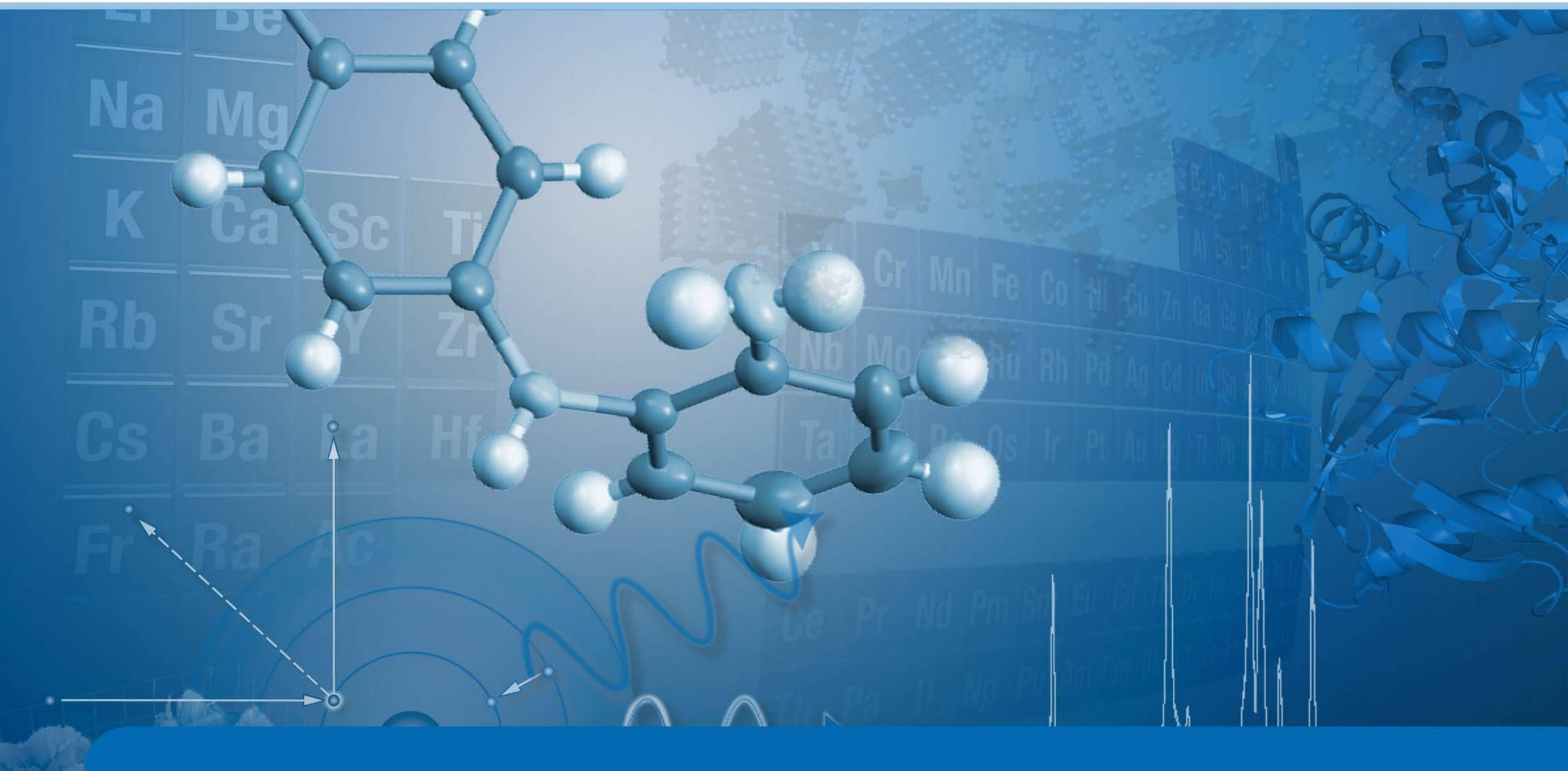
Practical Assessment of Merits of Methods for QPA

Arnt Kern, Ian Madsen, Nicola Scarlett



This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

Sponsored by The International Centre for Diffraction Data

Suggested Reading
Round Robins

Rietveld Refinement Round Robin (http://www.iucr.org/iucr-top/comm/cpd/)

- Hill, R.J. (1992): "*Rietveld Refinement Round Robin. I. Analysis of Standard X-ray and Neutron Data for* $PbSO_4$". J. Appl. Cryst., 25, 589-610
- Hill, R.J. & Cranswick, L.M.D (1994): "*Rietveld Refinement Round Robin. II. Analysis of Monoclinic* ZrO_2". J. Appl. Cryst., 27, 802-844

QPA Round Robin (http://www.iucr.org/iucr-top/comm/cpd/)

- Madsen, I.C. et al. (2001): "*Outcomes of the International Union of Crystallography Commission on Powder Diffraction Round Robin on Quantitative Phase Analysis: samples 1a to 1h*". J. Appl. Cryst., 34, 409-426
- Scarlett, N.V.Y. et al. (2002): "*Outcomes of the International Union of Crystallography Commission on Powder Diffraction Round Robin on Quantitative Phase Analysis: samples 2, 3, 4, synthetic bauxite, natural granodiorite and pharmaceuticals*". J. Appl. Cryst., 35, 383-400

Biannual "Reynold's Cup" series (http://www.clays.org/SOCIETY%20AWARDS/RCintro.html)

Quantitative Rietveld Phase Analysis of Pharmaceuticals"

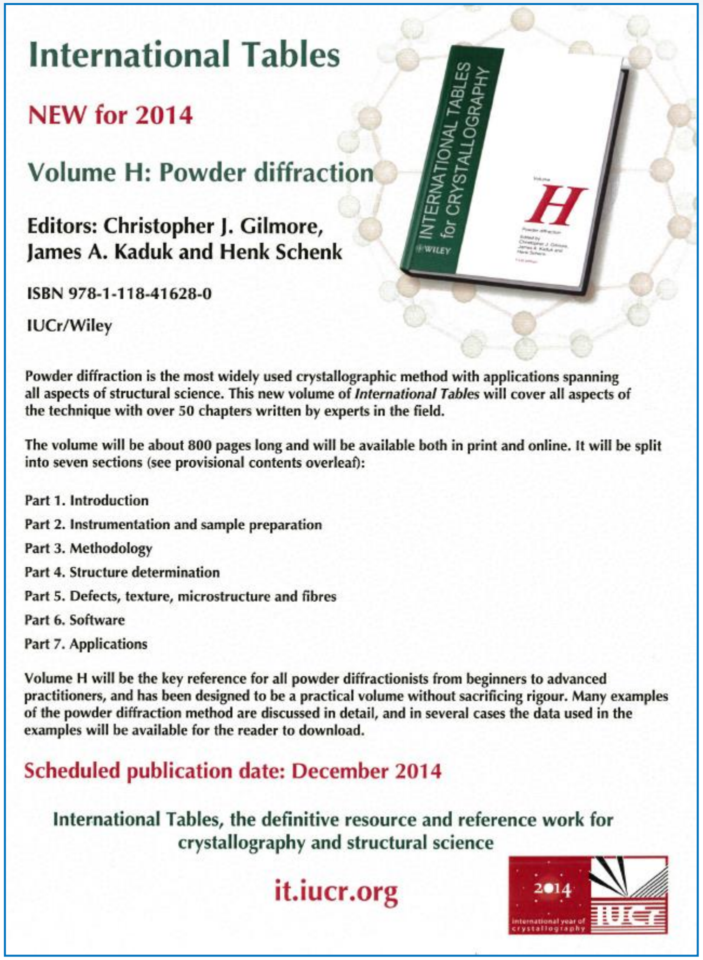
- Fawcett T.G., Needham, F., Faber, J.N. & Crowder, C.E. (2010): "*International Centre for Diffraction Data Round Robin on Quantitative Rietveld Phase Analysis of Pharmaceuticals*". Powder Diffraction, 25 (1), 1-8

Suggested Reading
Recent Reviews

Quantitative phase analysis

- Madsen, I.C. and Scarlett, N.V.Y. (2008)
  Quantitative Phase Analysis
  In "Powder Diffraction: Theory and Practice." Dinnebier, R.E. and Billinge, S.J.L., Editors. The Royal Society of Chemistry: Cambridge, UK, 582 pages.
- Madsen, I.C., Scarlett, N.V.Y. and Kern, A. (2011)
  Description and survey of methodologies for the determination of amorphous content via X-ray powder diffraction.
  Z. Krist., 226, 944-955.
- Kern, A., Madsen, I.C. and Scarlett, N.V.Y. (2012)
  Quantifying amorphous phases.
  Uniting Electron Crystallography and Powder Diffraction.
  Editors: Kolb, U., Shankland, K., Meshi, L., Avilov, A. & David, W.
  Springer, 434 pages.
- Madsen, I.C. and Scarlett, N.V.Y., Riley, D.P. and Raven, M.D. (2012)
  Quantitative Phase Analysis using the Rietveld Method
  In "Modern Diffraction Methods", Mittemeijer, E.J. and Welzel, U., Editors. Wiley-VCH, 554 pages.
- Madsen, I.C., Scarlett, N.V.Y. and Webster, N.A.S. (2012)
  Quantitative phase analysis.
  Uniting Electron Crystallography and Powder Diffraction.
  Editors: Kolb, U., Shankland, K., Meshi, L., Avilov, A. & David, W.
  Springer, 434 pages.

Suggested Reading
International Tables Volume H



International Tables

NEW for 2014

Volume H: Powder diffraction

Editors: Christopher J. Gilmore,
James A. Kaduk and Henk Schenk

ISBN 978-1-118-41628-0

IUCr/Wiley

Powder diffraction is the most widely used crystallographic method with applications spanning all aspects of structural science. This new volume of *International Tables* will cover all aspects of the technique with over 50 chapters written by experts in the field.

The volume will be about 800 pages long and will be available both in print and online. It will be split into seven sections (see provisional contents overleaf):

Part 1. Introduction
Part 2. Instrumentation and sample preparation
Part 3. Methodology
Part 4. Structure determination
Part 5. Defects, texture, microstructure and fibres
Part 6. Software
Part 7. Applications

Volume H will be the key reference for all powder diffractionists from beginners to advanced practitioners, and has been designed to be a practical volume without sacrificing rigour. Many examples of the powder diffraction method are discussed in detail, and in several cases the data used in the examples will be available for the reader to download.

Scheduled publication date: December 2014

International Tables, the definitive resource and reference work for crystallography and structural science

it.iucr.org

Part 2. Instrumentation and sample preparation

- *Instrumentation - laboratory X-rays*
  (A. Kern)
- ...
- *Sample preparation*
  (P. Whitfield and A. Huq)

Part 3. Methodology

- ...
- *Quantitative phase analysis*
  (I. Madsen, N. Scarlett, R. Kleeberg and K. Knorr)

Quantitative Phase Analysis by XRD
Classification

Methods described in this study

- Single peak method
- Whole pattern methods
  - Traditional Rietveld method
  - Internal Standard method
  - External Standard method
  - PONKCS method
  - Degree of Crystallinity (DOC)

Quantifying Amorphous Phases
Introduction

- Mathematical basis of quantitative phase analysis (QPA) is well established. Methods for QPA
  - are mature, extensively covered in literature, and enabled in many software packages
  - are the same for QPA of crystalline and amorphous content

- Amorphous content can be difficult to quantify
  - Intensity contribution to diffraction patterns is not always evident, especially at low concentrations
  - Broad diffraction halos resulting in an increased peak overlap problem
  - Discrimination of peak tail / amorphous band / background intensities

Quantitative Phase Analysis by XRD
Classification

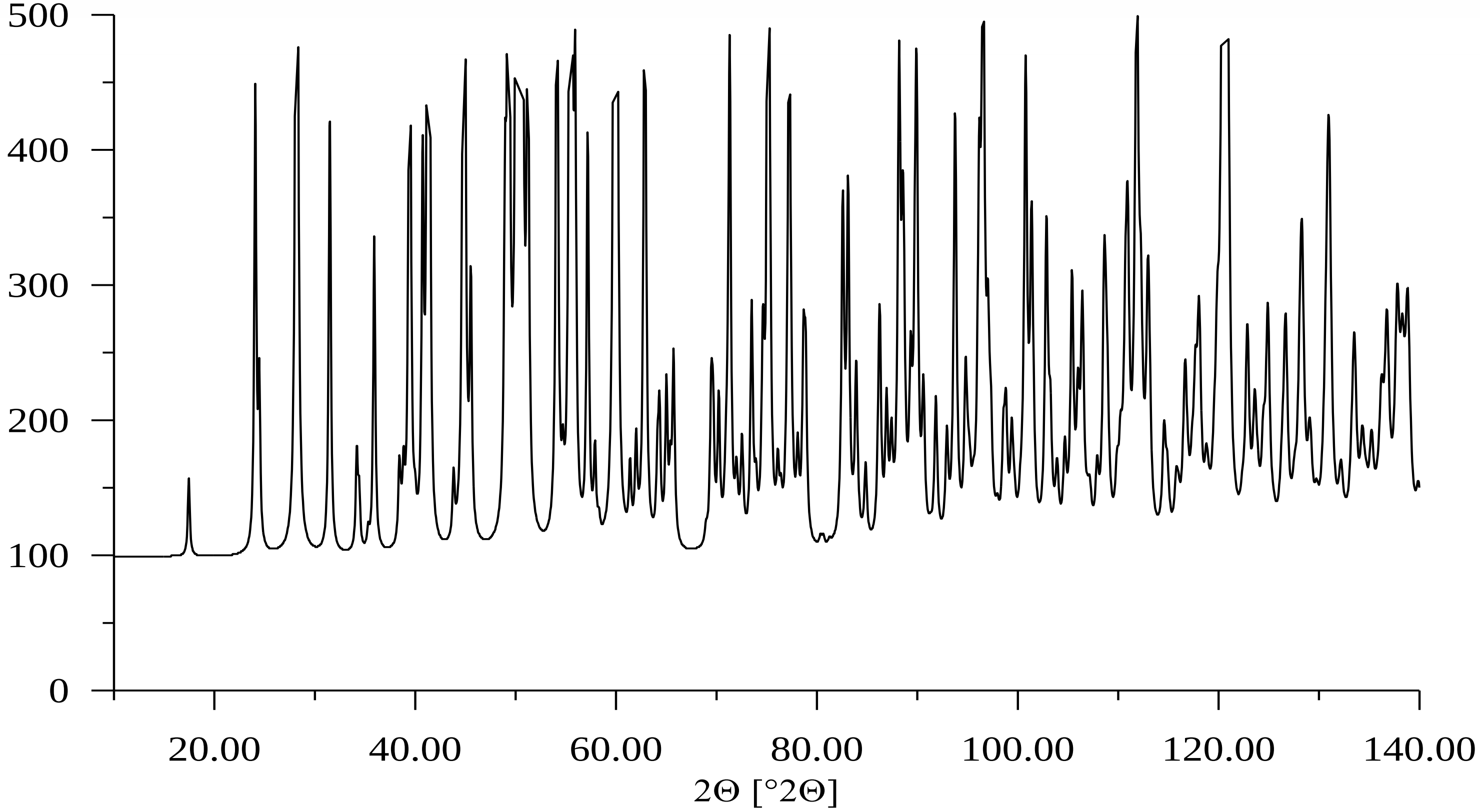
Classification of methods described in this study with respect to quantification of amorphous content

- Indirect measurement
    1. Analyse crystalline phases
    2. Put on absolute scale
    3. Calculate amorphous content by difference
- Direct measurement – estimate amorphous contribution to pattern
    - Calibrate using known standards, or
    - Include in whole sample analysis via modeling

    ➔ Relies on the ability to observe the intensity contribution of amorphous phases to the diffraction pattern

Quantifying Amorphous Phases

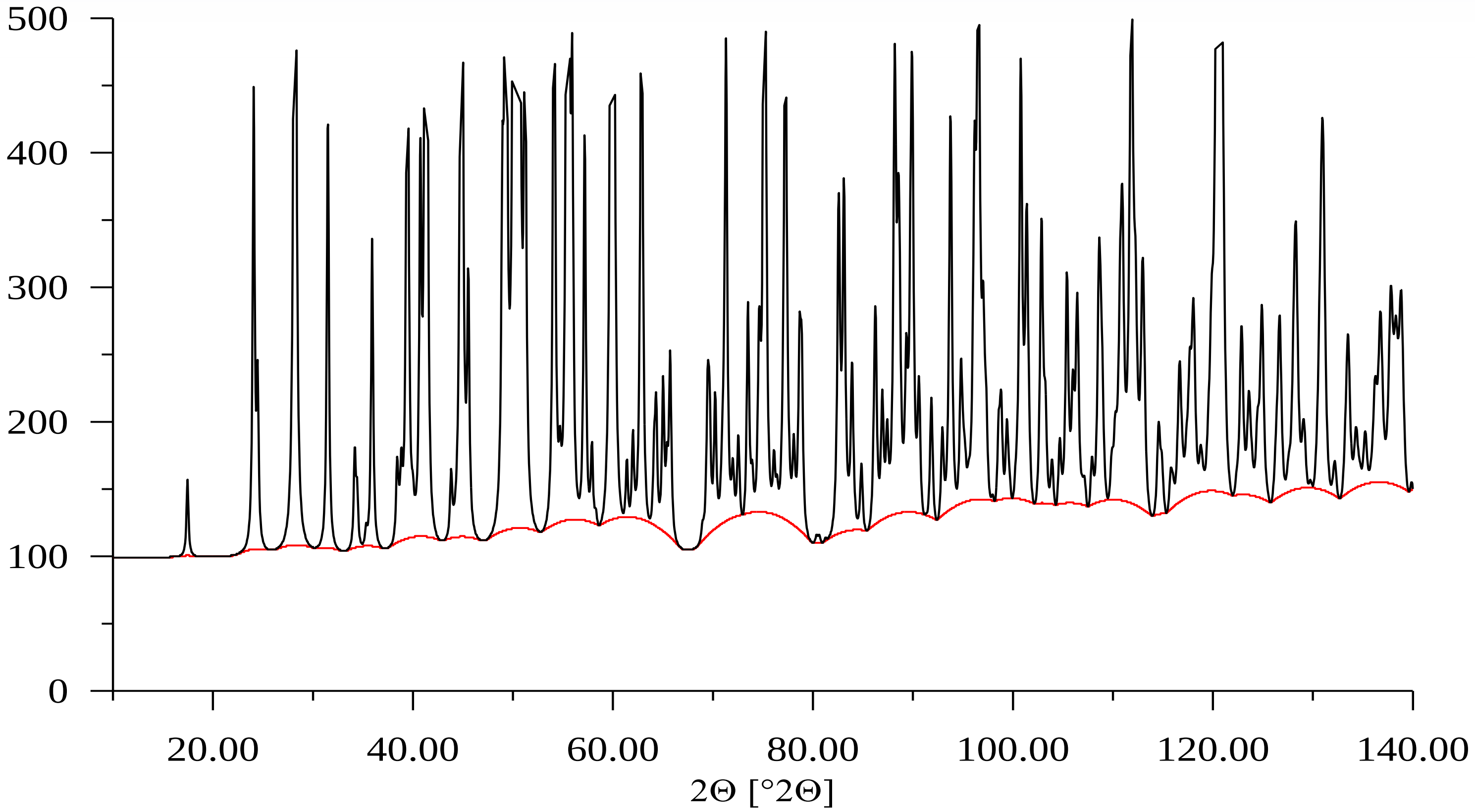
Introduction



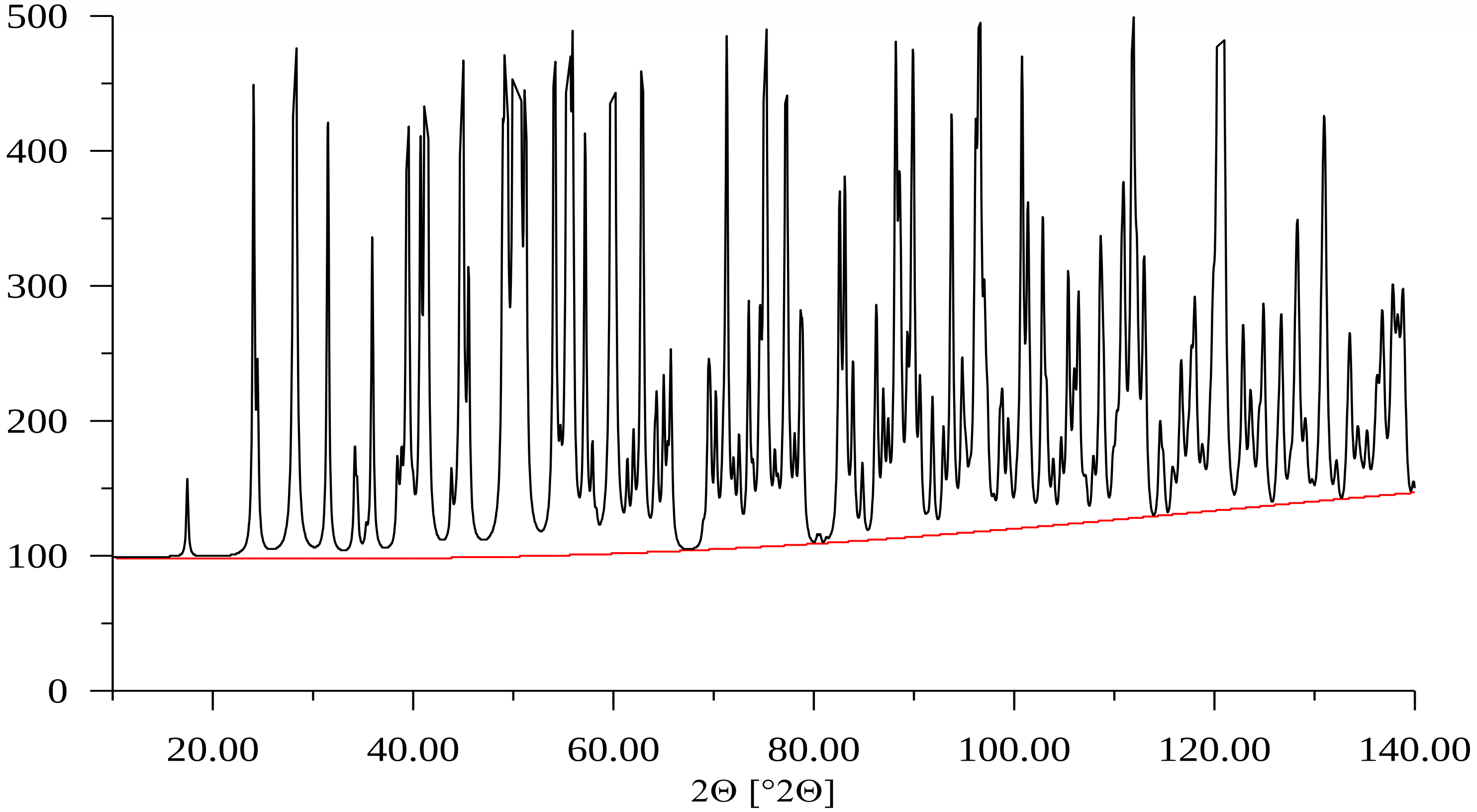
Can we easily discriminate between peak and background intensity?

Quantifying Amorphous Phases

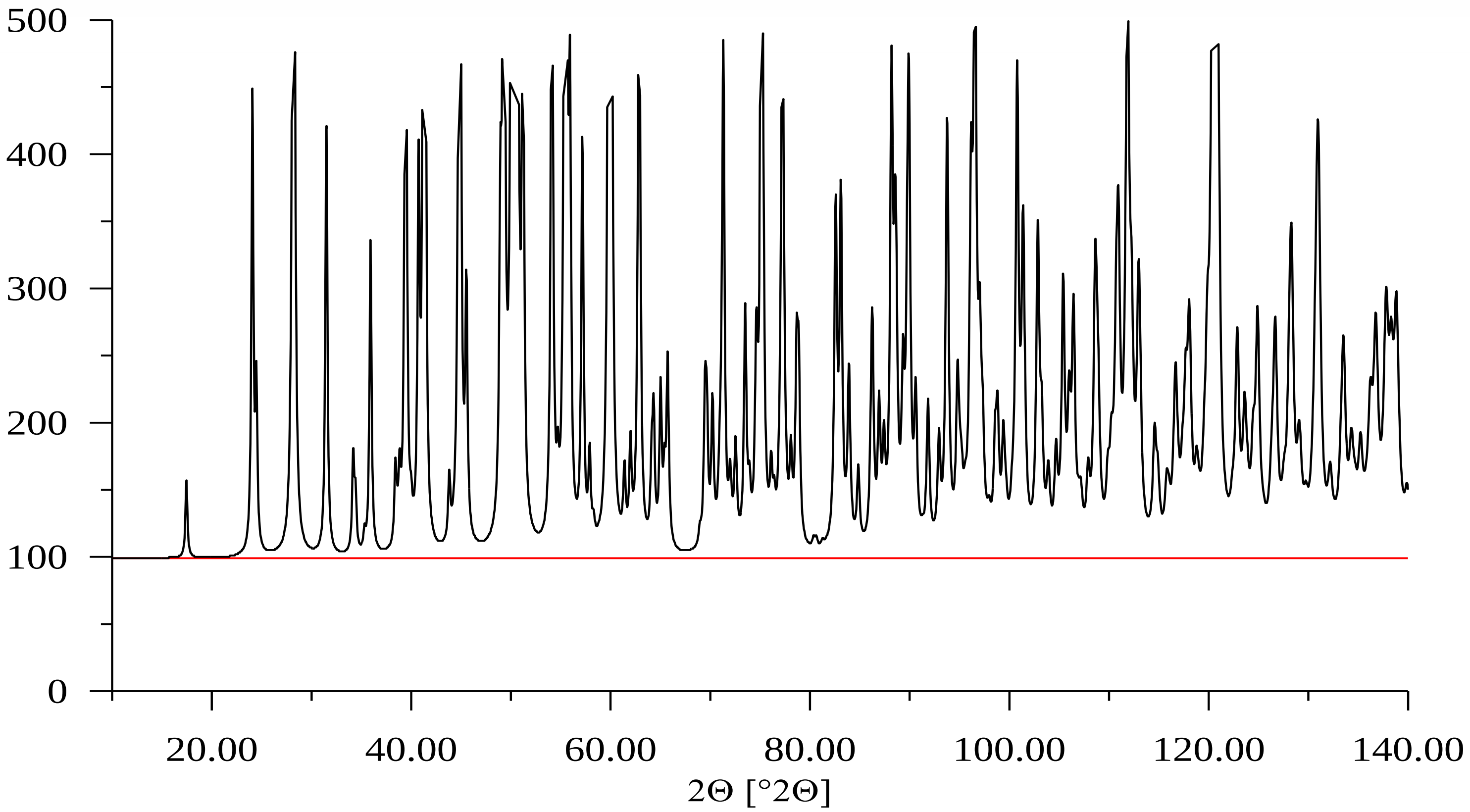
Introduction



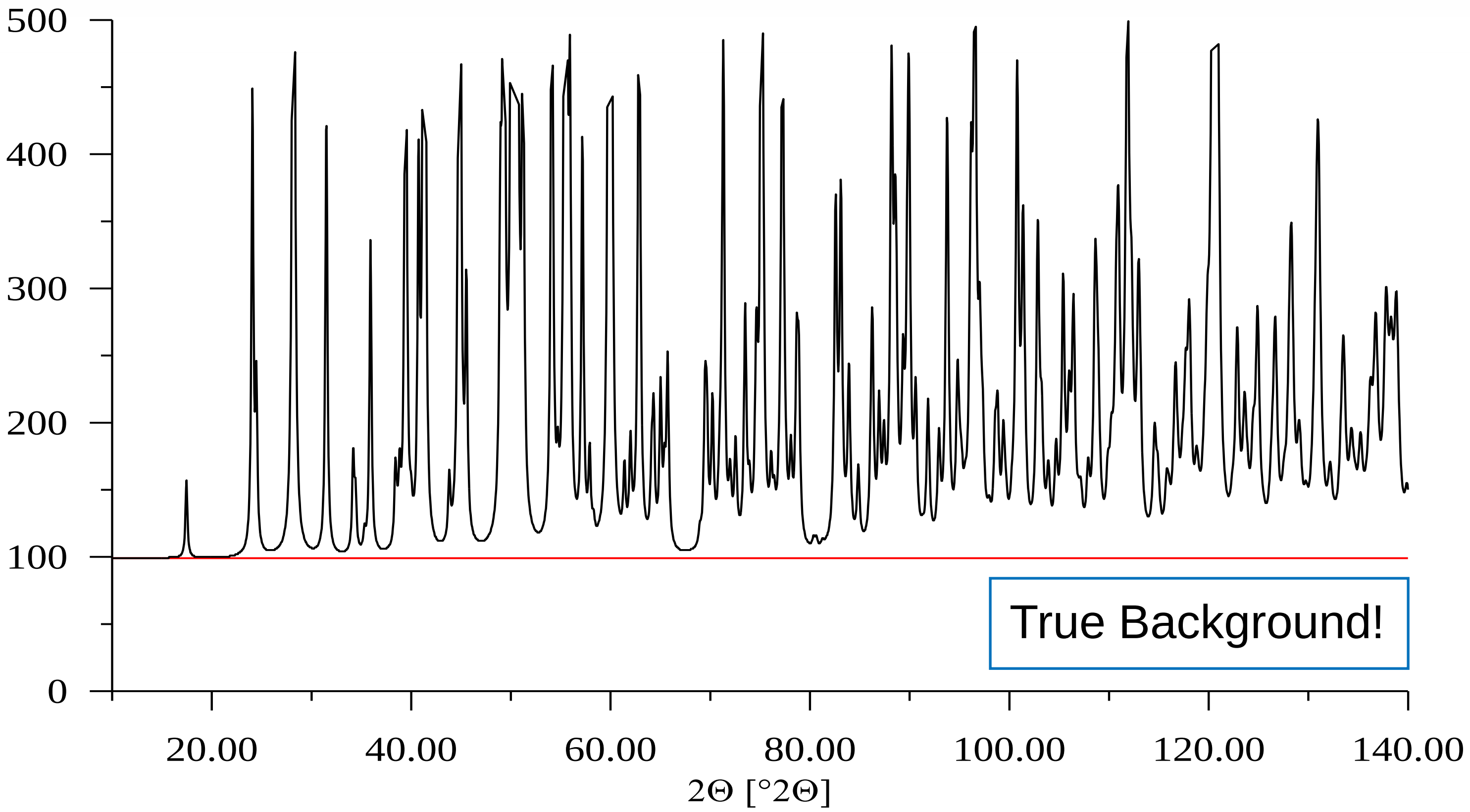
Quantifying Amorphous Phases
Introduction



Quantifying Amorphous Phases
Introduction

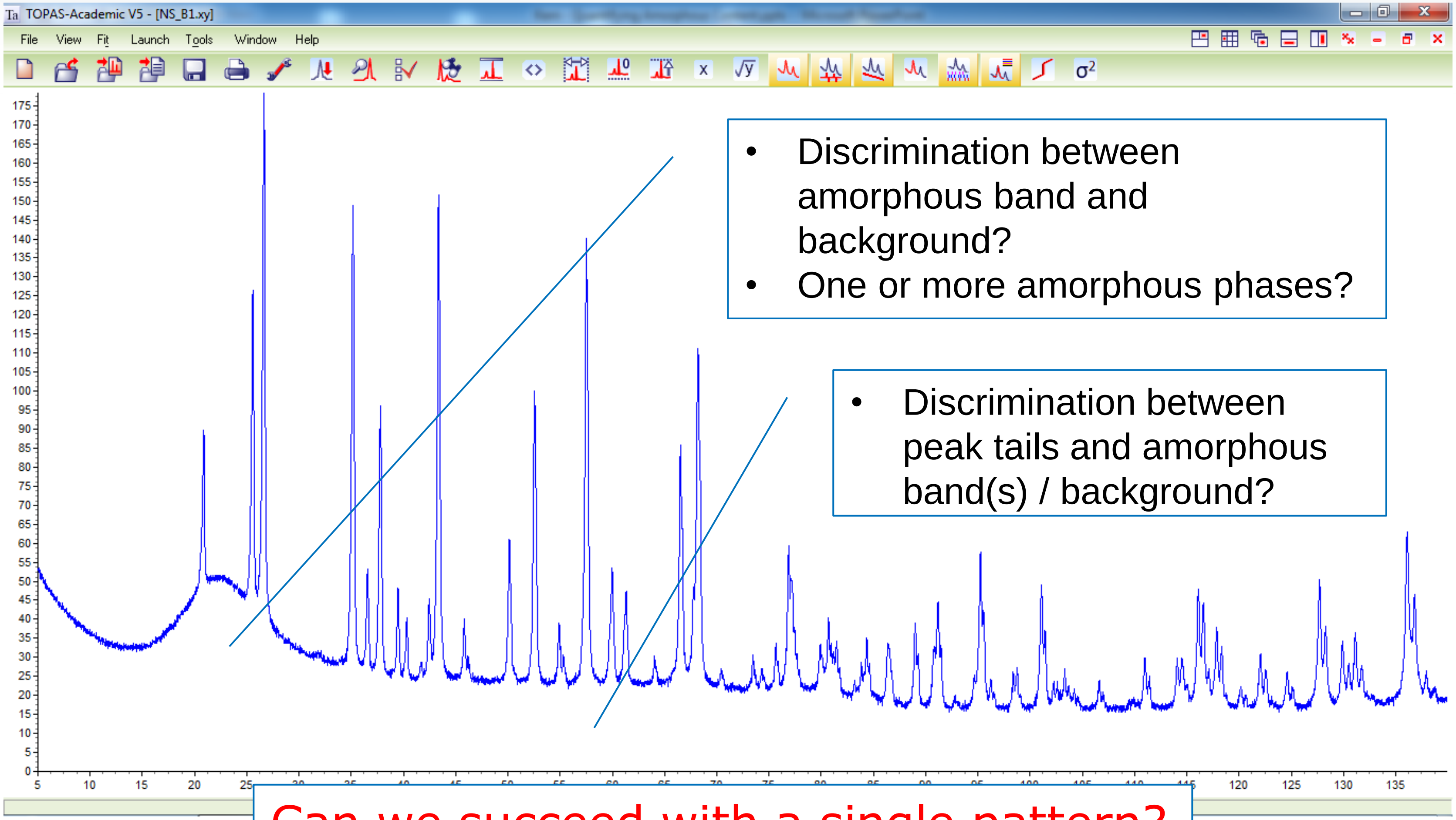


Quantifying Amorphous Phases
Introduction



True Background!

Quantifying Amorphous Phases
Introduction



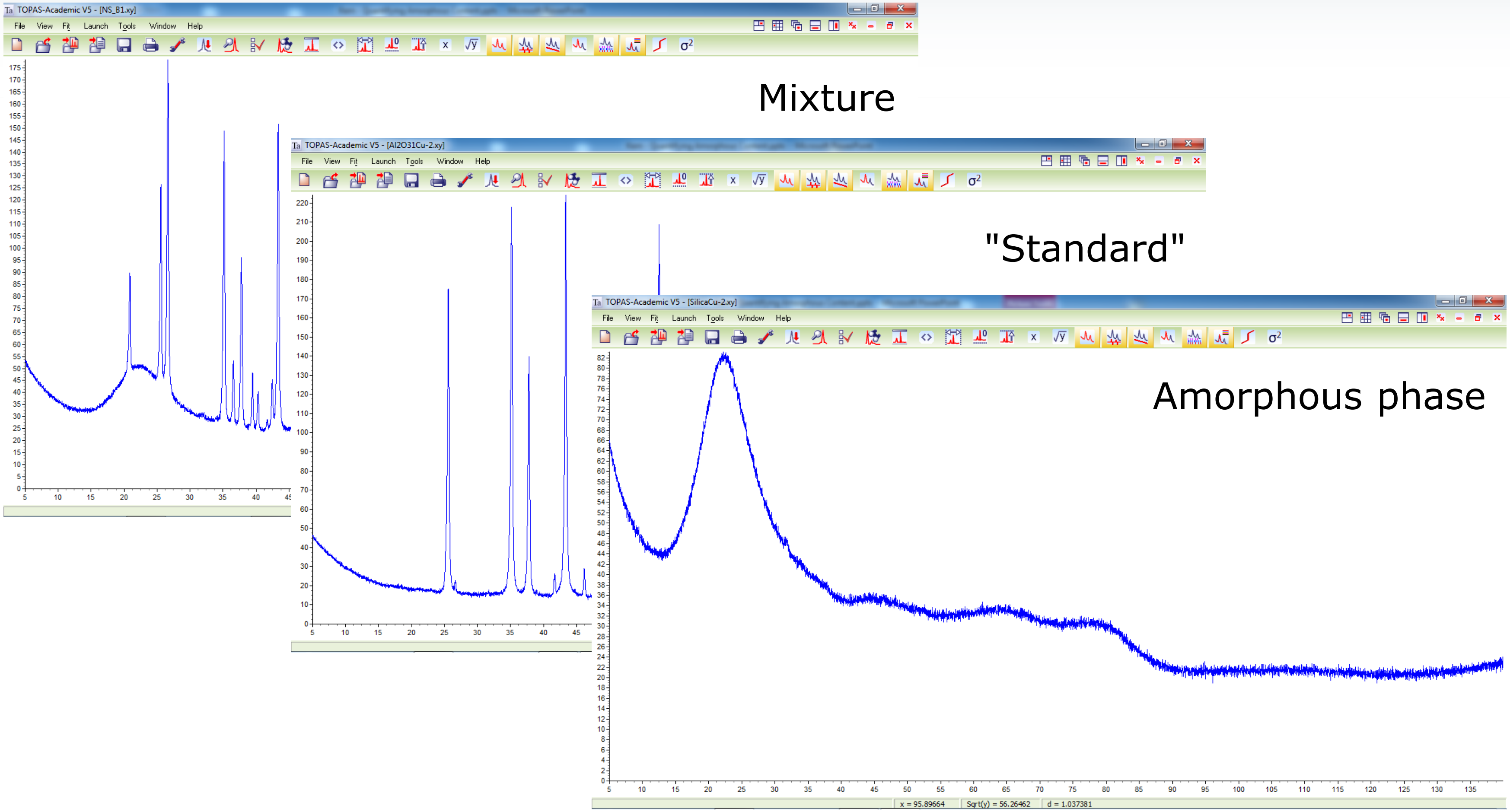
- Discrimination between amorphous band and background?
- One or more amorphous phases?

- Discrimination between peak tails and amorphous band(s) / background?

Can we succeed with a single pattern?

Quantifying Amorphous Phases

Intensity Discrimination

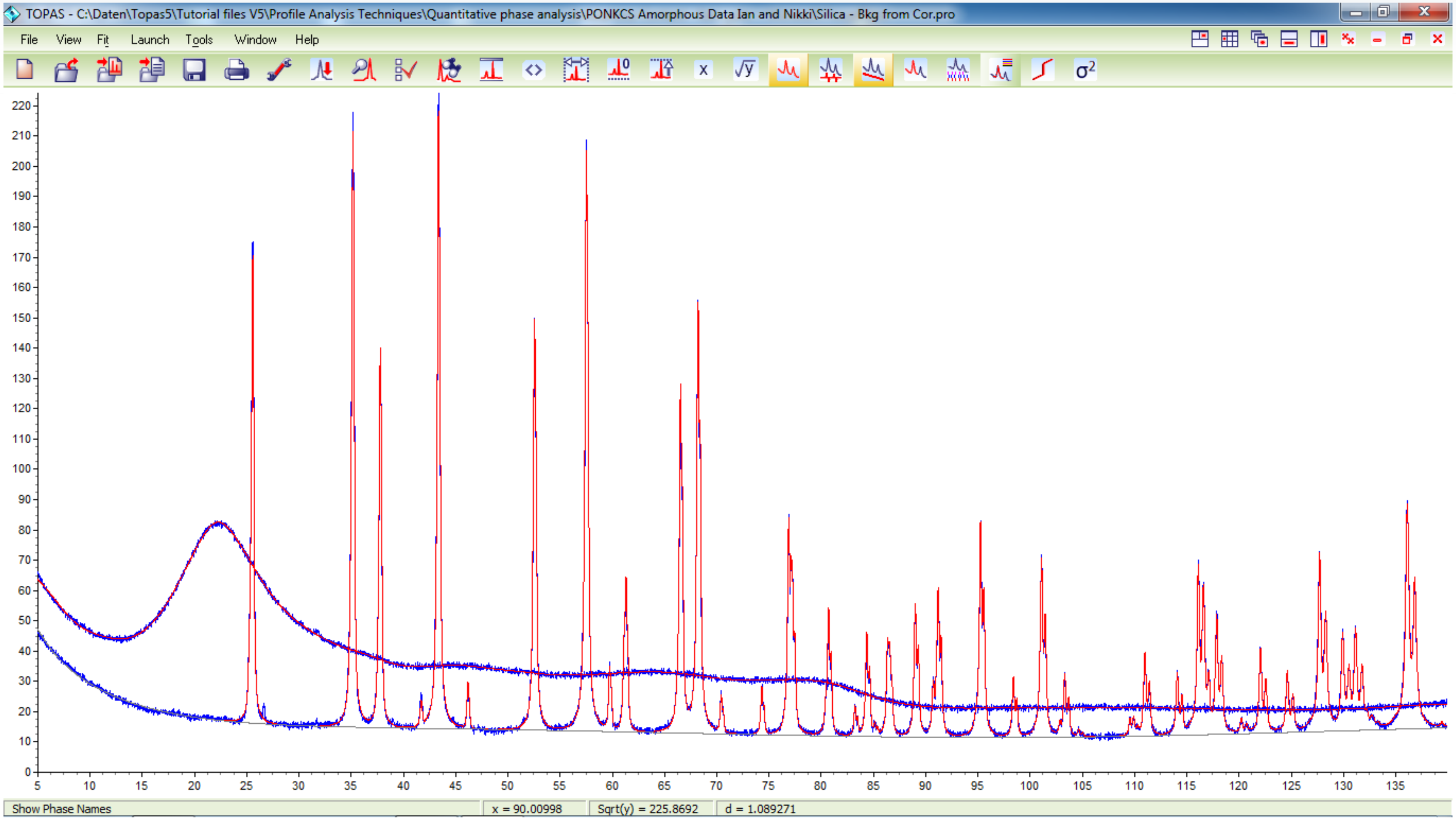


Mixture

"Standard"

Amorphous phase

Quantifying Amorphous Phases
Intensity Discrimination

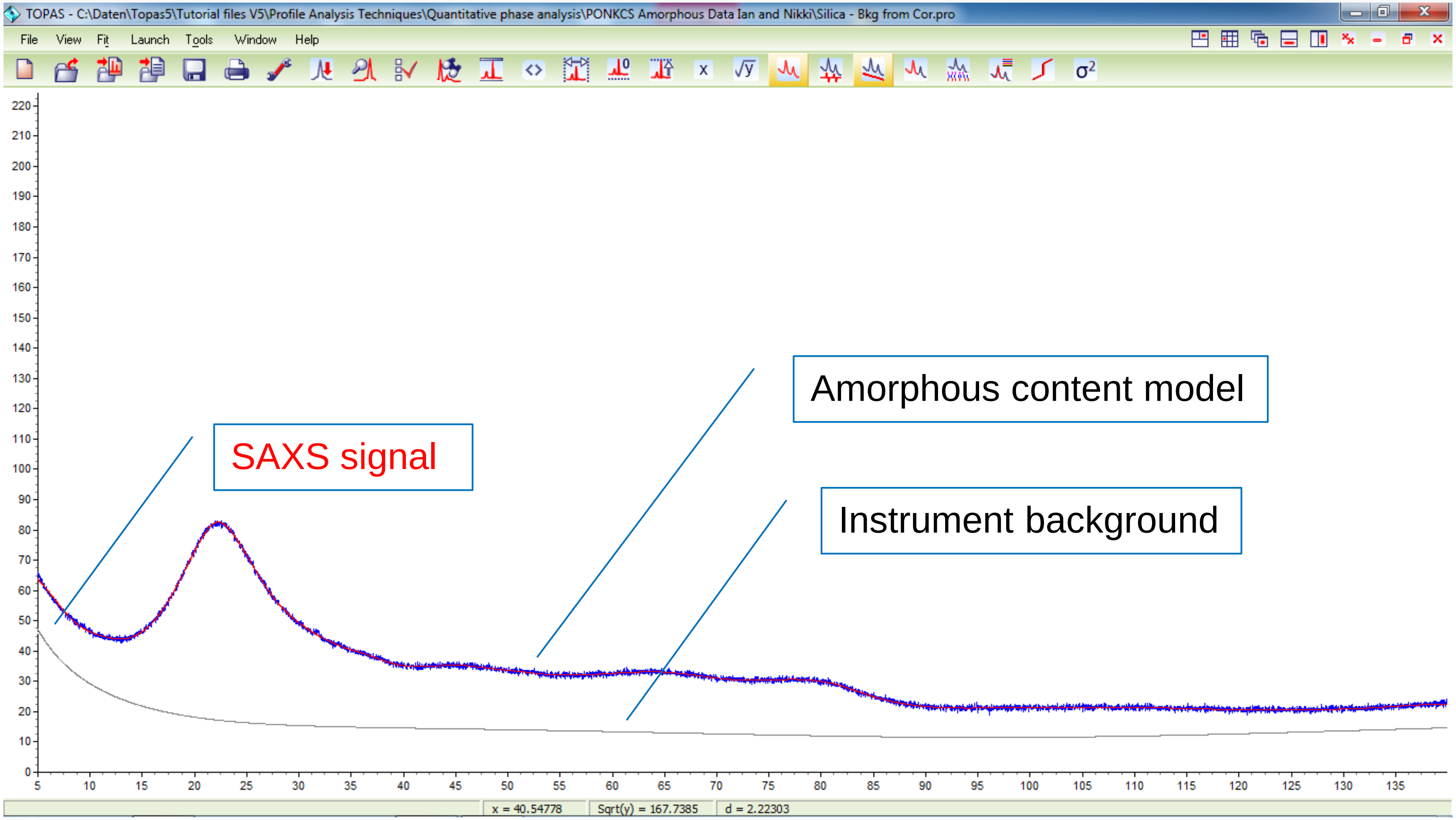


TOPAS - C:\Daten\Topas5\Tutorial files V5\Profile Analysis Techniques\Quantitative phase analysis\PONKCS Amorphous Data Ian and Nikki\Silica - Bkg from Cor.pro

x = 90.00998
Sqrt(y) = 225.8692
d = 1.089271

Quantifying Amorphous Phases

Intensity Discrimination


TOPAS - C:\Daten\Topas5\Tutorial files V5\Profile Analysis Techniques\Quantitative phase analysis\PONKCS Amorphous Data Ian and Nikki\Silica - Bkg from Cor.pro

SAXS signal

Amorphous content model

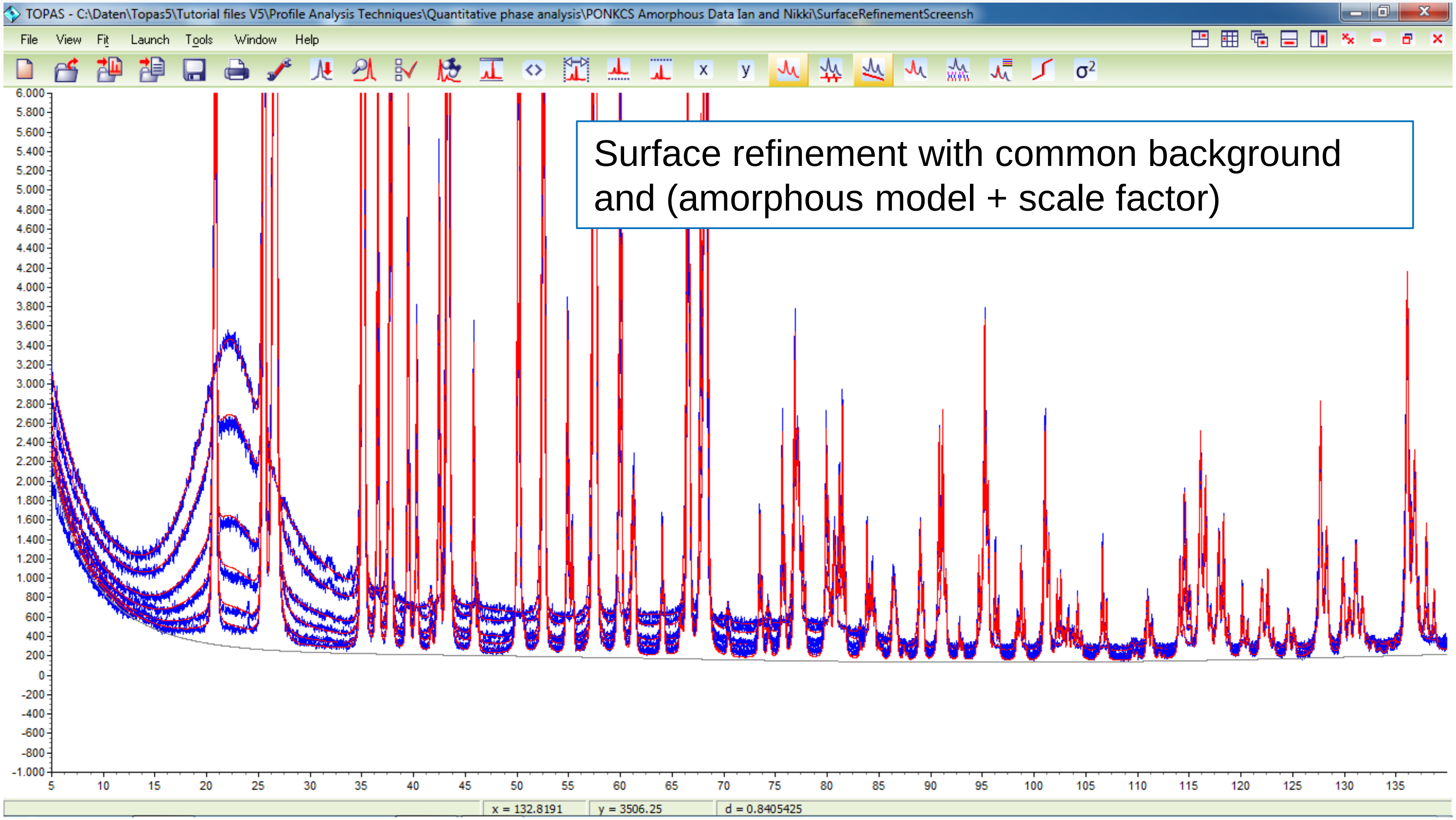
Instrument background

x = 40.54778

Sqrt(y) = 167.7385

d = 2.22303

Quantifying Amorphous Phases
Intensity Discrimination



Surface refinement with common background and (amorphous model + scale factor)

x = 132.8191
y = 3506.25
d = 0.8405425

Methodology

Single Peak Method

Single Peak Method

General procedure

1. Prepare a series of standards containing the crystalline or amorphous phase of interest at known concentrations
2. Obtain a measure of the crystalline or amorphous phase's intensity which is related to its concentration
3. Generate a calibration curve, e.g.

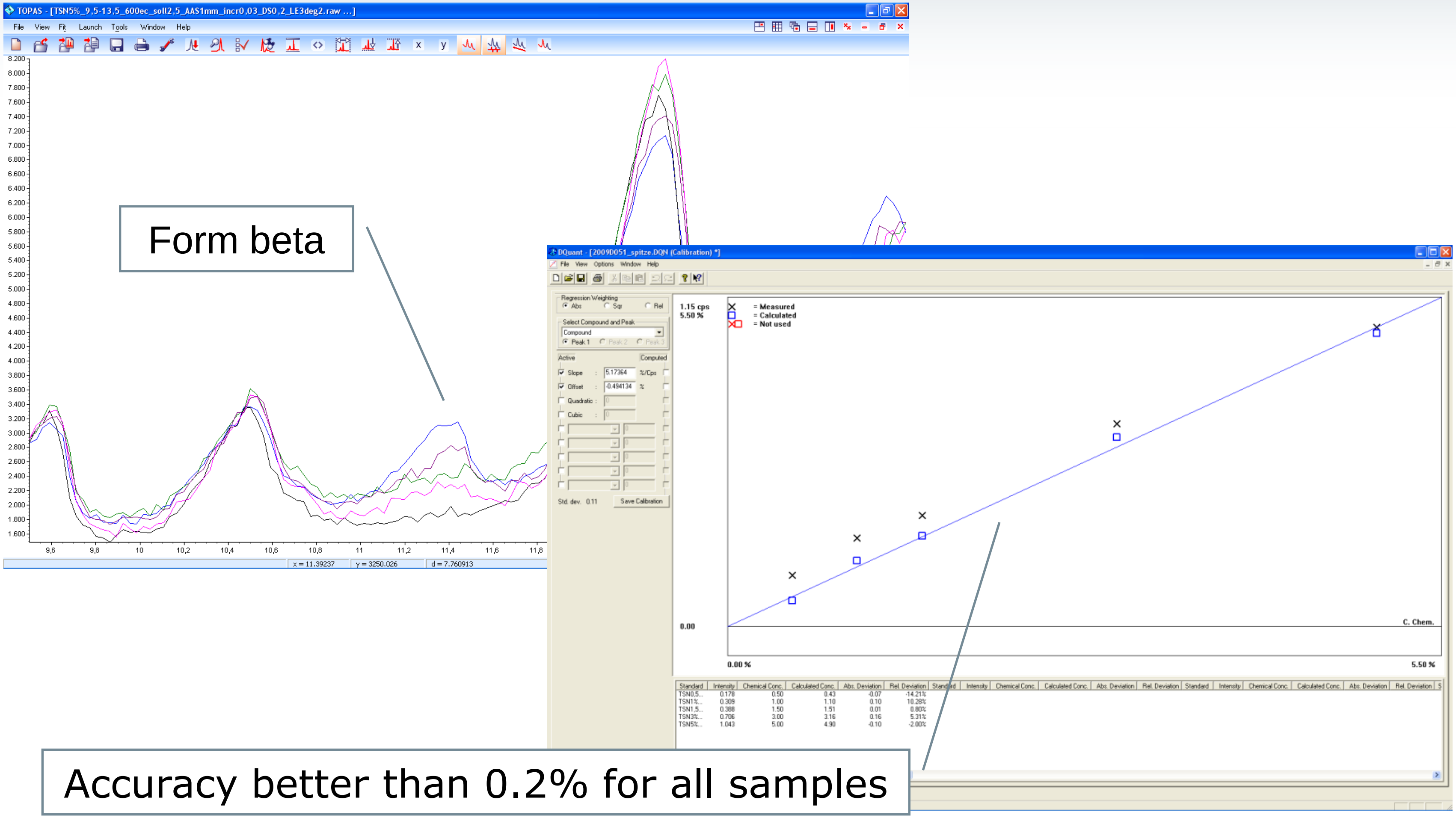
$$W_a = A * I_a + B$$

where W_α is the fraction of the crystalline or amorphous phase and I_α is the measure of the intensity of the crystalline or amorphous phase

‼ Needs redetermination to compensate for tube ageing and any instrument configuration change

Telmisartane

Form Beta in Form Alpha



Regression Weighting: ● Abs ○ Sqr ○ Rel

Select Compound and Peak: Compound ● Peak 1 ○ Peak 2 ○ Peak 3

Active				Computed
☑	Slope	5.17364	%/Cps	☐
☑	Offset	-0.494134	%	☐
☐	Quadratic	0		☐
☐	Cubic	0		☐

Std. dev. 0.11

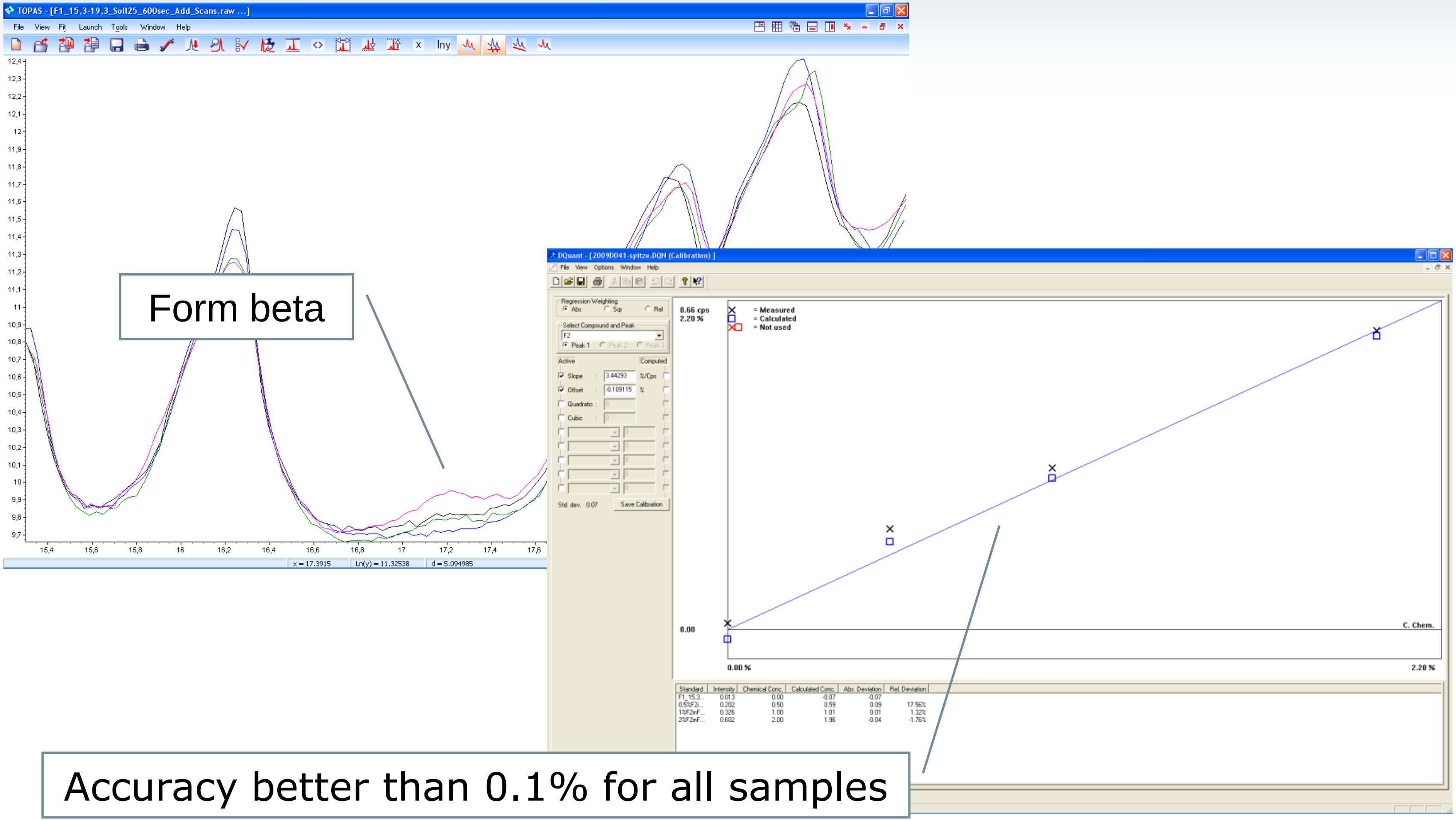
Save Calibration

Standard	Intensity	Chemical Conc.	Calculated Conc.	Abs. Deviation	Rel. Deviation
TSN0,5...	0.178	0.50	0.43	-0.07	-14.21%
TSN1%...	0.309	1.00	1.10	0.10	10.28%
TSN1,5...	0.388	1.50	1.51	0.01	0.80%
TSN3%...	0.706	3.00	3.16	0.16	5.31%
TSN5%...	1.043	5.00	4.90	-0.10	-2.00%

Form beta

Accuracy better than 0.2% for all samples

Undisclosed
Form 2 in Form 1



TOPAS - [F1_15,3-19,3_Soll25_600sec_Add_Scans.raw ...]

x = 17.3915 | Ln(y) = 11.32538 | d = 5.094985

DQuant - [2009D041-spitze.DQN (Calibration)]

Regression Weighting
● Abs ○ Sqr ○ Rel

Select Compound and Peak
F2
● Peak 1 ○ Peak 2 ○ Peak 3

Active / Computed
☑ Slope : 3.44293 %/Cps ☐
☑ Offset : -0.109115 % ☐
☐ Quadratic : 0 ☐
☐ Cubic : 0 ☐

Std. dev. 0.07

Standard	Intensity	Chemical Conc.	Calculated Conc.	Abs. Deviation	Rel. Deviation
F1_15,3...	0.013	0.00	-0.07	-0.07	
0,5%F2i...	0.202	0.50	0.59	0.09	17.56%
1%F2inF...	0.326	1.00	1.01	0.01	1.32%
2%F2inF...	0.602	2.00	1.96	-0.04	-1.76%

Form beta

Accuracy better than 0.1% for all samples

Single Peak Method

Benefits

- Highly accurate, specifically for phases close to the detection limit
- There is no need to characterize all phases in the mixture
- No need to determine the background.
  Note: If so, the calibration curve wont go through the origin
- More than one amorphous phase can be analyzed (this will usually require profile fitting)

Limitations

- Need access to region of pattern free from excessive peak overlap
- Requires access to materials for preparation of standards
- Method only applicable to mixtures similar to calibration suite
  - Sample properties must not change (chemistry, preferred orientation, ...)
  - Needs redetermination to compensate for tube ageing and any instrument configuration changes
- Direct method for determination of amorphous content

Methodology

Traditional Rietveld method
Internal Standard method
External Standard method
PONKCS method
Degree of Crystallinity

Whole Pattern Methods
Traditional Rietveld Method

- The basic principle of the Rietveld method is the description of all data points of a powder pattern using an appropriate refinement model
- The parameters of this model, consisting of crystal structure, sample, instrument and background parameters, are refined simultaneously using least squares methods
  - Minimize the differences between the calculated and measured powder diffraction pattern
- Rietveld analysis is a standardless1) method and thus does not require any standards or calibration

1) Note:
Instead of standards, accurate crystal structure are required for each crystalline phase in the sample. The impact of poor or wrong crystal structures on QPA results is widely underestimated.

Whole Pattern Methods
Traditional Rietveld Method

Benefits

- Requires no standards or calibration[1)]

[1)] Note:
Instead of standards, crystal structures are required for each crystalline phase in the sample. The impact of poor or wrong crystal structures on QPA results is widely underestimated.

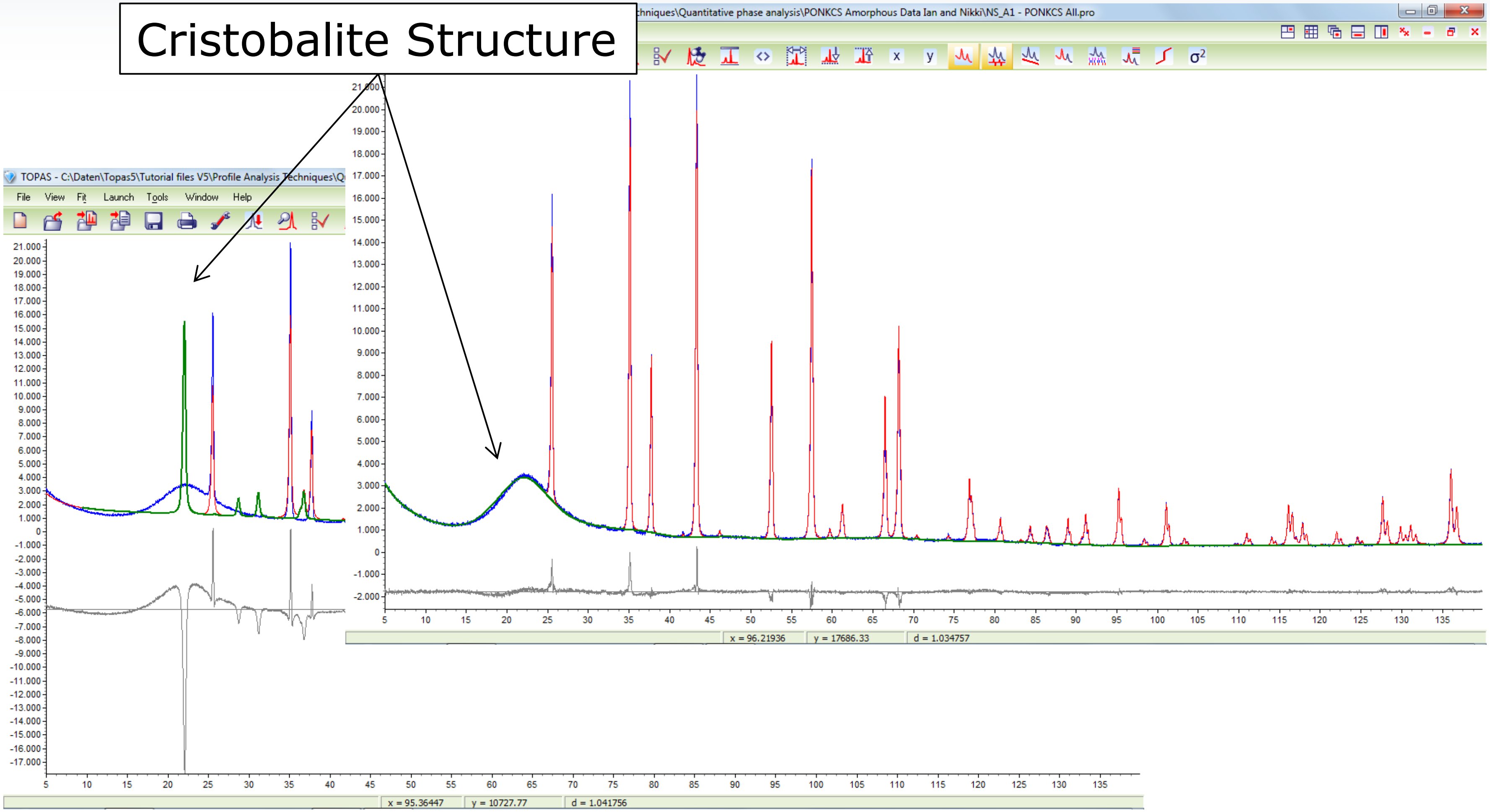
Limitations

- The Rietveld method assumes that all phases are crystalline and included in the analysis
  - Accurate crystal structure required for all phases
  - Amorphous components cannot be considered
- Produces only relative phase abundances
  - The relative weight fractions of the crystalline phases are normalized to 100%
  - Crystalline phases may be overestimated if non-identified and/or amorphous phases are present

Whole Pattern Methods
Traditional Rietveld Method - Quantifying Amorphous Phases

- Relies on finding a crystal structure which adequately models the positions and relative intensities of the observable bands of an amorphous component in a diffraction pattern
  - e.g. Le Bail, 1995; Lutterotti et al., 1998
- Allowance for extreme peak broadening provides peak widths and shapes which represent those of the amorphous bands in the observed data
- Since this approach treats all components as crystalline and includes them in the analysis, the amorphous phase abundance can be obtained using the traditional Rietveld methodology
(Hill and Howard, 1987):

Whole Pattern Methods
Traditional Rietveld Method - Quantifying Amorphous Phases



Cristobalite Structure

Madsen et al. (2011), Kern et al. (2012)

Whole Pattern Methods
Traditional Rietveld Method - Quantifying Amorphous Phases

Benefits

- Requires no standards or calibration
- More than one amorphous phase can be analyzed

Limitations

- Direct method for determination of amorphous content
- Some amorphous material will not have a representative crystal structure
  - Available crystal structures (with long-range order) may not accurately represent material which only has short-range order (e.g. glasses).

Methodology

Traditional Rietveld method
Internal Standard method
External Standard method
PONKCS method
Degree of Crystallinity

Whole Pattern Methods
Internal Standard

- The sample is "spiked" with a known mass of standard material and the QPA normalized accordingly
- The weight fractions of the crystalline phases present in each sample are estimated using the Rietveld methodology
- Concentrations to be corrected proportionately according to:

$$Corr(W_\alpha) = W_\alpha \frac{STD_{known}}{STD_{measured}}$$

where *Corr(*W_α*)* is the corrected weight percent, STD_{known} the weighed concentration of the standard in the sample and $STD_{measured}$ the analyzed concentration

- The amount of amorphous material $W_{amorphous}$ can then be derived from:

$$W_{amorphous} = 1 - \sum_{j=1}^{n} Corr(W_j)$$

Whole Pattern Methods
Internal Standard

Benefits

- Indirect method for determination of amorphous content
- The Internal Standard Method is enabled in many Rietveld analysis packages

Limitations

- Only the sum of all amorphous and unidentified phases can be reported
- The sample is contaminated
- The standard addition process is laborious (weighing, mixing), and not feasible in industrial, automated sample preparation environments

Methodology

Traditional Rietveld method
Internal Standard method
External Standard method
PONKCS method
Degree of Crystallinity

Quantifying Amorphous Phases
External Standard Method

- An external standard is used to determine a "normalisation constant" *K* for the experimental setup
  - Independent of sample and phase related parameters
  - A single measurement is sufficient for analysis
  - Requires the mass absorption coefficient for the entire sample – $\mu_m{}^*$

$$W_{\alpha(abs)} = \frac{S_\alpha (ZMV)_\alpha \mu_m^*}{K}$$

- Amorphous content derived in same way as internal standard method
  - Puts the determined crystalline components on an absolute scale and derives the amorphous content by difference

O’Connor and Raven (1988), Powder Diffraction, 3(1), 2-6

Quantifying Amorphous Phases
External Standard Method

- μ_m^* can be calculated e.g. from the elemental composition of the sample, determined, for example, by X-ray fluorescence (XRF)
- K requires regular redetermination to compensate for tube ageing

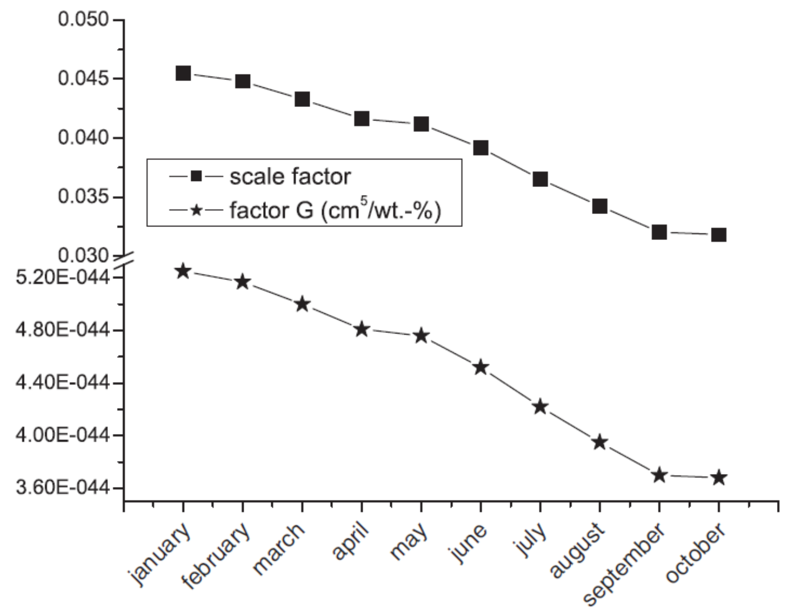


Fig. 1. Change in the scale factor and factor G over time (10 month).

Jansen et al., 2011

Quantifying Amorphous Phases
External Standard Method

Benefits

- Indirect method for determination of amorphous content
- Uses an external standard, the sample is not contaminated

Limitations

- Requires the mass absorption coefficient for the entire sample
  - ⇨ Cannot be used in transmission geometry; sample holder (capillary, foils, etc.) contribute to pattern!
- Only the sum of all amorphous and unidentified phases can be reported
- The normalization constant *K* is dependent on the instrumental conditions
  - Needs redetermination to compensate for tube ageing and any instrument configuration changes

Methodology

Traditional Rietveld method
Internal Standard method
External Standard method
PONKCS method
Degree of Crystallinity

Whole Pattern Methods

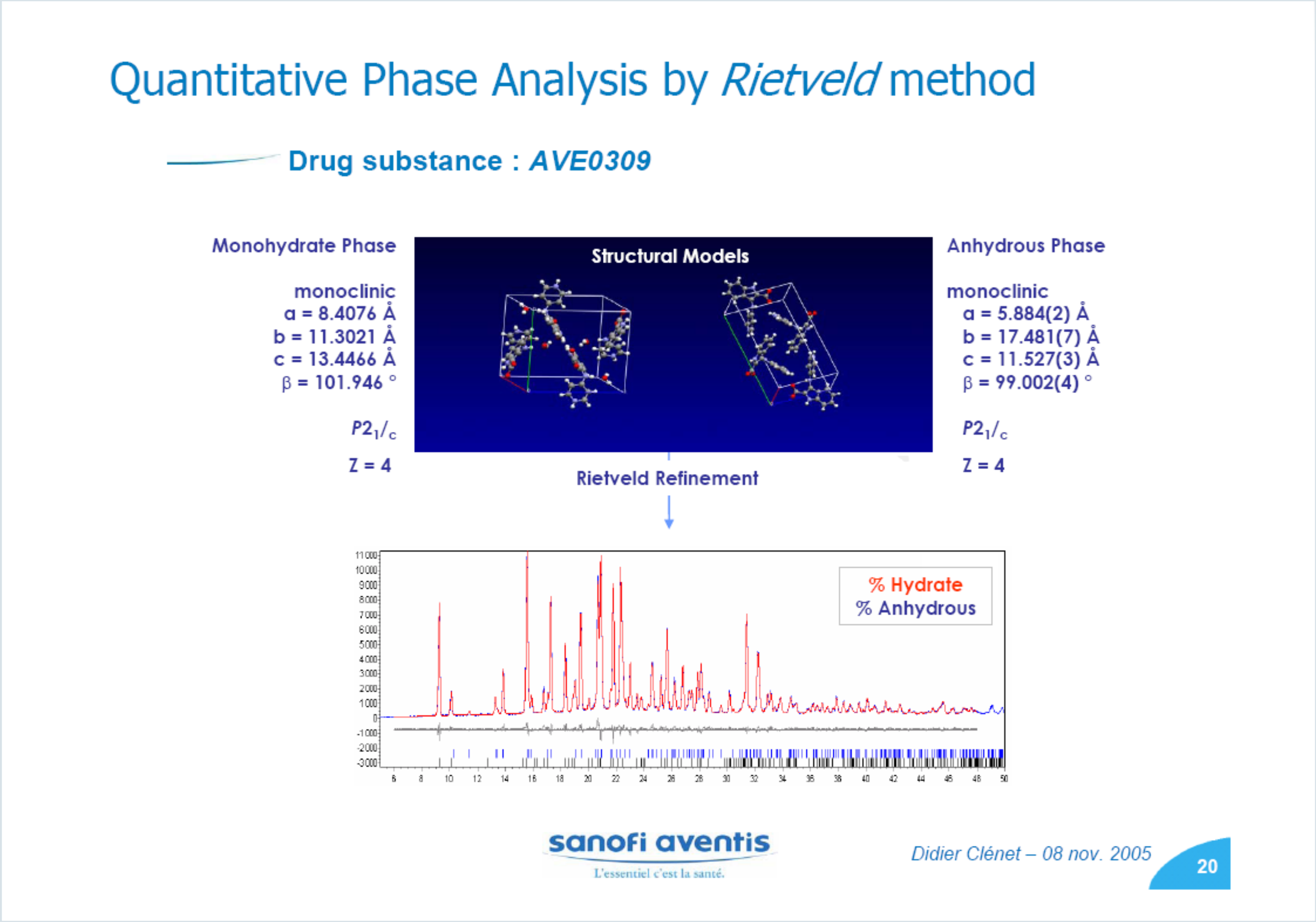
PONKCS

- Phases with Partial Or No Known Crystal Structure are characterized by measured rather than calculated structure factors
- Follows the same general form as that used in the Rietveld Method but now includes all crystalline and amorphous phases characterized by either calculated or empirical structure factors
- For all phases α using empirically derived structure factors ZMV "calibration constants" must be derived, e.g. via an internal standard *s*

$$(ZMV)_\alpha = \frac{W_\alpha}{W_s}\frac{S_s}{S_\alpha}(ZMV)_s$$

- A one time calibration per phase with a single standard mixture is usually sufficient

Example
AVE0309



Quantitative Phase Analysis by *Rietveld* method

Drug substance : *AVE0309*

Monohydrate Phase

monoclinic
a = 8.4076 Å
b = 11.3021 Å
c = 13.4466 Å
β = 101.946 °

$P2_1/c$

Z = 4

Structural Models

Anhydrous Phase

monoclinic
a = 5.884(2) Å
b = 17.481(7) Å
c = 11.527(3) Å
β = 99.002(4) °

$P2_1/c$

Z = 4

Rietveld Refinement

% Hydrate
% Anhydrous

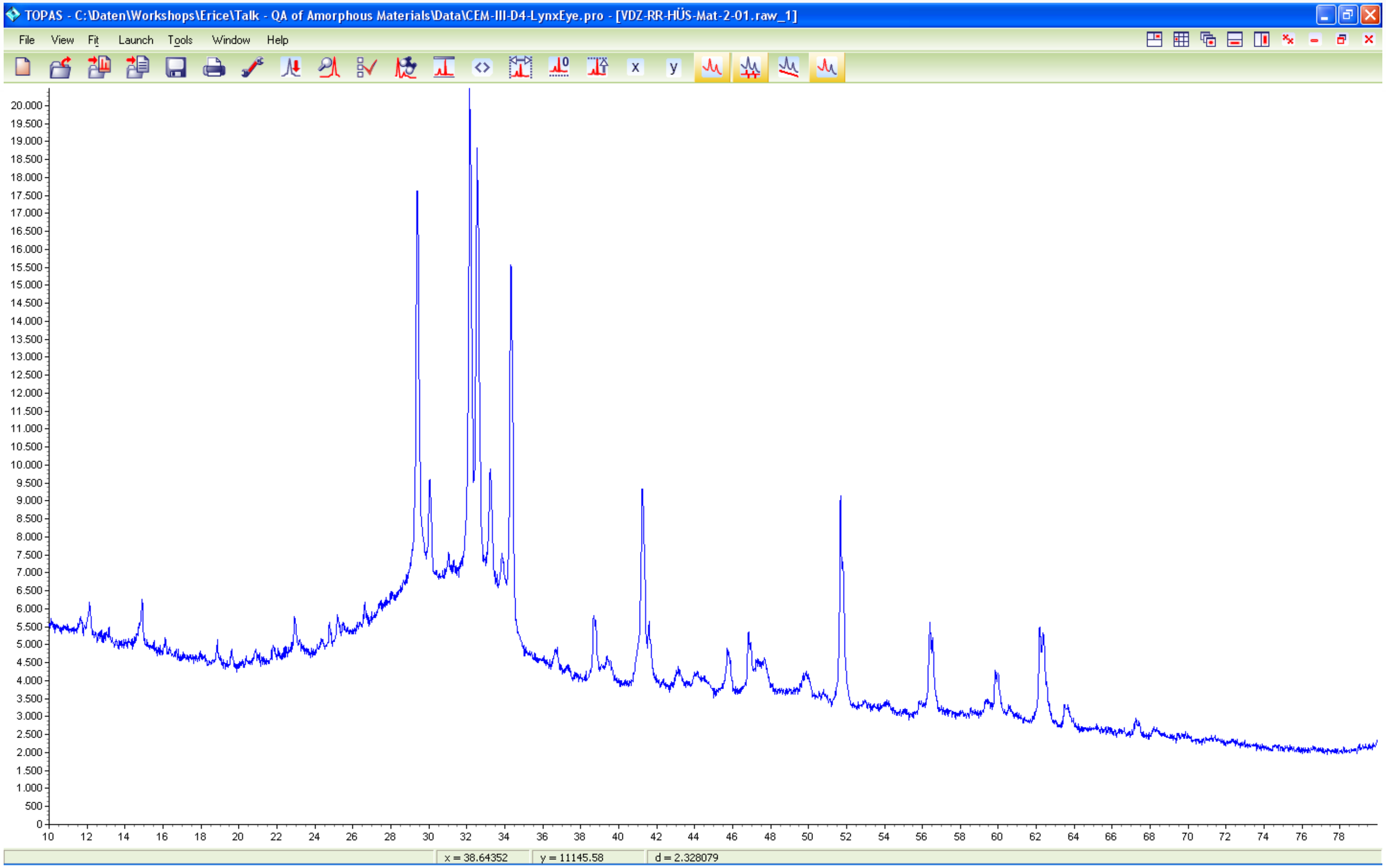
sanofi aventis
L'essentiel c'est la santé.

Didier Clénet – 08 nov. 2005

Example AVE0309

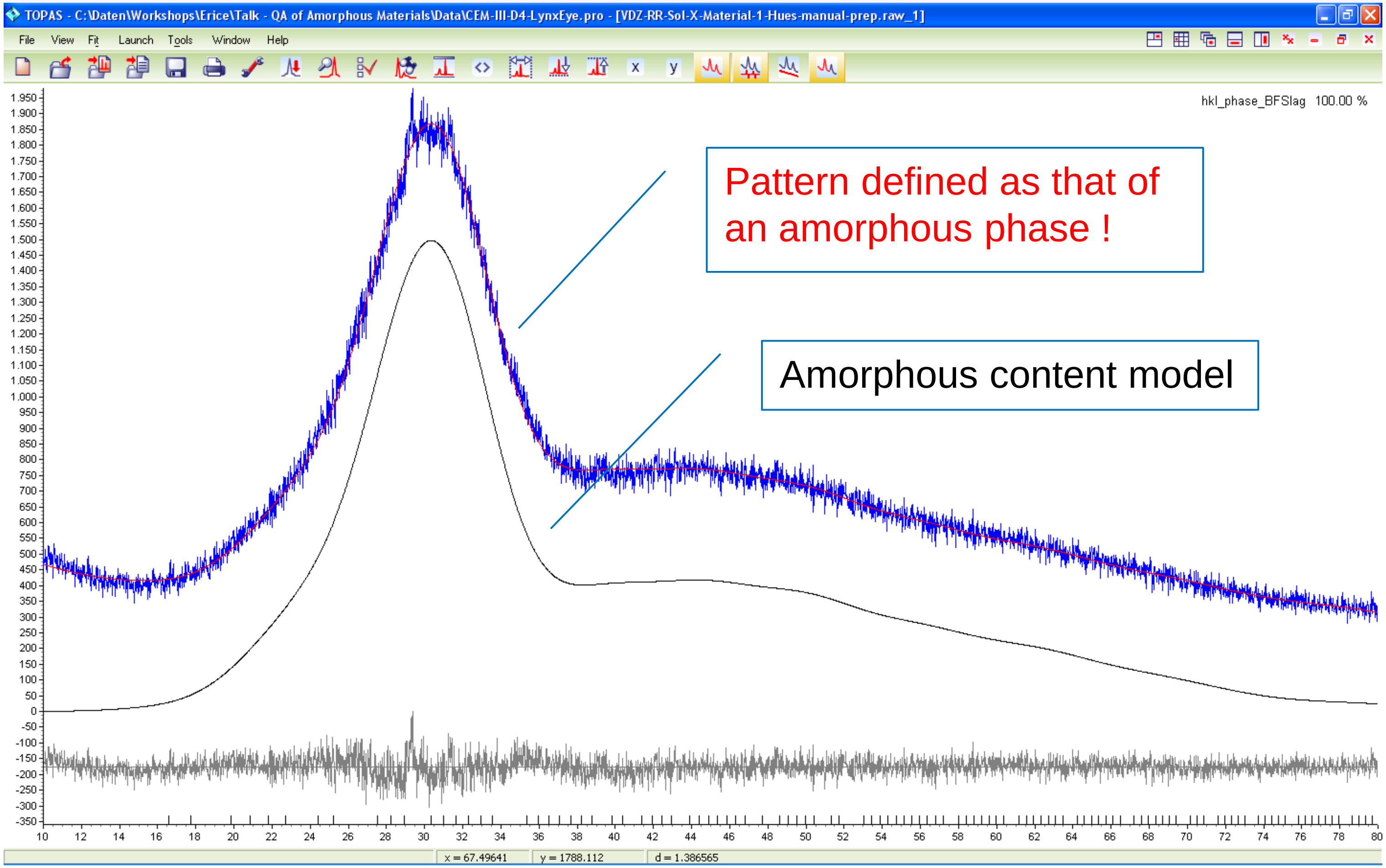
	Known composition **Clenet (2005)**	**Rietveld** **Clenet (2005)**	**PONKCS**
1) Hydrate **Anhydrate**	13.6 % 86.4 %	14.6 % 85.4 %	14.05 % 85.95 %
2) Hydrate **Anhydrate**	50.3 % 49.7 %	50.1 % 49.9 %	50.69 % 49.31 %
		Δ_{max} ~ 1%	Δ_{max} ~0.4%

Whole Pattern Methods
PONKCS


TOPAS - C:\Daten\Workshops\Erice\Talk - QA of Amorphous Materials\Data\CEM-III-D4-LynxEye.pro - [VDZ-RR-HÜS-Mat-2-01.raw_1]

x = 38.64352 y = 11145.58 d = 2.328079

Whole Pattern Methods
PONKCS



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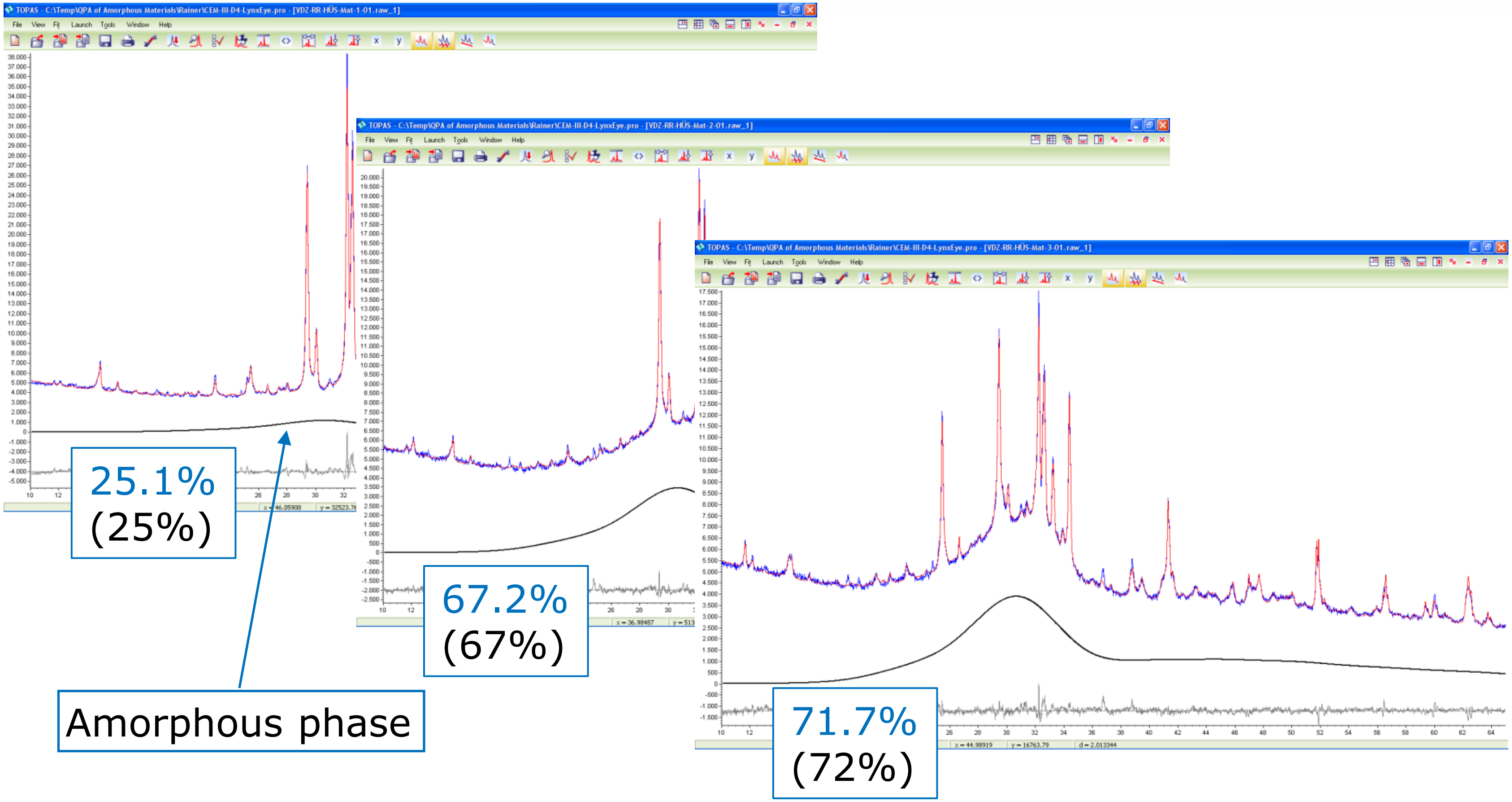
hkl_phase_BFSlag 100.00 %

x = 67.49641 y = 1788.112 d = 1.386565

Pattern defined as that of an amorphous phase !

Amorphous content model

Whole Pattern Methods
PONKCS



25.1%
(25%)

67.2%
(67%)

71.7%
(72%)

Amorphous phase

Whole Pattern Methods
PONKCS

Benefits

- Allows quantification of phases without known crystal structure
- Crystalline and amorphous phases are included in the analysis model
- More than one amorphous phase can be analyzed

Limitations

- Requires availability of a standard mixture to derive an empirical ZMV
- Direct method for determination of amorphous content

Methodology

Traditional Rietveld method
Internal Standard method
External Standard method
PONKCS method
Degree of Crystallinity

Whole Pattern Methods
Degree of Crystallinity

- Based on the estimation of the total intensity or area contributed to the overall diffraction pattern by each component in the analysis
- The degree of crystallinity, *DOC*, is calculated from the total areas under the defined crystalline and amorphous components from

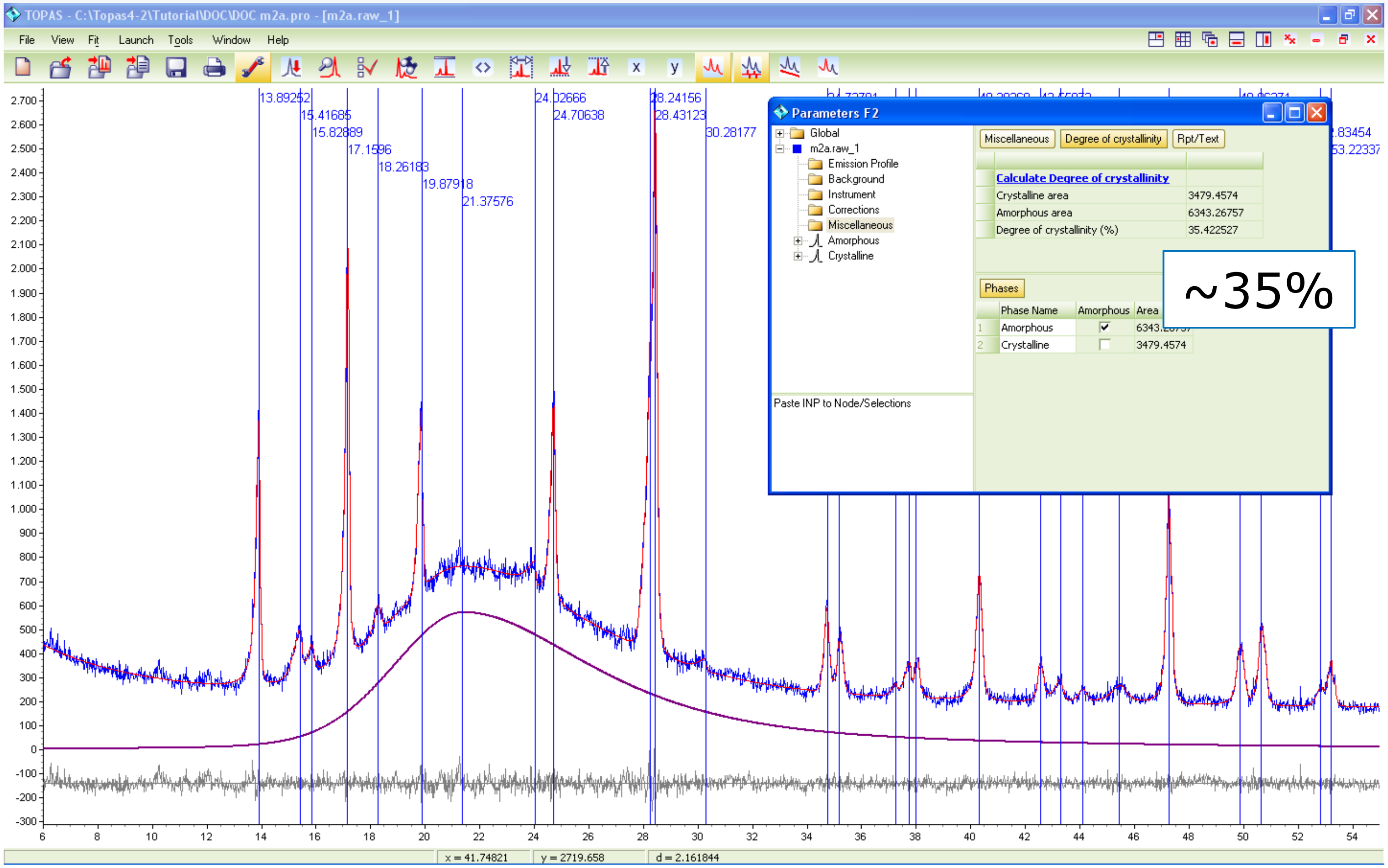
$$DOC = \frac{Crystalline\ Area}{Crystalline\ Area + Amorphous\ Area}$$

- The weight fraction of the amorphous material, W_{amorph}, can be calculated from

$$W_{amorph} = 1 - DOC$$

- The method only delivers accurate results, if the chemistry of the amorphous phase is identical to that of the whole sample
  - If this is not the case, then an additional calibration step is required to obtain absolute phase amounts

Whole Pattern Methods
Degree of Crystallinity - Example: M2A



Calculate Degree of crystallinity	
Crystalline area	3479.4574
Amorphous area	6343.26757
Degree of crystallinity (%)	35.422527

	Phase Name	Amorphous	Area
1	Amorphous	☑	6343.
2	Crystalline	☐	3479.4574

~35%

Whole Pattern Methods
Degree of Crystallinity

Benefits

- More than one amorphous phase can be analyzed
- The method is enabled in many software packages

Limitations

- Direct method for determination of amorphous content

Summary

Summary

Method	Calculation of amorphous content	Requires calibration suite or standard	Can deal with more than one amorphous phase	Singular samples
Single Peak	Direct	Calibration suite	Yes	
Rietveld Method	Direct	No	Yes	+
Internal Standard	Indirect	Internal standard	No	+
External Standard	Indirect	External standard	No	+
PONKCS	Direct	One-time calibration with single mixture	Yes	
DOC	Direct	Case dependent	Yes	+

Summary

- Lower limits of detection / accuracy / precision:
  - Detection, identification and quantification of crystalline phases less than 0.1% possible
  - Detection, identification and quantification of amorphous phases less than 1% possible
- Limitations are the same for quantitative analysis of crystalline and as well as amorphous phases and are dictated by sample properties and the analytical technique used

For the determination of crystalline and / or amorphous material, the problem will dictate the methodology used

Summary

- The traditional Rietveld method only delivers relative phase amounts by default; in the presence of amorphous and/or any amount of unidentified crystalline phases, the analyzed crystalline weight fractions may be significantly overestimated
- Most phase abundances reported in literature, obtained via Rietveld analysis, are provided in a manner suggesting absolute values

⇨ Where no allowance of amorphous and/or unidentified phases has been made/reported, it is reasonable to assume relative phase abundances instead

Summary

- Calibration based methods usually have the potential to achieve the highest accuracy, as most aberrations are included in the calibration function
- Any calibration sample and standard will contain amorphous materials which, if not accounted for, will decrease accuracy
  - Any material possesses a non-diffracting surface layer with some degree of disorder / inclusion of surface reaction products and adsorbed species
  - Such a layer can easily account for a mass fraction of several percent in a finely divided solid

Summary

- Singular samples do not afford the luxury of making a calibration suite
- Intensity contributions of amorphous phases to the diffraction pattern are not always evident, especially at low concentrations
    - Indirect methods will usually perform better
- Where intensity contributions of amorphous phases are evident, any method based on modeling amorphous bands provides improved accuracy (direct methods)
    - Usually a sample of pure amorphous material, or a sample where the amorphous content is high, is required to establish an accurate model.