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detecting the future

Instrumentation for tackling current and future challenges in pharmaceutical R&D

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Agenda

Where does laboratory XRPD analysis stand?

1. ***Old problems - new challenges?***
2. ***MYTHEN: Microstrip detector***
3. ***MYTHEN + STOE Stadi MP***
   - ***Higher accuracy in XRPD analysis***
   - ***PDF!***
4. ***New opportunities***

Old problems - new challenges?

1. Qualitative analysis

2. Quantitative analysis

Old problems - new challenges?

1. Data collection

- *Laboratory*
- *Synchrotron*

- Overlap
- Data statistics
- Radiation damage
- High throughput

Old problems - new challenges?

1. Data collection

- *Laboratory*
- *Synchrotron*

2. Identification

- *Crystalline materials*
- *"structurally challenged samples"*
- *Mixture*

- Overlap
- Data statistics
- Radiation damage
- High throughput

- Single crystal *vs* bulk
- Crystal structure *vs* material
- Polymorphs
- Excipients
- Interactions thereof

Old problems - new challenges?

1. ***Data collection***
   - *Laboratory*
   - *Synchrotron*
2. ***Identification***
   - *Crystalline materials*
   - *"structurally challenged samples"*
   - *Mixtures*
3. ***Detection limit***
4. ***Quantification limit***

- Overlap
- Data statistics
- Radiation damage
- High throughput

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Old problems - new challenges

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- Excipients
- Interactions thereof

3. Detection limit

4. Quantification limit

MAX ACCURACY

Old problems - new challenges

1. Data collection

- *Laboratory*
- *Synchrotron (Fabia Gozzo)*

- Overlap
- Data statistics
- Radiation damage
- High throughput

2. Identification

- *Crystalline materials*
- *"structurally challenged samples"*
- *Mixtures*

- Single crystal *vs* bulk
- Crystal structure *vs* material
- Polymorphs
- Excipients
- Interactions thereof

3. Detection limit (F. Gozzo)

4. Quantification limit (F. Gozzo)

MAX ACCURACY

MIN QUANTITY

Old problems - new challenges

1. Data collection

- *Laboratory*
- *Synchrotron*

2. Identification

- *Crystalline materials*
- *"structurally challenged samples"*
- *Mixtures*

3. Detection limit

4. Quantification limit

- Overlap
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- Single crystal *vs* bulk
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- Interactions thereof

MAX ACCURACY

MIN QUANTITY

Accuracy in XRPD: important factors

1. Instrumentation
2. Physical properties of a material
3. Expertise of an analyst
4. Software support
5. Computing power

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Accuracy in XRPD: important factors

1. Instrumentation
2. Physical properties of a material
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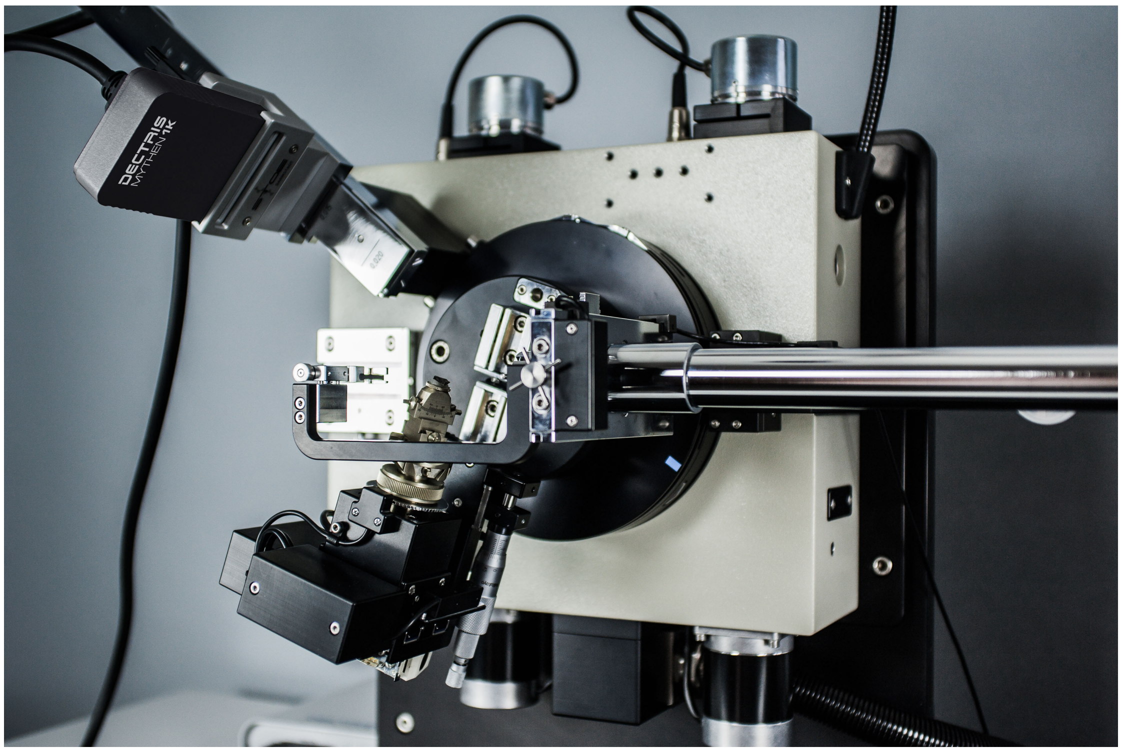
5. Computing power

Where are the limits of laboratory XRPD analysis?

Accuracy in XRPD: Instrumentation

Stoe Stadi MP + MYTHEN 1K detector



Accuracy in XRPD: Instrumentation

1. Source
2. Detector (F. Gozzo)
3. Geometry (M. Ermrich)
4. Optics
5. Mechanics (positioning)

Accuracy in XRPD: Instrumentation

Stoe Stadi MP Diffractometer

Basic parameters of Stoe Stadi MP diffractometer	
Tube	Cu,(Mo), Ag
Monochromator	Ge 111
Geometry	Debye-Scherrer
Mode	Continuous scan
Radius [mm]	190
Software	WinX^{pow}
Detector	MYTHEN 1K

Accuracy in XRPD: Instrumentation

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Radius [mm]	190
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Detector	**MYTHEN 1K**

Accuracy in XRPD: Instrumentation

MYTHEN detectors

PAUL SCHERRER INSTITUT

SINCE 1887

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Accuracy in XRPD: Instrumentation

Pixel/microstrip detectors operating in single-photon counting mode

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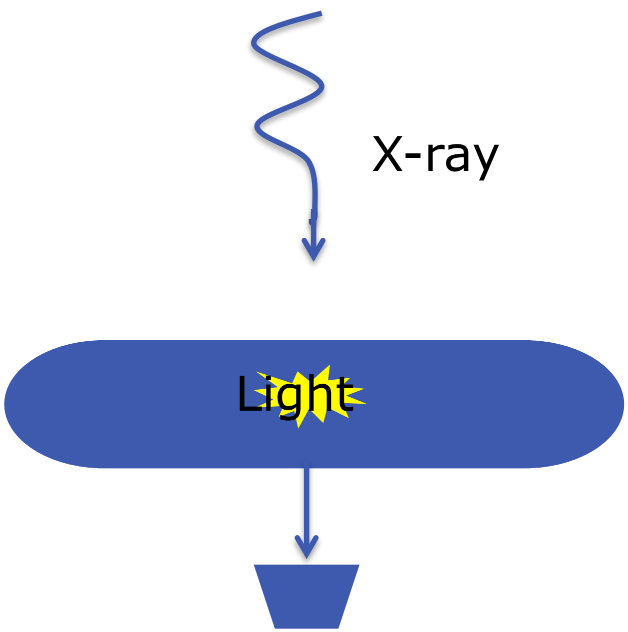
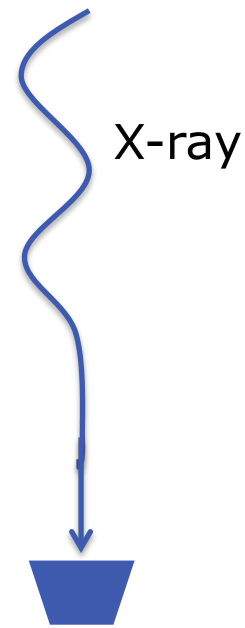
Accuracy in XRPD: Instrumentation

MYTHEN detectors



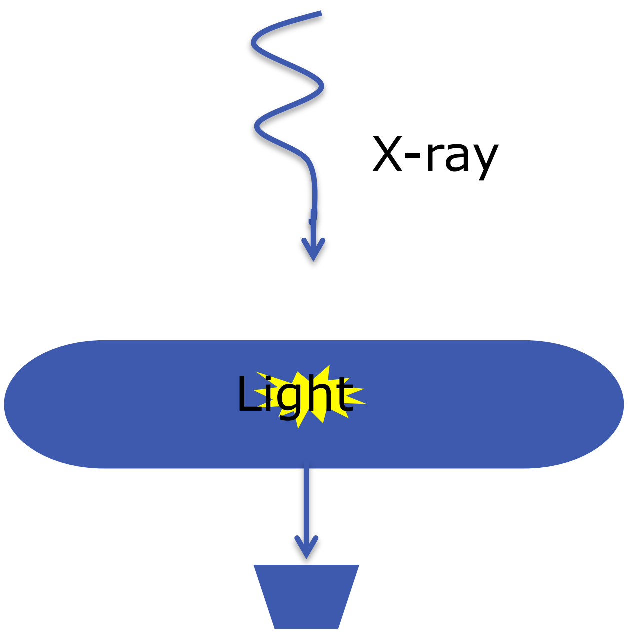
Indirect detection of X-rays
Traditional detectors

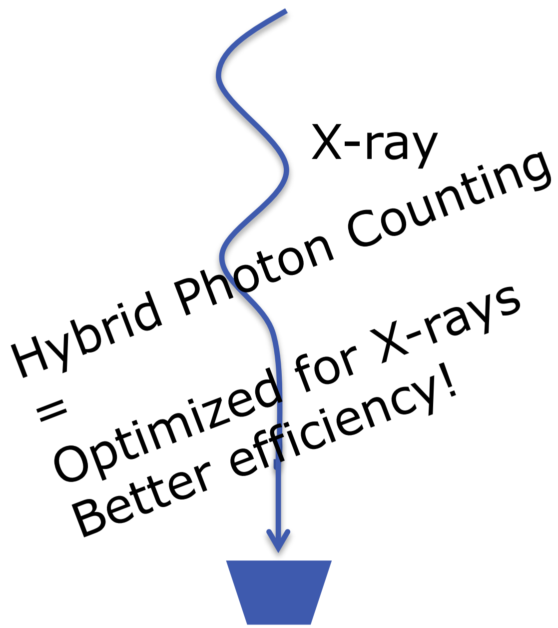


Direct detection of X-rays
Pixel/microstrip detectors

Accuracy in XRPD: Instrumentation

MYTHEN detectors





Indirect detection of X-rays
Traditional detectors

Direct detection of X-rays
Pixel/microstrip detectors

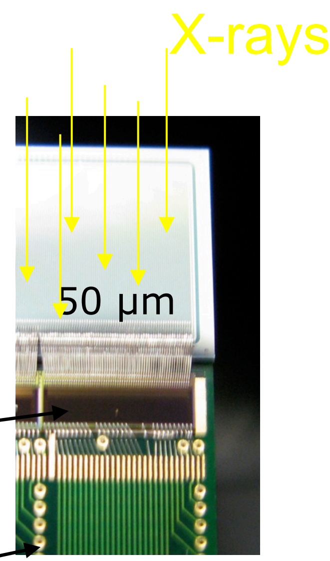
Accuracy in XRPD: Instrumentation

MYTHEN detectors

Silicon sensor:
Microstrips

Wire-bonds

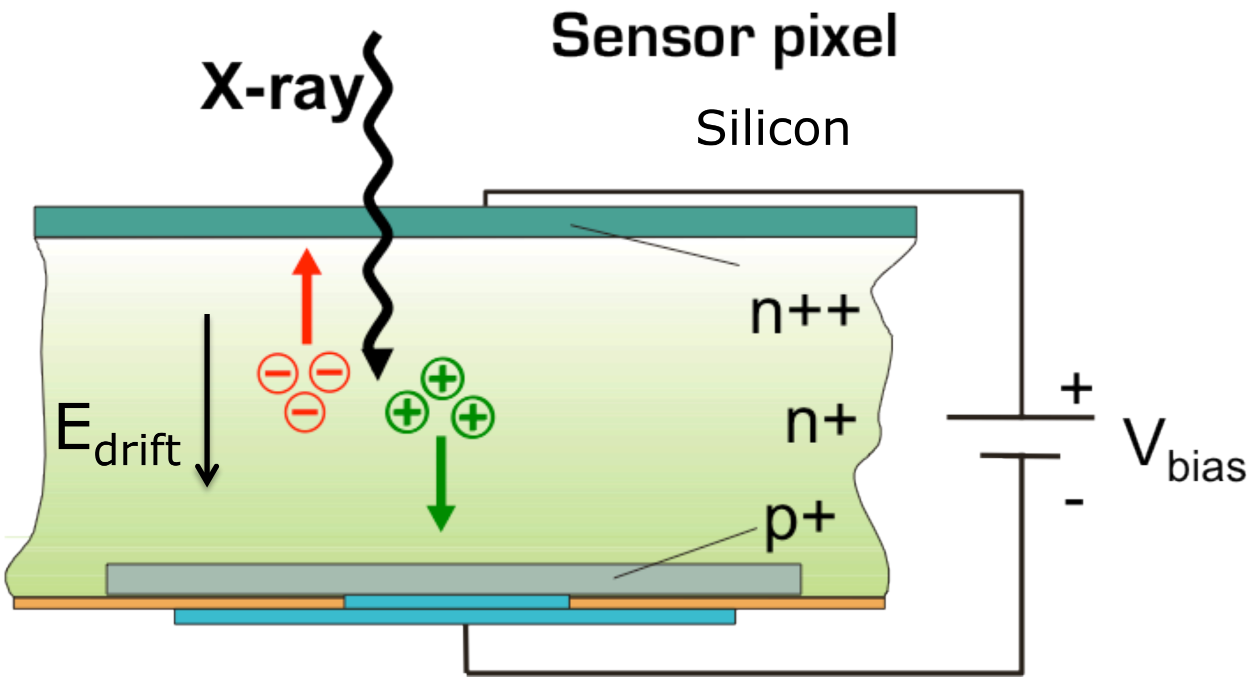
Readout chip



MYTHEN

Accuracy in XRPD: Instrumentation

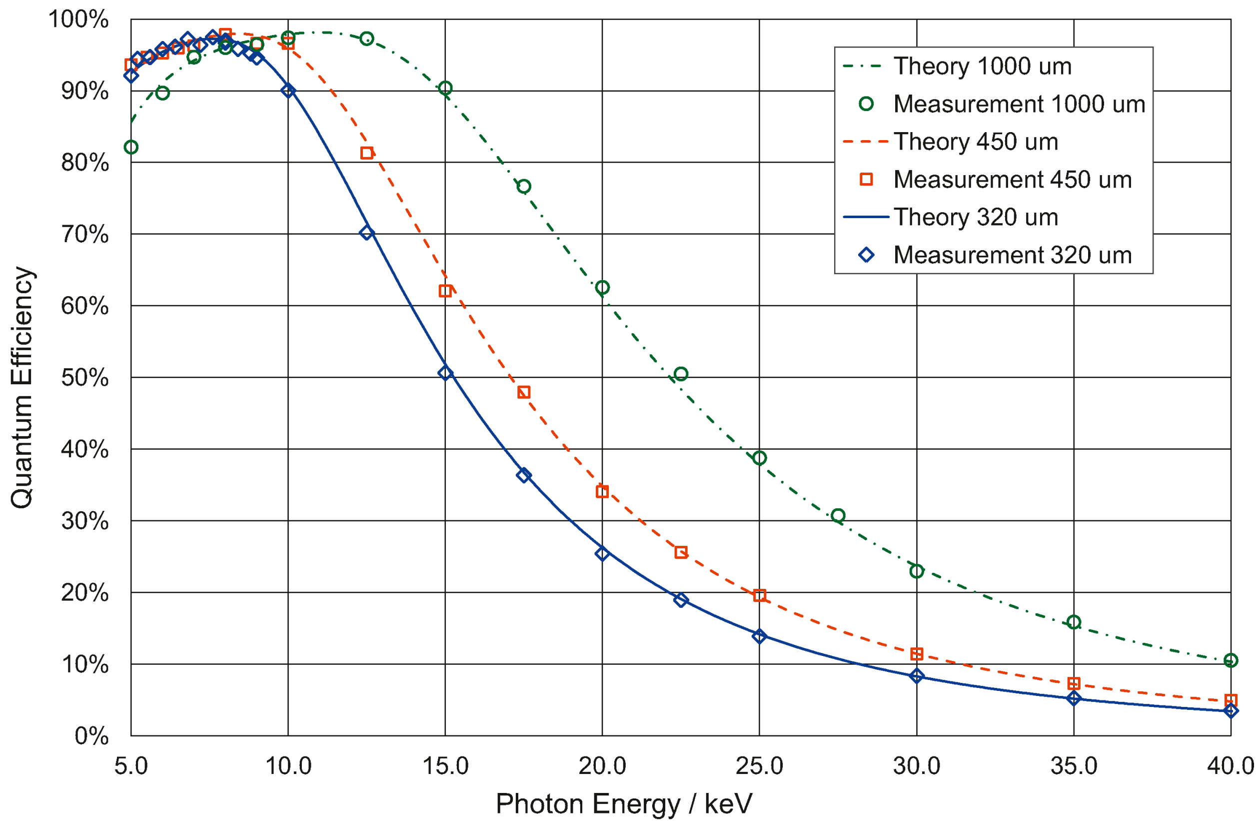
MYTHEN detectors



Interaction of X-rays and Si produces charge. Charge drifts through the sensor.

Accuracy in XRPD: Instrumentation

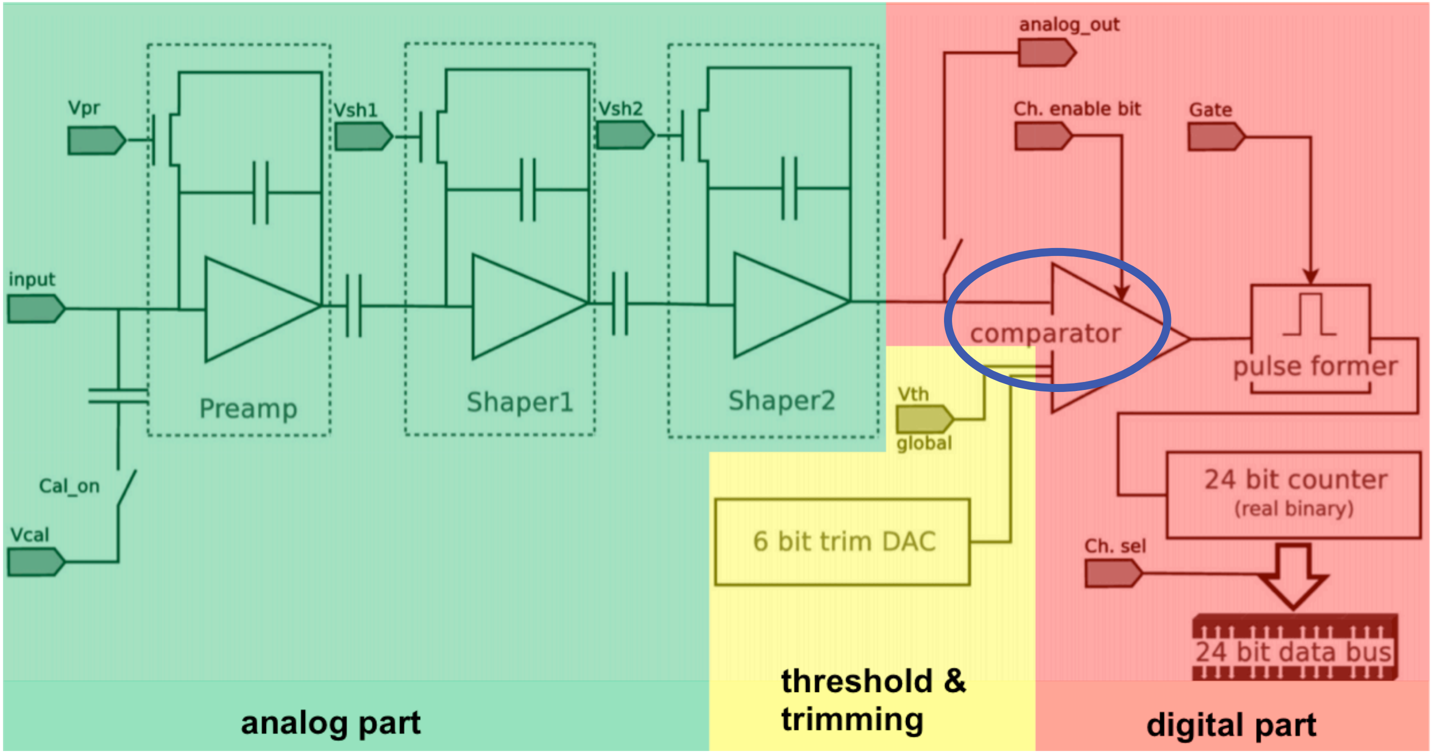
MYTHEN detectors



Efficiency of the silicon sensor depends on its thickness and X-ray energy.

Accuracy in XRPD: Instrumentation

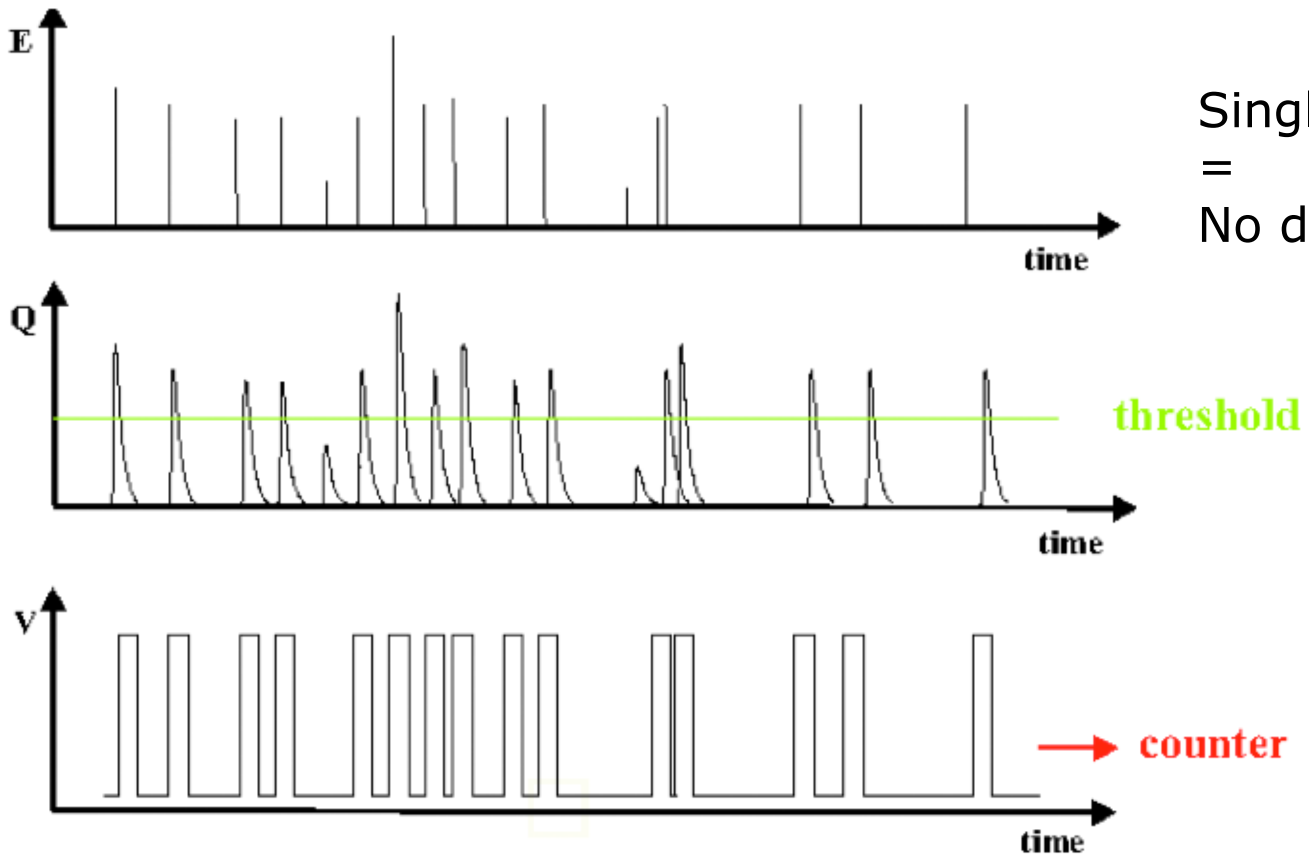
MYTHEN detectors



Signals with Energy higher than the threshold are accepted for counting.

Accuracy in XRPD: Instrumentation

MYTHEN detectors



Single photon counting
=
No dark current

Energy threshold
=
No noise
Fluorescence suppression

Calibration, trimming
= best quality data

Accuracy in XRPD: Instrumentation

MYTHEN detectors

Basic technical data: MYTHEN 1K detector	
Sensor	Silicon
No. strips	1280
Strip width [µm]	50
Dynamic range [bit]	24
Energy range [keV]	5-40
Point spread function	1 strip
Adjustable energy threshold	Yes
Readout time [ms]	0.3
Sensor thickness [µm]	320, 450, 1000

Accuracy in XRPD: Instrumentation

MYTHEN detectors

Basic technical data: MYTHEN 1K detector		in Stoe Stadi MP
Sensor	Silicon	
No. strips	1280	19.2° coverage
Strip width [μm]	50	0.015° sampling
Dynamic range [bit]	24	$1:16.8 \times 10^6$
Energy range [keV]	5-40	
Point spread function	1 strip	No blurring
Adjustable energy threshold	Yes	No noise
Readout time [ms]	0.3	22 Hz
Sensor thickness [μm]	320, 450, 1000	Cr, Cu, Mo, Ag

Accuracy in XRPD

1. ***Crystalline samples***

2. ***"Structurally challenged samples"***

Accuracy in XRPD: crystalline samples

1. Instrumental set up

- Cu radiation
- MYTHEN 1K, 1000 µm sensor thickness
- Variable data collection time

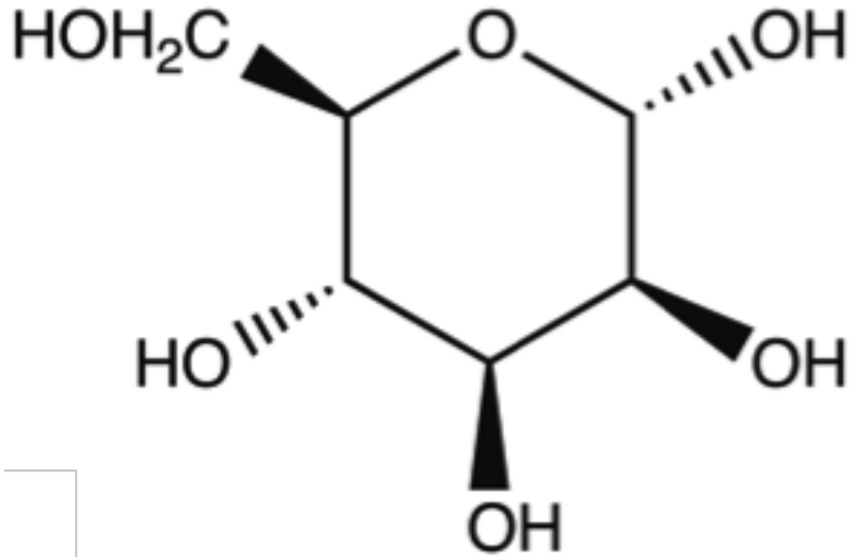
2. Structure determination and refinement

- Level of details
- Accuracy

Accuracy in XRPD: crystalline samples

Test case: D-mannose

- ***Known crystal structure***
  - *Solved from single crystal data*
  - *Z′ = 2 (24 atoms/a.u.)*
  - *A few ambiguities (Hydrogens missing, ADP values)*

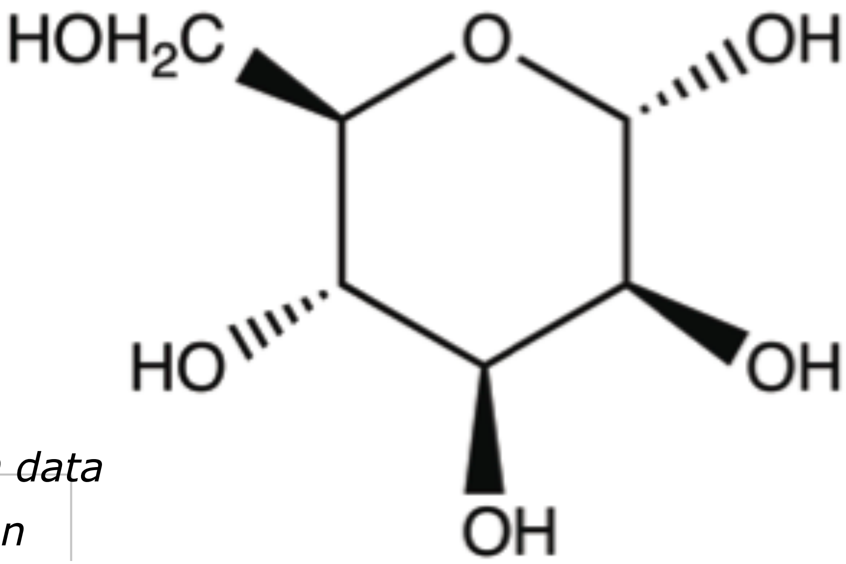


- ***Commercial sample***
  - *Controlled crystallite size*
  - *Uniform morphology*

Accuracy in XRPD: crystalline samples

Test case: D-mannose

- ***Procedure***
  - *Measure XRPD data*
  - *Refine single-crystal model against XRPD data with minimal model bias*
  - *Evaluate results*
    - *Compare models obtained from single-crystal and XRPD data*
    - *independent XRPD evaluation*



Accuracy in XRPD: crystalline samples

Test case: D-mannose

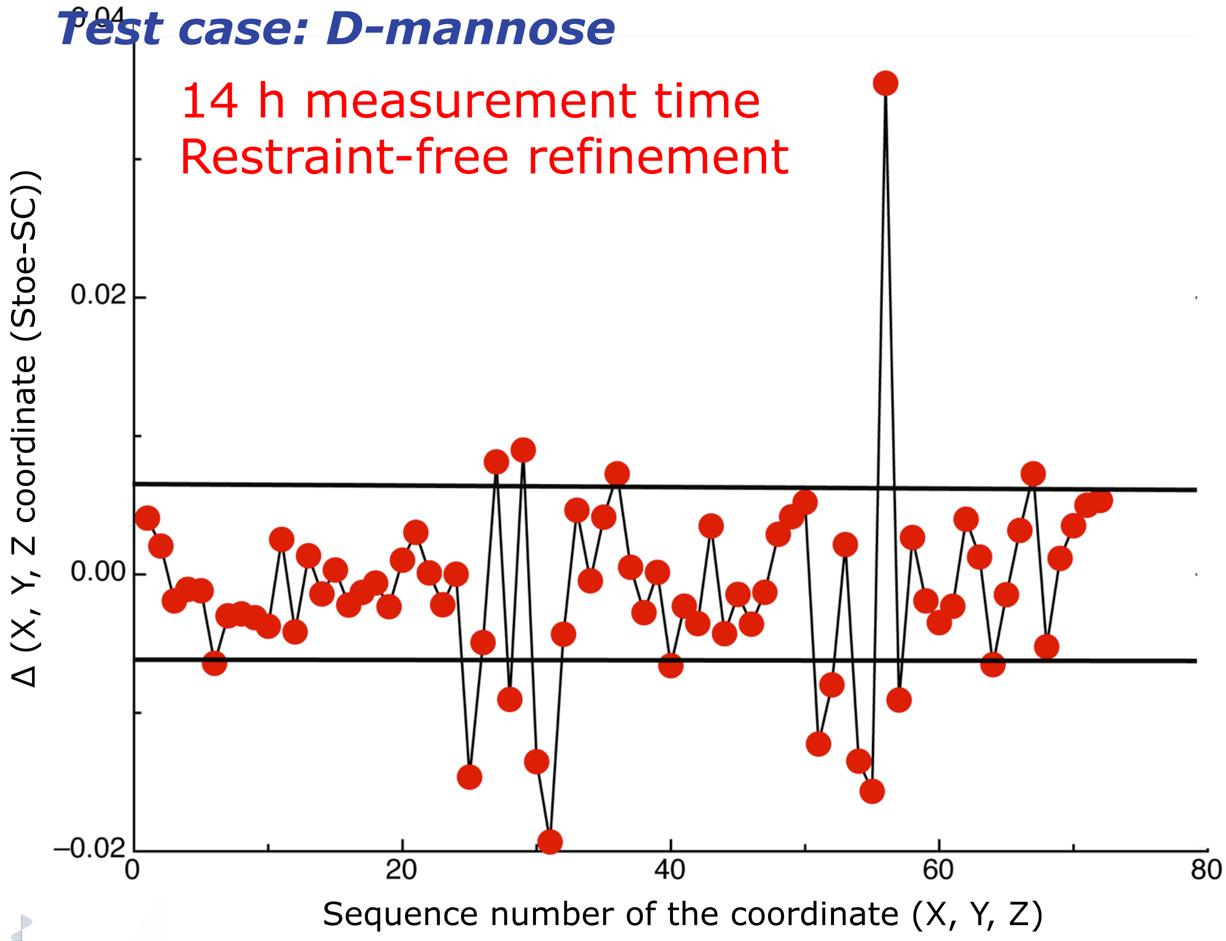
14 h measurement time
Restraint-free refinement

Δ (X, Y, Z coordinate (Stoe-SC))

Sequence number of the coordinate (X, Y, Z)

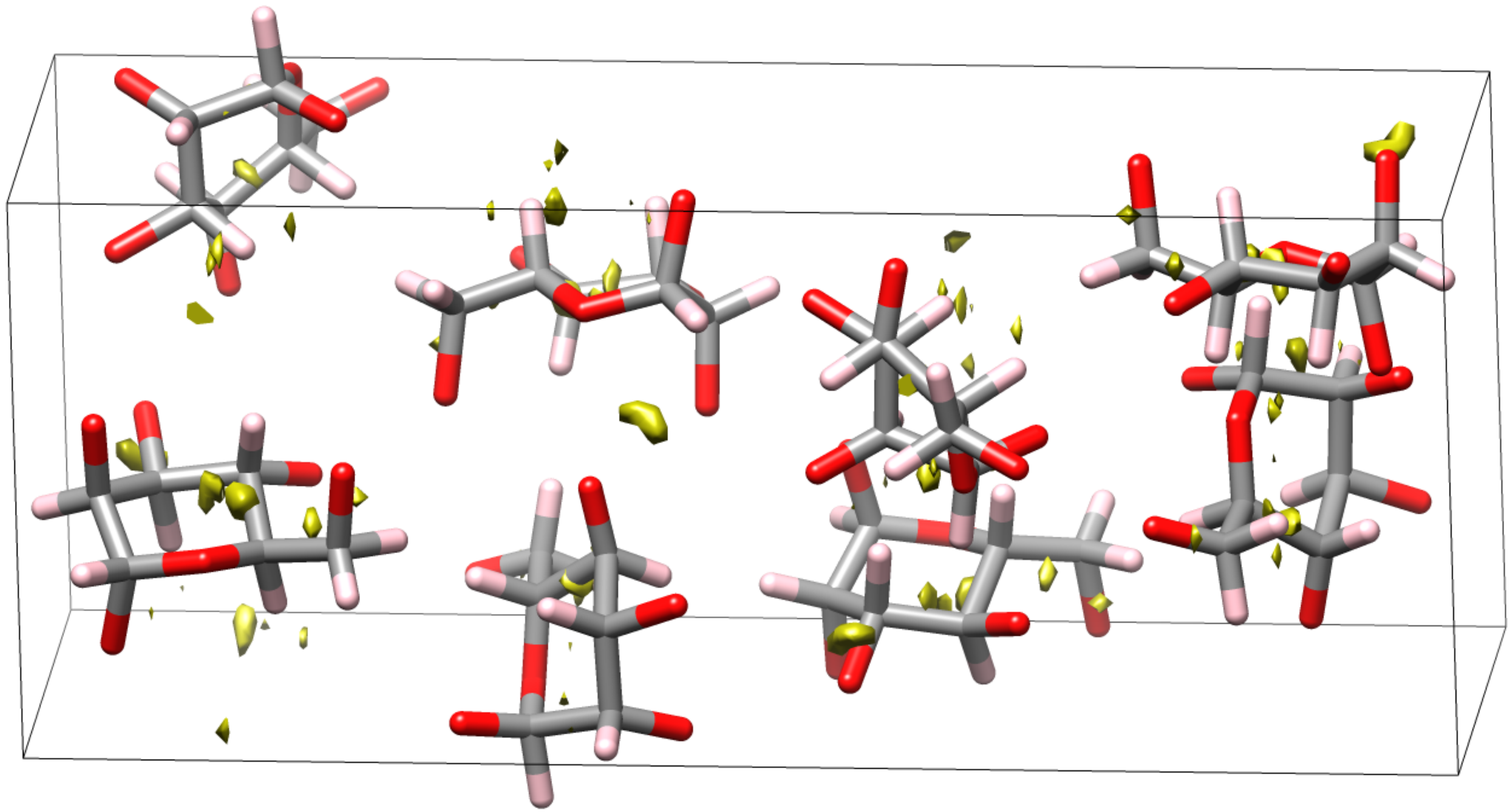
Accuracy in XRPD: crystalline samples

Test case: D-mannose



Accuracy in XRPD: crystalline samples

Test case: D-mannose



Accuracy in XRPD: crystalline samples

Test case: D-mannose[1]

Enhancing accuracy in structural analysis:

- Reducing a model-bias by restraint-free refinement
- Accuracy comparable to single-crystal data
- Fine level of structural details (residual el. densities)
- Evaluation of the success of the refinement *via* diff. Fourier map

[1]Šišak Jung, D.,Hörmann, Ch. Adv. X Ray Anal. 58, in press

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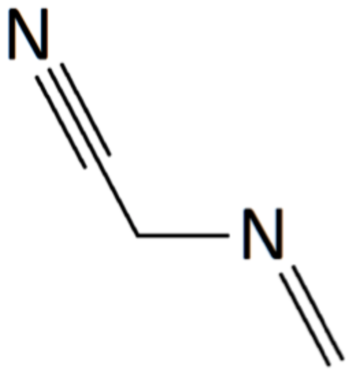
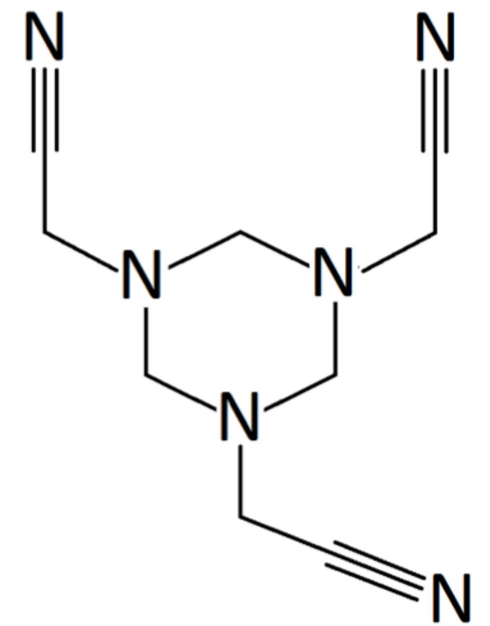
Accuracy in XRPD: crystalline samples

Monomer-trimer ambiguity

- ***Unknown crystal structure***
  - *Monomer, with ability to polymerize*
- ***Commercial sample***
  - *Controlled crystallite size*
  - *Uniform morphology*
  - *Spectroscopic studies*
  - *Name suggests monomeric specie*



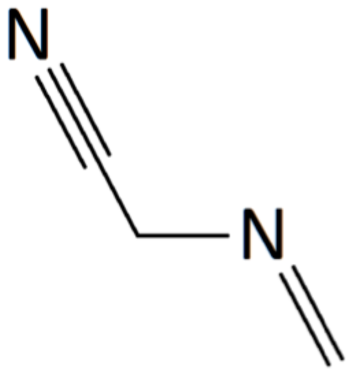


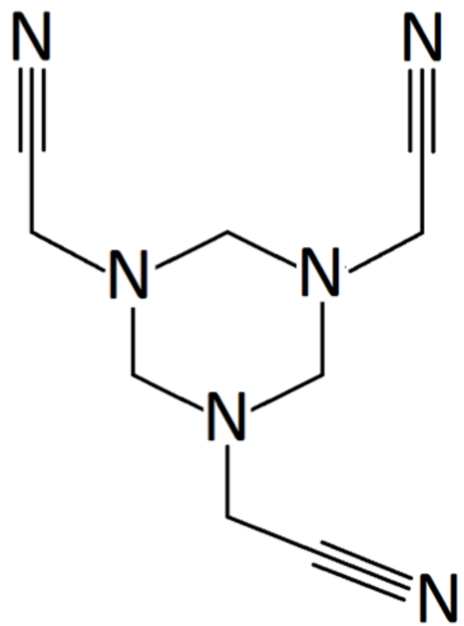
Accuracy in XRPD: crystalline samples

Monomer-trimer ambiguity

- ***Procedure***

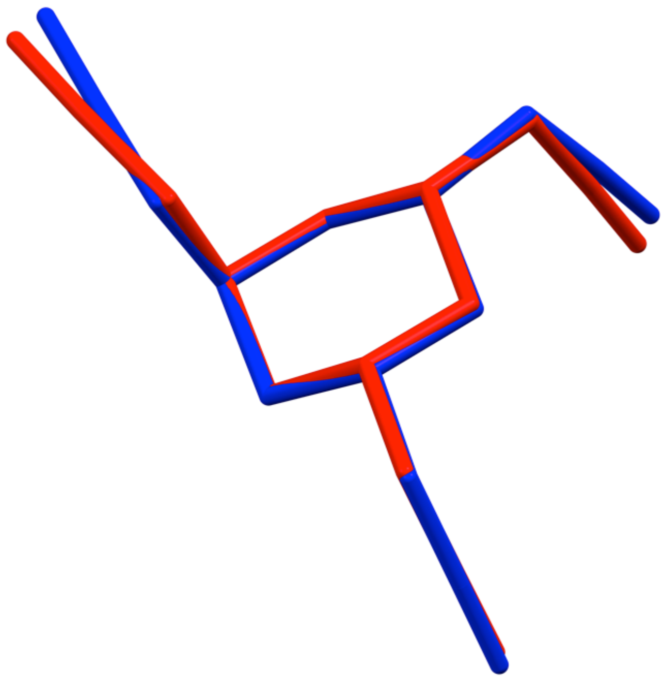
  - *Measure XRPD data*
  - *Construct several models using DFT approach*
  - *Solve the structure using direct-space methods*
  - *Refine the model(s) using variable weights on geometrical restraints*
  - *Evaluate results*
    - *Compare models obtained from DFT and XRPD data*





Accuracy in XRPD: crystalline samples

Monomer-trimer ambiguity[1]



Comparison of the molecular structure obtained from XRPD data (red) and Molecular structure obtained by the DFT optimization of the most stable conformer

[1]Hrenar, T., Kalinovčić, P., Jović, O., Šišak Jung, D., J. Powd. Diffr., proceedings of EPDIC – accepted

Accuracy in XRPD: structurally challenged samples

1. **Problem: local structure with Pair Distribution Function**

2. **Instrumentation setup**

   – Source, Detector

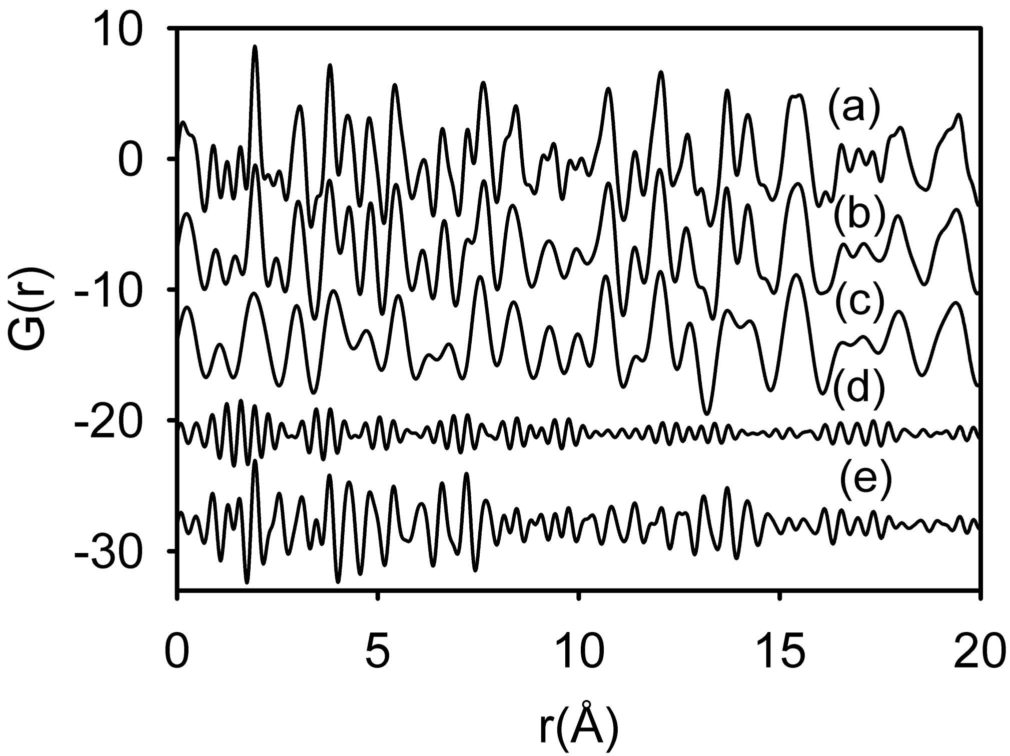
   – Calibration

3. **Data collection and processing**

4. **Accuracy of the results**

Accuracy in XRPD: structurally challenged samples

General considerations: PDF at Australian Synchrotron



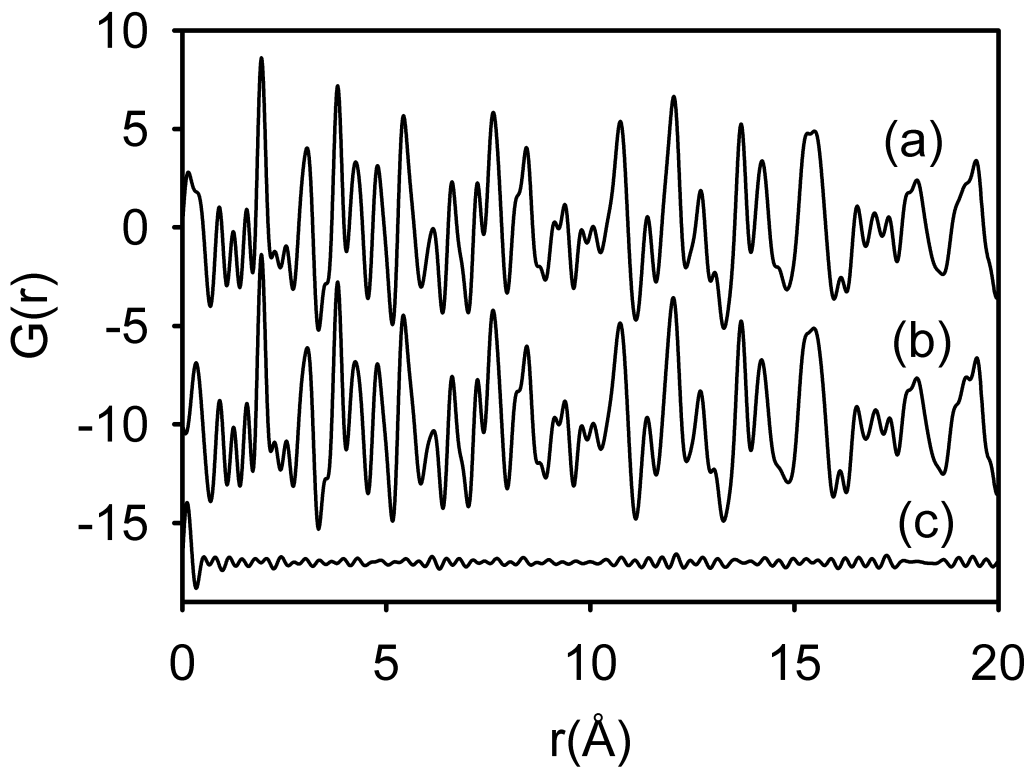
(a) E = 21 keV, 2θ = 149°
(b) E = 21 keV, 2θ = 80°
(c) E = 15.4 keV, 2θ = 149°
(d), (e) difference curves

PDF analysis requires high energy to be used and high angles to be measured

Haverkamp, R.G., Wallwork, K.S. (2009) *J. Synch. Rad.* **16**, 849-856

Accuracy in XRPD: structurally challenged samples

General considerations: PDF at Australian Synchrotron



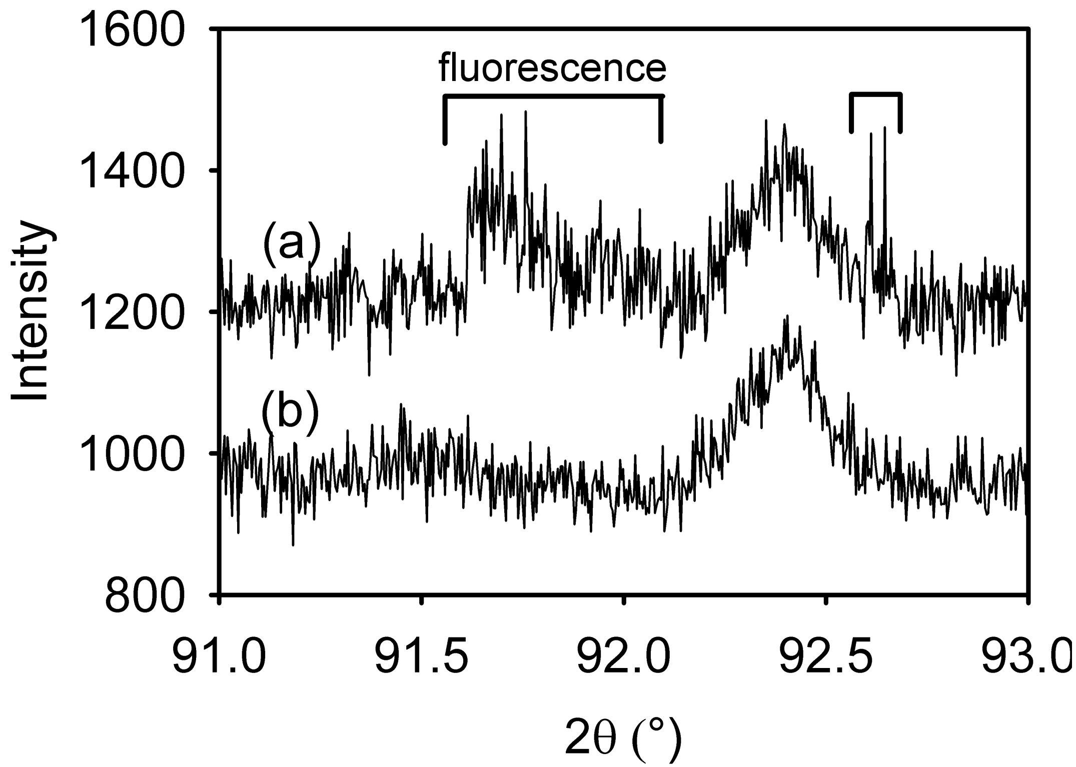
(a) t = 120 s
(b) t = 10 s
(c) Difference curve

PDF analysis does not necessarily require long exposure times

Haverkamp, R.G., Wallwork, K.S. (2009) *J. Synch. Rad.* **16**, 849-856

Accuracy in XRPD: structurally challenged

General considerations: PDF at Australian Synchrotron



(a) Flourescence
(b) Fluorescence suppression

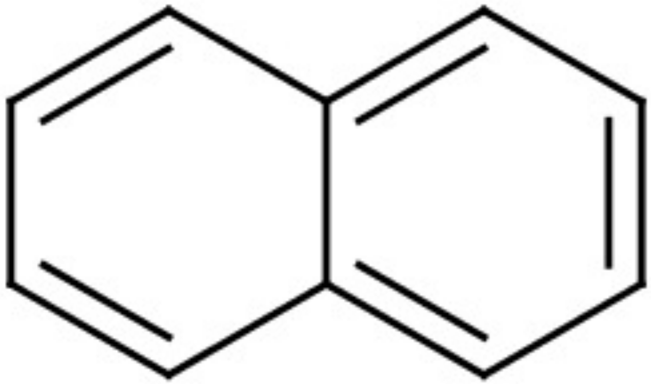
Adjustable energy threshold (MYTHEN) allows for fluorescence suppression

Haverkamp, R.G., Wallwork, K.S. (2009) *J. Synch. Rad.* **16**, 849-856

Accuracy in XRPD: structurally challenged samples

1. Problem: PDF in Stoe Stadi MP instrument

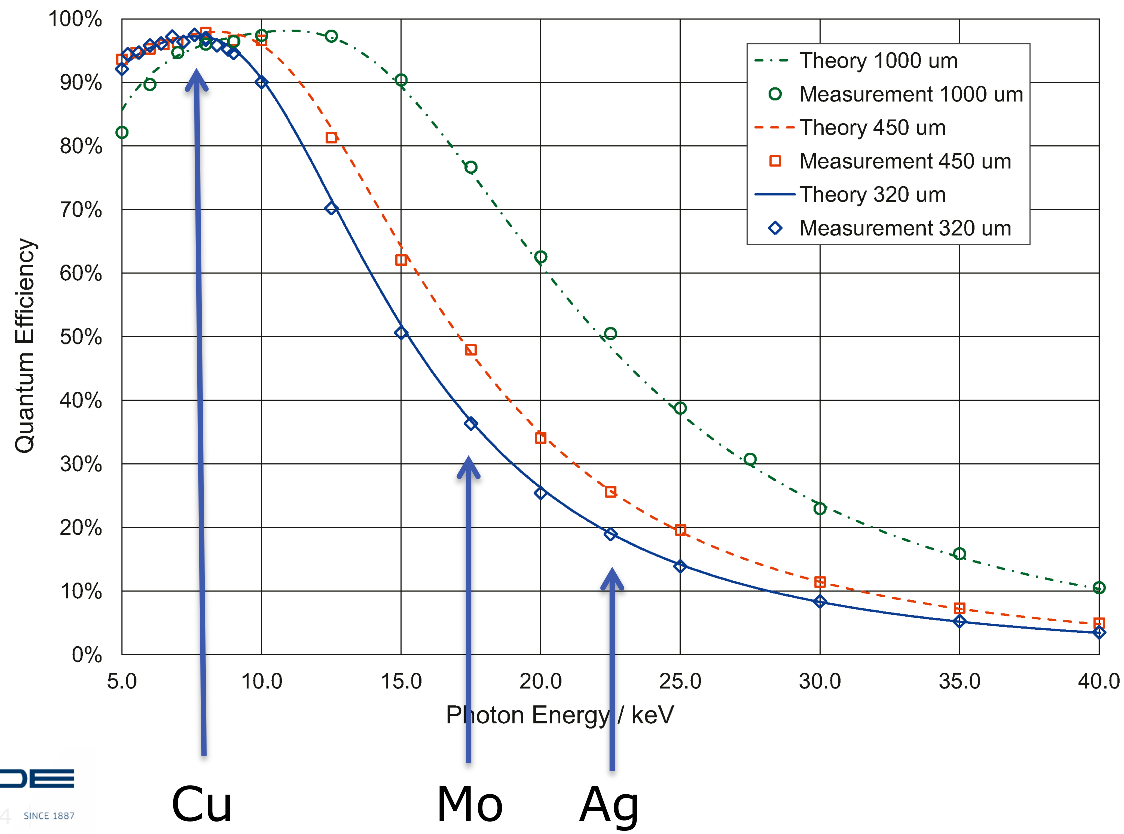
- *Naphtalene sample*



Accuracy in XRPD: structurally challenged samples

2. Instrumentation setup

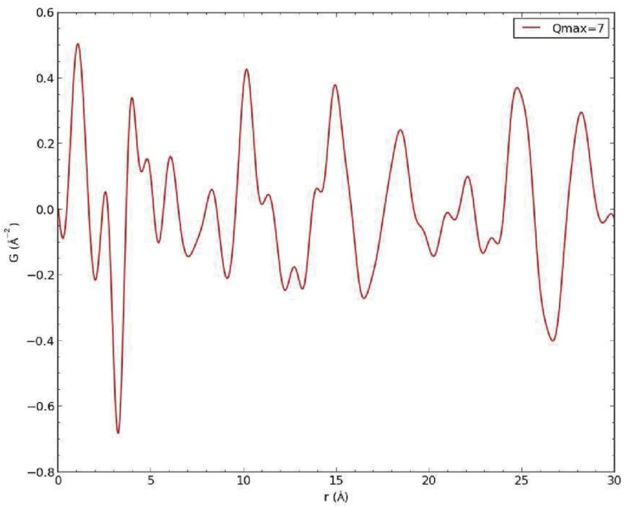
– *Optimizing instrumental set up: Source, Detector*



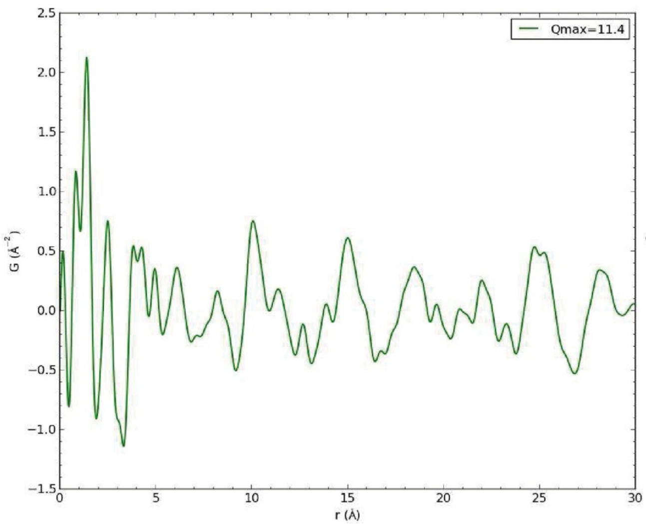
Accuracy in XRPD: structurally challenged samples

2. Instrumentation setup

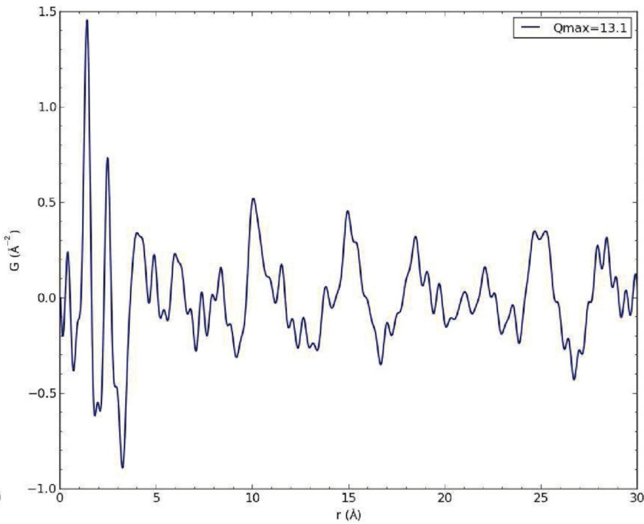
- *Source, Detector*
- *Calibration: proper trimming and flat-field files*



G(r), Cu



G(r), Mo



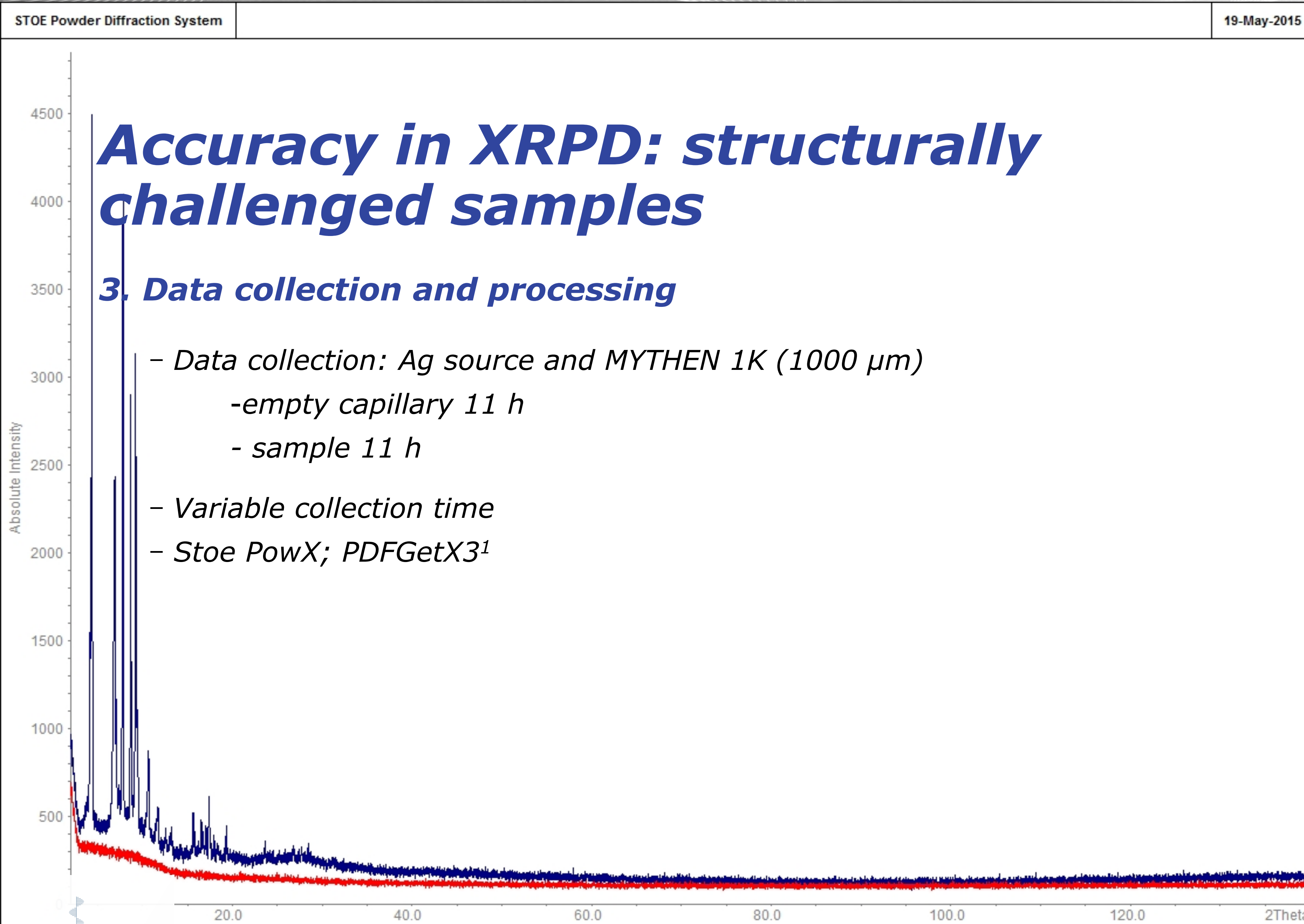
G(r), Ag

PDFs calculated for the data collected with different sources. Combination of Ag-source and MYTHEN 1K (1000 µm) is the best choice for the measurement.

Accuracy in XRPD: structurally challenged samples

3. Data collection and processing

- Data collection: Ag source and MYTHEN 1K (1000 µm)
  - -empty capillary 11 h
  - - sample 11 h
- Variable collection time
- Stoe PowX; PDFGetX3[1]



[1] Juhas, P., Davis, T., Farrow, C.L. and Billinge, S .J. L., *J. Appl. Cryst*. **2013**, *46*, 560-566.

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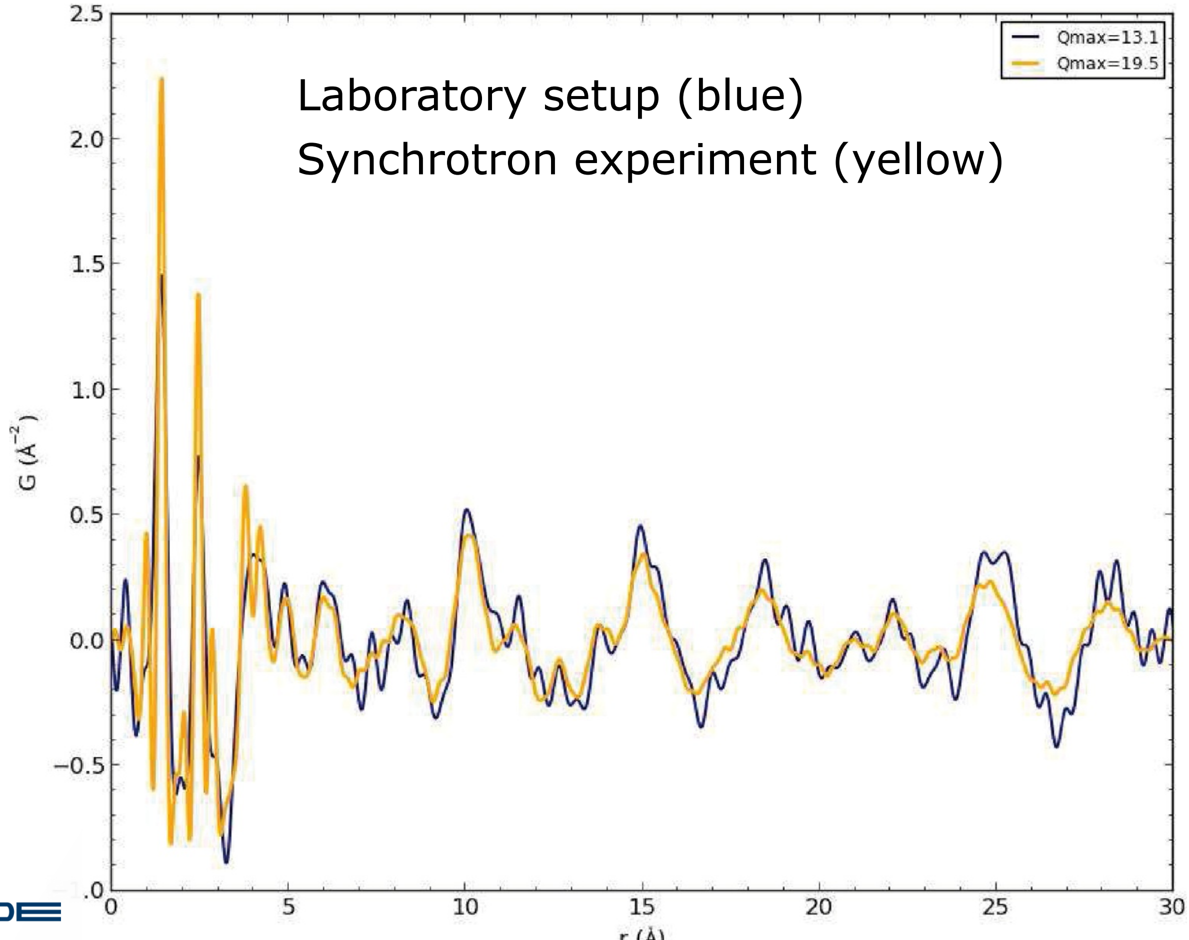
Accuracy in XRPD: structurally challenged samples

4. Accuracy of the results



New opportunities for new challenges

1. MYTHEN2

2. PILATUS3 CdTe

New opportunities for new challenges

1. MYTHEN2

1. Higher frame rates

2. Symmetric&compact design

3. Lower price

New opportunities for new challenges

2. PILATUS3 CdTe

1. 2D detector
2. Energy range 8 – 100 keV
3. 500 Hz

PILATUS3 X CdTe - Hard X-ray detection without compromise

A few guidelines

1. **Never trust a chemist**

2. **Define what it is goal of your analysis**

3. **Think carefully about your instrument set up**

4. **Make sure you understand details**

5. **High accuracy in structure analysis can be obtained with laboratory XRPD data:**
   - *Ab initio structure determination and restraint-free refinement reduces model bias*
   - *Results can be comparable to single-crystal case*
   - *XRPD data is sensitive to fine structural details*
   - *Collecting laboratory XRPD data doesn't take long -> avoid unnecessary radiation damage!*

6. **Ask your diffractometer provider**

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Thank you for your attention!

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