

QM-Polarized Ligand Docking

Schrödinger Suite 2009

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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	<code>\$SCHRODINGER/maestro</code>	File names, directory names, commands, environment variables, and screen output
Italic	<i>filename</i>	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`.

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 5.5 and QSite 5.5 (including Jaguar 7.6). In addition, to set up jobs from Maestro you must have Maestro 9.0 installed. You must also set the `SCHRODINGER` environment variable to point to the installation directory.

Running Schrödinger Software

To run any Schrödinger program on a UNIX platform, or start a Schrödinger job on a remote host from a UNIX 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:

```
cshtcsh:      setenv SCHRODINGER installation-directory  
bash/ksh:    export SCHRODINGER=installation-directory
```

Once you have set the `SCHRODINGER` environment variable, you can start Maestro 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. For more information on starting Maestro, including starting Maestro on a Windows platform, see [Section 2.1](#) of the *Maestro User Manual*.

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 two sections. The upper section contains controls for specifying the grid and the ligands. The lower section contains controls for the stages of the workflow. 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. Set up the receptor grid in the Glide grid generation section of the panel, or select an existing grid.
2. Select the ligands to be docked in the Ligands to be docked section.
3. Set the initial docking options in the Initial Glide docking section.
4. Select the level and type of quantum mechanical treatment in the QM charge calculation section.
5. Enter the number of poses to keep for each ligand in the redocking of each of the poses selected for QM charge evaluation, and select the docking accuracy.
6. Select the energy parameter by which the final poses are scored.
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, but you must run each application separately.

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.

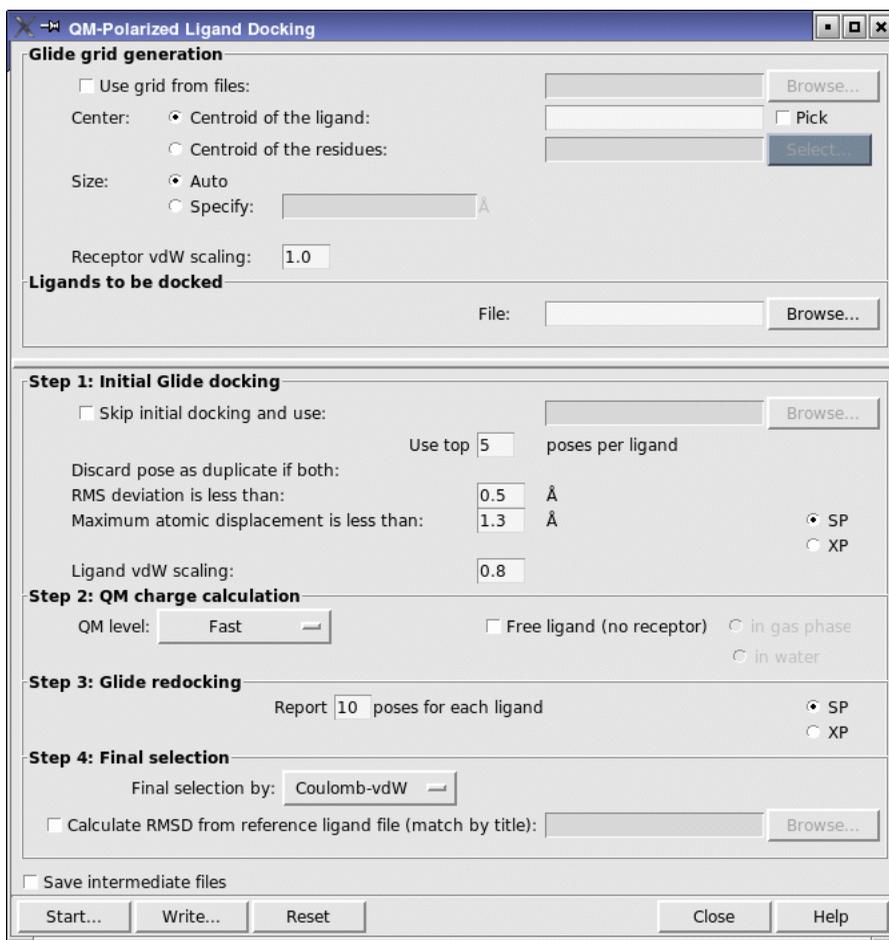


Figure 1. The QM-Polarized Ligand Docking panel.

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

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. 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 grid from files**, 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 enclosing 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 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 enclosing box are:

- **Centroid of the ligand**—Center the enclosing 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.
- **Centroid of the residues**—Center the enclosing 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.
- **Specify**—set the size of the enclosing box. Enter the desired side length in the text box, in angstroms. The enclosing box has sides of equal length given by the value in the text box.

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 vdW scaling** text box. For more information on the purpose of scaling these radii, see [Section 4.2.2](#) of the *Glide User Manual*.

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, in the **Ligands to be docked**

section, enter a file name in the text box, or click **Browse** and navigate to the file containing the ligands. You can use predocked poses instead, and skip the initial Glide docking. The ligands are taken from the pose viewer file, and the controls in this section are disabled.

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

Setting Initial Glide Docking Parameters

The tasks in the Initial Glide docking section are to set parameters for the elimination of duplicate poses, scale the van der Waals radii if necessary, select the docking mode, and decide how many poses to keep per ligand. The defaults represent reasonable choices.

If you want to skip the initial Glide docking step and use a set of predocked poses, you can select the **Skip initial docking and use option**, then click **Browse** to navigate to a pose viewer file. This option disables the controls in the **Ligands to be docked** section. This file is used instead of a ligand file.

Use top N poses per ligand text box

Enter the 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.

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.

Ligand vdW 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*.

Docking mode options

Select SP or XP docking mode. For more information on the docking modes, see [Section 5.2.2](#) of the *Glide User Manual*.

Selecting a QM Treatment

In the QM charge calculation section, 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.

The selection of the QM level is a trade-off between speed and accuracy. 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 “Ultrafine” SCF accuracy level (*iacc*=1, *iacscf*=2).

If you want to treat the ligand as a free ligand, rather than in the field of the receptor, select the **Free ligand** option. The calculation on the ligand will be performed without the receptor. When you select this option, you can also choose to treat the ligand as a gas-phase molecule (in **gas phase**) or solvated in water (in **water**) using a continuum solvation model.

Setting Glide Redocking Parameters

In the **Glide redocking** section, you can choose the docking mode (SP or XP) for redocking of the ligands with updated QM charges, and enter the number of poses to keep for each redocked ligand.

Specifying the Final Selection

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

The **Final selection** by option menu offers the choice of three quantities by which the poses are ranked: the Coulomb-vdW 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.

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 the usual controls for the job name, username, and host selection. There are no incorporation options: the results are written to the output file and a Maestro file in the working directory.

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). You can choose whether to run the driver on the local host, or on the host used for the computations. The master job will not use a lot of CPU time, so it can be inefficient to run it on a processor that is not running other tasks.

If you want to keep the intermediate files for the calculation, you can select **Save intermediate files** in the main panel before clicking **Start**. These files are archived in a gzipped tar file, and copied back to the directory from which the job was started.

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. The `-WAIT` option, described in [Table 2.2](#) of the *Job Control Guide*, is also supported.

Citing QM-Polarized Ligand Docking in Publications

Schrödinger Suite 2009 QM-Polarized Ligand Docking protocol; Glide version 5.5, Schrödinger, LLC, New York, NY, 2009; Jaguar version 7.6, Schrödinger, LLC, New York, NY, 2009; QSite version 5.5, Schrödinger, LLC, New York, NY, 2009.

Table 1. Options for the `qpld` command.

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

Getting Help

Schrödinger software is distributed with documentation in PDF format. If the documentation is not installed in `$(SCHRODINGER)/docs` on a computer that you have access to, you should install it or ask your system administrator to install it.

For help installing and setting up licenses for Schrödinger software and installing documentation, see the *Installation Guide*. For information on running jobs, see the *Job Control Guide*.

Maestro has automatic, context-sensitive help (Auto-Help and Balloon Help, or tooltips), and an online help system. To get help, follow the steps below.

- Check the Auto-Help text box, which is located at the foot of the main window. If help is available for the task you are performing, it is automatically displayed there. Auto-Help contains a single line of information. For more detailed information, use the online help.
- If you want information about a GUI element, such as a button or option, there may be Balloon Help for the item. Pause the cursor over the element. If the Balloon Help does not appear, check that Show Balloon Help is selected in the Maestro menu of the main window. If there is Balloon Help for the element, it appears within a few seconds.
- For information about a panel or the tab that is displayed in a panel, click the Help button in the panel, or press F1. The help topic is displayed in your browser.
- For other information in the online help, open the default help topic by choosing Online Help from the Help menu on the main menu bar or by pressing CTRL+H. This topic is displayed in your browser. You can navigate to topics in the navigation bar.

The Help menu also provides access to the manuals (including a full text search), the FAQ pages, the New Features pages, and several other topics.

If you do not find the information you need in the Maestro help system, check the following sources:

- *Maestro User Manual*, for detailed information on using Maestro
- *Maestro Command Reference Manual*, for information on Maestro commands
- *Maestro Overview*, for an overview of the main features of Maestro
- *Maestro Tutorial*, for a tutorial introduction to basic Maestro features
- *Glide User Manual*, for information on using Glide
- *Glide Quick Start Guide*, for Glide tutorials
- *QSite User Manual*, for information on using QSite

- Frequently Asked Questions pages on the Schrödinger [Support Center](#).
- Known Issues pages, available on the [Support Center](#).

The manuals are also available in PDF format from the Schrödinger [Support Center](#). Local copies of the FAQs and Known Issues pages can be viewed by opening the file `Suite_2009_Index.html`, which is in the `docs` directory of the software installation, and following the links to the relevant index pages.

Information on available scripts can be found on the [Script Center](#). Information on available software updates can be obtained by choosing Check for Updates from the Maestro menu.

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
- Computer platform type
- Operating system with version number
- Version numbers of products installed for QM-Polarized Ligand Docking
- Maestro version number
- mmshare version number

On UNIX you can obtain the machine and system information listed above by entering the following command at a shell prompt:

```
$SCHRODINGER/utilities/postmortem
```

This command generates a file named `username-host-schrodinger.tar.gz`, which you should send to help@schrodinger.com. If you have a job that failed, enter the following command:

```
$SCHRODINGER/utilities/postmortem jobid
```

where *jobid* is the job ID of the failed job, which you can find in the Monitor panel. This command archives job information as well as the machine and system information, and

includes input and output files (but not structure files). If you have sensitive data in the job launch directory, you should move those files to another location first. The archive is named `jobid-archive.tar.gz`, and should be sent to help@schrodinger.com instead.

If Maestro fails, an error report that contains the relevant information is written to the current working directory. The report is named `maestro_error.txt`, and should be sent to help@schrodinger.com. A message giving the location of this file is written to the terminal window.

More information on the `postmortem` command can be found in [Appendix A](#) of the *Job Control Guide*.

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