

OpenEye
SCIENTIFIC

SZYBKI

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CHAPTER

ONE

OVERVIEW

SZYBKI consists of four applications that carry out force field calculations on small molecule ligands or protein-ligand complexes with small molecule ligands. The main program, **SZYBKI**, is a general purpose program with a wide spectrum of force field functionalities. Input for **SZYBKI** is all-atom molecular structures for the ligands (and, if desired, a protein) with plausible 3-dimensional atomic coordinates. The other program, **Freeform**, calculates some thermodynamic properties for small molecules that are useful for drug discovery. Input for **Freeform** is a file of molecular structures for the ligands in a variety of formats ranging from SMILES strings to all-atom multiconformer formats. The output from both programs is all-atom molecular structures with associated information in the log output on the details of the calculations.

> **Note**
>
> Units of energy in various **SZYBKI** outputs are in kcal/mol.

CHAPTER

TWO

APPLICATIONS

The **SZYBKI** distribution comprises two applications:

SZYBKI

- Performs force field energy evaluations or geometry optimizations
- Operates on ligands alone or ligands posed in a protein active site
- Can include the effects of solvation within two continuum dielectric approximations
- Has multiprocessor capability using MPI

Freeform

- Calculates important minima in the unbound aqueous ensemble of a ligand
- Provides the free energy of going from an ensemble of solution phase conformers to a single, bioactive conformation
- Calculates the hydration free energy of unbound ligands
- Calculates the strain free energy of any conformation of a ligand

As input, **SZYBKI** and **Freeform** will often take ligand conformer databases generated by **OMEGA**. For protein-ligand calculations, output from **OEDocking** is also often used as input for **SZYBKI** and **Freeform**. The output from these two programs is often directly actionable, or it can be used as input for further physics-based modeling such as **SZMAP**.

CHAPTER

THREE

UTILITY PROGRAMS

The following utility programs are also included in this distribution:

- *OptLigandInDU*: Optimizes a ligand in a rigid protein active site, making it suitable for large scale screening.
- *OptimizeDU*: Optimizes a protein-ligand complex in a design unit, allowing the protein to be partially flexible, making it suitable for lead optimization.

CHAPTER

FOUR

SZYBKI

4.1 Overview

SZYBKI is a general purpose program with a wide spectrum of force field functionalities including, but not limited to, ligand, protein, and protein-ligand complex optimization in gas and solvent phases.

4.2 Example Commands

This section has several examples of typical **SZYBKI** command line executions.

4.2.1 Protein Preparation

X-ray protein structures rarely contain all hydrogen atoms coordinates. It is therefore necessary to prepare the protein structure before any protein-bound ligand calculations are done.

```
prompt> szybki -optGeometry Honly -prefix ex1 -neglect_frozen protein.pdb proteinH.mol2
```

In this command, the input protein file `protein.pdb` is assumed to contain all heavy atoms. Option *-optGeometry* followed by the string `Honly` fixes all heavy atoms at their positions given in the input file. For larger proteins, it is recommended to increase the total number of optimizer iterations beyond the default value of 1000 using the option *-max_iter*. It might be particularly important if a tight convergence of 1e-6 or smaller is required (see *-grad_conv*). The output protein file is `proteinH.mol2`. Note: All ionizable residues are assumed to be in their standard ionization states. If other than standard ionization states are needed, the input file has to be edited accordingly before the **SZYBKI** run is done.

4.2.2 Ligand Optimization in Solution

The equilibrium geometry of a molecule in solution is sometimes drastically different than in vacuum. This is because of solvent forces. The most efficient way to optimize a large set of ligands in solution is the usage of the *-sheffield* option.

```
prompt> szybki -sheffield -am1bcc -prefix ex2 ligands.sdf ligands_optimized.sdf
```

In the run above, a set of molecules from the input file `ligands.sdf` is optimized with the MMFF94 force field in solution. AM1BCC charges are optionally used for the Sheffield solvation model. Skipping the *-am1bcc* would result in the usage of MMFF94 atomic charges. Optimized structures are written to the `ligands_optimized.sdf` file. One can also optimize the ligand in solution using a physically more rigorous model by solving the Poisson-Boltzmann equation at every step. The command line below is equivalent to using the widely known PBSA model:

```
prompt> szybki -solvent` ``PB`` -solventCA 0.005 -prefix ex3 ligands.sdf ligands_
↪optimizedPB.sdf
```

4.2.3 Optimization with Fixed Atoms

This example illustrates the use of the option *-fix_file*.

```
prompt> szybki -fix_file f.txt -prefix ex4 mymolecule.mol2 molecule_opt.sdf
```

Text file `f.txt` contains molecules names followed by atom numbers in the (0,1…N-1) numbering convention. For example, the `f.txt` file contains the following six lines:

Molecule1
0
15
Molecule2
5
9

This informs **SZYBKI** that atoms 0 and 15 for molecule `Molecule1` and atoms 5 and 21 for molecule `Molecule2` should be fixed during optimization. This flag is useful when the user wants to fix atoms which are not directly bonded; for example, they belong to different functional groups in the optimized molecule. In the case a common substructure has to be fixed, an option *-fix_smarts* is more convenient to use:

```
prompt> szybki -fix_smarts fix_smarts.txt -prefix ex4a mymolecule.mol2 molecule_opt1.sdf
```

where file `fix_smarts.txt` contains a single line with the SMARTS pattern `c1ccccc1` that defines the substructure to be fixed.

4.2.4 Ligand Entropy Calculation in Solution

Assuming that the molecule conformations are given in the `molecule.oeb` file, the command line execution:

```
prompt> szybki -entropy AN -sheffield -prefix ex8  molecule.oeb
```

will result in the standard molar entropy estimation of the input molecule in solution. The meaning of the parameter value `AN` is explained in the description of the option *-entropy*. Option *-sheffield* informs **SZYBKI** that the calculation will be done in solution with the use of the Sheffield Solvation Model. The entropy results will be written in the `ex8.log` file. If the input file `molecule.oeb` does not contain the complete ensemble of conformations, the resultant entropy value may not be accurate. We recommend therefore that the input conformations are generated with the OpenEye tool **OMEGA**, with the `omega -rms` option set at 0.1 value, and `omega -maxconfs` set to at least 1000.

4.2.5 Protein-bound Ligand Entropy Calculation

Run:

```
prompt> szybki -p protein.mol2 -entropy AN -prefix ex9 ligand.mol2
```

will generate the estimation of ligand entropy in the active site of the protein. Input file `ligand.mol2` might be a docked structure or preferentially the X-ray structure.

4.2.6 Binding Entropy Calculation

A workflow for estimating binding entropy is shown in the figure below.

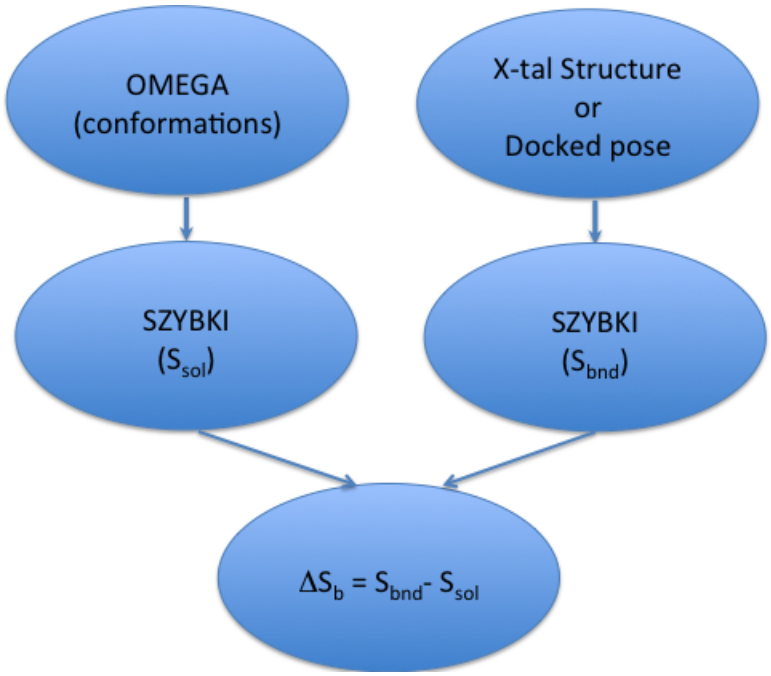


Fig. 1: **Figure 1.** A basic workflow for binding entropy estimation.

As Figure 1 shows, estimating binding entropy, ΔS_b, requires two separate **SZYBKI** runs: one for the estimation of ligand entropy in solution (S_{sol}) and another one to calculate protein-bound ligand entropy (S_{bnd}). It is possible to calculate binding entropy (ΔS_b) in a single **SZYBKI** run

```
prompt> szybki -complex complex.oeb -entropy AN  -prefix ex10 -sheffield -in ligand.oeb
```

where `complex.oeb` is a molecular file of the protein-ligand complex and `ligand.oeb` contains an ensemble of conformations of the ligand in solution. Note: The docked ligand in the `complex.oeb` file must represent a single pose and must be the same molecule as in the `ligand.oeb` input file. In the case where two or more docked poses are used, calculation of binding entropy requires two separate runs as shown in Figure 1.

4.3 Command Line Help

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

```
prompt> szybki --help
```

will generate the following output:

```
Simple parameter list

  Execute Options
     -param : A parameter file
```

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```
  Input Molecules
    Input Files Option 1 : Input molecule and optional protein
      -in : Name of the input molecule file. Aliases are -in and -i
      -protein : Name of the input protein file (not required)

  Input Files Option 2 : Ligand-protein complex
      -complex : Name of the input protein file with ligand(s)


  Output
    Output File Options
      -prefix : Replaces the default prefix for log, status, param and rpt
                files

    Explicitly specify individual file names
      -out : Name of the output molecular file


  Potential Function
    -ff : Force field to be used. Overwrites selection made with "-MMFF94S"


  Optimization
    -optGeometry : Specification of degrees of freedom used for optimization


Additional help functions:
  szybki --help simple      : Get a list of simple parameters (as seen above)
  szybki --help all         : Get a complete list of parameters
  szybki --help defaults    : List the defaults for all parameters
  szybki --help <parameter> : Get detailed help on a parameter
  szybki --help html        : Create an html help file for this program
  szybki --help versions    : List the toolkits and versions used in the application
```

4.4 Required Parameters

4.4.1 Input Files Option

Either option *-in* or option *-complex* must be used to perform a **SZYBKI** run.

-in <filename>

Molecular input file name containing 3D coordinates in any format supported by **OEChem**. In order to comply with previous **SZYBKI** releases, an alias *-i* can be used instead of *-in*. This option might be used as a keyless parameter without the `-in` or `-i` keys but only when used last or next to last when the last option on the command line is *-out*. Warning: The file name `szybki_out.oeb` is used as the default output file name, so it should be avoided as an input file name.

-i <filename>

An alias to *-in*.

-ligands <filename>

An alias to *-in*.

-protein <filename>

Protein input file with 3D coordinates in any format supported by **OEChem**. This works in combination with the *-in* option. No removal of preexisting ligands in the file `filename` will be done as in the case of the *-complex* option. This option can be aliased with *-p* for compatibility with previous **SZYBKI** releases.

-p <filename>

An alias to *-protein*.

-complex <filename>

Input file with 3D coordinates of a protein-ligand complex in any format listed in the table above. All ligands contained in the molecule file `filename` will be optimized one by one in the presence of all others.

4.4.2 Input File Formats

SZYBKI can handle molecular files in the following formats.

Table 1: *SZYBKI File Format Support*

File extension	Description
mol	MDL Mol File
mmd, mmod	Macromodel
mol2	Tripos Sybyl mol2 file
oeb	New Style OEBinary
pdb	Protein Databank PDB file
sd, sdf	MDL SD File
xyz	XMol XYZ format

4.5 Optional Parameters

4.5.1 Execute Options

-param <filename>

Command line options will be read from the specified file. This file may have been generated from a previous run or may be constructed de novo. The default name of the file is `szybki.param`. Any parameter in the parameter setup file is superseded by the parameter on the command line. For example, running `szybki -param szybki.param -i my.pdb` will perform calculations for the molecule `my.pdb` while using all other parameters taken from `szybki.param`.

-mpi_np <n>

Specifies the number of processors `n` when **SZYBKI** is run in MPI mode.

-mpi_hostfile <filename>

Specifies the name of the file containing processors configuration. For every host, this file should contain a line `host_name n` where `n` is the number of processors on the host.

4.5.2 Molecule Preparation Options

-strip_water

Causes removal of water molecules from the input protein when options *-protein* or *-complex* are used.

-largest_part

Calculations are performed only for the largest fragment of the noncovalent input complex. For example, when the input file contains coordinates for the salt, $[Large_cation^{+}] \cdot [Cl^{-}]$, the use of the *-largest_part* will cause the Cl^{-} anion to be ignored. By default, calculations are done for the entire complex.

4.5.3 Output Options

-silent

By default, the names of the processed molecules are displayed. The use of the option *-silent* will suppress this output.

-verbose

An extensive general output will be generated containing initial and final energy and gradient data, as well as an optimization report.

-prefix <pn>

Replaces the `szybki` prefix in .log, .rpt (report), .status , .param, and _out.oeb files, with the input string `pn`.

-report

An output file in tabular form of final energy components for every molecule/conformer will be generated. The name of the file is fixed as `prefix.rpt`, where `prefix` is `szybki` by default or determined by the *-prefix* option.

-sdtag <string>

In the case when the output file is in the SD format, an energy tag can be added. For single molecules, by default all energy terms (MMFF, solvation, and constraint) plus `Total energy` are added, so the option has no effect. "Total energy" always contains the constraint terms. In the case of protein-ligand systems, only the relevant terms (`Ligand-Protein Energy` and all of its components) are attached as SD tags by default. The option can be used therefore to add one of the remaining terms from the list below. If `string` is set to `all`, all energy terms are tagged as SD tags.

1. `VdW`
2. `Coulomb`
3. `Bond`
4. `Bend`
5. `StretchBend`
6. `Torsion`
7. `Improper Torsion`
8. `L VdW`
9. `L Coulomb`
10. `L Bond`
11. `L Bend`
12. `L StretchBend`
13. `L Torsion`
14. `L Improper Torsion`
15. `P VdW`
16. `P Coulomb`
17. `P Bond`
18. `P Bend`
19. `P StretchBend`
20. `P Torsion`

21. P Improper Torsion
22. PL VdW
23. PL Coulomb
24. Ligand-Protein Energy
25. Sheffield Solvation
26. Constraint Potential
27. PB Solvent
28. Area Solvent
29. __VdW
30. __Coulomb
31. __Protein desolv
32. __Ligand desolv
33. __Solvent screening
34. __Grid Coulomb
35. __Exact Coulomb
36. P/L energy
37. __AMBER VdW
38. __AMBER Coulomb
39. Torsion Constraint
40. IEFF Interaction
41. InterLigand IEFF

If the parameter `string` does not correspond to one of the available energy terms, no tag will be written. Tags starting with L, P, PL and __ are:

- L: ligand intramolecular terms only
- P: protein intramolecular terms only
- PL: protein-ligand intermolecular terms only
- __: protein-ligand interaction terms

-keepFailures

By default, molecules which failed during processing are store in the file `prefix.FAIL.input_format` where `input_format` is that of the input molecule used in option *-ligands*. If the flag is set to `true`, those failed molecules are written to the molecule output file.

-heavy_rms

By default, the RMSD of all atoms after optimization is reported in the log file. This option replaces the default with the heavy atoms RMSD.

-l <filename>

An alias to *-log*.

-log <prefix>

Prefix of the log file name, `prefix.log`. If omitted, the prefix `szybki` is used by default. This option is aliased to *-l*.

-o <filename>

An alias to *-out*.

-out <filename>

Output file name, in any format supported by **OEChem**, for an optimized ligand. If not specified, `szybki_out.oeb` or `prefix_out.oeb` (when *-prefix* is used) will be generated. Alias `-o` can be used instead of `-out`. This can be used as a keyless parameter without the `-out` key when it is last on the command line just after the *-in* (or *-i* or *-ligands*) option.

-out_protein <filename>

Partially optimized protein will be saved in a file named `filename`. By default, this option is not used; however, modified coordinates of a protein are still saved in the form of a generic data attached to the optimized ligand when it is output in the oeb format, under the tag `saveprot`. One can easily extract coordinates of the optimized protein using **OEChem TK** or **VIDA**.

-out_complex <filename>

Protein-ligand complex for partially optimized protein will be saved in a file named `filename`.

-reportFile <filename>

Sets user-selected file name, `filename`, for the tab file. Supersedes the *-report* option described above.

4.5.4 Force Field Options

-ff

Force field to be used. Valid options are: `mmff94`, `mmff94s`, `amber_mmff94`, `amber_mmff94s`, `ieff_mmff94`, `ieff_mmff94s`, `smirnoff99frosst`, `parsley_openff`, `sage_openff`, `ff14sb_parsley`, and `ff14sb_sage`.

Upper case options are also accepted. In addition to the above, this command also accepts any SMIRNOFF force field parameter file in XML format.

This option overwrites the deprecated option `-MMFF94s` when both are used simultaneously. The combined potential AMBER-MMFF94 (or AMBER-MMFF94s) can be applied only for protein-ligand interactions using a rigid protein model. All intramolecular ligand interactions are described by the MMFF94 (or MMFF94s) force field while intermolecular protein-ligand interactions are handled by the Amber force field. `ieff_mmff94` and `ieff_mmff94s` potentials can be used only for intermolecular interactions provided that electrostatic multipoles are assigned to the molecules. Combined potential `ff14sb_parsley` or `ff14sb_sage` can be applied for optimization of a protein system which might contain cofactors and ligands. In such a case, the protein part is handled with the ff14SB version of AMBER while ligands and cofactors by the latest `parsley` or `sage` force field. Currently selecting `ff14sb_parsley` or `ff14sb_sage` cannot be combined with *-protein* option. In order to optimize a part of a protein-ligand complex (e.g., the ligand), with the `ff14sb_parsley` or `ff14sb_sage` potential, one can specify a list of flexible atoms using *-flex_file*.

-exact_vdw

By default, the van der Waals protein-ligand interaction is calculated with the use of lookup tables in order to speed up the calculations. This option allows using the exact analytical van der Waals potential for the optimization of a ligand in the protein binding site.

-mod_vdw

Regular MMFF *Van der Waals Interactions* equation will be replaced with:

$$V_{vdw} = \begin{cases} \epsilon_{ij} \left(\frac{1.07 R_{ij}}{r_{ij} + 0.07 R_{ij}} \right)^7 \left(\frac{1.12 R_{ij}^7}{r_{ij}^7 + 0.12 R_{ij}} - 2 \right) & \text{for } r_{ij} < R_{ij} \\ -\epsilon_{ij} & \text{for } r_{ij} \geq R_{ij} \end{cases}$$

in which no attractive van der Waals forces are present. This type of van der Waals potential prevents a so-called "hydrophobic collapse."

-neglect_frozen

After an optimization with frozen terms, the default behavior calls for a full single-point calculation of the whole system. The *-neglect_frozen* option will skip this final calculation of the whole system, thus yielding results for only the non-frozen pieces. When there is a large frozen section, this can drastically reduce memory and CPU usage.

-noCoulomb

Electrostatic terms defined in the *electrostatic interactions* section will be excluded from the force field potential. This option might be useful to prevent generation of folded structures.

-protein_vdw <r>

Calculation of van der Waals protein-ligand interaction energy will be limited to a sphere of radius `r`. The default value is 18.0 Å. In many applications, a value as small as 10 Å can be used with essentially no effect on the final optimized ligand geometry. The legal range is 5–500 Å.

-strict

Enforces strict atom typing. This is a default behavior. When the value of the flag is selected to be `false`, this enforcement is removed.

-vdw_cutoff

Sets distance for intramolecular van der Waals interactions. By default, all atom pairs in the molecules contribute to the molecule's van der Waals energy. The legal range is 5–500 Å.

4.5.5 Charging Options

-am1bcc

AM1BCC charges [Jakalian-2002] are calculated for every conformation and used for the PB or Sheffield solvation energy only. Those charges are therefore conformation-dependent, and reflect changes of molecular density with molecular geometry. Note that AM1BCC charges are conventionally calculated for just one conformer or a few conformers of a multiconformer molecule, those conformers with electrostatically least-interacting functional (ELF) groups, so calculating AM1BCC charges for every conformer with this option is unconventional. For conventional behavior, apply AM1BCC ELF charges to the molecule separately and then use that as the input structure with the `-current_charges` option.

-current_charges

During optimization of molecules in solution with the use of the Poisson-Boltzmann solvation model, the free energy of solvation and solvent forces can be calculated with the use of atomic partial charges other than MMFF. The option *-current_charges* allows the use of partial charges read from the input molecular file. In the case where the ligand is optimized inside a protein, protein-ligand electrostatic interactions (coulomb and/or Poisson-Boltzmann) could be calculated based on ligand and protein partial charges read from the molecular input files. When input partial charges are not found, the MMFF94 partial charges will be used.

4.5.6 Solvent Options

-inner_dielectric <d>

The default value for the protein or ligand dielectric constant of 1.0 can be changed to a user-selected value `d`. This option is aliased as `-protein_dielectric`. The upper allowed limit is 20.0.

-shefA <a>

Parameter `a` in the Sheffield solvation potential given in option *-sheffield*. If the option is not used, a value of 1.553149 is assigned [Grant-2007].

-shefB <b>

Parameter b in the Sheffield solvation potential given in option *-sheffield*. If the option is not used, a value of 0.735694 is assigned [Grant-2007].

-sheffield

Use of this option will result in adding an additional electrostatic term in order to mimic the solution environment according to [Grant-2007]. This term is of the form: $f_\epsilon/(8\pi\epsilon_0)\sum_{i,j} q_i q_j/\sqrt{(ar^2 + bR_iR_j)}$, where $f_\epsilon = (1/\epsilon_{in} - 1/\epsilon_{out})$, q_i, and q_j are partial charges, and R_i and R_j are van der Waals radii of atoms i and j. While less accurate than Poisson-Boltzmann, this method is very fast and offers analytic first and second derivatives. Because of the latter, it is the only solvation option for entropy calculations.

-solv_dielectric <d>

Allows changing the default value for solvent dielectric constant used for Poisson-Boltzmann and Sheffield solvation energy calculations. The allowed range is 1 to 100. Default value is 80.

-solventCA <s>

This option can only be used in combination with *freeform -solvent* PB or *-sheffield*. It causes inclusion of a molecular surface solvation term (sometimes called cavity solvation term) in the total energy. The value of parameter s (microscopic surface tension coefficient) is in the range 0.005–0.030 kcal/(mol Å^2). This option is aliased as *-solventMA* for compatibility with previous releases.

-solventPB

For optimization of small molecules in solution, the electrostatic part of molecule-solvent interactions will be calculated using Poisson-Boltzmann model.

-protein_elec <m>

This option provides four choices for calculating protein-ligand electrostatic interaction energies: m = None, ExactCoulomb, GridCoulomb, and PB. The option m = None eliminates electrostatic interactions. Values of m set at ExactCoulomb and GridCoulomb result in the usage of coulomb exact potential and digitized on the grid, respectively. Option m = PB provides a more realistic potential which accounts for solvent forces, calculated according to the Poisson-Boltzmann model at every iteration step. This option requires substantially higher CPU time, particularly for large proteins. By default, m = ExactCoulomb.

-radii <type>

Determines types of atomic radii used for PB calculations (options: *freeform -solvent* PB and *-protein_elec*). By default, the parameter type is set to Bondi. Two other choices are ZAP9 and ZAP7 [Nicholls-2010].

-salt <c>

Allows to all PB calculations to be performed at a specified salt concentration in M, up to 0.08M. By default, the salt concentration is zero.

4.5.7 Saving and Loading Coulombic Grids

-loadPG <filename>

In the case when the electrostatic component of the protein-ligand interaction energy has been precalculated on a grid, this option forces **SZYBKI** to read the grid potential from the file filename, and use it for ligand optimization inside the protein. This option is available only when *-protein_elec* is set with GridCoulomb.

-savePG <filename>

Saves a potential grid in the file named filename. Allows a significant saving in CPU time for runs when coulomb grids are used to optimize a number of ligands inside the same protein. This option is available only when *-protein_elec* is set with GridCoulomb.

4.5.8 Optimization Options

-optDOF

An alias to *-optGeometry*.

-optdof

An alias to *-optGeometry*.

-optGeometry <dof>

Optimization in specified degrees of freedom will be done. The possible choice for the parameter `dof` are `cart` for Cartesian coordinates, `tor` or `torsions` for torsion optimization, `solid` for rigid ligand optimization inside a protein receptor, `none` or `sp` for single point calculation, `Honly` for hydrogen atoms only optimization, and `calculationDependent`. The value `calculationDependent`, which is selected by default when an option is not used, sets the type of degrees of freedom: free ligands by default are optimized in Cartesian coordinates, while protein-bound ligands are in translational-rotational coordinates. The option is aliased with *-optDOF* and *-optdof*.

-grad_conv <c>

Optimization is terminated when the RMS gradient reaches the input value `c`, unless it is finished earlier because of other reasons. When omitted, the default convergence criteria is 0.1 on gradient vector norm: $\sqrt{\sum_i g_i g_i}$, where g_i is the `i-th` gradient component.

-max_iter <m>

Optimization will be terminated when the number of iteration cycles reaches input number `m`. The default value is 1000.

-optMethod <type>

Selects optimization type. The value of `type` replaces the default BFGS optimizer for small molecules and the conjugate gradient for systems with 500 or more degrees of freedom. Allowed values of `type` are `BFGS` or `bfgs` for BFGS optimization; `CG`, `cg`, or `conj` for conjugate gradient; `SD`, `sd`, or `steepest` for steepest descent optimization; `sd_bfgs` for pre-optimization with five steps of steepest descent followed by BFGS optimization; `sd_cg` for pre-optimization with five steps of steepest descent followed by conjugate gradient optimization; and "newton" or "NEWTON" for Newton-Raphson optimization if analytic second derivatives are available. Entropy estimation requires a BFGS or Newton-Raphson type of optimization, so all values of the parameter `type` which represent different optimization methods are ignored for entropy runs. In addition, when a quasi-Newton method of entropy estimation is requested (see *-entropy*), the usage of BFGS is enforced.

4.5.9 Fixing Ligand Atoms

-fix_file <filename>

The text file `filename` should contain a list of molecule names followed by atom numbers to be fixed. An example of the command line for a **SZYBKI** run with the use of this option is given below in the *Example Commands* subsection.

-fix_smarts <file_name>

All atoms which belong to a SMARTS pattern specified in a single line of the text file `file_name` will be fixed. For example, if the input string is [!#1], all heavy atoms will be fixed and a **SZYBKI** run will optimize all hydrogen atom positions.

-flex_file <filename>

The text file `filename` should contain a list of molecule names followed by atom numbers to be optimized. All non-listed atoms will be fixed. The atom numbering convention used is from 0 to n-1, where n is the molecule's total number of atoms.

4.5.10 Constraining Ligand Atoms

-harm_constr1 <k>

Constrained potential of the form kr^2 will be imposed on all heavy atoms, where k is the force constant. By default, no constraint is applied ($k = 0$), and the upper allowed limit is 1000 kcal/(mol Å^2).

-harm_constr2 <d>

Constrained potential of the form $V = k(r - d)^2, r > d$ and $V = 0, r \leq d$ will be imposed on all heavy atoms, where d is the constraining distance in angstroms. This can be used only together with *-harm_constr1*. The default value is 0, while the upper allowed value is 5 Å.

-harm_smarts <file.txt>

All atoms which belong to a SMARTS pattern read from the file `file.txt` will be constrained. For example, when the file `file.txt` contains a single line `c0`, the input option `-harm_smarts file.txt` will result in constraining all aromatic carbon atoms and oxygen atoms bonded to them. This must be used in conjunction with *-harm_constr1*.

4.5.11 Constraining Torsion Angles

-tor_constr <fn>

File name containing a single line which determines the torsion to be constrained, reference torsion angle, and a force constant. The constraining potential is in the form $V = k_c(cos(phi) - cos(phi0))^2$, where k_c is the user-specified force constant, and $phi0$ is the reference torsion dihedral angle. The input data in the file `fn` should be in the following order: SMARTS $phi0$ k_c. SMARTS might be replaced with atom indices: i_1 i_2 i_3 i_4 $phi0$ k_c.

Examples of valid inputs are: `[C:1][N:2][c:3][s:4] 0.0 2.0 5 0 10 25 0.0 2.0` Notice that atom indices are numbered from 0 to $N - 1$, where N is the number of atoms in the molecule.

4.5.12 Protein Flexibility

-flexdist <d>

Specifies the distance `d` from the ligand that determines the flexible residues of a protein receptor in the optimization of a ligand inside the protein binding side. This has to be used together with *-flextype*.

-flexlist <fn>

Similar to *-flexdist*, but instead of using distance from the ligand as partial protein flexibility criteria, provides a file name `fn` containing flexible residues. Every line of this file should contain a PDB residue name, residue number, and chain ID. For example, a two-line file:

ILE 78 A
Phe 114 B

informs **SZYBKI** that Ile78 of chain A and Phe114 from chain B will be flexible during ligand optimization. This has to be used together with *-flextype*.

-flextype <type>

Allows the user to specify the type of partial protein flexibility. The possible values of parameter `type` are a string `polarH`, `sideC`, or `residue`, with respective meanings of polar hydrogens, side chains, and complete residues. This must be used together with *-flexdist* or *-flexlist*. The molecular potential used for optimization consists of three components:

1. Ligand intramolecular MMFF potential

2. Protein-ligand potential
    a. MMFF terms for interactions between polar protein hydrogens and the ligand
    b. Interaction between fixed protein atoms and the ligand
3. Protein intramolecular potential
    a. MMFF terms involving polar protein hydrogens and atoms up to three bonds apart

3.2. Interaction between the rest of the protein and flexible polar hydrogens

The sum of the components 2b and 3b might be called a "protein-pseudoligand" interaction and is evaluated according to the model selected with the *-protein_elec* option above.

4.5.13 Entropy Calculation Options

-entropy <type>

Estimation of the entropy of a ligand will be done. The parameter `type` can take three values: "None" (default), "QN" (Quasi-Newton Hessian), and "AN" (analytical). The input ligand is assumed to be in the form of a multiconformational molecule. The environment is determined by the *-sheffield* option (solution), *-protein* option (in the binding site), or neither one, indicating a gas phase.

-t

Sets the temperature (in °C) of the system for entropy estimation. The default temperature is 25°C (298K).

CHAPTER

FIVE

FREEFORM

5.1 Overview

Freeform calculates some thermodynamic properties for small molecules that are useful for drug discovery.

> **Caution**
>
> *freeform -calc conf* takes over 6 gigabytes of memory by default.

The conformer generation step of *freeform -calc conf* uses a default maximum conformer limit of 40,000 conformers, leading to a high memory usage of over 6 GB of memory. Reducing the maximum conformer limit with the *-maxconfs* flag will significantly reduce memory usage, although this may reduce the accuracy of the conformer free energies, especially with molecules containing many rotatable bonds. If memory usage is an issue, we recommend running a calculation using *maxconfs 20000*. If this maximum is not reached in the initial conformer generation step (check the line containing "generating conformers…" in the log file), then there will be no loss in accuracy compared to the default 40,000.

> **Note**
>
> The graph in the PDF output of *freeform -calc conf* may not show all minima.

The "dG vs Erel" graph in the PDF output of *freeform -calc conf* uses default axes spanning only 0 to 7 kcal/mol for conformer dG and 0 to 5 kcal/mol for Erel; generally the whole unbound ensemble contains minima above these ranges (sometimes the majority of minima). The data for all the minima are contained in both the output log and CSV files; the graph is intended only to show minima that could potentially contribute significantly to the room temperature ensemble, hence the limited range of the axes. The axes are extended somewhat to show tracked minima, but beyond 30 kcal/mol in either dG or Erel not even these data are shown in the graph.

> **Note**
>
> It is possible to get a negative local strain energy with `-solvent` PB.

Ordinarily, local strain energy can never be negative because the energy can only decrease once the restraints are removed and the ligand is allowed to freely minimize. With `-solvent` PB, PB single-point solvation energies are taken of the restrained minimum and the corresponding freely minimized minimum. There are two reasons why this could result in a negative local strain energy. The first is due to the precision of the PB calculation being around 0.2 kcal/mol: if the true restrained and free minima are within 0.2 kcal/mol, the restrained minimum could end up with a slightly higher PB solvation energy simply due to the imprecision. The second reason is that the Sheffield solvation energy

used in minimizing from the restrained to the free minimum may simply differ in the opposite direction from the PB solvation energy for the same minima.

> **Note**
>
> AM1BCC ELF10 charging may use fewer than 10 conformers for charging.

AM1BCC ELF10 charging is designed to average the AM1BCC charges from 10 conformers chosen from the 2% of the conformer population having the electrostatically least-interacting functional (ELF) groups. Ten conformers from 2% means there must be at least 500 conformers to start with; ligands which have fewer rotatable bonds may not have this many. In such cases, the AM1BCC ELF10 method is designed to take all the conformers in the 2% ELF population. For example, if the starting conformer set has 327 conformers, all 6 conformers in the 2% ELF population will be used. With 50 or fewer conformers, a single ELF conformer will be used. When more than one conformer is used, the log file line starting with "Semi-empirical charge averaging" tells how many were used.

5.2 Example Commands

5.2.1 Conformer Free Energies

The default calculation type in **Freeform** is `-calc conf`, so this is what it will run if no `-calc` option is specified. However, in the following examples we will specify this calculation type explicitly. The two main types of conformer free energy calculations are 1) when the input 3D structure is not known or not of special significance, and for example, if they are believed to be bioactive conformers. In the latter case, `-track` is specified, and **Freeform** reports specifically on the global and local strain energies for these conformers.

> **Note**
>
> The numbers and values in the examples below are just for illustration and can change as we improve the applications.

Example 1

Let us begin with case 1 above: when the input 3D structure is not known or not of special significance. In this example, the input is the SMILES string for Januvia in file `januvia.smi`:

(Fc1cc(c(F)cc1F)C[C@@H]([NH3+])CC(=O)N3Cc2nnc(n2CC3)C(F)(F)F)

The command is:

```
prompt> freeform -calc conf -in januvia.smi -prefix januvia.pfn
```

This produces five output files:

januvia.pfn.pdf: the results report summarizing key results for each molecule in the run.

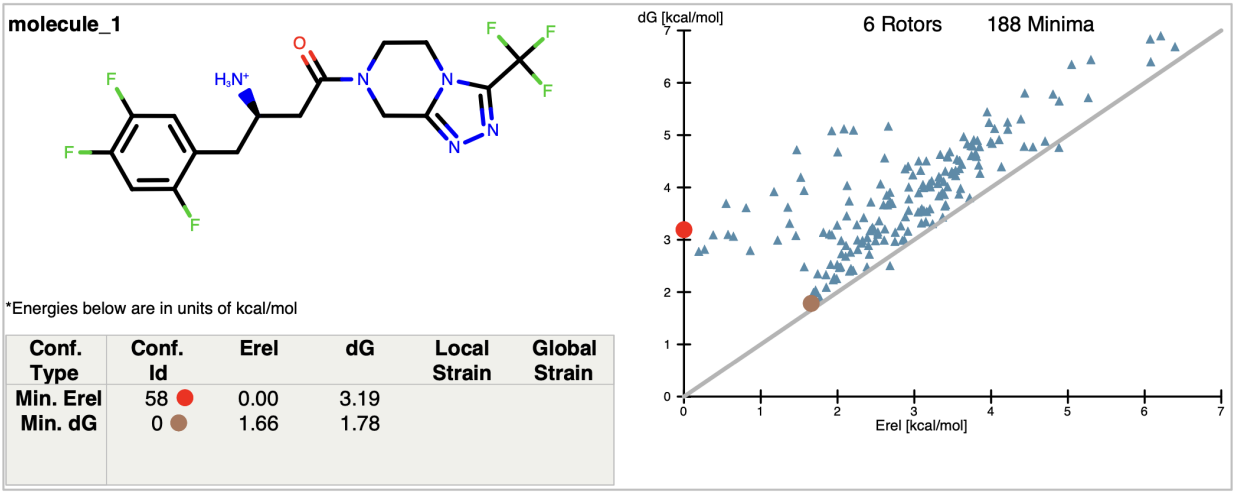
januvia.pfn.log: the log file of per-molecule results. This also shows the progress of the calculation if it is taking a long time, for example, if the run has to minimize a conformer ensemble containing 20,000 conformers (this can take over half an hour).

januvia.pfn.csv: the CSV file of per-conformer results (energies, entropies, and free energies)

januvia.pfn.oeb: the file of all the final minima for the molecule.

januvia.pfn.param: all the input parameters of the calculation are written here.

Let us first look at an example of a results report in the file `januvia.pfn.pdf`, as shown below.



Conf. Type	Conf. Id	Erel	dG	Local Strain	Global Strain
Min. Erel	58	0.00	3.19		
Min. dG	0	1.66	1.78		

Fig. 1: **Figure 1.** Results report from Januvia SMILES input.

A 2D depiction of the molecule is shown on the left, with a table that gives the relative energies (E(MMFF) + E(solv)) and conformer free energies (including entropy) for the relative energy (Erel) and free energy (dG) minimum conformations. All the energy units in *freeform* are in kcal/mol. The strain information (local strain and global strain) is empty in this example. The graph on the right-hand side shows the conformer free energy versus the relative energy for all the conformers produced in the calculation for the unbound ensemble. At the top of the graph, we note the number of rotors (rotatable bonds) sampled in the conformation generation for this molecule (six), and the number of unique minimal in the entropy calculation for this molecule (188 in this example). The red dot on the graph corresponds to the relative energy minimum (see the conformer also labeled with a red dot in the logfile table; the conformer ID can be used to reference it in the .oeb file, and in the .csv file). We can also see that while it is the global energy minimum in terms of enthalpy, it would cost the dG amount in conformer free energy to select this conformer from the aqueous free ligand ensemble. In contrast, the Min dG conformer has the lowest free energy (corresponding to the brown dot on the graph) to select it from the ensemble.

Example 2

In the second example, the input file is `sitagliptin.mol2`; it is in .mol2 format and contains the X-ray crystal coordinates for Januvia (sitagliptin). Here we are particularly interested in the conformer free energy for this input X-ray structure since it is the bioactive conformation. We would like to know how much free energy it costs to select this bioactive conformation from the aqueous free ligand ensemble. To track the input conformation throughout the calculation, we specify `-track` *sitagliptin.mol2* to indicate that we wish to use the 3D coordinates of the input structure and to track this conformer. Note that `-in` *sitagliptin.mol2* must also be specified so that we use the same structure to derive the conformers for the unbound aqueous ensemble. Just to be clear: the `-in` is always required to specify the molecule to be used for the unbound aqueous ensemble; the `-track` is optional, only needed for tracking one or more specific conformers. The command is thus:

```
prompt> freeform -calc conf -track sitagliptin.mol2 -in sitagliptin.mol2 \
-prefix sitagliptin.3D.pfn
```

This produces five output files analogous to those above for Januvia and in addition produces these three files related to the tracked conformer, each with:

sitagliptin.3D.pfn.tracked_input.oeb, the input tracked conformer.

sitagliptin.3D.pfn.tracked_rstr.oeb, the restrained minimum from the input tracked conformer.

sitagliptin.3D.pfn.tracked_free.oeb, the unrestrained minimum from the input tracked conformer.

The results report is in the file sitagliptin.3D.pfn.pdf.

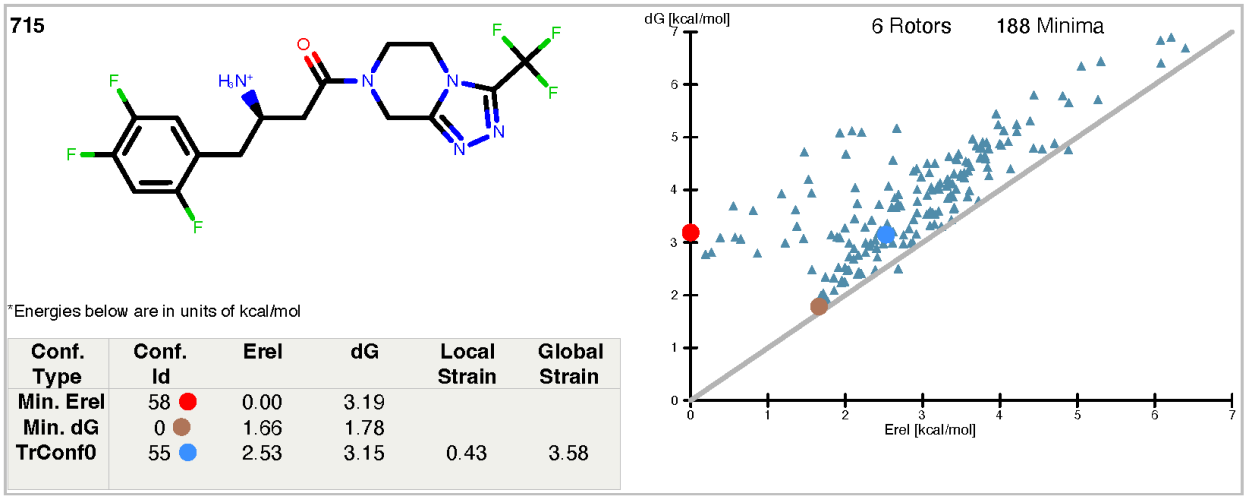


Fig. 2: **Figure 2.** The results report from sitagliptin.mol2, using the "-track" flag.

The results report in this case looks very similar to that of our first example except for the extra line added to the table and the corresponding blue dot on the graph. The extra line in the table relates to the bioactive conformer specified in the input with the `-track` flag. "TrConf0" is an abbreviation for "Tracked Conformer 0", that is, the first of the tracked conformers (in this case there was only one). The line beginning "TrConf0" gives information on the nearest unbound minimum to the tracked conformer, locating the unrestrained minimum from that conformer (in file **sitagliptin.3D.pfn.tracked_free.oeb**) and the corresponding relative energy (Erel) and conformer free energy (dG). The additional columns for this line give the local strain energy and the global strain energy associated with the tracked conformer.

These quantities are defined in the *Freeform Theory* section and depicted there in *Figure 3*, but we will briefly summarize here. The local strain energy is the relative energy difference (internal energy + solvation energy) between the restrained energy minimum (the structure in file **sitagliptin.3D.pfn.tracked_rstr.oeb**) and the nearest unbound minimum (the structure in file **sitagliptin.3D.pfn.tracked_free.oeb**). Conceptually, it corresponds to the energy required to distort the nearest unbound minimum to fit into the active site. The global strain energy is the sum of the local strain energy and the conformer free energy of the nearest unbound minimum.

Example 3

The third example is like the second except that PB single-point solvation energies are requested with the `-solvent` PB option. This is a higher level of continuum solvation theory compared to Sheffield solvation and so the solvation energies are expected to be more accurate. Sheffield solvation is still used in finding the minima for the unbound ensemble because it is fast and has the necessary analytic second derivatives. The command is:

```
prompt> freeform -calc conf -solvent PB -track sitagliptin.mol2 \
-in sitagliptin.mol2 -prefix sitagliptin.3D.pb.pfn
```

This produces eight output files analogous to those above for Example 2.

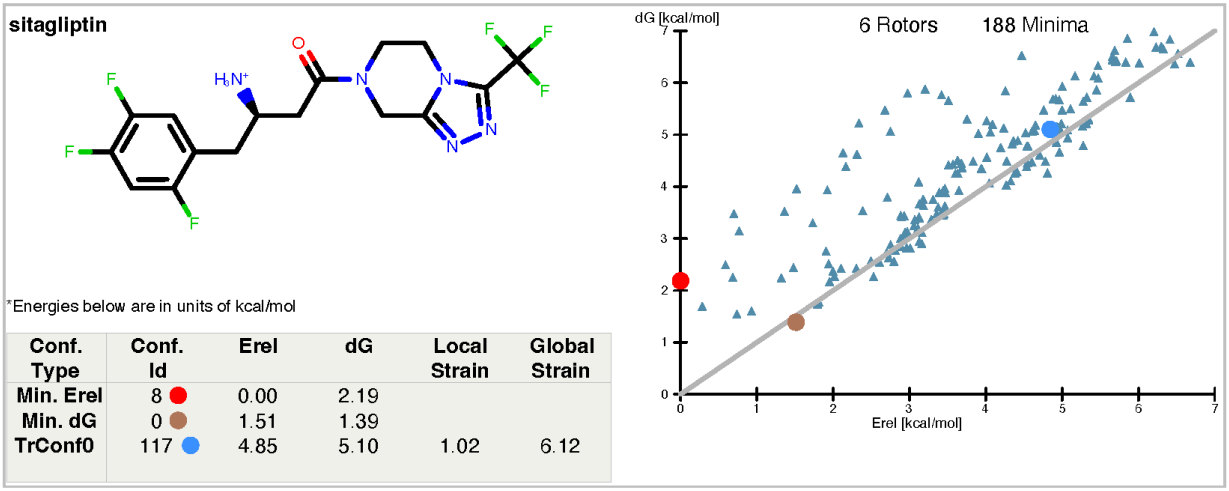


Fig. 3: **Figure 3.** The results report from sitagliptin.mol2, using "-solvent PB".

Note that the energies and the graph differ markedly from that of Example 2. The partial charges, the number of unique minima, and the minima themselves in both Example 2 and Example 3 are found using the Sheffield solvation. The difference is the solvation energy for each conformer: in Example 2, the Sheffield solvation energy is used, whereas in this example the Sheffield solvation energy has been replaced with a PB single-point solvation energy evaluated at the coordinates of the Sheffield-based minimum. The impact of changing to a PB energy is more pronounced with charged ligands.

Example 4

In the fourth and final example for *`freeform -calc conf`*, the same input file is used as in the second example, but now we would like to use the input charges in that file for the solvation energies. Note that in addition to specifying *-solvcharges input*, we also need to include *-ionic input* because the default behavior of potentially changing the ionic state for pH 7.4 cannot be allowed with input charges. The command is thus:

```
prompt> freeform -calc conf -solvcharges input -ionic input -track sitagliptin.mol2 \
-in sitagliptin.mol2 -prefix sitagliptin.3D.inp.pfn
```

The results report is in the file sitagliptin.3D.inp.pfn.pdf.

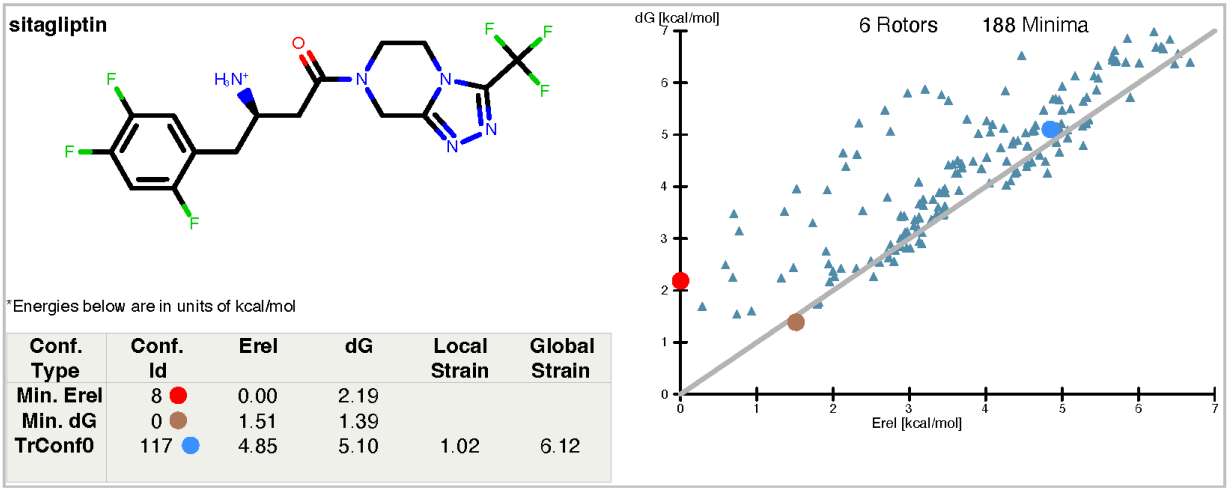


Fig. 4: **Figure 4.** The results report using "-solvcharges input``.

Given that only the atomic partial charges differ between this example and Example 2, we see significant changes in all the energies, yielding quite a different profile for the conformational ensemble. This includes changes to the conformer free energy and global strain energy values for the nearest unbound minimum to TrConf0. These differences reflect the impact of using different charge models, especially on charged ligands; we recommend the default AM1BCC ELF10 charges.

5.2.2 Solvation Free Energies

Example 5

In order to estimate solvation free energy, the user must use the option *-calc* followed by the value `solv`. The default charge state of the input compound corresponds to pH = 7.4 (see option *-ionic*), so the following run:

```
prompt> freeform -calc solv -prefix januvia_ph74 januvia.smi
```

will estimate the Januvia solvation free energy at physiological pH. The graphical output file for this run is displayed in Figure 5. On the left the result of the solvation free energy calculation is shown, including a depiction of the group-wise decompositions of the solvation free energy. It suggests that, as expected, the cationic NH_3 group is responsible for almost all of the strongly negative solvation free energy of this molecule (-53.6 kcal/mol), while the trifluorophenyl fragment is the most hydrophobic part of this drug, adding to the solvation free energy (2.4 kcal/mol). To the right, the calculated XlogP partition coefficient is given together with its fragment decomposition into group contributions. Note that the calculated XlogP partition coefficient is always done relative to the uncharged molecule irrespective of its ionic state in water at any pH.

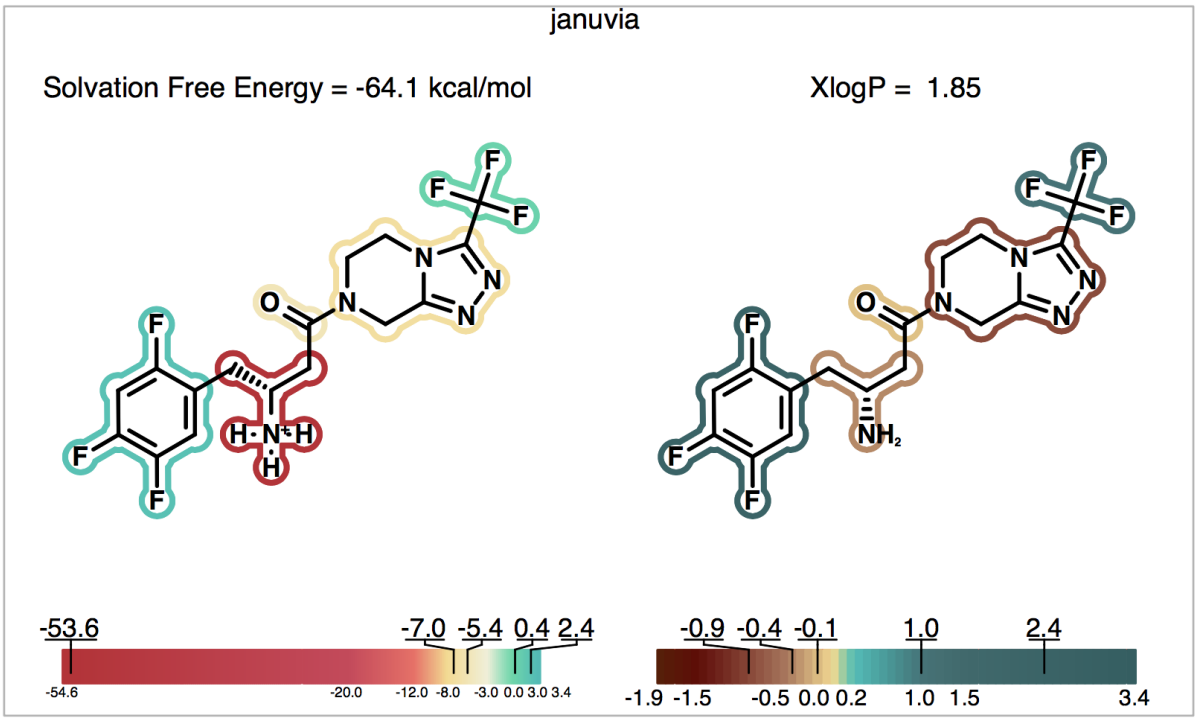


Fig. 5: **Figure 5.** Solvation of Januvia at physiological pH.

Example 6

In the next example, the solvation free energy of Januvia in its uncharged form is performed with:

```
prompt> freeform -calc solv -ionic uncharged -prefix januvia_neu januvia.smi
```

The output is shown in Figure 6. Note that changing the ionic state of the ligand only affects the solvation free energy on the left-hand side; the calculated XlogP partition coefficient is always done relative to the uncharged molecule so it is unchanged from the previous example. Now since the solvation free energy is also on the uncharged form, in this example (unlike the last), the solvation free energy and XlogP calculations correspond to the same (uncharged) form of Januvia.

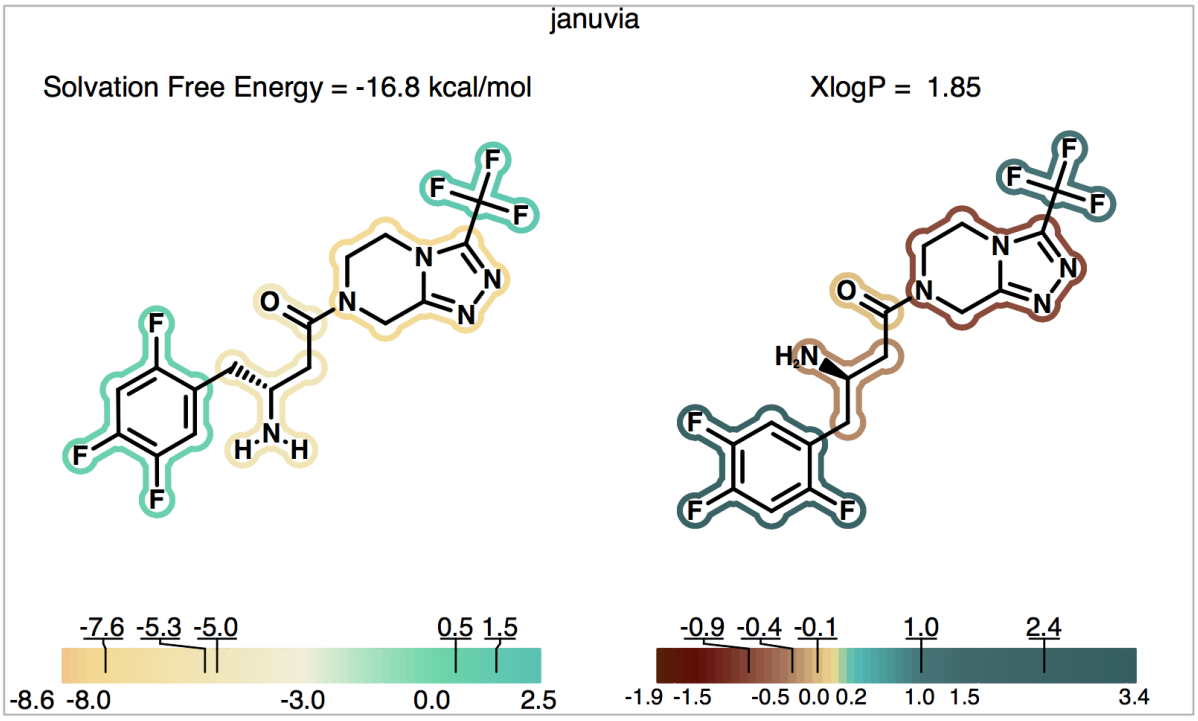


Fig. 6: **Figure 6.** Solvation of the neutral form of Januvia.

5.3 Command Line Help

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

```
> freeform --help
```

will generate the following output:

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

5.4 Required Parameters

`-calc` <run_type>

Selects type of calculations to be performed. There are two possible strings for parameter `run_type`: `conf` and `solv`. The first one asks *freeform* for the evaluation of conformational free energies while the second one tells *freeform* that solvation free energy is to be calculated. The default flag value is set at `conf`.

`-in` <filename>

Molecular input file name in any format supported by the OpenEye **OMEGA** Application. Warning: The file name `freeform.oeb` is used as the default output file name, so it should be avoided as an input file name.

-i <filename>

An alias to *-in*.

5.5 Optional Parameters

5.5.1 Basic Options

-out <filename>

Molecular output file name in any format supported by **OEChem**. The default name is `freeform.oeb`. For free energy estimation of the conformations for the input molecule, the output file contains all unique solution conformations structures identified by *freeform*. In the case of solvation free energy estimation, the output file contains the lowest energy vacuum conformation for which the PB solvation calculation was actually done.

-param <filename>

Command line options will be read from the specified file. This file may have been generated from a previous run or may be constructed de novo. The default name of the file is `freeform.param`. Any parameter in the parameter setup file is superseded by the parameter on the command line.

-prefix <p>

Replaces `freeform` prefix in .log, .param, .oeb and .pdf output files with the input string `p`.

-report <filename>

Name of the graphical output file. Currently only PDF and PS formats are allowed. The default name is `freeform.pdf`.

-track <filename>

The molecular input of conformers to be tracked is read from the file name; any 3D molecule file format supported by OpenEye is acceptable. Of critical importance is that the molecule graph be identical to that specified in the *-in* input file, and that atom and bond ordering also be identical. For the most common uses of *freeform*, the same input file is specified for both the *-in* and *-track* options.

5.5.2 Advanced Options

-ensemble

The ensemble of conformations is read from the *-in* input file instead of being generated internally. In both cases of *-calc* option, this ensemble is treated as if it already contains all the conformations needed. In conformer free energy estimation, when used together with *-track*, the tracked conformations are included with the ensemble.

-ewindow

The *-ewindow* flag sets the energy window (in kcal/mol) used as an energy cutoff in the initial conformation generation stage of *freeform*. An ewindow of at least 15.0 is encouraged to better cover accessible conformational space; increasing *-ewindow* will increase the number of conformers. [Default=15.0]

-ff <type>

This option specifies which force field to use in the energy minimizations and thermodynamics calculations following the initial conformer search. Choices include `mmff94s`, `mmff94`, `smirnoff99frosst`, `parsley_openff`, and `sage_openff`. Default: `sage_openff`.

In addition to the above, this command accepts any SMIRNOFF force field parameter file.

-ionic <type>

By default, a charge state used in calculations corresponds to pH = 7.4 (the value of parameter `type` is set at `pH74`). Two remaining values are `uncharged` and `input`. The former corresponds to an uncharged ionic state (i.e., no formal charges); the latter to the preexisting ionic state determined from the molecule input file.

-maxconfs <value>

The *-maxconfs* flag sets the maximum number of conformations to be generated using **OMEGA** for the initial conformation generation stage of *freeform*. A large set is desirable to cover the conformational space necessary to include all reasonable conformers that might contribute to the partition function. When this initial set is minimized, a large reduction is expected in the number of unique minima. [Default=40000]

-rms <value>

RMS threshold for conformation generation using **OMEGA**. The default value is `calculationDependent` meaning that the RMS threshold used depends on whether "-calc conf" or "-calc solv" is being run. 0.3 Å is used with "-calc conf" and 0.6 Å with "-calc solv". Values ranging from 0 to 5 are accepted.

-solvent <type>

By default, Sheffield solvation is used with dielectric 80.0 to account for aqueous solvation of the unbound ensemble; this can be specifically requested by setting the parameter `type` to `sheffield`. Setting `type` to `PB` will result in Poisson-Boltzmann (PB) single-point solvation energies being calculated at the Sheffield-based minima. The default solvent dielectric for the PB calculation is 80.0, but this can be changed with the *-PBsolvent_dielectric* option. Setting `type` to `vacuum` means that no solvation energy will be calculated.

-PBsolvent_dielectric <value>

This option allows the user to change the solvent dielectric used in the PB single-point solvation energies requested with *-solvent* `PB`. The default value is 80.0 to approximate aqueous solvation; it can adopt any value between 1.0 and 80.0 .

-solvcharges <type>

Selects the type of partial charges to be used for the solvent forces. By default, the value of `type` is `calculationDependent`, meaning that the charge type used depends on whether "-calc conf" or "-calc solv" is being run. AM1BCC charges that are AM1-optimized (Opt) (constrained to starting geometry) and symmetric by 2D-bond symmetry (Sym) are used for conformer free energy estimation and nonsymmetric (NoSym) AM1-single-point (SPt) for solvation free energy calculations. For net-charged species however, MMFF94 charges are used for the conformer free energy estimation, even if the flag value selected is different than `mmff94`. The defaults are different because the science behind the solvation free energy calculation [Nicholls-2010] was specifically developed using the "NoSymSPt" variant of AM1BCC charges, whereas the conformer free energies require the robustness of the canonical AM1BCC charging scheme (symmetric charges from a constrained AM1 optimization) towards large changes in conformation over the course of geometry optimization. In addition to the default `calculationDependent`, the other possible values of the parameter `type` are `am1bccSymOpt`, `am1bccNoSymOpt`, `am1bccSymSPt`, `am1bccNoSymSPt`, `mmff94`, and `input`. The first four refer to different variants of the AM1BCC charging scheme; the next applies MMFF94 charges and the last is used to specify user-defined charges (which are read in from the input structure). If `input` is selected, then the value of "-ionic" is automatically set to `input`.

CHAPTER

SIX

THEORY

6.1 SZYBKI Theory

6.1.1 MMFF94 Force Field

The MMFF potential expression is

$$V_{MMFF} = \sum_b V_b + \sum_a V_a + \sum_s V_s + \sum_o V_o + \sum_t V_t + \sum_v V_v + \sum_c V_c,$$

where the seven terms describe bond stretching (*b*), angle bending (*a*), stretch-bending (*s*), out-of-plane bending (*o*), torsion (*t*), van der Waals (*v*) and electrostatic (*c*) interactions. Their functional forms are given below.

Bond Stretching

For a bond *b* between atoms *i* and *j*, the stretching potential is

$$V_b = 143.9325 \frac{k_{ij}}{2} \Delta r_{ij}^2 (1 + c_s \Delta r_{ij} + 7/12 {c_s}^2 \Delta r_{ij}^2),$$

where k_{ij} is the force constant, Δr_{ij} is the difference between the actual and reference bond lengths, and c_s is a so-called "cubic-stretch" constant for which the value is -2 Å^{-1}.

Angle Bending

The bending potential of a bond angle *a* made by the bonds between the atoms *i* and *j* and the atoms *j* and *k* is given by

$$V_a = 0.043844 \frac{k_{ijk}}{2} \Delta \vartheta_{ijk}^2 (1 + c_b \Delta \vartheta_{ijk}),$$

where k_{ijk} is the force constant, $\Delta \vartheta_{ijk}$ is the difference between the actual and reference bond angles, and c_b is the so-called "cubic-bend" constant for which the value is $-0.4 rad^{-1}$.

Stretch-Bend Interaction

The coupling between the stretching potential of two bonds forming a bond angle and bending that angle is described by

$$V_s = 2.5121 (k_{ijk} \Delta r_{ij} + k_{kji} \Delta r_{kj}) \Delta \vartheta_{ijk},$$

where k_{ijk} and k_{kji} are force constants which couple stretches of *i-j* and *k-j* to the *i-j-k* bend respectively. Δr and $\Delta \vartheta$ are defined above.

Out-of-Plane Bending

For a trigonal center *j*, the potential of displacement for an atom *l* bonded to atom *j* out of plane *i-j-k* is

$$V_o = 0.043844 \frac{k_{ijkl}}{2} \chi_{ijkl}^2$$

where k_{ijkl} is the force constant and χ_{ijkl} is an angle formed by the bond *j-l* and the plane *i-j-k*.

Torsion Interactions

For every four bonded atoms *i-j-k-l*, the torsion interaction is described by the term

$$V_t = 0.5(V_1(1 + \cos\Phi) + V_2(1 - \cos 2\Phi) + V_3(1 + \cos 3\Phi),$$

where V_1, V_2 and V_3 are constants depending on atoms *i*, *j*, *k*, and *l*, and Φ is the dihedral angle formed by bonds *i-j* and *k-l*.

Van der Waals Interactions

For a pair of atoms *i* and *j* separated by three or more bonds, where the distance between them is r_{ij}, MMFF adopts the following van der Waals potential

$$V_v = \epsilon_{ij} \left(\frac{1.07 R_{ij}}{r_{ij} + 0.07 R_{ij}} \right)^7 \left(\frac{1.12 R_{ij}^7}{r_{ij}^7 + 0.12 R_{ij}} - 2 \right),$$

where R_{ij} and ϵ_{ij} are defined as follows:

$$R_i = A_i \alpha_i^{0.25}$$

$$R_{ij} = 0.5(R_i + R_j)(1 + B(1 - \exp(-12\gamma_{ij}^2)))$$

$$\gamma_{ij} = (R_i - R_j)/(R_i + R_j)$$

$$\epsilon_{ij} = \frac{181.16 G_i G_j \alpha_i \alpha_j}{(\alpha_i/N_i)^{0.5} + (\alpha_j/N_j)^{0.5}} \frac{1}{R_{ij}^6}$$

where α_i is the atomic polarizability of atom *i*, *B* is 0.2 or 0.0 if one of the atoms is polar hydrogen, N_i and N_j are the Slater-Kirkwood effective numbers of valence electrons, and G_i, G_j and A_i are scale factors.

Electrostatic Interactions

The electrostatic interaction between two charged atoms *i* and *j* separated by at least three bonds is calculated from the standard Coulombic expression

$$V_c = f \frac{332.0716 q_i q_j}{D(r_{ij} + \delta)}$$

where *D* is the dielectric constant for which the default value is 1, q_i and q_j are the MMFF partial charges on atoms *i* and *j*, r_{ij} is the interatomic distance, and δ is the "electrostatic buffering" constant of 0.05 Å. The scaling factor f is 0.75 for 1,4 interactions and 1.0 otherwise.

Protein-Ligand Amber Potential

Protein-ligand interactions can be described by the Amber force field instead of MMFF potential,

$$V_{Amber} = \sum_{i,j} \left\{ \epsilon_{ij} \left[\left(\frac{R_{ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right\},$$

where the summation is over protein-ligand atom pairs. r_{ij} is the interatomic distance, R_{ij} is the VdW distance for a pair of atoms, q_i and q_j are the Amber partial charges on atoms *i* and *j*, and ϵ_0 is the vacuum permittivity. VdW parameters R_{ij} and ϵ_{ij} and partial charges are taken from work by Wang and coworkers [Wang-J-2000].

6.1.2 SMIRNOFF99Frosst and OPENFF

SMIRNOFF (SMIRKS Natural Open Force Field) is a kind of small molecule force field springing from the Open Force Field Initiative (OFF Initiative or OFFI). The key feature of this force field is its chemical representation of parameters by using extended SMARTS patterns. "Extended" here means that the SMARTS patterns also use atom assignment syntax from SMIRKS. For example, `[*:2]~[*:1]~[#1]` specifies three atoms, where the first is assigned to be atom 2, the second atom is assigned to be atom 1, and the third atom is not assigned. This format frees the force field from using atom types; instead it uses the direct chemical perception of the extended SMARTS patterns [Mobley-2018]. Compared to traditional atom typing approaches, this representation greatly reduces the number of parameters needed to specify a general small molecule force field and makes each parameter more independent.

While it currently has a traditional "Amber" type functional form as specified below, future versions expect to modify the functional form. The OPENFF Initiative release periodic revisions of the parameters which include changes to the chemical specifications (i.e., the extended SMARTS patterns) as well as the numerical parameters. The revision used by the API points will be given with the results.

SMIRNOFF99Frosst OPENFF1.0.0 (released in October 2019) force fields have six terms

$$V_{SMIRNOFF} = \sum_b V_b + \sum_a V_a + \sum_o V_o + \sum_t V_t + \sum_v V_v + \sum_c V_c$$

describing bond stretching (*b*), angle bending (*a*), out-of-plane displacement (*o*), torsion (*t*), van der Waals (*v*), and electrostatic (*c*) interactions. Their functional forms are similar to those in the AMBER force field and are given below.

Bond Stretching

For *a* bond *b* the stretching potential has a simple harmonic form:

$$V_b = k_b(r - r_0)^2$$

where k_b is the force constant and r, and r_0 are the actual and reference bond lengths, respectively.

Angle Bending

For bond angle *a*, the angle bending potential form is

$$V_a = k_a(\alpha - \alpha_0)^2$$

where k_a is the force constant and α, and α_0 are the actual and reference bond angle values, respectively.

Torsion Interactions

Every four bonded atoms defines a torsion whose energy is represented with one to six terms of a Fourier series

$$V_t = \sum_n V_n/d_n(1 + \cos(p_n\theta - \gamma_n)),$$

where V_n, d_n, p_n, and γ_n are the barrier height, degeneracy, periodicity and phase, respectively, for the *n* component of a torsion whose dihedral angle is θ.

Out-of-Plane Bending

It is defined as the potential of a displacement of the trigonal center atom *a* bonded to three other out-of-plane atoms, *b*, *c*, and *d*. Its functional form is similar to a regular torsion with a single term. Sometimes it is also called an *improper torsion*:

$$V_o = V_n(1 + \cos(p_n\theta - \gamma_n)).$$

Since one can define three improper torsions of moving a trigonal atom *a* out of a plane defined by atoms *b*, *c*, and *d*, the energy of such a displacement is calculated as one third of the sum of those torsions.

Van der Waals Interactions

For a pair of nonbonded atoms *i* and *j*, a SMIRNOFF force field adopts Lennard-Jones potential

$$V_v = \epsilon_{ij}\left[\left(\frac{R_{ij}}{r_{ij}}\right)^{12} - 2\left(\frac{R_{ij}}{r_{ij}}\right)^{6}\right],$$

where ϵ_{ij} is well depth and R_{ij} and r_{ij} are the equilibrium and actual distance between atoms *i* and *j*, respectively.

Electrostatic Interactions

A simple coulomb term

$$V_c = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

represents coulomb interactions, where q_i and q_j are partial atomic charges, ϵ_0 is the vacuum permittivity, and r_{ij} is the distance between atoms *i* and *j*.

6.1.3 Entropy Evaluation

Ligand entropy is evaluated as a sum of configurational entropy (S_c) and solvation entropy (ΔS_s):

$$S = S_c + \Delta S_s$$

Configurational Entropy

Configurational entropy is calculated as

$$S_c = kN\left[1 + \ln\left(\frac{q}{N}\right) + \frac{T}{q}\frac{\partial q}{\partial T}\right],$$

where q is the conformation dependent partition function:

$$q = q_t \sum_{i=1}^{n_c} e^{-\frac{\epsilon_i}{kT}} q_{iv} q_{ir}.$$

Here q_t, $q_i r$, and $q_i v$ are the translational, rotational, and vibrational partition functions, respectively, and n_c is the number of unique conformations in the ensemble. All three partition functions are calculated from the classical statistical mechanics expressions which could be found in *Statistical Mechanics* by Donald McQuarrie ([McQuarrie-1976]). Vibrational frequencies for each conformation, needed for evaluation of q_{ir} are derived from diagonalization of a Hessian matrix obtained from quasi-Newton optimization when convergence is achieved. Eigenvalues λ_i of the mass-weighted Hessian

$$\mathbf{H}^m = \mathbf{M}^{-1/2}\mathbf{H}\mathbf{M}^{-1/2}$$

are converted into wave numbers $\tilde{\nu}_i$ according to

$$\tilde{\nu}_i = \frac{1}{2\pi c}\sqrt{\lambda_i}.$$

Solvation Entropy

Solvation entropy is split into electrostatic and hydrophobic parts:

$$\Delta S_s = \Delta S_{s,elec} + \Delta S_{s,hyd}$$

The electrostatic part of solvation entropy is divided into the bulk component and tight electrostatic polar solute-water interactions (hydrogen bonds). The bulk contribution is estimated from the temperature dependence of the solvent dielectric constant as

$$\Delta S_{s,elec_bulk} = -\left(\frac{\partial \Delta G_s}{\partial \epsilon_{solv}}\right)\left(\frac{\partial \epsilon_{solv}}{\partial T}\right).$$

The second term of the electrostatic solvation entropy is estimated as a constant of 28 J/(mol K).

The hydrophobic term, $\Delta S_{s,hyd}$, is evaluated as

$$\Delta S_{s,hyd} = -\left(\frac{\partial \Delta G_{s,hyd}}{\partial T}\right),$$

where $\Delta G_{s,hyd}$ consists of three components

$$\Delta G_{s,hyd} = \Delta G_{cav} + \Delta G_{VdW} + \Delta G_{Ind},$$

describing the free energy of cavitation, solute-solvent van der Waals, and inductive terms, respectively. The cavity formation term is calculated from Scaled Particle Theory [Pierotti-1976]. Analytical expressions for ΔG_{VdW} and ΔG_{Ind} terms are also taken from the 1976 Pierotti review.

Protein-Bound Ligand Entropy

The configurational entropy of a protein-bound ligand is calculated totally as vibrational entropy for 3N modes, assuming that three rotational and three translational degrees of freedom of a solution ligand are transformed into low vibrational degrees of freedom for the bound ligand.

Solvation entropy for a ligand in the active site is assumed to be a sum of its fractional value in solution determined by the percentage of the ligand surface exposed to the solvent, $f\Delta S_s$, and a partial desolvation entropy of the protein active site, ΔS_{des},

$$S_{protein} = S_v + f\Delta S_s + \Delta S_{des},$$

where f is the fraction of ligand surface exposed to the solvent. It is important to notice that $S_{protein}$ is not an experimentally measurable value, and that only the difference between $S_{protein}$ and $S = S_c + \Delta S_s$ might be compared with experimental binding entropy.

6.2 Nonplanar Aromatic Rings in Protein-Bound Ligands

Optimization of a ligand in a protein active site, especially if the protein conformation is held fixed during optimization, can often lead to distortions of the aromatic ring structures. Aromatic rings in optimized ligands are more prone to distortions when the initial pose structures are the output of docking, since tools such as **OEDocking** or **POSIT** try to accommodate a ligand into a rigid receptor pocket. Optimization of a ligand in the protein pocket helps relieve both intramolecular close contacts within the ligand and intermolecular clashes between the ligand and the protein. However, such relaxation of the van der Waals clashes can sometimes come at the expense of nonplanarity in the aromatic ring structures.

Ligand force fields used in optimization, such as `Sage`, `Parsley`, and `MMFF`, put a low energy constant in defining the out-of-plane potential of aromatic rings. The low energy penalty for aromatic rings to deviate from planarity in the force fields is also supported by quantum mechanical calculations which estimate only a 0.5 kcal/mol penalty for ~5 degrees of deviation for a benzene ring. The out-of-plane potential being the lowest vibrational motion during optimization means it can easily be bent by a few degrees during optimization.

6.3 Freeform Theory

freeform has two distinct functions:

“freeform -calc conf…”: Evaluation of the conformer free energy in solution, meaning the free energy required to select a particular conformer out of the whole conformational ensemble in solution.

“freeform -calc solv…”: Fast estimation of the small molecule solvation free energy and the XlogP calculated partition coefficient (with graphical representation of fragment-based contributions to these physical quantities).

6.3.1 Conformer Free Energies

Calculating the Partition Function

The method is based upon combining ligand conformational search, energy minimization, and entropy estimation in the workflow shown in Figure 1 below.

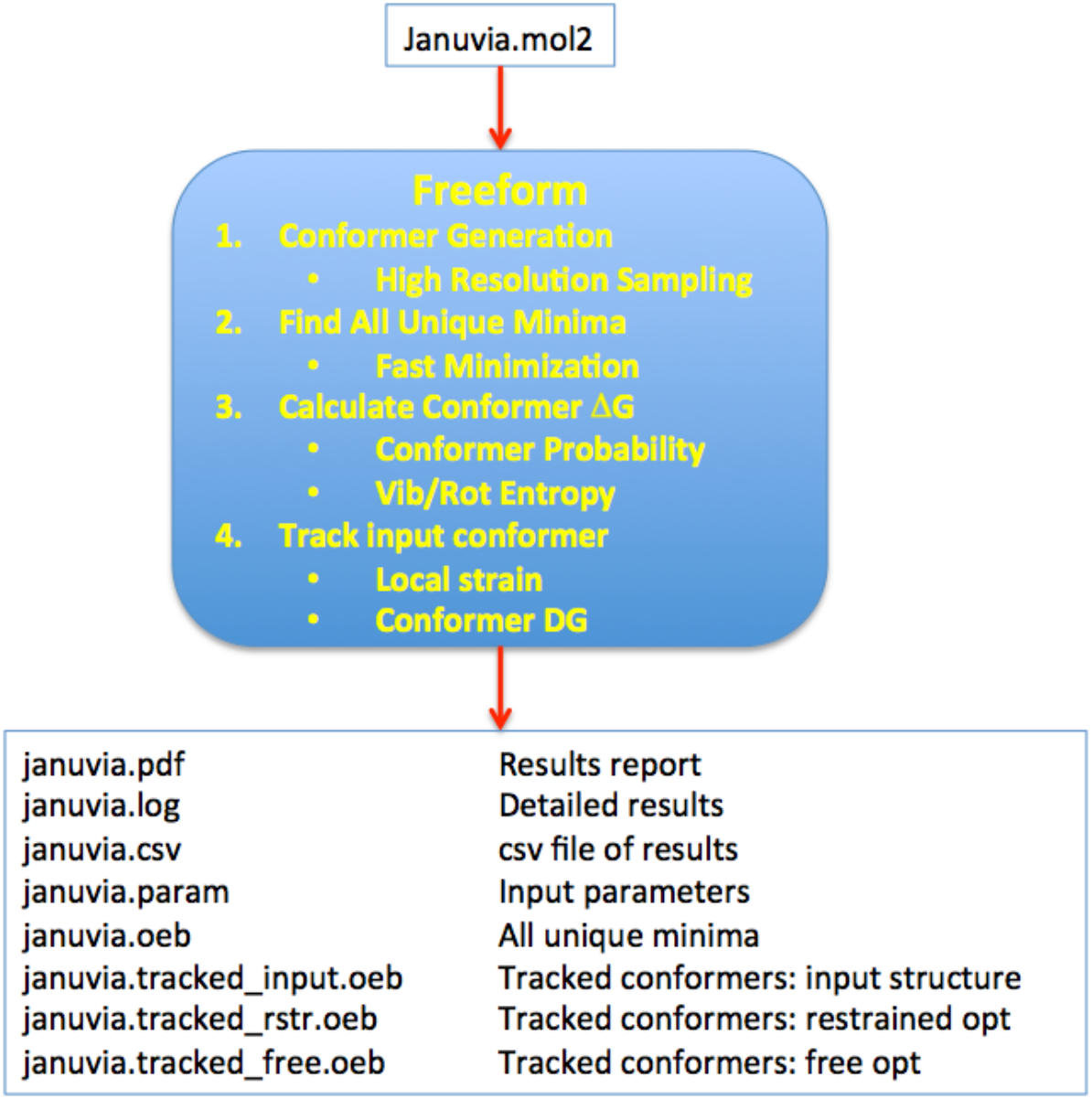


Fig. 1: **Figure 1.** Stages and workflow in the conformer free energy calculation.

The conformational search is done at a very high resolution using the conformation generator **OMEGA** [Hawkins-2010]. The energy minimization uses Halgren's MMFF94s force field [Halgren-VI-1999] and consists of several stages, all aimed at arriving at the most thorough sampling of the accessible conformational space of the ligand. Duplicate conformers are removed from the final minimized set, leaving an ensemble of n_c unique conformers, referred to below as the *Ensemble of Unbound Minima*, which we use to create an approximation to the partition function of the unbound ligand. This is illustrated conceptually in Figure 2.

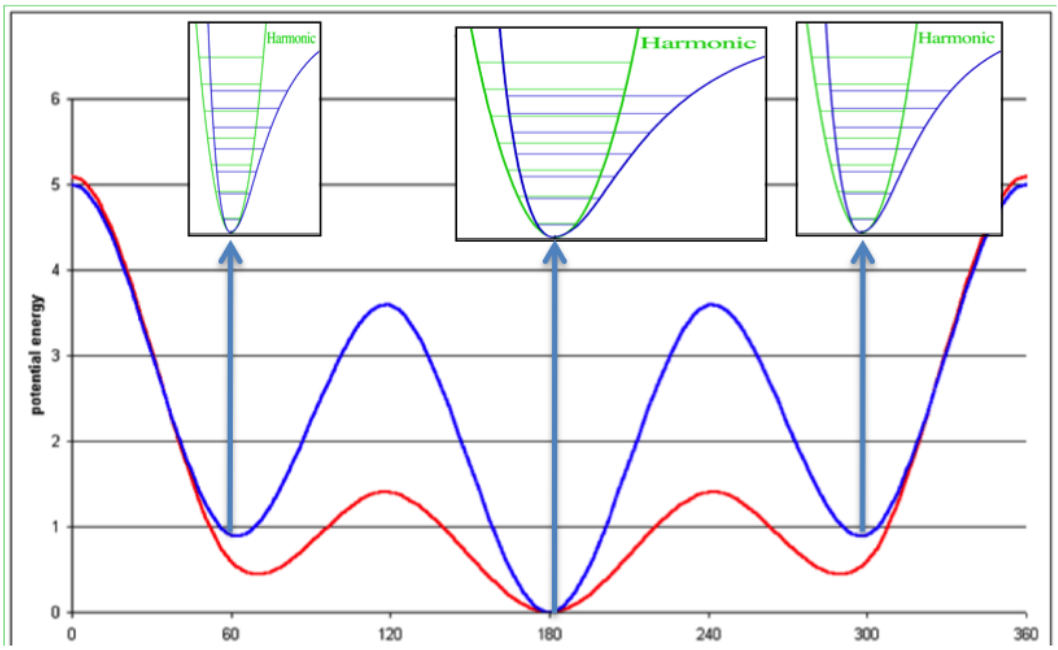


Fig. 2: **Figure 2.** Concept of ligand entropy as a sum-over-states of conformer entropies.

To the molecule's gas phase potential based on the MMFF94 force field (shown by the red line), Sheffield solvation energies are added to give a solvation-corrected potential (shown by the blue line) for which the minima are identified. The analytic second derivative of each minimum is then used to calculate the entropy contribution of each energy well according to Wlodek and coworkers [Wlodek-2010]. An energy minimum with a wider than average energy well will have a higher entropy, which will decrease the conformer free energy to select that conformer, while the converse will be true for a narrower than average energy well.

With this, the contribution Q_i of each energy minimum to the overall partition function Q can be calculated as

$$Q_i = q_t q_{ir} q_{iv} e^{-\epsilon_i / RT}$$

$$Q = \sum_{i=1}^{n_c} Q_i$$

Here ϵ_i is the relative internal energy (including solvation and zero-point energies) of the conformer relative to the global minimum conformation. q_t, $q_i r$, and $q_i v$ are the translational, rotational, and vibrational partition functions, respectively, describing the entropic contributions from that conformation. n_c is the number of unique conformations in the ensemble. More details on these terms are given in the *SZYBKI theory section*. In practice, we do not compute the translational partition function q_t because it is constant for all conformers, so it cancels out of the conformer free energies.

Computing the Conformer Free Energies

Based upon this approximation of the partition function, we calculate conformer free energies: the free energy required to select a particular conformation from the unbound ensemble of all conformers equilibrating in aqueous solution. Strictly speaking, this is a Helmholtz free energy, not a Gibb's free energy, because we are neglecting the differential PV (pressure*volume) contribution between conformers, but this should be negligible. Based on the above conformer and ensemble partition functions, the conformer free energy for any conformer is calculated straightforwardly as:

$$\Delta A_i = -RT(\ln Q_i - \ln Q).$$

In addition to the graphic output file, which shows a plot of the calculated free energies of conformations versus their relative internal and solvation energies, energetic and thermodynamic results are stored in the log and CSV files.

Tracking Conformers

Often we are interested in one or more particular conformers, such as a known or hypothetical bound conformer of a ligand (the "bioactive" conformer), or perhaps a number of top-scoring poses from a docking run. One of **Freeform**'s main purposes is to estimate the free energy cost of selecting such conformers out of the unbound ensemble, a quantity we will refer to as the *Global Strain Energy*. **Freeform** tracks these conformers using the `freeform -track` flag, followed by the filename containing the input conformers for which ligand strain energies are desired. Note that this is distinct from the input file specified with the `-in` flag, which specifies the molecule from which to construct the unbound ensemble. All conformers in the file specified after the `freeform -track` flag will be tracked by `freeform`, and the user will get a direct readout of the energy required to select that particular conformation out of the aqueous ensemble. Figure 3 shows how the various components of *Local and Global Strain Energies* are calculated.

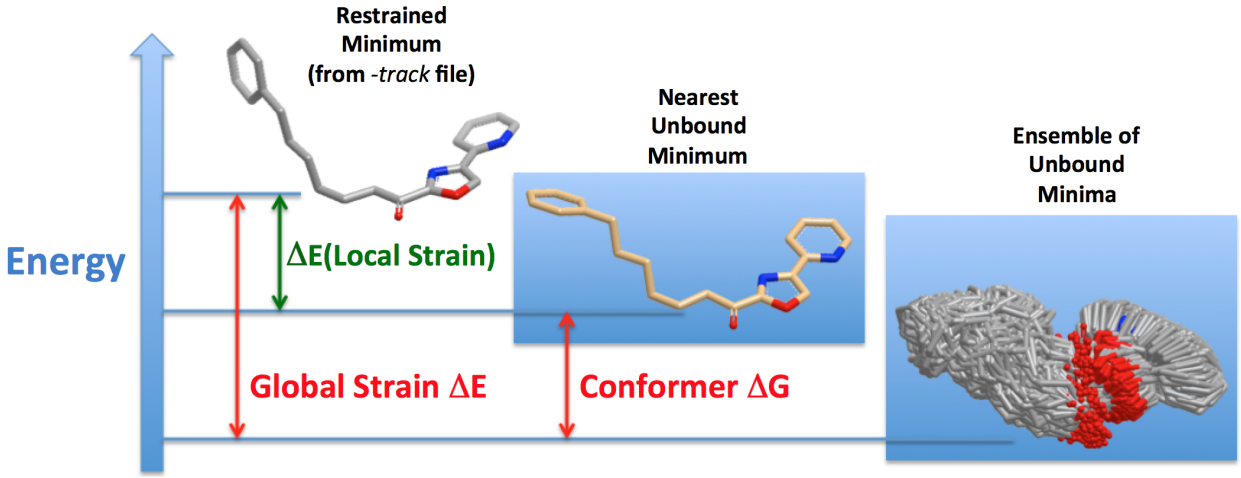


Fig. 3: **Figure 3.** The components of *Local and Global Strain Energies*.

A key issue is that the input 3D coordinates of the tracked conformer may be of artificially high energy, usually due to small deviations of bond lengths and bond angles from the force field's optimum values; this is often true particularly of ligands from X-ray structures. For this reason, the input structure is cleaned up with a restrained optimization using strong harmonic restraints to the input coordinates. The strong restraints retain the shape of the ligand (usually to within 0.2 Å RMSD) but resolve the artificially high energy. The energy of this restrained minimum structure is used in calculating the *Local Strain Energy* as shown in Figure 3 above.

Since conformer free energies must be calculated from energy minima in order to characterize the entropy, an unconstrained minimization is now required to find the *Nearest Unbound Minimum* to the input structure. This minimization allows the torsions in the input structure to relax away from where they may have been distorted from the nearby local minimum in order to fit into the active site. **Freeform** keeps track of this "distortion" strain energy as *Local Strain Energy*. From this point, **Freeform** simply includes the *Nearest Unbound Minimum* as just another energy minimum in the aqueous ensemble and calculates its conformer free energy, which is specifically reported in the PDF and log output (see examples). Thus, within **Freeform**, the *Global Strain Energy* for the input 3D structure would be considered to consist of a) the *Local Strain Energy* required to distort the *Nearest Unbound Minimum*, so the ligand can adopt the shape of the input tracked conformer, and b) the conformer free energy required to select the *Nearest Unbound Minimum* (i.e., the closest local minimum to the input structure) from the entire *Ensemble of Unbound Minima*.

6.3.2 Solvation Energy Estimation

How It Is Calculated

The term "solvation energy" is defined here as the standard free energy of transferring a compound from the gaseous phase into dilute aqueous solution, ΔG^0_{solv}.

Solvation energy is a crucial component of the solubility energetics and is directly related to hydrophilicity/hydrophobicity of a compound; therefore one can expect it is correlated with another measure of hydrophobicity, logP, as illustrated in Figure 4 below. Such a correlation, particularly when a functional group's contribution is considered, might not exist. **Freeform** shows the graphical group contributions to solvation free energy and XlogP.

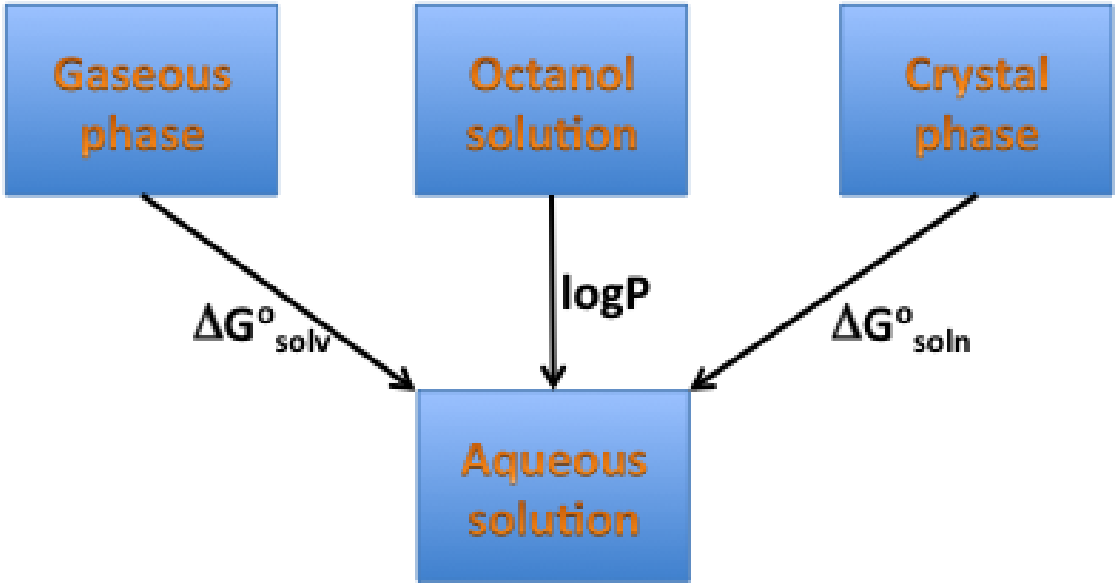


Fig. 4: **Figure 4.** Solvation, solubility, and hydrophobicity.

The method is based on the continuum solvent model in which a Poisson–Boltzmann (PB) solver ZAP [Grant-2001] is used. The calculation is performed on the lowest energy gas-phase conformation found with the MMFF94 force field from the optimized set of conformations generated by the conformation generator **OMEGA** [Hawkins-2010]. A set of atomic radii ZAP9 and AM1BCC partial charges as described by Nicholls [Nicholls-2010] is applied for all PB calculations. Atomic and group contributions to the free energy of solvation for the input compound are calculated from atomic electrostatic potentials and atomic area terms representing the hydrophobic part of solvation. Assuming that a functional group has n atoms, its calculated solvation free energy ΔG_s is

$$\Delta G_s = \sum_i^n [(V_{i,s} - V_{i,v})q_i + S_i],$$

where $V_{i,s}$ and $V_{i,v}$ are calculated electrostatic potentials on atom i in solution and in vacuum, respectively, q_i is atom partial charge, and S_i is atomic contribution to hydrophobic part of solvation evaluated from a simple surface area model assuming 6.3 cal/(mol Å) as a value for the microscopic surface tension coefficient. Graphical representation of group (or atomic) contributions to the free energy of solvation is performed with the OpenEye tools **OEDepict TK** and **Grapheme™ TK**.

Counterintuitive group contributions to solvation energies

Solvation free energy for molecular ions might not be trivial to interpret because of very strong intrinsic electrostatic interactions. One can most easily begin to understand these effects by considering zwitterions. A common zwitterion will contain both a group with a positive formal charge and a group with a negative formal charge. It is well known that zwitterions, though still having high solvation energies, have significantly smaller solvation energies than compounds with two formal charges of the same sign. In fact, zwitterion solvation energies are typically smaller than the solvation energy of the analog molecule with a single charge. For instance, as the examples in Figure 5 show, the solvation energy of zwitterionic phenylalanine is -35.4 kcal/mol, while the solvation energy of the formamide analog and the methyl ester analog are -74.9 and -64.6 kcal/mol, respectively.

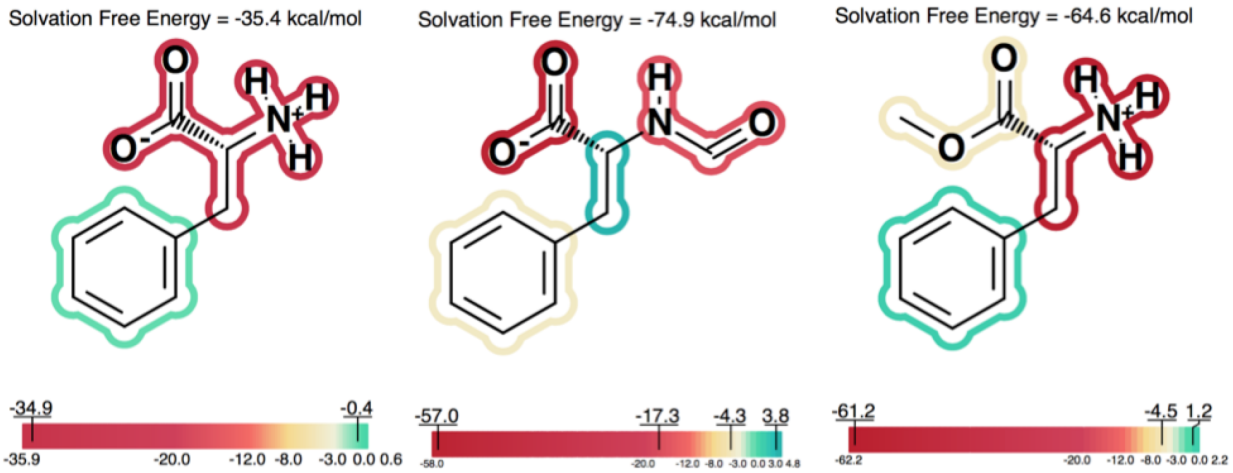


Fig. 5: **Figure 5.** Solvation energy of zwitterionic phenylalanine and two singly charged analogs.

One can consider, then, that adding a charge of the opposite sign of the current molecular ion contributes a positive 30 to 40 kcal/mol to the solvation energy. A similar situation, perhaps even more dramatic, occurs in the case of intramolecular salt bridges, where positively and negatively charged groups are positioned in a very short distance. That kind of interaction does not only exist in macromolecules: NMR and hydrogen exchange rate experiments have also confirmed the presence of salt bridges between arginine or lysine and aspartate or glutamate side chains in short peptides ([Mayne-1998]; [Otter-1989]). Making positive contributions to the solvation energy is generally considered a hydrophobic effect, yet here the contribution is made by a charged species, which is somewhat counterintuitive at first. Nevertheless, in this context, one can understand how, under the right conditions, a normally hydrophilic functional group can make a significant positive contribution to the solvation energy. The more confusing circumstance is when, rather than a simple zwitterion, we see a similar effect in a molecule with either multiple charges of one type (either positive or negative) and a single charge of the opposite sign. Consider a molecule with 2 negative ions, one positive ion and a total charge of -1, like the one shown in Figure 6.

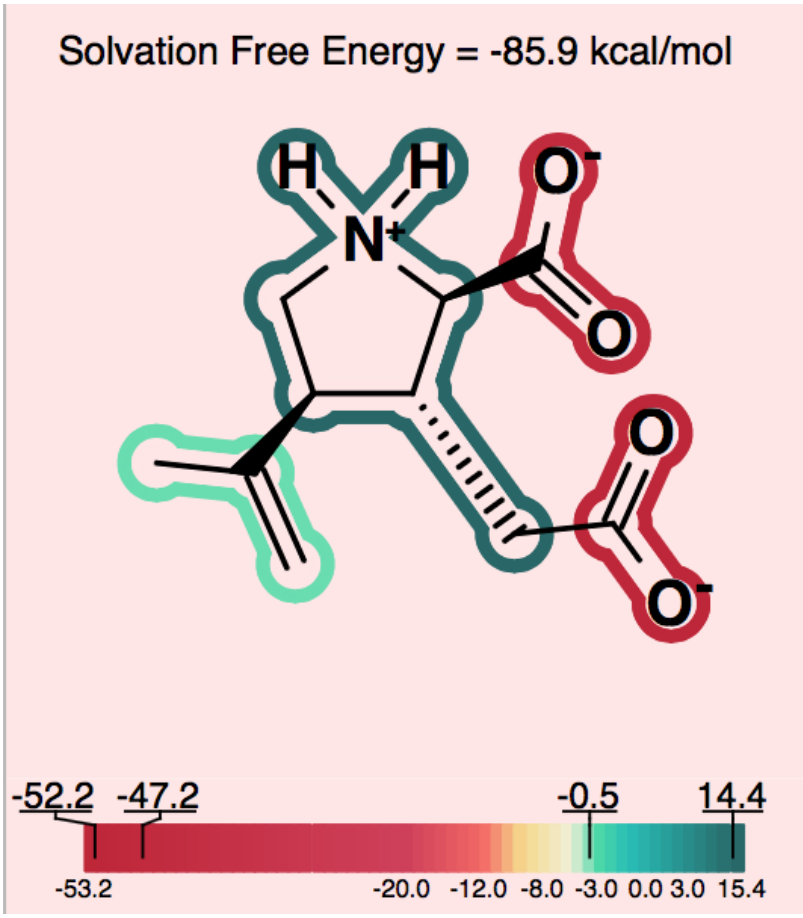


Fig. 6: **Figure 6.** Counterintuitive group contributions to solvation.

In this case, the positive ion will change the formal charge from -2 to -1. This will make the total solvation energy significantly less negative (a positive contribution to the solvation energy). The positive ionic functional group in this case will have a large positive solvation energy. While a charged group is indeed not hydrophobic, in this instance, one can understand that it makes the solvation energy less negative in a manner similar to the way a hydrophobic group might, but to a larger degree. In more subtle cases, one can observe a similar though less dramatic hydrophobicity in a molecule with a single charge, either positive or negative, and another fragment that makes a large neutralizing contribution to the partial charge of the molecule.

In order to alert the user, species which contain strong intramolecular electrostatic interactions of the nature described above are depicted on a light pink background. This should act as a reminder to users to consider the net charge of the molecule in interpreting the relative contribution of each fragment to the solvation energy.

CHAPTER

SEVEN

UTILITIES

7.1 OptLigandInDU

7.1.1 Overview

OptLigandInDU is an application to optimize a ligand or a series of ligands in a rigid protein active site. This is suitable for screening a large amount of docked ligands into a protein receptor.

7.1.2 Example Commands

Ligand Optimization in a Protein Active Site

This optimizes the ligands in a protein active site using the FF14SB-Parsley force field.

Input files

- **1H1Q_AB_receptor.oedu**: OEDU file containing the protein active site
- **1H1Q_AB_fred_docked.oeb**: OEB file containing the ligand to optimize

Command line

```
prompt> optligandindu 1H1Q_AB_receptor.oedu 1H1Q_AB_fred_docked.oeb 1H1Q_AB_
↪fred_docked_opt.oeb
```

Output files

- **1H1Q_AB_fred_docked_opt.oeb**: OEB file containing optimized ligands
- **OptLigandInDU_rpt.csv**: CSV file containing optimization report

7.1.3 Report File

The CSV report file contains the following fields.

- **Molecule**: SMILES representation of the ligand molecule.
- **Title**: Title of the ligand molecule.
- **ConfID**: Ligand conformer index.
- **Inter Ene**: Final intermolecular energy between the protein target and the ligand (kcal/mol).
- **Ligand Ene**: Final intramolecular energy of the ligand (kcal/mol).
- **Ligand RMSD**: Root mean square deviation of the ligand between initial and final structures (Å).
- **ElapsedTime(s)**: Elapsed time for the optimization process (seconds).
- **Status**: Status of the optimization. (Reported only when the optimization fails. Otherwise, this field is empty.)

Optimize a Ligand Pose in a Rigid Protein

This performs a constrained optimization of the ligand in the rigid protein active site, using the FF14SB-Parsley force field.

Input files

- **1H1Q_AB_receptor.oedu**: OEDU file containing the protein active site
- **1H1Q_AB_fred_docked.oeb**: OEB file containing the ligand to optimize

Command line

```
prompt> optligandindu -du 2IKO.oedu -in 1H1Q_AB_fred_docked.oeb -out 1H1Q_AB_
↪fred_docked_opt.oeb -optimize poseCartesian
```

Output files

- **1H1Q_AB_fred_docked_opt.oeb**: OEB file containing optimized ligand

7.1.4 Command Line Help

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

```
> optligandindu --help
```

will generate the following output:

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

7.1.5 Required Parameters

-du <filename>

An OEDU file with a design unit, containing the protein active site. If the file contains multiple design units, only the first one is used.

[keyless parameter 1]

-in <filename>

Molecular input file name containing 3D coordinates in any format supported by **OEChem**.

[keyless parameter 1]

Acceptable molecule file formats are listed below.

Table 1: *SZYBKI File Format Support*

File extension	Description
mol	MDL Mol File
mmd, mmod	Macromodel
mol2	Tripos Sybyl mol2 file
oeb	New Style OEBinary
sd, sdf	MDL SD File
xyz	XMol XYZ format

7.1.6 Optional Parameters

7.1.7 File Options

-log

The argument for this flag specifies the name of the log file. The level of detail for logfile information can be altered using the *-verbose* flag. Generation of an output log may be disabled by providing `nul` as a argument in Windows and `/dev/null` as an argument on Linux and macOS. [default = `prefix` _log.txt]

-prefix

The argument for this flag defines the prefix to be used for various information and data files generated. Most important among these is the '*prefix_parm.txt*' file which includes a copy of all the parameters used in the run. The prefix is also used to generate a default log file name if not explicitly specified with the *-log* flag. [default = <app_name>].

-verbose

This is a boolean flag that controls the level of detail written to the log file. By default only minimal information is written to the log file. Verbose logging will cause more information to be written to the log file in order to follow behavior during program execution. [default = false]

-molNames

This parameter takes a text file containing a list of molecule names (one name per line in the file). If this parameter is set then only molecules in the input file(s) (see parameter *-in*) with names that match those in the text files will be read in.

The general purpose of this flag is to provide an easy mechanism for reading a few specific molecule(s) that are contained in a large file, without having to extract those molecules by hand from the input molecules file. [default = NONE].

-progress

Show progress on screen. Options are 'none', 'dots', 'log' and 'percent'. The 'dots' options will displays dots on screen to show molecules completed. The 'log' option will duplicate the log file on screen. The 'percent' option will track progress through the input file. [default = none]

Input Options

-proteinMask

Design unit components mask defining the subset of design unit components to be used as `protein` during optimization. Multiple components can also be combined as a comma-separated string to create the input.

Possible values include cofactors, counter_ions, excipients, lipids, metals, nucleic, other_cofactors, other_ligands, other_nucleics, other_proteins, packing_residues, polymers, post_translational, protein, solvent, and sugars.

Predefined multicomponent values:

- **targetComplex** = protein,nucleic,cofactors,solvent,metals,counter_ions,lipids,other_proteins, other_nucleics,other_ligands,other_cofactors.
- **targetComplexNoSolvent** = protein,nucleic,cofactors,metals,lipids,other_proteins, other_nucleics,other_ligands,other_cofactors.
- **macroMolComponents** = protein,nucleic,other_proteins,other_nucleics.

[Default=targetComplex]

`-receptorMask` `[Default=True]`

Flag indicating if the `Design unit components mask` defining the subset of design unit components to be used as the `protein` during optimization should be picked up based on the mask defined in the receptor. If the input `Design Unit` does not contain a receptor, the optimizer automatically falls back to using the `-proteinMask`.

`-ignoreAroBent` `[Default=False]`

Flag indicating if optimization should not fail due to excess deviation from planarity for aromatic rings in optimized ligands. By default, optimization would fail if aromatic rings deviate from planarity in an optimized ligand by more than five degrees on average, or if certain torsion exceeds a maximum of 10 degrees.

Output Options

`-out` `<filename>`

Output file name, in any format supported by OEChem, for an optimized ligand.

[keyless parameter 2]

Optimization Options

`-optimize` `[Default=poseCartesian]`

Optimization type. Choices: [0] cartesian: performs a full cartesian optimization, or [1] poseCartesian: performs a constrained cartesian optimization, ensuring to hold the ligand pose.

`-ff` `[Default=ff14sb_sage]`

The force field to use for optimization. A predefined force field can be used by choosing one from the list of choices. A different SMIRNOFF/OpenFF formatted small molecule force field can be used with ff14SB by passing in the small molecule force field OFFXML file as the argument. Choices: `mmff94`, `mmff94s`, `mmff_amber`, `mmffs_amber`, `ff14sb_parsley`, and `ff14sb_sage`.

`-ligandCharge` `[Default=current]`

Charges to be assigned for the ligand. The default value of `current` refers to using the existing charges on the ligand. Choices: [0] current, [1] am1bcc [2], am1bccelf10, or [3] MMFF.

`-gradTol` `[Default=1.0e-6]`

Root mean squared (RMS) gradient tolerance for convergence and termination of optimization.

`-maxIter` `[Default=1000]`

Maximum number of iterations for termination of optimization. Optimization is terminated if either the gradient tolerance `gradTol` or the maximum iterations limit, whichever occurs first, is reached.

`-solventModel` `[Default=vacuum]`

Solvent model to be used during optimization. Choices: [0] vacuum, [1] sheffield, or [2] pb.

7.2 OptimizeDU

7.2.1 Overview

OptimizeDU is an application to optimize a protein-ligand complex inside a design unit. This is suitable for lead optimization, where a complete optimization which includes solvent forces and possibly partial relaxation of the protein residues in the direct proximity to the ligand desired.

7.2.2 Example Commands

Protein-Ligand Optimization in a Design Unit

This optimizes the protein-ligand complex in the design unit using the FF14SB-Parsley force field. Complete protein residues within 2 angstroms from the ligand are considered flexible by default.

Input files

- **1H1Q_AB_receptor.oedu**: OEDU file to optimize protein-ligand complex

Command line

```
prompt> optimizedu 1H1Q_AB_receptor.oedu 1H1Q_AB_opt.oedu
```

Output files

- **1H1Q_AB_opt.oedu**: OEDU file containing optimized protein-ligand complex
- **OptimizeDU_rpt.csv**: CSV file containing optimization report

7.2.3 Report File

The CSV report file contains the following fields.

- **Molecule**: SMILES representation of the ligand molecule.
- **Title**: Title of the ligand molecule.
- **Inter Ene**: Final intermolecular energy between the protein target and the ligand (kcal/mol).
- **Ligand Ene**: Final intramolecular energy of the ligand (kcal/mol).
- **Protein Ene**: Final intramolecular energy of the flexible part of the protein target (kcal/mol).
- **Ligand RMSD**: Root mean square deviation of the ligand between initial and final structures (Å).
- **Protein RMSD**: Root mean square deviation of the protein target between initial and final structures (Å).
- **ElapsedTime(s)**: Elapsed time for the optimization process (seconds).
- **Status**: Status of the optimization. (Reported only when the optimization fails. Otherwise, this field is empty.)

Optimize a Ligand Pose in a Partially Flexible Protein

This performs a constrained optimization of the ligand in the partially flexible protein active site, using the FF14SB-Parsley force field. Complete protein residues within 2 angstroms from the ligand are considered flexible by default.

Input files

- **1H1Q_AB_receptor.oedu**: OEDU file to optimize protein-ligand complex

Command line

```
prompt> optimizedu -in 1H1Q_AB_receptor.oedu -out 1H1Q_AB_opt.oedu -optimize␣
↪poseCartesian
```

Output files

- **1H1Q_AB_opt.oedu**: OEDU file containing optimized protein-ligand complex

7.2.4 Command Line Help

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

```
> optimizedu --help
```

will generate the following output:

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

7.2.5 Required Parameters

-in <filename>

An OEDU file containing one or more design units, containing protein and ligand.

[keyless parameter 1]

7.2.6 Optional Parameters

7.2.7 File Options

-log

The argument for this flag specifies the name of the log file. The level of detail for logfile information can be altered using the *-verbose* flag. Generation of an output log may be disabled by providing `nul` as a argument in Windows and `/dev/null` as an argument on Linux and macOS. [default = `prefix` _log.txt]

-prefix

The argument for this flag defines the prefix to be used for various information and data files generated. Most important among these is the '*prefix_parm.txt*' file which includes a copy of all the parameters used in the run. The prefix is also used to generate a default log file name if not explicitly specified with the *-log* flag. [default = <app_name>].

-verbose

This is a boolean flag that controls the level of detail written to the log file. By default only minimal information is written to the log file. Verbose logging will cause more information to be written to the log file in order to follow behavior during program execution. [default = false]

-molNames

This parameter takes a text file containing a list of molecule names (one name per line in the file). If this parameter is set then only molecules in the input file(s) (see parameter *-in*) with names that match those in the text files will be read in.

The general purpose of this flag is to provide an easy mechanism for reading a few specific molecule(s) that are contained in a large file, without having to extract those molecules by hand from the input molecules file. [default = NONE].

`-progress`

Show progress on screen. Options are 'none', 'dots', 'log' and 'percent'. The 'dots' options will displays dots on screen to show molecules completed. The 'log' option will duplicate the log file on screen. The 'percent' option will track progress through the input file. [default = none]

Input Options

`-proteinMask`

Design unit components mask defining the subset of design unit components to be used as `protein` during optimization. Multiple components can also be combined as a comma-separated string to create the input.

Possible values include cofactors, counter_ions, excipients, lipids, metals, nucleic, other_cofactors, other_ligands, other_nucleics, other_proteins, packing_residues, polymers, post_translational, protein, solvent, and sugars.

Predefined multi-component values:

- **targetComplex** = protein,nucleic,cofactors,solvent,metals,counter_ions,lipids,other_proteins, other_nucleics,other_ligands,other_cofactors.
- **targetComplexNoSolvent** = protein,nucleic,cofactors,metals,lipids,other_proteins, other_nucleics,other_ligands,other_cofactors.
- **macroMolComponents** = protein,nucleic,other_proteins,other_nucleics.

[Default=targetComplex]

`-receptorMask` `[Default=True]`

Flag indicating if the `Design unit components mask` defining the subset of design unit components to be used as `protein` during optimization should be picked up based on the mask defined in the receptor. If the input `Design Unit` does not contain a receptor, the optimizer automatically falls back to using the `-proteinMask`.

`-ignoreAroBent` `[Default=False]`

Flag indicating if optimization should not fail due to excess deviation from planarity for aromatic rings in optimized ligands. By default, optimization would fail if aromatic rings deviate from planarity in an optimized ligand by more than five degrees on average, or if certain torsion exceeds a maximum of 10 degrees.

Output Options

`-out` `<filename>`

An OEDesignUnit file containing the optimized protein-ligand complexes.

[keyless parameter 2]

Optimization Options

`-optimize` `[Default=poseCartesian]`

Optimization type. Choices: [0] cartesian: performs a full cartesian optimization, or [1] poseCartesian: performs a constrained cartesian optimization, ensuring to hold the ligand pose.

`-ff` `[Default=ff14sb_sage]`

The force field to use for optimization. A predefined force field can be used by choosing one from the list of choices. A different SMIRNOFF/OpenFF formatted small molecule force field can be used with ff14SB by passing in the small molecule force field OFFXML file as the argument. Choices: `mmff94`, `mmff94s`, `mmff_amber`, `mmffs_amber`, `ff14sb_parsley`, and `ff14sb_sage`.

-ligandCharge [Default=current]

Charges to be assigned for the ligand. The default value of `current` refers to using the existing charges on the ligand. Choices: [0] current, [1] am1bcc, [2] am1bccelf10, and [3] MMFF.

-gradTol [Default=1.0e-6]

Root mean squared (RMS) gradient tolerance for convergence and termination of optimization.

-maxIter [Default=1000]

Maximum number of iterations for termination of optimization. Optimization is terminated if either the gradient tolerance `gradTol` or the maximum iterations limit, whichever occurs first, is reached.

-solventModel [Default=vacuum]

Solvent model to be used during optimization. Choices: [0] vacuum, [1] sheffield, or [2] pb.

Protein Flexibility Options

-flexRange [Default=2.0]

Distance at which protein residues should be considered flexible. The distance is measured between all ligand atoms and the protein residues. The protein is completely rigid when a value of `0.0` is used.

-residueID [Default=None]

Regular expression (Regex) strings describing residues that should be considered flexible. When a value for `residueID` is provided, it overrides the `-flexRange` (i.e., the flexRange is ignored).

CHAPTER

EIGHT

RELEASE HISTORY

8.1 SZYBKI 2.9.2

Minor internal improvements have been made.

8.1.1 Related Toolkit Information

8.2 Szybki TK 2.9.2

Minor internal improvements have been made.

8.3 SZYBKI 2.9.1

Minor internal improvements have been made.

8.3.1 Related Toolkit Information

Szybki TK 2.9.1

Minor internal improvements have been made.

8.4 SZYBKI 2.9.0

8.4.1 New Features

- The following two new options have been added to both **OptLigandInDU** and **OptimizeDU**:
  - *-receptorMask* enables the use of `proteinMask` from the design unit receptor.
  - *-ignoreAroBent* enables the ability to ignore failure due to excess deviation from planarity for aromatic rings.
- The default for *-optimize* for both **OptLigandInDU** and **OptimizeDU** has been changed to `poseCartesian` to perform constrained Cartesian optimization, ensuring holding of the ligand pose.

8.4.2 Minor Bug Fixes

- **OptimizeDU** no longer crashes when a nonexistent `.lst` or `.list` file is passed as an argument to *-in*.

8.4.3 Related Toolkit Information

Szybki TK 2.9.0

New Features

- A new class, OEOELigandChargeOptions, has been added that provides options related to ligand charge assignment. The following classes now derive from OEOELigandChargeOptions, enabling greater flexibility in ligand charge assignment:
  - OEProteinLigandOptOptions
  - OETorsionScanOptions
  - OEBoundEntropyOptions
  - OELigandEntropyOptions
- The default optimization type has been changed to PoseCartesian in both OEFixedProteinLigandOptimizer and OEFlexProteinLigandOptimizer.
- The following two new constants have been added to the OESzybkiReturnCode namespace:
  - AromaticRingDev: refers to failure due to excessive aromatic distortion.
  - OptimizerFailed: refers to the optimizer failing to find a solution.
- The following class methods now take an optional predicate describing residues that should be considered as part of the protein target during optimization:
  - SetProtein in OEFixedProteinLigandOptimizer
  - Optimize in OEFlexProteinLigandOptimizer
  - Energy in OEFlexProteinLigandOptimizer
- The following new preliminary API classes have been added, enabling optimization of a ligand with torsion constraints:
  - OELigandEnergy
  - OELigandOptOptions
  - OELigandOptResults
  - OETorConstraintOptimizer
  - OETorConstraintOptOptions

Major Bug Fixes

- OEFixedProteinLigandOptimizer and OEFlexProteinLigandOptimizer no longer fail to optimize with the ExcessiveOverlap error code prematurely.

Minor Bug Fixes

- OEFreeFormConfOptions now sets the latest Sage force field as the default.
- An issue has been fixed in OETorsionScan where scanning using the option SetUseInternalCoord set to `true` would occasionally produce large unphysical energies at certain angles.

8.5 SZYBKI 2.8.0

Minor internal improvements have been made.

8.6 Szybki TK 2.8.0

8.6.1 New features

- The constant SAGE_OPENFF refers to the latest version of the Sage OpenFF force field.

8.7 SZYBKI 2.7.1

Minor internal improvements have been made.

8.8 Szybki TK 2.7.1.3

- The constant OESz_OEForceFieldType_SAGE_OPENFF refers to the 2.2.0 version of the Sage-OpenFF force field.

8.9 Szybki TK 2.7.1.0

- OEFixedProteinLigandOptimizer and OEFlexProteinLigandOptimizer now propagate error better when optimization fails.

8.10 SZYBKI 2.7.0

8.11 Szybki TK 2.7.0

8.11.1 New features

- The ability has been added to perform optimization in internal coordinates, with fixed torsions, during a torsion scan. Accordingly, the following additional commands have been added to OETorsionScanOptions:
  - SetUseInternalCoord
  - GetUseInternalCoord
  - SetTolerance
  - GetTolerance
  - SetMaxIter
  - GetMaxIter
- The ability to apply a nonbonded interactions cutoff in OEProteinLigandOptOptions has been added. The following two methods are also available in the class:
  - SetNonBondCutoff
  - GetNonBondCutoff
- Both OEFixedProteinLigandOptimizer and OEFlexProteinLigandOptimizer now apply a nonbonded interactions cutoff of *40.0* by default.

- A new class, OETorsionScanner, has been added to provide greater flexibility over the existing function OETorsionScan in extracting intermediate results from the scanning.

8.11.2 Major bug fixes

- An issue where the overloaded method SetTorsionConstraint would occasionally fail has been fixed.

8.11.3 Minor bug fixes

- Validation of user-selected torsion in torsion scan has been added. If a torsion passed to function OETorsionScan or method Scan does not exist, the torsion scan code stops with a message that the torsion does not exist in the input molecule.

8.12 SZYBKI 2.6.0

8.12.1 Minor bug fixes

- **OptLigandInDU** no longer attempts to write an empty molecule in the output file when the optimization fails.
- **OptimizeDU** now fails with an appropriate message when attempting to optimize an apo design unit.

8.13 Szybki TK 2.6.0.1

- New constant SAGE_OPENFF210 has been introduced that refers to the Sage 2.1.0 force field. The constant SAGE_OPENFF now refers to this latest version of Sage force field.

8.14 Szybki TK 2.6.0.0

8.14.1 New features

- Three classes have been added to facilitate using ff14SB/OpenFF potential for bound ligands and to bypass using OESzybki:
  - OEBoundEntropyOptions
  - OELigandEntropyOptions
  - OEEntropyResults
- A new function, OEBoundLigandEntropy, has been added to calculate the entropy of a bound ligand.
- A new function, OELigandEntropy, has been added to calculate the entropy of a free ligand.
- A new pair of options has been added to the OETorsionScanOptions to address hysteresis in torsion scanning. These provide the ability to increase the number of starts (SetNumStarts) and address the overlaps between scans (SetOverlapDiv) to avoid doing full 360-degree scans for many starts unless desired.

8.14.2 Major bug fixes

- An issue with the torsion scan (OETorsionScan) in solution with PB solvation has been fixed. It no longer incorrectly uses the MMFF94S potential even when scanning is done with the OpenFF force field.
- An issue with hysteresis that in certain cases caused asymmetric torsion scans has been addressed by resetting to the starting angle before starting reverse scans.

8.14.3 Minor bug fixes

- Better diagnostics have been added to OEFixedProteinLigandOptimizer when the optimization of a ligand in a fixed protein receptor fails due to an initial clash. An appropriate error code is now returned for such cases.
- OEFlexProteinLigandOptimizer now provides an appropriate error code when asked to optimize a design unit that does not contain a ligand.

8.15 SZYBKI 2.5.1

Fall 2022

8.15.1 New features

- Output for *freeform -calc* `conf` now adds dG, local strain, and global strain values to tracked conformer output files as SD data.

8.15.2 Minor bug fixes

- A misleading error message produced by **SZYBKI** when run with *freeform -ff* `ieff_mmff94` or *freeform -ff* `ieff_mmff94s`, without specifying the receptor with either *szybki -protein* or *szybki -complex*, has been improved.
- Values of dG, local strain, and global strain have been added to the `tracked_rst` file when freeform is run with the *freeform -track* option.
- Case-insensitive values for *freeform -ff* are now accepted in *SZYBKI*.

8.16 Szybki TK 2.5.1.2

- Possible crashes in OEFixedProteinLigandOptimizer_Optimize and OEFlexProteinLigandOptimizer_Optimize methods have been fixed.

8.17 Szybki TK 2.5.1.1

8.17.1 New features

- Optimization of bound ligands with ff14SB/Sage and ff14SB/Parsley force fields with PB solvation forces in rigid and partially flexible receptors is now available.
- Setting the force field to PARSLEY_OPENFF131 or SAGE_OPENFF200 now references the most recent official versions of those two parameterizations which are OpenFF_1.3.1 and OpenFF_2.0.0 respectively. Older versions are still available from the OEForceFieldType namespace.
- Final ligand geometry is now checked when large initial clashes occur while using OEFixedProteinLigandOptimizer and OESz_OEFlexProteinLigandOptimizer for optimization of a ligand inside a protein receptor. In most cases, clashes are successfully relaxed; however, in some cases they can lead to a nonphysical minimum which is characterized with distorted geometry. Such results can now be detected by checking the return values of methods OEFixedProteinLigandOptimizer_Optimize and OEFlexProteinLigandOptimizer_Optimize.

8.17.2 Major bug fixes

- An issue with torsion scan for alkanes using MMFF has been fixed.

- OEFixedProteinLigandOptimizer_Optimize and OEFlexProteinLigandOptimizer_Optimize now fails properly when optimization leads to a nonphysical state of a molecule, characterized with distorted geometry. Such nonphysical optimization can sometimes happen when the starting configuration of a protein-ligand complex contains high overlaps.

8.17.3 Minor bug fixes

- A warning regarding 'invalidation of receptor' upon optimization using the OEFlexProteinLigandOptimizer class has been removed.

8.18 SZYBKI 2.5.0

Spring 2022

8.18.1 New features

- A new command-line parameter, `-solventModel`, has been added to *OptLigandInDU*, and *OptimizeDU* to support the Sheffield solvation model.

8.18.2 Minor bug fixes

- An issue has been fixed where failure to assign atom vdw parameters were ignored resulting in calculations being performed with values of zero being assigned as the parameters. The effect of this fix can be observed in calculations performed using *SZYBKI*, *FREEFORM*, *OptLigandInDU*, and *OptimizeDU*.
- An issue causing the `optimizedu --help`, or any related commands, to segfault has been fixed.

8.19 Szybki TK 2.5.0

8.19.1 New Features

- The ability to use the Sheffield Solvation Model has been added to OEFlexProteinLigandOptimizer and OEFixedProteinLigandOptimizer.
- Two additional methods have been added to the OEProteinLigandOptOptions class:
  - GetSolventModel
  - SetSolventModel

8.20 SZYBKI 2.4.0

Fall 2021

8.20.1 New Features

- A new option, `sage_openff2.0.0`, has been added as a possible value for the `-ff` parameter in **SZYBKI** and in **Freeform**.
- **Freeform** uses the latest version of the Open Force Field by default. For this release that is `sage_openff2.0.0`.

8.20.2 Minor Bug Fixes

- *OptLigandInDU* now operates with expected keyless entries in the command line.
- An issue where "MMFF94S" was logged to the logfile regardless of what force field was used has been fixed.

8.20.3 Documentation Changes

- *Freeform Examples* has been updated.

8.21 SZYBKI 2.3.1

July 2021

8.21.1 New Features

- A new option, `parsley_openff1.3.1` has been added as a possible value for the `-ff` parameter in **SZYBKI** and in **Freeform**.

8.21.2 Minor Bug Fixes

- The log file for **SZYBKI** has been updated with a note that option `-exact_vdw` might be used to improve convergence for ligand optimization inside a protein receptor when MMFF94 or MMFF94S force fields are used.

8.22 Szybki TK 2.3.1

July 2021

8.22.1 New features

- The latest version of the Open Force Field Initiative, Parsley 1.3.1, has been added to the OEForceFieldType namespace as built-in force field PARSLEY_OPENFF131.
- Support for user-defined force fields has been added to the OETorsionScan function. Two new API points, SetForceField and GetForceField, have been added for setting and getting this value.
- Support for user defined dihedral angles has been added to OETorsionScan. Two new API points, SetUserDefinedAngles and GetUserDefinedAngles, have been added for setting and getting this value.

8.23 SZYBKI 2.3.0.2

March 2021

- A new parameter, `-proteinMask`, has been added to both *OptimizeDU* and *OptLigandInDU* to provide flexibility in identifying the target protein components of a design unit for optimization.

8.24 SZYBKI 2.3.0.0

Fall 2020

8.24.1 New Features

- A new utility, *OptLigandInDU*, has been added that optimizes a ligand against a rigid protein active site in a design unit. Optimization can be performed with `fff14sb_parsley`, `mmff_amber`, or `mmff` force fields.
- A new utility, *OptimizeDU*, has been added that optimizes a protein-ligand complex inside a design unit. The protein can be treated as partially flexible during the optimization, and can be performed with `fff14sb_parsley`, `mmff_amber`, or `mmff` force fields.
- New options, `parsley_openff1.2.1` and `ff14sb_parsley`, have been added to the -ff command in **SZYBKI**. The `ff14sb_parsley` is only meaningful when optimizing a protein or a part of a protein that includes cofactors.
- A new option, `parsley_openff1.2.1`, , has been added to the `-ff` command in **Freeform -conf**.

8.24.2 Major Bug Fixes

- An issue that delivered incorrect results from binding entropy calculation with **SZUBKI**, when the `-complex` flag was used has been fixed.
- Depiction of **Freeform -solv** results now shows the breakdown of group contributions.

8.24.3 Minor Bug Fixes

- Protein-ligand optimization with `OpenFF-Parsley` force fields using **SZYBKI** no longer fails even when the initial gradient norm is 1e15 kcal/(mol A) or larger.
- The **SZYBKI** log file for protein-ligand complexes optimized with `OpenFF-Parsley` force fields no longer provides the misleading message `mmff94 partial charges were used`.
- The log file for default **Freeform -conf** calculations that runs with default charges has been improved to correctly say that the `ELF10` partial charges were used.
- Unnecessary warnings in entropy calculations with **SZYBKI** have been removed.

8.25 Szybki TK 2.3.0

Fall 2020

8.25.1 New features

- A new SMIRNOFF force field from the Open Force Field Initiative, Parsley 1.2.1, has been added as a built-in force field. It is defined as PARSLEY_OPENFF121.
- A protein or part of a protein can now be optimized with the FF14SB force field. Cofactors with the exception if HEME are handled by the OpenFF/Parsley force field (for example Parsley 1.2.1), while parameters for HEME are taken from Bryce Group.
- The following preliminary classes have been added that enable optimizing protein-ligand complexes, with or without partial flexibility of the proteins, using the new OEFF14SBParsleyComplex force fields, among others:
  - OEFixedProteinLigandOptimizer
  - OEFlexProteinLigandOptimizer
- A new preliminary class, OEProteinLigandOptResults, has been added that represents results of a protein-ligand complex optimization.
- Two new preliminary classes, OEProteinLigandOptOptions and OEProteinFlexOptions, have been added that provide choices for protein-ligand optimization and protein flexibility.

- A new namespace, OESzybkiReturnCode, and a corresponding function, OEGetSzybkiError, have been added that correspond to return codes from the new optimizer classes.

8.25.2 Minor bug fixes

- Protein-ligand optimization with OpenFF/Parsley force fields using OESzybki no longer fails, even when the initial gradient norm is 1e^15 kcal/(mol A) or larger.

8.26 SZYBKI 2.2.0

Spring 2020

- This version of **SZYBKI** has been built using **OEToolkits 2020.0**.
- As part of the integration of **OEToolkits** and **OEApplications** into a single release, the version number of **SZYBKI** has been upgraded to 2.2.0 to make it consistent with that of **Szybki TK**.

8.26.1 New features

- **SZYBKI** applications can now use SMIRNOFF force fields with the built-in parameters `parsley_1.0.0` and `parsley_1.1.1`. In addition, the applications can now use custom OpenFF parameters from an XML file.

8.26.2 Major bug fixes

- An issue with **Freeform** results that occurred when the output was in `sd` format combined with the option `-track` has been fixed.

8.27 SZYBKI 1.11.0

Nov 2019

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

8.27.1 New features

- Two SMIRNOFF (SMIRks Native Open Force Field) specification-based force fields, `Smirnoff99Frosst` and `OpenFF1.0.0`, have been added as legal values for the command line option `-ff` for both **SZYBKI** and **FreeForm**. These force fields use extended SMARTS patterns for chemical representation of parameters. See https://openforcefield.org/ for more information.

8.27.2 Minor bug fixes

- **SZYBKI** now exits cleanly with invalid inputs in MPI mode.
- **SZYBKI** now works with pipes.
- **SZYBKI** now works in MPI mode when there is more than one protein in the input file, which is consistent with its behavior in single processor mode. Previously, **SZYBKI** threw a fatal error in MPI mode.
- Issue with molecule count when running `freeform -calc solv` has been fixed.

8.28 SZYBKI 1.10.1

May 2019

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

8.28.1 Major bug fixes

- `freeform -calc solv` has been fixed to properly calculate solvation energy when used with `-solvcharges input`.

8.28.2 Minor bug fixes

- Occasional overflow of table contents in the `freeform -calc conf` generated report file has been eliminated.
- Unreasonably high energy conformers information are clipped from the energy plots in the report generated from `freeform -calc conf`.
- **SZYBKI** entropy calculation with `-entropy AN` no longer produces a crash.

8.29 SZYBKI 1.10.0

November 2018

- This version of **SZYBKI** has been built using **OEToolkits 2018.Oct**. The previous version was built using **OEToolkits 2015.Oct**.

8.29.1 New features

- The **Freeform** application has been re-implemented to take advantage of the re-engineered functionality in **Szybki TK**.
- The `PDF` report generated with **Freeform** has been improved for clarity.

8.29.2 Minor bug fixes

- An issue that caused a **SZYBKI** entropy job to terminate if a molecule in a multi-molecule input file failed to process successfully has been fixed. If the entropy calculation fails on a particular molecule, the next molecule is now processed.

8.30 SZYBKI 1.9.0

8.30.1 Major Changes in Freeform (`freeform -calc conf`)

- Tracking input conformers is no longer controlled by the `-input3D` flag (which has been removed). This is now done by specifying the file containing the conformers to track after the `-track` command line flag.
- Tracking multiple input conformers at once is now possible.
- Better solvation energies are now accessible as Poisson-Boltzmann single-point solvation energies at the Sheffield-solvation minima.
- Better conformational sampling in Freeform's first stage.

8.30.2 New Features

New features in SZYBKI

- A SMARTS pattern is no longer required to constrain torsion with harmonic potential (option *-tor_constr*). This can now be done by providing 4 atom indices that define the torsion.
- Options `-residue`, `-sideC` and `-polarH` are now deprecated and have been replaced by a combination of the *-flextype* option and *-flexdist* or *-flexlist*. The latter allows user selected residues to be become flexible during bound ligand optimization.
- Beginning with this release, the default value of the *-protein_elec* option is `ExactCoulomb`. In all previous versions, no protein-ligand electrostatic interactions were used by default.

New features in `freeform -calc conf`

- The method for tracking input conformers has been changed. The input file containing these conformers must now be specified after the *-track* flag. The old method of using the flag `-input3D` or `-useInput3D` will not work and will cause a command line error.
- The command-line flag `-input3D` or `-useInput3D` has been removed; the equivalent functionality is now performed by specifying an input file with the `-track` flag.
- More than one input conformer per molecule can now be tracked in one run. The input conformers must either be successive conformers in an OEB file or successive structures of identical chemical graph, atom ordering, and bond ordering in another acceptable format.
- A new flag `-solvent` has been added, allowing users to control whether they want a Poisson-Boltzmann corrected Sheffield solvation or no solvent at all (i.e., gas phase) as alternatives to Sheffield solvation (the default).
- The new default method for applying partial charges to a ligand is AM1BCC ELF10, allowing up to 10 diverse conformers to be selected from conformers having the Electrostatically Least-interacting Functional groups (ELF). These conformers are then charged with the AM1BCCSym method and the charge sets averaged to come up with a single charge set applied to all conformers. This yields good-quality charge sets even for charged ligands. Previously, neutral versus charged ligands behaved differently: neutral ligands were charged using AM1BCCSym on a single ELF conformer, while charged ligands received MMFF94 charges for the sake of consistency.
- The initial conformational search is now performed using the full MMFF94S forcefield with Sheffield solvation, and with an energy window increased to 15 kcal/mol. This leads to improved performance particularly for molecules having internal hydrogen bonds.
- A new flag `-ewindow` has been added. This flag sets the energy window used to accept or reject conformers in the initial conformational search stage in a manner strictly analogous to the flag of the same name used in **OMEGA** or the *SetEnergyWindow* parameter in **Omega TK**.
- A new flag `-maxconfs` has been added. This flag sets the maximum number of conformers allowed in the initial conformational search stage in a manner strictly analogous to the flag of the same name used in **OMEGA** or the *SetMaxConfs* parameter in **Omega TK**.
- A new flag `-solvent_dielectric` has been added, allowing users to specify a dielectric other than 80.0 (the default) for the solvent dielectric of the Poisson-Boltzmann calculations in PB corrected solvation energies.
- A new flag `-forcefield` has been added, allowing users to specify the MMFF94 forcefield instead of MMFF94S (the default) for the *freeform -calc conf* energy minimizations. The conformational search still uses MMFF94S.
- To aid in analyzing the results of tracked conformers, three new output files have been added, with suffixes **.tracked_input.oeb*, **.tracked_rstr.oeb*, and **.tracked_free.oeb*. These contain the structures and key output values (as SD tags) for the tracked conformers' input structures, restrained-optimized minima, and freely-optimized minima, respectively.

- Zero-point energy is now included together with the internal energy and solvation energy when calculating the partition function. This quantity is calculated based on the same vibrational states used for the vibrational entropy.
- The output log file has changed its contents and format to make it easier to locate and extract key values.
- The output CSV file has several fields that contain additional values relevant to conformer free energies.

Bug fixes

- A discontinuity has been removed in flat-bottom potentials (*-harm_constr1* followed by *-harm_constr2*) that caused poor convergence during optimization and/or incorrect values of the harmonic potential to be reported in the log file.
- With the *-flextype* option set with `polarH` the printed list now includes protein polar hydrogens that are flexible during bound ligand optimization. Previously, only a list of side chains or complete flexible residues was printed.
- An error message is now generated when trying to use Newton optimization when
  - a protein-ligand electrostatic model is not `ExactCoulomb` or `None`,
  - a free ligand is not in vacuum or other than Sheffield solvation model is used,
  - a subset of atoms is fixed, or
  - a harmonic constraint potential is applied.
- When AM1BCC charges are selected in Sheffield or PB solvation models for multiply charged species (with option *-am1bcc*), the SCF procedure in AM1 might not converge within 20 cycles. To make sure that the calculated atomic charges are stable, up to 1000 SCF iterations are allowed for multiply charged molecules.
- Option *-max_iter* no longer can be set to a value of zero.
- **SZYBKI** output molecular files in OEB format contain a number of calculated numeric data. Previously, if such files had been used as input files in a subsequent **SZYBKI** run, the results reported in the log file could have been wrong. This problem has been fixed.
- In `freeform -calc conf`, using an existing input ensemble was previously restricted to molecules with 20 or fewer rotatable bonds. This limitation has been removed.

8.31 SZYBKI 1.8.0

8.31.1 New features

- New utility program called `FreeForm` is available for Szybki users. It provides two distinct functionalities: evaluation of the solvation free energy of the input molecules and free energies of solution conformations.
- A new forcefield for protein-ligand interactions is available upon selecting a new option *-ff* followed by `Amber_MMFF94` or `Amber_MMFF94S`. It is a combination of MMFF94 (or MMFF94S) with Amber. In this combined force field, MMFF94 (or MMFF94S) is used to describe the intramolecular interactions of the ligand and the Amber force field is used for the VdW and Coulomb interactions between ligand and protein. Currently, this force field can be used only for ligands inside rigid proteins.
- Entropy estimation based on analytical MMFF Hessian is extended for ligands bound in a rigid protein using the option *-entropy*.
- Constraining torsion potential in the form: $V = k_c(cos(phi) - cos(phi0))^2$, where k_c is the user specified force constant and $phi0$ is the reference torsion dihedral angle is available with the use of the input flag *-tor_constr*.
- New option *-optMethod* is introduced for optimization method selection. The possible choices of optimizers type are BFGS, conjugate gradient, steepest descent and mixtures of steepest descent preoptimization followed by BFGS of conjugate gradient. Option `-conj` is no longer supported.

- Optimization of molecular systems with large number of degrees of freedom (>= 500) is by default done with the conjugate gradient method unless specifically requested with the option *-optMethod*.
- New option *-optGeometry* is introduced for selection of coordinate system to be used during optimization. It replaces no longer supported options *-opt_cart* `, `-opt_torsions`, `-solid` and `-no_opt`. It can be also used to optimize hydrogen atoms positions only, instead of using for that purpose *-fix_smarts*.
- Molecules from the input file which failed during processing are by default written to the separate molecular file. See the description of new option *-keepFailures*.
- Starting from this release flags *-fix_smarts* and *-harm_smarts* are followed by the name of the text file containing a single line with a SMARTS pattern used to fix or constrain atoms. Input of SMARTS strings on the command line for those flags are not used anymore because some SMARTS strings may contain special characters which may be interpreted incorrectly on some platforms.

8.31.2 Bug fixes

- A few numerical errors in the calculation of analytical second derivatives (Hessian matrix) in MMFF torsion and out-of plane terms have been fixed.
- When preoptimized ligands are used for entropy estimation it is necessary to gently moved the ligand out of minimum. The gradient norm below which such a perturbation was done was raised from 1 kcal/(mol Å) to 10 kcal/(mol Å). Our research showed that for some conformations the above limit was too low which resulted in overestimation of its vibrational entropy.
- The usage of AM1BCC charges for PB, Sheffield and Coulomb protein-ligand interactions (option *-am1bcc*) produces the output molecule which preserves the existing partial charges from the input molecule. In previous versions MMFF94 charges were attached to the output molecule.
- Output ligand molecule in the oeb format in a run when protein was partially flexible and when a flags *-out_protein* or *-out_complex* were used, had attached a protein molecule. This bug was fixed in the current release.

8.31.3 Other changes

- PVM (parallel virtual machine) is no longer supported. OpenMPI version 1.6 is supported on all platforms. The *-mpi_np* and *-mpi_hostfile* flags are now used to run SZYBKI in MPI mode. These new flags replace the oempirun script.
- This will be the last release to support SuSe 10.

8.32 SZYBKI 1.7.0

8.32.1 New features

- An extension of the MMFF94 force field for three coordinated boron compounds is offered in this release. Most compounds containing B-X bonds where X=C,N,O,S, and H are covered with the following exceptions: X=N(imine),N(sulfonamide), N(pyridinium) and N(quaternary). Also not supported are compounds in which boron is bonded to X=F,Cl,Br,I,B and Si, or makes a bond angle BYX. Compounds in which boron is a part of four-membered rings of B1CCC1 type are also not available in the current parameterization because their existence is questionable: Ab initio calculations at the MP2/6-31G** level failed to identify stable structures for them (highly polar structures in which boron is four-coordinated are formed).
- New input flag `-solv_dielectric` is added. It controls solvent dielectric for all PB and Sheffield calculations. Default value is 80. Flag `-prot_dielectric` is changed into `-inner_dielectric`. Previous flag `-prot_dielectric` can be used.

- New option flag `-salt x` which sets the salt concentration for PB calculations is added. x is concentration in mM. Default value is 0.
- New option `-flex_file` which allow to specify only those atoms which will be optimized is added.
- Starting from the current release, binding entropy ($T\Delta S$), can be calculated in a single run:

  szybki -entropy QN -complex pl_complex.oeb -ligands ligands.oeb

  where pl_complex.oeb is a protein-ligand complex file, and ligands.oeb contains an ensemble of ligand conformations in solution.
- Entropy calculation of protein-bound ligands has been modified. Specifically, the fraction f of ligand surface exposed to the solvent used in the entropy component term: $f\Delta S_s$, is calculated currently as $f = A_{Lexp}/A_L$, where A_{Lexp} and A_L are ligand solvent accessible surfaces in the protein complex and solution respectively. The reason for a change is the recent OpenEye internal study which show that the above fraction f calculated according to the equation: $f = 0.5(A_L - A_P + A_{PL})/A_L$ ([Wlodek-2010]) is for many protein-ligand complexes overestimated.
- The default value of microscopic surface tension used for protein entropy desolvation calculation is now 6 $cal/(molA^2)$ (previously default value was set at 5 $cal/(molA^2)$. The flag `-sfp x`, where x is microscopic surface tension for protein desolvation entropy calculation, allows to overwrite the default value.
- Two more flags have been introduced: `-t x` and `-rws`. The first of them sets the temperature x in C for entropy calculations (the default value is 25C). The second flag removes water molecules from all solvent accessible surface calculations used for the evaluation of protein-bound ligand entropy, in the case the input protein contains water molecules.
- More entropy terms are reported in the log file. In earlier SZYBKI versions only the total entropy was reported. Starting from 1.7.0 release in addition to total entropy, configurational, solvation (or partial solvation) and protein desolvation entropy terms are reported.
- flag `-mol2charges` is replaced with `-current_charges`. `-mol2charges` is now an alias to the new flag.
- The format of the log file has been changed. Its readability is significantly improved.
- A new option `-out_complex` is added. It allows to output a protein-ligand complex after ligand optimization in partially flexible protein.

8.32.2 Bug fixes

- Optimization of polar hydrogens with the `-polarH` option when the input protein was in the PDB format resulted occasionally in mangling PDB atom names in the protein output file. This bug has been fixed.
- Combination of flags `-complex`, `-protein_elec PB` and `-exact_vdw` caused a crash on Windows platform. This bug has been fixed.
- Previous Szybki versions produced the parameter and status files even when Szybki was run without any user option. This problem has been fixed in the current release.
- Optimization of ligands in the partially flexible protein receptors in the case when the input file contained more than one ligand, stopped after processing the first ligand. This bug has been fixed.
- Information on the selected user options was written to the stdout. That was making piping impossible. This behavior has been eliminated in the current release.
- Input molecular files with badly specified geometry (with atom clashes), were not handled properly. Starting from the current release such an input is caught and the processing of such a molecule is skipped.
- Optimization of large molecules (e.g. optimization of hydrogen positions in very large proteins) can lead to memory exhaustion on some platforms, due to too large amount of VdW interactions or inability to allocate Hessian matrix in the quasi-Newton optimization. Previous Szybki releases terminated on such cases with the bad_alloc

crash. This has been corrected by terminating the run and generating information on the mentioned above cases, so the user might decrease the number of VdW interactions or switch to conjugate gradient optimization method.

8.33 SZYBKI 1.5.2

8.33.1 New features

- Entropy calculation of protein-bound ligands has been modified. Specifically, the fraction f of ligand surface exposed to the solvent used in the entropy component term: $f\Delta S_s$, is calculated currently as $f = A_{Lexp}/A_L$, where A_{Lexp} and A_L are ligand solvent accessible surfaces in the protein complex and solution respectively. The reason for a change is the recent OpenEye internal study which show that the above fraction f calculated according to the equation: $f = 0.5(A_L - A_P + A_{PL})/A_L$ ([Wlodek-2010]) is for many protein-ligand complexes overestimated. The previous way of protein-bound ligands entropy calculation is available with the option: "-ent 151".
- The default value of microscopic surface tension used for protein entropy desolvation calculation is now 6 $cal/(molA^2)$ (previously default value was set at 5 $cal/(molA^2)$. The flag "-sfp x", where x is microscopic surface tension for protein desolvation entropy calculation, allows to overwrite the default value.
- Two more flags have been introduced: "-t x" and "-rws". The first of them sets the temperature x in C for entropy calculations (the default value is 25C). The second flag removes water molecules from all solvent accessible surface calculations used for the evaluation of protein-bound ligand entropy, in the case the input protein contains water molecules.
- More entropy terms are reported in the log file. In earlier SZYBKI versions only the total entropy was reported. Starting from 1.5.2 release in addition to total entropy, configurational, solvation (or partial solvation) and protein desolvation entropy terms are reported.

8.34 SZYBKI 1.5.1

8.34.1 Bug fixes

- Ligand optimization in the active site with the use of the flag *-protein_elec* set at PB ended prematurely. This problem has been fixed.
- In the previous (1.5.0) release the entropy calculation of the protein-bound ligand worked only when a single molecule in the ligand input file was present. In the case when the ligand input file contained two or more molecules, the calculation was performed for the first molecule and died on next one with segmentation fault. This bug is fixed.
- Calculated entropy of the protein-bound ligand was underestimated by up to 0.5 kcal/mol due to the underestimation of the buried protein surface area upon binding. This error is corrected in the current release.
- Using options: *-exact_vdw* and *-protein_elec* set at PB resulted in minimization with Coulomb and VdW potential only. This has been corrected in the current release.
- Parameter file was written without the user command line flags. This bug is fixed.
- A tiny memory leak in the calculations of protein-ligand interaction has been removed.
- Two subsections in documentation has been added. That includes the theory of entropy estimation adopted by SZYBKI and several examples of command line SZYBKI executions.

8.35 SZYBKI 1.5.0

8.35.1 New features

- Starting from the current release, certain classes of divalent selenium compounds can be handled by Szybki. Currently only some compounds in which selenium is bonded to the hydrogen or carbon atoms can be processed. Those compounds include selenols (RSeH) and selenides (RSeR1) in which Se is bonded to alkyl or aromatic carbon atoms, with the exception when Se makes a bond with alkyl C which belongs to the 3- or 4-membered ring.
- Previous Szybki releases attempted to assign the "closest" MMFF94 atom type to those atoms for which a unique MMFF94 type could not be found. Starting from the 1.5.0 release this feature is removed, so consequently the input molecules containing such atoms will not be processed.
- Ligand RMSD which is reported in the log file, can optionally refer to the heavy atoms only. The new option used for that purpose is *-heavy_rms*.
- Entropy calculations of a ligand in different environments can be performed based on the methods described in the recent paper of Wlodek *et. al.* ([Wlodek-2010]). This is done with the option *-entropy* described in the section 4.1 of this manual.
- Default VdW protein-ligand potential used for the optimization of a ligand inside the protein binding site is precalculated in the form of a lookup table. This is done for the purpose of speed. The exact VdW protein-ligand potential can be used with the option *-exact_vdw*.

8.35.2 Bug fixes

- Memory leak in ligand torsion optimization inside the partially flexible protein receptor was removed.

8.36 SZYBKI 1.3.4

8.36.1 New features

- Calculation of the constant potential terms at the end of adapted optimization can be optionally eliminated, by the use of the *-neglect_frozen* flag. This feature allows for less memory and cpu usage in the case of partial optimization of large molecules.
- The corresponding atom symbols, bond symbols, and torsion angles are now printed on a line under the matching smarts pattern.

8.36.2 Bug fixes

- Input proteins with only partial information about residues were not handled properly. As a result, none of the side chains which were supposed to be made flexible with the use of an option `-sideC` were optimized. This problem was fixed.
- A bug causing memory corruption in the case of ligand optimization in partially flexible protein receptor is fixed.
- Residues with nonstandard name `CYX` were not properly handled in the situation when their side chains were included into the flexible part of the protein receptor. This bug has been fixed.

8.37 SZYBKI 1.3.3

8.37.1 Bug fixes

- Until current release, molecular output files in the .oeb format had MMFF aromaticity. In practice, such a situation lead to the visual change between the input and output aromaticity of some molecules. Starting from now

OpenEye aromaticity model is used in the .oeb output files.

8.38 SZYBKI 1.3.2

8.38.1 Bug fixes

- A bug which occasionally caused errors in fixing a subset of atoms, was fixed.
- When using PVM, Szybki now runs a mechanism for checking versions used by master and slaves. This mechanism prevents the situation of different versions of Szybki running on the master and slaves.
- Molecules containing atoms for which MMFF types are not properly typed are not processed. In previous versions attempts were made to assign for such atom the closest MMFF type, however this procedure almost always lead to errors. This situation occurred for example in the case of bad pdb files. For proteins, better diagnostics (residue name and number, atom name) are included as output.
- Reading protein data in .oeb binary format containing additional untagged information (FRED receptor files) is allowed. Until now using such a file in pvm mode caused a fatal error.

8.39 SZYBKI 1.3.1

8.39.1 Bug fixes

- The combination of options `-complex if1` and `-ligands if2` run in the pvm mode caused incorrect behavior in the case when the preexisting ligand in the macromolecule (in the file if1) overlapped with one or more ligands from the input file if2.
- Run time license for the shape toolkit is added. It is required when the combination of options `-complex if1` and `-ligands if2` is used.
- Redundant warnings generated upon `-protein_elec none` and `-strip_water` were removed.
- Spelling in the log file was fixed.
- Year 2008 was added to the Szybki banner.
- In the documentation description for the `-fix_smarts` option an example was added which illustrates the adjustment of hydrogen atom positions.
- Examples of log files generated upon ligand optimization in the partially flexible protein followed by a single point PB calculations are given.

8.40 SZYBKI 1.3.0

8.40.1 New features

- Optimization using conjugate gradient method was added as an alternative to the default quasi-Newton method with the BFGS Hessian update scheme. In Szybki toolkit this is done by the usage of a new function `void SetOptimizerType(unsigned int type)`. In Szybki application a flag `-conj` has been added for that purpose.
- Default value of the protein dielectric constant is 1. Previous default value for that parameter was 2, however it was not consistent with the default value of MMFF94 force field.
- Protein-electrostatic models in Szybki application are selected with descriptive strings. Available options are:
  - `None` - no electrostatic potential used (default option)
  - `ExactCoulomb` - exact MMFF Coulomb potential

- `GridCoulomb` - MMFF Coulomb potential on grid
- `PB` - PP solvent forces used at every step

8.40.2 Bug fixes

- A bug causing crash in the case of combined usage of partial protein flexibility and protein electrostatic model OEProteinElectrostatics::SolventPBForces was fixed.
- A bug causing different behavior and/or occasional crash depending of the order of calls: SetProtein(const OEChem::OEMolBase&), SetRunType(unsigned int) and SetResidueFlexibility(double) has been fixed.
- Modification of the potential function after the usage of coordinate adaptors could occasionally result in crash, for example when function FixAtoms() was followed by SetRemoveCoulombTerms(). This bug was fixed.
- Running in the pvm mode requires now setting the PVM_PATH variable, which points at the directory where the Szybki script is located. For example if Szybki was untarred in the directory `mydir`, then using bash shell one can set the above variable with: export PVM_PATH=mydir/openeye/bin

8.41 SZYBKI 1.2.2

8.41.1 New features

- Two new functions are added to the API:

  void SetResidueFlexibility(double dist); double GetResidueFlexibility() const;

  These allow the user to introduce and query for the flexibility of entire residues around the ligand.

8.41.2 Bug fixes

- In the case when protein electrostatic model was set at `OEProteinElectrostatics::NoElectrostatics` and partial protein flexibility was allowed with the `void SetSideChainsFlexibility(double)` or `void SetPolarHFlexibility(double)` functions, Coulombic terms describing the interaction between the ligand and flexible protein atoms were included during optimization. This was inconsistent with the meaning of `NoElectrostatics`, therefore those Coulombic terms were eliminated in the current release
- Using the function `void SetSideChainsFlexibility(double)` resulted occasionally in double counting of some residues. This bug was fixed.
- Fixing atoms with a function `bool FixAtoms(std::string)` where the passed string is SMARTS pattern, was based on MMFF aromaticity types. Starting from the current release OE aromaticity model is used.

CHAPTER

NINE

CITATION

Note

To cite SZYBKI please use the following:

SZYBKI 2.9.2.0. OpenEye, Cadence Molecular Sciences, Santa Fe, NM. http://www.eyesopen.com

CHAPTER

TEN

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CHAPTER

ELEVEN

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12.2 Orion Floes

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- OEFF TK
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- FastROCS TK
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- Lexichem TK
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- MolProp TK
- Omega TK
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- Shape TK
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- Spruce TK
- Szmap TK
- Szybki TK
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- AFITT Application
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- OMEGA Application
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- SZYBKI Application
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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.

12.4 Publications for Bibliographies

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

12.4.1 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

12.4.2 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

12.4.3 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

12.4.4 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

12.4.5 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

12.5 OpenEye MMDS Web Service

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

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

CHAPTER

THIRTEEN

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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
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Table 1 – continued from previous page

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

13.1 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.

13.1.1 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

13.1.2 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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share and change all versions of a program--to make sure it remains free
software for all its users.  We, the Free Software Foundation, use the
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want it, that you can change the software or use pieces of it in new
free programs, and that you know you can do these things.

  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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  No covered work shall be deemed part of an effective technological
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11 of the WIPO copyright treaty adopted on 20 December 1996, or
similar laws prohibiting or restricting circumvention of such
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  When you convey a covered work, you waive any legal power to forbid
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users, your or third parties' legal rights to forbid circumvention of
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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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    requiring that modified versions of such material be marked in
    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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  If you add terms to a covered work in accord with this section, you
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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