Haptimol FlexiDock: Quick Start Guide

1 Prerequisites

1.1 Biomolecular Data

In order to model protein interactions using Haptimol FlexiDock, the following biomolecular information is required:

For the receptor and ligand:

1. Protein Data Bank (*.pdb) file.
2. Protein Topology (*.top) file.
3. The molecular forcefield used by the topology file. Currently the Amber03 and GROMACS 54a7 forcefields are supported, as used with GROMACS.

In addition to the above information, a molecular dynamics simulation of the receptor is required, from which a covariance matrix needs to be calculated. The eigendecomposition of the covariance matrix then needs to be performed, and the eigenvalues and eigenvectors stored in .CSV format. The eigenvalues and eigenvectors should be ordered largest to smallest.

The CSV file containing the eigenvalues should contain the diagonal of the calculated eigenvalue matrix as a single column. The eigenvector matrix should be stored in the form 3N by M, where N is the number of atoms and M is the number of eigenvectors to be used in the docking session.

An example receptor and ligand, complete with the required eigenvalues and relevant forcefield is available to download from http://www.haptimol.co.uk/flexidock/haptimolflexidockfiles.zip.

1.2 Hardware Requirements

The size of the biomolecules and the number of eigenvectors included during docking dictate the specification of the hardware required. Currently, the only supported operating systems are 64-bit versions of Microsoft Windows 7, 8 and 10.

Whilst performing docking between a receptor of modest size and a small ligand using a mouse and keyboard, NVIDIA GPUs from the 700 series or later *should* be compatible, as well as Intel Graphics Chipsets from the 500 series or later. AMD graphics cards are untested. Please insure your graphics card drivers are up to date before installing Haptimol FlexiDock. NVIDIA drivers prior to version 387.66 are unsupported.

For haptic-assisted docking, a much more powerful GPU is required, ideally a NVIDIA GTX 980 or better. A modest CPU should be sufficient in all scenarios. A 3D systems haptic device (formally known as the Phantom Omni by SensAble Technologies) is required in order to perform haptic-assisted docking.

The memory requirements of Haptimol FlexiDock again vary depending on the size of the biomolecules being rendered. 4 GB should be sufficient in most scenarios.

2 Installation

Installation is straight forward. Run the executable "haptimolflexidockinstaller.exe" within this directory. The window depicted in Figure 1 should open. Simply follow the on screen instructions.

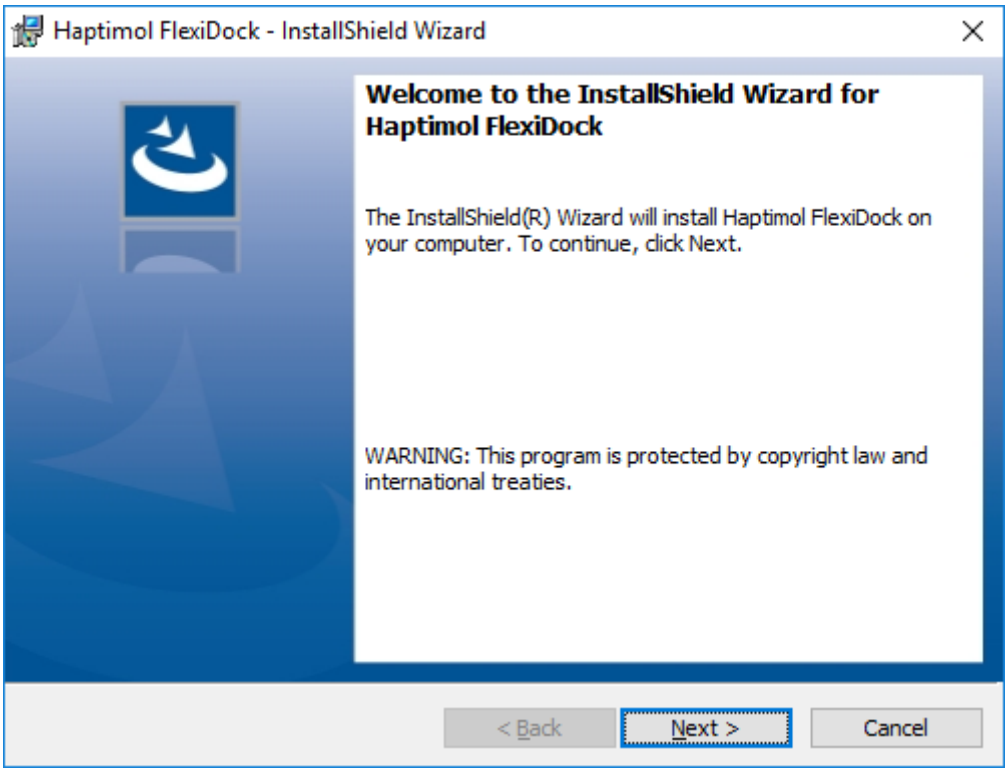

Figure 1: Haptimol FlexiDock installer window

3 Initial Setup

Once installation is complete, launch the application. Before performing a docking experiment, the application needs to know the location of the forcefields compatible with the receptor and ligand topology files. For evaluation purposes, an example receptor and ligand, complete with the required eigenvalues and relevant forcefield is available to download from http://www.haptimol.co.uk/flexidock/haptimolflexidockfiles.zip.

This is set by opening the applications settings window (See Figure 2) and clicking the the "Browse For Path" button (3.

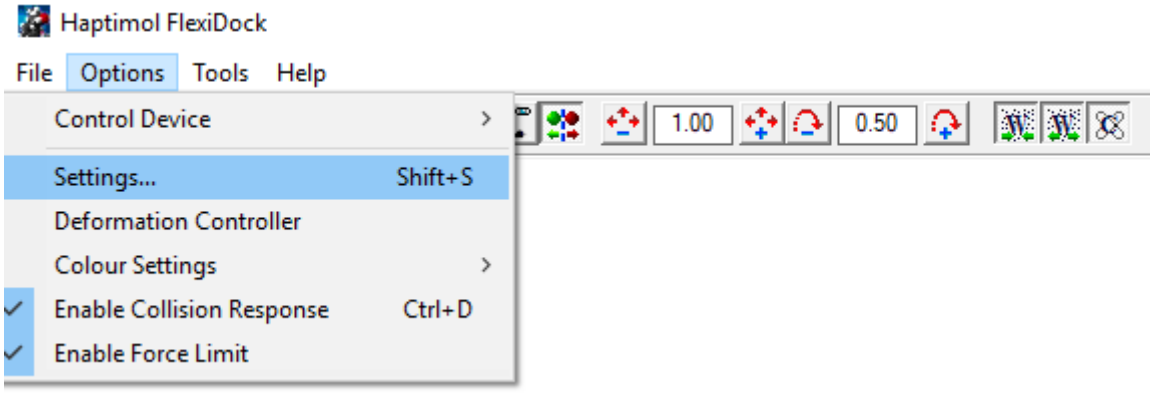

Figure 2: Opening the settings dialogue within Haptimol FlexiDock

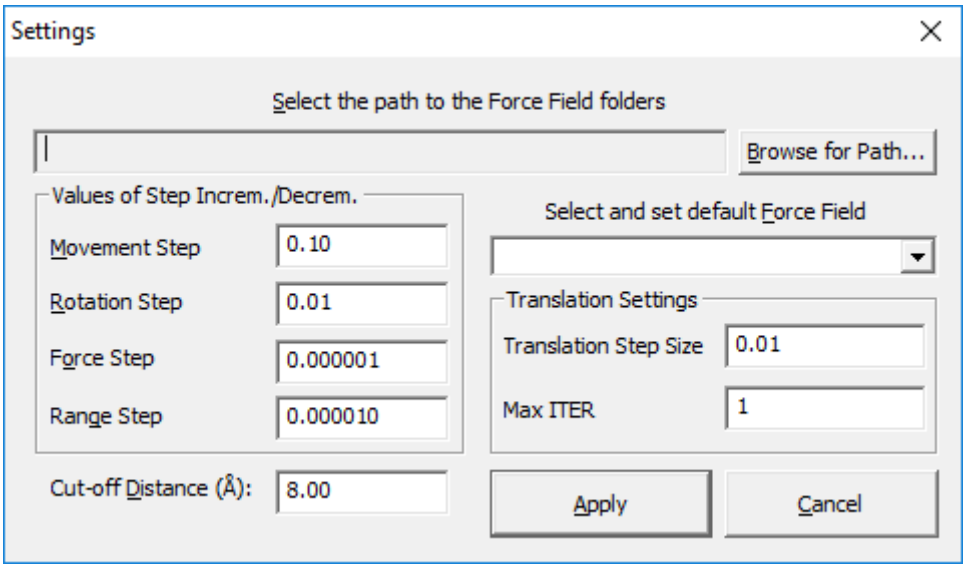

Figure 3: Unconfigured settings dialogue. Select "Browse for path," and select directory containing the molecular forcefield.

Within the browse window, navigate to the root folder, in which a folder containing each forcefield is contained (As seen in Figure 4).

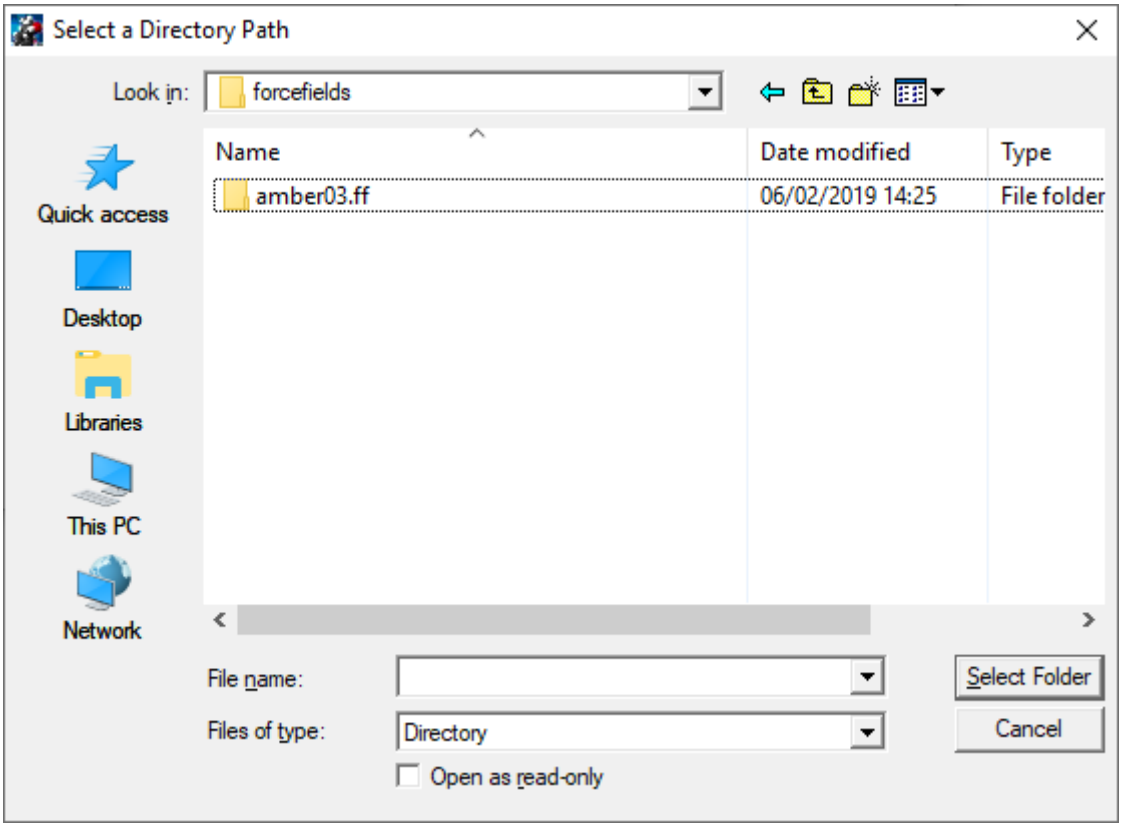

Figure 4: Example valid forcefield directory

The names of each folder should be the same as they are within the proteins topology files.

When the path to the forcefields has been set, the cut-off distance used in the intermolecular force calculations can be configured, and should be set to the largest value your system can support. This value can be adjusted later. An example of the final, configured Settings window is shown in Figure 5.

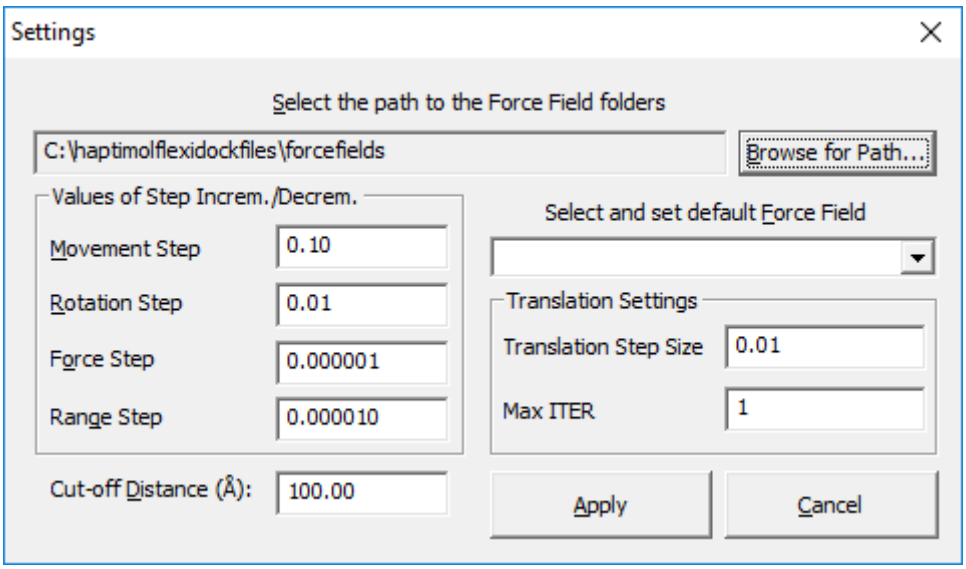

Figure 5: Complete settings window. Note the configured forcefield directory and increased cut-off distance.

4 Loading Biomolecules

After the path to the forcefields has been set, biomolecules can be loaded. The receptor should comprise an equal number, or more atoms than the ligand. To open the load window, press F5, or either the L or R buttons on the application toolbar, pictured in Figure 6.

Figure 6: Load Buttons (R/L) and save button within Haptimol FlexiDock's toolbar.

The load window, Pictured in Figure 7 will open. The receptor and ligands PDB and topology files should be provided, as well as the CSV files containing the eigenvalues and eigenvectors. Note, not all of eigenvalues/vectors need be loaded:- the fewer provided, the faster the application will load, and the less memory it will consume.

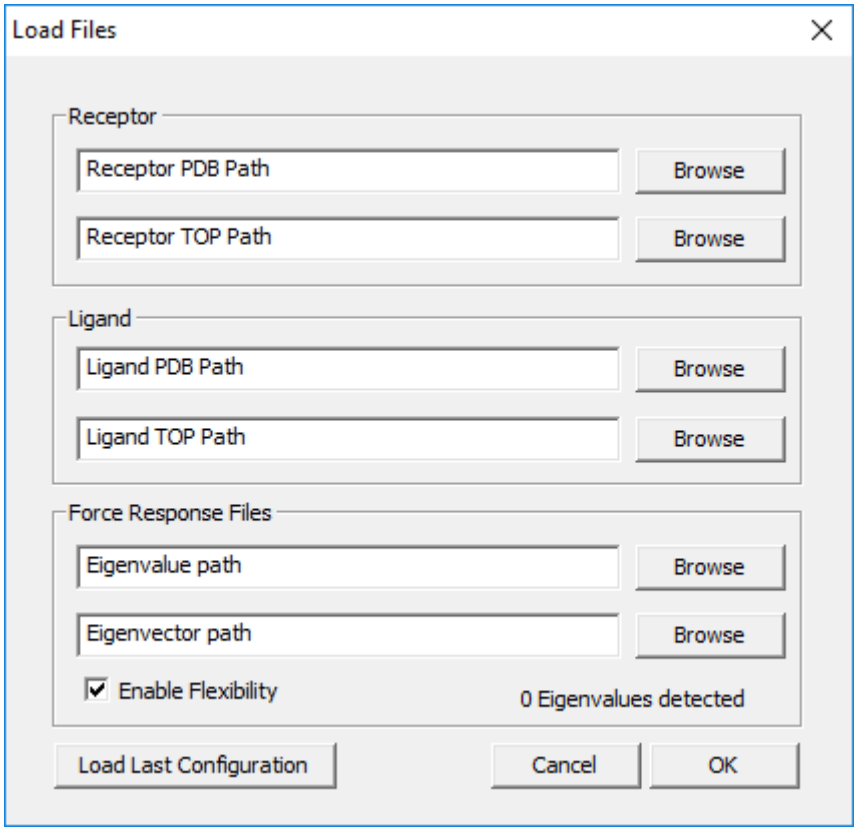

Figure 7: Empty load window. Set the paths to the PDB and Topoloy files for the receptor and ligand, and, if flexibility is desired, the path to the eigenvalues and eigenvectors relating to the receptor.

When the window has been populated, it should resemble something like that pictured in Figure 8. Pressing cancel will save the information that you have specified but will not start the load process. Pressing OK will load the structures specified into the application.

Whilst the files are loading, "LOADING" will be displayed in the bottom left hand corner of the main application window. Wait for this to disappear before attempting to move the biomolecules.

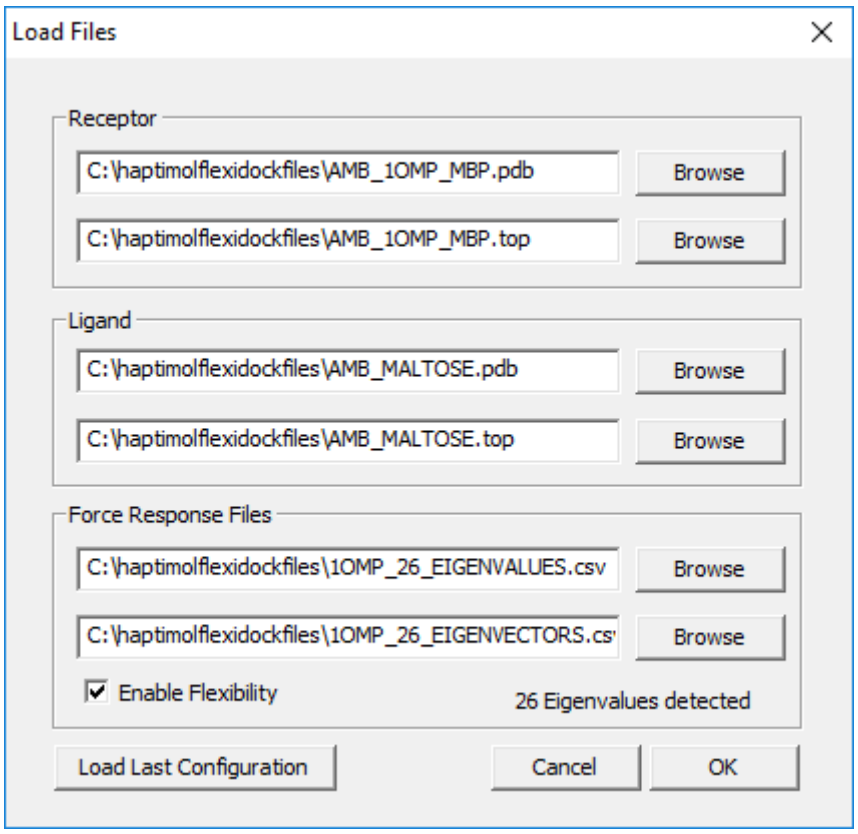

Figure 8: Load window populated ready to begin a docking session.

If one of the topology files contains an atom type not listed in the specified forcefield, or the forcefield could not be found, a pop-up like that in Figure 9 will be displayed. Check the forcefield has been specified (Section 3), and if it has, check that the molecular topology aligns with the PDB file and forcefield.

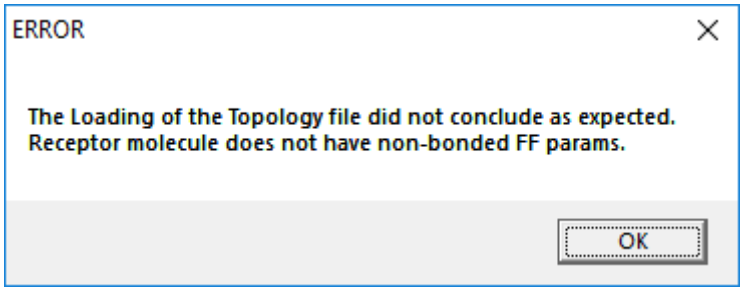

Figure 9: Pop-up window indicating that FlexiDock has failed to load force parameters for one of the structures. Check the forcefield is correctly configured.

5 Using the application

When loading is complete, the "LOADING" message will disappear from the application status bar, and docking can begin (See Figure 10.

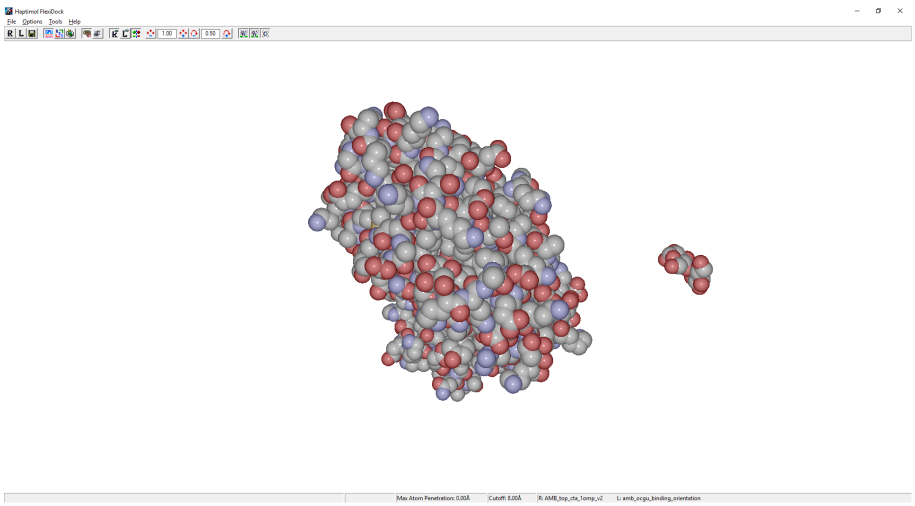

Figure 10: Main window of Haptimol FlexiDock

In Figure 10, the ligand is on the right, and the receptor is on the left.

5.1 Keyboard Controls

To change a biomolecules orientation:

- Ligand: Click the left mouse button, and move the mouse.
- Receptor: Press ctrl , then left click and move the mouse.
- Global: Press shift , then left click and move the mouse.

To change the global position of the ligand:

- Movement in X axis: Left and Right directional arrows
- Movement in Y axis: Up and down directional arrows.
- Movement in Z axis: Z and X character keys.

The speed the ligand moves can be configured within the main tool bar (Figure 11).

Figure 11: Use these buttons to change the speed of the movement and rotation of the ligand.

5.2 Haptics

To enable Haptic assisted docking, press the haptic device button (Figure 12), and then the lower button on the haptic device's stylus.

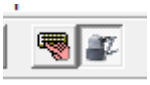

Figure 12: Select the haptic device button to switch to haptic-controlled docking.

The space bar can be used to change the force scaling method used. F9 can be used to declutch the haptic device from the ligand. Pressing it again re-engages control. F11 and F12 can be used to pause/reanimate the molecular deformation.

5.3 Interactive Docking

During the docking session, the receptor will deform in response to the force interaction between it and the ligand. The deformation controller (Figure 13) can be used to control the rate at which the receptor changes conformation and also the number of Eigenvectors used during the deformation calculation.

Further, the controller provides the facility to limit both the maximum force permissible, and also the maximum amount of overlap between receptor and ligand atoms, before the deformation of the receptor is halted. If, during docking, the receptors response becomes unrealistically extreme, or appears to be lacking, altering these values may help.

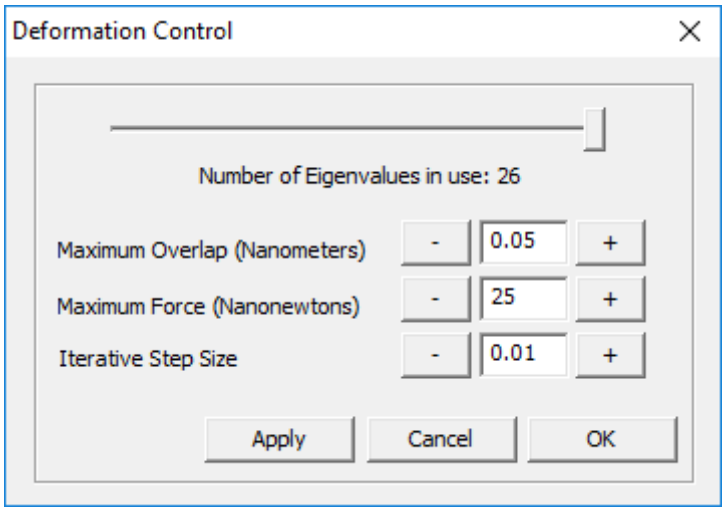

Figure 13: Deformation controller window. The scrollbar can be used to change how many eigenvectors are used during the docking session. The maximum overlap and maximum force indicate the maximum values tolerated by the deformation calculation before deformation is halted. The iterative step size controls the speed at which the protein deforms.

Finally, whilst performing docking, the ligand may become stuck within the receptor - if, for example, the receptor closes around the ligand. Pressing the collision response button (Figure 14, will allow the ligand to move through the receptor atoms. Be sure to re-enable it before beginning docking again.

Figure 14: Button to enable/disable collision detection. Deselecting it will allow the ligand to pass through the receptor.