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Empirical Potential Structure Refinement

Data-driven structural modelling of total scattering data

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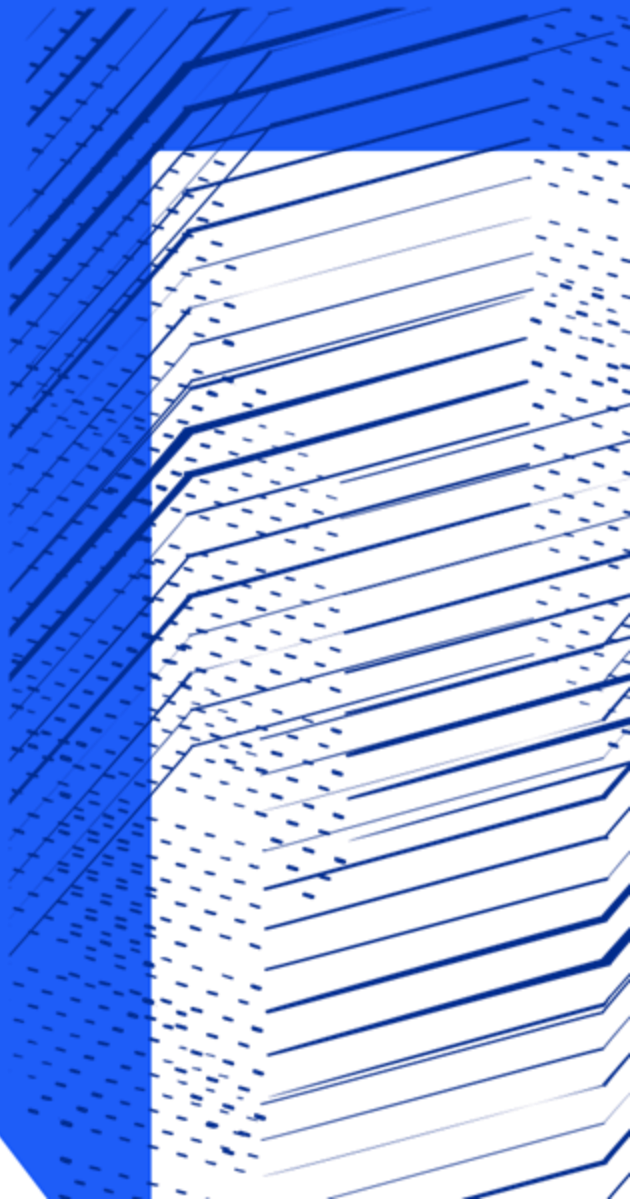
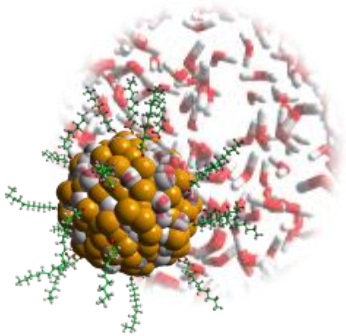


Disordered Materials

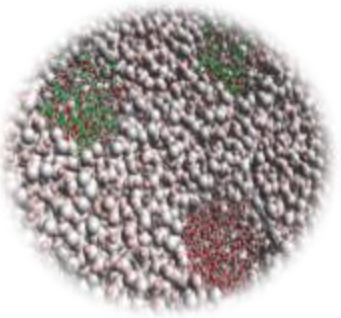
- Show predominantly local ordering (i.e. on the scale of atoms or molecules)
- Show primarily diffuse scattering (“soft” features in measured data)
- Are typically dynamic (e.g. liquids) – average structural picture is obtained
- May show long-range order (i.e. Bragg scattering)
- May contain large length-scale correlations (e.g. micelles, lamellae)

Liquids

Glasses

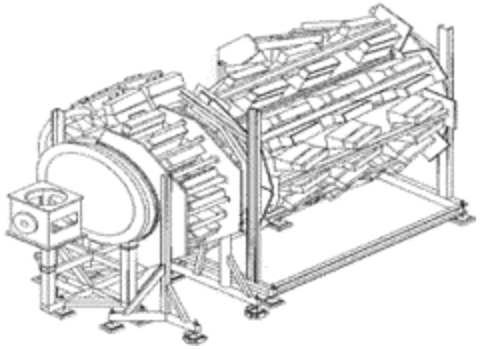


Solutions



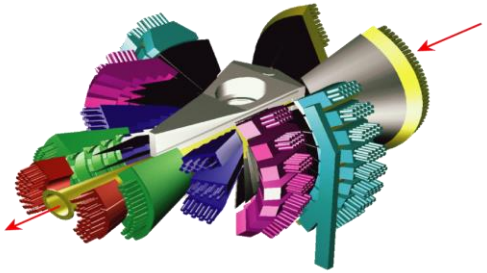
Condensed phases under confinement

Total Scattering Instruments @ ISIS



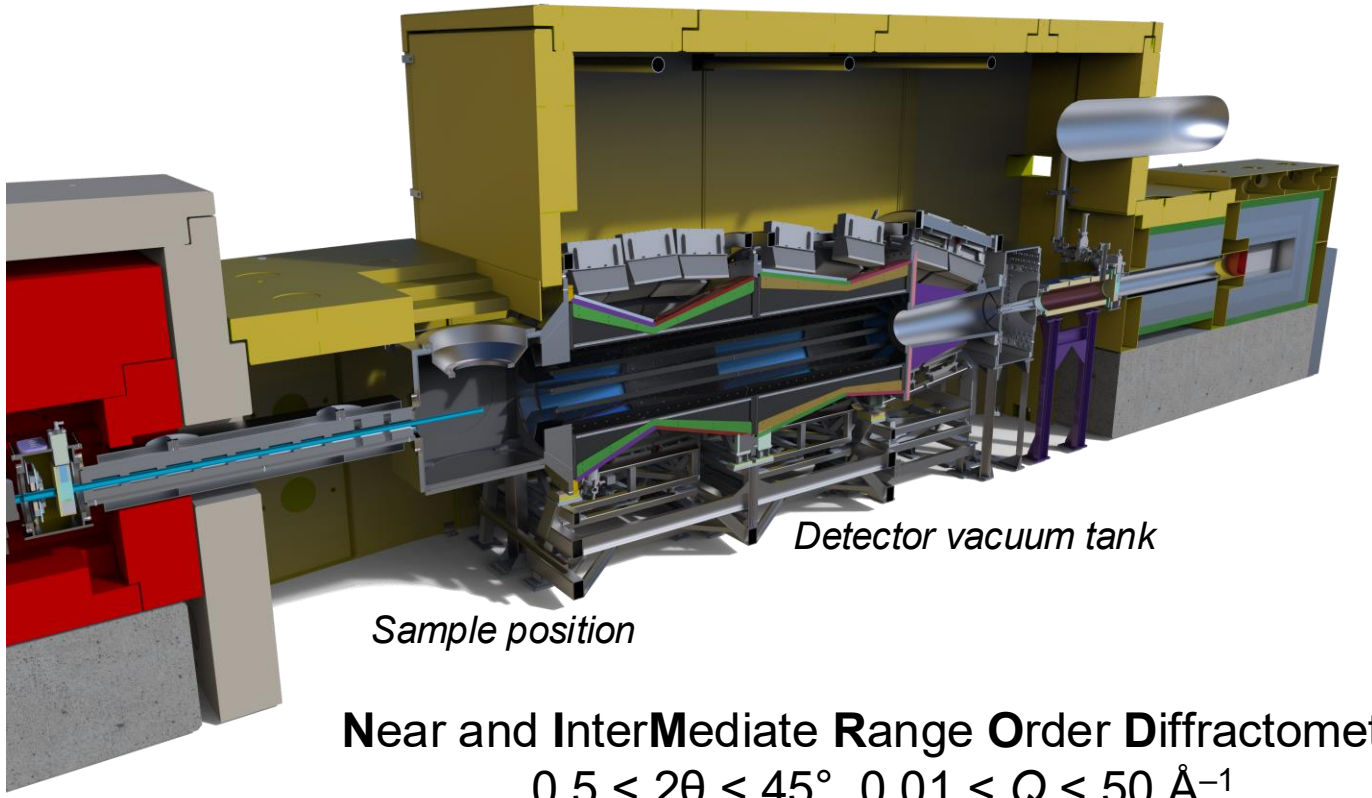
Small **A**ngle **N**eutron **D**iffractometer for **A**morphous and **L**iquid **S**amples

$3 < 2\theta < 38^\circ$, $0.1 < Q < 50$ Å^{-1}



General **M**aterials Diffractometer

$1.21 < 2\theta < 171.4^\circ$, $0.04 < Q < 50$ Å^{-1}



Near and **I**nter**M**ediate **R**ange **O**rder **D**iffractometer

$0.5 < 2\theta < 45^\circ$, $0.01 < Q < 50$ Å^{-1}

All three instruments exist to probe and understand material structure

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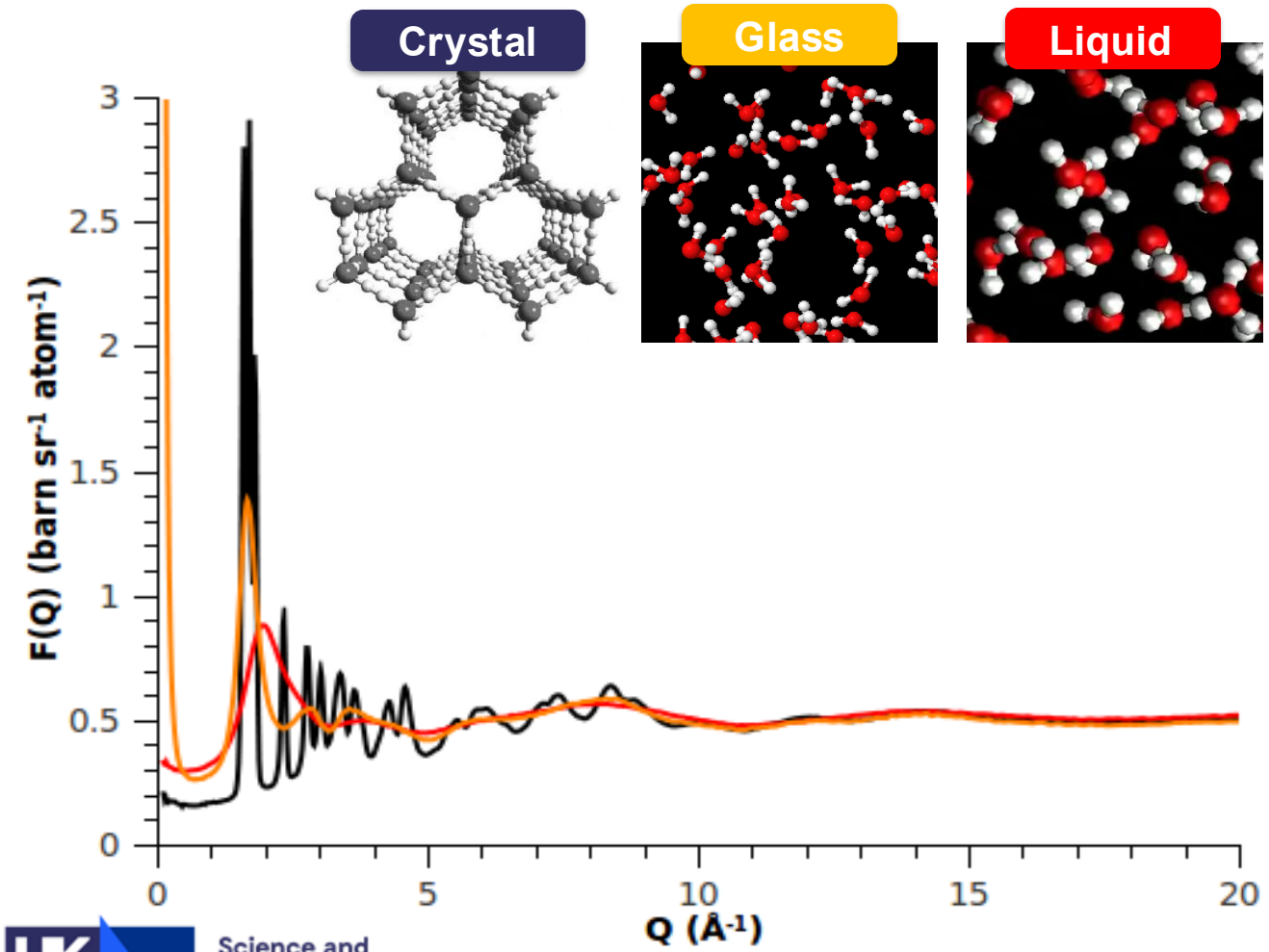
Total Structure Factor F(Q)



- Contains all correlation information between all "objects" in the system
- Also includes Bragg scattering
- Also includes any SANS

"A single dataset encompassing structural information on the target sample, no matter the phase, complexity, or composition of the system."

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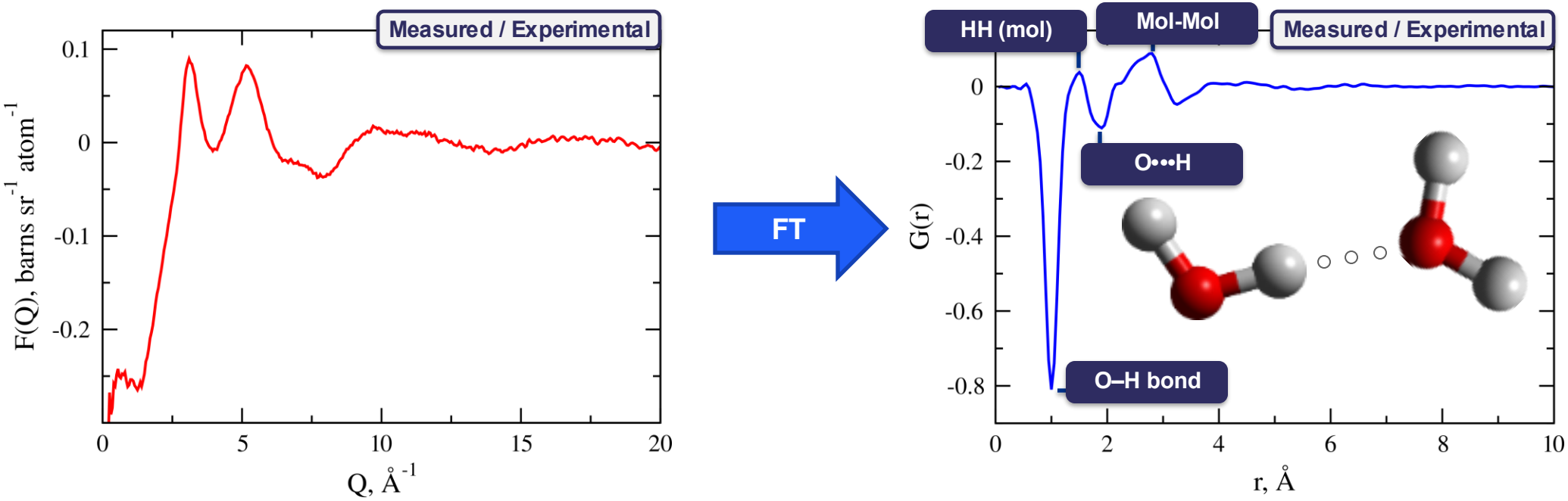
Interpreting F(Q)

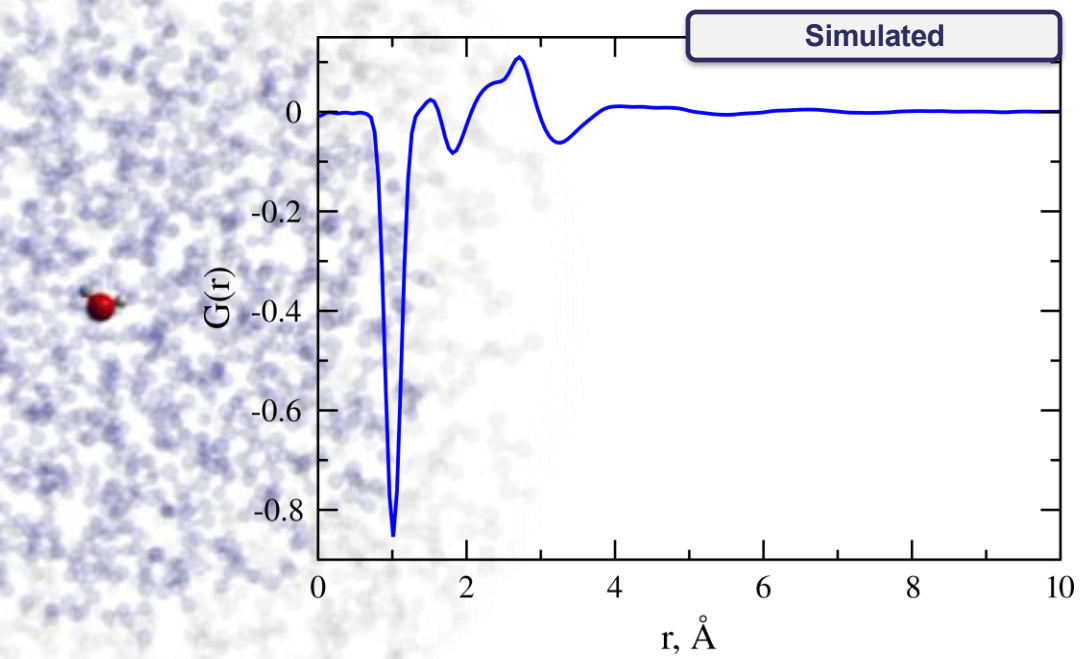
Can Fourier transform data from *Q*-space (instrument) to *r*-space (real)



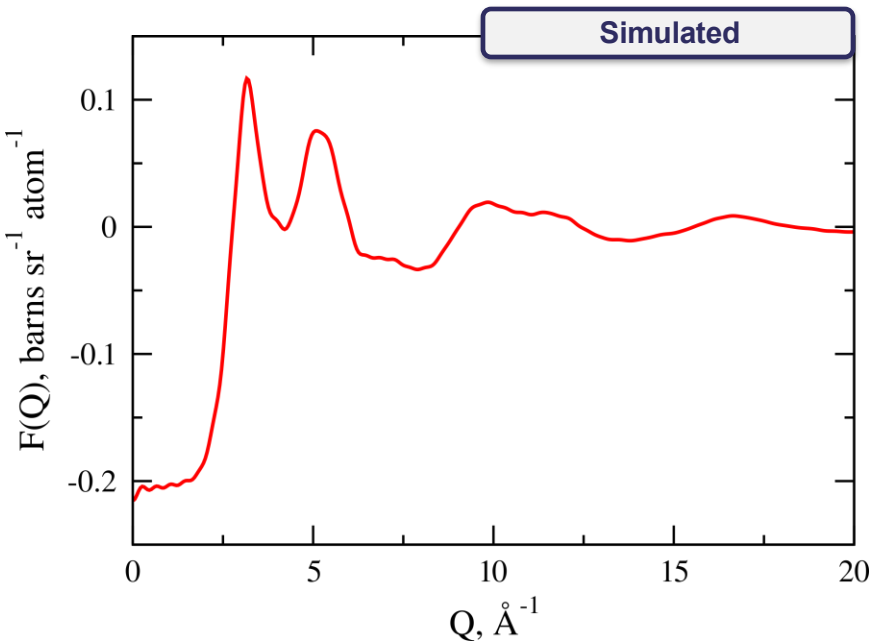
Non-trivial to analyse by inspection. Angular correlations? 3D structure?

Simulating F(Q)

Atomistic simulation – molecular dynamics, Monte Carlo – using off-the-shelf forcefield or *ab initio*.



FT

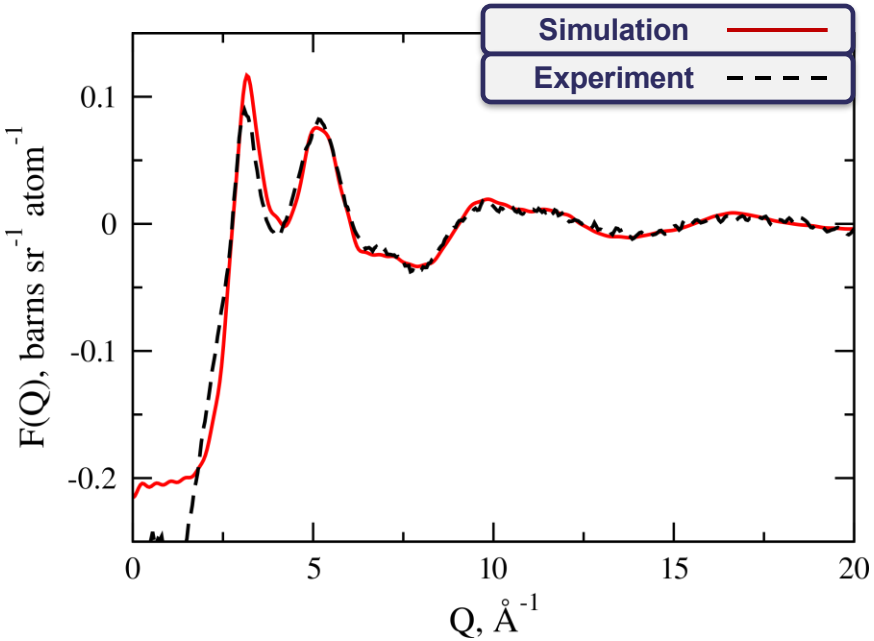


Can calculate any correlation I want from a simulation, but does it reflect reality?

Simulation vs Reality

Pure simulations can give results close to experiment, but are not guaranteed to reproduce the details of the experiment.

- Forcefields parameterised against phase data etc. rarely against bulk structure



Solution?

- Modify the forcefield to improve it
- By hand? Tedious, impractical…
- Automatically, using the data? How?

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Data-Driven Simulation with Empirical Potential Structure Refinement

The Goal

- Make a simulation of a system of arbitrary complexity
- Compare available experimental F(Q) with simulated F(Q)

- **Adjust the underlying forcefield to get good / better / acceptable agreement with the experimental measurements**

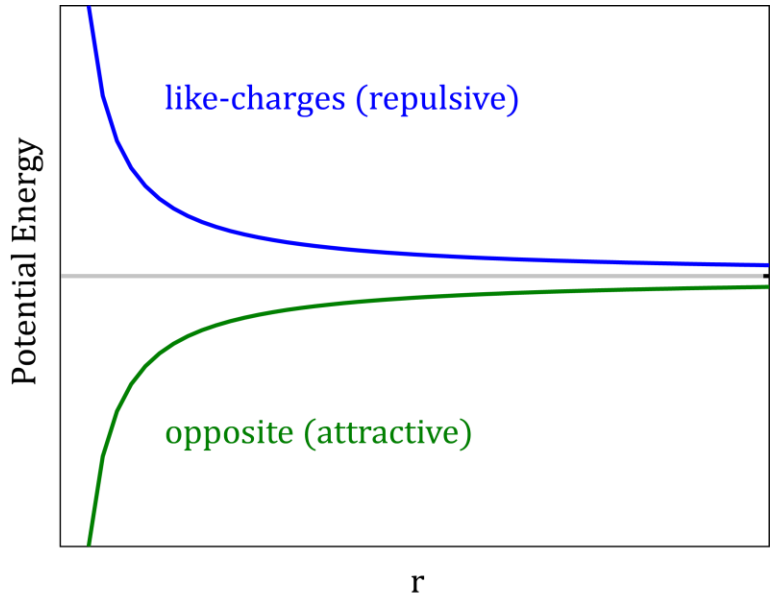
- Calculate structural properties of interest
- Write a paper
- Go home

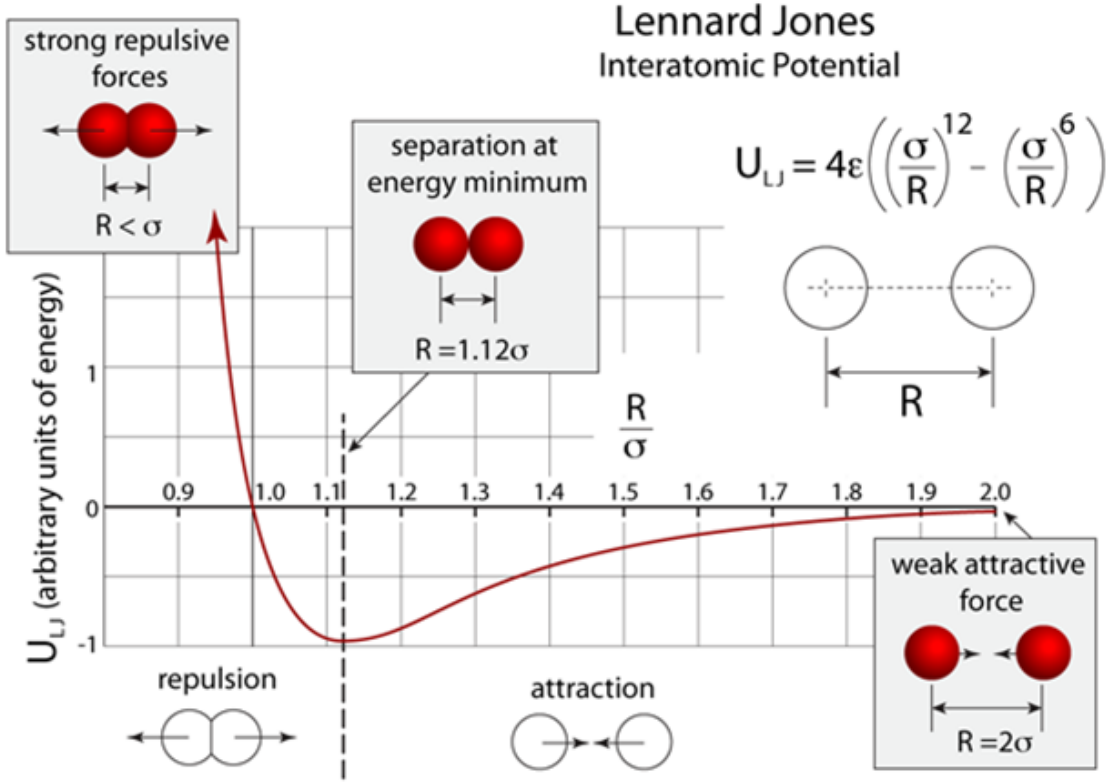
The Target: Pair Potentials

- Describes the interactions between atoms “through space”
- Parameters from:
  - Existing forcefields (LJ+q)
  - Calculated via QM / DFT (q)

Coulomb:

$$U = \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}^2}$$





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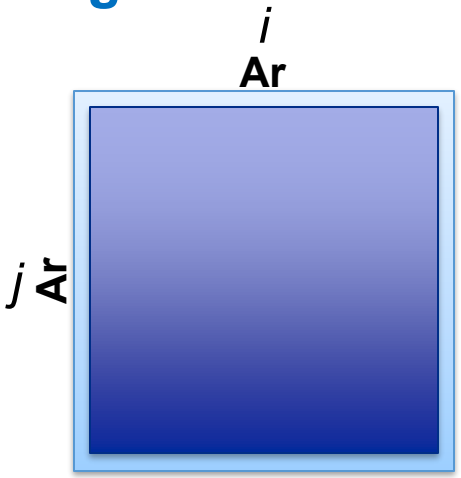
Atom Types

- A specific kind of atom *in the simulation*
  - Depends at least on the element. Can be split by chemical environment.
  - Does not depend on isotope...

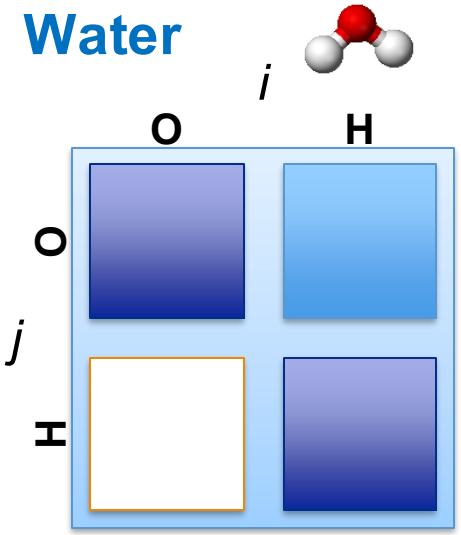
Argon



***N* = 1**

Also N_2, O_2…

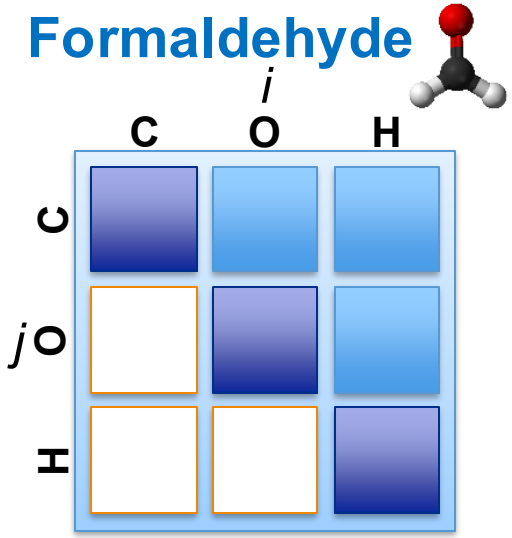
Water



***N* = 3**

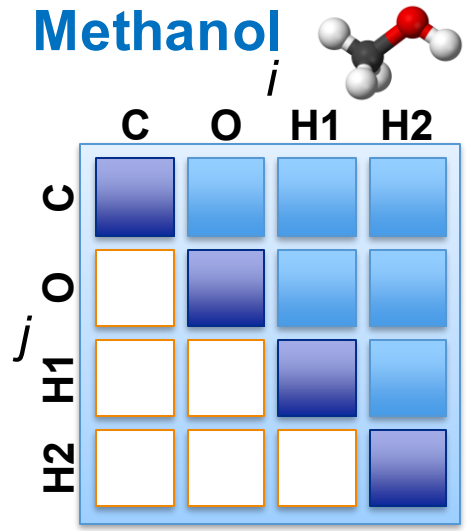
Also benzene, silica…

Formaldehyde



***N* = 6**

Methanol



***N* = 10**

$$F(Q) = \sum_{i,j} (2 - \delta_{ij}) c_i c_j b_i b_j S_{ij}(Q)$$

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Constructing the F(Q)

$$F(Q) = \sum_{i,j} (2 - \delta_{ij}) c_i c_j b_i b_j S_{ij}(Q)$$

Total Structure Factor
(Experimental Observable)

$$c_i = \frac{n_i}{N} \qquad b_i = scattering\ length$$

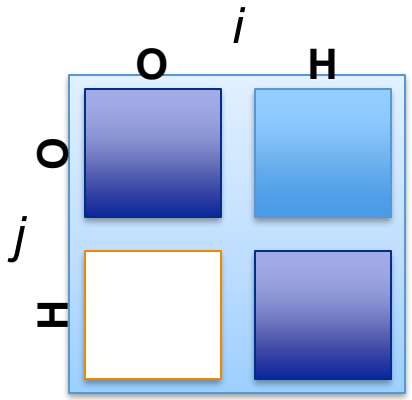
$$S_{ij}(Q) = \rho \int_0^\infty 4\pi r^2 g_{ij}(r) \frac{\sin Qr}{Qr} \mathrm{d}r$$

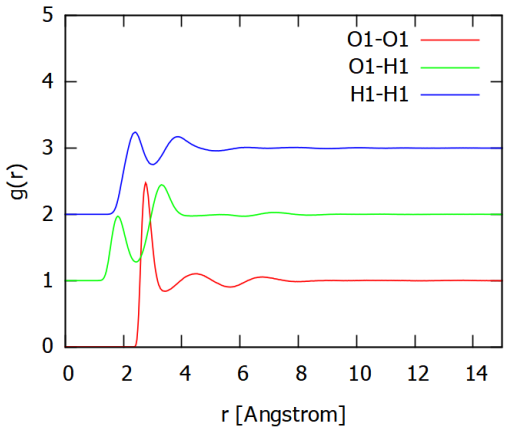
Partial Structure Factor

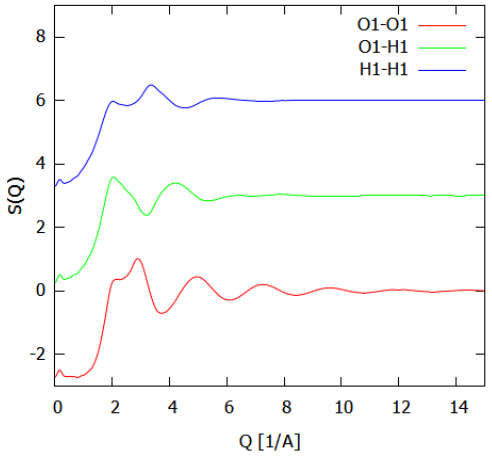
(Simulation Observable)

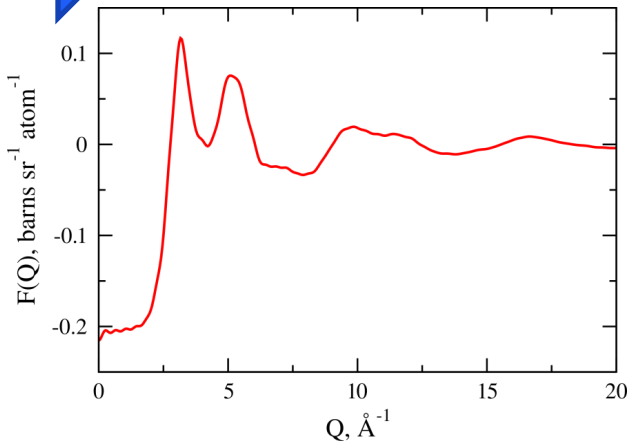
So…

Simulation Potentials U(r) → MC/MD → Simulated g(r) → FT → Simulated S(Q) → Weight → Simulated F(Q)









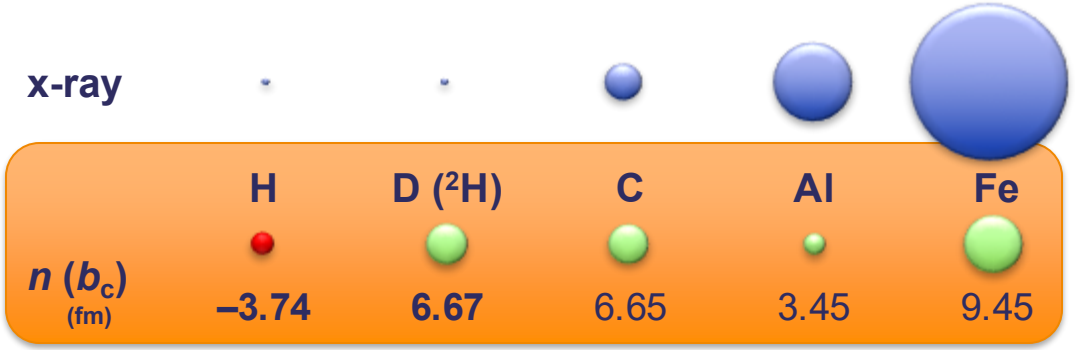
$$w_{ij} = c_i c_j \boldsymbol{b_i b_j}$$

$$\begin{bmatrix} 0.0374 & -0.0964 & 0.0622 \end{bmatrix} \begin{bmatrix} S_{OO}(Q) \\ S_{OH}(Q) \\ S_{HH}(Q) \end{bmatrix} = F_{H_2O}(Q)$$

"Real" Potentials U(r) ← Inversion ← Experimental g(r) ← FT⁻¹ ← Experimental S(Q) ← Weight⁻¹ ← Experimental F(Q)

Using Neutrons? Isotopic Substitution!

$$F(Q) = \sum_{i,j} (2 - \delta_{ij}) c_i c_j \underbrace{\boldsymbol{b_i b_j}}_{\text{Scattering Lengths}} S_{ij}(Q)$$

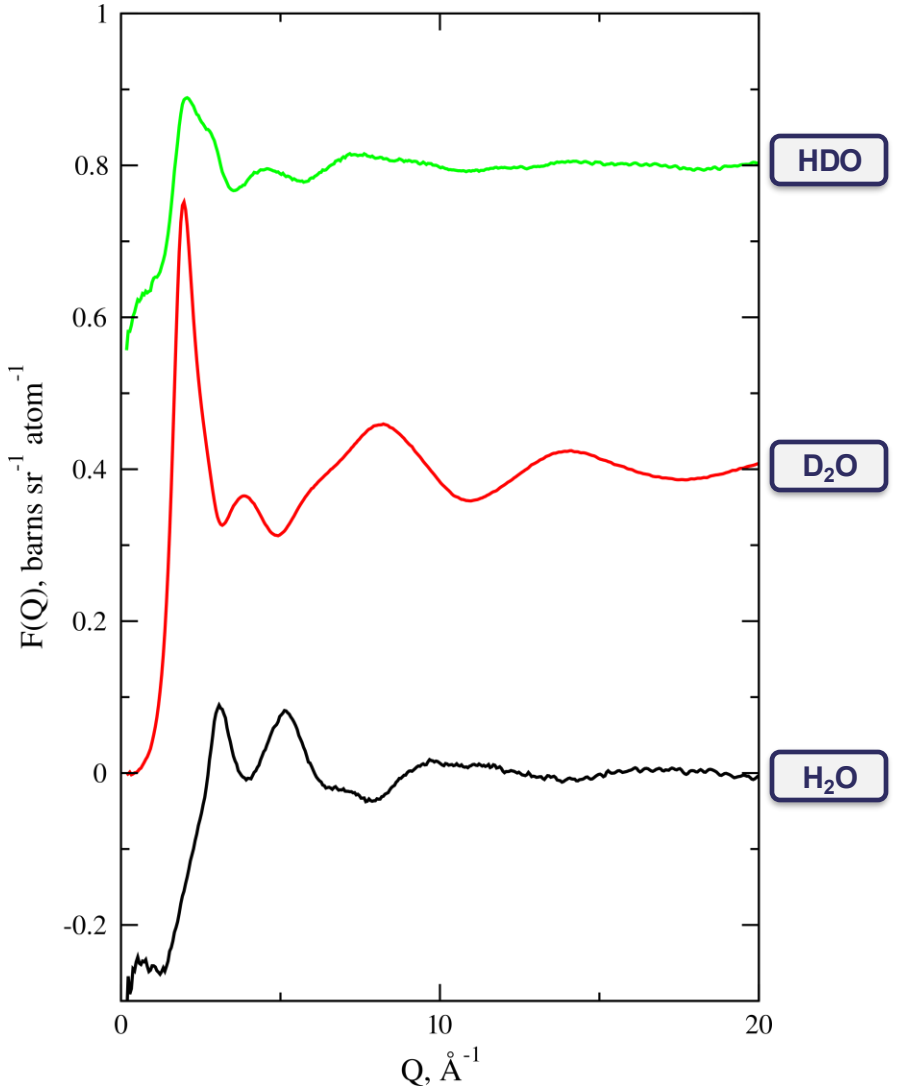


- Partial $S(Q)$ weighted by coherent scattering length, $\boldsymbol{b}$
- For neutrons, $\boldsymbol{b}$ is dependent on isotope
  - e.g. ^{2}H for H, ^{15}N for N, ^{6}Li for Li
- Key assumption: structure is independent of isotopes used
- Perform multiple measurements on the same system, with different isotopic substitutions

Isotopic Water

- Swapping H for ^{2}H (D) we can get three distinct datasets (i.e. three different measurements *of the same structure*):
  - H_2O
  - D_2O
  - 50:50 mix of H_2O and D_2O

N.B. Swapping isotopes always needs to involve enough atoms to produce a noticeable change in the F(Q)



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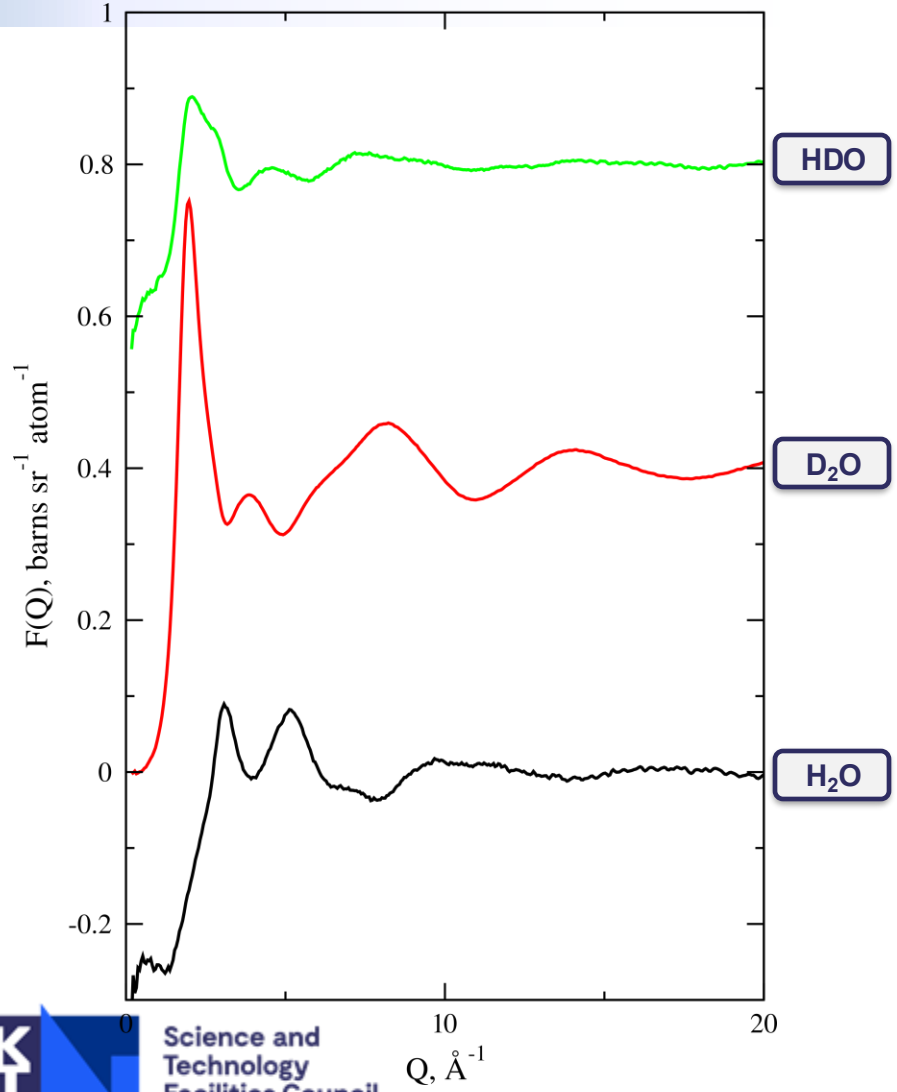
Great! So what?



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Experimental F(Q) $\quad w_{ij} \quad$ **Experimental S(Q)**

$$\begin{bmatrix} F_{H_2O}(Q) \\ F_{D_2O}(Q) \\ F_{HDO}(Q) \end{bmatrix} = \begin{bmatrix} 0.0374 & -0.0964 & 0.0622 \\ 0.0374 & 0.1722 & 0.1980 \\ 0.0374 & 0.0378 & 0.0096 \end{bmatrix} \begin{bmatrix} S_{OO}(Q) \\ S_{OH}(Q) \\ S_{HH}(Q) \end{bmatrix}$$

Invert

Experimental S(Q) $\quad w_{ij}^{-1} \quad$ **Experimental F(Q)**

$$\begin{bmatrix} S_{OO}(Q) \\ S_{OH}(Q) \\ S_{HH}(Q) \end{bmatrix} = \begin{bmatrix} 4.8238 & -2.7037 & 24.6061 \\ -5.8227 & 1.6265 & 4.1962 \\ 4.1525 & 4.1525 & -8.3050 \end{bmatrix} \begin{bmatrix} F_{H_2O}(Q) \\ F_{D_2O}(Q) \\ F_{HDO}(Q) \end{bmatrix}$$

FT^{-1}

Experimental g(r)

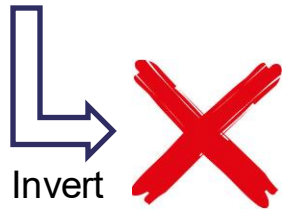
"Real" Potentials U(r)

The General Case

- For an “ideal” system such as H_2O where enough isotopic substitutions can be made, direct matrix inversion is possible
- What about cases where one or more partials only contribute weakly?
- What about cases where not enough isotopic substitutions can be made?

For example, silica:

$$\begin{bmatrix} F_{SiO_2}(Q) \end{bmatrix} = \begin{bmatrix} 0.0191 & 0.1070 & 0.1497 \end{bmatrix} \begin{bmatrix} S_{SiSi}(Q) \\ S_{SiO}(Q) \\ S_{OO}(Q) \end{bmatrix}$$



The Augmented Scattering Matrix

- We have a simulation which we assume gives us a good "guess" of the $F(Q)$ and hence a good guess for the partial $S(Q)$
- Define a feedback factor, $0 < f < 1$, and write new weighting factors

$$w_{ij} = f c_i c_j b_i b_j$$

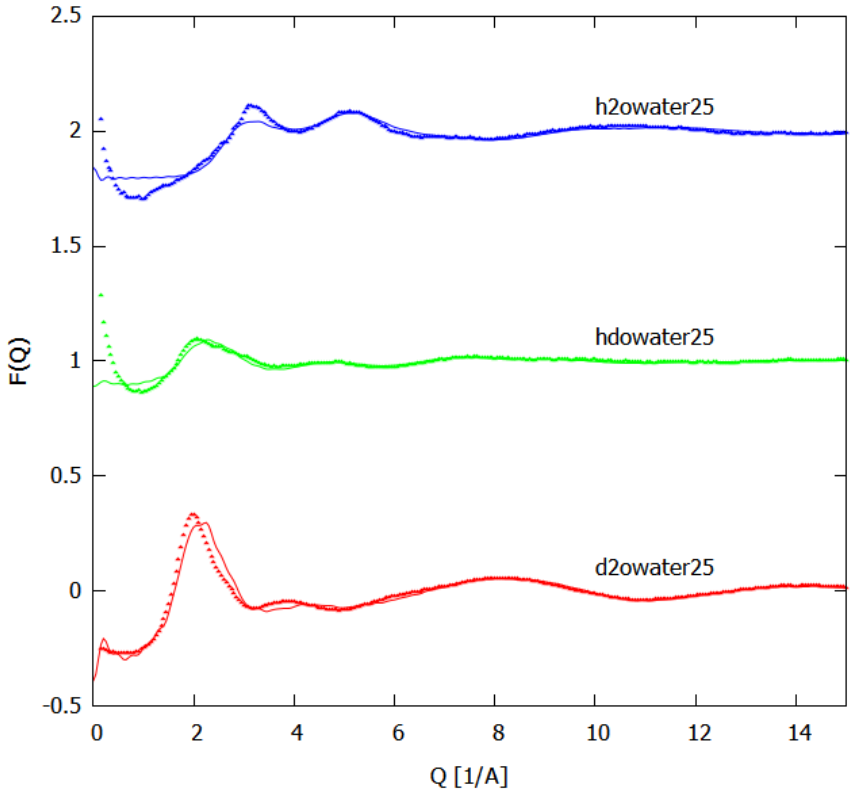
$$\begin{bmatrix} F_{SiO_2}(Q) \\ S^{sim}_{SiSi}(Q) \\ S^{sim}_{SiO}(Q) \\ S^{sim}_{OO}(Q) \end{bmatrix} = \begin{bmatrix} 0.0172 & 0.0963 & 0.1347 \\ 0.1 & 0.0 & 0.0 \\ 0.0 & 0.1 & 0.0 \\ 0.0 & 0.0 & 0.1 \end{bmatrix} \begin{bmatrix} S_{SiSi}(Q) \\ S_{SiO}(Q) \\ S_{OO}(Q) \end{bmatrix}$$

$$w_{ij} = (1 - f)$$

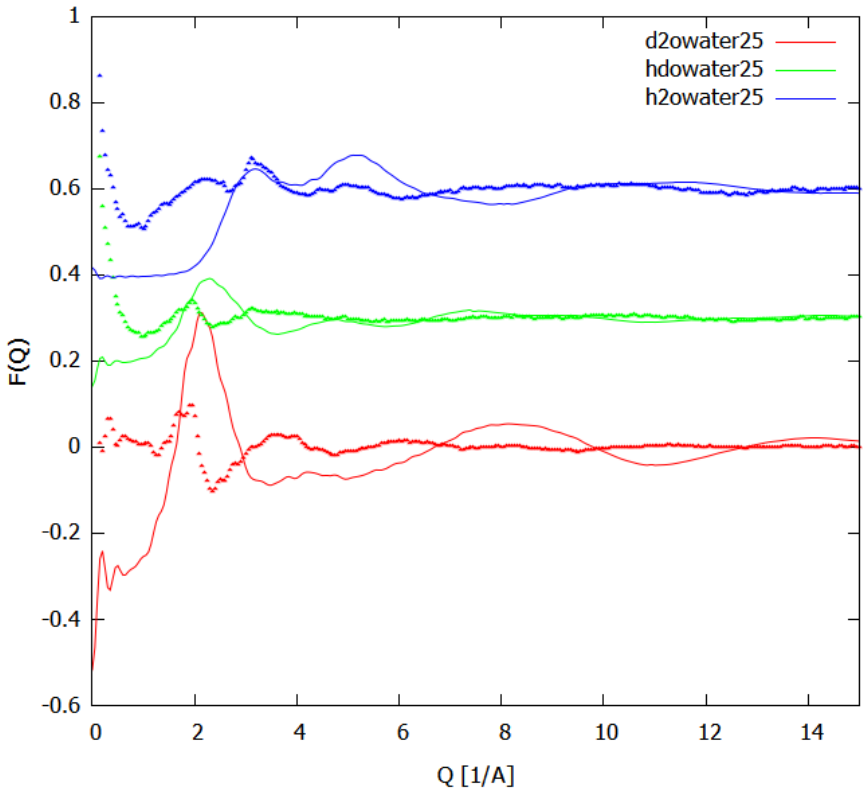
- Now we have an overdetermined matrix for which we can find a pseudoinverse

The EPSR Method

1) Take differences between experimental and simulated $F(Q)$ to get $\Delta F(Q)$



F(Q) from simulation and experiment



ΔF(Q) between simulation and experiment

The EPSR Method

1) Take differences between experimental and simulated $F(Q)$ to get $\Delta F(Q)$
2) Enter these $\Delta F(Q)$ into the inverse scattering matrix to generate $\Delta S(Q)$

$$\begin{bmatrix} \Delta S_{OO}(Q) \\ \Delta S_{OH}(Q) \\ \Delta S_{HH}(Q) \end{bmatrix} = \begin{bmatrix} 4.8238 & -2.7037 & 24.6061 \\ -5.8227 & 1.6265 & 4.1962 \\ 4.1525 & 4.1525 & -8.3050 \end{bmatrix} \begin{bmatrix} \Delta F_{H_2O}(Q) \\ \Delta F_{D_2O}(Q) \\ \Delta F_{HDO}(Q) \end{bmatrix}$$

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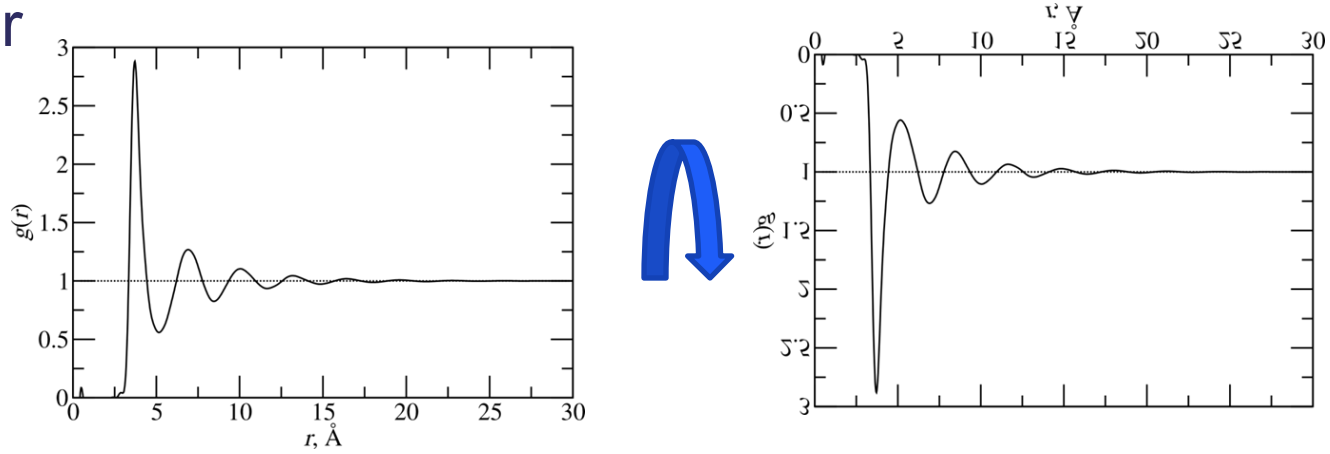
3) Transform the $\Delta S(Q)$ into $\Delta g(r)$ and use these to form an additional, empirical potential for each atom type pair



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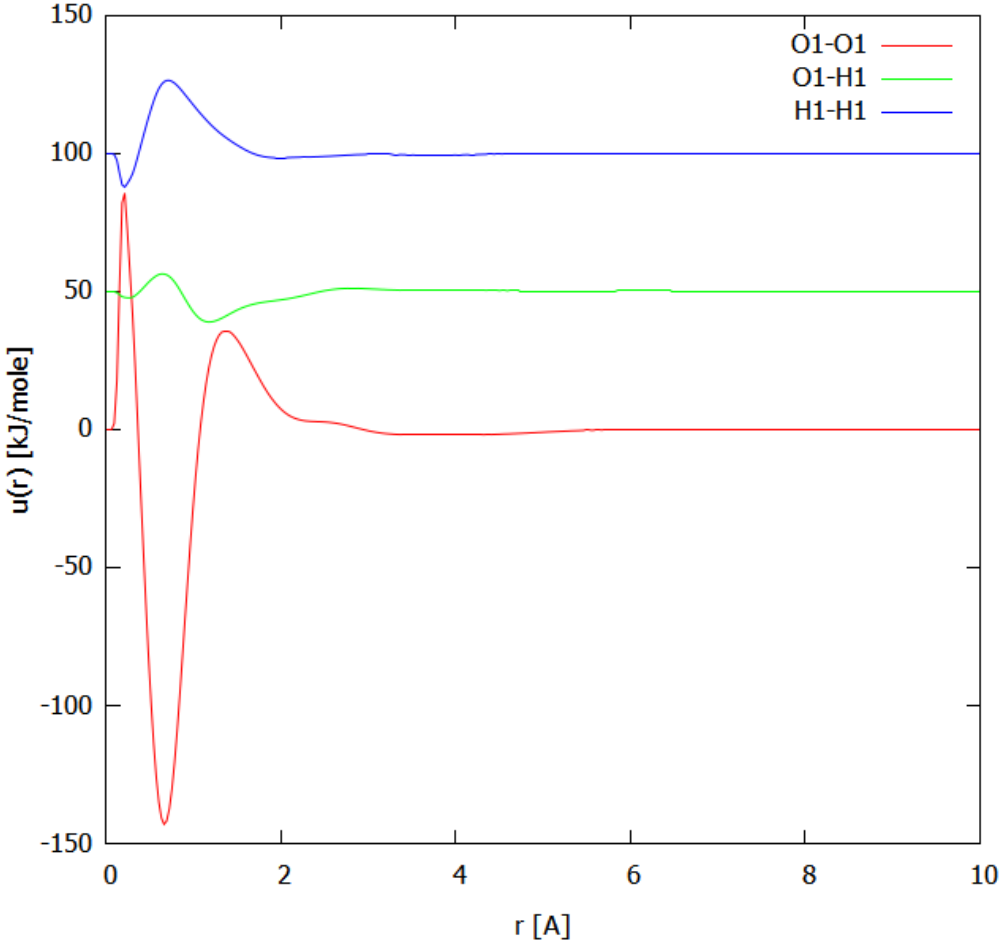
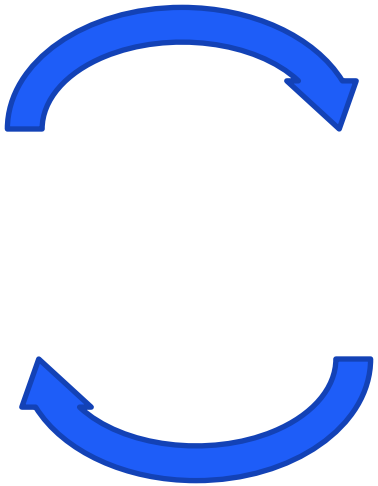
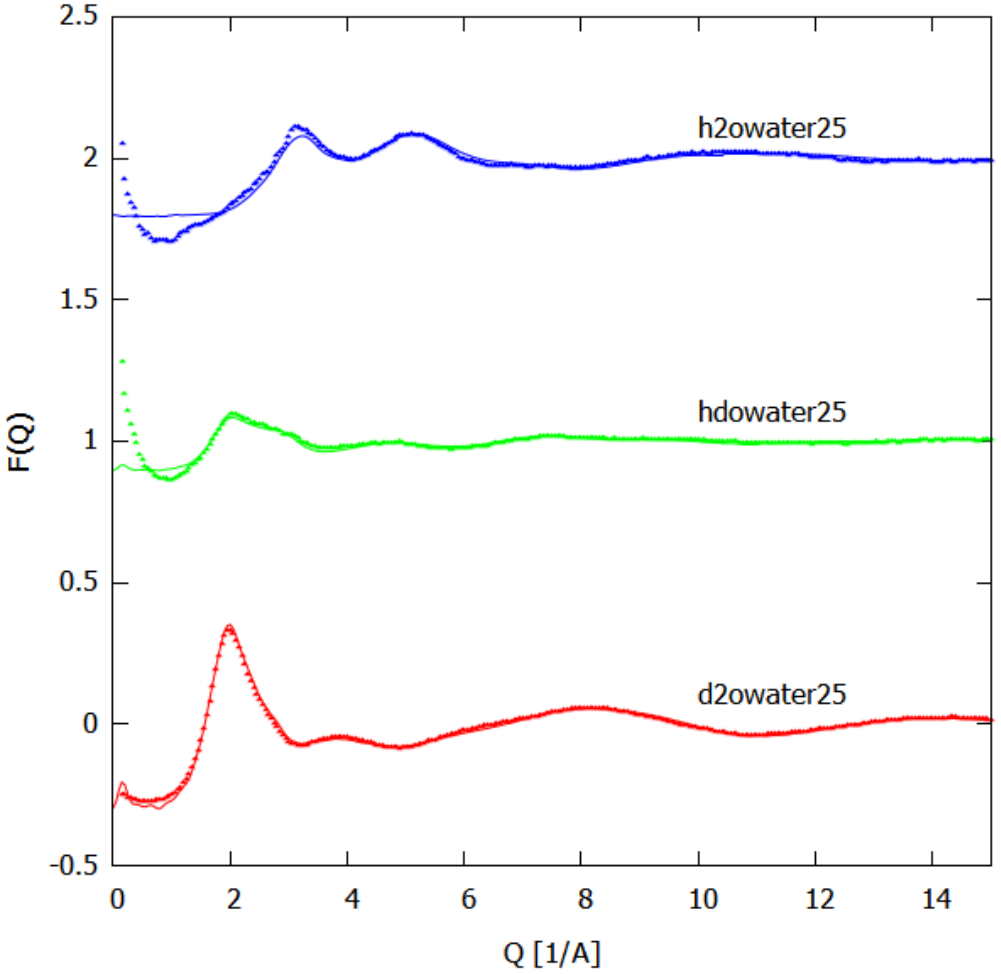
3) Transform the $\Delta S(Q)$ into $\Delta g(r)$ and use these to form an additional, empirical potential for each atom type pair
4) Repeatedly run the simulation and refine **additional potentials** until the experimental and simulated $F(Q)$ 'match'

Potential Refinement: EPSR results







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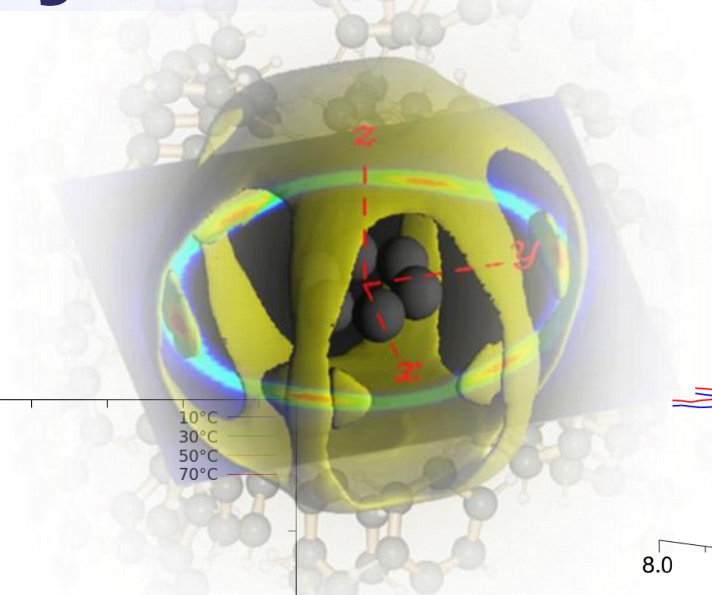
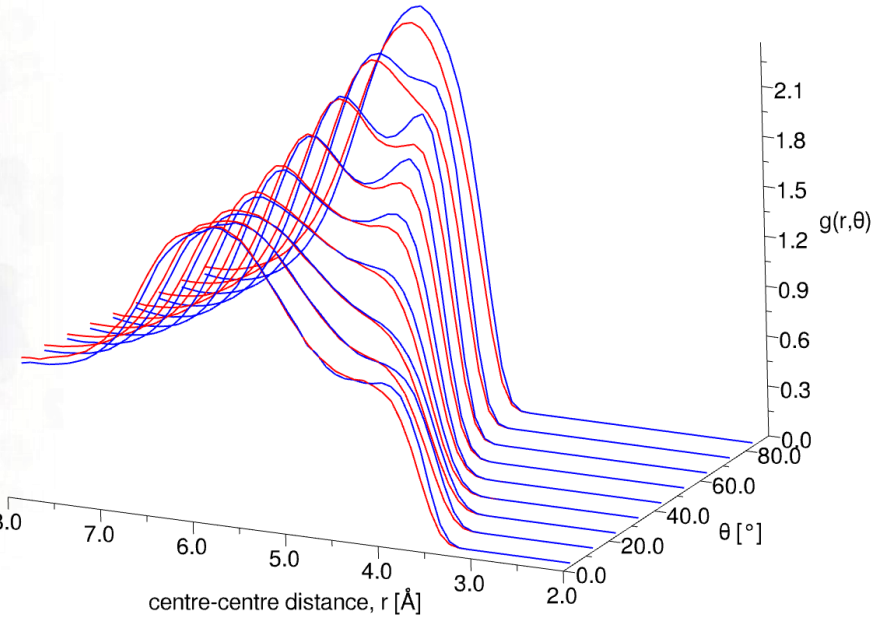
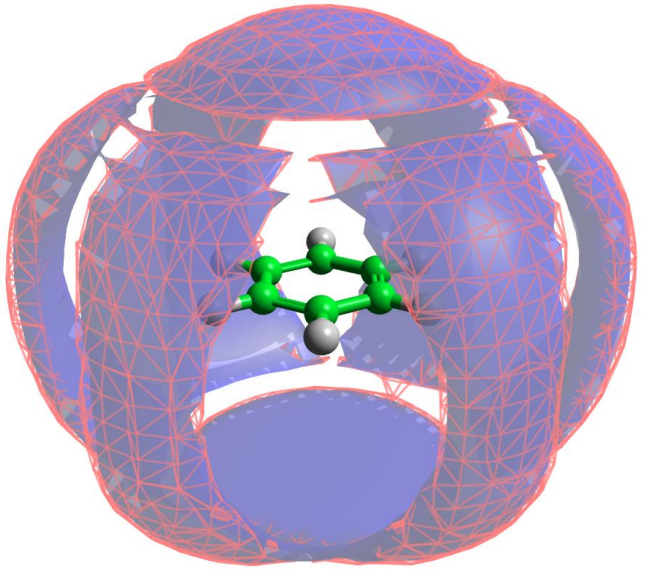
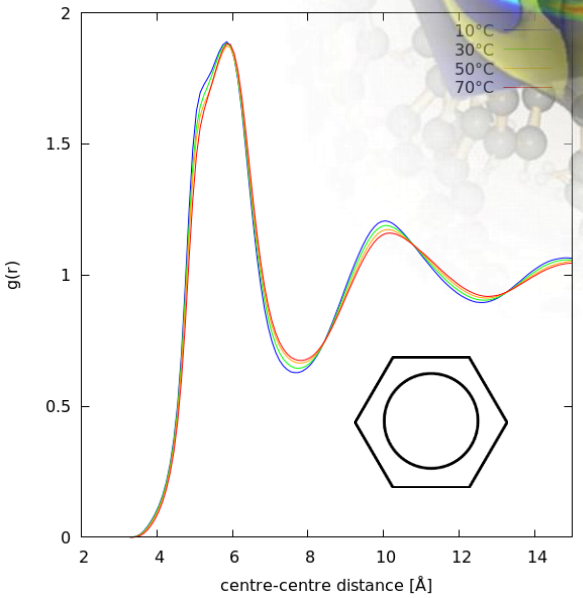
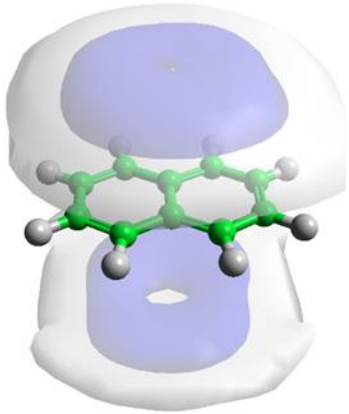
Analyse the Refined Simulation

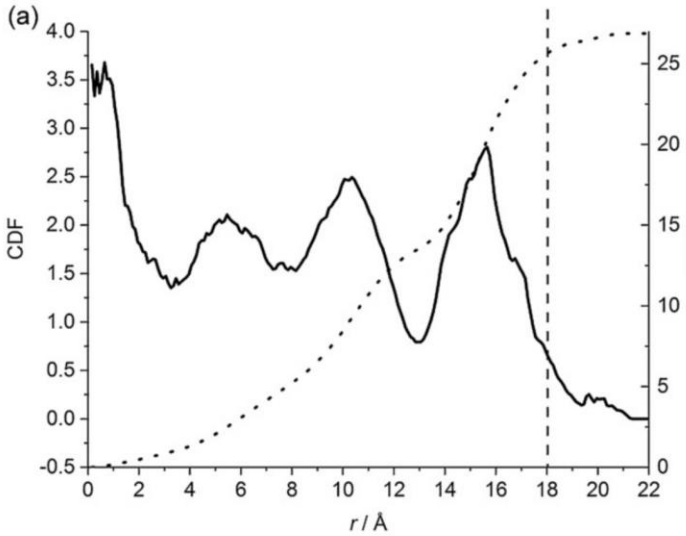


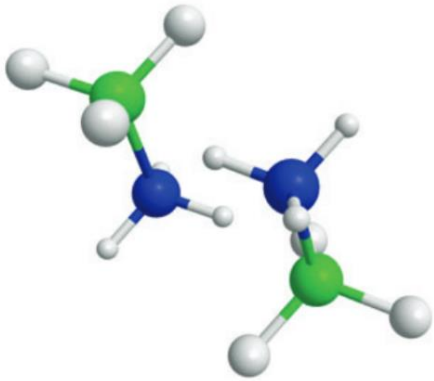


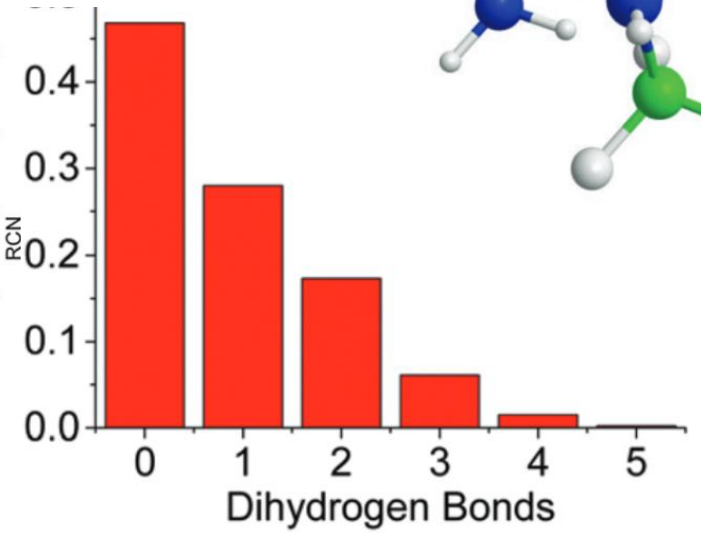












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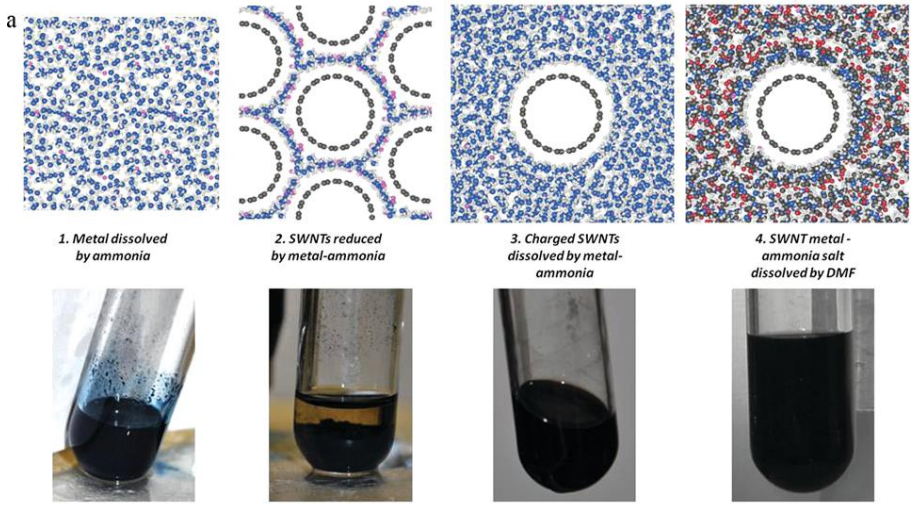
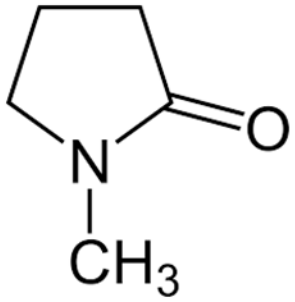
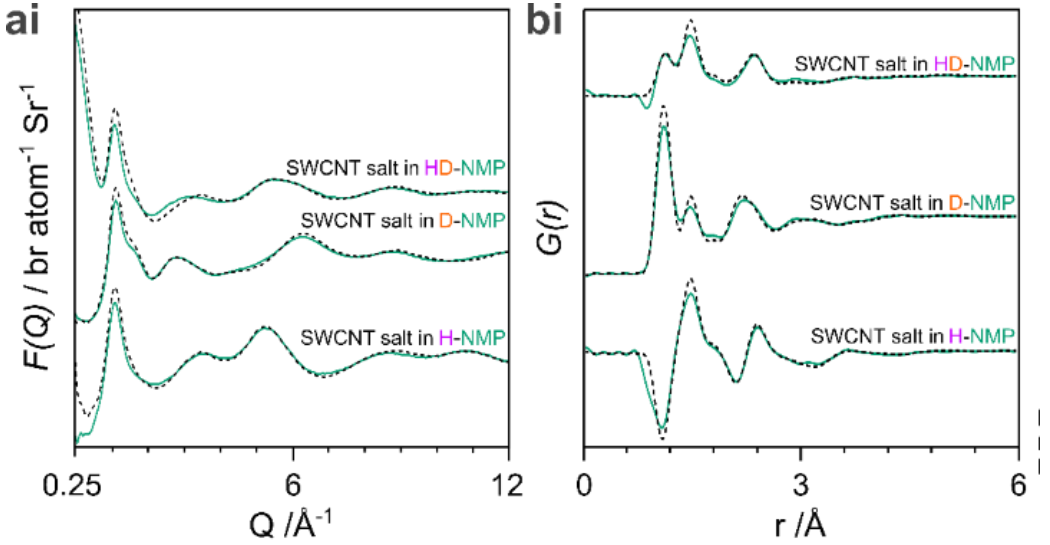
Brief Examples

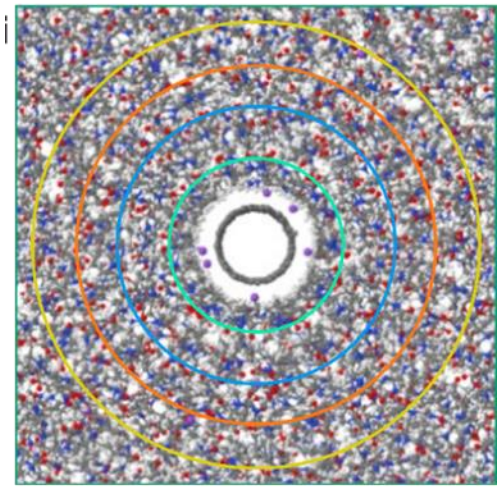
Nanotubide solutions: NT solvation

Di Mino (Oxford), Skipper/Howard/Clancy (UCL), Headen (ISIS)









di Mino, C *et al.* (2025) *Nature Nanotechnology 2025*, 1–7.

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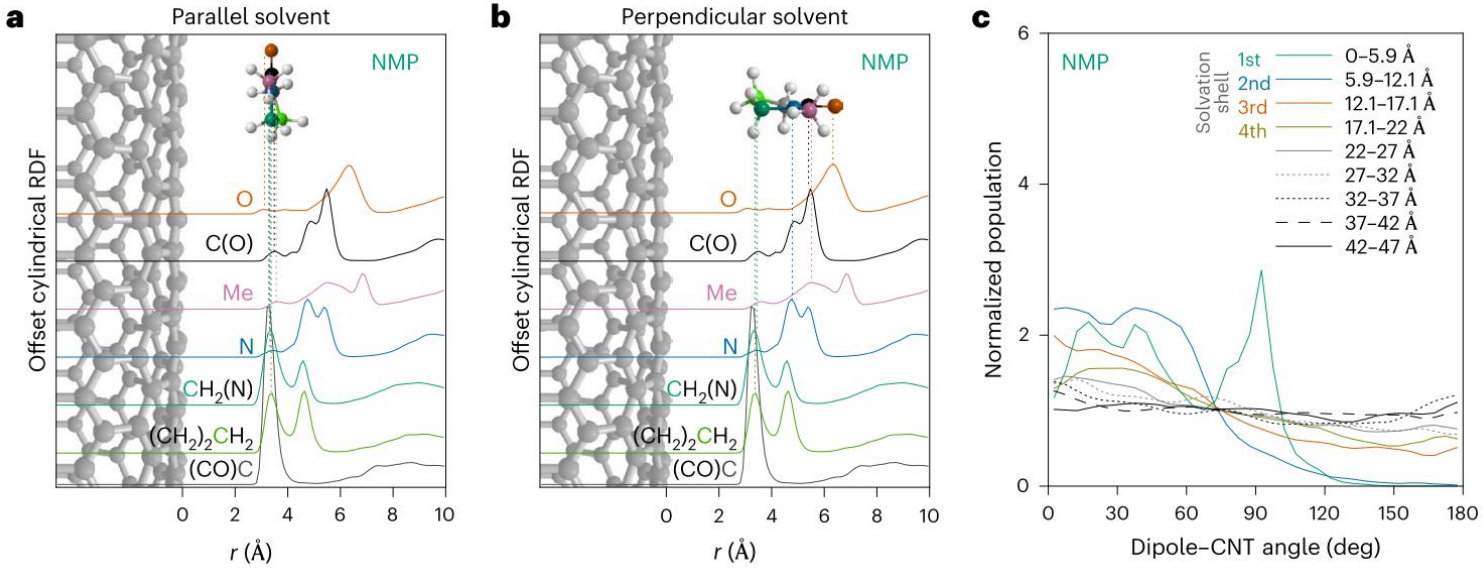


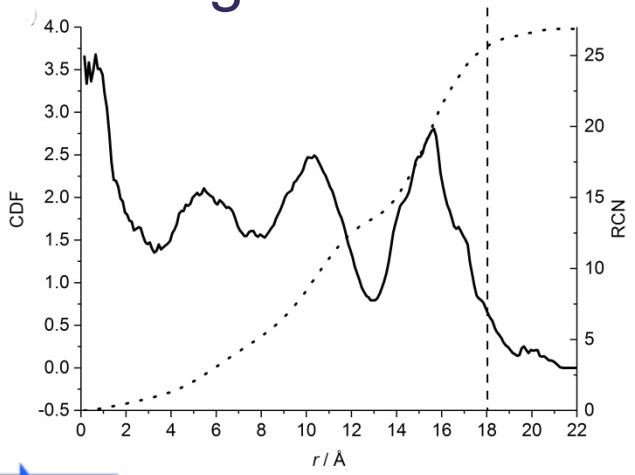
Confined Molecular Liquids

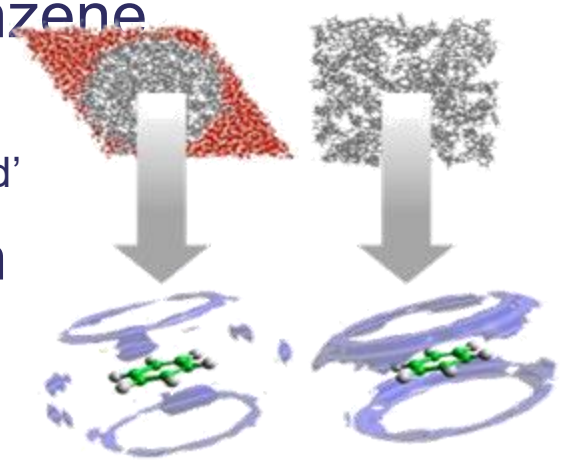
Falkowska/Hardacre (Manchester/ISIS), Hughes/Youngs/Bowron (ISIS)

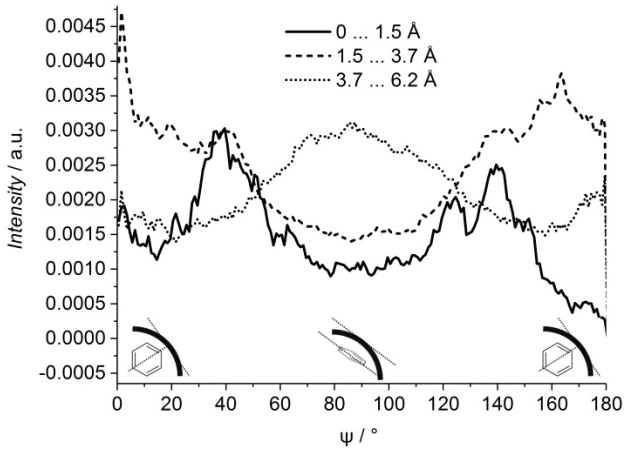
Measurement of confined structure of a model aromatic liquid benzene

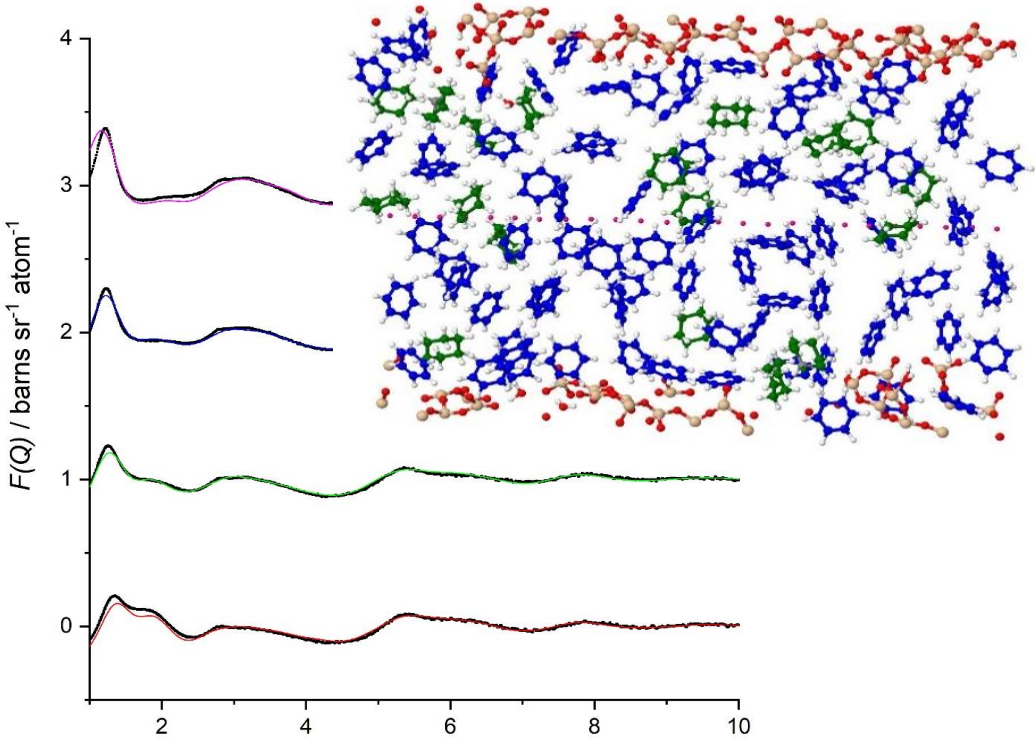
- Layering across pore
- Molecules closest to wall are ‘canted’

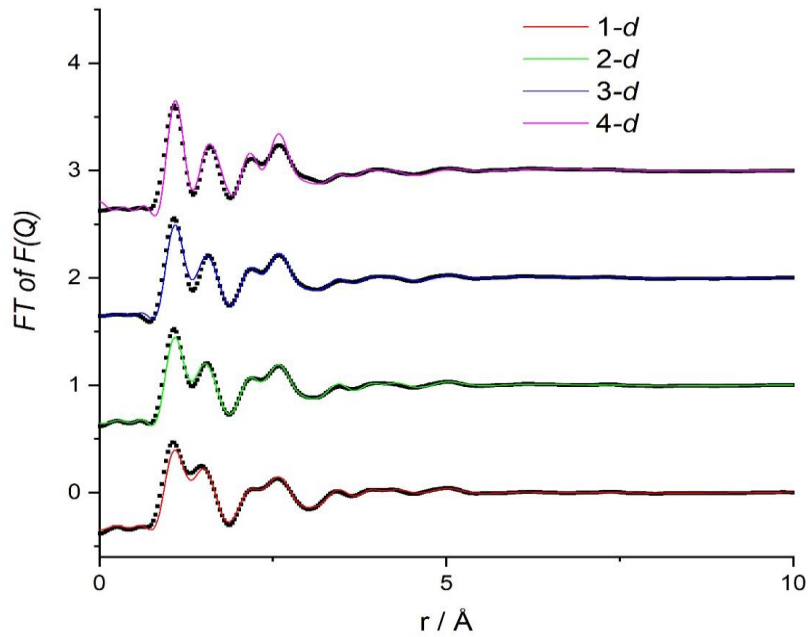
First steps towards reaction modelling











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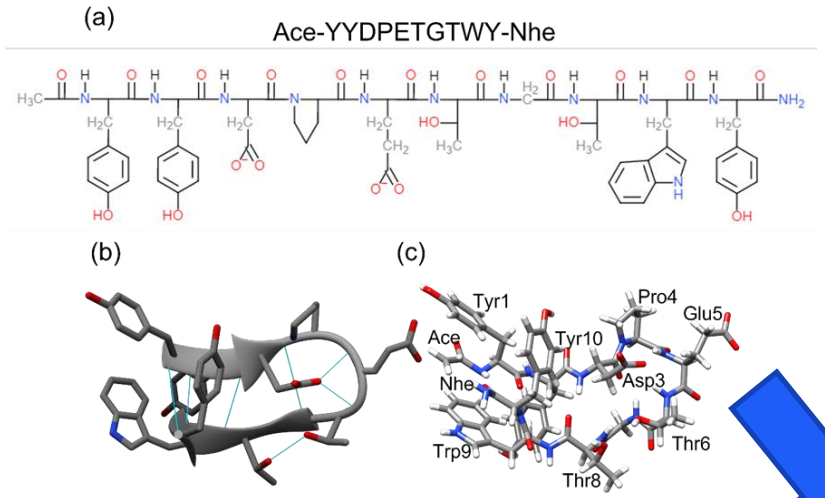
Falkowska *et al* ***Angew. Chem. Int. Ed.*** **2018**. 57,4565 –4570

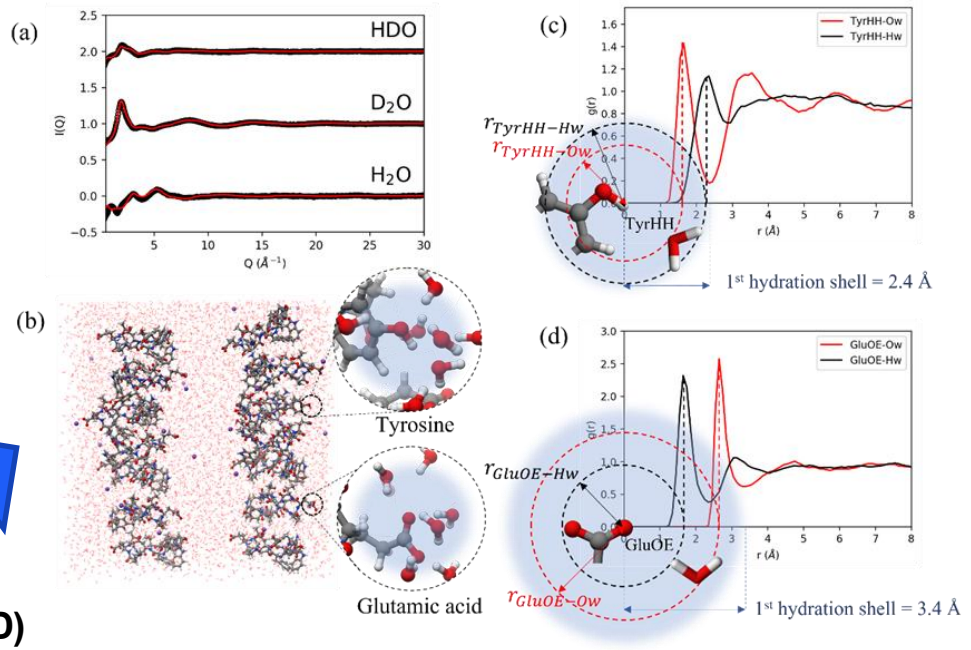
Biomolecule structure and hydration

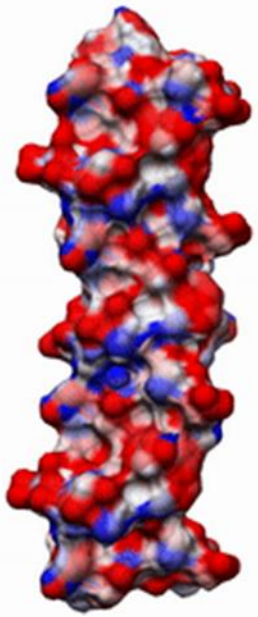
Dougan/Laurent (Leeds), Headen (ISIS)



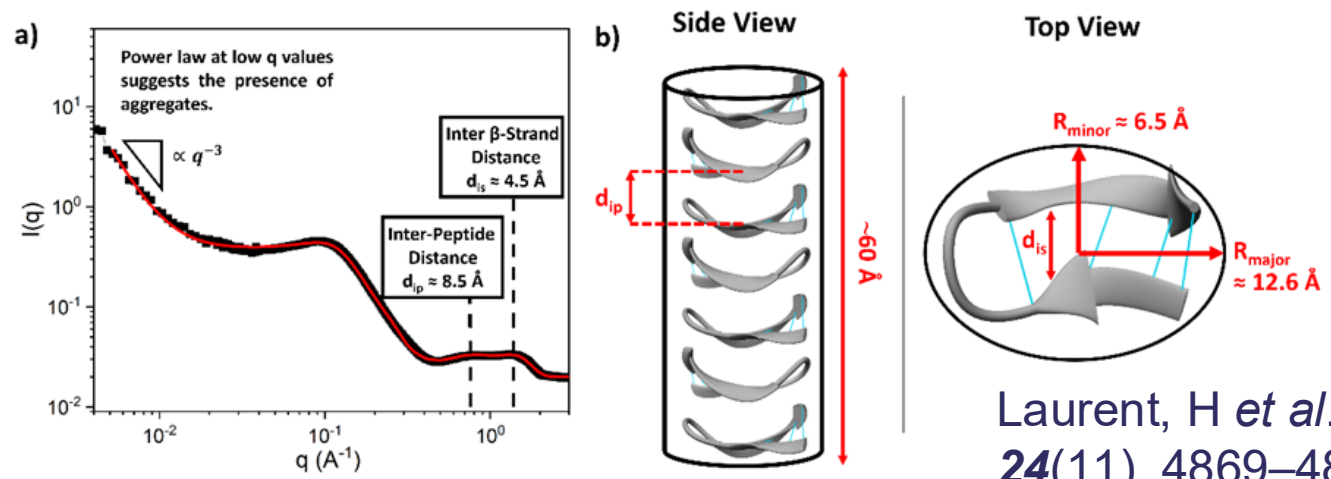
Beta-hairpin polypeptide

SANS data (Zoom and NIMROD)





Informs atomistic hydration model



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Laurent, H *et al*. *Biomacromolecules*, ***24***(11), 4869–4879.

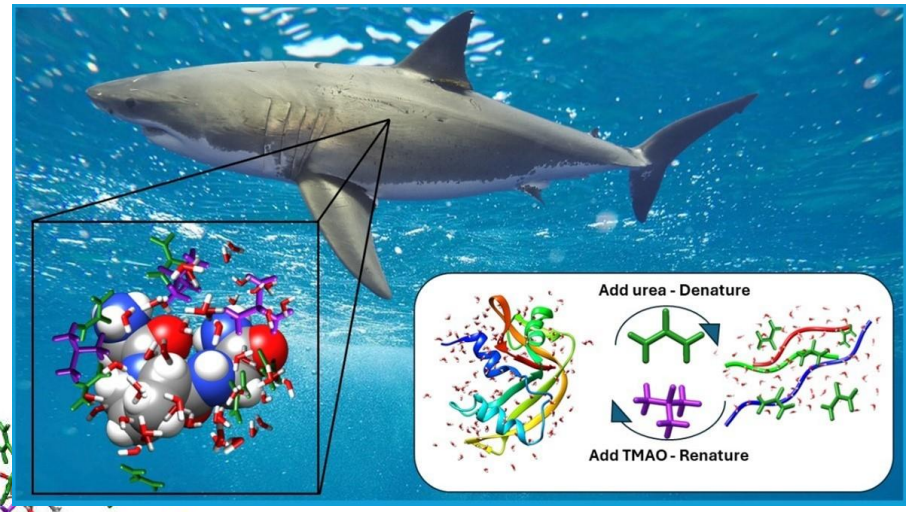
Peptide Solvation

PNAS RESEARCH ARTICLE | BIOPHYSICS AND COMPUTATIONAL BIOLOGY OPEN ACCESS

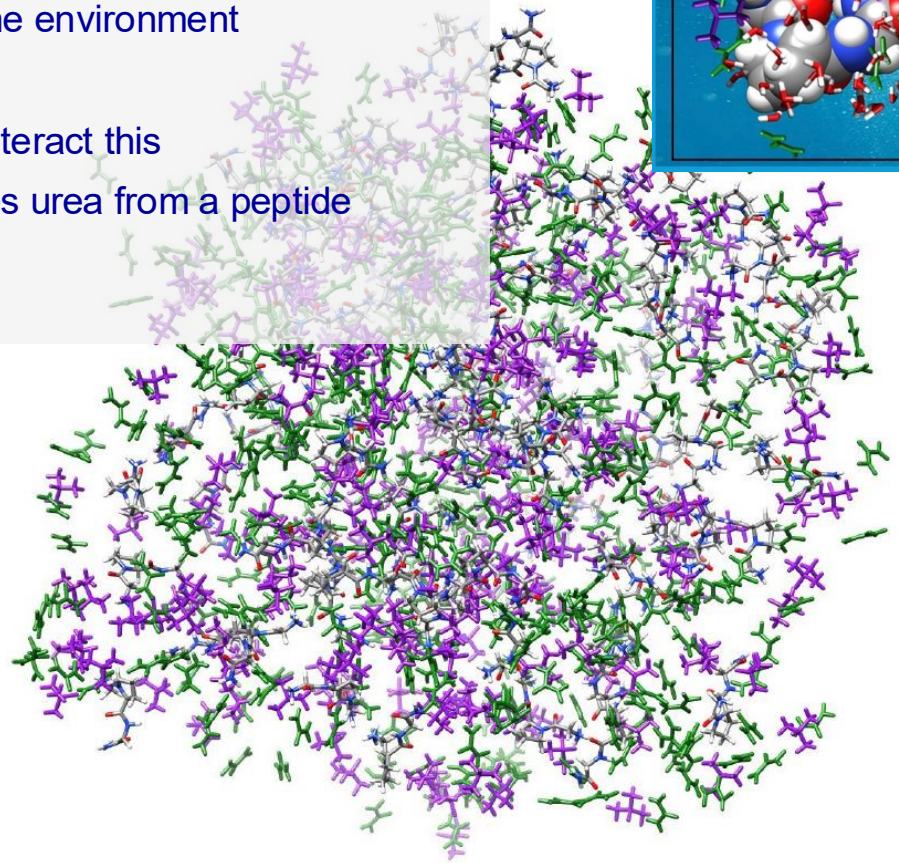
Trimethylamine-N-oxide depletes urea in a peptide solvation shell

Mazin Nasralla[a], Harrison Laurent[a], Oliver L. G. Alderman[b], Thomas F. Headen[b], and Loma Dougan[a,1]

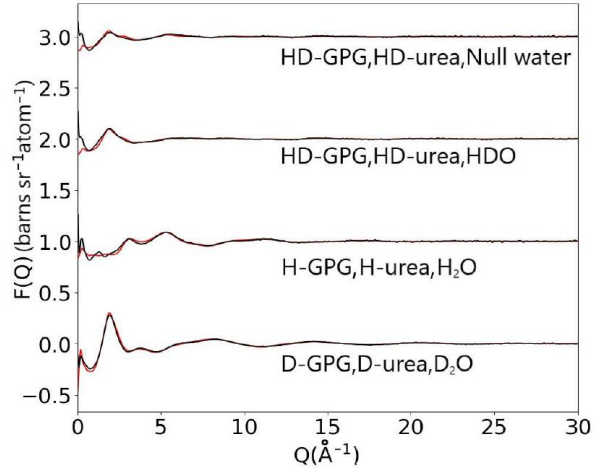
Edited by Valeria Molinero, The University of Utah, Salt Lake City, UT; received October 13, 2023; accepted February 15, 2024



- Urea an osmolyte allowing sharks to live in saline environment
- But urea denatures proteins
- Sharks have adapted to produce TMAO to counteract this
- This work demonstrated the how TMAO depletes urea from a peptide surface, allowing it to renature



- Two ternary + one quaternary solution
- 18 H-D isotopologues in total



Nasralla, M., *et al.*, Proc. Natl. Acad. Sci. USA, **2024**. **121**(14): e2317825121.

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Zwitterionic Osmolytes

Chemical Science

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Cite this: *Chem. Sci.*, 2025, **16**, 6770

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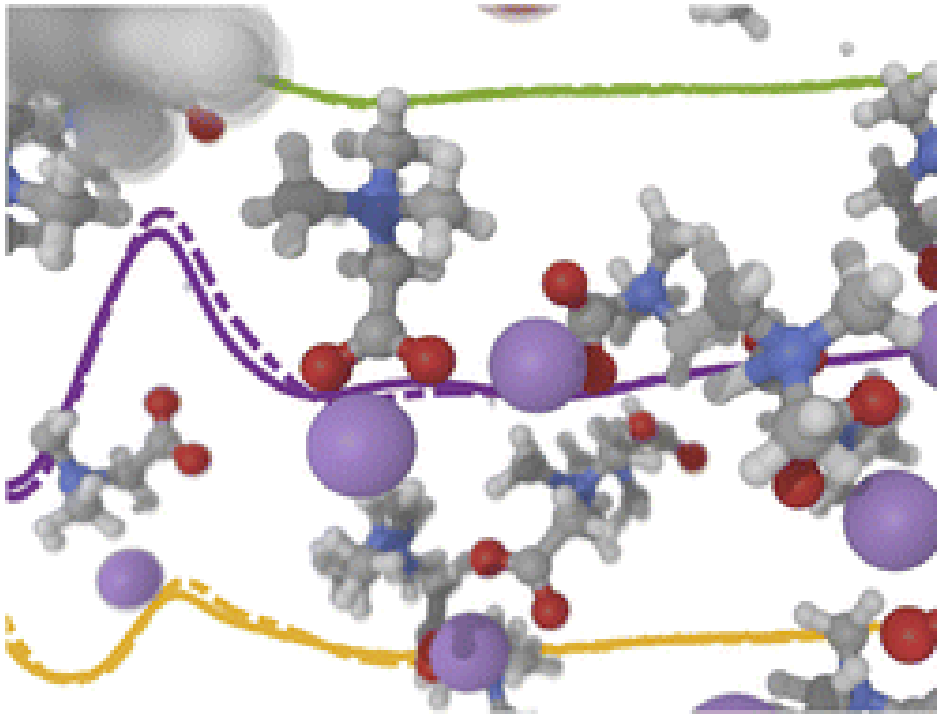
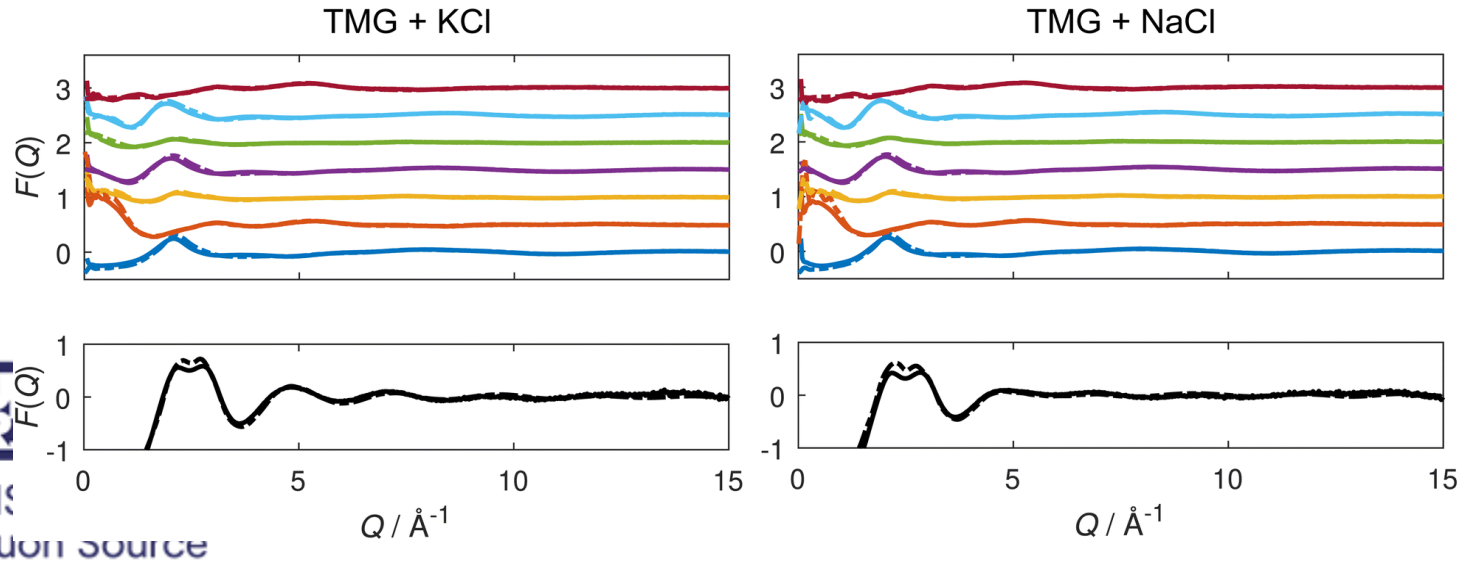
Specific ion effects enhance local structure in zwitterionic osmolyte solutions†

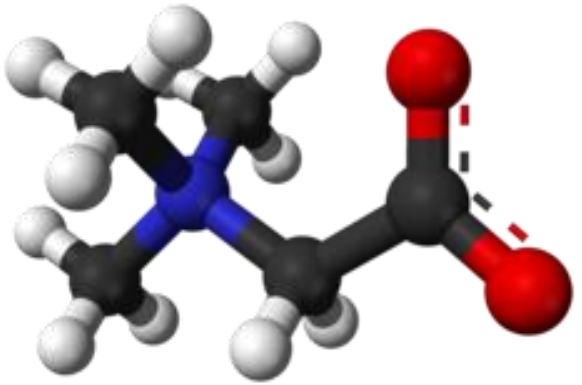
Kieran J. Agg, [a] Timothy S. Groves, [a] Shurui Miao, [a] Y. K. Catherine Fung, [a] Oliver L. G. Alderman,[b] Thomas F. Headen, [b] Terri-Louise Hughes,[b] Gregory N. Smith, [b] Tristan G. A. Youngs,[b] James P. Tellam, [b] Yao Chen,[b] Susan Perkin [a] and James E. Hallett *[c]





Neutrons
7x H/D isotopologues

Ag-Source X-rays



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Summary & Outlook

Current Capability

- Investigating pure liquids and solvated species (at decent concentration) with these techniques essentially “standard practice”
- Tertiary etc. systems possible, but need judicious use of isotopes
- Confined liquid structure accessible with TNS (+NMR)
- Process kinetics of confined system accessible with TNS

- “Static” reactions (vapour deposition followed by exposure to reactant gas)
- “Flow” reactions (continual vapour deposition with carrier gas)

- Gas uptake (low pressure surface adsorption)

Limitations / Caveats

Theory can link measured scattering intensities to real-space simulation data – but is **idealised**.

Must have good data (reduction):

- Quantified composition
- Quantified isotopic levels
- Backgrounds removed
- Multiple scattering / attenuation
- Remove self-scattering – interference scattering only
- Remove inelastic scattering
- Reduce to normalised intensity

It's just a simulation:

- Pairwise interactions and potential forms
- Finite system size (coarse-graining would be nice)
- Heterogeneity of e.g. porous systems?
- All standard limitations of classical simulation apply!

Ackowledgements

Daniel Bowron, Tom Headen, Terri-Louise Hughes, Oliver Alderman, Marta Falkowska, Zac Amato (DM)

Alan Soper FRS

Kieran Agg, Harrison Laurent, Lorna Dougan, Camilla Di Mino, Mazin Nasralla, Chris Hardacre, Neil Skipper, Adam Clancy, Chris Howard

DM @ ISIS - https://www.isis.stfc.ac.uk/Pages/Disordered-Materials.aspx

Dissolve – https://projectdissolve.com

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