Chemical Crystallography and Structural Chemistry

(VO 270287)

5th March 2020

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- personal Homepage: https://homepage.univie.ac.at/tim.gruene/
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Course Details

5 March	lecture № 1	19 March	lecture № 2
26 March	lecture № 3	2 April	exercise № 1
23 April	lecture № 4	30 April	lecture № 5
7 May	lecture № 6	14 May	exercise № 2
28 May	lecture № 7	4 June	lecture № 8
25 June	lecture № 9	18 June	exercise № 3

- Group exercises: same place, same time
- Lecture notes and exercises will be made available online
- https://homepage.univie.ac.at/tim.gruene/teaching/chemcryst

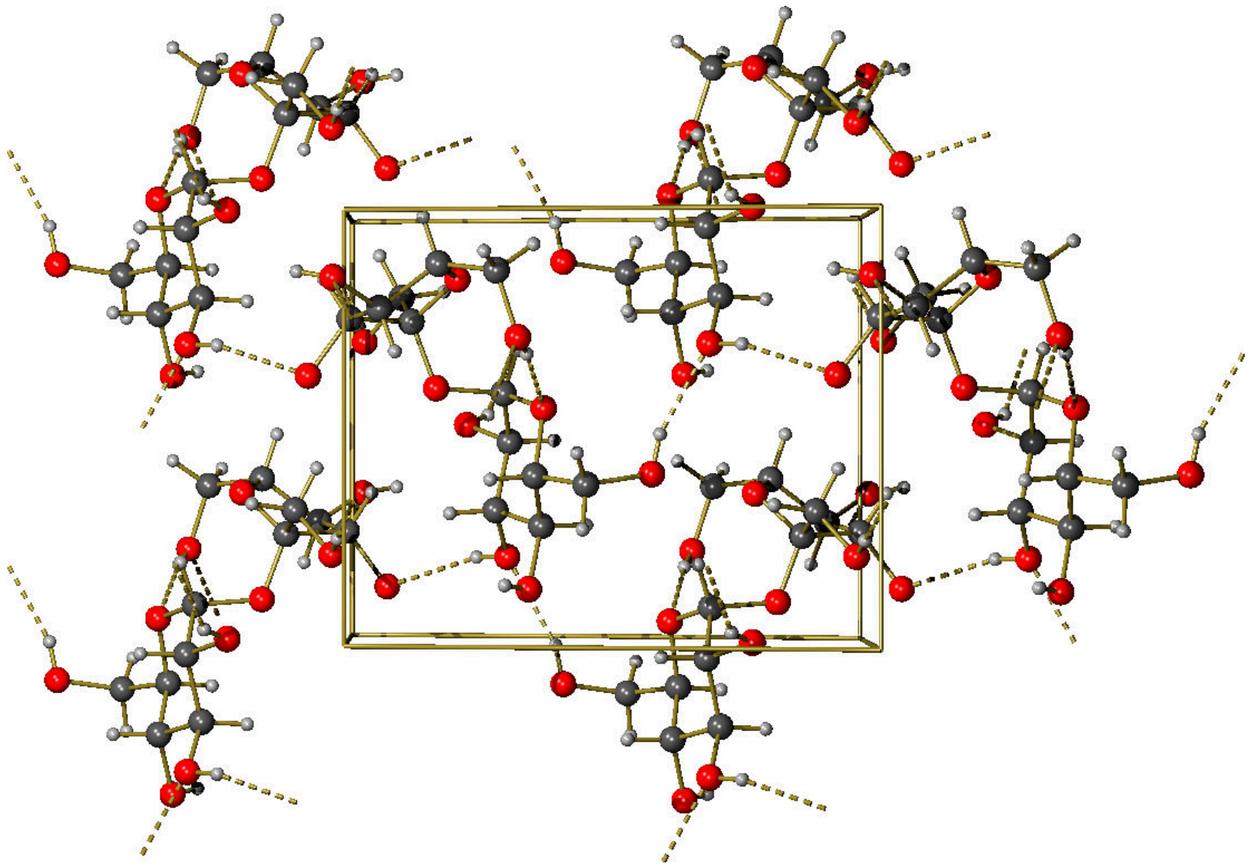
Examination

There will be an **oral** exam.

Course Objective

Chemical Crystallography:

Determination of the 3-dimensional structure of chemical compounds with single crystal diffraction



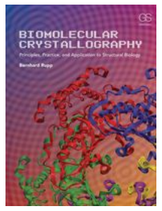
Crystal structure of sucrose, with hydrogen bonds

- what do we learn from a crystal structure?
- what are the **limits** of crystallography

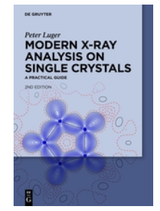
Content of today's Lecture

1. (Teaching) Resources for crystallography
2. (public) data bases for crystallography
3. what are crystals
4. X-rays and X-ray diffractometers
5. Conducting a diffraction experiment

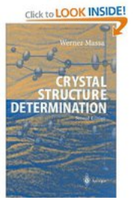
Resources: Literature for Crystallography



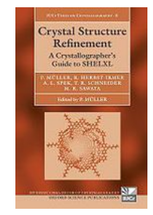
B. Rupp, *Biomolecular Crystallography*, Garland Science



P. Luger “Modern X-Ray Analysis on Single Crystals” De Gruyter

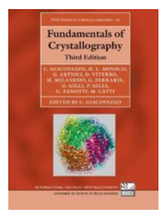


W. Massa, *Crystal Structure Determination*, Springer



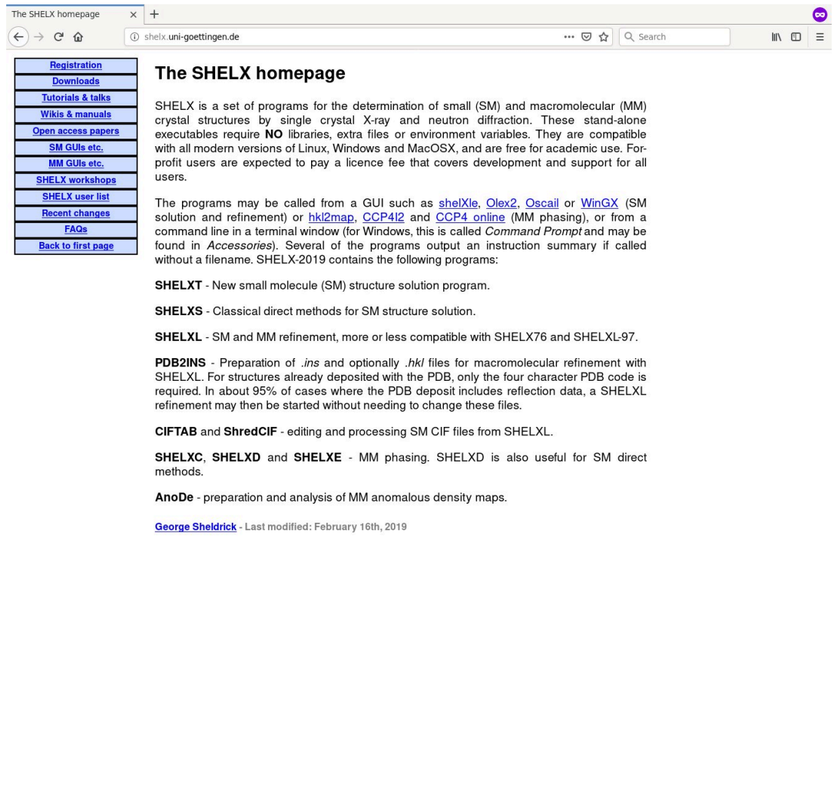
P. Muller *et al.*, “Crystal Structure Refinement — A Crystallographer’s Guide to SHELXL” Oxford University Press

International Tables of Crystallography A–F `http://www.iucr.org`

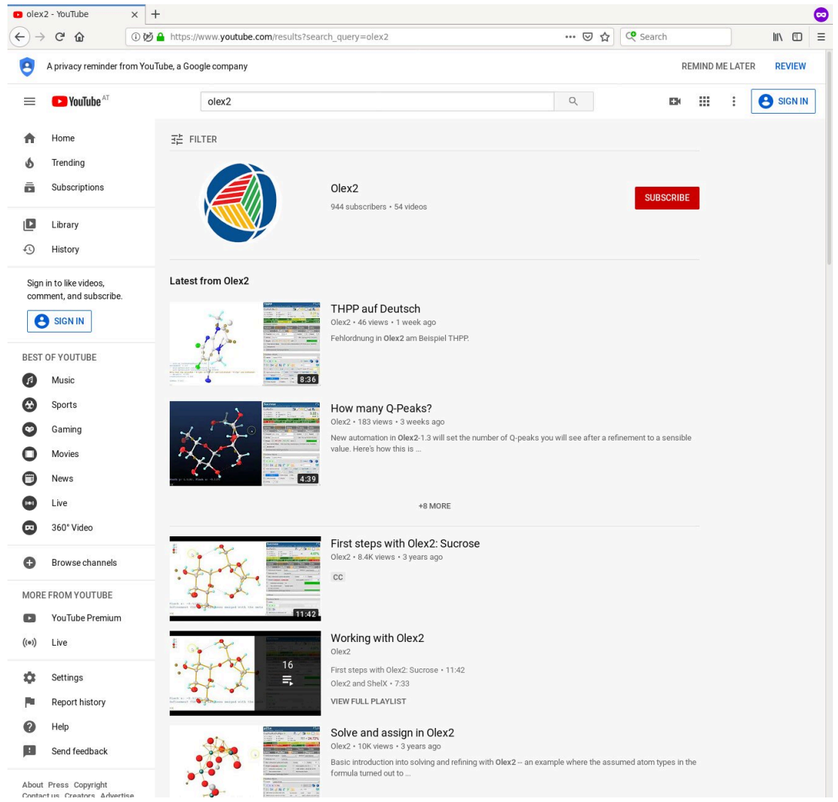


C. Giacovazzo *et al.*, *Fundamentals of Crystallography*, Oxford Science Publications

Online Resources



http://shelx.uni-goettingen.de



Olex2 *etc* on youtube

Journals for Chemical Crystallography

JACS, Journal of the American Chemical Society
`https://pubs.acs.org/journal/jacsat`

Angewandte Chemie Int. Ed.
`https://onlinelibrary.wiley.com/doi/full/10.1002/anie.201811318`

Acta Crystallographica A-F
`journals.iucr.org`: International Union of Crystallography

and most other journals for chemistry

Crystallographic databases

Most journals require the deposition of structural data structures at publicly available data bases. Crystallography has long been a pioneering discipline of open access data.

Cambridge Structural Database

Crystallography Open Database

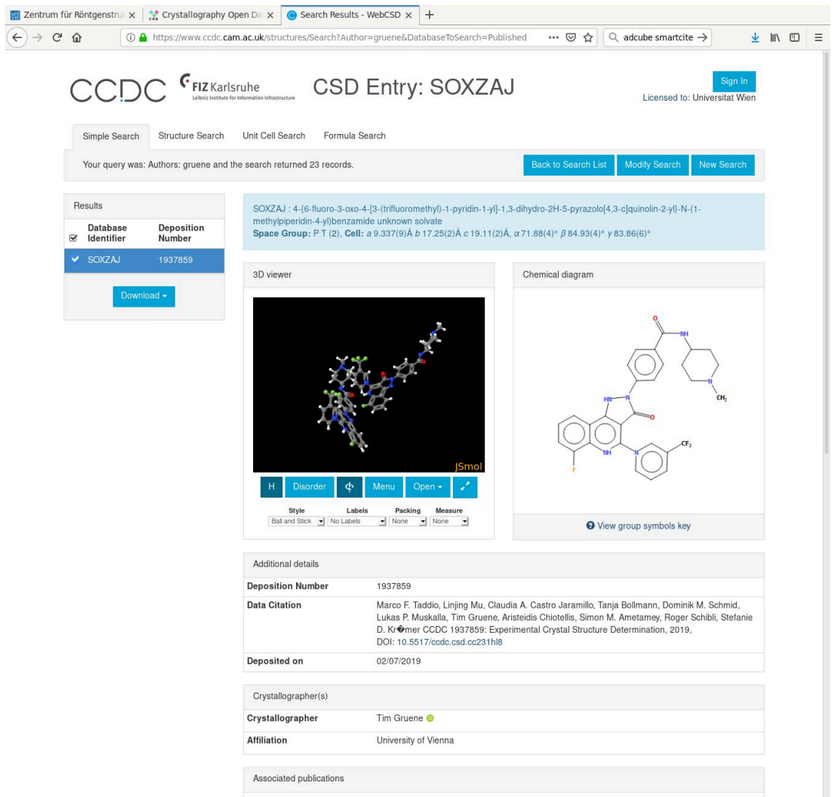
Inorganic Crystal Structure Database

Protein Data Bank

CRYSTMET ®

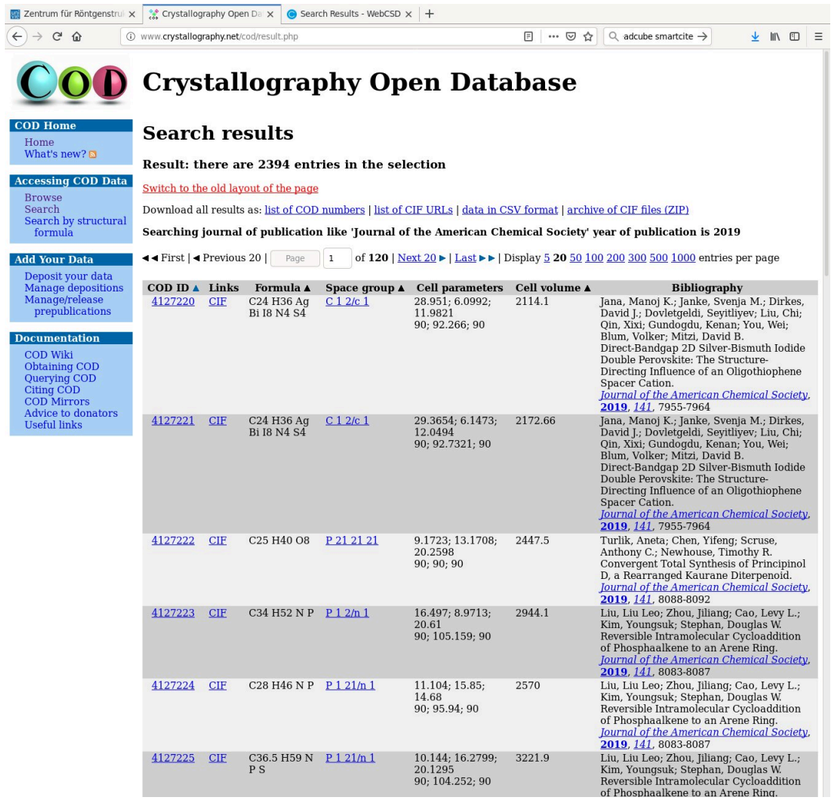
Cambridge Structural Database (CSD)

- `http://www.ccdc.cam.ac.uk`
- “The world repository of small molecule crystal structures”
- founded 1965
- curated
- organic and metal-organic compounds
- X-ray, neutron, (and electron diffraction)
- Single crystal and powder diffraction
- publication of a synthesis usually requires deposition of the product structure at the CSD
- $> 1,000,000$ entries, $\approx 50,000$/year



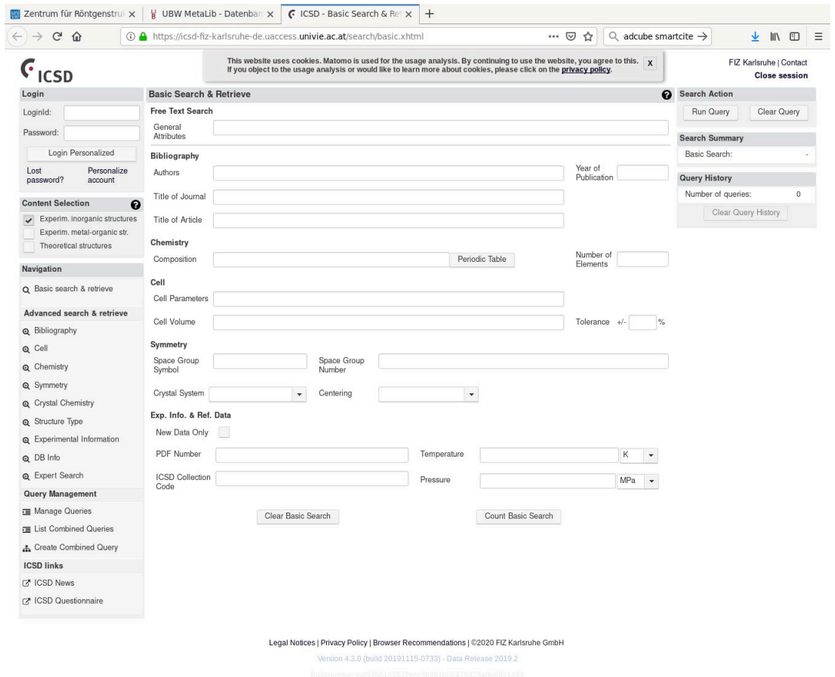
Crystallography Open Database (COD)

- `http://www.crystallography.net`
- “Open-access collection of crystal structures of organic, inorganic, metal-organics compounds and minerals, excluding biopolymers.”
- Local version available free of charge
- Organic and inorganic structures (minerals)
- Can be browsed (by journal, by year,...)
- All data from IUCr journals, and from American Mineralogist CSD
- $> 450,000$ entries, $\approx 50,000$/year



Inorganic Crystal Structure Database (ICSD)

- `https://icsd.fiz-karlsruhe.de/`
- inorganic and intermetallic structures
- only licensed access
- $> 215,000$ entries

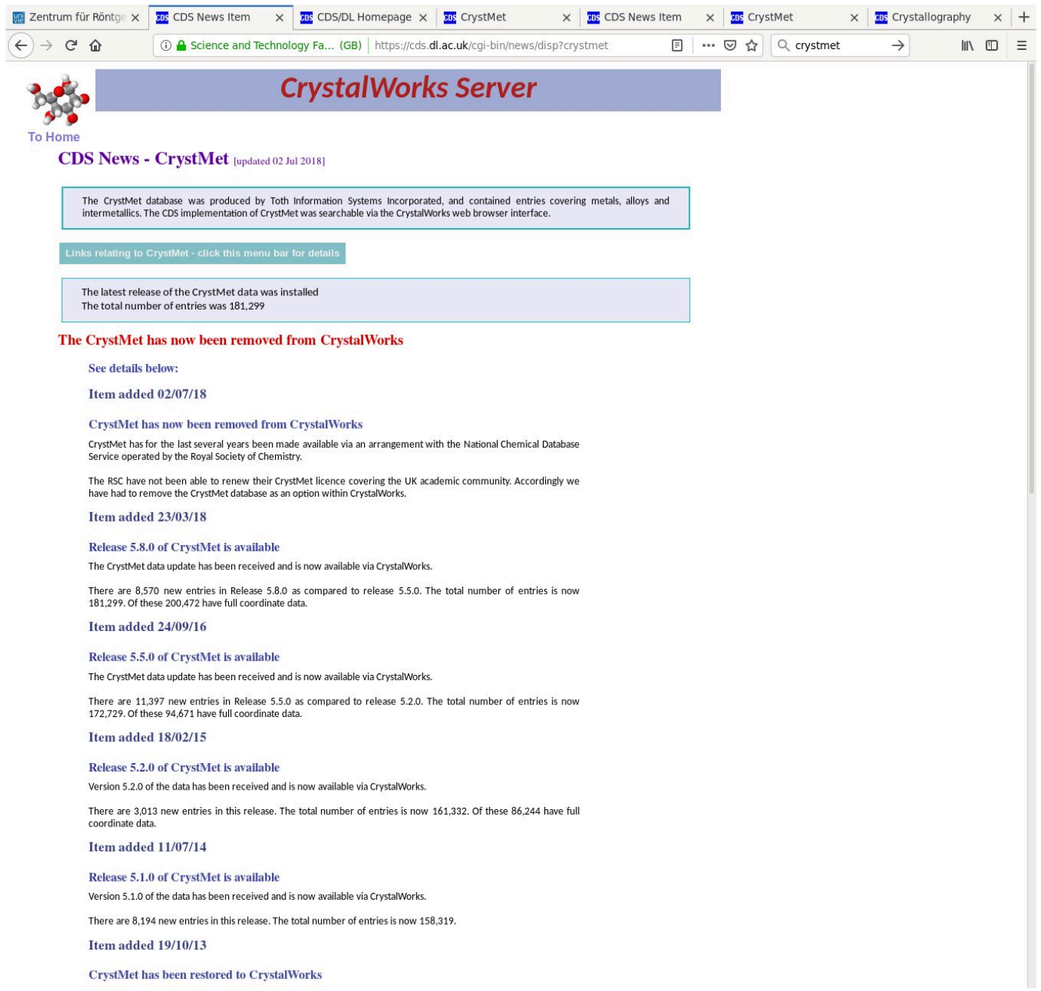


Protein Data Bank (PDB)

- `https://www.pdb.org`
- Search from `www.rcsb.org` or `https://www.ebi.ac.uk/pdbe` or `https://pdbj.org` (Japanese)
- polypeptides (proteins) and polysaccharides (nucleic acids)
- Crystal structures, NMR structures, EM structures
- Since 2007: data **must** be submitted along with co-ordinates
- $> 160,000$ structures

CrystMET

- `https://cds.dl.ac.uk/cds/datasets/crys/mdf/llmdf.html`
- Crystal structure data for metals and alloys
- licensed access only



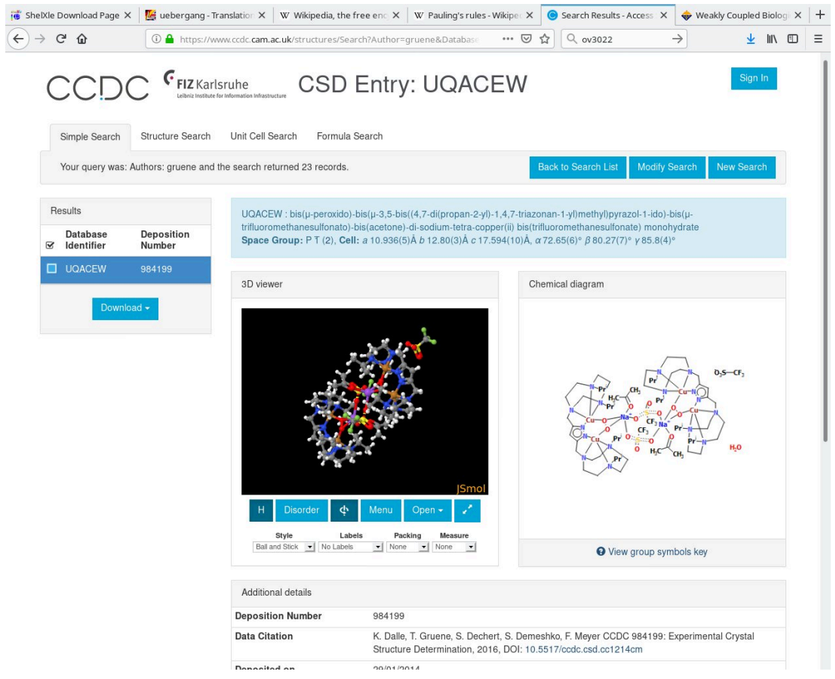
Structure, Data, Data Formats, and Visualisation Software

Structural Data: the CIF-file

- Main file format for published structures
- available from CSD, COD, ICSD, journal web-sites, etc
- pure text file
- Can contain both structure information (coordinates) and experimental data (hkl-file)

Example: CSD entry UQACEW, name of CIF-file: 984199.cif

K. Dalle *et al.*, J. Am. Chem. Soc. (2014), 136, 7428, DOI 10.1021/ja5025047: “Weakly Coupled Biologically Relevant $Cu^{II}_2(\mu\text{-}\eta^1:\eta^1\text{-}O_2)$ *cis*-Peroxo Adduct that Binds Side-On to Additional Metal Ions”

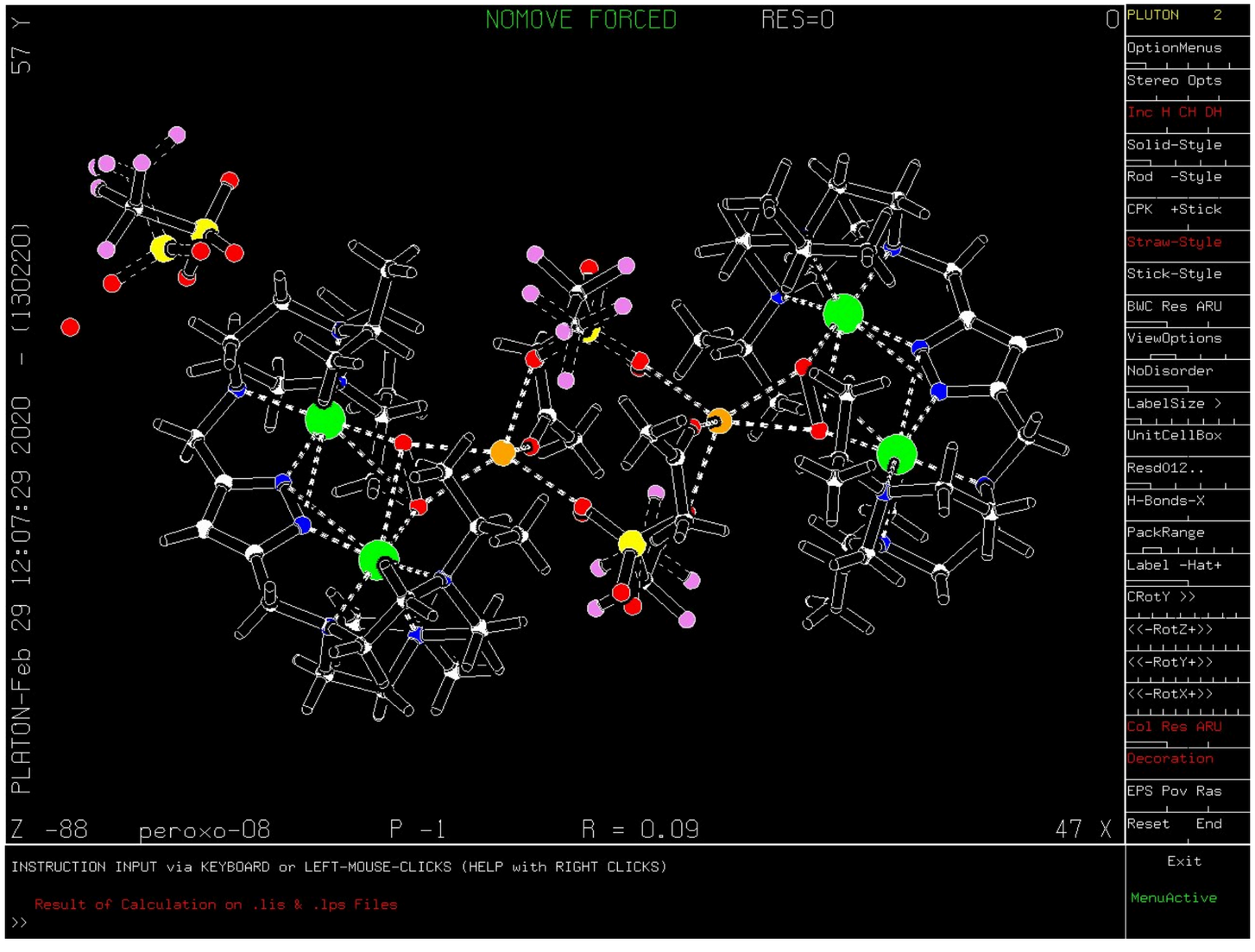


Structural Data: the RES-file

- RES/INS text file: chemical structure in computer language
- developed by George Sheldrick (SHELX programs), late 1960s
- still the most sophisticated format for chemical compounds
- “work” format: refinement and model building

Platon: Validation, format conversion

http://www.cryst.chem.uu.nl/spek/platon

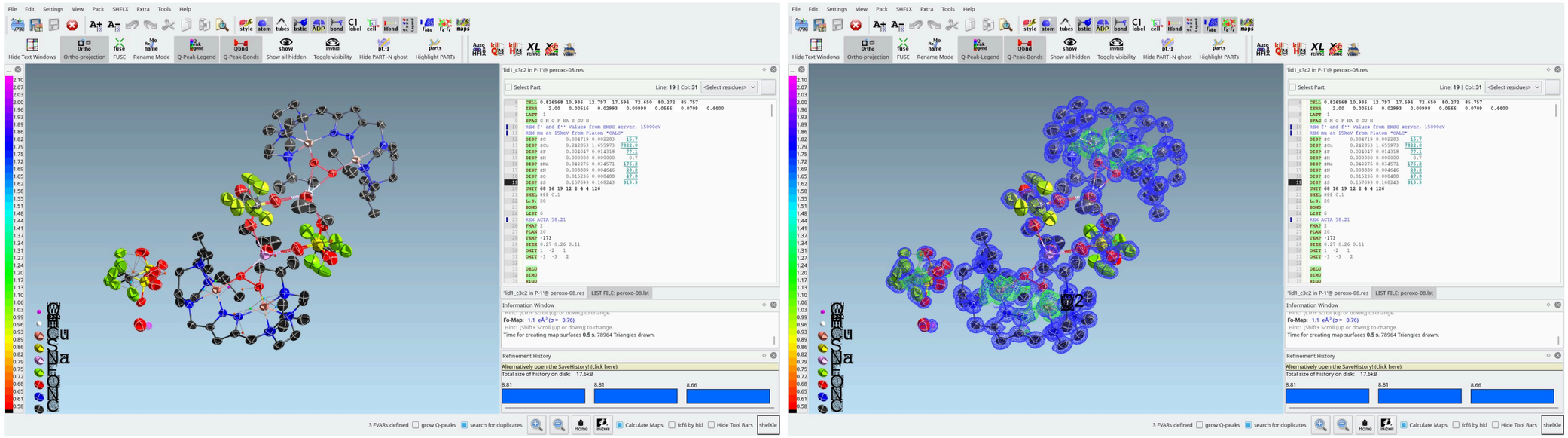


→ `984199_sx.ins` and `984199_sx.hkl`

ShelXle: Visualisation and Modelling

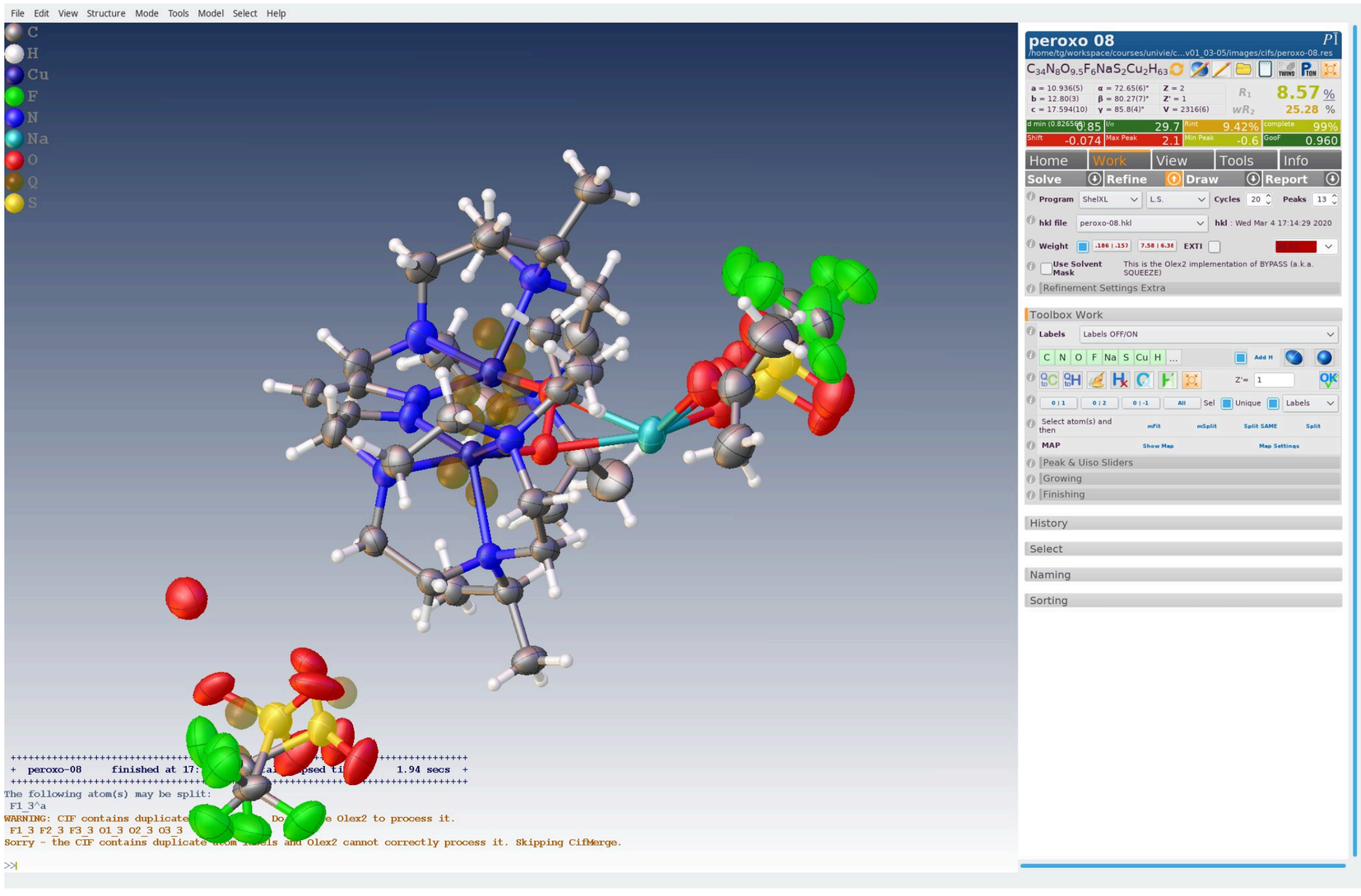
https://www.shelxle.org/shelx

```
#> shredcif 984199.cif
peroxo-08.res extracted, checksum O.K.
peroxo-08.hkl extracted, checksum O.K.
```



Olex2: Visualisation and Modelling

https://www.olexsys.org/



Crystals and Crystal Growth

Crystal Types

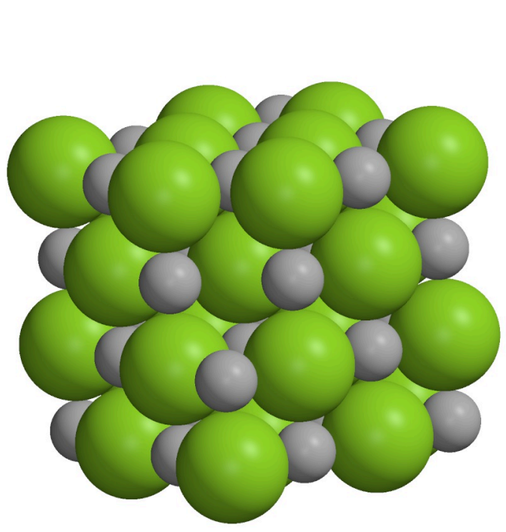
- Crystal = Solid state compound with regular composition
- interactions responsible for crystallisation
  1. ionic bond
  2. metallic bond
  3. covalent bond
  4. van-der-Waals interaction
- often not a clear cut between these types

Ionic Crystals

- Composed of anions (negative charge) and cations (positive charge)
- Geometry according to Pauling's rules

Simple example: $NaCl$:

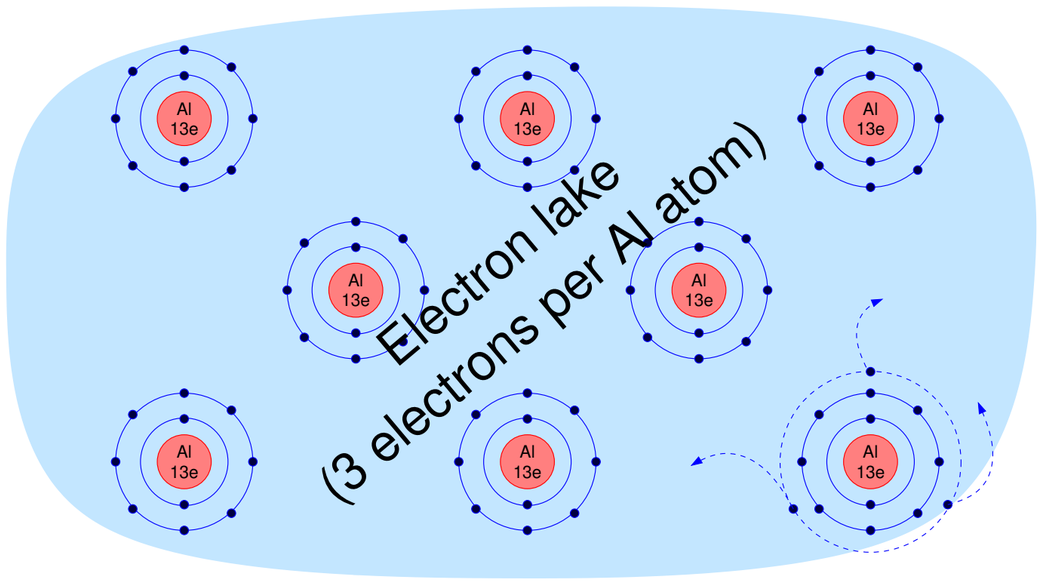
- cubic lattice
- energy difference $Na + Cl \rightarrow Na^+ + Cl^-$: $-6.4eV$



kubischer Aufbau von $NaCl$

Chrome alum,
alias Chromium(III) potassium sulfate
$KCr(SO_4)_2$

Metallic Crystals



Valence electrons dissociate from individual atoms and form an **electron lake** (conduction band)

→ electrical conductivity

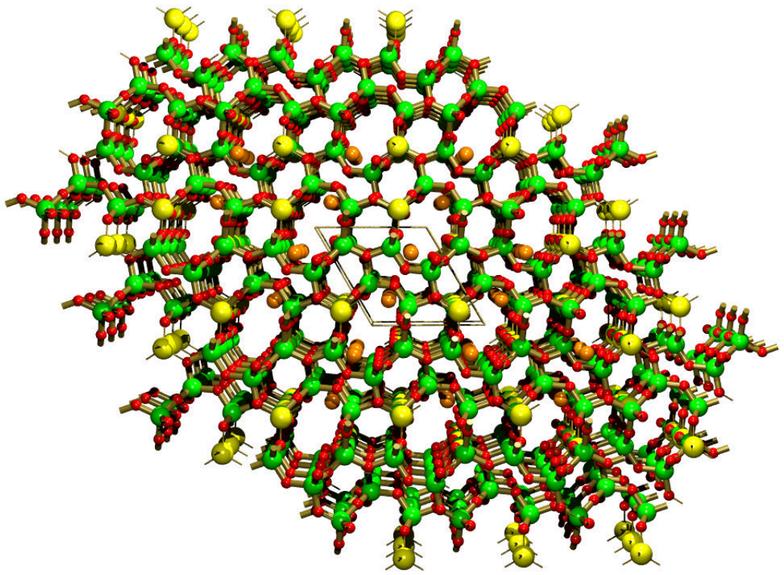
→ thermal conductivity (copper)

→ shiny surface

→ plasticity

http://commons.wikimedia.org/wiki/File:Iron_electrolytic_and_1cm3_cube.jpg

Covalent bond



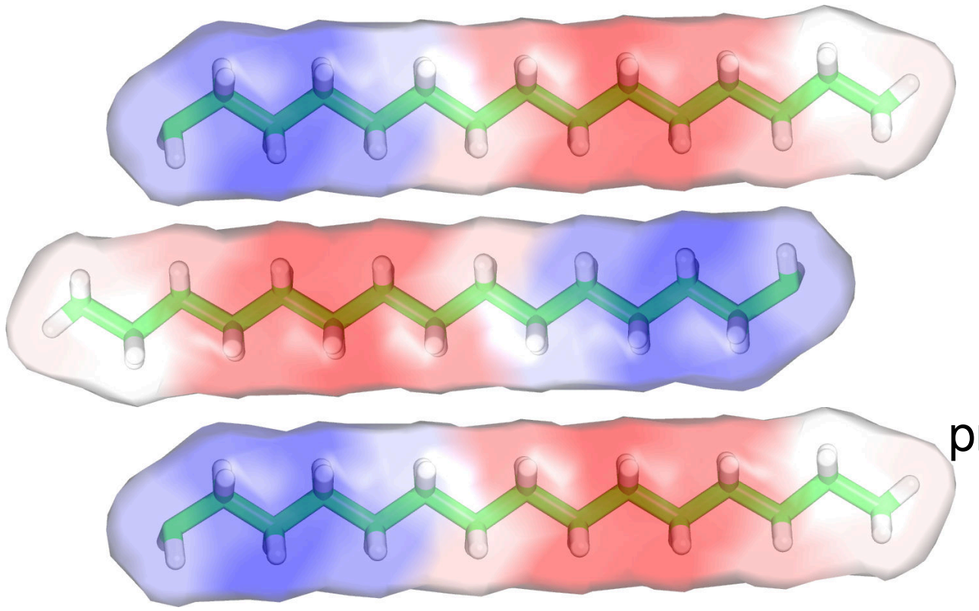
Feldspar Albite ($NaAlSi_3O_8$)

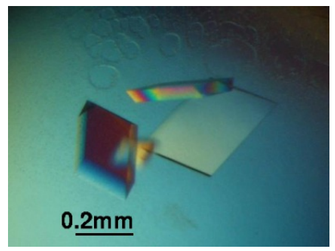
Two atoms share an electron to reach noble gas configuration.
Examples: zeolites, MOFs, diamond, quartz
$\Rightarrow$ high stability

By Rob Lavinsky, iRocks.com – CC-BY-SA-3.0, CC BY-SA 3.0
https://commons.wikimedia.org/w/index.php?curid=10137563

van-der-Walls interaction

- mostly organic and macromolecular compounds
- stochastic charge distribution (dipole moments) causes mutual attraction between molecules
- weak interaction





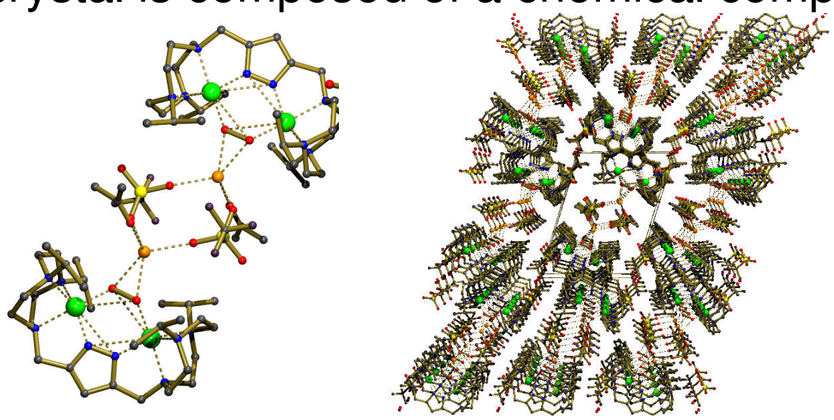
protein crystals in saturated solution

Crystals in Crystallography

Definition *International Union of Crystallography*:

> "A material is a crystal if it has essentially a sharp diffraction pattern."

Crystal in the context of this lecture:
A crystal is composed of a chemical compounds that repeats periodically in all three directions.



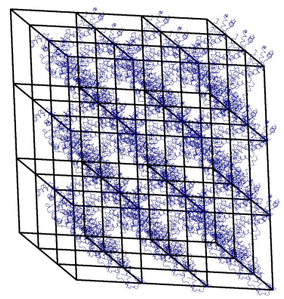
http://de.wikipedia.org/wiki/Parallelflach

- The periodicity results in the diffraction pattern of the crystal
- The periodicity act like an amplifier
- The smallest unit of the periodicity is an inclined box. It is called the **unit cell of the crystal**.

Crystal Growth

Crystals are

1. solid state materials
2. highly ordered, *i.e.* their entropy is very low compared to amorphous material



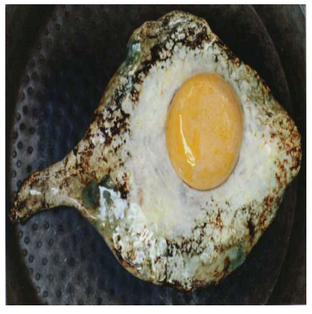
Especially for large molecules: weak interaction, *i.e.* low energy gain through crystallisation $\Rightarrow$ Crystal growth can be difficult

Crystal Growth

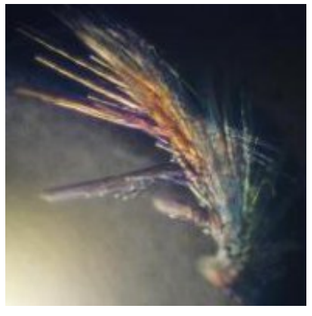
Usually: Precipitation from solution
Some means for precipitation (*cf.* LeChatelier's principle)

- Changes in temperature or pressure
  - sugar: better soluble in warm water
- precipitant
  - sugar: ethanol

Requirements for **structure determination**



crystallisation (instead of amorphous precipitation)

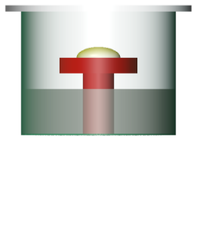


crystallise as single crystal

Examples for Crystallisation

1. Dissolve in Tetrahydrofuran (THF) in glass vial
2. Cover with parafilm: slow evaporation of THF
3. Store at $-80°$C

1. Dissolve in organic solvent (EtOH, Isopropanol, . . .)
2. Store sealed on water reservoir
3. Uptake of water (vapour) reduces solubility of compound



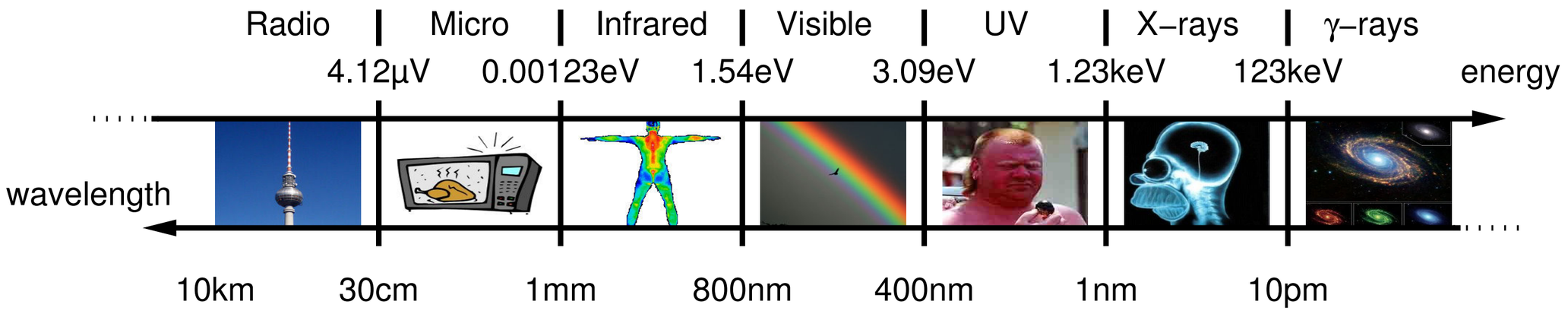
Twinned structures (cf. end of term) can often be improved with elevated temperature during crystal growth (30-40°C).

(see *e.g.* W. Massa, *Crystal Structure Determination*, Ch. 7)

X-rays and Diffraction

X-rays as electromagnetic radiation

X-rays are one type electromagnetic radiation — like visible light, UV-radiation, or radio waves



- Energy E and wavelength λ are equivalent ($E = h\frac{c}{\lambda} = 12.4keV\text{Å}/\lambda$):
- Long wavelength $\lambda \leftrightarrow$ low energy E.
- Short wavelength $\lambda \leftrightarrow$ high Energie E.
- Typical wavelength range for structure determination: 0.5-2 Å (24.8 - 6.2 keV).
- Inhouse X-ray instruments:
  - CuK_α: 1.54 Å $\leftrightarrow$ 8.0 keV
  - MoK_α: 0.71 Å $\leftrightarrow$ 17.3 keV
- 1 Å = 10^{-10} m = 100 pm

Generation of X-rays

1. **X-ray fluorescence** (mainly laboratory sources) electron beam at specific energy hits metal surface (Cu or Mo). This creates
   a) Bremsstrahlung (background)
   b) X-ray fluorescence

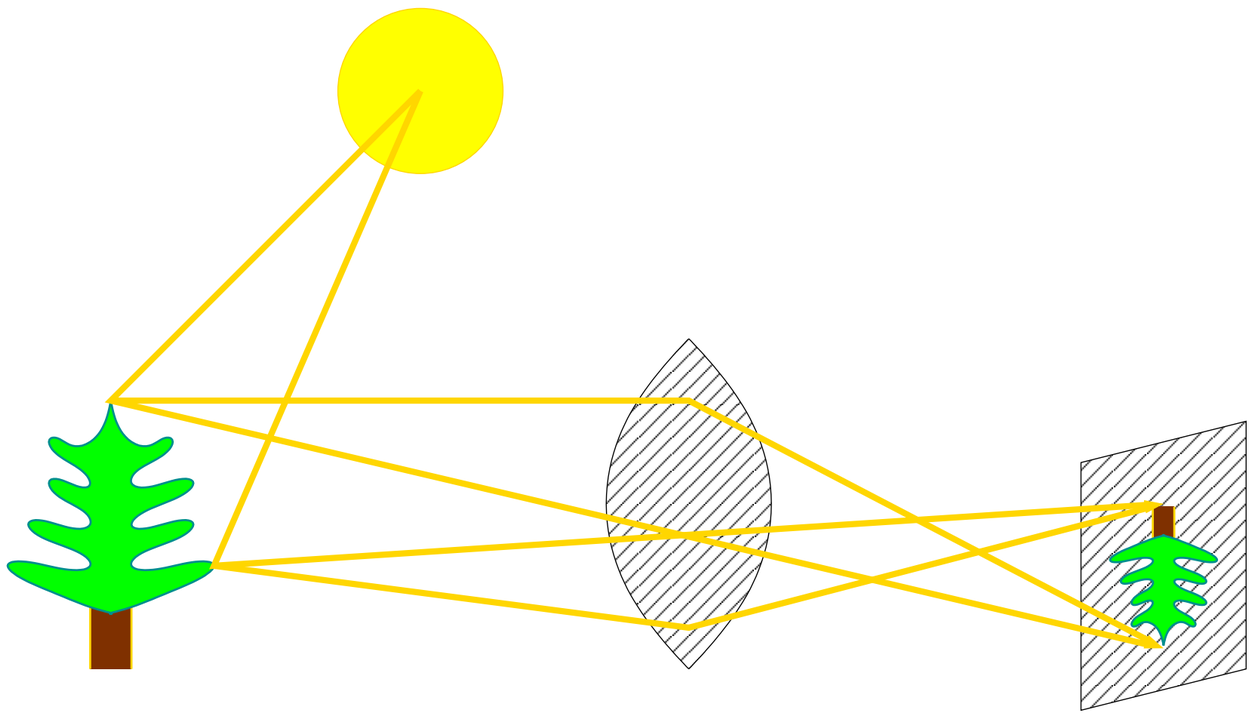
   Examples: rotating anode, liquid jet anode
2. **Synchrotron radiation** Acceleration of electron bunches in a magnetic field

Why X-rays?

Atom distances of molecules about 1–2 Å: required resolution d
Optical instruments are limited in resolution to $d > \lambda/2$ (later: derivation *via* Bragg's law)

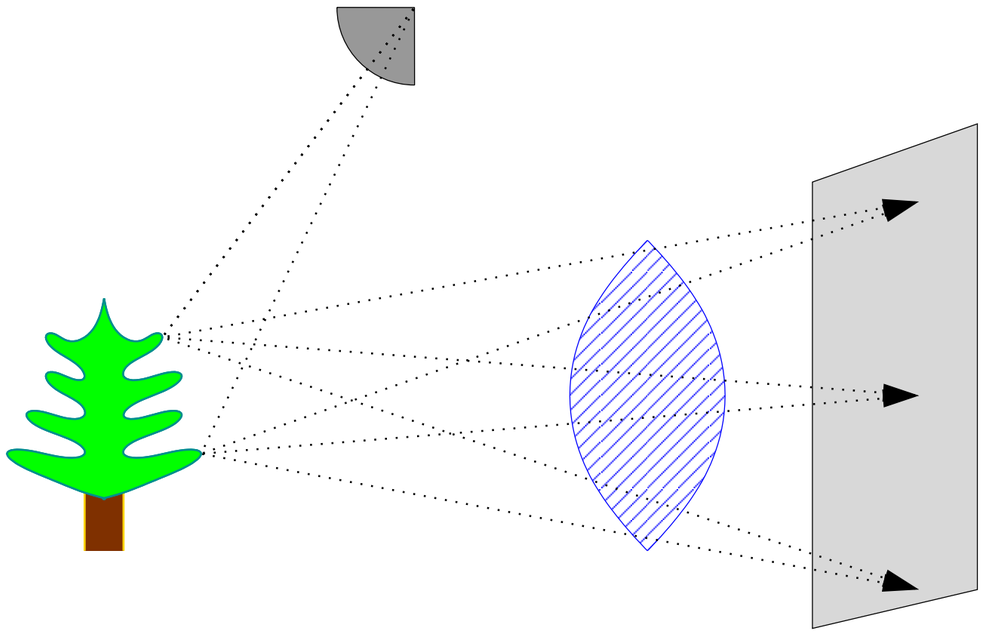
Why Crystals?

Optics and Imaging (Microscope / Telescope)



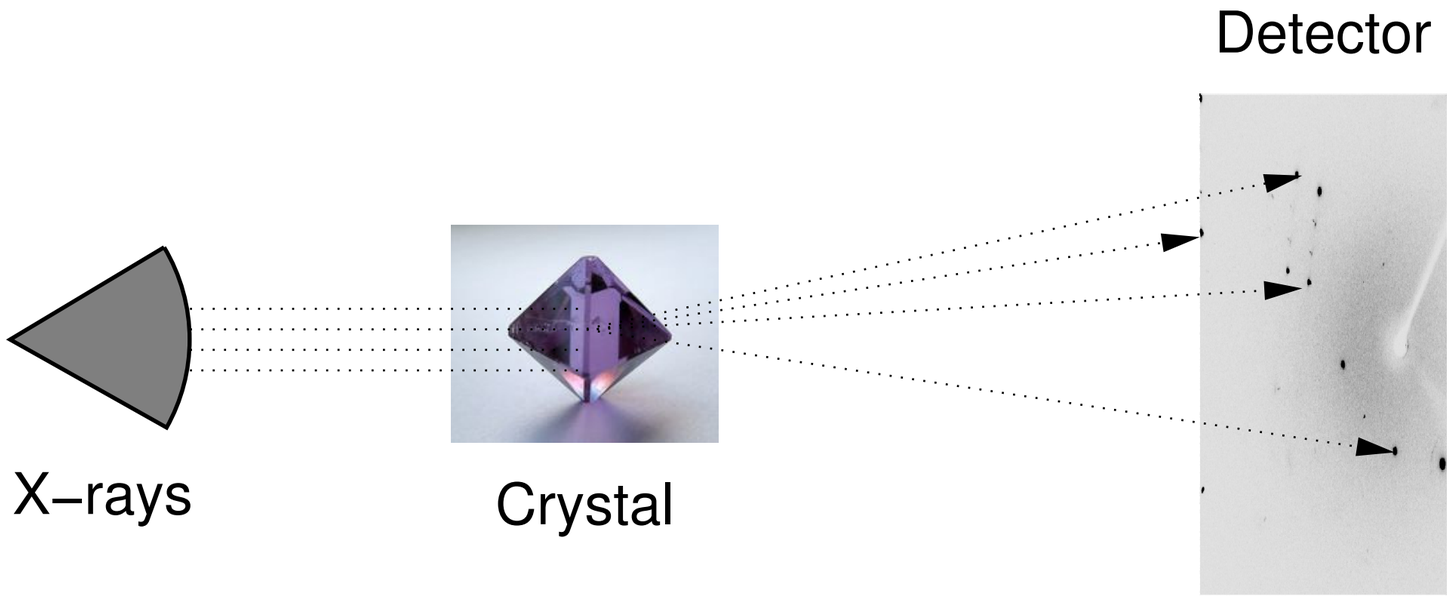
Objects scatter light. In order to see the object, the scattered light must be focused by **at least** one lens

X-ray Scattering



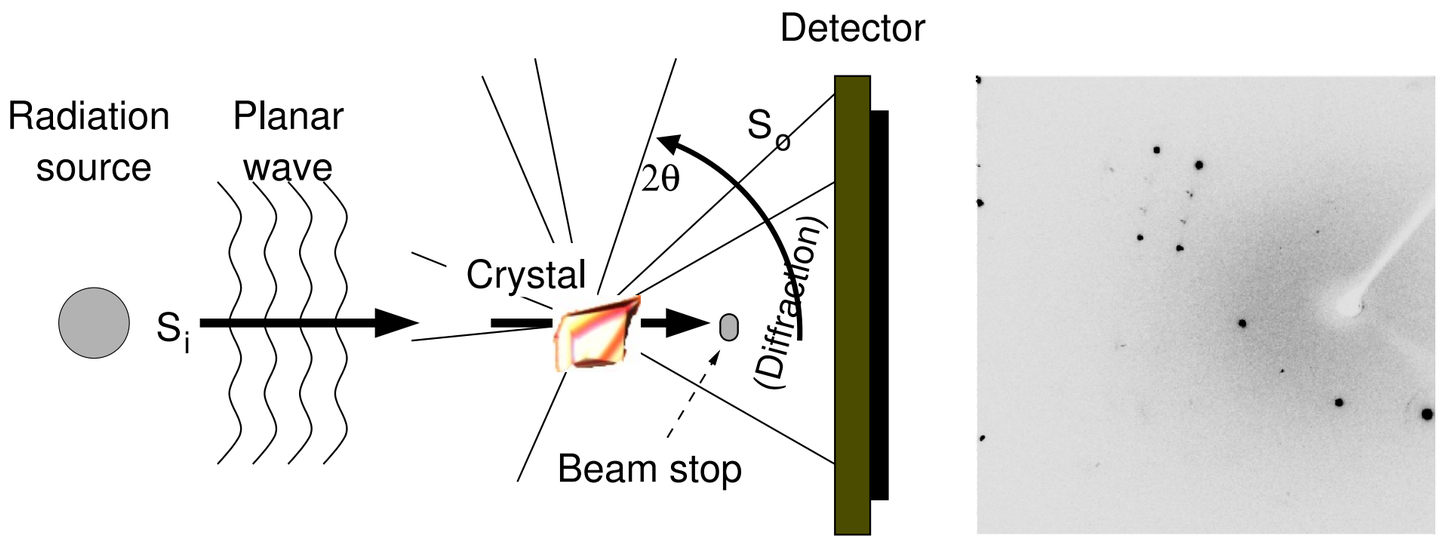
X-ray lenses do not exist: It is not possible to create a direct image of an object with X-rays.

X-ray Scattering by Crystals: Diffraction



The periodicity of the crystal results in a focussing of the scattered X-rays into **discrete spots**. The spots (reflections) can be measured without lenses. The crystal acts like a signal amplifier.

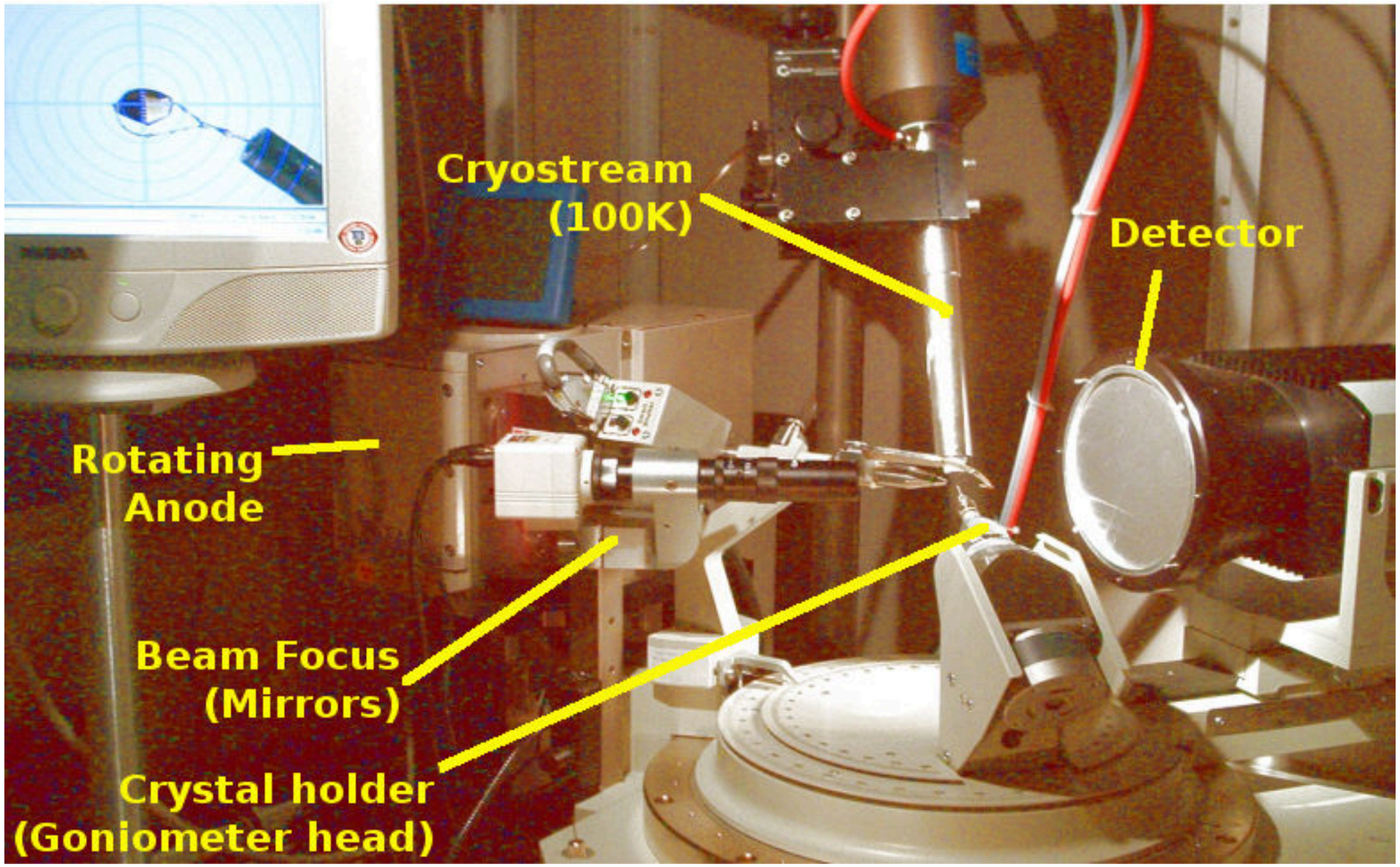
The X-ray Diffraction Experiment



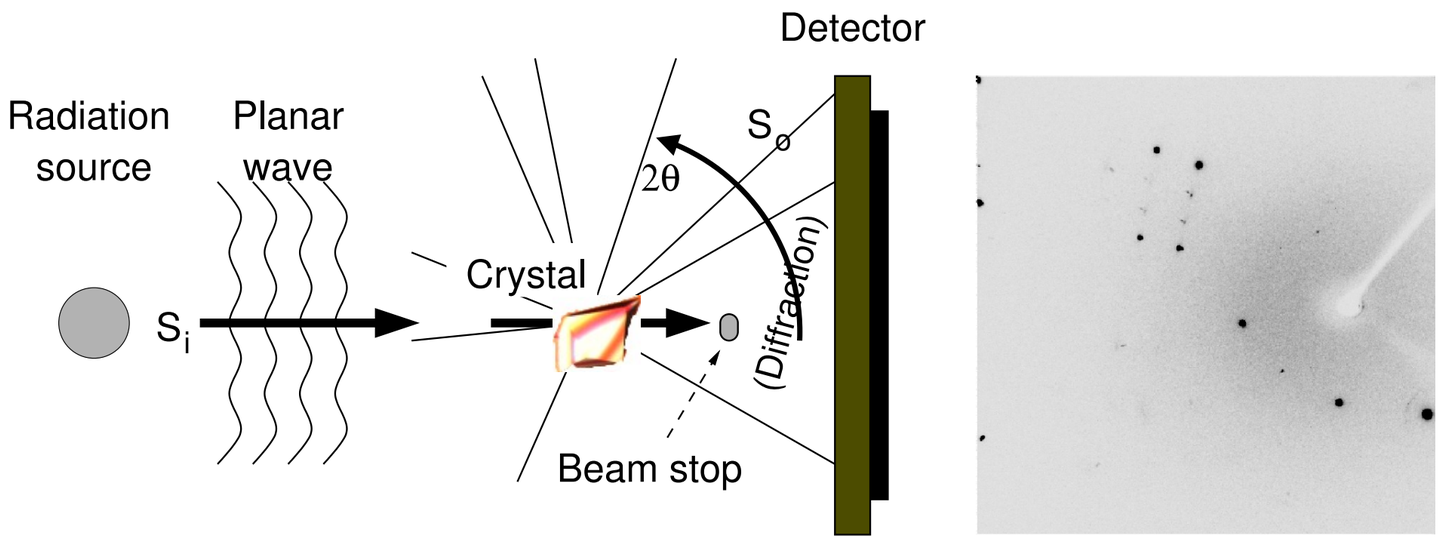
The crystal diffracts X-rays. This creates a **diffraction pattern** recorded by the detector.

The reflection spots are not images of the atoms

Typical laboratory X-ray Diffractometer



Data Collection experiment

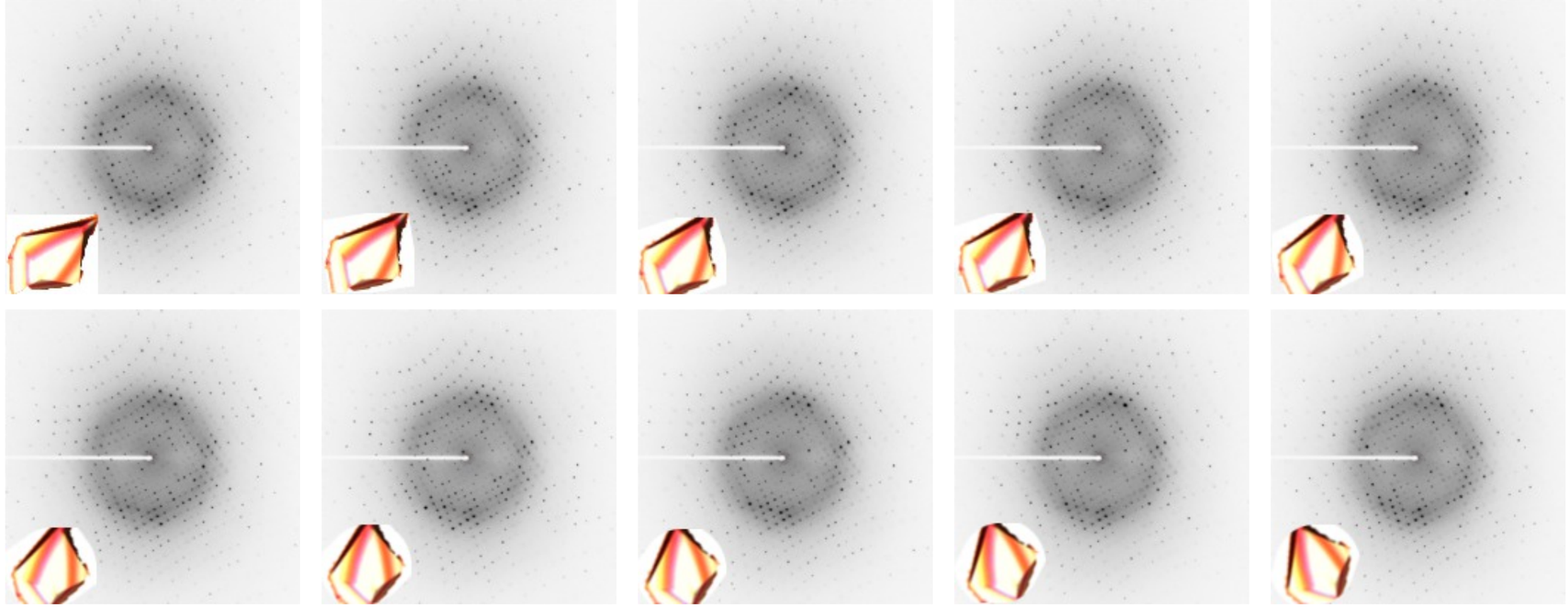


Reflections are data point. Each one contains different information. In order to collect as many data points as possible:

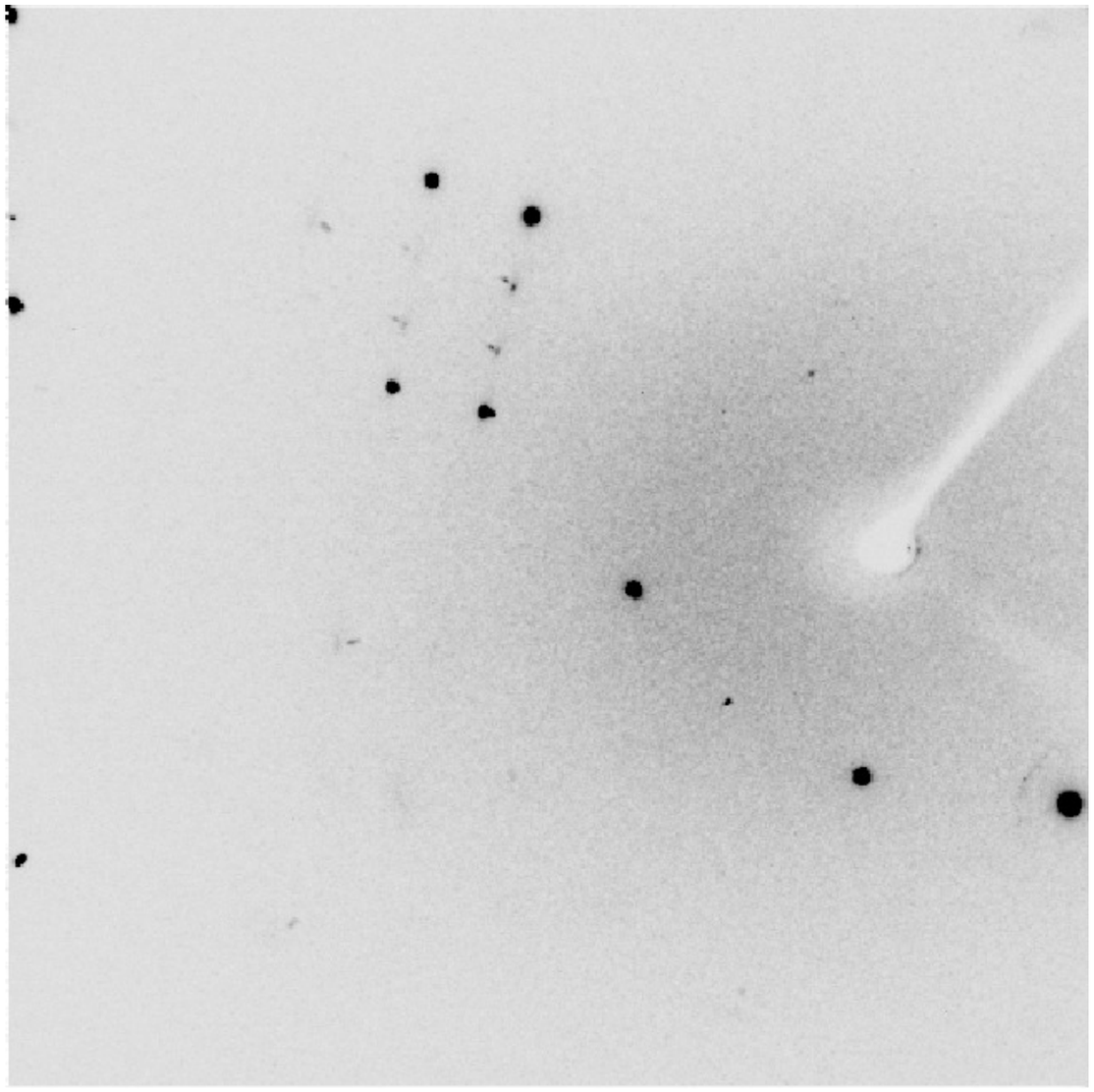
1. Rotation of the crystal (about one of three different axes, called ϕ–, ω–, and χ–circles)).
2. Rotation of the detector around the crystal, called 2θ–circle. This is parallel to the ω–circle).

The Data Set

The reflections can be described as three dimensional **reciprocal lattice**. The two dimensional detector records an intersection of the three dimensional lattice.
The full experiment results in a **data set**.
One data set consists of several runs (1–20). One run is the rotation of the crystal about a single axis. Per run, 180–2,000 **frames** are recorded. One frame corresponds typically to 0.1° – 1° rotation of the crystal.

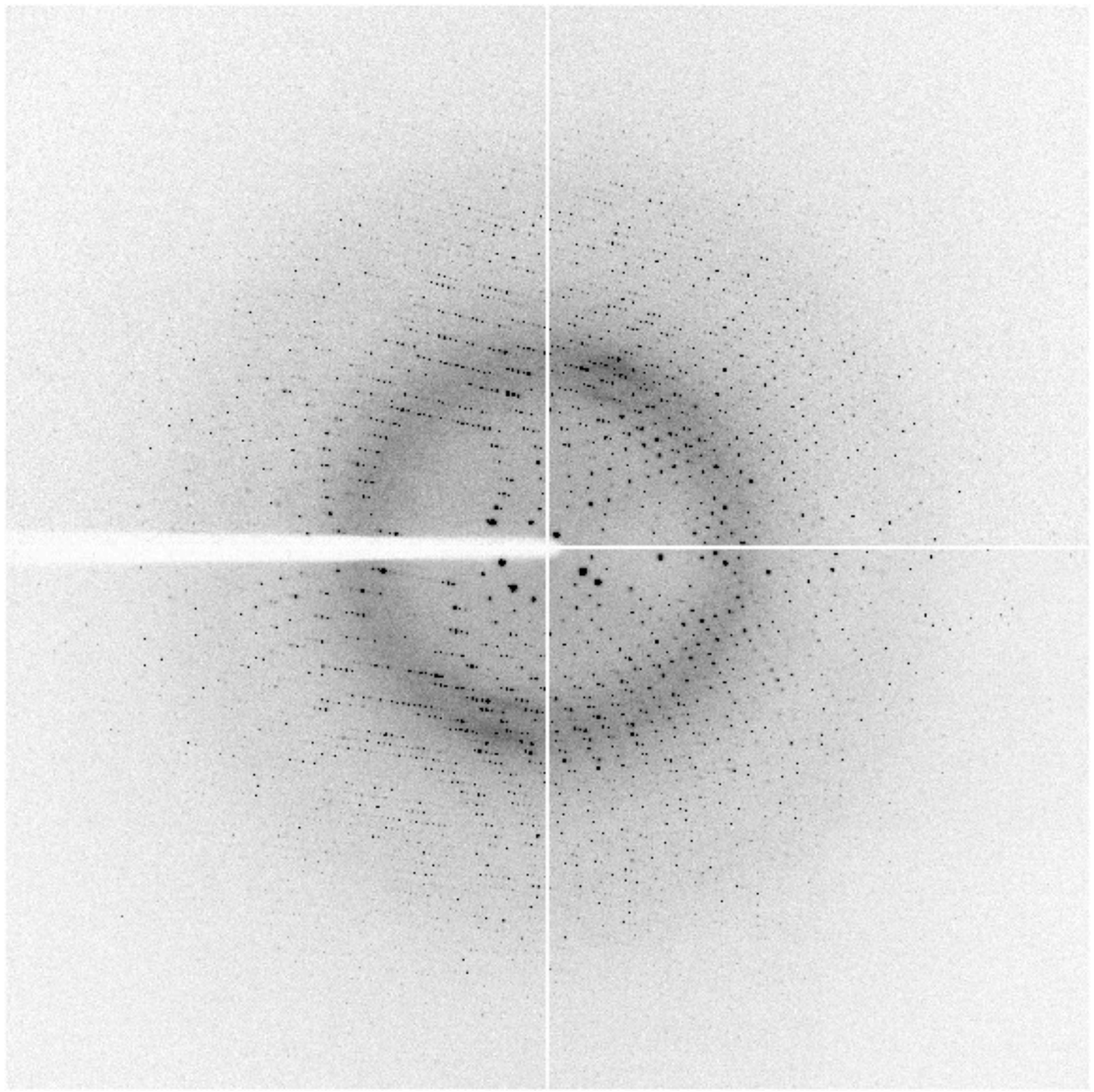


Examples of Data Frames



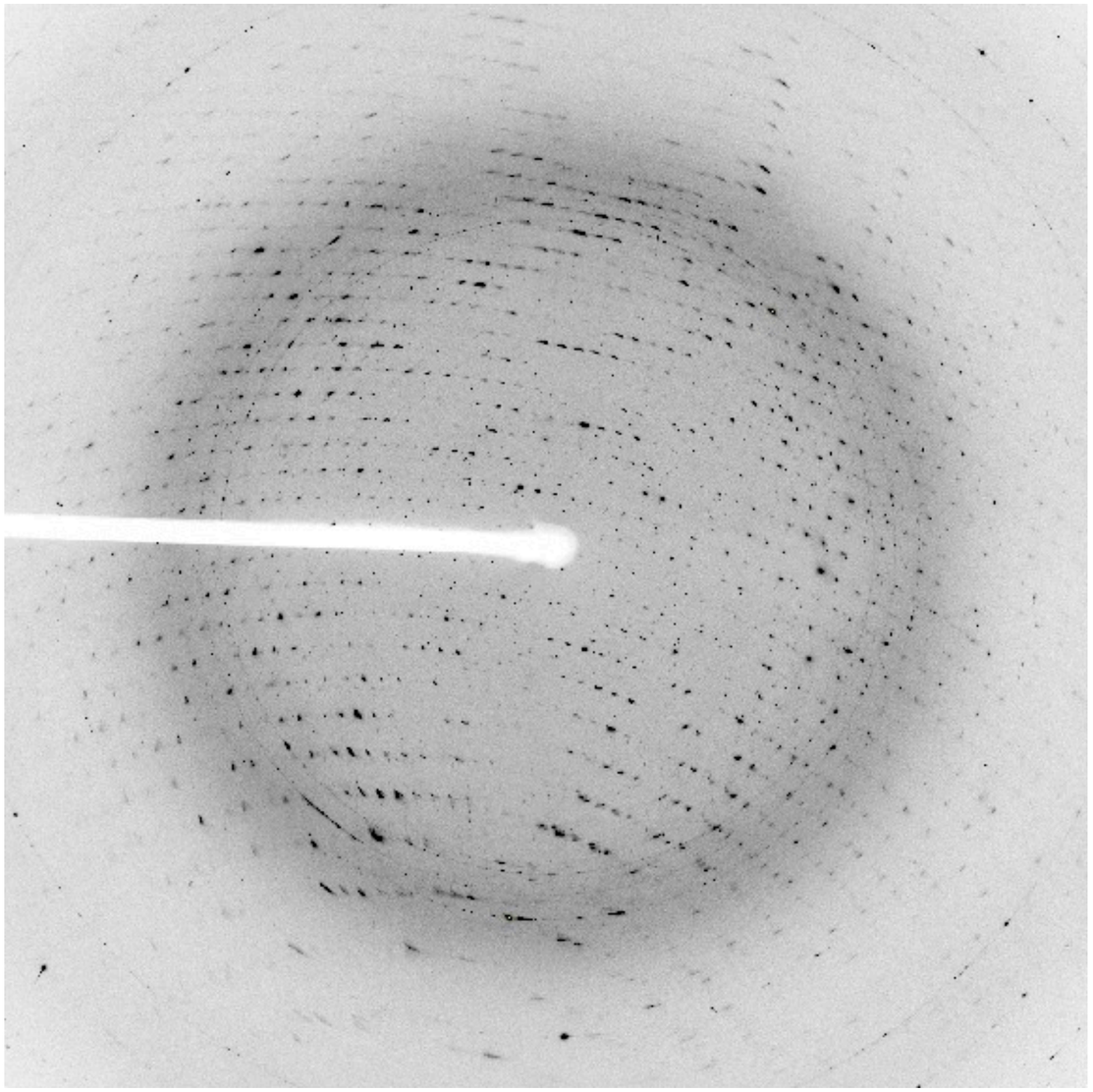
- Small molecule, unit cell dimensions: $a = 10.56$Å, $b = 11.64$Å, $c = 16.14$Å, $\alpha = \beta = \gamma = 90°$
- Small unit cell: $\Rightarrow$ few reflections
- Reflections beyond edge of detector: $\rightarrow 2\theta$ offset of detector necessary
- black reflections = data; grey regions: noise, neglectable

Examples of Data Frames



- Macromolecule. unit cell dimensions: $a = 92.6$Å, $b = 92.6$Å, $c = 128.9$Å, $\alpha = \beta = 90°, \gamma = 120°$
- Many more reflections
- Reflexes form patterns Muster (lunes, “Kugeldreiecke”)
- Intensity reduces towards edge of detector

Examples of Data Frames



- Macromolecule. unit cell dimensions: $a = 111.7$Å, $b = 80.5$Å, $c = 70.3$Å, $\alpha = \gamma = 90°, \beta = 94.2°$
- smeared reflexes
- ice rings (formed during measurement, or due to poor shock-freezing conditions)
- Closer look: small spots between “patterns”: twinned crystal, not a single crystal.

Purpose of a Crystal Structure

Why Crystal Structure Determination?

The Structure provides atom coordinates: arrangement of elements in 3D space

Organic Chemistry:

- Purity of synthesis
- Success (or failure) of synthesis
- Determination of absolute structure

Inorganic Chemistry"

- Bonding geometry, coordination geometry (of metals . . .)

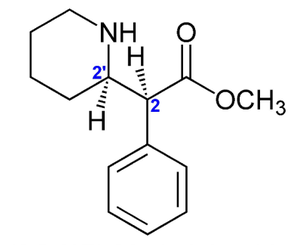
Comparison with other Structural Methods

NMR : chemical environment, sum formula. Not absolute structure

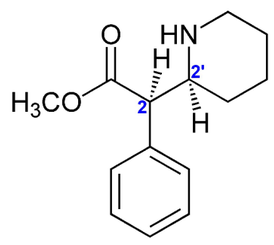
Rotational spectroscopy: (and gas phase electron diffraction): bond distances (**much more precise** than crystal structure)

Crystallography : Virtually no size limit (protein complexes $>$ 1.5 MDa; differentiation of element types

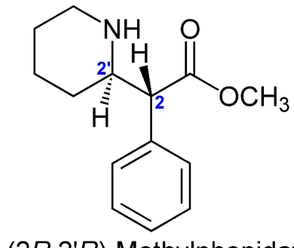
Examples: Absolute structure and degree of purity



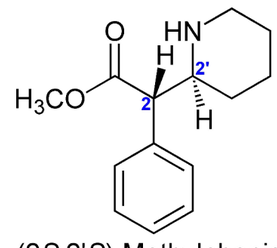
(2*S*,2'*R*)-Methylphenidat



(2*R*,2'*S*)-Methylphenidat



(2*R*,2'*R*)-Methylphenidat



(2*S*,2'*S*)-Methylphenidat

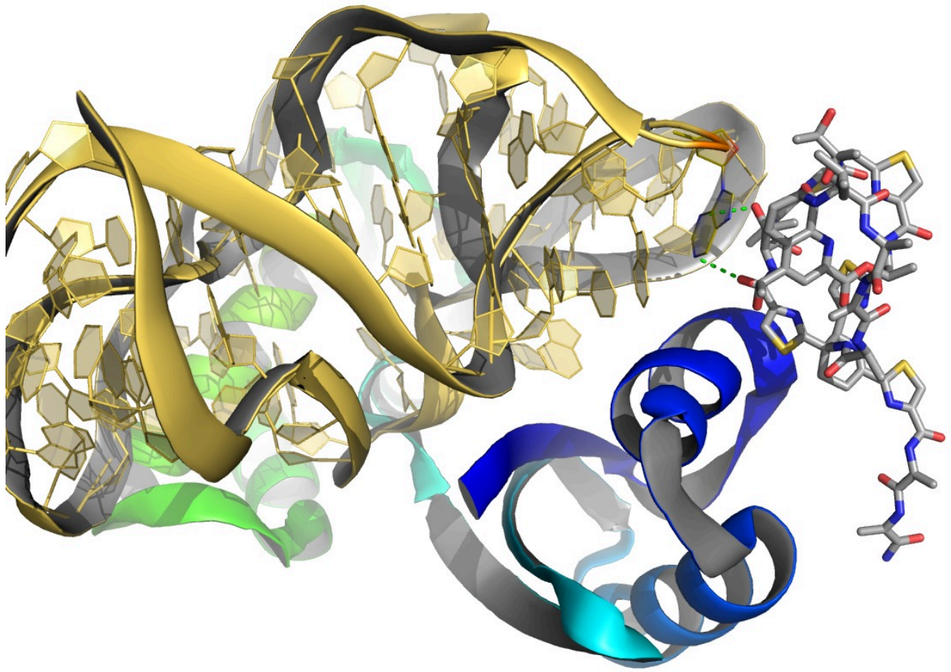
- Methylphenidate (*alias* Ritalin): medication to treat Attention Deficit Hyperacticyt Disorder (ADHD).
- Two chiral centres, *four* stereoisomers
- Typical: only one stereoisomer with desired effect.
- Remaining stereoisomers: side effects

(E. J. Ariëns:*Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology*, European Journal of Clinical Pharmacology, **26** (1984), pp. 663–668).

`http://de.wikipedia.org/wiki/Methylphenidat`

The crystal structure is the only method to determine the absolute structure and the degree of purity of mixtures.

Structure based Drug Development



The antibiotic *Thiostrepton* together with its target DNA. Dr. K. Pröpper.

Knowledge of structure of ligand and target:

- Improvement of chemical interaction
- Improvement of shape / surface: Functionality and access to cell or nucleus.
- Uptake in body (cf. `http://de.wikipedia.org/wiki/Insulinpräparat`)