Strike 3.0

User Manual

Schrödinger Press

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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 to Strike

1.1 Strike Overview

Strike is a chemically-aware statistical package which is integrated with Maestro to provide a flexible and intuitive interface. Employing molecular data generated by Schrödinger software such as QikProp, Glide, Liaison, or MacroModel, or from other sources such as experimental data or third-party software, Strike can be used to do the following:

- Generate basic univariate and bivariate statistics such as mean, median, mode, covariance, and correlations
- Generate structure-activity relationship hypotheses using rigorous statistical methods
- Run validation tools to assess the validity and predictive power of generated QSAR/ QSPR models
- Employ such models as filters and predictive tools
- Perform similarity analysis in molecular property or 2-dimensional structural space.

This document provides a set of tutorial exercises using the capabilities of Strike, a description of the Strike GUI in Maestro, a command line reference chapter, and definitions of some statistics terms and methods.

1.2 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

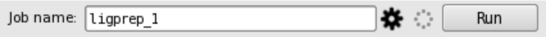
```
defaults write ~/.MacOSX/environment variable "value"
```

and on OS X 10.8, 10.9, and 10.10 use the command

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

1.3 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.



Job name: ligprep_1

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.

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.

Jobs are run under the Job Control facility, which manages the details of starting the job, transferring files, checking on status, and so on. For more information about this facility and how it operates, as well as details of the Job Settings dialog box, see the *Job Control Guide*.

1.4 Citing Strike in Publications

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

Strike, version 3.0, Schrödinger, LLC, New York, NY, 2015.

Strike Tutorial

This chapter is designed to help you become familiar with the functionality of Strike 3.0. Once you have worked through these exercises, you will have an understanding of the basic Strike features.

The Strike workflow for QSAR model generation/validation generally consists of three steps: data preparation, model generation and validation, and model application. The Strike workflow for similarity analysis using molecular properties also consists of three steps: data preparation, similarity calculation, and application of calculated similarities. For similarity analysis using two-dimensional structures (atom-pair similarity), two steps are required: the similarity calculation and application of calculated similarities. These steps will be illustrated in the tutorial exercises, which demonstrate how to do the following:

- Generate or import molecular data into Maestro for use by Strike
- Generate, validate, and apply QSAR/QSPR models
- Perform similarity analysis

Three tutorial examples are provided to demonstrate Strike workflows:

- Generating and testing a QSPR model for estimating aqueous solubility using a small number of molecular properties
- Developing a QSAR model for predicting activities of folate-based thymidylate synthase ligands
- Calculating similarities using 2-dimensional structures and molecular properties, and with these similarities extracting known actives for thermolysin from a ligand dataset.

To perform these exercises, you must have access to an installed version of Maestro. For installation instructions, see the *Installation Guide*.

2.1 Preparing for the Exercises

To run the exercises, you need a working directory in which to store the input and output, and you need to copy the input files from the installation into your working directory. This is done automatically in the Tutorials panel, as described below. To copy the input files manually, just unzip the `strike` zip file from the `tutorials` directory of your installation into your working directory.

On Linux, you should first set the SCHRODINGER environment variable to the Schrödinger software installation directory, if it is not already set:

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

sh/bash/ksh: `export SCHRODINGER=`*installation-path*

If Maestro is not running, start it as follows:

- **Linux:** Enter the following command:

  ```
  $SCHRODINGER/maestro -profile Maestro &
  ```

- **Windows:** Double-click the Maestro icon on the desktop.

  You can also use Start → All Programs → Schrodinger-2015-2 → Maestro.

- **Mac:** Click the Maestro icon on the dock.

  If it is not on the dock, drag it there from the SchrodingerSuites2015-2 folder in your Applications folder, or start Maestro from that folder.

Now that Maestro is running, you can start the setup.

1. Choose Help → Tutorials.

   The Tutorials panel opens.

2. Ensure that the Show tutorials by option menu is set to Product, and the option menu below is labeled Product and set to All.

3. Select Strike Tutorial in the table.

4. Enter the directory that you want to use for the tutorial in the Copy to text box, or click Browse and navigate to the directory.

   If the directory does not exist, it will be created for you, on confirmation. The default is your current working directory.

5. Click Copy.

   The tutorial files are copied to the specified directory, and a progress dialog box is displayed briefly.

If you used the default directory, the files are now in your current working directory, and you can skip the next two steps. Otherwise, you should set the working directory to the place that your tutorial files were copied to.

6. Choose Project → Change Directory.
7. Navigate to the directory you specified for the tutorial files, and click OK.

You can close the Tutorials panel now, and proceed with the exercises.

2.2 Setting Preferences

To keep the property list in the Project Table manageable, Maestro shows only the properties designated as “primary” for each application. In this tutorial, however, you will need access to all the properties, which you can do by setting a preference, as follows:

1. Click the Table button on the Project toolbar.

   The Project Table panel opens.

2. Choose Table → Preferences.

   The Preferences panel opens at the Project Table – Properties section.

3. Under When new entries are added, select Show all properties.
4. Close the Preferences panel.

2.3 Generating and Testing a QSPR Model for Aqueous Solubility

The aqueous solubility of organic molecules plays a key role in ADME processes, especially absorption, distribution, and excretion. To experimentally measure accurate aqueous solubilities (logS) is difficult and requires a synthesis of the compound of interest. Because of this, a number of *in silico* approaches have been developed to estimate this key molecular property, including fragment-based approaches, linear models, and non-linear models. QikProp, Schrödinger's molecular property predictor which estimates 44 molecular properties, uses a linear method for estimating logS.

The QikProp model, as with all linear or non-linear models, was fit to a finite set of compounds. When examining molecules outside the chemical space used in the fitting process, high accuracy in logS predictions might not be obtained. Consequently it may be desirable to generate local QSPR (quantitative structure-property relationship) models relevant to the compounds of interest. This tutorial provides an example of generating a local model for logS prediction using only molecular properties.

2.3.1 Importing Data

1. Click the Import button on the Project toolbar.

2. In the Import dialog box, select the Maestro-format structure file `aq_sol_ligs.maegz`.

   This file contains 1144 molecules for which experimental measurements of logS have been taken, as well as a set of calculated properties for each molecule.

3. If the import options are not displayed, click Options.

4. Ensure that Import all structures is selected.

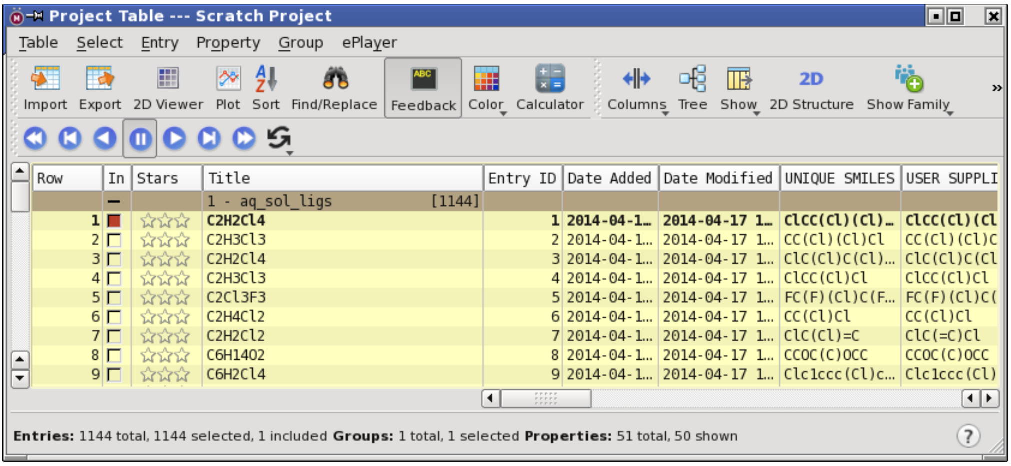
5. Click Open.

   The dialog box closes and the 1144 molecular structures in the file are imported. The import operation may take a minute to finish. When it has finished, the first structure in the file is displayed in the Workspace.

6. If the Project Table panel is not open, click the Table button on the Project toolbar.

   The Project Table panel opens.

As shown in Figure 2.1, each structure in the imported file is now an entry in the Project Table, represented by a row. The selected entries counter in the status bar of the panel reads 1144 selected. A long series of columns displays a number of molecular properties, or *descriptors*, which were calculated in advance for each entry. All but the first four columns (Row, Stars, In, and Title) can be scrolled into or out of view.


Project Table --- Scratch Project
Table Select Entry Property Group ePlayer
Import Export 2D Viewer Plot Sort Find/Replace Feedback Color Calculator Columns Tree Show 2D Structure Show Family

Row	In	Stars	Title	Entry ID	Date Added	Date Modified	UNIQUE SMILES	USER SUPPLI
	—		1 - aq_sol_ligs [1144]					
1	■	☆☆☆	**C2H2Cl4**	**1**	**2014-04-1...**	**2014-04-17 1...**	**ClCC(Cl)(Cl)...**	**ClCC(Cl)(Cl**
2	□	☆☆☆	C2H3Cl3	2	2014-04-1...	2014-04-17 1...	CC(Cl)(Cl)Cl	CC(Cl)(Cl)C
3	□	☆☆☆	C2H2Cl4	3	2014-04-1...	2014-04-17 1...	ClC(Cl)C(Cl)...	ClC(Cl)C(Cl
4	□	☆☆☆	C2H3Cl3	4	2014-04-1...	2014-04-17 1...	ClCC(Cl)Cl	ClCC(Cl)Cl
5	□	☆☆☆	C2Cl3F3	5	2014-04-1...	2014-04-17 1...	FC(F)(Cl)C(F...	FC(F)(Cl)C(
6	□	☆☆☆	C2H4Cl2	6	2014-04-1...	2014-04-17 1...	CC(Cl)Cl	CC(Cl)Cl
7	□	☆☆☆	C2H2Cl2	7	2014-04-1...	2014-04-17 1...	ClC(Cl)=C	ClC(=C)Cl
8	□	☆☆☆	C6H14O2	8	2014-04-1...	2014-04-17 1...	CCOC(C)OCC	CCOC(C)OCC
9	□	☆☆☆	C6H2Cl4	9	2014-04-1...	2014-04-17 1...	Clc1ccc(Cl)c...	Clc1ccc(Cl)

Entries: 1144 total, 1144 selected, 1 included **Groups:** 1 total, 1 selected **Properties:** 51 total, 50 shown

Figure 2.1. The Project Table after importing 1144 structures

Strike does not generate descriptors. The descriptors in this exercise came from three sources:

- Most of the descriptors in the table were determined by QikProp, a program distributed by Schrödinger that generates a widely applicable set of molecular properties. For more information on QikProp, see the *QikProp User Manual*.
- A few descriptors were obtained from the `ligparse` utility (`$SCHRODINGER/utilities/ligparse`), including the Aromatic proportion and the Non-carbon proportion. The aromatic proportion is the fraction of heavy atoms that are aromatic while the non-carbon proportion is the fraction of heavy atoms that are not carbon.
- Also included are experimentally determined logS values in the measured log(solubility:mol/L) descriptor.

2.3.2 Preparing Test and Training Sets

The next step is to separate the 1144 molecules into two sets, a test set and a training set, using a random selection method that is part of the Project Table facility.

1. In the Project Table panel, choose Select → Random.

   The Random Selection dialog box opens.

2. Ensure that the value in the Randomly select *n* % of entries text box is 50, the default.

   By default, the random set is chosen from only the selected entries. When the structure file was imported, all entries were selected, but this may not always be the case.

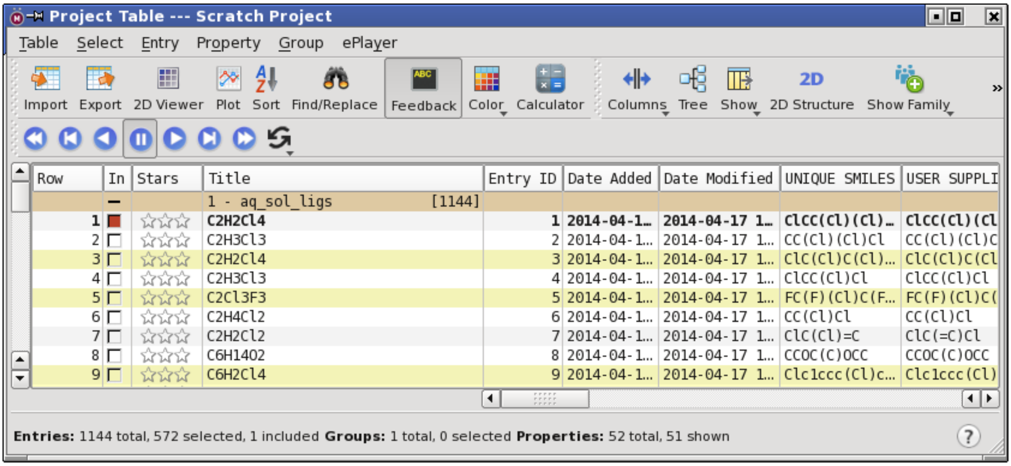
3. Change the Select from option from Selected entries to All entries and click Select.

   After a moment, the Project Table is redisplayed with random entries selected. The selected entries counter in the bottom of the panel now reads 572 selected.

To keep track of the newly selected entries, which will be used as the training set, add a column to the Project Table that labels the currently selected molecules.

4. Choose Property → Add to open the Add Property panel.
5. In the Name text box, type `Population`.
6. Choose String from the Type option menu.
7. In the Initial value text box, type `training`. Click Add.

   A column is added to the Project Table to the right of QPlogKhsa, as shown in Figure 2.2. Scroll to the far right to see this column. Under the column header Population, only the currently selected entries have a value of training.



Row	In	Stars	Title	Entry ID	Date Added	Date Modified	UNIQUE SMILES	USER SUPPLI
	—		1 - aq_sol_ligs [1144]					
1	■	☆☆☆	**C2H2Cl4**	**1**	**2014-04-1...**	**2014-04-17 1...**	**ClCC(Cl)(Cl)...**	**ClCC(Cl)(Cl**
2	□	☆☆☆	C2H3Cl3	2	2014-04-1...	2014-04-17 1...	CC(Cl)(Cl)Cl	CC(Cl)(Cl)C
3	□	☆☆☆	C2H2Cl4	3	2014-04-1...	2014-04-17 1...	ClC(Cl)C(Cl)...	ClC(Cl)C(Cl
4	□	☆☆☆	C2H3Cl3	4	2014-04-1...	2014-04-17 1...	ClCC(Cl)Cl	ClCC(Cl)Cl
5	□	☆☆☆	C2Cl3F3	5	2014-04-1...	2014-04-17 1...	FC(F)(Cl)C(F...	FC(F)(Cl)C(
6	□	☆☆☆	C2H4Cl2	6	2014-04-1...	2014-04-17 1...	CC(Cl)Cl	CC(Cl)Cl
7	□	☆☆☆	C2H2Cl2	7	2014-04-1...	2014-04-17 1...	ClC(Cl)=C	ClC(=C)Cl
8	□	☆☆☆	C6H14O2	8	2014-04-1...	2014-04-17 1...	CCOC(C)OCC	CCOC(C)OCC
9	□	☆☆☆	C6H2Cl4	9	2014-04-1...	2014-04-17 1...	Clc1ccc(Cl)c...	Clc1ccc(Cl)

Entries: 1144 total, 572 selected, 1 included **Groups:** 1 total, 0 selected **Properties:** 52 total, 51 shown

Figure 2.2. The Project Table with a randomly selected training set

Because the random selection generator is machine-dependent, your training set is unlikely to be a precise match to that shown in Figure 2.2, and therefore your results could differ from those shown in this document. Other results will also differ slightly because of differences in the random selections made.

The data has now been prepared. In the next section, it will be used to generate a model.

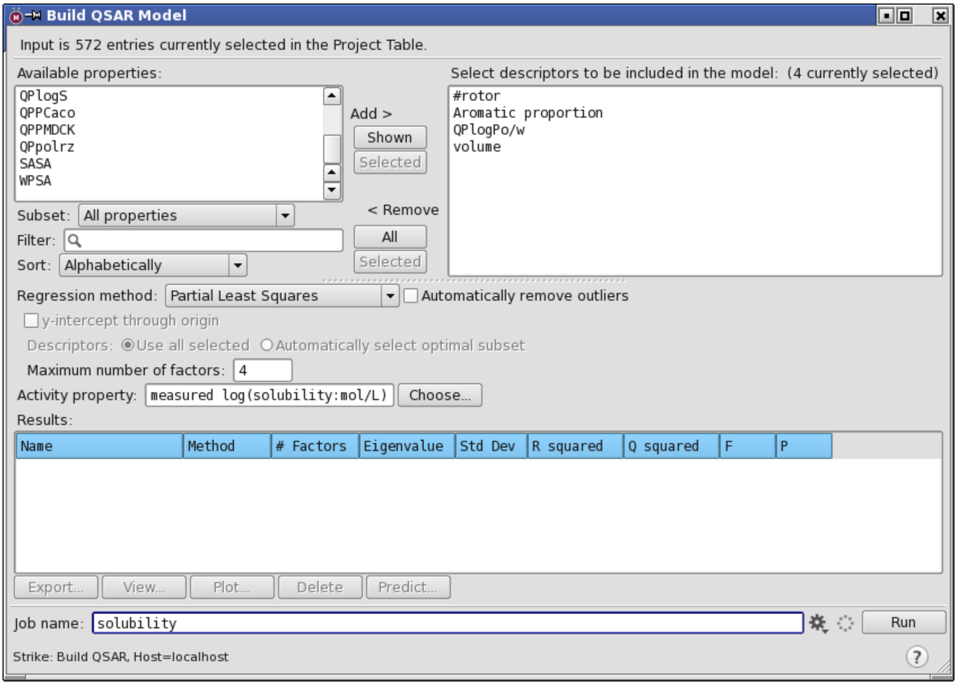
2.3.3 Building a Partial Least Squares Model

It is known from the general solubility equation that a relationship exists between a compound's aqueous solubility and its logP and melting points. We will use this idea in generating our model by including the logP estimate from QikProp along with a handful of molecular properties chosen to fulfill the role of the melting point.

Your first model will use the Partial Least Squares (PLS) method, which is described briefly in Chapter 5. Linear equations are generated that describe the relationship between a group of factors (derived from a set of independent descriptors) and a dependent descriptor (the predicted property). The goal of PLS is to find factors that explain the variance in both the independent and the dependent descriptors.

1. In the main Maestro window, choose Applications → Strike → Build QSAR Model or Tasks → QSAR → Property-Based → Build Model.

   The Build QSAR Model panel opens. As shown in Figure 2.3, the input counter under the panel title bar reads Input is 572 entries currently selected in the Project Table.



Build QSAR Model

Input is 572 entries currently selected in the Project Table.

Available properties:

```
QPlogS
QPPCaco
QPPMDCK
QPpolrz
SASA
WPSA
```

Select descriptors to be included in the model: (4 currently selected)

```
#rotor
Aromatic proportion
QPlogPo/w
volume
```

Subset: All properties

Filter:

Sort: Alphabetically

Regression method: Partial Least Squares ☐ Automatically remove outliers

☐ y-intercept through origin

Descriptors: ● Use all selected ○ Automatically select optimal subset

Maximum number of factors: 4

Activity property: measured log(solubility:mol/L)

Results:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P

Job name: solubility

Strike: Build QSAR, Host=localhost

Figure 2.3. The Build QSAR Model panel settings for the PLS model

2. Under Available properties, control-click on the following properties:

    - #rotor
    - Aromatic proportion
    - QPlogPo/w
    - volume

3. Under Add >, click Selected to move them to the Select descriptors to be included in the model list.

    The descriptor count is displayed: (4 currently selected) These four descriptors will be the independent variables.

4. Ensure that the Regression method selected is Partial Least Squares.

5. Ensure that Automatically remove outliers is deselected (the default).

6. Enter 4 as the Maximum number of factors.

    The Maximum number of factors should be less than or equal to the number of independent variables. If the Maximum number of factors is greater than the number of independent variables, Strike automatically reports the maximum number of factors extracted from the data, which is generally equal to the number of independent descriptors.

7. Select the Activity property (the dependent variable to be fit) by clicking Choose.

    The Choose Activity Property dialog box opens.

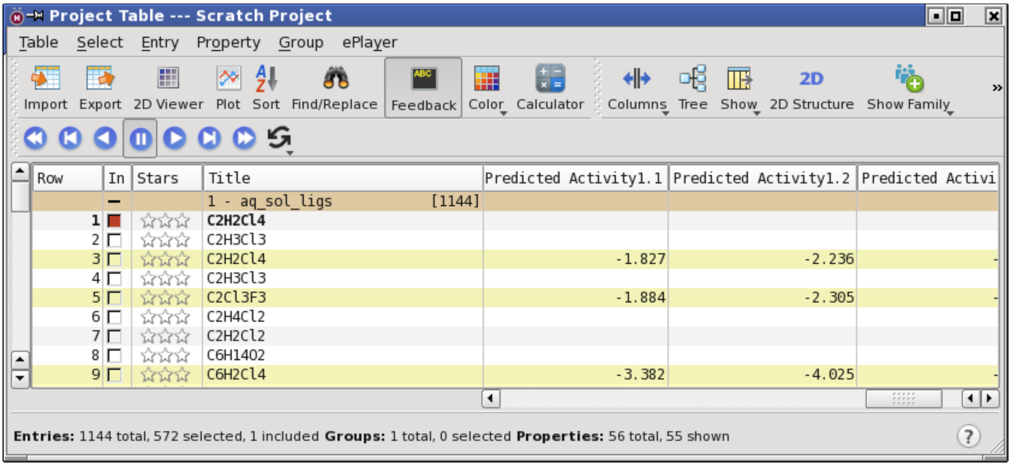
8. Select measured log(solubility:mol/L) and click OK.

    These settings mean that the model will attempt to correlate the number of rotatable bonds (#rotor), fractional aromatic proportion, molecular volume and logP (QPlogPo/w) to experimentally measured aqueous solubilities (measured log(solubility:mol/L)).

9. Enter `solubility` in the Job name text box.

10. Click Run to begin the calculation.

    The job takes only a few moments to finish. When the model has been generated, the results are incorporated into the Project Table, shown in Figure 2.4.



Row	In	Stars	Title	Predicted Activity1.1	Predicted Activity1.2	Predicted Activi
	–		1 - aq_sol_ligs [1144]			
1	■	☆☆☆	**C2H2Cl4**			
2	□	☆☆☆	C2H3Cl3			
3	□	☆☆☆	C2H2Cl4	-1.827	-2.236	-
4	□	☆☆☆	C2H3Cl3			
5	□	☆☆☆	C2Cl3F3	-1.884	-2.305	-
6	□	☆☆☆	C2H4Cl2			
7	□	☆☆☆	C2H2Cl2			
8	□	☆☆☆	C6H14O2			
9	□	☆☆☆	C6H2Cl4	-3.382	-4.025	-

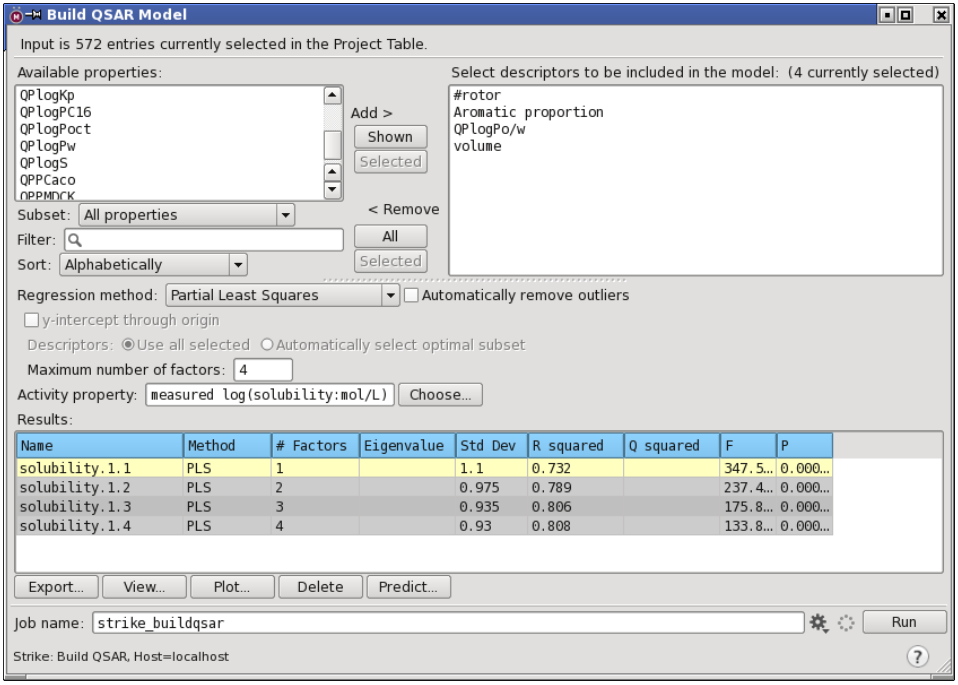
Entries: 1144 total, 572 selected, 1 included **Groups:** 1 total, 0 selected **Properties:** 56 total, 55 shown

Figure 2.4. The Project Table with training-set predicted activities

2.3.4 Examining PLS Model-Building Results

In the Project Table there are four new columns, headed Predicted Activity*X.Y*, where *X* represents the model and *Y* the number of factors used in the prediction. This is the first model built in this project, so *X* = 1, and a maximum of 4 factors were used, so *Y* = 1, 2, 3, or 4. The values in each column are the predicted values of logS generated using *Y* factors.

In this document, the particular set of diagnostic statistics generated by model *X* with *Y* factors is called a *predictor*. Four predictors are listed in the Results table of the Build QSAR Model panel after the model-building job has finished, as shown in Figure 2.5. Along with the Name in the format *jobname.X.Y*, the Method, and the number of factors (# Factors), statistical information is given for an immediate appraisal of the predictors: standard deviation, R-squared, F-value, and P-factor.



Input is 572 entries currently selected in the Project Table.

Available properties:
QPlogKp
QPlogPC16
QPlogPoct
QPlogPw
QPlogS
QPPCaco
QPPMDCK

Select descriptors to be included in the model: (4 currently selected)
#rotor
Aromatic proportion
QPlogPo/w
volume

Subset: All properties

Filter:

Sort: Alphabetically

Regression method: Partial Least Squares ☐ Automatically remove outliers

☐ y-intercept through origin

Descriptors: ● Use all selected ○ Automatically select optimal subset

Maximum number of factors: 4

Activity property: measured log(solubility:mol/L)

Results:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P
solubility.1.1	PLS	1		1.1	0.732		347.5...	0.000...
solubility.1.2	PLS	2		0.975	0.789		237.4...	0.000...
solubility.1.3	PLS	3		0.935	0.806		175.8...	0.000...
solubility.1.4	PLS	4		0.93	0.808		133.8...	0.000...

Job name: strike_buildqsar

Strike: Build QSAR, Host=localhost

Figure 2.5. The Build QSAR Model panel with a four-predictor PLS model

The five buttons below the Results table are now available. When a predictor is selected, the buttons can be used to perform the following tasks. Some tasks affect only the selected predictor; others operate on the model as a whole, including any other predictors belonging to the model:

Export	Export the model for use in another project
View	View the output file for the model-building job that generated the predictor
Plot	Plot the predicted versus experimental results for the selected predictor
Delete	Delete the model that generated the predictor
Predict	Make further predictions using the selected predictor

Here, you will examine the 4-factor predictor by plotting its predictions for the training set versus measured log(solubility:mol/L).

1. Select the row named solubility.1.4 in the Results table and click Plot.

   After a few moments, the Scatter Plot panel appears, showing measured logS values plotted against predicted values, with the line of best fit drawn.

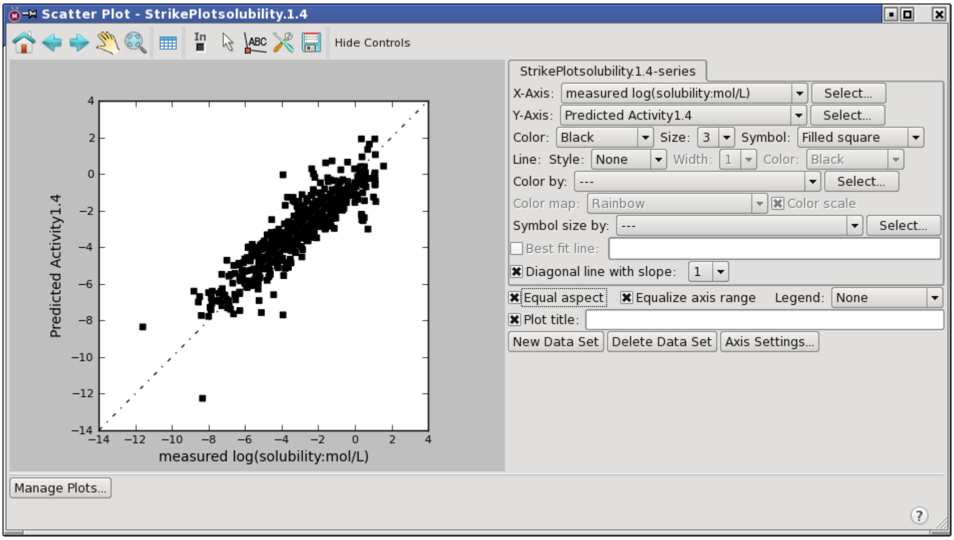
By default, the plot facility automatically sets the range for the X and Y axes of the plot. However, it is easier to spot outlying points when the X and Y axes share a common scale.

2. Select Equalize axis range.

   The axis range changes so that both axes have the same range.

3. Select Equal aspect.

   The plot is now drawn to a common scale, as in the example in Figure 2.6. Because the training set is selected randomly, some plot details will differ from yours.



Scatter Plot - StrikePlotsolubility.1.4

StrikePlotsolubility.1.4-series

X-Axis: measured log(solubility:mol/L)

Y-Axis: Predicted Activity1.4

Color: Black Size: 3 Symbol: Filled square

Line: Style: None Width: 1 Color: Black

Color by: ---

Color map: Rainbow ☒ Color scale

Symbol size by: ---

□ Best fit line:

☒ Diagonal line with slope: 1

☒ Equal aspect ☒ Equalize axis range Legend: None

☒ Plot title:

Figure 2.6. Plot of predicted vs. measured logS for the training set

For most of the molecules in this training set, the generated model does a good job of reproducing experimental logS values, as can be seen in Figure 2.6. Next you will examine some of the cases where the model generates less accurate predictions:

1. In the Scatter Plot panel, click the Pick to include entries toolbar button.

2. Pick one of the data points for which the model is most in error.

   The corresponding molecule is now included in the Workspace.

3. Pick other data points where the model is in error and look at their molecular structures in the Workspace.

The particular molecules you view will depend on the training set, but you should find that the model does less well for molecules that contain long alkyl chains, sugar-like molecules, and a few fused-ring heterocycles.

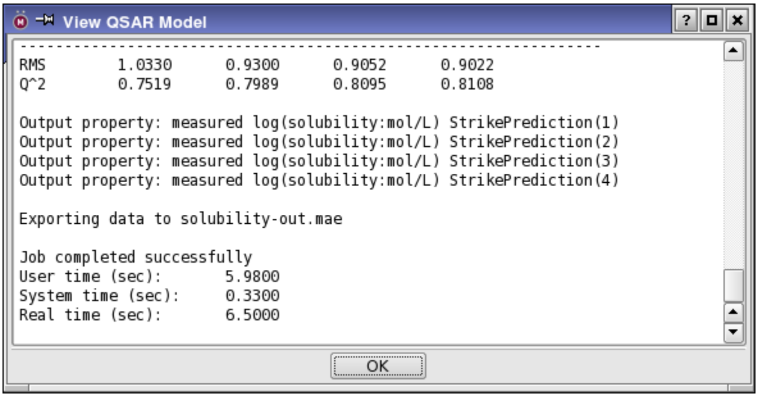
For information about other features of the Scatter Plot panel, click the Help button.

4. When you have finished working with the plot, close the panel.

More information about the model and the predictors is given in the output file of the model-building job, *jobname*`.out`, which can be examined using the View button:

1. In the Build QSAR Model panel, click the View button.

   The View QSAR Model dialog box opens. This dialog box displays the output file for the Strike model-building job—see Figure 2.7.



```
-----------------------------------------------------------------
RMS        1.0330      0.9300      0.9052      0.9022
Q^2        0.7519      0.7989      0.8095      0.8108

Output property: measured log(solubility:mol/L) StrikePrediction(1)
Output property: measured log(solubility:mol/L) StrikePrediction(2)
Output property: measured log(solubility:mol/L) StrikePrediction(3)
Output property: measured log(solubility:mol/L) StrikePrediction(4)

Exporting data to solubility-out.mae

Job completed successfully
User time (sec):       5.9800
System time (sec):     0.3300
Real time (sec):       6.5000
```

Figure 2.7. The View QSAR Model dialog box

2. Examine the output file, noting the following points of interest:

   - The Correlation Matrix for input variables (the four independent descriptors).
   - PLS Regression Statistics, listing standard deviation (S.D.), R-squared, F-factor, and P-value by #Factors. The large F-factors and small P-values indicate this model was likely not achieved by chance and that the descriptors chosen are significant as a set.
   - Cross Validation leave-*N*-out Results over *M* Cycles. Large differences between calculated q^2 and r^2 values reflect significant dependence of the model on the molecules included in the regression and in general are unfavorable.
   - T-values and coefficients.
   - Predicted values for logS at each #Factors for each of the molecules in the training set.

3. Click OK to close the View QSAR Model dialog box.

2.3.5 Applying the Model to the Test Set

The true test of any model is to check its predictions against a set of molecules not included during its training. The exercise performed in this section would typically be considered part of model generation and validation, but for the purposes of this tutorial, it will be used to demonstrate the model application step of the Strike workflow.

The first step is to create a test set of molecules. In this example, the test set will be those molecules in the Project Table that were not members of the training set:

1. In the Project Table, confirm that the training set is selected by examining the Population column. If so, skip to the next step.

   If for any reason the training set is no longer the selected set—for example, if a single entry has been selected instead—you can restore the selection by performing these steps:

   a. Choose Select → Only from the Project Table.

      The Entry Selection panel opens.

   b. In the Properties list, select Population.

   c. Select the option Is defined (any value).

      Only the training set has a defined value (training) in the Population column.

   d. Click Add, then OK.

   The molecules in the training set, and only those molecules, are now selected.

2. In the Project Table, choose Select → Invert.

   The selected molecules are now those that were not part of the training set. This will be the test set.

Now you can run a prediction job on the test set molecules:

3. In the main window, choose Applications → Strike → Predict.

   The Predict based on QSAR model panel opens. If it was open, the Build QSAR Model panel closes.

   In the Predict panel, the four predictors previously generated are listed in the Select model to use for prediction table.

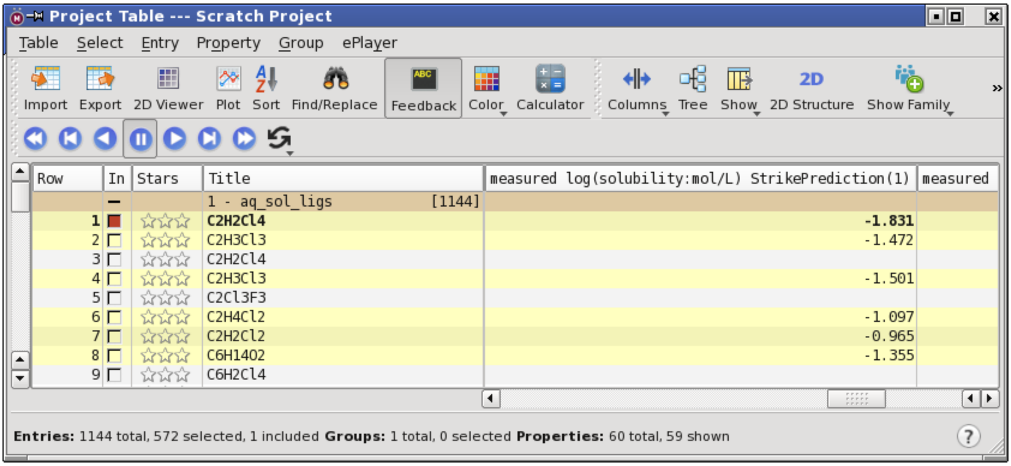
4. Select the model with 4 factors.

5. Click Run to launch the `strike_predict` job.

The job takes a few seconds to run.

6. When the job is finished, view the Project Table.

   There are four new columns to the right of the table: measured log(solubility:mol/L) StrikePrediction(*N*), where *N*=1, 2, 3, or 4. These columns hold predicted logS values for the test set, as shown in Figure 2.8.



Row	In	Stars	Title	measured log(solubility:mol/L) StrikePrediction(1)	measured
	—		1 - aq_sol_ligs [1144]		
1	■	☆☆☆	**C2H2Cl4**	**-1.831**	
2	□	☆☆☆	C2H3Cl3	-1.472	
3	□	☆☆☆	C2H2Cl4		
4	□	☆☆☆	C2H3Cl3	-1.501	
5	□	☆☆☆	C2Cl3F3		
6	□	☆☆☆	C2H4Cl2	-1.097	
7	□	☆☆☆	C2H2Cl2	-0.965	
8	□	☆☆☆	C6H14O2	-1.355	
9	□	☆☆☆	C6H2Cl4		

Entries: 1144 total, 572 selected, 1 included **Groups:** 1 total, 0 selected **Properties:** 60 total, 59 shown

Figure 2.8. The Project Table with test-set predicted solubilities.

Using the data in the fourth predicted values (*N*=4) column of the Project Table as the predicted logS, plot the predicted logS versus measured log(solubility:mol/L) for the test set molecules.

7. If the Manage Plots panel is not already open, open it by clicking the Plot button on the Project Table toolbar:

   or choosing Table → Manage Plots.

8. Click New Scatter Plot.

   A new Scatter Plot panel opens.

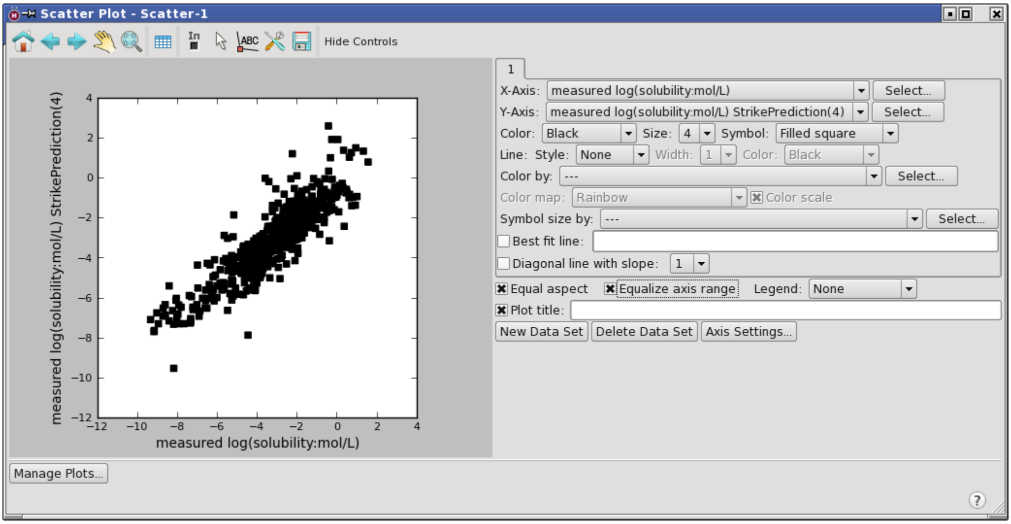
9. Choose measured log(solubility:mol/L) from the X-Axis option menu.

10. Choose measured log(solubility:mol/L) StrikePrediction(4) from the Y-Axis option menu.

    The points are plotted in the plot area.

11. Select Equal aspect and Equalize axis range.

    The plot should resemble that shown in Figure 2.9. The good agreement between calculated and experimental values found for the training set remains quite good for the test set.



Scatter Plot - Scatter-1

X-Axis: measured log(solubility:mol/L)
Y-Axis: measured log(solubility:mol/L) StrikePrediction(4)
Color: Black Size: 4 Symbol: Filled square
Line: Style: None Width: 1 Color: Black
Color by: ---
Color map: Rainbow ☒ Color scale
Symbol size by: ---
□ Best fit line:
□ Diagonal line with slope: 1
☒ Equal aspect ☒ Equalize axis range Legend: None
☒ Plot title:

Figure 2.9. Plot of predicted vs. measured logS for the test set

12. Click the Pick to include entries toolbar button

    In

13. Click on one or more of the less well-treated members of the test set.

    As they appear in the Workspace, note that many are fused heterocycles, sugar-like molecules, or molecules with large aliphatic chains, as was observed in the training set.

14. When you have finished working with the plot, click Delete in the Manage Plots panel, then close the panel.

2.3.6 Calculating Univariate and Bivariate Statistics

The Strike statistics script calculates univariate and bivariate statistics of selected descriptors for the set of entries currently selected in the Project Table. The Strike Univariate and Bivariate Statistics panel allows you to select from a list of the descriptors found in the Project Table. When you have run a statistics job, the results are displayed in the dialog box, from which information can be copied and pasted to an open file as reference material or for printing.

If for any reason the test set is no longer the selected set—for example, if a single entry has been selected instead—you can restore the selection by performing these steps:

a. Choose Select → Only from the Project Table.

   The Entry Selection panel opens.

b. In the Properties list, select Population.

c. Select the option Is defined (any value).

   Only the training set has a defined value (training) in the Population column.

d. Click Add.

e. Click Invert and then OK.

   The molecules in the test set, and only those molecules, are now selected.

1. Choose Applications → Strike → Statistics.

2. Select Aromatic_proportion from the list under Select one or two descriptors from the following list.

   The selected descriptor is highlighted. This will be a univariate statistics calculation, so the only input needed is the single descriptor you have selected.

3. Click Run to launch the job under the default name, strikeStats_1.

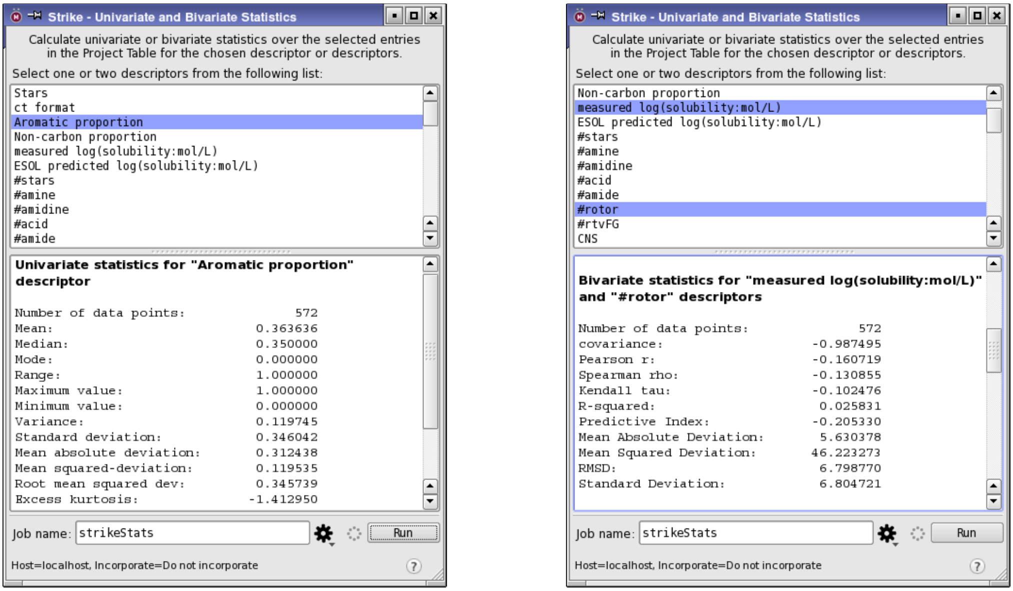
   After a moment, the job results appear in the Results text area, as shown in Figure 2.10. These univariate statistics describe the range and variance of the descriptor values and the shape of the distribution for the test set of molecules (the currently selected entries in the Project Table). See Chapter 5 for definitions of statistics terms.

Now set up a bivariate statistics calculation.

4. In the descriptor list, select measured_log(solubility:mol/L), then control-click on #rotor.

5. Click Run.

   After a few moments, the new results are appended to the Results table. They include a small set of bivariate statistics for the pair of descriptors, followed by the univariate statistics for each, as shown in Figure 2.10. See Chapter 5 for definitions of statistics terms.



Strike - Univariate and Bivariate Statistics

Calculate univariate or bivariate statistics over the selected entries in the Project Table for the chosen descriptor or descriptors.

Select one or two descriptors from the following list:

```
Stars
ct format
Aromatic proportion
Non-carbon proportion
measured log(solubility:mol/L)
ESOL predicted log(solubility:mol/L)
#stars
#amine
#amidine
#acid
#amide
```

```
Univariate statistics for "Aromatic proportion"
descriptor

Number of data points:              572
Mean:                          0.363636
Median:                        0.350000
Mode:                          0.000000
Range:                         1.000000
Maximum value:                 1.000000
Minimum value:                 0.000000
Variance:                      0.119745
Standard deviation:            0.346042
Mean absolute deviation:       0.312438
Mean squared-deviation:        0.119535
Root mean squared dev:         0.345739
Excess kurtosis:              -1.412950
```

Job name: strikeStats Run

Host=localhost, Incorporate=Do not incorporate

Strike - Univariate and Bivariate Statistics

Calculate univariate or bivariate statistics over the selected entries in the Project Table for the chosen descriptor or descriptors.

Select one or two descriptors from the following list:

```
Non-carbon proportion
measured log(solubility:mol/L)
ESOL predicted log(solubility:mol/L)
#stars
#amine
#amidine
#acid
#amide
#rotor
#rtvFG
CNS
```

```
Bivariate statistics for "measured log(solubility:mol/L)"
and "#rotor" descriptors

Number of data points:              572
covariance:                   -0.987495
Pearson r:                    -0.160719
Spearman rho:                 -0.130855
Kendall tau:                  -0.102476
R-squared:                     0.025831
Predictive Index:             -0.205330
Mean Absolute Deviation:       5.630378
Mean Squared Deviation:       46.223273
RMSD:                          6.798770
Standard Deviation:            6.804721
```

Job name: strikeStats Run

Host=localhost, Incorporate=Do not incorporate

Figure 2.10. The Univariate and BIvariate Statistics panel with univariate statistics (left) and bivariate statistics (right)

2.3.7 Model-Building Using Principal Component Analysis

In this exercise, you will generate a model using one of the other alternative regression methods available in Strike, Principal Component Analysis.

1. In the Project Table, the test set is currently selected. Choose Select → Invert to select the training set.

2. Open the Build QSAR Model panel.

   The Predict panel closes. The Build QSAR Model panel retains the selected descriptors, number of factors, and regression method used to generate the previous model. The four predictors generated by the PLS model-building job remain in the Results table.

3. Choose Principal Component Analysis from the Regression method option menu.

4. In the Job name text box, change the name to `solubility_pca` and click Run to launch the calculation.

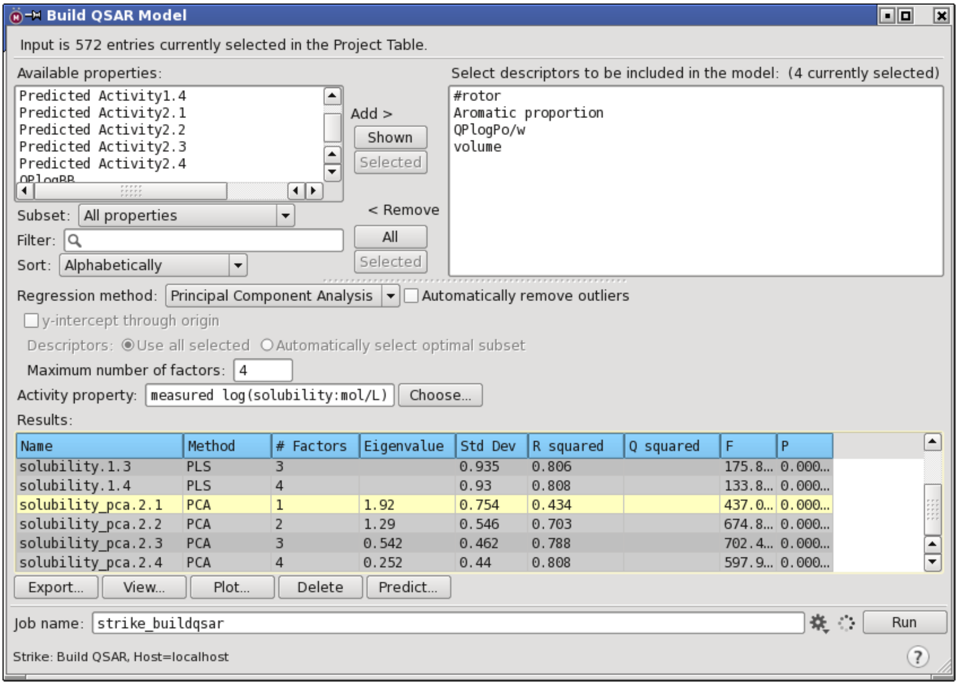
   When the job has finished, the new model will be added to the Results table as a set of predictors with # Factors equal to 1, 2, 3, and 4, as was the PLS model. In the Eigenvalue column, a number is associated with each of the four PCA-model predictors. The eigenvalue represents the portion of the total variance accounted for by the *n*-factor predictor.

In the Project Table, the four new columns Predicted Activity2.*n* are added to the table, with values only for the training set of molecules.

If you were using this PCA model in a real project, you could continue by carrying out the analysis and prediction steps that were performed for the PLS model earlier in this chapter.

The PCA method is frequently used for data reduction by retaining only those factors needed to account for most of the total variance. The variance of each of the independent variables used in the model is taken to be 1.0, and the total variance is defined as the sum of the variances of each independent variable. Typically it is sufficient to retain only those factors with an eigenvalue greater than 1.0. These are the factors that account for more of the variance than does any single original variable.

In the Results table in the Build QSAR Model panel, the *n*-factor predictor of a PCA model accounts for a portion of the total variance equal to the sum of the first *n* eigenvalues. For example, in the table shown in Figure 2.11, the first eigenvalue is 1.92 and the second 1.29, while the third and fourth eigenvalues are less than 1.0. The total variance is 4.0, and the two-factor predictor is sufficient to account for (1.92 + 1.29)/4.00 = 80% of the total variance.



Input is 572 entries currently selected in the Project Table.

Available properties:

```
Predicted Activity1.4
Predicted Activity2.1
Predicted Activity2.2
Predicted Activity2.3
Predicted Activity2.4
QPlogBB
```

Select descriptors to be included in the model: (4 currently selected)

```
#rotor
Aromatic proportion
QPlogPo/w
volume
```

Subset: All properties

Filter:

Sort: Alphabetically

Regression method: Principal Component Analysis ☐ Automatically remove outliers

☐ y-intercept through origin

Descriptors: ● Use all selected ○ Automatically select optimal subset

Maximum number of factors: 4

Activity property: measured log(solubility:mol/L)

Results:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P
solubility.1.3	PLS	3		0.935	0.806		175.8...	0.000...
solubility.1.4	PLS	4		0.93	0.808		133.8...	0.000...
solubility_pca.2.1	PCA	1	1.92	0.754	0.434		437.0...	0.000...
solubility_pca.2.2	PCA	2	1.29	0.546	0.703		674.8...	0.000...
solubility_pca.2.3	PCA	3	0.542	0.462	0.788		702.4...	0.000...
solubility_pca.2.4	PCA	4	0.252	0.44	0.808		597.9...	0.000...

Job name: strike_buildqsar

Strike: Build QSAR, Host=localhost

Figure 2.11. Build QSAR Model panel with four-predictor PCA model

2.3.8 Model-Building Using Multiple Linear Regression

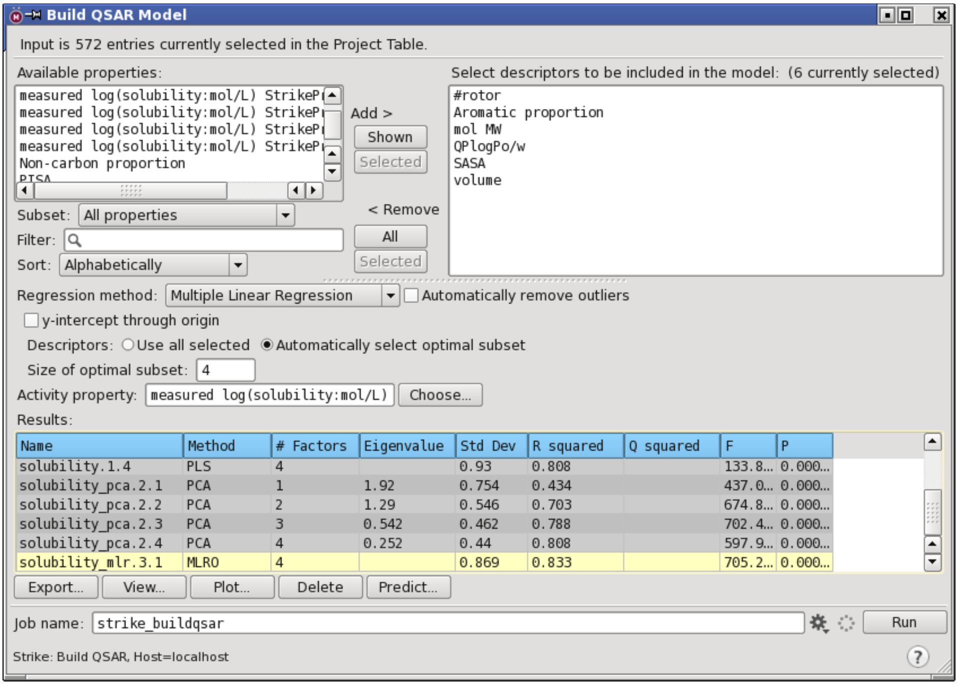
The third regression method available for model-building in Strike is multiple linear regression (MLR). In this section, you will generate an MLR model that uses an algorithm to select the optimal set of descriptors for use.

1. Ensure that the training set is selected in the Project Table.
2. In the Build QSAR Model panel, use control-click to select two more descriptors, mol MW and SASA
3. Click Selected to add them to the Select descriptors to be included in the model list.
4. Choose Multiple Linear Regression from the Regression method option menu.
5. Select the Descriptors option Automatically select optimal subset.
6. Ensure that the Size of optimal subset is 4.

   These settings instruct the MLR algorithm to use the best subset of four descriptors from the six selected.
7. Change the job name to `solubility_mlr`.
8. Click Run to launch the calculation.

   The job takes only a few moments to finish. When the model has been generated, it appears in the Results table in the Build QSAR Model panel as a single row with MLRO (MLR optimal subset) as the Method. See Figure 2.12.

   The results are also incorporated into the Project Table as the column Predicted Activity3.1.



Build QSAR Model

Input is 572 entries currently selected in the Project Table.

Available properties:

```
measured log(solubility:mol/L) StrikeP
measured log(solubility:mol/L) StrikeP
measured log(solubility:mol/L) StrikeP
measured log(solubility:mol/L) StrikeP
Non-carbon proportion
PISA
```

Select descriptors to be included in the model: (6 currently selected)

```
#rotor
Aromatic proportion
mol MW
QPlogPo/w
SASA
volume
```

Subset: All properties

Filter:

Sort: Alphabetically

Regression method: Multiple Linear Regression □ Automatically remove outliers

□ y-intercept through origin

Descriptors: ○ Use all selected ● Automatically select optimal subset

Size of optimal subset: 4

Activity property: measured log(solubility:mol/L) Choose...

Results:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P
solubility.1.4	PLS	4		0.93	0.808		133.8...	0.000...
solubility_pca.2.1	PCA	1	1.92	0.754	0.434		437.0...	0.000...
solubility_pca.2.2	PCA	2	1.29	0.546	0.703		674.8...	0.000...
solubility_pca.2.3	PCA	3	0.542	0.462	0.788		702.4...	0.000...
solubility_pca.2.4	PCA	4	0.252	0.44	0.808		597.9...	0.000...
solubility_mlr.3.1	MLRO	4		0.869	0.833		705.2...	0.000...

Job name: strike_buildqsar

Strike: Build QSAR, Host=localhost

Figure 2.12. Build QSAR Model panel with an MLR model

Again, you could continue with analysis and prediction using this model, as you did with the PLS model.

You can now close the Build QSAR Model panel.

2.4 Extracting Actives Using Atom-Pair Similarities

It is often useful to identify molecules that are "similar" in a chemically significant way to structures of interest. Strike can be used to analyze similarity in either two-dimensional structural (atom-pair connectivity) or molecular descriptor space. Using the atom-pair connectivity method has the advantage of requiring only structural (connectivity) information for a set of probe molecules and for the molecules for which calculated similarities are desired.

In this section, you will use Strike to calculate atom-pair similarities, then use those similarities to extract known actives for thermolysin from a ligand data set.

- If Maestro is already running, choose Close from the Project menu.

  If the project is a scratch project from the previous exercises, you may discard it.

2.4.1 Importing Active and Decoy Ligands

First we need to create a ligand database which is seeded with a subset of the known active ligands. Using the remaining active ligands as probe molecules, we will attempt to extract the seeded actives out of the database.

1. Click the Import button on the Project toolbar.

2. In the Import dialog box, select the Maestro structure file `1tmn_actives.maegz`.

   This file contains nine known active ligands for thermolysin.

3. If the import options are not displayed, click Options.

4. Ensure that Import all structures is selected.

5. Click Open.

   The first active ligand structure appears in the Workspace.

6. Open the Project Table panel.

   There are nine entries, each with a Title identifying the ligand. Each row also has columns of calculated molecular properties from QikProp. These properties will not be used in this exercise, as they are not needed to generate atom-pair similarities.

7. Display each of the ligands in turn in the Workspace.

   These structures show some diversity though many have peptide moieties.

   Note: if the Workspace appears empty, click the Fit to Workspace toolbar button

   to bring the ligand into view.

8. Click the Import button on the Project toolbar.

9. In the Import dialog box, select the file `dl-400mw.maegz` and click Open.

   This file contains the Maestro-format structures of 998 decoy ligands with an average molecular weight of 400.

After a few moments, the first decoy structure appears in the Workspace and 998 new entries are added to the Project Table. These entries also have molecular properties calculated by QikProp, which will not be used in this exercise.

2.4.2 Seeding the Database and Designating Probes

At this point, all of the decoy ligands and none of the actives are selected in the Project Table. In this exercise, you will include three active ligands in the Workspace and add the other six active ligands to the selection to create the seeded ligand set.

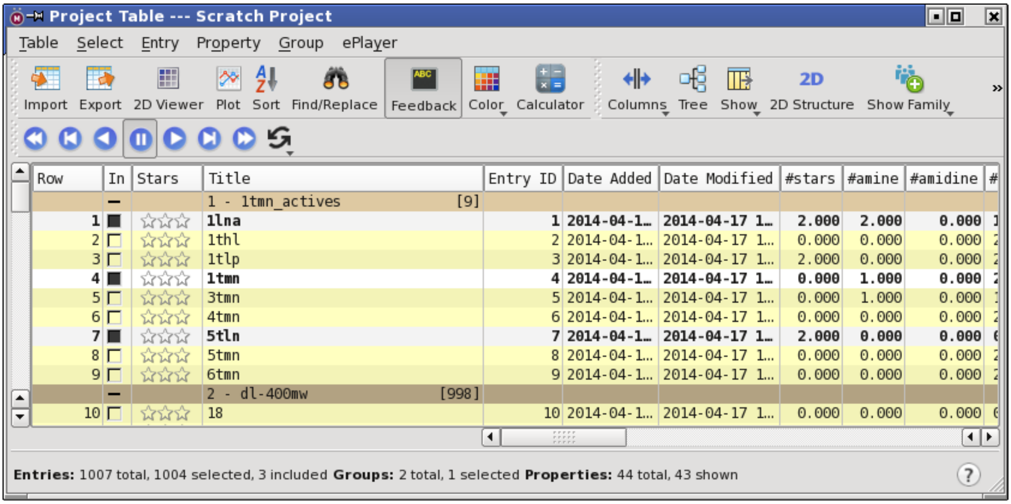
1. Include the three active ligands, `1lna`, `1tmn`, and `5tln` in the Workspace

   Use control-click for the second and third ligands.

   These three entries are *not* selected in the Project Table.

2. Add the six active ligands that are not included in the Workspace (`1thl`, `1tlp`, `3tmn`, `4tmn`, `5tmn`, and `6tmn`) to the selected entries by control-clicking their rows.

   The database for which similarities will be calculated now contains 1004 entries, of which six are known actives. The resulting Project Table is shown in Figure 2.13.



Row	In	Stars	Title	Entry ID	Date Added	Date Modified	#stars	#amine	#amidine	#
	–		1 - 1tmn_actives [9]							
1	■	☆☆☆	**1lna**	**1**	**2014-04-1...**	**2014-04-17 1...**	**2.000**	**2.000**	**0.000**	**1**
2	□	☆☆☆	1thl	2	2014-04-1...	2014-04-17 1...	0.000	0.000	0.000	2
3	□	☆☆☆	1tlp	3	2014-04-1...	2014-04-17 1...	2.000	0.000	0.000	2
4	■	☆☆☆	**1tmn**	**4**	**2014-04-1...**	**2014-04-17 1...**	**0.000**	**1.000**	**0.000**	**2**
5	□	☆☆☆	3tmn	5	2014-04-1...	2014-04-17 1...	0.000	1.000	0.000	1
6	□	☆☆☆	4tmn	6	2014-04-1...	2014-04-17 1...	0.000	0.000	0.000	2
7	■	☆☆☆	**5tln**	**7**	**2014-04-1...**	**2014-04-17 1...**	**2.000**	**0.000**	**0.000**	**6**
8	□	☆☆☆	5tmn	8	2014-04-1...	2014-04-17 1...	0.000	0.000	0.000	2
9	□	☆☆☆	6tmn	9	2014-04-1...	2014-04-17 1...	0.000	0.000	0.000	2
	–		2 - dl-400mw [998]							
10	□	☆☆☆	18	10	2014-04-1...	2014-04-17 1...	0.000	0.000	0.000	6

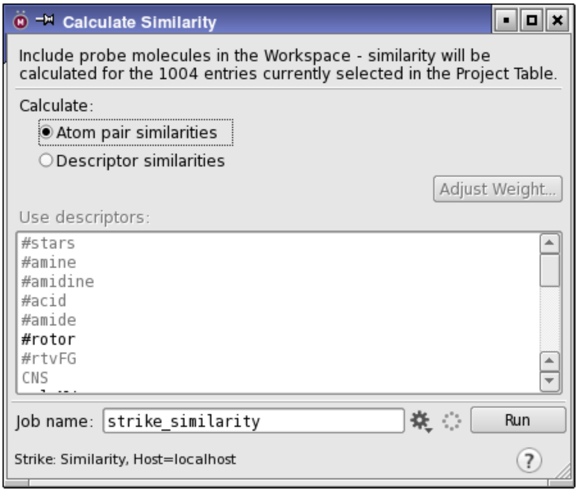
Entries: 1007 total, 1004 selected, 3 included **Groups:** 2 total, 1 selected **Properties:** 44 total, 43 shown

Figure 2.13. The Project Table with 1004 entries selected, 3 probes included.

2.4.3 Running the Calculate Similarity Job

1. Choose Applications → Strike → Similarity in the main window.

   The Calculate similarity panel opens, as shown in Figure 2.14. As noted in the panel, similarity will be calculated for the entries selected in the Project Table, using the entries included in the Workspace as probe molecules.



Include probe molecules in the Workspace - similarity will be calculated for the 1004 entries currently selected in the Project Table.

Calculate:

● Atom pair similarities
○ Descriptor similarities

Use descriptors:

```
#stars
#amine
#amidine
#acid
#amide
#rotor
#rtvFG
CNS
```

Job name: strike_similarity

Strike: Similarity, Host=localhost

Figure 2.14. The Calculate Similarity panel with atom pair similarities specified.

2. Ensure that the Atom pair similarities option is selected.

3. Click Run.

Two columns are added to the Project Table upon completion of the job. For each entry, the Max AP Similarity is the maximum atom-pair similarity of that structure to any of the probe molecules, and the Mean AP Similarity is the mean of the atom-pair similarities to each of the probes.

By default, atom-pair similarities are calculated on a scale from 0.0 to 1.0, with 0.0 indicating no structural similarity and 1.0 indicating maximum structural similarity.

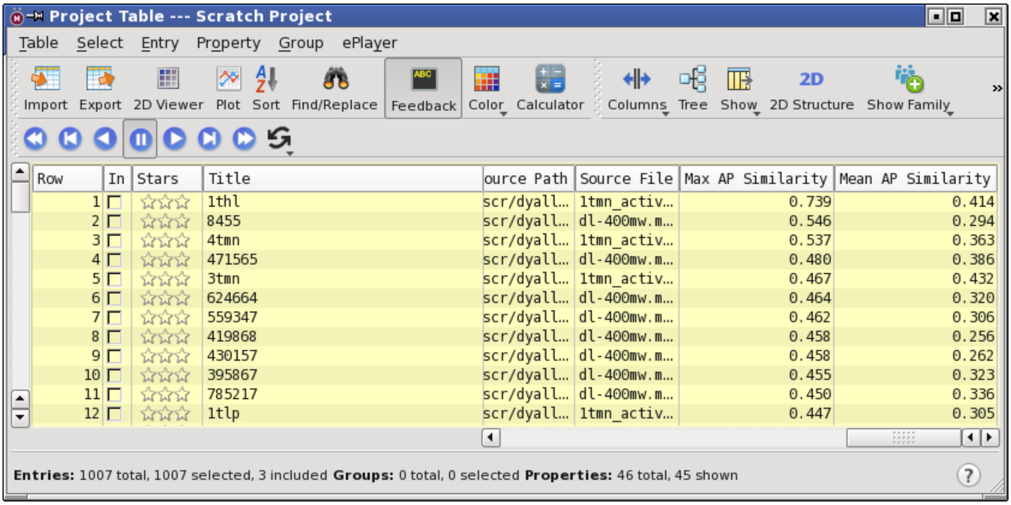
2.4.4 Applying Atom-Pair Similarity

In this exercise, you will examine how well atom-pair similarity performs in extracting the six active ligands (those not used as probes) from the set of decoy ligands. To do this, you will sort the entries in the Project Table by similarity. Project Table entries (rows) can be sorted by multiple user-specified properties (columns) called primary, secondary, and tertiary keys.

When you imported the entries, they were grouped according to the file they were imported from. To sort the entries they must first be ungrouped.

1. In the Project Table, select the 1tmn_actives group, and the dl-400mw group.
2. Choose Entry → Group → Ungroup.
3. Right-click the Max AP Similarity column heading in the Project Table and choose Sort All (Z to A).

   The Project Table is sorted by descending Max AP Similarity, as in Figure 2.15.



Row	In	Stars	Title	ource Path	Source File	Max AP Similarity	Mean AP Similarity
1	□	☆☆☆	1thl	scr/dyall...	1tmn_activ...	0.739	0.414
2	□	☆☆☆	8455	scr/dyall...	dl-400mw.m...	0.546	0.294
3	□	☆☆☆	4tmn	scr/dyall...	1tmn_activ...	0.537	0.363
4	□	☆☆☆	471565	scr/dyall...	dl-400mw.m...	0.480	0.386
5	□	☆☆☆	3tmn	scr/dyall...	1tmn_activ...	0.467	0.432
6	□	☆☆☆	624664	scr/dyall...	dl-400mw.m...	0.464	0.320
7	□	☆☆☆	559347	scr/dyall...	dl-400mw.m...	0.462	0.306
8	□	☆☆☆	419868	scr/dyall...	dl-400mw.m...	0.458	0.256
9	□	☆☆☆	430157	scr/dyall...	dl-400mw.m...	0.458	0.262
10	□	☆☆☆	395867	scr/dyall...	dl-400mw.m...	0.455	0.323
11	□	☆☆☆	785217	scr/dyall...	dl-400mw.m...	0.450	0.336
12	□	☆☆☆	1tlp	scr/dyall...	1tmn_activ...	0.447	0.305

Entries: 1007 total, 1007 selected, 3 included **Groups:** 0 total, 0 selected **Properties:** 46 total, 45 shown

Figure 2.15. The Project Table sorted by Max AP Similarity.

   All six actives were found within the first 41 compounds (4.1% of the data set), and five in the first 28 compounds (2.8% of the data set). The probe molecules are at the end of the Project Table.

4. As a second test, sort the Project Table again, repeating the previous step, but this time using Mean AP Similarity as the Primary Key.

   Using the mean atom-pair similarities, all six actives are found in the first 21 compounds (2.1% of the data set).

It is not surprising that the mean atom-pair similarity does a better job of extracting actives from the data set than the maximum atom-pair similarity. Because all actives are at least slightly structurally similar, their mean values are raised compared to decoy ligands, which may share common features with only one active molecule.

This example shows that Strike can be used to extract compounds similar to a set of molecules using 2D-geometry atom-pair similarities. Next, you will perform this extraction using descriptor similarity instead of atom-pair similarity.

2.5 Extracting Actives Using Descriptor Similarities from Molecular Properties

Now you will use calculated molecular properties to test the ability to extract actives from the data set using descriptor similarities. The molecular properties for the thermolysin active ligands and decoy ligands were previously determined using QikProp. From this set of molecular properties, four descriptor-based similarities can be calculated: *Euclidean similarity*, *Euclidean squared similarity*, *Manhattan similarity*, and *Tanimoto similarity*. Each of these methods calculates the descriptor-space distance between two molecules as a function of their molecular properties. For a summary of each of these methods, see Chapter 5.

The calculated similarities for all but Tanimoto similarity are expressed as distances on an arbitrary scale, where the smaller the value (the shorter the distance), the more similar the two molecules. High values for these quantities correspond to longer distances in descriptor space, indicating less similarity.

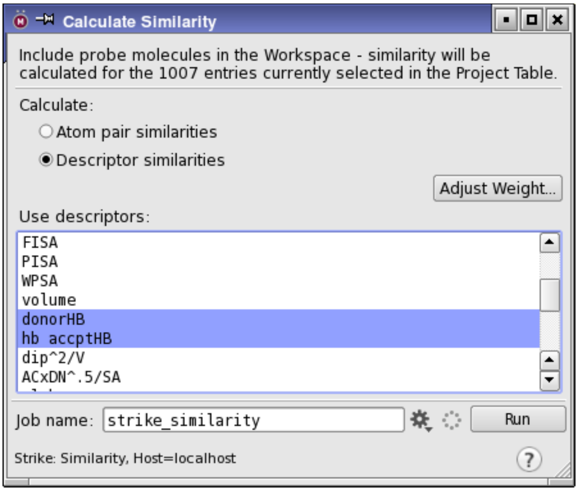
The Tanimoto similarity is calculated on a scale from 0.0 to 1.0 with 1.0 indicating maximum similarity and 0.0 indicating no similarity.

Like atom-pair similarity, Strike calculates descriptor similarities for a set of molecules relative to one or more probe molecules. The molecules included in the Workspace are used as probes; these molecules must also be included in the selected set (test set) of molecules.

1. In the Project Table, choose Select → All to select all entries.
2. Ensure that ligands `1lna`, `1tmn`, and `5tln` are included in the Workspace.

   If you are continuing from the previous exercise, they should be already included. These are the probe molecules, which must be both selected in the Project Table and included in the Workspace.
3. If the Calculate similarity panel is not open, open it by choosing Applications → Strike → Similarity in the main window.
4. Select Descriptor similarities.

   The Use descriptors list becomes available for choosing molecular properties to use in calculating similarities.
5. Select the donor HB and hb accptHB descriptors as shown in Figure 2.16 and click Run.



Include probe molecules in the Workspace - similarity will be calculated for the 1007 entries currently selected in the Project Table.

Calculate:

○ Atom pair similarities

● Descriptor similarities

Use descriptors:

FISA
PISA
WPSA
volume
donorHB
hb accptHB
dip^2/V
ACxDN^.5/SA

Job name: strike_similarity

Strike: Similarity, Host=localhost

Figure 2.16. The Calculate Similarity panel with descriptor similarities specified

After a few seconds the job finishes. In the Project Table, the calculated descriptor similarities have been added as properties. These properties include maximum and minimum distances as well as the similarity measures.

In the descriptor similarity calculation, the molecular properties of the probe molecules are averaged so they can be treated as a single virtual probe molecule. Similarity is calculated with respect to only the selected properties. You will now examine how well descriptor similarity based only on the number of hydrogen-bond acceptors and donors extracts known actives from the data set.

6. Right-click on the Euclidean sq property heading and choose Sort All (A to Z) to sort the property in ascending order.

   The smallest values, corresponding to the greatest similarity to the probes, appear at the top of the table. Of the 6 non-probe active ligands, 5 are found within the top 375 ligands. The remaining active, 1tlp, is ranked as last, due to its very large number of hydrogen-bond acceptor sites.

   To find the actives:

   a. Choose Table → Find/Replace or click the Find/Replace toolbar button.

   b. Enter `t` in the Find text box.

c. From the Options menu, choose Selected properties only, and select the Title property in the dialog box.

d. Click Next.

7. Now sort based on Tanimoto in Descending order (sort twice).

   Of the 6 non-probe actives, 5 are found in the top 560 compounds. The 1tlp ligand is again the lowest-ranked active. You can find the actives by clicking Next on the Find toolbar, as the search is already set up.

8. Close the Calculate Similarity panel, and hide the Find toolbar.

These very simple examples were designed to show possible applications of Strike similarity calculations in descriptor and 2D-similarity space.

2.6 Estimating Activity by Creating a QSAR Model

In this tutorial, you will build a QSAR model and use it to predict activity. The most significant difference between this exercise and the QSPR model-building exercise in Section 2.2 on page 7 is that the property being predicted is a biological activity. The workflow and steps that follow are similar to the QSPR exercise.

Thymidylate synthase is an anticancer drug target as it catalyses the generation of deoxythymidine monophosphate given dUMP and a cofactor, 5,10-methylene tetrahydrofolate, an essential step in de novo DNA replication. The widely used anticancer agent 5-fluorouracil targets thymidylate synthase and is active against solid tumors like breast, head, neck, and colon cancers. Activities (EC_{50} and IC_{50}) have been experimentally determined for a large series of compounds. You will use the set of broadly applicable descriptors generated by QikProp in order to develop a QSAR model with Strike.

For this tutorial, a set of 188 known inhibitors were selected. All of these ligands have experimentally-determined L1210 IC_{50} activities that range from 141 to 0.00052 µM. This set of ligands is well suited for QSAR as the structures have similar cores with a large variety of substitution in shared side chains which leads to a wide activity range. The ligands were prepared from 2D geometries using LigPrep, then neutralized, prior to being run through QikProp to produce 36 predicted properties.

The Maestro format file `thymidylate_synthase_ligands.maegz` contains the 188 ligand structures with their QikProp properties, their raw IC_{50} values, and their -log(IC_{50}) values. Because the goal is a free energy relationship between activities and properties, you will use the -log(IC_{50}) or log(1/IC_{50}) values rather than the raw IC_{50} values.

- If Maestro is already running, choose Project → Close.

  If the project is a scratch project from the previous exercises, you may discard it.

2.6.1 Preparing the Data

The ligand data must be imported into the project and divided into a test set and a training set.

1. Click the Import button.

2. In the Import panel, select the file `thymidylate_synthase_ligands.maegz`.
3. If the import options are not displayed, click Options.
4. Ensure that Import all structures is selected.
5. Click Open.

   After a moment, the first ligand in the file appears in the Workspace.
6. Open the Project Table panel.

   There are 188 entries in the project, all selected.
7. Choose Select → Random.

   The Random Selection dialog box opens.
8. Ensure that the value in the text box is `50` and % of entries is chosen, then click Select.

   After a moment, the Project Table is redisplayed with half the entries deselected at random. The selected entries counter in the status bar now reads 94 selected.

To keep track of the newly selected entries, which will be used as the training set, add a column to the Project Table that labels the currently selected molecules:

1. Choose Property → Add to open the Add Property panel.
2. In the Name text box, type `Population`.
3. Choose String from the Type option menu.
4. In the Initial value text box, type `training`.
5. Click Add.

   Under the column heading Population, only the currently selected entries have a value of training.

2.6.2 Model Generation

You will now build a QSAR model employing all of the relevant QikProp descriptors:

1. Choose Applications → Strike → Build QSAR Model in the main window.

   The Build QSAR Model panel opens. The input counter under the title bar reads Input is 94 entries currently selected in the Project Table.

2. If the Select descriptors to be included in the model list has any descriptors in it, click All under < Remove.

3. Under Available properties, select all the descriptors (CTRL+A, ⌘A).

4. Control-click to deselect the following descriptors: Activity (-log[IC50]), #stars, #rtvFG, CNS, QPlogBB, and #metab.

   The latter five descriptors are omitted because they are expected to be unrelated to the binding process; the first will be the dependent variable.

5. Under Add >, click Selected.

   The descriptors are transferred to the Select descriptors to be included in the model list. The Available properties list shows the properties you deselected.

6. Ensure that the Regression method is Partial Least Squares and that Automatically remove outliers is not selected.

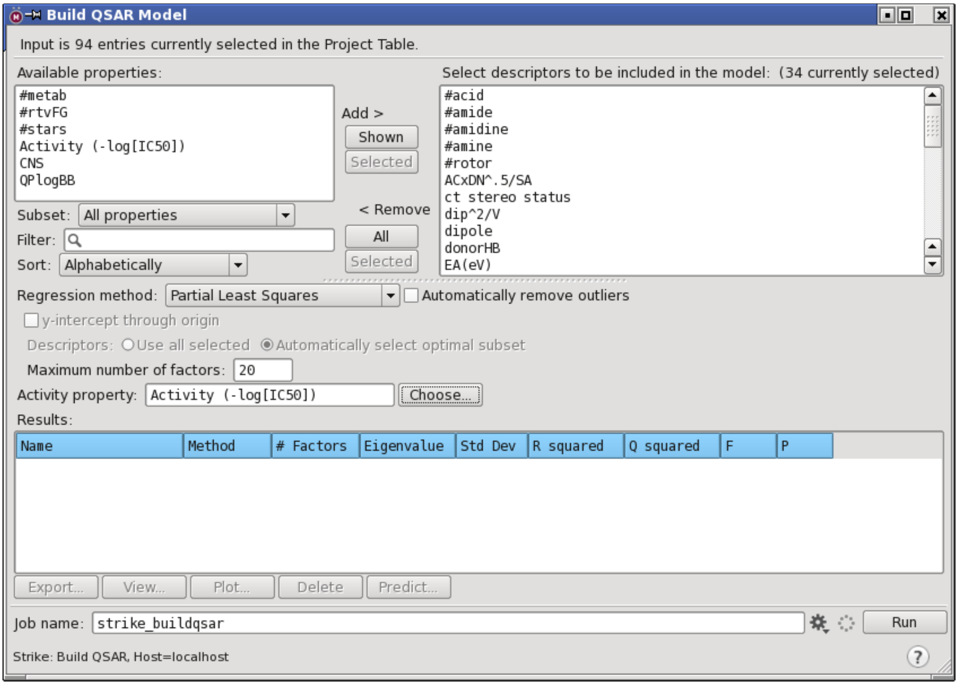
7. In the Maximum number of factors box, type `20`.

8. Click Choose.

   The Choose Activity Property dialog box opens.

9. Select Activity (-log[IC50]) from the list and click OK.

   See Figure 2.17 to check your settings.



Build QSAR Model

Input is 94 entries currently selected in the Project Table.

Available properties:

```
#metab
#rtvFG
#stars
Activity (-log[IC50])
CNS
QPlogBB
```

Add > Shown Selected

< Remove All Selected

Select descriptors to be included in the model: (34 currently selected)

```
#acid
#amide
#amidine
#amine
#rotor
ACxDN^.5/SA
ct stereo status
dip^2/V
dipole
donorHB
EA(eV)
```

Subset: All properties

Filter:

Sort: Alphabetically

Regression method: Partial Least Squares ☐ Automatically remove outliers

☐ y-intercept through origin

Descriptors: ○ Use all selected ● Automatically select optimal subset

Maximum number of factors: 20

Activity property: Activity (-log[IC50]) Choose...

Results:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P

Export... View... Plot... Delete Predict...

Job name: strike_buildqsar Run

Strike: Build QSAR, Host=localhost

Figure 2.17. Build QSAR Model panel showing settings for activity model

10. In the Job name text box, enter `strike_buildqsar`.

11. Click Run to start the job.

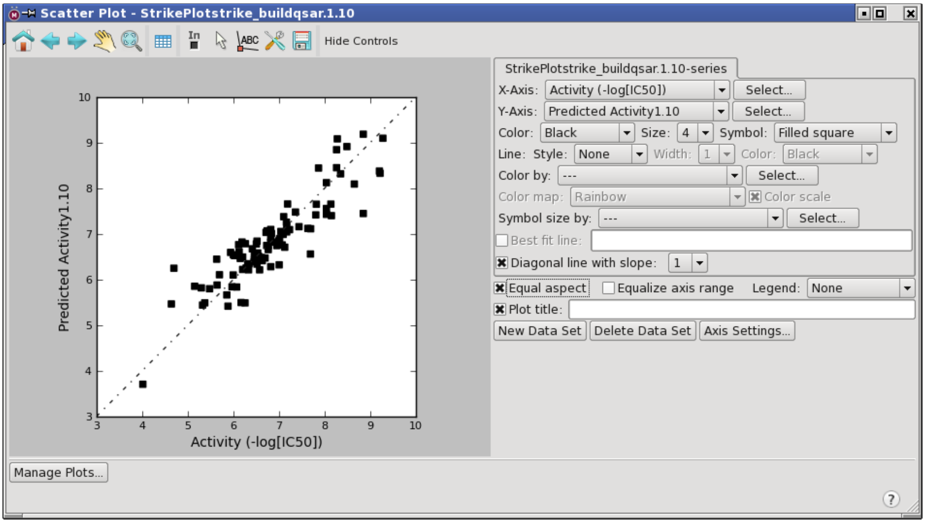
When the job is finished, 20 potential models representing the 20 factors extracted are shown in the Results section of the Build QSAR Model panel. The predicted activities for all 20 factors are added to the Project Table under the headers Predicted ActivityX.Y.

With 20 factors, the model fit to the 94 molecules in the training set should have a high R squared, a large F-statistic and a very small P-factor. The standard deviation (Std Dev) should decrease from 1 to about 10 factors and then become somewhat constant while the R squared value should increase continuously as more factors are included, leveling off at about 10 factors. Thus, much of the predictive information is contained in the first 10 factors.

Inspect the results for the training set using the 10-factor predictor:

1. Select the 10-factor predictor (#Factors equal to 10) in the Results table.

2. Generate a plot of predicted activities versus experimental activities for the training set by clicking Plot. See Figure 2.18.



StrikePlotstrike_buildqsar.1.10-series

X-Axis: Activity (-log[IC50]) Select...
Y-Axis: Predicted Activity1.10 Select...
Color: Black Size: 4 Symbol: Filled square
Line: Style: None Width: 1 Color: Black
Color by: --- Select...
Color map: Rainbow ☒ Color scale
Symbol size by: --- Select...
□ Best fit line:
☒ Diagonal line with slope: 1
☒ Equal aspect □ Equalize axis range Legend: None
☒ Plot title:
New Data Set | Delete Data Set | Axis Settings...

Figure 2.18. Plot of predicted vs. measured activity for the training set

3. When you have finished working with the plot, close the plot panel.

2.6.3 Applying the Model to the Test Set

The true test of any model is to check its predictions against a set of molecules not included during its training. The exercise performed in this section would typically be considered part of model generation and validation, but for the purposes of this tutorial, it will be used to demonstrate the model application step of the Strike workflow.

The first step is to create a test set of molecules. In this example, the test set will be those molecules in the Project Table that were not members of the training set.

1. In the Project Table, confirm that the training set is selected by examining the Population column.

   If so, skip to the next step. If for any reason the training set is no longer the selected set — for example, if a single entry has been selected instead — you can restore the selection by performing these steps:

   a. Choose Only from the Select menu of the Project Table.

      The Entry Selection panel opens.

   b. In the Properties list, select Population.

   c. Select the option Is defined (any value).

      Only the training set has a defined value (training) in the Population column.

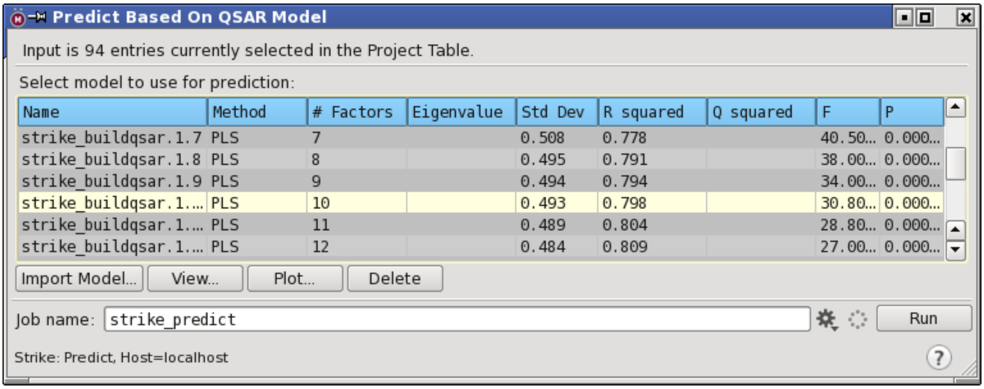
d. Click Add, then click OK.

The molecules in the training set, and only those molecules, are now selected. The molecules that were in the training set cannot be part of the test set, so you will invert the selection.

2. In the Project Table, choose Select → Invert.
3. In the Build QSAR Model panel, with the 10-factor predictor 1.10 selected, click Predict.

   The Predict based on QSAR model panel opens showing all the models.

4. Ensure that the 10-factor predictor is selected as shown in Figure 2.19 and click Run.



Predict Based On QSAR Model

Input is 94 entries currently selected in the Project Table.

Select model to use for prediction:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P
strike_buildqsar.1.7	PLS	7		0.508	0.778		40.50...	0.000...
strike_buildqsar.1.8	PLS	8		0.495	0.791		38.00...	0.000...
strike_buildqsar.1.9	PLS	9		0.494	0.794		34.00...	0.000...
strike_buildqsar.1....	PLS	10		0.493	0.798		30.80...	0.000...
strike_buildqsar.1....	PLS	11		0.489	0.804		28.80...	0.000...
strike_buildqsar.1....	PLS	12		0.484	0.809		27.00...	0.000...

Job name: strike_predict

Strike: Predict, Host=localhost

Figure 2.19. Predict based on QSAR Model panel with 10-factor predictor selected

5. When the prediction job is finished, open the Project Table to view the new series of predicted activities for the test set.

Now plot the results for the test set:

1. If the Manage Plots panel is not already open, open it by clicking the Plot button on the Project Table toolbar:

   or selecting Plot from the Table menu.

2. Click New Scatter Plot.

   A new Scatter Plot panel opens.

3. Choose Activity (-log[IC50]) from the X-Axis option menu.

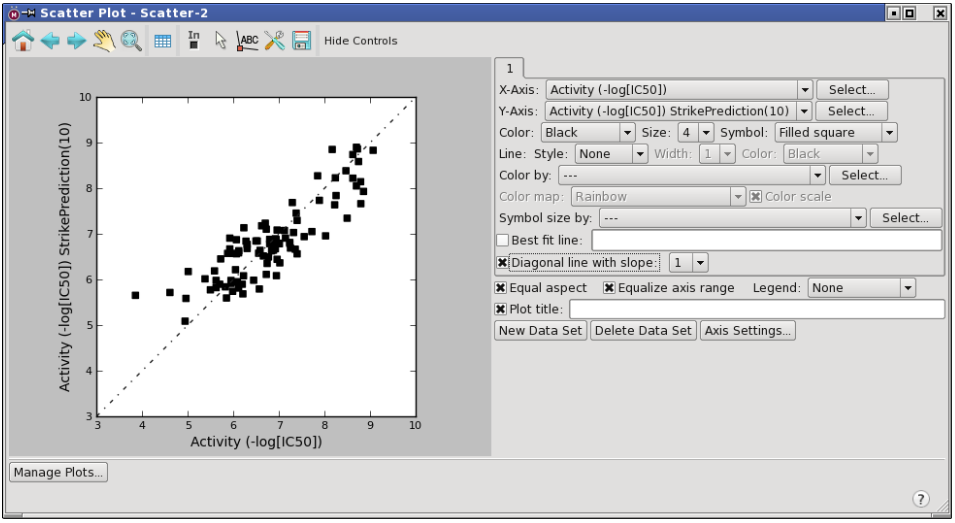
4. Choose Activity (-log[IC50]) StrikePrediction(10) from the Y-Axis option menu.

   The points are plotted in the plot area.

5. Select Equal aspect and Equalize axis range.

6. Select Diagonal line with slope.

   A line with a slope of 1 (the default) is drawn on the plot. This is the line of perfect agreement. A sample plot is shown in Figure 2.20.



X-Axis: Activity (-log[IC50])

Y-Axis: Activity (-log[IC50]) StrikePrediction(10)

Color: Black Size: 4 Symbol: Filled square

Line: Style: None Width: 1 Color: Black

Color by: ---

Color map: Rainbow ☒ Color scale

Symbol size by: ---

□ Best fit line:

☒ Diagonal line with slope: 1

☒ Equal aspect ☒ Equalize axis range Legend: None

☒ Plot title:

Figure 2.20. Plot of predicted vs. measured activity for the test set

The agreement between calculated and experimental values remains good for the test set. Individual data points of interest (outliers, high or low activity molecules) can be viewed in the Workspace by clicking the In button, then choosing data points.

Running Strike from Maestro

Before using Strike, molecular data (also referred to as “descriptor data”) should be obtained and imported into the Maestro Project Table. This data can be generated using QikProp or other Schrödinger programs. Descriptors for ligands that bind to a receptor can be generated using the Ligand & Structure-Based Descriptors panel. This panel provides an interface to Liaison, Prime, MacroModel (eMBrAcE and `ligparse`), and QikProp to generate descriptors. For more information, see the document *Ligand and Structure-Based Descriptors*. Descriptors generated by external programs or sources may be imported using standard comma-separated value (CSV) format files.

Once the data is incorporated in the Project Table, you can perform statistical analyses and create and use QSAR models using the Strike panels in Maestro.

The Strike interface in Maestro consists of five panels:

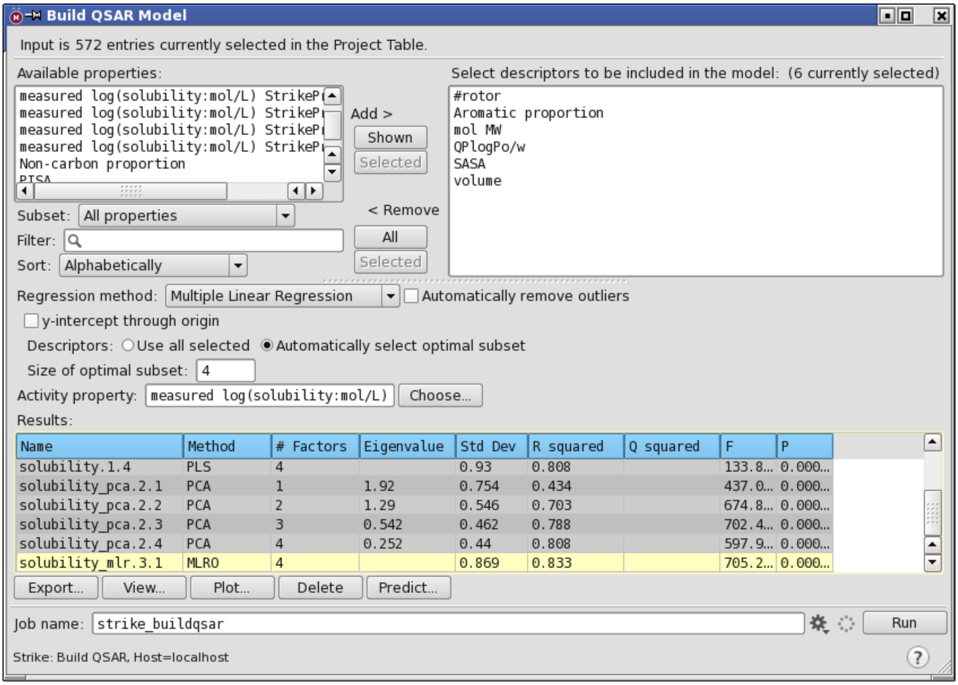
- Build QSAR Model—Generate a QSAR model using a training set of molecules selected from the Maestro Project Table, a set of independent descriptors, and a dependent descriptor chosen from those available in the data.
- Predict based on QSAR model—Import a model or select one from the table of generated models, then perform property predictions for molecules that were not part of the training set. Results can be viewed and unsatisfactory models can be deleted from the table.
- Similarity—Determine similarities in descriptor or 2D-structure space. Several distance-based descriptor similarity measures are available. Similarity in 2D-structure space is determined using an atom-pair-based approach.
- Factor Analysis—Perform a principal component analysis and display scores and loadings plots for the principal components.
- Statistics—Display univariate and bivariate statistics.

These panels can be opened in Maestro from either Applications → Strike or Tasks → QSAR → Property-Based.

3.1 Building a QSAR Model

You can use the Build QSAR Model panel to generate a QSAR model, given a training set of molecules selected from the Project Table, a set of independent descriptors, and a dependent variable for which a prediction will be made.

To open the Build QSAR Model panel, choose Applications → Strike → Build QSAR Model or Tasks → QSAR → Property-Based → Build Model. It may also be useful to open the Project Table containing your molecular data.



Input is 572 entries currently selected in the Project Table.

Available properties:

```
measured log(solubility:mol/L) StrikeP
measured log(solubility:mol/L) StrikeP
measured log(solubility:mol/L) StrikeP
measured log(solubility:mol/L) StrikeP
Non-carbon proportion
PISA
```

Select descriptors to be included in the model: (6 currently selected)

```
#rotor
Aromatic proportion
mol MW
QPlogPo/w
SASA
volume
```

Subset: All properties

Filter:

Sort: Alphabetically

Regression method: Multiple Linear Regression ☐ Automatically remove outliers

☐ y-intercept through origin

Descriptors: ○ Use all selected ● Automatically select optimal subset

Size of optimal subset: 4

Activity property: measured log(solubility:mol/L) Choose...

Results:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P
solubility.1.4	PLS	4		0.93	0.808		133.8...	0.000...
solubility_pca.2.1	PCA	1	1.92	0.754	0.434		437.0...	0.000...
solubility_pca.2.2	PCA	2	1.29	0.546	0.703		674.8...	0.000...
solubility_pca.2.3	PCA	3	0.542	0.462	0.788		702.4...	0.000...
solubility_pca.2.4	PCA	4	0.252	0.44	0.808		597.9...	0.000...
solubility_mlr.3.1	MLRO	4		0.869	0.833		705.2...	0.000...

Job name: strike_buildqsar

Strike: Build QSAR, Host=localhost

Figure 3.1. The Build QSAR Model panel

In this panel you can select the descriptors and activity property and choose a regression method. When you have finished selecting options, you can name the job in the Job name text box and click Run to run the job. For more information on starting jobs, including job settings, see Section 1.3 on page 3.

As the job starts, the job status icon on the Job toolbar rotates, indicating that a job is in progress. If you want to view the job's progress, click the job status icon (or choose Applications → Monitor Jobs). Most model-building jobs take only a few seconds to run.

Once a model has been built, 2D plots of predicted properties versus the dependent descriptor data can be created. Clicking points in a plot brings the molecule or molecules selected into the Maestro 3D Workspace for viewing and manipulation. (For more information about these and other Maestro plots, see Chapter 11 of the *Maestro User Manual*.)

From the Build QSAR Model panel you can proceed directly to the Predict based on QSAR model panel or save the generated models in the project for later use.

3.1.1 Choosing Molecules and Descriptors

The first task in building a QSAR model is to select a training set of molecules in the Project Table. You can use the tools on the Select menu of the Project Table panel for this purpose. This menu includes a Random item that allows you to make a random selection of a percentage of either all molecules or the current selection of molecules. When you have made the selection, the number of entries selected is displayed at the top of the Build QSAR Model panel.

The next step is to select a set of descriptors, which you do with the standard property selection tools in the panel. Select the descriptors in the Available properties list, and click Selected to move them to the Select descriptors to be included in the model list. You should choose an appropriate set of independent descriptors that is likely to correlate with the activity property. The number of descriptors chosen is displayed above the list. For the multiple linear regression method, you have the option of choosing the optimal subset of these descriptors of a given size.

3.1.2 Choosing a Regression Method

Strike provides three regression methods: multiple linear regression (MLR), partial least squares regression (PLS), and principal component analysis (PCA). You can choose the regression method from the Regression Method option menu. These methods have some common options, and some unique options that are displayed or activated when you select the method.

Partial Least Squares (PLS)

When this method is selected, the Maximum number of factors text box is displayed. The range for Maximum number of factors is from 1 to the number of selected descriptors. The number of molecules selected to be used in building the model must be greater than or equal to the maximum number of factors. For more information about the method, see Section 5.3.2 on page 66.

Principal Component Analysis (PCA)

When this method is selected, the Maximum number of factors text box is displayed. The range for Maximum number of factors is from 1 to the number of selected descriptors. The number of molecules selected must be greater than or equal to the number of descriptors chosen. For more information about the method, see Section 5.3.3 on page 66.

Multiple Linear Regression (MLR)

When this method is selected, the Descriptors options become available, and the Size of optimal subset text box is displayed. The number of molecules selected must be greater than or equal to the number of initial descriptors. It is recommended that the number of molecules be at least five times greater than the number of descriptors.

If you want to use all descriptors, select the Descriptors option Use all selected descriptors[1]. If you want Strike to determine the optimal subset of the selected descriptors, select Automatically select optimal subset[2], and enter a value in the Size of optimal subset text box. For more information about the method, see Section 5.3.4 on page 67.

If you want to force the regression line to pass through the origin, select y-intercept through origin.

3.1.3 Removing Outliers

Strike provides a means of automatically removing outliers, using the LOCI algorithm. To remove outlying molecules before the model is built, select Automatically remove outliers. By default, this option is not selected and outliers are not removed. For samples of 500 members or more, selecting this option greatly increases the time needed for the model-building job. See Section 5.5 on page 68 for a description of the algorithm. Note that this option does *not* remove outliers based on the model. If you wish to do so, you must run Strike from the command line with the keyword `printMLROutliers` set.

3.1.4 Choosing an Activity Property

For the dependent variable, you must select a property that serves as the activity. This can be any property, experimental or computed. To select the property, click Choose. A property selector opens, in which you can select a single property from the Project Table. This is the property that you want the model to predict. When you choose the property, it is displayed in the Activity Property text box.

3.1.5 Examining and Using Results

The Results table lists the models that have been calculated in the current Maestro project. You can select a single model to export, view, plot, delete, or use for prediction. Along with the name of each model, the table includes the regression method used, the number of PLS/PCA factors or MLR descriptors, the eigenvalue for PCA models, and standard statistics values.

[1] command-line keyword value `MLRS`
[2] command-line keyword value `MLRO`

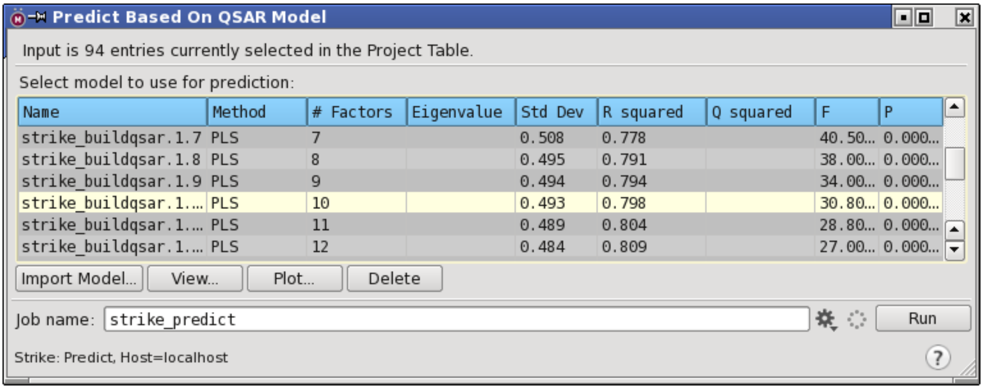
Below the Results table are action buttons that provide various functions:

- Export—Export the currently selected model to an external file.
- View—Click View to display the output file of the model-building job for the selected model, which contains all the data needed to completely describe the model. If the job fails, the View button will not display the output file but you can examine the output file *jobname*`.out` in a text editor or the Monitor panel instead.
- Plot—Generate a scatter plot of the predicted versus experimental activity for the currently selected model. This button opens the Manage Plots panel, then creates a new plot that includes the line of best fit for the model. For more information on plotting, see Chapter 11 of the *Maestro User Manual*. For an example, see Section 2.6.2 on page 33.
- Delete—Delete the currently selected model from the table.
- Predict—Open the Predict Based On QSAR Model panel with the currently selected model chosen, to make a prediction of a property with some other set of molecules.

3.2 Predicting Properties Based on a QSAR Model

The Predict Based On QSAR Model panel allows you to make predictions of molecular properties based on a QSAR or QSPR model. Models to be used for property predictions can be imported from another project or generated in the current project. You must have data for all independent descriptors used in the model.

To open the Predict Based On QSAR Model panel, choose Applications → Strike → Predict or Tasks → QSAR → Property-Based → Predict. The Predict Based On QSAR Model panel can also be opened from the Build QSAR Model panel once one or more models have been generated, using the Predict button in the lower portion of the panel.



Input is 94 entries currently selected in the Project Table.

Select model to use for prediction:

Name	Method	# Factors	Eigenvalue	Std Dev	R squared	Q squared	F	P
strike_buildqsar.1.7	PLS	7		0.508	0.778		40.50...	0.000...
strike_buildqsar.1.8	PLS	8		0.495	0.791		38.00...	0.000...
strike_buildqsar.1.9	PLS	9		0.494	0.794		34.00...	0.000...
strike_buildqsar.1....	PLS	10		0.493	0.798		30.80...	0.000...
strike_buildqsar.1....	PLS	11		0.489	0.804		28.80...	0.000...
strike_buildqsar.1....	PLS	12		0.484	0.809		27.00...	0.000...

Job name: strike_predict

Strike: Predict, Host=localhost

Figure 3.2. The Predict based on QSAR Model panel.

If you want to import a model into the table, click Import Model and navigate to the model (which has the extension `.model`). For example, you can import a model that was exported from the Build QSAR Model panel in an earlier Strike session.

To make predictions:

1. Select the desired molecules in the Project Table.

   The number of entries selected is displayed at the top of the panel.

2. Select the model to use for the prediction from the table.

   This table contains information about each model in the current project. If you want to view complete information about the model, click View. The output file from the model generation is displayed in a separate panel.

3. Name the job and click Run.

   When the job finishes, the predictions are imported into the Project Table and are displayed in the table.

To delete a model from the table, select it and click Delete.

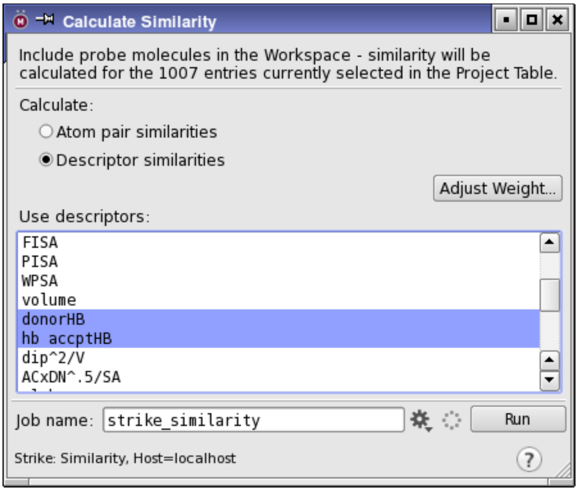
To plot the results for a model, click Plot. This button opens the Manage Plots panel, then creates a new, empty plot. You can then select the predicted and experimental properties to plot on the *x* and *y* axes, and display a linear regression line. For more information on plotting, see Chapter 11 of the *Maestro User Manual*. For an example, see Section 2.6.3 on page 35.

3.3 Calculating Similarities

The Calculate Similarity panel can be used to determine similarities in descriptor or 2D-structure space. Several distance-based descriptor similarity measures are available. Similarity in 2D-structure space is determined using an atom-pair-based approach.

Similarity, either atom-pair-based or descriptor-based, is calculated with respect to probe molecules. You select the probe molecules by including them in the Workspace. At least one molecule must be included in the Workspace, and at least one entry must be selected in the Project Table, before similarity calculations can proceed. For descriptor similarities, the probe molecules must also be selected in the Project Table.

To open the Calculate similarity panel, choose Applications → Strike → Similarity or Tasks → QSAR → Property-Based → Similarity.



Include probe molecules in the Workspace - similarity will be calculated for the 1007 entries currently selected in the Project Table.

Calculate:

○ Atom pair similarities

● Descriptor similarities

Use descriptors:

FISA
PISA
WPSA
volume
donorHB
hb accptHB
dip^2/V
ACxDN^.5/SA

Job name: strike_similarity

Strike: Similarity, Host=localhost

Figure 3.3. The Calculate Similarity panel with descriptor similarities specified.

When you open the panel, the number of selected entries is displayed at the top of the panel. There are two options for the type of similarity to be calculated:

- Atom pair similarities—A similarity property will be created for each selected entry in the Project Table, based on the similarity of the atoms in the structure.
- Descriptor similarities—Similarity in terms of properties will be calculated for the selected Project Table entries in terms of the properties chosen from the Use Descriptors list. When you choose this option, the Use Descriptors list becomes available. and you can choose the properties you want to include in the similarity calculation. If you want to adjust the weights of the chosen descriptors in the evaluation of the similarity, click Adjust Weight and set the desired weights in the Adjust Weight dialog box. The default weight is 1.0 for all descriptors.

3.4 Principal Component Factor Analysis

The Factor Analysis panel provides tools for performing principal component analyses of various sets of descriptors taken from a set of entries that is selected in the Project Table. Once an analysis is done, you can plot the scores and the loadings for selected pairs of principal components, or make use of the principal component decomposition for further model generation. For background on principal component analysis, see Section 5.3.3 on page 66.

The scores plot shows clustering of molecules from plotting one set of principal components against another. Each point on the plot represents a molecule. Molecules with similar data are found together. Often it is possible to visually cluster molecules on the basis of the scores plot.

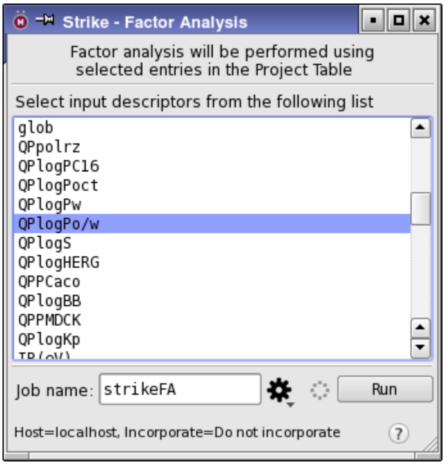
The loadings plot (also known as a weights plot) shows the influence of individual variables (descriptors) on the principal components. Each point on the plot represents a variable from the input data. Larger values for a given point indicates it has more weight in a given principal component. Often it is possible to visually cluster the effect of variables on the principal components.

By looking at a score and loading plot side-by-side it is possible to identify relationships between molecules and variables. For instance, if a number of molecules cluster with large values of the first principal component (PC1) in the scores plot, you can use the loadings plot to determine which variables have the most weight in PC1. These molecules will then cluster nicely on the basis of those variables.

To generate the principal components:

1. Select the entries in the Project Table for which you want to perform the analysis.
2. Choose Factor Analysis from the Strike submenu of the Applications menu.

   The Factor Analysis panel opens. The descriptor list is populated with the properties available in the Project Table. The visualization tools are hidden until an analysis job is run.



Factor analysis will be performed using selected entries in the Project Table

Select input descriptors from the following list

```
glob
QPpolrz
QPlogPC16
QPlogPoct
QPlogPw
QPlogPo/w
QPlogS
QPlogHERG
QPPCaco
QPlogBB
QPPMDCK
QPlogKp
```

Job name: strikeFA

Host=localhost, Incorporate=Do not incorporate

Figure 3.4. The Factor Analysis panel before analysis

3. Select a set of descriptors from the descriptor list.

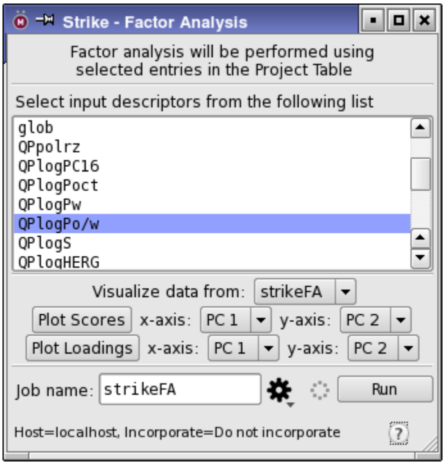
   You can use shift-click and control-click in the usual way to select multiple list items.

4. Name the job in the Job name text box.

   It is a good idea to choose a name that has some relation to the set of descriptors selected, since the name is displayed in the Visualize data from option menu once the first analysis job finishes.

5. Click Generate Factors.

   After a short time, the job finishes, and the visualization tools are displayed in the lower part of the panel.



Strike - Factor Analysis

Factor analysis will be performed using selected entries in the Project Table

Select input descriptors from the following list

```
glob
QPpolrz
QPlogPC16
QPlogPoct
QPlogPw
QPlogPo/w
QPlogS
QPlogHERG
```

Visualize data from: strikeFA

Plot Scores x-axis: PC 1 y-axis: PC 2

Plot Loadings x-axis: PC 1 y-axis: PC 2

Job name: strikeFA

Run

Host=localhost, Incorporate=Do not incorporate

Figure 3.5. The Factor Analysis panel after analysis

6. Repeat Step 3 through Step 5 for each set of descriptors that you want to analyze.

To display the results of an analysis:

1. Select the job from the Visualize data from option menu.

2. Select the principal components for the *x* and *y* axes for the desired plot types.

   By default, component 1 and component 2 are selected.

3. Click the Plot Scores button.

   The Manage Plots panel opens, and a new scatter plot with the selected data plotted is displayed. You do not need to close this panel to display another plot. For more information on these panels and plotting, see Chapter 11 of the *Maestro User Manual*.

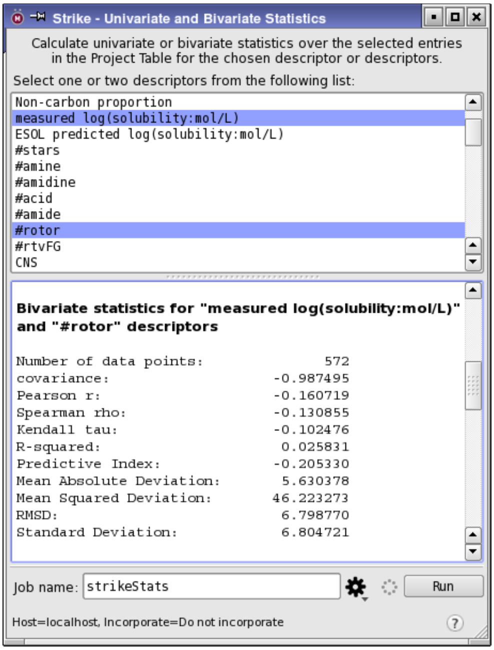
4. Click the Plot Loadings button.

   A panel opens with the loadings plotted and labeled.

3.5 Calculating Univariate and Bivariate Statistics

The Univariate and Bivariate Statistics panel enables you to calculate univariate statistics or bivariate statistics over the entries that are selected in the Project Table. To display univariate statistics for a particular descriptor, select the descriptor from the list of descriptors, then click Start. To display univariate and bivariate statistics for a particular descriptor, select two descriptors from the list of descriptors (click the first, control-click the second), then click Start. The results are displayed in the Results text area. The statistics given are described in Section 5.1 on page 59 and Section 5.2 on page 62.

This panel obtains its descriptor information from the Project Table. If you subsequently add or remove properties (descriptors) from the Project Table, you need to close the panel and then reopen it to capture the new information.



Calculate univariate or bivariate statistics over the selected entries in the Project Table for the chosen descriptor or descriptors.

Select one or two descriptors from the following list:

```
Non-carbon proportion
measured log(solubility:mol/L)
ESOL predicted log(solubility:mol/L)
#stars
#amine
#amidine
#acid
#amide
#rotor
#rtvFG
CNS
```

```
Bivariate statistics for "measured log(solubility:mol/L)"
and "#rotor" descriptors

Number of data points:              572
covariance:                   -0.987495
Pearson r:                    -0.160719
Spearman rho:                 -0.130855
Kendall tau:                  -0.102476
R-squared:                     0.025831
Predictive Index:             -0.205330
Mean Absolute Deviation:       5.630378
Mean Squared Deviation:       46.223273
RMSD:                          6.798770
Standard Deviation:            6.804721
```

Job name: strikeStats

Host=localhost, Incorporate=Do not incorporate

Figure 3.6. The Univariate and Bivariate Statistics panel with bivariate statistics

Running Strike from the Command Line

Strike can also be run using the `strike` command. This chapter lists keywords for the input file and gives two examples of command blocks that can be used in input files.

4.1 Usage Summary

`$SCHRODINGER/strike` [*options*] *inputfile*

inputfile	The `strike` input script file containing the commands to be performed.
`-HOST` *host*	Run job on a remote host.
`-LOCAL`	Run the job in the current directory, rather than in a temporary scratch directory.
`-WAIT`	Do not return until the job completes.
`-NICE`	Run the job at reduced priority.
`-HELP`	Print this message and exit.

4.2 Input File Examples

The `strike` input script consists of blocks of commands, each consisting of a series of *keyword=value* pairs and terminated by a line beginning with #. The termination line beginning with # is mandatory, even if there is only one block of data in the input script. Each command block is then executed sequentially. Comment lines must begin with `!!`. Two examples of command blocks are given below.

```
!! Section to train a model
dataFile=input_files/strike_mlro_fit.csv
runMode=train
model=MLRO
activityLabel=activity
numOptDescript = 4
# End of Section 1

!! Section to use a previously created model
runMode=test
dataFile=input_files/strike_pls_fit.csv
modelFile=input_files/strike_pls_fit.model
# End of Section 2
```

4.3 Input File Keywords

The following *keyword=value* pairs are accepted input for `strike`. Boolean values must be expressed as `yes` or `no`.

4.3.1 Mode Selection

All Strike jobs must use the `runMode` keyword with one of these values.

Value	Description
`train`	Generate a QSAR model.
`test`	Predict properties using a QSAR model.
`simil`	Run a descriptor similarity calculation.
`apsimil`	Run an atom-pair (2D structure space) similarity calculation.
`stats`	Generate statistics.
`factorGen`	Extract factors from PCA model.
`factorRed`	Reduce data using extracted PCA factors.
`factorExp`	Expand reduced data using extracted PCA factors.

4.3.2 File Specification Commands

Keyword	Value	Description/Relevant Job Types
`dataFile`	*datafilename*	Keyword required for all jobs except atom-pair similarity (`apsimil`). File must be in CSV or Maestro format.
`outputFile`	*outputfilename*	Default is *jobname*`.out`. All jobs.
`modelFile`	*modelfilename*	Default is *jobname*`.model`. File containing QSAR model. QSAR jobs (`train` and `test`) and factor reduction jobs (`factorGen`, `factorRed`, `factorExp`).
`csvFile`	*csvoutfilename*	Default is *jobname*`.csv`. Output file containing all data used and generated in current command block. All jobs except `apsimil`.
`plotFile`	*qsaroutfilename*	File containing output from `train` with predicted vs. dependent data. QSAR jobs.
`apPredFile`	*filename*	File of molecules whose similarity to the probes are to be determined. `apsimil` jobs.
`apActivesFile`	*activesfilename*	File of probe molecules. `apsimil` jobs.

Keyword	Value	Description/Relevant Job Types
`apInactivesFile`	*inactivesfilename*	File of decoy molecules. `apsimil` jobs.
`apWeightsFile`	*weightsfilename*	Weights file. When generated, default is *jobname*`.csv`. `apsimil` jobs.
`descriptorWeightFile`	*weightsfilename*	Weights file. When generated, default is *jobname*`-weights.tab`. `simil` jobs.

4.3.3 Alternative Naming Convention Commands

Keyword	Value	Description/Relevant Job Types
`modelTitle`	*modelname*	Alternative title for QSAR model generation. Otherwise defaults to *jobname*.
`baseName`	*basename*	Alternative basename for all jobs. All output files will be *basename*`.*`, and `modelTitle` will default to *basename*.

4.3.4 Commands for Reading/Writing CSV Files

Keyword	Value	Description/Relevant Job Types
`delim`	*string*	Delimiter character for reading `.csv` file. All jobs except `apsimil`.
`includeColumns`	*X:Y, Z* column numbers or column labels	X, Y, Z can be numbers or labels (headers). Use colon for ranges, For example, `includeColumns=2:6,9,15` includes columns 2-6, 9, and 15 from the input file. All jobs except `apsimil`.
`excludeColumns`	*X:Y, Z* column numbers or column labels	X, Y, Z can be numbers or labels (e.g., labels: `excludeColumns=IP(ev):QPlogKhsa` Properties in `.csv` file between IP(ev) and QPlogKhsa, inclusive, will not be used). All jobs except `apsimil`.
`includeRows`	*X:Y, Z* row numbers or row labels	Include molecules (rows) specified. All jobs except `apsimil`.
`excludeRows`	*X:Y, Z* row numbers or row labels	Exclude molecules (rows) specified (e.g., `excludeRows=25` excludes molecule 25). All jobs except `apsimil`.
`activityColumn`	*integer*	Identify dependent property by column number. Build QSAR model jobs.
`activityLabel`	*label*	Identify dependent property by column label. Build QSAR model jobs.

Keyword	Value	Description/Relevant Job Types
`rowHeaderColumn`	*integer*	Set the column in the `.csv` file that contains row labels, by column numbering beginning at 1. For all jobs if needed.
`rowHeaderLabel`	*label*	Set the column in the `.csv` file that contains row labels by column label. For all jobs if needed.
`descriptorWeightRow`	*integer*	Set by **number** the row that contains the weight for each descriptor. For descriptor similarity jobs.
`descriptorWeightLabel`	*label*	Set by **label** the row that contains the weight for each descriptor. For descriptor similarity jobs.

4.3.5 Commands for Build QSAR Model (train) Jobs

Keyword	Value	Description/Relevant Job Types

`model`	`PLS`
	`PCA`
	`MLRS`
	`MLRO`
	`NNET`
		Specify type of regression to be employed.

`autoScale`	`yes` `no`	Set whether data is to be converted to a common scale. Default is `yes`.
`maxFactors`	*integer*	Maximum number of factors to return. PLS, PCA.
`numOptDescript`	*integer*	Number of descriptors to be retained, determined by optimization. MLRO.
`removeOutliers`	`no` `yes`	Run prior to importing data into model building. Compare relative densities in descriptor space for included molecules to predict outliers. Recommended for sample size < 500 only. Default is `no`.
`printMLROutliers`	`no` `yes`	Set to `yes` to output possible outliers with respect to the MLR model. Default is `no`. MLRS, MLRO.
`MLROutlierCutoff`	*integer*	Integer from 0 to 5 giving the number of MLR outlier tests that need to fail before a data point is identified as a possible model outlier. Default is 4. MLRS, MLRO.
`lgoPercent`	*double*	For leave-group-out (LGO) validation, percentage of fitting set to use as test set for each regression. Default is 5.0%
`lgoCycles`	*integer*	Number of cycles of LGO validation to perform. Default is 10.
`RandCycles`	*integer*	Number of randomization cycles to perform. Default is 10 times the number of independent descriptors. MLRS, MLRO, PLS, and PCA.

Keyword	Value	Description/Relevant Job Types
supYintercept	no yes	Suppress inclusion of the *y* intercept as a dependent variable for regression generation. The default is no, which means that the *y* intercept is included. MLRS, MLRO.
nnetNumUnitsInHiddenLayer	*integer*	Number of units in the hidden layer. NNET.
nnetCrossValPer	*integer*	Percent of input data to be kept in the cross validation set. Default is 5%. NNET.
nnetExtValPer	*integer*	Percent of input data to be kept in the external validation set. Default is 10%. NNET.
nnetNumTrainCycles	*integer*	Number of training cycles for each neural network. Default is 200. NNET.
nnetNumNetworks	*integer*	Number of neural networks to train of which the best nnetumNetworksEnsem will be selected to create an ensemble neural network that is presented to the user. Default is 20. NNET.
nnetNumNetworksEnsem	*integer*	Number of the best neural networks to use in generating an ensemble neural network that is presented to the user. Default is 5. NNET.

4.3.6 Commands for Descriptor Similarity (simil) Jobs

Keyword	Value	Description
probes	*X:Y, Z*	Specify the probe molecules to use from the input file. *X, Y, Z* can be the molecule row indexes from the input file or, if rowHeaderColumn is defined, molecule titles.
simil	euclidean	Similarity

4.3.7 Commands for Atom-Pair Similarity (apsimil) Jobs

Keyword	Value	Description
apPredFormat	mae sdf	Format of apPredFile.
apActivesFormat	mae sdf	Format of apActivesFile.
apInactivesFormat	mae sdf	Format of apInactivesFile.
inactivePercent	*nn.n*	Percentage of inactives, e.g., for 99%: inactivePercent=99.0

Keyword	Value	Description
readWeights	yes no	Read weights from apWeightsFile.
genWeights	yes no	Generate weights in apWeightsFile.
normalize	range z-score none	Specify normalization approach. Default (range) normalizes data to 0.0 - 1.0 scale; required for Tanimoto coefficient calculation. Specify z-score to scale data in standard deviation units. Specify none to perform no normalization.

4.3.8 Commands for Factor Reduction Jobs

Keyword	Value	Description
facRedAuto	yes no	Determines if the factors are to be generated using scaled (yes) or unscaled (no) input data.
facRedNumFactors	*n*	Number of factors to generate. Range is from 0 to the number of input data columns.

4.3.9 Other Commands

Keyword	Value	Description/Relevant Job Types
enrich	Euclidean Euclidean_sq Tanimoto Manhattan	Calculate enrichment factors for extracting probe molecules from the entire data set, using the specified similarity measure. For simil and apsimil jobs.
stats	*label*	Calculate univariate statistics for the descriptor *label*. Any job.
	label1, *label2*	Calculate bivariate statistics for the descriptors *label1* and *label2*. Any job.

4.3.10 Keyword Requirements for Various Job Types

Table 4.1. Minimum Strike Keywords by Job Type

Job Type	Keywords Required	Comments
Build QSAR model	Keywords depend on chosen model.	Column containing dependent data can be specified by column number (`activityColumn`) *or* by column label (`activityLabel`).

Build QSAR model Partial Least Squares	`runMode=train`
	`model=PLS`
	`dataFile`
	`activityColumn` *or*
	`activityLabel`
	`maxFactors`	

Build QSAR model Principal Component Analysis	`runMode=train`
	`model=PCA`
	`dataFile`
	`activityColumn` *or*
	`activityLabel`
	`maxFactors`	

Build QSAR model Multiple Linear Regression Analysis	`runMode=train`
	`model=MLRS`
	`dataFile`
	`activityColumn` *or*
	`activityLabel`	

Build QSAR model MLRS with optimum number of descriptors	`runMode=train`
	`model=MLRO`
	`dataFile`
	`activityColumn` *or*
	`activityLabel`
	`numOptDescript`	

Build QSAR model Neural Network	`runMode=train`
	`model=NNET`
	`dataFile`
	`activityColumn` *or*
	`activityLabel`
	`nnetNumUnitsInHiddenLayer`	

Validation or prediction using any model	`runMode=test`
	`dataFile`
	`modelFile`
		Model is entirely specified in `modelFile`.

Table 4.1. Minimum Strike Keywords by Job Type (Continued)

Job Type	Keywords Required	Comments

Descriptor similarity calculation	`runMode=simil`
	`dataFile`
	`probes`
	(`rowHeaderColumn` *or* `rowHeaderLabel`)
		One of the keywords in parentheses needed to specify probe molecules if probes not specified by molecule number.

Atom-pair similarity calculation.
No weights
	`runMode=apsimil`
	`apActivesFile`
	`apActivesFormat`
	`apPredFile`
	`apPredFormat`	

Atom-pair similarity. Weights are generated and used in same command block	`runMode=apsimil`
	`apActivesFile`
	`apActivesFormat`
	`apPredFile`
	`apPredFormat`
	`apInactivesFile`
	`apInactivesFormat`
	`inactivePercent`
	`genWeights`	

Atom-pair similarity using weights that were generated previously	`runMode=apsimil`
	`apActivesFile`
	`apActivesFormat`
	`apPredFile`
	`apPredFormat`
	`readWeights`
	`apWeightsFile`	

PCA factor generation	`model=PCA`
	`runMode=factorGen`
	`facRedNumFactors`
	`facRedAuto=yes`
	`dataFile`
		Also generates reduced data set for the input.

Table 4.1. Minimum Strike Keywords by Job Type (Continued)

Job Type	Keywords Required	Comments

PCA factor reduction	`model=PCA`
	`runMode=factorRed`
	`facRedNumFactors`
	`facRedAuto=yes`
	`dataFile`
	`modelFile`
		`modelFile` must be output of a factor generation job. `dataFile` must contain the same descriptors as used in the factor generation, but need not contain data for the same structures.

PCA factor expansion	`model=PCA`
	`runMode=factorExp`
	`facRedNumFactors`
	`facRedAuto=yes`
	`dataFile`
	`modelFile`
		`modelFile` must be output of a factor generation job. `dataFile` must be a file with reduced factors from a factor generation or reduction job.

Statistical Definitions and Methods

This chapter defines statistical quantities, algorithms, and regression methods used in Strike.

5.1 Univariate Statistics

This section defines some symbols, definitions, and equations relating to the statistics of a single variable.

5.1.1 Symbols

N

Number of data points (observations) in a sample. There is no hard limit on sample size (number of molecules) in Strike, but for large samples (millions of molecules) practical issues such as system memory limitations may apply.

x_i —value of data point i in a sample of variable x

$\overline{x}$ —mean of variable x

5.1.2 Mean, Median, and Mode

These statistics describe the “central tendency” of a variable.

Mean

The *mean* of variable x is defined by Equation (1).

$$\bar{x} = \sum_{i}^{N} x_i / N \tag{1}$$

Median

- For an even number of data points, the *median* is the mean of the middle-most two values in the ordered sample.
- For an odd number of data points, the *median* is the middle-most value in the ordered sample.

One-half of the ranked values for a variable will lie above and one-half below the value of the median.

Mode

The *mode* is the value of a variable that occurs with the greatest frequency in a sample. If more than one value shares the highest frequency of occurrence, the term “mode” is not applicable.

5.1.3 Variance and Deviation

The statistical quantities defined in this section are measures of the spread of values in a sample about the mean.

Variance

The *variance* is defined as:

$$\sigma^2 = \sum_i^N (x_i - \bar{x})^2 / (N - 1) \tag{2}$$

If $\bar{x}$ is known or if one is examining a complete population, the *N*–1 term reverts to *N*. Strike calculates all variances assuming a sample, i.e. using *N*–1, which is suitable for the vast majority of cases. The *mean squared deviation*, also defined in this section, reports the variance for a population.

Standard Deviation

The *standard deviation* is the square root of the variance, defined in Equation (2).

If $\bar{x}$ is known or if one is examining a complete population, the *N*–1 term reverts to *N*. Strike calculates all standard deviations assuming a sample, i.e. using *N*–1, which is suitable for the vast majority of cases. The *root mean squared deviation*, also defined in this section, reports the standard deviation for a population.

The standard deviation measures the spread of values about the mean. If the sample exhibits a normal distribution, then 68.3% of values will lie within 1σ from the mean, 95.4% of values will lie within 2σ of the mean, and 99.7% of values will lie within 3σ of the mean.

Mean Absolute Deviation

$$\text{MAD} = \sum_i^N |x_i - \bar{x}| / (N - 1) \tag{3}$$

Mean Squared Deviation

$$\mathrm{MSD} = \sum_{i}^{N} (x_i - \bar{x})^2 / N \tag{4}$$

If $\bar{x}$ is known or if one is examining a complete population, the *mean squared deviation* reports the variance for the complete population.

Root Mean Squared Deviation

$$\mathrm{RMSD} = \sqrt{\sum_{i}^{N} (x_i - \bar{x})^2 / N} \tag{5}$$

If $\bar{x}$ is known or if one is examining a complete population, the *root mean squared deviation* reports the standard deviation for the complete population.

5.1.4 Skewness and Kurtosis

These statistics are measures of the extent to which a sample differs from a normal distribution. Both have a value of zero for a normal distribution.

Skewness

$$\mu = \frac{\sum_{i}^{N} (x_i - \bar{x})^3 / N}{\mathrm{RMSD}^3} \tag{6}$$

Strike calculates the Fisher Skewness for a sample. Normal distributions have a skewness of zero as they are perfectly symmetrical about the mean. A positive value of the skewness indicates, relative to a normal distribution, that the sample being examined is asymmetric and skews towards larger values, i.e. has a larger tail to the right. A negative value of the skewness indicates, relative to a normal distribution, that the sample being examined skews toward smaller values, i.e. has a larger tail to the left. A significant skewness value indicates that the sample does not have a normal distribution.

Kurtosis

$$\text{kurtosis} = \frac{\sum_i (x_i - \bar{x})^4 / N}{\text{RMSD}^4} - 3 \qquad (7)$$

Strike calculates the excess kurtosis using the formula of Snedecor and Cochran. The kurtosis for a normal distribution is three. By subtracting three, Strike reports the excess kurtosis where a normal distribution has a kurtosis of zero. A positive kurtosis indicates the distribution is strongly peaked about the mean while a negative kurtosis indicates the distribution is flat. A significant kurtosis value indicates the sample does not have a normal distribution.

5.2 Bivariate Statistics: Covariance and Correlation

The statistics in this section describe the relationship between two variables in terms of covariance and correlation. These statistics are also applied to pairs of variables in models with multiple independent variables.

Correlation coefficient

See *Pearson r* or *r-squared*

Correlation matrix

The *correlation matrix* generates the Pearson *r* values for the half matrix of all pairs of selected variables.

Covariance

$$\text{cov}(x, y) = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{N - 1} \qquad (8)$$

The covariance measures the extent to which two variables vary together. A positive value of the covariance indicates that larger than average values of one variable tend to be paired with larger than average values of the second variable. A negative value of the covariance indicates that larger than average values of one variable tend to be paired with smaller than average values of the second variable. A zero covariance indicates the two variables vary independently from one another. The covariance is dependent on the magnitude of the variables involved and is most useful when the variables have the same magnitude.

For a scatter plot of *x* and *y* the covariance measures how close the scatter is to a line. A negative covariance indicates a downward sloping line to the right, a positive covariance indicating an upward sloping line to the right, and a zero covariance indicating the best line lies along the horizontal axis.

Pearson r

$$r = \frac{\mathrm{cov}(x, y)}{\sigma_x \sigma_y} \tag{9}$$

The *Pearson r* is a correlation coefficient that determines the extent that two variables are proportional to one another. In other words, the Pearson *r* provides a measure of linear association between variables. Calculated Pearson *r* values lie on a scale from -1.0 to +1.0 with negative values indicating the best least-squares line between variables *x* and *y* is downward sloping to the right and positive values indicating the best line is upward sloping to the right. A value of zero indicates no correlation between the two variables. The Pearson *r* is independent of the magnitude of variables (unlike the covariance). Note that *R* is sometimes used instead of *r*.

R-squared

In Strike, *r-squared* is the square of the Pearson *r* correlation coefficient. Its value ranges from 0.0 to 1.0 with a value of zero indicating the two variables have no correlation and a value of one indicating the variables are perfectly correlated. Like the Pearson *r*, the *r*-squared is independent of the magnitude of the two variables.

Spearman rho

The *Spearman rho* is a rank-order correlation coefficient. It measures the proportion of variability accounted for between two variables using the ranking of the data rather than the data values themselves. The Spearman rho is interpreted in an identical fashion to the Pearson r statistic.

Ties in ranking (data points with the same value) are given the mean rank of the tied observations. i.e. if three points are identified as having equal values with ranks of 5, 6, 7, and 8 in the sample, the average rank assigned to all four would be 6.5. In the definitions below, rank(x_i) is the rank of the point x_i, ties(x_i) is the number of times the value x_i occurs, and in $\varepsilon(x)$ the sum is over the number of tied values.

$$D = \sum_{i}^{N} [\mathrm{rank}(x_i) - \mathrm{rank}(y_i)]^2 \tag{9a}$$

$$\varepsilon(x) = \sum_i \mathrm{ties}(x_i)^3 - \mathrm{ties}(x_i) \tag{9b}$$

$$\rho = \frac{1 - [6D + (\varepsilon(x) + \varepsilon(y))/2]/(N^3 - N)}{\sqrt{1 - \varepsilon(x)/(N^3 - N)}\,\sqrt{1 - \varepsilon(y)/(N^3 - N)}} \tag{9c}$$

Kendall tau

The *Kendall tau* is a rank-order correlation coefficient. It measures the proportion of variability accounted for between two variables using the ranking of the data rather than the data values themselves. The Kendall tau is interpreted in an identical fashion to the Pearson r statistic. It is defined in Equation (10), where:

P is the number of concordant pairs of ranks

Q is the number of discordant pairs of ranks

Y_0 is the number of ties in the ranks of two x's

X_0 is the number of ties in the ranks of two y's

$$\tau_b = \frac{P - Q}{\sqrt{P + Q + X_0}\sqrt{P + Q + Y_0}} \tag{10}$$

To calculate the Kendall tau the half matrix of data pairs is analyzed, i.e. (x_i,y_i) and (x_j,y_j) are compared for all i and j pairs. Each pair that shows the same rank order between the two data sets is counted as concordant. Each pair that shows a different rank order between the two data sets is counted as discordant. The rank order can be determined by the following expression:

$$\begin{array}{rl} (\mathrm{rank}(x_i) - \mathrm{rank}(x_j))(\mathrm{rank}(y_i) - \mathrm{rank}(y_j)) > 0 & \text{concordant} \\ < 0 & \text{discordant} \\ = 0 & \text{tie in } x \text{ or } y \end{array} \tag{11}$$

Ties are counted in the Y_0 and X_0 variables.

Predictive index

This index is a predictor of rank ordering [1], with values from +1 to –1. A value of +1 indicates perfect prediction of rank; a value of -1 indicates predictions that are completely wrong, and a value of 0 indicates random predictions.

$$\mathrm{PI} = \left(\sum_{j>i} w_{ij} c_{ij}\right) \Big/ \left(\sum_{j>i} w_{ij}\right) \tag{12}$$

where:

$$w_{ij} = \mathrm{abs}(E_i - E_j)$$

$$c_{ij} = \begin{cases} 1, & (E_i - E_j)/(P_i - P_j) > 0 \\ -1, & (E_i - E_j)/(P_i - P_j) < 0 \\ 0, & (P_i - P_j) = 0 \end{cases}$$

and E_i are the experimental values, P_i are the predictions.

5.3 Model-Building Methods

This section defines terms and methods used in building QSAR/QSPR models. It briefly introduces the three regression methods available for model-building in Strike: partial least squares, principal component analysis, and multiple linear regression.

5.3.1 Independent and Dependent Variables

Dependent variable

The *dependent variable* (or *response variable*) is the variable that is being fitted to in a regression model. It is referred to as dependent as it is assumed that its values are dependent on the values of independent variables that will be used to generate the predictive model. In Strike, this variable is also referred to as the dependent descriptor or the activity property.

Independent variables

The *independent variables* are the variables that are being used to fit a regression to a dependent variable in partial least squares, principal component analysis, or multiple linear regression. They are referred to as independent as their values are assumed not to depend on the values of the dependent variable. In Strike, the term *independent descriptors* is often used.

5.3.2 Partial Least Squares

The *partial least squares* (PLS) method generates linear equations that describe the relationship between a number of factors derived from a set of independent descriptors and a dependent descriptor. The PLS procedure works by extracting successive linear combinations of the factors (also called components or latent vectors), which explain independent and dependent variations. In particular, the method of partial least squares balances these objectives, seeking factors that explain both response variation and predictor variation.

Partial least squares is particularly valuable because it can be applied in cases where the number of independent descriptors is greater than the number of molecules.

Partial least squares is similar to *principal component analysis*, but the goals of the two methods in extracting factors differ. In PLS one is concerned with the variance in both the dependent and independent descriptors, while in PCA one is trying to explain the maximum variance possible in only the dependent descriptors.

While it is possible to use PLS to generate models to fit multiple dependent variables, Strike is limited to fitting a single dependent variable.

5.3.3 Principal Component Analysis

Principal component analysis (PCA) transforms a number of independent variables into a number of uncorrelated factors that explain the variance of the dependent variable. The first factor accounts for as much of the variability in the data as possible, and each succeeding factor accounts for as much of the remaining variability as possible. The eigenvalues of the covariance matrix from PCA indicate the portion of the total variance accounted for by each factor, where the total variance is generally defined as equal to the number of independent variables.

Principal component analysis can be applied in cases where the number of independent descriptors is greater than the number of molecules.

Principal component analysis is similar to partial least squares, but it focuses on explaining the maximum variance possible in only the dependent descriptors, while PLS considers the variance in both the dependent and independent descriptors.

While it is possible to use PCA to generate models to fit multiple dependent variables, Strike is limited to fitting a single dependent variable.

5.3.4 Multiple Linear Regression

Multiple linear regression (MLR) generates linear equations that describe the relationship between a set of independent descriptors and a dependent descriptor. Strike may only be used to fit a single dependent descriptor. As used in Strike, MLR fits a straight line to the dependent descriptor using the following linear relationship:

$$P_j = \sum_i c_i \chi_{ij} + c_0 \tag{13}$$

In the above equation, P_j is the property or activity that is to be predicted for each molecule j, the c_i values are the regression coefficients, χ_{ij} is the ith independent property for molecule j, and c_0 is a constant. Values of the coefficients and c_0 are fitted to give P_j values that reproduce the dependent value for the jth molecule.

In general, when fitting data using MLR it is advisable to use a data set with at least five times as many molecules as there are independent descriptors.

5.4 Model Analysis and Validation

The statistics in this section are used to analyze and validate QSAR/QSPR models built using regression techniques.

Cross-validation or leave-*n*-out validation

Cross-validation tests how dependent a generated regression is on the samples used to generate the regression. In leave-group-out (LGO) or leave-*n*-out cross-validation, the original set of samples is divided into *k* randomly chosen subsets, each consisting of *n* data points. Then *k* regressions are generated, each time omitting a different subset. Each of these regressions is then used to predict the expected dependent values for the omitted subset. In *k* regressions all molecules will have had their dependent value predicted, and the r-squared from comparing the predicted dependent values against the true dependent values is referred to as the *q-squared*. To reduce the dependence of cross-validation on the composition of the subsets, which are randomly generated, the cycle is repeated *c* times. The mean of the *c* values of q-squared is reported by Strike. A q-squared value that deviates significantly from the r-squared for a regression generally indicates that the regression is overly dependent on the set of points included in the training set and may not have the desired predictive power.

By default, Strike uses a subset size (`lgoPercent`) of 5% of the sample, giving $k = 20$ for the number of subsets, and a number of cycles *c* (`lgoCycles`) = 10. When Strike is run from the command line, the `lgoPercent` and `lgoCycles` keywords can be used to specify non-default values. See Section 4.3.5 on page 52.

F-statistic

The *F-statistic* is used in regression analysis to determine if the variances between the means of two populations are significantly different. In other word, the F-statistic provides an indication of the lack of fit of the data to the estimated values of the regression. A strong relationship between two variables gives a high F-ratio.

Leave-*n*-out validation

See *cross validation*.

P-value

The *p-value* is the probability that the regression was obtained not from correlations between the dependent and independent variables, but instead by chance. Generally p-values of < 0.05, which indicate a 1 in 20 probability that the regression was obtained by chance, are considered statistically significant.

Q-squared

The *q-squared* is the r-squared determined by comparing the dependent variable against predictions made using a model. See *cross validation* for details.

T-value

The *t-value* is the ratio of the coefficient of a variable to its standard error in the regression. A small t-value means that the variable's contribution to the regression is not very significant: a t-value of 1 means that the value of the coefficient is equal to its error, and hence the coefficient is in the "noise" of the regression. The higher the t-value, the more significant is the contribution of the variable to the regression.

5.5 Outlier Detection

Local Correlation Integral Outlier (LOCI) Detection

The LOCI outlier detection methodology uses a density-based approach to identifying outliers within a sample. It works by comparing the density of points surrounding a given point with the densities of the surrounding neighbor points. Significant differences in densities lead to the identification of outliers. It provides an automatic, data dictated cut-off to identify outliers without the need for user input. This method does not suffer from either the local density problem or the multi-granularity problem. It should be noted that our implementation of the LOCI algorithm does not scale well for larger sample sizes, and as such should only be used on samples of less than about 500 members.

Outliers Identified in Multiple Linear Regression

A second outlier detection method is used in conjunction with multiple linear regression (MLR). In this case, the model is run first and a set of five statistical tests on the final MLR model is run to identify the outliers. The five tests are:

- Standardized residual
- Studentized residual
- Leverage
- DFFITS
- Cook’s test

A molecule must be flagged by at least 2 of the five MLR outlier tests by default to be flagged for a molecule before listing it as being a possible outlier.

5.6 Similarity Statistics

The statistics defined in this section are measures of similarity.

5.6.1 Atom-Pair Similarity

m_{AB} is the total number of unique atom pair types found on molecules A and B

freq_k^A is the number of times atom pair type k was found on molecule A

w_i is the weight for atom pair type k

$$\mathrm{sim}_{AB} = \frac{\sum_{k}^{m_{AB}} w_k \min(\mathrm{freq}_k^A, \mathrm{freq}_k^B)}{0.5\sum_{k}^{m_{AB}} w_k(\mathrm{freq}_k^A + \mathrm{freq}_k^B)} \qquad (14)$$

To calculate the atom-pair similarity of two molecules, a set of atom-pair types is developed for each molecule. The atom-pair types are determined using the hydrogen-suppressed graph of the chemical structure and combining a simple atom typing scheme with the shortest path distances to arrive at the set of atom-pair types in the form, $type_i$-d_{ij}-$type_j$. The number of atom-pair types the two molecules share will determine their atom-pair similarities, with 0.0 indicating no similarity and 1.0 indicating all atom pairs of the two molecules are shared. The atom-pair weights are all 1.0 by default though they may be fitted to bias important atom pairs. Weight fitting and application in Strike can only be done from the command line. See Section 4.3.7 on page 53.

5.6.2 Similarity Measures in Descriptor Space

The four quantities defined here are measures of distance in descriptor space.

Manhattan Distance

$$\text{dist} = \sum_i w_i \left| x_i - x_i^{\text{probe}} \right| \tag{15}$$

The Manhattan distance metric, also known as the city-block distance, is a measure of the sum of geometric distances between points measured along axes at right angles. The distance being measured is summed over all variables. Put another way, the distance is calculated between all descriptors for a molecule and the probe value for each of those descriptors. For descriptor similarities, the probe value for each descriptor is the mean of the values of each probe molecule for that descriptor. Different weights for each descriptor, w_i, may be included only in command-line Strike calculations, otherwise all weights have the value of one. A value of zero indicates the probe molecule and test molecules are identical.

Euclidian Squared Distance

$$\text{dist} = \sum_i w_i (x_i - x_i^{\text{probe}})^2 \tag{16}$$

The Euclidean squared distance metric is a measure of the sum of geometric distances between points. The distance being measured is summed over all variables. Put another way, the distance is calculated between all descriptors for a molecule and the probe value for each of those descriptors. For descriptor similarities, the probe value for each descriptor is the mean of the values of each probe molecule for that descriptor. Different weights for each descriptor, w_i, may be included only in backend Strike calculations, otherwise all weights have the value of one. A value of zero indicates the probe molecule and test molecules are identical.

Euclidian Distance

The Euclidean distance is the square root of the expression in Equation (16).

Tanimoto Similarity

$$\text{dist} = \frac{\sum_i x_i x_i^{\text{probe}}}{\sum_i x_i x_i + \sum_i x_i^{\text{probe}} x_i^{\text{probe}} - \sum_i x_i x_i^{\text{probe}}} \tag{17}$$

The Tanimoto distance metric is a normalized measure of the similarity in descriptor space between a test molecule and a probe molecule. Similarities lie between one and zero with a value of one indicating identical molecules and a value of zero indicating completely dissimilar molecules.

5.7 References

1. Pearlman, D. A.; Charifson, P. S. *J. Med. Chem.* **2001**, *44*, 3417. Note that the inequalities in eq. 5 should be inverted.

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
- Strike purchaser (company, research institution, or individual)
- Primary Strike 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.

Index

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