X-ray powder diffraction measurements as a means to determine stability of non-crystalline forms.

Triclinic Labs May 2015

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Outline of presentation:

- 1.) Stability to re-crystallization and XRPD data.
- 2.) Crystalline and Non-crystalline.
- 3.) Universality and Liquid models.
- 4.) Review of basic Debye modeling concepts.
- 5.) ‘Lattice’ functions for ‘Liquid’ models.
- 6.) Normalizing experimental data to electron units
- 7.) Case studies:
  - i. Mannitol Melt
  - ii. Fructose Melt-Quench
  - iii. Simvastatin Melt-Quench & Cryo-Grind
- 8.) Thoughts on Stable Non-Crystalline Forms

1.) Stability of non-crystalline forms I

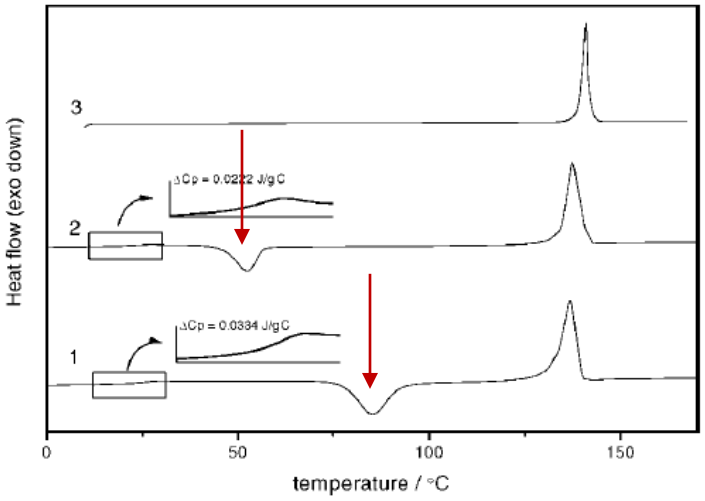
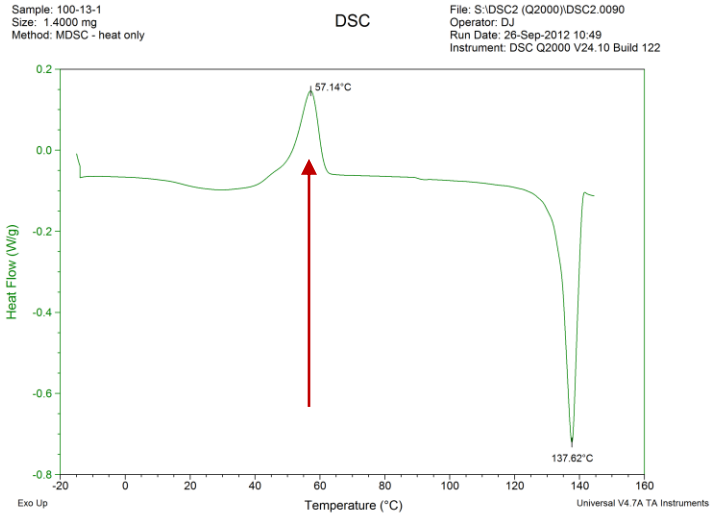
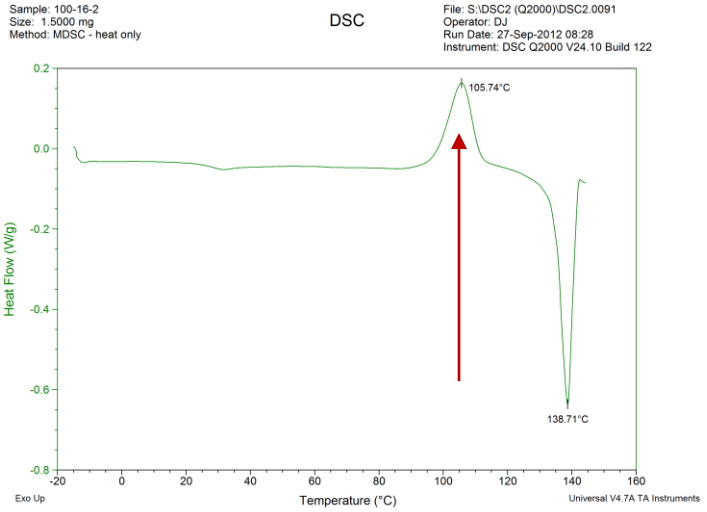


Figure 4. MTDSC thermograms of crystalline and amorphous forms of simvastatin: (1) quench-cooled, (2) cryo-milled, and (3) crystalline simvastatin.





Non-crystalline Simvastatin melt-quench and cryo-ground exhibit very different re-crystallization behavior. No visible difference in XRPD. Graeser et al Cryst Growth Des 2008 v8 p128

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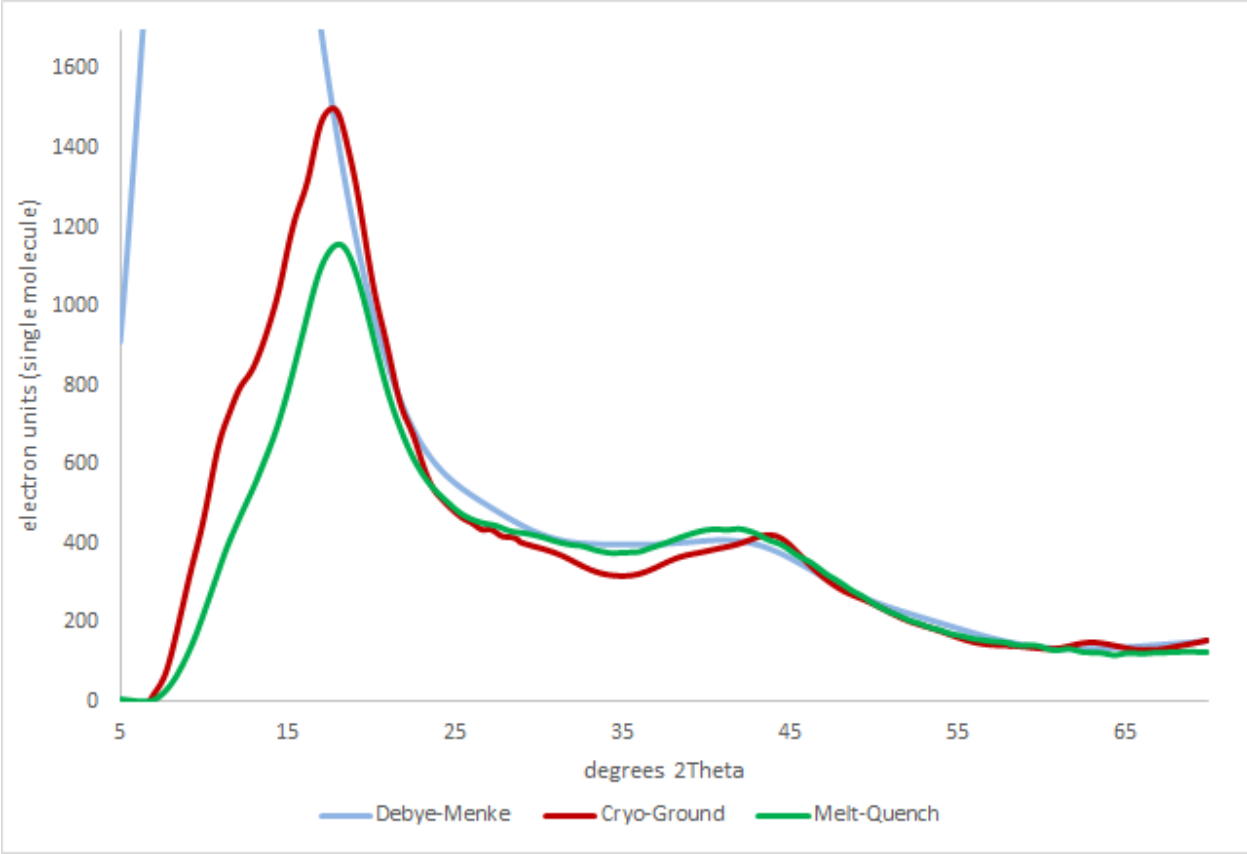
1.) Study of stability of non-crystalline forms II

Simvastatin exhibits 2 subtly different XRPD traces depending on whether material non-crystalline form is generated by melt-quench or cryo-grinding.

XRPD does show a difference between simvastatin non-crystalline forms but what does it mean?

Normalized XRPD data for simvastatin



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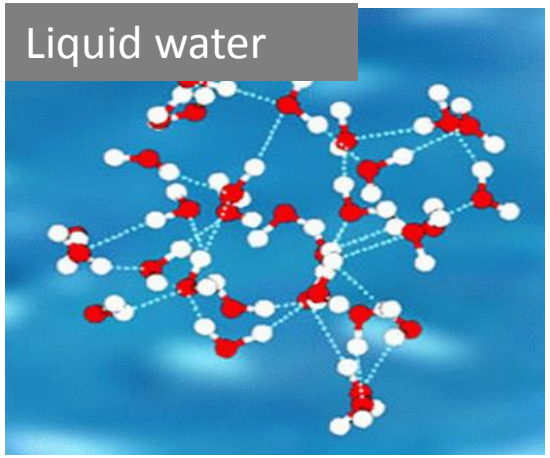
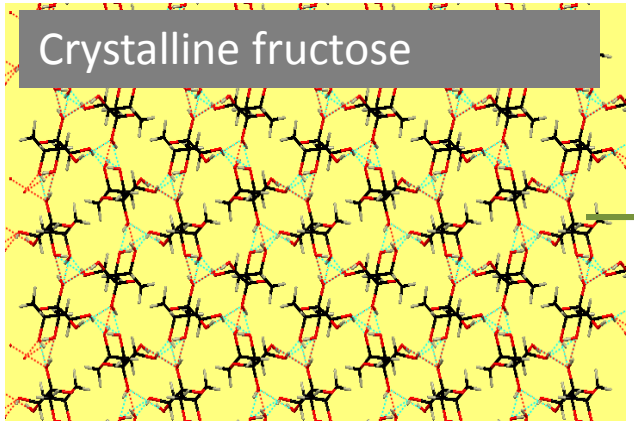
2.) Crystalline and Non-crystalline

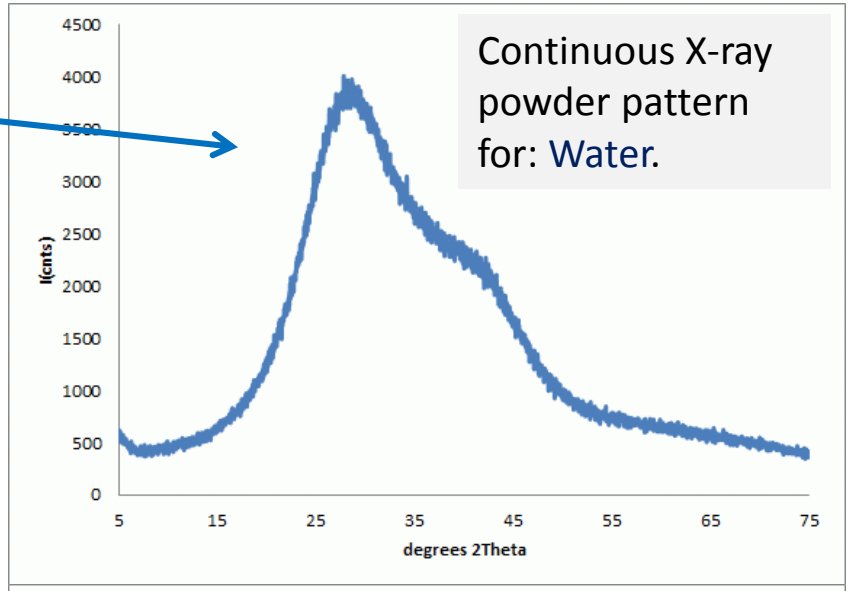
Liquid water

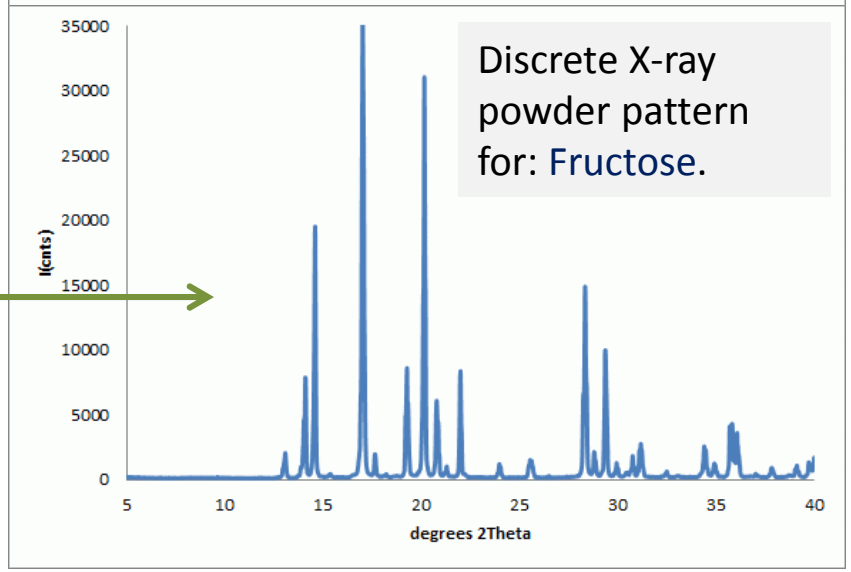


Crystalline: “any solid having an essentially discrete diffraction diagram” IUCr 1992

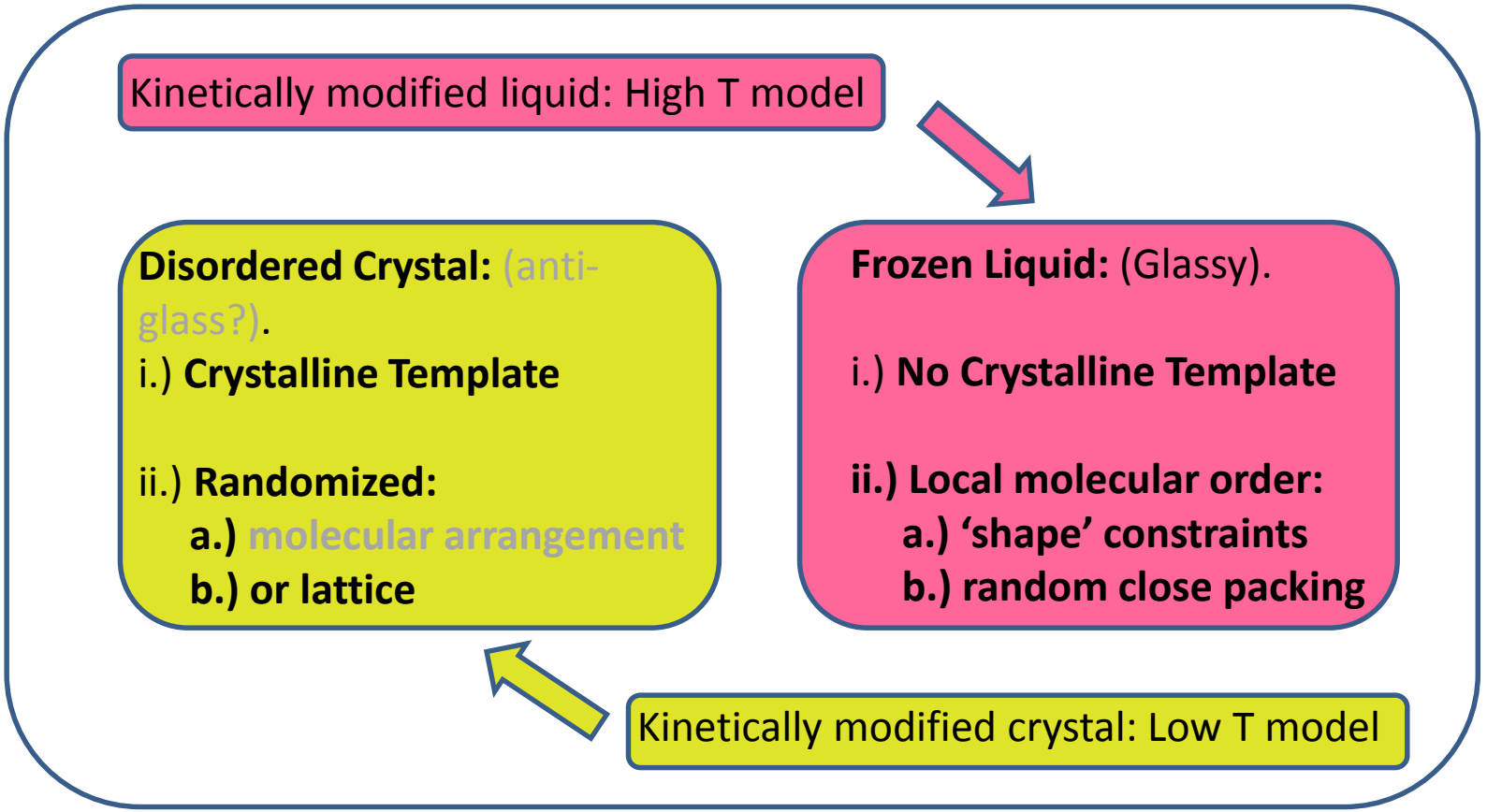
Crystalline fructose



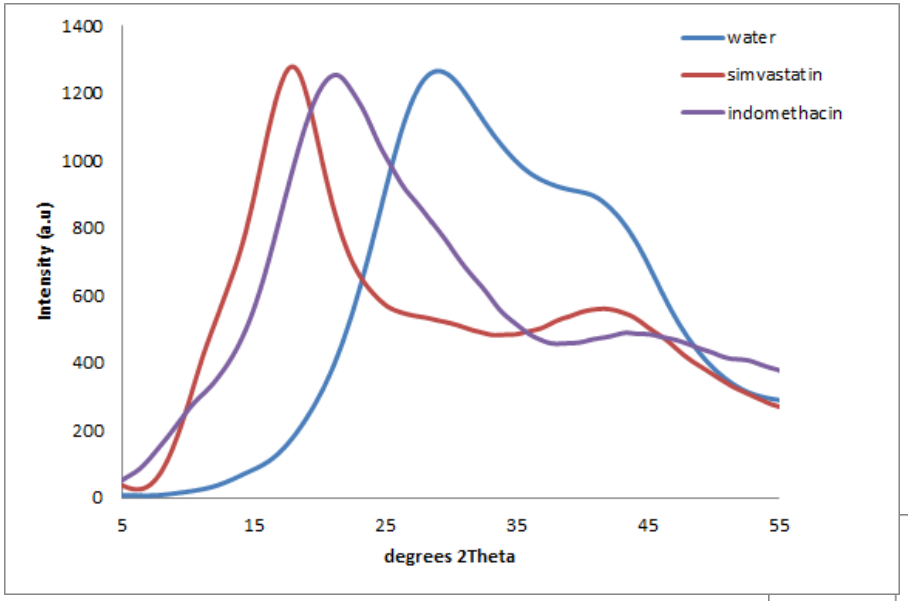




2.) The Ying-Yang of non-Crystalline Materials

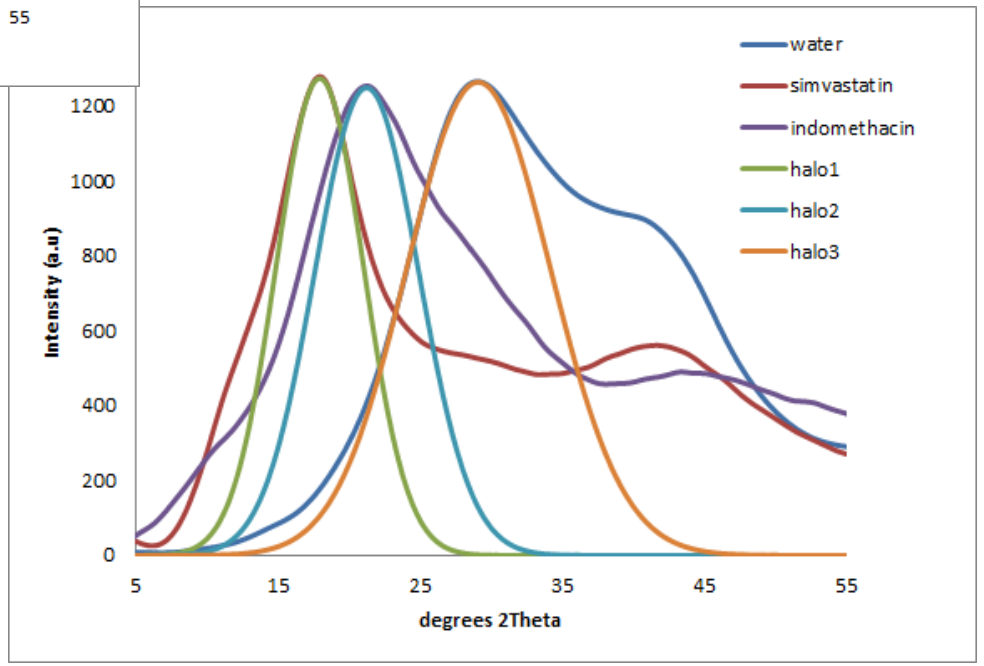


3.) Universal non-crystalline properties I



A ‘universal’ observation for non-crystalline materials is that halos that are occur at lower angles appear narrower than halos that occur at higher angles.

Using the Stokes & Wilson strain broadening model (crystalline materials), Universal halo width can be described by ~ 22% strain.



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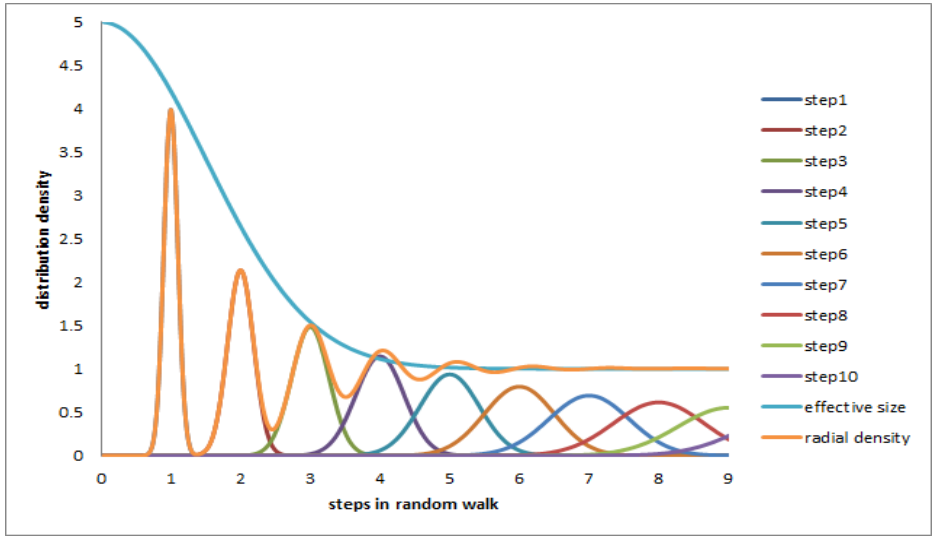
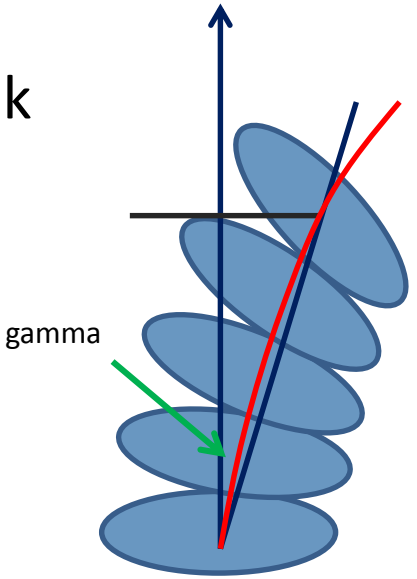
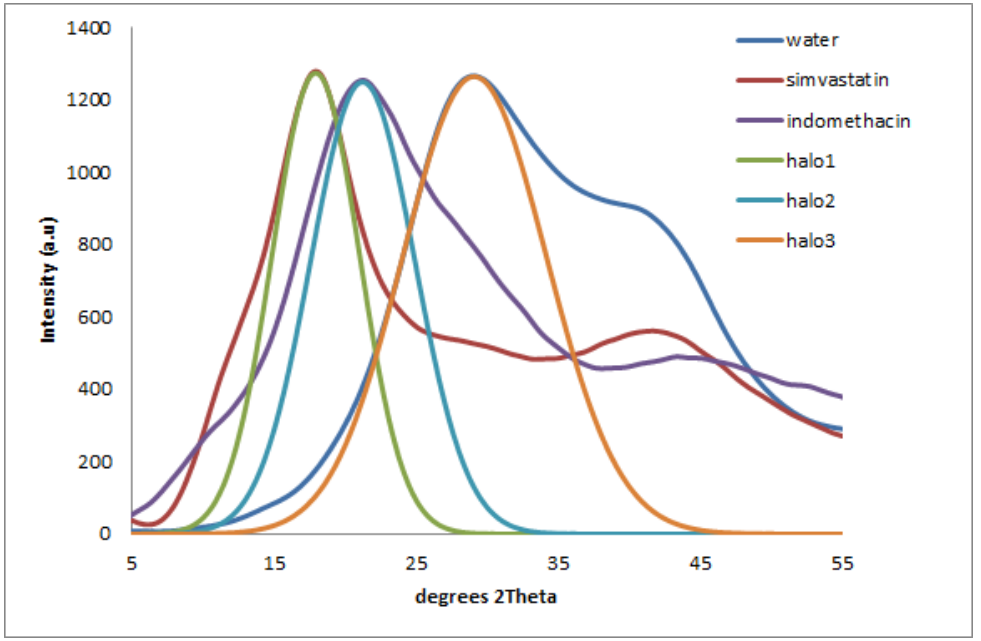
3.) Universal non-crystalline properties II



A random walk close-packing model of Local order



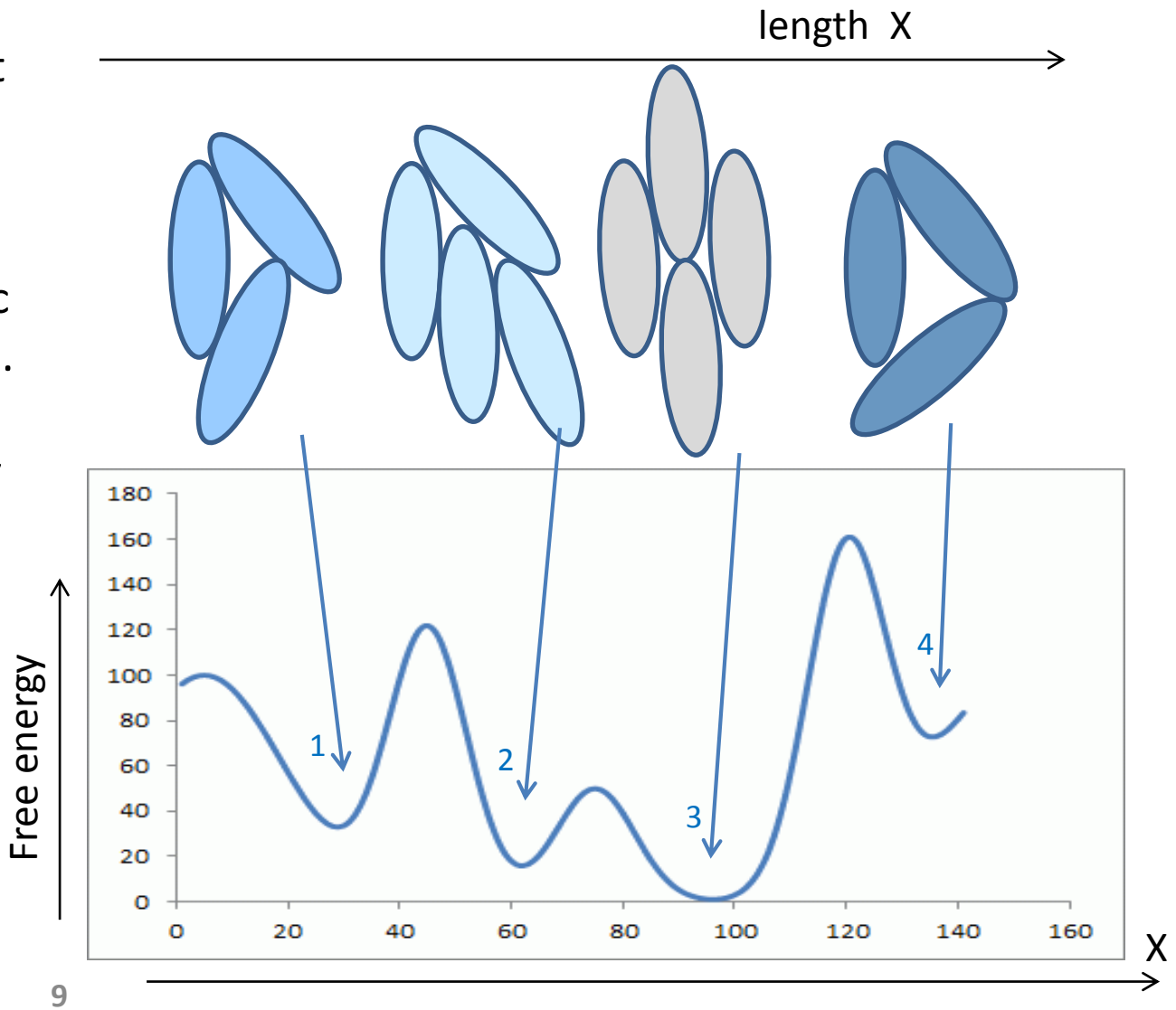
Universal halo width behavior can be described by a characteristic random walk coherence length N of ~ 1. (Liquid Model)



3.) Liquid models for non-crystalline systems

Within the N~1 constraint from the universal halo width observation, a 'liquid' model can be considered to be a mosaic of locally ordered clusters. The clusters explore all configurations allowed by the local energy conditions.

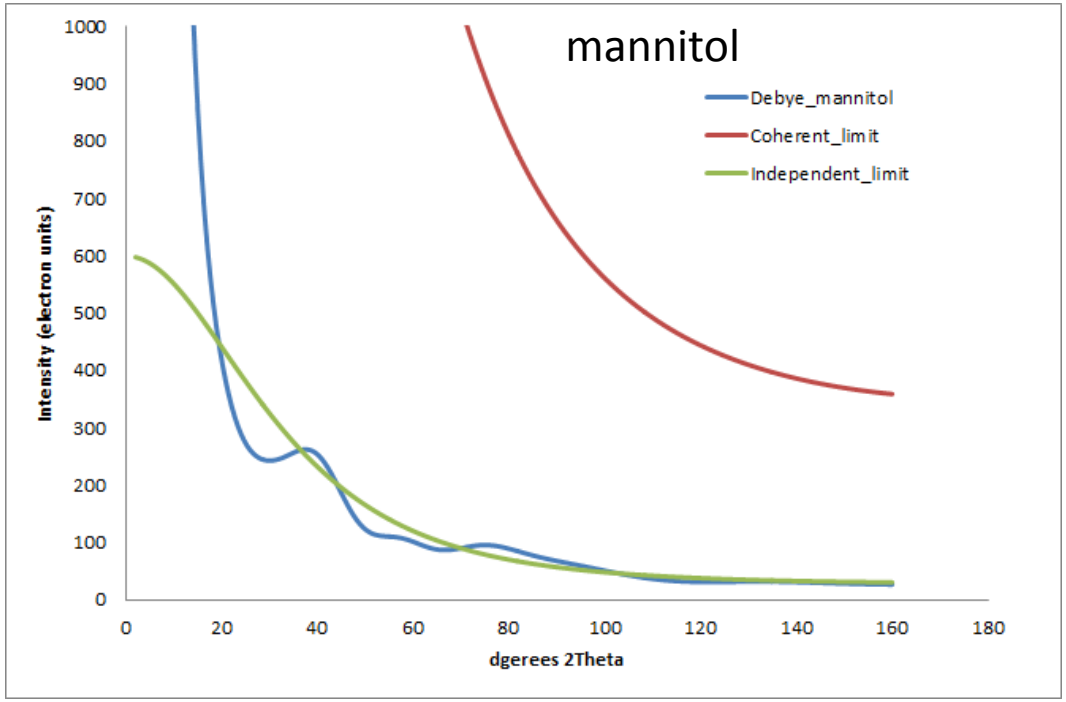
Configurational Entropy
Sc ~ log(Nf)/Nf
'Nf' ~ number of different free energy states available.

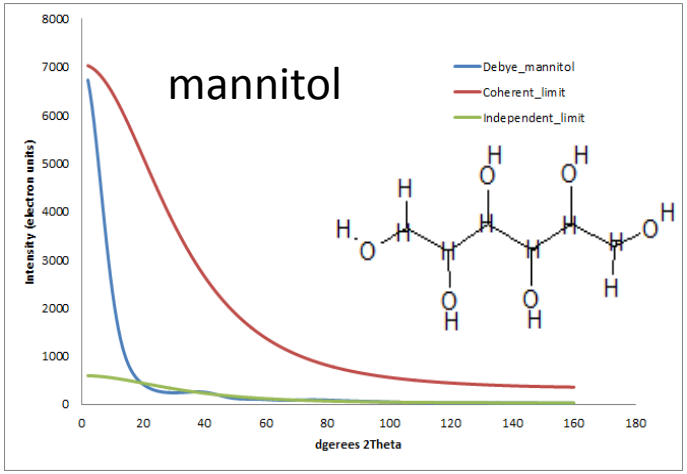


4.) Debye Diffraction Model of rigid molecule I

For a rigid molecule system – will the Debye response of a single molecule describe the observed XRPD trace for an ideal glassy system? (e.g. no local intra-molecular order)

$$I_{DM} = \sum_{i=1}^{n} f_i^2 + 2 \sum_{i,j\ i\neq j\ 1}^{n} f_i f_j \sin(Q\ d_{ij})/(Q\ d_{ij})$$



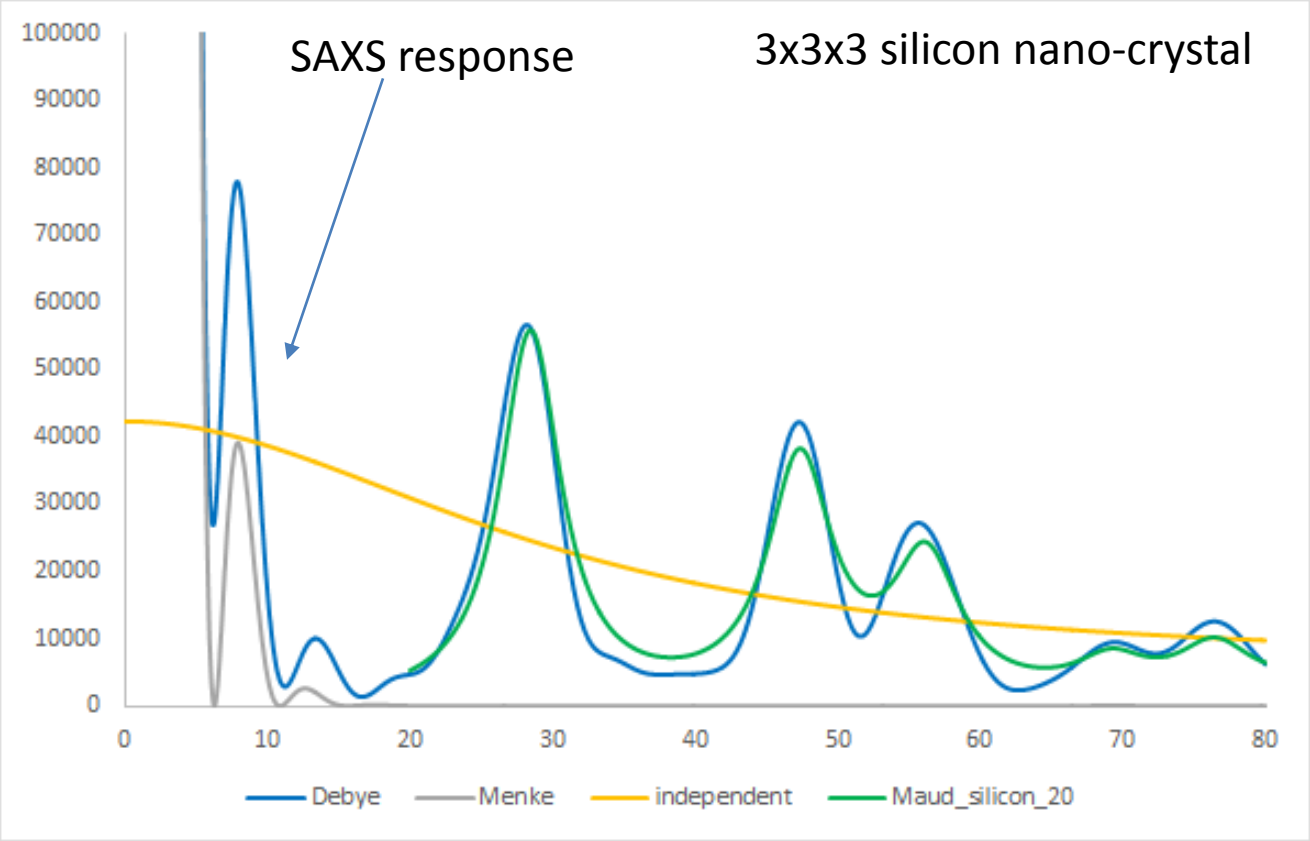


$$Independent\ limit = \sum_{i=1}^{n} f_i^2$$

$$Coherent\ limit = \left(\sum_{i=1}^{n} f_i \right)^2$$

Debye response is ideal gas response.

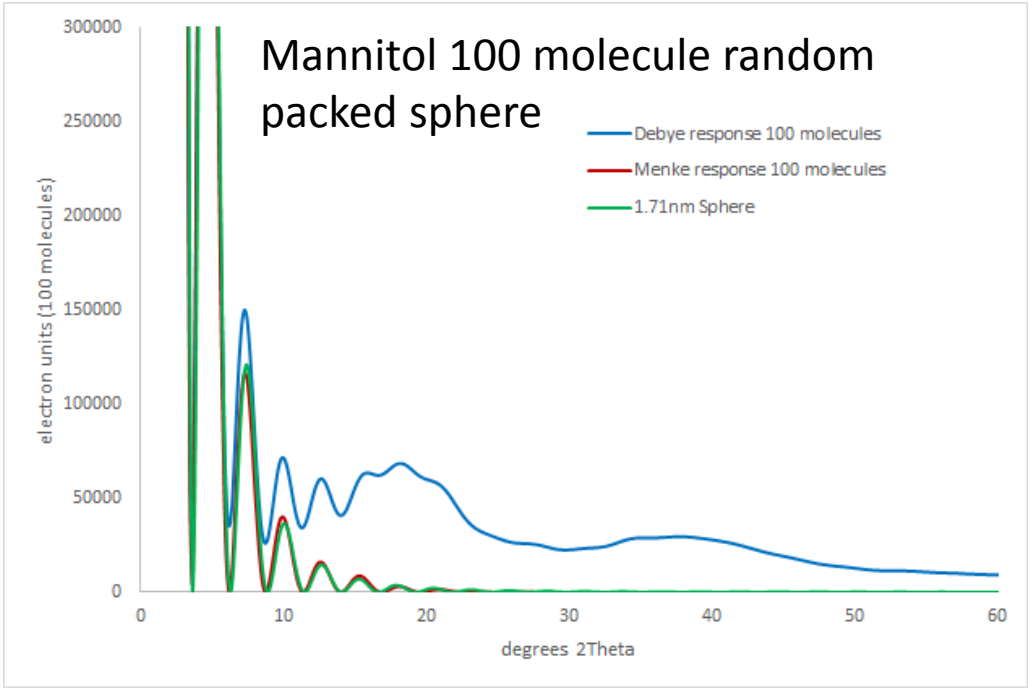
4.) Debye vs Bragg Diffraction Models



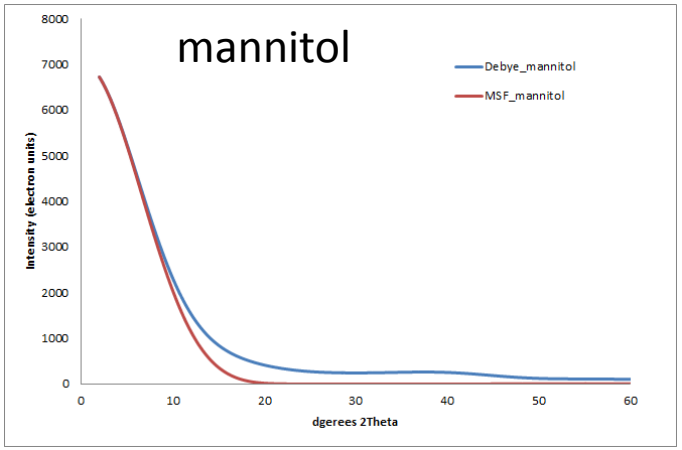
Calculated powder patterns for a 3x3x3 silicon nano-crystal using both Debye and Bragg diffraction equations. The Bragg calculation (Green) has been scaled and modified by multiplying by the $\sin(\theta)^2$ Lorentz difference. Originally calculated using MAUD.

4.) Debye Diffraction Model of rigid molecule II

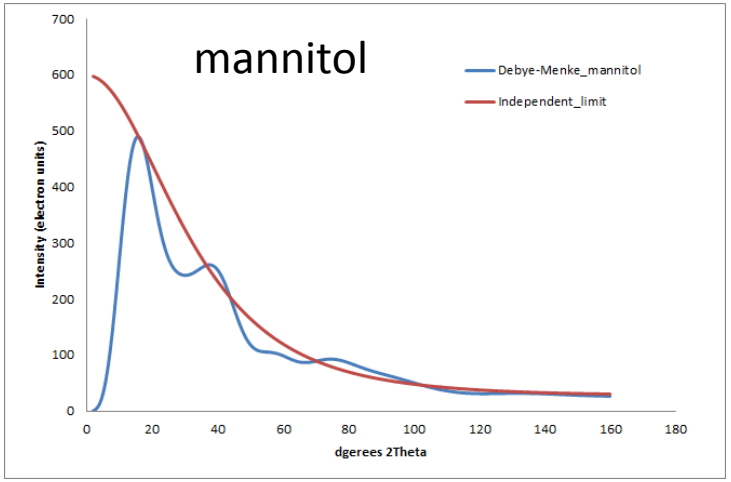
$$Menke\ Correction = \sum_{i=1}^{n}\sum_{j=1}^{n} f_i f_j \frac{\sin(Ql_{ci})}{Ql_{ci}} \frac{\sin(Ql_{cj})}{Ql_{cj}}$$



Debye and Menke response for 100 mannitol molecules packed into a 1.71 nm sphere



Menke correction used to remove Coherent SAXS response due to shape and mean number density.



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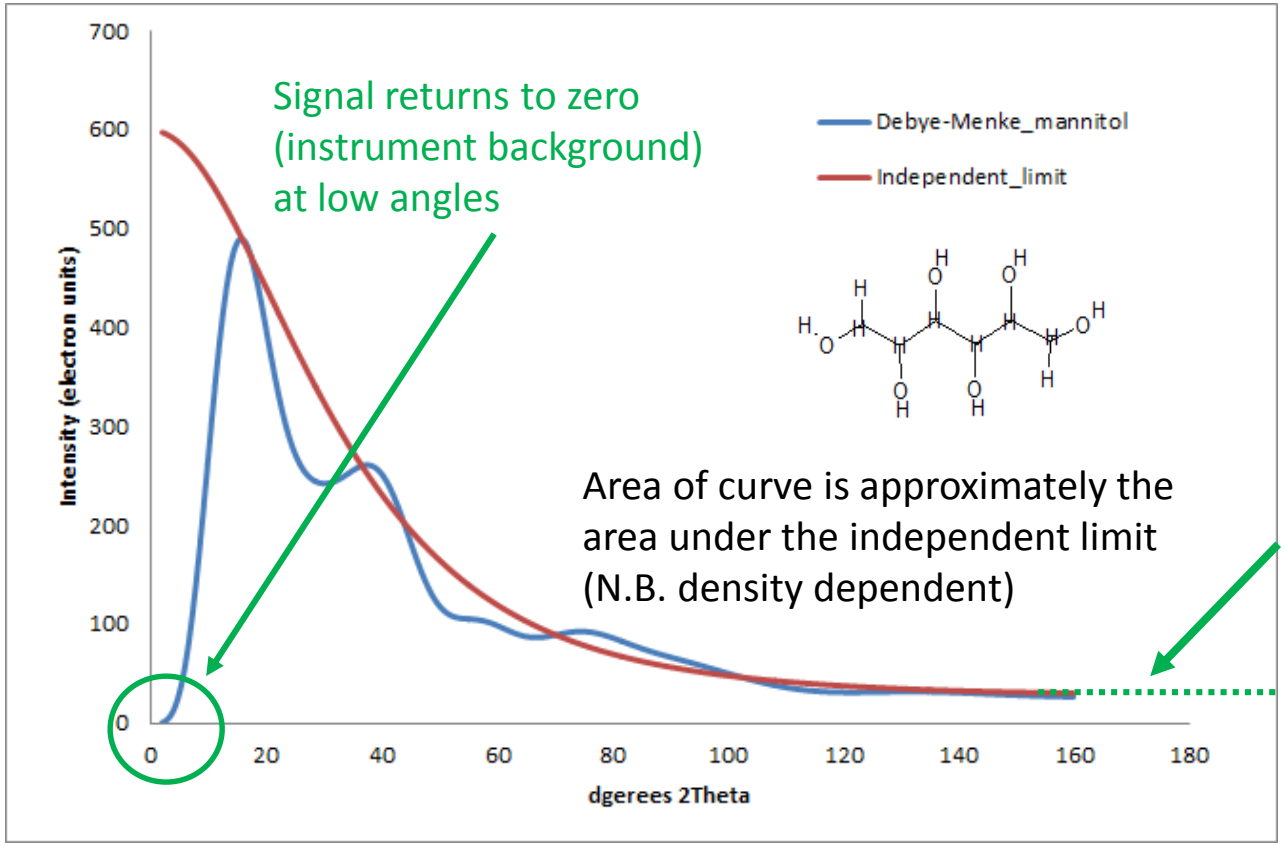
4.) Debye Diffraction Model of rigid molecule III

Debye diffraction model suggests a data normalization procedure.

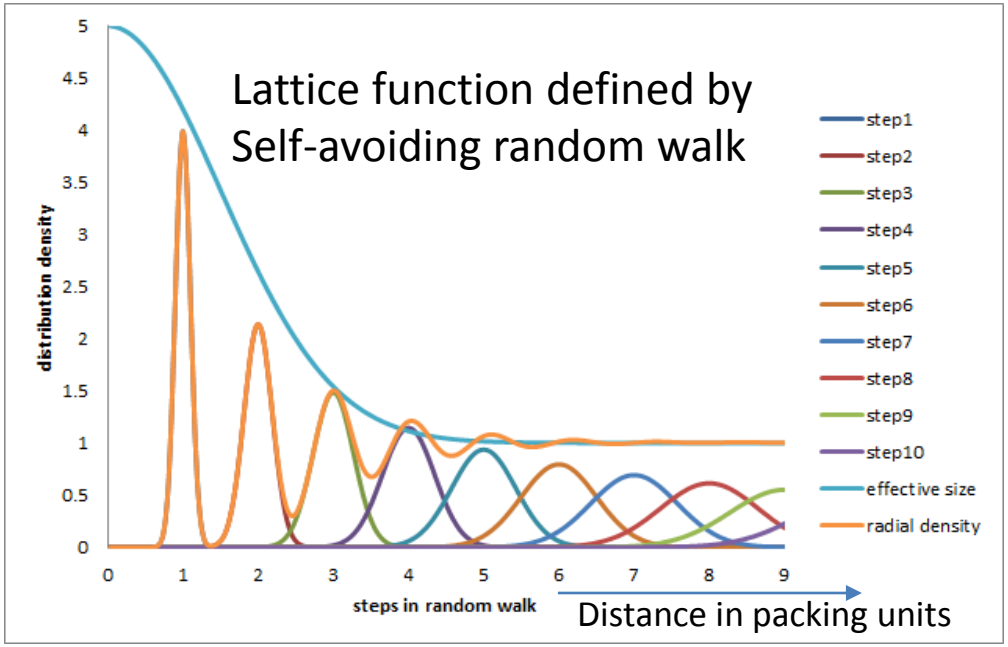


Debye-Menke response is ideal liquid response.

5.) Lattice Functions in the Debye Model

Exclusion zones and lattice functions – ideal solid glass.

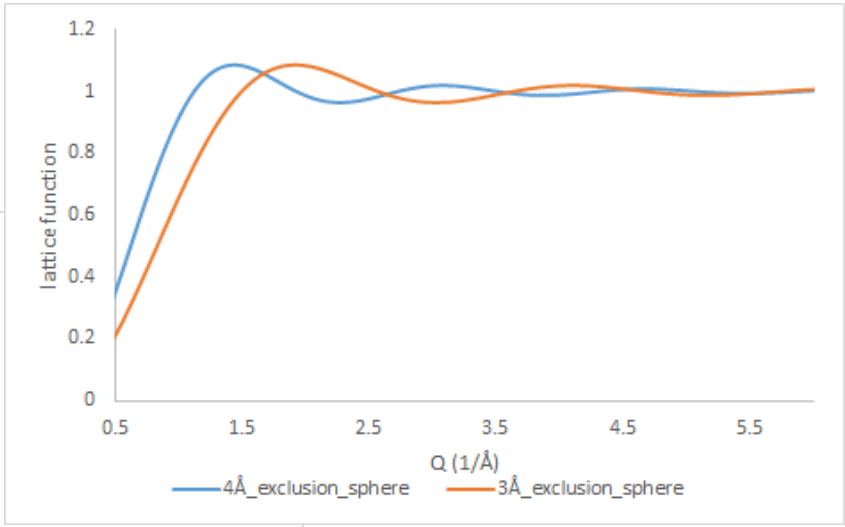
A Lattice Function for ‘solid-liquid’ defines the local molecular distribution probability. A frequently used example is an exclusion zone.

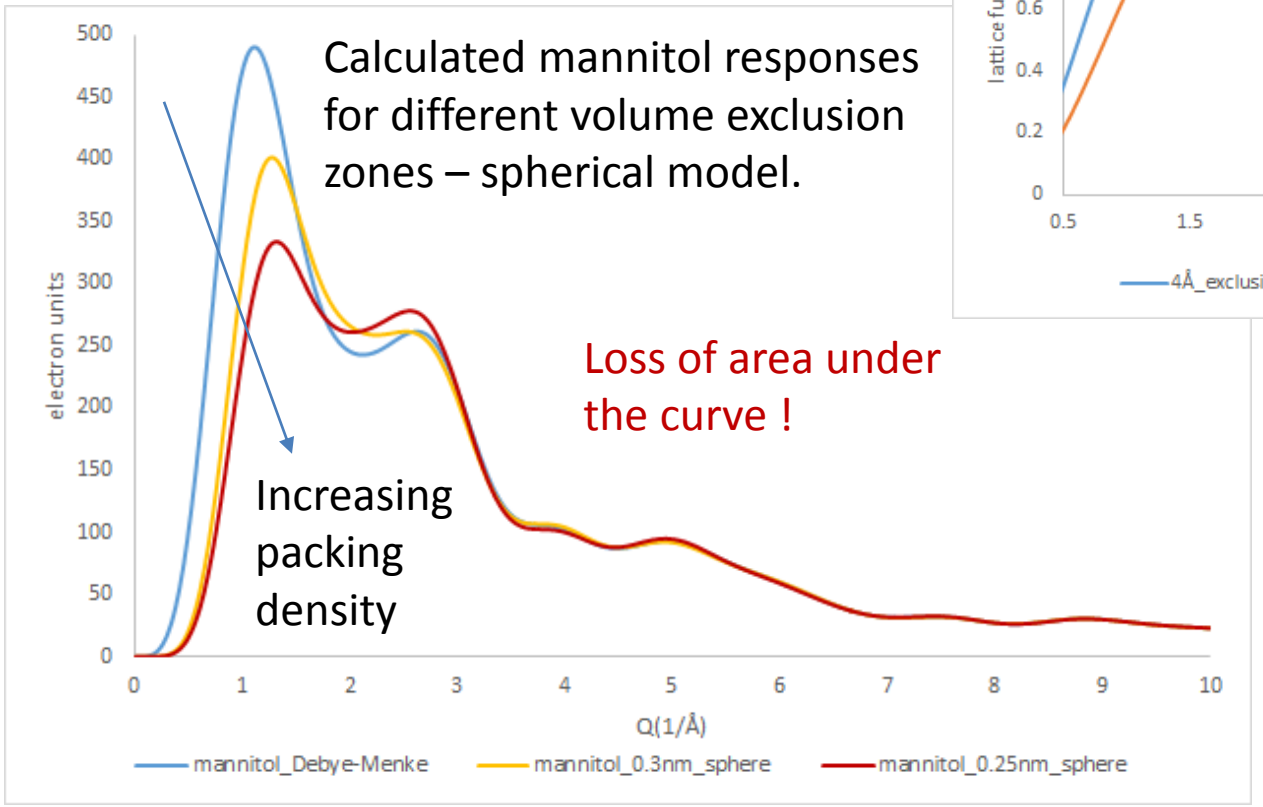


Ideal_Gass(Q) → Debye(Q)
Ideal_Liquid(Q) → Debye(Q) - Menke(Q)
Ideal_Glass(Q) → (Debye(Q) - Menke(Q)) . Lattice_Function(Q)
All ideal classes of non-crystalline material considered to be spherically symmetric and isotropic.

5.) Exclusion zone model of packing density

Packing density and exclusion zone.



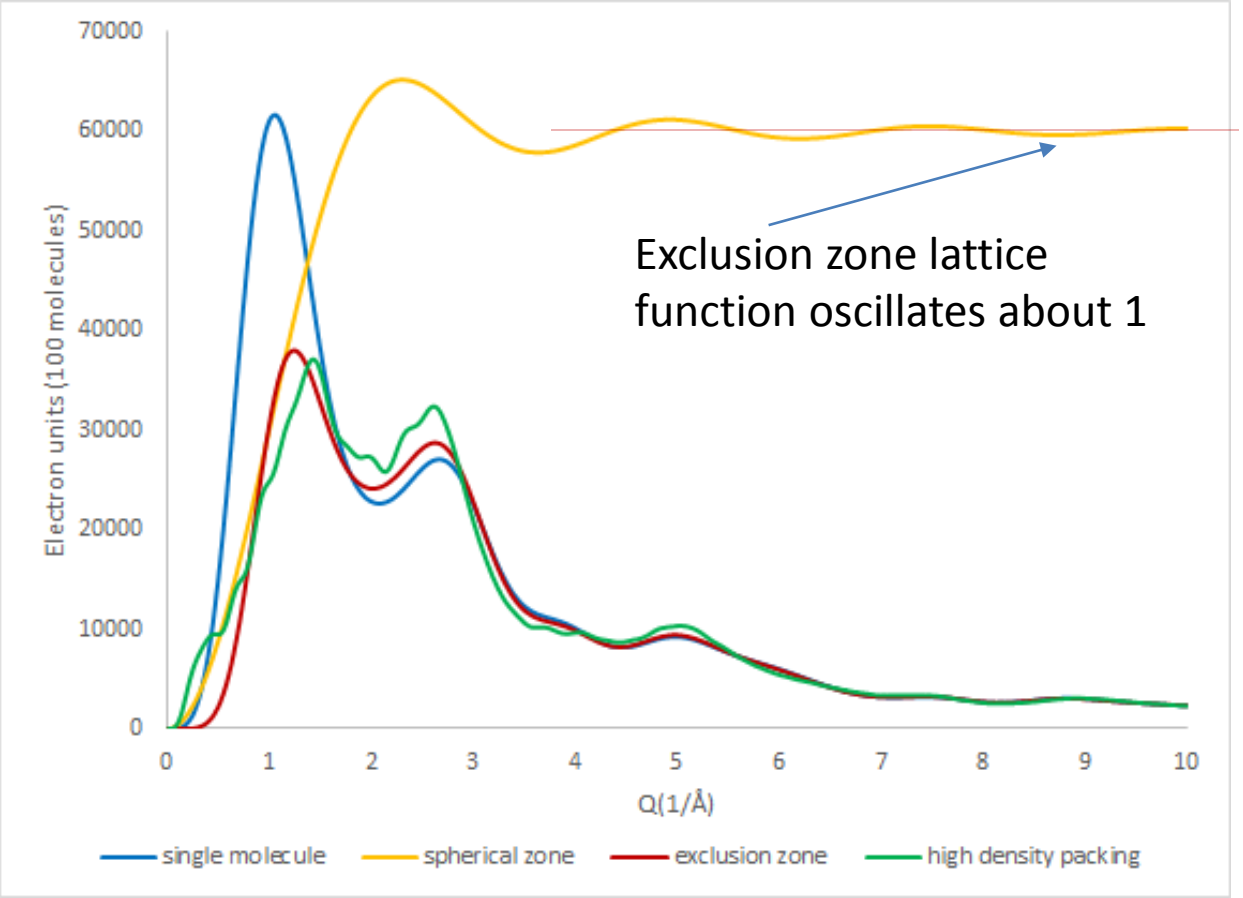


An exclusion zone can only be occupied by a single basic unit.

5.) Random Molecular packing model

Molecular simulation of 100 mannitol molecules randomly packed inside hollow sphere.

Using (packmol+tinker) 100 mannitol molecules randomly packed into spheres of different volumes. Must be repeated multiple times to approach true random behavior.



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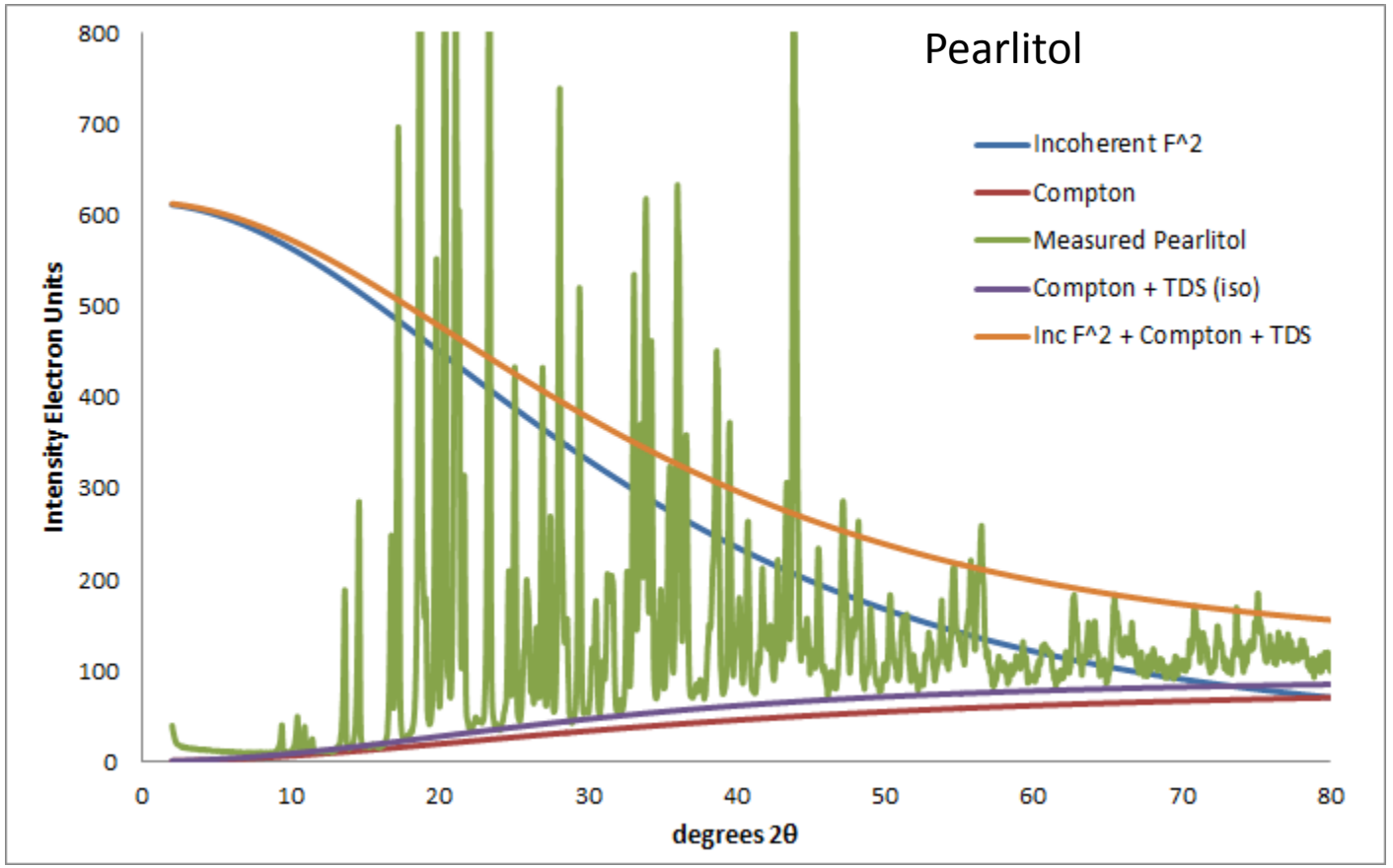
6.) Utility of diffraction limits: Total Diffraction

Data Scaled to give asymptotic convergence to calculated atomic scattering parameters at high Q (2Theta).

Forces data to an absolute Electron Units scale independent of instrument used or experimental technique



TDS derived from simple isotropic independent atom model. RMS deviation ~ 0.11Å

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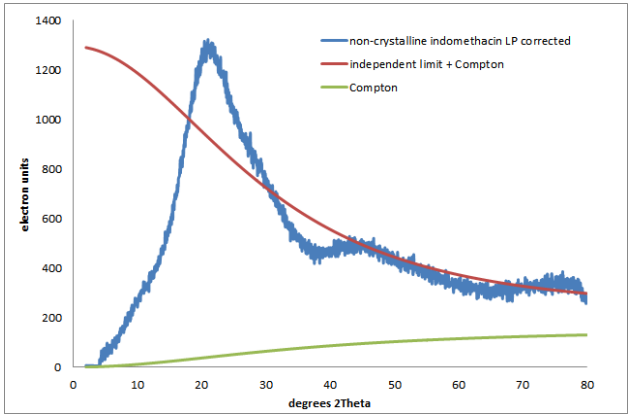
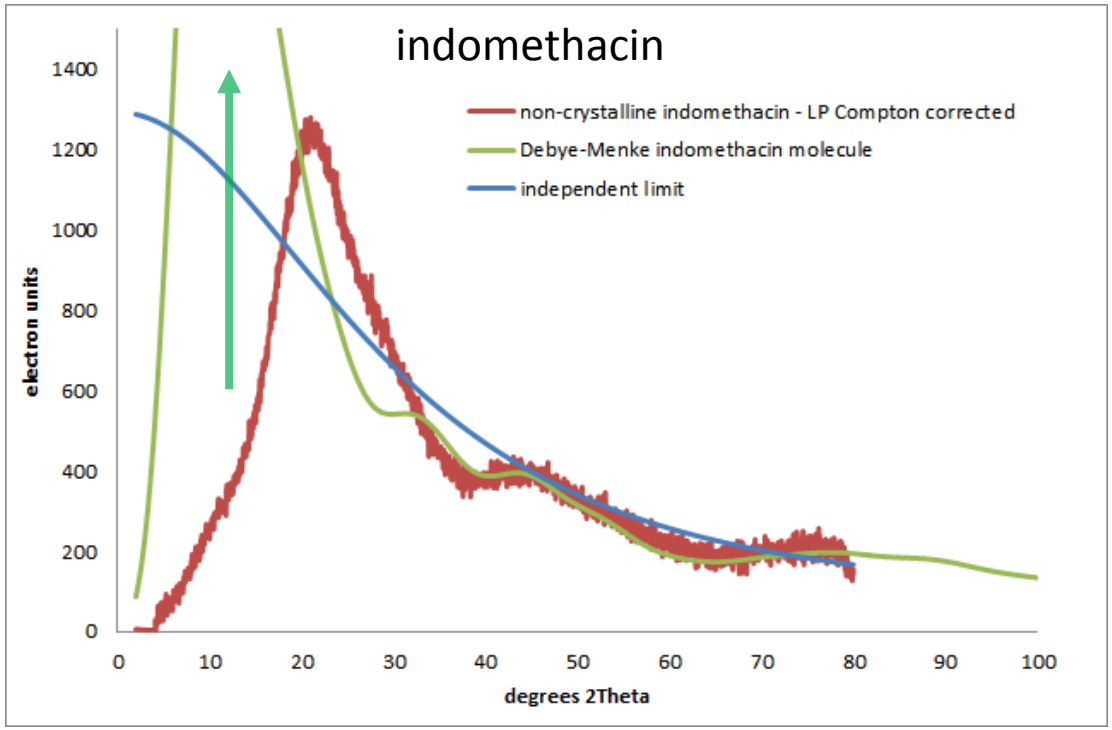
6.) Application of limits for non-crystalline XRPD

In addition to normalizing to the Independent limit And diffuse limit, the Debye-Menke curve can be used to confirm scaling.



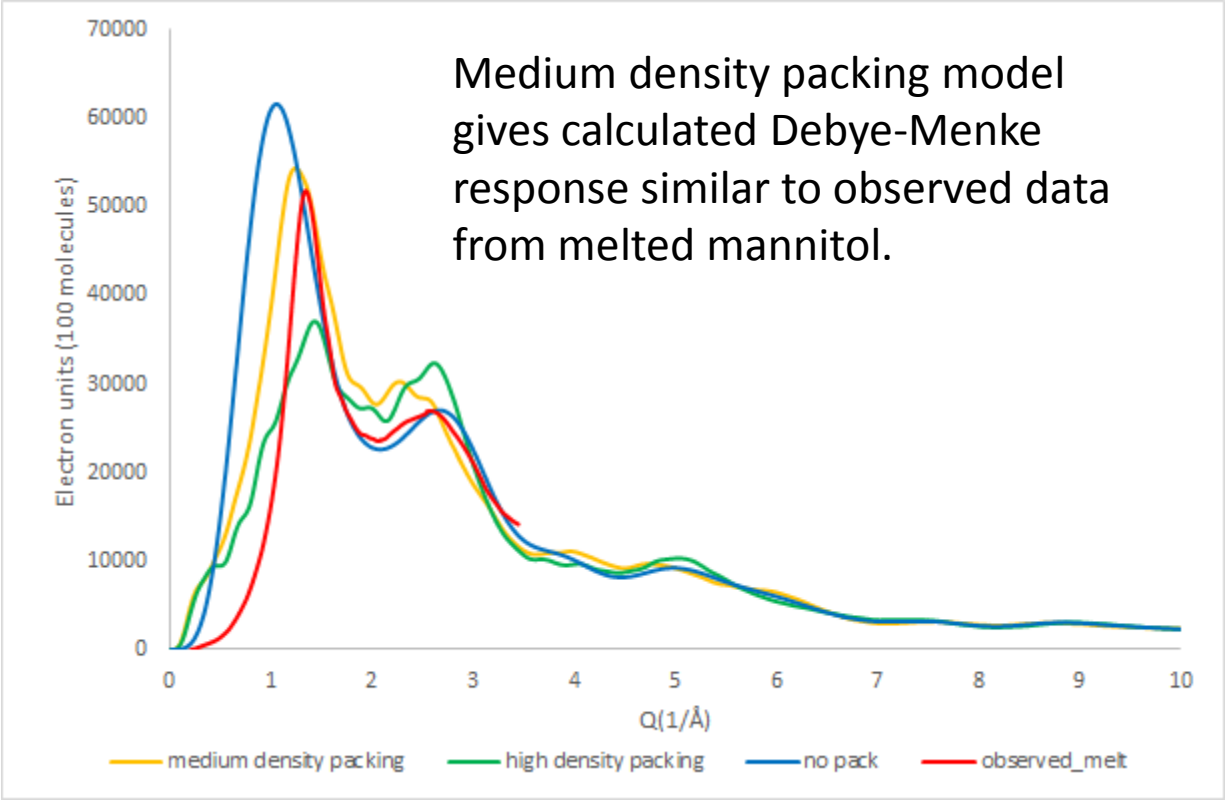


Indomethacin closely follows the high angle Debye-Menke curve but diverges significantly at lower angles.

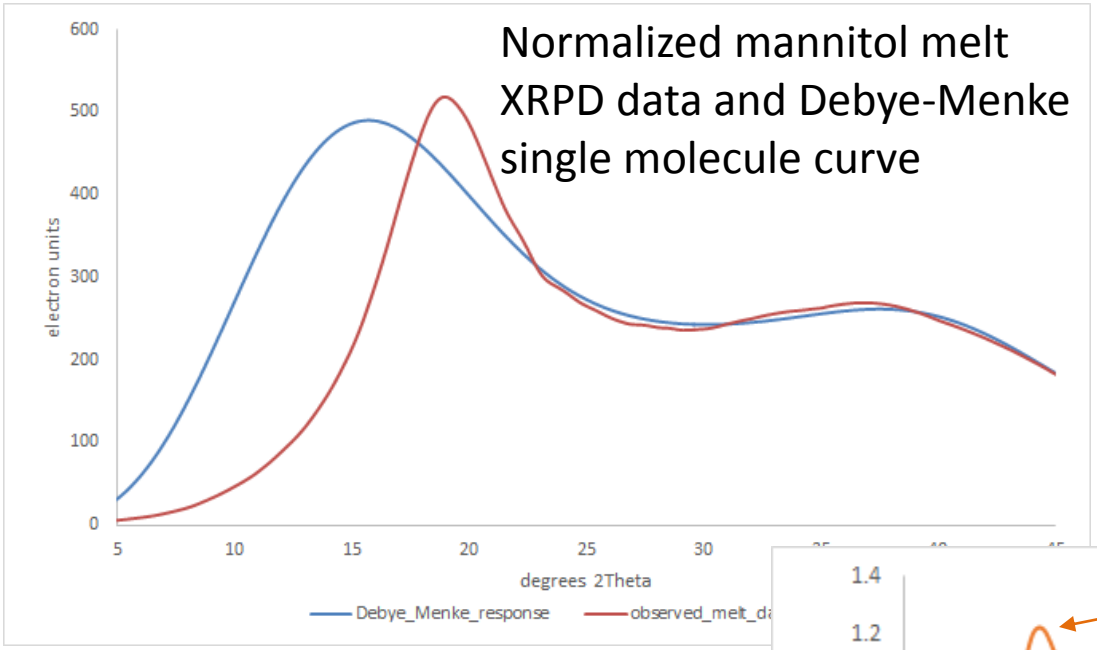
7.i.) Case Study i: Mannitol Melt (in-situ)

Molecular simulation of 100 mannitol molecules randomly packed inside hollow sphere to simulate low and high density packing.

Results of random molecular packing (+ constrained optimization) for a rigid mannitol molecule compared with actual data from melted mannitol.

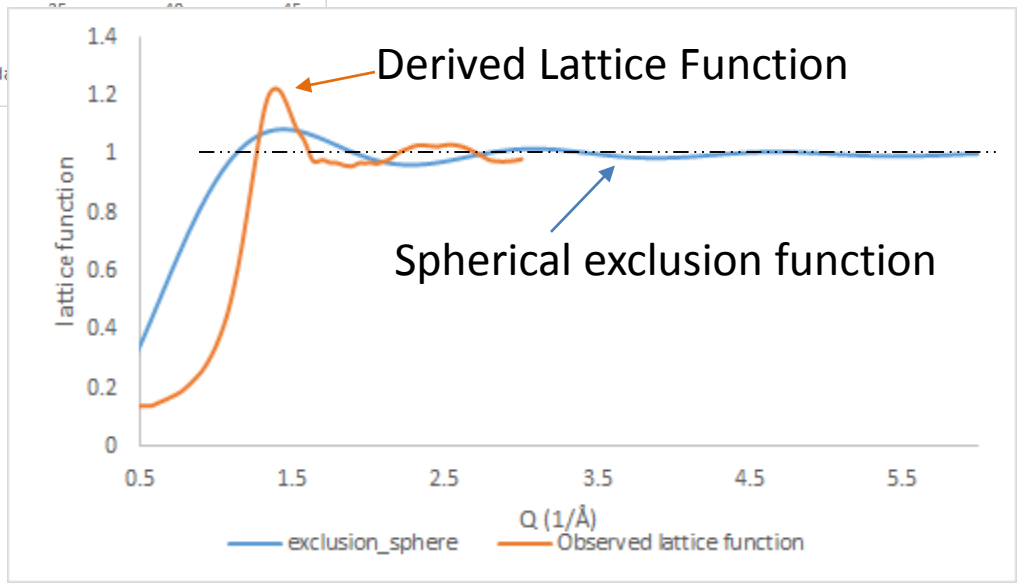


7.i.) Case Study i: Mannitol Melt (in-situ)



Effective Lattice Function an be derived from the effective single molecule Debye-Menke curve and normalized observed XRPD data.

Glassy mannitol unstable to crystallization. Derived lattice function has well defined nearest neighbor peak.



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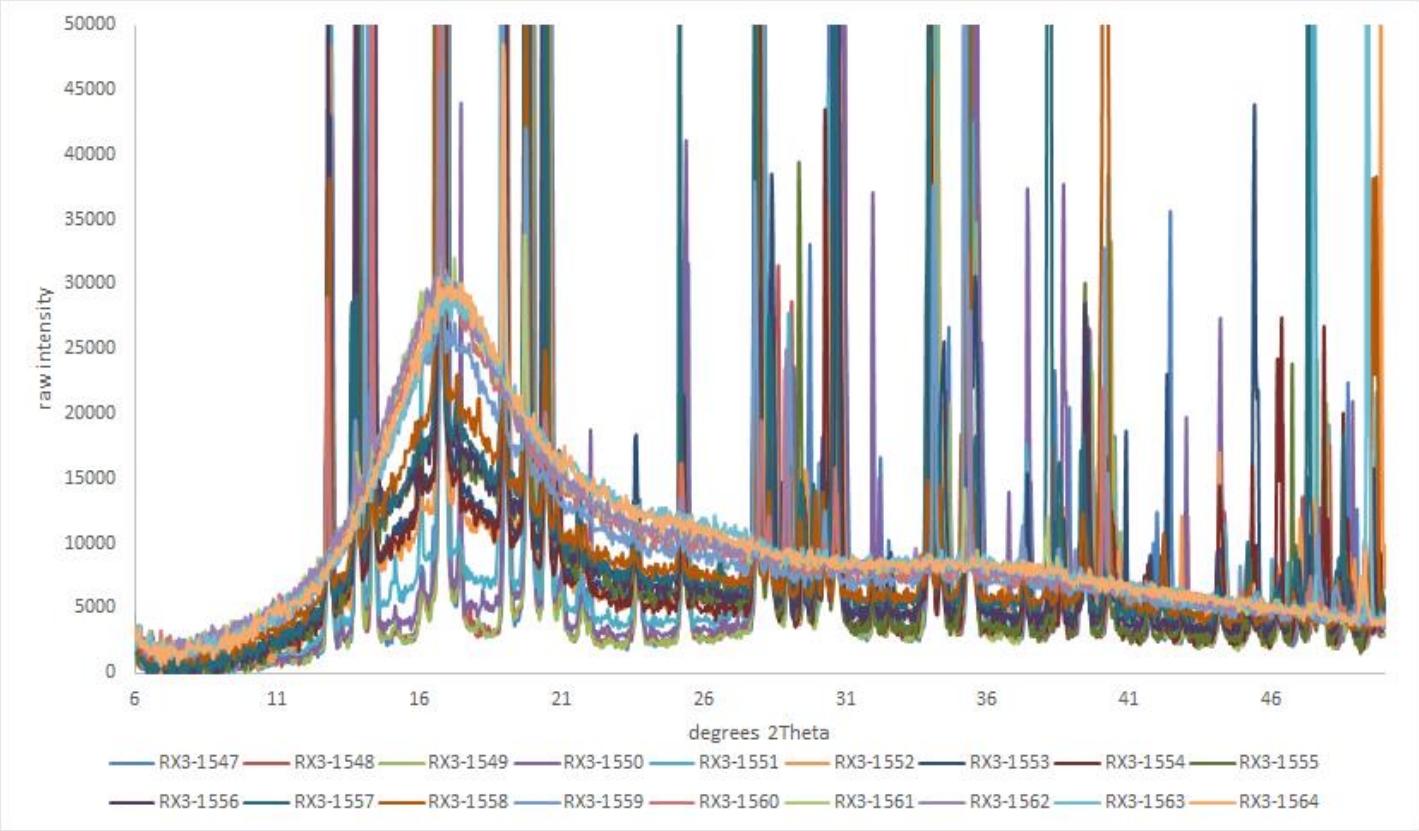
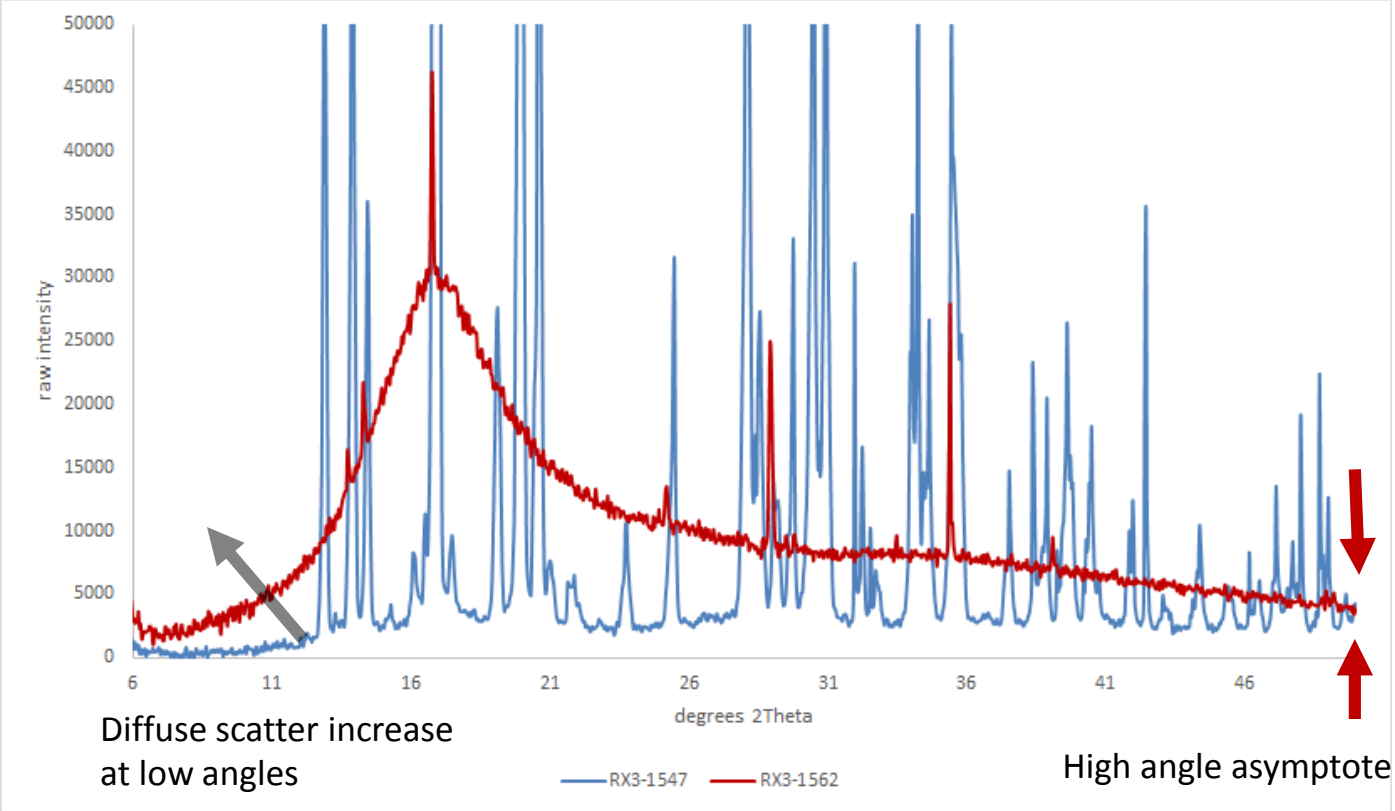
7.ii.) Study of fructose melt-quench (in-situ) I

Melt-Quench experiment for fructose using transmission X-ray optics and transmission non-ambient stage.



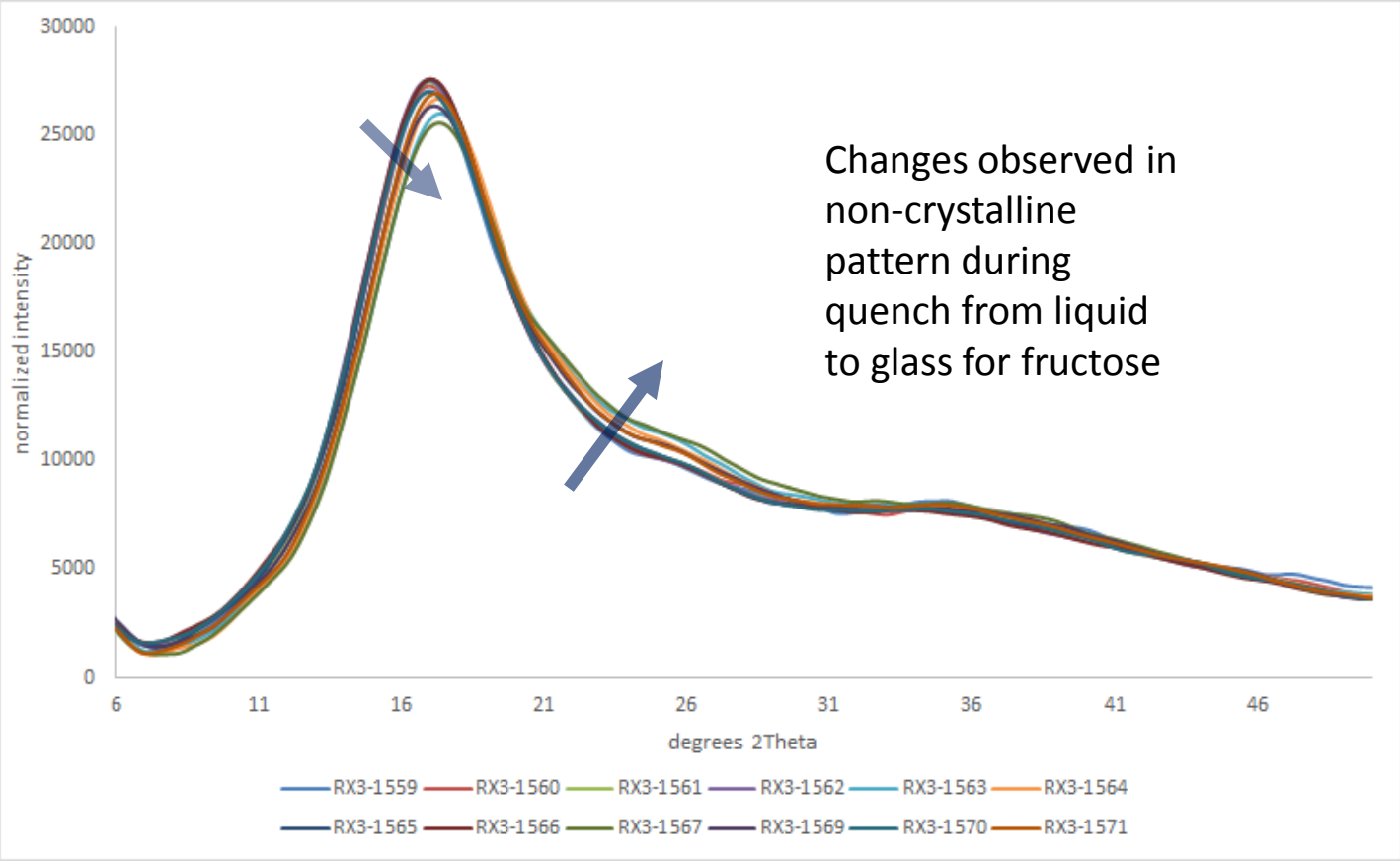
7.ii.) Study of fructose melt-quench (in-situ) II

The use of transmission optics with a contained sample allows a direct study of absolute changes in diffraction data from samples undergoing melt/quench



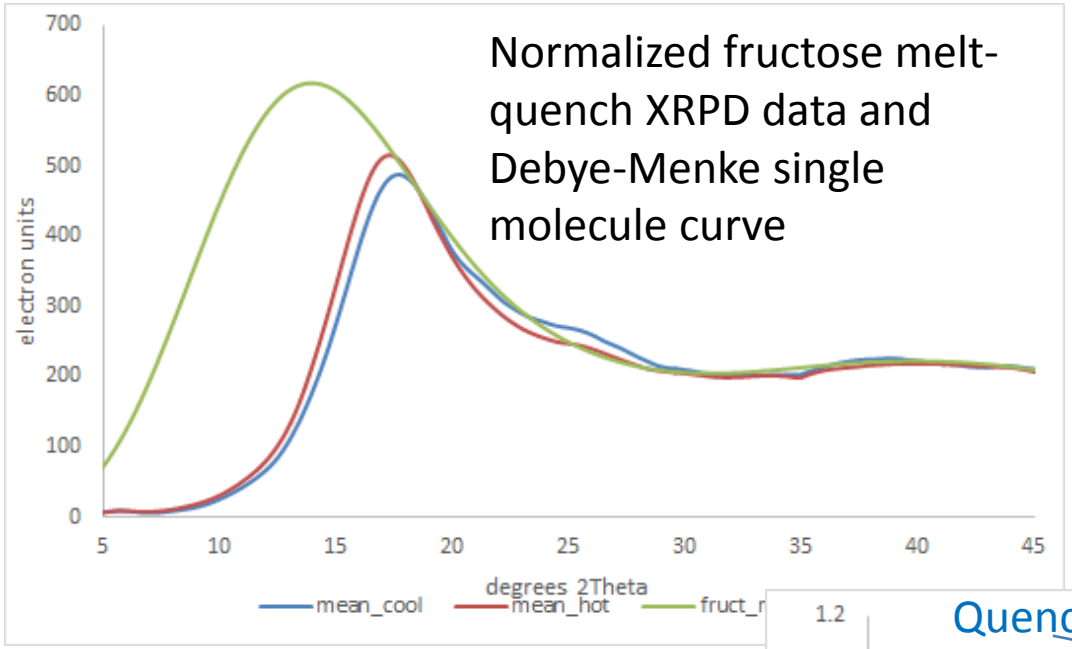
7.ii.) Study of fructose melt-quench (in-situ) III

Consistent changes observed in XRPD pattern for liquid and quench cooled glassy material



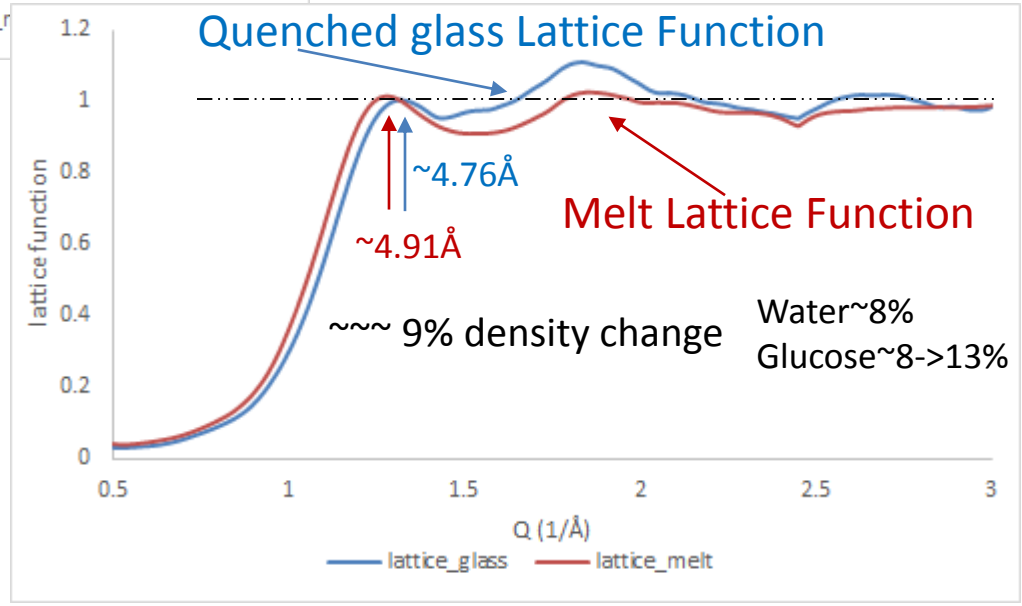
Changes observed in non-crystalline pattern during quench from liquid to glass for fructose

7.ii.) Study of fructose melt-quench (in-situ) IV

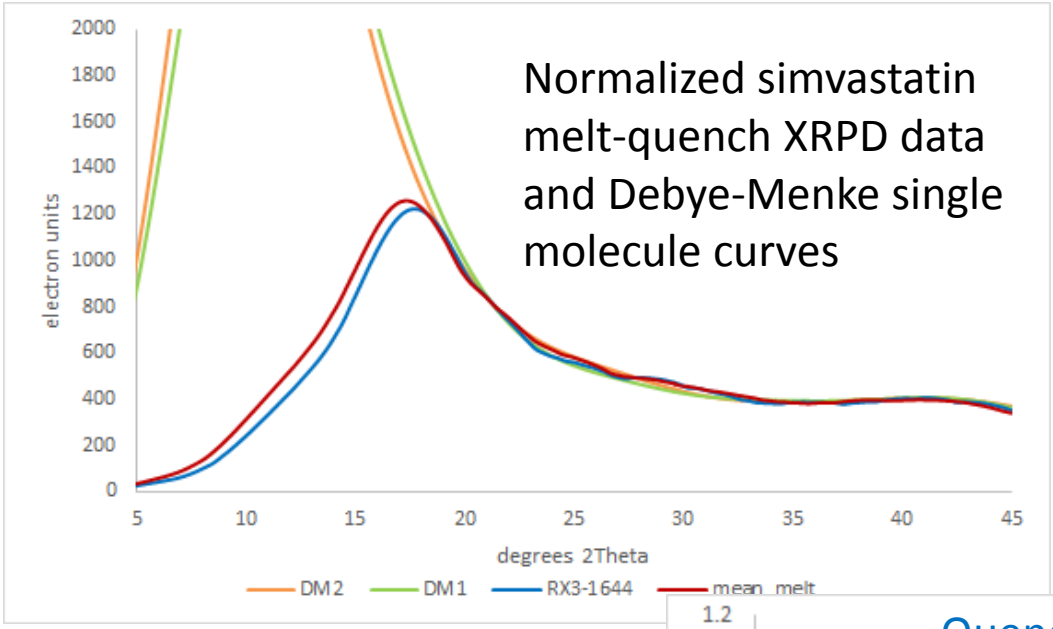


Calculation of Debye-Menke curve for fructose is complicated by the dynamic interchange of straight chain and ring forms in the melt. A fixed ratio was taken to derive the Debye-Menke curve.

Glassy fructose more stable than mannitol to re-crystallization. Derived lattice function has less well defined nearest neighbor peak. NN distance ~4.76Å for quench and ~4.91Å for melt.



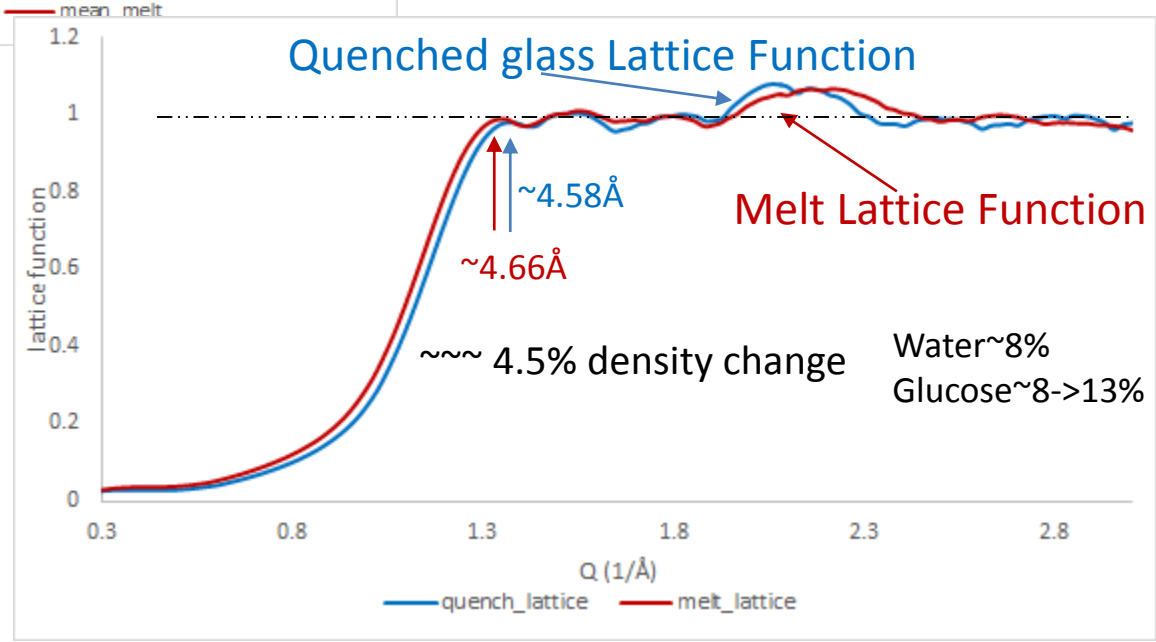
7.iii.) Study of simvastatin melt-quench (in-situ) I



Normalized simvastatin melt-quench XRPD data and Debye-Menke single molecule curves

Slightly different Debye-Menke curves can be generated for simvastatin due to its torsional flexibility. A mean Debye-Menke curve is taken for the lattice function derivation.

Glassy simvastatin is stable against re-crystallization.
Derived lattice function has no clearly defined nearest neighbor peak.
Exclusion zone cut-off ~4.58Å for quench and ~4.66Å for melt.



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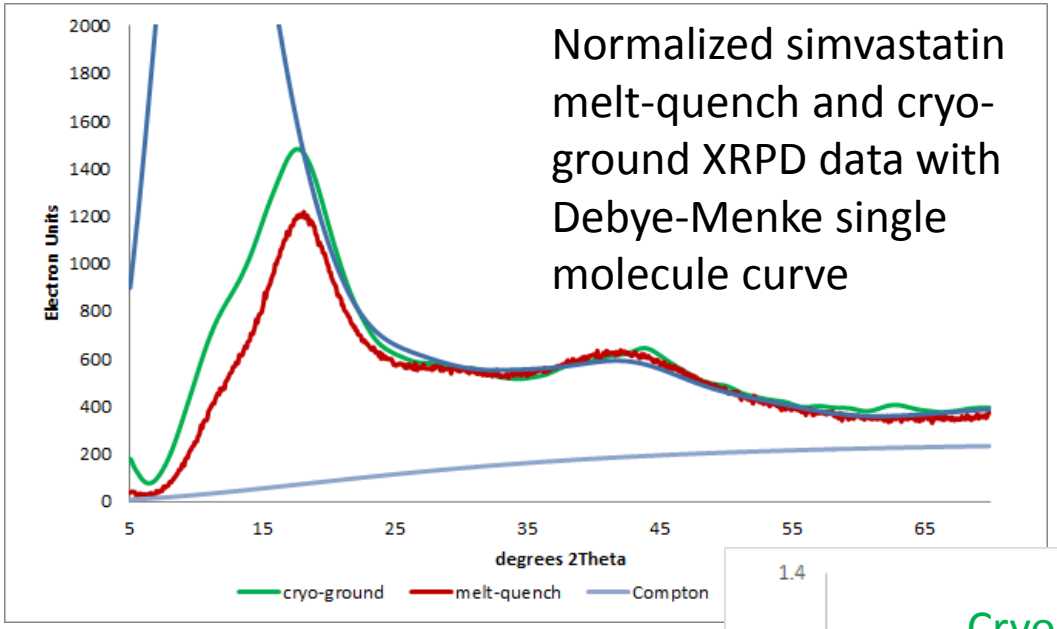
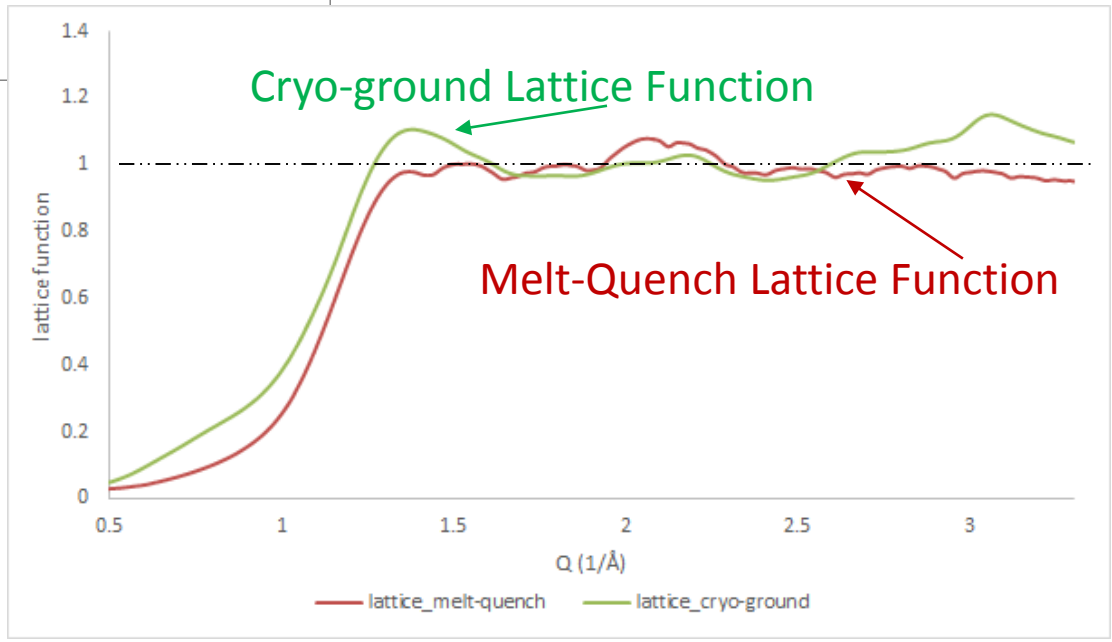
7.iii. Simvastatin melt-quench and cryo-ground I



Normalized simvastatin melt-quench and cryo-ground XRPD data with Debye-Menke single molecule curve

Difference between cryo-ground and melt-quench XRPD data for simvastatin (off-line) is more significant than difference between melt and quench XRPD data.

Cryo-ground material (unstable) exhibit a significant derived lattice function nearest-neighbor peak not observed for the melt-quench derived lattice function.



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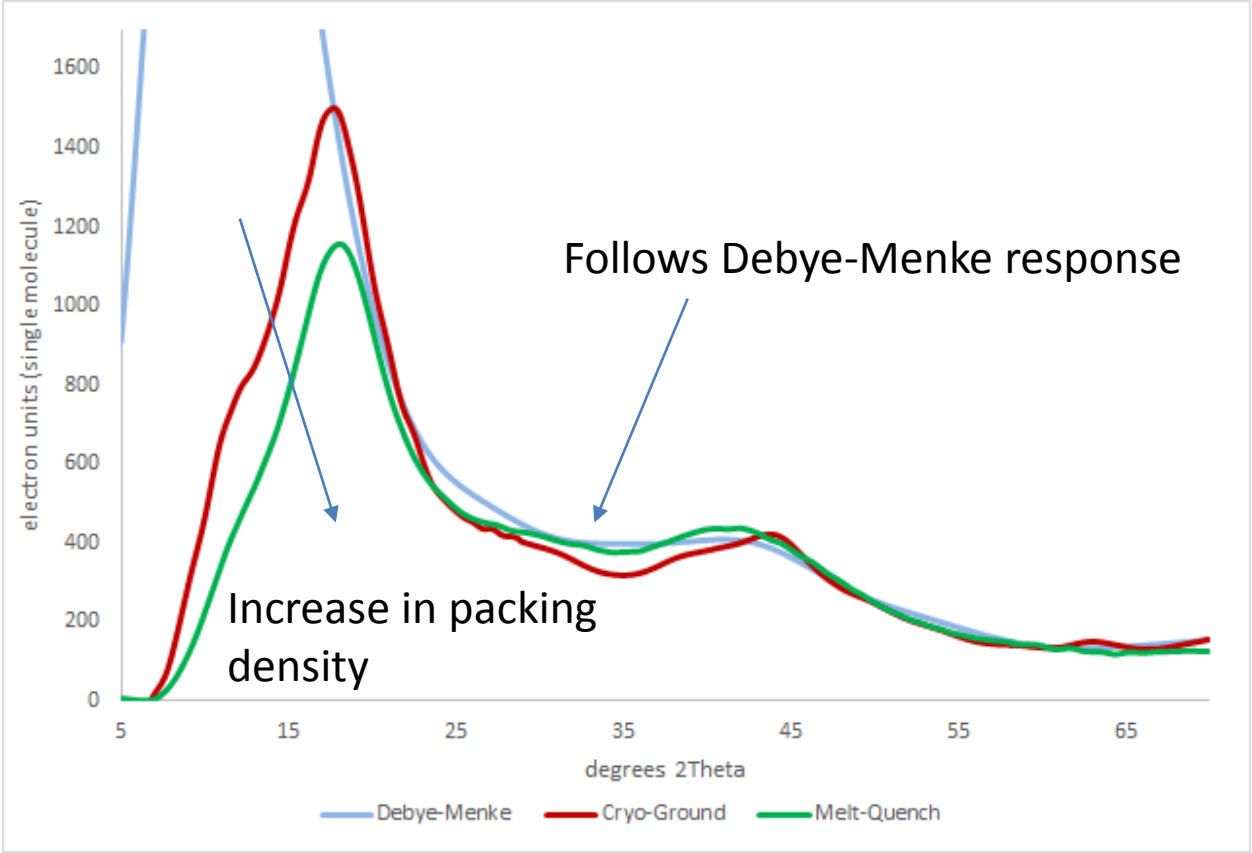
7.iii.) Simvastatin melt-quench and cryo-ground II

Melt-Quench form exhibits a higher packing density and more closely follows the predicted Debye-Menke curve.

No additional inter-molecular order induced by increased packing density.



Melt-Quench simvastatin is closer to the high symmetry state than cryo-ground simvastatin → increased stability.

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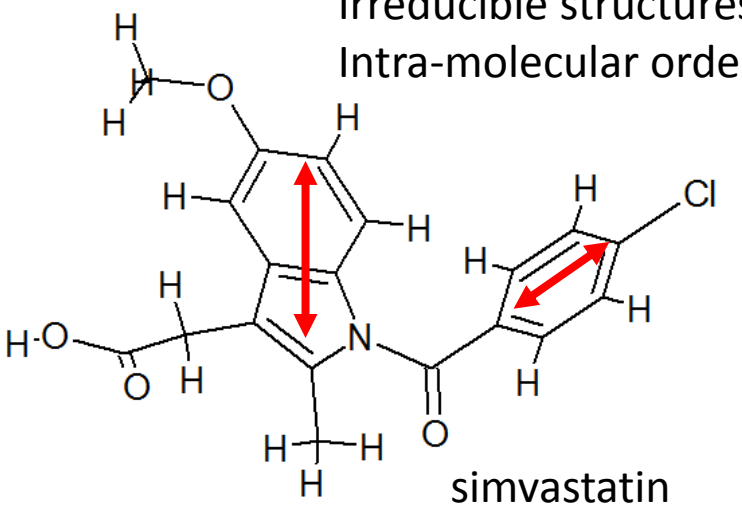
8.) Stability and Hypothetical Ideal Non-Crystalline

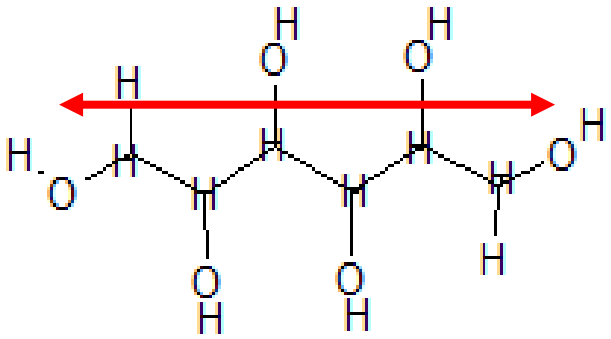
The highest symmetry state for a liquid/glassy system will be one within which every atom is equivalent to every other atom. Beyond the atomic level granularity there is, therefore, no local order and the system is isotropic.

Irreducible structures
Intra-molecular order



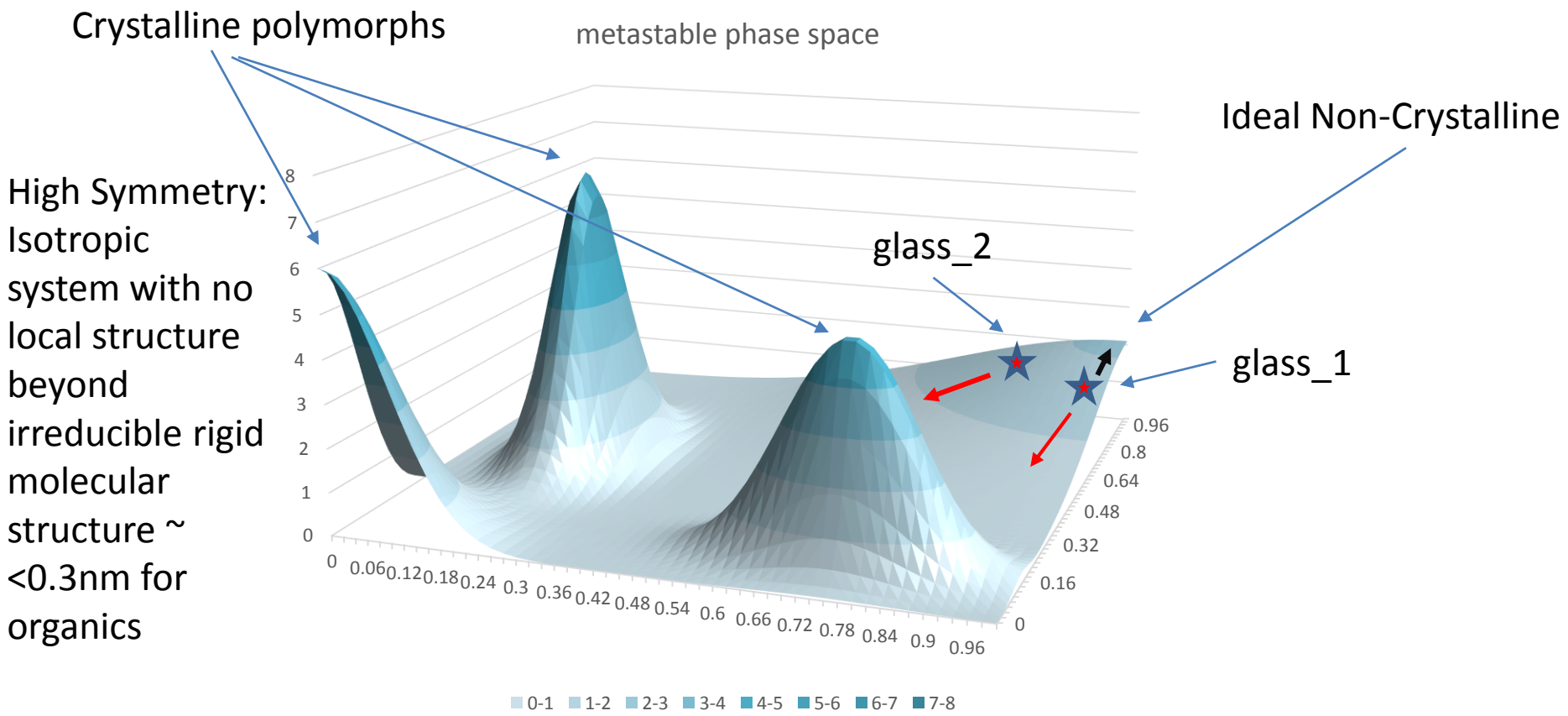
simvastatin

For organic molecules, the closest possible approach to the high symmetry state will still retain the irreducible local structure associated with rigid molecular segments.



mannitol

8.) Stability and Hypothetical Ideal Non-Crystalline



Ideal non-crystalline :: High Packing density + High Symmetry → increased physical stability.

Triclinic Labs