Investigation of local structures of organic compounds using pair-distribution function analysis

Prof. Dr. Martin U. Schmidt

Institut für Anorganische und Analytische Chemie
Goethe-Universität
Frankfurt am Main
m.schmidt@chemie.uni-frankfurt.de
Phone +49 69 798 29171

= Confidential. Not to be published =

Amorphous compounds: The dream of a crystallographer

Amorphous pharmaceutical powder

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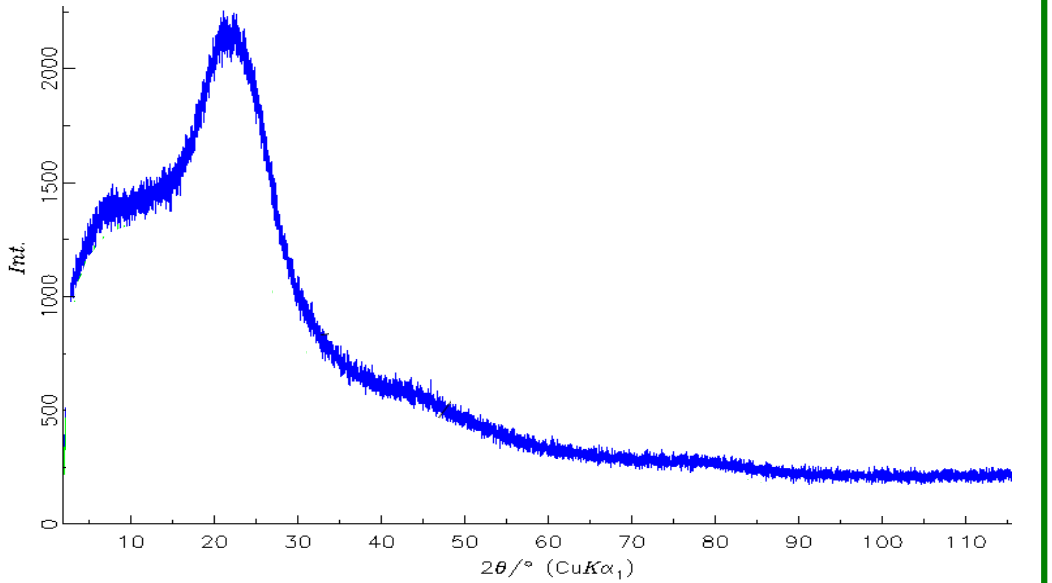
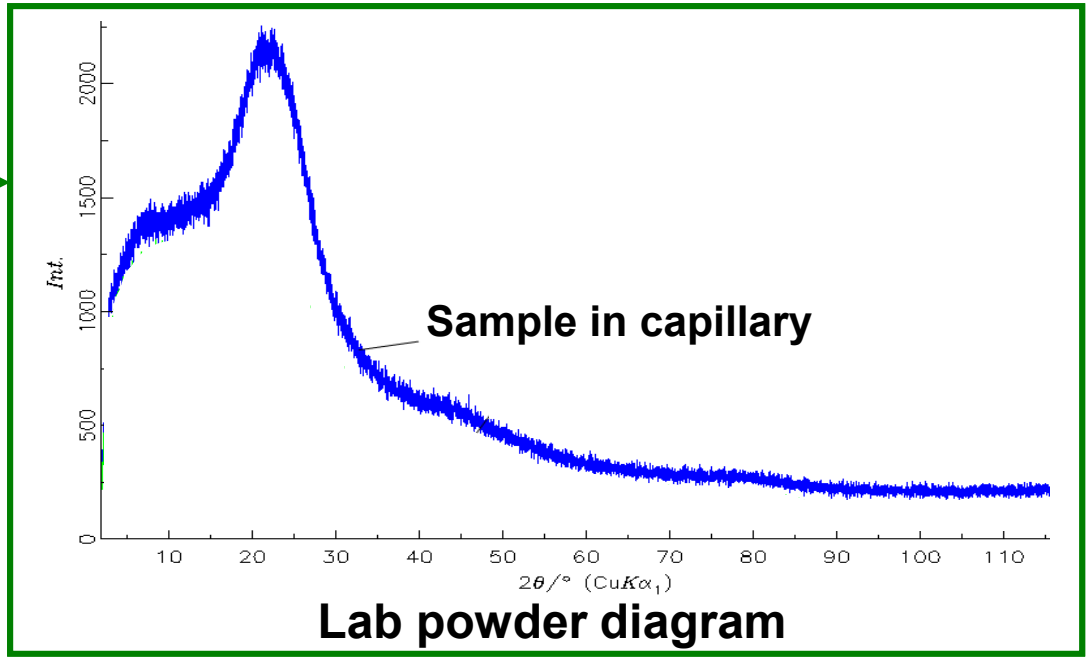
Amorphous pharmaceutical powder



Lab powder diagram

Amorphous compounds: The dream of a crystallographer

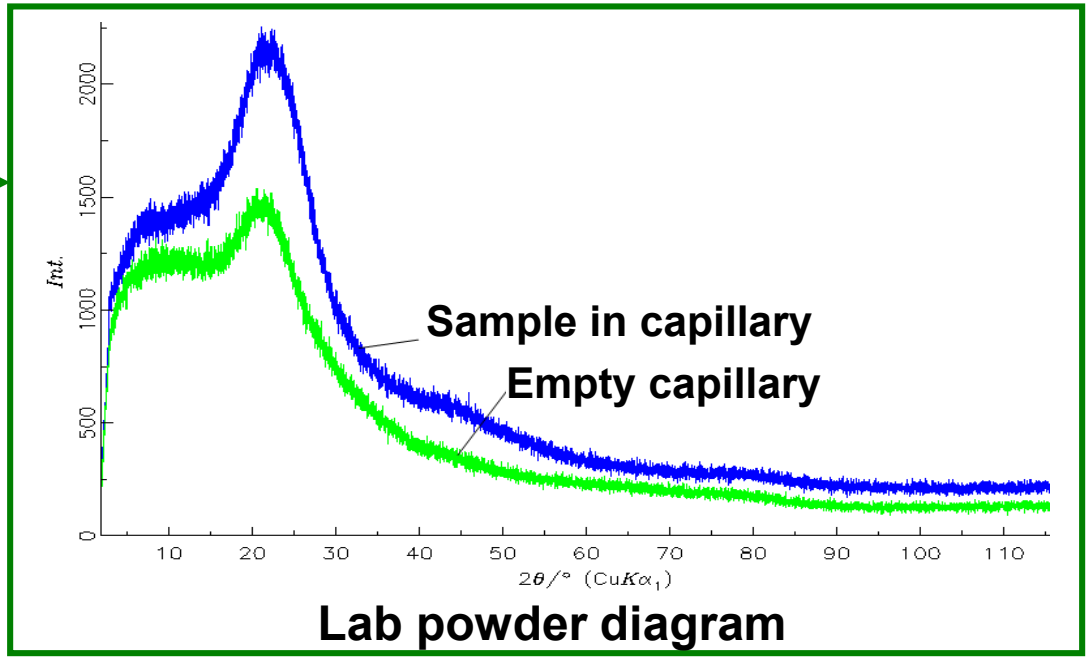
Amorphous pharmaceutical powder



Lab powder diagram

Amorphous compounds: The dream of a crystallographer

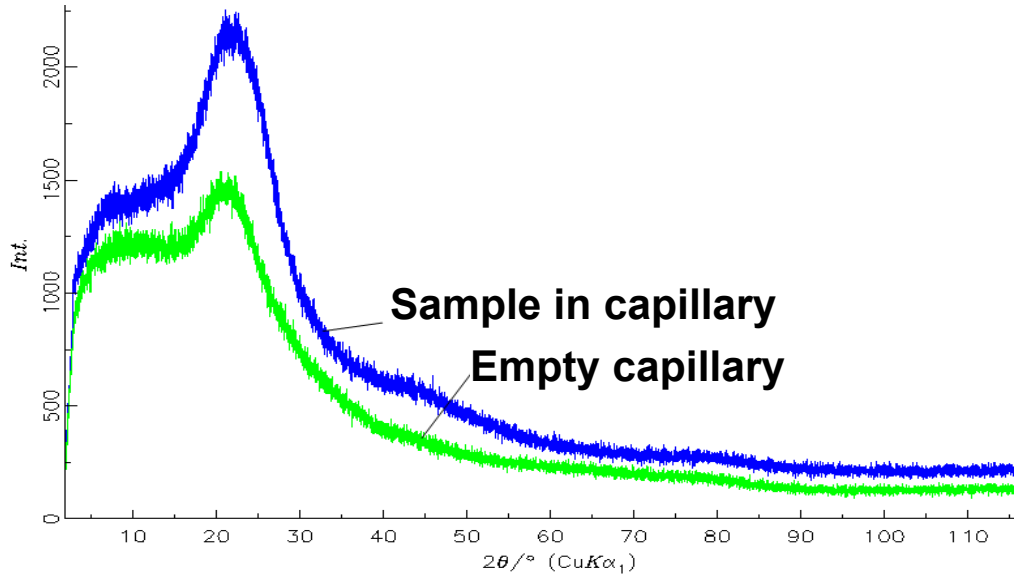
Amorphous pharmaceutical powder



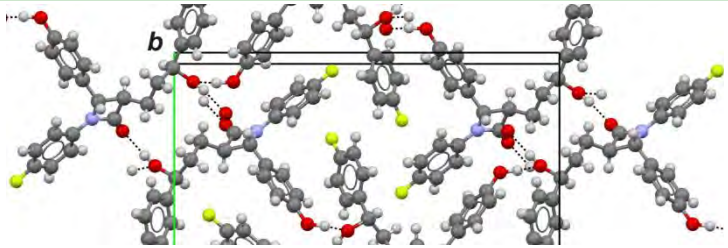
Lab powder diagram

Amorphous compounds: The dream of a crystallographer

Amorphous pharmaceutical powder



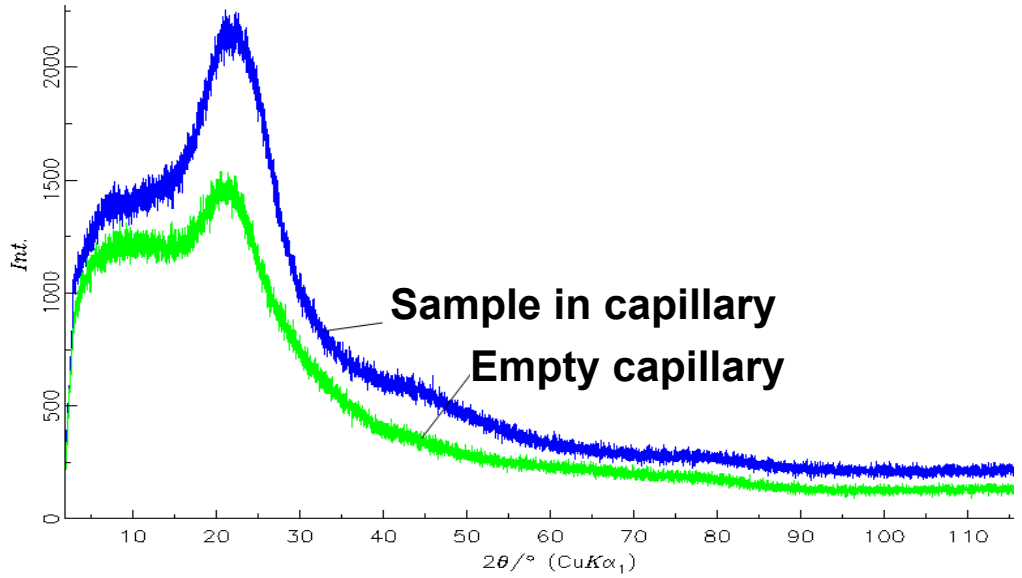
Lab powder diagram



Crystal structure

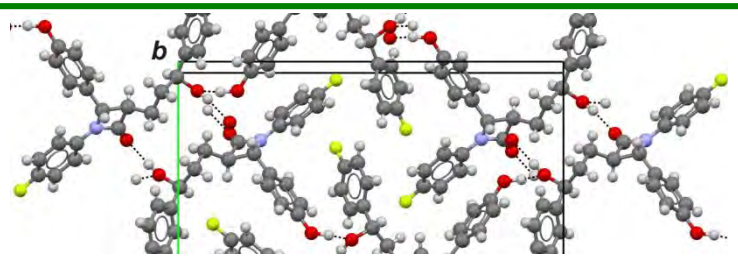
Amorphous compounds: The dream of a crystallographer

Amorphous pharmaceutical powder



Lab powder diagram

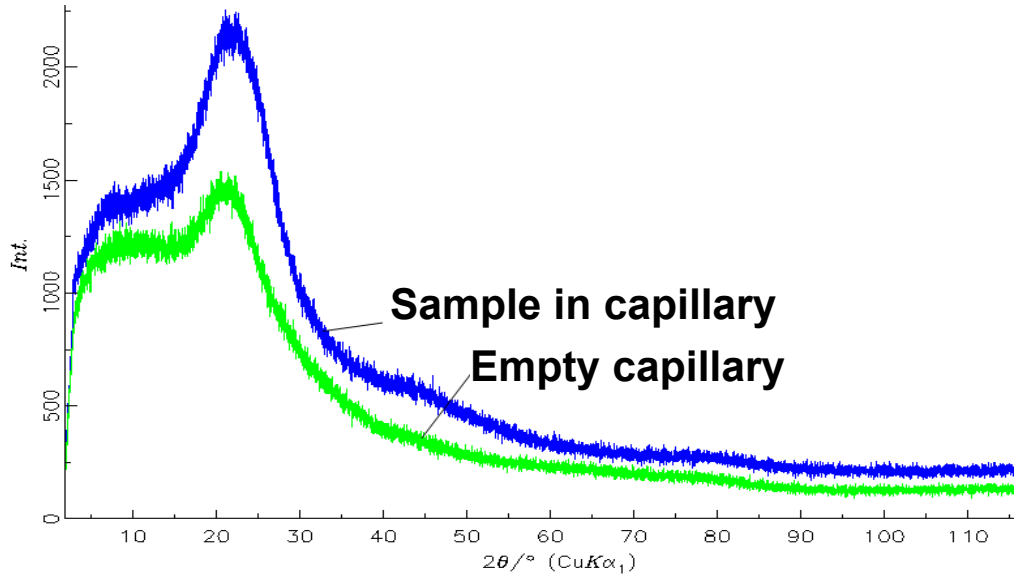
Here occurs a miracle



Crystal structure

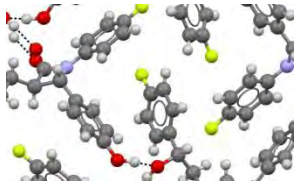
Amorphous compounds: What is possible?

Amorphous pharmaceutical powder



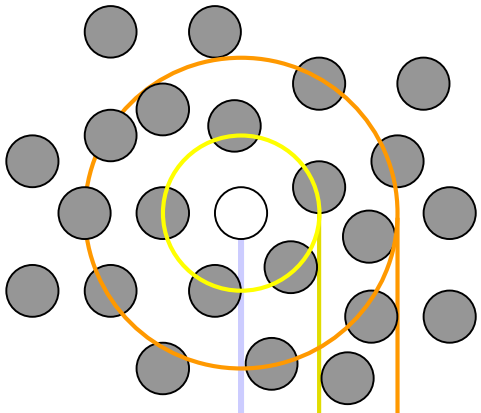
Lab powder diagram

Pair-distribution function analysis

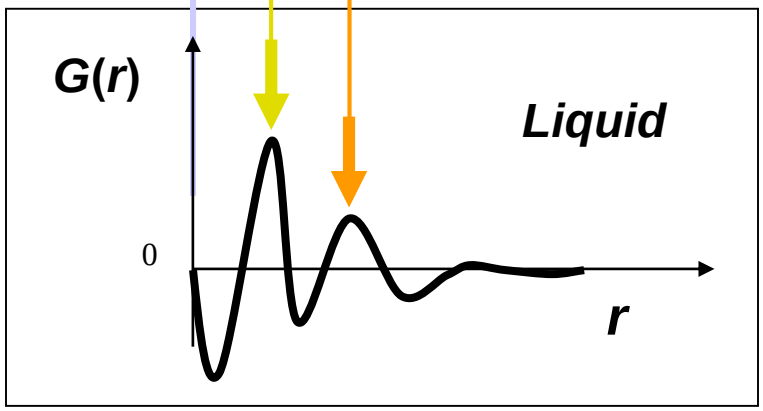


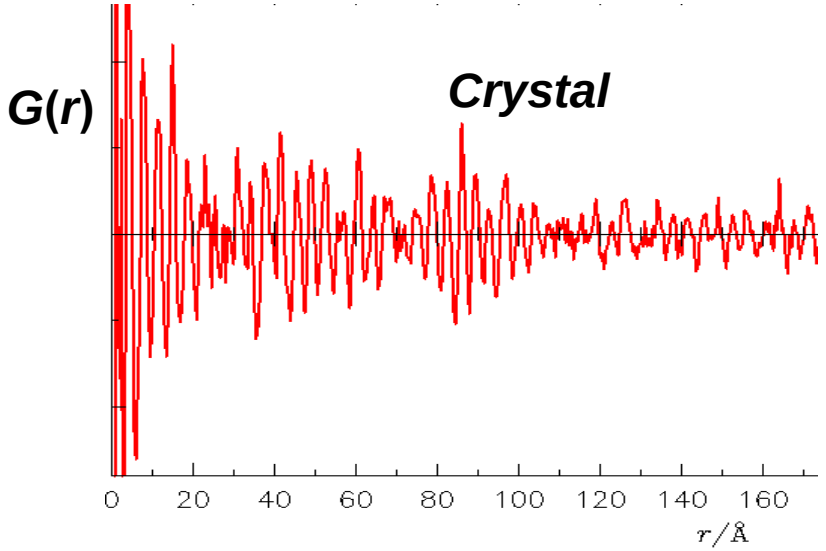
Information on the local structure

Pair Distribution Function (PDF)



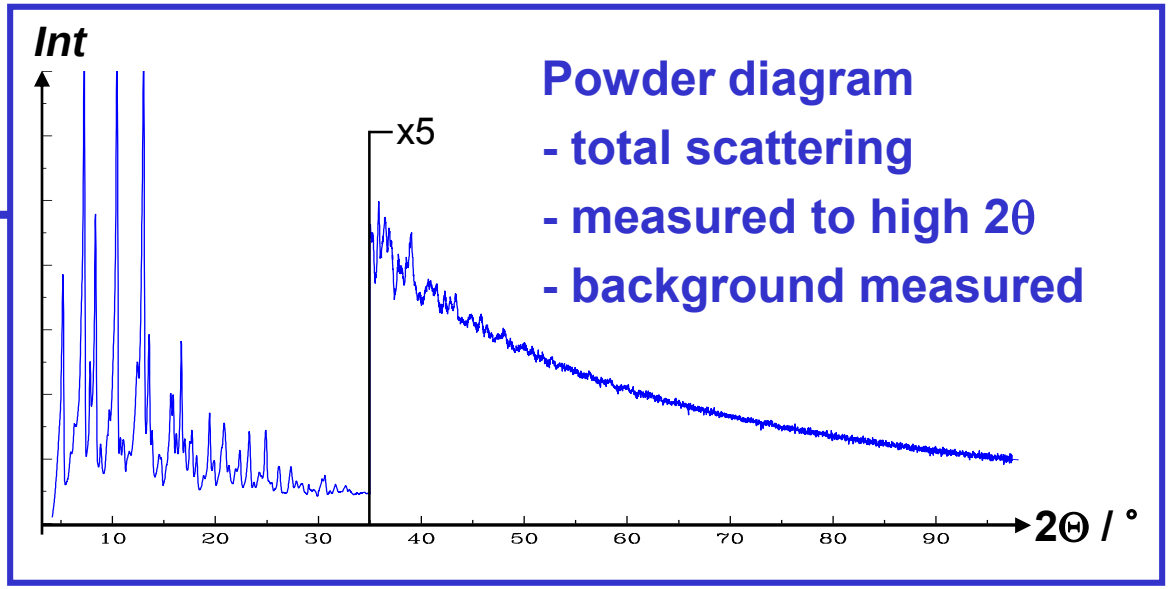
PDF, G(*r*):
Probability to find two atoms with a distance *r*
- weighted with the scattering power
- summed over all atoms
- normalised to a homogeneous atom density
- similar to the "radial distribution function"





$$G(r) = 4\pi r[\rho(r) - \rho_0] = \frac{2}{\pi}\int_{\min}^{\max} Q[S(Q) - 1]\sin(Qr)\,\mathrm{d}Q$$

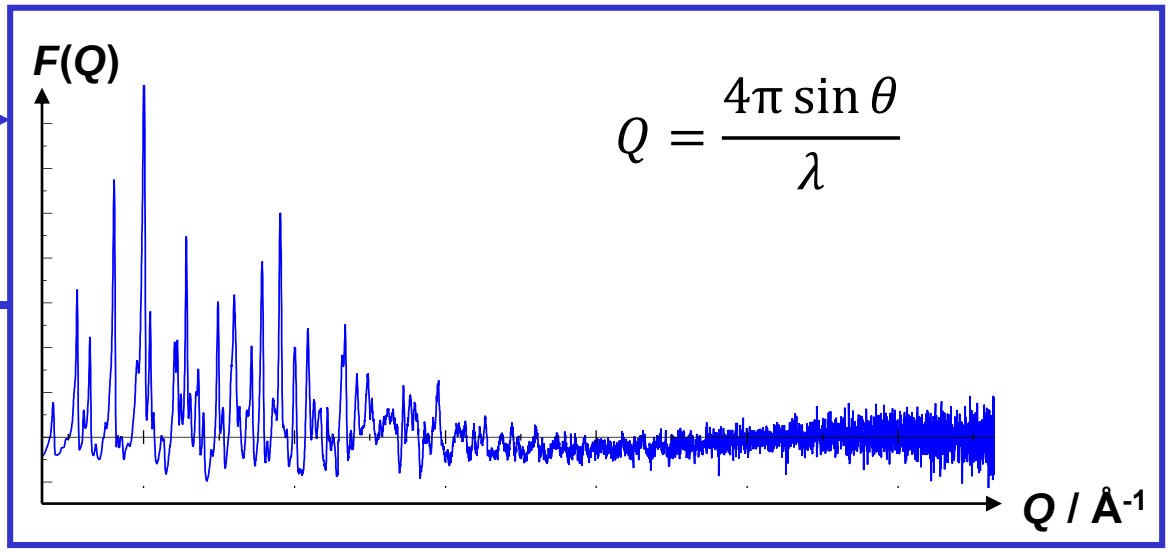
How to get the PDF



Powder diagram
- **total scattering**
- **measured to high 2θ**
- **background measured**

Careful background correction

Normalisation

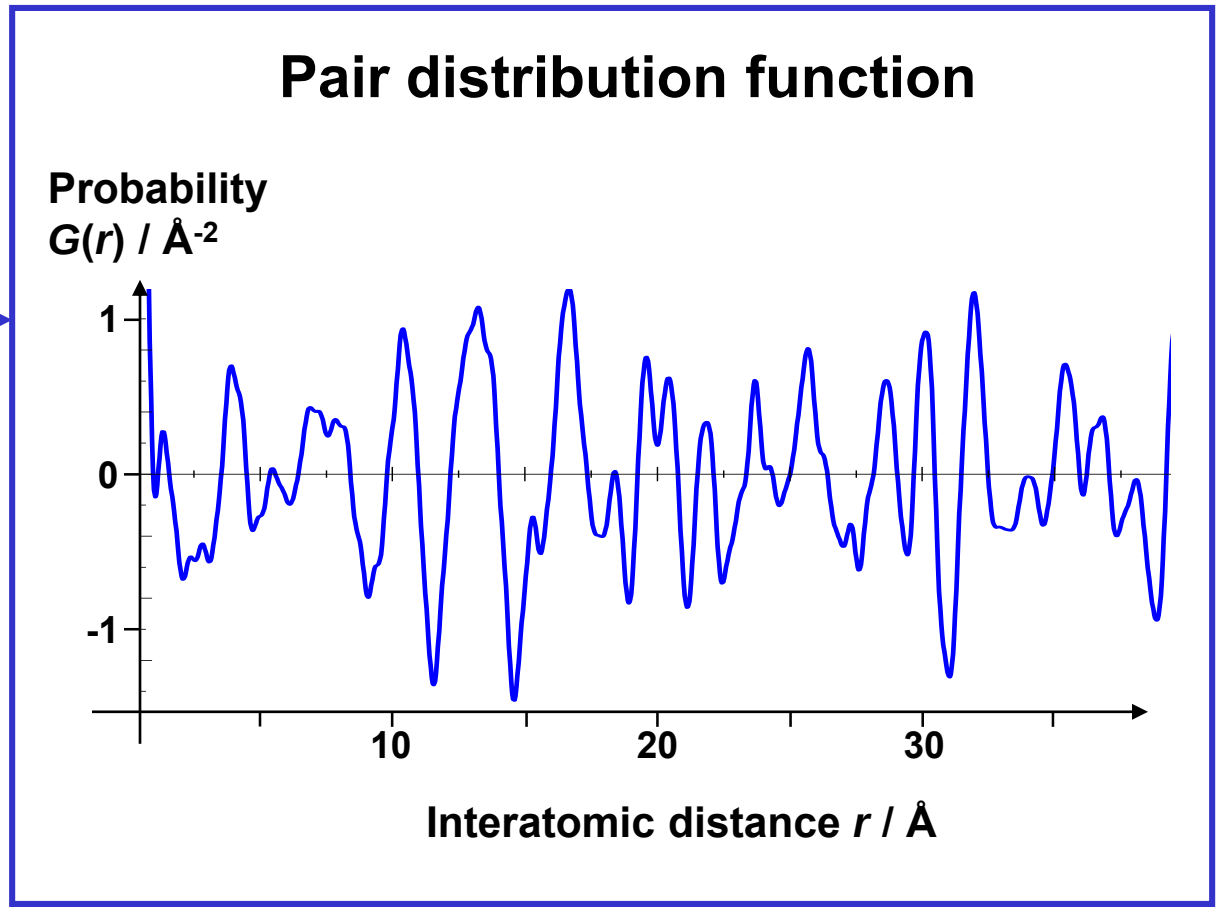


$$Q = \frac{4\pi \sin\theta}{\lambda}$$

Fourier transformation

How to get the PDF

$$G(r) = 4\pi r[\rho(r) - \rho_0] = \frac{2}{\pi}\int_{\min}^{\max} Q[S(Q) - 1]\sin(Qr)\,\mathrm{d}Q$$



Pair Distribution Function

Classical applications:

Local structures of

- glasses

- liquids

- nanocrystalline inorganic compounds

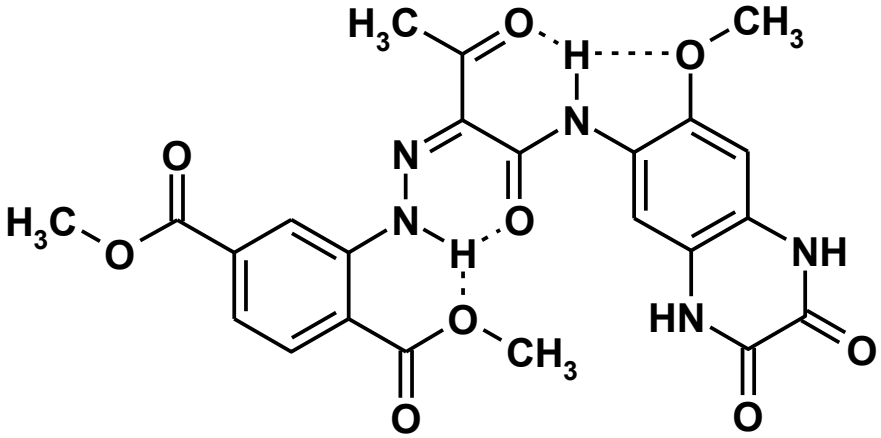
- amorphous inorganic compounds

- quasicrystals

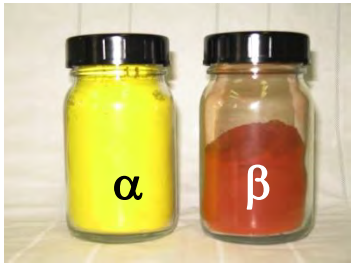
- disordered crystals

New: PDF on nanocrystalline and amorphous organic compounds

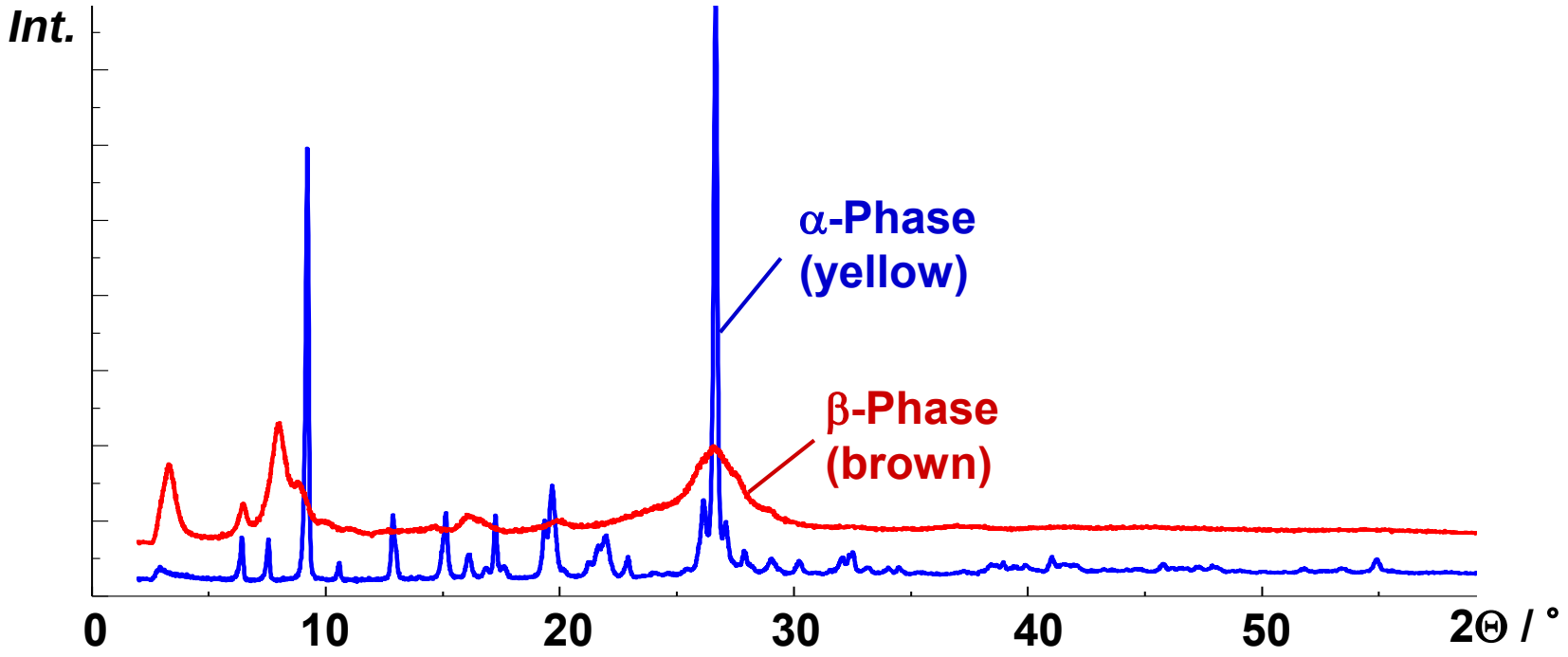
PDF on a nanocrystalline pigment



Pigment Yellow 213
(PY 213)



PDF on a nanocrystalline pigment

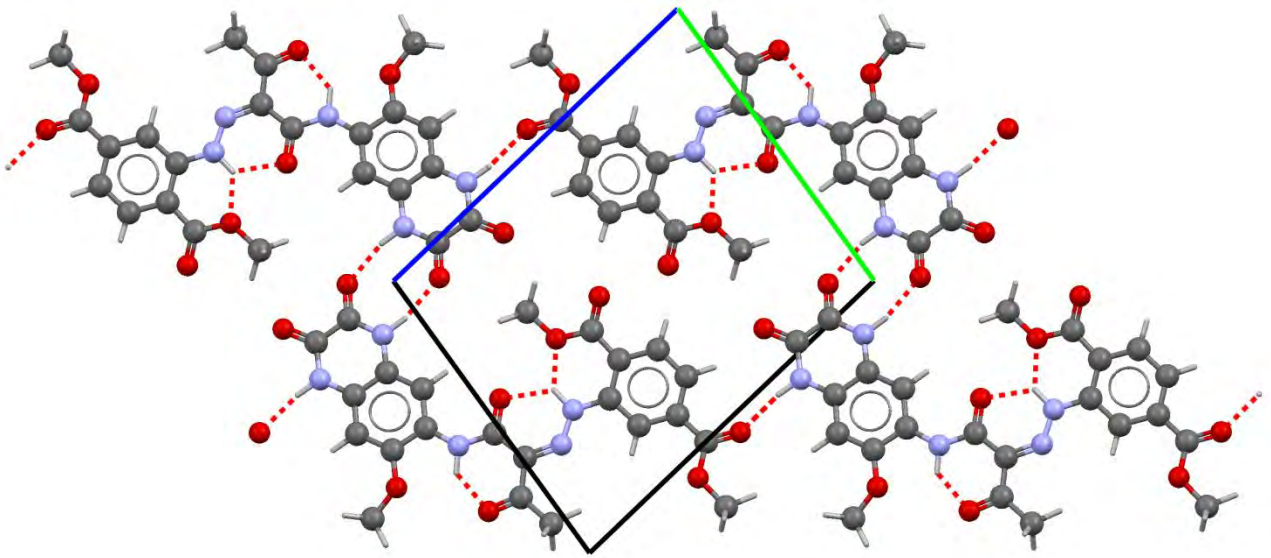


α-Phase:
Structure determined by combination of electron diffraction and X-ray powder diffraction

M. U. Schmidt, S. Brühne, A. K. Wolf, A. Rech, J. Brüning, E. Alig, L. Fink, C. Buchsbaum, J. Glinnemann, J. van de Streek, F. Gozzo, M. Brunelli, F. Stowasser, T. Gorelik, E. Mugnaioli, U. Kolb, *Acta Cryst. B* **2009**, *65*, 189-199.

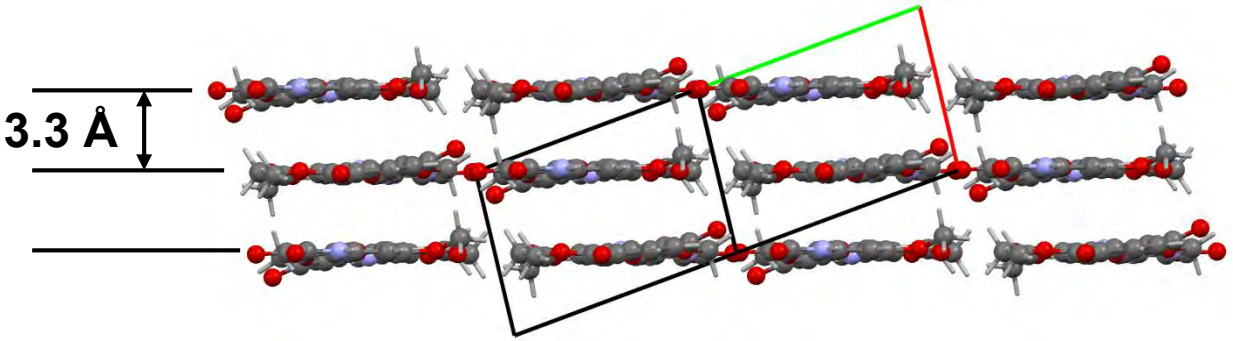
PDF on a nanocrystalline pigment

a = 6.9006(3) Å
b = 11.8347(6) Å
c = 14.0592(7) Å
α = 81.811(4) °
β = 81.032(9) °
γ = 87.541(10) °
V = 1122.3(1) Å^3
$P\bar{1}$, Z = 2



View direction [100]

Layer structure



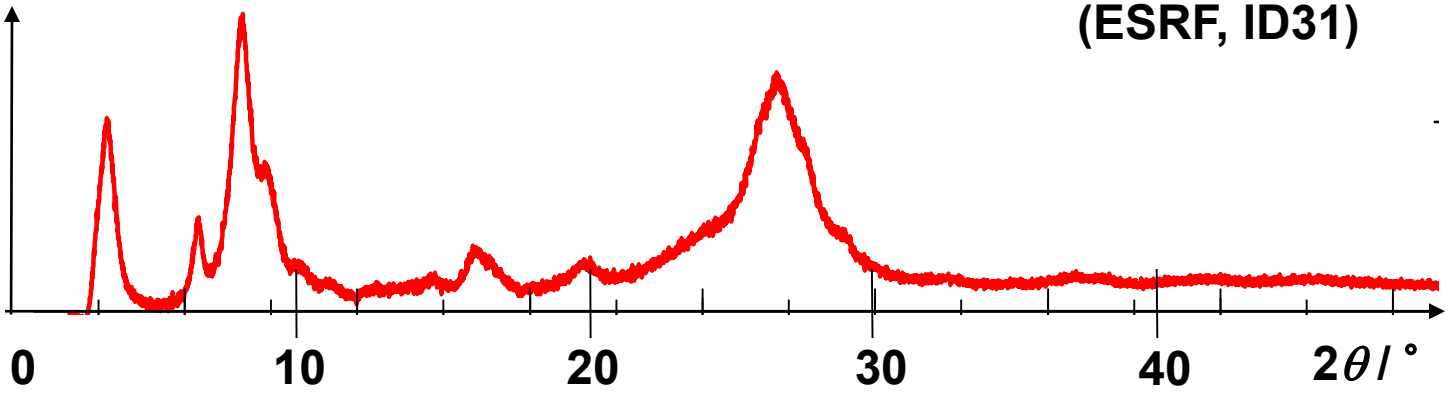
View direction [011]

M. U. Schmidt, S. Brühne, A. K. Wolf, A. Rech, J. Brüning, E. Alig, L. Fink, C. Buchsbaum, J. Glinnemann, J. van de Streek, F. Gozzo, M. Brunelli, F. Stowasser, T. Gorelik, E. Mugnaioli, U. Kolb, *Acta Cryst. B* **2009**, *65*, 189-199.

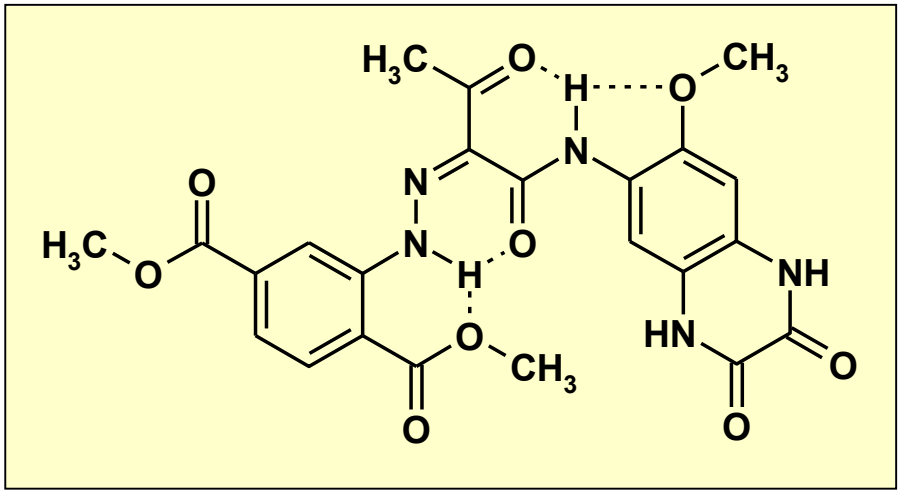
PDF on a nanocrystalline pigment

β-Phase: Best sample ever obtained

Synchrotron data
(ESRF, ID31)



(for λ = 1.54 Å)



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PDF on a nanocrystalline pigment

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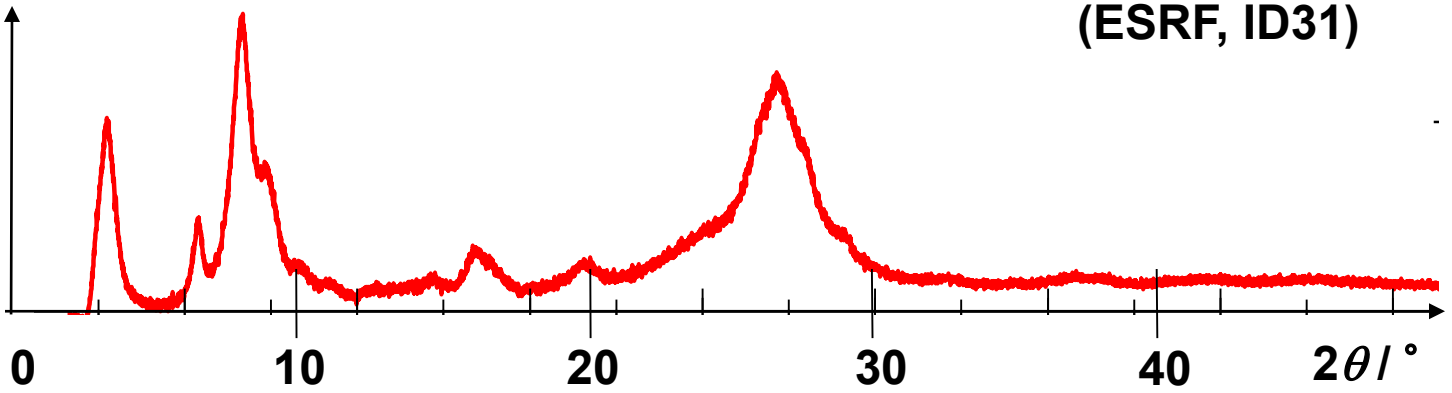

(for λ = 1.54 Å)

Does this diagram contain any usefull information?

Yes!

Use Pair Distribution Function Analysis (PDF)!

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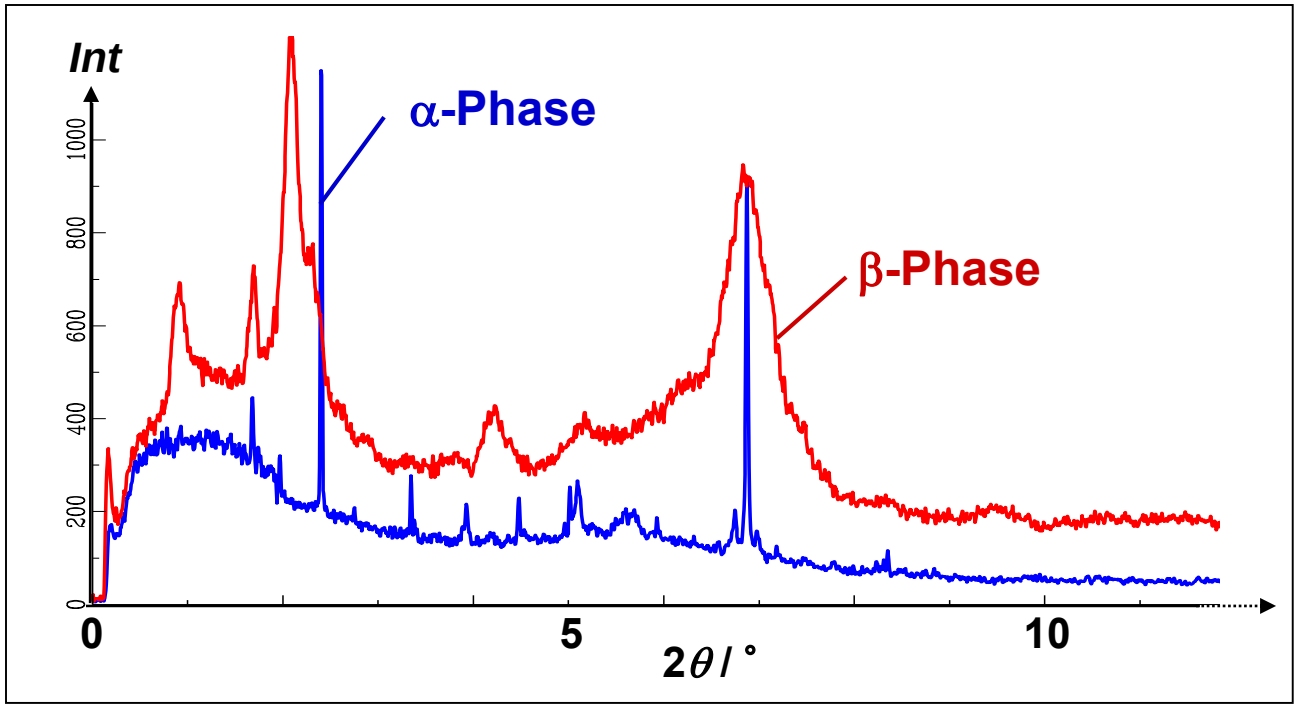
PDF on a nanocrystalline pigment

Synchrotron data (ESRF, ID31):

- **λ = 0.40 Å**
- **2θ(max) = 120°**
- **longer counting time at high 2θ**



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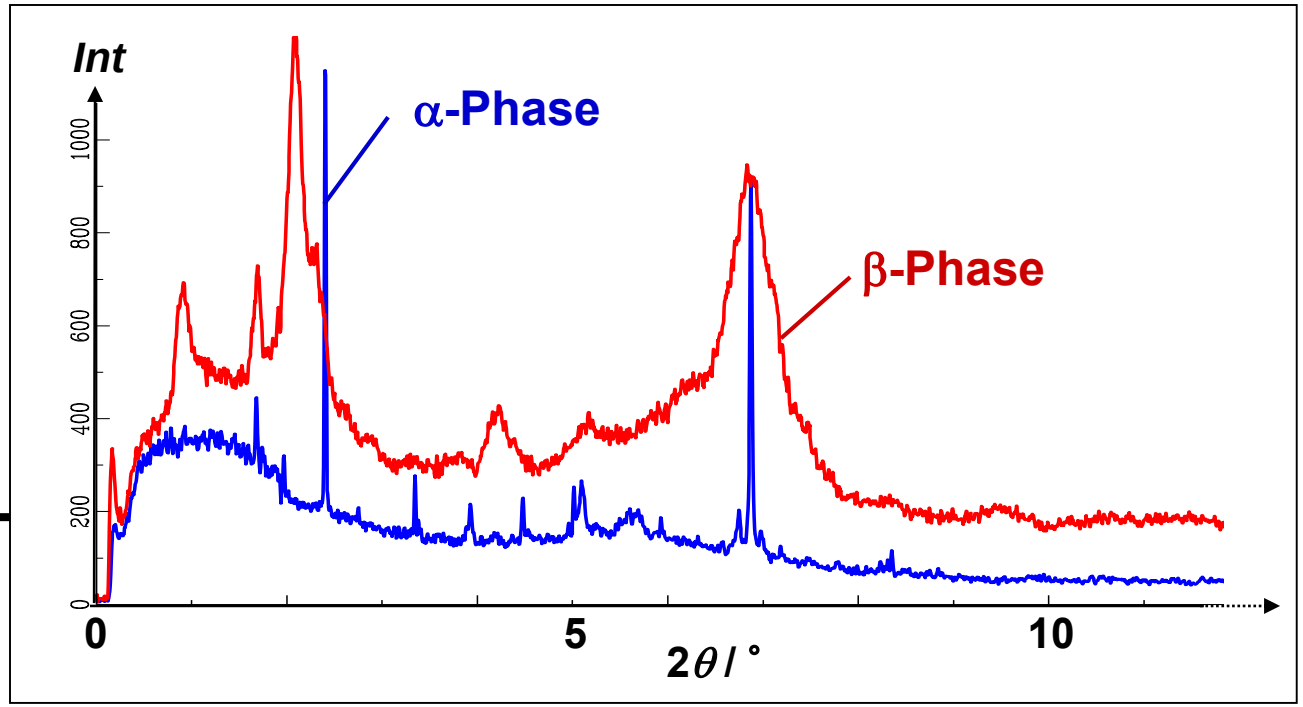
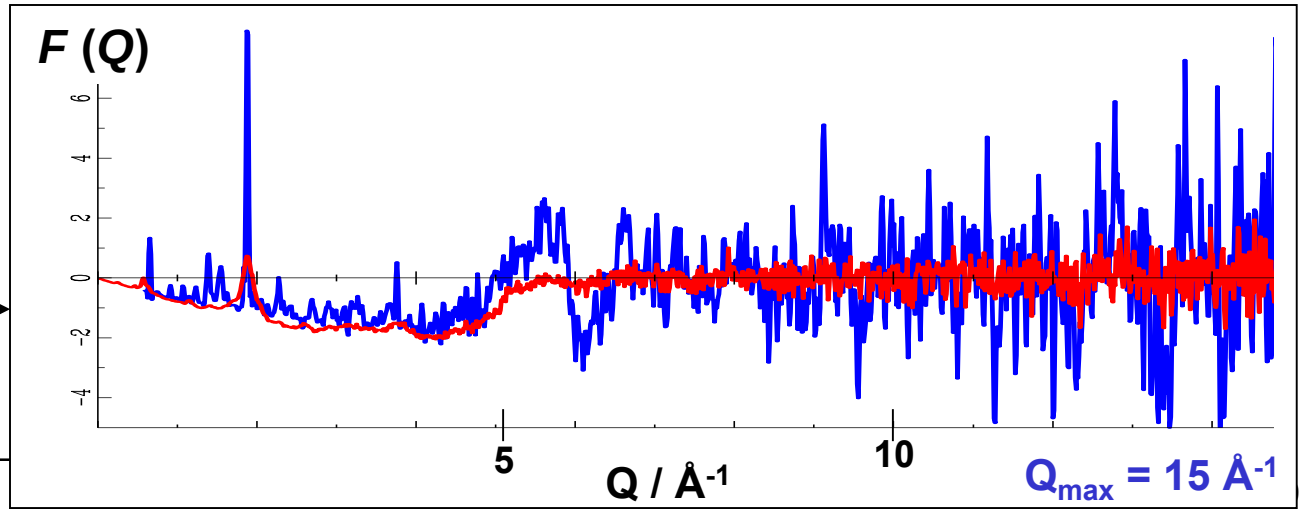
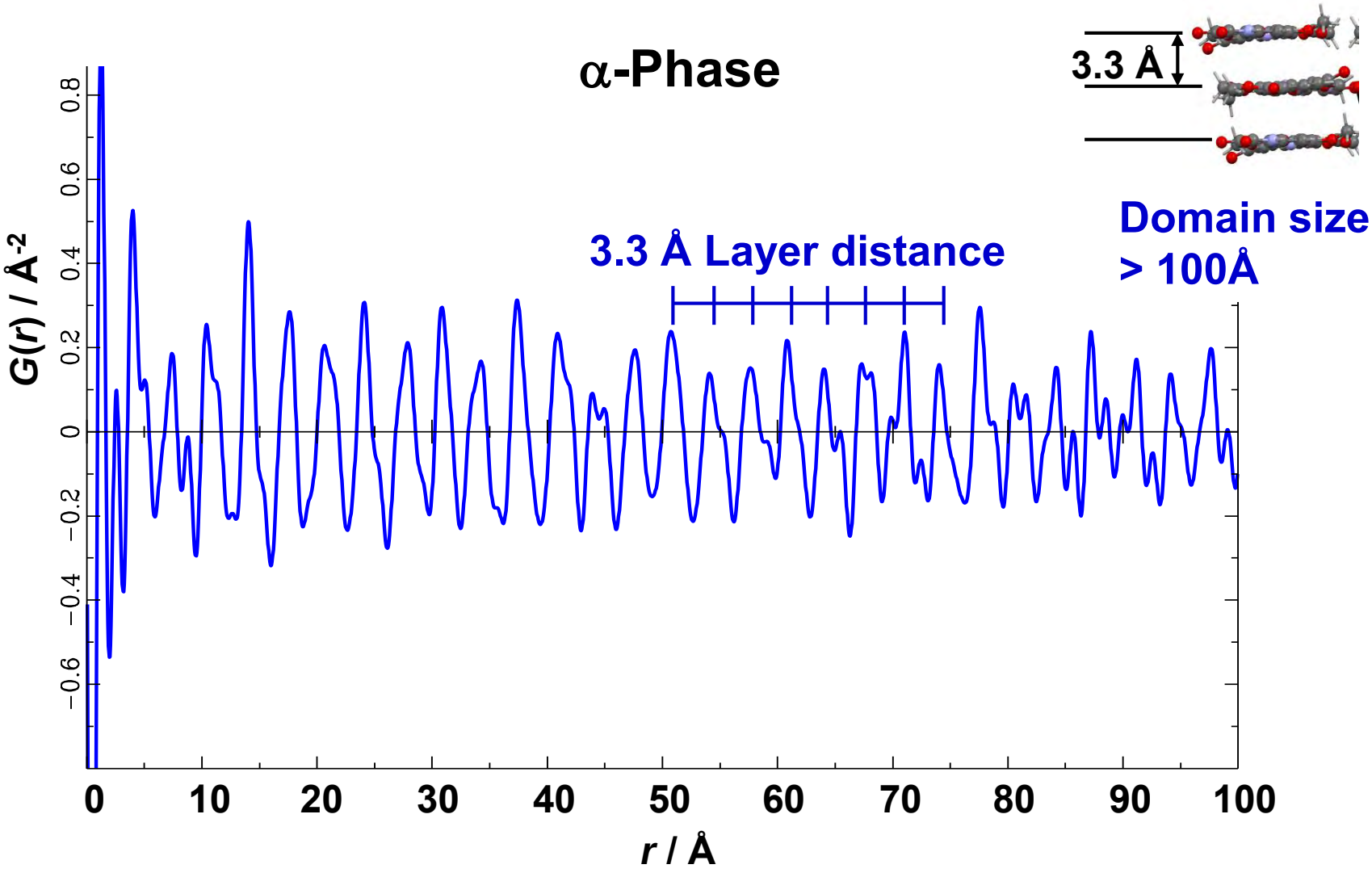


Carefull background correction

Normalisation



PDF on a nanocrystalline pigment



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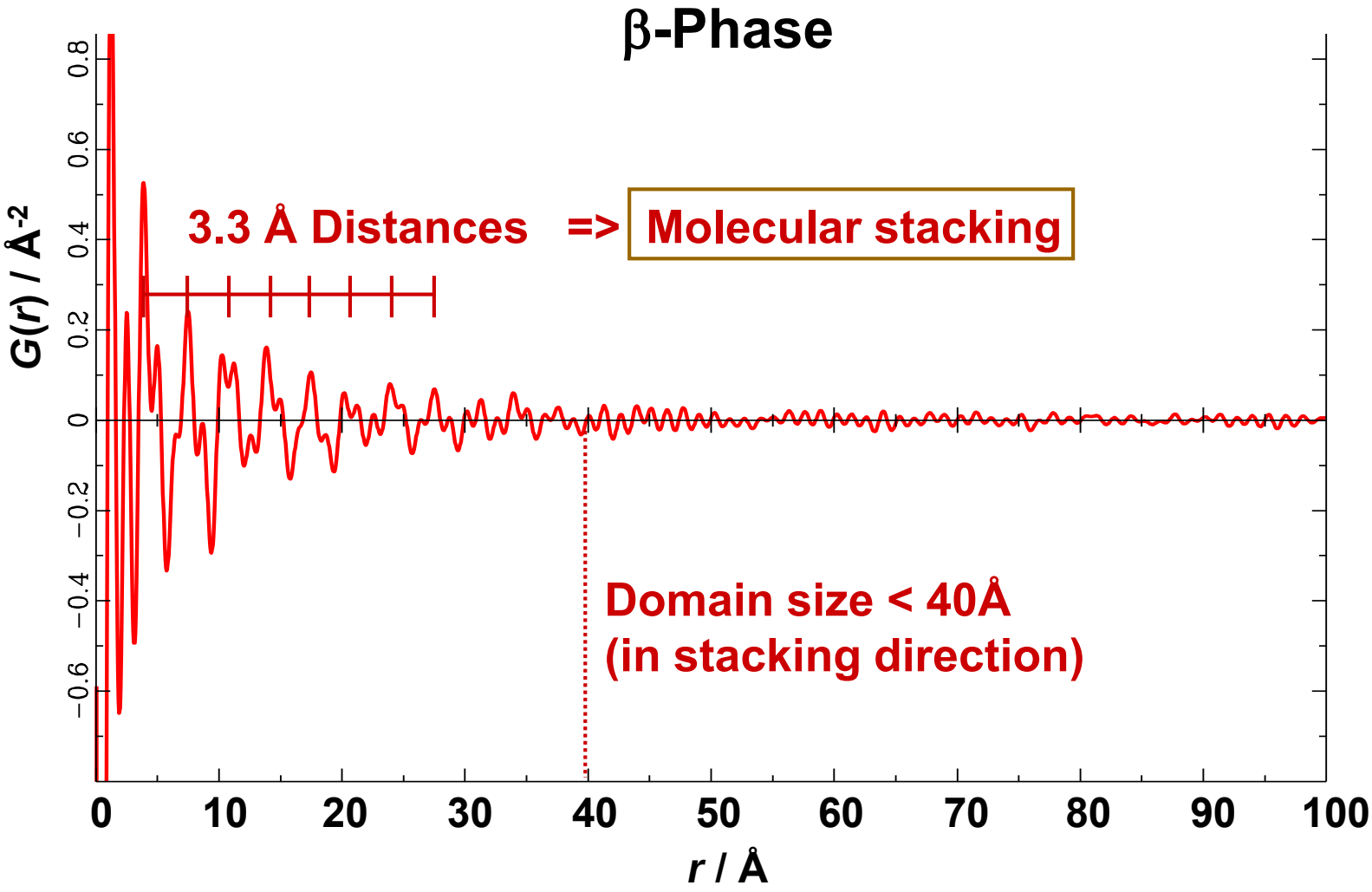

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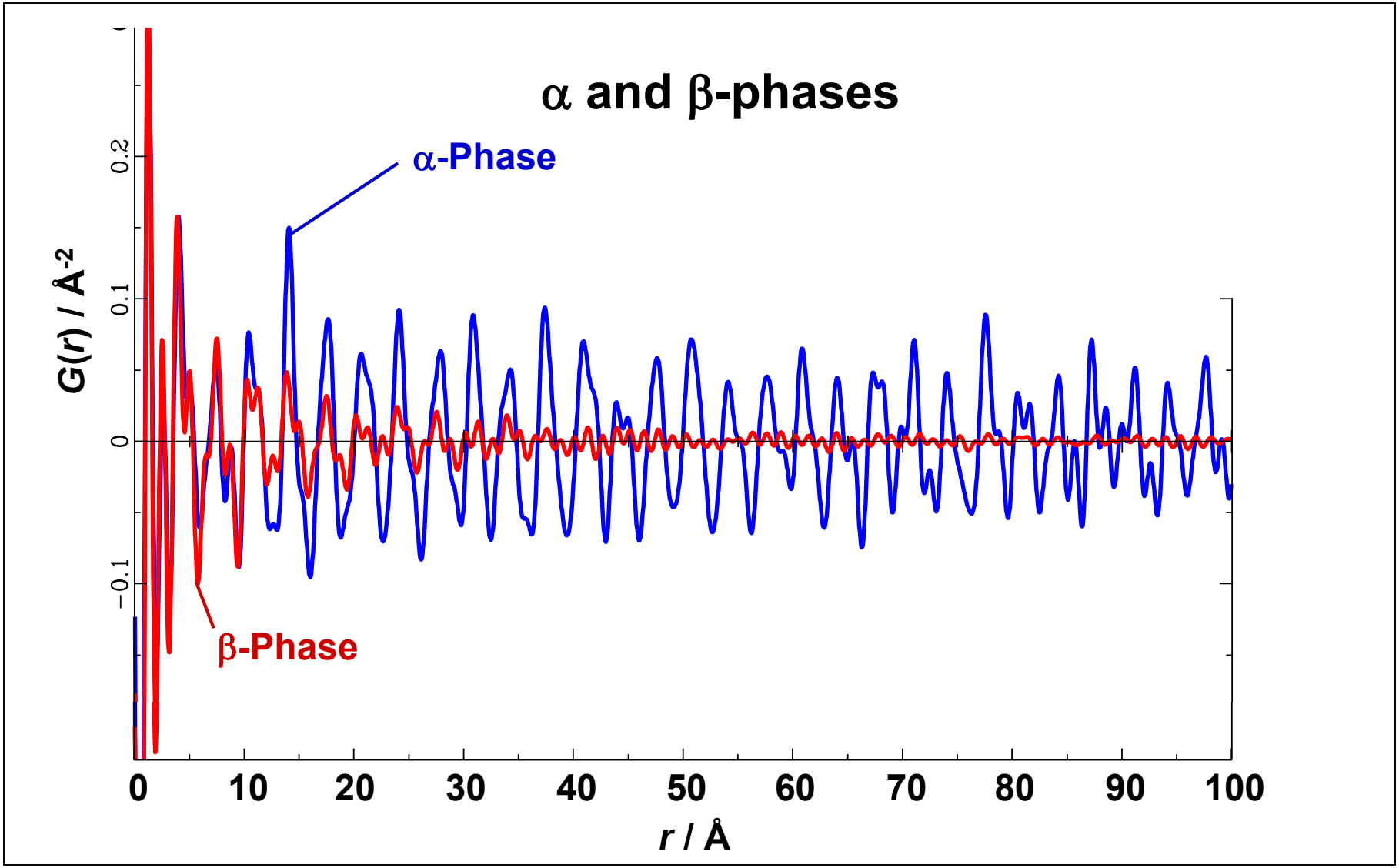

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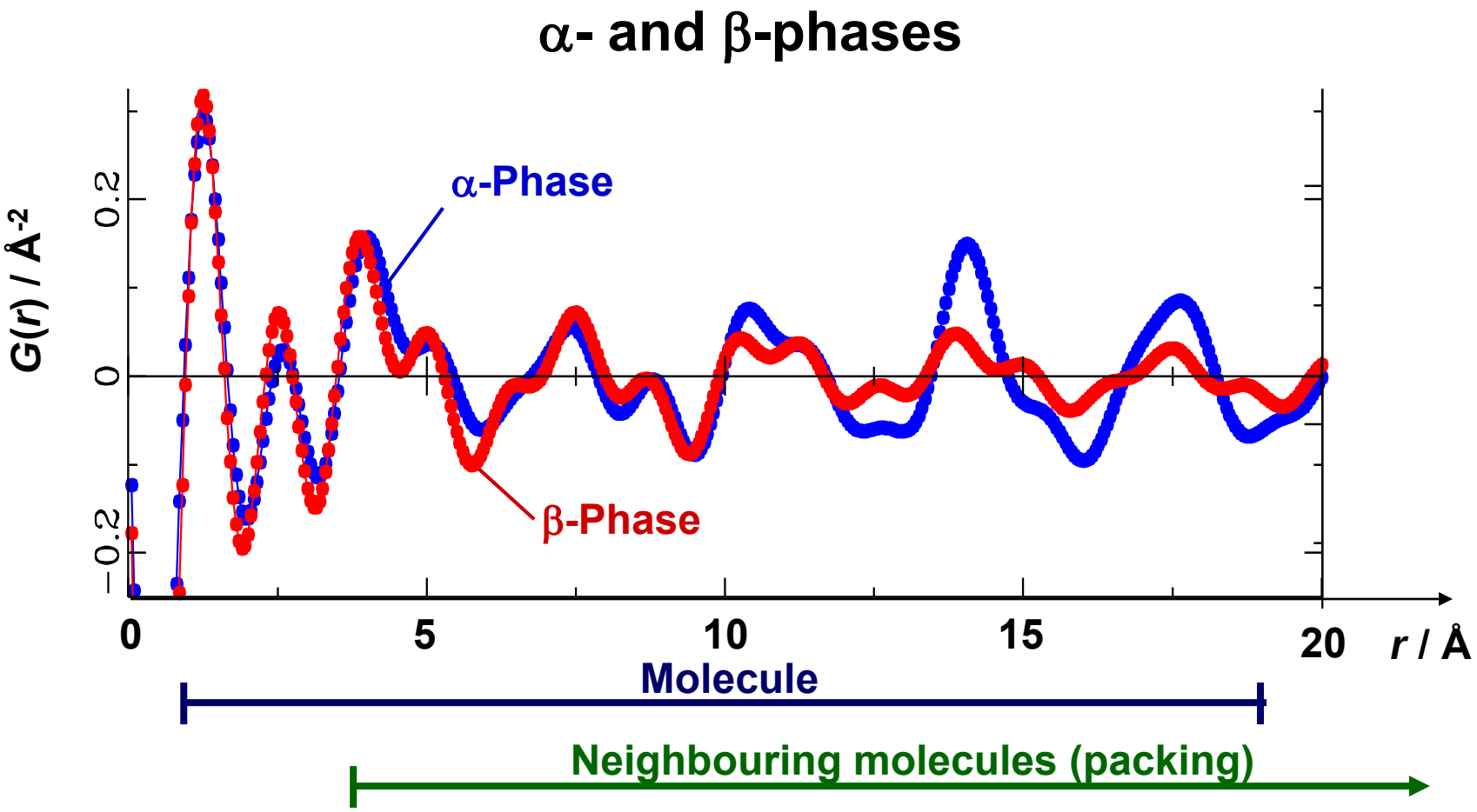


=> Local structures of α- and β-phases similar

General remarks on PDF of organic compounds

Problems with organic compounds:

1) Only light atoms

- Weak scattering
- Bad signal-to-noise ratio at high 2θ angles
- Longer measurement times required, esp. at high 2θ
- Nevertheless (esp. with lab data):
  Frequently too much noise at high 2θ
  => Truncation at high 2θ necessary => Limited Q_{max}

2) Sample in capillary or between polymer films

- Measurement of an empty capillary or empty sample holder
- Always careful background correction required
- Scaling of background vs. sample ambiguous

General remarks on PDF of organic compounds

Problems with organic compounds (continued):

3) Radiation damage

- May cause amorphisation or decomposition

The PDF of organic compounds strongly depends on:

- The sample
- The measurement
- The program used for calculating the PDF
- Background correction
- Parameters in the Fourier transformation, e.g. Q_{min}, Q_{max}, various corrections, ...

The PDF strongly depends on the user and his/her experience

General remarks on PDF of organic compounds

Caution with artefacts!

Origin of artefacts, e.g.:

- noise

- data corrections

- Fourier transformation

Artefacts are frequent at:

- r = 0 - 2 Å (suggesting unusual atom-atom distances)

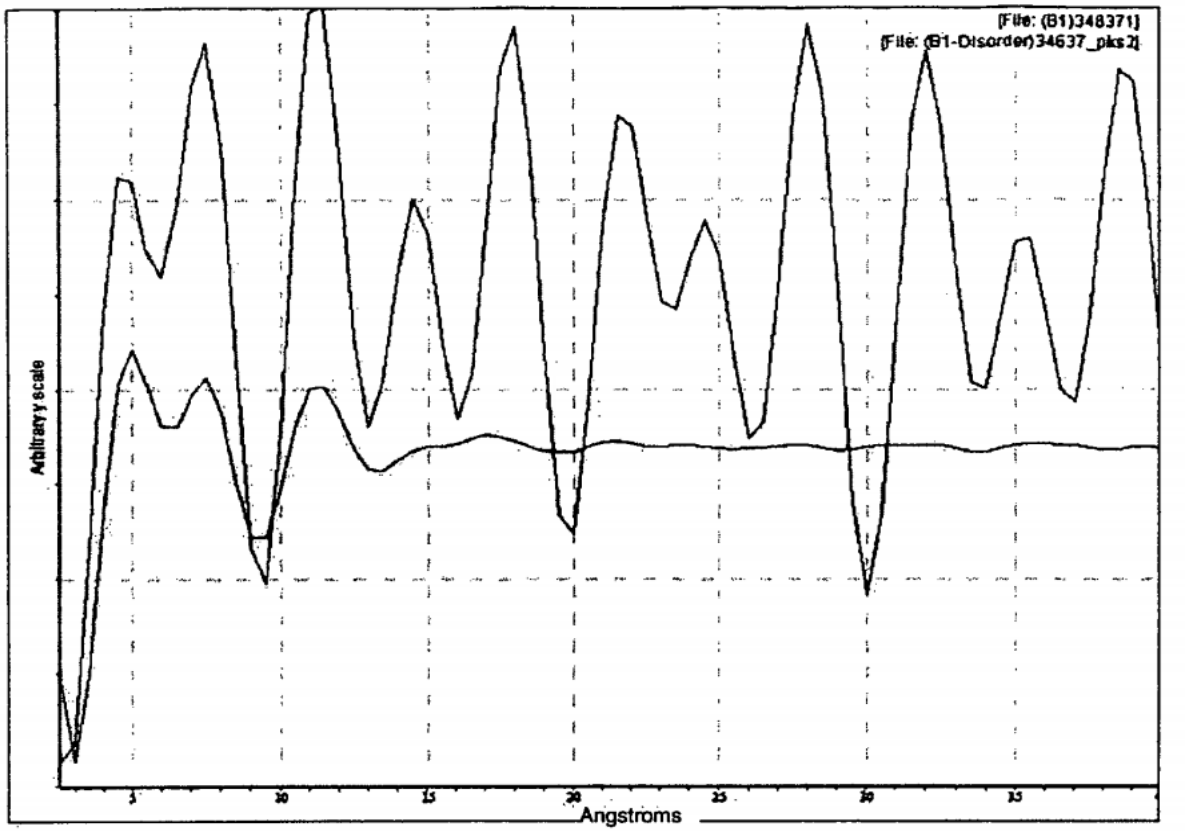
- high r, e.g. sine waves in the PDF

General remarks on PDF of organic compounds

Caution with artefacts!

The literature contains many examples with

- unreliable data



PDF from Cu radiation with $2\theta_{max} = 40^{\circ}$

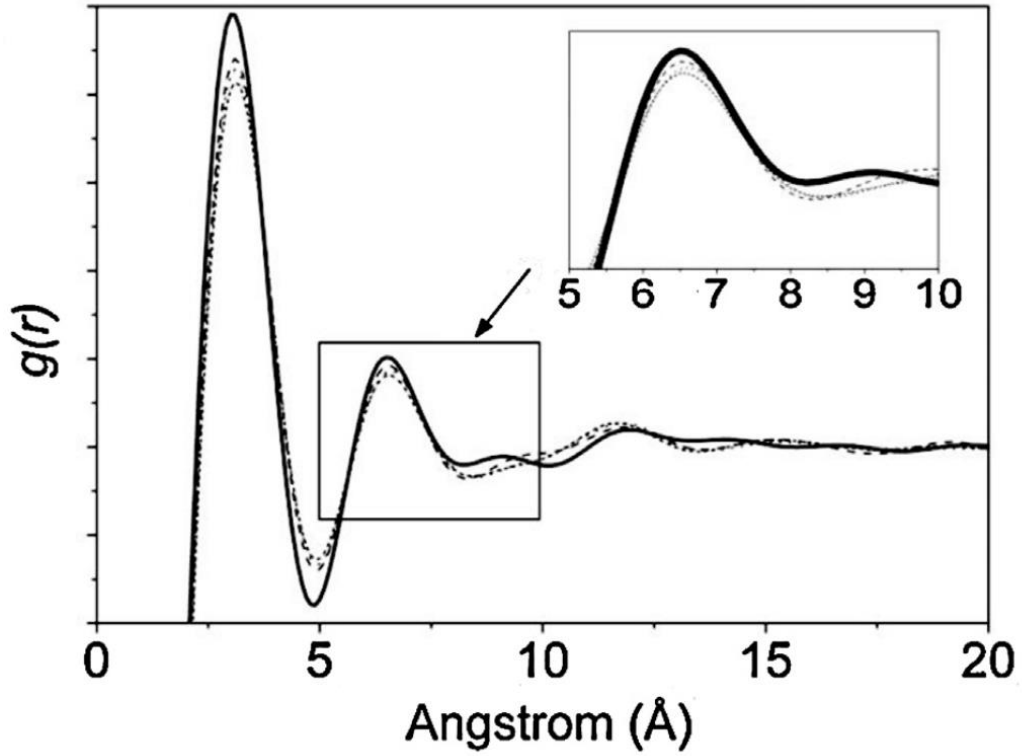
[Patent, 2005]

General remarks on PDF of organic compounds

Caution with artefacts!

The literature contains many examples with

- unreliable data



PDF from Cu radiation with $2\theta_{max} = 35^{\circ}$

[*Int. J. Pharm.*, 2013]

General remarks on PDF of organic compounds

Caution with artefacts!

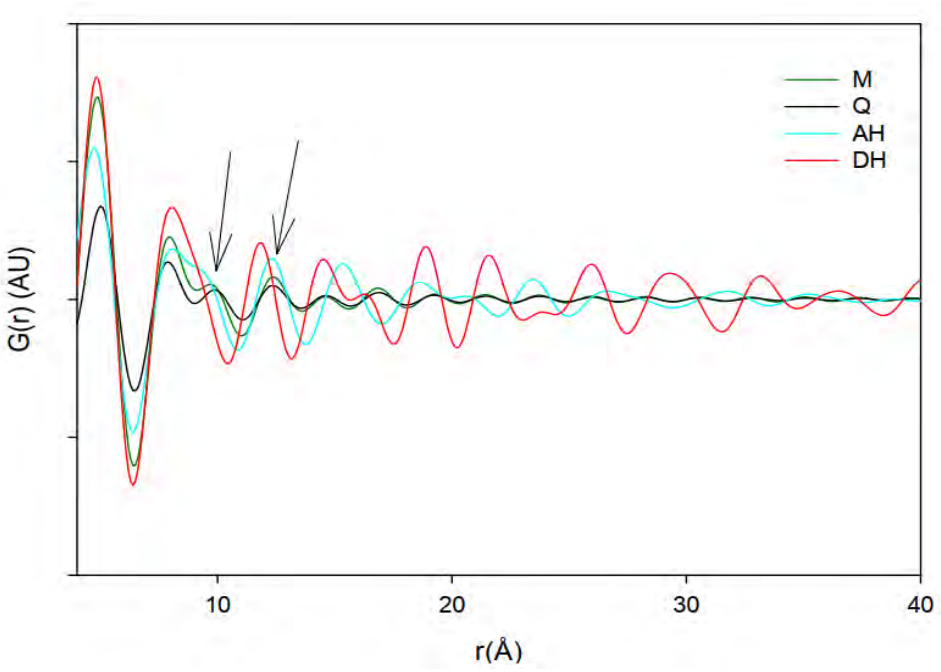
The literature contains many examples with

- unreliable data

- unreliable data processing
(e.g. no background correction, generation of artefacts, ...)

Interpretation of PDFs from Cu radiation with $2\theta_{max} = 40^{\circ}$

[*Pharmaceutics,* 2012]



General remarks on PDF of organic compounds

Caution with artefacts!

The literature contains many examples with

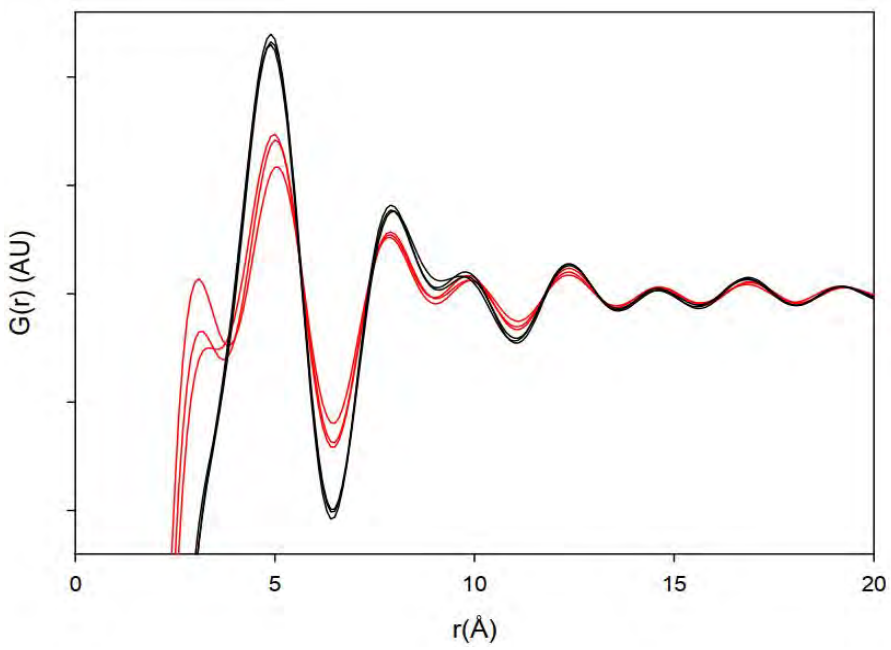
- unreliable data

- unreliable data processing (e.g. no background correction, generation of artefacts, ...)

- Interpretation of artefacts (very frequent)

Interpretation of PDFs from Cu radiation with $2\theta_{max} = 40^{\circ}$

[*Pharmaceutics,* 2012]



General remarks on PDF of organic compounds

My recommendations for PDF of organic compounds:

- **Sample holder: capillary or between films: both possible**
- **2θ as high as possible**
- **Background measurement**
  (of course measured under the same conditions as the sample)
- **Longer counting time at high 2θ (especially on lab instruments)**
- **Good signal-to-noise ratio**
  On lab diffractometers: long measurement times
- **Careful corrections and Fourier transform by experienced people**
- **No interpretation of distances less than ca. 2Å**
- **Lab data are sufficient, if PDF is used as "finger print",**
  (e.g. phase analysis, domain sizes, crystallinity,
  comparison of local structures, ...)
- **Structure refinement by PDF fit: Synchrotron data required**

Nanocrystalline and amorphous API

3 samples:

- Crystalline, unmilled

- Nanomilled

- Amorphous

Nanocrystalline and amorphous API

3 samples:

- Crystalline, unmilled

- Nanomilled

- Amorphous

All measurements:

STOE Stadi-P diffractometer

Ge(111) monochromator

Linear PSD

Cu-$K\alpha_1$ radiation

Capillary

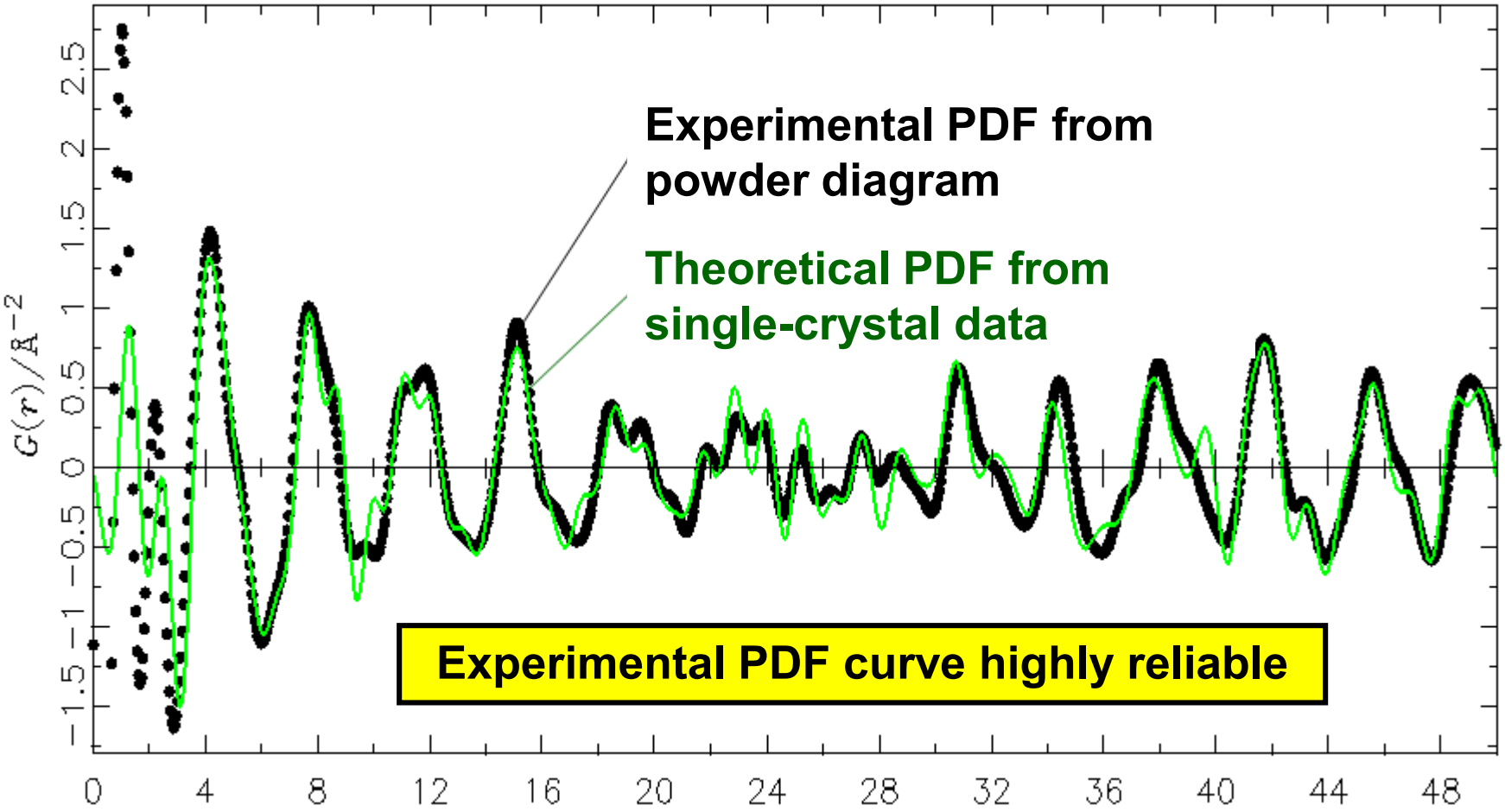
Transmission mode

2θ = 2 - 120°

Room temperature

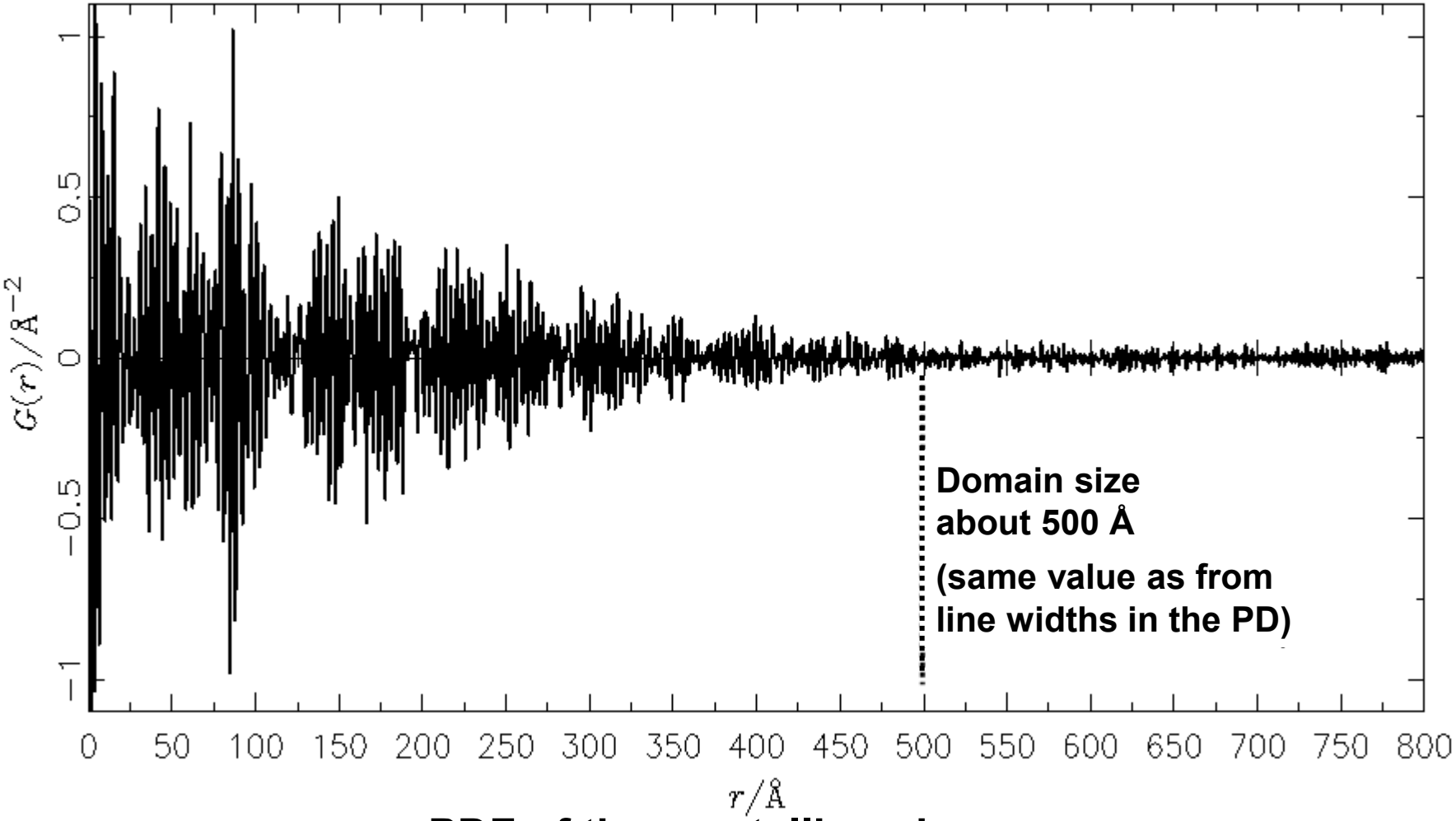
Background correction:
empty capillary

Nanocrystalline and amorphous API



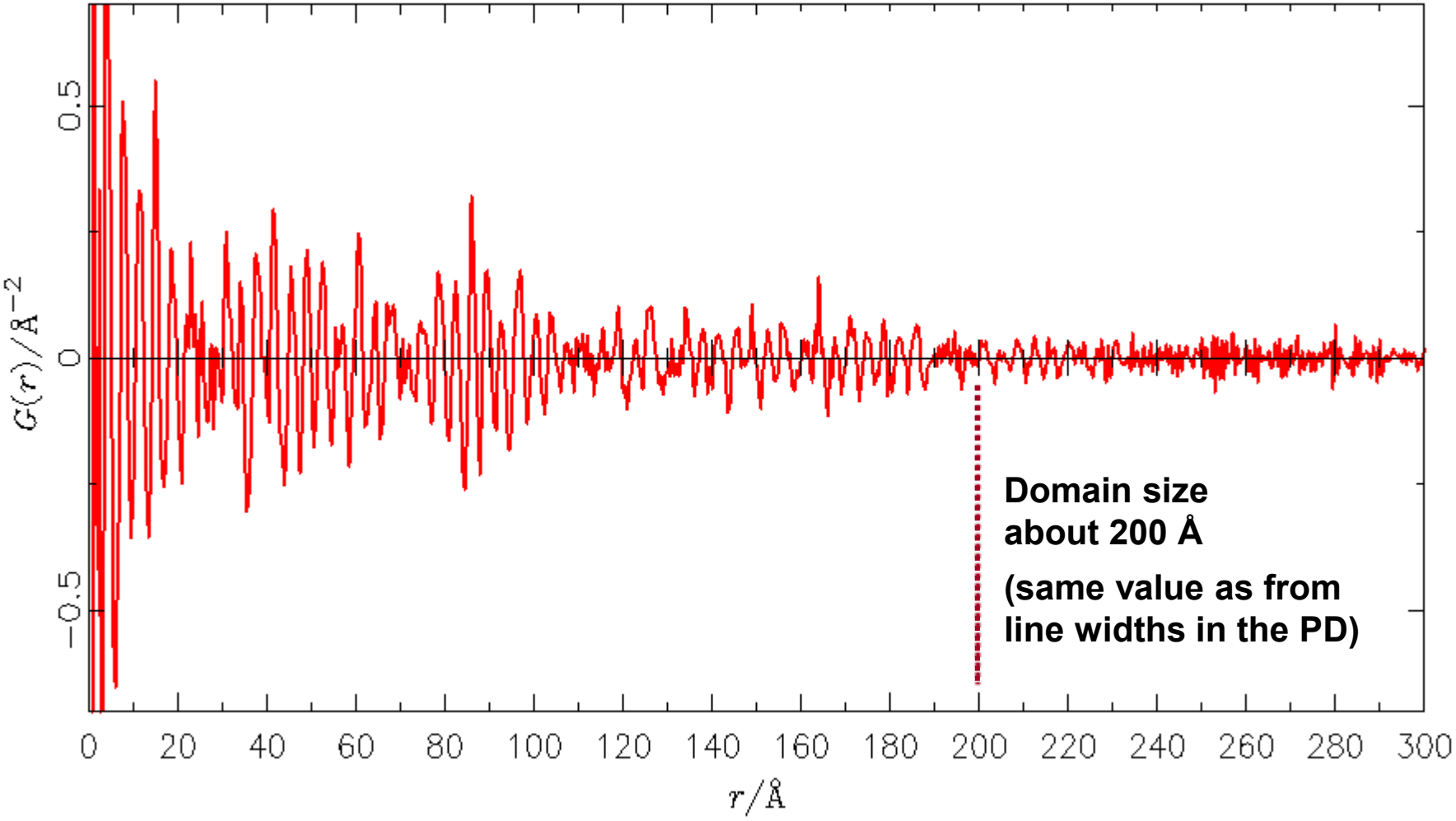
Comparison of experimental and theoretical PDF

Nanocrystalline and amorphous API



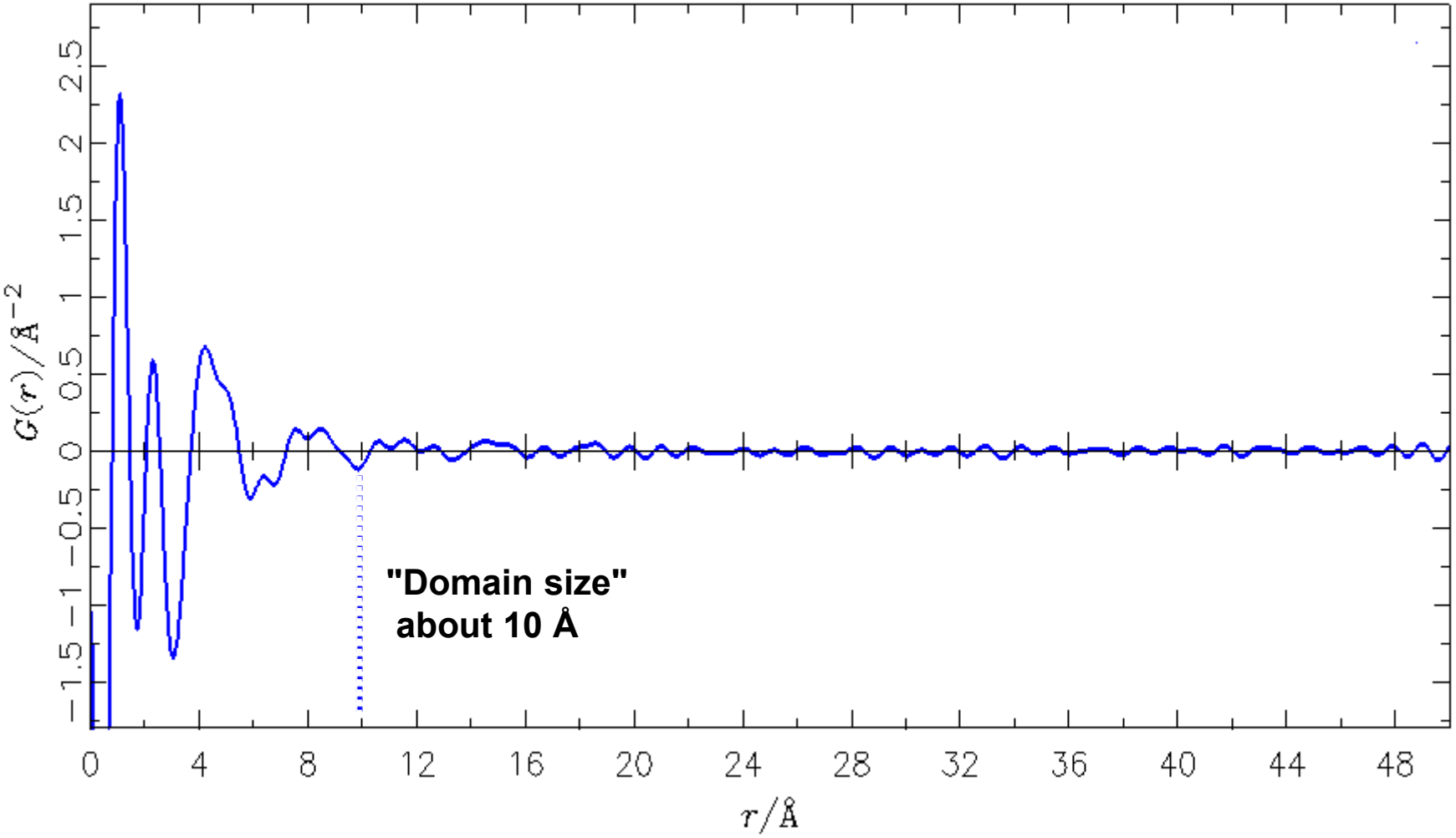
PDF of the crystalline phase

Nanocrystalline and amorphous API



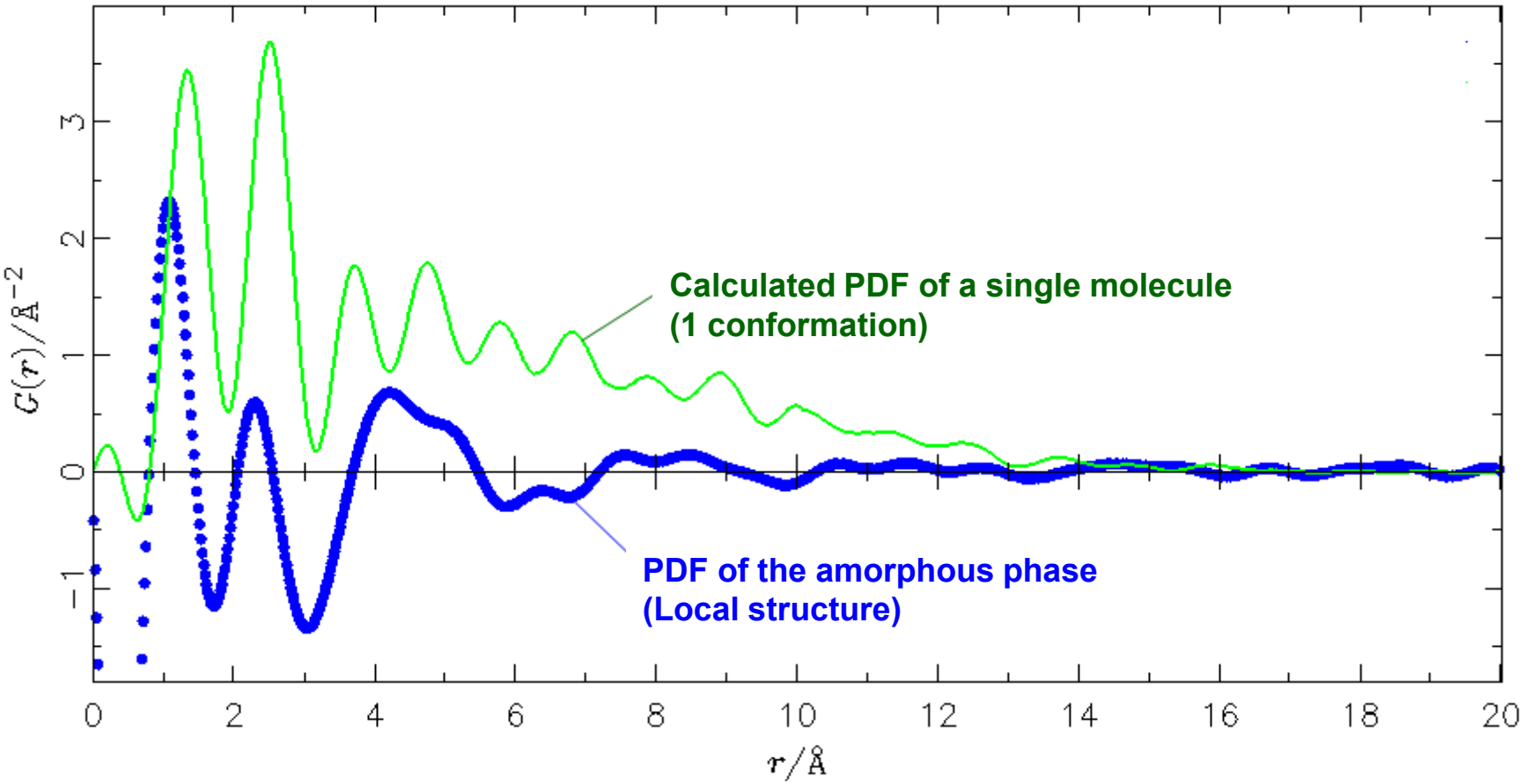
PDF of the nanomilled phase

Nanocrystalline and amorphous API



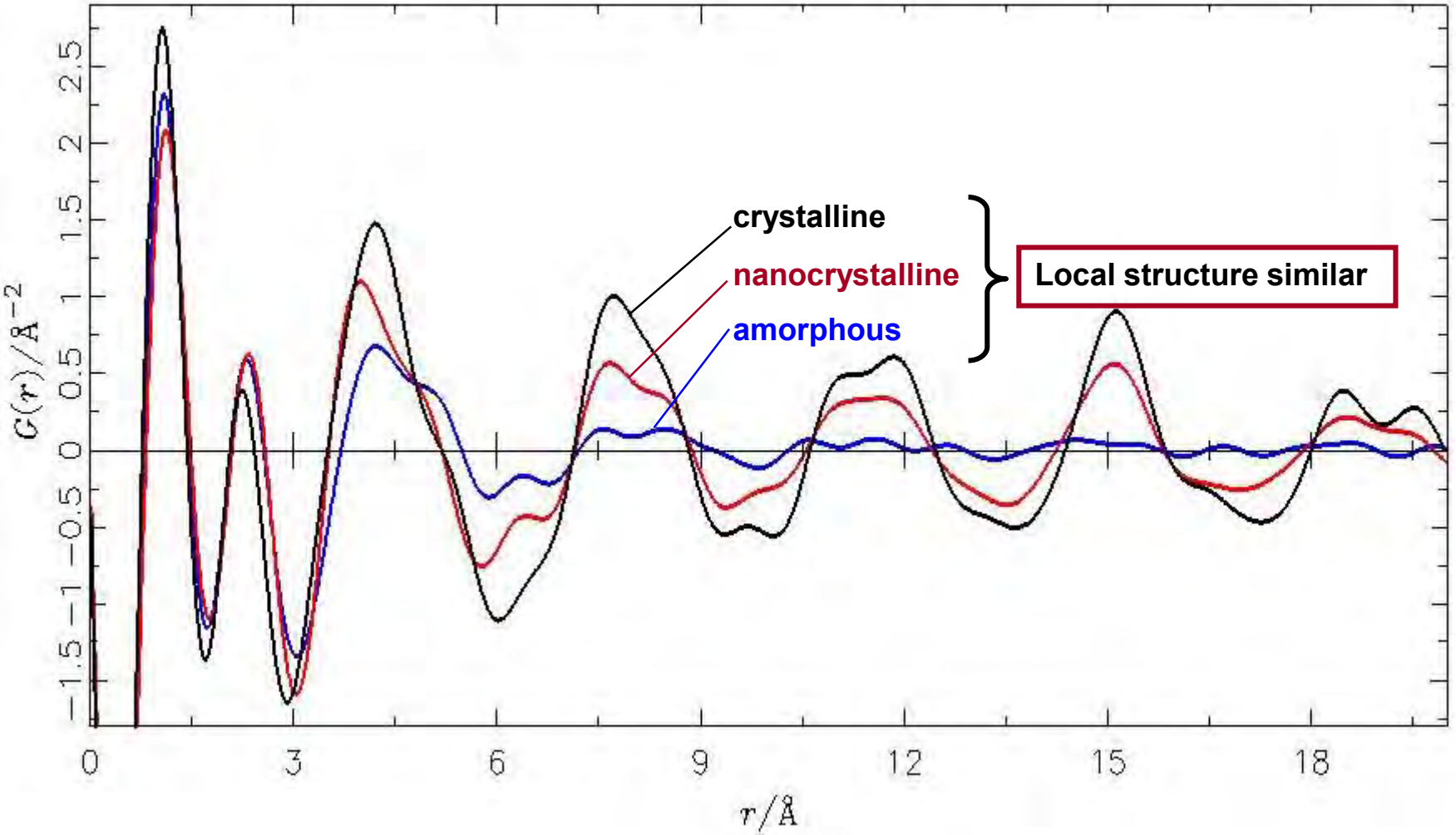
PDF of the amorphous phase

Nanocrystalline and amorphous API



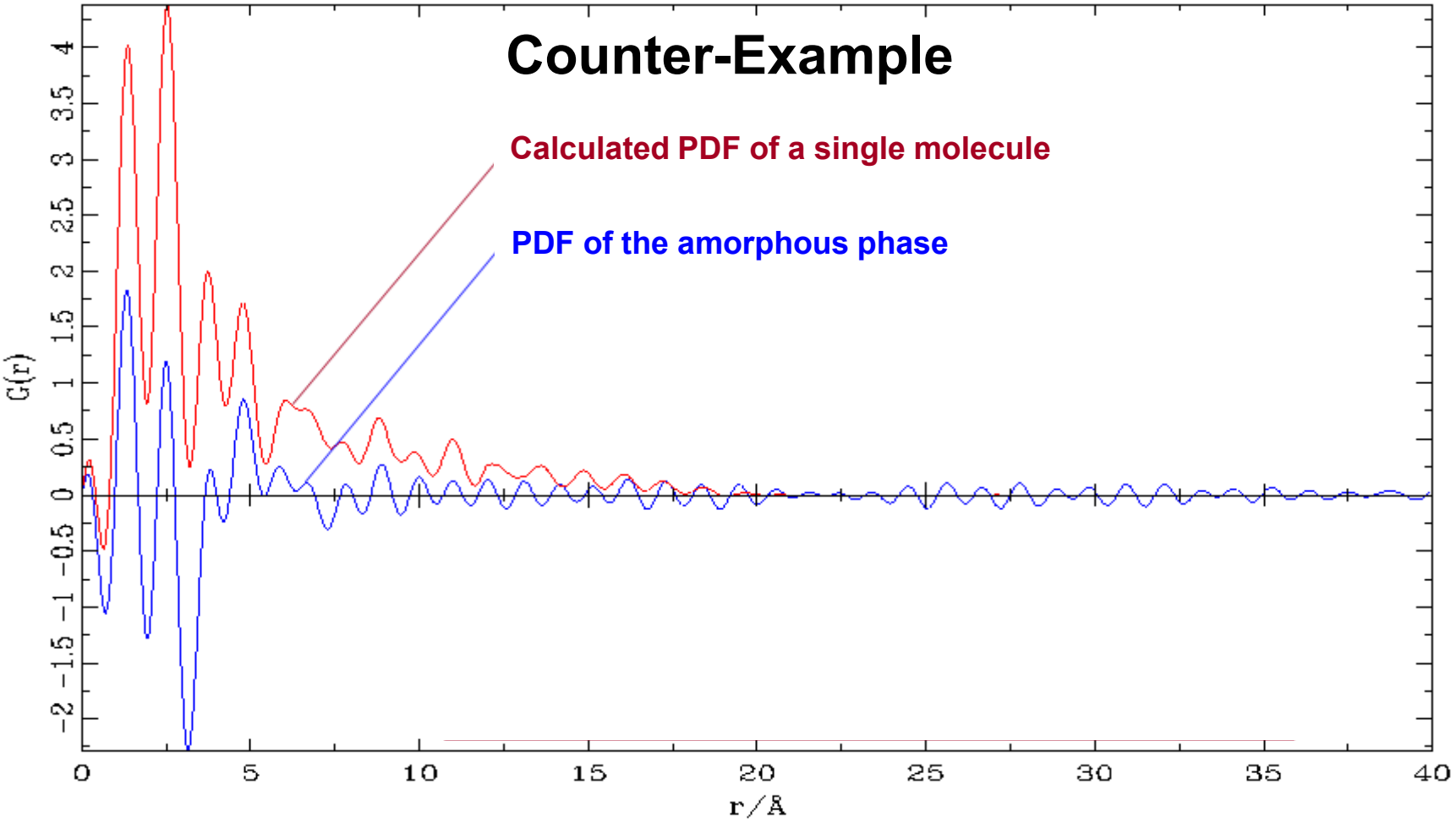
PDF of the amorphous phase

Nanocrystalline and amorphous API



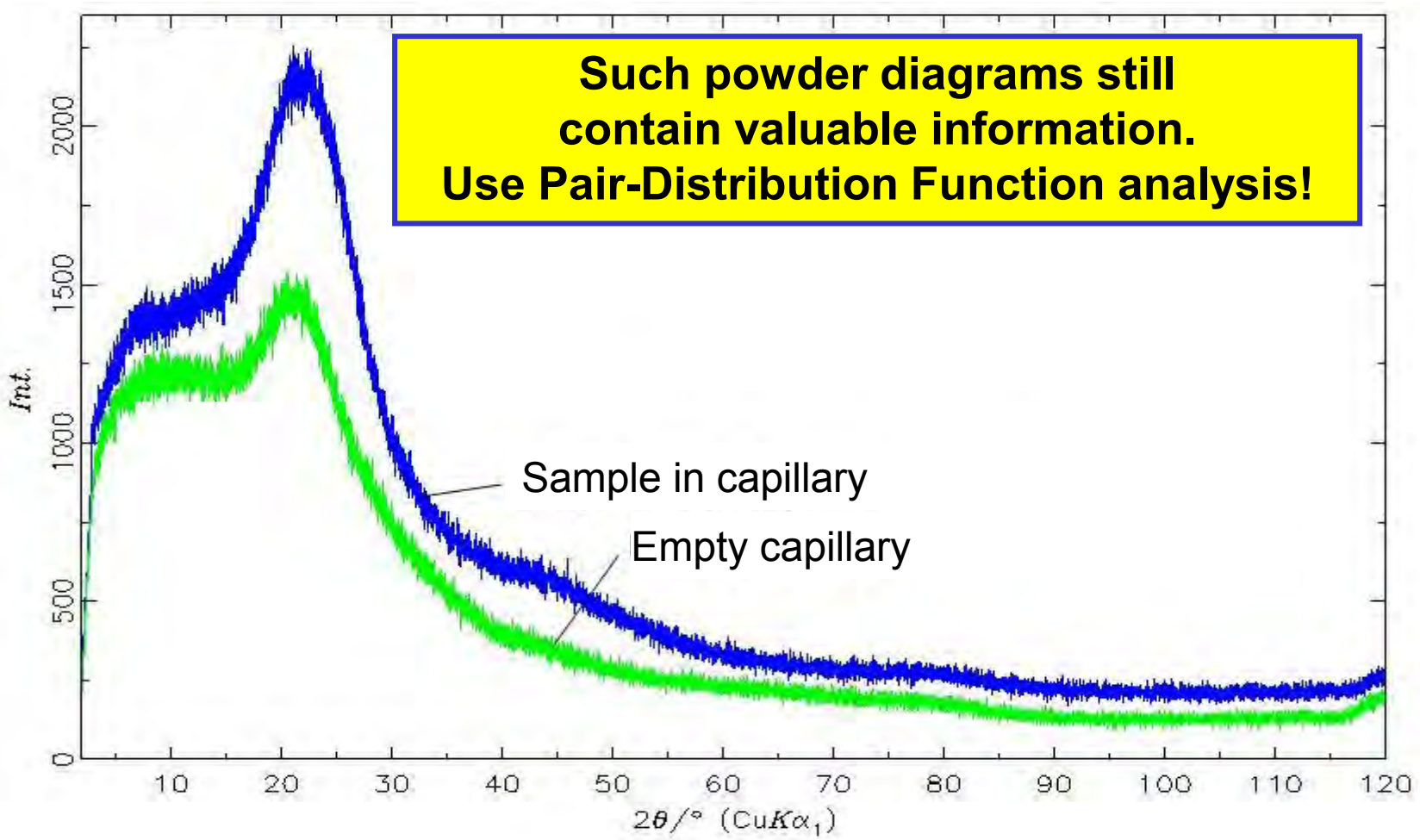
PDF: comparison (0 - 20 Å)

Nanocrystalline and amorphous API



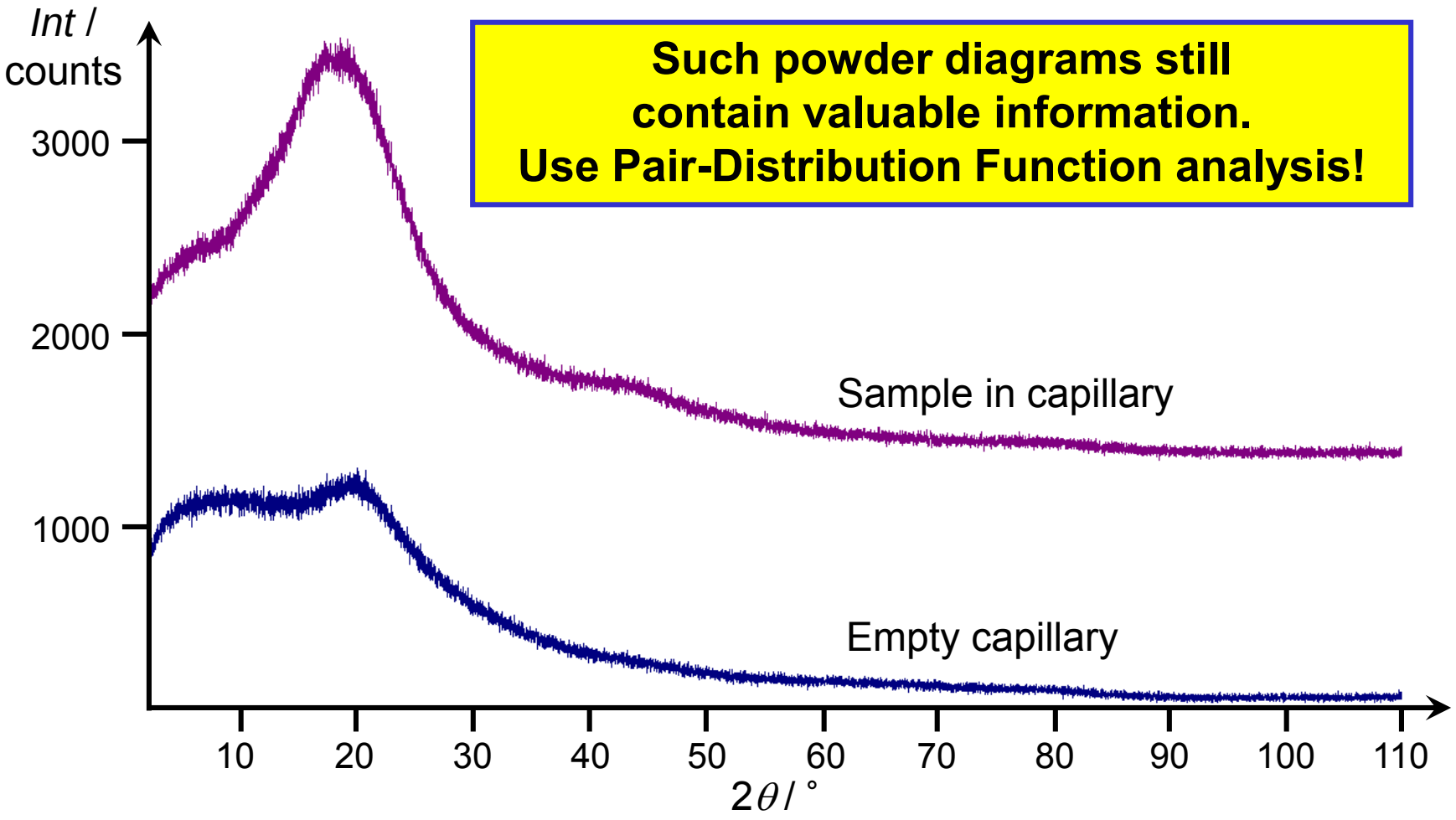
"Really amorphous".
No visible ordering of neighbouring molecules.

Nanocrystalline and amorphous API



Amorphous with local structure

Nanocrystalline and amorphous API



Cocrystal

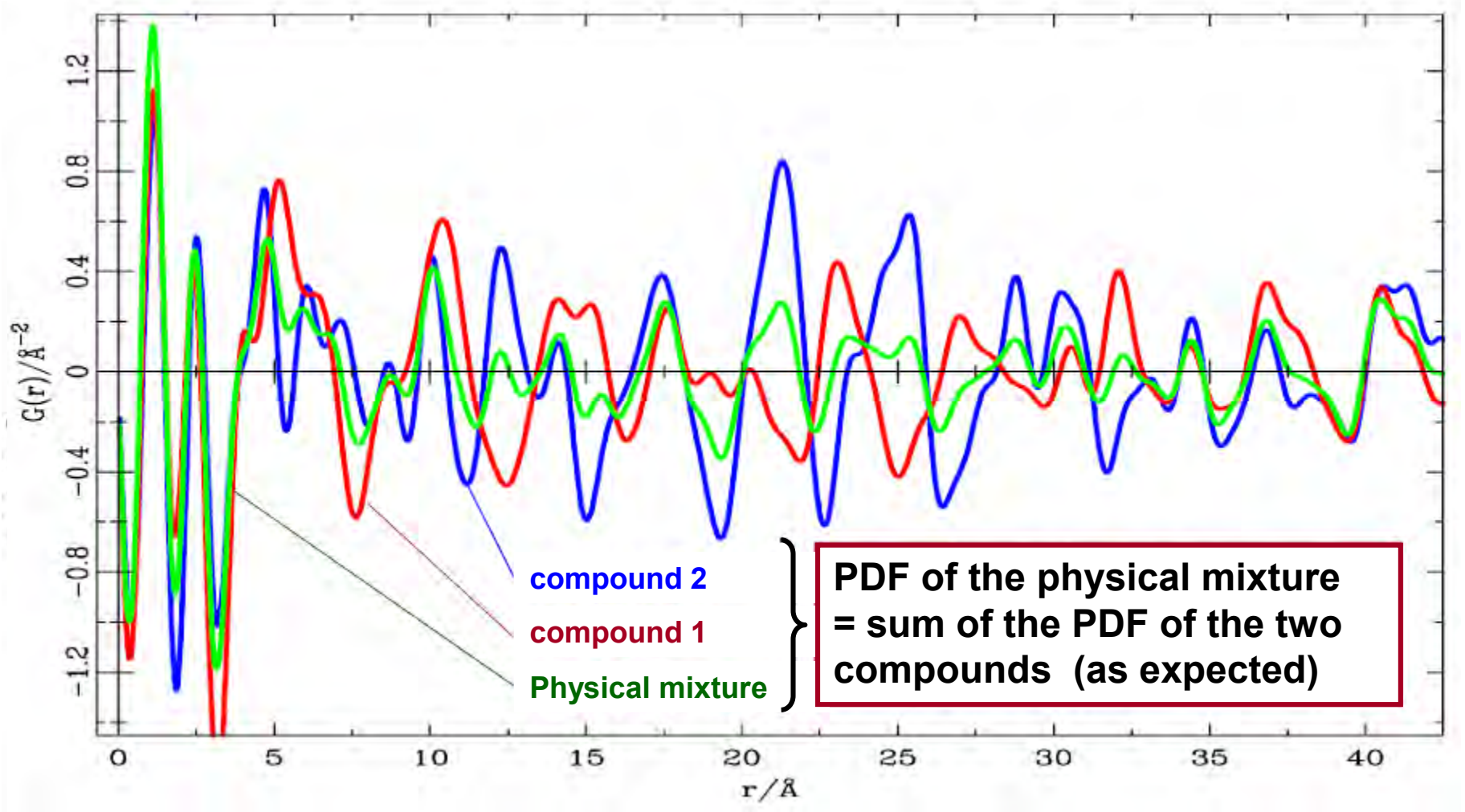
Cocrystal of 2 organic compounds

Questions:

- Cocrystal or physical mixture?

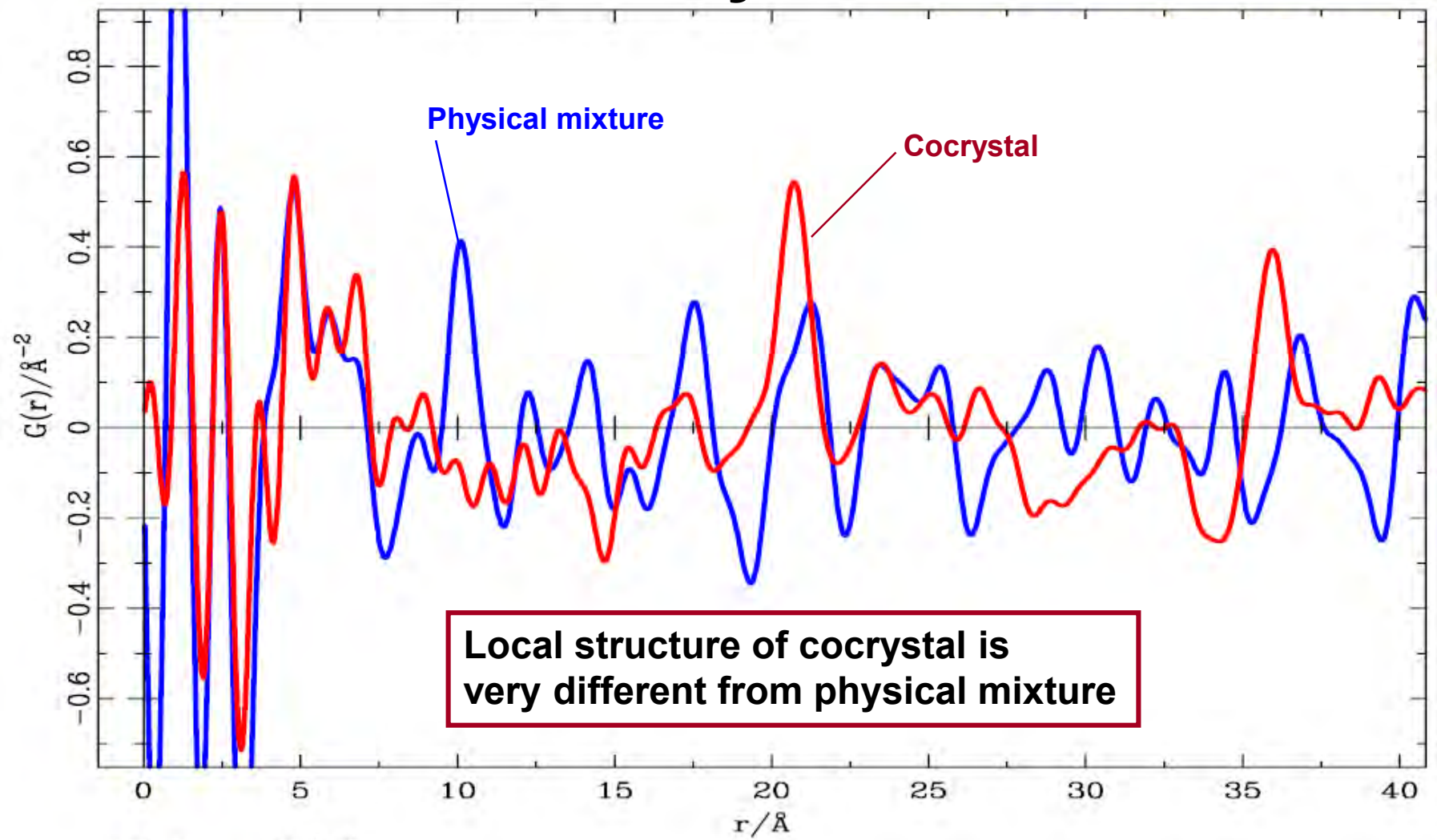
- Is it still a cocrystal after grinding or micronising?

Physical mixture



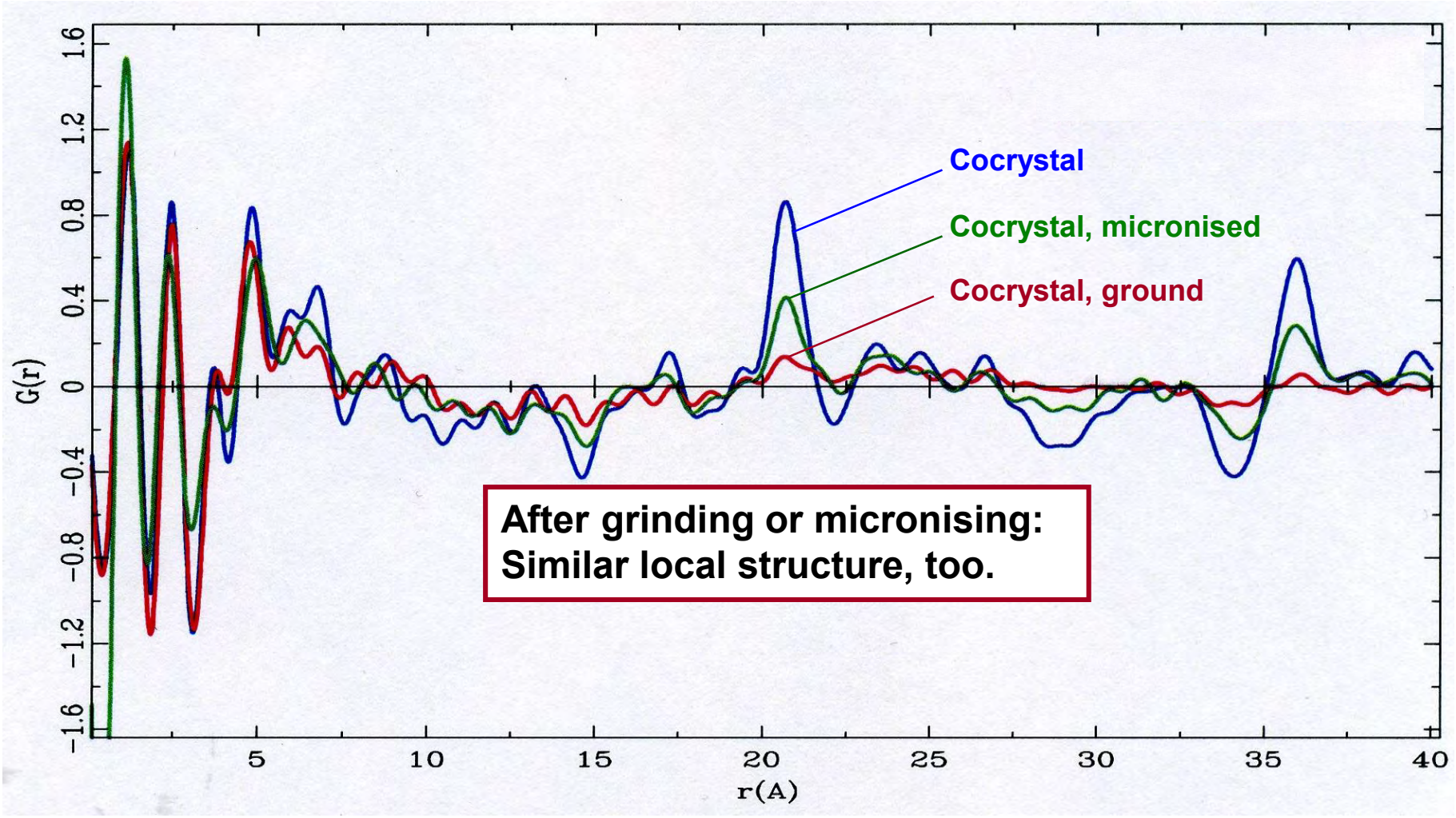
PDF of the physical mixture

Cocrystal



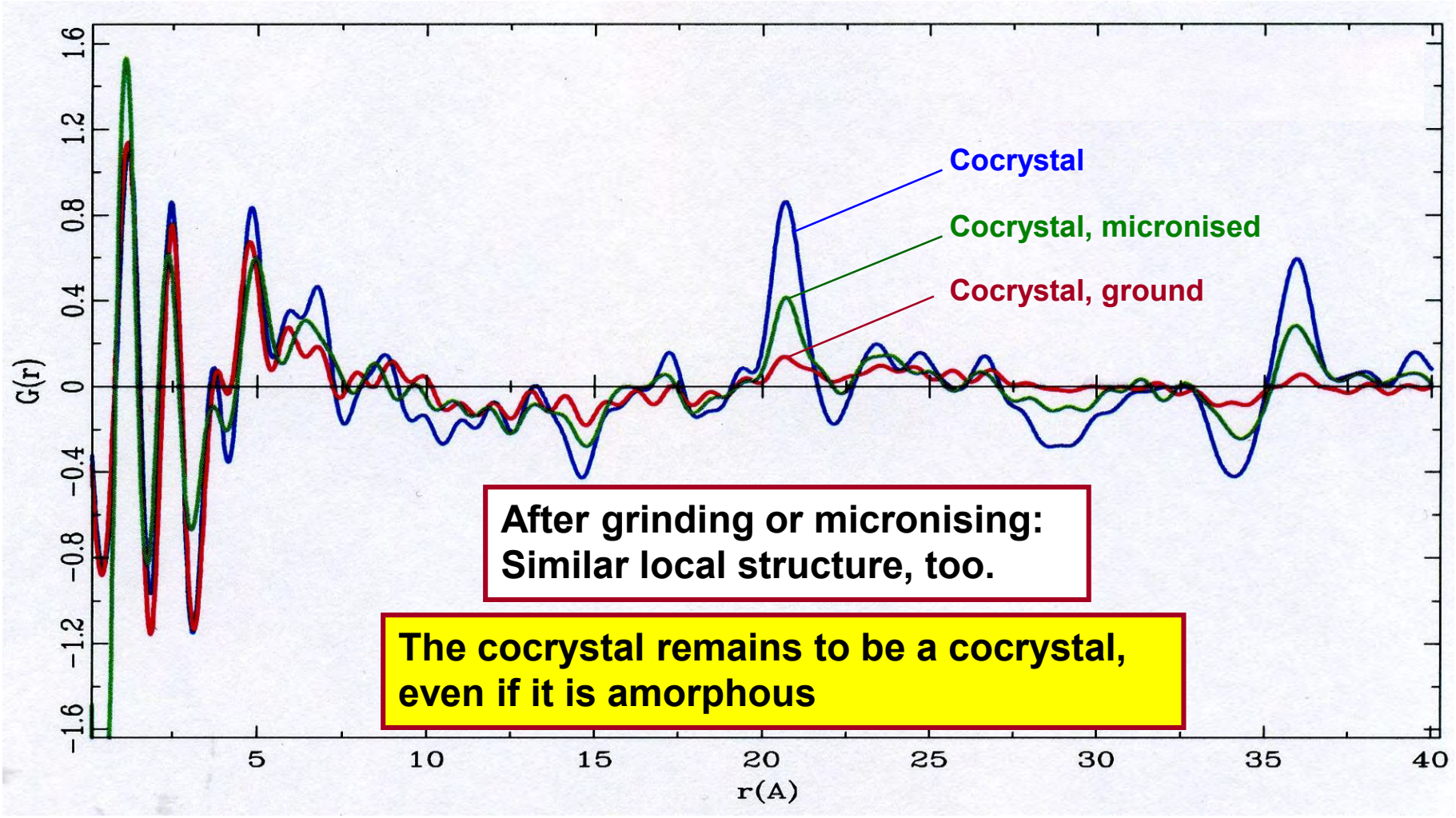
PDF of cocrystal and physical mixture

Cocrystal



Cocrystal: PDF

Cocrystal



Cocrystal: PDF

PDF of a pharmaceutical formulation

Formulation:

- Felodipine (well crystalline API)
- in two different types of "Eudragit" polymers (polyacrylates)
- Melt extrusion

Experimental observation:

10 % API
90 % polymer 1 (Eudragit E)

Poor dissolution behaviour

10 % API
90 % polymer 2 (Eudragit NE)

Poor dissolution behaviour

10 % API
85 % polymer 1
5 % polymer 2

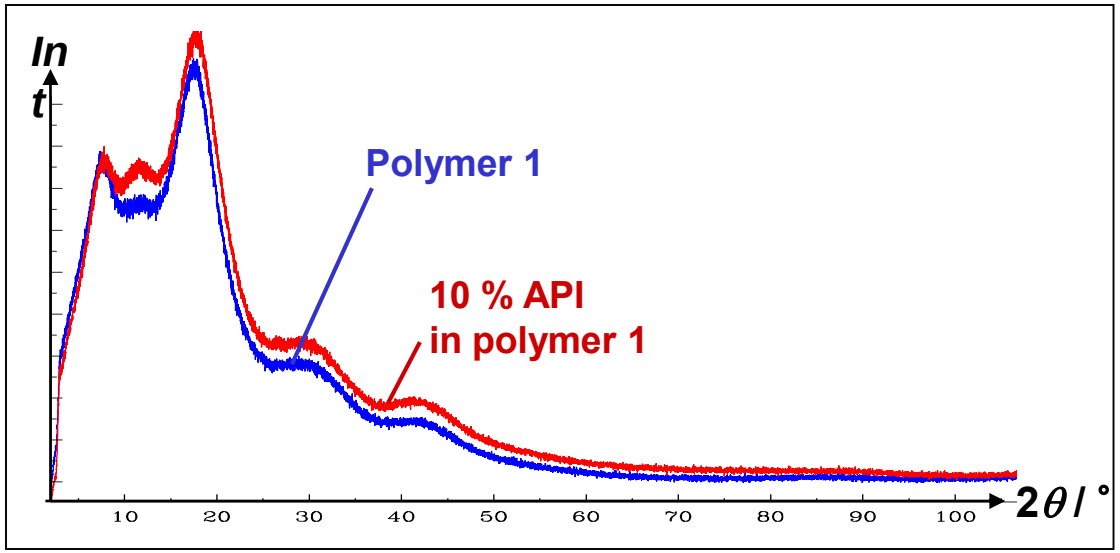
Much better dissolution behaviour

Why?

[K. Nollenberger, A. Gryczke, Ch. Meier, J. Dressman, M. U. Schmidt, S. Brühne, J. Pharm. Sci., **2009**, 98, 1476-1486]

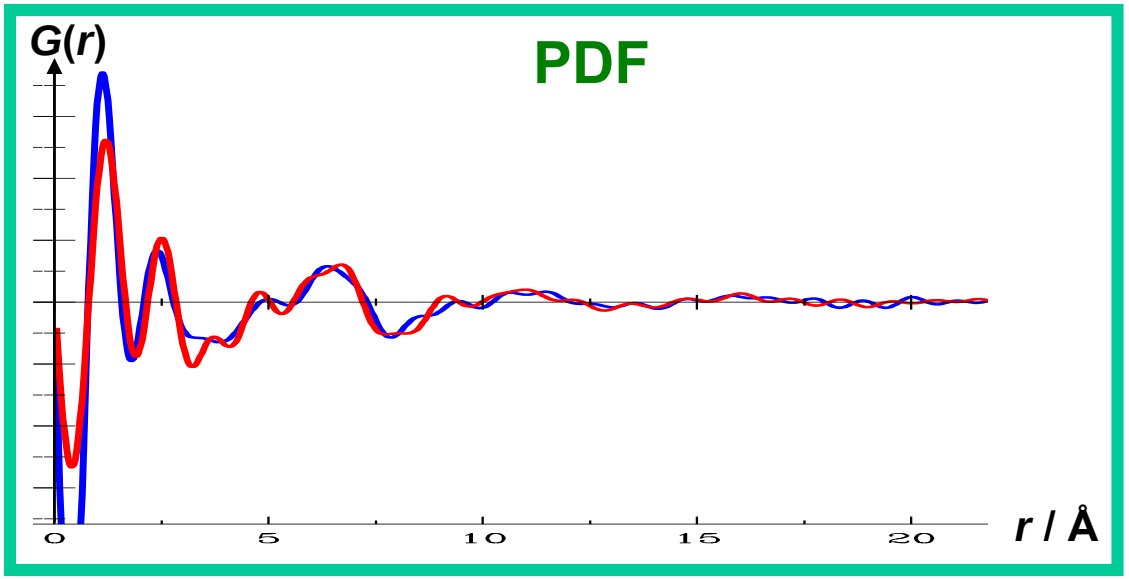
PDF of a pharmaceutical formulation

10 % API
in polymer 1



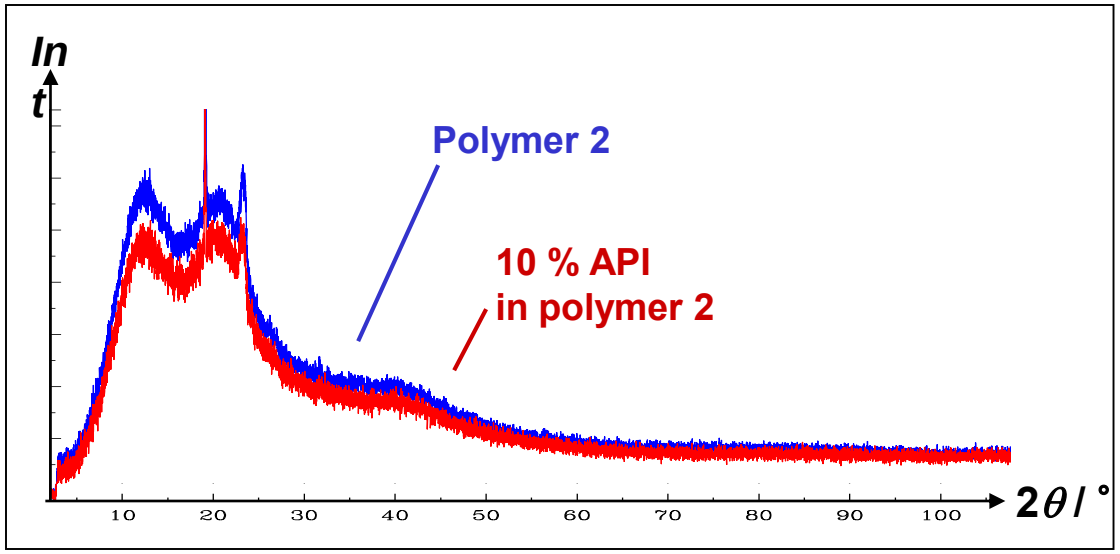
=> API is dissolved

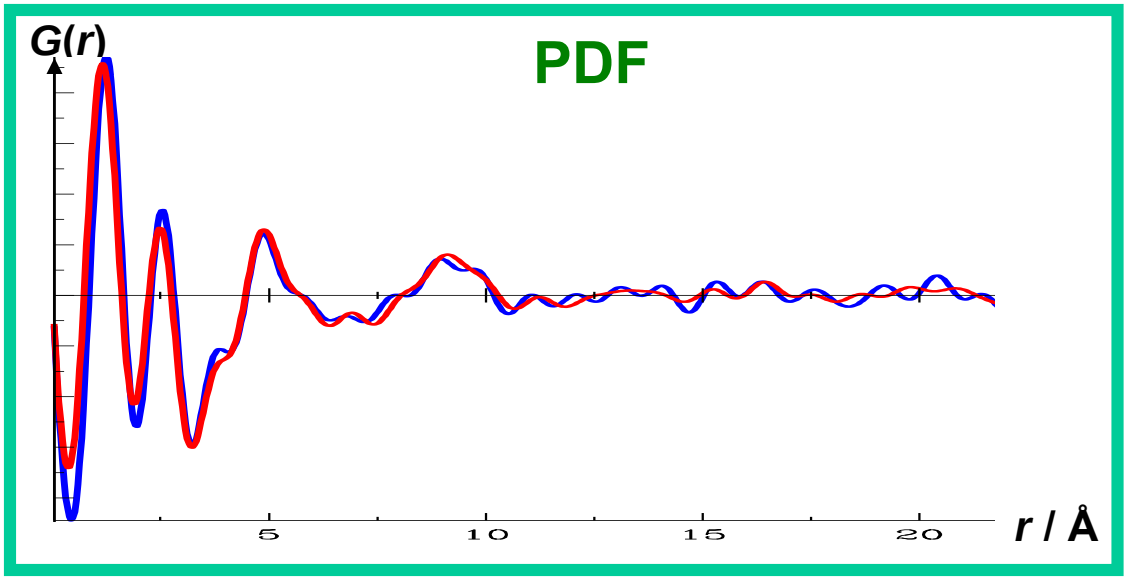
No structural changes
of polymer 1



PDF of a pharmaceutical formulation

10 % API
in polymer 2





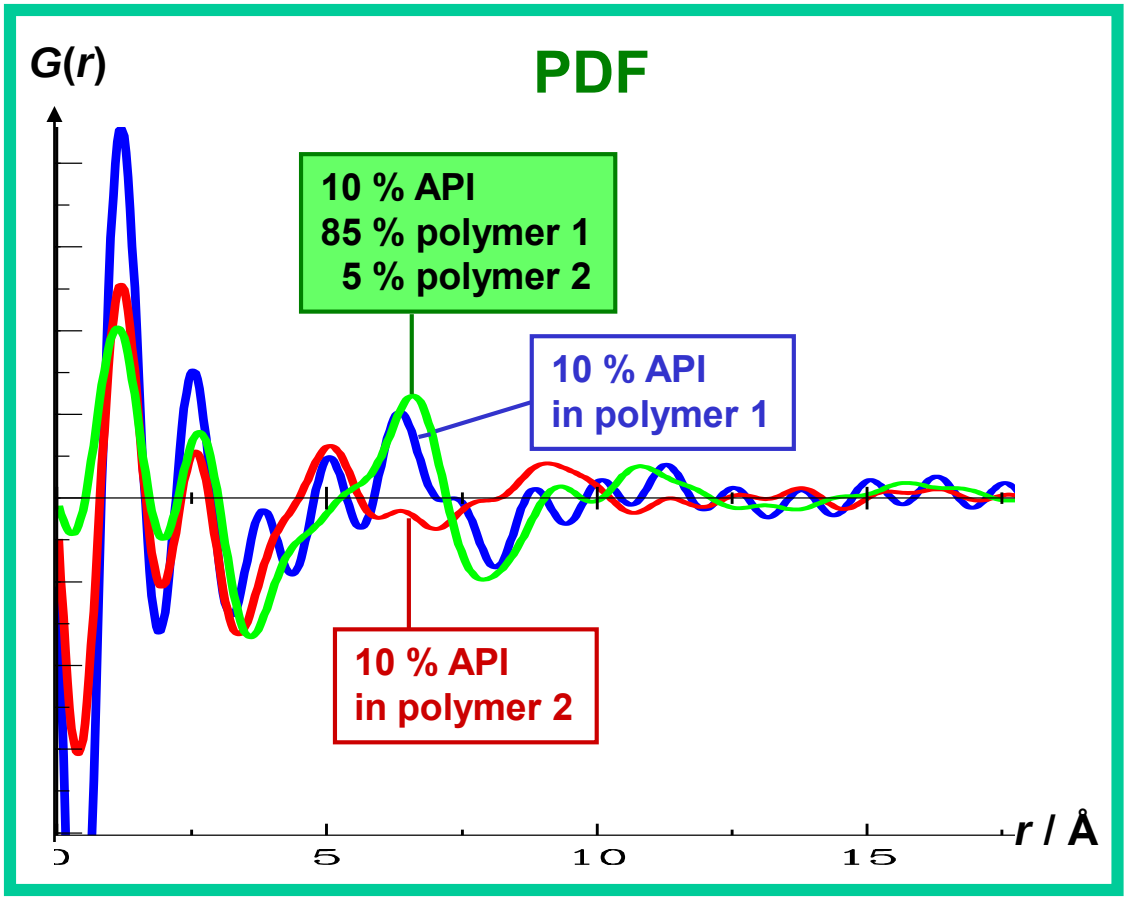
=> API is dissolved

No structural changes
of polymer 2

[K. Nollenberger, A. Gryczke, Ch. Meier, J. Dressman, M. U. Schmidt, S. Brühne, J. Pharm. Sci., **2009**, 98, 1476-1486]

PDF of a pharmaceutical formulation

10 % API
85 % polymer 1
5 % polymer 2



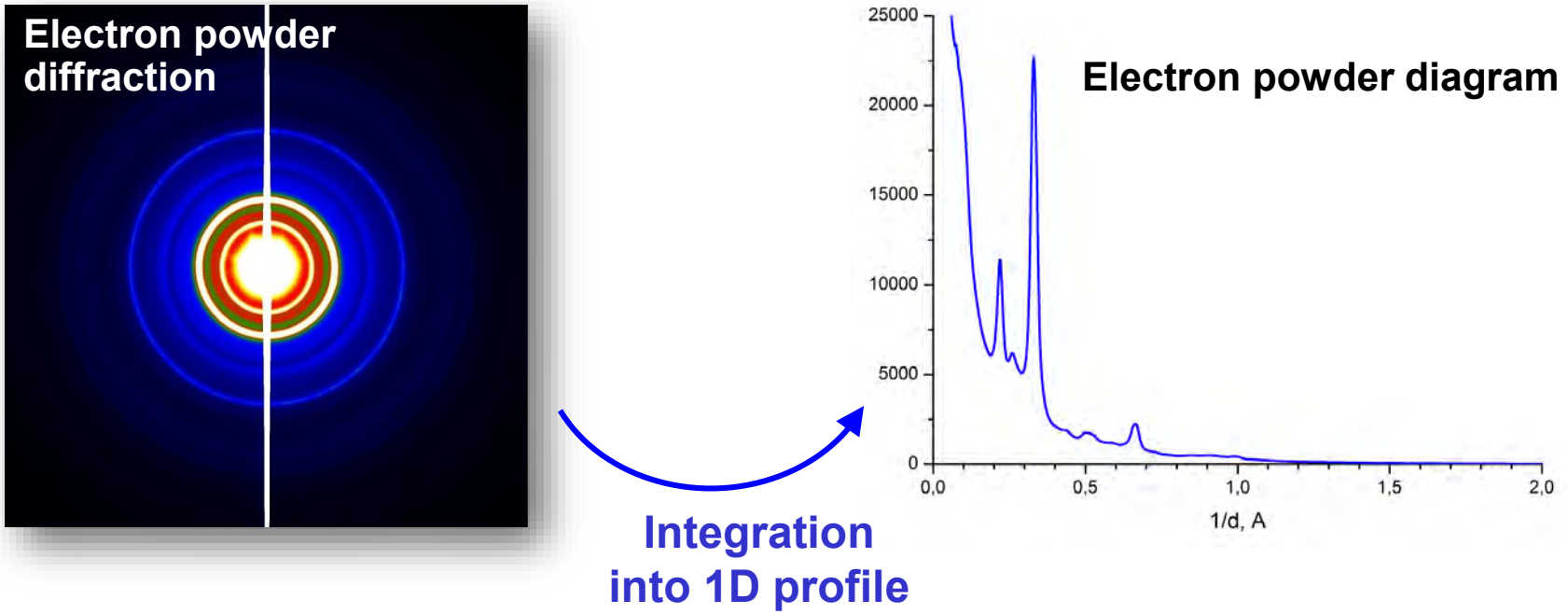
Structure of the mixture changes considerably.

This explains the observed differences in the dissolution behaviour.

[K. Nollenberger, A. Gryczke, Ch. Meier, J. Dressman, M. U. Schmidt, S. Brühne, J. Pharm. Sci., **2009**, 98, 1476-1486]

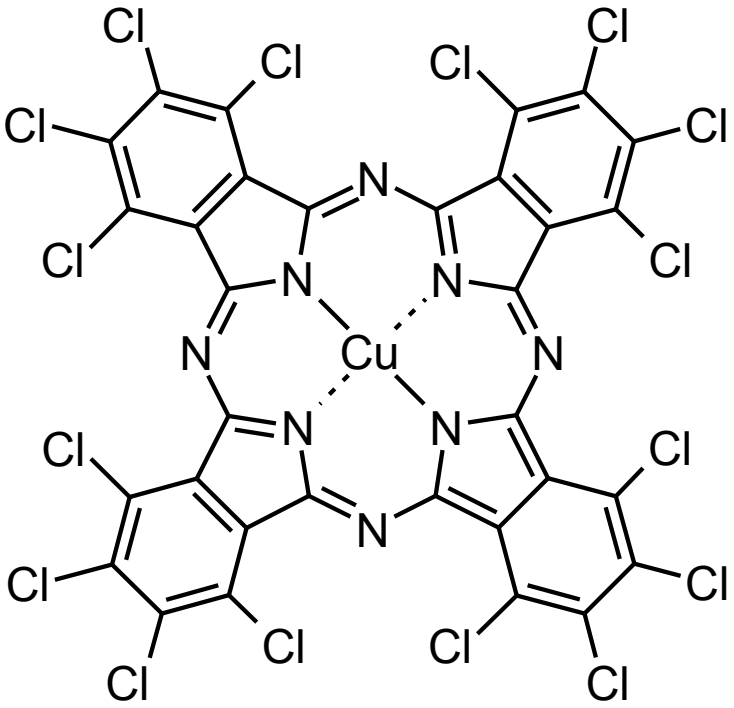
PDF from electron diffraction data (ePDF)

- **Polycrystalline thin films**
- **Amorphous thin films**



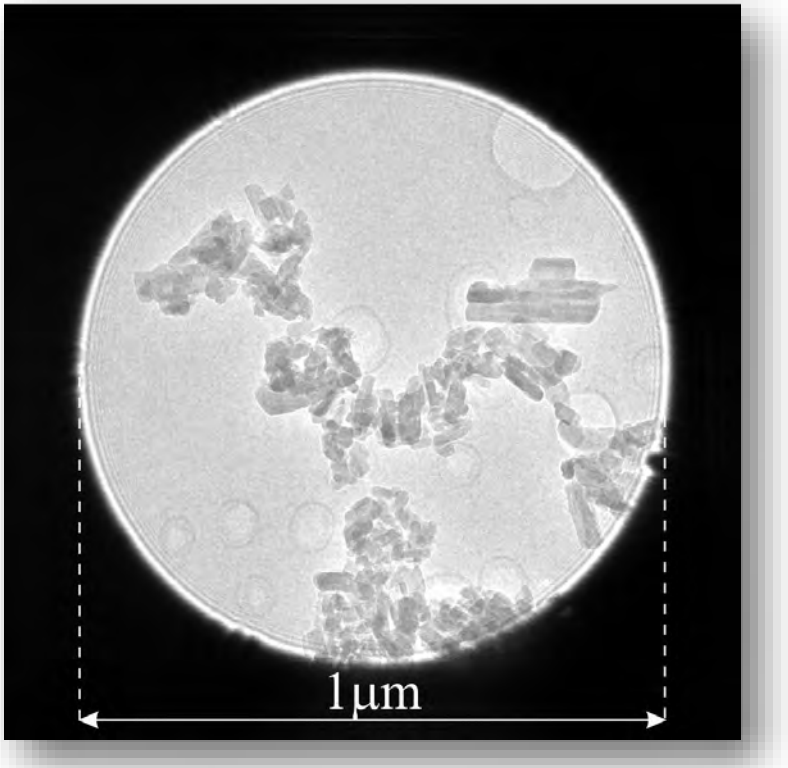
[S. Billinge, C. Farrow, M. Kanatzidis, T.E. Gorelik, M.U. Schmidt, *Patent* US 8921783 B2, **2014.**
T.E. Gorelik, M.U. Schmidt, U. Kolb, S.J.L. Billinge, *Microsc. Microanal.*, **2015**, 21, 459-471]

PDF from electron diffraction data (ePDF)



$CuPcCl_{16}$
(Chlorinated Cu-phthalocyanine)

Pigment Green 7

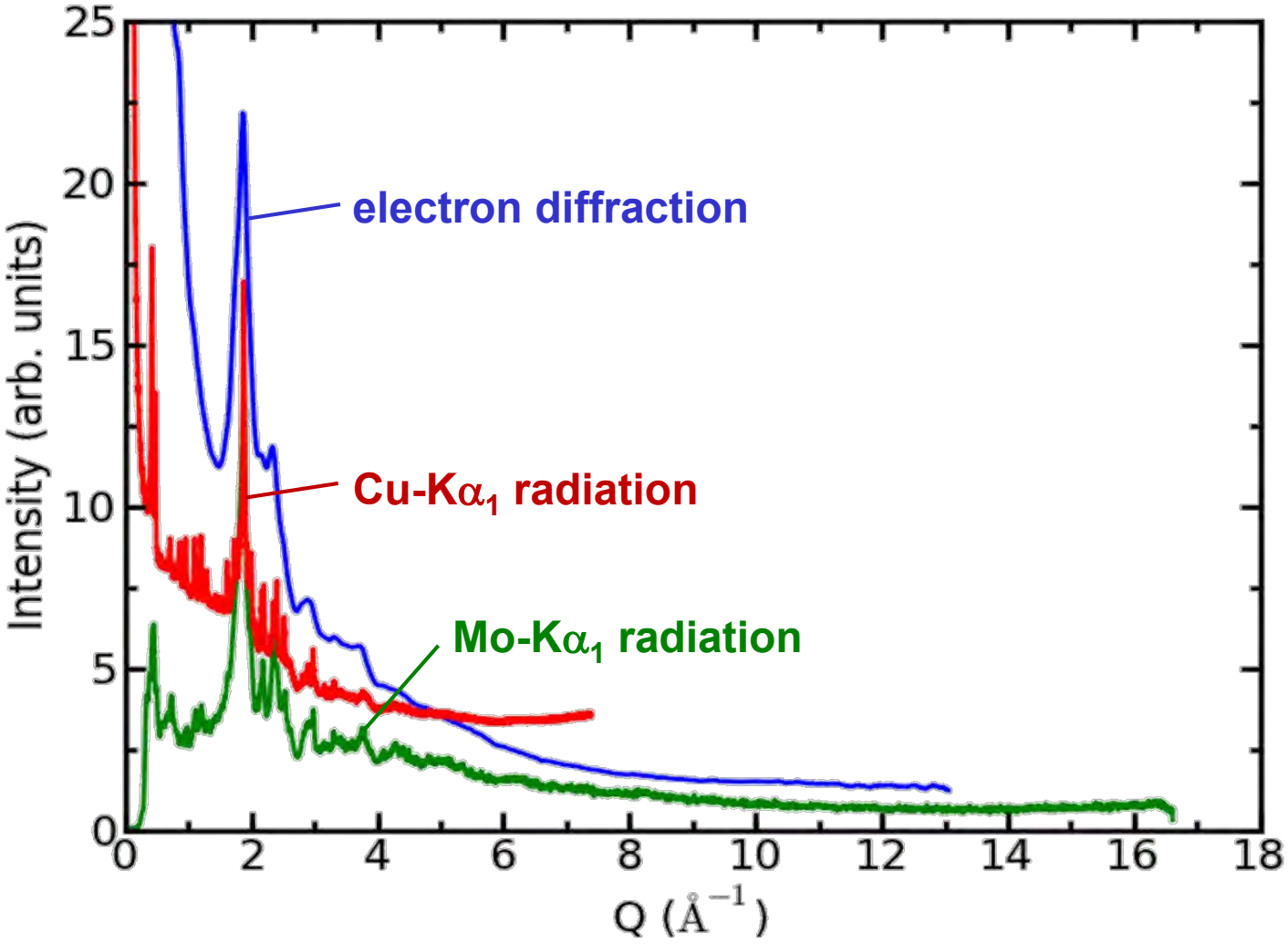


Data collection:

- **good counting statistics**
- **good orientation statistics**

[S. Billinge, C. Farrow, M. Kanatzidis, T.E. Gorelik, M.U. Schmidt, *Patent* US 8921783 B2, **2014.**
T.E. Gorelik, M.U. Schmidt, U. Kolb, S.J.L. Billinge, *Microsc. Microanal*., **2015**, 21, 459-471]

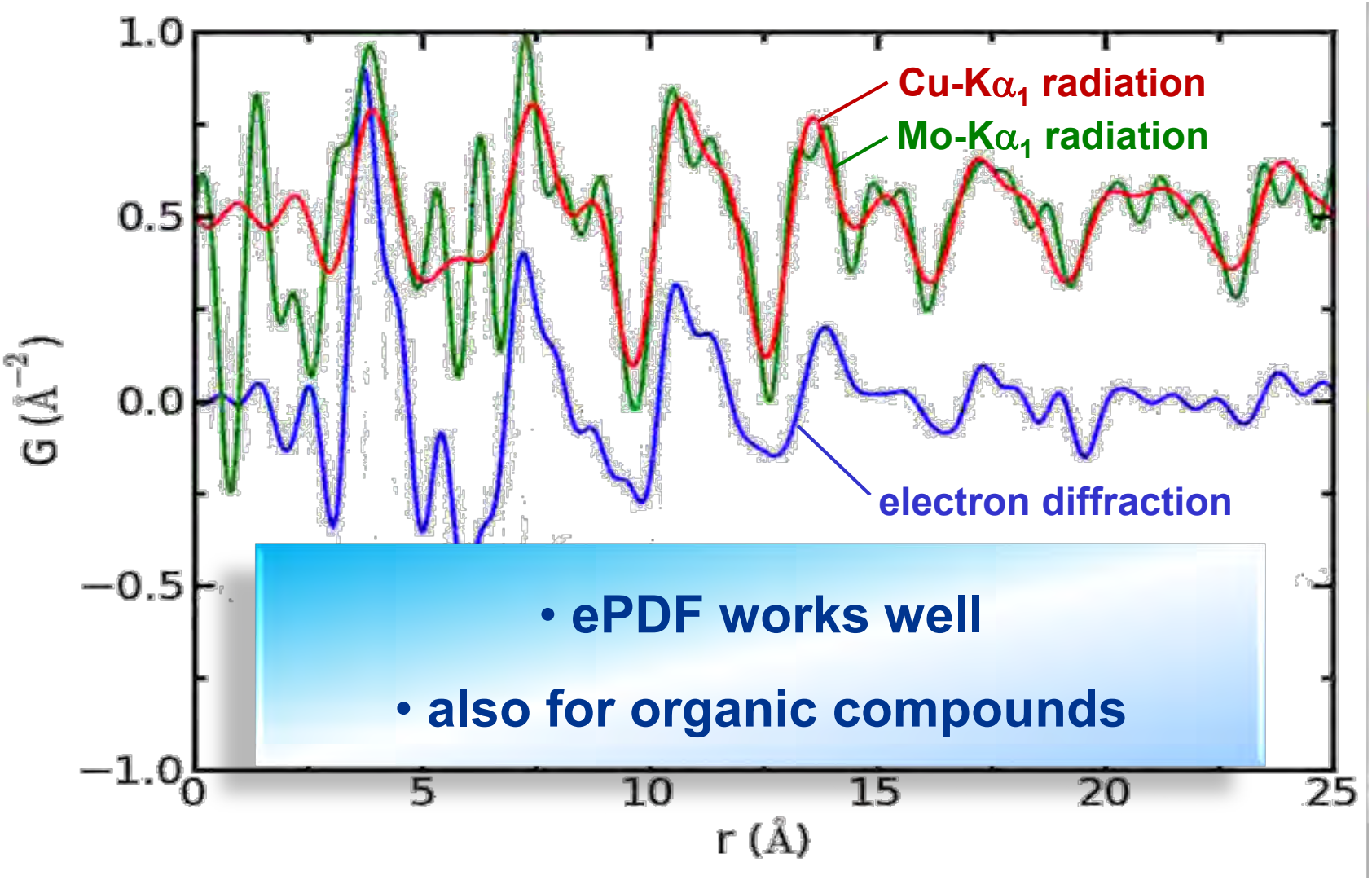
PDF from electron diffraction data (ePDF)



Powder diagrams of $CuPcCl_{16}$

[S. Billinge, C. Farrow, M. Kanatzidis, T.E. Gorelik, M.U. Schmidt, *Patent* US 8921783 B2, **2014.**
T.E. Gorelik, M.U. Schmidt, U. Kolb, S.J.L. Billinge, *Microsc. Microanal.*, **2015**, 21, 459-471]

PDF from electron diffraction data (ePDF)



PDF of $CuPcCl_{16}$

[S. Billinge, C. Farrow, M. Kanatzidis, T.E. Gorelik, M.U. Schmidt, *Patent* US 8921783 B2, **2014.**
T.E. Gorelik, M.U. Schmidt, U. Kolb, S.J.L. Billinge, *Microsc. Microanal.*, **2015**, 21, 459-471]

Applications of the PDF

- **Investigation of local structures and packing motifs in**
  - **nanocrystalline organic compounds.** ***(Done)***
  - **amorphous organic compounds.** ***(Done)***
  - **disordered organic and organometallic compounds.** ***(Done)***
- **Comparing the local structures in hydrates, solvates, and polymorphs.** ***(Done)***

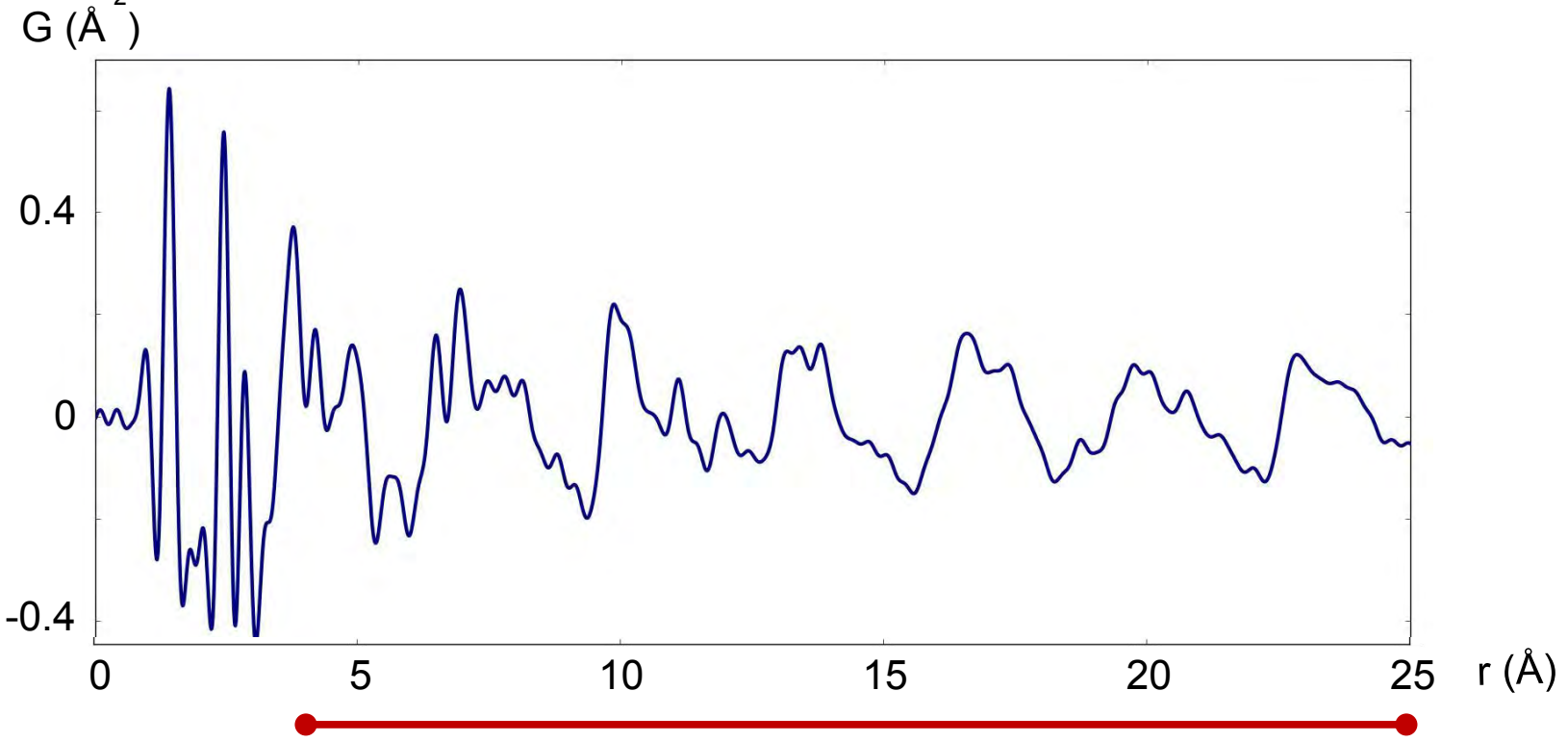
  Hydrate → Anhydrate (amorphous): Similar local structure?
- **Detecting the crystallisation of amorphous compounds (PDF: more sensitive than X-ray powder pattern).** ***(Done)***
- **Pharmaceutical cocrystals:**
  Proving that a micronized cocrystal remains to be a cocrystal, even if it is amorphous. ***(Done)***
- **Do different amorphous states exist?** ***(Done)***

Applications of the PDF

- **Determination of crystal structures of nanocrystalline organic compounds by fit to the PDF curve *(Done)*.**
  [D. Prill, P. Juhás, S.J.L. Billinge, M.U. Schmidt, Acta Cryst. **2016**, A72, 62-72]

Structure determination by fit to the PDF curve

PDF of organic compounds



Intramolecular atom-atom distances
- covalent bonds (hard)
- small vibrational amplitudes
- small variation of distances

Sharp signals

B_{intra}

Intermolecular atom-atom distances
- van der Waals bonds (soft)
- large vibrational amplitudes
- large variation of distances

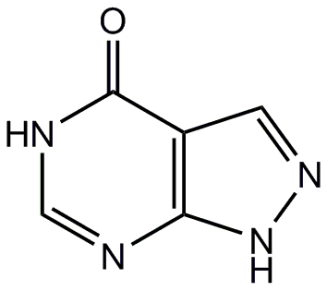
Broad signals

B_{inter}

[N. Rademacher, L. L. Luke, E. L. Chronister, Th. Proffen, J. Appl. Cryst. (2012), 45, 482-488]

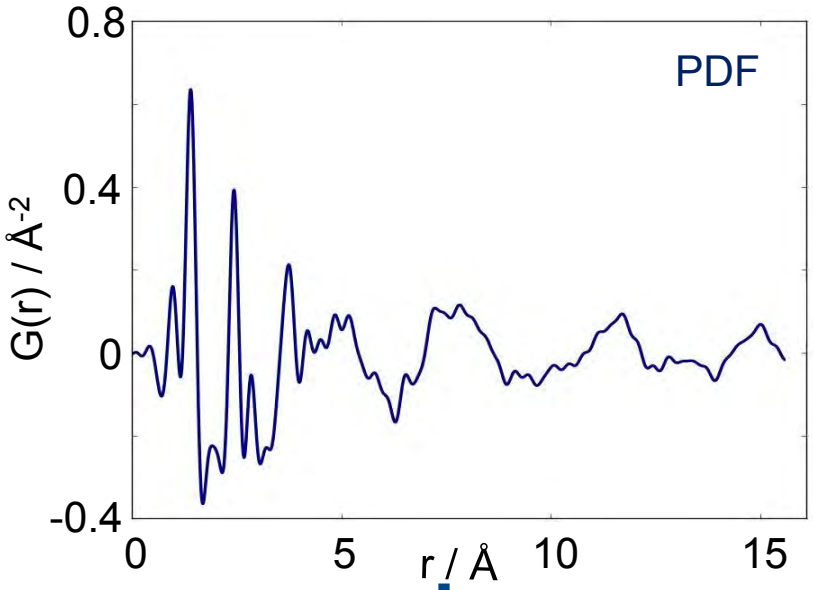
[D. Prill, P. Juhas, M. U. Schmidt, S. J. L. Billinge, J. Appl. Cryst. (2015), 48, 171-178]

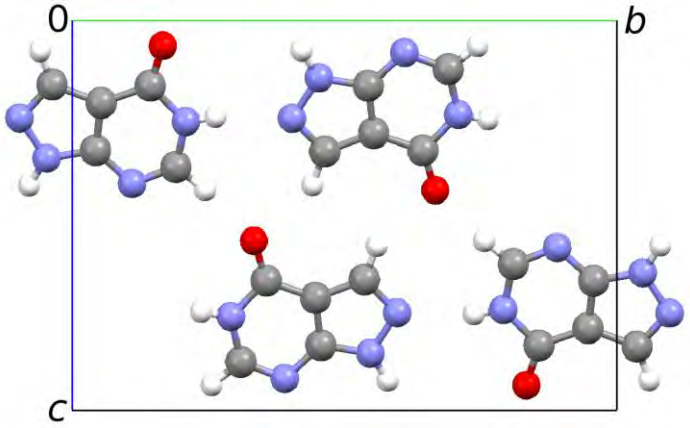
Structure determination by fit to the PDF data



Molecular structure

+





[D. Prill, P. Juhas, S. J. L. Billinge, M. U. Schmidt, Acta Cryst. A 72, 62 (2016)]

Structure determination by fit to the PDF data

Fit of a structural model to the PDF:

- Inorganic compounds: move individual atoms
- Organic compounds: move whole molecules

Structure determination by fit to the PDF data

Given:

- PDF data (reliable, high resolution) => Synchrotron data
- Molecular geometry (with flexible torsions)

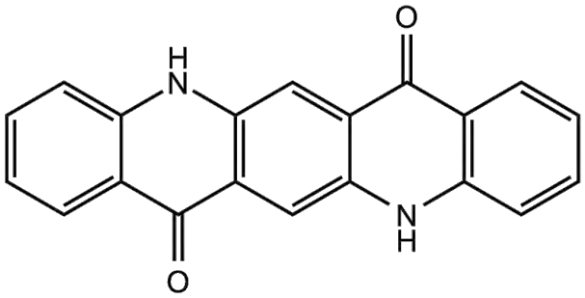
To be determined:

- Space group
- Lattice parameters
- Position of the molecule
- Orientation of the molecule
- Intramolecular degrees of freedom
- B_{intra} , B_{inter} , Scale factor

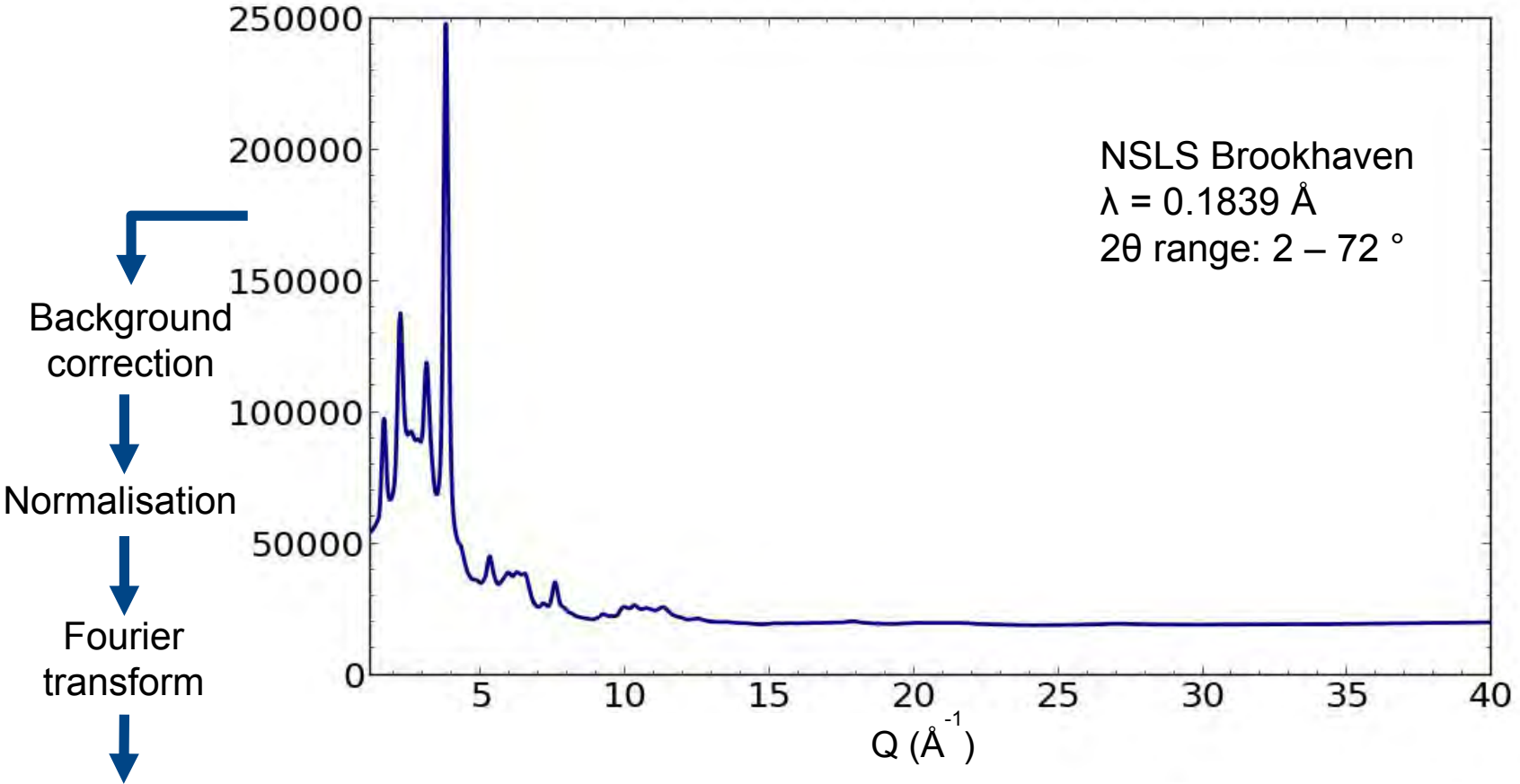
[D. Prill, P. Juhas, S. J. L. Billinge, M. U. Schmidt, Acta Cryst. A 72, 62 (2016)]

Structure determination by fit to the PDF data

Example 1:
- lattice parameters given
- space group given

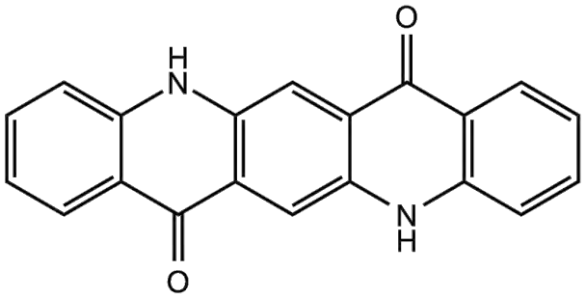


Quinacridone

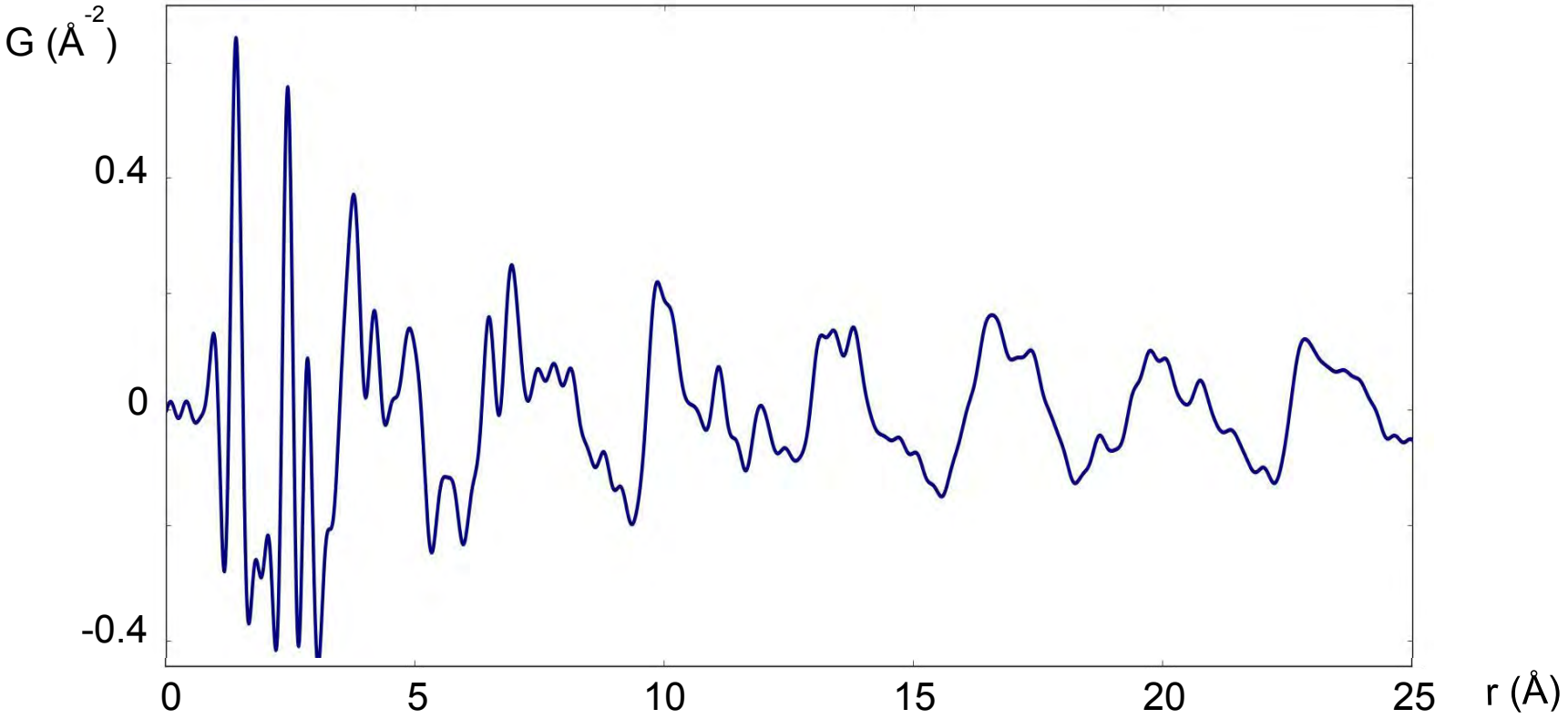


Structure determination by fit to the PDF data

Example 1:
- lattice parameters given
- space group given



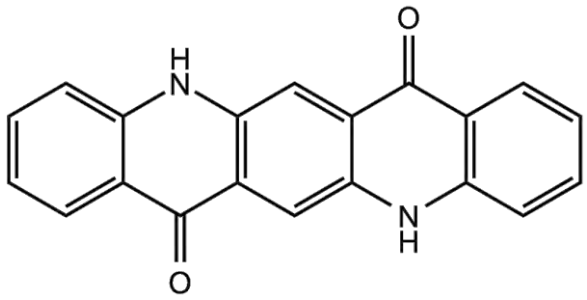
Quinacridone



[D. Prill, P. Juhas, S. J. L. Billinge, M. U. Schmidt, Acta Cryst. A 72, 62 (2016)]

Structure determination by fit to the PDF data

Example 1:
- lattice parameters given
- space group given



To be determined:

- position of the molecule (starting from random values)

- orientation of the molecule (starting from random values)

- B_{intra} , B_{inter}

- scale factor

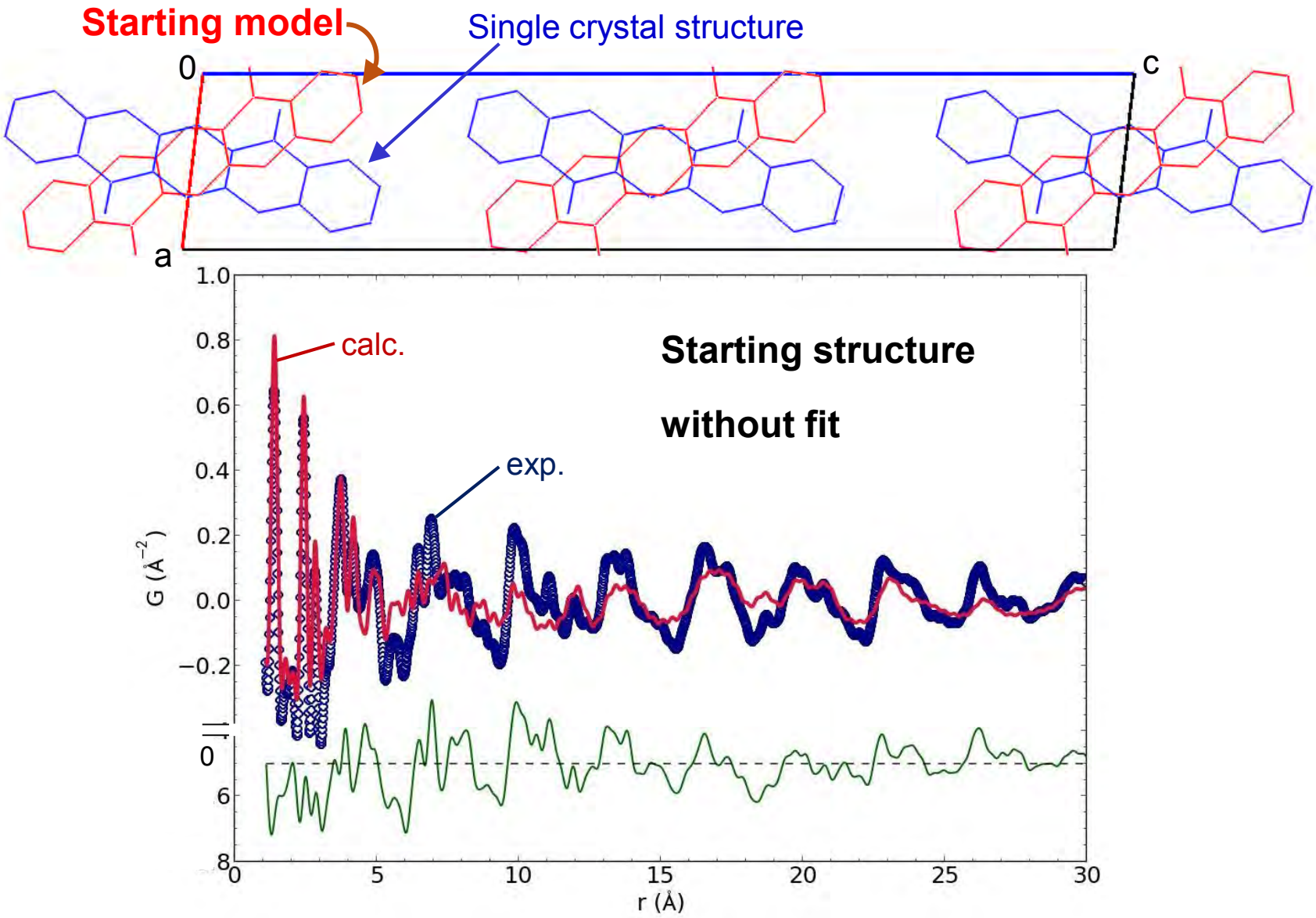
- lattice parameters re-refined

Programs:

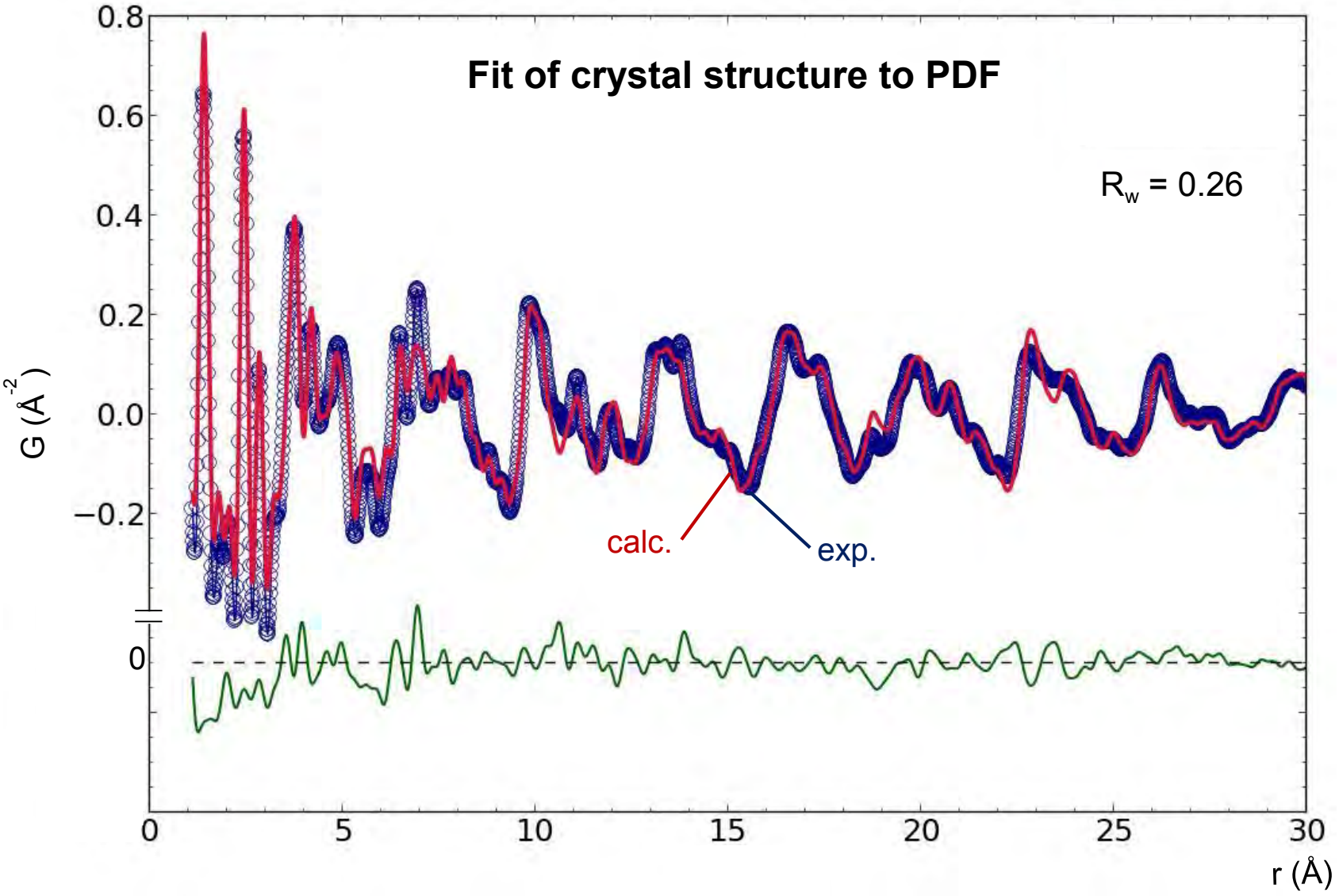
- DiffPy-CMI (Group of Simon Billinge)
- TOPAS-6 (Alan Coelho / Bruker)

[D. Prill, P. Juhas, S. J. L. Billinge, M. U. Schmidt, Acta Cryst. A 72, 62 (2016)]

Structure determination by fit to the PDF data

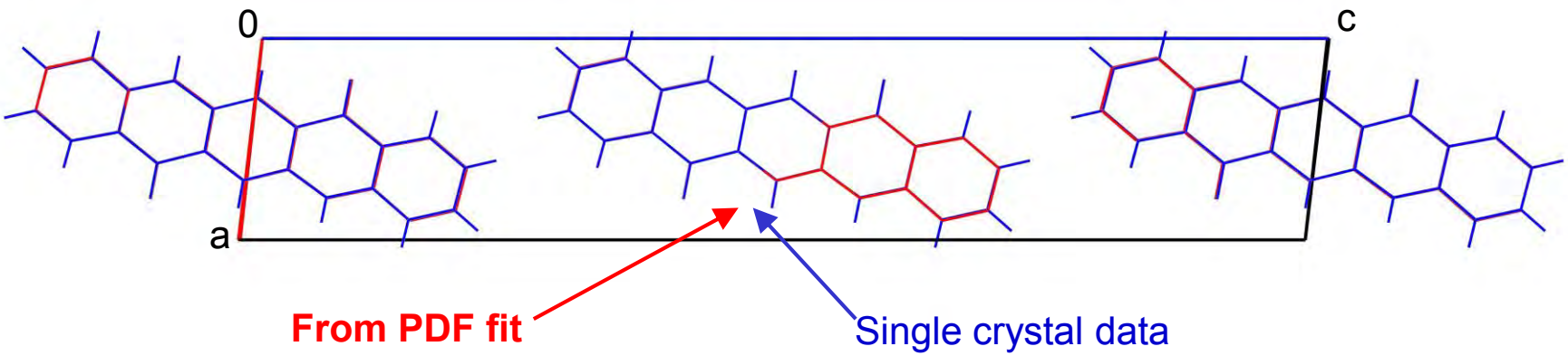


Structure determination by fit to the PDF data



Structure determination by fit to the PDF data

Fit of crystal structure to PDF



From PDF fit

a = 5.700 Å
b = 3.931 Å
c = 29.957 Å
β = 96.31 °

Single crystal data

a = 5.692 Å
b = 3.975 Å
c = 30.02 Å
β = 96.76 °

Also works for Z' = 4

Structure solved by fit to the PDF

(Lattice parameters and space group used as input)

[D. Prill, P. Juhas, S. J. L. Billinge, M. U. Schmidt, Acta Cryst. A 72, 62 (2016)]

Structure determination from scratch by fit to the PDF data

Structure determination from scratch

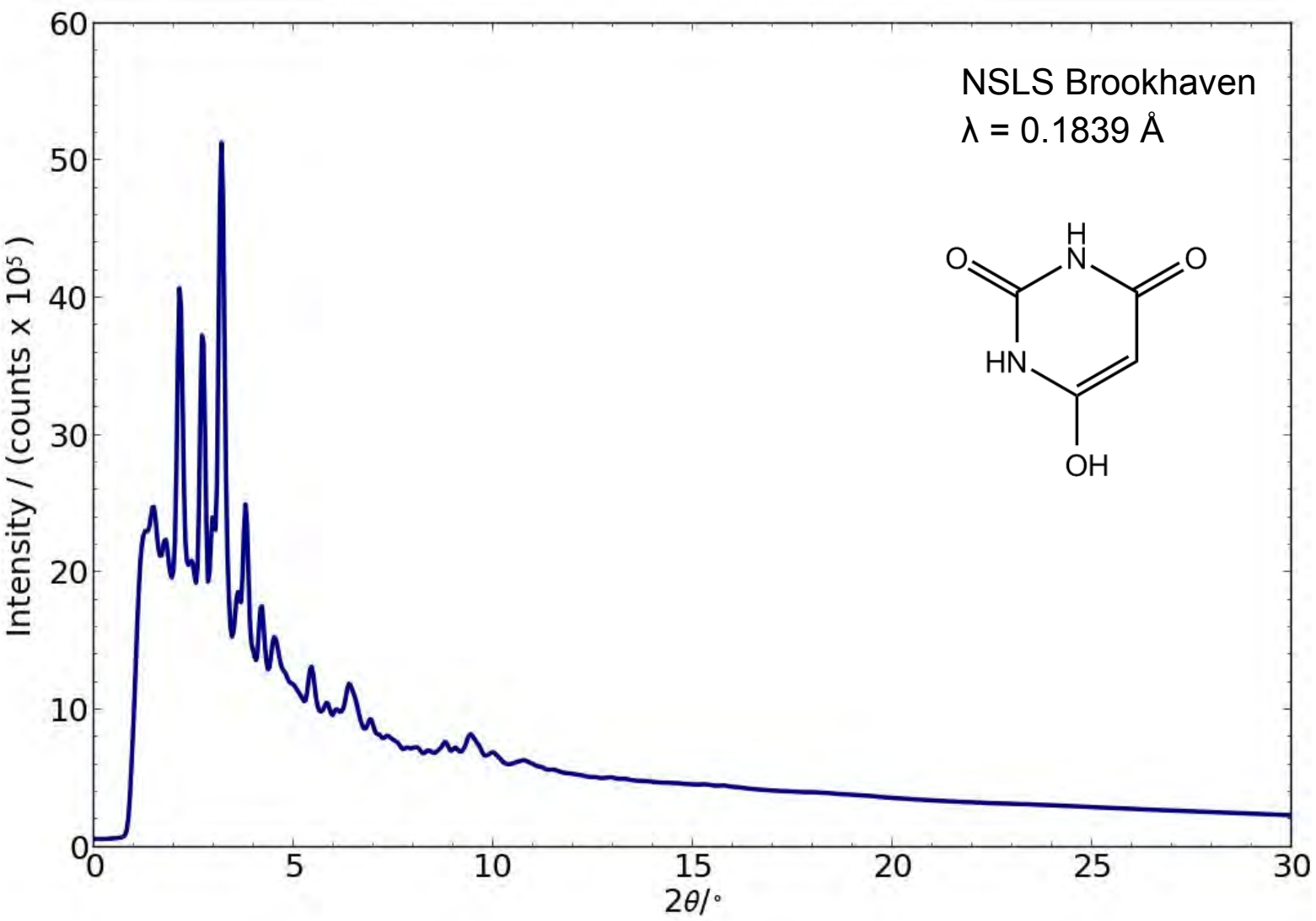
Input:
- Molecular geometry
- PDF curve

To be determined:
- Space group (Statistically frequent space groups)
- Lattice parameters
- Position of the molecule
- Orientation of the molecule
- B_{intra} , B_{inter}
- Scale factor

} **Starting from random values (About 1 Mio trials)**

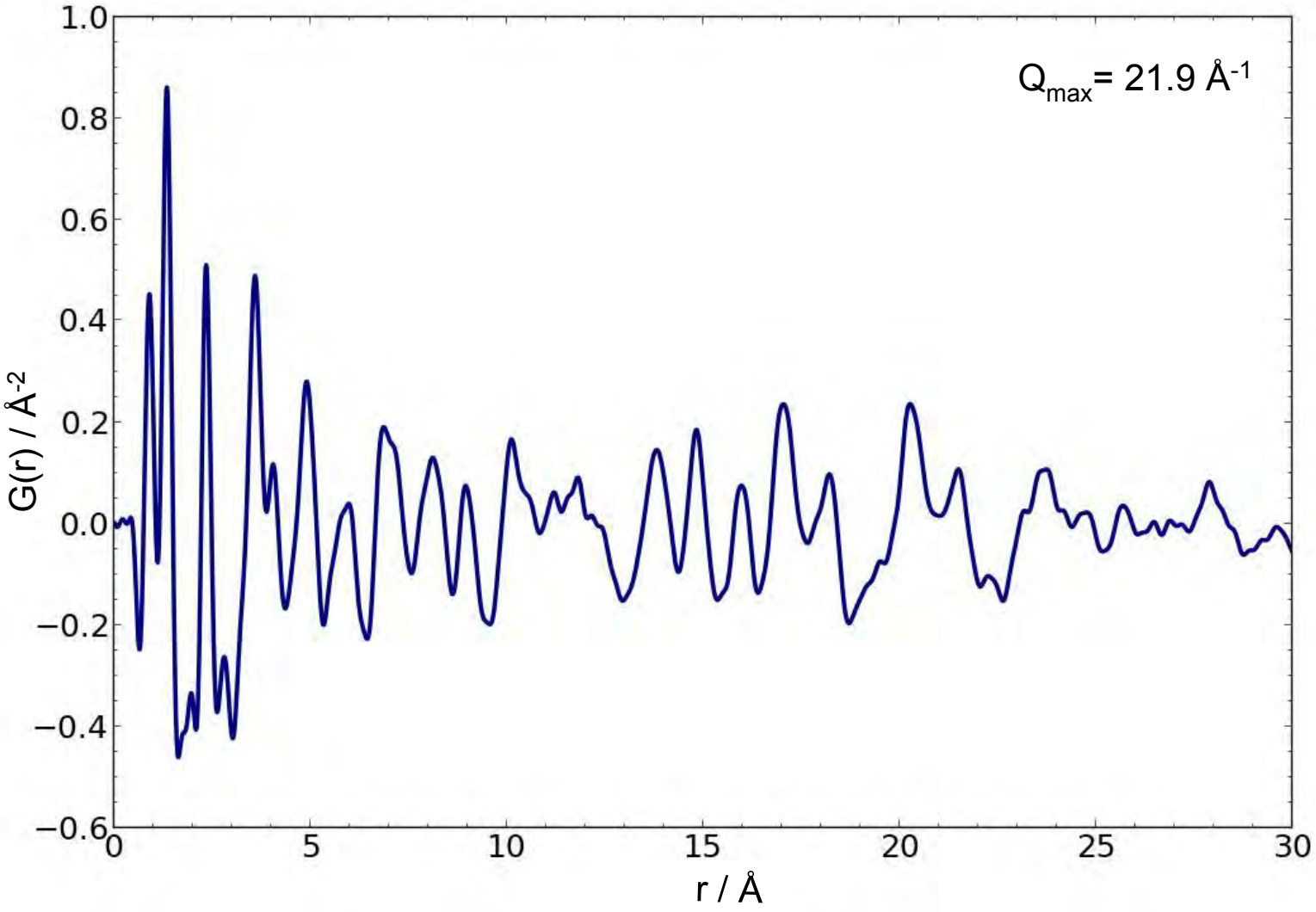
Programs:
- Set up and structure generation: self-developed software FIDEL
- PDF fit: TOPAS-6

Structure determination from scratch by fit to the PDF data



[Schlesinger, Habermehl, Prill, *J. Appl. Cryst.* 2021, 54, 776–786]

Structure determination from scratch by fit to the PDF data

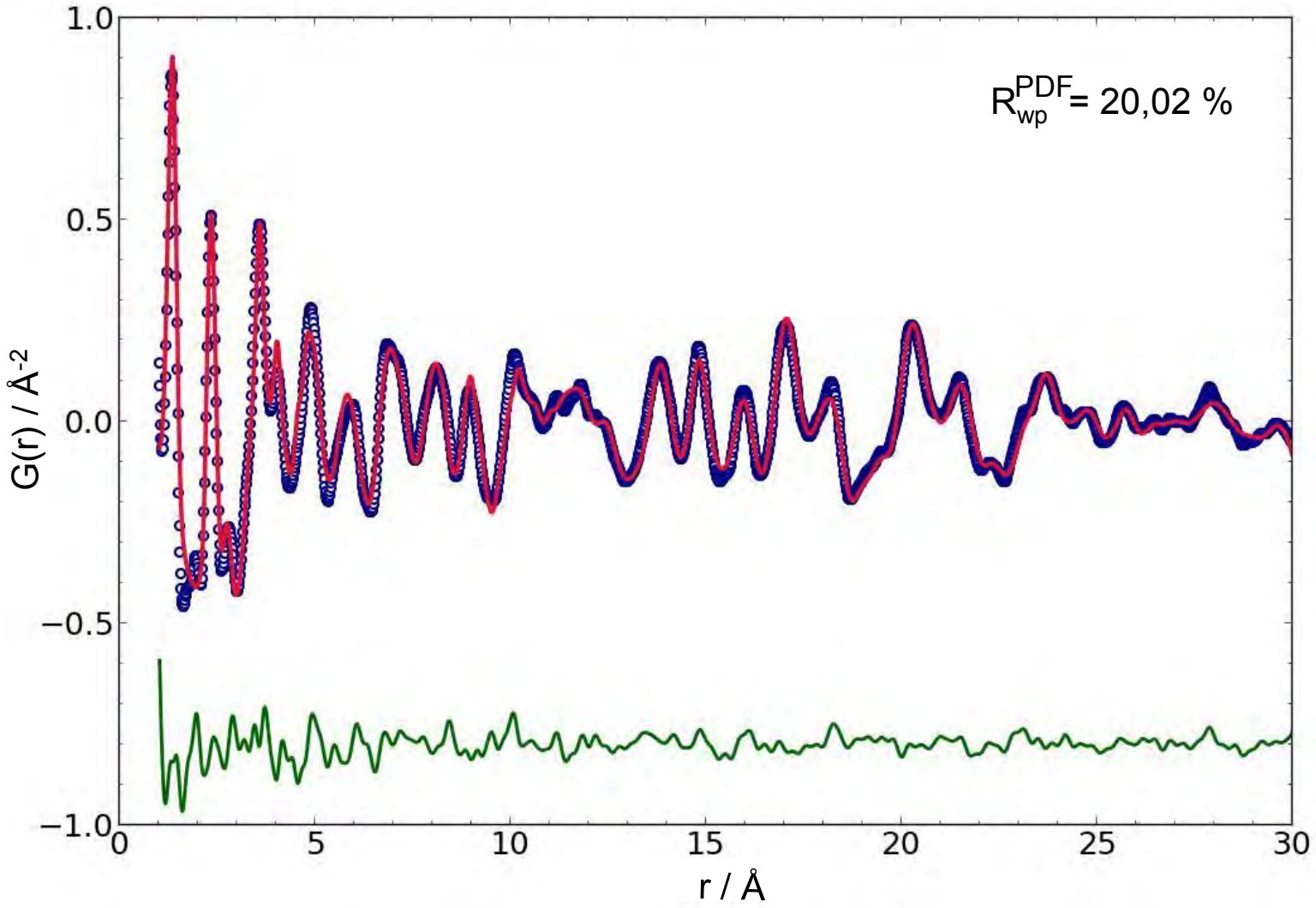


PDF derived by PDFgetX3[*]

[*] P. Juhas at al., J. Appl. Cryst. (2013), 46, 560-566.

Structure determination from scratch by fit to the PDF data

Best solution in $P2_1/n$, Z = 4 (Correct space group)

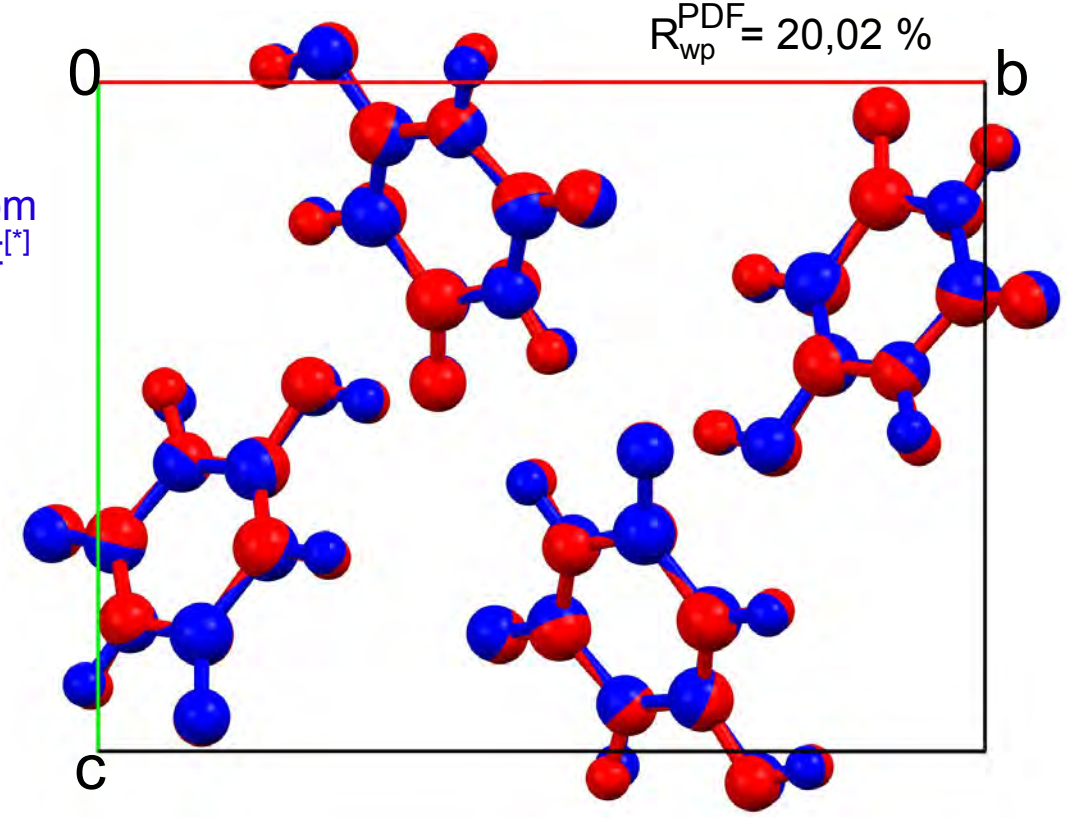


[Schlesinger, Habermehl, Prill, *J. Appl. Cryst.* 2021, 54, 776–786]

Structure determination from scratch by fit to the PDF data

Best solution in $P2_1/n$, Z = 4 (Correct space group)

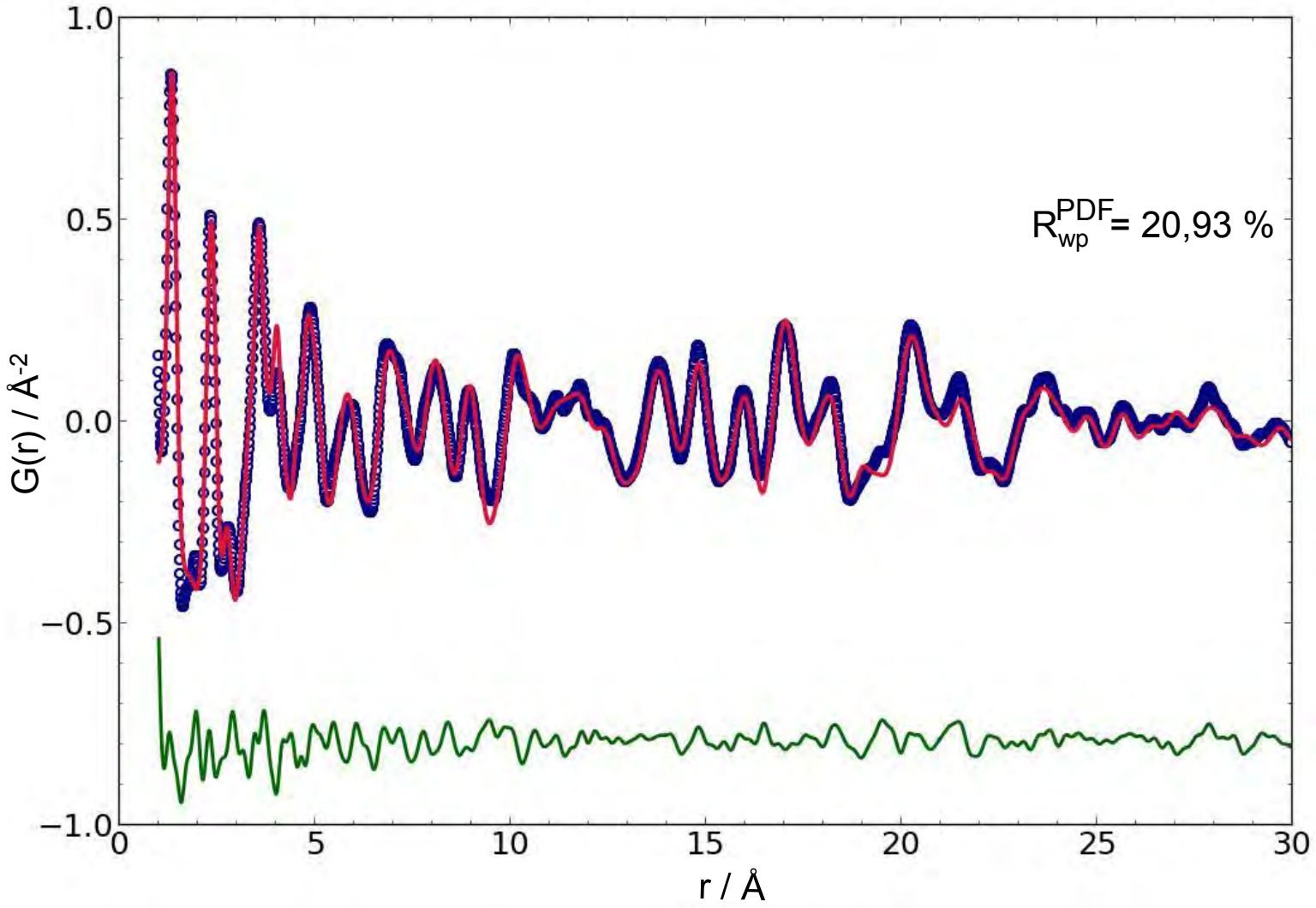
PDF structure	Crystal structure from Rietveld refinement[*]
a = 11.872 Å	a = 11.876 Å
b = 8.937 Å	b = 8.915 Å
c = 4.825 Å	c = 4.834 Å
β = 95.06 °	β = 95.08 °



[*] Schmidt et al., Angew. Chem. (2011), 50, 7924.

Structure determination from scratch by fit to the PDF data

Test with Z' = 2 (P $\bar{1}$, Z = 4)

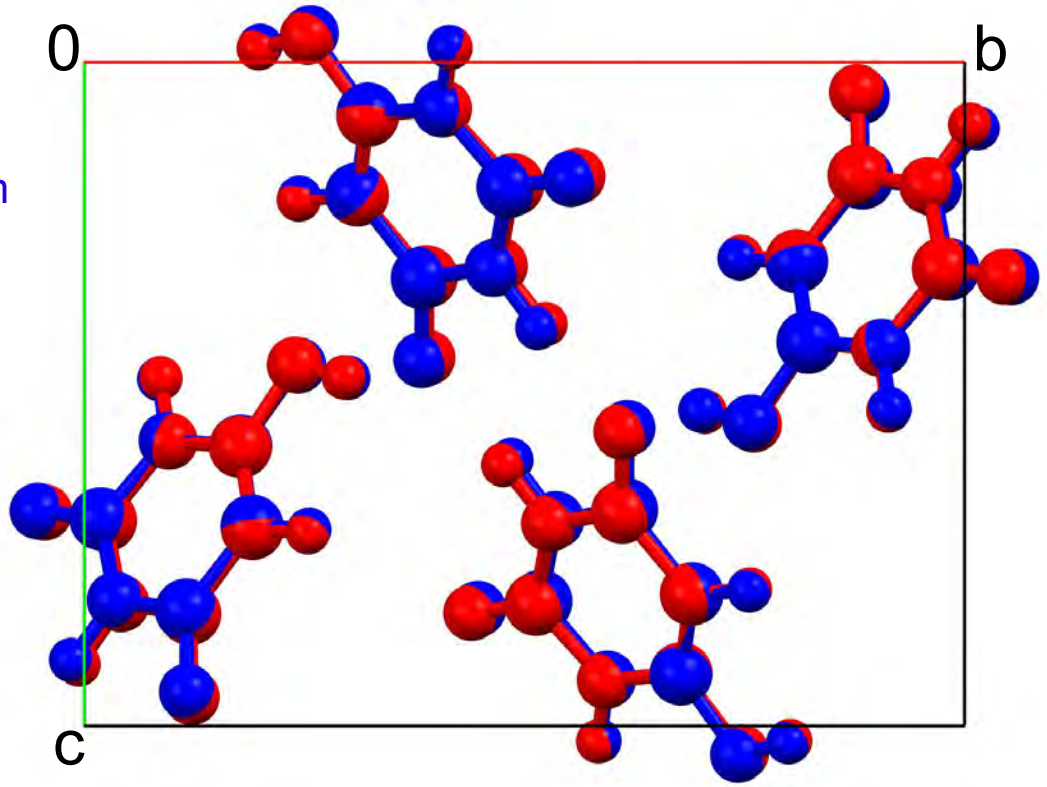


Structure determination from scratch by fit to the PDF data

Test with Z' = 2 (P $\bar{1}$, Z = 4)

PDF structure	Crystal structure from Rietveld refinement
a = 11.869 Å	a = 11.876 Å
b = 8.941 Å	b = 8.915 Å
c = 4.836 Å	c = 4.834 Å
α = 90.00 °	α = 90.00 °
β = 95.13 °	β = 95.08 °
γ = 90.00 °	γ = 90.00 °

R_{wp}^{PDF} = 20,93 %



Structure determination from scratch by fit to the PDF data

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PDF structure	Crystal structure from Rietveld refinement
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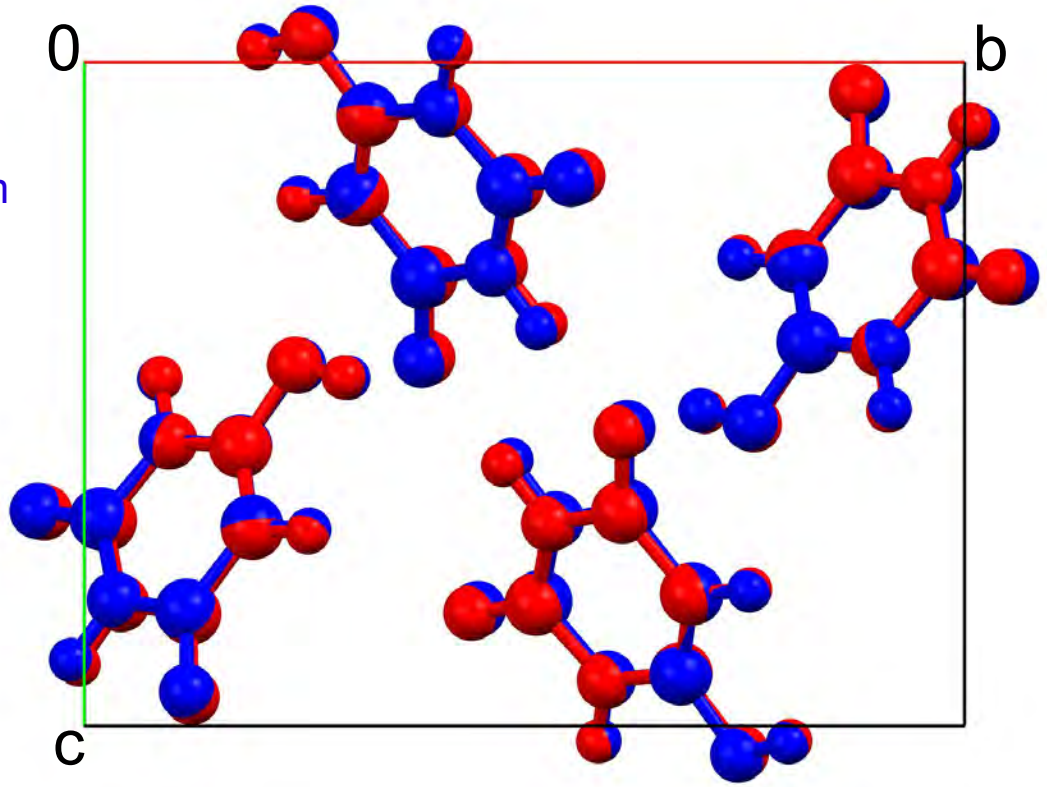
R_{wp}^{PDF} = 20,93 %



Second best solution:

R_{wp}^{PDF} = 24,62 %

- Similar lattice parameters
- 2 of 4 molecules rotated by 180° (Typical effect, also observed by real-space methods)

Conclusion

Organic crystal structures can be solved and refined

by a fit to the PDF curve, if the molecular structure is given.

Even if the lattice parameters and space group are unknown.

Method development ongoing

Acknowledgements

Alan Coelho (TOPAS)

Billinge group (PDF programs)

Colleagues from pharmaceutical industry

ESRF, NSLS, PSI

Goethe University:

Dr. Dragica Prill

Dr. Carina Schlesinger

Stefan Habermehl

Dr. Stefan Brühne

Edith Alig

Dr. Lothar Fink

Acknowledgements

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Synthesis, polymorph screening, crystallisation, X-ray powder diffraction (9 diffractometers), structure determination from powder data, PDF analysis, crystal structure prediction (incl. method development)

Dr. Lothar Fink, Edith Alig, Dr. Natalia Sennova, Dr. Stephanie Cronje, Dr. Dragica Podgorski, Dr. Christian Buchsbaum, Stefan Habermehl, ...

Former coworkers: Dr. Jacco van de Streek, Dr. Jürgen Glinnemann, Dr. Detlef Hofmann, Dr. Stephan Brühne, Dr. Sonja Hammer, Dr. Chunhua Hu, Dr. Jaroslaw Teteruk, Dr. Jürgen Brüning, Dr. Nadine Rademacher, Dr. Alexandra Wolf, Dr. Sándor Bekö, Dr. Philipp Mörschel, Dr. Christian Czech, Dr. Silke Thoms, Dr. Haishuang Zhao, Dr. Yasar Krysiak, Dr. Miriam Heine, Dr. Lukas Tapmeyer, Dr. Carina Schlesinger, Tanja Trepte, Daniela Hempler, Maurice Beske, ...

Synchrotron data:

ESRF, PSI, APS, NSLS, Elettra, Desy

Cooperation (samples + €€):

Colleagues from the pharmaceutical industry, pigments industry, ...