QM-Polarized Ligand Docking

Schrödinger Suite 2012 Update 2

Schrödinger Press

Revision A, September 2012

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].

QM-Polarized Ligand Docking

The QM-Polarized Ligand Docking protocol aims to improve the partial charges on the ligand atoms in a Glide docking run by replacing them with charges derived from quantum mechanical calculations on the ligand in the field of the receptor. In this way the polarization of the charges on the ligand by the receptor is accounted for, and redocking of the ligands with these new charges can result in improved docking accuracy. The protocol works by taking a small set of the best-scoring poses for each ligand, calculating charges using QSite, redocking each of these poses, and selecting the best poses from the set.

To run the QM-Polarized Ligand Docking protocol you must have an installed and licensed version of Glide 5.8 and QSite 5.8 (including Jaguar 7.9). In addition, to set up jobs from Maestro you must have Maestro 9.3 installed.

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"
```

2 The QM-Polarized Ligand Docking Panel

In the QM-polarized ligand docking protocol, ligands are docked with Glide, then charges on the ligand induced by the protein are calculated with QSite, and a set of the best ligand poses are redocked. The QM-Polarized Ligand Docking panel collects the relevant controls for each part of the protocol, with judicious selection of defaults for options that are not presented in the panel. To open this panel, choose QM-Polarized Ligand Docking from the Workflows menu on the main menu bar.

The panel is divided into five tabs, each of which deals with a stage of the protocol. Above the tabs is a section that contains controls for specifying the ligands. At the foot of the panel is a row of action buttons.

A summary of the setup process is given below. The steps in the process are described in more detail in the following sections.

To set up a QM-polarized ligand docking calculation:

1. Specify the ligands to be docked with the Dock ligands from option menu.
2. Set up the receptor grid or select an existing grid in the Receptor tab.
3. Set the initial docking options in the Initial docking tab.
4. Set the level and type of quantum mechanical treatment in the QM charge tab.
5. Set options for the redocking of the ligands in the Redocking tab.
6. Select the energy parameter by which the final poses are scored in the Final selection tab.
7. Click Start, set job options in the Start dialog box, and click Start.

When the job finishes, a pose viewer file is generated with the final selections. In addition, a *jobname*`.log` file is generated.

If you want to change any of the options for which controls are not provided in this panel, you can click Write, and the files for the calculation are written. You can then run the calculations from the command line.

If you are docking a single ligand and want to calculate the RMSD of the resultant poses from a reference ligand, select Calculate RMSD from reference ligand file and specify a Maestro, SD, or PDB file that contains the reference ligand, which must have the same structure as the input ligand. The results are written to a *jobname*`_rmsd.out` file.

If you want to start the setup process again with the default options, click Reset.

3 Selecting Ligands To Be Docked

The ligands to be docked must be properly prepared (for example, by using LigPrep) and must be in a Maestro, SD, or PDB file. Because the QSite step takes much more time than the Glide docking steps, you should restrict the number of ligands to a relatively small set, which might be the results of a previous docking run. To select the ligands, choose an option from the Dock ligands from option menu. If you choose Project Table (selected entries), the required entries must be selected before you start the job. If you choose File, enter a file name in the text box, or click Browse and navigate to the file containing the ligands.

For more information on preparing ligands, see the *LigPrep User Manual*.

4 Setting Up the Grid

The grid for the QM-polarized ligand docking job can be set up as part of the job, or it can be read from a previous Glide grid generation job. The QM-Polarized Ligand Docking panel offers a limited range of options for setting up the grid, in the Receptor tab. If you want greater flexibility, you should set up the grid using the Glide Receptor Grid Generation panel, which is described in Chapter 4 of the *Glide User Manual*.

If you want to use an existing grid, select Use existing grid, and enter the name of the grid file in the text box, or click Browse and navigate to the grid file (`.grd` or `.zip`).

If you want to set up the grid as part of the job, you can specify the center and size of the grid box, and apply van der Waals radii scaling to the receptor. All other parameters take their default values. To set up the grid, the receptor must be displayed in the Workspace, with or without the ligand. If a ligand is displayed, you must identify it, either by entering the molecule number in the Ligand molecule number text box, or selecting Pick and picking a ligand atom. If a ligand is not displayed, you must define the center of the enclosing box in terms of receptor residues. The protein must be properly prepared for a Glide calculation. See Chapter 3 of the *Glide User Manual* and the *Protein Preparation Guide* for more information on protein preparation, and Chapter 4 of the *Glide User Manual* for more information on grid generation.

The options for the center of the grid box are:

- Centroid of the Workspace ligand—Center the grid box on the ligand centroid. The centroid is the mean position of the non-hydrogen atoms in the ligand. To specify the ligand, select Pick and click on a ligand atom in the Workspace. The molecule number for the ligand is displayed in the text box.

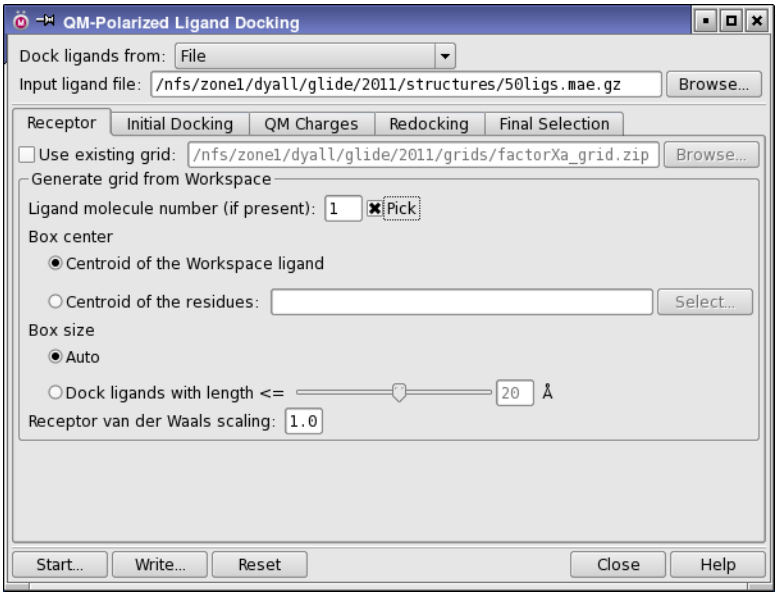

Figure 1. The Receptor tab of the QM-Polarized Ligand Docking panel.

- Centroid of the residues—Center the grid box on a group of receptor residues. To select residues for the centroid, click the Select button. The Atom Selection dialog box opens, in which you can select the residues to define the centroid. The ASL expression for the residues is displayed in the text box.

The options for the size of the enclosing box are:

- Auto—automatically determine the size of the enclosing box. If the Center option is Centroid of the ligand, the enclosing box size is calculated automatically from the size of the ligand. If the Center option is Centroid of the residues, the enclosing box size is set to 26 Å on each side.
- Dock ligands with length—set the size of the ligands to dock by adjusting the slider or entering a value in the text box. This is the same as in the Glide Receptor Grid Generation panel.

To set the scaling factor for the van der Waals radii of the nonpolar part of the receptor, enter the desired value in the Receptor van der Waals scaling text box. For more information on the purpose of scaling these radii, see Section 4.2.2 of the *Glide User Manual*.

5 Setting Initial Glide Docking Parameters

In the Initial docking tab, you can select the docking mode, set parameters for the elimination of duplicate poses, scale the van der Waals radii if necessary, and decide how many poses to keep per ligand. The defaults represent reasonable choices. The remaining Glide docking options are set to their default values, which includes post-docking minimization.

If you want to skip the initial Glide docking step and use a set of predocked poses, you can select the Use existing pose-viewer file, then click Browse to navigate to a pose viewer file. This option disables the controls in the Initial Glide docking section.

The pose-viewer file is only used as input to charge generation. The input file is the file that is used for the redocking stage, so the two sets of structures must be matched in order to apply the charges from the QM calculation to the structures in the input ligand file. For this reason, the structure titles in the pose-viewer file must match the titles in the input ligand file. Structures with the same title must be conformers, and have the same atom numbering. This file is only used as input to charge generation. To ensure that the matching is done correctly, we recommend that you choose the input ligand file to be the input file for the Glide docking run that you used to generate the pose viewer file.

The Initial Glide docking section contains the following controls:

Generate initial charges with semiempirical method option

Instead of using the charges from the force field, you can generate initial charges from a semiempirical NDDO calculation, by selecting this option.

Precision options

Select SP or XP precision. For more information on the docking precision, see Section 5.2.2 of the *Glide User Manual*.

Ligand van der Waals scaling text box

Specify scaling factors for the van der Waals terms for the ligand in this text box. For more information on the scaling, see Section 5.3.4 of the *Glide User Manual*.

Discard pose as duplicate text boxes

These two text boxes specify the thresholds for discarding a pose as a duplicate. Both thresholds must be met for a pose to be discarded. Specify the RMS deviation and the maximum atomic displacement thresholds in angstroms.

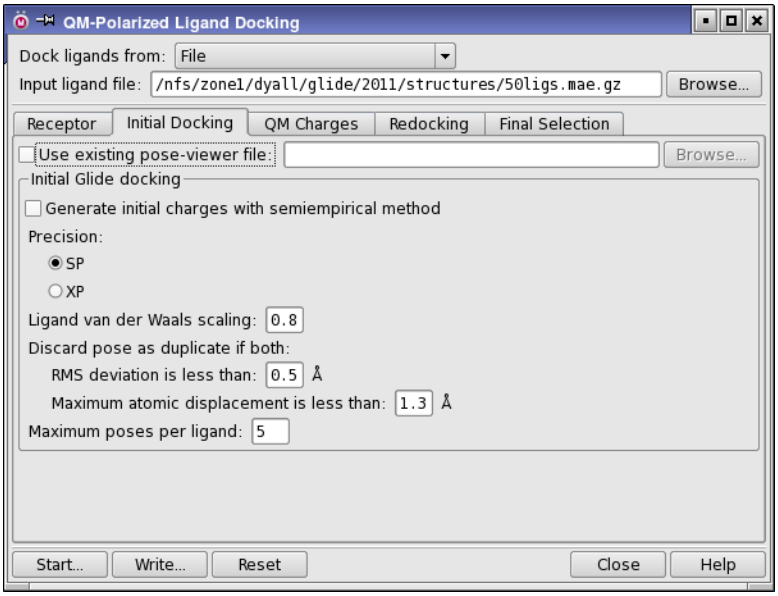

Figure 2. The Initial Docking tab of the QM-Polarized Ligand Docking panel.

Maximum poses per ligand text box

Enter the maximum number of poses to retain for the QSite ESP calculations. The QSite calculation is time-consuming, so only a small number of poses should be retained. The default value is 5, a value that has been optimized based on our research.

6 Selecting a QM Treatment

In the QM charges tab, you can select a level of quantum-mechanical treatment of the ligand, and choose whether to treat the ligand in the field of the receptor or as a free ligand, in the gas phase or in water.

To calculate charges for the free ligand, select Calculate charges for free ligand. You can then choose to calculate charges for the ligand in the gas phase by selecting In gas phase, or in aqueous solution using a continuum solvation model, by selecting In water.

The selection of the QM level is a trade-off between speed and accuracy. The fastest method is the semiempirical NDDO method, which you choose by selecting Use semiempirical method. With this option, you have a choice of three charge models: Coulson, Mulliken, or ESP, which you choose from the Charge type option menu.

The full QM methods take longer than the semiempirical methods. The charges are calculated from the electrostatic potential energy surface of the ligand, which is generated from a single-point calculation using density functional theory for the QM region, as follows:

- Fast—Uses the 3-21G basis set, BLYP functional, and "Quick" SCF accuracy level.
- Accurate—Uses the 6-31G*/LACVP* basis set, B3LYP density functional, and "Ultra-fine" SCF accuracy level (`iacc=1`, `iacscf=2`).

7 Setting Glide Redocking Parameters

In the Redocking tab, you can choose the docking precision (SP or XP) for redocking of the ligands with updated QM charges, set the van der Waals scaling, set criteria for the elimination of duplicate poses, and enter the maximum number of poses to keep for each redocked ligand. These controls are the same as in the Initial docking tab. The remaining Glide docking options are set to their default values, which includes post-docking minimization.

8 Specifying the Final Selection

In the Final selection tab, you can specify how the poses are ranked and calculate an RMSD from a reference ligand.

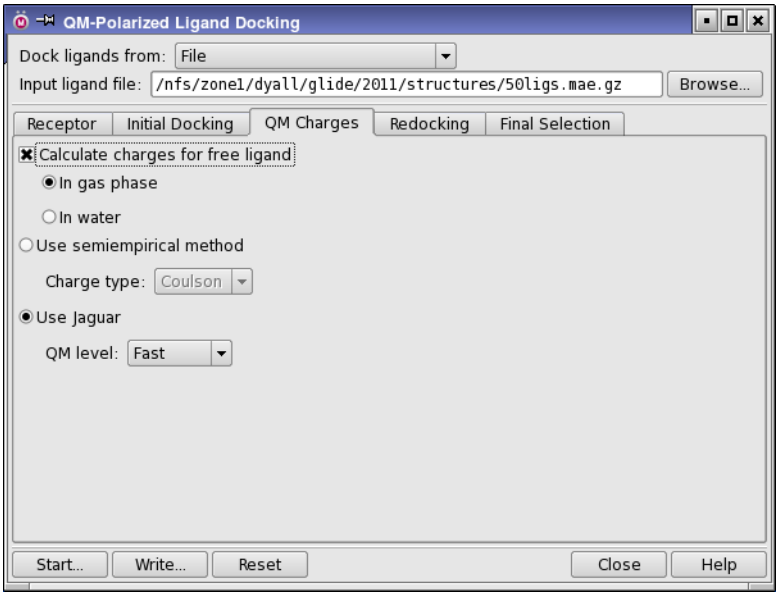

Figure 3. The QM Charges tab of the QM-Polarized Ligand Docking panel.

The Final selection by option menu offers the choice of three quantities by which the poses are ranked: the Coulomb-van der Waals energy, the GlideScore, and Emodel. For a description of these quantities, see Chapter 2 of the *Glide User Manual*.

The Calculate RMSD from reference ligand file option allows you to calculate the RMSD of the various poses of the redocked ligands relative to a set of reference ligands, which is read from file. Specify the path to the file, or click Browse to navigate to the file. The reference ligands must have the same structure (atom types and order) as the input ligands, and are matched to the poses for the RMSD calculation by title (by default). The poses are listed in rank order with their RMSD values in the file *jobname*`-RMSD.log`, and the RMSD value is added to the output structure file, *jobname*`-RMSD_OUT.mae`.

If you do not calculate the RMSD, the output structures are stored in the file *jobname*`-SORT_OUT.mae`.

9 Running the Job

When you are ready to run the job, click Start to open the Start dialog box. In this dialog box, you can make job settings and start the job. The dialog box has an Output section in which you can choose an option from the menu for incorporating the results into the project, from Append new entries and Do not incorporate. The usual controls are available for the job name and host selection.

QPLD jobs can be divided into multiple subjobs and run on multiple processors. The ligands are divided between the subjobs, and each subjob runs the entire protocol for each of its ligands. Multiple CPUs are not used for QSite (Jaguar) parallel calculations. Setting the number of subjobs to some multiple of the number of CPUs allows for better load balancing. The subjobs are managed by a master job (or driver) on the local host.

If you want to run the job from the command line, write out the input file to the working directory by clicking Write and supplying a job name (which becomes the stem of the file name) in the dialog box that is displayed. You can then run the job with the `qpld` command:

`$SCHRODINGER/qpld` [*options*] *input-file*

The options are listed in Table 1. The standard Job Control options, which are listed in Table 2.1 of the *Job Control Guide*, are supported. This includes the `-HOST` option, which is used to specify the hosts for the job, and the ability to run the driver job on a remote host. The `-WAIT` option, described in Table 2.2 of the *Job Control Guide*, is also supported.

The input file is described in detail in Chapter 2 of the *Python Pipeline Manual*. This manual gives details on the running of workflows from the command line, including information on restarting jobs.

Table 1. Options for the qpld command.

Option	Description
`-adjust`	Adjust the number of subjobs so that the estimated job length is between 10 minutes and 20 hours.
`-NJOBS` *n*	Number of subjobs to generate without adjusting. If not specified, the number of subjobs is set to the number of processors and the `-adjust` option is set.
`-host_glide` *hosts*	Run Glide jobs on the specified hosts. Default: run on hosts specified by `-HOST`.
`-host_qsite` *hosts*	Run QSite jobs on the specified hosts. Default: run on hosts specified by `-HOST`.
`-DRIVERHOST` *host*	Run the driver job on the specified host. By default, the driver (master) job runs on first host specified by `-HOST`.
`-LOCALDRIVER`	Run the driver job on the local host. Same as specifying `-DRIVERHOST localhost`.
`-LOCAL`	Run the driver job in local directory (default if the driver is run on the local host).
`-NOLOCAL`	Run the driver job in the scratch directory (default if he driver is run on a remote host). Jobs run with this option cannot be restarted.
`-REMOTEDRIVER`	Run the driver job on the first host specified by `-HOST`.
`-RESTART`	Restart the job. Restarting runs any subjobs that did not finish in the previous execution of the job.
`-RESTARTBEG`	Restart the job from the first uncompleted stage. All subjobs from the failed stage are run from the beginning.
`-OVERWRITE`	Overwrite any existing files when running the job.
`-local`	Do not create a temporary directory for each subjob.
`-no_cleanup`	Do not remove intermediate files.
`-max_retries` *n*	Maximum number of times to restart subjobs if they fail. If not specified, the value specified by `SCHRODINGER_MAX_RETRIES` value is used, if defined, otherwise the default is 2.
`-v`	Display the version number and exit.
`-h[elp]`	Print usage message and exit.

10 Citing QM-Polarized Ligand Docking in Publications

Schrödinger Suite 2012 QM-Polarized Ligand Docking protocol; Glide version 5.8, Schrödinger, LLC, New York, NY, 2012; Jaguar version 7.9, Schrödinger, LLC, New York, NY, 2012; QSite version 5.8, Schrödinger, LLC, New York, NY, 2012.

Please also cite the following reference:

Cho, A. E.; Guallar, V.; Berne, B.; Friesner, R. A., "Importance of Accurate Charges in Molecular Docking: Quantum Mechanical/Molecular Mechanical (QM/MM) Approach," *J. Comput. Chem.*, **2005**, *26*, 915-931.

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
- QM-Polarized Ligand Docking purchaser (company, research institution, or individual)
- Primary QM-Polarized Ligand Docking 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
Germany

Quatro House
Frimley Road
Camberley GU16 7ER
United Kingdom

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