Basics of Protein Ligand Docking using GOLD

CCDC Virtual Workshop November 2021 – Session 2

Rupesh Chikhale, Francesca Stanzione, Abhik Mukhopadhyay, Ilaria Gimondi, Suzanna Ward, Yinka Olatunji-Ojo

9 November 2021

CCDC
advancing structural science

Learning outcomes for today

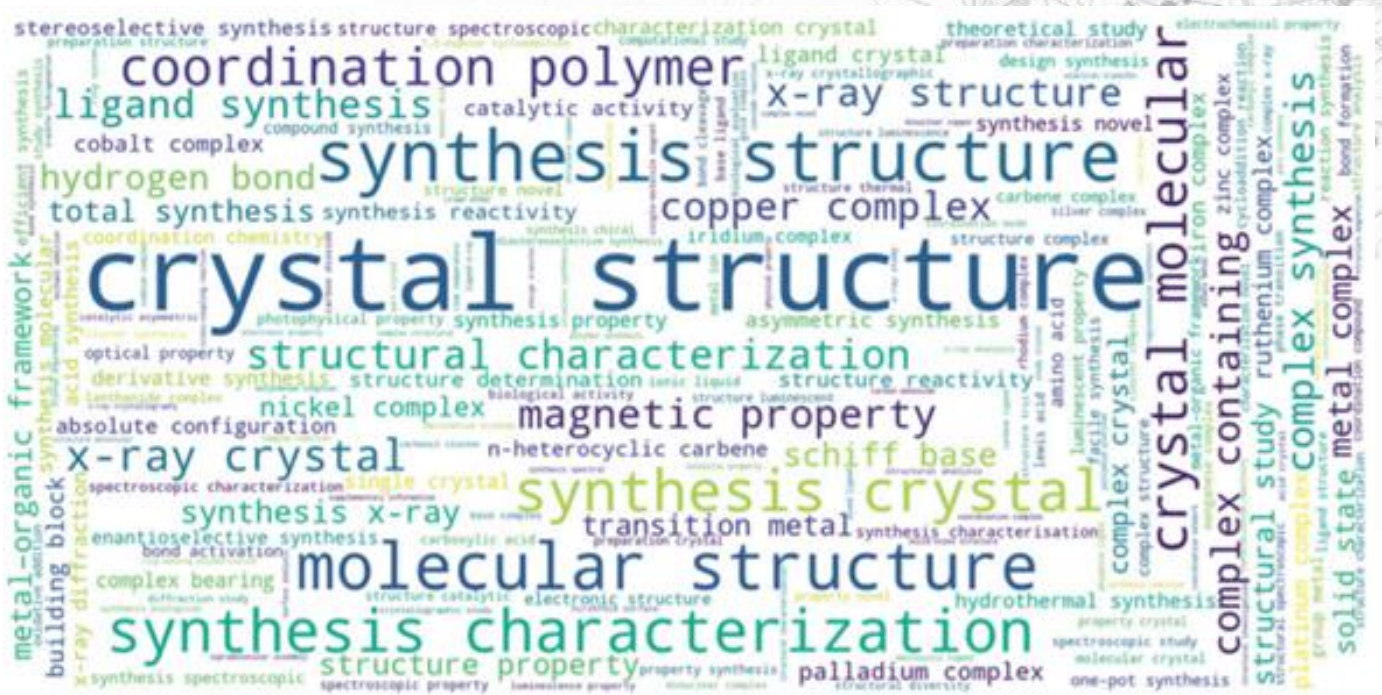
- The basics of GOLD and our Hermes interface.
- How to run a standard protein ligand dock.
- How to identify the correct binding modes reliably and with confidence.
- The basics of how GOLD can be used in virtual screening and lead optimisation.

CCDC

The CSD in research

The *Web of Science* subject categories that cite the 2006-2016 CCDC standard references most frequently

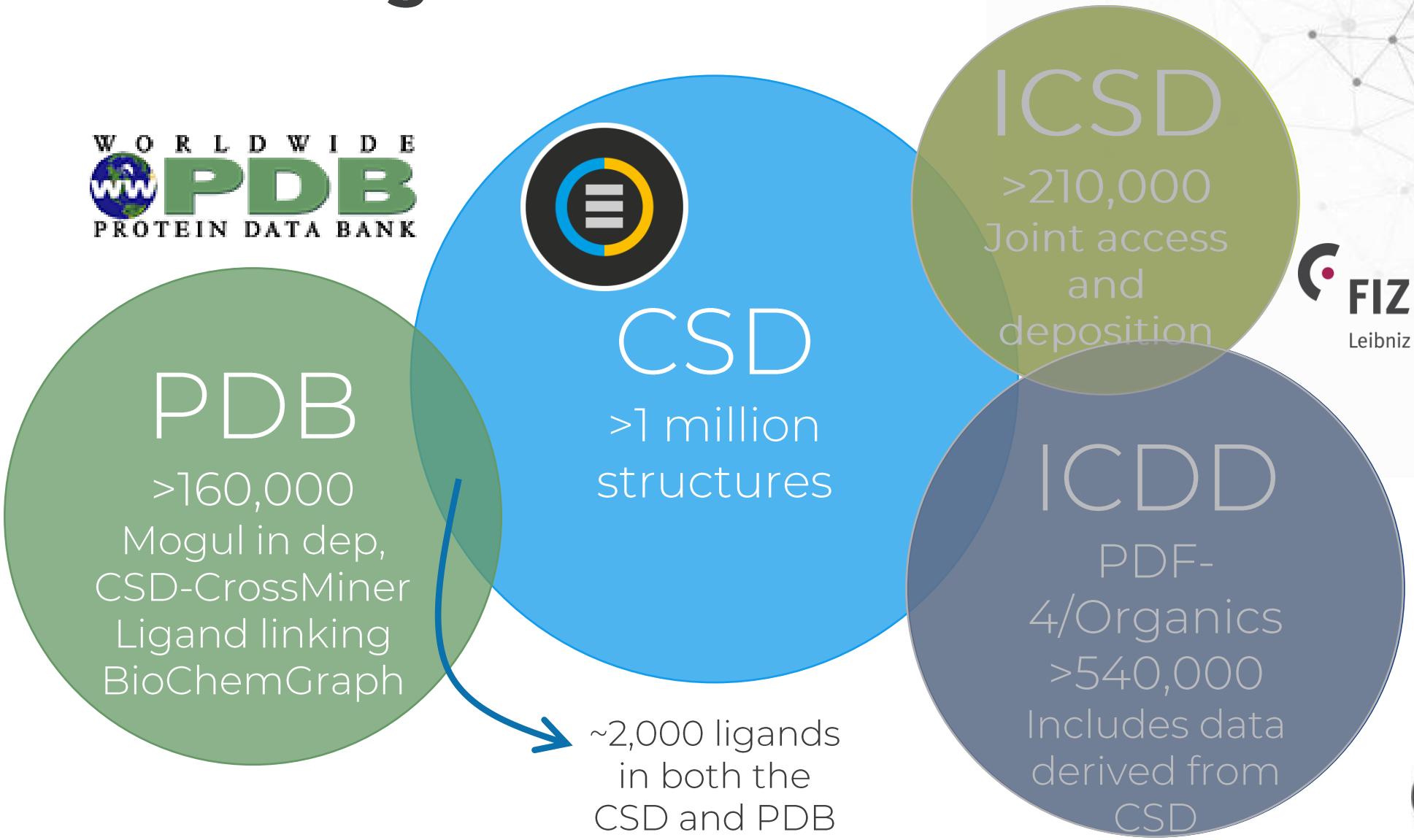
Subject category	Citations
Crystallography	5256
Chemistry Multidisciplinary	3275
Chemistry Inorganic Nuclear	1931
Chemistry Physical	1148
Materials Science Multidisciplinary	864
Chemistry Organic	568
Biochemistry Molecular Biology	307
Physics Atomic Molecular Chemical	203
Chemistry Medicinal	185
Spectroscopy	181



A word cloud of common bigrams in the titles of publications containing CSD-compliant crystal structures.

Willett P. et al, CrystEngComm, 2020,22, 7233-7241 DOI:10.1039/D0CE00045K

More integrated structural databases



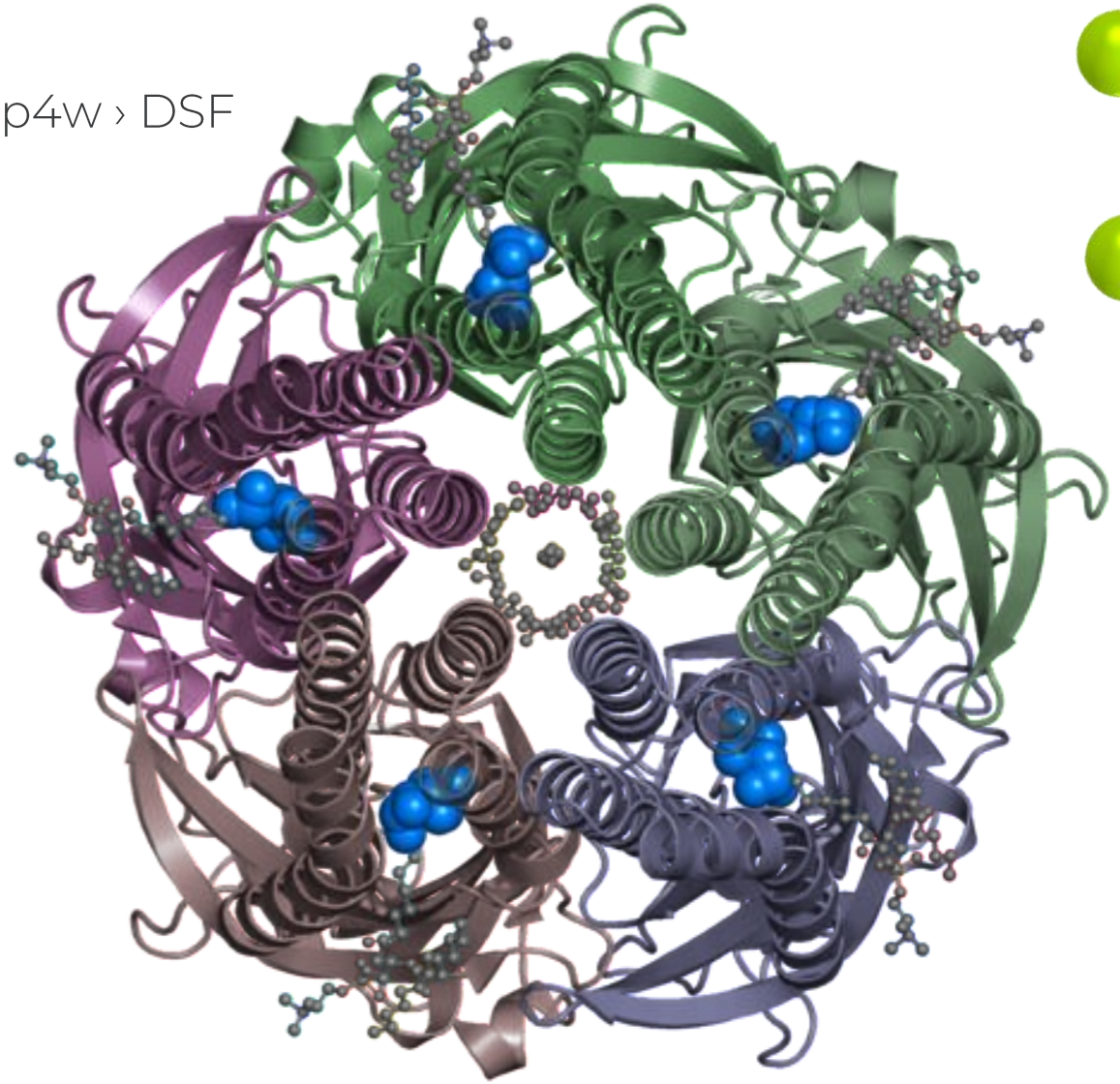
FIZ Karlsruhe
Leibniz Institute for Information Infrastructure

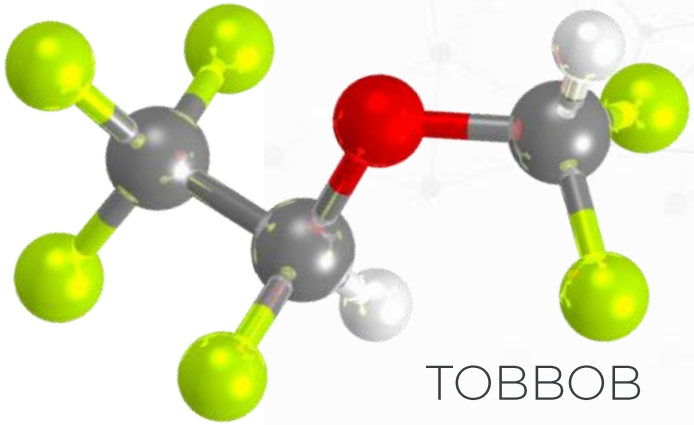
ICDD

CCDC

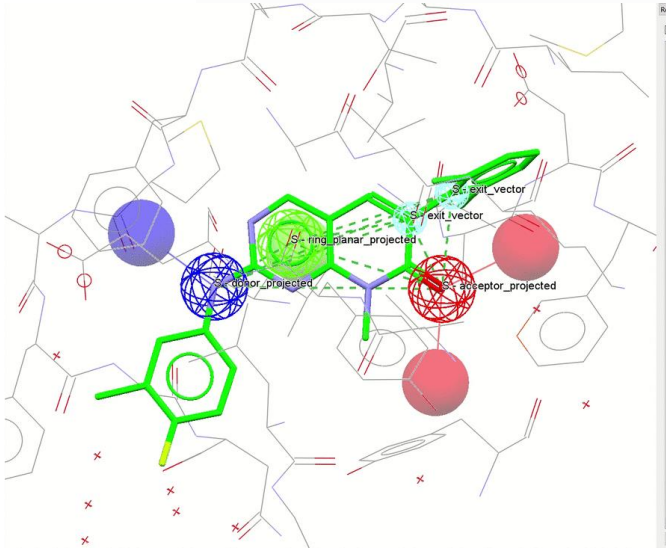
Connecting chemistry and biology

3p4w › DSF



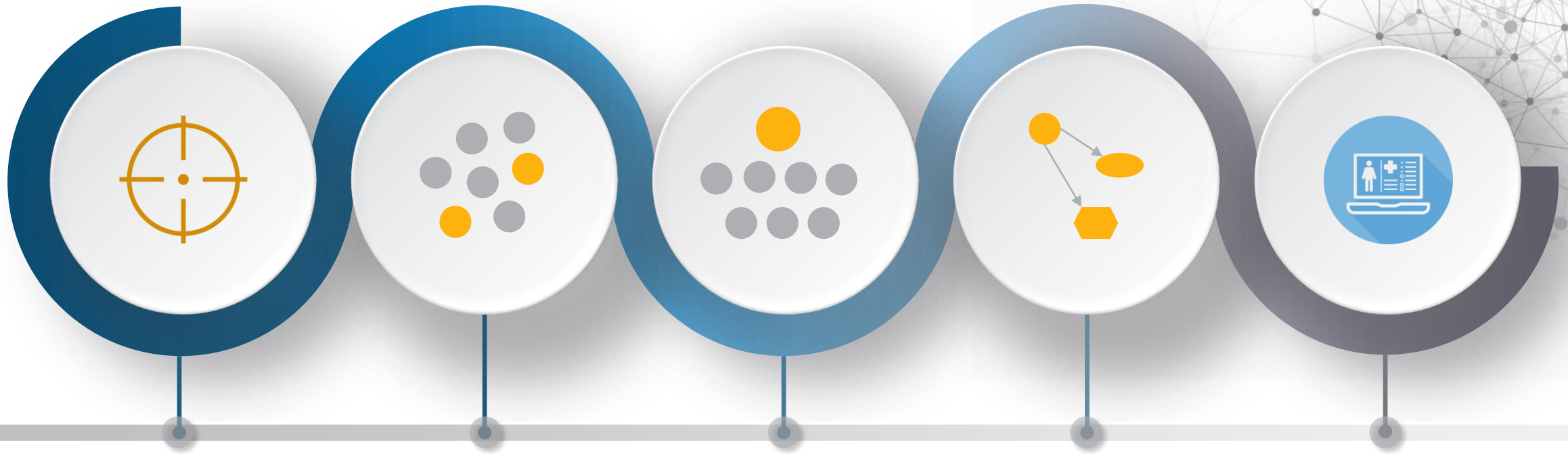


TOBBOB



CCDC

Drug Discovery Pipeline



TARGET SELECTION

HIT IDENTIFICATION

Structure- based virtual screening.

HIT TO LEAD

Assess how changes affect binding.
Optimize compound geometry.
Predict binding of small molecules to active pockets in proteins.

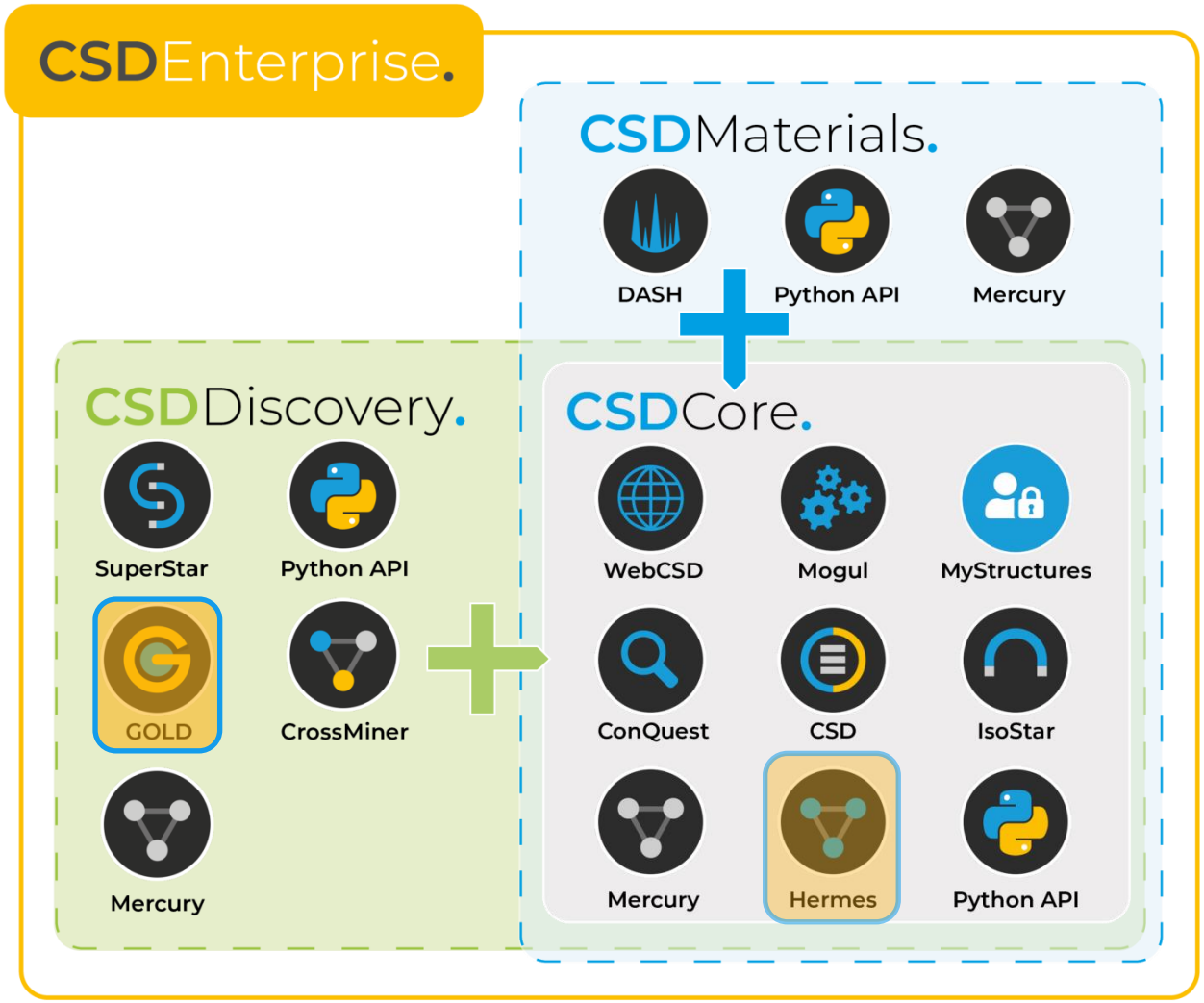
LEAD OPTIMISATION

Check the impact of changes with docking pose prediction.
Understand how changes affect conformations.

DRUG DEVELOPMENT

CCDC

The CSD software

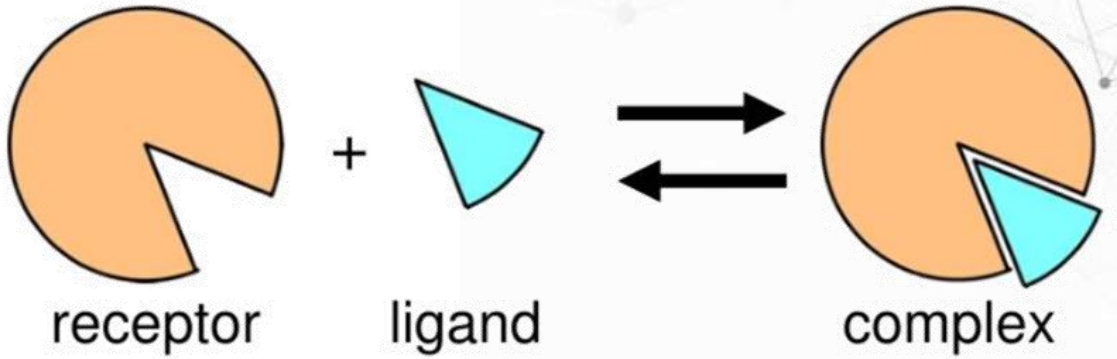


Professional Services

Research & Knowledge partnerships

CCDC

Docking



Docking studies are computational techniques for the exploitation of the possible binding modes of a substrate to a given receptor, enzyme or other binding site.

Ref: IUPAC, 1997, 69, 1137.

CCDC

GOLD: Protein-Ligand Docking Software

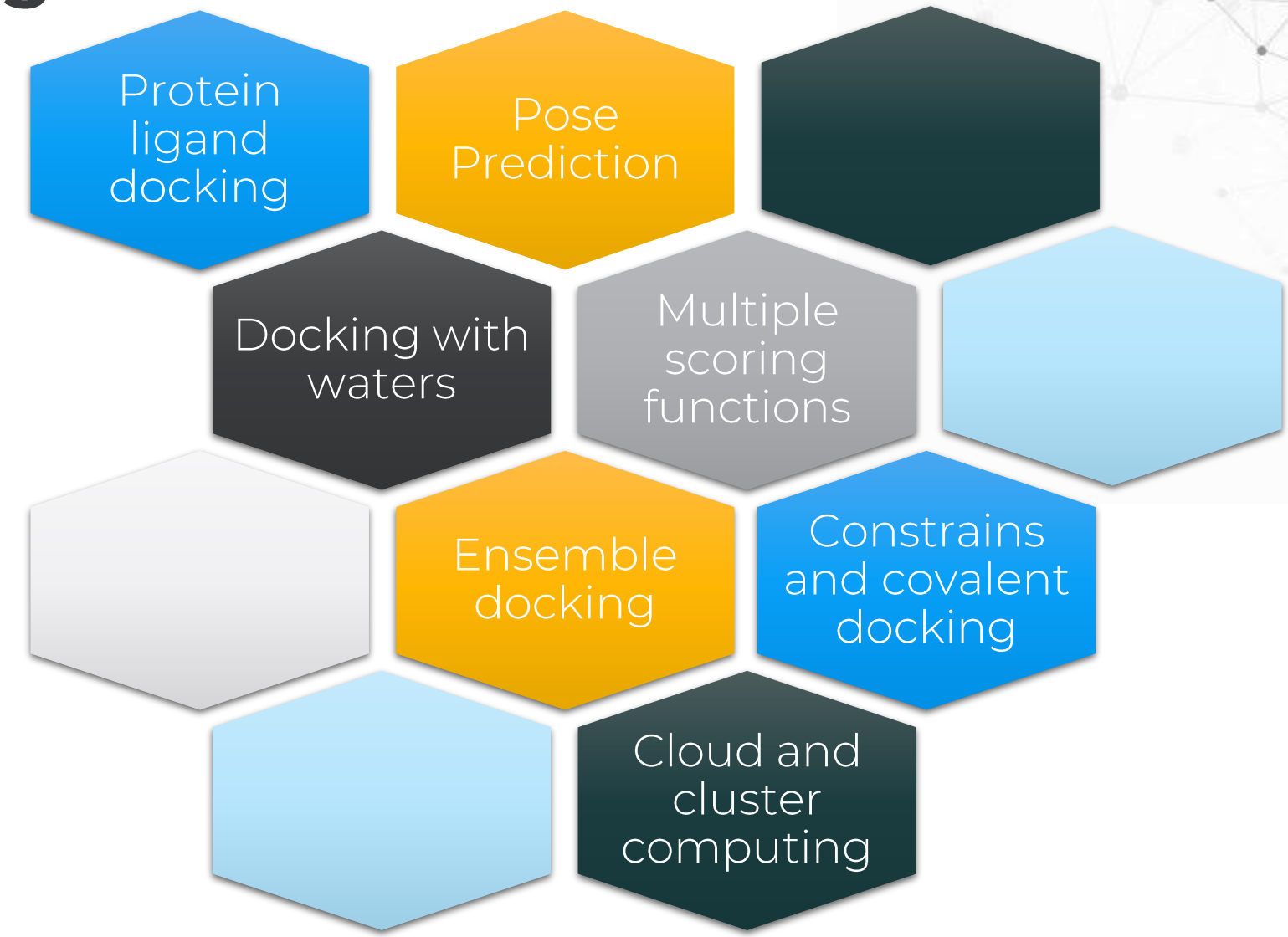
- GOLD has proven success in virtual screening, lead optimisation, and identifying the correct binding mode of active molecules.

- Relied on by researchers in academia and industry worldwide.

- Reliable
- Flexible
- Configurable

CCDC

GOLD: The all in one molecular docking package



CCDC

What are we going to learn today?

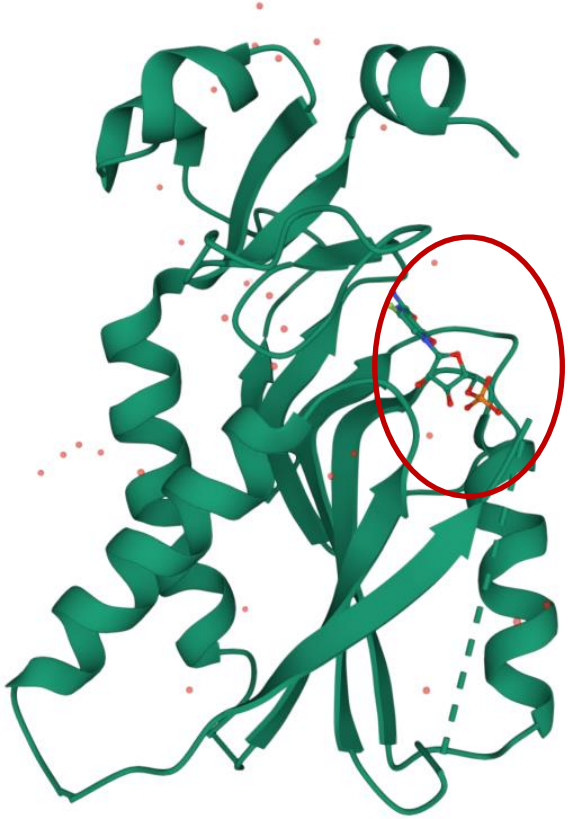
- Protein-ligand docking in the presence of water molecules
  - Water molecules in the binding site of a protein could form hydrogen-bonded networks and stabilise the protein-ligand interaction
  - Adds to specificity of ligand recognition
  - Stabilises the conformation of the active site of enzymes

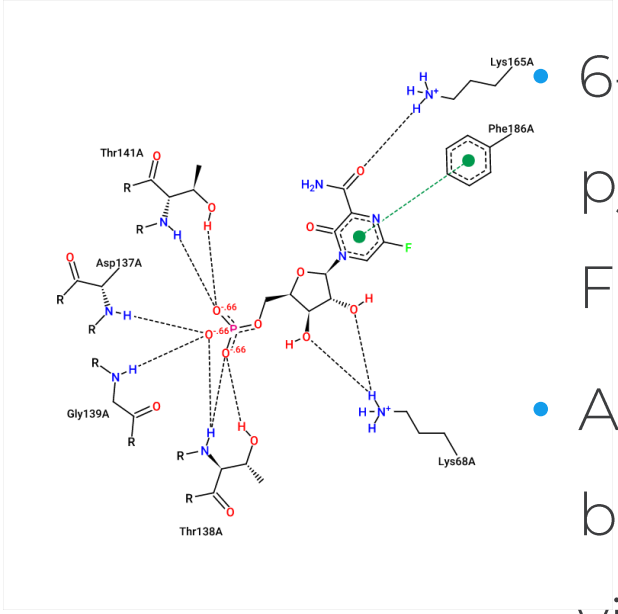
Ladbury, J E., *Chem.Biol.* (1996), 3, 973-980.

CCDC

Docking with GOLD: Case Study

PDB: 4KN6





- Human hypoxanthine-guanine phosphoribosyl transferase.
- 6-Fluoro-3-hydroxy-2-pyrazinecarboxamide (T-705), aka Favipiravir.
- A novel antiviral compound with broad activity against influenza virus and diverse RNA viruses.

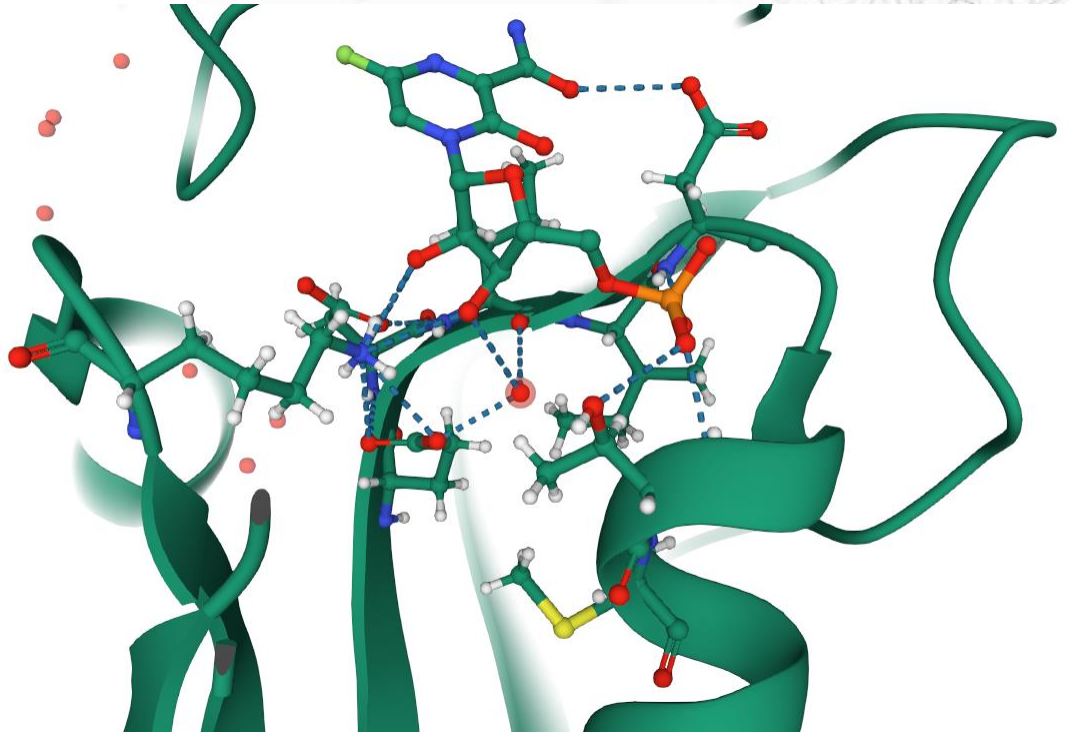
Balzarini, J. (2013) *Mol Pharmacol* 84: 615-629.

CCDC

Docking with GOLD: Case Study

- T705 is a prodrug, it is converted to T-705-ribose-5'-triphosphate (T-705-RTP).
- Water molecule HOH405 forms interactions with ILE134 and GLU132.
- The presence of this water molecule HOH405 affects the binding conformation of the ligand.

PDB: 4KN6

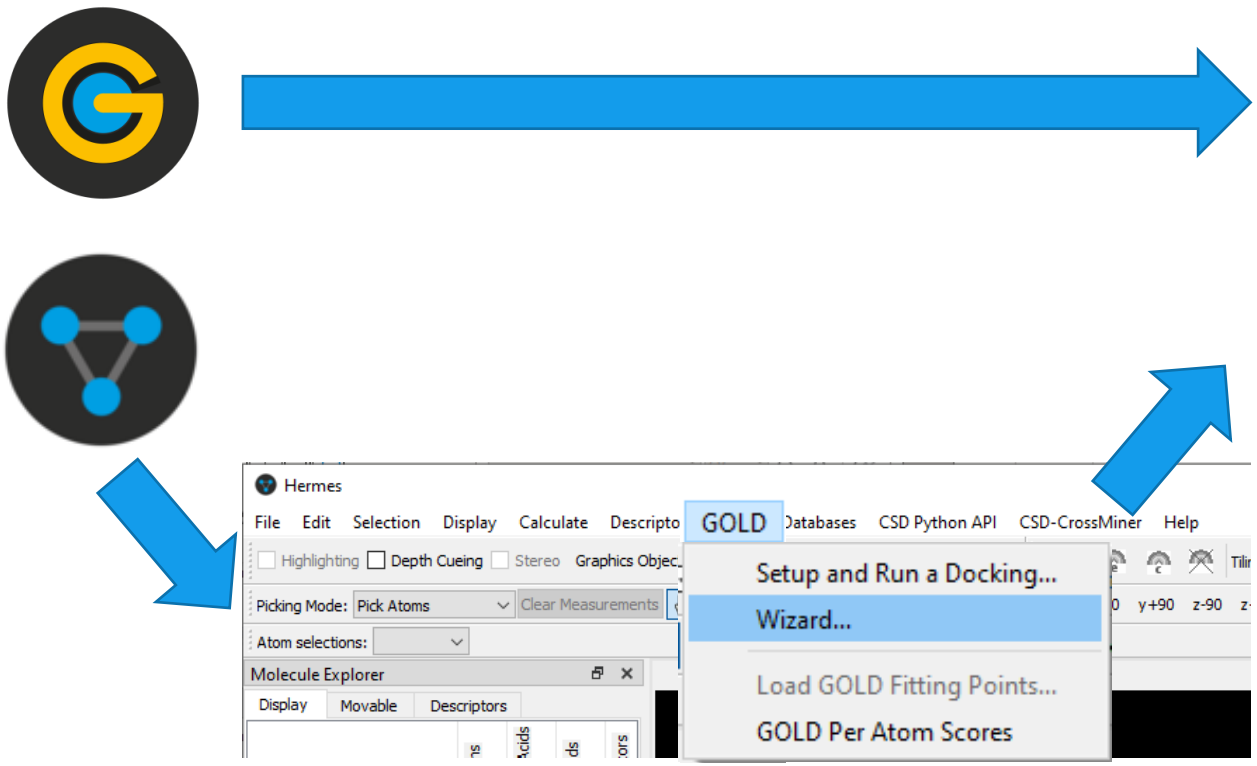


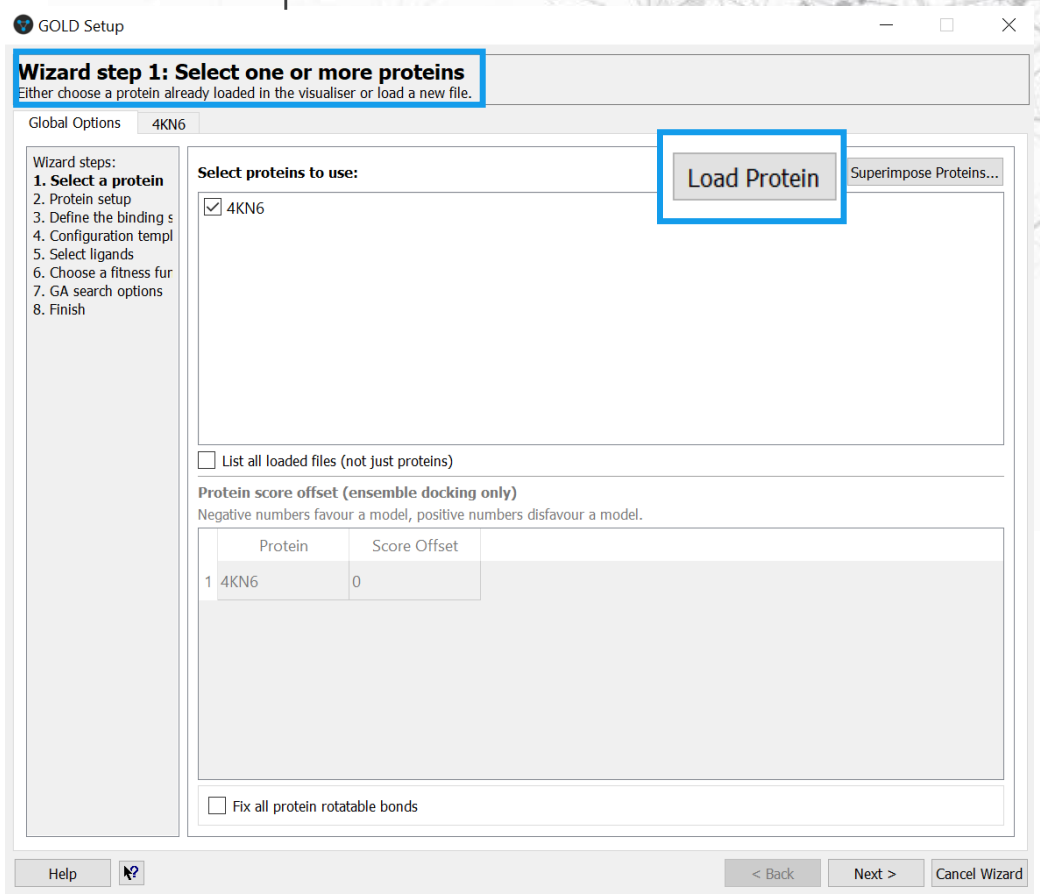
Balzarini, J. (2013) *Mol Pharmacol* 84: 615-629.

CCDC

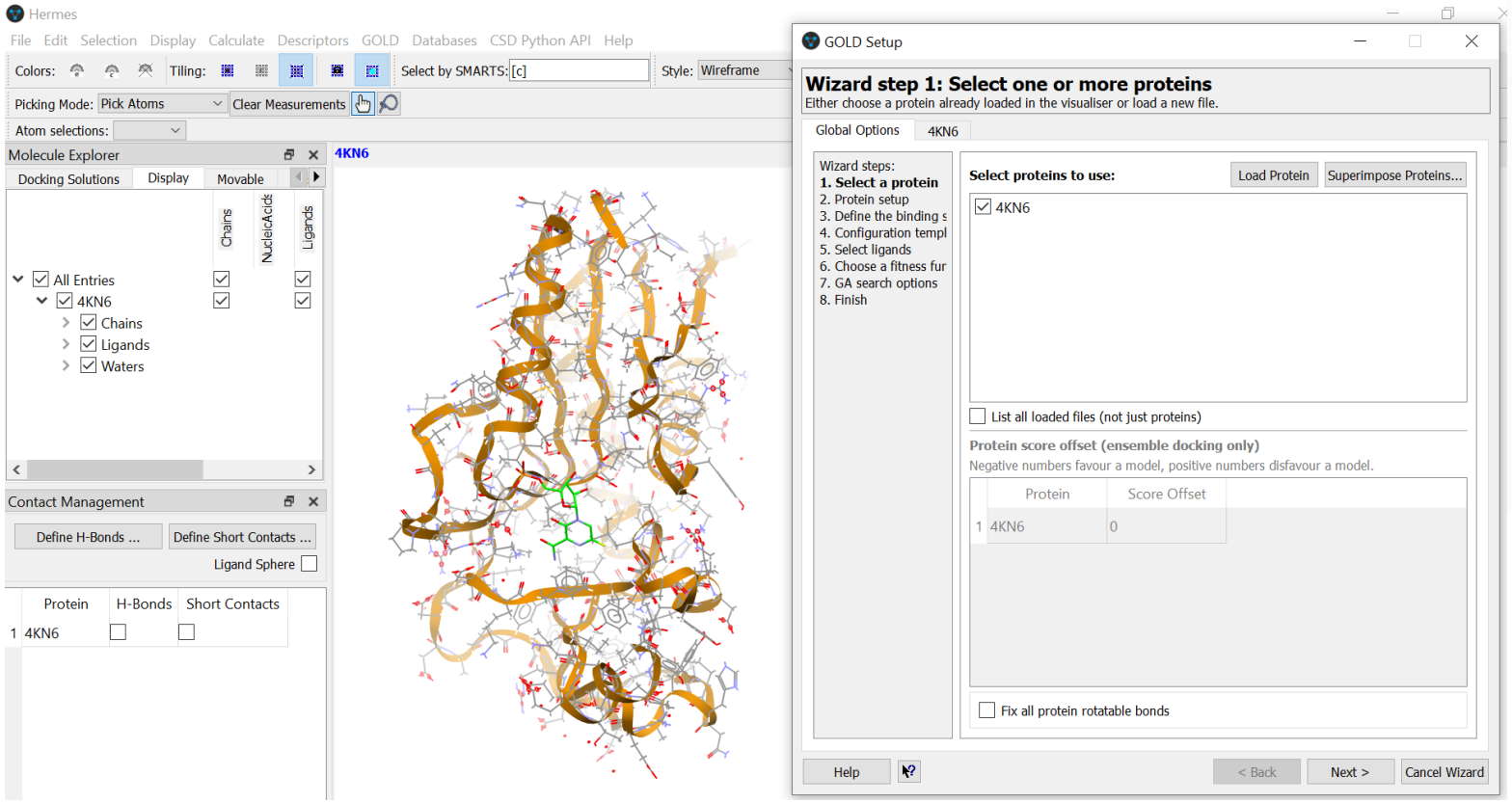
Docking with GOLD: Protein preparation

- Open the GOLD docking wizard…
- …and load the protein.



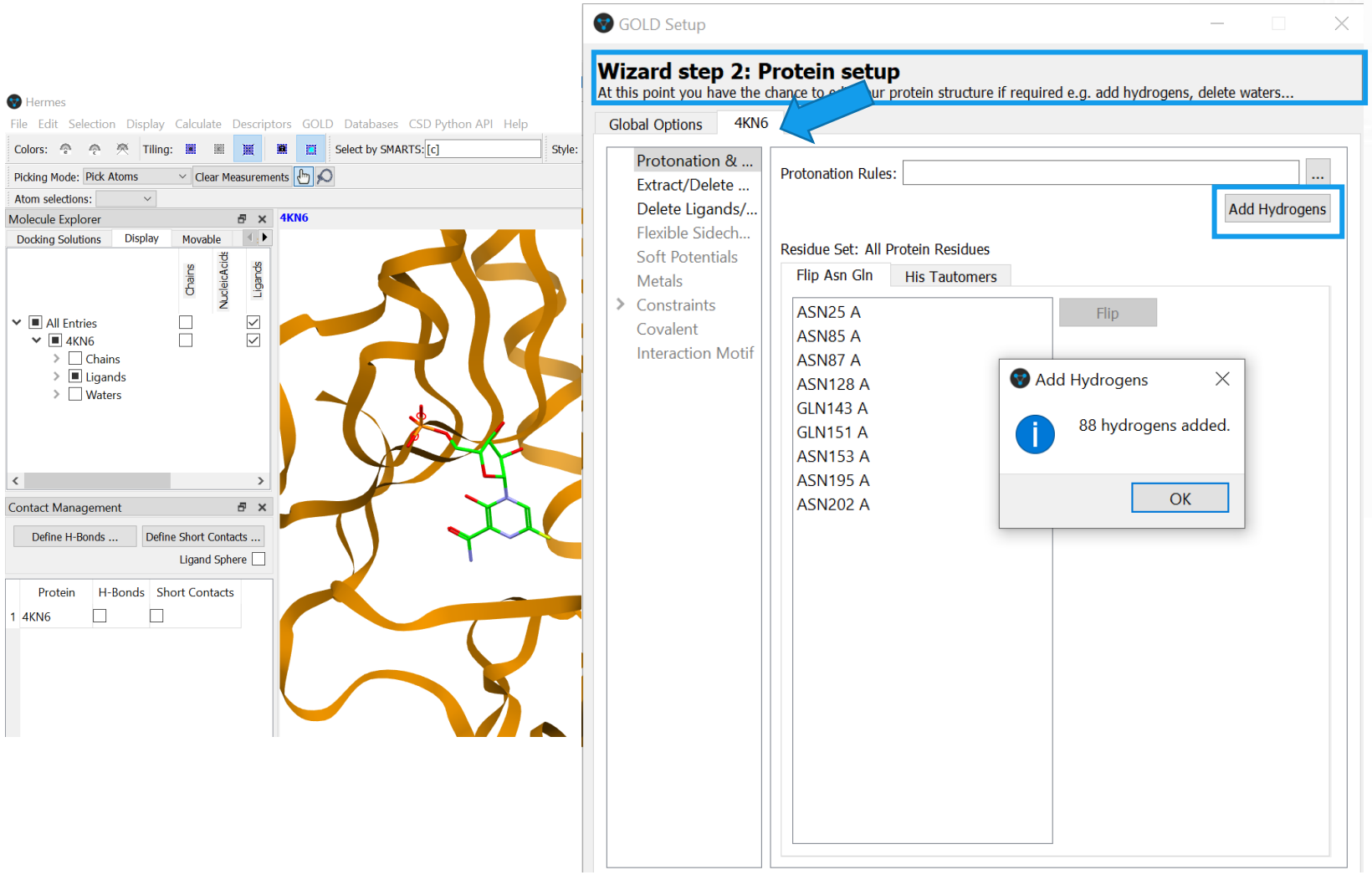


Docking with GOLD: Protein preparation



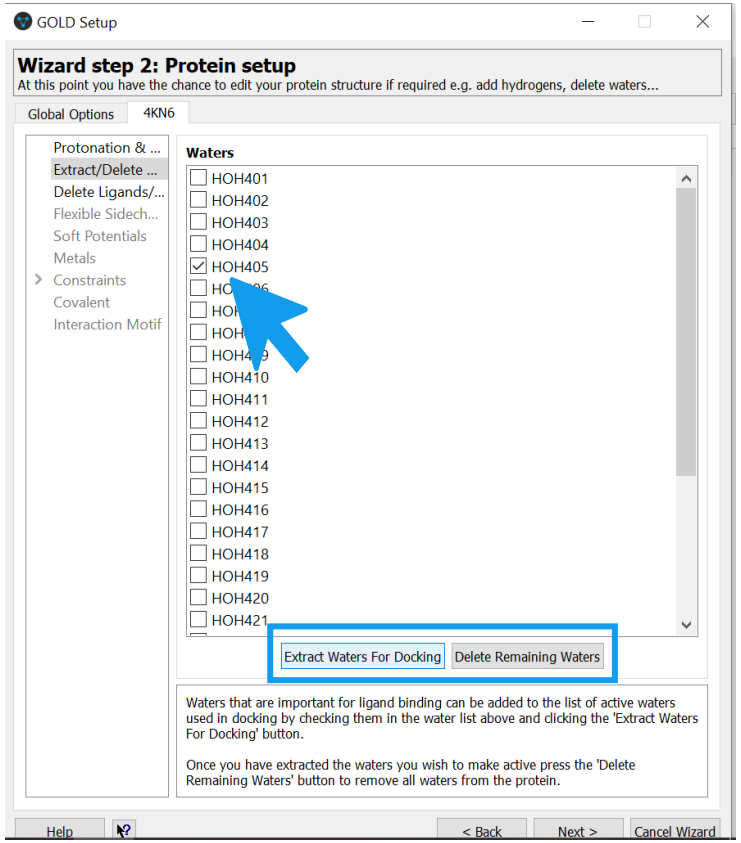
- The protein structure can be visualised in various representations.

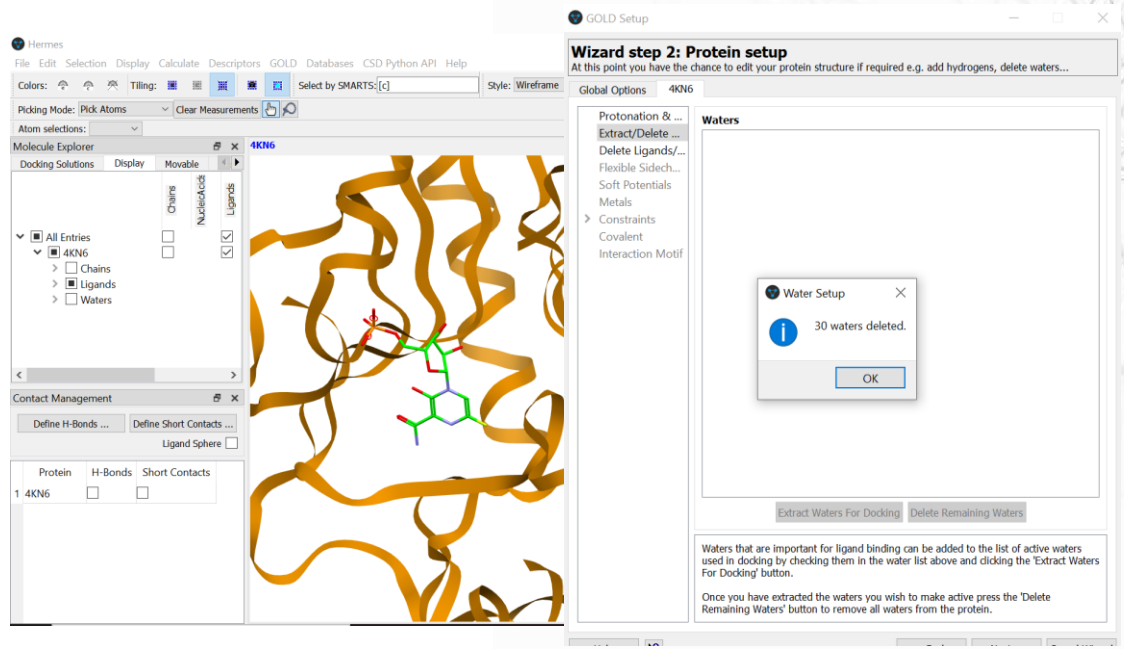
Docking with GOLD: Protein preparation



- Visual inspection of the protein structure, bound ligand and water molecules.
- Add missing hydrogens.

Docking with GOLD: Protein preparation

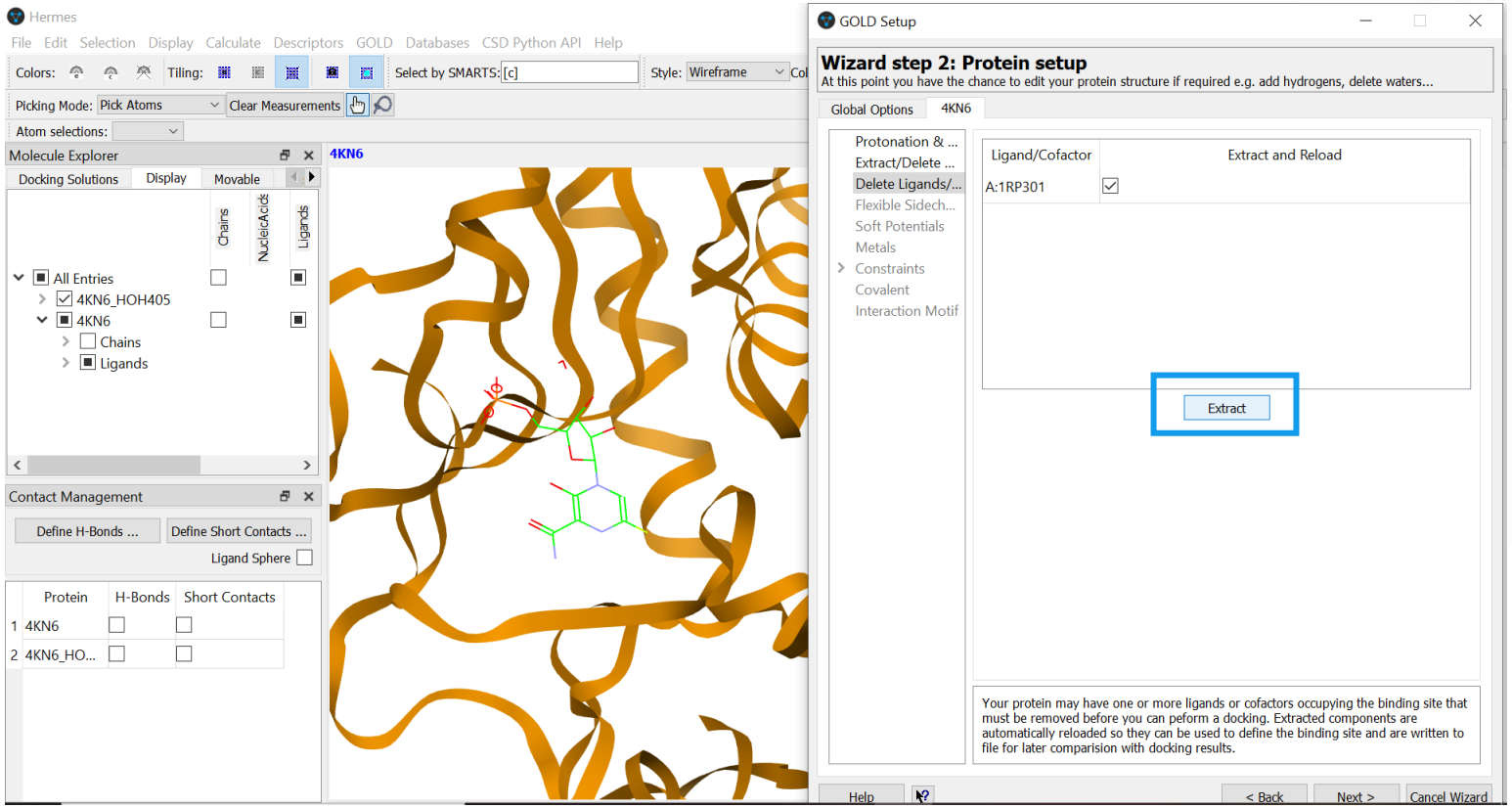




- Select water molecules that are important for the ligand interaction, i.e. functional waters.
- Extract the required water molecules and delete the excess ones. The selected water molecule is saved automatically in the working folder.

CCDC

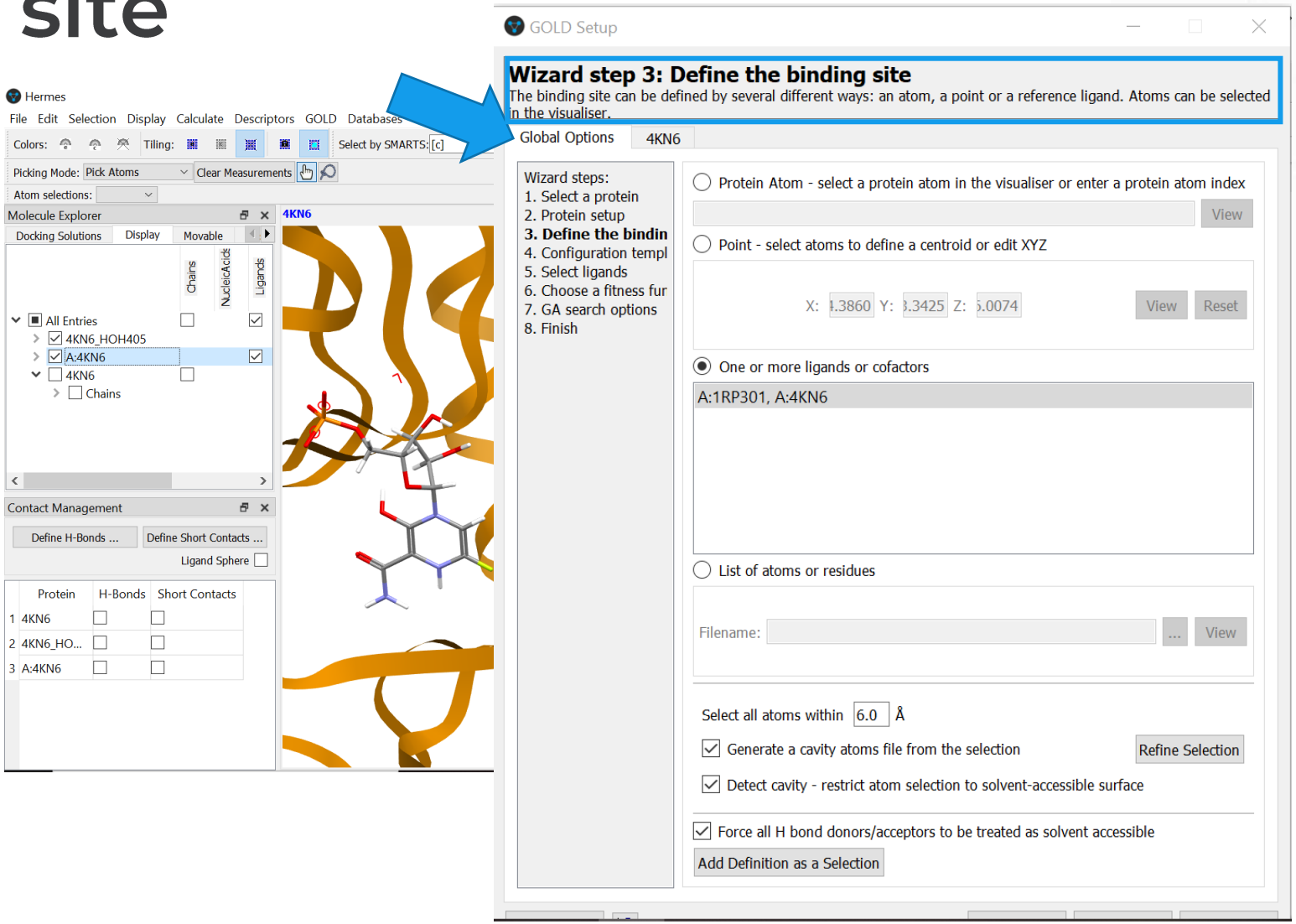
Docking with GOLD: Protein preparation



- Look for ligands and cofactors.
- Extract the ligand of your interest.
- Save the ligand.

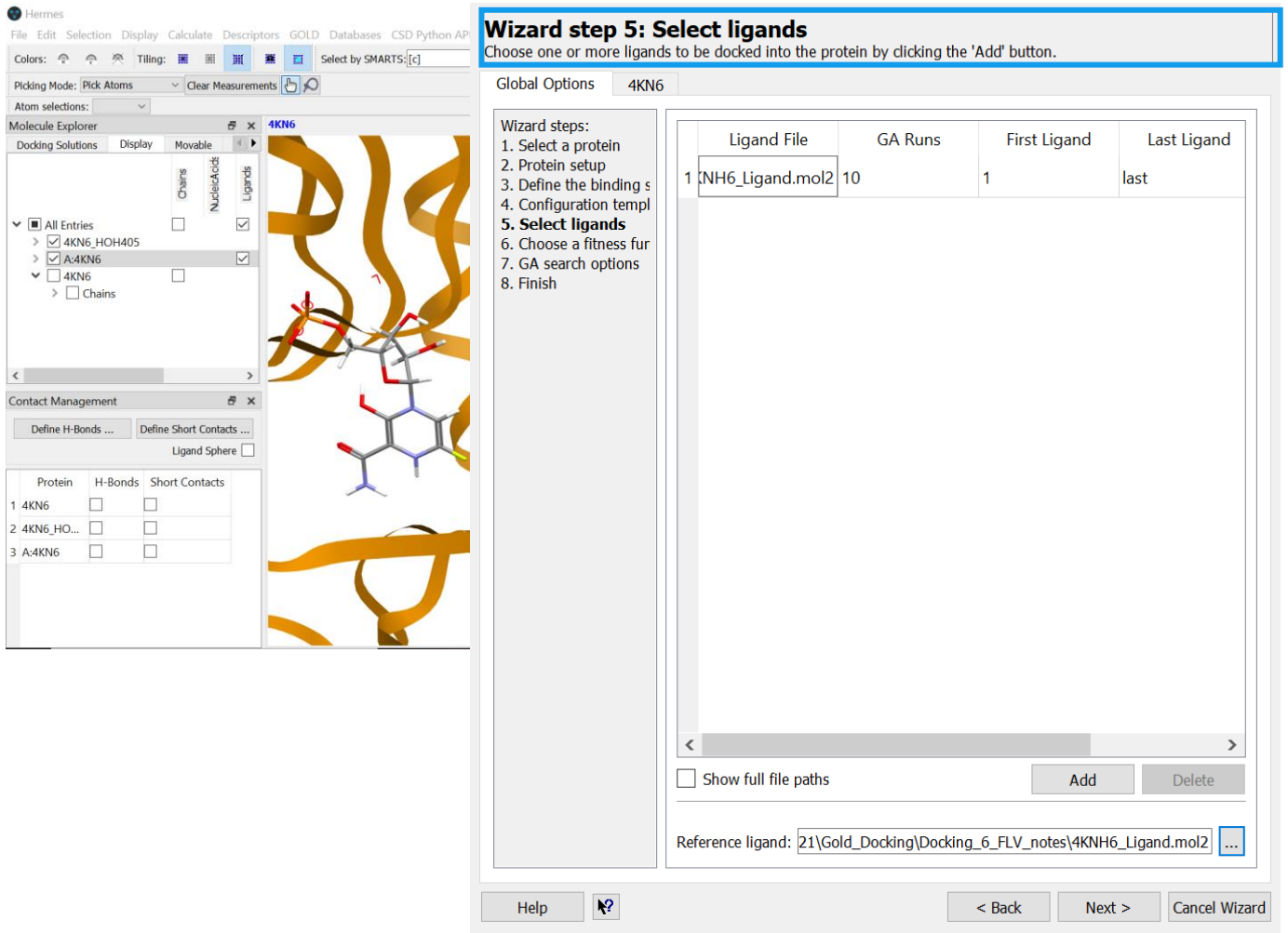
CCDC

Docking with GOLD: Defining the binding site



- There are various ways in which you can define the binding site.
- Decide and select the one depending on the target protein or specific needs.

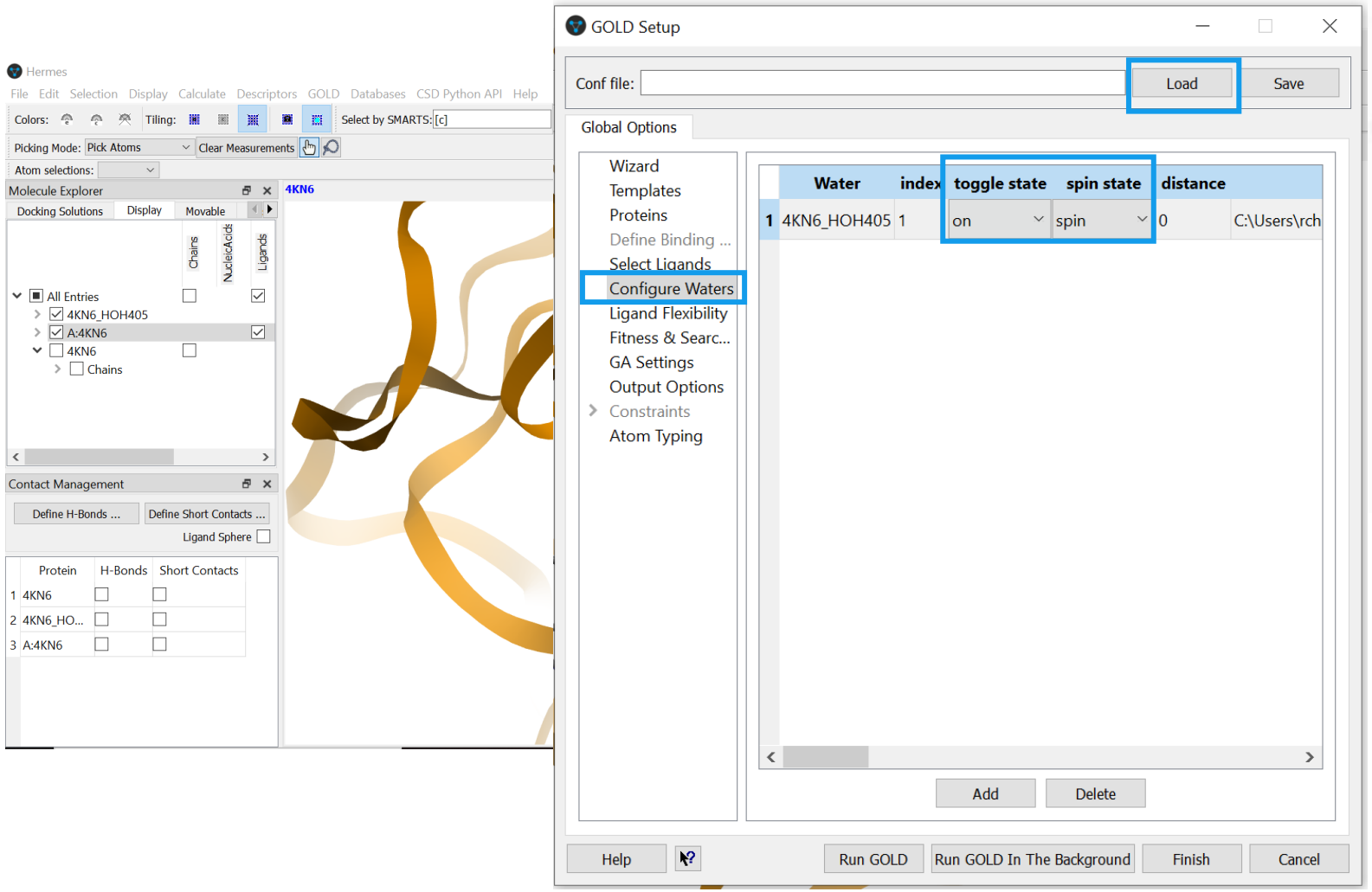
Docking with GOLD: Select ligand/s



- You can select the ligands to be docked.
- Ligand file could contain one or more than one molecule in .sdf or .mol format.
- Instead of continuing with the Wizard, cancel the wizard now to further configure.

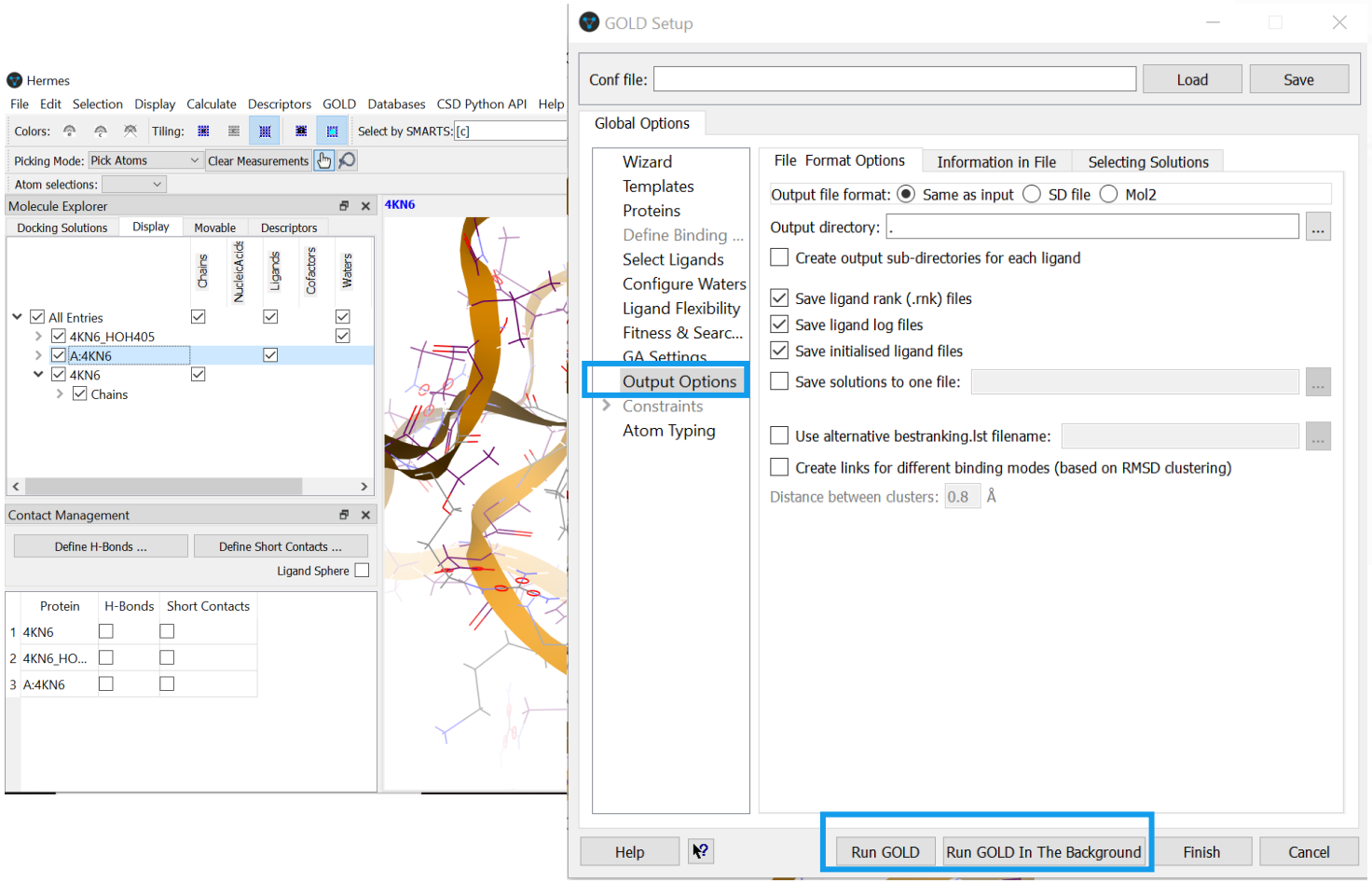
CCDC

Docking with GOLD: Settings for Water



- Now select the *Configure* water option and load the water molecule saved earlier.
- Select *toggle* and spin *on* options.

Docking with GOLD: Run the setup

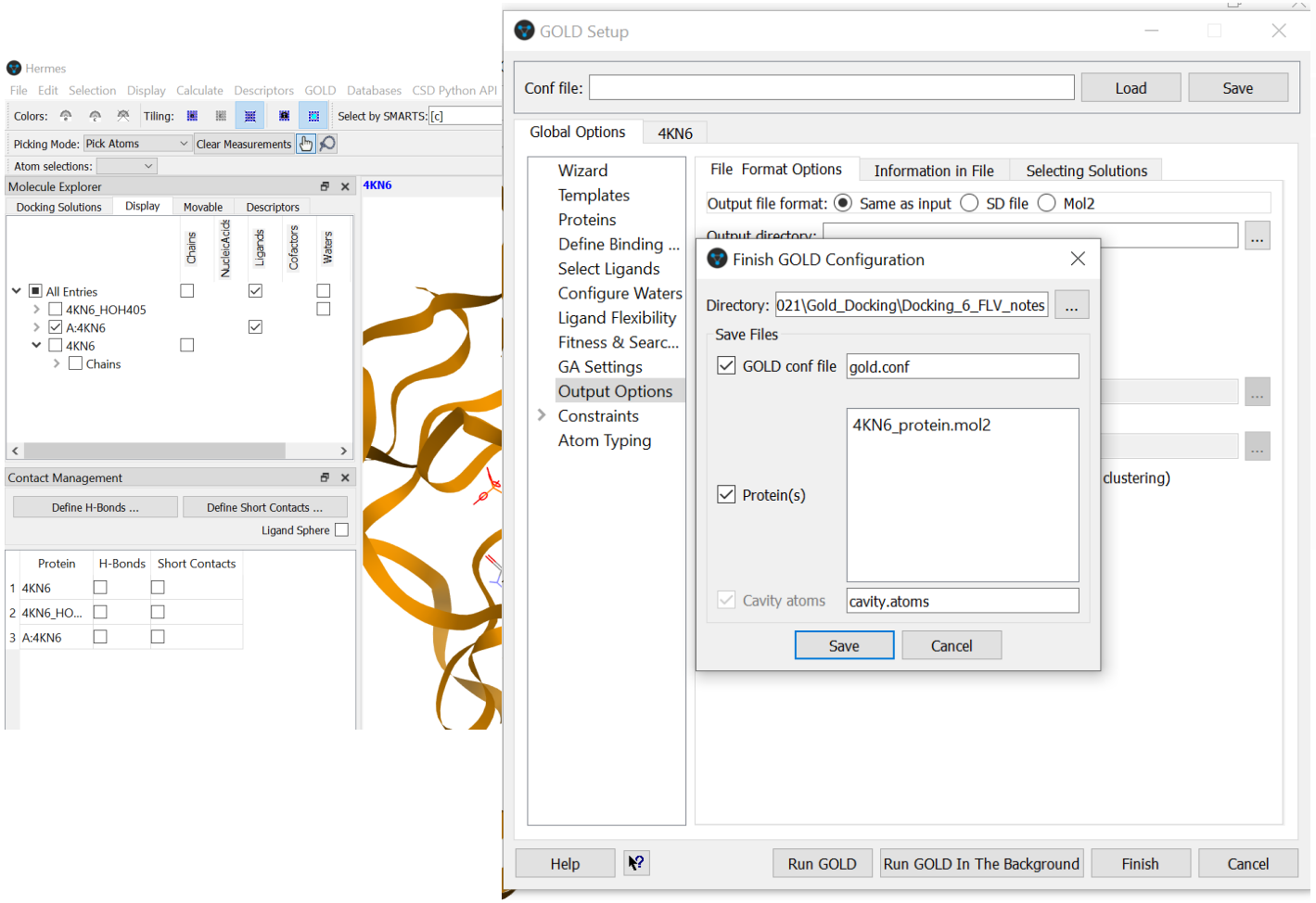


- Select output destination/directory.
- Format of output you require.
- Run the GOLD calculations.
- Two options are available;

1. Run Gold: Interactive mode.

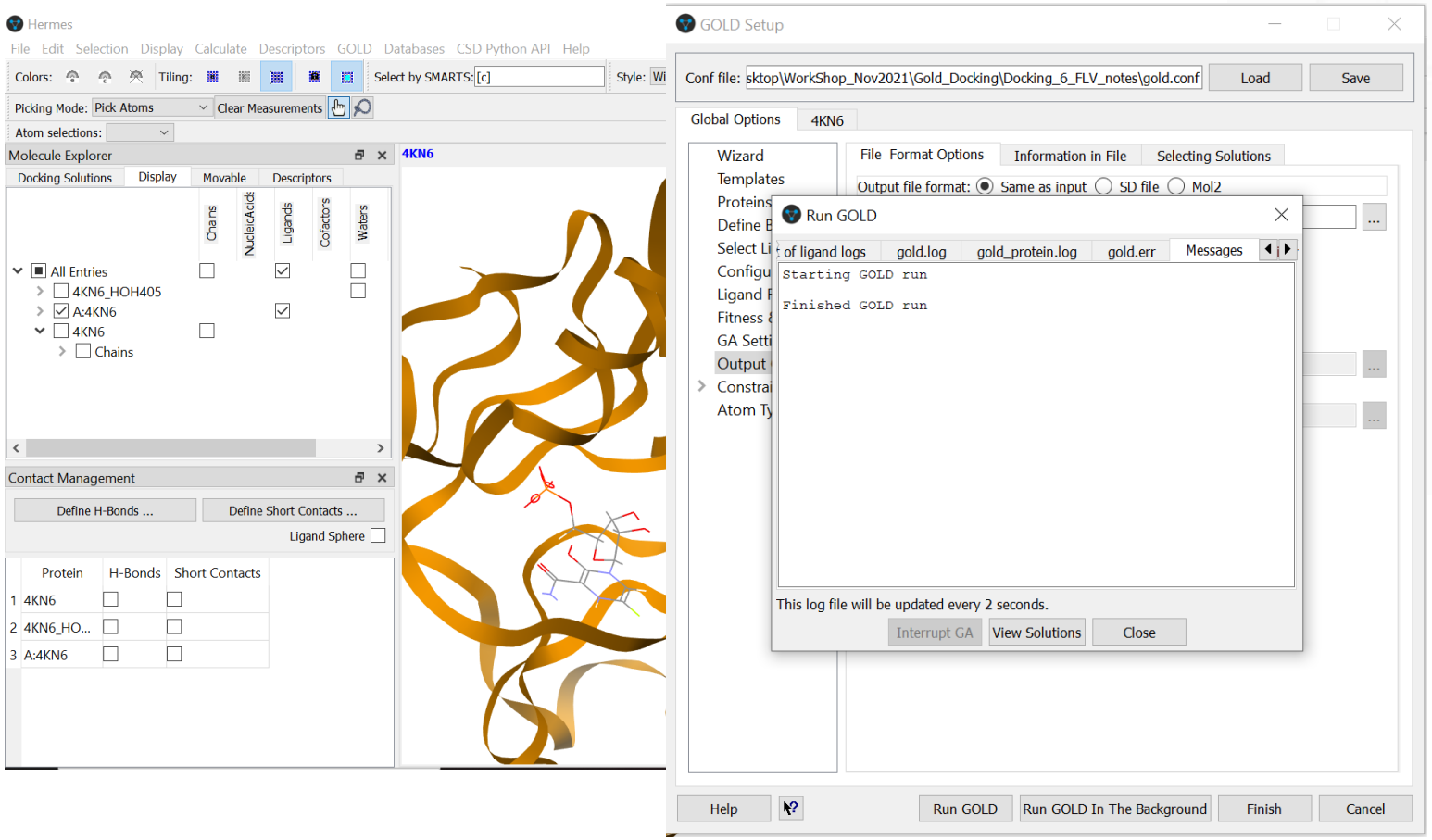
2. Run GOLD in Background: Results are seen in the output folder.

Docking with GOLD: Run the setup



- The run function asks for various options.
- The *gold.conf* file is the one with all the details. It is an editable file.

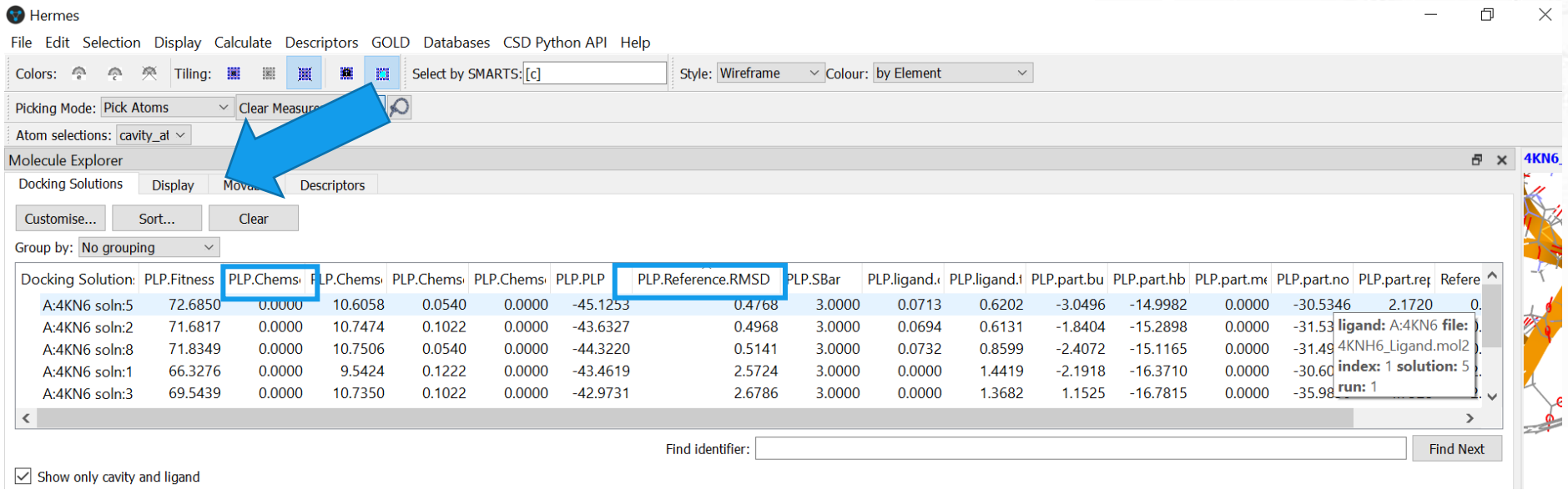
Docking with GOLD: Docking calculations



- You can check the progress of the calculation.
- The *Run GOLD* window has various tabs, these provide with on the fly status of your calculations.

Docking with GOLD: Analysis of results

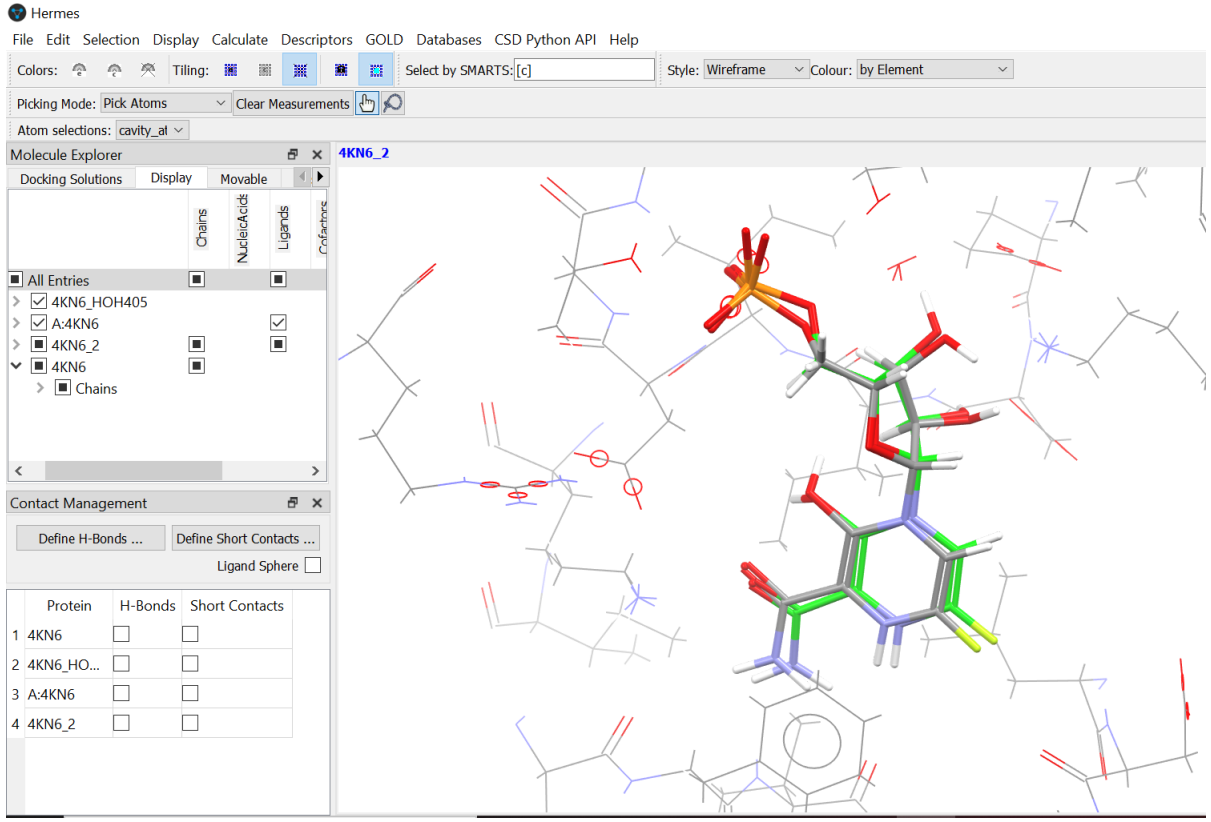
- Results are displayed in the *Molecular Explorer*.



- In most cases we are interested in the fitness score and the RMSD.
- For PLP scoring function, higher scores and lower RMSD is mean better results.
- PLP: Piecewise Linear Potential, it is an empirical fitness functions optimised for pose prediction.

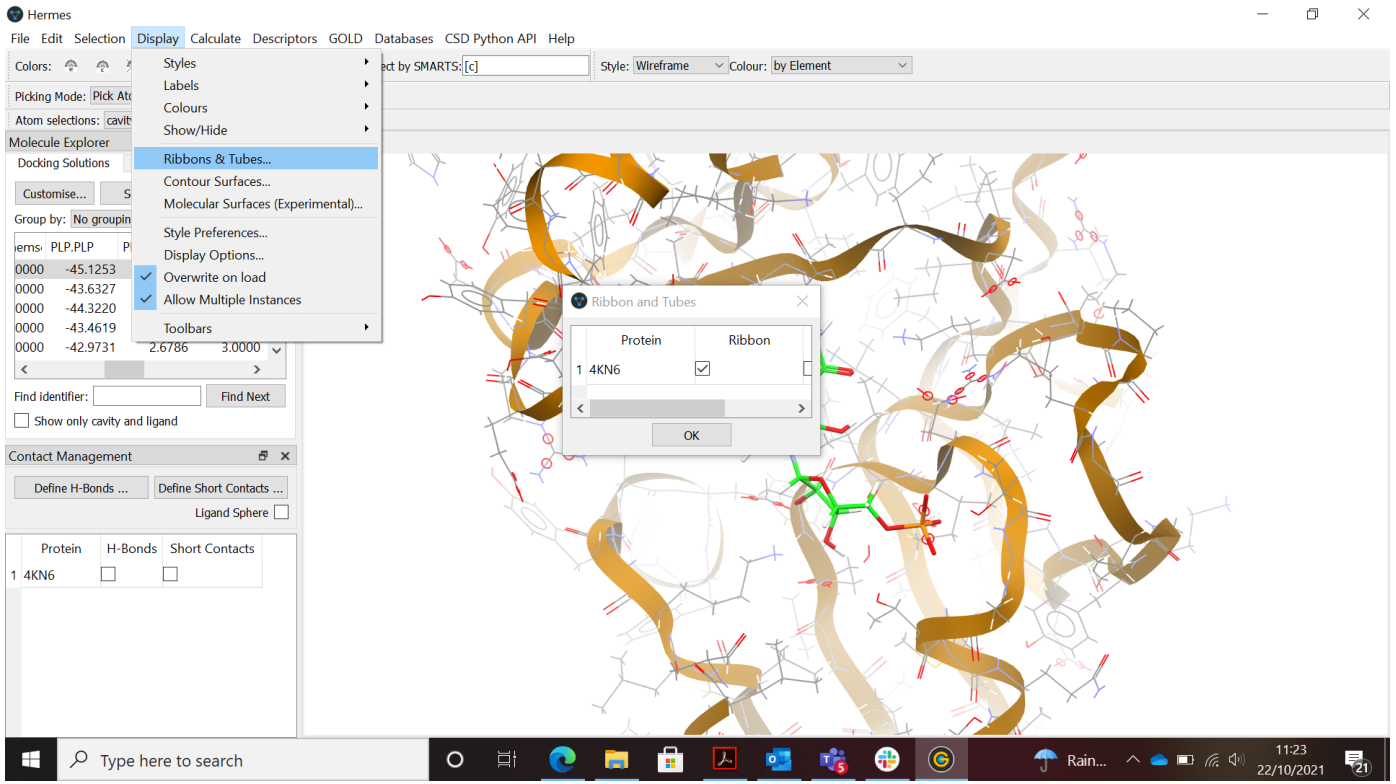
CCDC

Docking with GOLD: Analysis of results



- Use the *Molecular Explorer* to display docking solutions, component of the system and the molecules.
- Manage the views and study the interactions.

Docking with GOLD: Analysis of results



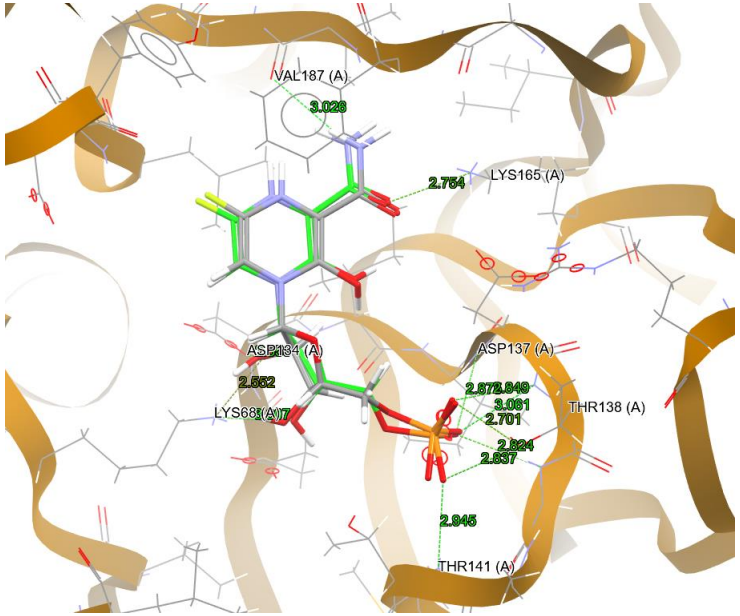
- Select Display

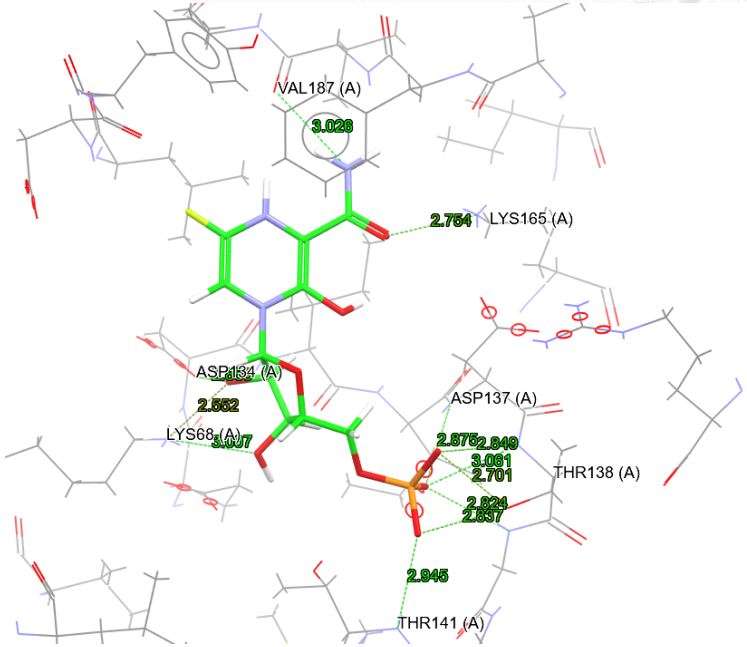
Ribbons and Tubes

Explore various options to create various colour combinations and displays

CCDC

Docking with GOLD: Analysis of results

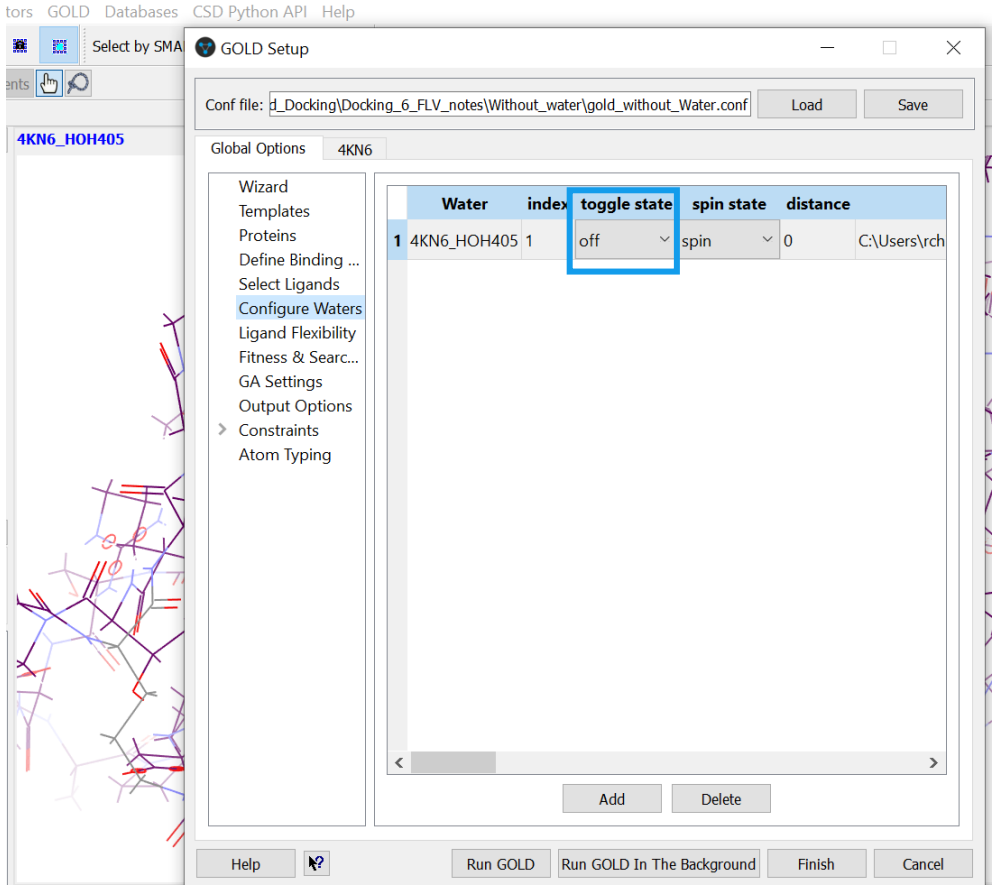




- Results can be visualised in various ways and representations.
- Can display hydrogen bonds for the docked and reference ligands.

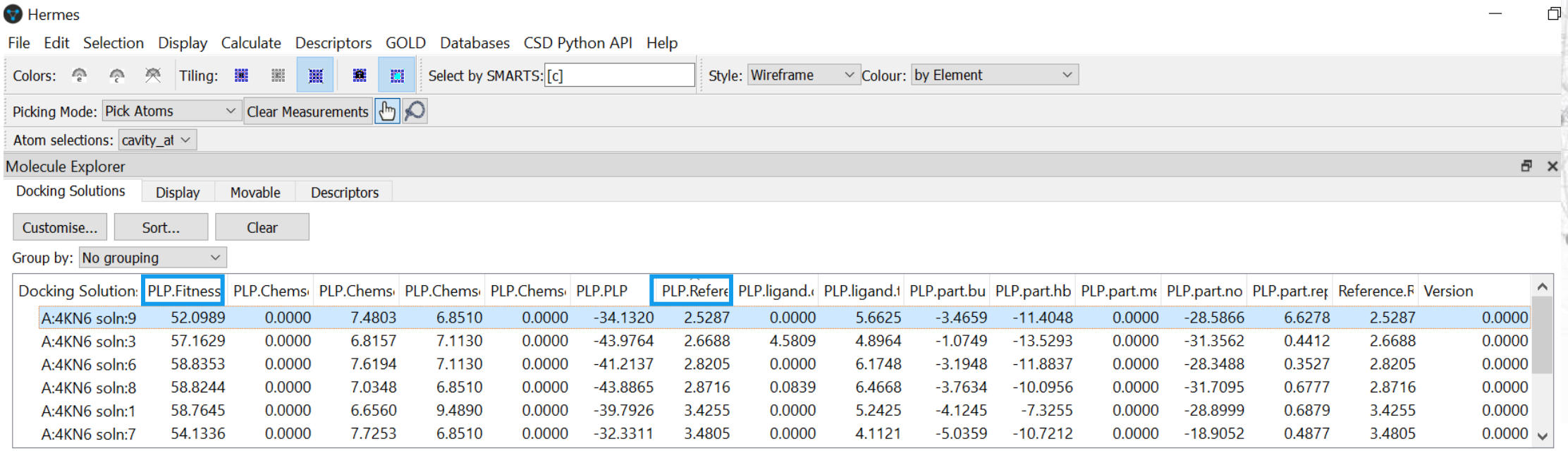
CCDC

What happens when we turn the water off!



- Now let us see the effect of docking without the water molecule on the docked pose.
- To see the effect, we switch off the '*toggle state*' in the configure water tab.

What happens when we turn the water off!

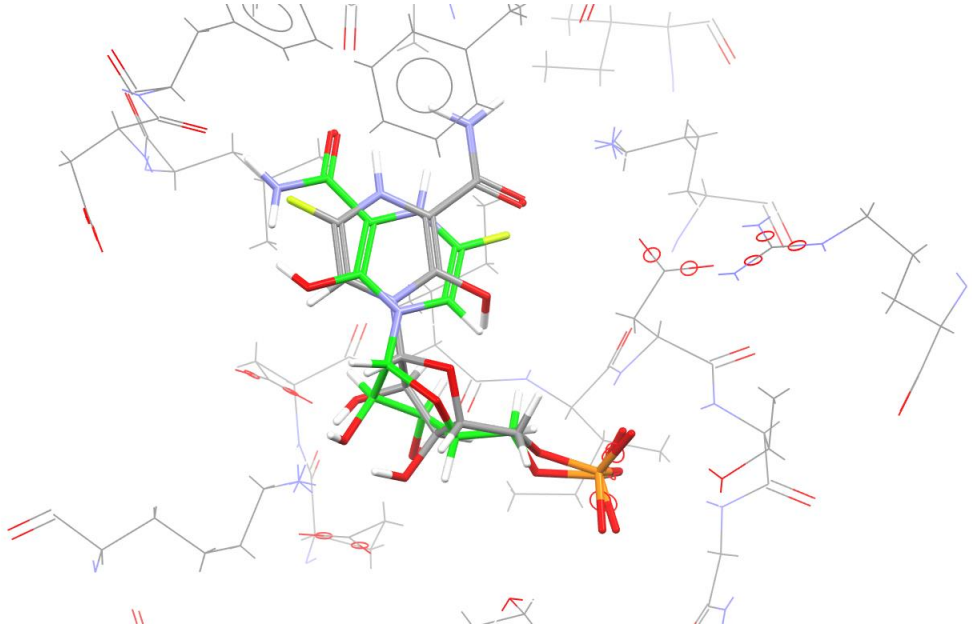


Docking Solution	PLP.Fitness	PLP.Chems	PLP.Chems	PLP.Chems	PLP.Chems	PLP.PLP	PLP.Refere	PLP.ligand.(	PLP.ligand.1	PLP.part.bu	PLP.part.hb	PLP.part.me	PLP.part.no	PLP.part.rep	Reference.R	Version
A:4KN6 soln:9	52.0989	0.0000	7.4803	6.8510	0.0000	-34.1320	2.5287	0.0000	5.6625	-3.4659	-11.4048	0.0000	-28.5866	6.6278	2.5287	0.0000
A:4KN6 soln:3	57.1629	0.0000	6.8157	7.1130	0.0000	-43.9764	2.6688	4.5809	4.8964	-1.0749	-13.5293	0.0000	-31.3562	0.4412	2.6688	0.0000
A:4KN6 soln:6	58.8353	0.0000	7.6194	7.1130	0.0000	-41.2137	2.8205	0.0000	6.1748	-3.1948	-11.8837	0.0000	-28.3488	0.3527	2.8205	0.0000
A:4KN6 soln:8	58.8244	0.0000	7.0348	6.8510	0.0000	-43.8865	2.8716	0.0839	6.4668	-3.7634	-10.0956	0.0000	-31.7095	0.6777	2.8716	0.0000
A:4KN6 soln:1	58.7645	0.0000	6.6560	9.4890	0.0000	-39.7926	3.4255	0.0000	5.2425	-4.1245	-7.3255	0.0000	-28.8999	0.6879	3.4255	0.0000
A:4KN6 soln:7	54.1336	0.0000	7.7253	6.8510	0.0000	-32.3311	3.4805	0.0000	4.1121	-5.0359	-10.7212	0.0000	-18.9052	0.4877	3.4805	0.0000

- Follow the steps showed earlier to complete the setup, then run the docking calculation.
- We will look at the ligand RMSD and fitness score to understand the impact of docking with and without water.

CCDC

What happens when we turn the water off?

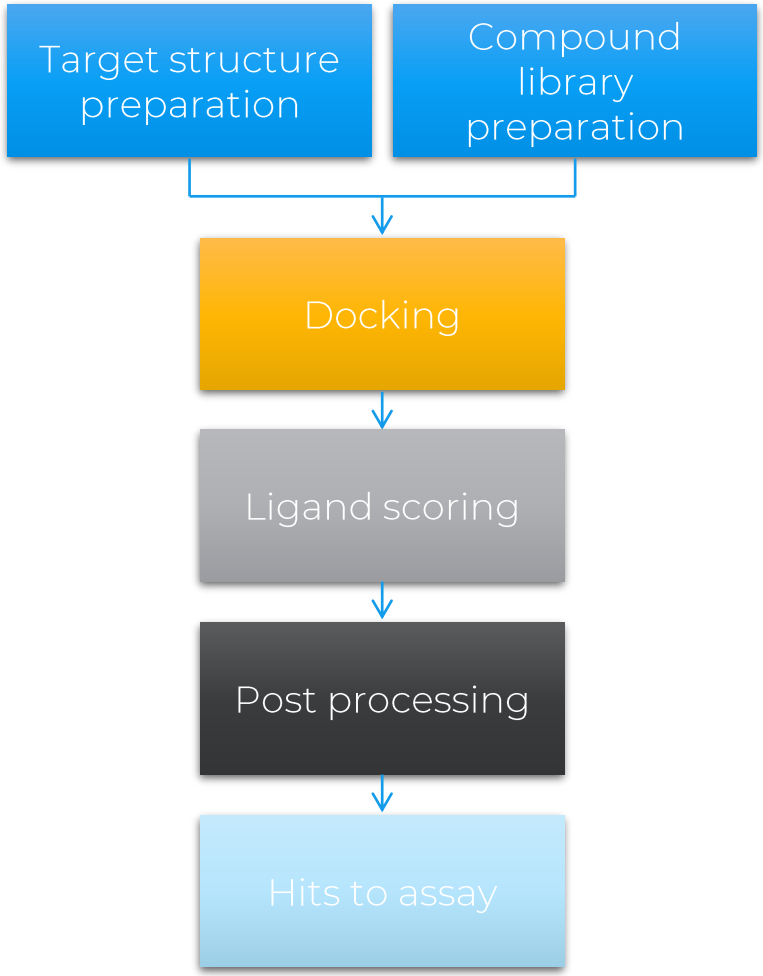


Docking pose with the lowest RMSD

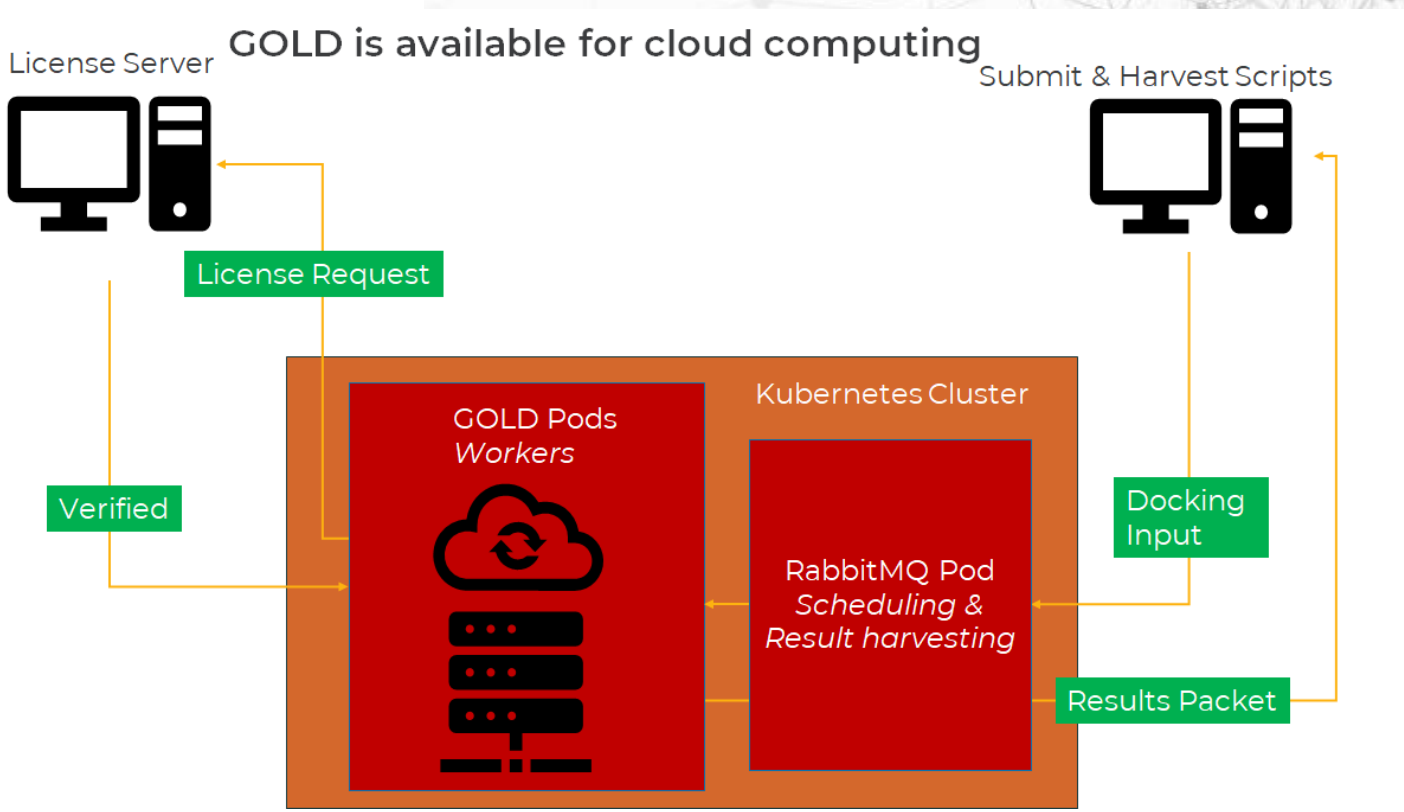
- Ligand orientation different from the experimental conformation.
- Only when docking with explicit water molecule(s) we were able to reproduce the crystallographic conformation.

CCDC

Docking virtual screening (VS) with GOLD



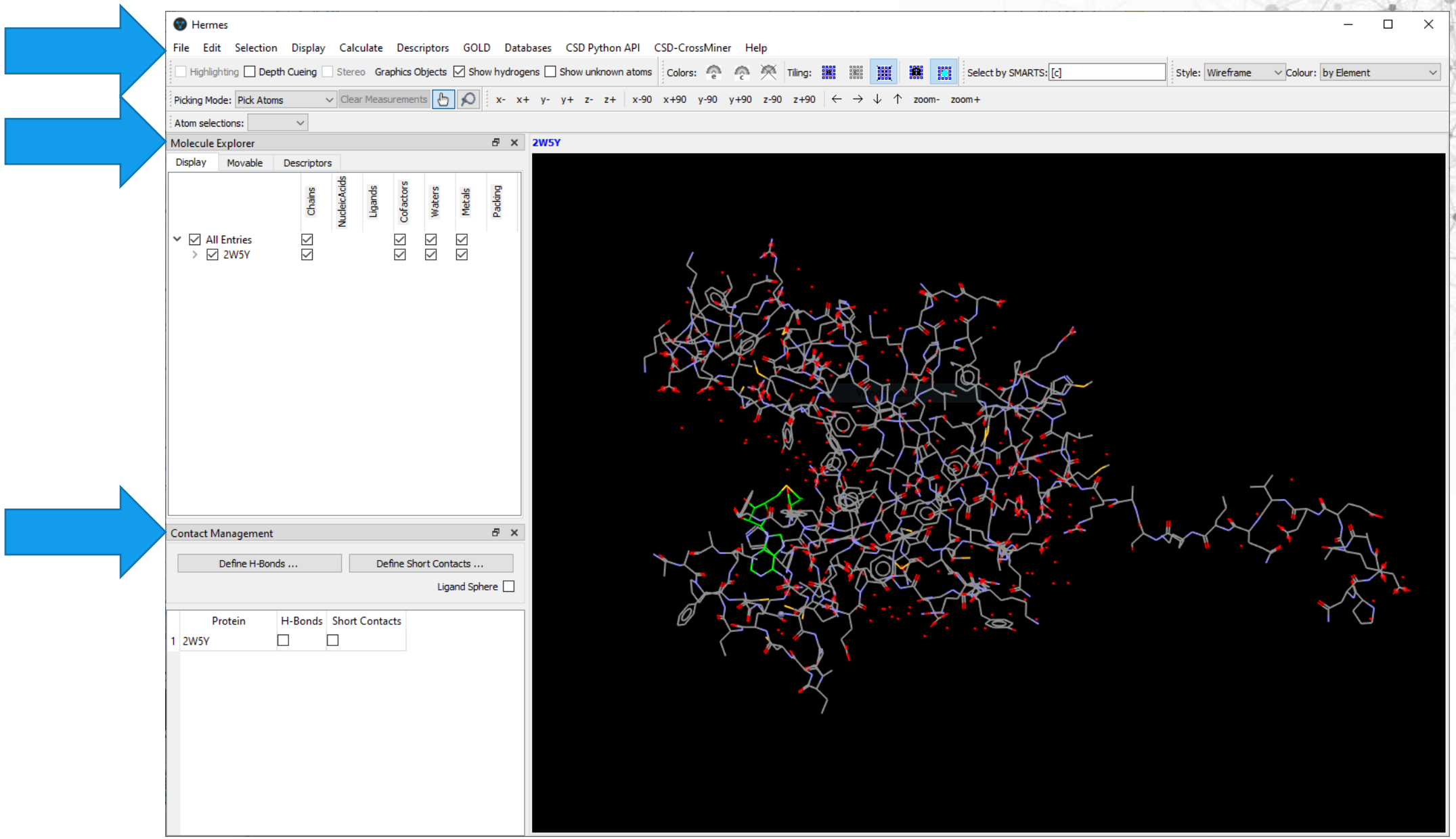
Typical workflow of a docking-based VS



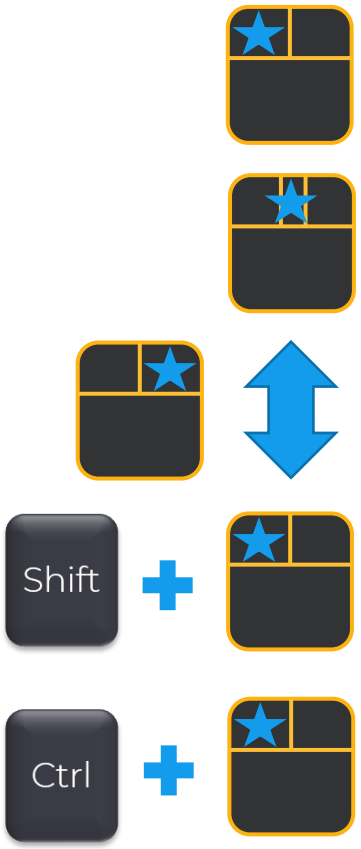
Gold cloud computing

CCDC

Show One: Hermes Interface



The 3D window basics

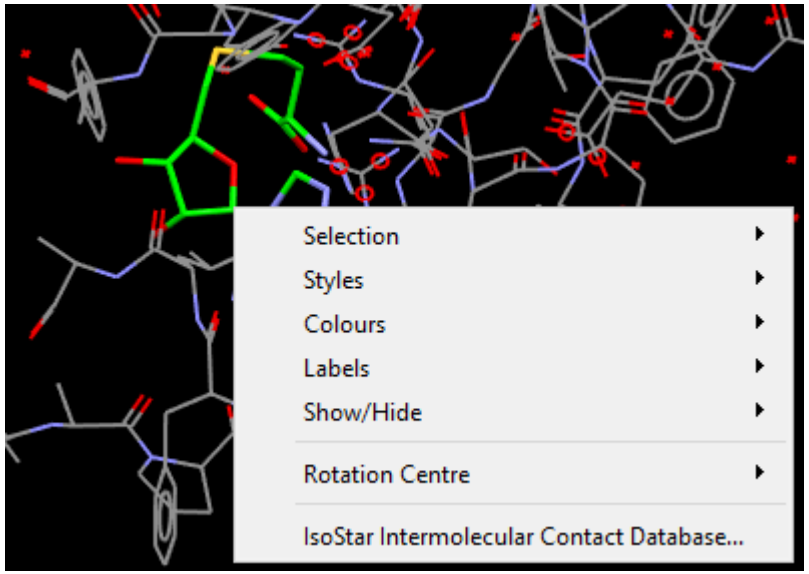


- Left mouse button and move – rotate molecules
- Middle Mouse wheel – move molecules up and down
- Right mouse button and move up and down – zoom in and out of molecules
- Shift + Left mouse button and move - rotate in the plane molecules
- Ctrl + Left mouse button and move - translate molecules

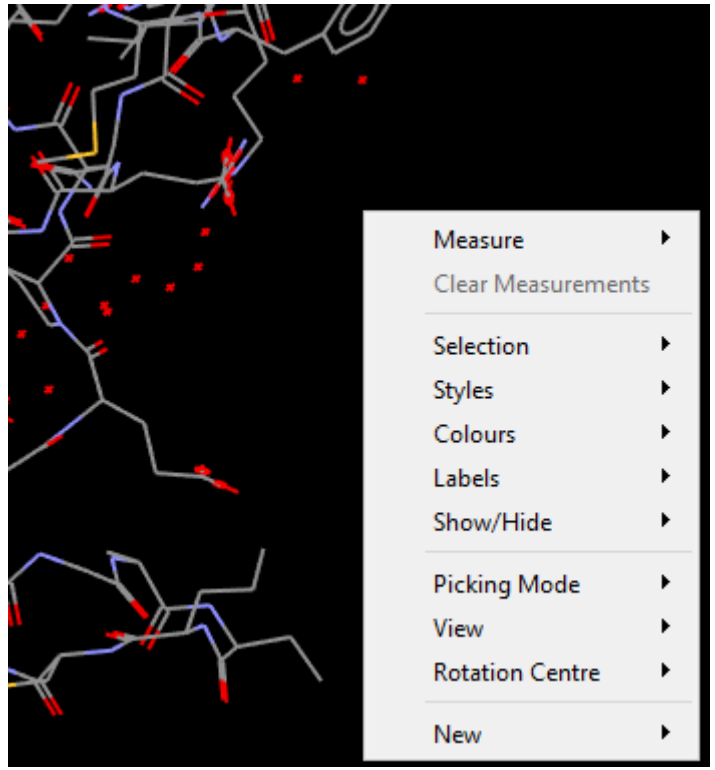
CCDC

The 3D window basics – Right click

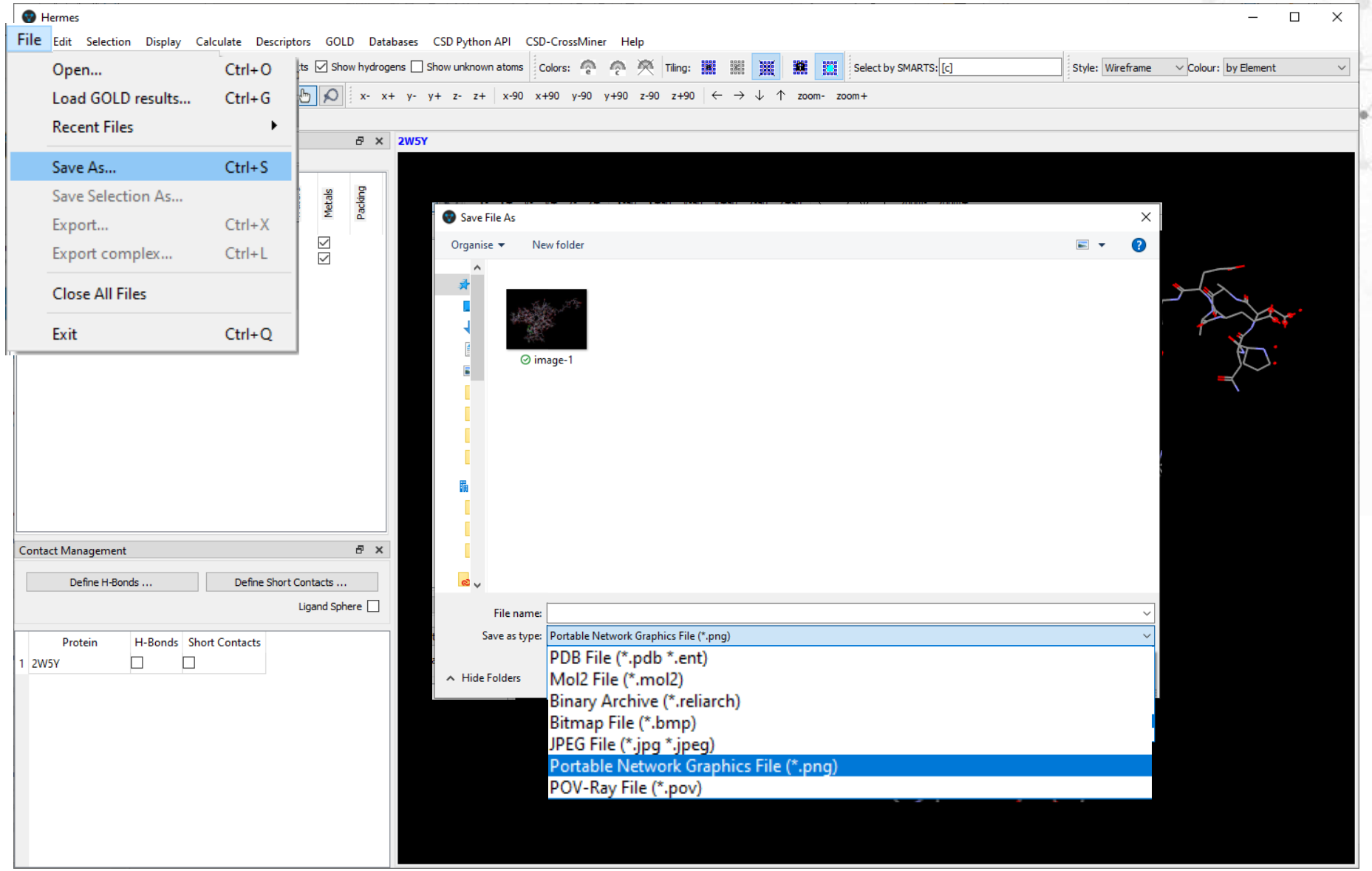
On a feature



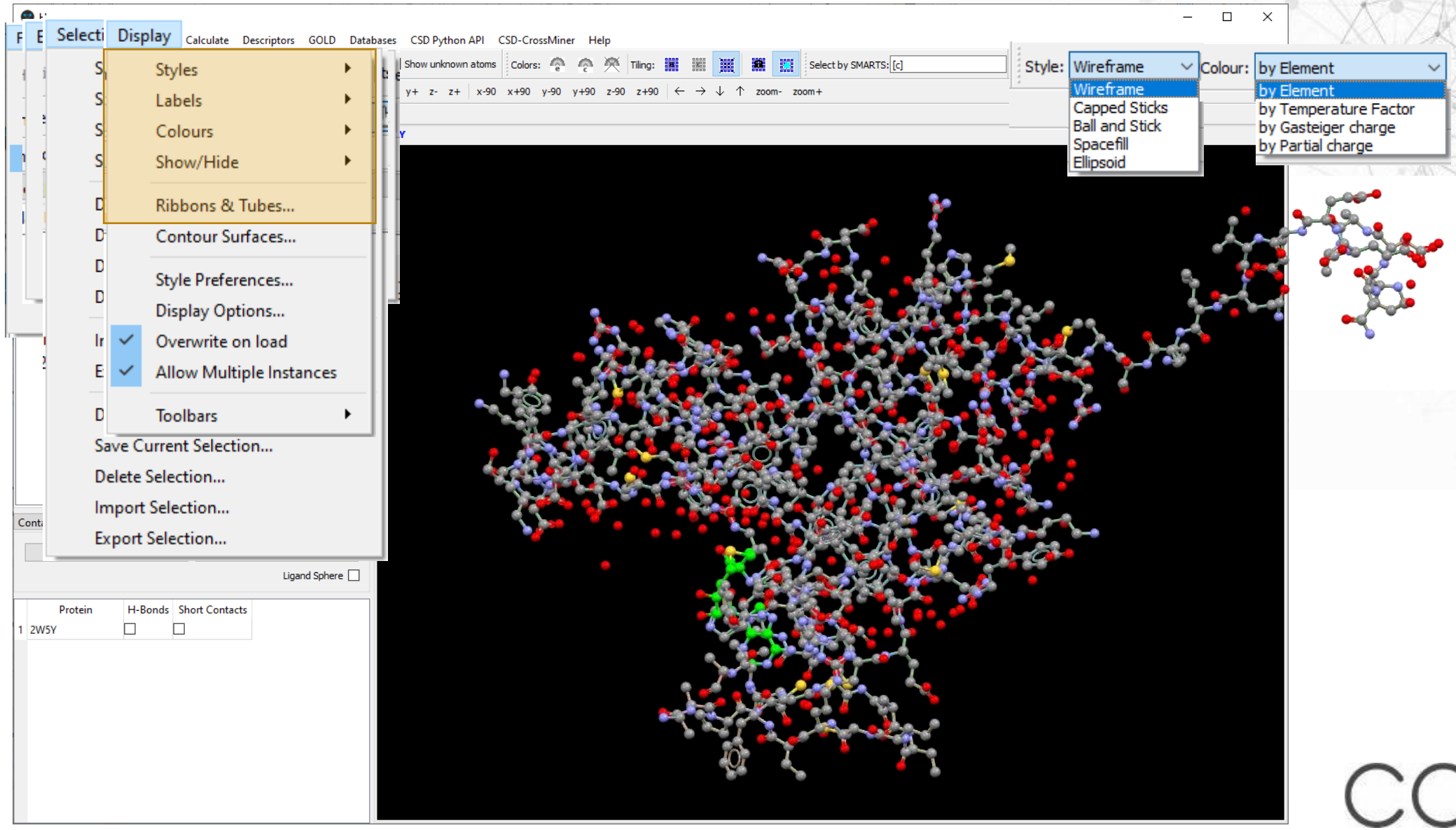
Away from a feature



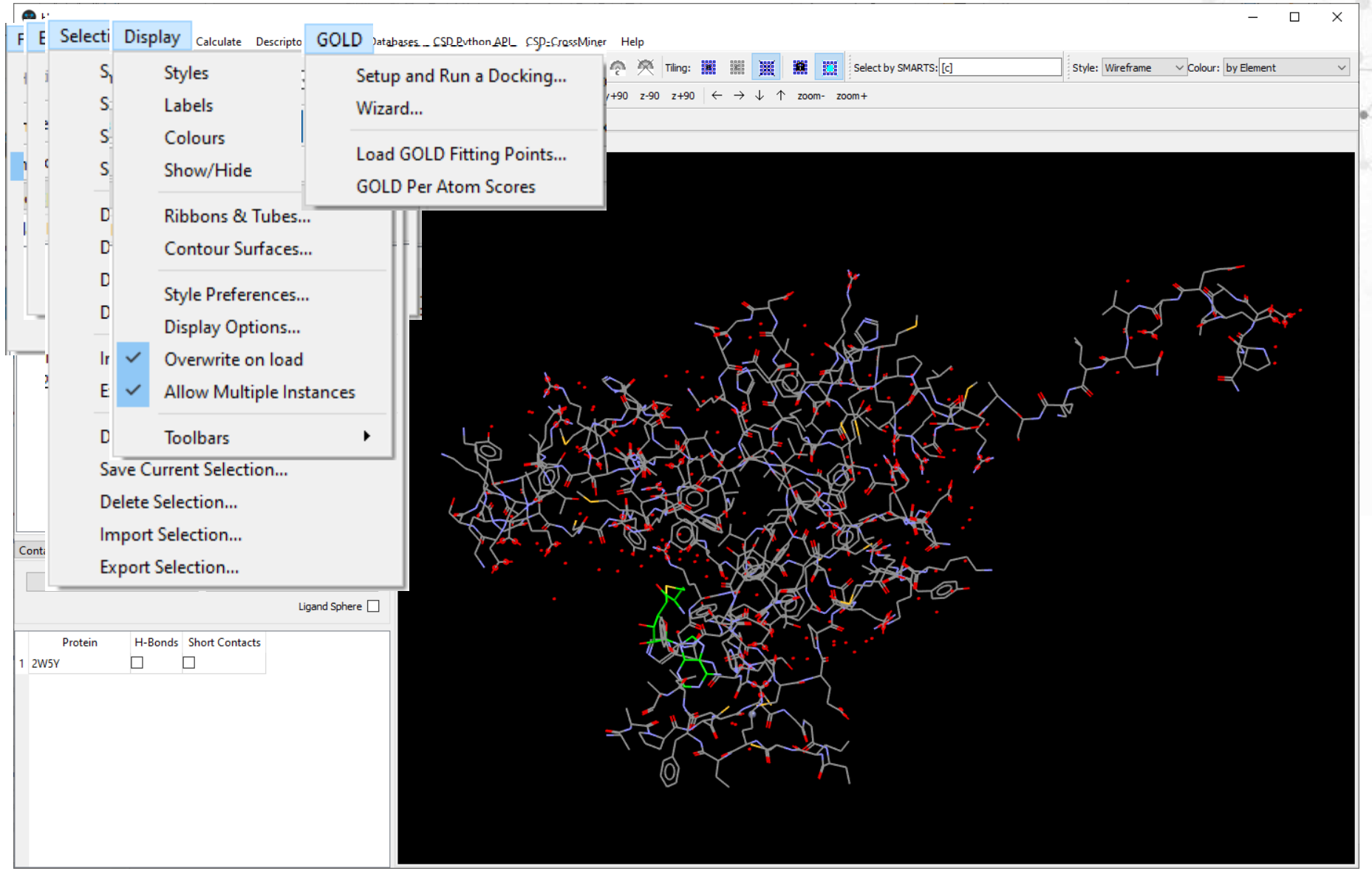
Show One: Hermes interface



Show One: Hermes interface



Show One: Hermes interface



CCDC

Want to explore more?

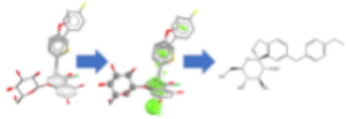
Training and Educational Resources

The wealth of information contained within the Cambridge Structural Database (CSD) extends far beyond a collection of crystal structures. Knowledge derived from these materials informs much of chemistry, biochemistry, and biology. Chemical and structural concepts are often difficult to grasp without real world, interactive examples for students to explore.

The CCDC and our colleagues continually produce educational materials for use in classroom and computer lab settings, or as independent study modules. Many of these materials make use of the Teaching Subset - a freely available set of over 750 structures that can be investigated with the free version of our Mercury visualisation and analysis program. Of database of over one million entries are available for free through our Access Structures portal.

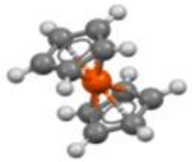
n educator looking for supplementary teaching materials, find out more about the Teaching Database **here**. If you have developed your own modules using the CSD and o share them with the broader community, please contact us at education@ccdc.cam.ac.uk.

to date with the latest news from education and outreach at the CCDC, sign up for the Education and Outreach Newsletter **here**.

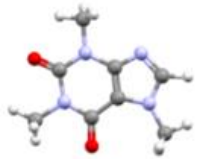


CSD-Discovery

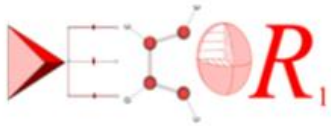
For pharmaceutical and agrochemical researchers, tools for discovering new molecules and performing protein docking studies.



formation on the Teaching Subset



Access a series of teaching modules for use in the classroom



DECOR: Educational Resources for Teaching Crystallography

Register for E&O newsletter

Self-guided workshops

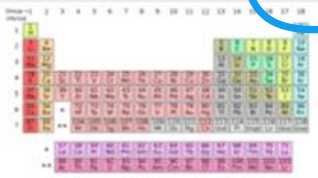
Download a series of self-guided workshop materials for CCDC tools and features

Watch software training and support videos

CSDU modules

On-demand modules with completion certificate

Access fun science activities for kids through the CCDC Home learning page



Explore the Periodic Table through Crystal Structures

YouTube and LabTube channels

CCDC