DockIT User Guide

CONTENTS

TO INSTALL

- Before Installing ensure you have an OpenCL 1.2 compliant GPU and have an OpenGL 4.0 ready driver installed for your graphics card. (Please check troubleshooting if you are unsure how to do this).
- Double-click on the DockIT_Setup.msi file included in the Setup folder.
- Go through the instructions on your screen to install it. The default installation folder is *C:\Program Files\HaptiMOL\DockIT*.
- The software can be used with a keyboard and mouse. However, you can also use a haptic device from 3D Systems (https://www.3dsystems.com/haptics).

- When using VR Mode you will need a compatible VR Headset. Meta Quest 2 (with link cable), Oculus Rift and Oculus Rift S are currently supported.

TO LAUNCH THE SOFTWARE

- Go to Start menu -> All Programs -> DockIT

The application should then launch.

GETTING STARTED

You are now ready to open two molecules one as the receptor and the other as the ligand. DockIT may be used with or without force parameters depending on whether you wish to calculate the interaction forces between the molecules. We suggest starting by loading gmx_Alanine.pdb and gmx_Alanine.top for the coordinate and topology files for both the receptor and the ligand to test with the force parameters.

- Click on the "R" in the top-left corner to start the steps for loading the receptor. Figure 1 shows the dialog that will appear.

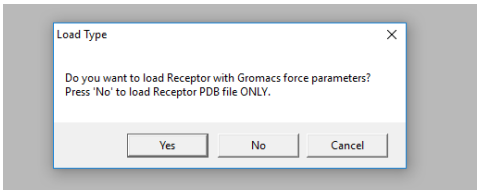


Figure 1 Load a receptor by clicking on the "R" in the top-left of the toolbar.

- Click *Yes* to include the force field parameters. (You can select *No* if you only wish to load the pdb and not perform any docking)
- Now you can set the PDB and TOP files in the dialog box as shown in Figure 2 by clicking on the *Browse for PDB…* and *Browse for TOP...* Several example files have been included with your installation including the ones mentioned above. They have been named to indicate which pairs could be used together as receptor and ligand.
- DockIT also supports receptor flexibility and to enable this feature tick the *Apply Flexibility* option to enable the eigen values and eigen vectors for the receptor to be loaded. Example files are included in the installation folder entitled *flexibility.*

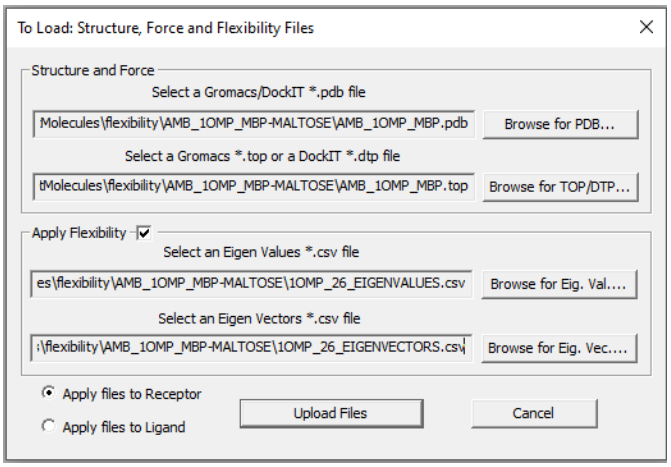


Figure 2 To load a pdb with the force parameters you need to load the pdb and the corresponding top file. For flexibility you need to add the appropriate eigen values and eigen vectors stored in CSV files.

Figure 2 shows the example files that have been installed with the application in *C:\Program Files\HaptiMOL\DockIT\TestMolecules.*

- Click on *Utilize Gromacs Files* to load in the receptor.
- Click on the "L" in the top left of the screen and repeat the above steps to load in the ligand with its force parameters.
- Currently we only support topology files that use the Gromos54a7 force-field. If you do not have a topology file for your system you can use the following *Gromacs* command to generate one:

  pdb2gmx -f xxxx.pdb -o gmx_xxxx.pdb -p gmx_xxxx.top -ff gromos54a7 -ignh -water none -merge all

  If a topology file for your compound is not available from the standard Gromos library then a topology file can be generated automatically at, for example, the ATb server (https://atb.uq.edu.au/).

Now you are ready to begin using the software. The software defaults to using a keyboard and mouse.

- To use a haptic device click on the haptic device icon on the taskbar (or press Ctrl + H).
- Press and release the button on the haptic stylus to start moving the ligand and feeling the interaction forces.

MOVING THE LIGAND AND RECEPTOR

You can move the ligand using the keyboard and mouse or the haptic device as explained in the following sections. Figure 3 highlights the buttons used to toggle between Keyboard and Haptic modes (Ctrl + K and Ctrl + H can also be used).

Figure 3 The DockIT interface with the haptic interaction mode selected.

MOVING THE LIGAND AND RECEPTOR USING THE KEYBOARD AND MOUSE

The following table details the keyboard and mouse controls.

Key / Mouse control	**Action**
Translation	
Arrow Keys	To move the ligand in the x and y axes
X	To move the ligand away from you (along the z-axis)
Z	To move the ligand closer to you (along the z-axis)
Shift + Arrow keys or Shift + middle mouse drag	To move the entire scene in the x and y axes
+ or mouse scroll wheel	To zoom in on the entire scene
- or mouse scroll wheel	To zoom away from the entire scene.
F9 (when using a haptic device)	To clutch the haptic interface point so that it doesn't directly affect the movement of the ligand.
Rotation	

Click and drag the mouse	To rotate the ligand about its centre
Shift + left click and drag the mouse	To rotate the ligand and receptor about the centre of the receptor
Ctrl + click and drag the mouse	To rotate the receptor about its centre.
F1	To toggle the rotations so they are only about the x axis
F2	To toggle the rotations so they are only about the y axis
F3	To toggle the rotations so they are only about the z axis.
Ctrl + R	To reset the scene transformations as they were originally loaded.

MOVING THE LIGAND AND RECEPTOR USING THE HAPTIC DEVICE

To use the haptic device after selecting haptic mode on the interface (or Ctrl + H) you need to press the button on the stylus of the haptic device to start controlling the ligand.

The concept of a Navigation Cube (see Stocks et al. [1] and enhanced in Iakovou et al. [3]) is used to control the ligand. The Navigation Cube defines a volume which is slightly smaller than the volume of the haptic workspace. When moving the haptic device in the Navigation Cube you will have direct control of the ligand. This means when you move the haptic device the ligand will move as if directly linked to the haptic stylus. However, when you reach the edge of the haptic workspace the ligand will start to translate and will continue to do so whilst your stylus is in the edge of the workspace. This approach enables you to move the ligand anywhere around the receptor whilst also giving direct control. Figure 4 illustrates this process.

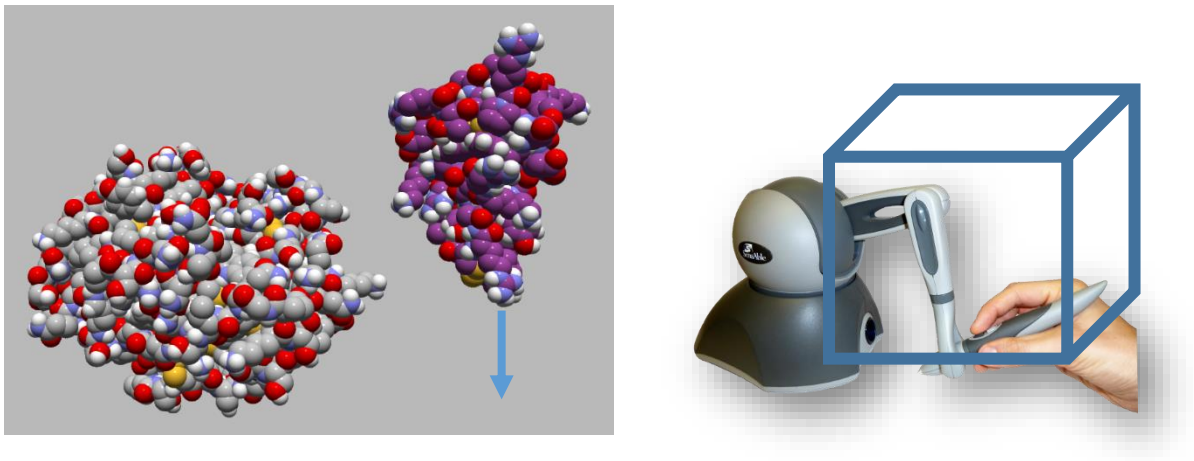


Figure 4 When you move the haptic stylus within the Navigation Cube (indicated by the blue cube on the right) you will move the ligand directly as if the stylus is attached to it. When you move the stylus outside of the volume the ligand will continue to translate. It will translate down in the y axis in the case of the position shown in this figure and the ligand will continue to move down until the stylus is moved back within the haptic workspace.

To rotate the ligand you can press the button on the haptic stylus and move the haptic stylus. You can rotate the receptor or the entire scene by pressing the button on the stylus and moving it whilst holding the Ctrl key or Shift key, respectively.

It can be useful to be able to move the haptic stylus without controlling the ligand acting like a clutch. You can do this by pressing F9. To resume direct control again press F9.

ADJUSTING THE SENSITIVITY OF THE MOVEMENTS AND ROTATIONS

Sometimes you may wish to adjust the rate of translation or rotation to be able to manipulate the molecules more precisely. You can achieve this using the *movement multiplier* and *rotation step value* settings available on the toolbar. Figure 5 shows the controls on the toolbar highlighted by the ellipse.

Figure 5 You can adjust the rates of movements with the movement multiplier and rotation step value settings highlighted in the blue ellipse here.

COLLISION RESPONSE MODE

The button to the left enables and disables the *Collision Response mode* which prevents the molecules from becoming too close. The movement can be limited by distance or by force and the mode is chosen from the *Options menu* and *Collision Response Mode*. When limited by force the movement is restricted when the maximum interaction force between the structures exceeds a specified force in nano Newtons. If you move the ligand so that the interaction force is exceeded a message will appear in the top left to indicate they cannot be moved closer together. A yellow highlighting will also appear on the ligand. As a consequence this response mode limits the maximum overlap of the atoms. The Spatial Overlap mode limits movement when two atoms become closer than a preset value. For the spatial overlap the hydrogens are not included in the calculation. The limiting force and spatial overlap distance can be set from *Options* and *Settings* (see Figure 7). It is recommended to use the Force-based collision response mode when docking with receptor flexibility.

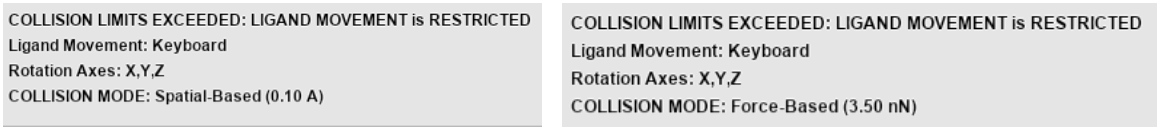


Figure 6 The messages shown here appear when the movement is limited by the (left) Spatial Overlap mode and (right) force based mode.

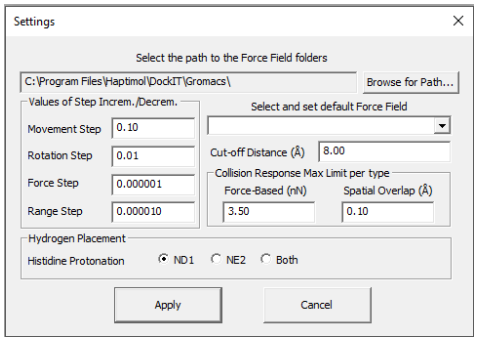


Figure 7 The *Settings* dialog is used to modify key settings. For Collision Response mode the limits for the forces and spatial overlap can be set here.

ROTATION AT COLLISION POINT

The button to the right is used to enable or disable the *Rotation At Collision Point*. When the structures are limited by the *Collision Response Mode* and this feature is enabled, the ligand will rotate about the

point of the collision rather than the centre of the ligand. Figure 8 illustrates an example movement. This feature is currently not supported in VR mode.

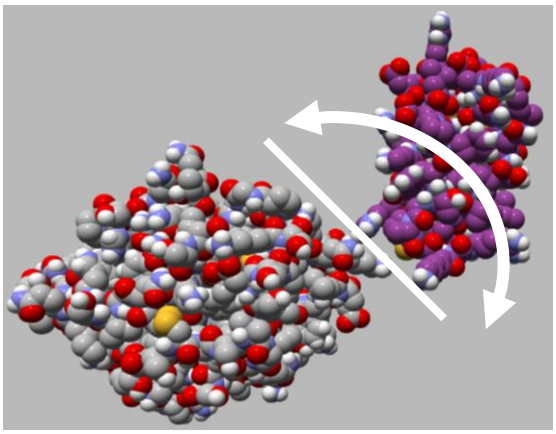
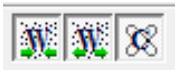


Figure 8 In Collision Response Mode the Rotation At Collision Point feature can be used to rotate the ligand about the collision point. The white arrow illustrates the direction of a possible rotation. The line indicates a potential axis of rotation which is through the collision point.

FORCE CALCULATIONS

During interaction van der Waals repulsive, van der Waals attractive and Coulombic forces are calculated. The force calculations use the Gromos54a7 force field parameters and these are provided with the DockIT installation and are located in the Gromacs folder within your installation directory. All three of these forces



are calculated by default, however, they can be switched on and off using the buttons in the toolbar as shown below. When using a haptic device this allows you to feel the effect of van der Waals repulsive and attractive terms as well as the effect of electrostatic interactions.

The interaction forces are best computed on a GPU, but the software will perform the force calculations on the CPU by disabling the GPU processing option.

To ensure better performance when handling larger structures a cut-off distance is used in the force calculation. The default cut-off distance is 8A and this can be changed from the *Settings* dialog available under the *Options* menu.

To visualise the forces and energy during the interaction the force graph option can be used. Figure 9 shows the force-graph which appears when clicking the button shown to the left. The energy axis is shown on the left and force axis on the right. Simulation steps occur every 200 milliseconds.

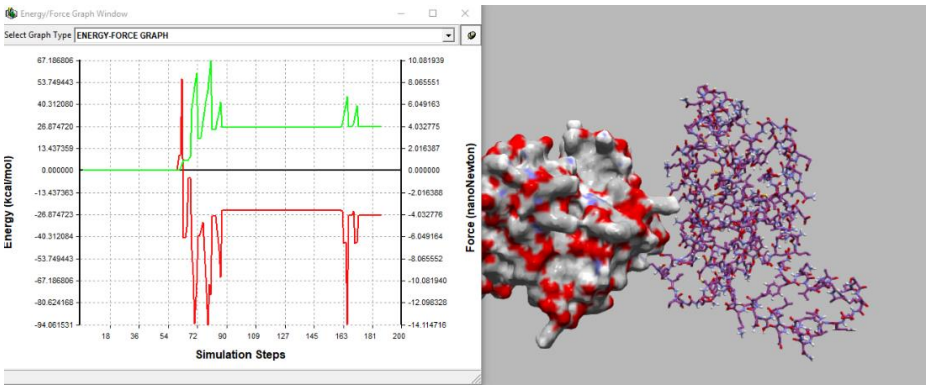
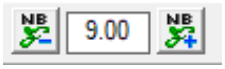


Figure 9 Force-graph displayed to show Force and Energy during interaction.

Further details on how the force is calculated can be found in Iakovou et al. [2].

FORCE SCALING

As the forces are calculated in nanoNewtons these need to be scaled if you are using a haptic device. Force scaling can be performed in three different ways in DockIT when using haptics and the scaling mode is selected by pressing the space bar. The current force scaling mode is indicated in the bottom left of the status bar.

Additional UI	Force Scaling Approach
	FIXED Scaling mode In fixed scaling mode, the molecular force in nanoNewtons (nN) is scaled by 10^9 to give the force in Newtons (N) applied to the haptic device. If the magnitude of the interaction force is greater than 3nN then the force on the haptic device is capped at 3N. The exponent here can be scaled using the UI controls.
	MIN/MAX RANGE Scaling Mode In this mode the total interaction force is mapped linearly to a user defined min-max range of force magnitudes. The min-max values can be adjusted with the UI and this method enables the user to focus on a specific range of intermolecular forces.
	VARIABLE Scaling Mode The variable scaling method follows an approach as described by Bolopian et al. [4] which amplifies small amplitude forces using a series of arctangent functions.

Further details on the Force Scaling methods can be found in Iakovou et al. [3].

HYDROGEN BONDING

Both intramolecular and intermolecular Hyrdrogen Bonds are calculated and can be visualised with broken lines. In order to display hydrogen bonds you must load the structures with the topology files. If you are using a non-protein molecule hydrogen bond donors and acceptors can be added to those already assigned for the amino acids by editing the files "HBDonorInfo.hbd" and "HBAcceptorInfo.hba" supplied with the installation and located in *C:\Program Files\HaptiMOL\DockIT\ Gromacs*.

For hydrogen bond donors the format is:

GROMOS;<3 letter compound code>;RG;<atom name of donor>;<number of hydrogens donated>;<atom name of hydrogen>…

For hydrogen bond acceptors the format is:

GROMOS; <3 letter compound code>;RG; <atom name of acceptor>

For example, for a non-terminal ("RG" stands for regular, i.e. non-terminal) asparagine, they are:

GROMOS;ASN;RG;N;1;H
GROMOS;ASN;RG;ND2;2;1HD2;2HD2

for the hydrogen bond donors, and

GROMOS;ASN;RG;O
GROMOS;ASN;RG;OD1
for the hydrogen bond acceptors.

By default the intermolecular hydrogen bonding is highlighted as shown in Figure 10. This can be disabled by pressing Shift+B or using the *Highlight Inter-molecular Hydrogen Bonds* menu item within Options. Figure 11 shows an example of the intra-molecular hydrogen bonding and also inter-molecular without highlighting.

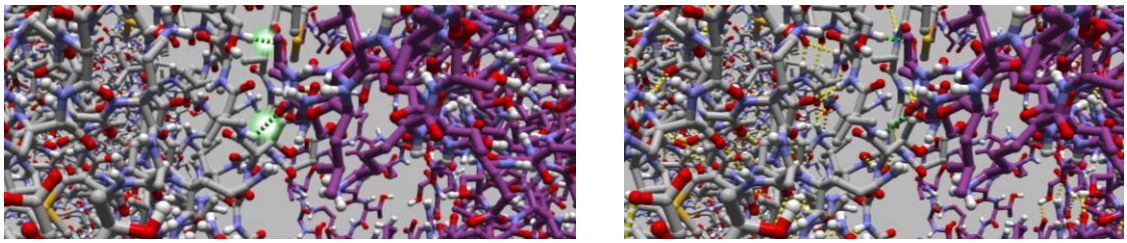


Figure 10 Left, Inter-molecular hydrogen bonding with highlighting and, right, inter-molecular hydrogen bonding without highlighting and intra-molecular hydrogen bonding.

FIND DISTANCES BETWEEN ATOM PAIRS

You can determine the distance, in Angstroms, between atoms on the same or different molecules. Hold Ctrl and click with the right mouse to select an atom and then hold Ctrl and right click a second atom to make a pair of atoms. The distance in Angstroms will be displayed as shown for the three selected line pairs in Figure 11.

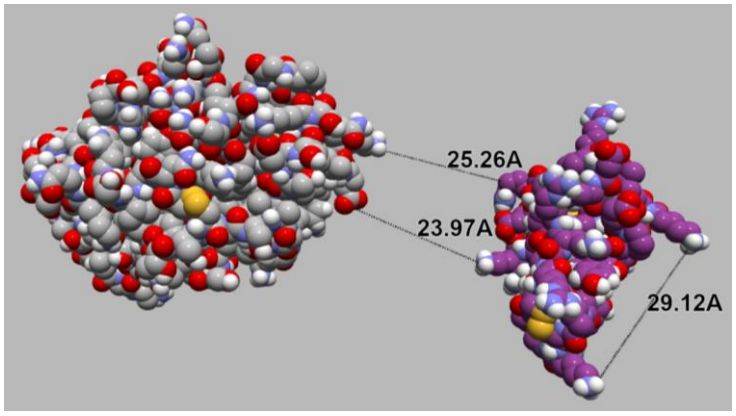


Figure 11 Three line pairs are selected with the length of the lines displayed in Angstroms.

VISUALISATION MODES

To change the representation of the molecules you can right click and select the options as shown in the table below.

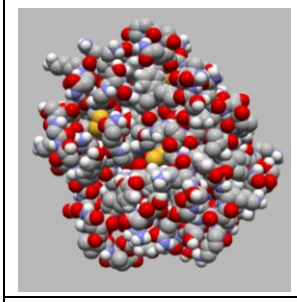
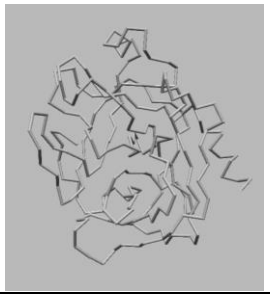
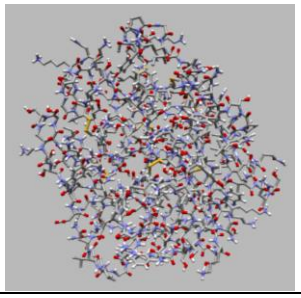
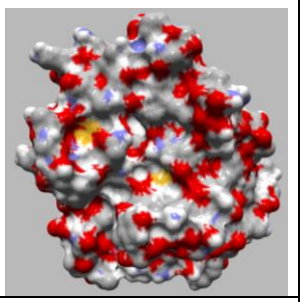
			
Spacefill	Backbone	Ball and stick	Surface

Table 1 The different molecule representations supported in DockIT

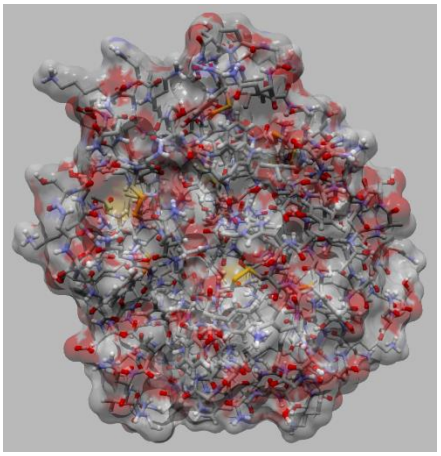


Figure 12 A molecule viewed with partially transparent molecular surface and opaque ball and stick.

You can also select to view a partially transparent molecular surface with any of the other three representations by selecting *View Transparent Surface*. If you select *View Transparent Surface* and *Surface* representation you will only see a partially transparent surface.

Figure 12 shows the transparent molecular surface with the ball and stick representation.

WHOLE MOLECULE AND CARBON ONLY COLOURING

Right-click on the molecule and you can select two whole molecule colouring options. Each option will bring up a colour picker to select the colour. *Change Whole Molecule Colour* is used to change the colour of all the atoms in the structure, whilst *Change Whole Molecule Carbon Colour* can be used to change the colour of only the carbon atoms. You can return the structure to its original CPK colouring system using *Reset Whole Molecule Colour to CPK*.

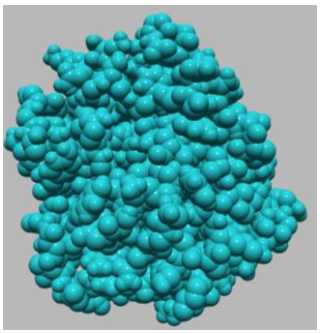


Figure 13 Shows the effect of changing the colour of all the atoms

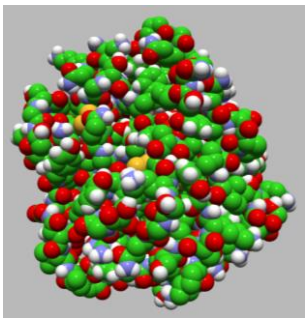


Figure 14 Shows the effect of just changing the carbon atoms and the other atoms keep their original CPK colouring

RESIDUE SELECTION

COLOURING

You can select residues and modify their colour in two ways. The first is by directly clicking on the residue to select it.

- Then, right-click to bring up the menu.
- Hover over the receptor or ligand options in the menu depending on which structure you clicked on (if you right click when hovering over a structure this selection will be inferred).
- Hover over Selection in the menu and then you can choose to colour all atoms in the selected residue(s) or just the carbon atoms.
- You can repeat this process and select *Reset Selection to CPK Colour* to return the residue colouring back to the original CPK Colours.

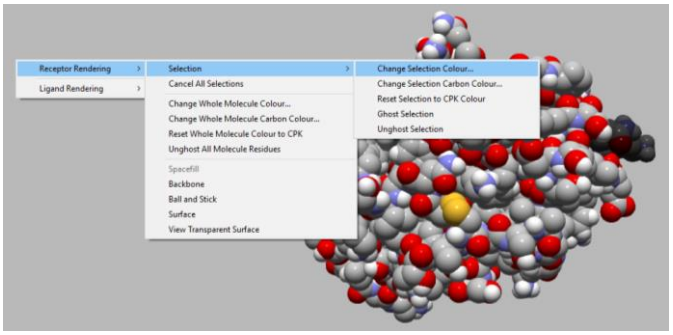


Figure 15 A molecule with a residue selected. The right-menu options are displayed for changing the colours of the selected residue(s)

You can also select residues using the Residue Selection Area. The Figure below shows the residue selection area displayed and being used to select residues in the receptor.

- Left-click or drag over the residue labels to select them.
- Right-click and then use the menu options to modify the colours.

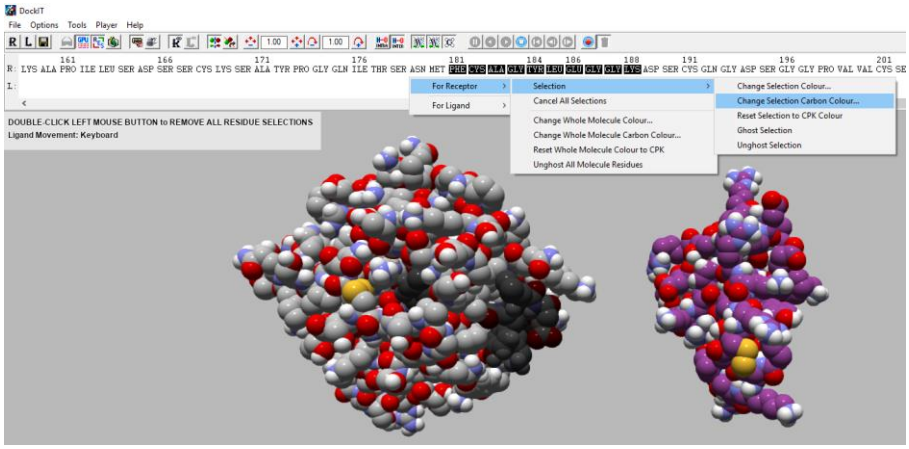


Figure 16 A sequence of residues are selected in the receptor using the Residue Selection Area. The right-click menu is shown for modifying the appearance of the residues.

If you selected something by mistake you can click on it again to toggle off the selection or you can right-click and select *Cancel All Selections* to deselect all currently selecting residues.

GHOSTING

Sometimes it can be useful to be able to remove a residue or selection of residues from the force calculation. The ghost feature will do this. Ghosted residues are seen in transparent rendering and not felt using a haptic

device. They are removed from the collision force calculation. The main use of ghosting is to enable you to access sites that might be blocked by particular residues. You can select the residues you wish to "Ghost" using the *Residue Selection Area* or by clicking on the residues directly. Further details on residue selection are covered in the section on colouring above.

RECORDING YOUR SIMULATION

You can record the movements you make during docking so that you can keep a copy of the paths you took and also to share with colleagues using DockIT.

Figure 17 Record and replay simulation controls

To start recording you can click on the *Start Simulation Recording* button shown next to the tool tip in Figure 17. All the movements of ligand and receptor will then be recorded. Once you have completed what you would like to record, click the *Stop Simulation Recording* button, shown as the square on the blue circle.

You can now save or replay the simulation from the *Player* menu. The simulation can be loaded back in to DockIT. In order to replay the simulation you must ensure you have loaded in the same ligand and receptor files that were used to create the simulation and then enter *Replay* mode from the *Player* menu. The current simulation can be removed using the icon on the tool bar or by pressing *Shift* + E.

SAVING MOLECULES(S)

You can save the current positions of the ligand and receptor separately or both as a single PDB file using the *Save Molecule(s)* option (*Ctrl* + S) from the File menu. This will save PDB files of the selected molecules in the positions they are within DockIT. You can select the molecules and the units using the *Save Molecule(s)* dialog, as shown below.

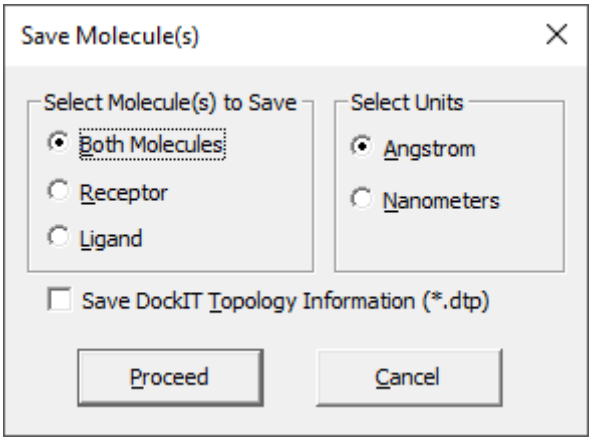


Figure 18 Save Molecule(s) dialog for saving PDB files for receptor, ligand or both molecules.

By ticking Save DockIT Topology Information you can save out the non-bonded force parameters in a DockIT topology file (*.dtp). This checkbox will become enabled only when the respective molecules or complexes have their non-bonded force parameters (*.top or *.dtp) loaded.

SETTING THE MOLECULAR COMPLEX AS THE RECEPTOR

After docking a ligand to a receptor you can combine them to form a single "receptor" molecule. This enables you to load in another ligand to dock against the new receptor allowing you to rapidly build up large complexes comprising many molecules. To do this you can press  or can choose File and Set Mol Complex

As Receptor (Ctrl + Return). The current ligand and receptor will become a single receptor and their non-bonded force parameters will be combined.

3D STEREOSCOPIC VIEWING

If you have an NVidia Quadro GPU then the *3D Stereoscopic viewing* option is available for viewing the molecules in 3D when using a 3D display device (e.g. 3D projector). You can enable the 3D Stereoscopic viewing using the Enable Stereo Viewing option on the toolbar. You can also toggle stereoscopic viewing using F5.

Key	**3D Viewing Control**
F5	To toggle Stereoscopic viewing
F6	To increase the eye separation.
F7	To decrease the eye separation.

VIEWING IN VR WITH A COMPATIBLE HEADSET

If you have a VR headset which is a Meta Quest 2 (with link cable), Oculus Rift S or Oculus Rift then you can explore molecules using the VR Mode. To do this first ensure your headset is plugged in and the appropriate setup has been done prior to starting DockIT. Then click the Start VR mode button and then you can put on your VR headset to continue exploring the molecules in VR. When you are finished in VR you can remove the head set and click the VR button to return to standard use of DockIT.

Once entering the VR mode you can use the touch controllers to perform the operations described in the table below. When you first put on the VR headset you will see instructions summarising the function of the touch controllers.

Controller keys and movements	**Operation**
Hold left grip and move the left thumbstick	Global translation of the molecules in the xy plane
Hold left grip and move the right thumbstick	Global translation of the molecules in the z axis.
Hold right grip and rotate the controller	Global rotation of both molecules
Hold left trigger + left grip and rotate the controller	Rotation of the receptor only
Hold right trigger + right grip and rotate the controller	Rotation of the ligand only
Hold left trigger + left grip and move the controller	Translation of the receptor only
Hold right trigger + right grip and move the controller	Translation of the ligand only
B on the controller (right)	To toggle display of the transparent surface on the ligand.
Y on the controller (left)	To toggle display of the transparent surface on the receptor.
X on the controller (left)	To toggle the display the status text on the screen.
A on the controller (right)	To toggle the display of the VR menu

 In the VR UI you can point at the buttons with the left controller. When you are highlighting them (target turns blue) press trigger to toggle the option.	VR UI can be used to toggle the following features: Show intermolecular hydrogen bonds Show intramolecular hydrogen bonds Toggle Collision Detection mode to prevent molecules overlapping. Adjusting the force components Replay mode features
Enter on the controller (left)	To toggle the instructions summarising the VR controls

What you are seeing in the Oculus Rift will be displayed on the regular monitor to allow others to see a 2D view of what is shown inside VR.

It is also possible to use standard DockIT whilst wearing the VR headset using the controller to manipulate the usual interface if you wish to reduce taking on and off the headset. This can be done by selecting to view the Desktop when wearing your headset

REPLAYING AND RECORDING SIMULATIONS IN VR

From the VR menu you can also control the recording and playback of simulations. This can be useful when wishing to explore what you or others have recorded using a VR headset.

To record in VR

- Press 'A' on the right controller to display the VR Menu.
- Then select the record button  using the trigger for button selection.
- *To record movements you need to hide the menu (Press 'A' on the controller).*
- When finished bring the VR menu up again and select the stop button.

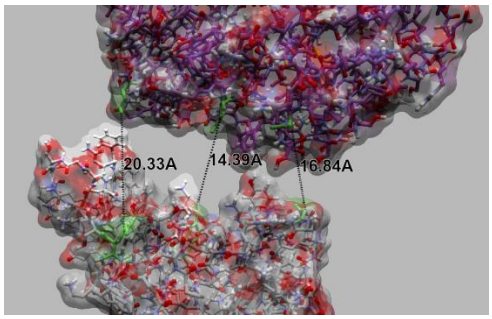
To replay the simulation in VR.

- To enter replay mode select the "Replay Mode" check box on the VR menu.
- You can then use the play and stop buttons on the VR menu (you need to hide the VR menu for the replay to begin.

You can also control the playback of the simulation using the thumbsticks when the VR menu is hidden. The table below describes the playback controls.

VR Control	**Action**
Move the Left Thumbstick to the right.	To play the simulation forwards.
Move the Left Thumbstick to the left.	To play the simulation in reverse.
Move the Right Thumbstick down	To decrease the speed of playback
Move the Right Thumbstick up	To increase the speed of playback.

TUTORIALS



Within the installation folder you will find some tutorials to help you get started with the software and to explore features for rigid docking and docking where receptor flexibility is enabled. Figure 19 illustrates the task for one of the available tutorials.

Figure 19 A tutorial is available to illustrate rigid docking of SARS-CoV-2 RBD protein and an antibody.

TROUBLESHOOTING

Minimum Specification Computer is as follows:

OpenGL 4.0 or Higher GPU

OpenCL 1.2 or Higher compliant GPU

2GB of GPU memory or 4GB of shared memory. A dedicated GPU is recommended for improved performance.

The following table lists some common issues and potential solutions.

Issue	Potential Solution
OpenGL 4.0 or above is required. A message will appear if you don't have sufficient version of OpenGL: *Invalid OpenGL version! This station supports a version lower than 4.x*.	OpenGL 4.0 or higher is required. Please check that your graphics card supports OpenGL 4.0. To do this go to Start menu and type *System Information".* From here you can go to *Components* and select *Display.* On the right you can see the *Adapter Description*, which is the name of your Graphics card and then you can check the specification online. Alternatively you can install a third party tool, https://www.geeks3d.com/dl/show/635, GPU Caps Viewer to check your version of OpenGL. Installing the latest driver may improve your version, but if the GPU doesn't support it then unfortunately you would need a different GPU to use the software.
OpenCL 1.2 capable device is required. If you don't have an OpenCL capable device the following message will appear: *FATAL ERROR: The application cannot create the appropriate OpenCL context!*	DockIT requires an OpenCL compliant device. Ideally a 1.2 compliant device is recommended with at least 2GB of RAM. The GPU Caps Viewer mentioned above will show the OpenCL version and available Global memory.
The loading of a structure appears to work but nothing is displayed on the screen.	If you experience difficulties viewing a structure you can try to update your graphics driver. The latest graphics driver for your system may improve the rendering of structures.
The Loading of the Topology file did not conclude as expected	When loading a structure the following error will occur if there is something incorrect with the topology file. A common mistake is loading a topology file for a different structure that is in the PDB file you are loading.

The ligand becomes stuck unable to be moved.	This can occur when collision response mode is on and the arrangement of atoms in contact make it difficult to move to a free space. The solution is to try moving the ligand in small movements to free it. If it is stuck you can switch off the collision response and move the ligand to a free location before turning it back on and continuing with docking.
There is insufficient GPU memory to support the Molecular Surface for the ligand and receptor.	When trying to build the molecular surface for structure being loaded the OpenCL device ran out of memory. The software can continue to be used without the Molecular Surface depiction. To load the same structures and view the Molecular Surface an OpenCL device with more memory would be required.
VR Mode doesn't work or isn't enabled in the interface.	Only a compatible VR headset may be used. Currently DockIT supports use of Meta Quest 2 (with oculus link cable), Oculus Rift and Oculus Rift S. When using a compatible headset ensure you plug it in and run the appropriate device set up prior to opening DockIT. For Meta Quest 2 ensure you connect the Oculus link cable and launch the quest link to view the Oculus Dashboard prior to starting DockIT. For Oculus Rift or Rift S ensure you run the Device setup.
I can't get a 3d projector to work with DockIT.	To use a 3D Projector DockIT uses Quad buffer stereo and requires an Nvidia Quadro GPU.

REFERENCES

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4 Bolopion, A.; Cagneau, B.; Redon, S.; Regnier, S. Variable gain haptic coupling for molecular simulation. World Haptics Conference (WHC), 2011 IEEE. 2011; pp 469–474.