Analysing intermolecular interactions 101 – Full Interaction Maps

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advancing structural science

Learning outcomes

- Learn how informatics and data-driven approaches can be used to understand the solid state.
- Familiarise yourself with what tools are available in the CSD-Materials suite and what they can be used to do.
- Learn how to use Full Interaction Maps to analyse a structure.

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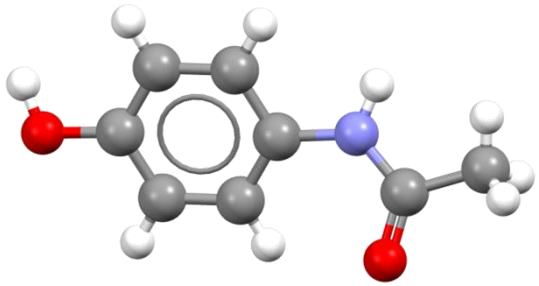
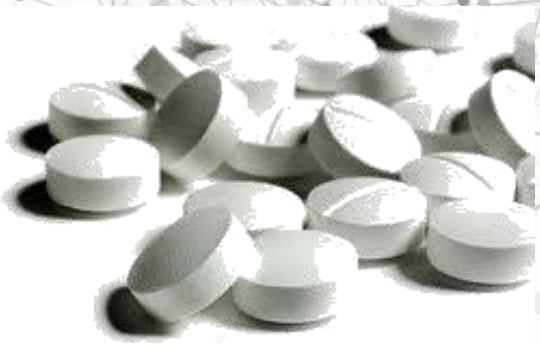
Solid form selection in product development

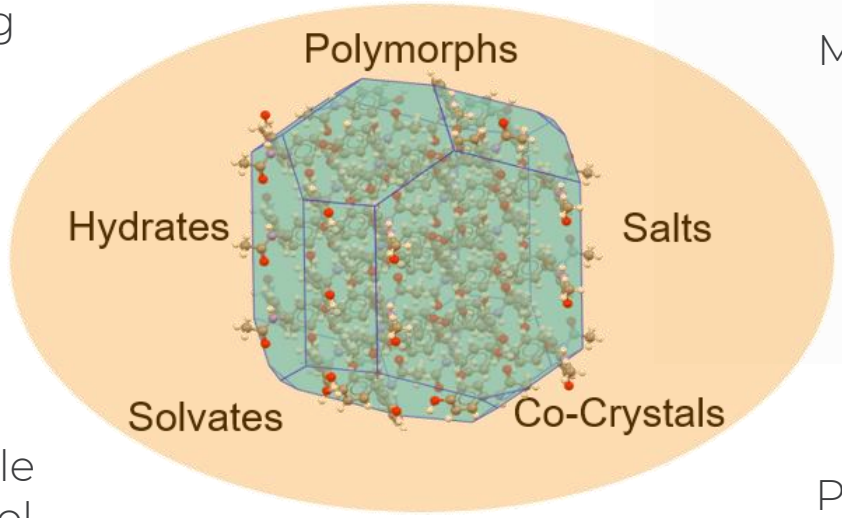


Chemical & Physical Stability

Melting Point

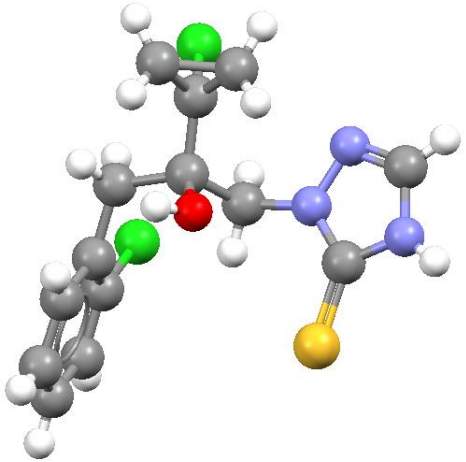
Morphology





Solubility

Mechanical Properties



Particle Control

Purification

Product Process Control

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A wealth of data in the CSD

Growth of co-crystals

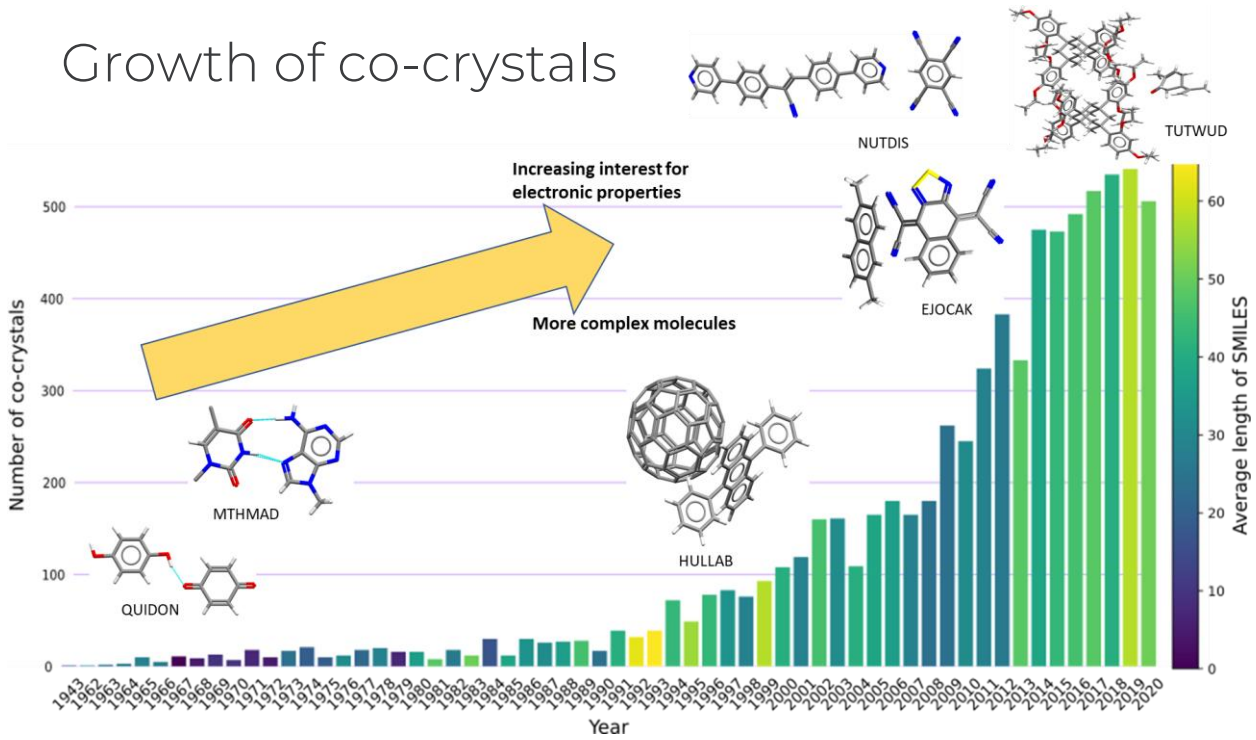
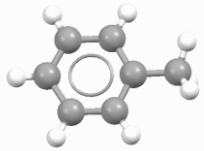


Chart showing the number of co-crystals in the CSD by year and colour coded by the average SMILES length. Image created by Katerina Vriza*, a CCDC sponsored PhD student.

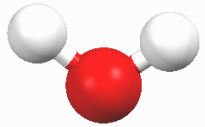


Solvates

>230,000

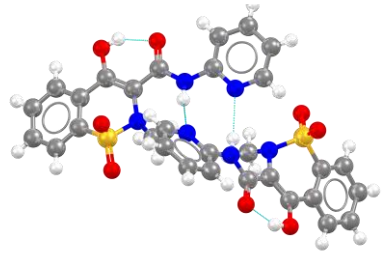
Hydrates

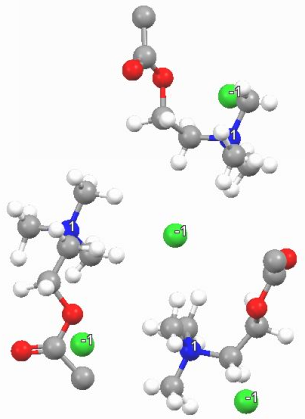
>140,000



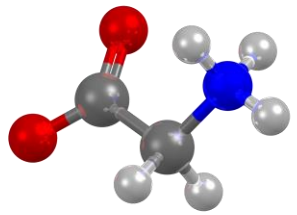
Polymorphs

>11,000 polymorphic families





Salts



Refcode families

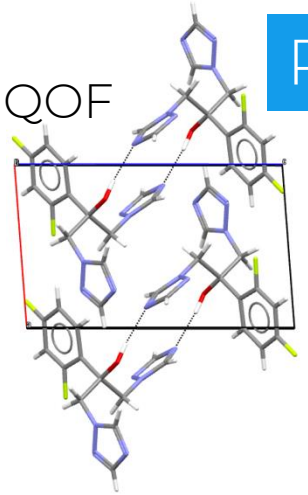
>1,000,000

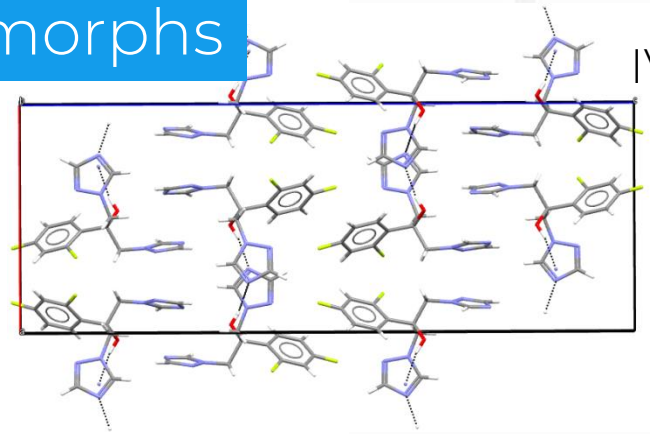
*Katerina Vriza, University of Liverpool, PhD on Data driven discovery of functional molecular co-crystal

A solid form landscape

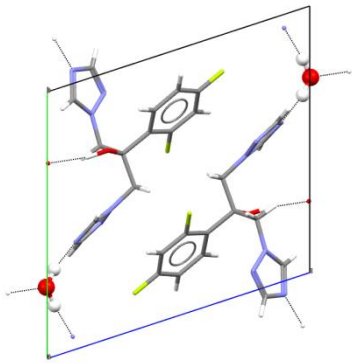
Polymorphs

IVUQOF



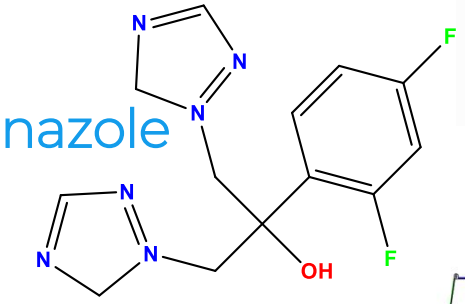


IVUQOF02

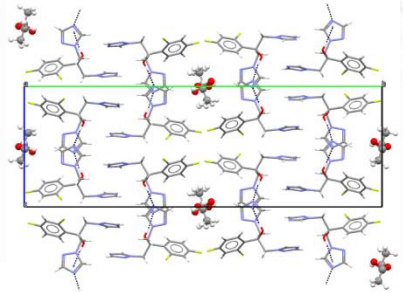


IVUQIZ

Hydrates

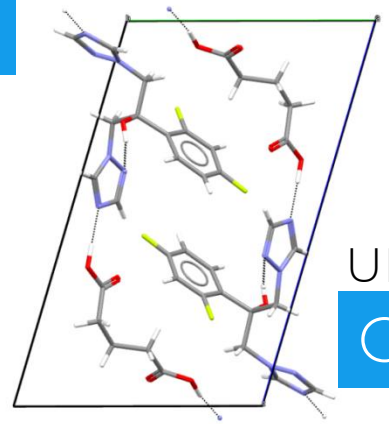


fluconazole



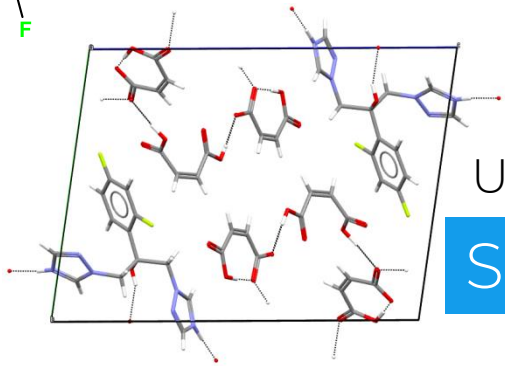
IVUQEV

Solvates



UPOQEW

Co-crystals



UPOQAS

Salts

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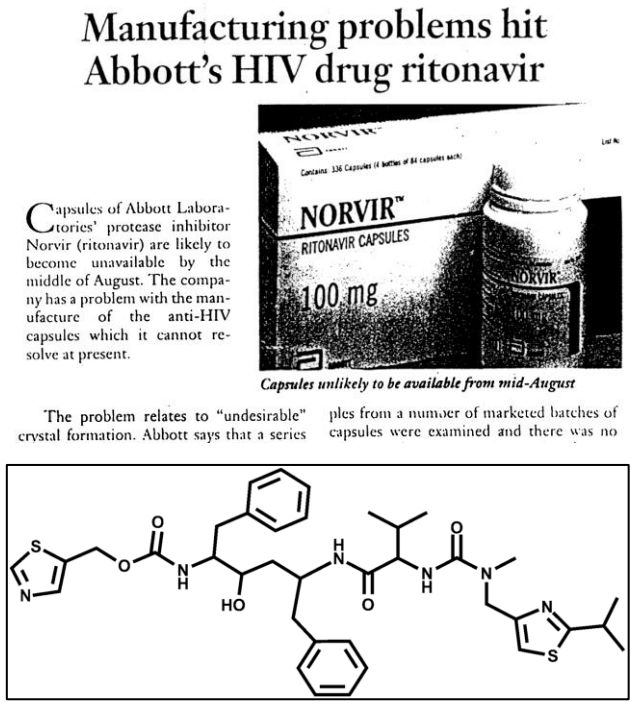
Impact of Hydrogen Bonding on lattice stability -The Ritonavir story



Manufacturing problems hit Abbott's HIV drug ritonavir

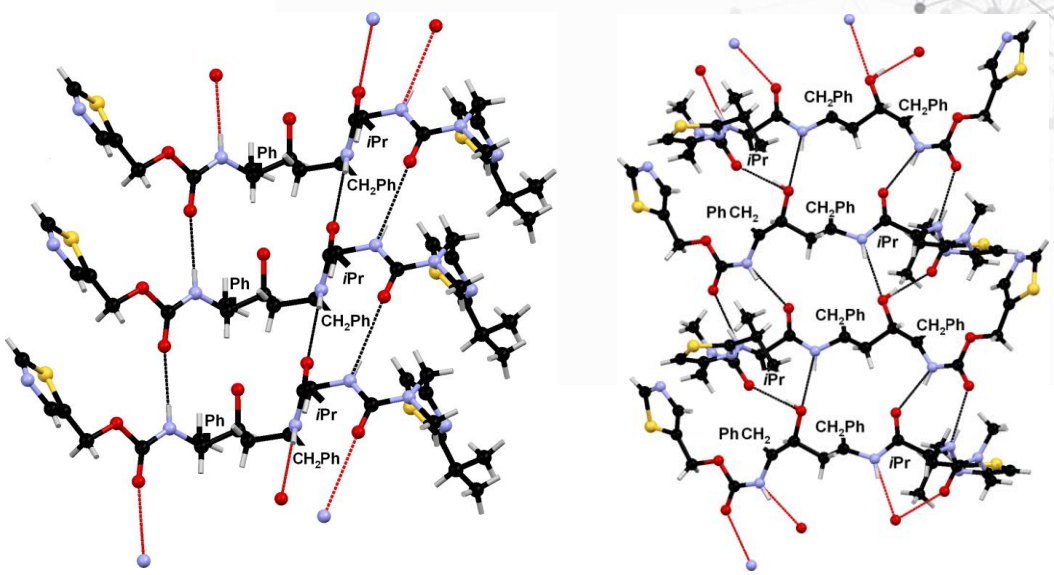
Capsules of Abbott Laboratories' protease inhibitor Norvir (ritonavir) are likely to become unavailable by the middle of August. The company has a problem with the manufacture of the anti-HIV capsules which it cannot resolve at present.

NORVIR™ RITONAVIR CAPSULES 100 mg

Capsules unlikely to be available from mid-August

The problem relates to "undesirable" crystal formation. Abbott says that a series of samples from a number of marketed batches of capsules were examined and there was no

- ~5-fold decrease in solubility
- Change in Hydrogen Bonding



"Since the strength and completeness of the hydrogen bonding has attained the maximum possible in the Form II lattice, it is not thought possible that another undiscovered polymorph of ritonavir would exist with equivalent or lower solubility than that of Form II."

Org. Process Res. Dev. (2000), 4(5), 413-417. Pharmaceutical Research (2001), 18(6), 859-866.

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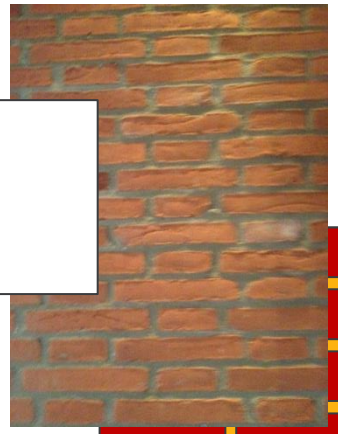
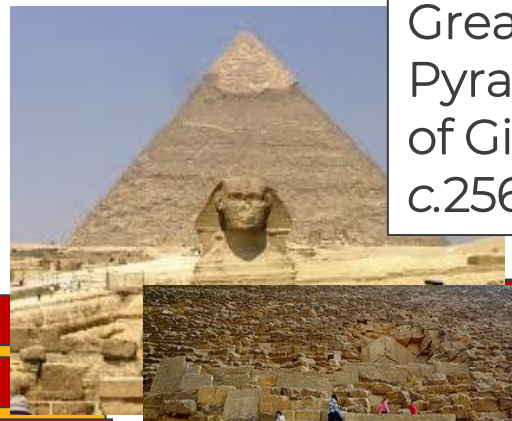
Structural Informatics

Which is the stable wall?



The CCDC c.1992



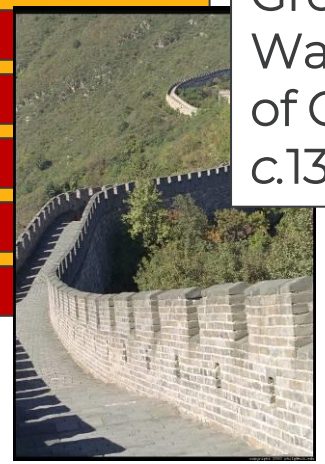
Great Pyramid of Giza c.2560 BC

Hadrian's Wall c.122

A

B

My House c.1967



Great Wall of China c.1368

The database of walls indicates that A is the frequently observed arrangement and therefore we can predict it is the most stable form

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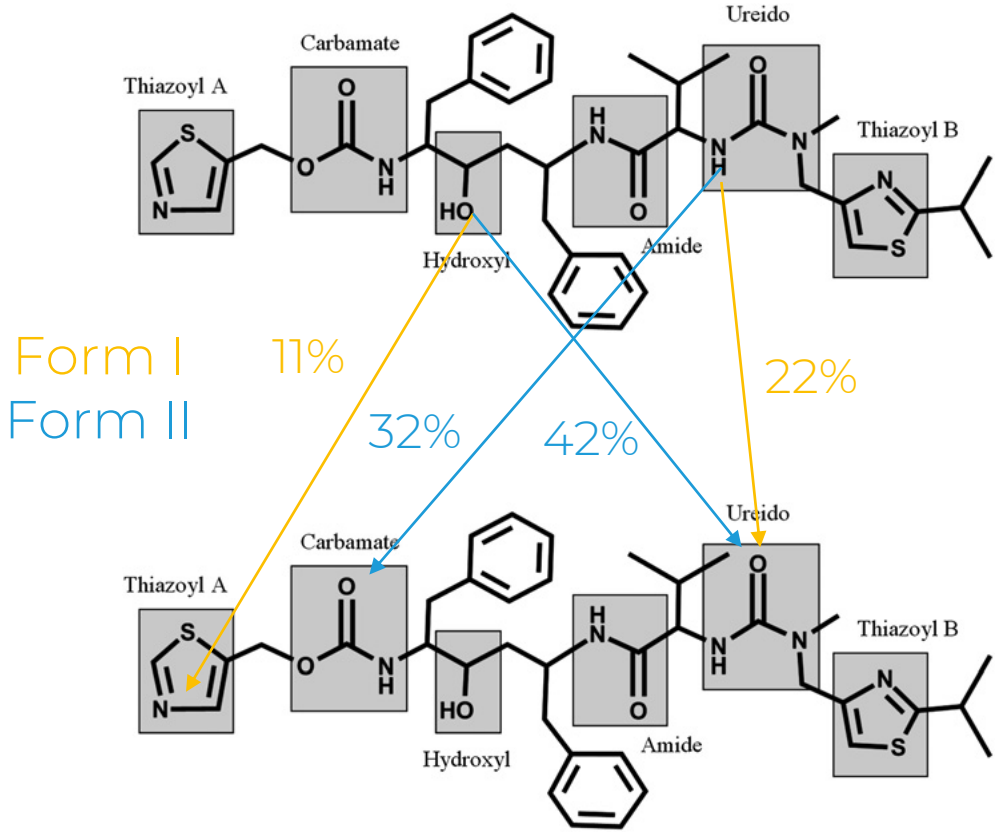
Predicting unlikely interactions

Predictive analytics is used to identify the likelihood of specific molecular interactions occurring from similar crystal structures



The integration of solid-form informatics into solid-form selection

Neil Feeder[a], Elna Pidcock[a], Anthony M. Reilly[a], Ghazala Sadiq[a], Cheryl L. Doherty[b], Kevin R. Back[b], Paul Meenan[c] and Robert Docherty[b]

One in half a million: a solid form informatics study of a pharmaceutical crystal structure

Peter T. A. Galek,*[a] Elna Pidcock,[a] Peter A. Wood,[a] Ian J. Bruno[a] and Colin R. Groom[a]

Navigating the Solid Form Landscape with Structural Informatics

Peter T. A. Galek, Elna Pidcock, Peter A. Wood, Neil Feeder, Frank H. Allen

Book Editor(s): Yuriy A. Abramov

Knowledge-based H-bond prediction to aid experimental polymorph screening

Peter T. A. Galek,*[ab] Frank H. Allen,[a] László Fábián[ab] and Neil Feeder[c]

Galek *et al*, *CrystEngComm*, (2009), 11, 2634 - 2639

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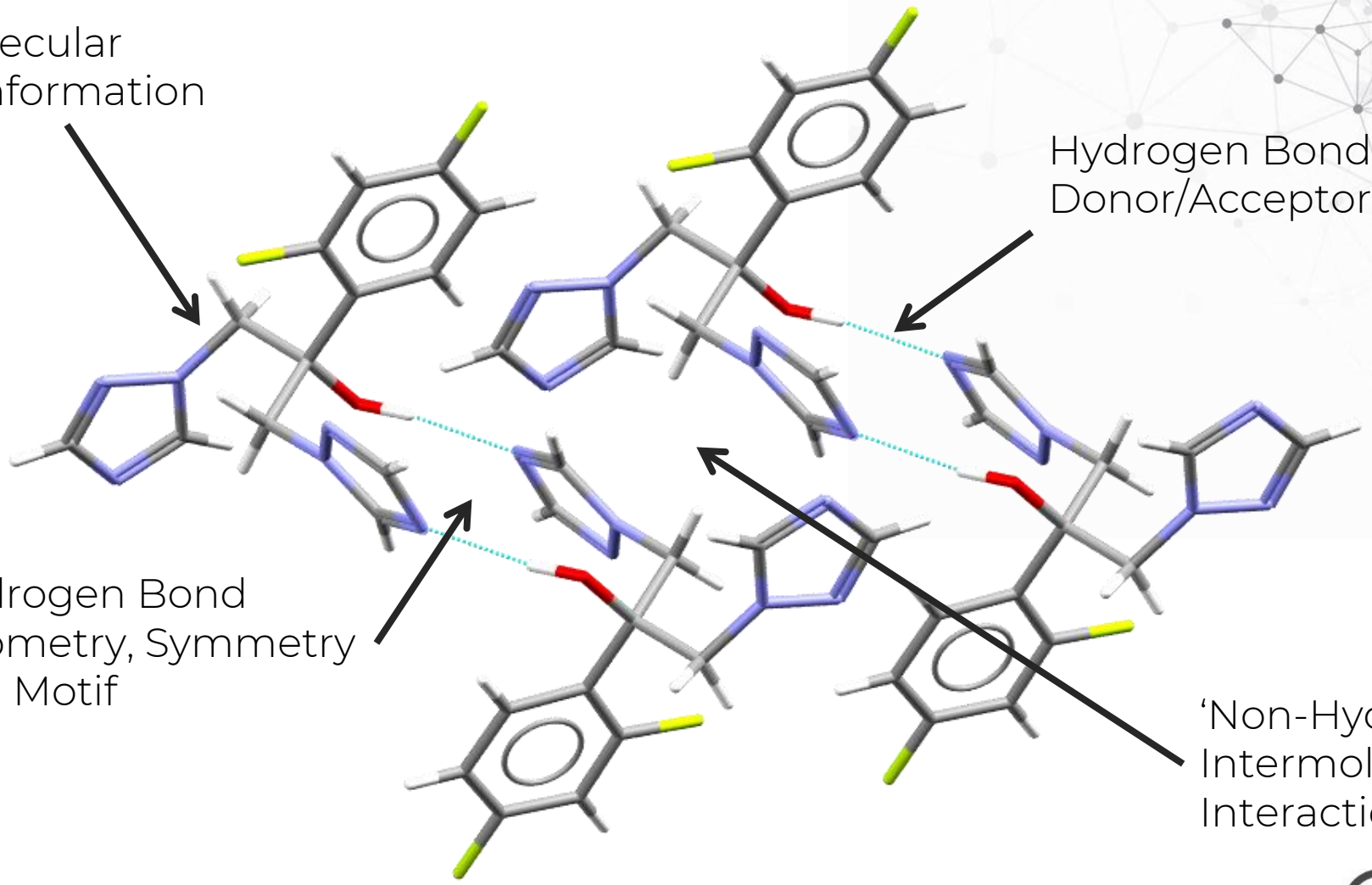
Characteristics that influence stability



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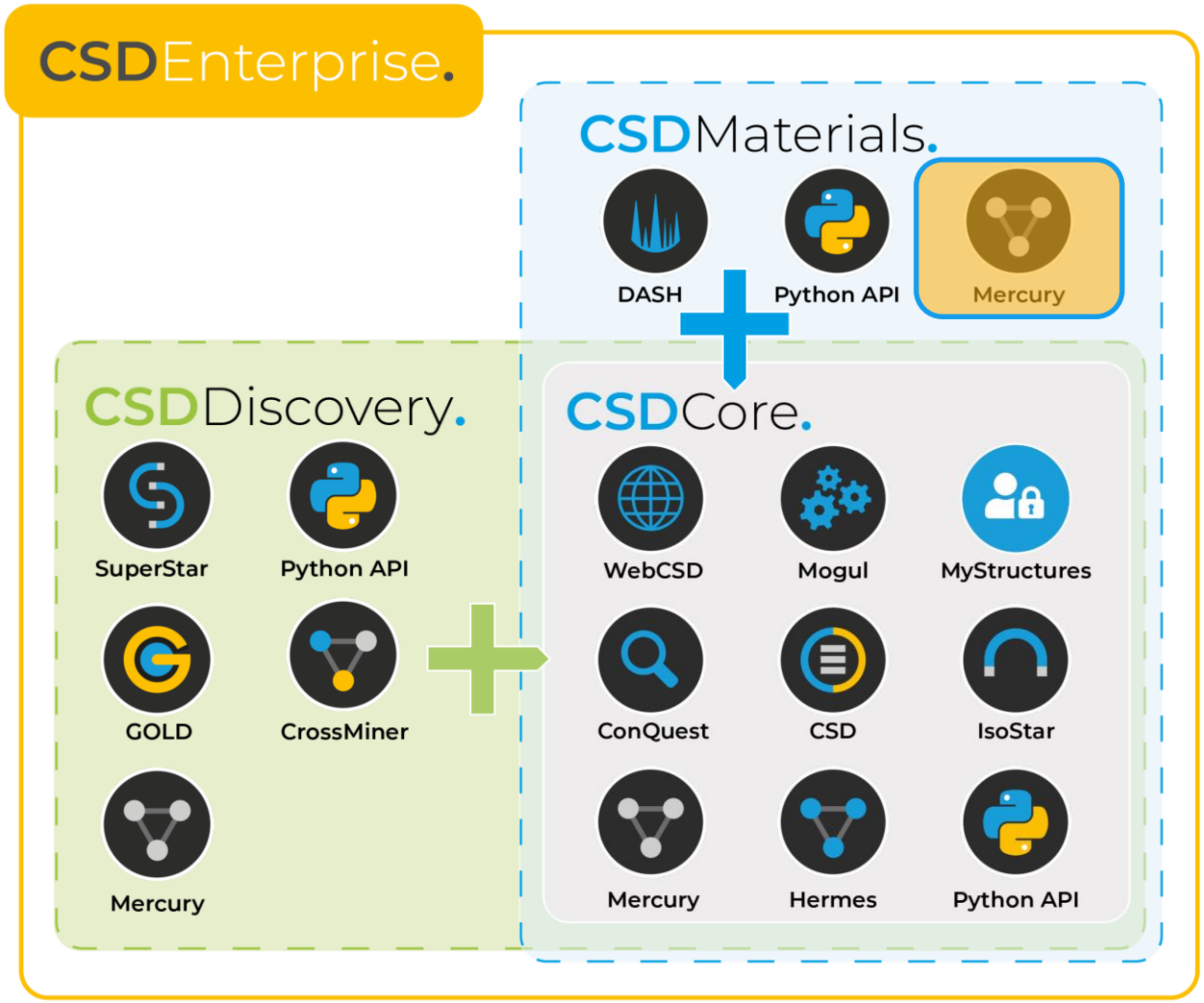
The CSD software



Professional Services

Research & Knowledge partnerships

CSDCommunity.

Mercury
enCIFer
Symmetry
Deposit
CellCheck
Educational
Access
MyStructures

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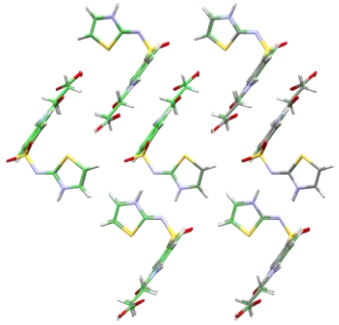
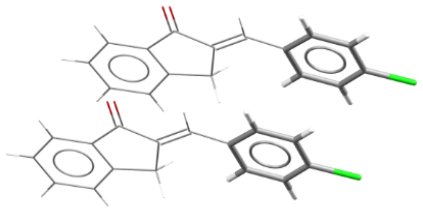
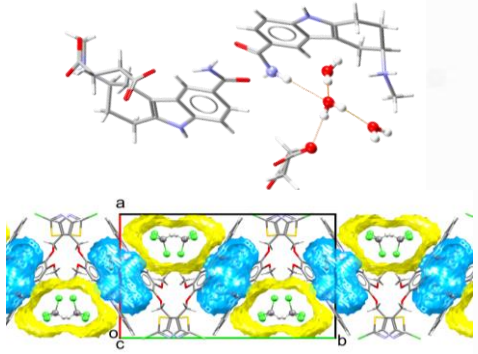
CSD-Materials overview



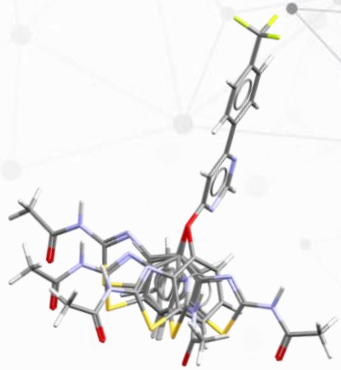
Crystal Packing Similarity



Motif Search & Packing Feature Search



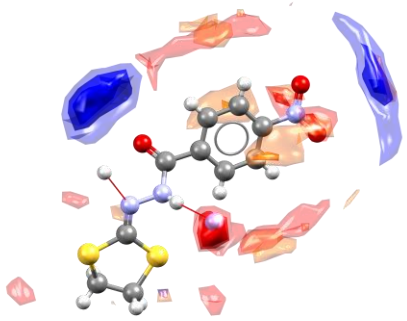
Hydrate Analyser & Solvate Analyser



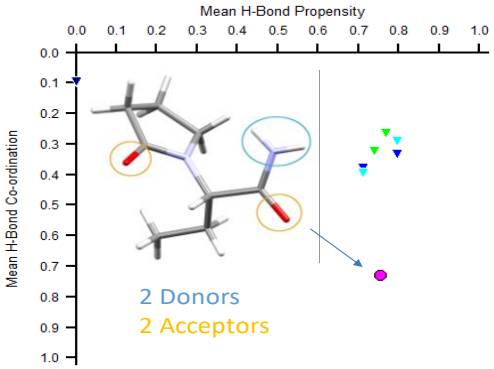
CSD Conformer Generator

Detailed Structural Analysis

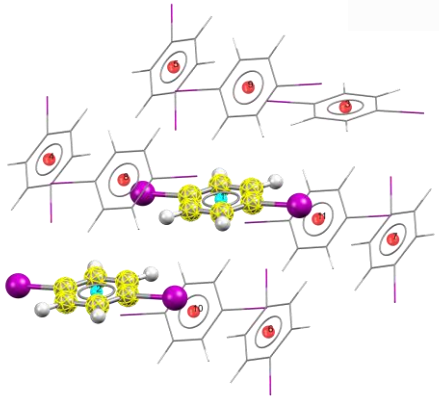
Solid Form Design



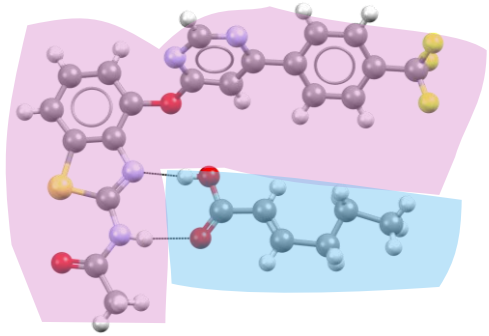
Full Interaction Maps



Hydrogen Bond Propensity



Aromatics Analyser



Molecular Complementarity

Solid Form Risk Assessment

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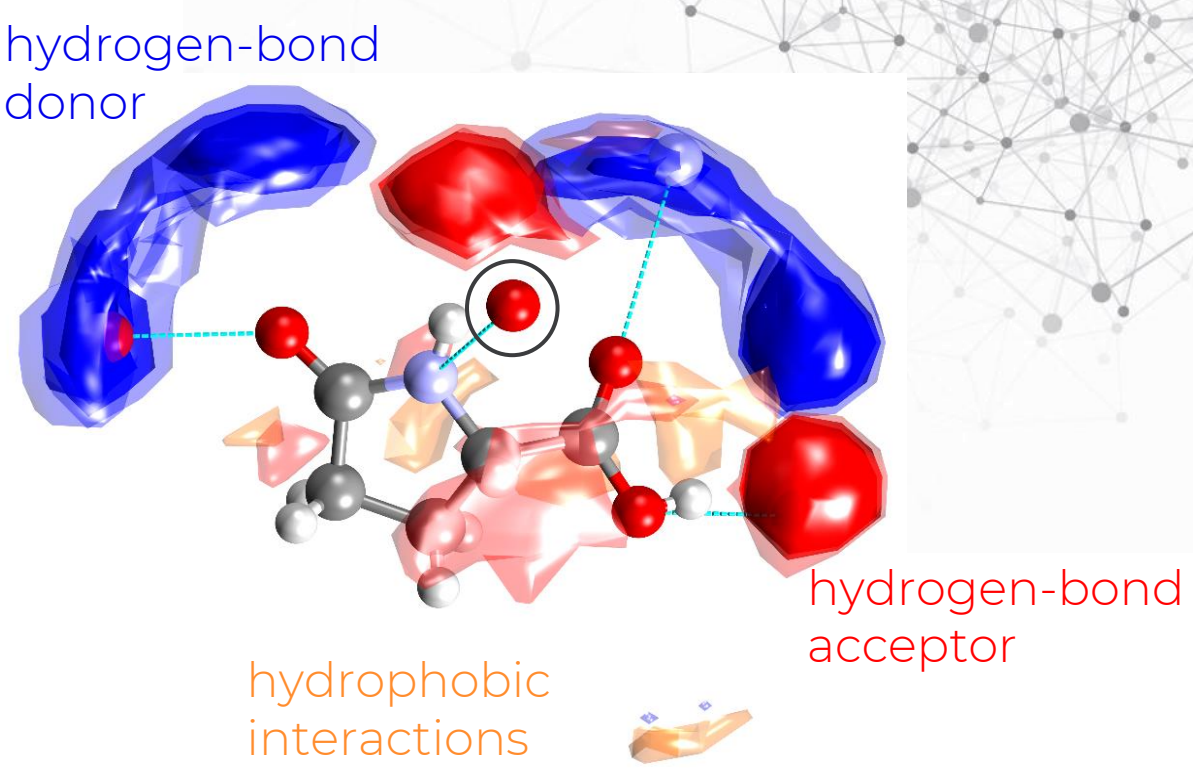
Full Interaction Maps (FIMs)

- Map interaction preferences around complete molecules in a crystal structure.
- Visualise observed atom-atom contacts with respect to likely geometries in 3D space.
- Identify interaction hot-spots around chemical groups.



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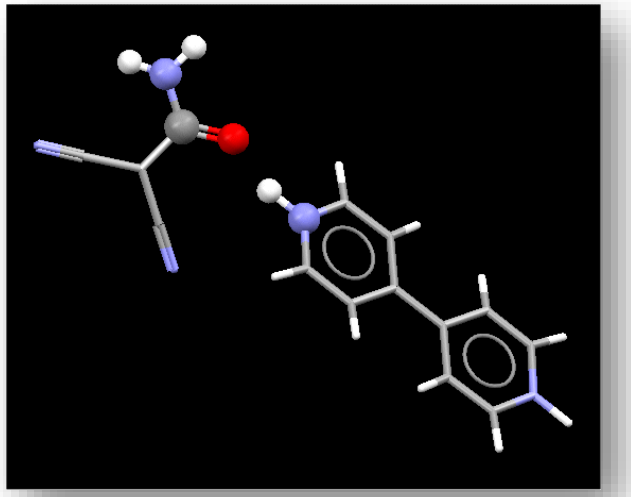
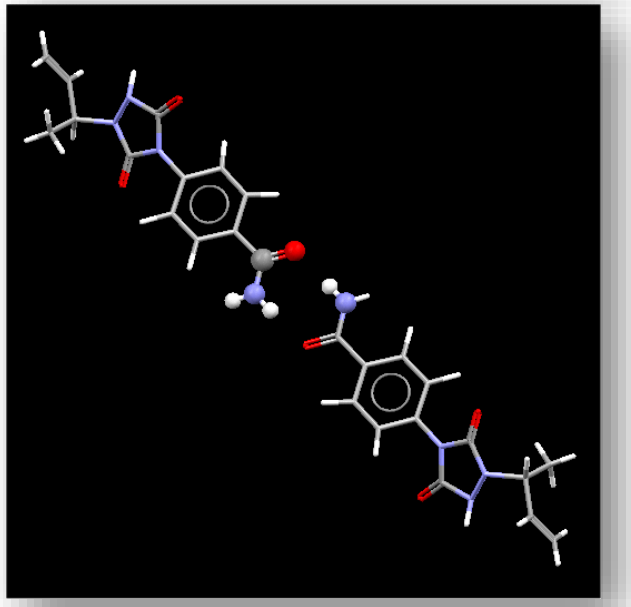
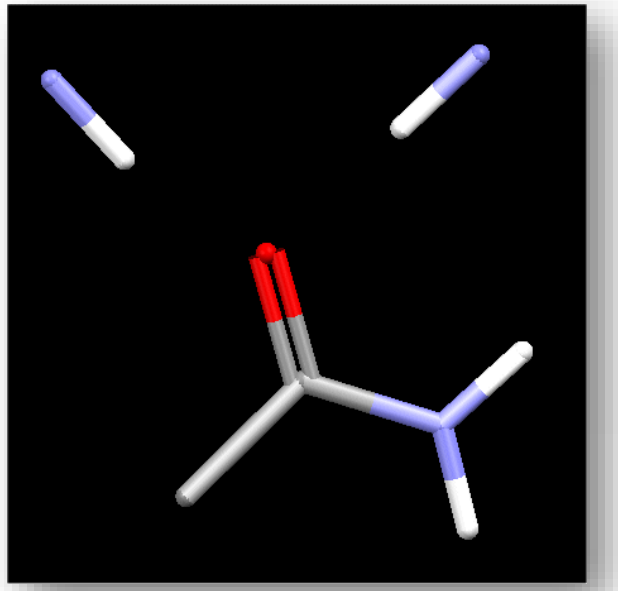
Understanding intermolecular interactions

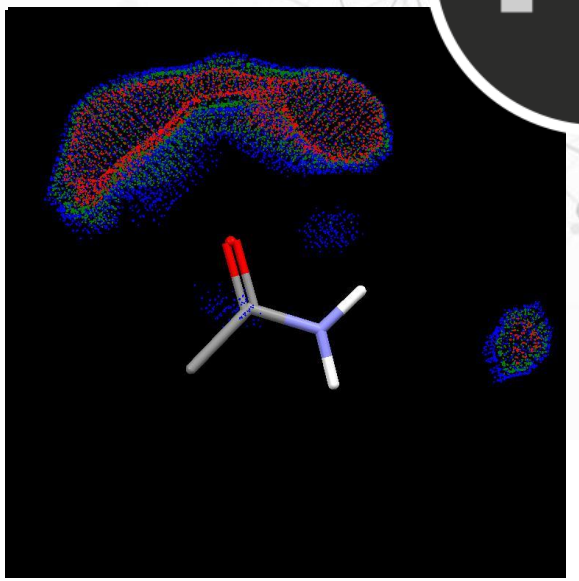




central group: -$CONH_2$

contact group: NH





Search for structures containing desired contact

Superimpose hits and display as scatterplots or contour plots

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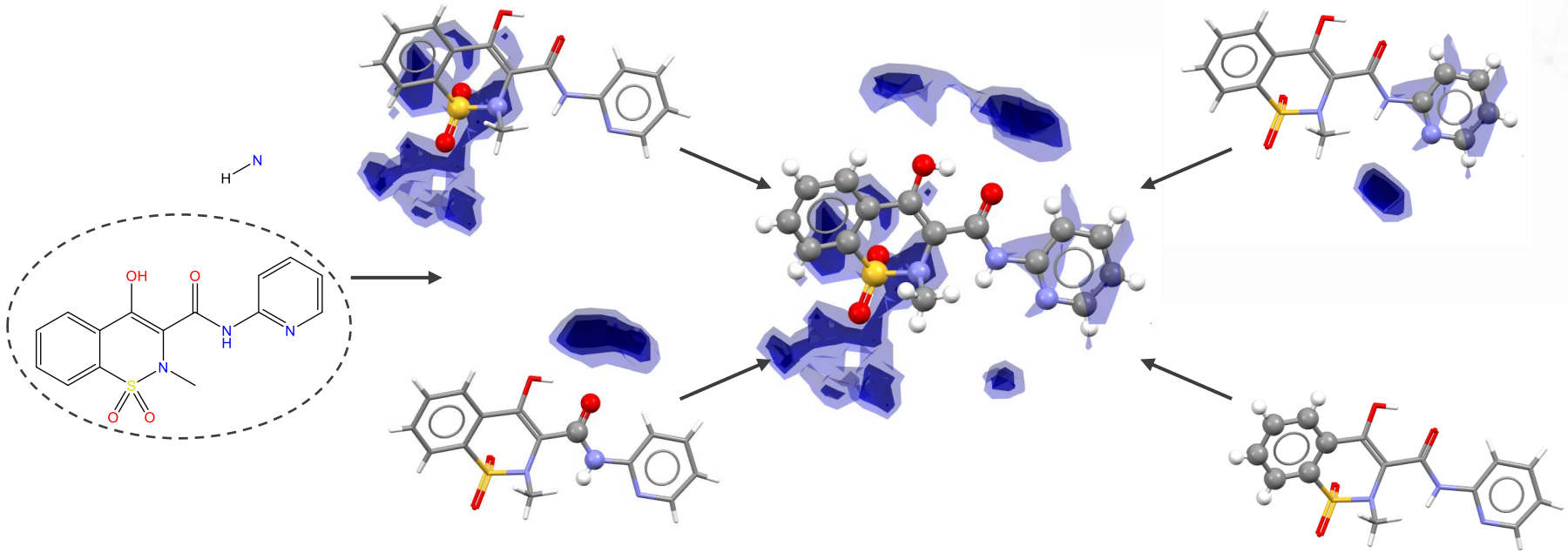
Combining plots into Full Interaction Maps

- Molecule is broken down into fragments
- IsoStar maps for each fragment are combined to give the Full Interaction Map



- Multiple maps can be generated for different probes

P. A. Wood *et al.*, *CrystEngComm* (2013), **15**, 65–72

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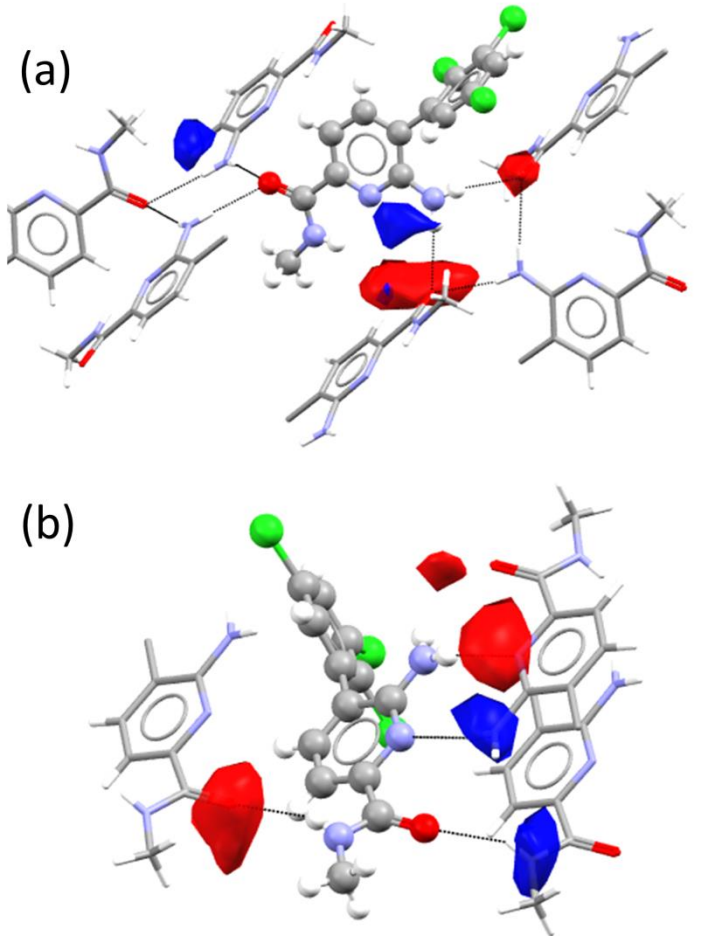
Predicting intermolecular interaction geometries

- “Early development candidate”
  - Two polymorphs, metastable (a) and stable (b)
  - Packing arrangement of stable form (b) satisfies Full Interaction Map particularly well
  - Packing arrangement of (a) does not



N. Feeder *et al.*, *J. Pharm. Pharmacol.* (2015), **67**(6), 857-868

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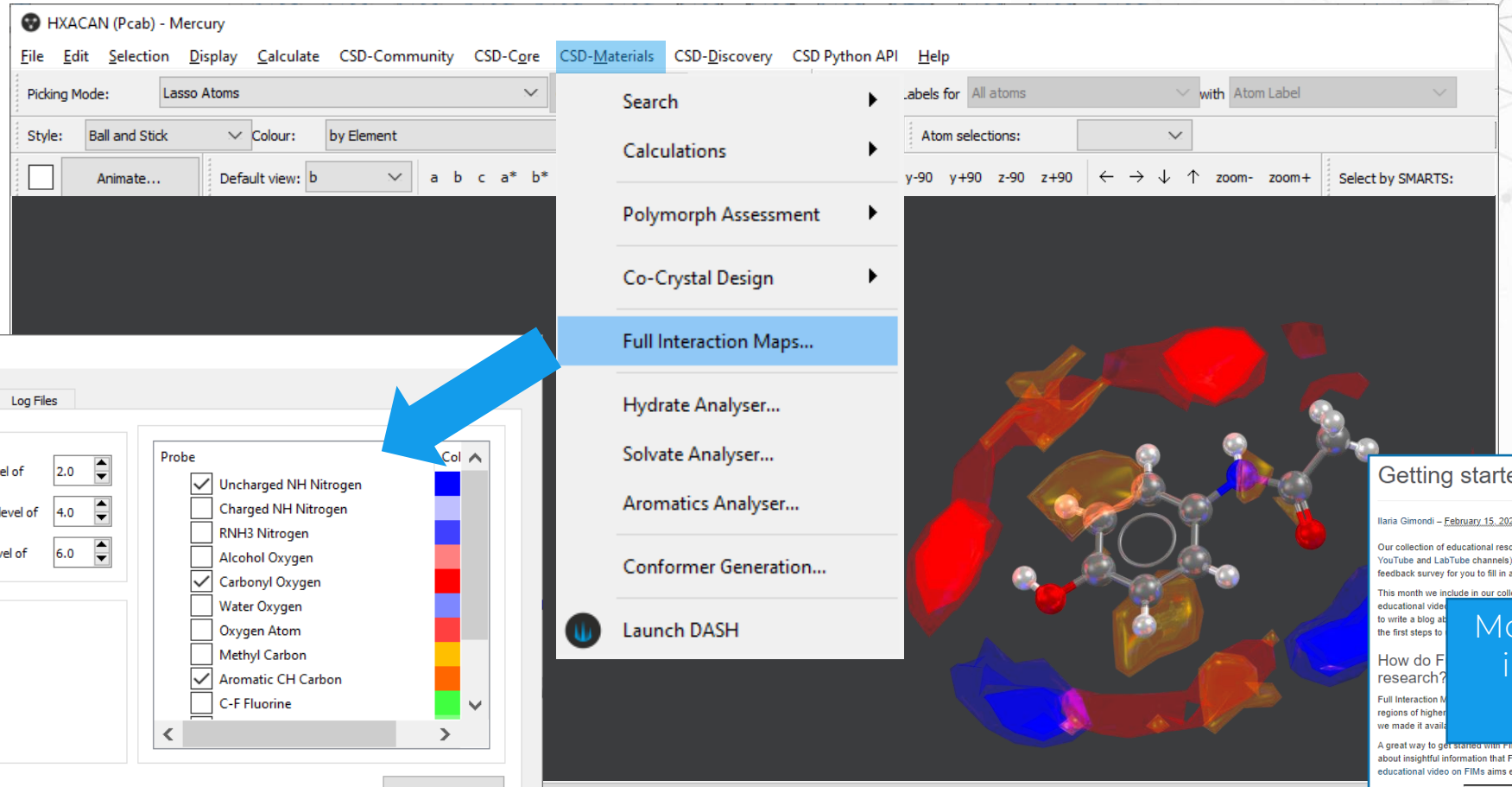
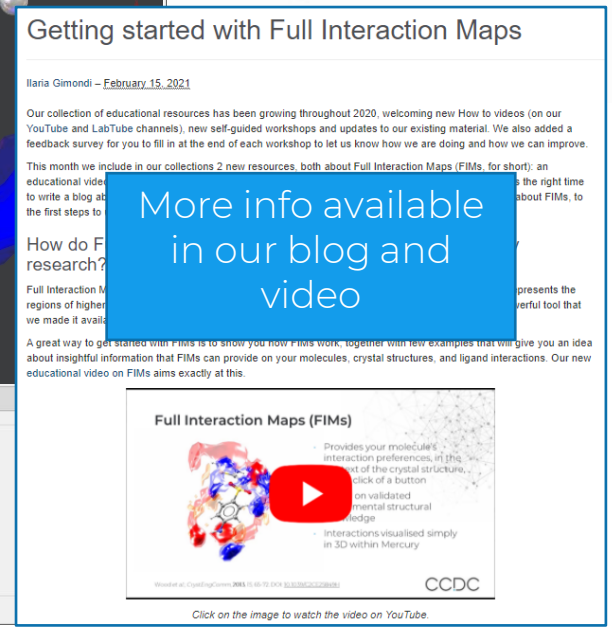
Creating a FIM

FIMs enable you to generate a 3D interaction map around a molecule representing regions of higher probability to find interactions with certain functional groups

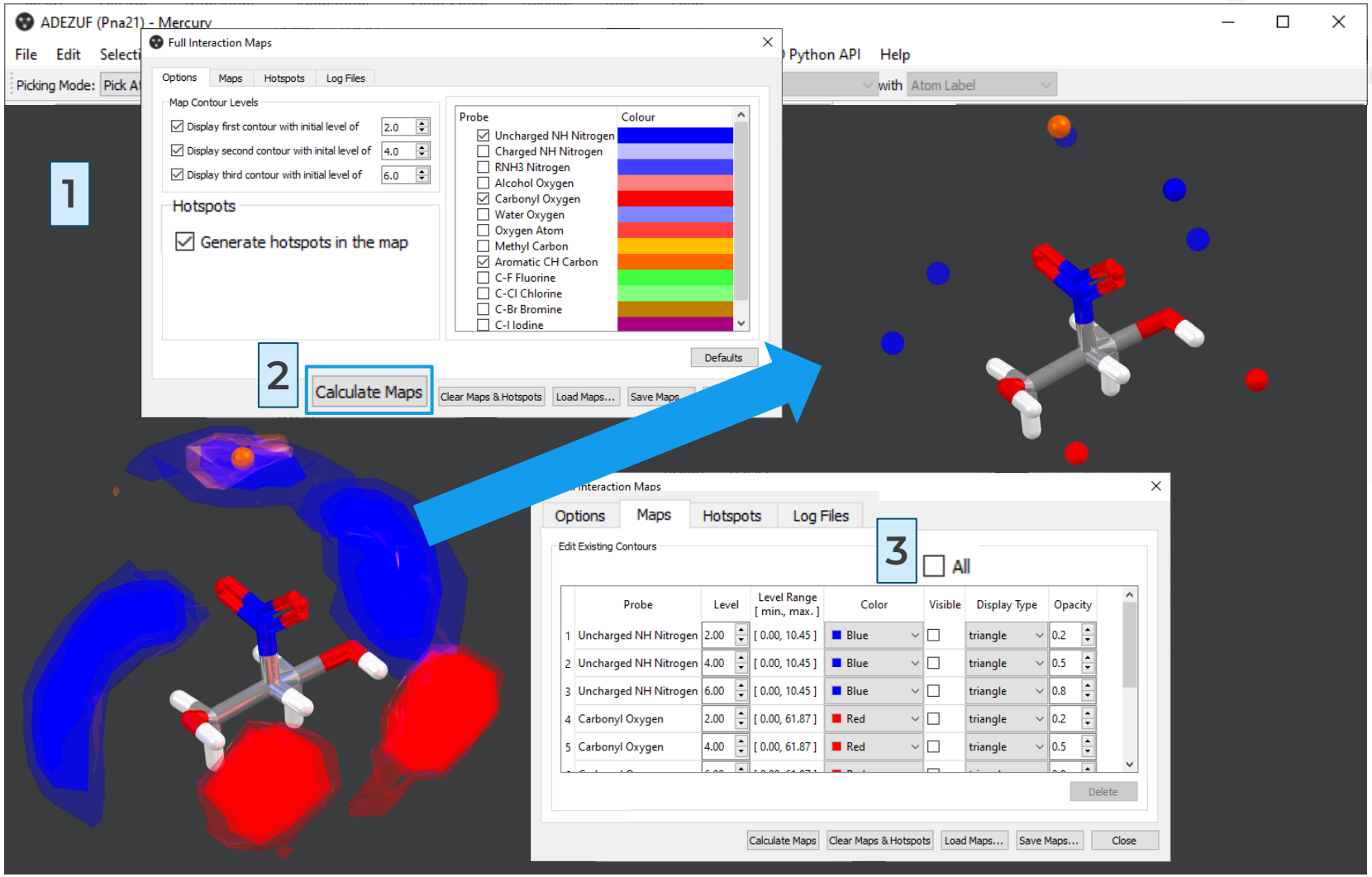




More info available in our blog and video

https://www.ccdc.cam.ac.uk/Community/blog/getting-started-with-FIMS/

Creating a hotspot



Hotspots represent the positions of highest local density for each contour Surface. Find this in our *Glossary*.

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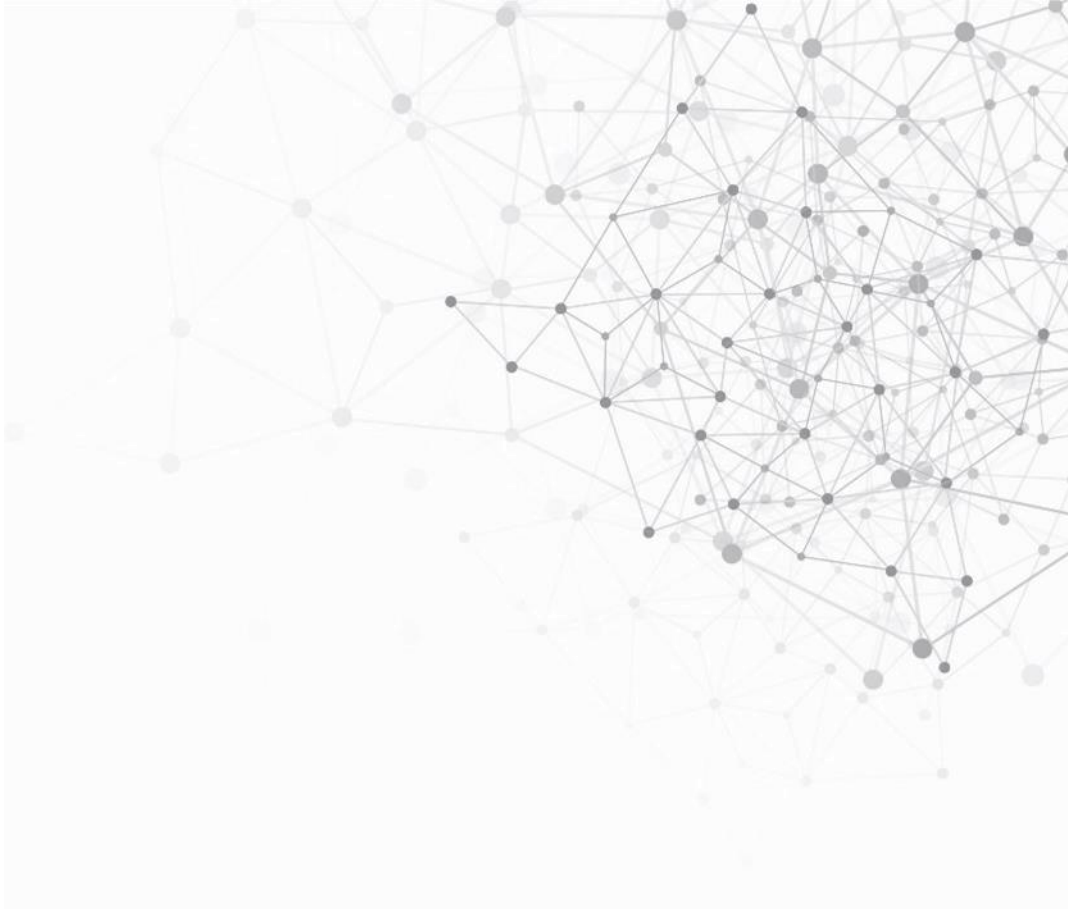
Tips and Tricks



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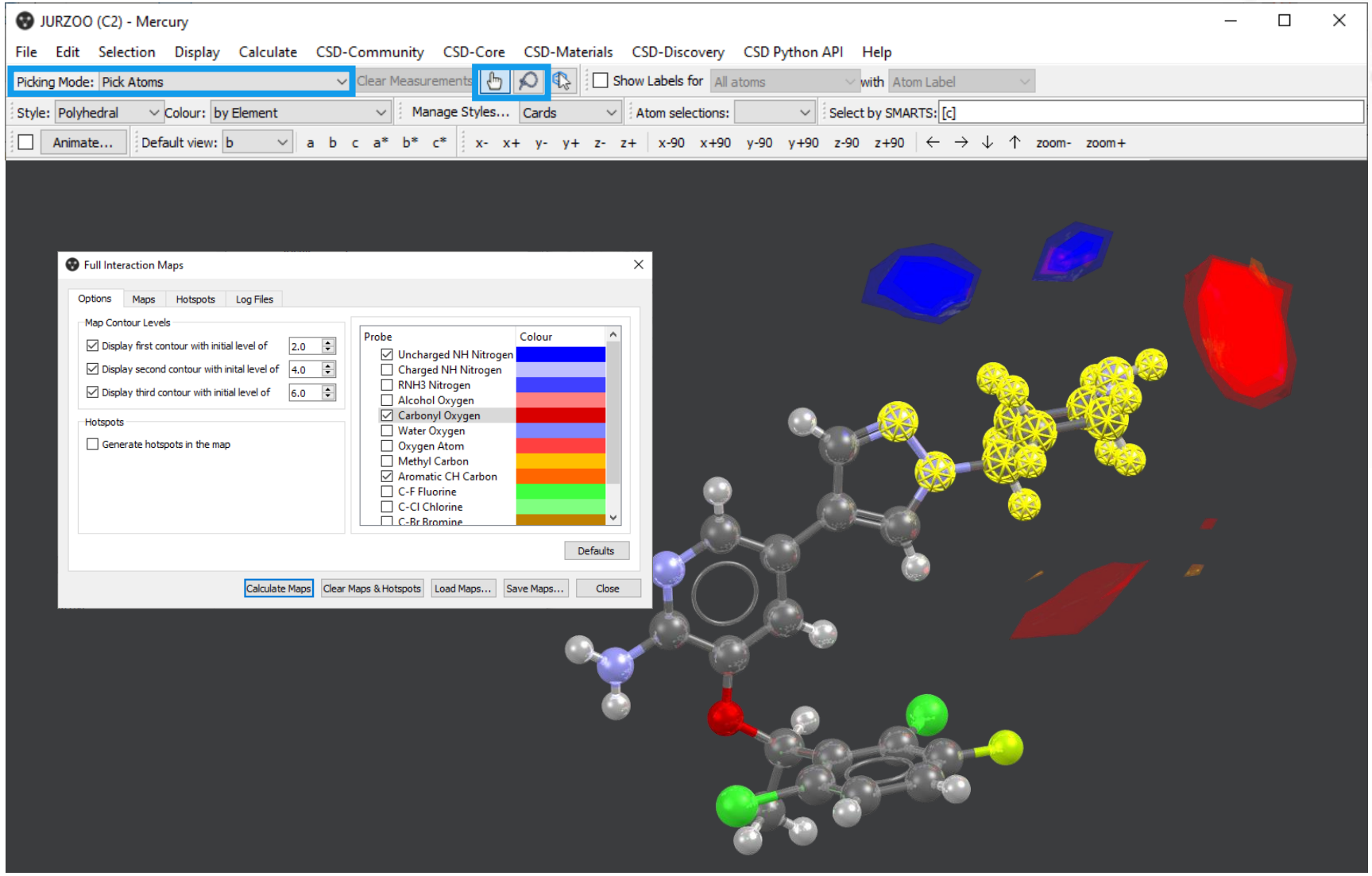
advancing structural science

Generate FIMs for selected atoms



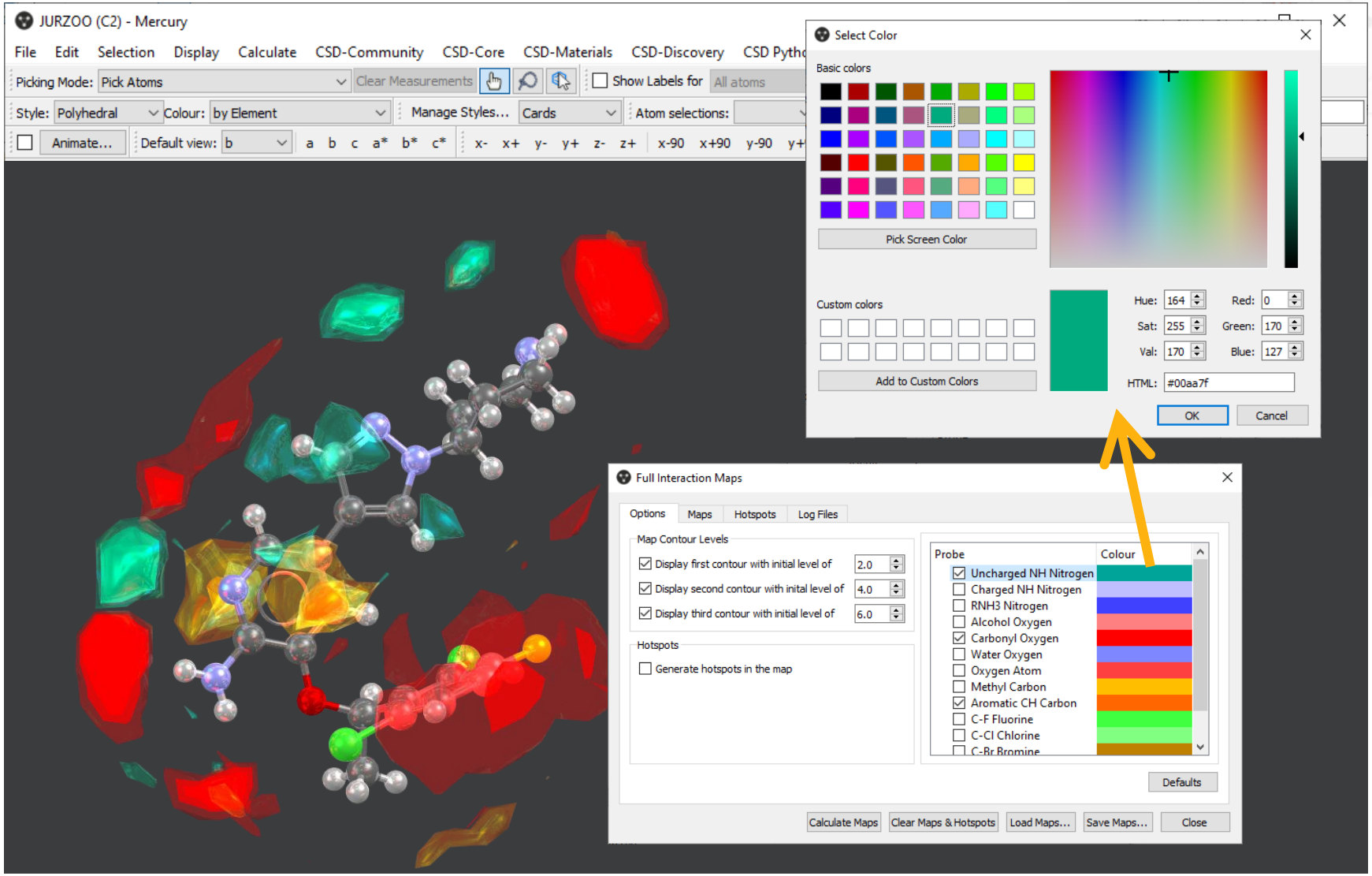
You can generate FIMs for a portion of a molecule.

Select the relevant atoms before calculating the maps.

Reminder: To select atoms you can:

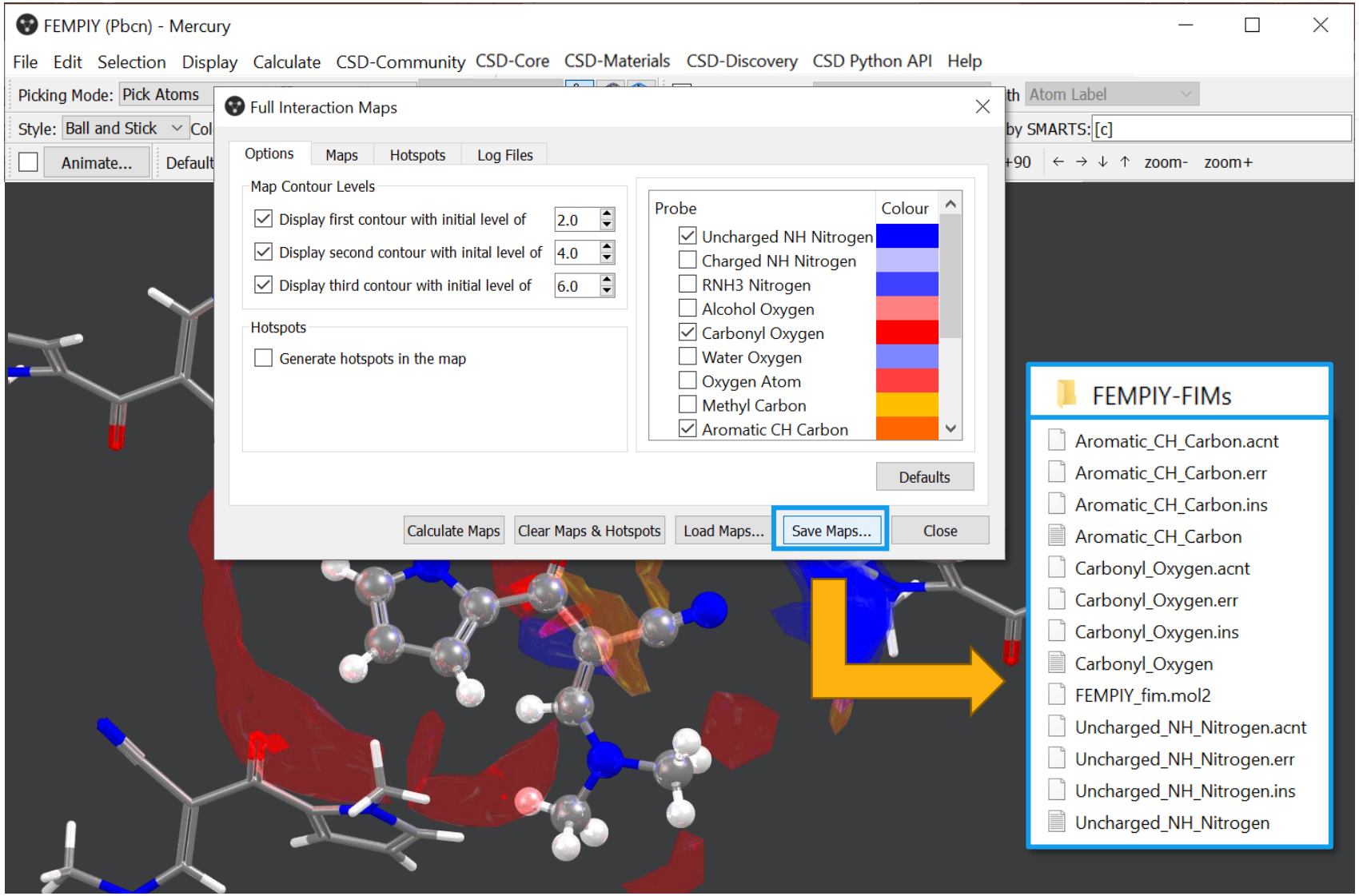
- Change the picking mode to Pick Atoms or Lasso Atoms
- Use the Lasso button
- Go to Selection > Select Atoms or
- Right click for visualiser menu > Selection > select atoms

Change the colour of probes



You can change the colour for each probe by clicking on the Colour in the Full Interaction Maps Options tab

Save FIMs



You can save a FIM in the Full Interaction Maps Options tab by clicking Save Maps...

Reminder: To save a high resolution image of what is displayed in your Mercury window go to File > POV-Ray Image... then click Preview to check the image before clicking Render

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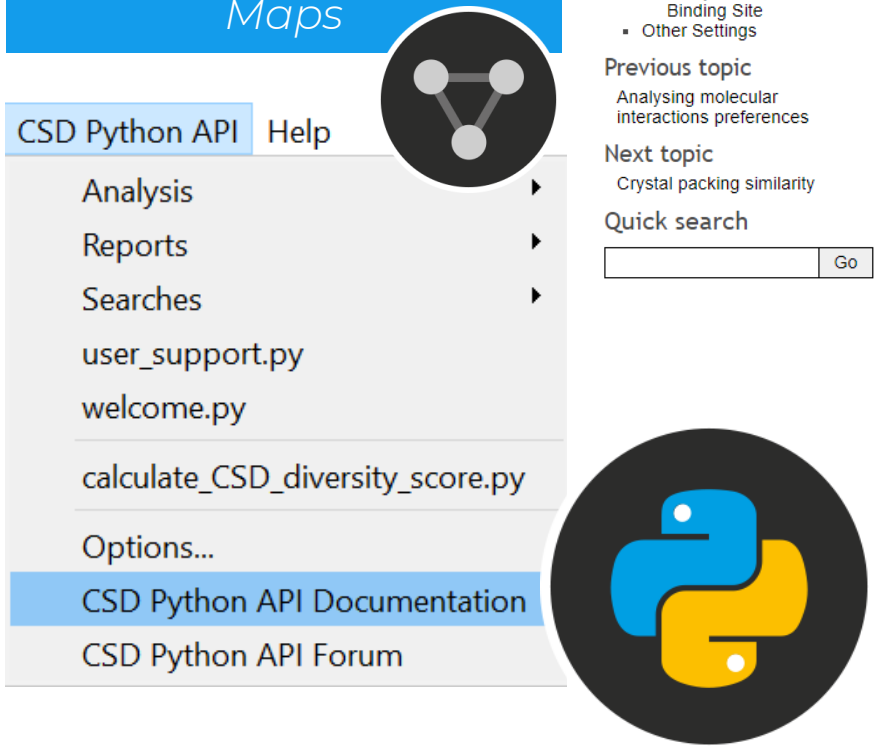
Programmatic access to FIMs in our API

For API documentation in Mercury go to CSD Python API > CSD Python API Documentation the navigate to Interaction Maps



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Note: the `ccdc.interaction.InteractionMapAnalysis` is available only to CSD-Discovery, CSD-Materials and CSD-Enterprise users.

ccdc.interaction.InteractionMapAnalysis

Introduction

The `ccdc.interaction.InteractionMapAnalysis` uses crystallographic information about non-bonded interactions to generate interaction maps around small molecules or within protein binding site. Depending on the settings used, the calculated maps provide the interaction preferences for your molecule as a whole in the context of the crystal structure, or the interaction preferences for all or selected cavities in a protein.

Note: For more information on the details of the fundamental methodology please see:

"SuperStar: A knowledge-based approach for identifying interaction sites in proteins.", M. L. Verdonk, J. C. Cole and R. Taylor, J. Mol. Biol., 289, 1093-1108, 1999, DOI: 10.1006/jmbi.1999.2809.

"Evaluation of molecular crystal structures using Full Interaction Maps", P. A. Wood, T. S. G. Olsson, J. C. Cole, S. J. Cottrell, N. Feeder, P. T. A. Galek, C. R. Groom, E. Pidcock, CrystEngComm, 15, 65?72, 2013, DOI: 10.1039/C2CE25849H.

See also: API documentation for the interaction module

Use Cases

Analyse Crystal and Small Molecule

One common use for `ccdc.interaction.InteractionMapAnalysis` is to analyse a crystal to determine the preferred binding sites of particular functional groups. We will exemplify this by considering paracetamol. Firstly, let us import the relevant modules and classes:

```
>>> from ccdc import io
>>> from ccdc.interaction import InteractionMapAnalysis
```

Then we will load a crystal structure for paracetamol:

```
>>> csd = io.EntryReader('csd')
>>> paracetamol = csd.crystal('HXACAN')
```

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