

Eliminating Finite-size Effects on the Calculation of X-ray Scattering from Molecular Dynamics Simulations

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Abstract

Structural studies using x-ray scattering methods for investigating molecules in solution are shifting focus towards describing the role and effects of the surrounding solvent. However, forward models based on molecular dynamics (MD) simulations to simulate structure factors and x-ray scattering from interatomic distributions such as radial distribution functions (RDFs) face limitations imposed by simulations, particularly at low values of the scattering vector q . In this work, we show how the value of the structure factor at $q = 0$ calculated from RDFs sampled from finite MD simulations is effectively dependent on the size of the simulation cell. To eliminate this error, we derive a new scheme to renormalize the sampled RDFs based on a model of the excluded volume of the particle-pairs they were sampled from, to emulate sampling from an infinite system. We compare this new correction method to two previous RDF-correction methods, developed for Kirkwood-Buff theory applications. We present a quantitative test to assess the reliability of the simulated low- q scattering signal, and show that our RDF-correction successfully recovers the correct $q = 0$ limit for neat water. We investigate the effect of MD-sampling time on the RDF-corrections, before advancing to a molecular example system, comprised of a transition metal complex solvated in a series of water cells with varying densities. We show that our correction recovers the correct $q = 0$ -behaviour for all densities. Furthermore, we employ a simple continuum scattering model to dissect the total scattering signal from the solvent-solvent structural correlations in a solute-solvent model system to find two distinct contributions: a non-local density-contribution from the finite, fixed cell size in NVT simulations, and a local contribution from the solvent shell. We show how the second contribution can be approximated without also including the finite-size contribution. Finally, we provide a 'best-practices'-checklist for experimentalists planning to incorporate explicit solvation MD simulations in future work, offering guidance for improving the accuracy and reliability of structural studies using x-ray scattering methods in solution.

Introduction

The term *solvation* describes the processes of how solvent molecules interact with solute molecules in a solution. Solvation and solvation dynamics can significantly influence the properties and function of a solute. Since so much chemistry takes place in solution, studying the role of solvation dynamics on a molecular level can be the key to obtaining a complete understanding of reaction mechanisms that are central within (photo)chemical processes with sought-after applications such as light-harvesting [1–5], charge-transfer [6–8], catalysis [9,10], or photoswitching [11–14]. Lastly, studies of

the neat solvent alone [15] are especially pertinent when that solvent is water [16,17], simply because of its unquestionable importance both in biology, chemistry, and elsewhere. Direct structural probes such as (time-resolved) x-ray scattering have proved a crucial tool for obtaining mechanistic understanding on an atomic scale [10, 18–21]. However, the random orientation of solutes in a solution results in the scattered signal being comprised of an average of all possible orientations of the solute and its solvation shell, which thus reduces the extractable information content in the recorded signal, necessitating support from theoretical and computational modeling. Often, classical molecular dynamics (MD), driven by either quantum [22–24], classical [8, 18, 23, 25, 26], or mixed potentials [23, 27, 28], provide molecular structures or trajectories that evolve in time, predicting the process of interest. These predictions need to be linked to experiment through a forward model, calculating the theoretical experimental signal from the molecular simulations [29,30]. As the focus moves further towards the role of the solvent [8,19,26,31–35], it should be noted that the structural changes of solvation shells are more diffuse than for, say, covalent bond-lengths in a molecule. This necessitates more accurate forward models that fully capture these subtle effects across the entire range of the scattering vector q . Furthermore, the models need to be able to discern between real changes in distributions of interatomic distances and artificial contributions to the predicted scattering signals. Such artificial contributions arise from approximations in the simulations, such as the finite size of the simulation cell, and density fluctuations in the solvent that cannot fully be averaged out within reasonable simulation times.

In a previous study, we presented the fundamentals of deriving a forward model for calculating coherent x-ray scattering signals from solute-solvent systems, based on pairwise radial distributions (RDFs) sampled from molecular dynamics simulations [29]. In the present work, we investigate how finite-size simulation cells introduce errors in the long-range behaviour of the sampled RDFs (finite-size artefacts), and what effects this has on the predicted scattering signal. We present a new method for eliminating these artefacts by re-normalizing the RDFs based on an estimation of the excluded volume of the particle-pairs the RDFs are sampled between, to emulate them being sampled from infinite systems. We then critically assess this new correction scheme alongside two previous methods developed for correcting the RDFs for Kirkwood-Buff Integrals, here employed instead for scattering. We present methods to discern features in the simulated signal corresponding to real interatomic structure from finite-size artefacts, and analyse a method to obtain contributions to the total x-ray scattering term from solvent-solvent correlations within solvation shells [26].

The paper is structured as follows: First, we present the theoretical background for calculating x-ray scattering from RDFs sampled from finite-size systems and introduce our new correction. Then, we briefly introduce two previously developed correction methods. We then test the performance of all the corrections on systems of increasing complexity, going from a simple Lennard-Jones liquid, to neat water, to a single-atom solute in water, before ending up with a many-atom complex solvated in water. Finally, we go into detail in analysing further contributions to the total x-ray scattering signal from solvent shells, before presenting a best-practices recipe for future forward modeling.

The methods described and used in this work have been implemented in Python and is available from the The Python Package Index [36]. The data, plots, and code to reproduce them can be found in an online data-repository [37].

Background

It is well known that the isotropic x-ray scattering can be simulated from radial distribution functions (RDFs) which describe the ratio of local probability density to the bulk density, $g(r) = \rho(r)/\rho$

[38–40]. We define an ‘atom type’ as an element belonging to a certain region w of the system. Thus, e.g. an Oxygen belonging to the solute can be a different atom type than an Oxygen belonging to the solvent. For a pair of atom types l, m the pairwise RDF, $g_{lm}(r)$ can be sampled from molecular dynamics (MD) trajectories of $i \in l$ and $j \in m$ atom positions, sampled in spherical shells along r from the i ’th particle to every j ’th particle, $\delta(|\mathbf{r}_i - \mathbf{r}_j| - r)$:

$$g_{lm}(r) = \frac{1}{\rho_m} \left\langle \sum_{j \neq i}^{N_m} \delta(|\mathbf{r}_i - \mathbf{r}_j| - r) \right\rangle_i = \lim_{dr \rightarrow 0} \frac{N_{lm}(r)}{\rho_m 4\pi r^2 dr} = \frac{\rho(r)}{\rho_m}, \quad (1)$$

where $\rho_m = N_m/V$ is the average density of m -type particles in a simulation cell of volume V , and $N_{lm}(r)$ is the number of m -type atoms found at distance $r + dr$ from atoms of type l , most often averaged over a set of MD frames. As we want to separate the various contributions to the total scattering signal, we introduce the indices w_l, w_m , since for a solute in a solvent, the atom types can be further classified as belonging to either the solute, $w_l = u$, or the solvent: $w_l = v$. Then, the total scattered x-ray intensity $I(q)$ as a function of the scattering vector q from a solute in a solvent can be calculated as the double sum of the individual terms (the form of which we shall return to in eq. 3):

$$I(q) = \sum_{w_l}^{\{u,v\}} \sum_{w_m}^{\{u,v\}} I_{w_l w_m}(q) = I_{uu}(q) + I_{uv}(q) + I_{vu}(q) + I_{vv}(q). \quad (2)$$

As discussed previously [29], the diagonal terms constitute solute-solute scattering $I_{uu}(q)$, which will not be addressed further in this work, and solvent-solvent scattering, $I_{vv}(q)$. The off-diagonal, or ‘‘cross’’ terms constitute the scattering terms from the solute-solvent correlations, $I_{uv}(q) + I_{vu}(q) = I_c(q)$. These terms are sometimes also called ‘‘solvent cage’’ scattering, which is misleading, as the total scattering signal from the solvent cage *also* includes scattering from solvent-solvent correlations in e.g. a denser solvent shell around a solute. This part of the ‘‘cage’’ is encoded in the *solvent-solvent* term, $I_{vv}(q) = I_v(q)$. In addition, the solvent-solvent term includes the bulk signal (which resembles the signal from a neat liquid), as well as the solvent-solvent interactions across the solute, which will constitute a ‘hole’ in the solvent, which we will return to in the second part of this work.

The $I_{w_l w_m}(q)$ terms can be calculated from the RDFs via [29, 40]:

$$I_{w_l w_m}(q) = \delta_{w_l w_m} \sum_l N_l f_l(q)^2 + \sum_l \sum_m f_l(q) f_m(q) \frac{N_l(N_m - \delta_{lm})}{V} 4\pi \int_0^\infty (g_{lm}(r) - g_{w_l w_m}^0) \frac{\sin(qr)}{qr} r^2 dr, \quad (3)$$

where l (m) runs over all atom types belonging to w_l (w_m). The atomic form factors $f_l(q)$, $f_m(q)$ can be parameterized within the Independent Atom Model (IAM) [41] and N_l (N_m) the number of atoms of type l (m) in the simulation cell. $g_{w_l w_m}^0 = 0$ when $w_l = u$ and $w_m = u$, and 1 otherwise [29]. The equation is split up in two terms: the first term is the self-scattering and the second term contains the interatomic structure. The Kronecker delta, $\delta_{w_l w_m}$, assures there is no double-counting of self-scattering terms.

For this work, the two relevant contributions are the solvent and cross terms, $I_{vv}(q)$ and $I_c(q)$, i.e. with $g_{w_l w_m}^0 = 1$. The fundamental measurable quantity for these two terms, agnostic to the nature of the scatterer, is the structure factor $S_{lm}(q)$, which for uniform, isotropic systems comprised of particles of type m and l (with at least one type within the solvent) can be defined as [42]:

$$S_{lm}(q) = 1 + \rho_m 4\pi \int_0^\infty (g_{lm}(r) - 1) \frac{\sin(qr)}{qr} r^2 dr. \quad (4)$$

We can express the x-ray scattering signal as a function of structure factors for the different pairs of atom types in our simulation. Keeping in mind that $N_l(N_m - \delta_{lm}) = (N_l - \delta_{lm})N_m$, we can rewrite eq. 3 as:

$$I_{w_l w_m}(q) = \delta_{w_l w_m} \sum_l N_l f_l(q)^2 + \sum_l \sum_m f_l(q) f_m(q) (N_l - \delta_{lm}) (S_{lm}(q) - 1) \quad (5)$$

Note that with the definition of the structure factor in eq. 4, this expression is only valid for the cross- and solvent-solvent terms. Lastly, while $g_{lm}(r) = g_{ml}(r)$, the same is not true for $S_{lm}(q)$ and $S_{ml}(q)$, as N_m and N_l should also switch place, and thus we have not reduced the double sum further. In the following, we will use the shorthand index c to label the total cross-term scattering and structure factors, and v for the solvent-solvent term. Note that since the first term in eq. 3 is zero for $I_c(q)$, this term can be negative.

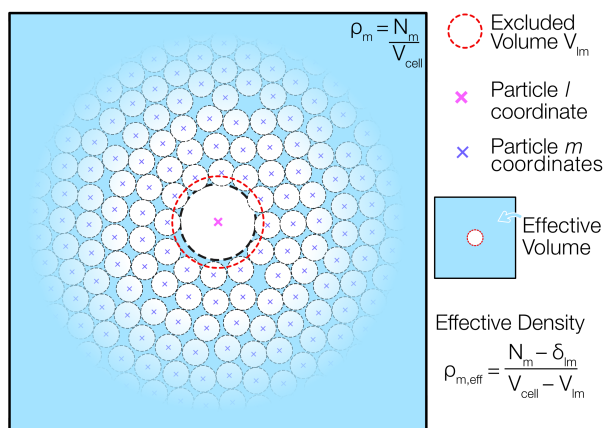


Figure 1: Illustration of the central concepts of volume and densities in a finite (periodic) system with volume V_{cell} . Particle l takes up space in the simulation cell, where the other particles cannot exist. This volume is dependent on the extension of both of the particle types, as the volume is defined by the interaction potential between the particles. Thus, for a potential of non-interacting hard spheres, the volume would be a sphere with radius $R_{lm} = R_l + R_m$, but for all other differentiable potentials, the volume will be less well defined. When scaling the RDF to ρ_m , the excluded volume of particle type-pair l, m , V_{lm} , is included in V_{cell} , even though it is not available to the m -type particles. Instead, the "effective volume", i.e. the total volume of the simulation cell minus V_{lm} should be used to obtain an "effective" density $\rho_{m,\text{eff}}$ with which $\rho(r)$ in eq. 1 should be normalized.

If we let $q \rightarrow 0$, the integral term in eq. 4, except for the density ρ_m , is recognized as the Kirkwood-Buff Integral (KBI) [43]:

$$G_{lm} = 4\pi \int_0^\infty (g_{lm}(r) - 1) r^2 dr = V \frac{\langle N_l N_m \rangle - \langle N_l \rangle \langle N_m \rangle}{\langle N_l \rangle \langle N_m \rangle} - \frac{\delta_{lm}}{\rho_l}. \quad (6)$$

The KBI links atomic scale interactions - as expressed through RDFs - to fluctuations (r.h.s of eq. 6), and therefore also to thermodynamic properties of fluids [44]. For a single atom-type system, $l = m$, we can combine eqs. 4 and 6 to relate the structure factor at $q = 0$ to fluctuations in the liquid:

$$S(0) = \frac{\langle N^2 \rangle - \langle N \rangle^2}{\langle N \rangle} = \rho k_B T \chi_T, \quad (7)$$

for $\rho = \langle N \rangle / V$. The r.h.s of eq. 7 above equates fluctuations to the experimentally measurable isothermal compressibility χ_T (at temperature T , where k_B is the Boltzmann constant), and has been derived elsewhere [45, 46].

The problem arises as KBIs are only defined for infinite systems [43]. In infinite systems, the theoretical long- r limit of the RDF is 1. This means, that for the integrals in eqs. 3, 4, and 6, when the RDF has converged to this limit at some distance $r = R$, we can safely truncate the integral at R , since the integrand above this R will be 0. However, the limit of the RDF when sampled in a finite-size system of N particles, even if periodic, becomes different from 1. As an example of this, statistical mechanics analysis show that for an ideal gas system, $g(r) = 1 - (1/N)$ [46, 47].

Finite-size corrections

Our interpretation of why the deviation from 1 arises is because the statistical mechanics analysis that leads to the $g(r) = 1 - (1/N)$ result for a ideal gas does not take into account that in a *real* system, the particles have a finite volume. Thus, the probability of finding a particle in the volume element dr_j , given that another particle is in the element dr_i *must* take into account the (excluded) volume taken up by particle i , since the two particles cannot occupy the same volume (see fig. 1). As the system size increases, the ratio between the excluded volume and the total simulation volume decreases, which makes the limit approach the infinite-size limit of 1. This means that when we sample RDFs from finite-system molecular dynamics simulations, we must modify the calculation scheme to obtain the infinite-size limit of 1. For RDFs sampled in finite systems, $g_{lm}^N(r)$, the RDF in eq. 1, the RDF is normalized to the average density of particles m , $\rho_m = N_m / V_{\text{cell}}$. We must therefore rescale the RDF with the difference between the cell volume and the effectively accessible volume to recover the RDF as if sampled from an infinite system, $g_{lm}^\infty(r)$:

$$g_{lm}^\infty(r) = \frac{\rho_m}{\rho_{\text{eff}}} g_{lm}^N(r) = g_{lm}^N(r) \rho_m \frac{V_{\text{cell}} - V_{lm}}{N_m - \delta_{lm}}, \quad (8)$$

where V_{lm} is the excluded volume, i.e. the volume taken up by particle of type l in which particles m cannot be found. This volume is nontrivial to obtain exactly, but as a first-order approximation, we assume it to be spherical $V_{lm} = (4/3)\pi R_{lm}^3$, with a radius R_{lm} that has to be estimated either by inspection of the RDFs or by fitting (*vide infra*). Note that V_{lm} is the volume inaccessible to the remaining particles, and not just the total volume divided by the total number of particles (which would be larger than V_{lm} , c.f. close-packing of equal spheres only uses 74% of the total volume).

An alternative route is presented by P. Ganguly and N. F. van der Vegt, developed for correcting KBIs. The authors state that "excess (depletion) of particles of type m around particles of type l at a local scale is compensated by depletion (excess) of particles of type m at long distances, as the total number of particles is fixed." [48] Based on this observation, the authors propose to correct the error in the ρ -normalization of the RDF by correcting the number N of particles throughout r :

$$\begin{aligned} g_{lm}^\infty(r) &= g_{lm}^N(r) \frac{N_m}{N_m - \left[(\Delta N_{lm}(r) + \delta_{lm}) \left(1 - \frac{(4/3)\pi r^3}{V_{\text{cell}}} \right)^{-1} \right]} \\ &= g_{lm}^N(r) \frac{N_m \left(1 - \frac{(4/3)\pi r^3}{V_{\text{cell}}} \right)}{N_m \left(1 - \frac{(4/3)\pi r^3}{V_{\text{cell}}} \right) - (\Delta N_{lm}(r) + \delta_{lm})}, \end{aligned} \quad (9)$$

The parameter $\Delta N_{lm}(r)$ is defined as "the excess number of particles of type m within a sphere of radius r around particle of type l ". Usually [49–51] one estimates this quantity via:

$$\Delta N_{lm}(r') = 4\pi\rho_m \int_0^{r'} (g_{lm}^N(r) - 1)r^2 dr, \quad (10)$$

for r' -values less than half the simulation box length.¹

Another N -focused correction uses a Taylor expansion of the difference between the finite- and infinite-system RDF long- r behaviour [53], using an unknown function to describe the deviation, which is estimated from two simulations with differing number of molecules [49, 54]. This method thus requires twice the amount of simulations, and relies on the difference between RDFs sampled from almost identical systems, making it very sensitive to sampling noise. Thus, we will not be employing this method here.

Lastly, Perera *et al* propose a more heuristic correction to the RDF between particles of type l and m [55]:

$$g_{lm}^\infty(r) = g_{lm}^N(r) \left[1 + \frac{1 - g_{lm}^{N,0}}{2} \left(1 + \tanh \left(\frac{r - \kappa_{lm}}{\alpha_{lm}} \right) \right) \right]. \quad (11)$$

The difference between the correct asymptotic limit, 1, and the sampled, $g_{lm}^{N,0}$, $1 - g_{lm}^{N,0}$ is used in a smooth switching function, where α_{lm} controls the smoothness of the switch from $g_{lm}^{N,0}$ to 1. κ_{lm} represents an effective diameter with which particle of type l and m displace each other, as it is taken to be twice the distance at which $g_{lm}(r)$ starts to be different from zero. This RDF-correction grows in at larger r , and leaves the local structure untouched. However, from the definition of the RDF in eq. 1, the $1/\rho_m$ normalization should be applied over the entire r -range. This correction is more akin to the often applied "damping" or "windowing" functions used ubiquitously in forward modeling as well as in inversion methods [8, 9, 16, 26, 56–58], which we will address in the next section.

Damping functions

As we shall see in the following sections, none of the above physics-based corrections are guaranteed to make the RDF go *exactly* to 1 at long r , we thus cannot be certain that the integral in eq. 3 (or in eq. 4) will converge. Therefore, in practice, we must often employ a window function (or 'damping function') to the integral in eq. 3, $\omega(r)$, which is not grounded in physical considerations about the RDF. One such window function is used by Lorch [59]:

$$\omega_{\text{Lorch}}(r) = \frac{\sin(\pi r/R)}{\pi r/R}, \quad (12)$$

where R is the largest r -value of the sampled RDF (most often half of the simulation cell sides). However, to ensure optimal results when combined with any of the previously mentioned RDF-corrections, one should take care that the applied damping function minimally alters the structure encoded in the RDF, avoiding excessive adjustments to it.

¹Some programs, such as VMD [52] uses an average density in the normalization of the RDF that does not count the particle from which the histogramming starts, in cases of $l = m$, i.e. $\rho_m = (N_m - \delta_{lm})/V$. If such a normalization is used, then the Kronecker delta should be omitted from eq. 9.

Dhabal and coworkers compared the correlation functions of water simulated using the TIP4P/2005 potential with experimental results using the following windowing function:

$$\omega_{\text{Dhabal}}(r) = \begin{cases} 1 - 3(r/R)^2, & \text{if } r < R/3 \\ 3/2 (1 - 2(r/R) + (r/R)^2), & \text{if } R/3 < r < R \\ 0, & \text{if } r > R \end{cases} \quad (13)$$

which was later modified into an smooth step function from R_{cut} to $R_{\text{cut}} + R$, which leaves the RDF completely untouched before R_{cut} [5]:

$$\omega_{\text{ZK}}(r) = \begin{cases} 1, & \text{if } r < R_{\text{cut}} \\ 1 - 3 \left(\frac{r - R_{\text{cut}}}{R - R_{\text{cut}}} \right)^2, & \text{if } R_{\text{cut}} < r \leq \frac{2R_{\text{cut}} + R}{3} \\ \frac{3}{2} \left(1 - \frac{r - R_{\text{cut}}}{R - R_{\text{cut}}} \right)^2, & \text{if } R > r > \frac{2R_{\text{cut}} + R}{3} \\ 0, & \text{if } r > R, \end{cases} \quad (14)$$

Which reduces to $\omega_{\text{Dhabal}}(r)$ for $R_{\text{cut}} = 0$. For large cells, the Lorch-like damping might be most appropriate, as a very slow change in the RDF is less aggressive than a more abrupt cut provided by a smooth step function, but in other cases, where e.g. smaller cells have been sampled, it might in some cases be more important to avoid damping the local structure encoded at shorter r values in the RDF, than to enforce a smoothly changing damping window. See fig. 2 for a comparison of the shapes of the functions.

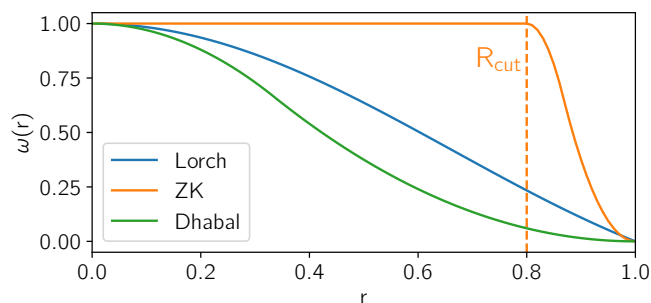


Figure 2: Illustration of the shapes of the three window functions described in the main text, with $R = 1$, and in the case of the ZK-damping, $R_{\text{cut}} = 0.8$

In the last two decades, much work has gone into developing corrections for the RDF that recovers the correct KBI [48–51, 53, 54, 60–69]. In this work, we will analyse our own correction-scheme based on the excluded volume, as well as the van der Vegt- and Herera-corrections, focusing on x-ray scattering. MD simulations and subsequent RDF sampling are often carried out in a "black box"-fashion as just one of many steps in a complex structural modeling strategy. Thus, we have limited ourselves to corrections that can be applied to RDFs sampled from MD simulations carried out in readily available and highly efficient MD codes, and RDFs sampled from already available codes, where no (cost-increasing or otherwise) modifications have to be implemented in either methodology in order to apply the correction.

Testing the Corrections

Based on the considerations in the previous sections, we can devise a useful test of the various corrections by evaluating

$$S_{lm}(q; R) = 1 + \rho_m 4\pi \int_0^R \omega(r) (g_{lm}^\infty(r) - 1) \frac{\sin(qr)}{qr} r^2 dr \quad (15)$$

at $q = 0 \text{ \AA}^{-1}$, for increasing values of R , since a successful recovery of $g_{lm}^\infty(r)$ from $g_{lm}^N(r)$ will make this integral converge, as previously discussed. The test systems in the following are chosen to gradually increase in complexity, starting from a neat LJ liquid, a solute-solvent LJ liquid system, then switching to liquid water before finally ending up with solute-solvent water systems. For the systems with many l, m -combinations, we will use eq. 5 at $q = 0$ instead, to judge the overall convergence.

Computational Details

The test systems were chosen to gradually increase in complexity, starting from a neat LJ liquid, a solute-solvent LJ liquid system, then switching to liquid water before finally ending up with solute-solvent water systems.

All MD simulations were carried out in OpenMM [70]. The LJ simulations were set up using OpenMMTools [71], placing 20713 particles in a (100 x 100 x 100) \AA cell with the LJ-parameters $\sigma_{\text{solvent}} = 3.4 \text{ \AA}$ and $\epsilon = 0.238 \text{ kcal/mol}$. The σ_{solute} values were manually changed before starting each separate simulation. All simulations were equilibrated for 1 ns each in the NVT ensemble using a Langevin thermostat with a 2 fs timestep at 94.4 K. Each production run was carried out with the same thermostat for 100 ns, as recommended elsewhere [48], saving all particle positions every 0.5 ps. The RDFs were sampled using VMD with a numerical dr of 0.05 \AA .

The neat water system was created using Packmol [72] to place 4095 water molecules in a (50 x 50 x 50) \AA cell, and AmberTools22 [73] to generate the topology for the TIP4P_{EW} potential [74]. The simulation was equilibrated for 1 ns, and sampled for 99 ns, both in the NVT ensemble at 300 K, using a Langevin thermostat with a 2 fs timestep. Then two simulations were spawned from the end of the first: one in which the cell side lengths were reduced each by 0.2 \AA , and the other where they were increased by the same amount. The new simulations were again equilibrated for 1 ns, and sampled for 99 ns. The process was then repeated for further reductions and expansions of the cell. The RDFs were sampled using VMD with a numerical dr of 0.01 \AA .

The first water-based solute-solvent system was chosen to be a single Ag^+ in water, but could have been any single-atom ion. The Ag^+ -Water cells were created with AmberTools22 [73], placing a single ion in 17535 water molecules, using the non-bonded Ag^+ parameters optimized for TIP4P_{EW} from Li & Merz [75]. Since the solvent-cell routine in AmberTools creates water with a very low density, the system was equilibrated for 2 ns in the NPT ensemble at 1 bar, maintained by a Monte Carlo barostat, and then propagated in 2 fs timesteps at 300 K by the Langevin integrator. The final cell dimensions for the production runs were 85.8 \AA x 85.8 \AA x 85.8 \AA . The RDFs were sampled using VMD with a numerical dr of 0.05 \AA .

For the final solute-solvent system, we chose the $[\text{Fe}(\text{bpy})_3]^{2+}$ (bpy = 2,2'-bipyridine) complex in water, as it has been central to many previous x-ray solution scattering experiments [21, 25, 76] and theoretical studies of solute-solvent interactions [22, 24, 77]. The complex was parameterized within

the General AMBER (GAFF) potential, using the 'MCPB.py' method, as described elsewhere [78]. The complex was then solvated in a box of 7329 water molecules modelled with the TIP4P_{EW} potential [74], using the 'leap' program from the 'Ambertools' toolbox [73]. Two Cl⁻ counterions were also added using leap, to charge-neutralize the system. The complex was restrained in the center of the box, and the counterions were restrained roughly 22 Å away from the complex using positional restraints with 500 kcal/mol force constants. The NPT equilibration resulted in a final cell size of (58.7 x 61.1 x 61.4) Å. The density and temperature were equilibrated using OpenMM for 500 ps in the NPT ensemble, using a Monte Carlo Thermostat to keep the pressure at 1 bar, and a Langevin propagator to keep the temperature at 300 K [70]. As with the previous set of simulations the simulation cell size was changed to sample each global density in the NVT ensemble for 20 ns.

Results and Discussion

Test System 1: The Lennard-Jones Liquid

This section analyses the effects on calculating the cross-term structure factor from finite-system sampled RDFs of Lennard-Jones (LJ) liquids, and tests the ability of the chosen corrections to eliminate finite-size artefacts. The liquid structure of LJ liquid is governed by the well-known potential between particles i and j :

$$E(r_{ij}) = 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right], \quad (16)$$

where σ_{ij} determines the distance at which the potential becomes repulsive, and ϵ the depth of the minimum. Each atom type (element) are assigned their own σ and ϵ parameters, and are combined via simple geometric combination rules, $\sigma_{ij} = (\sigma_i + \sigma_j)/2$ and $\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$, also called the Lorentz-Berthelot combination rules [79, 80]. By employing the LJ potential, we prioritize computational conveniences such as differentiability over a completely well-defined hard-sphere excluded volume, meaning that pressure and density will affect the resulting excluded volume.

First, we simulate a 'neat' LJ liquid where all particles are assigned $\sigma = 3.4$ Å, sample the RDFs, and calculate the structure factor using eq. 15 at $q = 0$ Å⁻¹ for gradually increasing truncations of the integral, R , $S_{lm}(0; R)$, towards convergence if the correction is successful. This type of plot is therefore a helpful tool in judging whether the low- q behaviour of the structure factor (and thus the scattering signal) will be influenced by finite-size sampling errors of the RDF. Since $l \in v, m \in v$, we label this structure factor $S_v(0; R)$. The top plot in fig.3 shows the LJ-potential (red line) used in sampling the RDF shown in black. The middle plot in the figure shows the structure factor $S_v(0; R)$, using the 'raw' RDF in the top plot, before applying any RDF-corrections (black dashed line). The plot also shows structure factors calculated from RDFs corrected with the three main methods described previously (solid lines). The uncorrected $S_v(0; R)$ -value starts a smooth increase from around roughly 40 Å, while the structural correlations die out. This indicates that the RDF is converging towards a value slightly above 1 such that the value of the integral truncated at R is increasing proportionally to R^3 , and the low- q structure factor intensity will be entirely dependent on when one chooses to stop sampling the RDF, a choice often governed by the size of the MD simulation cell. For the Perera-correction, k_{lm} is simply set to the first r -value that gives $g_{lm}(r) > 0$, as suggested in the original paper [55]. Due to the finite bin-size of 0.05 Å in sampling the RDF, as well as the fact that an LJ particle is not completely hard, the value is associated with some inaccuracy. Having this in mind, we set the value to 2.925 Å. For the volume correction, R_{lm} was

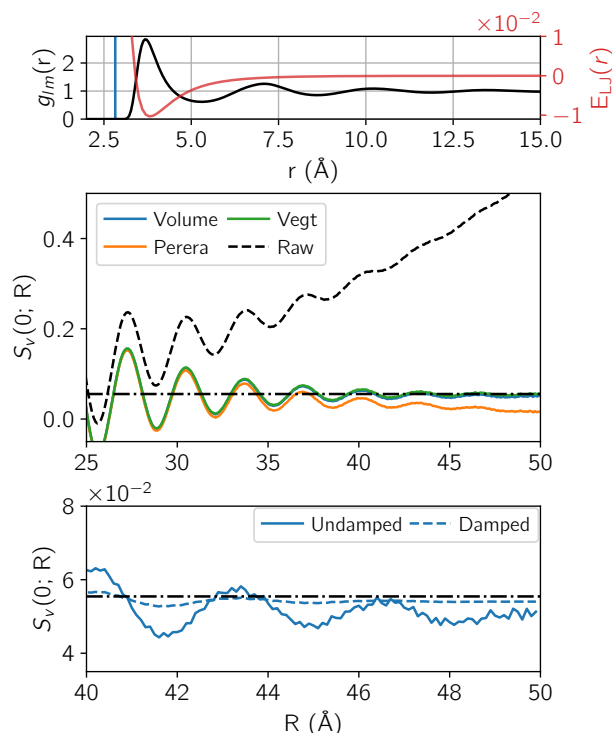


Figure 3: Top: The RDF of a neat Argon LJ liquid with $\sigma = 3.4$ Å. The RDF is sampled for 100 ns in a 100 Å box. The red curve shows the energy from the corresponding LJ potential. Middle: $S_v(0; R)$ for the corrections presented in the previous section, calculated without damping ($\omega(r) = 1$), as well as from the uncorrected ('raw') RDF. The R represents the truncation length of the integral in eq. 15. The dash-dotted line shows the average $S_v(0; R)$ -value for $r > 40$ Å of the van der Vegt-corrected result. Bottom: Zooming in on the $R > 40$ Å region, and comparing two Volume-corrected results, the same, undamped calculation as found in the main bottom plot, and a calculation that also employed the Lorch-like damping with $L = 50$ Å.

set to 2.8240 Å using a simple fitting-method to find the excluded volume which we will describe in the next section on solute-solvent LJ systems. The volume- and van der Vegt correction both flatten out $S_v(0; R)$ at R -values roughly above 40 Å to slightly oscillate around their average value in this region. The Perera-correction seems to have slightly overcorrected the RDF such that the $S_v(0; R)$ -value starts to systematically decrease at long R -values. This small overcorrection can most likely be eliminated by further tuning the involved parameters.

The volume- and van der Vegt correction both make the $S_v(0; R)$ -value converge. However, in practice, the small oscillations still present even at these large distances will cause an unwanted truncation-distance dependence of the resulting predicted scattering signal. The bottom plot in the fig. 3 shows how employing the Lorch-like damping window converges the integral to a constant value such that it can be safely truncated. This procedure will be used throughout the rest of this work.

Fig. 4 shows the low- q behaviour of the structure factor, with and without corrections, as well as the structure factor up to $q = 4$ Å⁻¹ in the inset. The uncorrected structure factor artificially increases as q goes toward zero, consistent with $S_v(0; R)$ from fig. 3. The black dashed curves with gradually increasing opacity represents results from integral-truncation distances ranging from

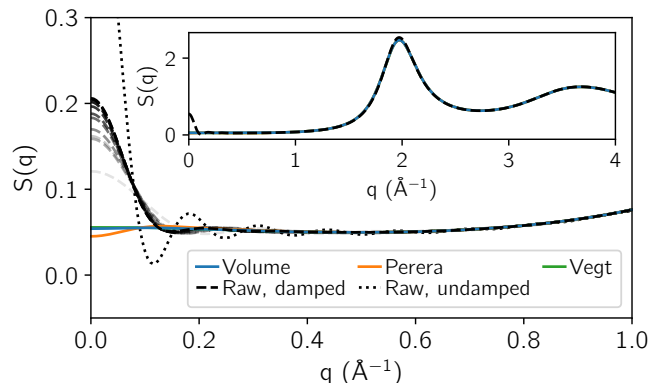


Figure 4: The performance of the three corrections on the low- q behaviour of the structure factor. The structure factor calculated from the uncorrected RDF artificially increases as q goes toward zero, as a result of the finite-size RDF-sampling. The dashed black curves increase in opacity according to R values going from 30 Å to 50 Å. Note that the Volume- van der Vegt corrections produce results that are almost identical, which means the green curve is hidden behind the blue.

30 Å to 50 Å, showing how the low- q amplitude is entirely dependent on the (arbitrarily) chosen truncation distance. By correcting the RDFs for their finite-sampling, these low- q artefacts can be removed. The van der Vegt- and the volume-corrections are in closest agreement on the $q < 0.2$ Å⁻¹ signal shape and magnitude, whereas the Perera-correction produces a slightly smaller signal in this region. For these large 100 Å cells, the artificial increase in the uncorrected signal sets in around $2\pi/(50 \text{ Å}) = 0.125 \text{ Å}^{-1}$, with some ringing (i.e. truncation oscillations) present up until $\sim 0.2 \text{ Å}^{-1}$. However, not all types of simulation are inexpensive enough to allow cells of these sizes to be employed, making corrections crucial, even at higher q . Especially *ab initio* molecular dynamics (AIMD) simulations, where the particles are classically propagated from gradients of *ab initio* potentials [21, 22, 24], are still too expensive to perform using such large cells. Multiscale methods that couple Quantum Mechanical / Molecular Mechanical (QM/MM) potentials can employ larger (MM) cells [3, 10, 81, 82], but not without increasing the coupling cost in evaluating the interactions between the two subsystems, and introducing approximations in how the coupling is carried out [83].

Solute-Solvent LJ systems

We now extend the analysis by systematically varying the σ -value of a single 'solute' particle in a series of separate MD simulations, to simulate how an increase of the effective particle-size affects the resulting estimated excluded volume, RDF convergence, and corrections. To find the excluded volume for an l -type particle in an m -type solvent, we fitted $V_{lm} = 4/3\pi R_{lm}^3$ of the volume-correction in eq. 8 by optimizing R_{lm}^3 to produce an RDF that minimizes the residual between $g_{lm}(r > r_{\max})$ and 1, where the parameter r_{\max} was chosen such that correlations within the liquid have died out. This will circumvent the limit imposed by the finite bin-size when numerically sampling the RDF, but the fit will be sensitive to the numerical sampling noise, which even for 100 ns trajectories is relatively large compared to the difference between the actual asymptotic limit of the RDF and 1. The first 5 rows of fig. 5 again uses the $S(0; R)$ method to analyse the results, this time labeled $S_c(0; R)$, since $l \in u$ and $m \in v$. Since the differences between the RDF value and 1 are so small, the sampling noise makes the fit sensitive to the choice of r_{\max} , but generally, 7σ proved adequate in fitting volumes that converges $S_c(0; R)$. The bottom plot shows a linear increase in the excluded

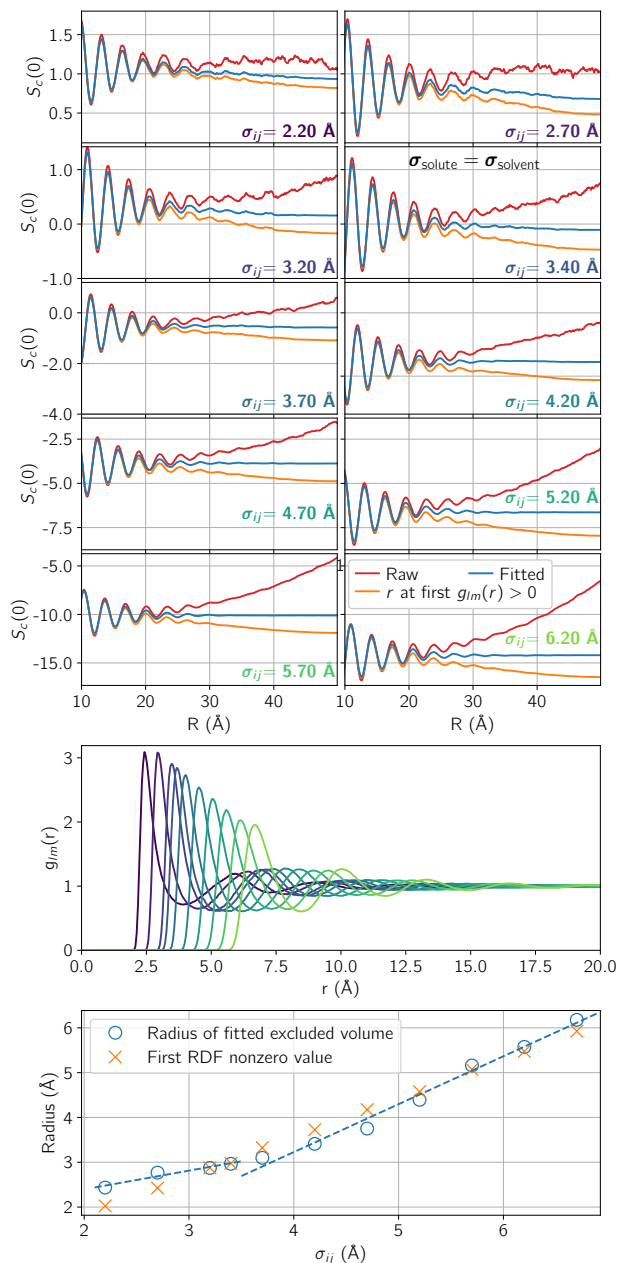


Figure 5: Top 5 rows: Comparing the volume-correction for $S_c(0; R)$ for a selection of the entire set of simulations. The excluded volume is either approximated with a sphere with radius r equal to the r at which $g(r) > 0$ (yellow curves), or via the fitting procedure described in the main text (blue curves). Note that we only calculate the cross-term. The actual measured signal would also contain both particle self-scattering and all the other terms apart from the term shown here. Middle: Solute-solvent RDFs used in the plots above. Bottom: Fitted radii of the excluded volume V_{lm} as a function of solute-solvent σ values (blue circles). The blue dashed lines show linear fits to the two regions $\sigma_{\text{solute}} < \sigma_{\text{solvent}}$ and $\sigma_{\text{solute}} > \sigma_{\text{solvent}}$ (with $\sigma_{\text{solvent}} = 3.4 \text{ \AA}$). The yellow crosses represent the radii used for the yellow curves in the top 5 rows.

volume with increasing σ_{solute} , with two distinct slopes depending on whether $\sigma_{\text{solute}} > \sigma_{\text{solvent}}$ or vice versa: When the solute is smaller than the solvent, the extension of the neighbouring solvent molecules play a larger role in how close they can pack around the solute, as their own extensions in space hinder closer packing, showing the m -dependence on V_{lm} .

Test System 2: Water

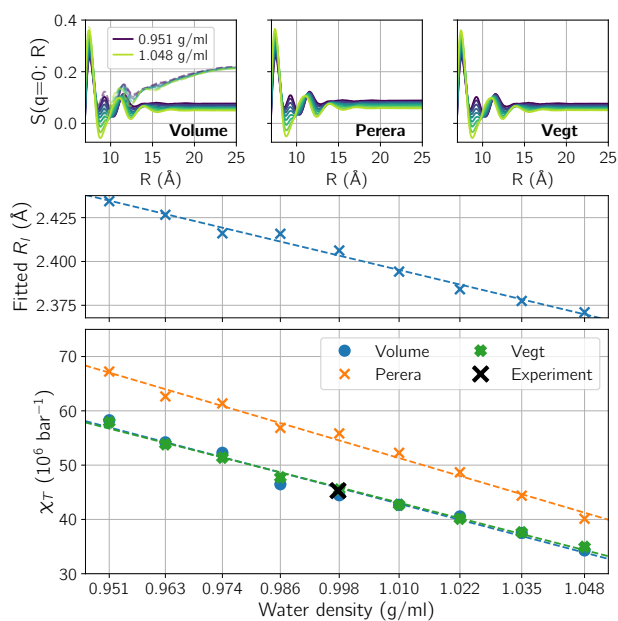


Figure 6: Top: The three corrections of the $S(0; R)$ -value, for each density of 4095 molecules of TIP4P_{EW} water sampled for 100 ns each, in cells of decreasing size. The leftmost plot also shows the uncorrected curves as dashed lines. Middle: The fitted radius of the excluded volume as a function of density, where the fit minimizes the residual of $g(r > r_{\text{max}}) - 1$, where an r_{max} -value of 22 Å was used. Bottom: The isothermal compressibility χ_T as a function of the water density.

We now focus on neat water as a test system. As shown in eq. 7, the isothermal compressibility can be obtained from $S(q = 0)$. Therefore, we can calculate the isothermal compressibility χ_T from the simulations and compare to its experimental value. Fig. 6 collects the results from simulating neat water at a range of densities.

As the main contribution to the scattering will come from the O-O correlation, we calculate the $q = 0$ structure factor of this atom-type pair, and correct it with the three previous corrections, again fitting the excluded volume as explained in the previous section. The middle plot shows how the excluded volume decreases as expected with increasing the density. The lowest plot shows how this translates into a linearly decreasing isothermal compressibility. Heuristically, the more we have already compacted the water, the less it is willing to be further compacted. As we are only using the O-O pair, and using the relatively simple TIP4P_{EW} water model that e.g. employs rigid water molecules, we cannot expect a complete agreement with the experimental value, yet both the van der Vegt- and volume correction produces compressibilities very close to the experimental value of ambient water density at room temperature [84, 85]. This shows that the corrections not only make the integral converge, but also reproduce the experimental value, whereas the Perera correction seems to slightly overestimate it. This does not change whether we set κ_{lm} from eq. 11

to the value found using our excluded-volume fitting method, or the first non-zero $g_{lm}(r)$ r -value, but we cannot rule out that further adjustments would increase the accuracy with respect to the experimental result. However, our result is consistent with the previous finding that the van der Vegt- and Perera- methods give different KBIs [48], most likely since the Perera-correction leaves the RDFs unchanged at shorter r -values, even though the sampled RDF should be corrected across all r .

Test System 3: A Single-atom Ion in Water - Sampling Convergence

In the previous section we took advantage of the fact that there are $N(N - 1)$ water-water correlations in the simulation cell, which greatly increases the sampling statistics. However, many scenarios involve a single solute molecule in solution, where the cross term RDFs are then sampled on only N correlations per independent MD frame. Fig. 7 tests the three corrections on a simple

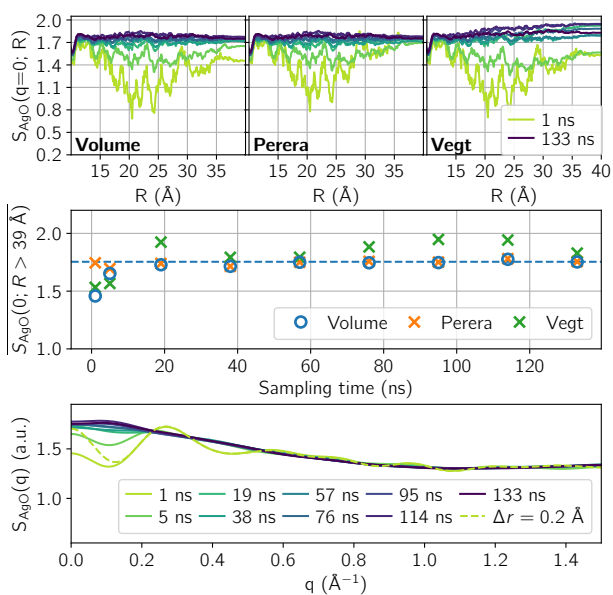


Figure 7: Top row: Performance of the volume, Perera, and van der Vegt corrections on the Ag^+ -O RDF, with respect to sampling time. Middle: the average $S_c(0; R > 39\text{\AA})$ as a function of sampling time. The Perera correction converges fastest, but our Volume-correction also reaches convergence if sampled more than roughly 20 ns. The dashed blue line shows the total average of all $S_c(0; R > 39\text{\AA})$ averages for sampling times of 60 ns or more. Bottom: The structure factor at low q as a function of sampling time, calculated from RDFs corrected using the Volume correction. The dashed line shows the result of reducing the sampling noise of the 1 ns sample by calculating the scattering using a numerical dr of 0.2 \AA .

solute-solvent system comprised of a single Ag^+ ion in water, with RDFs sampled from between 1 ns to 133 ns. If the sampling is too short, the corrections cannot converge the integral. The $S_c(0; R > 39\text{\AA})$ values converge with simulation time when either the Volume- and Perera correction is applied, whereas the van der Vegt correction is more unstable. For the 1 ns sampling, the bottom plot shows large artificial oscillations at low q with some ringing even above 1\AA^{-1} . The dashed curve represents scattering calculated from an RDF sampled with $dr = 0.2 \text{\AA}$ instead of 0.05\AA , showing that a 4 x increase in numerical bin size of dr in eq. 1 only affects the oscillatory artefacts significantly at $q < 0.2 \text{\AA}^{-1}$.

Molecular Solutes: Simulation cell sizes

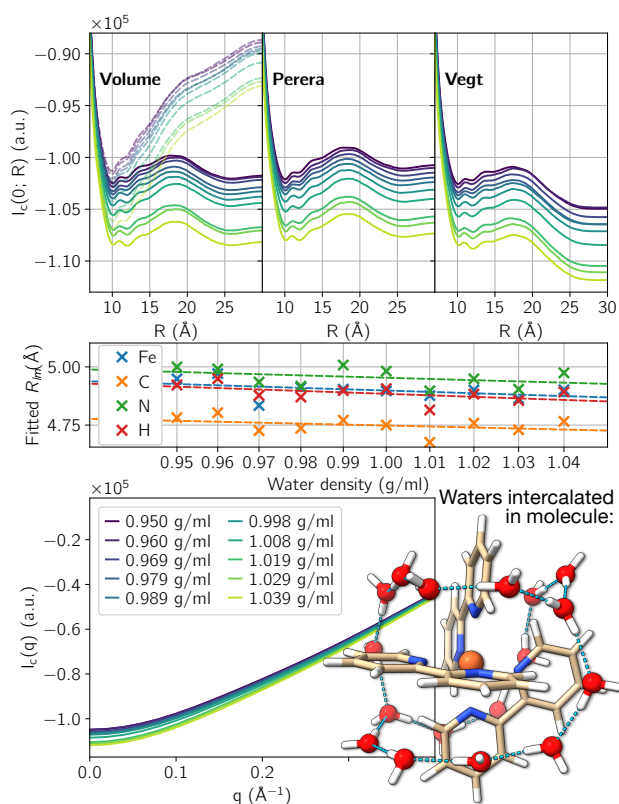


Figure 8: Top row: Performance of the three corrections tested on the total coherent cross-scattering term $I_c(q = 0)$ as a function of the integral truncation distance R , calculated from all solute-solvent pairwise RDFs of the $[\text{Fe}(\text{bpy})_3]^{2+}$ molecule in water. Middle: The fitted excluded volume of the different solute atom types as a function of water density. Bottom left: the cross-term at low q as a function of water density. Bottom right: Illustration of the (hydrogen bonded) network of intercalated water molecules in the first solvation shell of the molecule.

Real systems, like a molecule in solution, will most often be comprised of many different elements. This section will use the transition metal complex $[\text{Fe}(\text{bpy})_3]^{2+}$ as an example, as it has been the center for many experimental studies using x-ray techniques [76, 86, 87], including scattering [18, 21, 25], as well as computational investigations [22, 24, 77]. The complex is shown in the lower right corner of fig. 8. From the geometry of the complex, it is evident that the simple spherical approximation of the excluded volume will be much less accurate than previously. The complex is comprised of a single Fe atom, plus atoms of the elements C, N, and H, and according to eq. 3 the coherent cross term scattering signal $I_c(q)$ is a stoichiometrically weighed sum of the integrals over the cross-term RDFs, each term multiplied with the atomic form factors of the atom types of the RDF. It is thus clear that each pairwise correlation does not contribute equally to the recorded signal, but that its intensity is dependent on the number of atoms of each type present in the system, as well as the number of electrons in each atom type. But $I_c(0; R)$ will show the same behaviour as $S_c(0; R)$, as the form of the integral is the same. Therefore, to make a single assessment of the convergences of *all* the integrals that are evaluated to obtain $I_c(q)$, taking into account how much each term contributes to the total cross-term signal, we use $I_c(0; R)$ instead of all

the individual $S_c(0; R)$ terms. The top three plots in fig.8 shows the results of applying each of the three corrections to each of the cross-term RDFs. For the volume-correction, the excluded volume was fitted separately for each RDF. For this relatively large molecule, the first thing we observe is how the two first corrections struggle to make the running integral reach convergence within the limited box size. However, close inspection of the results from the van der Vegt correction shows that the curves seem to flatten out above ~ 27 Å, indicating that convergence might be reached for this correction. We repeated the strategy of performing the simulations at increasing densities in order to study the robustness of the fitted excluded volume from the long- r RDF asymptote. The middle plot shows the result of these fits. We first note that the excluded-volume values are larger than expected for a single atom of the same type in a solution. This is because the rest of the particles in the solute will hinder access of the solvent molecules. Yet, in spite of the now somewhat crude spherical approximation of the excluded volume, we still observe the expected behaviour of the volume decreasing with increased density, no matter which of the solute-solvent RDFs we fit. While all pairs produce excluded volumes of similar sizes for each water density, the intercalation of water molecules between the ligands of the complex (see the inset in fig. 8) means that the waters of the first solvation shell can get closer to especially the carbon atoms of the complex. This effect causes the smaller fitted excluded volume values from those correlations.

The solid curves in the bottom plot show the total cross-term scattering signal at low q -values, corrected using the van der Vegt correction. The signal is negative since there is no atomic self-scattering for this term in eq. 3, but while this term can easily be calculated, it evidently cannot be measured without *also* measuring the rest of the scattering terms, which make the total signal positive for all q .

We conclude this section by emphasizing that larger solute molecules create larger excluded volumes, which again require larger total simulation cell sizes if one is to robustly assess and correct the RDFs to calculate reliable signals in the low- q region. Overall, this section has given examples on how to use evaluation of $S(0; R)$ and $I(0; R)$ to assess how artefacts from finite-size sampling affects the low- q region, and how well one can correct for them. We thus put forward the strategy presented in the above analysis as an effective way to gauge the trustworthiness of simulated scattering signals and discern artifacts from physical information, in work where high accuracy in the low- q region is required. The strategy is summarized in the summary and outlook section of this work.

Solvent-Solvent Contributions to Scattering

Since our RDF-correction is based on an estimation of the excluded volumes in a finite simulation cell, we will now try to isolate the contribution of the excluded volume *itself* to the total scattering signal. For a solute-solvent system, we can choose to tally up contributions to the scattering arising from the interaction between the two subsystems in the following terms: (1) $I_{uv}(q) + I_{vu}(q) = I_c(q)$ from the solute-solvent RDFs (see eq. 2), (2) The part of the solvent-solvent scattering term $I_{vv}(q) = I_v(q)$ that encodes the local structure in the shell around the solute, and (3) the part of I_v due to the excluded volume 'hole'. While the second and third contributions aren't directly available in isolation from eq. 2, both contributions are encoded in the solvent-solvent RDFs and thus in $I_v(q)$. However, the hole, and the subtle changes in average pairwise particle distances within the solvation shell compared to the bulk solvent are averaged out over the bulk-solvent average pairwise particle distances, and are thus extremely sensitive to numerical sampling noise. Furthermore, calculating $I_v(q)$ from RDFs sampled in fixed-cell simulations can give rise to an additional finite-size effect, separate from the one discussed in the previous sections. Let us suppose one wishes to analyse a system where the overall extension of the solute changes upon some perturbation to it (for example

an electronic excitation), such that the solvation shell expands. For fixed cell (NVT) simulations, such a local expansion will lead to a *decrease* in effective volume available to the solvent, resulting in a bulk-solvent density *increase*. The scale of this effect is dependent on the size of the simulation cell, as in a(n equilibrium) simulation of an infinite system, the solvent would have space (and time) to reorganize itself to its preferred density. If preferred, such an effect could be eliminated by re-equilibrating the system after the solvent shell expansion in the NPT ensemble. However, the density fluctuations in such runs will make it difficult to eliminate this effect in a systematic manner. Instead, we will focus on a different route that does not rely on the solvent-solvent RDFs.

Small-Angle X-ray Scattering (SAXS) methods estimate the scattering from the excluded volume by constructing form factors from an average density of the surrounding solvent to model the scattering from it [88–91]. The same central principle has been employed elsewhere [26, 35] by using the cross-term RDFs to construct an 'excluded volume' form factor $f_{l \in u, \text{EV}}(q)$:

$$f_{l \in u, \text{EV}}(q) = 4\pi \sum_{m \in v} f_m(q) \frac{N_m}{V} \int (g_{lm}(r) - 1) \frac{\sin(qr)}{qr} r^2 dr, \quad (17)$$

which was then used in the discrete Debye-formulation on all solute distances [26], effectively using the solute-atomic positions to approximate the size and shape of the excluded volume. The solute in the original study of Panman et al. was comprised of particles of a single atom type, but as we observed in fig.8, when different atom types make up the solute, the excluded volume experienced by each atom type can be slightly different, thus requiring an $f_{l, \text{EV}}(q)$ per atom type $l \in u$. Due to the equivalence of the discrete Debye equation and eq. 3 [29], we can generalize this procedure to obtain the excluded-volume scattering from solute-solute radial distribution functions:

$$I_{\text{EV}}(q) = \sum_{l \in u} N_l f_{l, \text{EV}}(q)^2 + \sum_{l \in u} \sum_{m \in u} f_{l, \text{EV}}(q) f_{m, \text{EV}}(q) \frac{N_l(N_m - \delta_{lm})}{V} 4\pi \int_0^R g_{lm}(r) \frac{\sin(qr)}{qr} r^2 dr. \quad (18)$$

We can assess this method by comparing it to the direct solvent-solvent term $I_v(q)$ for our simple LJ liquid with varying solute sizes. We thus return to the LJ liquid system and calculate $I_v(q)$, as well as the scattered intensity using $f_{l, \text{EV}}(q)$. As our system only contains a single particle, the excluded-volume intensity is simply the self-scattering term.

$$I_{\text{EV}}(q) = \sum_{l \in u} N_l f_{l, \text{EV}}(q)^2 = f_{l, \text{EV}}(q)^2. \quad (19)$$

The contribution of the solvation shell to the total solvent-solvent term $I_v(q)$ will be completely overshadowed by the bulk solvent signal. Thus we first calculate the *difference*-scattering signal from a solute-expansion by subtracting the solvent-scattering of the 'neat' LJ liquid from that of the system with the biggest solute: $\Delta I_v(q) = I_v^{6.7}(q) - I_v^{3.4}(q)$, where both simulations were performed with identical box sizes.

The black curve in fig. 9 shows this calculated signal. The signal has two distinct features, a $q < 1 \text{ \AA}^{-1}$ peak and a $1 \text{ \AA}^{-1} < q < 3 \text{ \AA}^{-1}$ oscillation, which we call the 'low-q' and 'high-q' feature, respectively. As mentioned in the introduction to this section, there are two events that affect $I_v(q)$: (I) The increase in the excluded volume inaccessible to the solvent due to the increase in solute size, and (II) the increase in average density of the bulk solvent as the effectively accessible volume to the solvent decreases as the excluded volume of the solute *increases*. The latter can be isolated by simply running a simulation of 'neat' $\sigma_{ij} = 3.4 \text{ \AA}$ -particles in a *smaller* box, where we have reduced the volume with the same amount as the total accessible volume has decreased for $\sigma = 3.4$

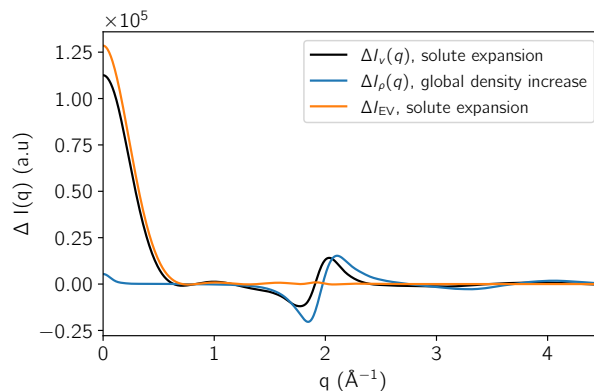


Figure 9: Difference-scattering curves of the individual contributions to the solvent-solvent term (black curve), calculated from the difference of the scattering of the LJ RDFs containing the $\sigma_{ij} = 6.7 \text{ \AA}$ solute, and the 'neat' LJ liquid, where all particles have a σ_{ij} of 3.4 \AA . The blue curve shows the global density difference from calculating $\Delta I(q)$ from reducing the NVT box volume with the same amount as we estimate the excluded volume increases in the $\sigma = 6.7 \text{ \AA}$ case. The orange curve shows the excluded volume term calculated via eq. 17.

\AA -particles in the original box, due to the single $\sigma_{ij} = 6.7 \text{ \AA}$ -solute. We estimate this volume by using the fitted radius of the excluded volume in fig. 5. For 100 \AA box sides, this change constitutes a reduction of the total volume by less than 0.1 %. Yet, this minute change gives the difference-scattering signal $\Delta I_\rho(q)$, displayed with blue in fig. 9. There is a noticeable agreement between the high- q solvent-solvent feature in $I_v(q)$ and the global average density increase, indicating that this feature arises from the global density increase of the bulk solvent. The differences between the black and blue curve in the high- q feature must arise from the inaccuracies in exactly determining the excluded volume from the simple model discussed previously (see fig. 5 and accompanying text), as well as the fact that the signal from the global density increase does not contain any local solvent shell structure. We thus conclude that the high- q feature is a finite-size effect due to the fixed volume of the simulation cell.

The low- q feature of $I_v(q)$ is not present in the global density term $\Delta I_\rho(q)$, but it is present in $\Delta I_{EV}(q) = I_{EV}^{6.7}(q) - I_{EV}^{3.4}(q)$. Thus, the excluded-volume scattering expression in eq. 18 describes the local structural changes in the shell and of the 'hole' left by the solute, for this simple test system. We can test this characterization by comparing the absolute I_{EV} term to an analytical 'hole'-shell model, inspired by SAXS-methodologies [90]. This approach is based on homogeneous volumes, and not scattering from distributions of discrete particles with preferred interatomic distances, so we cannot expect a 1:1 agreement between scattering from an analytic hole-shell model and the I_{EV} term. Nevertheless, we re-purpose a well-known core-shell model [90]. Here, the analytical form factor $F(q)$ of a core particle with scattering length density ρ_c and volume V_c , surrounded by a shell of scattering length density ρ_s and volume V_s , is [90] (see fig. 10):

$$F(q) = \frac{3}{V_s} (V_c(\rho_c - \rho_s)\Psi(qr_c) + V_s(\rho_s - \rho_{\text{bulk}})\Psi(qr_s)), \quad (20)$$

with

$$\Psi(qr) = \frac{\sin(qr) - qr \cos(qr)}{(qr)^3},$$

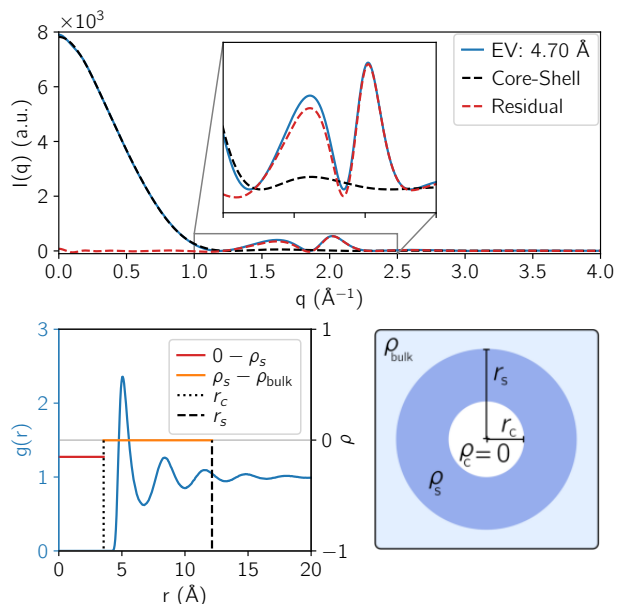


Figure 10: Top left: The blue curve shows the excluded volume term for the $\sigma_{ij} = 4.7 \text{ \AA}$ LJ solute system, calculated with eq. 22. The dashed black line shows scattering from the analytical core-shell model, calculated from fitting the scattering length densities and shell radii in eq. 21, as well as the overall scaler α in eq. 19 to minimize the difference (red dashed curve) to the EV term. The inset shows a zoom-in on the high- q features. The analytic model can capture the low- q feature, but not the later oscillations. Top right: Core-hole continuum model scattering densities, made from subtracting a core sphere with the same scattering length density as in the shell, ρ_s from a bigger sphere of ρ_s , such that $\rho_c = 0$. Bottom plot: Comparison of the RDF used to obtain the EV form factor in eq. 17 to the fitted scattering length densities and radii of the core-hole r_c , as well as the shell r_s .

where ρ_{bulk} is the scattering length density of the bulk solvent. In our case, the scattering length density of the core particle is zero, since the solute particle scattering should not be included twice (both here, and in the solute-term). Thus, the form factor becomes:

$$F(q) = \frac{3}{V_s} (V_s(\rho_s - \rho_{\text{bulk}})\Psi(qr_s) - V_c\rho_s\Psi(qr_c)), \quad (21)$$

and we see that the second term indeed gives the negative scattering length density of the 'hole' left in the shell. Since the local density of particles in the shell will differ slightly from the bulk solvent, the first term of the form factor needs to reflect the change in scattering contrast between these two (albeit not very well-defined) regions of solvent, $\rho_s - \rho_{\text{bulk}}$, as is indeed the case in eq. 21. The model is illustrated in the top right part of fig. 10. We calculate the scattered intensity as

$$I(q) = \alpha F(q)^2, \quad (22)$$

with α being a free parameter to scale the total intensity to account for the number of particles used in the MD simulations. We can thus now fit the core (hole) and shell radii, r_c and r_s , as well as the scattering length densities to the excluded volume scattering signal, to see if the fitted values give reasonable estimates while reproducing I_{EV} . Fig. 10 shows this for the absolute scattering of the solute- $\sigma_{ij} = 4.70 \text{ \AA}$ LJ liquid, which was chosen since the both its high- and low- q features are

visible within the same scale. The top left plot in fig. 10 shows the results of this fit. The plot shows the $I_{\text{EV}}^{4,7}(q)$ signal (blue curve) and the scattering from the analytical form factor as dashed black lines. The bottom plot shows the fitted radii and scattering length densities. The fitted radii corresponds well with the structure of the shell encoded in the RDF, even for this simple description. The difference in fitted scattering length densities between the bulk solvent and the shell is only around 1%, which is to be expected as the two regions are made up of the same type of particles. Returning to the top left plot, we observe how the model captures the low- q increase arising from the excluded volume, but not the oscillations at longer q (see also the inset). We thus assign them to the non-homogeneous structure of the solvent shell, which cannot be captured by a continuum model, but is encoded in the cross-term RDF from which the excluded volume signal is constructed.

In conclusion, this analysis has identified the two main contributions of the excluded volume term of eq. 18 as the solvent-solvent scattering from the excluded volume created by the solute, as well as the local structure of the solvent shell. The excluded volume formulation thus provides a method for calculating the local solvent-solvent scattering from the shell (and hole). For difference-scattering analyses, this method can prove advantageous for fixed-cell simulations, since it is free from the finite-size effect of global density changes that arise from changes in the excluded volume changing the average solvent-solvent distances in the bulk solvent.

Summary and Outlook

With this work, we have analysed the effect of the excluded volume on the global density normalization in the sampling of RDFs from finite systems on the low- q behaviour of the structure factor and the coherent x-ray scattering signal. We have done so in order to design a robust set of best practices for the forward modelling of coherent x-ray scattering across the entire q -range, all the way to 0 \AA^{-1} . We showed how the density normalization of the RDFs sampled from particles l in finite size systems does not take into account the excluded volume of the l -type particles themselves, and how this makes the RDFs converge to a value different from 1. This causes the integral in the central scattering equations (3, 4) to diverge if the RDFs are not corrected for this type of finite-size artifacts. We developed a conceptually simple way of correcting finite-size sampled RDFs, by accounting for this excluded volume in the density normalization of the RDF. Our correction was then evaluated alongside two previously published corrections which we repurposed for x-ray scattering. We have also shown the evaluation of $S(0; R)$ and $I(0; R)$ at increasing cutoff-values R of the central integral in the scattering equations as a robust way of assessing whether or not the low- q region of the resulting scattering signal has converged to its final value, as these quantities converge to a constant value with increasing R . We hope that this method will be used to include more of the low- q region in future work that focuses on the solvent-shell structure and changes therein.

In simple test-systems, we were able to use the volume-correction to identify the size of the excluded volume and correct the RDFs to provide converged scattering signals across the entire q -range. However, both the volume-correction and the correction provided by Perera and coworkers are reliant on parameters that have to be fitted or estimated, whereas the van der Vegt correction is parameter-free. We have used the isothermal compressibility of water to test the corrections against experimental results, and found the volume- and van der Vegt correction to recover the experimental isothermal compressibility with the best accuracy.

We also assessed the effects of MD-sampling time on the effectiveness of the RDF corrections, and

have shown that for the cross-term RDFs, the significant reduction in particle-pairs that can be sampled for each frame compared to the solvent-solvent RDFs necessitates higher requirements on sampling-time for the corrections to make $S(0; R)$ converge. For the Ag^+ ion in water, roughly 20 ns sampling time was needed. Water correlations are on the 1-10 ps range, meaning that roughly 2,000-20,000 uncorrelated frames were needed for robust evaluations of the corrections. Since the computational cost of classical MD simulations has been greatly reduced with the advent of performing calculations on GPUs, it has become a routine operation to produce >20 ns trajectories on a single GPU node, and we therefore recommend always assessing the convergence of the corrections against sampling time, before continuing to employ the simulated signal in further modeling, if the computational cost of the employed potential allows for it.

We furthermore evaluated the corrections on a more intricate system, namely the $[\text{Fe}(\text{bpy})_3]^{2+}$ complex in water. We observe that larger excluded volumes require larger R -values to reach convergence, thus requiring larger simulation cells. For this system, only the van der Vegt correction managed to flatten out the $I(0; R)$ -signal within the limits of the range of the sampled RDF. This system also illustrated the intricate nature and m -extension dependence of the excluded volume concept for real systems.

While there only exists a single *correct* RDF, the differences between the RDFs after applying the various corrections are so small that it can be advantageous to test multiple corrections from an operational perspective, before deciding on which to use going forward.

Finally, we analysed $I_{EV}(q)$ as an alternative to the solvent-solvent term $I_v(q)$ for including scattering from the local structure of the solvation shell and its excluded volume. We identified two different features of the $I_{EV}(q)$ term, arising from (1) the scattering from the contrast between the solvent and the hole left by the excluded volume, and (2) from the local structure in the solvent shell around the solute. We showed that, for analysis of difference scattering signals, e.g. from time-resolved experiments, the $I_{EV}(q)$ term is less affected by perturbations in the bulk solvent density that can manifest themselves when the overall extension of the solute is modified but the simulation cell is kept constant over both simulations.

Based on our findings in this work, we propose the following best-practices guidelines to minimize low- q oscillations from finite size systems:

1. Perform MD (equilibrium) production runs in the NVT ensemble if possible, to keep the cell volume fixed throughout the simulation. Non-equilibrium simulations should be carried out in the NVE ensemble [92].
2. If computationally tractable (i.e. as with classical MD), thoroughly sample the RDFs to avoid buildup of statistical noise - i.e. test convergence of $S(0; R)$ as a function of sampling time as in fig. 7 - and use simulation cells big enough to allow for the $S(0; R)$ analysis.
3. If using 'black-box' RDF-sampling codes and the van der Vegt correction, use a density-normalization for the RDF-sampling consistent with the correction (or vice versa). Similarly, if NPT production runs were performed, the $N_{lm}(r)$ histograms of the RDFs should be normalized with the current volume of the cell at each frame.
4. Perform the $S(0; R)$ or $I(0; R)$ -analysis to ascertain converged integrals at long R -values and to benchmark the corrections.
5. Various window functions should be tested in conjunction with the RDF-corrections. There unfortunately isn't a 'one-size-fits-all' solution to all simulation cell sizes and systems, so their influence on the entire scattering signal should be minimized.

6. If reliability all the way to $q = 0$ is desired, either the calculated value should be tested against the isothermal compressibility if such an experimental quantity is available, or the $S(q = 0)$ -dependence on density should be assessed to ensure that the $S(q = 0)$ limit exhibits the expected behaviour with respect to density changes.
7. If modeling dynamics or large structural changes of a solute in a solvent in the NVT ensemble, any significant changes to the size of the solute will be reflected in an overall change of the average solvent-solvent distances, creating a 'density'-contribution in the solvent-solvent scattering signal, as shown in fig. 9. Further treatment of this term is highly dependent on the specifics of the desired analysis. For ultra-fast studies of, say, an expanding solute, the surrounding solvent molecules might not have had time to re-arrange themselves to re-obtain the density it had before the expansion of the solute, and the term might also be present in experimental data. One can imagine other cases where the solvent has had enough time to re-equilibrate, and thus including the density term can be avoided by calculating $I_{EV}(q)$ from eq. 22 instead. The density term can also be eliminated by expanding the simulation cell with the increase in excluded volume, or by re-equilibrating the cell size in an NPT simulation, stopping at the same density for the previous simulation of the non-expanded solute.

The software package 'grsq' has been developed to apply the corrections and simulate the signals. It is available through the Python Package Index [36]. Further examples on how to use it apart from the ones already included can be found in the data-repository accompanying this work [37].

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