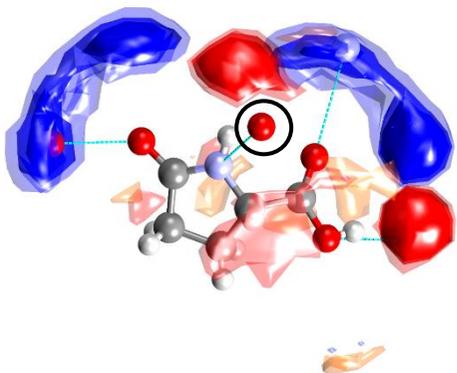


Full Interaction Maps

2020.3 CSD Release



CCDC
advancing structural science

MER-002 1

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Introduction

This tutorial will introduce you to the Full Interaction Maps feature included with Mercury under the CSD-Materials/CSD-Discovery toolsets.

The Full Interaction Maps tool will generate a picture of the interaction landscape of your molecule from its three-dimensional coordinates. Using statistical distributions from the hundreds of thousands of structures included in the CSD, we can predict the most likely locations for a variety of functional groups. By comparing this distribution against a 3D packing diagram, we can determine whether a crystal structure fulfills the desired interactions of a particular conformation of a particular molecule. The Full Interaction Maps tool is instrumental in highlighting the potential for polymorphism of a given compound, assisting in the development of co-crystals, and understanding solid form stability.

Objectives

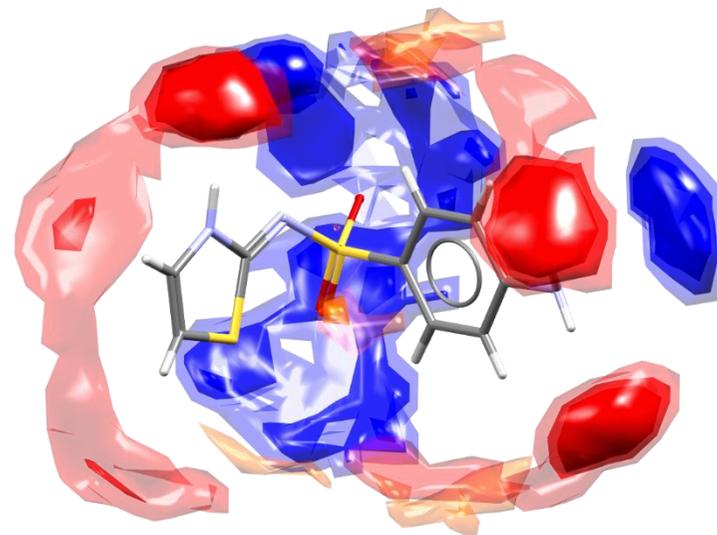
In this workshop you will:

- Learn how to produce Full Interaction Maps (FIMs) for a given molecule and how to interpret the results.
- See how the FIMs analysis can be used for co-crystal design.
- See how FIMs can be used to investigate the differences in the interaction preferences of a molecule when substitutions are made across a series.

This workshop will take approximately **1.5-2** hours to be completed.

Pre-required skills

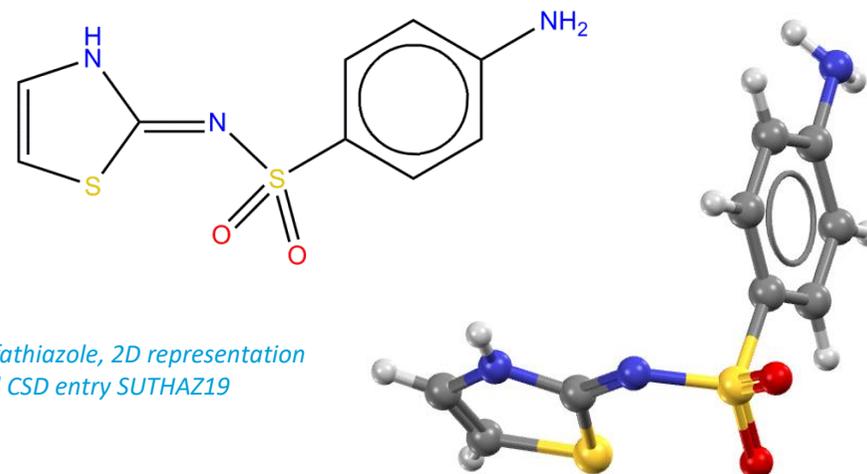
The following exercises assume you have a working knowledge of the program Mercury, namely, how to display and manipulate structures from a 3D coordinates file. There are many other features included with Mercury that are beyond the scope of this tutorial. You can find the Visualisation workshop in the [CSD-Core workshop area on our website](#).



Example 1. Using Full Interaction Maps to assess polymorph stability

The stability of a given crystal structure is a balance between the intramolecular conformation and the intermolecular packing of the molecules in the crystalline state. One method for understanding the relative stability of crystal structures is to compare the observed intermolecular interactions with preferred geometries for that type of interaction.

This example will look at two known polymorphs of sulfathiazole to answer the question: **How do the interactions in each polymorph compare with what is expected?** You will learn how to produce a Full Interaction Map for a given structure and how to interpret this map.



Sulfathiazole, 2D representation and CSD entry SUTHAZ19

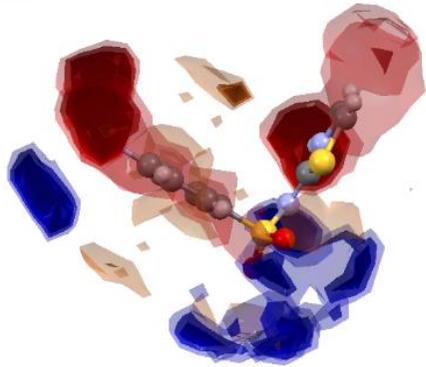
1. Launch Mercury by clicking its icon . In the Structure Navigator toolbar, type SUTHAZ19 to bring up the structure for the Form V polymorph of sulfathiazole.
2. Click on the *CSD-Materials* menu or *CSD-Discovery* menu and select *Full Interaction Maps...* Note: If the *CSD-Materials* menu bar is inactive, click on "Help" and "Activate CSD-Materials" before proceeding further.
3. In the *Full Interaction Maps* dialogue box, you will see several options. On the left you will find options to change the display contour levels. On the right, you will see a list of functional groups to be used as probes. For the purposes of this tutorial, we will keep the default options. These typically work well for most situations, but if you know you are looking for a specific functional group, or if you want to change the look of the map, you will want to change these settings.
4. Click the **Calculate Maps** button to start.

The screenshot illustrates the software interface for generating a Full Interaction Map. It is divided into four numbered steps:

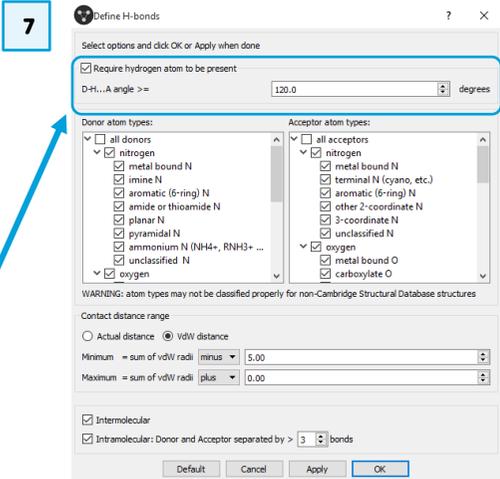
- 1**: The Structure Navigator window shows the search for 'SUTHAZ19' in the Crystal Structures list, with 'SUTHAZ19 P21/n' selected.
- 2**: The CSD-Materials menu is open, and 'Full Interaction Maps...' is selected.
- 3**: The Full Interaction Maps dialog box is shown. The 'Map Contour Levels' section has three checkboxes checked: 'Display first contour with initial level of 2.0', 'Display second contour with initial level of 4.0', and 'Display third contour with initial level of 6.0'. The 'Probe' list on the right includes 'Uncharged NH Nitrogen', 'Charged NH Nitrogen', 'RNH3 Nitrogen', 'Alcohol Oxygen', 'Carbonyl Oxygen', 'Water Oxygen', 'Oxygen Atom', 'Methyl Carbon', 'Aromatic CH Carbon', 'C-F Fluorine', 'C-Cl Chlorine', 'C-Br Bromine', and 'C-I Iodine'. The 'Uncharged NH Nitrogen' probe is selected, and its color is set to blue.
- 4**: The 'Calculate Maps' button at the bottom of the dialog box is highlighted.

- The generated map will now be displayed in the main Mercury window. Notice the three different colours in the map. **Red** regions of the map denote areas in which there is a high probability of locating a hydrogen bond **acceptor**. **Blue** regions denote hydrogen bond **donors**, and **brown** regions indicate **hydrophobic** preferences.
- Now we want to see how the overall packing of this polymorph fits with the Full Interaction Map we have generated. Tick the box for *H-Bond* in the Display Options toolbar.
- Double click the *H-Bond* line to launch the *Define H-bonds* dialogue. In this dialogue, tick the box for “Require hydrogen atom to be present”. Click **OK** to apply the change.
- Now you will see dashed **red** lines in the Mercury window that indicate where hydrogen bonding interactions/contacts are present.
- Click on these contacts to generate nearby molecules. You will see that in each case, the interaction falls within the contour range for the expected type. This indicates that the packing of Form V satisfies the expected interaction landscape of this conformation of sulfathiazole.
- Now let’s look at the Form I polymorph. In the Structure Navigator toolbar, type SUTHAZ16 to load this structure.
- Click the **Reset** button in the Display Options toolbar to remove all the hydrogen bonding interactions.
- Note that $Z' = 2$ for Form I; meaning there are two unique molecules in the asymmetric unit. We will focus on one unique molecule in the Form I structure.
- Tick the box to Label atoms in the Display Options toolbar. Locate which molecule contains N1. This is the molecule we will focus on. Once you have located it, remember which one it is, but untick the Label atoms box to keep the display clean.

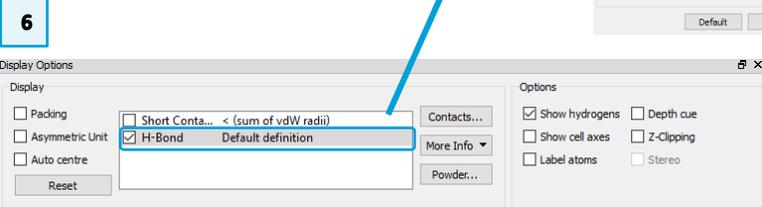
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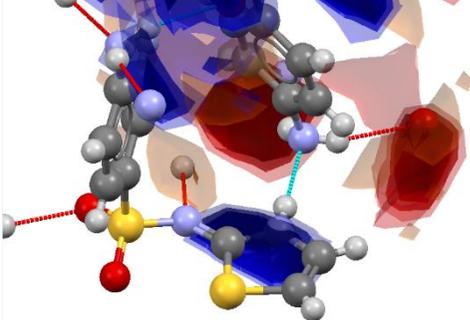
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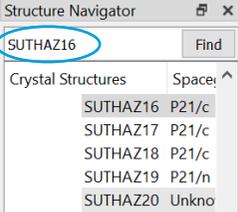
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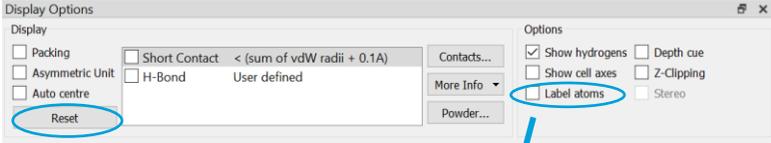
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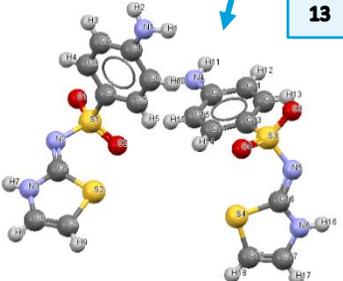
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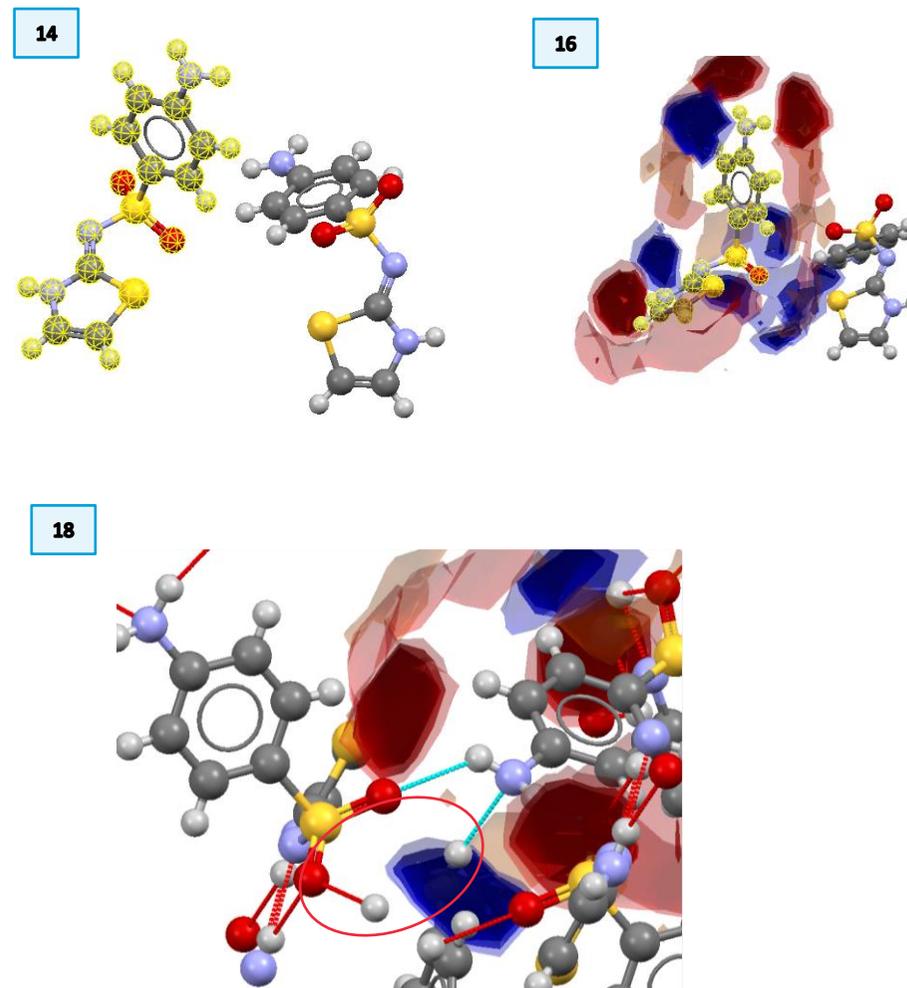


14. Hold the Shift key and click the molecule that contains N1. This will select the entire molecule.
15. If the *Full Interaction Maps* dialogue is still open, simply click **Calculate Maps** again. Otherwise, follow steps 2-4 to re-open the dialogue.
16. You should now have a Full Interaction Map surrounding molecule 1.
17. Following steps 6-9 above, turn on the hydrogen bonding interactions and click to expand the interaction around N1.
18. Notice that one of the three interactions falls well outside the predicted region for a hydrogen bond acceptor. This suggests that this interaction has a non-ideal geometry and is likely to be significantly less stabilising than the interactions in Form V.

Conclusions

The observed polymorphs of sulfathiazole exhibit different interactions, but also noticeably different geometries for those interactions. We can use knowledge-based approaches to compare the observed intermolecular interactions in two polymorphs with the preferred geometries for these interaction types. Full Interaction Maps indicate that Form V (known to be the most stable of the sulfathiazole polymorphs) has interactions which are near to ideal, whereas Form I (known to be metastable) has non-ideal interactions.

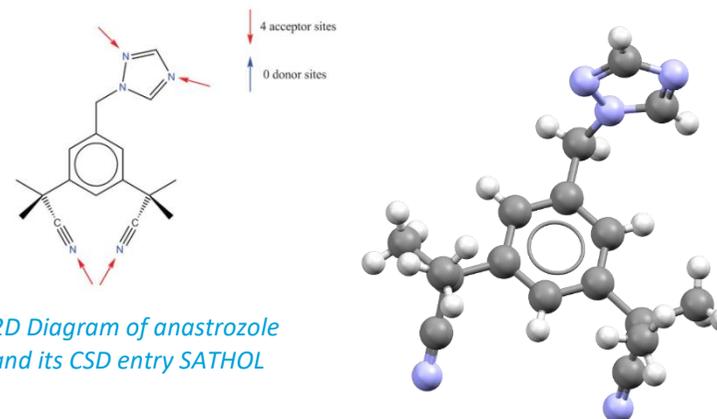
You should now know how to generate a Full Interaction Map of a molecule through Mercury and how to explore hydrogen bonding interactions in a crystal structure in relation to the predicted interaction landscape.



Example 2. Investigating the potential for co-crystallisation

For this tutorial, we will investigate the molecule anastrozole. This compound is a non-steroidal aromatase inhibitor used to treat breast cancer. The only published crystal structure is of the pure form. The molecule also contains no conventional hydrogen bond donors.

In this example, you will generate a Full Interaction Map for this molecule and investigate the interaction landscape. You will see how this information can be used to design a co-crystal.



1. In the Mercury window, type SATHOL in the Structure Navigator toolbar to load the structure of anastrozole.
2. Click the *CSD-Materials* menu or *CSD-Discovery* menu and select *Full Interaction Maps...* from the dropdown menu.
3. Keep the default settings.
4. Click **Calculate Maps** to generate the Full Interaction Map for SATHOL.
5. The resulting map shows several areas for hydrogen bond donors (**blue regions**); two high-probability areas near the nitrogen atoms of the triazole ring, and two slightly lower probability regions near the cyano groups.
6. While there are no true hydrogen bond donors in this structure, the C-H groups in the triazole ring could interact with possible hydrogen bond acceptors (**red regions**).
7. There is also a small **brown** region indicating the possibility for a hydrophobic or $\pi-\pi$ interaction.

1

Structure Navigator

SATHOL| Find

Crystal Structures	Space
SATHOL	C2/c
SATHOM	C2/c
SATHON	P41
SATHUR	P-1
SATHUS	C2/c
SATHUT	P43

2

CSD-Materials CSD-Discovery CSD-Materials CSD-Discovery CSD Python API He

Search

Calculations

Polymorph Assessment

Co-Crystal Design

Full Interaction Maps...

Hydrate Analyser...

Solvate Analyser...

Aromatics Analyser...

Conformer Generation...

Launch DASH

Full Interaction Maps...

Conformer Generation...

Launch GOLD Docking

Launch Protein Interactions

Launch Ligand Overlay

3

Full Interaction Maps

Options Maps Hotspots Log Files

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

Hotspots

Generate hotspots in the map

Probe

Uncharged NH Nitrogen

Charged NH Nitrogen

RNH3 Nitrogen

Alcohol Oxygen

Carbonyl Oxygen

Water Oxygen

Oxygen Atom

Methyl Carbon

Aromatic CH Carbon

C-F Fluorine

C-Cl Chlorine

C-Br Bromine

C-I Iodine

Colour

4

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

5

6

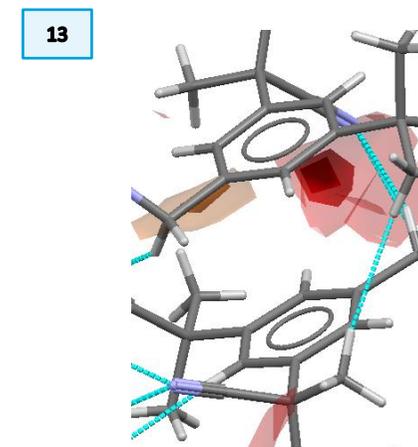
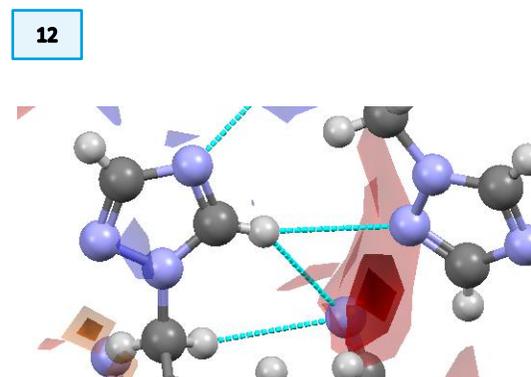
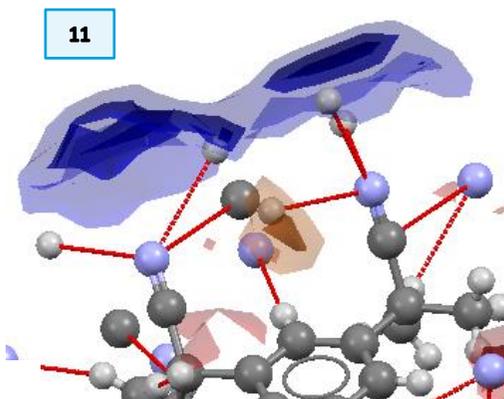
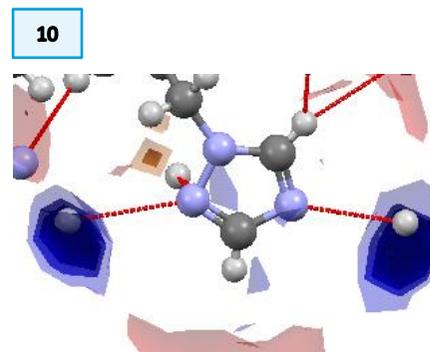
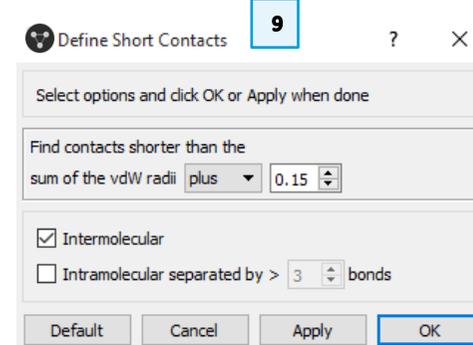
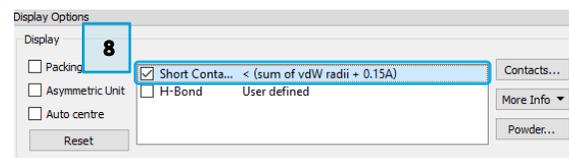
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8. As there are no conventional hydrogen-bond donors in this structure, there will be nothing to display by ticking the H-Bond box in the Display Options toolbar. Instead, tick the Short Contact box.
9. Double click this bar to open the *Define Short Contacts* dialogue box. Change this so that we find contacts shorter than the sum of the vdW radii **plus** 0.15Å. Click **OK** to save your changes.
10. Let's first look at the region around the triazole ring. We can see that there are two C-H donors that will satisfy the interaction preferences of the two N acceptors in the triazole ring. Click on the two contacts (dashed red lines) to generate the neighbouring molecules.
11. Looking at the region around the cyano groups, there are some short contacts available for interactions, but these are not directed toward the high-probability areas.
12. From the acceptor probe maps (red contours), we can see that the main region of acceptor preference is only weakly satisfied by the cyano group from one molecule and the triazole ring from another. Click the contacts to expand nearby molecules. The other acceptor regions are not satisfied at all.
13. Finally, there is a weak π — π interaction between the two phenyl rings that matches with one of the hydrophobic regions.

Conclusions

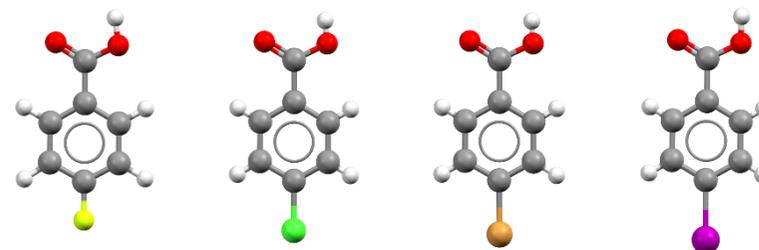
The Full Interaction Maps for SATHOL show that the highest probability regions for interactions, the donor regions for the triazole N atoms, are quite nicely satisfied. However, this comes at the cost of satisfying the interactions that would fulfill the acceptor sites. Since anastrozole has no classical H-bond donors of its own to fulfill those interactions, a molecule with one or more H-bond donors would be a good choice for a potential co-crystallisation agent.

There are no co-crystals or solvates of anastrozole yet found in this CSD.



Example 3. Investigating a series of halogenated molecules

When designing molecules to fit a specific purpose, chemists will often make subtle changes to a single functional group; for example, replacing fluorine with chlorine, bromine or iodine. We can use Full Interaction Maps to investigate the differences in the interaction preferences of a molecule when these substitutions are made across a series.



A series of halogenated benzoic acids

This example will look at the series of halogenated benzoic acids to compare what differences there are across the series.

1. Launch Mercury and type PFBZAD15 in the Structure Navigator tool bar to bring up one of the parafluorobenzoic acid entries.
2. Click the *CSD-Materials* menu or *CSD-Discovery* menu and choose *Full Interaction Maps...* from the drop-down menu.
3. We will again use the default settings.
4. Click **Calculate Maps** to generate the Full Interaction Map for parafluorobenzoic acid.
5. Repeat steps 1-4 for the other molecules in this series. Open a new instance of Mercury each time so you can easily compare the results. Use refcodes CLBZAP10 for the Cl analogue, BRBZAP01 for the Br analogue, and BENMOW07 for the I analogue. These particular entries were chosen because they are relatively recent crystal structure determinations at low temperatures. To open multiple Mercury windows on a Mac, open a terminal window and run this command:

```
open -n -a "/Applications/CCDC/CSD_2020/mercury.app"
```

 This command tells the system to open a new instance (the "-n" flag) of an application (the "-a" flag) that is the given name in quotes.
6. Now let's compare the maps for each molecule in the series.

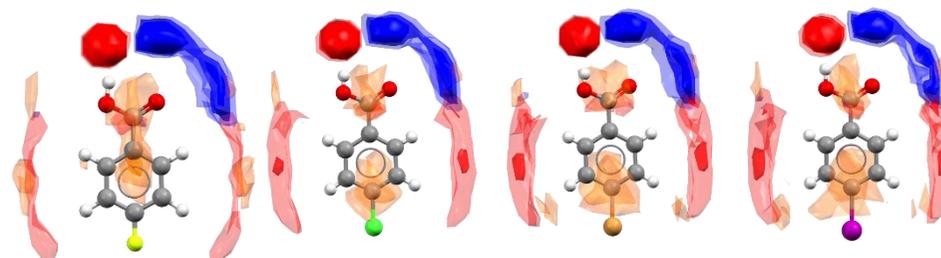
The screenshot illustrates the workflow in Mercury:

- 1:** The Structure Navigator window shows 'PFBZAD15' entered in the search bar. Below it, a list of crystal structures is displayed:

Crystal Structures	Space
PFBZAD15	P21/c
PFBZAD16	P21/c
PFBZCY	P-1
PFCHDC	P21/n
PFCYGU10	C2
PFD0CT	P2121

- 2:** The 'CSD-Materials' menu is open, and 'Full Interaction Maps...' is selected.
- 3:** The 'Full Interaction Maps' dialog box is shown with the 'Options' tab active. The 'Map Contour Levels' section has three checked options: 'Display first contour with initial level of 2.0', 'Display second contour with initial level of 4.0', and 'Display third contour with initial level of 6.0'. The 'Hotspots' section has 'Generate hotspots in the map' unchecked. The 'Probe' list on the right includes 'Uncharged NH Nitrogen' (checked), 'Charged NH Nitrogen', 'RNH3 Nitrogen', 'Alcohol Oxygen', 'Carbonyl Oxygen', 'Water Oxygen', 'Oxygen Atom', 'Methyl Carbon', 'Aromatic CH Carbon' (checked), 'C-F Fluorine', 'C-Cl Chlorine', 'C-Br Bromine', and 'C-I Iodine'. A color scale legend is visible on the right.
- 4:** The 'Calculate Maps' button at the bottom of the dialog is highlighted.

7. Look at the maps generated across the series. You should notice that as the size of the halogen increases across the series, there is an increased likelihood of finding an acceptor interacting with the halogen. This interaction is non-existent for the fluoro species, but fairly well-defined for the bromo and iodo analogues.
8. Now we will investigate how this affects the packing in each crystal structure.
9. Start with the iodo analogue. In the Display Options make sure the Short Contact settings are for “sum of vdW radii **plus** 0.15Å.” If not, double click that line to open the Define Short Contacts dialog and change the settings. Click **OK** to accept these changes. Then tick the box to display Short Contacts.
10. With the short contacts displayed, you should see that most of the interactions are satisfied. The two high-probability donor and acceptor sites near the carboxylic acid group are satisfied, as are the weaker acceptor sites near the aromatic hydrogen atoms on the phenyl ring. The iodine from a neighbouring molecule serves as the acceptor for a halogen-halogen interaction.
11. Click the interactions highlighted in Figure 10 to expand these neighbouring molecules. You will notice that while the acceptor (red) contours on either side of the phenyl ring are roughly equivalent, only one region is satisfied well by an interaction. Iodine atoms from neighboring molecules fill this region on the opposite side.



9

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Short Conta... < (sum of vdW radii + 0.15Å)

Short Contact

H-Bond

User defined

Contacts...

More Info

Powder...

Define Short Contacts

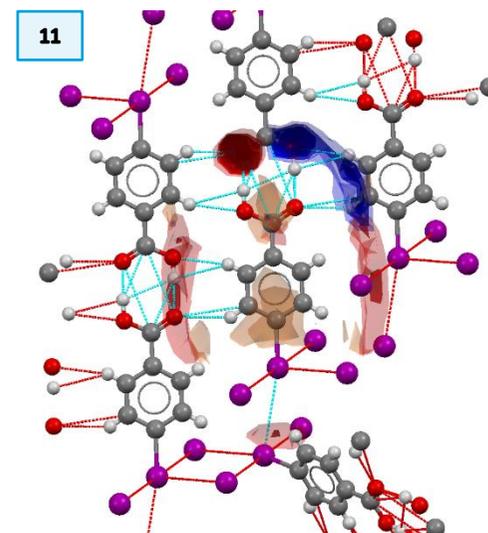
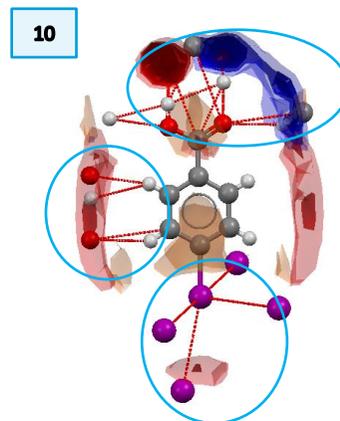
Select options and click OK or Apply when done

Find contacts shorter than the sum of the vdW radii plus 0.15

Intermolecular

Intramolecular separated by > 3 bonds

Default Cancel Apply OK



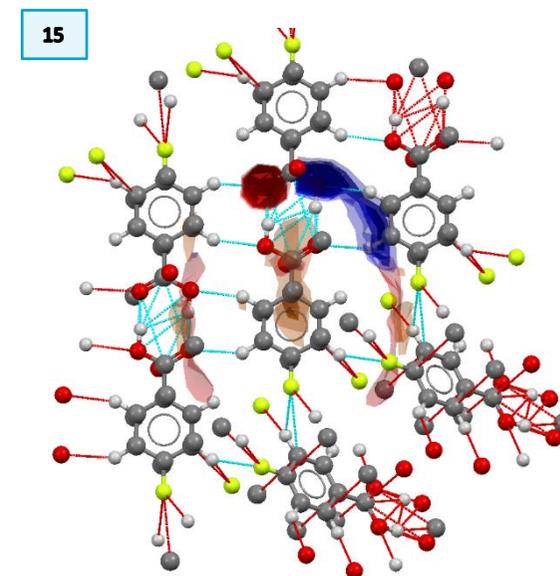
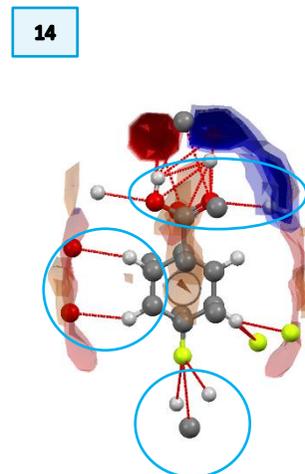
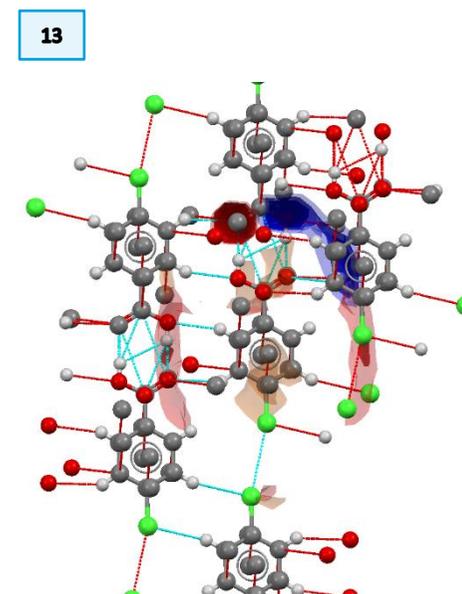
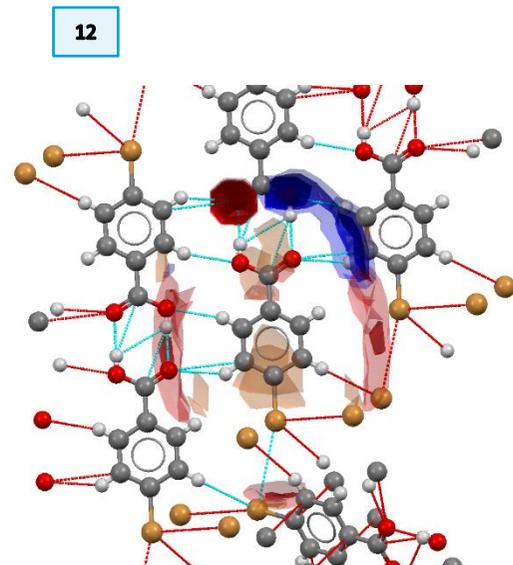
12. Repeat steps 9-11 for the Br and Cl analogues. What similarities and differences do you see across the series so far? What do you expect to see for the fluoro analogue?
13. For the fluoro analogue, follow step 9 to generate the short contacts.
14. You will see that the interactions for the carboxylic acid group and for the two weak C-H donors on the phenyl ring are satisfied. However, there is no probability of an acceptor for the fluorine, and consequently there is only C and H in this region.
15. Click these contacts to expand the neighbouring molecules. Now you can see that there is no halogen-halogen interaction involving the fluorine.

Conclusions

It is well understood that iodine forms halogen-halogen interactions more so than the other halogen atoms. Using Full Interaction Maps, we can clearly see how the probability of these interactions affects the overall packing in a crystal structure.

Further Exercises

- Try calculating Full Interaction Maps using only the C-F and C-Cl probes. Do the results match your expectations?
- Investigate the hydrophobic interactions among the halogenated benzoic acid molecules in this series.
- Try looking at ortho- or meta- substituted halogenated benzoic acid species. Do your results match your expectations?
- Use Full interaction maps for a crystal that exhibits jumping properties, L-pyroglutamic acid, before (LPYGLU07) and after a phase transition (LPYGLU08). What do you observe for the phase transition structure?
- Run a Full Interaction Maps calculation on your own molecules.
- **Advanced:** Try designing a ConQuest search to return just the molecules we used for this example. How close can you get? *Tips: You may want to try using the **Formula** and **Author/Journal** query types, too.*



Conclusions

After this workshop you will:

- Know how to produce Full Interaction Maps (FIMs) for a given molecule and how to interpret the results.
- Have experience in exploring and assessing the hydrogen bonding interactions in a crystal structure in relation to the interaction landscape predicted by FIMs.
- Be familiar with how the FIMs analysis can be used for co-crystal design.
- Be familiar with how FIMs can be used to investigate the differences in the interaction preferences of a molecule when substitutions are made across a series.

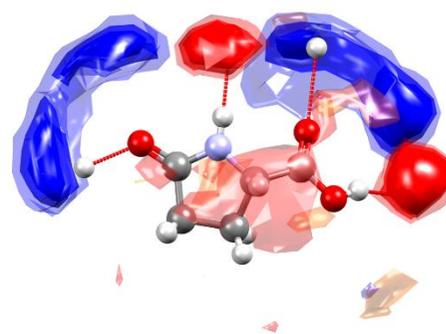
Next steps

After this workshop, you can explore more exercises in the self-guided workshops available from the [CSD-Materials workshops area](#) and the [CSD-Discovery workshops area](#) on our website. If you are interested in CSD-Materials, We suggest trying the Hydrogen Bond Propensity workshop, which presents complementary tools to the Full Interaction Maps in assessing solid forms.

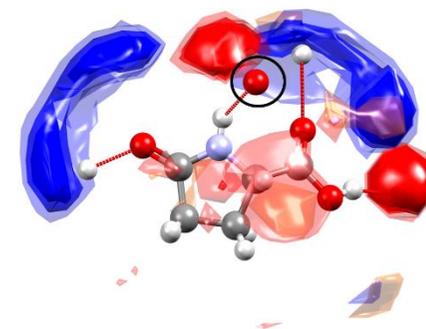
<https://www.ccdc.cam.ac.uk/Community/educationalresources/workshop-materials/>

Feedback

We hope this workshop improved your understanding of *Full Interaction Maps* and you found it useful for your work. As we aim at continuously improve our training materials, we would love to hear your feedback. Click on [this link](#) to a survey (link also available from workshops webpage), 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 MER-002. Thank you!



LPYGLU07



LPYGLU08