Quantitative Phase Analysis with Diffraction Methods

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QPA literature: a selection

Books


Articles & Reviews

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IV. Whole patterns QPA methods → Rietveld and Rietveld-like methods
I. Defining the QPA problem

Qualitative *versus* Quantitative phase analysis

Principal use of powder diffraction technique is the identification of crystalline or disordered structures (or phases)

Why?

A powder diffraction pattern is **DIRECTLY** produced by the structure of the component phases and can, therefore, fingerprint them
What do we learn from a powder pattern of a crystalline structure?

- Position of the diffracted peaks ➔ size and dimension of the unit cell
- Intensity ratios of the diffracted peaks ➔ type and location of atoms in the unit cell
- Full Width at Half Maximum (FWHM) of the diffracted peaks ➔ intrinsic properties of the materials (i.e. microstructural analysis)
I. Defining the QPA problem

**Polymorphism of drugs**

Polymorphism is the ability of substances with **identical chemical composition** to crystallize in solid state phases according to different arrangements or conformations of the basic molecule(s) in the crystal lattice.

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**Example of Bupivacaine Hydrochloride**

Forms B and D share the same chemical composition, but have different solid forms → They are different polymorphs!
I. Defining the QPA problem

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 important and needs to be kept under control

- **Degree of Crystallinity** in amorphous/crystalline mixtures
I. Defining the QPA problem

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

Majority phase (intensity up to 1.5 M counts): Haloperidol

Minority phase: Indomethacin

Diffracted intensity (a.u.)

2θ (degree)
I. Defining the QPA problem

QPA analytical methods

Several are the analytical methods used to obtain quantitative phase related information:

• Based on chemical composition (so-called *normative calculation*)

• Based on properties specific to the phases of interest (e.g. magnetism, selective dissolution, density)

• Spectroscopic methods (e.g. Raman and Infrared spectroscopy, Mass spectroscopy, Nuclear Magnetic Resonance spectroscopy)

• Thermal Methods (e.g. Differential Scanning Calorimetry, ThermoGravimetric Analysis)

• Diffraction Methods  \( \rightarrow \) XRPD  
  
  **Direct method**

**Diffraction information is directly produced by the crystal structure of the component phases in the mixture**
I. Defining the QPA problem

QPA ↔ determining the contribution (typically in % weight) of each component phase in a mixture
DIFFRACTION-BASED QPA METHODS

I. Defining the QPA problem

Single-peak methods:

- Intensity ratio $I_{\text{unknown}}/I_{\text{standard}}$ of one or more reflections
- No need of structural information but prone to systematic errors (e.g. caused by preferential orientation and peak overlapping)
- Need ad-hoc mixtures for calibration curves

Whole-pattern methods:

- Use of full diffraction patterns
- Minimization of systematic errors (e.g. due to peak overlap)
- Preferential Orientation (PO) can be modeled
- Accuracy close to X-Ray fluorescence elemental analysis, with the advantage of being sensitive to structural differences $\rightarrow$ direct QPA of polymorphs
I. Defining the QPA problem

DIFFRACTION-BASED QPA METHODS

**Single-peak methods:**
(adapted from Cullity, *Elements of X-Ray Diffraction*)

- Intensity ratio $I_{\text{unknown}}/I_{\text{standard}}$ of one or more reflections
- No need of structural information but prone to systematic errors (e.g. caused by preferential orientation and peak overlapping)
- Need *ad-hoc* mixtures for calibration curves

**Rietveld-based methods:**
(adapted from Madsen & Scarlett in *Powder Diffraction-Theory and Practice*)

- Use of full diffraction patterns
- Minimization of systematic errors (e.g. due to peak overlap)
- Preferential Orientation (PO) can be modeled
- Accuracy close to X-Ray fluorescence elemental analysis, with the advantage of being sensitive to structural differences $\rightarrow$ direct QPA of polymorphs
II. Math background: the diffracted integrated intensity

QPA with diffraction methods: math background

The diffracted intensity distribution is defined by:

**Structural factors** → crystal structure

**Specimen factors** → preferential orientation, grain size, shape and distribution, microstructure

**Instrumental factors** → properties of radiation, optics geometry, properties of detectors, slits and/or monochromator

![Graph showing diffracted intensity distribution](image)

Si NIST 640C at 12.4 keV
0.5 mm capillary diameter

2θ (degrees)
II. Math background: the diffracted integrated intensity

For a powder diffraction pattern of a pure phase we can write:

\[ I_{hkl} = K \cdot M_{hkl} \cdot L_{\theta} \cdot P_{\theta} \cdot A_{\theta} \cdot PO_{hkl} \cdot E_{hkl} \cdot |F_{(hkl)}|^2 \cdot \exp \left( -2B \left( \frac{\sin \theta}{\lambda} \right) \right) \]

- **Integrated intensity** of reflection \( hkl \)
- **Multiplicity factor**
- **Lorentz factor** for powders = \( \frac{1}{\sin^2 \theta \cdot \cos \theta} \)
- **Scale factor**
- **Polarization factor** = \( \begin{cases} 1 & \text{Synchrotron: vertical scattering plane} \\ \cos^2 2\theta & \text{Synchrotron: horizontal scattering plane} \\ \frac{1 + \cos^2 2\theta}{2} & \text{Unpolarized/unmonochromatized source} \end{cases} \)
- **Structure factor** (or amplitude)
- **Preferential Orientation factor**
- **Extinction factor**

Absorption multiplier factor: experimental geometry dependent (see: Ch.8 in Pechasky & Zavalij; Ch.11 in Dinnebier & Billinge)
II. Math background: the diffracted integrated intensity

For a powder diffraction pattern of a pure phase we can write:

\[ I_{hkl} = K \cdot M_{hkl} \cdot L_{\theta} \cdot P_{\theta} \cdot A_{\theta} \cdot PO_{hkl} \cdot E_{hkl} \cdot |F_{(hkl)}|^2 \cdot \exp \left( -2B \left( \frac{\sin \theta}{\lambda} \right) \right) \]

**Lorentz factor**

for powders

\[ \text{Lorentz factor} = \frac{1}{\sin^2 \theta \cdot \cos \theta} \]

**Polarization factor**

\[ \text{Polarization factor} = \begin{cases} 
1 & \text{Synchrotron: vertical scattering plane} \\
\cos^2 2\theta & \text{Synchrotron: horizontal scattering plane} \\
\frac{1 + \cos^2 2\theta}{2} & \text{Unpolarized/unmonochromatized source}
\end{cases} \]
II. Math background: the diffracted integrated intensity

For a powder diffraction pattern of a pure phase we can write:

\[ I_{hkl} = K \cdot M_{hkl} \cdot L_\theta \cdot P_\theta \cdot A_\theta \cdot P_0_{hkl} \cdot E_{hkl} \cdot |F_{(hkl)}|^2 \cdot \exp \left( -2B \left( \frac{\sin \theta}{\lambda} \right) \right) \]

Lorentz-Polarization factor for powders

\[ \text{Lorentz-Polarization factor} = \frac{1 + \cos^2 2\theta \cos^2 2\theta_M}{\sin^2 \theta \cdot \cos \theta} \]

**Lab diffractometer:**

2\( \theta_M \) is the Bragg angle of the reflection from a monochromator, 2\( \theta_M = 0 \) for unpolarized unmonochromatized source, 2\( \theta_M \neq 0 \) (e.g. 26.5° graphite mono +CuK\( \alpha \) radiation)

**Synchrotron radiation:**

2\( \theta_M \) is the angle between the scattering direction (where we place our detector!) and the direction of acceleration of the electron (e.g. the direction of the electric field of the synchrotron e.m. radiation). In the vertical plane this is always 90°.
II. Math background: the diffracted integrated intensity

For a powder diffraction pattern of a pure phase we can write:

\[
I_{hkl} = K \cdot M_{hkl} \cdot L_\theta \cdot P_\theta \cdot A_\theta \cdot P_O_{hkl} \cdot E_{hkl} \cdot |F_{(hkl)}|^2 \cdot \exp \left( -2B \left( \frac{\sin \theta}{\lambda} \right) \right)
\]

negligible

Under the hypothesis of A, PO and E negligible, transmission (Debye-Scherrer) geometry, synchrotron radiation with vertical diffraction plane (as at the SLS-MS-PD), with powders loaded in capillaries and a 1D display detector (e.g. Mythen II):

\[
I_{hkl} = \left[ \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4} \right] \cdot \left[ \frac{M_{hkl}}{V^2} \right] \cdot |F_{(hkl)}|^2 \cdot \left( \frac{1}{\sin^2 \theta \cdot \cos \theta} \right) \cdot \exp \left( -2B \left( \frac{\sin \theta}{\lambda} \right) \right) \cdot \left[ \frac{1}{\mu} \right]
\]

\begin{align*}
I_0 & \quad \text{incident beam intensity} \\
\lambda & \quad \text{photon beam wavelength} \\
\sigma & \quad \text{cross sectional area of incident beam} \\
e & \quad \text{charge of the electron} \\
m_e & \quad \text{mass of the electron} \\
c & \quad \text{speed of light} \\
V & \quad \text{unit cell volume} \\
\mu & \quad \text{linear absorption (attenuation) coefficient of the pure phase} \\
\rho & \quad \text{density of the pure phase} \\
\mu^* & \quad \text{mass absorption coefficient} \\
\exp(-2B\left(\frac{\sin \theta}{\lambda}\right)) & \quad \text{thermal factor, B is the mean atomic displacement parameter (ADP)}
\end{align*}
III. Single-peak or single-line QPA methods

For a powder diffraction pattern of a **mixture** (e.g. binary $\alpha+\beta$ mixture), for a hkl intensity line of phase $\alpha$, we can write:

$$I_{(hkl)\alpha} = \left[ \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4} \right] \cdot \left[ \frac{M_{hkl}}{V_{\alpha}^2} \cdot |F_{hkl}| \alpha \right]^2 \left( \frac{1}{\sin^2 \theta \cdot \cos \theta} \right) \cdot \exp \left( -2B\alpha \left( \frac{\sin \theta}{\lambda} \right) \right) \cdot \left[ \frac{c_{\alpha}}{\mu_m} \right]$$

- $I_0$: incident beam intensity
- $\lambda$: photon beam wavelength
- $\sigma$: cross sectional area of incident beam
- $e$: charge of the electron
- $m_e$: mass of the electron
- $c$: speed of light
- $r$: distance scattering electron-detector
- $V_{\alpha}$: unit cell volume of phase $\alpha$
- $c_{\alpha}$: volume fraction of phase $\alpha$
- $\mu_m$: linear absorption (attenuation) coefficient of the mixture
- $\rho_m$ and $\mu_m^*$: density of the mixture and the mass absorption coefficient
- $B\alpha$: thermal factor, with $B$ mean Atomic Displacement Parameter (ADP)

And similarly, for a $h'k'l'$ line of phase $\beta$, we can write:

$$I_{(h'k'l')\beta} = \left[ \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4} \right] \cdot \left[ \frac{M_{hkl}}{V_{\beta}^2} \cdot |F_{(h'k'l')}| \beta \right]^2 \left( \frac{1}{\sin^2 \theta \cdot \cos \theta} \right) \cdot \exp \left( -2B\beta \left( \frac{\sin \theta}{\lambda} \right) \right) \cdot \left[ \frac{c_{\beta}}{\mu_m} \right]$$
III. Single-peak or single-line QPA methods

For a powder diffraction pattern of a mixture (e.g. binary $\alpha+\beta$ mixture), for a hkl intensity line of phase $\alpha$, we can write:

$$I_{(hkl)\alpha} = \left[ \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m e^2 c^4} \right] \cdot \left[ \frac{M_{hkl}}{V_\alpha} \right]^2 \cdot |F_{hkl}|^2 \left( \frac{1}{\sin^2 \theta \cdot \cos \theta} \right) \cdot \exp \left( -2B_\alpha \left( \frac{\sin \theta}{\lambda} \right) \right) \cdot \left[ \frac{c_\alpha}{\mu_m} \right]$$

All factors are constant and independent of the concentration of the $\alpha$ phase with the exception of $c_\alpha$ and $\mu_m$

$$I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m}$$

and equivalently:

$$I_{(hkl)\beta} = \frac{K_{1,\beta} \cdot c_\beta}{\mu_m}$$
III. Single-peak or single-line QPA methods

The simplified expression: \( I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m} \) can also be written in terms of weight fractions \( w_\alpha \) (and \( w_\beta \)): \[
I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha \cdot \rho_m}{\mu_m \cdot \rho_\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \frac{\mu_m}{\rho_m}} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m} \]

with \( \rho_\alpha \) the density of phase \( \alpha \) and \( \mu_m * \) the mass absorption coefficient \( (= \frac{\mu_m}{\rho_m}) \).

DEMO:
Assuming a unit volume of mixture \((V_m=1)\): \( \rho_m \) = density of mixture = weight of mixture \( \rightarrow \) \( w_\alpha \rho_m \) and \( w_\beta \rho_m \) represent the weights of the \( \alpha \) and \( \beta \) contents in our binary mixture with \( w_\alpha \) and \( w_\beta \) the weight fractions \( \rightarrow \rho_\alpha = \frac{w_\alpha \rho_m}{c_\alpha} \rightarrow c_\alpha = \frac{w_\alpha \rho_m}{\rho_\alpha} \) and equivalently \( c_\beta = \frac{w_\beta \rho_m}{\rho_\beta} \rightarrow c_\alpha = \frac{w_\alpha \rho_m}{\rho_\alpha \mu_m} \rightarrow \frac{c_\alpha}{\mu_m} = \frac{c_\alpha}{\rho_\alpha \mu_m} = \frac{c_\alpha}{\mu_m} \cdot \frac{1}{\mu_m^*} \) with \( \mu_m \) linear absorption (or attenuation) coefficient and \( \mu_m^* \) mass absorption coefficient.
III. Single-peak or single-line QPA methods

The simplified expression: \( I_{(hkl)} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m} \), can also be written in terms of weight fractions \( w_\alpha \) (and \( w_\beta \)): \( I_{(hkl)} = \frac{K_{1,\alpha} \cdot w_\alpha \cdot \rho_m}{\mu_m \cdot \rho_\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \frac{\mu_m}{\rho_m}} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m \ast} \) with \( \rho_\alpha \) the density of phase \( \alpha \) and \( \mu_m \ast \) the mass absorption coefficient (\( = \frac{\mu_m}{\rho_m} \)).

**DEMO:**
Assuming a unit volume of mixture (\( V_m = 1 \)): \( \rho_m \) = density of mixture = weight of mixture → \( w_\alpha \rho_m \) and \( w_\beta \rho_m \) represent the weights of the \( \alpha \) and \( \beta \) contents in our binary mixture with \( w_\alpha \) and \( w_\beta \) the weight fractions → \( \rho_\alpha = \frac{w_\alpha \rho_m}{c_\alpha} \to c_\alpha = \frac{w_\alpha \rho_m}{\rho_\alpha} \) and equivalently \( c_\beta = \frac{w_\beta \rho_m}{\rho_\beta} \to c_\alpha = \frac{w_\alpha \rho_m}{\rho_\alpha \mu_m} = \frac{w_\alpha}{\rho_\alpha} \cdot \frac{1}{\mu_m \ast} \) with \( \mu_m \) linear absorption (or attenuation) coefficient and \( \mu_m \ast \) mass absorption coefficient.
III. Single-peak or single-line QPA methods

The simplified expression: \( I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_{\alpha}}{\mu_m} \)

\[ \text{can also be written in terms of weight fractions } w_\alpha \text{ (and } w_\beta) : \]
\[ I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha \cdot \rho_m}{\mu_m \cdot \rho_\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \frac{\mu_m}{\rho_m}} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m} \]

\[ \text{with } \rho_\alpha \text{ the density of phase } \alpha \text{ and } \mu_m \cdot \rho_m \text{ the mass absorption coefficient (} = \frac{\mu_m}{\rho_m} \). \]

If we can access a powder sample of pure phase \( \alpha \):
\[ I_{(hkl)\alpha,\text{pure}} = \frac{K_{1,\alpha}}{\rho_\alpha \mu_\alpha} = \frac{K_{1,\alpha}}{\mu_\alpha} \]

and we can write:
\[ \frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,\text{pure}}} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \frac{\mu_m}{\rho_m} \cdot K_{1,\alpha}} = \frac{w_\alpha (\frac{\mu_\alpha}{\rho_\alpha})}{(\frac{\mu_m}{\rho_m})} = \frac{w_\alpha (\frac{\mu_\alpha}{\rho_\alpha})}{w_\alpha (\frac{\mu_\alpha}{\rho_\alpha} - \frac{\mu_\beta}{\rho_\beta}) + \frac{\mu_\beta}{\rho_\beta}} \]

[\text{[demo p.389-390 Cullity]}]
QPA of a binary mixture can, therefore be performed provided that we can access:

- the mass absorption coefficients of the two phases (if not, a calibration curve can be prepared using mixtures of known composition)
- one pure phase (or a mixture with a known amount of that phase)
- No need of structural information, $K_{1,\alpha}$ cancels out

\[
\frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,pure}} = \frac{w_\alpha \left( \frac{\mu_\alpha}{\rho_\alpha} \right)}{w_\alpha \left( \frac{\mu_\alpha}{\rho_\alpha} - \frac{\mu_\beta}{\rho_\beta} \right) + \frac{\mu_\beta}{\rho_\beta}}
\]
III. Single-peak or single-line QPA methods

What can we observe?

\[
\frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,\text{pure}}} = \frac{w_\alpha(\frac{\mu_\alpha}{\rho_\alpha})}{w_\alpha(\frac{\mu_\alpha}{\rho_\alpha} - \frac{\mu_\beta}{\rho_\beta}) + \frac{\mu_\beta}{\rho_\beta}}
\]

- The intensity of a particular diffraction line depends on the mass absorption coefficient of the other phase

- For binary mixtures of phases with the same mass absorption coefficient: \( \frac{I_{(hkl)\alpha}}{I_{(hkl)\alpha,\text{pure}}} = w_\alpha \)

The binary mixture case that we have worked out together is an example of the so-called **single-line** or **single-peak methods of QPA**, for which the measurement of the weight fraction of phase in a mixture depends on the measurement of the ratio of the intensity of a diffraction line from that phase to the intensity of some standard reference line!

In the case discussed, the reference standard is the pure phase \( \alpha \)!
III. Single-peak or single-line QPA methods

DIRECT COMPARISON METHOD

INTERNAL STANDARD METHOD
III. Single-peak or single-line QPA methods

DIRECT COMPARISON METHOD

Let us again consider a \( \alpha+\beta \) binary mixture:

\[
I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m} \quad \quad I_{(hkl)\beta} = \frac{K_{1,\beta} \cdot c_\beta}{\mu_m} = \frac{K_{1,\beta} \cdot w_\beta}{\rho_\beta \mu_m}
\]

Let us separate in \( K_{1,\alpha} \) the phase-dependent from the phase-independent part:

\[
K_{1,\alpha} = K_2 \cdot R_{1,\alpha}
\]

K_2 is a constant independent of the kind and amount of diffracting substance; R depends on \( \theta, \) hkl, kind of substance

\[
I_{(hkl)\alpha} = \frac{K_2 \cdot R_{\alpha} \cdot c_\alpha}{\mu_m} \quad \frac{I_{(hkl)\alpha}}{I_{(hkl)\beta}} = \frac{R_{\alpha} \cdot c_\alpha}{R_\beta \cdot c_\beta} \quad \frac{c_\alpha}{c_\beta} = \frac{I_{(hkl)\beta} \cdot R_\beta}{I_{(hkl)\alpha} \cdot R_{\alpha}}
\]

Details here: \( K_2 = \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4} \) and \( R_{\alpha} = \left[ \frac{M_{hkl}}{V_\alpha^2} \cdot |F_{(hkl)}|_\alpha \frac{2}{2} \right] \cdot \exp \left( -2B_\alpha \frac{\sin \theta}{\lambda} \right) \)
III. Single-peak or single-line QPA methods

DIRECT COMPARISON METHOD

Let us again consider a $\alpha+\beta$ binary mixture:

$$I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot c_\alpha}{\mu_m} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \mu_m} \quad I_{(h\ell\ell\ell)\beta} = \frac{K_{1,\beta} \cdot c_\beta}{\mu_m} = \frac{K_{1,\beta} \cdot w_\beta}{\rho_\beta \mu_m}$$

Let us separate in $K_{1,\alpha}$ the phase-dependent from the phase-independent part:

$$K_{1,\alpha} = K_2 \cdot R_{1,\alpha} \quad K_2 \text{ is a constant independent of the kind and amount of diffracting substance; } R \text{ depends on } \theta, \text{ hkl, kind of substance}$$

$$I_{(hkl)\alpha} = \frac{K_2 \cdot R_\alpha \cdot c_\alpha}{\mu_m} \quad I_{(h\ell\ell\ell)\beta} = \frac{R_\alpha \cdot c_\beta}{R_\beta \cdot c_\beta} \quad \frac{w_\alpha}{w_\beta} = \frac{I_{(hkl)\beta}}{I_{(h\ell\ell\ell)\alpha}} \cdot \frac{\rho_\alpha \cdot R_\beta}{\rho_\beta \cdot R_\alpha}$$

Details here: $K_2 = \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4}$ and $R_\alpha = \left[ \frac{M_{hkl}}{V_\alpha^2} \cdot |F_{(hkl)}|_\alpha^2 \cdot \left( \frac{1 + \cos^2 2\theta}{2} \right) \right] \cdot \exp \left( -2B_\alpha \left( \frac{\sin \theta}{\lambda} \right) \right)$
III. Single-peak or single-line QPA methods

INTERNAL STANDARD METHOD

A diffraction line from the phase that we need to quantify in a given mixture (e.g. \( I_{hkl,a} \)) is compared with a line from a standard (e.g. \( I_{h'k'l',s} \)) mixed with our original mixture in known proportion → the ISM method is only applicable to powders!

Let us consider a mixture M of n phases \( \alpha, \beta, \gamma \ldots \)

We need to quantify the **amount of phase** \( \alpha \) in a series of mixtures of type M in which the relative proportion of the other phases \( \beta, \gamma \ldots \) might change from mixture to mixture.
III. Single-peak or single-line QPA methods

INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture $M$ with a known amount of a known standard $S$ and form a new mixture $M' = M + S$ (e.g. 50% $M + 50\%$ $S$)

![Diagram of Mixture M, Standard S, and M'=M+S with phases α, β, γ, and Standard S represented by different colors](image)

ii. Let $c_\alpha$ and $c'_\alpha$ the volume fractions of phase $\alpha$ in $M$ and $M'$ (both unknown!) and $c_S$ the volume fraction of the standard $S$ (that we know!)
INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture M with a known amount of a known standard S and form a new mixture M’=M+S (e.g. 50% M + 50% S)

ii. Let $c_\alpha$ and $c'_\alpha$ the volume fractions of phase a in M and M’ (both unknown!) and $c_S$ the volume fraction of the standard S (that we know!)

iii. From a powder diffraction pattern recorded on the new mixture M’, we obtain:

$$I_{(hkl)\alpha} = I_\alpha = \frac{K_{1,\alpha} \cdot c_\alpha'}{\mu_m}$$

and similarly:

$$I_{(hkl)S} = I_S = \frac{K_{1,S} \cdot c_S}{\mu_m}$$

Note that $\mu_m$ cancels out!

$$\frac{I_\alpha}{I_S} = \frac{K_{1,\alpha} \cdot c_\alpha'}{K_{1,S} \cdot c_S}$$

It physically means that the variation of absorption due to the variation of the relative amounts of the other phases present in the original mixture ($\beta, \gamma, ...$) does not affect the $I_\alpha/I_S$ ratio since such variations equivalently affects $I_\alpha$ and $I_S$!
III. Single-peak or single-line QPA methods

INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture M with a known amount of a known standard S and form a new mixture M’=M+S (e.g. 50% M + 50% S)

ii. Let \( c_\alpha \) and \( c'_\alpha \) the volume fractions of phase \( \alpha \) in M and M’ (both unknown!) and \( c_S \) the volume fraction of the standard S (that we know!)

iii. From a powder diffraction pattern recorded on the new mixture M’, we obtain:

\[
\frac{I_\alpha}{I_S} = \frac{K_{1,\alpha} \cdot c'_\alpha}{K_{1,S} \cdot c_S} \quad \text{with} \quad \frac{c'_\alpha}{c_S} = \frac{w'_\alpha \cdot \rho_S}{\rho_\alpha \cdot w_S} \quad \rightarrow \quad \frac{I_\alpha}{I_S} = \frac{K_{1,\alpha} \cdot w'_\alpha \cdot \rho_S}{K_{1,S} \cdot \rho_\alpha \cdot w_S}
\]

If \( w_S \) is kept constant in all mixtures of type M’, then

\[
\frac{K_{1,\alpha}}{K_{1,S}} \cdot \frac{\rho_S}{\rho_\alpha \cdot w_S} = K_3
\]

\[
\frac{I_\alpha}{I_S} = K_3 \cdot w'_\alpha \quad \rightarrow \quad \frac{I_\alpha}{I_S} = K_4 \cdot w_\alpha \quad \text{being:} \quad w'_\alpha = w_\alpha (1 - w_S)
\]
III. Single-peak or single-line QPA methods

INTERNAL STANDARD METHOD: how does it work?

i. We mix a known amount of original mixture M with a known amount of a known standard S and form a new mixture M’=M+S (e.g. 50% M + 50% S)

ii. Let \( c_\alpha \) and \( c'_\alpha \) the volume fractions of phase a in M and M’ (both unknown!) and \( c_S \) the volume fraction of the standard S (that we know!)

iii. From a powder diffraction pattern recorded on the new mixture M’, we obtain:

\[
\frac{I_\alpha}{I_\text{S}} = K_4 \cdot w_\alpha
\]

- The intensity ratio \( \frac{I_\alpha}{I_\text{S}} \) is therefore a **linear function** of the weight fraction \( w_\alpha \) of phase \( \alpha \).

- A calibration curve can be prepared from XRPD measurements on a set of *ad-hoc* synthetic samples containing **known** concentrations of phase \( \alpha \) and a **constant** concentration \( w_S \) of a suitable standard.

- The concentration of \( \alpha \) in an unknown mixture is obtained by measuring the ratio \( \frac{I_\alpha}{I_\text{S}} \) in a mixture of type M’ (so-called *spiked* sample) containing the unknown original mixture and the standard in the same proportion as used to build up the calibration curve.
III. Single-peak or single-line QPA methods

**Generalization of the Internal Standard Method** →

**The Reference Intensity Ratio (RIR)**

\[
\frac{I_{\alpha}}{I_S} = K_4 \cdot w_\alpha
\]

The calibration constant \(K_4\) depends on: \(\alpha, S, (hkl)_\alpha, (h'k'l')_S\) and \(w_S\)

(remember: \(I_\alpha = I_{(hkl)\alpha}\) and \(I_S = I_{(h'k'l')_S}\))

For a more reliable quantification, the use of several analyte-line/internal standard-line pair is preferable → each pair requires a calibration constant!

The use of relative intensities \(I_{rel}\) and so-called **Relative Intensity Ratio (RIR)** allows us to use multiple analyte/standard reflection pairs without the need of multiple reference standards:

\[
\frac{I_{i\alpha}}{I_{jS}} \cdot \frac{I_{jS}}{I_{i\alpha}} \cdot \frac{w_S}{w_\alpha} = K = RIR_{\alpha,S}
\]

**Super-easy example**

**Pair A:**

\[
\frac{200}{40} \cdot \frac{100}{100} \cdot \frac{0.5}{0.2} = 12.5 = K = RIR_{\alpha,S}
\]

**Pair B:**

\[
\frac{100}{10} \cdot \frac{25}{50} \cdot \frac{0.5}{0.2} = 12.5 = K = RIR_{\alpha,S}
\]

---

Hubbard & Snyder, (1988)
Powder Diffraction 3, 74-78.

**Diffraction pattern from a \(M'\)-type mixture with 50% standard and (for example) 20% \(\alpha\)-phase**

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www.excels.us
III. Single-peak or single-line QPA methods

The Reference Intensity Ratio (RIR)

\[ K = RIR_{\alpha,S} = \frac{I_{i\alpha}}{I_{js}} \cdot \frac{I_{js}^{rel}}{I_{i\alpha}^{rel}} \cdot \frac{w_S}{w_\alpha} \]

Universal calibration constant relating the scattering power of phase \( \alpha \) to that of the standard S

→ So-called Reference Intensity Ratio or RIR

Standard S → NIST Corundum → RIR=I/I_C

The Powder Diffraction File (PDF) contains I/I_C ratios for more than 2500 phases!

Quantitative Phase Analysis with I/I_C (RIR or Chung Method)

\[ w_\alpha = \frac{I_{i\alpha}}{I_{jc}} \cdot \frac{I_{jc}^{rel}}{I_{i\alpha}^{rel}} \cdot \frac{w_S}{RIR_{\alpha,C}} = \frac{I_{i\alpha}}{I_{jc}} \cdot \frac{I_{jc}^{rel}}{I_{i\alpha}^{rel}} \cdot \frac{w_S}{(I/I_C)_\alpha} \]

With the addition of a known %wt of corundum, no calibration curves needed!

Or standardless QPA, if all phases in the mixture are crystalline, identified, and the RIR values known for each of them!
DIFFRACTION-BASED METHODS

Single-peak methods:
(adapted from Cullity, *Elements of X-Ray Diffraction*)

- Intensity ratio $I_{\text{unknown}}/I_{\text{standard}}$ of one or more reflections
- No need of structural information but prone to systematic errors caused by PO and peak overlapping
- Need ad-hoc mixtures for calibration curves

Rietveld-based methods:
(adapted from Madsen & Scarlett in *Powder Diffraction-Theory and Practice*)

- Use of full diffraction patterns
- Minimization of systematic errors (e.g. due to peak overlap)
- Preferential Orientation (PO) can be modeled
- Accuracy close to X-Ray fluorescence elemental analysis, with the advantage of being sensitive to structural differences $\rightarrow$ direct QPA of polymorphs
IV. Rietveld-based QPA methods

Rietveld QPA METHOD

“The Rietveld method uses a model to calculate a diffraction pattern which is then compared with observed data. The difference between the two patterns is then reduced through least square minimization. The refinable parameters used in the models provide the analyst with information regarding the crystal structure of the component phases, the crystalline size and strain and, importantly, their relative proportions. The Rietveld scale factor $S$, which is a multiplier for each components’ contribution to the pattern, is related to the relative abundance of that phase and can be used in the quantification of phases.”

(textual citation from Quantitative Phase Analysis using the Rietveld Method, Madsen, Scarlett, Riley & Raven, Ch.10 in Modern Diffraction Methods, Mittemeijer & Welzel Edts, 2013)
IV. Rietveld-based QPA methods

Rietveld QPA METHOD

\[ I_{(hkl)\alpha} = \left( \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4} \right) \cdot \left[ \frac{M_{hkl}}{V_\alpha} \cdot |F_{hkl}|^2 \left( \frac{1}{\sin^2 \theta \cdot \cos \theta} \right) \right] \cdot \exp \left( -2B_\alpha \left( \frac{\sin \theta}{\lambda} \right) \right) \cdot \left[ \frac{w_\alpha}{\rho_\alpha \mu_m^*} \right] \]

D-S geometry with capillary, assuming absorption, PO and extinction negligible

\[ I_{(hkl)\alpha} = \frac{K_{1,\alpha} \cdot w_\alpha}{\rho_\alpha \cdot \mu_m^*} \quad \implies \quad w_\alpha = \frac{I_\alpha \cdot \rho_\alpha \cdot \mu_m^*}{K_{1,\alpha}} = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K} \]

- \[ K_{1,\alpha} \propto \frac{1}{V_\alpha^2} \]

- \[ I_\alpha \propto S_\alpha \]  
  R. J. Hill, Powder Diffr. 1991, 6, 74-77

- \[ \rho_\alpha = 1.6604 \cdot \frac{ZM_\alpha}{V_\alpha} \]  
  Z=number of formula units  
  M=molecular mass of the formula unit
IV. Rietveld-based QPA methods

Rietveld QPA METHOD

\[ I_{(hkl)}^{(\alpha)} = \left[ \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4} \right] \cdot \left[ \frac{M_{hkl}}{V^2} \cdot |F_{hkl}|^{2} \left( \frac{1}{\sin^2 \theta \cdot \cos \theta} \right) \right] \cdot \exp \left( -2B_{\alpha} \left( \frac{\sin \theta}{\lambda} \right) \right) \cdot \left[ \frac{w_{\alpha}}{\rho_{\alpha} \mu^*_m} \right] \]

D-S geometry with capillary, assuming absorption, PO and extinction negligible

\[ w_{\alpha} = \frac{S_{\alpha} \cdot (ZMV)_{\alpha} \cdot \mu^*_m}{K} \]

**IMPORTANT RELATION**

In 1988, O’Connor & Raven demonstrated that the scaling factor K is independent of individual phases and overall sample-related parameters (Powder Diffr. 3, 2-6).

This implies that K only needs to be estimated once for a given instrumental configuration and using an appropriate standard

⇒ EXTERNAL STANDARD METHOD for absolute QPA analysis

**Warning:** the term “instrumental configuration” really refers to all experimental details ⇒ in DS geometry with powders in capillaries it would imply also the same powder packing!
IV. Rietveld-based QPA methods

**Rietveld QPA METHOD**

\[
I_{(hkl)\alpha} = \left[ \frac{I_0 \lambda^3}{32 \pi r} \cdot \frac{\sigma e^4}{m_e^2 c^4} \right] \cdot \left[ \frac{M_{hkl}}{V_\alpha^2} \cdot |F_{hkl}| \alpha^2 \left( \frac{1}{\sin^2 \theta \cdot \cos \theta} \right) \right] \cdot \exp \left(-2B_\alpha \left( \frac{\sin \theta}{\lambda} \right) \right) \cdot \left[ \frac{w_\alpha}{\rho \alpha \mu_m^*} \right]
\]

D-S geometry with capillary, assuming absorption, PO and extinction negligible

\[
w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K}
\]

**IMPORTANT RELATION**

\((ZMV)_\alpha\) is the so-called *calibration constant* for phase \(\alpha\) that can be calculated from the structural model (either from crystallographic database or the refinement of the pure \(\alpha\) phase)

Absolute QPA analysis can, then, be obtained provided we correctly estimate \(K\) and \(\mu_m^*\) for all our mixtures and calibration standards (the latter for \(K\) determination)
QPA by XRPD
13th PPXRD Workshop
May 18th, 2015 - Bad Herrenalb

IV. Rietveld-based QPA methods

Rietveld QPA METHOD: Questions & Answers

Q1: Can we still perform absolute QPA analyses without estimating $K$ and $\mu_m^*$?

A1: Yes, we can, if we “spike” our unknown mixture with a known amount $w_s$ of an appropriate reference standard $S$ of well known crystallographic structure (INTERNAL STANDARD METHOD)

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

$$w'_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S}$$

$$w'_\alpha = w_\alpha (1 - w_S)$$

Remark: note that there is no need of a calibration curve as for the Internal Standard Method as implemented in the single-line diffraction method in virtue of performing here a Rietveld refinement!
IV. Rietveld-based QPA methods

Rietveld QPA METHOD: Q&A

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

$$w'_\alpha = w_s \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_s \cdot (ZMV)_s}$$

$$w'_\alpha = w_\alpha (1 - w_s)$$

**Q2:** What if we do **NOT** dispose of the whole composition of the unknown mixture?

**A2:** We have 2 possibilities:

> if we can reasonably estimate $K$ and $\mu_m^*$, we apply ★, that is the External Standard Method.

> we spike the sample with a known amount of a known standard and apply the ★★ (Internal Standard Method)
IV. Rietveld-based QPA methods

Rietveld QPA METHOD: Q&A

\[ w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K} \]

\[ w'_\alpha = w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S} \]

\[ w'_\alpha = w_\alpha (1 - w_S) \]

Q₂: What if we dispose of the whole composition of the unknown mixture?

A₂: For a mixture of n crystalline phases \( \alpha, \beta, \gamma, \delta \ldots \) we can write:

\[ w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1 \]

\[ w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i} \]

and equivalent expressions for \( w_\beta, w_\gamma \ldots \)

**Hill & Howard** (JAC (1987). 20, 467-474) modification of the Rietveld QPA method, known as the \textit{ZMV approach} inspired by the \textit{Matrix Flushing Method} of \textbf{Chung} (JAC, 1974, 7, 519-525 and 526-531)
IV. Rietveld-based QPA methods

Rietveld QPA METHOD: Q&A

\[ w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu_m^*}{K} \]

External Standard Method

\[ w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1 \]

Hill & Howard (ZMV) Approach

\[ w'_\alpha = w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S} \]

\[ w'_\alpha = w_\alpha(1 - w_S) \]

Internal Standard Method

**Warning:** the (ZMV) approach assumes that:

- All phases in the mixtures are crystalline!
- We have identified them all!

If our mixture has unknown crystalline phases or amorphous components, a QPA analysis via (ZMV) approach inevitably **overestimates** the \( w_i \) weight fractions.
IV. Rietveld-based QPA methods

Rietveld QPA METHOD: Q&A

\[ w_\alpha = \frac{S_\alpha \cdot (ZMV)_\alpha \cdot \mu^*_m}{K} \]

External Standard Method

\[ w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1 \]

Hill & Howard (ZMV) Approach

\[ w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i} \]

\[ w'_\alpha = w_s \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_s \cdot (ZMV)_S} \]

Internal Standard Method

\[ w'_\alpha = w_\alpha (1 - w_s) \]

What do we do in such cases?

We apply the Internal Standard Method:

- We add a known amount of an appropriate standard S

- We write ★★★ for all identified crystalline phases i and for S

- For each phase i we can write: \( Corrected(W_i) = W_{i,Rietveld} \frac{w_{S,true}}{w_{S,Rietveld}} \)

- \( W_{unknown}=1.0-\sum_{k=1}^{n} Corrected(W_k) \)
IV. Rietveld-based QPA methods

What if a **structural model is NOT available** or if it does not work well with our experimental data?
Partial Or No Known Crystal Structure (PONKCS) Method
Madsen & Scarlett, Powder Diffr. 21(4), 2006, 278-284;
Madsen, Scarlett & Kern, Z. Kristallogr.226 (2011) 944-955

• If partial structure available (i.e. unit cell and SG) → real structure factors substituted with empirical values derived from a Pawley or LeBail refinement performed on pure phases → an hkl_Is phase in Topas

• If partial structure NOT available → real structure factor substituted by fictitious phases consisting each of a series of related peaks with FIXED relative intensities and GROUP-SCALED as a single entity during the QPA analysis → a x0_Is phase or peak-phase in Topas

• Compute empirical ZM or ZMV calibration constants from the refinement of ad-hoc mixtures of pure phases with a known amount of a known standard (e.g. via spiking) → so-called PONKCS phases.

Requirements:
• Pure phases (or pure phases with known impurities) must be available
• Ad-hoc mixtures of pure phases with an appropriate standard in known %wt must be available to build the so-called PONKCS phase

Benefits:
• No need of a valid structural model
• PONKCS phases can be “re-used” provided the QPA analyses are conducted at the same photon energy! → Careful with SR-XRPD data!
• PONKCS works for crystalline as well as amorphous phases
Whole-patterns QPA Methods

- **QUANTO+**

  - If *partial structure available* (i.e. unit cell and SG) → for each phase in the mixture a reflection intensity file is built via whole pattern decomposition (e.g. Le Bail refinement) performed on pure phases
  - This «external» file is used instead of the calculated structural factors from the model ($|F_c|^2$) for the absolute scaling of the diffracted intensity via a Wilson plot

**Requirements:**
- Pure phases must be available
- Partial structure (unit cell and SG) must be known
- Crystalline phases

**Benefits:**
- No need to have a valid structural model
- No need to prepare *ad-hoc* mixtures with an appropriate standard!

→ implemented in Quanto (CNR-IC)
Additional topics not covered during the lecture plus a few examples of application
Factors influencing QPA

For a detailed and exhaustive discussion and references citation see:
- Madsen & Scarlett (Ch. 11, Powder Diffraction – Theory and Practice), 2009
- Madsen, Scarlett, Riley & Raven (Ch.10, Modern Diffraction Methods), 2013

Accurate QPA ↔ Accurate integrated intensity
(ca. 1-2% relative)
Factors influencing QPA and QPA accuracy

Sources of errors

Instrument related
- **Experimental geometry**: 
  BB (reflection) \( \theta \rightarrow 2\theta \)
  BB fixed-\( \theta \)
  DS (transmission) capillary or thin layer
- **Counting errors** (random and systematic)

Sample related
- **Particle statistics**
- **Preferential Orientation**
- **Absorption** and **microabsorption**
- Incorrect or insufficient **crystal structure** model
- Crystallite size and strain broadening

Operator related
- **Analyst choices** during QPA analysis affect the results \( \rightarrow \) QPA Round Robin 1996-2002 (see Madsen & Scarlett)
- Dangerous side of easy-to-use QPA software
- Importance of setting up QPA guidelines

Accuracy & Precision associated to QPA
What sets QPA accuracy and precision?
What does a Rietveld (or Rietveld-like) refinement return?
Factors influencing QPA and QPA accuracy

Sources of errors

Instrument related

- Experimental geometry:
  - BB (reflection) θ–2θ
  - BB fixed-θ
  - DS (transmission) capillary or thin layer
- Counting errors (random and systematic)

Sample related

- Particle statistics
- Preferential Orientation
- Absorption and microabsorption
- Incorrect or insufficient crystal structure model
- Crystallite size and strain broadening

Operator related

- Analyst choices during QPA analysis affect the results → QPA Round Robin 1996-2002 (see Madsen & Scarlett)
- Dangerous side of easy-to-use QPA software
- Important of setting up QPA guidelines

The accuracy in the $I_{hkl}$ estimate is strongly influenced by $N_{\text{diff}}$ in a powder sample

$V \sim 3 - 5 \text{ mm}^3 \rightarrow N_{\text{diff}} \sim 3 \rightarrow \sigma_{PS} \sim 0.6$

Table 11.1  Relationship between crystallite diameter and the number diffracting 
(after Smith24).

<table>
<thead>
<tr>
<th>Crystallite diameter (μm)</th>
<th>40</th>
<th>10</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystallites (20 mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number diffracting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$N_{\text{diff}}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_{PS}$</td>
<td>0.289</td>
<td>0.036</td>
<td>0.005</td>
</tr>
</tbody>
</table>

From Madsen&Scarlett, Powder Diffraction-Theory and Practice, p. 309
Factors influencing QPA and QPA accuracy

Instruments related

- Experimental geometry:
  - BB (reflection) θ–2θ
  - BB fixed-θ
  - DS (transmission) capillary or thin layer
- Counting errors (random and systematic)

Sample related

- Particle statistics
- Preferential Orientation
- Absorption and microabsorption
- Incorrect or insufficient crystal structure model
- Crystallite size and strain broadening

Operator related

- Analyst choices during QPA analysis affect the results → QPA Round Robin 1996-2002 (see Madsen & Scarlett)
- Dangerous side of easy-to-use QPA software
- Important of setting up QPA guidelines

The accuracy in the \( I_{\text{hkl}} \) estimate is strongly influenced by \( N_{\text{dифfr}} \) in a powder sample

\[ V \sim 3 - 5 \, \text{mm}^3 \rightarrow N_{\text{dифfr}} \sim 3 \rightarrow \sigma_p \sim 0.6 \]

Glass capillary

Remedies:

- Increase instrument beam divergence
- Sample spinning or oscillation
- Increase the powder volume analyzed or powder repacking
- Mechanical comminution (grinding, milling)
Factors influencing QPA and QPA accuracy

Sources of errors

Instrument related
- Experimental geometry:
  - BB (reflection) \( \theta-2\theta \)
  - BB fixed-\( \theta \)
  - DS (transmission) capillary or thin layer
- Counting errors (random and systematic)

Sample related
- Particle statistics
- Preferential Orientation
- Absorption and microabsorption
- Incorrect or insufficient crystal structure model
- Crystallite size and strain broadening

Operator related
- Analyst choices during QPA analysis affect the results \( \rightarrow \) QPA Round Robin 1996-2002 (see Madsen & Scarlett)
- Dangerous side of easy-to-use QPA software
- Important of setting up QPA guidelines

DS geometry + capillary + 1D position sensitive detectors:
- intensity modulation due to inhomogeneous capillary packing
- inhomogeneous photon beam distribution

Remedies:
- Partial photon beam focusing
- Analysis of a large number of powder volumes
Factors influencing QPA and QPA accuracy

Sources of errors

Instrument related
- Experimental geometry:
  BB (reflection) θ–2θ
  BB fixed-θ
  DS (transmission) capillary or thin layer
- Counting errors (random and systematic)

Sample related
- Particle statistics
- Preferential Orientation
- Absorption and microabsorption
- Incorrect or insufficient crystal structure model
- Crystallite size and strain broadening

Operator related
- Analyst choices during QPA analysis affect the results → QPA Round Robin 1996-2002 (see Madsen & Scarlett)
- Dangerous side of easy-to-use QPA software
- Important of setting up QPA guidelines

- The need of absorption corrections should be minimized and corrections appropriate for the given experimental geometry applied

- Microabsorption (i.e. absorption contract) occurs when the phases in a mixture are characterized by different mass absorption μ* coefficients and/or different crystallite size → the %wt of the phase with higher μ* and/or larger crystallite size would be underestimated

Remedies:
- Choose an appropriate λ
- Reduce crystallite size
Factors influencing QPA and QPA accuracy

Sources of errors

- Instrument related
  - Experimental geometry:
    - BB (reflection) θ–2θ
    - BB fixed-θ
    - DS (transmission) capillary or thin layer
  - Counting errors (random and systematic)

- Sample related
  - Particle statistics
  - Preferential Orientation
  - Absorption and microabsorption
  - Incorrect or insufficient crystal structure model
  - Crystallite size and strain broadening

- Operator related
  - Analyst choices during QPA analysis affect the results → QPA Round Robin 1996-2002 (see Madsen & Scarlett)
  - Dangerous side of easy-to-use QPA software
  - Important of setting up QPA guidelines

- Strong correlation between the Rietveld scale factor and the Atomic Displacement Parameters (ADP, \( B_{\text{iso}} \), \( U_{\text{iso}} \)).

WARNING: very often .cif files in the crystallographic database DO NOT report such parameters → commercial programs use in such cases default values (i.e. 1 Å²)

Be careful: most programs require as input \( B_{\text{iso}} \) (e.g. Topas, FullProf), often you find in literature and database \( U_{\text{iso}} \) → \( B_{\text{iso}} = 8\pi^2 U_{\text{iso}} \)
EXAMPLES
Example 1: Quantification of wt% of Corundum ($\alpha$-$\text{Al}_2\text{O}_3$), Fluorite ($\text{CaF}_2$) and Zincite ($\text{ZnO}$) using *ad-hoc* synthetic mixtures: CPD-2.RAW

Source: IUCr CPD Round Robin on Quantitative Phase Analysis

Rietveld QPA - No Preferential Orientation correction

Corresponding to the (001) direction of brucite, the calculated diffracted intensity clearly poorly matches the experimental data

$\rightarrow$ PO effects presumably decreases the accuracy of quantification!
Example 1: Quantification of wt% of Corundum ($\alpha$-$\text{Al}_2\text{O}_3$), Fluorite ($\text{CaF}_2$) and Zincite ($\text{ZnO}$) using ad-hoc synthetic mixtures: CPD-2.RAW

Source: IUCr CPD Round Robin on Quantitative Phase Analysis

The modeling of the PO for (001) direction of brucite improves the refinement and the QPA accuracy.
The accuracy of the quantitative phase analysis strongly depends on:

- The quality of the refinement models (e.g. background, instrumental contribution, crystal structure, microstructure)

- How close to the correct values of all these refinement parameters we start the quantitative analysis
Example 2: A good description of the extrinsic background with a limited number of parameters
Example 3: Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum ($\alpha$-Al$_2$O$_3$) as an internal standard (spiking method)

Expected values: 28.41% Fluorite+27.45% Zincite + 44.14% Glass

Source: IUCr CPD Round Robin on Quantitative Phase Analysis

Help:

$$w'_\alpha = w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S}$$

$$w'_\alpha = w_\alpha (1 - w_S)$$

$$w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i}$$

$$w_\alpha + w_\beta + w_\gamma + \cdots = \sum_{i=1}^{n} w_i = 1$$

$$Corr(W_i) = W_i \frac{w_{S, true}}{w_{S, Rietveld}}$$

$$W_{unknown} = 1.0 - \sum_{k=1}^{n} Corr(W_k)$$

Step I: We spike the original mixture M of Fluorite and Zincite with a known amount of a known internal standard (30.79% Corundum) $\rightarrow$ Mixture of type M’=30.79% IS+69.21% M
Example 3: Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum (α-Al$_2$O$_3$) as an internal standard (spiking method)

Expected values: 28.41% Fluorite+27.45% Zincite + 44.14% Glass

Source: IUCr CPD Round Robin on Quantitative Phase Analysis

Help:

\[
\begin{align*}
w'_\alpha &= w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S} \\
w'_\alpha &= w_\alpha (1 - w_S)
\end{align*}
\]

\[
w_\alpha + w_\beta + w_\gamma + \ldots = \sum_{i=1}^{n} w_i = 1
\]

\[
w_\alpha = \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i}
\]

\[
Corr(W_i) = W_i \frac{w_{S,\text{true}}}{w_{S,\text{Rietveld}}}
\]

\[
W_{\text{unknown}} = 1.0 - \sum_{k=1}^{n} Corr(W_k)
\]

**Mixture M**  
Fluorite • Zincite  
Phase Standard Corundum 30.79% wt  

**Standard S**  
Phase Standard Corundum 30.79% wt  

**Mixture M’=M+S**  
M’=Corundum 30.79%wt Corundum + 69.21% (Fluorite+Zincite)
Rietveld-based QPA methods

Example 3: Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum ($\alpha$-Al$_2$O$_3$) as an internal standard (spiking method)

Expected values: 28.41% Fluorite+27.45% Zincite + 44.14% Glass

Source: IUCr CPD Round Robin on Quantitative Phase Analysis

Help:

\[
\begin{align*}
 w'_\alpha &= w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S} \\
 w'_\alpha &= w_\alpha (1 - w_S) \\
 w_\alpha + w_\beta + w_\gamma + \cdots &= \sum_{i=1}^{n} w_i = 1 \\
 w_\alpha &= \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i} \\
 Corr(W_i) &= W_i \frac{w_{S,true}}{w_{S,Rietveld}} \\
 W_{unknown} &= 1 - \sum_{k=1}^{n} Corr(W_k)
\end{align*}
\]

Step I: We spike the original mixture M of Fluorite and Zincite with a known amount of a known internal standard (30.79% Corundum) \(\rightarrow\) Mixture of type M'=30.79% IS+69.21% M

Step II: We perform a Rietveld QPA using the structural information of Fluorite, Zincite and Corundum
Example 3: Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum ($\alpha$-Al$_2$O$_3$) as an internal standard (spiking method)

Expected values: 28.41% Fluorite + 27.45% Zincite + 44.14% Glass

Source:
IUCr CPD Round Robin on Quantitative Phase Analysis

\[
 w'_\alpha = w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S}
\]

\[
 w'_\alpha = w_\alpha (1 - w_S)
\]

\[
 w_\alpha + w_\beta + w_\gamma + \ldots = \sum_{i=1}^{n} w_i = 1
\]

\[
 c_{corr}(W_i) = W_i \cdot \frac{w_{S,true}}{w_{S,Rietveld}}
\]

\[
 W_{unknown} = 1.0 - \sum_{k=1}^{n} c_{corr}(W_k)
\]

Hypothesis: only crystalline phases in the mixture

Corr: Corundum 45.44 % Fluorite 27.65 % Zincite 26.91 %

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Example 3: Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum ($\alpha$-Al$_2$O$_3$) as an internal standard (spiking method)

Expected values: 28.41% Fluorite+27.45% Zincite + 44.14% Glass

Source:
IUCr CPD Round Robin on Quantitative Phase Analysis

Help:

\[
\begin{align*}
    w'_\alpha &= w_S \cdot \frac{S_\alpha \cdot (ZMV)_\alpha}{S_S \cdot (ZMV)_S} \\
    w'_\alpha &= w_\alpha (1 - w_S) \\
    w_\alpha + w_\beta + w_\gamma + \cdots &= \sum_{i=1}^{n} w_i = 1 \\
    w_\alpha &= \frac{w_\alpha}{\sum_{i=1}^{n} w_i} = \frac{S_\alpha \cdot (ZMV)_\alpha}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i} \\
    Corr(W_i) &= W_i \frac{w_{S,\text{true}}}{w_{S,Rietveld}} \\
    W_{\text{unknown}} &= 1.0 - \sum_{k=1}^{n} Corr(W_k)
\end{align*}
\]

Step I: We spike the original mixture M of Fluorite and Zincite with a known amount of a known internal standard (30.79% Corundum) \(\rightarrow\) Mixture of type M’=30.79% IS+69.21% M

Step II: We perform a Rietveld QPA using the structural information of Fluorite, Zincite and Corundum \(\rightarrow\) 45.44% Corundum+27.65% Fluorite+26.91% Zincite

The overestimation of Corundum of our Rietveld QPA clearly tells us that we DO have an unknown in our original mixture M!
Rietveld-based QPA methods

**Example 3:** Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum ($\alpha$-Al$_2$O$_3$) as an internal standard (spiking method)

**Expected values:** 28.41% Fluorite + 27.45% Zincite + 44.14% Glass

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**Help:**

\[
\begin{align*}
\omega' &= \omega_S \frac{S_a \cdot (ZMV)_a}{S_s \cdot (ZMV)_s} \\
\omega_a &= \omega_a (1 - \omega_s)
\end{align*}
\]

\[
\omega_a + \omega_B + \omega_Y + \cdots = \sum_{i=1}^{n} w_i = 1
\]

\[
\begin{align*}
\omega_a &= \frac{w_a}{\sum_{i=1}^{n} w_i} = \frac{S_a \cdot (ZMV)_a}{\sum_{i=1}^{n} S_i \cdot (ZMV)_i} \\
\text{Corr}(W_i) &= W_i \frac{w_{S,\text{true}}}{w_{S,\text{Rietveld}}} \\
W_{\text{unknown}} &= 1.0 - \sum_{k=1}^{n} \text{Corr}(W_k)
\end{align*}
\]

**Step III:** We calculate the correction factor

\[
\frac{w_{S,\text{true}}}{w_{S,\text{Rietveld}}} = \frac{w_{\text{Corundum, true}}}{w_{\text{Corundum, Rietveld}}} \approx \frac{30.79\%}{45.44\%} \approx 0.68
\]

**Step IV:** We calculate the corrected % wt:

\[
\begin{align*}
\text{Corr}(W'_{\text{Fluorite}}) &= W'_{\text{Fluorite}} \frac{w_{S,\text{true}}}{w_{S,\text{Rietveld}}} \approx 27.65 \cdot 0.68 \approx 18.80\% \\
\text{Corr}(W'_{\text{Zincite}}) &= W'_{\text{Zincite}} \frac{w_{S,\text{true}}}{w_{S,\text{Rietveld}}} \approx 26.91 \cdot 0.68 \approx 18.30\% \\
\rightarrow W'_{\text{unknown}} &= 1.0 - \sum_{k=1}^{n} \text{Corr}(W_k) \approx 32.11\% \\
\rightarrow \text{In original mixture: } w_{\text{unknown}} &= w'_{\text{unknown}} / (1 - \omega_s) \approx 46.40\%
\end{align*}
\]
Rietveld-based QPA methods

**Example 3:** Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum (α-Al$_2$O$_3$) as an internal standard (spiking method)

**Expected values:** 28.41% Fluorite + 27.45% Zincite + 44.14% Glass

**Source:** IUCr CPD Round Robin on Quantitative Phase Analysis

\[
\begin{align*}
\text{Help:} & \\
\end{align*}
\]

\[
\begin{align*}
\frac{w'_a}{w_S} &= \frac{S_{a} \cdot (ZMV)_{a}}{S_{S} \cdot (ZMV)_{S}} \\
w'_{a} &= w_a(1 - w_S) \\
w'_a &= w_a + w_{\beta} + w_{\gamma} + \ldots = \sum_{i=1}^{n} w_i = 1 \\
\frac{w_a}{w_{S,true}} &= \frac{w_{Corundum,true}}{w_{Corundum,Rietveld}} \approx \frac{30.79\%}{45.44\%} \approx 0.68 \\
Corr(W_i) &= W_i \frac{w_{S,true}}{w_{S,Rietveld}} \\
W_{unknown} &= 1.0 - \sum_{k=1}^{n} Corr(W_k) \\
\end{align*}
\]

**Step III:** We calculate the correction factor

\[
\begin{align*}
\text{Step III:} & \\
\text{We calculate the corrected % wt:} & \\
Corr(W'_{Fl}) &= W'_{Fl} \frac{w_{S,true}}{w_{S,Rietveld}} \approx 27.65 \cdot 0.68 \approx 18.80\% \Rightarrow w_{Fluorite} \approx 27.16\% \text{ in original mixture } M \\
Corr(W'_{Zin}) &= W'_{Zin} \frac{w_{S,true}}{w_{S,Rietveld}} \approx 26.91 \cdot 0.68 \approx 18.30\% \Rightarrow w_{Zincite} \approx 26.44\% \text{ in original mixture } M \\
\Rightarrow W'_{unknown} &= 1.0 - \sum_{k=1}^{n} Corr(W_k') \approx 32.11\% \\
\Rightarrow \text{In original mixture: } w_{unknown} &= w'_{unknown} / (1 - w_S) \approx 46.40\% \\
\end{align*}
\]
Rietveld-based QPA methods

**Example 3:** Quantification of wt% of an Amorphous phase in a mixture of Fluorite (CaF$_2$) and Zincite (ZnO) using Corundum ($\alpha$-Al$_2$O$_3$) as an internal standard (spiking method)

Expected values: 28.41% Fluorite+27.45% Zincite + 44.14% Glass

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\end{align*}
\]

Quantification of amorphous phase with an internal standard