ADDOPT

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

The Cambridge Crystallographic Data Centre

Applying structural informatics approaches to pharmaceutical supply chain processes

Andrew G.P. Maloney, Mathew J. Bryant and Ian J. Bruno

The Cambridge Crystallographic Data Centre

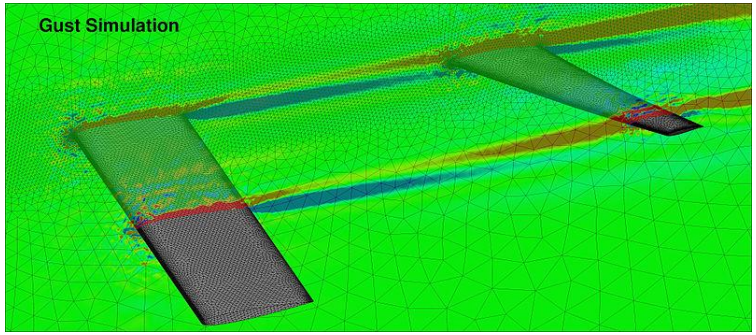
Thursday 12th April 2018

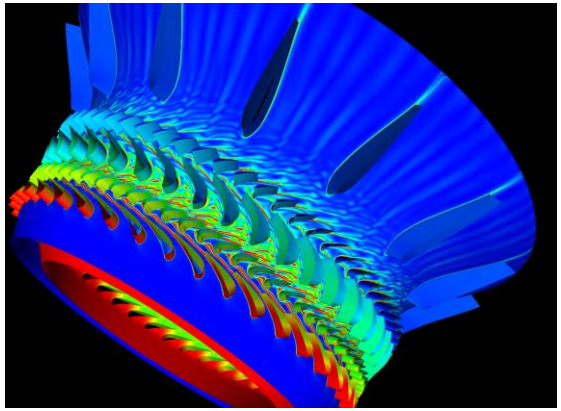
The ADDoPT Project

- **A**dvanced **D**igital **D**esign of **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**

Digital Design

If we designed drugs like we design airplanes…





"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?"

W.S Woltosz, *J. Comput. Aided Mol. Des.* (2012), **26**, 159-163

Digital Design: Molecules to medicines

Product and Process Design

Upstream

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

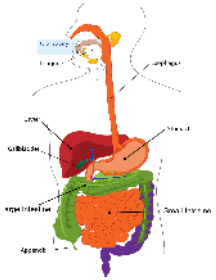
Product Performance

Downstream

Primary Manufacturing - Secondary Manufacturing

Active Ingredient (API) → Crystallisation, Filtration, Washing, Drying → Milling, Blending, Compaction, Coating →

→

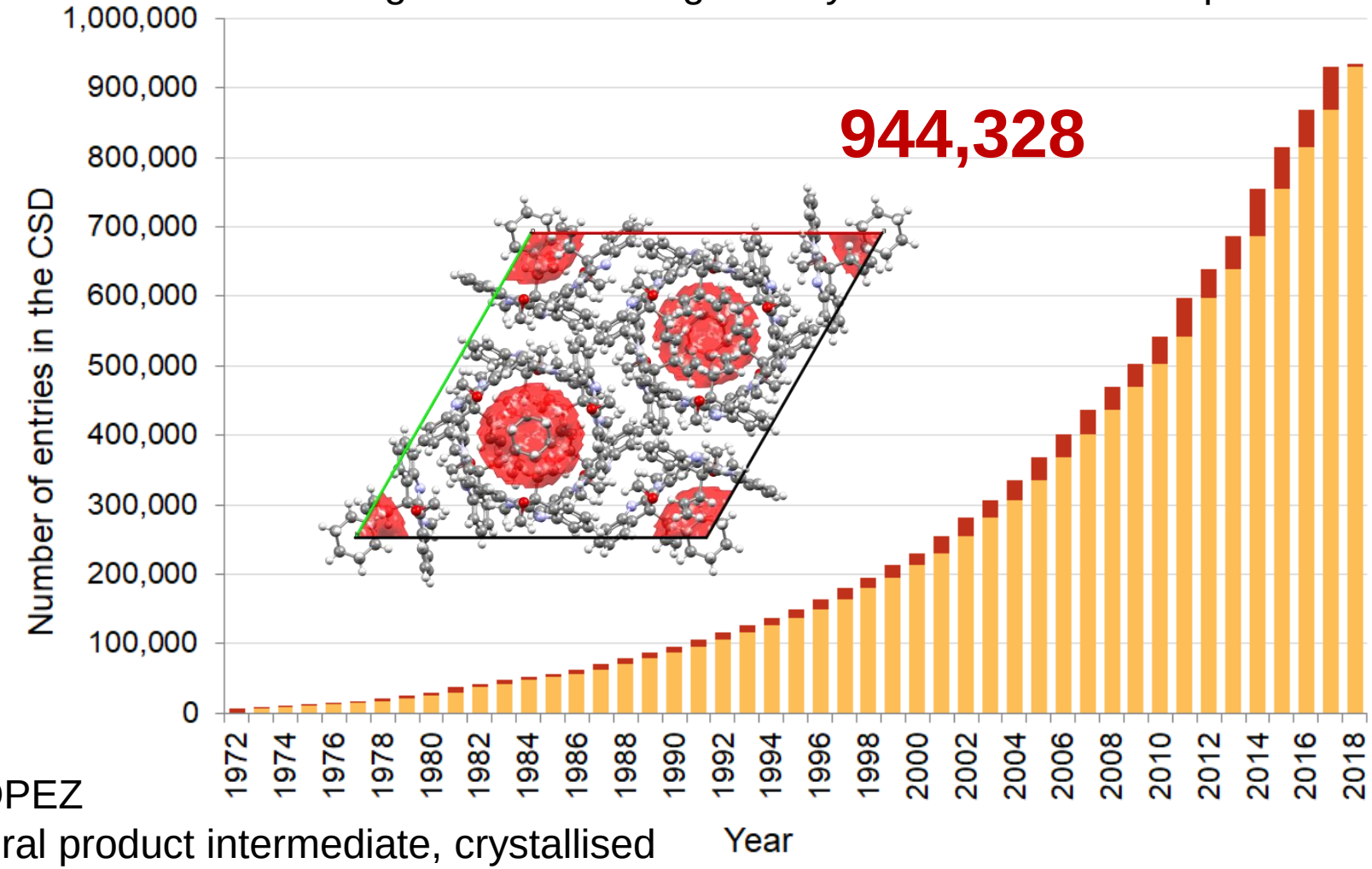


Processes | **Products** | **Performance**

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

The Cambridge Structural Database

All small-molecule organic & metal-organic crystal structures ever published.

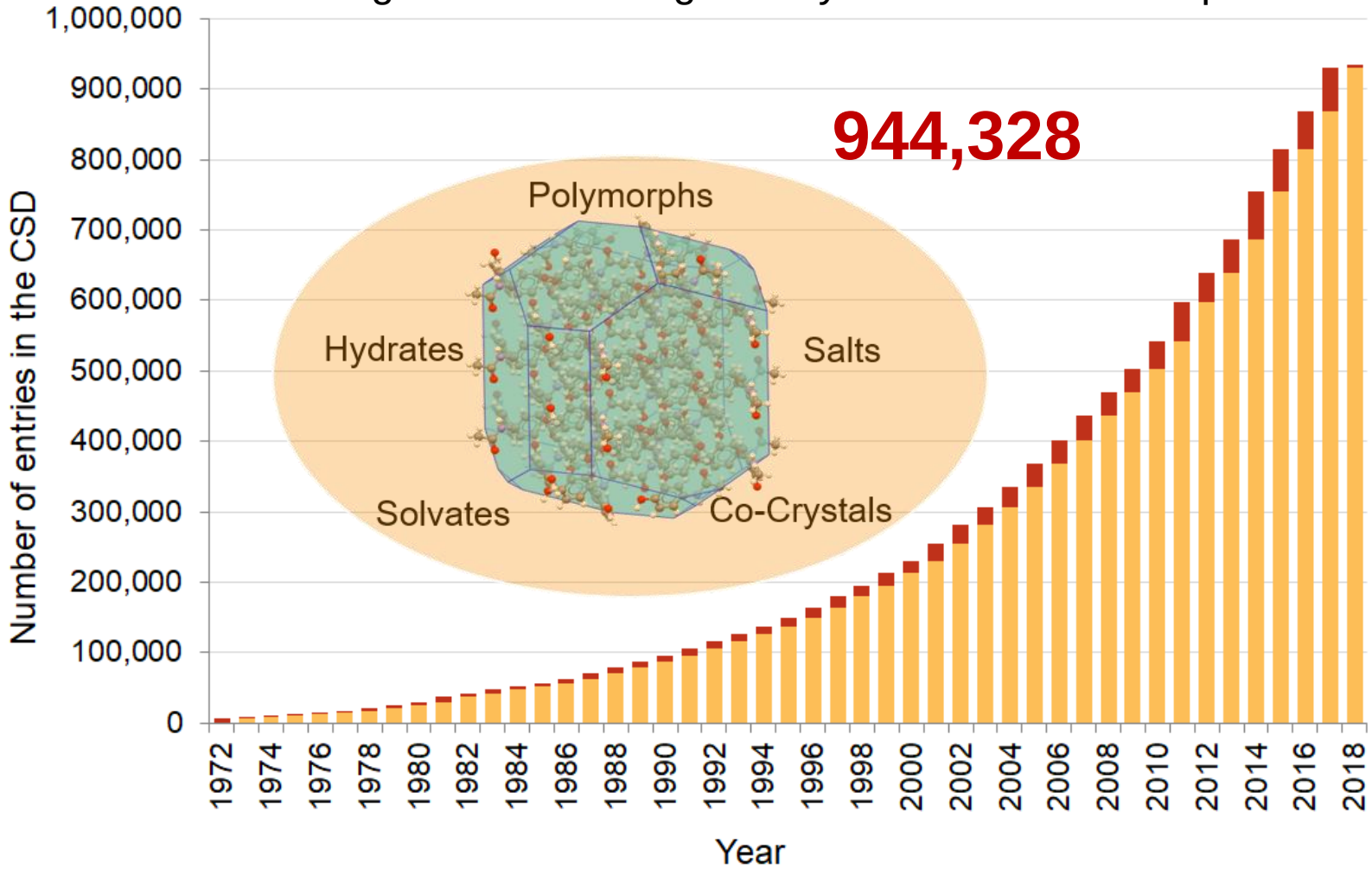


USOPEZ
Natural product intermediate, crystallised as a cyclohexane solvate

R. P. Wilkie *et al.*, *Chem. Commun.* (2016), **52**, 10747-10750

The Cambridge Structural Database

All small-molecule organic & metal-organic crystal structures ever published.



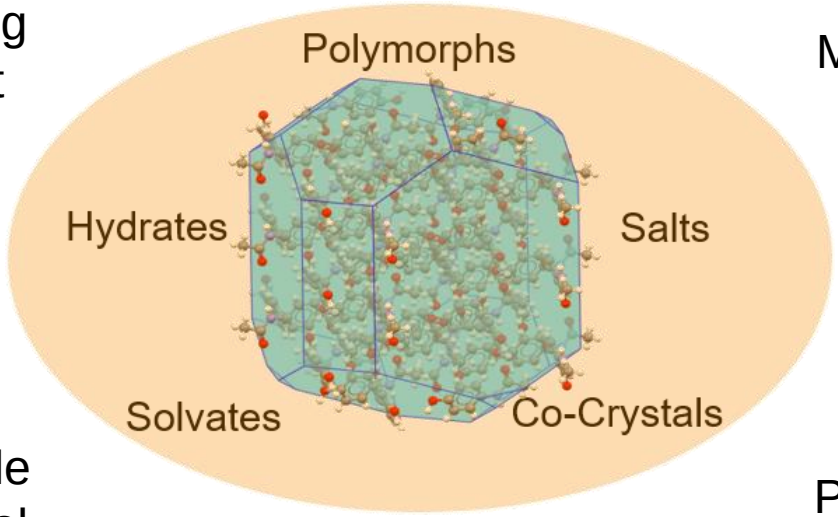
R. P. Wilkie *et al.*, *Chem. Comun.* (2016), **52**, 10747-10750

Crystal structure is important…

Chemical & Physical Stability

Melting Point

Morphology



Solubility

Mechanical Properties

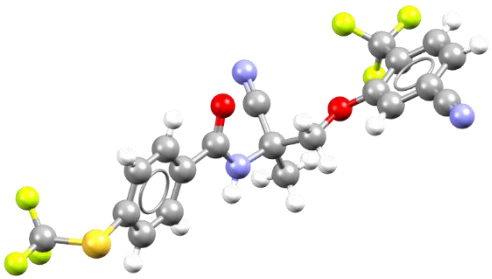
Particle Control

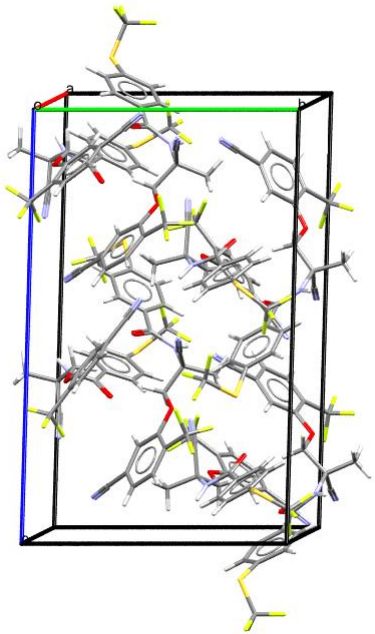
Purification

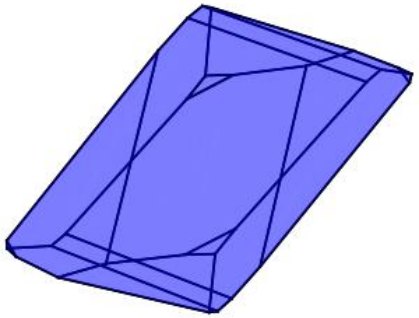
Product Process Control

R. P. Wilkie *et al.*, *Chem. Comun.* (2016), **52**, 10747-10750

Drug product design and development







Molecule **Form** **Particle**

Making a CSD Drug Subset

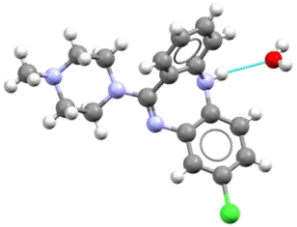
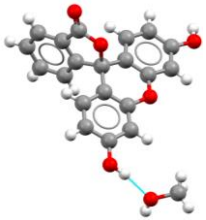
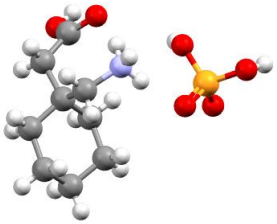
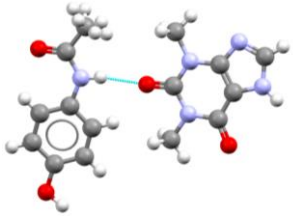
- Drug definition taken from the approved drug database of Drugbank.ca

DRUGBANK
Open Data Drug & Drug Target Database

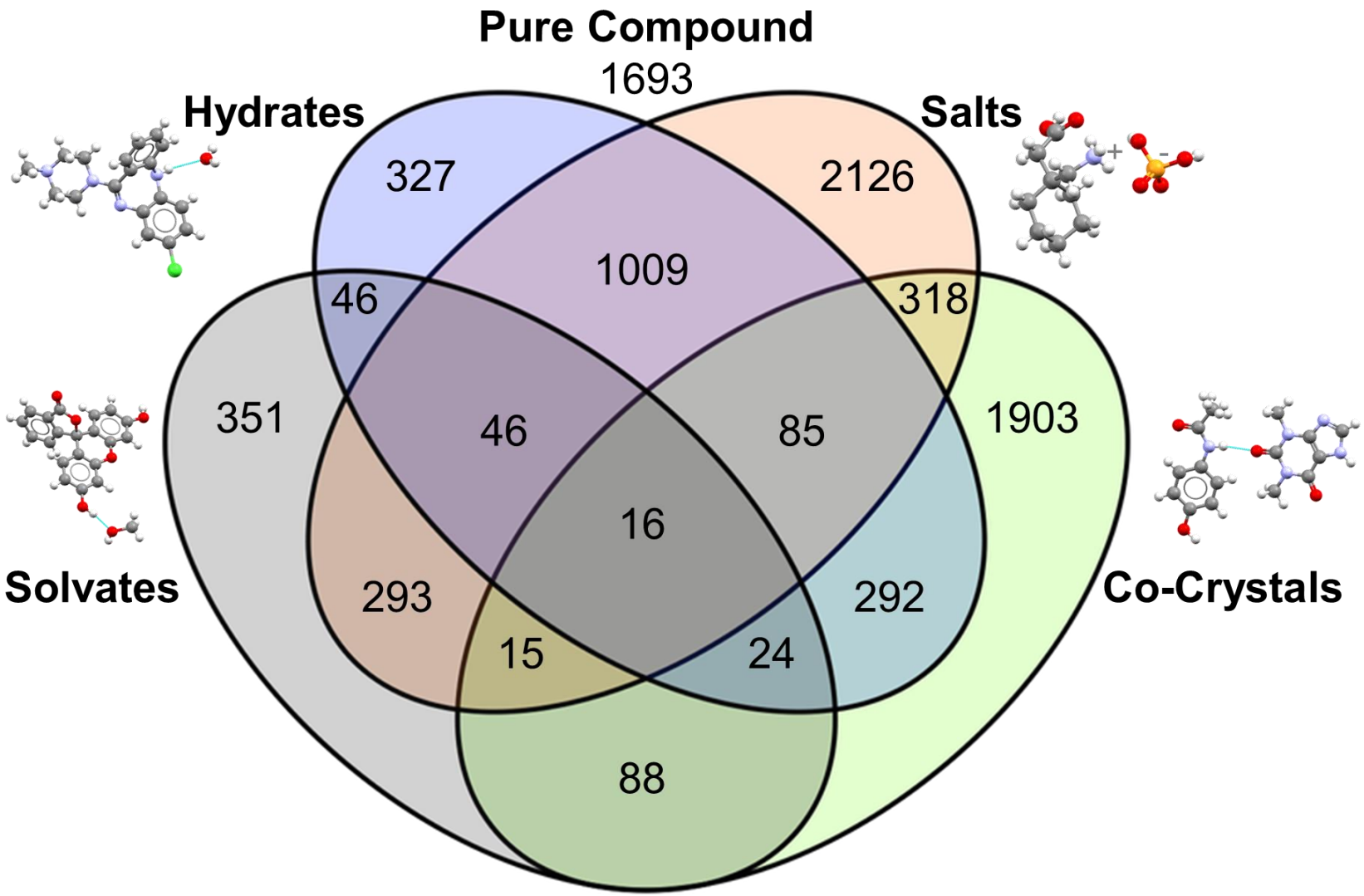
- Generated using InChI strings and the CSD Python API

- 8632 crystal structures representing 785 drug molecules

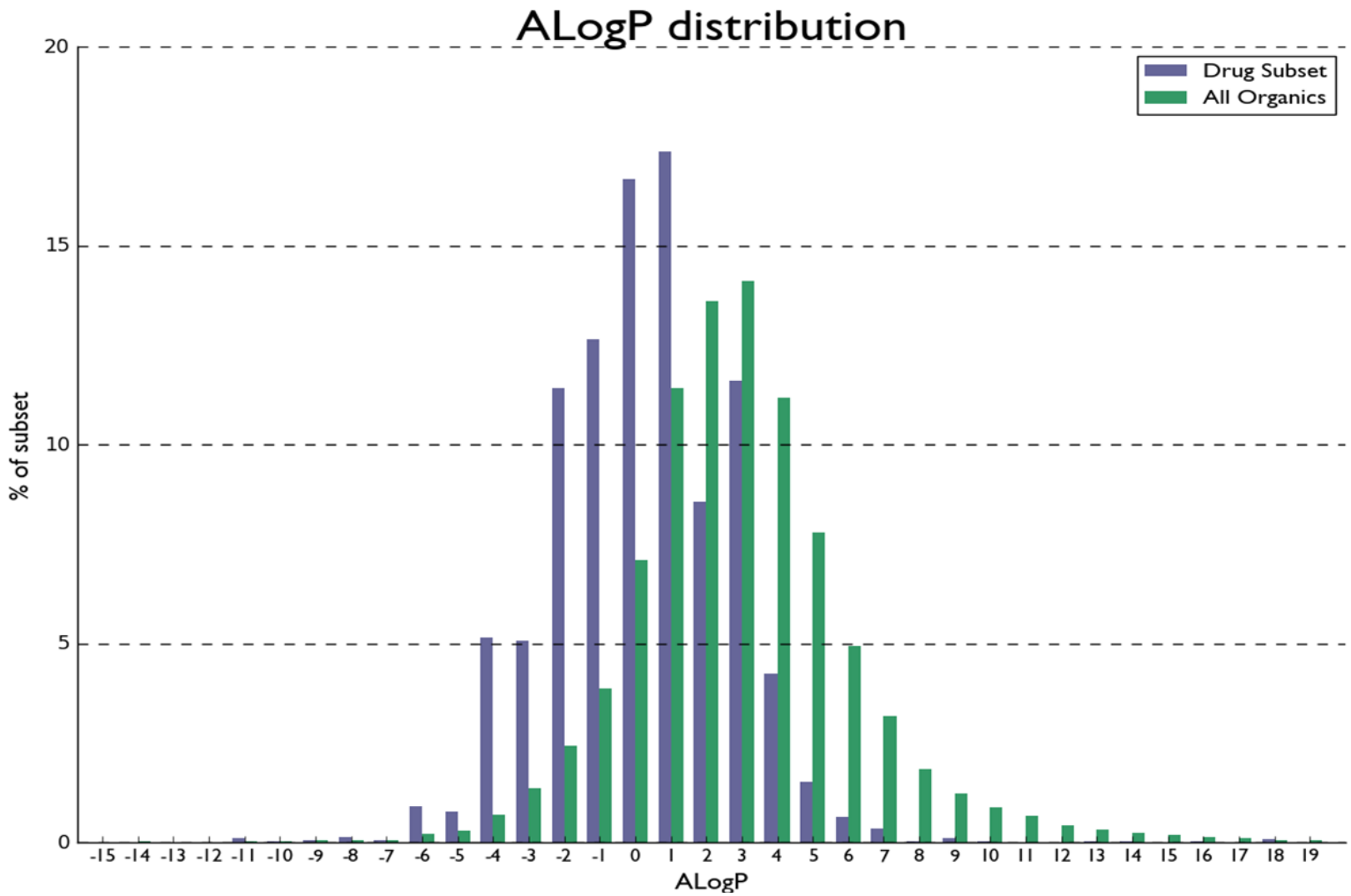
- Searchable and sortable by categories like hydrates, solvates, salts, co-crystals, pure drug (or any combination of these)

Making a CSD Drug Subset



Comparison to organic molecules in the CSD



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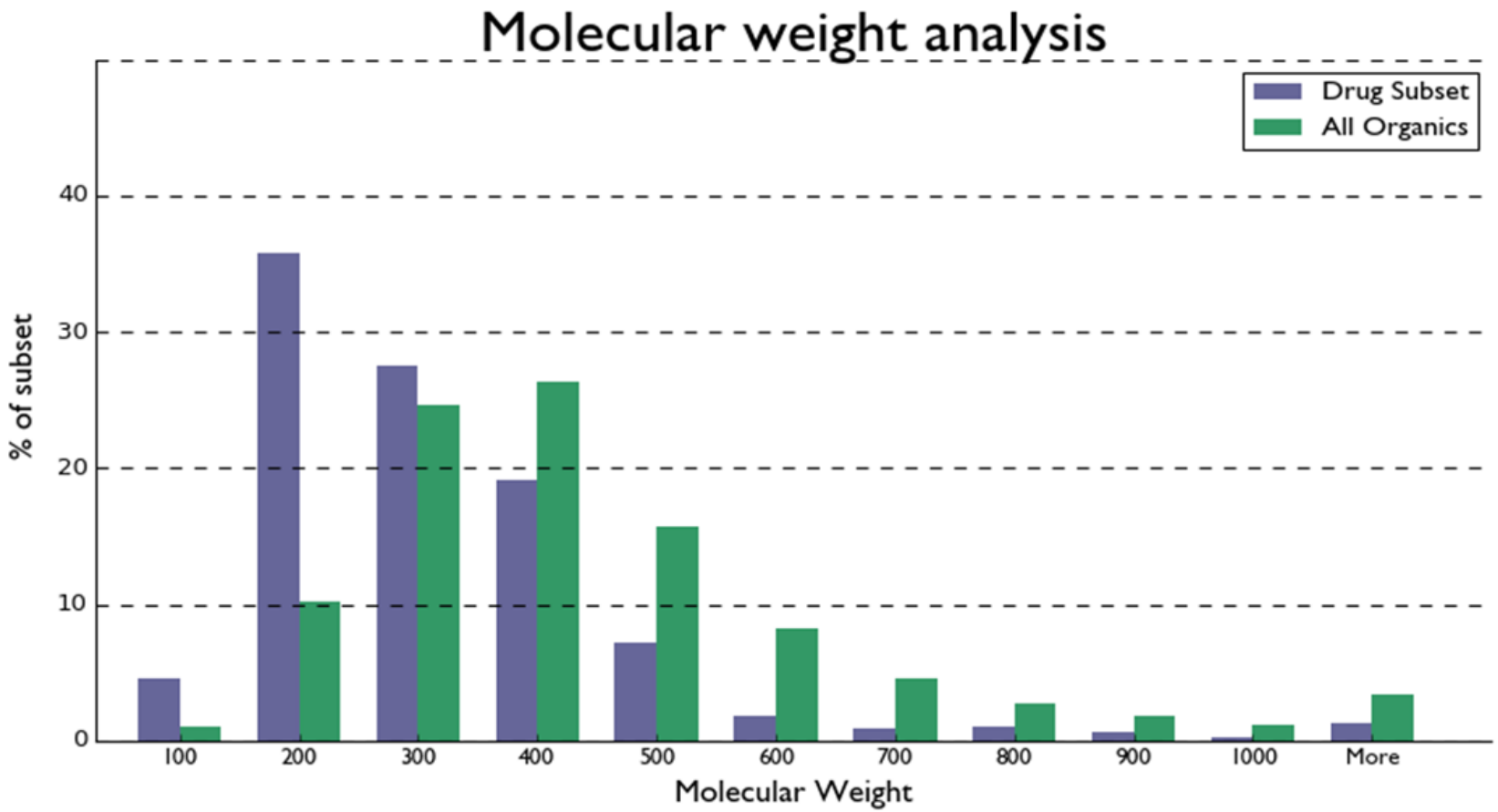
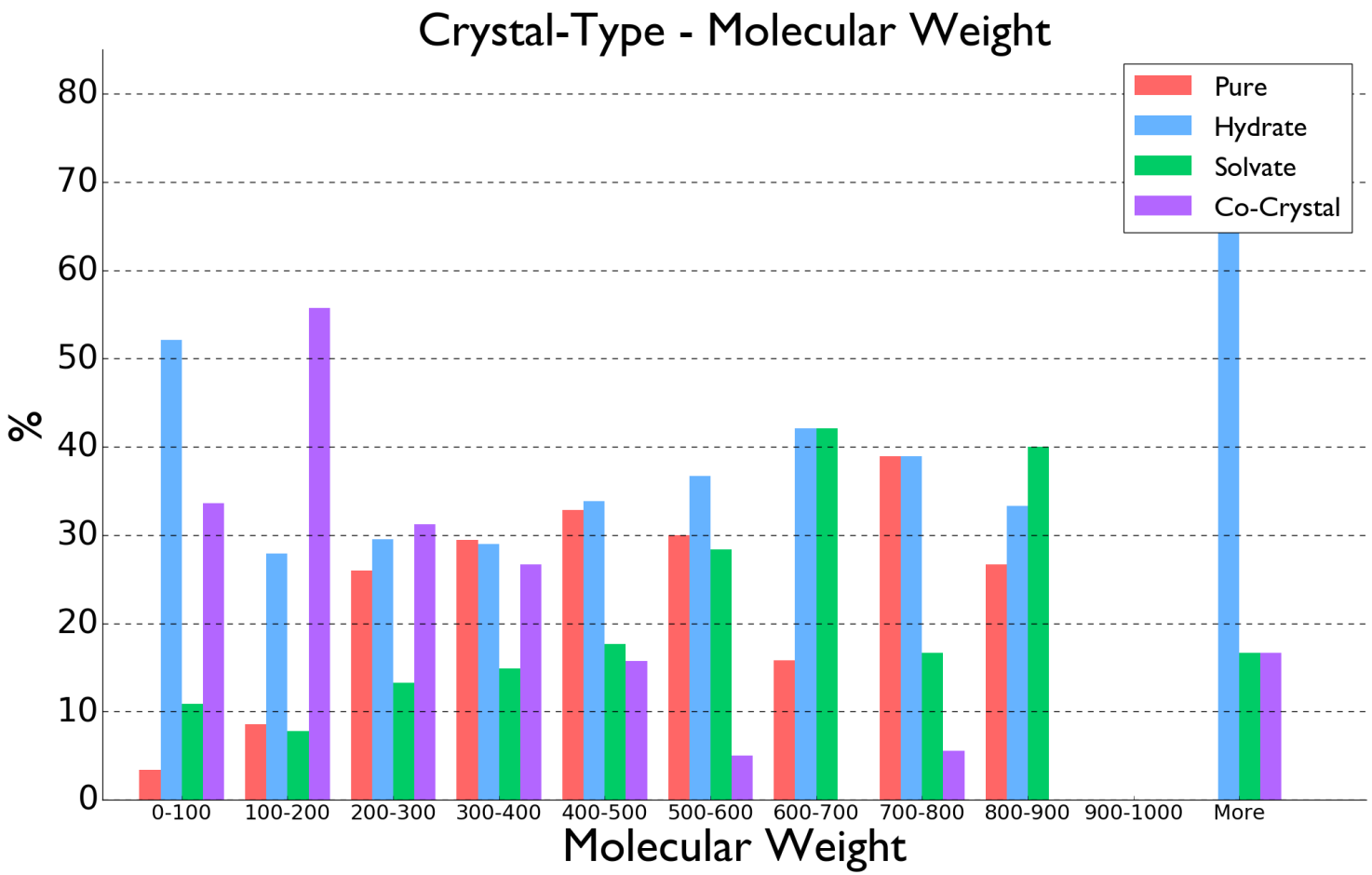
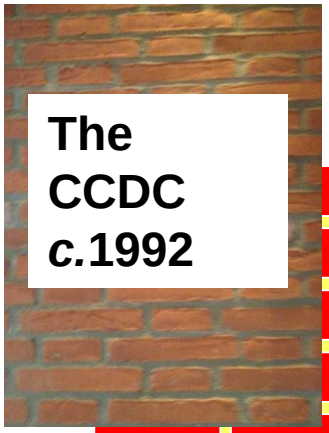


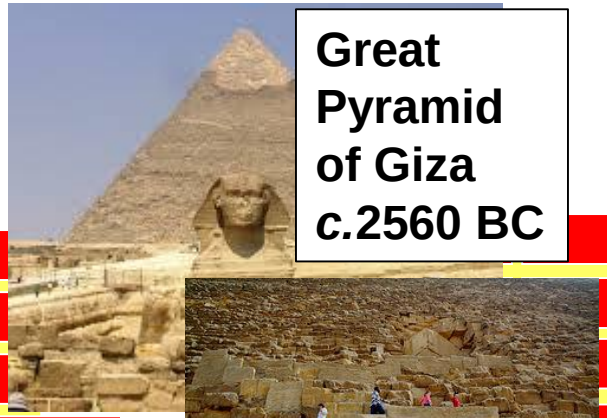
Solid form and molecular descriptors



Structural Informatics

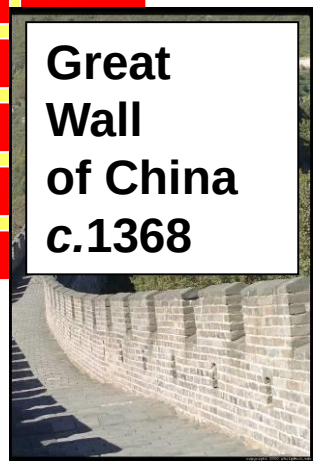
Which is the stable wall?





A

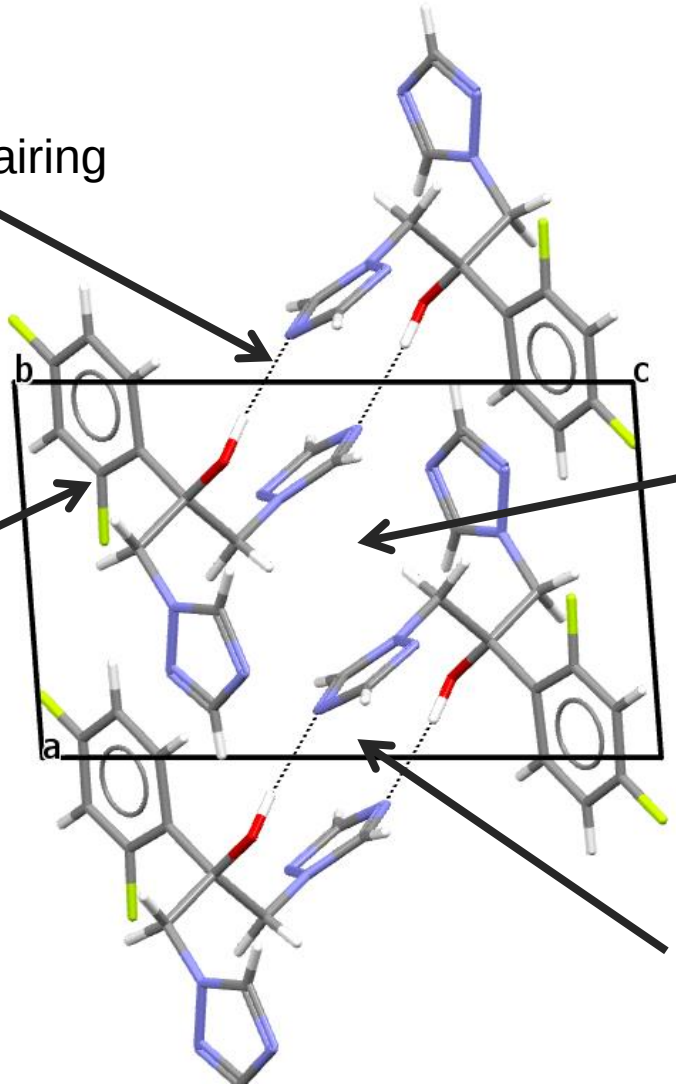
B



The database of walls indicates that <u>A</u> is the frequently observed arrangement and therefore the one that achieves stability.

Crystal Structure Characteristics that Influence Stability

Hydrogen Bond
Donor/Acceptor Pairing



'Non-Hydrogen Bond'
Intermolecular
Interactions

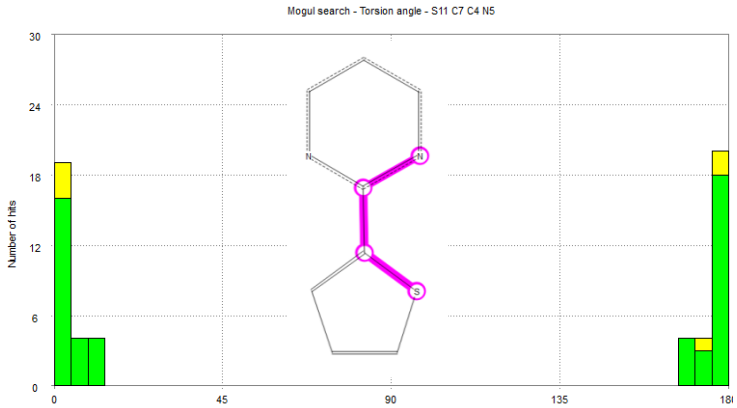
Molecular
Conformation

Hydrogen Bond
Geometry, Symmetry
and Motif

We mine the CSD to identify these intra and intermolecular geometric preferences.

CSD derived knowledge bases

Number of hits



Tosion angle (º)

Mogul

Molecular geometry distributions

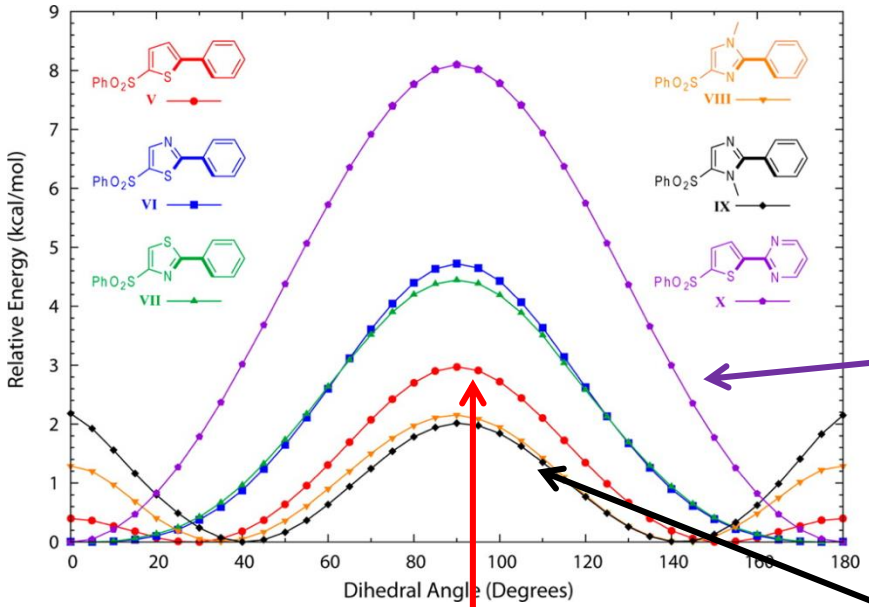
- Bond lengths
- Valence angles
- Torsion angles
- Rings

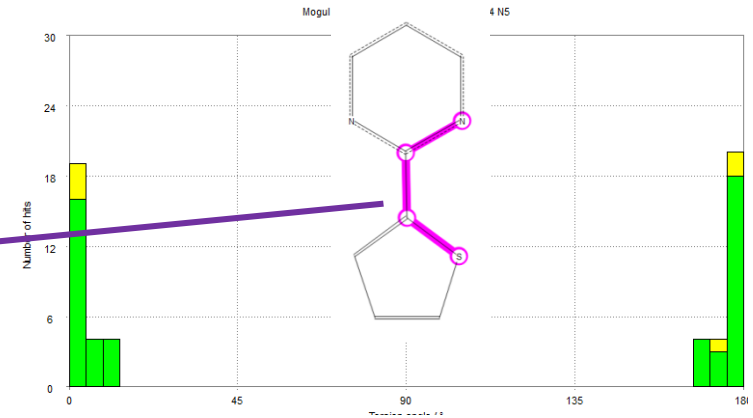
IsoStar

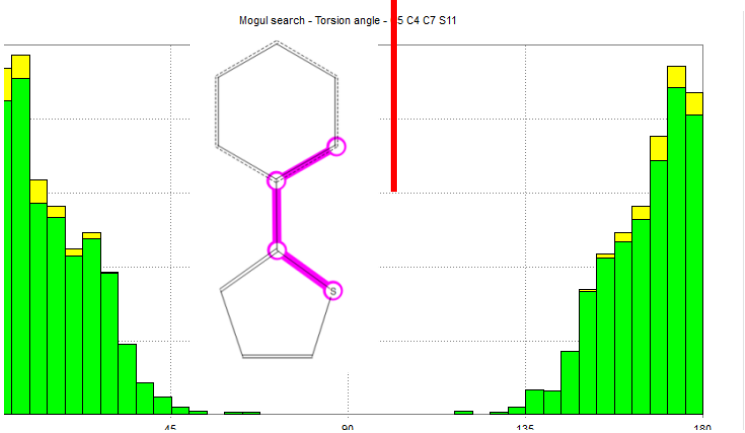
Intermolecular geometry analysis

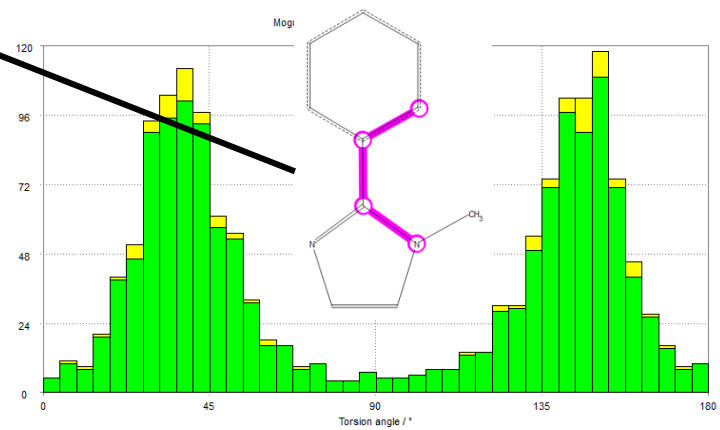
- Interaction distributions displayed as scatterplots or contour surfaces
- 18,000 pre defined interaction scatter plots

Understanding conformational complexity





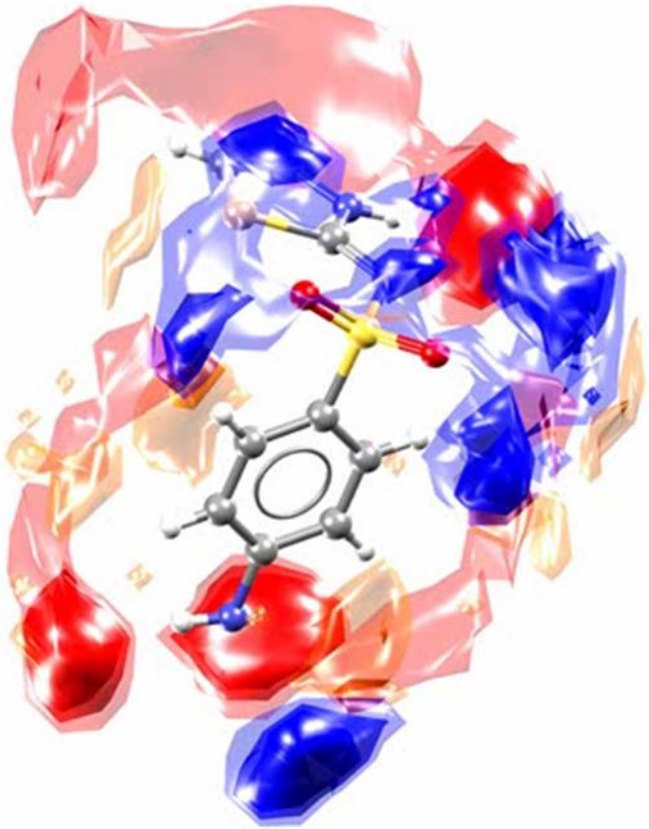




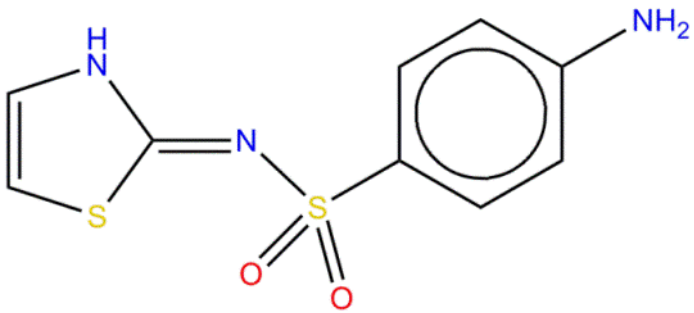
Tamayo *et al., J. Med. Chem.* (2015), **58**, 4462–4482
Pennington *et al., J. Med. Chem.* (2015), **58**, 9663−9679

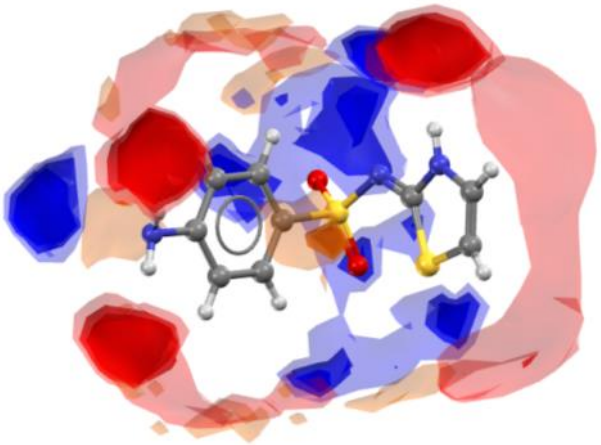
Full Interaction Maps (FIMs)

- IsoStar libraries used to map interaction preferences around complete molecules in a crystal structure
- The satisfaction of the Full Interactions Maps by the packing shell of the crystal structure can then be used to assess stability



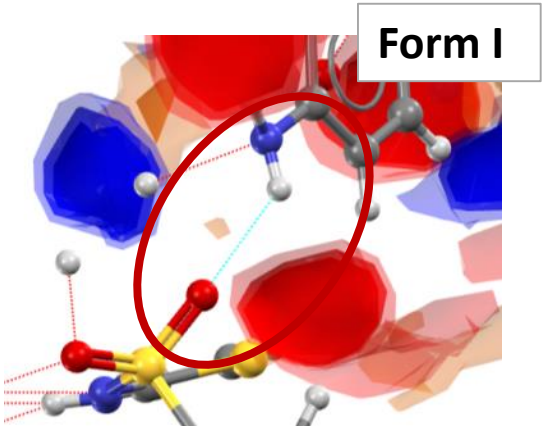
Using FIMs to assess stability





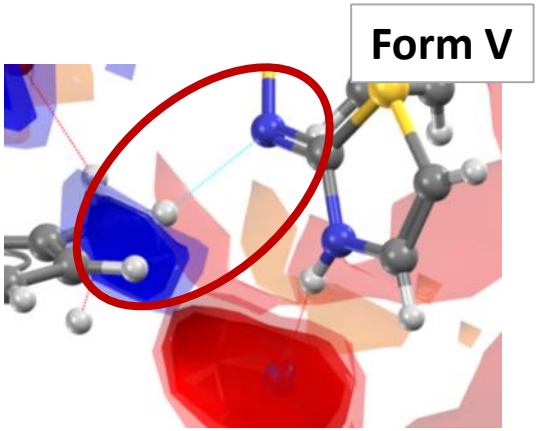
Donor probe
Acceptor Probe
Hydrophobic Probe

SUTHAZ16



Low satisfaction – Metastable

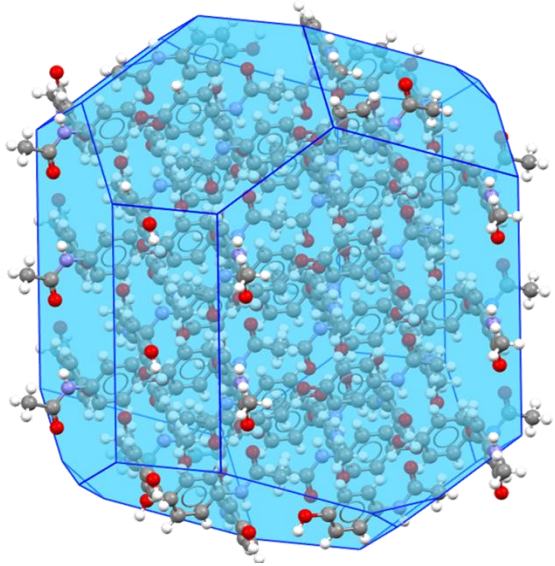
SUTHAZ19



High satisfaction – Stable

N. Blagden *et al.*, *Int. J. Pharm.* (1998), **172**, 169–177
D. S. Hughes *et al.*, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* (1999), **55**, 1831–1833

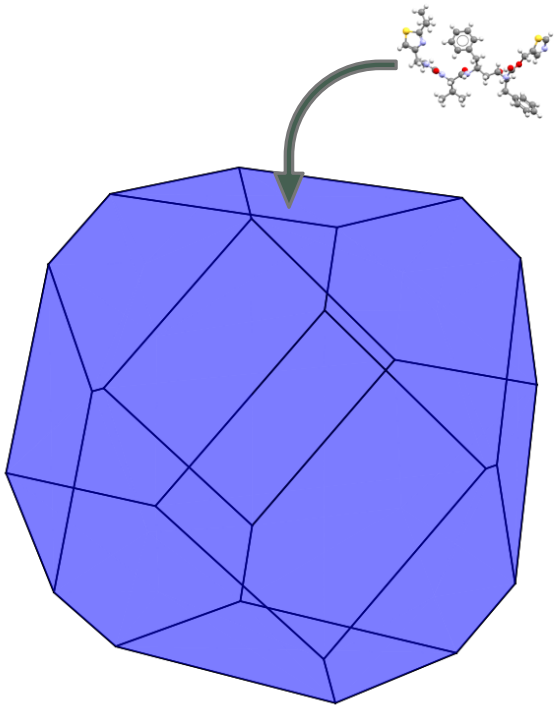
Crystal structure directs…



- Morphology/crystal growth
- Surface chemistry
- Mechanical properties
- Solubility
- Stability
- Melting point

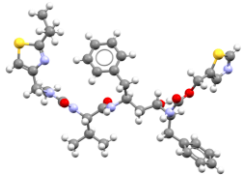
Predicting morphologies

- Start from a base morphology prediction
- Assume nucleation onto existing faces to be the rate limiting step in further crystal growth
- Use a forcefield to quantify the most favourable site of interaction
- As growth rate is proportional to the nucleation rate, this allows us to use nucleation kinetics, including a term for supersaturation

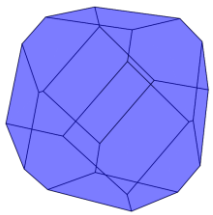


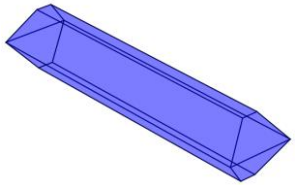
D. Vatvani, *"Predicting the morphology of crystals of organic molecules"*, PhD Thesis (2014)

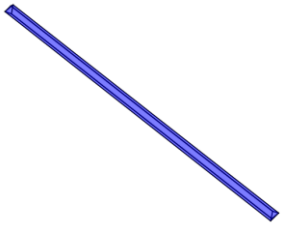
Predicting morphologies

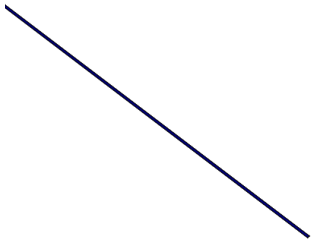


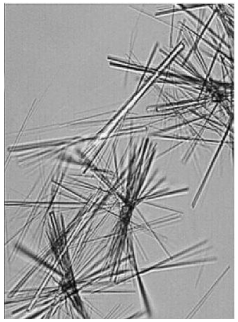
Ritonavir Form-II



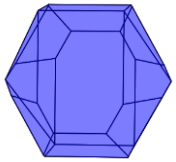


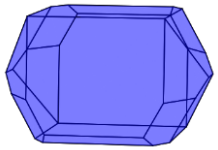


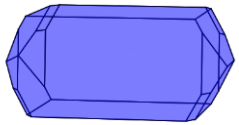


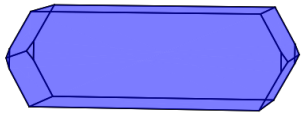


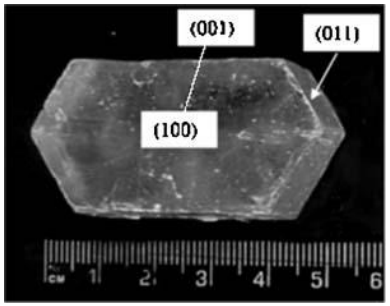
Supersaturation

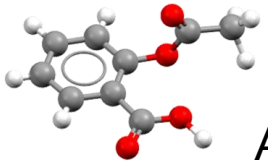










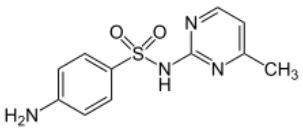


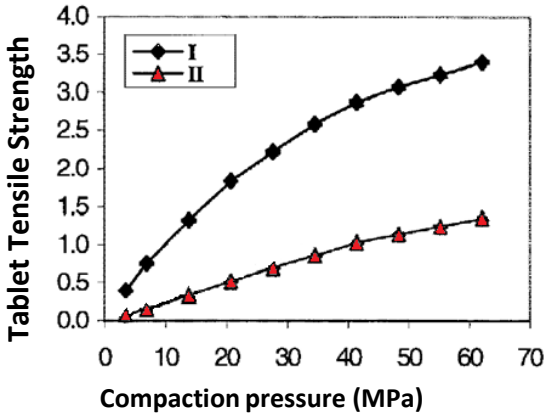
Aspirin

J.F. Bauer, *J. Valid. Technol.* (2009), **15**, 37 - 44
J.Y.Y. Heng, *J. Pharm. Sci.* (2007), **96**(8), 2134 - 2144

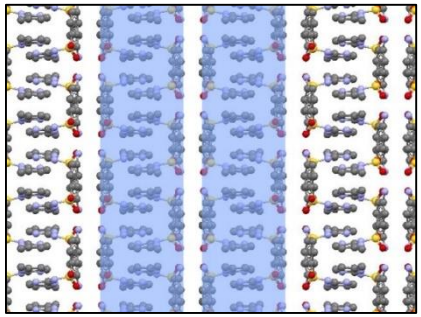
Mechanical properties from structure

Sulfamerazine

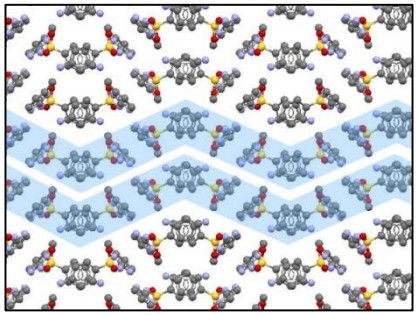




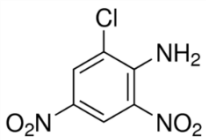
Form-I

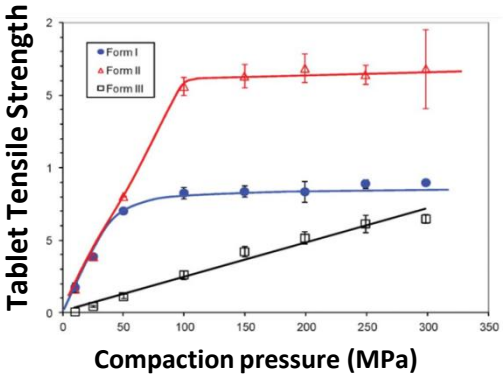


Form-II

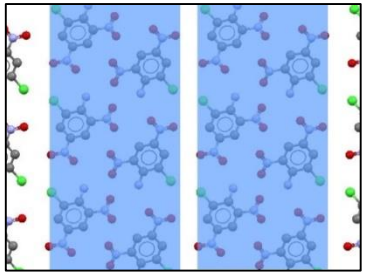


6-chloro-2,4-dinitroanilene

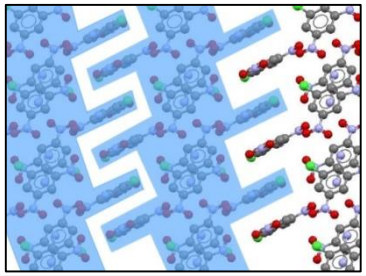




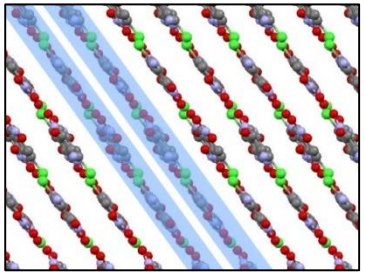
Form-I



Form-III

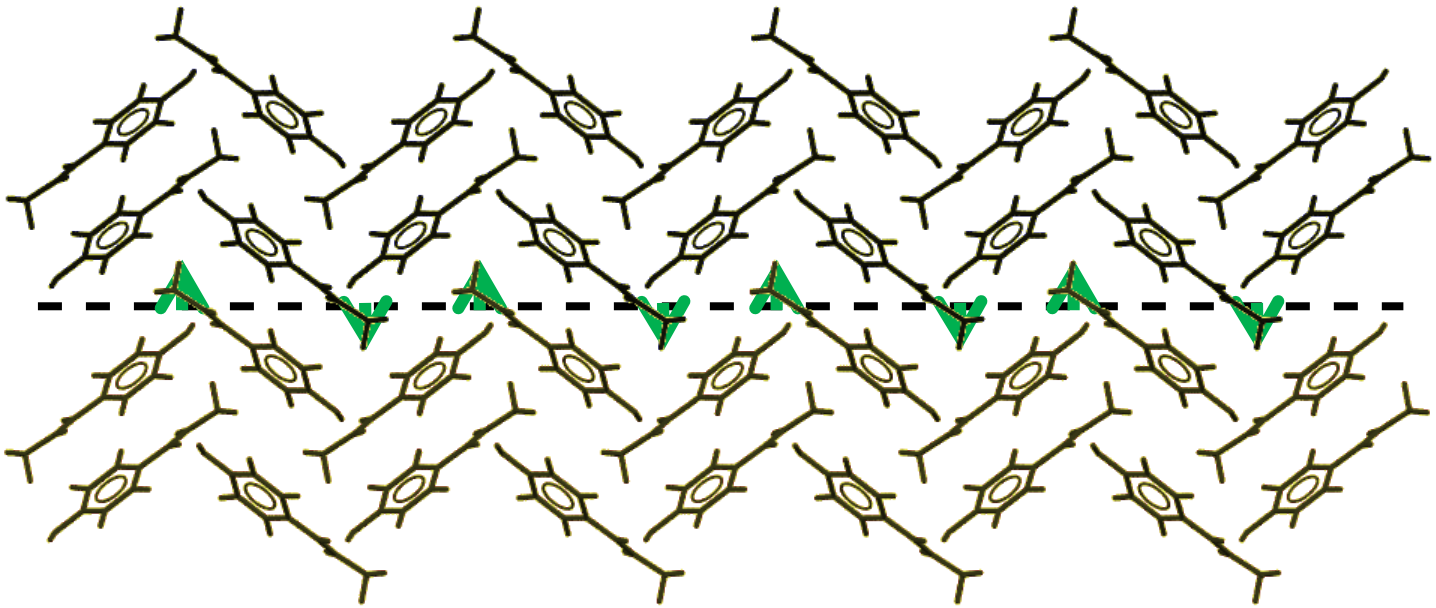


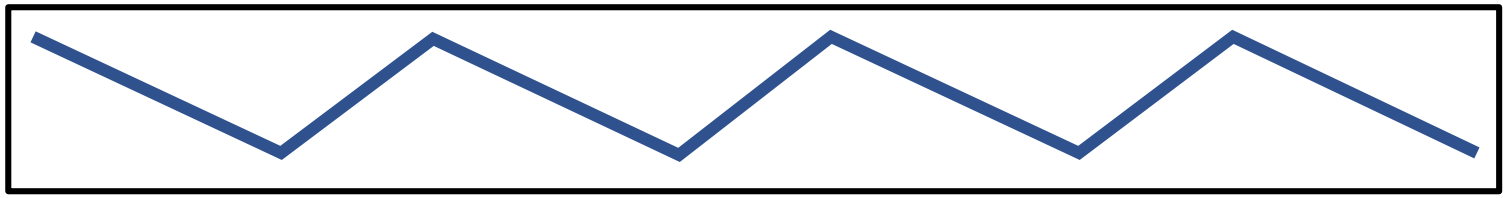
Form-II



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

Predicting slip planes



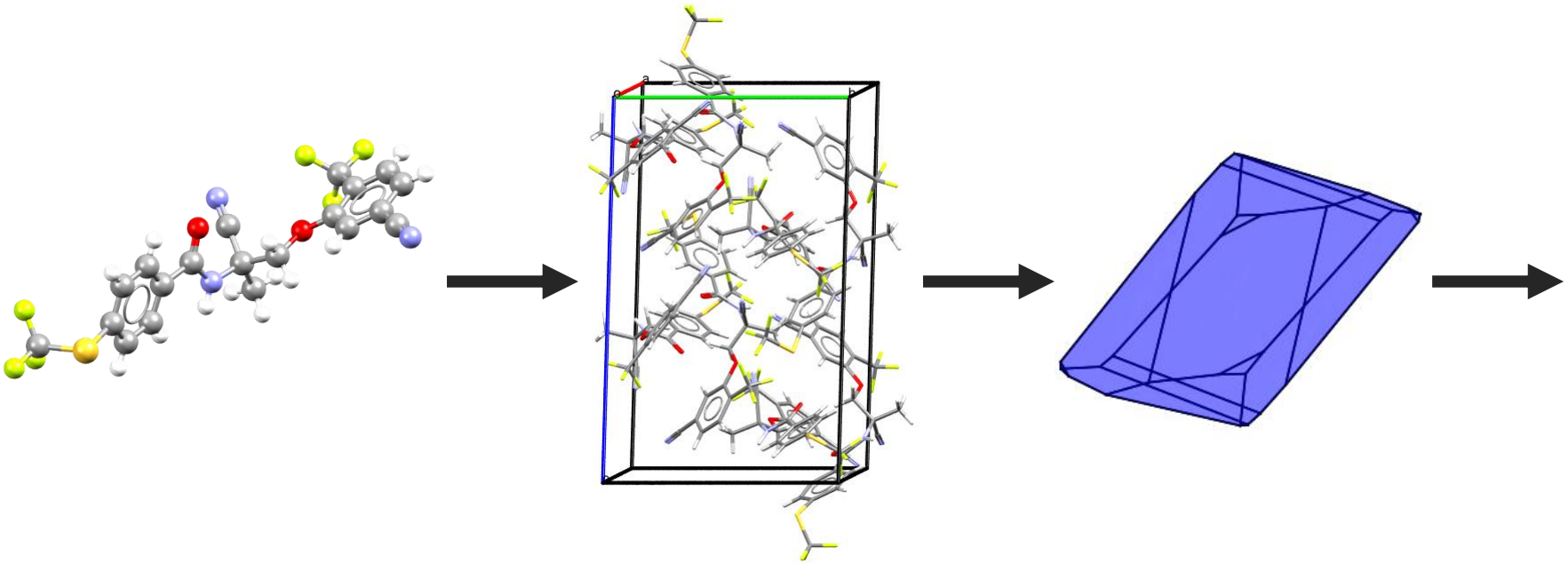


Predicting slip planes

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**

C.C. Sun and Y.-H. Kiang, *J. Pharm. Sci.* (2008), **97**, 3456-3461

Making the most of every crystal structure ever published



Molecule **Form** **Particle**

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ADDOPT

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS