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The role of powder diffraction in populating the crystal structure landscape: status and methods

Dr. Kenneth Shankland

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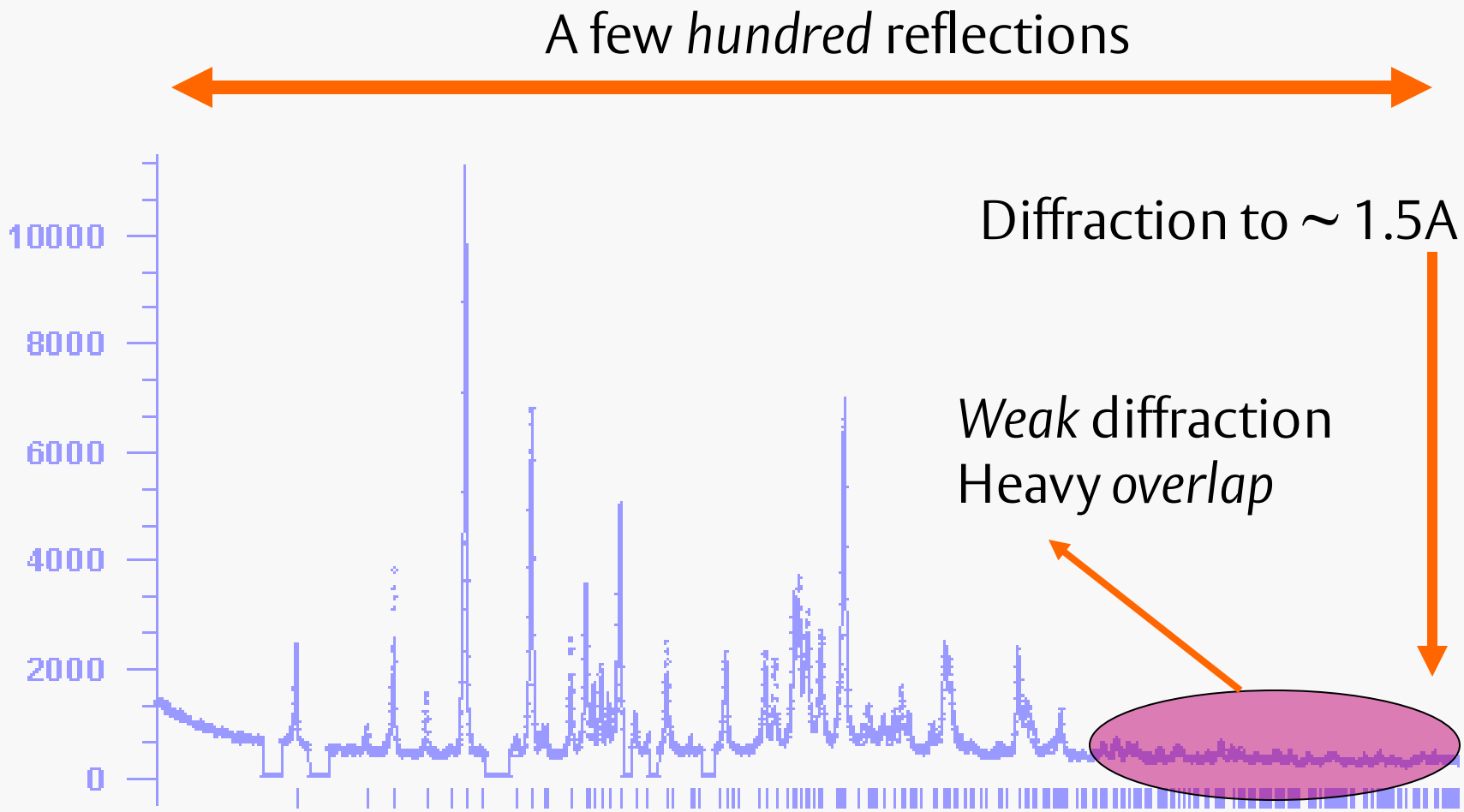
Overview

- Quick review of PXRD limitations
- DM & the global optimisation approach
- SDPD in context, challenging examples
- Checking the structures
- Co-crystals

- *Emphasis on laboratory X-ray data*

Anatomy of a powder pattern



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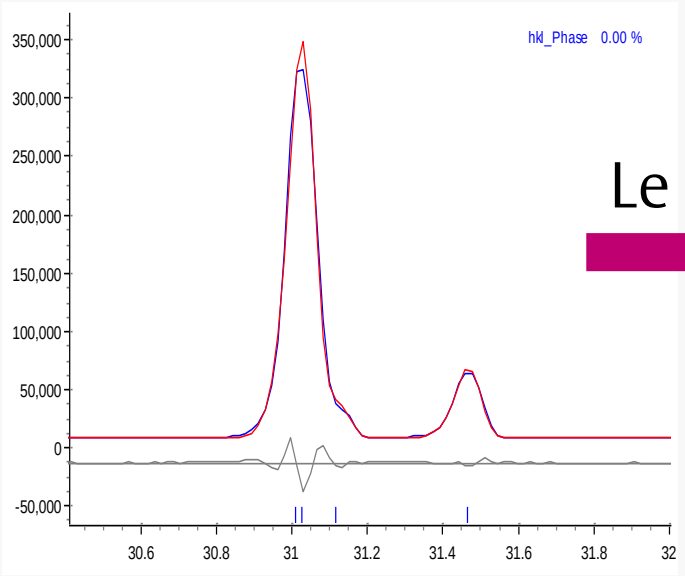
SX vs. PXRD (typical)

	Single crystal	PXRD
Number of refs.	Thousands	Hundreds
Accuracy of intensities	Excellent	Good to very poor
Resolution	< 1 Angstrom	Ca. 1.3 Angstom

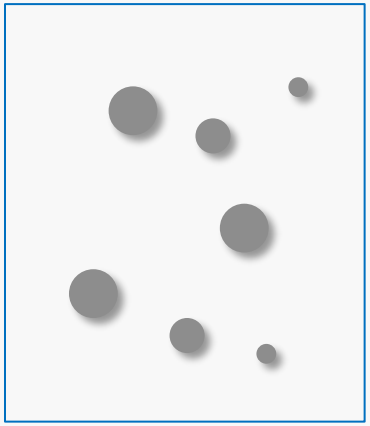
Net result: *standard* DM of structure solution tend not to work very well with powder data

Modified DM

- As exemplified by the EXPO program of the Bari group



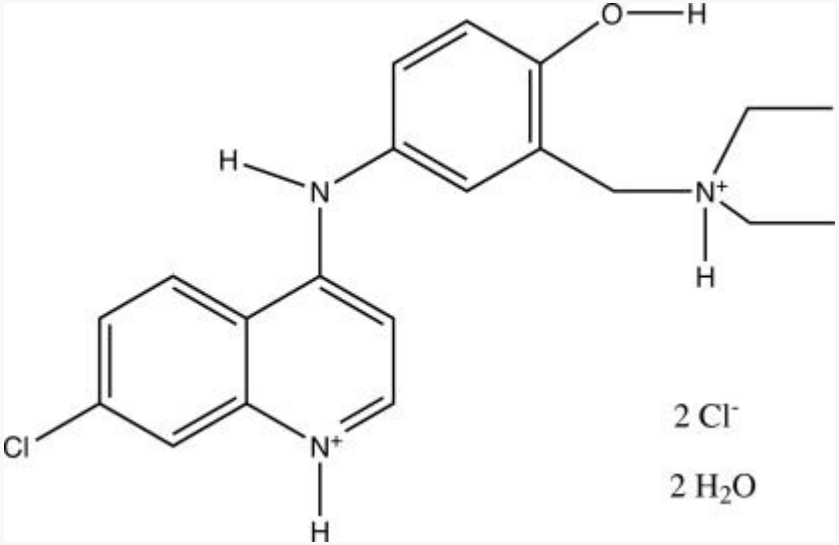
Le Bail → {h k l F^2} → DM →



recycle

Coupled with

- Fourier map interpretation *plus*



Amodiaquinium dichloride dihydrate (*)

$P2_1/c$ V = 2284Å^3

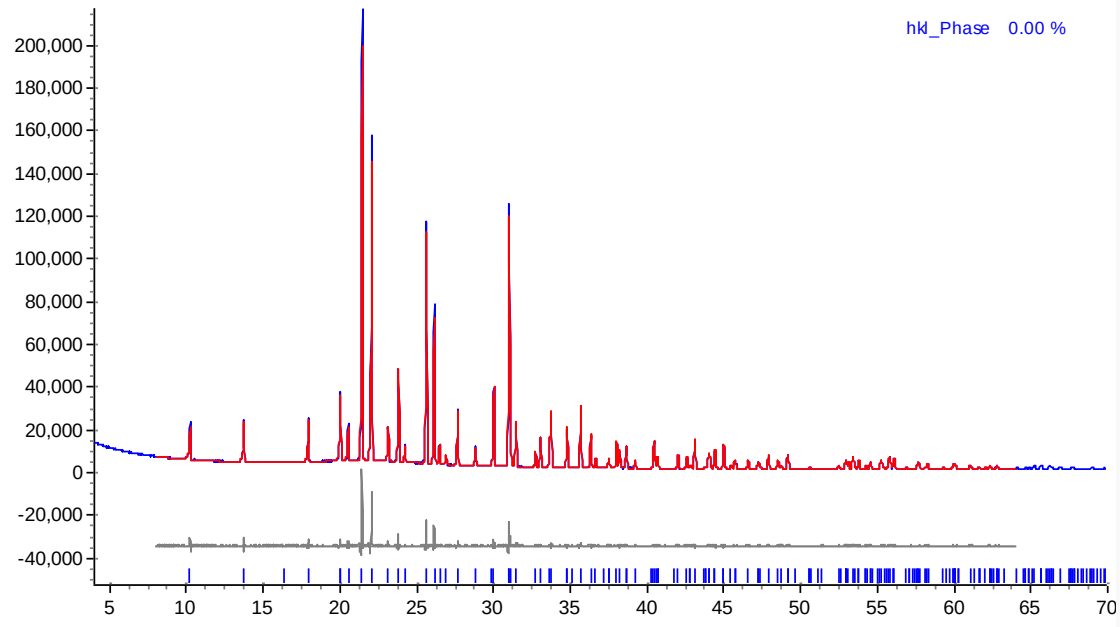
30 non-H atoms

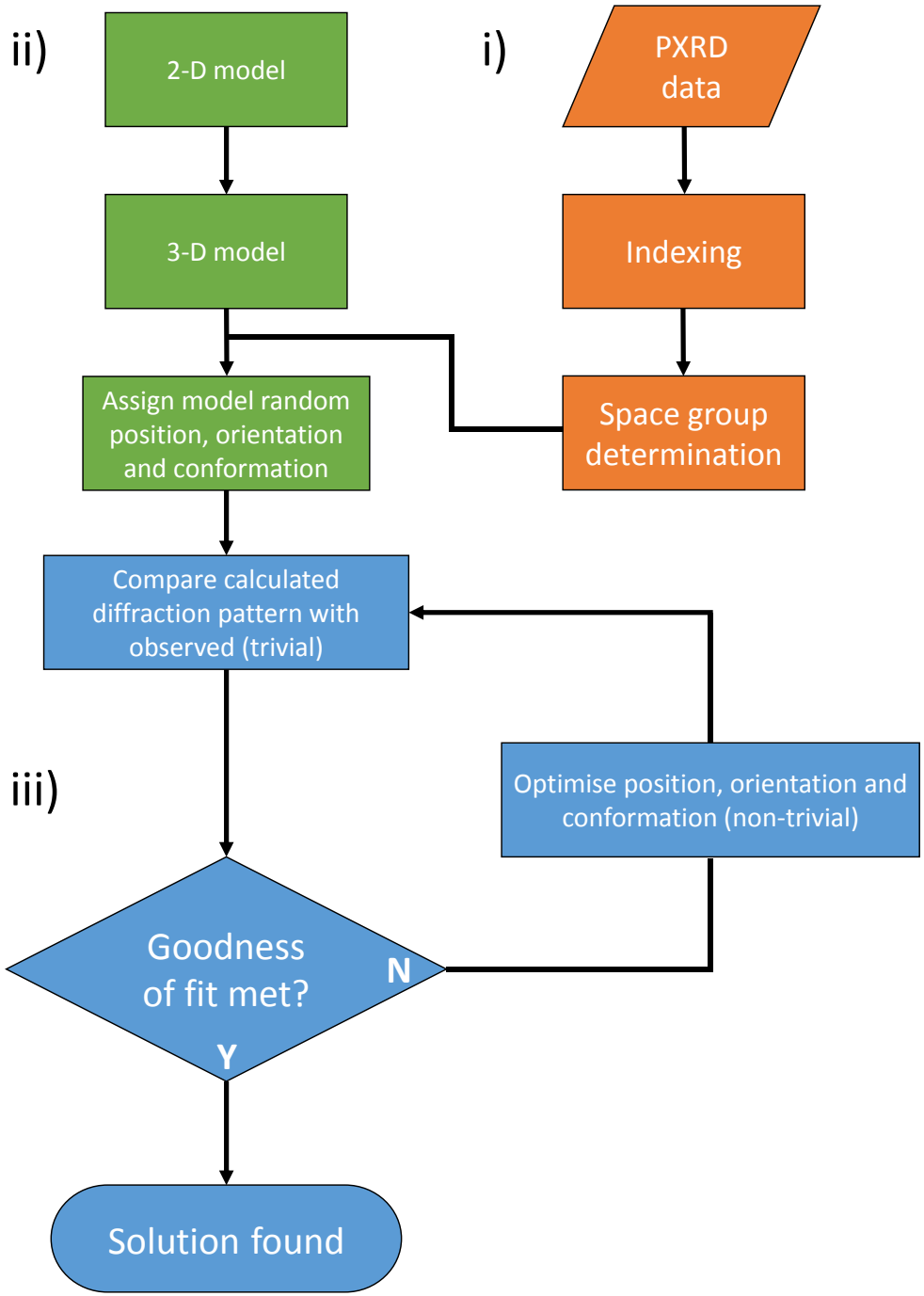
And many more…

(*) www.powderdata.net

The global optimisation alternative

- Assumptions
  - Data have been collected and indexed
  - Space group has been determined
  - Data have been fitted in a **model independent** Pawley or LeBail type fit
  - Molecular connectivity is known





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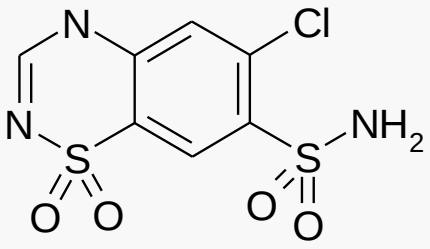
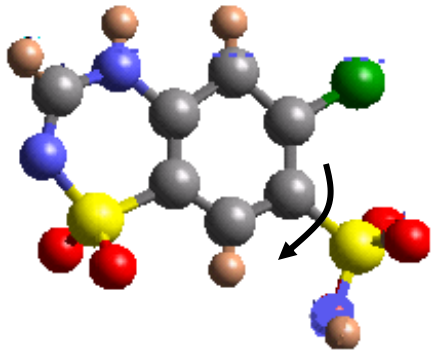
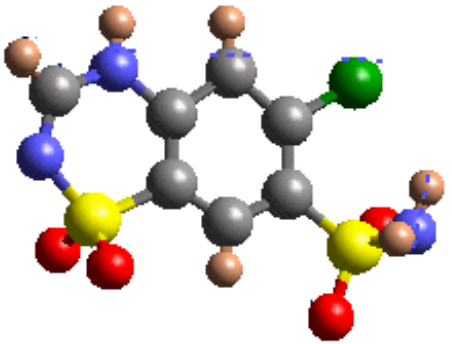
Global optimization

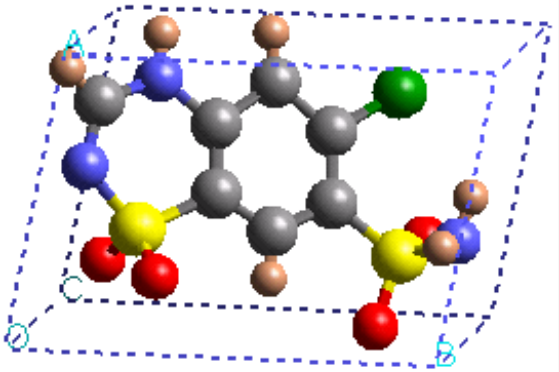
Basic global optimisation

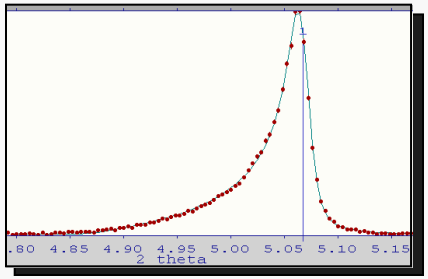






7 DoF





Compare & update 10000 times a sec.

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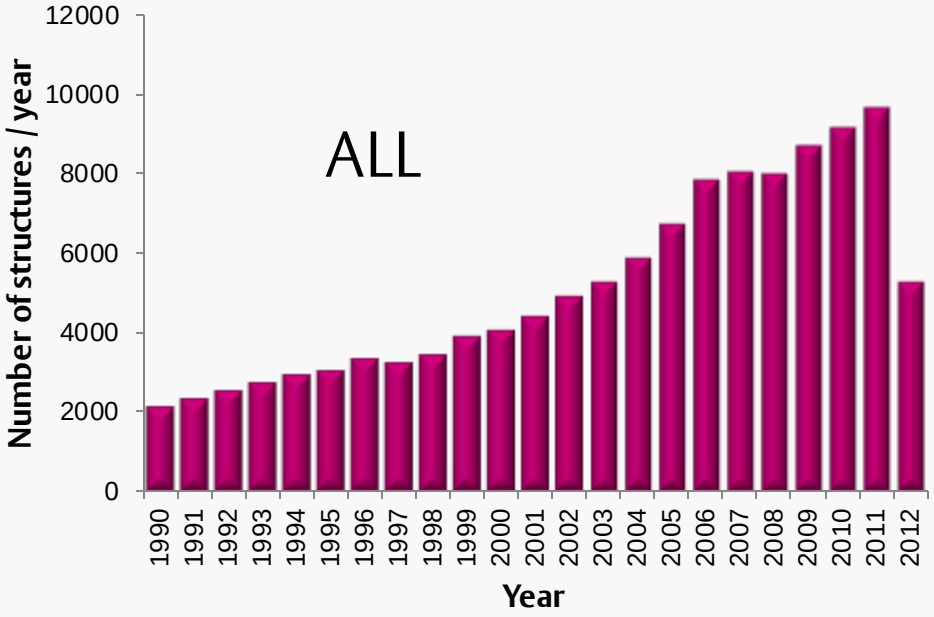
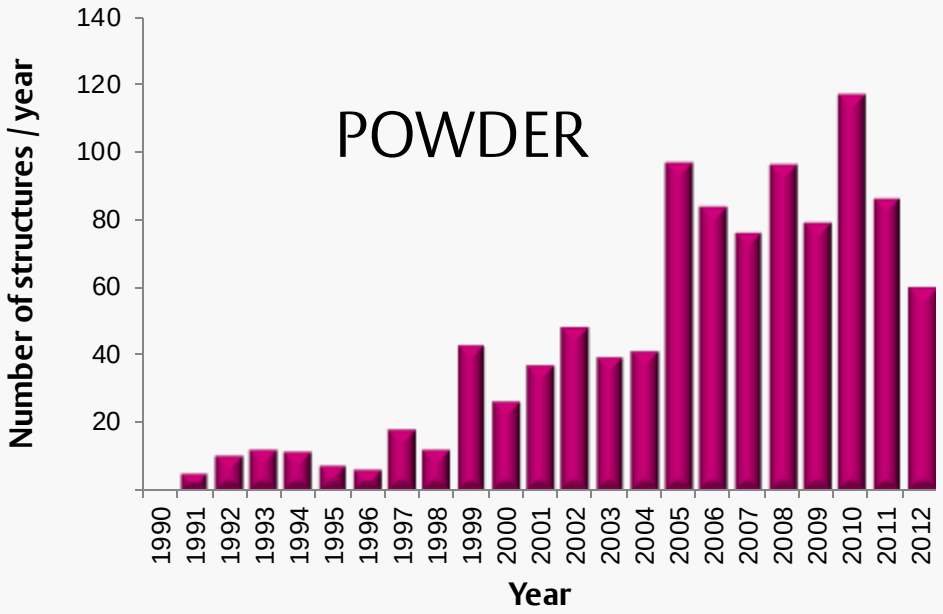
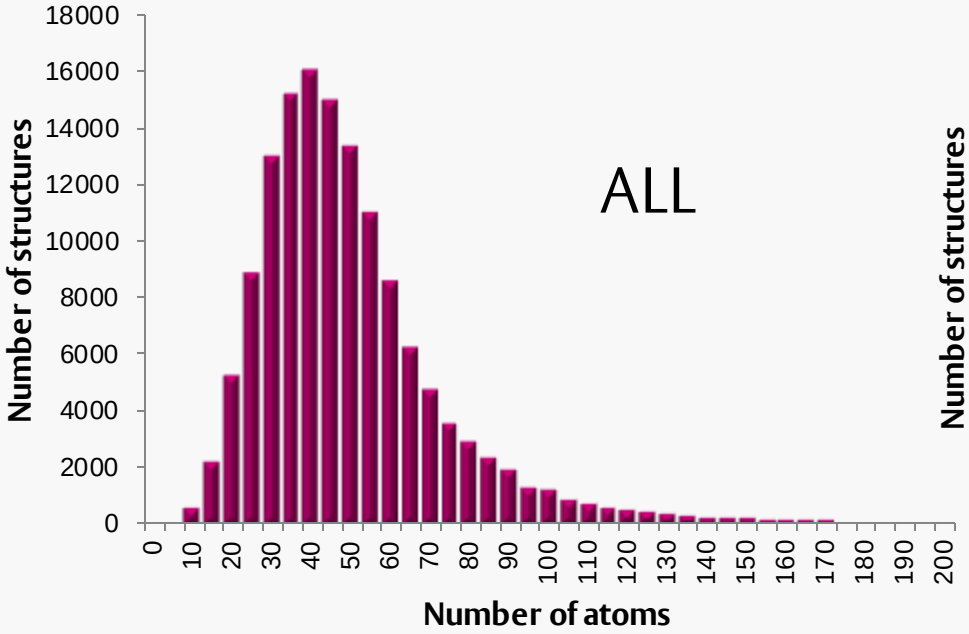
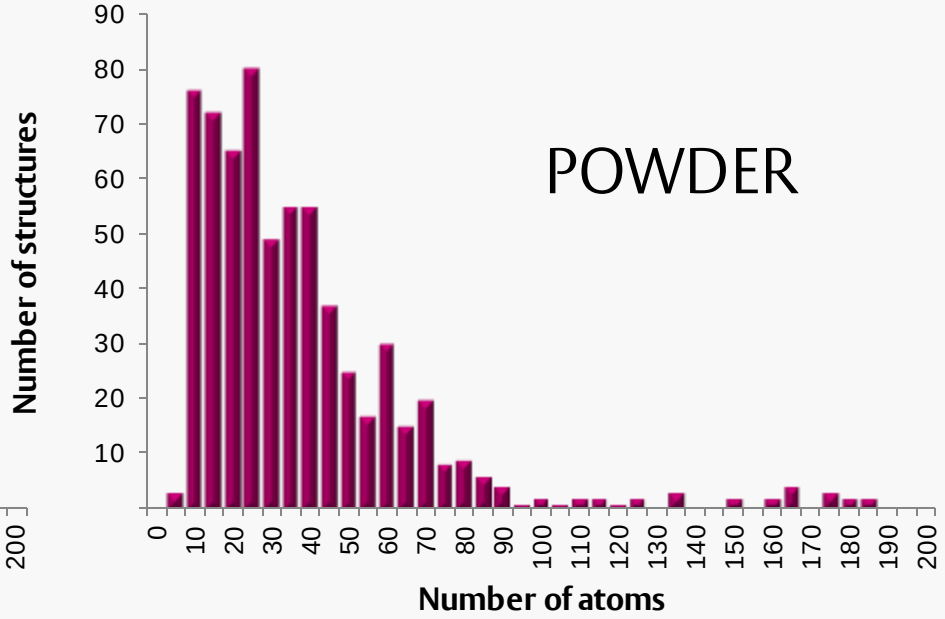
Molecular crystal structures since 1990





As a function of atoms in the a.s.u.





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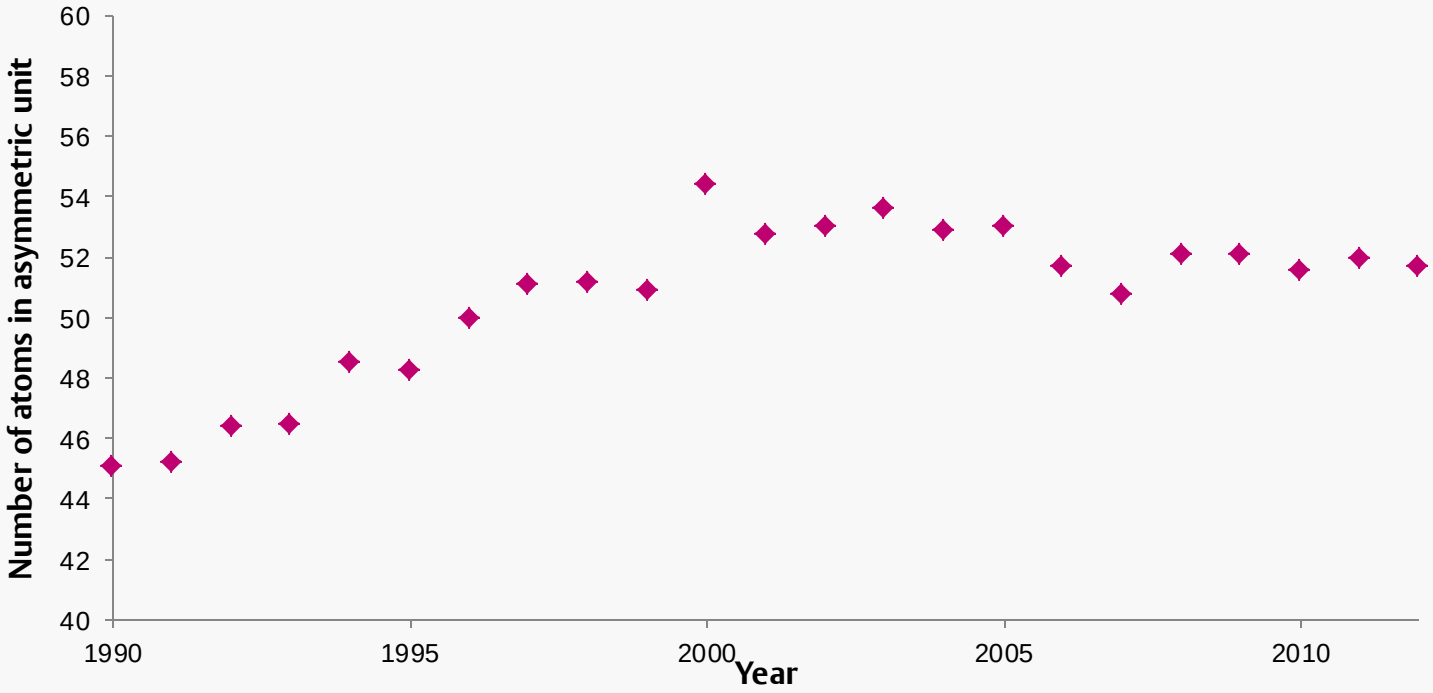
Average complexity in atom terms



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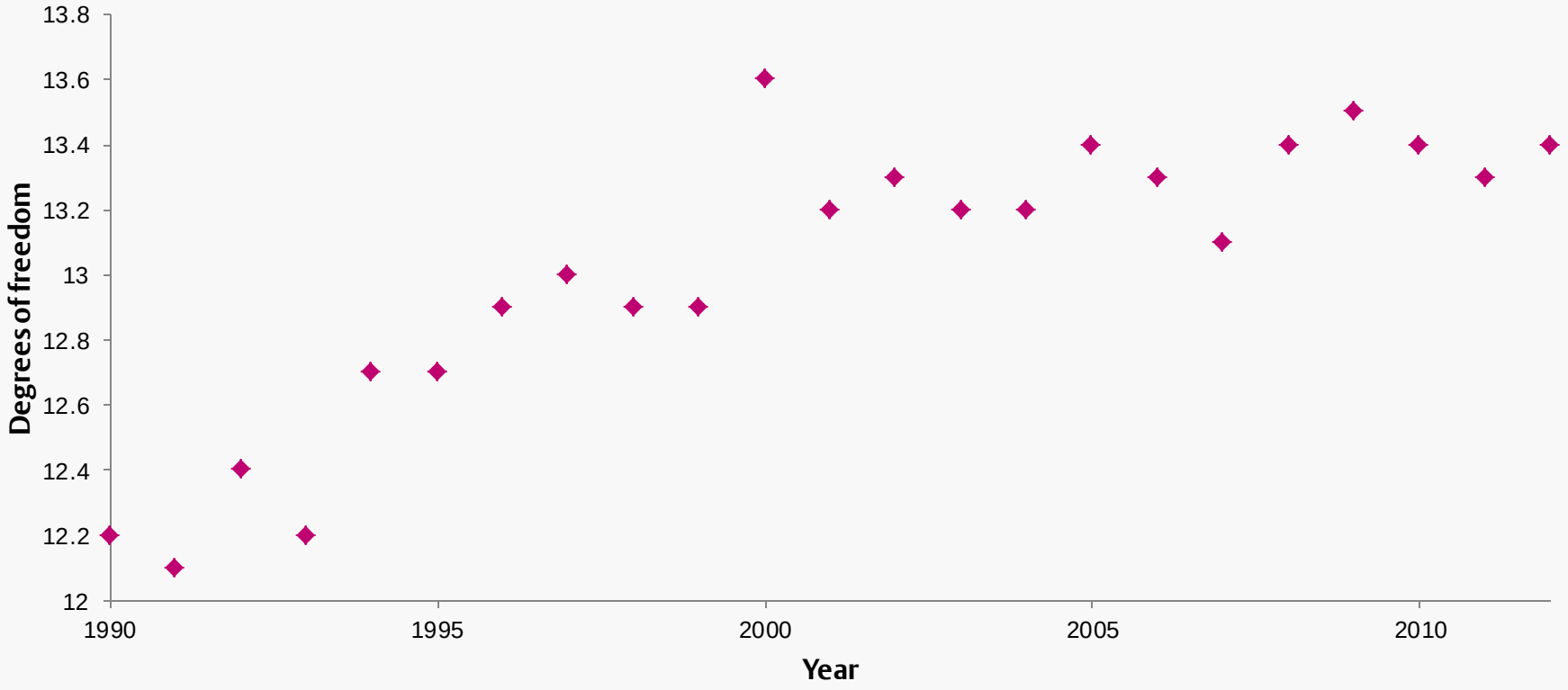
Average complexity in DoF terms



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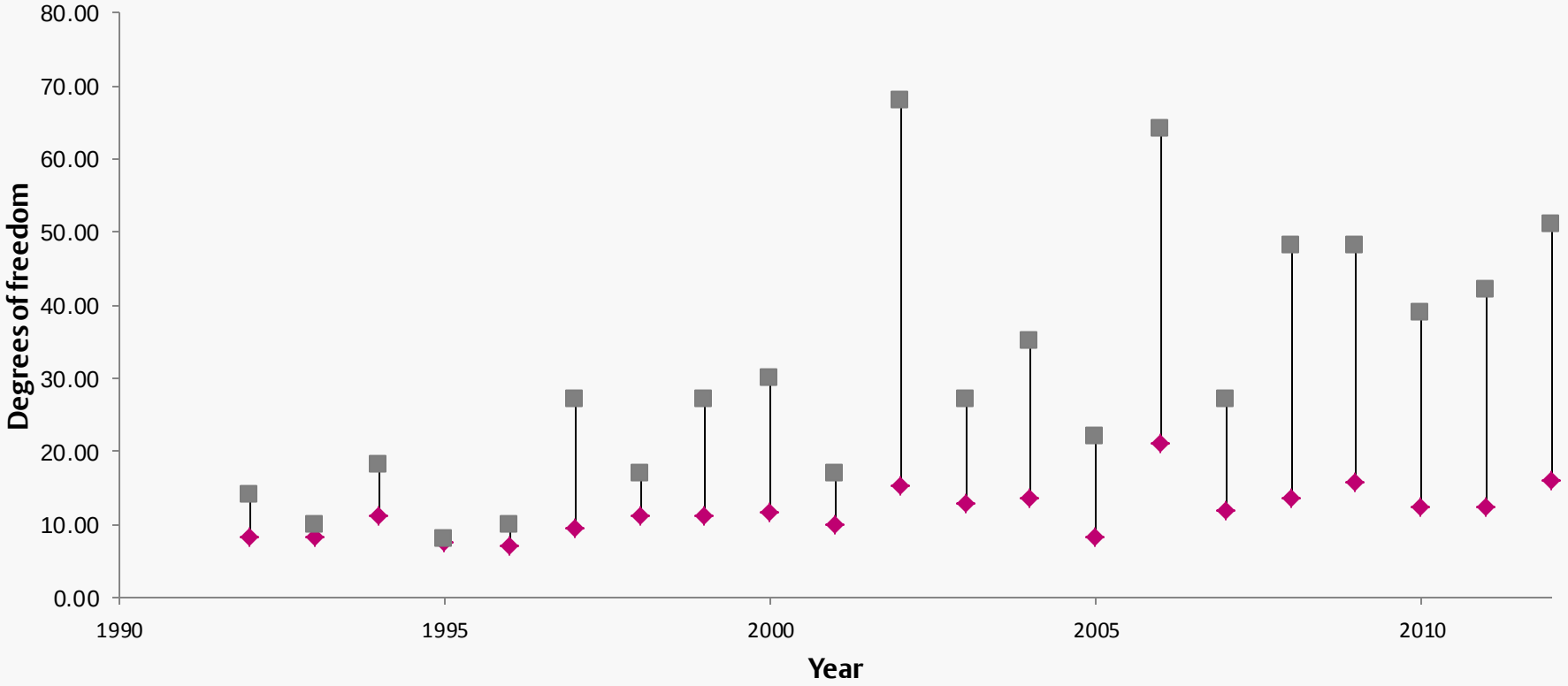
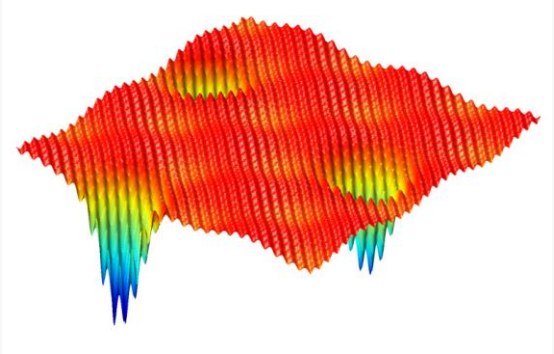
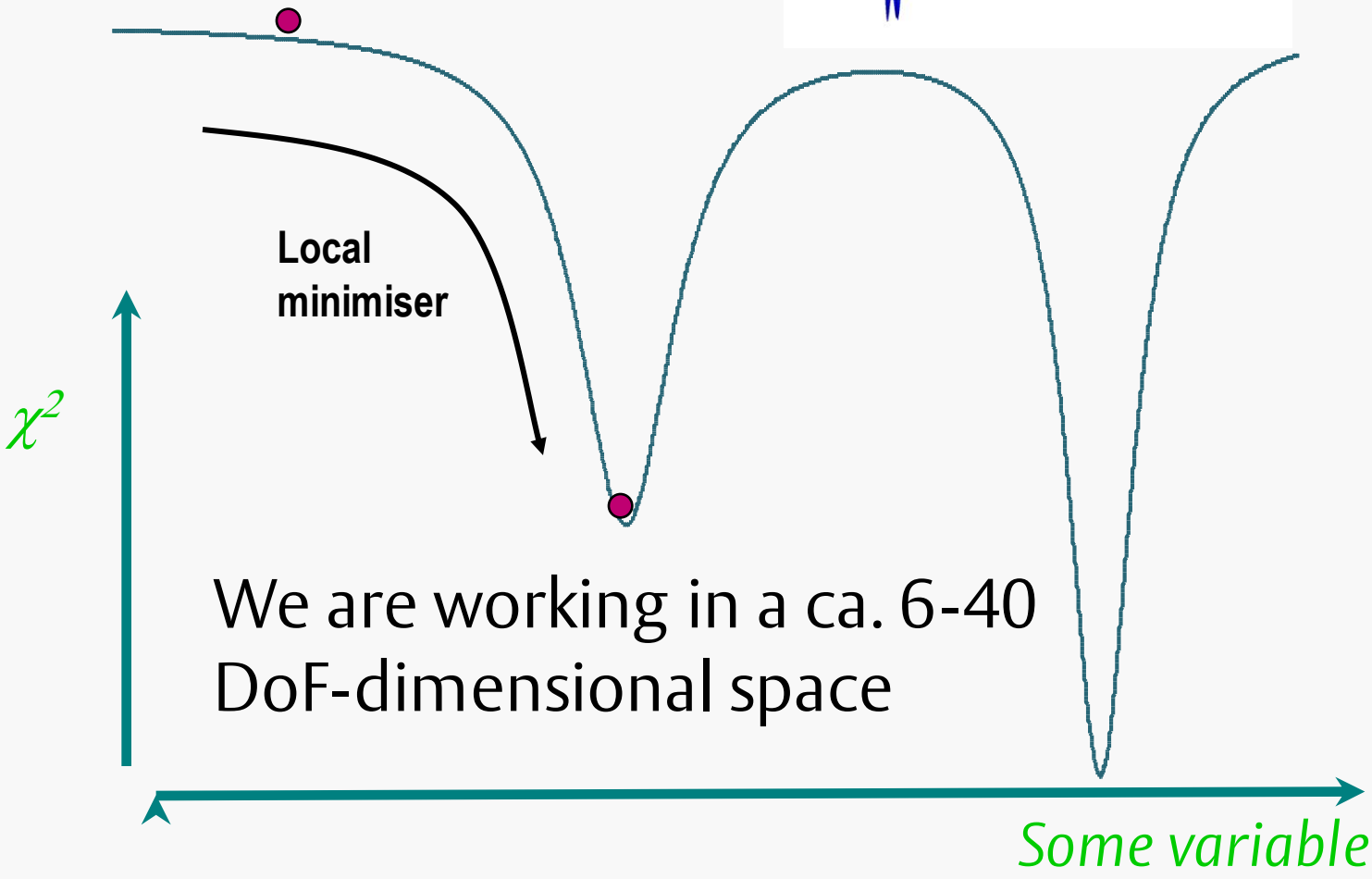
Context – Powder average & max DoF



Why global search?





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Global search methods

- Simulated annealing
  - Mimics the annealing of molten systems into an ordered state
- Genetic algorithms / evolutionary algorithms
  - Mimics Darwinian (or Lamarckian) evolution
- Swarm / ant colony
  - Mimic the movement behaviour of bees / birds / ants etc….

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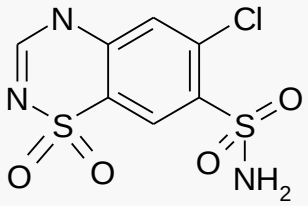
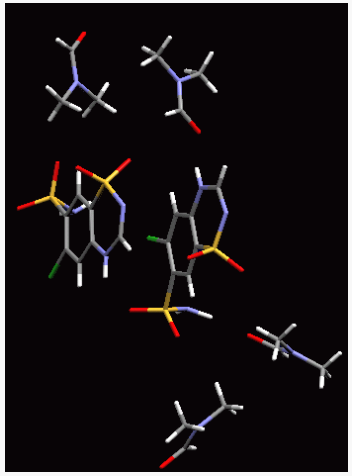
Big structures from lab XRPD

Chlorothiazide $(DMF)_2$ solvate

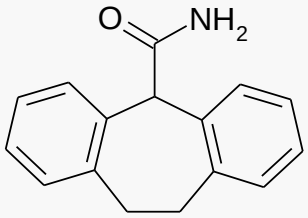
- V=3816 Å^3
- $P2_1/c$, Z'=2
- N_{frag}=6, N_{atoms}=94

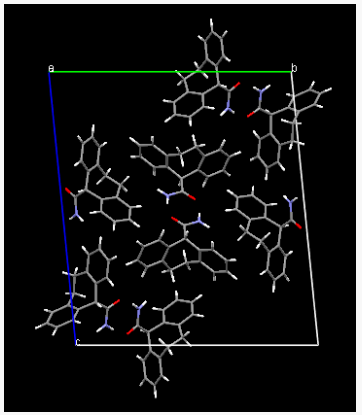




Cyheptamide form II

- V= 2412 Å^3
- P-1, Z'=4
- N_{frag}=4, N_{atoms}=128

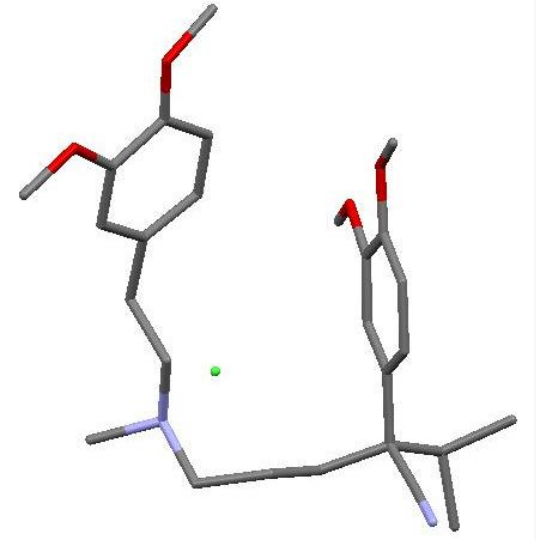


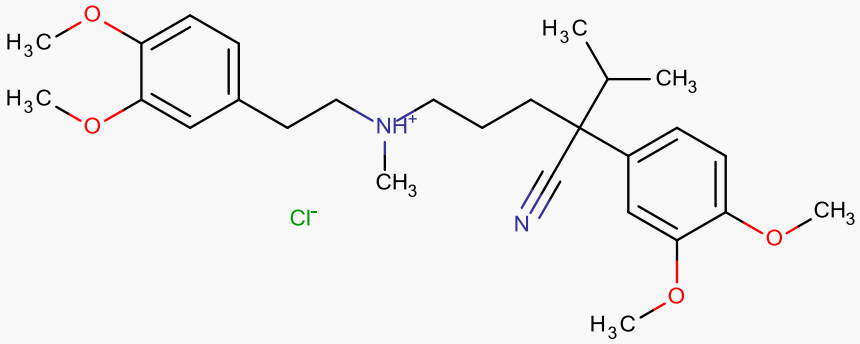


Big structures from lab XRPD

Verapamil hydrochloride

- V=1384 Å^3
- *P*-1, Z'=1
- N_{frag}=2, N_{atoms}=73





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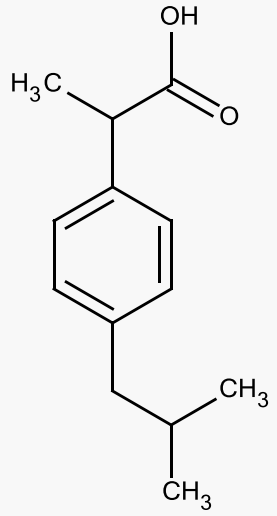
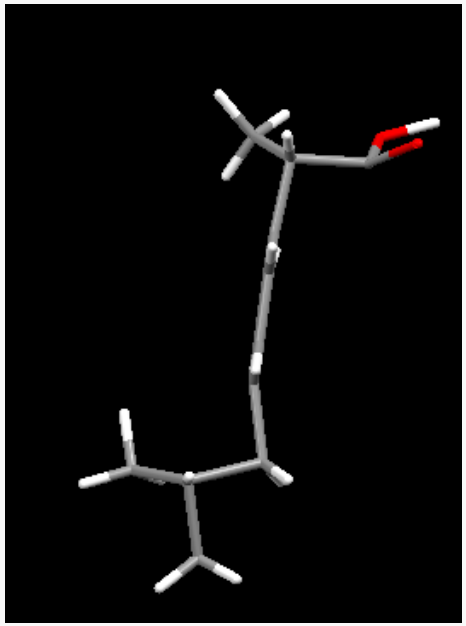
Problems and solutions

- Success rate drops as number of atoms increases
  - E.g. for verapamil hydrochloride, only a few % of SA runs reach the global minimum
  - Time taken to obtain solution increases
- Addressing this issue
  - Optimise the SA optimiser
  - Increase the level of parallelisation
  - Improve starting model accuracy
- Take home message
  - Chances of solving a typical structure are good, and set to get better

A warning

- Refinement stage becomes increasingly difficult as we solve larger and larger structures
- Chemical sense, not just fit to data, is the ultimate arbiter





IBPRAC04

α-Hydroxyglycine

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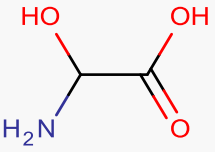
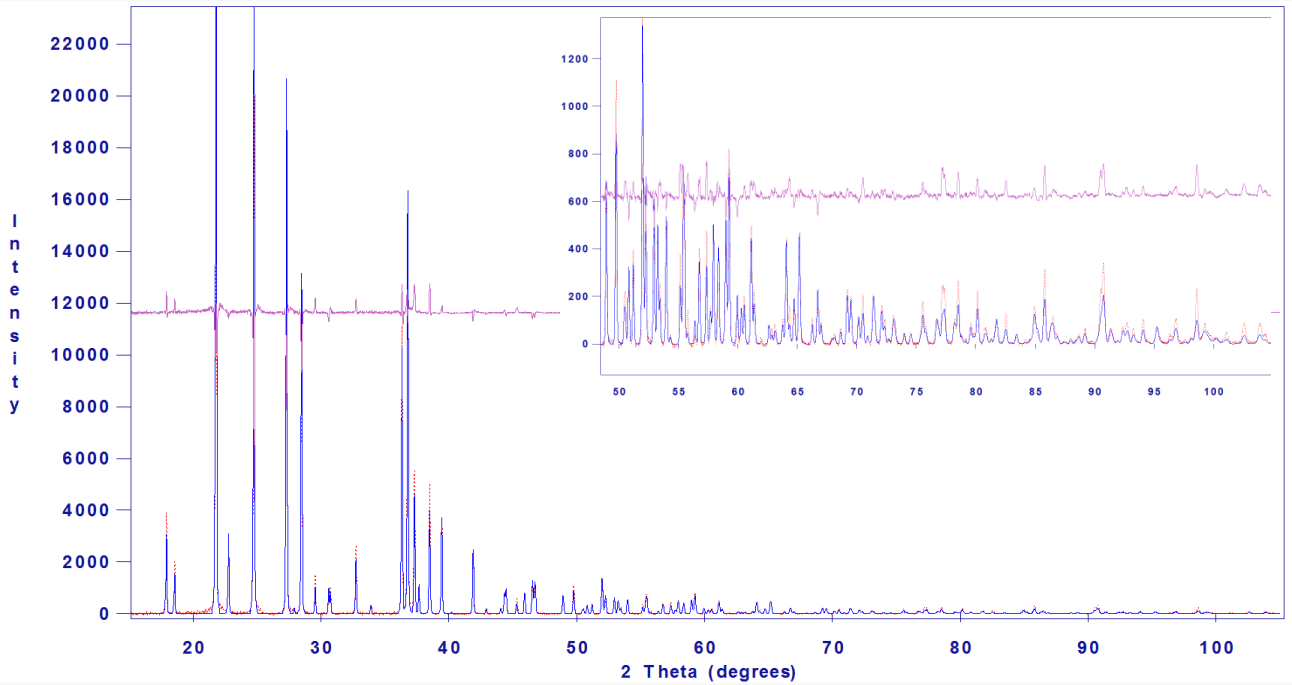
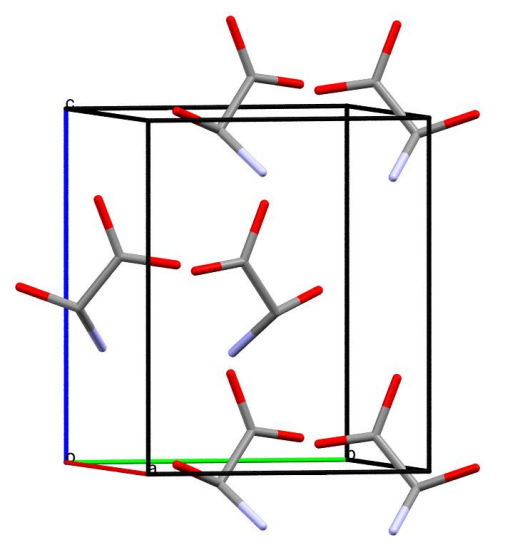
Structure solution attempted with a Marvin model







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How best to check?

- DFT
- Lund, A. M *et al*. Optimization of Crystal Structures of Archetypical Pharmaceutical Compounds: A Plane-Wave DFT-D Study Using Quantum Espresso. *Crystal Growth & Design* **2013,** *13* (5), 2181-2189.
- Attention grabbed by:
  - Modest computing (dual 6 core Xeons, 24Gb RAM)
  - Modest run times (3 – 80 hrs for typical small molecule organics)

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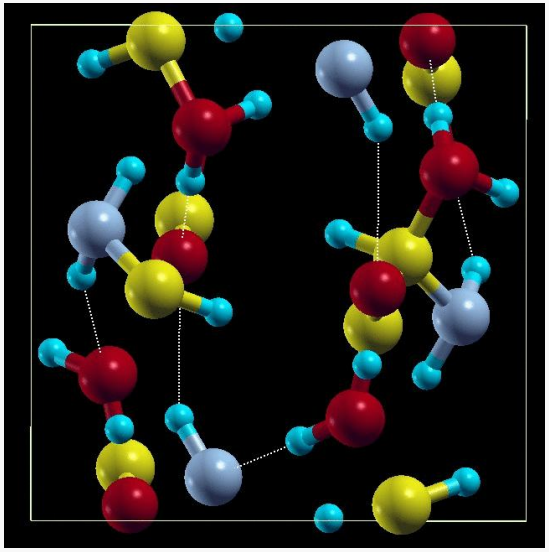
DFT-D of AHG

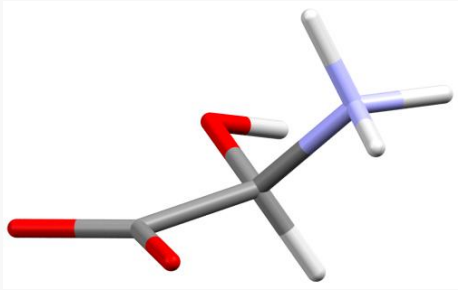
- AHG structure optimised using DFT-D calculations.
- Calculations were carried out with parallelised Quantum Espresso v5.0.2 installed on Ubuntu 13.09 utilising 12 core nodes (dual 6-core Intel Xeon E5-2630 processors, 2.3GHz) and 32GB RAM. [ca. £2000]

P. Giannozzi, et al J.Phys.:Condens.Matter, 21, 395502 (2009) http://dx.doi.org/10.1088/0953-8984/21/39/395502

Model optimisation



- Crystal structure optimised with DFT-D using a fixed cell calculation, 'relax'.
- AHG forms a lower energy crystal structure as a zwitterion
  than the uncharged molecule
- The zwitterionic model was then recycled into the SA and gave a significantly improved fit to the PXRD data



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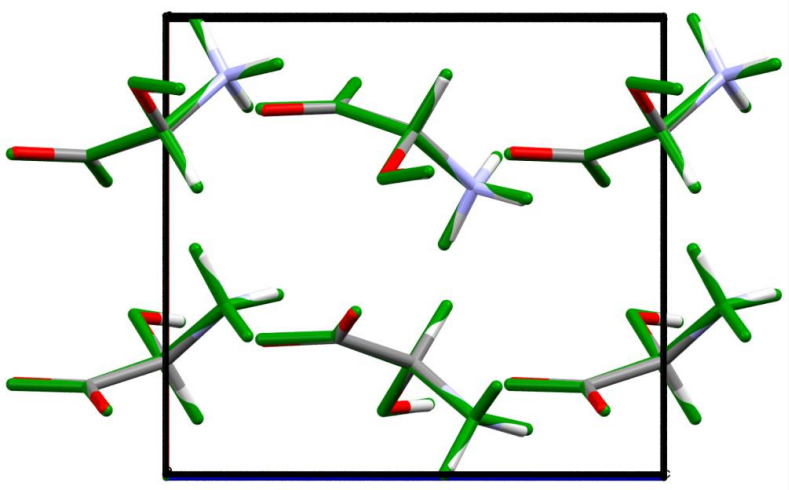
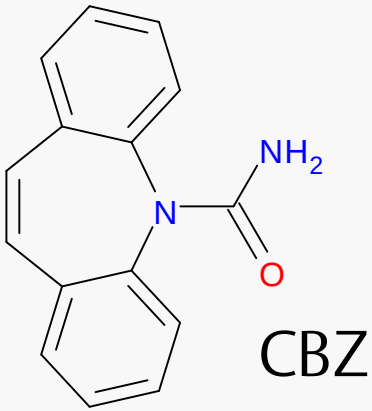
Structural verification

- Minimise SA structure and lattice parameters
- 'Variable-cell relax' calculation took 29 mins 30 seconds; reduced the total energy by 0.475382 Ry.

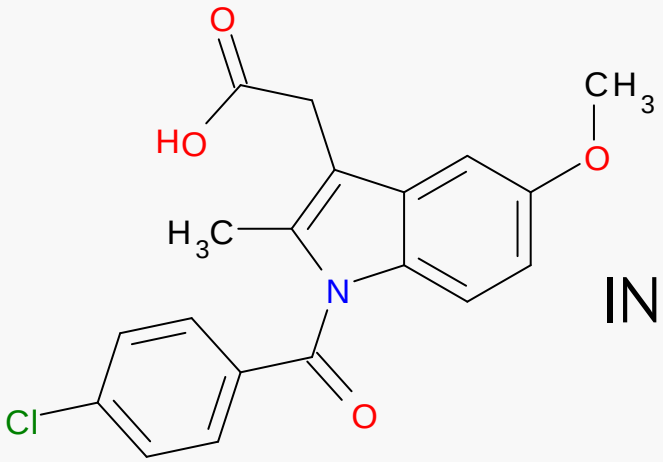


Crystal structure of AHG (coloured) & DFT-D optimised structure (green), confirming SA structure RMSD=0.043Å^2

A co-crystal example: CBZ:IND



CBZ

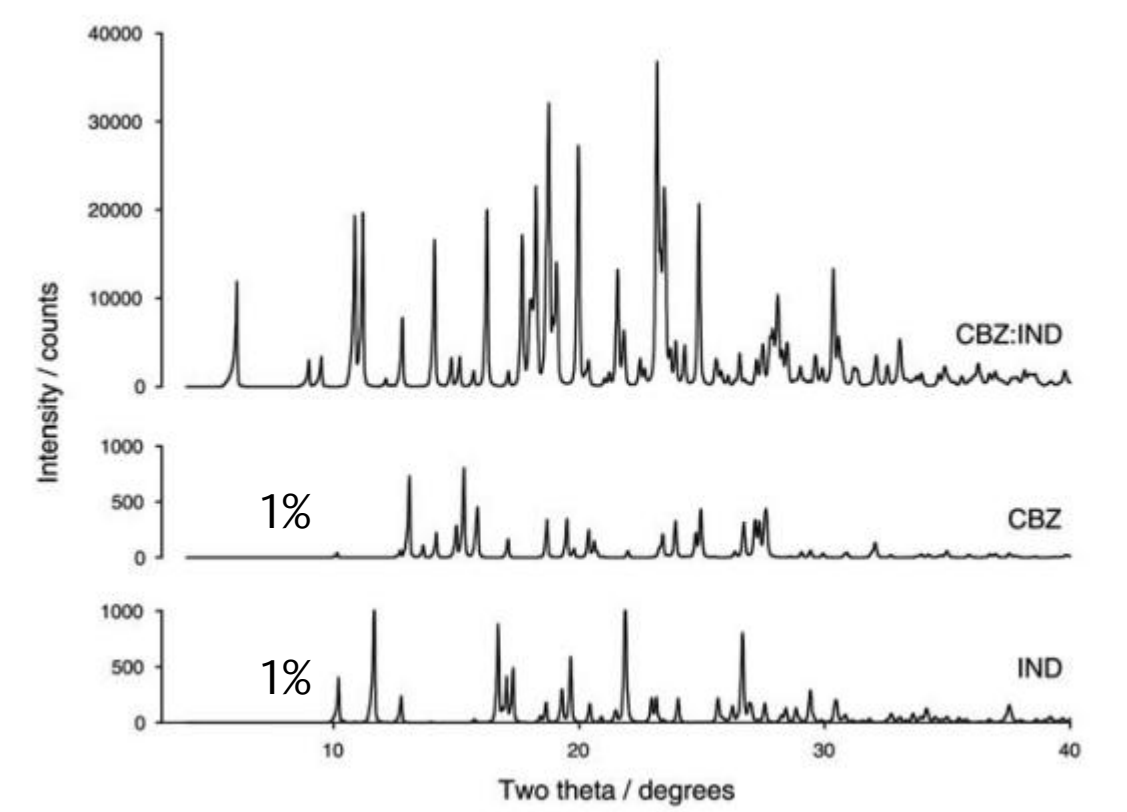


IND

- Ground 1:1 molar mixture of β-CBZ and γ-IND for 4 hrs in a ball mill
- Stored 40°C / 75% RH for 21 days
- At *t*=0, resultant powder appears 'X-ray amorphous'
- At *t*=21 days, powder displays 'novel' PXRD pattern

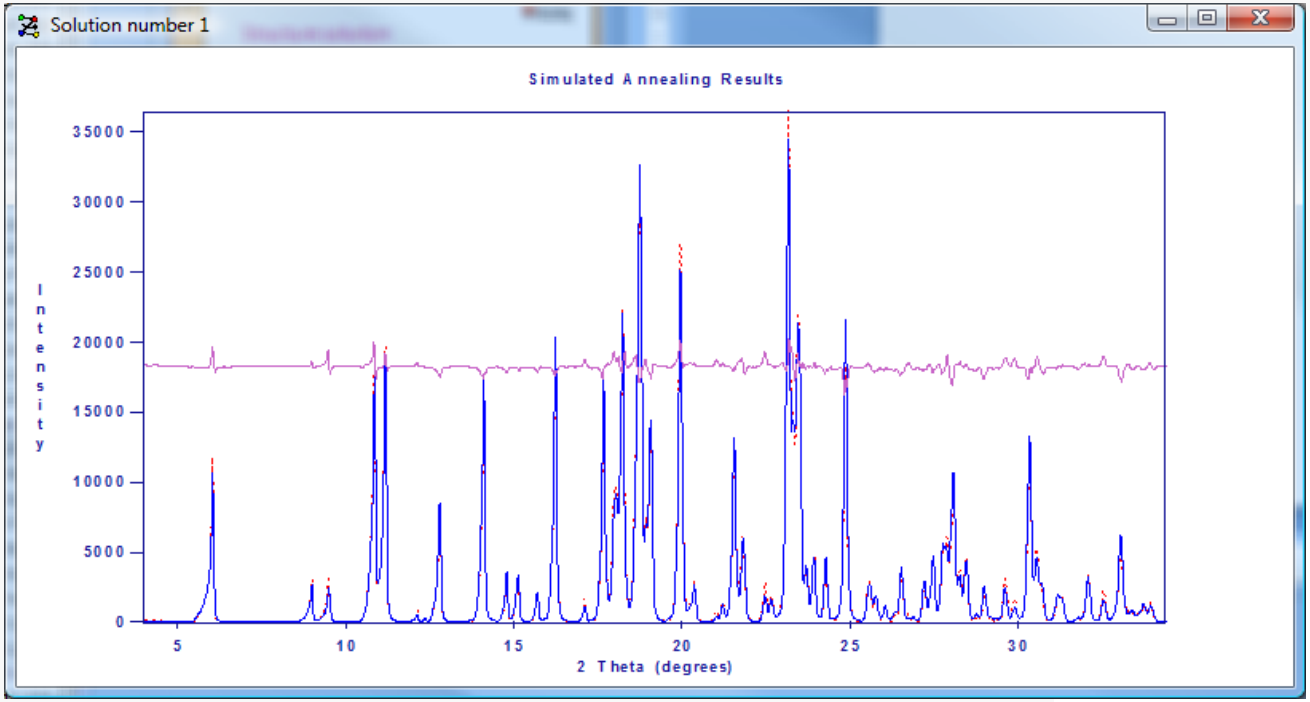
CBZ:IND

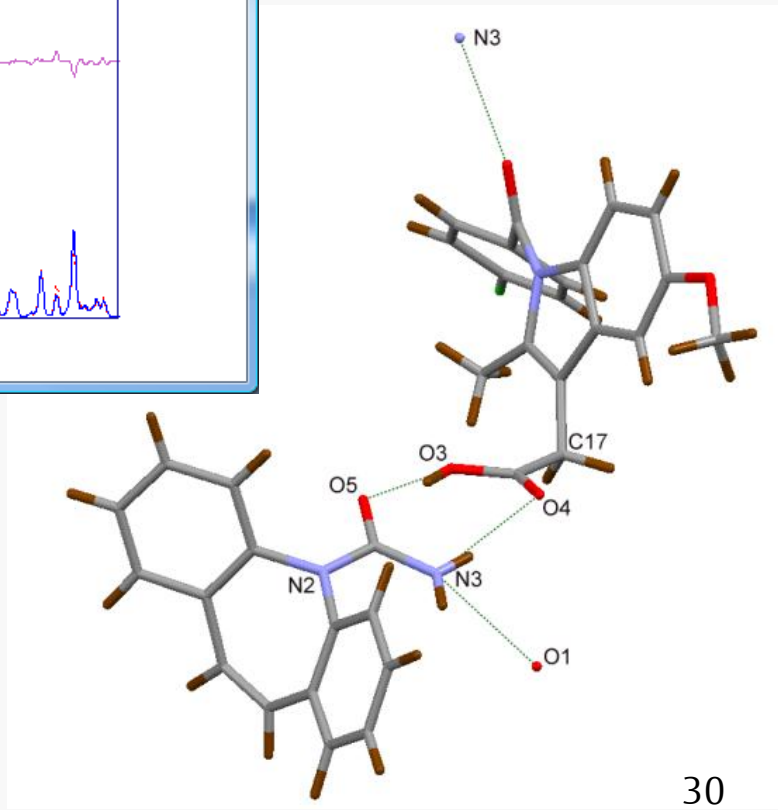
- $P2_1/c$, V=2920Å^3 (indicative of 1:1 cocrystal)



'pure' CBZ:IND pattern extracted using TOPAS after simultaneous Pawley / Rietveld

CBZ:IND – Easily solved

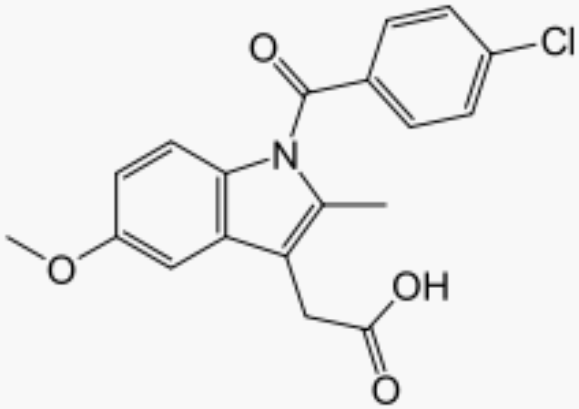


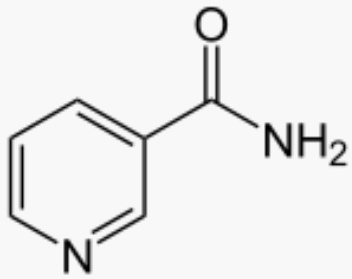


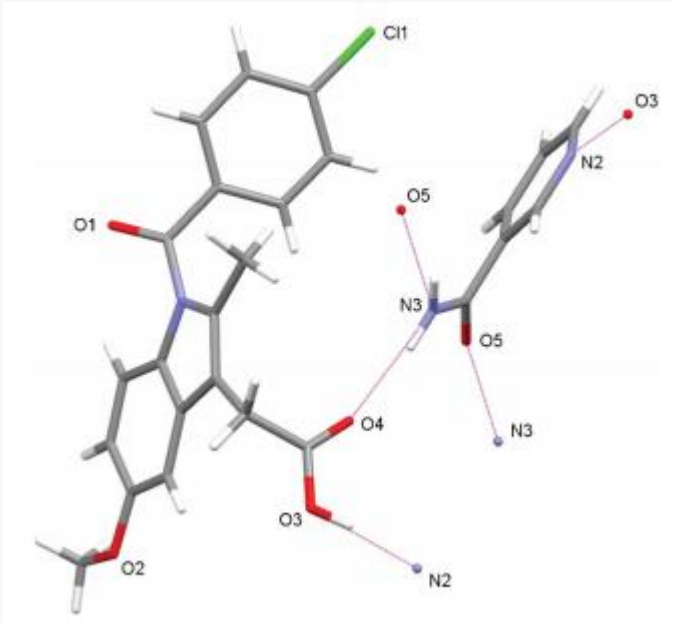
DoF = 18

IND:NIC

- Easily solved
- Hydrogen bonding propensity (Mercury, CCDC)







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Thanks to…

- **STFC**: Data Analysis Group
- **Reading**: Mark Spillman, Elena Kabova, David Edgeley, Mridul Majumder
- **CCDC**: Jason Cole, Jacco van de Streek, Elna Pidcock, Oliver Korb
- DASH – CCDC
- SDPD Context: Acta C (2013) 69, 11, 1251
- CBZ:IND: CrystEngComm (2011) 13, 6327
- IND: NIC : CrystEngComm (2013) 15, 4041