Glide 6.7

User Manual

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Contents

Document Conventions

In addition to the use of italics for names of documents, the font conventions that are used in this document are summarized in the table below.

Font	Example	Use
Sans serif	Project Table	Names of GUI features, such as panels, menus, menu items, buttons, and labels
Monospace	`$SCHRODINGER/maestro`	File names, directory names, commands, environment variables, command input and output
Italic	*filename*	Text that the user must replace with a value
Sans serif uppercase	CTRL+H	Keyboard keys

Links to other locations in the current document or to other PDF documents are colored like this: Document Conventions.

In descriptions of command syntax, the following UNIX conventions are used: braces { } enclose a choice of required items, square brackets [ ] enclose optional items, and the bar symbol | separates items in a list from which one item must be chosen. Lines of command syntax that wrap should be interpreted as a single command.

File name, path, and environment variable syntax is generally given with the UNIX conventions. To obtain the Windows conventions, replace the forward slash / with the backslash \ in path or directory names, and replace the $ at the beginning of an environment variable with a % at each end. For example, `$SCHRODINGER/maestro` becomes `%SCHRODINGER%\maestro`.

Keyboard references are given in the Windows convention by default, with Mac equivalents in parentheses, for example CTRL+H (⌘H). Where Mac equivalents are not given, COMMAND should be read in place of CTRL. The convention CTRL-H is not used.

In this document, to *type* text means to type the required text in the specified location, and to *enter* text means to type the required text, then press the ENTER key.

References to literature sources are given in square brackets, like this: [10].

Introduction

The *Glide User Manual* is intended to help you perform ligand database screening and high-accuracy docking with Glide. Glide is run primarily from the Maestro graphical user interface, but can also be run from the command line. Online help for Glide is available in Maestro, although the information in this manual is generally more comprehensive.

Chapter 2 introduces the scientific methods and computational procedures used in Glide.

Chapter 3 describes the preparation of the protein and the ligands for use in Glide.

Chapter 4 describes the use of the Receptor Grid Generation panel to calculate the grids that represent the receptor.

Chapter 5 describes the use of the Ligand Docking panel to set up and run docking jobs, and the use of Glide constraints and distributed processing of multiple-ligand docking calculations.

Chapter 6 contains information on visualizing the results of Glide docking runs, using the Pose View mode in the Project Table and the Glide XP Visualizer.

Chapter 7 contains information about running Glide, and its associated applications and utilities, from the command line.

The *Glide Quick Start Guide* contains tutorials intended to familiarize you with protein preparation, receptor grid generation, ligand docking, and viewing poses.

1.1 Running Schrödinger Software

Schrödinger applications can be run from a graphical interface or from the command line. The software writes input and output files to a directory (folder) which is termed the *working directory*. If you run applications from the command line, the directory from which you run the application is the working directory for the job.

Linux:

To run any Schrödinger program on a Linux platform, or start a Schrödinger job on a remote host from a Linux platform, you must first set the `SCHRODINGER` environment variable to the

installation directory for your Schrödinger software. To set this variable, enter the following command at a shell prompt:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

Once you have set the `SCHRODINGER` environment variable, you can run programs and utilities with the following commands:

```
$SCHRODINGER/program &
$SCHRODINGER/utilities/utility &
```

You can start the Maestro interface with the following command:

```
$SCHRODINGER/maestro &
```

It is usually a good idea to change to the desired working directory before starting the Maestro interface. This directory then becomes the working directory.

Windows:

The primary way of running Schrödinger applications on a Windows platform is from a graphical interface. To start the Maestro interface, double-click on the Maestro icon, on a Maestro project, or on a structure file; or choose Start → All Programs → Schrodinger-2015-2 → Maestro. You do not need to make any settings before starting Maestro or running programs. The default working directory is the Schrodinger folder in your Documents folder.

If you want to run applications from the command line, you can do so in one of the shells that are provided with the installation and have the Schrödinger environment set up:

- Schrödinger Command Prompt—DOS shell.
- Schrödinger Power Shell—Windows Power Shell (if available).

You can open these shells from Start → All Programs → Schrodinger-2015-2. You do not need to include the path to a program or utility when you type the command to run it. If you want access to Unix-style utilities (such as `awk`, `grep`, and `sed`), preface the commands with `sh`, or type `sh` in either of these shells to start a Unix-style shell.

Mac:

The primary way of running Schrödinger software on a Mac is from a graphical interface. To start the Maestro interface, click its icon on the dock. If there is no Maestro icon on the dock, you can put one there by dragging it from the SchrodingerSuite2015-2 folder in your Applications folder. This folder contains icons for all the available interfaces. The default working

directory is the Schrodinger folder in your Documents folder (`$HOME/Documents/Schrodinger`).

Running software from the command line is similar to Linux—open a terminal window and run the program. You can also start Maestro from the command line in the same way as on Linux. The default working directory is then the directory from which you start Maestro. You do not need to set the `SCHRODINGER` environment variable, as this is set in your default environment on installation. To set other variables, on OS X 10.7 use the command

`defaults write ~/.MacOSX/environment` *variable* `"`*value*`"`

and on OS X 10.8, 10.9, and 10.10 use the command

`launchctl setenv` *variable* `"`*value*`"`

1.2 Starting Jobs from the Maestro Interface

To run a job from the Maestro interface, you open a panel from one of the menus (e.g. Tasks), make settings, and then submit the job to a host or a queueing system for execution. The panel settings are described in the help topics and in the user manuals. When you have finished making settings, you can use the Job toolbar to start the job.

You can start a job immediately by clicking Run. The job is run on the currently selected host with the current job settings and the job name in the Job name text box. If you want to change the job name, you can edit it in the text box before starting the job. Details of the job settings are reported in the status bar, which is below the Job toolbar.

If you want to change the job settings, such as the host on which to run the job and the number of processors to use, click the Settings button. (You can also click the arrow next to the button and choose Job Settings from the menu that is displayed.)

You can then make the settings in the Job Settings dialog box, and choose to just save the settings by clicking OK, or save the settings and start the job by clicking Run. These settings apply only to jobs that are started from the current panel.

If you want to save the input files for the job but not run it, click the Settings button and choose Write. A dialog box opens in which you can provide the job name, which is used to name the files. The files are written to the current working directory.

The Settings button also allows you to change the panel settings. You can choose Read, to read settings from an input file for the job and apply them to the panel, or you can choose Reset Panel to reset all the panel settings to their default values.

You can also set preferences for all jobs and how the interface interacts with the job at various stages. This is done in the Preferences panel, which you can open at the Jobs section by choosing Preferences from the Settings button menu.

Note: The items present on the Settings menu can vary with the application. The descriptions above cover all of the items.

The icon on the Job Status button shows the status of jobs for the application that belong to the current project. It starts spinning when the first job is successfully launched, and stops spinning when the last job finishes. It changes to an exclamation point if a job is not launched successfully.

Clicking the button shows a small job status window that lists the job name and status for all active jobs submitted for the application from the current project, and a summary message at the bottom. The rows are colored according to the status: yellow for submitted, green for launched, running, or finished, red for incorporated, died, or killed. You can double-click on a row to open the Monitor panel and monitor the job, or click the Monitor button to open the Monitor panel and close the job status window. The job status is updated while the window is open. If a job finishes while the window is open, the job remains displayed but with the new status. Click anywhere outside the window to close it.

Jobs are run under the Job Control facility, which manages the details of starting the job, transferring files, checking on status, and so on. For more information about this facility and how it operates, as well as details of the Job Settings dialog box, see the *Job Control Guide*.

1.3 Using Glide

The Glide task most frequently performed is ligand docking. The grid files produced by a single receptor grid generation task can be used for any number of jobs that dock ligands to that receptor. Before generating receptor grids, it is strongly recommended that you prepare the protein. Therefore, the first steps of a typical project beginning with an unprepared protein-ligand complex structure (e.g., from PDB) might proceed using the Glide panels as follows:

1. Prepare the receptor using the Protein Preparation Wizard panel. See Chapter 3 for details.
2. Ensure that the ligands to be docked are in the right form. See Chapter 3 for details.

3. With the prepared receptor-ligand complex in the Workspace, use the Receptor Grid Generation panel to specify settings, optionally define constraints, and start the receptor grid generation job. Details of setting up receptor grid generation jobs are given in Chapter 4.
4. Specify the base name for the receptor grid files you want to use in the Ligand Docking panel, and use the other settings and options in the panel to set up and start a ligand docking job. As many docking jobs as you want can be set up in this panel, using the current receptor grids or specifying a different set of grids to use. Details of setting up ligand docking jobs are given in Chapter 5.

1.4 Documentation

For information related to the installation and use of Glide, see the following documentation:

- The *Installation Guide*, which includes installation instructions for all Schrödinger products and documentation.
- The *Job Control Guide*, which includes instructions for running and managing Schrödinger jobs.
- The *Glide Quick Start Guide*, which contains tutorials intended to familiarize you with receptor grid generation, ligand docking, and visualization of results.
- The *Impact Command Reference Manual*, which contains syntax and keywords for Impact command input files.
- The *Maestro User Manual*, which describes how to use the features of Maestro, including the Atom Selection dialog box.
- The *Maestro Command Reference Manual*, which contains commands, options, and arguments for running Maestro from the command line, including the Atom Specification Language (ASL) and the Entry Specification Language (ESL).

1.5 Citing Glide in Publications

The use of this product should be acknowledged in publications as:

Glide, version 6.7, Schrödinger, LLC, New York, NY, 2015.

In addition, please cite the following papers:

- Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shaw, D. E.; Shelley, M.; Perry, J. K.; Francis, P.; Shenkin, P. S. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy, *J. Med. Chem.* **2004**, *47*, 1739-1749.

- Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 2. Enrichment Factors in Database Screening. *J. Med. Chem.* **2004**, *47*, 1750–1759.
- Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D. T. Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes. *J. Med. Chem.* **2006**, *49*, 6177–6196.

Glide Overview

This chapter contains an overview of the Glide (Grid-based Ligand Docking with Energetics) program, its scientific methods and computational procedures.

Glide searches for favorable interactions between one or more ligand molecules and a receptor molecule, usually a protein. Each ligand must be a single molecule, while the receptor may include more than one molecule, e.g., a protein and a cofactor. Glide can be run in rigid or flexible docking modes; the latter automatically generates conformations for each input ligand. The combination of position and orientation of a ligand relative to the receptor, along with its conformation in flexible docking, is referred to as a *ligand pose*.

The ligand poses that Glide generates pass through a series of hierarchical filters that evaluate the ligand's interaction with the receptor. The initial filters test the spatial fit of the ligand to the defined active site, and examine the complementarity of ligand-receptor interactions using a grid-based method patterned after the empirical ChemScore function [1].

Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of a grid approximation to the OPLS-AA nonbonded ligand-receptor interaction energy.

Final scoring is then carried out on the energy-minimized poses. By default, Schrödinger's proprietary GlideScore multi-ligand scoring function is used to score the poses. If GlideScore was selected as the scoring function, a composite *Emodel* score is then used to rank the poses of each ligand and to select the poses to be reported to the user. Emodel combines GlideScore, the nonbonded interaction energy, and, for flexible docking, the excess internal energy of the generated ligand conformation.

2.1 Introduction to Glide

Glide uses a hierarchical series of filters to search for possible locations of the ligand in the active-site region of the receptor. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses.

Conformational flexibility is handled in Glide by an extensive conformational search, augmented by a heuristic screen that rapidly eliminates unsuitable conformations, such as conformations that have long-range internal hydrogen bonds.

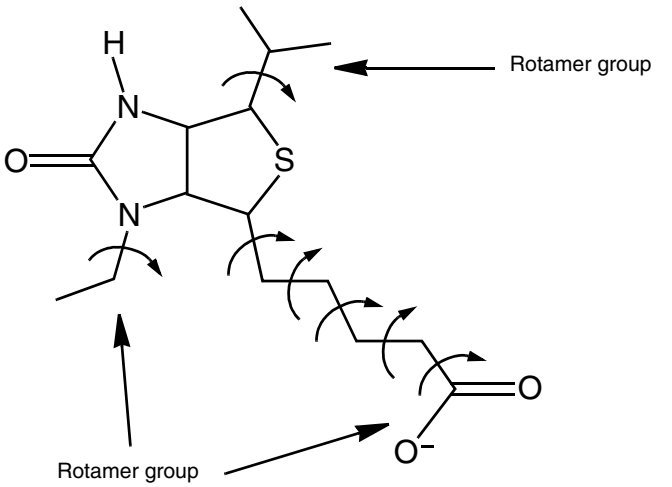

Figure 2.1. Definition of core and rotamer groups.

As illustrated in Figure 2.1, each ligand is divided into a *core* region and some number of *rotamer groups*. Each rotamer group is attached to the core by a rotatable bond, but does not contain additional rotatable bonds. The core is what remains when each terminus of the ligand is severed at the "last" rotatable bond. Carbon and nitrogen end groups terminated with hydrogen (—CH_3, —NH_2, —NH_3^+) are not considered rotatable because their conformational variation is of little significance. In Figure 2.1, the four central torsions are part of the core, and the methyl groups are not considered rotatable.

During conformation generation, each core region is represented by a set of core conformations, the number of which depends on the number of rotatable bonds, conformationally labile 5– and 6–membered rings, and asymmetric pyramidal trigonal nitrogen centers in the core. This set typically contains fewer than 500 core conformations, even for quite large and flexible ligands, and far fewer for more rigid ligands. Every rotamer state for each rotamer group attached to the core is enumerated. The core plus all possible rotamer-group conformations is docked as a single object. Glide can also dock sets of pre-computed conformations. However, Glide offers its greatest value when conformations are generated internally.

For each core conformation (or for rigid docking, each ligand), an exhaustive search of possible locations and orientations is performed over the active site of the protein. The search begins with the selection of "site points" on an equally spaced 2 Å grid that covers the active-site region (Stage 1 in Figure 2.2). This selection is made as follows. Distances from the site point to the receptor surface are evaluated at a series of pre-specified directions and sorted into

distance ranges (“bins”) of width 1 Å. Likewise, distances from the ligand center (the midpoint of the two most widely separated atoms) to the ligand surface are sorted into bins of width 1 Å. For a given site point, the distance ranges from the site point to the receptor are compared with those from the ligand center to the ligand surface. Glide positions the ligand center at the site point if there is a good enough match, but skips over the site point if there is not.

The second stage of the hierarchy begins by examining the placement of atoms that lie within a specified distance of the line drawn between the most widely separated atoms (the *ligand diameter*). This is done for a pre-specified selection of possible orientations of the ligand diameter (Step 2a). If there are too many steric clashes with the receptor, the orientation is skipped.

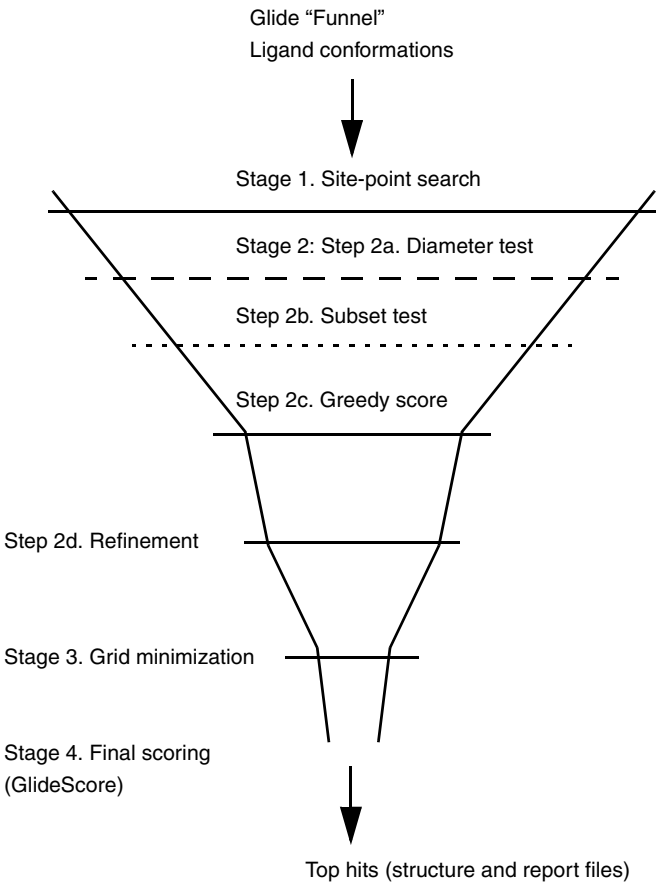

Figure 2.2. The Glide docking hierarchy.

Next (Step 2b), rotation about the ligand diameter is considered, and the interactions of a subset consisting of all atoms capable of making hydrogen bonds or ligand-metal interactions with the receptor are scored (*subset test*). If this score is good enough, all interactions with the receptor are scored (Step 2c).

The scoring in these three tests is carried out using Schrödinger's discretized version of the ChemScore empirical scoring function [1]. Much as for ChemScore itself, this algorithm recognizes favorable hydrophobic, hydrogen-bonding, and metal-ligation interactions, and penalizes steric clashes. This stage is called "greedy scoring," because the actual score for each atom depends not only on its position relative to the receptor but also on the best possible score it could get by moving ±1 Å in *x*, *y*, or *z*. This is done to mute the sting of the large 2 Å jumps in the site-point/ligand-center positions. The final step in Stage 2 is to re-score the top greedy-scoring poses via a "refinement" procedure (Step 2d), in which the ligand as a whole is allowed to move rigidly by ±1 Å in the Cartesian directions.

Only a small number of the best refined poses (typically 100-400) is passed on to the third stage in the hierarchy—energy minimization on the pre-computed OPLS van der Waals and electrostatic grids for the receptor. The energy minimization typically begins on a set of van der Waals and electrostatic grids that have been "smoothed" to reduce the large energy and gradient terms that result from too-close interatomic contacts. It finishes on the full-scale OPLS nonbonded energy surface ("annealing"). This energy minimization consists only of rigid-body translations and rotations when external conformations are docked. When conformations are generated internally, however, the optimization also includes torsional motion about the core and end-group rotatable bonds. Unless otherwise specified, a small number of the top-ranked poses are then subjected to a sampling procedure in which alternative local-minima core and rotamer-group torsion angles are examined to try to improve the energy score.

Finally, the minimized poses are re-scored using Schrödinger's proprietary *GlideScore* scoring function. GlideScore is based on ChemScore, but includes a steric-clash term, adds other rewards and penalties such as buried polar terms (devised by Schrödinger to penalize electrostatic mismatches), amide twist penalties, hydrophobic enclosure terms, and excluded volume penalties, and has modifications to other terms:

GScore = 0.05*vdW + 0.15*Coul + Lipo + Hbond + Metal + Rewards + RotB + Site

The components of the GlideScore (GScore) are described in Table 2.1.

The choice of best-docked structure for each ligand is made using a model energy score (*Emodel*) that combines the energy grid score, the binding affinity predicted by GlideScore, and (for flexible docking) the internal strain energy for the model potential used to direct the conformational-search algorithm. Glide also computes a specially constructed Coulomb-van der Waals interaction-energy score (CvdW) that is formulated to avoid overly rewarding charge-charge interactions at the expense of charge-dipole and dipole-dipole interactions. This

Table 2.1. GlideScore components.

Component	Description
vdW	Van der Waals energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Coul	Coulomb energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.
Lipo	Lipophilic term, which is a pairwise term in SP but is derived from the hydrophobic grid potential for XP. Rewards favorable hydrophobic interactions.
HBond	Hydrogen-bonding term. This term is separated into differently weighted components that depend on whether the donor and acceptor are neutral, one is neutral and the other is charged, or both are charged.
Metal	Metal-binding term. Only the interactions with anionic or highly polar acceptor atoms are included. If the net metal charge in the apo protein is positive, the preference for anionic or polar ligands is included; if the net charge is zero, the preference is suppressed.
Rewards	Rewards and penalties for various features, such as buried polar groups, hydrophobic enclosure, correlated hydrogen bonds, amide twists, and so on. This category covers all terms other than those explicitly mentioned.
RotB	Penalty for freezing rotatable bonds.
Site	Polar interactions in the active site. Polar but non-hydrogen-bonding atoms in a hydrophobic region are rewarded.

score is intended to be more suitable for comparing the binding affinities of different ligands than is the "raw" Coulomb-van der Waals interaction energy. In addition to the GlideScore, a "docking score" is reported, which is the GlideScore supplemented by Epik state penalties, if used, and strain corrections, if used.

This hierarchical search gives Glide exceptionally high accuracy in predicting the binding mode of the ligand. At the same time, the computational cost is dramatically reduced compared to what would be required for a complete systematic search. The key to this reduction is that the algorithm allows the rotamer groups to be optimized one at a time for a given core conformation and location of the ligand. For example, if there are five rotamer groups and each has three rotamer states, the total number of conformers in the ensemble based on this core conformation/location is $3^5 = 243$. However, if the rotamer groups are optimized one at a time, the number of conformational combinations is only $3 \times 5 = 15$, for a savings of about a factor of 15 in computational effort. While many other time-saving algorithms in Glide contribute to its performance advantages, this fundamental qualitative feature allows large libraries to be screened at an affordable computational cost.

2.2 Glide Constraints

A *Glide constraint* is a ligand-receptor interaction requirement. The constraint usually means that a ligand atom must lie within a certain region defined in relation to features of the receptor that are responsible for ligand binding. To use Glide constraints, you must specify receptor sites for possible ligand interactions when you set up a receptor grid generation job. When you run a ligand docking job, you can select Glide constraints to apply from the list of receptor constraint sites that you defined for the receptor.

Other constraints that reflect ligand-receptor interactions indirectly are applied during docking. These include superposition of the ligand core on a reference core, and restriction of specified ligand torsions.

In Glide constraint docking jobs, Glide incorporates satisfaction of these constraints into several of its hierarchical filters, allowing prompt rejection of docked poses that fail to meet the requirements.

The first constraint filter is a simple one involving the atoms of the ligand. If a ligand does not contain atoms of the right types to make the required interactions with the receptor constraint atoms, Glide simply skips that ligand—for instance if a selected receptor constraint atom is a polar hydrogen and the ligand has no hydrogen-bond acceptors. If there are qualifying atoms in the ligand, Glide keeps a list of the possible "partner atoms" for each constraint, for use in subsequent filters. For hydrophobic constraints, this filter checks that the ligand contains a sufficient number of hydrophobic heavy atoms; the sum of the minimum numbers specified for all the selected constraints of this type. In addition, Glide locates centroids of ligand hydrophobic groups, which take the role of partner atoms in subsequent filters.

Other filters operate further down the funnel. These include matching distances between partner atoms (or hydrophobic group centroids) for different constraints against the corresponding distances between receptor atoms; matching distances from the ligand center to partner atoms against those from receptor site points to constraint atoms, and restricting orientations of, and rotations about, the ligand diameter to those that bring partner atoms into appropriate proximity with receptor atoms or regions. In addition, a restraining potential is used in grid optimizations (for hydrogen-bond and metal constraints only) to bring or keep constraint-satisfying ligand-receptor atom pairs at appropriate distances, and torsional sampling moves are not tried if they would move any ligand atom currently in a constraint-satisfying position. Finally, grid-optimized poses are rejected if they don't strictly satisfy all selected constraints.

Core constraints are applied by a "snap and refine" algorithm. The core pattern is identified in the ligand, and the matching atoms are placed at exactly the same coordinates as the reference ligand. The rest of the molecule is rebuilt, preserving the internal coordinates of the non-core atoms. The rotatable bonds are then sampled, and passed through rough scoring, but the refine-

ment part is skipped, as the core is placed exactly and no translation of the ligand is needed. The refinement (grid minimization) is performed, in which the non-core torsions are minimized, and sampling of torsions is then applied to improve poses, if possible. Finally, post-docking minimization is performed, with steep, flat-bottomed constraints on the core atoms. This last step may change the RMSD with respect to the reference core; prior to that, it is zero.

For information on using Glide constraints, see Section 4.4, Section 4.6, Section 5.5, Section 5.6, and Section 5.7.

2.3 Glide Extra-Precision Mode

The extra-precision (XP) mode of Glide combines a powerful sampling protocol with the use of a custom scoring function designed to identify ligand poses that would be expected to have unfavorable energies, based on well-known principles of physical chemistry. The presumption is that only active compounds will have available poses that avoid these penalties and also receive favorable scores for appropriate hydrophobic contact between the protein and the ligand, hydrogen-bonding interactions, and so on. The chief purposes of the XP method are to weed out false positives and to provide a better correlation between good poses and good scores.

Extra-precision mode is a refinement tool designed for use only on good ligand poses. The more extensive XP docking method and specialized XP scoring method are strongly coupled: the more precise poses produced by XP docking are necessary for the more demanding XP scoring method. Because XP docking mode requires considerably more CPU time, you should screen large sets of ligands first in standard-precision (SP) mode or in high-throughput virtual screening (HTVS) mode. Only the top-scoring ligands should be docked using XP mode.

In any grid-based docking method, the receptor is essentially frozen. Some degree of flexibility can be introduced by scaling parts of the potential, as is done in SP mode, but such techniques cannot represent larger adjustments to the receptor, like conformational changes. XP mode is less forgiving than SP mode so that it can screen out false positives, and is designed to locate active compounds that bind to a particular conformation of the receptor. Active compounds can be prevented from docking if these compounds are not compatible with the particular conformation of the receptor that is being used. To ensure that actives are not eliminated you should if possible dock into multiple receptor conformations and combine the results of the individual docking runs.

The XP sampling method is based on an anchor and refined growth strategy. Anchor fragments of the docked ligand, typically rings, are chosen from the set of SP poses and the molecule is re-grown bond by bond from these anchor positions. Complete minimizations and XP scoring are carried out on the large ensemble of poses generated by this growing method. At various cycles the growing is focused to attempt to relieve any XP scoring penalties as well as to opti-

mize the best scoring poses. This focused sampling is essential for allowing the use of the hard XP scoring function as well as for finding the best scoring basins of attraction. It is important to note that the coupling between the extra sampling and the XP scoring means that it is not recommended to just score the SP poses with XP scoring.

The scoring function (GlideScore XP) includes additional terms over the SP scoring function, and a more complete treatment of some of the SP terms, as described below.

To model solvation, explicit water molecules are docked into a list of protein-ligand complexes that otherwise receive good GlideScores, and descriptors based on the interaction of these water molecules with various charged and polar groups of the ligand and protein are used as a measure of whether the complex is physically realistic. Penalties are assigned to structures where statistical results indicate that one or more groups is inadequately solvated. A large database of co-crystallized structures has been used to optimize the parameters associated with the penalty terms. The explicit-water technology and descriptors are also used in Glide SP scoring. However, the improved sampling allows XP docking to assign substantially higher penalties to serious violations of physical principles.

GlideScore XP specifically rewards occupancy of well-defined hydrophobic pockets by hydrophobic ligand groups. Hydrophobic reward terms are employed in empirical scoring functions such as ChemScore and the SP version of GlideScore in the form of lipophilic-lipophilic pair terms, while other empirical scoring functions use lipophilic surface-area contact terms for this purpose. Investigations have shown that simple pair terms underestimate hydrophobic effects in certain well-defined cases. The hydrophobic term in GlideScore XP was developed to offset this underestimation. The term can confer up to several kcal/mol of additional binding energy in favorable cases, and substantially improves enrichment factors GlideScore XP also includes improvements to the scoring of hydrogen bonds as well as detection of buried polar groups, and detection of pi-cation and pi-pi stacking interactions.

For information on using XP mode, see Section 5.4. For information on visualizing the various XP scoring terms, see Section 6.2.

2.4 Glide/Prime Induced Fit Docking

Glide docking uses the basic assumption of a rigid receptor. Scaling of van der Waals radii of nonpolar atoms, which decreases penalties for close contacts, can be used to model a slight “give” in the receptor or the ligand or both, and specified hydroxyl groups can be allowed to reorient to optimize hydrogen bonding. This may not be sufficient to treat systems where ligand binding induces substantial conformation changes in the receptor (“induced fit”). Schrödinger has developed a procedure for such cases which uses Prime and Glide to perform induced fit docking. For more information about Schrödinger’s Induced Fit Docking protocol, see the document *Induced Fit Docking*.

Protein and Ligand Preparation

The quality of Glide results depends on reasonable starting structures for both the protein and the ligand. Schrödinger offers a comprehensive protein preparation facility in the Protein Preparation Wizard, which is designed to ensure chemical correctness and to optimize protein structures for use with Glide and other products. Likewise, Schrödinger offers a comprehensive ligand preparation facility in LigPrep. It is strongly recommended that you process protein and ligand structures with these facilities in order to achieve the best results.

3.1 Choosing the Most Appropriate Protein Site

Glide relies on the rigid-receptor approximation in order to treat protein-ligand binding. However, protein conformations are in general flexible and can occupy a continuum of states. Proteins can exhibit induced fit effects on binding of a ligand, in which the protein conformation changes significantly. This effect can be seen in cases where more that one co-crystallized complex is available. Since Glide docking experiments employ only a single protein geometry, two approaches are commonly taken. One is to select a single well-suited representative protein structure to dock into. The other is to use an ensemble of representative structures, into which each of the candidate ligands is docked.

If more than one co-crystallized complex is available, you must decide whether to select a single protein site or to choose two or more sites for use in independent docking experiments. This choice may depend on whether the protein site is rigid or mobile, as well as on the resources available and the objectives of the docking study. A single representative site should suffice for a rigid protein. Cases in which the site changes substantially as different ligands bind may require the use of two or more sites, if finding the maximum number of promising ligands is the main objective.

Some proteins are known to be rigid. To determine whether a single site is likely to be sufficient in other cases, you can transpose the known protein-ligand complexes into the coordinate frame of a “reference” complex. The objective is to judge whether the reference site is compatible with all the co-crystallized ligands or whether another site appears more suitable. A procedure for making this determination is as follows:

1. Choose a reference complex and superimpose all the other complexes to it.

   You can perform this task in Maestro with the Superposition panel. The atoms you choose to superimpose could be the alpha carbons, or all the backbone atoms for residues

in common, or the Cα or backbone atoms for selected active-site residues. Alternatively, you can use the Protein Structure Alignment facility to perform the superposition in an automated fashion.

2. Display the protein for the reference complex and the ligand for each of the other complexes, in turn. Examine the active-site region to determine whether the superimposed ligand can fit into the reference site without steric clashes that could not reasonably be relieved by minor repositioning. You can use the tools on the Measurements toolbar or in the Non-Bonded Interactions panel to examine contacts.
3. Display the protein for the reference complex and the protein for each of the other complexes in turn. Note whether any residues in the superimposed protein differ appreciably in position or conformation from those in the reference site.
4. From the above steps, judge whether the reference site appears compatible with all the co-crystallized ligands or, if not, whether another site appears more compatible.
5. Choose a most representative (i.e., fairly generous) site for docking—or choose two or more sites if there are large differences between the sites and the objective is to find as many prospective strong binders as possible.
6. Write out a separate file for the protein or proteins that will be prepared. Also write out separate files for the superimposed ligands.

For example, an initial screening of the CDK-2 kinase receptor used 1hck as the docking site, the co-crystallized ligand for which is ATP. Other known co-crystallized complexes include 1aq1, 1di8, 1dm2, 1fvt, and 1fvv. Superimposing these five complexes onto 1hck using all Cα atoms in common revealed that at least four of the five ligands (all active binders) cannot fit into the 1hck site because its active-site channel is too short. The reason is that ATP and a Mg^{2+} ion bound to its terminal phosphate group pull glutamate and lysine sidechains more deeply into the 1hck cavity, where they form an ion pair that closes off the cleft. Based on this visual examination, the 1dm2 site was chosen instead. This site is considerably more open than the 1hck site, though somewhat less so than the 1aq1 or 1fvv sites. Glide was far more successful in docking the known binders into the 1dm2 site than into 1hck, and was even more successful when the still more open 1aq1 site was used.

3.2 Protein Preparation

A typical PDB structure file consists only of heavy atoms, can contain waters, cofactors, and metal ions, and can be multimeric. The structure generally has no information on bond orders, topologies, or formal atomic charges. Terminal amide groups can also be misaligned, because the X-ray structure analysis cannot usually distinguish between O and NH_2. Ionization and tautomeric states are also generally unassigned. Glide calculations use an all-atom force field

for accurate energy evaluation. Thus, Glide requires bond orders and ionization states to be properly assigned and performs better when side chains are reoriented when necessary and steric clashes are relieved.

This section provides an overview of the protein preparation process. The entire procedure can be performed in the Protein Preparation Wizard panel, which you open from the Workflows menu on the main toolbar. This tool and its use is described in detail in Chapter 2 of the *Protein Preparation Guide*.

After processing, you will have files containing refined, hydrogenated structures of the ligand and the ligand-receptor complex. The prepared structures are suitable for use with Glide. In most cases, not all of the steps (outlined below) need to be performed. See the descriptions of each step to determine whether it is required, and make the appropriate selections in the Protein Preparation Wizard panel.

You may on occasion want to perform some of these steps manually. Detailed procedures for manual preparation are described in Chapter 3 of the *Protein Preparation Guide*.

The steps in the procedure, which can be performed either in the Protein Preparation Wizard panel or manually, are listed below.

1. Import a ligand/protein cocrystallized structure, typically from PDB, into Maestro.

   The preparation component of the protein preparation facility requires an identified ligand.

2. Simplify multimeric complexes.

   For computational efficiency it is desirable to keep the number of atoms in the complex structure to a minimum. If the binding interaction of interest takes place within a single subunit, you should retain only one ligand-receptor subunit to prepare for Glide. If two identical chains are both required to form the active site, neither should be deleted.

   - Determine whether the protein-ligand complex is a dimer or other multimer containing duplicate binding sites and duplicate chains that are redundant.
   - If the structure is a multimer with duplicate binding sites, remove redundant binding sites and the associated chains by picking and deleting molecules or chains.

3. Locate any waters you want to keep, then delete all others.

   These waters are identified by the oxygen atom, and usually do not have hydrogens attached. Generally, all waters (except those coordinated to metals) are deleted, but waters that bridge between the ligand and the protein are sometimes retained. If waters are kept, hydrogens will be added to them by the preparation component of the protein preparation job. Afterwards, check that these water molecules are correctly oriented.

4. Adjust the protein, metal ions, and cofactors.

   Problems in the PDB protein structure may need to be repaired before it can be used. Incomplete residues are the most common errors, but may be relatively harmless if they are distant from the active site. Structures that are missing residues near the active site should be repaired.

   Covalent bonds from metal ions to the protein should be changed to zero-order bonds, and the formal charges on the metal and the ligating groups should be adjusted to appropriate values.

   Cofactors are included as part of the protein, but because they are not standard residues it is sometimes necessary to use Maestro's structure-editing capabilities to ensure that multiple bonds and formal charges are assigned correctly.

   - Fix any serious errors in the protein.
   - Check the protein structure for metal ions and cofactors.
   - If there are bonds to metal ions, change the bonds to zero-order bonds and adjust the formal charges of the metal and the atoms that were attached to it.
   - Set charges and correct atom types for any metal atoms, as needed.
   - Set bond orders and formal charges for any cofactors, as needed.

5. Adjust the ligand bond orders and formal charges.

   If the complex structure contains bonds from the ligand or a cofactor to a protein metal, they must be deleted. Glide models such interactions as van der Waals plus electrostatic interactions. Glide cannot handle normal covalent bonds to the ligand, such as might be found in an acyl enzyme.

   If you are working with a dimeric or large protein and two ligands exist in two active sites, the bond orders have to be corrected in both ligand structures.

6. Run a restrained minimization of the protein structure.

   This is done with `impref`, and should reorient side-chain hydroxyl groups and alleviate potential steric clashes. The minimization is restrained to the input protein coordinates by a user-selected RMSD tolerance.

7. Review the prepared structures.

   - If problems arise during the restrained minimization, review the log file, correct the problems, and rerun.
   - Examine the refined ligand/protein/water structure for correct formal charges, bond orders, and protonation states and make final adjustments as needed.

3.3 Checking the Protein Structures

After you have completed the protein preparation, you should check the completed ligand and protein structures.

3.3.1 Checking the Orientation of Water Molecules

You only need to perform this step if you kept some structural waters. Reorienting the hydrogens is not strictly necessary, as their orientation should have been changed during refinement, but it is useful to check that the orientation is correct.

If the orientation is incorrect, reorient the molecules by using the procedure outlined in Section 3.9 of the *Protein Preparation Guide*.

When you have corrected the orientation of the retained water molecules, you should run a refinement on the adjusted protein-ligand complex.

3.3.2 Checking for Steric Clashes

You should make sure that the prepared site accommodates the co-crystallized ligand in the restraint-optimized geometry obtained from the structure preparation.

Steric clashes can be detected by displaying the ligand and protein in Maestro and using the Measurements toolbar or the Non-Bonded Interactions panel to visualize bad or ugly contacts. Maestro defines bad contacts purely on the basis of the ratio of the interatomic distance to the sum of the van der Waals radii it assigns. As a result, normal hydrogen bonds are classified as bad or ugly contacts. By default, Maestro filters out contacts that are identified as hydrogen bonds, and displays only the genuine bad or ugly contacts.

If steric clashes are found, repeat the restrained optimization portion of the protein preparation procedure, but allow a greater rms deviation from the starting heavy-atom coordinates than the default of 0.3 Å. Alternatively, you can apply an additional series of restrained optimizations to the prepared ligand-protein complex to allow the site to relax from its current geometry.

3.3.3 Resolving H-Bonding Conflicts

You should look for inconsistencies in hydrogen bonding to see whether a misprotonation of the ligand or the protein might have left two acceptor atoms close to one another without an intervening hydrogen bond. One or more residues may need to be modified to resolve such an acceptor-acceptor or donor-donor clash.

Some of these clashes are recognized by the preparation process but cannot be resolved by it. The preparation process may have no control over other clashes. An example of the latter typi-

cally occurs in an aspartyl protease such as HIV, where both active-site aspartates are close to one or more atoms of a properly docked ligand. Because these contact distances fall within any reasonable cavity radius, the carboxylates are not subject to being neutralized and will both be represented as negatively charged by the preparation process. However, when the ligand interacts with the aspartates via a hydroxyl group or similar neutral functionality, one of the aspartates is typically modeled as neutral.

If residues need to be modified, follow these steps:

1. Place the refined protein-ligand complex in the Workspace.
2. Examine the interaction between the ligand and the protein (and/or the cofactor).
3. Use your judgment and chemical intuition to determine which protonation state and tautomeric form the residues in question should have.
4. Use the structure-editing capabilities in Maestro to resolve the conflict (see Section 3.8 of the *Protein Preparation Guide* for procedures).
5. Re-minimize the structure.

It is usually sufficient to add the proton and perform about 50 steps of steepest-descent minimization to correct the nearby bond lengths and angles. Because this optimizer does not make large-scale changes, the partial minimization can be done even on the isolated ligand or protein without danger of altering the conformation significantly. However, if comparison to the original complex shows that the electrostatic mismatch due to the misprotonation has appreciably changed the positions of the ligand or protein atoms during the protein-preparation procedure, it is best to reprotonate the original structure and redo the restrained minimization.

3.3.4 Docking the Native Ligand

Once you have prepared the protein and generated grids (see Chapter 4), you should dock the native ligand both rigidly and flexibly. If either run fails to produce a low-rms structure, the structure or structures obtained from the docking should be scored in place, and the outcomes in the `*.rept` files for the doc king runs and in the `*.scor` files for the score-in-place runs should be checked.

Before running a docking job, you can run a score-in-place Glide calculation on the complex and check that the metal-ligation energy is reasonable. If it is highly positive, you may have to re-adjust the charge and protonation states in the active site manually.

- If rigid docking fails to give a low-rms pose, there may be a problem with the structure. Double-check the protein preparation. Such a failure may also reflect incomplete sampling by Glide. If the problem is sampling, there are some settings in the GUI, and others that can be made in the input file, that can be used to increase the amount of sampling.

- If rigid docking succeeds but flexible docking gives a high-rms pose that has a poor Coulomb-vdW energy, there may also be a sampling problem.
- If rigid docking succeeds but flexible docking finds a high-rms solution that has a more negative Coulomb-vdW energy than the ligand pose generated in the structure preparation, there may be a scoring problem, that is, Glide may have chosen the wrong solution because its Coulomb-vdW and Emodel energies are more favorable than those for the correct solution. There usually is no way you can fix such a problem. However, if the GlideScore value computed for the misdocked ligand is similar to that obtained for the co-crystallized ligand, the database screen may still be effective in identifying ligands that can bind tightly. The ligand may just have found a plausible alternative binding mode.

3.4 Ligand Preparation

To give the best results, the structures that are docked must be good representations of the actual ligand structures as they would appear in a protein-ligand complex. This means that the structures supplied to Glide must meet the following conditions:

1. They must be three-dimensional (3D).
2. They must have realistic bond lengths and bond angles.

   Glide only modifies the torsional internal coordinates of the ligand during docking, so the rest of the geometric parameters must be optimized beforehand.
3. They must each consist of a single molecule that has no covalent bonds to the receptor, with no accompanying fragments, such as counter ions and solvent molecules.
4. They must have all their hydrogens (filled valences).
5. They must have an appropriate protonation state for physiological pH values (around 7).

   For example, carboxylic acids should be deprotonated and aliphatic amines should be protonated. Otherwise a neutral aliphatic amine could improperly act as a hydrogen-bond acceptor in the docking calculations, or could occupy a hydrophobic region without incurring the large desolvation penalty that XP Glide docking would have assessed if the amine had been properly protonated.

   Protonation states are particularly crucial when the receptor site is a metalloprotein such as thermolysin or a MMP. If the metal center and its directly coordinated protein residues have a net charge, Glide assigns a special stability to ligands in which anions or polar groups coordinate to the metal center.
6. They must be supplied in Maestro, SD, Mol2, or PDB format.

Maestro transparently converts SD, MacroModel, Mol2, PDB, and other formats to Maestro format during structure import. However, Glide has no direct support for other formats, so you should ensure that your structures are in Maestro, SD, Mol2, or PDB format before starting Glide jobs.

All of the above conditions can be met by using LigPrep to prepare the structures. Use of LigPrep is described in the next section.

3.4.1 Using LigPrep for Ligand Preparation

The Schrödinger ligand preparation product LigPrep is designed to prepare high quality, all-atom 3D structures for large numbers of drug-like molecules, starting with 2D or 3D structures in SD, Maestro, or SMILES format. LigPrep can be run from Maestro or from the command line. For detailed information on LigPrep, see the *LigPrep User Manual*.

To run LigPrep, you must have a LigPrep license. The MacroModel commands `premin` and `bmin` require LigPrep licenses when run in a LigPrep context, and are limited to a restricted set of commands when run using a LigPrep license. LigPrep can be run from Maestro or from the command line.

The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures, and optimize the structures. Many of the steps are optional, and are controlled by selecting options in the LigPrep panel or specifying command-line options. The steps are listed below.

1. Convert structure format.
2. Select structures.
3. Add hydrogen atoms.
4. Remove unwanted molecules.
5. Neutralize charged groups.
6. Generate ionization states.
7. Generate tautomers.
8. Filter structures.
9. Generate alternative chiralities.
10. Generate low-energy ring conformations.
11. Remove problematic structures.
12. Optimize the geometries.

13. Convert output file.

The LigPrep panel allows you to set up LigPrep jobs in Maestro. Choose LigPrep from the Applications menu to open the panel. For details of panel options and operation, see Chapter 2 of the *LigPrep User Manual*.

The simplest use of LigPrep produces a single low-energy 3D structure with correct chiralities for each successfully processed input structure. LigPrep can also produce a number of structures from each input structure with various ionization states, tautomers, stereochemistries, and ring conformations, and eliminate molecules using various criteria including molecular weight or specified numbers and types of functional groups present.

The default options in the LigPrep panel remove unwanted molecules, add hydrogens, and minimize the ligand structure (performing a 2D-3D conversion, if necessary). Below are notes on panel options that produce more than one output structure per input structure.

The Ionization options allow you to generate all the ligand protonation states that would be found in the specified pH range. The Ionization options are:

- Retain original state—Retain the original ionization state rather than attempting to ionize the ligand.
- Neutralize—Neutralize the ligand by adding or removing protons from ionizable groups.
- Generate possible states at target pH *target* +/- *range*—This is the default, and can generate several different output structures for each input structure. The default pH *target* is 7.0 with a +/- *range* of 2.0, so the default pH range is 5.0 – 9.0. Both the target and range settings can be changed. You can use either the `ionizer` or Epik to generate ionization states. Epik generally yields more accurate states, because it uses a more sophisticated algorithm and performs ionization and tautomerization together. In addition, Epik generates a set of states that are more appropriate for metal binding when you select Add metal binding states, and calculates penalties for these states to use in the docking score. Epik is a separate product, so you must purchase this product to use it.

Generate low energy ring conformations: *number* per ligand. The default is to generate only the lowest energy conformation.

Desalt is selected by default.

Generate tautomers is selected by default. The `tautomerizer` generates up to 8 tautomers per ligand, selecting the most likely tautomers if more than 8 are possible. If you are sure that the input structures are already in the correct tautomeric form for docking to a particular target, then the `tautomerizer` should be turned off by deselecting Generate tautomers.

The `stereoizer` can generate two stereoisomers per chiral center in the ligand, up to a specified maximum. There are three Stereoisomers options:

The first two options, Retain specified chiralities (the default) and Determine chiralities from 3D structure, generate both isomers only at chiral centers where chirality is unspecified or indeterminate; centers with known chirality retain that chirality. The difference is that Retain specified chiralities takes its chirality data from the input file (SD or Maestro), while Determine chiralities from 3D structure ignores input file chiralities and takes chirality information from the 3D geometry.

Generate all combinations varies the stereochemistry up to a maximum number of structures specified by Generate at most *max* per ligand. The default maximum is 32.

3.4.2 Using Other Programs for Ligand Preparation

If you prefer to prepare the ligands with other programs, you can do so. Schrödinger software installations include a number of utilities that can be used to perform some of the above tasks. These utilities are also used by LigPrep. One of these, the Ionizer, can be used to prepare ligands in the required protonation states. Some of the other tasks can be performed as follows:

- Hydrogen atoms can be added in Maestro with either the Add H toolbar button:

  

  or the Add Hydrogens - Advanced panel (choose Edit > Hydrogen Treatment > Advanced).

  Hydrogen atoms can also be added (or removed) using the utility `applyhtreat`, which is described in Section 4.1 of the *General Utilities* manual.

- Structure file format conversion can be done from the command line with utilities such as `structconvert`, `pdbconvert`, and `sdconvert`—see Section 1 of the *General Utilities* manual.

Receptor Grid Generation

Glide searches for favorable interactions between one or more ligand molecules and a receptor molecule, usually a protein. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses. For receptors that adopt more than one conformation on binding, you might want to prepare grids for each conformation, to ensure that possible actives are not missed. Glide can, however, handle different hydroxyl conformations with a single grid generation.

The receptor grid can be set up and generated from the Receptor Grid Generation panel. The options in each tab of this panel allow you to define the receptor structure by excluding any cocrystallized ligand that may be present, determine the position and size of the active site as it will be represented by receptor grids, set up Glide constraints, and set up flexible hydroxyl groups. Ligand docking jobs cannot be performed until the receptor grids have been generated.

Receptor grid generation requires a “prepared” structure: an all-atom structure with appropriate bond orders and formal charges. Information on structure preparation is given in Chapter 3.

The force field used for grid generation is the OPLS_2005 force field, which allows a proper treatment of metals and has a wider range of atom types defined than its predecessor, OPLS_2001.

A tutorial example of setting positional and H-bond constraints is given in Chapter 2 of the *Glide Quick Start Guide*.

4.1 The Receptor Grid Generation Panel

To open the Receptor Grid Generation panel, choose Receptor Grid Generation from the Glide submenu of the Applications menu. The Receptor Grid Generation panel has five tabs, which you use to specify settings for the receptor grid generation job:

- Receptor
- Site
- Constraints
- Rotatable Groups
- Excluded Volumes

These tabs are described in later sections of this chapter.

Below the tabs are controls for starting the job, which are described in general in Section 1.2 on page 3. Some details are given here.

The Run button starts the job immediately with the current settings for the job, including the job name and the host.

The Job name text box allows you to specify the job name without opening the Job Settings dialog box. When you click the Start button, the job is run with the name in this text box.

The Settings button opens the Receptor Grid Generation - Job Settings dialog box.

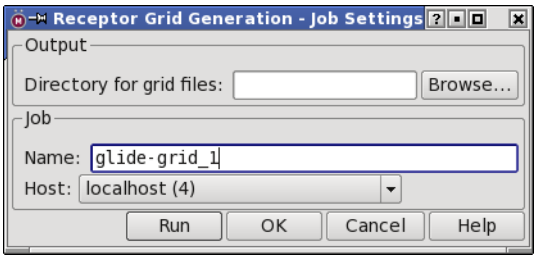

Figure 4.1. The Job Settings dialog box for grid generation jobs.

The dialog box has two sections: Output and Job. In the Output section you can specify the location for the grid files, which are written as zip files.

In the Job section, you can name your job by typing the name into the Name text box, and you can specify the Host to run the job. To save settings, click OK; to save settings and start the job, click Run. For more information on this dialog box, see Section 2.2 of the *Job Control Guide*.

The Settings button has an option menu (arrow to the right of the icon) with the following items:

Write

Choose Write to write the input files without starting the job. The job name is taken from the Job name text box. This name is used to create a directory in which the input files are written, and to name the files. The Glide input file is written to the file *jobname*`.in`, and the receptor is written to the file *jobname*`.maegz`. A script is also written to the file *jobname*`.sh`, containing the command for running the job in a Unix shell.

Reset Panel

Choose Reset Panel to restore the default settings in all tabs.

4.2 The Receptor Tab

In this tab you define the part of the Workspace system for which receptor grids should be calculated. You can also scale receptor atom van der Waals radii in this tab, and choose whether to use partial charges from the force field or from the input structure. The tab has three sections, Define receptor, Van der Waals radii scaling, and an unlabeled section with several options in it. Some more advanced settings that are not commonly needed are in a dialog box, which you open by clicking Advanced Settings.

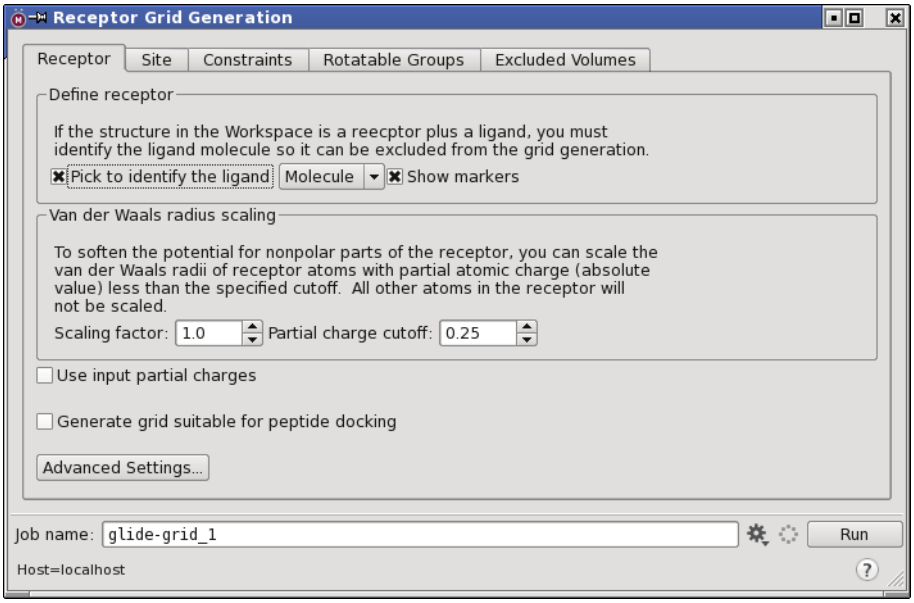

Figure 4.2. The Receptor tab of the Receptor Grid Generation panel.

4.2.1 Defining the Receptor

The Define receptor section contains options for defining the part of the system in the Workspace to be treated as the receptor. If only the receptor is included in the Workspace, and no ligand is present, you can ignore the Define receptor options.

- If the Workspace includes both a receptor and a ligand, use these options to pick the ligand molecule. The ligand will be excluded from receptor grid generation. Everything not defined as the ligand will be treated as part of the receptor. The ligand can be identified either as a molecule or as an entry in the Workspace.
- If you want to use a binding site from a SiteMap calculation, you can do so by treating it as a ligand and including it in the Workspace. Each site from SiteMap is a separate entry.

However, the site points in the site are not connected, so the site must be selected as an entry.

To select the ligand, ensure that Pick to identify ligand molecule is selected, choose an option from the option menu, then pick an atom in the ligand molecule or SiteMap site. The ligand (or site) is now distinguished from the receptor. If Show markers is selected, the ligand molecule is marked with green markers. Deselect the option to remove the markers.

4.2.2 Global Van der Waals Radius Scaling

Glide does not allow for receptor flexibility in docking (apart from hydroxyl rotations), but scaling of van der Waals radii of nonpolar atoms, which decreases penalties for close contacts, can be used to model a slight "give" in the receptor and the ligand. Scaling of other interactions can also help to model flexibility of parts of the receptor.

If you have a receptor in which there is substantial movement upon docking, such as a change in side-chain conformation, backbone location or loop conformation, you should consider docking to multiple protein conformations. You can also use the Induced Fit Docking protocol to account for receptor flexibility. This protocol uses Glide and Prime, and is much more computationally demanding than Glide docking alone. It is therefore mainly useful for docking a small number of ligands. See the document *Induced Fit Docking* for more information.

If you have a receptor that has Ser, Thr, or Tyr residues in the active site and the rotation of the hydroxyls on these groups is important, you can specify the hydroxyls as rotatable groups in the Rotatable Groups tab—see Section 4.5 on page 41 for details.

Glide has two means of accounting for protein flexibility by scaling of van der Waals radii. The first is described here; the second is described in the next section.

For nonpolar receptor atoms, you can use the controls in the Van der Waals radius scaling section to scale the van der Waals radius of those receptor atoms. The definition of nonpolar atoms is determined by a partial charge threshold that you can set. For ordinary Glide docking, it is recommended that receptor radii be left unchanged, and any scaling be carried out on ligand atoms. Receptor scaling is probably most useful when the active site is tight and encapsulated.

The Scale by text box specifies the scaling factor. Van der Waals radii of nonpolar receptor atoms are multiplied by this value. The default value is 1.00, for which no scaling is done. Scaling of van der Waals radii is performed only on nonpolar atoms, defined as those for which the absolute value of the partial atomic charge is less than or equal to the number in the text box. Since this is an absolute value, the number entered must be positive. The default is 0.25.

4.2.3 Selection of Partial Charges

You can use partial charges from the input structure, rather than from the force field, by selecting Use input partial charges. This option is useful if, for example, you have obtained improved partial charges around the active site, such as those from a QSite calculation or a QM-Polarized Ligand Docking calculation.

4.2.4 Grids for Peptide Docking

If you want to dock peptides with Glide, the grid must be prepared for this purpose. To do so, select Generate grid suitable for peptide docking. The grid can only be used in SP-Peptide docking mode.

4.2.5 Per-Atom Van der Waals Radius and Charge Scaling

For a more flexible method of softening the receptor potential, you can specify van der Waals radii and charges on a per-atom basis. This is done in the Per-atom van der Waals radius and charge scaling section of the Receptor - Advanced Settings dialog box, which you open by clicking Advanced Settings in the Receptor tab. If you specify per-atom scaling, the global scaling of nonpolar atoms is only performed on those atoms for which per-atom scaling factors are not specified.

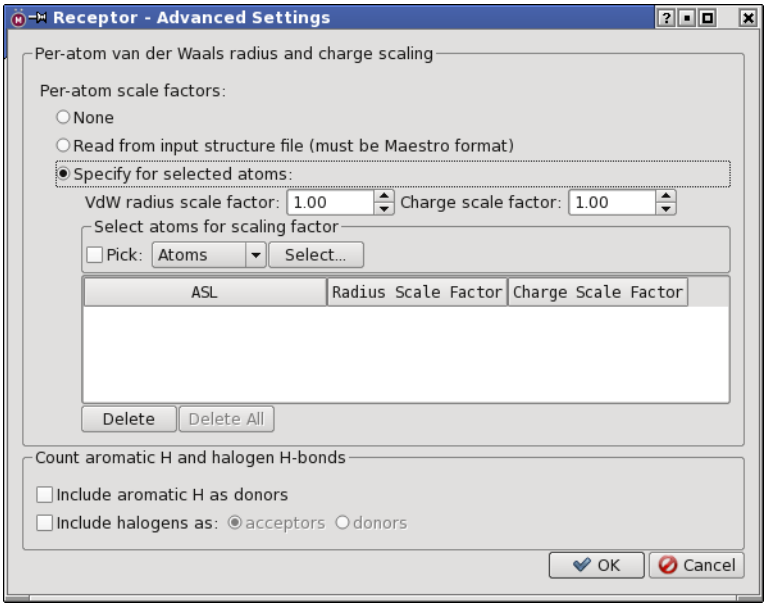

Figure 4.3. The Receptor - Advanced Settings dialog box.

There are three choices for the source of per-atom scale factors:

- None—do not use per-atom scale factors.
- Read from input structure file—Read the radius and charge scaling factors from the input file for the receptor. This file must be in Maestro format, and must have the properties VdW radius scale factor (`r_glide_atom_vdwscale`) and Charge scale factor (`r_glide_atom_coulscale`) defined. These properties must have a value for each atom in the receptor. They are defined if you have previously set per-atom scaling factors.
- Specify for selected atoms—Specify the scaling factors for selected atoms. You can make multiple selections and apply scaling factors to each, using the Select atoms for scaling factor picking tools. The selections should be mutually exclusive. A row is added to the table for each pick, with the scale factors specified in the van der Waals radius scale factor text box and Charge scale factor text box. You can subsequently edit the factors in the table.

4.2.6 Hydrogen Bonds with Aromatic Hydrogens and Halogens

In addition to normal hydrogen bonds, you might want to account for other noncovalent interactions that are generally weaker, but could be important. You can choose to include three types of interactions in the grid generation: hydrogen bonds to aromatic hydrogens, hydrogen bonds to halogens (halogen as an acceptor), and halogen bonds (halogen as a donor). The options to include these interactions are in the Count aromatic H and halogen H-bonds section of the Receptor - Advanced Settings dialog box, which you open by clicking Advanced Settings in the Receptor tab. (Strictly speaking, halogen bonds aren't H-bonds, but they are included here as a class of weak noncovalent interactions.) Currently you can only choose to have halogens treated as donors or as acceptors, but not both.

4.3 The Site Tab

The settings in the Site tab determine where the scoring grids are positioned and how they are prepared from the structure in the Workspace. To make these settings, you need to understand how Glide sets up grids.

Glide uses two "boxes" to organize the calculation:

- The grids themselves are calculated in the space defined by the *enclosing box*, or *grid box* or *outer box*. This is also the box within which all the ligand atoms must be contained.
- During the site point search, the ligand center is allowed to move within the *ligand diameter midpoint box*, or *inner box*. This box gives a truer measure of the effective size of the search space. However, ligands can move outside this box during grid minimization.

The only requirement on the grid box is that it is big enough to contain all ligand atoms when the ligand center is placed at an edge or vertex of the inner box. Grid boxes that are larger than this are not useful: they take up more space on disk and in memory for the scoring grids, which take longer to compute. The maximum size of the grid box is 80 Å.

The ligand center is defined in a rigid-docking run as the midpoint of the line drawn between the two most widely separated atoms. The definition changes slightly for flexible docking, where the ligand center becomes the midpoint between the two most widely separated atoms of the *core region*—the part of the ligand remaining after each of the end-groups has been stripped off at the terminal end of the connecting rotatable bond.

The two boxes share a common center. Thus, the operations in the tab that center one box also center the other. Information on the two boxes is written to the Maestro file for the receptor.

Each rigidly docked ligand or flexibly docked conformation has an associated length, L, which can be defined as twice the distance from the ligand center to its farthest atom. The required relationship between L and the lengths E and B of the outer and inner boxes for successful placement of the ligand center anywhere within the inner box is:

$$E \geq B + L$$

The grid box must be large enough in each dimension to hold the length of the inner box plus the maximum length of any ligand. If a larger ligand is encountered, not all positions for the center of the ligand in the inner box are accessible. The effective inner box for that ligand will be smaller than the dimension nominally specified. In any docking job using these receptor grids, ligands are confined to the grid box.

If the structure in the Workspace consists of a receptor and the ligand molecule you identified in the Receptor tab, Glide uses the position and size of the ligand to calculate a default center and a default size for the grid box. When you open the Site tab, the Workspace displays the center of the grid box as a set of coordinate axes colored bright green, and the boundaries of the region as a purple wire-frame cube.

If the Workspace includes a SiteMap binding site, you might want to reduce the size of the grid box, because it is likely that the site is larger than defined by a ligand. You might also want to specify the center of the box by selection of a few residues from the receptor, as the centroid of the site might not be in the optimal location. This is particularly so if the site is not well defined or the site points extend over a broad region.

If the Workspace structure consists of a receptor only, there is no default center for the grid box. The box will not be displayed until you have specified a grid center by selecting residues.

By default, the purple grid box outline and the green axes at the center are displayed when you enter the tab. Deselect Display Box to undisplay the box and its center.

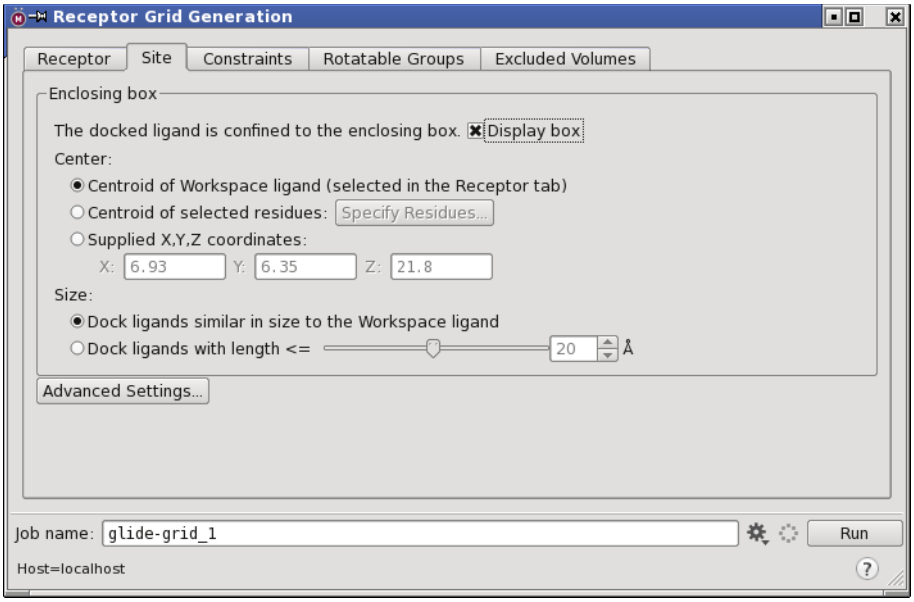

Figure 4.4. The Site tab of the Receptor Grid Generation panel.

4.3.1 Selecting a Box Center

Select one of the options under Center to determine how the center of the grid is defined:

- Centroid of Workspace ligand

  This option centers grids at the centroid of the ligand molecule that was defined in the Receptor tab, also called the Workspace ligand. If a Workspace ligand has been defined, this option is the default. The Advanced Settings button is available with this option.

- Centroid of selected residues

  This option centers grids at the centroid of a set of residues that you select. With this option you can define the active site (where grids should be centered) with only the receptor in the Workspace. The Specify Residue button is only available when you choose this option; the Advanced Settings button is not available with this option.

  To select the residues, click Specify Residues. The Active Site Residues dialog box opens. Using the picking controls, you can pick the residues that best define the active site. The list of selected residues is displayed in the table. You can delete residues by selecting them in the list, and clicking Delete. To delete all residues, click Delete All.

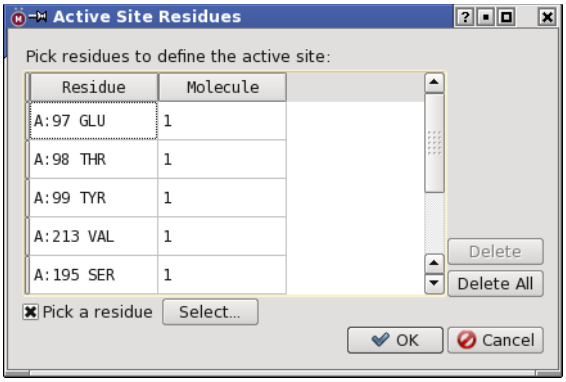

Figure 4.5. The Active Site Residues dialog box.

- Supplied X, Y, Z coordinates

  This option centers the grid at the Cartesian coordinates that you specify in the X, Y, and Z text boxes. These text boxes are only available when you choose this option. The Advanced Settings button is available with this option.

4.3.2 Setting the Box Sizes

The Size section provides options for the size of the grid box. The default option is Dock ligands similar in size to the Workspace ligand when a ligand is used for the grid center. This choice is suitable when the ligands to be docked are of the same size as, or smaller than, the Workspace ligand. If you expect to dock larger ligands, or if there is no Workspace ligand, select Dock ligands with length <= and use the slider to choose an appropriate maximum ligand length. The slider is set to 20 Å by default. If you use the centroid of specified residues, or supplied coordinates, Dock ligands with length <= is the default option.

To change the size of the inner box, click Advanced Settings. The Site - Advanced Settings dialog box opens, and the inner box, or *ligand diameter midpoint box,* is displayed as a cube outlined in bright green. The diameter midpoint of each docked ligand remains within this box in the site-point search stage, but can move outside this box in the grid minimization stage (see Figure 2.2 on page 9). You can use the Size sliders to increase or decrease the dimensions of each side of the box. The default is 10 Å on each side; the allowed range is 6 Å to 14 Å.

A larger inner box can be useful to allow ligands to find unusual or asymmetric binding modes in the active site. Conversely, if the default inner box allows ligands to stray into regions you know to be unfruitful, you can confine their midpoints to a smaller box, eliminating some of the less useful poses and saving calculation time. Changing the shape of the box can be useful when the active site is spatially extended in one or more directions.

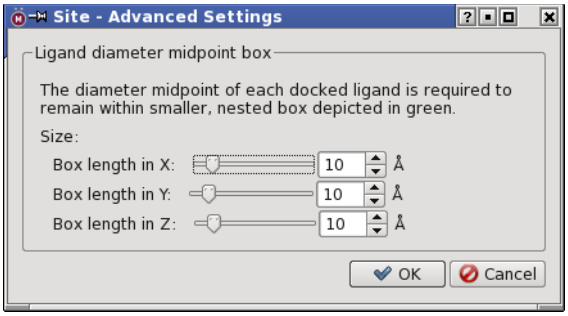

Figure 4.6. The Site - Advanced Settings dialog box.

4.4 The Constraints Tab

The Constraints tab of the Receptor Grid Generation panel is used to define Glide constraints for the receptor grids to be generated. Glide constraints are receptor-ligand interactions that you believe to be important to the binding mode, based on structural or biochemical data. Setting constraints enables Glide to screen out ligands, conformations, or poses that do not meet these criteria early on in their evaluation for docking suitability.

There are five types of Glide constraints that are set up during grid generation: positional constraints, NOE constraints, H-bond constraints, metal constraints, and metal coordination constraints. Two other types, core constraints and torsional constraints, only depend on the ligand and are specified during docking setup (see Section 5.5 on page 58 and Section 5.7 on page 69).

- A positional constraint is a requirement that one or more ligand atoms occupy a spherical volume that is centered at a particular position. This is a maximum distance constraint.
- A NOE (nuclear Overhauser effect) constraint is a requirement that one or more ligand atoms occupy a spherical shell (the region between two spheres) that is centered at a particular position. This is a constraint to a distance range.
- An H-bond constraint is a requirement that a particular receptor-ligand hydrogen bond be formed.
- A metal constraint is a requirement that a particular metal-ligand interaction is present when the ligand is docked. The ligand atom must lie in a sphere around a specified receptor metal atom, and therefore the constraint on the ligand atom has no directionality.
- A metal coordination constraint is a requirement that a ligand atom lie within a given distance of an optimal coordination site for a metal atom. It differs from a metal constraint in that the constraint sphere is centered on a potential ligand coordinating atom rather than on the metal, and is thus directional.

The constraints tab has three subtabs, Positional/NOE, H-bond/Metal, and Metal Coordination, for setting up the constraints. The number of constraints of each type is reported on the subtab tab, and the total number of constraints is reported at the top of the tab. The maximum number of constraints that you can define for a given grid is ten constraints, distributed among positional, H-bond, metal, and metal coordination constraints.

When constraints setup is complete and the grid generation job is run, Glide writes a file containing the information about the constraints. Subsequent docking jobs use this file to determine whether a given ligand pose satisfies the constraints. If the base name for writing grid files is *gridbase*, the constraints file is named *gridbase*`.cons`. Not all of these constraints are used in a given docking job: when you set up the docking job, you can choose which constraints to apply.

To use Glide constraints, you must define the constraints during grid generation setup and then apply the constraints during docking setup (see Section 5.6 on page 61). Any Glide constraints that you want to apply in docking must be defined when the receptor grids are generated.

Note: You cannot use flexible receptor groups for constraints.

When you are setting up constraints, it may be helpful to undisplay most of the receptor, leaving only residues within a short distance of the ligand visible.

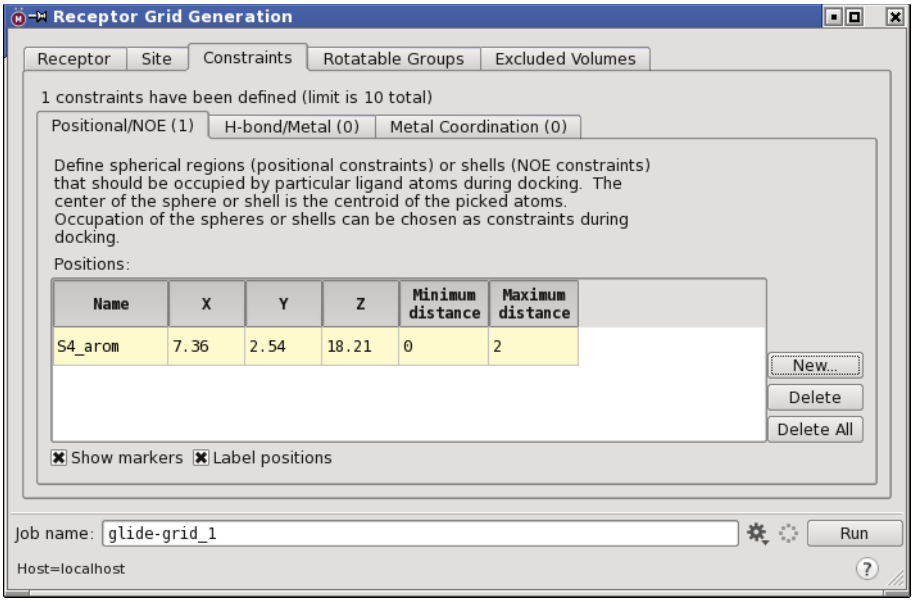

Figure 4.7. The Constraints tab of the Receptor Grid Generation panel showing the Positional/NOE subtab.

4.4.1 Setting Positional and NOE Constraints

Positional constraints define a region that must contain a particular kind of ligand atom. The specific kind of atom is defined during docking setup, using SMARTS patterns. Positional constraints allow you to require interactions between any kind of receptor and ligand atoms, while at the same time placing tighter restrictions on the ligand atom position than is typical with other constraint types.

For example, a hydrogen-bond acceptor in the receptor might be capable of forming hydrogen bonds in two directions, but only one of these results in good binding. While setting an H-bond constraint in this case allows a ligand hydrogen atom to lie in either of these directions, a positional constraint can require it to be in the "good" direction. The constraint could be set by selecting a hydrogen atom that bonds in the "good" direction to define the position of the constraint. For reasons such as this, we suggest that you display a model ligand in the Workspace to aid in selecting appropriate positions for constraints.

NOE constraints are similar to positional constraints, but require that the ligand atoms lie in a given distance range from the constraint center, i.e. in the "shell" between two spheres.

To add a positional or NOE constraint, click New. This button opens the New Position/NOE dialog box, in which you can pick atoms with the standard picking controls to define a constraint center, name the constraint, and specify its radius or minimum and maximum distances. To choose the constraint type, select Position or NOE under Constraint type.

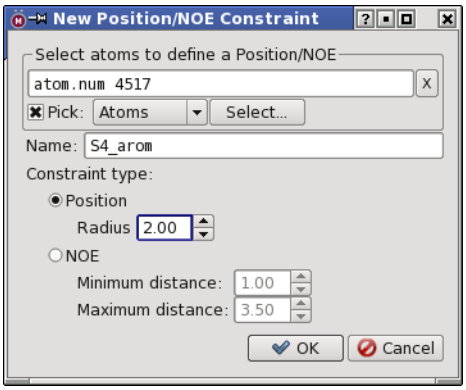

Figure 4.8. The New Position/NOE dialog box.

The center of the sphere or spheres for a constraint is the centroid of the selected atoms, and must be inside the grid box. While picking is in progress, the constraint is marked with a gray sphere. If you make the constraint an NOE constraint, both spheres are displayed. When you click OK, the constraint is added to the Positions table if it is inside the grid box; otherwise a warning is displayed.

To delete a constraint, select it in the Positions table and click Delete; to delete all constraints, click Delete all.

The Positions table displays the constraints you have chosen, giving the name, coordinates, and radii of the constraint spheres for each constraint. The coordinates and the radii are given in angstroms. You can select a single constraint in the table, and edit the name, coordinates, and sphere radii by clicking in the table cell and changing the value. If you want to convert a positional constraint to an NOE constraint, you can do so by providing a minimum distance.

To view the constraints in the Workspace, select Markers. The selected constraint is marked by one or two yellow spheres. The other positional or NOE constraints are marked by red spheres. If Markers is selected, selecting the Label positions option displays the name of the constraint in the Workspace. The labels are colored the same as the constraints.

4.4.2 Setting H-Bond and Metal Constraints

Up to ten symmetry-distinct receptor atoms can be chosen as possible H-bond or metal constraint sites.

For hydrogen-bonding interactions, the receptor atom must be a polar hydrogen (including thiol H in cysteine), nitrogen, or oxygen. If you choose an atom with one or more symmetry-equivalent atoms in its functional group, the symmetry-equivalent atoms are all selected as well by default, and collectively count as one constraint. For example, if you create a constraint by picking one oxygen atom of a carboxylate group, Glide includes the other oxygen atom in the same constraint. A ligand interaction with either oxygen atom satisfies that single constraint. However, you can turn off the use of symmetry so that only the chosen atom is used.

For metal-ligand interaction constraints, the receptor atom must be a metal ion.

The receptor atoms selected must also be close enough to the ligand that satisfying the constraints is possible. You do not need to specify limits on distances or angles between receptor and ligand atoms for the constraint: Glide sets these values internally, to H-acceptor distances of 1.2 to 2.5 Å; donor angles greater than 90°, and acceptor angles greater than 60°. For metal constraints the ligand-metal distance must be no greater than the sum of the van der Waals radii of the metal and ligand atoms plus 0.4 Å.

These values are looser than those employed by Maestro. General distance requirements are incorporated using the grid box for the ligand. The receptor atoms selected for constraints must be inside the grid box (which is displayed in purple) or within bonding range of it.

To display hydrogen bonds in the Workspace, choose Inter from the Display H-bonds button menu and click on a ligand atom. The hydrogen bonds between the ligand and the receptor are displayed. This should make it easier to locate the relevant receptor atoms. If you want to use

the looser criteria for hydrogen bonds employed by Glide, you can do so in the Preferences panel. Choose Maestro → Preferences and under Nonbonded Interactions – Criteria, click Glide in the H-Bonds section.

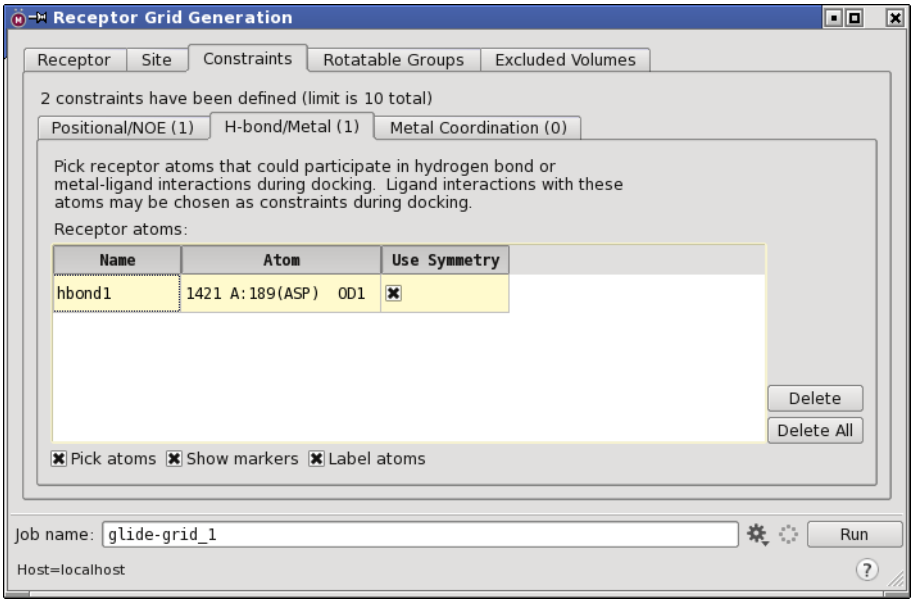

Figure 4.9. The Constraints tab of the Receptor Grid Generation panel showing the H-bond/Metal subtab.

To set H-bond or metal constraints, ensure that Pick atoms is selected in the H-bond/Metal constraints tab, and pick the desired atoms in the Workspace. By default, symmetry-equivalent atoms such as the other oxygen in a carboxylate group are included in the constraint. If you only want to use the picked atom for the constraint, clear the check box in the Use Symmetry column. If Show markers is selected, a red cross and red padlock appear next to each atom picked. If the picked atom is one of a set of symmetry-equivalent atoms, all the atoms in the set are marked, provided Use Symmetry is selected. If Show markers is selected, selecting Label atoms displays the constraint name in the Workspace.

As you select atoms in the receptor, they appear in the Receptor atoms table. The Atom column gives detailed information on the atom selected in the format

atom-number:*chain*:*residue-name* *residue-number* :*atom-name* : *symmetry-set*

where

- *atom-number* is the Maestro atom number
- *chain* is the chain name
- *residue-name* is the name of the residue
- *residue-number* is the residue number and the insertion code, if any
- *atom-name* is the PDB atom name
- *symmetry-set* is the atom name or symmetry-equivalent atom set

for example,

341:C:ASN 239 : OD1 : ODn

If the picked atom is part of a symmetry-equivalent set and Use Symmetry is selected, its identification is followed by square brackets enclosing the number and name of each atom in the set, separated by commas.

The Name column gives a label that is used when displaying the possible constraints from the Ligand Docking panel. The format of the name is:

chain : *residue-name* : *residue-number* : *atom-name* (*type*)

where the quantities except type are defined above, and *type* is either `hbond` or `metal`, for example,

C:ASN:239:OD1(hbond)

This name can be changed by editing the table cell.

The Use Symmetry column indicates whether symmetry-equivalent atoms are included with the picked atom for a constraint or not.

To delete a single H-bond or metal constraint, select it in the list and click Delete; to delete all the listed constraints, click Delete All.

4.4.3 Setting Metal Coordination Constraints

Metal coordination constraints require a ligand atom to lie within a specified distance of a coordination site, which is the location that a ligand atom should occupy for optimal bonding with the metal. For each metal, the possible coordination sites are identified, and a constraint sphere is placed at the ideal location of a ligand donor atom at the available site. This differs from the metal constraint feature, in which a constraint sphere is placed on the metal. The metal coordination constraint has directionality, whereas the metal constraint has none. You can choose to use any or none of the sites found for a given metal.

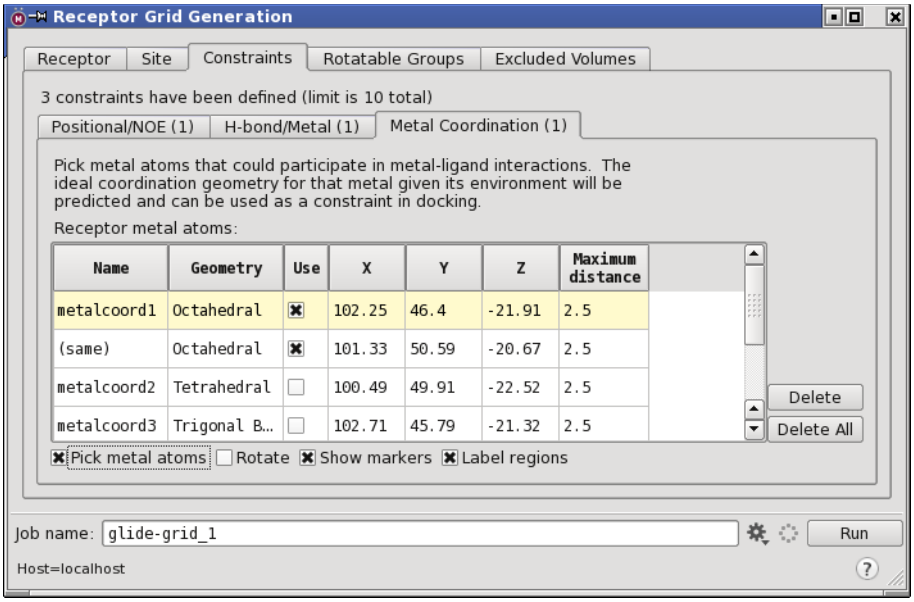

Figure 4.10. The Constraints tab of the Receptor Grid Generation panel showing the Metal Coordination subtab.

To choose a metal for a coordination constraint, select Pick metal atoms (the default), then pick a receptor metal atom in the Workspace. (The atom is identified in the status bar when the pointer is over the atom.) When a metal is picked, the possible coordination sites are identified and rows are added to the Receptor metal atoms table with the coordinates of the site and the maximum distance. Each of the possible coordination constraints is shown in the Workspace as a sphere centered at the coordination site, with the radius equal to the maximum distance. If there is more than one possible coordination geometry, all geometries are listed.

All of the sites for the first coordination geometry are selected for use by default, but you can choose which ones you want to use by checking or clearing the check box in the Use column.

When you select a row in the table, all the sites associated with the metal atom for that coordination geometry are also selected, and highlighted in the Workspace in red. Any other spheres are colored gray. You can edit the constraint name and the coordinates and radii of the constraint spheres by clicking in the appropriate table cell and changing the value, or you can delete the set of sites for a given metal by clicking Delete. You cannot delete individual sites: instead, you should clear the Use check box to remove them from consideration. When the check box is cleared, the sphere in the Workspace turns gray.

It may be necessary to adjust the orientations of the sites from their initial locations, so that the constraint spheres cover the desired regions of space. As coordination orientations can vary

considerably in a complex structure such as a protein, it may be necessary to make some adjustments. To do this, select Rotate, and then rotate the orientation of the coordination sites around the metal with the usual actions for Workspace rotation.

You can hide the constraint spheres in the workspace by deselecting Show markers. You can also hide the label on the constraint spheres by deselecting Label regions. This label is the constraint name, and is the same for all constraint spheres belonging to a particular metal atom.

4.5 The Rotatable Groups Tab

The hydroxyl groups in residues such as Ser, Thr, and Tyr and the thiol group in Cys can adopt different orientations with different ligands. Glide can allow such groups to adopt different orientations when ligands are docked, to produce the most favorable interaction. For Ser and Thr, the hydroxyls can be oriented in any of the three local minima, and likewise for the thiol of Cys; for Tyr, they can be in either of the two local minima. The Rotatable Groups tab allows you to choose which of these groups should be treated flexibly.

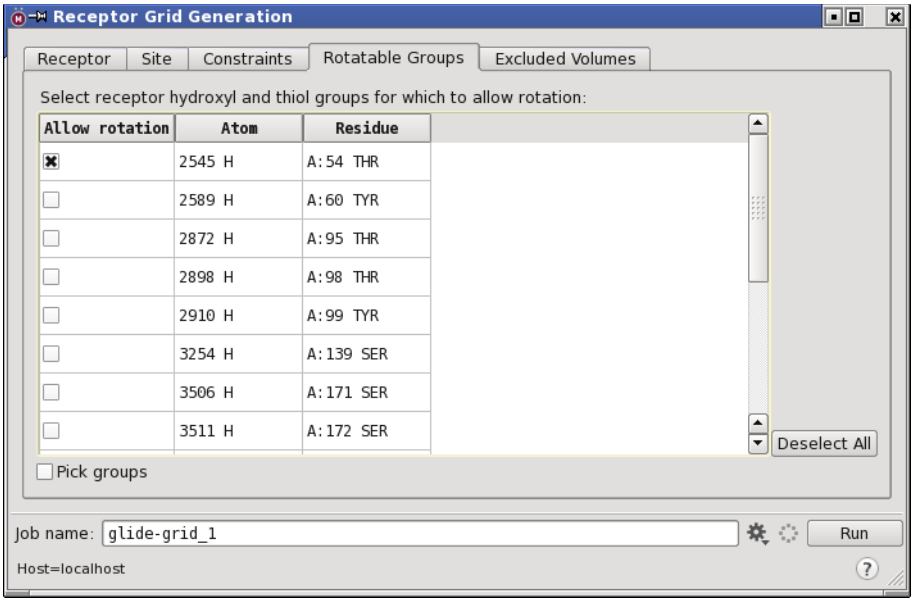

Figure 4.11. The Rotatable Groups tab of the Receptor Grid Generation panel.

The Available groups table is loaded by default with a list of all rotatable groups within the grid box. The group is identified by the hydrogen atom number and the residue (chain, number, name). By default, none of them are selected for use. You can then choose the groups that you want to include in the grid generation either by selecting them in the Allow rotation column of

the table, or by selecting Pick groups and picking the hydrogens of the groups in the Workspace. The selected groups are marked in the Workspace. Clicking a second time, either in the column or in the Workspace, deselects the group. Clicking Deselect All deselects all groups (which has the effect of turning off the use of rotatable groups).

If you have previously prepared grids with flexible groups, and you are using the receptor from a file that was written by Glide, the existing selection is loaded by default. The rotatable group information is added to the receptor structure when it is written out by Glide.

You cannot create constraints to flexible groups.

When docking ligands with flexible groups, the time taken is longer than for a non-flexible docking calculation, but significantly shorter than docking with all possible combinations of flexible group orientations. For example, with 4 flexible groups, an SP docking run takes about twice as long as a run with no flexible groups, and an XP docking run takes about 4 times longer. If each of these groups can take two possible orientations, there are 16 combinations. To dock to all of these combinations without allowing flexibility would therefore require 16 grid calculations and 16 non-flexible docking runs, and the results from the individual runs would have to be collated at the end.

Note: Once you have set up a grid with flexible groups, the flexibility is used in docking, and cannot be turned off.

4.6 The Excluded Volumes Tab

In some situations, you might want to prevent ligands from occupying certain regions of space. For example, if you have a pocket near the active site where ligands are known not to bind, you might want to stop ligands from occupying that pocket. Another situation is searching for ligands that might be immune to drug-resistant mutations, to check the alignment by ensuring that the drug only occupies the space that is occupied by the substrate. A third case is where parts of a protein are missing, and you want to prevent the ligand from occupying that region.

In the Excluded Volumes tab, you can set up regions of space from which the ligands will be excluded during docking. These regions are composed of a set of spheres, which you can define by picking atoms for the centroid of a sphere (e.g. atoms on either side of a pocket you want to exclude), and then setting the radius of the sphere. You would not normally need to place spheres on regions occupied by the protein, because these are already excluded in the docking process (due to the potentials).

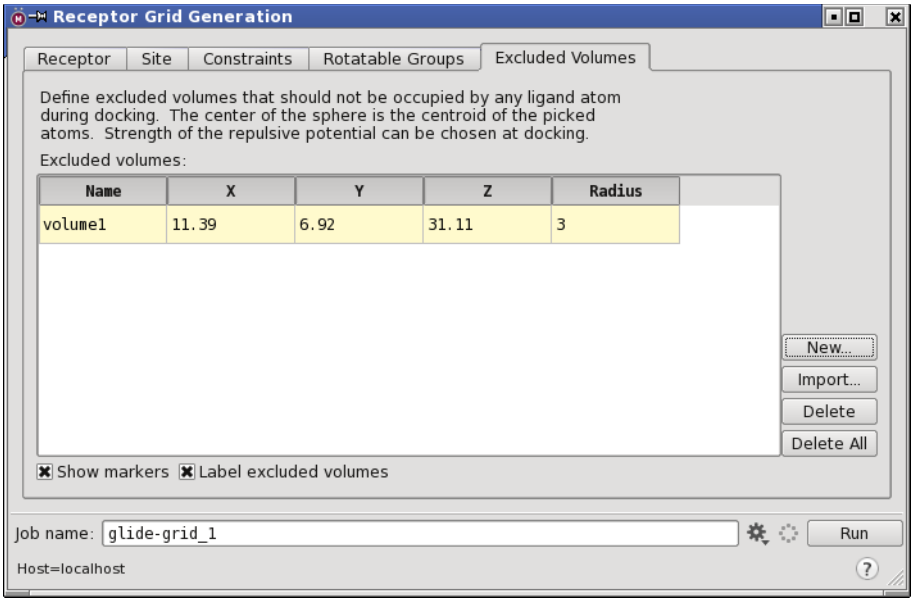

Figure 4.12. The Excluded Volumes tab of the Receptor Grid Generation panel.

To set up an excluded volume:

1. Click New.

   The New Excluded Volume dialog box opens.

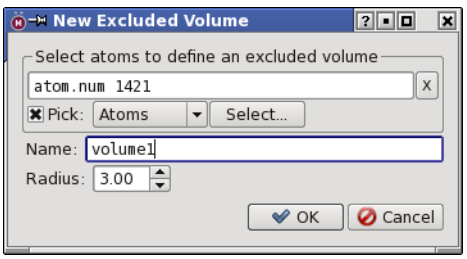

Figure 4.13. The New Excluded Volume dialog box.

2. Pick atoms in the Workspace to define the center of the excluded volume sphere.

   When you start to pick, a sphere is placed in the Workspace. The sphere center is placed at the centroid of the picked atoms, and moves to the new centroid as you pick more atoms.

3. Enter a name for the excluded volume in the Name text box.

4. Enter the sphere radius in the Radius text box.
5. Click OK.

   The dialog box closes, and a new row is added to the Excluded volumes table.

You can change the sphere parameters by editing the table cells for the excluded volume. You can define as many excluded volumes as you like.

Phase also allows you to define excluded volumes for a pharmacophore hypothesis. You can import a Phase excluded volume file (`.xvol`) to use with a Glide grid, by clicking Import and navigating to the file. Importing Phase excluded volumes is only likely to be useful if the ligand you are using as the reference ligand for Glide is the same as that used for the Phase hypothesis, or at least has pharmacophore features that superimpose well on the Glide ligand. To check the alignment, you should include both the Phase hypothesis with its reference ligand and the Glide native ligand in the Workspace.

Glide excluded volume files (`.gxvol`) cannot be used with Phase, however, because the format is not compatible, and they contain information other than the sphere coordinates and radii.

Ligand Docking

Glide ligand docking jobs require a set of previously calculated receptor grids and one or more ligand structures. The ligand structures must satisfy the conditions listed on page 21. Information on setting up grid generation jobs is given in Chapter 4. For docking tutorial examples, see Chapter 3 of the *Glide Quick Start Guide*.

Preparation of the ligands before docking is strongly recommended. LigPrep or MacroModel can be used to prepare ligands—see Chapter 3 for more information.

If a correct Lewis structure cannot be generated for a ligand, it is skipped by the docking job. Glide also automatically skips ligands containing unparametrized elements, such as tin, or atom types not supported by the OPLS force fields, such as explicit lone pair "atoms."

This chapter contains a detailed description of the Ligand Docking panel in Maestro and each of its tabs, including instructions for applying Glide constraints, using extra-precision Glide docking (Glide XP), and distributed processing.

5.1 The Ligand Docking Panel

To open the Ligand Docking panel, choose Ligand Docking from the Glide submenu of the Applications menu. The Ligand Docking panel has several tabs:

- Ligands
- Settings
- Core
- Constraints
- Torsional Constraints
- Output

These tabs are described in the following sections of this chapter. You use the options in these tabs to specify settings for the ligand docking job. When you have completed your setup, the Job toolbar at the bottom of the panel allows you to process your job.

- Specify the name for the job in the Job name
- Click the Settings button (gear icon) to make other job settings.
- Click the Settings button arrow and choose Write to write the input files to disk without starting the job, or choose Reset to discard settings and restore the defaults in all tabs.

When you write the input files, you can choose a standard job name, type in a name, or browse to the desired location. The input files are written to the current working directory by default.

The Ligand Docking - Job Settings dialog box provides controls for the running of the job. You can name the job by entering text in the Name text box. If you want to incorporate the results into the current Maestro project, you can select an option from the Incorporate option menu. Incorporation can take some time if you have a large number of poses.

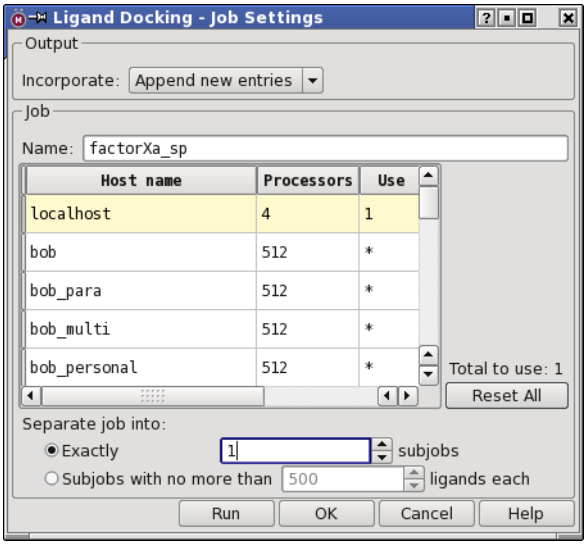

Figure 5.1. The Job Settings dialog box for ligand docking jobs.

You can also specify options for distributed processing, by splitting the job into subjobs and distributing the subjobs over multiple processors. To separate the docking job into a specific number of subjobs, select Exactly under Separate job into and enter the number of subjobs in the text box. To separate the docking job into subjobs of a maximum size (number of ligand), select Subjobs with no more than and enter the maximum number of ligands in the text box. To use multiple processors, select the hosts and enter number of processors to use on each host in the host table. You can edit the cells in the Use column to set the number of processors to use for each host. For details on the use of this table, see Section 2.2 of the *Job Control Guide*.

The number of subjobs cannot be set to less than the number of processors. For optimal load balancing and for restartability, the number of subjobs should be several times the number of processors—even if you are running on a single processor. It is recommended that you split any docking job into subjobs with no more than about 50,000 ligands, to minimize the loss of work in the event of a job failure (which could be due to network problems or hardware failure). Glide tries to restart failed subjobs, and if there is only one subjob, it restarts the failed job from the beginning.

See Section 2.2 of the *Job Control Guide* for more information on the Job toolbar and the Job Settings dialog box.

5.2 Specifying the Receptor Grid

To specify the receptor grid for the docking job, click Browse in the Receptor grid section of the Settings tab to open a file selector and choose a compressed grid archive (`.zip`) or a grid file (`.grd`). Note that the grid archive cannot be renamed, otherwise the docking job will fail. The file name is displayed in the Receptor grid text box. You can also enter the file name directly into the text box. The grid file must be accessible on the local host; if it is not, the job will not be submitted. If you want to use a grid that is not accessible on the local host, you can do so by submitting the job from the command line. If you plan to use SP-Peptide docking mode, you must select a grid that was generated for this mode.

If you want to display the receptor in the Workspace, select Display receptor. If you want to see the grid box, the ligand center box, and the grid center, select Show grid boxes. (The grid boxes are only displayed for grids generated with the Suite 2011 release onward).

5.3 The Ligands Tab

In the Ligands tab you specify the source of ligands to be docked or scored and set size limits for skipping ligands. You can also choose the partial charges to use and change the settings for van der Waals radii scaling of nonpolar ligand atoms.

5.3.1 Specifying the Source of the Ligands

In the Ligands to be docked section you specify the source of ligands to be docked (or scored in place). The ligands must satisfy the criteria given in Section 3.4 on page 21. To specify the source, choose one of the following options from the Use ligands from option menu:

- Files—If you select Files as the source of ligands, you can type the file names in the File name text box, or click the Browse button to open a file selector, in which you can choose the format and navigate to and select the ligand files. The file must be in Maestro, SD, MOL2, or PDB format. Maestro and SD files can be in compressed form.

  By default, all structures in all files are docked. If you specify a single file, you can select a contiguous subset of ligands from the file, by entering values in the Range text boxes. To enter the upper limit, deselect End. The End option allows you to dock all ligands from a particular ligand to the end of file.

  Selecting a subset of ligands is useful if a problem with Glide or with the input ligand causes a Glide job to fail. Then you can set the initial ligand number when you restart the

job to pick up at the point in the ligand file at which the problem occurred. This only applies if a single file is selected for docking.

- Project table (selected entries)—Select this option to dock ligands that are selected entries in the Project Table.
- Workspace (included entries)—Select this option to dock the structures in the Workspace. If you select this option, the entries in the Workspace must satisfy the criteria for valid ligand entries.

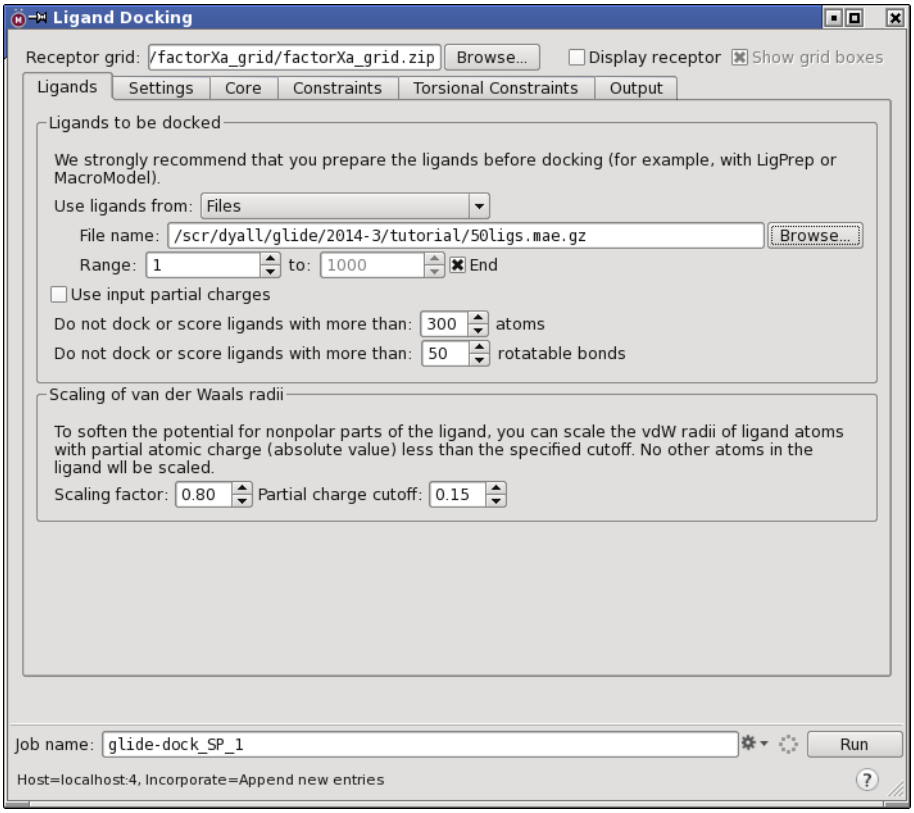

Figure 5.2. The Ligands tab of the Ligand Docking panel.

5.3.2 Selecting the Source of Ligand Partial Charges

Partial charges for the ligand atoms are obtained from the force field. These partial charges do not reflect the influence of the environment on the atomic charges. To compensate, you can use pregenerated partial charges from some other source. To use the partial charges that are supplied with the ligand, select Use input partial charges.

The QM-polarized ligand docking solution provides a way of using quantum mechanical charges from a QSite calculation to dock ligands. For more information, see the document *QM-Polarized Ligand Docking*.

5.3.3 Setting Restrictions on the Type of Ligands

In the text boxes at the end of the Ligands to be docked section, you can set limits on structural feature counts to screen out structures before docking. These text boxes are described below.

Do not dock or score ligands with more than *a* atoms

Set the maximum number of atoms a ligand structure may have if it is to be docked. Ligand structures in the input file that have more than the specified number of atoms will be skipped. The default is also the maximum, 500 atoms. You can reduce the maximum number of atoms *a*, if the active-site region is small and enclosed, to speed up a docking calculation.

Do not dock or score ligands with more than *r* rotatable bonds

Set the maximum number of rotatable bonds a ligand structure may have if it is to be docked flexibly. Ligand structures in the input file that have more than this number of rotatable bonds are skipped. The default is also the maximum, 100 rotatable bonds. If only relatively small or rigid ligand "hits" are wanted, you can decrease the value of *r*. If you use torsional constraints, the rotatable bonds that are constrained are excluded from the number of rotatable bonds.

5.3.4 Van der Waals Radii Scaling

Glide does not generally allow for flexible receptor docking, except for reorientation of selected hydroxyl and thiol groups (see Section 4.5 on page 41).[1] However, successful docking sometimes requires that the ligand and the receptor "give" a bit in order to bind. To model this behavior, Glide can scale the van der Waals radii of nonpolar atoms (where nonpolar is defined by a partial charge threshold you can set), thereby decreasing penalties for close contacts. Scaling is performed for qualifying atoms in the ligand, but not those in the receptor. Ligand atom radii scaling settings can be changed using the options in this section. To scale receptor atom radii, you must choose the appropriate options in the Receptor tab of the Receptor Grid Generation panel prior to grid generation.

Scaling factor

Specify the scaling factor. The default is 0.80. To turn van der Waals radii scaling off, set the scaling factor to 1.0. Full penalties for close contacts of nonpolar ligand atoms will then be used.

1. Flexible receptor docking can be performed with the Induced Fit Docking solution, which uses Glide with Prime to allow for receptor flexibility. For more information, see the document *Induced Fit Docking*.

Partial charge cutoff

Scaling is performed only on nonpolar atoms, defined as those for which the absolute value of the partial atomic charge is less than or equal to the number in the text box. Since this is an absolute value, the number entered must be positive. The default for ligand atoms is 0.15.

5.4 The Settings Tab

The Settings tab defines the basic options for docking ligands: specifying the grid, selecting the precision, and setting flexibility options. You can also make settings for the selection of initial poses and for the energy minimization of the poses that pass the initial selection in the Settings - Advanced Settings dialog box. To open this dialog box, click Advanced Settings. The settings, both basic and advanced, are described in the following subsections.

The force field used for docking is the OPLS_2005 force field.

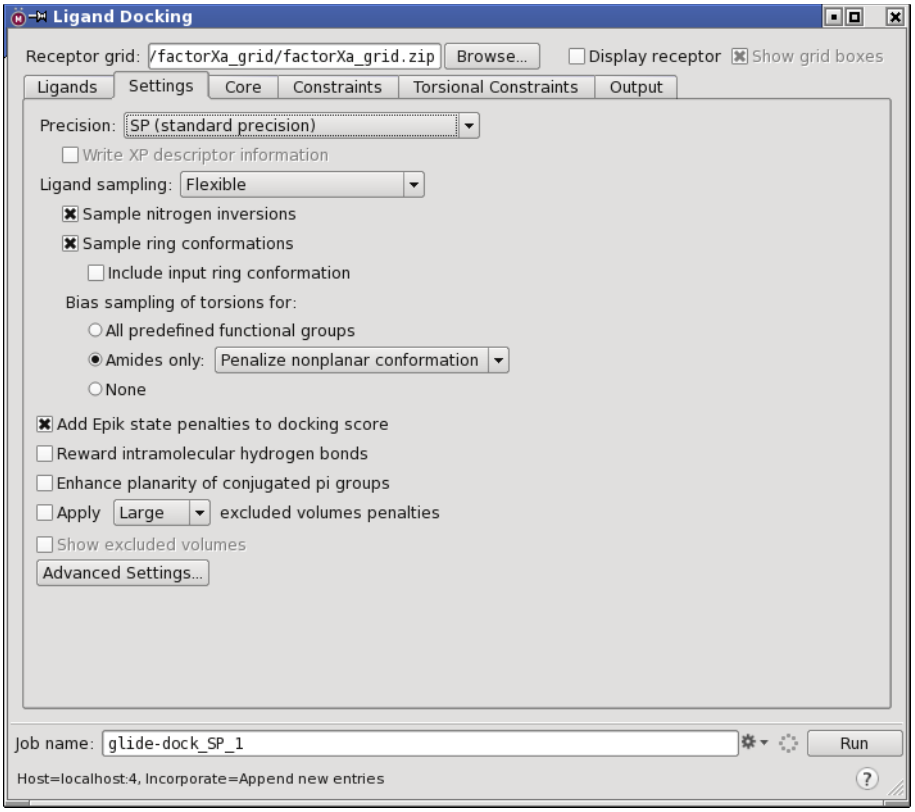

Figure 5.3. The Settings tab of the Ligand Docking panel.

5.4.1 Selecting the Docking Precision

There are three choices of docking precision, given on the Precision option menu in the Docking section.

- HTVS (high-throughput virtual screening)—High-throughput virtual screening (HTVS) docking is intended for the rapid screening of very large numbers of ligands. HTVS has much more restricted conformational sampling than SP docking, and cannot be used with score-in-place. Advanced settings are not available for HTVS, as they are predetermined.
- SP (standard precision)—Standard-precision (SP) docking is appropriate for screening ligands of unknown quality in large numbers. Standard precision is the default.
- XP (extra precision). Extra-precision (XP) docking and scoring is a more powerful and discriminating procedure, which takes longer to run than SP. XP is designed to be used on ligand poses that have a high score using SP docking. We recommend that you run your database through SP docking first, then take the top 10% to 30% of your final poses and dock them using XP, so that you perform the more expensive docking simulation on worthwhile ligands. For more information on XP docking, see Section 2.3 on page 13.
- SP-Peptide—Standard-precision docking for peptide ligands uses the same general settings as for regular standard precision but changes some of the settings to enhance the retention of poses. Specifically, it keeps 100000 poses in the initial docking stage, and uses 1000 poses per ligand for energy minimization, and sets the number of poses for post-docking minimization to 100. Although this option was designed for peptides, it is not restricted to peptides: you can dock any kind of ligand.

  If you select this option, the grid must be one that was generated for this mode, i.e. with Generate grid suitable for peptide docking selected.

If you want to dock a set of ligands using a progression of precision, you can use the Virtual Screening Workflow to set up and run the docking jobs. See the *Virtual Screening Workflow* document for details.

5.4.2 Setting Ligand Sampling Options

From the Ligand Sampling option menu you can choose whether ligands are docked flexibly or rigidly, refined in place, or simply scored in place; and set options for conformation generation for flexible docking. The choices are described below.

Flexible

This is the default option, and directs Glide to generate conformations internally during the docking process; this procedure is known as *flexible docking*. Conformation generation is limited to variation around acyclic torsion bonds and pyramidal nitrogen inversions such as in

amines and sulfonamides. For a set of predefined functional groups, such as amides and esters, you can bias sampling of the torsion around the bond that normally adopts a particular conformation so that it adopts the desired conformation. These variations are controlled by the following options:

- Sample nitrogen inversions—Sample inversions at pyramidal nitrogen atoms. This option is on by default.
- Sample ring conformations—Sample ring conformations, using the same technology as in LigPrep—see Section 4.11 of the *LigPrep User Manual* for details. This option is selected by default. Only low-energy conformations are kept. You can choose to include the original ring conformation by selecting Include input ring conformation. (This conformation is of course used if you do not sample ring conformations.)
- Bias sampling of torsions for—Choose an option for sampling of torsions that should normally be restricted to a particular conformation. The biasing can include retention of the input conformation, setting the torsion to a particular value, applying a penalty for deviating from the desired conformations, or allowing only a particular conformation to within a small angle range. The options cover different selections of functional groups:
  - Predefined functional groups—Bias the sampling of torsions for a set of functional groups that is defined in a resource file. The choice of biasing method, as outlined above, is set in the resource file. The resource file can be customized—see Section 7.6.2 on page 111.
  - Amide bonds—Bias the sampling of torsions around the C–N bond of amides only. You can choose the biasing method from the option menu:
    - Penalize nonplanar conformation—Apply penalties to amide bonds that are not cis or trans, rather than freezing them entirely.
    - Retain original conformation—Fix amide bonds in their input conformation.
    - Allow trans conformation only—Enforce the trans conformation to within a small angle range (20° by default). Ligands that do not dock in a trans conformation are rejected.

    The default is to penalize nonplanar conformations.
  - None—Do not apply any biasing, but allow the conformation to be determined by the conformation generator via the force field.

Rigid

Rigid docking does not generate conformations of the input ligand. It only allows the input conformation of the ligand to be translated and rigidly rotated relative to the binding site.

None (refine only)

When this option is selected, Glide does no docking, but rather uses the input ligand coordinates to perform an optimization of the ligand structure in the field of the receptor, and then the ligand is scored. The goal of this docking method is to find the best-scoring pose that is geometrically similar to the input pose. For HTVS and SP, a minimization is performed; for XP, the ligand is regrown in place. This option is not a substitute for a full docking calculation, and requires accurate initial placement of the ligand with respect to the receptor.

None (score in place only)

When this option is selected, Glide does no docking, but rather uses the input ligand coordinates to position the ligands for scoring. It therefore requires accurate initial placement of the ligand with respect to the receptor.

This option is useful to score the native ligand in its cocrystallized or modeled position, or as a post-processing step on Glide-generated poses to obtain individual components of the GlideScore prediction of the binding affinity. It can also be used to check whether the scores of the known binders in their native proteins are similar enough to their scores when cross-docked to the chosen receptor protein. If this is the case, it is reasonable to expect that similar structures would also score well.

Score in place should not be used with Glide XP, as full XP sampling is normally needed to avoid strong XP penalties for ligands that should be able to dock correctly.

Note: You cannot use score in place for the ligand that is defined as the reference ligand for calculation of the RMSD in conformational comparisons.

5.4.3 Writing XP Descriptor Information

If you want to visualize the various scoring terms from the XP scoring function in the XP Visualizer panel, select Write XP descriptor information. These terms are written to a file that can be read by the XP Visualizer. You can write these terms only for XP docking runs.

Note: To generate XP descriptor information, you must have a license for this feature.

5.4.4 Adding Epik State Penalties to the Docking Score

If the ligands were prepared using Epik for ionization and tautomerization, the Epik penalties for adopting higher-energy states (including those where metals are present) are added to the docking score when the Add Epik state penalties to docking score option is selected. Ligands that do not have this information are not penalized and will therefore have better scores, so you should ensure that the ligand set is consistent. This option is selected by default.

If the ligand interacts with a metal (distance less than 3.0 Å), the metal penalties that are computed when Epik is run with the metal binding option are used. If multiple ligand atom-metal interactions are found, the smallest value of the metal-specific penalty is used.

5.4.5 Rewarding Intramolecular Hydrogen Bonds

Ligands with intramolecular hydrogen bonds pay a smaller entropic penalty upon binding, so forming intramolecular hydrogen bonds can be important for binding. You can add a reward for each intramolecular hydrogen bond to the GlideScore, by selecting Reward intramolecular hydrogen bonds. A reward is also added to Emodel for each intramolecular H-bond, to favor selection of poses with intramolecular hydrogen bonds.

5.4.6 Improving Planarity Around sp^2 Atoms

Groups such as aromatic rings, amides, and esters can adopt a geometry that is nonplanar. This happens because the torsional potential has a finite barrier which can be overcome to some extent by other interactions, and is a physically reasonable effect. In Glide docking, nonplanarity can also be a result of the approximations made to reduce clashes with the receptor. Selecting Enhance planarity of conjugated pi groups increases the torsional potential around bonds between atoms whose geometry should be planar (i.e. sp^2 atoms). This option should make aromatic rings, amides, esters, and so on, less likely to adopt a nonplanar geometry.

To some extent, planarity can be enforced in flexible docking by choosing one of the biasing options for sampling torsions. However, if you want to improve planarity in post-docking minimization or for non-flexible docking, you should select this option.

5.4.7 Applying Excluded Volumes

If the grid that you chose contains excluded volume data, you can choose to apply the excluded volumes when docking the ligands, and set the penalty for occupying the excluded volume. To do so, select the option Apply *size* excluded volume penalties, and choose a size for the penalty. The sizes available are large, medium, and small, which correspond to particular choices of the penalty value. The penalty ramps up linearly from zero at the edge of the sphere to the value specified, over a shell of width 10% of the sphere radius, and remains at that value over the rest of the sphere. Each atom that occupies the excluded volume incurs the penalty, and the penalty is applied in both the rough scoring stage and the final docking. You can also view the excluded volumes in the Workspace, by selecting Show excluded volumes. The excluded volumes controls are not available if the grid does not have excluded volumes.

5.4.8 Advanced Settings

Further options for controlling the docking process are available in the Settings - Advanced Settings dialog box, which opens when you click Advanced Settings in the Settings tab. You will not normally need to change these options from their defaults.

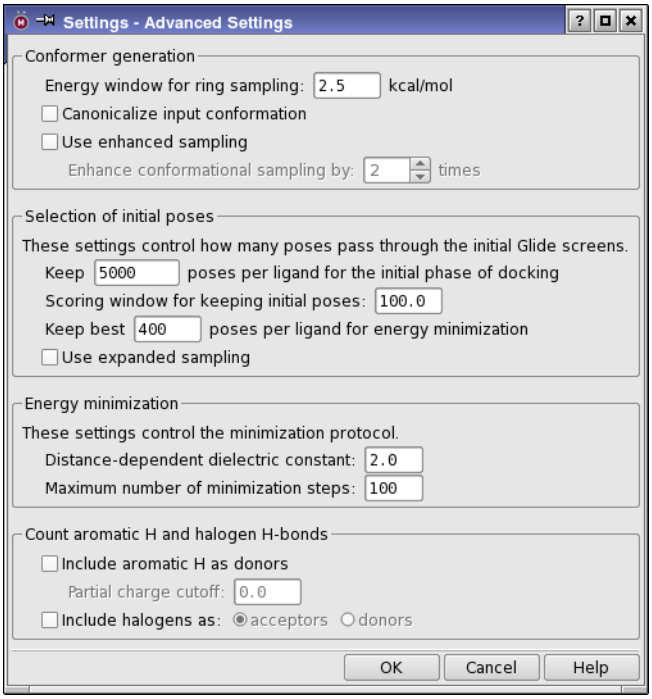

Figure 5.4. The Settings - Advanced Settings dialog box.

5.4.8.1 Conformer Generation

When you sample ring conformations, only the low-energy ring conformations are kept. The threshold for keeping or discarding ring conformations can be set in the Conformer generation section of the dialog box. Ring conformations are discarded if their energies are higher than that of the lowest conformation by more than the amount specified in the Energy window for ring sampling text box.

The poses obtained in docking can depend on details of the input structure. Sometimes this is useful, to obtain a wider range of poses, but it can also prevent comparisons between docking runs that should not depend on the detailed structure of the input ligands. To remove the dependency on the input structure, you can select Canonicalize input conformation. The input coordinates of the ligand are then discarded and regenerated, based only on the connectivity (including bond orders) and the stereochemistry.

While variation in docked poses with the input structure can be a problem, it can also be used to enhance conformational sampling. You can add variations to the input structure that are used as input to the conformational sampling, by selecting Use enhanced sampling, and specifying the enhancement factor in the Enhance conformational sampling by *N* times text box. This factor is the number of structures (including the input structure) that are used as seed structures for conformational sampling.

5.4.8.2 Selection of Initial Poses

The options in the Selection of initial poses section of the dialog box control the way poses pass through the filters for the initial geometric and complementarity "fit" between the ligand and receptor molecules. The grids for this stage contain values of a *scoring function* representing how favorable or unfavorable it would be to place ligand atoms of given general types in given elementary cubes of the grid. These cubes have a constant spacing of 1 Å. The "rough score" for a given *pose* (position and orientation) of the ligand relative to the receptor is simply the sum of the appropriate grid scores for each of its atoms. By analogy with energy, favorable scores are negative, and the lower (more negative) the better.

The initial "rough scoring" is done on a coarse grid, on which the possible positions for placing the ligand center are separated by 2 Å, twice the elementary cube spacing, in *x*, *y*, and *z*. The "refinement" step rescores the successful rough-score poses after the particular rigid translational repositioning of –1.0 Å or +1.0 Å in *x*, *y*, and *z* that gives the best possible score. This procedure effectively doubles the resolution of the scoring screen.

Poses that pass these initial screens enter the final stage of the algorithm, which involves evaluation and minimization of a grid approximation to the OPLS-AA nonbonded ligand-receptor interaction energy.

This section contains three text boxes and an option for controlling the initial screening:

Keep *n* initial poses per ligand for the initial phase of docking

This text box sets the maximum number of poses per ligand to pass to the grid refinement calculation. The value must be a positive integer. The default setting depends on the type of docking specified and whether Glide constraints have been applied:

- 5000 poses for flexible docking jobs in general
- 500 poses for flexible docking jobs to which Glide constraints are applied
- 1000 poses for rigid docking jobs (Glide constraints do not change this value)
- 100000 poses for peptide docking jobs

Scoring window for keeping initial poses

This text box sets the rough-score cutoff for keeping initial poses, relative to the best rough score found so far. The value must be positive. The default window is 100.0 kcal/mol, meaning that to survive, a pose must score within 100.0 kcal/mol of the best pose. Using the default window, for example, if the best pose found so far has a score of -60.0 kcal/mol, poses with a score more positive than 40.0 kcal/mol are rejected.

Keep best *m* poses per ligand for energy minimization

This text box specifies the number of poses per ligand to be energy minimized on the OPLS-AA nonbonded-interaction grid. The default setting depends on the type of docking specified:

- 400 poses for flexible SP docking jobs, 800 poses for flexible XP docking jobs.
- 40 poses for flexible docking jobs to which Glide constraints are applied.
- 100 poses for rigid docking jobs (Glide Constraints do not change this value).
- 1000 poses for peptide docking jobs.

The range for this value is 1 to *n*, where *n* is the value in the Keep *n* initial poses per ligand for the initial phase of docking text box, with the exception that for XP docking, the number can be adjusted between 800 and 1000.

Use expanded sampling

This option bypasses the elimination of poses based on the rough score, so that many more poses are passed on to the subsequent stages. This option is particularly useful for fragment docking to ensure that good poses are found.

5.4.8.3 Energy Minimization Settings

The energy minimization stage of the docking algorithm minimizes the energy of poses that are passed through the Selection of initial poses scoring phase. The Energy minimization section of the Settings - Advanced Settings dialog box contains two options:

Distance-dependent dielectric constant

Glide uses a distance-dependent dielectric model in which the effective dielectric "constant" is the supplied constant multiplied by the distance between the interacting pair of atoms. The default setting is 2.0, and Glide's sampling algorithms are optimized for this value. Although this text box allows you to set the dielectric constant to any real value greater than or equal to 1.0, changing this setting is not recommended. This relatively strong dielectric is sometimes needed to "hold" a hydrogen bond in the energy-grid optimization phase of the algorithm.

Maximum number of minimization steps

This text box specifies the maximum number of steps taken by the conjugate gradient minimization algorithm. The value must be greater than or equal to 0; the default value is 100. Setting the value to 0 results in a single-point energy calculation on each pose that survives rough-score screening, or on the single initial pose if no screening was done.

5.4.8.4 Hydrogen Bonds with Aromatic Hydrogens and Halogens

In addition to normal hydrogen bonds, you might want to account for other noncovalent interactions that are generally weaker, but could be important. You can choose to include three types of interactions in your docking run: hydrogen bonds to aromatic hydrogens, hydrogen bonds to halogens (halogen as an acceptor), and halogen bonds (halogen as a donor). The options to include these interactions are in the Count aromatic H and halogen H-bonds section. (Strictly speaking, halogen bonds aren't H-bonds, but they are included here as a class of weak noncovalent interactions.) Currently you can only choose to have halogens treated as donors or as acceptors, but not both. These interactions contribute to the scoring and constraints in the same way as normal hydrogen bonds.

For aromatic hydrogens, you can set a cutoff for the partial charge, to filter out hydrogens that have small partial charges. To be considered as a donor, the partial charge on an aromatic hydrogen must be greater than the value given in the Partial charge cutoff text box.

5.5 The Core Tab

In the Core tab, you can specify the "core" of a ligand, and use this core to constrain the docking of other ligands or to calculate the rms deviation from the defined core for all docked ligands. The core is specified in terms of a *reference ligand*.

The constraint that you apply here is a *ligand-based* constraint, which means that the ligands that are subject to the constraint are those that have the same core moiety as the reference ligand. Ligands that do not match the core can be screened out in the first docking stage. In later stages, ligands that match the core pattern but do not meet the rms tolerance for the position of the core can be screened out. Receptor-based constraints can be applied in the Constraints tab, which is described in the next section.

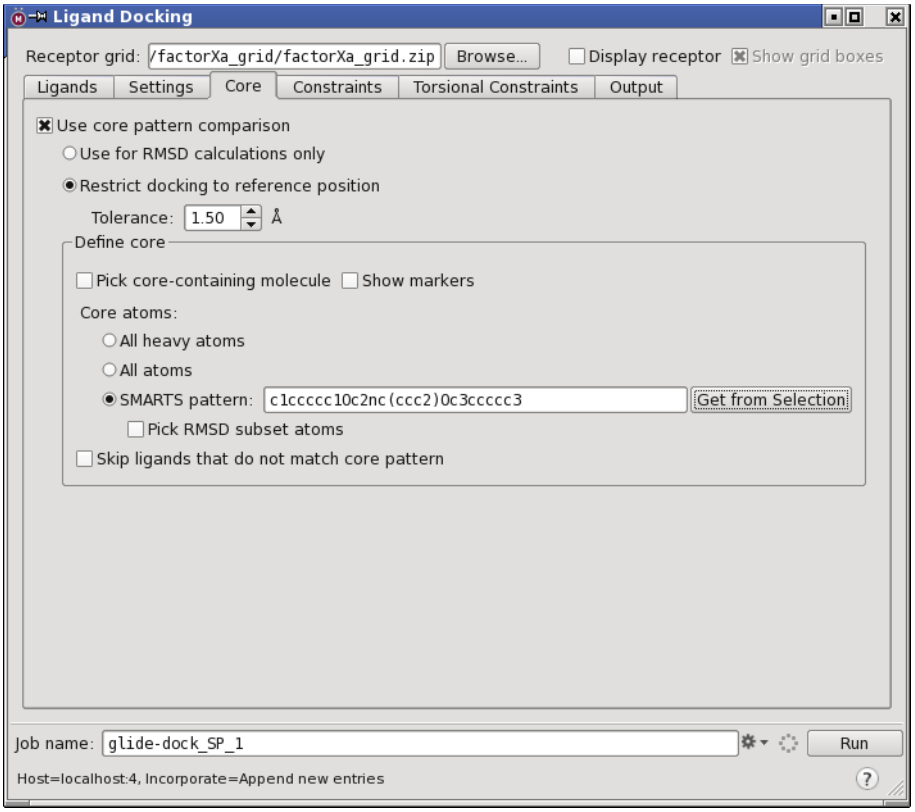

Figure 5.5. The Core tab of the Ligand Docking panel.

To use a core definition, select Use core pattern comparison, then select an option for how to use the core definition:

- Use for RMSD calculations only—Use the core definition for computing the RMSD from the reference ligand, but not for restricting docking.
- Restrict docking to reference position—Restrict the docking of ligands so that the ligand core lies within a given RMSD of the core in the reference ligand. The core is defined in terms of a set of atoms or a SMARTS pattern; if the ligand does not contain the topology defined in the core, it can be skipped. You can enter a tolerance for the RMSD in angstroms for restricting the docking to the reference position in the Tolerance text box.

The Core tab offers a great deal of flexibility in defining the core. You can use the entire molecule (or its heavy atoms) for the RMSD evaluation, or you can define a subset of the molecule, both for the matching and for the RMSD, in terms of SMARTS patterns. Choosing the core molecule and setting up the core pattern is done in the Define core section of the Core tab. The

controls in this section become available when you choose Use for RMSD calculations only or Restrict docking to reference position.

If you plan to use the entire reference ligand for the core (or its non-hydrogen atoms), ensure that Pick core-containing molecule is selected, then pick an atom in the Workspace that belongs to the core molecule. The molecule is marked in purple in the Workspace if Show markers is selected. Pick core-containing molecule is automatically selected when the controls in this section become available. You can then proceed to choose All heavy atoms or All atoms for the core, under Core atoms.

If you want to define the core in terms of a smaller set of atoms, select SMARTS pattern under Core atoms. Pick core-containing molecule is automatically deselected if you make this choice, because you can choose any atoms and picking a molecule is no longer relevant. You can then enter a SMARTS pattern into the text box, or you can select atoms in the Workspace with the Select atoms tool,

then click Get From Selection to create a SMARTS pattern for the selected atoms. The atoms in the core molecule that match the pattern are marked in the Workspace with green markers if Show markers is selected. Note that it is advisable not to have the receptor displayed when you click Get From Selection, because it can slow the generation of the SMARTS pattern.

You might not want to use all the atoms in the SMARTS pattern for the RMSD calculation. If this is the case, you can choose Pick RMSD subset atoms, and pick atoms in the Workspace that are in the SMARTS pattern to define a subset of atoms for the RMSD calculation. A lock symbol appears next to the atoms you pick. Each pick adds to the set; picking an atom again deletes it. The RMSD atoms are used both when calculating only the RMSD and when restraining the core: it is the RMSD of these atoms that must fall below the prescribed tolerance in the latter case.

Finally, you can select Skip ligands that do not match core pattern if you want to strictly apply the core pattern filter. This option is selected by default. When it is selected, ligands that do not match the core are discarded in the first stage of the funnel. If this option is not selected, ligands that do not match the core pattern are docked anyway, the core constraints are not applied, and the RMSD is only calculated for those ligands that do match the core pattern.

5.6 The Constraints Tab

The Constraints tab lists all the Glide constraints that are defined for the receptor grid file you specified in the Settings tab, and provides the means to apply these constraints in docking. The available constraints are shown in the Workspace if Show markers is selected and the receptor is displayed. To display the receptor, select Display Receptor. Positional and NOE constraints are marked with gray spheres. Atoms for which H-bond/metal constraints are defined are marked with a red asterisk.

Constraints are applied during or after docking by identifying the relevant features in the ligand, and requiring specified atoms in those features to be spatially confined to the constraint region. The ligand features and the atoms in those features that must be constrained are defined in terms of SMARTS patterns. You can customize the features in the Edit Feature dialog box, which is described in Section 5.6.2 on page 64. For positional constraints, no default features are defined, so you must provide a feature definition in the Edit Feature dialog box.

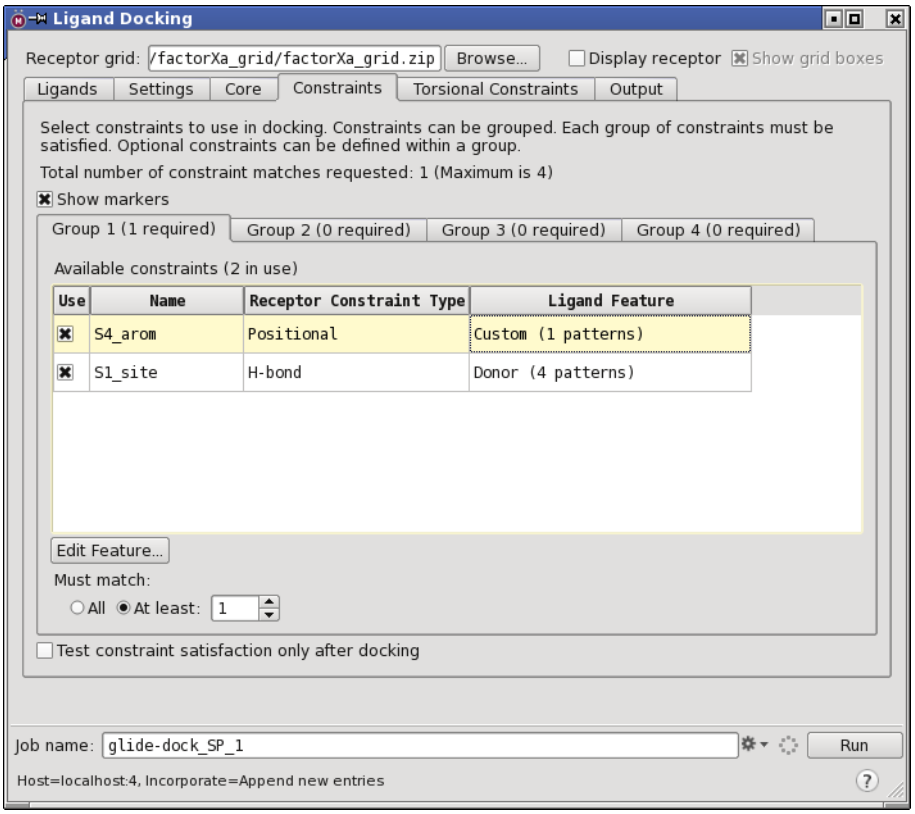

Figure 5.6. The Constraints tab of the Ligand Docking panel.

Glide constraints can be used in HTVS mode, but may result in poor pose recovery relative to unconstrained HTVS docking.

Only the constraints you select will be applied in the ligand docking job you are setting up. If there are no constraints selected when you start the docking job, no constraints will be applied.

5.6.1 Setting Constraints

To allow some flexibility in setting constraints, including optional constraints, Glide provides four constraint groups, presented in subtabs labeled Group 1 through Group 4. If you want to set simple constraints you can do so in the Group 1 tab, which is displayed by default, and ignore the remaining groups.

Each subtab contains a table of all the available constraints (described in Table 5.1), an Edit Feature button, and two Must match options. To set constraints within a tab, first click the Use column for each of the desired constraints. An X appears in the check box. If the receptor is displayed and Show markers is selected, the hydrophobic and positional constraint markers turn red when the constraint is selected, and the H-bond and metal constraint markers turn turquoise. The number of constraints you selected is displayed next to the table title.

Table 5.1. Description of the Available constraints table.

Column	Description
Use	Check box to select the constraint for use in docking. Click to select or deselect.
Name	Constraint name. This is the name defined in the Constraints tab of the Receptor Grid Generation panel.
Receptor Constraint Type	Type of receptor constraint. Hydrogen bond constraints are classified into H-bond for hydrogen-bond acceptors and Polar Hydrogen for hydrogen-bond donors (i.e. hydrogen atoms).
Ligand Feature	Name of the feature in the ligand that must match the constraint. The available features are: Acceptor, Charged Acceptor, Neutral Acceptor, Donor, Hydrophobic, and Custom. By default, the feature that matches a receptor polar hydrogen is set to Acceptor; for a receptor H-bond type it is Donor, for a receptor hydrophobic feature it is Hydrophobic, and for a positional constraint it is Custom. Custom is undefined by default, so you must edit this feature to define the patterns that match the desired ligand atoms.
Number of Ligand Atoms	In this column, the number of ligand atoms that must occupy a hydrophobic region can be set. The value is only meaningful for hydrophobic constraints.

Next, decide whether all the constraints should be applied, or only some of them.

- If you want all of the chosen constraints to be applied, select All under Must match.
- If you want some of the chosen constraints to be applied, select At least under Must match, and enter the number of constraints that must be satisfied in the text box. For example, if you chose three hydrogen-bond acceptors, and you want any two out of the three to be satisfied, you would enter 2 in the text box.

The number of constraints that are required is displayed in the subtab tab, and is added to the total, which is displayed in the upper part of the Constraints tab.

To clear a constraint, click the Use column again. The X in the check box disappears.

More complex constraints can be applied by using more than one constraint group. If you set constraints in more than one group, each group of constraints is applied to the ligand (that is, a Boolean AND is applied between groups). The general syntax of the constraints is (N1 required from Group 1) AND (N2 required from Group 2) AND (N3 required from Group 3) AND (N4 required from Group 4).

For example, suppose the grid contains a hydrogen bond constraint hbond1 and two positional constraints pos1 and pos2. If you want to enforce the hydrogen bond constraint, and require only one of the two positional constraints, you would use two groups. In Group 1, you would click the Use check box for hbond1 and select All under Must match. In Group 2, you would click the Use check boxes for pos1 and pos2, select At least under Must match, and enter 1 in the text box. Both groups are applied. The resulting constraints can be represented as "hbond1 AND (pos1 OR pos2)".

If your desired constraint specification cannot be put in the general form above, you might be able to achieve your goal by running more than one docking job with a separate constraint specification for each. For example, if you want to apply the constraints "(hbond1 AND pos1) OR (hbond2 AND pos2) OR (hbond3 AND pos3)", you could run three separate docking jobs, one with (hbond1 AND pos1) set, one with (hbond2 AND pos2) set, and one with (hbond3 AND pos3) set.

The total number of required constraints, summed over all groups, must be four or fewer. The number in parentheses after the group name in the subtab tab is the number of constraints that must be satisfied in this group. If you selected All, it is the number of constraints you chose. If you selected At least, it is the value in the At least text box.

A default ligand feature definition is supplied and assigned to each receptor constraint type, with the exception of positional constraints, for which the Custom feature is undefined. To change either the assignment or the feature definitions, use the Edit Feature dialog box, as described in the next section. You can select the same constraint in more than one group, but the assignment and the feature definitions are the same for each group.

To use positional constraints, you *must* define the ligand feature that it should match. No default feature definition is provided, and the job cannot be run until a feature definition is provided. To define the ligand feature, select the appropriate row in the Available constraints table and click Edit Feature. The feature can then be defined in the Edit Feature dialog box.

5.6.2 Defining Ligand Features

Ligand features are identified by matching to a collection of SMARTS patterns that defines a feature type. The available feature types are:

- Acceptor—Neutral or charged acceptor.
- Charged Acceptor—Acceptor that has a formal charge. Includes $O^{\bullet}$, $S^{\bullet}$, $F^{\bullet}$, $Cl^{\bullet}$. Both oxygens in a carboxylate are included as charged acceptor atoms.
- Neutral Acceptor—Acceptor that does not have a formal charge. Includes a range of groups containing N and O.
- Acceptor Including Halogens—Acceptor or a neutral halogen (F, Cl, Br, I).
- Donor—Hydrogen attached to any neutral nitrogen, oxygen or sulfur; also includes $OH^{\bullet}$
- Donor Including Aromatic H—Donor as defined above and any hydrogen attached to an aromatic carbon.
- Donor Including Halogens—Donor as defined above and any neutral halogen other than F. Halogens can make nonbonded interactions with acceptor groups.
- Donor Including Aromatic H + Halogens—Donor, hydrogen attached to aromatic carbon, or halogen, as defined above.
- Hydrophobic—A range of patterns of aliphatic and aromatic carbons, and neutral halogens other than F.
- Custom—Specify your own feature type by defining SMARTS patterns that match the feature.

The donor or acceptor feature type is coordinated with the settings for aromatic and halogen H-bonds in the Settings - Advanced Settings dialog box (see Section 5.4.8.4 on page 58). A change in either place changes the setting in the other.

The feature definitions for these types form a *feature set*, which can be imported and exported. Each constraint can have its own feature definition, so you can have a different definition of a given feature type for each constraint. However, the same feature definition from the same set is used for a given constraint in all groups. For each feature definition, you can add patterns, edit and delete custom patterns, and define patterns for exclusion of functional groups. Feature

sets can be imported and exported. These tasks are carried out in the Edit Feature dialog box, which you open by clicking Edit Feature.

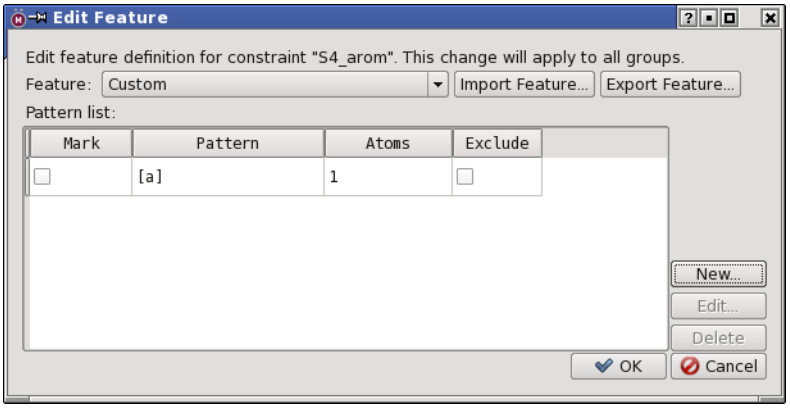

Figure 5.8. The Edit Feature dialog box.

To change the feature type assigned to the constraint or to edit the feature definition for a particular constraint, select the row in the Available constraints table, and click Edit Feature.

If you only want to change the feature type assigned to the constraint, choose the feature type from the Feature menu, and click OK. The change is reflected in the Ligand Feature column of the Available constraints table, and applies to all groups. If you want to edit the feature definition, follow the instructions in Section 5.6.2.2 and Section 5.6.2.3.

5.6.2.1 Loading and Saving Feature Sets

Built-in feature sets are stored with the distribution, so you do not need to create your own, except for positional constraints.

You can import a feature set for the selected constraint from a file by clicking Import, and navigating to the feature file. When you import a feature set, the definitions of all feature types are replaced, not just the feature type chosen from the Feature menu. The feature definitions are replaced only for the selected constraint, but are replaced for that constraint in all groups.

Feature sets can be saved to a file by clicking Export, and specifying the file location in the file selector that is displayed.

5.6.2.2 Adding, Editing, and Deleting Patterns

The patterns that define a feature are displayed in the Pattern list table (see Table 5.2) when you choose the feature type from the Feature option menu.

If the patterns in a given feature definition do not cover all the functional groups that you want to include in the definition, you can add extra patterns. Matching of patterns to ligand structures is done in the order specified in the Pattern list table. You cannot change the order of the patterns once they are in the table, so you must add new patterns at the appropriate point. If you want to move a pattern, you must delete it and add it again.

To add a new SMARTS pattern, click the table row above which you want the pattern to be inserted, then click New. In the New Pattern dialog box, you can provide a SMARTS pattern and define the atoms that must satisfy the constraint: the acceptor or donor atoms, for example.

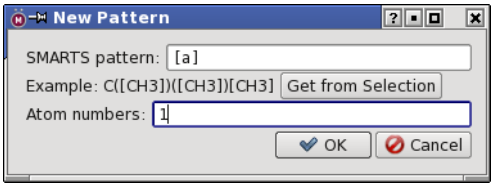

Figure 5.10. The New Pattern dialog box.

There are two ways to provide a SMARTS string. The first is to type the string into the SMARTS pattern text box. The second is to select atoms in the Workspace, then click Get from selection. Maestro generates a SMARTS string for the selected atoms and places it in the SMARTS pattern text box. You can then edit it if you like. You should make sure that you have a suitable molecule, such as a known active ligand, in the Workspace before you open the Edit Feature dialog box. This second procedure can be slow if large molecules, such as a receptor, are displayed in the Workspace.

Table 5.2. Description of Pattern list table.

Column	Description
Mark	Column of check boxes. Selecting a check box marks the pattern on any structures that are displayed in the Workspace.
Pattern	Pattern definition. The definitions are SMARTS strings.
Atoms	The list of atoms that may be constrained, numbered according to the SMARTS string.
Exclude	Column of check boxes. If a check box is selected, the atoms in other patterns are matched only if they do not match this pattern. This is essentially a NOT operator. Excluded patterns are processed before other patterns.

To specify the atoms in the ligand that must satisfy the constraint, enter the atom numbers as a comma-separated list in the Atom numbers text box. The atom numbers are given relative to the SMARTS pattern: atom 1 is the first atom in the SMARTS pattern, and so on.

For positional, metal, and H-bond constraints, you can specify multiple atoms, but only one of the specified atoms is constrained. Normally, only one atom should be specified, to ensure that the correct atom is constrained. However, if the functional group contains multiple acceptors or donors, for example, you can specify all of them if you want any one of them to be constrained. This is not necessary for groups such as carboxylates, where the local symmetry of the functional group is used and either of the oxygen atoms in the carboxylate can be selected for the constraint, even though only one of them is specified.

For hydrophobic constraints, the non-hydrogen atoms of the hydrophobic group should be specified. The number of atoms that is constrained is specified in the Required Ligand Atoms column of the Available constraints table.

When you click OK, a new row is added to the Pattern list table.

To edit a pattern, select the table row for the pattern, then click Edit. In the Edit Pattern dialog box, you can modify the SMARTS pattern or get a new pattern from the Workspace selection, and change the atoms in the pattern that must satisfy the constraint. The Edit Pattern dialog box is identical to the New Pattern dialog box except for the title.

To delete a pattern, select the table row for the pattern, then click Delete.

5.6.2.3 Excluding Functional Groups from a Feature

If you want to ensure that certain functional groups are not matched, you can select the check box in the Exclude column for the pattern for that group. For example, you might want to exclude a carboxylic acid group from being considered as a hydrogen bond donor, because it will be ionized under physiological conditions. Excluded patterns are processed first, regardless of their position in the Pattern list table. Thus, an excluded pattern prevents the atoms that match it from being matched by any other pattern.

5.6.2.4 Visualizing Patterns

If you want to see a pattern for a given ligand or group of ligands, you can select the check box in the Mark column for the pattern. Any occurrences of the pattern are marked in the Workspace. You can display markers for more than one pattern, but the markers do not distinguish between patterns. If you want to see the atoms and bonds as well as the markers, select Apply marker offset.

5.6.3 Choosing When To Apply Constraints

Constraints can be applied during the docking process, or only after the ligands have been docked. When testing for constraint satisfaction after docking, constraints are used as a post-docking filter and have no influence on the docking or scoring. You can therefore compare results from such a run directly with an unconstrained docking run. To apply constraints only

after docking, select Test constraint satisfaction only after docking. This option applies only to the constraints available in the Constraints tab, not to core constraints or torsional constraints.

5.6.4 Using Multiple Constraints

When you use multiple constraints with complex optional constraint specifications and many ways of satisfying the constraints, it is possible to lose poses because Glide cannot track all possible ways a given pose can satisfy the constraints, due to memory limitations. Under these circumstances, Glide truncates the list of poses or the selections of constraint-satisfying atoms per pose, or both. The result is that poses that would ultimately satisfy the constraints are lost.

There are several ways in which you can alleviate this problem:

- Select Test constraint satisfaction only after docking in the Constraints folder when setting up the docking job. (If you run from the command line, add the keyword `finalonly` after `constraints` in the *jobname*`.inp` file.) This avoids the memory explosion needed to track complicated constraint combinations through the Glide funnel, but still ensures that the final docked poses satisfy the required constraints.
- Use more restrictive SMARTS patterns to define the kinds of ligand atoms that can satisfy the constraints. This can reduce the memory requirements for tracking constraint satisfaction in a given ligand to a point where all constraint-satisfying poses can be kept. If you need to allow more general chemistry to satisfy your constraints, you can run multiple Glide jobs to cover the various possibilities.
- Split your job into several jobs with tighter restrictions on which constraints must be satisfied, while still spanning all the desired possibilities. For instance, suppose you want your ligands to make hydrogen bonds to each of three protein hydroxyl groups, but don't care which molecule is the donor and which is the acceptor for each group. A single job to cover all the possibilities would have three groups of two constraints each, each group consisting of H-bond constraints to the hydrogen and oxygen of one of the protein hydroxyls, and would require one of the two constraints in each group to be satisfied. This job is likely to run into the memory problems and lose poses, particularly for ligands that have multiple H-bonding groups (e.g. sugars). Instead, you could run eight Glide jobs, one for each specific combination of donors and acceptors among the three protein hydroxyls. Each job would specify a single group of three constraints, all required, and would be less likely to lose poses due to memory restrictions.

5.7 The Torsional Constraints Tab

There are situations in which you want to constrain some of the torsional degrees of freedom in the ligand. For example, a ligand in the binding site might have only one conformation of a particular rotatable group, while other groups can exist in several conformations. Or the ligand might have a large number of rotatable bonds, such as in a polypeptide. Glide provides a means of constraining selected torsional degrees of freedom in the Torsional Constraints tab. The groups that are constrained are defined in terms of SMARTS patterns, and you can constrain all of the torsions in the group or only selected torsions in the group.

This tab is only available when either Dock flexibly or Refine is selected in the Settings tab.

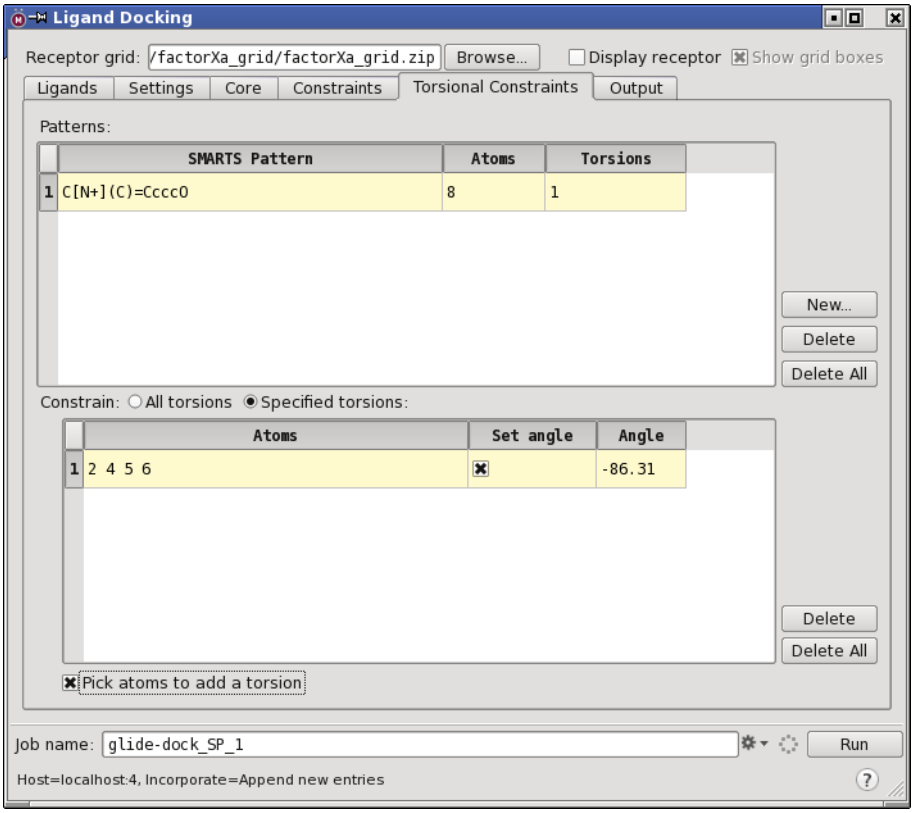

Figure 5.11. The Torsional Constraints tab of the Ligand Docking panel.

To set up and apply the constraints, you need to define the rotatable groups, and for each group, the torsions to constrain. The easiest way of defining the groups is to include a ligand in the Workspace and select the atoms in the group with the Select atoms tool:

When you have selected the atoms, click New. The New Torsion Pattern dialog box opens, and you can click From Workspace Selection to get the SMARTS pattern from the atoms that you selected in the Workspace. You can also type in a SMARTS pattern directly. When you click OK, a new row is added to the Patterns table that shows the SMARTS pattern the number of atoms in the pattern and the number of torsions defined (which is initially zero). The pattern is marked on the matching atoms in the Workspace.

The SMARTS pattern cannot be changed. If you want to modify it, you will have to create a new pattern, and delete the old one.

To delete a pattern, select it in the Patterns table, and click Delete. To delete all patterns, click Delete All.

Once you have entered a SMARTS pattern, you can then select it in the table to define the torsions that are constrained within that pattern. If you want to constrain all the torsions for this pattern, select All torsions. The Torsions column in the Pattern table then shows All. If you want to choose the torsions to constrain, select Specified torsions, and then you can do so by picking atoms.

1. Select Pick atoms to add a torsion.
2. Pick four atoms in the Workspace to define the torsion.

   The atoms must form a contiguous set of three bonds when you have finished picking, and must not define a ring torsion. They must also be atoms in the SMARTS pattern for which you are defining torsions.

When you have picked the torsion, the atom numbers are shown in the table. The torsion is marked in the Workspace with the number in the table and the current value of the angle, and the number of torsions in the Torsions column of the Patterns table is updated.

No checking is done for the validity of the torsion prior to docking, so you must make sure that it meets the criteria given above. The torsion cannot be changed once you have defined it, so if it is in error, you must delete it.

To delete a torsion, select it in the table and click Delete.

See Section 3.11 of the *Glide Quick Start Guide* for an example of setting and using torsional constraints.

5.8 The Output Tab

The options in the Output tab control the final output of ligand poses that pass successfully through Glide's various scoring stages. The features of this tab are options in a section called Structure output and an Advanced Settings button. Clicking the button opens the Output - Advanced Settings dialog box.

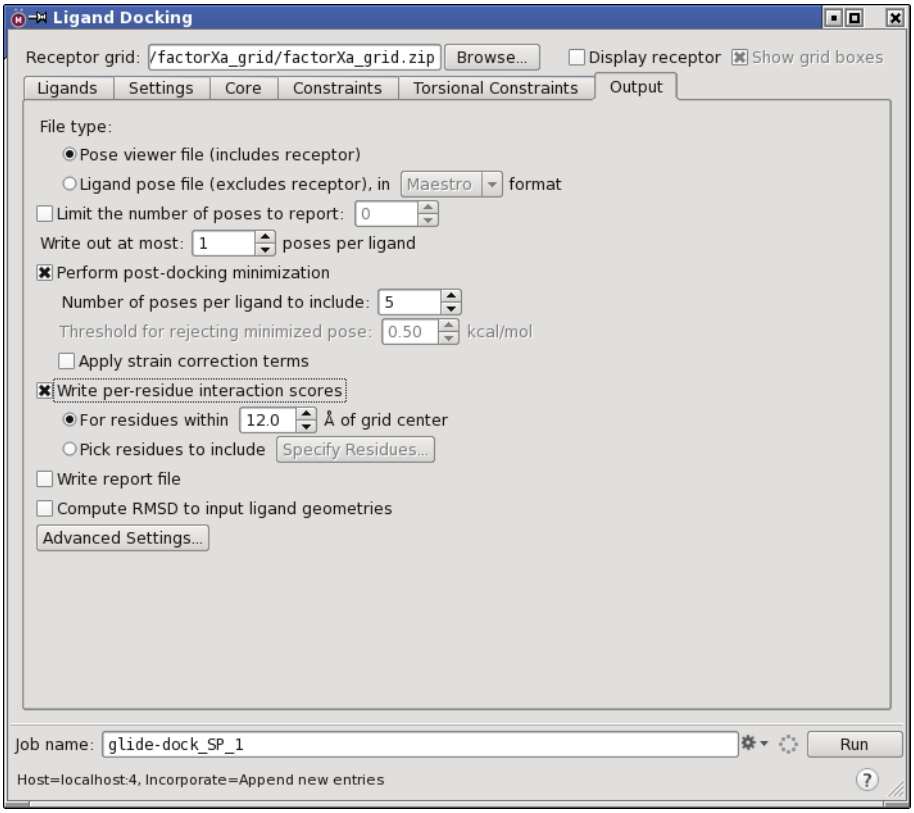

Figure 5.12. The Output tab of the Glide panel.

5.8.1 Structure Output Options

In flexible docking runs, Glide appends docked poses to a file named *jobname*`_raw.`*suffix*, where *suffix* depends on the output file format (`.maegz` or `.sdfgz`). The "raw" in the filename indicates that these poses are not sorted by GlideScore. Once the Glide job has docked all the ligands, it runs the `glide_sort` utility script to sort the raw poses and write them to *jobname*`_pv.`*suffix* or *jobname*`_lib.`*suffix*. The *jobname*`_raw.`*suffix* file is then deleted.

Rigid docking runs sort the poses internally, then, at the end of the job, the sorted poses are written to either *jobname*_pv.*suffix* or *jobname*_lib.*suffix*. The glide_sort utility is not automatically used in rigid docking jobs.

For score-in-place jobs, the structure output file contains the input structures, since they are not altered.

The output files for the job are written to a subdirectory of the current directory, which is named with the job name.

The glide_sort utility can sort any pose file, whether _raw.*suffix*, _pv.*suffix*, or _lib.*suffix*, using default or alternate criteria—see Section 7.5.1 on page 109.

The options in the Structure output section are described below.

File type

The final list of poses that pass Glide's criteria are written to a multi-structure compressed pose file. You can select one of two options for the file type:

- Pose viewer file (includes receptor)

  This option includes the receptor and the poses in the output pose file, and is intended for use with the Pose Viewer. It is in Maestro format and is named *jobname*_pv.maegz.

- Ligand pose file (excludes receptor), in *format* format

  This option includes only the ligand structures in the output pose file. This file cannot be used with the Pose Viewer, but may be useful if the output poses are intended for input to a subsequent Glide job, or for some other purpose. It is named *jobname*_lib.*suffix*, where *suffix* is determined by the choice of output format made from the option menu. The choices are Maestro and SD, resulting in a .maegz or an .sdfgz suffix.

You cannot write ligand pose files with XP descriptors, with per-residue interactions, or if you have rotatable groups in the grid. These features require a pose viewer file.

Limit the number of poses to report

This option limits the total number of the predicted best-binding poses written to the sorted pose file to the specified value. The default is to report all poses that pass all the filters.

Write out at most *m* poses per ligand

This text box limits the number of poses per ligand written to the sorted pose file. The default choice of 1 pose per ligand is intended for database screening applications. A larger choice may be appropriate for lead-optimization studies or whenever several "reasonable" poses are wanted; for example, to generate a variety of docked poses for study with Liaison or another

post-docking program. However, if you have a small binding pocket or ligands with few rotatable bonds, choosing a larger number might simply retain poor poses.

Compute RMSD to input ligand geometries

This option enables the computation of the RMSD between the docked poses and the corresponding input ligand geometries. The RMSD calculation is done in place with heavy atoms only. The value is recorded as a Maestro property named glide rmsd to input (internal name `r_i_glide_rmsd_to_input`).

Write report file

A report file in plain text format that lists information about the scoring of the retained poses is written to *jobname*`.rept` if this option is selected. Like the pose viewer file or ligand pose file, the report file lists the poses in rank order by the selected final-scoring function. The report file is not written for distributed jobs.

For score-in-place jobs, instead of the `.rept` file, a `.scor` file is produced, containing scoring information for the input structures.

5.8.2 Post-Docking Minimization

The docking process relies on rapid generation of ligand conformers and use of a grid to represent the receptor. The ligand poses generated during docking are rarely exactly at a local minimum, and post-minimization can improve the geometry of the poses. The Grid Minimization step of the Glide funnel (see Figure 2.2 on page 9) does not perform a full force-field minimization and excludes interactions beyond 1,5 interactions. The full force-field minimization performed by post-docking minimization penalizes highly strained ligand geometries and eliminates poses with eclipsing interactions, many intraligand close contacts, and so on.

The Perform post-docking minimization option specifies a full force-field minimization of top-ranked poses following the final docking. This minimization optimizes bond lengths and angles as well as torsional angles, and rescores the poses using the scaled Coulomb-van der Waals term and the GlideScore. You can perform the post-docking minimization for both flexible and rigid docking.

When you perform post-docking minimization, you can select the number of poses per ligand to minimize. Testing has indicated that the rescoring of poses after post-docking minimization generally finds a lower GlideScore than is reported in the top few poses from docking. Thus, it is strongly recommended to apply the minimization to a number of poses. You can enter the number in the Number of poses per ligand to include text box. This number must not be less than the number of poses per ligand that is written to the output file. The default is 10 for XP, 5 for SP or HTVS, and 100 for SP-Peptide. If the binding pocket is small, or the ligands are

fairly rigid, the post-docking minimization will not improve the results for poses that do not fit or are already poorly aligned to the receptor.

For HTVS and SP docking, the minimized poses replace the original poses. For XP docking, the pose is kept if the GlideScore is no higher than that of the original pose by less than a certain threshold, otherwise the original pose is kept. This threshold is specified in the Threshold for rejecting minimized pose text box.

The time taken for post-docking minimization is less than 1% of the total docking time for SP and XP docking, and can be around 10% for HTVS.

In addition to minimizing, you can choose to calculate and apply a strain correction when doing the final scoring, by selecting Apply strain correction terms. These terms are evaluated by optimizing each ligand pose as a free ligand, first with constraints on all torsions, then without these constraints. The difference is used to compute a penalty term for unreasonably high strain: the strain correction is only added if it is above a threshold, and the excess strain above this threshold is scaled before adding it to the GlideScore. You can set the threshold and the scaling factor in the Output - Advanced Settings dialog box.

5.8.3 Per-Residue Interaction Scores

To examine interactions between a ligand and individual, nearby receptor residues, you can write out per-residue interaction scores for selected residues or for residues within a chosen distance of the grid center. The Coulomb, van der Waals, and hydrogen bonding scores, the sum of these scores (interaction energy, Eint), and the minimum distances are calculated between the ligand and the specified residues. These values are written as properties for each ligand to the output file, as well as to the log file.

To enable writing of the scores, select Write per-residue interaction scores, then choose an option to specify the residues:

- For residues within *N* Å of grid center—Write scores for complete residues that have any atom within the specified distance of the grid center.
- Pick residues to include—Pick residues for which the scores are written. Click Specify Residues and use the picking controls in the dialog box that opens to pick residues.

Per-residue interactions can be visualized in the Workspace when viewing poses. See Section 6.1 on page 79 for more information.

5.8.4 Advanced Settings

In the Output - Advanced Settings dialog box, you can set options to screen out poses that either have too high an energy or are too similar to other poses, and change the parameters associated with strain correction. The thresholds for rejection of poses are set into two sections, Filter and Clustering; the strain correction thresholds are set in the Strain Correction section.

The Filter section contains a single option, Reject poses with Coulomb-vdW energy greater than *x* kcal/mol. If the pose has a coulomb-vdW score greater (more positive) than this value, the pose is rejected. The default value is 0.0 kcal/mol. This means that poses that interact favorably with the protein site, however weakly, are retained, whereas poses that interact unfavorably are rejected. Change *x* to a negative value to reject poses with weakly favorable interactions, or to a positive value to keep poses with mildly unfavorable interactions.

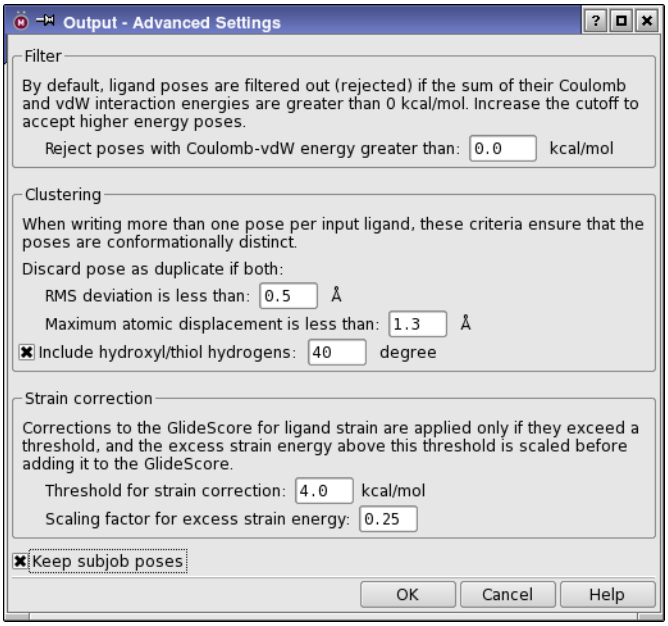

Figure 5.13. The Output - Advanced Settings dialog box.

The clustering options determine which ligand poses are sufficiently alike to be considered duplicates. To determine whether a pose is a duplicate, Glide uses a sophisticated algorithm for recognizing "number reorderings" that need to be taken into account—for example, to accommodate trivial variations such as a 180º rotation of a phenyl group. Ligand poses are compared to those previously selected for inclusion in the reported output, and are discarded as duplicates if either of the following criteria are met. This ensures that reported poses are conformationally distinct. The criteria are:

- RMS deviation is less than *d* Å

  For a pose to be considered a duplicate of one already scored the heavy-atom (nonhydrogen) RMS deviation must be less than *r* Å. The default RMS deviation threshold for *r* is 0.5 Å; choose any value greater than 0.0 Å.

- Maximum atomic displacement is less than *d* Å

  For a pose to be considered a duplicate the maximum atomic displacement must be less than *d* Å. The default is 1.3 Å; choose any value greater than 0.0 Å.

The use of symmetry is somewhat time-consuming, so there is a limit of 100 on the number of poses that are compared by this method.

In addition, the torsions of hydroxyl and thiol can be checked independently, by selecting Include hydroxyl/thiol torsions. If the difference in all such torsional angles is less than the value given in the text box, and one of the RMSD or MAD criteria is also met, the pose is considered a duplicate.

The GlideScore is corrected for excessive strain of the ligand by adding to it a fraction of the strain energy that exceeds a threshold value. This correction is made only if you have selected Apply strain correction terms in the Output tab. The threshold value is specified in the Threshold for strain correction text box, and the fraction of the excess strain energy, expressed as a decimal number, is specified in the Scaling factor for excess strain energy text box. The default value of the threshold is 4.0 and of the scaling factor is 0.25.

You can also set an option to keep the zip archive, *jobname*`_subjob_poses.zip`, which contains the pose files from all the subjobs of a distributed docking job. The archive is copied back to your working directory. This archive may be useful if you limit the number of poses to report for the job too severely and want to examine other poses without doing the entire docking run again. You can run `glide_merge` using the contents of this archive with the `-n` option to set a new number of poses to report. If disk space is an issue, deselect this option.

5.9 Docking Output Properties

In addition to the docked poses, HTVS and SP docking runs generate a number of Maestro properties, including terms in the scoring function; various indexes; and ligand efficiency metrics, which allow discrimination on the basis of size for ligands that have similar docking score values. These properties are listed in Table 5.3. See page 10 for a description of the GlideScore terms and energy components.

Table 5.3. Maestro properties generated by HTVS and SP docking runs.

Property	Description
glide lignum	Ligand number
docking score	Docking score, including all additional terms.
glide gscore	GlideScore
glide lipo	Lipophilic contact plus phobic attractive term in the GlideScore.
glide hbond	Hydrogen-bonding term in the GlideScore.
glide metal	Metal-binding term in the GlideScore.
glide rewards	Various reward or penalty terms
glide intrahb reward	Rewards for ligand intramolecular hydrogen bonds. Also included in glide rewards.
glide evdw	Van der Waals energy.
glide ecoul	Coulomb energy.
glide erotb	Penalty for freezing rotatable bonds in the GlideScore.
glide esite	Term in the GlideScore for polar interactions in the active site.
glide emodel	Model energy, Emodel.
glide energy	Modified Coulomb-van der Waals interaction energy
glide einternal	Internal torsional energy
ligand efficiency	(docking score) / (number of heavy atoms)
ligand efficiency sa	(docking score) / (number of heavy atoms)$^{2/3}$. This efficiency metric approximates the effect of surface area.
ligand efficiency ln	(docking score) / (1 + ln(number of heavy atoms))
glide confnum	Conformer index for the pose
glide posenum	Pose index of the pose
glide RMSD to input	RMSD between the docked poses and the input geometries. Only present if Compute RMSD to input ligand geometries was selected in the Output tab.
conssat *constraint*	Boolean reporting whether the constraint labeled *constraint* was satisfied. The label includes the name specified for the constraint, and if multiple constraint groups were used, includes a suffix (Group *n*) to indicate the group in which the constraint was satisfied.

Visualizing Docking Results

Several tools are provided to help visualize the results of docking runs. The View Poses facility in the Project Table panel enables you to display the ligand poses with the receptor in the Workspace, along with hydrogen bonds, bad and ugly contacts, and per-residue interaction information. This facility is described in the next sections.

For Glide SP and XP docking runs, you can visualize the contributions to the XP docking score, provided that descriptor information was requested in the docking run. Visualization in the Workspace is done using the Glide XP Visualizer panel, which is described in Section 6.2.

6.1 Viewing Poses

Maestro has a special facility for viewing poses from a pose viewer file (`_pv.mae[gz]`) or an ensemble pose viewer file (`_epv.mae[gz]`). This facility allows you to step through poses with the receptor fixed in the Workspace. You can also define and display hydrogen bonds, contacts, and per-residue interactions, and count hydrogen bonds and contacts. If you have flexible hydroxyl or thiol groups ("rotatable groups") in the receptor, these are shown in the correct orientation for each pose, and you can export the receptor and poses for given orientations of the rotatable groups. If you have multiple receptors from an ensemble pose viewer file, the best receptor for each ligand is shown as you step through the ligands.

These capabilities are available in the Pose Viewer panel, which you can open by choosing Entry → View Poses in the Project Table panel, or by choosing Tasks → Docking → Pose Viewer or Applications → Glide → Pose Viewer in the main window. You can also right-click on an entry group in the Entry List panel or the Project Table panel and choose View Poses to select the group and open the Pose Viewer panel.

6.1.1 Setting Up Pose Viewing

To use the pose-viewing facility to step through poses, you must select a single entry group in the Project Table. The group must contain the receptors at the beginning of the group, followed by the ligands, and the entries in the group must have the appropriate properties. This is the normal situation when you import a pose viewer file or ensemble pose viewer file into the project. Ensemble pose-viewer files have multiple receptors at the beginning of the file, and a property that associates each ligand pose with its receptor. You can create an ensemble pose-viewer file from separate pose-viewer files with the `glide_merge` utility, using the `-epv` option. (Hereafter, both kinds of files are referred to as pose viewer files.)

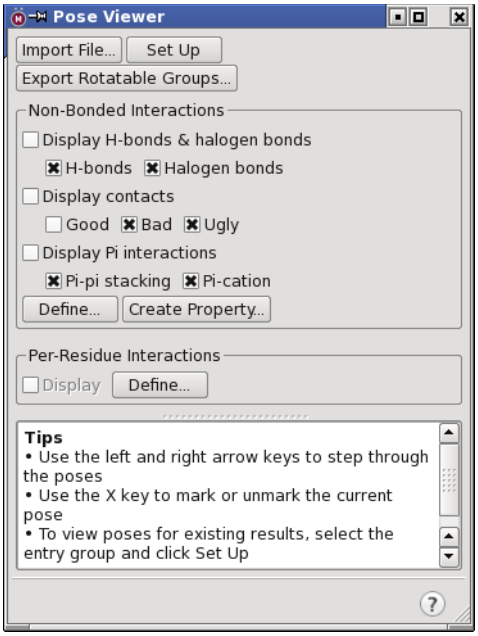

Figure 6.1. The Pose Viewer panel.

To set up pose viewing for a set of poses in the Project Table:

1. Select the entry group in the Project Table that contains the poses.

   The receptor or receptors must be at the beginning of the group, followed by the ligands. This is the normal situation when you import a pose viewer file into the project.

2. Choose Entry → View Poses.

   The Pose Viewer panel opens.

3. Click Set Up.

   The first ligand entry is included in the Workspace, the receptor is fixed in the Workspace, the and the view zooms to the ligand.

To import poses and set up pose viewing from the Pose Viewer panel:

1. Open the Pose Viewer panel.
2. Click Import File.
3. Navigate to and import the pose-viewer file.

   Setup is performed automatically.

To import poses in the Import dialog box and set up pose viewing:

1. Open the Preferences panel (Maestro → Preferences).
2. Under Project – Importing structures, ensure that For pose-viewer files, turn on pose viewing is selected.

   Once you have done this, you can skip the steps above the next time.
3. Open the Import dialog box, for example by clicking the Import toolbar button.

   
4. Navigate to and import the pose-viewer file.

   When the file is imported into the project, the Pose Viewer panel opens and setup is performed automatically.

6.1.2 Stepping Through Poses

You can step through the poses using the RIGHT ARROW and LEFT ARROW keys, or the ePlayer controls on the ePlayer toolbar. For example, you can use the ePlayer to play through the poses automatically, and perform actions on the poses with a script. For more information on the ePlayer, see Section 9.7 of the *Maestro User Manual*.

If your docking run used Epik to expand tautomeric or ionization states in your input ligands, or you generated conformers outside Glide (e.g. with ConfGen or MacroModel), or you chose to write out more than one pose per ligand, you might want to step through the top poses for each ligand rather than all poses. Maestro provides some ways of selecting the top ligands if the ligands are identified by the value of a property, such as the title. Here we assume that it is the Title property that identifies the ligands. If the ligands are already sorted by the GlideScore or the docking score, you can use these two simple steps:

1. Select the entry group containing the ligands.
2. Right-click on the Title column and choose Deselect Duplicate Values.

The first ligand for each value of the property is selected, and the entries for all other occurrences of the property are deselected. You can now step through the ligands with the left and right arrow keys.

If the ligands are not sorted by the desired property, you can use another approach, which selects the ligands after sorting:

1. Select the entry group containing the ligands.

2. Click the Sort button on the Project Table toolbar.

   

   The Sort Project Table panel opens.

3. Choose the property to sort by from the list on the left, e.g. docking score or glide gscore.
4. Make sure Sort entries is selected.
5. Click the arrow button under Sort entries, to add the property to the sort list, and ensure that the sort direction is correct. (If not, click the Direction cell to change it).
6. On the lower right, select After sorting, select top.
7. Select Unique entries in each group, by property.
8. Click the button with the table icon (to the right of the text box) and choose the property that distinguishes different ligands (e.g. Title)
9. Click Sort Selected.

   The Sort Project Table panel closes.

The entries in the group should now be sorted and the top entry for each ligand should be selected. You can now step through the entries with the left and right arrow keys.

If you want to compare the results of two different docking runs by including one ligand from each run in the Workspace and stepping through the poses for each run simultaneously, you can do so as follows.

1. Select all the poses for all the ligands of interest.

   If you want the ligands for each run to correspond (same ligand in each run), you will have to ensure that you select the corresponding ligands and place them in the desired order—for example, sort them by title.

2. If you want to view the receptor, fix it in the Workspace (right-click on it and choose Fix).
3. Include the first ligand from each run in the Workspace (click the In column for the first, control-click the In column for the rest).
4. Step through the poses with the RIGHT ARROW and LEFT ARROW keys.

   Each time you press one of these keys, each entry in the Workspace is replaced by the next (or previous) selected entry in the Project Table.

You can also set up the comparison using the pose-viewing mode, which is merely a shortcut for doing the required setup. The instructions below demonstrate how to do this for two sets of poses, which are in two entry groups.

1. Set up pose-viewing mode for the first entry group (select it and choose Entry → View Poses → Set Up).
2. Select the second entry group (control-click) and include the first pose in this entry group (control-click the In column).

   If you want the ligands for each group to correspond (same ligand in each group), you will have to ensure that you select the ligands that correspond to the first group and place them in the desired order—for example, sort them by title in both groups.
3. Step through the poses with the RIGHT ARROW and LEFT ARROW keys.

6.1.3 Displaying Nonbonded and Per-Residue Interactions

In addition to displaying the poses, you can display nonbonded interactions, such as hydrogen bonds, halogen bonds, contacts, pi-pi interactions and pi-cation interactions. You can also display per-residue interactions if they have been calculated. To do so, choose the appropriate options in the Pose Viewer panel. The nonbonded interactions between the ligand and the receptor are turned on for each ligand in the entry group.

If you want to set the parameters that define H-bonds, halogen bonds, and contacts or change the appearance of the interaction markers, you can do so under Non-bonded interactions in the Preferences panel (Maestro → Preferences).

Display of per-residue interactions can only be done if you selected Write per-residue interaction scores in the Output tab of the Ligand Docking panel. The display is turned on by selecting Display in the Per-Residue Interactions section of the Pose Viewer panel. The per-residue interactions are represented by coloring the residues by the value of the interaction, using a color ramp with white at zero.

To select the residues that are colored and which interactions are visualized, click Define in the Per-Residue Interactions section of the Pose Viewer panel, and make settings in the Per-Residue Interactions panel. In this panel you can select the interaction type, and pick residues for which the interaction is displayed.

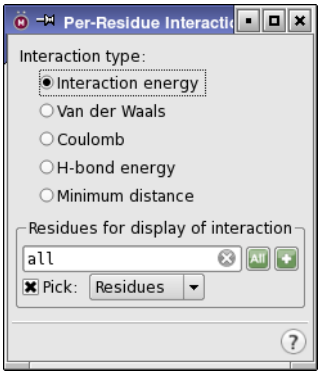

Figure 6.2. The Per-Residue Interactions panel.

6.1.4 Exporting Poses for Rotatable Groups

If you defined a set of receptor rotatable groups (hydroxyls in Ser, Thr, and Tyr residues) in the Rotatable Groups tab of the Receptor Grid Generation panel (see Section 4.5 on page 41), you can export the receptor with different orientations of these groups. The coordinates of the receptor in the pose viewer file are written for the original orientation, but the receptor includes information on the alternative orientations. This option allows you to write a file with the coordinates for alternative orientations, which you can then use in other applications. (Note that the receptor is locked in the Project Table, i.e. made read-only, as well as fixed in the Workspace.)

To do so, first include one of the poses that has this orientation in the Workspace. Next, in the Pose Viewer panel, click Export Rotatable Groups. In the Export Rotatable Groups dialog box you can choose to export just the receptor, the receptor and the included pose, or the receptor and all poses for which the receptor has that particular orientation of the rotatable groups.

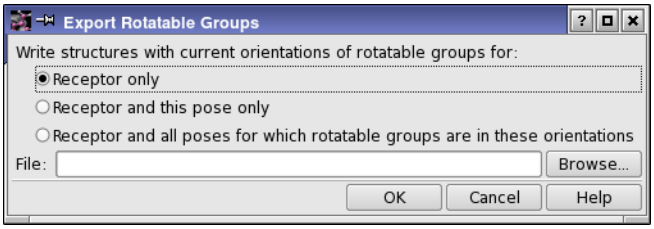

Figure 6.3. The Export Rotatable Groups dialog box.

6.2 The Glide XP Visualizer

The Glide XP Visualizer panel provides a way to visualize and analyze the results of a Glide XP docking run. The main functions of this panel are:

- To display the Glide XP results from a pose viewer file (*jobname*_pv.mae) in a table of XP terms for each ligand.
- To provide 3D visualizations for XP terms. Information for these visualizations is read from the pose viewer file. The descriptor file (*jobname*.xpdes), which is also generated by Glide XP, can be used instead; it must be in the same directory as the pose viewer file.
- To allow selective evaluation of ligands (and groups of ligands) within the table. This helps you analyze ligands separately during the screening process.

Before you can use the Glide XP Visualizer, you must generate the descriptor information. This information is not included in a normal XP run. To generate it, select Write XP descriptor information in the Settings tab of the Ligand Docking panel. You should also select Write pose viewer file in the Output tab of the Ligand Docking panel to write the required pose viewer file.

Note: Generation of XP descriptor information requires a separate license.

To open the Glide XP Visualizer panel, choose XP Visualizer from the Glide submenu of the Applications menu.

When the panel opens, click Open to select the pose viewer file. If you want to read the descriptor file instead, select .xpdes before clicking Open. The descriptor file must have the same base name as the corresponding pose viewer file. The file name and receptor name are displayed in the File and Receptor text boxes.

After the data has been loaded, the Select Activity Property dialog box opens so that you can select an activity property to display in the table. Choose a property from the list and click OK if you want to display the activities in the ligands table, or click Cancel if you do not want to display an activity property. If you do not choose a property, the Activity column is present, but shows '--' for the activity. You can change an activity value by clicking in the table cell. When you do so, the Edit Activity dialog box opens, and you can enter a new value.

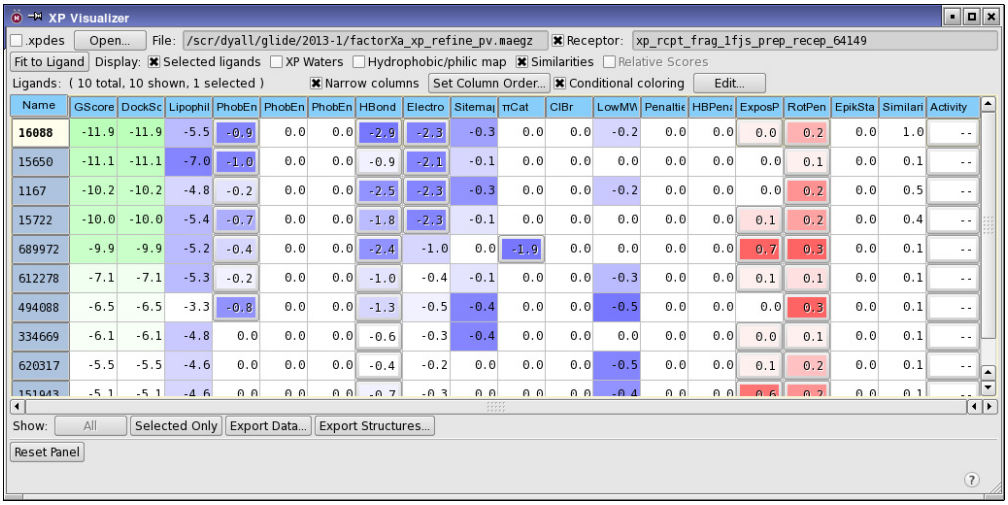

Figure 6.4. The Glide XP Visualizer panel.

6.2.1 The Ligands Table

When you open a file, the ligands are loaded into the table, with the name of the ligand in the far left column, along with the XP terms in the rest of the columns. If the same ligand name is listed twice in the pose viewer file, then a *-N* is added to the ligand name, where *N* is an integer starting with 2 that is incremented for each successive instance of a ligand name. By default the first ligand is selected.

To sort the rows of the table by the values in a column, click on the column heading. There are three sort settings: ascending (+), descending(-), and the original pose viewer order. These settings can be changed by successively clicking on the column heading. One column can be sorted at a time. The sorting mechanisms work on the ligands shown in the table.

To change the order of the columns in the table, click Set Column Order, which opens the Set Column Order dialog box. In this dialog box, you can select the columns from a list and move them up and down in the list. When you click OK, the columns are reordered with the top column in the list at the left of the table. You can also order the columns by decreasing values of the variance, which is listed in the list along with the column name.

The background color of the cells can be chosen to reflect the values of the XP terms. To color the cells, select Conditional Coloring. To set up the coloring scheme, click Edit, and make changes in the Edit Conditional Coloring dialog box:

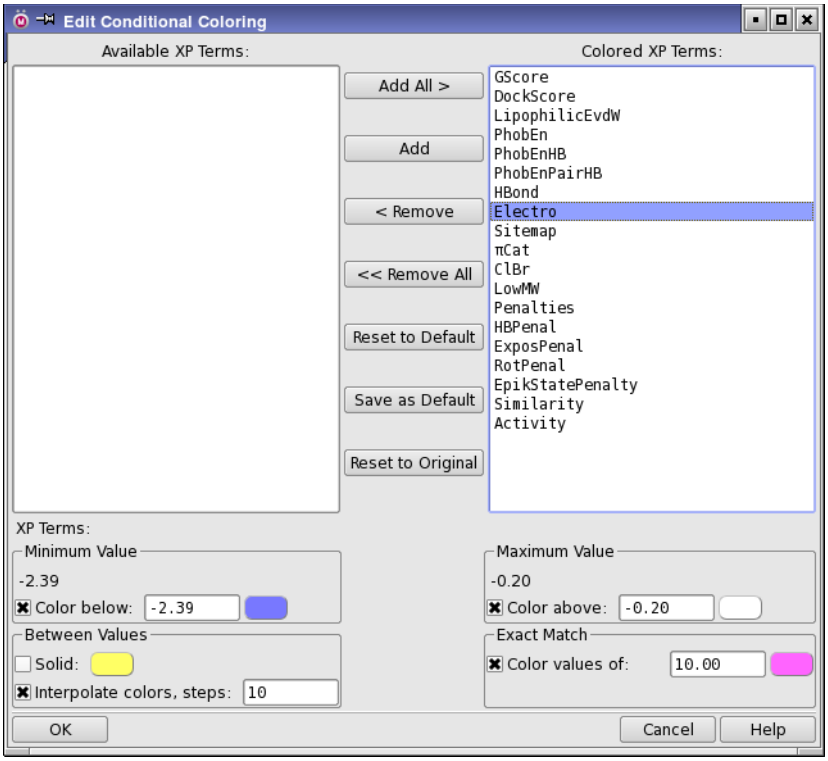

Figure 6.5. The Edit Conditional Coloring dialog box.

- To remove coloring for XP Terms, select them in the Colored XP Terms list, and click Remove. The terms are transferred to the Available XP Terms list, and the color scheme is no longer displayed. (The color scheme is still associated with the terms, so it can be reinstated).
- To reinstate coloring for XP Terms, select them in the Available XP Terms list, and click Add. The terms are transferred to the Colored XP Terms list, and the color scheme is displayed.
- To change the color scheme for a term, select it in the Colored XP Terms list, and use the controls in the lower half of the panel to set up the scheme. You can choose to apply a color to terms that are below or above a given value, to color between these thresholds either with a single color or a color ramp, and to color particular values.

Clicking on cells in the table produces two different functions depending on the cell type:

- XP Term Cells—Cells that have a gray border around them indicate XP term values for which a visualization exists. By clicking on one of these cells, the cell is highlighted and the visualization is displayed in the Workspace. These visualizations depend on the XP term and are described below.
- Ligand Name Cells—You can select multiple ligands by clicking in the Name column, using shift-click and control-click. If Selected ligands is selected in the Display section, then Maestro shows the selected ligands and the view changes each time the selection is changed. There is a limit on the number of ligands you can display. If you select more than 100 ligands, a warning is posted, and Selected ligands is turned off.

You can step through the ligands in the table using the LEFT ARROW and RIGHT ARROW keys. If a cell is selected, the arrow keys move up or down the column for that cell, displaying the visualization if a cell has an associated visualization.

The table columns can be widened so that the entire heading is displayed by deselecting Narrow columns. The column descriptions are displayed in tooltips. If you want to change the column order, click Set Column Order and use the tools in the Set Column Order dialog box to move the columns in the list. You can select multiple columns and move them to the top or bottom of the list, or move them up or down in the list.

In addition to selecting ligands in the table, you can limit what is shown in the table by using the Show buttons. The Selected Only button shows only the selected ligands in the table, and the sorting mechanisms now work exclusively on the ligands shown in the table. The All button shows all ligands in the table.

The Ligands table also lists a set of fragments that maximize the values of the XP descriptors, if these have been docked along with the ligands. These fragments are a special set of fragments that are docked using the Virtual Screening Workflow, by selecting Compute maximum values by docking fragments in the Docking Options tab. The fragments are displayed in the Workspace with purple carbons, to distinguish them from the ligands. You can display the scores for the ligands relative to the maximum value for each descriptor by selecting Relative Scores. Positive values of the relative score mean that the ligand score does not achieve the maximum as obtained from the fragment set, and indicates room for improvement.

6.2.2 Controlling the Display

The normal Workspace controls to rotate, translate, and zoom in on the structure can be used. The Glide XP Visualizer panel provides some additional control over the display.

To change the view so that the ligands that are displayed occupy the entire Workspace, click the Fit to Ligand button.

To control what is displayed in the Workspace, you can use the Display options:

- Receptor—Display or undisplay the receptor. By default, the receptor is displayed. Only the residues within 5 Å of the ligand are displayed.
- Selected ligands—Display the ligands that are selected in the table. If this option is selected, the Workspace is updated whenever the selection of ligands is changed.

  Note: If multiple ligands are selected, changing the view might take a considerable amount of time. Unless it is necessary to view many ligands at once, it is recommended that this option is used infrequently.

- XP Waters—Waters are shown as small red spheres in the visualizations and can be displayed or hidden using this option. By default, waters are not displayed.
- Hydrophobic/philic map—Hydrophobic and hydrophilic surfaces can be shown in the visualizations by selecting this option. The first time this option is selected, the HPPMap job is run, and the button flashes until the job finishes. The surfaces are stored for subsequent use. The job takes 1–2 minutes.

6.2.3 Exporting Data and Structures

You can export the information shown in the table to a CSV file. To do so, click Export Data. A file chooser opens, in which you can navigate to a location and name and save the file. If you want to export data for a selection of ligands, select them in the table and click Selected Only before clicking Export Data.

You can also export structures from the table to a Maestro file, along with the receptor structure. The receptor is the first structure, followed by the ligands, just as in a pose-viewer file. All selected ligands are exported, or if there is no selection, all ligands that are shown in the table are exported.

6.2.4 XP Terms and Their Visualizations

The XP terms and a description of their visualizations is given in Table 6.1. In the visualizations, hydrogen atoms are not generally displayed, and the ligand carbon atoms are colored green.

In addition to the XP terms, you can display similarities between the ligands in XP descriptor space, by selecting Similarities. The similarity is only displayed if a single ligand is selected in the table.

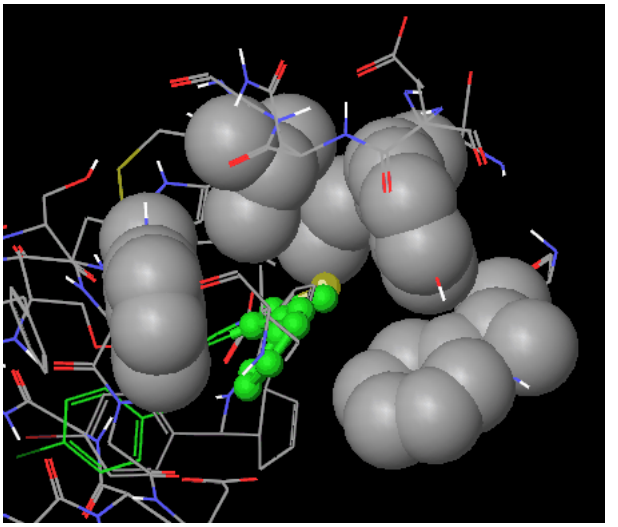

Figure 6.6. Visualization of hydrophobic enclosure terms.

Table 6.1. Glide XP terms and their visualizations

XP Term	Description	Visualization
GScore	Total GlideScore; sum of XP terms	None
LipophilicEvdW	Lipophilic term derived from hydrophobic grid potential at the hydrophobic ligand atoms.	None
PhobEn	Hydrophobic enclosure reward	Hydrophobic atoms on the protein that are necessary for recognition of hydrophobic enclosure are displayed in CPK representation in gray. Hydrophobic atoms on the ligand necessary for hydrophobic enclosure are displayed in green in ball and stick representation.
PhobEnHB	Reward for hydrophobically packed H-bond	H-bonds are displayed as pink dotted lines. Hydrophobic atoms on the protein that enclose hydrophobic groups on the ligand are displayed in gray in CPK representation. Hydrophobic atoms on the ligand are displayed in ball and stick representation.

Table 6.1. Glide XP terms and their visualizations (Continued)

XP Term	Description	Visualization
PhobEnPairHB	Reward for hydrophobically packed correlated H-bonds	H-bond are displayed as pink dotted lines. Hydrophobic atoms on the protein that enclose hydrophobic groups on the ligand are displayed in gray in CPK representation. Hydrophobic atoms on the ligand are displayed in ball and stick representation.
HBond	ChemScore H-bond pair term	H-bonds are displayed as yellow dotted lines.
Electro	Electrostatic rewards; includes Coulomb and metal terms.	Relevant atoms in the ligand are displayed in ball-and-stick representation.
SiteMap	SiteMap ligand-receptor non-H-bonding polar-hydrophobic terms	Hydrophobic (orange) and hydrophilic (turquoise) surfaces are displayed, representing the field of the receptor. These are the same as the Maestro Hppmap surfaces.
π Cat	Reward for pi-cation interactions	The relevant aromatic groups in the protein are displayed in CPK representation and in the ligand in ball and stick representation.
ClBr	Reward for Cl or Br in a hydrophobic environment that pack against Asp or Glu	None
LowMW	Reward for ligands with low molecular weight	None
Penalties	Polar atom burial and desolvation penalties, and penalty for intra-ligand contacts	Atoms are labeled with the penalties. The labels and their descriptions and the associated visualizations are as follows: Charge+*value*—Charge penalty. Penalty for putting a ligand charge in a region without water and with the charge not in a salt bridge. Ball and stick representation for ligand atoms. Water+*value*—Water-protein and water-ligand penalties. Penalties for desolvating (via presence of ligand) a polar group on the protein or ligand and not making an H bond to the polar group. Ball and stick representation for ligand and protein atoms

Table 6.1. Glide XP terms and their visualizations (Continued)

XP Term	Description	Visualization
		DDpen+*value*—Donor-donor penalty. Penalty for non-H-bonded donors on the ligand and protein too close together and with semi-collinear NH--HN. Blk+*value*—Penalty for burial of charged group on the protein by the ligand with no H bonds made to the charged group by the ligand or protein. Ball and stick representation for protein atoms Polar+*value*—Penalty for desolvation of a polar ligand atom in a hydrophobic protein environment. Similar to water-ligand penalty but specific to phobic environments. Ball and stick representation for protein atoms Contact+*value*—Penalty for intraligand contacts. Ball and stick representation for ligand atoms PhoBl+*value*—Phobic ligand-protein blockage. Penalty for putting a phobic group of the ligand against polar (donor/acceptor) groups of the protein in a protein region which normally would give a favorable phobic packing score (PhobEn). Ball and stick representation for protein atoms Twisted amide linkages in the ligand are also displayed in ball-and-stick, but not labeled.
HBPenal	Penalty for ligands with large hydrophobic contacts and low H-bond scores	None
ExposPenal	Penalty for solvent-exposed ligand groups; cancels van der Waals terms.	The molecular surface of the protein around the ligand is displayed as a semi-transparent surface. Ligand groups that are exposed are rendered in ball-and-stick representation
RotPenal	Rotatable bond penalty	Rotatable bonds in the ligand are displayed in tube representation.

Running Glide from the Command Line

This chapter contains information on running Glide from the command line. Although you will usually set up Glide jobs using the controls and settings in the Maestro GUI, you sometimes might want to submit jobs from the command line for the following reasons:

- The command-line scripts can run all full-featured jobs written using the Glide panels in Maestro, and also allow you to override specific run-time values that are not accessible through the Maestro interface.
- Command-line scripts allow you to run Glide jobs when you want.
- Input files and scripts can be modified and jobs can be re-run without reconfiguring and reloading job settings in Maestro.

Using Maestro is the best way to write Glide input files, even if you intend to run them from the command line, because the files are syntactically correct. To create the input files needed to run a job from the command line, set up the job in Maestro, click the panel's Write button, and modify the files that are generated.

Glide jobs are ultimately run using the Impact program, but they are started with the `glide` command. This command reads a Glide input file, processes it and runs the Impact executable. You can run both single-processor and distributed Glide docking jobs with this command.

Glide jobs can also be run with the `impact` and `para_glide` commands, but these commands require a DICE (Impact) input file, and `para_glide` is deprecated. See Appendix A for information on these commands.

Glide also has three command-line utilities, kept in the `utilities` subdirectory of the installation: `glide_sort`, `glide_merge`, and `glide_rescore`, which are also described in this chapter.

For information about general-purpose utilities, see the *General Utilities* manual.

7.1 Running Jobs

To run jobs on Linux or Mac, open a terminal window and set the SCHRODINGER environment variable to the Schrödinger software installation directory, as follows:

csh/tcsh: `setenv SCHRODINGER` *installation-directory*

bash/ksh: `export SCHRODINGER=`*installation-directory*

Once you have defined this environment variable, you should use it to define the paths to the applications and utilities, e.g. `$SCHRODINGER/glide`. In the text below, the path will not be given.

On Windows, you can use a Schrödinger Command Prompt (or Power Shell) and `sh` to run Linux commands (see Section 1.1 on page 1). When you open this shell, the SCHRODINGER environment variable is already set and in your path, as is the `utilities` folder, so you can run applications and utilities with just the name.

Command-line applications are located in the main Schrödinger installation directory; command-line *utilities* are located in the `utilities` subdirectory. For usage summary information on any application or utility, use the `-h` (help) option:

command `-h`
utilityname `-h`

Schrödinger applications and utilities run under Schrödinger's Job Control facility. To run jobs on remote hosts, you must set up a hosts file. For information on this file and other aspects of configuring hosts and Job Control, see Chapter 7 of the *Installation Guide*. You can force Impact to run outside Job Control, but you are then responsible for managing all the files.

Jobs are automatically run in the background. You need not add an `&` at the end of the commands to have them run and immediately display the command prompt. The `-WAIT` option forces the shell to wait until the job is finished, so you can embed such commands in other scripts.

Once your jobs are launched, you can monitor their progress using the Monitor panel in Maestro. The command `jobcontrol` can also be used. It has many options, but the two most useful options are:

```
jobcontrol -list
```

which shows the status of all your jobs, and:

```
jobcontrol -kill jobid
```

to terminate any job and its subjobs, if any exist.

For a summary of `jobcontrol` options, use:

```
jobcontrol -h
```

For more information, see the *Job Control Guide*.

7.2 Job Files and Directories

Location of Files and Working Directory

For Glide jobs, Maestro normally writes input files to a subdirectory of the directory from which you launched Maestro (the *Maestro working directory*). This subdirectory (folder) is named with the job name. The output files are also written to this subdirectory. For grid generation, the Glide interface allows you to specify an arbitrary location for the grid zip file.

File Name Conventions

A typical job has one command-script file (*jobname*`.in` or *jobname*`.inp`), one or more structure files (*jobname*`.mae`, *jobname*`.pdb`, or *jobname*`.sdf`), and after execution, several output files (e.g., *jobname*`.out` for textual data). Docking jobs can also use structures from a Phase database (`.phdb`), which must be specified in the input file instead of the ligand files, and must be present on the host the job is run on (it is not copied).

If a file already has the name of an output file, in many cases the old file is renamed with a numerical extension (*filename*`.out.01`, *filename*`.out.02`, and so on) for archival purposes. The new job's output is then written to the base name (*filename*`.out`). If you do not need the old files, you can remove them.

Some files, such as *jobname*`.log` files, are newly written each time a calculation is run. Likewise, old *jobname*`_pv.`*suffix* files are overwritten. Glide writes intermediate Maestro-format structure output to *jobname*`_raw.`*suffix* files, which are incremented. Output structure files can be written in Maestro or SD format, and can be compressed or uncompressed.

Table 7.1 and Table 7.2 contains descriptions of the various files generated during Glide grid generation and Glide docking. For more information, see the Maestro online help or the *Impact Command Reference Manual*.

Table 7.1. Input and output files for Glide grid generation jobs

File	Description
jobname.in	Glide input file, required as input to the glide command. Glide input files are formatted plain-text files. Maestro creates Glide input files for job submission. You can create or edit them manually with a text editor.
jobname.inp	Impact input file, required as input to the impact command. Impact input files are formatted plain-text files written in the Impact input file language, DICE. You can create or edit them manually with a text editor.
jobname.mae, *jobname*.mae.gz, *jobname*.maegz	Maestro format file containing the receptor structure, compressed or uncompressed. If written by Maestro, this file is named *jobname*.maegz.
jobname.zip	Zip file containing the receptor grid.
jobname.log	Log file, which captures standard output and standard error messages in text form. This file is overwritten during subsequent runs.
jobname.out	Output file, containing output from standard output but not standard error. Output files are appended with numerical extensions when the input file is used again. Up to 99 output files are retained.

Table 7.2. Input and output files for Glide docking jobs.

File	Description
jobname.in	Glide input file, required as input to the glide command. Glide input files are formatted plain-text files written in the Glide simplified input format. Maestro creates Glide input files for job submission. You can create or edit them manually with a text editor.
jobname.inp	Impact input file, required as input to the impact command. Impact input files are formatted plain-text files written in the Impact input file language, DICE. You can create or edit them manually with a text editor.
jobname.mae[[.]gz]	Maestro format file containing input structures for docking.
jobname.log	Log file. If specified, a .log file captures standard output and standard error messages in text form. This file is overwritten during subsequent runs.
jobname.out	Output file, containing output from standard output but not standard error. Output files are appended with numerical extensions when the input file is used again. Up to 99 output files are retained.
jobname.rept	Plain text file containing a table of ranked poses, scores, and score components.

Table 7.2. Input and output files for Glide docking jobs. (Continued)

File	Description
*jobname*_lib.maegz or *jobname*_lib.sdfgz	Glide ligand structure output file, in Maestro or SD format, compressed.
*jobname*_pv.maegz	Glide pose viewer file, in Maestro format, compressed. Contains the receptor structure, followed by all output ligand poses ranked by their score.
*jobname*_raw.maegz or *jobname*_raw.sdfgz	Glide's intermediate structure files, containing unranked ligand poses.
*jobname*_subjob_poses.zip	Zip archive containing pose files for subjobs, when the docking job is distributed. The subjob pose files are removed after they are successfully archived.

7.3 The glide Command

The `glide` command is used for both receptor grid generation and ligand docking jobs. For ligand docking, it can run both single processor and distributed docking jobs. The syntax of the command is as follows:

`glide` [*options*] *input-file*

For a description of the command options, run the command `glide -h`.

The input file is a Glide input file, whose default extension is `.in`. This file contains keyword-value pairs that define the parameters of the calculation. These keywords are listed in the tables below. Table 7.3 contains keywords for grid generation jobs, and Table 7.4 contains keywords for ligand docking jobs. The keywords for grid generation and ligand docking are grouped according to the tabs (and associated Advanced Settings dialog boxes) in the Receptor Grid Generation and Ligand Docking panels in which they are set. Defaults are available for many of the keywords, so you do not need to include all the keywords in the input file.

Boolean values in the input file can be represented by `True` or `False`, `Yes` or `No`, `1` or `0`. The last two pairs are converted internally to `True` or `False`. The values are case-insensitive. A Boolean value is denoted by *boolean* in the tables below, and the value is represented by `True` or `False`, which you can change as you will.

Table 7.3. Glide input file keywords for grid generation jobs.

Keyword	Description
GRIDFILE *filename*	Filename of the grid .zip file, if compressed, or the .grd file.
OUTPUTDIR *path*	Output directory. Must be a path that is accessible on the host that runs the job. The default is the job launch directory.
CV_CUTOFF *value*	Coulomb-van der Waals cutoff.
Receptor keywords	
RECEP_FILE *filename*	Receptor file name. Must be a Maestro file (.mae, .maegz, .mae.gz). If LIGAND_MOLECULE is used, it must contain the ligand as well, which is removed for the grid generation.
RECEP_VSCALE *value*	General van der Waals radius scaling factor. Default: 1.0.
RECEP_CCUT *value*	General van der Waals radius scaling partial charge cutoff. Default: 0.25.
GLIDE_RECEP_MAESCALE *boolean*	Read per-atom scale factors from the input structure file if set to True. Default: False.
GLIDE_RECEP_ASLSCALE *boolean*	Specify per-atom scale factors by ASL if set to True. Default: False.
ASLSTRINGS *list*	Comma-separated list of quoted ASL expressions, one expression for each set of residues to be scaled. Only used if GLIDE_RECEP_ASLSCALE is set to True.
GLIDERECEPTORSCALECHARGES *list*	Comma-separated list of charge scaling factors, one factor for each set of residues that is defined in the ASLSTRINGS list.
GLIDERECEPTORSCALERADII *list*	Comma-separated list of van der Waals scaling factors, one factor for each set of residues that is defined in the ASLSTRINGS list.
REC_MAECHARGES *boolean*	Use partial charges from the input structure if set to True. Default: False.
HBOND_ACCEP_HALO *boolean*	Accept halogens (neutral or charged, F, Cl, Br, or I) as H-bond acceptors. Default: False.
HBOND_DONOR_HALO *boolean*	Accept the halogens (Cl, Br, I, but not F) as potential "H-bond" (noncovalent interaction) donors. Default: False.
HBOND_DONOR_AROMH *boolean*	Accept aromatic hydrogens as potential H-bond donors. Default: False.
HBOND_DONOR_AROMH_CHARGE *value*	Partial charge cutoff for accepting aromatic hydrogens as potential H-bond donors. The cutoff is applied to the actual (signed) charge, not the absolute value. Default: 0.0.

Table 7.3. Glide input file keywords for grid generation jobs. (Continued)

Keyword	Description
PEPTIDE *boolean*	Set up grids for peptide docking. Required if peptides are to be docked.
Site keywords	
INNERBOX *x,y,z*	Comma-separated list of the *x*, *y*, and *z* dimensions of the inner (ligand centroid bounding) box in angstroms. These values must be integers. Written to the receptor Maestro file as r_glide_gridbox_lig*q*range, where *q* is x, y, or z.
ACTXRANGE *value*	Outer box *x* dimension. Must be set to the same as for the OUTERBOX keyword.
ACTYRANGE *value*	Outer box *y* dimension. Must be set to the same as for the OUTERBOX keyword.
ACTZRANGE *value*	Outer box *z* dimension. Must be set to the same as for the OUTERBOX keyword.
OUTERBOX *x,y,z*	Comma-separated list of the *x*, *y*, and *z* dimensions of the outer (grid) box in angstroms. These values can be floating-point numbers. Written to the receptor Maestro file as r_glide_gridbox_*q*range, where *q* is x, y, or z.
GRID_CENTER *x,y,z*	Comma-separated list of the *x*, *y*, and *z* coordinates of the center of the grid. These values can be floating-point numbers. Written to the receptor Maestro file as r_glide_gridbox_*q*cent, where *q* is x, y, or z.
GRID_CENTER_ASL *asl*	Specify the grid center with the ASL expression *asl*. The center is placed at the centroid of the atoms defined in the ASL expression.
LIGAND_MOLECULE *number*	Specify the molecule number of the ligand that defines the grid center.The center is placed at the centroid of the ligand atoms. If this keyword is used, the receptor file must contain the ligand, which is removed for the grid generation.
Constraints keywords	
GLIDECONS *boolean*	Define constraints if set to True. Default: False.
GLIDE_NTOTALCONS *ncons*	Total number of constraints defined (Positional/NOE+H-bond/Metal+Hydrophobic+Metal Coordination).
GLIDE_NUMPHOBCONS *nhpc*	Number of hydrophobic constraints defined.
GLIDE_NUMPOSITCONS *npc*	Number of positional constraints defined.

Table 7.3. Glide input file keywords for grid generation jobs. (Continued)

Keyword	Description
GLIDECONSATOMS *list*	Comma-separated list of atom numbers that define H-bond/ Metal constraints.
GLIDECONSNAMES *list*	Comma-separated list of constraint names.
GLIDECONSUSESYMATOMS *list*	Include symmetry-related atoms when applying constraints. List of Booleans for each H-bond or metal constraint, which matches the list given for GLIDECONSATOMS. Default: True for all H-bond and metal constraints.
GLIDE_NUMMETCOORDCONS *value*	Number of metal-coordination constraints (number of metals selected for coordination constraints).
GLIDE_NUMMETCOORDSITES *list*	List of the number of available coordination sites for each metal coordination constraint.
GLIDE_CONS_XMETCOORD *list* GLIDE_CONS_YMETCOORD *list* GLIDE_CONS_ZMETCOORD *list*	Comma-separated list of coordinates of the metal coordination sites. The coordinates of the sites for each metal center should be contiguous, and they should be in the order implied by the list defined by GLIDE_NUMMETCOORDSITES.
GLIDE_CONS_RMETCOORD *list*	Comma-separated list of radii of the metal coordination spheres, which represent the maximum allowed distance of a ligand atom from the coordination site.
Rotatable groups keywords	
USEFLEXMAE *boolean*	Include flexible groups in the grid generation, as specified in the Maestro file for the receptor. Only one of USEFLEXMAE and USEFLEXASL can have the value True.
USEFLEXASL *boolean*	Include flexible groups in the grid generation, as specified by the FLEXASL keyword. Only one of USEFLEXMAE and USEFLEXASL can have the value True.
FLEXASL *asl*	ASL expression that specifies the hydrogens on the flexible groups. The expression must specify only the required hydroxyl and thiol hydrogens.
Excluded volumes keywords	
GLIDE_NUMEXVOL *value*	Number of excluded volumes. For each excluded volume, the coordinates of the center and the radius must be defined, at a minimum.
GLIDE_XEXVOL *list* GLIDE_YEXVOL *list* GLIDE_ZEXVOL *list*	Comma-separated list of coordinates of the centers of the excluded volume spheres.

Table 7.3. Glide input file keywords for grid generation jobs. (Continued)

Keyword	Description
GLIDE_REXVOL *list*	Comma-separated list of radii of the excluded volume spheres.
GLIDEXVOLNAMES *list*	Comma-separated list of names of the excluded volumes.
GLIDE_REXVOLIN *list*	Comma-separated list of the inner radii of the excluded volume spheres (the radii at which the penalties have their full values). Default is 90% of the sphere radius.

Table 7.4. Glide input file keywords for ligand docking jobs.

Keyword	Description
GRIDFILE *filename*	File name of the grid .zip file, if compressed, or the .grd file.
Settings keywords	
DOCKING_METHOD {confgen|rigid|mininplace|inplace}	Docking method: confgen—Dock flexibly. rigid—Dock rigidly. mininplace—Refine (do not dock) inplace—Score in place (do not dock)
PRECISION {XP|SP|HTVS}	Docking precision mode. Set in the Settings tab.
CANONICALIZE *boolean*	Canonicalize the input structure by discarding the coordinates and regenerating the structure from the connectivity and stereochemistry. Takes about 1 sec per ligand. Default: False.
SAMPLE_N_INVERSIONS *boolean*	Sample nitrogen inversions if set to True and DOCKING_METHOD is set to confgen. Default: True.
SAMPLE_RINGS *boolean*	Sample rings if set to True and DOCKING_METHOD is set to confgen. Default: True.
INCLUDE_INPUT_RINGS *boolean*	Include the input structure along with any generated ring conformations. Only applies if SAMPLE_RINGS is set to True (otherwise the input structure is the only structure). Default: False.
RINGONFLY *boolean*	Generate templates dynamically for unrecognized rings of up to 14 atoms. Only available with OPLS_2005. Default: False.
AMIDE_MODE {penal|free|fixed|trans}	Amide bond sampling mode. Only set when DOCKING_METHOD is set to confgen. penal—penalize nonplanar conformation free—vary conformation fixed—retain original conformation trans—allow trans conformation only gen[eralized]—use generalized torsion controls defined in torcontrol.txt.

Table 7.4. Glide input file keywords for ligand docking jobs. (Continued)

Keyword	Description
AMIDE_TRANSTOL *angle*	Maximum angle deviation in degrees from 180° for an amide to be considered trans. Default: 20.
EPIK_PENALTIES *boolean*	Apply penalties for ionization or tautomeric states calculated by Epik. Default: False.
SKIP_EPIK_METAL_ONLY *boolean*	Skip Epik-generated states of ligands that are designed for binding to metals. This option is useful if the receptor has a metal but the ligand does not bind to it. These states are skipped by default if the receptor does not have a metal.
EXPANDED_SAMPLING *boolean*	Expand the sampling by bypassing the elimination of poses in the rough scoring stage. Useful for fragment docking. Default: False.
REWARD_INTRA_HBONDS *boolean*	Reward intramolecular ligand hydrogen bonds by adding a contribution for each intramolecular hydrogen bond to the GlideScore, and a contribution to Emodel. Default: False.
HBOND_DONOR_AROMH *boolean*	Accept aromatic hydrogens as potential H-bond donors. Default: False.
HBOND_DONOR_AROMH_CHARGE *value*	Partial charge cutoff for accepting aromatic hydrogens as potential H-bond donors. The cutoff is applied to the actual (signed) charge, not the absolute value. Default: 0.0.
HBOND_ACCEP_HALO *boolean*	Accept halogens (neutral or charged, F, Cl, Br, or I) as H-bond acceptors. Default: False.
HBOND_DONOR_HALO *boolean*	Accept the halogens (Cl, Br, I, but not F) as potential "H-bond" (noncovalent interaction) donors. Default: False.
GLIDEUSEALLEXVOL *boolean*	Apply all excluded volumes that are included with the grid.
GLIDE_EXVOL_PENAL_STRENGTH *value*	Set the strength of the penalty for occupying an excluded volume. Allowed values: large, medium, small. These values are translated into a numeric value for each volume. Default: large.
GLIDE_NUMUSEXVOL *value*	Number of excluded volumes to use in docking. Must not be greater than the total number, specified by GLIDE_NUMEXVOL. for grid generation.
GLIDEUSEXVOLNAMES *list*	Comma-separated list of names of the excluded volumes to use in docking.
GLIDE_EXVOL_PENAL_NUM *list*	Comma-separated list of maximum penalty values for each excluded volume used in docking.
WRITE_XP_DESC *boolean*	Write XP descriptor information if set to True. Default: False.

Table 7.4. Glide input file keywords for ligand docking jobs. (Continued)

Keyword	Description
FLEXTORS *boolean*	Set to False for rigid, refineinput and inplace jobs.
MAXKEEP *nposes*	Number of poses per ligand to keep in initial phase of docking. Default: 5000.
SCORING_CUTOFF *cutoff*	Scoring window for keeping initial poses. Default: 100.0.
MAXREF *nposes*	Number of poses to keep per ligand for energy minimization. Maestro sets this number to 800 for XP. Default: 400.
GLIDE_DIELCO *constant*	Distance-dependent dielectric constant. Default: 2.0.
FORCEPLANAR *boolean*	Scale force-field parameters for planar (sp^2) systems such as rings to strongly penalize nonplanar conformations. Default: False.
MAX_ITERATIONS *niter*	Maximum number of conjugate gradient steps. Default:100.
PEPTIDE *boolean*	Set parameters for improving docking results for polypeptides. The following settings are made if the keywords are not already set: MAXKEEP 100000 MAXREF 1000 POSTDOCK_NPOSE 100 Other keywords are set internally: the maximum number of conformers is increased by a factor of 10, and the number of diameter directions is increased by about a factor of 3. It is recommended to follow docking with Prime MM-GBSA postprocessing, for minimization of the peptide and for scoring. Not available for HTVS docking precision.
Ligands keywords	
GLIDECONSUSEMET *boolean*	Use individual metal and ligand radii to determine the cutoff for metal-ligand constraints ($r_{metal}+r_{ligand}+0.4$), rather than a single global value of 2.4 Å. Default: False.
GLIDESCORUSEMET *boolean*	Use individual metal radii for the cutoff in the scoring function, rather than a single ramp from 2.2 to 2.6 Å. Default: False.
LIGANDFILE *filenames*	Comma-separated list of ligand file names. File names that include commas can be quoted; leading and trailing spaces are ignored. Files can be in any of Maestro, SD, MOL2, or PDB format.If LIGAND_START and LIGAND_END are used, they refer to the ligand indices as if the input files were concatenated in the order specified.
LIGAND_START *firstlig*	First ligand from the ligand file to be docked. Default: 1.

Table 7.4. Glide input file keywords for ligand docking jobs. (Continued)

Keyword	Description
LIGAND_END *lastlig*	Last ligand from the ligand file to be docked. Default: last in file.
PHASE_DB *dbpath*	Full path to Phase database to use for the ligands. The first conformer of each ligand is extracted from the database for docking. Use instead of LIGANDFILE, LIGAND_START, LIGAND_END.
PHASE_SUBSET *filename*	Name of subset file to use in the Phase database. Only the ligands whose records are listed in the subset file are docked. If omitted, all ligands in the database are docked.
LIG_MAECHARGES *boolean*	Take charges from input structures if set to True. Default: False.
MAXATOMS *maxatoms*	Maximum number of atoms per ligand. Default (and maximum): 300.
MAXROTBONDS *maxrotbonds*	Maximum number of rotatable bonds per ligand. Default (and maximum): 50
LIG_VSCALE *factor*	Scaling factor for van der Waals radii scaling. Default: 0.8.
LIG_CCUT *cutoff*	Partial charge cutoff for van der Waals radii scaling. Default: 0.15.
RINGCONFCUT *cutoff*	Energy window for retention of ring conformers. Default: 2.5 kcal mol^{-1}.
Core keywords	
USE_REF_LIGAND *boolean*	Use core pattern for comparison or restraint if set to True. Default: False.
REF_LIGAND_FILE *filename*	File name for reference ligand. File format can be Maestro, SD, MOL2 or PDB.
CORE_DEFINITION {all|smarts|allheavy}	Specify how the core is defined. all—use all atoms in the reference ligand allheavy—use all nonhydrogen atoms in the reference ligand smarts—use the SMARTS pattern defined by the CORE_ATOMS keyword.
CORE_ATOMS *list*	List of core atoms to use for the RMSD calculation. Only set when CORE_DEFINITION is set to smarts.
CORE_SMARTS *pattern*	Smarts pattern for core. Only set when CORE_DEFINITION is set to smarts. Set in the Core tab.
CORE_RESTRAIN *boolean*	Restrict docking to reference position if set to True. Default: False.

Table 7.4. Glide input file keywords for ligand docking jobs. (Continued)

Keyword	Description
CORE_SNAP *boolean*	When using core constraints, "snap" the core of the ligand to exactly match the reference ligand and rebuild the rest of the ligand with the new core, if set to True. If set to False, use the filter-and-restrain approach. Not compatible with CORE_DEFINITION all. Default: True if CORE_POS_MAX_RMSD < 0.75, False otherwise.
CORE_POS_MAX_RMSD *value*	Tolerance on the RMSD to use when restricting docking to the reference position.
CORE_FILTER *boolean*	Skip ligands that do not match the core pattern if set to True. Default: False.
Constraints keywords	
[FEATURE:*n*]	Define a feature block. A feature is use to define the ligand atoms that match a given constraint, and is defined by a set of SMARTS patterns and rules. The feature block consists of one or more PATTERN lines. The index *n* is used to associate the feature with a constraint specified by USE_CONS. The square brackets must be included.
PATTERN*i* *string*	Define a ligand matching pattern in a feature block. The index *i* must be unique within a block. The string consists of the following components, separated by spaces: 1. SMARTS pattern. 2. Comma-separated list of atoms in the SMARTS pattern that must be matched by the ligand. 3. Optional keyword include or exclude, for including or excluding matched atoms. Default is include. exclude can only be used to limit the scope of an included pattern. 4. For hydrophobic constraints, number of atoms required in the constraint region. Must be preceded by include.
[CONSTRAINT_GROUP:*m*]	Define a constraint group. Must be followed by a USE_CONS keyword and a NREQUIRED_CONS keyword. The square brackets must be included. All constraints must be defined as part of a group. The ligand must satisfy the constraints in each group.
USE_CONS *list*	Apply the specified constraints as part of the constraint group. The list is a comma-separated list of constraints. Each constraint is specified in the format *title*:*n*, where *n* must match the index of a FEATURE block, and *title* is the label of the constraint in the .cons file for the grid.

Table 7.4. Glide input file keywords for ligand docking jobs. (Continued)

Keyword	Description
NREQUIRED_CONS *nreq*	Number of constraints in the USE_CONS list that are required to match. The sum of *nreq* values over all constraint groups must not exceed 4.
GLIDE_CONS_FINALONLY *boolean*	Test constraint satisfaction only after docking if set to True. Default: False.
HAVEGLIDECONSFEAT *boolean*	Deprecated, but retained for backward compatibility. A feature file is already available if set to True. Default: False.
GLIDECONS *boolean*	Deprecated, but retained for backward compatibility. Use constraints if set to True. Default: False.
GLIDE_CONS_FEAT_FILE *filename*	Deprecated, but retained for backward compatibility. Specify the name of the constraints feature file. Default: *jobname*.feat.
GLIDEUSECONSFEAT *boolean*	Deprecated, but retained for backward compatibility. Use the constraints feature file for the application of constraints if set to True. If set to False, the constraint information is in the Impact .inp file.
Torsional constraints keywords	
[TORCONS:*index*]	Define a torsional constraint block. If a torsion matches a constraint definition in more than one block, the match in the block with the highest index. is used. These blocks must be contiguous and be placed at the end of the input file.
SMARTS "*pattern*"	Define part of a molecule in which torsional constraints can be defined by the specified SMARTS pattern. The pattern must be enclosed in quotes.
ATOMS *list*	Define torsions to be constrained. The list of atoms that define the torsions is a comma-separated list of quoted atom number quartets. The atom numbers are separated by hyphens. For example: ATOMS "1-2-3-4","2-3-4-5","4-5-6-7" The atom numbering is given relative to the SMARTS pattern.
USEVAL *list*	Specify which torsions should be set to the corresponding values given in the list for the TORVAL keyword. The list is a comma-separated list of integer values. The default is 0 for all values, which means that the input value of the torsion will be used.
TORVAL *values*	Specify the angle values to which the torsions should be set before constraining them, if the corresponding boolean value in the USEVAL list is True. The angle values are a comma-separated list.

Table 7.4. Glide input file keywords for ligand docking jobs. (Continued)

Keyword	Description
ALLBONDS *boolean*	Constrain torsions about all bonds for which a dihedral (defined by four atoms) is fully contained in the SMARTS pattern, using the value for each torsion from the input structure. Any ATOMS, SETVAL, and TORVAL keywords in the constraint block are ignored.
Output keywords	
COMPRESS_POSES {TRUE|FALSE}	Compress the output pose files. Default: TRUE.
NOSORT {TRUE|FALSE}	Do not sort the poses by score (using glide_sort), but return the poses as generated in *jobname*_raw.maegz.
CV_CUTOFF *cutoff*	Reject poses with Coulomb-van der Waals energy greater than *cutoff* kcal/mol. Default: 0.0.
HBOND_CUTOFF *cutoff*	Reject poses with H-bond score greater than *cutoff*. Default: 0.0.
METAL_CUTOFF *cutoff*	Reject poses with metal score greater than *cutoff*. Default: 10.0.
POSE_OUTTYPE {poseviewer|ligandlib|poseviewer_sd|ligandlib_sd}	Type of output file to produce. Default: poseviewer. poseviewer—Write pose viewer file (_pv.maegz); includes receptor as first structure. poseviewer_sd—Write pose viewer file in SD format (_pv.sdfgz); receptor stored in V3000 format. ligandlib—Write ligand pose file (_lib.maegz); does not contain receptor. ligandlib_sd—Write ligand pose file in SD format (_lib.sdfgz). SD format is not available with flexible groups in the grid or with XP descriptors.
POSE_RMSD	RMS deviation used in clustering to discard poses, in angstroms. Default: 0.5.
POSE_DISPLACEMENT	Maximum atomic displacement used in clustering to discard poses, in angstroms. Default: 1.3.
NMAXRMSSYM	Maximum number of poses to compare taking local symmetry into account, when detecting duplicates. A negative value means that there is no limit. Default: 100.
NREPORT *maxposes*	Maximum number of poses to write out from the docking run. Default: 0, meaning write out all poses.
OUTPUTDIR *path*	Directory for output files. Must be a path that is accessible on the host that runs the job. The default is the job launch directory.

Table 7.4. Glide input file keywords for ligand docking jobs. (Continued)

Keyword	Description
POSES_PER_LIG *maxperlig*	Maximum number of poses to write per ligand. Default: 1.
POSTDOCK *boolean*	Use post docking minimization if set to True. Default: True.
POSTDOCK_NPOSE *npose*	Number of poses to use in post-docking minimization. Maestro sets this number to 10 for XP. Default: 5.
POSTDOCKSTRAIN *boolean*	Apply strain correction terms if set to True. Default: False.
WRITE_RES_INTERACTION *boolean*	Generate per-residue interaction terms if set to True. Default: False.
ASL_RES_INTERACTION *asl*	ASL expression defining residues to be used for per-residue interactions. Takes precedence over RADIUS_RES_INTERACTION.
RADIUS_RES_INTERACTION *r*	Radius for per-residue interaction terms, in angstroms. Only set if WRITE_RES_INTERACTION is set to True. Default: 12.0
WRITEREPT *boolean*	Write report text file (.rept for docking and .scor for score-in-place). Default: False.
KEEPSKIPPED *boolean*	Write a file *jobname*_skipped.maegz containing the ligands that were skipped or rejected at any point in the docking process. Default: False.
KEEP_SUBJOB_POSES *boolean*	Keep the zip archive, *jobname*_subjob_poses.zip, and copy it back to the job launch directory. This archive contains the pose files from all the subjobs of a distributed docking job. Default: True.
CALC_INPUT_RMS *boolean*	Calculate RMSD between each pose and its input structure. Default: False.

7.4 Restarting Glide Docking Jobs

The Job Control facility can automatically restart failed Glide subjobs that were run with the `glide` command. The number of times a failed subjob is retried is set by the `SCHRODINGER_MAX_RETRIES` environment variable, whose default is 3. This environment variable is described in Table B.1 of the *Job Control Guide*.

If you still have failed subjobs when the master job finishes, you can restart the job to run the subjobs that failed. To do so, use the command that you used to run the job originally with the `-RESTART` option added. This restart mechanism only applies to distributed jobs.

7.5 Glide Utilities

This section describes the utilities that are available in the `utilities` directory of the installation.

7.5.1 glide_sort

Re-ranks Glide poses by custom criteria or combines job outputs into one file. The "best" pose is defined by the property used for sorting. If you set any of the custom scoring function terms, sorting is done only on this custom function instead of the standard sorting options. The syntax of the command is:

`glide_sort` *mode* [*options*] *pose-files*

The input pose files can be in Maestro or SD format, uncompressed (`.mae` or `.sdf`) or compressed (`.maegz`,`.mae.gz`, `.sdfgz`). The same format must be used for all files, both input and output. You can combine pose-viewer files (`_pv.mae[gz]`) into ensemble pose-viewer files (`_epv.mae[gz]`).

At least one of these modes is required:

`-o` *output-file*	Write the best-scoring poses to *output-file* in Maestro or SD format, compressed or uncompressed. The output format must match the input format, except that `_pv.mae[gz]` files can be combined into an `_epv.mae[gz]` file.
`-r` *report-file*	Create a report of the best scores in *report-file.*
`-R`	Write a report of the best scores to standard output.

For a description of the command options, run the command `glide_sort -h`. If multiple `-use_prop[_a|d]` options are given, a multi-key sort is used, with the first property specified as the primary key, the second property as the secondary key, and so on.

7.5.2 glide_merge

This utility merges results from a list of pose files (such as from `glide` subjobs) into a single pose file, sorted by the docking score or a specified property. The pose files must be already sorted by the docking score or the specified property. The syntax of the command is as follows:

`glide_merge` *mode* [*options*] *pose-files*

The input and output pose files can be in Maestro or SD format, uncompressed (`.mae` or `.sdf`) or compressed (`.maegz`,`.mae.gz`, `.sdfgz`). The same format must be used for all files, both input and output. You can combine pose-viewer files (`_pv.mae[gz]`) into ensemble pose-viewer files (`_epv.mae[gz]`).

At least one of these modes is required:

`-o` *output-file*	Write the poses to *output-file*. If `.xpdes` files exist for the input pose files, an output `.xpdes` file is also created with the same base name.
`-r` *report-file*	Create a report of the best scores in *report-file.*
`-R`	Write a report of the best scores to standard output.

For a description of the command options, run the command `glide_merge -h`.

7.5.3 glide_rescore

This utility replaces the docking score properties in Glide pose output files with different values, so that the `glide_sort` "best-by-title" option can be used to combine different screens. See Section 7.5.1. The syntax of the command is as follows:

`glide_rescore` [*options*] *pv-or-lib-files*

For a description of the options, run the command `glide_rescore -h`. Only one of `-rank`, `-offset`, and `-average` can be used at a time. If none is specified, `-rank` is assumed. Using `-top` or `-every` implies `-average` mode.

7.6 Customizing Glide Calculations

The controls in the Glide panels provide a limited number of options for customizing the docking calculations. You can make more extensive customizations by adding commands and keywords to the Impact input file. The syntax of this input file is described in detail in the *Impact Command Reference Manual*. You cannot make these customizations with the Glide input file.

The subsections below describe two customizations that are done by changing resource files.

7.6.1 Changing the Glide Atom Typing

Glide uses SMARTS patterns to define the atom types ("ptypes") and hybrid types used in grid generation and docking. By default, these patterns are read from `$SCHRODINGER/impact-v`*version*`/data/opls/ptype.def`. If you want to change the atom types, you can copy and edit this file, and then add the appropriate keywords under the `PARAMETER` subtask in the Impact (Dice) input file. There are two keywords: `ptype`, which specifies the file to be used and must be followed by the file name, and `prntptypes`, which prints out the ptypes and the hybrid types.

To customize a grid generation job, an additional parameter statement should be included at the beginning of the `DOCK` task:

`parameter prntptypes ptype "`*filename*`"`

For docking jobs, during the first `DOCK` task when reading the grid files, include:

`parameter prntptypes ptype "`*filename*`"`

The quotes are required to preserve the case of the file name.

Since Glide no longer uses the Dice input file by default, you must convert your Glide input file to a Dice input file by running `glide` with the `-write_inp` option.

7.6.2 Defining Torsional Controls for Planar and Other Groups

The mechanism for controlling rotations about amide bonds in earlier Glide releases has been generalized to allow control of any class of torsions—for example, around ester linkages. The torsions and the type of control applied are defined in a resource file, `torcontrol.txt`, which is included in the `impact-v`*version*`/data` directory of the installation. You can override the default definitions by copying this file to the `impact` directory in your user resources area (`$HOME/.schrodinger` on Linux or Mac, `%APPDATA%\Schrodinger` on Windows), or to your working directory, and editing the file to provide your own definitions. The file has a summary of the syntax at the top.

Each torsion control is defined by a keyword for the control type, a unique name, a SMARTS pattern, and four atom numbers to define the torsion, then values that depend on the control type. These must all be on the same line, separated by spaces. The control type syntax is:

```
free         name smarts atoms
freezeinput  name smarts atoms
freeze       name smarts atoms angle
force        name smarts atoms angle tolerance
penalize     name smarts atoms angle multiplicity penalty barrier exponent
```

The various fields in the torsion control are described in Table 7.5.

Table 7.5. Description of fields in the definition of a torsion control.

Field	Description
keyword	Case-insensitive control type. Allowed values: `free`—do not constrain the torsion `freezeinput`—freeze the torsion at its input value `freeze`—freeze the torsion at the specified angle `force`—reject poses for which the torsion does not lie within the given tolerance of the specified angle. `penalize`—penalize torsions during scoring that do not adopt the given angle, using a periodic penalty function with a global minimum (zero penalty) and other penalized minima.
name	Name of the torsion (case-sensitive). Must be unique within the file, and cannot contain spaces.
smarts	SMARTS pattern that defines the torsion.
atoms	Indexes of the four atoms in the SMARTS pattern that define the torsion.
angle	Value of the angle (in degrees) to which the torsion is frozen or forced, or at which the penalty is at its minimum (zero).
tolerance	Tolerance for the angle to which the torsion is forced, in degrees. The tolerance defines the range of acceptable angles.
multiplicity	Number of maxima (or minima) in the torsional potential. Must be 1, 2, 3, 4, or 6. If the number is 4 or 6, the potential is assumed to have two global minima separated by 180°, with higher energies for the other minima.
penalty	Penalty value for torsions at the nonglobal minima.
barrier	Maximum value of the torsional potential, which is the barrier between the global minimum and the next minimum.
exponent	Power to which the torsional potential function is raised (while maintaining the barrier heights. Useful for flattening the potential around the minima. A value of 2 is recommended to enable some flexibility around the minima.

The order in which the torsions are included in the file matters: the last torsion that is matched is the one that is used. This means that you should put the more general SMARTS patterns first, followed by the more specific patterns. You can even include torsions around double bonds, as the torsion patterns are matched to determine the bonds to be restricted before determining the rotatable bonds.

When looking for matches to a pattern in a molecule, it is possible to find multiple matches—for example, the pattern CN(=O)cc to constrain the CNcc dihedral angle for an aromatic amide

matches a molecule that has a benzene ring attached to the amide in two ways, and therefore the penalty could be applied in two different ways. In such cases, the "favored" orientation is chosen to be the one that is closest to the input dihedral angle from the molecule.

The `freeze` and `freezeinput` controls on the torsions are only applied during docking: they make the bond non-rotatable. However, post-docking minimization can change these frozen torsions. The `force` and `penalize` controls are applied after post-docking minimization.

An example of a torsion control is given below, for an ester.

```
penalize  ester  O=C(-O[#6])  1 2 3 4   0.0  2  4.0  9.0  2.0
```

If a penalty is applied, the name of the torsion control and the penalty value are added as bond properties (`s_glide_torcontrol_name`, `r_glide_torcontrol_penalty`) to the output structure.

7.7 Docking Log Messages

When a ligand is docked, its fate is reported in messages in the log file. These messages are described below.

- `DOCKING RESULTS FOR LIGAND` *n*—Docking succeeded and at least one pose was written to the `_raw.mae` file.
- `NO POSES STORED`—Nothing was written to the `_raw.mae` file for this ligand. This usually only happens in constrained jobs, if none of the minimized poses satisfies constraints.
- `NO POSES SURVIVED ROUGH-SCORE`—There are actually several messages similar to this (one of which mentions "refinement" as well as "rough-score"). For all of them, poses have been eliminated somewhere in the rough-score part of the funnel.
- `NO GOOD POSES FOUND`—This message should occur in conjunction with one of the two previous messages.
- `PROBLEM IN CONFGEN`—Problems occured in the conformation generator.
- `INVALID ATOMIC NUMBER`—An atom in the ligand has an atomic number for which no atom type can be assigned.
- `TOO MANY ROTATABLE BONDS`—The user-specified limit on the number of rotatable bonds was exceeded.
- `LIGAND TOO BIG`—The ligand has more atoms than either the absolute maximum allowed (200 atoms) or the maximum set by the user.

- FAILED INTERCONSTRAINT DIST—More than one constraint was required and the atoms that could satisfy each constraint individually are in positions that cannot possibly satisfy the constraints simultaneously.
- TOO MANY ROTAMERS—More conformations were generated for a given rotatable group than the constraint algorithm can handle. (The limit is 6.)
- HYDROPHOBIC/PERIPHERAL ASSIGNMENT FAILED—Assignment of hydrophobic regions on the ligand for application of hydrophobic constraints failed.
- ATOMIC COORDINATES OVERLAP—Ligand atoms are too close to each other. This message might indicate poor ligand preparation.
- STRUCTURE INCOMPATIBLE WITH FORCE FIELD—The ligand cannot be used with the force field selected because the bonding patterns could not be assigned.
- STRUCTURE HAS TOO MANY ATOMS—The ligand has more atoms than Impact can handle. (The limit is 300.)
- INVALID ATOM(S)—The ligand has atoms for which no force field parameters are available.
- ERROR GETTING LIGAND DATA—Glide encountered an error parsing the ligand line of the (Dice) input file. Usually preceded by a more specific error message.
- ROUGH POSE REFINE FAILED—The preminimization step on the rough poses failed. This step involves displacing the ligand and sampling rotatable bonds by small amounts about the generated values.

Old Commands for Running Glide

This appendix provides information on commands for running Glide that are superseded by the `glide` command. The `impact` command can be used to run Glide jobs on a single processor with a DICE input file. The `para_glide` command can be used to run Glide jobs on multiple processors. This command is deprecated and will be removed in a future release. You should change any scripts that use this command to use the `glide` command instead.

A.1 The impact Command

The syntax of the command is as follows:

`impact [`*options*`] [[-i]` *input-file*`]`

For a description of the command options, run the command `impact -h`.

If your protein has more than 8000 atoms and you are making grid files (but not if you are just docking ligands), you must specify a larger executable with the `-s` option. See Table 6.1 of the *Impact User Manual* for more information. If you have a large number of ligands, you can use `para_glide` to distribute the docking job over multiple processors

The `impact` command is also used to run other applications. For more information on the input file syntax, see the *Impact Command Reference Manual*.

A.2 The para_glide Command

The para_glide application divides the ligands into batches of ligand structures and submits these batches to multiple processors for docking. The syntax of the `para_glide` command is:

`para_glide -i` *input-file* `[`*options*`]`

For a description of the command options, run the command `para_glide -h`. All other options, such as options for the `impact` command, are passed to the subjobs.

The `para_glide` application splits the Glide job specified in the *input-file* into smaller subjobs for distributed execution. The ligands from *firstlig* to *lastlig* are separated into *njobs* equal-sized batches. By default, *njobs* is set to 1, *firstlig* is set to 1 and *lastlig* is set to 0, which is interpreted as the final ligand in the ligands file.

For example, to submit a job with 50 subjobs to be run on 10 processors, you could use the following command:

```
$SCHRODINGER/para_glide -n 50 -HOST mycluster:10 -i myjob.inp
```

This job would run on the host `mycluster` using 10 processors.

Each use of `para_glide` creates two scripts: *jobname*`_report.sh` and *jobname*`_status.sh`. The *jobname*`_report.sh` script collects the output (poses) from subjobs created by `para_glide`, and produces a single pose file and a single report file that summarizes the best poses in the entire job suite. The subjob results are stored in subdirectories of the working directory, named *jobname_firstlig_lastlig*, where *firstlig* and *lastlig* are the indexes of the first and last ligands in the subjob. The *jobname*`_status` script can be run at any time to obtain a summary of the disposition of each job: whether it finished normally, died, was terminated, stopped, and so on, using the conventional Schrödinger job control terms. (See Chapter 3 of the *Job Control Guide* for information about job monitoring and job control.)

The `-job` option is useful for preparing only a single subjob. A value of 0 is equivalent to not specifying `-job` at all, and all subjobs will be prepared. Negative values are not permitted.

By default, a new ligand file is written for each subjob, containing only the ligands for that subjob. If the `-nosplit` option is given, all jobs use the same input ligand file, and each job reads out of it just the ligands pertinent to that job. Splitting the ligand file is likely to be more efficient if there is a large number of ligands, but requires extra disk space to store the ligand files.

A.3 Recovering Failed Docking Jobs

For jobs run with `impact` or `para_glide`, you can reclaim the work that has been done to date and rerun jobs for the ligands that have not yet been docked. The results to the point of failure are stored in a `_raw.mae` file, which can be used in conjunction with the results of a new docking run that completes the task to generate the final output file, using `glide_sort`. There are several scenarios to consider.

If you ran a single-processor job:

1. Examine the log file to obtain the number of the ligand being docked when docking failed.
2. Copy the log file to a safe location.
3. Start a `para_glide` job, specifying the first ligand to be docked as the one that failed.

   You can run a `para_glide` job on a single processor. The results will be in a subdirectory created by `para_glide`.

If you ran a para_glide job and isolated subjobs failed or didn't run:

1. Change to the subdirectory for each subjob that failed or didn't run in turn, and start an `impact` job, with the files for the subjob as input. The output is placed in the same subdirectory as the job was started from.

If you ran a para_glide job and a contiguous block of subjobs failed or didn't run:

1. Determine which subjobs ran from the log files.
2. Run a `para_glide` job for the block of subjobs that didn't run.

For subjobs that failed but produced some results, you can rerun them from the point of failure with `para_glide`. This procedure creates another subdirectory for the results.

When all the restarted jobs finish, run a `glide_sort` job from the parent directory, specifying all the `_raw.mae` files as input.

References

1. Eldridge, M. D.; Murray, C. W.; Auton., T. R.; Paolini, G. V.; Mee, R. P. Empirical scoring functions: I. The development of a fast empirical scoring function to estimate the binding affinity of ligands in receptor complexes. *J. Comput.-Aided Mol. Des.* **1997,** *11,* 425–445.

2. Maggiora, G. M.; Johnson, M. A. *Concepts and Applications of Molecular Similarity.* Wiley & Sons: New York, 1990, pp 99–117.

3. Moreau, G.; Broto, P. The Autocorrelation of a Topological Structure: A New Molecular Descriptor. *Nouv. J. Chim.* **1980,** *4,* 359–360.

4. Carhart, R. E.; Smith, D. H.; Venkataraghavan, R. Atom Pairs as Molecular Features in Structure-Activity Studies: Definitions and Applications. *J. Chem. Inf. Comput. Sci.* **1985,** *25,* 65–73.

5. Wagener, M.; Sadowski, J.; Gasteiger, J. Autocorrelation of Molecular Surface Properties for Modeling Corticosteroid Binding Globulin and Cytosolic Ah Receptor Activity by Neural Networks. *J. Am. Chem. Soc.* **1995,** *117,* 7769–7775.

6. Sheridan, R. P.; Miller, M. D.; Underwood, D. J.; Kearsley, S. K. Chemical Similarity Using Geometric Atom Pair Descriptors. *J. Chem. Inf. Comput. Sci.* **1996,** *36,* 128–136.

7. Kearsley, S. K.; Sallmack, S.; Fluder, E. M.; Andose, J. D.; Mosley, R. T.; Sheridan, R. P. Chemical Similarity Using Physicochemical Property Descriptors. *J. Chem. Inf. Comput. Sci.* **1996,** *36,* 118–127.

8. Pearlman, R. S.; Smith, K. M. Novel Software Tools for Chemical Diversity. *Perspectives Drug Discovery Design* **1998,** *9,* 339–353.

9. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shaw, D. E.; Shelley, M.; Perry, J. K.; Francis, P.; Shenkin, P. S. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy, *J. Med. Chem.* **2004**, *47*, 1739–1749.

10. Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 2. Enrichment Factors in Database Screening. *J. Med. Chem.* **2004**, *47*, 1750–1759.

11. Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D. T. Extra Precision Glide: Docking and Scoring

Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes. *J. Med. Chem.* **2006**, *49*, 6177–6196.

Getting Help

Information about Schrödinger software is available in two main places:

- The `docs` folder (directory) of your software installation, which contains HTML and PDF documentation. Index pages are available in this folder.
- The Schrödinger web site, http://www.schrodinger.com/, In particular, you can use the Knowledge Base, http://www.schrodinger.com/kb, to find current information on a range of topics, and the Known Issues page, http://www.schrodinger.com/knownissues, to find information on software issues.

Finding Information in Maestro

Maestro provides access to nearly all the information available on Schrödinger software.

To get information:

- Pause the pointer over a GUI feature (button, menu item, menu, ...). In the main window, information is displayed in the Auto-Help text box, which is located at the foot of the main window, or in a tooltip. In other panels, information is displayed in a tooltip.

  If the tooltip does not appear within a second, check that Show tooltips is selected under General → Appearance in the Preferences panel, which you can open with CTRL+, (⌘,). Not all features have tooltips.

- Click the Help button in the lower right corner of a panel or press F1, for information about a panel or the tab that is displayed in a panel. The help topic is displayed in the Help panel. The button may have text or an icon:

  

- Choose Help → Online Help or press CTRL+H (⌘H) to open the default help topic.
- When help is displayed in the Help panel, use the navigation links in the help topic or search the help.
- Choose Help → Documentation Index, to open a page that has links to all the documents. Click a link to open the document.

- Choose Help → Search Manuals to search the manuals. The search tab in Adobe Reader opens, and you can search across all the PDF documents. You must have Adobe Reader installed to use this feature.

For information on:

- Problems and solutions: choose Help → Knowledge Base or Help → Known Issues → *product*.
- New software features: choose Help → New Features.
- Python scripting: choose Help → Python Module Overview.
- Utility programs: choose Help → About Utilities.
- Keyboard shortcuts: choose Help → Keyboard Shortcuts.
- Installation and licensing: see the *Installation Guide*.
- Running and managing jobs: see the *Job Control Guide*.
- Using Maestro: see the *Maestro User Manual*.
- Maestro commands: see the *Maestro Command Reference Manual*.

Contacting Technical Support

If you have questions that are not answered from any of the above sources, contact Schrödinger using the information below.

Web:	http://www.schrodinger.com/supportcenter
E-mail:	help@schrodinger.com
Mail:	Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone:	+1 888 891-4701 (USA, 8am – 8pm Eastern Time)
	+49 621 438-55173 (Europe, 9am – 5pm Central European Time)
Fax:	+1 503 299-4532 (USA, Portland office)
FTP:	ftp://ftp.schrodinger.com

Generally, using the web form is best because you can add machine output and upload files, if necessary. You will need to include the following information:

- All relevant user input and machine output
- Glide purchaser (company, research institution, or individual)
- Primary Glide user
- Installation, licensing, and machine information as described below.

Gathering Information for Technical Support

The instructions below describe how to gather the required machine, licensing, and installation information, and any other job-related or failure-related information, to send to technical support. Where the instructions depend on the profile used for Maestro, the profile is indicated.

For general enquiries or problems:

1. Open the Diagnostics panel.
   - **Maestro:** Help → Diagnostics
   - **Windows:** Start → All Programs → Schrodinger-2015-2 → Diagnostics
   - **Mac:** Applications → Schrodinger2015-2 → Diagnostics
   - **Command line:** `$SCHRODINGER/diagnostics`
2. When the diagnostics have run, click Technical Support.

   A dialog box opens, with instructions. You can highlight and copy the name of the file.
3. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.

If your job failed:

1. Open the Monitor panel, using the instructions for your profile as given below:
   - **Maestro/Jaguar/Elements:** Tasks → Monitor Jobs
   - **BioLuminate/MaterialsScience:** Tasks → Job Monitor
2. Select the failed job in the table, and click Postmortem.

   The Postmortem panel opens.
3. If your data is not sensitive and you can send it, select Include structures and deselect Automatically obfuscate path names.
4. Click Create.

   An archive file is created, and an information dialog box with the name and location of the file opens. You can highlight and copy the name of the file.
5. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.

6. Copy and paste any log messages from the window used to start the interface or the job into the web form (or an e-mail message), or attach them as a file.
   - **Windows:** Right-click in the window and choose Select All, then press ENTER to copy the text.
   - **Mac:** Start the Console application (Applications → Utilities), filter on the application that you used to start the job (Maestro, BioLuminate, Elements), copy the text.

If Maestro failed:

1. Open the Diagnostics panel.
   - **Windows:** Start → All Programs → Schrodinger-2015-2 → Diagnostics
   - **Mac:** Applications → SchrodingerSuite2015-2 → Diagnostics
   - **Linux/command line:** `$SCHRODINGER/diagnostics`
2. When the diagnostics have run, click Technical Support.

   A dialog box opens, with instructions. You can highlight and copy the name of the file.
3. Upload the file specified in the dialog box to the support web form.

   If you have already submitted a support request, use the upload link in the email response from Schrödinger to upload the file. If you need to submit a new request, you can upload the file when you fill in the form.
4. Upload the error files to the support web form.

   The files should be in the following location:

- **Windows:** `%LOCALAPPDATA%\Schrodinger\appcrash`
  (Choose Start → Run and paste this location into the Open text box.)
  Attach `maestro_error_`*`pid`*`.txt` and `maestro.exe_`*`pid_timestamp`*`.dmp`.
- **Mac:** `$HOME/Library/Logs/CrashReporter`
  (Go → Home → Library → Logs → CrashReporter)
  Attach `maestro_error_`*`pid`*`.txt` and `maestro_`*`timestamp_machinename`*`.crash`.
- **Linux:** `$HOME/.schrodinger/appcrash`
  Attach `maestro_error_`*`pid`*`.txt` and `crash_report_`*`timestamp_pid`*`.txt`.

If a Maestro panel failed to open:

1. Copy the text in the dialog box that opens.
2. Paste the text into the support web form.

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