Physics-Based ADME/Tox

Schrödinger Software Release 2015-2

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Contents

Document Conventions

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

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

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

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

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

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

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

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

Introduction

The Physics-Based ADME/Tox suite is a set of tools for evaluating ADME/Tox properties. The current suite contains two tools:

- P450 Site of Metabolism—a tool for identifying likely sites of metabolism based on Hammet and Taft- type rules and 3D spatial information in several P450 isoforms.
- Membrane Permeability—a tool for evaluating membrane permeability based on conformational analysis and desolvation penalties.

For ADME predictions based on molecular descriptors, see the *QikProp User Manual*.

1.1 Running Schrödinger Software

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

Linux:

To run any Schrödinger program on a Linux platform, or start a Schrödinger job on a remote host from a Linux platform, you must first set the `SCHRODINGER` environment variable to the installation directory for your Schrödinger software. To set this variable, enter the following command at a shell prompt:

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

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

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

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

You can start the Maestro interface with the following command:

```
$SCHRODINGER/maestro &
```

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

Windows:

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

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

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

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

Mac:

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

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

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

and on OS X 10.8, 10.9, and 10.15 use the command

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

1.2 Starting Jobs from the Maestro Interface

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

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

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

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

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

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

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

Note: The items present on the Settings menu can vary with the application. The descriptions above cover all of the items. Jaguar has an Edit item and extra functions for the Read and Write items, which are described later in the manual.

The icon on the Job Status button shows the status of jobs for the application that belong to the current project. It starts spinning when the first job is successfully launched, and stops spinning

when the last job finishes. It changes to an exclamation point if a job is not launched successfully.

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

1.3

P450 Site of Metabolism

Cytochrome P450 enzymes play an integral role in the metabolism pathway of drugs. These heme-containing enzymes catalyze a variety of reactions, such as hydroxylation, dealkylation, and double-bond oxidation, that result in the degradation of small molecules. Predicting the sites of metabolism of drug-like molecules would give medicinal chemists better control of the metabolic stability of molecules they design.

For the 3A4 isoform of cytochrome P450, ligand-based reactivity models have been shown to be highly predictive. The success of these predictions is thought to be due to the lack of orientational preference of ligands in the 3A4 binding site, which is highly flexible. For other isoforms with regioselective preferences, it is more difficult to predict the reactivity with ligand-based models. This is particularly true for differentiating ligands with very subtle differences, such as inversions of stereo centers and small functional group modifications away from the sites of metabolism. In such cases, a model that includes information about the binding mode to the isoform of interest is necessary.

For a given atom of a molecule to be a significant site of metabolism by a P450 enzyme, it must have some degree of reactivity in the absence of the enzyme and also be accessible to the reactive heme iron center. To address both of these requirements, the P450 Site of Metabolism workflow combines induced-fit docking (IFD) for the determination of accessibility to the reactive center with a rule-based approach to intrinsic reactivity.

2.1 Methodology

The reactivity rules have been parameterized to predict atomic reactivity profiles for promiscuous P450 enzymes that are thought to be mostly independent of structural restrictions on the binding poses. The reactivity is predicted with a linear free energy approach based on the Hammett and Taft scheme, where the reactivity of a given atom is the sum of a baseline reactivity rate and a series of perturbations determined by the connectivity.

The induced-fit docking approach is a variation on the current protocol (see the *Induced Fit Docking* manual). The initial sampling is enhanced by generating multiple starting conformations, so that a wider range of poses is found in the initial docking stage. The initial docking includes van der Waals scaling of the receptor and alanine mutation of the most flexible residues. In the Prime refinement stage, any residue with an atom within 5 Å of any ligand pose is selected for side-chain prediction. The subsequent minimization includes the ligand, side chains, and backbones of the flexible residues. The ligand is then redocked into each of the

low-energy protein conformations, determined by a 40 kcal/mol cutoff. There is no final scoring stage, since all poses are considered in determining which atoms are sufficiently accessible to the reactive heme iron. Any atom within the cutoff distance of 5 Å from the heme iron is considered as a potential site of metabolism.

2.2 Running the Calculation

The calculation can be set up from the P450 Site of Metabolism - Perform Calculation panel, which you open by choosing Applications → Physics-Based ADME/Tox → P450 Site of Metabolism → Perform Calculation or Tasks → ADME/Tox → Structure-Based P450 Site of Metabolism → Perform Calculation.

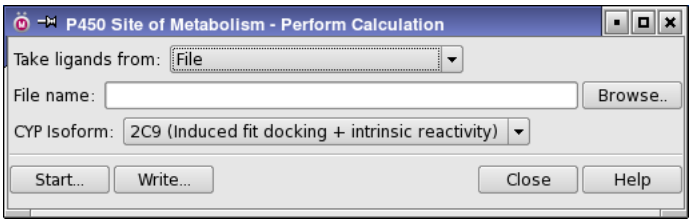

Figure 2.1. The P450 Site of Metabolism - Perform Calculation panel

The ligands can be taken from the Workspace (included entries), the selected entries in the Project Table, or from a file. You can make this selection from the Take ligands from option menu. If you choose File, click Browse to locate the file, which must be in Maestro format. The ligands must be properly prepared before you run the calculation: 3D structures with all hydrogens. If you have 2D structures, or SMILES strings for the structures, you can prepare them with LigPrep (Applications → LigPrep)—see the *LigPrep User Manual* for details.

Next, choose the isoform that you are interested in from the CYP Isoform option menu. Three isoforms are available: 2C9, 2D6, and 3A4. For 3A4, only the intrinsic reactivity is calculated. For the others, an induced-fit docking calculation is also performed.

When you have made your choices, click Start to start the calculation. The Start P450 Job dialog box opens, in which you can name the job, choose a host, and set the number of processors used for the Prime and the Glide stages of the induced-fit docking calculation. The induced-fit docking run can take some time, so you should consider running it on multiple processors. When you click Start in this dialog box, the job is started.

If you want to adjust the induced-fit protocol, you can click Write to write the input file for modification. The Write P450 Job dialog box opens. It is identical in function to the Start P450 Job dialog box, because all the job information is included in the input file. See Chapter 5 of the *Induced Fit Docking* manual for information on the input file.

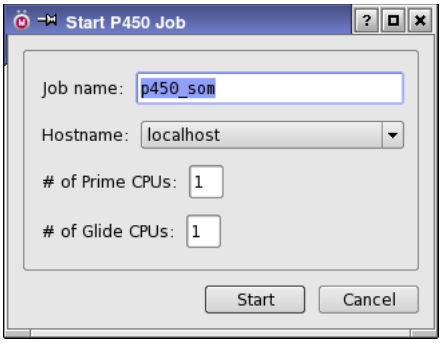

Figure 2.2. The Start P450 Job dialog box

When you have modified the input file, you can run the calculation with the command

`$SCHRODINGER/ifd` *jobname*`.inp`

2.3 Examining the Results

When the job finishes, you can examine the results in the P450 Site of Metabolism - Examine Results panel, which you open by choosing Workflows > P450 Site of Metabolism > Examine Results or Tasks > P450 Site of Metabolism > Examine Results.

First, the results must be imported. To do so, click Import Results, and navigate to the file *jobname*`-CYPligs-out.maegz`. When you import the file, the first ligand in the file is displayed in the display area as a 2D structure, annotated with reactivity information. The ligand name and the CYP isoform are shown above the display area.

The type of annotation can be set by choosing a Show reactivity option:

- Fe-accessibility from IFD—Label atoms with the accessibility of the atoms to the iron. This is defined as the natural logarithm of the number of poses for the atom in which the atom was within 5 Å of Fe. Larger values indicate greater accessibility.
- Intrinsic reactivity—Label atoms with the intrinsic reactivity for 3A4, calculated with Hammett and Taft methodology. Positive values are more reactive, negative values are less reactive.
- Overall SOM score—Linear combination of the accessibility and the intrinsic reactivity. The results are displayed as green circles, in which the radius is proportional to the score. Larger scores mean higher reactivity. When you display this score, you can click on one of the green circles to view a representative pose for that site in the Workspace.

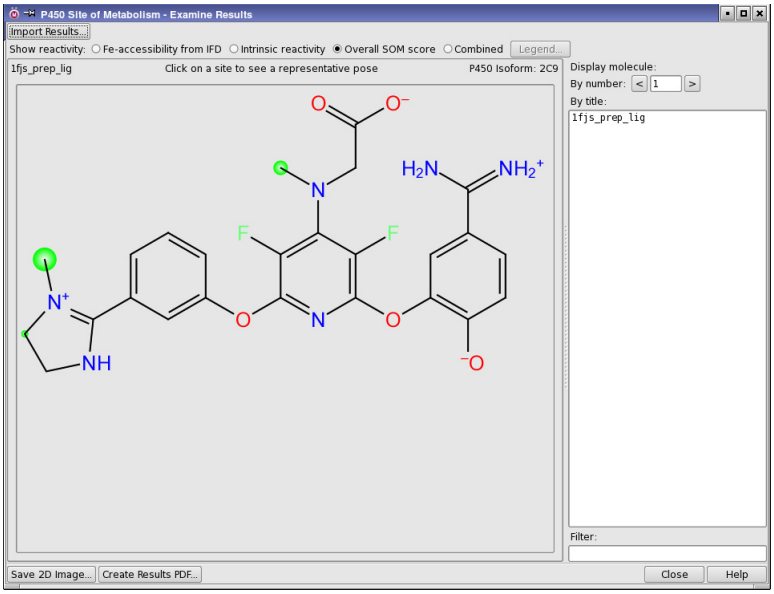

Figure 2.3. The Examine Results panel, showing the Overall SOM score.

- Combined—Show all three annotations at the same time, in graphical form. An explanation of the annotations is given in a panel when you click Legend. The description of the annotations is summarized below.

  The Fe-accessibility is indicated by a set of green rays drawn out from the atom to a given maximum length. Each full-length ray represents one unit of accessibility, so the number of full-length rays is the integer part of the score. The remaining partial ray represents the decimal part of the score.

  The circles represent the overall score and the intrinsic reactivity. The radius of the circle is proportional to this score. The intensity of the red color of the circle is proportional to the intrinsic reactivity. The blue perimeter indicates whether the atom passed the filtering stage, which has cutoffs for the intrinsic reactivity and the number of poses.

If you ran predictions on more than one molecule, you can step through the molecules with the controls to the left of the display area. Click the arrow buttons to display the next or previous molecule, enter the molecule number (index in the input file) in the text box, or select the molecule by its title in the By title list. You can filter the list by entering text in the Filter text box.

You can save a copy of the annotated 2D structure as an image, in TIFF, JPEG, or PNG format. Click Save 2D Image, navigate to the desired location, and name the file. The format is determined automatically by the file extension. The images are illustrated in Figure 2.4.

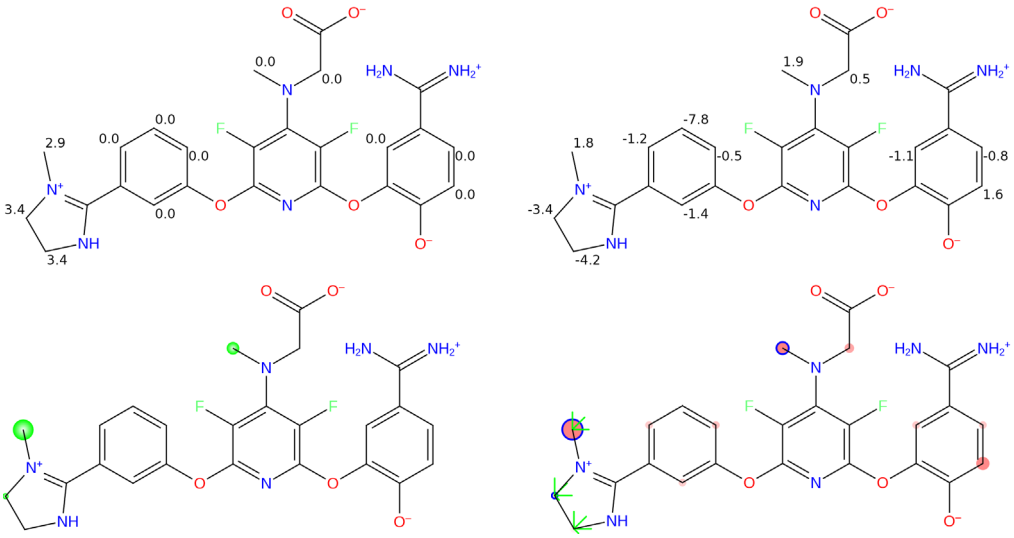

Figure 2.4. 2D images of scoring displays. Top to bottom, left to right: Fe-accessibility, Intrinsic reactivity, Overall SOM score, Combined.

You can also export the results for all molecules to a PDF file. The results are arranged in three columns, one for each property.

Membrane Permeability

The membrane permeability tool allows you to calculate the passive membrane permeability of a set of molecules. It is primarily intended for use on congeneric series of ligands to evaluate the relative permeability of similar ligands.

The calculations are based on a physical model with the assumptions that the permeability is dominated by the free energy of desolvation and change of state (neutralization and tautomerization) on passing into the membrane. The membrane is modeled as a low-dielectric continuum, and water as a high-dielectric continuum. A conformational search is performed in both the high-dielecric and low-dielectric continuum and the low-energy conformers from each are evaluated. Macrocycles are handled with a specialized sampling method. The highest value of the permeability found from this ensemble is used as the permeability for that molecule.

For a fuller description of the background and methodology, see Leung et al., *J. Chem. Inf. Model.* **2012**, *52*, 1621.

The calculations can take several minutes per molecule. The molecules should be all-atom 3D structures in a reasonable geometry. You can use LigPrep to convert 2D structures or SMILES strings to 3D structures—see the *LigPrep User Manual* for details.

You can set up and run calculations from the Membrane Permeability panel, which you can open with one of the following:

- Choose Applications → Physics-based ADME/Tox → Membrane Permeability.
- Choose Tasks → ADME/Tox → Physics-Based Membrane Permeability.

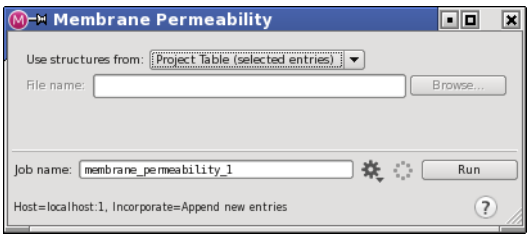

Figure 3.1. Membrane Permeability panel.

To set up a calculation:

1. Specify the source of the ligands, with the Use structures from option menu.

   The ligands can be in the Project Table or in a file.

2. Make job settings.

   If you want to use the default settings, which are to run the job locally as a serial job, and append the resulting structures to the Project Table, set the job name and click Run.

   If you want to distribute the job over multiple processors, click the Settings (gear) button, and choose the host, specify the number of processors and the number of subjobs, and set the job name, then click Run

The main results of the calculation are the structures of the ligands in the conformation that is predicted to be the most likely conformation inside the membrane, and four Maestro free energy properties, given in kcal/mol. The ligands are scored with a function that is optimized to predict RRCK permeability assay results. This score is also added as a property, which is the logarithm of the permeability in cm/s. The output properties are described in Table 3.1.

Table 3.1. Membrane permeability properties.

Property	Description
Membrane dG Insert	The total free energy penalty for the ligand to change state and enter the membrane. This is the sum of Membrane HDLD and Membrane State-Penalty, described below.
Membrane HDLD	The free energy penalty for the neutral form of the ligand in its conformation inside the membrane to enter the membrane (i.e., move from the high dielectric region to the low dielectric region, hence HDLD).
Membrane StatePenalty	The free energy penalty for neutralizing (or tautomerizing) the ligand.
Membrane HDLD alternate	The free energy penalty for the neutral form of the ligand to enter the membrane and change conformation between the most likely conformation in each phase. This is an alternative that allows for conformational change on entering the membrane.
Log Perm RRCK	Logarithm of the RRCK permeability in cm/s. This property is optimized to reproduce RRCK permeability assay results, with fitted energy and volume terms.

You can visualize the contributions to the Membrane HDLD property by atom in the Prime Energy Visualizer panel, which you can open with one of the following:

- Choose Applications → Prime → Energy Visualizer.
- Choose Tasks → Protein Analysis → Energy Visualization.

In the Visualize section of the panel, choose Membrane Permeability from the Family option menu. Only one property is shown, labeled Total Membrane Permeability.

To visualize this property on a ligand, include the ligand in the Workspace and click Update Workspace. The ligand is colored according to the contribution of each atom to the permeability. If you want to step through the ligands that you calculated the property for to visualize each in turn, select Automatically update Workspace. You can then use the left and right arrow keys to step through the ligands in the Project Table.

The visualization allows you to locate parts of the ligand that are most important for the membrane permeability. It could also help to identify parts of the ligand that you might want to modify to increase or decrease the permeability.

See Chapter 9 of the *Prime User Manual* for more information on the Prime Energy Visualizer panel.

If you want to run the calculation from the command line, you can use the following command:

`structurebased_adme permeability` *structure_file*

See Section 1.1 on page 1 for information on running jobs from the command line.

The membrane permeability facility has a special sampling method for macrocycles, which is used automatically.

Amphiphilic Moment

The structure-based adme tool allows you to calculate the amphipilic moment of one or more positively charged molecules. This property often correlates with certain ADME/Tox end points, such as phospholipidosis.

The algorithm involves calculation of ClogP contributions (octanol/water partition coefficient) for the atoms or groups in the structure and then produces a moment value by summing the product of the ClogP value for the atom and the vector from the positive center to the atom. A conformational search is performed on each structure, and the conformer with the highest amphiphilic moment is returned. If a structure has multiple positively-charged centers, the centroid of charges is used as the "positive center". If the structure is neutral, a zero moment is returned. See Fischer et al. *J. Med. Chem.* **2012**, *55*, 3227, for more information on the method.

The molecules should be positively charged, all-atom 3D structures in a reasonable geometry. You can use LigPrep to convert 2D structures or SMILES strings to 3D structures—see the *LigPrep User Manual* for details.

The calculations can be set up and run from the Amphiphilic Moment panel, which you can open with one of the following:

- Choose Applications → Physics-based ADME/Tox → Amphiphilic Moment.
- Choose Tasks → ADME/Tox → Amphiphilic Moment.

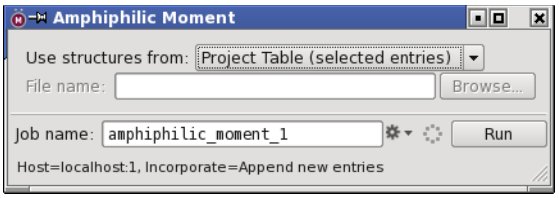

Figure 4.1. Amphiphilic Moment panel.

To set up a calculation:

1. Specify the source of the ligands, with the Use structures from option menu.

   The ligands can be in the Project Table or in a file.

2. Make job settings.

If you want to use the default settings, which are to run the job locally as a serial job, and append the resulting structures to the Project Table, set the job name and click Run.

If you want to distribute the job over multiple processors, click the Settings (gear) button, and choose the host, specify the number of processors and the number of subjobs, and set the job name, then click Run

The main results of the calculation are the structures of the ligands in the conformation that has the largest amphiphilic moment, and the moment property (`r_adme_amphiphilic_moment`).

You can visualize the contributions to the Amphiphilic moment property by atom in the Prime Energy Visualizer panel, which you can open with one of the following:

- Choose Applications → Prime → Energy Visualizer.
- Choose Tasks → Protein Analysis → Energy Visualization.

In the Visualize section of the panel, choose Amphiphilic Moment from the Family option menu. Only one property is shown, labeled Amphiphilic Moment.

To visualize this property on a ligand, include the ligand in the Workspace and click Update Workspace. The ligand is colored according to the contribution of each atom to the moment. If you want to step through the ligands that you calculated the property for to visualize each in turn, select Automatically update Workspace. You can then use the left and right arrow keys to step through the ligands in the Project Table.

The visualization allows you to locate parts of the ligand that are most important for the moment. It could also help to identify parts of the ligand that you might want to modify to increase or decrease the moment.

See Chapter 9 of the *Prime User Manual* for more information on the Prime Energy Visualizer panel.

If you want to run the calculation from the command line, you can use the following command:

`structurebased_adme amphiphilic` *structure_file*

See Section 1.1 on page 1 for information on running jobs from the command line.

Getting Help

Information about Schrödinger software is available in two main places:

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

Finding Information in Maestro

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

To get information:

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

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

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

  

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

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

For information on:

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

Contacting Technical Support

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

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

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

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

Gathering Information for Technical Support

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

For general enquiries or problems:

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

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

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

If your job failed:

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

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

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

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

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

If Maestro failed:

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

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

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

   The files should be in the following location:

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

If a Maestro panel failed to open:

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

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