The Cambridge Structural Database (CSD): An invaluable resource for drug discovery

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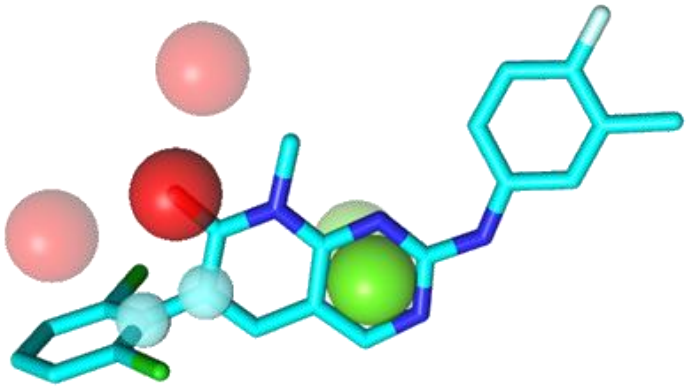
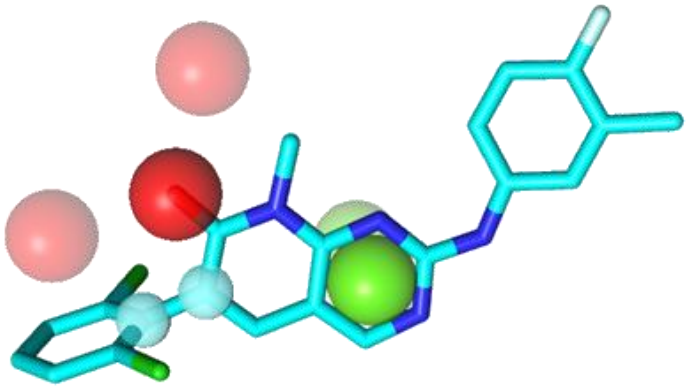
The 18th Annual Meeting of the Protein Science Society of Japan

28-Jun-2018, Niigata



Talk Outline

- **Introduction to the CCDC and the CSD**
- Introduction to CSD-CrossMiner software
- CSD-CrossMiner application example
- CSD-CrossMiner software demo



The Cambridge Crystallographic Data Centre (CCDC)

International Data Repository
Archive of crystal structure data
High quality scientific database

Scientific Software Provider
Search/analysis/visualisation tools
Scientific applications

Collaborative Research Organisation
New methodologies
Fundamental research

Education and Outreach
Workshops, Training
Teaching Materials

Employer of ~60 staff

Scientific editors
Software developers
Applications scientists

Cambridge UK

Princeton NJ USA

Originated in 1965

Financially self-supporting, not-for-profit

UK Registered Charity

University of Cambridge Partner Institute

Unlocking Knowledge

International Data Repository
Archive of crystal structure data
High quality scientific database

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Search/analysis/visualisation tools
Scientific applications

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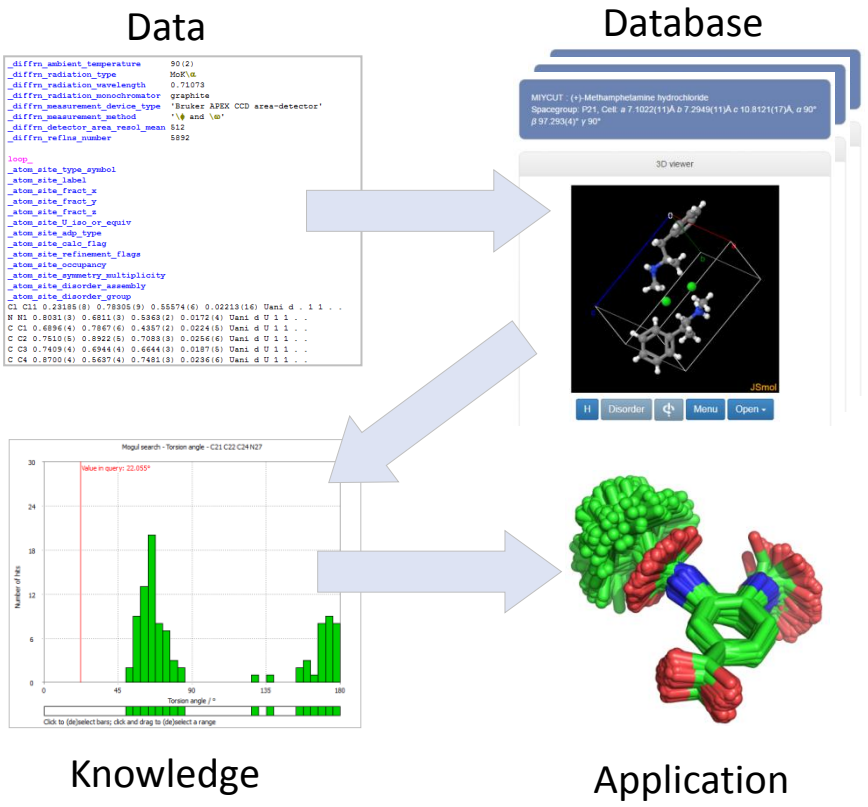
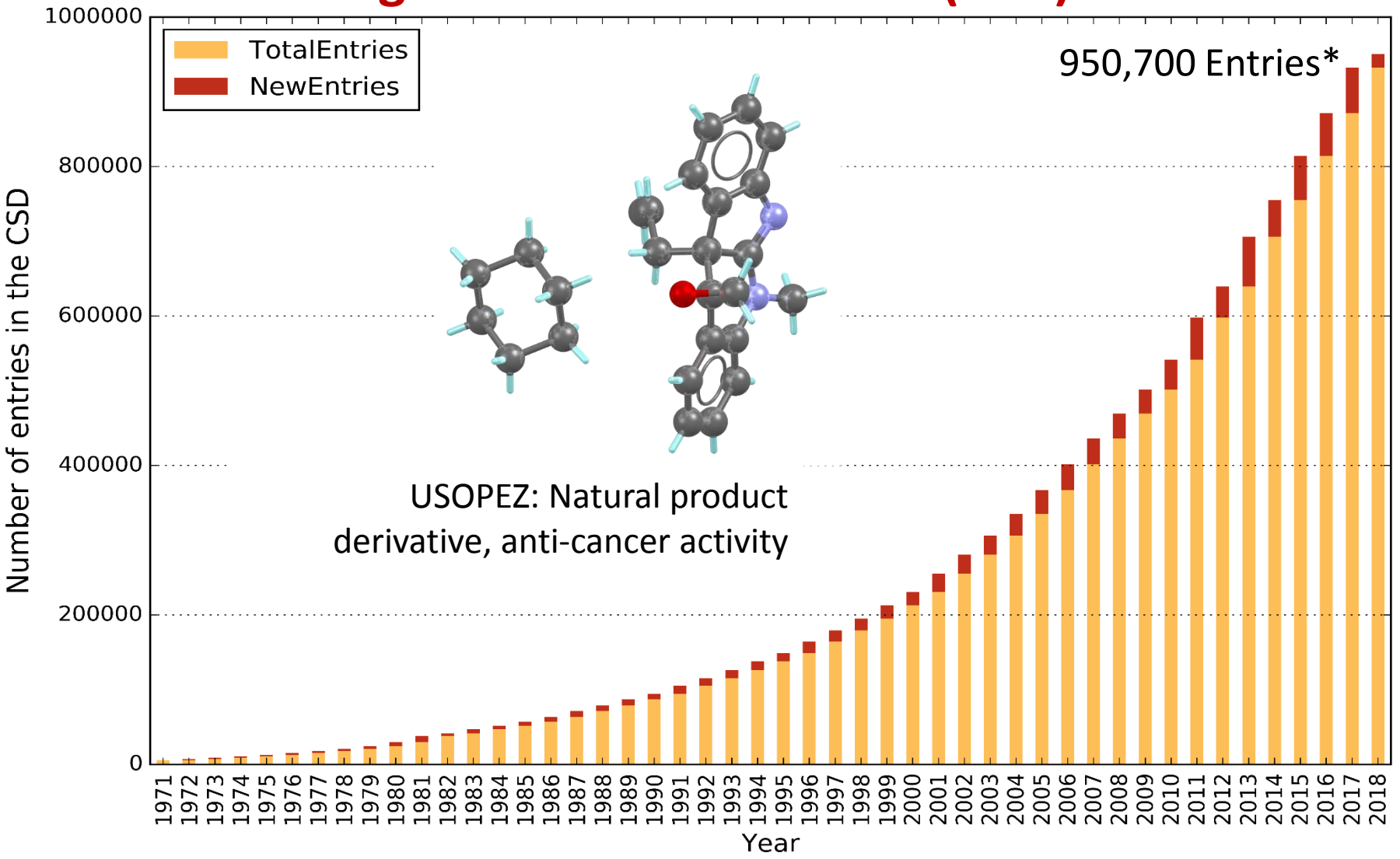


Chemistry plus crystallography enables discovery and application of new knowledge

The Cambridge Structural Database (CSD)



*As of 17-May-2018, adding ~60,000/year

Groom, C. R.;. Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater. 2016, 72 (2), 171–179. DOI: 10.1107/S2052520616003954

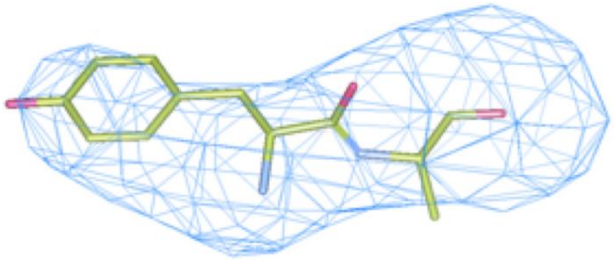
Top 200 small molecule drugs of 2015

Green = Exact Matches in the CSD (118 drugs)

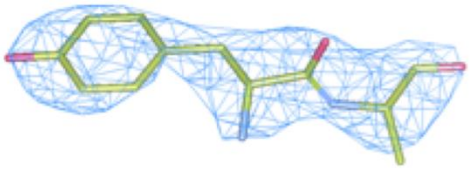
Grey = No exact match in CSD, it is likely something very similar is in the CSD

Crystallographic Resolution

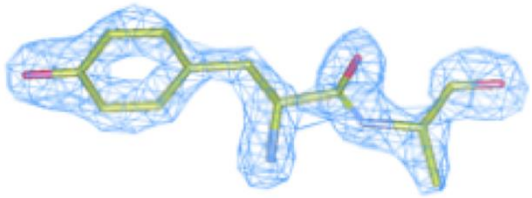
Crambin
PDB: 3nri
Experimental resolution: 0.48Å



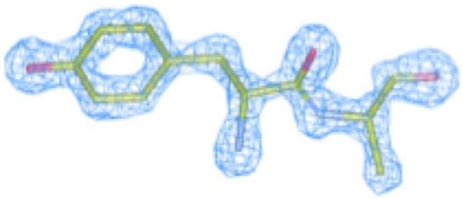
5.0 Å



3.0 Å

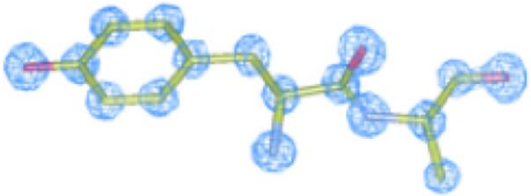


2.0 Å

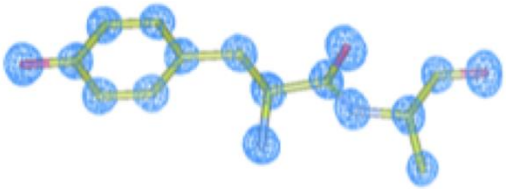


1.5 Å

Typical PDB Structures



1.0 Å



0.6 Å

Typical CSD Structures

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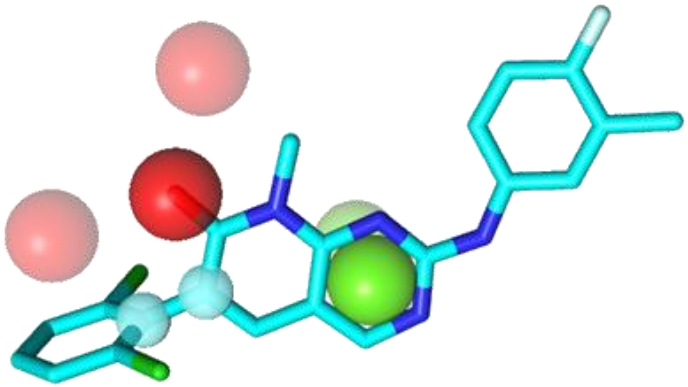
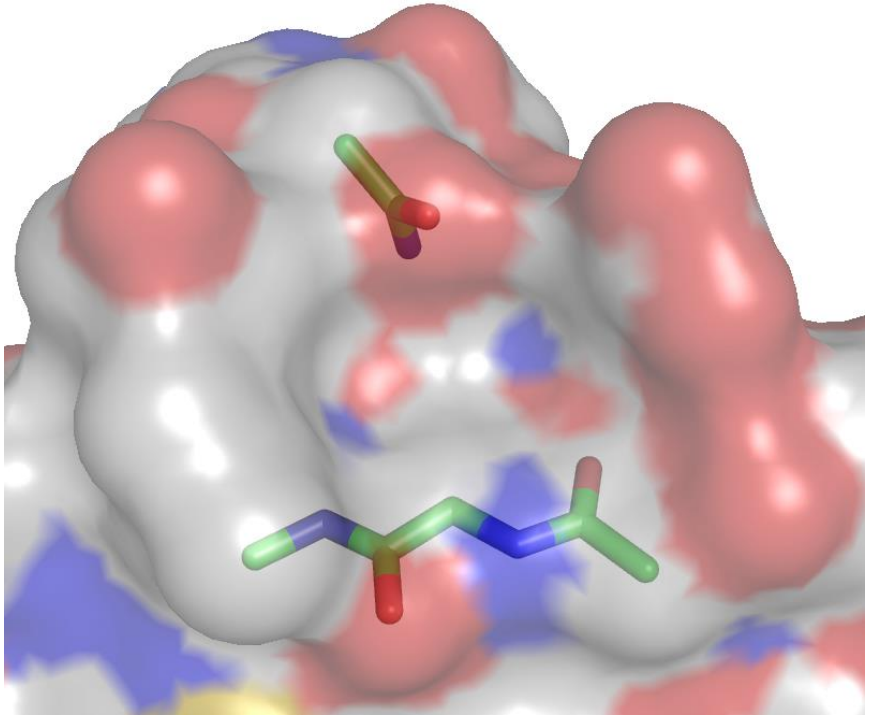
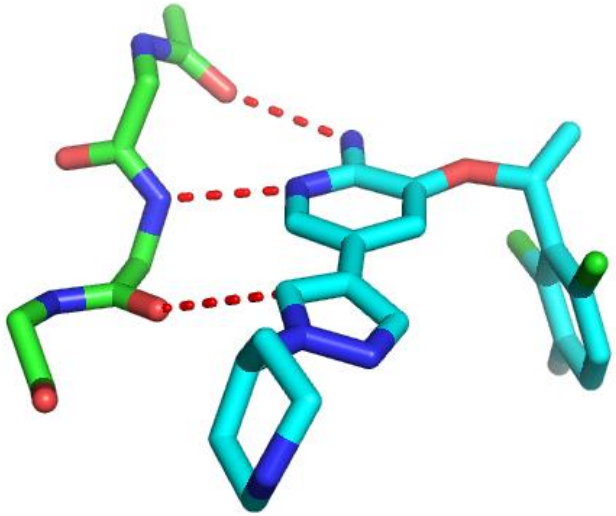
NEW!



Typical Questions Arising in Drug Design Projects

- Which structural motifs bind in a similar environment?





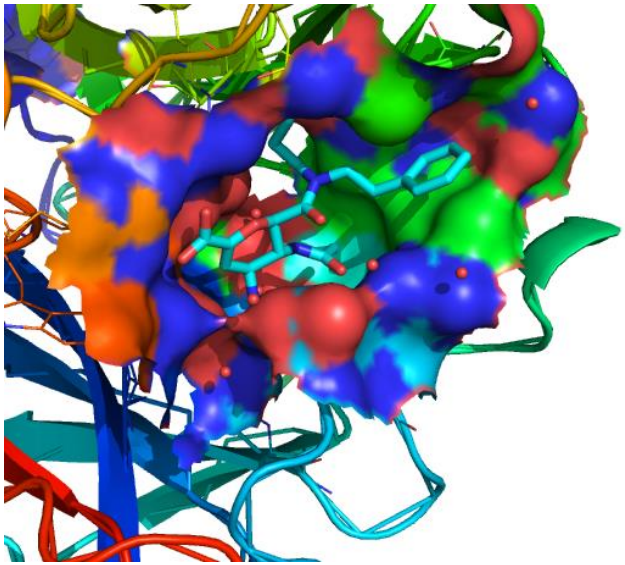
- Which ligand motifs have similar protein interaction pattern?
- Are there molecules with similar interacting groups in the database?

Grand Challenge: Enable a More Effective Usage of Structural Data in Drug Design Projects

protein-ligand binding sites

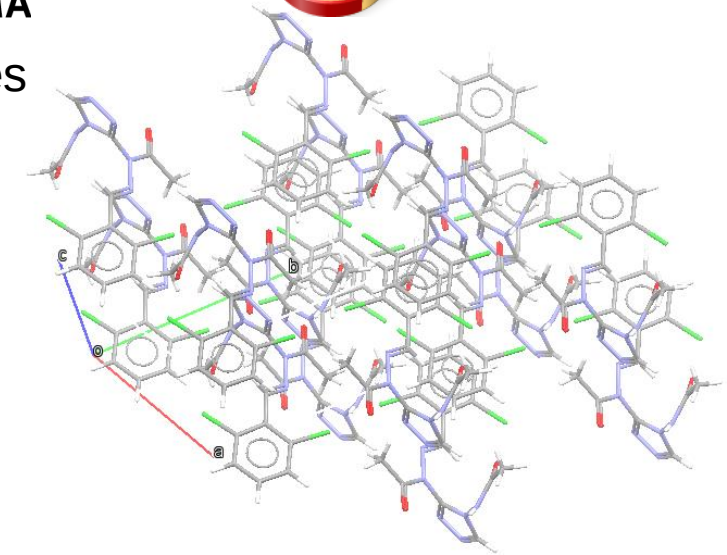
organic small molecules

PDBj
Protein Data Bank Japan



PS PHARMA

In-house databases



[1]Berman, *et al.*, *Nucl. Acids Res.*, **2000**, *28*, 235-242. DOI: 10.1093/nar/28.1.235
[2]Groom, *et al.*, *Acta Cryst. B*, **2016**, *72*, 171-179. DOI: 10.1107/S2052520616003954

CSD-CrossMiner: Pharmacophore Search Tool

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Interactive and Versatile Navigation of Structural Databases

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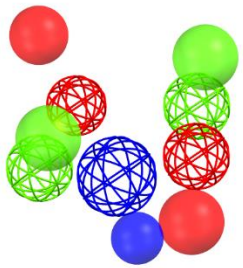
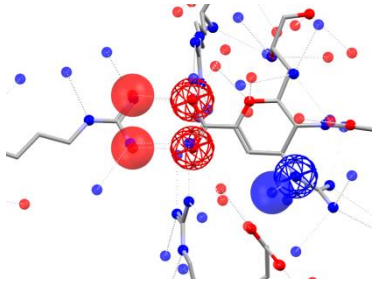
[§]Desert Scientific Software Pty Ltd., Level 5 Nexus Building, Norwest Business Park, 4 Columbia Court, Baulkham Hills, NSW 2153, Australia

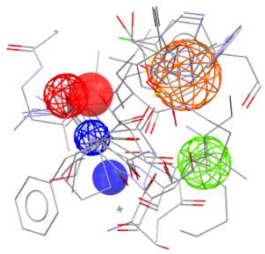
- Tool for pharmacophore-based searches in the PDB and CSD
  - From IUPAC: “an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions”
  - Wikipedia: “abstract description of molecular features”
- Modify a hypothesis/results on the fly

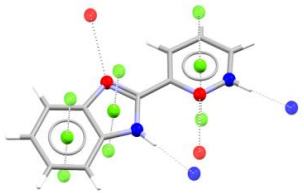
Why use Pharmacophores?

donor
acceptor
planar ring





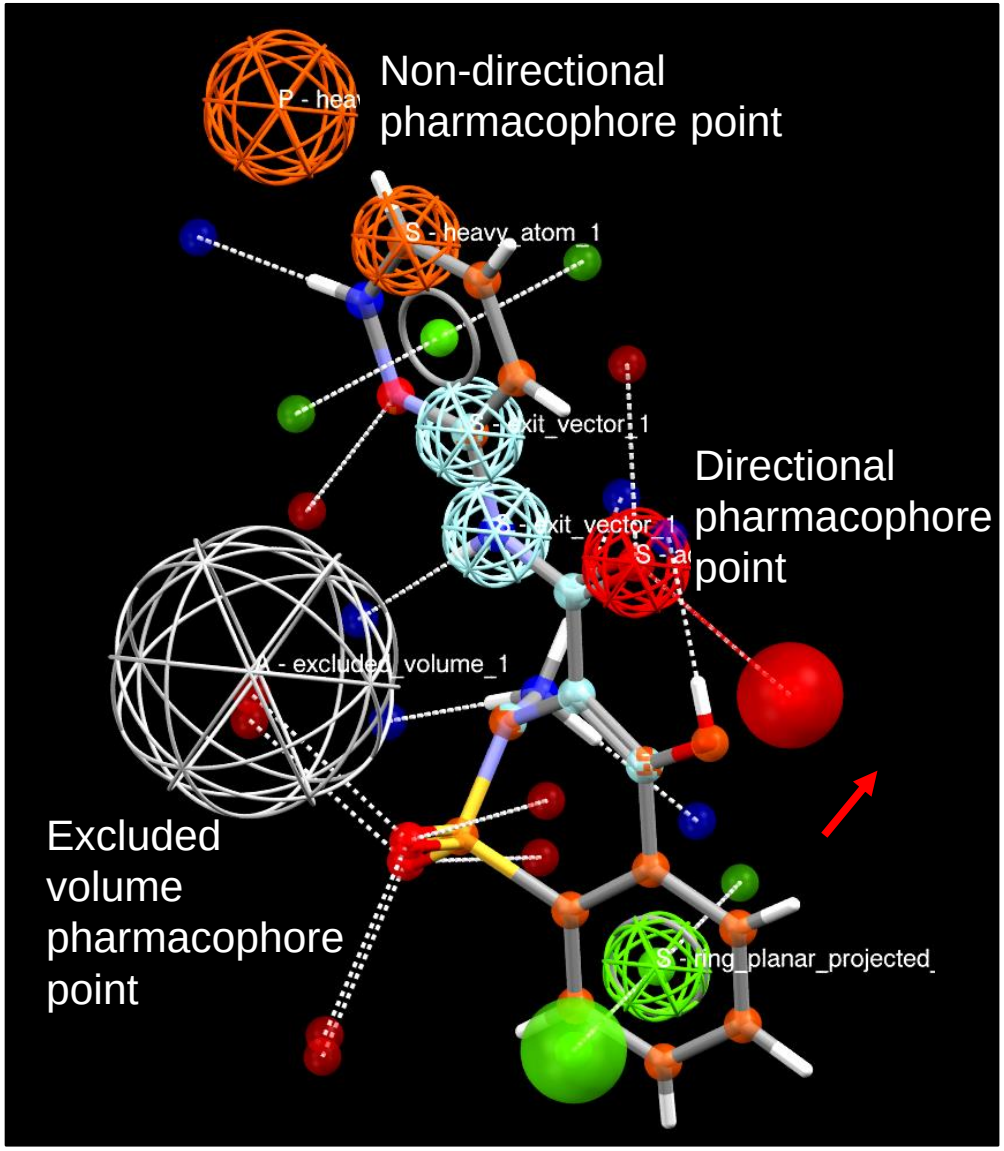




- Intuitive as the query can be specified relative to a 3D structure
  a) Can easily be refined
- *"what you see is what you get"*
  a) Hits will be overlaid onto the query and can be analysed in the same context
- Concept well-understood by medicinal chemists
- Flexible feature definitions
  a) User can control the level of chemical abstraction

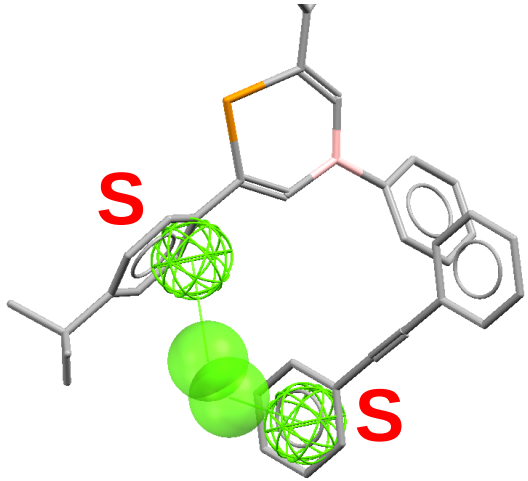
From Features to Pharmacophores

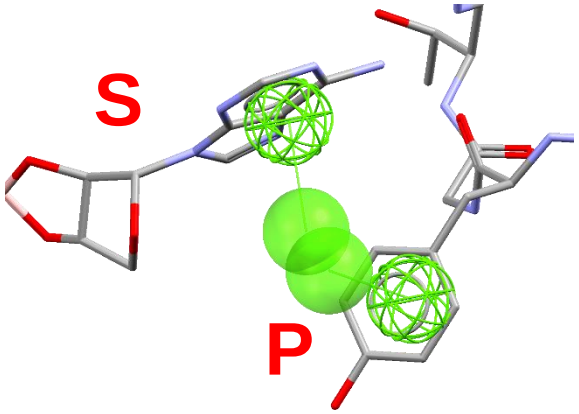
- Molecular structures are annotated with *features*
  - Based on SMARTS patterns
  - Stored in feature database
- Pharmacophore query is based on *tolerance spheres*
  - Sphere radii reflect uncertainty in the position of the features
- Pharmacophore points can be
  - Single point
  - Directional (two points)

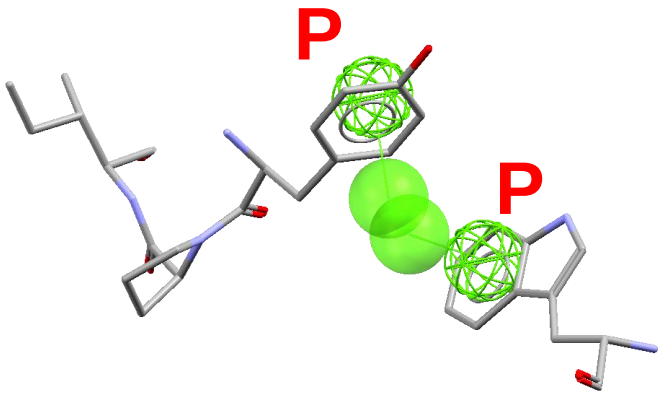


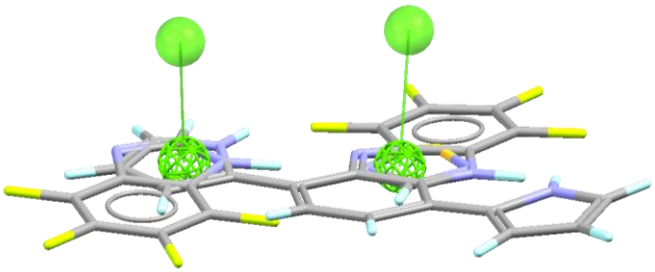
Constraints

Protein (P)
Small molecule (S)

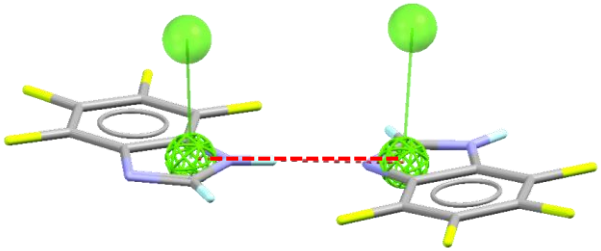




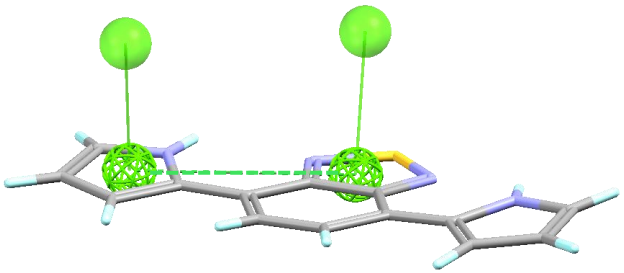




No constraint

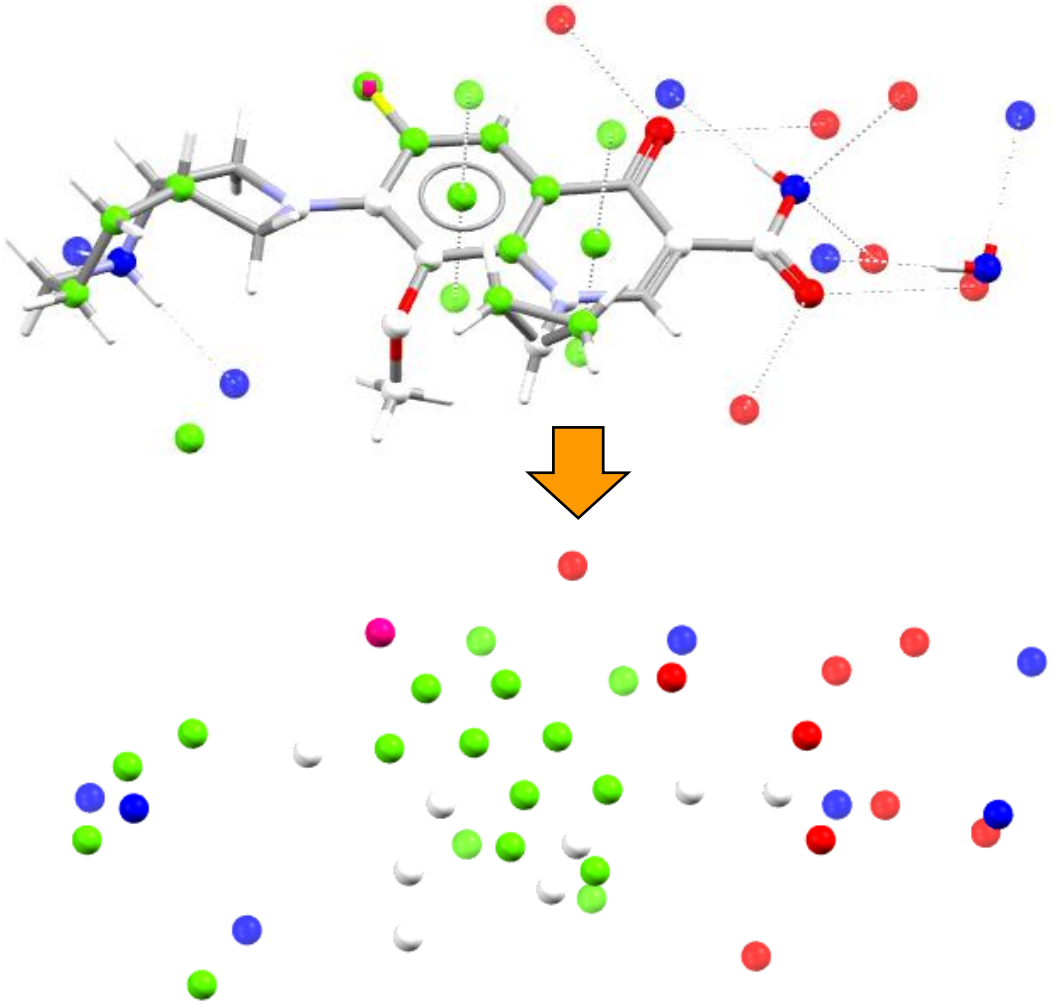


Inter-molecular constraint



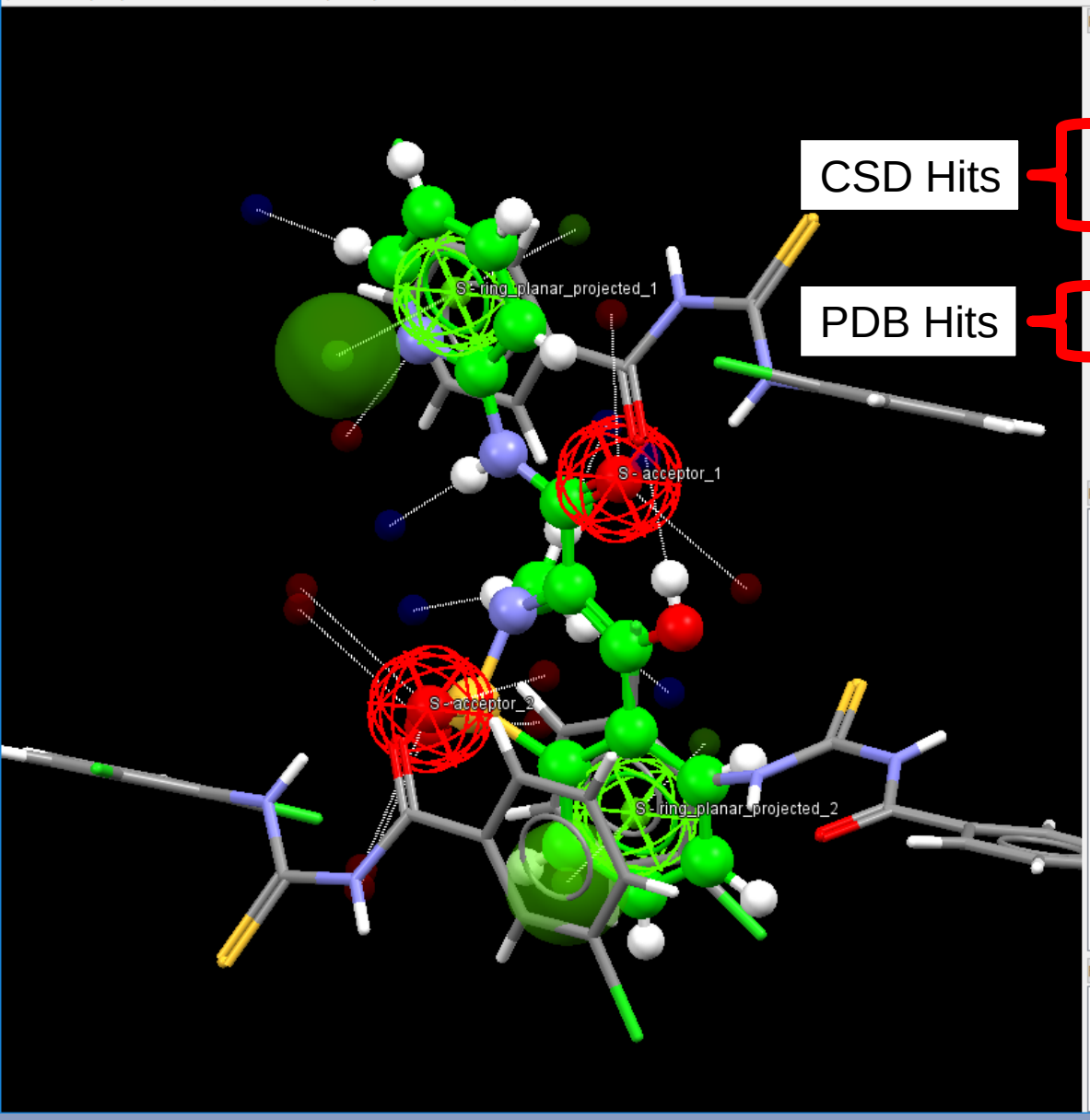
Intra-molecular constraint

Feature Abstraction



the actual search algorithm doesn’t know about molecules

Software Interface



BIYSEH - CSD-CrossMiner

File Edit Display Feature Database Help

Style: Ball and Stick Colour: by Element Picking Mode:

Show: reference hits constraints features pharmacophore pharm. labels hydrogens Search: Edit: intra

x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 zoom- zoom+

CSD Hits

PDB Hits

Results Hitlist

1st in cluster Settings... Tanimoto: 0.70 Number of hits: 370 Show all

mark	identifier	cluster	rmsd	chain	deposition_date	ec_number
	MEHLUH_1	36	0.802			
	MEHMER	37	0.929			
	MEHMIW_1	38	0.713			
	MEHMOC_1	39	0.766			
	MEHNAP	40	0.981			
	1EO3_m1_A-B_...	41	0.812	B	2000-03-21	3.1.21.4
	MEHNIY_1	42	0.759			
	5OE3_m1_D_bs_...	43	0.971	D	2017-07-07	6.2.1.32
	5P91_m1_A_bs_...	44	0.975	A	2016-08-29	2.1.1.6
	5P9H_m1_A_bs...	45	0.865	A	2016-09-20	2.7.10.2
	5PAC_m1_B_bs...	46	0.837	B	2016-11-10	3.4.21.21
	MEHPAR_1	47	0.79			

#hits: 795/10000

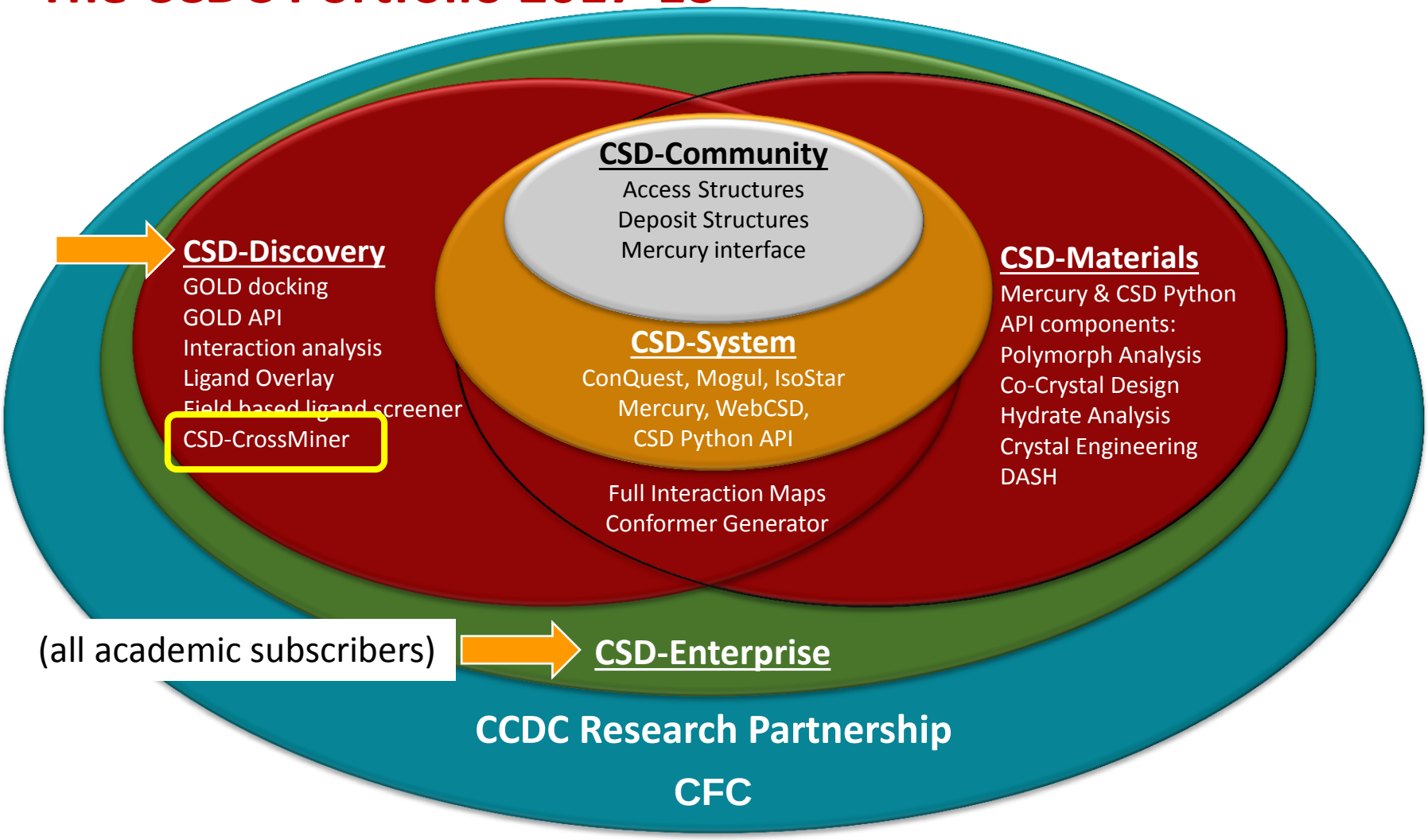
Pharmacophore Features

feature name	tolerance radius	show in reference	show in pharmacophore
acceptor_1			☑
B	1.00		
acceptor_2			☑
B	1.00		
acceptor_projected		☑	
donor_ch_projected		☑	
donor_projected		☑	
heavy_atom		☑	
hydrophobe		☐	
ring		☐	
ring_non_planar		☐	
ring_planar_projected		☑	
ring_planar_project...			☑
B	1.00		
V	1.00		

Feature Databases

database	size
pdb_crossminer	205194
csd539_crossminer	285437

The CCDC Portfolio 2017-18



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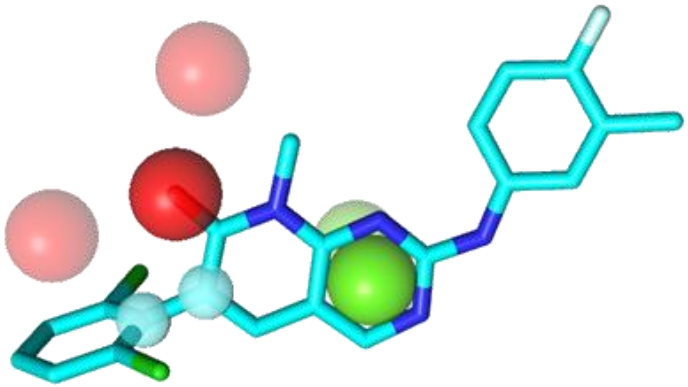
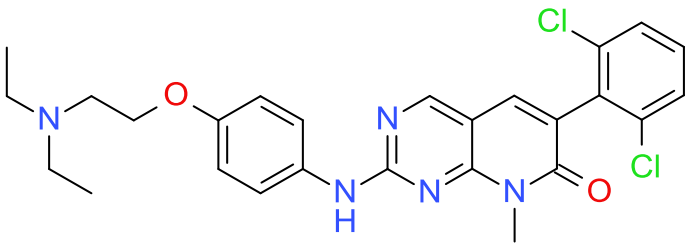
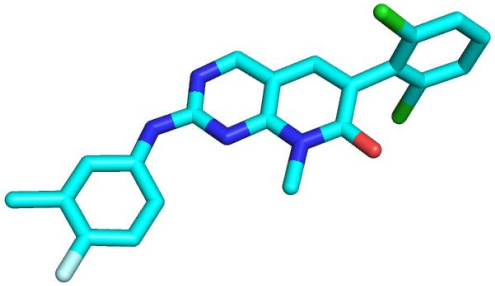


Kinase Inhibitor Scaffold Hopping based on Ligand Features

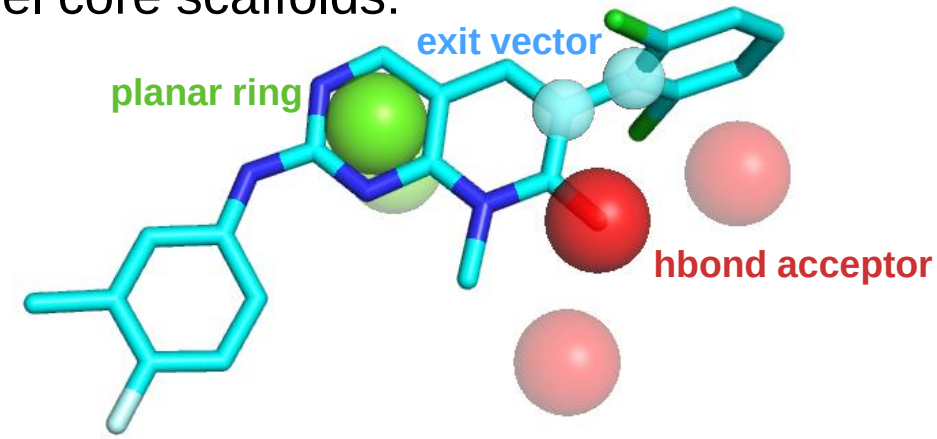


PD166285 is known tyrosine kinase inhibitor



PDB:2hzi
(Abl kinase)

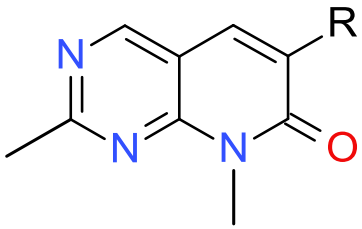
Search for novel core scaffolds:

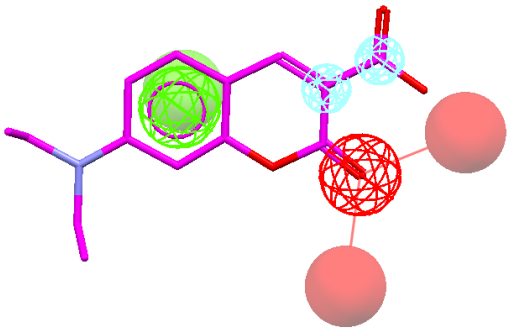


Furet et al., *Bioorg. Med. Chem. Lett.* 2008, *18*, 897 DOI: 10.1016/j.bmcl.2007.12.041 (Novartis)

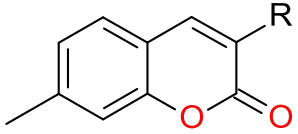
Top-ranking Hit Structures in CSD

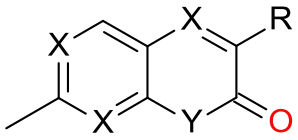
Template:



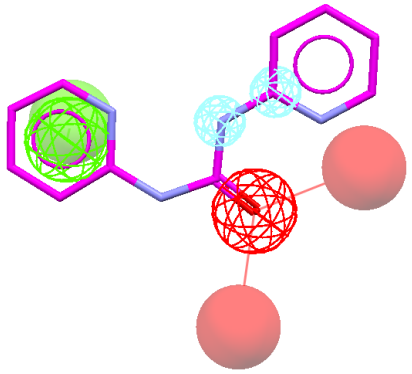


IDUQOO_1

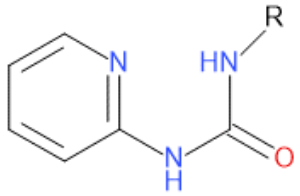


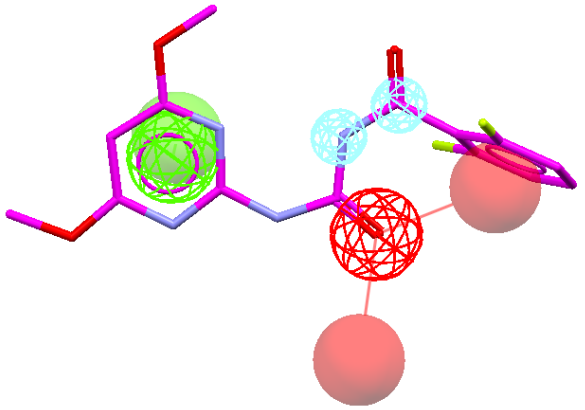


X: C,N
Y: O,N

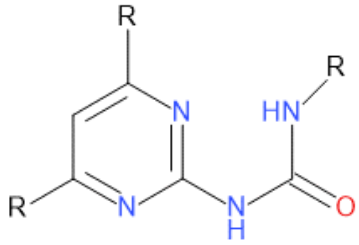


ALOJIW_1





IFAFEB_1



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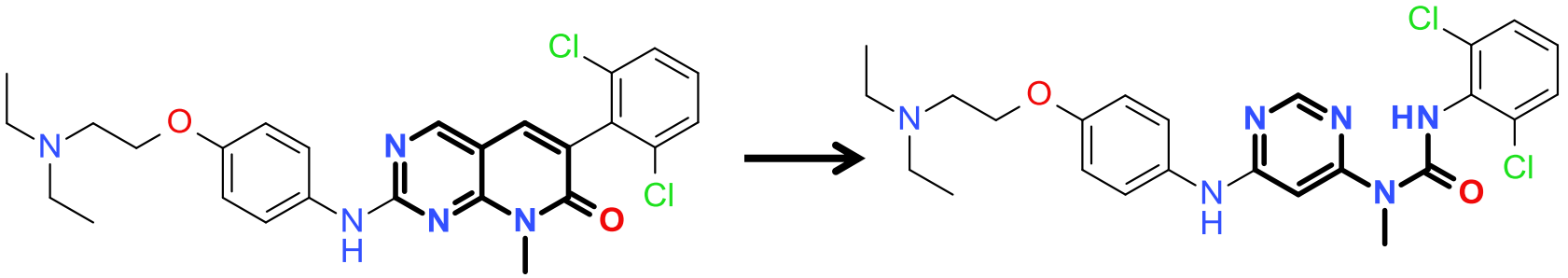
Scaffold Hopping Example from Novartis



These pseudo rings are considered to be particularly stable and represent a new and non-conventional strategy to mimic established lead compounds.

IC_{50} < 1 uM against different kinases

c-Src	0.066
EGF-R	0.38
c-Abl	0.25
FGFR-1	0.57
c-Kit	0.93
KDR	0.96
Tie-2	0.30
p38	0.35
EphB4	0.43

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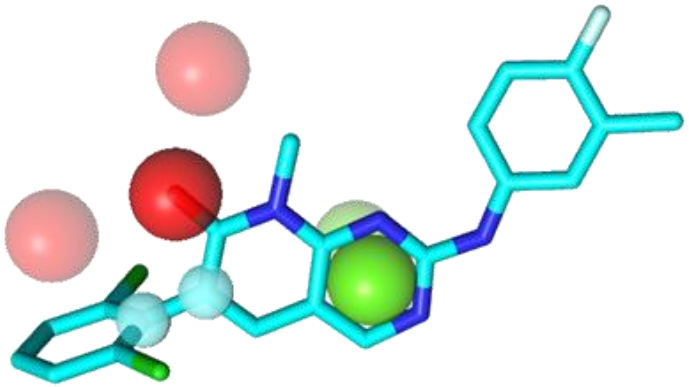
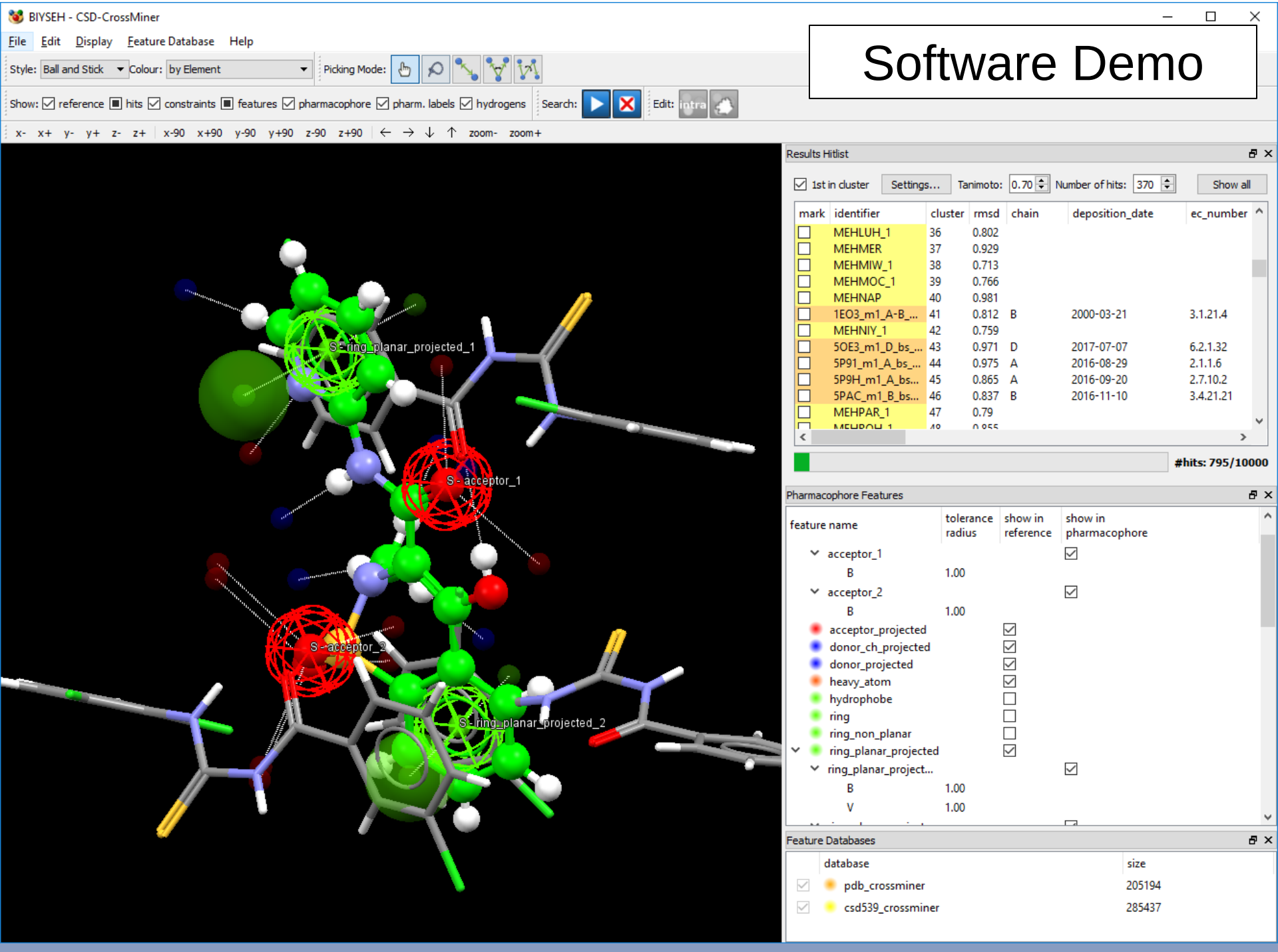
- CSD-CrossMiner application example
- **CSD-CrossMiner software demo**

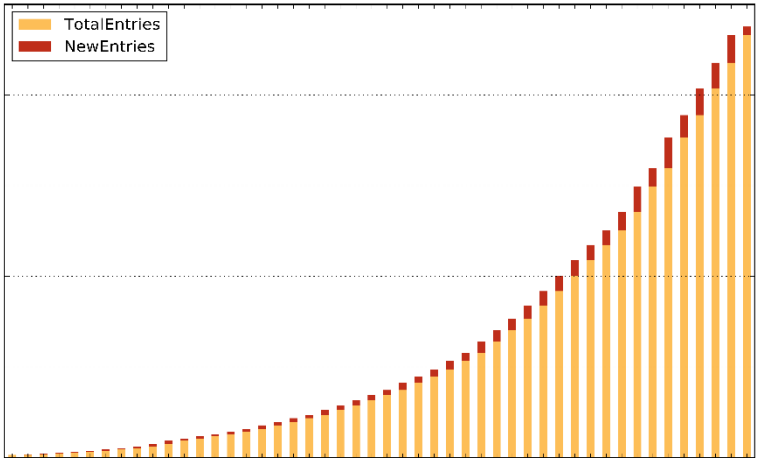


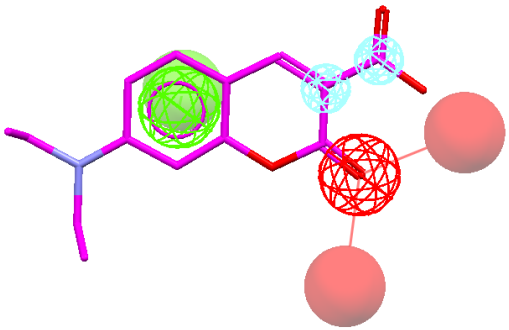
Software Demo

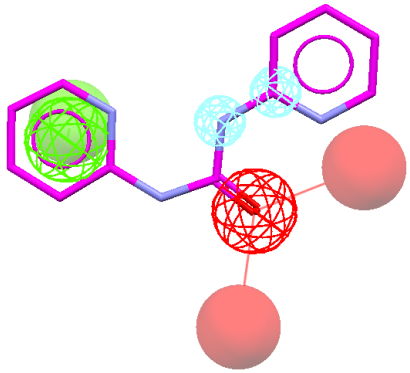


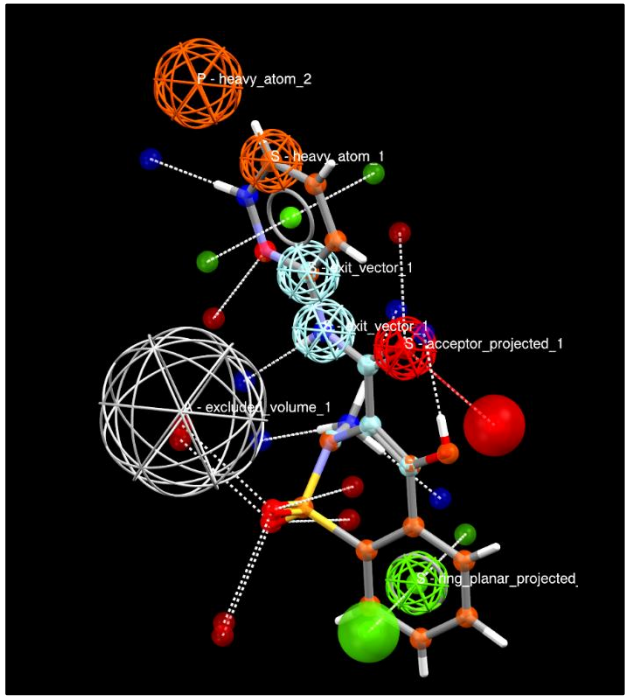
Summary

- Introduction to the CCDC and the CSD
- Introduction to CSD-CrossMiner software
- CSD-CrossMiner application example
- CSD-CrossMiner software demo









Thank you
どうもありがとうございました

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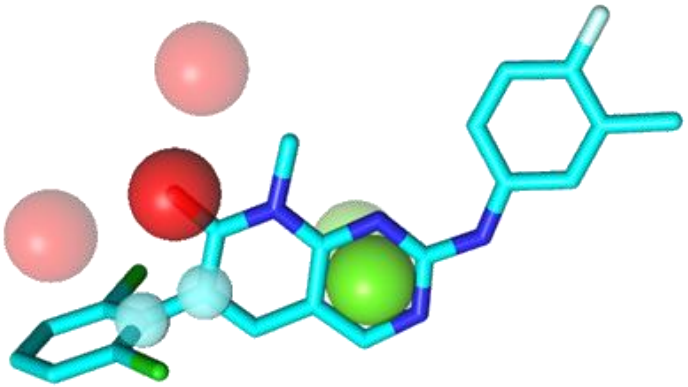
アカデミック向け：大阪大学蛋白質研究所

下家 <kshimoke@protein.osaka-u.ac.jp>



【CSDパッケージソフトの構成】

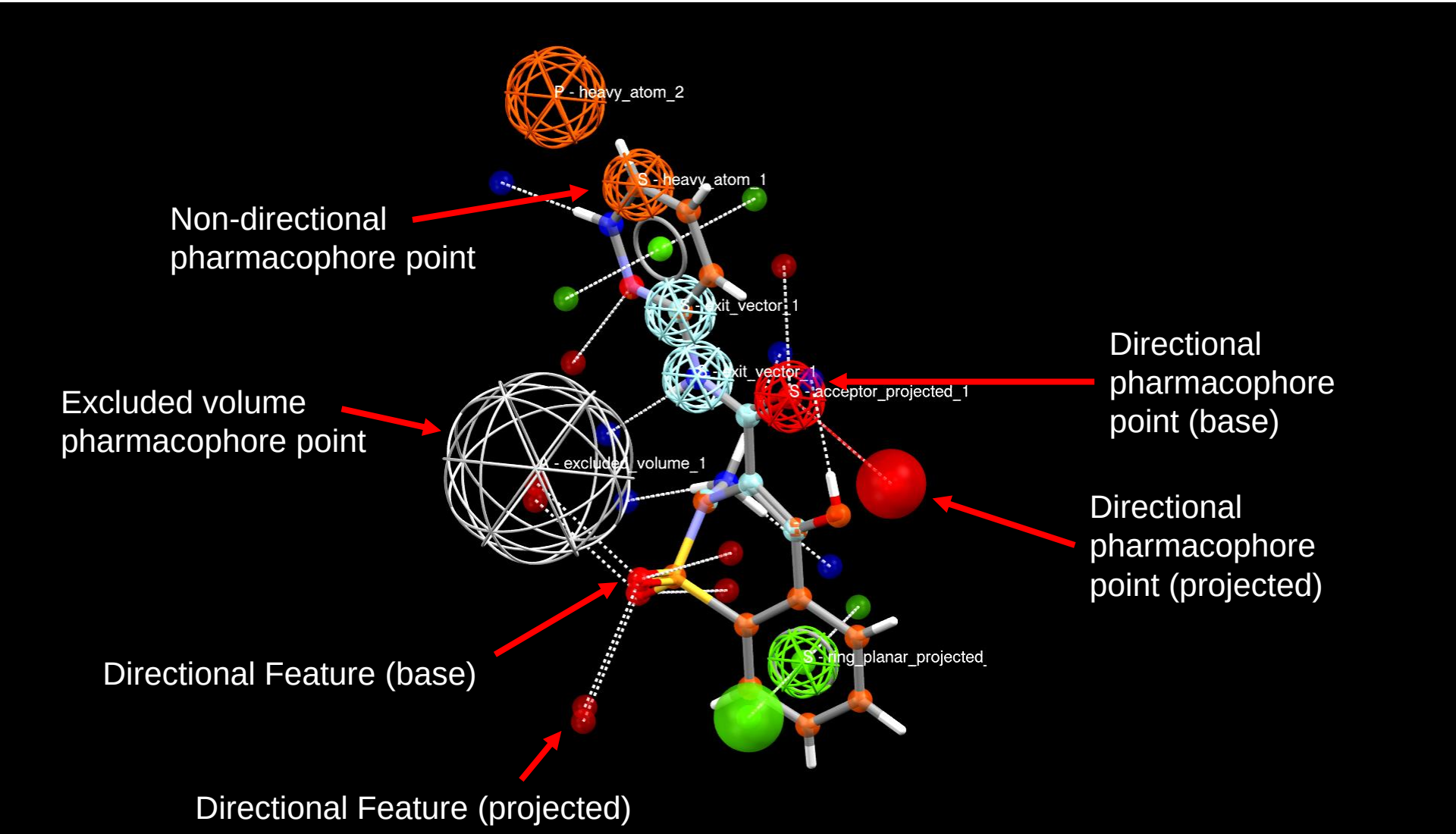
◆The Cambridge Structural Database (CSD): 90万件を超える有機分子の結晶構造を集めたデータベース.
◆CSD-System: CSDの基本セット．データ，検索，解析，表示ソフト付．分子間相互作用のライブラリー
分子ジオメトリーのsubライブラリーMogul付．(企業向け)
◆CSD-Discovery: CSD-System + 創薬向けツールが付属．(企業向け， CSDのアップグレード版)
◆CSD-Materials: CSD-System + 製剤系ツールが付属．(企業向け， CSDのアップグレード版)
◆CSD-Enterprise: CSD-System + すべてのツールが付属.
(アカデミック向けは，これ1本に統合．企業はCSDのアップグレード版として利用可)

	CSD-System	GOLD	Relibase+	CSD-CrossMiner	SuperStar	Conformer Generator/Full Interaction Maps	Materials module	DASH
CSD-System	●							
CSD-Discovery	●	●	●	●	●	●		
CSD-Materials	●					●	●	●
CSD-Enterprise	●	●	●	●	●	●	●	●

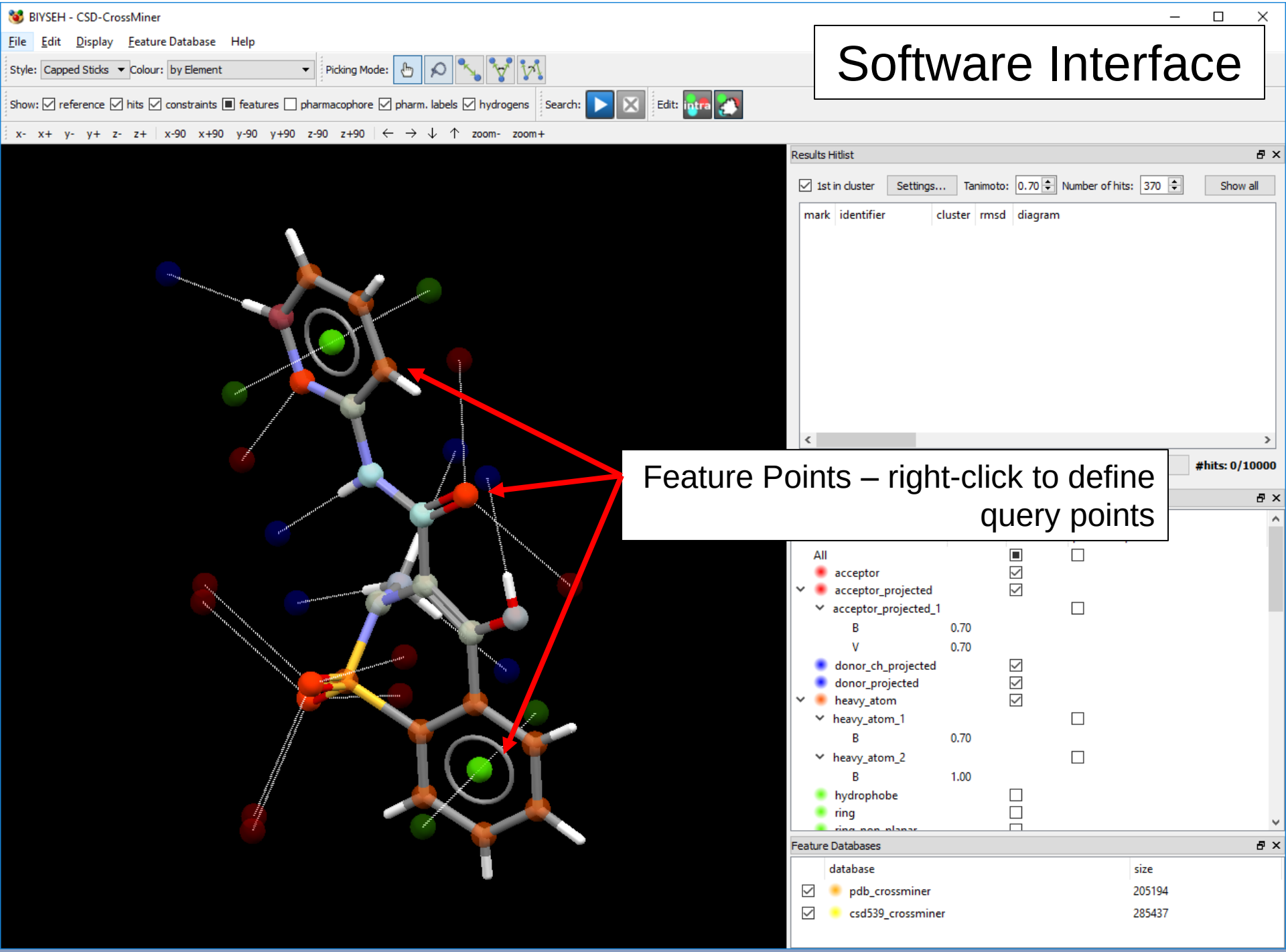
◇GOLD: 遺伝的アルゴリズムを使ったドッキングプログラム．多様なconstrainが容易に設定可能.
◇Relibase+: PDBの3Dを自在に検索可能．PDBの構造も定期的にupdate．(2018年11月頃をもって提供終了を予定)
◇CSD-CrossMiner: 今回リリースされた，CSDおよびPDBのデータをPharmacophoreを元に検索.
◇SuperStar: 注目している蛋白質の結合部位に対し，相互作用のhotspotをCSDのデータをもとに視覚化.
◇Conformer Generator: CSDの実験データをもとにconformerを自動発生．経験値からの配座発生のため，瞬時に発生可能.
◇Full Interaction Map:注目している分子に対して，周りの相互作用をCSDのデータをもとに視覚化.
◇Materials Module: 類似パッキングの検索，水素結合様式に基づく，多形結晶の可能性プロット，水和物の解析など，
固体結晶の解析に役立つツール.
◇DASH: 粉末結晶構造解析ソフト．粉末パターンから結晶構造を導きます.

詳細，お問い合わせは，https://www.ccdc.cam.ac.uk/solutions/
アカデミック：http://www.protein.osaka-u.ac.jp/csd/csd.html
企業：https://www.jaici.or.jp/wcas/csdpackage.htm

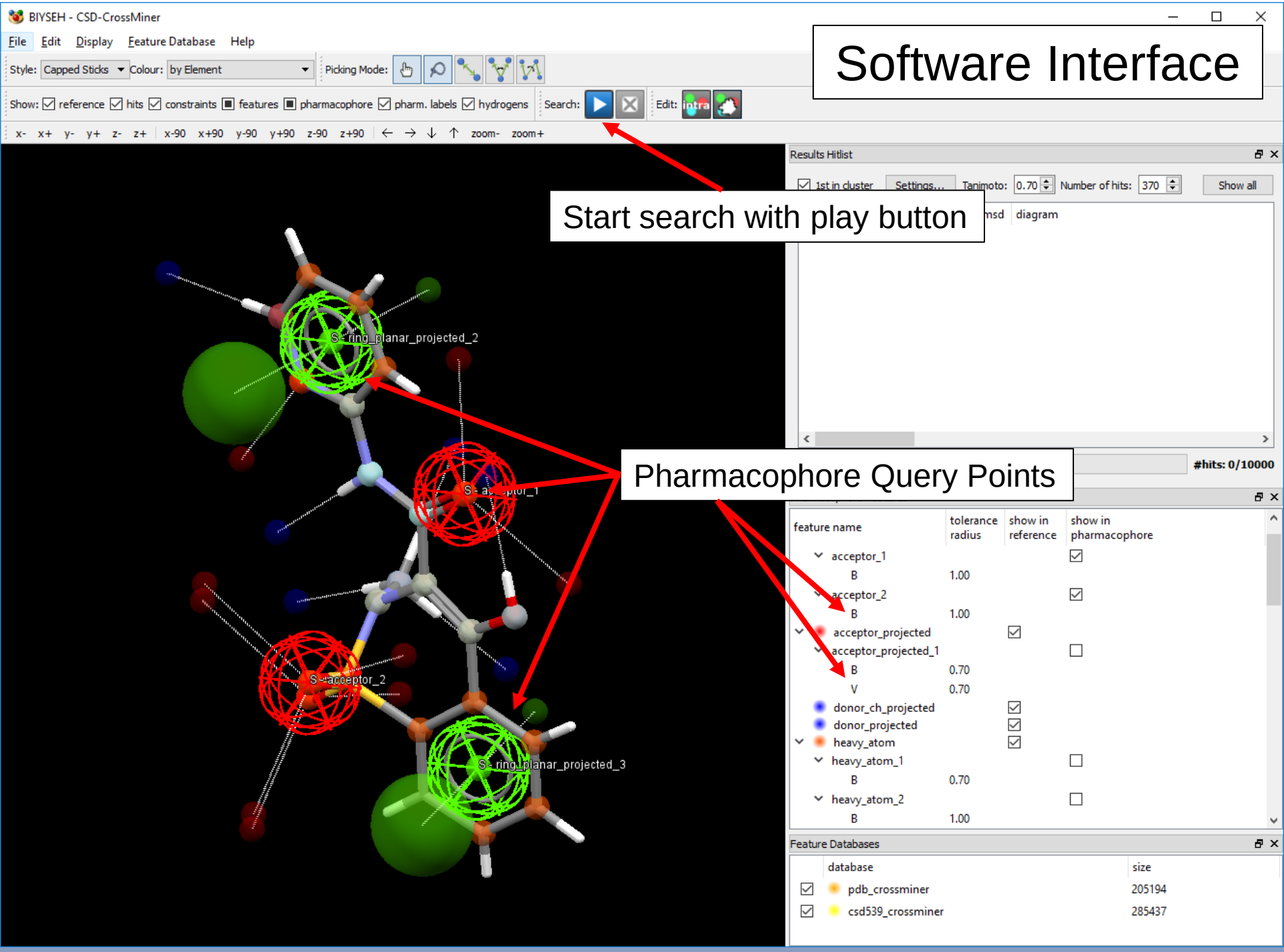
Feature and Pharmacophore Representation



Software Interface



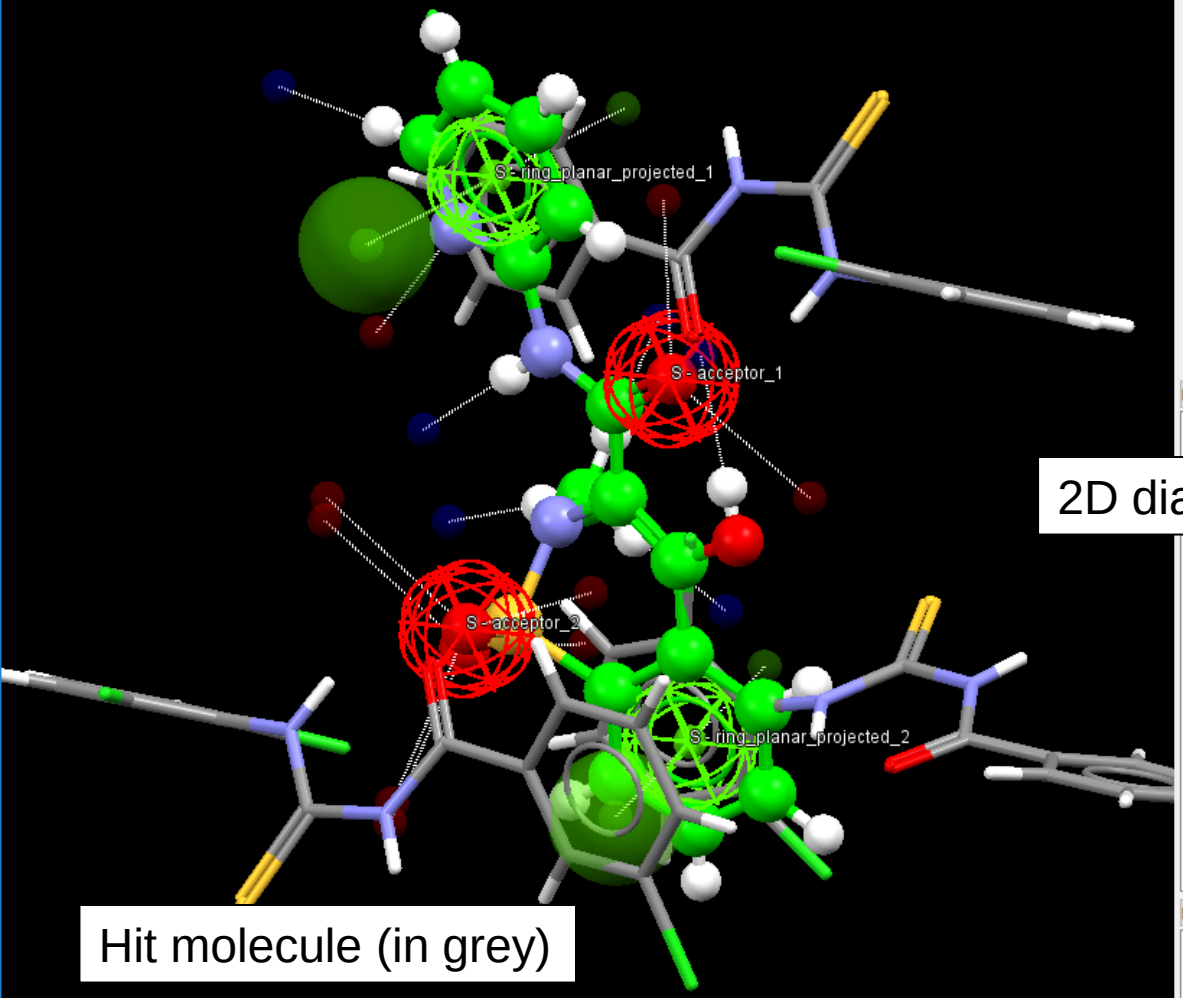
Feature Points – right-click to define query points


BIYSEH - CSD-CrossMiner
File Edit Display Feature Database Help
Style: Capped Sticks Colour: by Element Picking Mode:
Show: reference hits constraints features pharmacophore pharm. labels hydrogens Search: Edit:
x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 zoom- zoom+
Software Interface
Start search with play button
Pharmacophore Query Points
S - ring_planar_projected_2
S - acceptor_2
S - ring_planar_projected_3
Results Hitlist
1st in cluster Settings... Tanimoto: 0.70 Number of hits: 370 Show all
msd diagram
#hits: 0/10000
feature name tolerance radius show in reference show in pharmacophore
acceptor_1
B 1.00
acceptor_2
B 1.00
acceptor_projected
acceptor_projected_1
B 0.70
V 0.70
donor_ch_projected
donor_projected
heavy_atom
heavy_atom_1
B 0.70
heavy_atom_2
B 1.00
Feature Databases
database size
pdb_crossminer 205194
csd539_crossminer 285437

Software Interface

As search is running, hits appear as they are found

Reference molecule in green



Hit molecule (in grey)

2D diagram with query points aligned

BIYSEH - CSD-CrossMiner

File Edit Display Feature Database Help

Style: Ball and Stick Colour: by Element Picking Mode:

Show: reference hits constraints features pharmacophore pharm. labels hydrogens Search: Edit: intra

x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 zoom-

1st in cluster Settings... Tanimoto: 0.70 Number of hits: 370 Show all

mark	identifier	cluster	rmsd	diagram
☐	MEHJUF_1	33	0.808	

#hits: 795/10000

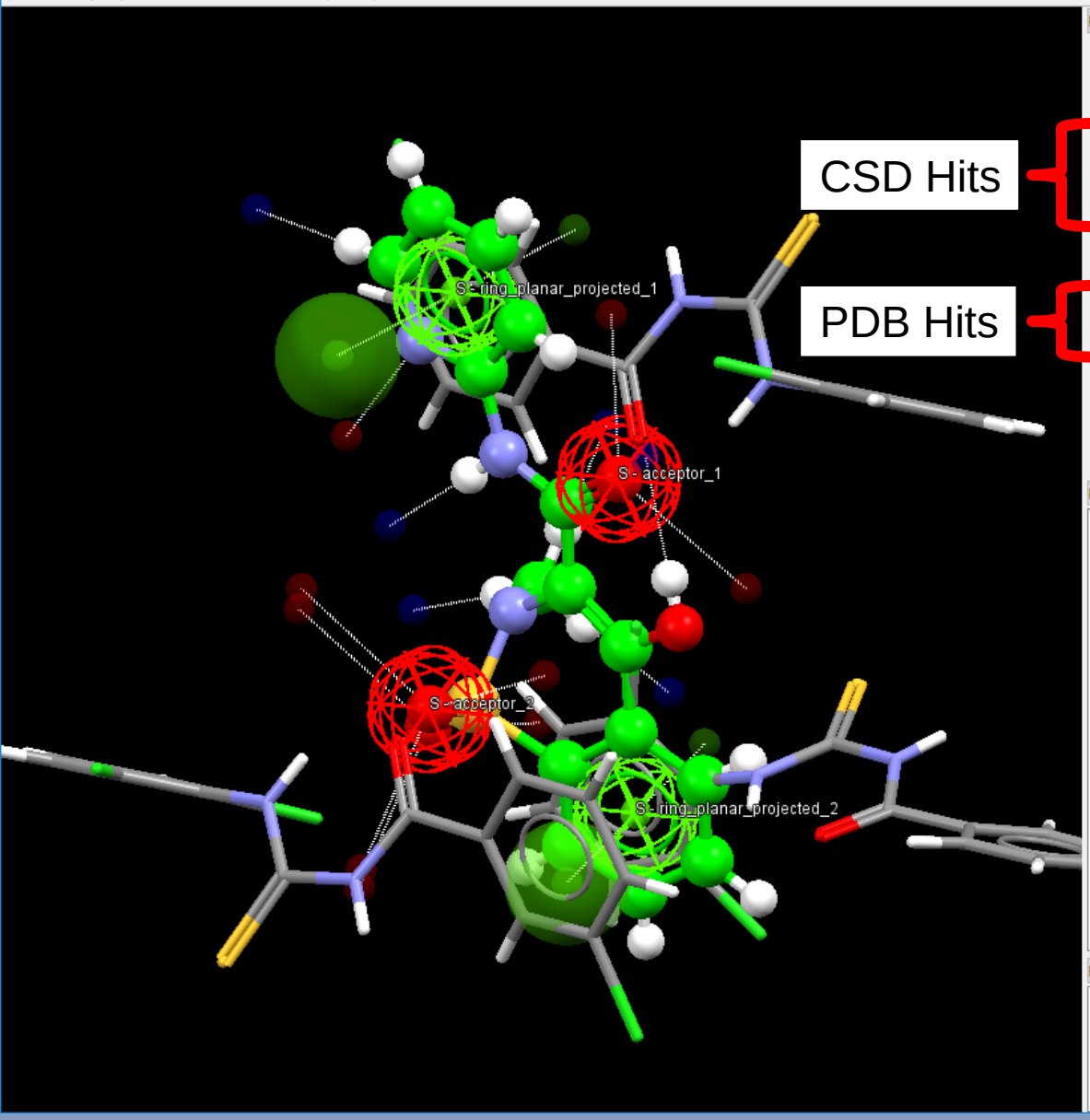
Pharmacophore Features

feature name	tolerance radius	show in reference	show in pharmacophore
acceptor_2			☑
B	1.00		
acceptor_projected		☑	
donor_ch_projected		☑	
donor_projected		☑	
heavy_atom		☑	
hydrophobe		☐	
ring		☐	
ring_non_planar		☐	
ring_planar_projected		☑	
ring_planar_project...			☑
B	1.00		
V	1.00		

Feature Databases

database	size
pdb_crossminer	205194
csd539_crossminer	285437

Software Interface



BIYSEH - CSD-CrossMiner

File Edit Display Feature Database Help

Style: Ball and Stick Colour: by Element Picking Mode:

Show: reference hits constraints features pharmacophore pharm. labels hydrogens Search: Edit: intra

x- x+ y- y+ z- z+ x-90 x+90 y-90 y+90 z-90 z+90 zoom- zoom+

CSD Hits

PDB Hits

Results Hitlist

1st in cluster Settings... Tanimoto: 0.70 Number of hits: 370 Show all

mark	identifier	cluster	rmsd	chain	deposition_date	ec_number
	MEHLUH_1	36	0.802			
	MEHMER	37	0.929			
	MEHMIW_1	38	0.713			
	MEHMOC_1	39	0.766			
	MEHNAP	40	0.981			
	1EO3_m1_A-B_...	41	0.812	B	2000-03-21	3.1.21.4
	MEHNIY_1	42	0.759			
	5OE3_m1_D_bs_...	43	0.971	D	2017-07-07	6.2.1.32
	5P91_m1_A_bs_...	44	0.975	A	2016-08-29	2.1.1.6
	5P9H_m1_A_bs...	45	0.865	A	2016-09-20	2.7.10.2
	5PAC_m1_B_bs...	46	0.837	B	2016-11-10	3.4.21.21
	MEHPAR_1	47	0.79			

#hits: 795/10000

Pharmacophore Features

feature name	tolerance radius	show in reference	show in pharmacophore
acceptor_1			☑
B	1.00		
acceptor_2			☑
B	1.00		
acceptor_projected		☑	
donor_ch_projected		☑	
donor_projected		☑	
heavy_atom		☑	
hydrophobe		☐	
ring		☐	
ring_non_planar		☐	
ring_planar_projected		☑	
ring_planar_project...			☑
B	1.00		
V	1.00		

Feature Databases

database	size
pdb_crossminer	205194
csd539_crossminer	285437