Maestro Elements 1.3 Tutorial: Tasks

Legal Notices

March 2012

Getting Started

Requirements

Before starting this tutorial, please ensure that you have:

- Maestro Elements installed on your Linux or Windows machine
- A 3-button wheel mouse
- Tutorial-specific files, which can be found in your Schrodinger software installation directory, chosen by the person who installed your software. On Windows this directory is likely to be the default: `C:\Schrodinger2012\`

  Please copy these directories of tutorial files to your Desktop:

`<installation directory>/impact-v`*version*`/tutorial/structures/`

`<installation directory>/impact-v`*version*`/tutorial/grids/`

Starting Maestro Elements

If you haven't already, please launch Maestro Elements.

On Windows: double-click the Maestro Elements icon on your desktop.

On Mac: click the Maestro Elements icon in your Applications folder, in the Schrodinger subfolder. Or launch from the commandline as described below for Linux.

On Linux, set the SCHRODINGER environment variable to point to your Schrodinger installation location and run on the command-line: `$SCHRODINGER/maestro -elements &`

Maestro Elements Tasks

Maestro Elements tasks are available in the Tasks menu, as shown in Figure 1. This tutorial will help familiarize you with some of the available Maestro Elements Tasks: 2D ligand analysis, 3D ligand modeling, and ligand-protein complex modeling. However, your available Tasks may be different from the set described here.

Please import the structure files *1fjs_prep_lig.mae.gz* and *1fjs_prep_recep.mae.gz* from the tutorial structures directory. These are prepared structures of the 1FJS PDB structure of factorXa. To do this, go to the File menu and choose Import Structures…. Navigate to your Desktop, then to the structures/ directory you placed there. Select both files and press Open.

Your Maestro Elements Workspace should now look like Figure 1.

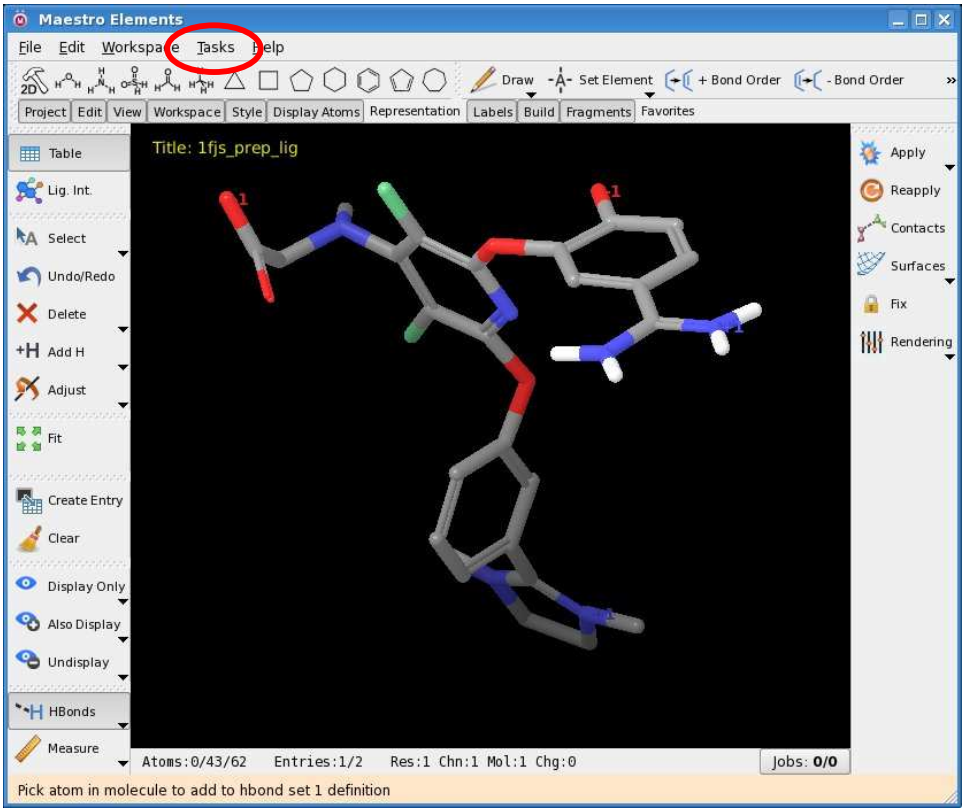

Figure 1: Maestro Elements after files 1fjs_prep_lig.mae.gz and 1fjs_prep_recep.mae.gz have been imported. The Tasks menu is highlighted.

Note that although only one structure is displayed in the Workspace, two structures have been loaded into the Project Table. You can always view the Project Table by pressing the Open/Close Project table button on the toolbar.

More information about working with the Project Table is available in the Maestro Elements Visualization tutorial.

Molecular Properties

The **Interactive Molecular Properties** task automatically displays the properties shown in Figure 2 for the current workspace ligand. This is true even if there is both a ligand and a receptor in the workspace – the panel will detect the ligand. This allows you to interactively design a ligand with goal properties in mind. Include the 1fjs_prep_lig entry in the Workspace to see its properties as shown in Figure 2. Note that the checkbox Show only Medchem properties hides other properties in the Project Table. Uncheck this box to view all properties.

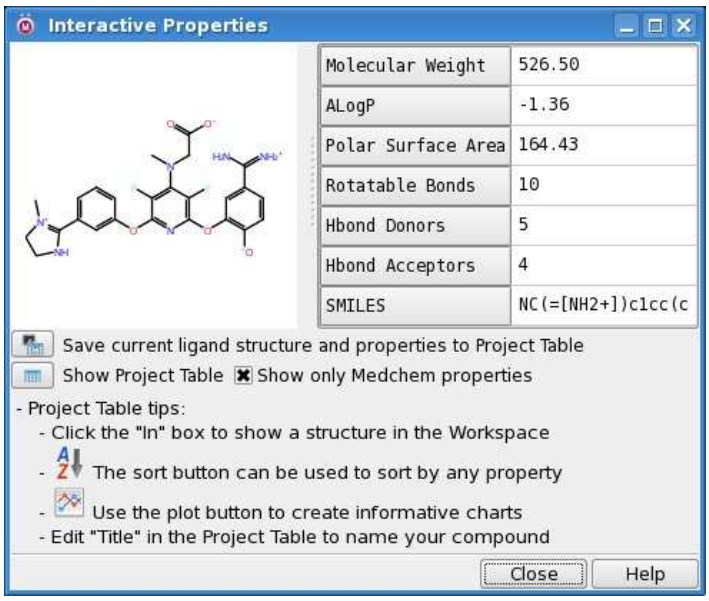

Figure 2: Interactive Molecular Properties shown for file 1fjs_prep_lig.mae.gz

The **ADME prediction (QikProp)** task can predict additional absorption, distribution, metabolism, and excretion (ADME) properties. This program was designed by Professor William L. Jorgensen. To run ADME prediction on multiple compounds, choose as input Project Table (selected entries) or File. These compounds must have been prepared using the **Prepare Ligands (LigPrep)** task. More information on these properties is available in the QikProp User Manual.

R-group Analysis

The R-group Analysis task analyzes a series of ligands with a common core. You can define the core for your series manually using SMARTS or by letting the panel automatically detect your core using maximum common substructure.

Import the file *sar_series.mae.gz* to do an R-group analysis. As a reminder, go to the File menu and choose Import Structures…. Navigate to your tutorial structures/ directory. Double-click the *sar_series.mae.gz* file to open it. Make sure the entries from this file are all selected (their rows will be yellow in the Project Table when they are selected).

Compute a few properties for these ligands using the Project Table so we have something to analyze. In the Project Table go to the Property menu and choose Calculate... and choose Property-based. Select Molecular Weight and press Calculate. Then select Number of Heavy Atoms and press Calculate. Then press Close to close the Calculate panel.

In the Tasks menu under Ligand Tools choose the R-group Analysis... task. Choose to Use structures from: Project Table (selected entries) as shown in Figure 3. Press Start. When the job is finished, the R-group Viewer panel will open.

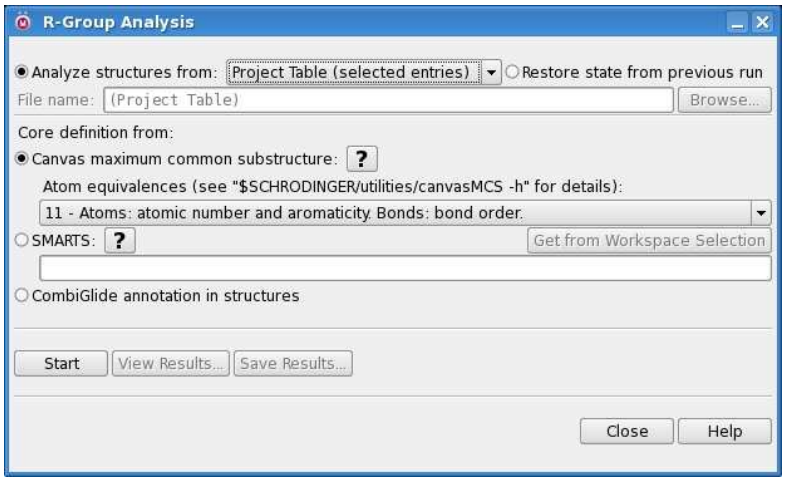

Figure 3: R-group Analysis panel

We will view a heat map and an SAR table to analyze these compounds. Press the Heat Map button. At first, R7 is shown on the X-axis and R2 is shown on the Y-axis. These are chosen as the most important R positions because for the property of interest (number of structures by default) these positions have the largest range of this property over the structures (averaged over each R-group at this position). At the top left, choose to show the property Molecular Weight and to color by the Average to view the panel as shown in Figure 4. Note that although the RGA panel chooses the most important R-group positions based on this new property, you can click on the colored boxes in the upper right graphic to plot other R positions on the X or Y axes. You can use this panel to notice interesting correlations between

R groups and properties and also helps visualize what other combinations of R groups it may be useful to try.

Press the SAR Table button to show a view like that in Figure 5. This allows you to view all the R positions and properties at once. The Select Properties button can be used to display a subset of your available properties. You can save an image of this layout if you like.

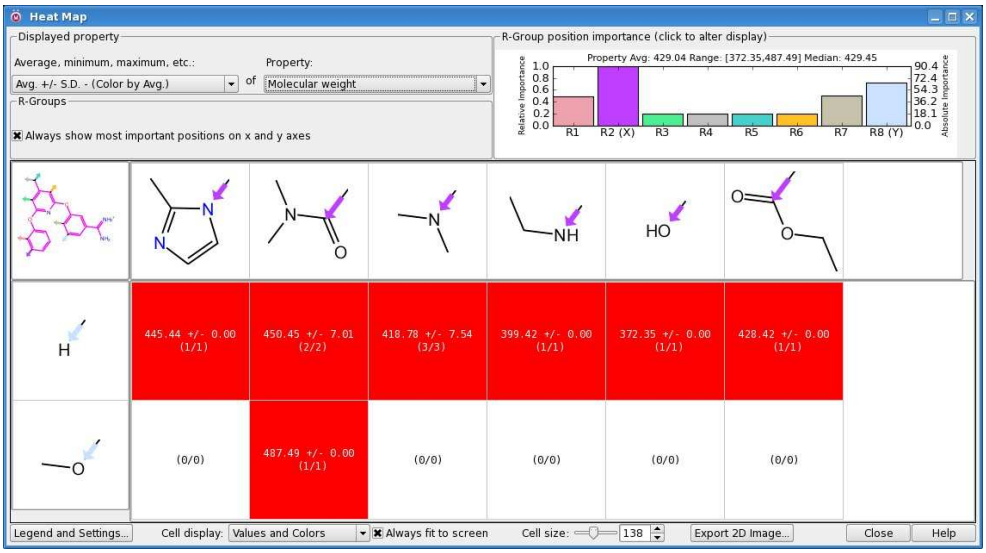

Figure 4: Heat Map panel

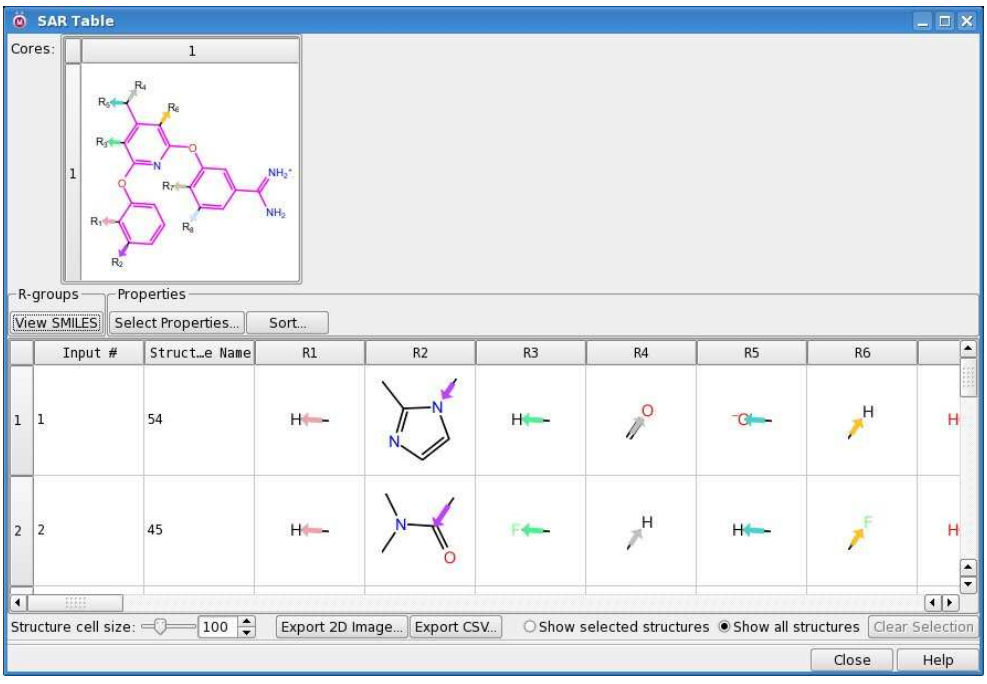

Figure 5: SAR Table panel

Prepare Ligands

The Prepare Ligands task prepares SMILES, 2-dimensional and 3-dimensional ligands for use in a 3-dimensional modeling environment. It creates plausible tautomers and protonation states for drug-like compounds. It can also vary chiral centers and rings if the user so chooses.

Input

The input for LigPrep is specified with the Use structures from option menu. It can come from the Workspace, selected entries in the Project Table, or from a file. The file can be in Maestro (.mae) or SD format, compressed or uncompressed, 2D or 3D, or it can be in one of two SMILES formats: .smi file (a text file with one SMILES string and an optional title per line) or .csv file (a comma-separated file with the SMILES string as the first field, title as the second, followed by optional properties).

For this tutorial, we will prepare the sar_series.mae.gz ligands we used for R-group analysis. Make sure these compounds are selected (yellow rows) in the Project Table. In the Tasks menu choose Ligand Tools and open the Prepare Ligands (LigPrep) task. We recommend that you choose Epik instead of Ionizer for generating protonation states, as shown in Figure 6.

Output

By default, results will be incorporated as new entries in your Project Table. However, you may also choose to save them to a file. If you provide the jobname ligprep_sar_series as shown in Figure 6, the output file will be called ligprep_sar_series-out.maegz and the results will appear in the Project Table in a group called ligprep_sar_series-out1.

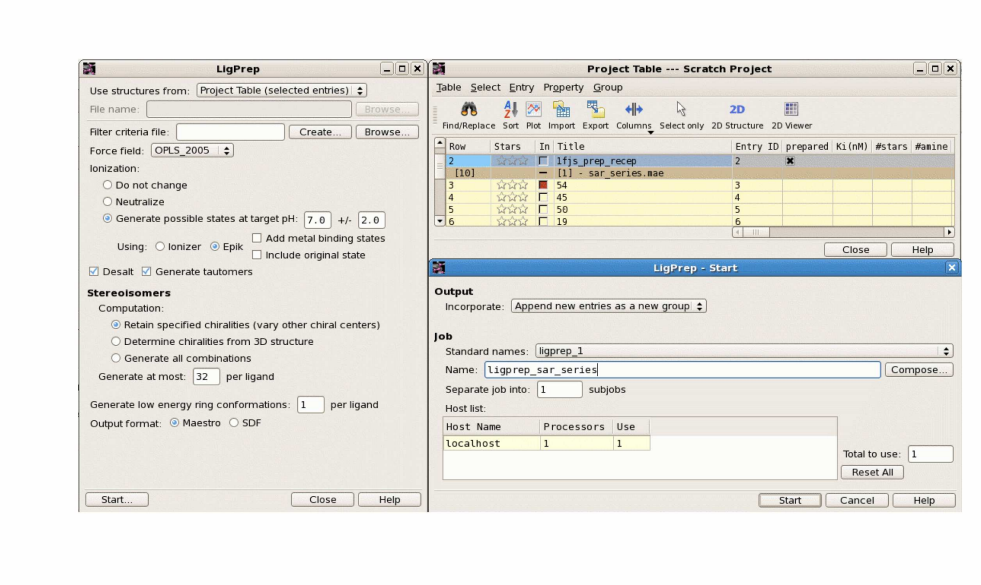

Figure 6: LigPrep panel. Input is selected entries in the Project Table. Results will be incorporated into the Project Table.

Minimization

Include the 1fjs_prep_lig Project Table entry in the Workspace by checking the In box next to this entry.

To do a complete minimization of this ligand, choose the Minimization task in the Tasks menu. Change the Solvent option to Water as shown in Figure 7. (This option changes the handling of the ligand electrostatic interactions.) Press Run to start the minimization job.

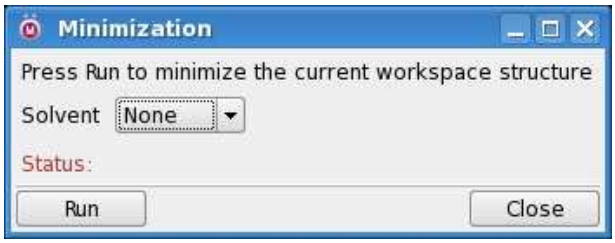

Figure 7: Minimization panel

When your job finishes, you will have a new entry in the Project Table with the same name as the ligand you started with (1fjs_prep_lig in this tutorial example) but with the minimized structure. To keep track of which structure is which, click on the title of this entry in the Project Table to give it a new name, such as minimized_1fjs_ligand. Scroll to the right side of the Project Table to see the new energy properties you calculated. Include both the new and old ligand structures in the Workspace to see the difference between them.

For a new or edited ligand you could press the Clean up geometry button in the Build panel to do a quick minimization of your ligand using the OPLS_2005 forcefield.

CONTROL-M to Minimize selected atoms

The Minimize selected atoms task can be particularly useful when modifying a protein-ligand complex. Include both the 1fjs_prep_recep and the 1fjs_prep_lig entries in the Workspace. Press the L button on your keyboard to center the workspace on the ligand.

Modify the ligand in the workspace, for example by adding a methoxy group. Select some of the ligand atoms. Hold down the CONTROL key and press M on the keyboard to minimize the selected atoms with the OPLS_2005 forcefield.

Conformational Search

Using the same ligand you used for the minimization task, start a Conformational Search task. This will generate a variety of low-energy conformations of the ligand and provide you with an energy ranking of the conformers. Change the Solvent option to Water as shown in Figure 8, then press Run. When the job is done it will plot the energy of each conformer. At the top of the plot panel you can choose the In button and select a point in the plot to view that ligand conformation in the Workspace.

Figure 8. Conformational Search panel

Electrostatic Potential

In the Tasks menu in the Ligand Tools submenu, choose Electrostatic Potential... to compute ligand charges and electrostatic potential surface using the quantum mechanics program Jaguar. Include one ligand in the Workspace (for example the entry minimized_1fjs_ligand from the Minimization task). We will use the default settings as shown in Figure 9. This will use Medium accuracy so that the job takes only a few minutes. (Low accuracy uses a semi-empirical calculation and High accuracy uses a higher level of quantum mechanics theory than the Medium level does.)

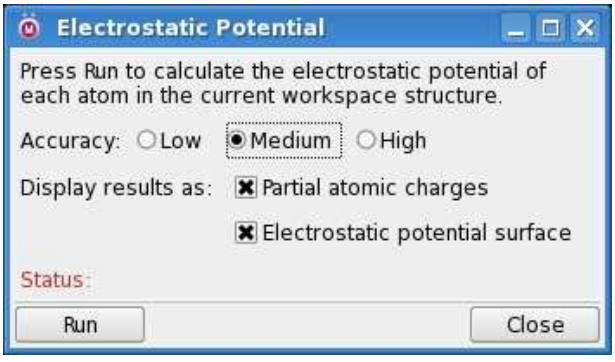

Figure 9: Electrostatic Potential panel

When the job finishes, the predicted charge density on each atom and the electrostatic potential surface will be shown as in Figure 10. In the Project Table, the availability of a surface is indicated by a blue S. You can right-click on this blue S and choose to undisplay the surface if you desire. Left click on the blue S opens the Manage Surfaces panel. More information on surfaces is included in the Maestro Elements Visualization tutorial.

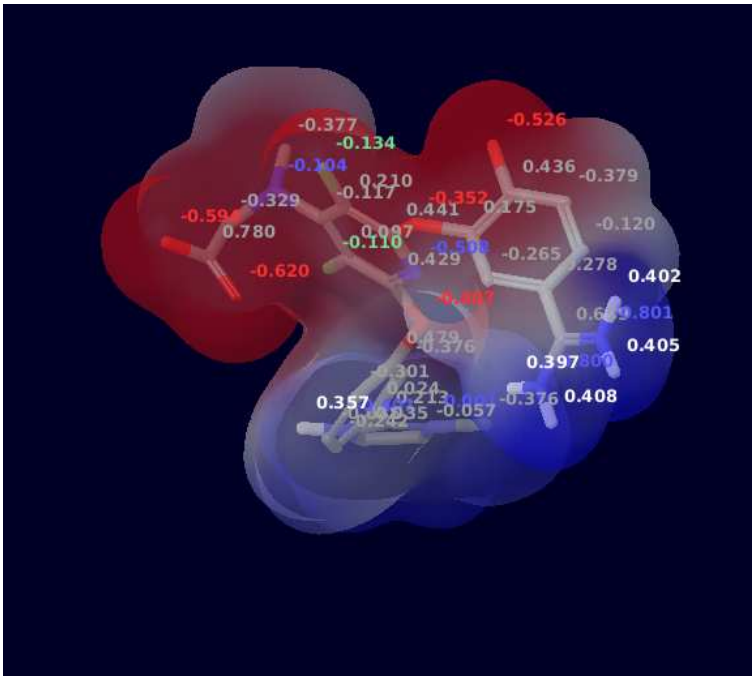

Figure 10: Electrostatic Potential results: partial charges and electrostatic potential surface

Ligand Alignment

Flexible Ligand Alignment

To start our ligand-based design tasks, duplicate the ligand entry 1fjs_prep_lig to create a new entry, which we'll call ligand_based_design. (Right-click on 1fjs_prep_lig and choose Duplicate then choose In Place. Click on the new title to change the name.) The Flexible Ligand Alignment task will help us align a set of ligands to our crystal structure ligand. We can evaluate the results to look at the similarity between our ligands and evaluate their poses in the 1fjs_prep_recep binding site.

Import the file *sar_series.mae.gz* for the Flexible Ligand Alignment Task. As a reminder, go to the File menu and choose Import Structures…. Navigate to your tutorial structures/ directory. Double-click the *sar_series.mae.gz* file to open it. The Flexible Ligand Alignment will use the workspace structure as the query, meaning the structure that will not move during the alignment. Your Project Table should look like Figure 11, where the the ligand_based_design entry is included in the workspace, and then the ligands to align are

selected in the table. Then, in the Flexible Ligand Alignment panel, click on the Align Selected Entries button.

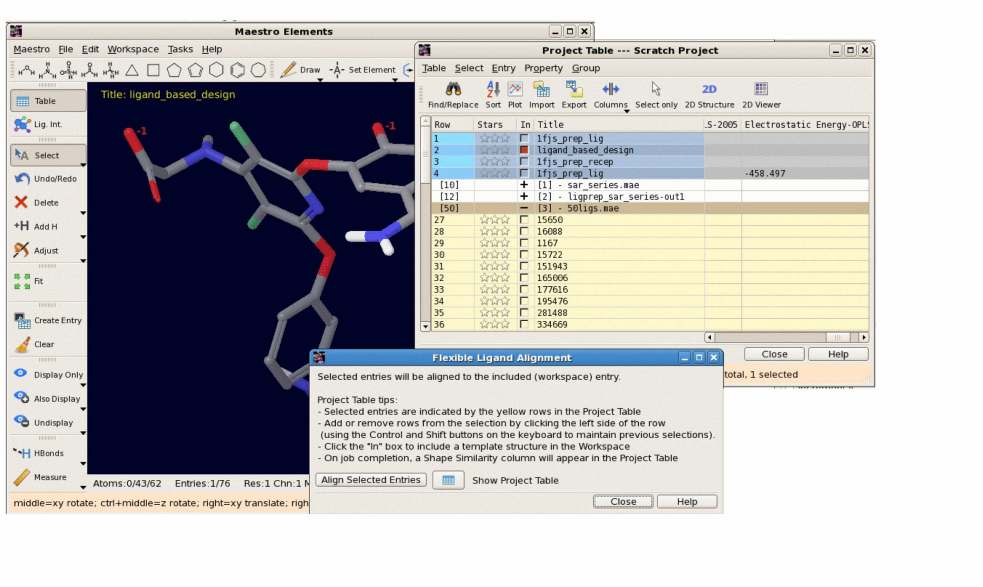

Figure 11: Flexible Ligand Alignment panel and Project Table layout

While the job is running the Aligning Ligands status dialog will pop up. When the job is done you can include other entries in the workspace, including the 1fjs_prep_recep entry to compare your new ligand poses to the crystal structure ligand.

Figure 12 shows the Project Table and workspace after including the query and one of the aligned results in the workspace to view the overlay. The ligands have different carbon colors because Workspace Style was used. More details on Workspace Style are provided in the Visualization tutorial.

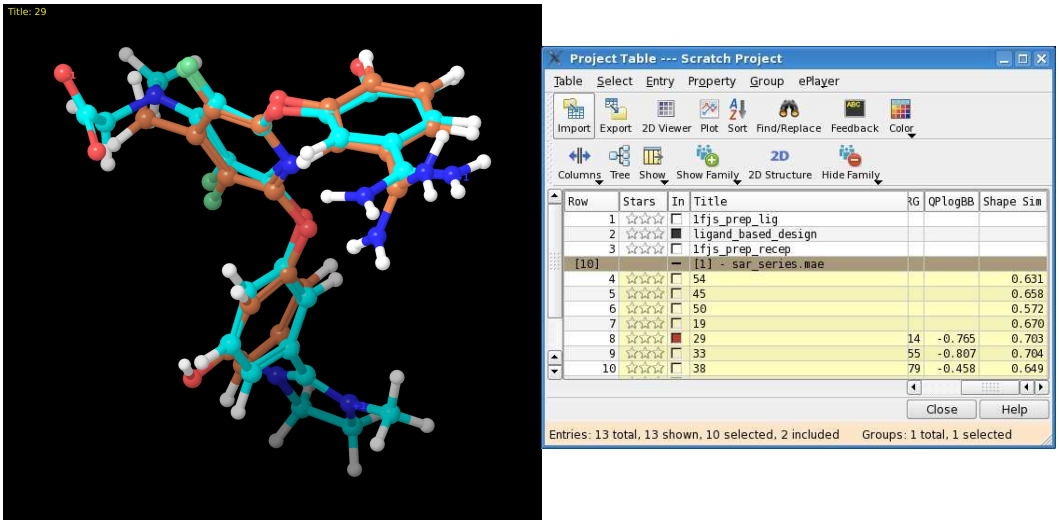

Figure 12: Flexible Ligand Alignment result and Project Table layout

Shape-based Similarity Screening

For more control over the ligand alignment, use the Shape-based Similarity Screening task. This works like the Flexible Ligand Alignment task but provides additional options for alignment such as alignment by pharmacophore features or atom-by-atom weights to bias the alignment toward some ligand atoms and away from others.

Superposition

For alignment of specific sets of atoms, use the Superposition task. To align specific atoms in two ligands: include the ligand_based_design entry in the workspace, and include one of the ligands you imported from 50ligs.mae.gz. Open the Superposition task and confirm that the default Included entries radio button is checked and the Atom Pairs tab is displayed. Click on 3 pairs of atoms in the workspace, where one from each pair comes from one ligand and one from each pair comes from the other ligand. Press Superimpose Atom Pairs to superimpose the ligands.

Torsion scan

For the Torsion scan Task, include a ligand and protein in the workspace, such as the 1fjs_prep_lig and the 1fjs_prep_recep entries. Focus the view on the ligand by pressing the letter L on the keyboard. Open the Torsion scan panel and check the box for Pick ligand bond to rotate. Pick a ligand bond. When the rotation and energy generation are done, the lowest-energy ligand state is displayed in the workspace. Press Plot to view the energies for each bond rotation, as shown in Figure 12. Select rows in the panel to view and choose other rotations of the ligand.

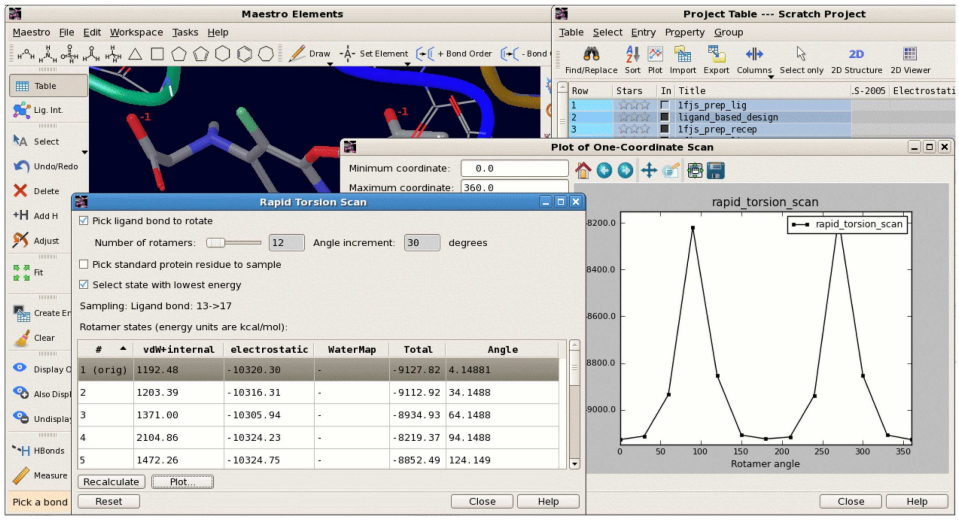

Figure 12: Torsion scan panel with Project Table layout and energy plot

Core hopping

In this task, a portion of the crystal structure ligand will be replaced by new potential cores. We will use the ligand_based_design entry in our Project Table as the starting ligand. However, we need to obtain a set of new possible cores for replacement. An example set of these can be downloaded from the Schrodinger website:

http://www.schrodinger.com/downloadcenter

Choose Core Hopping Library and download. The downloaded file must be unzipped.

Include the ligand_based_design entry in the Workspace and open the Core Hopping task in the Tasks menu in the Ligand Tools submenu. First we must define the part of the original ligand we want to replace. Click Start Defining Template and click on bonds in the workspace to create green arrows to define the core, as shown in Figure 13. Note that all the arrows must point outward from the core to be replaced. If an arrow points the wrong direction along a bond, just click the bond again and the arrow will change directions. When you are done choose Stop Defining Template.

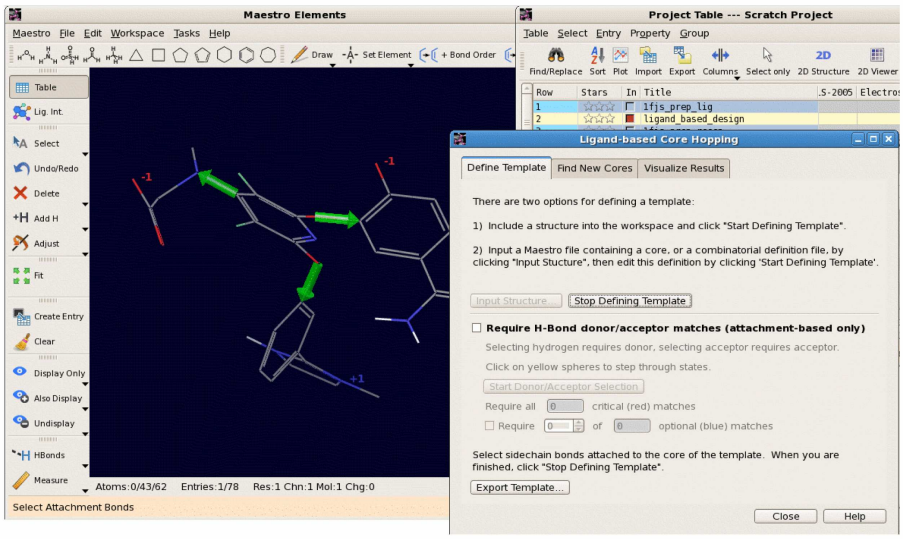

Figure 13: Ligand-Based Core Hopping panel with core-definition arrows shown in green

Then go to the Find New Cores tab to choose the new cores you want to use for replacement. The example cores you downloaded contain sets with zero or more methylene linkers attached. Since our example core is small we will choose the example cores with 0 linkers.

Press Start to run the job.

The Results Preview window will open when the job is finished and will display new core matches that are found while the job is running. Click on a square in the Results Preview GUI to show the new and old compounds aligned in the Maestro Workspace.

Protein preparation

Protein structures must be prepared with the Protein Preparation Wizard, found in the Tasks menu under Protein Tools. Preparation of the 1FJS crystal structure is shown in Figures 16-18. Protein preparation ensures that a protein structure (from the PDB or from your internal database) has properly-assigned bond orders and the correct number of hydrogens to make the structure compatible with the OPLS forcefields. An unprepared or poorly-prepared protein structure will lead to poor results or may even prevent modeling jobs from running.

In the Maestro Elements workspace, choose File, Save Project As to save your current project. Each step you do with the Protein Preparation Wizard will be saved in this project. In the File menu choose Get PDB and type 1FJS and click Download to import that crystal structure.

On the Import and Process panel of the Protein Preparation Wizard, press the **Preprocess** button to perform the checked actions on the workspace structure. In addition to properly assigning bond orders and hydrogens, by default this will convert selenomethionine to methionine and delete any waters that are more than 5 Å from het groups (such as ligands, cofactors, or detergents). The program will also look for problems in the protein structure such as unrealistic atom-atom distances and geometries. Press **View Problems** to view each problem and decide if you wish to continue with protein preparation or manually fix the protein structure first. In the case of 1FJS the Protein Preparation Wizard will notify you that atoms 3272 and 4619 are overlapping. If you click in the error message it will automatically zoom to the part of the structure with the problem. You can see these are both hydrogen atoms which will be refined in the next steps, so this is not a cause for concern.

Next, on the Review and Modify tab, observe the detected chains and het groups in your protein structure. If there are any chains, waters, or het groups that are not necessary for your modeling task, you may remove them now by selecting the row to delete and press Delete. Press **Generate States** to generate alternate tautomers and protonation states of your het groups near pH 7.0. Click on a het group row in the table to view the het group more closely in the Maestro Elements workspace. Choose the het group tautomer and protonation state that is most consistent with the hydrogen-bonding pattern you observe in the 3D structure. The appropriate state of the het group may be different in the context of the protein than it would be in solvent.

Move to the Refine tab to automatically assign the water and protein hydrogen-bonding network (your het group hydrogen assignment from the Review and Modify tab will not be changed). Press **Optimize** to rotate water hydrogens and protein hydroxyl hydrogens, and to flip asparagine, glutamine, and histidine sidechains to optimize the protein hydrogen-bonding network. When the optimization is done, look at the 3D structure in the Maestro Elements workspace in particular focus on the hydrogen-bonding network near your het groups of interest. You may use the **Interactive Optimizer** to manually fix any problem with the hydrogen-bonding network and re-run the optimization with constraints.

Finally, press **Minimize** to minimize the protein structure. The minimization will stop when the heavy-atom RMSD has reached 0.3 Å, so the atoms will not move very far. This minimization helps to relieve small clashes in the protein structure.

Open the Project Table to notice that each step you performed has been recorded in the Project Table. Scroll to the far right of the table to view the properties indicating the tasks that have been performed, such as *added hydrogens* and *ran protassign*.

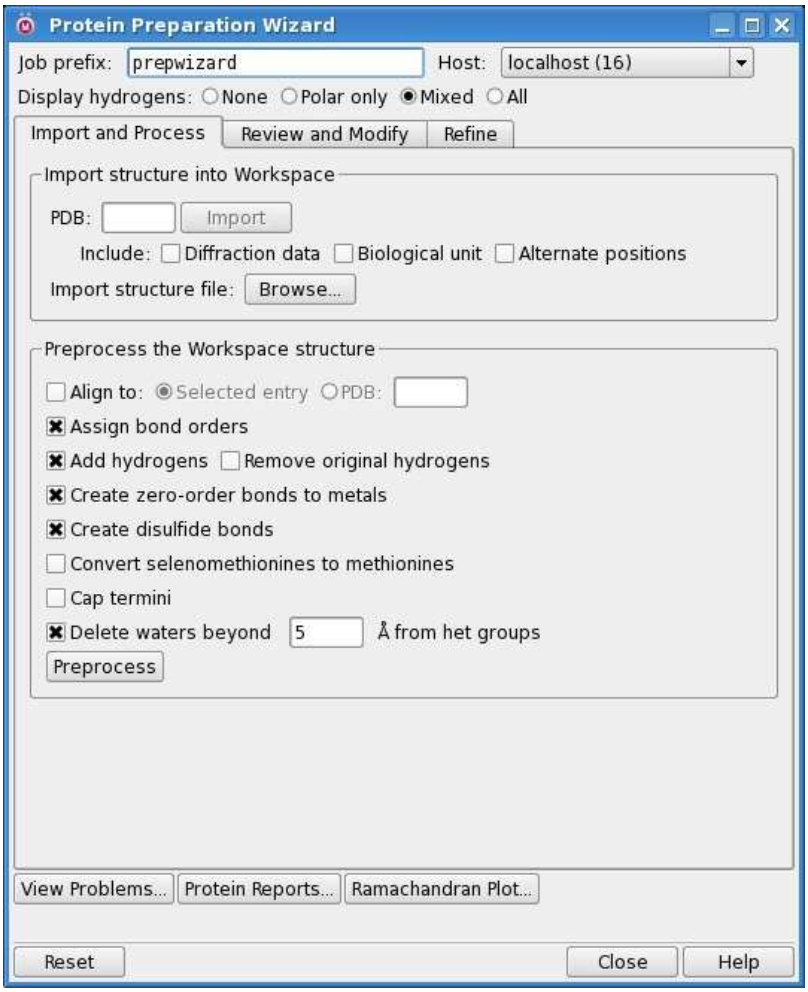

Figure 16: Protein Preparation Wizard: Import and Process panel

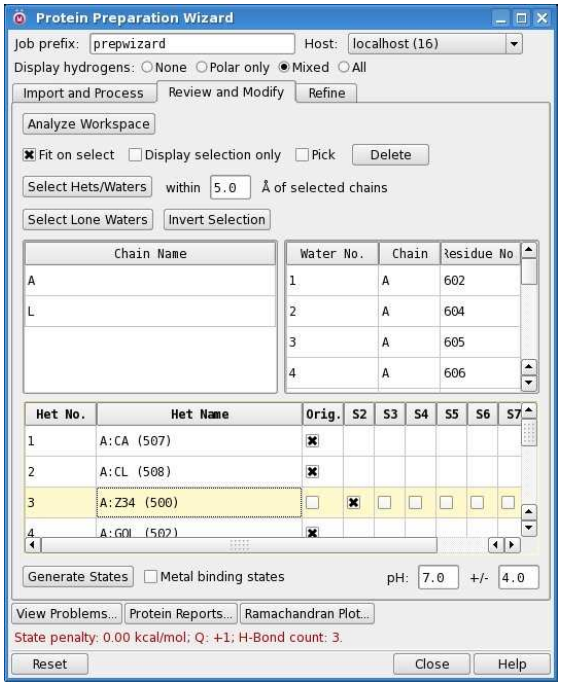

Figure 17: Protein Preparation Wizard: Review and Modify panel

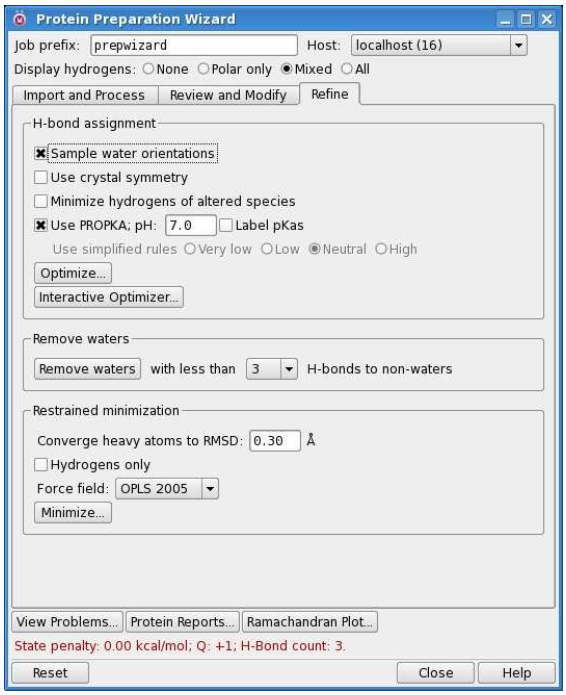

Figure 18: Protein Preparation Wizard: Refine panel

Binding Site Characterization

The Binding Site Characterization (SiteMap) task analyzes protein binding sites to characterize each part of the pocket as most preferring a hydrophobic group, a donor, or an acceptor. It can also be used to detect binding sites when the Identify top-ranked potential receptor binding sites option is used and it can predict the druggability of those sites. We will use Binding Site Characterization to characterize the 1fjs_prep_recep binding site.

Open the Binding Site Characterization (SiteMap) task from the Tasks menu and the Protein Tools submenu. Include both the 1fjs_prep_recep and the 1fjs_prep_lig entries in the Workspace. The 1fjs_prep_lig entry will only be used to define the binding site location and will not be used in the calculation. Choose the radio button in the panel to Evaluate a single binding site region. The checkbox for Pick (Molecule) should already be checked, so just click an atom of the ligand in the workspace. Then press Start to run the job.

When the job completes, only one binding site surface will be shown in the Workspace. However, four new entries have been added to the Project Table as shown in Figure 19. As shown, please include all four entries in the workspace to view the protein, the ligand, and both sitemaps.

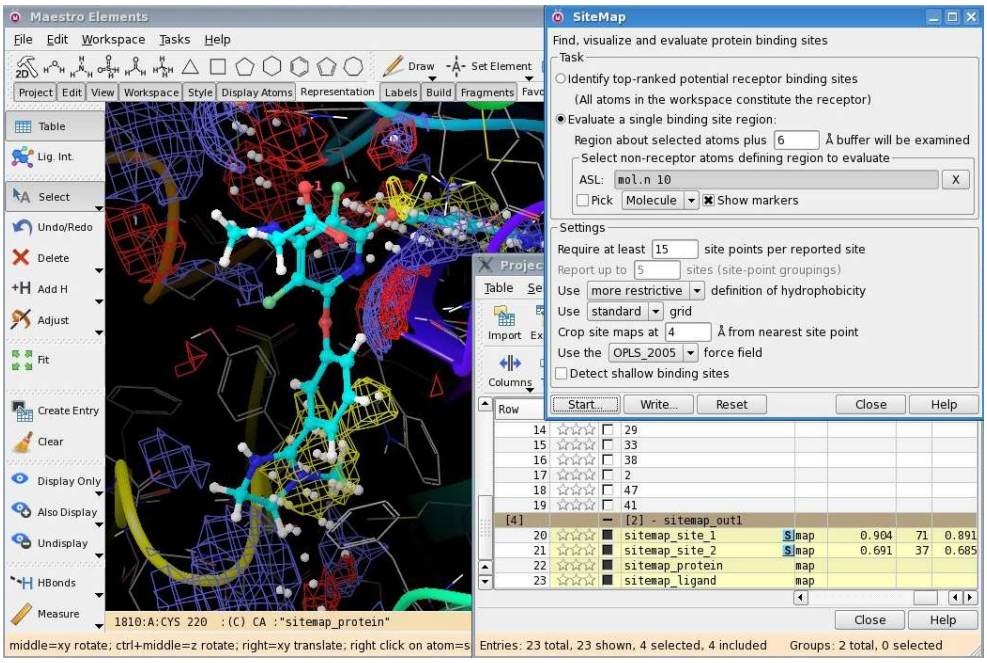

Figure 19: Binding Site Characterization (SiteMap) panel with all results included in Workspace

Note that two sites have been reported, which correspond roughly to the S1 and S4 factorXa pockets. The two blue S's in the Project Table indicate that surfaces are available. These are associated with white SiteMap points that were used during the calculation. To undisplay these, right-click on a blue S in the Project Table, select Display and choose Surface Only.

Design and Scoring

Ligand Design: Rigid Binding Site

The Ligand Designer tasks allow design and scoring of a ligand in a protein binding site. Starting with a protein-ligand complex, the user manually alters the ligand using the Build panel in Maestro Elements and refines each new ligand position. With Ligand Designer: Rigid Binding Site (uses Glide), the ligand is refined with the GlideScore docking scoring function. With Ligand Designer: Flexible Binding Site (uses Embrace), the ligand and protein are refined using Macromodel minimization with the OPLS-2005 forcefield.

Open the Glide Ligand Designer, found in the Tasks menu under Design and Scoring, and Ligand Designer: Rigid Binding Site (uses Glide). We will start with a pre-prepared protein grid: check the radio button for Use receptor from pre-generated grid file:. Press Browse and navigate to your Desktop, then to the grids/ directory you placed there. Choose the *factorXa_grid.zip* file you find there. It is important to start with a prepared protein – when working on any structure without a pre-prepared grid, please see the section on **Protein Preparation**.

Please import the structure files *1fjs_prep_lig.mae.gz* and *1fjs_prep_recep.mae.gz* from the tutorial structures directory. These are prepared structures of the 1FJS PDB structure of factorXa and correspond to the grid you already used. As a reminder, go to the File menu and choose Import Structures…. Navigate to your Desktop, then to the structures/ directory you placed there. Select both files and press Open. Although only one structure is displayed in the Workspace, two structures have been loaded into the Project Table. View the Project Table by pressing the Open/Close Project table button on the toolbar. 

Include both the 1fjs_prep_recep and the 1fjs_prep_lig entries in the Workspace by pressing SHIFT and checking the In box for the 1fjs_prep_recep entry. The 1fjs_prep_lig entry will be the starting ligand for this exercise. Check the box Pick reference ligand. Your workspace should look like Figure 20.

Click on any ligand atom in the workspace. This will launch a Glide scoring job for this ligand. When this is finished, your workspace should look like Figure 21. The yellow squares in the workspace indicate the ligand of interest. The table in the Glide Ligand Designer panel shows the GlideScore for this ligand.

Now, make a small modification to the ligand. For example, add a methyl fragment to one of the rings: click on the methyl  fragment and then click on one of the ring hydrogens.

Press Score Workspace Ligand to refine and score the new ligand. You may make additional modifications and press Score Workspace Ligand after each change. The Results table will collect each structure and score you create. Press the Export button to save all these results to the Project Table. There, you may include different ligands with the receptor in the workspace and evaluate their interactions as described in the Maestro Elements Visualization tutorial.

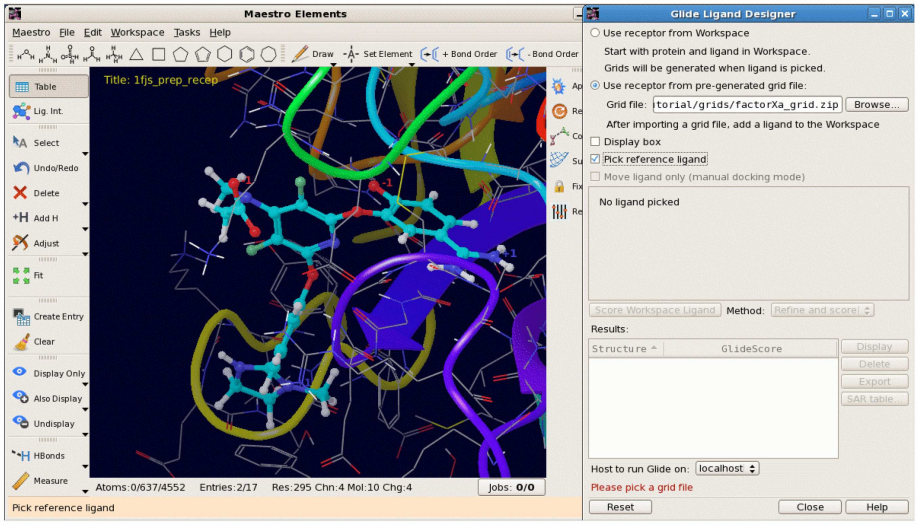

Figure 20: Glide Ligand Designer panel with pre-prepared receptor-ligand complex loaded

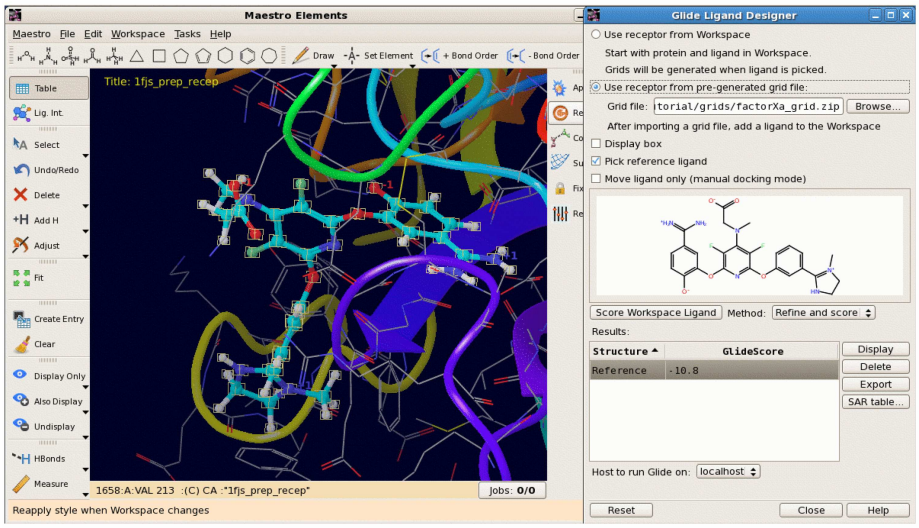

Figure 21: Glide Ligand Designer after scoring the ligand

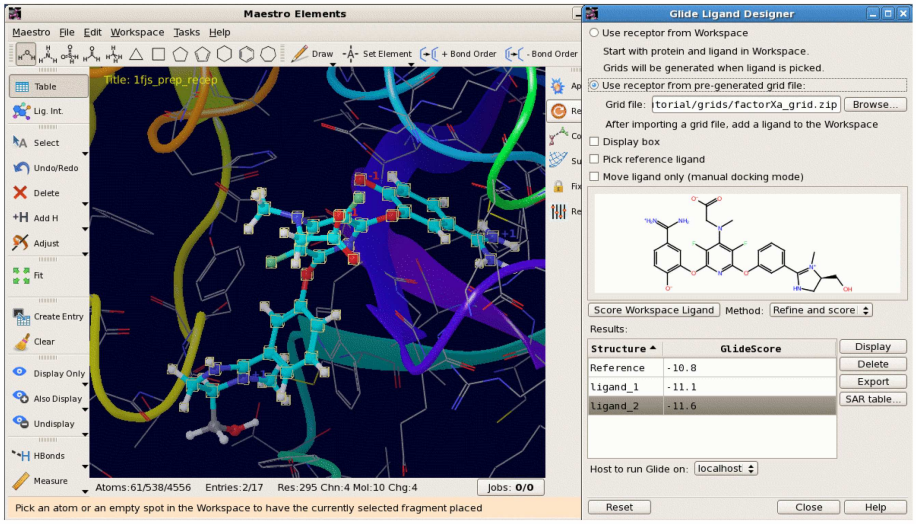

Figure 22: Glide Ligand Designer after modifying and scoring the ligand twice.

Glide grid generation and flexible docking

In this example we will dock a single ligand into the FactorXa binding site. Instead of using a pre-prepared Glide grid this time we will generate one as part of the task.

Please import the structure files *1fjs_prep_lig.mae.gz* and *1fjs_prep_recep.mae.gz* from the tutorial structures directory. These are prepared structures of the 1FJS PDB structure of factorXa, and the native ligand will be used to define the binding site location. As a reminder, go to the File menu and choose Import Structures…. Navigate to your Desktop, then to the structures/ directory you placed there. Select both files and press Open. Although only one structure is displayed in the Workspace, two structures have been loaded into the Project Table.

View the Project Table by pressing the Open/Close Project table button on the toolbar.

Include both the 1fjs_prep_recep and the 1fjs_prep_lig entries in the Workspace by pressing SHIFT and checking the In box for the 1fjs_prep_recep entry. The 1fjs_prep_lig entry will define the binding site for this exercise. Press the letter L on your keyboard to zoom in on the ligand.

Open the panel Glide grid generation and docking from the Tasks menu and the Design and Scoring submenu. Check the box Pick ligand (for box center and to exclude) and click on the 1fjs_prep_lig ligand. Then, we must select one row from the Project Table to define the ligand to be docked. In this example I have chosen the first ligand from the sar_series.mae.gz series.

Your Maestro Elements workspace should look like Figure 23. Press Start to dock the selected ligand. Choose to Append new entries for the output when the job finishes. The job will take several minutes; when it finishes the results will be included in the Project Table and shown in the Maestro Workspace.

Notice that in this tutorial example, the 1fjs_prep_recep structure was already prepared with the Protein Preparation Wizard. Flexible docking will not work with an unprepared protein structure. When working on any new structure, please see the section on **Protein Preparation**.

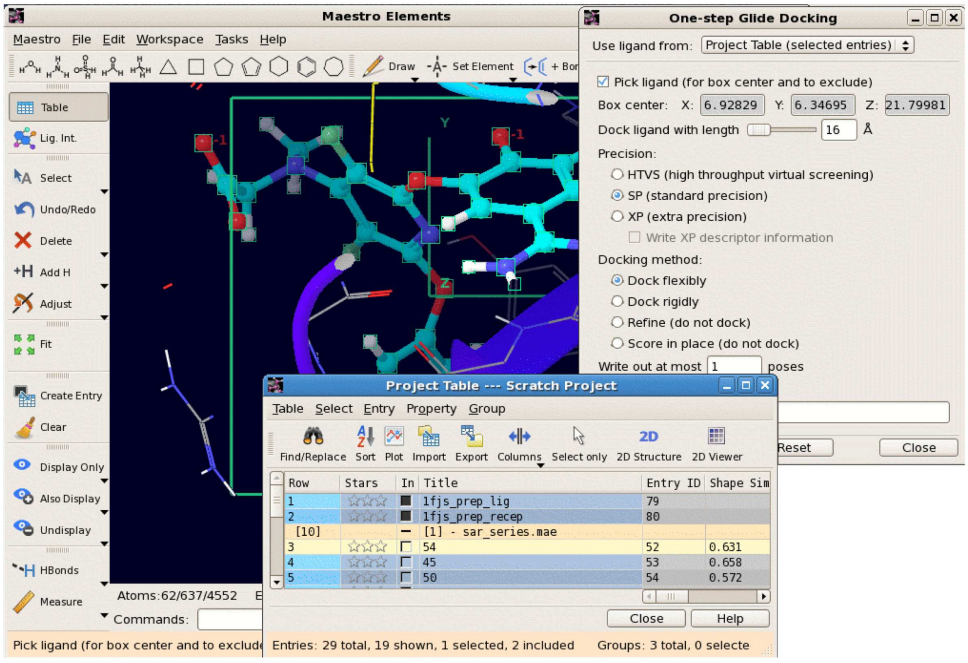

Figure 23: Glide Grid generation and docking: job setup to dock 1 ligand to a prepared protein

Other methods for ligand design

Ligand alignment

If one has a ligand already in a protein binding site, other ligands can be placed in the binding site using the tools described in the **Ligand Alignment** section of this document. This method works best when the new ligands are very similar to the ligand already in the binding site.

Pharmacophore Search

Maestro Elements provides tools for searching a database with a pharmacophore hypothesis. The Phase user manual is accessible from the Help menu in Maestro Elements. Choose Manuals Index, then under the Phase product choose Phase User Manual. This manual has more information on creating a manual hypothesis with the Create Hypothesis panel (in section 2.2 on Building aor Editing Hypotheses) and on searching a database with the Find Matches to Hypothesis panel (in section 2.4 on Finding Matches to a Hypothesis). The full Phase product is not included with Maestro Elements.

Ligand group placement

After manually editing a ligand in a protein binding site, various tools can be helpful in moving and evaluating the edited ligand. For example the **Torsion Scan** task can be used to rotate an added functional group and find the lowest energy position for that group. The **Minimize selected atoms** task can be used to minimize only the edited part of the ligand.

The **Adjust** button allows manual rotation of torsions. Hold down the Adjust button in the toolbar or choose Adjust from the Edit menu for more ligand adjustment options. Hydrogen bonds and contacts will be displayed during ligand adjustment.

Various tools exist for by-eye analysis of the ligand as well. For example the **Measurements** task may be helpful for evaluating the quality of hydrogen bonds as well as distances and angles of other atoms. The **Contacts and H-bonds** panel in the Workspace Style toolbar may also be useful for evaluating hydrogen bonds and contacts. These panels are described in more detail in the Visualization tutorial.