Glide 6.7

Quick Start Guide

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Contents

Document Conventions v

Chapter 1: Getting Started 1

1.1 About Glide and Maestro 1

1.2 Preparing for the Exercises 2

Chapter 2: Receptor Grid Generation 5

2.1 Importing and Displaying the Prepared Structures 5

2.2 Defining the Receptor 6

2.3 Defining the Active Site 7

2.4 Setting Up Glide Constraints 9

2.4.1 Setting the Display for Constraint Definition 9

2.4.2 Defining a Positional Constraint 9

2.4.3 Defining an H-bond Constraint 11

2.5 Setting Up Excluded Volumes 13

2.6 Starting and Monitoring the Grid Calculation 13

Chapter 3: Ligand Docking 15

3.1 Specifying the Grid 15

3.2 Specifying Ligands To Dock 16

3.3 Setting Basic Options 17

3.4 Specifying Output Quantity and File Type 18

3.5 Starting the Ligand Docking Job 19

3.5.1 Running on a Single Processor 20

3.5.2 Running on Multiple Processors 21

3.6 Docking in High-Throughput Virtual Screening Mode 22

3.7 Using Excluded Volumes 22

3.8 Using Ionization and Tautomeric State Penalties 23

3.9 Docking Ligands Using Positional and H-Bond Constraints 26
3.10 Docking Ligands Using Core Constraints 28
3.11 Docking Ligands Using Torsional Constraints 31
3.12 Refining Docked Ligands with Glide XP 35

Chapter 4: Examining Poses 37

4.1 Importing and Selecting Pose Data 37
4.2 Viewing Poses 38
4.3 Displaying Atoms by Proximity 39
4.4 Visualizing Hydrogen Bonds and Contacts 40
4.5 Visualizing Per-Residue Interactions 41
4.6 Visualizing Glide XP Descriptors 43
4.7 Finishing the Exercises 44

Chapter 5: Docking to a SiteMap-Based Grid 45

5.1 Running the SiteMap Calculation 45
5.2 Generating a Grid from a Site Map 46
5.3 Docking the Native Ligand 48

Getting Help 51

Glossary 55

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].

Getting Started

This manual contains tutorials designed to help you quickly become familiar with the functionality of Glide, using the Maestro interface. This chapter contains a brief overview of the software and some setup instructions for the tutorials. The tutorial begins in Chapter 2 with the generation of grids from a prepared protein to represent the receptor for docking. In Chapter 3, a set of ligands is docked and scored, and the receptor and ligand poses are examined in Chapter 4. Protein preparation is not covered in this manual: see the *Protein Preparation Guide* for details of this task.

Panel-specific online help is available for all Glide panels. If you need help with a Glide task, click the Help button or see the *Glide User Manual*.

Exercises in some chapters produce structure files that are needed in subsequent exercises. To allow you to begin at any exercise you choose, these and other necessary files (ligand files, for example) are included with the Glide distribution.

1.1 About Glide and Maestro

Glide is designed to assist you in high-throughput screening of potential ligands based on binding mode and affinity for a given receptor molecule. You can compare ligand scores with those of other test ligands, or compare ligand geometries with those of a reference ligand. Additionally, you can use Glide to generate one or more plausible binding modes for a newly designed ligand. Once you locate favorable structures or bonding conformations with Glide, you can use Liaison or QSite to obtain binding energies for ligand-receptor pairs.

Protein Preparation is usually required for Glide calculations. It can be performed for most protein and protein-ligand complex PDB structures using the Protein Preparation Wizard panel in Maestro. For detailed information, see the *Protein Preparation Guide*.

Maestro is Schrödinger's powerful, unified, multi-platform graphical user interface (GUI). It is designed to simplify modeling tasks, such as molecule building and data analysis, and also to facilitate the set up and submission of jobs to Schrödinger's computational programs. The main Maestro features include a project-based data management facility, a scripting language for automating large or repetitive tasks, a wide range of useful display options, a comprehensive molecular builder, and surfacing and entry plotting facilities. For more detailed information about the Maestro interface, see the Maestro online help or the *Maestro User Manual*.

Maestro comes with automatic context-sensitive help (Auto-Help), Balloon Help (tool tips), an online help facility, and a user manual. For more information on getting help, see page 51. You can also undo some operations in Maestro. For more information, see Section 2.11 of the *Maestro User Manual*.

The **Impact** computational engine is the underlying computational program for Glide. It can perform molecular mechanics calculations, either through the Maestro interface or from the command line. For information on running basic Impact jobs, see the *Impact User Manual* or the *Impact Command Reference Manual*.

1.2 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 `glide` and `sitemap` zip files 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 Glide Quick Start Guide 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.

Note: These exercises are intended to be run from the default version of Maestro. If you are using one of the other Maestro profiles (such as BioLuminate), the instructions for opening panels and using toolbars might not match the profile you are using.

Receptor Grid Generation

This chapter contains exercises that demonstrate how to use the Receptor Grid Generation panel to set up and start a grid file calculation job. Grid files represent physical properties of a volume of the receptor (specifically the active site) that are searched when attempting to dock a ligand. You will use the grid files calculated in this chapter to dock ligands in later Glide exercises.

If you have not started Maestro or copied the tutorial files, do so now. See Section 1.2 on page 2 for instructions on how to do these tasks.

2.1 Importing and Displaying the Prepared Structures

The complex for this exercise is actually in two files, one containing the receptor and one containing the ligand.

1. Click the Import button on the Project toolbar.

   

   The Import dialog box opens.
2. From the Files of type option menu, ensure that Common is chosen.
3. If the options are not displayed, click Options.
4. Ensure that Import all structures and Replace Workspace are selected.
5. Select the files `1fjs_prep_recep.mae.gz` and `1fjs_prep_lig.mae.gz`.
6. Click Open.

   The Import dialog box closes. Only one of the structures is displayed in the Workspace.
7. In the Entry List panel, control-click the check box for the entry that is not in the Workspace.

   Now both structures are displayed. The protein structure is displayed in ribbon representation with the backbone shown. The protein structure entry includes solvent molecules (glycerine) and ions (Ca^{2+} and Cl^{-}). The ligand is displayed in tube representation.

2.2 Defining the Receptor

The receptor structure used for grid generation is taken from the Workspace, so you need to exclude the ligand atoms from consideration as part of the receptor.

1. In the main window, choose Tasks → Docking → Grid Generation

   The Receptor Grid Generation panel opens with the Receptor tab displayed.

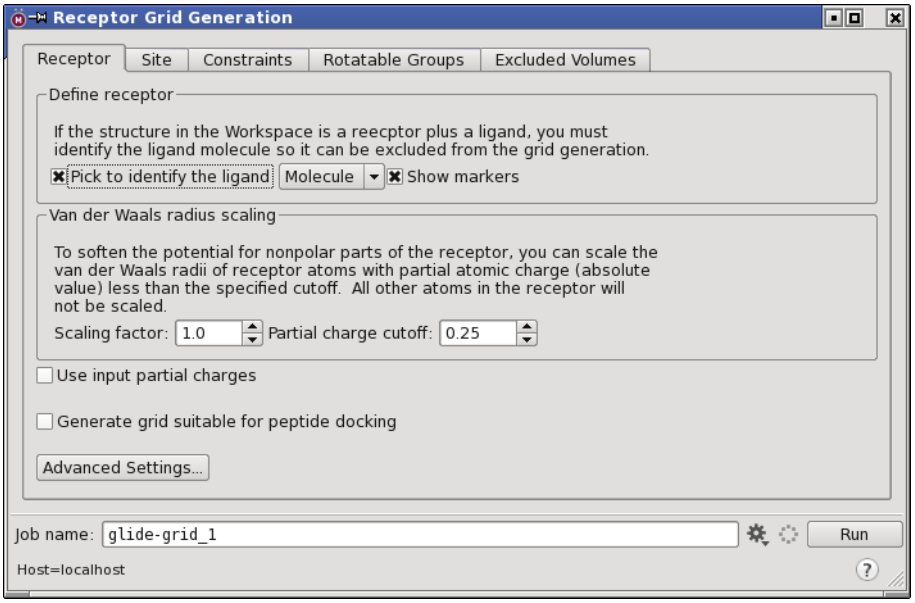

Figure 2.1. The Receptor Grid Generation panel.

2. In the Define receptor section, ensure that Pick to identify ligand and Show markers are selected, and that Molecule is chosen in the option menu.
3. With the pointer in the Workspace, press the L key.

   The view zooms in and centers on the ligand.
4. Pick an atom in the ligand molecule.

   Green markers appear on the ligand.
5. In the Van der Waals radii scaling section, ensure that Scaling factor is set to the default value of 1.0 (no scaling.)

2.3 Defining the Active Site

Now that the ligand has been excluded, the volume for which grids will be calculated can be defined:

1. Click the Site tab.

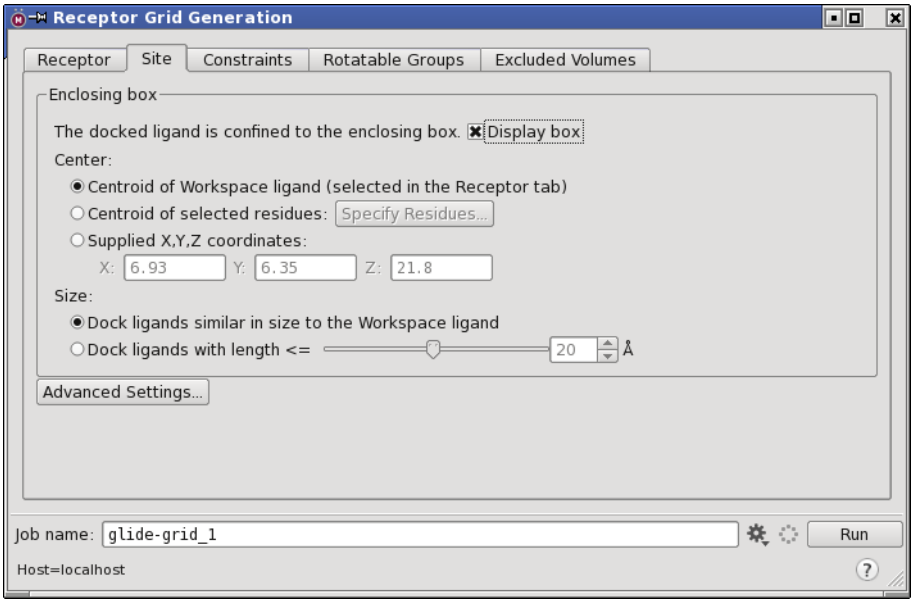

Figure 2.2. The Site tab of the Receptor Grid Generation panel.

The complex is shown in the Workspace with several types of markers: the green ligand molecule markers that appeared when the ligand was identified, and the new markers that appeared when the Site tab was opened:

- The *enclosing box* is shown in purple.
- The center of the enclosing box is marked by green coordinate axes.

The purple enclosing box represents the volume of the protein for which grids will be calculated. Generally, you should make the enclosing box as small as is consistent with the shape and character of the protein's active site and with the ligands you expect to dock.

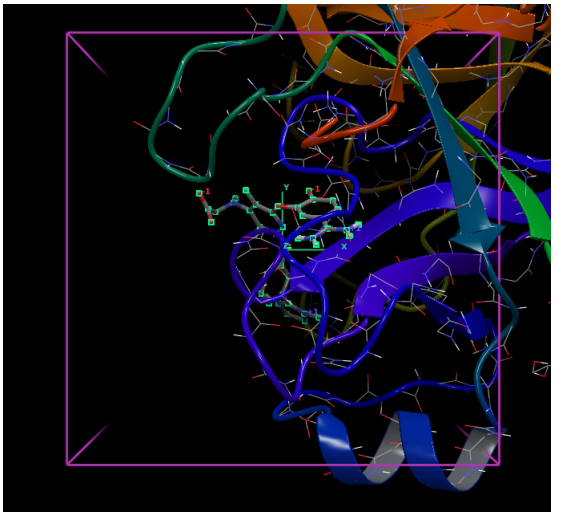

Figure 2.3. The marked ligand with the enclosing box and axes.

2. Ensure that the Center option selected is Centroid of Workspace ligand.
3. Ensure that the Size option selected is the default, Dock ligands similar in size to the Workspace ligand.

   If you have a representative ligand in the active site, the default generates an enclosing box that is large enough for most systems. However, if you think that conformations of active ligands may exist that are significantly larger than the cocrystallized ligand, you should consider enlarging the enclosing box using the Dock ligands with length <= option.

2.4 Setting Up Glide Constraints

The Constraints tab of the Receptor Grid Generation panel is used to define Glide constraints. In this exercise, you will define two constraints: a positional constraint and an H-bond constraint. To make it easier to see the parts of the receptor close to the ligand and to see the ligand atoms, you will first change the display.

For more information on using Glide constraints, see Section 4.4 of the *Glide User Manual*.

2.4.1 Setting the Display for Constraint Definition

1. If the Display Atoms and Representation toolbars are not displayed, click their buttons on the Manager toolbar, or choose Window → Toolbars → *toolbar*.
2. From the Ribbons button menu on the Representation toolbar, choose Delete Ribbons.

   

   The ribbons are removed and the protein backbone remains displayed.
3. From the Display Only button menu on the Display Atoms toolbar, choose Ligands.

   

   The protein is removed from the display, leaving only the ligand.
4. From the Within button menu, choose +3 Å.

   

   The residues that are closest to the ligand are displayed, with only their polar hydrogens. Nonpolar hydrogens are not displayed, by default. This makes it easier to see the polar hydrogens that are likely to form hydrogen bonds.

   You can hide the Representation and Display Atoms toolbars if you want.

2.4.2 Defining a Positional Constraint

Positional constraints are spherical regions placed at the centroid of a set of picked atoms. The constrained atoms in the ligand must lie inside this region. You can also define NOE constraints, for which the constrained atoms must line between two spheres: that is, they must be within a given distance range of the centroid. In this exercise, you will define a positional constraint.

1. In the Constraints tab of the Receptor Grid Generation panel, click the Positional/NOE tab.

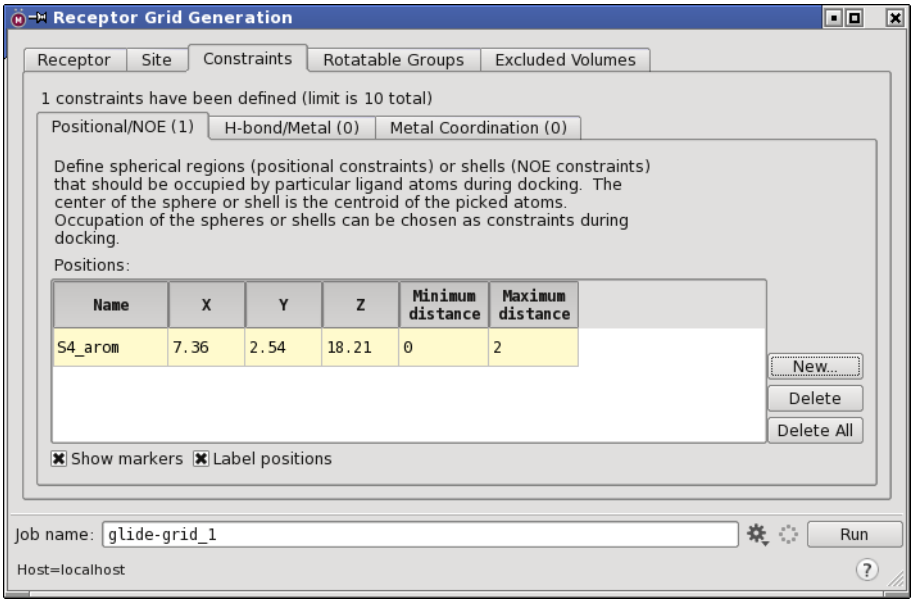

Figure 2.4. The Constraints tab of the Receptor Grid Generation panel showing the Positional/NOE subtab.

2. Click New.

   The New Position/NOE Constraint dialog box opens.

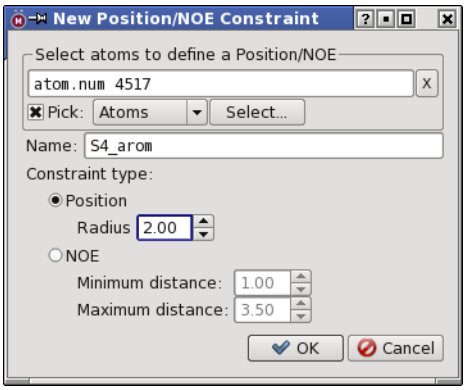

Figure 2.5. The New Position/NOE Constraint dialog box.

3. In the Select atoms to define a position/NOE section, ensure that Pick is selected; and from the Pick option menu, ensure that Atoms is selected.
4. Click the carbon atom that is between the two nitrogen atoms in the imidazole ring in the ligand.

   A semi-transparent gray sphere is displayed around the atom, labeled `position1`. The atom number in the text box depends on whether you included the protein or the ligand in the Workspace first.
5. Change the Name to `S4_arom`.

   The name in the Workspace changes as well.
6. Enter `2.0` in the Radius text box.
7. Click OK.

   The constraint is added to the Positions table in the Positional tab, and the sphere changes to red. The name is displayed next to the sphere.

2.4.3 Defining an H-bond Constraint

Next, you will define an H-bond constraint, for the carboxylate that is H-bonded to the amidine of the ligand. To aid the picking of the constraint, H-bonds to the ligand will be displayed.

1. If the Measurements toolbar is not displayed, click Measurements on the Manager toolbar, or choose Window → Toolbars → Measurements.
2. From the HBonds button menu on the Measurements toolbar, choose Ligand-Receptor, and ensure that Display is selected.

   

   The hydrogen bonds between the ligand and the receptor appear as yellow dashed lines.
3. In the Constraints tab, click on the H-bond/Metal tab.

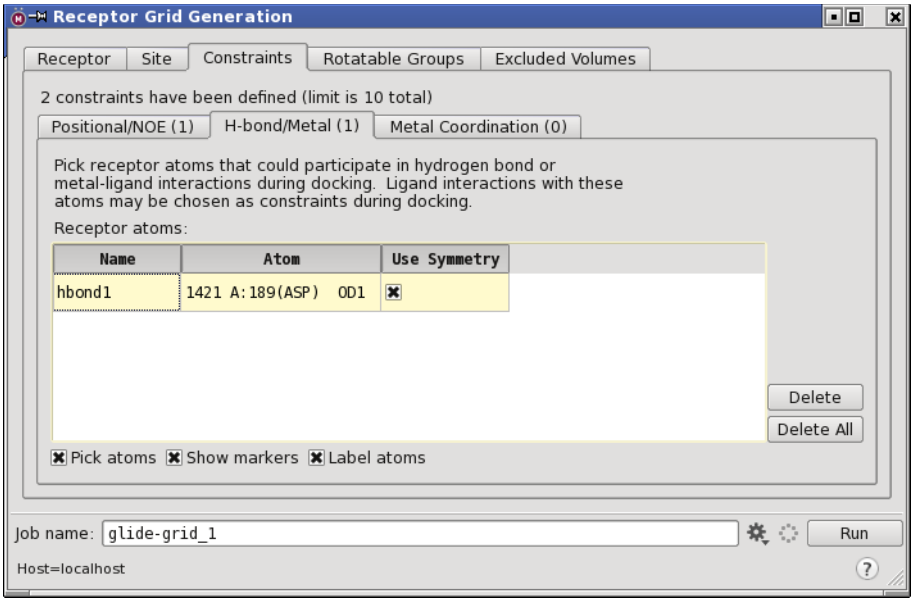

Figure 2.6. The Constraints tab of the Receptor Grid Generation panel showing the H-bond/Metal subtab.

4. Ensure that Pick atoms is selected.
5. Click on the carboxyl oxygen that is hydrogen-bonded to the amidine of the ligand.

   This atom is the OD1 atom of ASP 189. When you have picked the atom, an entry is added to the Receptor atoms table. The Name column shows the name as hbond1. In the Atom column, both oxygen atoms of the carboxylate are listed, because Glide includes symmetry-related atoms as part of the constraint. Both atoms are marked in the Workspace, if Show markers is selected, and the name is also displayed if Label atoms is selected.
6. Name the constraint `S1_site`, by editing the text in the Name column.
7. From the HBonds button menu, deselect Display.

2.5 Setting Up Excluded Volumes

In this exercise you will add an excluded volume to exclude ligands from a particular region of the bonding site.

1. Click the Excluded Volumes tab.
2. Click New.

   The New Excluded Volume dialog box opens. This dialog box is similar to that for positional and NOE constraints.

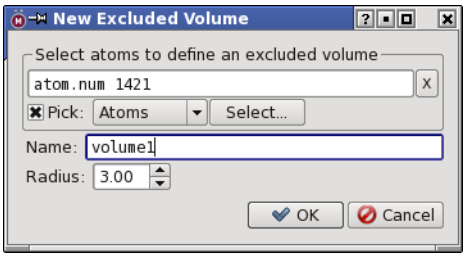

Figure 2.7. The New Excluded Volume dialog box.

3. Ensure that Pick is selected and Atoms is chosen from the Pick option menu (the default).
4. Pick the carbonyl oxygen atom that is hydrogen-bonded to the amidine of the ligand.

   This is the same atom as you picked for the H-bond constraint in Step 5 of Section 2.4.3.
5. Ensure that the radius is set to 3.0 Å (the default).
6. Click OK.

   An excluded volume named `volume1` is added to the table in the Excluded Volumes tab.

2.6 Starting and Monitoring the Grid Calculation

With the ligand and the active site defined, and constraints set up, the grid generation job can be started.

1. In the Job name text box at the bottom of the Receptor Grid Generation panel, change the name to `factorXa_grid`.
2. Click Run.

   You might see a dialog box that warns about an unidentified ligand. This is a check for ligand-sized molecules in the active site. It has found the glycerine molecules, which are not a problem for docking. You can therefore ignore the warning and click Continue.

When the job starts, the job status icon starts spinning. You can click this icon to display information about the job status. The job can also be monitored in the Monitor panel, which is not displayed by default. To open it, click the Jobs button in the status bar in the Workspace, or choose Applications → Monitor Jobs. While the job is in progress, the Status column displays "running." When the job is complete, the status is changed to "completed : finished".

The job takes approximately 3 minutes on a 2.33 GHz core2 duo processor; this time may vary depending on your particular system configuration and workload.

Before the job is launched, these job input files are written:

`factorXa_grid.in`	Command input for grids job
`factorXa_grid.maegz`	Receptor structure input for grids job

When the calculation is complete, the `grids` directory will contain the following output files:

`factorXa_grid.log`	Log summary file from grids job
`factorXa_grid.out`	Output summary file from grids job
`factorXa_grid.zip`	Archive containing grid files

The zip archive contains the following grid files:

`factorXa_grid.csc`	`factorXa_grid.gsc`
`factorXa_grid.site`	`factorXa_grid.save`
`factorXa_grid_greedy.save`	`factorXa_grid.cons`
`factorXa_grid_recep.mae`	`factorXa_grid.grd`
`factorXa_grid_coul2.fld`	`factorXa_grid_vdw.fld`
`factorXa_grid.vdwc`	`factorXa_grid.gxvol`

Ligand Docking

The exercises in this chapter demonstrate the use of Glide to screen a multiple-ligand file for structures that interact favorably with a receptor active site. The receptor grid files you calculated in the previous chapter will be used to dock ligands from the file `50ligs.mae`. Most of the 50 ligands in the file are decoys, selected as a representative sample from a database of drug-like molecules using the `ligparse` utility. Four ligands out of the total of 50 are active ligands for the chosen receptor. These ligands have all been prepared for docking with LigPrep—see Section 3.4 of the *Glide User Manual* or the *LigPrep User Manual* for more information on ligand preparation.

Typically, Glide standard-precision docking is used to find probable good binders in a large set; the top-scoring 10% to 30% can then be investigated more intensively using Glide extra-precision (XP) docking or other methods available from Schrödinger. In these exercises, you will use all three docking modes (HTVS, SP, and XP), and also investigate the use of constraints.

If you have not started Maestro or copied the tutorial files, do so now (see Section 1.2).

3.1 Specifying the Grid

In this exercise, you will select the grid that you calculated in Chapter 2 for the ligand docking job.

1. Click the Clear button on the Workspace toolbar.

   

2. Choose Tasks → Docking → Glide Docking.

   The Ligand Docking panel opens with the Settings tab displayed.

3. Click the Browse button for the Receptor grid.

   A file selector opens.

4. Navigate to the factorXa_grid folder, choose `factorXa_grid.zip`, and click Open.

   The full name of the grid file is displayed in th eReceptor grid text box.

3.2 Specifying Ligands To Dock

There are several methods for specifying ligand structures to be docked with receptor grids. In this tutorial, you will specify a file containing a set of 50 ligands.

1. In the Ligands tab, for Use ligands from, ensure that Files is selected.
2. Click Browse.

   A file selector is displayed. Ensure that Files of type is set to Maestro
3. Navigate to the tutorial directory, choose `50ligs.mae.gz`, and click Open.
4. Ensure that the selected Range is from `1` to End (the default).
5. Ensure that van der Waals radii scaling for ligand atoms is set to the default values: Scaling factor to 0.8 and Partial charge cutoff to 0.15.

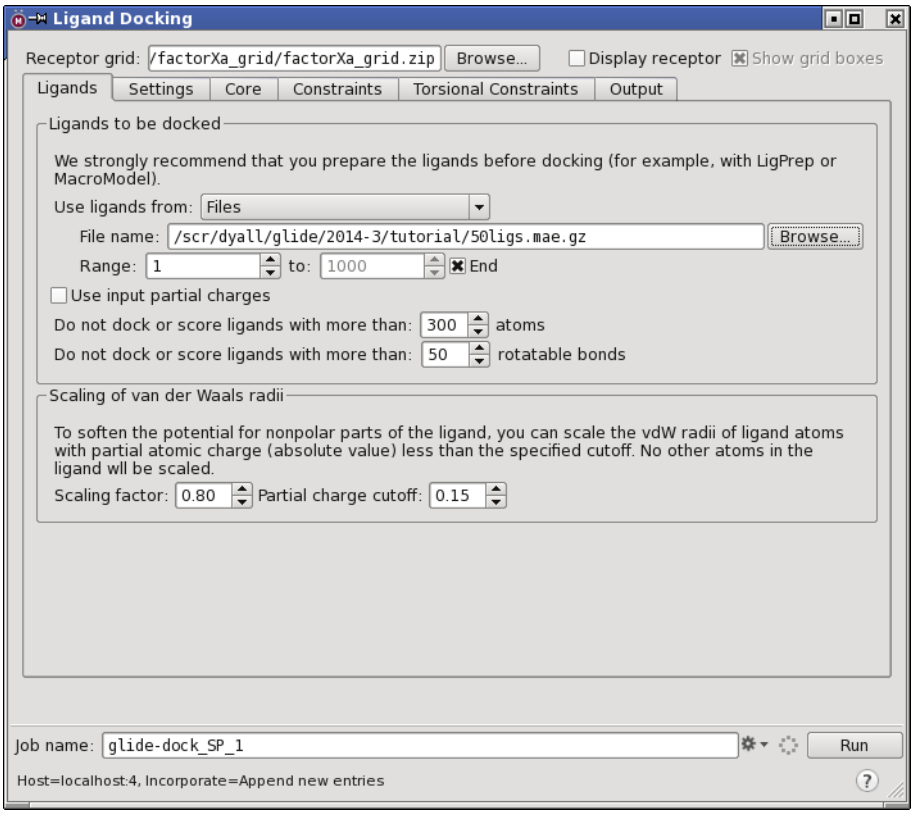

Figure 3.1. The Ligands tab of the Ligand Docking panel.

3.3 Setting Basic Options

In this exercise you will set and check the basic options for docking ligands.

1. In the Settings tab, ensure that the Precision option is SP (standard precision).

   This is usually the best choice for docking large numbers of ligands. For more rapid screening you can use the HTVS (high throughput virtual screening) option. You will do this in a later exercise.

2. Ensure that Ligand sampling is set to Flexible.

3. Ensure that Sample ring conformations and Sample nitrogen inversions are selected.

4. Ensure that Amides only is selected and Penalize nonplanar conformation is chosen from its option menu.

5. Ensure that Apply [Large] excluded volumes penalties is not selected.

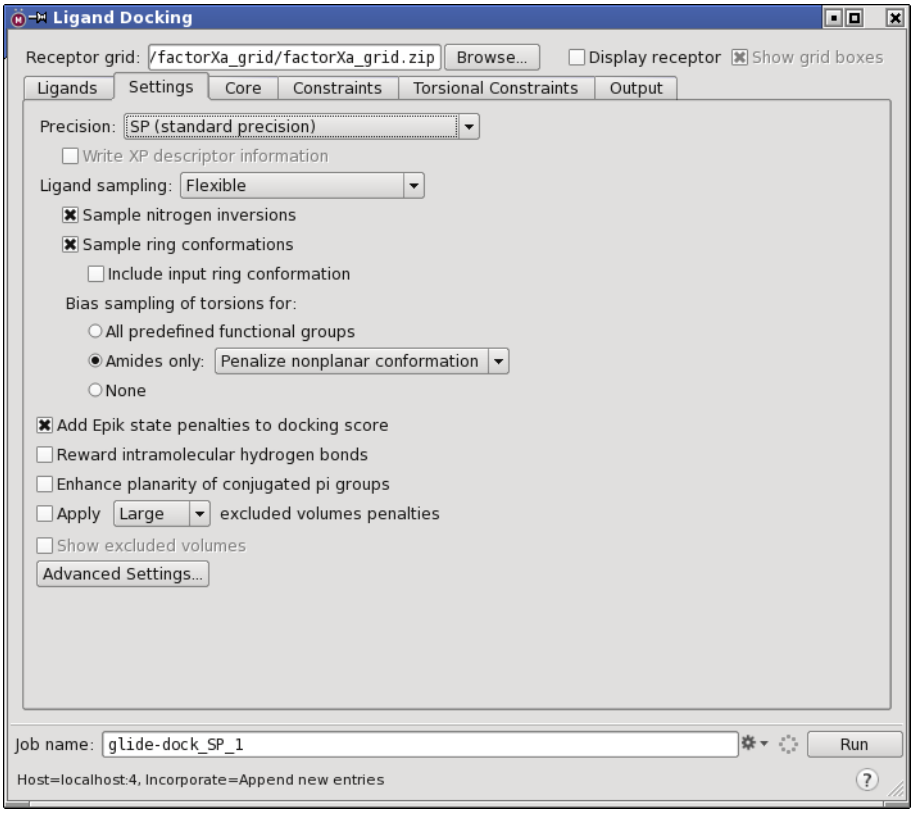

Figure 3.2. The Settings tab of the Ligand Docking panel.

These are the default settings. The grid, ligands, and basic Glide settings for the ligand docking job are now specified. In the next section, you will specify output options. The options in the remaining tabs can be left at their defaults for this exercise.

In this docking job the constraints that were specified in the grid generation will not be used. In a later exercise you will use the constraints to dock the same ligands.

3.4 Specifying Output Quantity and File Type

The Output tab allows you to specify the type of file to create for the output ligand poses, to determine how many poses to write, per ligand and per docking job, and to set various options for processing the output or providing information on the output structures.

1. In the Output tab, under File type, ensure that Pose viewer file (includes receptor) is selected.

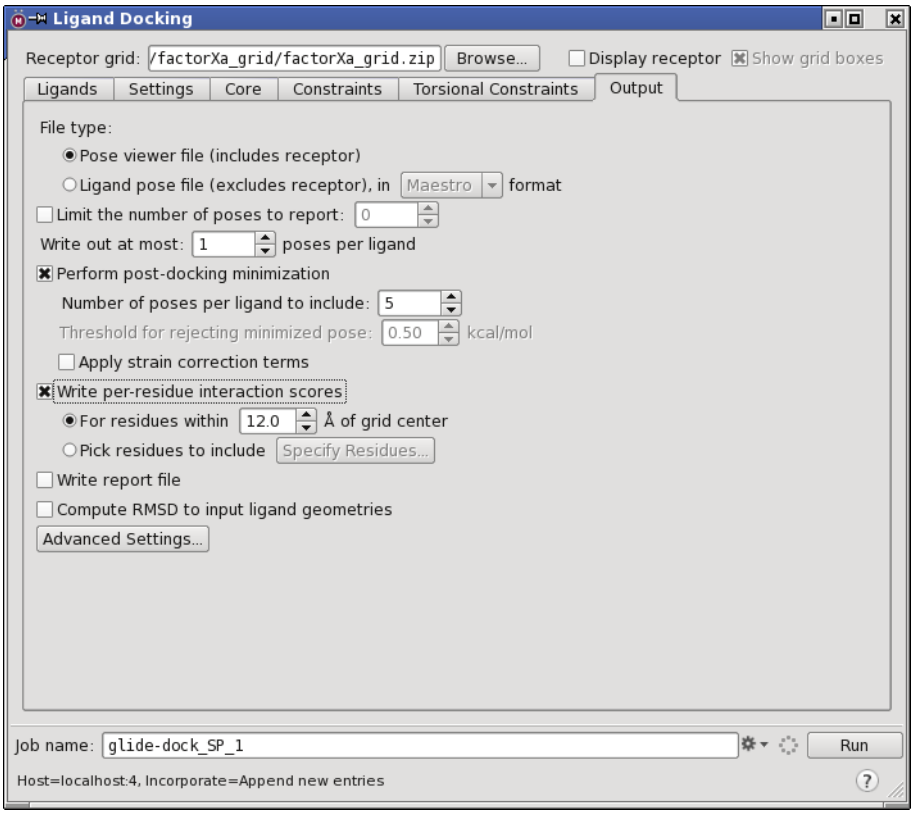

Figure 3.3. The Output tab of the Ligand Docking panel.

You are specifying that the structural output from the docking job be written to a "pose viewer" file, a file of ligand poses that begins with the structure of the receptor. Having the receptor structure included in the file is convenient for displaying hydrogen bonds and contacts between the ligand and the receptor. In Chapter 4, you will use some tools to examine the poses in the file `factorXa_sp_pv.maegz`.

2. Ensure that the value of *m* in the Write out at most *m* poses per ligand text box is 1, the default.

   Because there are only 50 ligands in the input file, this setting ensures that no more than 50 poses, one for each ligand, will be collected and written to the pose viewer file.

3. Ensure that Perform post-docking minimization is selected, with the default number of poses per ligand (which is 5).

   Post-docking minimization in the field of the receptor produces better poses and only adds a small amount to the time taken.

4. Select Write per-residue interaction scores and ensure that For residues within *N* Å of grid center is also selected (the default).

   You can leave the number in the text box at its default. The per-residue interaction scores will be used in the visualization exercises in Chapter 4.

3.5 Starting the Ligand Docking Job

In this section you will start the docking job. Glide can divide a multiple-ligand docking job into subjobs that can be distributed over multiple processors.

The time required for Glide docking jobs depends on the processor speed and workload, the size and flexibility of the ligands, and the volume specified by the enclosing box. The current 50-ligand docking job takes about 10 minutes on a 2.33 GHz core2 duo processor. As 10 subjobs distributed over 5 similar processors, the docking job should finish in about 2 minutes.

You can choose to run the job on a single processor, or distribute it across multiple processors. If you have access to a host machine with multiple CPUs and want to distribute the job, follow the instructions in Section 3.5.2. Otherwise, to run on a single processor, follow the instructions in Section 3.5.1.

When the job finishes, examine the results in the Project Table panel. The four active ligands (glide lignum 1 through 4) are ranked highest.

3.5.1 Running on a Single Processor

Use the instructions below to run the job on a single processor.

1. Click the Settings button.

   

   The Job Settings dialog box opens.

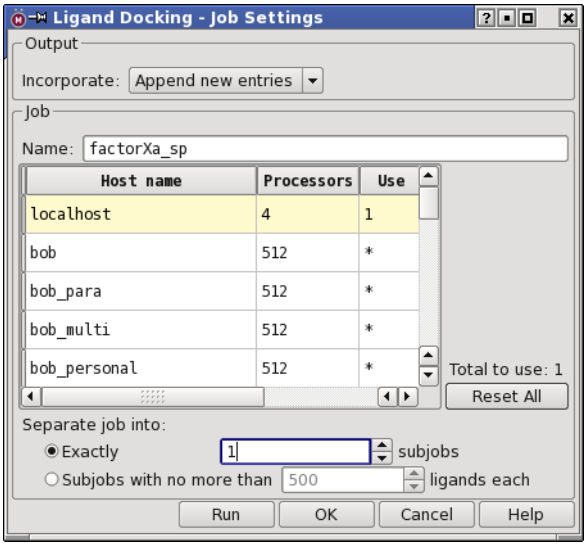

Figure 3.4. The Job Settings dialog box with settings for a single processor.

2. From the Incorporate option menu, choose Append new entries.
3. Change the job name in the Name text box to `factorXa_sp`.
4. Select a host from the Host list.
5. Ensure that the value in the Use column for the selected host is 1.

   The value in the Exactly *N* subjobs text box changes to 1 automatically. You can run multiple subjobs on a single processor, but you will have to set the number of subjobs explicitly.

6. Click Run.

   The docking job starts. By default, the Monitor panel is not displayed, but if you want to monitor the job, click the Jobs button in the status bar in the main window, or choose Applications → Monitor Jobs.

3.5.2 Running on Multiple Processors

The instructions below describe how to distribute the docking job over multiple processors. Job distribution is set up in the Start dialog box, which allows you to specify the number of subjobs and the number of processors to use. For efficient load balancing it is a good idea to set the number of subjobs to a multiple of the number of processors.

1. Click the Settings button.

   

   The Job Settings dialog box opens.

2. Change the job name to `factorXa_sp`.

3. From the Incorporate option menu, choose Append new entries.

4. Under Separate job into, select Exactly *N* subjobs and set the value in the text box to 10.

   The docking job will be split into 10 subjobs, each one docking 5 ligands. For the sake of speed, the number of ligands per subjob in this exercise is much smaller than would be typical in actual use. The default for *N* is 1, meaning that the job is run as a single job.

5. Choose a multiprocessor host from the Host list table.

   The number of processors on each host is shown in the Processors column.

6. Edit the value in the Use column for the selected host to specify the number of processors to use.

   By default, the value is set to the number of processors on the host. We suggest using a value of 5, but you can choose any number that is not greater than 10, the number of subjobs. The value shown by the Total to use text is updated to reflect the value you entered. If you want to use multiple hosts, you can select multiple table rows, and specify the number of processors to use on each. The total number is given by the Total to use text.

   The 10 subjobs will be distributed over the number of processors you specify. If you use five processors, the first five subjobs are run first, followed by each of the remaining five as processors become available.

7. Click Run.

As soon as the `factorXa_sp` job has been launched, it is divided into subjobs. As each subjob is launched on a processor, it is listed in the Monitor panel. When one subjob is finished, the next one is launched. To view the log for any subjob, select it in the job table and click Monitor. If the subjob is already finished, the entire log can be scrolled through in the File tab of the Monitor panel. The results for each subjob are stored in subdirectories of the output directory, and collected at the end into the output directory.

3.6 Docking in High-Throughput Virtual Screening Mode

Glide has a set of predetermined options that can speed up the docking by a factor of about seven over the standard precision (SP) docking mode. In this exercise, you will run an HTVS docking job on the same set of ligands as used in the SP docking exercise.

1. In the Settings tab, select HTVS from the Precision option menu.

   The other settings will be left as they were for the SP docking job.

2. In the Output tab, deselect Write per-residue interaction scores for residues within *N* Å of grid center.

3. Under File type, select Ligand pose file (excludes receptor).

4. In the Job name text box, set the job name to `factorXa_htvs`.

5. If you ran the job on a single processor in the previous exercise, click Run. If you ran the job on multiple processors, do the following:

   a. Click the Settings button.

   b. Select a host, and set the number of processors and subjobs to 1.

   c. Click Run.

The job should take only a minute to run. When the job finishes, examine the results in the Project Table panel. The four active ligands are ranked in the top 9 ligands. Their scores differ a little from those in the SP docking run.

3.7 Using Excluded Volumes

In this exercise you will apply the excluded volume penalties for the excluded volume in the S1 pocket. This should prevent ligands from binding in this very favorable part of the receptor. The settings from the previous exercise will be used.

1. In the Settings tab, ensure that HTVS (high throughput virtual screening) is selected.

2. Select Apply [Large] excluded volumes penalties.

   The other settings will be left as they were for the previous HTVS docking job, including the ligand file.

3. Change the job name to `factorXa_exclvol`.

4. Click Run.

The job should take only a minute to run. When the job finishes, examine the results in the Project Table panel.

5. Compare the docking score from this run for the ligand 16088 to that from the previous run (entry group factorXa_htvs_lib1).

   Note that the score has gone from around –9 to around –7, a penalty of about 2 kcal/mol due to the exclusion of this ligand from the S1 binding site.

6. Include in the Workspace the receptor and ligand 16088 from this run and the previous run (use control-click).

7. Click the Apply button on the Style toolbar.

   

   The ligand carbon atoms are colored differently, allowing you to distinguish the ligands.

8. Click the HBonds button on the Measurements toolbar.

   

9. Check that Ligand-receptor and H-Bonds are selected, and select Display.

   Hydrogen bonds are now displayed between the receptor and the two poses of the ligand.

The protonated amidine in the ligand from the previous run is hydrogen bonded to the carboxylate of ASP 189 in the S1 pocket, which is strongly favored. It also has a naphthyl group in the S4 pocket, which is also favored. In this run the amidine cannot form a hydrogen bond with the carboxylate because this is the region that was excluded. The napthyl group instead occupies this pocket, but outside the excluded volume, and the amidine is in the S4 pocket.

3.8 Using Ionization and Tautomeric State Penalties

When the ligands are prepared using Epik, state penalties for the ionization and tautomeric states can be added to the structure properties. These penalties can be applied in docking to produce an adjusted score, the *docking score*. In this exercise, you will run an HTVS docking job on the same ligands as in the previous exercise, but with state penalties generated by Epik.

1. In the Settings tab, ensure that Add Epik state penalties to docking score is selected.

2. Ensure that HTVS (high throughput virtual screening) is selected.

3. Deselect Apply [Large] excluded volumes penalties.

   The other settings will be left as they were for the previous HTVS docking job.

4. In the Ligands tab, click Browse.

   A file selector opens.

5. Choose `50ligs_epik.mae.gz`, and click Open.
6. Ensure that the selected Range is from `1` to End (the default).
7. Change the job name to `factorXa_epik`.
8. Click Run.

The job takes only a few minutes to run. The results include more poses because of the ionization and tautomeric states that were generated by Epik. Next, you will examine the scores for the ligand titled 15650 Known Active, which is one of the active ligands. This ligand has a protonated amine group; Epik generated both the protonated and the unprotonated form of this ligand. The protonated form is the normal form at physiological pH.

9. Click the Table toolbar button in the main window (if the Project Table panel is not open).

   

   The Project Table panel opens.

10. Choose Group → Expand → Only Selected.

    The entry groups from the previous runs are now collapsed, and only the current results are displayed.

11. Right-click on the Title column heading and choose Sort Selected (A to Z). Repeat this action if necessary to bring the ligands into ascending order of title (molecule ID).

    The two forms of ligand 15650 now appear near the top of the entry group.

12. Scroll the properties in the Project Table panel so that you can see both the docking score and the glide gscore (GlideScore) properties.

    Note that there is no difference between these two properties for the first ligand in the entry group, ligand 1167, which has no ionization or tautomeric states, but that there is a difference for both forms of ligand 15650. The docking score is less negative for the neutral form, because this state is heavily penalized by Epik, due to the fact that aliphatic amines are typically protonated in an aqueous environment.

13. Fix the receptor entry (1fjs_prep_recep) in the Workspace by right-clicking on it and choosing Fix.
14. Include both of the ligand 15650 forms in the Workspace (use control-click).

15. Click the Tile toolbar button.

    The two ligands are displayed side-by-side in separate tiles, with the receptor shown in each tile.

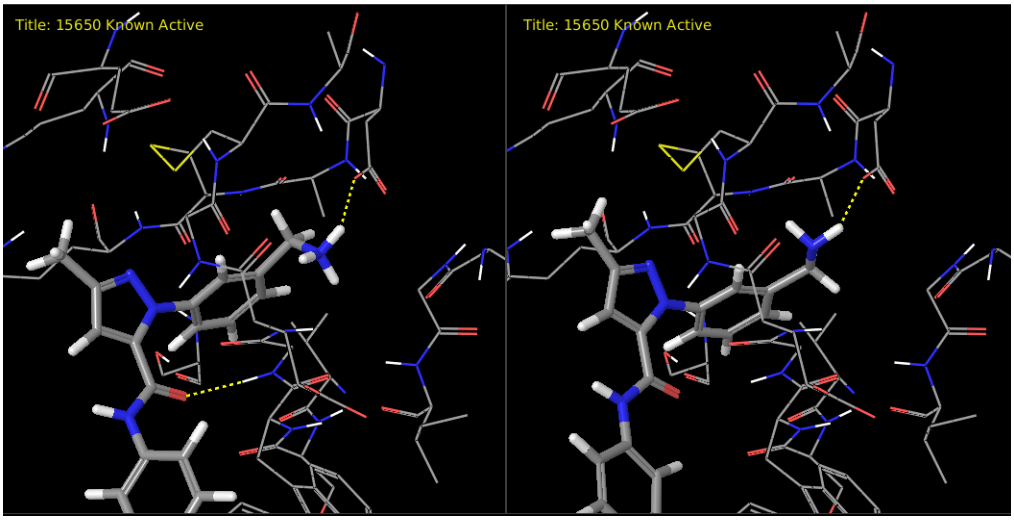

Figure 3.5. Docked poses of ligand 15650, protonated (left) and unprotonated (right).

16. Adjust the location and orientation of the view so that you can see the protonated amine group clearly.

    Both tiles are updated as you do the adjustment. This allows you to see the ligand from the same angle in both poses.

17. Click the HBonds button on the Measurements toolbar.

18. Check that Ligand-receptor and H-Bonds are selected, and select Display.

    The hydrogen bonds are displayed. Both forms of the ligand bond to the carboxylate of ASP 189, but the protonated form has much stronger binding and is not penalized for water displacement, as the unprotonated form is. In addition, the neutral form is penalized by Epik for its very low concentration at physiological pH.

3.9 Docking Ligands Using Positional and H-Bond Constraints

In this exercise, you will apply the constraints you defined in the grid generation to the docking of the same set of ligands as for the standard SP job. By default, no constraints are applied, even if they are defined. Here, you will require any one of the three constraints to be applied.

1. In the Settings tab, select SP (standard precision).

   The other settings will be left as they were for the HTVS docking job.

2. In the Ligands tab, click Browse.

   A file selector opens.

3. Choose `50ligs.mae.gz`, and click Open.

4. In the Constraints tab, click both check boxes in the Use column.

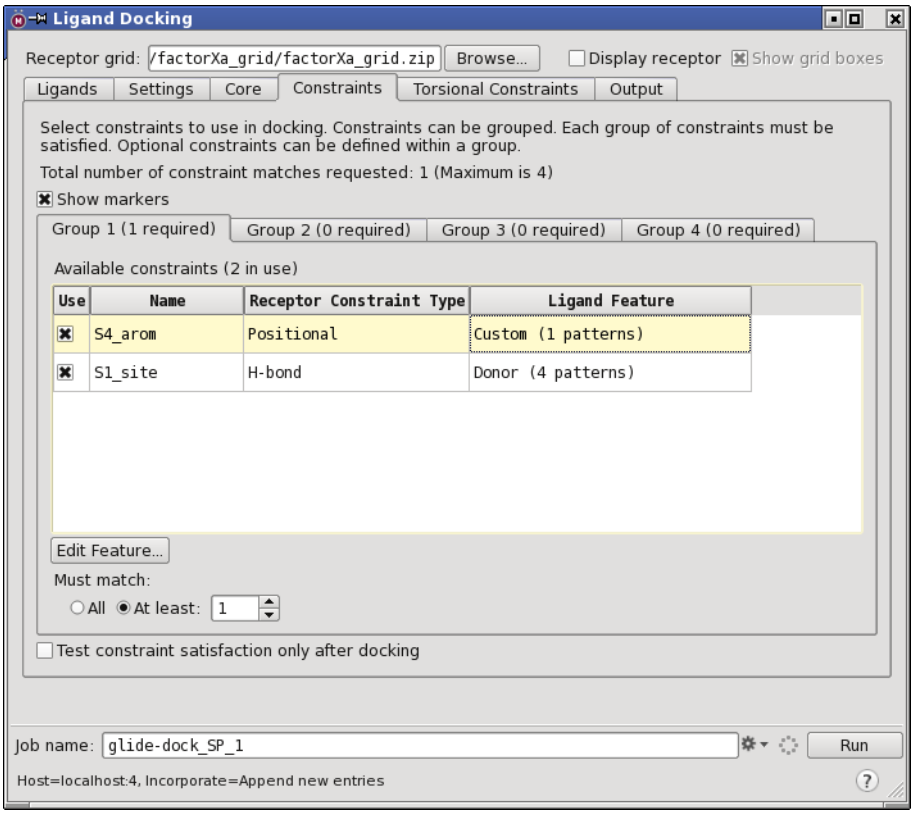

Figure 3.6. The Constraints tab of the Ligand Docking panel.

These check boxes mark the constraints for use in docking.

5. Under Must match, select All.

For H-bond and hydrophobic constraints, the ligand features that must match these constraints are predefined. You can edit them if you want, but this is not necessary. For positional constraints, you must define the ligand feature that matches the constraint. Features are defined in terms of SMARTS patterns.

6. From the Available constraints table, select the S4_arom row and click Edit Feature.

   The Edit Feature dialog box opens. There are no SMARTS patterns in the Pattern list table, because the Custom feature type is undefined by default.

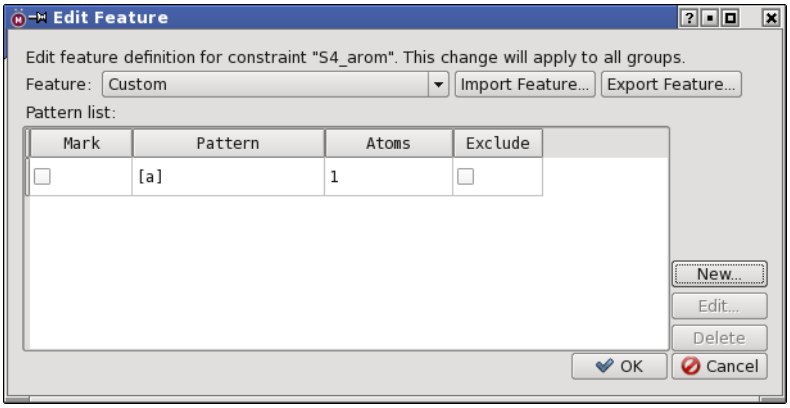

Figure 3.7. The Edit Feature dialog box.

7. Click New.

   The New Pattern dialog box opens.

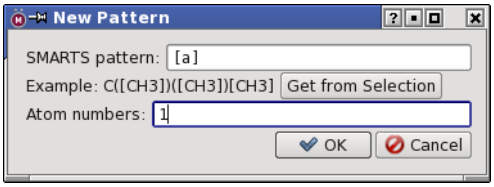

Figure 3.8. The New Pattern dialog box.

8. Enter the following text into the SMARTS pattern text box:

   ```
   [a]
   ```

   This pattern matches all aromatic atoms.

9. Enter `1` into the Atom numbers text box.

   This is the index of the atom in the SMARTS pattern that is matched by the constraint. Since there is only one atom in the pattern, this is the only possible choice.

10. Click OK.

    The New Pattern dialog box closes, and a row is added to the Pattern list table in the Edit Feature dialog box.

11. Click OK.

    The Edit Feature dialog box closes. This completes the definition of the Custom feature. If you did not define this feature, the docking job would not be started.

12. Change the job name to `factorXa_sp_cons`.

13. Click Run to run the job on a single processor, or if you want to run the job on multiple processors, follow the instructions in Section 3.5.2 on page 21.

14. When the job finishes, examine the results in the Project Table.

Of the 50 ligands, poses are reported for only six ligands, of which the first four are the actives, and the others did not score very well. The remaining ligands did not satisfy the constraints. These results indicate that the application of constraints serves to discriminate between ligands that bind in the proper mode, and ligands that don't.

3.10 Docking Ligands Using Core Constraints

In this exercise, you will apply core constraints defined by a pattern in the reference ligand, and use these to dock a set of structures. Structures that do not include the core pattern will not be docked. The first task is to import the reference ligand.

1. In the main window click the Import button on the Project toolbar.

   

   The Import panel opens.

2. From the Files of type menu, ensure that Common is chosen.

3. Ensure that Import all structures and Replace Workspace are selected.

4. Select the file `sar_reference.mae.gz`.

5. Click Open.

   The reference ligand is displayed in the Workspace.

Next, the settings for the previous constraints job need to be cleared.

6. In the Ligand Docking panel, click the Settings tab, and select SP (standard precision).

   The other settings will be left as they were for the previous docking job.

7. In the Constraints tab, clear all check boxes in the Use column.

   Receptor-based constraints will no longer be applied; instead you will be using ligand-based constraints.

The core constraint is defined in the following steps.

8. In the Core tab, select Use core pattern comparison.

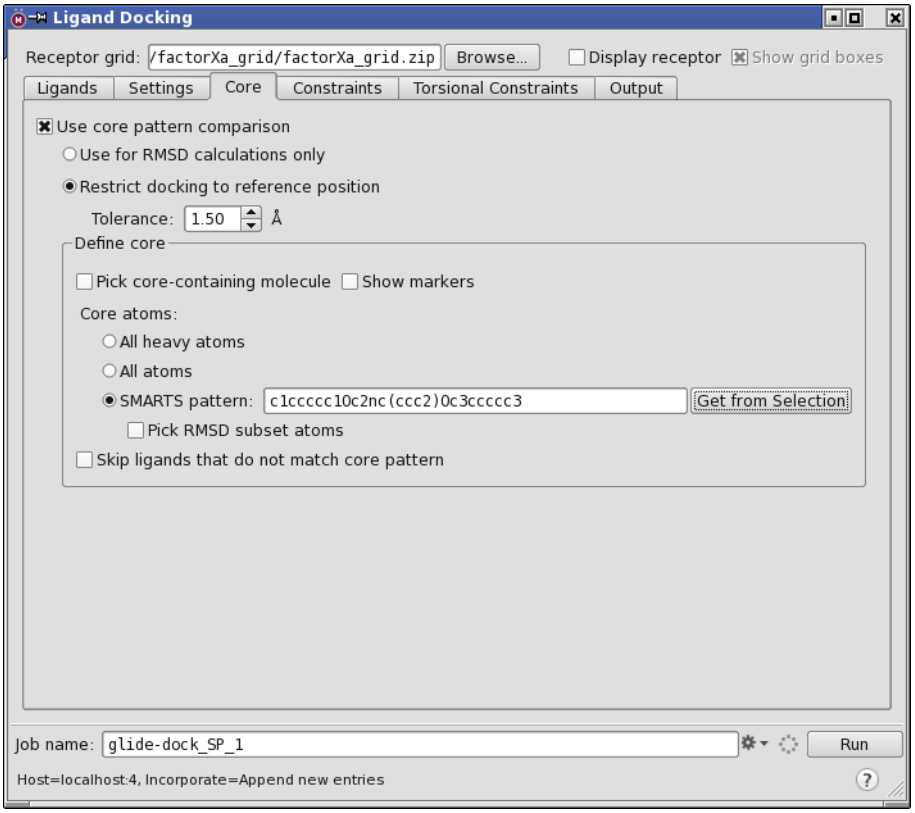

Figure 3.9. The Core tab of the Ligand Docking panel.

9. Select Restrict docking to reference position.

   The first few controls in the Define core section become available.

10. Enter `1.5` in the Tolerance text box.
11. Select Pick core-containing molecule.
12. Click an atom in the reference ligand (in the Workspace).

    The ligand is marked with purple markers, and the remaining controls in the Define core section become available.
13. Under Core atoms, select SMARTS pattern.
14. In the main window, from the Undisplay button menu, choose Nonpolar hydrogens.

    
15. Rotate the structure so that you can clearly see the three six-membered rings.
16. Ensure that the Select button is selected (indented) and displays an A (for picking atoms).

    
17. Select the three six-membered rings with their ether linkages, and the amidine group on the terminal ring.

    Do not include the carboxyl on the middle ring or the hydroxyl on the terminal ring.

    You can drag to make the first selection, then hold down SHIFT and drag or click to add atoms to the selection. The selected atoms are marked in yellow rather than in purple.
18. In the Ligand Docking panel, click Get From Selection.

    The Smarts pattern text box is filled in with the pattern that corresponds to the atoms selected in the Workspace. The markers on the Workspace selection turn green.

Finally, the ligands to be docked need to be selected. A different set is used from the set used for the previous runs.

19. In the Ligands tab, ensure that File is selected.
20. Click Browse.

    A file selector is displayed. Ensure that Files of type is set to Maestro.
21. Choose `sar_series.mae.gz`, and click Open.
22. Ensure that the selected Range is from `1` to End (the default).
23. Start the job with the name `factorXa_sp_core`.

    The job takes a similar time to the constraints job.

24. When the job finishes, examine the results in the Project Table.

3.11 Docking Ligands Using Torsional Constraints

If you have flexible ligands and want to constrain some of their torsions, or you want to enforce a particular orientation of a group in the ligands, you can use torsional constraints. The constraints are applied to any ligand that matches a supplied SMARTS pattern; ligands that do not match are docked without applying the torsional constraints. You can define multiple patterns, and for each pattern you can define multiple torsional constraints. In this exercise, you will only define one pattern and one torsion.

In this exercise you will dock the native ligand for 1fjs, but with the imidazole ring flipped by applying a torsional constraint to the flipped geometry. The ligand is imported first. It serves as the template for the SMARTS patterns.

1. Click the Import button on the Project toolbar.

   

   The Import panel opens, showing the contents of the working directory.
2. From the Files of type menu, choose Common.
3. Select the file `1fjs_prep_lig.mae.gz`.
4. Click Open.

   The ligand is displayed in the Workspace.

Next, any settings from the previous exercise are reset for the current exercise.

5. In the Ligands tab under Use ligands from, select Workspace.
6. In the Settings tab of the Ligand Docking panel, select SP (standard precision).
7. In the Core tab, deselect Use core pattern comparison.

Next you will set up the pattern to be matched in the ligand and the torsion within that pattern that is to be constrained. The pattern to be matched in the ligand must usually extend beyond the torsion to be constrained, so that only the desired torsion is constrained, and not other torsions that would match. For instance, the pattern `cccn` would restrict both the imidazole ring torsion and the amidine, and here we only want to restrict the imidazole ring torsion.

8. Click the Torsional Constraints tab.

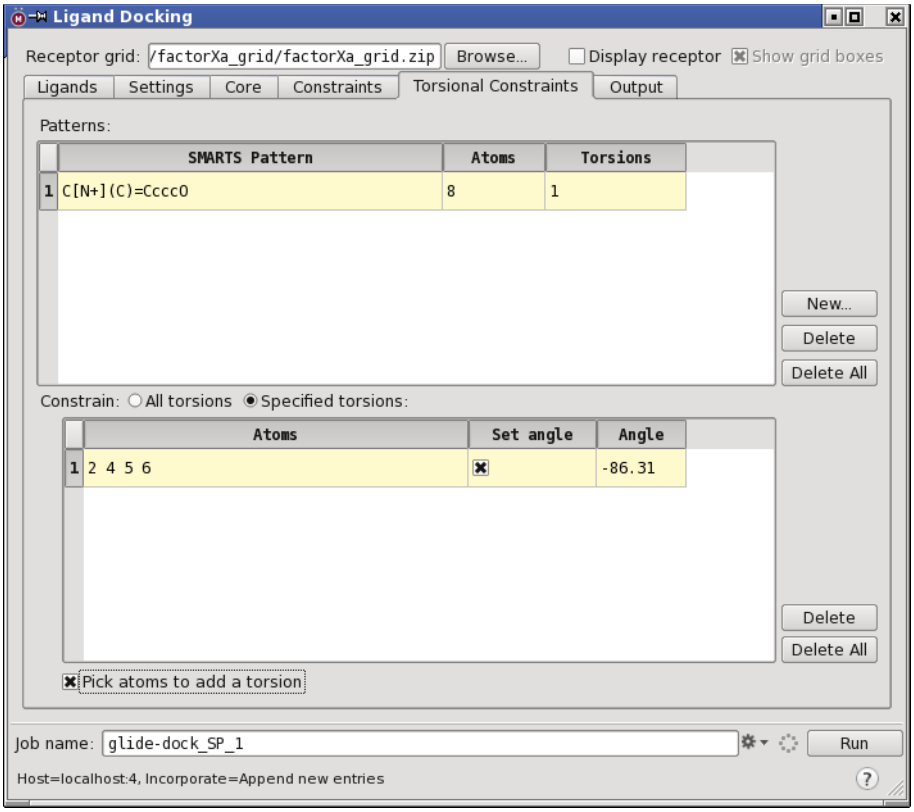

Figure 3.10. The Torsional Constraints tab of the Ligand Docking panel.

9. In the Workspace, select the following atoms. (Use shift-click to add to the selection):

   - The imidazole nitrogen that has a methyl attached and the three carbon atoms attached to it.
   - The phenyl carbon attached to the imidazole ring, the one attached to the oxygen, and the carbon in between.
   - The oxygen attached to the phenyl ring.

   The atoms to pick are shown in Figure 3.11. The oxygen atom is included to avoid symmetry within the phenyl ring.

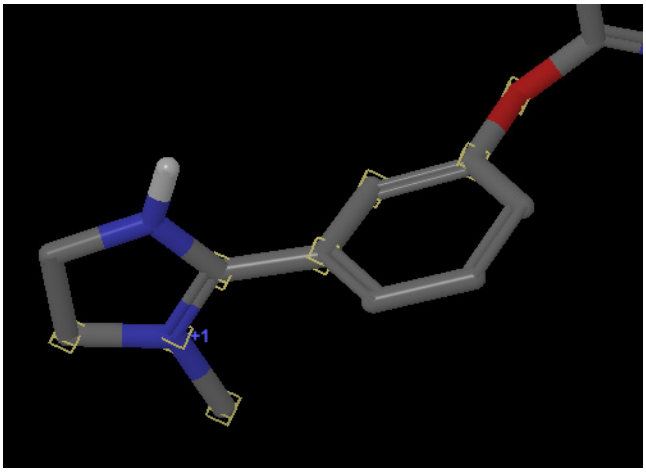

Figure 3.11. The 1fjs ligand, showing the atoms to select for a torsional constraint.

10. In the Torsional Constraints tab, click New.

    The New Torsion Pattern dialog box opens.

11. Click From Workspace Selection, then click OK.

    A row is added to the Patterns table with the following SMARTS pattern:

    `C[N+](C)=CcccO`

12. For Constrain, select Specified torsions.

13. Ensure that Pick atoms to add a torsion is selected.

14. In the Workspace, pick the marked imidazole nitrogen, the two carbons in the bond joining the imidazole to the phenyl ring, and the marked carbon next to it in the phenyl ring.

    A row is added to the torsions table. The Atoms column should show 2 4 5 6, which are the atom numbers in the SMARTS pattern that correspond to the picked atoms.

15. Select the check box in the Set angle column.

    The current angle value is displayed in the Angle column, and is close to 90°.

16. Edit the Angle cell to change the sign of the angle.

17. In the Output tab, ensure that Ligand pose file (excludes receptor) is selected.

18. Enter `dock_torcons_flip` in the Job name text box.

19. Click Run.

    The job should take less than a minute to finish.

Now you will redock the ligand without the torsional constraint.

20. Include in the Workspace just the ligand structure that you imported.

    The ligand in the Workspace is the result of the previous docking run, so to compare results, the same ligand needs to be used in each docking run.

21. In the Torsional Constraints tab, click Delete All to delete all patterns.

22. Run the job with the name `dock_notorcons`.

23. When the job finishes, display the poses obtained with and without the constraints.

    The pose with the imidazole ring flipped docks in a very similar pose to the pose obtained without the constraint, except that one of the groups is rotated in the unconstrained pose. This is not surprising since the group is exposed to the solvent and can easily adopt different conformations.

Finally you will dock the ligand with all torsions constrained (rigid docking).

24. Include in the Workspace just the ligand structure that you imported.

25. Select all atoms in the ligand (by dragging over the entire molecule).

26. In the Torsional Constraints tab, click New.

    The New Torsion Pattern dialog box opens.

27. Click From Workspace Selection, then click OK.

    A new pattern is added, that has 43 atoms. This pattern includes polar hydrogens, but does not include nonpolar hydrogens, which are not displayed.

28. Under Constrain, select All torsions.

29. Start the job with the name `dock_torcons_all`.

30. When the job finishes, add the pose obtained with the ring flipped to the Workspace (control-click).

    The pose with all torsions constrained is very similar to that in which only the ring was flipped.

3.12 Refining Docked Ligands with Glide XP

In this exercise, you will use Glide XP to refine a set of ligands from the first SP docking run. The results of this exercise are used later in a visualization exercise.

1. In the Torsional Constraints tab, deselect Apply torsional constraints.

   Torsional constraints are now turned off.

2. In the Settings tab, choose XP (extra precision) from the Precision option menu.
3. Select Write XP descriptor information.

   Note: This option requires a special license. If you do not have this license, do not select the option. You will obtain results without the license, but you will not be able to complete the exercise in Section 4.6.

4. From the Ligand sampling option menu, choose None (refine only).
5. In the Ligands tab, ensure that File is selected.
6. Click Browse.

   A file selector is displayed.

7. Ensure that Files of type is set to Maestro or Common.
8. Choose `refine_xp_entries.mae.gz`, and click Open.
9. Ensure that the selected Range is from `1` to End (the default).
10. If you did not select Write XP descriptor information, in the Structure output section of the Output tab, select Pose viewer file (includes receptor).

    If you did select this option, the Pose viewer file option is automatically selected.

11. Start the job with the name `factorXa_xp_refine`.

This job may take up to 30 minutes to run on a 2 GHz processor.

Examining Poses

In this chapter, Glide results are examined with an emphasis on visual rather than numerical appraisal. The first set of exercises use the Project Table to display the results of the SP Glide docking job, examine individual ligand poses and their contacts with the input receptor structure. The second set of exercises uses the Glide XP Visualizer panel to display information on the terms in the Glide XP scoring function that contribute to the ligand binding.

If you have not started Maestro, start it now (see Section 1.2).

4.1 Importing and Selecting Pose Data

If you are continuing on from the previous chapter, the poses are already available in the Project Table, and you only need to select them. Otherwise, you will need to import the poses.

If you are continuing from the previous chapter:

- In the Project Table panel, select the entry group factorXa_sp_pv1.

If you need to import the poses:

1. Click the Import button on the Project toolbar.

   

   The Import panel opens, displaying the contents of the directory where your docking results were written.

2. Ensure that Maestro is chosen from the Files of type menu.

3. Ensure that Import all structures, Replace Workspace, and Fit to Workspace following import are all selected.

4. In the Import panel, select the file `factorXa_sp_pv.maegz` and click Open.

   The receptor and the ligands are imported as an entry group named factorXa_sp_pv. The receptor is displayed in the Workspace.

5. If the Project Table panel is not open, open it.

   You can do this by clicking the Table toolbar button.

   

   The entry group factorXa_sp_pv that you imported should be already selected. If not, click in the Row column for this entry group.

4.2 Viewing Poses

The Project Table panel has a facility for viewing poses, using an entry group that consists of a receptor and a set of ligands. This facility is available in the Pose Viewer panel, which you open with Entry → View Poses, when you have a single entry group selected. It is also available in the main window: Applications → Glide → View Poses.

1. Choose Entry → View Poses.

   The Pose Viewer panel opens, docked into the Workspace by default. The receptor is fixed in the Workspace, and the first pose is included in the Workspace. A Mark property is added to the Project Table so you can mark poses as being of special interest. To mark a Workspace entry, type X. The property is not shown by default.

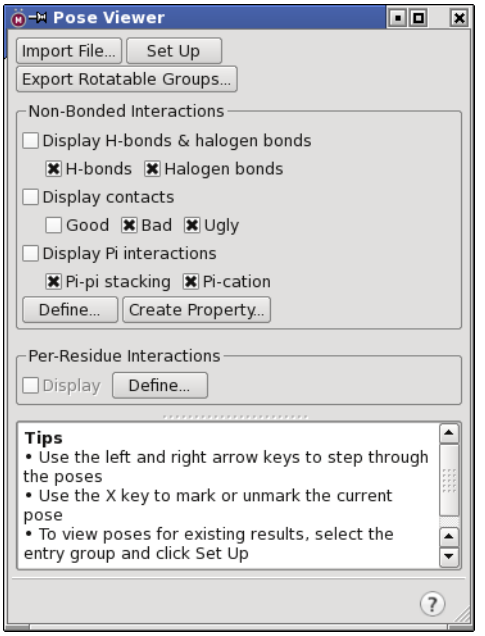

Figure 4.1. The Pose Viewer panel.

2. If Workspace feedback is not displayed, type S.

   By default Workspace feedback appears in the upper right corner of the Workspace, and includes the entry title.

Now you are ready to view the poses.

3. Press the RIGHT ARROW key.

   The second pose replaces the first in the Workspace. The RIGHT ARROW and LEFT ARROW keys can be used to step through the selected poses.

4. Shift-click the entry for the first pose.

   The first pose is added to the Workspace, and the Workspace feedback is removed.

5. Press the RIGHT ARROW key.

   The third pose replaces the first two, and the Workspace feedback is displayed.

6. Reselect the first pose by clicking its In column.

4.3 Displaying Atoms by Proximity

In this section, you will select a display that includes the ligand and the receptor residues nearest the ligand. This is useful for examining contacts and hydrogen bonds between the ligand and the active site of the receptor.

1. From the Display Only button menu on the Display Atoms toolbar, choose Ligands.

   

   The ligand molecule is displayed, and all other atoms are undisplayed.

2. From the Within button menu on the Display Atoms toolbar, choose +5 Å.

   

   Only the ligand and the nearby residues are displayed. All residues that do not have any atoms within 5 Å of the ligand are undisplayed. Hiding the residues that do not come into contact with the ligand makes it easier to examine the ligand-receptor interactions.

   If you want more flexibility in picking the residues, you can open the Atom Selection dialog box from the Display only button menu to pick the ligand and add atoms within a given radius of a particular set of atoms.

4.4 Visualizing Hydrogen Bonds and Contacts

In this exercise, you will display hydrogen bonds between the ligand and the receptor. (To display hydrogen bonds or contacts between any two sets of atoms, click Define to open the Non-Bonded Interactions panel, where you can make the desired settings.)

1. In the Pose Viewer panel, select Display H-bonds & halogen bonds in the Non-bonded interactions section, and deselect Halogen bonds.

   Hydrogen bonds to the currently displayed pose are displayed as yellow dashed lines.

   If you want to change the cutoffs for defining hydrogen bonds, you can do so in the Preferences panel, under Non-bonded interactions – Criteria.

   If you want a count of hydrogen bonds between the ligands and the receptor, click Create Property in the Non-bonded interactions section, select H-bonds and halogen bonds and clear other options in the Create Properties dialog box. The count may take a few seconds to finish. When it does, an HBond property is added to the Project Table.

2. Use the RIGHT ARROW and LEFT ARROW keys to step through the poses.

   The hydrogen bonds are displayed as each pose is included in the Workspace. Note the difference in hydrogen bonding patterns between the ligands.

3. In the Pose Viewer panel, select Display contacts.

   The contacts are shown as dashed lines connecting Workspace atoms. Ugly contacts are shown in red and Bad contacts are shown in orange. By default, atoms that are hydrogen bonded are not considered to have bad or ugly contacts.

   If you want to change the distance cutoff criteria for Good, Bad, and Ugly contacts, you can do so in the Preferences panel, under Non-bonded interactions – Criteria.

   If you want a count of contacts between the ligands and the receptor, click Create Property in the Non-bonded interactions section, select Cutoffs and clear other options in the Create Properties dialog box. The count may take a few seconds to finish, and three new properties are added to the Project Table: Good vdW, Bad vdW, and Ugly vdW.

   In the pose list, 309 Good vdW, 7 Bad vdW, and 0 Ugly vdW contacts are reported for `687624`. Even the least-good ligand pose has many more good contacts than bad or ugly ones. The default is to display only Bad or Ugly contacts between the ligand and the receptor.

4. Use the RIGHT ARROW and LEFT ARROW keys to step through the poses.

4.5 Visualizing Per-Residue Interactions

In this exercise you will visualize the per-residue interactions that you generated in the SP docking run. After turning the display on and selecting the interaction, you need to choose the residues for which the interaction is displayed.

1. In the Pose Viewer, select Display in the Per-Residue Interactions section.
2. Click Define in the Per-Residue Interactions section.

   The Per-Residue Interactions panel opens. By default, the interaction type selected is Interaction energy.

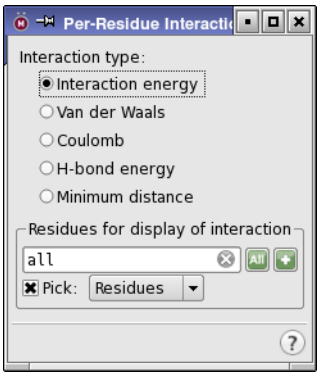

Figure 4.2. The Per-Residue Interactions panel.

3. Click the Atom selections button, then choose Select.

   

   The Atom Selection dialog box opens.
4. In the Molecule tab, choose Molecule number.
5. Enter `10` in the Molecule number text box, and click Add.

   The ligand is highlighted with light blue markers in the Workspace.
6. Click Proximity.

   The Proximity dialog box opens.
7. Type 5 in the text box.
8. Under Fill, select Residues.

9. Click OK.

   The Proximity Dialog box closes, and the residues within 5 Å of the ligand are marked in the Workspace.

10. Click OK in the Atom Selection dialog box.

    The dialog box closes, and the residues are colored in the Workspace according to the value of the interaction.

11. Use the RIGHT ARROW and LEFT ARROW keys in the Workspace to step through the first eight poses.

    The active ligands have very similar interactions, and a particularly favorable interaction (colored red) with ASP 189, to which they are hydrogen-bonded. The decoy ligands have favorable interactions with a variety of residues, and as the color scheme is relative to the range of values for the ligand, the quality of the most favorable (red) interaction varies from ligand to ligand. The color scheme is therefore of most use in picking out the residues with which there is the most favorable or unfavorable interactions. Given that ASP 189 is important for binding, ligands that don't have a favorable interaction with this residue are likely to be poor binders.

12. In the Per-Residue Interactions panel, select Van der Waals.

13. Use the RIGHT ARROW and LEFT ARROW keys in the Workspace to step through the first eight poses.

    The active ligands all have a lot of favorable van der Waals interactions (red and pink), particularly with TRP 215. They also have an unfavorable van der Waals interaction with ASP 189, but this is the residue to which they are hydrogen bonded. By contrast, the decoys have more unfavorable interactions and fewer favorable interactions.

14. Close the Per-Residue Interactions panel, and turn off the display of per-residue interactions.

    Turning off the display returns the coloring of the receptor to the Element color scheme.

4.6 Visualizing Glide XP Descriptors

In this exercise, you will use the Glide XP Visualizer to examine the contributions of various terms to the XP scoring function. The terms are given a spatial representation that you can display together with the ligand and the receptor.

Note: This exercise uses the results obtained from the exercise in Section 3.12 on page 35, which requires a special license for XP descriptor generation. However, the results of this exercise are included with the tutorial files, so you can still do the exercise.

1. Click the Clear button on the Workspace toolbar.

2. Choose Tasks → Docking → Visualize XP Interactions.

   The Glide XP Visualizer panel opens.

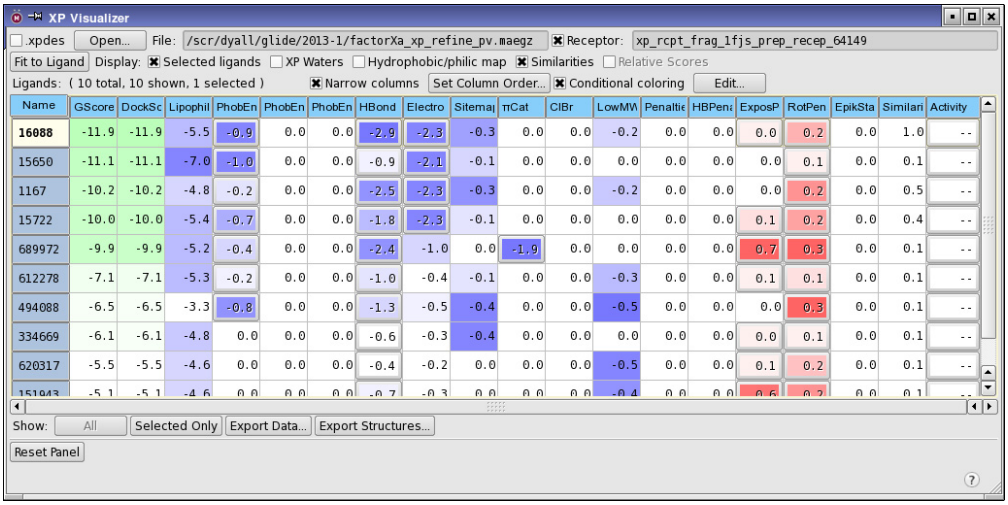

Figure 4.3. The Glide XP Visualizer panel.

3. Ensure that the .xpdes box is *not* selected, then click Open.
4. Select `factorXa_xp_refine_pv.maegz` in the file selector that opens, and click Open.

   The Select Activity Property dialog box opens, so you can choose an activity property. For this exercise, no activity property is required.

5. Click Cancel.

The receptor and the highest-scoring ligand are displayed in the Workspace, and the table in the panel is filled in. The outlined values indicate that there is a corresponding visualization for this value.

6. Click the PhobEn cell for ligand 16088.

   You might want to deselect Narrow columns to see the entire column heading. This column displays the hydrophobic enclosure rewards. After a few seconds, the naphthalene of the ligand is displayed in ball-and-stick, and the hydrophobic atoms on the protein surrounding this ring are displayed in CPK in gray.

7. Click the PhobEn cell for ligand 612278.

   Note that for this ligand there is only a benzene ring rather than a naphthalene.

8. Click the HBond cell for ligand 16088.

   The hydrogen bonds are displayed as pink dotted lines and annotated with their lengths.

9. Click the Electro cell for ligand 16088.

   The amidine nitrogens are displayed in ball-and-stick, to indicate their contribution to electrostatic rewards.

10. Click the RotPenal cell for ligand 16088.

    The bonds that contribute to the rotatable bond penalty are displayed as tubes.

11. Close the Glide XP Visualizer panel.

12. Clear the Workspace, deleting the scratch entry.

4.7 Finishing the Exercises

Close the scratch project you are working in. Because you have written the output structure files to your directory tree, you do not need to save the scratch project or Workspace structures. Click OK to delete any scratch entries.

Choose Maestro → Quit, and click Quit in the Quit dialog box.

Docking to a SiteMap-Based Grid

If you do not have information on the active site, you can use SiteMap to locate possible active sites on a protein, and use the results to identify the active site for docking. In these exercises, you will use the site map for 1ke8, for which a site and a ligand are known, to illustrate how well the use of a site map performs.

If you have not started Maestro or copied the tutorial files, do so now. See Section 1.2 on page 2 for instructions on how to do these tasks.

If you have already created the site map by running the *SiteMap Tutorial*, you can skip Section 5.2, but first you should change your working directory to the directory that contains the SiteMap results (Project → Change Directory).

5.1 Running the SiteMap Calculation

In this exercise, you will set up and run the SiteMap calculation to locate sites on 1ke8.

1. Click the Import button on the Project toolbar.

   

   The Import panel opens.

2. From the Files of type option menu, ensure that Common is chosen.
3. Select the file `1ke8_protein.maegz` and click Open.

   The protein is displayed in the Workspace.

4. Choose Tasks → Protein Analysis → Binding Site Detection (or Applications → SiteMap).

   The SiteMap panel opens.

5. In the Task section, ensure that Identify top-ranked potential receptor binding sites is selected.

   You can leave the settings at their defaults.

6. Click the Settings button.
7. Ensure that Append new entries is selected from the option menu in the Output section.

8. Name the job `1ke8_sitemap_find`, and click Run.

The job takes only a few minutes. When it finishes, the first (top-ranked) site found is included in the Workspace, along with the surfaces.

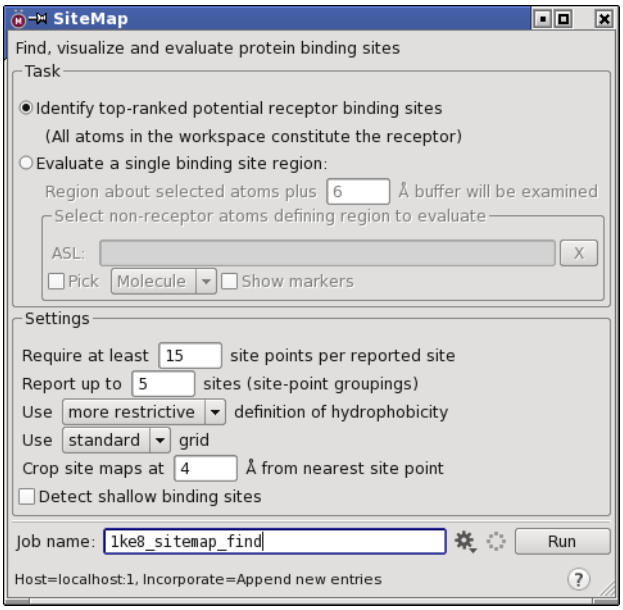

Figure 5.1. The SiteMap panel.

5.2 Generating a Grid from a Site Map

In this exercise, you will generate a grid from the site map for the top site that was located in the previous exercise (or in the SiteMap Tutorial).

If you are continuing from Section 5.2, skip to Step 4. Otherwise, you must first import the files, as follows.

1. Click the Import button on the Project toolbar.

   

   The Import panel opens.

2. From the Files of type option menu, ensure that Common is chosen.
3. Select the file `1ke8_sitemap_find_out.maegz` and click Open.

4. Include in the Workspace the entries with the titles 1ke8_sitemap_find_protein and 1ke8_sitemap_find_site_1.
5. Choose Tasks → Docking → Grid Generation.

   The Receptor Grid Generation panel opens at the Receptor tab.
6. Select Pick to identify ligand, and choose Entry from the option menu.
7. Pick a site point near the center of the point in the hydrophobic surface region (yellow) of the SiteMap surface.

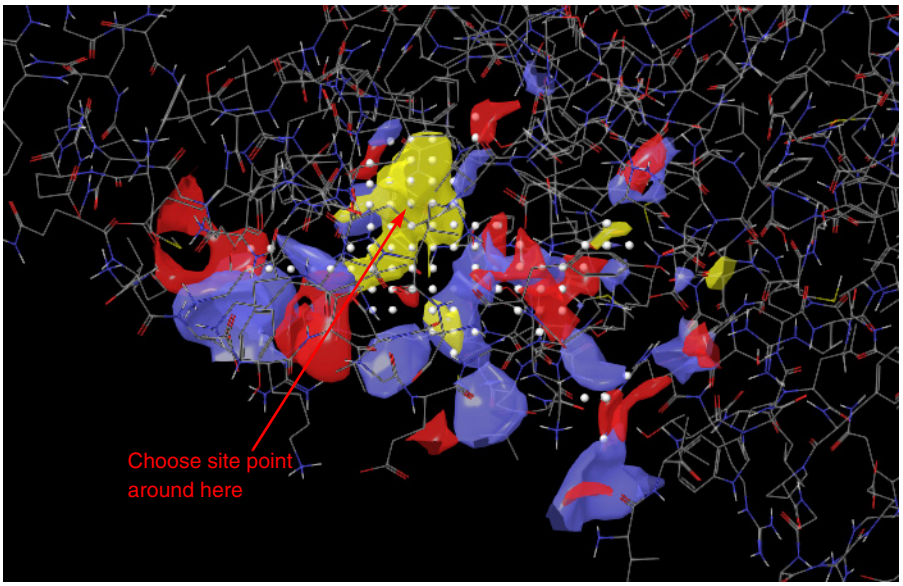

Figure 5.2. The site for 1ke8 with the ligand.

   The "ligand" is now defined, and its size is defined by the site map.

   If the site points are distributed over a broad region and you want to limit the grid to a smaller region, you can pick a site point at the center of the desired grid box, then in the Site tab, select Supplied X,Y,Z coordinates under Center to set the center to the picked site point and select Dock ligands with length under Size to set the size of the ligands to be docked (and hence the size of the grid box). You should exclude the site map entry from the Workspace before starting the job.
8. Name the job `1ke8_sitemap_entry`.
9. Click Run.

5.3 Docking the Native Ligand

In this exercise, you will dock the native ligand for 1ke8 into the grid that was generated from a site map.

1. Choose Tasks → Docking → Glide Docking.

   The Ligand Docking panel opens.

2. From the Settings button menu, choose Reset Panel.

   The options are set to their defaults, which includes clearing the name of the receptor file and the ligand file. This step is only necessary if you have used the panel before in the Maestro session, but it does no harm.

3. In the Receptor grid section, click the Browse button.

   A file selector opens.

4. Choose `1ke8_sitemap_entry.zip`, and click Open.

5. In the Ligands tab, click Browse.

   A file selector opens.

6. Choose `1ke8_ligand.maegz`, and click Open.

7. In the Output tab, ensure that Write ligand pose file (excludes receptor) is selected.

8. Run the job with the name `dock_1ke8_sitemap_entry`.

   When the job finishes, the docked ligand is included in the Workspace.

9. In the main window click the Import button on the Project toolbar.

   

   The Import panel opens, showing the contents of the tutorial directory.

10. From the Files of type menu, ensure that Maestro is chosen.

11. Deselect Replace Workspace.

12. Select the file `1ke8_ligand.maegz`, and click Open.

    The native ligand is imported and placed in the Workspace along with the docked pose. The two structures superimpose well. In the next steps, you will calculate the RMSD to see how well they superimpose.

13. Choose Tools → Superposition.

14. Ensure that Included entries is selected.
15. Select Calculate 'in place'.
16. In the ASL tab, click All.

    The results of the RMSD calculation between all atoms in the molecules is reported in the RMSD text area—it is about 0.2 Å, and the maximum difference is less than 0.5 Å.

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

Glossary

Base Name—The name entered in the Base name for grid files text box that is used to write grid files during a grid file calculation, or to find pre-existing grid files during a docking job.

Contacts—Graphical representations of the van der Waals interactions between the atoms of two or more molecules. Within Maestro, contacts are categorized as "Good," "Bad," and "Ugly." Good contacts are those that have van der Waals radii consistent with the experimentally determined values for the involved atom types. Bad contacts depict those interactions that are experimentally improbable. Ugly contacts represent van der Waals interactions that are disallowed in experimental systems.

Enclosing Box—The purple, cube-shaped marker that appears in the Workspace after you specify active residue sites, coordinates, or a ligand to be used as a bounding box center using the Glide panel. The enclosing box represents the space that any part of any specified ligand can sample during a docking calculation. Compare this with the green *ligand center box*, which represents the space that the center of each specified ligand must be confined to during a docking calculation.

Flexible Docking—A job type in which alternate conformations for each ligand are generated during the docking process, and then the interactions between the receptor and the conformers are analyzed. After docking jobs are complete, the conformers, or "poses," are ranked according to their overall interaction with the receptor. The results can be posted to a pose view file, which can be examined using the View Poses panel.

GlideScore—Glide's scoring function (based on ChemScore). GlideScore is used in ranking ligand poses found in docking. In Liaison, GlideScore is used in an alternative binding energy model.

Grid Files—Files written by Glide during grid setup. These files contain data about the properties of the associated receptor and are used during docking.

Ligand Center Box—The green, cube-shaped marker that appears in the Workspace during Glide docking job setup after you select active site residues, coordinates, or a ligand to be used as the box's center. The box represents the space in which ligands are allowed to move during docking. Increasing the size of this box increases the space that can be sampled by the docked ligands, and consequently increases the CPU time required for the calculation.

Ligand Centroid—Used to define the grid box center, a ligand centroid is the point whose x, y, and z coordinates are the mean of the minimum and maximum *x*, *y*, and *z* coordinates of all the atoms in the ligand.

Reference Ligand—A user-specified structure whose ligand/receptor docking score will be compared with all other docked ligands.

Rigid Docking—A job type in which only supplied conformations of the specified ligands will be docked, scored, and displayed in a pose view file. This job type is useful if you have already performed a conformational search on the ligands that you want to dock.

120 West 45th Street
17th Floor
New York, NY 10036

101 SW Main Street
Suite 1300
Portland, OR 97204

245 First Street
Riverview II, 18th Floor
Cambridge, MA 02142

8910 University Center Lane
Suite 270
San Diego, CA 92122

155 Gibbs St
Suite 430
Rockville, MD 20850-0353

Dynamostraße 13
D-68165 Mannheim
Germany

Zeppelinstraße 73
D-81669 München
Germany

Potsdamer Platz 11
D-10785 Berlin
Germany

Quatro House
Frimley Road
Camberley GU16 7ER
United Kingdom

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

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

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