Total Scattering Pair Distribution Functions (TSPDF) for Fingerprinting Amorphous Pharmaceuticals

S.J.L. Billinge

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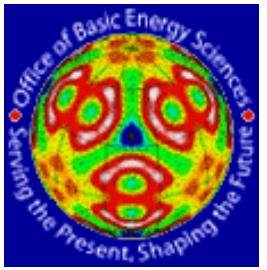
Columbia University,

CMPMS, Brookhaven National Laboratory



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

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Brookhaven National Laboratory

National Synchrotron Light Souce (NSLS) =>
New PDF beamline X17A

- 75 keV
- Superconducting wiggler

NSLS-II under construction

- XPD beamline

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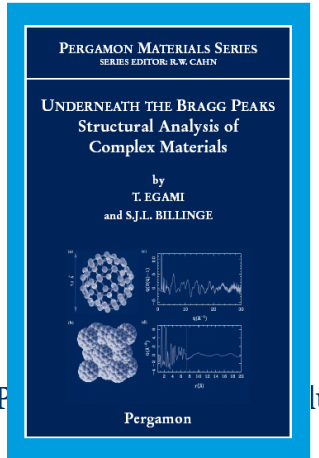
A little background about myself

- Professor of Materials Science, Applied Physics and Applied Mathematics at Columbia University
- Scientist at Brookhaven National Laboratory, Long Island, NY
- 13 years as faculty member in Physics and Astronomy at Michigan State University
- Been working on developing and applying the PDF method for 22 years

- First looked at a few drug molecules a long time ago (when Valeri was a post-doc with me!) but not seriously
- Became more seriously interested in amorphous pharmaceuticals 4-5 years ago when I discovered that Pharma was interested in amorphous pharmaceuticals



A little PDF history

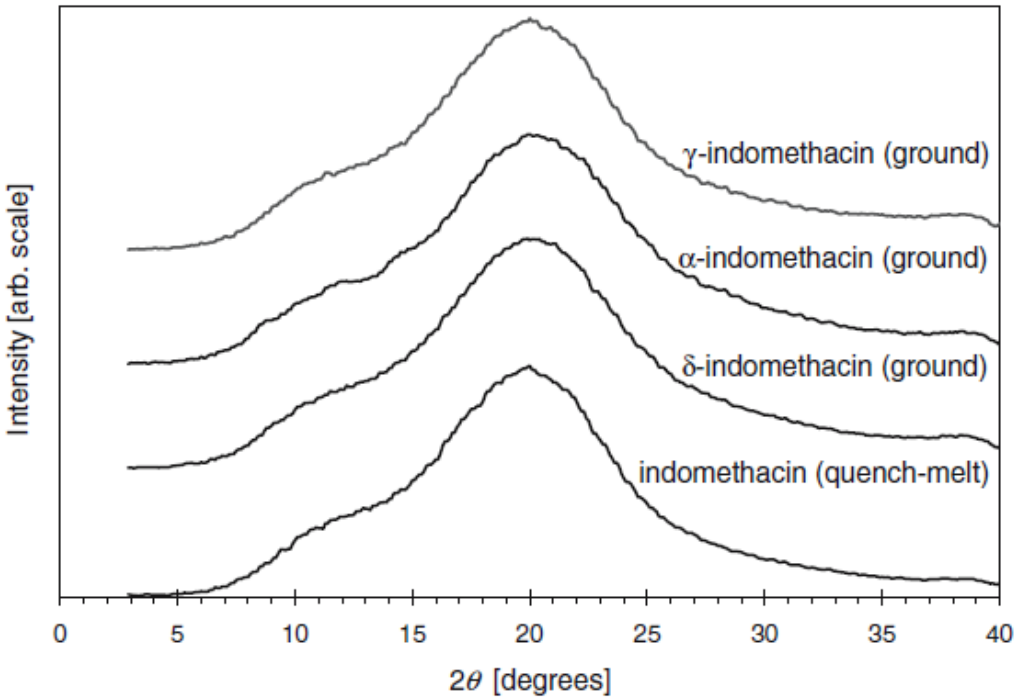
- 1915: Debye Equation
  - Scattering intensity from non crystalline isotropic samples
- 1920's pair correlation functions derived
- 1930's first measured PDFs from liquid metals and glasses
- Intermediate decades: lots of work on glasses.
- 1987 PDFs applied to study disorder in crystals (Egami)
- 1990's high resolution x-ray PDFs with high x-ray energy data (us)
- 2000's 2D detectors and rapid throughput PDFs (us)
- 2000's PDFs applied to pharma (Simon Bates et al., and now us)

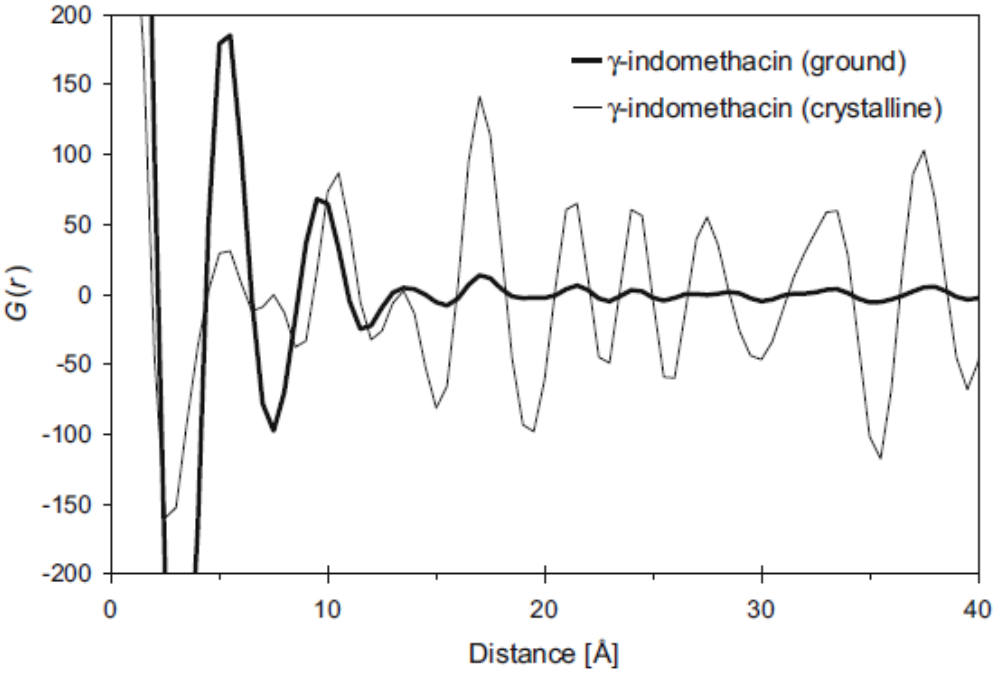
Pharmaceutical Research, Vol. 23, No. 10, October 2006 (© 2006)
DOI: 10.1007/s11095-006-9086-2

Research Paper

Analysis of Amorphous and Nanocrystalline Solids from Their X-Ray Diffraction Patterns

Simon Bates,[1] George Zografi,[2] David Engers,[3] Kenneth Morris,[3] Kieran Crowley,[4] and Ann Newman[1,5]





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IJP-11590; No. of Pages 8

ARTICLE IN PRESS

International Journal of Pharmaceutics xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Assessment of crystalline disorder in cryo-milled samples of indomethacin using atomic pair-wise distribution functions

Johan P. Bøtker[a,1], Pranav Karmwar[b,1], Clare J. Strachan[b], Claus Cornett[a], Fang Tian[c], Zoran Zujovic[c], Jukka Rantanen[a], Thomas Rades[b,*]

[a] Faculty of Pharmaceutical Sciences, Department of Pharmaceutics and Analytical Chemistry, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen Ø, Denmark
[b] School of Pharmacy, University of Otago, 18 Frederick Street, Dunedin 9054, New Zealand
[c] Department of Chemistry, University of Auckland, Science Centre, Building 301, 23 Symonds St., Auckland, New Zealand

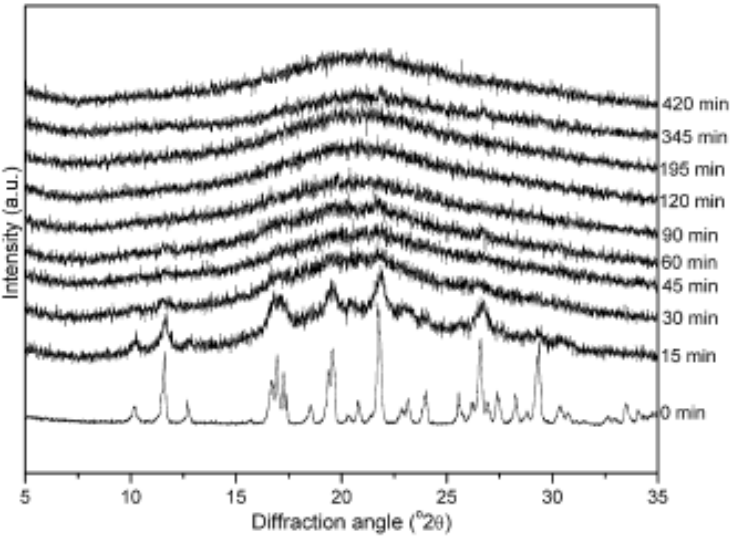

Fig. 2. XRPD diffractograms of the cryo-milled samples of γ-indomethacin milled for different times (time in the figure correspond to the milling times).

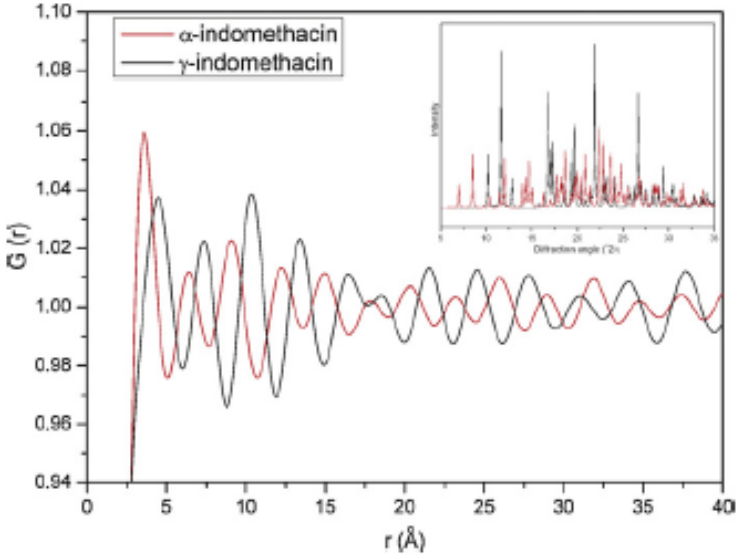

Fig. 3. PDF of the γ-form and α-form of indomethacin. XRPD diffractograms of γ-form and α-form of indomethacin are shown in the inset.

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Pharmaceutical Research, Vol. 26, No. 11, November 2009 (© 2009)
DOI: 10.1007/s11095-009-9954-7

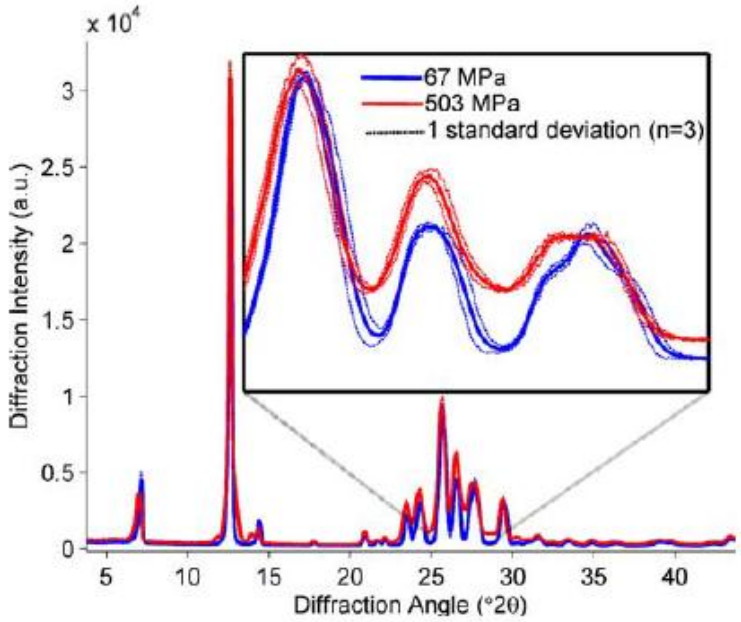
Research Paper

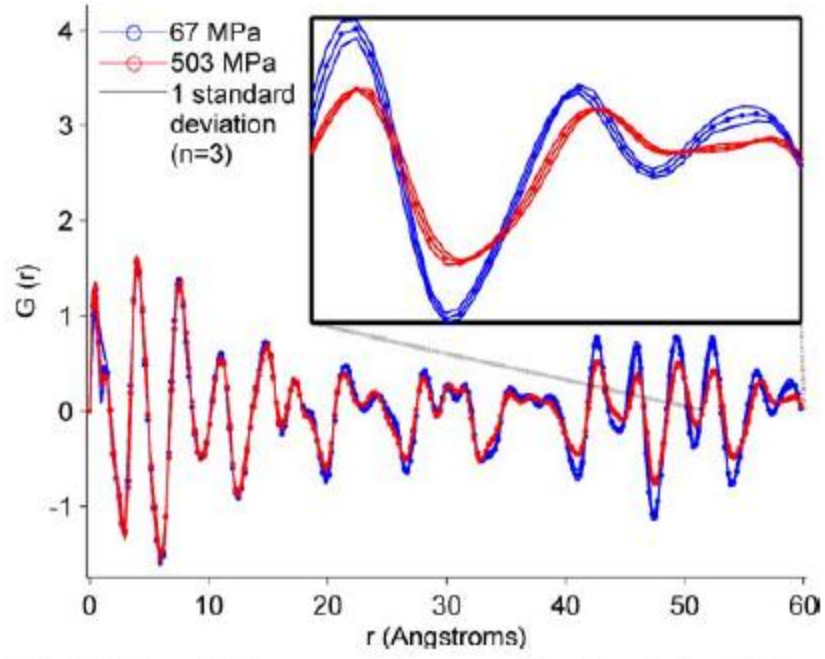
A Structural Investigation into the Compaction Behavior of Pharmaceutical Composites Using Powder X-ray Diffraction and Total Scattering Analysis

Michael D. Moore,[1] Alison M. Steinbach,[1] Ira S. Buckner,[1] and Peter L. D. Wildfong[1,2]

Received April 23, 2009; accepted August 10, 2009; published online August 28, 2009

Purpose To use advanced powder X-ray diffraction (PXRD) to characterize the structure of anhydrous



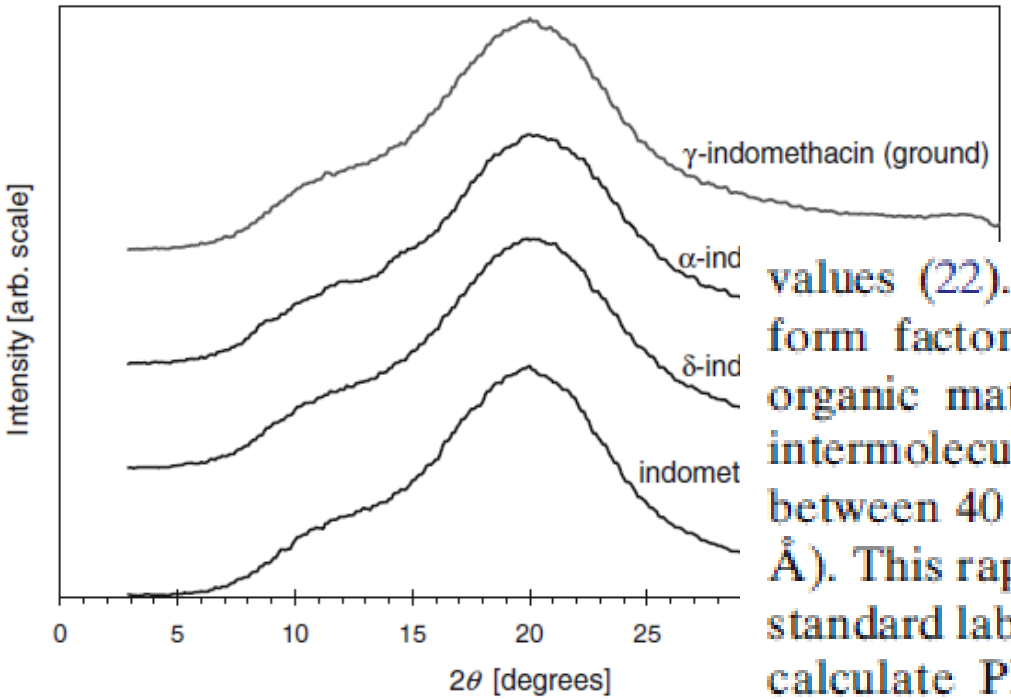


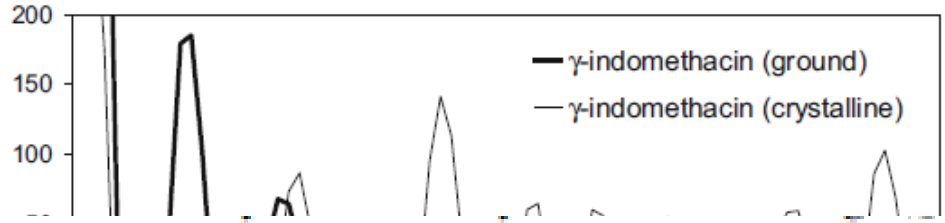
Pharmaceutical Research, Vol. 23, No. 10, October 2006 (© 2006)
DOI: 10.1007/s11095-006-9086-2

Research Paper

Analysis of Amorphous and Nanocrystalline Solids from Their X-Ray Diffraction Patterns

Simon Bates,[1] George Zografi,[2] David Engers,[3] Kenneth Morris,[3] Kieran Crowley,[4] and Ann Newman[1,5]





values (22). However, the combination of atomic/molecular form factors and thermal vibrations present in molecular organic materials causes the measured X-ray intensity for intermolecular correlation to fall off to background levels between 40 or 60°2θ when using Cu Kα radiation (λ~1.5406 Å). This rapid intensity fall off means that data collected on standard laboratory powder diffraction systems is sufficient to calculate PDFs that capture the relevant intermolecular ordering information. The reduced measurement range does

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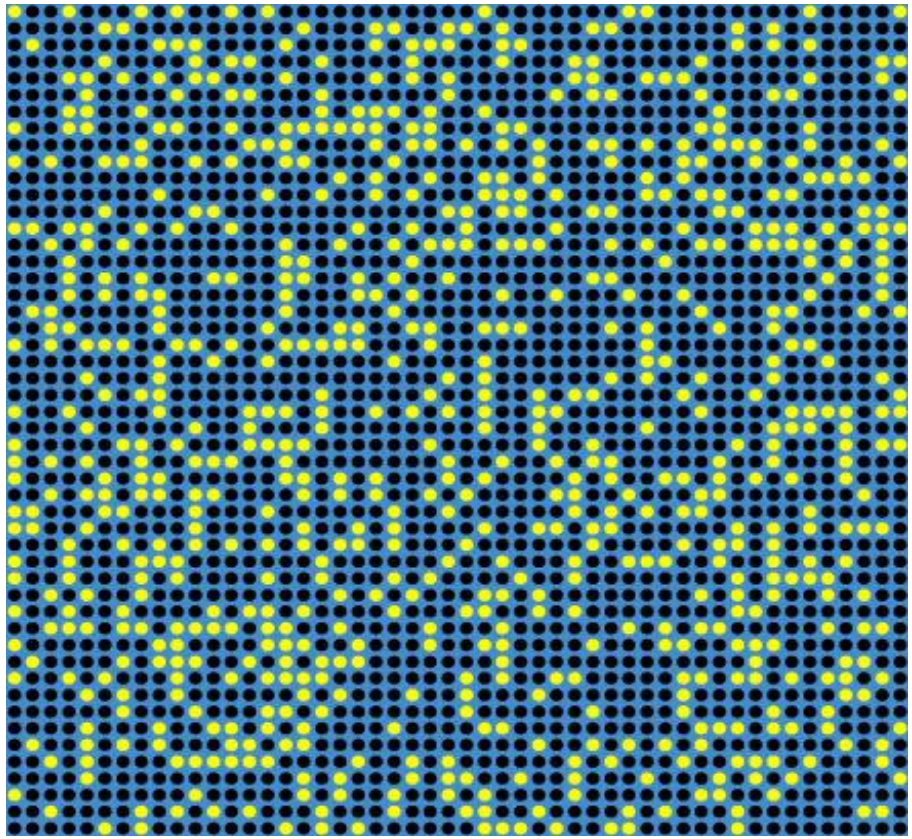
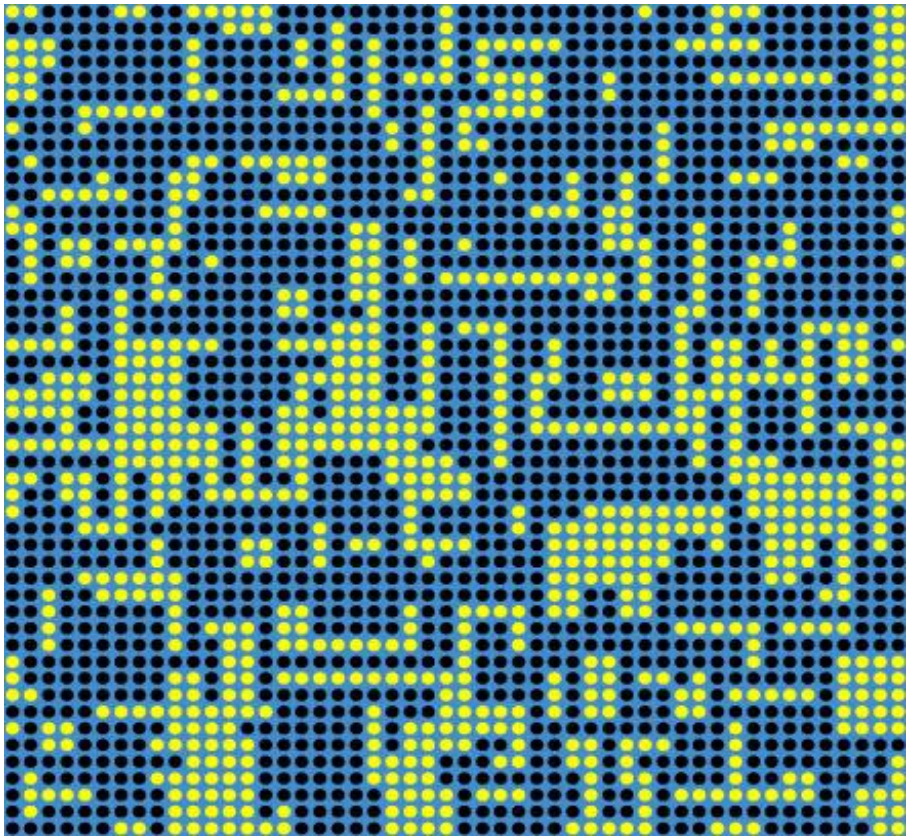
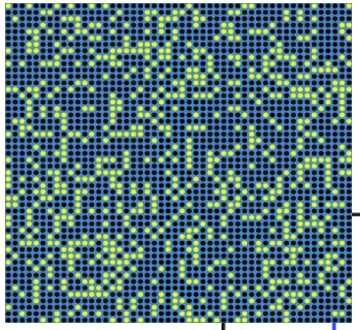
Why is diffuse scattering important?



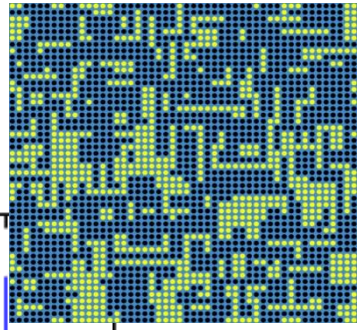


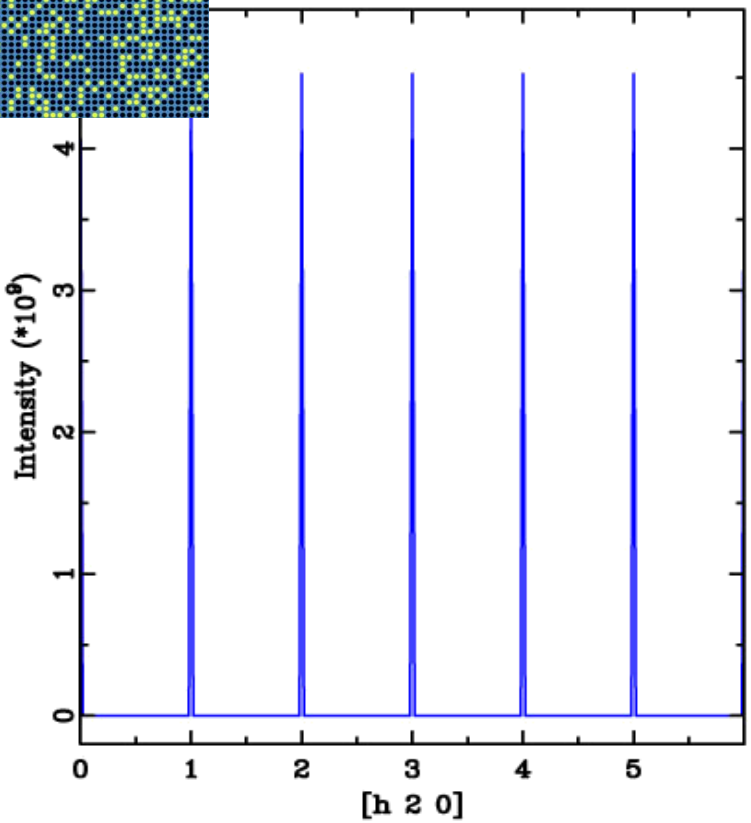
Cross section of 50 x 50 x 50 unit cell model crystal with 70% black atoms and 30% yellow, Simulation using DISCUS courtesy of Thomas Proffen

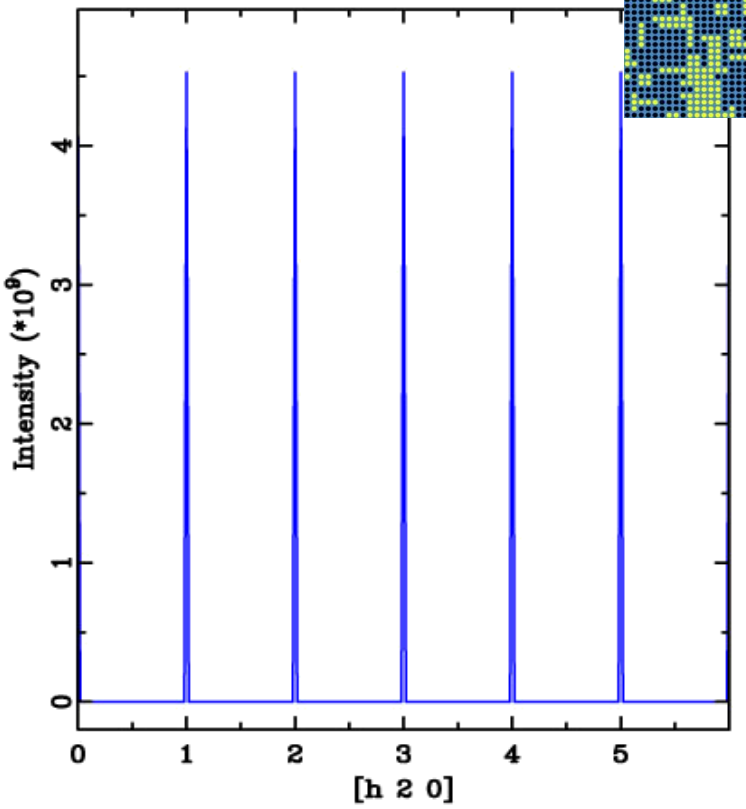
Bragg peaks are blind to the nanoscale order



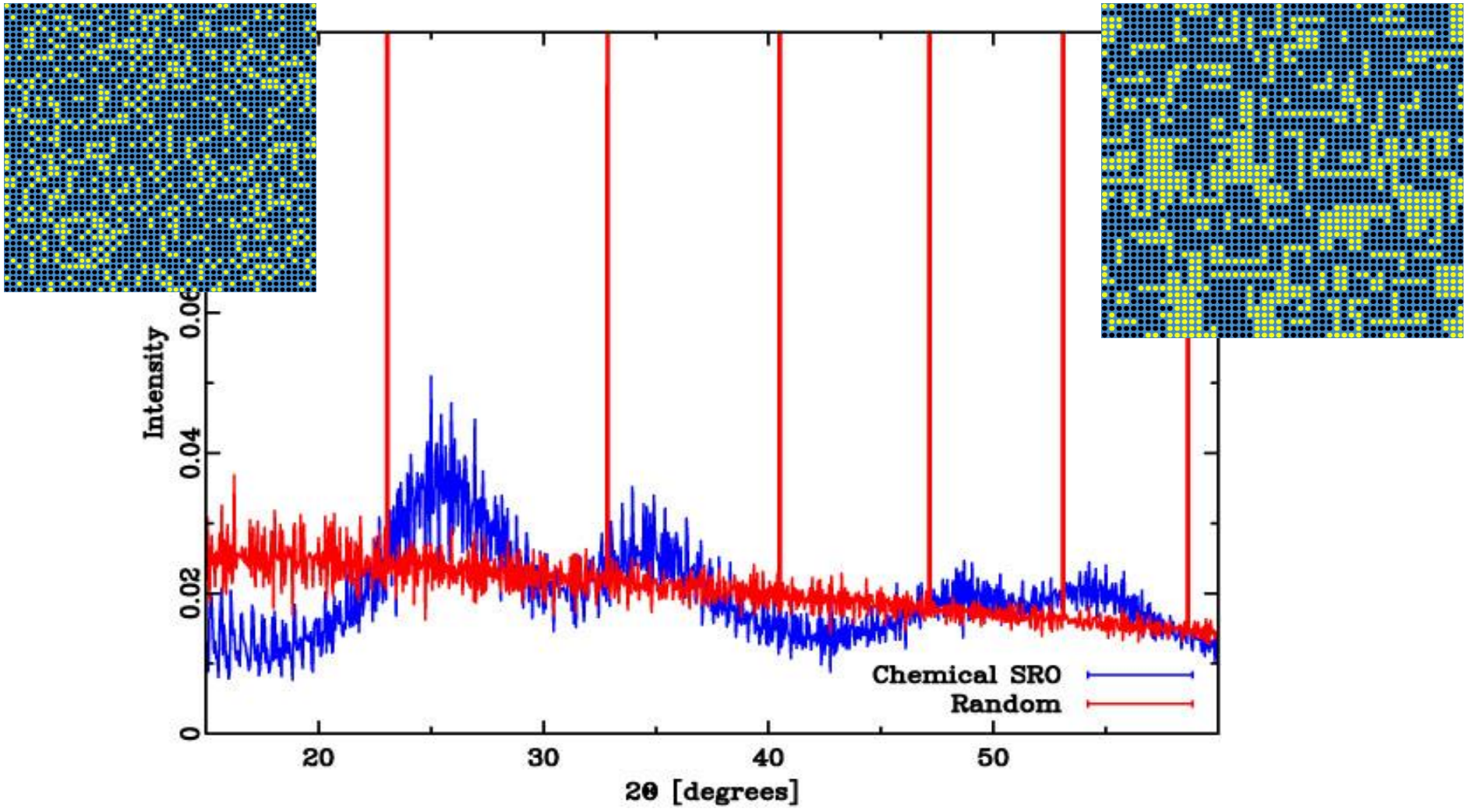
Bragg scattering: Information about the *periodic* component structure, e.g. average positions, displacement parameters and occupancies.



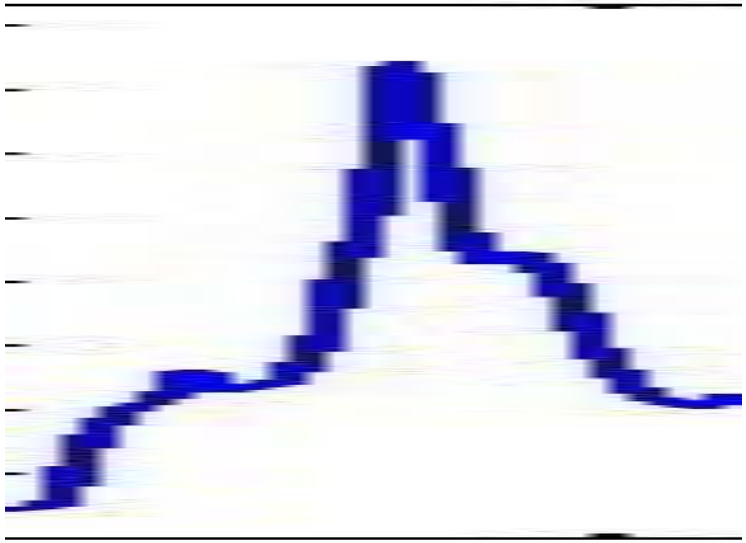


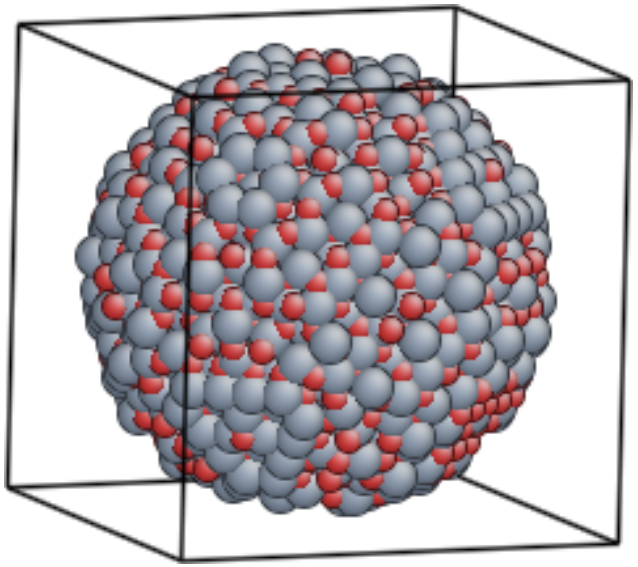


Diffuse scattering: Underneath the Bragg-peaks
Total Scattering: Bragg + diffuse



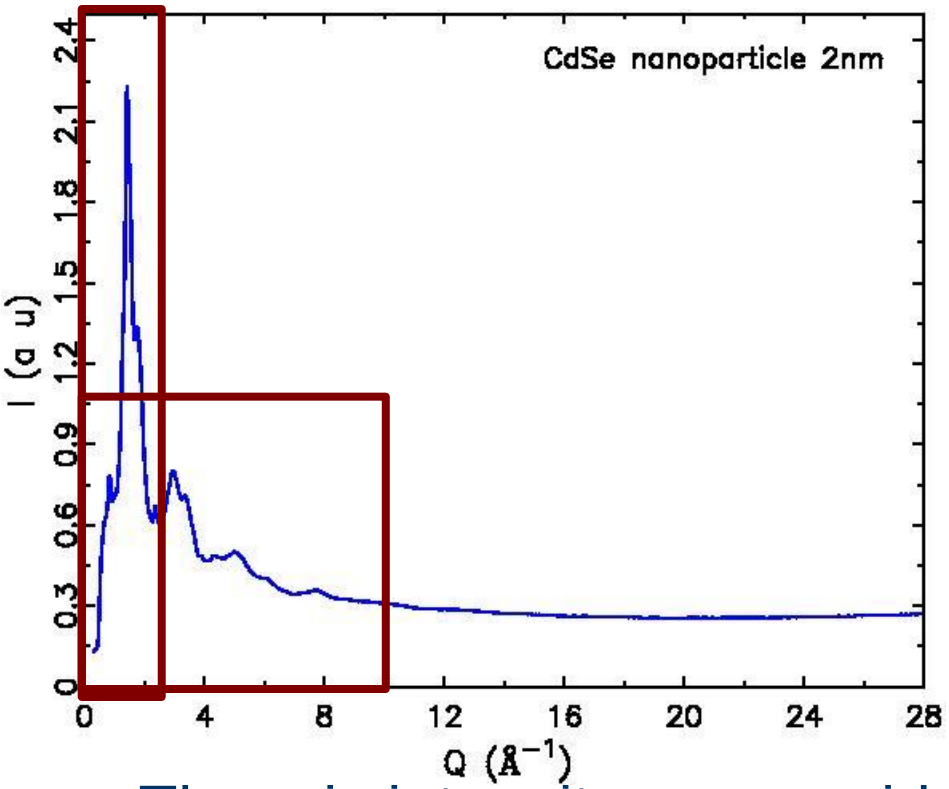
But there is no information at high-Q…?

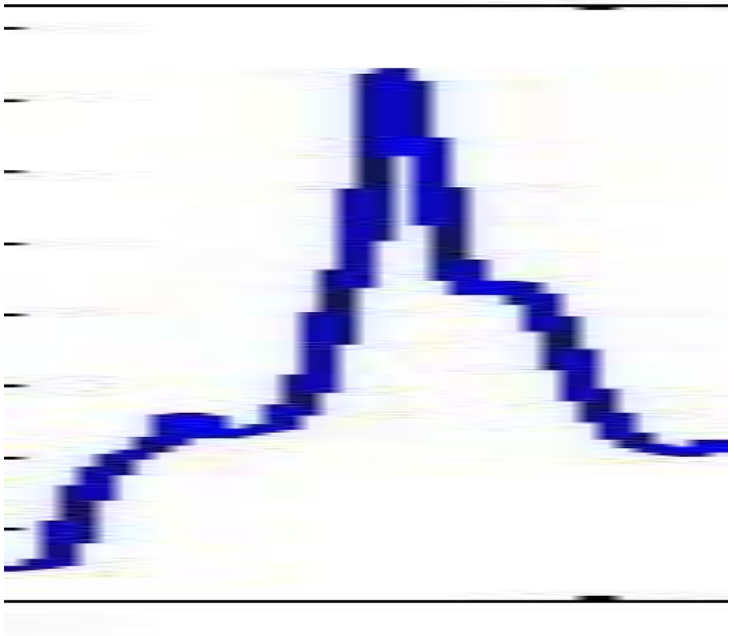




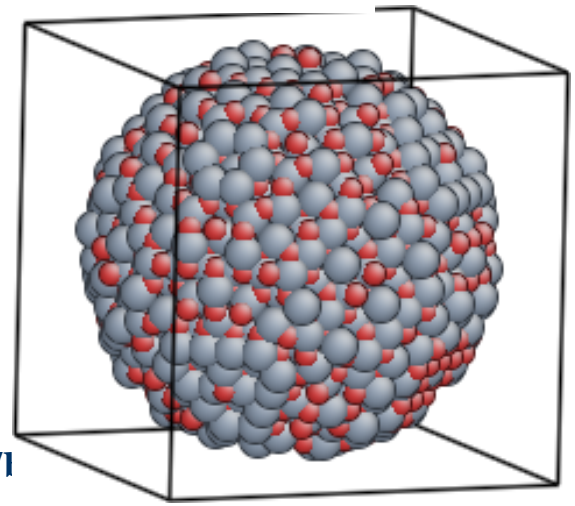
- CdSe nanoparticle, 2 nm diameter
- “X-ray amorphous”
- “Amorphous halo” viewed over range to 40^{o} 2θ for Cu Kα radiation

But there is no information at high-Q…?



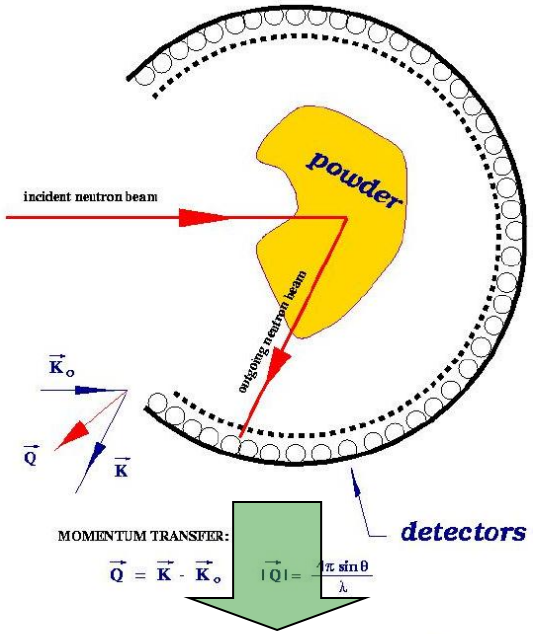


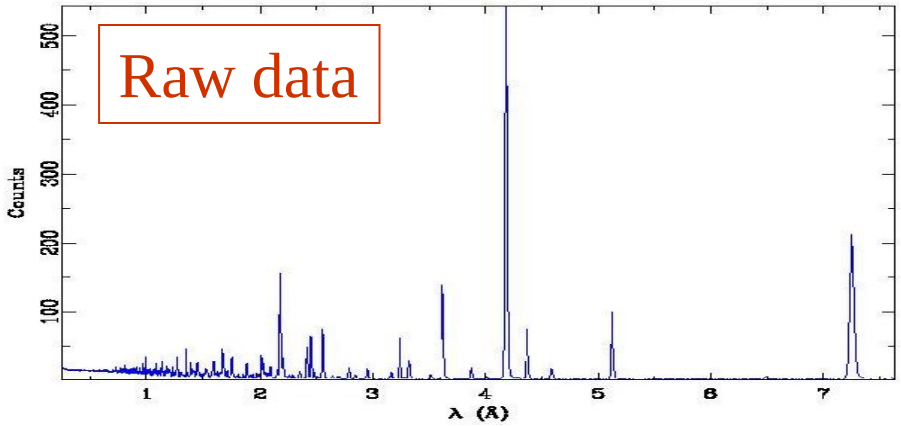
- There is intensity over a wider Q-range
- Furthermore, as part of the data processing to obtain the PDF we divide by the x-ray atomic form factor squared

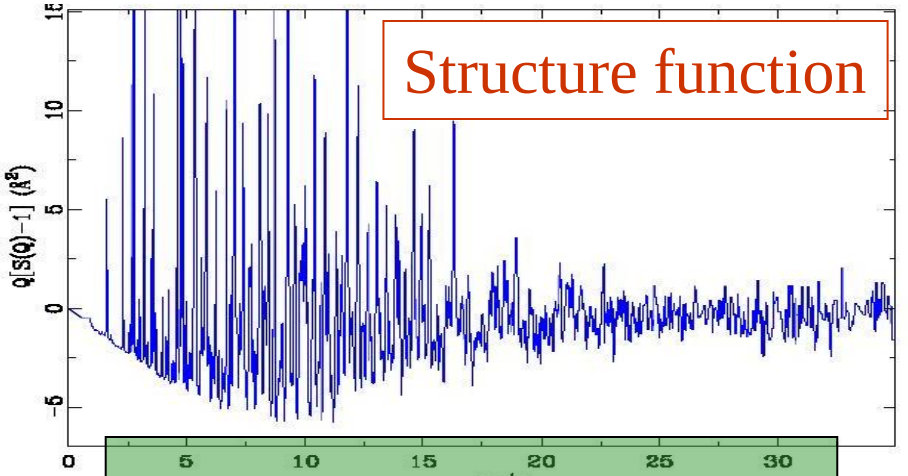


HTTP://I

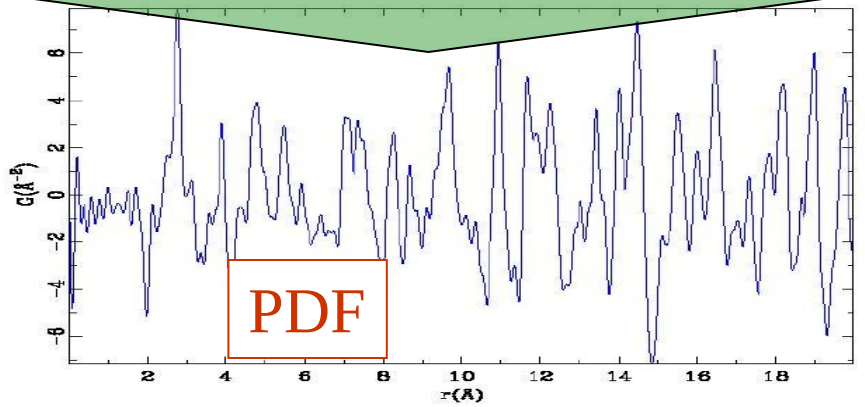
Obtaining the PDF



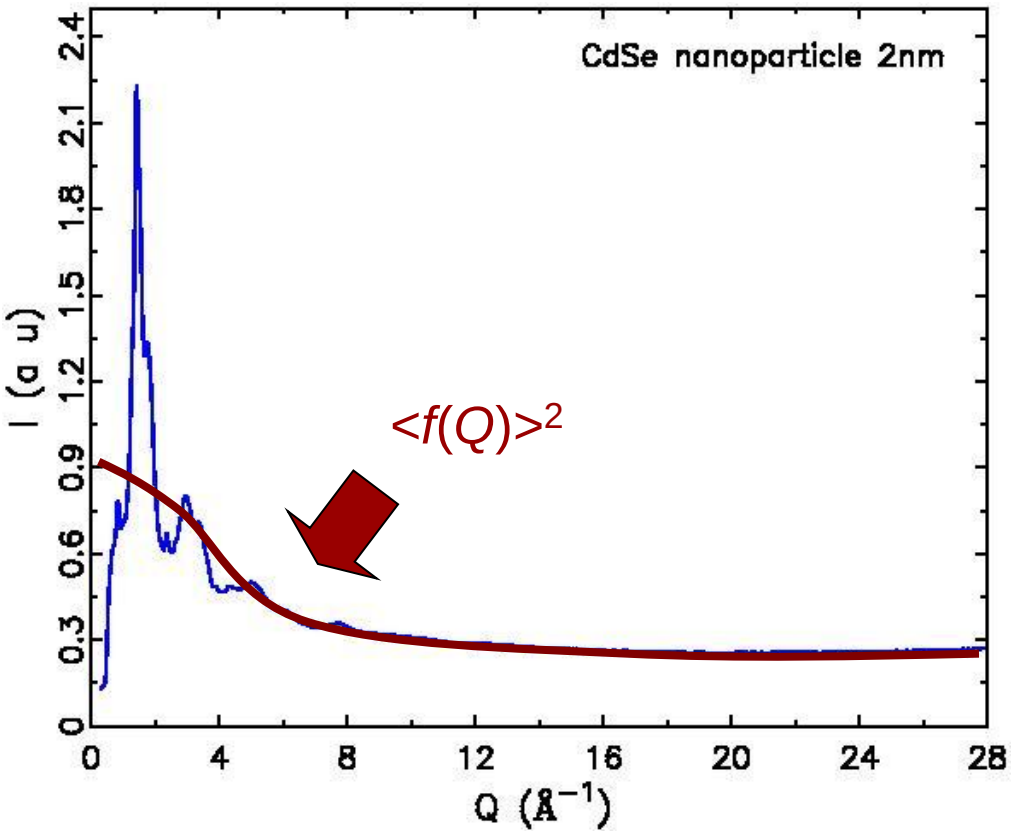


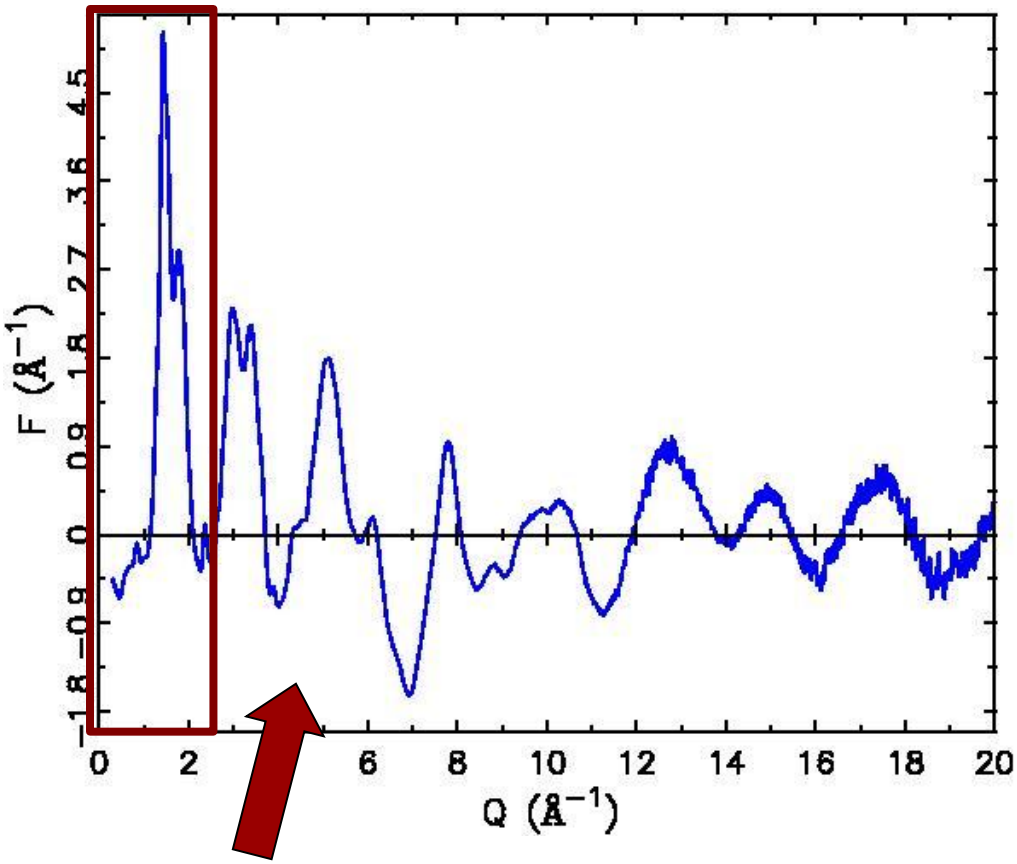


$$G(r) = \frac{2}{\pi}\int_0^\infty Q[S(Q)-1]\sin Qr\,dQ$$



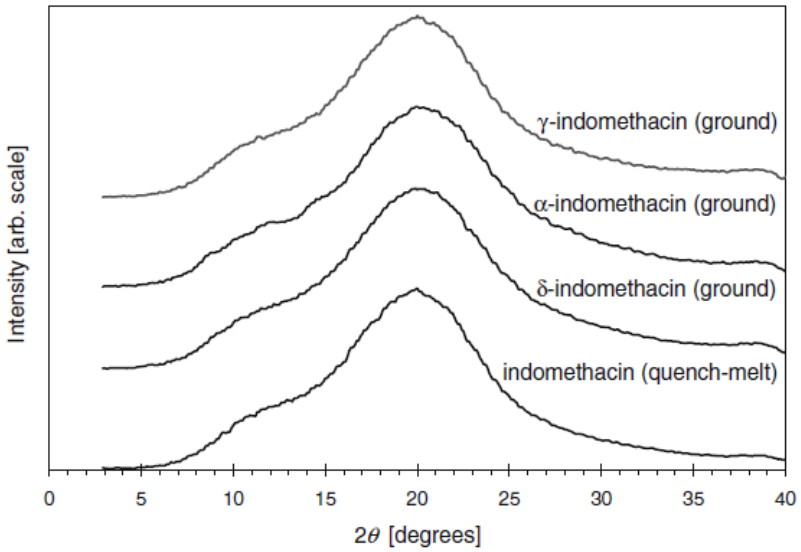
But there is no information at high-Q…?

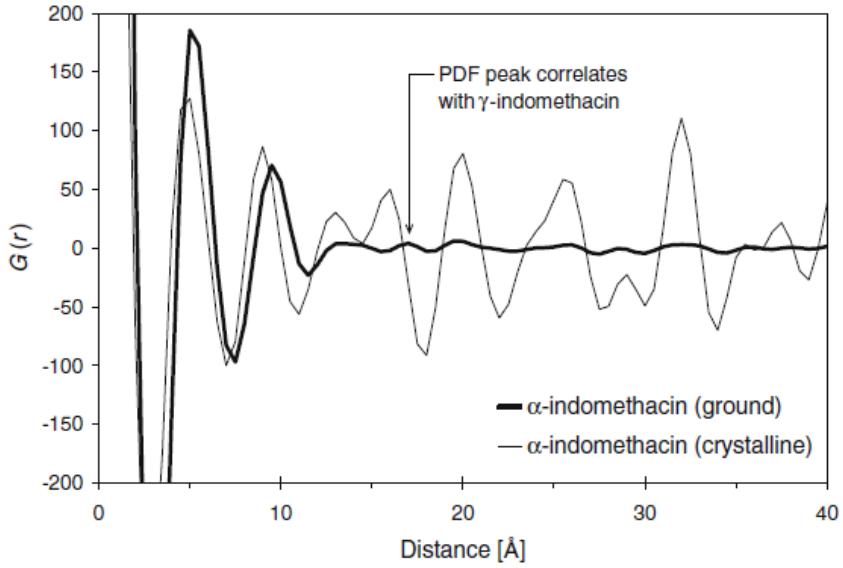


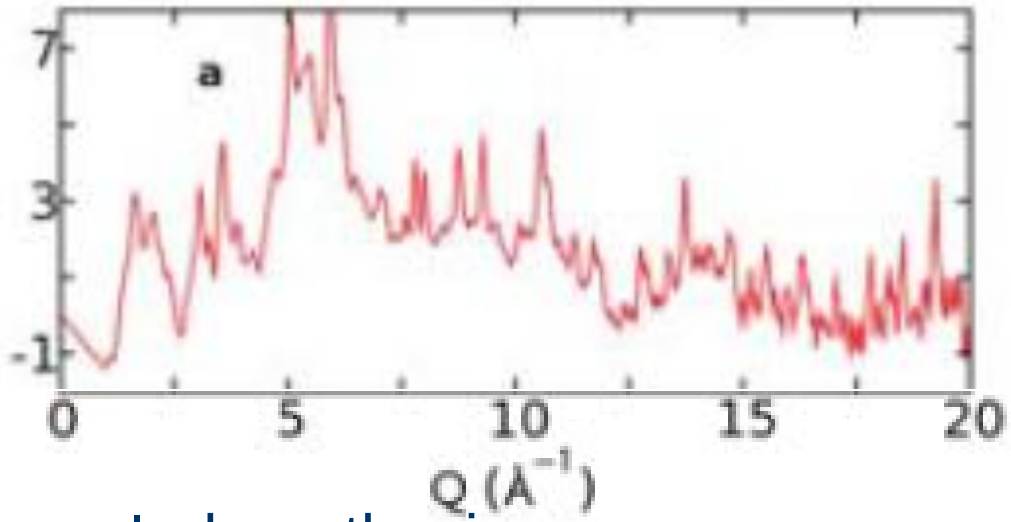


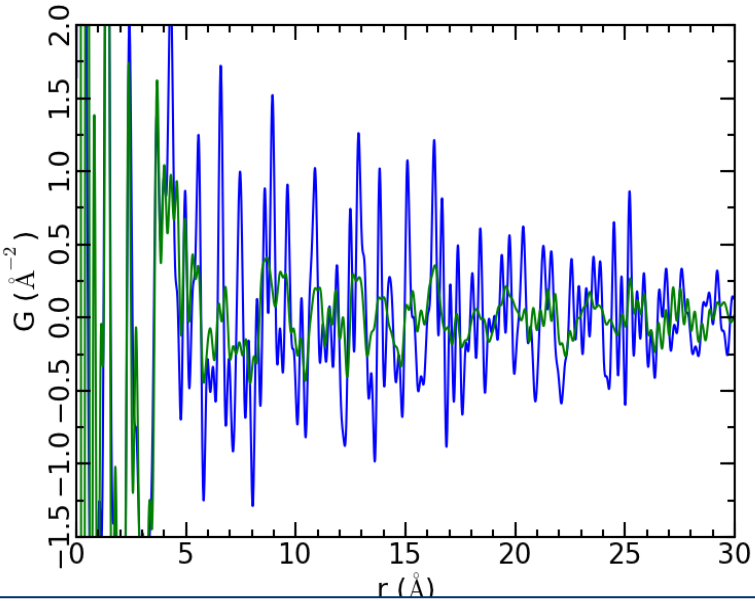
$$G(r) = \frac{2}{\pi}\int_0^\infty Q[S(Q)-1]\sin Qr\,\mathrm{d}Q$$

What about the pharmaceuticals?



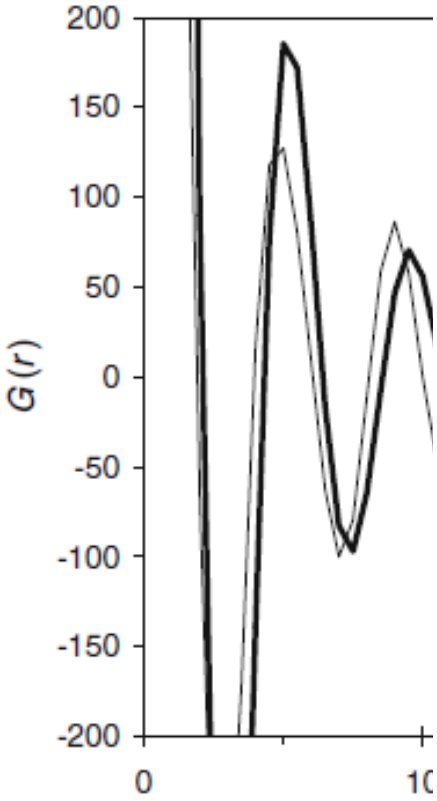


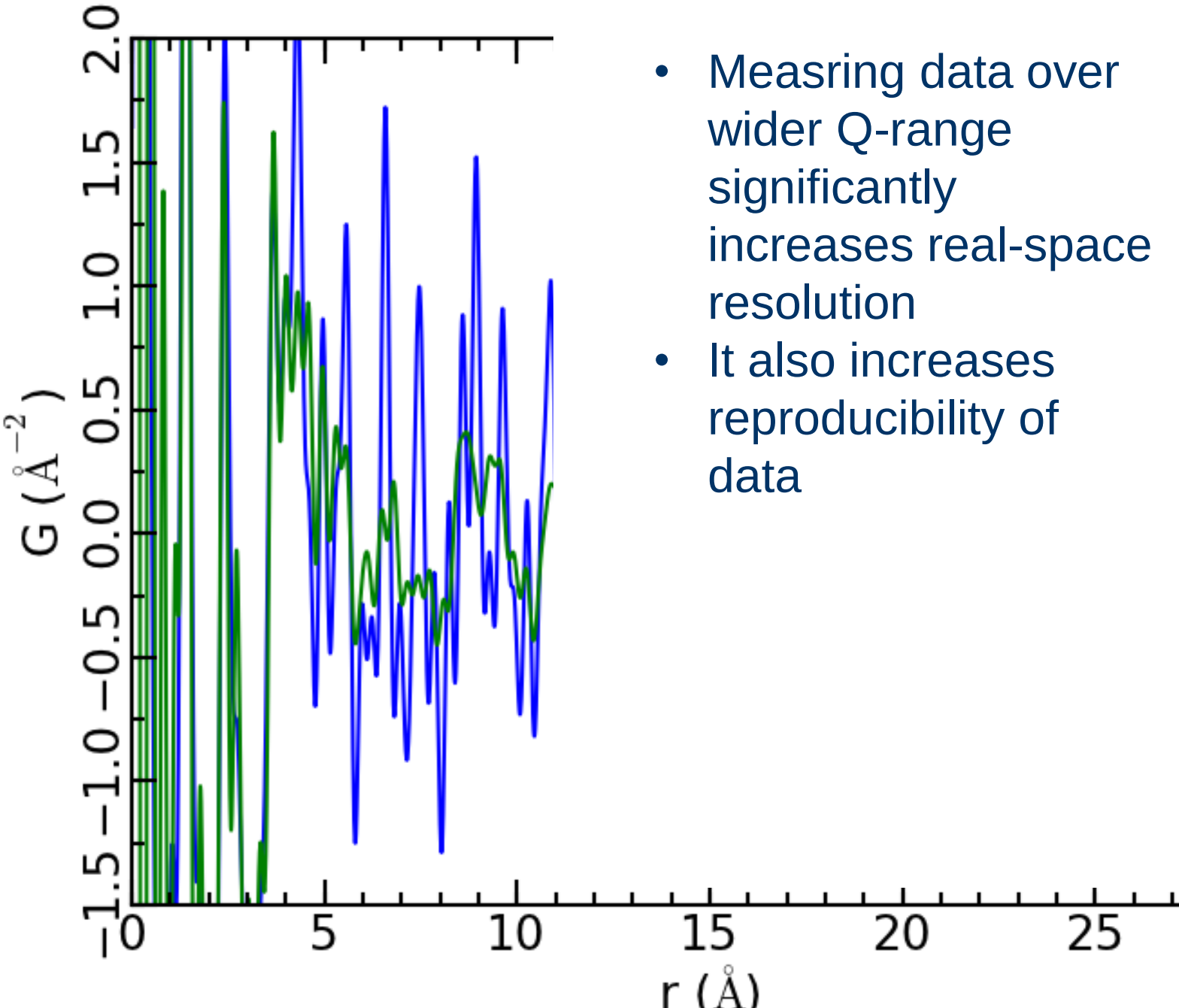




α-Indomethacin

Billinge et al., CrystEngComm 12, 1366-1368 (2010)





- Measring data over wider Q-range significantly increases real-space resolution
- It also increases reproducibility of data

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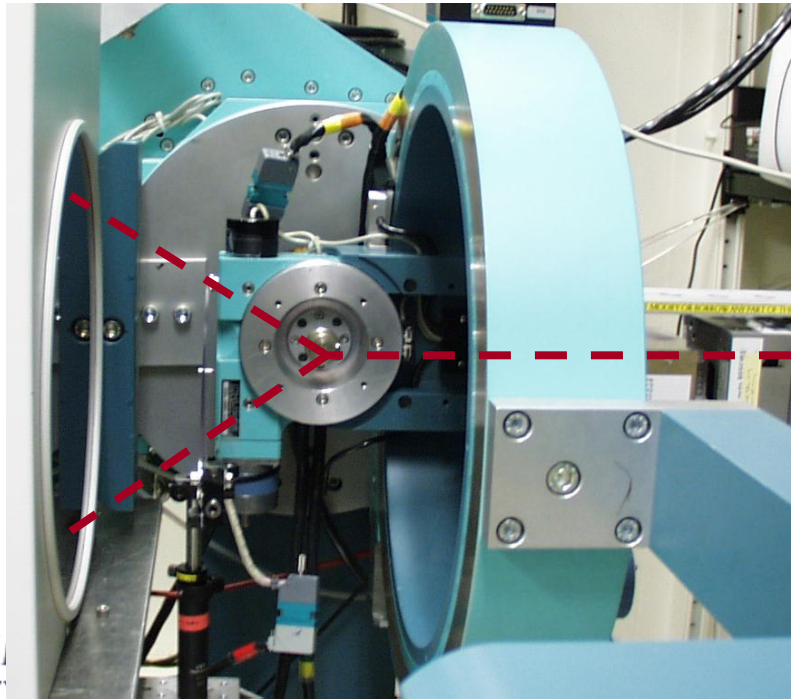
The Atomic Pair Distribution Function (PDF) Method

- Use modern high intensity x-ray and neutron sources to collect unprecedentedly precise data
- Utilize all the information: Bragg and diffuse scattering
- Use modern computing capabilities to analyze, model and visualize the data



- Chupas et al., J. Appl. Crystallogr. (2003)
- Billinge-group, BNL, SUNY-SB, APS collaboration
- Main developments thanks to Pete Chupas and Xiangyun Qiu

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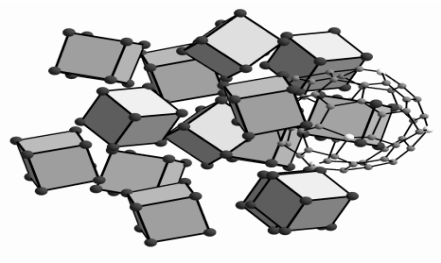
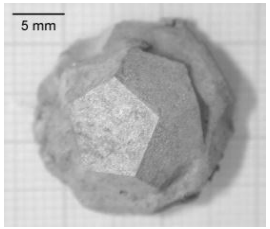
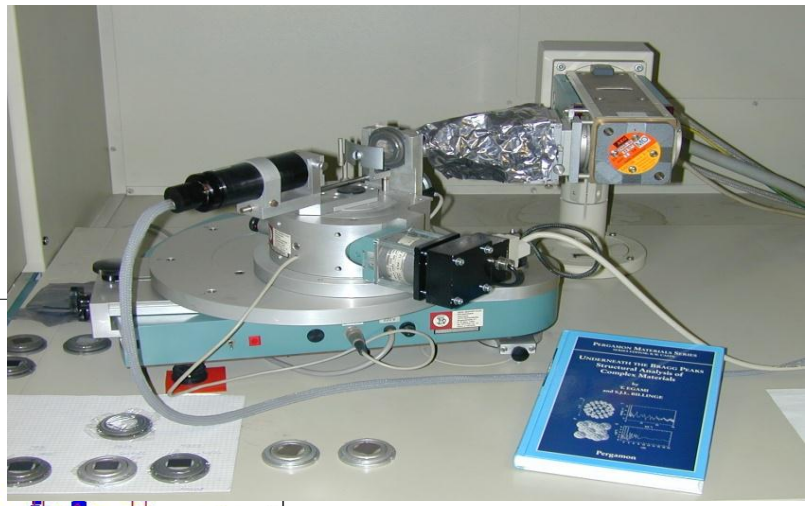
X-ray PDF: In-house measurements

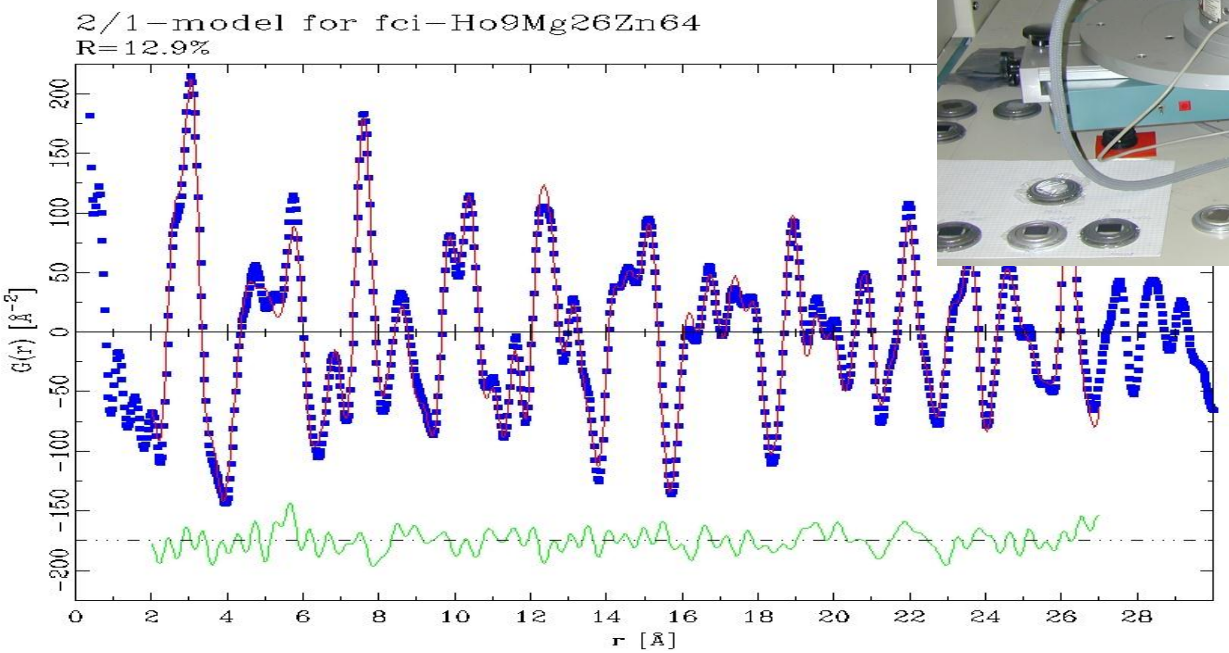


***fci*-Ho-Mg-Zn**



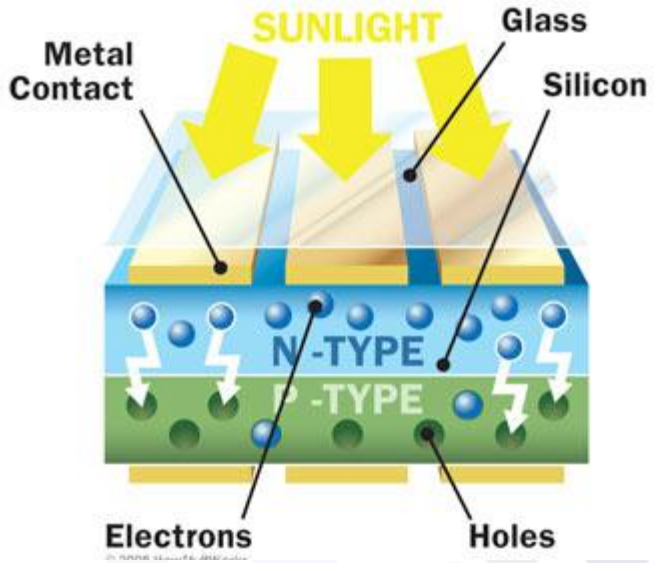
Huber Gunier diffractometer
Q_{max} = 13.5Å^{-1}

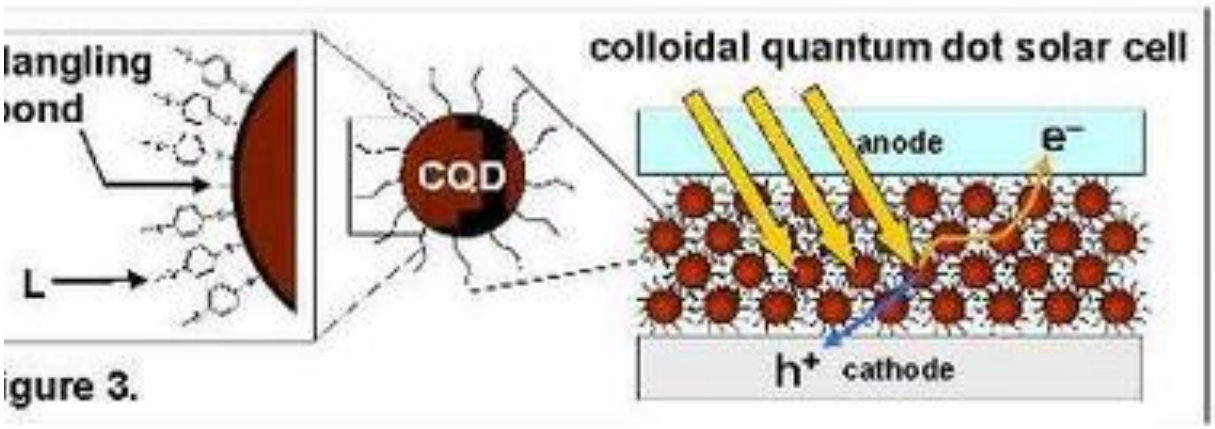


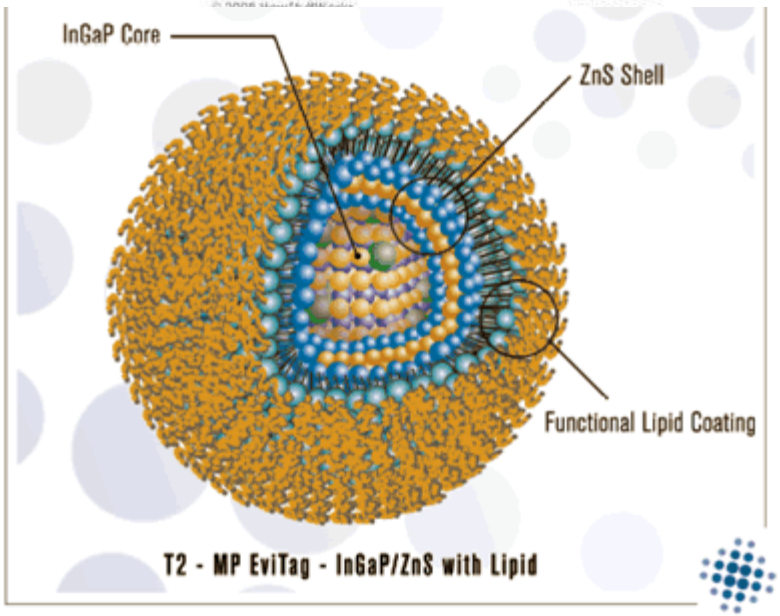


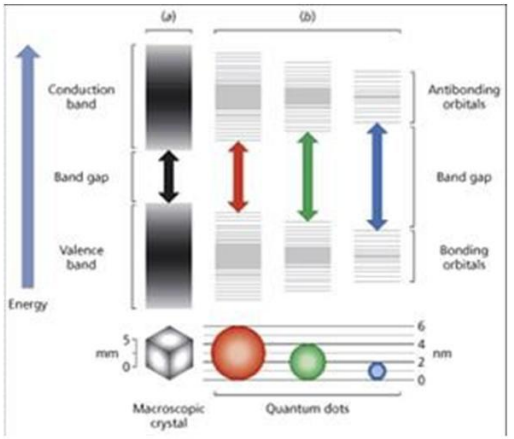
Brühne et al., *Z. Kristallogr.* **219** (2004) 245-258

Quantum Dot solar cells

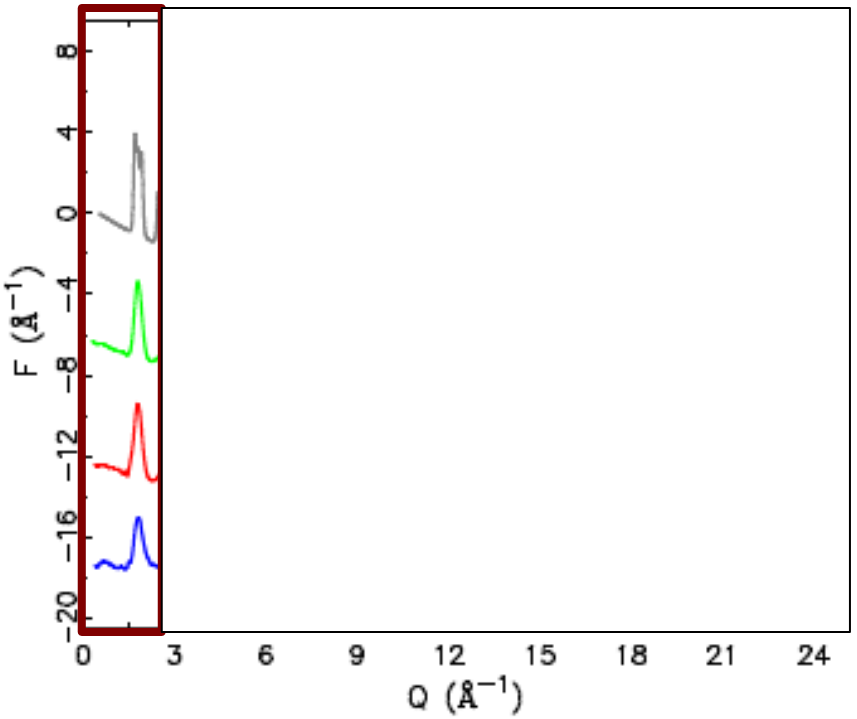


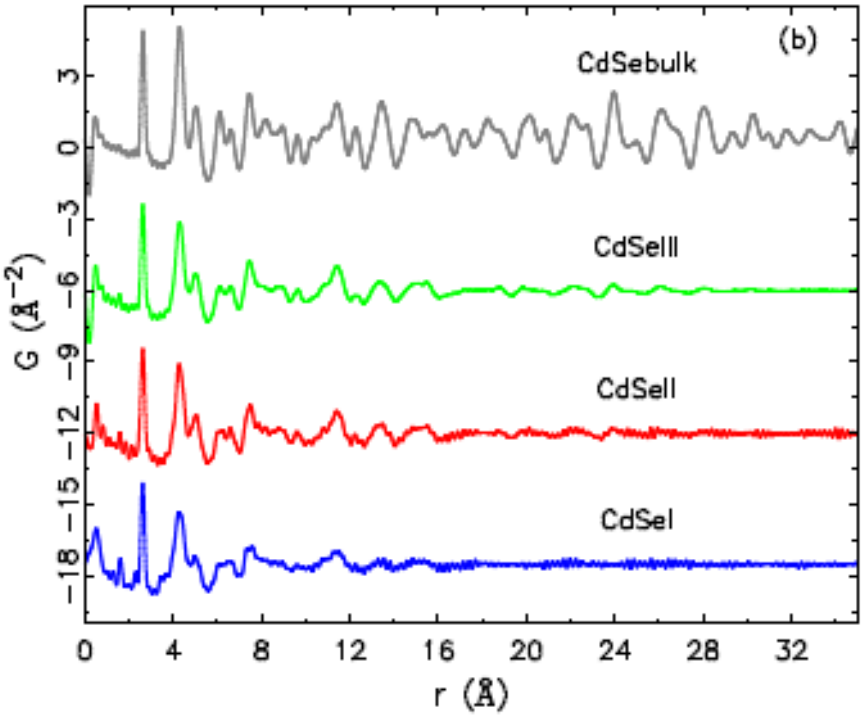




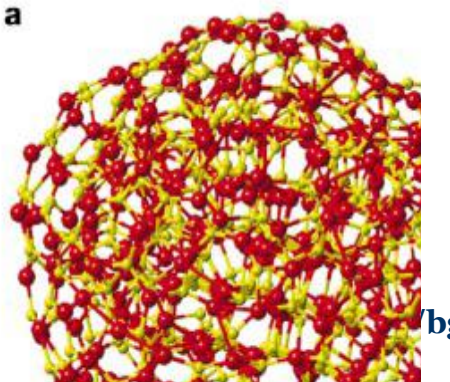


CdSe quantum dots





- RAPDF experiments at APS, Sector 6
- Work of grad student Ahmad Masadeh
- Masadeh, SJB *et al.* PRB **76**, 115413 (2007)



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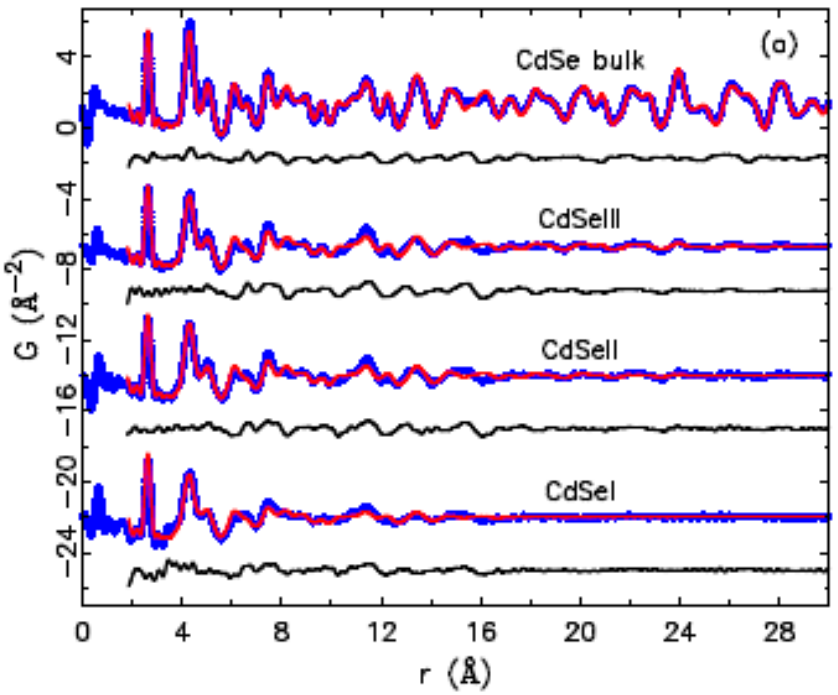
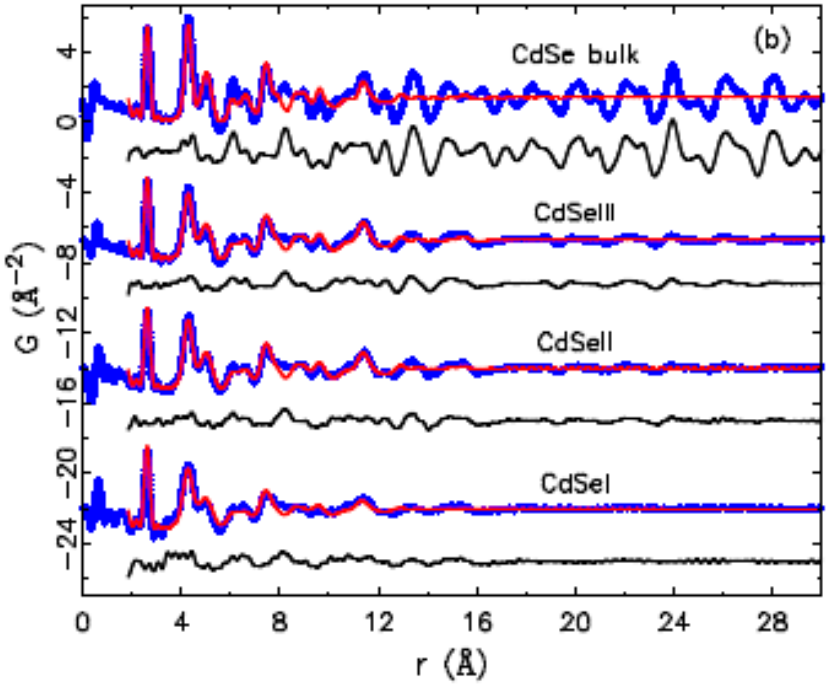
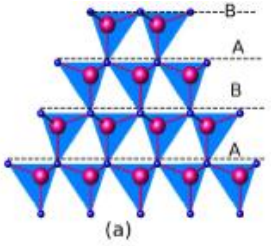
Structure of the CdSe core

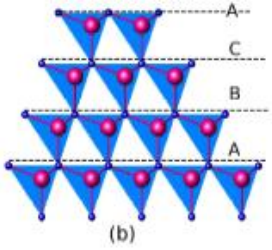


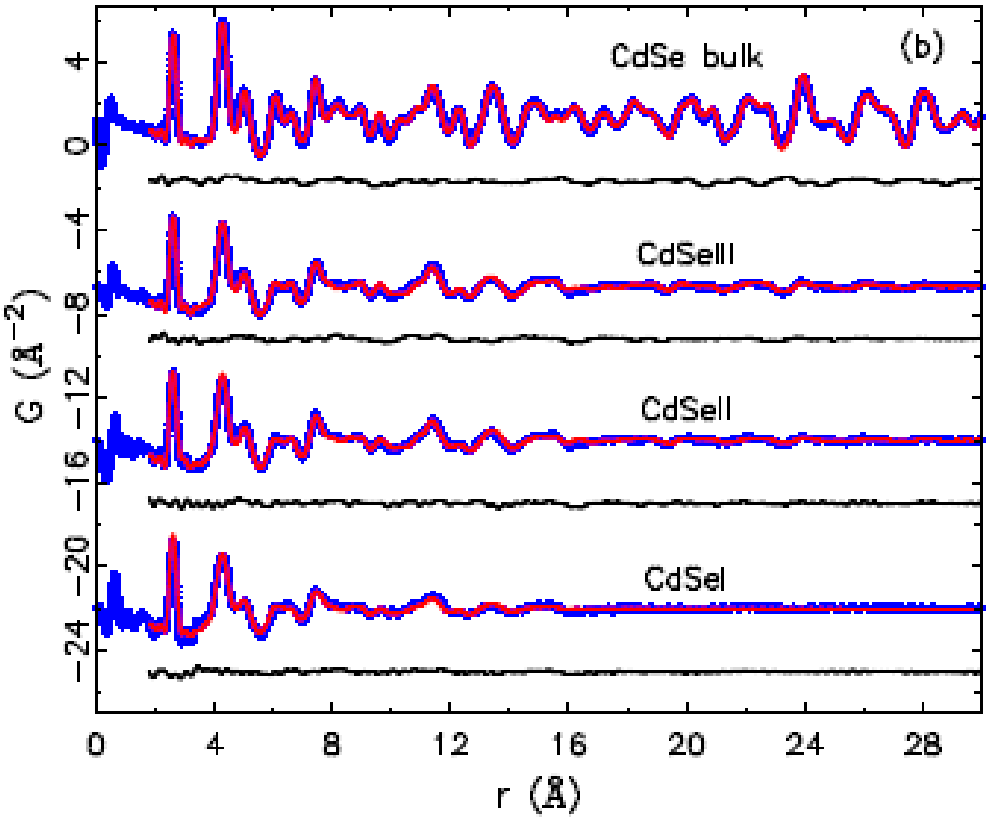


- Wurtzite structure



- Zinc blende structure



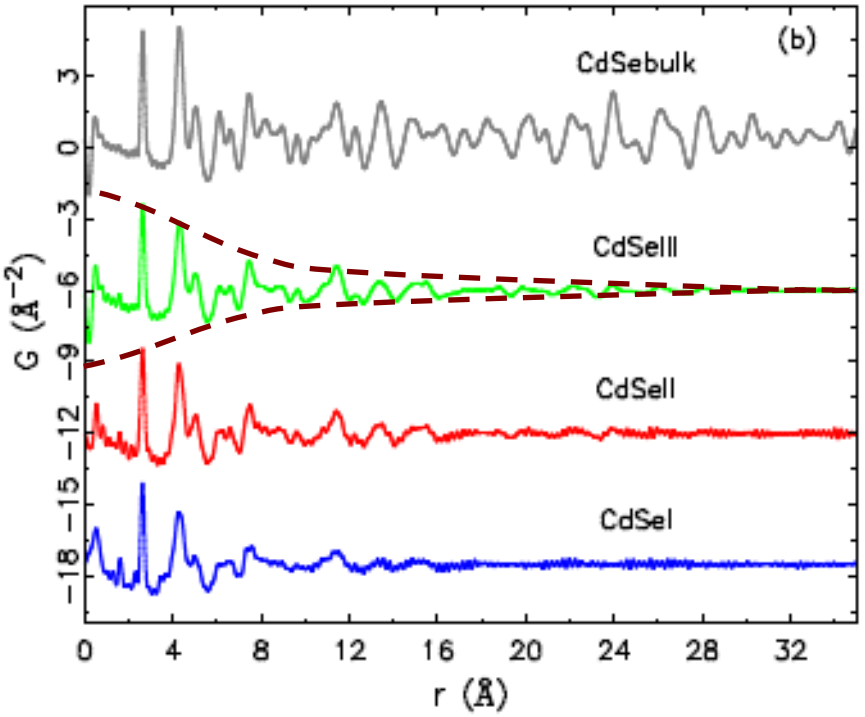


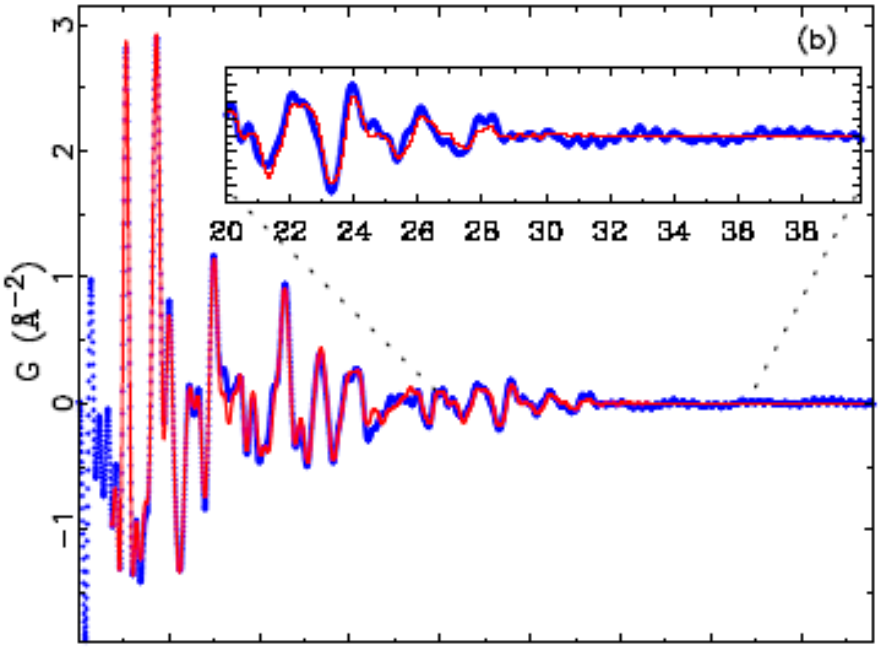
Masadeh, SJB *et al.* PRB **76**, 115413 (2007)

Thanks to Reinhard Neder for help with stacking fault models

	CdSe-bulk		CdSeIII		CdSeII		CdSeI	
Stacking fault density (%)	0.0	33.0	0.0	50.0	0.0	50.0	0.0	50.0
a (Å)	4.3014(4)	4.3012(4)	4.2997(9)	4.2987(9)	4.3028(9)	4.3015(9)	4.2930(9)	4.2930(8)
c (Å)	7.0146(9)	7.0123(9)	7.0145(4)	7.0123(4)	6.9987(9)	6.9975(9)	6.9405(9)	6.9405(7)
Se *Z-frac.*	0.3774(3)	0.3771(3)	0.3761(9)	0.3759(9)	0.3751(6)	0.3747(6)	0.3685(9)	0.3694(9)
Cd $U_{11} = U_{22}$ (Å^2)	0.0108(2)	0.0102(2)	0.0146(7)	0.0149(7)	0.0149(6)	0.0112(5)	0.0237(9)	0.0213(8)
U_{33} (Å^2)	0.0113(3)	0.0112(3)	0.0262(9)	0.0241(9)	0.0274(9)	0.0271(9)	0.0261(9)	0.0281(9)
Se $U_{11} = U_{22}$ (Å^2)	0.0109(9)	0.0102(9)	0.0077(7)	0.0138(7)	0.0083(7)	0.0121(7)	0.0110(9)	0.0191(9)
U_{33} (Å^2)	0.0462(9)	0.0115(9)	0.1501(9)	0.02301(9)	0.1628(9)	0.0265(9)	0.1765(9)	0.0311(9)
NP[a] diameter (nm)	∞	∞	3.7(1)	3.7(1)	3.1(1)	3.1(1)	2.4(2)	2.2(2)
R_w	0.12	0.09	0.20	0.14	0.18	0.15	0.27	0.21

Size of the structural core





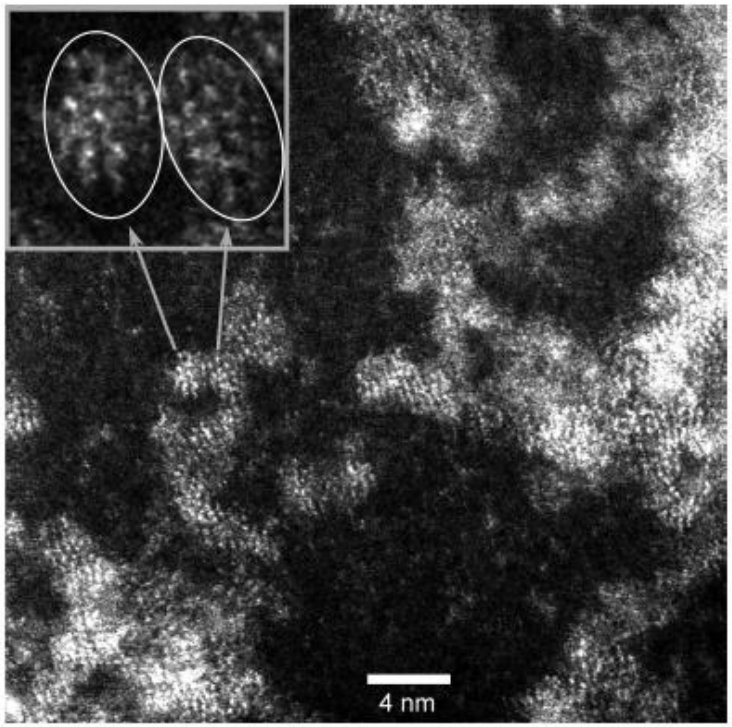
$$f\,(r,d) = \left[1 - \frac{3r}{2d} + \frac{1}{2}\left(\frac{r}{d}\right)^3\right]\Theta(d-r),$$

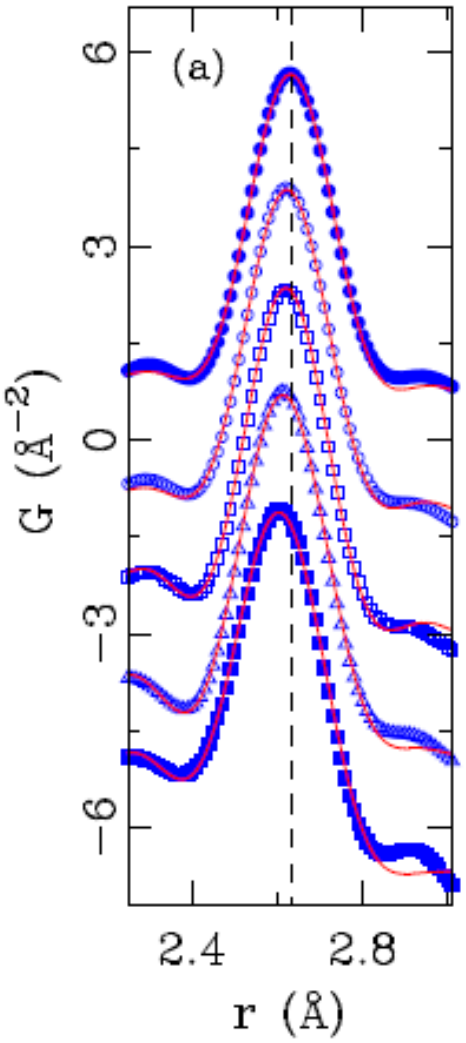
TABLE I: CdSe nanoparticle diameter as determined using various methods.

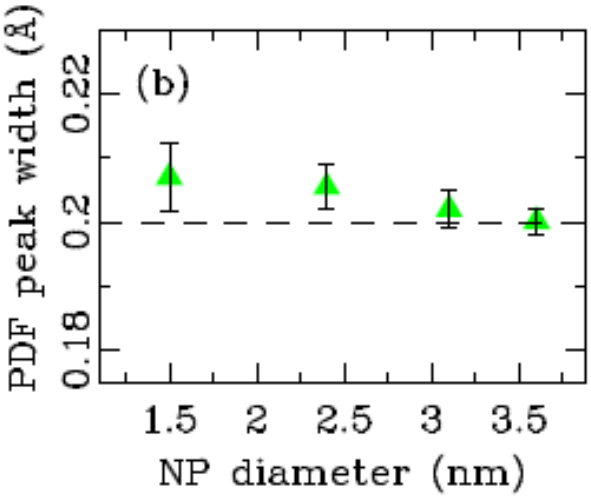
	CdSeIII	CdSeII	CdSeI
Nucleation time (s)	1200	630	15
Diameter (nm)			
TEM	3.5(2)	2.7(2)	2.0(2)
UV-vis	3.5(4)	2.9(3)	$\leq$ 1.90
PL	3.6(4)	2.9(3)	$\leq$ 2.1
PDF	3.7(1)	3.1(1)	2.2(2)

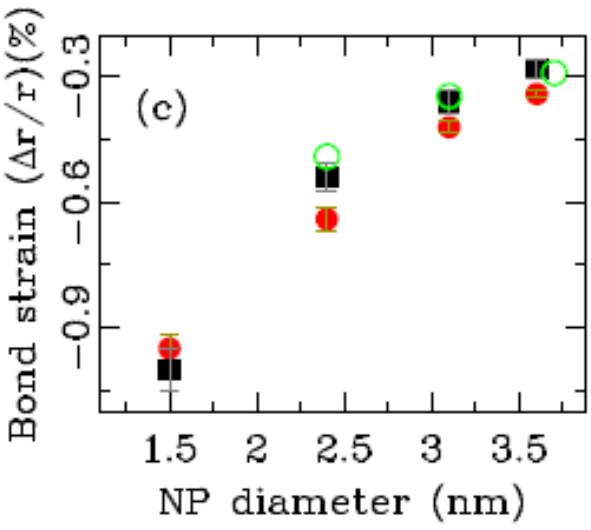
- Masadeh, SJB *et al.* PRB **76**, 115413 (2007)
- Also see Shamoto paper, JAC 2007

White Light Nanoparticles









- Samples are from Sandy Rosenthal (Vanderbilt)
- Unpublished work

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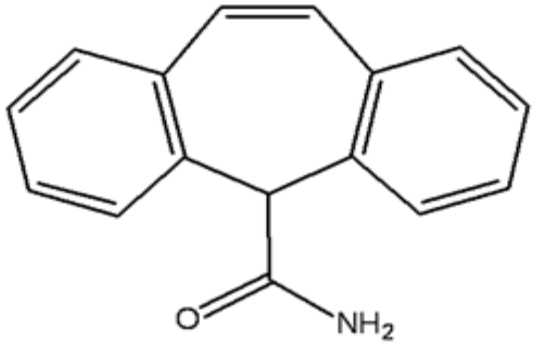
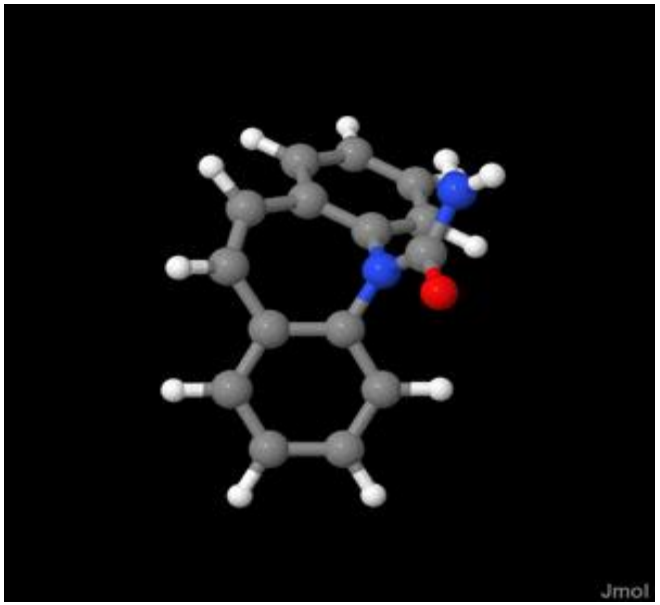
Applying PDF to small molecule systems

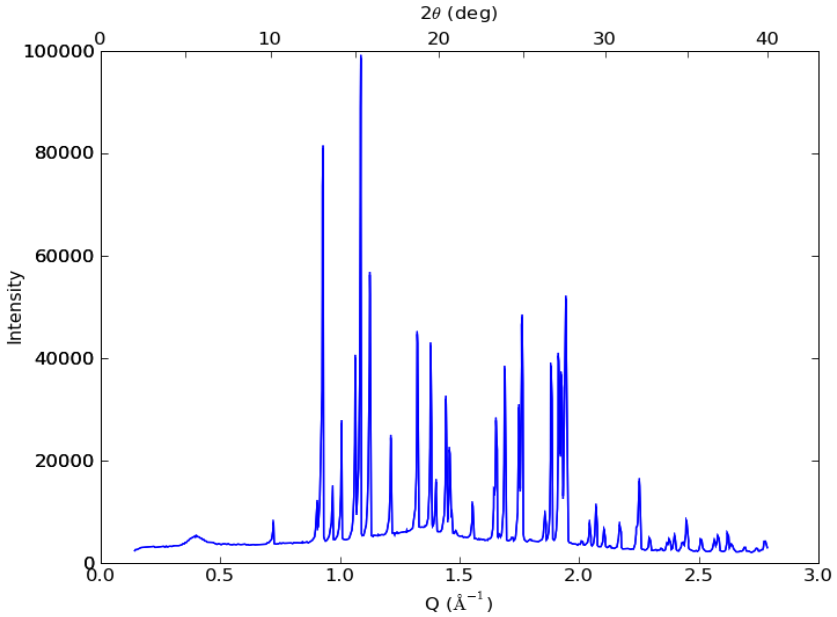
- Collaboration with Alastair Florence, U. Strathclyde and Ken Shankland (U. Reading)
- Carbamezapine (CBZ) is a mood stabilizing drug used in the treatment of epilepsy, bipolar disorder, and seizures.
- CBZ has two crystalline polymorphs and a dihydrate form. We will focus on the polymorphs.



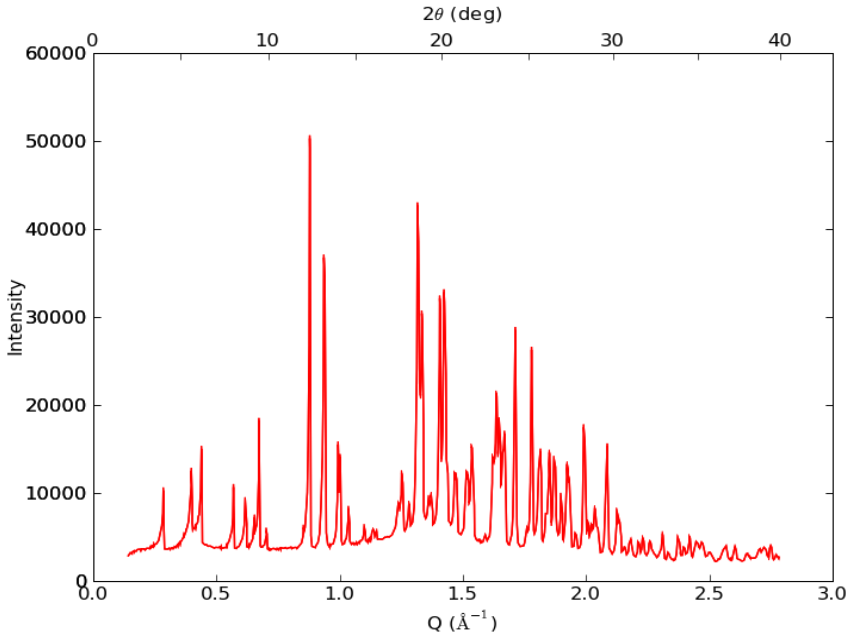


Fingerprinting example

Take two crystalline forms of a drug molecule, e.g., CBZ: β-phase and γ-phase.

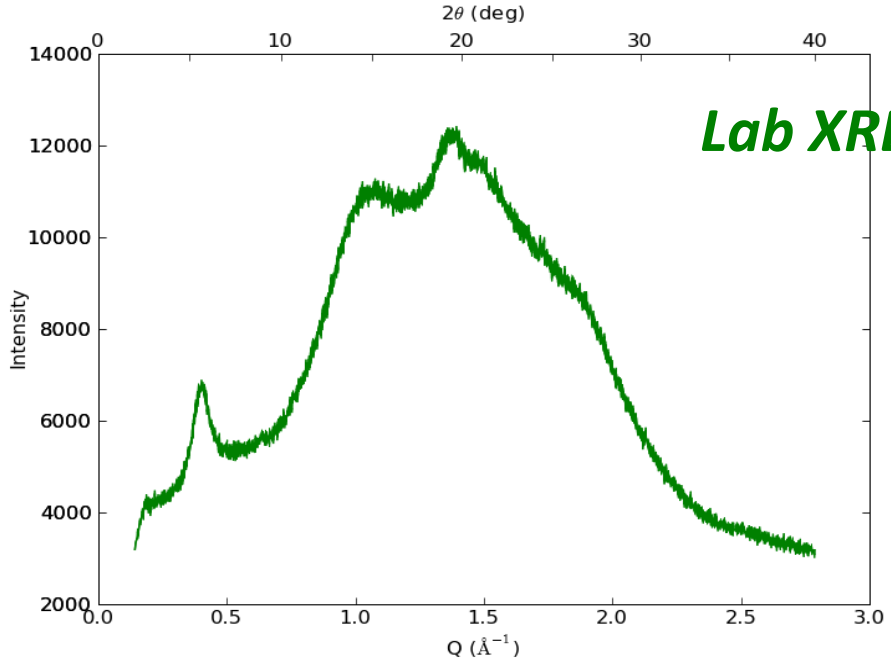


Lab XRD of CBZ-β



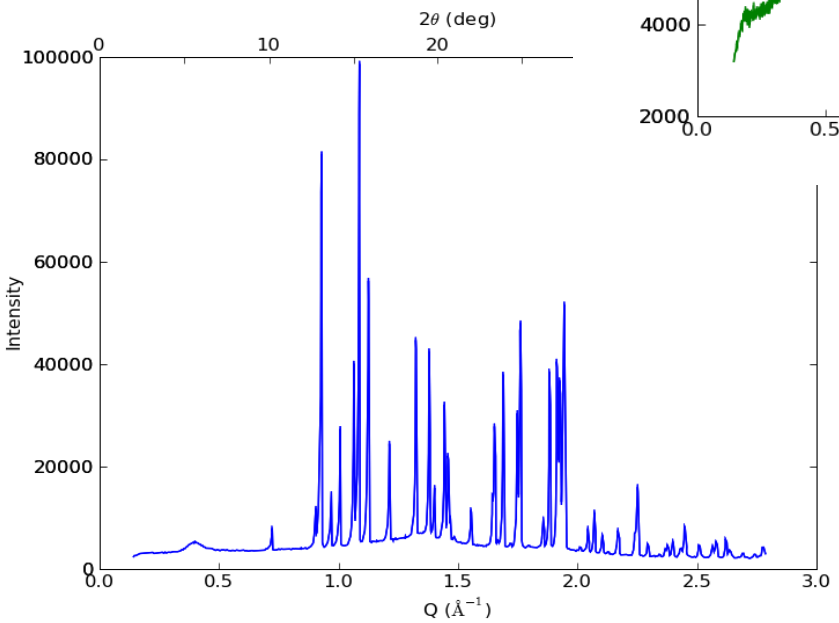
Lab XRD of CBZ-γ

Fingerprinting example: what about amorphous a-form?

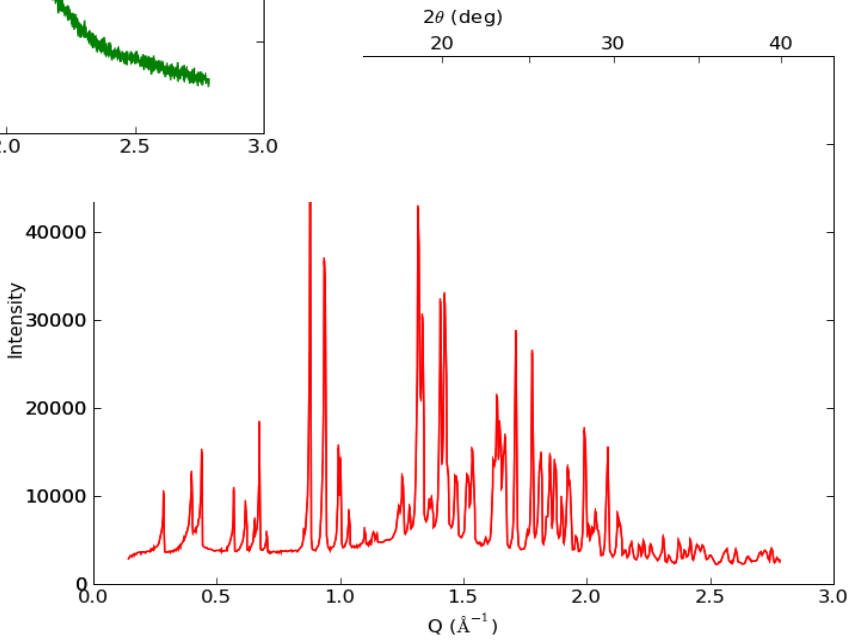


Lab XRD of a-CBZ

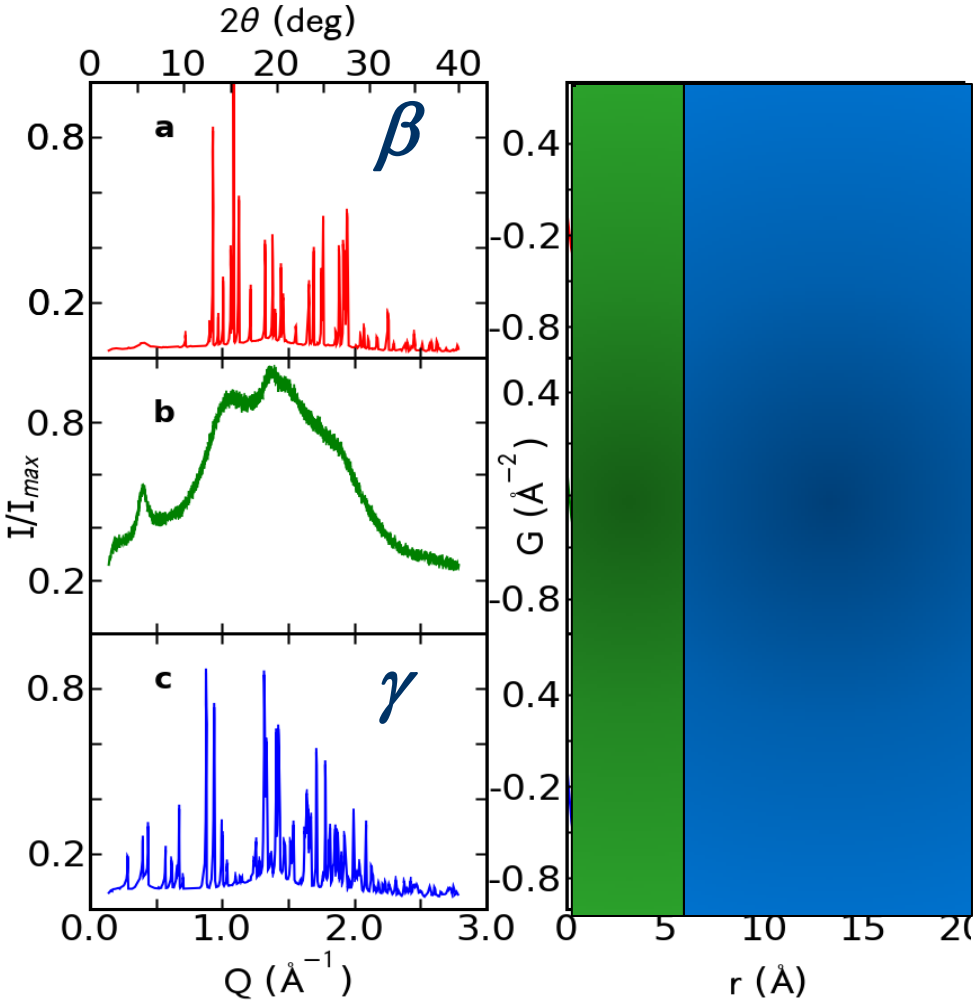
Lab XRD of CBZ-β



ab XRD of CBZ-γ



Try Fourier transforming to get the PDF



- Fourier transforming the lab data to get a PDF is inconclusive
- Beta and gamma have different PDFs (good!) but what about melt-quenched?

HTTP://

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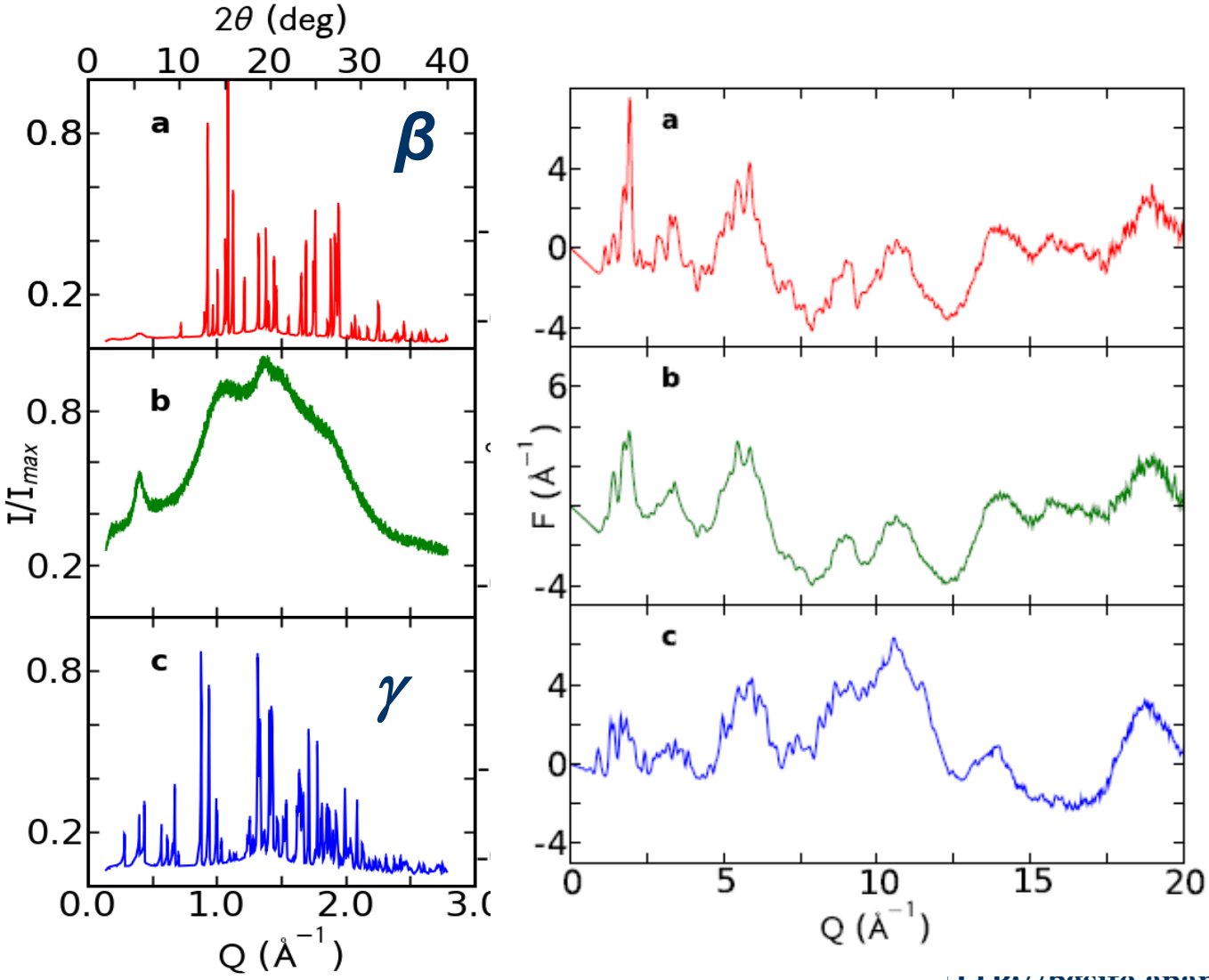
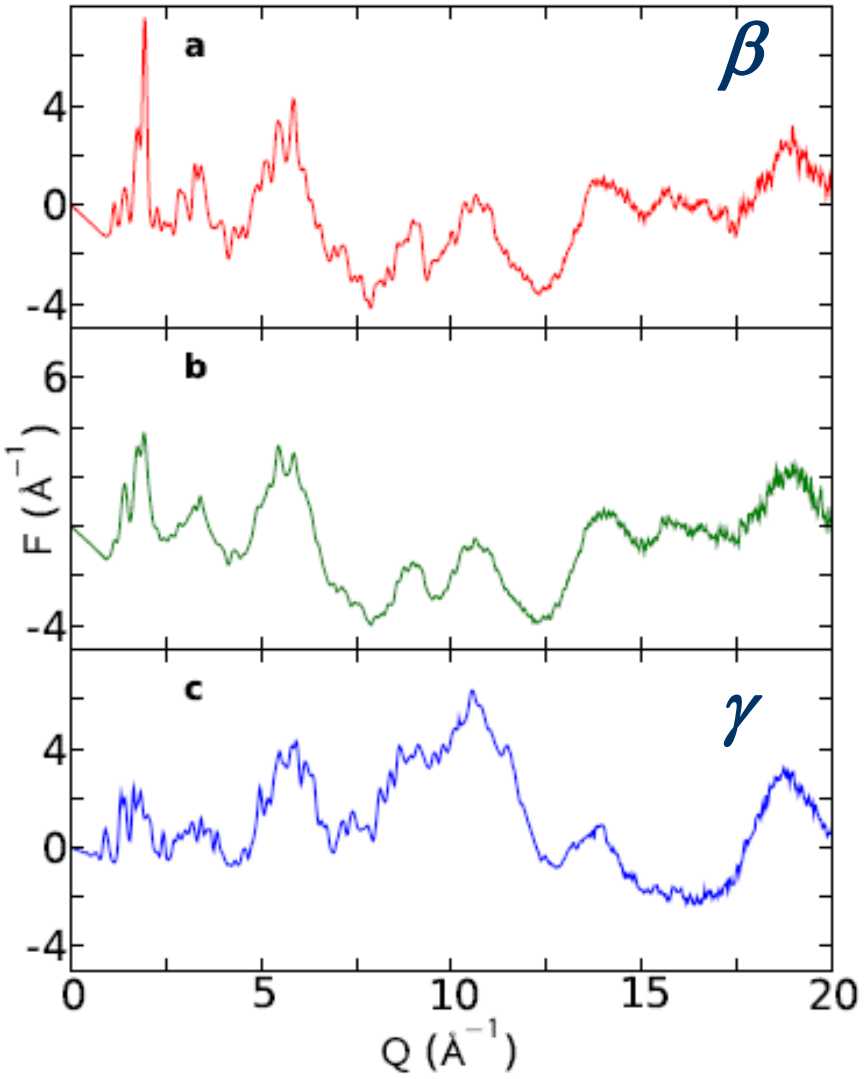
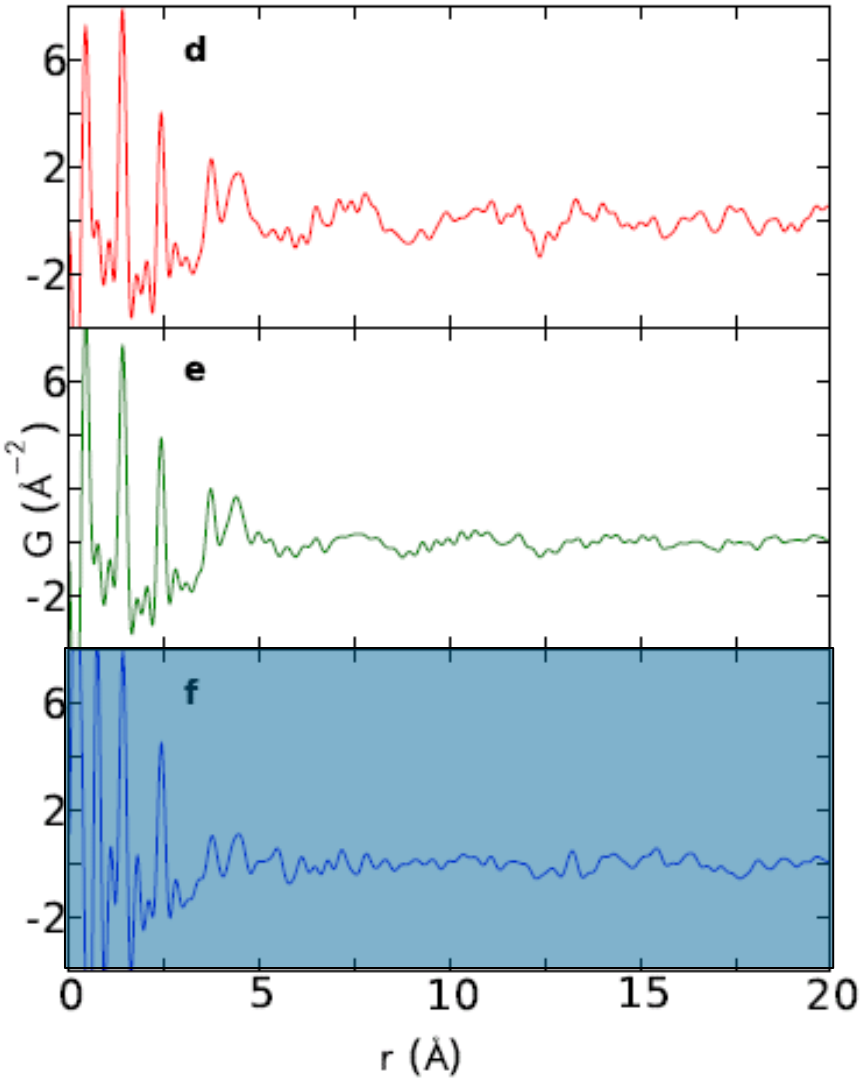
Total scattering PDFs



Total scattering PDFs





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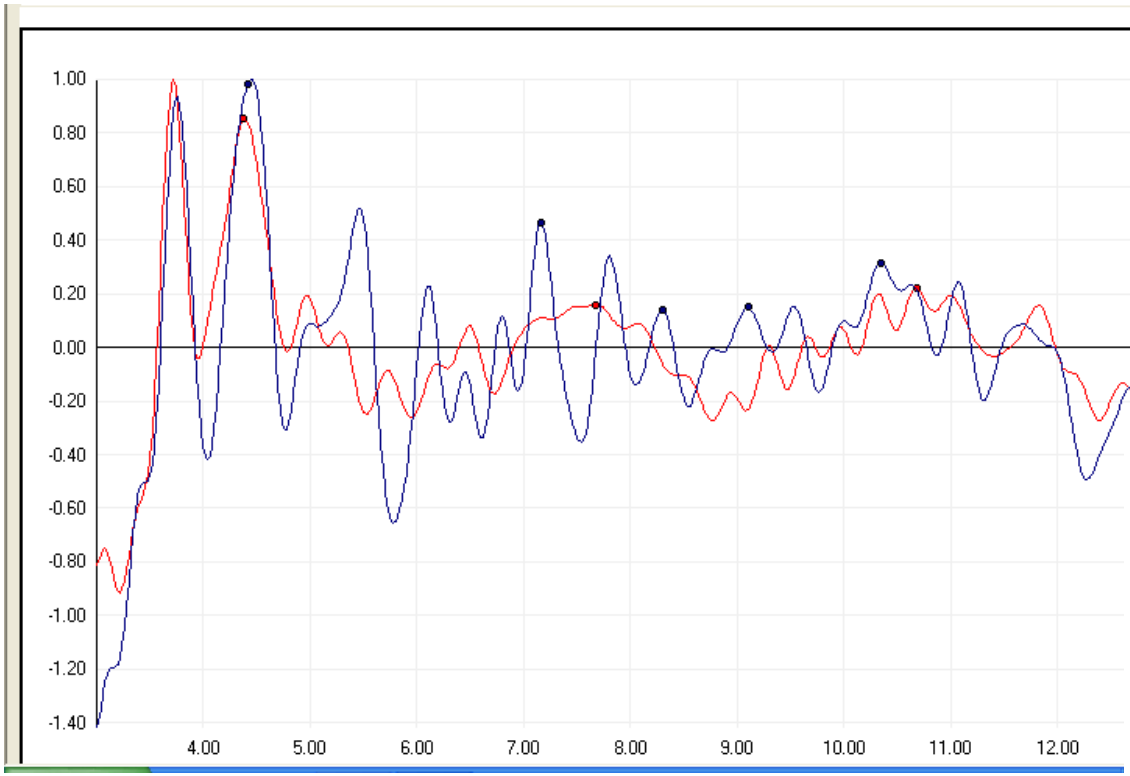
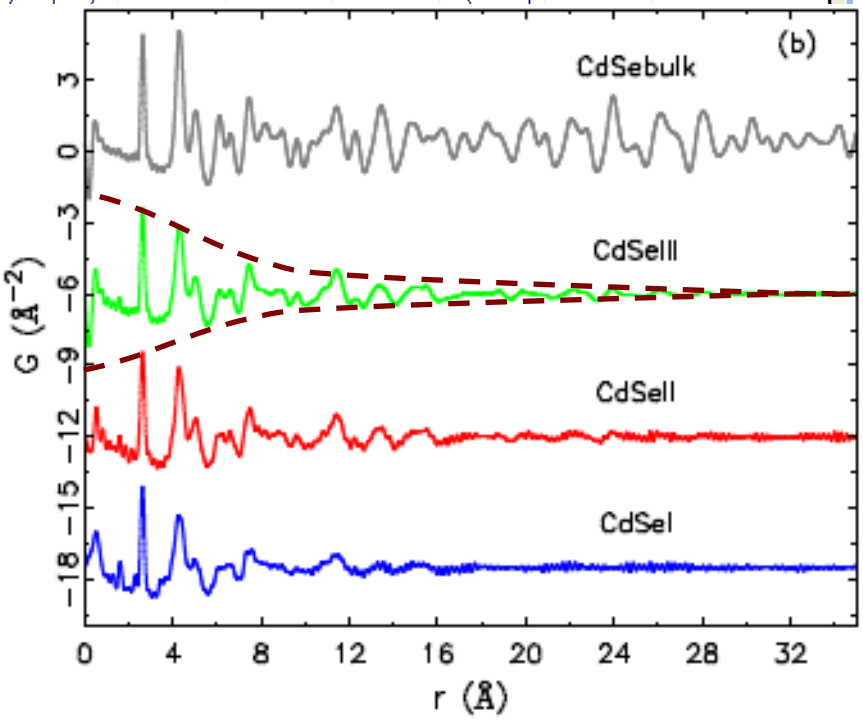
Comparison of CBZ beta (blue) and melt-quenched in Polysnap



$$f\,(r,d) = \left[1 - \frac{3r}{2d} + \frac{1}{2}\left(\frac{r}{d}\right)^3\right]\Theta(d-r),$$



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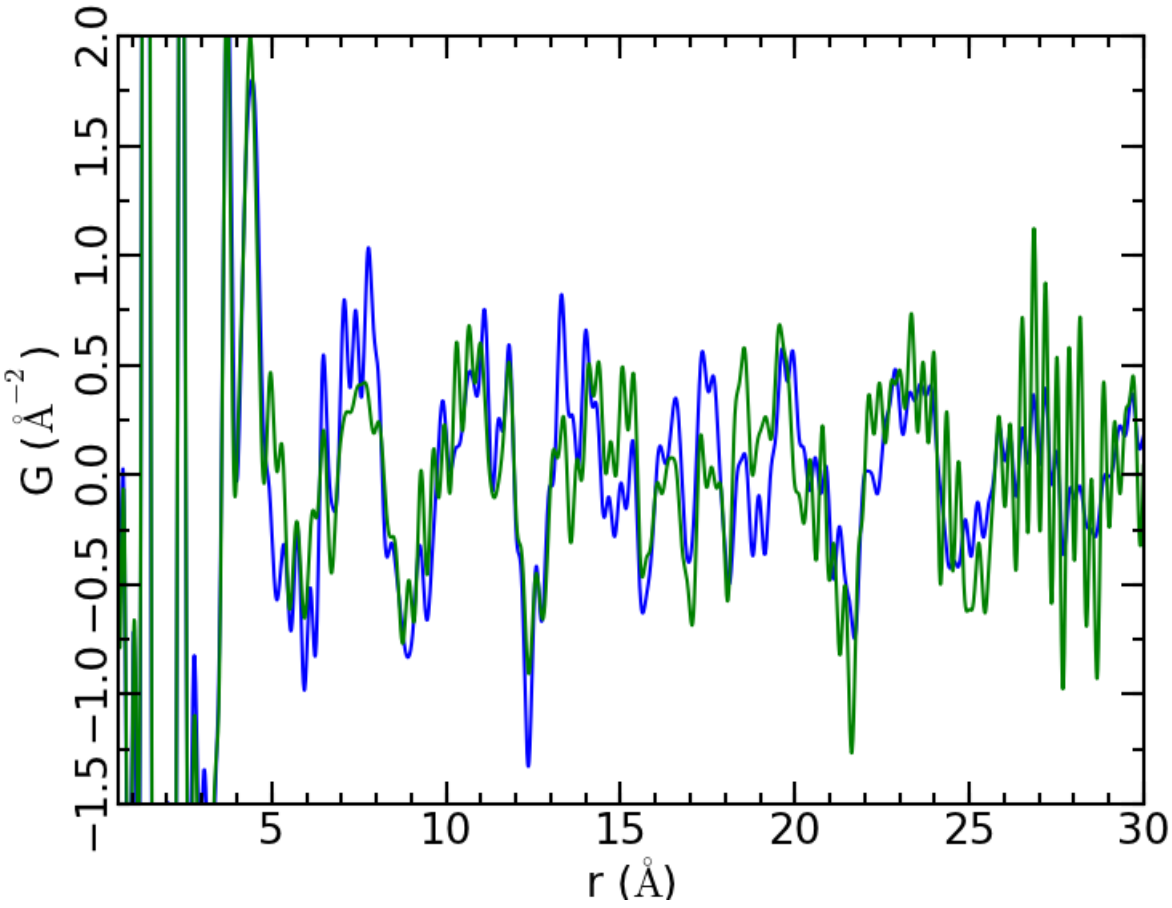
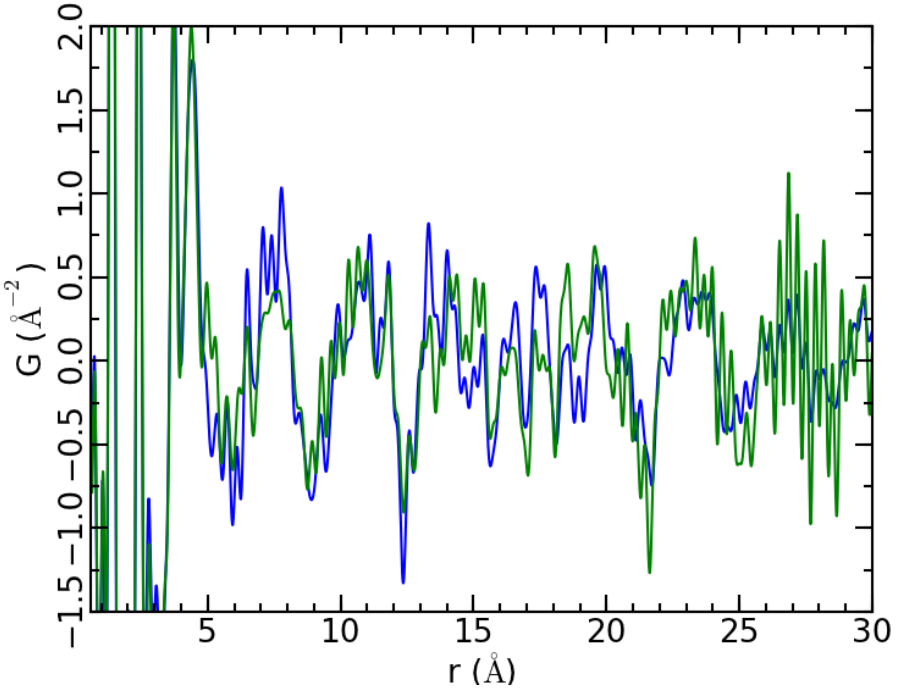
Visual comparison of melt-quenched CBZ

- (blue) Crystalline Carbamezapine-beta (Form III)
- Plotted to emphasize intermediate-r range
- Melt quenched Carbamezapine
- Melt quenched Carbamezapine corrected for 4.5 nm nanoparticle size effects



Fingerprinting using Pearson product momentum correlation function



$$R = \frac{1}{1-n}\sum_{i=0}^{n}\left(\frac{X_i-\overline{X}}{\sigma_x}\right)\left(\frac{Y_i-\overline{Y}}{\sigma_y}\right)$$

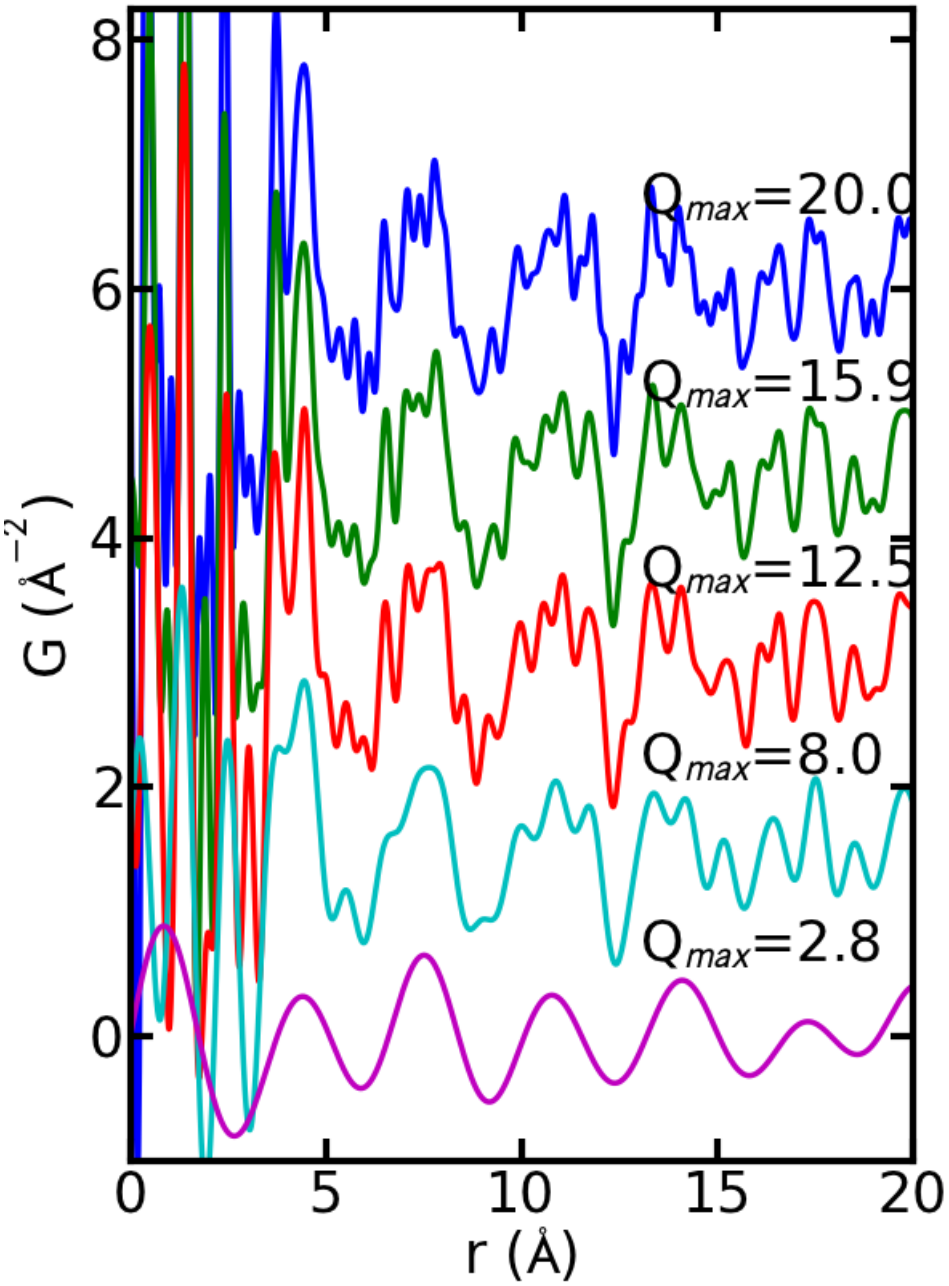
- Pearson correlation function
  - Value 1 => curves are perfectly correlated (the same)
  - Value -1 => curves are perfectly anticorrelated
  - Value 0 => curves are uncorrelated
- A higher number means more correlated
- Rule of thumb: >0.8 means the samples are the same form

	CBZ-III	CBZ-a	CBZ-I
CBZ-III	I	**0.881**	0.580
CBZ-a		I	0.722
CBZ-I			I

- Dykhne, SJB et al *Pharmaceut. Res.* **28**, 1041-1048 (2011)

Sensitivity to Qmax

- Melt-quenched Carbamezapine
- Synchrotron data
- Silver anode lab source
- Mo anode lab source
- Cu anode, $2\theta = 180^{o}$
- Cu anode, $2\theta = 40^{o}$



- Melt-quenched Carbamezapine, low-r region vs Q_{max}

- Synchrotron data
- Silver anode lab source
- Mo anode lab source
- Cu anode, $2\theta = 180^{o}$
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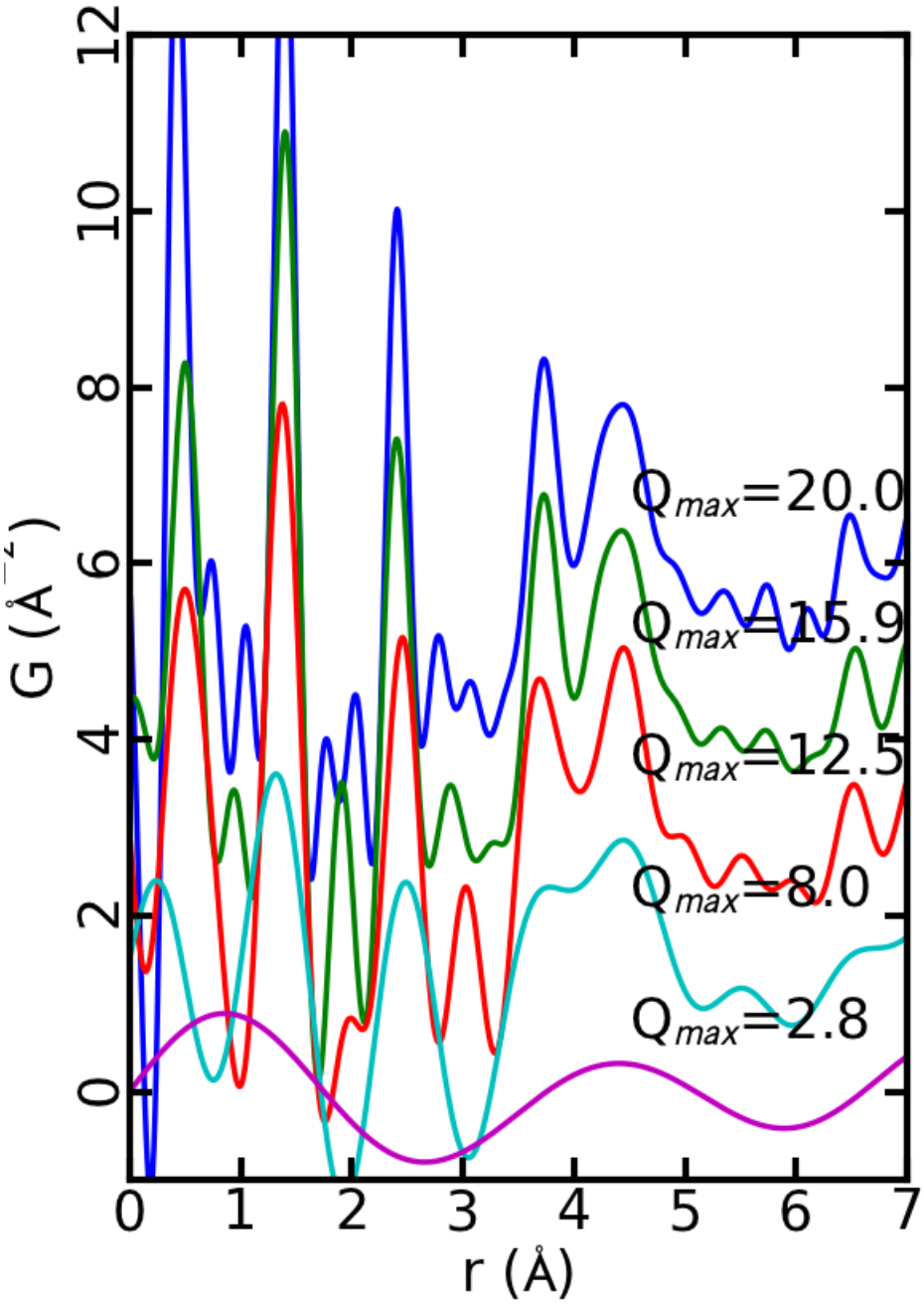

- Melt-quenched Carbamezapine

- Synchrotron data
- Silver anode lab source
- Mo anode lab source
- Cu anode, $2\theta = 180^{o}$
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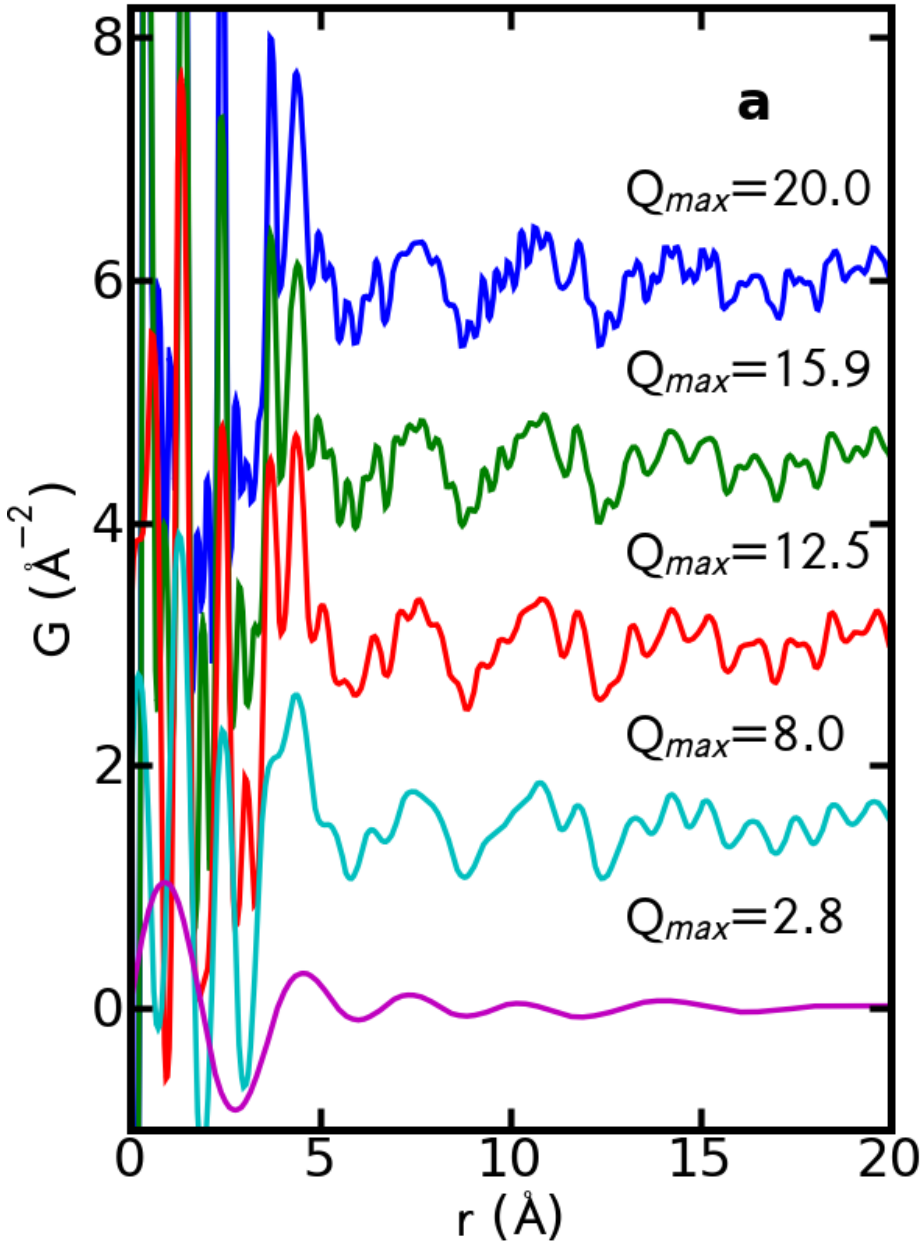

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- Synchrotron
- Silver anode source
- Mo anode source
- Cu anode source 2θ = 180°
- Cu anode source 2θ = 40°

	CBZ-III	CBZ-a	CBZ-I	IND-α	IND-a	IND-γ
$Q_{max} = 20 Å^{-1}$						
CBZ-III	1	**0.88121**	0.580032	0.36072	0.520868	0.535466
CBZ-a		1	0.721854	0.499347	0.692577	0.585051
CBZ-I			1	0.4143	0.607663	0.353945
IND-α				1	0.706309	0.477629
IND-a					1	0.648231
IND-γ						1

- Synchrotron
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- Mo anode source
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IND-a					I	0.648231
IND-γ						I
$Q_{max} = 15.9Å^{-1}$						
CBZ-III	I	**0.88806**	0.587318	0.408013	0.540808	0.554994
CBZ-a		I	0.735184	0.528379	0.711449	0.603083
CBZ-I			I	0.461576	0.633917	0.371975
IND-α				I	0.747408	0.512554
IND-a					I	0.656109
IND-γ						I
$Q_{max} = 12.5Å^{-1}$						
CBZ-III	I	**0.884121**	0.602841	0.414968	0.532329	0.552159
CBZ-a		I	0.743738	0.550489	0.694594	0.596248
CBZ-I			I	0.493308	0.642929	0.385381
IND-α				I	0.796457	0.546241
IND-a					I	0.648245
IND-γ						I

- Synchrotron
- Silver anode source
- Mo anode source
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IND-a					1	0.648245
IND-γ						1
$Q_{max}=8.0Å^{-1}$						
CBZ-III	1	**0.896121**	0.609902	0.488752	0.541615	0.588639
CBZ-a		1	**0.803586**	0.611696	0.717735	0.620615
CBZ-I			1	0.567149	0.668514	0.403731
IND-α				1	**0.874273**	0.593747
IND-a					1	0.660049
IND-γ						1

- Synchrotron
- Silver anode source
- Mo anode source
- Cu anode source 2θ = 180°
- Cu anode source 2θ = 40°

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CBZ-I			I	0.567149	0.668514	0.403731
IND-α				I	**0.874273**	0.593747
IND-a					I	0.660049
IND-γ						I
$Q_{max}=2.8Å^{-1}$						
CBZ-III	I	0.592352	0.56047	0.242189	0.301645	0.315372
CBZ-a		I	0.738592	**0.815624**	**0.889357**	0.291114
CBZ-I			I	0.749409	0.688959	0.128833
IND-α				I	**0.95458**	0.25323
IND-a					I	0.324015
IND-γ						I

Qmax sensitivity conclusion

- Synchrotron is best
- ….. But at the very least use Mo source and get a Qmax of 12.5 or more

Conclusions

- Ongoing study
- Cryomilled Salbutamol sulphate is not nanocrystalline, but “truly” amorphous. Correlations do not extend beyond 10A, 1 nm.
- Highly reproducible datasets from different samples and different diffractometers
- Temperature effects:
  - Strong effects for crystalline materials
  - Weak effects for amorphous (because of the presence of significant static disorder)

Concluding remarks

- TSPDF (PDF to high enough Q) looks very promising for characterizing pharmaceuticals
- Data:
  - Get synchrotron data if you can
    - Work with a synchrotron expert if you can
    - Dedicated beamlines at APS, Diamond, NSLS, also non dedicated at ESRF
    - ~$1000 per dataset for proprietary data
    - ~ 30 mins per dataset
  - Or get a Mo or Ag lab source
    - ~$250,000 for a dedicated source or $50,000 to convert and existing source
    - ~ few hours to a day to get a dataset

Concluding remarks

- Software:
  - Software for converting data to PDFs
    - PDFgetX2 (strictly you need to pay MSU for a license for commercial use). Hard to learn and use
    - RAD. Hard to learn and use
    - PDFgetO on the horizon. Online app, easy to use and little learning but will need a license
  - Correlation analysis
    - POLYSNAP: commercial
    - Pearson: we use Python scripts. Can consider releasing it if there is interest
  - Modeling, calculating PDFs
    - PDFgui (www.diffpy.org)
- Contact info
  - Simon Billinge: sb2896@columbia.edu

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