

OEDOCKING

Release 2026.1.0

Cadence Design Systems, Inc.

August 06, 2026

CONTENTS

1 Introduction **1**
- 1.1 Overview . . . 1
- 1.2 Applications . . . 1
- 1.3 Utility Programs . . . 1

2 Tutorials **3**
- 2.1 Overview . . . 3
- 2.2 Receptor Preparation Tutorial . . . 4
- 2.3 CombineReceptors tutorial . . . 6
- 2.4 FRED tutorial . . . 7
- 2.5 HYBRID tutorial . . . 10
- 2.6 POSIT tutorial . . . 12
- 2.7 POSIT MPI tutorial . . . 13

3 Theory **15**
- 3.1 Receptors . . . 15
- 3.2 FRED Theory . . . 17
- 3.3 HYBRID Theory . . . 18
- 3.4 Scoring Functions . . . 19
- 3.5 POSIT Theory . . . 20
- 3.6 Posit How to . . . 24

4 FRED **27**
- 4.1 Overview . . . 27
- 4.2 Input Preparation . . . 27
- 4.3 Example Commands . . . 28
- 4.4 Command Line Help . . . 29
- 4.5 Required Parameters . . . 30
- 4.6 Optional Parameters . . . 30

5 HYBRID **35**
- 5.1 Overview . . . 35
- 5.2 Input Preparation . . . 35
- 5.3 Example Commands . . . 36
- 5.4 Command Line Help . . . 38
- 5.5 Required Parameters . . . 38
- 5.6 Optional Parameters . . . 39

6 POSIT **45**
- 6.1 Overview . . . 45
- 6.2 Input Preparation . . . 46

6.3 Example Commands . . . 47
6.4 Command Line Help . . . 48
6.5 Required Parameters . . . 49
6.6 Optional Parameters . . . 49

7 Make Receptor **57**
7.1 Overview . . . 57
7.2 GUI Layout . . . 58
7.3 Setting up a Receptor . . . 60

8 Utilities **67**
8.1 ReceptorInDU . . . 67
8.2 OEB2DUReceptor . . . 69
8.3 DockingReport . . . 71
8.4 ScorePose . . . 75
8.5 ReceptorToolbox . . . 81
8.6 combine_receptors . . . 84
8.7 DU2OEBReceptor . . . 87

9 Release History **91**
9.1 OEDocking 4.3.5 . . . 91
9.2 OEDocking TK 4.3.5 . . . 91
9.3 OEDocking 4.3.4 . . . 91
9.4 OEDocking 4.3.3 . . . 91
9.5 OEDocking 4.3.2 . . . 91
9.6 OEDocking TK 4.3.2 . . . 92
9.7 OEDocking 4.3.1 . . . 92
9.8 OEDocking TK 4.3.1.3 . . . 92
9.9 OEDocking TK 4.3.1.0 . . . 93
9.10 OEDOCKING 4.3.0 . . . 93
9.11 OEDocking TK 4.3.0 . . . 93
9.12 OEDOCKING 4.2.1.1 . . . 94
9.13 OEDOCKING 4.2.1.0 . . . 94
9.14 OEDocking TK 4.2.1 . . . 94
9.15 OEDOCKING 4.2.0 . . . 95
9.16 OEDocking TK 4.2.0 . . . 95
9.17 OEDOCKING 4.1.2 . . . 95
9.18 OEDocking TK 4.1.2 . . . 96
9.19 OEDOCKING 4.1.2 . . . 96
9.20 OEDocking TK 4.1.2 . . . 96
9.21 OEDOCKING 4.1.0 . . . 96
9.22 OEDocking TK 4.1.0 . . . 96
9.23 OEDOCKING 4.0.0.2 . . . 97
9.24 OEDOCKING 4.0.0.0 . . . 97
9.25 OEDocking 3.5.0 . . . 98
9.26 OEDocking 3.4.0 . . . 98
9.27 OEDocking 3.3.1 . . . 99
9.28 OEDocking 3.3.0 . . . 100
9.29 OEDocking 3.2.0 . . . 100
9.30 OEDocking 3.0.1 . . . 100
9.31 OEDocking 3.0.0 . . . 101
9.32 POSIT 3.1.0 . . . 104
9.33 POSIT 1.0.3 . . . 105
9.34 POSIT 1.0.2 . . . 105

9.35 POSIT 1.0.1 . . . 105
9.36 POSIT 1.0.0 . . . 106
9.37 FRED 2.2.5 . . . 106
9.38 FRED 2.2.4 . . . 107
9.39 FRED 2.2.3 . . . 107
9.40 FRED 2.2.2 . . . 107
9.41 FRED 2.2.1 . . . 107
9.42 FRED 2.2.0 . . . 108

10 Citation **111**

11 Copyright and Trademarks **113**

12 Sample Code **115**

13 Citation **117**
13.1 Orion® . . . 117
13.2 Orion Floes . . . 117
13.3 Toolkits and Applications . . . 117
13.4 Publications for Bibliographies . . . 119
13.5 OpenEye MMDS Web Service . . . 120

14 Technology Licensing **121**
14.1 GCC . . . 193

Index **209**

CHAPTER

ONE

INTRODUCTION

1.1 Overview

OEDocking is a suite of programs and utilities that dock small drug-like molecules into a protein receptor site. The input to these programs is one (or more) crystallographic structures of the target protein (possibly including the ligand with which the protein was crystallized) and one or more drug-like molecules to be docked. The output is the docked structure of the molecules and information about the score or confidence in the docked structure.

1.2 Applications

The **OEDocking** distribution contains 3 primary command line programs for docking molecules:

FRED

- Docks multiconformer molecules using an exhaustive search algorithm
- Uses the structure of a target protein to dock and score molecules
- Uses one structure of the target protein

HYBRID

- Docks multiconformer molecules using an exhaustive search algorithm
- Uses the structure of a target protein and the structure of a bound ligand to dock and score molecules
- Uses either one or multiple protein-ligand complexes

POSIT

- Docks molecules by overlaying onto a similar ligand with a known docked pose (generally derived from X-ray crystallography)
- Compares predicted poses to observed bound ligands in related co-crystals
- Supplies a robust probability that the given pose is reasonable

1.3 Utility Programs

The following utility programs are also included in this distribution:

- *Make Receptor*: A GUI utility for setting up a receptor.
- *ReceptorInDU*: Creates a receptor inside a prepared OEDesignUnit from Spruce.
- *OEB2DUReceptor*: Creates a design unit with a receptor (inside the design unit), converting a receptor OEB or OEB.GZ file.

- *DockingReport*: Creates a PDF report for one or more docked molecules.
- *ScorePose*: Rescores and optionally optimizes poses in an active site with the **FRED** scoring function.
- *ReceptorToolbox*: A utility program for receptors that reports information about a receptor and can make simple edits of the receptor file
- *combine_receptors*: Makes a single receptor using multiple ligands that may be a better target for predicting some ligands.
- *DU2OEBReceptor*: Converts a design unit with a receptor into a receptor OEB or OEB.GZ file.

CHAPTER

TWO

TUTORIALS

2.1 Overview

The OEDocking suite contains three docking programs, *FRED*, *HYBRID* and *POSIT*, and associated utilities. The input to *FRED*, *HYBRID* or *POSIT* is one (or more) crystallographic structures of the target protein (possibly including the co-crystallized ligand) and one or more drug-like molecules to be docked. The output is the docked structure of the molecules and information about the score or confidence in the docked structure.

At the end of these tutorials, you will be able to run:

- SPRUCE to prepare receptor files from PDB or MMCIF files for docking.
- *COMBINE_RECEPTORS* to take disparate but sequence related proteins and combine the complexes into new receptors with more thorough binding information.
- *FRED* to dock multi-conformer molecules into the structure of a target protein and score the molecules.
- *HYBRID* to dock multi-conformer molecules into the structure(s) of a target protein and the structure of a bound ligand and score the molecules.
- *POSIT* to generate potential poses of ligands against *OEDocking* receptor targets.
- *DOCKING_REPORT* to generate a PDF report for one or more molecules docked by *FRED* , *HYBRID* or *POSIT* .

The basic workflow for docking ligands using *FRED*, *HYBRID* or *POSIT* is as follows:

- Generate *OEDocking* receptors with bound ligands.
- Dock ligands into receptor.
- Analyze results.

> **Note**
>
> Data for the tutorials is included in the application bundle. Please see Example and Tutorial Data for platform specific information regarding the data's location.

Note

For the following tutorials, the OpenEye application banner and run settings have been omitted for brevity.

2.2 Receptor Preparation Tutorial

The first step in using *FRED*, *HYBRID*, or *POSIT* is the creation of an **OEDocking** receptor, which is a collection of docking-related information connected to a protein. A typical receptor is shown in Figure 1 below.

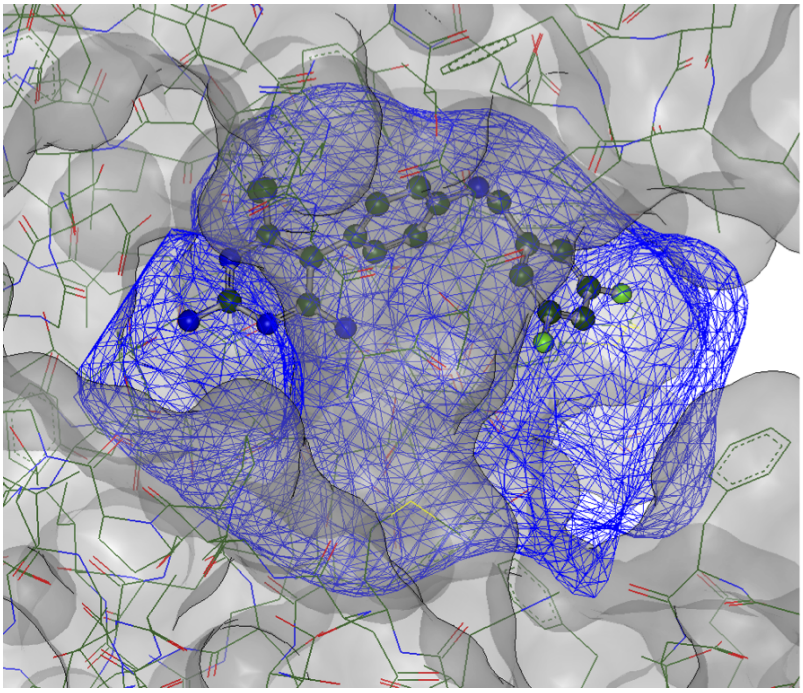


Fig. 1: **Figure 1.** The **OEDocking** receptor and typical docking information.

There is an *automated* way to prepare **OEDocking** receptor files using SPRUCE. Alternatively, the graphical utility *Make Receptor* provides an *interactive* approach for flexible and customizable receptor preparation.

2.2.1 SPRUCE (Recommended)

The SPRUCE application provides functionality for automated biomolecule preparation for modeling applications. The preparation functions include tautomer evaluation, charge normalization, receptor grid generation, and missing protein loop building. A typical receptor generation session could begin with the retrieval of a set of coordinates and an experimental electron density map from the PDB (in this case, the RCSB). To automatically retrieve the data files from the PDB, the Get Structure utility in SPRUCE can be given a four character accession code.

For example, to retrieve the PDB entry 5TMG:

```
> getstructure 5TMG
```

The above command downloads `5tmg.pdb`, `5tmg.cif`, `5tmg.mtz` files from RCSB database directly. Once the files have been downloaded, SPRUCE can be used to generate design units (DUs) and other receptor components. DUs are explained in the theory chapter of **Spruce TK**.

```
> spruce -in 5tmg.cif -map 5tmg.mtz
```

The above command creates the following intermediate DU files:

- `5TMG_A__DU__7EK_A-402.oedu`
- `5TMG_B__DU__7EK_B-402.oedu`

DU files are generated for each of the monomers in the crystallographic asymmetric unit; in this example, there are two copies in the asymmetric unit. If the user has supplied the electron density map (in this example, `5tmg.mtz`) to the **Spruce** command, the quality of the structure is evaluated using the Iridium protocols.

When there is no bound ligand detected, an error message is written into `spruce_output.log`. The parameter `enumsites -site_residue` is required to specify a protein residue in the active site for apo structures.

This command creates **OEDocking** receptor files that are readily used as docking input:

```
> receptorindu -in 5TMG_A__DU__7EK_A-402.oedu -out rec_5TMG.oedu
```

The above command then creates receptors inside the DU `rec_5TMG.oedu` as an input receptor file for *FRED*, *HYBRID*, and *POSIT*.

2.2.2 Interactive Modification of a Receptor

The *Make Receptor* GUI can be used to examine or modify a previously created receptor. The GUI can be used if a user wants to define constraints or include specific water molecules in the receptor. The implementation of **Make Receptor** generates an OEDesignUnit file (`.oedu`) for input to any of the **OEDocking** applications. If using a legacy docking receptor (`.oeb` or `.oeb.gz`), conversion between the two file types can be done using the **OEDocking** utility programs *OEB2DUReceptor* and *DU2OEBReceptor*. For example:

```
> du2oebreceptor -in rec_5TMG.oedu -out rec_5TMG.oeb.gz
> oeb2dureceptor -in rec_5TMG.oeb.gz -out converted_rec_5TMG.oedu
```

The OEReceptor files, such as `rec_5TMG.oedu`, can be visualized using **VIDA**. The components are shown in Figure 2.

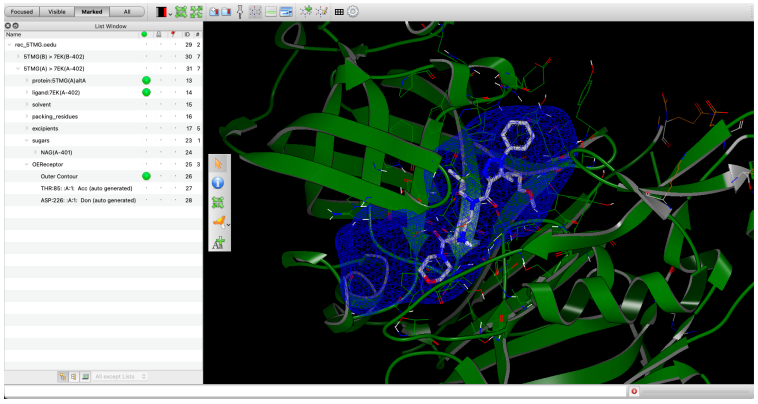


Fig. 2: **Figure 2.** The view of the **OEDocking** receptor and components in **VIDA**.

This **OEDocking** receptor includes the protein structure and a description of the binding site. This description includes an *outer contour* (highlighted in the *List Window*), which limits the placement of heavy atoms during the *FRED*, *HYBRID*, or *POSIT* search procedures.

See the *Make Receptor* section for generating receptors from structure coordinates instead of from previously generated **OEDocking** receptor files.

2.3 CombineReceptors tutorial

Combining receptors is an optional step that can be used to take information found in multiple receptors to create a new, merged, receptor.

combine_receptors is intended to be used in an automated fashion where the output aligned receptors should be included with the original receptors when running *POSIT*. As such, the output receptor files are automatically named based on the input filenames and only receptors that are capable of merging produce output.

This is particularly helpful when using small bound fragments to try and predict binding poses for larger ligands. Combining receptors works by supplying a list of potential receptors and only receptors that are deemed worthy or merging are output. To be worthy of merging:

1. It must be possible to align the protein sequences.
2. The ligands must overlap, but be different enough to indicate that the combined receptor has more information content than each independently.

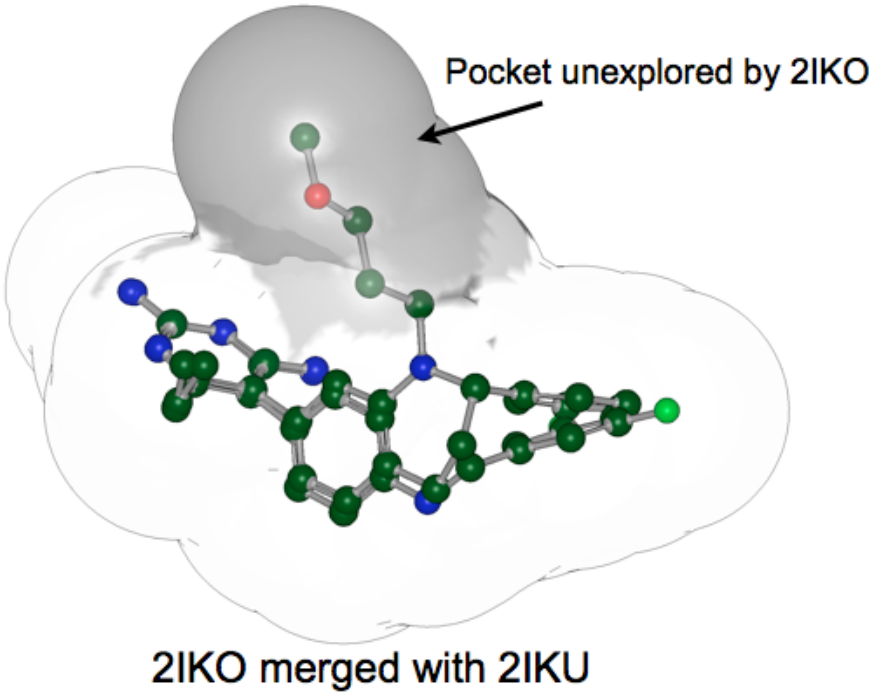


Fig. 3: **Merged Receptors:** Merging the receptors 2IKO and 2IKU capture more potential interaction constraints than either does alone

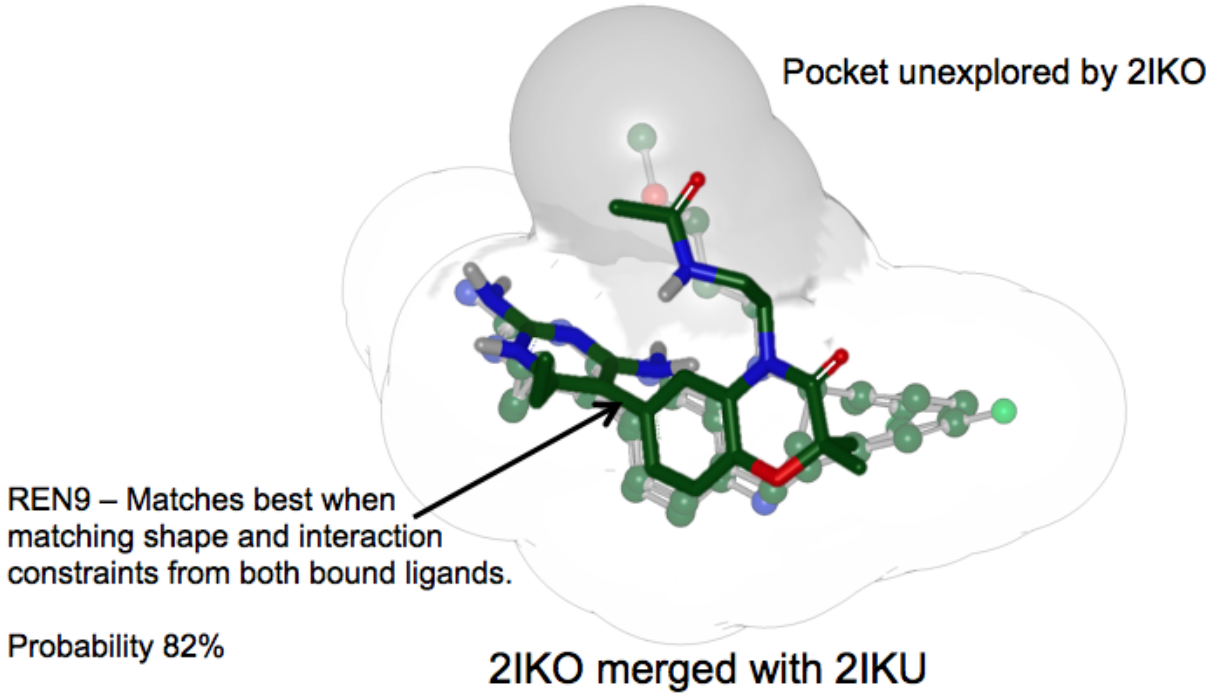


Fig. 4: **Ligand Posed to Merged Receptors:** REN9 is correctly predicted by the merged receptor

For example, consider the merged receptor shown in figure: *Merged Receptors*. In this case, one of the ligands binds to a pocket that is not present in the other. The expectation is that the combination of both ligands has more information content than either alone.

For each valid merge, two output files are generated, one in each reference frame. See the *combine_receptors* section for more details.

2.4 FRED tutorial

FRED requires a protein to be docked into, a definition of a region in that protein in which the docking will take place and a multi-conformer database of molecules to be docked. The most common format for database file(s) is a multi-conformer OEBinary file created by OpenEye's OMEGA application, however, this file can be one of several 3D formats. These formats include SDF, MOL2 and PDB. *FRED* determines the database file format from the file extension, .sdf or .mol for SDF, .mol2 for MOL2, .pdb or .ent for PDB. Gzip compressed files of these same formats are allowed as well. *FRED* will interpret *infile.sdf.gz* as a gzip'ed SDF file.

Note

Even though all these formats are supported, using SDF, PDB or MOL2 can result in a loss of speed due to the I/O penalty of these formats.

FRED requires a single receptor to dock ligands into. Receptors may be created with the following programs: *Make Receptor*, *ReceptorInDU*, *OEB2DUReceptor*, and *Receptor preparation tutorial* .

> **Note**
>
> Receptors are encapsulated inside a `OEDesignUnit` in .oedu files.

To dock a set of ligands into the receptor `2IKO_rec.oedu`:

```
> fred -receptor renin/receptors/2IKO_rec.oedu -dbase renin/all.oeb.gz
```

By default, *FRED* generates several output files. Unless you specify a different *Output prefix* during setup, *FRED* will use the prefix `fred` for all output files.

- `fred_docked.oeb.gz` - top 500 scoring molecules of `all.oeb.gz` docked into `2IKO_rec.oedu`.
- `fred_undocked.oeb.gz` - molecules of `all.oeb.gz` that could not be docked into the active site (generally occurs if the molecules are too big for the site). This file will not be present if all molecules were successfully docked to the active site.
- `fred_score.txt` - a tab separated text file containing the name and score of each of the top 500 ligands.
- `fred_report.txt` - a text report of the docking process.
- `fred_settings.param` - a text file containing the parameters used for this run.
- `fred_status.txt` - a text file that is written periodically during the run with the status of the run.

If you have a multi-processor machine, you can harness the extra computing power by using OpenMPI. To re-run the job on a host with 4 processors, you enter the following:

```
> fred -mpi_np 4 -receptor renin/receptors/2IKO_rec.oedu -dbase renin/all.oeb.
↪gz -prefix 2IKO_fred
```

The output from the docking runs may be viewed in VIDA, as depicted in figure *2IKO FRED Docked*.

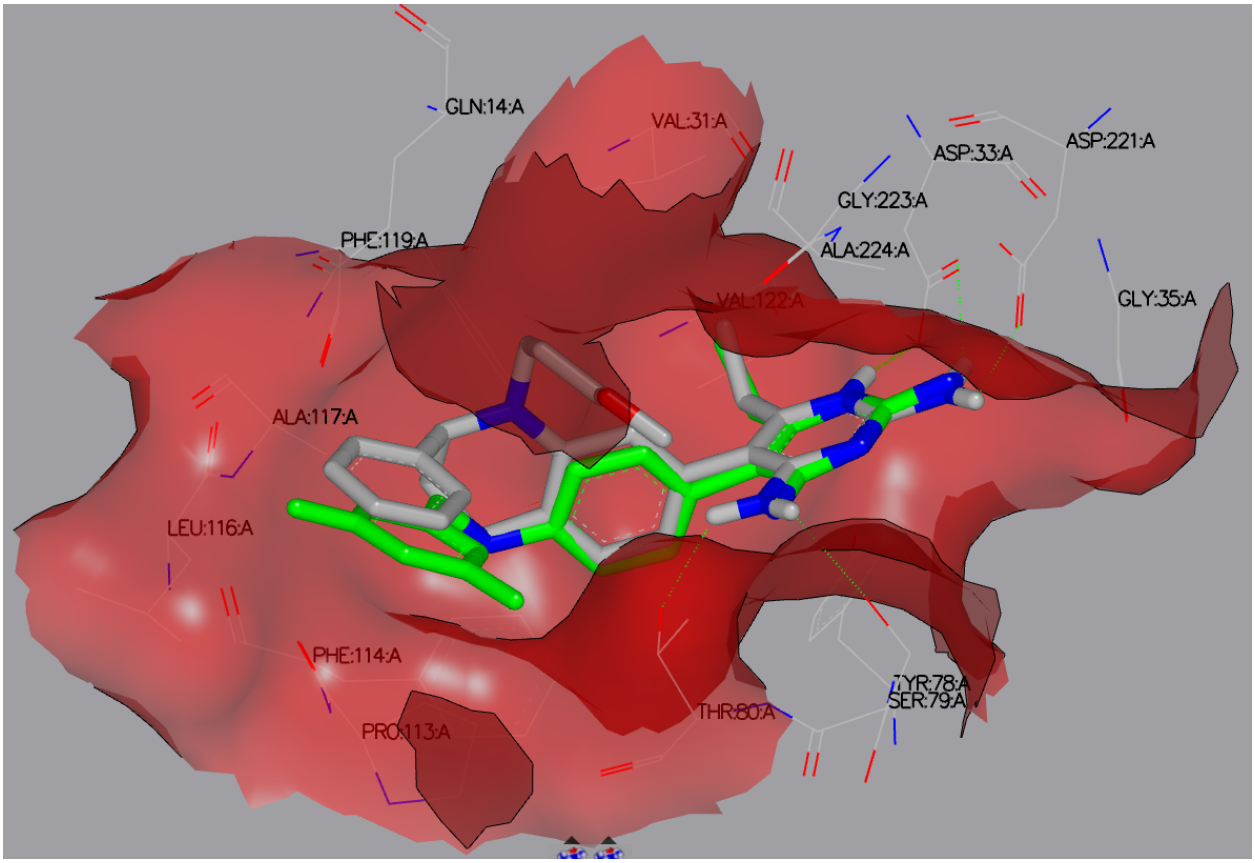


Fig. 5: **2IKO FRED Docked results showing the reference ligand (green) and the top docked ligand**

In addition to analyzing and visualizing the output from a docking run in VIDA, a summary PDF report can be generated using *DockingReport*.

```
> docking_report -docked_poses 2IKO_fred_docked.oeb.gz \
                  -receptor renin/receptors/2IKO_rec.oedu  -report_file 2IKO_
↪fred_docked_report.pdf
```

The result of running the above command is depicted in figure *2IKO FRED Docking Report*.

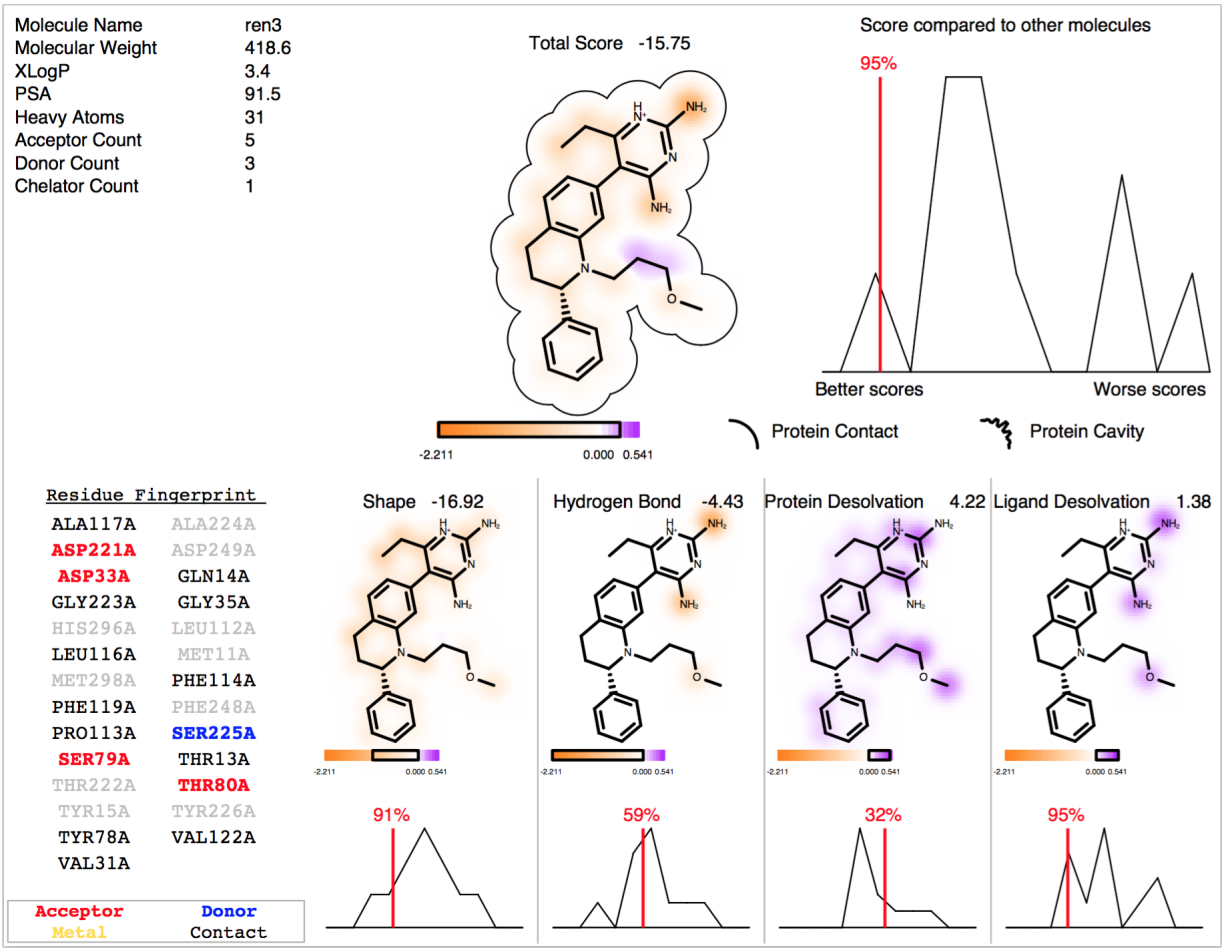


Fig. 6: **2IKO FRED Docking Report**

The PDF report includes a 2D depiction of each molecule, a breakdown of the docking score components by atom, a comparison of the molecule's score compared to the other docked molecules, and a 'Residue Fingerprint' which highlights which residues in the receptor site the ligand is interacting with. Greyed out residues are residues in the site that other ligands interact with, but the current ligand does not.

2.5 HYBRID tutorial

HYBRID docks molecules using a single receptor or using multiple structures of the target protein. When using a single structure, the input files are simply the receptor and the ligand database. However, when using multiple structures of the target protein, the input files are all of the receptor files and the ligand database.

- `receptor1.oedu` - a receptor file containing the structure of the target protein and a bound ligand.
- `receptor2.oedu` - a receptor file containing the structure of the second target protein and a bound ligand. This receptor file should have a different structure of the same target protein in `receptor1.oedu`, generally with a different bound ligand.
- `multiconformer_ligands.oeb.gz` - conformationally expanded 3D ligands to dock.

See the usage for multiple receptor files in *Hybrid Docking with Multiple Crystal Structures*.

Setting up and running a *HYBRID* job is similar to *FRED* job. As a comparison to *FRED*, *HYBRID* is used to dock a set of ligands into the same receptor `2IKO_rec.oedu`:

```
> hybrid -receptor renin/receptors/2IKO_rec.oedu -dbase renin/all.oeb.gz
```

By default, *HYBRID* generates several output files. Unless you specify a different *Output prefix* during setup, *HYBRID* will use the prefix `hybrid` for all output files.

- `hybrid_docked.oeb.gz` - top 500 scoring molecules of `all.oeb.gz` docked into `2IKO_rec.oedu`.
- `hybrid_undocked.oeb.gz` - molecules of `all.oeb.gz` that could not be docked into the active site (generally occurs if the molecules are too big for the site). This file will not be present if all molecules were successfully docked to the active site.
- `hybrid_score.txt` - a tab separated text file containing the name and score of each of the top 500 ligands.
- `hybrid_report.txt` - a text report of the docking process.
- `hybrid_settings.param` - a text file containing the parameters used for this run.
- `hybrid_status.txt` - a text file that is written periodically during the run with the status of the run.

If you have a multi-processor machine, you can use the OpenMPI option.

```
> hybrid -mpi_np 4 -receptor renin/receptors/2IKO_rec.oedu -dbase renin/all.
↪oeb.gz -prefix 2IKO_hybrid
```

As with the output from *FRED* docking runs, *HYBRID* results may be viewed and analyzed in VIDA as shown in figure *2IKO HYBRID DOCKED*.

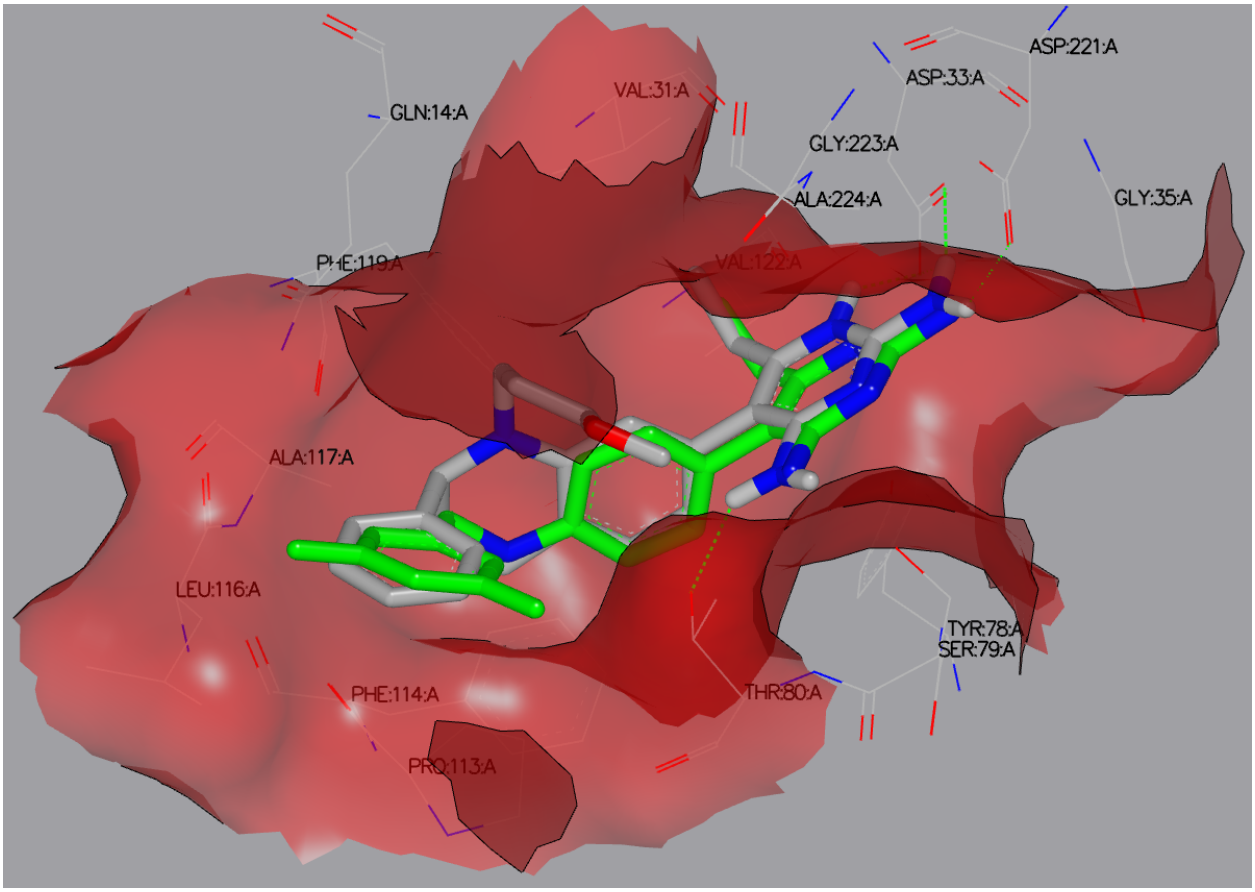


Fig. 7: **2IKO HYBRID DOCKED results showing the reference ligand (green) and the top docked ligand**

Likewise, you also can create a summary PDF report for the *HYBRID* results using *DockingReport*.

2.6 POSIT tutorial

Given receptors, using *POSIT* is very straightforward. There are two basic ways to input molecules to *POSIT*.

- `-in` - converts input to 3D conformers (if 3D structures are input, these initial structures are retained)
- `-dbase` - takes the input conformations as is (these are normally generated with OMEGA.)

For usage of `-dbase` see *POSIT MPI Tutorial*.

Given a set of input smiles strings:

```
> posit -receptor renin/receptors/*.oedu renin/merged/*.oedu -in renin/all.smi
```

Note

On *Microsoft Windows* systems, you need to expand the wildcard:

```
> posit -receptor renin\receptors\2IL2_rec.oedu renin\receptors\2IKU_rec.
↪oedu \
      renin\receptors\2IKO_rec.oedu reninmerged\combine_receptors_2IKO_rec_
↪merged_2IKU_rec.oedu \
      renin\merged\combine_receptors_2IKU_rec_merged_2IKO_rec.oedu -in renin\
↪all.smi
```

The following files are output:

- `posit_docked.oedu` - contains all successful poses
- `posit_score.txt` - contains the scores of all successful poses
- `posit_report.txt` - contains the report of the run
- `posit_status.txt` - a periodic status file generated during a run
- `posit_settings.param` - parameters used in the run

The following files are output only if non-empty:

- `posit_clashed.oeb.gz` - contains all poses with good enough probability but clash
- `posit_undocked.oeb.gz` - contains all unsuccessful poses
- `posit_rejected.txt` - list of rejected structures and status of rejection

There is more than one reason a pose may be unsuccessful. The most common is that the probability of the predicted binding mode is too low. To control this behavior use the *`posit -outputall`* flag, which writes all output to the file specified by `-out` in order of input molecule.

POSIT by default writes docked structure results to `.oedu` file which can be viewed using **VIDA 5**. If an `.oeb` or `.oeb.gz` file is desired use the *`hybrid -docked_molecule_file`* flag.

To specify the *-prefix* option to add a prefix to all files output by *POSIT* or use the *-docked_molecule_file* option to output a pose file with particular name.

When *POSIT* is finished, it prints the final status and indicates what new data was added to the results that are output.

The `posit_score.txt` file contains the scores and ranking of docked structures.

The `posit_rejected.txt` file can be used to identify the status of rejected molecules, for instance "All conformers clashed with protein" indicates that while the probability was good, the protein could not accept the desired pose.

Note

While *POSIT* can take most molecule formats as input, with large datasets it is fastest to use a pre-generated database of OMEGA [Hawkins-2010] generated conformers. It is recommended, above two rotatable bonds, to generate 100 conformers per rotatable bond when running OMEGA:

```
> omega2 -in renin/all.smi -out renin/all.oeb.gz -rangeIncrement 1 \
   -maxConfRange 200,200,300,400,500,600,700,800,900,1000,1100,1200,1300,
↪1400,1500,1600
> posit -receptor renin/receptors/*.oedu -dbase renin/all.oeb.gz \
   -prefix renin
```

See the *posit usage* section for more details.

2.7 POSIT MPI tutorial

Running *POSIT* on multiple cores is a simple matter of adding the *-mpi_np* argument and specifying the number of cores desired. When *POSIT* is run on a small job as shown above (with 11 molecules and 6) receptors, using a large number of cores is overkill.

```
> posit -mpi_np 3 -receptor renin/receptors/*.oedu -dbase renin/all.oeb.gz \
    -prefix renin
```

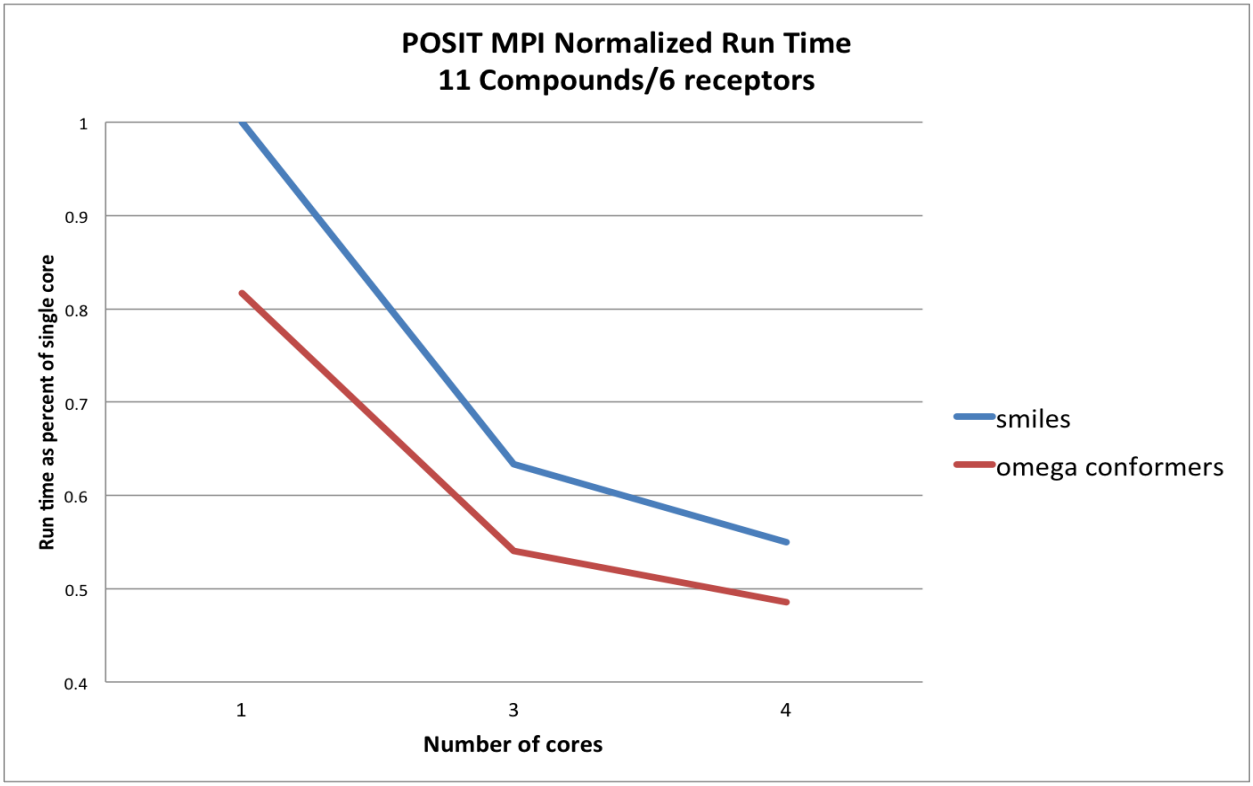


Fig. 8: **POSIT performance varying the number of cores against a small lead-optimization example.**

As seen in figure *Posit Performance*, running with 3 cores gives a large boost in the run-time and adding another is only marginally faster. Note that running under two cores is not recommended as one core is always the master so, in effect, this is the slowest way to run *POSIT*.

Also note that using OMEGA conformations as input is the fastest way to run *POSIT*.

CHAPTER

THREE

THEORY

3.1 Receptors

3.1.1 Overview

A receptor is an integral part of a Design Unit (see Spruce Introduction) and contains information about the location and characteristics of the binding pocket. Receptors are used by every program in the OEDocking suite of programs.

A receptor always contains:

- The *target mask* that describes the target protein.
- A *negative image* that describes the shape of the active site.

A receptor may contain:

- Docking *constraints* specifying required protein-ligand interactions.
- A *score cache* to speed up the startup of *FRED*, *HYBRID* or *ScorePose*.

3.1.2 Contents of a Receptor

Target Mask

The target mask defines the subset of design unit components that should be included in defining the *protein structure* for docking or pose prediction.

The protein structure includes all molecules that a ligand being docked or scored interacts with. This generally only includes the protein, but may also include key cofactors or solvent molecules (e.g. a crystallographic water). All parts of the receptor structure are static during both docking and scoring and any cofactors or solvent molecules in the receptor structure are not displaceable.

Negative Image

The negative image describes the shape of the active site. It is stored as a potential grid surrounding the active site. The negative image has high potentials where ligand atoms make many contacts with atoms of the active site without clashing and in positions some ligand atoms are likely to occupy when other atoms of the ligand make good contacts with the receptor (e.g. bridging positions ligand atoms will likely occupy when a ligand is stretched between two pockets).

During docking two shapes are created by contouring the negative image potential grid. The two shapes control the docking process as follows:

Outer Contour Shape

> During docking any pose examined by the exhaustive search that does not fit within this shape will be rejected. A pose is considered to fit if the center of every heavy atom is within this shape. The volume of this shape is typically between 500 and 2000 cubic Ångströms.

Inner Contour Shape

> During docking any pose examined by the exhaustive search that does not touch this shape is rejected. A pose is considered to touch if the center of at least one heavy atom falls within this shape. The volume of this shape is typically 50 to 100 cubic Ångströms.

The negative image of the receptor is setup when the receptor is created. When a receptor is made the contour levels are automatically set for both the inner contour and outer contour, however the inner contour will be disabled. The receptor inner contour can be enabled using the *ReceptorToolbox* program, which will slightly improve docking speed at the expense of some sampling.

Constraints

Constraints define key interactions ligands are required to make when docking into the active site. They are optional and user defined.

Constraints do not affect how a given pose scores, however they do affect how the docking algorithm chooses poses to score during the docking process. Any pose that does not match the docking constraints will be rejected and replaced by the next best scoring pose. If no poses of a ligand match the docking constraints the ligand will not be docked. If multiple constraints are specified every constraint must be satisfied or the pose will be rejected.

> **Note**
>
> The docking process used by both *FRED* and *HYBRID* has a resolution of approximately 1 Ångström, and thus the constraints have a similar resolution. Therefore it is possible that poses docked with a constraint may have small violations of the constraint distance, up to approximately 1 Ångström.

Receptors support two general classes of constraints; protein constraints and custom constraints. There may be any number of either class of constraint.

> **Note**
>
> Each individual custom or protein constraint has an enabled flag. A disabled constraint is ignored during the docking process.

Protein Constraints

A protein constraint specifies an interaction that must be made with a heavy atom of the protein structure (i.e. protein constraints cannot be placed on hydrogen atoms). There are five types of protein constraints.

Contact

> A contact constraint is satisfied when any ligand heavy atom is within 4 Ångströms of the protein heavy atom.

Lipophilic

> A lipophilic constraint is satisfied when any non-polar heavy atom on the protein is within 4 Ångströms of the protein heavy atom.

Donor

> A donor constraint is satisfied when a donor on the ligand makes a hydrogen bond interaction with the protein heavy atom.

Acceptor

An acceptor constraint is satisfied when an acceptor on the ligand makes a hydrogen bond interaction with the protein heavy atom. Acceptor constraints must be placed on the protein heavy atom the donor hydrogen is interacting with.

Chelator

A chelator constraint is satisfied when a chelator on the ligand makes a metal-chelator interaction with the protein heavy atom.

Only one protein constraint is allowed per protein heavy atom. If a protein constraint is set on a protein atom that already has a protein constraint the original protein constraint will be discarded and replaced by the new constraint.

Custom Constraints

A custom constraint requires that docked poses have at least one atom within a sphere (or set of spheres). Any heavy atom on the docked pose can satisfy the constraint, unless the constraints has SMARTS patterns with it, in which case on atoms matching one of the smarts patterns can satisfy the constraint.

A custom constraint always has at least one sphere. If it has multiple spheres then a matching atom within any of the spheres will satisfy the constraints.

If the custom constraint has no associated SMARTS patterns then any heavy atom on the ligand will satisfy the constraint if it is in one of the constraints associated spheres. If one SMARTS pattern is specified then only an atom matching the SMARTS pattern will be able to satisfy the constraint. If multiple SMARTS patterns are specified then an atom matching any of the SMARTS patterns will be able to satisfy the constraint.

Score Cache

A receptor may optionally contain a score cache. A score cache is scoring setup information usable by either *FRED*, *HYBRID* or *ScorePose* to speed up the initialization process prior to docking and scoring. Using a score cache will not change the docking or scoring results.

A score cache is most useful when *FRED*, *HYBRID* or *ScorePose* are started and stopped often to dock one or a small number of ligands as the initialization cost must be paid each time the program is started, and using a score cache can substantially reduce this time.

3.2 FRED Theory

FRED docks multiconformer molecules into a single *receptor* using an exhaustive search that systematically searches rotations and translations of each conformer of the ligand within the active site. Following the exhaustive search the top scoring poses are optimized and assigned a final score. These two steps are described in more detail below

Exhaustive Search

1. Enumerates, to given resolution, every possible rotation and translation of each conformer of the ligand being docked within a box enclosing the active site. The resolution of the exhaustive search is determined by the overall resolution setting of `fred -dock_resolution` flag.
2. Discard poses that either clash with the protein or extend too far from the binding site using the receptor's negative image outer contour (see *Negative Image* section).
3. If the negative image inner contour is enabled discard any poses that do not have at least one heavy atom that falls within the inner contour. (see *Negative Image* section).
4. Discard any poses that do no match any user specified constraints. (see *Constraints* section).
5. Score all remaining poses using *Chemgauss3*.
6. Sort poses by score and pass the top scoring poses to optimization.

Optimization

1. Enumerate nearby positions of each pose by having the initial pose take one positive and one negative step for each translational and rotational degree of freedom (729 poses total). The resolution of these steps is half that of the exhaustive search, and is determined by the setting of the `-dock_resolution` flag.
2. Each pose is scored with *Chemgauss4*.
3. The best scoring poses are retained. The number of poses retained is determined by the setting of the `-num_poses` parameter.
4. The overall score of the molecule, used to rank the molecule against other molecules in the docking database, is set to the best scoring pose's score.

3.3 HYBRID Theory

HYBRID docks multiconformer molecules into one or more *receptors* with bound ligands using an exhaustive search that systematically searches rotations and translations of each conformer of the ligand within the active site. Following the exhaustive search the top scoring poses are optimized and assigned a final score. These two steps are described in more detail below

Receptor Selection

Note

If there is only one receptor this these steps are skipped and all ligands are docked to the receptor.

1. For each ligand in the docking `database` the similarity of the ligand to each of the receptor's bound ligands is calculated based on the 3D shape and chemical similarity of the docking ligand and bound ligand.
2. Each ligand is then docked to the single receptor that has the most similar bound ligand as described in the following steps.

Exhaustive Search

1. Enumerates, to given resolution, every possible rotation and translation of each conformer of the ligand being docked within a box enclosing the active site. The resolution of the exhaustive search is determined by the overall resolution setting of `-dock_resolution` flag.
2. Discard poses that either clash with the protein or extend to far from the binding site using the receptor's negative image outer contour (see *Negative Image* section).
3. If the negative image inner contour is enabled discard any poses that do not have at least one heavy atom that falls within the inner contour. (see *Negative Image* section).
4. Discard any poses that do no match any user specified constraints. (see *Constraints* section).
5. Score all remaining poses using *Chemical Gaussian Overlay*.
6. Sort poses by score and pass the top scoring poses to optimization.

Optimization

1. Enumerate nearby positions of each pose by having the initial pose take one positive and one negative step for each translational and rotational degree of freedom (729 poses total). The resolution of these steps is half that of the exhaustive search, and is determined by the setting of the `-dock_resolution` flag.
2. Each pose is scored with *Chemgauss4*.
3. The best scoring poses are retained. The number of poses retained is determined by the setting of the `-num_poses` parameter.

4. The overall score of the molecule, used to rank the molecule against other molecules in the docking database, is set to the best scoring pose's score.

3.4 Scoring Functions

3.4.1 Chemgauss3

The Chemgauss3 scoring function uses Gaussian smoothed potentials to measure the complementarity of ligand poses within the active site. Chemgauss3 recognizes the following types of interactions.

- Shape
- Hydrogen bonding between ligand and protein
- Hydrogen bonding interactions with implicit solvent
- Metal-chelator interactions.

All interaction potentials in Chemgauss are initially constructed using step functions to describe the interaction of atom pairs (or other chemical points) as a function of distance. These interactions are mapped onto a grid that is then convoluted with a spherical Gaussian function, which smoothes the potential making it less sensitive to small changes in the ligand position. Smoothing the score in this way serves two purposes. First docking can be run at lower resolution than would be required if the score were not smooth since small changes in position to do not cause large changes in score. Second it reduces the error associated with the rigid protein approximation by effectively accounting for the ability of the protein to make small structural re-arrangements to accommodate the ligand.

Shape interactions in Chemgauss are based on a united atom model (*i.e.* only heavy atoms are relevant to the shape calculation). Each ligand heavy atom is assigned a fixed clash penalty score if the distance between it and a protein heavy atom is less than the sum of the VdW radii, otherwise it is assigned a score proportional to the count of the number of protein heavy atoms within 1.25 and 2.5 times the sum of the VdW radii (atoms within 2.5 count one tenth as much as those within 1.25). From this score a penalty equal to two close protein atom contacts is subtracted to represent the VdW interactions with solvent water that are lost when the ligand docks. This score is pre-computed at grid points throughout the active site and the resulting grid is then smoothed.

Hydrogen bonding groups are modeled with one or more lone-pair or polar-hydrogen position(s) that describe the directionality of potential hydrogen bonds (with respect to the hydrogen bonding group's heavy atom). Donor groups have lone pair positions representing the possible location of the donor hydrogen atoms relative to the donating molecule, while acceptors have lone-pair positions representing the possible locations of the donated hydrogen relative to the acceptor. A hydrogen bond is detected and assigned a constant score when a hydrogen bonding position on the ligand is within 1.0 Angstrom of a complementary hydrogen bonding position on the protein (*i.e.* when the polar-hydrogen position of a donor overlaps the lone-pair position of an acceptor). If the ligand hydrogen bonding group has multiple polar-hydrogens and/or lone-pair positions (groups can be both donors and acceptors) then this calculation is performed for each position and the result is summed. As with all Chemgauss terms the hydrogen bond potential is pre-computed at grid points throughout the site and then smoothed.

Hydrogen bonds to solvent molecule that break when the ligand docks into the active site are penalized by the Chemgauss scoring function. Broken protein-solvent hydrogen bonds are accounted for by calculating how many hydrogen bonds water can make with the protein at the position of each heavy atom of the docked ligand, and a penalty score is assigned which is proportional to the number of hydrogen bonds. Broken ligand-solvent hydrogen bonds are accounted for by calculating desolvation positions around each hydrogen-bonding group on the ligand that represent the positions water could occupy when making a hydrogen bonding interaction with the protein. A penalty is then assessed that is proportional to the number of desolvation positions that can no longer be occupied by water because the water in these positions would clash with the protein. As before, this potential is placed on a grid and smoothed.

Chelating interactions between protein metals and ligand chelating groups are accounted for by Chemgauss (protein-chelator and ligand-metal chelating interactions are not). For each chelator on the ligand one or more chelating-positions are calculated. If a protein metal is within 1.0 Angstrom of any chelating-position of a chelating group then a fixed score is assigned, otherwise a zero score is assigned. As before this potential is placed on a grid and smoothed.

3.4.2 Chemgauss4

The Chemgauss4 is a modification of the Chemgauss3 scoring function that has improved hydrogen bonding and metal chelator terms (The shape and implicit solvent interaction terms are identical to those in Chemgauss3). The new hydrogen bonding and metal chelator terms have better perception of the directionality of these interactions and also account for hydrogen bond networking effects.

To calculate the hydrogen bonding score for a ligand-protein hydrogen bond two distances are measured.

1. How far the donor heavy atom is from the position the acceptor atom would consider to be an ideal for a hydrogen bonding to form.
2. How far the acceptor heavy atom is from the position the donor atom would consider to be ideal for a hydrogen bonding interaction to occur.

The score for the hydrogen bond interaction is a product of two Gaussian functions of these distances scaled by the strength of the hydrogen bonding groups involved in the interaction.

HBscore = strength*g(distance1)*g(distance2)

To compute the total hydrogen bonding score for the ligand-protein complex the individual pairwise scores are calculated for all protein-ligand donor-acceptor pairs. Individual HB interaction are then eliminated if either the donor or acceptor exceeds the maximum number of interactions allowed (e.g., a hydroxyl with one hydrogen is not allowed to make more than one donor interaction), with the lowest scoring interactions eliminated first. The final hydrogen bond score is then calculated by summing the scores of the remaining individual acceptor-donor interactions.

3.4.3 Chemical Gaussian Overlay

The Chemical Gaussian Overlay function (or CGO) is primarily a ligand-based scoring function although some information from the protein structure is used as well. The similarities computed are based on the overall shape of the molecules as well as the position of hydrogen bonding and metal chelating groups. This scoring function requires a bound ligand pose along with the structure of the target protein. Typically the ligand structure is obtained from X-ray crystallography along with the structure of the target protein, although a docked ligand could also, in principal, be used.

CGO represents molecules as a set of spherical Gaussian functions describing the shape and chemistry (acceptors, donors and chelators) of the molecule. The Gaussians representing the shape of the molecule are centered at the heavy atom positions, those for donors are centered on polar-hydrogen positions (*i.e.* positions where the donating hydrogen could be when it is involved in a hydrogen bond), those for acceptors are centered on lone-pair positions (*i.e.* positions where a donating hydrogen could be when a hydrogen bond is formed) and those for chelators are centered at chelating positions (*i.e.* locations where a metal could have a chelating interaction). The overlap of the Gaussians on the docked ligand to those on the bound ligand are computed for each type of Gaussian (*e.g.* shape, donor, acceptor and chelator) by summing the overlap of individual pairs of Gaussian. The overlap of each individual pair is calculated by integrating the product of the two. To prevent chemistry not relevant to binding from contributing to the overall score, when calculating the chemistry overlaps (*i.e.* acceptor, donor and chelator) only groups that make the interaction with the protein are accounted for (*e.g.* a chelator that does not interact with a metal on the protein is ignored in the overlap calculation). The sum of all four types of overlaps is the CGO score.

3.5 POSIT Theory

POSIT is a pose-prediction tool primarily based on the assumption that similar ligands bind similarly. Pose prediction is the process of determining the structure of a ligand bound in the active site of a target protein. Pose prediction with *POSIT* assumes that the incoming ligand binds to the given protein and makes the best effort in correctly placing it in the active site. In conjunction to the predicted pose, **POSIT** also provides an estimate of confidence, in terms of an estimated probability, that the docked pose is within 2.0 Ångströms of the actual binding pose.

> **Note**
>
> Note that this probability is not the probability of binding, rather, the probability that the pose is correct given the ligand actually binds to the receptor.

POSIT consists of multiple *Docking* or *Pose Prediction* methods intentionally and automatically chooses the best method to use for any particular ligand based on the 2D (graph) and 3D (structure) similarity of the docked ligand to the bound ligand. The methods *POSIT* uses to dock are:

1. ShapeFit - Shape-guided ligand minimization into the receptor site
2. Hybrid - hybrid method that uses ligand and protein information
3. Fred - Standard docking method that uses no ligand information

If there is no bound ligand in the receptor, the *Fred* method is used by default since it does not rely upon the pressence of the bound ligand.

3.5.1 Handling of isomerisms and chirality

Stereo, and notably nitrogen aniline stereo centers, are currently somewhat problematic for *POSIT*. Many crystal structures have flat geometries for some stereo centers due to time-averaging during data collection. This makes stereo centers appear to have flat geometries in the 3D coordinates.

Because the POSIT algorithm internally expands conformations during the flexible fitting procedure, the full molecule must be labeled with stereo - either in the 3D coordinate sense or the 2D coordinate sense. This means that some pdb ligand structures will unfortunately be failed by the POSIT algorithm.

To get around this, posit can be told to ignore nitrogen stereo during the conformer generation phase.

> **Note**
>
> Output structures of *Posit* are not guaranteed to have the same conformations of the input molecule. This is due to the fact that force-field minimization is occasionally performed during pose prediction.

3.5.2 Estimated Pose Probability

During a drug discovery campaign, thousands of small molecule inhibitors are made in the course of optimizing molecular properties. For projects that have X-Ray crystallographic (XRC) coordinates, structure-based designs help guide the medicinal chemistry efforts. In many cases XRC provides a detailed picture of the binding of a small-molecule inhibitor into the binding site.

Many techniques exist for pose-prediction and are well documented [Erickson-2004] . However, very few provide a probability that the generated pose is correct where correct is typically considered to be less than 2.0 Ångströms RMSD (root mean square distance) from experimental crystal structure. In fact, many docking scores such as Chemscore, Chemgauss3, PLP [Tuccinardi-2010] are not very correlated with correct ligand pose, and worse are not transferable between systems. The best docking score in one system may not even be close to the best docking score in another.

POSIT overcomes these issues by comparing predicted poses to observed bound ligands in related co-crystals. As the observed ligand becomes more similar to the the predicted pose, both the binding mode and the shape of the receptor pocket itself tends to become more similar.

The similarity measures being used are 2D path-based fingerprints and the 3D *TanimotoCombo* [Hawkins-2010] that compares shape and the Mills-Dean approximation of electrostatics [Mills-Dean-1996] . These similarity measures choose the most appropriate system to dock against (when multiple receptors are available) and provide a prediction of the quality of the result. The *TanimotoCombo* measure is agnostic of how the poses in question are generated; it can be used to validate and provide a pose prediction probability regardless of how the pose was generated.

POSIT probabilities were generated using a large test set containing many pose predictions and verified against an independent set of predictions that were then validated with X-Ray crystallography. It is important to note that *POSIT* does not give a probability of binding. Rather it gives a probability that **if the ligand does actually bind**, what is the likelihood of the *POSIT* pose being the actual pose.

Figure *POSIT Probability MAP* shows how the beliefs given by the 2D and 3D measures are combined into a probability of having a good pose. Remember that this probability has been generated from ligands that actually bind, hence, it is not a probability of binding.

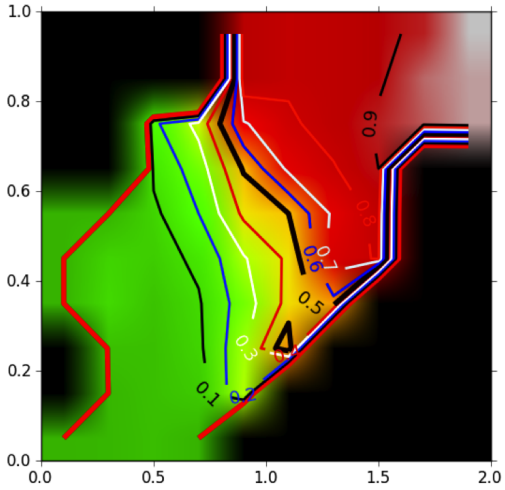


Fig. 1: **POSIT Probability Map:** Given a 2D similarity (in this case the MACCS 166 descriptor set [Durant-2002]) and a 3D similarity (*TanimotoCombo*) *posit* computes a probability of finding the correct pose based on an analysis of historical and experimental data.

This result is different from the result shown in [Tuccinardi-2010] , where they reported that having a high *Tanimoto-Combo* to the known bound ligand did not dramatically increase the quality of the resulting pose (even for *FRED*). The reason is subtle: Tuccinardi *et al* were computing the highest *TanimotoCombo* that the two molecules could obtain, while *Posit* computes the actual, docked, in-place *TanimotoCombo* of the fitted pose. That is, if the docking algorithm produces an alignment of fit molecule to known bound ligand that overlaps with a given *TanimotoCombo*, one can look up the probability the docking was successful. In point of fact, *Posit* is specifically designed so that the docked pose obtains the highest *TanimotoCombo* score possible while simultaneously minimizing induced strain and maintaining interactions with the protein.

Categorically the data shown in *POSIT Probability MAP*, for each pose can be binned into the following results:

Result	Meaning
GREAT	Computed pose is likely (75%-100% probability) to be within 2.0 Å of experimentally-derived pose.
GOOD	Computed pose may be (50%-75% probability) to be within 2.0 Å of experimentally-derived pose.
MEDIOCRE	Take with a grain of salt (33%-50% probability)
POOR	Take with a huge grain of salt (<33% probability)

3.5.3 Additional MCS Constraints

Walter's *et al* noted that a large portion of ligands bound to the same protein kinase share a large maximum common substructure (MCS). This was the basis for their **CORES** algorithm [Hare-2004] . *Posit* can optionally identify matching regions and use them as additional constraints during conformer generation. *Posit* performs the MCS match to the bound ligand by default.

3.5.4 On Clashes

The definition of *clashes* is somewhat problematic for purposes of pose prediction. In general, serious clashes where interpenetration with the protein should be avoided at all costs. However, when docking into a rigid protein that does not have the appropriate conformation, rigid docking ignores that fact that the active site may adopt a conformation suitable to the posed ligand.

Posit uses the definitions from OEClashInteractionHint to identify clashes. *Posit* allows the users to specify three allowable clash levels.

Allowed Clash	Description
noclashes (none)	No clashes are allowed.
hydrogen (mild clashes)	Only hydrogen clashes are allowed.
allclashes	All clashes are allowed.

3.5.5 Using Multiple Receptors

Using multiple receptors to dock or pose molecules has been shown to greatly increase the reliability of docking.

When multiple receptors are provided *Posit* chooses the appropriate reference system based on the 2D/3D similarity to the bound ligand. The best reference, in general, has the highest 2D/3D similarity of the input molecule to the chosen bound ligand. The similarity measure used here are similar to those used in determining the best docking method in *Posit*.

3.5.6 Receptor Flexibility

Incorporating multiple receptors is the simplest way to account for receptor flexibility during pose prediction. With multiple receptors, *Posit* would pick the best suitable conformer of the receptor for a particular docked ligand.

Pose generated from *Posit* with provided receptor conformers can still sometimes contain clashes. Option is available to trigger post pose prediction relaxation, that relaxes both the posed ligand and protein residues around it.

Note that optimization of a protein-ligand complex can sometimes be time consuming, especially if the target protein and associated components are large.

3.5.7 TanimotoCombo

Posit uses the *TanimotoCombo* measure to compare (and optimize) predicted and bound ligands. The *TanimotoCombo* measure is simply two separate Tanimoto measures added together. While most uses of Tanimoto have been to compare fingerprints together, there is a direct relation between the 1D fingerprint bit vector and 3D space:

The basic equation for a field Tanimoto between two fields A and B is:

$$Tanimoto_{A,B} = \frac{\int A(\vec{r}) * B(\vec{r})}{\int A(\vec{r}) * A(\vec{r}) + \int B(\vec{r}) * B(\vec{r}) - \int A(\vec{r}) * B(\vec{r})}$$

In the case of *Posit*, the field in question can be thought of as field of voxel space. For $Tanimoto_{shape}$, where A and B are now molecules: if two objects fill the same voxels, then the Tanimoto value is 1.0. If two objects overlap by half, the Tanimoto value is 0.5 and so on. (The term voxel is used for purposes edification, in actuality the volumes estimated using a fast approximate method)

$$\text{Overlap(q,t)} = \text{Intersection of Volumes q and t}$$

$$\text{T=} \frac{\text{Overlap(q,t)}}{\text{Overlap(q,q)} + \text{Overlap(t,t)} - \text{Overlap(q,t)}}$$

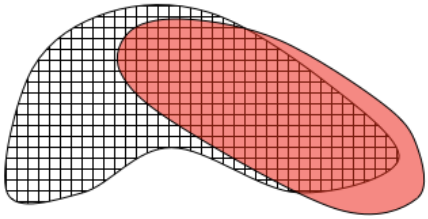


Fig. 2: **Voxel Representation of Shape:** Similar to fingerprint bits in 1D, voxels can be used to represent 3D space and compared with the Tanimoto measure. The numerator *Overlap(q,t)* is essentially the volume of the **intersection** of *q* and *t* and the denominator *Overlap(q,q)* + *Overlap(t,t)* - *Overlap(q,t)* is essentially the volume of the **union** of *q* and *t*.

The field can also contain colored representations of chemistry. For example, if two voxels are colored as hydrogen bond donors and overlap, the $Tanimoto_{color}$ increases.

Hence, *TanimotoCombo* is:

$$TanimotoCombo = Tanimoto_{shape} + Tanimoto_{color}$$

TanimotoCombo values range from 0 (no overlap) to 2.0 (full shape overlap and full color or chemistry overlap).

3.6 Posit How to

3.6.1 Ignore Nitrogen stereo

Nitrogen stereo can be ignored in *Posit* by setting the *-ignore_nitrogen_stereo* parameter to `true`.

3.6.2 Prepare molecules for Posit

With default settings, *Posit* internally generates the required input conformers and *Posit* can be used with 2D input molecules. However, if it is desired to pass a pre-generated set of conformers to *Posit*, following are the recommended ways to supply or prepare molecules for POSIT.

1. Use *OMEGA* or the *OMEGA toolkit* to prepare molecules or expand the stereo chemistry using *OEFlipper*. *POSIT* is guaranteed to work correctly if the input molecules have been generated by *OMEGA*.
2. Pass the *OMEGA* generated 3D conformers through the *-dbase* parameter. This method of running *POSIT* is not recommended as a large portion of the flexible methodology will be deactivated.

3.6.3 Use multiple receptors

Multiple receptors can be passed to *Posit* through the *-receptor* command-line parameter.

3.6.4 Obtain clash-free pose

Pose generated from **Posit** with the default options can sometimes contain clashes. Users have the option to perform pose relaxation, either on the clashed poses or on all generated poses, with the *-relax* command-line parameter

CHAPTER

FOUR

FRED

4.1 Overview

FRED is a docking program that docks molecules from a multiconformer database into a *receptor* site using an exhaustive search algorithm.

4.2 Input Preparation

> **Note**
>
> It is not required to calculate the ligand charges and protein charges explicitly. The scoring functions do not utilize partial charges.

4.2.1 Ligand Preparation

The most common use of *FRED* is to dock a large collection of molecules into the active site of a target protein. For the purposes of this document, we'll call the file(s) of molecules the database file(s), or dbase file(s). The most common format for database file(s) is a multi-conformer OEBinary file created by OpenEye's **OMEGA** program, however, this file can be one of several 3D formats. These formats include SDF, MOL2 and PDB. *FRED* determines the database file format from the file extension, `.sdf` or `.mol` for SDF, `.mol2` for MOL2, `.pdb` or `.ent` for PDB. Gzip compressed files of these same formats are allowed as well. *FRED* will interpret `infile.sdf.gz` as a gzip'ed SDF file.

> **Note**
>
> Note that even though all these formats are supported, using SDF, PDB or MOL2 can result in a loss of speed due to the I/O penalty of these formats.

FRED has no provision for conversion of 1D/2D molecules to 3D. **The database file(s) must be in a conformationally expanded 3D format**. Within the OpenEye tool chain the program OMEGA can be used to generate conformers.

By default *FRED* will interpret conformers in the database file(s) as part of a single multi-conformer molecule as long as they:

- Are contiguous in the input file.
- Have the same numbers of atoms and bonds in the same order
- Have identical atom and bond properties with their order correspondent in the subsequent connection table
- Have the same atom and bond stereochemistry

While this may appear to be a restrictive list, many programs write multi-conformer molecules into SDF or MOL2 files such that the above rules will be satisfied. If the conformers are named differently, (*i.e.* they have a conformer number appended to the base name like acetsali_1, acetsali_2), *FRED* will still consider them part of a single multi-conformer molecule if the criteria above are met.

4.2.2 Receptor Preparation

Note

Beginning with *FRED* 4.0.0, *FRED* now only accepts an OEDU with receptor as the receptor input file.

FRED requires a single *receptor* to dock ligands into. The contents of a receptor are described in the *receptor theory* section. Receptors can be created with the following programs

Program	Type	Description
Make Receptor	GUI	Interactive GUI for creating a receptor.
ReceptorInDU	Command Line	Generates a receptor inside a prepared OEDesignUnit in an OEDU file.
OEB2DUReceptor	Command Line	Converts a molecule based receptor OEB or OEB.GZ file into a receptor inside an OEDesignUnit, in an OEDU file

Note

Receptors can also be created using the Docking Toolkit (see the Docking Toolkit documentation).

4.3 Example Commands

4.3.1 Basic docking example

This example docks molecules on a single processor using default parameters.

Input files for 1DWD

- **receptor.oedu** : A receptor file containing the structure of the prepared target protein. (see *Receptor Preparation* section).
- **multiconformer_ligands.oeb.gz** : Conformationally expanded ligands to dock. (see *Ligand Preparation* section).

Command line

```
prompt> fred -receptor receptor.oedu -dbase multiconformer_ligands.oeb.gz
```

Output files

- **fred_docked.oeb.gz** : Top 500 scoring molecules of *multiconformer_ligands.oeb.gz* docked into *receptor.oedu*.
- **fred_undocked.oeb.gz** : Molecules of *multiconformer_ligands.oeb.gz* that could not be docked into the active site (generally occurs if the molecules are too big for the site). This file will not be present if all molecules were successfully docked to the active site.
- **fred_score.txt :**
  A tab separated text file containing the name and score of each of the top 500 ligands.

- **fred_report.txt** : A text report of the docking process.
- **fred_settings.param** : A text file containing the parameters used for this run.
- **fred_status.txt** : A text file that is written periodically during the run with the status of the run.

4.3.2 MPI docking example

This example docks molecules on 4 processors of the host machine.

Input files

- **receptor.oedu** : A receptor file containing the structure of the prepared target protein. (see *Receptor Preparation* section).
- **multiconformer_ligands.oeb.gz** : Conformationally expanded ligands to dock. (see *Ligand Preparation* section).

Command line

```
prompt>fred -mpi_np 4  -receptor receptor.oedu \
                           -dbase multiconformer_ligands.oeb.gz
```

Output files

- **fred_docked.oeb.gz** : Top 500 scoring molecules of *multiconformer_ligands.oeb.gz* docked into *receptor.oedu*.
- **fred_undocked.oeb.gz** : Molecules of *multiconformer_ligands.oeb.gz* that could not be docked into the active site (generally occurs if the molecules are too big for the site). This file will not be present if all molecules were successfully docked to the active site.
- **fred_score.txt** : A tab separated text file containing the name and score of each of the top 500 ligands.
- **fred_report.txt** : A text report of the docking process.
- **fred_settings.param** : A text file containing the parameters used for this run.
- **fred_status.txt** : A text file that is overwritten periodically during the run with the status of the run.

4.4 Command Line Help

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

```
> fred --help
```

will generate the following output:

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

4.5 Required Parameters

-receptor <receptor file>

All molecules will be docked to this receptor. The receptor file must be in OEDocking receptor format (`.oedu`).

[Aliases=**-rec**]

-dbase <input filename1> [<input filename2> ...]

File(s) containing ligands to dock (see section *Ligand Preparation*).

The following file formats are supported.

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

More than one file can be specified.

[Aliases=**-database**,**-in**]

4.6 Optional Parameters

4.6.1 Input Options

-param <parameter filename> [No Default]

A parameter file is a text file that lists parameter settings to be used during a run. If a parameter is specified both on the command line and in the parameter file, the value specified on the command line is used.

The format of the parameter file is as follows:

- One parameter per line
- For non-list parameters one key-value pair per line. (*e.g., -receptor rec.oedu*).
- For list parameters a key followed by all the values (*e.g., -dbase lig1.oeb.gz ligs2.oeb.gz*)
- Boolean parameters must be listed as a key followed by true or false (*e.g. -annotate_poses true*).
- The parameter file may not contain the *-param* parameter.
- Lines beginning with # are considered comments

-molnames <input filename> [No Default]

This parameter specifies 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 database file(s) (see parameter *-dbase*) 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 database, without having to extract those molecules by hand from the database.

4.6.2 Dock Options

-dock_resolution <setting> [Default: Standard]

The parameter controls the resolution of the docking both during the exhaustive search and the optimization. The resolution of the exhaustive search at each setting is as follows.

Setting	Translational Stepsize	Rotational Stepsize
High	1.0 Ångström	1.0 Ångström
Standard	1.0 Ångström	1.5 Ångströms
Low	1.5 Ångströms	2.0 Ångströms

During the optimization step the resolution is half that of the exhaustive search.

[Aliases = **-res**]

See also

- OEDocking::OEDockOptions::SetResolution in the **OEDocking TK** manual.

4.6.3 Output File

-docked_molecule_file <filename> [Default=docked.oeb.gz]

File docked molecules will be written to. The file format is controlled by the extension of the filename. The following output formats are supported.

Format	Extension
OEBinary	.oeb
SDF	.sdf
Gzipped OEBinary	.oeb.gz
Gzipped SDF	.sdf.gz

Scores will be attached as SD data to each pose with the tag *FRED Chemgauss4 Score*, unless the *-score_tag* option is used to specify another tag.

The number of top scoring molecules outputted is controlled by the *-hitlist_size* option (which has a default value of 500).

Note

If this flag is not set by the user the default filename (i.e., docked.oeb.gz) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases=**-docked_mol_file**,**-docked_file**,**-docked**,**-out**]

-undocked_molecule_file <filename> [Default: undocked.oeb.gz]

Specifies an output file in which to place molecules that could not be docked into the active site (this generally occurs when a molecule is too large to fit in the site, or unable to match user specified docking constraints). The format of this file is determined by the filename extension. The following output formats are supported.

Format	Extension
OEBinary	.oeb
SDF	.sdf
Isomeric SMILES	.ism
Gzipped OEBinary	.oeb.gz
Gzipped SDF	.sdf.gz
Gzipped Isomeric Smiles	.ism.gz

> **Note**
>
> If this flag is not set by the user the default filename (i.e., undocked.oeb.gz) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-undocked_mol_file**, **-undocked_file**, **-undocked**]

-score_file <filename> [Default: score.txt]

Specifies a tab separated text file with the name and scores of the molecules.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., score.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases : **-score**]

-report_file <filename> [Default: report.txt]

Specifies a file that a text report of the run will be written to.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., report.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases : **-report**]

-settings_file <filename> [Default: settings.param]

Writes the settings of all parameters of the run to the specified output file. The settings will be listed in plain text with one parameter name follow by its value(s). This format is compatible with the format of parameter files, and therefore a settings file from a previous run can be passed to the *-param* flag to re-run the program with the same settings.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., settings.param) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-settings**]

-status_file <filename> [Default: status.txt]

If this parameter is set then the status of the run will be written to the given output file every few seconds (the previous contents of the file will be overwritten) during the run.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., status.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-status**]

4.6.4 Output Options

-hitlist_size <num> [Default: 500]

This parameter controls the number of top scoring molecules that will be outputted at the end of the run (sorted by score), or can be used to specify that all molecules should be outputted as they are processed (unsorted).

If -hitlist_size is non-zero a sorted hitlist of the best scoring molecules is produced that will be maintained and output at the end of the run. The maximum size of the hitlist is *-hitlist_size*. If more than this number of molecules are in the input database only the top scoring molecules will be outputted and the rest will be discarded.

If *-hitlist_size* is zero the run will be in serial mode, *i.e.* each molecule will be outputted as it is processed (unsorted). For single processor runs this will be the order the molecules appear in the database file(s). For MPI runs the order will not be strictly the order the molecules appear in the database file(s).

There is no formal limit on the number of molecules that can be sorted and outputted at the end of the run. However, retaining a large number of molecules significantly increases the memory requirements. A good rule of thumb is that the setting *-hitlist_size* times the setting of *-num_poses* should not be larger than 10,000.

[Aliases = **-hitlist_size**, **-hitlist**]

-num_poses <num> [Default: 1]

Specifies the maximum number of docked poses to output for each docked molecule.

There is no formal limit on the number of poses per molecule that can be outputted, however, retaining a large number of alternate poses significantly increases the size of the molecules in memory and when outputted to disk. A good rule of thumb is that the setting *-hitlist_size* times the setting of *-num_poses* should not be larger than 10,000.

[Aliases = **-numposes**]

-score_tag <score tag> [No Default]

This parameter overrides the default SD data tag used to store molecule scores.

[Aliases=**-scoretag**]

-annotate_scores [Default: false]

If the value of this flag is set to true VIDA score annotations will be added to the processed molecules. These annotations are visible in VIDA (OpenEye's molecular visualization program) and show a per atom breakdown of the score.

> **Note**
>
> The docked molecule output file format (see *fred -docked_molecule_file*) must be OEBinary when using score annotations.

[Aliases = **-annotate**]

-save_component_scores [Default: false]

If the value of this flag is set to true individual components of the total score will be saved to SD data on each pose and appear in the score file (see *-score_file*).

[Aliases = **-component_scores**, **-component**]

-no_extra_output_files [Default=false]

When this flag is set to true the only default output to the program will be the docked structure file (see *-docked_molecule_file*).

Using this flag suppresses the default output of the following

Output filename	Default	Parameter
Undocked molecule file	undocked.oeb.gz	*-undocked_molecule_file*
Text score file	score.txt	*-score_file*
Report file	report.txt	*-report_file*
Settings file	fred.param	*-settings_file*
Status file	status.txt	*-status_file*

Only default output is suppressed. If any of these output parameters are explicitly set by the users the relevant output file will still be written even if this switch is turned on.

[Aliases=**-no_extra**,**-noextra**,**-noextraoutputfiles**,**-no_extra_output**,**-noextraoutput**]

-no_dots [Default: false]

When this flag is set to true, a dot is being written to standard error for each docking molecule (or x in the case of a failure). Setting this flag to false to suppress dot/x writing.

[Aliases = **-nodots**]

-prefix <value> [Default=fred]

This flag prefixes all default output filenames with the specified value.

> **Note**
>
> This flag does not affect output filenames explicitly set by the user.

-nostructs [Default=false]

When this flag is set to true, both the docked and undocked structure files will be suppressed. The flag overrides *-docked_molecule_file* and *-undocked_molecule_file*.

CHAPTER

FIVE

HYBRID

5.1 Overview

HYBRID is a docking program that also uses elements of ligand based design to enhance performance. Typically, the protein structure is determined with X-ray crystallography in the presence of a known binding ligand (or bound ligand). The *HYBRID* program uses the information present in both the structure of the protein and the bound ligand to enhance docking performance. *HYBRID* **requires that the structure of a bound ligand be known**, if it is not known *FRED* can then be used to do traditional docking.

HYBRID also allows multiple structures/conformations of the target protein to be used. In this case *HYBRID* will determined the best structure/conformation to use for each ligand in the docking database.

5.2 Input Preparation

Note

It is not required to calculate the ligand charges and protein charges explicitly. The scoring functions do not utilize partial charges.

5.2.1 Ligand Preparation

The most common use of *HYBRID* is to dock a large collection of molecules into the active site of a target protein. For the purposes of this document, we'll call the file(s) of molecules the database file(s), or dbase file(s). The most common format for database file(s) is a multi-conformer OEBinary file created by OpenEye's **OMEGA** program, however, this file can be one of several 3D formats. These formats include SDF, MOL2 and PDB. *HYBRID* determines the database file format from the file extension, `.sdf` or `.mol` for SDF, `.mol2` for MOL2, `.pdb` or `.ent` for PDB. Gzip compressed files of these same formats are allowed as well. *HYBRID* will interpret `infile.sdf.gz` as a gzip'ed SDF file.

Note

Note that even though all these formats are supported, using SDF, PDB or MOL2 can result in a loss of speed due to the I/O penalty of these formats.

HYBRID has no provision for conversion of 1D/2D molecules to 3D. **The database file(s) must be in a conformationally expanded 3D format**. Within the OpenEye tool chain the program **OMEGA** can be used to convert 1D/2D to 3D and generate conformers.

By default *HYBRID* will interpret conformers in the database file(s) as part of a single multi-conformer molecule as long as they:

- Are contiguous in the input file.
- Have the same numbers of atoms and bonds in the same order
- Have identical atom and bond properties with their order correspondent in the subsequent connection table
- Have the same atom and bond stereochemistry

While this may appear to be a restrictive list, many programs write multi-conformer molecules into SDF or MOL2 files such that the above rules will be satisfied. If the conformers are named differently, (*i.e.* they have a conformer number appended to the base name like acetsali_1, acetsali_2), *HYBRID* will still consider them part of a single multi-conformer molecule if the criteria above are met.

5.2.2 Receptor Preparation

Note

Beginning with *HYBRID* 4.0.0, *HYBRID* now only accepts an OEDU with receptor as the receptor input file.

HYBRID can use either a single *receptor* or multiple *receptors* each of which contains a different structure/conformation of the target protein. Each *receptor* must also have a bound ligand. Receptors with bound ligands can be created with the following programs.

Program	Type	Description
Make Receptor	GUI	Interactive GUI for creating a receptor.
ReceptorInDU	Command Line	Generates a receptor inside a prepared OEDesignUnit in an OEDU file.
OEB2DUReceptor	Command Line	Converts a molecule based receptor OEB or OEB.GZ file into a receptor inside an OEDesignUnit, in an OEDU file

Note

Receptors can also be created using the Docking Toolkit (see the Docking Toolkit documentation).

5.3 Example Commands

5.3.1 Basic Hybrid Docking Example

This example hybrid docks molecules using a single processor.

Input files for 1DWD

- **receptor.oedu :**
  A receptor file containing the structure of the target protein and a bound ligand. (see *Receptor Preparation* section).
- **multiconformer_ligands.oeb.gz :**
  Conformationally expanded 3D ligands to dock. (see *Ligand Preparation* section).

Command line

```
prompt> hybrid -receptor receptor.oedu -dbase multiconformer_ligands.oeb.gz
```

Output files

- **hybrid_docked.oeb.gz** : Top 500 scoring molecules of *multiconformer_ligands.oeb.gz* docked into *receptor.oedu*.
- **hybrid_undocked.oeb.gz** : Molecules of *multiconformer_ligands.oeb.gz* that could not be docked into the active site (generally occurs if the molecules are too big for the site). This file will not be present if all molecules were successfully docked to the active site.
- **hybrid_score.txt** : A tab separated text file containing the name and score of each of the top 500 ligands.
- **hybrid_report.txt** : A text report of the docking process.
- **hybrid_settings.param** : A text file containing the parameters used for this run.
- **hybrid_status.txt** : A text file that is overwritten periodically during the run with the status of the run.

5.3.2 Hybrid Docking with Multiple Crystal Structures

In this example *HYBRID* docks molecules using multiple structures of the target protein.

Input files for 2AA2 and 2AA7

- **receptor1.oedu :**
  A receptor file containing the structure of the target protein and a bound ligand. (see *Receptor Preparation* section).
- **receptor2.oedu :**
  A receptor file containing the structure of the second target protein and a bound ligand. This receptor file should have a different structure of the same target protein in *receptor1.oedu*, generally with a different bound ligand. (see *Receptor Preparation* section).
- **multiconformer_ligands.oeb.gz :**
  Conformationally expanded 3D ligands to dock. (see *Ligand Preparation* section).

Command line

```
prompt> hybrid -receptor receptor1.oedu \
               -receptor receptor2.oedu \
               -dbase multiconformer_ligands.oeb.gz
```

Output files

- **hybrid_docked.oeb.gz** : Top 500 scoring molecules of *multiconformer_ligands.oeb.gz* docked into either *receptor1.oedu* or *receptor2.oedu*. The title and filename of the receptor docked to will be tagged to the SD data of each docked ligand (see the *report.txt* file).
- **hybrid_undocked.oeb.gz** : Molecules of *multiconformer_ligands.oeb.gz* that could not be docked into the active site (generally occurs if the molecules are too big for the site). This file will not be present if all molecules were successfully docked to the active site.
- **hybrid_score.txt** : A tab separated text file containing the following information for each of the top 500 ligands.
  - Name of the ligand
  - Score of the ligand
  - Title of the receptor site the ligand docked to.
  - Filename of the receptor site the ligand docked to.
- **hybrid_report.txt** : A text report of the docking process.
- **hybrid_settings.param** : A text file containing the parameters used for this run.
- **hybrid_status.txt** : A text file that is written periodically during the run with the status of the run.

5.3.3 MPI docking example

In this example *HYBRID* docks molecules to a single receptor on 4 processors of the host machine.

Input files

- **receptor.oedu :**
  A receptor file containing the structure of the target protein and a bound ligand. (see *Receptor Preparation* section).
- **multiconformer_ligands.oeb.gz :**
  Conformationally expanded ligands to dock. (see *Ligand Preparation* section).

Command line

```
prompt> hybrid -mpi_np 4 -receptor receptor.oedu \
                              -dbase multiconformer_ligands.oeb.gz
```

Output files

- **hybrid_docked.oeb.gz** : Top 500 scoring molecules of *multiconformer_ligands.oeb.gz* docked into *receptor.oedu*.
- **hybrid_undocked.oeb.gz** : Molecules of *multiconformer_ligands.oeb.gz* that could not be docked into the active site (generally occurs if the molecules are too big for the site). This file will not be present if all molecules were successfully docked to the active site.
- **hybrid_score.txt** : A tab separated text file containing the name and score of each of the top 500 ligands.
- **hybrid_report.txt** : A text report of the docking process.
- **hybrid_settings.param** : A text file containing the parameters used for this run.
- **hybrid_status.txt** : A text file that is overwritten periodically during the run with the status of the run.

5.4 Command Line Help

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

```
> hybrid --help
```

will generate the following output:

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

5.5 Required Parameters

-receptor <receptor file1> [<receptor file2> ...]

Receptor file(s) to dock to. Each receptor must have a bound ligand and must be in OEDocking receptor format (`.oedu`).

If multiple receptors are specified each docking ligand will be docked into the single receptor with the bound ligand most similar to it, as measured by 3D shape and chemical similarity.

[Aliases=**-rec**]

-dbase <input filename1> [<input filename2> ...]

File(s) containing conformationally expanded ligands to dock (see section *Input Preparation*).

The following file formats are supported.

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

More than one file can be specified.

[Aliases=**-database**,**-in**]

5.6 Optional Parameters

5.6.1 Input Options

-param <parameter filename> [No Default]

A parameter file is a text file that lists parameter settings to be used during a run. If a parameter is specified both on the command line and in the parameter file, the value specified on the command line is used.

The format of the parameter file is as follows:

- One parameter per line
- For non-list parameters one key-value pair per line. (*e.g., -receptor rec.oedu*).
- For list parameters a key followed by all the values (*e.g., -dbase lig1.oeb.gz ligs2.oeb.gz*)
- Boolean parameters must be listed as a key followed by true or false (*e.g. -annotate_poses true*).
- The parameter file may not contain the *-param* parameter.
- Lines beginning with # are considered comments

-molnames <input filename> [No Default]

This parameter specifies 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 database file(s) (see parameter *-dbase*) 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 database, without having to extract those molecules by hand from the database.

5.6.2 Dock Options

-dock_resolution <setting> [Default: Standard]

The parameter controls the resolution of the docking both during the exhaustive search and the optimization. The resolution of the exhaustive search at each setting is as follows.

Setting	Translational Stepsize	Rotational Stepsize
High	1.0 Ångström	1.0 Ångström
Standard	1.0 Ångström	1.5 Ångströms
Low	1.5 Ångströms	2.0 Ångströms

During the optimization step the resolution is half that of the exhaustive search.

[Aliases = **-res**]

See also

- OEDocking::OEDockOptions::SetResolution in the **OEDocking TK** manual.

5.6.3 Output Files

-docked_molecule_file <filename> [Default=docked.oeb.gz]

File docked molecules will be written to. The file format is controlled by the extension of the filename. The following output formats are supported.

Format	Extension
OEBinary	.oeb
SDF	.sdf
Gzipped OEBinary	.oeb.gz
Gzipped SDF	.sdf.gz

Scores will be attached as SD data to each pose with the tag **HYBRID Chemgauss4 Score**, unless the *-score_tag* option is used to specify another tag.

By default all docked molecules will be outputted in the order in which they were docked. Molecules can also be outputted in sorted order by using the *-hitlist_size* option.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., docked.oeb.gz) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases=**-docked_mol_file**,**-docked_file**,**-docked**,**-out**]

-undocked_molecule_file <filename> [Default: undocked.oeb.gz]

Specifies an output file in which to place molecules that could not be docked into the active site (this generally occurs when a molecule is too large to fit in the site, or unable to match user specified docking constraints). The format of this file is determined by the filename extension. The following output formats are supported.

Format	Extension
OEBinary	.oeb
SDF	.sdf
Isomeric SMILES	.ism
Gzipped OEBinary	.oeb.gz
Gzipped SDF	.sdf.gz
Gzipped Isomeric Smiles	.ism.gz

> **Note**
>
> If this flag is not set by the user the default filename (i.e., undocked.oeb.gz) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-undocked_mol_file**, **-undocked_file**, **-undocked**]

-score_file <filename> [Default: score.txt]

Specifies a tab separated text file with the name and scores of the molecules.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., score.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases : **-score**]

-report_file <filename> [Default: report.txt]

Specifies a file that a text report of the run will be written to.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., report.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases : **-report**]

-settings_file <filename> [Default: settings.param]

Writes the settings of all parameters of the run to the specified output file. The settings will be listed in plain text

with one parameter name follow by its value(s). This format is compatible with the format of parameter files, and therefore a settings file from a previous run can be passed to the *-param* flag to re-run the program with the same settings.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., settings.param) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-settings**]

-status_file <filename> [Default: status.txt]

If this parameter is set then the status of the run will be written to the given output file every few seconds (the previous contents of the file will be overwritten) during the run.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., status.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-status**]

5.6.4 Output Options

-hitlist_size <num> [Default: 500]

This parameter controls the number of top scoring molecules that will be outputted at the end of the run (sorted by score), or can be used to specify that all molecules should be outputted as they are processed (unsorted).

If -hitlist_size is non-zero a sorted hitlist of the best scoring molecules is produced that will be maintained and output at the end of the run. The maximum size of the hitlist is *-hitlist_size*. If more than this number of molecules are in the input database only the top scoring molecules will be outputted and the rest will be discarded.

If *-hitlist_size* is zero the run will be in serial mode, *i.e.* each molecule will be outputted as it is processed (unsorted). For single processor runs this will be the order the molecules appear in the database file(s). For MPI runs the order will not be strictly the order the molecules appear in the database file(s).

There is no formal limit on the number of molecules that can be sorted and outputted at the end of the run. However, retaining a large number of molecules significantly increases the memory requirements. A good rule of thumb is that the setting *-hitlist_size* times the setting of *-num_poses* should not be larger than 10,000.

[Aliases = **-hitlist_size**, **-hitlist**]

-num_poses <num> [Default: 1]

Specifies the maximum number of docked poses to output for each docked molecule.

There is no formal limit on the number of poses per molecule that can be outputted, however, retaining a large number of alternate poses significantly increases the size of the molecules in memory and when outputted to disk. A good rule of thumb is that the setting *-hitlist_size* times the setting of *-num_poses* should not be larger than 10,000.

[Aliases = **-numposes**]

-score_tag <tag> [No Default]

This parameter overrides the default SD Data Tag used to store molecule scores (the default is **HYBRID Chemgauss4 Score**).

[Aliases=**-scoretag**]

-annotate_scores [Default: false]

If the value of this flag is set to true VIDA score annotations will be added to the processed molecules. These annotations are visible in VIDA (OpenEye's molecular visualization program) and show a per atom breakdown of the score.

> **Note**
>
> The docked molecule output file format (see *fred -docked_molecule_file*) must be OEBinary when using score annotations.

[Aliases = **-annotate**]

-save_component_scores [Default: false]

If the value of this flag is set to true individual components of the total score will be saved to SD data on each pose and appear in the score file (see *-score_file*).

[Aliases = **-component_scores**, **-component**]

-no_extra_output_files [Default=false]

When this flag is set to true the only default output to the program will be the docked structure file (see *-docked_molecule_file*).

Using this flag suppresses the default output of the following

Output	Default filename	Parameter
Undocked molecule file	undocked.oeb.gz	*-undocked_molecule_file*
Text score file	score.txt	*-score_file*
Report file	report.txt	*-report_file*
Settings file	hybrid.param	*-settings_file*
Status file	status.txt	*-status_file*

Only default output is suppressed. If any of these output parameters are explicitly set by the users the relevant output file will still be written even if this switch is turned on.

[Aliases=**-no_extra**,**-noextra**,**-noextraoutputfiles**,**-no_extra_output**,**-noextraoutput**]

-no_dots [Default: false]

When this flag is set to true, a dot is being written to standard error for each docking molecule (or x in the case of a failure). Setting this flag to false to suppress dot/x writing.

[Aliases = **-nodots**]

-prefix <value> [Default=hybrid]

This flag prefixes all default output filenames with the specified value.

> **Note**
>
> This flag does not affect output filenames explicitly set by the user.

-nostructs [Default=false]

When this flag is set to true, both the docked and undocked structure files will be suppressed. The flag overrides *-docked_molecule_file* and *-undocked_molecule_file*.

CHAPTER

SIX

POSIT

6.1 Overview

POSIT works best when fitting to a collection of co-crystal ligands, however, it can be used for a single ligand targets. Each pose that **POSIT** generates is analyzed with a simple heuristic and marked with a probability (seen below).

The structures output by **POSIT** are annotated with information about the best-fit receptor and with various metrics describing the details of the pose. These details are stored in SDDATA and can be viewed with most molecular structure viewers.

The details are as follows:

Name	Description
Docking Input Order	The input order from the original file
Result	GREAT, GOOD, MEDIOCRE or POOR detailing the quality of the result
POSIT receptor title	the name of the receptor (taken from the original protein)
POSIT receptor filename	the filename of the original receptor
POSIT::Probability	Estimated probability of being within 2 Ångström RMSD of the real structure (assuming binding)
POSIT::Method	The underlying method used (SHAPEFIT, HYBRID, FRED)
Dock Type	The docking type used (which is *POSIT* in this case)

These values are also written to the report file in a tab separated format, see `-prefix` for details.

The probability that the computed pose is a correct pose is generated as described in *the section about estimated pose probability*.

The values in the Result field are as follows:

Result	Meaning
GREAT	Computed pose is likely (75%-100%) probability) to be within 2.0 Å of experimentally-derived pose.
GOOD	Computed pose may be (50%-75%) probability) to be within 2.0 Å of experimentally-derived pose.
MEDIOCRE	Take with a grain of salt (33%-50%) probability)
POOR	Take with a huge grain of salt (<33% probability)

By default, **POOR** poses are not written out, they are rejected as unsuitable. The number of rejected molecules is recorded in the status file.

6.2 Input Preparation

6.2.1 Ligand Preparation

The most common use of *POSIT* is to dock molecules into the active site of a target protein. For the purposes of this document, we'll call the file(s) of molecules the database file(s), or dbase file(s). The most common format for database file(s) is a multi-conformer OEBinary file created by OpenEye's **OMEGA** program, however, this file can be one of several 3D formats. These formats include SDF, MOL2 and PDB. *POSIT* determines the database file format from the file extension, `.sdf` or `.mol` for SDF, `.mol2` for MOL2, `.pdb` or `.ent` for PDB. Gzip compressed files of these same formats are allowed as well. *POSIT* will interpret `infile.sdf.gz` as a gzip'ed SDF file.

> **Note**
>
> Note that even though all these formats are supported, using SDF, PDB or MOL2 can result in a loss of speed due to the I/O penalty of these formats.

POSIT internally generates 3D conformations **OMEGA** if a 1D/2D molecule is supplied.

By default *POSIT* will interpret conformers in the database file(s) as part of a single multi-conformer molecule as long as they:

- Are contiguous in the input file.
- Have the same numbers of atoms and bonds in the same order
- Have identical atom and bond properties with their order correspondent in the subsequent connection table
- Have the same atom and bond stereochemistry

While this may appear to be a restrictive list, many programs write multi-conformer molecules into SDF or MOL2 files such that the above rules will be satisfied. If the conformers are named differently, (*i.e.* they have a conformer number appended to the base name like acetsali_1, acetsali_2), *POSIT* will still consider them part of a single multi-conformer molecule if the criteria above are met.

6.2.2 Receptor Preparation

> **Note**
>
> Beginning with *POSIT* 4.0.0, *POSIT* now only accepts an OEDU with receptor as the receptor input file.

POSIT can use either a single *receptor* or multiple *receptors* each of which contains a different structure/conformation of the target protein. Each *receptor* must also have a bound ligand. Receptors with bound ligands can be created with the following programs.

Program	Type	Description
Make Receptor	GUI	Interactive GUI for creating a receptor.
ReceptorInDU	Command Line	Generates a receptor inside a prepared OEDesignUnit in an OEDU file.
OEB2DUReceptor	Command Line	Converts a molecule based receptor OEB or OEB.GZ file into a receptor inside an OEDesignUnit, in an OEDU file

Note

Receptors can also be created using the Docking Toolkit (see the Docking Toolkit documentation). Since **POSIT** can generate poses using various methods, constraints present in the receptor may or may not play any role for the specific pose generation. Constraints only affect the generated pose when `FRED` or `HYBRID` is the underlying method.

6.3 Example Commands

POSIT always requires a bound-ligand in a receptor to fit against and an output file. The ligand (or ligands) to fit is specified with the *-dbase* option or the *-in* option, and the structures to fit are specified with *combine_receptors -receptors*. Multiple receptors can be input at a time, in fact this is the preferred mode of running **POSIT**.

Note

-dbase accepts only 3D molecules, normally generated by **OMEGA**.

-in accepts most formats and generates 3D conformations when applicable. When in doubt, use the *-in* option.

6.3.1 Basic Usage

The basic form of running **POSIT** is to fit against multiple receptors. The best fit receptor will be chosen for the final pose. Assuming that you have made receptors and combined them as shown above:

```
> posit -receptors renin/receptors/*.oedu renin/merged/*.oedu -in renin/all.smi \
        -docked_molecule_file results.oedu
```

Note

On *Microsoft Windows* systems, you need to expand the wildcard:

```
> posit -receptor renin\receptors\2IL2_b.rec.oedu renin\receptors\2IL2_a.rec.
↪oedu \
      renin\receptors\2IL2_c.rec.oedu renin\receptors\2IKO.rec.oedu \
      renin\receptors\2IKU_a.rec.oedu renin\receptors\2IKU_b.rec.oedu \
      renin\merged\2IKU_a.rec._merge_2IKO.rec.oedu renin\merged\2IKO.rec._
↪merge_2IKU_a.rec.oedu \
      -in renin\all.smi -docked_molecule_file results.oedu
```

All results are written to the specified output file.

Any predicted ligand that has a good probability but clashes with the protein will either be ignored or, if the *-clashed_molecule_file* output is specified on the command line, it will be output to the specified file.

```
> posit -receptors renin/receptors/*.oedu renin/merged/*.oedu -in renin/all.smi \
        -docked_molecule_file results.oedu -clashed_molecule_file clashed.smi
```

6.3.2 Ignoring Nitrogen Stereo

By default, **POSIT** ignores nitrogen stereo to make it easier to dock input x-ray models which may be time-averaged resulting in planar nitrogens.

If desired, this flag can be set to false in order to only fit explicit nitrogen stereo:

```
> posit -receptors renin/receptors/*.oedu renin/merged/*.oedu -in all.smi \
         -docked_molecule_file results.oedu -ignore_nitrogen_stereo false
```

Note

POSIT 1.0 defaulted to not ignoring nitrogen stereo. This was changed due to the nature of crystallographic structures tending to produce time-averaged planar nitrogens.

Sometimes you may see warnings like the following:

```
Warning: Input stereochemistry different from output after fitting
in: CCc1c(c(nc([nH+]1)N)N)c2ccc3c(c2)N(CCC3)CCCOC
out: CCc1c(c(nc([nH+]1)N)N)c2ccc3c(c2)[N@](CCC3)CCCOC
Warning: Input stereochemistry different from output after fitting
in: CCc1c(c(nc([nH+]1)N)N)c2ccc3c(c2)N(CCC3)CCCOC
out: CCc1c(c(nc([nH+]1)N)N)c2ccc3c(c2)[N@@](CCC3)CCCOC
```

These simply serve as a warning that stereochemistry was added or modified during the fitting/optimization process.

6.3.3 Advanced Usage

To run **POSIT** on absolutely everything and not worry about clashes or probabilities:

```
> posit -receptors renin/receptors/*.oedu -in renin/all.smi \
 -docked_molecule_file results.oedu  -outputall
```

This runs **POSIT** and outputs all docked molecules regardless of score in the order they exist in the input file.

6.4 Command Line Help

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

```
> posit --help
```

will generate the following output:

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

6.5 Required Parameters

-receptor <filenames>

List of receptors used to predict the pose of the input molecules. Receptors must include a bound ligand.

Multiple receptors can be input:

```
> posit -receptor rec*.oedu
```

Will use all files that start with rec and end with `.oedu`.

```
> posit -receptor  receptors.lst
```

Will use all receptors files specified in the receptors.lst file. If any entry in the specified file is not a valid receptor, **POSIT** will halt.

Supported *-receptor* file formats are:

File type	Extension
OEDesignUnit	.oedu
list	.lst

Multiple receptor files and list files can be used simultaneously.

[Aliases=**-rec**,**-receptors**]

-in <filename>

Input molecules to pose-predict. If 3D molecules are input, the original conformations are retained for optimization as well as the expanded conformational ensemble.

[Aliases=**-lig**]

POSIT uses an internal conformation sampling to generate high-quality conformations. However, input ring structures (chair/boat) may not be reproduced as **POSIT** may choose a lower energy ring template during the sampling process.

Supported input file formats are:

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

6.6 Optional Parameters

6.6.1 Input Options

-dbase <filename>

Input molecules to pose-predict. 3D molecules must be input as conformational expansion is not performed prior to fitting.

-dbase is the fastest way to run **POSIT** on large datasets. The expected input is a pre-generated database of **OMEGA** generated conformers.

```
> omega2 -in renin/all.smi -out all.oeb.gz -rangeIncrement 1 \
   -maxConfRange 200,200,300,400,500,600,700,800,900,1000,1100,1200,1300,1400,1500,
↪1600

> posit -receptor receptor.oedu -dbase all.oeb.gz
```

Supported input file formats are:

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

[Aliases=**-db**,**-database**]

-molnames

This flag specifies a text file with the names of one or more molecules in supplied to the *-dbase* flag. If specified, only molecules with matching names will be read by the *-dbase* flag. If this flag is not specified all molecules will be read normally. Molecules names should be listed one per line.

The general purpose of this flag is to provide an easy mechanism for reading a few specific molecules that are contained in a large database, without having to extract those molecules by hand from the database.

6.6.2 Multiprocessing Options

Execute Options

-param

The argument for this flag is the name of a file containing control parameters. The control parameter file acts to either replace or augment the command line interface. All parameters necessary for program execution may be provided in the control parameter file, although any command given explicitly on the command line will supersede options found in the parameter file. The application generates a new parameter file containing the full set of execution parameters upon every execution. The name of the parameter file is created by combining the prefix base name with the *'.param'* extension.

-mpi_np <n>

Specifies the number of processors `n` when the application 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 slots=n` where `n` is the number of processors on the host.

6.6.3 Dock Options

-ignore_nitrogen_stereo

When examining the ligands to pose predict for stereo, ignore any missing nitrogen chirality. (This is normally caused by time averaging of crystal structures).

When expanding stereo, nitrogen stereo centers will not be assigned.

POSIT now always expands missing stereo.

> **Note**
>
> **POSIT** may complain about stereo centers being changed by the optimization, this is more likely when ignoring nitrogen stereo centers since the optimization may decide a different stereo configuration is optimal.

[Default=true]

[Aliases=**-ignoreNitrogenStereo**]

> **See also**
>
> - OEDocking::OEPositOptions::SetIgnoreNitrogenStereo in the **OEDocking TK** manual.

`-minimum_probability`

Minimum probability for poses of interest. **POSIT** only outputs poses that has the minimum required probability. To output all poses, set *-minimum_probability* to 0.

[Default=0.33]

[Aliases=**-minProbability**]

> **See also**
>
> - OEDocking::OEPositOptions::SetMinProbability in the **OEDocking TK** manual.

`-allowed_clashes`

Clashes allowed in the generated poses. There are three levels:

Allowed Clash	Description
noclashes	No clashes are allowed. Actually there is a little wiggle room here less than 0.2 Å penetration is not considered a clash.
mildclashes	Clashes involving hydrogen are allowed, but
hclashes	those between heavy atoms are disallowed.
allclashes	All clashes are allowed.

All poses that are accepted by the probability calculation yet clash with the protein are written to the fail file (if specified).

[Default=mildclashes]

[Aliases=**-allowedClashes**]

> **See also**
>
> - OEDocking::OEPositOptions::SetAllowedClashType in the **OEDocking TK** manual.

-relax

Flag indicating if post pose prediction relaxation should be performed. The relaxation is performed by allowing flexibility to the ligand and parts of the receptor. Turning on relaxation can significantly slow down the calculations. There are three options:

Relax Mode	Description
none	No relaxation is performed.
clashed	Relaxation is performed on poses that contains clashes.
all	Relaxation is performed on all poses.

[Default=none]

See also

- OEDocking::OEPositOptions::SetPoseRelaxMode in the **OEDocking TK** manual.

-num_poses

Number of alternative poses to be generated for each docked molecule. The default is to only generate a single most probable pose.

[Default=1]

[Aliases=**-numposes**]

-best_Receptor_Pose_Only

If this flag set to `false` the pose prediction is performed using all of the receptors and the best set of poses from all of the receptors combined is provided as the results. With the default setting of `true` pose prediction is only performed on the `best receptor` for any given ligand. Note that, setting the flag to `false` could increse the runtime significantly depending on the number of receptors used for the calculation.

[Default=true]

[Aliases=**-bestReceptorPoseOnly**]

See also

- OEDocking::OEPositOptions::SetBestReceptorPoseOnly in the **OEDocking TK** manual.

6.6.4 Output File Options

POSIT writes docked structure results to a single file, *-docked_molecule_file* – Ligand only output in one file.

By default, not all poses may be written to the output, to see where ligands were placed, consult the log file for more details. To control this behavior use the *-outputall* flag, which writes all output to the file specified by *-docked_molecule_file* in order of input molecule.

-docked_molecule_file <filename>

If specified, this flag overrides the default name of the docked molecule output file. Only .oedu, .oeb, and .oeb.gz formats are allowed. An .oedu file is generated by default, and is the preferred output format.

> **Note**
>
> The default file is posit_docked.oedu, or <-prefix>_docked.oedu if the *-prefix* flag is specified.

Ligands are written to the output file based on the desired sort order (see the `flynn -sortBy` flag).

[Aliases=**-docked_mol_file**,**-docked_file**,**-docked**,**-out**]

`-undocked_molecule_file`

If specified this flag overrides the default name for the undocked molecule file.

> **Note**
>
> The default filename is posit_undocked.oeb.gz, or <-prefix>_undocked.oeb.gz if *-prefix* is specified.

[Aliases=**-undocked_mol_file**,**-undocked_file**,**-undocked**]

`-score_file`

If specified overrides the default name of the output text file containing the scores of the docked molecules.

> **Note**
>
> The default filename is posit_score.txt or <-prefix>_score.txt if the *-prefix* flag is specified.

[Aliases=**-scorefile**,**-score**]

`-report_file`

If specified overrides the default output filename for the report file.

> **Note**
>
> The default filename for the report file is posit_report.txt or <-prefix>_report.txt if the *-prefix* flag is specified.

[Aliases=**-report**]

`-status_file`

If specified overrides the default filename for the status file.

> **Note**
>
> The default status file name is posit_status.txt or <-prefix>_status.txt if the *-prefix* flag is specified.

[Aliases=**-statusfile**,**-status**]

-rejected_file

If specified overrides the default filename for the reject file.

The reject file is a tab separated file containing the input ligand number, the ligand title and the reason for the ligand being undocked.

Example output:

```
Ligand #        Title#Status
0       lig1    No conformers above minimum probability
1       lig2    No conformers above minimum probability
2       lig3    No conformers above minimum probability
3       lig4    No conformers above minimum probability
```

> **Note**
>
> The default status file name is posit_rejected.txt or <-prefix>_rejected.txt if the *-prefix* flag is specified.

[Aliases=**-rejected**]

-settings_file

If specified overrides the default output filename for the setting file.

> **Note**
>
> The default settings filename is posit_settings.param or <-prefix>_settings.param if the *-prefix* flag is specified.

[Aliases=**-settingsfile**,**-settings**]

-clashed_molecule_file <filename>

Occasionally **POSIT** rejects ligands that probably have the correct binding mode but also display uncorrectable clashes. If this flag is set, clashed molecules will be written to this file in no specific output order.

It is important to be aware that because these are likely binding modes there is a chance that the clashed poses are still correct but the protein has reconfigured to accept the clashed pose.

[Aliases=**-clashed_mol_file**,**-clashed_file**,**-clashed**,**-clash**]

6.6.5 Output Options

-score_tag

Overrides the default tag used to attach the score to the output molecules

[Aliases=**-scoretag**]

-no_extra_output_files

Suppress the default output of the score, status, settings, report and undocked files.

[Aliases=**-no_extra**,**-noextra**,**-noextraoutputfiles**,**-no_extra_output**,**-noextraoutput**]

-no_dots

Suppress writing a dot (.) to standard error for each docking molecule (or *x* in the case of a failure).

[Aliases=**-nodots**]

-prefix

The text passed to this parameter will be preappended to all default output filenames (it does not affect output filenames explicitly set by the users).

[Default=posit]

-outputall

Shorthand to write all output including clashed or nonprobable molecules.

-verbose

Set verbose output for logging.

[Default=false]

CHAPTER

SEVEN

MAKE RECEPTOR

7.1 Overview

Make Receptor is a graphical utility for creating or modifying a *receptor*. *Receptors* are specialized design unit (OEDU) files used by *FRED* and *HYBRID* that contain the location and shape of the active site, and optionally the docking constraints.

Receptors can also be created using the SPRUCE and *ReceptorInDU* command line utilities. These utilities create receptors with default settings with fairly minimal user input and are generally very effective.

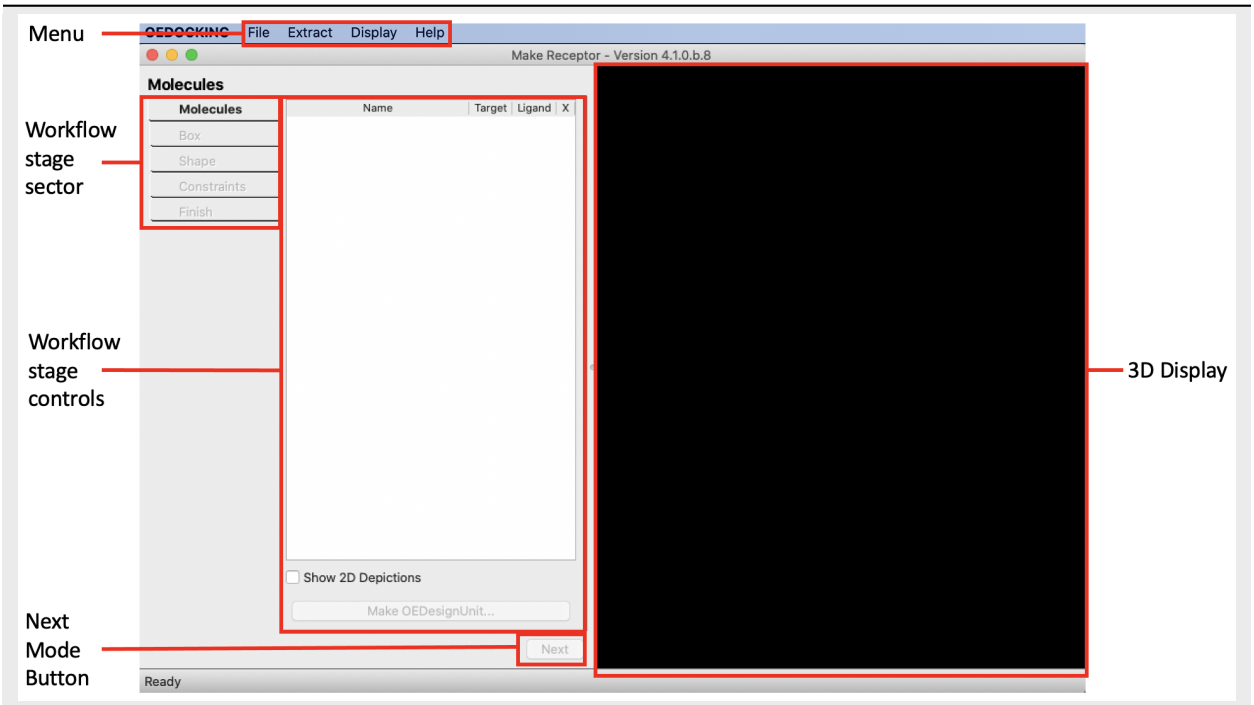
> **Note**
>
> Receptors created with the command line utilities can be edited with the **Make Receptor** GUI.

Make Receptor provides the users with more control over the receptor creation process than the command line utilities, as well as a way to visualize all the information contained in a receptor. The following capabilities of the **Make Receptor** program are either unavailable or difficult to execute from the command line tools.

- Creating a receptor with crystallographic water that ligands will interact with.
- Creating a receptor with constraints or adding constraints to an existing receptor.
- Visualizing and editing the size of the inner and outer contour shapes (see *Receptor Theory*).

To start **Make Receptor**, type "make_receptor" on the command line or click on the **Make Receptor** icon from Dock on OSX; type "make_receptor" on the DOS prompt or click on the **Make Receptor** shortcut from Desktop on Windows; or type "make_receptor" on the command line on Linux.

7.2 GUI Layout



Make Receptor Layout

The layout of the **Make Receptor** GUI, shown above, is divided into five general areas.

- **Menu**
  - **File**
    - **New**
      Open molecule file(s) to create a new design unit receptor.
    - **Open Design Unit/Receptor**: Open an existing design unit or receptor.
    - **Open Recents**: Opens a recently opened OEDU file.
    - **Save Receptor**: Saves the receptor to a file. The receptor shape must be defined before this option can be used.
    - **Save DU**: Saves the design unit(s) to a file. A design unit must exist before this option can be used.
    - **Clear** :Deletes all receptor data and molecules and opens the molecules edit mode.
    - **Quit**: Quits **Make Receptor**.
  - **Extract**
    - **Target**

      Extract the receptor target into a molecule file.
    - **Protein**

      Extracts the protein structure from the design unit into a molecule file.
    - **Ligand**

      Extracts the bound ligand from the design unit into a molecule file.

        * **Box**

          Extracts the box enclosing the receptor site into a molecule file. The molecule file will have eight carbon atoms, one at each vertex of the box.

    - **Display**

      These options all relate to the 3D display window.

        * **Hydrogens**

          Turn on and off display of hydrogens in the 3D window.

        * **Protein**

          Sets the protein display mode.

        * **Ligand**

          Sets the ligand display mode.

        * **Box**

          Sets the box display mode.

        * **Outer Contour**

          Sets the display mode of the outer contour.

        * **Inner Contour**

          Sets the display mode of the inner contour.

        * **Constraints**

          Sets the display mode of the constraints.

        * **Disable Hardware Rendering**

          Disables OpenGL hardware rendering. Useful for Windows machines experiencing driver-related 3D graphical issues.

    - **Help**

        * **About**

          Reports the version of the program.

        * **Documentation**

          Opens a browser window to OpenEye's web documentation.

- **Workflow Stage Selector**

  These buttons control the overall workflow to set up a receptor. Most stages of the workflow must be finished before progressing to the next stage. When the next stage of the workflow is available, its button will highlight here and the next button (described below) will become available. The workflow for setting up a receptor is described in detail in the *setting up a receptor section*.

- **Workflow Stage Controls**

  The controls for each stage of the workflow setup are located in this area. As you progress through the stages of the setup process, controls for each stage will appear here. The workflow for setting up a receptor is described in detail in the *setting up a receptor section*.

- **3D Display**

  A 3D display of the current state of the receptor and its associated data.

- **Next Mode Button**

  Selects the next stage of the setup receptor workflow once the current stage has been properly setup.

7.3 Setting up a Receptor

7.3.1 New DU/Receptor

Use the `File->New...` menu option to create a new design unit or receptor. This provides two separate paths to creating a new design unit. Choose the `PDB/MMCIF` option to create a design unit starting from a PDB or MMCIF file (with or without an associated MTZ file). The `Molecules` option should be used when various molecule components of the design unit contains in separate files.

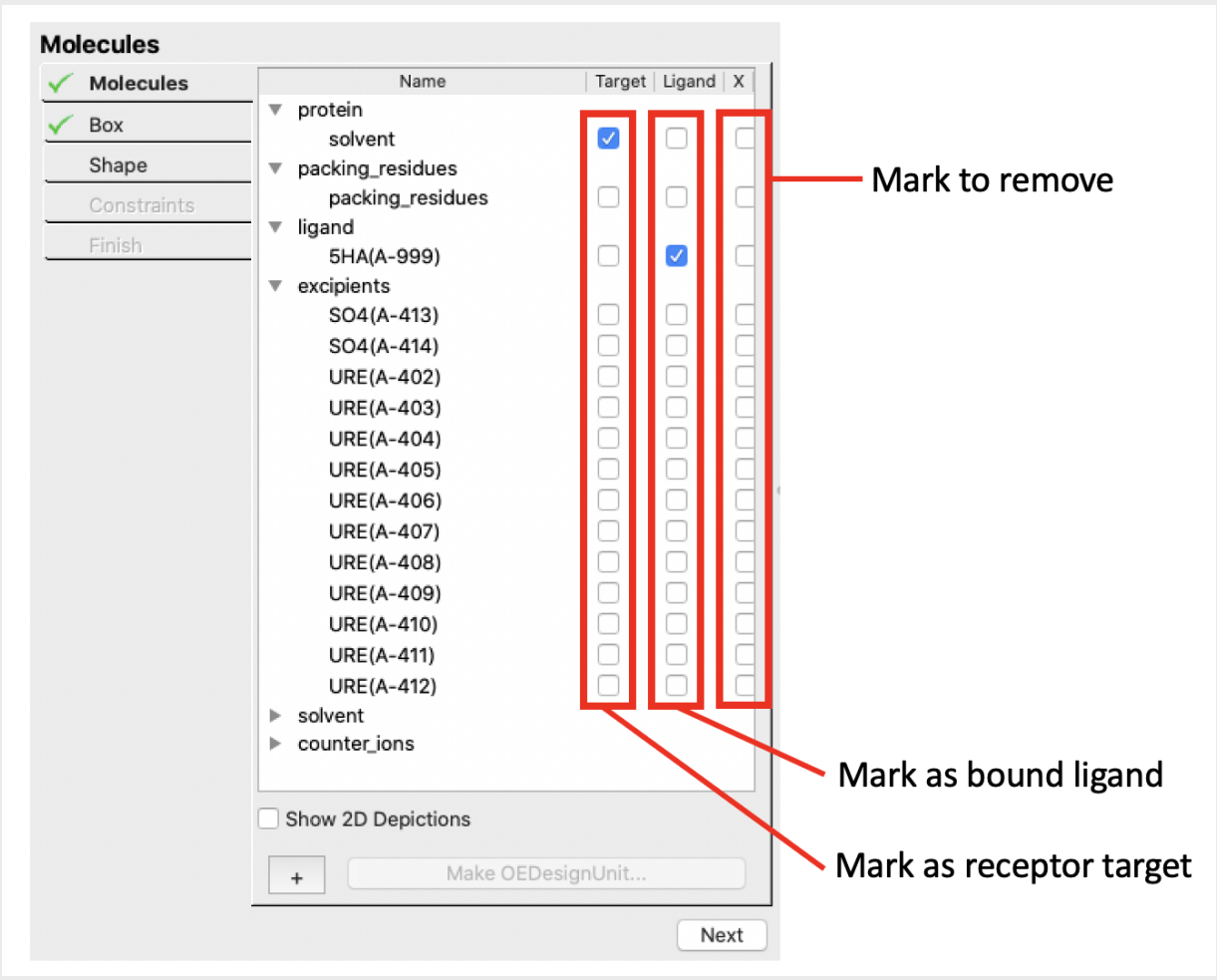
7.3.2 Existing DU/Receptor

Use the `File->Open Design Unit/Receptor...` menu option to open an existing design unit or receptor. This option allows opening both an OEDU file or a receptor containing in an OEB or OEB.GZ file.

The *HYBRID* program requires that a receptor have a bound ligand, while *FRED* does not. Waters and other crystallographic solvents, that are a aprt of the design unit, are ignored during the docking process of both *HYBRID* and *FRED*, unless the user designates them as part of the receptor target. (See the following *molecules* section).

> **Note**
>
> If a receptor is chosen using File->Open menu option *Make Receptor* will switch to *finish mode* to show a summary of the information on the receptor. You can then select any of the setup steps to modify the receptor as desired.

7.3.3 Molecules



Molecules controls

The purpose of the molecules workflow stage is to classify molecules. A molecule is a covalently connected set of atoms that is not covalently bound to any other molecule.

> **Note**
>
> Covalently bound ligands are not supported.

Each molecule can have one of three classifications.

- **Target**

  These molecules make up the structure of the target (protein) that docking ligands interact with. The structure is treated as rigid during the docking process, except for rotatable hydrogens (e.g., hydroxyls) which are rotated to form optimal hydrogen bonding interactions during the docking process (this rotation is an internal calculation that is reflected in the docked scores, but not in any output structure).

- **Bound Ligand**

  This molecule is a ligand bound into the active of the protein. Generally the bound ligand structure is deter-

mined by x-ray crystallography, although a docked molecule structure could also be used instead if there is high confidence in the correctness of the docked structure.

This molecule is required by *HYBRID* during the docking process to guide docking molecules into a docking mode similar to the bound ligand. It is not required by *FRED* and is ignored by *FRED* if present.

- **Excess Molecules**

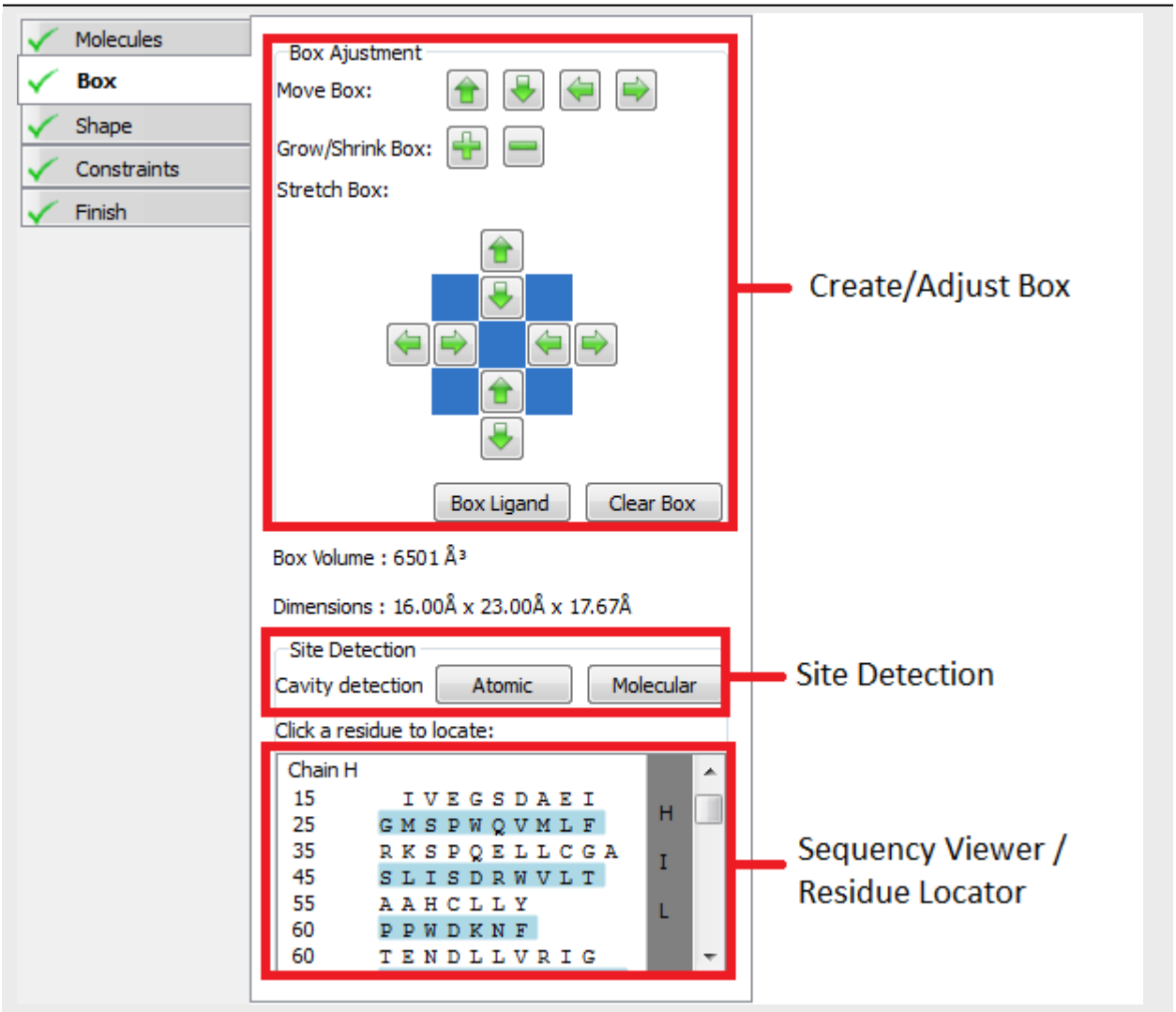
  Excess molecule are those that should not be included as part of the design unit. Once a set of molecules are marked to be removed (**X**), and design unit is prepared, those molecules are removed from the system.

Molecule classification is done using the *Mark as bound ligand*, *Mark as receptor target*, and *Mark to remove* checkboxes (see the *molecule controls figure*).

Listed molecules can be identified in the 3D window by clicking their names in the list. Selected molecules are depicted in CPK rather than wireframe mode. Molecule selection can also be done on a molecule in the 3D window to identify which molecule it is in the molecule list.

At least one molecule must be classified as a receptor target molecule before moving on to the next stage of the workflow.

7.3.4 Box



Box controls

The goal in this stage of the receptor setup workflow is to define a box enclosing the active site. The box should enclose the entire region active site where heavy atoms of the docking ligand can be placed. Any docked pose with any heavy atom that lies outside the box will be rejected.

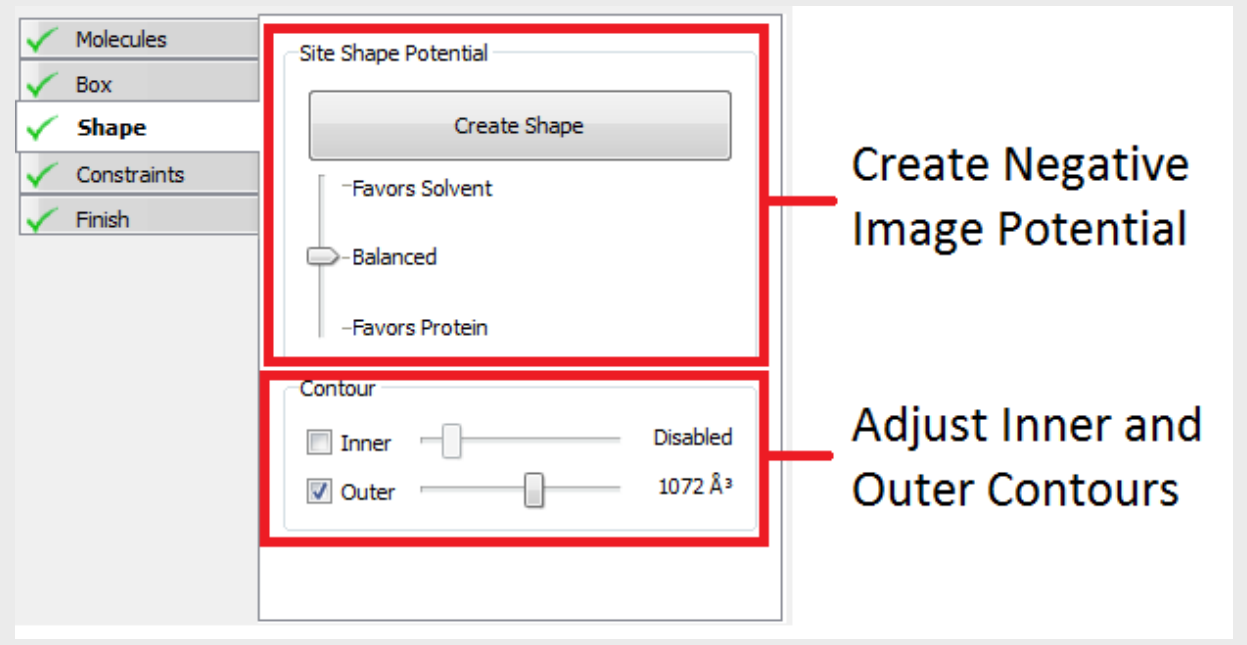
If a bound ligand was specified in the previous stage a default box will automatically be setup around the bound ligand, otherwise an initial box can be created by clicking on a protein residue in the 3D window.

Once created a box and be adjusted using the Create/Adjust box controls. Clicking on a protein residue will also automatically extend the box to enclose the clicked reside.

Two cavity detection routines are also provided. Both the Atomic and Molecular cavity detection routines create blobs in the 3D windows in the grooves and pockets around the protein that could potentially be active sites. The box can then be extended or created around a blob by clicking on it. The Molecular cavity detection uses a better algorithm, but takes much longer to run than the Atomic detection algorithm. The sensitivity slider adjusts the contour level of created blobs.

The sequence viewer can be used to locate specific residues on the protein. When a residue is clicked in the sequence viewer a label on the corresponding residue is shown in the 3D window.

7.3.5 Shape



Shape controls

The Shape stage of the receptor setup workflow defines the *inner and outer contours* of the receptor. Both contours are always enclosed by the box setup in the previous stage of the setup workflow.

The "Create Shape" button sets up a shape potential and automatically selects reasonable inner and outer contours (the former is disabled by default, see below). The slider below the "Create Shape" can be used to select the type of shape potential that will be generated when the "Create Shape" button is pushed. If "Favors Protein" is selected the contours will tend to extend closer to the protein before extending out into solvent, while "Favors Solvent" will cause the reverse to happen. Balanced, the default, is reasonable in most cases.

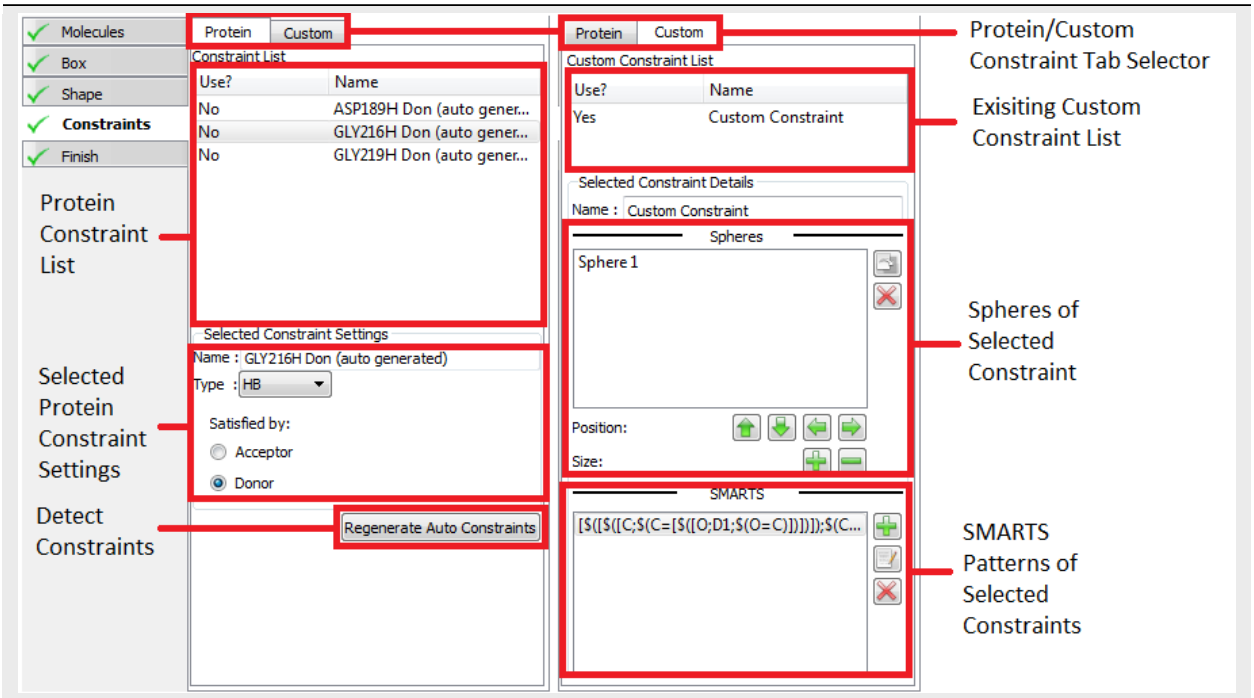
Once the contours are created, their size can be adjusted using the inner and outer contour sliders. The sliders control the inner and outer contour levels (while the slider below the "Create Shape" button controls the underlying potential being contoured). Either contour can be disabled to increase the space of poses searched for each docking ligand.

Disabled is the recommended, and default setting, for the inner contour. The inner contour should be enabled only if the active site is extremely large. In these cases using the inner contour can increase docking speed by ~25% at the cost of reduced docking accuracy.

The outer contour should only be disabled in cases where the active site is flat with no well defined shape. **Docking without the outer contour can increase docking time by as much as 100 fold**.

> **Note**
>
> In general the outer contour should be between 500 and 2000 cubic Ångströms and the inner contour between 25 and 100 cubic Ångströms.

7.3.6 Constraints



Constraints controls

Constraints are a way of ensuring that receptor-ligand interactions known to be associated with activity are present in a docked pose. This inclusion of prior knowledge has been shown to be effective in improving the performance for pose prediction and virtual screening of docking programs including *FRED* [Warren-2006]. While the use of constraints can improve performance it can also degrade performance if the constraints used are not chosen wisely. The current recommended practice is to use the smallest number of constraints possible that describe the interaction associated with activity and to validate that the results generated (poses and virtual screening performance) are an improvement versus using no constraints. For this release, validation must be done using either *FRED* or *HYBRID* using a saved receptor file.

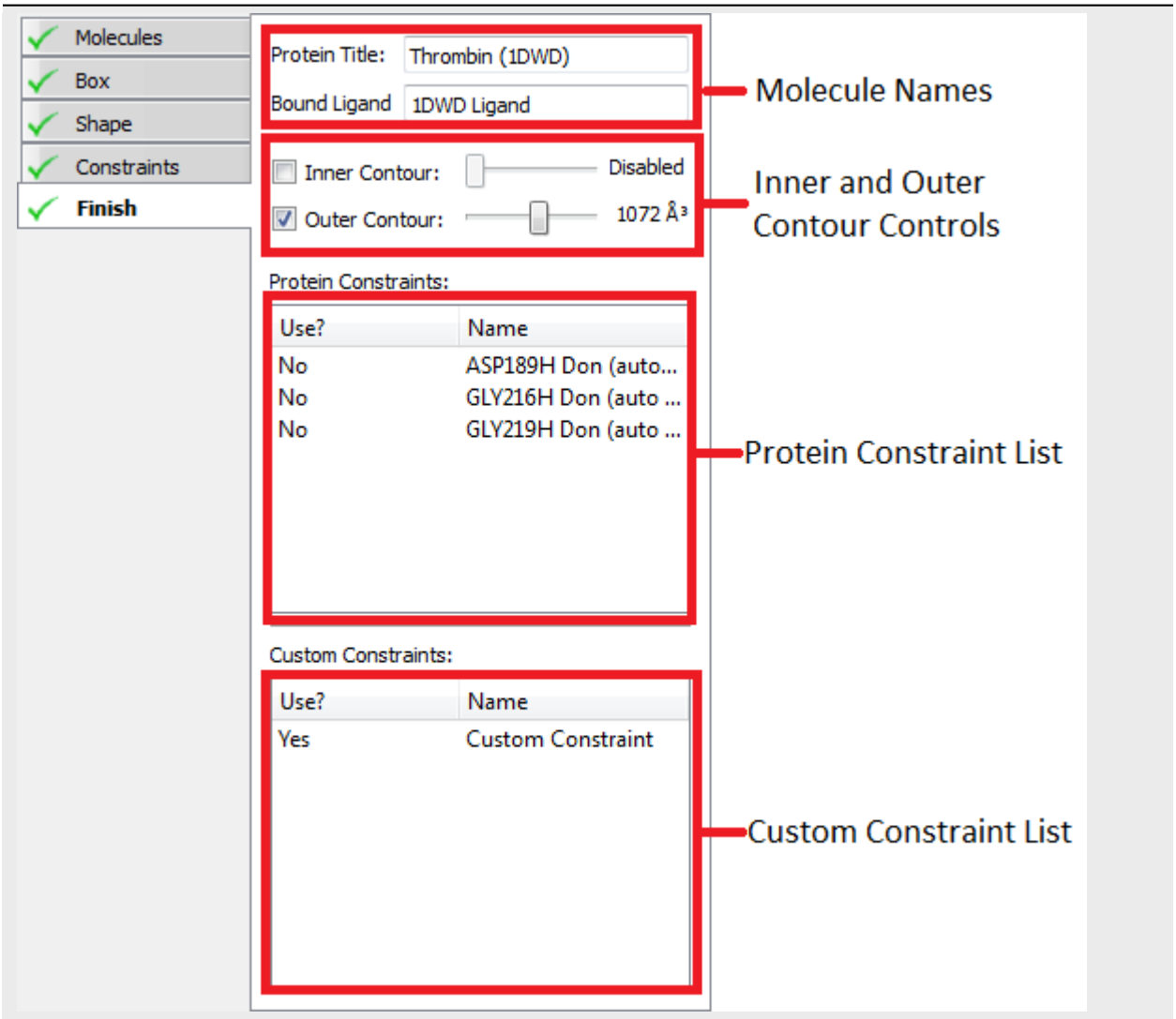
Adding constraints to a receptor is optional. Constraints are user specified interactions that docked poses are required to make with the protein. Once created a constraint can be enabled or disabled. A disabled constraint has no effect on the docking process of either *FRED* or *HYBRID*. Any docked pose that does not satisfy an enabled constraint will be rejected. If multiple enabled constraints are specified poses must satisfy every one. It is not possible for instance to only require that only 3 out of 4 constraints be satisfied.

There are two types of constraint that can be specified; Protein and Custom constraints. Protein constraints are easy to use constraints that are associated with a particular protein atom and are satisfied when a docked poses makes a specified type of interaction with it (hydrogen bond, metal-chelator or contact). Custom constraints are defined by spheres within the active site and optionally one or more SMARTS patterns. Custom constraints are satisfied when a heavy atom of a docked pose falls with one of the spheres if no SMARTS pattern is satisfied, or when an atom on the docked pose matching one of the SMARTS patterns falls with a sphere.

To edit, view or create protein constraints click on the proteins tab at the top of the window. If the receptor contains a bound ligand, **Make Receptor** may automatically detect potential constraints. Auto-detected constraints appear in the constraint list like any other protein constraint and are disabled by defaults. To enable them click the *Use* field next to the constraint you wish to enable in the protein constraint list. To see where the constraint is located in the 3D window and view the constraint setting click on the name of the constraint in the protein constraint list. To create a new protein constraint simple click on a protein atom in the receptor site and use the protein constraint setting to select the type of constraint desired.

To edit, view or create custom constraints select the custom tab at the top of the window. Select and edit custom constraints by clicking on their name in the custom constraint list. To create a new constraint click on an atom in the 3D window, which will create an initial sphere around the clicked atom and prompt you to name the constraint. To add SMARTS patterns click on the + button in the "SMARTS Pattern of Selected Constraint" list. As with protein constraints they can be enabled and disabled by clicking the *Use* column next to the constraint name.

7.3.7 Finish



Finish controls

This stage of the workflow provides a summary of the information stored on the receptor. You should now save your receptor using either the button at the bottom of the screen or the File->Save menu option.

If you load a receptor using the File->Open menu option, the **Make Receptor** will automatically load all the receptor information at set the workflow to this stage.

To edit any part of the receptor click on the appropriate workflow mode button on the left (e.g., Molecules, Box, Shape or Constraints).

CHAPTER

EIGHT

UTILITIES

8.1 ReceptorInDU

8.1.1 Overview

ReceptorInDU is a utility program to make a receptor inside a prepared OEDesignUnit.

Note

While *ReceptorInDU* is good at automatically setting up receptors, it is recommended that the *Make Receptor* GUI be used to examine/modify the receptor created by *ReceptorInDU* prior to using it with *FRED*, *HYBRID* or *POSIT*. Particularly, if a user wants to define constraints or include specific water molecules in the receptor. This step is not required, however.

See also

- The SPRUCE chapter

8.1.2 Example Commands

Make receptor version of OEDU file for 5MM6

Converts the prepared OEDU file into a receptor containing OEDU file.

Input files

- **5MM6_HIL__DU__32U_H-311.oedu** : OEDU file to convert into a receptor.

Command line

```
prompt> receptorindu 5MM6_HIL__DU__32U_H-311.oedu rec_5MM6_HIL__DU__32U_H-311.
↪oedu
```

Output files

- **rec_5MM6_HIL__DU__32U_H-311.oedu** : Receptor version of 5MM6 design unit.

8.1.3 Command Line Help

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

```
> receptorindu --help
```

will generate the following output:

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

8.1.4 Required Parameters

-in <filename>

An OEDesignUnit file generated by Spruce.

[keyless parameter 1]

8.1.5 Optional Parameters

Input Options

-molnames

This parameter specifies a text file containing a list of molecule names (one name per line in the file). If this parameter is set then only molecule 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 database, without having to extract those molecules by hand from the database.

Output Options

-out <filename>

An OEDesignUnit file containing the receptor.

[keyless parameter 2]

-prefix

Prefix used to name output files.

-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]

Receptor Options

-targetMask [Default=targetComplexNoSolvent]

Design unit components mask defining the subset of design unit components to be used as targets for the receptor. Multiple components can also be combined as a comma separated string to create the input.

Possible values:

- cofactors, counter_ions, excipients, lipids, metals, nucleic, other_cofactors, other_ligands, other_nucleics, other_proteins, packing_residues, polymers, post_translational, protein, solvent, sugars

Multi component choices:

- 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)

-targetPred

Residue-based selection predicate to subset components of the design unit targetMask. The predicate is only enforced on a component of the targetMask if it matches something in that component from the design unit. Input like: "HOH:1024: :A|HOH:567: :A|" with a targetMask that includes the solvent from the designunit, will subset the solvent component to only include these specific water molecules in the receptor generation, however, since this does not match anything in the Protein component of the design unit it will leave that component as is.

-negImageType `[Default=standard]`

The type of negative image to create in generating the receptor grid. Choices: large, standard, small

-box `<box file> [No Default]`

A file describing a box enclosing the active site. All docked poses will be required to fit within this box.

The box must be in a 3D molecular format. SDF, MOL2, OEBinary and several other common molecular formats are supported.

The box will always be aligned along the X, Y and Z axis of the coordinate system and the edges of the box will be the maximum and minimum X, Y and Z value of any atom in the box file.

> **Note**
>
> The bound ligand is ignored for active site detection, when this flag is specified.

-addbox `<distance> [No Default]`

This flag adjusts the box created by the *-box* flag by extending each edge of the box by the specified number of Angstroms. Thus each dimension of the box will be enlarged by twice the setting of this parameter.

If *-box* is not specified this flag has no effect.

8.2 OEB2DUReceptor

8.2.1 Overview

OEB2DUReceptor is a utility program to convert a molecule based receptor OEB or OEB.GZ file into a receptor inside OEDesignUnit, in OEDU file.

> **Note**
>
> The *OEB2DUReceptor* is not an utility to make a receptor. This is merely a converter for old receptor files, in OEB or OEB.GZ format, into a new OEDU format receptor.
>
> To make a receptor, use the *ReceptorInDU* or the *Make Receptor*.

8.2.2 Example Commands

Convert a receptor OEB.GZ file into an OEDU receptor

Converts the OEB.GZ receptor file into an OEDU receptor.

Input files

- **receptor.oeb.gz** : OEB.GZ file to convert into an OEDU receptor.

Command line

```
prompt> oeb2dureceptor receptor.oeb.gz receptor.oedu
```

Output files

- **receptor.oedu** : OEDU version of the receptor.

8.2.3 Command Line Help

A description of the command line interface can be obtained by executing **OEB2DUReceptor** with the *–help* option.

```
> oeb2dureceptor --help
```

will generate the following output:

```
Help functions:
  oeb2dureceptor --help simple      : Get a list of simple parameters
  oeb2dureceptor --help all         : Get a complete list of parameters
  oeb2dureceptor --help defaults    : List the defaults for all parameters
  oeb2dureceptor --help <parameter> : Get detailed help on a parameter
  oeb2dureceptor --help html        : Create an html help file for this program
  oeb2dureceptor --help versions    : List the toolkits and versions used in the␣
↪application
```

8.2.4 Required Parameters

-in <filename>

An OEB or OEB.GZ file containing a receptor.

[keyless parameter 1]

8.2.5 Optional Parameters

Input Options

-molnames

This parameter specifies a text file containing a list of molecule names (one name per line in the file). If this parameter is set then only molecule 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 database, without having to extract those molecules by hand from the database.

Output Options

-out <filename>

An OEDesignUnit file containing the receptor.

[keyless parameter 2]

-prefix

Prefix used to name output files.

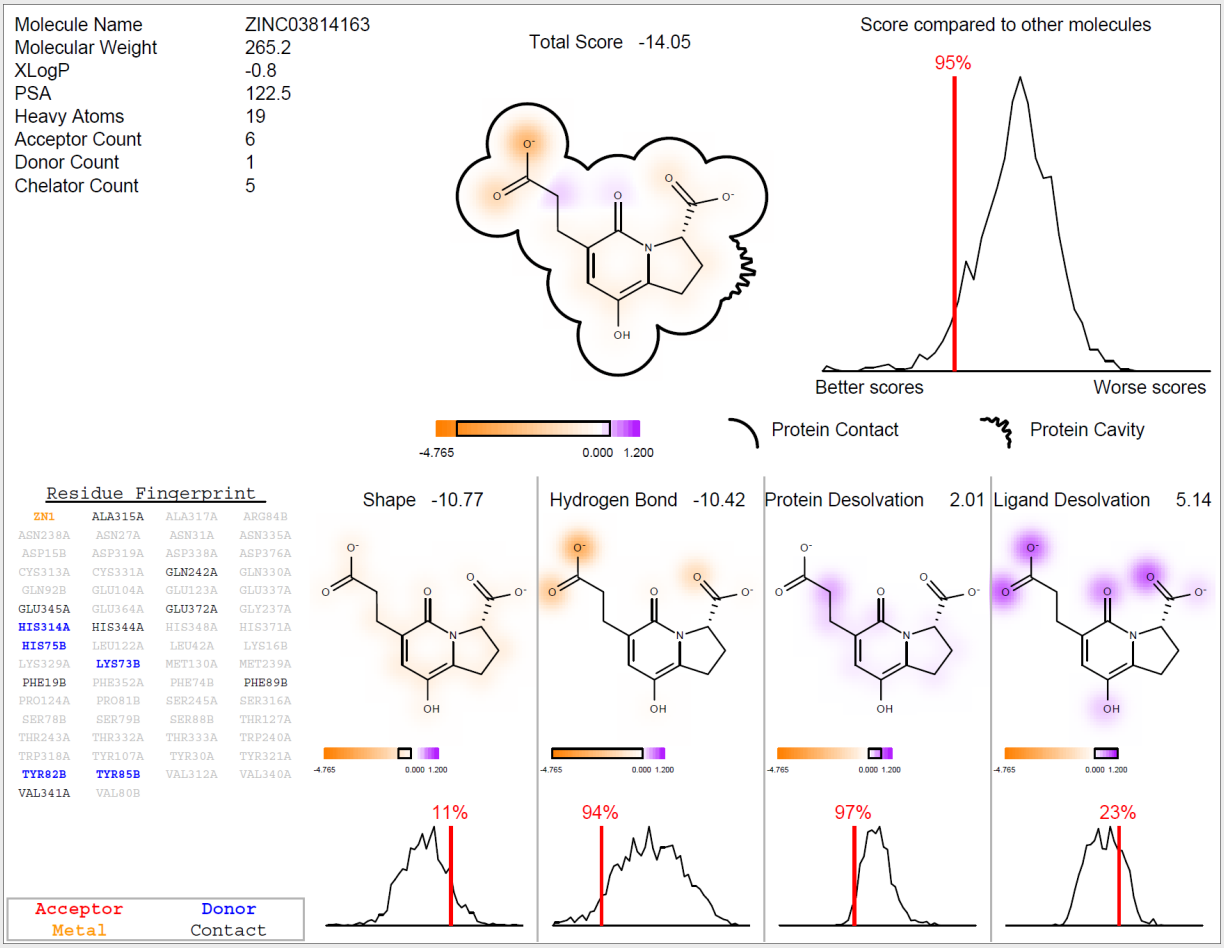
-progress

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]

8.3 DockingReport

8.3.1 Overview

DockingReport is a utility program that creates a PDF report for one or more molecules docked by *FRED* or *HYBRID*. The PDF report lists includes a 2D depiction of each molecule, a breakdown of the score by atom, a breakdown of the score components by atom, a comparison of the molecule's score compared to the other docked molecules, SD data tagged to the molecule and other general molecule properties (e.g., molecular weight). *DockingReport* also includes a 'Residue Fingerprint' which highlights which residues in the receptor site the ligand is interacting with (greyed out residues are residues in the site that other ligands interact with, but the current ligand does not).



Example dock report

8.3.2 Example Commands

Creating a report for named molecules

Creates a report for 2 molecules *blockbuster1* and *blockbuster2* that were docked by *FRED*.

Input files

- **fred_docked.oeb.gz**

  Molecules docked by *FRED* including two molecules named *blockbuster1* and *blockbuster2* respectively.

- **receptor.oedu**

  The receptor file the molecules in **docked.oeb.gz** were docked to.

Command line

```
prompt> docking_report -docked_poses fred_docked.oeb.gz \
                       -receptor receptor.oedu \
                       -names blockbuster1 blockbuster2
```

Output files

- **docking_report.pdf**

  PDF dock report for *blockbuster1* and *blockbuster2*.

Creating a report for molecules identified by SMILES

Creates a report for molecules, docked by *HYBRID*, that have the same canonical smiles as molecules in a specified file.

Input files

- **hybrid_docked.oeb.gz**

  Molecules docked by *HYBRID*.

- **receptor1.oedu** and **receptor2.oedu**

  The receptor files *HYBRID* used to dock the molecules in **docked.oeb.gz**.

- **interesting_ligands.sdf**

  Set molecules to create reports for. The molecules in this file will be converted into canonical SMILES, and a report will be generated for each molecule in **docked.oeb.gz** that has the same canonical SMILES as any one of the molecules in **interesting_ligands.sdf**

Command line

```
prompt> docking_report -docked_poses hybrid_docked.oeb.gz \
                    -receptor receptor1.oedu receptor2.oedu \
                    -smiles_file interesting_ligands.sdf
```

Output files

- **docking_report.pdf**

  PDF dock report for all molecules in **docked.oeb.gz** that have the same canonical SMILES as one of the molecules in **interesting_ligands.sdf**.

8.3.3 Command Line Help

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

```
> docking_report --help
```

will generate the following output:

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

8.3.4 Required Parameters

Input

-docked_poses <filename>

A file with poses that were docked by either *FRED* or *HYBRID*.

[Aliases=**-poses**]

-receptor <filename> [<filename> ...]

Receptor file the poses passed to *-docked_poses* were docked too. If the poses were docked with hybrid *HYBRID* using multiple receptor structures then the same set of receptor structures should be passed to this flag.

[Aliases=**-rec**]

8.3.5 Optional Parameters

Input Options

-names <molecule name> [<molecule name> ...] [No Default]

This option identifies one or more molecules passed to the *-docked_poses* option by name. Molecules specified with this flag will have a report generated for them.

> **Note**
>
> Either this flag or *-smiles_file* must be specified.

[Aliases=**-title**]

-smiles_file <filename> [No Default]

This option identified molecules passed to the *-docked_poses* option by canonical SMILES. Molecules identified with this flag will have a report generated for them.

> **Note**
>
> Either this flag or *-names* must be specified.

[Aliases=**-smiles**]

-sd_tags <Tag> [<Tag> ...] [No Default]

This flag specifies a specific set of SD tagged data to include in the dock report. If this flag is not specified all the SD data will be include in the dock report.

> **Note**
>
> The dock report has a limited amount of space for SD data and can only include 10 pieces of SD data for each docked molecule (additional SD data will not appear in this report).

[Aliases=**-sdtags**]

Output Options

-report_file <filename> [Default=docking_report.pdf]

Name of the docked report file to generate.

The file must be a PDF file (i.e., have a .pdf extension).

[Aliases=**-report**]

8.4 ScorePose

8.4.1 Overview

ScorePose scores poses in a `-dbase` database in the context of a single *receptor*, using the *Chemgauss4* scoring function. Poses may also optionally be optimized with the `-optimize` option vs. *Chemgauss4*.

> **Note**
>
> *ScorePose* does not dock molecules, it only rescores and optionally optimizes molecules within the context of a *receptor* site.

8.4.2 Input Preparation

Ligand Preparation

The ligand input to *ScorePose* should already be docked into the *receptor* site. For the purposes of this document, we'll call the file(s) of poses to be scored the database file(s), or dbase file(s). Supported formats of the database file include SDF, MOL2 and PDB. *ScorePose* determines the database file format from the file extension, `.sdf` or `.mol` for SDF, `.mol2` for MOL2, `.pdb` or `.ent` for PDB. Gzip compressed files of these same formats are allowed as well. *ScorePose* will interpret `infile.sdf.gz` as a gzip'ed SDF file.

> **Note**
>
> Note that even though all these formats are supported, using SDF, PDB or MOL2 can result in a loss of speed due to the I/O penalty of these formats. We recommend using Gzipped OEB format for maximum speed.

By default *ScorePose* will interpret conformers in the database file(s) as part of a single multi-conformer molecule as long as they:

- Are contiguous in the input file.
- Have the same numbers of atoms and bonds in the same order
- Have identical atom and bond properties with their order correspondent in the subsequent connection table
- Have the same atom and bond stereochemistry

While this may appear to be a restrictive list, many programs write multi-conformer molecules into SDF or MOL2 files such that the above rules will be satisfied. If the conformers are named differently, (*i.e.* they have a conformer number appended to the base name like acetsali_1, acetsali_2), *ScorePose* will still consider them part of a single multi-conformer molecule if the criteria above are met.

Receptor Preparation

> **Note**
>
> Beginning with *ScorePose* 4.0.0, *ScorePose* now only accepts an OEDU with receptor as the receptor input file.

ScorePose requires the *receptor* file that the ligands in the database were docked to. This should generally already be available if the ligands were docked with *FRED* or *HYBRID*. If the ligands were docked with another program a receptor can be created using one of the following programs.

Program	Type	Description
Make Receptor	GUI	Interactive GUI for creating a receptor.
ReceptorInDU	Command Line	Generates a receptor inside a prepared OEDesignUnit in an OEDU file.
OEB2DUReceptor	Command Line	Converts a molecule based receptor OEB or OEB.GZ file into a receptor inside an OEDesignUnit, in an OEDU file

> **Note**
>
> Receptors can also be created using the OpenEye Docking Toolkit (see the Docking Toolkit documentation).

8.4.3 Command Line Help

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

```
> scorepose --help
```

will generate the following output:

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

8.4.4 Required Parameters

-receptor <receptor file>

Receptor file to rescore poses with.

[Aliases=**-rec**]

-dbase <input filename1> [<input filename2> ...]

File(s) containing ligand poses to rescore (see section *Input Preparation*).

The following file formats are supported.

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

More than one file can be specified.

[Aliases=**-database**,**-in**]

8.4.5 Optional Parameters

Input Options

-param <parameter filename> [No Default]

A parameter file is a text file that lists parameter settings to be used during a run. If a parameter is specified both on the command line and in the parameter file, the value specified on the command line is used.

The format of the parameter file is as follows:

- One parameter per line
- For non-list parameters one key-value pair per line. (*e.g., -receptor rec.oedu*).
- For list parameters a key followed by all the values (*e.g., -dbase lig1.oeb.gz ligs2.oeb.gz*)
- Boolean parameters must be listed as a key followed by true or false (*e.g. -annotate_poses true*).
- The parameter file may not contain the *-param* parameter.
- Lines beginning with # are considered comments

-molnames <input filename> [No Default]

This parameter specifies 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 database file(s) (see parameter *-dbase*) 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 database, without having to extract those molecules by hand from the database.

Score Options

-optimize <level> [No Default]

If this parameter is specified each pose will be optimized with a systematic solid body optimization with a resolution given by the table below.

Level	Translational Stepsize	Rotational Stepsize
High	0.5 Ångström	0.5 Ångström
Standard	0.5 Ångström	0.75 Ångström
Low	0.75 Ångström	1.0 Ångström

If this parameter is not specified poses will not be optimized prior to scoring.

[Aliases=**-opt**]

See also

- OEDocking::OEDockOptions::SetResolution in the **OEDocking TK** manual.

Output Files

-prefix <value> [Default=rescore]

This flag prefixes all default output filenames with the specified value.

Note

This flag does not affect output filenames explicitly set by the user.

Note

Values in parenthesis are default values.

-rescored_molecule_file <output filename> [Default=scored.oeb.gz]

File rescored molecules will be written to. The file format is controlled by the extension of the filename. The following output formats are supported.

Format	Extension
OEBinary	.oeb
SDF	.sdf
Gzipped OEBinary	.oeb.gz
Gzipped SDF	.sdf.gz

Scores will be attached as SD data to each pose with the tag **FRED Chemgauss4 Score**, unless the *-score_tag* option is used to specify another tag.

By default the top 500 scoring molecules will be outputted to this file (see *-hitlist_size* flag).

Note

If this flag is not set by the user the default filename (i.e., scored.oeb.gz) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases=**-rescored_mol_file**,**-rescored_file**,**-rescored**,**-out**]

-score_file <filename> [Default: score.txt]

Specifies a tab separated text file with the name and scores of the molecules.

Note

If this flag is not set by the user the default filename (i.e., score.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases : **-score**]

-report_file <filename> [Default: report.txt]

Specifies a file that a text report of the run will be written to.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., report.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases : **-report**]

-settings_file <filename> [Default: settings.param]

Writes the settings of all parameters of the run to the specified output file. The settings will be listed in plain text with one parameter name follow by its value(s). This format is compatible with the format of parameter files, and therefore a settings file from a previous run can be passed to the *-param* flag to re-run the program with the same settings.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., settings.param) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-settings**]

-status_file <filename> [Default: status.txt]

If this parameter is set then the status of the run will be written to the given output file every few seconds (the previous contents of the file will be overwritten) during the run.

> **Note**
>
> If this flag is not set by the user the default filename (i.e., status.txt) will be automatically prefixed with the setting of the *-prefix* flag.

[Aliases = **-status**]

Output Options

-hitlist_size <num> [Default=500]

This parameter controls whether docked molecules are outputted as they are docked or in an internal hitlist and outputted at the end of the run.

If -hitlist_size is zero the run will be in serial mode, i.e. each molecule will be outputted as it is docked (unsorted). For single processor runs this will be the order the molecules appear in the database file(s). For MPI runs the order will not be strictly the order the molecules appear in the database file(s).

If -hitlist_size is non-zero a sorted internal hitlist of docked molecules that will be maintained and outputted at the end of the run. The maximum size of the hitlist is -hitlist_size. If more than this number of molecules are docking during the run only the top scoring molecules will be outputted and the rest will be discarded.

There is no formal limit on the number of molecule that can be sorted and outputted at the end of the run. However, retaining a large number of molecules significantly increases the memory requirements. A good rule of thumb is that the setting total number of poses retained should not be larger than 10,000.

[Aliases=**-hitlist_size**,**-hitlist**]

-sort_poses [Default=false]

If this option is selected the poses of each molecule will be sorted by score.

If the molecules in the database do not have multiple poses this flag has no effect.

[Aliases=**-sortposes**]

-score_tag <tag> [No Default]

This parameter overrides the default SD Data Tag used to store molecule scores (the default is **FRED Chemgauss4 Score**).

[Aliases=**-scoretag**]

-annotate_scores [Default: false]

If the value of this flag is set to true VIDA score annotations will be added to the processed molecules. These annotations are visible in VIDA (OpenEye's molecular visualization program) and show a per atom breakdown of the score.

> **Note**
>
> The docked molecule output file format (see *fred -docked_molecule_file*) must be OEBinary when using score annotations.

[Aliases = **-annotate**]

-save_component_scores [Default: false]

If the value of this flag is set to true individual components of the total score will be saved to SD data on each pose and appear in the score file (see *-score_file*).

[Aliases = **-component_scores**, **-component**]

-no_extra_output_files [Default=false]

When set the only default output to the program will be the docked structure file (see *-rescored_molecule_file*).

Using this flag suppresses the default output of the following

Output	Default file	Parameter
text score file	score.txt	*-score_file*
report file	report.txt	*-report_file*
settings file	settings.param	*-settings_file*
status file	status.txt	*-status_file*

Only default output is suppressed. If any of these output parameters are explicitly set by the users the relevant output file will still be written even if this switch is turned on.

[Aliases=**-no_extra**,**-noextra**,**-noextraoutputfiles**,**-no_extra_output**,**-noextraoutput**]

-no_dots [Default: false]

When this flag is set to true, a dot is being written to standard error for each docking molecule (or x in the case of a failure). Setting this flag to false to suppress dot/x writing.

[Aliases = **-nodots**]

8.5 ReceptorToolbox

8.5.1 Overview

ReceptorToolbox is a utility program for receptors that can do the following

- List information about the receptor
- Set the name of the receptor and/or bound ligand
- Extract molecules from the receptor
- Setup a scoring cache for *FRED*, *HYBRID* or *ScorePose*.
- Enable/Disable existing constraints.

8.5.2 Example Commands

Setup a receptor cache for *fred*

This example illustrates setting up a receptor cache for *FRED*.

Input files

- **receptor.oedu** : A file containing a receptor.

Command line

```
prompt> receptor_toolbox -receptor receptor.oedu -prepare_score_cache fred
```

Output files

- **receptor.oedu** : Receptor with score cache for *FRED* (overwrites input file).

8.5.3 Command Line Help

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

```
> receptor_toolbox --help
```

will generate the following output:

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

8.5.4 Required Parameters

Receptor File to Operate On

-receptor <receptor file>

ReceptorToolbox reads this receptor file, and if the receptor is edited in any way the modified receptor will be output to this file (overwriting the original).

[Aliases=**-rec**]

8.5.5 Optional Parameters

Score Caching

-prepare_score_cache <fred, **scorepose** or hybrid> [No Default]

Caches scoring setup for the specified program on the receptor. This is not required, however doing so will improve the initial speed of the program by not requiring it to do as much scoring setup.

A receptor can only have a score cache for one program at a time (previous score caches will be erased when this flag is used).

> **Note**
>
> Creating a score cache will substantially increase the size of the receptor file, typically on the order of 100 MBytes.

[Aliases=**-prepare**]

-clear_score_cache [Default=false]

If this flag is set to true any scoring cache on the receptor will be removed.

[Aliases=**-clear_cache**]

Inner Contour

-turn_inner_contour <on or off> [No Default]

If this flag is set the inner contour will be turned on or off, as specified. See *Receptor Theory Section* for an explanation of the inner contour.

[Aliases=**-inner_contour**,**-inner**]

Protein Constraints

-enable_protein_constraint <name> [<name> ...] [No Default]

Enables the specified protein constraints. The name can be either the name of the constraint or the name of the atom that the constraint is associated with.

[Aliases=**-enable_protein_constraints**]

-disable_protein_constraint <name> [<name> ...] [No Default]

Disables the specified protein constraints. The name can be either the name of the constraint or the name of the atom that the constraint is associated with.

[Aliases=**-disable_protein_constraints**]

-enable_all_protein_constraints [Default=false]

Enables all protein constraints.

[Aliases=**-enableallproteinconstraints**]

-disable_all_protein_constraints [Default=false]

Disables all protein constraints.

[Aliases=**-disableallproteinconstraints**]

Custom Constraints

-extract_custom_constraints <filename> [No Default]

Extracts the receptors custom constraints to this specified file.

-set_custom_constraints <filename> [No Default]

Sets the receptors custom constraints to be those in the specified file.

The format of the constraint file is a text file with lines of one of the two following forms

```
SPHERE <ID> <RAD> <X> <Y> <Z>
SMARTS <ID> <SMARTS Pattern>
```

- **SPHERE** creates a sphere associated with a given constraint
  - ID is an integer that uniquely identifies a constraint
  - RAD is the radius of the sphere
  - X, Y and Z is the sphere center
- **SMARTS** Creates a SMARTS pattern associated with the specified sphere.
  - ID is an integer that uniquely identifies a constraint
  - SMARTS Pattern is the SMARTS pattern to associate with the constraint.

The following example file

```
SPHERE 1 4.0 1.0 1.0 1.0
SMARTS 1 F
SPHERE 2 4.5 3.0 2.5 -1.0
```

Creates two constraints. Constraint 1 has one sphere centered at (1.0, 1.0, 1.0) with radius 4.0 and can only be satisfied by a fluorine atom on the ligand. Constraint 2 has one sphere centered at (3.0, 2.5, -1,0) with radius 4.5 and can be satisfied by any heavy atom on the ligand since the constraint as no associated smarts patterns.

See *Receptor Theory Section* for more information about constraints.

-enable_custom_constraint <constraint> [<constraint> ...] [No Default]

Enables the specified custom constraints.

[Aliases=**-enable_custom_constraint**,**-enable_custom_constraints**]

-disable_custom_constraint <constraint> [<constraint> ...] [No Default]

Disables the specified custom constraints.

[Aliases=**-disable_custom_constraints**]

-enable_all_custom_constraints [Default=false]

If this flag is set to true all custom constraints on the receptor are enabled.

-disable_all_custom_constraints [Default=false]

If this flag is set to true all custom constraints on the receptor are disabled.

8.6 combine_receptors

8.6.1 Overview

In many cases ligands from different receptors may be combined to yield more productive posing targets. For example, if, when the two proteins are aligned, two ligands overlap but occupy different spaces in the binding pocket, **combine_receptors** will make a single receptor using both ligands that may be a better target for predicting some ligands.

When given multiple receptors, **combine_receptors** will find the best matched pair for each input receptor. The best matched pair is the combination of two ligands that overlap but have a large difference in shape.

For each set of combined ligands, two receptors are output, one for each input protein. This also helps when analyzing clashes.

Output names are automatically generated so that if two receptors are merged, say `A_receptor.oeb.gz` and `B_receptor.oeb.gz`, two outputs are formed:

- `combine_receptors_A_receptor_merged_B_receptor.oeb.gz`
- `combine_receptors_B_receptor_merged_A_receptor.oeb.gz`

For example, consider the merged receptors shown in figures *Merged receptors* and *Matched to merged receptor*.

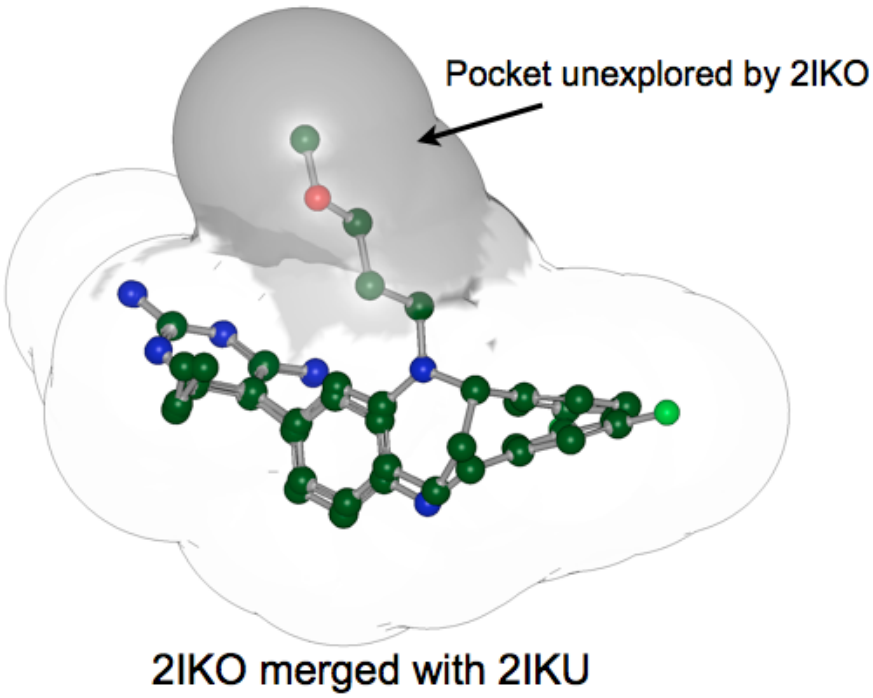


Fig. 1: **Merged Receptors:** Merging the receptors 2IKO and 2IKU capture more potential interaction constraints than either does alone

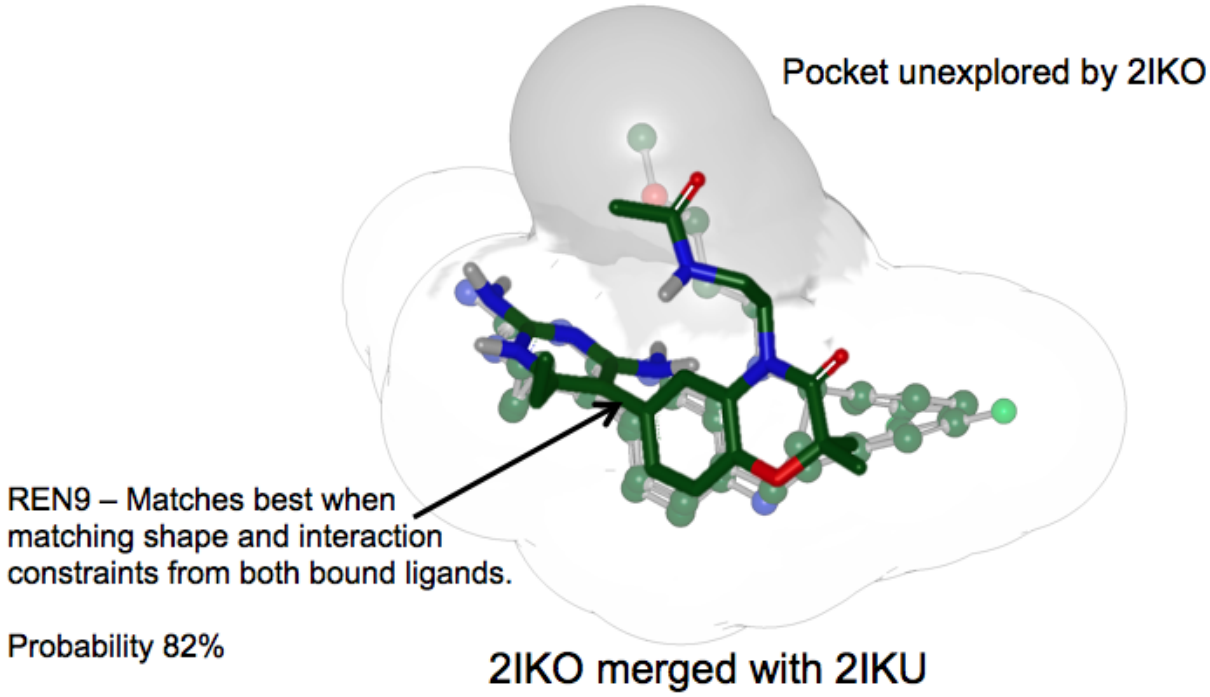


Fig. 2: **Matched to Merged Receptors:** REN9 is correctly predicted by the merged receptor

If a combined ligand has significant clashes with the protein a warning will also be output with the recommended setting when running *posit*. Serious clashes will not be output unless the user specifies the `-allowedClashes` option.

8.6.2 Example Commands

To run **combine_receptors**, simply provide a list of known receptors:

First, make some receptors:

```
> spruce -in renin/2IKO.pdb.gz
> spruce -in renin/2IKU.pdb.gz
```

To convert output `OEDesignUnit` files into `OEBinary` files:

```
> du2oebreceptor -in rec_2IKO_ABCDEFsym1__DU__7IG_A-601.oedu -out rec_2IKO_ABCDEFsym1__
↪DU__7IG_A-601.oeb.gz
> du2oebreceptor -in rec_2IKO_ABCDEFsym2__DU__7IG_A-601.oedu -out rec_2IKO_ABCDEFsym2__
↪DU__7IG_A-601.oeb.gz
...
> du2oebreceptor -in rec_2IKU_ABCDEF__DU__LIY_A-336.oedu -out rec_2IKU_ABCDEF__DU__LIY_A-
↪336.oeb.gz
> du2oebreceptor -in rec_2IKU_ABCDEF__DU__LIY_B-336.oedu -out rec_2IKU_ABCDEF__DU__LIY_B-
↪336.oeb.gz
...
```

```
> combine_receptors -receptors rec_*.oeb.gz
```

> **Note**
>
> On *Microsoft Windows* systems, you need to expand the wildcard:

```
> combine_receptors -receptors rec_2IKO_ABCDEFsym1__DU__7IG_A-601.oeb.gz  rec_2IKO_
↪ABCDEFsym2__DU__7IG_A-601.oeb.gz rec_2IKO_ABCDEFsym3__DU__7IG_A-601.oeb.gz  rec_2IKU_
↪ABCDEF__DU__LIY_A-336.oeb.gz rec_2IKU_ABCDEF__DU__LIY_B-336.oeb.gz rec_2IKU_ABCDEF__DU_
↪_LIY_C-336.oeb.gz rec_2IKU_ABCDEF__DU__LIY_D-336.oeb.gz rec_2IKU_ABCDEF__DU__LIY_E-336.
↪oeb.gz rec_2IKU_ABCDEF__DU__LIY_F-336.oeb.gz
```

The merged receptor files will be named `combine_receptors_rec_*`:

```
Wrote combined receptor:combine_receptors_rec_2IKU_ABCDEF__DU__LIY_E-336_merged_rec_2IKO_
↪ABCDEFsym1__DU__7IG_A-601.oeb.gz
Wrote combined receptor:combine_receptors_rec_2IKO_ABCDEFsym2__DU__7IG_A-601_merged_rec_
↪2IKU_ABCDEF__DU__LIY_E-336.oeb.gz ShapeTanimoto of merged ligands:0.690121
...
```

It is often useful to first collect the receptors ready for combining into a directory, and place the merged receptors into another directory which must already exist, to do this, simply use the *-outputdir* option.

```
> combine_receptors -receptors receptors/*.oeb.gz -outputdir merged
```

> **Note**
>
> Again, on *Microsoft Windows* systems, you need to expand the wildcard (this will be omitted for all future examples).

If a merged ligand has an unallowable clash with a protein, it will not result in a receptor.

8.6.3 Command Line Help

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

```
> combine_receptors --help
```

will generate the following output (omitting the OpenEye banner for space)

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

8.6.4 Required Parameters

-receptors <filenames>

List of receptors to combine. If a file is not a receptor, **combine_receptors** will halt.

8.6.5 Optional Parameters

-allowedClashes

Clashes allowed between the ligand and protein of a receptor. There are three levels:

Allowed Clash	Description
noclashes	No clashes are allowed. Actually there is a little wiggle room here less than 0.2 Ångström penetration is not considered a clash.
mild-clashes	Mild clashes are allowed (greater than 0.2 Ångström and less than 0.65 Ångström)
allclashes	All clashes are allowed.

The clash ranges have been tuned to account for average coordinate error in a sampling of PDB files, they are intended to be used as guidelines and may not be indicative of some clash states.

By default, receptors are not output if serious clashes exist between the specified ligand and protein. By specifying `-allowedClashes allclashes` all clashing receptors will be output.

[Default=mildclashes]

-param <filename>

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

-prefix

Controls the name of the default param file.

[Default=combine_receptors]

-outputdir

Write the merged receptors to the directory specified (the directory must already exist).

-verbose

Show that matching status of every receptor pair (whether it is merged or not)

[Default=false]

8.7 DU2OEBReceptor

8.7.1 Overview

DU2OEBReceptor is a utility program to convert a design unit, OEDU file, containing a receptor into a molecule based receptor, in OEB or OEB.GZ file.

Note

The molecule based OEB or OEB.GZ receptors are no longer the preferred form of receptor, and instead receptors inside design unit in OEDU are desired. The *DU2OEBReceptor* is provided for a handful of cases where receptors inside design units in OEDU format cannot still be used.

To make a receptor, use the *ReceptorInDU* or the *Make Receptor*.

8.7.2 Example Commands

Convert a receptor OEDU file into an OEB.GZ receptor

Converts the OEDU receptor file into an OEB.GZ receptor.

Input files

- **receptor.oedu** : OEDU file to convert into an OEB.GZ receptor.

Command line

```
prompt> DU2OEBReceptor receptor.oedu receptor.oeb.gz
```

Output files

- **receptor.oeb.gz** : OEB.GZ version of the receptor.

8.7.3 Command Line Help

A description of the command line interface can be obtained by executing **DU2OEBReceptor** with the *–help* option.

```
> du2oebreceptor --help
```

will generate the following output:

```
Help functions:
  du2oebreceptor --help simple      : Get a list of simple parameters
  du2oebreceptor --help all         : Get a complete list of parameters
  du2oebreceptor --help defaults    : List the defaults for all parameters
  du2oebreceptor --help <parameter> : Get detailed help on a parameter
  du2oebreceptor --help html        : Create an html help file for this program
  du2oebreceptor --help versions    : List the toolkits and versions used in the␣
↪application
```

8.7.4 Required Parameters

-in <filename>

An OEDU file containing a receptor.

[keyless parameter 1]

8.7.5 Optional Parameters

Input Options

-molnames

This parameter specifies a text file containing a list of molecule names (one name per line in the file). If this parameter is set then only molecule 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 database, without having to extract those molecules by hand from the database.

Output Options

-out <filename>

An OEB or OEB.GZ file containing receptor.

[keyless parameter 2]

-prefix

Prefix used to name output files.

-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]

CHAPTER

NINE

RELEASE HISTORY

9.1 OEDocking 4.3.5

Minor internal improvements have been made.

9.1.1 Related Toolkit Information

9.2 OEDocking TK 4.3.5

- An issue has been fixed that was causing OEPosit to pick the wrong method in posing some ligands.

9.3 OEDocking 4.3.4

Minor internal improvements have been made.

9.3.1 Related Toolkit Information

OEDocking TK 4.3.4

Minor Bug Fixes

- An issue has been fixed where a receptor grid could not be constructed for covalently bonded ligands.

9.4 OEDocking 4.3.3

Minor internal improvements have been made.

9.4.1 Related Toolkit Information

OEDocking TK 4.3.3

Minor internal improvements have been made.

9.5 OEDocking 4.3.2

Minor internal improvements have been made.

9.6 OEDocking TK 4.3.2

9.6.1 New features

- The method Optimize in OEPoseOptimizer now returns an `unsigned` code corresponding to any possible failure, instead of a `bool`. The method also takes additional arguments for protein and ligand masks in the OEDesignUnit.
- The following methods have been added to the OESinglePoseResult:
  - GetRelaxAttempted
  - GetRelaxStatus
  - GetRelaxStatusStr
- A new method, MethodChoice, has been added to OEPosit that provides information on the method that would be used for the pose prediction of a given ligand against a given receptor.
- The new methods GetTorLib and SetTorLib have been added to OEPositOptions to provide a choice for the torsion library that would be used for conformer generation during pose prediction.
- The following methods have been added to the OEShapeFitOptions:
  - GetMaxLocalStrain
  - SetMaxLocalStrain
  - GetTorLib
  - SetTorLib

9.6.2 Major bug fixes

- The method Optimize in OEPoseOptimizer is now more robust in optimizing a docked pose. Accordingly, Docking with relaxation in OEPosit is also now more robust.
- The function OEHasClash now properly recognizes all clashes between a ligand and a protein that were previously mistaken because of some misidentification of covalent bonds.

9.6.3 Minor bug fixes

- Selection of the best receptor has been improved in OEPosit, ensuring that the correct receptor will always be picked in case of a self-docking.
- The internal algorithm has been optimized to improve time requirements for OEPosit when working with many receptors and a few ligands.

9.7 OEDocking 4.3.1

Minor internal improvements have been made.

9.8 OEDocking TK 4.3.1.3

- An issue has been fixed in OEHasClash such that strong atom clashes are no longer mistakenly marked as covalent bonds causing failure to recognize those as actual clashes.

9.9 OEDocking TK 4.3.1.0

- An issue has been fixed that would occasionally cause segmentation faults when OEPosit would internally fail to generate conformers.
- New methods, GetPoseRelaxOptions and SetPoseRelaxOptions, have been added to OEPositOptions to allow more flexibility in relaxing the OEPosit generated poses.
- Internal algorithms have been improved in OEShapeFit to improve strain in generated poses.

9.10 OEDOCKING 4.3.0

9.10.1 Minor bug fixes

- **POSIT** now correctly outputs the status of relaxation, indicating if flexible optimization was performed on the generated pose.
- Closing out of the `save` dialog in **MakeReceptor** no longer causes a "Failed Save" message.
- Constraint spheres now appear with appropriate colors when viewed in the *Finish* tab of **MakeReceptor**.

9.11 OEDocking TK 4.3.0

9.11.1 New features

- Flexible **Posit** now uses `FF14SB-SAGE` force field for the protein/ligand complex optimization.
- A new overload of SetupRef has been added that allows using OEShapeFit with a bound ligand as the reference.
- The following new methods have been added to enable internal conformation generation in OEShapeFitOptions:
  - SetFullConformationSearch
  - GetFullConformationSearch
- A new class, OEShapeFitOptions, has been added that allows estimating pose prediction confidence against different reference systems. This new class is complementary to the existing function OEGetEstimatedPositProbability.

9.11.2 Major bug fixes

- An issue has been fixed where relaxation failed in OEPosit when the pose relaxation mode was set to either ALL or CLASHED.
- An issue causing generation of bent ring structures and high strain poses when performing OEPosit has been fixed.
- An issue has been fixed that caused flexible OEPosit with ALL relaxation mode to fail while generating non-clashing poses when NONE was successful.

9.11.3 Minor bug fixes

- An issue where Dock passed too many conformers for flexible optimization with relaxation in OEPosit has been fixed. Now, OEShapeFit no longer passes too many conformers for flexible optimization that could occasionally cause a less accurate conformer to become the top predicted pose.
- The Dock method with relaxation has been modified to be more aligned with other modes of failure when ligand charge assignments fail.

9.12 OEDOCKING 4.2.1.1

- An issue where the shape contour could extend out of the user-defined box has been fixed. The grid will fill the initial box adjusting for grid spacing, and the resulting re-drawn box will be slightly larger to sit at the edge of the generated grid.
- The generate shape contour button can now only be clicked a subsequent time if a different user selection has been made that would cause the contour to change.

9.13 OEDOCKING 4.2.1.0

9.13.1 Major bug fixes

- **Posit** now correctly provides only the nonclashing poses in the generated output file when running with `-num_poses` greater than one and results in a mix of clashed and nonclashed poses for a particular ligand.
- **Posit** now provides three-dimensional structures in the clashed output file.
- An issue in **Posit** that caused occasional relaxation of nonclashing poses when running with the `-relax` option set to `clashed` has been fixed.
- Possible inconsistent behavior and/or crashes in **MakeReceptor**, while editing custom constraints or selecting a constraint from the list of created constraints, have been fixed.

9.14 OEDocking TK 4.2.1

9.14.1 New features

- A new preliminary API class, OEShapeFitOptions, has been added to allow better control over option parameters for OEShapeFit. The constructor for the preliminary class OEShapeFit now takes OEShapeFitOptions as an argument instead of OEFlexiOverlayOptions. Also, SetFlexiOverlayOptions and GetFlexiOverlayOptions now accept and return OEShapeFitOptions.

9.14.2 Major bug fixes

- The Dock method in OEPosit now returns poses instead of a failure, if there is a failure during flexible optimization.
- An issue that caused intermittent crash for specific calculations on specific platforms when working with OEPosit has been fixed.
- OEPosit now accurately returns NoValidNonClashPoses as status when the predicted pose contains clashes based on the defined clash allowed type. Note that the clashed poses can still be retrieved from the resulting OESinglePoseResult if desired.

9.14.3 Minor bug fixes

- The RankDesignUnits method is now properly wrapped in python.

9.14.4 Documentation changes

- Documentation has been added for the function OEGetEstimatedPositProbability, which works with OEDesignUnit.
- Documentation has been added for the function OESetupBox, which supports OEMolBase and OEMCMolBase.

9.15 OEDOCKING 4.2.0

Fall 2022

9.15.1 New features

- The **Posit** application now uses the new OEShapeFit API for flexible fitting with Shape/Color and Forcefield. The new algorithm replaces the currently existing ShapeFit algorithm that uses adiabatic optimization. A modified ShapeFit algorithm optimizes the shape and chemical similarity between the fit molecule and bound ligand present in the reference design unit, along with intra-molecular forcefield energies of the fit molecule. The SAGE ligand force field is used during this optimization.
- Spruce Filter was added to **MakeReceptor**, to assist in structure standardization prior to structure preparation.

9.15.2 Minor bug fixes

- **Posit** now prints out more concise warning messages.

9.16 OEDocking TK 4.2.0

9.16.1 New features

- Two new preliminary API classes, OEShapeFit and OEShapeFitResults have been added which provides functionality for pose generation based on flexible fitting with Shape/Color and Forcefield.
- The adiabatic optimization algorithm of `ShapeFit` method for pose generation in OEPosit has been replaced by a new simultaneous flexible fitting algorithm, as implemented in OEShapeFit. The new algorithm uses Sage as the default forcefield, instead of MMFF.
- Two new methods, SetFlexiOverlayOptions and GetFlexiOverlayOptions, have been added to OEPositOptions to expose parameters related to OEShapeFit in OEPosit.

9.16.2 Major bug fixes

- An issue that caused a segmentation fault when using CacheScoringSetup has been fixed.

9.16.3 Documentation changes

- New C++ and Python examples have been added to the Flexible Overlay Optimization with OEShapeFit API section that demonstrate how to flexibly fit input multi-conformer molecules into a design unit that contains a bound ligand.

9.17 OEDOCKING 4.1.2

Spring 2022

9.17.1 Minor bug fixes

- Typos in the help text for **ReceptorInDU** have been fixed.
- Typos in the help text for **ReceptorToolbox** have been fixed.
- An issue causing **MakeReceptor** to crash when editing protein constraints has been fixed.

9.18 OEDocking TK 4.1.2

Spring 2022

- Minor internal improvements have been made.

9.19 OEDOCKING 4.1.2

Spring 2022

9.19.1 New Features

9.19.2 Major Bug Fixes

9.19.3 Minor Bug Fixes

9.20 OEDocking TK 4.1.2

Spring 2022

- Minor internal improvements have been made.

9.21 OEDOCKING 4.1.0

July 2021

9.21.1 New Features

- The *MakeReceptor* GUI application has been extended to be a fully functional DesignUnit and receptor builder. A new design unit can be created from a `PDB/MMCIF` file (with or without an associated `MTZ` file), or by combining molecules from various molecule files of any format. SPRUCE options are exposed through a graphical interface giving users control over the level of preparation the structure should go through. Existing receptors, both in `OEDU` or `OEB` format, can also be opened and edited in *MakeReceptor*.

9.21.2 Minor Bug Fixes

- Apps will now fail with error message if an invalid database with no molecules is provided.
- `Spruce4Docking` has been removed. We recommend using SPRUCE instead.
- *POSIT* output now contains receptor filename as SD data.
- *ReceptorInDU* now generates receptors and reports multiple design units in a single output `OEDU` file.
- *OEB2DUReceptor* now converts and reports multiple design units within a single output `OEDU` file.

9.22 OEDocking TK 4.1.0

July 2021

9.22.1 New features

- A predicate string can now be supplied to OEMakeReceptorOptions using SetTargetPred. This povides a way to specify a select set of water molecules in an OEDesignUnit to be part of the receptor when the docking grid is constructed and used in subsequent docking calculations.

- OEMakeReceptor now autogenerates protein constraints. The constraints are left disabled by default for the docking calculations. These can be enabled using the toolkits, or the Make Receptor GUI application. The autogeneration of the constraints can be turned off using the SetAutoConstraints method in OEMakeReceptorOptions.

9.22.2 Minor bug fixes

- The default value for the SetBoxMol has been set to `0.0` in the OEMakeReceptorOptions class.

9.23 OEDOCKING 4.0.0.2

March 2021

- The default value of the `-targetMask` parameter in *ReceptorInDU* has been changed to `targetComplexNoSolvent` to reflect best practices for receptor generation.
- The `-targetMask` parameter in *ReceptorInDU* now provides added flexibility to create user defined masks.
- Protein constraints, custom constraints, and extra molecules are now properly transferred and serialized when converting OEB format receptors to OEDU format receptors using *OEB2DUReceptor*.
- *POSIT* now properly handles `.lst` files containing empty lines as input to `-receptor` parameters.
- Component names are now consistent when converting between `OEChem::OEMolBase` and `OEBio::OEDesignUnit` receptors.
- Documentation regarding *Receptors* has been updated.

9.23.1 OEDocking Toolkit Information

For additional details, see OEDocking TK 4.0.0.2.

9.24 OEDOCKING 4.0.0.0

Fall 2020

9.24.1 New features

- A new utility, *ReceptorInDU*, has been added that makes a receptor inside a design unit OEDU file.
- A new utility, *OEB2DUReceptor*, has been added that converts a receptor OEB or OEB.GZ file into a OEDU receptor file.
- The GUI application *MakeReceptor* now reads OEDU files and outputs OEDU receptor files, with receptors created inside a design unit.
- The following programs in the **OEDocking** applications suite now expect OEDU files (with receptors inside a Design Unit), for receptors. These programs no longer support receptor input from OEB or OEB.GZ files.
  - *FRED*
  - *HYBRID*
  - *POSIT*
  - *ScorePose*
  - *ReceptorToolbox*
  - *DockingReport*

- **POSIT** now produces OEDU files as output containing design units consisting of pose ligand structures and protein active site structures.
- A new parameter, `-nostructs`, has been added to **FRED** and **HYBRID**. When this flag is set to `true`, both the docked and undocked structure files will be suppressed.
- A new utility, *DU2OEBReceptor*, has been added that converts an OEDU receptor file into a receptor OEB or OEB.GZ file.
- The utility `DU2Receptor` has been removed from the **OEDocking** application suite. The receptors are now created inside a design unit, and can be created using the *ReceptorInDU* utility application.

9.24.2 Documentation changes

- The Tutorials section has been updated.

9.25 OEDocking 3.5.0

Spring 2020

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

9.25.1 Minor bug fixes

- The Windows version of **Make Receptor** now displays the user's home directory when *File Open* is first clicked.
- **Make Receptor** file filters have been simplified to only include *Molecules*, *Receptors*, and *All Supported Formats*. The *Molecules* filter now includes CIF and CIF.gz file extensions.
- Users can now browse to find their license file.

9.25.2 Documentation changes

- The utilities section has been updated with accurate information on supported applications and their usage.

9.26 OEDocking 3.4.0

Nov 2019

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

9.26.1 New features

- New utility application, **Spruce4Docking**, has been added to properly prepare structures for receptor generation. The output from **Spruce4Docking** is an OEDesignUnit object serialized to a new `OEDU` file format. Alternatively, users with access to **SPRUCE** can take the **SPRUCE**-generated `OEDU` files directly and bypass **Spruce4Docking**.
- New utility application, **DU2Receptor**, has been added that can be used to create a receptor from design units contained in an `OEDU` file. With the addition of **DU2Receptor** and **Spruce4Docking**, previously existing utilities `ApoPdb2Receptor`, `Pdb2Receptor`, and `ReceptorSetup` are no longer required and has been removed from the **OEDocking** applications suite.
- **POSIT** has been rewritten to take advantage of the newly extended corresponding **POSIT** functionality in the **2019.Oct** release of the **OEDocking TK**. With this update, some of the previous application-specific functionality, including working with multiple receptors, finding the best receptor for a specific ligand, and clash checking, are now directly taken care of by the toolkit functionality. From a performance point of view, **POSIT** is now

more efficient in finding a pose for a ligand when working with multiple receptors. On the downside, there is a slight increase in memory usage and time with use of an increasing number of receptors.

- The ability to further refine generated poses has been added to **POSIT**. The optional relaxation allows for greater flexibility of the ligand and parts of the receptor. A new parameter, `-relax`, has been added that defines if and when this post-pose generation relaxation should be performed.
- Definition of "clash" and "clash types" have been redefined to be in sync with the definitions in the corresponding functionality in **OEDocking TK**. The new clash definitions are based on perceived protein-ligand interactions. Accordingly new type `hclashes` have been introduced in `-allowed_clashes` that redefines `mildclashes`.
- The `-conftest` parameter has been removed from all **OEDOCKING** applications.

9.26.2 Major bug fixes

- **POSIT** no longer gives up when the pose generated from the single best receptor produces a clash, and instead continues to generate poses with subsequent best receptors until a clash free pose is generated.

9.26.3 Minor bug fixes

- An issue regarding **POSIT** to fail to maintain SD Data from the input molecule has been fixed.
- An issue in **HYBRID** that caused a single molecule with enumerated nitrogen stereo to be treated as multiple molecules has been fixed.
- An issue that caused **HYBRID** to fail to output undocked molecules to the undocked molecule file for large runs has been fixed.
- An order dependent issue in **POSIT** that affected choosing the best receptor when working with multiple receptors has been fixed. **POSIT** now gives the same result regardless of the order in which receptors are provided.
- An issue regarding **POSIT** to fail to report the correct number of molecules process has been fixed.
- **POSIT** no longer crashes when a single atom input molecule is passed.
- **CombineReceptors** now recognizes the `-prealigned` flag.

9.27 OEDocking 3.3.1

May 2019

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

9.27.1 Major bug fixes

- **POSIT** now correctly uses the FRED method when there is no bound ligand in the receptor.
- **POSIT** now correctly uses the FRED method when the similarity between the bound ligand and posed ligand is very low.
- A bug that caused a memory issue in **FRED** has been fixed

9.27.2 Minor bug fixes

- The `hybrid_Score.txt` file now starts at 1 instead of 0 when labeling the poses, from a **Hybrid** calculation.

9.28 OEDocking 3.3.0

November 2018

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

9.28.1 Major bug fixes

- **ScorePose** no longer requires an **OEChem TK** license.

9.28.2 Minor bug fixes

- The `-force_planar_aromatic` flag has been removed from **POSIT**.

9.29 OEDocking 3.2.0

December 2015 Major Features ——————

- *posit* is now part of the *OEDocking* suite (a *posit* license is still required to run *posit*).
- Improved *posit*'s clash detection. *posit* now ignores on a per atom basis clashes with the protein that the crystallographic ligand also makes.
- OpenMPI version 1.6 is now supported on all platforms. The -mpi_np and -mpi_hostfile flags are now used to run *fred*, *hybrid* and *posit* in MPI mode. These new flags replace the oempirun script.
- `pdb2receptor` now incorporates all of *make_pose_receptor*'s functionality. *make_pose_receptor* has now been retired.
- `pdb2receptor` now supports the identification and selection of a desired ligand in a protein-ligand complex.

9.29.1 Minor Features

- *Make Receptor*, `pdb2receptor`, `apopdb2receptor`, *docking_report*, `receptor_setup` and *receptor_toolbox* now all accept either a posit or fred2 license.

9.29.2 Major Bug Fixes

- *Make Receptor* no longer routinely crashed under a Japanese version of Windows.
- Fixed a bug where pdf's generated by *docking_report* causes an error under Windows versions of Acrobat.

9.29.3 Minor Bug Fixes

- Fixed an off by one error in *hybrid*'s progress reporting of how many molecules have been docked.
- Fixed a bug where *fred*, *hybrid* or *posit* could crash if given a protein structure with non-sensical atom states.

9.30 OEDocking 3.0.1

September 2012

9.30.1 Changes

The program dock_report has been renamed to *DockingReport*.

The formatting of the *DockingReport* has been significantly improved.

Improved the geometry detection for hydrogen bond protein constraints. These constraints should now be tighter.

9.30.2 New Features

The output of *DockingReport* now includes

- Added a protein interaction fingerprint to the docking_report.
- XLogP
- Polar surface area (PSA)

9.30.3 Bug Fixes

Fix bug where clash detection between hydrogen bonding groups was occasionally to strict.

9.31 OEDocking 3.0.0

April 2012

9.31.1 Changes

The **OEDocking** 3.0.0 release is the first release of the **OEDocking** package, which is an upgrade of the previous *FRED* release packages. The **OEDocking** package includes *FRED* along with a suite of new docking tools.

As part of this **OEDocking** release the interface to *FRED* has been streamlined. Several functions of *FRED* have been split out into separate programs that are now part of the OEDocking suite, and several older features that have not proved to improve docking results (or in the worst case degrade docking results relative to the defaults) have been removed.

The features of **FRED** 2.2.5 that have been moved to separate utility programs in 3.0.0 are as follows

- **Receptor Creation**

  Receptors are now created either with the *Make Receptor* GUI or the `pdb2receptor`, `apopdb2receptor`, or `receptor_setup` command-line programs. Existing receptors can now also be edited or modified with the *Make Receptor* GUI or *ReceptorToolbox* command line program. These programs are all included in the OEDocking distribution.

  Relevant flags removed from FRED:

  - **-pro**
  - **-strip_water**
  - **-bound_ligand**
  - **-box**
  - **-addbox**
  - **-no_inner_contour**

- **Hybrid Docking**

  Hybrid docking is now available as a separate application, *HYBRID*, included in the OEDocking distribution.

- **Rescoring of poses**

  The feature to rescore existing poses is now available in a separate application, *ScorePose*, included in the OE-Docking distribution.

The features of FRED 2.2.5 removed in 3.0.0 are as follows

- **Alternate Scoring Functions**

  FRED now uses the improved Chemgauss4 scoring function. This scoring function has better virtual screening and pose prediction performance than any of the scoring functions available in FRED 2.2.5.

  Relevant flags removed from FRED:

  - **-exhaustive_scoring**
  - **-opt**
  - **-shapegauss**
  - **-plp**
  - **-chemgauss2**
  - **-chemgauss3**
  - **-chemscore**
  - **-oechemscore**
  - **-screenscore**
  - **-cgo**
  - **-cgt**
  - **-zapbind**
  - **-consensus**
  - **-shapegauss_masc**
  - **-plp_masc**
  - **-chemgauss2_masc**
  - **-chemgauss3_masc**
  - **-chemscore_masc**
  - **-oechemscore_masc**
  - **-screenscore_masc**
  - **-cgo_masc**
  - **-cgt_masc**
  - **-zapbind_masc**
  - **-consensus_masc**
  - **-assign_ligand_charges**

- **MASC**

  Multiple Active Site Correction (MASC) was introduced in **FRED** 2.1 as a method of compensating for the size bias in scoring functions. This size bias arises in many scoring functions where the interaction terms are all favorable interactions, and thus larger molecules score better since they can make more interactions. Chemgauss4 (and Chemgauss3), however, has both favorable interactions (i.e., shape, hydrogen bonding and metal-chelator)

and unfavorable interactions (i.e., desolvation and clash), and therefore does not have a significant size bias that necessitates the use of MASC.

Relevant flags removed from FRED:

- **-reference_receptors**
- **-no_masc_data**
- **-recalculate_masc_data**
- **-report_masc_failures**

- **Consensus Pose Selection**

  FRED 2.2.5 had slightly better pose prediction results when the best docked pose was selected using a consensus of three scoring function (Chemgauss3, Chemscore and PLP) rather than one (Chemgauss3). The new Chemgauss4 scoring function in the 3.0 release is not improved by this feature, and has therefore been removed.

  Relevant flags removed from **FRED**:

  - **-pose_select_weight_shapegauss**
  - **-pose_select_weight_plp**
  - **-pose_select_weight_chemgauss2**
  - **-pose_select_weight_chemgauss3**
  - **-pose_select_weight_chemscore**
  - **-pose_select_weight_oechemscore**
  - **-pose_select_weight_screenscore**
  - **-pose_select_weight_cgo**
  - **-pose_select_weight_cgt**

- **MMFF Refinement**

  Using this option in **FRED** 2.2.5 degraded the results for both pose prediction and virtual screening and significant increases the run time.

  Relevant flags removed from **FRED**:

  - **-refine**

9.31.2 New Features

- **Chemgauss4 scoring**

  Improved hydrogen bond detection vs. Chemgauss3. Hydrogen bond network effects are also now accounted for.

- **Hybrid docking**

  Dock using ligand and protein structural information simultaneously

- **MPI**

  MPI is now supported on all platforms except Windows.

- **Docking Report**

  Creates an Adobe PDF docked report for selected docked molecules.

- **Receptor tools**

  Streamlines the receptor setup GUI, and also added several command line tools for setting up receptors.

9.31.3 Bug Fixes

- Fixed a bug where large hit lists (> ~50,000) would result is very slow runtimes.
- SD tag data on the input ligand is now retained.
- Added an option to toggle hardware rendering in the Make Receptor GUI application to correct Windows driver related 3D graphics issues.

9.32 POSIT 3.1.0

June 2014

9.32.1 Major Features

- The *hybrid* and *fred* algorithms have been incorporated into *posit*, the appropriate method is determined by analyzing the ligand to pose against the input receptors.
- Multiprocessing has been enabled through the use of MPI, to speed calculations.
- *posit* now supports a *list of receptors files* or **.lst** file as input. This overcomes command-line limitations for the number of receptors that can be used simultaneously.
- Added a *MEDIOCRE* result rating for results between 33% and 50% probability.
- Command line parameters have been simplified and updated to be compatible with the *OEDocking* Suite of tools. The following command-line options have been removed, see the documentation for full details.
  - outcomplexes
  - outreceptors
  - clashcomplexes
  - clashreceptors
  - alternatePoses
  - cleanupWithProtein
  - mcs
  - minInitialProbability
  - minInitialTanimotoCombo
  - minTanimotoCombo
  - probabilityStop
  - scatter
  - selectReceptorBy
  - strain

9.32.2 Major Bug Fixes

- *posit* no longer automatically strips out incoming SDData fields.

9.32.3 Minor Bug Fixes

- The default for the option *-ignore_nitrogen_stereo* has been changed to *true* to account for the nature of time-averaged crystallographic structures.

9.33 POSIT 1.0.3

September 2012

9.33.1 Major Bug Fixes

- Stereo isomer detection was not handling bridgeheads properly, this caused some non-stereo molecules to be identified as such.

9.34 POSIT 1.0.2

July 2012

9.34.1 Major Features

- The optimizer has been enhanced to produce better aligned structures in certain cases.

9.34.2 Major Bug Fixes

- A memory leak in the optimizer has been fixed, **POSIT** now properly handles large streams of molecules.
- The -mcs flag has been turned off by default. In some cases, the mcs was taking far too long for no real benefit in pose prediction.

9.35 POSIT 1.0.1

February 2012

9.35.1 Major Bug Fixes

- In some rare cases the -mcs flag could cause a portion of the posed ligand to be fixed in space while the rest was optimized correctly, this causes very bad geometry molecules that can score very well. **POSIT** has been fixed to optimize the whole molecule in such cases.

9.35.2 Minor Bug Fixes

- The version numbers for make_pose_receptor and combine_receptors were being incorrectly output in the OpenEye Banner, this has been updated to reflect the correct **POSIT** version.

9.35.3 Minor Features

- -outputall flag has been added to send all computed output to the file specified by **-out**, **-outcomplexes** or **-outreceptors**. It as a shortcut for:

```
-minInitialTanimotoCombo 0.0 -minTanimotoCombo 0.0 -minProbability 0.0 \
  -allowedClashes allclashes
```

- if any of the input receptors has a clashing ligand, a warning will be output and POSIT will be set to accept clashes of the same severity as the receptor ligand.
- **POSIT can now stream output specified by the *-out* switch to stdout using the** command line switch *-out .sdf* or *-out .oeb*

9.36 POSIT 1.0.0

November 2011

First release of **POSIT**.

Traditional structure based pose-prediction has not been very accurate in reproducing crystallographic poses. This can be rectified by using all of the information present in a crystal structure - both ligand and protein structure. **POSIT** is a flexible docking technique that uses both the known protein and ligand structure to predict poses. Furthermore, using this information generates a probability that the predicted pose is indeed correct. This has far reaching implications for real world lead optimization scenarios including measuring confidence but also the ability to select the existing crystal structure that best predicts the docked pose for a given molecule.

9.36.1 Features

- Probability based pose-prediction
- Performs better than structure-based pose-prediction for poses similar to known bound ligands.
- All-atom optimization of poses based on known bound-ligands and ligand-protein interactions.
- Fast detection of best known receptor (complex) to determine pose.

9.37 FRED 2.2.5

9.37.1 New Features

- On Microsoft Windows platforms, the installer adds the ability to open command prompts that setup the user environment to run specific versions of **FRED** or the latest version of **FRED**.

9.37.2 Changes

- **FRED** and **FRED_RECEPTOR** are now versioned and shipped together.

9.37.3 Bug Fixes

- **FRED** licenser has been updated to work with licenses that expire past the year 2009.
- The **FRED** licenser supports having the license file located in the users home directory.
- SD files are now written with the 3D flag set.
- Fixed issue where Fred could crash if -nodock is specified and the poses given to Fred to score are not within the receptor site.

9.38 FRED 2.2.4

9.38.1 Bug Fixes

- Fixed crash when -refine and -no_dock were used together.
- Fixed crash when -clash_scale and a receptor without an inner contour is used.

9.39 FRED 2.2.3

9.39.1 Bug Fixes

- Fixed a bug when using two custom constraints that caused all molecules to fail to dock with a NoConstraintMatch code.

9.40 FRED 2.2.2

9.40.1 Bug Fixes

- Fixed a bug that causes the -pharm flag to be ignored.
- Cleaned up minor formatting issue when informing the user that a warning log has been opened.

9.41 FRED 2.2.1

9.41.1 New Features

- Added support for OEB rotor offset compression when writing the MASC tagged version of the input database (provided the initial input database used rotor offset compression).
- Chemscore's, OEChemscores's and Screenscores's hydrogen bonding terms now only allow one hydrogen bond per hydrogen. Also prevented two hydroxyls from making both and acceptor-donor interaction and a donor-acceptor interaction.

9.41.2 Changes

- Modified OEChemscore's hydrogen bonding term to be more forgiving of non-ideal geometries. The range of geometries considered ideal is unchanged.
- Corrected a deficiency in Chemgauss3 metal term and metal constraints. The metal chelator interaction function was picking up on some but not all of the allowable geometries for metal-chelator interactions.
- Improved Chemscore's, OEChemscore's and Screenscore's handling of rotatable hydrogens involved in hydrogen bonding by replacing the brute force torsion driving search for the optimal hydrogen position with an analytic solution for the best position.
- Added a new flag "-no_masc_data_calc" which will prevent Fred from calculating MASC data for ligands. Any ligands that missing needed masc data will not be docked. The purpose of this flag is to prevent it from doing a lengthy MASC calculation when all but a handful of ligands have the required MASC data.
- Extended initial list of atom types know to Chemgauss3. This should improve the startup speed of runs using Chemgauss3, by avoiding costly grid recalculations each time a new atom type is encountered. This change is only for speed, there is no change to the Chemgauss3 score value Fred calculates.
- When using constraints fred now defaults to effectively using a -clash_scale value of 0.6 if the -clash_scale flag has not been set by the user. This helps eliminate unusually close protein-ligand contacts that can occasionally

occur when constraints are used. The original behavior can be obtained by explicitly setting -clash_scale to 0. Runs without constraints are unaffected and behave as before.

- Chemgauss2 is no longer used by default in the consensus pose stage of docking. This has no real effect on docking performance and will reduces Fred's startup time.

9.41.3 Bug Fixes

- Important: Fixed a bug when using -pro and -box to create a receptor that causes the inner contour to be set to an extremely small value. The resulting receptor would produce extremely poor docking results without warning. In this release newly created receptors will now have reasonable inner contours. Additionally Fred now checks if the inner contour volume is extremely small (i.e., one that was produced by this bug), and if one is detected the inner contour is turned off and a warning is issued before proceeding with the run.
- Fixed a when requesting alternate poses during a PVM run, which caused the run to shutdown and not dock any molecules.
- Fixed a bug in screenscore when the receptor/protein it was initialized with did not have explicit hydrogens. The bug causes the initial setup to fail and the run to stop if screenscore was used. The error reported when this bug occurred was "Error! Screenscore::FindAcceptors (OH)".
- Fixed a crash bug when calculating MASC data for ligands on a 64bit machine.
- Fixed minor when reporting how many molecules in a database have MASC data. The percentage reported was erroneously divided by 100.
- Fixed a bug when using both the MASC and Non-MASC variants of a scoring function in the same run. The bug caused a shift in the Non-MASC score related to the precalculated MASC data, while the MASC variant score was correctly calculated. The error was especially damaging to CGT score.
- Fixed spelling error by changing parameter -recalculate_masc_data to -recalculate_masc_data. The original misspelling is now an alias to minimize impact on users with existing parameter files.
- Fixed bug checking for charges when -zapbind and -pro are used together. (Did not affect runs where -zapbind and -rec were being used). The bug caused the run to stop.
- Fixed a bug in -clash_scale flag, that causes the value passed to the flag to be ignored and a value of one to be used. If the -clash_scale flag was not used no bug occurred in this regard.
- Silenced the warning "OEInterface::Get, requesting value of unset parameter -addbox" when using the -box parameter without also specifying -addbox. The warning was spurious, no error occurred when it was issued.
- Slave of a multiprocessor run now longer require a license, only the master process requires a license now.

9.42 FRED 2.2.0

9.42.1 New Features / Improvements

Optional GUI setup and preparation of the active site (the actual docking remains command line). The GUI allows users to

- Separate bound ligands and solvent molecules from the protein structure.
- Detect active sites, and adjust the box defining the active site.
- Manually tweak residue protonation states.
- Visualize and adjust the complimentary shapes **FRED** uses during the exhaustive search.
- Specify constraints.

A new version of the Chemgauss scoring function, version 3, which includes new desolvation terms as well as improved typing.

Ligand based design scoring functions, C.G.O (Chemical Gaussian Overlay) and C.G.T. (Chemical Gaussian Tanimoto). These functions score be measuring how well a molecules shape and chemistry overlay a known bound ligand placed in the active site.

All new algorithm for generating the negative image of the active site using molecular shape probes, as opposed to the atomic probes uses earlier.

On the fly preparation of MASC data for runs using the MASC variant scoring functions is now an option. Precalculating MASC data is still available and most efficient when doing multiple runs.

9.42.2 Changes

FRED now uses a special receptor file to describe the active site. This file can be created interactively using the new fred_receptor GUI program, or on the fly with the command line using the same flags as the previous version of **FRED** (2.1.x).

The functionality of the masc_prep and ligand_info programs distributed with the previous version (2.1.x) have been merged into the main fred executable.

Version 1 of Chemgauss has been removed, Version 2 is deprecated but still available.

Individual hitlist -size and -cut flags have be replaced by a single -hitlist_size flag.

CHAPTER

TEN

CITATION

Note

To cite OEDOCKING please use the following:

OEDOCKING 4.3.5.0. OpenEye, Cadence Molecular Sciences, Inc., Santa Fe, NM. http://www.eyesopen.com.

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CHAPTER

ELEVEN

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CHAPTER

TWELVE

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CHAPTER

THIRTEEN

CITATION

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13.1 Orion®

To cite use of Orion, please use the following:

```
Orion <version-number>. OpenEye, Cadence Molecular Sciences, Santa Fe, NM. http://www.
↪eyesopen.com.
```

For example:

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

The version number for Orion appears in the product's release notes, for example, https://docs.eyesopen.com/orion-user-interface/releasenotes/index.html.

13.2 Orion Floes

To cite use of an Orion-based floe package, please use the following:

```
OpenEye <package-name> <version-number>. OpenEye, Cadence Molecular Sciences, Santa Fe,␣
↪NM. http://www.eyesopen.com.
```

For example:

```
OpenEye Large-Scale Floes 4.2.3. OpenEye, Cadence Molecular Sciences, Santa Fe, NM.␣
↪http://www.eyesopen.com.
```

The version number for a floe package is displayed on the first page of the package's release notes. For example: https://docs.eyesopen.com/floe/modules/large_scale_floes/docs/source/releasenotes_2025_1.html.

13.3 Toolkits and Applications

To cite OpenEye toolkits or applications used in your work, please use the following:

```
OpenEye Toolkits [or Applications] <version-number>. OpenEye, Cadence Molecular Sciences,
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```

For example:

```
OpenEye Toolkits 2024.2.1. OpenEye, Cadence Molecular Sciences, Santa Fe, NM. http://www.
↪eyesopen.com.
```

The Applications and Toolkits are released as a package, multiple times per year. The first part of the version number designates the calendar year. The version number appears on the summary document for the package.

If you want to cite an individual application or toolkit, you can use the syntax:

```
<product name> <version-number>. OpenEye, Cadence Molecular Sciences, Santa Fe, NM.␣
↪http://www.eyesopen.com.
```

where <*product name*> is:

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

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

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

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

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

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

13.4 Publications for Bibliographies

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

13.4.1 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

13.4.2 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

13.4.3 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

13.4.4 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

13.4.5 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

13.5 OpenEye MMDS Web Service

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

```
Macromolecular Data Service <version-number>. OpenEye, Cadence Molecular Sciences, Santa␣
↪Fe, NM. http://www.eyesopen.com.
```

For example:

```
Macromolecular Data Service 1.1. OpenEye, Cadence Molecular Sciences, Santa Fe, NM.␣
↪http://www.eyesopen.com.
```

The MMDS version number appears on the web service's release notes.

CHAPTER

FOURTEEN

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Some of the open source technologies we use are licensed under the GNU Public License (GPL) version 2 or 3. In all instances, these technologies are communicated with using the "at arms length" principle, using pipes and command line arguments.

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Table 1: Licensed Technology

Name of Project	Website	License URL
_libgcc_mutex	https://github.com/conda-forge/_libgcc_mutex-feedstock	https://github.com/conda-forge/_libgcc_mutex-feedstock/blob/master/LICENSE.txt
_openmp_mutex	https://github.com/conda-forge/_openmp_mutex-feedstock	https://github.com/conda-forge/_openmp_mutex-feedstock/blob/main/LICENSE.txt
ablang2	https://github.com/TobiasHeOl/AbLang2	https://github.com/TobiasHeOl/AbLang2/blob/main/LICENSE
abseil-cpp	https://github.com/abseil/abseil-cpp	https://github.com/abseil/abseil-cpp/blob/master/LICENSE
absl-py	https://github.com/abseil/abseil-py	https://github.com/abseil/abseil-py/blob/main/LICENSE

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Table 1 – continued from previous page

Name of Project	Website	License URL
aiohappyeyeballs	https://github.com/aio-libs/aiohappyeyeballs	https://github.com/aio-libs/aiohappyeyeballs/blob/main/LICENSE
aiohttp	https://docs.aiohttp.org/en/stable/	https://github.com/aio-libs/aiohttp/blob/master/LICENSE.txt
aiosignal	https://github.com/aio-libs/aiosignal	https://github.com/aio-libs/aiosignal/blob/master/LICENSE
Amazon Linux 2	https://aws.amazon.com/amazon-linux-2	N/A
AmberUtils	http://ambermd.org	N/A
ambit	https://github.com/khimaros/ambit	https://github.com/khimaros/ambit/blob/master/LICENSE
amqp	https://github.com/celery/py-amqp	https://github.com/celery/py-amqp/blob/master/LICENSE
anaconda-anon-usage	https://github.com/anaconda/anaconda-anon-usage	https://github.com/anaconda/anaconda-anon-usage/blob/main/LICENSE
angular	https://github.com/angular/angular.js	https://github.com/angular/angular.js/raw/master/LICENSE.md
angular-animate	https://github.com/angular/angular.js	https://github.com/angular/angular.js/raw/master/LICENSE.md
angular-cache	https://github.com/jmdobry/angular-cache	https://github.com/jmdobry/angular-cache/raw/master/LICENSE
angular-cookies	https://github.com/angular/angular.js	https://github.com/angular/angular.js/raw/master/LICENSE.md

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Table 1 – continued from previous page

Name of Project	Website	License URL
angular-loggly-logger	https://github.com/ajbrown/angular-loggly-logger	https://github.com/ajbrown/angular-loggly-logger/raw/master/LICENSE.md
angular-mocks	https://github.com/angular/angular.js	https://raw.githubusercontent.com/angular/angular.js/master/LICENSE
angular-resource	https://github.com/angular/angular.js	https://raw.githubusercontent.com/angular/angular.js/master/LICENSE
angular-toggle-switch	https://github.com/cgarvis/angular-toggle-switch	https://github.com/cgarvis/angular-toggle-switch/blob/master/LICENSE
angular-ui-grid	https://github.com/angular-ui/ui-grid	https://github.com/angular-ui/ui-grid
angular-ui-router	https://github.com/angular-ui/ui-router	https://github.com/angular-ui/ui-router/raw/master/LICENSE
angular-ui-tree	https://github.com/angular-ui-tree/angular-ui-tree	https://github.com/angular-ui-tree/angular-ui-tree/raw/master/LICENSE
angular-vs-repeat	https://github.com/kamilkp/angular-vs-repeat	https://raw.githubusercontent.com/kamilkp/angular-vs-repeat/master/LICENSE
aniso8601	https://bitbucket.org/nielsenb/aniso8601	https://bitbucket.org/nielsenb/aniso8601/src/master/LICENSE
annotated-types	https://github.com/annotated-types/annotated-types	https://github.com/annotated-types/annotated-types/blob/main/LICENSE
antlr4-python3-runtime	http://www.antlr.org OR https://pypi.org/project/antlr4-python3-runtin	https://github.com/conda-forge/antlr4-python3-runtin blob/master/LICENSE.txt

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Table 1 – continued from previous page

Name of Project	Website	License URL
anyio	https://github.com/agronholm/anyio	https://github.com/agronholm/anyio/blob/master/LICENSE
appdirs	http://github.com/ActiveState/appdirs	http://github.com/ActiveState/appdirs/blob/master/LICENSE.txt
appengine	https://google.golang.org/appengine	https://github.com/golang/appengine/blob/master/LICENSE
arabic-reshaper	https://github.com/mpcabd/python-arabic-reshape	https://github.com/mpcabd/python-arabic-reshape/blob/master/LICENSE
archspec	https://github.com/archspec/archspec/blob/master/README.md	https://github.com/archspec/archspec/blob/master/COPYRIGHT
argon2-cffi	https://github.com/hynek/argon2-cffi	https://github.com/hynek/argon2-cffi/blob/master/LICENSE
argon2-cffi-bindings	https://github.com/hynek/argon2-cffi-bindings	https://github.com/hynek/argon2-cffi-bindings/blob/master/LICENSE
arpack	https://www.caam.rice.edu/software/ARPACK/	https://www.caam.rice.edu/software/ARPACK/
arrow	https://github.com/arrow-py/arrow	https://github.com/arrow-py/arrow?tab=Apache-2.0-1-ov-file#readme
ascii85	https://github.com/huandu/node-ascii85	https://github.com/huandu/node-ascii85/raw/master/LICENSE
ase	https://wiki.fysik.dtu.dk/ase/	https://wiki.fysik.dtu.dk/ase/development/licenseinfo.html#license-info
asgiref	https://github.com/django/asgiref/	https://github.com/django/asgiref/blob/main/LICENSE

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Table 1 – continued from previous page

Name of Project	Website	License URL
asn1crypto	https://github.com/wbond/asn1crypto	https://github.com/wbond/asn1crypto/blob/master/LICENSE
assertions go-render	https://github.com/smartystreets/assertions/internal/go-render/render	https://github.com/smartystreets/assertions/blob/master/internal/go-render/LICENSE
assertions oglmatchers	https://github.com/smartystreets/assertions/internal/oglematchers	https://github.com/smartystreets/assertions/blob/master/internal/oglematchers/LICENSE
assertions	https://github.com/smartystreets/assertions	https://github.com/smartystreets/assertions/blob/master/LICENSE.md
asttokens	https://github.com/gristlabs/asttokens	https://github.com/gristlabs/asttokens/blob/master/LICENSE
astunparse	https://github.com/simonpercivall/astunparse	https://github.com/simonpercivall/astunparse/blob/master/LICENSE
async-lru	https://github.com/aio-libs/async-lru	https://github.com/aio-libs/async-lru/blob/master/LICENSE
async-timeout	https://github.com/aio-libs/async-timeout	https://github.com/aio-libs/async-timeout/blob/master/LICENSE
atk-1.0	https://docs.gtk.org/atk/	https://gitlab.gnome.org/GNOME/atk/-/blob/master/COPYING
atomic	https://github.com/uber-go/atomic	https://github.com/uber-go/atomic/blob/master/LICENSE.txt

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Table 1 – continued from previous page

Name of Project	Website	License URL
atomicwrites	https://github.com/untitaker/python-atomicwrites	https://github.com/untitaker/python-atomicwrites/blob/master/LICENSE
attrs	https://www.attrs.org/	https://github.com/python-attrs/attrs/blob/main/LICENSE
aws-sdk-go	https://github.com/aws/aws-sdk-go	https://github.com/aws/aws-sdk-go/blob/master/LICENSE.txt
babel	https://babel.pocoo.org/ OR https://github.com/python-babel/babel	https://github.com/python-babel/babel/blob/master/LICENSE OR https://babel.pocoo.org/en/latest/license.html#babel-license
Babel	https://github.com/python-babel/babel	https://github.com/python-babel/babel/blob/master/LICENSE
backcall	https://github.com/takluyver/backcall	https://github.com/takluyver/backcall/blob/master/LICENSE
backports	https://github.com/brandon-rhodes/backports	https://github.com/brandon-rhodes/backports/blob/master/LICENSE.TXT
backports.functools-lru-cache	https://github.com/jaraco/backports.functools_lru_cache	https://github.com/jaraco/backports.functools_lru_cache/blob/main/LICENSE
backports.zstd	https://github.com/rogdham/backports.zstd	https://github.com/rogdham/backports.zstd?tab=License-1-ov-file#readme
base62	https://github.com/kare/base62	https://github.com/kare/base62/blob/main/LICENSE
beautifulsoup4	https://www.crummy.com/software/BeautifulSoup/	https://www.crummy.com/software/BeautifulSoup/

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Table 1 – continued from previous page

Name of Project	Website	License URL
billiard	https://github.com/celery/billiard	https://github.com/celery/billiard/blob/master/LICENSE.txt
biopython	https://biopython.org	https://github.com/biopython/biopython/blob/master/LICENSE.rst
biotite	https://github.com/biotite-dev/biotite/blob/master/README.rst	https://github.com/biotite-dev/biotite/blob/master/LICENSE.rst
bitarray	https://github.com/ilanschnell/bitarray	https://github.com/ilanschnell/bitarray/blob/master/LICENSE
bitset	https://github.com/willf/bitset	https://github.com/willf/bitset/blob/master/LICENSE
blas	https://www.netlib.org/blas/	https://www.netlib.org/blas/#_licensing
bleach	https://github.com/mozilla/bleach	https://github.com/mozilla/bleach/blob/main/LICENSE
blessings	https://github.com/erikrose/blessings	https://github.com/erikrose/blessings/blob/master/LICENSE
blinker	https://pythonhosted.org/blinker/	https://github.com/pallets-eco/blinker/blob/master/LICENSE
bokeh	https://github.com/bokeh/bokeh	https://github.com/bokeh/bokeh/blob/branch-4.0/LICENSE.txt
blosc	https://github.com/Blosc/python-blosc	https://github.com/Blosc/python-blosc/blob/master/LICENSE.txt
blosc2	https://github.com/Blosc/python-blosc2	https://github.com/Blosc/c-blosc2/blob/main/LICENSE.txt

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Table 1 – continued from previous page

Name of Project	Website	License URL
boltons	https://github.com/mahmoud/boltons	https://github.com/mahmoud/boltons/blob/master/LICENSE
Boltz	https://boltz.bio	https://github.com/jwohlwend/boltz/blob/main/LICENSE
boost	https://www.boost.org/doc/libs/1_71_0/libs/python/doc/html/index.html	https://www.boost.org/LICENSE_1_0.txt
boost-cpp	https://www.boost.org/doc/libs/1_71_0/libs/python/doc/html/index.html	https://www.boost.org/LICENSE_1_0.txt
bootstrap-vue	https://github.com/bootstrap-vue/bootstrap-vue	https://github.com/bootstrap-vue/bootstrap-vue/raw/master/LICENSE
boto3	https://github.com/boto/boto3	https://github.com/boto/boto3/blob/develop/LICENSE
botocore	https://github.com/boto/botocore	https://github.com/boto/botocore/blob/develop/LICENSE.txt
Bottleneck	https://bottleneck.readthedocs.io/en/latest/index.html	https://bottleneck.readthedocs.io/en/latest/license.html
Brotli	https://github.com/google/brotli	https://github.com/google/brotli/blob/master/LICENSE
brotli-bin	https://github.com/google/brotli	https://github.com/google/brotli/blob/master/LICENSE
brotli-python	http://python-hyper.org/projects/brotlipy/en/latest/	https://github.com/python-hyper/brotlicffi/blob/main/LICENSE
brotlicffi	https://github.com/python-hyper/brotlicffi	https://github.com/python-hyper/brotlicffi?tab=MIT-1-ov-file#readme
brotlipy	https://github.com/python-hyper/brotlicffi	https://github.com/python-hyper/brotlicffi/blob/main/LICENSE

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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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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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Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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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Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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-file#readme

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Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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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Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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		

continues on next page

Table 1 – continued from previous page

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

continues on next page

Table 1 – continued from previous page

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		

continues on next page

Table 1 – continued from previous page

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

continues on next page

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

continues on next page

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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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

14.1 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).

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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.

14.1.1 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␣
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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.

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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␣
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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

14.1.2 GNU GENERAL PUBLIC LICENSE

```
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                       Version 3, 29 June 2007

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  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
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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.

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  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
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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
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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.

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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
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Component, and (b) serves only to enable use of the work with that
Major Component, or to implement a Standard Interface for which an
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"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
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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.

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   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,
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    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
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  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.

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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,
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INDEX

Symbols

-addbox
    ReceptorInDU command line option, 69
-allowedClashes
    combine_receptors command line option, 87
-allowed_clashes
    posit command line option, 51
-annotate_scores
    fred command line option, 33
    hybrid command line option, 43
    scorepose command line option, 80
-best_Receptor_Pose_Only
    posit command line option, 52
-box
    ReceptorInDU command line option, 69
-clashed_molecule_file
    posit command line option, 54
-clear_score_cache
    receptor_toolbox command line option, 82
-dbase
    fred command line option, 30
    hybrid command line option, 39
    posit command line option, 49
    scorepose command line option, 76
-disable_all_custom_constraints
    receptor_toolbox command line option, 83
-disable_all_protein_constraints
    receptor_toolbox command line option, 82
-disable_custom_constraint
    receptor_toolbox command line option, 83
-disable_protein_constraint
    receptor_toolbox command line option, 82
-dock_resolution
    fred command line option, 31
    hybrid command line option, 39
-docked_molecule_file
    fred command line option, 31
    hybrid command line option, 40
    posit command line option, 52
-docked_poses
    docking_report command line option, 73
-enable_all_custom_constraints
    receptor_toolbox command line option, 83
-enable_all_protein_constraints
    receptor_toolbox command line option, 82
-enable_custom_constraint
    receptor_toolbox command line option, 83
-enable_protein_constraint
    receptor_toolbox command line option, 82
-extract_custom_constraints
    receptor_toolbox command line option, 83
-hitlist_size
    fred command line option, 33
    hybrid command line option, 42
    scorepose command line option, 79
-ignore_nitrogen_stereo
    posit command line option, 50
-in
    DU2OEBReceptor command line option, 88
    OEB2DUReceptor command line option, 70
    posit command line option, 49
    ReceptorInDU command line option, 68
-minimum_probability
    posit command line option, 51
-molnames
    DU2OEBReceptor command line option, 88
    fred command line option, 30
    hybrid command line option, 39
    OEB2DUReceptor command line option, 70
    posit command line option, 50
    ReceptorInDU command line option, 68
    scorepose command line option, 77
-mpi_hostfile
    posit command line option, 50
-mpi_np
    posit command line option, 50
-names
    docking_report command line option, 74
-negImageType
    ReceptorInDU command line option, 69
-no_dots
    fred command line option, 34
    hybrid command line option, 43
    posit command line option, 54

scorepose command line option, 80
-no_extra_output_files
fred command line option, 34
hybrid command line option, 43
posit command line option, 54
scorepose command line option, 80
-nostructs
fred command line option, 34
hybrid command line option, 43
-num_poses
fred command line option, 33
hybrid command line option, 42
posit command line option, 52
-optimize
scorepose command line option, 77
-out
DU2OEBReceptor command line option, 89
OEB2DUReceptor command line option, 71
ReceptorInDU command line option, 68
-outputall
posit command line option, 55
-outputdir
combine_receptors command line option, 87
-param
combine_receptors command line option, 87
fred command line option, 30
hybrid command line option, 39
posit command line option, 50
scorepose command line option, 77
-prefix
combine_receptors command line option, 87
DU2OEBReceptor command line option, 89
fred command line option, 34
hybrid command line option, 43
OEB2DUReceptor command line option, 71
posit command line option, 55
ReceptorInDU command line option, 68
scorepose command line option, 78
-prepare_score_cache
receptor_toolbox command line option, 82
-progress
DU2OEBReceptor command line option, 89
OEB2DUReceptor command line option, 71
ReceptorInDU command line option, 68
-receptor
docking_report command line option, 74
fred command line option, 30
hybrid command line option, 38
posit command line option, 49
receptor_toolbox command line option, 81
scorepose command line option, 76
-receptors
combine_receptors command line option, 86
-rejected_file
posit command line option, 53
-relax
posit command line option, 51
-report_file
docking_report command line option, 74
fred command line option, 32
hybrid command line option, 41
posit command line option, 53
scorepose command line option, 79
-rescored_molecule_file
scorepose command line option, 78
-save_component_scores
fred command line option, 34
hybrid command line option, 43
scorepose command line option, 80
-score_file
fred command line option, 32
hybrid command line option, 41
posit command line option, 53
scorepose command line option, 78
-score_tag
fred command line option, 33
hybrid command line option, 42
posit command line option, 54
scorepose command line option, 80
-sd_tags
docking_report command line option, 74
-set_custom_constraints
receptor_toolbox command line option, 83
-settings_file
fred command line option, 32
hybrid command line option, 41
posit command line option, 54
scorepose command line option, 79
-smiles_file
docking_report command line option, 74
-sort_poses
scorepose command line option, 80
-status_file
fred command line option, 32
hybrid command line option, 42
posit command line option, 53
scorepose command line option, 79
-targetMask
ReceptorInDU command line option, 68
-targetPred
ReceptorInDU command line option, 69
-turn_inner_contour
receptor_toolbox command line option, 82
-undocked_molecule_file
fred command line option, 31
hybrid command line option, 41
posit command line option, 53
-verbose

combine_receptors command line option, 87
posit command line option, 55

C

combine_receptors command line option
-allowedClashes, 87
-outputdir, 87
-param, 87
-prefix, 87
-receptors, 86
-verbose, 87

D

docking_report command line option
-docked_poses, 73
-names, 74
-receptor, 74
-report_file, 74
-sd_tags, 74
-smiles_file, 74
DU2OEBReceptor command line option
-in, 88
-molnames, 88
-out, 89
-prefix, 89
-progress, 89

F

fred command line option
-annotate_scores, 33
-dbase, 30
-dock_resolution, 31
-docked_molecule_file, 31
-hitlist_size, 33
-molnames, 30
-no_dots, 34
-no_extra_output_files, 34
-nostructs, 34
-num_poses, 33
-param, 30
-prefix, 34
-receptor, 30
-report_file, 32
-save_component_scores, 34
-score_file, 32
-score_tag, 33
-settings_file, 32
-status_file, 32
-undocked_molecule_file, 31

H

hybrid command line option
-annotate_scores, 43
-dbase, 39
-dock_resolution, 39
-docked_molecule_file, 40
-hitlist_size, 42
-molnames, 39
-no_dots, 43
-no_extra_output_files, 43
-nostructs, 43
-num_poses, 42
-param, 39
-prefix, 43
-receptor, 38
-report_file, 41
-save_component_scores, 43
-score_file, 41
-score_tag, 42
-settings_file, 41
-status_file, 42
-undocked_molecule_file, 41

O

OEB2DUReceptor command line option
-in, 70
-molnames, 70
-out, 71
-prefix, 71
-progress, 71

P

posit command line option
-allowed_clashes, 51
-best_Receptor_Pose_Only, 52
-clashed_molecule_file, 54
-dbase, 49
-docked_molecule_file, 52
-ignore_nitrogen_stereo, 50
-in, 49
-minimum_probability, 51
-molnames, 50
-mpi_hostfile, 50
-mpi_np, 50
-no_dots, 54
-no_extra_output_files, 54
-num_poses, 52
-outputall, 55
-param, 50
-prefix, 55
-receptor, 49
-rejected_file, 53
-relax, 51
-report_file, 53
-score_file, 53
-score_tag, 54
-settings_file, 54

-status_file, 53
-undocked_molecule_file, 53
-verbose, 55

R

receptor_toolbox command line option
-clear_score_cache, 82
-disable_all_custom_constraints, 83
-disable_all_protein_constraints, 82
-disable_custom_constraint, 83
-disable_protein_constraint, 82
-enable_all_custom_constraints, 83
-enable_all_protein_constraints, 82
-enable_custom_constraint, 83
-enable_protein_constraint, 82
-extract_custom_constraints, 83
-prepare_score_cache, 82
-receptor, 81
-set_custom_constraints, 83
-turn_inner_contour, 82
scorepose, 82
ReceptorInDU command line option
-addbox, 69
-box, 69
-in, 68
-molnames, 68
-negImageType, 69
-out, 68
-prefix, 68
-progress, 68
-targetMask, 68
-targetPred, 69

S

scorepose
receptor_toolbox command line option, 82
scorepose command line option
-annotate_scores, 80
-dbase, 76
-hitlist_size, 79
-molnames, 77
-no_dots, 80
-no_extra_output_files, 80
-optimize, 77
-param, 77
-prefix, 78
-receptor, 76
-report_file, 79
-rescored_molecule_file, 78
-save_component_scores, 80
-score_file, 78
-score_tag, 80
-settings_file, 79
-sort_poses, 80
-status_file, 79