Pharmacophore constraints in GOLD (GLD-004)

2025.1 CSD Release
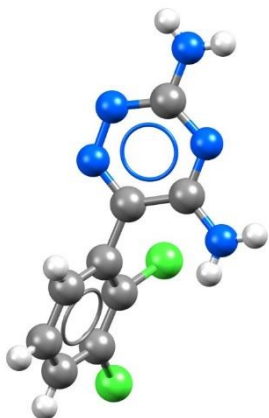
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Introduction: Pharmacophore Constraints in GOLD

Constraints are used to include in a *docking* experiment any known (*a priori*) information about the protein-ligand system. Constraint-driven docking has also been shown to improve the results of a docking calculation when docking a non-native ligand into a protein.

GOLD includes several types of constraints that can be applied to a protein, protein ensemble or to a protein-ligand system (see Setting Constraints in the GOLD User Guide). The latest constraint implemented in GOLD and developed with Astex Therapeutics Ltd. is the pharmacophore constraint. A pharmacophore constraint rewards docking poses when specific regions of the *binding site* are occupied by specific types of ligand atoms (for example, H-bond donor or acceptor, ring centre).

When using *pharmacophore* constraints GOLD will be biased towards finding solutions in which the specified constraint is satisfied. However, such a solution is not guaranteed, i.e. it is not possible to force a constraint to be satisfied in the final solution.

Learning Outcomes

In this workshop, we will explore a situation where a researcher has a crystal structure of a protein and wants to explore the binding site and/or secondary pockets of the binding site by rewarding ligand structures that interact with such pockets. After completing this workshop, you should be able to:

- Set and use pharmacophore constraints to reproduce the binding mode of a ligand in a small secondary pocket in the protein binding site.
- Compare results between docking with and without pharmacophore constraints.

This workshop will take approximately **50 minutes** to complete. **Note:** The words in *Blue Italic* in the text are reported in the Glossary at the end of this handout.

Pre-required Skills

This example assumes you are already familiar with how to setup protein(s) and ligands for docking calculations in GOLD. If not, please refer to the following sections of the GOLD User Guide and CSDU module:

- Setting Up the Protein
- Essential Steps
- Protein-ligand docking 101 - running a simulation in GOLD, covering the basics of protein-ligand docking with GOLD.

The basic visualisation options for Hermes are at the end of this handout.

Materials

For this workshop, we will use the files provided in this folder

Provided Input Files

- *1KE7_protein.mol2,* CDK2 protein coordinates derived from the crystallographic structure of CDK2 in complex with LS3 inhibitor. The protein structure has already been set up in accordance with the guidelines for the preparation of protein input files (see Setting Up the Protein(s)). The original PDB file *1ke7.pdb* has also been provided should you wish to set up the protein for yourself.

- *LS3_ideal.sdf,* LS3 inhibitor coordinates that will be used for the docking. *LS3_idea.sdf* represents the idealised version of LS3, downloaded from the PDB, which bears no resemblance to the docked conformation. The ligand has been set up in accordance with the guidelines for the preparation of input files (see Setting Up the Protein(s) and Setting Up Ligands).

- *reference_LS3.mol2,* this represents the coordinates of LS3 in complex with CDK2. We will use this structure as reference to calculate the RMSD of the docked solution compare d to the reference binding mode.

Case Study

Introduction

Cyclin-dependent kinase 2 (CDK2) is an important protein kinase required for promoting the cell division cycle and for successful progression through S and G2 phases. This role in the cell cycle progression has led to an active search of small molecule compounds inhibiting this enzyme as potential anticancer drugs.

Many studies have been published that describe various CDK inhibitors which mimic ATP by targeting the hinge region and the hydrophobic adenine region of the CDK2 binding site. They bind by hydrophobic interactions and by forming hydrogen bonds with the kinase, especially with the backbone of Glu81 and Leu83 in the structure of the apoenzyme (Figure 1).

Many structures of CDK2 in complex with different types of inhibitors have been deposited in the Protein Data Bank (PDB). Among them, of particular interest are the oxindole-based imidazo[1,2-*a*]pyridines and imidazo[1,2-*b*]pyridazines derivates.

These compounds, in addition to the common features of a CDK2 inhibitor, exploit a particular non-conserved region in the active site that provides selectivity for CDK2 over the other kinases and other members of CDK family. The selectivity is provided by the presence of sulfonyl or sulphonamide group that positions to interact with Asp86 or Lys89 respectively on the top edge of the binding site adjacent to a phenyl ring (Phe82) that packs into a small secondary hydrophobic pocket above the hinge region.

In this workshop we are going to use GOLD to reproduce the binding site of one of these CDK2 selective ligand, LS3 (3-{[(2,2-dioxido-1,3-dihydro-2-benzothien-5-yl)amino]methylene}-5-(1,3-oxazol-5-yl)-1,3-dihydro-2H-indol-2-one) in the CDK2 binding site. We will make use of pharmacophore constraints to optimise the docking poses of LS3.
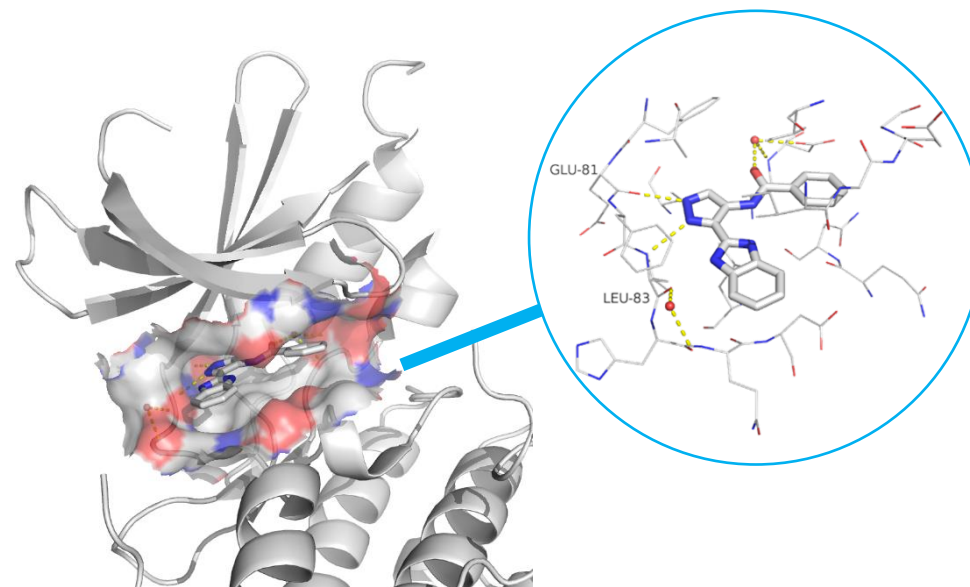

Figure1. CDK2 in complex with a fragment-like molecule. Hydrogen bond interactions are shown as dashed yellow lines.
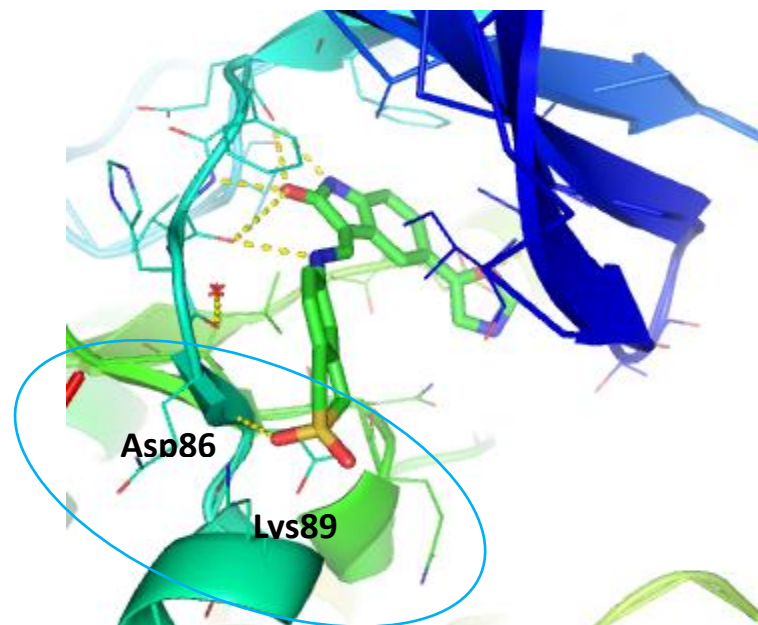

Figure2. CDK2 in complex with a LS3 ligand. Hydrogen bond interactions are shown as dashed yellow lines.

Docking with GOLD without constraints

1. Open Hermes and click on **File** and select **Open…** from the pull-down menu to load *1KE7_protein.mol2* (from the provided materials). The loaded structure will be displayed in Hermes 3D view and listed in *Molecule Explorer* window in the left-hand panel.

2. Click on **GOLD** from the top-menu bar and select **Wizard…**.

3. In the *GOLD Setup* window, select *1KE7* as protein to use by activating the tick-box adjacent to *1KE7.* This will add a tab corresponding to this protein to the right of the *Global Options* tab, labelled with the name taken from the protein file. Click **Next**.

4. The protein is already set-up for docking (e.g. hydrogen atoms were added, water molecules removed, the ligand removed from the binding site and the protonation of key residues in the binding site checked); click **Next** to move to the next step of the Wizard to define the binding site.
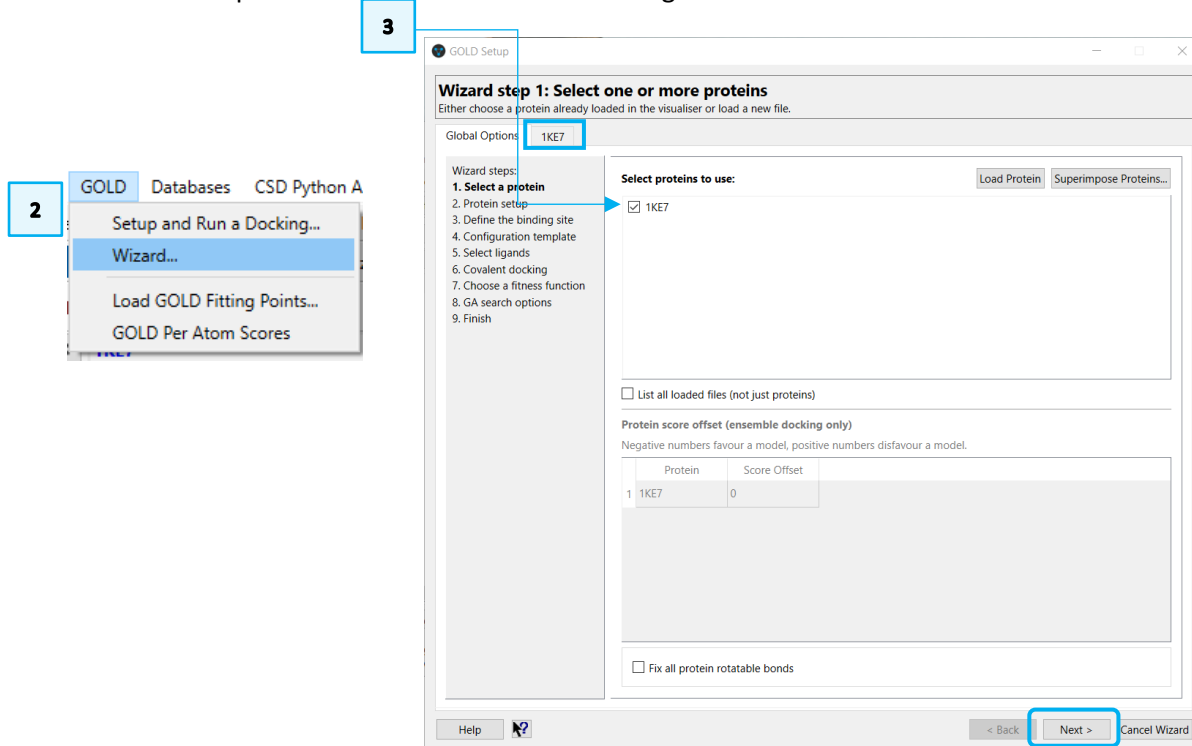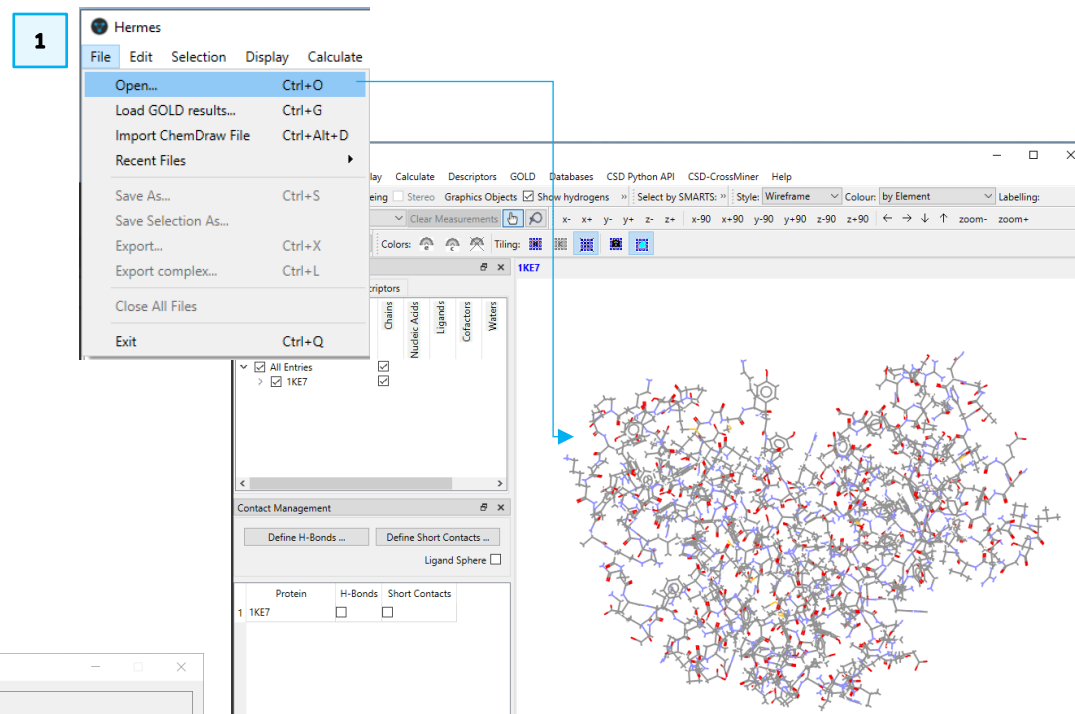
Defining the Binding Site

5. In the *GOLD Setup* window, in the *Define the binding site* step, select the *Point - select atoms to define a centroid or edit XYZ* radio button. We will use a set of coordinates to define the binding site.

    Enter −8.79212, 50.4067 and 13.7064 in the corresponding *X,Y,Z* text boxes, then click on the **View** button to visualise those atoms included in the binding site definition. Carbon atoms outside of the binding site will turn purple. Switch off the display of H-atoms using the **Show hydrogens** tick box in the Hermes toolbar.

6. Leave the default binding site radius of 10 Å around this point. This radius should be large enough to contain all possible binding modes of the LS3 ligand.

7. A cavity detection algorithm, LIGSITE, is used to restrict the region of interest to concave, solvent-accessible surfaces. Ensure that cavity detection is enabled by activating the **Detect cavity - restrict atom selection to solvent-accessible surface** tick-box. Click **Next** to continue setting up the calculation.

8. At this point you are given the option to load a configuration file template. These templates can be used to load recommended settings for a number of different types of docking protocols. In this example, we will specify all docking settings manually.

9. Click **Next** to proceed to the *Select ligands* step in the GOLD wizard.
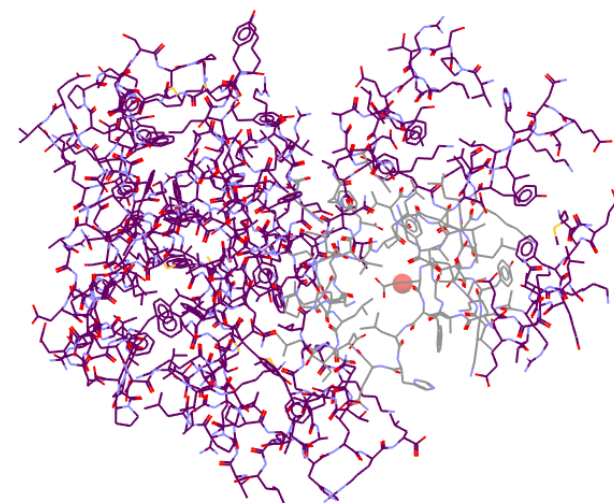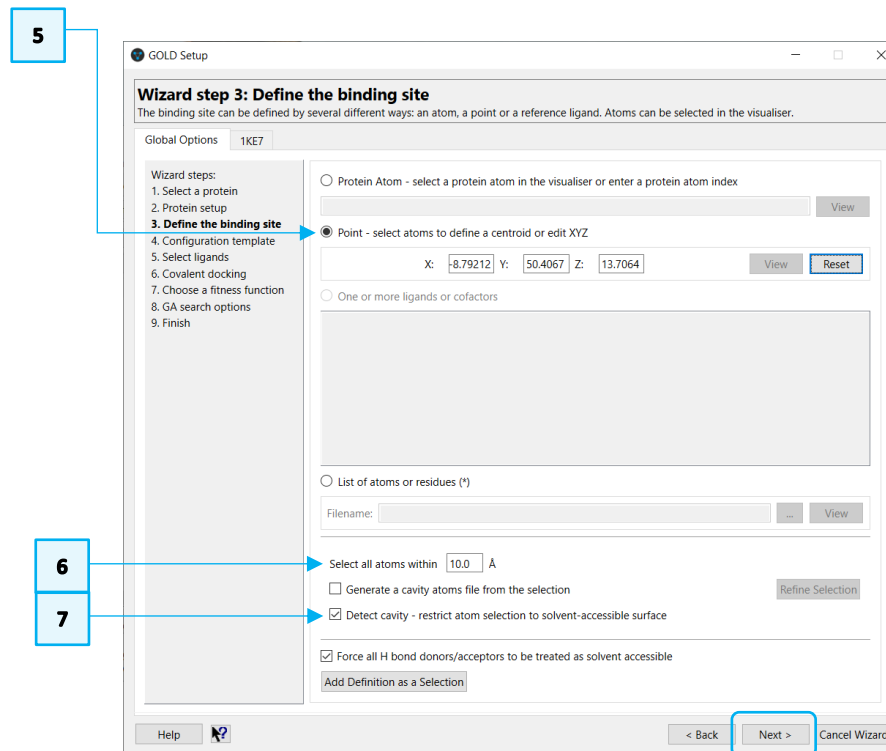
Selecting Ligand for Docking

To proceed with the GOLD setup, we need to specify the ligand that we want to dock into the protein.

The idealised version of the ligand LS3 (with no resemblance to the binding conformation) is available in the tutorial folder (*LS3_ideal.sdf*). As with the protein file, the ligand has been set up in accordance with the guidelines for the preparation of input file.

10. Specify the *LS3_ideal.sdf* ligand by clicking **Add** at the bottom of the *GOLD Setup* window. The *LS3_ideal.sdf* is now listed under *Ligand File.*

You also have the option to supply the file containing the reference ligand (i.e. the ligand in the conformation it adopts in its native binding site), which will be used to perform an automated RMSD calculation with respect to the reference ligand conformation. For each GOLD solution, the resultant RMSD value will be written out to the files containing the fitness function ranking, i.e. the ligand rank file (.rnk) and *bestranking.lst* file.

11. To specify the ligand reference file either enter the path and the filename of the file in the **Reference ligand** box, or click on the **…** button and use the file selection window to choose the *reference_LS3.mol2* file provided in the tutorial folder. This is the native conformation of LS3 in complex with the CDK2 protein. Click **Next** twice to proceed to *Choose a fitness function.*

12. In the *Choose a fitness function,* click on **More >>** button. Ensure that the default **CHEMPLP** *scoring function* is set. In addition, untick the **Allow early termination** tick-box, so that the 10 GA runs will lead to 10 docking poses. Click **Next** to proceed to *GA search options.*
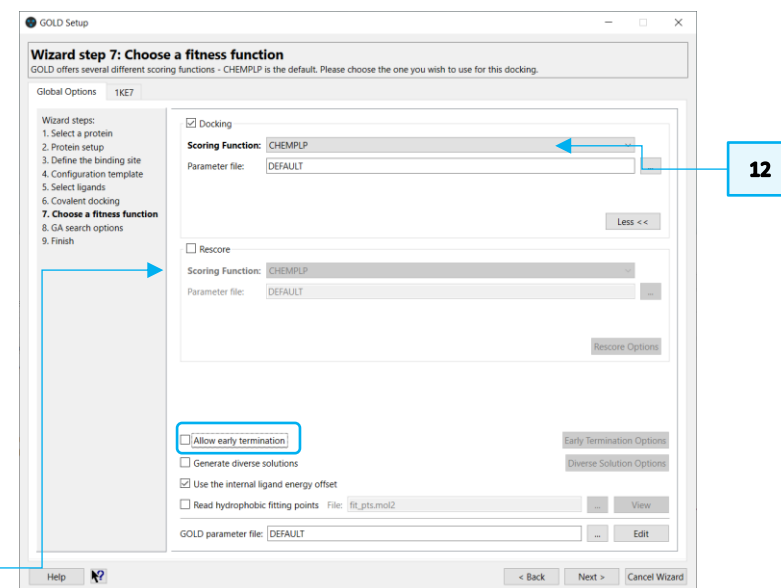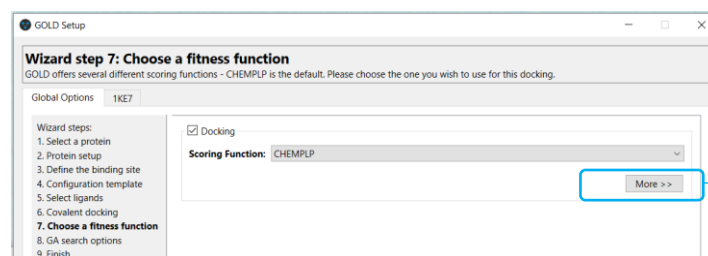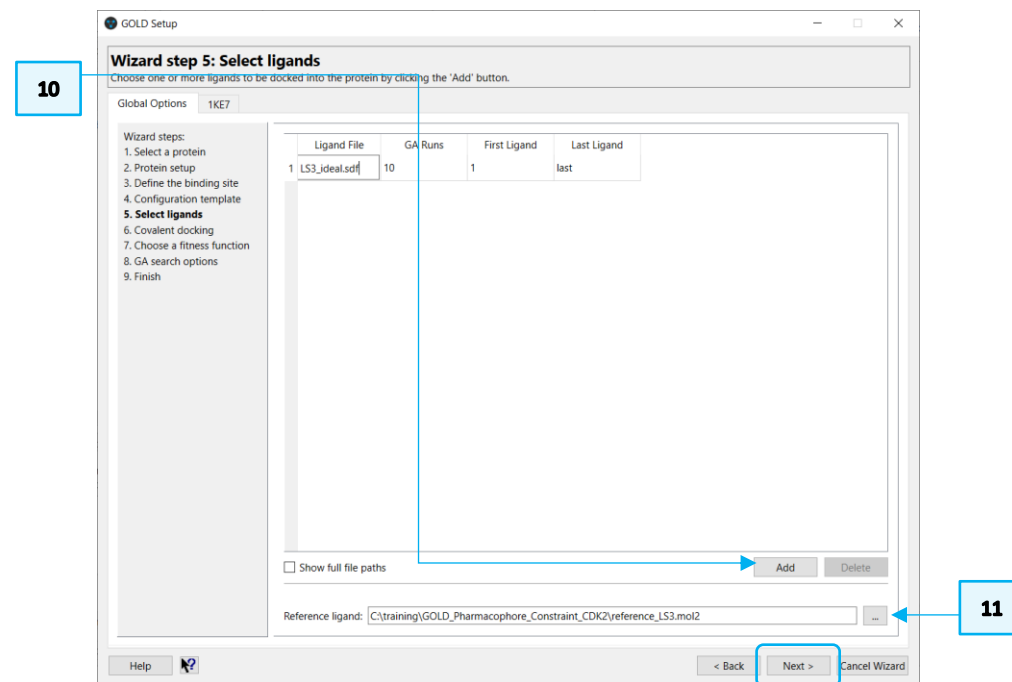
13. In *GA search options,* the user has access to a number of parameters that control the precise operation of the genetic algorithm. Click on the **More** button. Ensure that automatic *GA settings* are enabled (i.e. the **Automatic** radio button is selected) and that *Search efficiency* is set to 100%. This will make GOLD automatically calculate an optimal number of operations for a given ligand, thereby making the most efficient use of the search time.

The criteria used by GOLD to determine the optimal GA parameter settings for a given ligand include: the number of rotatable bonds in the ligand, ligand flexibility (i.e. number of flexible ring corners, flippable nitrogens, etc.), the volume of the protein binding site, and the number of water molecules considered during docking. Details of the exact settings used will be given in the ligand log file *gold_ligand_m1.log.*

14. Click **Next** to proceed to the *Finish* window.

15. Before proceeding to run GOLD, in the *Wizard step 8: Finish basic GOLD configuration*, click on **Advanced**. This will give the access to more advanced options for docking available outside the main Wizard.
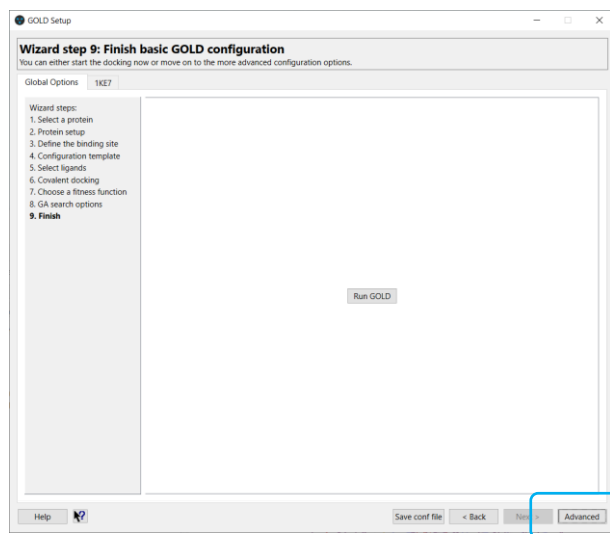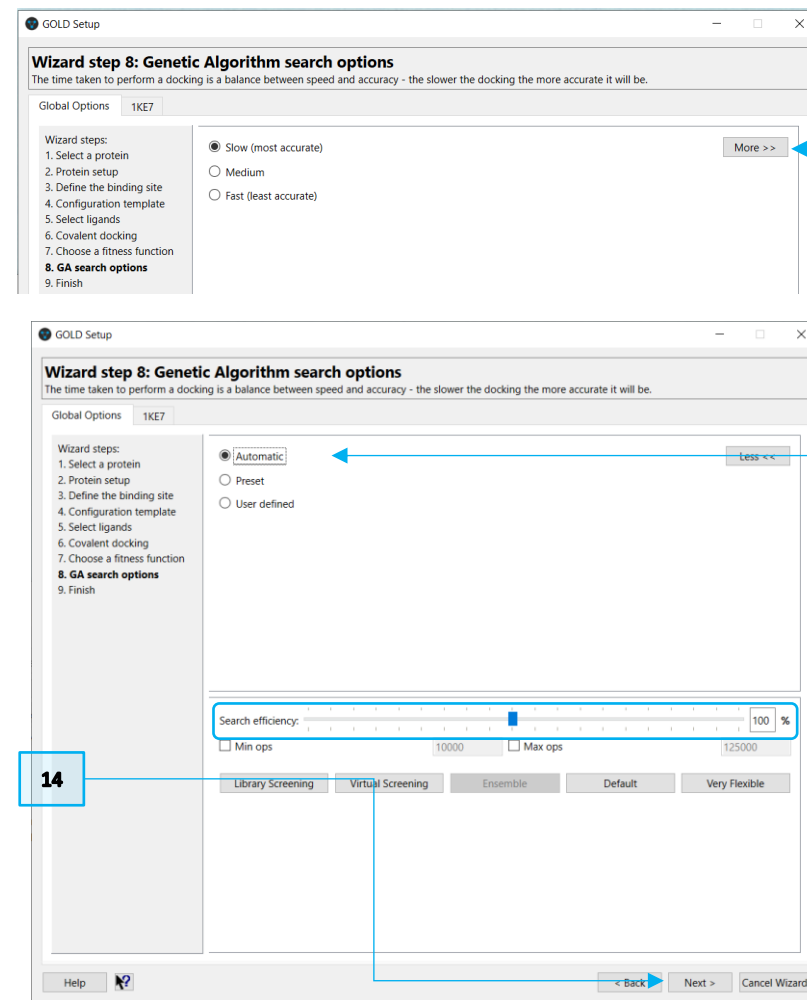
16. Select *Output Options* under *Global Options.* In the tab labelled *File Format Options*, activate the **Mol2** radio button adjacent to *Output file format*. This means the docking solutions will be written out in *MOL2* format.

17. Click the **…** button next to *Output directory* and either browse to or create a directory (*e.g. no_constraints*) where you have write permissions; this is where the GOLD output files will be written*.*

18. Click on *Ligand Flexibility* under *Global Options* and activate:

    - **Flip pyramidal N** check-box to allow pyramidal (i.e. non-planar sp^3) nitrogen atoms of the ligand to invert during docking;

    - **Flip amide bonds** check-box to allow amides, thioamides, ureas, and thioureas in the ligand to flip between *cis* and *trans* conformations during docking;

    - **Flip ring corners** check-box to allow GOLD to perform a limited conformational search of cyclic systems by allowing free corners of the rings in the ligand to flip above and below the plane of their neighbouring atoms.

19. We have now finished setting up our docking, so click on the **Run GOLD** button at the bottom of the GOLD interface. You will be presented with a *Finish GOLD Configuration* window containing *Save Files* options.
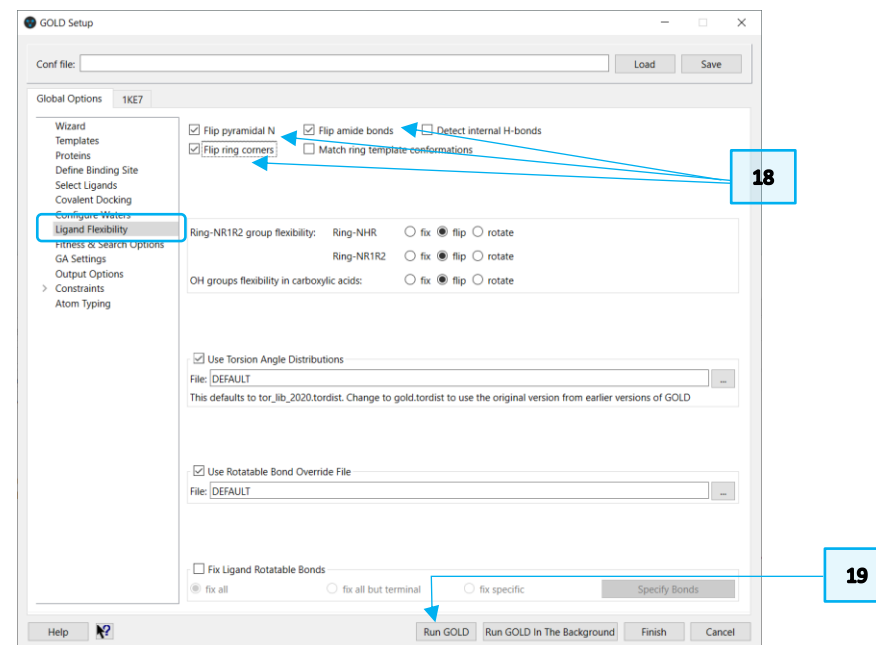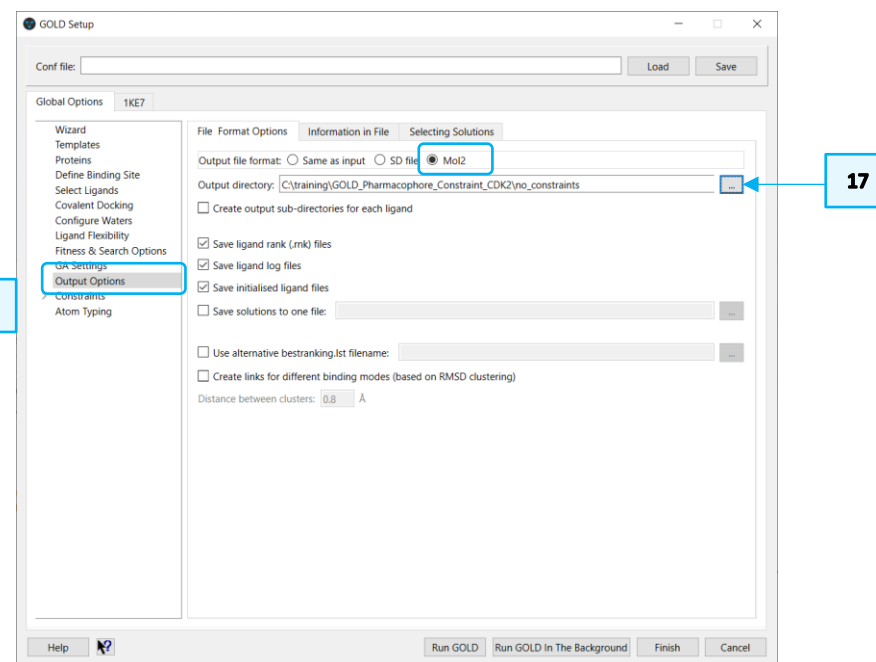
20. Ensure the **GOLD conf file** box is ticked in the *Save Files* section of the *Finish GOLD Configuration* window, and type in the filename box to rename the conf file as *no_constraints.conf.*

21. No edits were made to the protein therefore you can leave the **Protein(s)** check-box unticked. Click **Save** to start the docking run.

22. As the job progresses output will be displayed in several tabs in the *Run GOLD* window. Note that the docking calculation will take a few minutes to complete.

23. Once the job is complete, load the docking results into Hermes by clicking on the **View Solutions** button in the *Run GOLD* window.
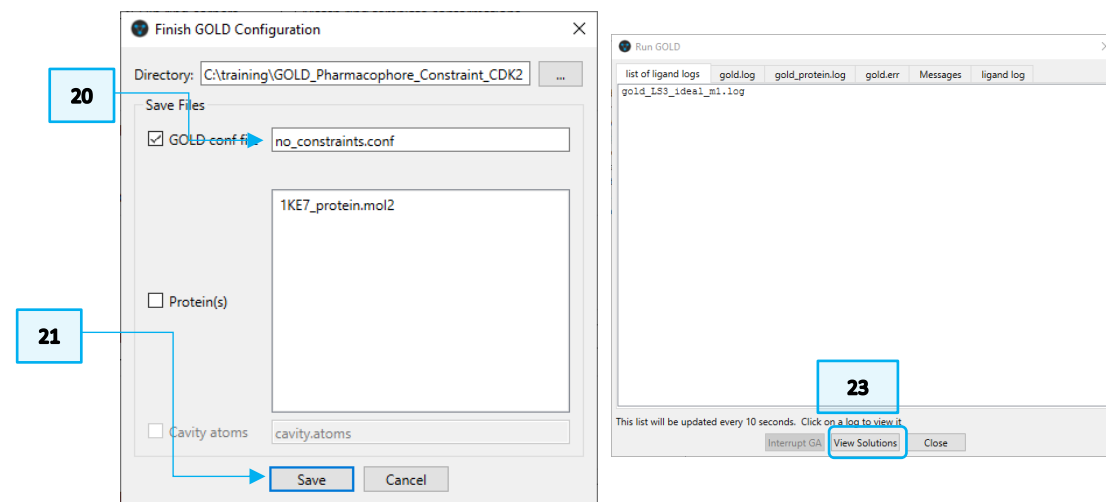
Analysing Docking Results

1. Return to the Hermes 3D view and look at the *Docking Solutions* tab in the *Molecule Explorer*. Use the Up and Down arrows on your keyboard to change between docking solutions.

2. Click on **File** > **Open…** to load the structure of LS3 in its native conformation within its native CDK2 protein (*reference_LS3.mol2*). We will use it to evaluate if GOLD was able to reproduce the binding mode of LS3 in complex with CDK2.

3. In the *Docking Solutions* tab, you will notice that the docking solutions are given in their docked order with their corresponding fitness score listed under the column headed *PLP.Fitness*. Order the solutions based on the fitness score by clicking on this *PLP.Fitness* header to list the highest scoring pose at the top of the list.

Please note: Due to the non-deterministic nature of GOLD, your results may vary from those described in this tutorial. In addition, the precise values of scoring functions terms in your docking will differ from the ones illustrated here.
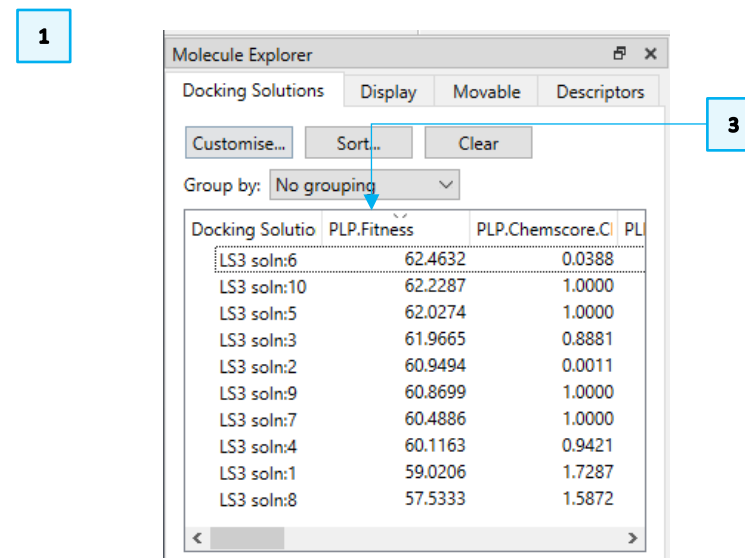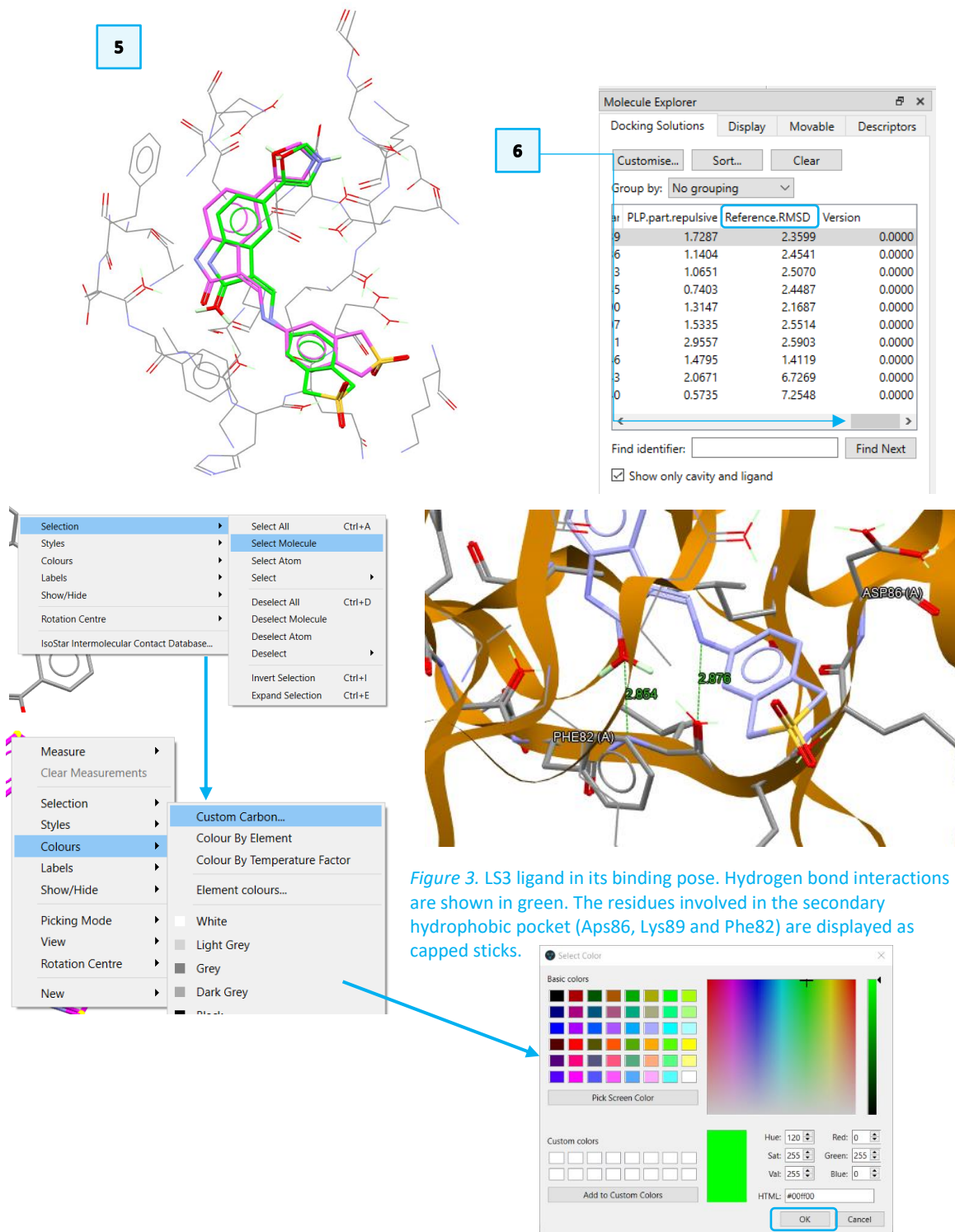
4. We have obtained 10 docking solutions, as expected because we deactivated the **Allow early termination** mode.

5. You will see that none of the solutions found by GOLD perfectly reproduces the binding mode of LS3. Comparing the reference crystallographic structure of LS3 (shown here in pink carbon atoms for clarity) and the best ranked docking pose (with green carbon atoms) you will see that GOLD fails to reproduce the orientation of the thiophene portion of the benzothiophene 2,2-dioxide moiety. Show only cavity and ligand has been ticked for easier viewing.

Tip: You can change the colour of Carbon atoms in a molecule by right clicking on any atom in the molecule, clicking on **Selection > Select Molecule**. Once the molecule is selected, right click on an atom or in the display window, select **Colours > Custom Carbon**...to open the *Select Color* window. Pick a color and *click OK* to apply the change to the selected molecule.

6. Use the scroll-bar in the *Docking Solutions* tab to have access to "*Reference.RMSD*" column. The best ranked docking solution shows an RMSD of 2.36 Å to the crystallographic pose of LS3.

GOLD tries to place the sulfonyl group toward the surface of the CDK2 binding site, whereas in the crystallographic binding pose of LS3, the sulfonyl moiety of the benzothiophene ring is positioned such that it interacts with Asp86 on the top edge of the binding site adjacent to a phenyl ring (Phe82) that packs into a small secondary hydrophobic pocket above the hinge region (See Figure 3).

In the next part of this tutorial, we will make use of a pharmacophore constraint to try and reproduce the binding mode of LS3 in complex with CDK2. The pharmacophore constraint will bias GOLD towards rewarding docking solutions with the benzothiophene ring of LS3 located in the secondary hydrophobic pocket.

PLP.part.repulsive	Reference.RMSD	Version
1.7287	2.3599	0.0000
1.1404	2.4541	0.0000
1.0651	2.5070	0.0000
0.7403	2.4487	0.0000
1.3147	2.1687	0.0000
1.5335	2.5514	0.0000
2.9557	2.5903	0.0000
1.4795	1.4119	0.0000
2.0671	6.7269	0.0000
0.5735	7.2548	0.0000

Figure 3. LS3 ligand in its binding pose. Hydrogen bond interactions are shown in green. The residues involved in the secondary hydrophobic pocket (Aps86, Lys89 and Phe82) are displayed as capped sticks.

Docking with Pharmacophore Constraints

Pharmacophore constraints in GOLD reward occupation of specific regions of the binding site by specific types of ligand atoms. A contribution (determined according to a user-specified weight) is added to the score for each specified pharmacophore constraint if the distance between the pharmacophore point and an atom of the same type in the ligand is less than the specified radius of the sphere. If a pharmacophore constraint point is not matched in the ligand, it will not be used during scoring.

Setting Pharmacophore Constraints

1. If you still have your docking results loaded, click on **File** > **Close All Files** to clear the Hermes 3D view.

2. From Hermes top-level menu click on **GOLD** > **Setup and Run a Docking** > **Load Existing** to load the previous *no_constraints.conf* configuration file.

3. Click on the "**>**" symbol next to *Constraints* in the list of *Global Options* to open a list of available constraints.

4. Select **Pharmacophore** from the *Constraints* list to set the requirement for the pharmacophore constraints.

Five types of pharmacophore points can be defined: *H-bond acceptor*, *H-bond donor, H-bond donor or acceptor*, *Aromatic ring centre* and *Ring centre.* For each pharmacophore point specified, a sphere is placed at an explicitly defined position within the binding site. For this tutorial, we are going to define an H-bond acceptor pharmacophore constraint.

5. Select **H-bond acceptor** from the list of available pharmacophore type. Then Click on **Define Pharmacophore Point**. An *Edit Sphere* pop-up window will allow to generate the pharmacophore sphere based on:

- *Centroid of protein subset*
- *Centroid of atoms selected in 3D viewer*
- *x,y,z coordinates*
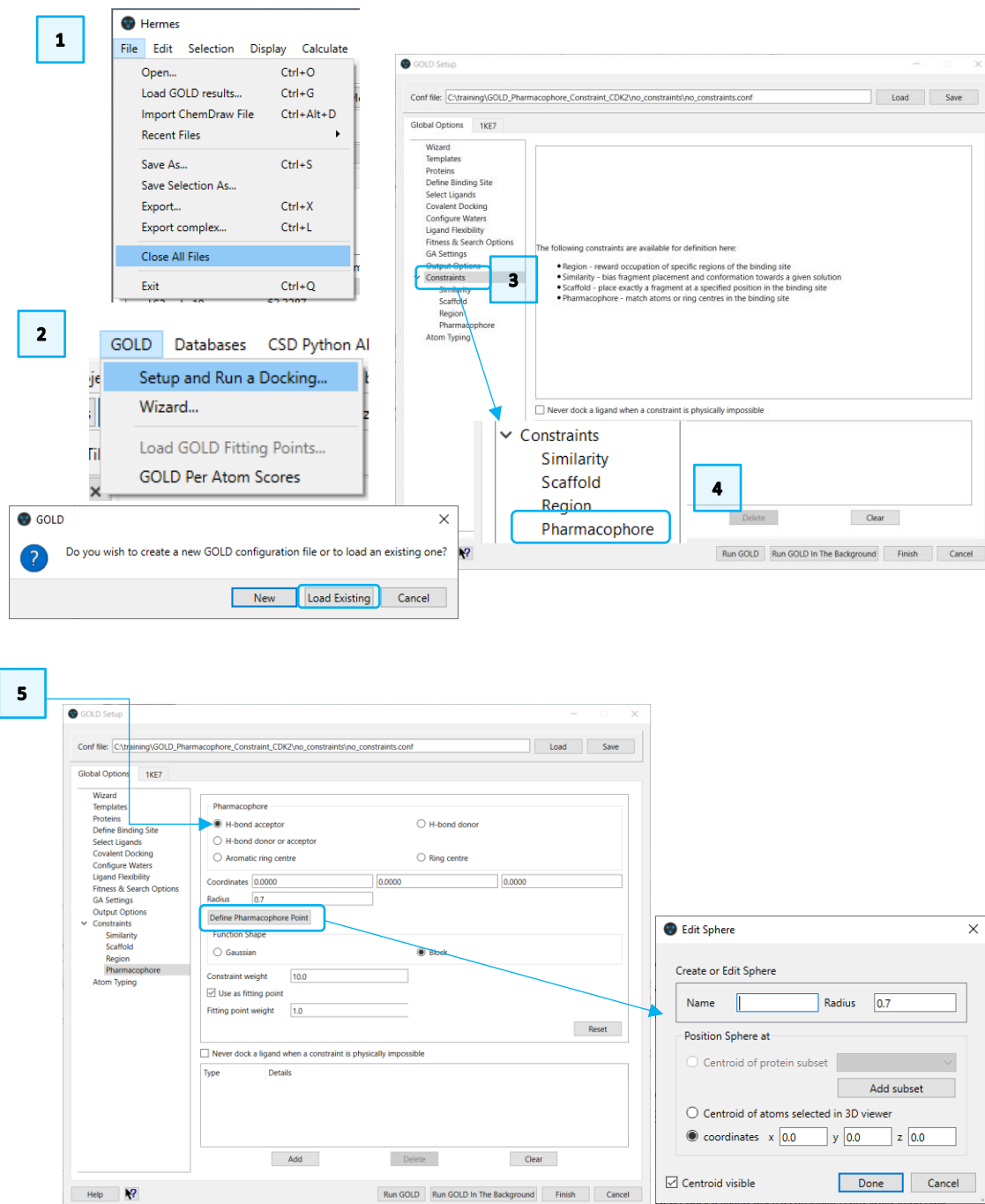
6. Click on the radio next to **Centroid of atoms selected in 3D viewer** to position the pharmacophore sphere based on a *Centroid of selected atoms*.

7. From the *Molecule Explorer* window click on ">" adjacent to *1KE7*, then on the ">" adjacent to *Chains* and then ">" adjacent to *A* to access all residues in the protein. Scroll through the list in the *Molecule Explorer* and select ASP86 and LYS89. Multi-selection is possible by using **CTRL + left-click**. With both residues highlighted, right click on either one, then click **Select** from the right-click menu.

8. The coordinates of the selected residues will be populated in the *coordinates* boxes. The coordinates should be −7.17575, 45.1085 and 4.29812 in the *x*, *y*, *z* boxes.

9. The H-bond acceptor pharmacophore sphere will be placed based on the *ASP86_LYS89* protein subset. Write *Acceptor* in the **Name** text-box and increase the radius of the pharmacophore sphere to 3 Å in the **Radius** text-box of the *Edit Sphere* window. This means that a contribution for the fulfilment of this pharmacophore constraint is added to the score if the distance between the pharmacophore point and an H-bond acceptor atom in the ligand is less than the specified 3 Å radius of the sphere. Then click **Done.**

10. This will update the *Pharmacophore* window with the coordinates of the H-bond acceptor pharmacophore point just defined.

11. The pharmacophore weight must also be specified. This is the value that will be added to the fitness score for matched ligand atoms satisfying the constraint. Leave the **Pharmacophore Weight** to the default value of 10.

12. Ensure the **Function Shape** is set to **Block.**

13. From here, click **Add** to create the pharmacophore constraint. An acceptor pharmacophore constraint will then be added to the list of constraints.

14. Now we are going to set a *Ring centre* pharmacophore constraint. To do so, first click **Reset**, then select **Ring centre** from the list of available pharmacophore types. Then click on **Define Pharmacophore Point.**

15. This time select the **coordinates** check-box and type −10.5647, 45.3358 and 7.6280 in the *x, y, z* text-boxes to define the coordinates of the pharmacophore ring centre. Name the pharmacophore point *Ring_centre* and define the pharmacophore radius to *1.5Å.* Then click **Done.**

16. Leave the pharmacophore weight and function shape as the defaults and click **Add** to create the *Ring centre* pharmacophore constraint.

17. Select *Output Options* from the *GOLD Setup* window. Click the **...** button next to *Output directory* and either browse to or create an appropriate directory, *e.g. pharmacophore_constraints* to which you have write permissions; this is where the GOLD output files will be written.

18. We have now finished setting up our docking, so click on the **Run GOLD** button. You will be presented with a *Finish GOLD Configuration* window containing *Save Files* options.

19. Ensure the **GOLD conf file** box is ticked in the *Save Files* section of *Finish GOLD Configuration* window and type in the filename box to rename the conf file as *pharmacophore_constraints.conf.* No edits were made to the protein therefore you can leave the **Protein(s)** check-box unticked. Click **Save** to run GOLD.

20. Once the GOLD job is complete, load the results into Hermes using the **View Solutions** button.
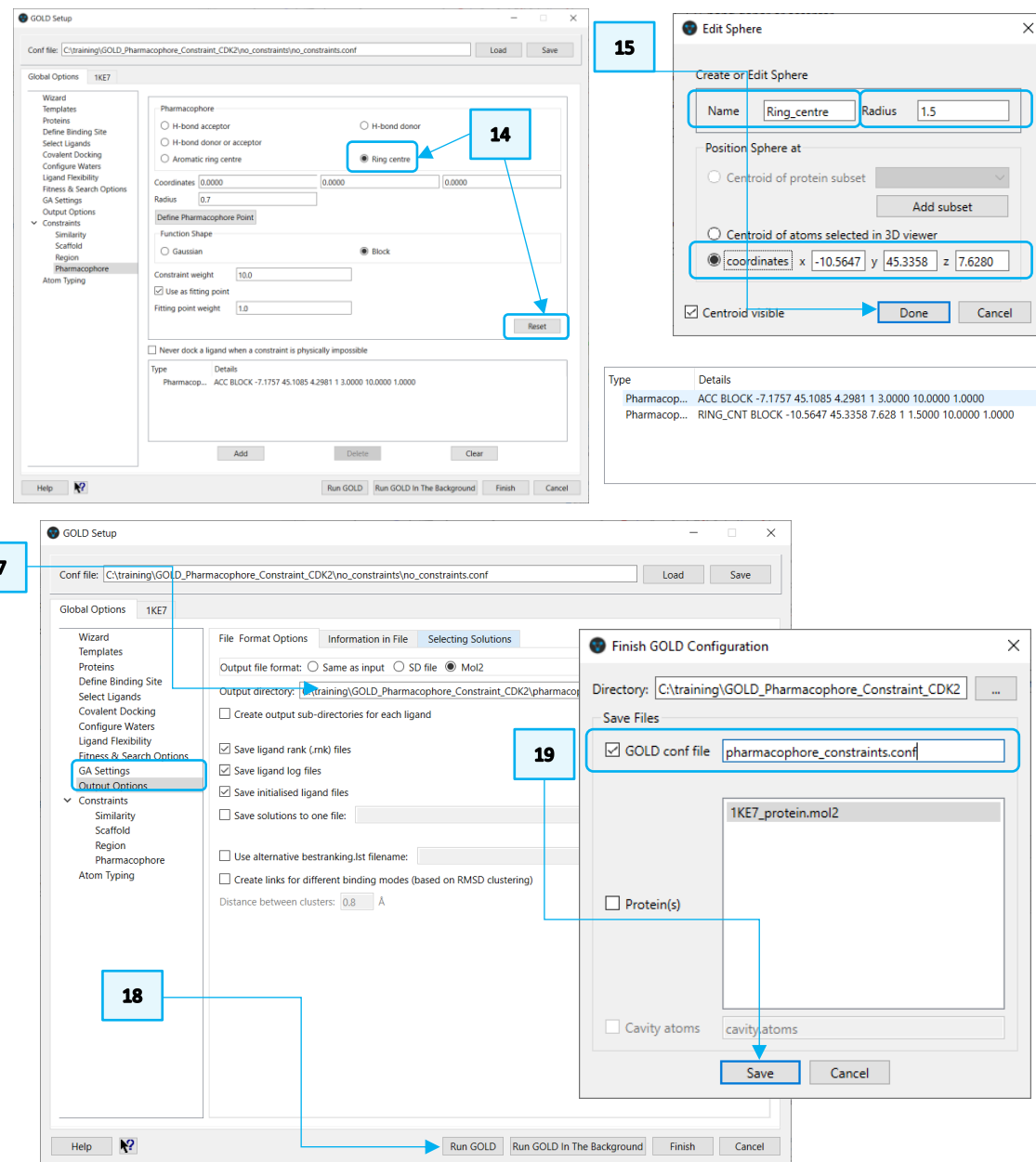
Analysing Docking Results with Pharmacophore Constraints

1. Return to the Hermes 3D view and look at the *Docking Solutions* tab in *Molecule Explorer*. Use the Up and Down arrows on your keyboard to change between the 10 docking solutions.

2. Click on **File** > **Open…** to load the structure of LS3 in its native conformation within its native CDK2 protein (*reference_LS3.mol2*). We will use it to evaluate if GOLD was able to reproduce the binding mode of LS3 in complex with CDK2.

3. In the *Docking Solutions* tab, order the solutions based on the fitness score by clicking on this *PLP.Fitness* header to list the highest scoring pose at the top of the list.

Please note: Due to the non-deterministic nature of GOLD your results may vary from those described in this tutorial. In addition, the precise values of scoring functions terms in your docking will differ from the ones illustrated here.

4. You will notice that the fitness score of the best ranked docking pose (i.e. 73.08 in our results) is higher than the fitness score of the best ranked docking pose without pharmacophore constraints (e.g. 62.46 in the previous run).

5. Click on the best ranked docking pose to load it in the Hermes 3D view. This time, GOLD is able to reproduce the binding mode of LS3 Comparing the reference crystallographic structure of LS3 (shown here in pink carbon atoms) and the best ranked docking pose (shown here in green carbon atoms). See the tip on page 10 for changing the atom colour.

6. Use the scroll-bar in the *Docking Solutions* tab to display the "*Reference.RMSD*" column. The best ranked docking solution shows an RMSD of 0.39 Å against the crystallographic pose of LS3. This RMSD is considerably lower than the previous docking run performed without pharmacophore constraints (2.36 Å).

7. Go in your specified output folder (e.g. *pharmacophore_constraints*) and inspect the *gold_LS3_ideal_m1.log* file (using any text editor) to see if GOLD has rewarded the best ranked docking pose.

This file gives the total fitness score and a breakdown of the fitness into its constituent energy terms for each docking run performed on the ligand. A constraint scoring term *DE(con)* is listed for each docking. If a solution predicted by GOLD satisfies the two pharmacophore constraints, then the user-defined pharmacophore weight (here, value of 10) for each pharmacophore constraint (see step 11 of Setting Pharmacophore Constraints) is added to the fitness score.

8. The *gold_soln_LS3_ideal_m1_3.mol2,* corresponding to the best ranked docking pose in our case (you may have different results), satisfies both pharmacophore constraints. Therefore, a *DE(con)* contribution of 20 is added to reward this solution.

9. An alternative way to access the contribution of these constraints to the fitness score of each docking solution is to navigate through the *Docking Solutions* tab in the *Molecule Explorer* window. You can use the scroll-bar to access the *PLP.Constraint* column that shows the contribution of the constraint(s) to the fitness score. The best ranked docking pose satisfies both pharmacophore constraints (with a constraint contribution of 20) whilst most of the lower ranked docking poses do not satisfy both or either constraint (with a constraint contribution of 10, and in one case zero).

Conclusions and Summary

- A docking calculation with GOLD can be guided by the inclusion of pharmacophore type constraints in an active site. This is particularly useful if information about how a ligand binds to a protein is already available and in other special cases where docking should be biased around an important area of the binding site.
- The inclusion of pharmacophore constraints in the docking calculation of LS3 in CDK2 significantly improved the docking results, with the RMSD obtained between the best ranking docking pose and the crystallographic pose of the ligand being much lower when implementing these pharmacophore constraints.

After this workshop, you should be able to:

- Set up docking in GOLD including pharmacophore constraints.
- Visualise and analyse docking results with Hermes.

Next Steps

After this workshop, you can continue learning about GOLD with more exercises available in the self-guided workshops available in the CSD-Discovery workshops area on our website.
https://www.ccdc.cam.ac.uk/community/training-and-learning/workshop-materials/csd-discovery-workshops/.

Feedback

We hope this workshop improved your understanding of GOLD and you found it useful for your work. As we aim to continuously improve our training materials, we would love to get your feedback. Click on this link to a survey, it will take less than **5** minutes to complete. The feedback is anonymous. You will be asked to insert the workshop code, which for this self-guided workshop is **GLD-004**. Thank you!

Glossary

Binding Site

A specific region (or atom) in a molecular entity that is capable of entering into a stabilizing interaction with another molecular entity. An example of such an interaction is that of an active site in an enzyme with its substrate. Typical forms of interaction are by hydrogen bonding, coordination and ion pair formation. Two binding sites in different molecular entities are said to be complementary if their interaction is stabilizing. *Source*: PAC, 1994, 66, 1077. (Glossary of terms used in physical organic chemistry (IUPAC Recommendations 1994)) on page 1089.
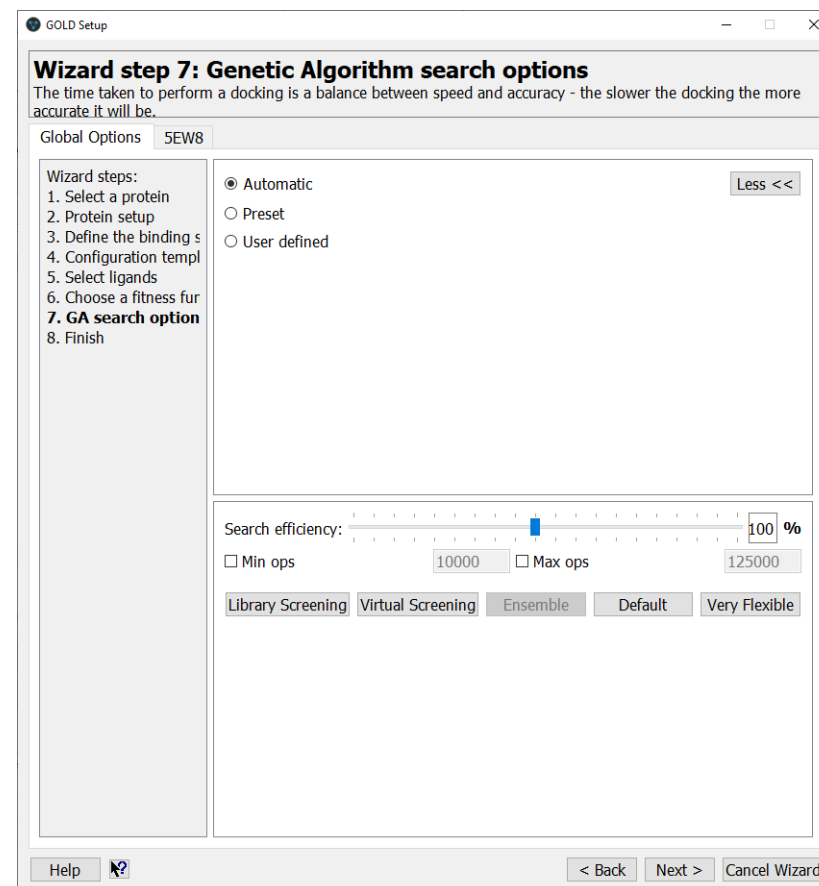
Docking

Docking studies are computational techniques for the exploration of the possible binding modes of a substrate to a given receptor, enzyme or other binding site. *Source*: PAC, 1997, 69, 1137. (Glossary of terms used in computational drug design (IUPAC Recommendations 1997)) on page 1142.

GA setting

A genetic algorithm is an optimization algorithm based on the mechanisms of Darwinian evolution which uses random mutation, crossover and selection procedures to breed better models or solutions from an originally random starting population or sample. *Source*: PAC, 1997, 69, 1137. (Glossary of terms used in computational drug design (IUPAC Recommendations 1997)) on page 1144.

In GOLD, the number of genetic operations performed (crossover, migration, mutation) is the key parameter in determining how long a GOLD run will take (i.e. this parameter controls the coverage of the search space). GOLD can automatically calculate an optimal number of operations for a given ligand, thereby making the most efficient use of search time, e.g. small ligands containing only one or two rotatable bonds will generally require fewer genetic operations than larger, highly flexible ligands. The criteria used by GOLD to determine the optimal GA parameter settings for a given ligand include:

- the number of rotatable bonds in the ligand,

- ligand flexibility, i.e. number of flexible ring corners, flippable nitrogens, etc. (see Ligand Flexibility),
- the volume of the protein binding site, and
- the number of water molecules considered during docking (see Water Molecules).

The exact number of GA operations contributed, e.g. for each rotatable bond in the ligand, are defined in the gold.params file (see Altering GOLD Parameters: the gold.params File). For further information please refer the GOLD user manual.

GOLD

GOLD (Genetic Optimisation for Ligand Docking) is a genetic algorithm for docking flexible ligands into protein binding sites. GOLD has been extensively tested and has shown excellent performance for pose prediction and good results for virtual screening.

Ligand

In this context, these are the molecules under investigation. These could be organic, inorganic and macromolecules.

Pharmacophore

A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or block) its biological response. *Source*: PAC, 1998, 70, 1129. (Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998)) on page 1140.

Scoring function

In the fields of computational chemistry and molecular modelling, scoring functions are mathematical functions used to approximately predict the binding affinity between two molecules after they have been docked. Most commonly one of the molecules is a small organic compound such as a drug and the second is the drug's biological target such as a protein receptor.

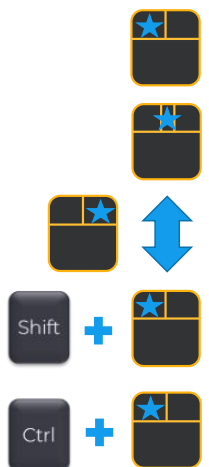# Basics of Hermes Visualisation

Hermes is the CCDC's visualization software to study protein-ligands interaction, and it is the interface for protein docking with GOLD.

In the following we will see some of the basics of navigation and visualization in Hermes that you will find helpful to support your analysis.

In the **Hermes interface** we find:

- **At the top**: list of menus from which we can access visualization and analysis options, and other CSD-Discovery components.
- **On the left-hand side**: the **Molecule Explorer**, where the proteins, ligands, water molecules, and other molecules present in the structures are listed in the *Display* tab. You can expand each entry to see the components, and tick or untick the corresponding boxes to display / not display them. The solutions from a GOLD run will also be displayed in the Molecule Explorer.
- **On the left-hand side**, below the Molecule Explorer: the **Contact Management** box, which allows to display H-bonds and short contacts for selected molecules by ticking the corresponding box.

Using the **mouse to enhance visualization**:

- Left mouse button and move – rotate molecules

- Middle Mouse wheel – move molecules up and down

- Right mouse button and move up and down – zoom in and out of molecules

- Shift + Left mouse button and move - rotate in the plane molecules

- Ctrl + Left mouse button and move - translate molecules
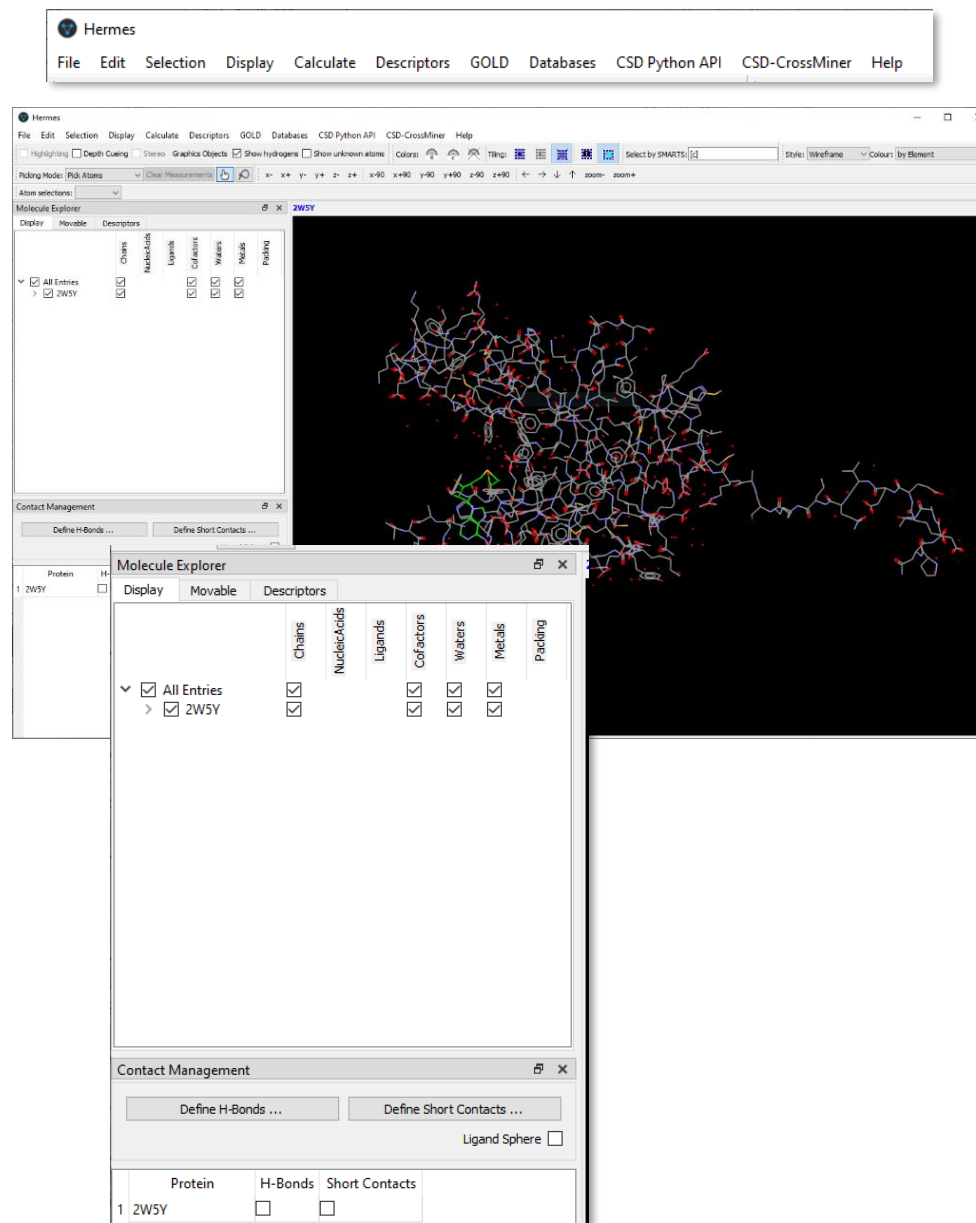
Right click:

a) On a feature

b) Away from a feature

Creating high-resolution images

1. Go to the top menus and click on **File**, then **Save A**s. Alternatively you can use the keyboard and do **Ctrl + S**.

2. In the *Save File As* window, select destination folder, file type and choose a name. Then click **Save**.

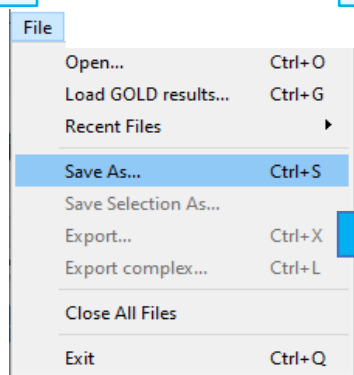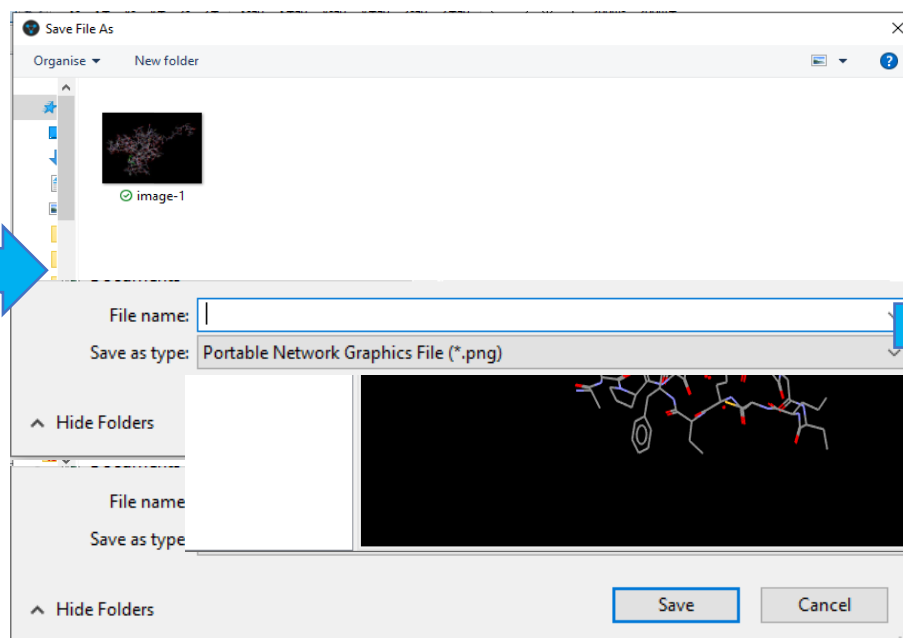3. This will bring up the *Save Image* menu. Here you can select the resolution and tick whether you want a transparent background. Click **Ok**.
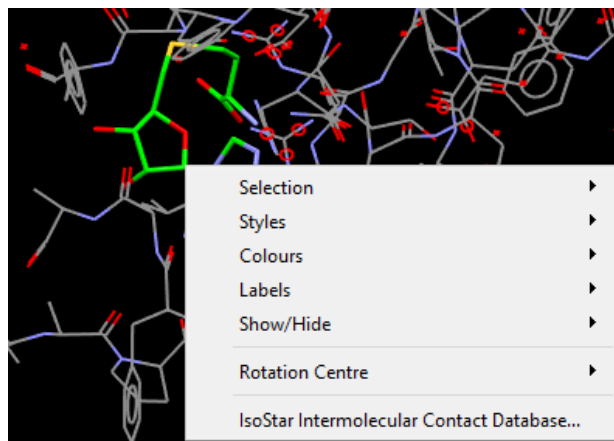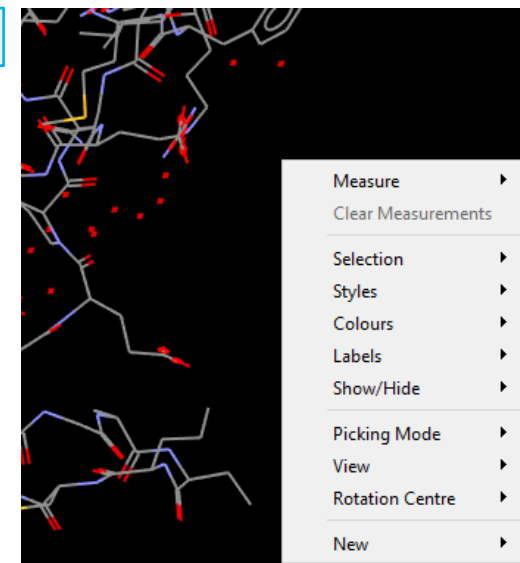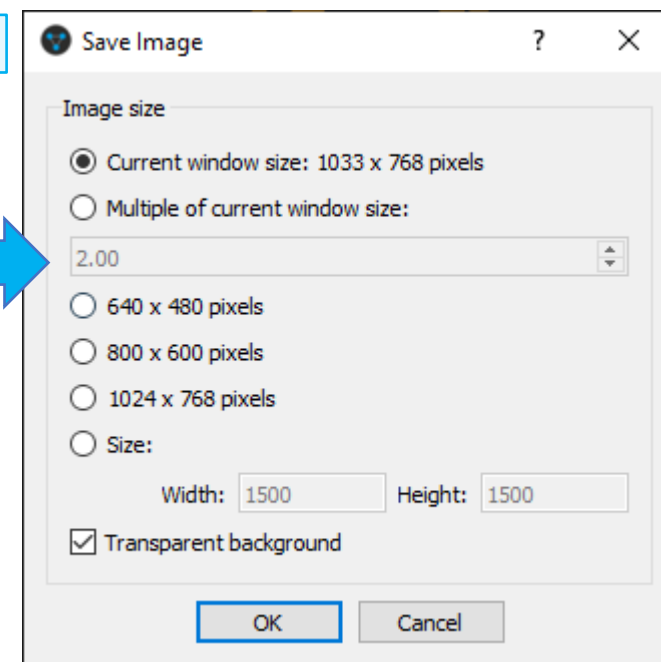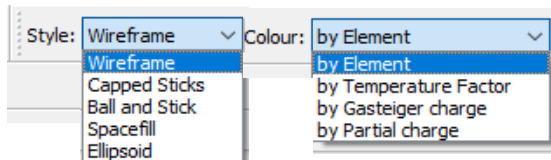
You can access visualization options from the **Display** menu.

- From **Display > Styles**, you can pick the representation style of atoms and bonds and change settings. **Note**: you can also access this feature from the dropdown menu at the top right of the 3D visualizer window.

- From **Display > Colours**, you can edit the colour for elements and object. **Note**: you can change the colouring style for the structure from the dropdown menu at the top right of the 3D visualizer window.

- Clicking on Display > Display Options brings up the Display Options menu, where you can edit settings for the 3D visualizer.
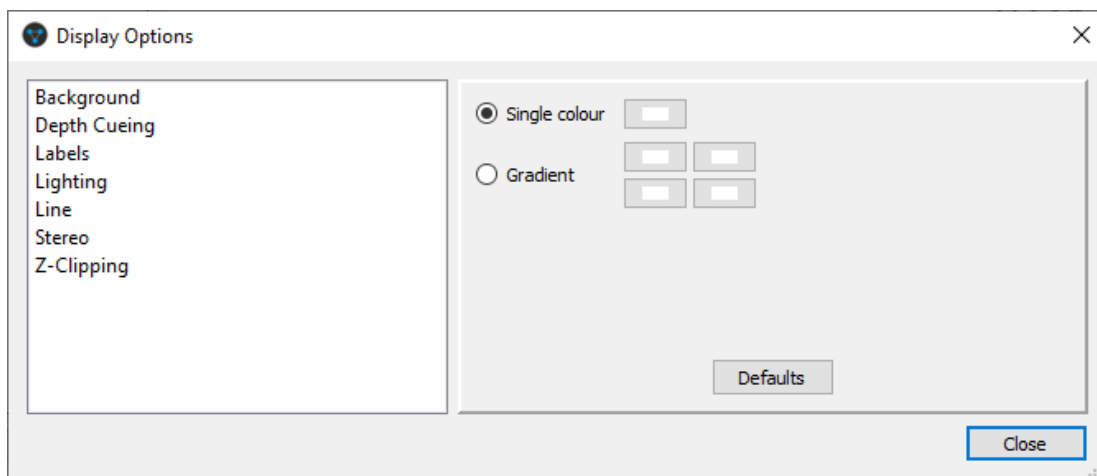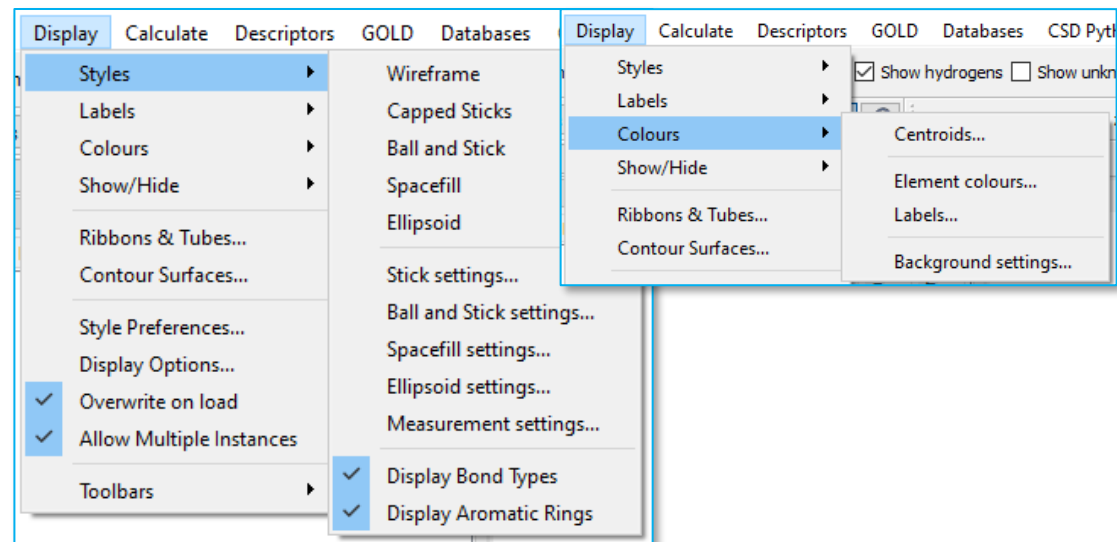
- If any of the toolbars at the top of the Hermes interface is not displayed and you wish to have it shown, or vice versa, you can do so from **Display > Toolbars**, where you can ensure to tick the ones you wish to have on.