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advancing structural science

What's Up

Customer Update Webinar

18th November 2021

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Today’s presenters

Pete Wood

Director of Product Management

Sophie Bryant

Marketing Manager

Francesca Stanzione

Research and Applications Scientist

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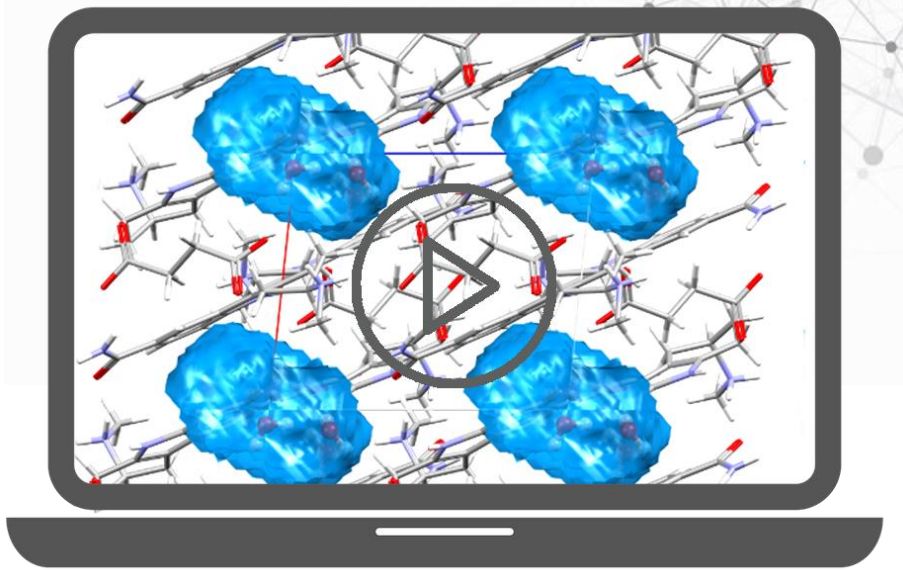
Overview

In this webinar we will discuss:

- Latest updates and news
- DASH: What has changed?
- CSD-CrossMiner: New features from the 2021.2 release
- Q&A: the floor is yours



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Latest updates

- Upcoming 2021.3 CSD release in December: DASH migration, new CSD subsets, and usability improvements for CSD-Core solutions.

- 7th CSP Blind Test: we released the 2D chemical structures of the target compounds.
  Learn more www.ccdc.cam.ac.uk/Community/initiatives/CSPBlindTests/

- CSDU new module available: Analysing molecular geometries 101 – basics of Mogul. www.ccdc.cam.ac.uk/Community/educationalresources/CSDU/

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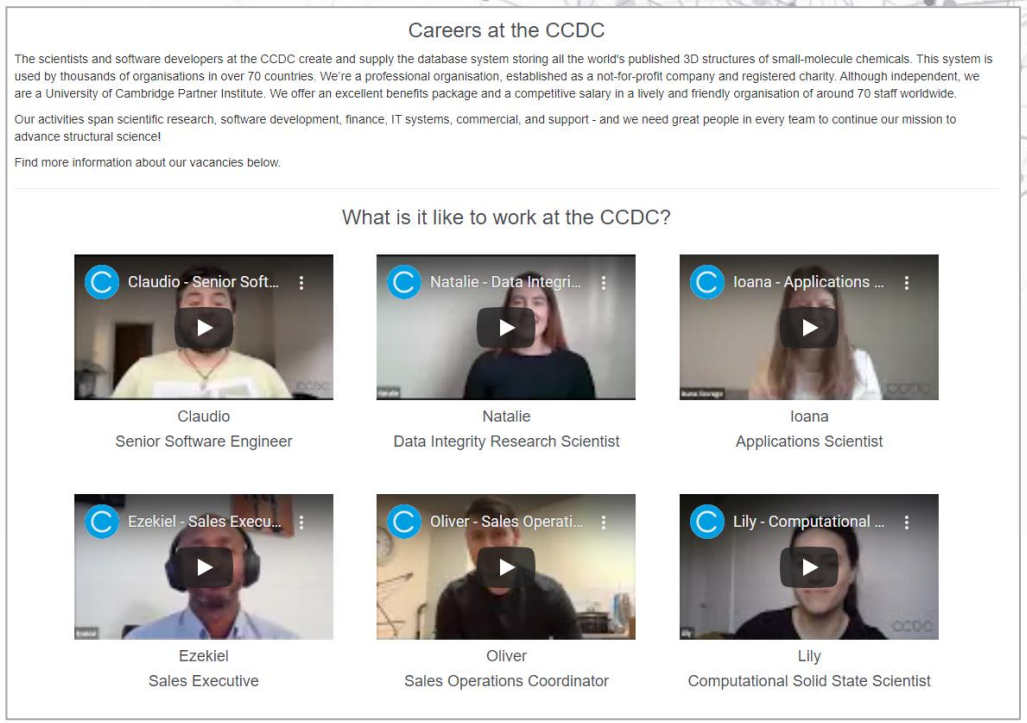
Time for a change?

- We are hiring!
  - Postdoctoral Research Associate – Interactions
  - Research and Applications Scientist – Materials Science
  - Product Manager
  - Technical Manager
  - USA – Research and Applications Scientist – Discovery Science

- Work for a registered charity, active research centre and partner institute of the University of Cambridge.
- Advancing structural science for the public benefit.

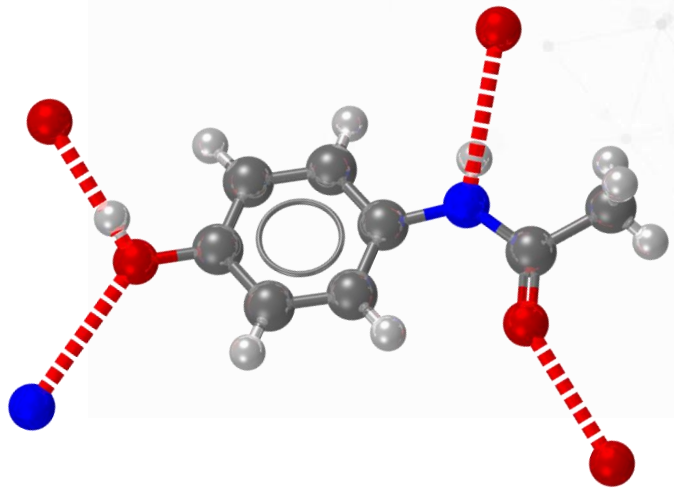
https://www.ccdc.cam.ac.uk/theccdcprofile/careers/



We need you

Are you interested in helping us to evolve WebCSD and our 3D visualiser?

- Let us know in the question box!
- Just drop us an email hello@ccdc.cam.ac.uk
- User research sessions should take < 1 hour



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DASH: What has changed?

Structure solution from powder data – *for the community*

Pete Wood

Director of Product Management

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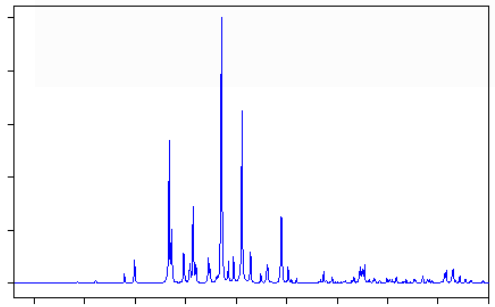
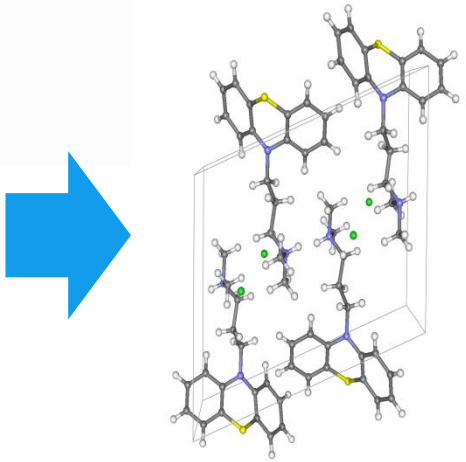
What is DASH?

- One of the most well-known and effective programs for crystal structure solution from power diffraction data
- DASH is named after the program's original authors Bill David and Kenneth Shankland
- First presented in a paper in 1998, then distributed by CCDC since April 2001 under licence from STFC Innovations Limited
- Designed with a user-friendly interface and extensive manual
- Powerful integration with Mogul for search space reduction





W. I. F. David, K Shankland, J. van de Streek, E. Pidcock, W. D. S. Motherwell, J. C. Cole. J. Appl. Cryst., 39, 910-915.

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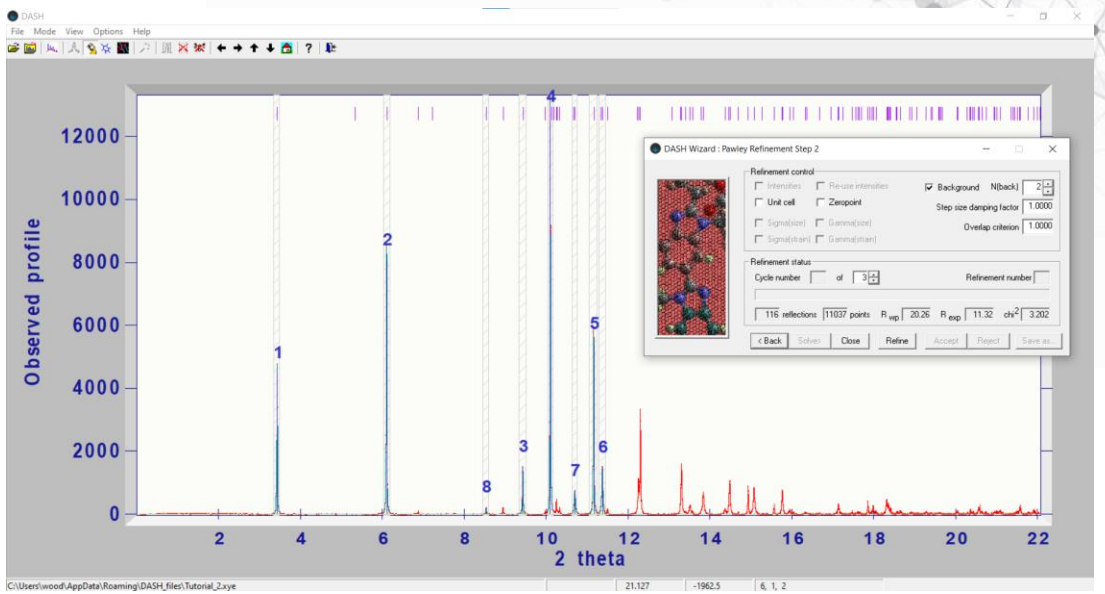
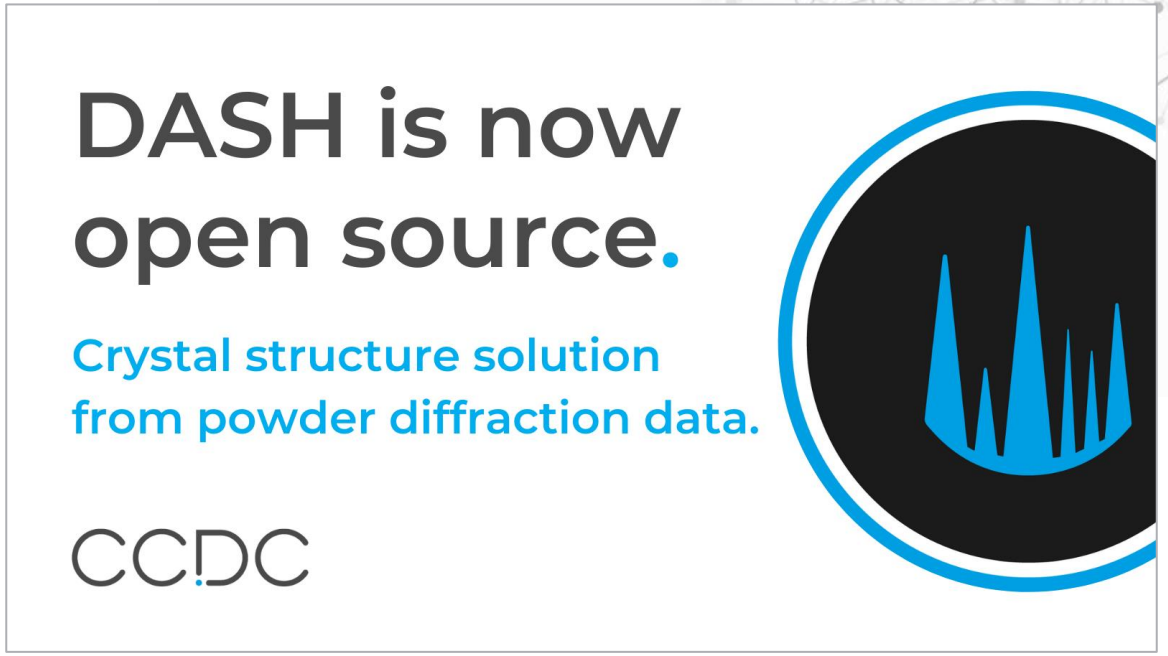
How does DASH work?

- DASH solves crystal structures from powder diffraction data
- The approach assumes you know the molecular formula of the material – you input this 3D model at the start
- The unit cell and space group are determined by indexing the pattern
- DASH generates many trial solutions and uses simulated annealing to adjust the molecular position and conformation until it agrees well with the pattern
- Mogul can help by dramatically reducing conformational search space
- All steps are guided using a UI Wizard



Why is the situation with DASH changing?

- As the CSD software portfolio has developed and expanded, DASH is now at the periphery
- The CCDC has not been able to spend much time developing its functionality in recent years
- There are still interesting directions that could be explored with DASH though
- To ensure DASH remains available to use, and can grow and change, the CCDC, STFC and DASH's co-authors have agreed to make it open to the community
- This will also allow our team more time to focus on other areas of CSD-Materials



https://www.ccdc.cam.ac.uk/solutions/open-source/dash-open-source/

What does that mean for me as a user?

- To install DASH, you will need to get the installer from the new DASH GitHub repository
- From the 2021.3 CSD Release (December 2021), DASH will no longer be installed as a part of the CSD software portfolio
- In March 2022, older versions of DASH will also stop working
- DASH is now available for free, for anyone to use and adapt, under the MIT licence

https://github.com/ccdc-opensource/dash

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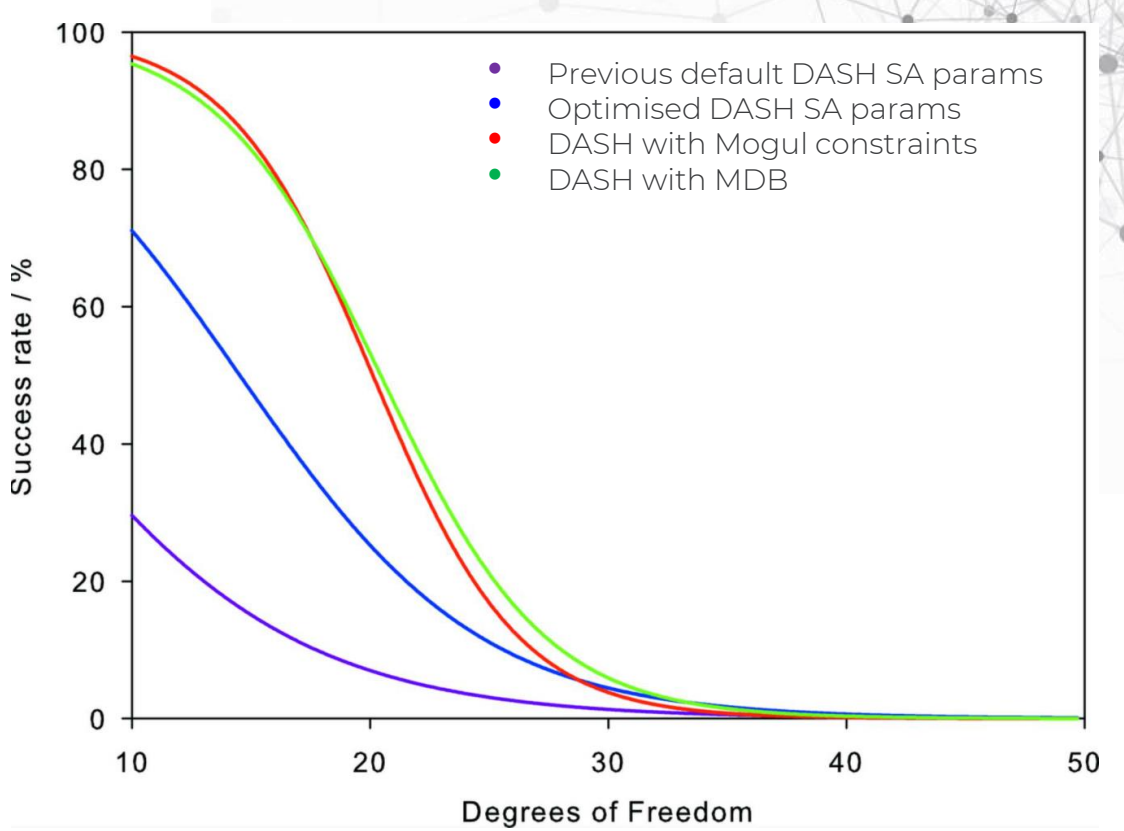
Will DASH still integrate with Mogul?

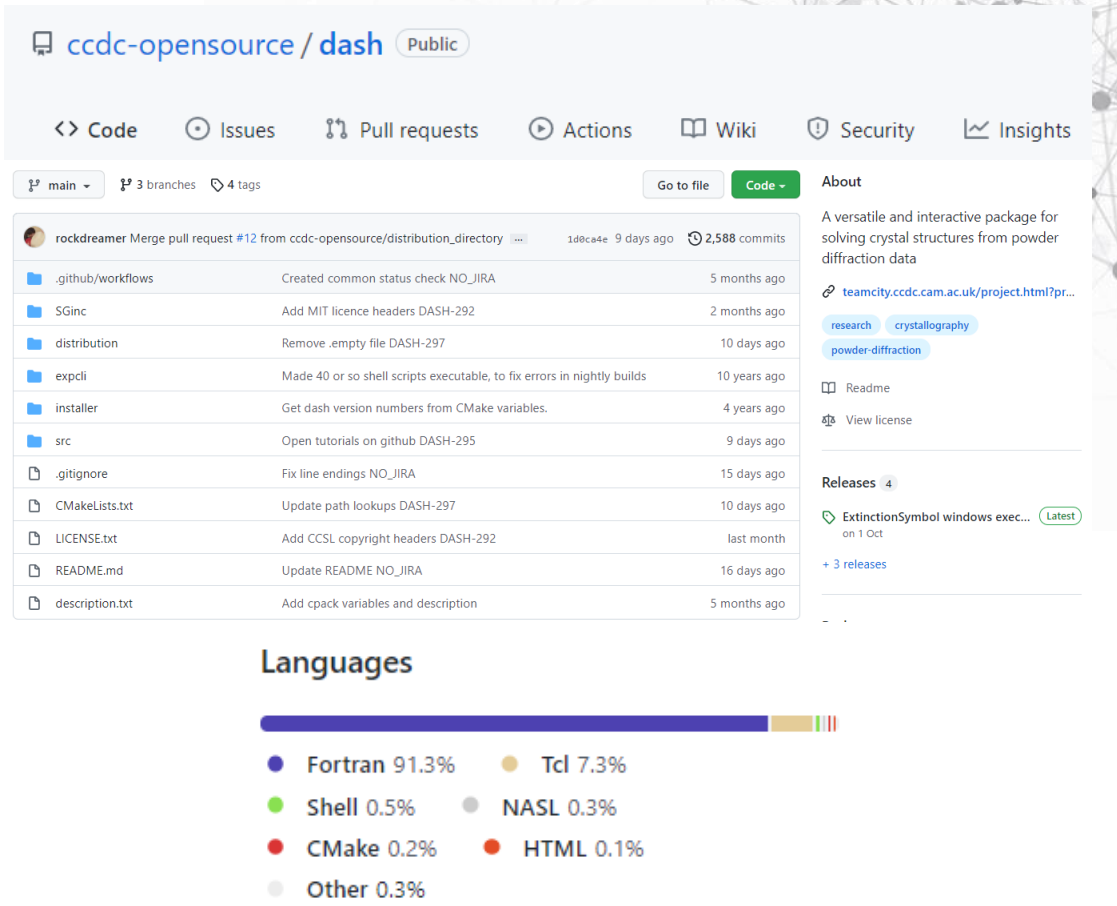
- Yes! This is a key integration that the CCDC will continue to test and maintain
- Users will need a valid licence for Mogul to make use of it
- Mogul will still have a major impact in improving the effectiveness of crystal structure solution
  - See Kabova et al., 2017



E. A. Kabova, J. C. Cole, O. Korb, A. C. Williams, K. Shankland, *J. Appl. Cryst*. (2017). 50, 1421-1427

How can the community progress DASH?

- All the code for DASH is now openly accessible under the MIT licence in GitHub
- This means that *anyone* can now work on improving or extending the DASH code
- The community can also report concerns, or improvement ideas, within GitHub
- To build DASH, you will need:
  - Intel Fortran compiler
  - CMake
  - Licence for Winteracter (the UI library)



https://github.com/ccdc-opensource/dash

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What directions might DASH take next?

- Further methods development
  - Use of GPUs for acceleration
  - Improved support for Cloud or Cluster usage
- Handling of alternative data sources
  - Neutron diffraction data
  - Electron diffraction data
- Support for alternative platforms
  - macOS version
  - Linux version
  - Command-line version

Where do *you* want to see DASH go now?

https://github.com/ccdc-opensource/dash

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CSD-CrossMiner

Improving user experience

Francesca Stanzione

Research and Applications Scientist

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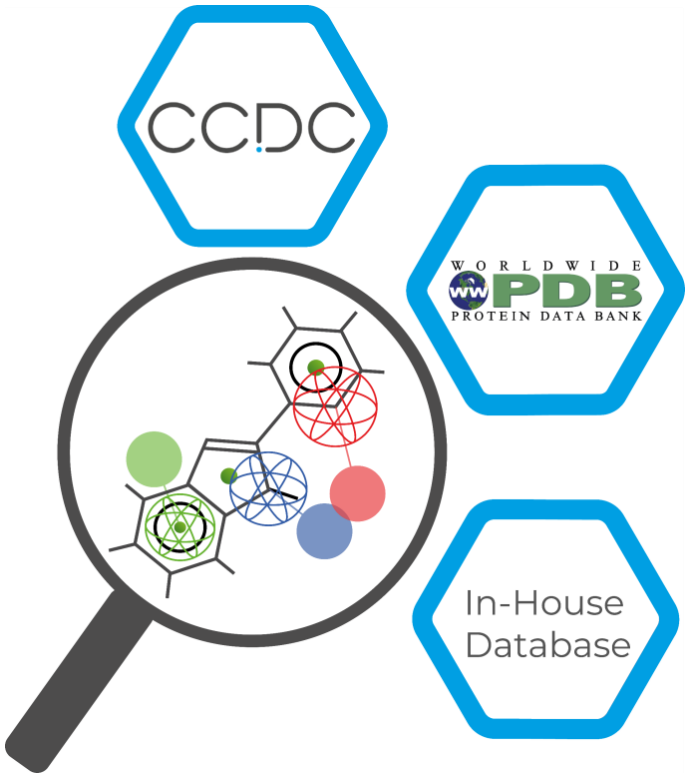
Background



- Pharmacophore-based searches of structural databases (CSD & PDB & any in-house databases, simultaneously) for early stage drug discovery
- Modify a hypothesis/results on the fly: interactive tool!
- Annotated for easy filtering of hits

Korb *et al,. J. Med. Chem.* 2016, 59, 4257-4266. DOI: 10.1021/acs.jmedchem.5b01756

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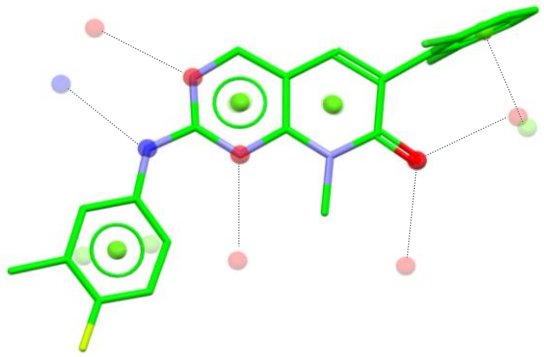
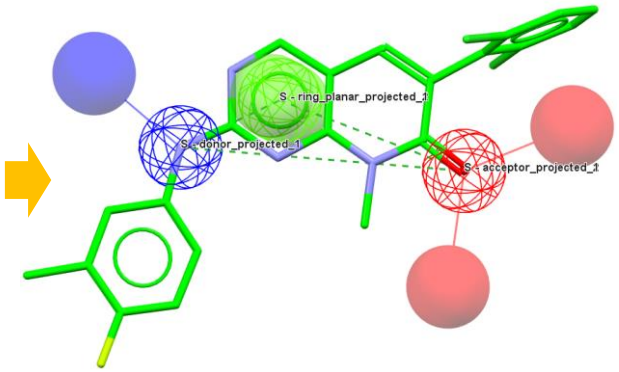
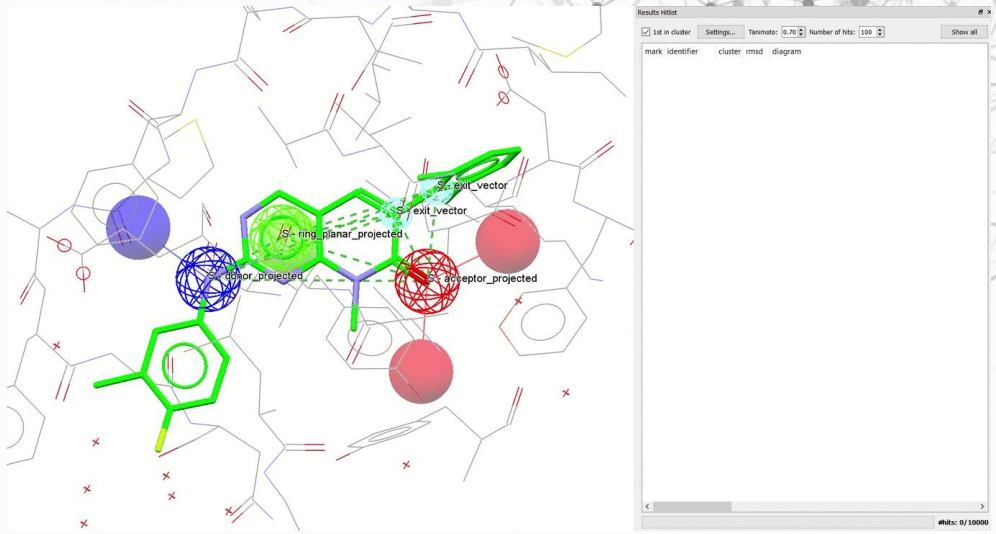
How does it work?



donor
acceptor
planar ring
hydrophobe





Molecules annotated with customisable SMARTS feature definition

Pharmacophore points are defined using the same types of features but with a tolerance sphere

Entries matching the pharmacophore query are overlaid in the 3D view and listed with the 2D diagram showing the features matching the pharmacophore query

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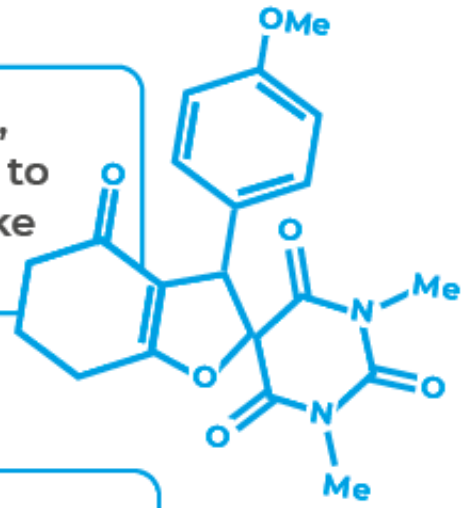
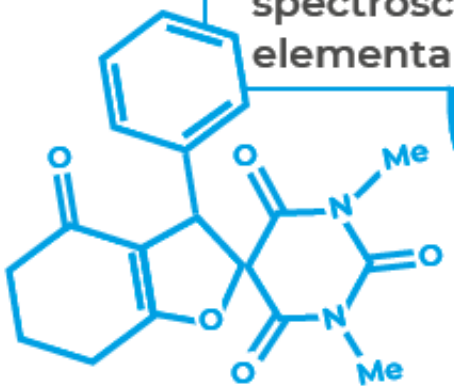
Elinson, M.N. *et al.*
J. Heterocycl. Chem., 2021, 1–12.
doi.org/10.1002/jhet.4274

Multicomponent, one-pot reaction to generate drug-like scaffold



Confirm structure with NMR, IR and Mass spectroscopy and elemental analysis



Scaffold-based search using CSD-CrossMiner of about 300K potential target proteins

Identify a protein (aldose reductase) in complex with a molecule of similar size with similar features

Note relevance of H-bonds and π-π interactions for designing future scaffolds

Further investigate use as aldose-reductase inhibitors via docking studies

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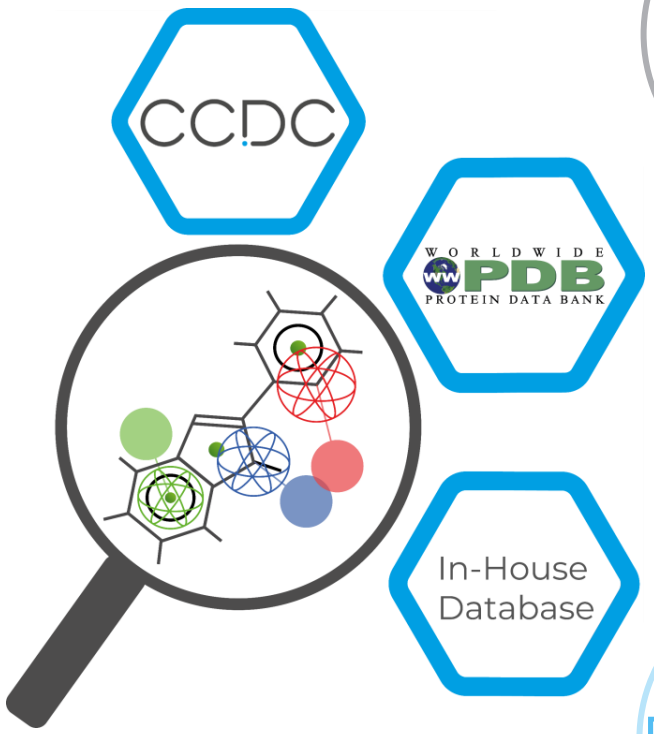
Why improving CSD-CrossMiner?

- From user feedback:
  - Difficult to distinguish between protein and ligand
  - Do I have access to CSD-CrossMiner?
  - Better integration with other tools
  - I don’t really need organo-metallic structures
  - Flexibility in the search – OR/NOT Boolean operators
  - Don’t let me think about SMARTS
  - Reusable sessions
  - More available databases
  - …

What?



Visibility

- One installer for CSD-Discovery suite
- Integration with Hermes (protein-ligand visualiser)

Usability

- Style & colour of different components
- Style & colour reference and hits

Flexibility

- Customisable excluded volume
- Exclude organometallic structures

https://www.ccdc.cam.ac.uk/solutions/whats-new/

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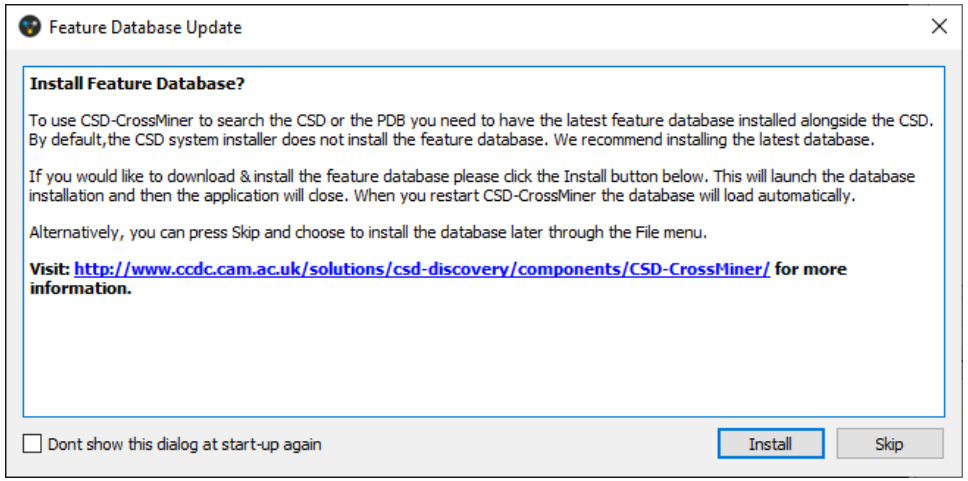
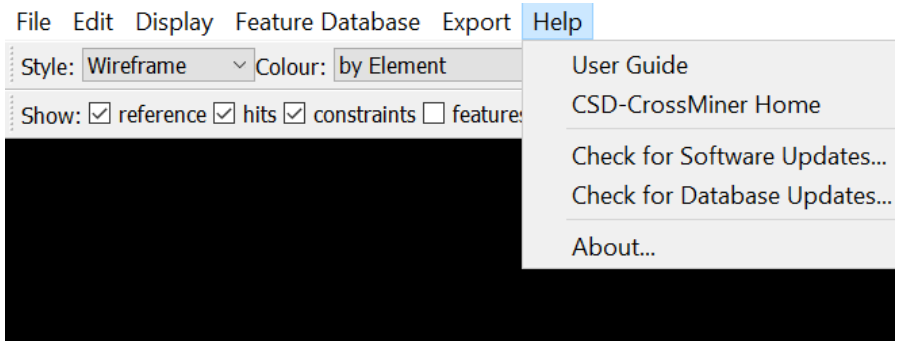
Visibility - Include CSD-CrossMiner in the CSDS installer

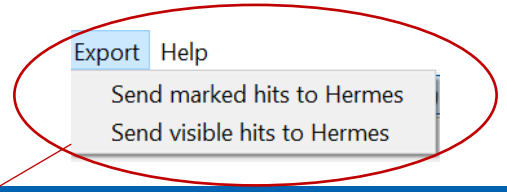
- Include CSD-CrossMiner software in the CSDS installer:
  - CSD-CrossMiner software added to the Discovery component of the CSD software portfolio
  - CSDS software update will also update CSD-CrossMiner software
  - When opening CSD-CrossMiner a pop-up window will guide you to download the feature database
  - Built-in auto-update mechanism that makes updating both the software and the database easy

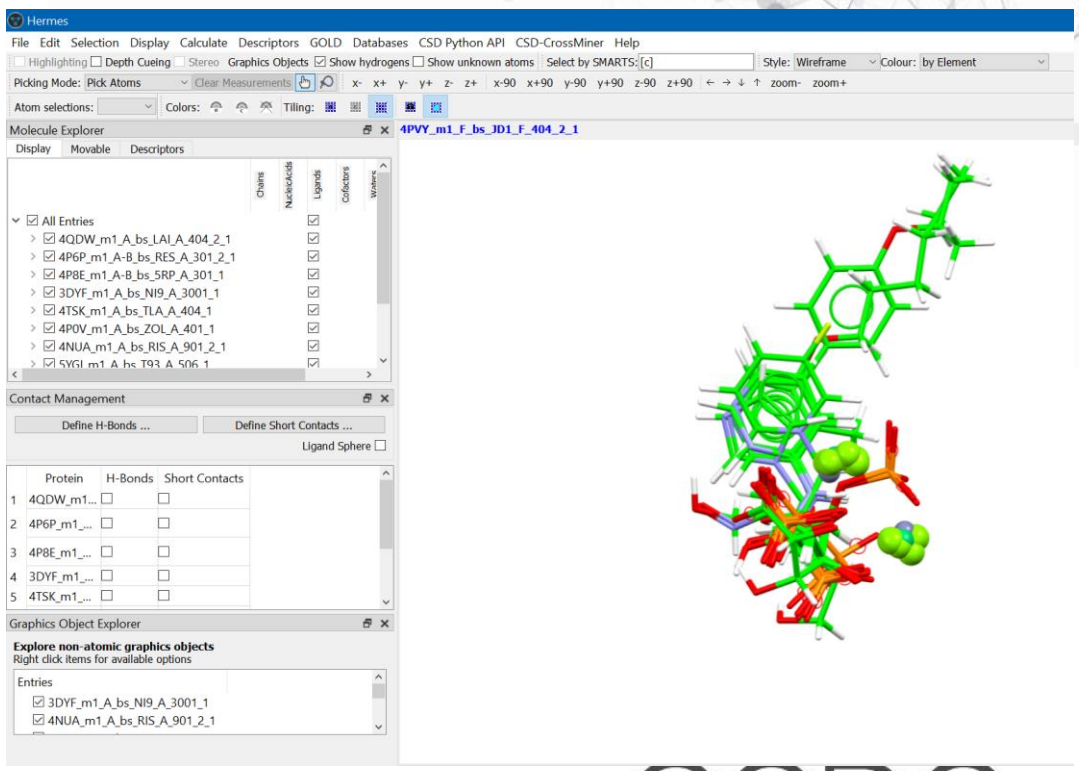




Visibility - Integration with Hermes

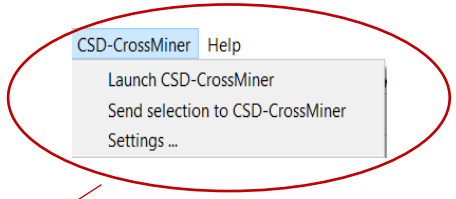
- Export hits to Hermes

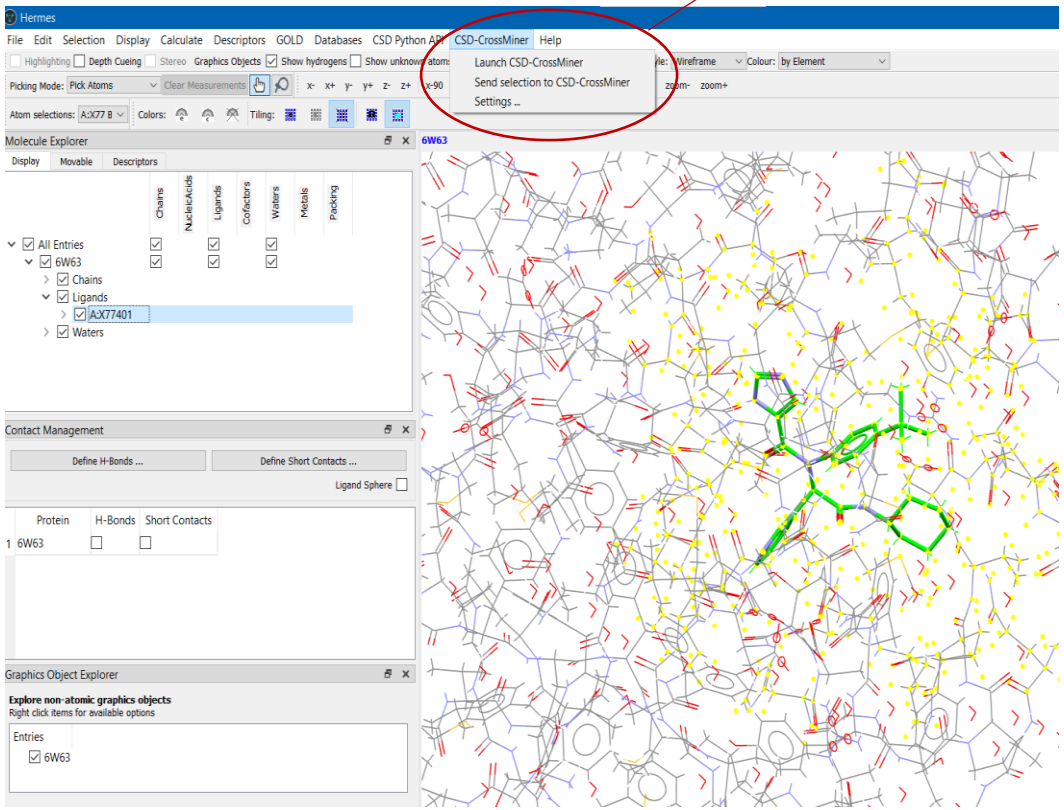


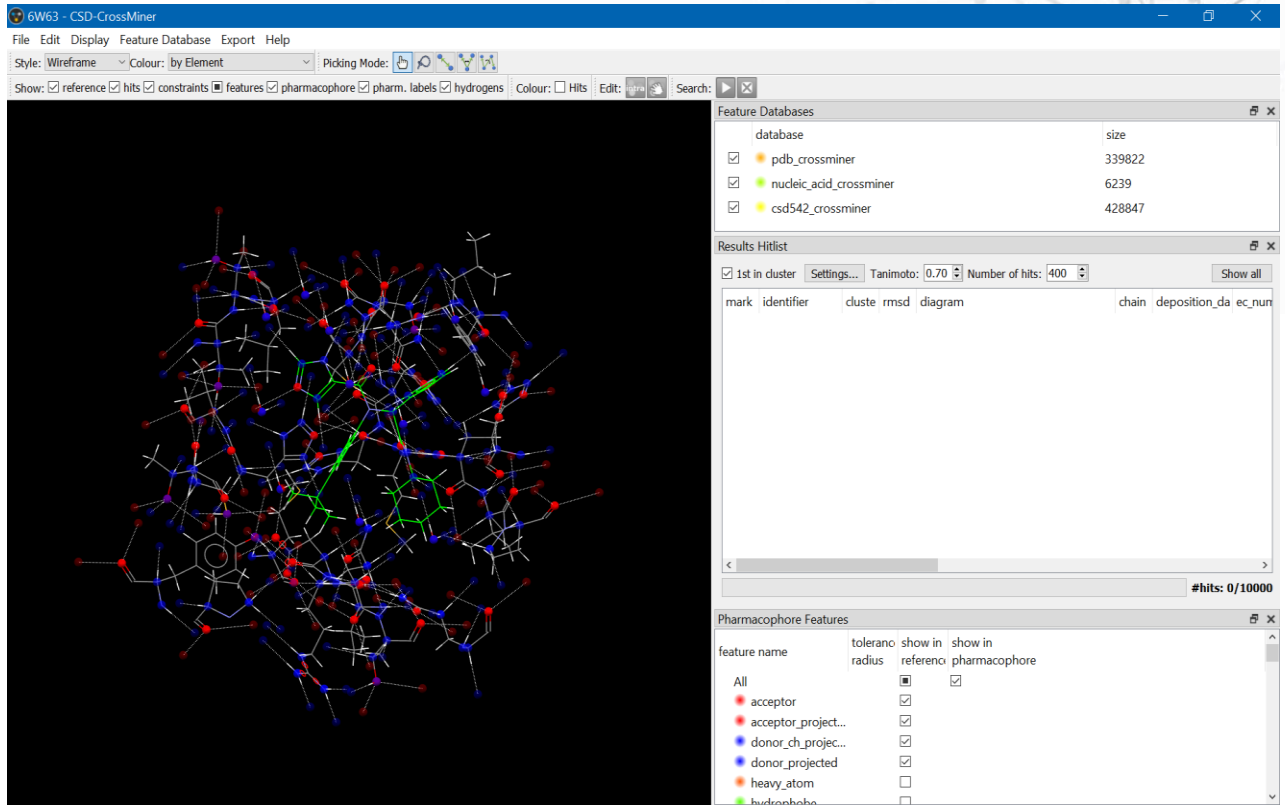


Visibility - Integration with Hermes

- Launching CSD-CrossMiner from Hermes

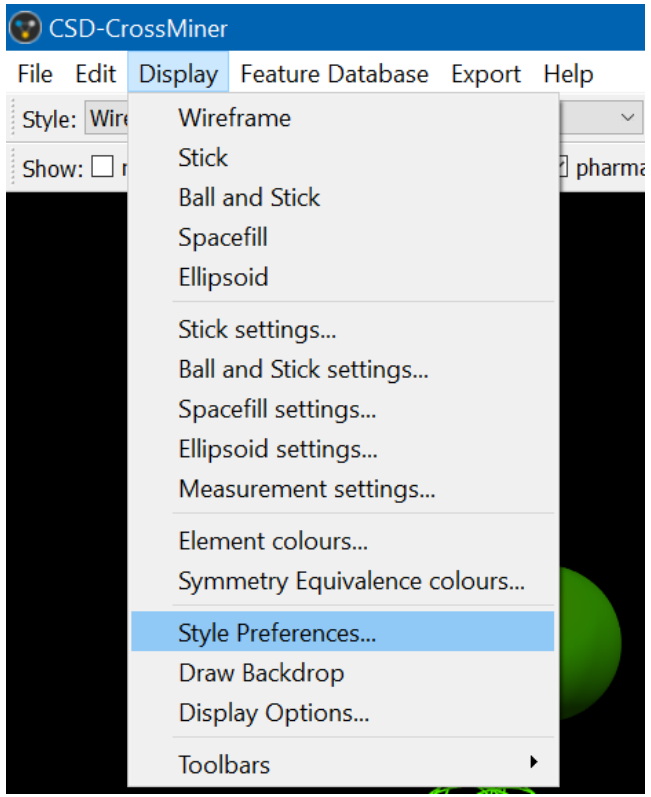


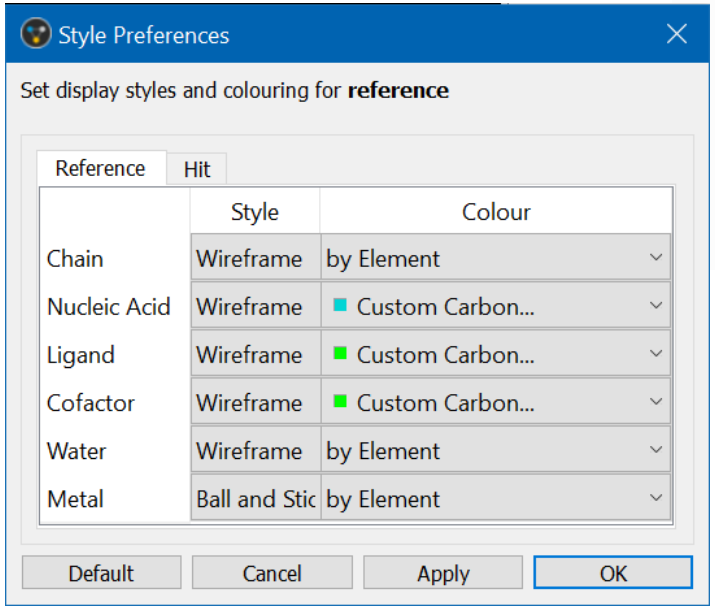


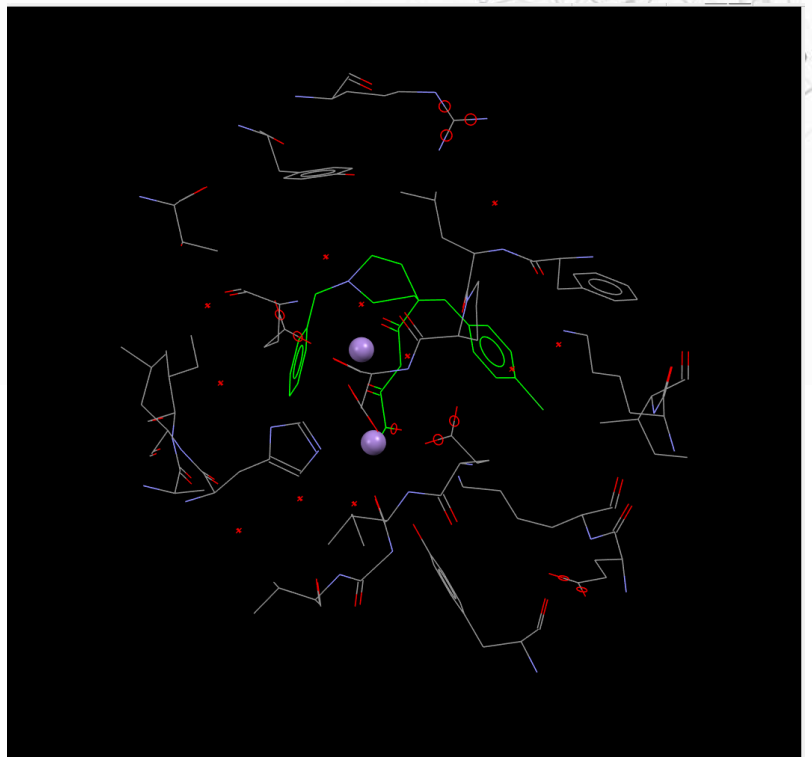


Usability – Style/colour of different components

- Style Preferences... menu to style and colour different components of both reference molecule and hits

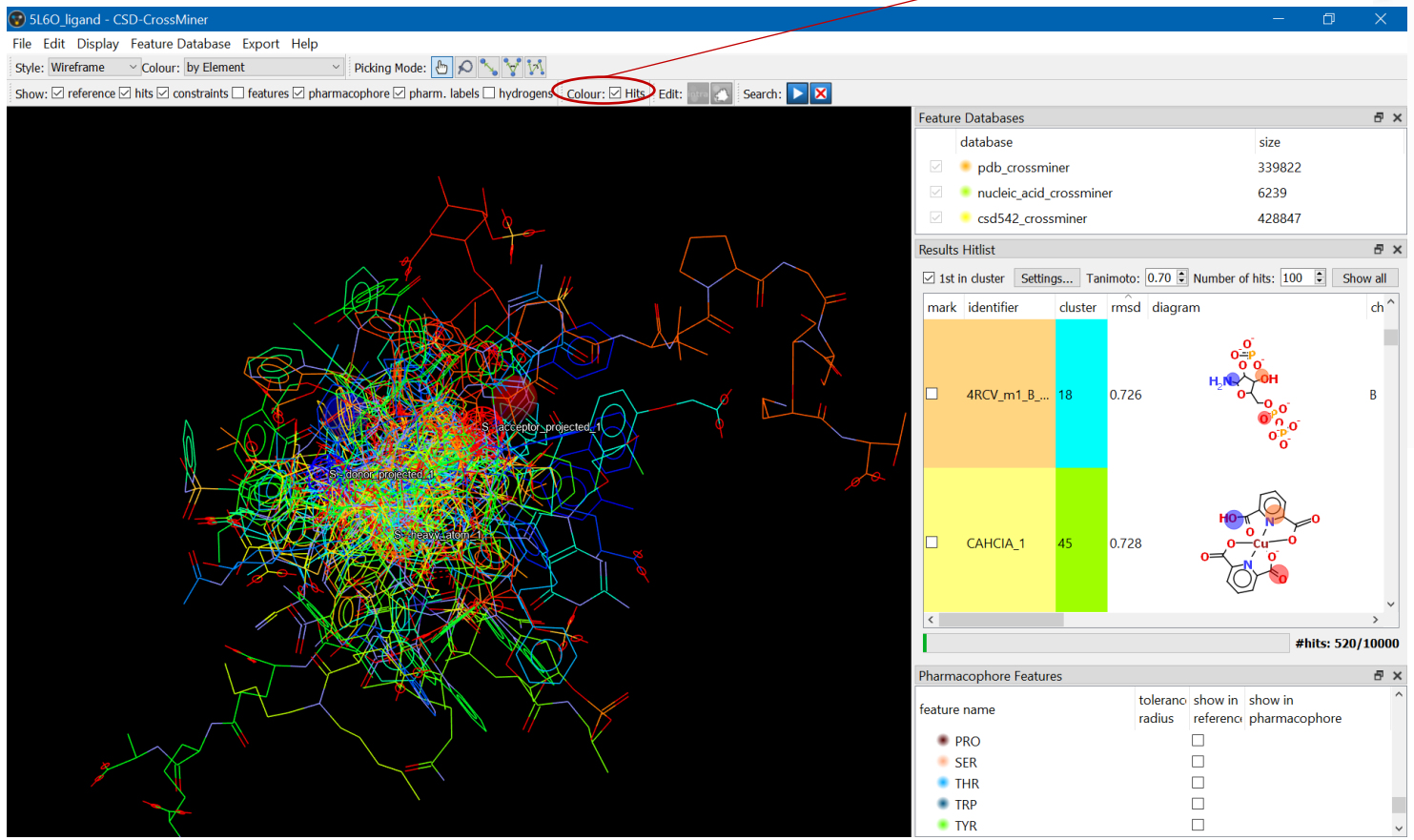






Usability – Colouring hits

- Colour hits by rainbow



- Colouring is applied when the pharmacophore search is paused or completed
- Colouring is applied to the cluster
- Hits of the same cluster have the same colour

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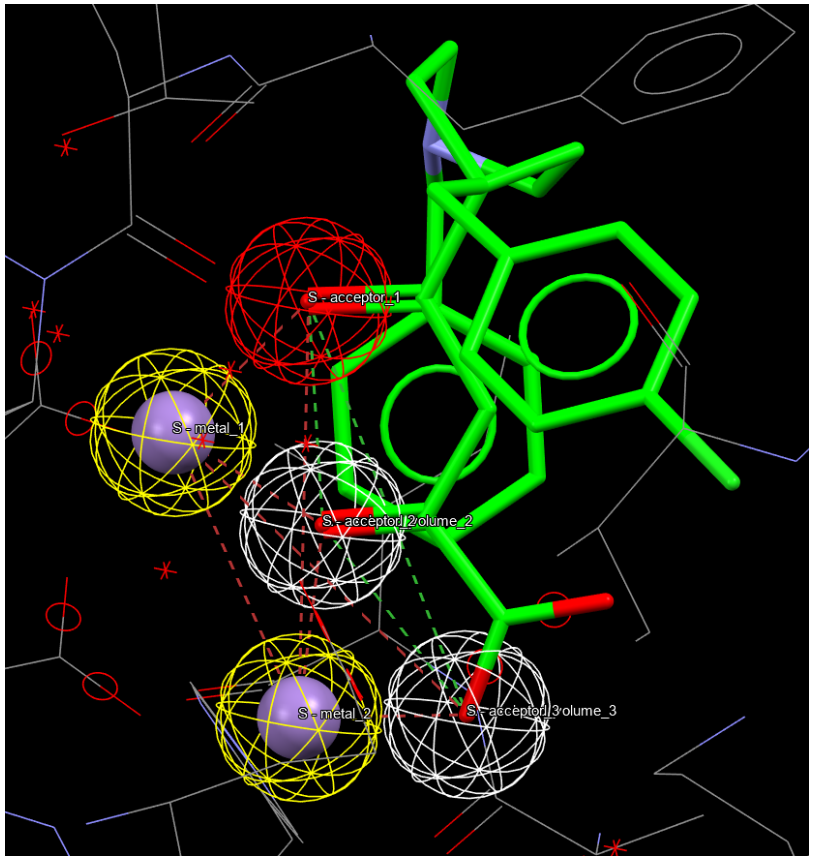
Flexibility – Customisable excluded volume

- Customisable exclude volume (NOT feature) – Exclusion sphere(s) such that only defined moieties are excluded from a region.



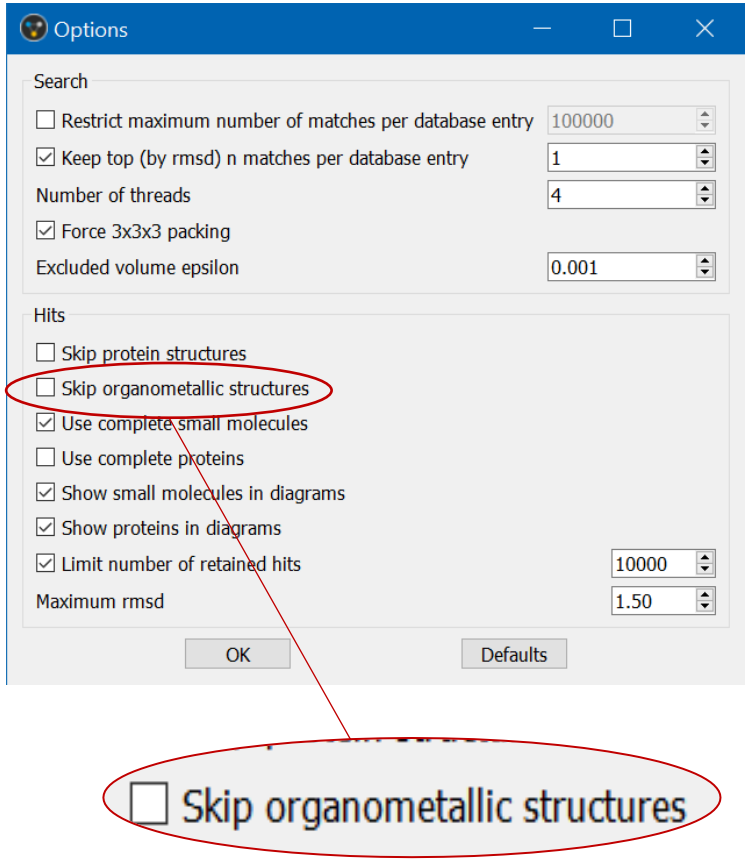
- Moieties are specified using SMARTS patterns.

Pharmacophore Features

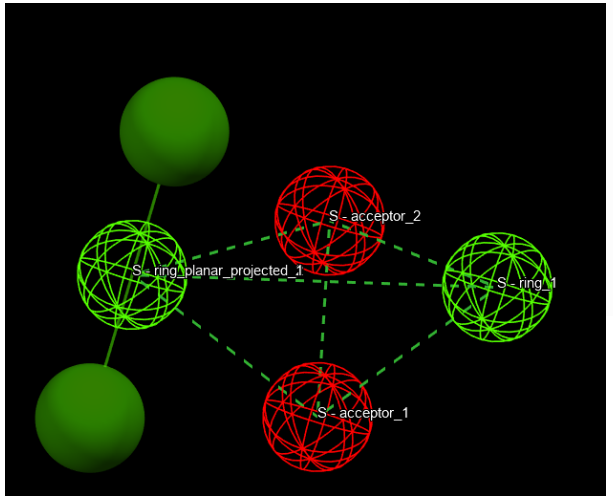
feature name	tolerance radius	show in referenc	show in pharmacophore
B	1.00		
Excluding atoms (SMARTS)	[#15]~[#8]		
excluded_volume_3			☑
B	1.00		
Excluding atoms (SMARTS)	[#15]~[#8]		
annotation_filter		☐	
substructure_filter		☐	

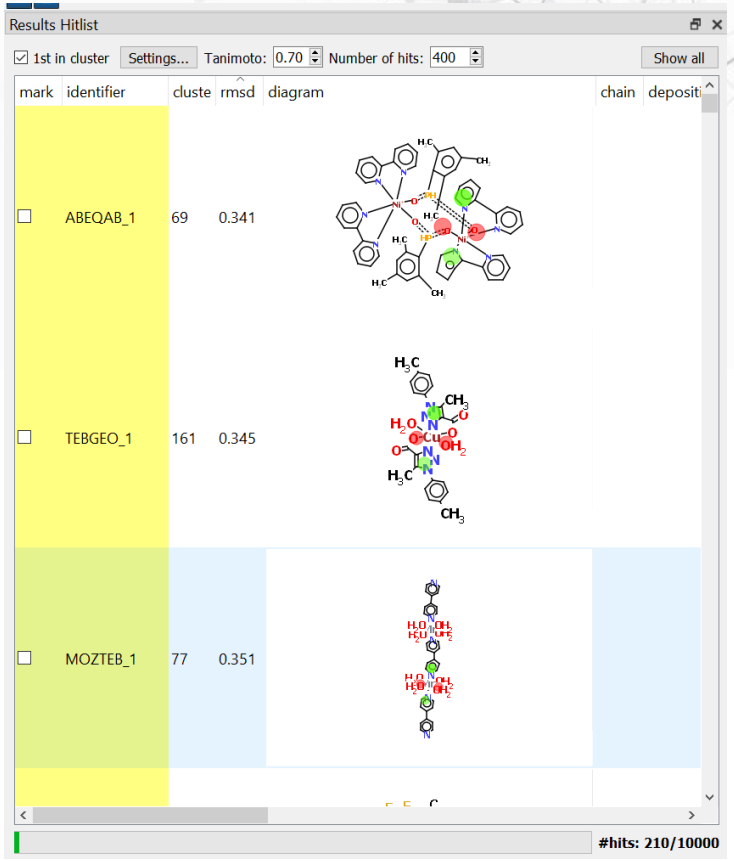
Flexibility – Excluding organometallic structures

- Provided the option to exclude organometallic structures from the search



- Hits containing at least one transition metal, lanthanide, actinide, or any Al, Ga, In, Tl, Ge, Sn, Pb, Sb, Bi, Po will be excluded from the search





Additional new features

- Easy way to select a reference molecule in CSD-CrossMiner
- Optimised the Style/Colour style behaviour
- Improved the generation of the feature database
- Easy way to select protein-ligand binding site in Hermes

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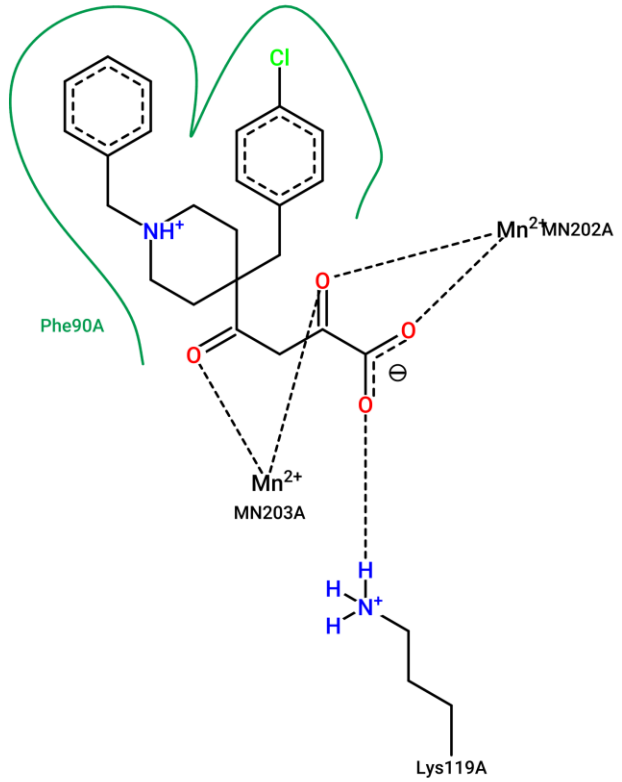
Demo

- Performing a pharmacophore search using CSD-CrossMiner



PDB code 5FDG

- Influenza polymerase acidic protein N-terminal domain (PAN) in complex with high potency endonuclease inhibitor (0N8)
- 0N8 chelate to the metal ions by its metal-chelation motifs
  - What other metal-chelation motifs are in the PDB?
  - What about in the organic subset of the CSD?

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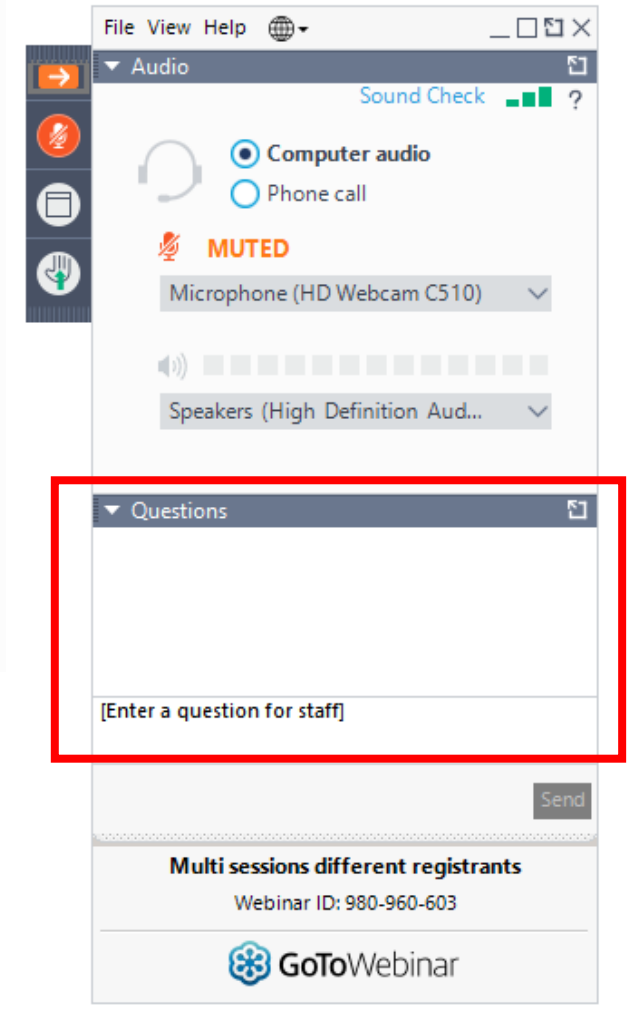
Q&A

- Type your questions in the box as shown



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Next What's Up Webinar

- Next webinar: **20th January 2022**

- Follow us on social media
- Send us your ideas and news

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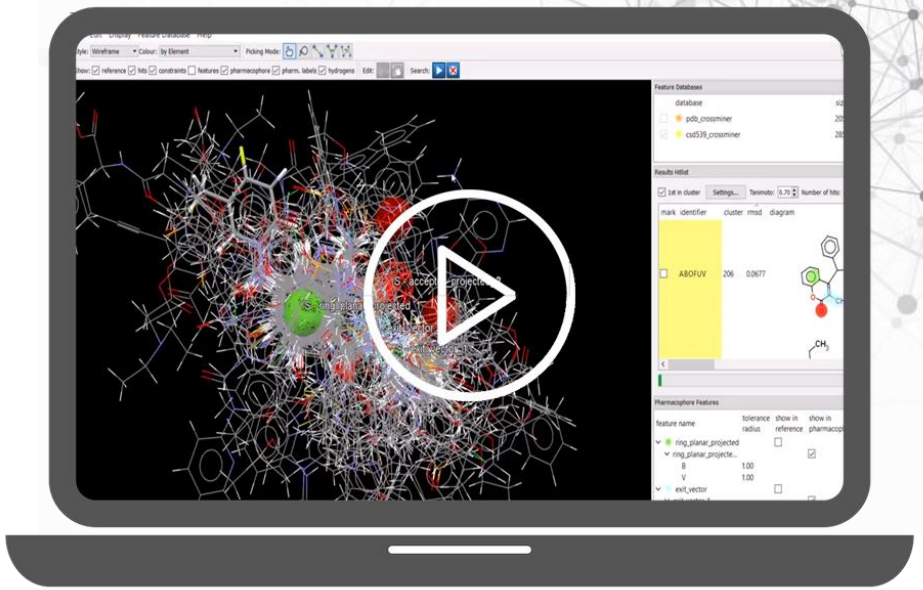

Thank you

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