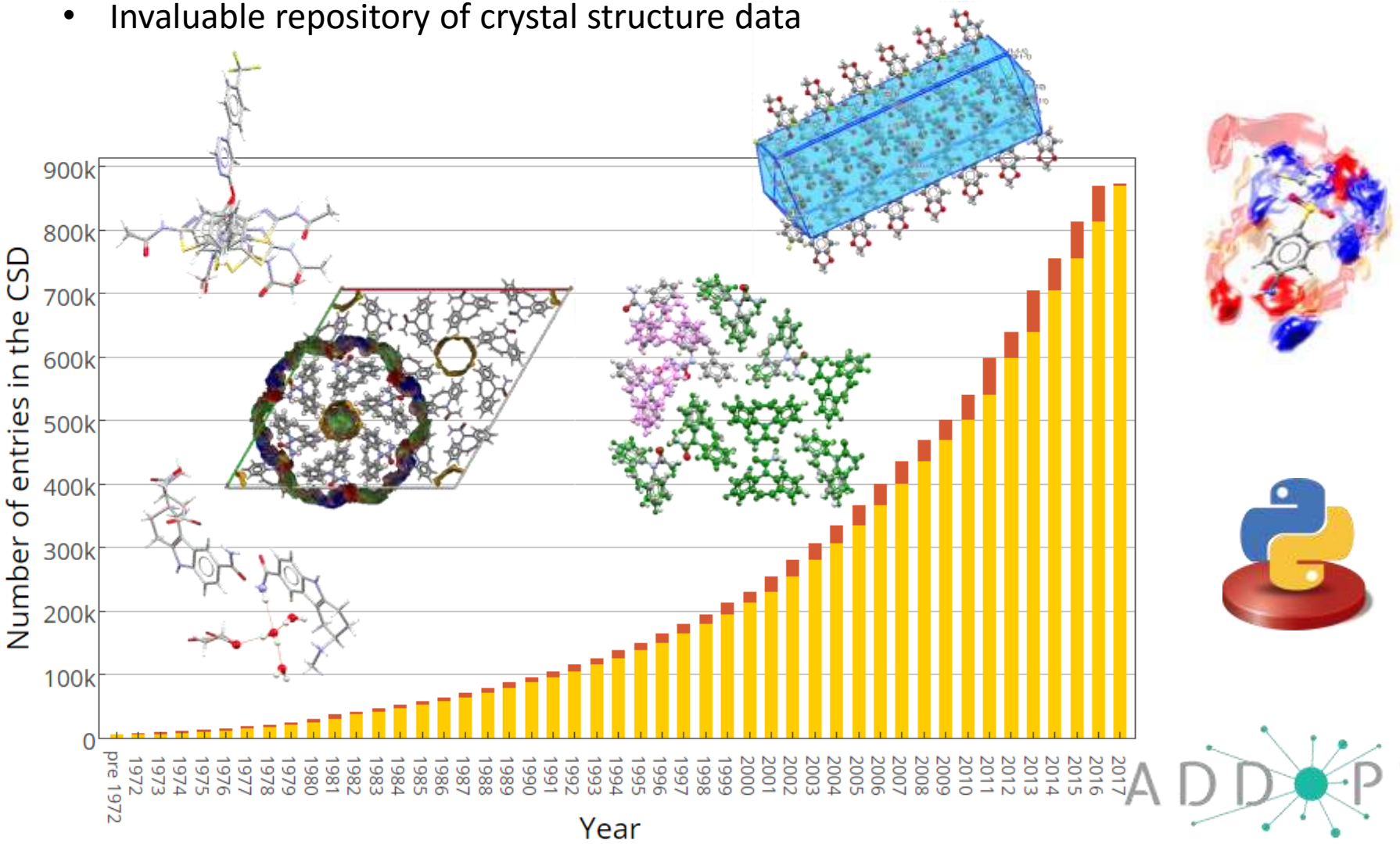
Streamlining pharmaceutical supply chain processes:

The emerging application of solid-state structural informatics

Mathew J. Bryant, Andrew G.P. Maloney and Neil Feeder

The Cambridge Structural Database

- All small-molecule organic & metal-organic crystal structures ever published.
- CSD contains over 875,000 crystal structures
- Invaluable repository of crystal structure data



The ADDoPT Project

- **A**dvanced **D**igital **D**esign **o**f **P**harmaceutical **T**herapeutics
  - Four year collaboration between government, industry and academia

  - Instigated by the Medicines Manufacturing Industry Partnership and part funded under the **Advanced Manufacturing Supply Chain Initiative**

ADDOPT

Digital Design: Molecules to Medicine

Product and Process Design

Upstream

Materials properties
Surface chemistry
Release profiles
Manufacturing classification
Particle attributes
Processing rules
Quality systems
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Product Performance

Downstream

Primary Manufacturing - Secondary Manufacturing

Active Ingredient (API)

Crystallisation
Filtration
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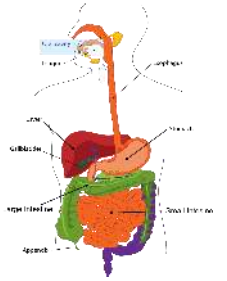


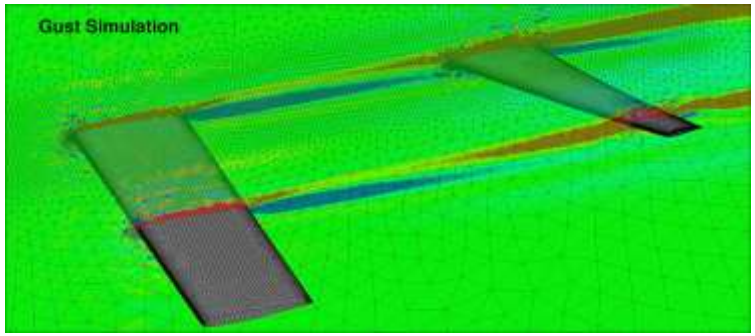
Processes **Products** **Performance**

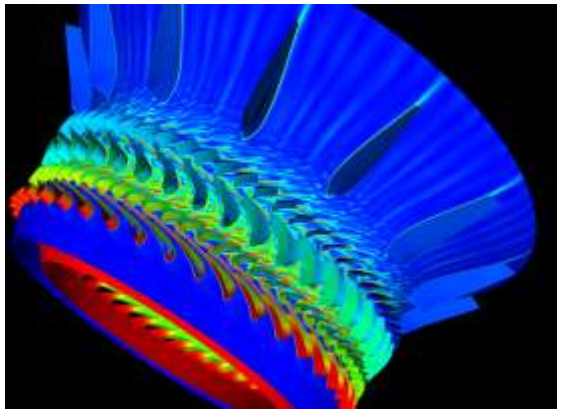
Design and control of optimised development & manufacturing processes through data analysis and first principle models

ADD PT

- If we designed airplanes like we design drugs…

Woltosz, W.S. J. Comput. Aided Mol. Des. (2012) 26: 159





"Why has pharmaceutical research and development lagged so far behind other industries in the development and application of simulation and modelling for research and development?"

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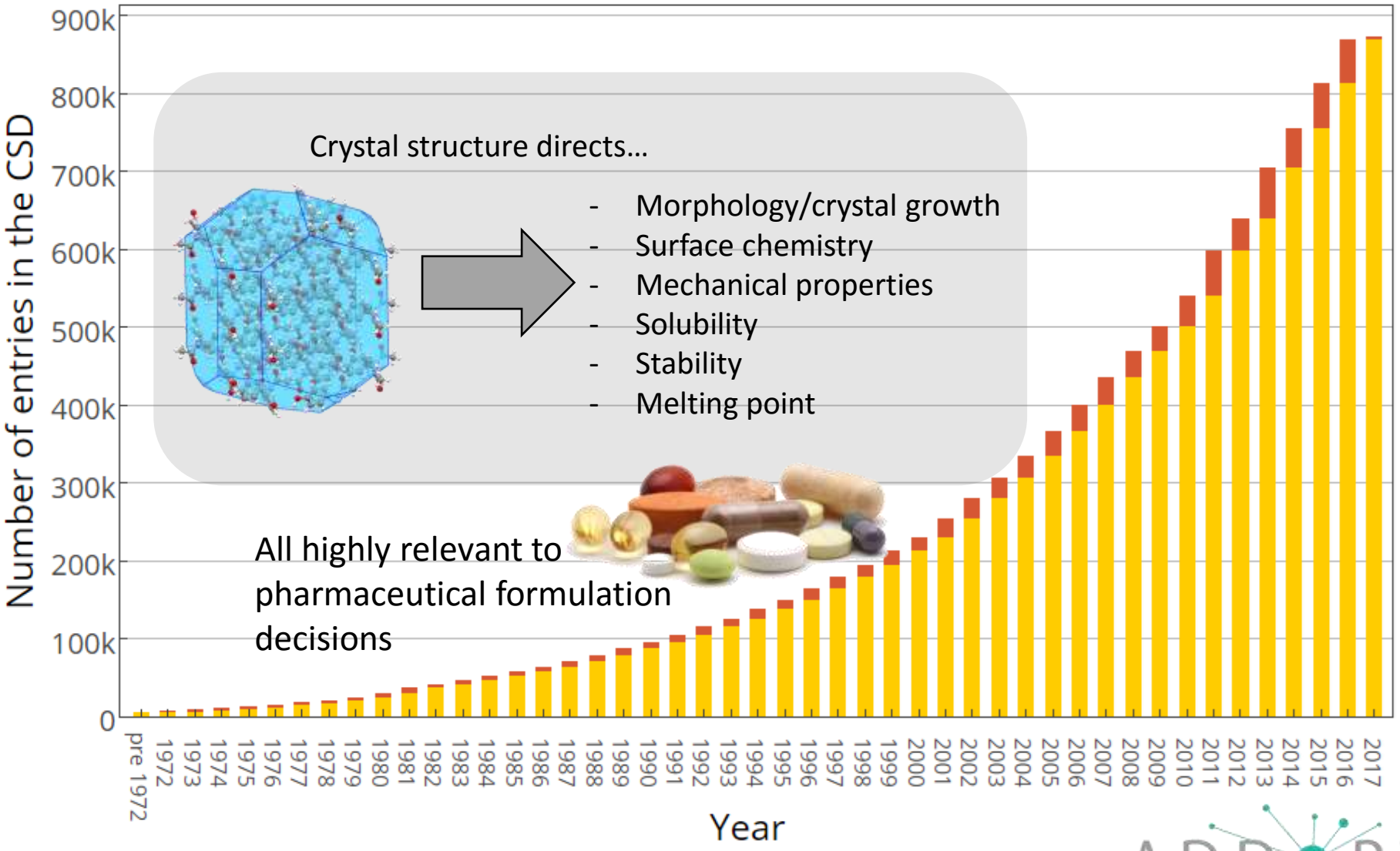
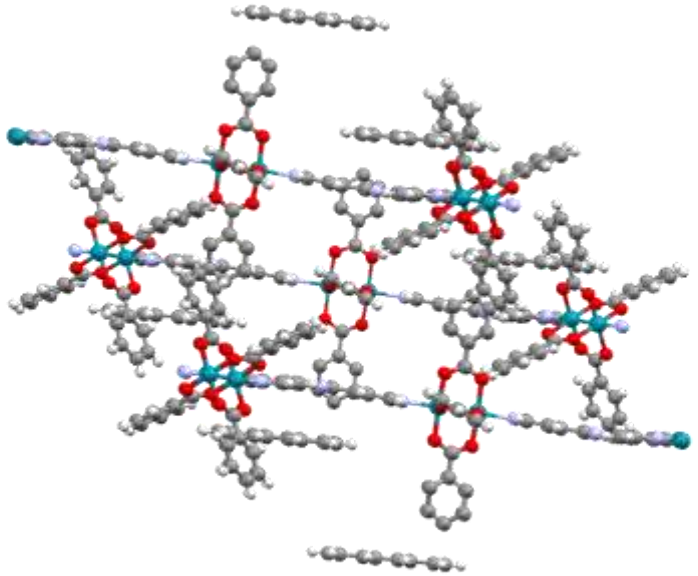
Digital design of pharmaceuticals using the CSD



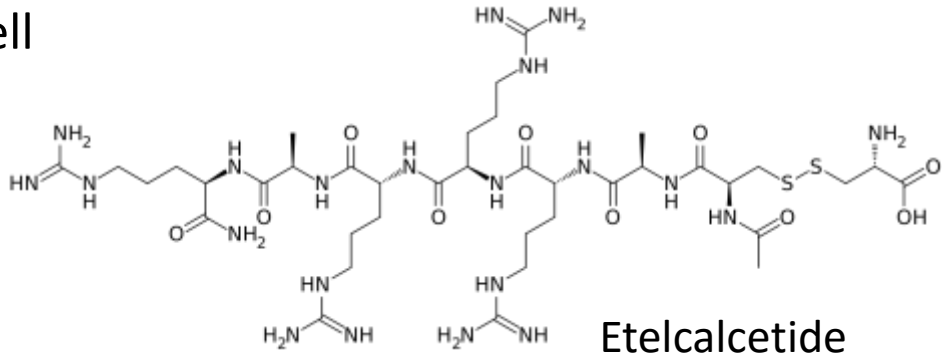
Making the CSD relevant to drugs

- 57% of structures in the CSD are metal-organic



- Currently working towards creating a ‘Drug like’ subset

- Lipinski's rule of 5 doesn’t apply well to modern drugs



Etelcalcetide

- Initially decided to look at actual approved drugs in the CSD

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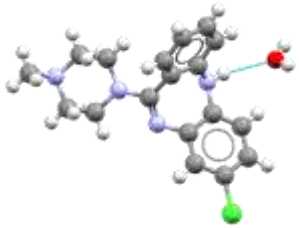
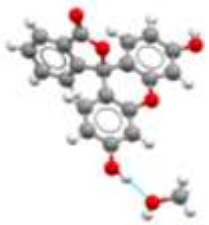
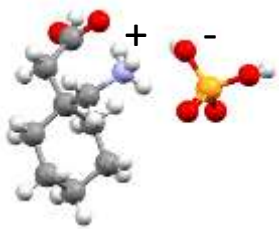
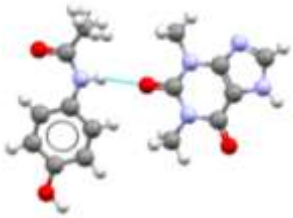
Making the CSD relevant to drugs

- CSD Drug Subset has now been established
- Drug definition taken from the approved drug database of Drugbank.ca

DRUGBANK
Open Data Drug & Drug Target Database

- Generated using InChI strings and the CSD Python API
- 8632 crystal structures representing 785 drug molecules
- Searchable and sortable by categories like hydrates, solvates, salts, co-crystals, pure drug (or any combination of these)



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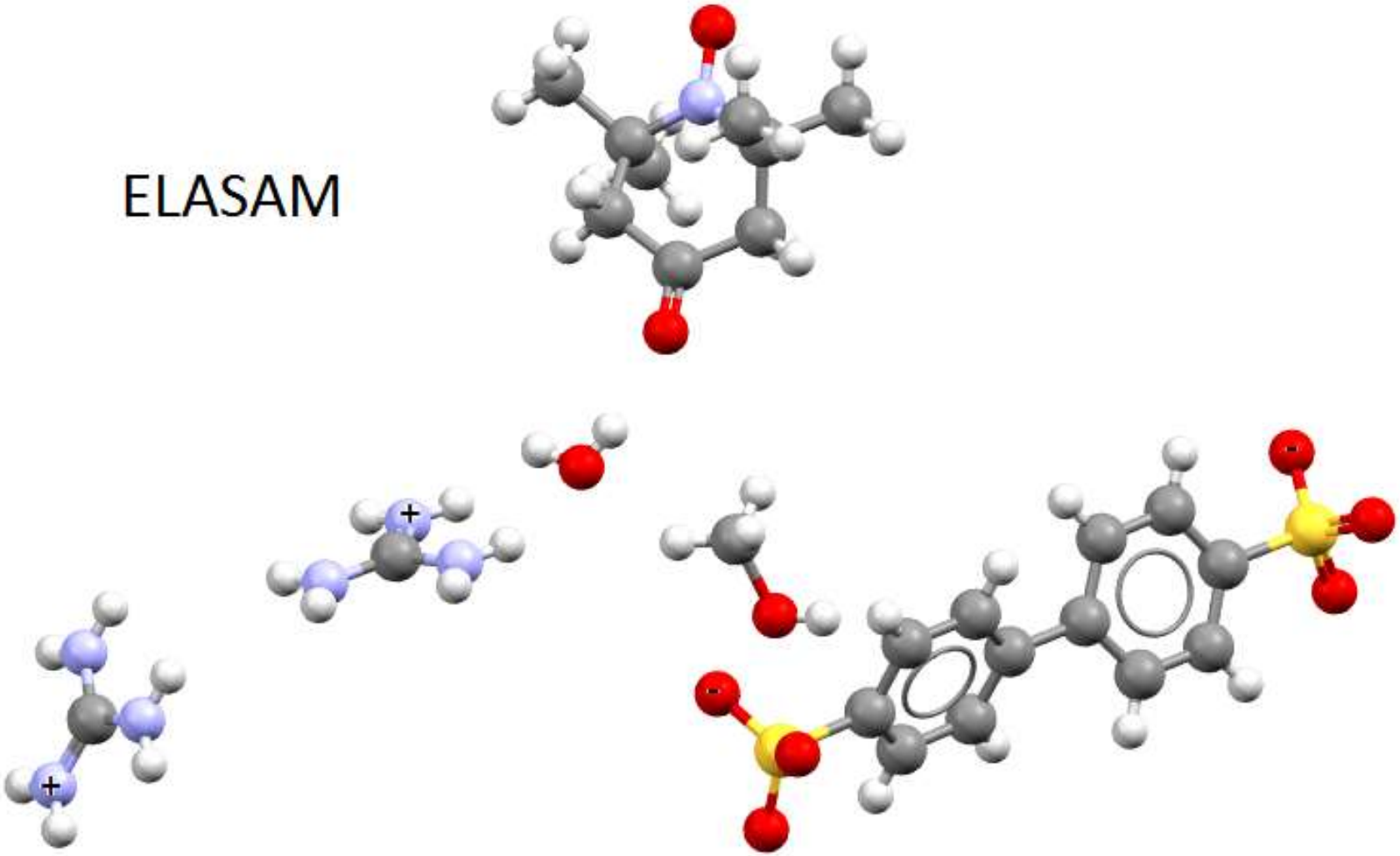
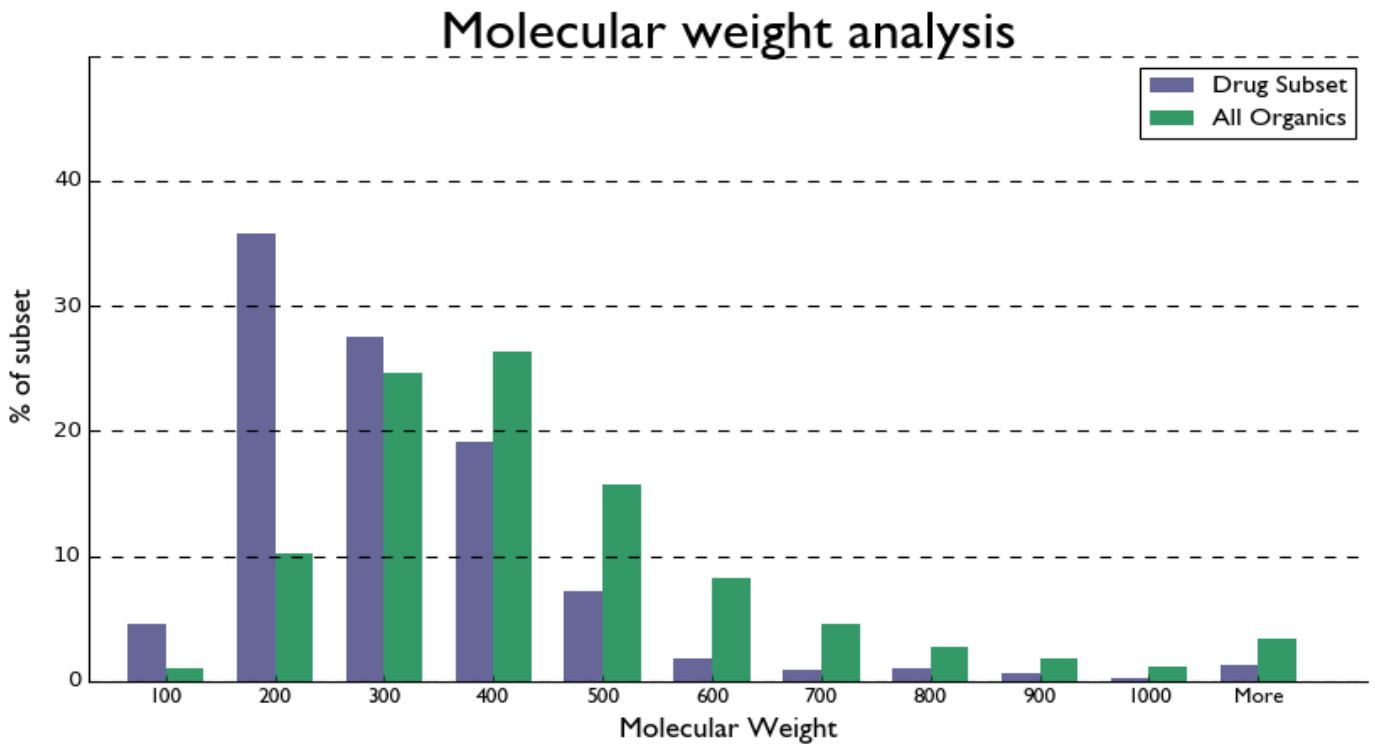
Proportions of each type in CSD Drug Subset

ELASAM

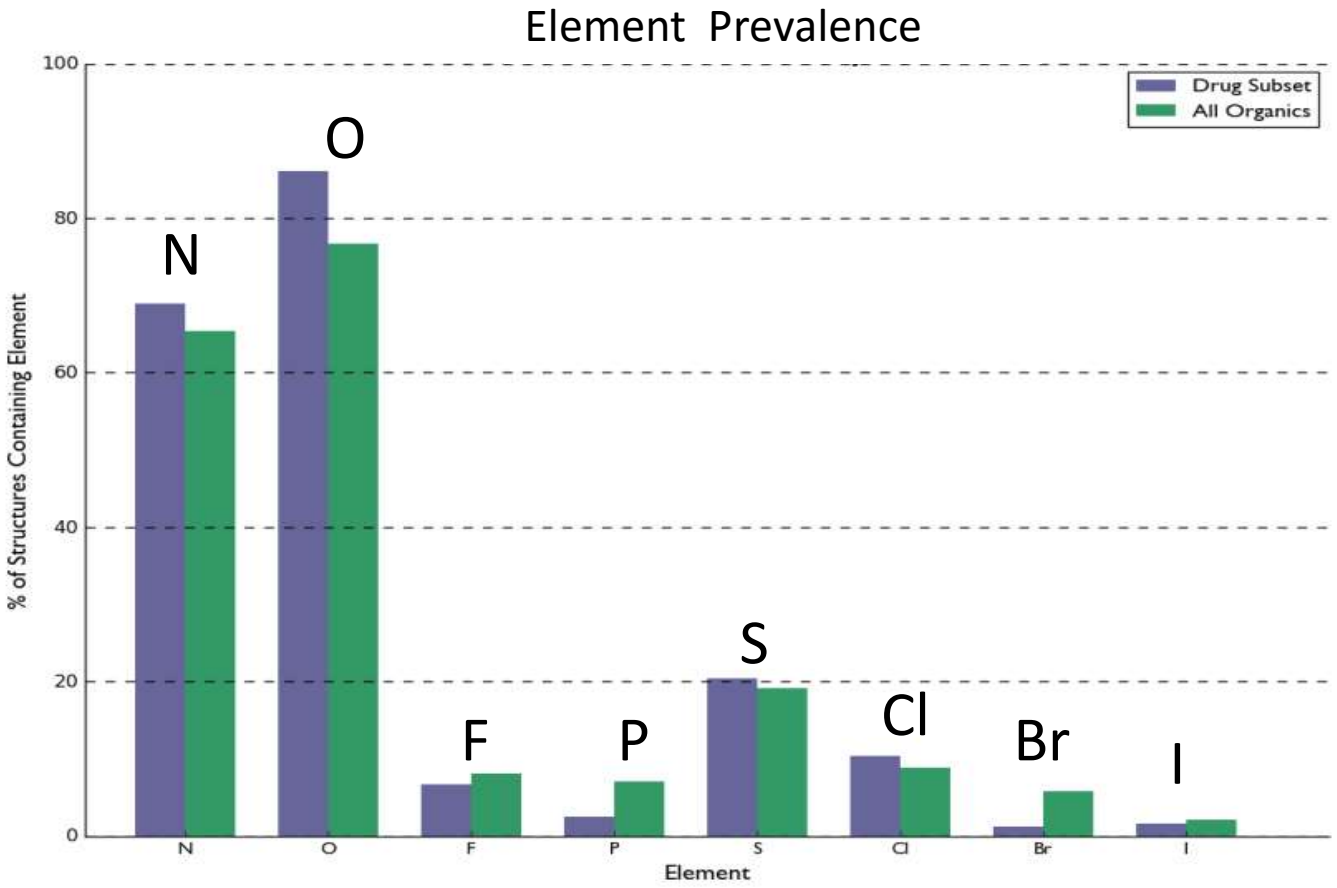


Comparison to organic molecules in the CSD – Molecular weight



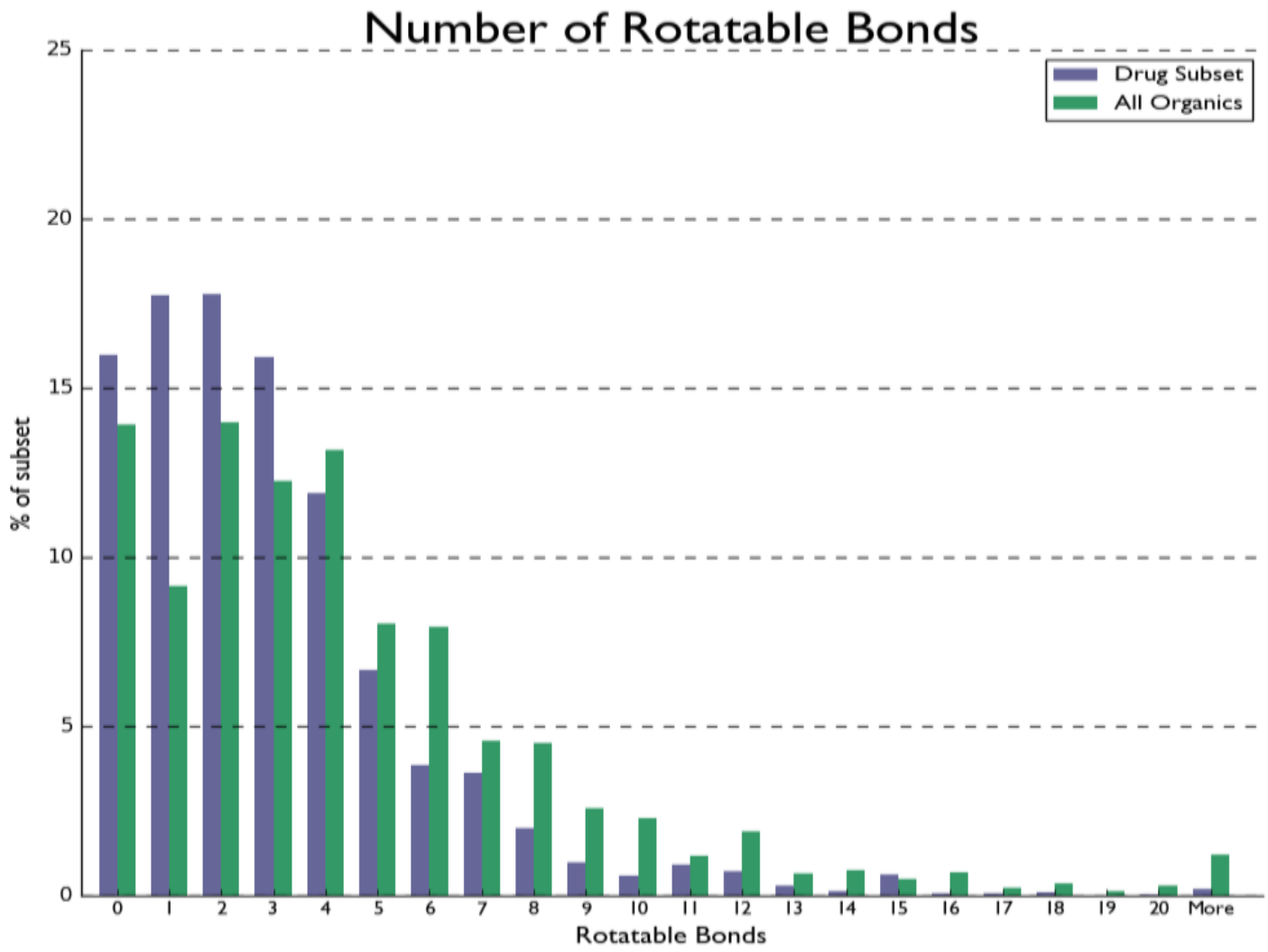
- Clear trend towards lower molecular weights for drug molecules
- Highest percentage of Drugs fall between 100 and 200 g/mol

Comparison to organic molecules in the CSD - Elements



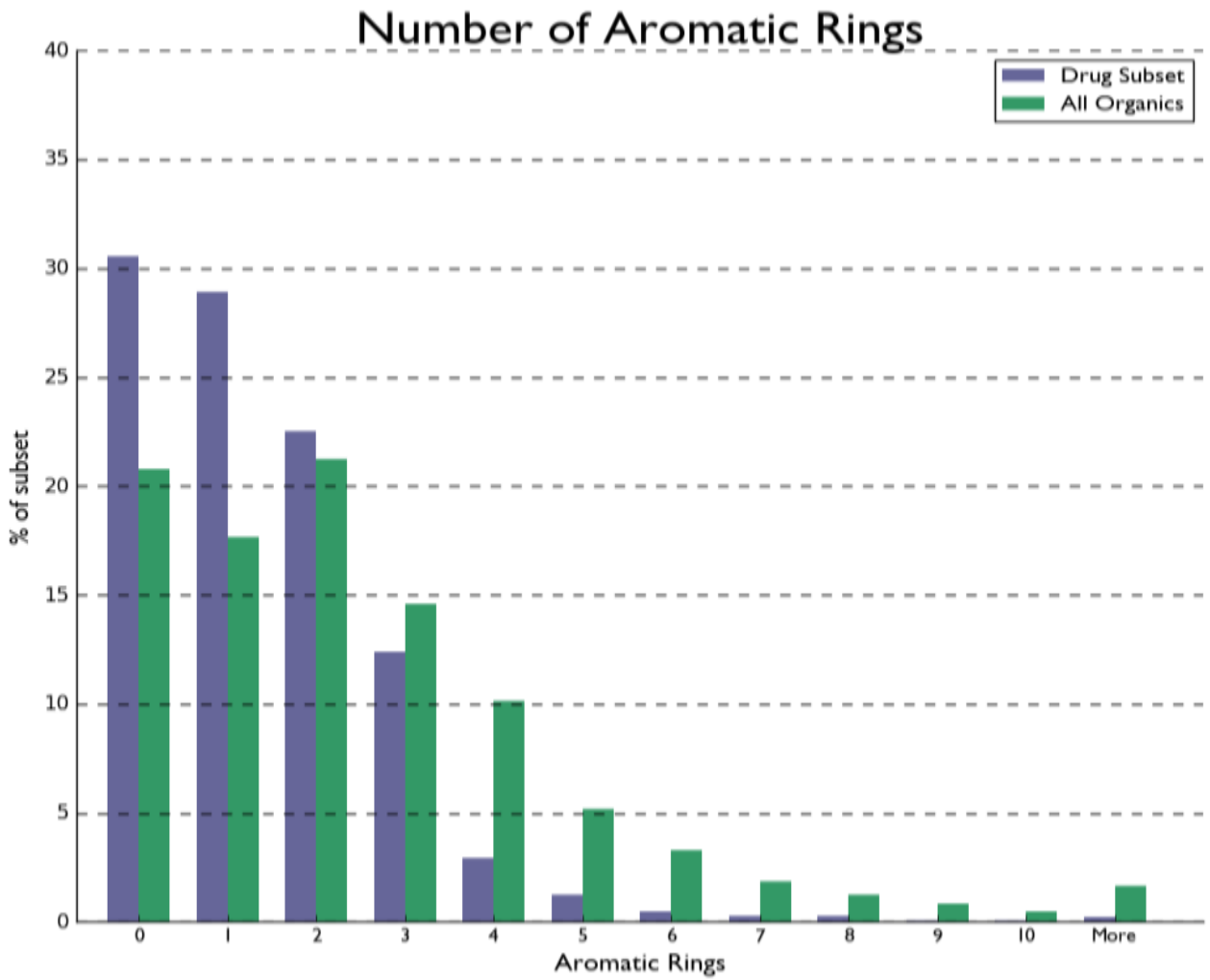
- Drugs show a different spread of elements
- Much lower prevalence of bromine and phosphorus

Comparison to organic molecules in the CSD - Flexibility



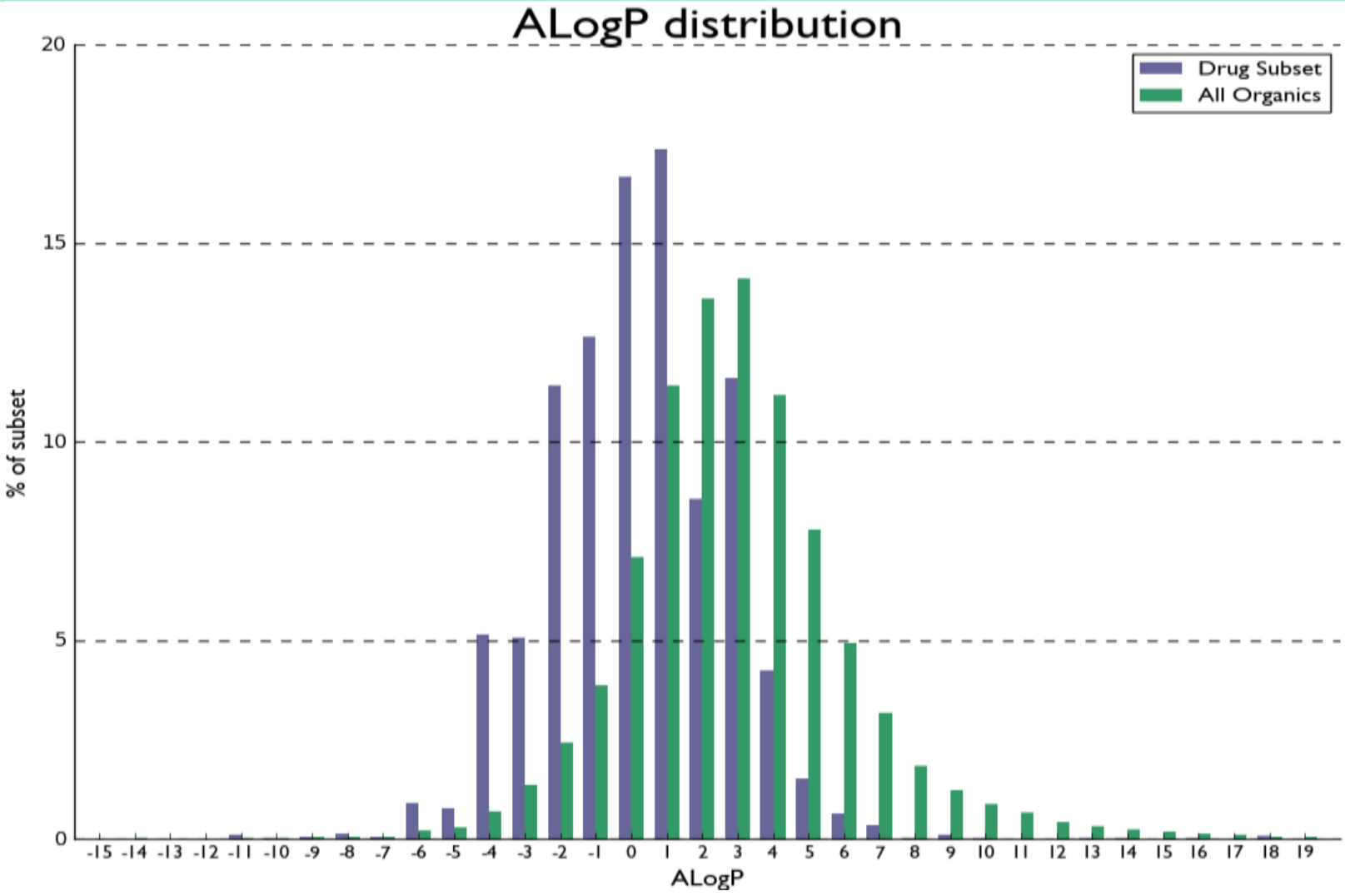
- Drugs have fewer rotatable bonds

Comparison to organic molecules in the CSD - Aromaticity



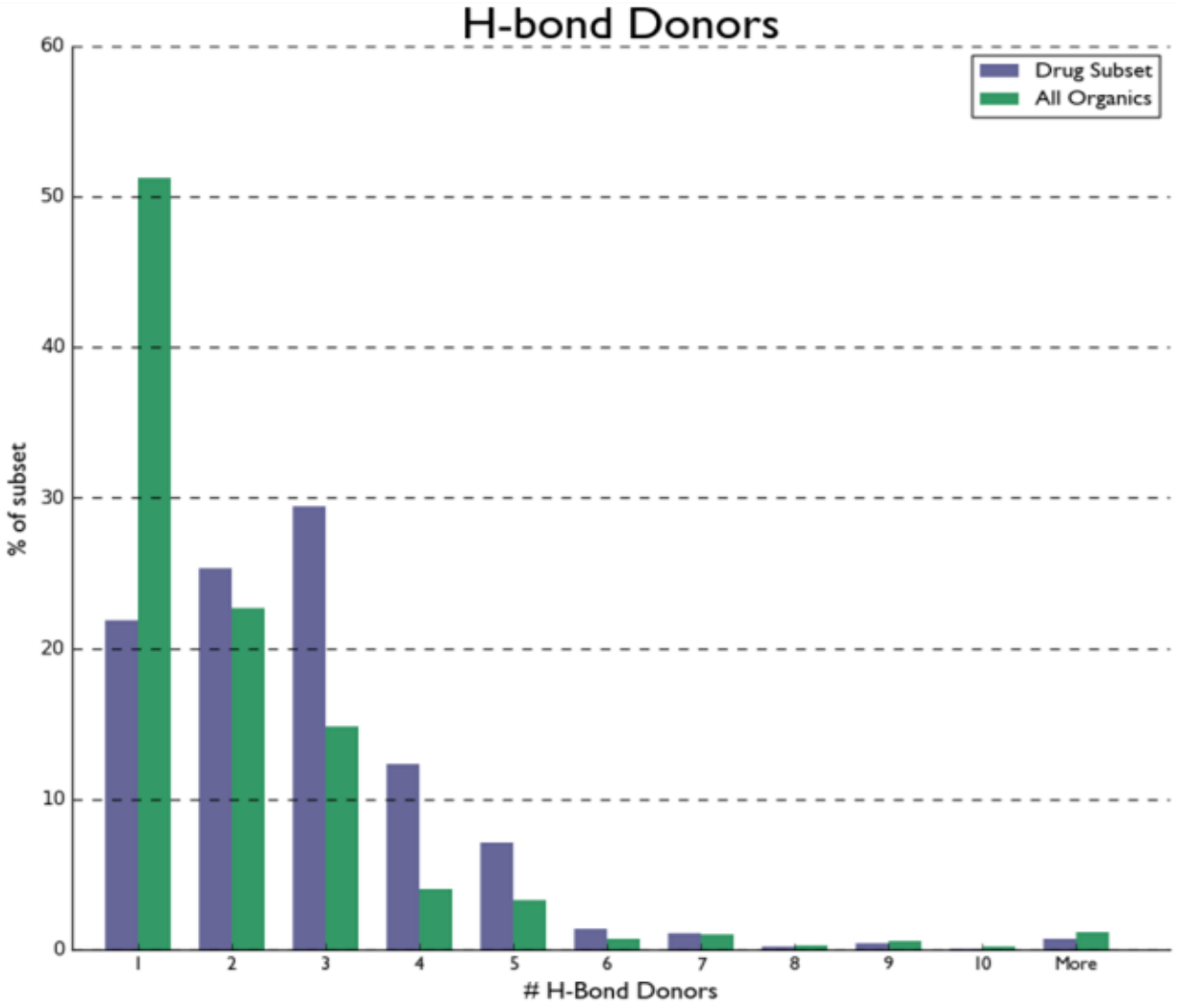
- Drugs have fewer aromatic rings

Comparison to organic molecules in the CSD - ALogP

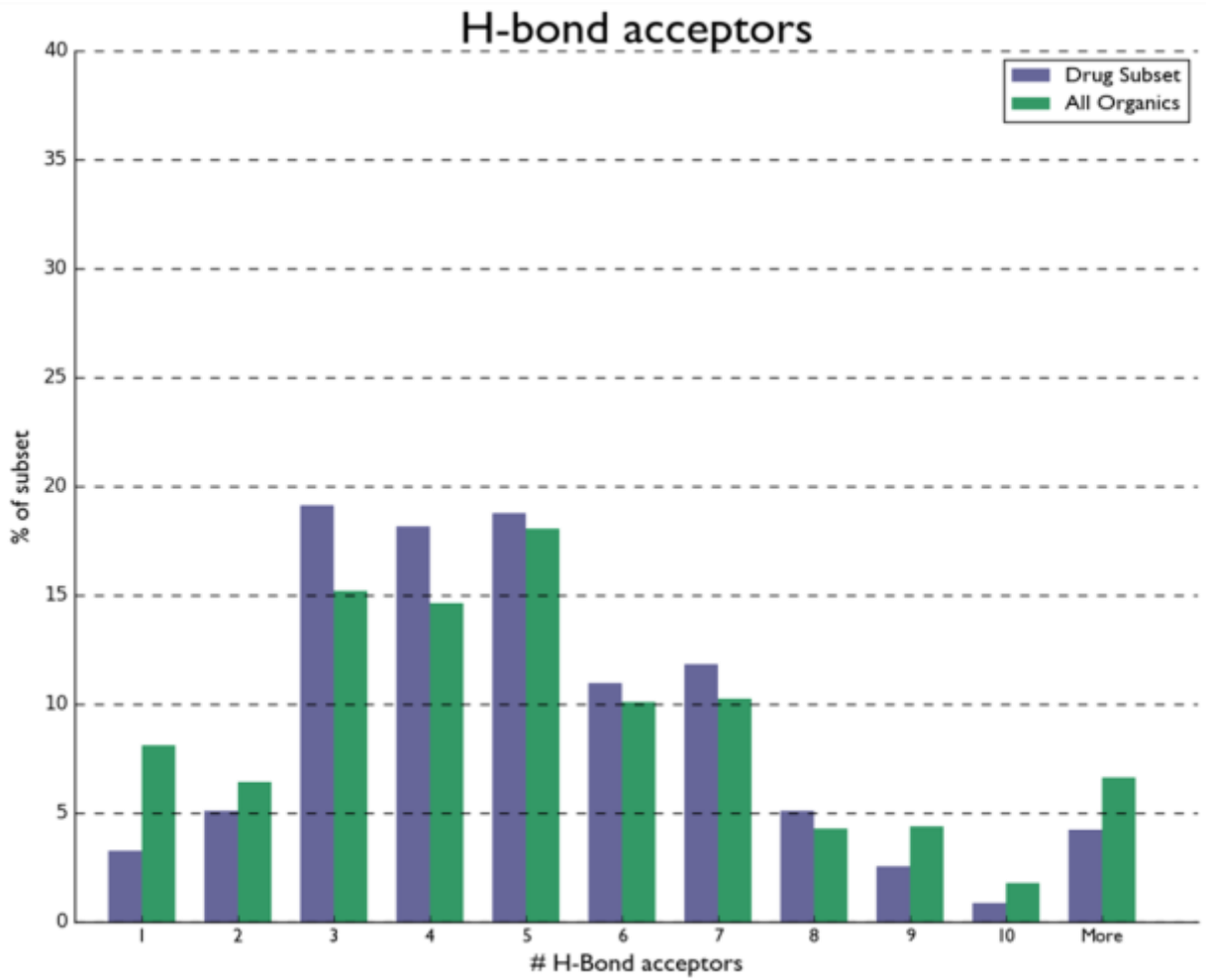


- Clear tendency towards greater water affinity for drug molecules

Comparison to organic molecules in the CSD – H-Bond Donors



Comparison to organic molecules in the CSD – H-Bond Acceptors



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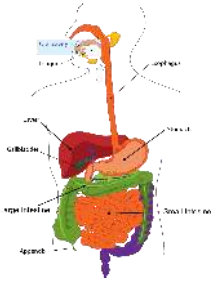

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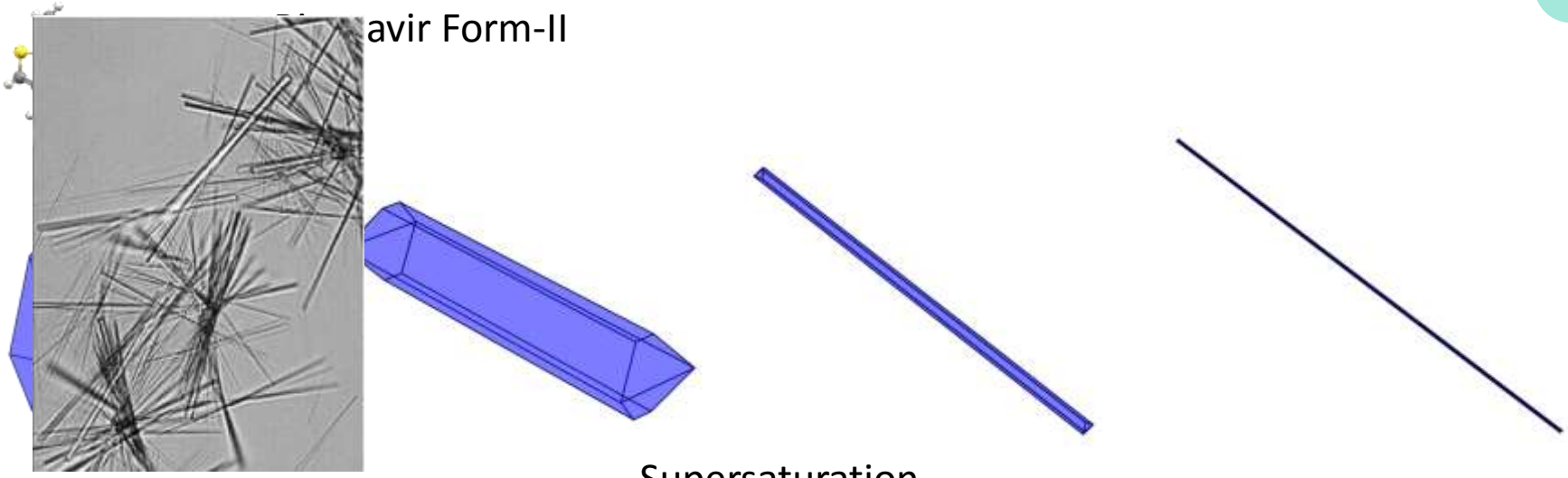
Crystal morphology

- A large aspect of the filtering, drying and flow properties of a solid crystalline form is influenced by the crystal habit or morphology
- Various ways to predict this, but very few take the crystallisation conditions into account, or tell you how dynamic this property is likely to be
- A tool we are currently working on, uses forcefield potentials to investigate the effects of supersaturation on the growth rates of crystal faces

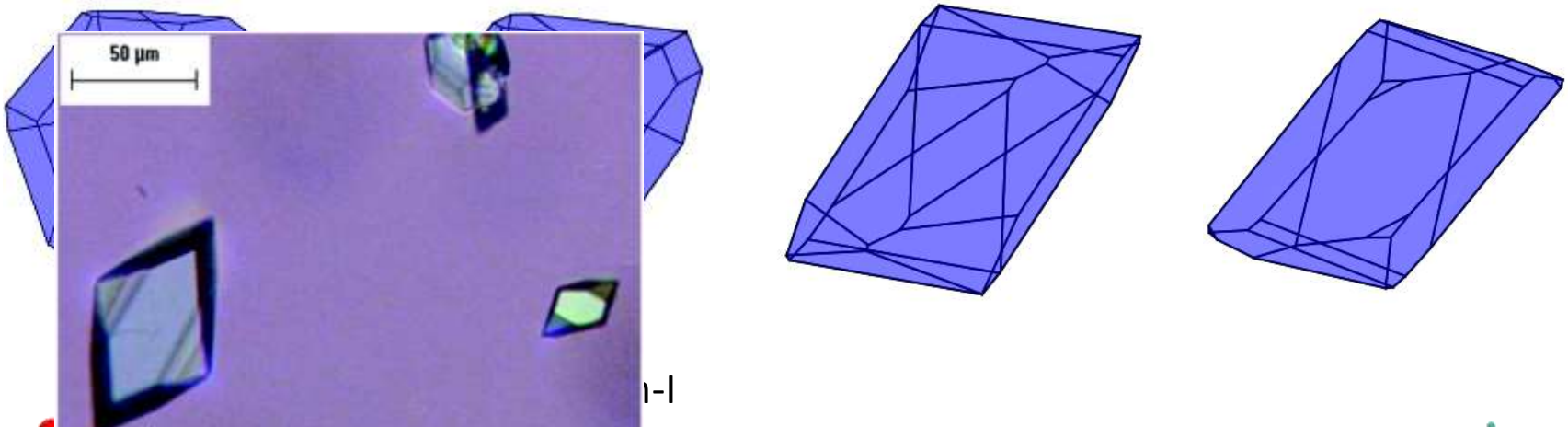
ADDOPT

Simulated impact of supersaturation

avir Form-II



Supersaturation

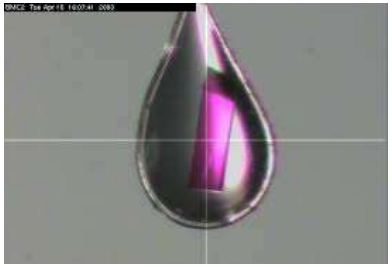


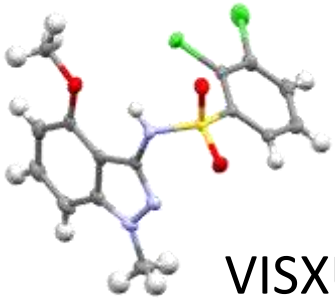
-I

- Bauer J.F., Pharmaceutical Solids, Journal of Validation Technology [**Winter 2009**]
- Cryst. Growth Des., 2008, 8 (9), pp 3316–3322

ADD PT

Linking experimental and predicted crystal morphology

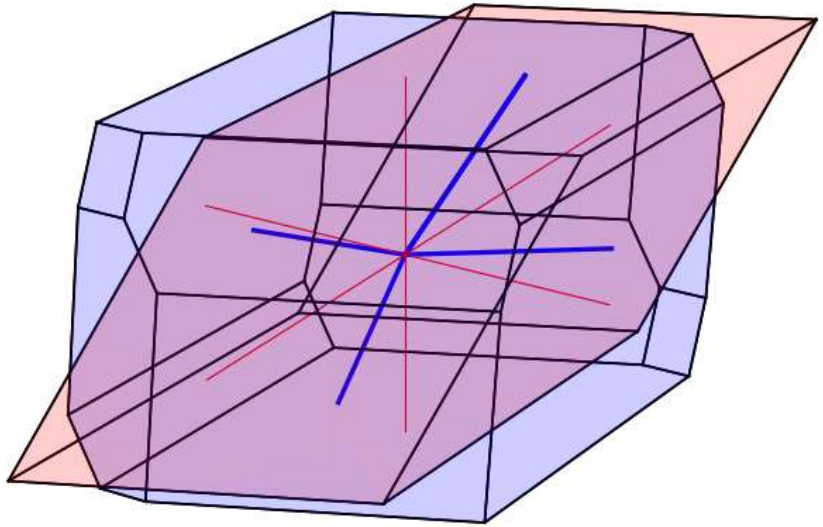




VISXUS

Crystal Face 1	Crystal Face 2	Dihedral angle
(-1, 1, 0)	(1, -1, -1)	155.8158
(-1, 1, 0)	(-1, 1, 1)	155.8158
(-1, 1, 0)	(1, 0, 0)	146.1096
(-1, 1, 0)	(1, -1, 0)	180
(-1, 1, 0)	(0, 0, 1)	95.45741
(-1, 1, 0)	(1, 0, -1)	140.2617
(-1, 1, 0)	(1, -1, -1)	155.8158

```
loop_
_exptl_crystal_face_index_h
_exptl_crystal_face_index_k
_exptl_crystal_face_index_
l_exptl_crystal_face_perp_dist
0.00 1.00 1.00 0.239
0.00 -1.00 2.00 0.451
0.00 -2.00 -1.00 0.216
0.00 0.00 -1.00 0.201
1.00 0.00 -1.00 0.574
-1.00 0.00 1.00 0.383
```



RMSD: 10.14

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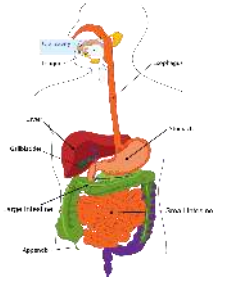

Processes **Products** **Performance**

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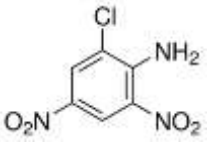
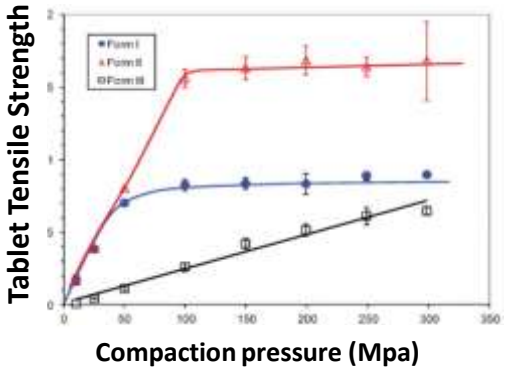
ADD PT

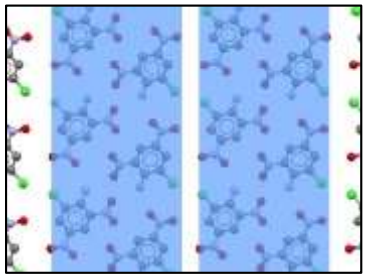
Mechanical properties from Structure

6-chloro-2,4-dinitroanilene

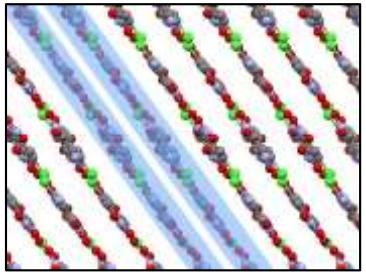




Form-I



Form-II



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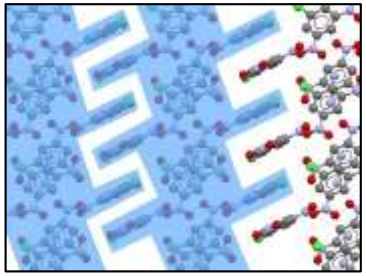
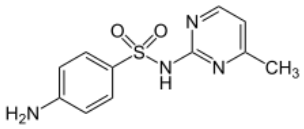
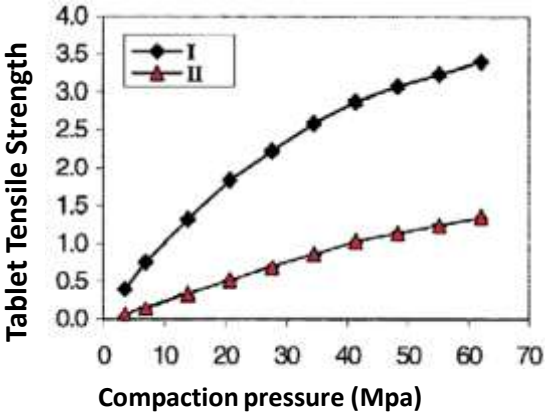
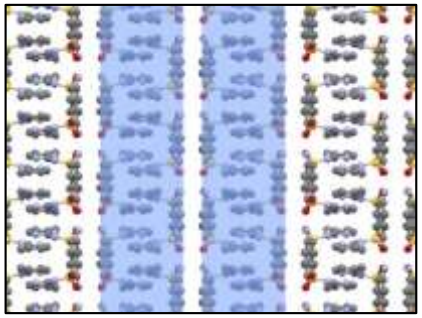


Sulfamerazine





Form-I



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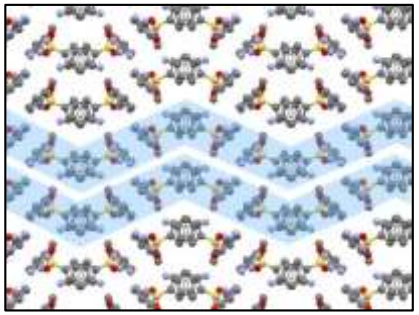


C. C. Sun, J. Adhes. Sci. Technol. 25 (2011) 483–499

Image analysis Approach: OpenCV

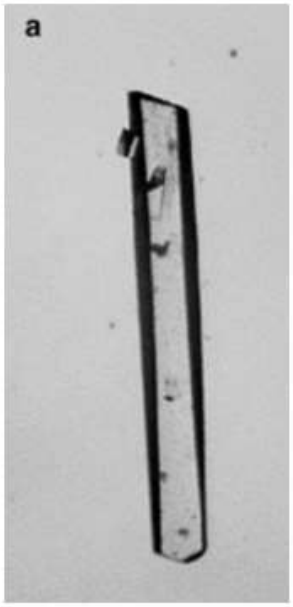
Crystal	Observed	Dreiding	cvff	compass	CCDC Rugosity tool
SLFNMA01	**020**	002	002	002	**010**
SLFNMA02	**020**	020	020	020	**010**
260457 (UCECAG03)	**001**	001	001	001	**001**
CITRAC10	**002**	002	002	002	**001**
260456 (UCECAG02)	**001**	001	001	001	**001**
PUPBAD01	**10-2**	10-2	020	011	**10-2**
PUPBAD02	**101**	10-1	011	020	**101**
HXACAN	**002**	002	200	200	**001**
HXACAN01	**010**	110	110	110	**010**
DIJVOH	**002**	200	200	200	**001**
260455 (UCECAG01)	**10-1**	100	100	100	**10-1**
ethyl paraben (FEGLEI)	**101**	100	100	100	**101**
propyl paraben (DUPKAB)	**101**	100	100	100	**101**

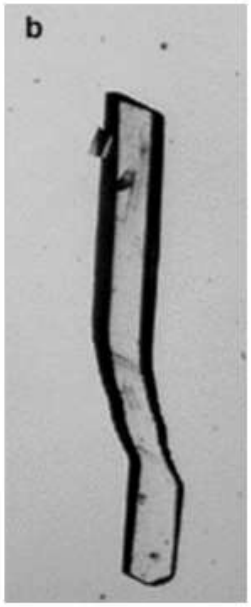
calculate the miller plane the line follows using the CSD Python API

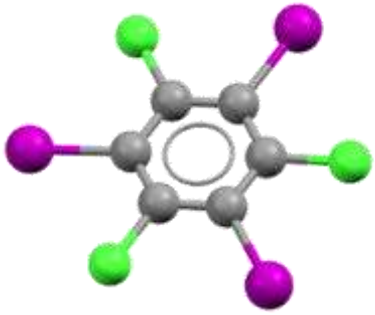
Plane [0 1 0]

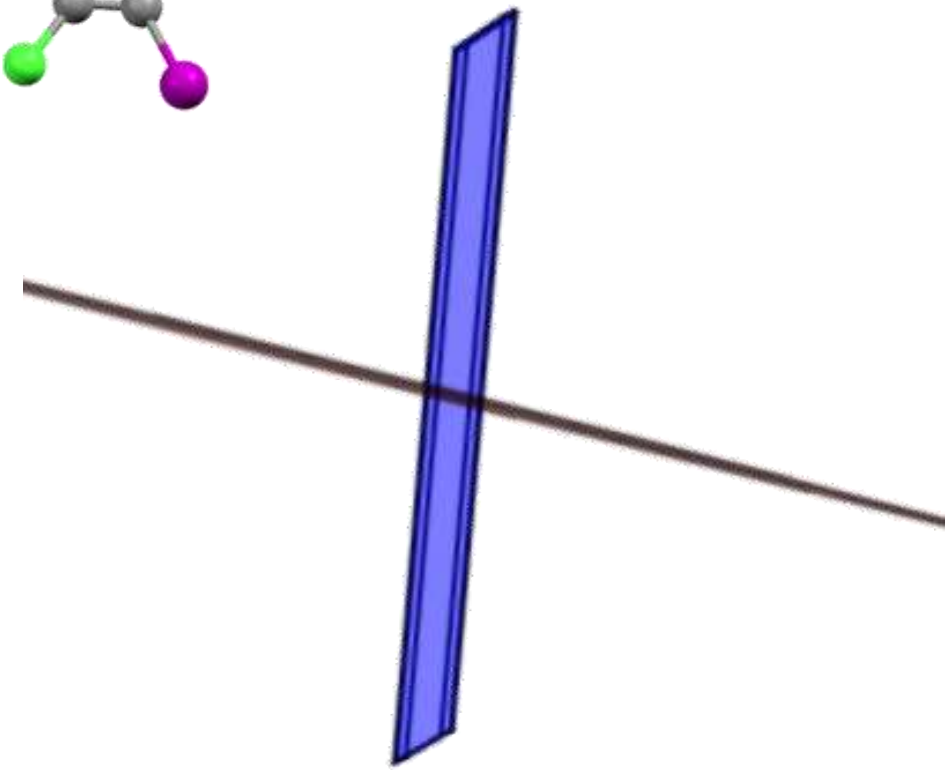
Rugosity = 1.30

Combining tools: Plane of weakness









Chem. Eur. J., 12: 2222–2234. doi:10.1002/chem.20050098

More to come…

- Lots more areas the CCDC are looking into developing tools for
- Looking at generating broad landscapes of hypothetical crystal structures to quantify the potential variance that might be encountered in the solid forms of a drug
- Working closely with ADDoPT partners to validate work done so far