Insights drawn from proprietary structural databases

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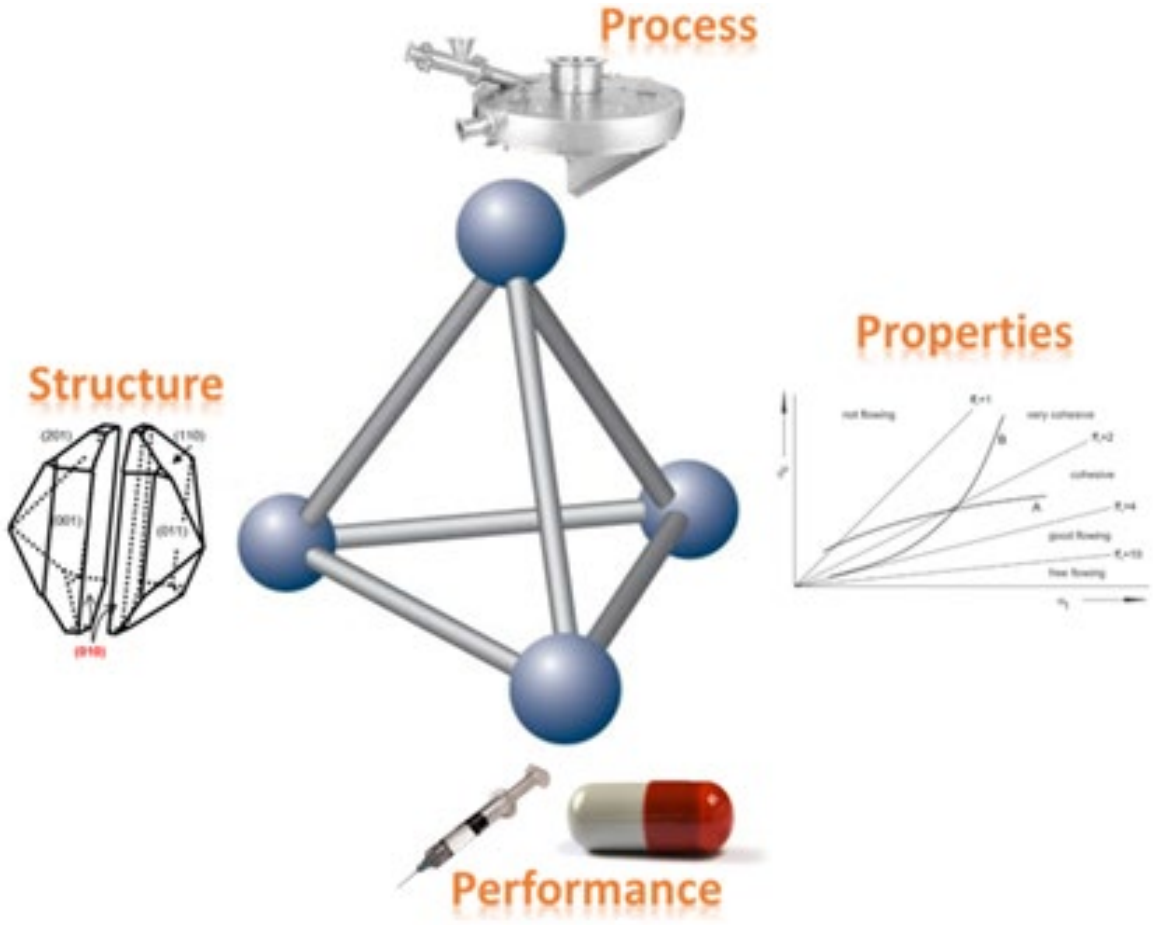
Pharmaceutical solid forms

The Materials Science Tetrahedron

- The properties, behaviour on processing and future performance of our drug products are intrinsically linked to their structural form.
- Understanding the structure by investigating the interactions, surfaces and particle formation is key to building a robust product.
- Regulatory agencies responsible for approving new drug applications around the world pay close attention to whether that new drug can be consistently delivered and that it will perform to expected standards.



C.C. Sun. Materials Science Tetrahedron—A Useful Tool for Pharmaceutical Research and Development, J Pharm Sci, 98, 5, 1671-1687.

Late appearing stable polymorphs

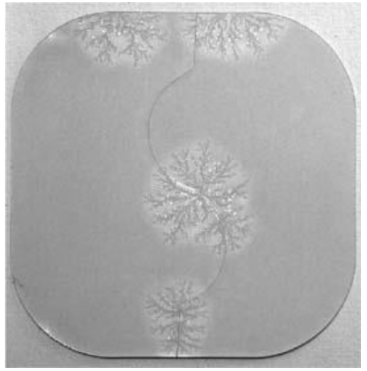
April 2, 2008

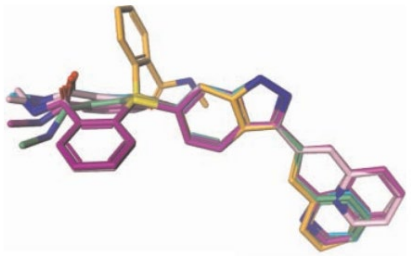
Neupro patches recalled

Neupro (rotigotine transdermal system, from UCB and Schwarz Pharma) patches are being recalled due to the formation of rotigoti crystallizes, less drug is available to be absorb efficacy of the affected product may vary.

Healthcare providers have been advised to no to begin down-titrating all patients currently u product label. It is strongly advised that patier therapy.Neupro will not be available after the

Neupro is indicated for the treatment of the si idiopathic Parkinson's disease.



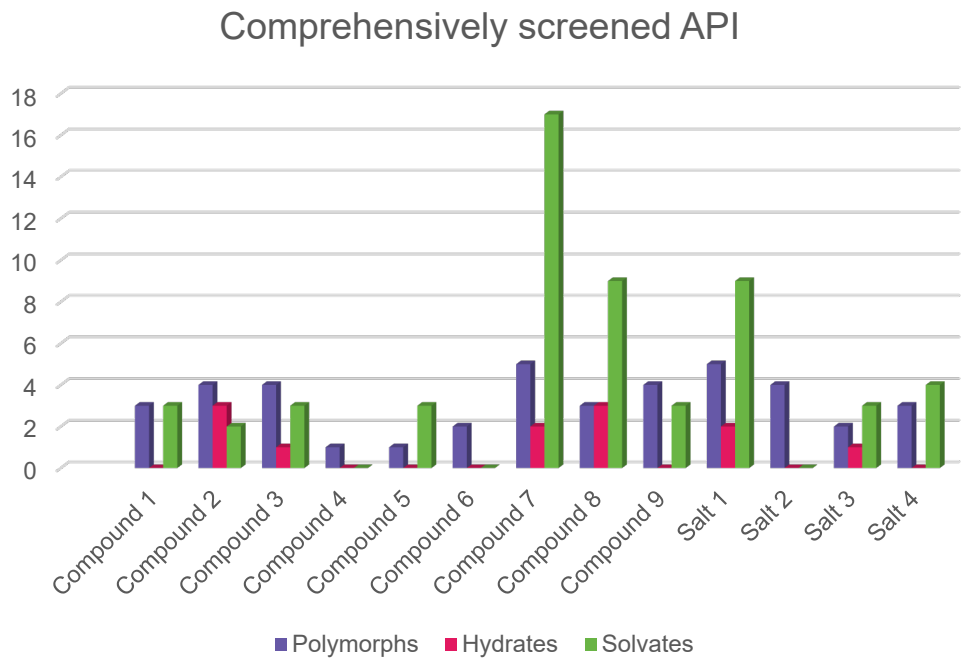


- In most cases, a thoroughly designed API form screen should typically identify the thermodynamically stable polymorph.
- However, there are numerous exceptions that describe the appearance of a lower energy form at late stages in development or even after launch.

Bauer J, Spanton S, Henry R, Quick J, Dziki W, Porter W, Morris J. 2001. Ritonavir: An extraordinary example of conformational polymorphism. Pharm Res 18:859–866. Desikan S, Parsons R, Jr., Davis WP, Ward JE, Marshall WJ, Toma PH. 2005. Chekal BP, Campeta AM, Abramov YA, Feeder N, Glynn PP, McLaughlin RW, Meenan PA, Singer RA. 2009. The challenges of developing an API crystallization process for a complex polymorphic and highly solvating system. Part I. Org Process Res Dev 13:1327–1337.

How common are pharmaceutical polymorphs and hydrates?

- Survey of 13 comprehensively screened GSK candidates shows prevalence of diverse solid form landscapes.
  - Most form > 1 anhydrous polymorph
  - Around half form at least one hydrate
  - Solvates are very common
  - Only one is monomorphic with no multi-component systems
- Most candidates will exhibit multiple solid forms and it is important we are prepared to manage them. Not all of these will have been identified in early phase screening.



McCrone, W.C., Fox, D., Labes, M.M., Weissberger, A. (1965) *Physics and Chemistry of the Organic Solid State*, 2, pp. 725-767. Griesser, U. J. The importance of solvates. In *Polymorphism in the Pharmaceutical Industry*; Wiley-VCH Verlag GmbH & Co., 2006.

Exploring a polymorph landscape

Complimentary methods

Experimental screening

- Carried out in multiple solvents/temperatures/ methods
- Requires several g of API
- Purity must be high

Structural Informatics

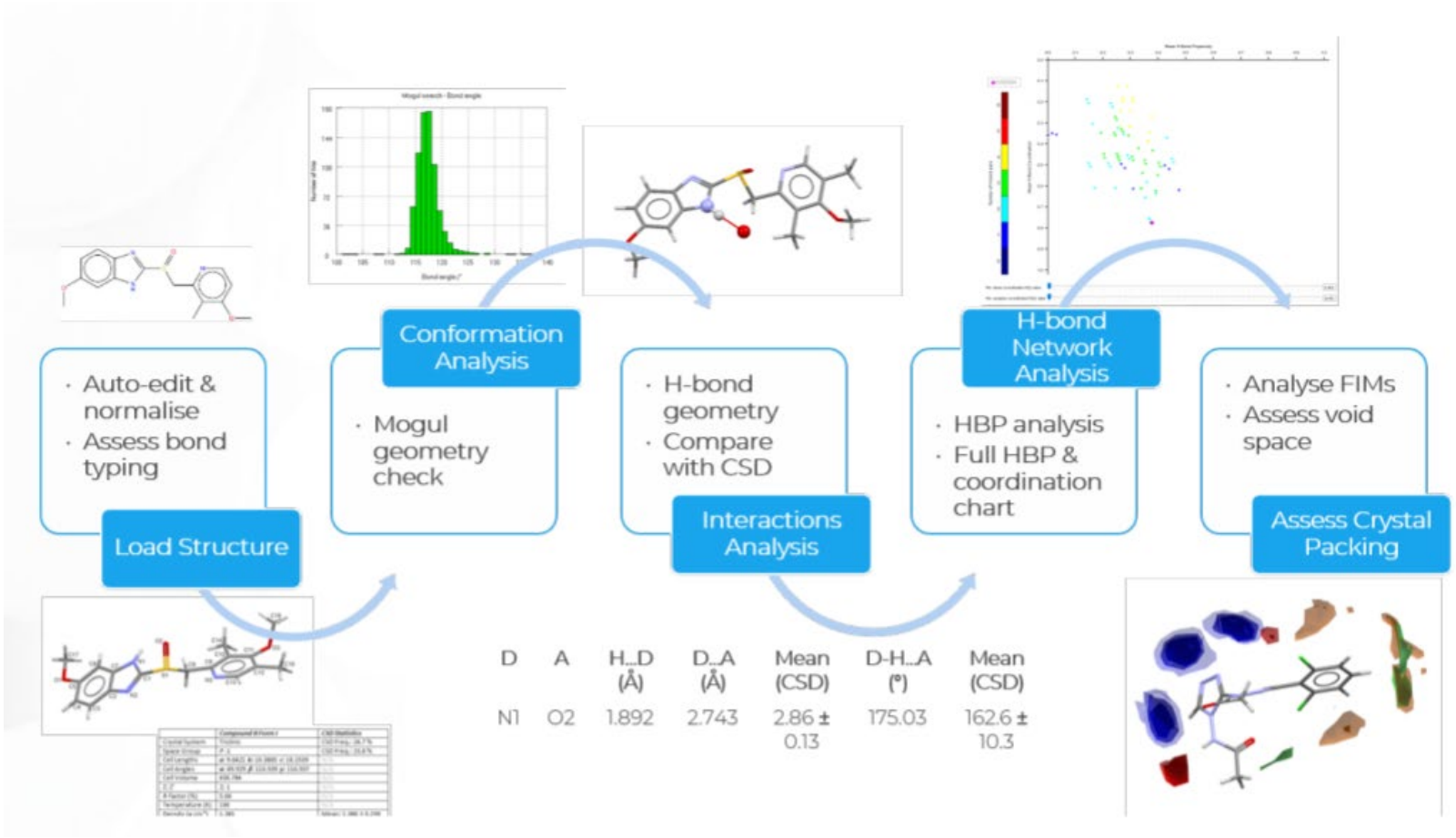
- Mining structural data to inform troubleshooting of solid form landscapes
- Obtain likelihoods, not definitive answers
- Inform additional screening
- Fast answer from very small amount of API (few mg, single crystal structure)

Crystal Structure Prediction

- Completely computational prediction of the energy landscape and packing
- Resource intensive (time, ££)
- Some very complex systems still not amenable

Healthcheck

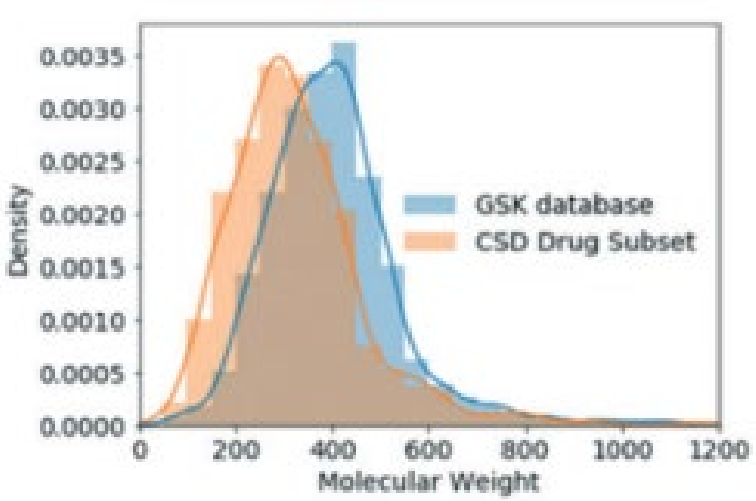
Mining structural data to inform troubleshooting of solid form landscapes

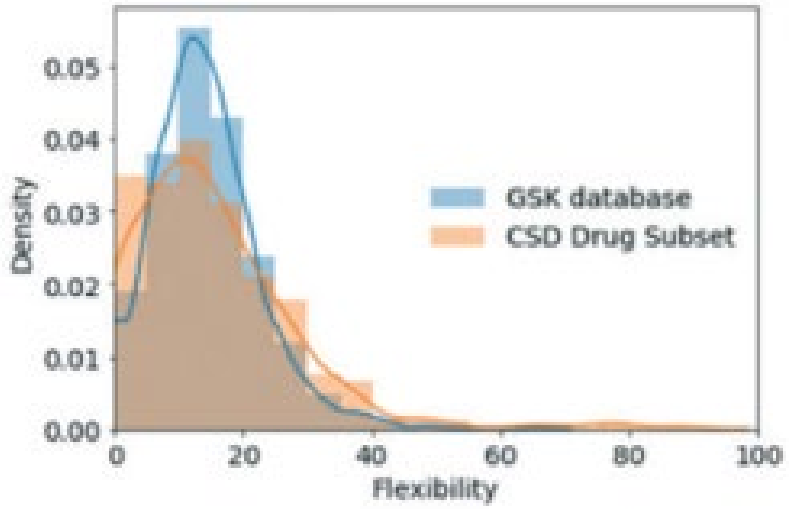


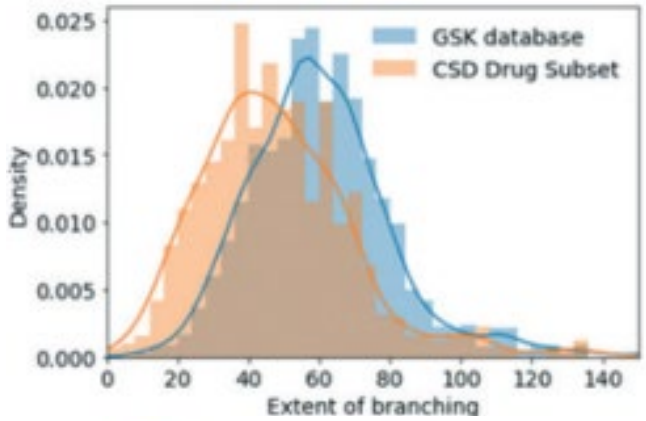
Healthcheck
Mercury tools package for stable form analysis and comparison

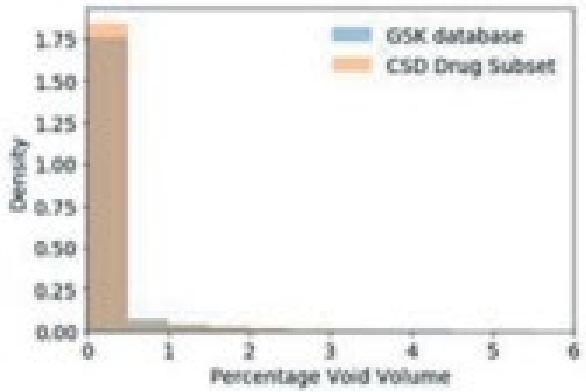
CSD drug subset

Molecular features

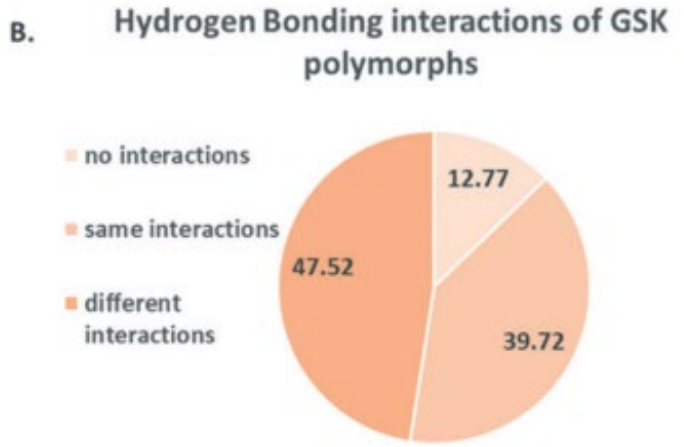








- Good coverage of relevant structural features in CSD
- Modern proprietary dataset is slightly more complex than the drug subset



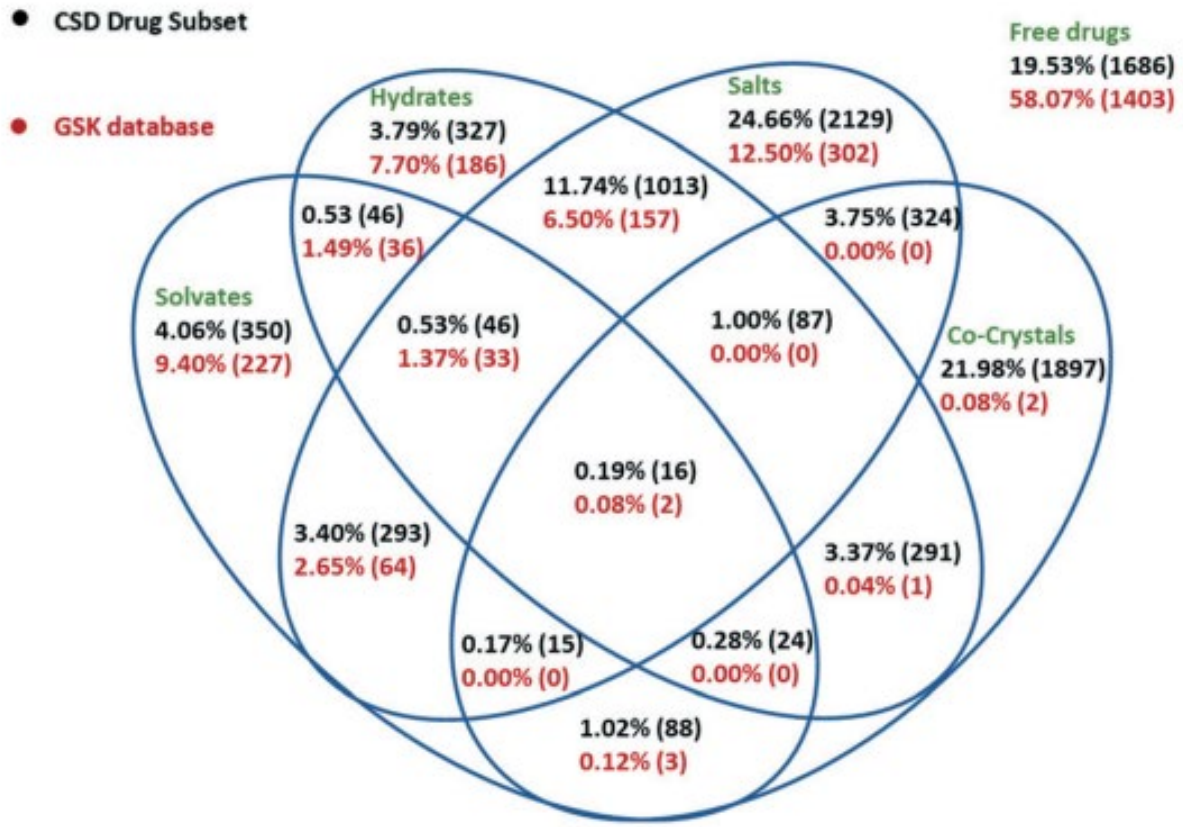
- HBP tool assesses different hydrogen bond motifs
- Almost half of the recorded polymorphs in the GSK dataset do have different interactions

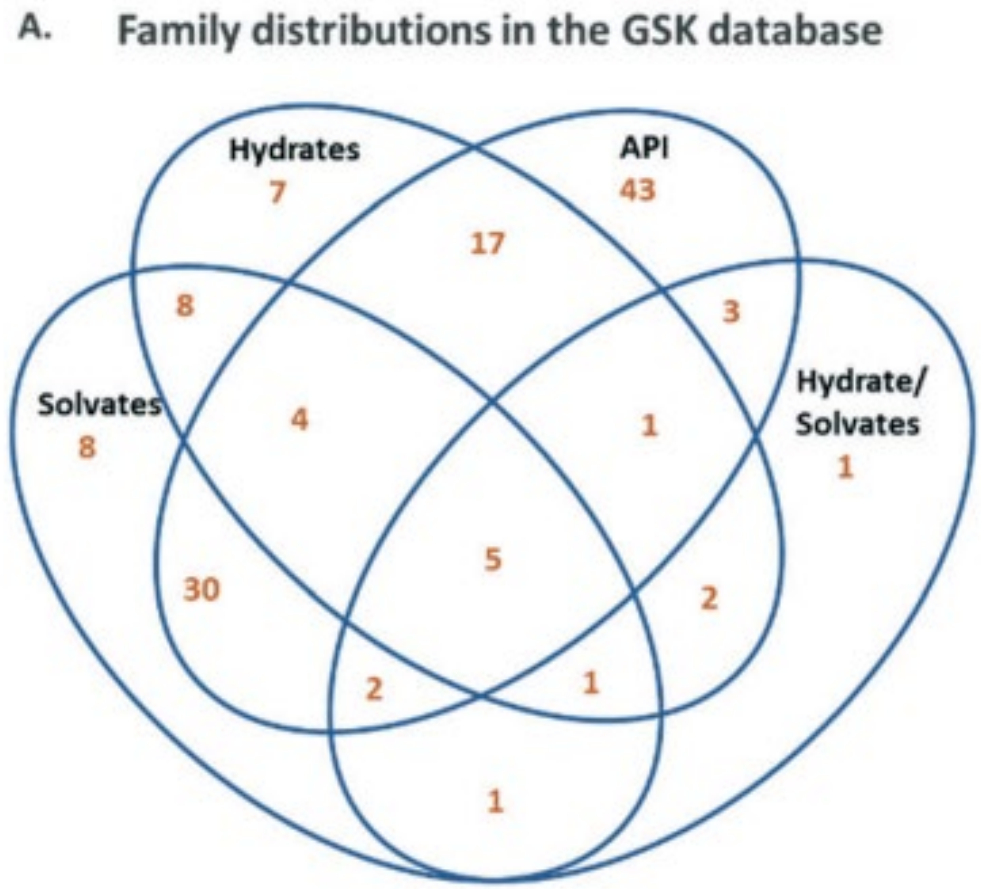
Leen Kalash et al. *CrystEngComm*, 2021, **23**, 5430-5442.

CSD drug subset

Solid form distributions

How comparable is the drug subset?

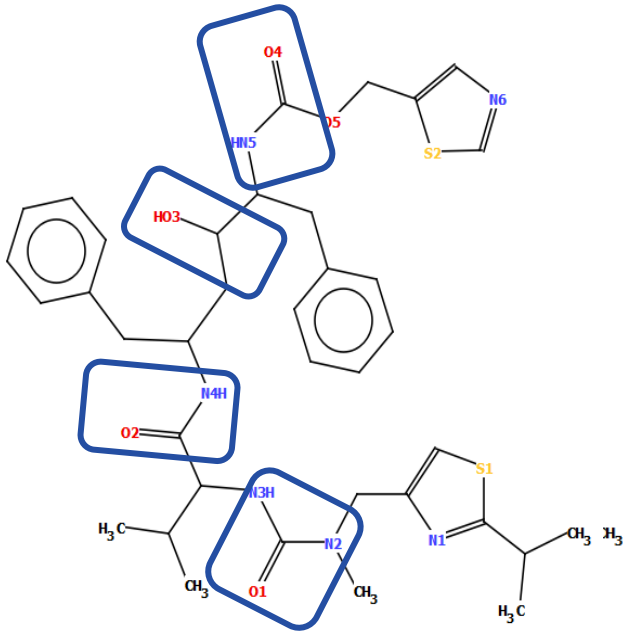


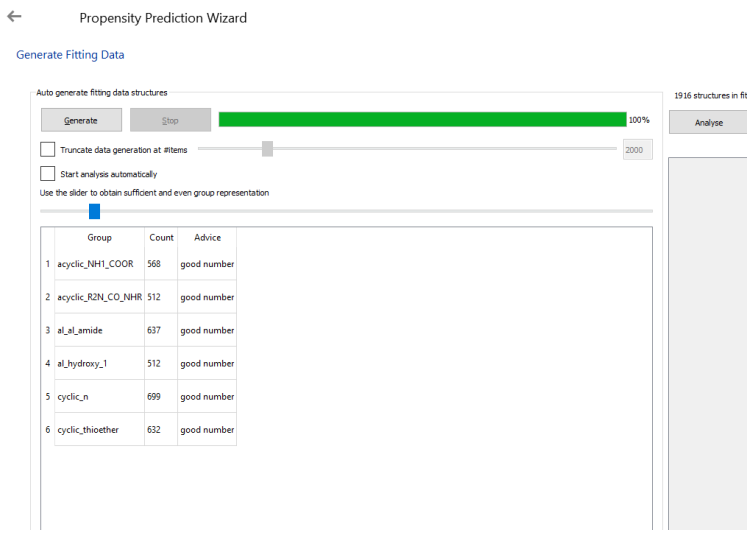


Hydrogen bond propensity models

Ritonavir

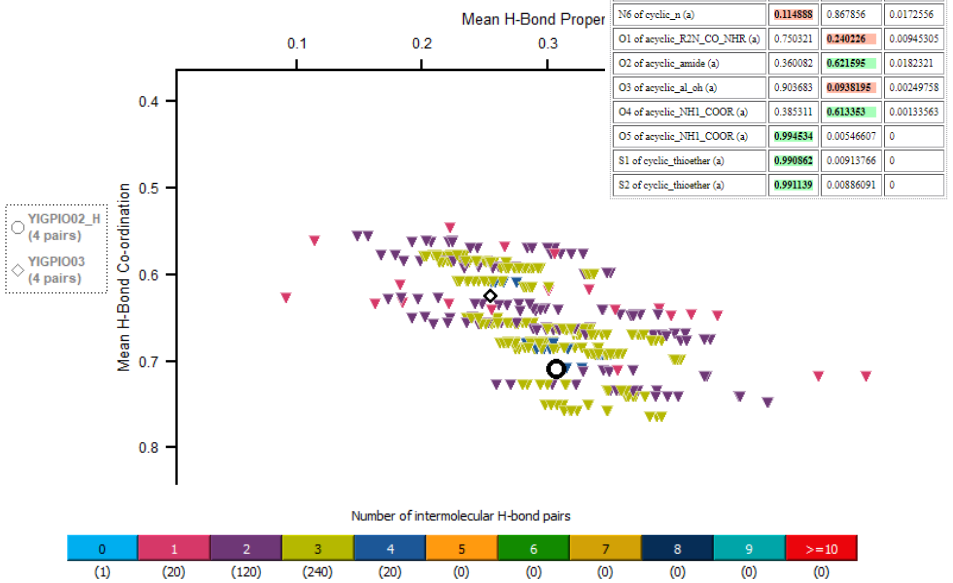
- HBP allows a comparison of the hydrogen bond pairings possible and the alternative motifs
- Uses a single crystal structure, available via the wizard in Mercury Materials or via Snapshot script.





YIGPIO03

Atom (D/A)	= 0	= 1	= 2
N3 of acyclic_R2N_CO_NHR (d)	0.713103	0.286897	0
N4 of acyclic_amide (d)	0.267946	0.728134	0.00391977
N5 of acyclic_NH1_COOR (d)	0.161496	0.838504	0
O3 of acyclic_al_oh (d)	0.138059	0.828856	0.0330856
N1 of cyclic_n (a)	0.815359	0.183215	0.00142641
N6 of cyclic_n (a)	0.114888	0.867856	0.0172556
O1 of acyclic_R2N_CO_NHR (a)	0.750321	0.240226	0.00945305
O2 of acyclic_amide (a)	0.360082	0.621595	0.0182321
O3 of acyclic_al_oh (a)	0.903683	0.0938195	0.00249758
O4 of acyclic_NH1_COOR (a)	0.385311	0.613353	0.00133563
O5 of acyclic_NH1_COOR (a)	0.994534	0.00546607	0
S1 of cyclic_thioether (a)	0.990862	0.00913766	0
S2 of cyclic_thioether (a)	0.991139	0.00886091	0

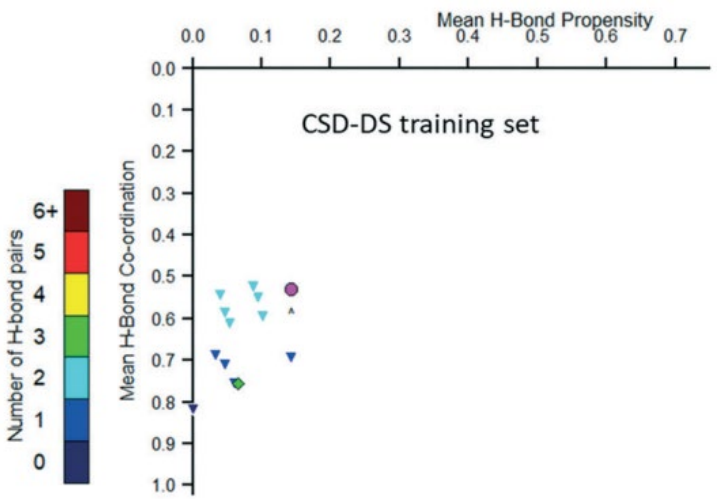


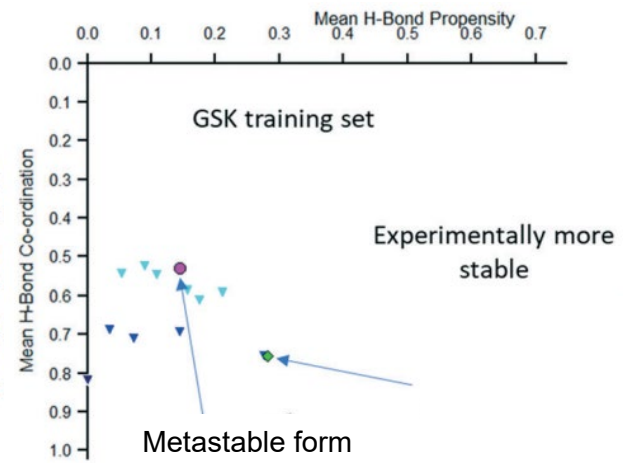
CCDC refcodes YIGPIO02, YIGPIO03. Peter Galek et al. ***CrystEngComm***, 2009,**11**, 2634-2639

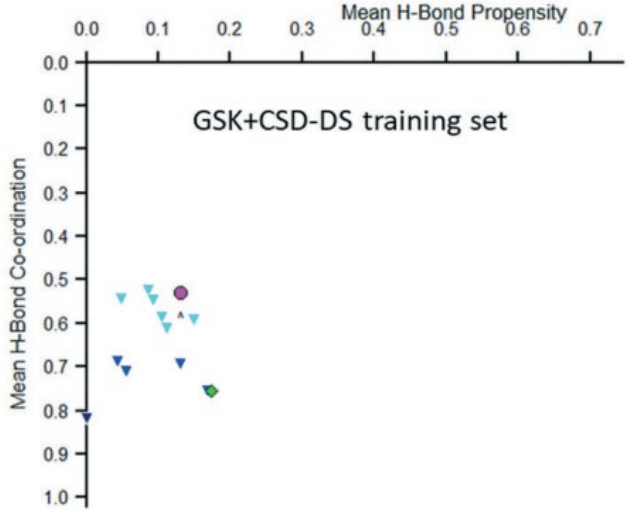
Benefits of in-house data to bolster hydrogen bond propensity models

Improving the accuracy of HBP models

- CSD contains many structures useful in training data sets.
- In-house databases are many orders of magnitude smaller, but the examples are so relevant that they can greatly boost the accuracy of the output model.



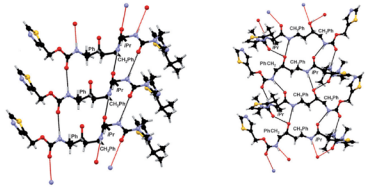




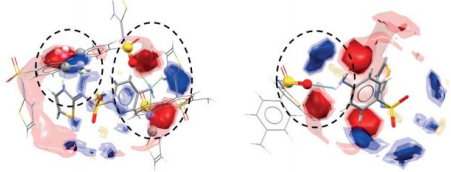
Structural Informatics

Moving on from retrospective rationalisation

Interpreting output
Not all the flags in a healthcheck tell the same story

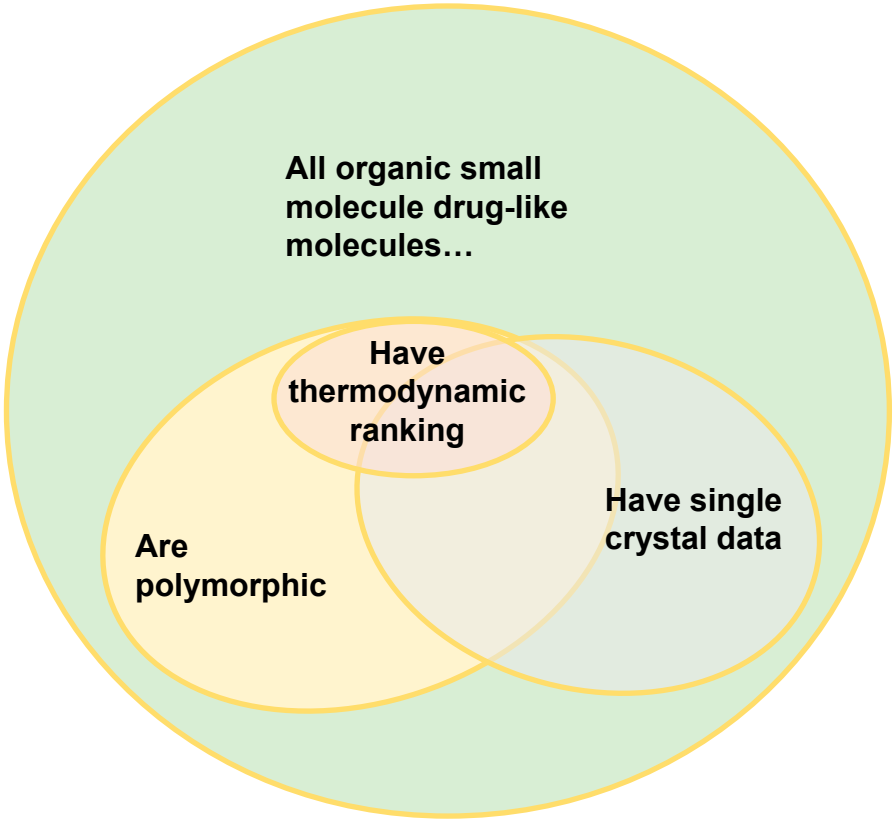


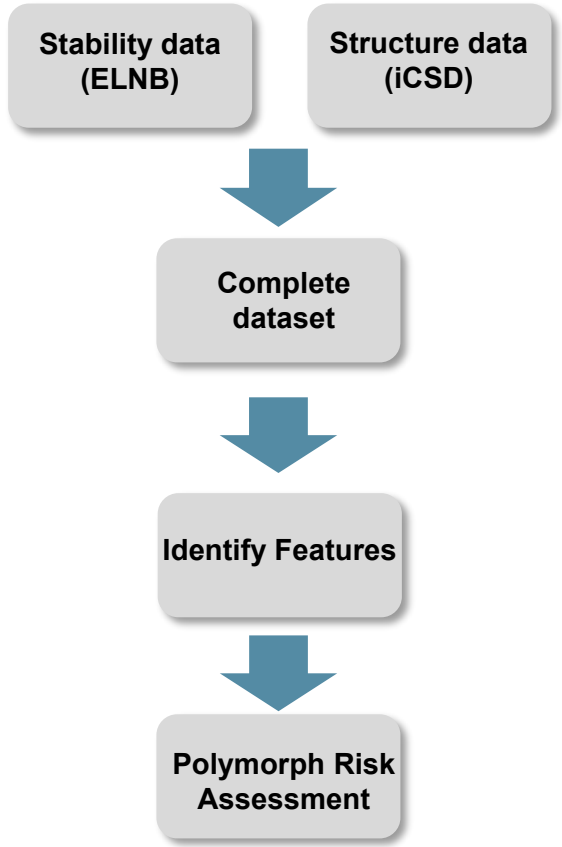
Ritonavir Forms I and II
Ranking interactions correctly identifies stable form



Sulfathiazole Forms V and I
Full interaction maps shows matching of donors and acceptors to rationalise stability ranking

CSD and iCSD
Contains real structures, but a mix of stable and metastable. What does “Unusual” mean?





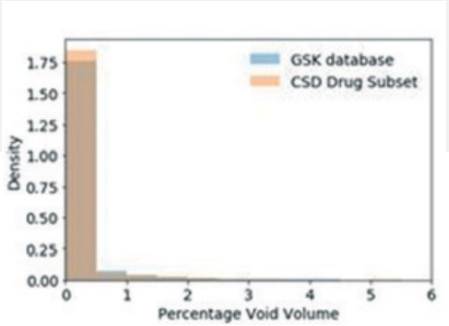
Improving model predictivity

Voids

Larger amounts of total voids are typically considered a higher risk.

The overall comparison of voids in structures in the GSK database looks very similar to that for the CSD subset.

By analysing the stability information at the same time we will get more clarity on how voids are related to solid form risk.



Unused donors

Hydrogen bond donors are typically expected to be used. Some donors exhibit low coordination scores.

How high a coordination score is acceptable in an unbonded potential donor?

	Atom (D/A)	= 0	= 1	= 2
1	O3 of cooh (d)	0.009	0.973	0.018
2	N1 of cyclic_n (a)	0.821	0.177	0.002

DB7/FOCWUR01: Braun et al. Cryst. Growth Des. 2014, 14, 4, 2056.

Conformation

In conformational polymorphs the same molecule the different conformations.

Predicting when a more stable conformational polymorph can appear would be of extreme value

Chandler Greenwell and Gregory J. O. Beran. *Cryst. Growth Des.* 2020, 20, 4875.

Conclusions

- **Automation:** Particularly for early phase candidates and pre-candidates fast and reliable analysis is needed to offer results on a timeline that can impact project decisions.
- **Leveraging legacy "big" data:** The CSD drug subset as well as in house databases hold valuable and relevant information about real crystal systems. Adding crystal structures of new polymorph families are valuable to this analysis.
- **Reliability:** A combined dataset comprising crystal structure data and the relative stability ranking for polymorph pairs allows the identification of structural features that are discriminatory with respect to thermodynamic stability. Basing decisions on real stable/metastable comparisons offers an opportunity to improve the accuracy of informatics predictions.

Acknowledgements

- Co-authors: Leen Kalash, Jason Cole, Royston Copley, Colin Edge, Alex Moldovan, Ghazala Sadiq
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