R-Group Analysis

Schrödinger Software Release 2015-2

Schrödinger Press

May 2015

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].

R-Group Analysis

If you have a set of structures that are built on a common or similar scaffold, by attaching different groups at one or more points on the scaffold, you might want to see the properties of the structures as a function of the groups at the various attachment points. The R-Group Analysis facility provides tools for identifying the scaffolds, the attachment points, and the R groups at each point, and displaying the R groups and property information in various forms.

1 Analyzing a Set of Structures

The analysis and display of R groups is done in the R-Group Analysis panel. The panel is available from Maestro, from Canvas, and from the command line.

- To open the R-Group Analysis panel from Maestro, choose Tools → R-Group Analysis in the main window.
- To open the R-Group Analysis panel from Canvas, choose Applications → R-Group Analysis in the master view.
- To open the R-Group Analysis panel from the command line, type the following command in a terminal window:

  `$SCHRODINGER/run r_group_analysis.py [`*input-file*`]`

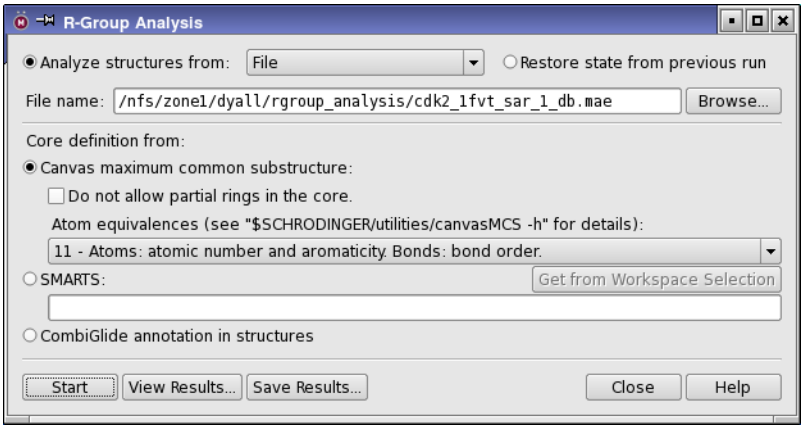

Figure 1. R-Group Analysis panel.

1.1 Specifying the Structures to Analyze

First, you must specify the source of the structures to analyze, which you can do by selecting Analyze structures from and choosing a source from the option menu. The sources are:

- Project Table (selected entries)—Use the structures that are selected in the Project Table. Only available from Maestro.
- All Rows—Use all rows in the spreadsheet. Only available from Canvas.
- Selected Rows—Use the rows that are selected in the spreadsheet. Only available from Canvas.
- File—Use the structures in a specified file. Enter the name of the structure file in the text box, or click Browse and navigate to the file in the file selector that opens. The file must be in Maestro or SD format, and can be compressed or uncompressed. The file name is displayed in the text box when you click Open.

1.2 Defining the Core

The second step in the analysis is to choose a method for the definition of the core of the structures. The analysis determines the R groups that are attached to this core. The core can be taken from CombiGlide attachment-bond labeling, specified by a SMARTS pattern, or determined by the maximum common substructure obtained from a Canvas MCS run. The options available under Core definition from are:

- Canvas maximum common substructure—Use the maximum common substructure as determined from a Canvas MCS calculation. When you choose this option, you must also choose a definition of equivalent atoms from the Atom equivalences option menu. The options are described in Table 5.2 of the *Canvas User Manual* and also in the help message for `canvasMCS`, which you can view with the following command:

  ```
  $SCHRODINGER/utilities/canvasMCS -h
  ```

  You can also select Do not allow partial rings in the core to ensure that the rings in the core are always complete, and are not broken when finding the substructure for the core.
- SMARTS—Specify a SMARTS pattern for the core in the text box. From Maestro, you can also select atoms in the Workspace and click Get from Workspace Selection to load a SMARTS pattern into the text box. You can edit the SMARTS pattern in the text box.
- CombiGlide annotation in structures—Use the core definition that has been added by CombiGlide. You should use this option only if you are using structures that were generated by CombiGlide.

The CombiGlide annotation for determining the core provides a unique definition, and one that is restricted to singly bonded terminal attachments. The use of SMILES or Canvas MCS to determine the core can result in cores with different atomic composition, multiply bonded R groups, R groups that are attached to the core in more than one location, and multiple core structures.

When Canvas MCS methods that allow different atom or bond types to be treated as equivalent are used, some cores may have attachment points to which no R group is attached. For example, the core might contain a pyridine ring in one structure, but a benzene ring in another. An attachment point in the benzene ring might be at the carbon atom corresponding to the nitrogen in the pyridine. In this case, the attachment at the nitrogen is considered a “null” attachment, and a dummy atom is used with the label “Null”.

R groups that are attached with multiple bonds are treated as any other group. You might, for example have a carbonyl group (XC=OX') in one structure where there is a substituted methylene group (e.g. $XCHCH_3X'$) in another. In the first structure the R group is =O, in the second it is $–CH_3$. The core in both structures involves the X-C-X' framework.

R groups that are attached at multiple attachment points (thus forming rings) are listed as groups for each attachment point.

When using these two methods, the program must decide which mapping to use for each input structure if the core substructure maps to some input structures in several ways. The program picks the best set of mappings chiefly by optimizing the fingerprint similarity of the side chains for pairwise alignments of the input structures. This choice usually also minimizes the number of R-group positions defined on the core.

1.3 Running the Analysis

When you have selected the input structures and chosen a method for defining the core, click Start to run the analysis. Once the analysis finishes, the R-Group Viewer panel opens. In this panel you can view the groups, export them, and open other panels that display various analyses of the properties. These panels are described in the following sections.

1.4 Saving and Loading Results of an Analysis

If you want to save the results of the analysis, click Save Results, and navigate to a location and save the results (as a zip file) in the file selector that opens. You can then read the results of this analysis back in at a later time, by selecting Read results from previous run, then clicking Browse and browsing to the zip file. When the results are read, you can click View Results to view the results of the analysis, as explained below. The analysis controls are dimmed when you select Read results from previous run.

2 Viewing and Exporting R-Groups

If you want to view the results of the analysis by displaying the structures with the R groups marked, you can do so in the R-Group Viewer panel. This panel displays the structures and the R groups for each structure. It also allows you to choose R groups at each position and display only the input structures containing them, and then export the restricted list of input structures. You can also export the R groups as individual molecules, capped with methyl groups.

To open the R-Group Viewer panel, click View Results in the R-Group Analysis panel. This panel opens automatically when the analysis of the structures in the R-Group Analysis panel finishes.

In the Input Structures section, you can view the individual input structures, annotated to display the attachments to the core. To step through the structures, click the arrow buttons. To display a particular structure, enter the structure index in the text box.

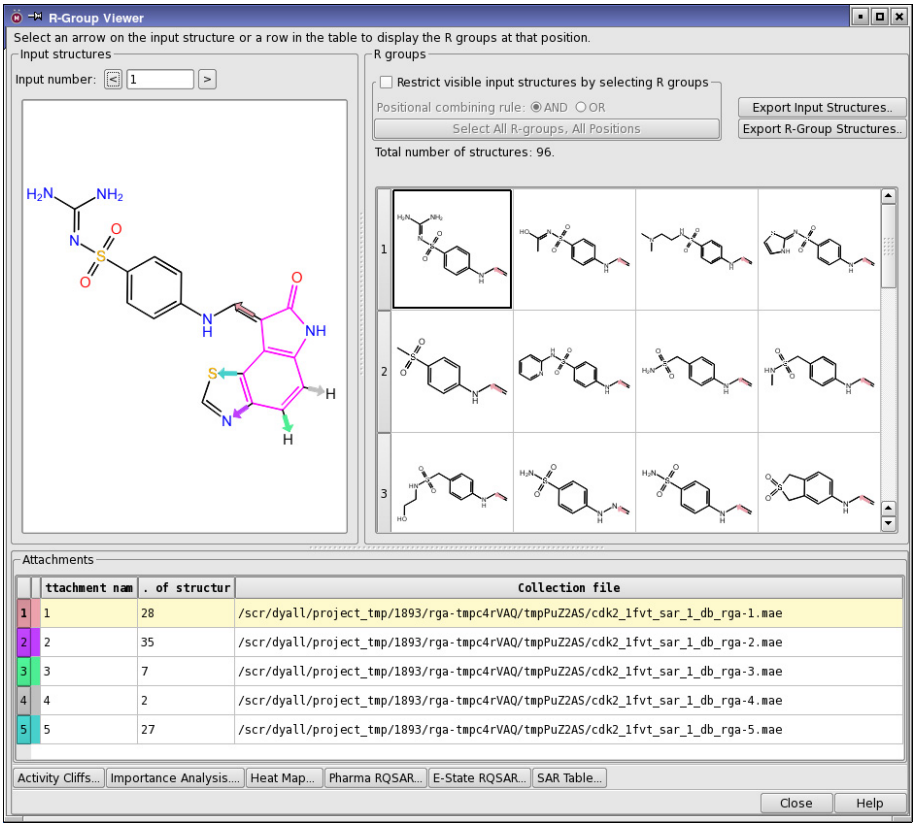

Figure 2. R-Group Viewer panel.

The structures are displayed as 2D images. The attachment points are marked with arrows pointing toward the R groups. The arrows are color-coded to match the rows in the Attachments table. The arrow is outlined for the current attachment, which is the attachment that is selected in the Attachments table, and whose R groups are displayed in the R Groups section.

In the R Groups section, you can view the R groups for a given attachment position, and restrict the structures that are shown by selecting R groups. The bond that connects an R group to the core is colored the same way and oriented in the same direction as the attachment bond in the input structure. You can export the structures or the R groups. The table in this section displays the 2D structures of the R groups at the current attachment position. The table cell for the R group that is displayed in the Input Structures section is outlined in black. When you pause the pointer over the table cell, an enlarged image of the R group is displayed. You can select cells in the table when restricting the visible input structures.

The Attachments table lists the attachment positions that were located in the analysis. The first column is an index and is color-coded to match the positions marked in the Input Structures display area. The remaining columns show the name given to the attachment, the number of R groups selected at the attachment position, and the name of the temporary file that stores the R groups. Selecting a table row populates the table in the R Groups section with the R groups found at that attachment position. The table is noneditable.

2.1 Restricting the Structures Displayed

To restrict the structures that are shown in the Input Structures section, select Restrict visible input structures by selecting R-groups. By default, all R groups are selected for display at each position. For each position you can choose the R groups that you want to display by selecting them in the table. To change the position whose R groups are shown in the table, select the position in the Attachments table.

There are two ways of combining the restrictions at each position, determined by the option chosen for the Positional combining rule:

- AND—Display only those structures that have a selected R group (fragment) at all attachment positions.
- OR—Display only those structures that have a selected R group (fragment) at one or more of the attachment positions.

To return to the default selection, click Select All R-Groups, All Positions. To remove the restrictions, deselect Restrict visible input structures by selecting R-groups.

2.2 Exporting Structures

If you want to export the input structures, click Export Input Structures. A dialog box opens, in which you can make the following choices:

- Export the structures to a file or to the Project Table (only available from Maestro).
- Export all structures or only the visible structures.
- Superimpose the structures by aligning the cores to that of the first input structure.

If the structures are exported to a Maestro file or to the Project Table, the annotations that identify the attachment points are kept; for file types other than Maestro, they are discarded. The allowed file types are Maestro (`.mae`, `.maegz`), SD (`.sdf`), and SMILES (`.smi`); the file type written is determined by the extension that you provide for the file name.

2.3 Exporting R-Groups

To export the R groups as separate molecules, capped with methyl groups, to a set of Maestro files or to the Project Table, click Export R-Group Structures. The set of R groups at each position is exported to a separate file or entry group. The base name of the file or the entry group is given in the Filename text box. To this name is added the suffix `_rga-`*N*, where *N* is the position number. This name is used for the entry group name, and the `.mae` extension is added to it for the file name. The titles of the structures are set to R-group *M*, where *M* is the index of the R group in the list for the given attachment.

There are two options that you can select:

- Save MCS .csv output—export the CSV output file produced by `canvasMCS`, if you ran a Canvas MCS calculation to define the core.
- Export for use in CombiGlide—Create the necessary extra files so that the R groups can be used in CombiGlide as reagents.

3 Analyzing Molecular Properties

The R-group analysis facility offers several ways of displaying information on molecular properties and their relationship to the R-groups and the cores: an activity cliff plot, importance analysis, a heat map, R-group QSAR based on either pharmacophore features or electrotopological states (Estates), and an SAR table, in separate panels. These features are described in the following subsections.

3.1 Activity Cliffs

When examining structure-activity relations, you may want to identify “activity cliffs”, where a small change in structure produces a large change in a property. This can be done in the Activity Cliffs panel, which you open by clicking Activity Cliffs in the R-Group Viewer panel.

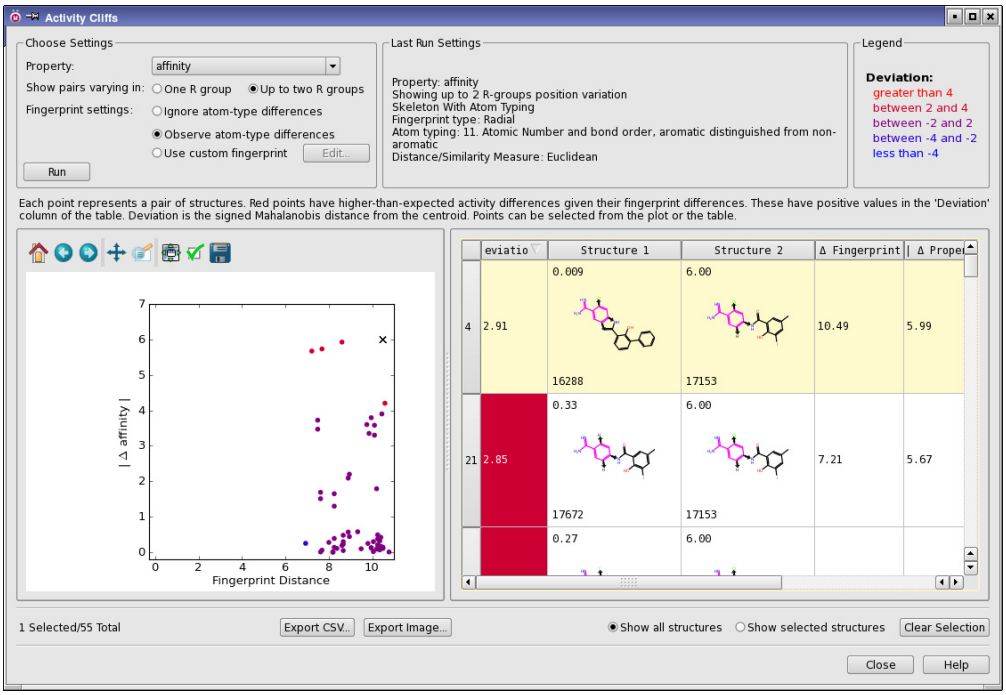

Figure 3. Activity Cliffs panel.

The first task is to select the property, which you can do from the Property option menu. Next, choose whether to examine property variations at a single attachment point (One R-group), or at up to two attachment points (Up to two R-groups). The latter is useful for analyzing the activity variation with structure when groups are exchanged between two sites, possibly resulting in different binding modes.

The structural differences are calculated using fingerprints, with a given similarity metric. There are three choices for the fingerprint settings:

- Ignore atom-type differences—Evaluate the fingerprint differences using radial fingerprints with no atom or bond type information, and exclude hydrogens. This choice means that the variations in structure that are considered are purely in the connectivity.
- Observe atom type differences—Evaluate the fingerprint differences using radial fingerprints, with atoms distinguished by element, and bonds distinguished by bond order and aromaticity. This choice produces larger variations in fingerprint differences, and distinguishes between similar structures that might differ only in the atom type, e.g. substitution of Cl for F, or NH_2 for OH.
- Use custom fingerprints—Choose the fingerprint type and precision, the atom typing scheme, and the similarity metric to use, from those available in Canvas. This choice allows the greatest flexibility in setting up the analysis. This button opens the Activity Cliffs Options dialog box, in which you can make the choices described.

After making settings, click Run to run the analysis. The settings you used are listed in the Last run settings section at the top of the panel.

As the calculation runs, a progress bar is displayed at the bottom of the panel. The calculation time varies quadratically with the number of structures. When the job finishes, the plot of change in property against fingerprint difference is displayed, and the table of structures and values is populated.

The plot displays the difference in property for pairs of structures as a function of the fingerprint difference. The points in the plot are colored by the Mahalanobis distance of the points from the centroid of all the points. Points within two standard deviations of the centroid are colored purple. Points outside this range with a larger property difference than average are colored red-purple if they lie within 4 standard deviations of the centroid, and red if they are outside 4 standard deviations. Likewise, points outside this range with a smaller property difference than the average are colored blue-purple if they lie within 4 standard deviations of the centroid, and blue if they are outside 4 standard deviations. The legend for the color scheme in the plot is displayed in the Legend section.

You can select points in the plot by clicking on them. The points are marked with an X, and the corresponding rows are selected in the table. To add points to the selection, use shift-click; to change the selection of one point without affecting the others, use control-click.

The plot toolbar contains a standard set of tools for adjusting the view of the plot, stepping through different views, and saving a plot image. The panel has a toolbar that you can use to

configure the plot or to save an image of the plot. The toolbar buttons are described below.

Reset
Reset the plot to the original pan and zoom settings.

Back
Display the previous view of the plot in the view history

Next
Display the next view of the plot in the view history

Pan/zoom
Pan the plot by dragging with the left mouse button, zoom by dragging with the right mouse button.

Zoom to rectangle
Drag out a rectangle on the plot to zoom in to that rectangle.

Configure subplots
Configure the margins and spacing of each plot in the panel.

Edit axis and curve parameters
Make settings for the title, range, labeling, and scale of the axes; the color, style, and width of lines; and the color, style, and size of markers.

Save image
Save an image of the plot to file. Opens a file selector in which you can browse to a location, select the image format, and name the image.

Copy to clipboard
Copy an image of the plot to the clipboard. You can then paste it into another application. This button is only available in some panels.

The structure and property table shows the pairs of structures represented in the plot and the relevant properties for each of the structures. You can select rows in the table, and the corresponding points are marked in the plot. You can show only the table rows that are selected, and hide the unselected rows. You can sort the rows by clicking in any of the column headings. The columns are described in Table 1.

You can export the contents of the table either as a CSV file, by clicking Export CSV, or as an image, by clicking Export Image. The structures in the CSV file are represented by the SMILES string for the structure. The SMILES string includes stereochemistry, and marks the attachment points with [Xe] and [Kr]. The image format can be one of PNG, TIFF, or JPEG.

Table 1. Columns in the structure and property table of the Activity Cliffs panel.

Column	Description
Deviation	Signed Mahalanobis distance from the centroid of the points in the plot. The sign indicates the relation of the activity difference to the activity difference of the centroid. The table cells are colored with the same scheme as the points in the plot.
Structure 1 Structure 2	2D structures. Pausing the pointer over the cell displays an enlarged image of the structure in a tool tip. The property value for the structure is shown at the top left.
Δ Fingerprint	Fingerprint distance between the two structures.
|Δ Property|	Absolute value of the difference in properties.
Substitutions	Number of positions at which the two structures differ. The range of values depends on the choice made for showing the position variation.

3.2 Importance Analysis

Importance analysis addresses the question of how sensitive the property of interest is to R-group variation at that position. A position is more important than another if varying the R group at that position leads to greater property differences than are observed when the R group at the other position is varied. The importance value of a position is the range of the property over the R groups at that position, averaged over all structures containing a given R group at that position. As an example of its use, a position in which the range of the property does not vary much as the R group is changed may not be very important for improving the potency of a lead compound, whereas a position in which the property varies a great deal may be considered much more important.

The Importance Analysis panel presents the results of importance analysis and also displays the average of the property for each R group. You can open the Importance Analysis panel by clicking Importance Analysis in the R-Group Viewer panel, or by choosing Show R Groups from the shortcut menu in the histogram display of the Heat Map panel.

The panel shows a histogram of the importance value of a chosen property for each position, normalized to one for the most important position. It also contains a table showing the values of a selected function of that property for each R group at a selected position. You can choose the property and the function in the Displayed property section. To select the position, click the position in the histogram. The current position is marked in the histogram with an asterisk. When you select a property, the current position is set to the most important position.

The properties for each R group are displayed as a heat map, colored by value. You can choose how the values in the cells is displayed from the Cell Display option menu. The choices are the same as in the Heat Map panel (see below). Likewise, you can set the color range and the numerical display by clicking Legend and Settings, and you can set the cell size. You can sort the property values in ascending or descending order, by clicking on the column heading.

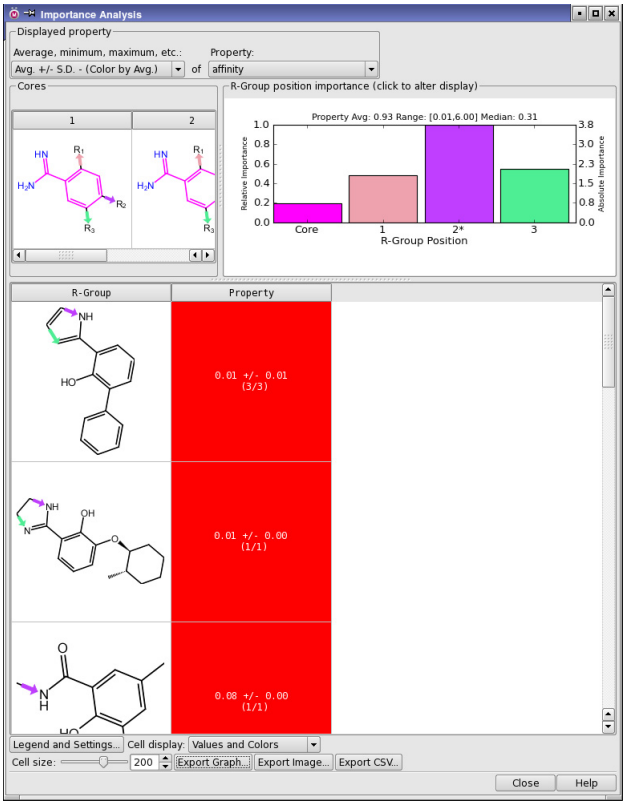

Figure 4. The Importance Analysis panel.

If you want to make a copy of the results, you can export them. Clicking Export Graph exports an image of the histogram in PNG, TIFF, or JPEG format; likewise clicking Export Image exports an image of the table, with the same choice of formats. Clicking Export CSV exports the table data to a CSV file, with a SMILES string for the structure. The SMILES string includes stereochemistry, and marks the attachment points with [Xe] and [Kr] (as the nominal capping group).

Ideally, we would like to interpret the importance measure as characteristic of a position. For example, positions that make intimate contact with a receptor might be expected to exhibit greater variation of a binding property when its R groups are altered than one which protrudes into the solvent. However, there are several caveats to this interpretation. Most SAR data sets have very different numbers of structures at the various positions. Even if all else were equal, we would expect positions with more R groups to exhibit greater property variation and therefore to appear more important. Even if all positions had the same number of R groups, we would expect positions whose R groups exhibit greater chemical variability to exhibit a greater

range of property values upon variation and hence a greater importance. For example, the chemists designing the SAR study might have had reason to believe that it is important to place hydrogen-bond donors at a given position. They might then sample only such R groups there, and this could in some cases lead to minimal property variation and low importance. These possibilities should be kept in mind when interpreting the importance measure.

3.3 Heat Maps

You can display a heat map of a selected property for R groups at two positions, as a function of the values at all other positions, in the Heat Map panel. To open the Heat Map panel, click Heat Map in the R-Group Viewer panel.

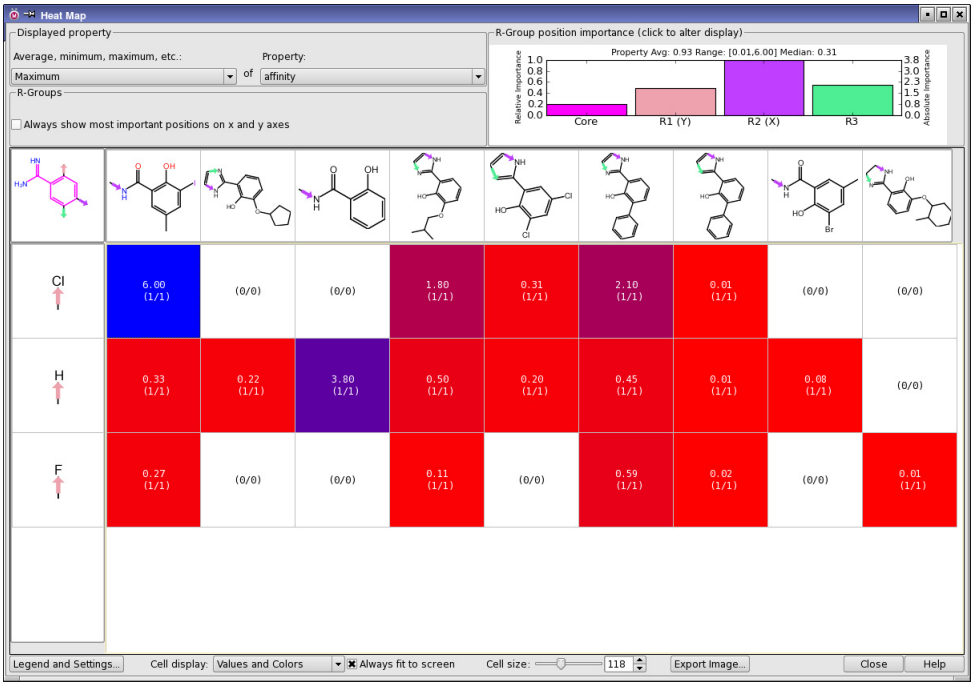

Figure 5. The Heat Map panel.

You can choose the property used in the heat map in the Displayed property section. Choose the property from the Property option menu. This option menu lists the properties that are available for the input structures. The way in which these properties are combined and displayed (the "function") is chosen from the Average, minimum, maximum option menu. You can display the average, the maximum, the minimum, or the median. You can also display the average and standard deviation, and color cells by either the average or the standard deviation.

Both values are displayed in each cell when you choose to display values. The heat map is updated when you choose a property or a function.

A histogram displaying the importance value of each position is displayed at the top right of the panel. The importance value of a position is the range of the property over the R groups at that position, averaged over all other positions. For more detail on the property values for each R group at that position, click on the position and choose Show R Groups from the shortcut menu, to open the Importance Analysis panel (see Section 3.2 on page 14).

By default, the positions that are selected for the axes are those that have the greatest importance value. If you deselect Always show most important positions on x and y axes, the selection of positions for the axes does not change when you change the property or function.

This histogram can be used for selecting positions, by clicking on a position and choosing Set as X Axis or Set as Y Axis from the shortcut menu. (It does not matter where you click on the plot: in the bar, above the bar, or on the label.) When you choose a new position, the R groups on the chosen axis are replaced with those for the new position, and the heat map is updated.

In the heat map, the top left cell of the table displays the core. Pausing the pointer above the core displays an enlarged image of the core in a tool tip. The rest of the first row displays the R groups at the position chosen for the *x* axis, and the rest of the first column displays the R groups at the position chosen for the *y* axis. You can adjust the size of the cells with the Cell size slider and text box, or you can ensure that the entire heat map is always visible by selecting Always fit to screen. To export an image of the heat map, click Export Image, and select the image format and name the file in the file selector that opens.

The remainder of the table displays the value of the selected property, evaluated over all R groups at the positions that are not selected for the two axes. If you click in a cell, the Structure panel opens, and allows you to display each of the structures represented in that cell, with the value of the property that is chosen for display in the heat map. Cells that do not have any structures are not colored, except when the number of structures is the property displayed.

The way in which the property value is displayed in the cells can be chosen from a range of possibilities, on the Cell display option menu:

- Values and colors—show the property value and the color.
- Cartwheels and colors—show a cartwheel colored by unique property values (see below), with the cell background colored by the average property value.
- Cartwheels only—show a “cartwheel” in which the sectors of the circle represent unique values of the property and are colored according to the property value.
- Values only—show the property value only.
- Colors only—show only the color corresponding to the property value.

When values are displayed, the number of structures for which the property is evaluated and the total number of structures for that cell are displayed in parentheses below the value.

You can configure the cell display by clicking Legend and Settings. In the Display Settings dialog box, you can set the number of decimals for the value and choose between floating point and scientific notation; you can adjust the range of values represented by the color ramp; and you can invert the ramp.

If you want to restrict the R groups that are included in the averaging of the property, or displayed on the axes, click in the histogram and choose Restrict structures. The Select R Groups panel opens, in which you can choose the position and select the R groups shown at that position, or to select all R groups at all positions. The heat map is updated when you make selections: for the displayed positions, rows or columns are removed from the table; for the undisplayed positions, the values of the properties are recomputed to reflect the selection.

3.4 R-Group QSAR Models

If you want some idea of what kinds of groups are most important for the properties of your compounds at each attachment position, you can generate a QSAR model, based either on pharmacophore features or E-state (electrotopological state) atom types. These two model types are supported in panels that you open by clicking the Pharma RQSAR button or the E-State RQSAR button. The panels are identical in their operation and only differ in the details of the model.

If you choose a model based on pharmacophore features, the model is built using counts of pharmacophore features present in the R groups at each position as the independent variables. The pharmacophore features are the standard features used in Phase QSAR models: hydrogen-bond acceptor (A), hydrogen-bond donor (D), hydrophobic (H), negatively-charged (N), positively-charged (P), and aromatic (R). When the calculation finishes, the attachment positions are labeled with a list of the six pharmacophore features, colored by significance: red for significant positive contributions, blue for significant negative contributions, and gray for insignificant contributions. If a pharmacophore feature is absent from an attachment position, a lower-case letter is used for the pharmacophore feature type.

If you choose a model based on E-state atom types, the model is built using counts of E-state atom types present in the R groups at each position as the independent variables. As the effect of hydrogen is absorbed into the attached E-state atom type, the R group includes the attached core atom so that an R group consisting of only a hydrogen can be treated. When the calculation finishes, the attachment positions are labeled with a list of letters representing the E-state atom types, colored by significance: red for significant positive contributions, blue for significant negative contributions, and gray for insignificant contributions. If an E-state atom type is absent from an attachment position, it is not included in the annotation for that position.

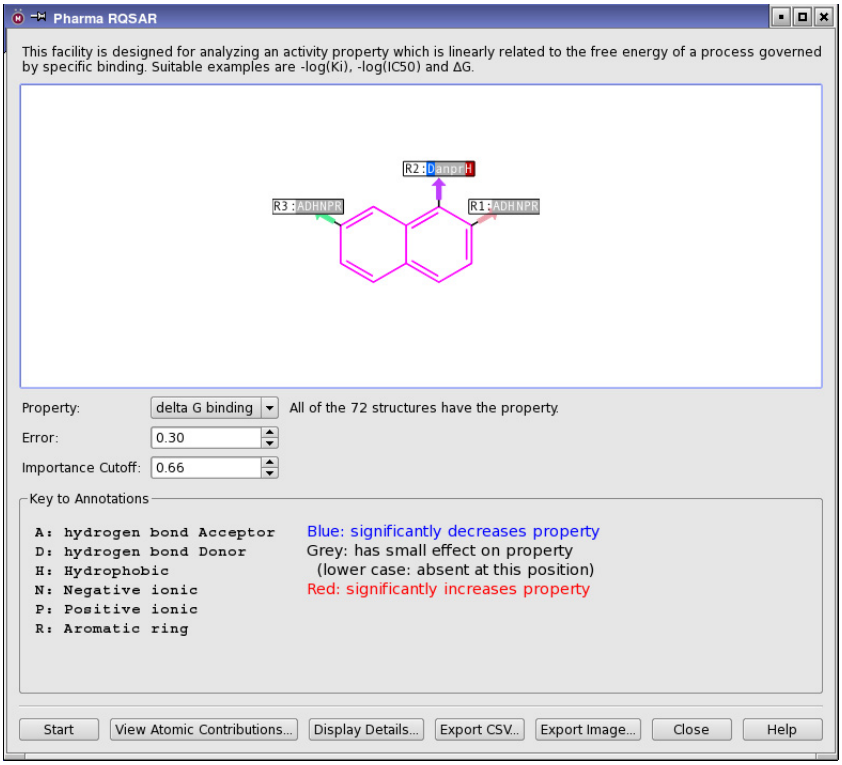

Figure 6. The Pharma RQSAR panel.

The letters used to represent the atom types are listed with the names of the atom types and the intrinsic E-state value (which increases with increasing effective electronegativity). The atom type names are represented by a string of bond types (s=single, d=double, t=triple, a=aromatic), followed by an element symbol, then a hydrogen count, then a letter that indicates the charge on the atom (p=plus, m=minus). For example, aasC represents a carbon connected to other atoms by two aromatic and one single bond, such as in biphenyl.

For both types of QSAR model, a partial-least-squares (PLS) procedure is used to fit the data, assigning 75% of the data to the training set and 25% to the test set at random. The fitting is repeated many times, each time picking the best model that does not overfit the data (which occurs when the standard deviation of the fit is smaller than the error in the property being fit). The mean of the coefficients from all of these trials is used to determine whether a feature at a given position contributes significantly to the property, either positively or negatively: if the absolute value of the mean is greater than the cutoff, the contribution is considered significant.

To generate a QSAR model:

1. Choose a property from the Property option menu.

   The number of structures that have this property is reported to the right.

2. Specify the estimated error in the property in the Error box.
3. Specify the cutoff for significant contributions in the Importance cutoff box.
4. Click Start.

When the model has been generated, the display area shows the 2D structure of the core, with the attachment points, and annotation at each attachment point.

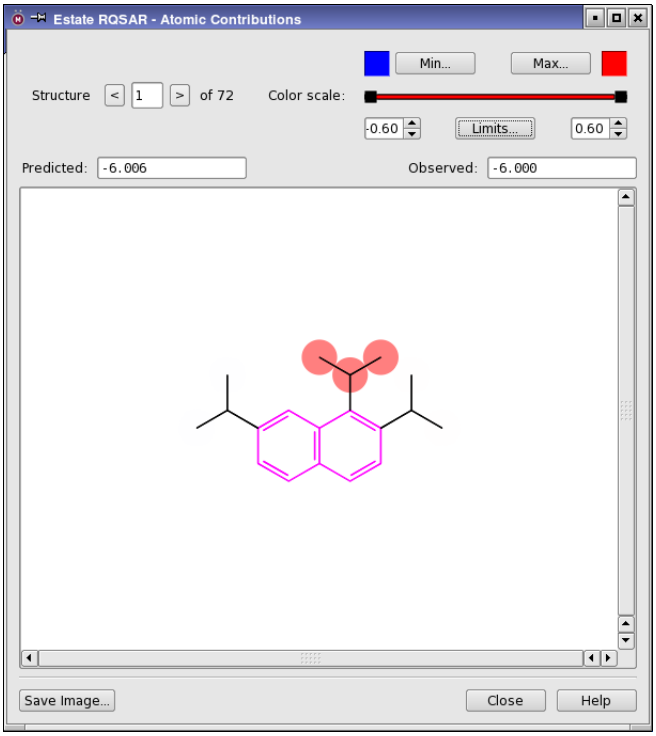

Figure 7. Estate RQSAR - Atomic Contributions panel.

You can view a breakdown of the contributions to the QSAR model at the atomic level, by clicking View Atomic Contributions. In the Atomic Contributions panel, the first of the structures is displayed in 2D in the viewing area, marked with circles on the atoms of the chosen R group. The circles are colored according to the sign and magnitude of the atomic contributions. The magnitude is represented by the color intensity, the sign by the color. Pausing the pointer over

an atom displays the pharmacophore type or the E-state atom type name (depending on the model) and the contribution to the property due to that atom. The predicted and observed values of the property for the molecule are displayed in text boxes. If you want to view the breakdown for other molecules in your set, use the Structure arrow buttons or text box to select the molecule. To save an image of the annotated structure in PNG, TIFF, or JPEG format, click Save Image, and choose the image format and the file name in the file selector that opens.

You can change the colors using the Min and Max buttons. You can also change the property value at which the circles have the maximum color intensity, in two ways. First, you can set the maximum and minimum property values that are represented, by clicking Limit and setting the value in the dialog box that opens. The color intensity for any value outside the range is set to the value for the limit. Second, you can use the Color scale slider to adjust the cutoff within these limits.

You can examine the data produced by the QSAR model by clicking Display Details. In the panel that opens, for each pharmacophore type or E-state atom type at each position, the minimum, maximum, mean, and standard deviation for the PLS coefficient is given, and the assessed effect on the activity is listed, as weak, positive, or negative. If you want a copy of this summary, click Export CSV in the parent RQSAR panel, and name the file in the file selector that opens.

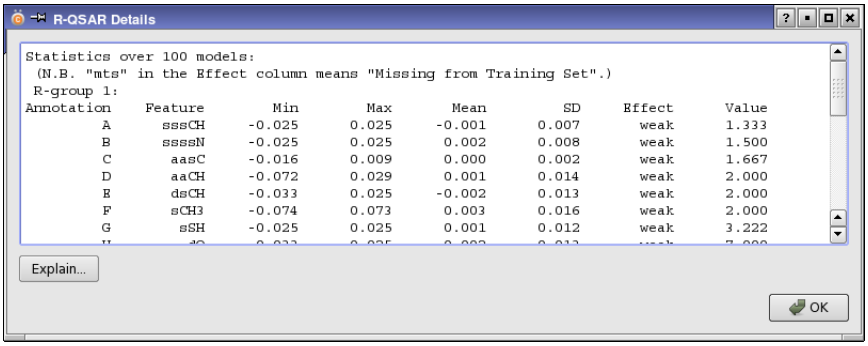

Figure 8. R-QSAR Details dialog box for an E-State RQSAR model.

To save an image of the annotated core structure in PNG, TIFF, or JPEG format, click Export Image, and choose the image format and the file name in the file selector that opens.

3.5 SAR Table

If you want to view the property values in tabular form along with the R groups, click SAR Table in the R-Group Viewer panel. The SAR Table panel shows the 2D structures of the cores, at the top, with the R groups and properties below. The attachment positions on the core structures have labels R_n, where n is the position index.

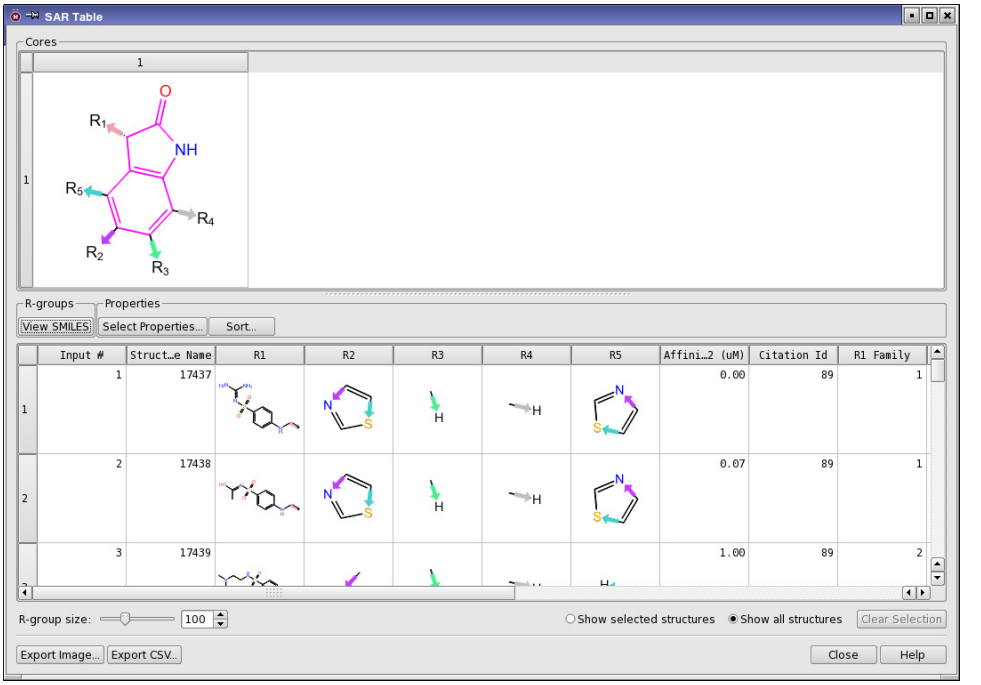

Figure 9. The SAR Table panel.

The first column in the table is a structure index, and the second contains the name of the input structure. Next come the R groups for each position, labeled R*n*, followed by the index of the core for each structure. Multiple cores can arise from the use of Canvas MCS methods that allow different atom or bond types to be treated as equivalent. The R groups can be viewed either as SMILES strings or as 2D structures. To change the representation, click View SMILES or View 2D Images. When you pause the pointer over a table cell, an enlarged image of the R group is displayed. To change the size of the R-group image in the table, use the R-group size slider and box.

Following the R groups and the core index are columns containing the index of the R-group families for each attachment position. An R-group family is a set of structures for which the R group varies at only one position. Each compound therefore only belongs to one such family at

each position. The families are numbered in decreasing order of size. Sorting on one of these columns arranges the structures by family.

The remaining columns of the table list the property values for each structure. You can select the properties that are shown by clicking Select Properties, and choosing which properties to display in the dialog box that opens. You can click the column heading to sort the rows by a single property. If you want to sort by multiple properties, click Sort, and choose the properties and the order in which they are used in the Sort Multiple Columns dialog box.

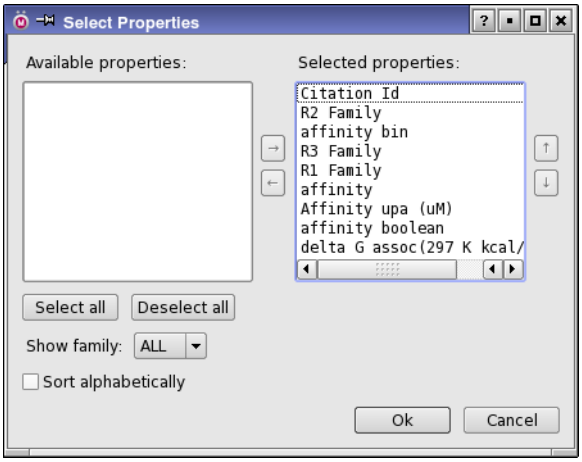

Figure 10. Select Properties dialog box.

You can limit the display to show only the selected structures, by making a selection and selecting Show selected structures. Rows can be selected with the usual shift-click and control-click for multiple row selection. To display all structures again, select Show all structures. To clear the row selection, click Clear Selection.

If you want to make a copy of the results, you can do so either in a CSV file or as an image. To export a CSV file, in which the input structures and the R groups are included as SMILES strings, click Export CSV. The SMILES string includes stereochemistry, and marks the attachment points with [Xe] and [Kr] (as the nominal capping group). The properties are exported for only the visible rows. To export an image, that contains the cores table and the main table (but not the controls), click Export Image. Both of these buttons open a file selector, in which you can navigate to a location and name the file. For images, the format is determined by the file extension.

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
- R-Group Analysis purchaser (company, research institution, or individual)
- Primary R-Group Analysis 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.

120 West 45th Street
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

8F Pacific Century Place
1-11-1 Marunouchi
Chiyoda-ku, Tokyo 100-6208
Japan

No. 102, 4th Block
3rd Main Road, 3rd Stage
Sharada Colony
Basaveshwaranagar
Bangalore 560079, India

SCHRÖDINGER®