

Cocrystals and Other Complex Pharmaceutical Materials: Structure Solution from Powder Diffraction

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Outline of method

Collect data



Peak positions: index pattern → unit cell



Intensities: solve structure → approximate structural model



Least-squares refinement → accurate structural model



What is powder diffraction

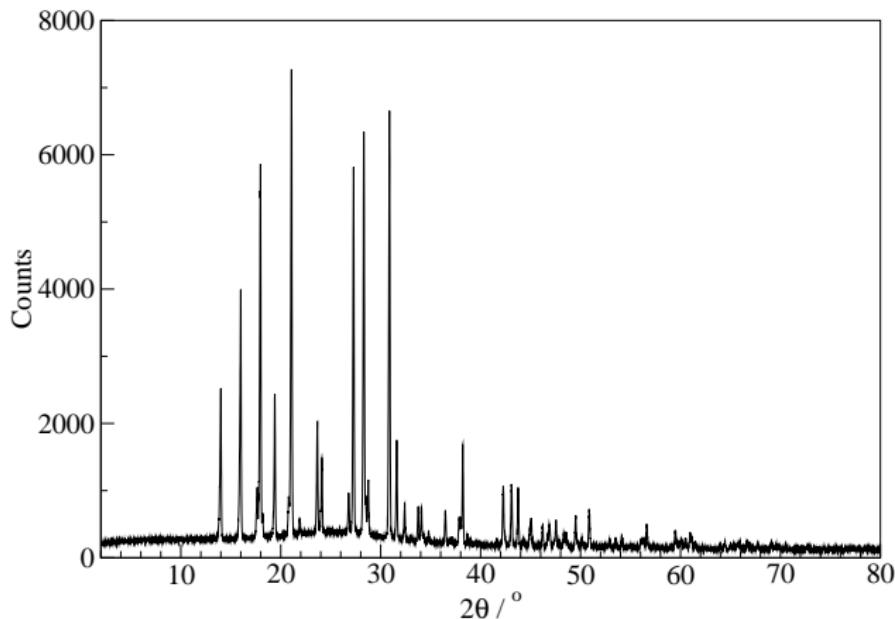
Single crystal:

- One crystal, known orientation

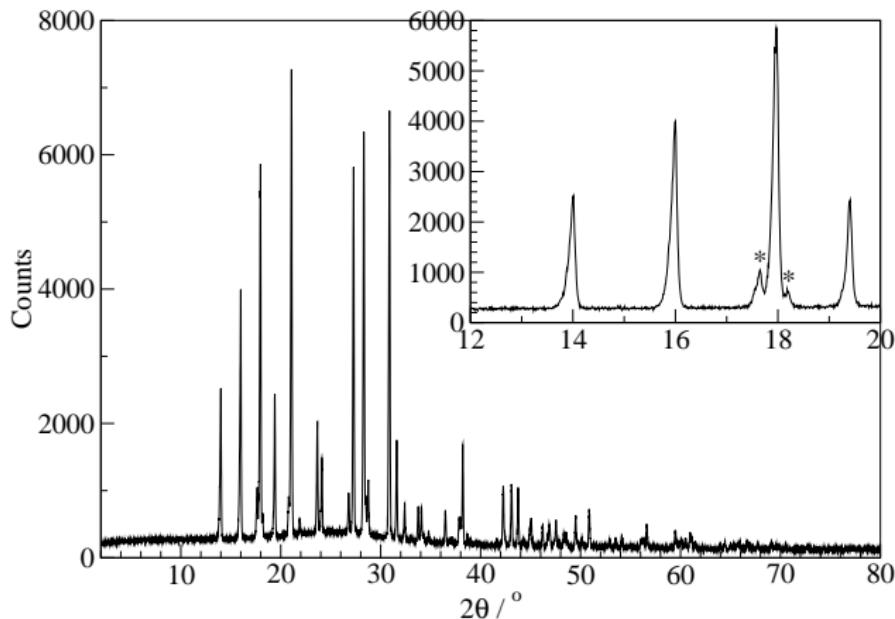
Powder:

- Many crystals, isotropic (average orientation)

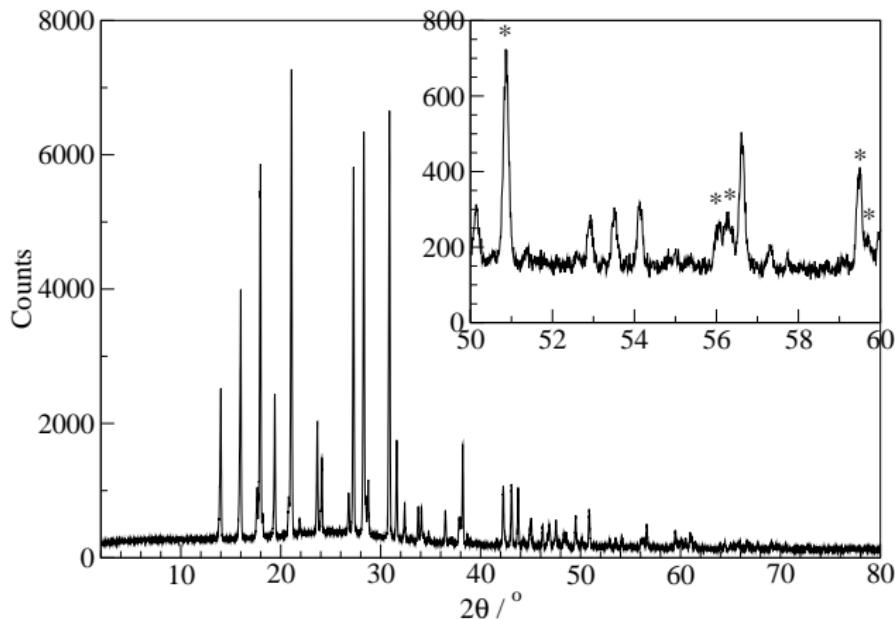
Typical powder diffraction pattern



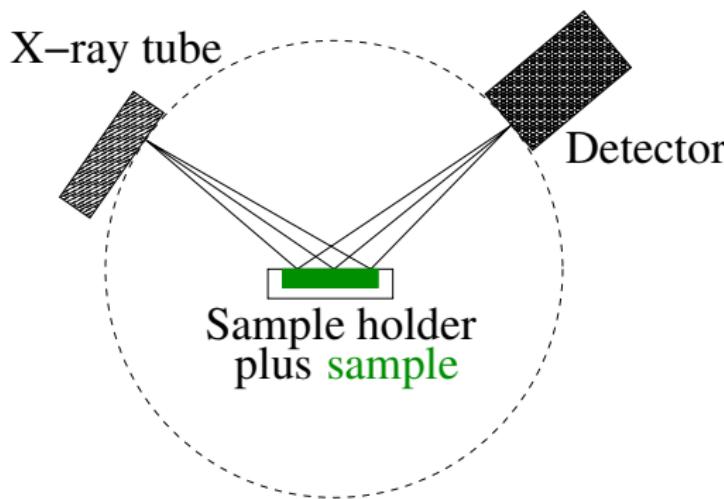
Typical powder diffraction pattern



Typical powder diffraction pattern

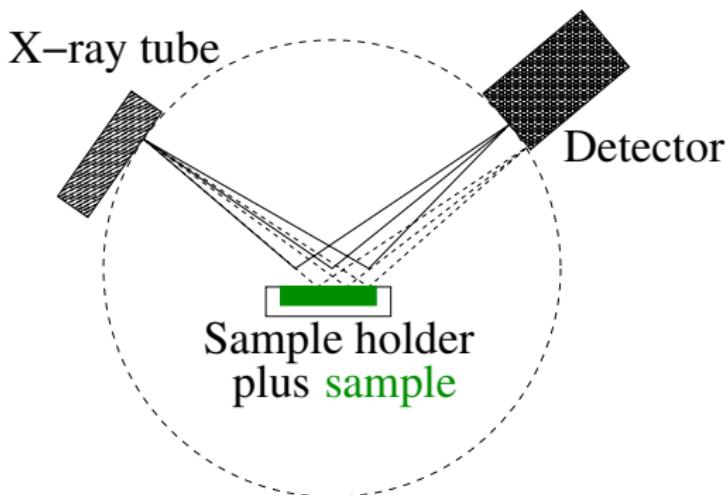


Bragg-Brentano geometry



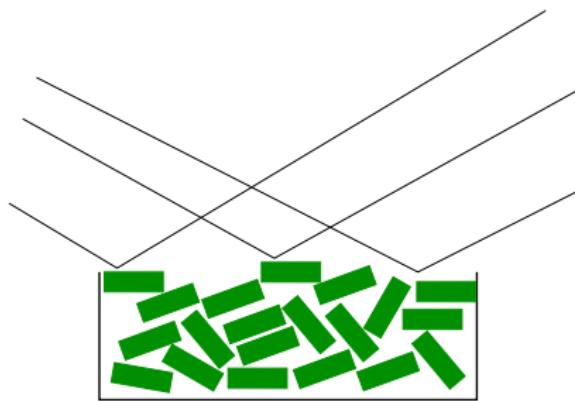
Assumption: all X-rays diffracted immediately at surface of sample, no penetration of X-rays into sample

Sample height effects



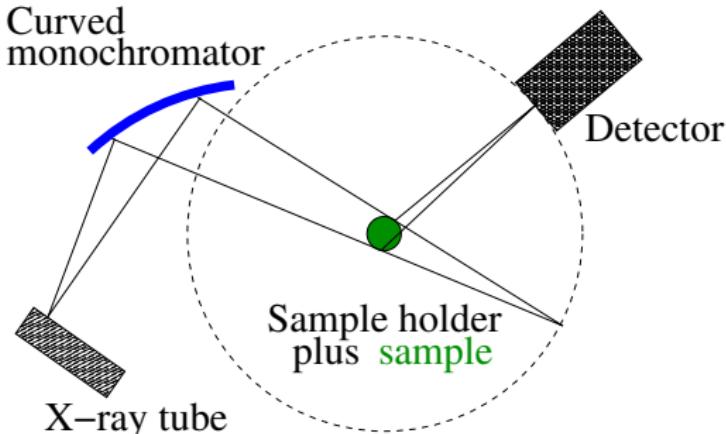
Net effect: peak positions out by factor $\Delta\theta$ of $S \cos \theta$, typically
 $0 \leq \Delta\theta / {}^\circ \leq 0.1$

Preferred orientation effects



Net effect: peak intensities do not correspond to ‘powder average’, certain classes of hkl (e.g. 00l) more intense than expected

Debye-Scherrer geometry



Sample position well-defined, sample spinning removes almost all preferred orientation

Data collection methods

Two main methods:

- Bragg-Brentano (flat-plate)
 - More common geometry
 - Simple sample prep
- Debye-Scherrer (capillary)
 - Less common geometry
 - Slightly fiddly sample prep

Key point: Debye-Scherrer method far superior peak positions and intensities

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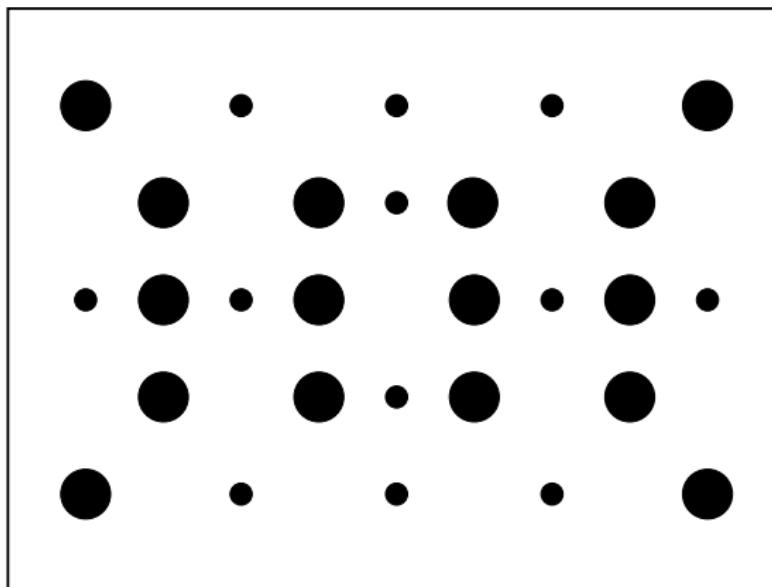
Intensities: solve structure → approximate structural model



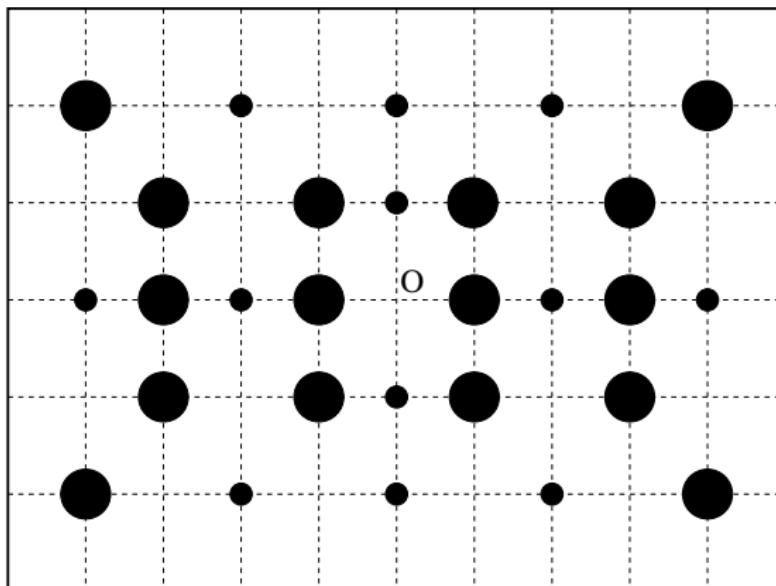
Least-squares refinement → accurate structural model



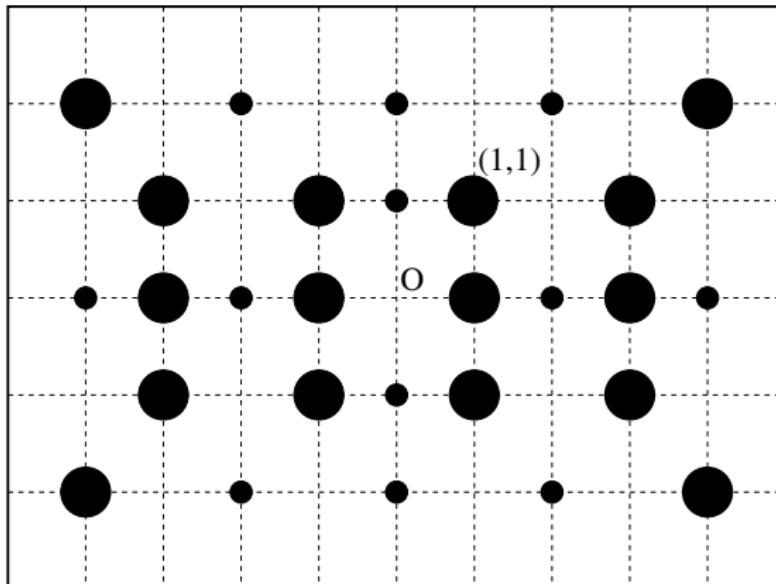
Indexing: 2D example



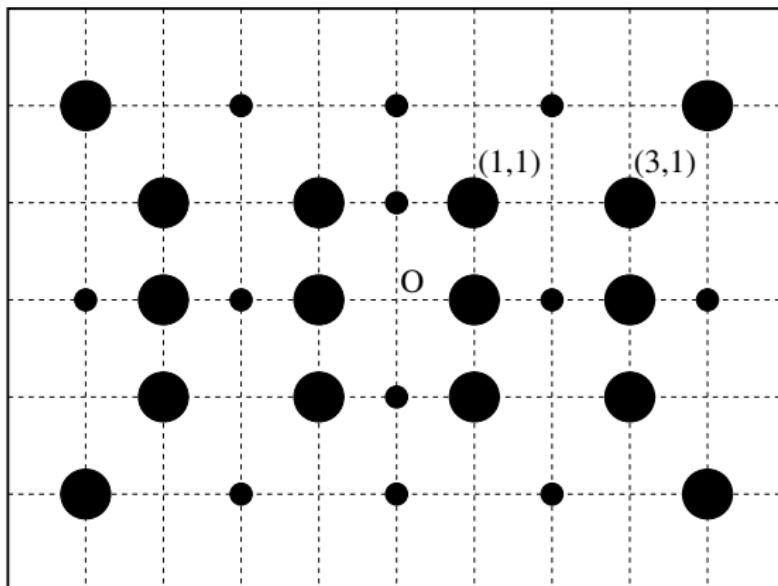
Indexing



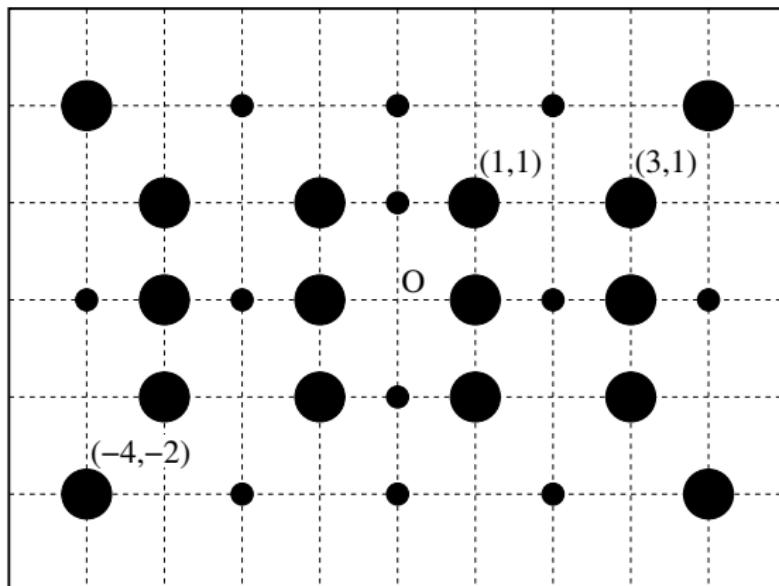
Indexing



Indexing



Indexing



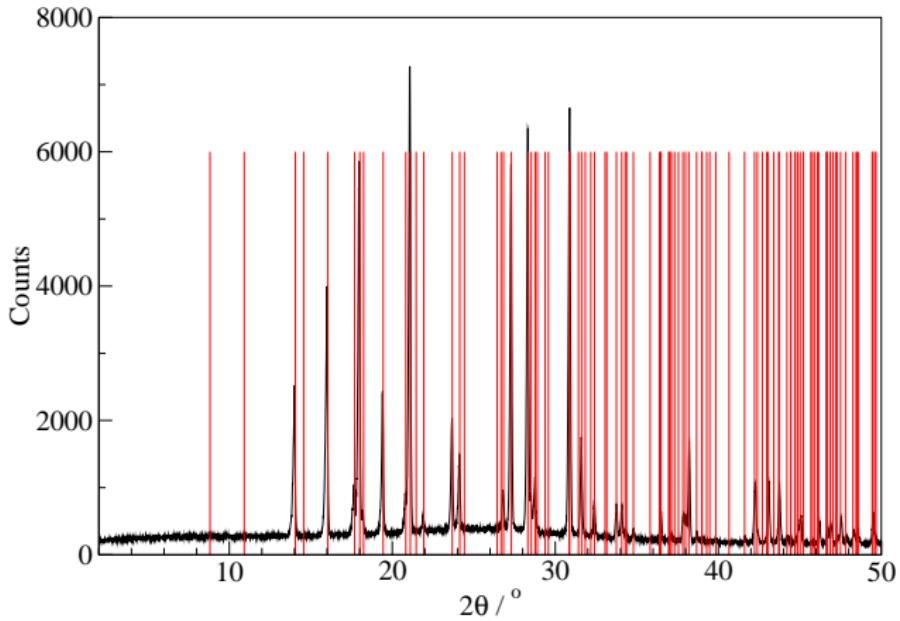
Indexing

Software readily available, either free of charge, open-source or commercial:

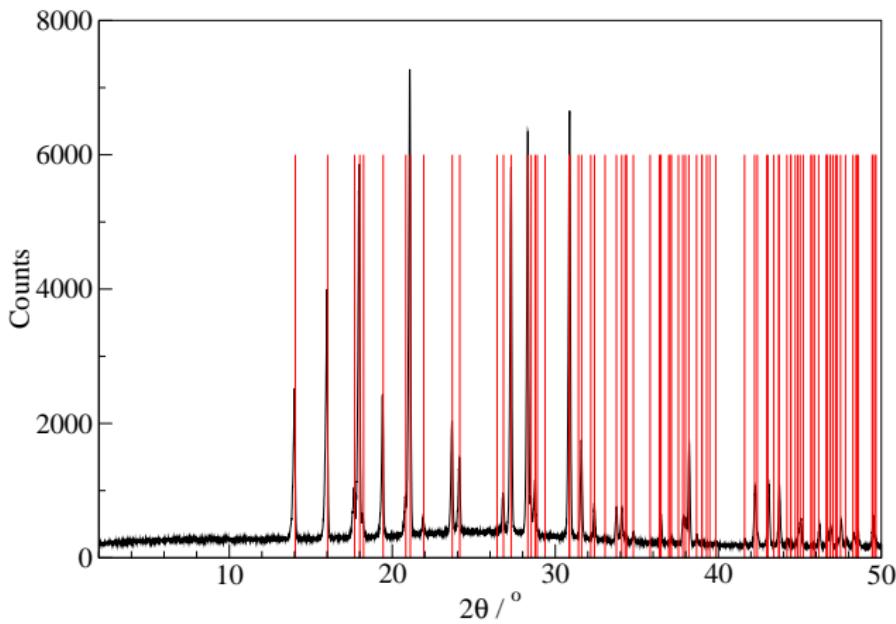
- treor
- ito
- dicvol & dicvol04

User-friendly, useable interface: cmpr

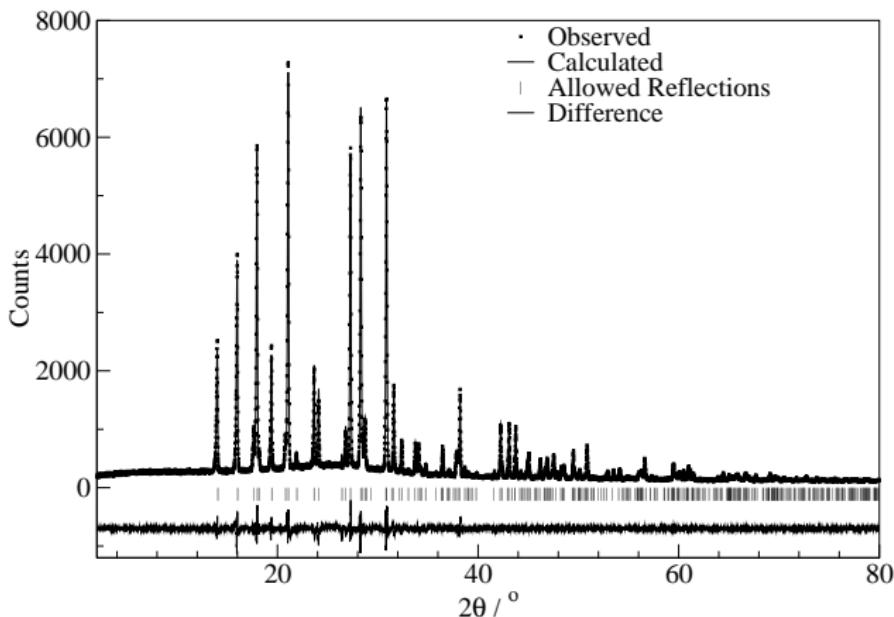
Indexing: powder example



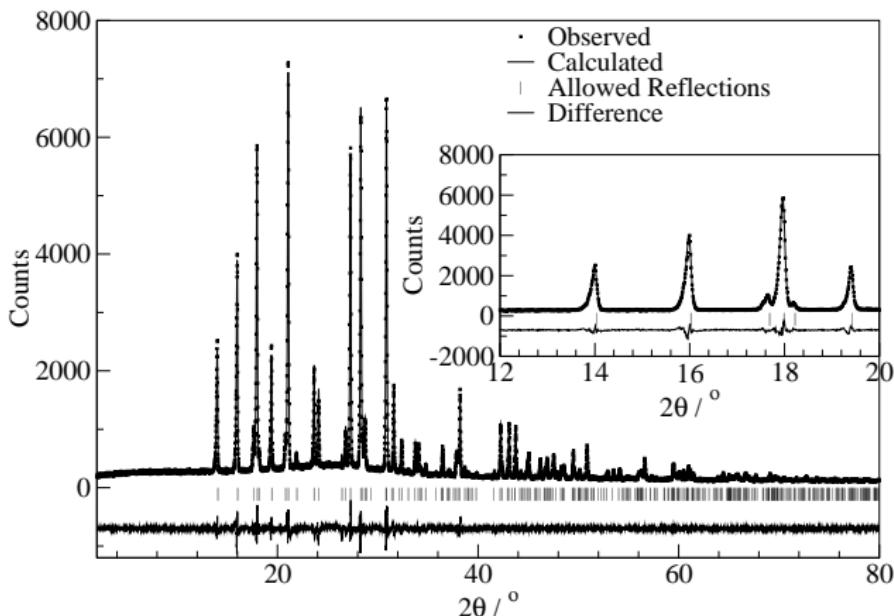
Indexing: powder example



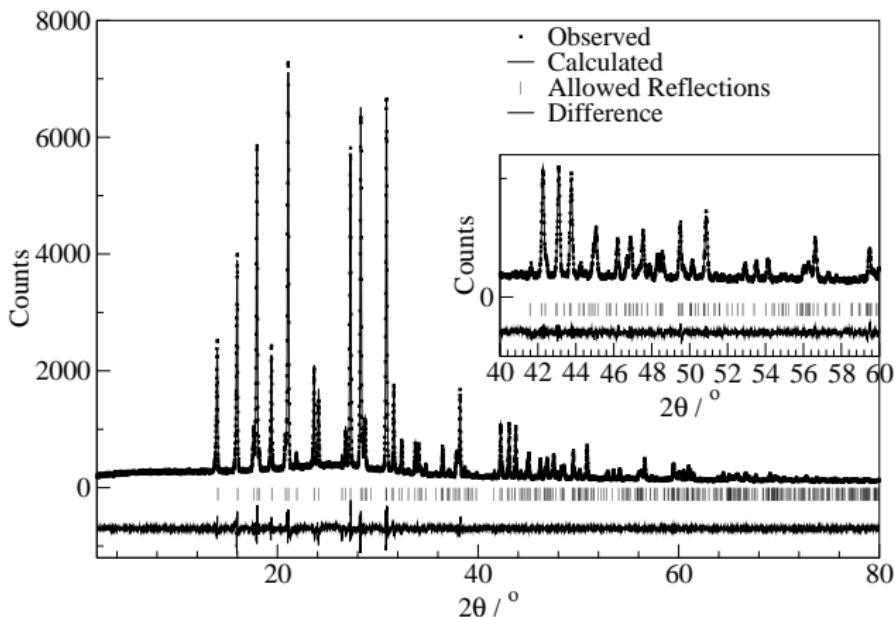
Whole-pattern fitting (LeBail or Pawley)



Whole-pattern fitting (LeBail or Pawley)



Whole-pattern fitting (LeBail or Pawley)



Powder vs single crystal data

	Powder	Single crystal
Defined intensities	Partially	Yes
Data dimensions	$2(2\theta, I)$	$4(hkl, I)$
Number hkl	50-150	2k-50k

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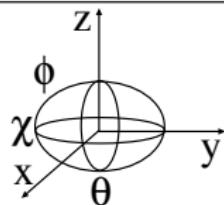
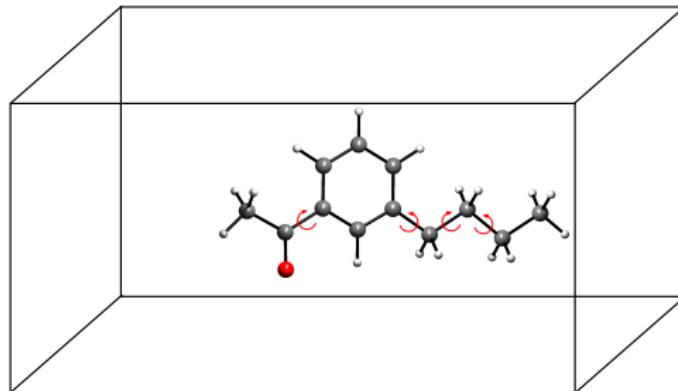
Intensities: solve structure → approximate structural model



Least-squares refinement → accurate structural model



Structure solution



Brute-force approach

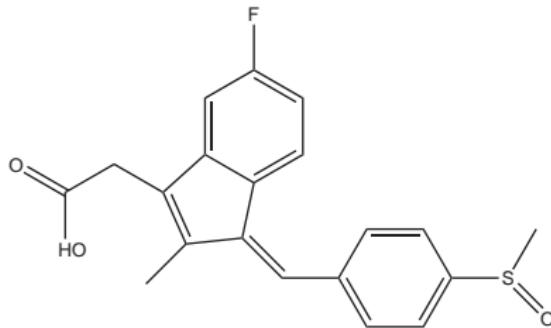
Minimise difference between observed and calculated data,
adjust structural parameters until good match obtained

Software readily available:

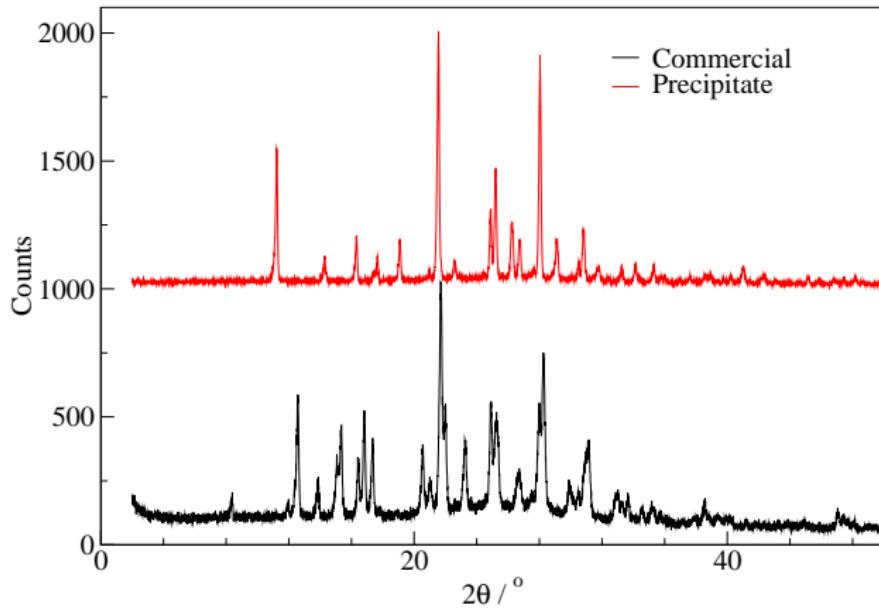
- DASH
- PSSP
- FOX

Sulindac

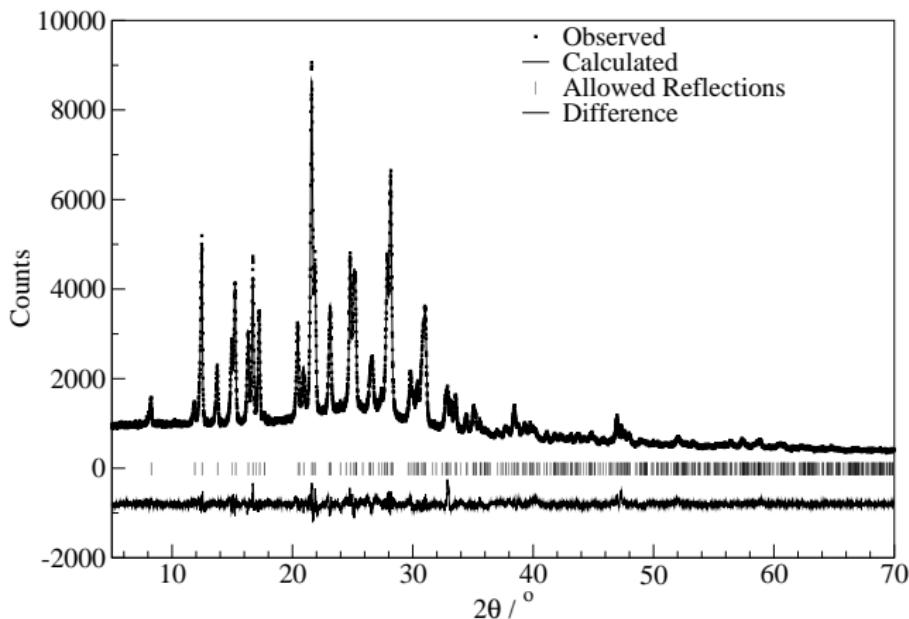
NSAID, anti-cancer



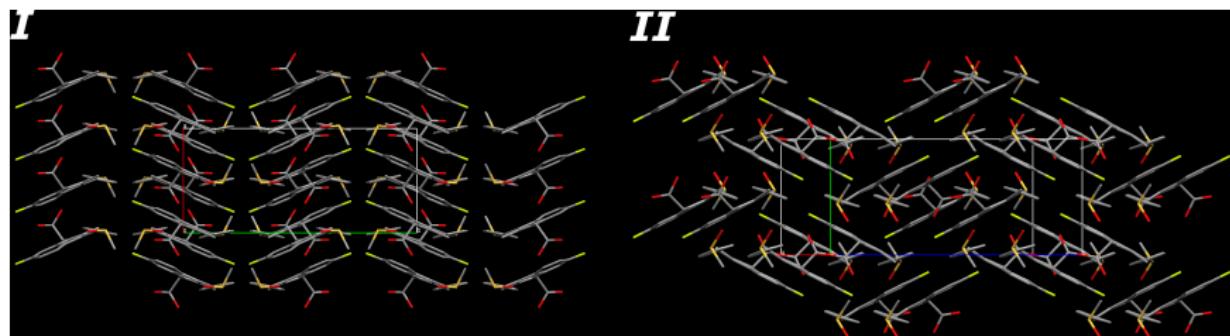
Sulindac: polymorphism



Sulindac: Rietveld

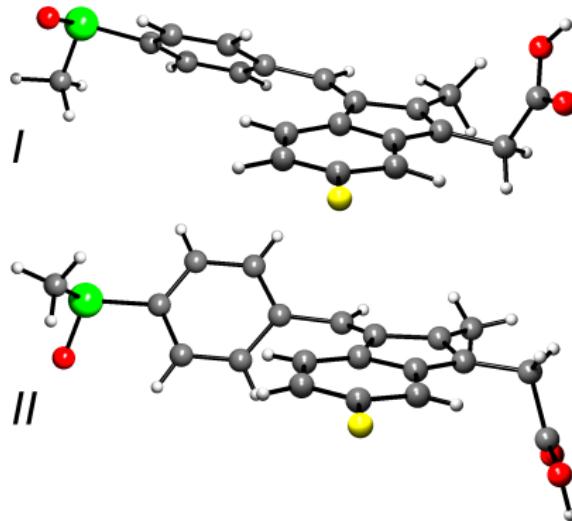


Sulindac: structures



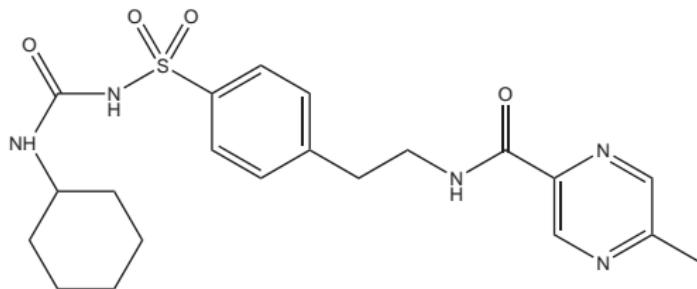
Two polymorphs, solubilities differ by factor of 7

Sulindac: structures

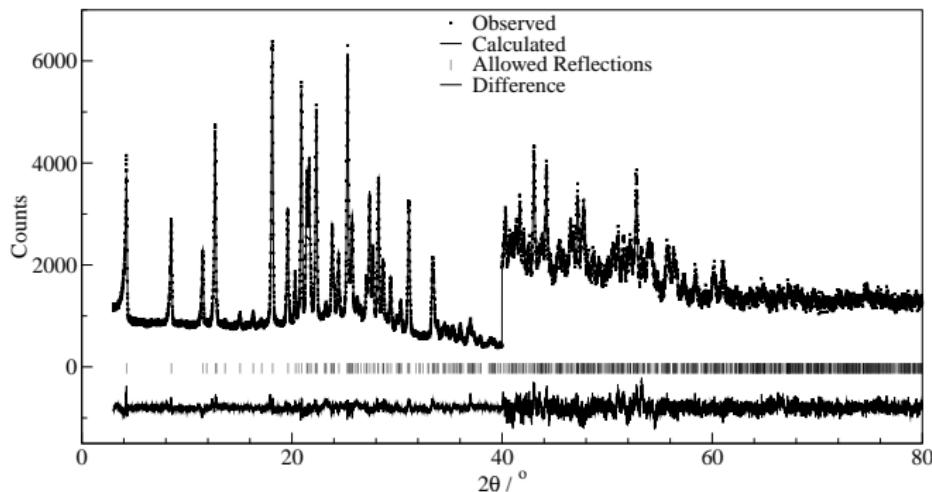


Glipizide

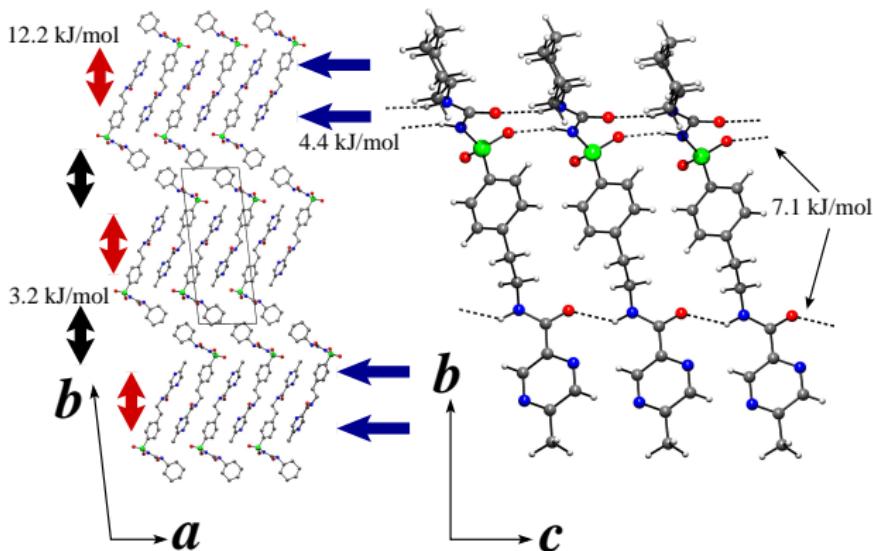
Diabetes treatment



Glipizide: Rietveld

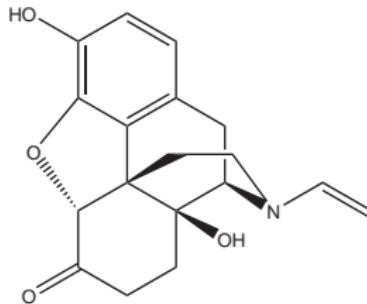


Glipizide: forces from thermal expansion

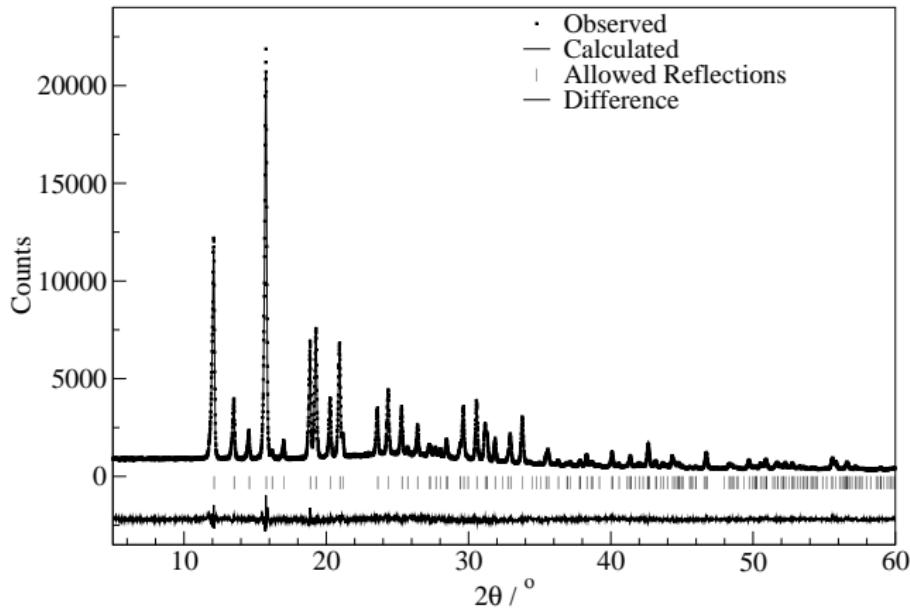


Naloxone

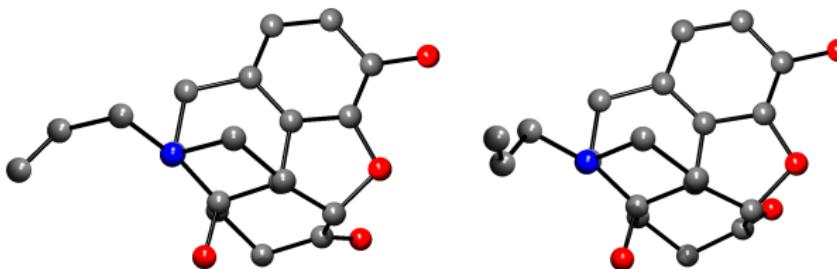
μ -opioid receptor competitive antagonist



Naloxone: Rietveld



Naloxone: comparison with salt hydrates

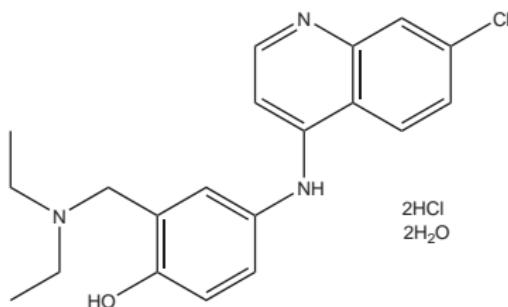


HCl hydrate

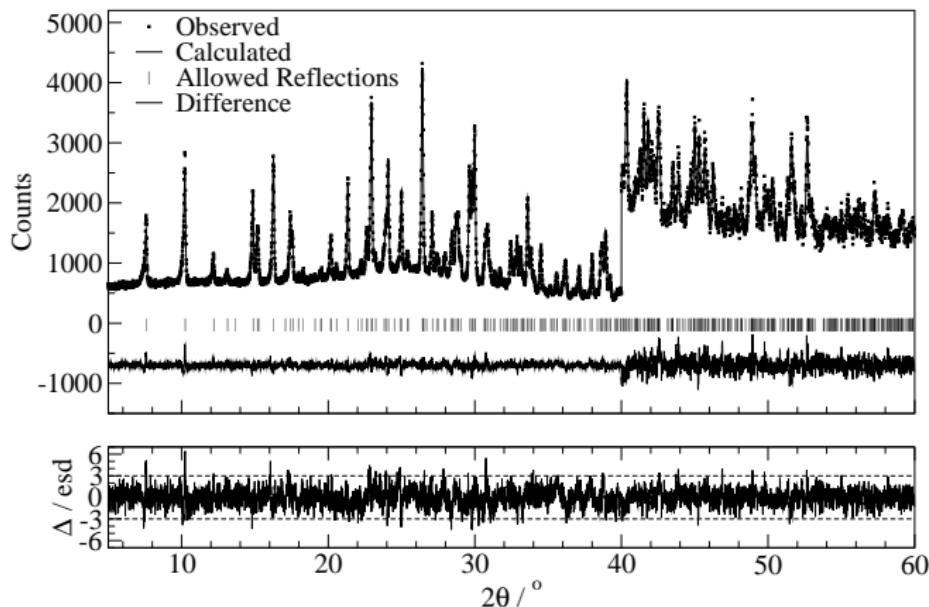
Neutral form

Amodiaquinium dichloride dihydrate

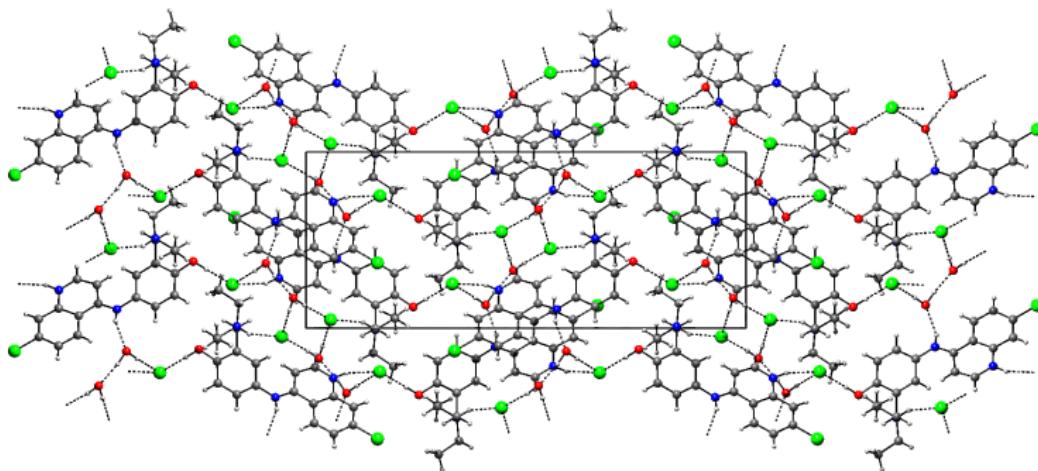
Malaria treatment



Amodiaquinium dichloride dihydrate: Rietveld

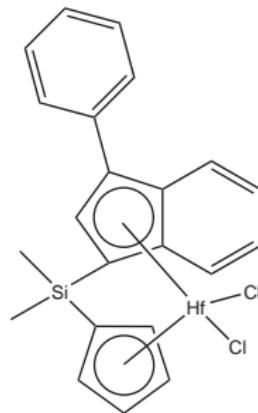


Amodiaquinium dichloride dihydrate: structure

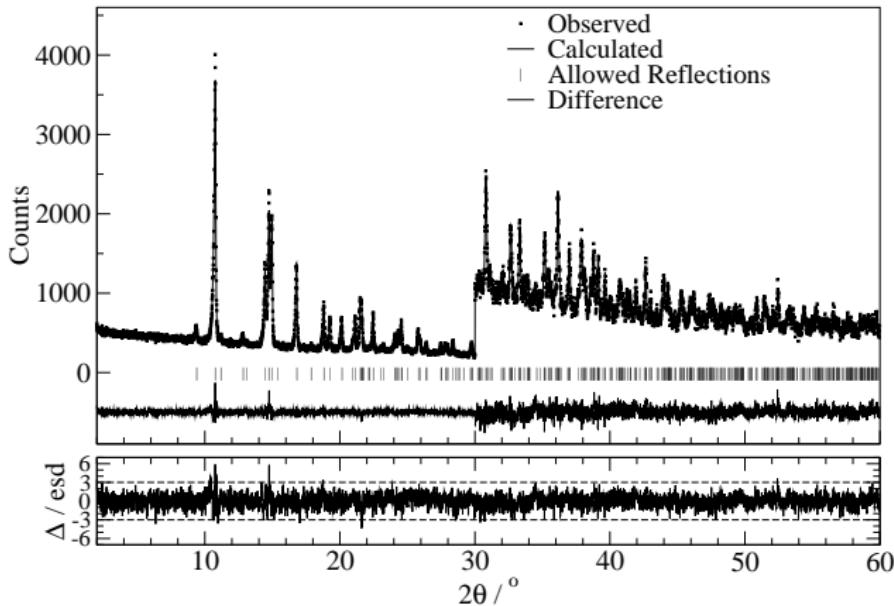


Hafnium cyclopentadienyl

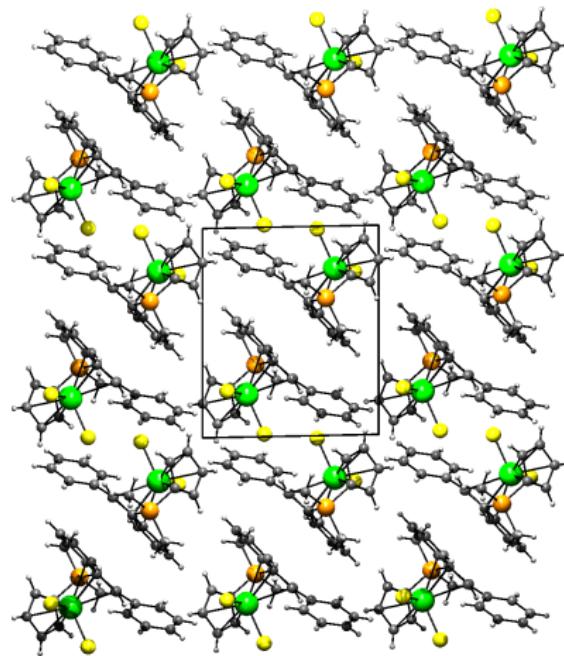
Propylene polymerisation catalyst



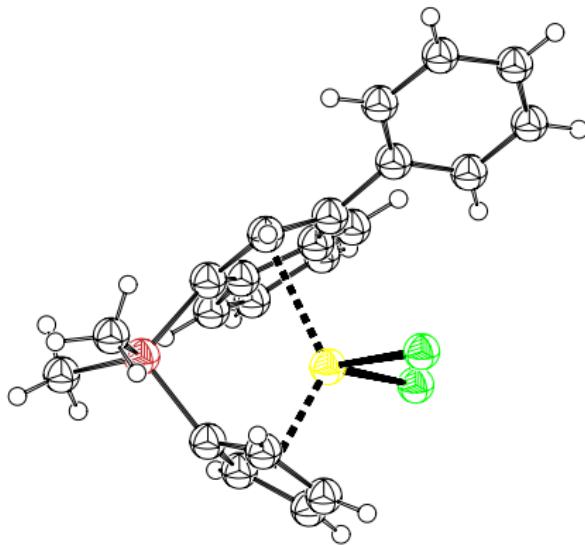
Organometallic: Rietveld



Organometallic: crystal packing

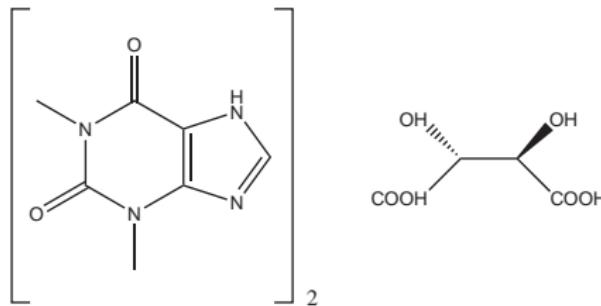


Organometallic: molecular conformation

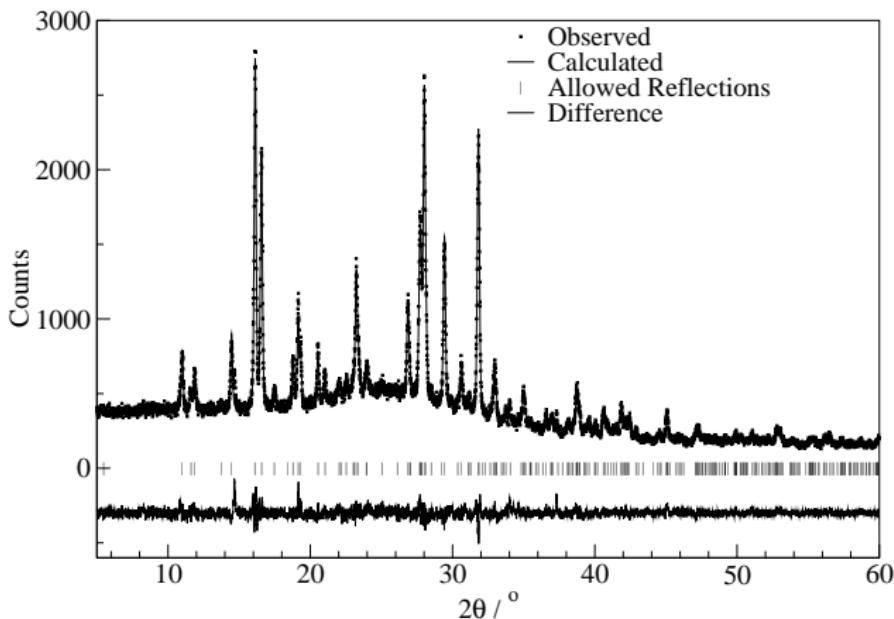


(theophylline)₂·(L-tartaric acid)

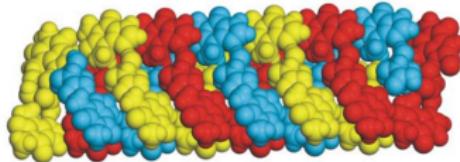
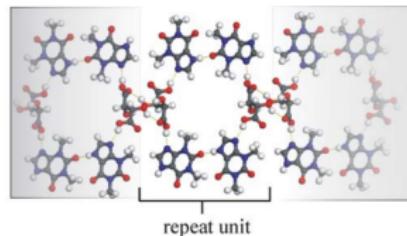
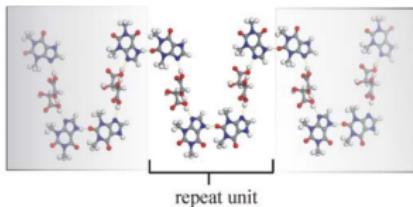
Cocrystal



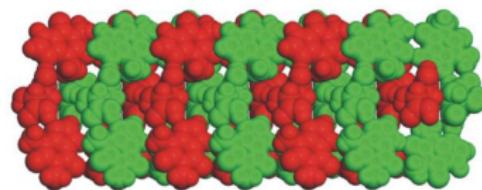
(theophylline)₂·(L-tartaric acid): Rietveld



(theophylline)₂·(L-tartaric acid): structure



Chiral



Racemate

Conclusions

Laboratory X-ray powder diffraction:

- Increasingly useful and powerful
- Applicable to a variety of problems

Start with high-quality data to maximise results!

Thanks & Acknowledgements

Cambridge chemistry:

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- Robert Glen
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- Robin Stein

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