Amorphous Materials: A Structural Perspective

Amorphous workshop PPXRD-11

Simon Bates: Triclinic Labs

Triclinic Labs

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

Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd

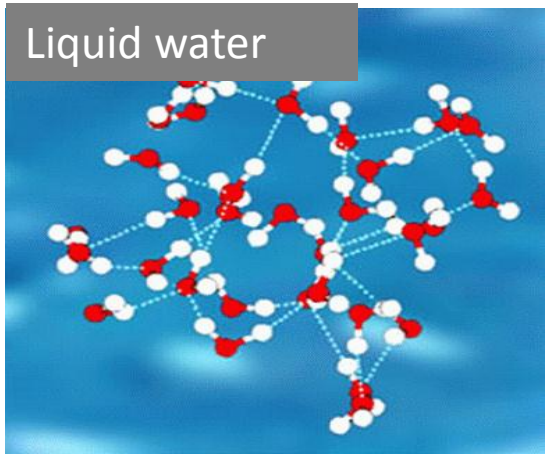
ICDD Website - www.icdd.com

Where to begin our study of structure in the amorphous state?

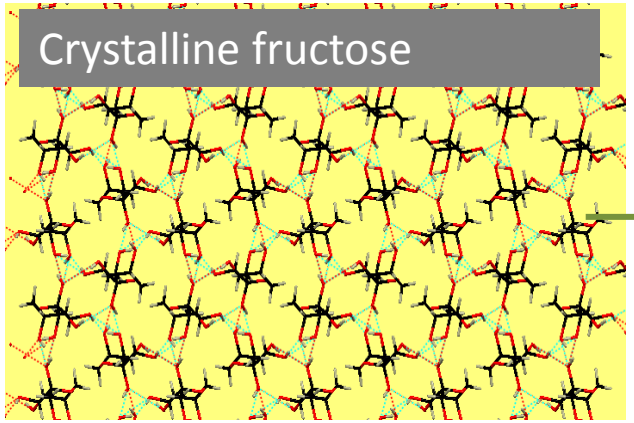
- A good place to start is to reference known boundaries to the definition of ‘structure’.
- Ideal Crystalline: A solid with long-range order (periodic or aperiodic)
  - “any solid having an essentially discrete diffraction diagram” IUCr 1992
- Ideal Non-crystalline: A liquid (or ‘*solid*’) possessing no long-range order.
  - “any sample having an essentially continuous diffraction diagram”
- The ideal solid crystal and ideal liquid non-crystal give two equilibrium thermodynamic reference points.

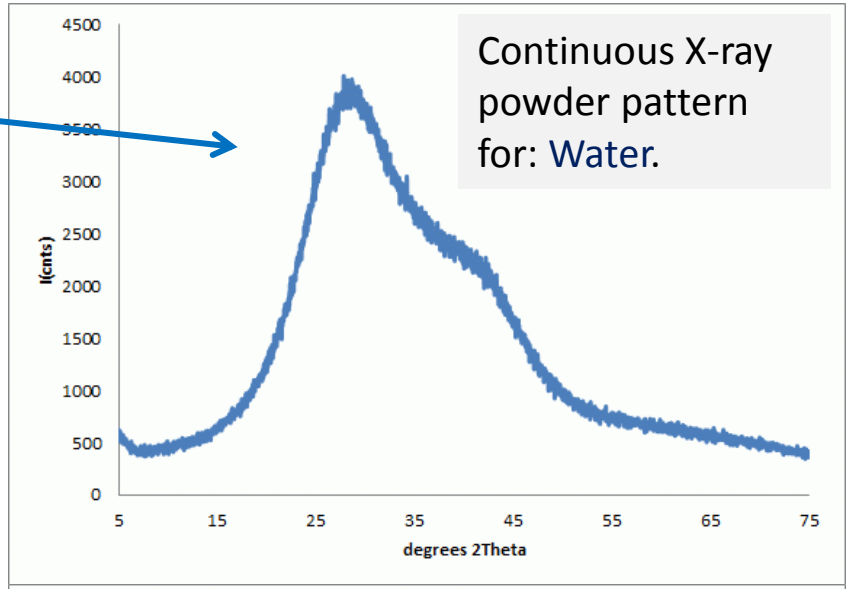
Triclinic Labs

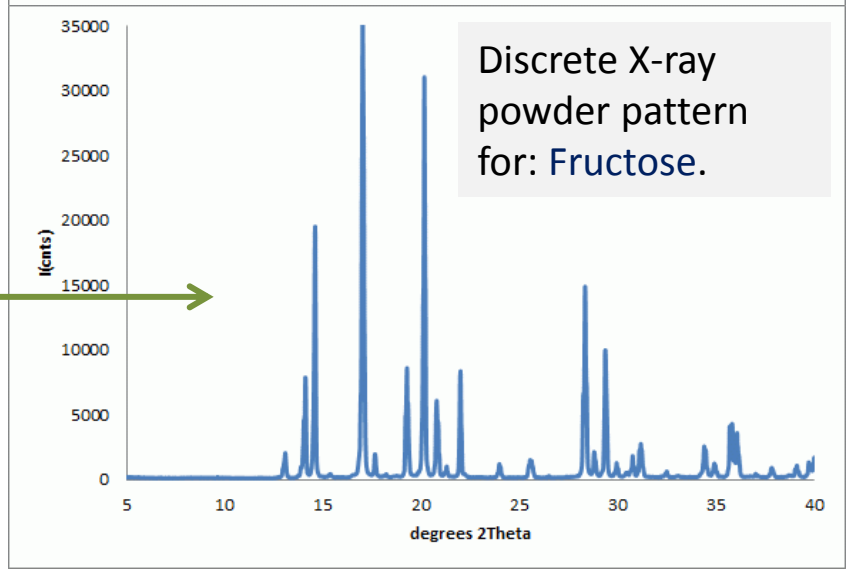
Crystalline and non-crystalline diffraction



Crystalline: “any solid having an essentially discrete diffraction diagram” IUCr 1992



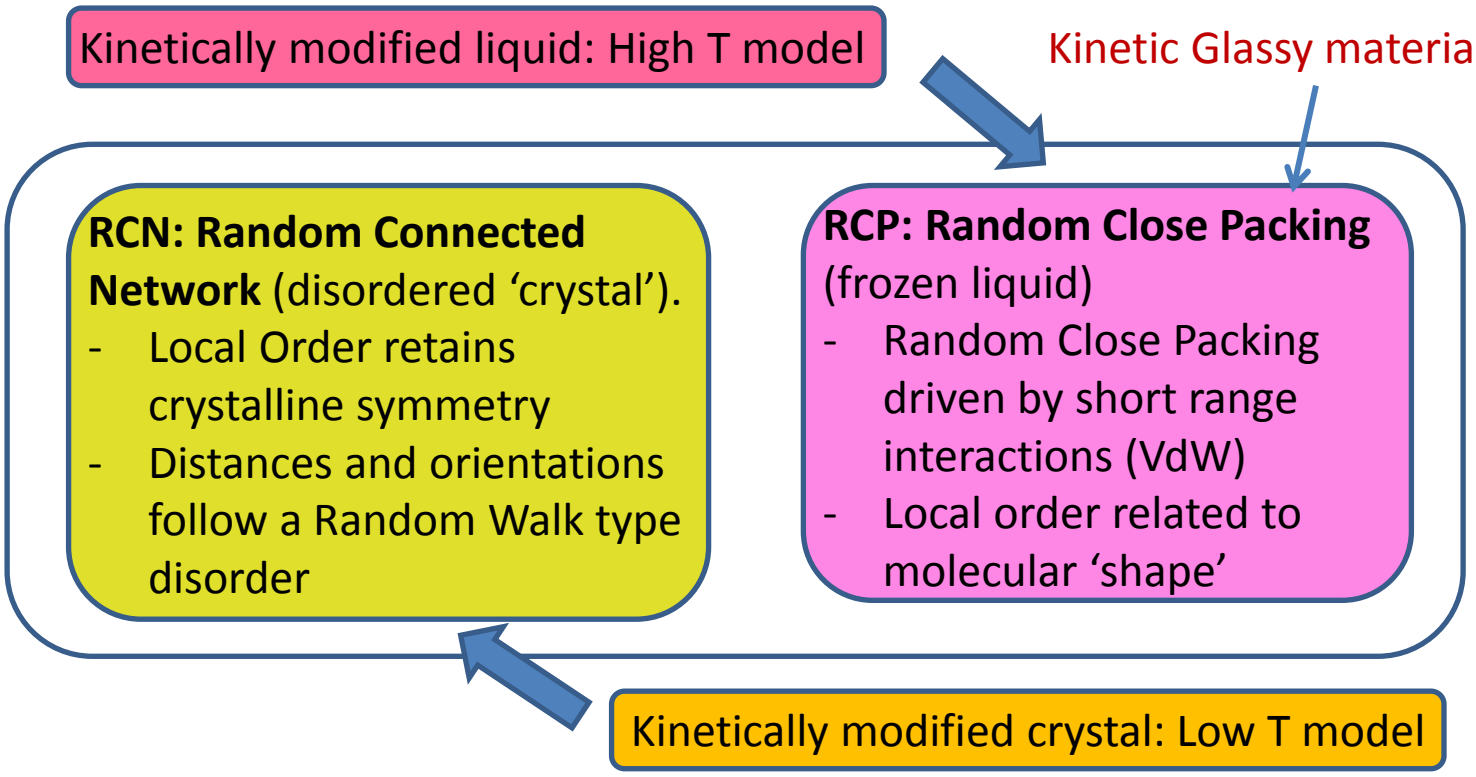




Triclinic Labs

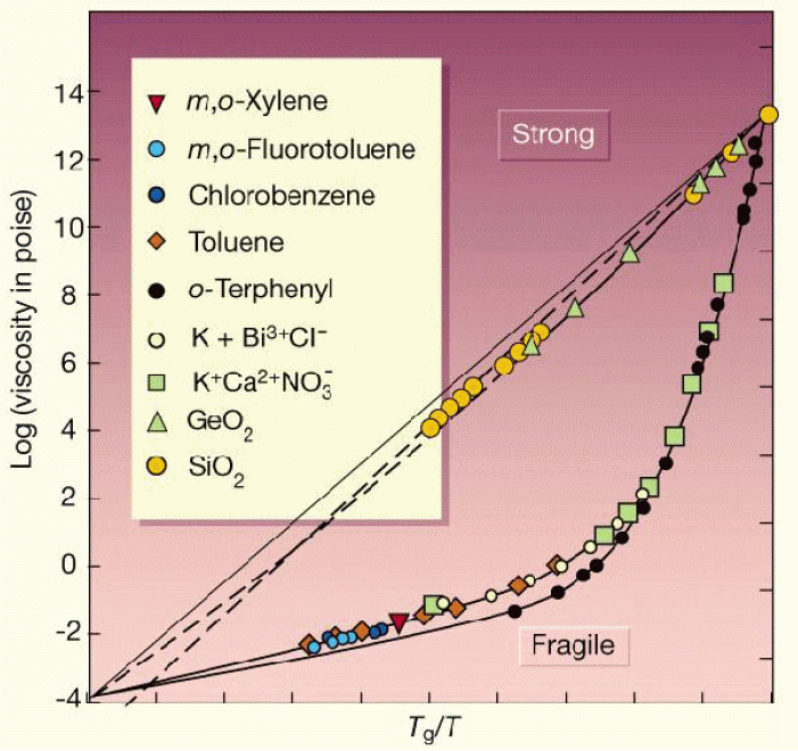
What is X-ray amorphous

X-ray amorphous powder patterns are continuous in nature (**non-crystalline**) indicating that the sample has no long-range order and is macroscopically isotropic in nature. However, the X-ray amorphous pattern is a finger print of the short-range order.



Triclinic Labs

Is the concept of ‘structure’ even important for kinetic glassy material?



Glass transition, Tg, viscosity ~ 10^13 Poise (~10^12 Pa.s)

Giulio Biroli: Seminaire Poincare XIII (2009) 37 - 67

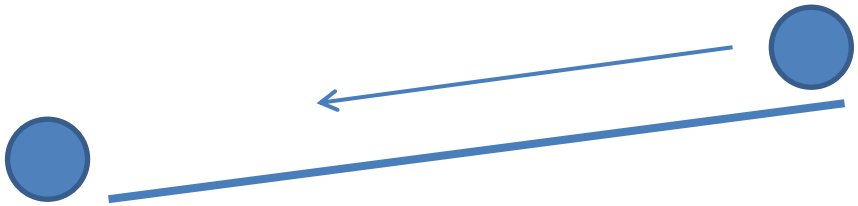
Triclinic Labs

Angell plot for super-cooled liquids scaled to glass transition temperature (Tg) shows the different behavior for ‘strong’ and ‘fragile’ glasses. Difference in behavior is thought to be related to differences in structural cooperativity.

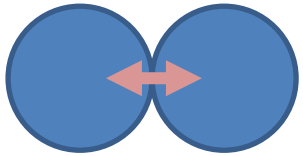
Strong glasses have the same local structure above and below Tg with viscosity related to bond breaking. Scales with the number of bonds.

Fragile glasses rapidly lose their local structure below Tg. Non linear viscosity change is related to the growth of cooperative local structure approaching Tg. Scales with length scale of cooperative order.

What is ‘structure’ in super-cooled liquids?



Molecules exert a long range attractive force on each other

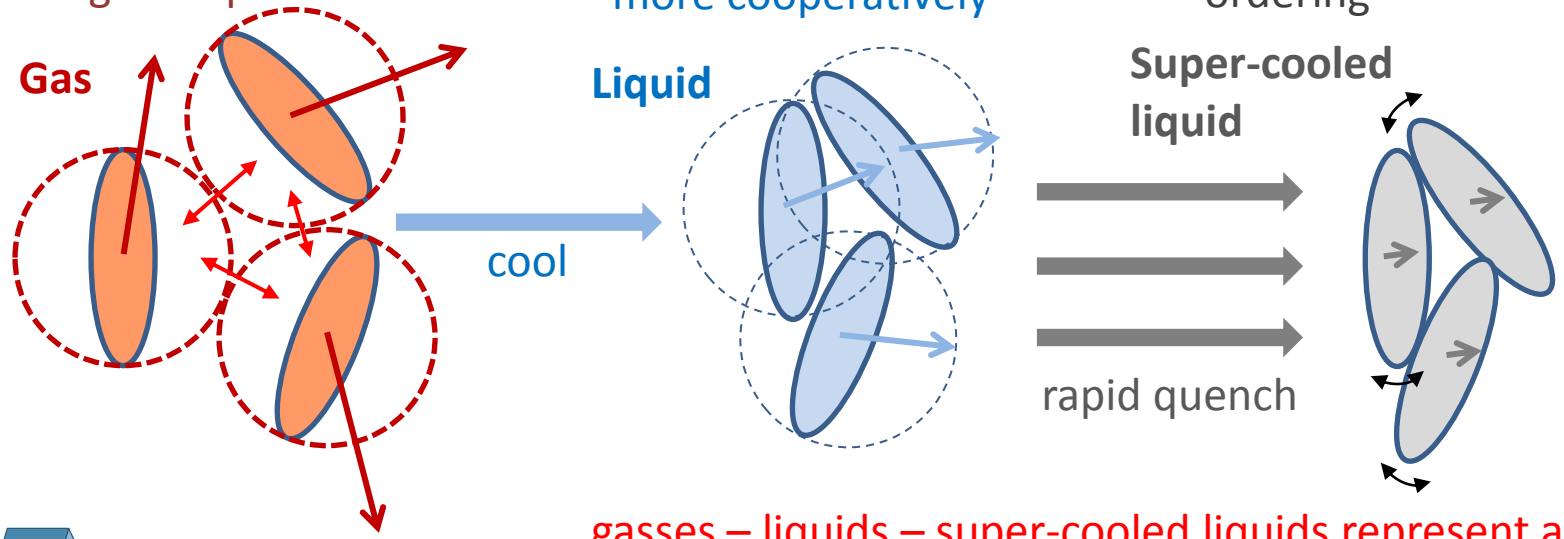


At short distances, molecules repel each other

Thermal motion tends to push molecules further apart at high temperatures

Cooling allows molecules to pack more closely and act more cooperatively

At low temperatures, short range repulsion drives local ‘ordering’



gasses – liquids – super-cooled liquids represent a continuum of isotropic systems with no long-range ‘order’.

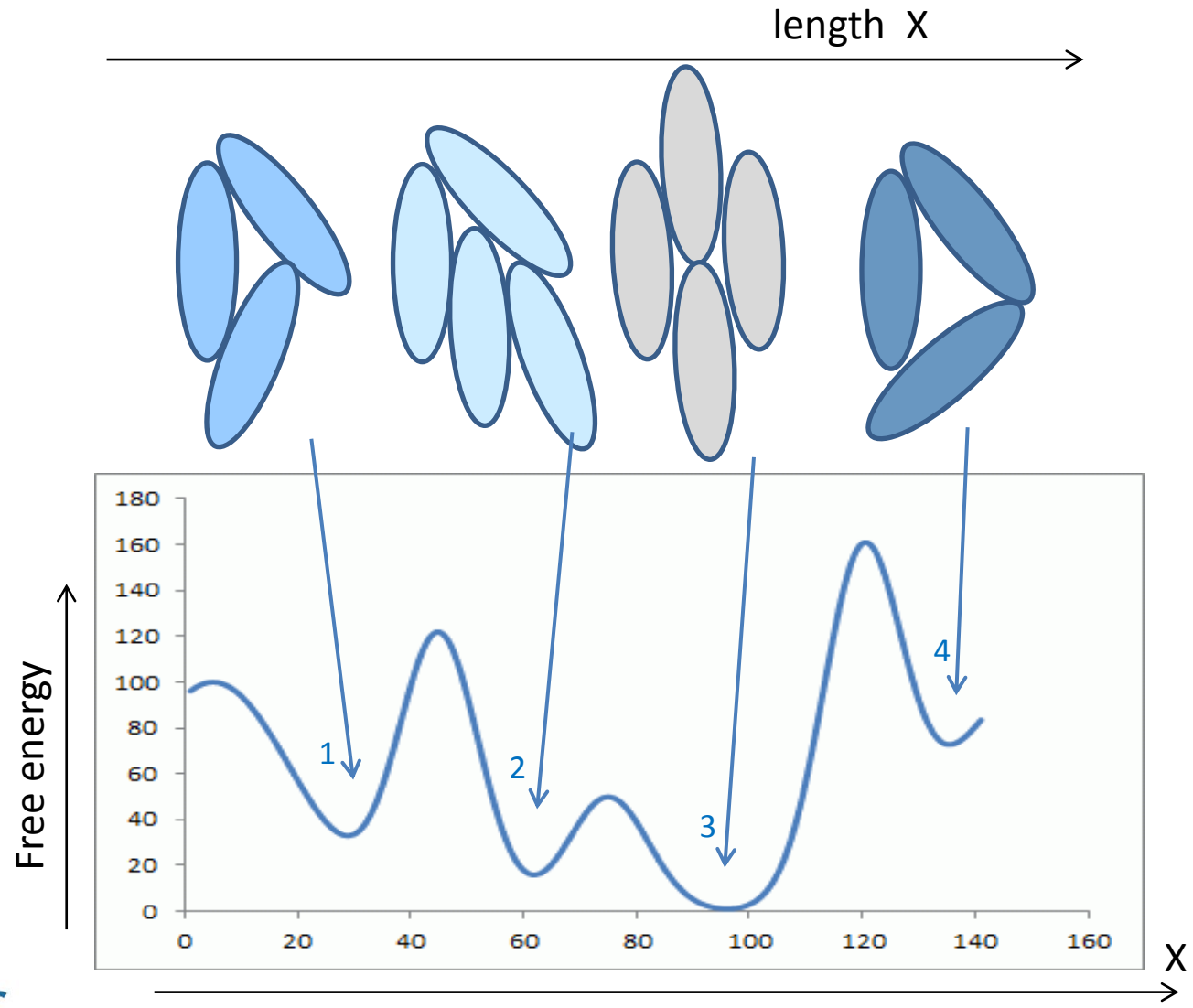
Triclinic Labs

Can we say anything about ‘long-range order’ in super-cooled liquids

Spatially, a super-cooled liquid can be considered to be a mosaic of locally ordered regions (each of which represents a local energy minima) isolated from each other by high energy barriers

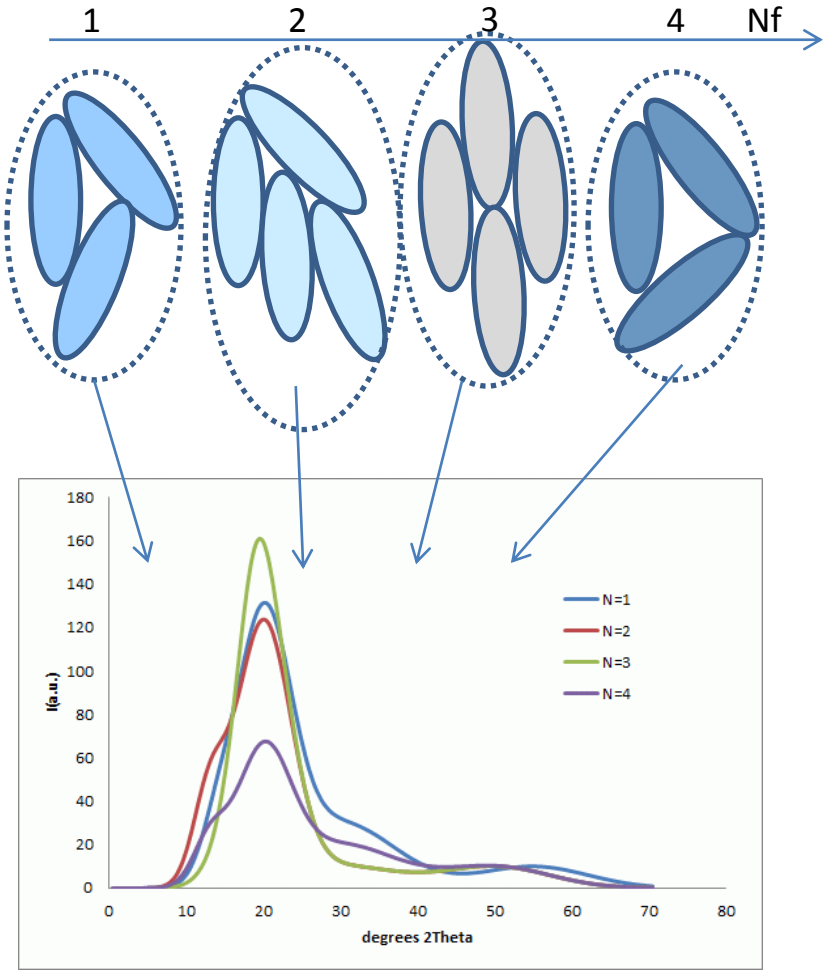
Configurational Entropy
Sc ~ log(Nf)/Nf
‘Nf’ ~ number of different free energy states available.

Experimental determination of local order will average over the huge number of local states



Triclinic Labs

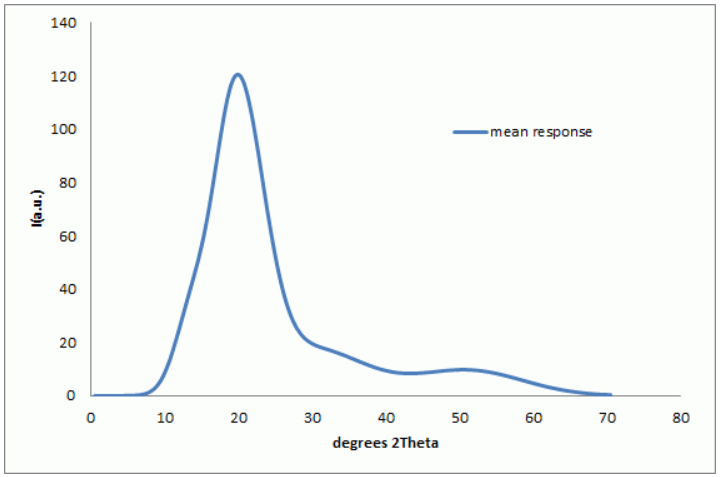
What does X-ray Powder Diffraction measure for a super-cooled liquid?



Coherent X-ray diffraction from each local packing minima will contribute an individual XRPD profile.

Each individual profile is incoherently averaged to give a single mean coherent XRPD response for the sample.

The mean response essentially represents the average local order in the sample.

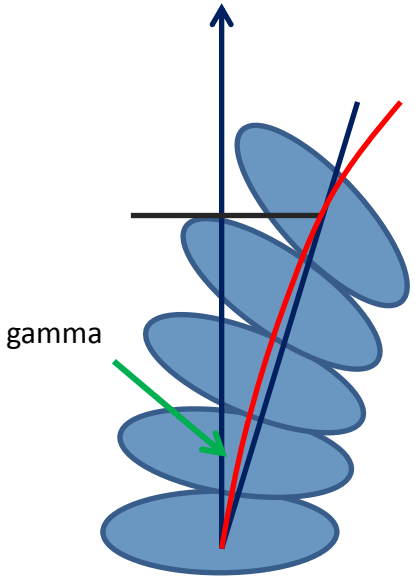


Triclinic Labs

Laboratory XRPD averages spatially and over the duration of the measurement →insensitive to Tg

In addition to averaging, what other limitations are introduced by the XRPD measurement?

Consider random close packing as a self-avoiding random walk

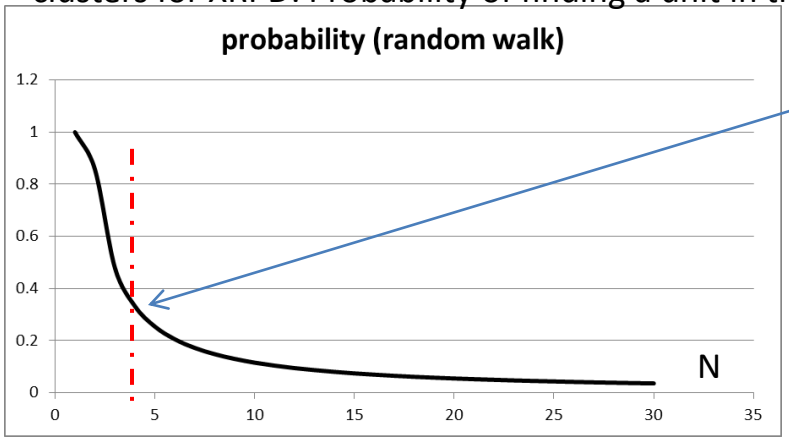


Half cone angle:: gamma
From self avoiding random walk

Cos(gamma) = (1/(N^(1-x))

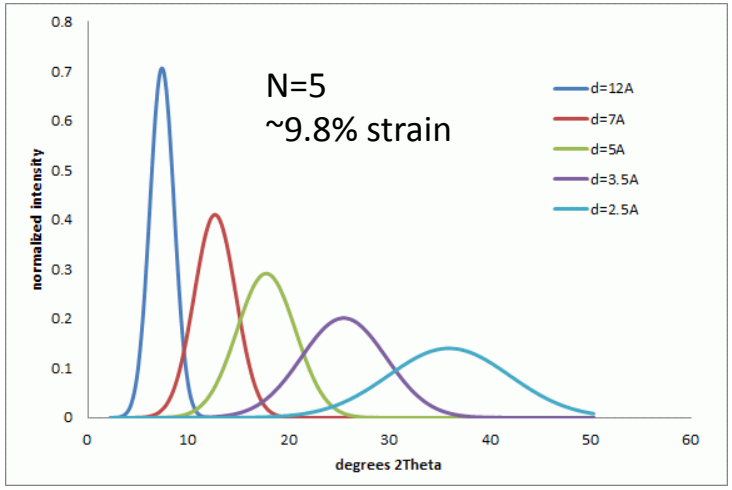
Where N is number of units and
(x) typically lies between 0.5 and 0.8

Evolution of gamma gives effective size limit to coherently diffracting clusters for XRPD: Probability of finding a unit in the correct place.



coherent limit ~ N d
Where N = number of units
and 'd' is size of packing unit

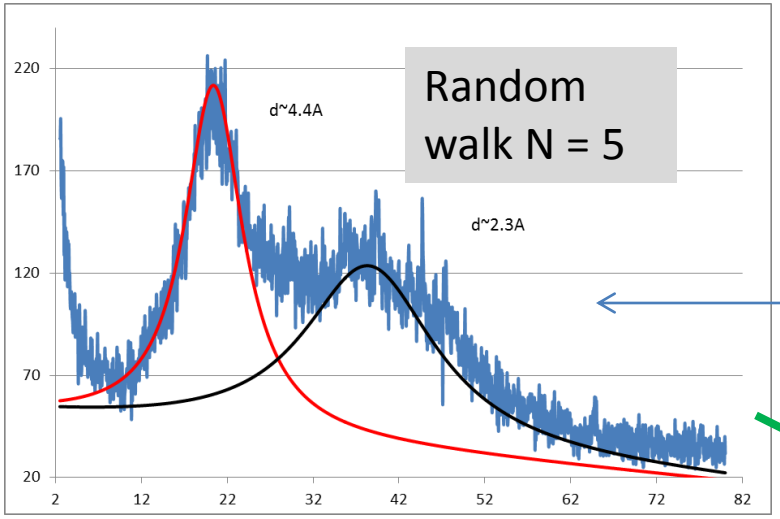
Scherrer equation
Peak_broadening ~ K λ/(N d cos(2θ)) (peak broadening in radians)



XRPD from a randomly close packed material will have a universal form where peak width is only a function of its position

Triclinic Labs

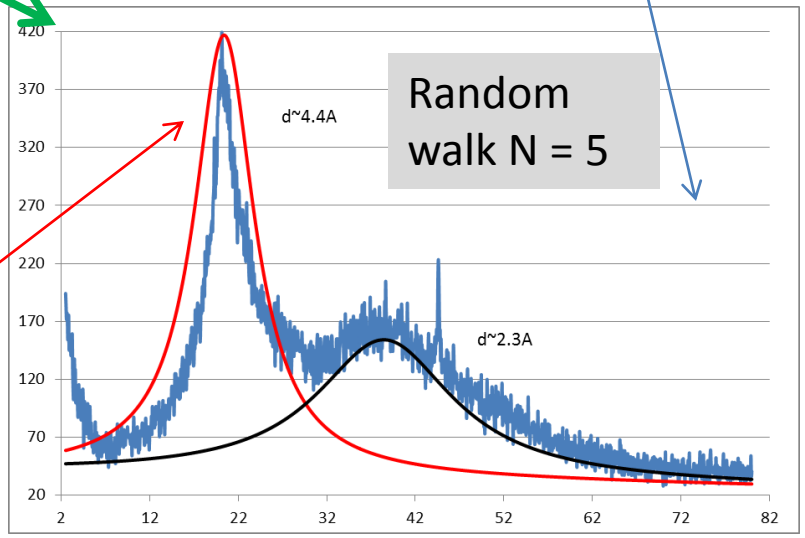
So XRPD patterns collected on randomly close packed systems will all look the same?



The universal nature of XRPD patterns from random systems is only with respect to the peak width as a function of peak position.

The actual peak position and peak area will be unique to the system of interest!

Change processing conditions



Crystalline materials also have a universal peak width determined by the instrument alone. For crystalline materials, peak broadening is related to 'micro-structure'.

Random materials also have a universal peak width where peak sharpening is related to 'micro-structure'.

Triclinic Labs

Are ‘amorphous’ forms that exhibit different ‘micro-structure’ and stabilities polyamorphic?

- Traditionally, changes in micro-structure are not consider to be new structural polymorphs.
  - The crystal structure is the thermodynamic state and any micro-structure is a ‘kinetic’ modification.
  - A kinetically modified crystal form can exhibit different physical and chemical properties like solubility but is not a new polymorph.

- For a glassy material, the super-cooled liquid is the underlying thermodynamic state.
  - Different glassy states with differing micro-structure and configurational entropy can be considered to be ‘kinetic’ modifications and may exhibit different physical and chemical properties.

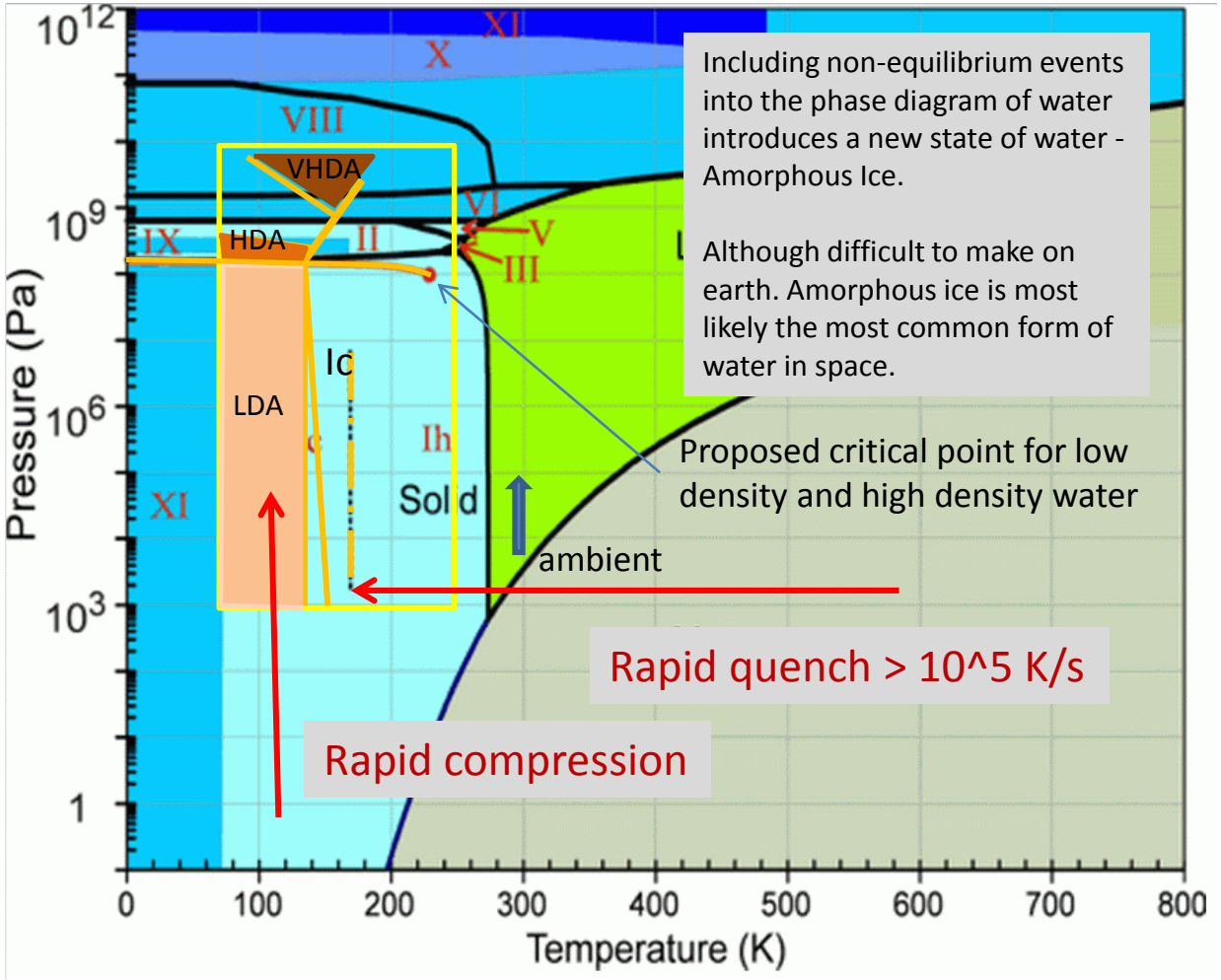
- One liquid form == One glassy form.
  - Water is believed to have 2 thermodynamic liquid forms and therefore can exhibit 2 glassy polymorphs.

Triclinic Labs

But water has more than 2 amorphous forms?

Water has many solid forms and at least 3 different X-ray amorphous forms: low density LDA, high density HDA, and very high density VHDA. LDA and HDA are considered to be glassy forms related to the proposed different low and high density water forms. VHDA is proposed to be a 'crushed' crystal form and often not considered to be a glass.

X-ray amorphous forms include any material where the mean structural coherence length is or the order of 5 basic units (e.g. atoms, molecules, unit cells). Includes: Liquids, Glasses, crushed Crystals (sometimes), Meso-phases (sometimes) and potentially very small Nano-crystals.



Triclinic Labs

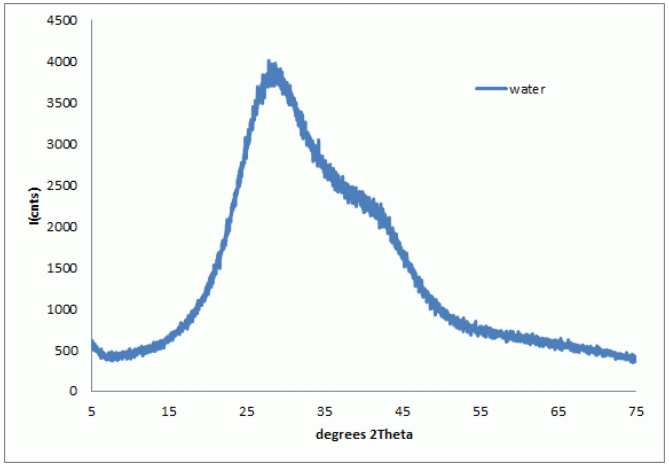
So how do we figure out which type of amorphous short range order we have?

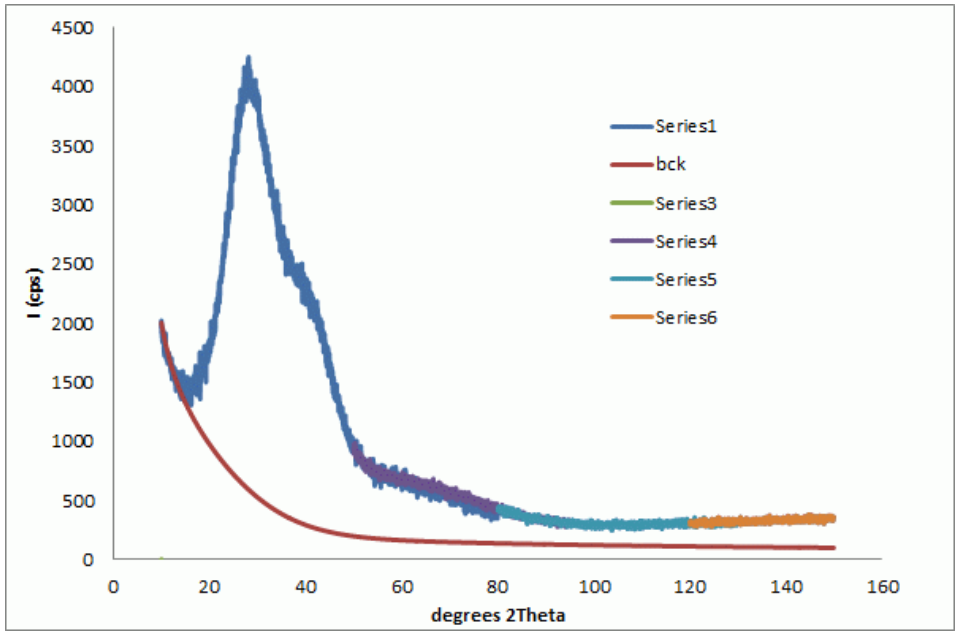
- The first step is to measure an appropriate XRPD pattern of the sample of interest.
  - Background at low angles → background at high angles.
  - You can use a larger step size 0.08 → 1.2 degrees 2Theta (Cu Kalpha)
  - Most important is to increase count time (> 4 – 10 seconds per point)
- Next step is to isolate the "Total Diffraction Response" from the sample by removing a calibrated instrumental background and binning the data to maximize information content per point.
  - When performing detailed PDF modeling, the background may need to be refined during the modeling.
- At this point, we can perform either direct analysis of the data or indirect analysis via a molecular model.

Triclinic Labs

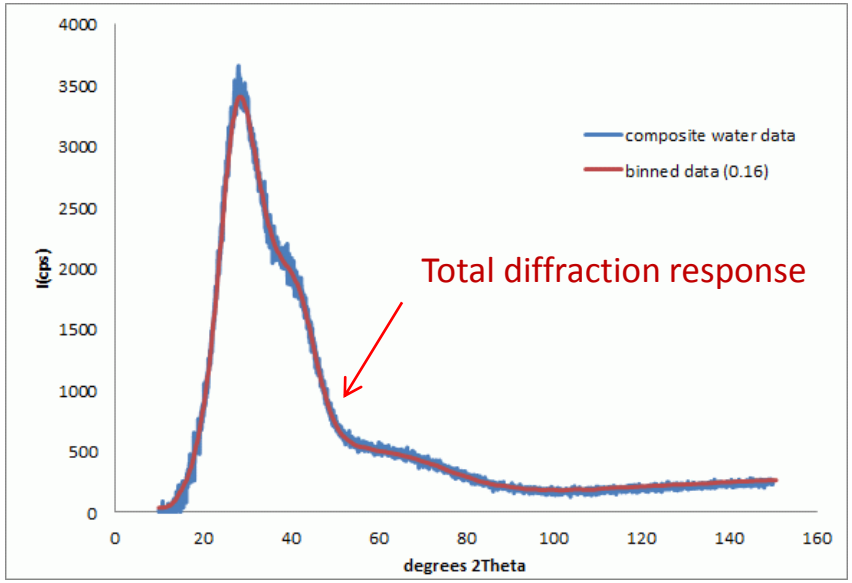
Examples of measured data for liquid water and data pre-processing

Typically, a measurement range of 2.0 → 80 degrees 2Theta is used (Cu Kalpha). For more accurate PDF type work, measurements to higher angles may be needed. Data collected at higher angles require longer count times.



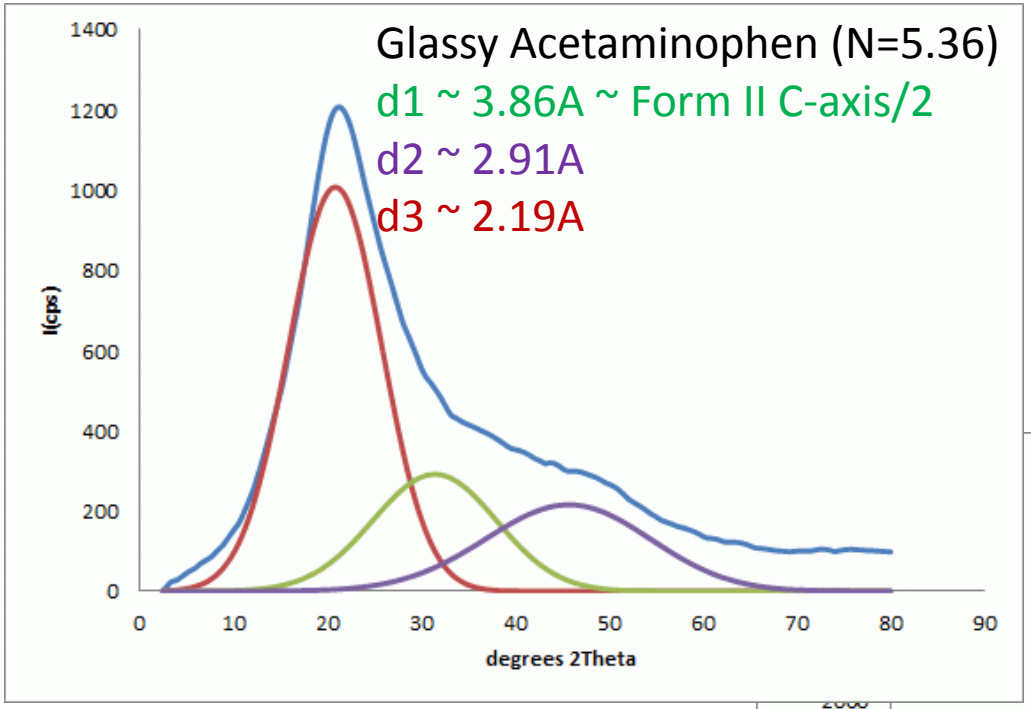


Data binning removes data points leaving only those required to define the XRPD pattern. Maximize information content per data point.

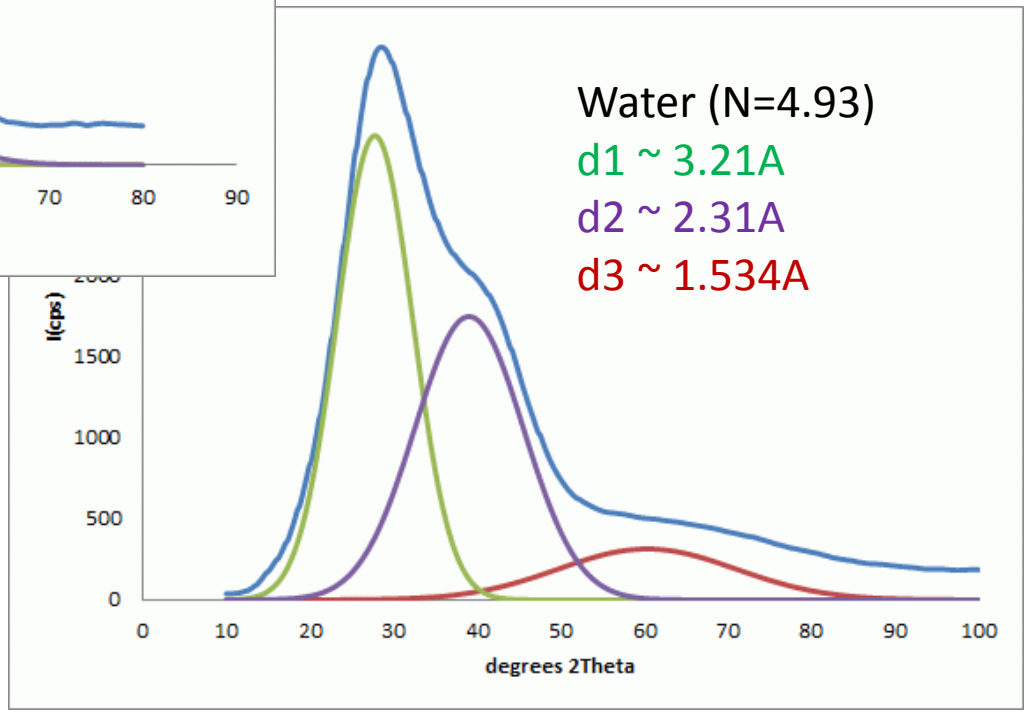


Triclinic Labs

Direct Analysis based upon universal random material halo shape



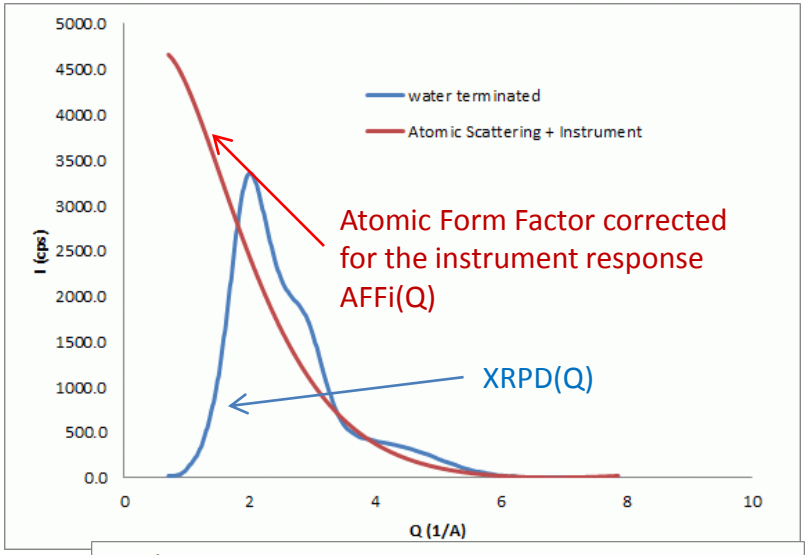
The universal peak width variation allows a measured XRPD pattern to be directly split into a number of discreet halos, each with their unique ‘d’ value.



The value of ‘N’ is the number of ‘units’ that are coherently related within the random close packing. N is an index of the degree of local order.

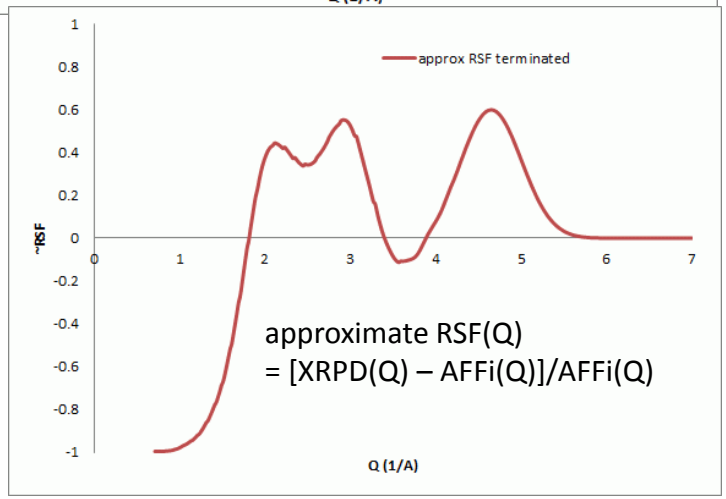
Triclinic Labs

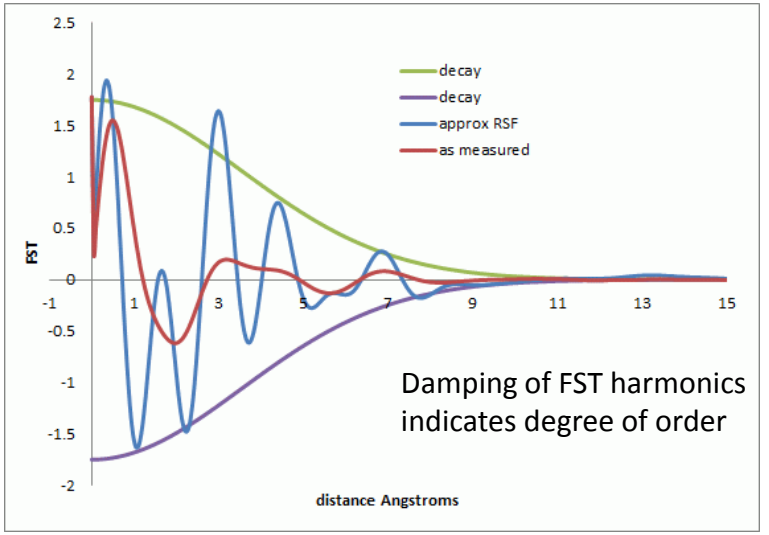
Direct analysis using the Fourier Sine Transform FST (poor man's PDF)



The direct FST approach uses the same Fourier transform as used to derive a PDF but is performed either on the terminated measured data or for better results the terminated approximate RSF.

$$FST1(d) = 2\ im[FT\{Q\ \Delta Q\ XRPD(Q)\}] / \pi$$
$$FST2(d) = 2\ im[FT\{Q\ \Delta Q\ RSF(Q)\}] / \pi$$



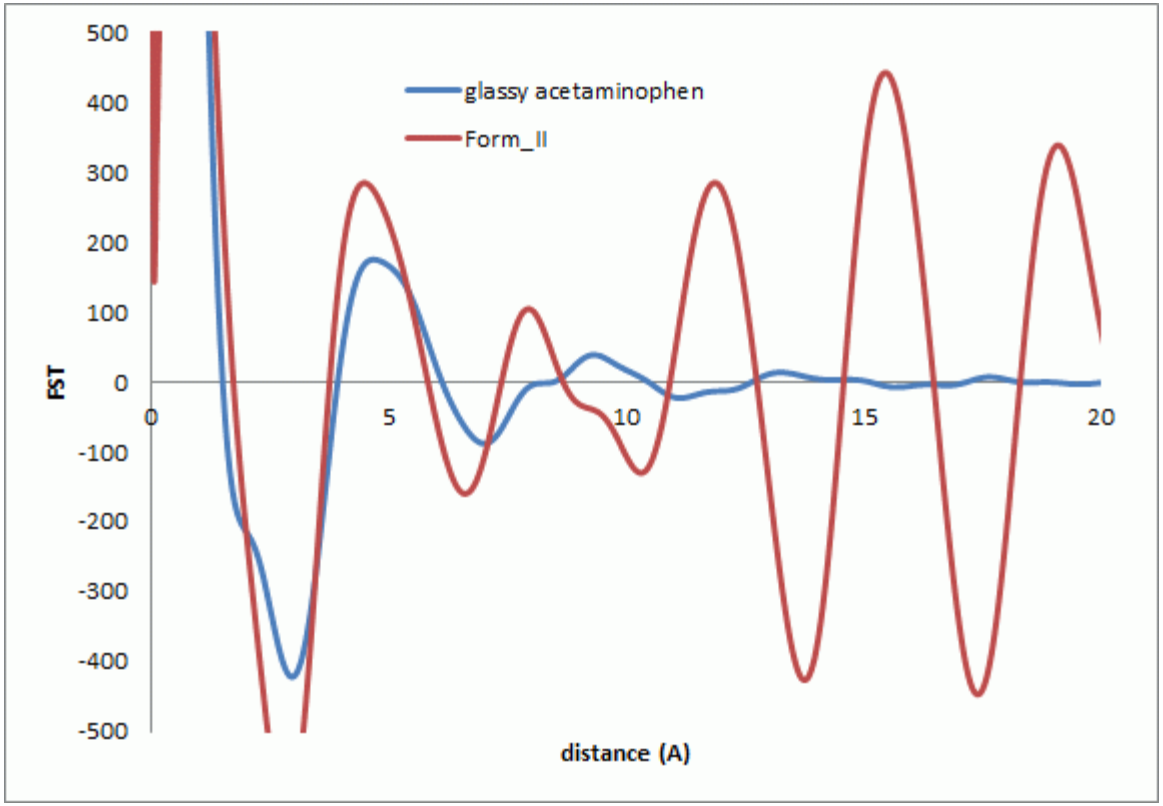


Triclinic Labs

Can the FST be used to match the local structure in an amorphous material to a polymorph?

FST calculated from measured powder patterns of glassy acetaminophen and crystalline Form II

The FST performed directly on the terminated total diffraction response can be used to give some indication as to whether a crystalline polymorph may provide a good description of the local amorphous order



Triclinic Labs

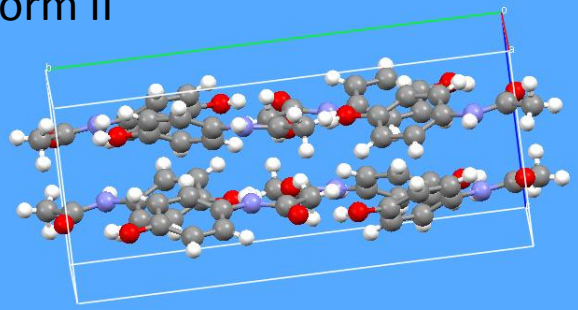
Indirect modeling methods require a molecular model of the proposed local structure.

- Within the spirit of the crystalline and liquid reference structures, the molecular models of local order for X-ray amorphous systems can be built up as either:
  - Kinetically modified crystalline solid (random defects → reduced long range order) (Low T model)
  - Kinetically modified liquid (super-cooled → glassy) (High T model)
- Once a model has been defined, the XRPD response has to calculated:
  - Modified Debye method (Menke modification: James p496)
  - PDF approach
  - Integration over Q space approach

Triclinic Labs

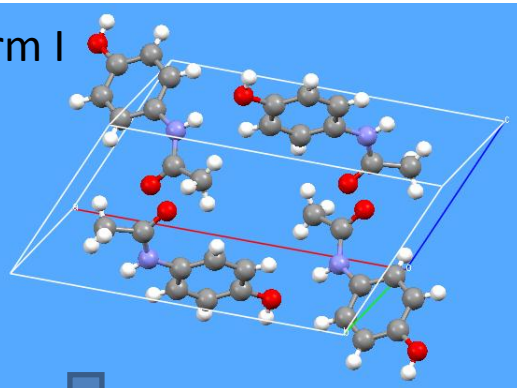
Using known crystal structures as a starting point for local amorphous structure

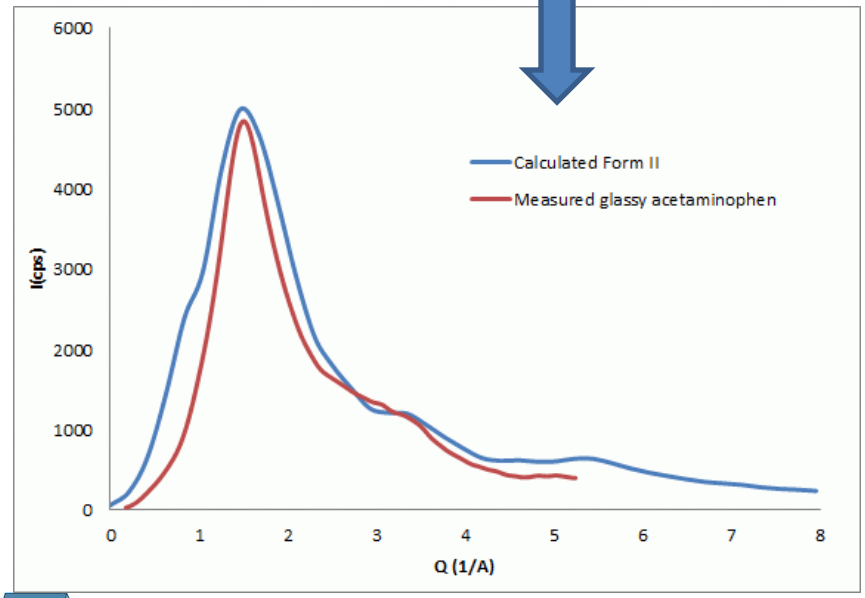
Form II

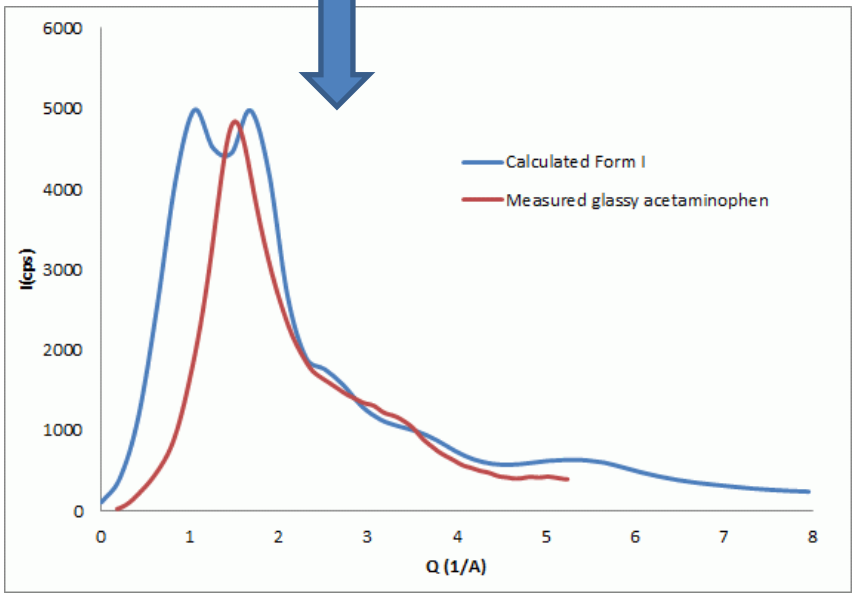


Acetaminophen: XRPD calculated via a smeared PDF to simulate kinetic disorder

Form I





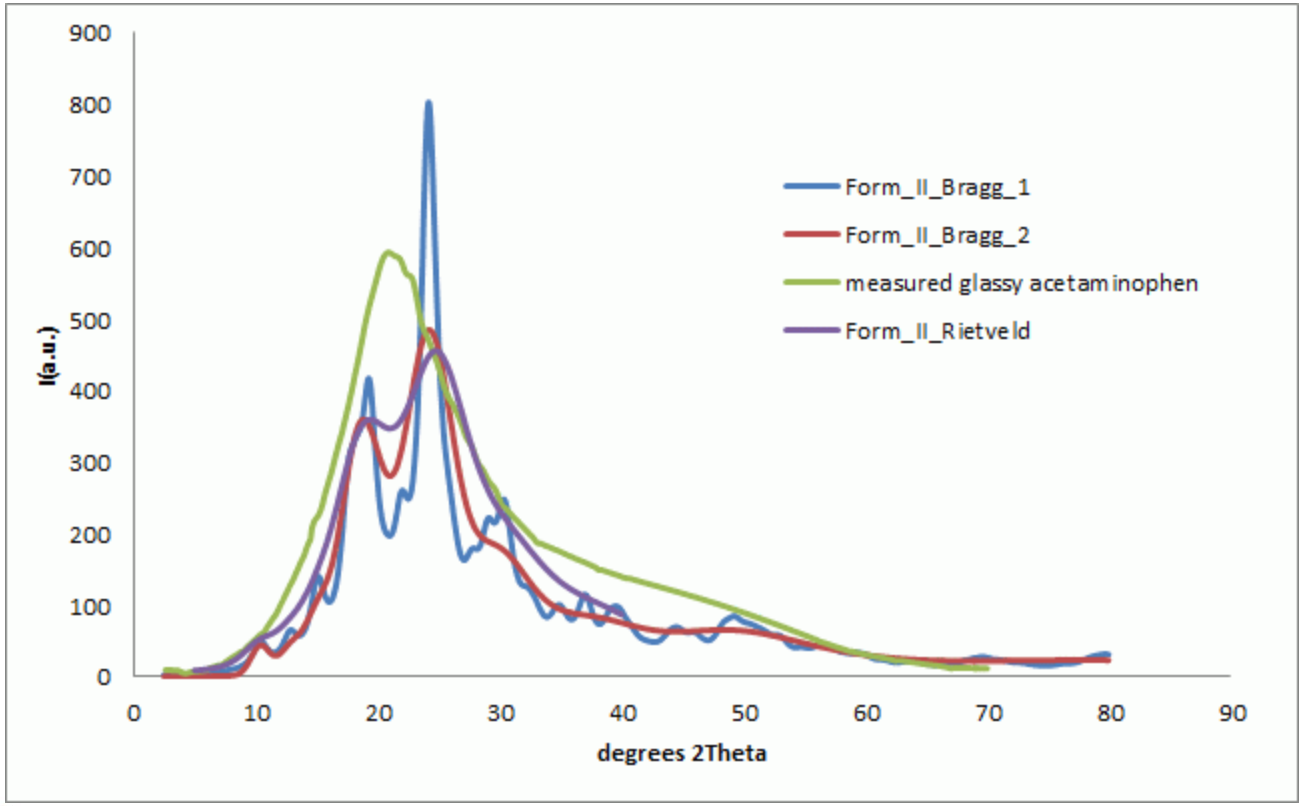


Triclinic Labs

Why can't I simply use a Rietveld program or Bragg calculation program?

Bragg calculations including Rietveld programs rely on a discreet structure factor that is only derived at the 'Bragg' position itself. Much of the profile shape in X-ray amorphous powder patterns cannot be reproduced unless a continuous structure factor is used.

Attempts to model the X-ray amorphous profile of acetaminophen using Bragg type calculations. In the Rietveld approach, the crystal structure must not be refined.



Triclinic Labs

The low T model for local structure for amorphous material: results

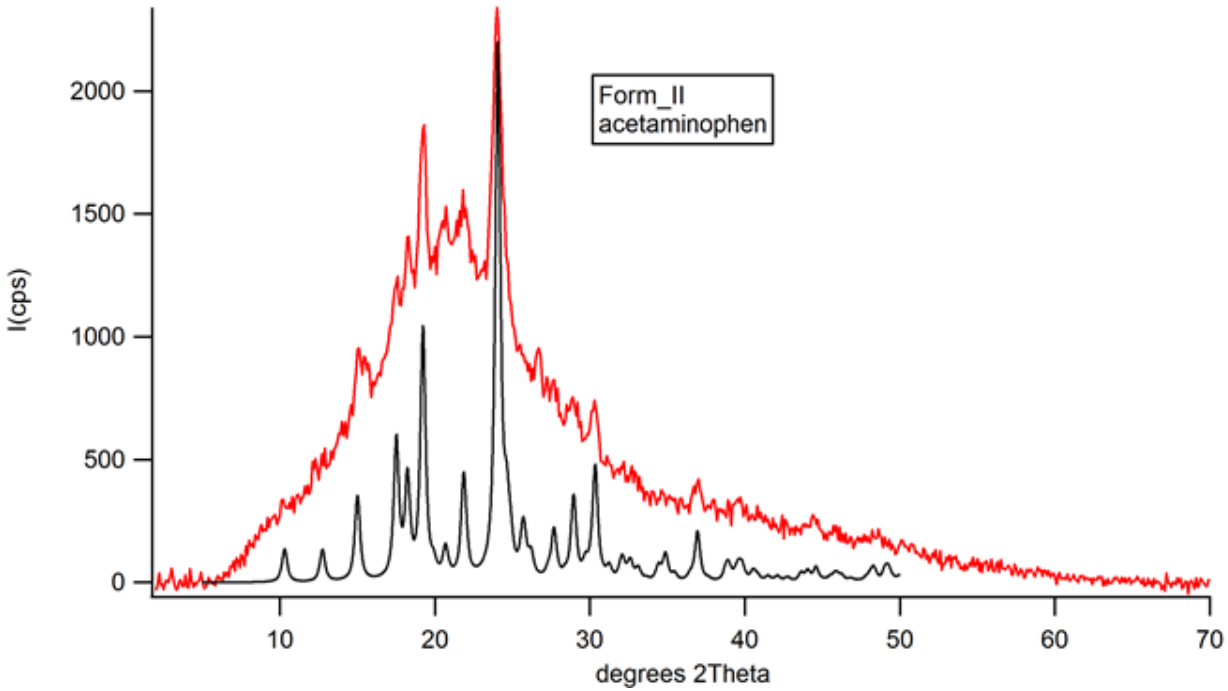
- The low T modeling has no variable parameters other than the kinetic microstructure (degree of disorder).
- Calculated XRPD patterns either match measured data or they do not match measured data.
- Rietveld type modeling may not give meaningful results due to the discreet structure factor used for Bragg calculations.

- After modeling a plethora of organic X-ray amorphous materials about 50% to 60% have XRPD patterns that can be adequately described by assuming that the local structure is a disordered variant of a crystalline polymorph.
  - The High temperature/pressure form is always the polymorph with the closest match

Triclinic Labs

And why is that important to me?

If the local structure in the X-ray amorphous phase is related to a crystalline polymorph, then the local packing minima may act as seeds. From the random walk model, these local minima may be 10's of nm in extent and contain a few hundred small molecules. (XRPD observes a reduced coherence length of ~2nm).



When glassy acetaminophen re-crystallizes, it generally goes to Form II if the glass is not perturbed mechanically.

Is this a violation of Ostwald's rule?

Triclinic Labs

How do we model the local structure from the perspective of a frozen liquid?

- Coherent XRPD will only contain information on the mean correlated structure within the sample. The X-ray amorphous powder pattern will be a fingerprint of the local structure that is common to the various local minima.

- For a small rigid molecule like acetaminophen, the smallest coherent unit is a single molecule.

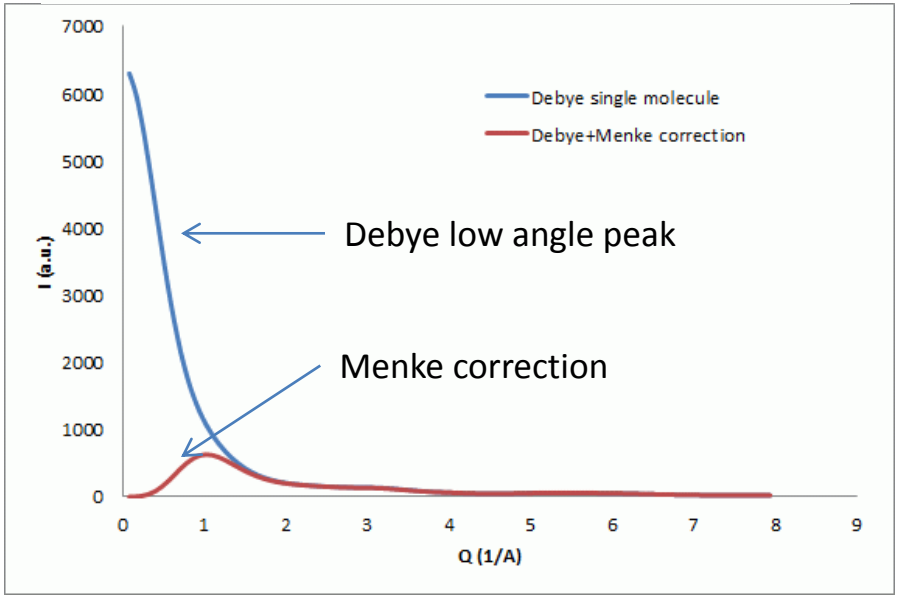
- As a first pass, let's assume that the structure of glassy acetaminophen consists of randomly packed single molecules.

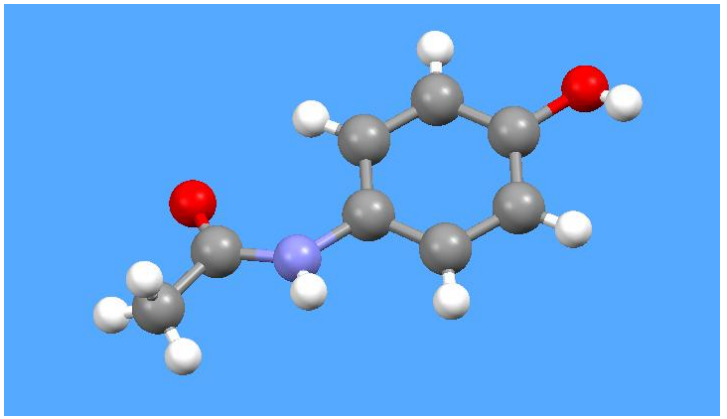
Triclinic Labs

How do we calculate the coherent XRPD profile for a single molecule?

The text book approach to calculating the XRPD profile for a liquid is to use the Debye equation to give the Debye Intensity :

$$I_{DM} = \sum_i F_i^2 + 2\sum_i \sum_{j \neq i} F_i F_j \sin(Q.d_{ij})/(Q.d_{ij})$$





The Debye calculation gives a huge peak at low angles due to the 'shape' of the molecule. (Mean electron density distribution)

The Menke modification to the Debye theory is one path to approximately remove the 'shape' effect.

$$I_{shape} = (N-1)\sum_i \sum_j F_i F_j \left[\sin(Q.l_i)/(Q.l_i)\right]\left[\sin(Q.l_j)/(Q.l_j)\right]$$

Triclinic Labs

What is the ‘shape’ effect and how to remove it?

Applying the Debye formula to a single molecule is equivalent to modeling an ideal gas where the molecule is in free space. For liquid and glassy materials, the molecule must be modeled within a high density matrix of other molecules. Within a high density matrix, the ‘shape’ of the molecule is no longer an abrupt change in electron density.

Calculation of a PDF from a molecular structure has the mean electron density matrix correction built in. One derivation of a PDF for XRPD work is as follows:

$$RDF(r) = F0_a \, F0_b \sum_{1}^{Na} \sum_{1}^{Nb} \delta(|r_{ab}| - r)$$

$$M(r) = 4 \pi r^2 \Delta r \, N_0$$

$$PDF(r) = (RDF(r) - M(r))/M(r)$$

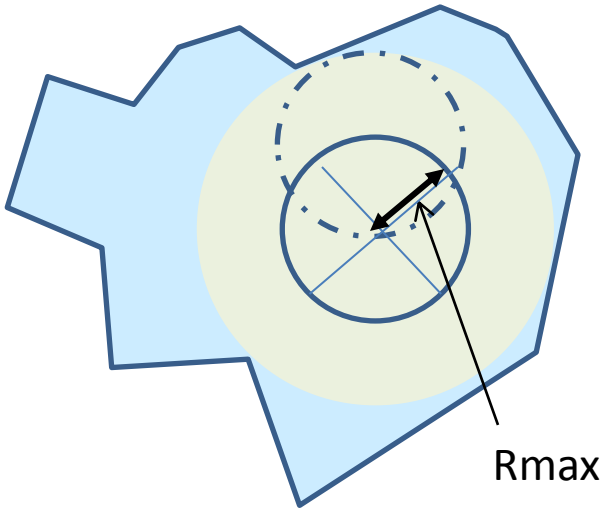
M(r) is the mean density matrix response - The only unknown term is the appropriate number density ‘N0’, which depends on how the RDF(r) has been defined.

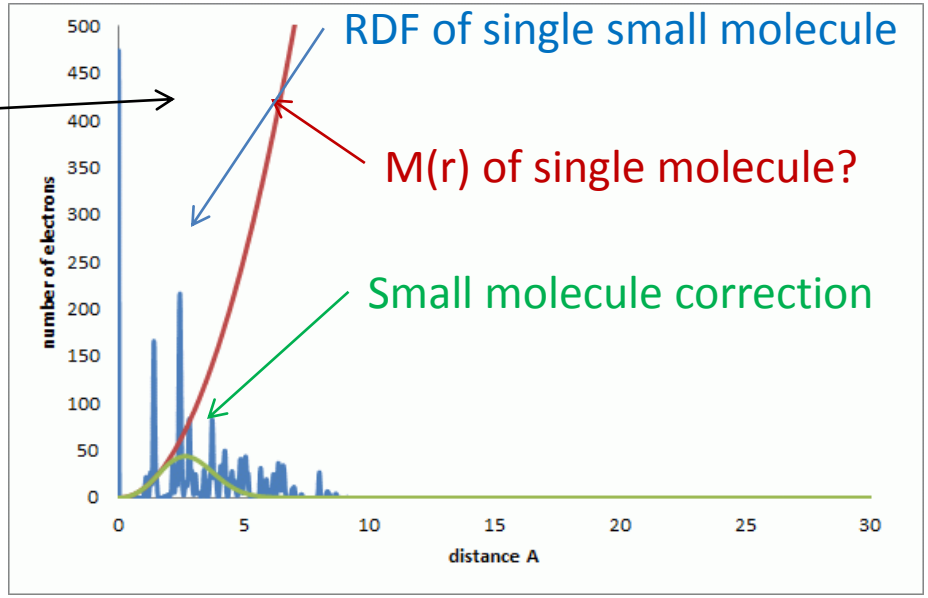
Triclinic Labs

So how do we derive the appropriate number density to make the matrix correction?

For a single molecule, the textbook number density matrix correction cannot be applied.

The very small size of the molecule leaves the pair-pair coordination shells only partially occupied

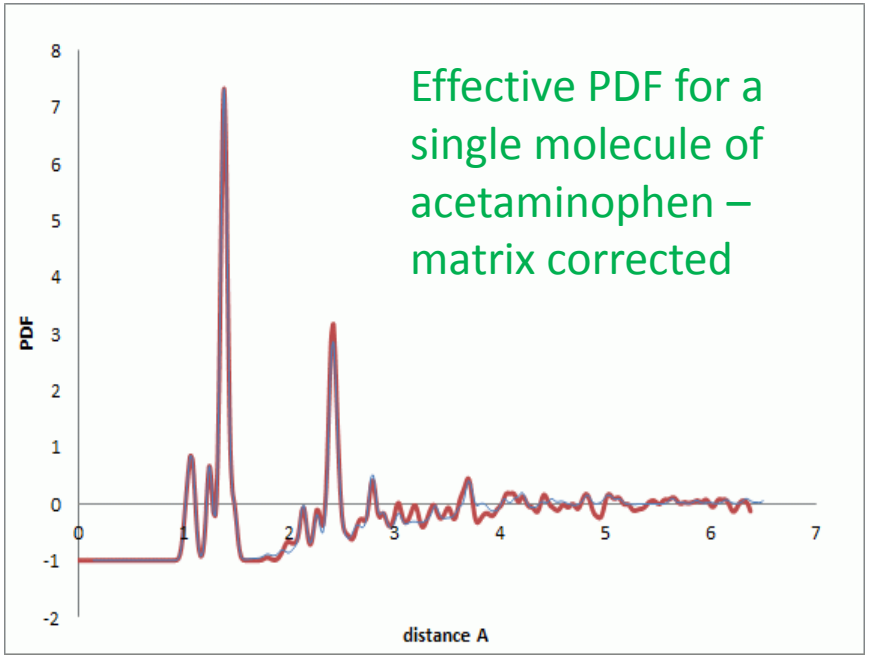


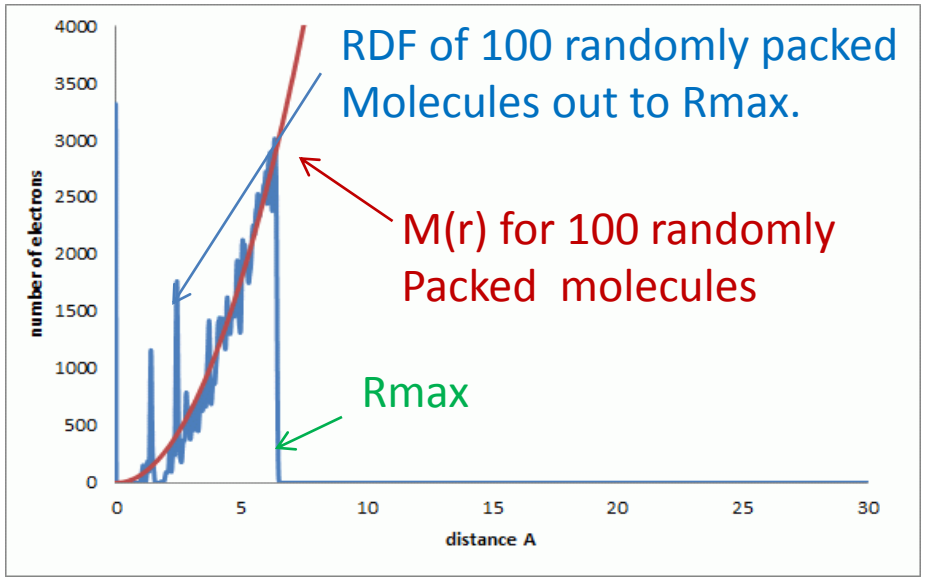


Need to create a much larger ensemble of molecules by randomly packing the single molecule. The random ensemble will have an Rmax within which all molecules will have fully occupied pair-pair coordination spheres. (Can use Packmol)

Triclinic Labs

With the appropriate number density, an effective PDF for a single molecule can be derived





The inverse Fourier sine transform can now be used to transform the effective PDF into an X-ray scattering function for our single molecule of acetaminophen.

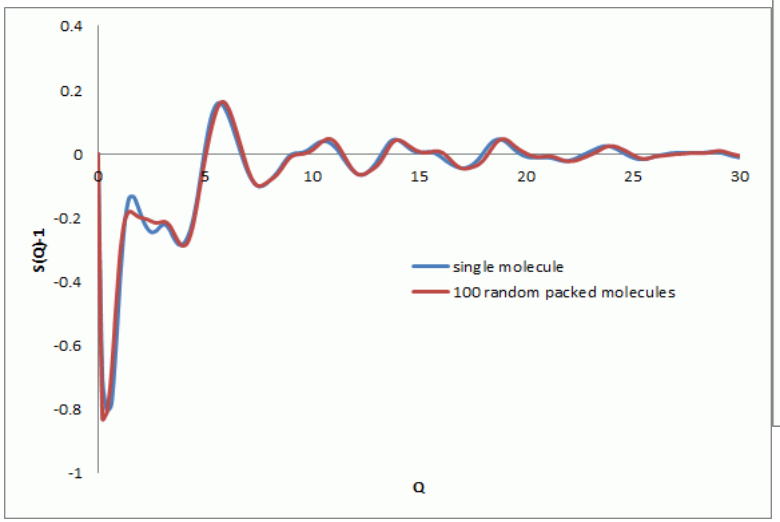
Triclinic Labs

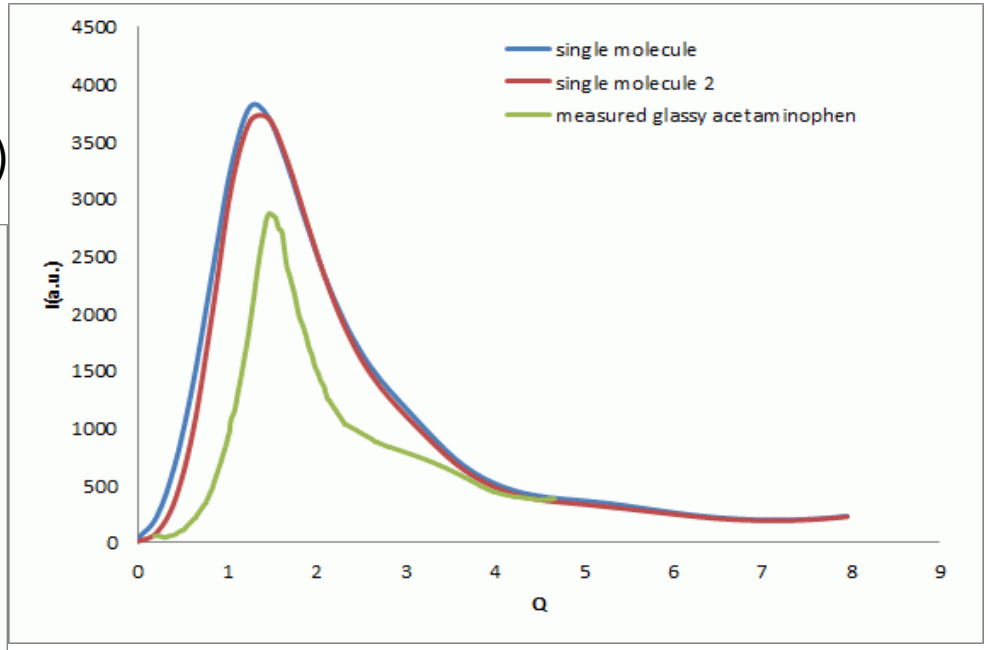
So what does the calculated XRPD pattern for a single molecule look like?

The inverse Fourier sine transform of the PDF gives us the reduced structure factor and the coherent scattering function S(Q). The instrument function needs to be applied to S(Q) before a comparison can be made to the measured data.

$Q\,(S(Q)-1) = \mathrm{im}[FT\{\Delta d\ PDF(r)\}]$

XRPD(Q) ~ InstrumentFunction x S(Q)





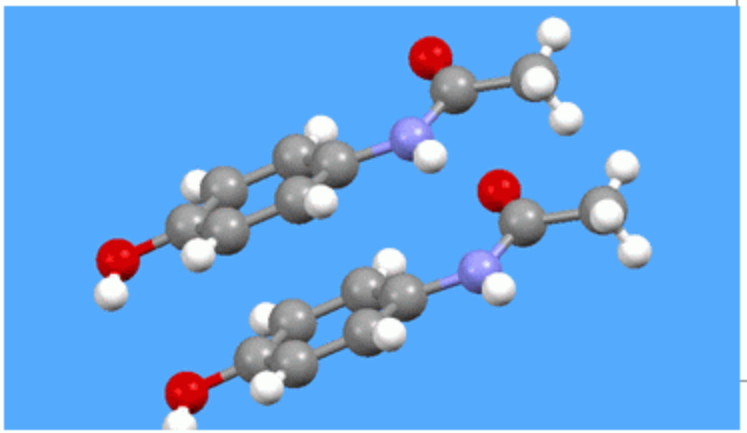
The single molecule XRPD pattern is too broad and is not representative of the measured data

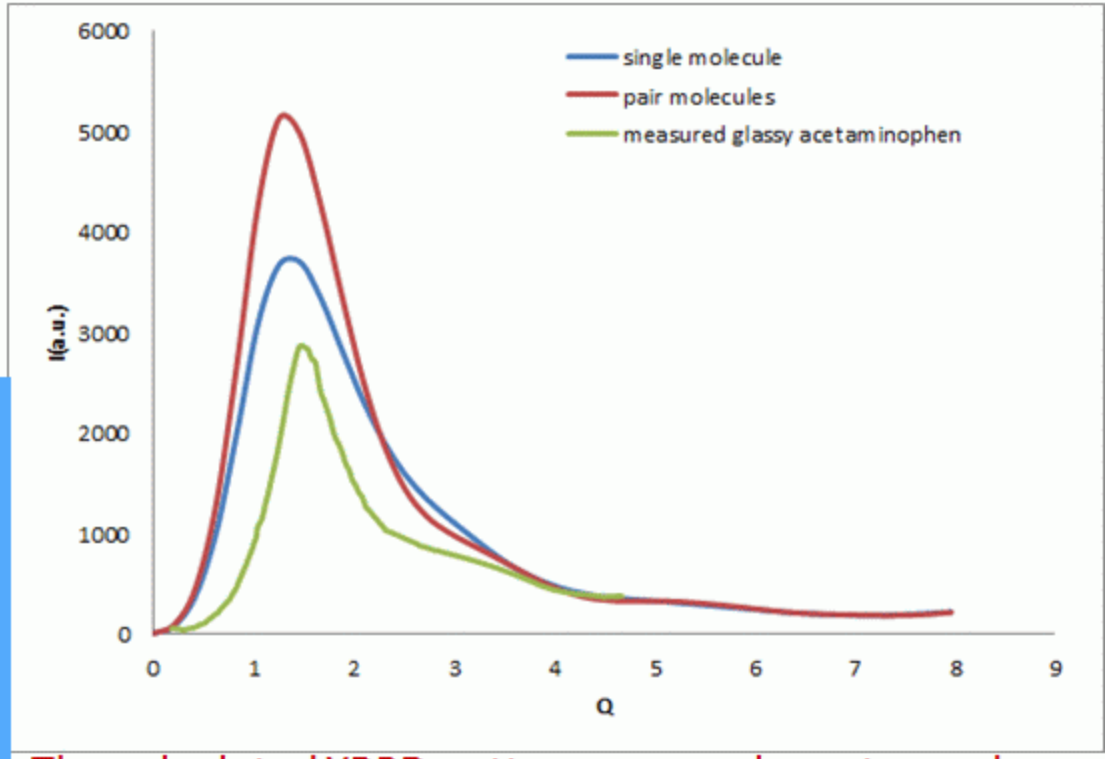
Triclinic Labs

Glassy acetaminophen is more complex than random single molecules – what is the structure?

The next step is either to build and pack more complex local structures or try to extract the local structure directly.

To illustrate both approaches, two molecules stacked using a simple translation of ~3.7A normal to the ring group form the next guess as to the local structure





The calculated XRPD pattern moves closer towards the measured data but is still not representative.

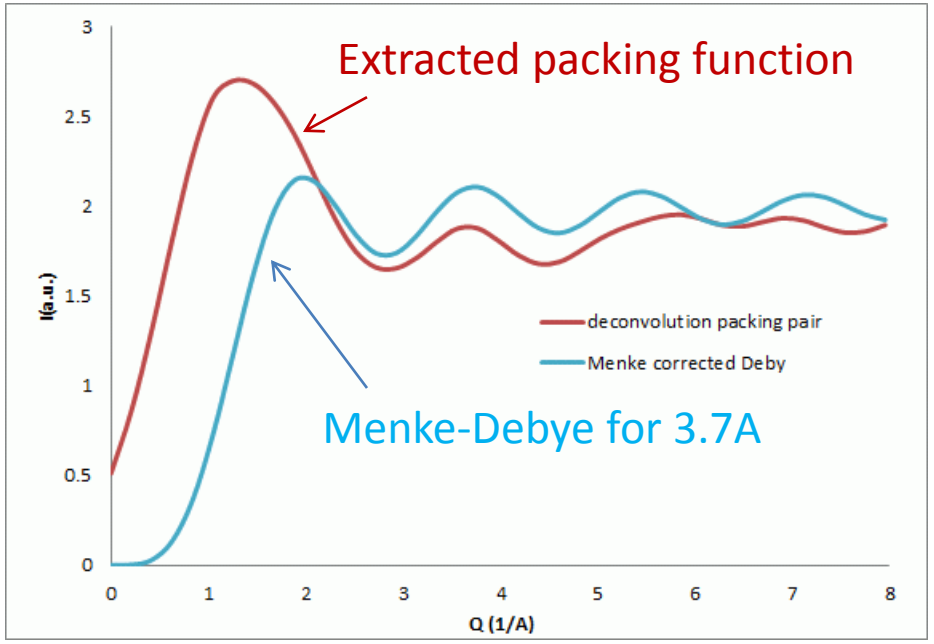
Triclinic Labs

Direct extraction of the finger print for complex local order

The simple molecule pair can be expressed mathematically as a single molecule convoluted with 2 delta functions. The delta functions correspond to the center positions of each molecule.

Structure(r) = molecule X (δ(a – r) + δ(b – r))
Calculating the scattering function using a Fourier transform
S(Q) = $|FT\{\text{molecule}\}|^2$ $|FT\{\delta(a - r) + \delta(b - r)\}|^2$
$|FT\{\text{molecule}\}|^2$ = single molecule scattering function

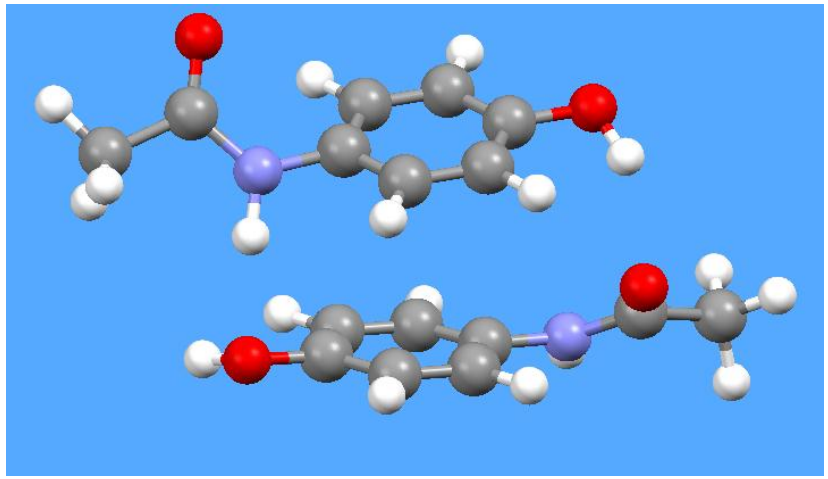
So dividing the scattering function of the pair of molecules by the scattering function of the single molecule should give the scattering function corresponding to the local packing function



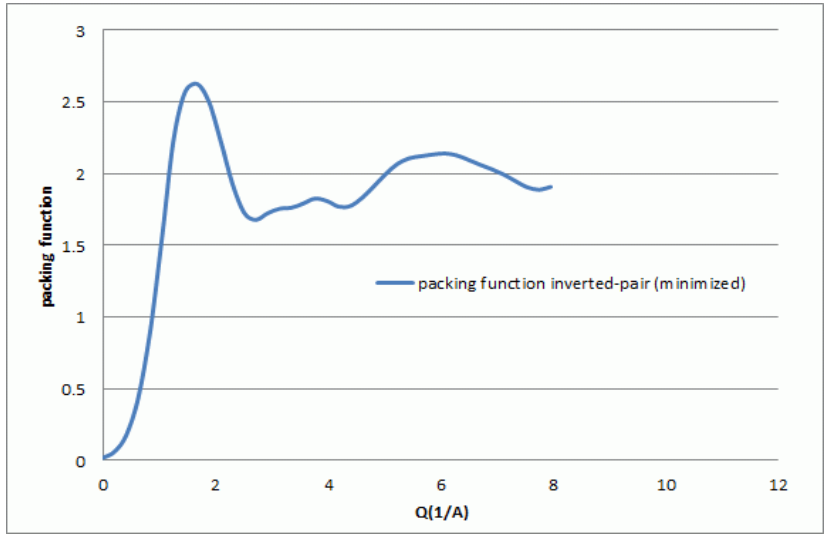
Triclinic Labs

Energy minimization used to derive more realistic packing clusters

Minimization of the packing energy for pairs of molecules (Tinker) gives essentially a single high density packing solution. This is an inverted pair packing with the ring groups packed on top of each other along the packing direction.



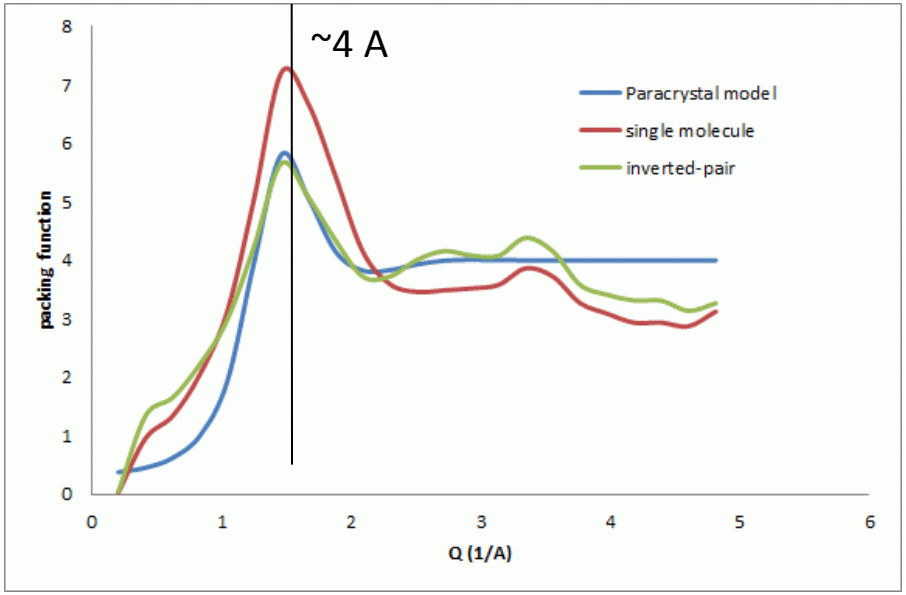
Calculating the scattering function for the inverted pair and then dividing through by the single molecule scattering function allows the packing function to be extracted.

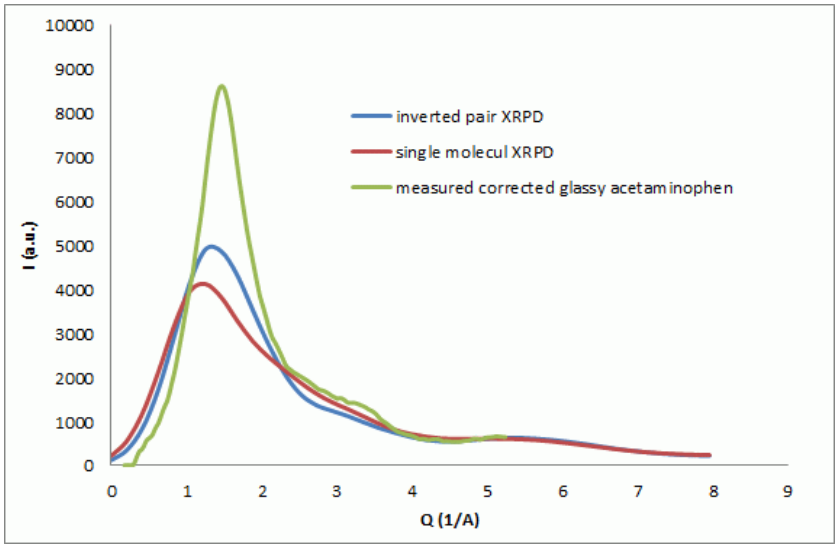


Triclinic Labs

Can the packing function corresponding to the measured glassy acetaminophen be extracted?

Before any modeling of the measured data can be performed, the measured data must be corrected to remove the instrumental artifacts and isolate the coherent diffraction response only.



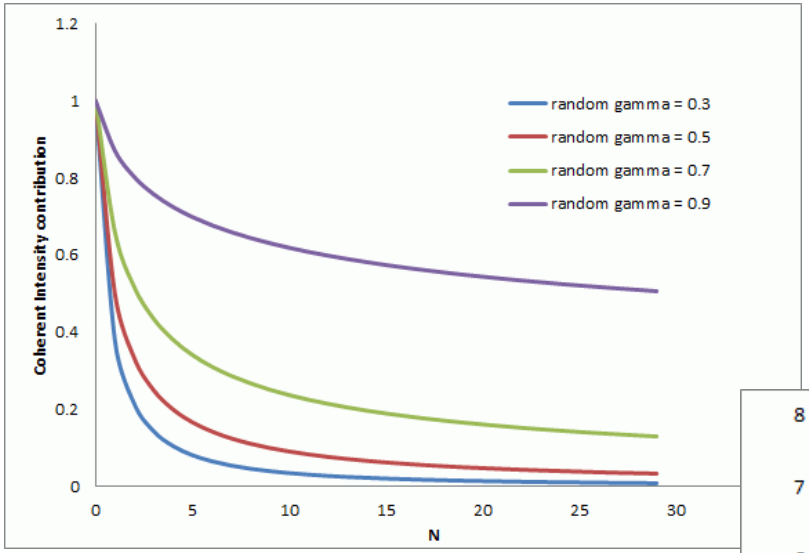


The packing function extracted for glassy acetaminophen using the inverted pair as the basic unit can be described by a para-crystalline function.

The local structure in glassy acetaminophen can be described as a para-crystalline type packing of inverted pairs of molecules.

Triclinic Labs

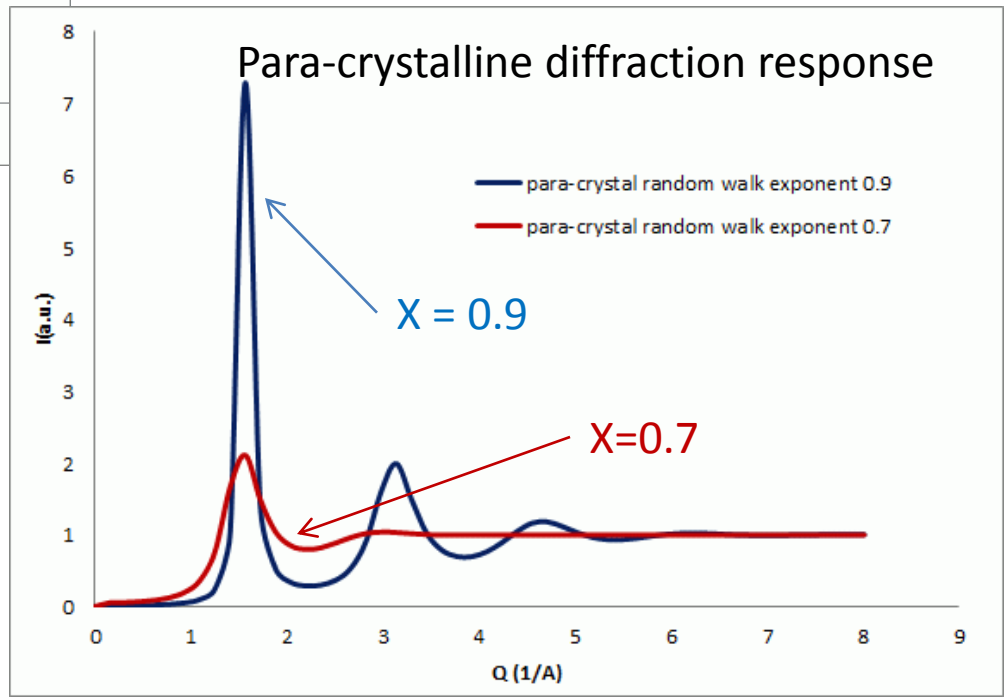
What has para-crystalline got to do with X-ray amorphous materials?



A para-crystalline lattice is one where along a specific lattice direction the disorder increases for each molecule you move away from any starting molecule – similar to a random walk.

The random walk gamma exponent can be used to define disorder in the para-crystalline lattice:

Cos(gamma) = 1(N^(1-X))
X is the gamma exponent

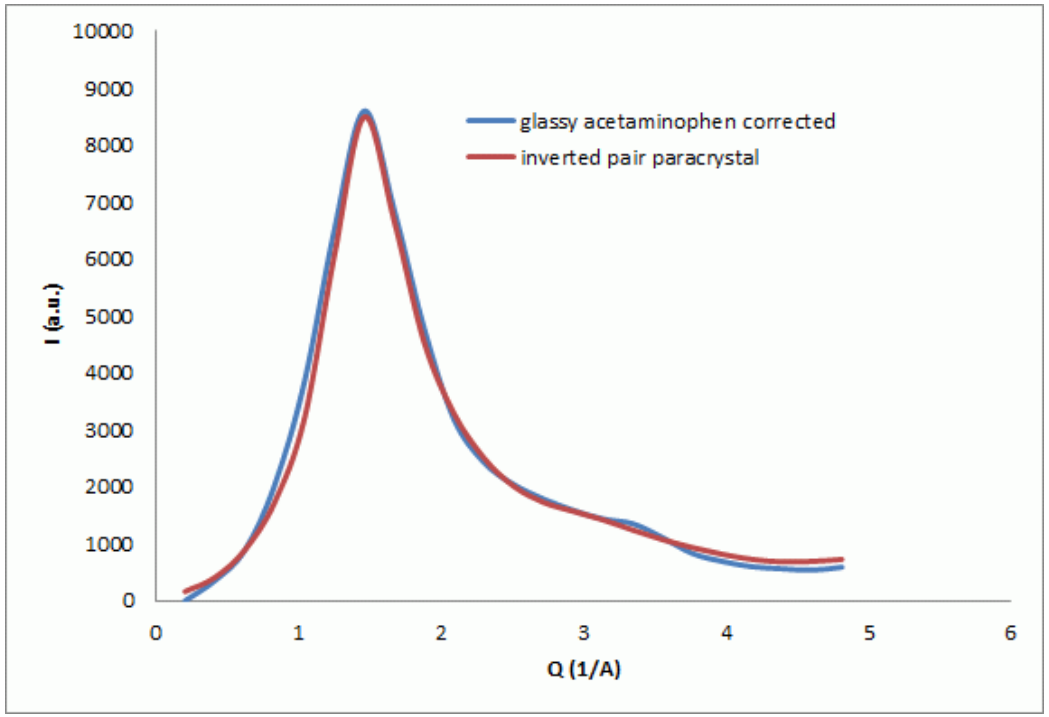


Triclinic Labs

Para-crystalline model + scattering function of basic unit can be used for direct modeling.

Glassy data is well described by the inverted-pair scattering including the para-crystalline scattering. About 40% of the intensity is due to inverted-pairs. The para-crystalline ‘d’ value ~ 4.01Å

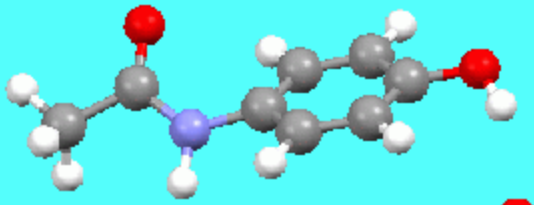
Now we have 2 reasonable models for glassy acetaminophen. One based upon the Form II polymorph and the other based upon a super cooler liquid



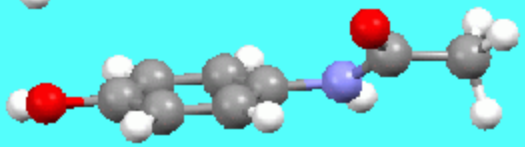
Triclinic Labs

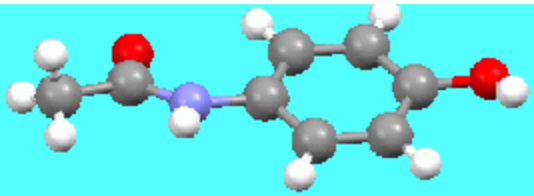
So which one is it, a kinetically modified liquid or a kinetically modified Form II?

Both the Form II crystal structure and the super cooled liquid have an inverted pair of molecules as their essential structural motif

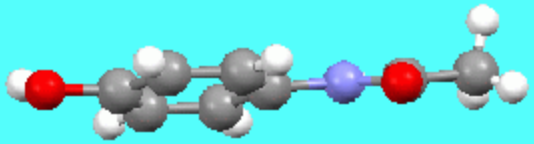


Liquid model





Form II



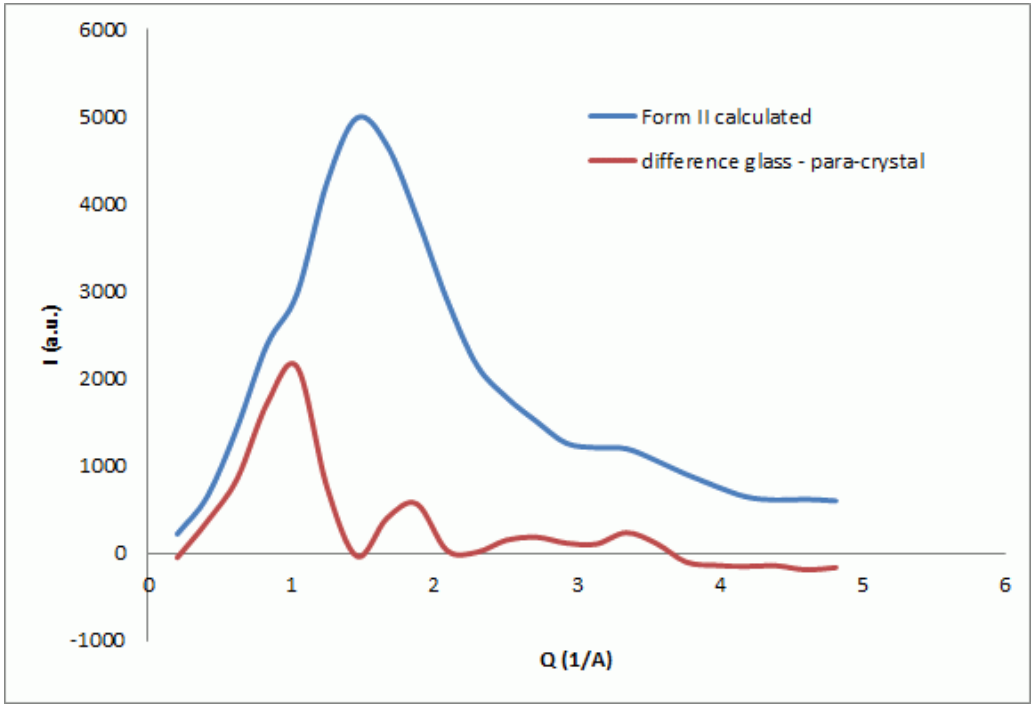
Within the coherence length probed by X-ray's for random materials, the dominant local structure is stacked inverted pairs.

Triclinic Labs

But which one is correct – Form II or Liquid?

Closer inspection of the calculated para-crystalline response for the inverted pair indicates that some components of the measured glassy data are not well described

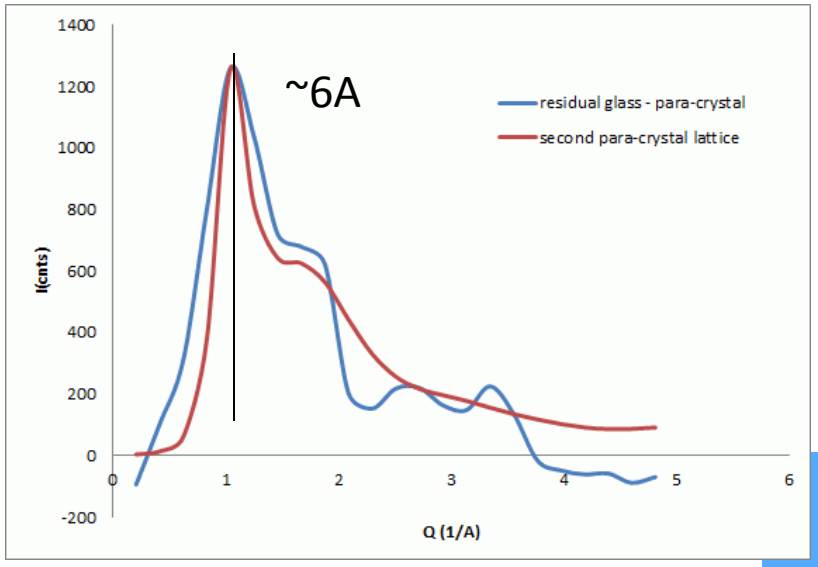
Plotting the difference between the glassy data and the calculated inverted-pair para-crystal against the calculated Form II pattern clearly demonstrates that the additional observed components are present in the Form II calculation



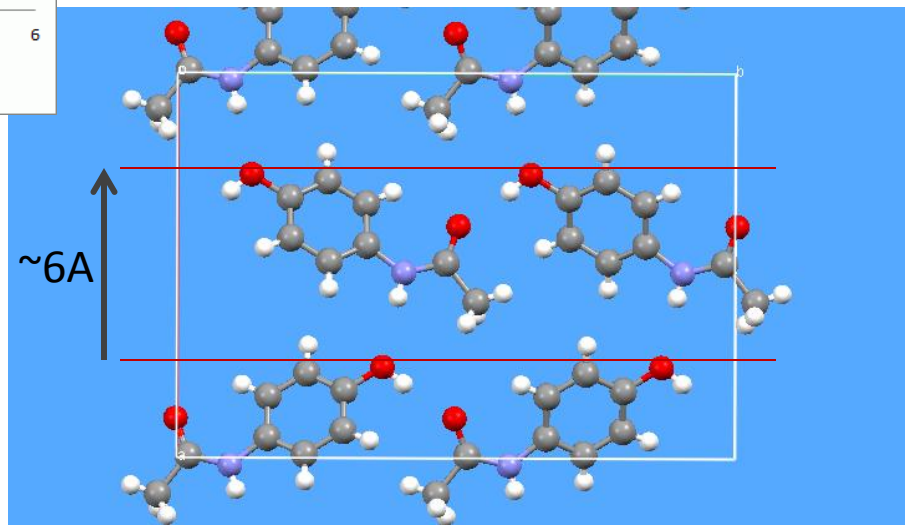
For acetaminophen, the Form II crystal structure provides the best available description of the measured glassy data. With the inverted-pair stackc hydrogen bonding to the neighboring stacks.

Triclinic Labs

Which additional structure from Form II describes the residual intensity?



The residual intensity can be described by a second para-crystalline lattice running normal to the inverted-pair stacks with an effective ‘d’ value of about 6Å.



An effective ‘d’ value of about 6Å is close to half the a-axis length for the Form II crystal structure and represents the closest packing for the inverted pair stacks.

Triclinic Labs

How doe we derive a ‘true’ PDF from laboratory data?

- The PDF method is usually used to either compare experimental data to a molecular model or to directly derive quantitative information concerning atomic/molecular coordination and local structure.
- Any approach that directly compares theory to experiment demands extensive corrections be applied to the measured data to carefully and precisely extract the coherent (total) diffraction profile.
  - Atomic Form Factor + Compton Scattering
  - Instrument intensity function
  - Instrumental background function.
  - Absorption by sample
  - Multiple Scattering by sample
- Corrections are applied iteratively using a recursive procedure where results are constrained to lie within theoretical limits to behavior.

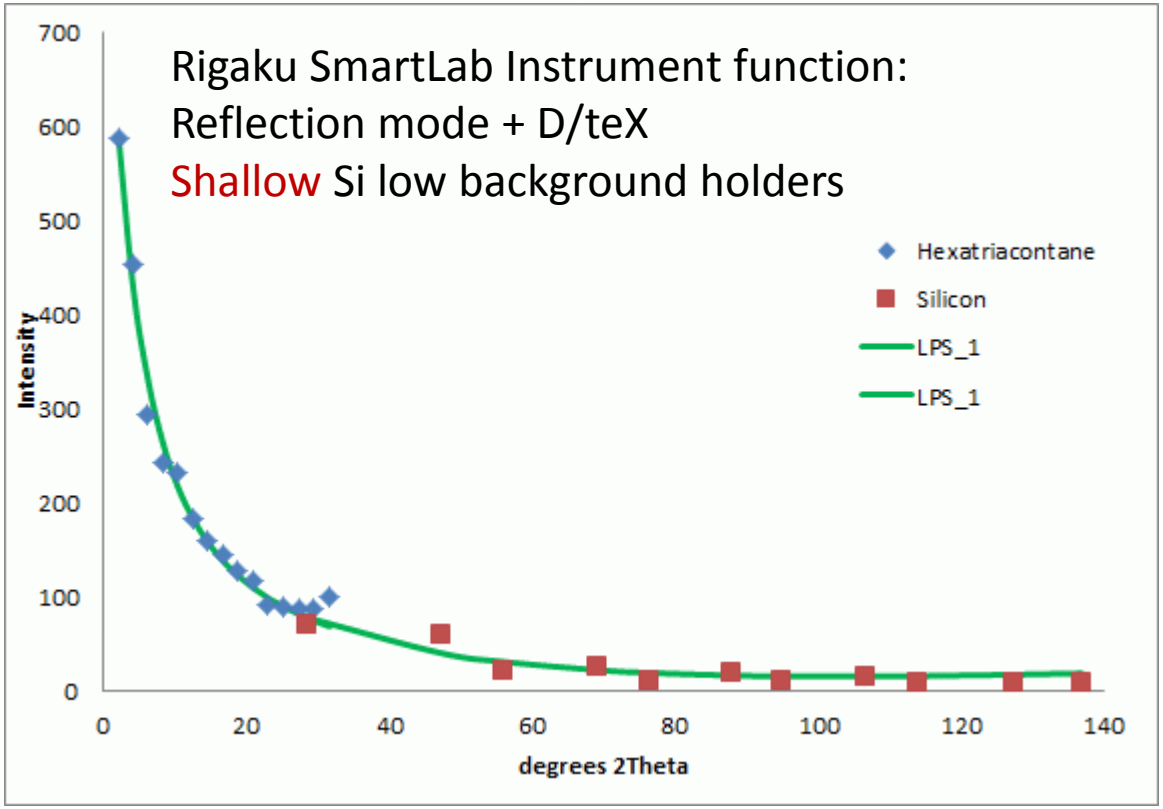
Triclinic Labs

How do you determine what is an appropriate instrumental intensity correction?

Instrumental intensity function:

- Lorentz Factor
  ~ sin(θ)^(-Y)
- Polarization Factor
  ~[1+cos(2θ)^2]/2
- Optical shadow factor
  ~[1+atan(Z*(Q-2π/X))/1.5]/2

Measuring a standard material with known structure factors allows removal of the atomic form factor contribution.
Remaining intensity variation is due to instrument response for the sample holder being used.



Triclinic Labs

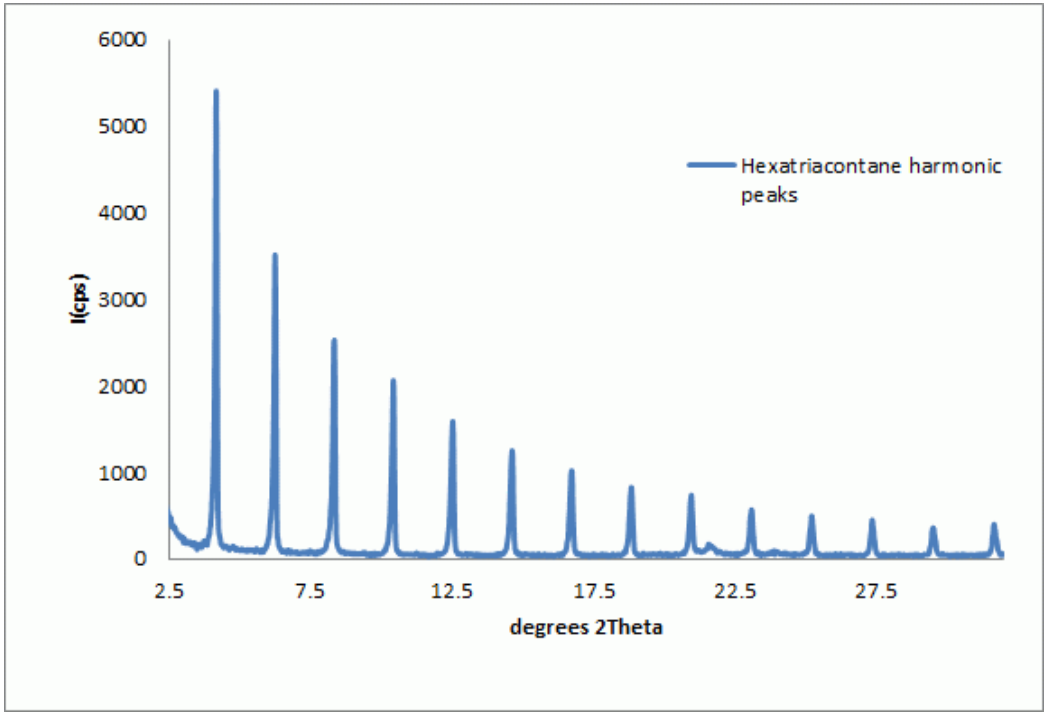
Why use hexatriacontane for instrumental calibration?

Hexatriacontane is an organic material that forms a multilayer like structure when packed. The multilayer 'd' value is ~43Å (variable) and gives 17 or 18 harmonic peaks from 1.5 to 40 degrees 2Theta.

Harmonic peaks should all have the same structure factor – so intensity function is easy to derive.

Harmonic peaks all have the same spacing (in Q) so linearity and zero errors are easy to remove.

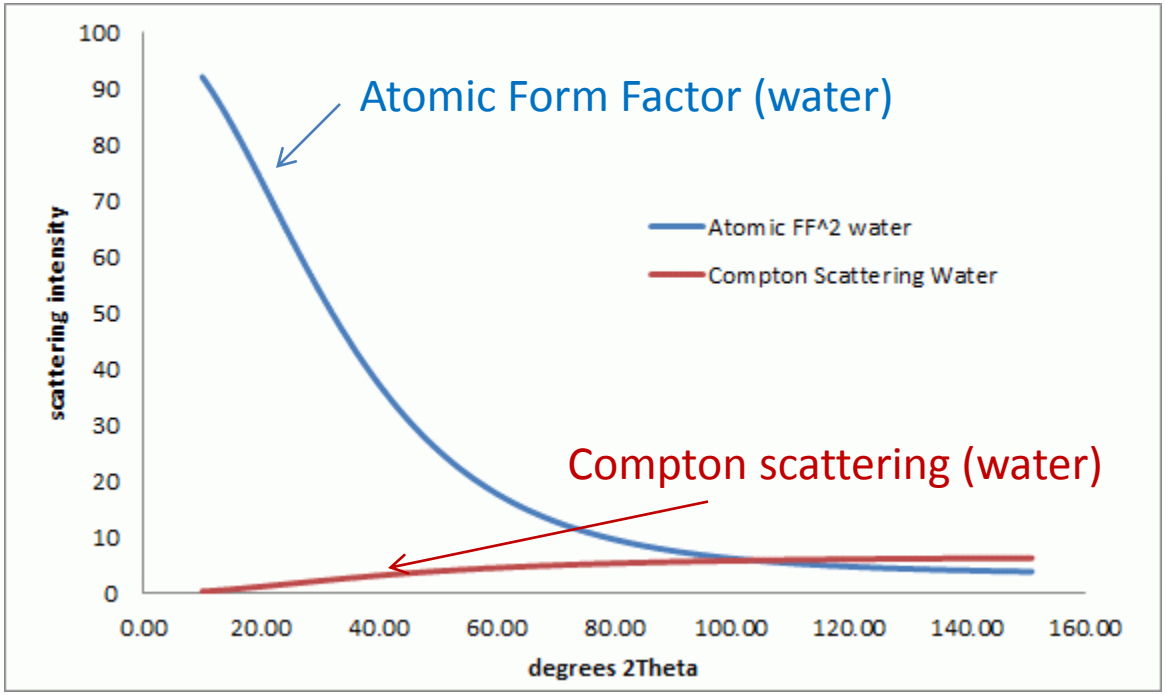
XRPD trace of hexatriacontane showing 14 harmonic peaks (Cu Kα)



Triclinic Labs

How are the atomic Form Factor and Compton scattering corrections applied?

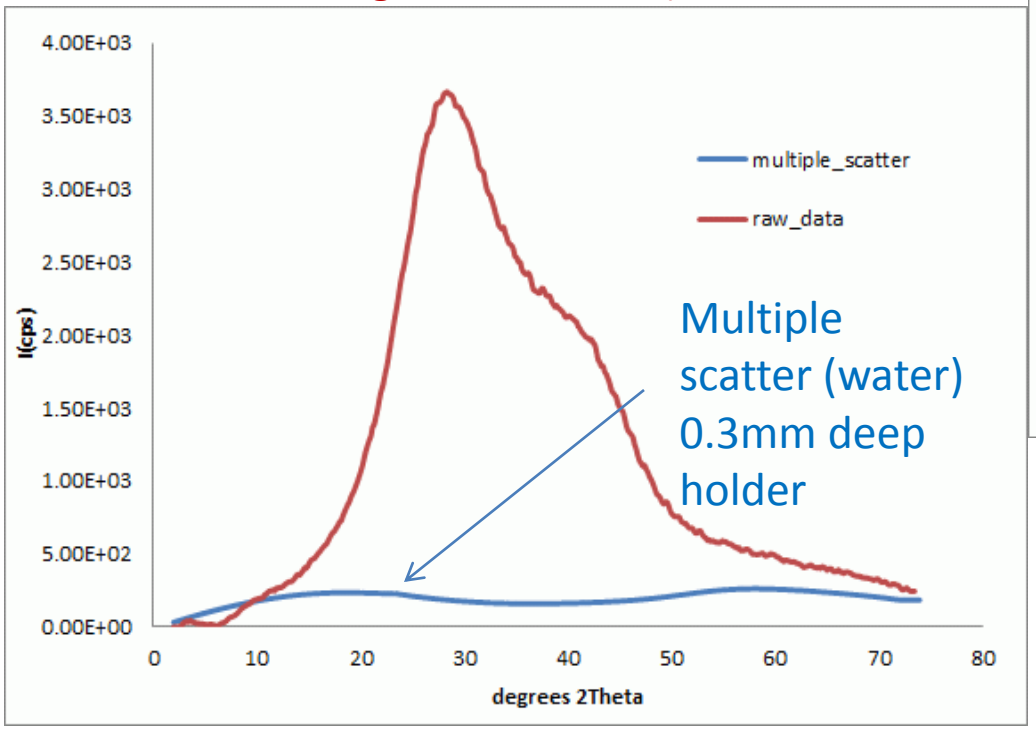
Atomic Form Factors and Compton scattering terms are tabulated in many text books (e.g. Warren). The atomic Form Factor is applied as an intensity modification similar to the instrument function. Compton scattering is a background correction (high angle). Both terms only depend on the atomic composition and X-ray wave-length used

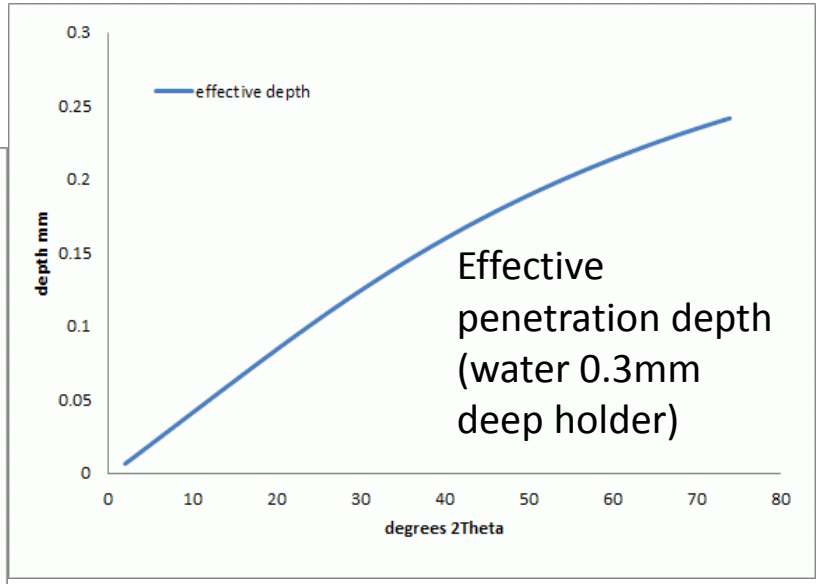


Triclinic Labs

Do you really need to correct for absorption and multiple scattering with organics?

Both absorption and multiple scattering strongly depend on the depth of the sample holder and the compaction of the sample (use shallow low background holders)





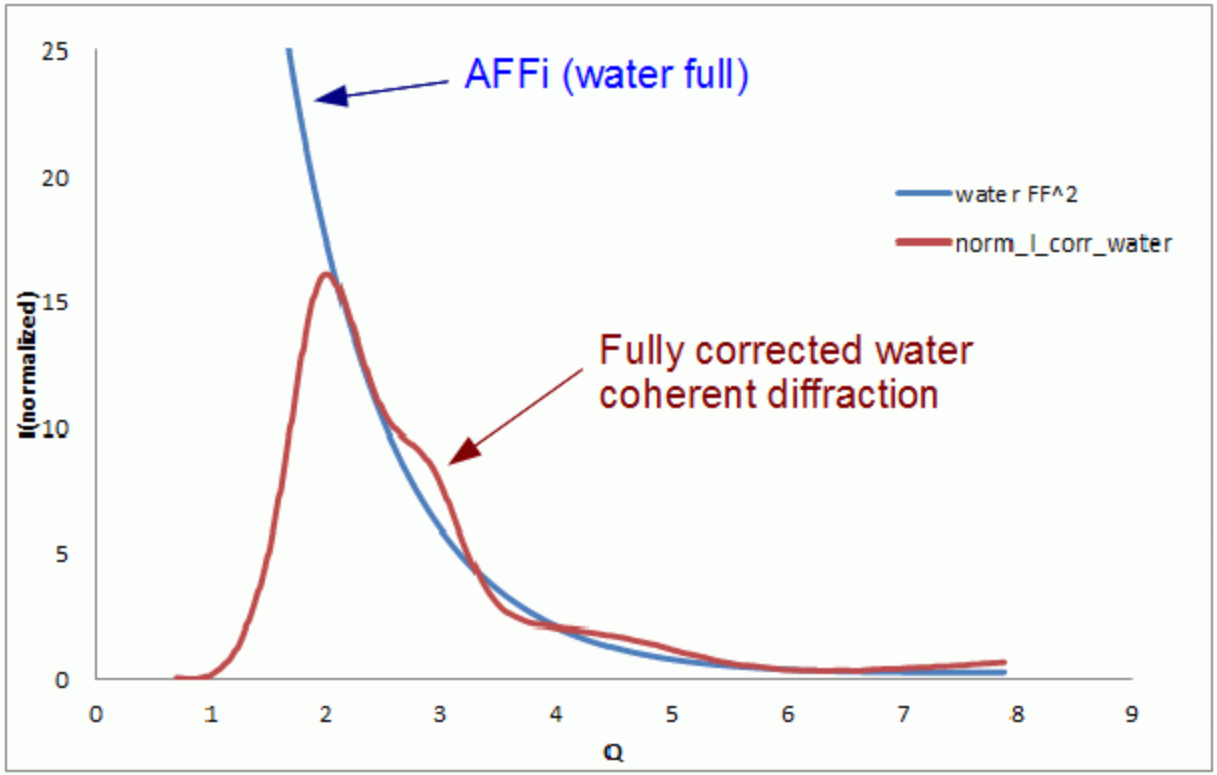
The absorption correction is a further overall intensity modification and multiple scattering is a background correction. The absorption correction can often be built into the instrument function

Triclinic Labs

OK we have fully corrected our measured data and isolated the coherent response– now what?

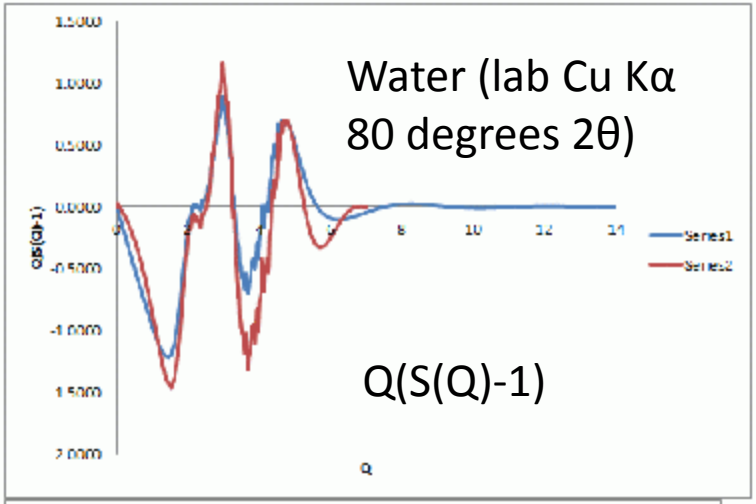
As with the approximate reduced structure factor derivation, the isolated coherent diffraction response is scaled to the atomic scattering function (AFFi) to put it on an absolute scale.

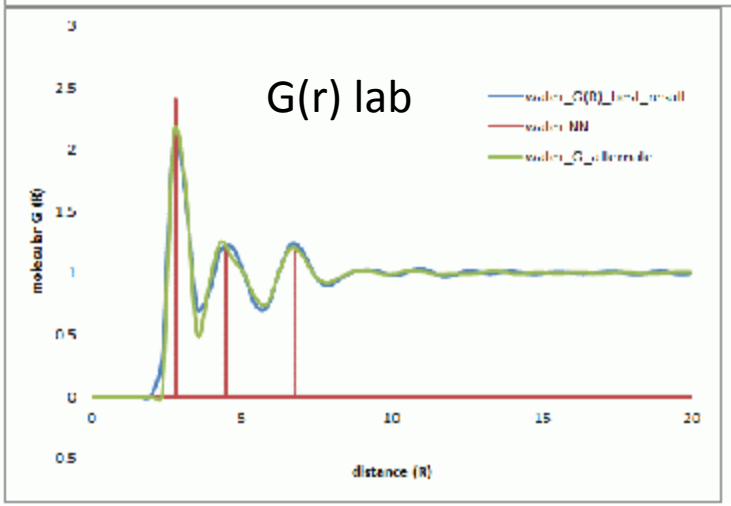
The reduced structure factor [S(Q)-1] is derived by then subtracting and normalizing by AFFi.

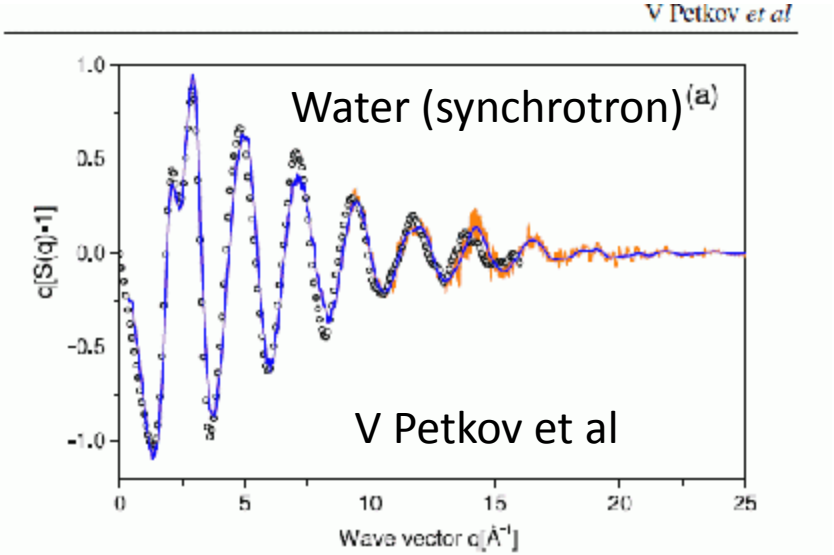


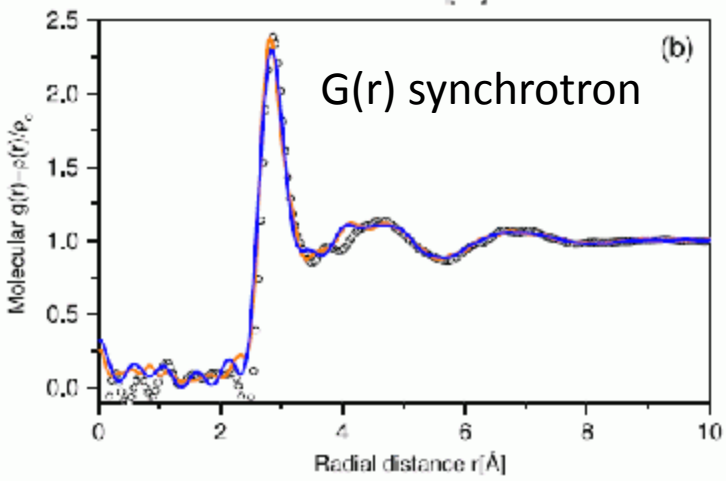
Triclinic Labs

What do the final results look like?









PDF peak positions in the lab data agree well with theory and the first peak area gives a coordination number ~ 4.4

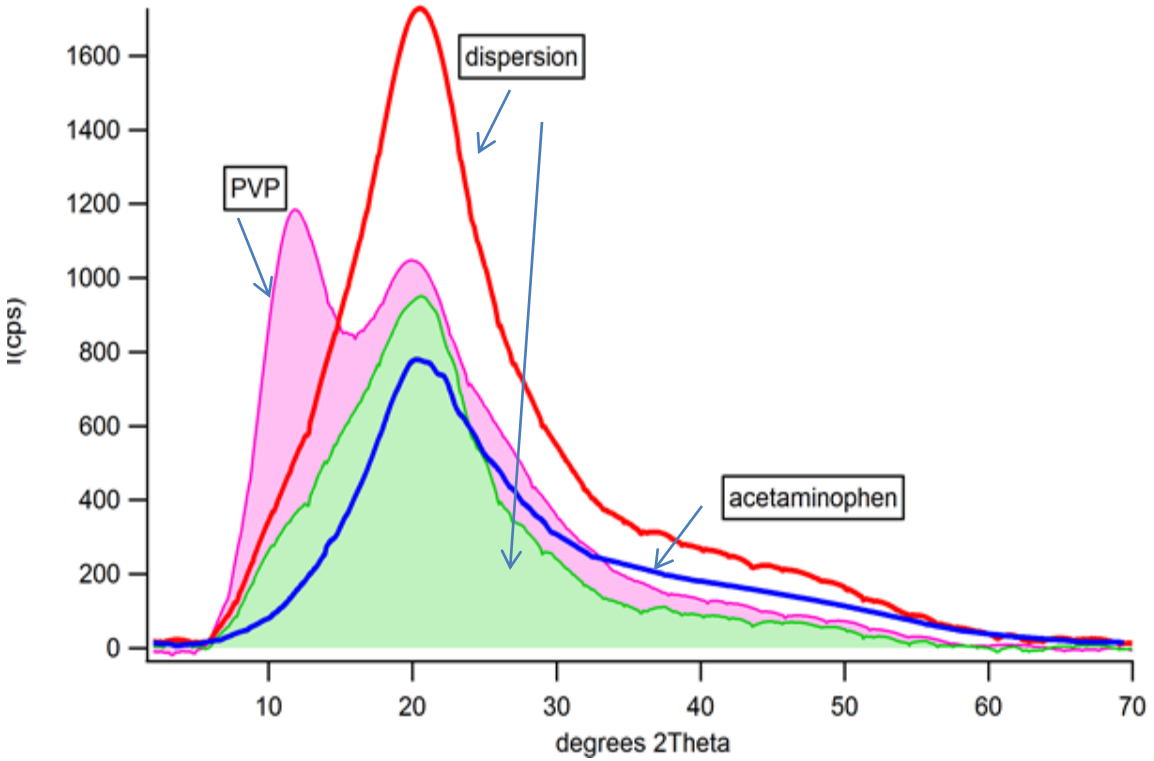
Triclinic Labs

Dispersions: identification of miscibility

Miscibility between 2 X-ray amorphous components can be identified when the powder pattern for the dispersion is not described by a linear combination of the powder patterns for both components.

For the 50:50 PVP:acetaminophen dispersion shown (red), the characteristic PVP halo at about 11 degrees 2Theta is absent from the dispersion data.

Change in the local PVP-PVP coordination – same as seen when dissolving PVP in water



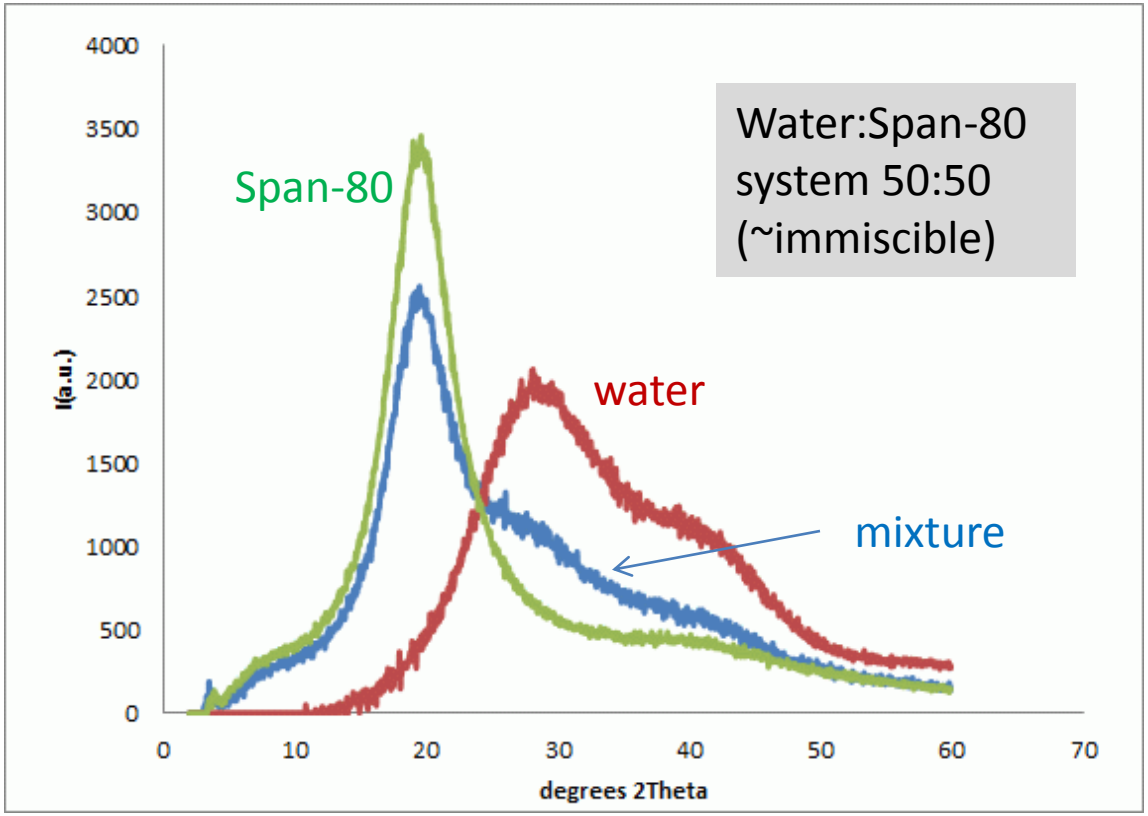
Triclinic Labs

How do we know this is a sign of miscibility?

Liquids are the underlying thermodynamic state for glassy materials. Many liquids are known to be either miscible or immiscible

Water and span-80 are essentially immiscible and tend to phase separate into large regions of either water or span-80.

The features of both single phase powder patterns are clearly visible in the mixed system data and the fit gives ~50:50 intensity ratio.

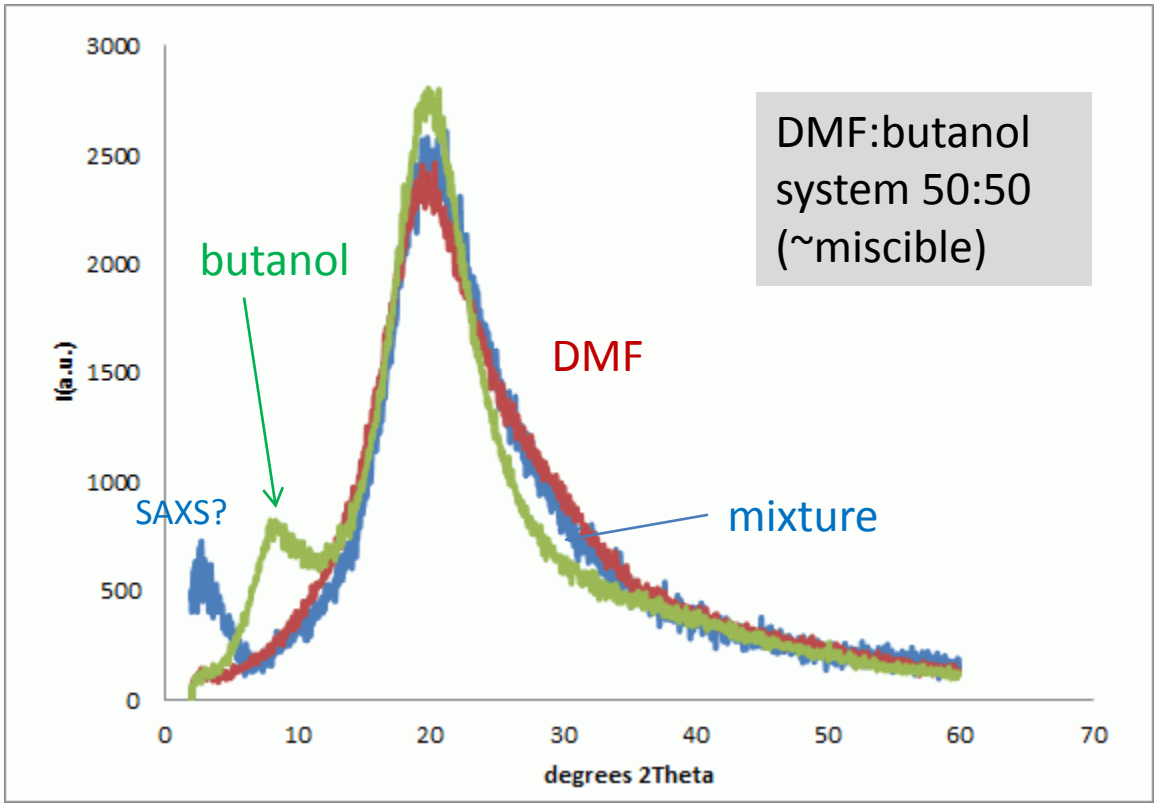


Triclinic Labs

What about liquids that are known to be miscible?

butanol and DMF are essentially miscible and form a system that is optically a single phase

The low angle halo of butanol is absent from the mixed system data. (like PVP in the PVP:acetaminophen dispersion). In addition a small angle contribution has formed.



Triclinic Labs