Synchrotron XRPD

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Outlook

I. LoD and LoQ

II. SR-XRPD: is a synchrotron source enough for trace analyses?

III. Dose-controlled SR-XRPD

IV. Qualitative and quantitative trace analyses of pharmaceuticals: requirements/difficulties

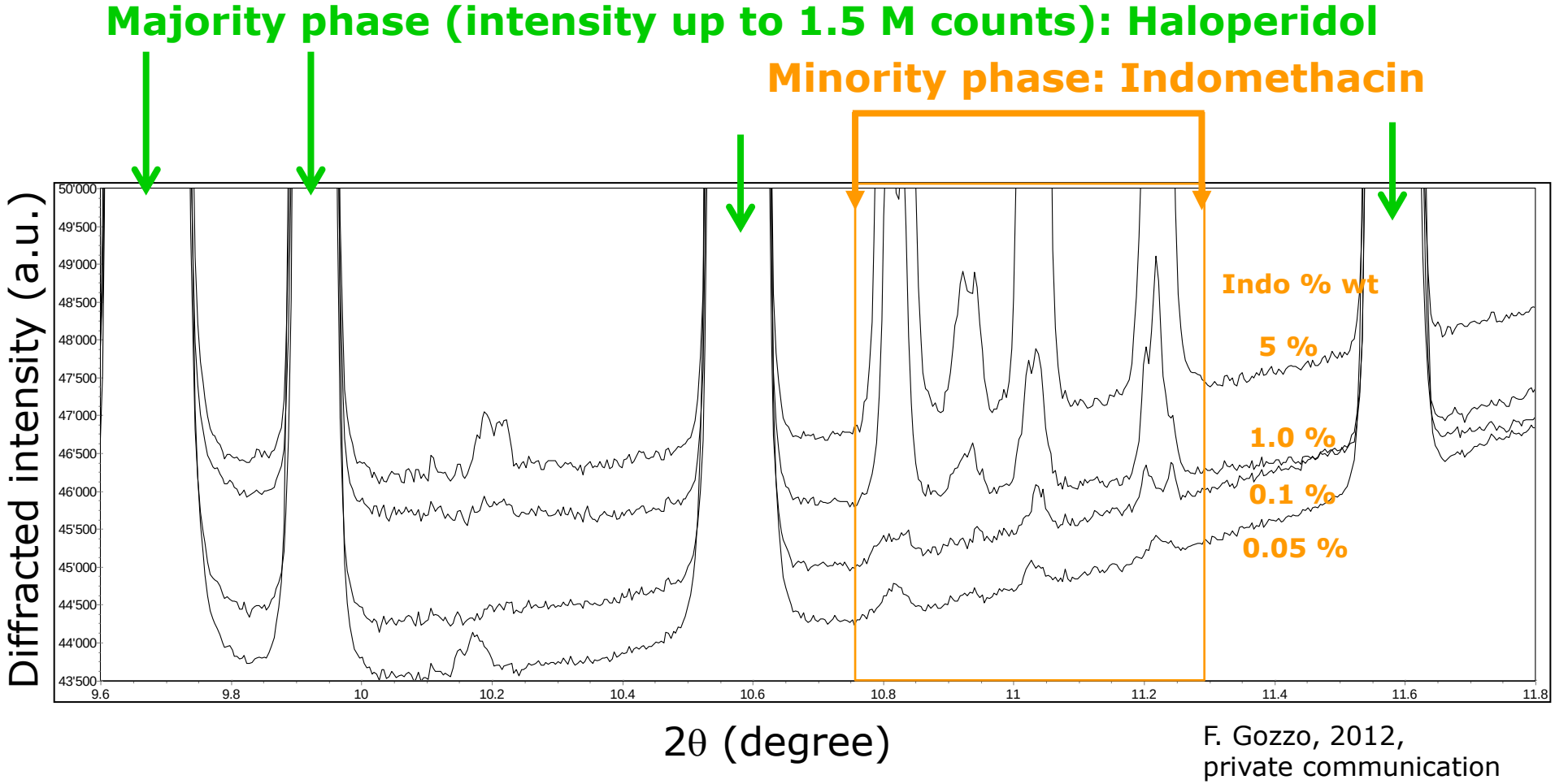
Quantitative Phase Analysis (QPA)

QPA refers to the ability of quantitatively state the abundance of the different phases that constitute a mixture.

Why is this relevant?

- Polymorphic purity: detect and quantify unwanted polymorphic forms in both drug substance and drug product
  - Level of Detection (LoD)
  - Level of Quantitation (LoQ)
- Assess the polymorphic composition in drug substance and product
- In formulated materials, the API/excipients relative proportion is paramount and needs to be kept under control
- Degree of Crystallinity in amorphous/crystalline mixtures

QPA of a binary API physical mixtures with fast SR-XRPD



F. Gozzo, 2012,
private communication

Aggressive LoD/LoQ require advanced instrumentation often combined with advanced/unconventional methodologies

- An intense photon beam for enhanced counting statistics
- Adequate angular (FWHM) resolution
- Adequate S/B and S/N

Aggressive LoD/LoQ require advanced instrumentation often combined with advanced/unconventional methodologies

Synchrotron XRPD

Our 3 ingredients for state-of-the-art SR-XRPD

A. An efficient synchrotron facility and beamline optics

B. State-of-the-art diffractometers

C. Outstanding detection systems

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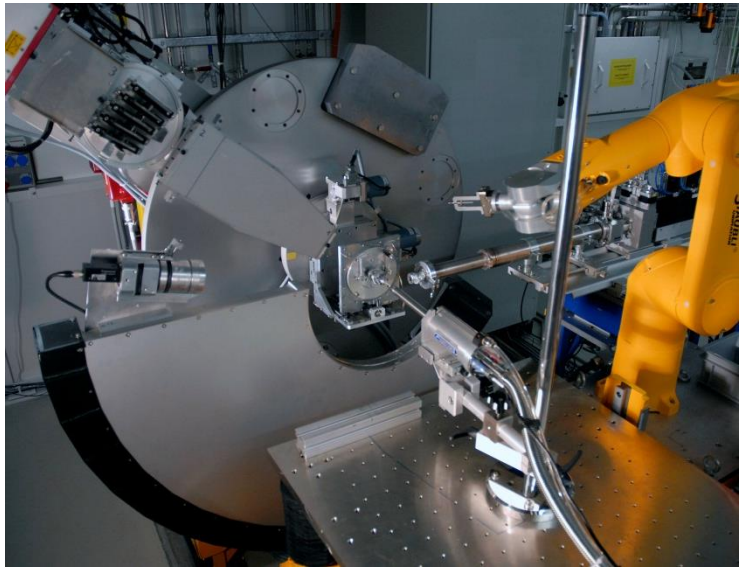

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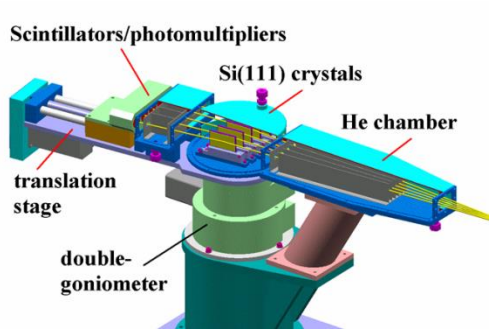
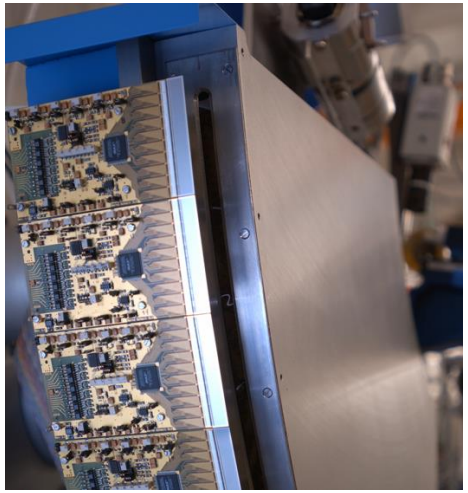
Hodeau et al, 1998



Multicrystal Analyser

Schmitt et al, 2003,
Bergamaschi, Schmitt et al, 2010



MYTHEN II

A. Synchrotron facility and beamline optics

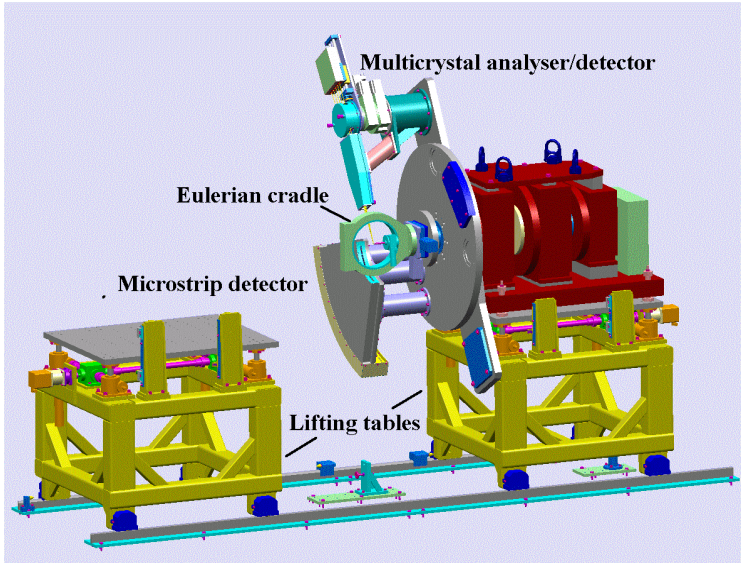
Properties:

- High Spectral Brightness: 10^{12}-10^{15} photons/sec in small beams (μm^2 to mm^2)
- Tuneable and monochromatic photon energy
- Polarization
- Time structure
- Coherence

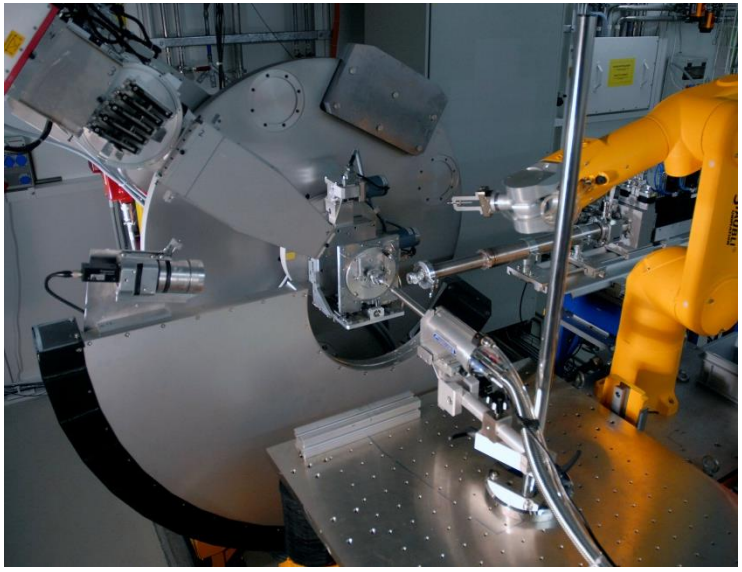
Benefits

- Efficient data collection, high statistics
- Time-resolved in-situ non ambient XRD
- Photon-consuming experimental set ups
- Penetration of highly absorbing materials
- Variable d-spacing resolution
- large unit cells (many reflections at very low angles)
- XRD near absorption edges (anomalous dispersion)

B. State-of-the-art diffractometers



Swiss Light Source-Materials Science beamline
Powder Diffraction station



Properties:

Resolution: 1 arcsec

Accuracy: ±2 arcsec

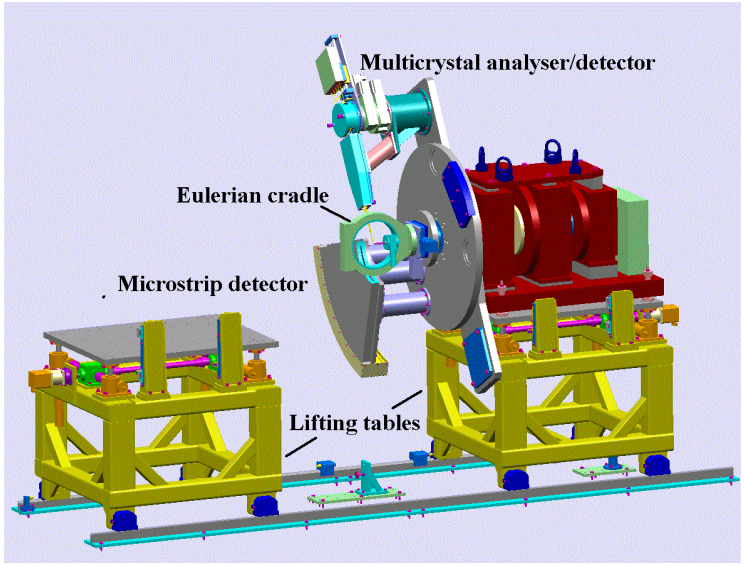
Precision: ±1 arcsec

Large working space and flexibility

Benefits

- Great mechanical stability
- Highest flexibility to accommodate all kinds of sample environments

B. State-of-the-art diffractometers



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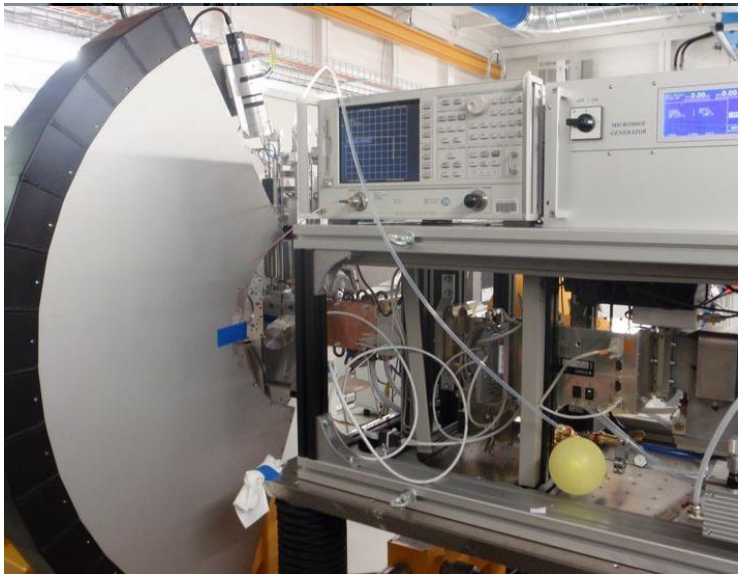

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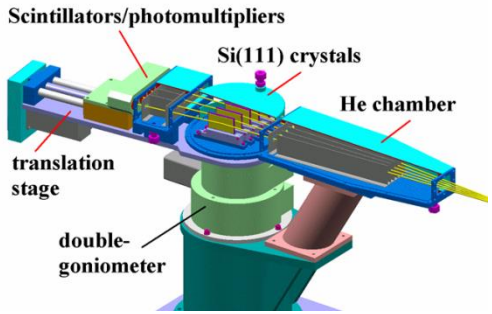


Multicrystal Analyser

Hodeau et al, 1998

Properties:

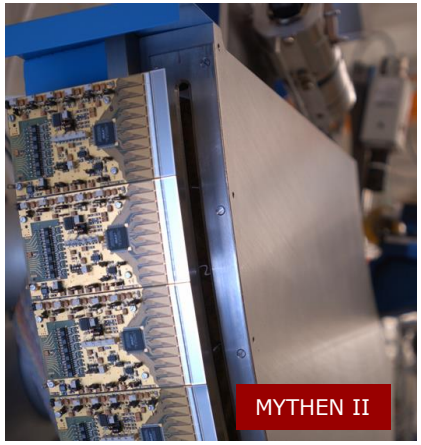
- Angular selection of diffracted beam
- Fluorescence suppression

Benefits:

- Ultra-high resolution (better than 0.003°)
- Angular resolution independent of sample dimension and position
- Independence of transparency effect
- High S/N and S/B

Trade-off:

Long measurements (min to hours) → radiation damage



Schmitt et al, 2003,
Bergamaschi, Schmitt et al, 2010

Properties:

- Solid state modular microstrip detector
- Large dynamic range (24 bits)
- Single photon counting read out
- Fluorescence suppression
- Very fast acquisition times (subsec)

Benefits:

- 120° angular coverage at SLS
- High d-spacing resolution
- 0.004° inherent angular resolution
- Capable of simultaneously detecting strong and weak signals
- Sub-sec time resolution XRPD for in-situ kinetic studies

Trade-off:

- Resolution limited by sample dimension
- Sensitive to the uniformity of both the beam intensity spatial distribution and the powder distribution in sample holder, granularity, statistical orientation

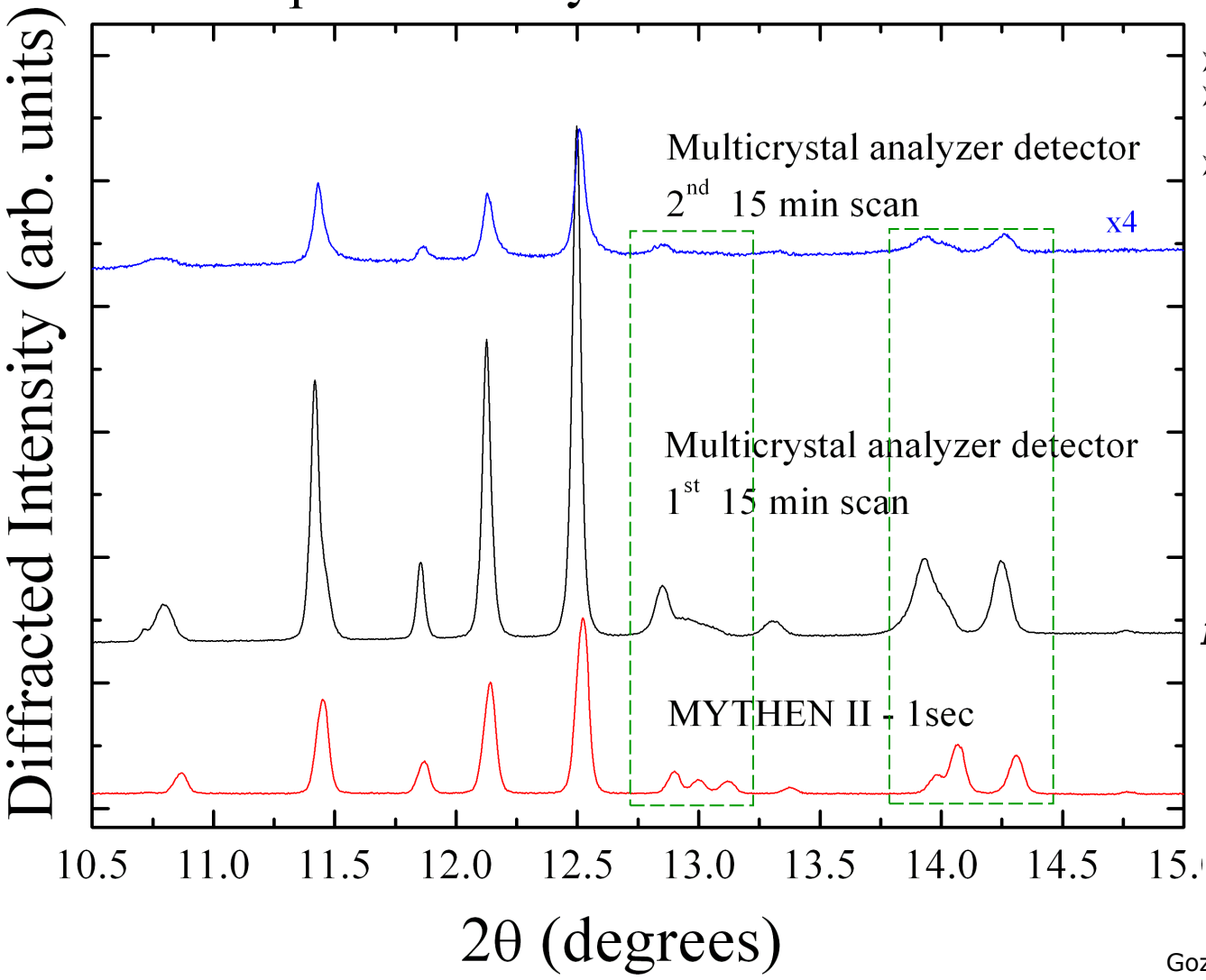
Minimization of radiation damage control with fast and dose-controlled SR-XRPD

- **Radiation Damage** is the **alteration of the structural and chemical properties** of the material under investigation induced by its exposure to electromagnetic radiation. It is **dose** and **energy** dependent
- In XRD patterns we observe shift (usually anisotropic) and broadening of reflections and their progressive disappearance → it usually undermines the success of structural solution

The effect is very serious at 3rd generation synchrotron facilities and affects the study of organic compounds, in particular pharmaceuticals

Our high-resolution, fast and dose controlled SR-XRPD measurements have opened a new gate to the systematic structural analyses of organic compounds!

Bupivacaine Hydrochloride - form D



- 1 mm capillary,
- Mythen data at 50% reduced intensity
- No radiation damage up to 3min

Large counting statistics in subsec acquisition times

In-situ kinetic studies of organic compounds!

Gozzo F. , 2008
See: Bergamaschi et al, J. Synchrotron Rad. (2010). 17, 653–668

With pharmaceuticals, radiation damage control is particularly critical when aiming at very low LoD and LoQ

What are the requirements/difficulties related to qualitative and quantitative trace analyses in pharmaceuticals?

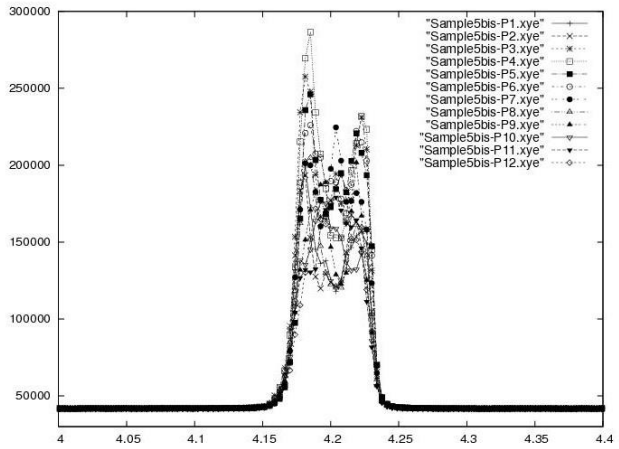
Trace analysis → signal from minority phase extremely weak

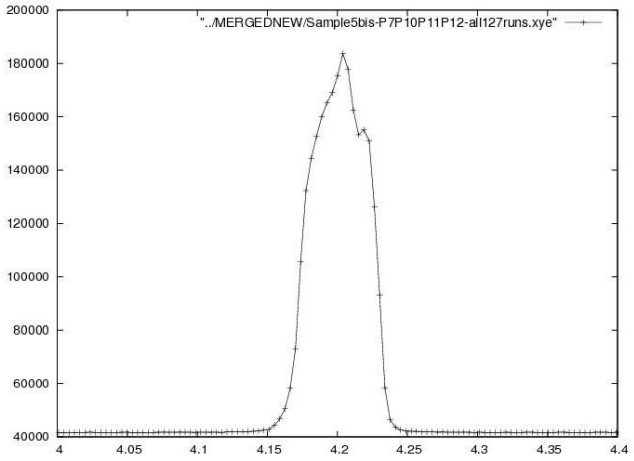
- Require unusual counting statistics (orders of hundreds of million of counts) → Is this enough?
- Reduced non-statistical noise → single photon counting detectors, reduced background, accurate flat field calibrations, tunable photon energy

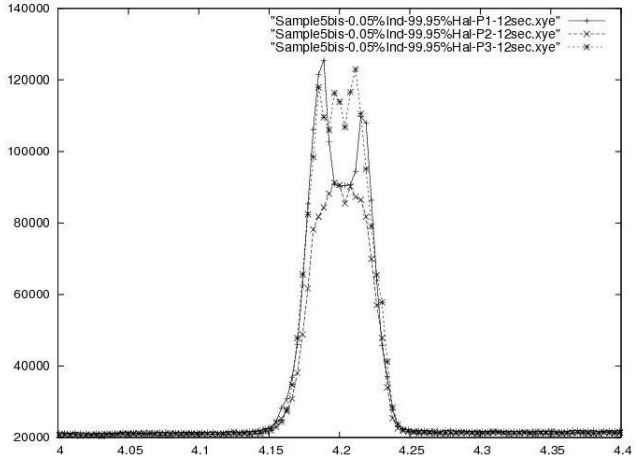
Trace analysis → dilution of the minority phase

- Particle Statistics, often combined with Preferential Orientation
- Peak line shape with position sensitive detectors

API mixture: 99.95% Haloperidol + 0.05% Indomethacin







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- Particle Statistics, often combined with Preferential Orientation
- Peak line shape with position sensitive detectors
- 'anisotropic' shifts of minority phase peaks

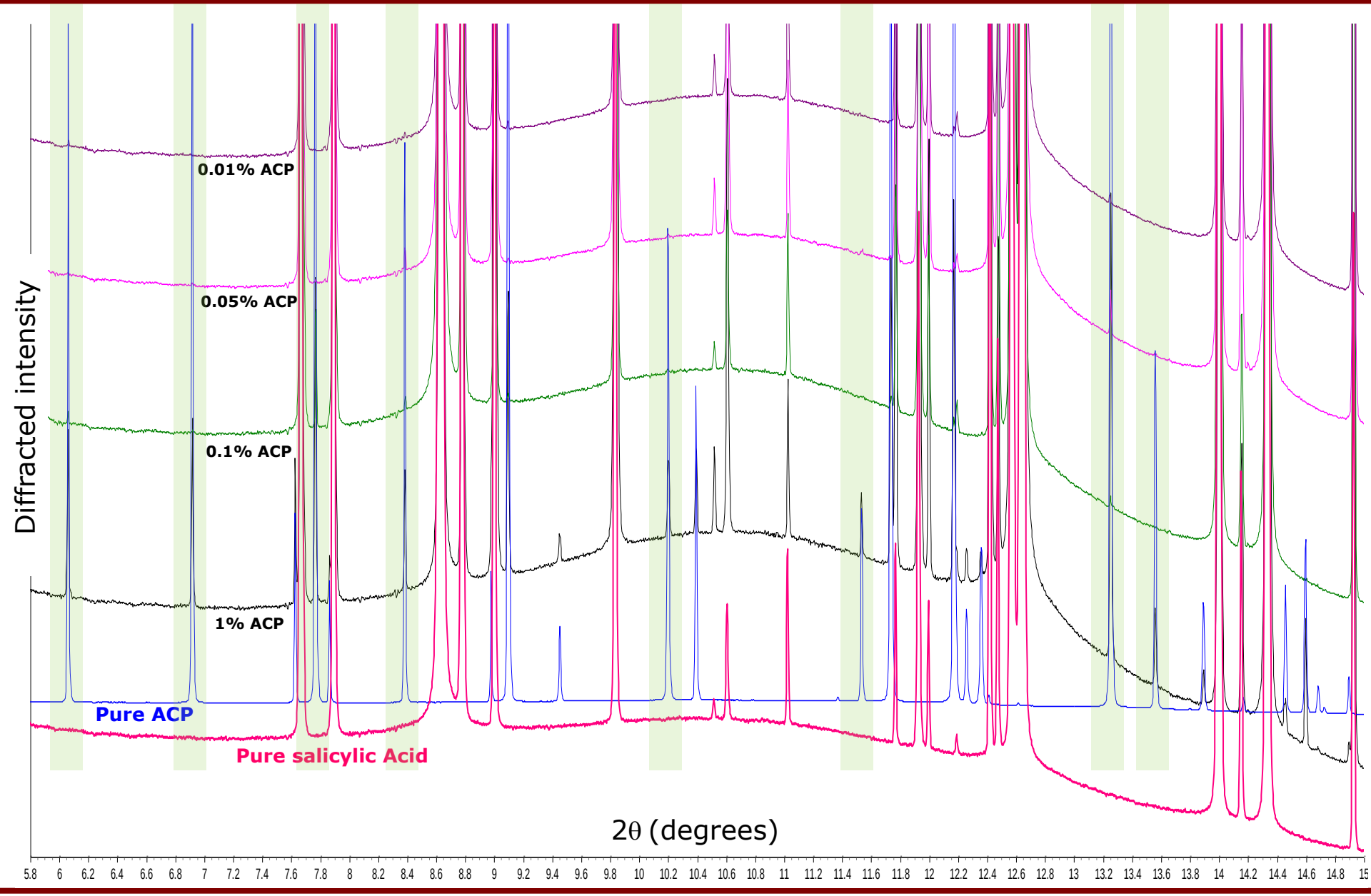
- Much larger volumes of powder should be analyzed → in transmission geometry with capillaries, larger diameter → reduced angular (FWHM) resolution
- Sample spun for improved orientation statistics
- Powder mechanical comminution (not always possible!)

Tuning the synchrotron optics to improve LoD and LoQ

(R&D work in progress)

Our pilot experiments have demonstrated LoD down to 0.01% in *ad-hoc* API mixtures

Unconventional beam optics



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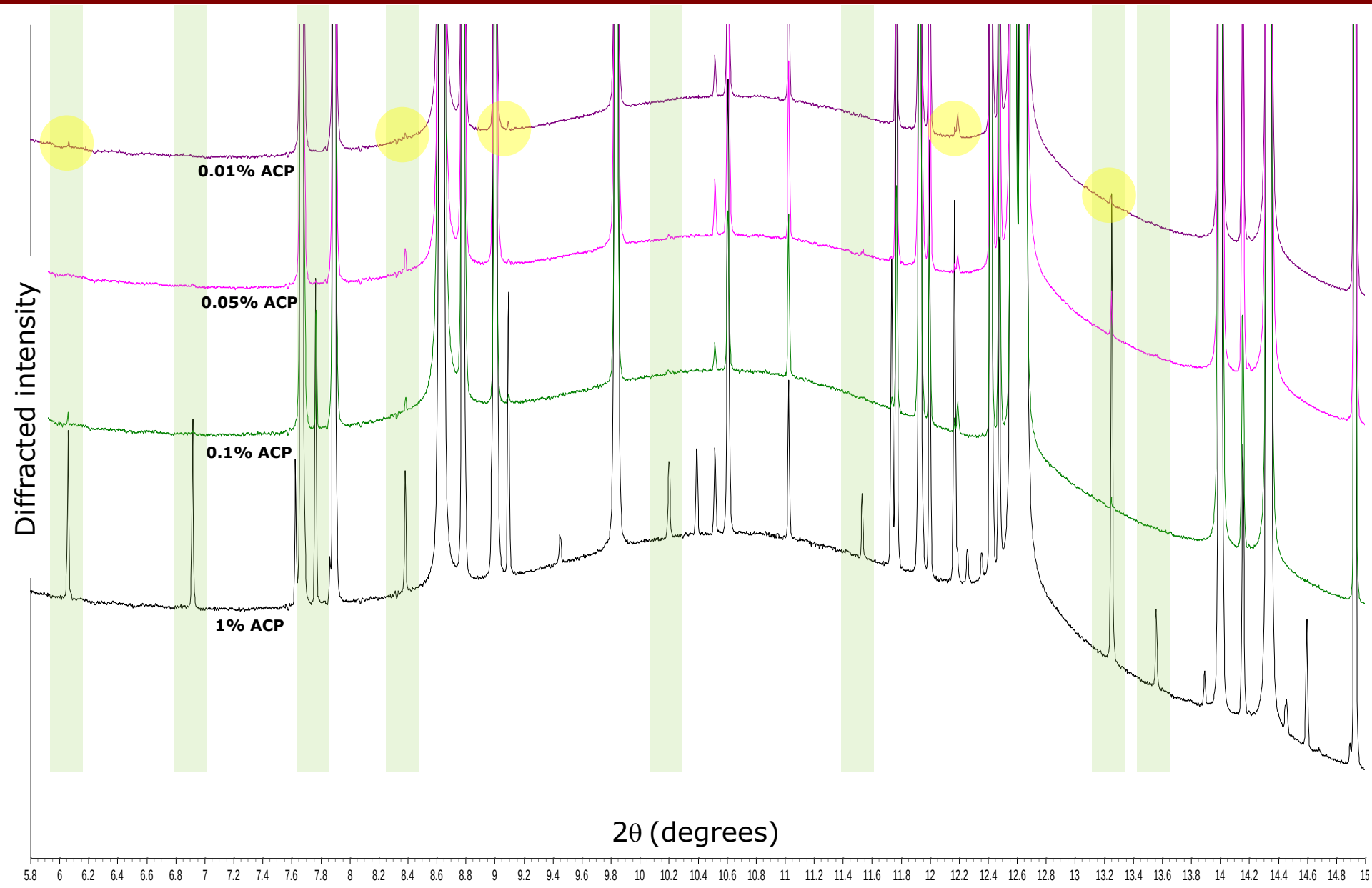

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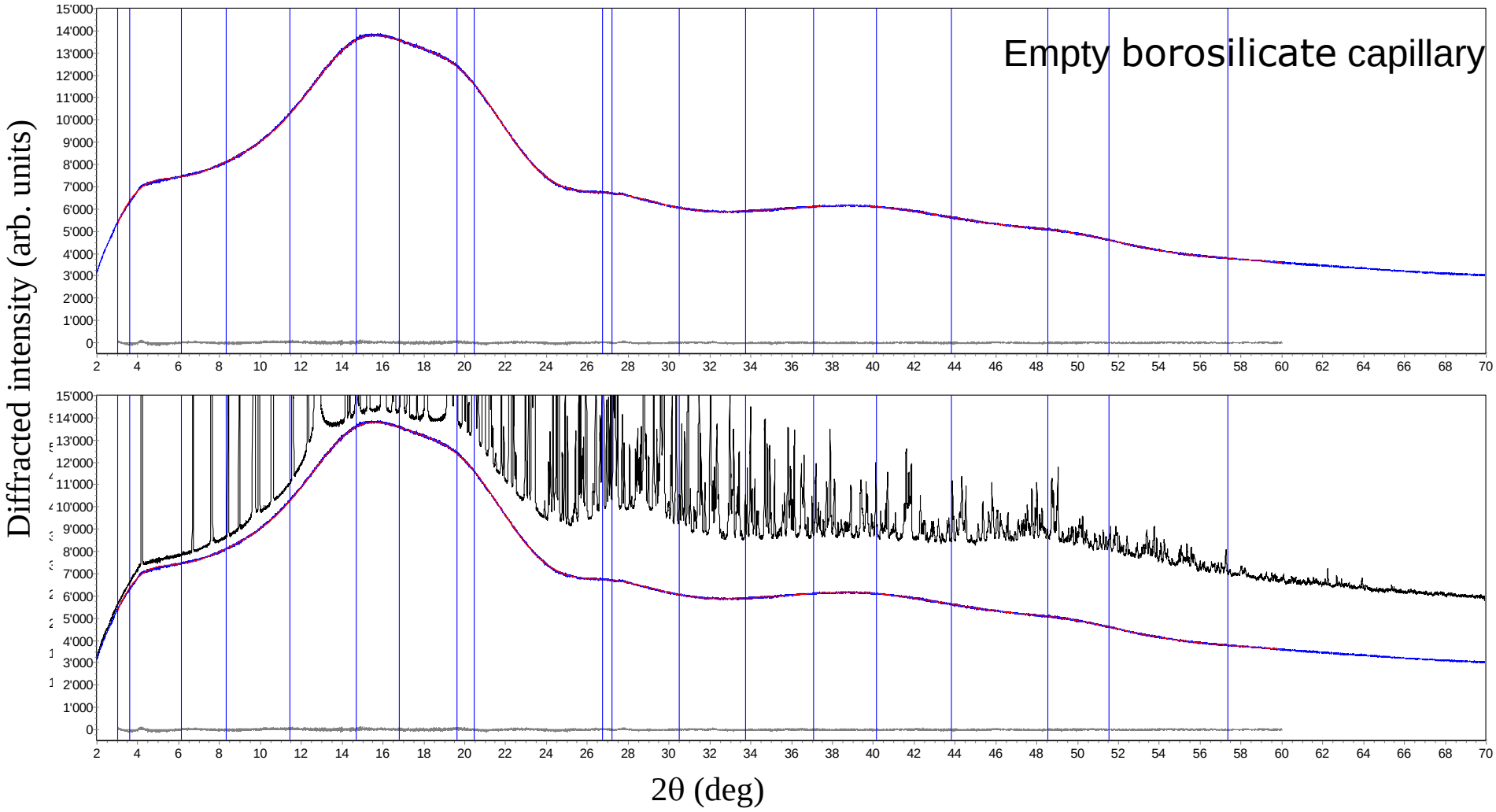
The accuracy of the quantitative phase analysis strongly depends on:

- The quality of the refinement models
- How close to the correct values of all these refinement parameters we start the quantitative analysis

When dealing with quantification of traces:

- All contributions in the diffraction pattern should be appropriately described to drastically reduce the number of refined parameters and the correlations of refined parameters during QPA
- The minority phase parameters do not support refinement during QPA analysis and should not be refined

A good description of the extrinsic background with a limited number of parameters



Thanks for your kind attention