Core Hopping 1.2

User Manual

Schrödinger Press

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Revision A, September 2012

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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 to Core Hopping

Improving the activity of a lead compound is often done by varying the side chains that are attached to a core part of the compound. The object of this strategy is to find the optimal side chains. Since in many cases it is the side chains that bind to the protein, it makes sense to vary the core, to find other molecules ("scaffolds") to which the side chains could be attached and result in enhanced binding. This capability is available in the Core Hopping facility.

The core-hopping strategy is to screen multiple potential scaffolds (also called *protocores*) against a template (a lead compound), and search for alignments of potential attachment points on the scaffold with the attachment points on the template.

If a receptor is available, the core-hopping strategy can take advantage of the receptor by docking the new compounds into the binding site, and use the docking score to rate the compounds. If a receptor is not available, the new compounds can be rated on alignment alone or on the matching of the shape of the new compound to the template.

1.1 Running Schrödinger Software

Schrödinger applications can be started 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 Maestro. This directory then becomes Maestro's 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-2012 > 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 (Documents on Windows 7/Vista, My Documents on XP).

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 that 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-2012. 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 SchrodingerSuite2012 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. If you need to set any other variables, use the command

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

1.2 Citing Core Hopping in Publications

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

Core Hopping, version 1.2, Schrödinger, LLC, New York, NY, 2012.

Core Hopping

If you have a receptor structure for your lead compound, you can take advantage of the known interactions with the receptor to screen out scaffolds that have clashes or unfavorable interactions, or do not have favorable interactions. This can be done by docking the core-substituted molecules with Glide, and is called Glide-based (or receptor-based) core hopping.

For other targets, such as GPCRs, a receptor may not be available. In these situations, you can do core hopping based on the ligand characteristics. As in receptor-based core hopping, the attachments on the core are identified, and a new set of cores is tried. The evaluation of the cores cannot be done by docking to a receptor, but instead is based either on a match of the shape of the new core to the template core (isosteric matching, or shape-based core hopping), or of the alignment of the new core to the template core (ligand-based or attachment-based core hopping).

Isosteric matching (shape-based core hopping) is useful when you want the cores to be similar to the template core. The similarity can be defined simply in terms of volume overlap, or can involve weighting different regions of the volume overlap, or requiring that certain atom types or pharmacophore types match. You might, for example, start with a natural substrate and want to make a drug-like molecule that is similar. Isosteric matching uses `phase_shape` for the alignment, for which a special license is provided as part of the licensing for Core Hopping.

In the attachment-based method, the alignment is based only on the attachment bonds, so this method is most suitable for scaffold-hopping applications where keeping the R-groups in place is the most important goal. It generally provides better alignments of the R groups than shape-based core hopping, because that is the criterion applied when assessing the new core-containing molecules. The attachment-based method can also insert linker groups between the core and the side-chains to allow a smaller replacement core to substitute for the original core.

Of course, you can use isosteric matching or ligand-based core hopping even if you do have a receptor.

Regardless of the strategy, the procedure is similar for each, and is reflected in a common structure for the panels that you use to set up and run the jobs. The panels have a tab for defining the template, a tab for selecting the cores, setting options, and running the job, and a a tab for viewing results. To open the panels, choose Applications → Core Hopping and then the panel for the strategy: Glide-Based, Ligand-Based, or Isosteric Matching.

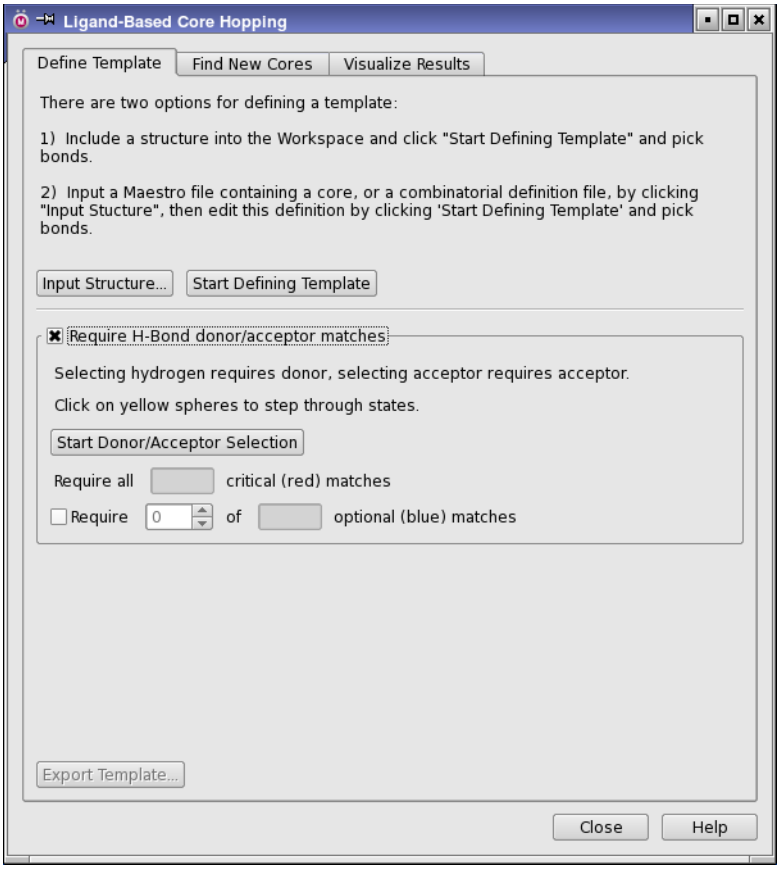

Figure 2.1. The Define Template tab of the Ligand-Based Core Hopping panel.

2.1 Defining the Template

The first step in ligand-based core hopping is to define a template, which you do in the Define Template tab. The template is derived from the molecule whose core you want to substitute. The basic task in this step is to identify the side chains (R groups) on the template molecule that you want to keep, while substituting the rest of the template with scaffolds from other molecules. The bonds to these side chains are called attachment bonds, and must be defined for all three approaches.

If you are performing ligand-based core hopping, you can also require that the scaffold matches specified hydrogen-bond donor or acceptor groups.

If you have a template molecule that was previously used for core hopping, or prepared for CombiGlide, you can import this molecule by clicking Input Structure and navigating to the file. If you are satisfied with the core definition in this file, you can proceed to the next tab.

Otherwise, you can edit the imported molecule, or display and edit a molecule in the Workspace to define the template. In either case, click Start Defining Template to define the attachment bonds.

Click the bonds to the side chains that you want to keep as part of the new structures. The bonds are marked with an arrow pointing towards the side chain. Multiple clicks on the first bond change the direction of the arrow, then clear the bond selection, then select it again. For the subsequent bonds, multiple clicks select and deselect the bond (as the core is determined by the first pick).

When you have finished selecting bonds, click Stop Defining Template to exit template definition mode.

If you are using ligand-based (attachment-based) core hopping to find new cores, you can also require that the new cores have hydrogen-bond donors or acceptors at certain locations that you choose. To apply these requirements, select Require H-Bond donor/acceptor matches. When you do, the controls for selecting the sites are available, and the possible sites are marked on the template as yellow spheres. These sites can be on the core or on the side chains (which can move to adjust to the new core).

To select the sites that you want to match in the new core-containing molecules, click Start Donor/Acceptor Selection, then pick spheres in the Workspace. The first click marks the site as an optional match (blue), the second marks it as a required match (red), and the third returns it to the unmarked state (yellow). When you have finished, click Stop Donor/Acceptor Selection. The number of required and optional matches are listed in the text boxes below this button, and you can set the minimum number of optional matches.

When a new core is created, the donor and acceptor sites are checked against the selected sites, to see if a match to within a certain distance is found (0.75 Å by default; it can be adjusted from the Find New Cores tab.) If all required sites are matched, and the minimum number of optional sites is matched, the new core is accepted.

If you want to save the template for later use, click Export Template to export the template to a Maestro file. The file includes the core definition information.

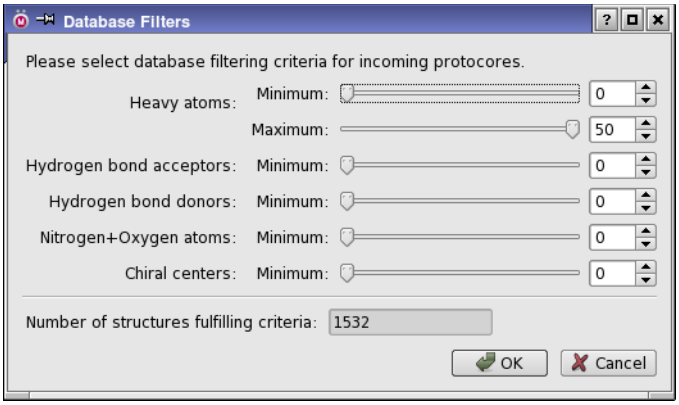

Figure 2.2. The Database Filters dialog box.

2.2 Finding New Cores

In the Find New Cores tab, you can specify the structures that contain the potential new cores, select the core-hopping method, select options, and run the job to generate the new cores.

The structures that contain the potential new cores ("protocores") can be taken from the Project Table or from a file, by choosing an option from the Use structures from option menu. If you choose File, click Browse to navigate to the file in a file selector. You can choose a Maestro file or an SQLite database (`.sqlite`) file. You can obtain an SQLite database of candidate cores from the Schrödinger web site (http://www.schrodinger.com/downloadcenter), or you can use the `corefinder` utility to generate a database from your own structures.

If your input comes from an SQLite database, you can filter the protocores on the basis of atom counts: minimum and maximum numbers of heavy atoms, and minimum numbers of hydrogen-bond acceptors, donors, nitrogen and oxygen atoms, and chiral centers. To apply the filter, click Database Filters, and make settings in the Database Filters dialog box.

The three core-hopping methods and their options are described in the following subsections.

2.2.1 Isosteric Matching

Isosteric matching uses Phase shape-based screening to find the new cores based on the similarity of their shape to the original core (see Chapter 14 of the *Phase User Manual*).

As well as matching the template shape, you can filter out structures that occupy forbidden regions of space ("excluded volumes") that might be occupied by the receptor. To do this, select Use Phase excluded-volume file, and click Browse to locate the file (`.xvol` or `.ev`).

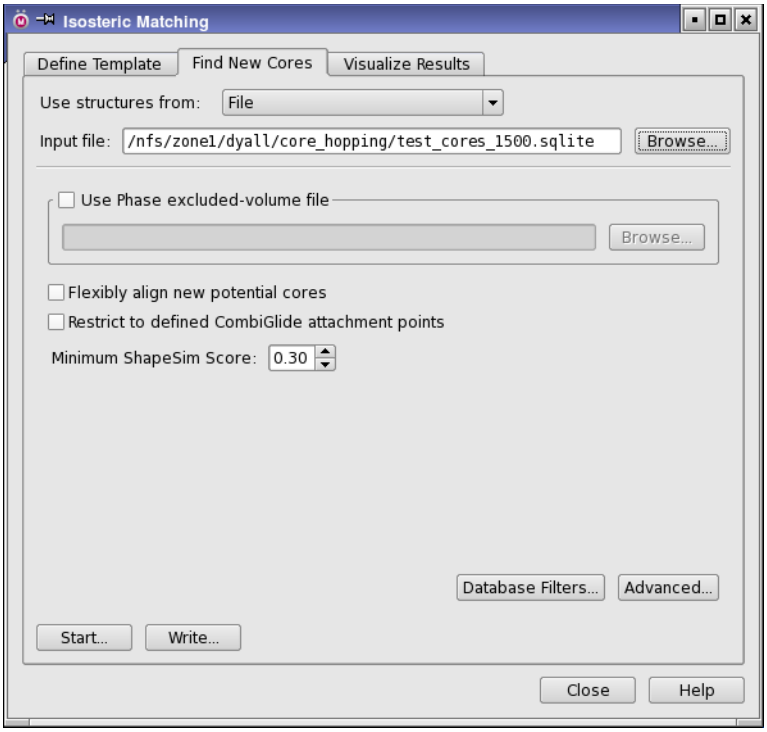

Figure 2.3. The Find New Cores tab of the Isosteric Matching panel.

There are several ways of creating excluded volume files, all of which require a Phase pharmacophore hypothesis. You can create a hypothesis from the template molecule by choosing Applications → Phase → Create Pharmacophore Hypothesis Manually, choose the template molecule for the reference structure, and choose at least 3 sites for the hypothesis in the New Hypothesis dialog box (which sites is not important for this purpose). The hypothesis is then available in the Manage Hypotheses panel, and you can create excluded volumes from this panel. See Chapter 8 of the *Phase User Manual* for details. It is useful to consider receptor rearrangement and flexibility when setting up excluded volumes.

To produce the best alignment of the new potential cores, you can perform a flexible alignment, which allows conformational changes, by selecting Flexibly align new potential cores.

Two ways of filtering out cores are also provided:

- Restrict to defined CombiGlide attachment points—Restrict the attachments to the atoms that are marked as attachment points in the structure. By default any bond to hydrogen can be used for an attachment.

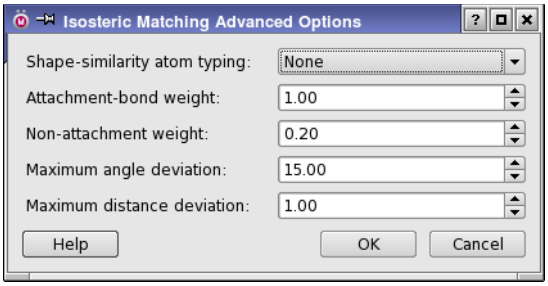

Figure 2.4. The Isosteric Matching Advanced Options dialog box.

- Minimum ShapeSim score—Specify the minimum shape similarity score for a core to be accepted. Cores that do not meet this threshold are rejected.

More options are available in the Isosteric Matching Advanced Options dialog box, which you open by clicking Advanced.

The atom typing scheme can be chosen from the Shape-similarity atom typing option menu. Volume overlaps are computed between atoms that have the same atom type as defined by the choice of atom typing scheme below.

- None—Don't distinguish different types of atoms when calculating volume overlaps: all atoms are treated the same.
- MacroModel—Calculate volume overlaps only between atoms that have the same MacroModel atom type. This is the most restrictive atom typing scheme.
- Elements—Calculate volume overlaps only between atoms of the same element.
- Pharmacophore—Calculate volume overlaps between atoms that have the same pharmacophore type (Acceptor, Donor, etc.) as defined for Phase QSAR models (see Section 7.1 of the *Phase User Manual*).

If you want to adjust the weights, enter new weights in the Attachment-bond weight and Non-attachment weight text boxes. The attachment-bond weight is applied to the atoms in the attachment bonds, whereas the non-attachment weight is applied to all other atoms in the core. The default values of 1.0 for the attachment bonds and 0.2 for all others produces results in which the attachment bonds overlap well, but the cores might not overlap very well. Increasing the non-attachment weight should increase the similarity of the cores, somewhat at the expense of the attachment bonds. For example, increasing the non-attachment weight to 0.7 should yield new cores that are similar to the template core.

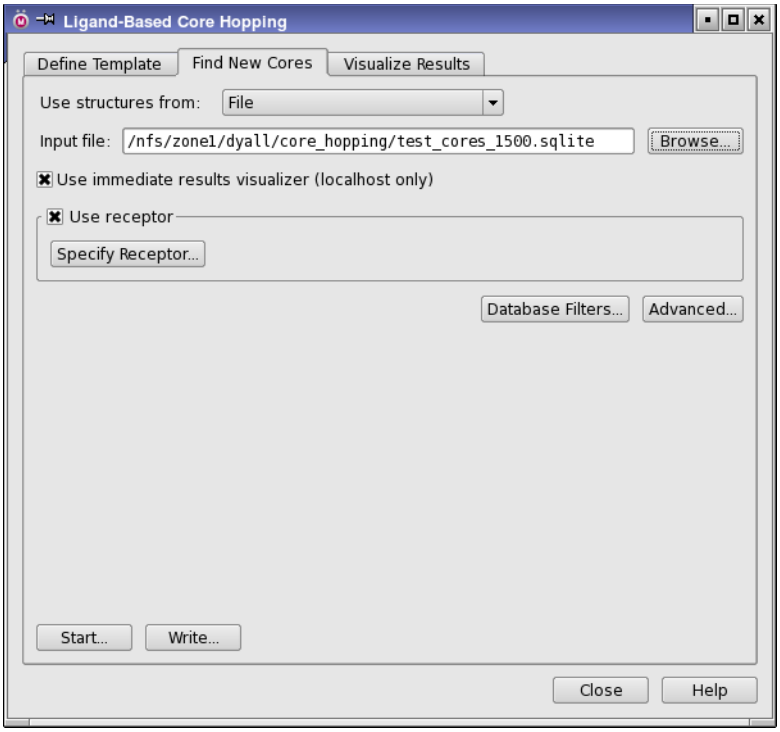

Figure 2.5. The Find New Cores tab of the Ligand-Based Core Hopping panel.

To ensure that the attachment bonds do not move too far from good alignment, you can require the alignment and position of the attachment bonds in the new core to be within a certain tolerance, which can be specified in the Maximum angle deviation and Maximum distance deviation text boxes. The maximum distance is measured between corresponding attachment bond atoms, the angle is the angle between the attachment bond vectors.

2.2.2 Ligand-Based Core Hopping

The alignment of the attachment bonds to find new cores works as follows. For each candidate replacement core, the program first determines which sets of attachments bonds align reasonably well with those in the template molecule. This is done using a spatial sampling method that allows for automatic addition of -CH_2- linkers. The R groups from the original template are then attached to the newly identified attachment bonds in the replacement core, and bond torsions between the new core and the R groups are adjusted to optimize the superposition of the R-group atoms upon their original positions.

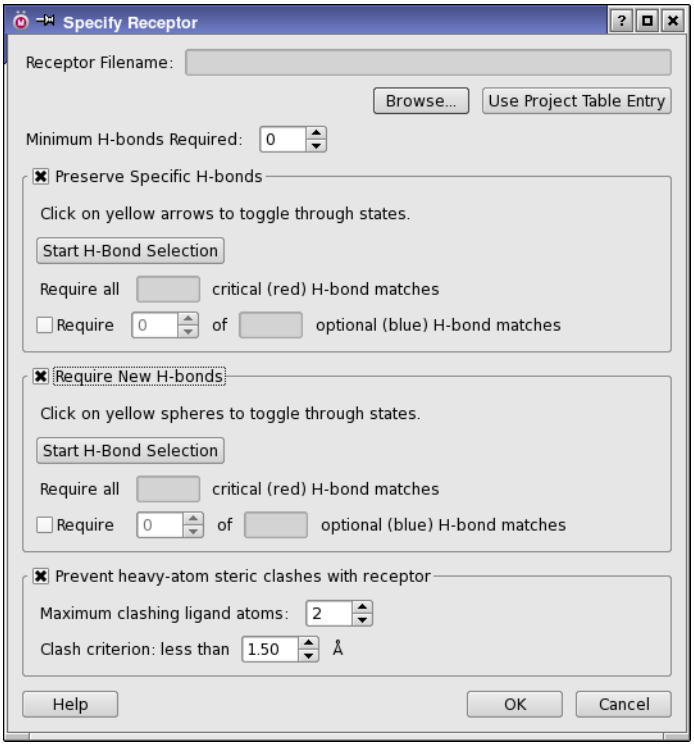

Figure 2.6. The Specify Receptor dialog box.

2.2.2.1 Using a Receptor to Filter Cores

A receptor can be used to enforce hydrogen bonding patterns and to eliminate cores that have too many steric clashes with the receptor. To make use of a receptor, select Use receptor, then click Specify Receptor to choose the receptor and set up constraints to the receptor.

In the Specify Receptor dialog box, you can set a general minimum on the number of hydrogen bonds to the receptor, and you can also pick existing template-receptor hydrogen bonds or define new receptor-core hydrogen bonds in the Workspace. These specific hydrogen bonds can be either required or optional.

To set up these hydrogen bonds, select Preserve specific H-bonds or Require New H-Bonds, then click Start H-Bond Selection and pick any of the arrows or spheres that mark candidate hydrogen bonds. The existing H-bonds are marked as arrows between the template and the receptor. Potential new H-bonds are marked on the receptor acceptor and donor atoms. The first click marks the H-bond as an optional match (blue), the second marks it as a required

match (red), and the third returns it to the unmarked state (yellow). When you have finished, click Stop H-Bond Selection.

Apart from requiring a minimum number of hydrogen bonds to ensure good binding to the receptor, the general minimum is useful for new cores that form hydrogen bonds to the receptor that are absent in the template, if you do not want to specify these in advance.

To avoid steric clashes, you can set a minimum allowed distance between heavy atoms in the new core molecule and the receptor. Smaller distances are considered a clash. It is not always necessary to exclude all such clashes, because of the flexibility of both the receptor and the ligand, so you can set a maximum on the number of ligand atoms that are permitted to clash with the receptor.

2.2.2.2 Setting Advanced Options

If you want to change any of the default settings of the method, click Advanced, and make settings in the Ligand-Based Advanced Options dialog box. General settings are at the top of the dialog box, and you can make settings for GPGPU use and sampling, and set cutoffs related to hydrogen bonding.

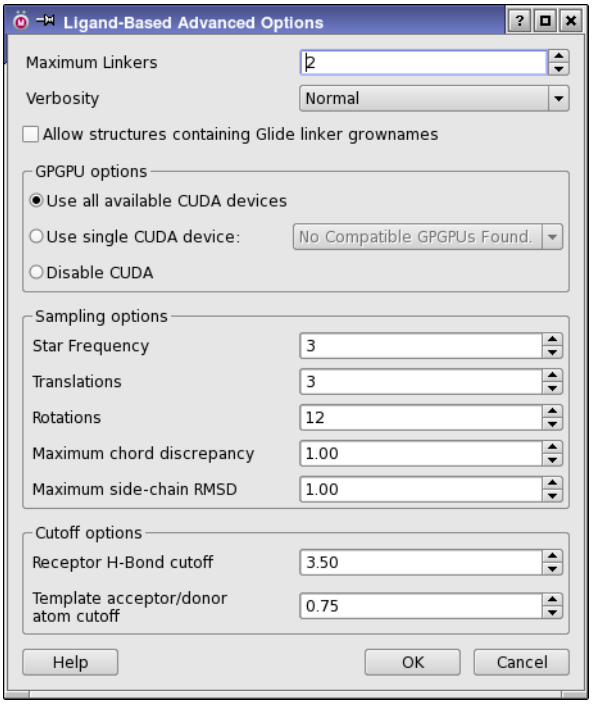

Figure 2.7. The Ligand-Based Advanced Options dialog box.

The general options include setting the maximum number of linkers that are added (up to 3 are permitted); select a verbosity level for the output; and allow the use of core candidates that already have linkers added in Glide-based core hopping (Allow structures containing Glide linker grow names): this is normally considered an error. and the maximum permissible root-mean-square interatomic deviation of the newly placed side chains from their original positions on the template. You can also select or deselect Allow side chains to be attached to polar atoms.

If you have a graphics card that supports CUDA-based computing, you can run the job on the graphics card. The GPGPU options allow you to use multiple graphics cards (if installed), or select one, or disable the user of the graphics card. If you want to use a GPGPU, you must run the job locally. You can also distribute the job on a multicore or multiprocessor host.

The sampling options in this dialog box affect the spatial sampling, and should not need to be set, except perhaps for Maximum side-chain RMSD, the maximum permissible root-mean-square interatomic deviation of the newly placed side chains from their original positions on the template. For more information on these options, contact help@schrodinger.com.

The cutoff options allow you to set the maximum length considered for a hydrogen bond to the receptor, if you are using one, and the maximum distance from a designated template acceptor or donor atom for a corresponding protocore acceptor or donor atom to be considered a match, when requiring acceptor/donor matches.

2.2.2.3 Previewing Results

The results of the calculation can be previewed and examined while they are being generated, in the Results Preview panel. To enable the use of previewing, select Use immediate results visualizer. At the top of the panel the template is displayed, along with statistics on the progress of the job. The top-scoring 20 structures are displayed in a table for two or three different scores: side-chain RMSD, core overlap, and synthesizability. The third of these is only available if you use an `.sqlite` file as input. The best, worst, average and standard deviation of the scores is displayed at the top of the table for each score.

The scores are defined as follows:

- Side chain RMSD score—RMSD of the side chains of the generated core structures with respect to the template, when superimposed on the template side chains.
- Core overlap score—Average of the fraction of atoms in the new core that have a template core atom within 0.5 Å and the fraction of atoms in the template core that have a new core atom within 0.5 Å, when the side chains are superimposed.
- Synthesizability score—Based on whether a particular substitution pattern has been observed in drug-like molecules, and how many of the attachment points are substituted in the new core molecule.

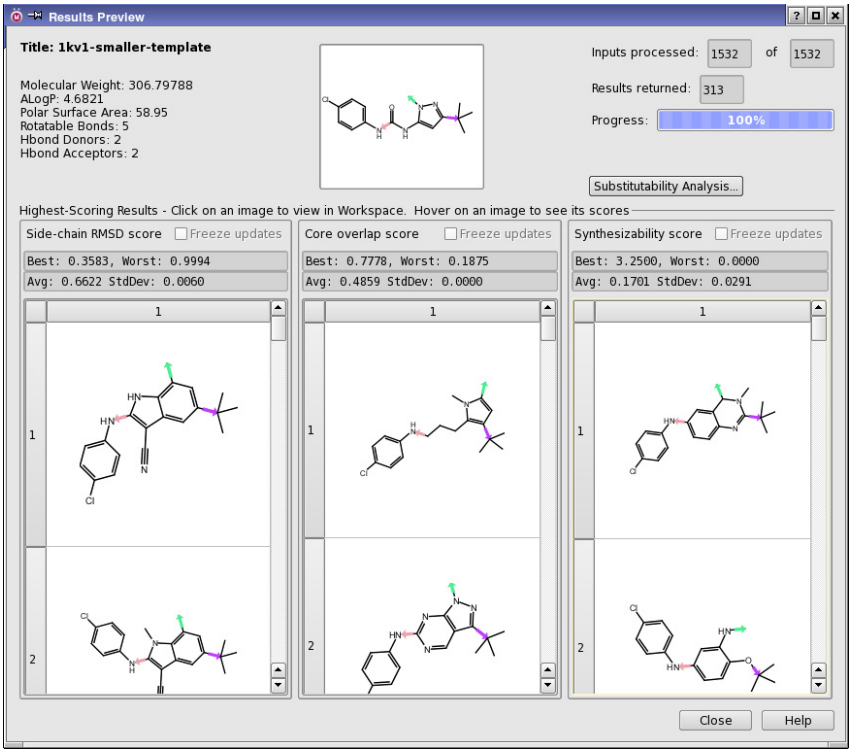

Figure 2.8. The Results Preview panel for an .sqlite input file.

The scores are evaluated as output structures are generated, and the results in the tables are updated. If you want to prevent the table for a particular score from being updated, select Freeze updates. The table is not updated until you deselect this option, and you can examine the structures in the table. The structures are ordered from the best score to the worst score.

To view one of the core structures in the Workspace, click on the cell for the structure. To display the scores and other information for a structure, pause the pointer over the structure.

2.2.3 Glide-Based Core Hopping

Glide-based core hopping first aligns the attachment bonds of the protocore (the input structure) to those of the template, using any selected Glide constraints, and writes out the resulting structures without any side chains at the attachment points. It then adds the template side chains at the attachment points of these structures, and docks them with Glide, again using any constraints that have been selected. During the alignment, methylene linkers can be added to the protocore to improve the alignment for cores that do not have the same size or shape as the template.

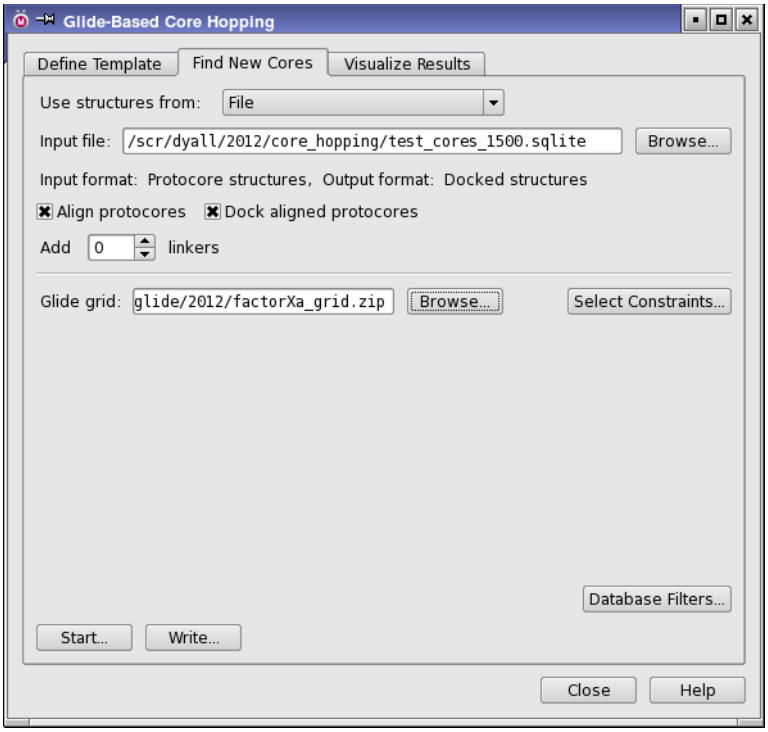

Figure 2.9. The Find New Cores tab of the Glide-Based Core Hopping panel.

You must generate the grid for the Glide docking before you start the core hopping job: the job does not generate the grids for you. See Chapter 4 of the *Glide User Manual* for details of grid generation. Constraints to the receptor can be used in both the alignment stage and the docking stage, so it is worth setting up the grid with the desired constraints.

You can perform the two stages of the process independently. By default, both are run.

- If you want to run just the alignment, ensure that Align protocores is selected and Dock aligned protocores is not selected. You can then inspect the aligned structures before proceeding with the docking, or use them as they are.
- If you want to run just the docking, ensure that Align protocores is not selected and Dock aligned protocores is selected. The input file must be a file containing aligned structures, and the output is a Glide pose file.

The input file and output file types are reported above these options, so that you can ensure you have the correct input, and know what kind of output to expect.

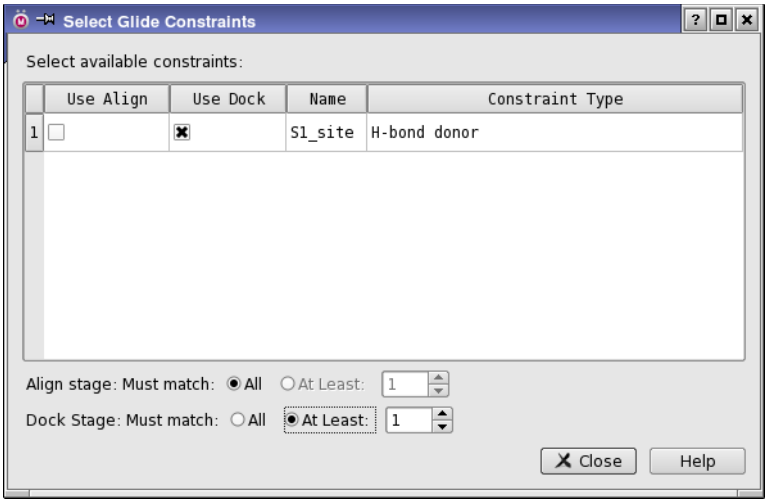

Figure 2.10. The Select Glide Constraints dialog box.

If you want to add linkers during the alignment, set the number of linkers to add in the Add *N* linkers box.

Next, you must choose the Glide grid that you want to use. Click Browse to locate and select the grid. The path to the grid file is displayed in the Glide grid text box.

If the receptor has H-bond constraints defined, you can select them for use in either the alignment stage or the docking stage. To do so, click Select Constraints and select them in the Select Glide Constraints dialog box. (The button is not available unless the grid has H-bond constraints.) The table lists the available constraints, and you can select each constraint for either stage. If you select multiple constraints, you can choose whether they all must be satisfied or whether a minimum number must be satisfied. To do this, select All for the appropriate stages to apply all the selected constraints, or select At least, and set the minimum number of constraints that must be satisfied in the box. When you have made your settings, close the dialog box.

2.2.4 Running the Job

When you have made all the settings you want to make, click Start to start the job. The Start dialog box opens, and you can choose a host for the job and provide a job name. The job is submitted to the host for execution when you click Start. If you are running a ligand-based or Glide-based core hopping job, you can distribute the job by choosing the number of CPUs to use.

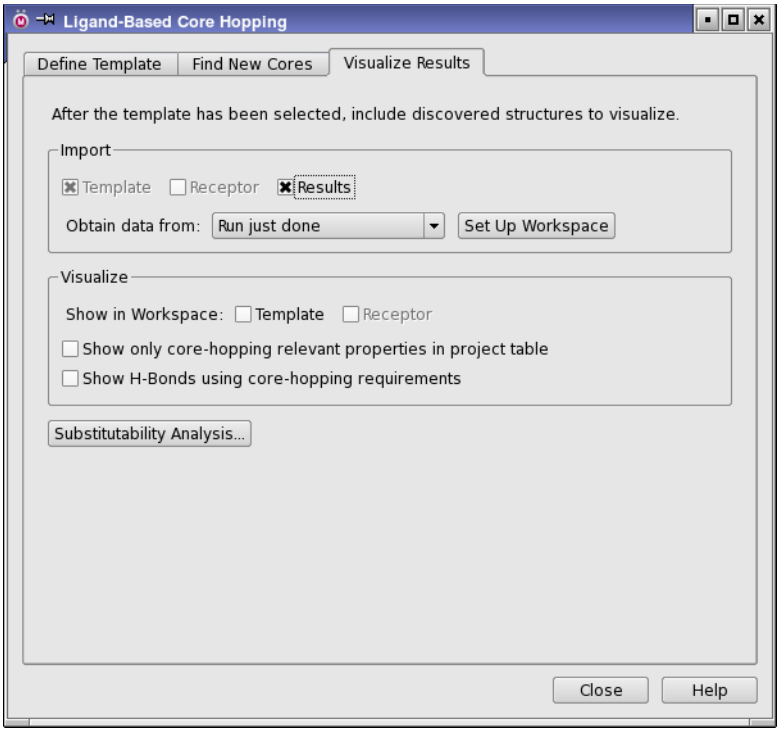

Figure 2.11. The Visualize Results tab of the Ligand-Based Core Hopping panel.

If you want to run the job from the command line, you can click Write. A dialog box opens, in which you can provide a job name, used for naming files, and select a host, just as in the Start dialog box. A shell script is written to the working directory that has the commands necessary to run the job. You can run this script from a terminal window on Linux or Mac hosts, and you can use a Schrodinger Command Prompt window on Windows, and prefix the command with `sh`.

2.3 Visualizing the Results

In the Visualize Results tab, you can set up the Workspace to examine the alignment of the new core-containing molecules with the template. To do this, you must import a set of results. The results can come from a run that has just been done, or they can come from a previous run, which can be either in a file or in the Project Table. This allows you to use the Visualize Results tab to examine results without having to perform another run. When you import data from a run, you can choose to import the receptor, the results, or both. The default is to import both. The template is always imported, and this cannot be changed.

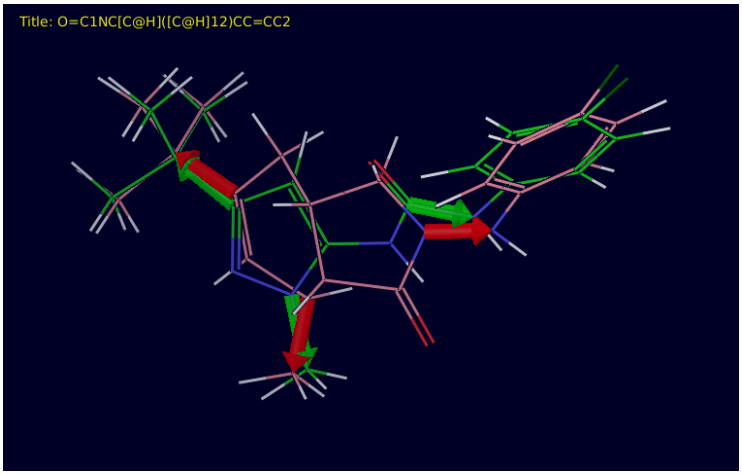

Figure 2.12. Example of ligand-based results visualization.

You can specify the source of the results by making a choice from the Obtain data from option menu. The button next to this menu depends on the choice that you make.

- For the run just completed, the results are already in the Project Table and selected. Click Set Up Workspace to fix the template or receptor in the Workspace and display the first result.
- For a previous run from a file, the results must be imported. Click Select Template in Job Directory to locate the template and import it, along with the results or the receptor or both. The template or the receptor structure or both are then fixed in the Workspace, and the first result is shown.
- For a previous run whose results are already in the Project Table, the template and the receptor must be selected. Click Select Entries in Project Table. If you do not have the template or the receptor selected in the Project Table, you are prompted to select entries for these structures when you click this button. The template or the receptor structure or both are then fixed in the Workspace, and the first result is shown.

You can step through the new core-containing molecules in the Project Table using the ePlayer or the arrow keys. The template is colored with green carbons and arrows for the attachment bonds and the new structures are shown with red carbons and arrows. If you want to display or undisplay the template or the receptor, you can do so in the Visualize section.

If a receptor is displayed, hydrogen bonds to the receptor are also displayed. If you chose a ligand-based core-hopping results set, and the receptor is displayed, you can show the hydrogen bonds to the receptor that satisfy the H-bond cutoff by selecting Show H-bonds using

core-hopping requirements. These requirements—distance of 3.5 Å between the donor and the acceptor heavy atoms, no angle requirements—are more generous than those used by Glide or by Maestro.

If you want to show only the properties that originate from core hopping in the Project Table, select Show only core-hopping relevant properties in Project Table. These properties include the sidechain rmsd, the number of linkers (nlinkers), and the largest number of linkers used in any side chain (linker sc max).

If you used an `.sqlite` database as input for the job, you can analyze the results to locate other molecules that have the same core pattern and are substituted at one or more of the same attachment points. This provides some information on whether the core has been used before in drug-like molecules, and if so whether the molecule might be synthesized. To run this analysis, click Substitutability Analysis, which opens the Substitutability Score Analysis panel (or in the Results Preview panel, if you are doing ligand-based core hopping).

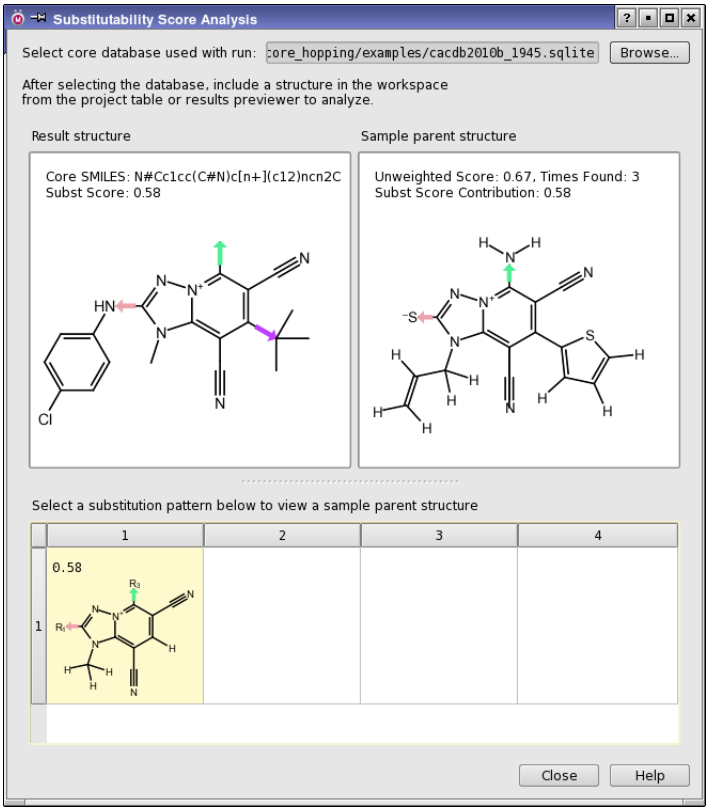

Figure 2.13. The Substitutability Score Analysis panel.

First, open the `.sqlite` database used to find the cores that you are visualizing in the Visualize Results tab (or Results Preview panel). You can then display the results in turn in the Workspace. As you display each result, the structure is analyzed and displayed in the Result structure section of the panel.

When a molecule is displayed in the Workspace, the database is searched for the core SMILES pattern. If it is found in a structure, the attachment points of the core in this structure are examined to see if there are any non-hydrogen groups (R groups, or substitutions) at the attachment points. If there are, it is considered to be a substitution pattern, even if not all the attachment points are substituted. The substitution patterns are displayed in the table at the bottom of the panel. If you click one of these patterns, an example of a known structure that has this substitution pattern is displayed in the Sample parent structure area, with a substitutability score and the number of times it was found.

Utilities

A.1 Protocore Preparation

The `protocore_prep` utility prepares a set of protocores by adding linkers and marking all possible attachment bonds on the protocores. The syntax of the command is as follows:

`$SCHRODINGER/utilities/protocore_prep` [*options*] *input-file output-file*

Both the input file and the output file must be Maestro files. The options are described in Table A.1.

Table A.1. Options for the protocore_prep command.

Option	Description
`-v[ersion]`	Display the program version and exit.
`-h[elp]`	Display the usage message and exit.
`-n` *GrowLength*	Set the maximum number of methylene linkers. The default is 0. Specifying more than two linkers is not recommended.
`-a`	Use the bonds that are already marked as attachment bonds in the input. By default, all nonpolar hydrogens are considered as attachment bonds.
`-p`	Use polar hydrogens. By default only nonpolar hydrogens are considered as attachment bonds.
`-e`	Grow linkers dendritically: the second and subsequent methylene insertions replace two hydrogens on the previous methylene rather than just one.
`-d` *level*	Set verbosity level (0-2)
`-l` *logfile*	Specify location of log file. The default is stdout.

A.2 Creating a Core Library

If you want to prepare a library of cores for use with ligand-based core hopping, you can do so with the `corefinder` utility. This utility produces either a Maestro file (`.mae` or `.maegz`) or an SQLite file (`.sqlite`). Its main intended use is for producing SQLite files, which include information that is used to derive synthetic feasibility scores that is absent from the Maestro file. The syntax is:

`$SCHRODINGER/utilities/corefinder` [*job-options*] `-o` *output-file input-files*

More than one input file can be specified, and the output is combined into a single file with elimination of redundancies. If the input files are SQLite files, they must be core-hopping library files produced by this utility, and they are combined into a single output file. Multiple structure files are processed in separate subjobs.

The utility accepts the standard Job Control job options, described in Section 2.3 of the *Job Control Guide*. In addition, the common options `-NOJOBID` (for running outside Job Control) and `-WAIT` are supported. You can specify subjob hosts with the `-SUBHOST` option.

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/, particularly the Support Center, http://www.schrodinger.com/supportcenter, and the Knowledge Base, http://www.schrodinger.com/kb.

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 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 your browser.
- Choose Help → Online Help or press CTRL+H (⌘H) to open the default help topic in your browser.
- When help is displayed in your browser, use the navigation links or search the help in the side bar.
- Choose Help → Manuals Index, to open a PDF file that has links to all the PDF 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*.
- Software updates: choose Maestro → Check for Updates.
- New software features: choose Help → New Features.
- Scripts available for download: choose Scripts → Update.
- 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.

E-mail: help@schrodinger.com
USPS: Schrödinger, 101 SW Main Street, Suite 1300, Portland, OR 97204
Phone: (503) 299-1150
Fax: (503) 299-4532
WWW: http://www.schrodinger.com
FTP: ftp://ftp.schrodinger.com

Generally, e-mail correspondence is best because you can send machine output, if necessary. When sending e-mail messages, please include the following information:

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

Gathering Information for Technical Support

This section describes how to gather the required machine, licensing, and installation information, and any other job-related or failure-related information, to send to technical support.

For general enquiries or problems:

1. Open the Diagnostics panel.
   - **Maestro:** Help → Diagnostics
   - **Windows:** Start → All Programs → Schrodinger-2012 → Diagnostics
   - **Mac:** Applications → Schrodinger2012 → 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. Attach the file specified in the dialog box to your e-mail message.

If your job failed:

1. Open the Monitor panel in Maestro.

   Use Applications → Monitor Jobs or Tasks → Monitor Jobs.
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 in your working directory, and an information dialog box with the name of the file opens. You can highlight and copy the name of the file.
5. Attach the file specified in the dialog box to your e-mail message.
6. Copy and paste any log messages from the window used to start Maestro (or the job) into the email 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-2012 → Diagnostics
   - **Mac:** Applications → Schrodinger2012 → 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. Attach the file specified in the dialog box to your e-mail message.

4. Attach the file `maestro_error.txt` to your e-mail message.

   This file should be in the following location:

   - **Windows:** `%LOCALAPPDATA%\Schrodinger\appcrash`
     (Choose Start → Run and paste this location into the Open text box.)
   - **Mac:** `Documents/Schrodinger`
   - **Linux:** Maestro's working directory specified in the dialog box (the location is given in the terminal window).

5. On Windows, also attach the file `maestro.EXE.dmp`, which is in the same location as `maestro_error.txt`.

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17th Floor
New York, NY 10036

101 SW Main Street
Suite 1300
Portland, OR 97204

245 First Street
Riverview II, 18th Floor
Cambridge, MA 02142

8910 University Center Lane
Suite 270
San Diego, CA 92122

155 Gibbs St
Suite 430
Rockville, MD 20850-0353

Dynamostraße 13
D-68165 Mannheim
Germany

Zeppelinstraße 73
D-81669 München
Germany

Potsdamer Platz 11
D-10785 Berlin
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Quatro House
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Camberley GU16 7ER
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