DataDog/sketches-py/blob/master/LICENSE
debugpy	https://aka.ms/debugpy	https://github.com/microsoft/debugpy/blob/main/LICENSE

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Name of Project	Website	License URL
decimal	https://github.com/shopspring/decimal	https://github.com/shopspring/decimal/blob/master/LICENSE
decorator	https://github.com/micheles/decorator	https://github.com/micheles/decorator/blob/master/LICENSE.txt
deepdiff	https://github.com/seperman/deepdiff	https://github.com/seperman/deepdiff/blob/master/LICENSE
deeptime	https://github.com/deeptime-ml/deeptime	https://github.com/deeptime-ml/deeptime/blob/main/LICENSE.txt
defusedxml	https://github.com/tiran/defusedxml	https://github.com/tiran/defusedxml/blob/main/LICENSE
dftd3	https://github.com/dftd3/tad-dftd3	https://github.com/dftd3/tad-dftd3/blob/main/LICENSE
dill	https://github.com/uqfoundation/dill	https://github.com/uqfoundation/dill/blob/master/LICENSE
distlib	https://distlib.readthedocs.io/en/latest/	https://github.com/pypa/distlib/blob/master/LICENSE.txt
distro	https://github.com/python-distro/distro	https://github.com/python-distro/distro/blob/master/LICENSE
Django	https://www.djangoproject.com/	https://github.com/django/django/blob/main/LICENSE
django-classy-tags	https://github.com/django-cms/django-classy-tags	https://github.com/django-cms/django-classy-tags/blob/master/LICENSE
django-cors-headers	https://github.com/adamchainz/django-cors-headers	https://github.com/adamchainz/django-cors-headers/blob/main/LICENSE

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Table 1 – continued from previous page

Name of Project	Website	License URL
django-csp	https://github.com/mozilla/django-csp	https://github.com/mozilla/django-csp/blob/main/LICENSE
django-extensions	https://github.com/django-extensions/django-extensions	https://github.com/django-extensions/django-extensions/blob/main/LICENSE
django-filter	https://github.com/carltongibson/django-filter/tree/master	https://github.com/carltongibson/django-filter/blob/main/LICENSE
django-redis	https://github.com/jazzband/django-redis	https://github.com/jazzband/django-redis/blob/master/LICENSE
django-taggit	https://github.com/jazzband/django-taggit	https://github.com/jazzband/django-taggit/blob/master/LICENSE
django-taggit-serializer	https://github.com/glemmaPaul/django-taggit-serializ	https://github.com/glemmaPaul/django-taggit-serializ blob/master/LICENSE
django-taggit-templatetags2	https://github.com/fizista/django-taggit-templat	https://github.com/fizista/django-taggit-templat blob/master/LICENSE.txt
djangorestframework	https://www.django-rest-framewor org/	https://github.com/encode/django-rest-framewor blob/master/LICENSE.md
dkh	https://psicode.org/psi4manual/master/dkh.html	https://github.com/psi4/dkh/blob/master/COPYING.LESSER
dm-tree	https://github.com/deepmind/tree	https://github.com/deepmind/tree/blob/master/LICENSE
docker-py	https://github.com/docker/docker-py/	https://github.com/docker/docker-py/blob/master/LICENSE

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Name of Project	Website	License URL
docker-pycreds	https://github.com/shin-/dockerpy-creds	https://github.com/shin-/dockerpy-creds/blob/master/LICENSE
docopt	https://docopt.org	https://github.com/docopt/docopt/blob/master/LICENSE-MIT
docutils	https://docutils.sourceforge.io	https://docutils.sourceforge.io/COPYING.html
drf-dynamic-fields	https://github.com/dbrgn/drf-dynamic-fields	https://github.com/dbrgn/drf-dynamic-fields/blob/master/LICENSE
DuckDB	https://duckdb.org/	https://github.com/duckdb/duckdb?tab=MIT-1-ov-file#readme
edgembar	https://rutgerslbsr.gitlab.io/fe-toolkit/edgembar/index.html	https://gitlab.com/RutgersLBSR/fe-toolkit/-/blob/master/LICENSE
editdistance	https://github.com/roy-ht/editdistance	https://github.com/roy-ht/editdistance/blob/master/LICENSE
eigen	https://eigen.tuxfamily.org/index.php?title=Main_Page	https://eigen.tuxfamily.org/index.php?title=Main_Page#License
einops	https://github.com/arogozhnikov/einops	https://github.com/arogozhnikov/einops/blob/master/LICENSE
einx	https://github.com/fferflo/einx	https://github.com/fferflo/einx/blob/master/LICENSE
entrypoints	https://github.com/takluyver/entrypoints	https://github.com/takluyver/entrypoints/blob/master/LICENSE
errors	https://github.com/pkg/errors	https://github.com/pkg/errors/blob/master/LICENSE

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Name of Project	Website	License URL
eslint-plugin	https://github.com/typescript-eslint/typescript-eslint	https://github.com/typescript-eslint/typescript-eslint/raw/master/LICENSE
et_xmlfile	https://foss.heptapod.net/openpyxl/et_xmlfile	https://foss.heptapod.net/openpyxl/et_xmlfile/-/blob/branch/default/LICENCE.rst
exceptiongroup	https://github.com/agronholm/exceptiongroup	https://github.com/agronholm/exceptiongroup/blob/main/LICENSE
execnet	https://execnet.readthedocs.io/en/latest/	https://github.com/pytest-dev/execnet/blob/master/LICENSE
executing	https://github.com/alexmojaki/executing	https://github.com/alexmojaki/executing/blob/master/LICENSE.txt
expat	https://libexpat.github.io	https://github.com/libexpat/libexpat/blob/master/expat/COPYING
fairscale	https://github.com/facebookresearch/fairscale	https://github.com/facebookresearch/fairscale/blob/main/LICENSE
fairseq	https://github.com/pytorch/fairseq	https://github.com/facebookresearch/fairseq/blob/main/LICENSE
fastjsonschema	https://github.com/horejsek/python-fastjsonschem	https://github.com/horejsek/python-fastjsonschem/blob/master/LICENSE
fastrlock	https://github.com/scoder/fastrlock	https://github.com/scoder/fastrlock/blob/master/LICENSE
fftw	https://www.fftw.org	commercial license

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Name of Project	Website	License URL
filebuffer	https://github.com/mattetti/filebuffer	https://github.com/mattetti/filebuffer/blob/master/LICENSE
filelock	https://py-filelock.readthedocs.io/en/latest/index.html	https://github.com/tox-dev/py-filelock/blob/main/LICENSE
finufft	https://github.com/flatironinstitute/finufft	https://github.com/flatironinstitute/finufft/blob/master/LICENSE
Flask	https://flask.palletsprojects.com/en/2.1.x/	https://flask.palletsprojects.com/en/2.1.x/license/
flatbuffers	https://google.github.io/flatbuffers/	https://github.com/google/flatbuffers/blob/master/LICENSE.txt
flexcache	https://github.com/hgrecco/flexcache	https://github.com/hgrecco/flexcache/blob/main/LICENSE
flexparser	https://github.com/hgrecco/flexparser	https://github.com/hgrecco/flexparser/blob/main/LICENSE
flit-core	https://github.com/pypa/flit	https://github.com/scientific-python/lazy_loader/blob/main/LICENSE.md
FLTK	https://www.fltk.org/index.php	https://www.fltk.org/COPYING.php
fmt	https://fmt.dev/latest/index.html	https://github.com/fmtlib/fmt/blob/master/LICENSE.rst
font-awesome	https://github.com/FortAwesome/Font-Awesome	https://github.com/FortAwesome/Font-Awesome
font-ttf-dejavu-sans-mono	https://dejavu-fonts.github.io	https://dejavu-fonts.github.io/License.html
font-ttf-inconsolata	https://fonts.google.com/specimen/Inconsolata	https://scripts.sil.org/cms/scripts/page.php?site_id=nrsi&id=OFL

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Name of Project	Website	License URL
font-ttf-source-code-pro	https://fonts.google.com/specimen/Source+Code+Pro	https://scripts.sil.org/cms/scripts/page.php?site_id=nrsi&id=OFL
font-ttf-ubuntu	https://fonts.google.com/specimen/Ubuntu	https://ubuntu.com/legal/font-licence
fontconfig	https://www.freedesktop.org/wiki/Software/fontconfig/	https://gitlab.freedesktop.org/fontconfig/fontconfig/-/blob/main/COPYING
fonts-conda-ecosystem	https://anaconda.org/conda-forge/fonts-conda-ecosyster	https://docs.conda.io/en/latest/license.html
fonts-conda-forge	https://anaconda.org/conda-forge/fonts-conda-forge/	https://creativecommons.org/licenses/by/4.0/
fonttools	https://github.com/fonttools/fonttools	https://github.com/fonttools/fonttools/blob/main/LICENSE
forcebalance	https://simtk.org/home/forcebalance OR https://github.com/leeping/forcebalance	https://github.com/leeping/forcebalance/blob/master/LICENSE
fqdn	https://github.com/ypcrts/fqdn	https://github.com/ypcrts/fqdn?tab=MPL-2.0-1-ov-file#readme
freetype	https://freetype.org	https://freetype.org/license.html
freetype-py	https://github.com/rougier/freetype-py	https://github.com/rougier/freetype-py?tab=License-1-ov-file#readme
fribidi	https://github.com/fribidi/fribidi	https://github.com/fribidi/fribidi/blob/master/COPYING
frozendict	https://github.com/Marco-Sulla/python-frozendict	https://github.com/Marco-Sulla/python-frozendict/blob/master/LICENSE.txt
frozenlist	https://github.com/aio-libs/frozenlist	https://github.com/aio-libs/frozenlist/blob/master/LICENSE

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Name of Project	Website	License URL
fsmlite	https://github.com/tkem/fsmlite	https://github.com/tkem/fsmlite/blob/master/LICENSE
fsspec	https://github.com/fsspec/filesystem_spec	https://github.com/fsspec/filesystem_spec/blob/master/LICENSE
funcy	https://github.com/Suor/funcy	https://github.com/Suor/funcy/blob/master/LICENSE
gast	https://github.com/serge-sans-paille/gast/	https://github.com/serge-sans-paille/gast/blob/master/LICENSE
gau2grid	https://github.com/dgasmith/gau2grid	https://github.com/dgasmith/gau2grid/blob/master/LICENSE
gax-go	https://github.com/googleapis/gax-go/v2	https://github.com/googleapis/gax-go/blob/main/LICENSE
gdk-pixbuf	https://gitlab.gnome.org/GNOME/gdk-pixbuf	https://gitlab.gnome.org/GNOME/gdk-pixbuf/-/blob/master/COPYING
gemmi	https://gemmi.readthedocs.io/en/latest/	https://github.com/project-gemmi/gemmi/blob/master/LICENSE.txt
genproto	https://google.golang.org/genproto/googleapis	https://github.com/googleapis/go-genproto/blob/main/LICENSE
geometric	https://openbase.com/python/geometric	https://openbase.com/python/geometric
giflib	https://giflib.sourceforge.net	https://github.com/mirrorer/giflib/blob/master/COPYING
gitdb	https://github.com/gitpython-developers/gitdb	https://github.com/gitpython-developers/gitdb/blob/master/LICENSE
GitPython	https://github.com/gitpython-developers/GitPython	https://github.com/gitpython-developers/GitPython/blob/main/LICENSE

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Name of Project	Website	License URL
glib	https://docs.gtk.org/glib/	https://gitlab.gnome.org/GNOME/glib/-/blob/main/LICENSES/LGPL-2.1-or-later.txt
GLM Library	https://github.com/g-truc/glm	https://github.com/g-truc/glm/blob/master/manual.md#section0
gls	https://github.com/jtolds/gls	https://github.com/jtolds/gls/blob/master/LICENSE
gmpy2	https://github.com/aleaxit/gmpy	https://github.com/gmpy2/gmpy2/blob/master/COPYING.LESSER
go-cleanhttp	https://github.com/hashicorp/go-cleanhttp	https://github.com/hashicorp/go-cleanhttp/blob/master/LICENSE
go-connections	https://github.com/docker/go-connections	https://github.com/docker/go-connections/blob/master/LICENSE
go-cpio	https://github.com/cavaliercoder/go-cpio	https://github.com/cavaliercoder/go-cpio/blob/master/LICENSE
go-getter	https://github.com/hashicorp/go-getter	https://github.com/hashicorp/go-getter/blob/master/LICENSE
go-homedir	https://github.com/mitchellh/go-homedir	https://github.com/mitchellh/go-homedir/blob/master/LICENSE
go-ini	https://github.com/go-ini/ini	https://github.com/go-ini/ini/blob/master/LICENSE
go-jmespath	https://github.com/jmespath/go-jmespath	https://github.com/jmespath/go-jmespath/blob/master/LICENSE

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Name of Project	Website	License URL
go-junit-report	https://github.com/jstemmer/go-junit-report	https://github.com/jstemmer/go-junit-report/blob/master/LICENSE
go-netrc	https://github.com/bgentry/go-netrc/netrc	https://github.com/bgentry/go-netrc/blob/master/LICENSE
go-ole	https://github.com/go-ole/go-ole	https://github.com/go-ole/go-ole/blob/master/LICENSE
go-pg	https://github.com/go-pg/pg	https://github.com/go-pg/pg/blob/master/LICENSE
go-redis	https://github.com/go-redis/redis/v8	https://github.com/go-redis/redis/blob/master/LICENSE
go-rendezvous	https://github.com/dgryski/go-rendezvous	https://github.com/dgryski/go-rendezvous/blob/master/LICENSE
go-safetemp	https://github.com/hashicorp/go-safetemp	https://github.com/hashicorp/go-safetemp/blob/master/LICENSE
go-sysconf	https://github.com/tklauser/go-sysconf	https://github.com/tklauser/go-sysconf/blob/master/LICENSE
go-testing-interface	https://github.com/mitchellh/go-testing-interface	https://github.com/mitchellh/go-testing-interface/blob/master/LICENSE
go-units	https://github.com/docker/go-units	https://github.com/docker/go-units/blob/master/LICENSE
go-version	https://github.com/hashicorp/go-version	https://github.com/hashicorp/go-version/blob/master/LICENSE
go-zglob	https://github.com/mattn/go-zglob	https://github.com/mattn/go-zglob/blob/master/LICENSE

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Name of Project	Website	License URL
go.opencensus	https://go.opencensus.io	https://github.com/census-instrumentatio opencensus-go/blob/master/LICENSE
gobrake.v2	https://gopkg.in/airbrake/gobrake.v2	https://github.com/airbrake/gobrake/blob/v2.0.9/LICENSE
goconvey	https://github.com/smartystreets/goconvey	https://github.com/smartystreets/goconvey/blob/master/LICENSE.md
golden-layout	https://github.com/deepstreamIO/golden-layout	https://github.com/deepstreamIO/golden-layout/raw/master/LICENSE
google-auth	https://google-auth.readthedocs.io/en/master/	https://github.com/GoogleCloudPlatform google-auth-library-p blob/master/LICENSE
google-auth-oauthlib	https://github.com/googleapis/google-auth-library-p	https://github.com/googleapis/google-auth-library-p blob/main/LICENSE
google-cloud-go	https://cloud.google.com/go	https://github.com/googleapis/google-cloud-go/blob/main/LICENSE
google-cloud-go/storage	https://cloud.google.com/go/storage	https://github.com/googleapis/google-cloud-go/blob/main/LICENSE
google-pasta	https://github.com/google/pasta	https://github.com/google/pasta/blob/master/LICENSE
google.golang.org/api	https://google.golang.org/api	https://github.com/googleapis/google-api-go-client/blob/main/LICENSE
gopsutil	https://github.com/shirou/gopsutil	https://github.com/shirou/gopsutil/blob/master/LICENSE

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Name of Project	Website	License URL
gorilla websocket	https://github.com/gorilla/websocket	https://github.com/gorilla/websocket/blob/master/LICENSE
gpytorch	https://gpytorch.ai	https://github.com/cornellius-gp/gpytorch?tab=MIT-1-ov-file#readme
graphite2	https://github.com/silnrsi/graphite	https://github.com/silnrsi/graphite/blob/master/LICENSE
graphviz	https://graphviz.org/	https://graphviz.org/license/
greenlet	https://greenlet.readthedocs.io/en/latest/	https://github.com/python-greenlet/greenlet/blob/master/LICENSE
groupcache	https://github.com/golang/groupcache	https://github.com/golang/groupcache/blob/master/LICENSE
grpc	https://google.golang.org/grpc	https://github.com/grpc/grpc-go/blob/master/LICENSE
grpc-cpp	https://github.com/grpc/grpc	https://github.com/grpc/grpc/blob/master/LICENSE
grpcio	https://github.com/grpc/grpc.io/blob/main/LICENSE	https://github.com/grpc/grpc.io/blob/main/LICENSE
gtk2	https://gitlab.gnome.org/GNOME/gtk	https://gitlab.gnome.org/GNOME/gtk/-/blob/main/COPYING
gts	https://sourceforge.net/projects/gts/	https://www.gnu.org/licenses/lgpl-3.0.html
h11	https://github.com/python-hyper/h11	https://github.com/python-hyper/h11/blob/master/LICENSE.txt
h2	https://github.com/python-hyper/h2	https://github.com/python-hyper/h2?tab=MIT-1-ov-file#readme

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Name of Project	Website	License URL
h5py	https://www.h5py.org	https://docs.h5py.org/en/stable/licenses.html
harfbuzz	https://github.com/harfbuzz/harfbuzz	https://github.com/harfbuzz/harfbuzz/blob/main/COPYING
hdbscan	https://hdbscan.readthedocs.io/en/latest/	https://github.com/scikit-learn-contrib/hdbscan/blob/master/LICENSE
hdf4	https://www.hdfgroup.org/solutions/hdf4/	https://github.com/HDFGroup/hdf4/blob/master/COPYING
hdf5	https://www.hdfgroup.org/solutions/hdf5/	https://github.com/HDFGroup/hdf5/blob/master/COPYING
he	https://github.com/mathiasbynens/he	https://github.com/mathiasbynens/he/raw/master/LICENSE-MIT.txt
hpack	https://github.com/python-hyper/hpack	https://github.com/python-hyper/hpack?tab=MIT-1-ov-file#readme
html-loader	https://github.com/webpack-contrib/html-loader	https://github.com/webpack-contrib/html-loader/raw/master/LICENSE
html5lib	https://github.com/html5lib/html5lib-python	https://github.com/html5lib/html5lib-python/blob/master/LICENSE
htslib	https://www.htslib.org	https://github.com/samtools/htslib/blob/develop/LICENSE
httpcore	https://www.encode.io/httpcore/	https://github.com/encode/httpcore/blob/master/LICENSE.md
httpx	https://github.com/encode/httpx	https://github.com/encode/httpx/blob/master/LICENSE.md

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Name of Project	Website	License URL
humanize	https://github.com/jmoiron/humanize	https://github.com/jmoiron/humanize/blob/master/LICENCE
hydra-core	https://github.com/facebookresearch/hydra	https://github.com/facebookresearch/hydra/blob/main/LICENSE
hyperframe	https://github.com/python-hyper/hyperframe	https://github.com/python-hyper/hyperframe?tab=MIT-1-ov-file#readme
icu	https://github.com/unicode-org/icu	https://github.com/unicode-org/icu/blob/main/icu4c/LICENSE
idna	https://github.com/kjd/idna	https://github.com/kjd/idna/blob/master/LICENSE.md
ihm	https://github.com/ihmwg/python-ihm	https://github.com/ihmwg/python-ihm/blob/main/LICENSE
imageio	https://github.com/imageio/imageio	https://github.com/imageio/imageio/blob/master/LICENSE
imagesize	https://github.com/shibukawa/imagesize_py	https://github.com/shibukawa/imagesize_py/blob/master/LICENSE.rst
ImmuneBuilder	https://github.com/oxpig/ImmuneBuilder/tree/main	https://github.com/oxpig/ImmuneBuilder/blob/main/LICENSE
importlib-metadata	https://github.com/python/importlib_metadata	https://github.com/python/importlib_metadata/blob/main/LICENSE
importlib_metadata	https://github.com/python/importlib_metadata	https://github.com/python/importlib_metadata/blob/main/LICENSE

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Name of Project	Website	License URL
importlib_resources	https://github.com/python/importlib_resources	https://github.com/python/importlib_resources/blob/main/LICENSE
InChI	https://iupac.org/who-we-are/divisions/division-details/inchi/	https://iupac.org/wp-content/uploads/2021/06/iupac-inchi-license_2020.pdf
inflection	https://github.com/jinzhu/inflection	https://github.com/jinzhu/inflection/blob/master/LICENSE
ini.v1	https://gopkg.in/ini.v1	https://github.com/go-ini/ini/blob/v1.66.2/LICENSE
iniconfig	https://github.com/pytest-dev/iniconfig	https://github.com/pytest-dev/iniconfig/blob/main/LICENSE
innersvg-polyfill	https://github.com/dnozay/innersvg-polyfill	https://github.com/dnozay/innersvg-polyfill/raw/master/LICENSE
intel-openmp	https://github.com/hermitcore/libomp_oss	https://github.com/hermitcore/libomp_oss/blob/hermit/LICENSE.txt
ipykernel	https://ipython.org	https://ipython.org
ipython	https://ipython.org	https://github.com/ipython/ipython/blob/master/LICENSE
ipython-genutils	http://ipython.org	https://github.com/ipython/ipython_genutils/blob/master/COPYING.md
ipython_pygments_le	https://github.com/ipython/ipython-pygments-lex	https://github.com/ipython/ipython-pygments-lex blob/main/LICENSE
ipywidgets	http://jupyter.org	https://github.com/jupyter-widgets/ipywidgets/blob/main/LICENSE

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Name of Project	Website	License URL
isodate	https://github.com/gweis/isodate/	https://github.com/gweis/isodate/blob/master/LICENSE
isoduration	https://github.com/bolsote/isoduration	https://github.com/bolsote/isoduration?tab=ISC-1-ov-file#readme
itsdangerous	https://palletsprojects.com/p/itsdangerous/	https://itsdangerous.palletsprojects.com/en/2.1.x/license/
jax	https://github.com/google/jax	https://github.com/google/jax/blob/main/LICENSE
jaxlib	https://github.com/google/jax	https://github.com/google/jax/blob/main/LICENSE
jaxtyping	https://github.com/patrick-kidger/jaxtyping	https://github.com/patrick-kidger/jaxtyping?tab=License-1-ov-file#readme
jedi	https://jedi.readthedocs.io/en/latest/	https://github.com/davidhalter/jedi/blob/master/LICENSE.txt
Jinja2	https://palletsprojects.com/p/jinja/	https://github.com/pallets/jinja/blob/main/LICENSE.rst
jmespath	https://github.com/jmespath/jmespath.py	https://github.com/jmespath/jmespath.py/blob/develop/LICENSE.txt
joblib	https://joblib.readthedocs.io/en/latest/	https://github.com/joblib/joblib/blob/master/LICENSE.txt
jpeg	https://www.ijg.org	https://www.ijg.org/files/README
json5	https://github.com/dpranke/pyjson5	https://github.com/dpranke/pyjson5/blob/main/LICENSE
jsonfield	https://github.com/dmkoch/django-jsonfield/	https://github.com/rpkilby/jsonfield/blob/master/LICENSE

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Name of Project	Website	License URL
jsonpatch	https://github.com/stefankoegl/python-json-patch	https://github.com/stefankoegl/python-json-patch/blob/master/LICENSE
jsonpickle	https://github.com/jsonpickle/jsonpickle	https://github.com/jsonpickle/jsonpickle/blob/main/LICENSE
jsonpointer	https://github.com/stefankoegl/python-json-pointer	https://github.com/stefankoegl/python-json-pointer/blob/master/LICENSE.txt
jsonschema	https://github.com/python-jsonschema/jsonschema	https://github.com/python-jsonschema/jsonschema/blob/master/COPYING
jsonschema-specifications	https://github.com/python-jsonschema/jsonschema-specificat	https://github.com/python-jsonschema/jsonschema-specificat blob/main/COPYING
jstat	https://github.com/jstat/jstat	https://www.opensource.org/licenses/mit-license.php
jupyter-client	https://jupyter.org	https://github.com/jupyter/jupyter_client/blob/main/COPYING.md
jupyter-core	https://jupyter.org	https://github.com/jupyter/jupyter_core/blob/master/COPYING.md
jupyter-events	https://github.com/jupyter/jupyter_events	https://github.com/jupyter/jupyter_events/blob/main/LICENSE
jupyter-lsp	https://github.com/jupyter-lsp/jupyterlab-lsp	https://github.com/jupyter-lsp/jupyterlab-lsp
jupyter-serverhttp://jupyter.or	https://github.com/jupyter-server/jupyter_server/blob/main/LICENSE	
jupyter_client	http://jupyter.org	https://github.com/jupyter/jupyter_client/blob/main/LICENSE

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Name of Project	Website	License URL
jupyter_core	http://jupyter.org	https://github.com/jupyter/jupyter_core/blob/master/LICENSE
jupyter_server	https://github.com/jupyter-server/jupyter_server	https://github.com/jupyter-server/jupyter_server/blob/main/LICENSE
jupyter_server_termin	https://github.com/jupyter-server/jupyter_server_terminals	https://github.com/jupyter-server/jupyter_server_terminals/blob/main/LICENSE
jupyterlab	https://github.com/jupyterlab/jupyterlab	https://github.com/jupyterlab/jupyterlab/blob/main/LICENSE
jupyterlab-pygments	http://jupyter.org	https://github.com/jupyterlab/jupyterlab_pygments/blob/main/LICENSE
jupyterlab-widgets	http://jupyter.org	https://github.com/jupyter-widgets/ipywidgets/blob/master/LICENSE
jupyter-lab_pygments	https://github.com/jupyterlab/jupyterlab_pygments	https://github.com/jupyterlab/jupyterlab_pygments?tab=BSD-3-Clause-1-ov-file#readme
jupyterlab_server	https://github.com/jupyterlab/jupyterlab_server	https://github.com/jupyterlab/jupyterlab_server/blob/main/LICENSE
jupyterlab_widgets	https://github.com/jupyter-widgets/ipywidgets	https://github.com/jupyter-widgets/ipywidgets?tab=BSD-3-Clause-1-ov-file#readme
kaleido	https://github.com/plotly/Kaleido	https://github.com/plotly/Kaleido/blob/master/LICENSE.txt
keras	https://github.com/keras-team/keras	https://github.com/keras-team/keras/blob/master/LICENSE

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Name of Project	Website	License URL
Keras-Preprocessing	https://github.com/keras-team/keras-preprocessing	https://github.com/keras-team/keras-preprocessing/blob/master/LICENSE
keras-tuner	https://github.com/keras-team/keras-tuner	https://github.com/keras-team/keras-tuner/blob/master/LICENSE
keyring	https://github.com/jaraco/keyring	https://github.com/jaraco/keyring/blob/main/LICENSE
keyutils	https://github.com/sassoftware/python-keyutils	https://github.com/sassoftware/python-keyutils/blob/master/LICENSE
kiwisolver	https://kiwisolver.readthedocs.io/en/latest/	https://github.com/nucleic/kiwi/blob/main/LICENSE
kombu	https://kombu.readthedocs.io	https://github.com/celery/kombu/blob/master/LICENSE
krb5	https://web.mit.edu/kerberos/	https://github.com/krb5/krb5/blob/master/src/lib/gssapi/LICENSE
kt-legacy	https://github.com/haifeng-jin/kt-legacy	https://github.com/haifeng-jin/kt-legacy/blob/main/LICENSE
lark	https://github.com/lark-parser/lark	https://github.com/lark-parser/lark?tab=MIT-1-ov-file#readme
lazy_loader	https://github.com/scientific-python/lazy_loader	https://github.com/scientific-python/lazy_loader/blob/main/LICENSE.md
lcms2	https://www.littlecms.com	https://github.com/sk1project/python-lcms2/blob/master/LICENSE
legacy-cgi	https://github.com/jackrosenthal/legacy-cgi	https://github.com/jackrosenthal/legacy-cgi?tab=License-1-ov-file#readme

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Name of Project	Website	License URL
lerc	https://github.com/Esri/lerc	https://github.com/Esri/lerc/blob/master/LICENSE
libarchive	http://www.libarchive.org	https://raw.githubusercontent.com/libarchive/libarchive/master/COPYING
libblas	https://www.netlib.org/blas/	https://www.netlib.org/blas/#_licensing
libbrotlicommon	https://github.com/google/brotli	https://github.com/google/brotli/blob/master/LICENSE
libbrotlidec	https://github.com/google/brotli	https://github.com/google/brotli/blob/master/LICENSE
libbrotlienc	https://github.com/google/brotli	https://github.com/google/brotli/blob/master/LICENSE
libcblas	https://anaconda.org/conda-forge/libcblas	N/A
libclang	https://github.com/sighingnow/libclang	https://github.com/sighingnow/libclang/blob/master/LICENSE.TXT
libcurl	https://curl.se/libcurl/	https://curl.se/docs/copyright.html
libcxx	https://github.com/llvm-mirror/libcxx	https://github.com/llvm-mirror/libcxx/blob/master/LICENSE.TXT
libdb	https://www.oracle.com/technology/software/products/berkeley-db/index.html	https://github.com/berkeleydb/libdb/blob/master/LEGAL
libdeflate	https://github.com/ebiggers/libdeflate	https://github.com/ebiggers/libdeflate/blob/master/COPYING
libedit	https://thrysoee.dk/editline/	http://www.netbsd.org/Goals/redistribution.html
libev	https://software.schmorp.de/pkg/libev.html	https://software.schmorp.de/pkg/libev.html

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Name of Project	Website	License URL
libexpat	https://libexpat.github.io/	https://github.com/libexpat/libexpat?tab=MIT-1-ov-file#readme
libffi	https://github.com/libffi/libffi	https://github.com/libffi/libffi/blob/master/LICENSE
libgcc	https://gcc.gnu.org/onlinedocs/gccint/Libgcc.html	https://gcc.gnu.org/onlinedocs/libstdc++/manual/license.html
libgcrypt	https://gnupg.org/software/index.html	https://git.gnupg.org/cgi-bin/gitweb.cgi?p=libgcrypt.git;a=blob;f=COPYING.LIB;hb=HEAD
libgd	https://libgd.github.io	https://libgd.github.io/manuals/2.2.1/files/license-txt.html
libglib	https://github.com/PolMine/libglib	https://github.com/PolMine/libglib/blob/master/include/glib-2.0/glib.h
libiconv	https://www.gnu.org/software/libiconv/	https://www.gnu.org/software/libiconv/#downloading
libint	https://tinyurl.com/yvw97wbw	https://tinyurl.com/yvw97wbw
liblapack	http://www.netlib.org/lapack/	https://www.netlib.org/lapack/LICENSE.txt
liblapacke	https://anaconda.org/conda-forge/liblapacke	https://www.netlib.org/lapack/LICENSE.txt
liblzma	https://tukaani.org/xz/	https://git.tukaani.org/?p=xz.git;a=blob;f=COPYING.0BSD
libmamba	https://medium.com/@QuantStack/open-software-packag	https://github.com/mamba-org/mamba/blob/main/LICENSE

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Name of Project	Website	License URL
libmambapy	https://www.anaconda.com/blog/a-faster-conda-for-a-g	https://github.com/conda/conda-libmamba-solv blob/main/LICENSE
libnetcdf	https://www.unidata.ucar.edu/software/netcdf/	https://www.unidata.ucar.edu/software/netcdf/copyright.html
libnghttp2	https://github.com/nghttp2/nghttp2	https://github.com/nghttp2/nghttp2/blob/master/COPYING
libnsl	https://github.com/thkukuk/libnsl	https://gcc.gnu.org/onlinedocs/libstdc++/manual/license.html
libopenblas	https://www.openblas.net/	https://github.com/xianyi/OpenBLAS/blob/develop/LICENSE
libpng	https://www.libpng.org/pub/png/libpng.html	https://www.libpng.org/pub/png/src/libpng-LICENSE.txt
libpq	https://www.postgresql.org/	https://www.postgresql.org/about/licence/
librsvg	https://gitlab.gnome.org/GNOME/librsvg	https://gitlab.gnome.org/GNOME/librsvg/-/blob/main/COPYING.LIB
libsolv	https://github.com/openSUSE/libsolv	https://github.com/openSUSE/libsolv/blob/master/LICENSE.BSD
libsqlite	https://github.com/mackyle/sqlite	https://github.com/mackyle/sqlite?tab=License-1-ov-file#readme
libssh2	https://github.com/libssh2/libssh2	https://github.com/libssh2/libssh2/blob/master/COPYING
libstdcxx	https://gcc.gnu.org/	https://gcc.gnu.org/onlinedocs/libstdc++/manual/license.html

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Name of Project	Website	License URL
libtiff	https://www.libtiff.org/	https://www.libtiff.org/misc.html
libtrust	https://github.com/docker/libtrust	https://github.com/docker/libtrust/blob/master/LICENSE
libuuid	https://sourceforge.net/projects/libuuid/	https://sourceforge.net/p/libuuid/code/ci/master/tree/COPYING
libuv	https://github.com/libuv/libuv	https://github.com/libuv/libuv/blob/v1.x/LICENSE
libwebp	https://chromium.googlesource.com/?format=HTML	https://chromium.googlesource.com/chromium/src/third_party/+/refs/heads/main/libwebp/LICENSE
libwebp-base	https://chromium.googlesource.com/?format=HTML	https://chromium.googlesource.com/chromium/src/third_party/+/refs/heads/main/libwebp/LICENSE
libxc	https://www.tddft.org/programs/libxc/	https://gitlab.com/libxc/libxc/-/blob/master/COPYING
libxcb	https://xcb.freedesktop.org	https://github.com/freedesktop/xcb-libxcb/blob/master/COPYING
libxcrypt	https://github.com/besser82/libxcrypt	https://github.com/besser82/libxcrypt?tab=LGPL-2.1-1-ov-file#readme
libxml2	https://git.gnome.org/browse/libxml2/	https://gitlab.gnome.org/GNOME/libxml2/-/blob/master/Copyright
libxmlsec1	https://github.com/lsh123/xmlsec	https://github.com/lsh123/xmlsec/blob/master/README
libxslt	https://gitlab.gnome.org/GNOME/libxslt/-/wikis/home	https://gitlab.gnome.org/GNOME/libxslt/-/blob/master/Copyright

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Name of Project	Website	License URL
libzlib	https://zlib.net	https://zlib.net/zlib_license.html
lightning-utilities	https://github.com/Lightning-AI/utilities	https://github.com/Lightning-AI/utilities?tab=Apache-2.0-1-ov-file#readme
lime	https://github.com/marcotcr/lime	https://github.com/marcotcr/lime/blob/master/LICENSE
linear-operator	https://github.com/cornellius-gp/linear_operator	https://github.com/cornellius-gp/linear_operator?tab=MIT-1-ov-file#readme
lit	http://llvm.org	https://releases.llvm.org/14.0.0/LICENSE.TXT
llvm-openmp	https://github.com/llvm-mirror/openmp	https://github.com/llvm-mirror/openmp/blob/master/LICENSE.txt
llvmlite	http://llvmlite.readthedocs.io	https://github.com/numba/llvmlite/blob/main/LICENSE
loader-utils	https://github.com/webpack/loader-utils	https://github.com/webpack/loader-utils/raw/master/LICENSE
logistro	https://github.com/geopozo/logistro	https://github.com/geopozo/logistro?tab=MIT-1-ov-file#readme
logomaker	https://logomaker.readthedocs.io/en/latest/	https://github.com/jbkinney/logomaker/blob/master/LICENSE
logrus	https://github.com/sirupsen/logrus	https://github.com/sirupsen/logrus/blob/master/LICENSE
logrus-airbrake-hook.v2	https://gopkg.in/gemnasium/logrus-airbrake-hook.v2	https://github.com/gemnasium/logrus-airbrake-hook/blob/v2.1.2/LICENSE
lxml	https://lxml.de	https://lxml.de/index.html#license

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Name of Project	Website	License URL
lz4-c	https://www.lz4.org/	https://github.com/lz4/lz4/blob/dev/LICENSE
lzo	https://www.oberhumer.com/opensource/lzo/	https://www.oberhumer.com/opensource/gpl.html
mamba	https://github.com/mamba-org/mamba	https://github.com/mamba-org/mamba?tab=BSD-3-Clause-1-ov-f readme
markdown	https://github.com/evilstreak/markdown-js	https://www.opensource.org/licenses/mit-license.php
markdown-it-py	https://github.com/executablebooks/markdown-it-py	https://github.com/executablebooks/markdown-it-py/blob/master/LICENSE
markupsafe	https://github.com/pallets/markupsafe/tree/main/src/markupsafe	https://github.com/pallets/markupsafe/tree/main?tab=BSD-3-Clause-1-ov-f
MarkupSafe	https://palletsprojects.com/p/markupsafe/	https://github.com/pallets/markupsafe/blob/main/LICENSE.rst
mashumaro	https://github.com/Fatal1ty/mashumaro	https://github.com/Fatal1ty/mashumaro
matplotlib	https://matplotlib.org	https://matplotlib.org/stable/users/project/license.html
matplotlib-base	https://matplotlib.org	https://matplotlib.org/stable/users/project/license.html
matplotlib-inline	https://github.com/ipython/matplotlib-inline	https://github.com/ipython/matplotlib-inline/blob/master/LICENSE
mda-xdrlib	https://github.com/MDAnalysis/mda-xdrlib	https://github.com/MDAnalysis/mda-xdrlib/blob/main/LICENSE

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Name of Project	Website	License URL
mda_xdrlib	https://github.com/MDAnalysis/mda-xdrlib	https://github.com/MDAnalysis/mda-xdrlib?tab=License-1-ov-file#readme
mdtraj	https://www.mdtraj.org/	https://www.mdtraj.org/1.9.8.dev0/index.html#license
mdurl	https://github.com/markdown-it/mdurl	https://github.com/markdown-it/mdurl/blob/master/LICENSE
menuinst	https://github.com/conda/menuinst	https://github.com/conda/menuinst/blob/main/LICENSE.txt
mergo	https://github.com/imdario/mergo	https://github.com/imdario/mergo/blob/master/LICENSE
mistune	https://github.com/lepture/mistune	https://github.com/lepture/mistune/blob/master/LICENSE
mkl	https://github.com/rust-math/intel-mkl-src	https://github.com/rust-math/intel-mkl-src/blob/master/License.txt
mkl-fft	https://github.com/IntelPython/mkl_fft	https://github.com/IntelPython/mkl_fft/blob/master/LICENSE.txt
mkl-random	https://github.com/IntelPython/mkl_random	https://github.com/IntelPython/mkl_random/blob/master/LICENSE.txt
mkl-service	https://github.com/IntelPython/mkl-service	https://github.com/IntelPython/mkl-service/blob/master/LICENSE.txt
mkl_fft	http://github.com/IntelPython/mkl_fft	https://github.com/IntelPython/mkl_fft?tab=BSD-3-Clause-1-ov-f readme

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Name of Project	Website	License URL
mkl_random	http://github.com/IntelPython/mkl_random	https://github.com/IntelPython/mkl_random?tab=BSD-3-Clause-1-ov-f readme
ml-dtypes	https://github.com/jax-ml/ml_dtypes	https://github.com/jax-ml/ml_dtypes/blob/main/LICENSE
ml_dtypes	https://github.com/jax-ml/ml_dtypes	https://github.com/jax-ml/ml_dtypes/blob/main/LICENSE
modelcif	https://github.com/ihmwg/python-modelcif	https://github.com/ihmwg/python-modelcif/blob/main/LICENSE
molecupy	https://molecupy.readthedocs.io/en/latest/	https://github.com/samirelanduk/atomium/blob/master/LICENSE
moment	https://github.com/moment/moment	https://github.com/moment/moment/raw/master/LICENSE
moment-precise-range-plugin	https://github.com/codebox/moment-precise-range	https://github.com/codebox/moment-precise-range raw/master/LICENSE.md
more-itertools	https://github.com/more-itertools/more-itertools	https://github.com/more-itertools/more-itertools/blob/master/LICENSE
mpiplus	https://github.com/choderalab/mpiplus	https://github.com/choderalab/mpiplus/blob/main/LICENSE
mpmath	http://mpmath.org/	https://github.com/mpmath/mpmath/blob/master/LICENSE
mrcfile	https://github.com/ccpem/mrcfile	https://github.com/ccpem/mrcfile/blob/master/LICENSE.txt

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Name of Project	Website	License URL
msgpack	https://msgpack.org/	https://github.com/msgpack/msgpack-python/blob/main/COPYING
multidict	https://github.com/aio-libs/multidict	https://github.com/aio-libs/multidict/blob/master/LICENSE
multierr	https://go.uber.org/multierr	https://github.com/uber-go/multierr/blob/master/LICENSE.txt
multiprocess	https://github.com/uqfoundation/multiprocess	https://github.com/uqfoundation/multiprocess/blob/master/LICENSE
munkres	https://software.clapper.org/munkres/	https://github.com/bmc/munkres/blob/master/LICENSE.md
myesui uuid	https://github.com/myesui/uuid	https://pkg.go.dev/github.com/myesui/uuid?tab=licenses
namex	https://github.com/bcgov/namex	https://github.com/bcgov/namex/blob/main/LICENSE
narwhals	https://github.com/narwhals-dev/narwhals	https://github.com/narwhals-dev/narwhals?tab=MIT-1-ov-file#readme
nbclassic	http://jupyter.org	https://github.com/jupyter/nbclassic/blob/main/LICENSE
nbclient	https://jupyter.org	https://github.com/jupyter/nbclient/blob/main/LICENSE
nbconvert	https://jupyter.org	https://github.com/jupyter/nbconvert/blob/main/LICENSE
nbformat	http://jupyter.org	https://github.com/jupyter/nbformat/blob/main/LICENSE

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Name of Project	Website	License URL
ncurses	https://invisible-island.net/ncurses/	https://invisible-island.net/ncurses/ncurses-license.html
ndfes	https://rutgerslbsr.gitlab.io/fe-toolkit/	https://gitlab.com/RutgersLBSR/fe-toolkit/-/blob/master/LICENSE
ndindex	https://quansight-labs.github.io/ndindex/	https://github.com/Quansight-Labs/ndindex?tab=MIT-1-ov-file#readme
nest-asyncio	https://github.com/erdewit/nest_asyncio	https://github.com/erdewit/nest_asyncio/blob/master/LICENSE
nest_asyncio	https://github.com/erdewit/nest_asyncio	https://github.com/erdewit/nest_asyncio?tab=BSD-2-Clause-1-ov-f readme
netcdf-fortran	https://www.unidata.ucar.edu/software/netcdf/	https://www.unidata.ucar.edu/software/netcdf/copyright.html
netCDF4	http://github.com/Unidata/netcdf4-python	https://github.com/Unidata/netcdf4-python/blob/master/LICENSE
nettle	https://git.lysator.liu.se/nettle/nettle	https://git.lysator.liu.se/nettle/nettle/-/blob/master/AUTHORS?ref_type=heads
networkx	https://networkx.org	https://github.com/networkx/networkx/blob/main/LICENSE.txt
nfpm	https://github.com/goreleaser/nfpm	https://github.com/goreleaser/nfpm/blob/master/LICENSE.md
ng-tags-input	https://github.com/mbenford/ngTagsInput	https://github.com/mbenford/ngTagsInput
ng-toast	https://github.com/tameraydin/ngToast	https://github.com/tameraydin/ngToast

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Name of Project	Website	License URL
ngdraggable	https://github.com/fatlinesofcode/ngDraggable	https://github.com/fatlinesofcode/ngDraggable/raw/master/LICENSE.txt
ngVue	https://github.com/ngVue/ngVue	https://github.com/ngVue/ngVue/raw/master/LICENSE
nh3	https://nh3.readthedocs.io/en/latest/	https://github.com/messense/nh3/blob/main/LICENSE
nlohmann_json	https://github.com/nlohmann/json	https://github.com/nlohmann/json?tab=MIT-1-ov-file#readme
nlopt	https://nlopt.readthedocs.io/en/latest/NLopt_Python_Reference/	https://nlopt.readthedocs.io/en/latest/NLopt_License_and_Copyright/
nodejs	https://nodejs.org/en/	https://raw.githubusercontent.com/nodejs/node/master/LICENSE
nomkl	https://github.com/conda-forge/nomkl-feedstock	https://github.com/conda-forge/nomkl-feedstock/blob/main/LICENSE.txt
notebook	http://jupyter.org	https://github.com/jupyter/notebook/blob/main/LICENSE
notebook-shim	https://github.com/jupyter/notebook_shim	https://github.com/jupyter/notebook_shim
notebook_shim	http://jupyter.org	https://github.com/jupyter/notebook_shim/blob/main/LICENSE
numba	https://numba.pydata.org	https://github.com/numba/numba/blob/main/LICENSE
numcpus	https://github.com/tklauser/numcpus	https://github.com/tklauser/numcpus/blob/master/LICENSE

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Name of Project	Website	License URL
numexpr	https://github.com/pydata/numexpr	https://github.com/pydata/numexpr/blob/master/LICENSE.txt
numpy	https://numpy.org	https://github.com/numpy/numpy/blob/main/LICENSE.txt
numpy-base	https://numpy.org	https://github.com/numpy/numpy/blob/main/LICENSE.txt
numpydoc	https://numpydoc.readthedocs.io/en/latest/index.html	https://github.com/numpy/numpydoc/blob/main/LICENSE.txt
nvidia-cublas-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cublas-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cuda-cupti-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cuda-cupti-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cuda-nvrtc-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cuda-nvrtc-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cuda-runtime-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cuda-runtime-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cudnn-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/deeplearning/cudnn/sla/index.html
nvidia-cudnn-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/deeplearning/cudnn/sla/index.html

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Name of Project	Website	License URL
nvidia-cuEquivariance	https://github.com/NVIDIA/cuEquivariance	https://github.com/NVIDIA/cuEquivariance/blob/main/LICENSES/LICENSE
nvidia-cufft-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cufft-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cufile-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html#
nvidia-curand-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-curand-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cusolver-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cusolver-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cusparse-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cusparse-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-cusparselt-cu12	https://docs.nvidia.com/cuda/cusparselt/index.html	https://docs.nvidia.com/cuda/cusparselt/license.html
nvidia-ml-py	https://pypi.org/project/nvidia-ml-py/	https://pypi.org/project/nvidia-ml-py/
nvidia-nccl-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/hpc-sdk/eula/index.html
nvidia-nccl-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/hpc-sdk/eula/index.html
nvidia-nvjitlink-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html

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Name of Project	Website	License URL
nvidia-nvshmem-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-nvtx-cu11	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
nvidia-nvtx-cu12	https://developer.nvidia.com/cuda-zone	https://docs.nvidia.com/cuda/eula/index.html
Oat++	https://oatpp.io/	https://github.com/oatpp/oatpp/blob/master/LICENSE
oauthlib	https://github.com/oauthlib/oauthlib	https://github.com/oauthlib/oauthlib/blob/master/LICENSE
ocl-icd	https://github.com/OCL-dev/ocl-icd	https://github.com/OCL-dev/ocl-icd/blob/master/COPYING
ocl-icd-system	https://github.com/conda-forge/ocl-icd-system-feedst	https://github.com/conda-forge/ocl-icd-system-feedst blob/main/LICENSE.txt
olefile	https://www.decalage.info/python/olefileio	https://olefile.readthedocs.io/en/latest/License.html
omegaconf	https://github.com/omry/omegaconf	https://github.com/omry/omegaconf/blob/master/LICENSE
OmegaFold	https://github.com/HeliXonProtein/OmegaFold/tree/main	https://github.com/HeliXonProtein/OmegaFold/blob/main/LICENSE
omnicanvas	https://omnicanvas.readthedocs.io/en/latest/	https://github.com/samirelanduk/omnicanvas/blob/master/LICENSE
OpenFF	https://openforcefield.org/	https://github.com/openforcefield/openff-forcefields
openff-amber-ff-ports	https://github.com/openforcefield/openff-amber-ff-ports	https://github.com/openforcefield/openff-amber-ff-ports blob/main/LICENSE

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Name of Project	Website	License URL
openff-forcefields	https://openforcefield.org	https://github.com/openforcefield/openff-forcefields/blob/master/LICENSE
openff-fragmenter	https://github.com/openforcefield/openff-fragmenter	https://github.com/openforcefield/openff-fragmenter/blob/main/LICENSE
openff-interchange	https://github.com/openforcefield/openff-interchange	https://github.com/openforcefield/openff-interchange/blob/main/LICENSE
openff-models	https://github.com/openforcefield/openff-models	https://github.com/openforcefield/openff-models/blob/main/LICENSE
openff-nagl	https://docs.openforcefield.org/projects/nagl/en/latest/?badge=latest	https://github.com/openforcefield/openff-nagl/blob/main/LICENSE
openff-nagl-models	https://github.com/openforcefield/openff-nagl-models	https://github.com/openforcefield/openff-nagl-models/blob/main/LICENSE
openff-toolkit	https://openforcefield.org	https://github.com/openforcefield/openff-toolkit/blob/master/LICENSE
openff-toolkit-base	https://openforcefield.org	https://github.com/openforcefield/openff-toolkit/blob/master/LICENSE
openff-units	https://github.com/openforcefield/openff-units	https://github.com/openforcefield/openff-units/blob/main/LICENSE
openff-utilities	https://github.com/openforcefield/openff-utilities	https://github.com/openforcefield/openff-utilities/blob/main/LICENSE
openjpeg	https://github.com/uclouvain/openjpeg	https://github.com/uclouvain/openjpeg/blob/master/LICENSE

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Name of Project	Website	License URL
openldap	https://www.openldap.org/software/repo.html	https://git.openldap.org/openldap/openldap/-/blob/master/LICENSE
OpenMM	https://openmm.org	https://docs.openmm.org/7.1.0/userguide/library.html#license
openmmtools	https://github.com/choderalab/openmmtools	https://github.com/choderalab/openmmtools/blob/main/LICENSE
openmoltools	https://github.com/choderalab/openmoltools	https://github.com/choderalab/openmoltools/blob/master/LICENSE
openpyxl	https://openpyxl.readthedocs.io/en/stable/	https://foss.heptapod.net/openpyxl/openpyxl/-/blob/branch/3.0/LICENCE.rst
openssl	https://www.openssl.org	https://github.com/openssl/openssl/blob/master/LICENSE.txt
opt-einsum	https://github.com/dgasmith/opt_einsum	https://github.com/dgasmith/opt_einsum/blob/master/LICENSE
opt_einsum	https://github.com/dgasmith/opt_einsum	https://github.com/dgasmith/opt_einsum/blob/main/LICENSE
OptKing	https://github.com/psi-rking/optking	https://github.com/psi-rking/optking/blob/master/LICENSE
optree	https://optree.readthedocs.io/en/latest/	https://github.com/metaopt/optree/blob/main/LICENSE
oscrypto	https://github.com/wbond/oscrypto	https://github.com/wbond/oscrypto/blob/master/LICENSE
overrides	https://github.com/mkorpela/overrides	https://github.com/mkorpela/overrides/blob/main/LICENSE

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Name of Project	Website	License URL
packaging	https://github.com/pypa/packaging	https://github.com/pypa/packaging/blob/main/LICENSE
packmol	https://leandro.iqm.unicamp.br/m3g/packmol/home.shtml	https://github.com/m3g/packmol/blob/master/LICENSE
packmol_memgen	http://cpclab.uni-duesseldorf.de/	https://gitlab.com/cbjh/memgen/py-memgen/-/blob/main/LICENSE
pandas	https://pandas.pydata.org	https://github.com/pandas-dev/pandas/blob/main/LICENSE
pandocfilters	http://github.com/jgm/pandocfilters	https://github.com/jgm/pandocfilters/blob/master/LICENSE
panedr	https://github.com/MDAnalysis/panedr	https://github.com/MDAnalysis/panedr/blob/master/LICENSE.txt
pango	https://pango.gnome.org	https://gitlab.gnome.org/GNOME/pango/-/blob/main/COPYING
ParmEd	https://parmed.github.io/ParmEd/html/index.html	https://github.com/ParmEd/ParmEd#license
parser	https://github.com/typescript-eslint/typescript-eslint	https://github.com/typescript-eslint/typescript-eslint/raw/master/LICENSE
parso	https://parso.readthedocs.io/en/latest/	https://github.com/davidhalter/parso/blob/master/LICENSE.txt
pathos	https://github.com/uqfoundation/pathos	https://github.com/uqfoundation/pathos/blob/master/LICENSE
patsy	https://patsy.readthedocs.io/en/latest/	https://github.com/pydata/patsy/blob/master/LICENSE.txt

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Name of Project	Website	License URL
pbkdf2	https://golang.org/x/crypto/pbkdf2	https://cs.opensource.google/go/x/crypto/+/master:LICENSE
pbr	https://docs.openstack.org/pbr/latest/	https://opendev.org/openstack/pbr/src/branch/master/LICENSE
pcmsolver	https://pcmsolver.readthedocs.io/en/stable/	https://github.com/PCMSolver/pcmsolver/blob/master/LICENSE
pcre	https://www.pcre.org	https://www.pcre.org/licence.txt
pcre2	https://www.pcre.org	https://github.com/PCRE2Project/pcre2/blob/master/LICENCE
pdb4amber	https://github.com/Amber-MD/pdb4amber	https://github.com/Amber-MD/pdb4amber/blob/master/LICENSE
pdbfixer	https://github.com/openmm/pdbfixer	https://github.com/openmm/pdbfixer/blob/master/LICENSE
pexpect	https://pexpect.readthedocs.io/	https://github.com/pexpect/pexpect/blob/master/LICENSE
pgconn	https://github.com/jackc/pgconn	https://github.com/jackc/pgconn/blob/master/LICENSE
pgio	https://github.com/jackc/pgio	https://github.com/jackc/pgio/blob/master/LICENSE
pgpassfile	https://github.com/jackc/pgpassfile	https://github.com/jackc/pgpassfile/blob/master/LICENSE
pgproto3	https://github.com/jackc/pgproto3/v2	https://github.com/jackc/pgproto3/blob/master/LICENSE
pgtype	https://github.com/jackc/pgtype	https://github.com/jackc/pgtype/blob/master/LICENSE
pgx	https://github.com/jackc/pgx/v4	https://github.com/jackc/pgx/blob/v4.0.1/LICENSE

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Name of Project	Website	License URL
phonopy	https://github.com/phonopy/phono3py	https://github.com/phonopy/phono3py/blob/develop/LICENSE
pickleshare	https://github.com/pickleshare/pickleshare	https://github.com/pickleshare/pickleshare/blob/master/LICENSE
Pillow	https://python-pillow.org	https://github.com/python-pillow/Pillow/blob/main/LICENSE
Pint	https://pint.readthedocs.io/en/stable/	https://github.com/hgrecco/pint/blob/master/LICENSE
pip	https://pip.pypa.io/	https://github.com/pypa/pip/blob/main/LICENSE.txt
pip-licenses	https://github.com/raimon49/pip-licenses	https://github.com/raimon49/pip-licenses/blob/master/LICENSE
pixman	https://pixman.org	https://cgit.freedesktop.org/pixman/tree/COPYING
pkginfo	https://launchpad.net/pkginfo	https://bazaar.launchpad.net/~tseaver/pkginfo/trunk/view/head:/LICENSE.txt
pkgutil-resolve-name	https://github.com/graingert/pkgutil-resolve-name	https://github.com/graingert/pkgutil-resolve-name?tab=License-1-ov-file#readme
pkgutil_resolve_name	https://github.com/graingert/pkgutil-resolve-name	https://github.com/graingert/pkgutil-resolve-name?tab=License-1-ov-file#readme
platformdirs	https://github.com/platformdirs/platformdirs	https://github.com/platformdirs/platformdirs/blob/main/LICENSE

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Name of Project	Website	License URL
plotly	https://plotly.com/python/	https://github.com/plotly/plotly.py/blob/master/LICENSE.txt
plotly-orca	https://github.com/plotly/orca	https://github.com/plotly/orca/blob/master/LICENSE
plotly.js	https://github.com/plotly/plotly.js	https://github.com/plotly/plotly.js/raw/master/LICENSE
pluggy	https://pluggy.readthedocs.io/en/stable/index.html	https://github.com/pytest-dev/pluggy/blob/main/LICENSE
pooch	https://github.com/fatiando/pooch	https://github.com/fatiando/pooch/blob/main/LICENSE.txt
portalocker	https://github.com/WoLpH/portalocker	https://github.com/wolph/portalocker/blob/develop/LICENSE
pox	https://github.com/uqfoundation/pox	https://github.com/uqfoundation/pox/blob/master/LICENSE
ppft	https://github.com/uqfoundation/ppft	https://github.com/uqfoundation/ppft/blob/master/LICENSE
pq	https://github.com/lib/pq	https://github.com/lib/pq/blob/master/LICENSE.md
ProDy	http://www.csb.pitt.edu/ProDy	https://github.com/prody/ProDy/blob/master/LICENSE.rst
prometheus-client	https://github.com/prometheus/client_python	https://github.com/prometheus/client_python/blob/master/LICENSE
prometheus_client	https://github.com/prometheus/client_python	https://github.com/prometheus/client_python/blob/master/LICENSE
prompt-toolkit	https://python-prompt-toolkit.readthedocs.io/en/stable/	https://github.com/prompt-toolkit/python-prompt-toolkit/blob/master/LICENSE

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Name of Project	Website	License URL
prompt_toolkit	https://github.com/prompt-toolkit/python-prompt-toolki	https://github.com/prompt-toolkit/python-prompt-toolki tab=BSD-3-Clause-1-ov-f readme
propcache	https://github.com/aio-libs/propcache	https://github.com/aio-libs/propcache?tab=Apache-2.0-1-ov-file#readme
protobuf	https://google.golang.org/protobuf	https://github.com/protocolbuffers/protobuf-go/blob/master/LICENSE
psi4	https://psicode.org	https://github.com/psi4/psi4/blob/master/COPYING.LESSER
psutil	https://psutil.readthedocs.io/en/latest/	https://github.com/giampaolo/psutil/blob/master/LICENSE
psycopg2	https://psycopg.org/	https://github.com/psycopg/psycopg2/blob/master/LICENSE
PTable	https://github.com/kxxoling/PTable	https://github.com/kxxoling/PTable/blob/master/COPYING
pthread-stubs	https://xcb.freedesktop.org	https://github.com/freedesktop/xcb-pthread-stubs/blob/master/COPYING
ptyprocess	https://ptyprocess.readthedocs.io/en/latest/	https://github.com/pexpect/ptyprocess/blob/master/LICENSE
pure-eval	http://github.com/alexmojaki/pure_eval	http://github.com/alexmojaki/pure_eval/blob/master/LICENSE.txt
pure_eval	http://github.com/alexmojaki/pure_eval	https://github.com/alexmojaki/pure_eval?tab=MIT-1-ov-file#readme

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Name of Project	Website	License URL
py	https://py.readthedocs.io/en/latest/	https://github.com/pytest-dev/py/blob/master/LICENSE
py-cpuinfo	https://github.com/workhorsy/py-cpuinfo	https://github.com/workhorsy/py-cpuinfo/blob/master/LICENSE
pyasn1	https://github.com/etingof/pyasn1	https://github.com/etingof/pyasn1/blob/master/LICENSE.rst
pyasn1-modules	https://github.com/etingof/pyasn1-modules	https://github.com/etingof/pyasn1-modules/blob/master/LICENSE.txt
pyasn1_modules	https://pyasn1.readthedocs.io/en/latest/contents.html	https://github.com/pyasn1/pyasn1-modules?tab=BSD-2-Clause-1-ov-file#readme
pybind11	http://pybind11.readthedocs.io/en/stable/	https://github.com/pybind/pybind11/blob/master/LICENSE
pybind11-abi	https://github.com/pybind/pybind11	https://github.com/pybind/pybind11/blob/master/LICENSE
pybind11_global	http://pybind11.readthedocs.io/en/stable/	https://github.com/pybind/pybind11/blob/master/LICENSE
pycairo	https://pycairo.readthedocs.io/en/latest/index.html	https://github.com/pygobject/pycairo/blob/master/COPYING
pycosat	https://github.com/conda/pycosat	https://github.com/conda/pycosat/blob/main/LICENSE
pycparser	https://github.com/eliben/pycparser	https://github.com/eliben/pycparser/blob/master/LICENSE
pydantic	https://pydantic-docs.helpmanual.io	https://github.com/samuelcolvin/pydantic/blob/master/LICENSE

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Name of Project	Website	License URL
pydantic-core	https://github.com/pydantic/pydantic-core	https://github.com/pydantic/pydantic-core
pyedr	https://github.com/MDAnalysis/panedr	https://github.com/MDAnalysis/panedr/blob/master/LICENSE.txt
pyEMMA	http://github.com/markovmodel/PyEMMA	https://github.com/markovmodel/PyEMMA/blob/devel/LICENSE.txt
Pygments	https://pygments.org	https://github.com/pygments/pygments/blob/master/LICENSE
pygments	https://pygments.org/	https://github.com/pygments/pygments?tab=BSD-2-Clause-1-ov-file#readme
pygraphviz	https://pygraphviz.github.io	https://github.com/pygraphviz/pygraphviz/blob/main/LICENSE
pygtop	https://pygtop.readthedocs.io/en/latest/	https://github.com/samirelanduk/pygtop/blob/master/LICENSE
pyHanko	https://github.com/MatthiasValvekens/pyHanko	https://github.com/MatthiasValvekens/pyHanko/blob/master/LICENSE
pyhanko-certvalidator	https://github.com/MatthiasValvekens/certvalidator	https://github.com/MatthiasValvekens/certvalidator/blob/master/LICENSE
PyJWT	https://github.com/jpadilla/pyjwt	https://github.com/jpadilla/pyjwt/blob/master/LICENSE
pymbar	https://pymbar.org	https://github.com/choderalab/pymbar/blob/master/LICENSE
pynvml	https://github.com/gpuopenanalytics/pynvml	https://github.com/gpuopenanalytics/pynvml/blob/master/LICENSE.txt

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Name of Project	Website	License URL
pyOpenSSL	https://pyopenssl.org/	https://github.com/pyca/pyopenssl/blob/main/LICENSE
pyparsing	https://pyparsing-docs.readthedocs.io/en/latest/	https://github.com/pyparsing/pyparsing/blob/master/LICENSE
PyPDF3	https://github.com/sfneal/PyPDF3	https://github.com/sfneal/PyPDF3/blob/master/LICENSE
pyrsistent	http://github.com/tobgu/pyrsistent/	https://github.com/tobgu/pyrsistent/blob/master/LICENSE.mit
pysam	https://github.com/pysam-developers/pysam	https://github.com/pysam-developers/pysam/blob/master/COPYING
PySocks	https://github.com/Anorov/PySocks	https://github.com/Anorov/PySocks/blob/master/LICENSE
pytables	https://www.pytables.org	https://github.com/PyTables/PyTables/blob/master/LICENSE.txt
python	https://www.python.org/	https://docs.python.org/3/license.html
python-bidi	https://github.com/MeirKriheli/python-bidi	https://github.com/MeirKriheli/python-bidi/blob/master/COPYING
python-constraint	https://github.com/python-constraint/python-constraint	https://github.com/python-constraint/python-constraint/blob/master/LICENSE
python-dateutil	https://dateutil.readthedocs.io	https://github.com/dateutil/dateutil/blob/master/LICENSE
python-json-logger	http://github.com/madzak/python-json-logger	https://github.com/madzak/python-json-logger/blob/master/LICENSE

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Name of Project	Website	License URL
python-pptx	https://github.com/scanny/python-pptx	https://github.com/scanny/python-pptx/blob/master/LICENSE
python-ldap	https://www.python-ldap.org/	https://github.com/python-ldap/python-ldap/blob/python-ldap-3.4.0/LICENCE
python3-saml	https://github.com/onelogin/python3-saml	https://github.com/onelogin/python3-saml/blob/master/LICENSE
python_abi	https://github.com/conda-forge/python_abi-feedstock	https://github.com/conda-forge/python_abi-feedstock/blob/main/LICENSE.txt
pytorch-lightning	https://github.com/Lightning-AI/pytorch-lightning	https://github.com/Lightning-AI/pytorch-lightning/blob/master/LICENSE
pytz	https://pythonhosted.org/pytz	https://git.launchpad.net/pytz/tree/LICENSE.txt
pytz-deprecation-shim	https://github.com/pganssle/pytz-deprecation-shim	https://github.com/pganssle/pytz-deprecation-shim/blob/master/LICENSE
PyWavelets	https://github.com/PyWavelets/pywt	https://github.com/PyWavelets/pywt/blob/master/LICENSE
PyYAML	https://pyyaml.org/	https://github.com/yaml/pyyaml/blob/master/LICENSE
pyyml	No longer available	No longer available
pyzmq	https://pyzmq.readthedocs.io/en/latest/	https://github.com/zeromq/pyzmq/blob/main/COPYING.BSD
qcelemental	https://github.com/MolSSI/QCElemental	https://github.com/MolSSI/QCElemental/blob/master/LICENSE

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Name of Project	Website	License URL
qcengine	https://github.com/MolSSI/QCEngine	https://github.com/MolSSI/QCEngine/blob/master/LICENSE
qrcode	https://github.com/lincolnloop/python-qrcode	https://github.com/lincolnloop/python-qrcode/blob/main/LICENSE
ramda	https://github.com/ramda/ramda	https://github.com/ramda/ramda/raw/master/LICENSE.txt
rapidjson	https://rapidjson.org/	https://github.com/Tencent/rapidjson/blob/master/license.txt
rdkit	https://www.rdkit.org	https://github.com/rdkit/rdkit/blob/master/license.txt
re2	https://github.com/google/re2	https://github.com/google/re2/blob/main/LICENSE
readme-renderer	https://github.com/pypa/readme_renderer	https://github.com/pypa/readme_renderer/blob/main/LICENSE
redis-py	https://github.com/andymccurdy/redis-py	https://github.com/redis/redis-py/blob/master/LICENSE
referencing	https://github.com/python-jsonschema/referencing	https://github.com/python-jsonschema/referencing
regex	https://github.com/mrabarnett/mrab-regex	https://github.com/mrabarnett/mrab-regex/blob/hg/LICENSE.txt
reportlab	https://www.reportlab.com	https://www.reportlab.com/dev/docs/faq/#1.3
reproc	https://github.com/DaanDeMeyer/reproc	https://github.com/DaanDeMeyer/reproc/blob/main/LICENSE
reproc-cpp	https://github.com/DaanDeMeyer/reproc	https://github.com/DaanDeMeyer/reproc/blob/main/LICENSE

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Name of Project	Website	License URL
requests	https://requests.readthedocs.io	https://github.com/psf/requests/blob/main/LICENSE
requests-oauthlib	https://github.com/requests/requests-oauthlib	https://github.com/requests/requests-oauthlib/blob/master/LICENSE
requests-toolbelt	https://toolbelt.readthedocs.org	https://github.com/requests/toolbelt/blob/master/LICENSE
resumable	https://github.com/stevvooe/resumable	https://github.com/stevvooe/resumable/blob/master/LICENSE
retrying	https://github.com/rholder/retrying	https://github.com/rholder/retrying/blob/master/LICENSE
rfc3339-validator	https://github.com/naimetti/rfc3339-validator	https://github.com/naimetti/rfc3339-validator/blob/master/LICENSE
rfc3339_validator	https://github.com/naimetti/rfc3339-validator	https://github.com/naimetti/rfc3339-validator?tab=MIT-1-ov-file#readme
rfc3986	https://rfc3986.readthedocs.io/en/latest/	https://github.com/python-hyper/rfc3986/blob/main/LICENSE
rfc3986-validator	https://github.com/naimetti/rfc3986-validator	https://github.com/naimetti/rfc3986-validator/blob/master/LICENSE
rfc3987-syntax	https://github.com/willynilly/rfc3987-syntax	https://github.com/willynilly/rfc3987-syntax?tab=MIT-1-ov-file#readme
rich	https://github.com/Textualize/rich	https://github.com/Textualize/rich/blob/master/LICENSE

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Name of Project	Website	License URL
rich-argparse	https://github.com/hamdanal/rich-argparse	https://github.com/hamdanal/rich-argparse/blob/main/LICENSE
rlPyCairo	https://pypi.org/project/rlPyCairo/	https://hg.reportlab.com/hg-public/rlPyCairo/file/tip/rlPyCairo/LICENSE.txt
RocksDict	https://github.com/rocksdict/RocksDict	https://github.com/rocksdict/RocksDict?tab=MIT-1-ov-file#readme
roman-numerals	https://github.com/AA-Turner/roman-numerals	https://github.com/AA-Turner/roman-numerals?tab=License-1-ov-file#readme
roman-numerals-py	https://github.com/AA-Turner/roman-numerals	https://github.com/AA-Turner/roman-numerals?tab=License-1-ov-file#readme
rotary-embedding-torch	https://github.com/lucidrains/rotary-embedding-tor	https://github.com/lucidrains/rotary-embedding-tor blob/main/LICENSE
rpds-py	https://github.com/crate-py/rpds	https://github.com/crate-py/rpds
rpmpack	https://github.com/google/rpmpack	https://github.com/google/rpmpack/blob/master/LICENSE
rsa	https://stuvel.eu/rsa	https://github.com/sybrenstuvel/python-rsa/blob/main/LICENSE
ruamel-yaml	https://sourceforge.net/p/ruamel-yaml/code/ci/default/tree/	https://sourceforge.net/p/ruamel-yaml/code/ci/default/tree/LICENSE
ruamel.yaml.clib	https://sourceforge.net/p/ruamel-yaml-clib/code/ci/default/tree/	https://sourceforge.net/p/ruamel-yaml-clib/code/ci/default/tree/LICENSE

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Name of Project	Website	License URL
s3transfer	https://github.com/boto/s3transfer	https://github.com/boto/s3transfer/blob/develop/LICENSE.txt
sacrebleu	https://github.com/mjpost/sacrebleu	https://github.com/mjpost/sacrebleu/blob/master/LICENSE.txt
sapiens	https://github.com/Merck/Sapiens	https://github.com/Merck/Sapiens/blob/main/LICENSE
sasl	https://mellium.im/sasl	https://github.com/mellium/sasl/blob/main/LICENSE
scikit-gstat	https://mmaelicke.github.io/scikit-gstat/	https://github.com/mmaelicke/scikit-gstat/blob/main/LICENSE
scikit-image	https://scikit-image.org	https://scikit-image.org/docs/dev/license.html
scikit-learn	https://scikit-learn.org/stable/	https://github.com/scikit-learn/scikit-learn/blob/main/COPYING
scikit-learn-extra	https://github.com/scikit-learn-contrib/scikit-learn-extra	https://github.com/scikit-learn-contrib/scikit-learn-extra/blob/main/LICENSE
scikit-network	https://github.com/sknetwork-team/scikit-network	https://github.com/sknetwork-team/scikit-network?tab=License-1-ov-file#readme
scipy	https://scipy.org	https://github.com/scipy/scipy/blob/main/LICENSE.txt
seaborn	https://seaborn.pydata.org	https://github.com/mwaskom/seaborn/blob/master/LICENSE
seaborn-base	https://seaborn.pydata.org	https://github.com/mwaskom/seaborn/blob/master/LICENSE

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Name of Project	Website	License URL
semver	https://github.com/Masterminds/semver/v3	https://github.com/Masterminds/semver/blob/v3.0.3/LICENSE.txt
Send2Trash	https://github.com/arsenetar/send2trash	https://github.com/arsenetar/send2trash/blob/master/LICENSE
sentry-sdk	https://github.com/getsentry/sentry-python	https://github.com/getsentry/sentry-python/blob/master/LICENSE
setproctitle	https://github.com/dvarrazzo/py-setproctitle	https://github.com/dvarrazzo/py-setproctitle/blob/master/LICENSE
setuptools	https://github.com/pypa/setuptools	https://github.com/pypa/setuptools/blob/main/LICENSE
setuptools-scm	https://github.com/pypa/setuptools_scm/	https://github.com/pypa/setuptools_scm/blob/main/LICENSE
sh	https://github.com/amoffat/sh	https://github.com/amoffat/sh/blob/develop/LICENSE.txt
shellingham	https://github.com/sarugaku/shellingham	https://github.com/sarugaku/shellingham/blob/master/LICENSE
simdjson	https://github.com/simdjson/simdjson/tree/master	https://github.com/simdjson/simdjson/blob/master/LICENSE
simint	https://www.bennyp.org/research/simint/	https://github.com/simint-chem/simint-generator/blob/master/LICENSE
simplejson	https://github.com/simplejson/simplejson	https://github.com/simplejson/simplejson/blob/master/LICENSE.txt
six	https://github.com/benjaminp/six	https://github.com/benjaminp/six/blob/master/LICENSE

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Name of Project	Website	License URL
smirnoff99frosst	https://github.com/openforcefield/smirnoff99frosst	https://github.com/openforcefield/smirnoff99Frosst/blob/master/LICENSE
smmap	https://github.com/gitpython-developers/smmap	https://github.com/gitpython-developers/smmap/blob/master/LICENSE
snappy	https://github.com/google/snappy	https://github.com/google/snappy/blob/main/COPYING
sniffio	https://github.com/python-trio/sniffio	https://github.com/python-trio/sniffio/blob/master/LICENSE.MIT
snowballstemmer	https://github.com/snowballstem/snowball	https://github.com/snowballstem/snowball/blob/master/COPYING
soupsieve	https://github.com/facelessuser/soupsieve	https://github.com/facelessuser/soupsieve/blob/main/LICENSE.md
spdlog	https://github.com/gabime/spdlog	https://github.com/gabime/spdlog?tab=License-1-ov-file#readme
spglib	https://spglib.readthedocs.io/	https://github.com/spglib/spglib/blob/develop/COPYING
sphinx	https://github.com/sphinx-doc/sphinx	https://github.com/sphinx-doc/sphinx/blob/5.x/LICENSE
sphinxcontrib-applehelp	https://github.com/sphinx-doc/sphinxcontrib-applehe	https://github.com/sphinx-doc/sphinxcontrib-applehe blob/master/LICENSE
sphinxcontrib-devhelp	https://github.com/sphinx-doc/sphinxcontrib-devhelp	https://github.com/sphinx-doc/sphinxcontrib-devhelp blob/master/LICENSE
sphinxcontrib-htmlhelp	https://github.com/sphinx-doc/sphinxcontrib-htmlhel	https://github.com/sphinx-doc/sphinxcontrib-htmlhel blob/master/LICENSE

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Name of Project	Website	License URL
sphinxcontrib-jsmath	https://github.com/sphinx-doc/sphinxcontrib-jsmath	https://github.com/sphinx-doc/sphinxcontrib-jsmath/blob/master/LICENSE
sphinxcontrib-qthelp	https://github.com/sphinx-doc/sphinxcontrib-qthelp	https://github.com/sphinx-doc/sphinxcontrib-qthelp/blob/master/LICENSE
sphinxcontrib-serializinghtml	https://github.com/sphinx-doc/sphinxcontrib-serializ	https://github.com/sphinx-doc/sphinxcontrib-serializ blob/master/LICENSE
SQLAlchemy	https://www.sqlalchemy.org	https://docs.sqlalchemy.org/en/14/copyright.html
SQLAlchemy	https://www.sqlalchemy.org/	https://github.com/sqlalchemy/sqlalchemy?tab=MIT-1-ov-file#readme
sqlite	https://sqlite.org/index.html	https://sqlite.org/copyright.html
sqlparse	https://github.com/andialbrecht/sqlparse	https://github.com/andialbrecht/sqlparse/blob/master/LICENSE
stack-data	http://github.com/alexmojaki/stack_data	https://github.com/alexmojaki/stack_data/blob/master/LICENSE.txt
stack_data	http://github.com/alexmojaki/stack_data	https://github.com/alexmojaki/stack_data?tab=MIT-1-ov-file#readme
starfile	https://github.com/alisterburt/starfile	https://github.com/teamtomo/starfile/blob/main/LICENSE
statsmodels	https://github.com/statsmodels/statsmodels	https://github.com/statsmodels/statsmodels/blob/main/LICENSE.txt
structlog	https://www.structlog.org/	https://github.com/hynek/structlog/blob/main/LICENSE

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Name of Project	Website	License URL
streamlit	https://github.com/streamlit/streamlit	https://github.com/streamlit/streamlit/blob/develop/LICENSE
svglib	https://github.com/deeplook/svglib	https://github.com/deeplook/svglib/blob/master/LICENSE.txt
sympy	https://sympy.org	https://github.com/sympy/sympy/blob/master/LICENSE
tables	https://www.pytables.org/	https://github.com/PyTables/PyTables/blob/master/LICENSE.txt
tabulate	https://github.com/astanin/python-tabulate	https://github.com/astanin/python-tabulate/blob/master/LICENSE
tbb	https://github.com/oneapi-src/oneTBB	https://github.com/oneapi-src/oneTBB/blob/master/LICENSE.txt
tenacity	https://github.com/jd/tenacity	https://github.com/jd/tenacity/blob/master/LICENSE
tensorboard	https://github.com/tensorflow/tensorboard	https://github.com/tensorflow/tensorboard/blob/master/LICENSE
tensorboard-data-server	https://github.com/tensorflow/tensorboard	https://github.com/tensorflow/tensorboard/blob/master/LICENSE
tensorboard-plugin-wit	https://github.com/pair-code/what-if-tool	https://github.com/PAIR-code/what-if-tool/blob/master/LICENSE
tensorboardX	https://github.com/lanpa/tensorboardX	https://github.com/lanpa/tensorboardX/blob/master/LICENSE
tensorflow	https://github.com/tensorflow/tensorflow	https://github.com/tensorflow/tensorflow/blob/master/LICENSE

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Name of Project	Website	License URL
tensorflow-estimator	https://github.com/tensorflow/estimator	https://github.com/tensorflow/estimator/blob/master/LICENSE
tensorflow-io-gcs-filesystem	https://github.com/tensorflow/io	https://github.com/tensorflow/io/blob/master/LICENSE
tensorflow-probability	https://github.com/tensorflow/probability	https://github.com/tensorflow/probability/blob/main/LICENSE
termcolor	https://github.com/hugovk/termcolor	https://github.com/hugovk/termcolor/blob/main/COPYING.txt
terminado	https://github.com/jupyter/terminado	https://github.com/jupyter/terminado/blob/main/LICENSE
testpath	https://github.com/jupyter/testpath	https://github.com/jupyter/testpath/blob/master/LICENSE
textangular	https://github.com/fraywing/textAngular	https://github.com/fraywing/textAngular
texttable	https://github.com/foutaise/texttable/	https://github.com/foutaise/texttable/?tab=MIT-1-ov-file#readme
tf_keras	https://github.com/keras-team/keras-io	https://github.com/keras-team/keras-io/blob/master/LICENSE
tf_keras	https://github.com/keras-team/keras-io	https://github.com/keras-team/keras-io/blob/master/LICENSE
threadpoolctl	https://github.com/joblib/threadpoolctl	https://github.com/joblib/threadpoolctl/blob/master/LICENSE
three	https://github.com/mrdoob/three.js	https://github.com/mrdoob/three.js/raw/master/LICENSE

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Name of Project	Website	License URL
tiffile	https://github.com/cgohlke/tiffile/	https://github.com/cgohlke/tiffile/blob/master/LICENSE
tinycss2	https://github.com/Kozea/tinycss2/	https://github.com/Kozea/tinycss2/blob/master/LICENSE
tinyxml2	https://github.com/leethomason/tinyxml2	https://github.com/leethomason/tinyxml2/blob/master/LICENSE.txt
tk	https://www.tcl.tk/	https://www.tcl.tk/software/tcltk/license.html
toml	https://github.com/toml-lang/toml	https://github.com/toml-lang/toml/blob/main/LICENSE
tomli	https://github.com/hukkin/tomli	https://github.com/hukkin/tomli/blob/master/LICENSE
toolz	https://github.com/pytoolz/toolz	https://github.com/pytoolz/toolz/blob/master/LICENSE.txt
torch	https://pytorch.org/	https://pypi.org/project/torch/#license
torch-geometric	https://pyg.org/	https://github.com/pyg-team/pytorch_geometric?tab=MIT-1-ov-file#readme
torcheval	https://github.com/pytorch/torcheval	https://github.com/pytorch/torcheval?tab=License-1-ov-file#readme
torchmetrics	https://github.com/Lightning-AI/torchmetrics	https://github.com/Lightning-AI/torchmetrics?tab=Apache-2.0-1-ov-file#readme
tornado	https://www.tornadoweb.org	https://github.com/tornadoweb/tornado/blob/master/LICENSE

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Name of Project	Website	License URL		
tqdm	https://github.com/tqdm/tqdm	https://github.com/tqdm/tqdm/blob/master/LICENCE		
tracy	https://github.com/gear-genomics/tracy	https://github.com/gear-genomics/tracy/blob/main/LICENSE		
traitlets	https://github.com/ipython/traitlets	https://github.com/ipython/traitlets/blob/main/COPYING.md		
triton	https://github.com/openai/triton/	https://github.com/openai/triton/blob/main/LICENSE		
truststore	https://github.com/sethmlarson/trus	https://github.com/sethmlarson/truststore/blob/main/LICENSE		
truststore	https://github.com/sethmlarson/truststore	https://github.com/sethmlarson/truststore/blob/main/LICENSEtruststore	https://github.com/sethmlarson/truststore	https://github.com/sethmlarson/truststore/blob/main/LICENSE
ts-jest	https://github.com/kulshekhar/ts-jest	https://github.com/kulshekhar/ts-jest/raw/master/LICENSE.md		
ts-loader	https://github.com/TypeStrong/ts-loader	https://github.com/TypeStrong/ts-loader/raw/master/LICENSE		
twine	https://github.com/pypa/twine	https://github.com/pypa/twine/blob/main/LICENSE		
twinj uuid	https://github.com/twinj/uuid	https://github.com/twinj/uuid/blob/master/LICENSE		
types	https://github.com/babel/babel	https://github.com/babel/babel/raw/master/LICENSE		
types-python-dateutil	https://github.com/python/typeshed	https://github.com/python/typeshed?tab=License-1-ov-file#readme		
types-requests	https://pypi.org/project/types-requests/	https://github.com/python/typeshed/blob/main/LICENSE		

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Name of Project	Website	License URL
typescript	https://github.com/Microsoft/TypeScript	https://github.com/Microsoft/TypeScript/raw/master/LICENSE.txt
typing-inspection	https://github.com/pydantic/typing-inspection	https://github.com/pydantic/typing-inspection?tab=MIT-1-ov-file#readme
typing-utils	https://github.com/bojiang/typing_utils	https://github.com/bojiang/typing_utils?tab=Apache-2.0-1-ov-file#readme
typing_extensions	https://github.com/python/typing	https://github.com/python/typing/blob/master/LICENSE
typing_utils	https://github.com/bojiang/typing_utils	https://github.com/bojiang/typing_utils?tab=Apache-2.0-1-ov-file#readme
tzdata	https://github.com/python/tzdata	https://github.com/python/tzdata/blob/master/LICENSE
tzlocal	https://github.com/regebro/tzlocal	https://github.com/regebro/tzlocal/blob/master/LICENSE.txt
umf	https://github.com/oneapi-src/unified-memory-fram	https://github.com/oneapi-src/unified-memory-fram tab=License-1-ov-file#readme
umi-tools	https://github.com/CGATOxford/UMI-tools	https://github.com/CGATOxford/UMI-tools/blob/master/LICENSE
unicodedata2	https://github.com/fonttools/unicodedata2	https://github.com/fonttools/unicodedata2/blob/master/LICENSE
uri-template	https://gitlab.linss.com/open-source/python/uri-template	https://gitlab.linss.com/open-source/python/uri-template/-/blob/main/LICENSE
uritools	https://github.com/tkem/uritools/	https://github.com/tkem/uritools/blob/master/LICENSE

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Name of Project	Website	License URL		
urllib3	https://urllib3.readthedocs.io/	https://github.com/urllib3/urllib3/blob/main/LICENSE.txt		
vine	https://github.com/celery/vine	https://github.com/celery/vine/blob/master/LICENSE		
vue	https://github.com/vuejs/vue	https://github.com/vuejs/vue/raw/master/LICENSE		
wadler_lindig	https://github.com/patrick-kidger/wadler_lindig	https://github.com/patrick-kidger/wadler_lindig?tab=Apache-2.0-1-ov-file#readme		
wadler_lindig	https://github.com/patrick-kidger/wadler_lindig	https://github.com/patrick-kidger/wadler_lindig?tab=Apache-2.0-1-ov-file#readmewcwidth	https://github.com/jquast/wcwidth	https://github.com/jquast/wcwidth/blob/master/LICENSE
wandb	https://github.com/wandb/wandb	https://github.com/wandb/wandb/blob/main/LICENSE		
webcolors	https://github.com/ubernostrum/webcolors	https://github.com/ubernostrum/webcolors?tab=BSD-3-Clause-1-ov-file#readme		
webencodings	https://github.com/gsnedders/python-webencodings	https://github.com/gsnedders/python-webencodings/blob/master/LICENSE		
websocket-client	https://github.com/websocket-client/websocket-client.git	https://github.com/websocket-client/websocket-client/blob/master/LICENSE		
Werkzeug	https://palletsprojects.com/p/werkzeug/	https://werkzeug.palletsprojects.com/en/2.1.x/license/		
westpa	http://github.com/westpa/westpa	https://github.com/westpa/westpa/blob/westpa2/LICENSE		
wheel	https://github.com/pypa/wheel	https://github.com/pypa/wheel/blob/main/LICENSE.txt		

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Name of Project	Website	License URL
widgetsnbextension	https://github.com/jupyter-widgets/ipywidgets#readme	https://github.com/jupyter-widgets/ipywidgets/blob/main/LICENSE
wrapt	https://github.com/GrahamDumpleton/wrapt	https://github.com/GrahamDumpleton/wrapt/blob/develop/LICENSE
wsutil	https://github.com/yhat/wsutil	https://github.com/yhat/wsutil/blob/master/LICENSE
x/lint	https://golang.org/x/lint	https://github.com/golang/lint/blob/master/LICENSE
x/mod	https://golang.org/x/mod/semver	https://cs.opensource.google/go/x/mod/+/master:LICENSE
x/net	https://golang.org/x/net	https://cs.opensource.google/go/x/net/+/master:LICENSE
x/oauth2	https://golang.org/x/oauth2	https://cs.opensource.google/go/x/oauth2/+/master:LICENSE
x/sys	https://golang.org/x/sys	https://cs.opensource.google/go/x/sys/+/master:LICENSE
x/text	https://golang.org/x/text	https://cs.opensource.google/go/x/text/+/master:LICENSE
x/tools	https://golang.org/x/tools	https://cs.opensource.google/go/x/tools/+/master:LICENSE
x/xerrors	https://golang.org/x/xerrors	https://cs.opensource.google/go/x/xerrors/+/master:LICENSE
xgboost	https://github.com/dmlc/xgboost	https://github.com/dmlc/xgboost/blob/master/LICENSE
xhtml2pdf	http://github.com/xhtml2pdf/xhtml2pdf	https://github.com/xhtml2pdf/xhtml2pdf/blob/master/LICENSE.txt

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Table 1 – continued from previous page

Name of Project	Website	License URL
xlrd	https://github.com/python-excel/xlrd	https://github.com/python-excel/xlrd/blob/master/LICENSE
xlsxwriter	https://github.com/jmcnamara/XlsxWriter	https://github.com/jmcnamara/XlsxWriter/blob/main/LICENSE.txt
xmlsec	https://github.com/mehcode/python-xmlsec	https://github.com/mehcode/python-xmlsec/blob/master/LICENSE
xmltodict	https://github.com/martinblech/xmltodict	https://github.com/martinblech/xmltodict/blob/master/LICENSE
xorg-kbproto	https://gitlab.freedesktop.org/xorg/proto/kbproto	https://gitlab.freedesktop.org/xorg/proto/kbproto/-/blob/master/COPYING
xorg-libice	https://gitlab.freedesktop.org/xorg/lib/libice	https://gitlab.freedesktop.org/xorg/lib/libice/-/blob/master/COPYING
xorg-libsm	https://gitlab.freedesktop.org/xorg/lib/libsm	https://gitlab.freedesktop.org/xorg/lib/libsm/-/blob/master/COPYING
xorg-libx11	https://gitlab.freedesktop.org/xorg/lib/libx11	https://gitlab.freedesktop.org/xorg/lib/libx11/-/blob/master/COPYING
xorg-libxau	https://gitlab.freedesktop.org/xorg/lib/libxau	https://gitlab.freedesktop.org/xorg/lib/libxau/-/blob/master/COPYING
xorg-libxdmcp	https://gitlab.freedesktop.org/xorg/lib/libxdmcp	https://gitlab.freedesktop.org/xorg/lib/libxdmcp/-/blob/master/COPYING

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Table 1 – continued from previous page

Name of Project	Website	License URL
xorg-libxext	https://gitlab.freedesktop.org/xorg/lib/libxext	https://gitlab.freedesktop.org/xorg/lib/libxext/-/blob/master/COPYING
xorg-libxrender	https://gitlab.freedesktop.org/xorg/lib/libxrender	https://gitlab.freedesktop.org/xorg/lib/libxrender/-/blob/master/COPYING
xorg-libxt	https://gitlab.freedesktop.org/xorg/lib/libxt	https://gitlab.freedesktop.org/xorg/lib/libxt/-/blob/master/COPYING
xorg-renderproto	https://gitlab.freedesktop.org/xorg/proto/renderproto	https://gitlab.freedesktop.org/xorg/proto/renderproto/-/blob/master/COPYING
xorg-xextproto	https://gitlab.freedesktop.org/xorg/proto/xextproto	https://gitlab.freedesktop.org/xorg/proto/xextproto/-/blob/master/COPYING
xorg-xproto	https://gitlab.freedesktop.org/xorg/proto/xproto	https://gitlab.freedesktop.org/xorg/proto/xproto/-/blob/master/COPYING
xxhash	https://github.com/cespare/xxhash/v2	https://github.com/cespare/xxhash/blob/main/LICENSE.txt
xz	https://github.com/ulikunitz/xz	https://github.com/ulikunitz/xz/blob/master/LICENSE
yaml	https://pyyaml.org/	https://github.com/yaml/pyyaml/blob/master/LICENSE
yaml-cpp	https://github.com/jbeder/yaml-cpp	https://github.com/jbeder/yaml-cpp/blob/master/LICENSE
yaml.v2	https://gopkg.in/yaml.v2	https://github.com/go-yaml/yaml/blob/v2.4.0/LICENSE
yaml.v3	https://gopkg.in/yaml.v3	https://github.com/go-yaml/yaml/blob/v3/LICENSE

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Table 1 – continued from previous page

Name of Project	Website	License URL
yarl	https://github.com/aio-libs/yarl/	https://github.com/aio-libs/yarl/blob/master/LICENSE
yaspin	https://github.com/pavdmyt/yaspin	https://github.com/pavdmyt/yaspin/blob/master/LICENSE
yfiles	https://www.yworks.com/products/yfiles	commercial license
yml	https://pypi.org/project/yml/	N/A
zap	https://go.uber.org/zap	https://github.com/uber-go/zap/blob/master/LICENSE.txt
zipp	https://github.com/jaraco/zipp	https://github.com/jaraco/zipp/blob/main/LICENSE
zlib	https://zlib.net/	https://zlib.net/zlib_license.html
zstandard	https://github.com/indygreg/python-zstandard	https://github.com/indygreg/python-zstandard/blob/main/LICENSE
zstd	https://facebook.github.io/zstd/	https://github.com/facebook/zstd/blob/dev/LICENSE
click-option-group	https://github.com/click-contrib/click-option-group	https://github.com/click-contrib/click-option-group/blob/master/LICENSE

16.1 GCC

On the Linux platform, The OpenEye toolkits are linked with the GCC libraries using an eligible compilation process under the terms of the GCC RUNTIME LIBRARY EXCEPTION (see below).

The OpenEye toolkits are NOT open source software and are NOT governed by GPL or other open source licenses. Your right to use the toolkits are governed by the OpenEye license which is binding to You.

For certain Linux distributions, GCC library components are included as object files. Your rights to use GCC library components (libstdc++, libgcc, and libgomp) included with these distributions are governed by the GPLv3 license as follows:

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- GCC is distributed in the hope that it will be useful, but WITHOUT ANY WARRANTY; without even the

implied warranty of MERCHANTABILITY or FITNESS FOR A PARTICULAR PURPOSE. See the GNU General Public License for more details.

You should have received a copy of the GNU General Public License along with GCC (see below). If not, see Licenses GNU Project .

Per GPLv3, section 6d, the source for GCC is available for download from the following location: GNU. The GCC library components included here are from version gcc-4.9.3 and are built using the standard instructions at Installing GCC.

16.1.1 GCC RUNTIME LIBRARY EXCEPTION

```
Version 3.1, 31 March 2009

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Everyone is permitted to copy and distribute verbatim copies of this license document,␣
↪but changing it is not allowed.

This GCC Runtime Library Exception ("Exception") is an additional permission under␣
↪section 7 of the GNU General Public License,
version 3 ("GPLv3"). It applies to a given file (the "Runtime Library") that bears a␣
↪notice placed by the copyright holder
of the file stating that the file is governed by GPLv3 along with this Exception.

When you use GCC to compile a program, GCC may combine portions of certain GCC header␣
↪files and runtime libraries with
the compiled program. The purpose of this Exception is to allow compilation of non-GPL␣
↪(including proprietary) programs
to use, in this way, the header files and runtime libraries covered by this Exception.

0. Definitions.

A file is an "Independent Module" if it either requires the Runtime Library for␣
↪execution after a Compilation Process,
or makes use of an interface provided by the Runtime Library, but is not otherwise based␣
↪on the Runtime Library.

"GCC" means a version of the GNU Compiler Collection, with or without modifications,␣
↪governed by version 3 (or a specified
later version) of the GNU General Public License (GPL) with the option of using any␣
↪subsequent versions published by the FSF.

"GPL-compatible Software" is software whose conditions of propagation, modification and␣
↪use would permit combination with
GCC in accord with the license of GCC.

"Target Code" refers to output from any compiler for a real or virtual target processor␣
↪architecture, in executable
form or suitable for input to an assembler, loader, linker and/or execution phase.␣
↪Notwithstanding that, Target Code
does not include data in any format that is used as a compiler intermediate␣
↪representation, or used for producing a
compiler intermediate representation.
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The "Compilation Process" transforms code entirely represented in non-intermediate␣
↪languages designed for human-written
code, and/or in Java Virtual Machine byte code, into Target Code. Thus, for example, use␣
↪of source code generators and
preprocessors need not be considered part of the Compilation Process, since the␣
↪Compilation Process can be understood
as starting with the output of the generators or preprocessors.

A Compilation Process is "Eligible" if it is done using GCC, alone or with other GPL-
↪compatible software, or if it is
done without using any work based on GCC. For example, using non-GPL-compatible Software␣
↪to optimize any GCC intermediate
representations would not qualify as an Eligible Compilation Process.

1. Grant of Additional Permission.

You have permission to propagate a work of Target Code formed by combining the Runtime␣
↪Library with Independent Modules,
even if such propagation would otherwise violate the terms of GPLv3, provided that all␣
↪Target Code was generated by
Eligible Compilation Processes. You may then convey such a combination under terms of␣
↪your choice, consistent with the
licensing of the Independent Modules.

2. No Weakening of GCC Copyleft.

The availability of this Exception does not imply any general presumption that third-
↪party software is unaffected by
the copyleft requirements of the license of GCC.
```

See also

- http://www.gnu.org/licenses/gcc-exception.html

16.1.2 GNU GENERAL PUBLIC LICENSE

```
                    GNU GENERAL PUBLIC LICENSE
                       Version 3, 29 June 2007

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                            Preamble

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 software and other kinds of works.

   The licenses for most software and other practical works are designed
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want it, that you can change the software or use pieces of it in new
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  To protect your rights, we need to prevent others from denying you
these rights or asking you to surrender the rights.  Therefore, you have
certain responsibilities if you distribute copies of the software, or if
you modify it: responsibilities to respect the freedom of others.

  For example, if you distribute copies of such a program, whether
gratis or for a fee, you must pass on to the recipients the same
freedoms that you received.  You must make sure that they, too, receive
or can get the source code.  And you must show them these terms so they
know their rights.

  Developers that use the GNU GPL protect your rights with two steps:
(1) assert copyright on the software, and (2) offer you this License
giving you legal permission to copy, distribute and/or modify it.

  For the developers' and authors' protection, the GPL clearly explains
that there is no warranty for this free software.  For both users' and
authors' sake, the GPL requires that modified versions be marked as
changed, so that their problems will not be attributed erroneously to
authors of previous versions.

  Some devices are designed to deny users access to install or run
modified versions of the software inside them, although the manufacturer
can do so.  This is fundamentally incompatible with the aim of
protecting users' freedom to change the software.  The systematic
pattern of such abuse occurs in the area of products for individuals to
use, which is precisely where it is most unacceptable.  Therefore, we
have designed this version of the GPL to prohibit the practice for those
products.  If such problems arise substantially in other domains, we
stand ready to extend this provision to those domains in future versions
of the GPL, as needed to protect the freedom of users.

  Finally, every program is threatened constantly by software patents.
States should not allow patents to restrict development and use of
software on general-purpose computers, but in those that do, we wish to
avoid the special danger that patents applied to a free program could
make it effectively proprietary.  To prevent this, the GPL assures that
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patents cannot be used to render the program non-free.

  The precise terms and conditions for copying, distribution and
modification follow.

                    TERMS AND CONDITIONS

  0. Definitions.

  "This License" refers to version 3 of the GNU General Public License.

  "Copyright" also means copyright-like laws that apply to other kinds of
works, such as semiconductor masks.

  "The Program" refers to any copyrightable work licensed under this
License.  Each licensee is addressed as "you".  "Licensees" and
"recipients" may be individuals or organizations.

  To "modify" a work means to copy from or adapt all or part of the work
in a fashion requiring copyright permission, other than the making of an
exact copy.  The resulting work is called a "modified version" of the
earlier work or a work "based on" the earlier work.

  A "covered work" means either the unmodified Program or a work based
on the Program.

  To "propagate" a work means to do anything with it that, without
permission, would make you directly or secondarily liable for
infringement under applicable copyright law, except executing it on a
computer or modifying a private copy.  Propagation includes copying,
distribution (with or without modification), making available to the
public, and in some countries other activities as well.

  To "convey" a work means any kind of propagation that enables other
parties to make or receive copies.  Mere interaction with a user through
a computer network, with no transfer of a copy, is not conveying.

  An interactive user interface displays "Appropriate Legal Notices"
to the extent that it includes a convenient and prominently visible
feature that (1) displays an appropriate copyright notice, and (2)
tells the user that there is no warranty for the work (except to the
extent that warranties are provided), that licensees may convey the
work under this License, and how to view a copy of this License.  If
the interface presents a list of user commands or options, such as a
menu, a prominent item in the list meets this criterion.

  1. Source Code.

  The "source code" for a work means the preferred form of the work
for making modifications to it.  "Object code" means any non-source
form of a work.
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  A "Standard Interface" means an interface that either is an official
standard defined by a recognized standards body, or, in the case of
interfaces specified for a particular programming language, one that
is widely used among developers working in that language.

  The "System Libraries" of an executable work include anything, other
than the work as a whole, that (a) is included in the normal form of
packaging a Major Component, but which is not part of that Major
Component, and (b) serves only to enable use of the work with that
Major Component, or to implement a Standard Interface for which an
implementation is available to the public in source code form.  A
"Major Component", in this context, means a major essential component
(kernel, window system, and so on) of the specific operating system
(if any) on which the executable work runs, or a compiler used to
produce the work, or an object code interpreter used to run it.

  The "Corresponding Source" for a work in object code form means all
the source code needed to generate, install, and (for an executable
work) run the object code and to modify the work, including scripts to
control those activities.  However, it does not include the work's
System Libraries, or general-purpose tools or generally available free
programs which are used unmodified in performing those activities but
which are not part of the work.  For example, Corresponding Source
includes interface definition files associated with source files for
the work, and the source code for shared libraries and dynamically
linked subprograms that the work is specifically designed to require,
such as by intimate data communication or control flow between those
subprograms and other parts of the work.

  The Corresponding Source need not include anything that users
can regenerate automatically from other parts of the Corresponding
Source.

  The Corresponding Source for a work in source code form is that
same work.

  2. Basic Permissions.

  All rights granted under this License are granted for the term of
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for you must do so exclusively on your behalf, under your direction
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your copyrighted material outside their relationship with you.

  Conveying under any other circumstances is permitted solely under
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  You may convey verbatim copies of the Program's source code as you
receive it, in any medium, provided that you conspicuously and
appropriately publish on each copy an appropriate copyright notice;
keep intact all notices stating that this License and any
non-permissive terms added in accord with section 7 apply to the code;
keep intact all notices of the absence of any warranty; and give all
recipients a copy of this License along with the Program.


  You may charge any price or no price for each copy that you convey,
and you may offer support or warranty protection for a fee.

  5. Conveying Modified Source Versions.

  You may convey a work based on the Program, or the modifications to
produce it from the Program, in the form of source code under the
terms of section 4, provided that you also meet all of these conditions:

   a) The work must carry prominent notices stating that you modified
   it, and giving a relevant date.

   b) The work must carry prominent notices stating that it is
   released under this License and any conditions added under section
   7.  This requirement modifies the requirement in section 4 to
   "keep intact all notices".
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    c) You must license the entire work, as a whole, under this
    License to anyone who comes into possession of a copy.  This
    License will therefore apply, along with any applicable section 7
    additional terms, to the whole of the work, and all its parts,
    regardless of how they are packaged.  This License gives no
    permission to license the work in any other way, but it does not
    invalidate such permission if you have separately received it.

    d) If the work has interactive user interfaces, each must display
    Appropriate Legal Notices; however, if the Program has interactive
    interfaces that do not display Appropriate Legal Notices, your
    work need not make them do so.

  A compilation of a covered work with other separate and independent
works, which are not by their nature extensions of the covered work,
and which are not combined with it such as to form a larger program,
in or on a volume of a storage or distribution medium, is called an
"aggregate" if the compilation and its resulting copyright are not
used to limit the access or legal rights of the compilation's users
beyond what the individual works permit.  Inclusion of a covered work
in an aggregate does not cause this License to apply to the other
parts of the aggregate.

  6. Conveying Non-Source Forms.

  You may convey a covered work in object code form under the terms
of sections 4 and 5, provided that you also convey the
machine-readable Corresponding Source under the terms of this License,
in one of these ways:

  a) Convey the object code in, or embodied in, a physical product
  (including a physical distribution medium), accompanied by the
  Corresponding Source fixed on a durable physical medium
  customarily used for software interchange.

  b) Convey the object code in, or embodied in, a physical product
  (including a physical distribution medium), accompanied by a
  written offer, valid for at least three years and valid for as
  long as you offer spare parts or customer support for that product
  model, to give anyone who possesses the object code either (1) a
  copy of the Corresponding Source for all the software in the
  product that is covered by this License, on a durable physical
  medium customarily used for software interchange, for a price no
  more than your reasonable cost of physically performing this
  conveying of source, or (2) access to copy the
  Corresponding Source from a network server at no charge.

  c) Convey individual copies of the object code with a copy of the
  written offer to provide the Corresponding Source.  This
  alternative is allowed only occasionally and noncommercially, and
  only if you received the object code with such an offer, in accord
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   with subsection 6b.

   d) Convey the object code by offering access from a designated
   place (gratis or for a charge), and offer equivalent access to the
   Corresponding Source in the same way through the same place at no
   further charge.  You need not require recipients to copy the
   Corresponding Source along with the object code.  If the place to
   copy the object code is a network server, the Corresponding Source
   may be on a different server (operated by you or a third party)
   that supports equivalent copying facilities, provided you maintain
   clear directions next to the object code saying where to find the
   Corresponding Source.  Regardless of what server hosts the
   Corresponding Source, you remain obligated to ensure that it is
   available for as long as needed to satisfy these requirements.

   e) Convey the object code using peer-to-peer transmission, provided
   you inform other peers where the object code and Corresponding
   Source of the work are being offered to the general public at no
   charge under subsection 6d.

  A separable portion of the object code, whose source code is excluded
from the Corresponding Source as a System Library, need not be
included in conveying the object code work.

  A "User Product" is either (1) a "consumer product", which means any
tangible personal property which is normally used for personal, family,
or household purposes, or (2) anything designed or sold for incorporation
into a dwelling.  In determining whether a product is a consumer product,
doubtful cases shall be resolved in favor of coverage.  For a particular
product received by a particular user, "normally used" refers to a
typical or common use of that class of product, regardless of the status
of the particular user or of the way in which the particular user
actually uses, or expects or is expected to use, the product.  A product
is a consumer product regardless of whether the product has substantial
commercial, industrial or non-consumer uses, unless such uses represent
the only significant mode of use of the product.

  "Installation Information" for a User Product means any methods,
procedures, authorization keys, or other information required to install
and execute modified versions of a covered work in that User Product from
a modified version of its Corresponding Source.  The information must
suffice to ensure that the continued functioning of the modified object
code is in no case prevented or interfered with solely because
modification has been made.

  If you convey an object code work under this section in, or with, or
specifically for use in, a User Product, and the conveying occurs as
part of a transaction in which the right of possession and use of the
User Product is transferred to the recipient in perpetuity or for a
fixed term (regardless of how the transaction is characterized), the
Corresponding Source conveyed under this section must be accompanied
by the Installation Information.  But this requirement does not apply
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if neither you nor any third party retains the ability to install
modified object code on the User Product (for example, the work has
been installed in ROM).

  The requirement to provide Installation Information does not include a
requirement to continue to provide support service, warranty, or updates
for a work that has been modified or installed by the recipient, or for
the User Product in which it has been modified or installed.  Access to a
network may be denied when the modification itself materially and
adversely affects the operation of the network or violates the rules and
protocols for communication across the network.

  Corresponding Source conveyed, and Installation Information provided,
in accord with this section must be in a format that is publicly
documented (and with an implementation available to the public in
source code form), and must require no special password or key for
unpacking, reading or copying.

  7. Additional Terms.

  "Additional permissions" are terms that supplement the terms of this
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be treated as though they were included in this License, to the extent
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    reasonable ways as different from the original version; or

    d) Limiting the use for publicity purposes of names of licensors or
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must place, in the relevant source files, a statement of the
additional terms that apply to those files, or a notice indicating
where to find the applicable terms.

  Additional terms, permissive or non-permissive, may be stated in the
form of a separately written license, or stated as exceptions;
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