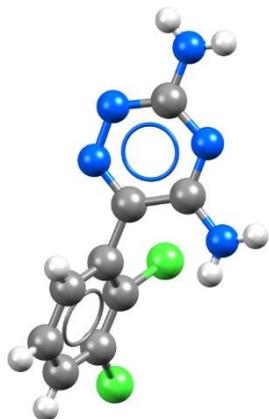


Understand protein-ligand interaction patterns using Full Interaction Maps (FIMs) (MER-004)

Developed using
2020.3 CSD Release



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Table of Contents	
Introduction.....	2
Objectives.....	2
Pre-required skills.....	3
Example. Using Full Interaction Maps to analyse docking solutions	3
Case Study	3
Material	4
Calculating FIMs in Mercury	4
Hermes: Loading the protein-ligand complex.....	6
Hermes: Analysing the Full Interaction Maps	7
Analysing Full Interaction Maps derived from a carbonyl oxygen probe.	9
Analysing Full Interaction Maps derived from an uncharged NH nitrogen probe... ..	12
Analysing Full Interaction Maps derived from an aromatic CH carbon probe.....	14
Conclusions.....	15
Further exercises	15
Conclusions.....	16
Next steps.....	16
Feedback.....	16

Introduction

This tutorial will introduce you to the Full Interaction Maps (FIMs) feature included with Mercury under the CSD-Materials/CSD-Discovery toolsets. In particular, we will show you how you can use this tool to analyse protein-ligand interactions.

The FIMs tool generates a visual representation of the interaction landscape of a molecule from its 3D coordinates. It shows the small molecule's interaction preferences by highlighting regions around the molecule (maps) where chemical functional groups (probes) are likely to come into contact with.

Using statistical distributions from hundreds of thousands structures included in the CSD, we can predict the most likely locations for a variety of functional groups.

Full Interaction Maps is instrumental in highlighting the potential for polymorphism of a given compound, assisting in the development of co-crystals, and understanding solid form stability.

It can also be used to understand likely interaction patterns between a ligand and a protein from the ligand's perspective. By generating these density maps for a bound conformation of a ligand to a protein binding site, we can determine whether it fulfills the desired interactions.

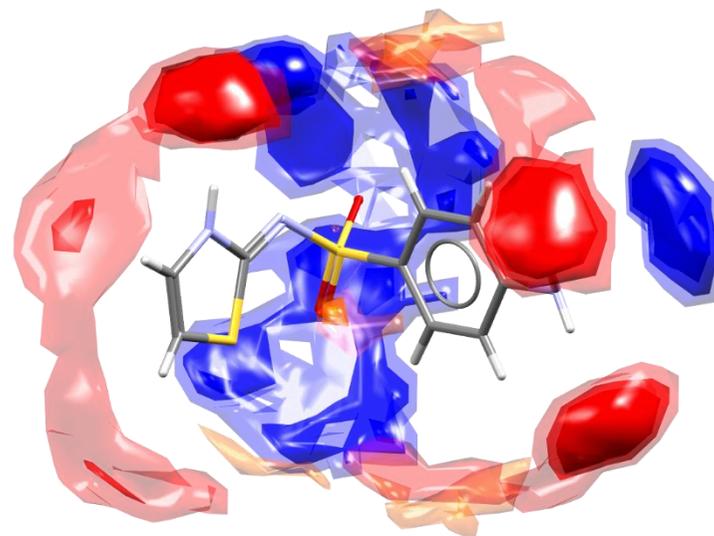
In addition, the comparison of contour maps for different fragments can be used to identify bioisosteres, i.e., functional groups which form similar intermolecular interactions and hence similar binding properties.

Objectives

In this workshop you will:

- Learn how to generate and save Full Interaction Maps (FIMs) for a given molecule.
- Visualise and analyse FIMs in Hermes in the protein context.
- See how FIMs can be used to analyse protein-ligand complexes.

This workshop will take approximately **1** hour to be completed.



Pre-required skills

The following workshop assumes you have some familiarity with the program Mercury and Hermes, namely, how to display and manipulate structures from a 3D coordinates file. For more information, please see the Structure Visualisations and Introduction to Hermes workshops in the [CSD-Core workshop area on our website](#).

Example. Using Full Interaction Maps to analyse docking solutions

In this workshop, you will use Full Interaction Maps (FIMs) to analyse the best docking solution generated by the docking program [GOLD](#).

Docking is commonly used in drug discovery to predict how ligands binds to protein targets and provides numerical scores to assess the quality of the solutions generated: the **higher the score the better the solution**.

In this context FIMs can help understand what are the key interactions that a ligand can form when binding to a protein. Such analysis will help rationalise the protein-ligand interactions observed in a docking solution, as well as suggest new modifications to a ligand during a lead optimisation programme.

Case Study

Indole-3-glycerol phosphate synthase (IGPS) catalyses the fifth reaction in the pathway for the biosynthesis of tryptophan, in which the substrate 1-(*o*-carboxyphenylamino)-1-deoxyribulose 5-phosphate (CdRP, Figure 1 (a)) undergoes a ring closure reaction to the product indole-3-glycerol phosphate (IGP, Figure 1 (d)). Hence, this enzyme has one substrate, CdRP, but three products: IGP, CO₂, and H₂O.

We used GOLD to dock IGP, in the IGPS protein and we obtained several solutions that correspond to the preferred orientations and conformations of the IGP ligand in the IGPS protein binding site. We will now use FIMs to understand if the best docking solution is making the most likely interactions when bound to the protein.

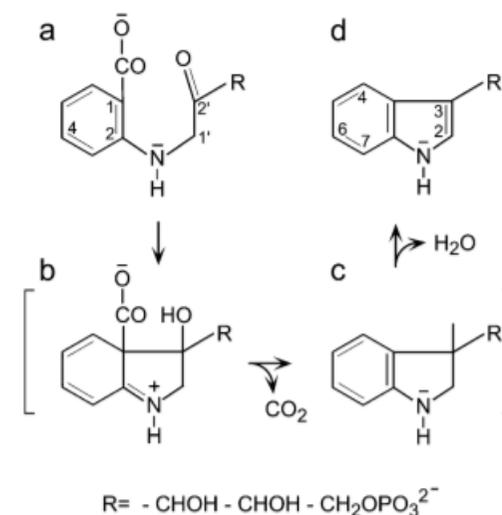


Figure 1. The mechanism of the indole-3-glycerol phosphate synthase reaction. (a) CdRP, 1-(*o*-carboxyphenylamino)-1-deoxyribulose 5-phosphate, undergoes a ring closure reaction (b,c) to the product indole-3-glycerol phosphate (IGP) (d).

Material

All files necessary to follow along with this workshop are provided in the workshop folder [here](#).

The workshop contains:

- 3D conformation of the ligand with the highest score obtained from docking (*docked_igp.mol2*)
- 3D structure of the top scoring docking solution in complex with the IGPS protein (*docked_complex.mol2*).

Calculating FIMs in Mercury

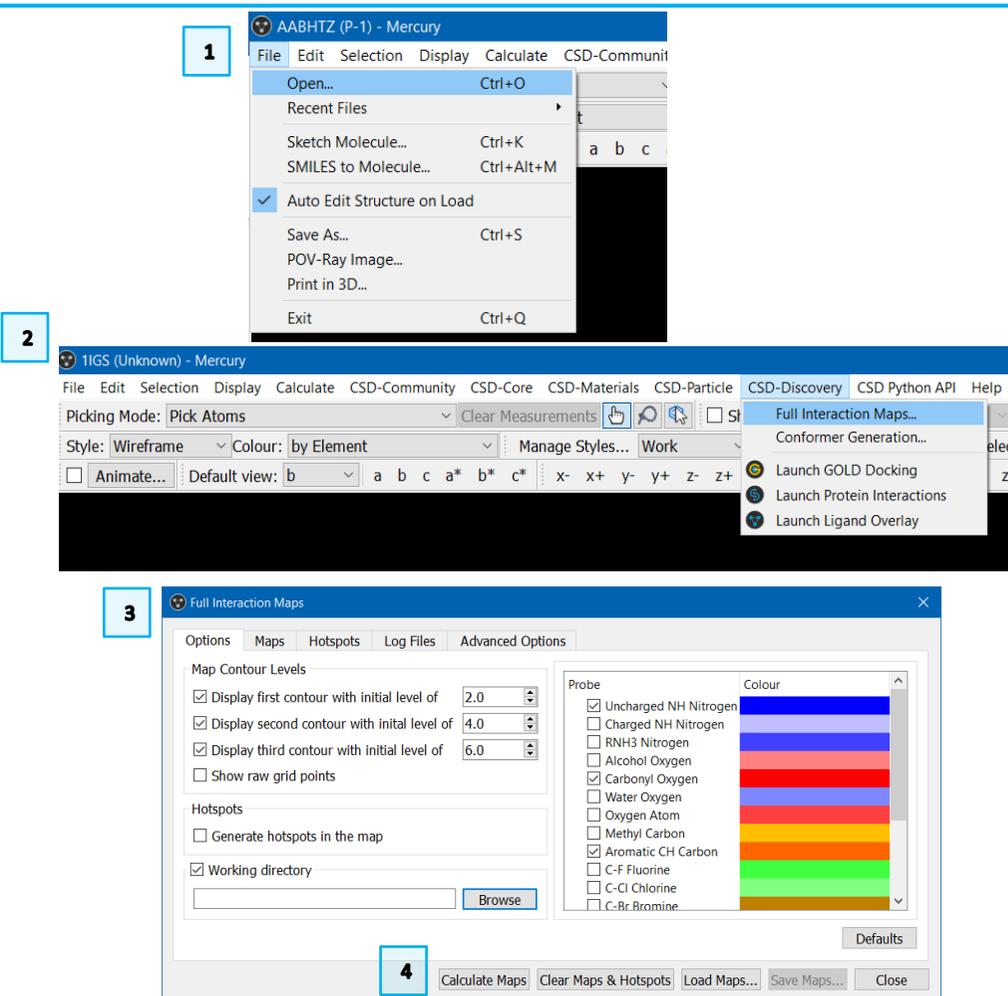
1. To use FIMs you need to first launch Mercury by clicking on its icon  (on MacOS click on mercury.app). From Mercury, click on **File** and select **Open...** from the pull-down menu to load the best ranking docking pose obtained with GOLD and available in the workshop folder (*docked_igp.mol2*).
2. Click on **CSD-Discovery** in the Mercury top-level menu and select **Full Interaction Maps...**

Note that Full Interaction Maps is also available under the **CSD-Materials** menu in Mercury.

3. In the *Full Interaction Maps* window, there are several options: on the left-hand side you will find options to change the display contour levels while, on the right, you will see a list of functional groups that can be used as probes.

For the purposes of this workshop, we will use the default probes: **Uncharged NH Nitrogen, Carbonyl Oxygen** and **Aromatic CH Carbon** and we will keep the default options. The default probes and options typically work well for most situations, but if you wish to look for the interaction preferences of the molecule with a specific functional group, or if you want to change the look of the map, you will want to edit these settings.

4. Click on **Calculate Maps** button in the *Full Interaction Maps* window.



5. The generated maps will now be displayed in the main Mercury window. Notice that:

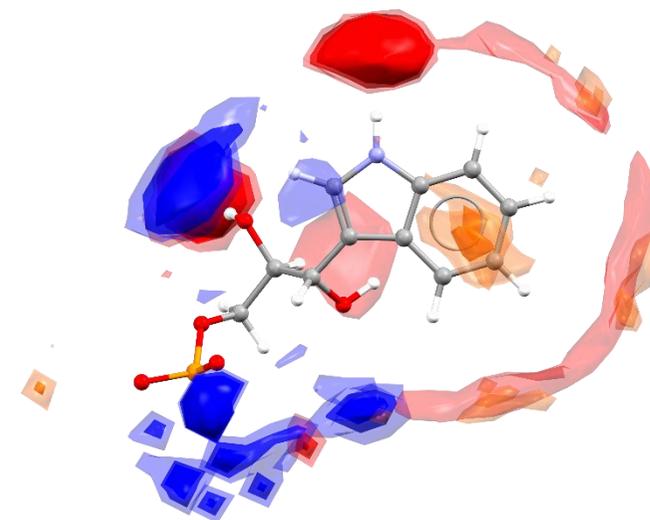
- **Red** regions of the maps denote areas in which there is a high probability of locating a hydrogen bond acceptor.
- **Blue** regions denote the preferred locations of an H-bond donor.
- **Brown** regions indicate hydrophobic preferences.

We are now going to save these generated maps and visualise them in our protein visualiser Hermes. This will allow us to see them in the context of the protein binding site.

6. Click on **Save Maps...** in the *Full Interaction Maps* window. Note that the **Save Maps...** option requires the selection (or creation) of an empty directory to save into. Navigate to your *workshop* folder and use the right-click menu to create a new folder (e.g., *FIMs*). Then click on **Select Folder**. The generated maps will then be saved in your defined folder.

7. Click on **Close** in the *Full Interaction Maps* window and you can also close Mercury if you wish by clicking on **File** and then select **Exit** from the pull-down menu.

5



Full Interaction Maps

Options Maps Hotspots Log Files Advanced Options

Map Contour Levels

Display first contour with initial level of 2.0

Display second contour with initial level of 4.0

Display third contour with initial level of 6.0

Show raw grid points

Hotspots

Generate hotspots in the map

Working directory

Probe

Probe	Colour
<input checked="" type="checkbox"/> Uncharged NH Nitrogen	Blue
<input type="checkbox"/> Charged NH Nitrogen	Light Blue
<input type="checkbox"/> RNH3 Nitrogen	Dark Blue
<input type="checkbox"/> Alcohol Oxygen	Red
<input checked="" type="checkbox"/> Carbonyl Oxygen	Red
<input type="checkbox"/> Water Oxygen	Light Blue
<input type="checkbox"/> Oxygen Atom	Light Blue
<input type="checkbox"/> Methyl Carbon	Yellow
<input checked="" type="checkbox"/> Aromatic CH Carbon	Green
<input type="checkbox"/> C-F Fluorine	Light Green
<input type="checkbox"/> C-Cl Chlorine	Light Green
<input type="checkbox"/> C-Br Bromine	Light Green

Calculate Maps Clear Maps & Hotspots Load Maps... Save Maps... Close

File Explorer: This PC > Toshiba (D:) > workshop

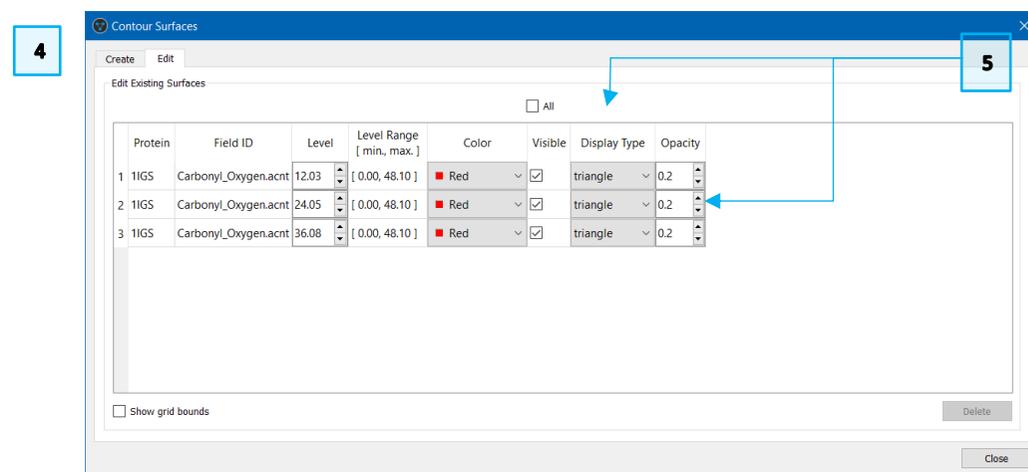
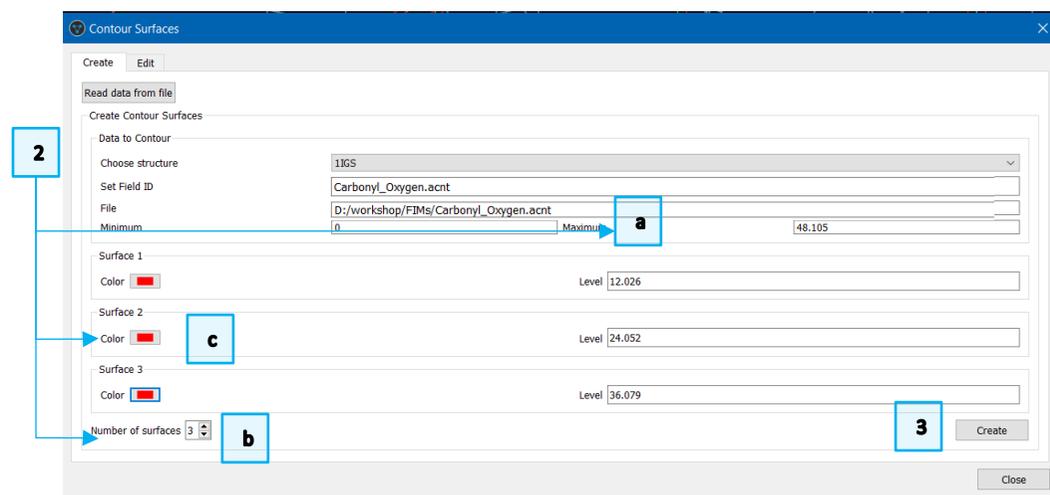
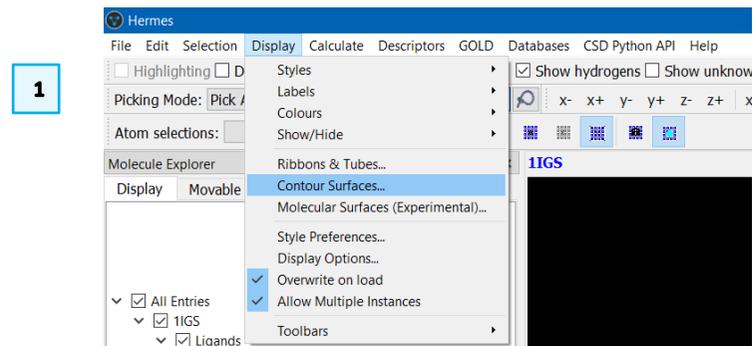
Folder: workshop

Select Folder Cancel

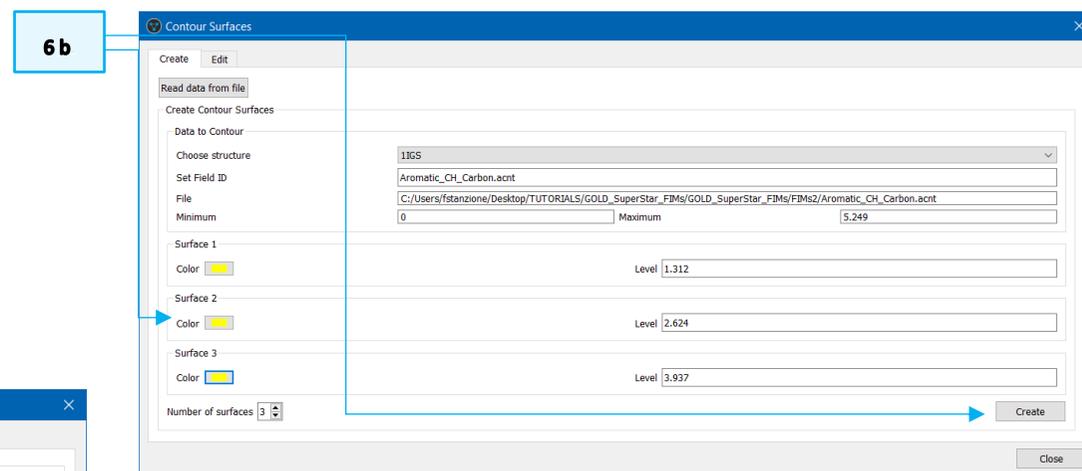
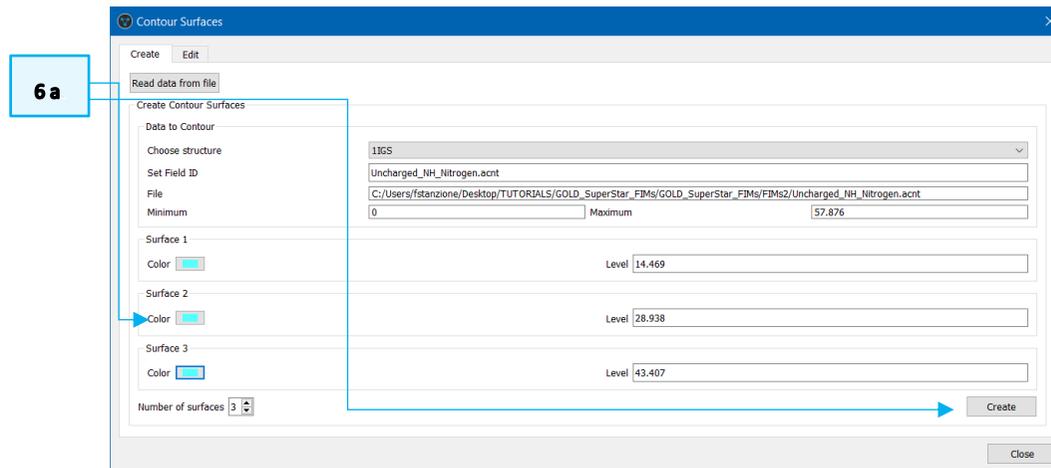
Hermes: Analysing the Full Interaction Maps

To analyse the Full Interaction Maps that we have generated in Mercury we will load the saved maps into the Hermes session.

- From the Hermes top-level menu click on **Display** and select **Contour Surfaces** from the pull-down menu.
- Click on the **Create** tab of the *Contour Surfaces* window and then click on **Read data from file**. Navigate to the folder where you saved your FIMs and select the *Carbonyl_Oxygen.acnt* file to open. The window will update to reflect the file that has been read.
 - The contour level range (**Maximum** and **Minimum** values can be specified). Note that Hermes provides an optimal range by default that has been extracted from the contour file.
 - The number of surfaces displayed: controlled using the **Number of surfaces** option at the bottom of the interface. Be sure that this is set to "3".
 - The surface colours can be changed by clicking on the **Color** button. Change the colour of all the Surfaces to **Red**.
- Click on **Create** button in the *Contour Surfaces* window. This will load the full interaction map obtained with carbonyl oxygen probe.
- The *Contour Surfaces* window will update displaying the loaded map.
- Customise the map corresponding to **Carbonyl_Oxygen.acnt** by:
 - changing its **Display Type** by clicking on **dot** and selecting **triangle** from the drop-down menu.
 - changing its **Opacity** from "1.0" to "0.2" using the **Opacity** spin-box

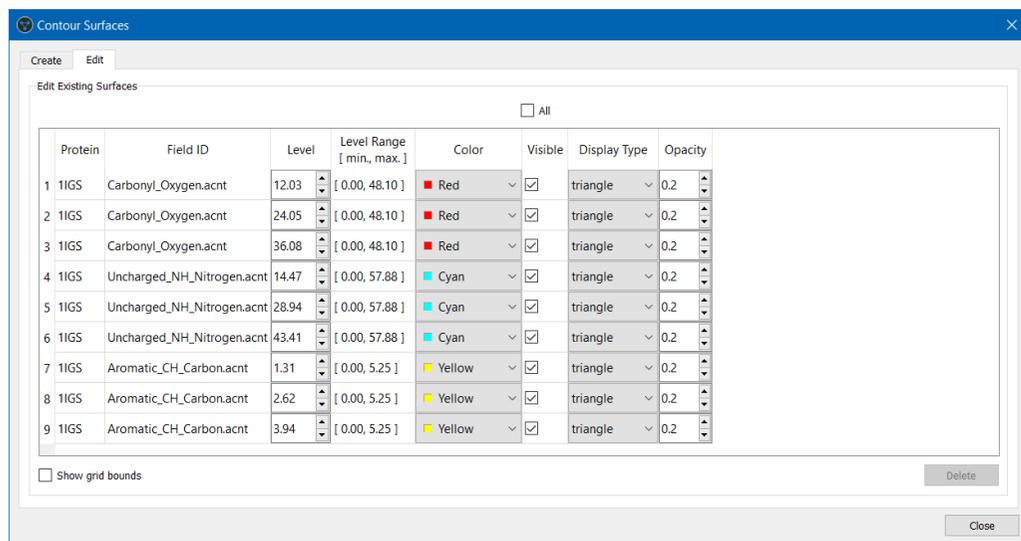


6. Repeat steps 1-2 for the other two maps saved in the FIMs folder (i.e., *Uncharged_NH_Nitrogen.acnt* and *Aromatic_CH_Carbon.acnt*). However,
 - a. For the **Uncharged_NH_Nitrogen.acnt** map set the colour of the three surfaces to **Cyan** and then click **Create**.
 - b. For the **Aromatic_CH_Carbon.acnt** map set the colour of the three surfaces to **Yellow** and then click **Create**.
7. As you did for the Carbonyl_Oxygen map, customise the **Uncharged_NH_Nitrogen** and **Aromatic_CH_Carbon** maps by:
 - a. changing the **Display Type** by clicking on **dot** and selecting **triangle** from the drop-down menu.
 - b. changing the **Opacity** from "1.0" to "0.2" using the **Opacity** spin-box
8. Your *Contour Surfaces* window should look like the one shown here on the bottom. Click on **Close** button in the window.



We will now analyse the interaction maps obtained using the different probes in Hermes 3D view.

8



Analysing Full Interaction Maps derived from a carbonyl oxygen probe.

Full Interaction Maps obtained using the carbonyl oxygen probe can be used to denote areas in which there is a high probability of locating a hydrogen bond acceptor.

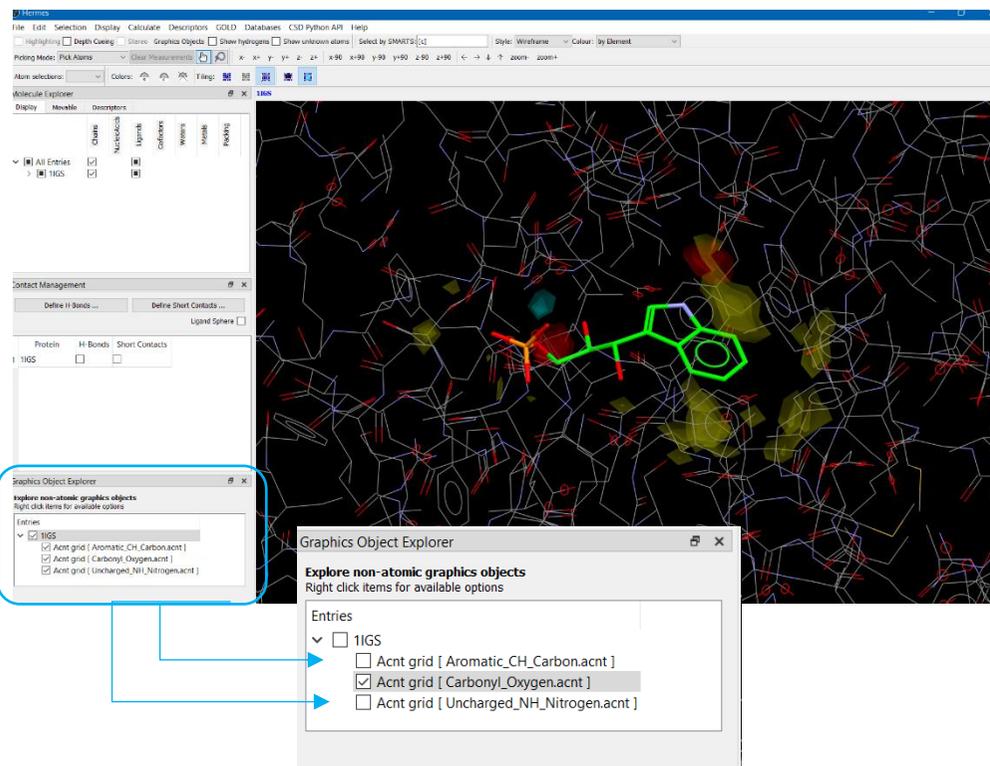
1. Ensure that *Graphics Object Explorer* is displayed by clicking **Display** then **Toolbars** and checking that **Graphics Object Explorer** is ticked.
2. Hide the FIMs of the aromatic CH carbon and that of the uncharged NH nitrogen by disabling the **Acnt grid [Aromatic_CH_Carbon.acnt]** and **Acnt grid [Uncharged_NH_Nitrogen.acnt]** tick-boxes in the **Graphics Object Explorer** window. You will now have only the full interaction map derived by using the carbonyl oxygen probe displayed in the Hermes 3D view.

Now we will look at the interaction map derived by using the carbonyl oxygen probe in the Hermes 3D view.

3. Hermes 3D-view should look like the picture on the right.
4. Enable the **H-bonds** tick-box in the *Contact Management* window. This displays all the hydrogen bonds formed between the IGP ligand and the IGPS protein.

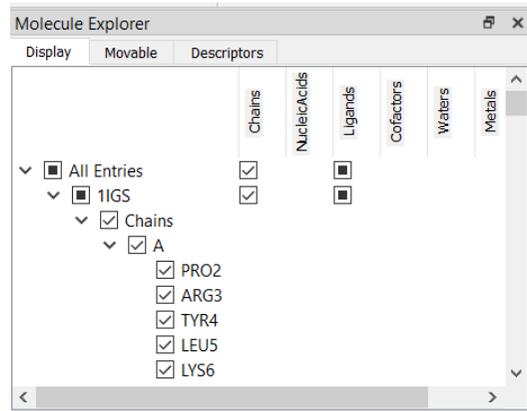
Note that if you don't have the *Contact Management* window you can easily display it by ticking the **Contact Management** in **Display>Toolbars** menu.

5. From the *Molecule Explorer* window, select *GLU159* and *SER211*. Multi-selection is possible using **CTRL + left-click**. You may use the ">" adjacent to *1IGS* under *All Entries* to have access to all the components.



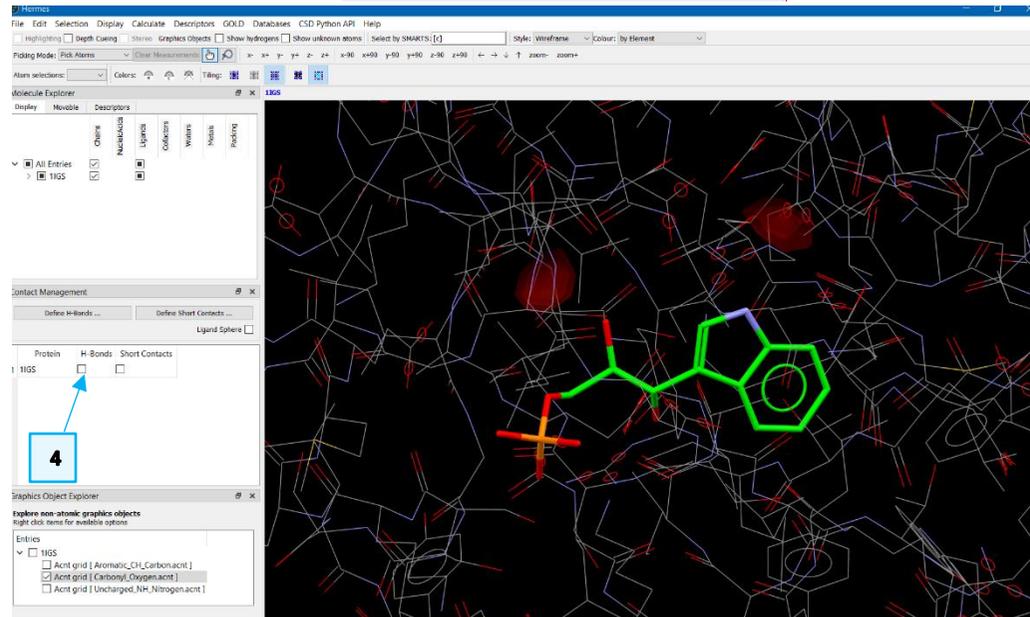
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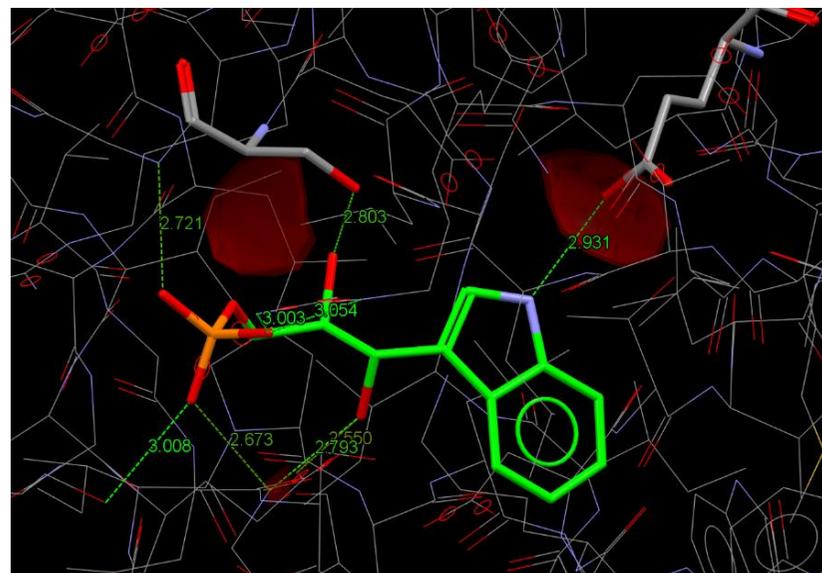
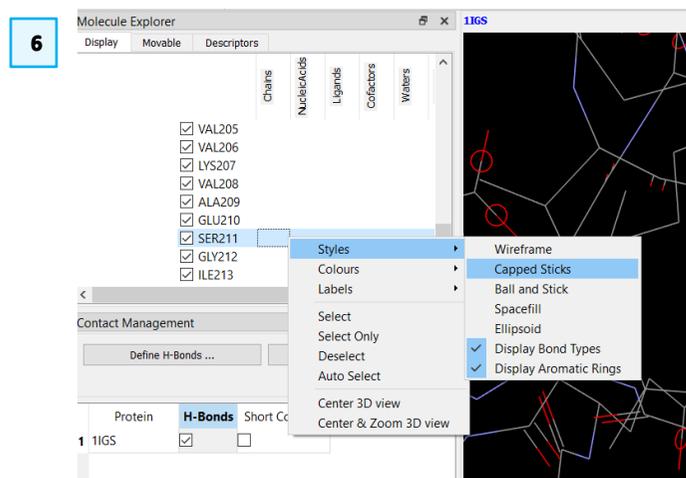
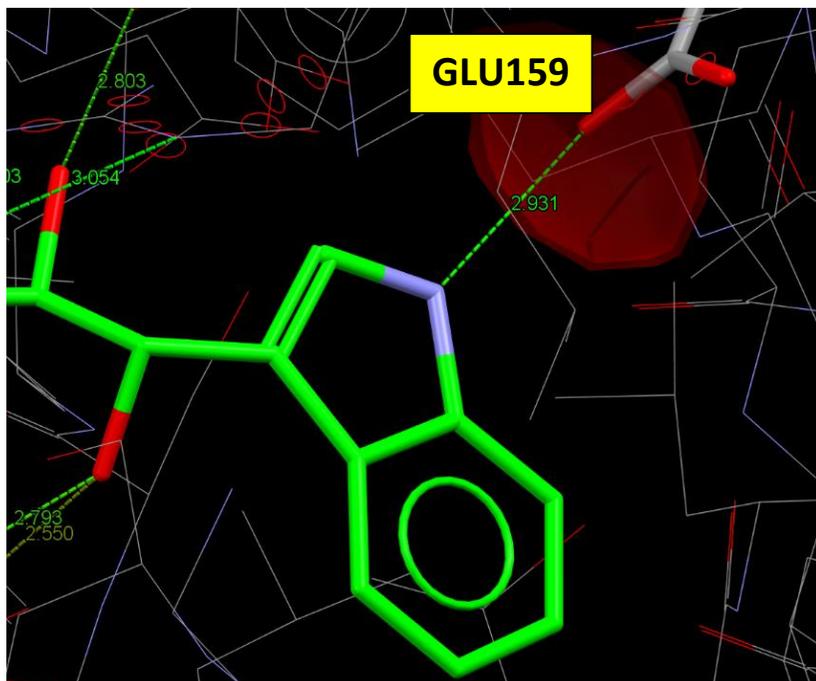
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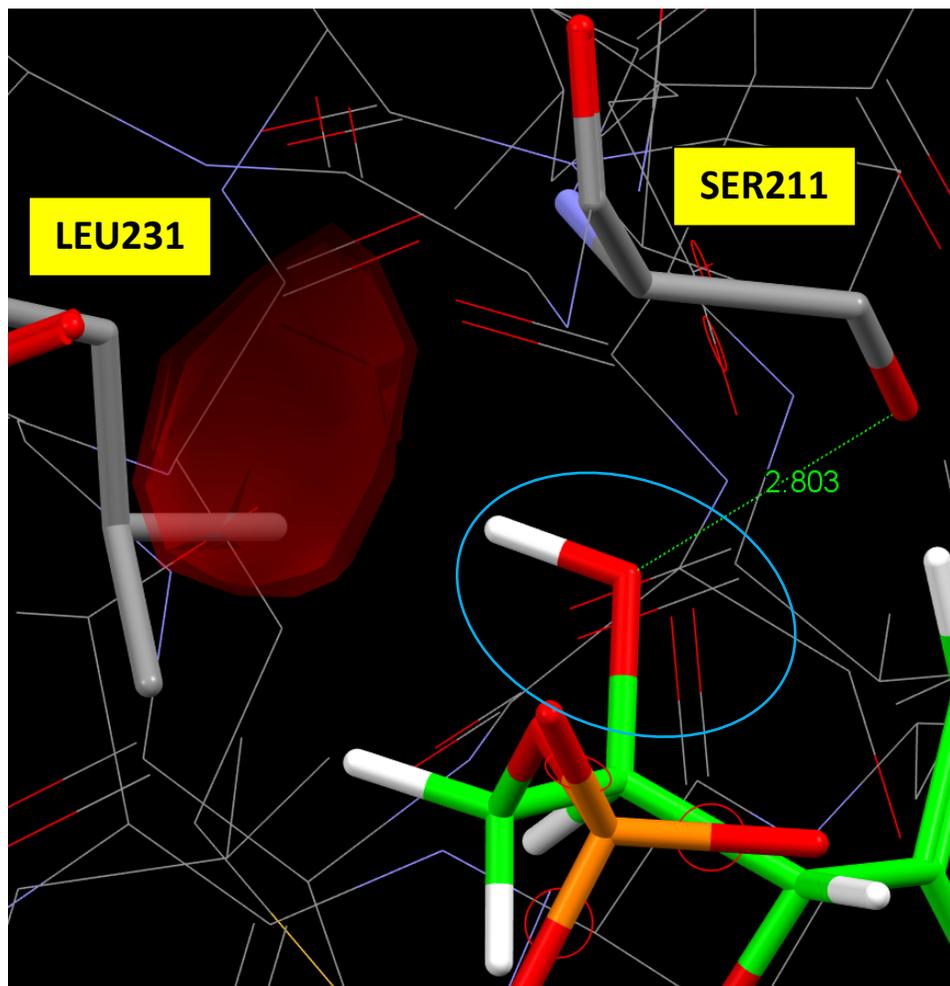
- Right-click in the *Molecule Explorer* area and select **Styles > Capped Sticks** from the pull-down menu. This will show the selected residues as capped sticks in the Hermes 3D view.
- Of the two H-bond acceptor interaction sites predicted by FIMs for the best scoring docking pose of compound IGP only one is satisfied by the protein:
 - The indole moiety of the IGP ligand acts as a H-bond donor and it forms an H-bond with the sidechain of GLU159.

7



8. The other predicted H-bond acceptor region could involve a H-bond between the ligand and the protein (see picture on the right), where the hydroxyl group acts as H-bond donor.

- The closer residue to the predicted H-bond acceptor location is LEU231, however there are not H-bond acceptors in that location.
- The hydroxyl group here acts as H-bond acceptor and form and H-bond with the sidechains of SER211 (see figure on the right). We will now see if this interaction is correctly predicted by looking at the Uncharged_NH_Nitrogen map.

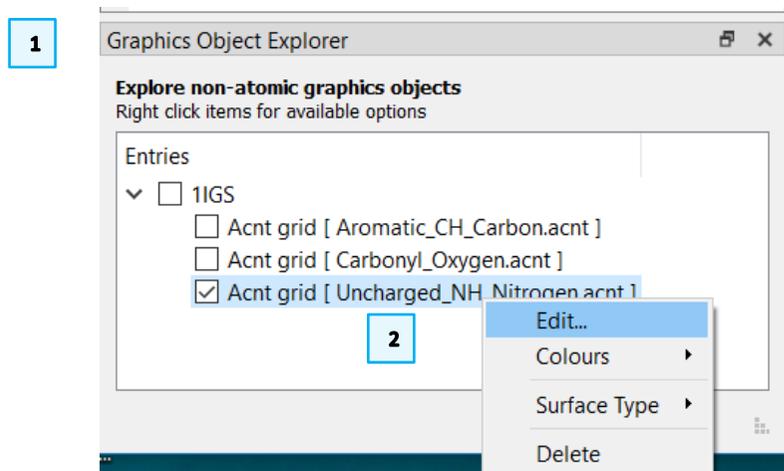
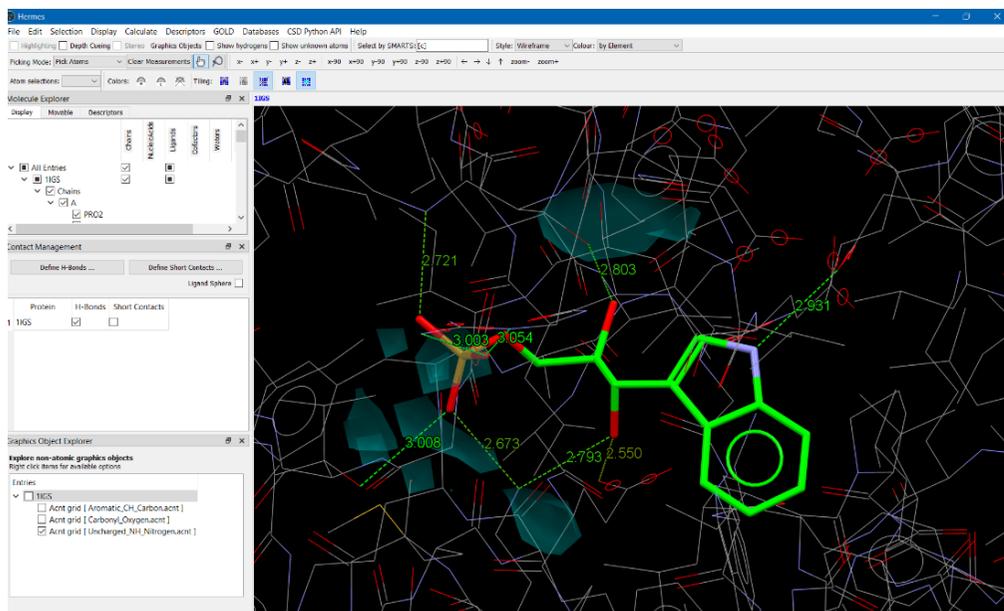


Analysing Full Interaction Maps derived from an uncharged NH nitrogen probe.

Full Interaction Maps obtained using an uncharged nitrogen probe can be used to identify areas of high probability for a hydrogen bond donor group.

1. In the *Graphics Object Explorer* window, hide the FIMs of the carbonyl oxygen and show the uncharged NH nitrogen map by disabling the **Acnt grid [Carbonyl_Oxygen.acnt]** tick-box and activating the **Acnt grid [Uncharged_NH_Nitrogen.acnt]** tick-box. You will now have only the full interaction map derived by using the carbonyl oxygen probe displayed in the Hermes 3D view.
2. Right-click on the **Acnt grid [Uncharged_NH_Nitrogen.acnt]** and select **Edit**, this will open the loaded maps in the *Graphic Object Editor Dialog* window.
3. Reduce the contour level of the **Uncharged_NH_Nitrogen.acnt** map to “2.89” by using the **Level** spin-box (row 4 in the figure on the right). This will show maps with lower probability in the Hermes 3D view. Then click **OK**.

You will now have only the full interaction map derived by using the uncharged NH nitrogen probe displayed in the Hermes 3D view.



The screenshot shows the Graphics Object Editor Dialog window. The table shows the configuration for the 'Acnt Fields'.

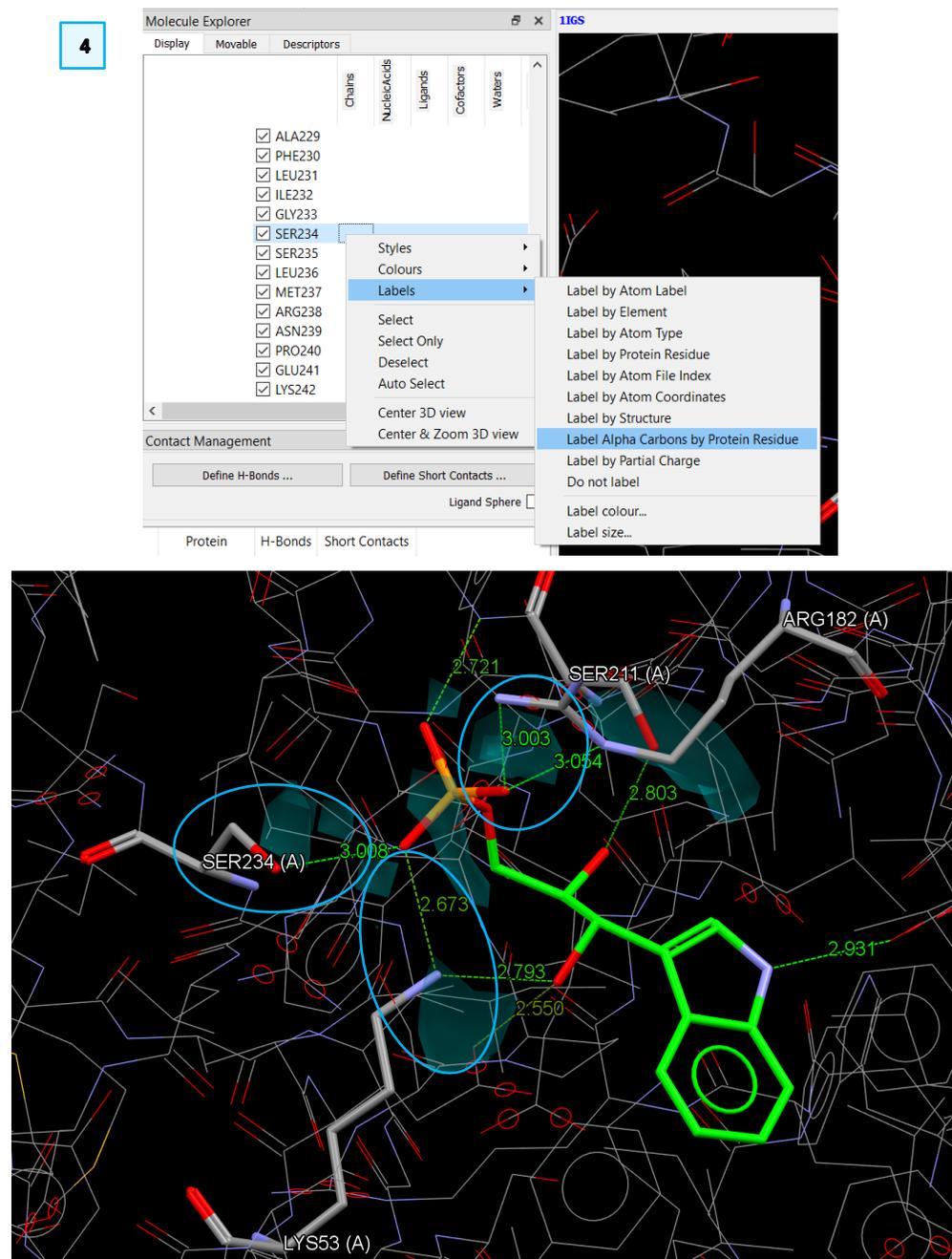
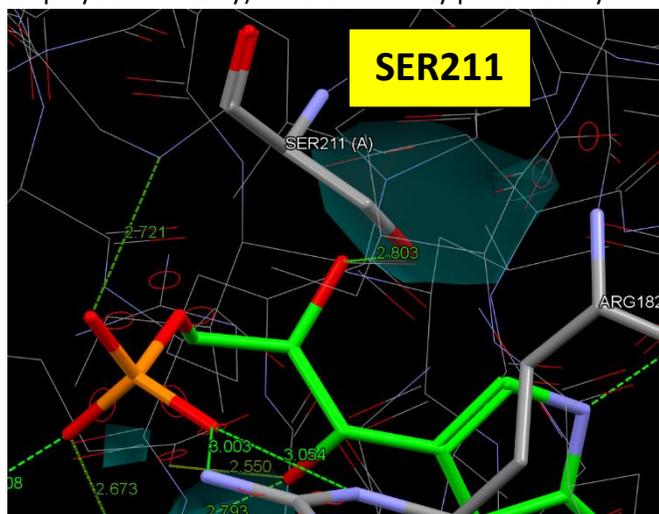
Entry	Field	Level	Level Range	Color	Visible	Display Type	Opacity
1	1IGS Carbonyl_Oxygen.acnt	12.03	[0.00, 48.10]	Red	<input type="checkbox"/>	triangle	0.2
2	1IGS Carbonyl_Oxygen.acnt	24.05	[0.00, 48.10]	Red	<input type="checkbox"/>	triangle	0.2
3	1IGS Carbonyl_Oxygen.acnt	36.08	[0.00, 48.10]	Red	<input type="checkbox"/>	triangle	0.2
4	1IGS Uncharged_NH_Nitrogen.acnt	2.89	[0.00, 57.88]	Cyan	<input checked="" type="checkbox"/>	triangle	0.2
5	1IGS Uncharged_NH_Nitrogen.acnt	28.94	[0.00, 57.88]	Cyan	<input checked="" type="checkbox"/>	triangle	0.2
6	1IGS Uncharged_NH_Nitrogen.acnt	43.41	[0.00, 57.88]	Cyan	<input checked="" type="checkbox"/>	triangle	0.2
7	1IGS Aromatic_CH_Carbon.acnt	1.31	[0.00, 5.25]	Yellow	<input type="checkbox"/>	triangle	0.2
8	1IGS Aromatic_CH_Carbon.acnt	2.62	[0.00, 5.25]	Yellow	<input type="checkbox"/>	triangle	0.2
9	1IGS Aromatic_CH_Carbon.acnt	3.94	[0.00, 5.25]	Yellow	<input type="checkbox"/>	triangle	0.2

The uncharged NH nitrogen contour map fitted on top of the IGP protein binding site overlap with several residues.

- From the *Molecule Explorer* window, select *LYS53*, *ARG182*, *SER211* and *SER234*. Multi-selection is possible using **CTRL + left-click**.
- Right-click in the *Molecule Explorer* area and select **Styles > Capped Sticks** from the pull-down menu. This will show the selected residues as capped sticks in the Hermes 3D view.
- You may wish to display the residue names in the Hermes 3D view. To do so select *LYS53*, *ARG182*, *SER211* and *SER234* and select **Label Alpha Carbons by Protein Residue** from the right-click menu.

Most of the predicted H-bond donor interaction sites of the best scoring docking pose of compound IGP are satisfied by the protein binding site and several key hydrogen bonds can be formed:

- The triosephosphate moiety of IGP can form H-bonds with the sidechains of ARG182, LYS53 and SER234.
- The hydroxyl group of the IGP ligand acts as H-bond acceptors forming an H-bond with hydroxyl group of the SER211 (H atoms not displayed for clarity). This is correctly predicted by FIMs.

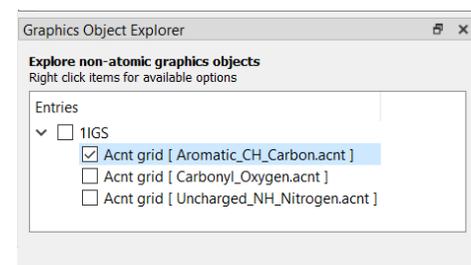


Analysing Full Interaction Maps derived from an aromatic CH carbon probe.

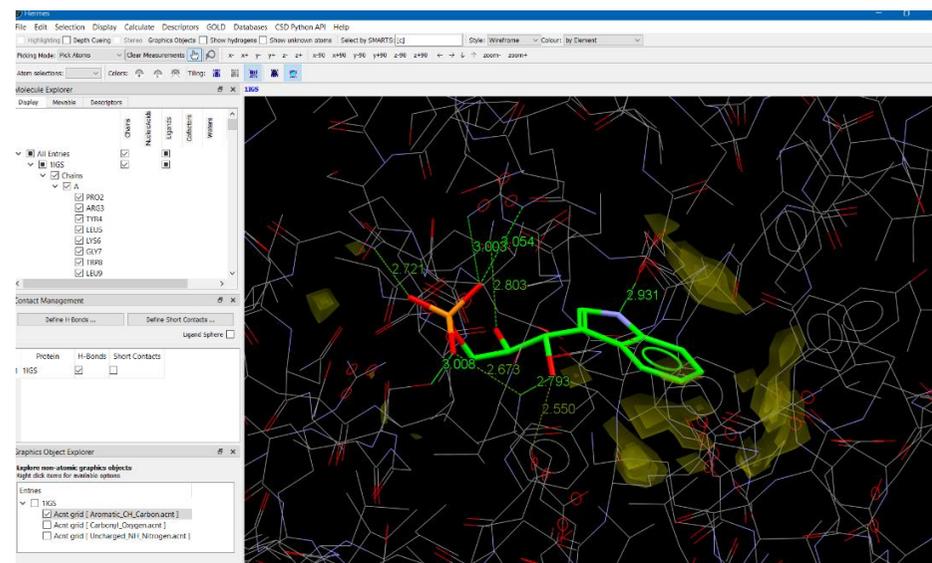
Full Interaction Maps obtained using an aromatic carbon probe can be used to denote areas in which there is a high probability of locating hydrophobic residues.

1. In the *Graphics Object Explorer* window, hide the FIMs of the uncharged NH nitrogen map by disabling the **Acnt grid [Uncharged_NH_Nitrogen.acnt]** tick-box and show the FIMs of the aromatic carbon by activating the **Acnt grid [Aromatic_CH_Carbon.acnt]** tick-box.
2. You will now have only the full interaction map derived by using the aromatic CH carbon probe displayed in the *Hermes 3D* view. FIMs reveals that the indole group has a propensity to interact with hydrophobic groups.
3. From the *Molecule Explorer* window, select *LEU83*, *PHE89*, *LYS110*, *PHE112* and *LEU184*. Multi-selection is possible using **CTRL + left-click**.
4. Right-click in the *Molecule Explorer* area and select **Styles > Capped Sticks** from the pull-down menu. This will show the selected residues as capped sticks in the *Hermes 3D* view.
5. Analysing the protein binding site, we can see that the indole moiety occupies a hydrophobic region of the IGPS binding site that nicely overlap with the FIMs density (see figure 5).

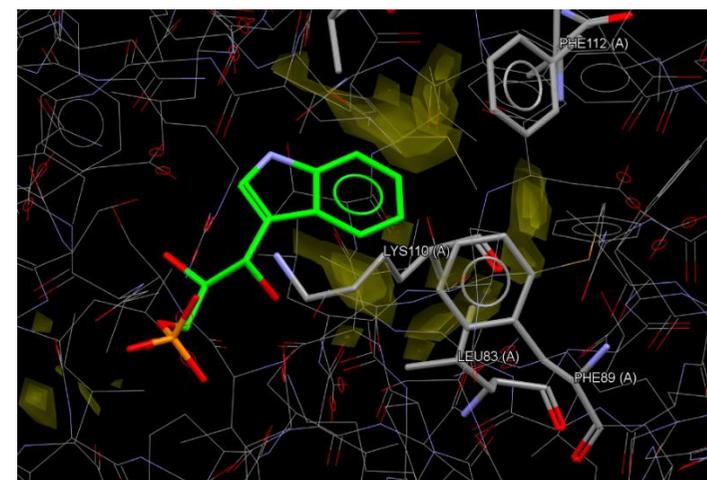
1



2



5



Conclusions

We used Full Interaction Maps to analyse the top scoring docking solution obtained by docking IGP ligand into IGPS protein.

- FIMs mapped the regions where the IGP ligand preferred to find H-bond acceptors/donors and hydrophobic groups.
- The generated maps obtained using the ligand as input structure were then analysed in the context of the protein-ligand complex in Hermes.
- The analysis showed that the binding mode of the best docking solution satisfied the ligand's preferred interaction sites predicted with FIMs. Several H-bonds can be formed that optimise the conformation and orientation of the ligand in the protein binding site.
- The conformation of the highest scoring ligand solution (with green carbon atoms in Figure 2) is comparable to the native binding mode of IGP ligand in sIGPS-IGP complex with a 2 Å resolution (pdb code 1A53.pdb, with magenta carbon atoms in Figure 2).

Further exercises

- Which other functional groups would be of interest for this molecule? You may wish to repeat FIMs calculation using other functional groups.
- We have seen how the protein is satisfying the ligand interaction preferences using FIMs. However, you may wish to further explore the protein-ligand interaction patterns: **is the IGP ligand satisfying the interactions that the protein wants to form?** Look at this [SuperStar tutorial](#) that describes how to identify regions within a protein binding site where particular functional groups (probes) are likely to interact.

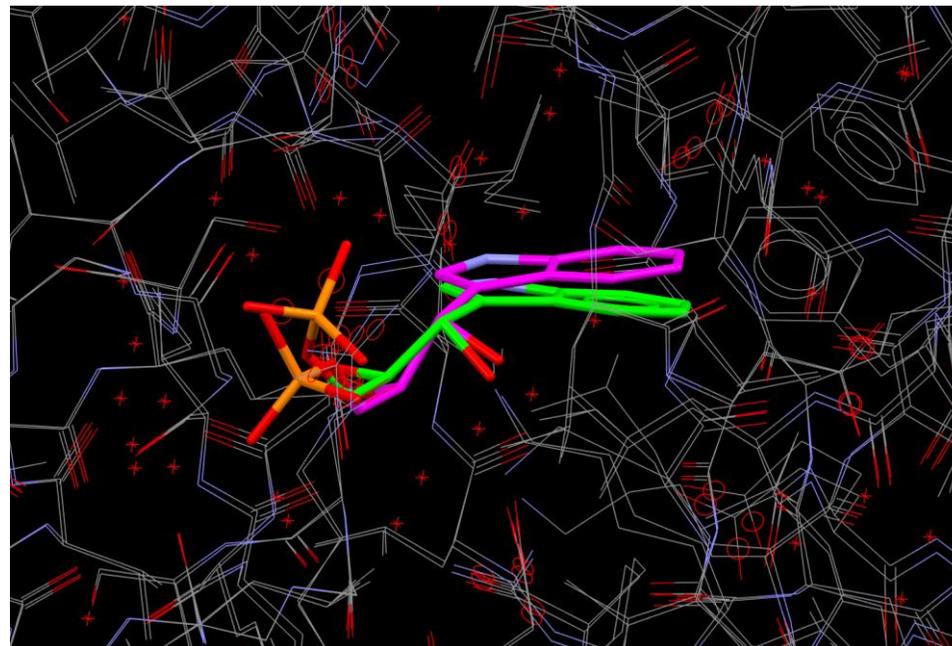


Figure 2. Comparison of the best docking solution of IGP ligand (green carbon atoms) and the crystallographic observed conformation of the ligand in the co-crystal structure of sIGPS-IGP (magenta carbon atoms).

Conclusions

After this workshop you know how to:

- Generate and save Full Interaction Maps (FIMs) for a given molecule in Mercury.
- Visualise and edit contour maps in Hermes.
- Analyse and interpret FIMs for a given molecule to analyse protein-ligand interactions.

For your reference, you can find the user manual at this [link](#).

Next steps

After this workshop, you can explore more exercises in the self-guided workshops available from the [CSD-Discovery workshops area](#) on our website. In particular, we recommend the SuperStar tutorial (see above).

Feedback

We hope this workshop improved your understanding of FIMs and you found it useful for your work. As we aim at continuously improve our training materials, we would love to hear your feedback. Follow the link on the workshop homepage and insert the workshop code, which for this self-guided workshop is *MER-004*. It will only take 5 minutes and your feedback is anonymous. Thank you!