

Appendix B

Molecular Solvation Through Correlation Functions

B.1 Introduction

It is particularly desirable to obtain the free energy of solvation, $\Delta\mu^{\text{solv}}$, of an arbitrary solute molecule in a solvent consisting of a mixture of molecular species. For example, this could be the free energy of solution of an oxygen molecule O_2 in a water solution. Theoretical methods for the accurate computation of this quantity for small molecules and proteins have a large impact on fields such as protein folding and rational drug design. They also provide descriptions of solvent and electrolyte interaction with various chemical groups and the potential effects of mutations in proteins.

There are currently many methods for the theoretical computation of $\Delta\mu^{\text{solv}}$ — molecular dynamics integration, Monte Carlo simulation, continuum electrostatics, semi-empirical quantum mechanics, and integral equation methods, to name a few. Integral equation methods have the advantageous feature of modeling the detailed solvent and solute structure while enabling fast analytic computation of the positional and orientational correlation functions between molecules. These functions can be used under certain approximations to compute the solvation free energy, enthalpy, energy, entropy, heat capacity, etc.

The free energy of solvation is defined in Section II. Distribution function theory for single- and multi-component fluids is derived in Section III, resulting in expressions for the free energy in terms of the 2-particle correlation functions. Section IV, following a short review of the calculus of functionals, gives derivations of several important integral equations, such as the Ornstein–Zernike equation, along with approximate methods of their solution. Finally, in Section V, these theoretical results are applied to the particular case where the intermolecular potential energy functions are written as a pair-wise sum of atomic energy functions. From this, a fast computational method is obtained for computing the radially averaged atom–atom correlation functions and the free energy of solvation.

B.2 Free Energy of Solvation

The free energy of solvation is defined as the free energy of transfer^a of the solute molecule from an ideal gas, in which the concentration of the solute molecules^b is 1 molar,^c to a solvent mixture in which the concentration of solute molecules is also 1 molar (see Chapter 2). The computation of $\Delta\mu^{\text{solv}}$ can be broken down to several smaller steps

$$\Delta\mu^{\text{solv}} = -\mu^{\text{ig}}(\rho = 1M) + \mu^{\text{noint}}(\rho = 1M) + \mu^{\Delta\text{int}}(\rho = 1M), \quad (\text{B.1})$$

where the chemical potential of an ideal gas in which solute molecules have a density ρ is denoted $\mu^{\text{ig}}(\rho)$ and can be computed from the ideal gas partition function. The other two terms represent the free energy of placing a non-interacting solute molecule into solution and the free energy change associated with allowing the solute molecule to interact with the solution. In the canonical ensemble of N rigid^d solute molecules in a volume V ($\rho = N/V$), the partition function is

$$Q = \frac{1}{N!\sigma^N} \int d\mathbf{r}d\mathbf{p}d\omega d\mathbf{J} e^{-\beta\mathcal{H}} \quad (\text{B.2})$$

where \mathbf{r} and \mathbf{p} are the position and momentum of the center of mass of a molecule, ω is the orientation of the molecule in terms of the relevant Euler angles^e (with $\Omega = \int d\omega$ and $s =$ total number of rigid degrees of freedom), and \mathbf{J} is the rotational angular momentum of the molecule. Also, σ is the symmetry factor representing the number of unique ways to rotate the molecule onto itself.^f For notational simplicity, let $\beta = 1/(kT)$, $\mathbf{x}_i = (\mathbf{r}_i, \omega_i)$ and $\mathbf{x}_{i\dots j} = (\mathbf{x}_i, \dots, \mathbf{x}_j)$.

Specializing to the ideal gas case of current interest, the classical Hamiltonian factors into separate linear and angular momentum terms with no intermolecular interaction, $\mathcal{H} = \mathcal{H}_p(\mathbf{p}_{1\dots N}) + \mathcal{H}_J(\mathbf{J}_{1\dots N})$. Eq. B.2 is then also separable into the product of 3 partition functions:

$$\begin{aligned} Q^{\text{ig}} &= \frac{1}{N!} \int d\mathbf{p}_{1\dots N} e^{-\beta\mathcal{H}_p} \int d\mathbf{J}_{1\dots N} e^{-\beta\mathcal{H}_J} \int \frac{d\mathbf{x}_{1\dots N}}{\sigma^N} \\ Q^{\text{ig}} &= \frac{Q_P^N Q_J^N}{N!} \left(\frac{V\Omega}{\sigma} \right)^N, \end{aligned} \quad (\text{B.3})$$

the single particle linear momentum (Q_P), angular momentum (Q_J), and configurational ($Z_1^{\text{ig}} = V\Omega/\sigma$) partition functions. The Hamiltonians for the translational and rotational degrees of freedom

^aAll ensembles involved in the transfers (ideal gas or non-ideal fluid) should have the same temperature and volume or pressure, depending on the statistical mechanical formalism chosen.

^bThe ideal gas can have any concentration of other molecular species without affecting the chemical potential of the solute species.

^c1 molar = 1M = 1 mole/liter = 6.02214×10^{-4} molecules/ \AA^3

^dMolecules are considered rigid because conformational freedom would result in many-body intramolecular constraints that are difficult to handle theoretically, especially when the system includes intermolecular potential functions. In fact, the major approximation to be made—that the potential energy functions can be pair-wise additive—would be violated by any non-rigidity except small amplitude bond vibrations. This condition is generally not too restrictive since many molecules of interest have only a few discrete conformations that can be explicitly included.

^eFor spherically symmetric molecules (i.e. atoms and monatomic ions), ω does not contain any variables, $s = 3$ and $\Omega = 1$ (there are no rotational degrees of freedom to normalize). For linear molecules, $\omega = (\theta, \phi)$ $s = 5$ and $\Omega = 4\pi$, and for nonlinear molecules, $\omega = (\theta, \phi, \xi)$, $s = 6$ and $\Omega = 8\pi^2$.

^fFor example, $\sigma = 1$ for a molecule of CO, 2 for H₂O or O₂, 12 for NH₄, etc.

are known so the integrals in Eq. B.3 can be analytically computed²⁰

$$\begin{aligned}
 Q_P &= \left(\frac{2\pi M k T}{h^2} \right)^{3/2} \\
 Q_J &= \begin{cases} 1 & \text{spherically symmetric molecules} \\ \frac{T}{\Omega \Theta} & \text{linear molecules} \\ \frac{\pi^{1/2}}{\Omega} \left(\frac{T^3}{\Theta_1 \Theta_2 \Theta_3} \right)^{1/2} & \text{nonlinear molecules} \end{cases} \quad (\text{B.4})
 \end{aligned}$$

where M denotes the total molecular mass and $\Theta_i = h^2/(8\pi^2 I_i k)$ is the rotational temperature about the molecule's i^{th} principle axis of inertia. The ideal gas partition function is commonly written as a product of translational and rotational partition functions. In Eq. B.3 the volume integral has been separated from the translational partition function leaving Q_P . Also, the angular integral has been separated from the rotational partition function leaving Q_J . This has been done in anticipation of the inclusion of intermolecular potential energy functions yielding a more complicated configurational partition function.

Now that the partition function of the ideal gas is known, the first term in Eq. B.1 can be derived

$$\mu^{\text{ig}}(N, V) = \left(\frac{\partial F}{\partial N} \right)_{T, V} = \frac{-kT}{Q} \left(\frac{\partial Q}{\partial N} \right)_{T, V} \quad (\text{B.5})$$

Substituting Eq. B.3 and Eq. B.4 into Eq. B.5, the ideal gas chemical potential is

$$\mu^{\text{ig}}(\rho) = \begin{cases} kT \ln \left[\frac{\rho}{Q_P} \right] & \text{spherically symmetric} \\ kT \ln \left[\frac{\rho \sigma \Theta}{Q_P T} \right] & \text{linear} \\ kT \ln \left[\frac{\rho \sigma (\Theta_1 \Theta_2 \Theta_3)^{1/2}}{Q_P T^{3/2} \pi^{1/2}} \right] & \text{nonlinear} \end{cases} \quad (\text{B.6})$$

For future reference, the system's entropy is

$$S_N = \left(\frac{\partial (kT \ln Q)}{\partial T} \right)_{N, V}, \quad (\text{B.7})$$

which, with the substitution of Eq. B.3 for Q , gives

$$S_N^{\text{ig}} = \begin{cases} Nk \ln \left[\frac{Q_P e^{5/2}}{\rho} \right] & \text{spherically symmetric molecules} \\ Nk \ln \left[\frac{Q_P e^{5/2}}{\rho} \right] + Nk \ln \left[\frac{T e}{\Theta} \right] & \text{linear molecules} \\ Nk \ln \left[\frac{Q_P e^{5/2}}{\rho} \right] + Nk \ln \left[\frac{\pi^{1/2} (T e)^{3/2}}{\sigma (\Theta_1 \Theta_2 \Theta_3)^{1/2}} \right] & \text{nonlinear molecules} \end{cases} \quad (\text{B.8})$$

The energy of an ideal gas is entirely kinetic because there is no intermolecular potential

$$E_N = - \left(\frac{\partial \ln Q}{\partial \beta} \right)_{N, V} \quad (\text{B.9})$$

$$E_N^{\text{ig}} = \frac{s N k T}{3}. \quad (\text{B.10})$$

The next term in $\Delta\mu^{\text{solv}}$ is $\mu^{\text{noint}}(\rho)$. This reflects the free energy cost of placing a non-interacting solute molecule into a solvent in which the solute density is already ρ . Note that the solute already present in solution is assumed to behave as an ideal gas. In other words, one assumes that the chemical potential of solute will be independent of solute density (see Chapter 2 for more on this

approximation). Therefore, solvent molecules are unperturbed by the presence of solute at concentration ρ and there are no solute–solute interactions. Based on this, the computation of $\mu^{\text{noint}}(\rho)$ involves placing an ideal-gas like solute molecule into a fluid containing fully interacting solvent and an ideal-gas solute of density ρ . Thus, since the solute molecule does not see the interacting fluid, the chemical potential of the addition of a non-interacting solute molecule is just $\mu^{\text{noint}}(\rho) = \mu^{\text{ig}}(\rho)$. This exactly cancels the first term of Eq. B.1 by design.[§] The overall change in energy and entropy from these terms is also zero. If the solute densities in the ideal gas and fluid phases were different, then $-\mu^{\text{ig}}(\rho_g) + \mu^{\text{ig}}(\rho_f) = kT \ln(\rho_f/\rho_g)$. Since $\Delta\mu = \Delta E - T\Delta S$, where the difference in energy per particle in the two systems, ΔE , is zero from Eq. B.10, one has that $\Delta S = -k \ln(\rho_f/\rho_g)$. In other words, the change in free energy $-\mu^{\text{ig}}(\rho_g) + \mu^{\text{noint}}(\rho_f)$ when $\rho_g \neq \rho_f$ is entirely entropic in origin.

The solvation free energy with $\rho_g = \rho_f$ is then given entirely by $\Delta\mu^{\text{solv}} = \mu^{\text{int}}$ (as discussed in Chapter 2). This term describes the change in free energy which results from allowing a solute molecule (at infinite dilution) to fully interact with the solvent molecules. If it were possible to accurately compute the free energy of the interacting and non-interacting states, then the job would be done. Describing the process in terms of a coupling parameter, λ , in which at $\lambda = 0$ the solute is non-interacting and at $\lambda = 1$ the solute is fully interacting, then formally,

$$\Delta\mu^{\text{solv}} = F(\lambda = 1) - F(\lambda = 0) = \int_0^1 d\lambda \left(\frac{\partial F(\lambda)}{\partial \lambda} \right). \quad (\text{B.11})$$

This procedure, in which the effect of the solute–solvent interaction is slowly turned on, is called *thermodynamic integration*. While not obvious from Eq. B.11, in combination with certain approximations, it allows for computation of $\Delta\mu^{\text{solv}}$ without the need for explicit evaluation of the absolute free energy of the system. In the next section a theory of molecular distribution functions will be developed for this task.

B.3 Distribution Function Theory

B.3.1 Homogeneous Molecular Fluid

To develop a basic understanding of distribution functions, a classical homogeneous fluid of N polyatomic rigid molecules in a volume V at a temperature T shall be treated first. In the next section, these results will be generalized to the case of a multicomponent molecular fluid. The relevant partition function

$$Q = \frac{Q_P^N Q_J^N Z_N}{N!} \quad (\text{B.12})$$

for the ensemble can be obtained from Eq. B.2 by including intermolecular interactions $\mathcal{V}(\mathbf{x}_{1\dots N})$ in the Hamiltonian. This simply results in the single particle ideal gas configurational partition functions $(Z_1^{\text{ig}})^N$ being replaced by the multi-particle configurational partition function for the interacting fluid

$$Z_N = \int \frac{d\mathbf{x}_{1\dots N}}{\sigma^N} e^{-\beta\mathcal{V}(\mathbf{x}_{1\dots N})}. \quad (\text{B.13})$$

[§]Here it is assumed that the internal degrees of freedom for the solute are the same in gas and fluid environments.

Because there is no external field, the intermolecular potential energy only depends on the relative distances and orientations between the molecules, i.e. the integrand in Eq. B.13 will depend only on these relative coordinates. Therefore, one can change variables to $\mathbf{X}_j = \mathbf{x}_j - \mathbf{x}_1$ for $j \neq 1$ so that the integrand is actually *independent* of \mathbf{r}_1 and ω_1 and Eq. B.13 becomes (after integrating out \mathbf{x}_1)

$$\mathcal{Z}_N = \frac{V\Omega}{\sigma} \int \frac{d\mathbf{X}_{2\dots N}}{\sigma^{N-1}} e^{-\beta\mathcal{V}(\mathbf{x}_{2\dots N})}. \quad (\text{B.14})$$

In this case, molecule one is assumed to be located at the origin with some convenient orientation.

The simplest distribution function describes the single molecule configurational density $\rho^{(1)}(\mathbf{r}, \omega)$, which gives the average density of particles with a given orientation at a given position in space

$$\rho^{(1)}(\mathbf{r}_1, \omega_1) = \frac{N}{\sigma\mathcal{Z}_N} \int \frac{d\mathbf{x}_{2\dots N}}{\sigma^{N-1}} e^{-\beta\mathcal{V}(\mathbf{x}_{1\dots N})}. \quad (\text{B.15})$$

The factor of N/σ accounts for the indistinguishability between various sets of molecular orientations and the indistinguishability of the molecules themselves. Somewhat more familiar is the positional density distribution function obtained by integrating $\rho^{(1)}(\mathbf{r}, \omega)$ over the Euler angles

$$\rho^{(1)}(\mathbf{r}_1) = \int d\omega_1 \rho^{(1)}(\mathbf{r}_1, \omega_1).$$

For the ideal gas, $\mathcal{V} = 0$ and so $\mathcal{Z}_N^{\text{ig}} = (V\Omega/\sigma)^N$. This results in $\rho^{(1)}(\mathbf{r}, \omega) = N/(V\Omega)$ and $\rho^{(1)}(\mathbf{r}) = \rho = N/V$. Therefore $\int \rho^{(1)}(\mathbf{r}) d\mathbf{r} = N$, as must happen in any fluid. The symbol ρ will always represent the positional density of particles so $\rho^{(1)}(\mathbf{x}) \equiv \rho/\Omega$.

Higher order distribution functions can be defined analogously to Eq. B.15. The n^{th} order configurational density function, where one asks for the density of n molecules simultaneously in configurations $\mathbf{x}_{1\dots n}$, is

$$\rho^{(n)}(\mathbf{x}_{1\dots n}) = \frac{N!}{(N-n)!\sigma^n \mathcal{Z}_N} \int \frac{d\mathbf{x}_{(n+1)\dots N}}{\sigma^{N-n}} e^{-\beta\mathcal{V}(\mathbf{x}_{1\dots N})}. \quad (\text{B.16})$$

Returning to the ideal gas case, $\rho^{(n)}(\mathbf{x}_{1\dots n}) = N!/((N-n)!V^n\Omega^n) \approx \rho^n/\Omega^n$ and $\rho^{(n)}(\mathbf{r}_{1\dots n}) \approx \rho^n$ for $N \gg 1$. For a non-ideal fluid, a *dimensionless* n -particle correlation function $g^{(n)}$ can be defined such that the deviation of the fluid from ideal gas behavior is

$$g^{(n)}(\mathbf{x}_{1\dots n}) = \frac{\rho^{(n)}(\mathbf{x}_{1\dots n})}{\rho^{(1)}(\mathbf{x}_1) \cdots \rho^{(1)}(\mathbf{x}_n)} \quad (\text{B.17})$$

$$= \frac{N!\Omega^n}{(N-n)!\sigma^n \rho^n \mathcal{Z}_N} \int \frac{d\mathbf{x}_{(n+1)\dots N}}{\sigma^{N-n}} e^{-\beta\mathcal{V}(\mathbf{x}_{1\dots N})}. \quad (\text{B.18})$$

In a slightly more useful form, this definition is also

$$\rho^{(n)}(\mathbf{x}_{1\dots n}) = \frac{N!}{(N-n)!\mathcal{Z}_N} \int \frac{d\mathbf{x}_{(n+1)\dots N}}{\sigma^N} e^{-\beta\mathcal{V}(\mathbf{x}_{1\dots N})} = \frac{\rho^n g^{(n)}(\mathbf{x}_{1\dots n})}{\Omega^n}. \quad (\text{B.19})$$

As the system approaches ideal gas behavior, $g^{(n)} \rightarrow 1$. In a hard core, excluded volume region where molecules are overlapping, $g^{(n)} \rightarrow 0$. In other regions $g^{(n)}$ oscillates, describing the local and long range structure of the fluid. From these limiting values and Eq. B.17, one sees that $g < 1$ corresponds to an anti-correlation among the n molecules with $g = 0$ representing the total exclusion

of the proposed n -molecule configuration from occurring. Likewise, $g > 1$ corresponds to a positive correlation where sets of n molecules will preferentially assume the given configuration.

For any distribution or correlation function, for example $F(\mathbf{x}_{1\dots n})$, one can apply the same symmetry arguments leading to Eq. B.14 to write $F(\mathbf{x}_{1\dots n}) = F(\mathbf{X}_{2\dots n})$ independent of \mathbf{x}_1 . In particular, this implies that the single particle configurational density will always be independent of its variables and thus rigorously assume its constant ideal gas value, $\rho^{(1)}(\mathbf{r}_1, \omega_1) \equiv \rho/\Omega$, independent of the intermolecular potential. Additionally, any 2-particle function will only depend on the relative position and orientation of the two particles. For spherically symmetric potentials, F will only depend on the relative distance between the particles. In general,

$$F(\mathbf{x}_1, \mathbf{x}_2) = F(\mathbf{X}_2) = F(\mathbf{r}_2 - \mathbf{r}_1, \omega_2 - \omega_1) = F(\mathbf{r}, \omega), \quad (\text{B.20})$$

where ω_1 is assumed fixed at some convenient orientation and \mathbf{r}_1 is taken to be the origin of the coordinate system so that ω represents the Euler angles of particle 2 and \mathbf{r} represents the center of mass of particle 2. A major consequence of Eq. B.20 is that while $F(\mathbf{x}_1, \mathbf{x}_2)$ can be a function of up to 12 parameters (for non-linear molecules), $F(\mathbf{r}, \omega)$ is a function of at most 6 parameters.^h

The 2-particle correlation function (GCF) will play a particularly important role in the evaluation of the solvation free energy.ⁱ The angularly averaged version

$$g^{(2)}(r_{12}) = \frac{1}{\Omega^2} \int d\omega_1 d\omega_2 g^{(2)}(\mathbf{r}_{ij} = \mathbf{r}_1 - \mathbf{r}_2, \omega_{ij} = \omega_2 - \omega_1) = \frac{1}{\Omega} \int d\omega_{ij} g^{(2)}(\mathbf{r}_{ij}, \omega_{ij}) \quad (\text{B.21})$$

is the highest order correlation function that can be obtained experimentally (through x-ray scattering and neutron diffraction). Note that once the angular average has been performed, the GCF will also be independent of the orientation of $\mathbf{r}_1 - \mathbf{r}_2$.^j Taking advantage of the translational and rotational uniformity of the equilibrium system, one can interpret $\rho g^{(2)}(r)$ as the density of molecules in the spherical shell between radii r and $r + dr$ about a central molecule and $4\pi r^2 \rho g^{(2)}(r) dr$ as the number of molecules in that shell. $g^{(2)}(r)$ is often referred to as the radial distribution function (RDF). For simplicity, the superscript 2 in the GCF and the RDF will be dropped except where necessary.

One major approximation commonly introduced into the theory of molecular fluids is that the intermolecular potential is pair-wise additive. That is

$$\mathcal{V}(\mathbf{x}_1, \dots, \mathbf{x}_2) = \sum_{i < j}^N u(\mathbf{r}_i - \mathbf{r}_j, \omega_i - \omega_j) = \sum_{i < j}^N u(\mathbf{r}_{ij}, \omega_{ij}). \quad (\text{B.22})$$

While this approximation simplifies the theoretical treatment of fluids, allowing the interactions to be described by a combination of Coulombic and van der Waals energies, it neglects important many-body effects such as atomic polarization. While many-body corrections to Eq. B.22 are available,

^hFor spherically symmetric molecules the reduction is from 6 variables to 1 and for linear molecules it is from 10 to 5.

ⁱG-Correlation Function. ‘‘G’’ stands for the g in $g^{(2)}(\mathbf{x}_1, \mathbf{x}_2)$. Other correlation functions shall be defined later.

^jThis is not true in the presence of an external field.

their incorporation into analytic theory is difficult. If these corrections are treated at all, it is only in direct Monte Carlo or molecular dynamics simulations or very detailed ab-initio quantum mechanical computations.

Assuming that Eq. B.22 provides a good qualitative description of fluid behavior, many thermodynamic functions can be derived in terms of the GCF. The total energy given by Eq. B.9 breaks up into the ideal-gas kinetic energy Eq. B.10 and the imperfect-fluid energy

$$\bar{V} = \frac{1}{\mathcal{Z}_N \sigma^N} \int d\mathbf{x}_{1\dots N} \mathcal{V}(\mathbf{x}_{1\dots N}) e^{-\beta \mathcal{V}(\mathbf{x}_{1\dots N})}. \quad (\text{B.23})$$

Substituting Eq. B.22 and noting that there are $N(N-1)/2$ equivalent pairs of molecules, Eq. B.23 becomes

$$\bar{V} = \frac{N(N-1)}{2 \mathcal{Z}_N \sigma^N} \int d\mathbf{x}_1 d\mathbf{x}_2 u(\mathbf{r}_2 - \mathbf{r}_1, \omega_2 - \omega_1) \int d\mathbf{x}_{3\dots N} e^{-\beta \mathcal{V}(\mathbf{x}_{1\dots N})}. \quad (\text{B.24})$$

Now, the definition of the GCF, Eq. B.19, can be substituted for the second integral to obtain

$$\begin{aligned} \bar{V} &= \frac{\rho^2}{2\Omega^2} \int d\mathbf{r}_1 d\mathbf{r}_2 d\omega_1 d\omega_2 u(\mathbf{r}_2 - \mathbf{r}_1, \omega_2 - \omega_1) g(\mathbf{r}_1 - \mathbf{r}_2, \omega_2 - \omega_1) \\ \bar{V} &= \frac{\rho N}{2\Omega} \int d\omega_2 d\mathbf{r}_2 u(\mathbf{r}_2, \omega_2) g(\mathbf{r}_2, \omega_2). \end{aligned} \quad (\text{B.25})$$

If one can measure the temperature dependence of $g(\mathbf{r}, \omega)$ then the heat capacity is

$$C_V = \frac{sNk}{2} + \frac{\rho N}{2\Omega} \int d\omega d\mathbf{r} u(\mathbf{r}, \omega) \frac{\partial g(\mathbf{r}, \omega, T)}{\partial T}. \quad (\text{B.26})$$

Another approximation sometimes made is the *Kirkwood superposition approximation* (SA).¹⁵¹ In this approximation, it is assumed that the n -particle correlation functions of order 3 or more can be written as products of the GCFs. For example, without approximation one can write the 3-particle correlation function as

$$g^{(3)}(\mathbf{x}_{1\dots 3}) = g^{(2)}(\mathbf{x}_1, \mathbf{x}_2) g^{(2)}(\mathbf{x}_1, \mathbf{x}_3) g^{(2)}(\mathbf{x}_2, \mathbf{x}_3) \delta g^{(3)}(\mathbf{x}_{1\dots 3}) \quad (\text{B.27})$$

where $\delta g^{(3)}(\mathbf{x}_{1\dots 3})$ is a correction term. The SA assumes $\delta g^{(3)} = 1$. This procedure can be performed similarly for all higher order correlation functions.^{152,153} One advantage of this approximation is that it allows one to compute the entropy directly from the GCF without having to compute the partition function or the free energy.^k In this manuscript, the SA approach will not be pursued, though it is worthy of further investigation.

^kThe general formulation for the entropy is

$$S_N = \frac{-k}{h^s N \sigma^N N!} \int P_N \ln P_N d\mathbf{x}_{1\dots N} d\mathbf{p}_{1\dots N} d\mathbf{J}_{1\dots N},$$

where $P_N = \exp(-\beta \mathcal{H}) / \mathcal{Q}$ is the dimensionless canonical probability distribution. It can be shown^{152,153} that under the SA approximation, the entropy becomes

$$S_N = S_N^{\text{ig}} - \frac{kN\rho}{2\Omega} \int d\omega d\mathbf{r} g(\mathbf{r}, \omega) \ln g(\mathbf{r}, \omega).$$

While this allows computation of the entropy and in principle can be combined with Eq. B.25 to obtain the overall free energy of the system, $F = E - TS$, it involves a somewhat less well tested approximation than the standard pair-wise addition of potential energy. In fact, the tests made show that it does not work well for large systems.

B.3.2 Multicomponent Molecular Fluid

Before addressing the actual computation of the solvation free energy, it will be of great value to generalize the definitions of the distribution and correlation functions to a heterogeneous fluid system. Let there be m species of molecules in a volume V . The number of particles of species $i \in \{1 \dots m\}$ is N_i , the partial density is $\rho_i = N_i/V$, the angular volume is Ω_i and the symmetry factor is σ_i . The configuration variable of particle j of species i shall be denoted $\mathbf{x}^{(i)}_j$ and the ideal gas partition functions will be $\mathcal{Q}_P^{(i)}$ and $\mathcal{Q}_J^{(i)}$. The partition function for the system is then

$$\mathcal{Q} = \left(\prod_{i=1}^m \frac{(\mathcal{Q}_P^{(i)} \mathcal{Q}_J^{(i)})^{N_i}}{N_i!} \right) \mathcal{Z}_{N_1, \dots, N_m}, \quad (\text{B.28})$$

where the configurational partition function is described by

$$\mathcal{Z}_{N_1, \dots, N_m} = \int \left(\prod_{i=1}^m \frac{d\mathbf{x}^{(i)}_{1 \dots N_i}}{\sigma_i^{N_i}} \right) \exp(-\beta \mathcal{V}(\mathbf{x}^{(1)}_{1 \dots N_1}, \dots, \mathbf{x}^{(m)}_{1 \dots N_m})). \quad (\text{B.29})$$

The single particle configurational density, $\rho_i^{(1)}(\mathbf{x})$ is still given by the constant ideal gas value of ρ_i/Ω_i . The GCF comes in two varieties now depending on whether or not the two molecules are of the same species. Analogous to Eq. B.18 the GCF for two molecules of the same species (which shall be denoted as species number 1 for simplicity) is

$$\begin{aligned} g_{11}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(1)}_2) &= \frac{N_1(N_1-1)\Omega_1^2}{\sigma_1^2 \rho_1^2 \mathcal{Z}_{N_1, \dots, N_m}} \int \frac{d\mathbf{x}^{(1)}_{3 \dots N_1}}{\sigma_1^{N_1-2}} \int \left(\prod_{i=2}^m \frac{d\mathbf{x}^{(i)}_{1 \dots N_i}}{\sigma_i^{N_i}} \right) \\ &\times \exp(-\beta \mathcal{V}(\mathbf{x}^{(1)}_{1 \dots N_1}, \dots, \mathbf{x}^{(m)}_{1 \dots N_m})). \end{aligned} \quad (\text{B.30})$$

Similarly, the GCF for molecules of different species (species 1 and 2) is

$$\begin{aligned} g_{12}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(2)}_1) &= \frac{N_1 N_2 \Omega_1 \Omega_2}{\sigma_1 \sigma_2 \rho_1 \rho_2 \mathcal{Z}_{N_1, \dots, N_m}} \int \left[\frac{d\mathbf{x}^{(1)}_{2 \dots N_1}}{\sigma_1^{N_1-1}} \frac{d\mathbf{x}^{(2)}_{2 \dots N_2}}{\sigma_2^{N_2-1}} \times \right. \\ &\left. \int \left(\prod_{i=3}^m \frac{d\mathbf{x}^{(i)}_{1 \dots N_i}}{\sigma_i^{N_i}} \right) \exp(-\beta \mathcal{V}(\mathbf{x}^{(1)}_{1 \dots N_1}, \dots, \mathbf{x}^{(m)}_{1 \dots N_m})) \right]. \end{aligned} \quad (\text{B.31})$$

From Eq. B.17, the configurational density distributions, $\rho_{11}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(1)}_2)$ and $\rho_{12}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(2)}_1)$, can be obtained by multiplying Eqs. B.30 and B.31 by ρ_1^2/Ω_1^2 and $\rho_1 \rho_2/\Omega_1 \Omega_2$, respectively. By symmetry, it is clear from Eq. B.31 that $g_{12}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(2)}_1) = g_{21}(\mathbf{x}^{(2)}_1, \mathbf{x}^{(1)}_1)$. However, if the symmetry arguments leading to Eq. B.20 are taken into account, so that one reduces the parameter space from up to 12 variables to at most 6 variables, $g_{12}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(2)}_1) = g_{12}(\mathbf{r}, \omega)$, then $g_{12}(\mathbf{r}, \omega) \neq g_{21}(\mathbf{r}, \omega)$. This is because in writing $g_{12}(\mathbf{r}, \omega)$, the dependence on the variables $\mathbf{x}^{(1)}_1$ has been removed from Eq. B.30, which breaks the symmetry of the equation. In all functions like $g_{12}(\mathbf{r}, \omega)$, the particle of species 1 is assumed to be fixed in some convenient orientation with its center of mass at the origin of the coordinate system.

With these definitions, one is prepared to obtain the free energy of solvation and the average solute–solvent interaction energy. Assume that species 1 is the solute species ($N_1 = 1$) and that the

other molecular species are fully-interacting solvent molecules (water with Na^+ and Cl^- ions, for example). The interaction energy Eq. B.22 can be generalized to

$$\mathcal{V} = \sum_{i < j}^N u_{ij}(\mathbf{r}_{ij}, \omega_{ij}), \quad (\text{B.32})$$

where the u_{ij} depends on the species of molecules i and j and $N = \sum_{i=1}^m N_i$. In particular, the solute-solvent potential energy of interaction will be

$$u_{1j}(\mathbf{r}_{1j}, \omega_{1j}) = \lambda U_j(\mathbf{r}_{1j}, \omega_{1j}), \quad (\text{B.33})$$

where the thermodynamic integration parameter has been re-introduced to describe the degree of interaction between the solute particle and the solvent molecules. The advantages of distribution function theory and the pair-wise additivity assumption now become apparent in that one can calculate $\partial F/\partial \lambda$ without computing F . To see this

$$\frac{\partial F}{\partial \lambda} = \frac{-kT}{\mathcal{Z}_{N_1, \dots, N_m}(\lambda)} \frac{\partial \mathcal{Z}_{N_1, \dots, N_m}(\lambda)}{\partial \lambda}, \quad (\text{B.34})$$

which, after plugging in Eq. B.29 for $\mathcal{Z}_{N_1, \dots, N_m}$ and taking the derivative, is

$$\begin{aligned} \frac{\partial F}{\partial \lambda} &= \frac{1}{\mathcal{Z}_{N_1, \dots, N_m}(\lambda)} \sum_{k=2}^m \sum_{j=1}^{N_k} \int \left(\prod_{i=1}^m \frac{d\mathbf{x}^{(i)}_{1 \dots N_i}}{\sigma_i^{N_i}} \right) U_{1k}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(k)}_j) \\ &\quad \times \exp(-\beta \mathcal{V}(\mathbf{x}^{(1)}_{1 \dots N_1}, \dots, \mathbf{x}^{(m)}_{1 \dots N_m}; \lambda)) \\ &= \frac{1}{\mathcal{Z}_{N_1, \dots, N_m}(\lambda)} \sum_{k=2}^m N_k \int \left[\frac{d\mathbf{x}^{(1)}_1 d\mathbf{x}^{(k)}_1}{\sigma_1 \sigma_k} U_{1k}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(k)}_j) \times \right. \\ &\quad \left. \int \frac{d\mathbf{x}^{(k)}_{2 \dots N_k}}{\sigma_k^{N_k-1}} \int \left(\prod_{i \neq 1 \text{ OR } k}^m \frac{d\mathbf{x}^{(i)}_{1 \dots N_i}}{\sigma_i^{N_i}} \right) \exp(-\beta \mathcal{V}(\mathbf{x}^{(1)}_{1 \dots N_1}, \dots, \mathbf{x}^{(m)}_{1 \dots N_m}; \lambda)) \right], \end{aligned} \quad (\text{B.35})$$

Comparing Eqs. B.35 and B.31, the final expression can be simplified considerably by substituting in GCFs

$$\begin{aligned} \frac{\partial F}{\partial \lambda} &= \frac{\rho_1}{\Omega_1} \sum_{k=2}^m \frac{\rho_k}{\Omega_k} \int d\mathbf{x}^{(1)}_1 d\mathbf{x}^{(k)}_1 U_k(\mathbf{x}^{(1)}_1, \mathbf{x}^{(k)}_j) g_{1k}(\mathbf{x}^{(1)}_1, \mathbf{x}^{(k)}_1; \lambda) \\ &= \sum_{k=2}^m \frac{\rho_k}{\Omega_k} \int d\omega_k d\mathbf{r}_k U_k(\mathbf{r}_k, \omega_k) g_{1k}(\mathbf{r}_k, \omega_k; \lambda), \end{aligned} \quad (\text{B.36})$$

Finally, the free energy of solvation can be written in terms of GCFs by substituting Eq. B.36 into Eq. B.11

$$\Delta \mu^{\text{solv}} = \sum_{k=2}^m \frac{\rho_k}{\Omega_k} \int_0^1 d\lambda \int d\omega_k d\mathbf{r}_k U_k(\mathbf{r}_k, \omega_k) g_{1k}(\mathbf{r}_k, \omega_k; \lambda). \quad (\text{B.37})$$

As mentioned before, $g_{1k}(\mathbf{r}, \omega; \lambda)$ can only be measured experimentally at $\lambda = 0$ and $\lambda = 1$.¹ Theoretical methods are needed to obtain the solute-solvent GCF analytically. One such method, integral equation theory, shall be developed in the following section. Once the $g_{1k}(\mathbf{r}, \omega; \lambda)$ has been

¹In fact, at $\lambda = 0$, $g_{1k}(\mathbf{r}, \omega; 0) \equiv 1$ because the solute is an ideal gas and thus there is no correlation between it and the solvent particles.

computed, not only can the free energy of solution be evaluated but the solute–solvent potential energy (as a function of the interaction parameter λ) can be obtained from the expectation value

$$\Delta U(\lambda) = \left\langle \sum_{k=2}^m \sum_{i=1}^{N_k} \lambda U_k(\mathbf{r}, \omega) \right\rangle_{Z_{N_1, \dots, N_m}(\lambda)}, \quad (\text{B.38})$$

where by comparing to Eqs. B.35 and B.29 one sees that

$$\begin{aligned} \Delta U(\lambda) &= \lambda \frac{\partial F}{\partial \lambda} \\ &= \lambda \sum_{k=2}^m \frac{\rho_k}{\Omega_k} \int d\omega_k d\mathbf{r}_k U_k(\mathbf{r}_k, \omega_k) g_{1k}(\mathbf{r}_k, \omega_k; \lambda). \end{aligned} \quad (\text{B.39})$$

This implies that another way to write the free energy of solvation is

$$\Delta\mu^{\text{solv}} = \int_0^1 d\lambda \frac{\Delta U(\lambda)}{\lambda} \quad (\text{B.40})$$

From the difference $T\Delta S = -\Delta\mu + \Delta U(\lambda = 1)$, the entropic contribution is also available.

B.4 Integral Equation Theory

In this section, the Ornstein–Zernike equation,¹⁵⁴ the direct correlation function, $c_{ij}(\mathbf{x}^{(i)}, \mathbf{x}^{(j)})$, and various expansions of the molecular fluid configurational partition function Eq. B.29 shall be derived. As a whole, they provide a solvable, though approximate, set of non-linear integral equations for the GCFs. Because much of the following derivation will rely heavily on the theory of functionals,^{28, 155} some of the formulae from the calculus of functionals shall be presented first.

B.4.1 The Calculus of Functionals

A *functional* is a function that maps a set of functions to a real or complex number. A functional, F , that depends on the functions $u(x)$ and $g(x)$ shall be denoted $F[u, g]$. Note that the dependent variable, x , is not specified in the definition of the functional. This is because a functional depends on the values of its dependent functions over a range of parameter values — not just at a single point, x . For example, a simple linear functional $F[u, g]$ could be written

$$F[u, g] = \int_a^b u(z)g(z)dz \quad (\text{B.41})$$

Given two functions, $u(x)$ and $g(x)$, Eq. B.41 maps the infinite-dimensional vector-spaces of the functions to a number.^m

The variation of Eq. B.41 with respect to the dependent function u is given by

$$\begin{aligned} \delta F[u, g] &= F[u + \delta u, g] - F[u, g] \\ &= \left(\int_a^b u(y)g(y)dy + \int_a^b \delta u(y)g(y)dy \right) - \int_a^b u(y)g(y)dy \\ &= \int_a^b \delta u(x)g(x)dx. \end{aligned} \quad (\text{B.42})$$

^mThese vector-spaces are the uncountably infinite-dimensional ordered sets $\{u(x)\}$ for $x \in [a, b]$ and $\{g(x)\}$ for $x \in [a, b]$.

In standard calculus, the differential of a function, f , of many variables is given by the chain rule

$$df = \sum_{i=1}^n \frac{\partial f}{\partial x_i} dx_i. \quad (\text{B.43})$$

In the calculus of functionals, the number of variables is infinite. If one divides the interval $[a, b]$ into small enough sub-intervals defined by the set $\{x_1 = a, x_2, \dots, x_{n-1}, x_n = b\}$ so that the variation $\delta u(x)$ is approximately constant in each interval, then Eq. B.42 is given approximately by

$$\delta F[u, g] \approx \sum_{i=1}^n g(x_i) [\delta u(x_i) \Delta x]. \quad (\text{B.44})$$

In the limit of $n \rightarrow \infty$, Eq. B.42 is recovered. Comparing Eqs. B.42 and B.43 one can identify $dx_i \rightarrow \delta u(x) dx$ and

$$\frac{\partial f}{\partial x_i} \rightarrow \frac{\delta F[u, g]}{\delta u(x)} = g(x). \quad (\text{B.45})$$

In the particular case when $g(x) = \delta(y - x)$ is substituted into Eq. B.41, $F[u] \equiv u(y)$ and from Eq. B.42, $\delta F[u, g] = \delta u(y)$, then one obtains from Eq. B.45 by taking the functional derivative of $F[u]$, the important relation

$$\frac{\delta u(y)}{\delta u(x)} = \delta(y - x). \quad (\text{B.46})$$

In more a more general form, the equivalent to the functional of the partition function in the next section, the functional depends nonlinearly on the function $u(x)$ and linearly on the function of n -variables, $f(x_{1\dots n})$,

$$G[u, f] = \int dx_{1\dots n} u(x_1) \cdots u(x_n) f(x_{1\dots n}). \quad (\text{B.47})$$

The functional derivative of $G[u, f]$ with respect to $u(x)$ is given by a form of the product rule applied to functionals. One must take the functional derivative with respect to each appearance of $u(x)$ in the functional and apply Eq. B.46

$$\begin{aligned} \frac{\delta G[u, f]}{\delta u(x)} &= \sum_{i=1}^n \int dx_{1\dots n} u(x_1) \cdots \frac{\delta u(x_i)}{\delta u(x)} \cdots u(x_n) f(x_{1\dots n}) \\ &= \sum_{i=1}^n \int dx_{1\dots i-1} dx_{i+1\dots n} u(x_1) \cdots u(x_{i-1}) u(x_{i+1}) \cdots u(x_n) f(x_{1\dots i-1}, x, x_{i+1}, n). \end{aligned} \quad (\text{B.48})$$

If f is symmetric in its dependence on its variables,ⁿ then the derivative simplifies to

$$\frac{\delta G[u, f]}{\delta u(x)} = n \int dx_{2\dots n} u(x_2) \cdots u(x_n) f(x, x_{2\dots n}). \quad (\text{B.49})$$

Multiple derivatives of Eq. B.47 can be obtained by repeated application of Eq. B.48

$$\frac{\delta^m G[u, f]}{\delta u(x_1) \cdots \delta u(x_m)} = \frac{n!}{(n-m)!} \int dx_{m+1\dots n} u(x_{m+1}) \cdots u(x_n) f(x_{1\dots n}). \quad (\text{B.50})$$

The most general form of the functional derivative takes into account the possible dependence of the functions on each other. The functional derivative is really a total derivative in the sense

ⁿFor example, $g(x) = \int f(x_1, x_2, x) dx_1 dx_2 = \int f(x, x_2, x_3) dx_2 dx_3 = \int f(x_1, x, x_3) dx_1 dx_3$, i.e. all variables are essentially equivalent.

of normal calculus. Therefore, for example, if the functions $v_i(x)$ depend on $u(x)$ in the functional $F[u, v_{1\dots n}]$, then the functional derivative with respect to $u(x)$ is

$$\left. \frac{\delta F[u, v_{1\dots n}]}{\delta u(x)} \right|_{total} = \left. \frac{\delta F[u, v_{1\dots n}]}{\delta u(x)} \right|_{partial} + \sum_{i=1}^n \int dy \left. \frac{\delta F[u, v_{1\dots n}]}{\delta v_i(y)} \right|_{partial} \left. \frac{\delta v_i(y)}{\delta u(x)} \right|_{total} \quad (\text{B.51})$$

Here, the type of derivative has been explicitly noted — partial and total functional derivatives. In particular, if $F[v_{1\dots n}]$ does not depend explicitly on $u(x)$, the functional derivative can still be obtained.

Applying the machinery just developed, one can generalize the Taylor series expansion of a function in standard calculus to the Taylor series of a functional with respect to a specific function. The standard Taylor series of a function f about a point x_0 can be written

$$f(x) = \sum_{n=0}^{\infty} \frac{1}{n!} \left. \frac{d^{(n)} f(x)}{dx^{(n)}} \right|_{x=x_0} (x - x_0)^n. \quad (\text{B.52})$$

To generalize this to a functional Taylor series of a functional $F[u]$ and to obtain the value of the functional at a function $u(x)$, one could expand about some function $u_0(x)$, obtaining a power series in $u(x) - u_0(x)$. The derivative of the function in Eq. B.52 would go over to a functional derivative integrated over the dependent variable x to get the total effect of the variation. The first few terms of this series are

$$\begin{aligned} F[u] &= F[u_0] + \int dx \left. \frac{\delta F[u]}{\delta u(x)} \right|_{u=u_0} (u(x) - u_0(x)) + \\ &\quad \frac{1}{2} \int dx dy \left. \frac{\delta^{(2)} F[u]}{\delta u(x) \delta u(y)} \right|_{u=u_0} (u(x) - u_0(x))(u(y) - u_0(y)) + \dots \end{aligned} \quad (\text{B.53})$$

The reason to have integrals in Eq. B.53 is because one needs to take the functional derivative for *all values* of the function $u(x) \forall x \in [a, b]$. Since there are an infinite number of these, what would be a sum of terms becomes an integral, just like in Eqs. B.44 and B.42.

B.4.2 The Ornstein–Zernike Equation

The Ornstein–Zernike equation^{28, 154} (OZE) is the fundamental formula in the integral equation theory of equilibrium fluids. It describes the GCF as a very intuitively understandable sum of the direct interaction between the two molecules and a sum of indirect interactions of the two with successively more and more intermediate molecules. There exist similar derivations to the one about to be presented;²⁸ however, they often use a different ensemble and always assume that the fluid is homogeneous. Here, a full multi-component fluid in the canonical ensemble will be assumed. In order to derive the OZE and other related equations, an external potential

$$W = \sum_{i=1}^m \sum_{j=1}^{N_i} w^{(i)}(\mathbf{x}^{(i)}_j) \quad (\text{B.54})$$

shall be introduced. In the end, W can be set to zero to obtain the field-free behavior of interest, but meanwhile it will provide a means to turn the partition function into a generating function for the

n -particle density distribution functions. Due to the notational complexity of the multi-component fluid equations, the definitions $\vec{\mathbf{X}} \equiv (\mathbf{x}^{(1)}_{1\dots N_1}, \dots, \mathbf{x}^{(m)}_{1\dots N_m})$ and $W^{(i)}(j) \equiv \exp(-\beta w^{(i)}(\mathbf{x}^{(i)}_j))$ shall be used. To further reduce index redundancy, the n -particle correlation and distribution functionals shall be written as, for example, $g_{ij}^{(2)}[W; \mathbf{x}^{(i)}_1, \mathbf{x}^{(j)}_2] \equiv g_{ij}[W; 1, 2]$, where explicit functional dependence on W is noted in the argument. The order of the molecular species labels in the subscript will always match the order of the particle indices in the argument.^o Furthermore, the order of the distribution function, n , shall be obvious from the number of dependent variables it has as its arguments.

The configurational partition function, Eq. B.29, in the presence of the external field W becomes

$$\mathcal{Z}[W] = \int d\vec{\mathbf{X}} \left(\prod_{i=1}^m \prod_{j=1}^{N_i} \frac{W^{(i)}(j)}{\sigma_i} \right) \exp(-\beta \mathcal{V}(\vec{\mathbf{X}})). \quad (\text{B.55})$$

Now the beauty of the calculus of functionals becomes apparent. Using Eq. B.50, the single particle configurational density function can be obtained from Eq. B.55. Starting with

$$\frac{\delta \mathcal{Z}[W]}{\delta W^{(k)}(1)} = \frac{N_k}{\sigma_k} \int \left(\prod_{i=2}^{N_k} \frac{d\mathbf{x}^{(k)}_i}{\sigma_k} W^{(k)}(i) \right) \int \left(\prod_{i \neq k}^m \prod_{j=1}^{N_i} \frac{d\mathbf{x}^{(i)}_j W^{(i)}(j)}{\sigma_i} \right) \exp(-\beta \mathcal{V}(\vec{\mathbf{X}})) \quad (\text{B.56})$$

and comparing with Eq. B.15 one can write

$$\rho_k[W; 1] = \frac{W^{(k)}(1)}{\mathcal{Z}[W]} \frac{\delta \mathcal{Z}[W]}{\delta W^{(k)}(1)}. \quad (\text{B.57})$$

Due to the presence of the external field, $\rho_k[W; 1]$ is not necessarily constant. Higher order configurational density functions can be obtained analogously

$$\rho_{k_1 \dots k_n}[W; 1, \dots, n] = \left(\frac{W^{(k_1)}(1) \dots W^{(k_n)}(n)}{\mathcal{Z}[W]} \right) \left(\frac{\delta^n \mathcal{Z}[W]}{\delta W^{k_1}(1) \dots \delta W^{(k_n)}(n)} \right), \quad (\text{B.58})$$

where k_i is the species of molecule i .^p The GCF is obtained from Eq. B.58 by applying Eq. B.17.

In an ideal gas, the GCF is identically equal to one; therefore, it makes sense to define another correlation function, the *total correlation function* (HCF), that describes the deviation of the GCF from ideal gas behavior

$$h_{ij}[W; 1, 2] = g_{ij}[W; 1, 2] - 1 = \frac{\rho_{ij}[W; 1, 2] - \rho_i[W; 1]\rho_j[W; 2]}{\rho_i[W; 1]\rho_j[W; 2]}. \quad (\text{B.59})$$

In the limit that there are only two particles in the system, the HCF will be a function only of the direct interaction between them (and any external fields) and not depend on the influence of intermediate particles. The *direct correlation function* (CCF), $c_{ij}[W; 1, 2]$, is defined as this limit of the HCF to the case of a system with just two particles. Thus, as $\rho_i \rightarrow 0 \forall i$, $h_{ij} = c_{ij} = g_{ij} - 1$. While not necessarily obvious at first, the functional form of the CCF can be written as

$$c_{ij}[W; 1, 2] = \frac{\delta}{\delta \rho_j[W; 2]} \ln \left(\frac{\rho_i[W; 1]}{W^{(i)}(1)} \right), \quad (\text{B.60})$$

^oIn the example, particle 1 is of species i and particle 2 is of species j .

^pTechnically, for Eq. B.58 to make sense, one must have $i \leq N_i \forall i \in [1 \dots n]$; however, one can always relabel in situations where this is not the case.

which, assuming molecules 1 and 2 are different, is simply the change in the average effect of the external field on particle 1 due to a change in the configurational density of particle 2 — an indirect way of measuring the direct interaction between the two particles. Using Eq. B.46 in evaluating Eq. B.60 one obtains

$$\frac{\delta \ln W^{(i)}(1)}{\delta \rho_j[W; 2]} = \frac{\bar{\delta}_{ij}(1-2)}{\rho_i[W; 1]} - c_{ij}[W; 1, 2], \quad (\text{B.61})$$

where

$$\bar{\delta}_{ij}(1-2) \equiv \delta_{ij} \delta(\mathbf{x}^{(i)}_1 - \mathbf{x}^{(j)}_2), \quad (\text{B.62})$$

δ_{ij} is the Kronecker delta function, and $\delta(\mathbf{x}^{(i)}_1 - \mathbf{x}^{(j)}_2)$ is the s -dimensional Dirac delta function.

Using the chain-rule Eqs. B.51 and B.46 and noting that $W^{(i)}(1)$ does not depend explicitly on $W^{(j)}(2)$ but that they are coupled in their effects on $\rho_k[W, 3]$, one can re-write the $\bar{\delta}_{ij}(1-2)$ in terms of the single-particle configurational density functions

$$\bar{\delta}_{ij}(1-2) = \frac{\delta \ln W^{(i)}(1)}{\delta \ln W^{(j)}(2)} = \sum_{k=1}^m \int d\mathbf{x}^{(k)}_3 \frac{\delta \ln W^{(i)}(1)}{\delta \rho_k[W; 3]} \frac{\delta \rho_k[W; 3]}{\delta \ln W^{(j)}(2)}. \quad (\text{B.63})$$

The first term in the integrand is given by Eq. B.61. The second can be obtained from the derivative of Eq. B.57

$$\begin{aligned} \frac{\delta \rho_k[W; 3]}{\delta \ln W^{(j)}(2)} &= W^{(j)}(2) \frac{\delta}{\delta W^{(j)}(2)} \left(W^{(k)}(3) \frac{\delta \ln \mathcal{Z}[W]}{\delta W^{(k)}(3)} \right) \\ &= W^{(j)}(2) \bar{\delta}_{jk}(2-3) \frac{\delta \ln \mathcal{Z}[W]}{\delta W^{(k)}(3)} + W^{(j)}(2) W^{(k)}(3) \frac{\delta^2 \ln \mathcal{Z}[W]}{\delta W^{(j)}(2) \delta W^{(k)}(3)} \\ &= \rho_j[W; 2] \bar{\delta}_{jk}(2-3) + \rho_j[W; 2, 3] - \rho_j[W; 2] \rho_k[W; 3] \\ &= \rho_j[W; 2] \bar{\delta}_{jk}(2-3) + h_{jk}[W; 2, 3] \rho_j[W; 2] \rho_k[W; 3]. \end{aligned} \quad (\text{B.64})$$

Now, substituting Eq. B.61 and Eq. B.64 into Eq. B.63, one finds

$$\begin{aligned} \bar{\delta}_{ij}(1-2) &= \sum_{k=1}^m \int d\mathbf{x}^{(k)}_3 \left\{ (\bar{\delta}_{ik}(1-3) \rho_i[W; 1] - c_{ik}[W; 1, 3]) \times \right. \\ &\quad \left. (\rho_j[W; 2] \bar{\delta}_{jk}(2-3) + h_{jk}[W; 2, 3] \rho_j[W; 2] \rho_k[W; 3]) \right\}. \end{aligned} \quad (\text{B.65})$$

After the delta functions in the integrals are evaluated and the left hand side is canceled by a term from the right. This yields the Ornstein–Zernike equation for multi-component molecular fluids

$$h_{ij}[W; 1, 2] = c_{ij}[W; 1, 2] + \sum_{k=1}^m \int d\mathbf{x}^{(k)}_3 c_{ik}[W; 1, 3] \rho_k[W; 3] h_{kj}[W; 3, 2]. \quad (\text{B.66})$$

The version of Eq. B.66 for $W = 0$ is also easily obtained

$$h_{ij}(\mathbf{x}^{(i)}_1 - \mathbf{x}^{(j)}_2) = c_{ij}(\mathbf{x}^{(i)}_1 - \mathbf{x}^{(j)}_2) + \sum_{k=1}^m \frac{\rho_k}{\Omega_k} \int d\mathbf{x}^{(k)}_3 c_{ik}(\mathbf{x}^{(i)}_1 - \mathbf{x}^{(k)}_3) h_{kj}(\mathbf{x}^{(k)}_3 - \mathbf{x}^{(j)}_2). \quad (\text{B.67})$$

The definition for the CCF holds true; in the limit of only two particles in the system, $\rho_k \rightarrow 0 \forall k$, the OZE implies that $h_{ij} \rightarrow c_{ij}$. The correction to this behavior for finite densities is given by the second term. This correction involves, essentially, the effective interaction due to the presence of other molecules near the two of interest.

The form of the OZE resembles a matrix equation. In fact, writing $m \times m$ matrices $\overset{\leftrightarrow}{\mathbf{c}} [W; 1, 2]$, $\overset{\leftrightarrow}{\mathbf{h}} [W; 1, 2]$ and $\overset{\leftrightarrow}{\mathbf{g}} [W; 1, 2]$ whose elements (i, j) are given by $c_{ij}[W; 1, 2]$, $h_{ij}[W; 1, 2]$ and $g_{ij}[W; 1, 2]$ respectively, one has from Eq. B.59 that $\overset{\leftrightarrow}{\mathbf{h}} [W; 1, 2] = \overset{\leftrightarrow}{\mathbf{g}} [W; 1, 2] - \overset{\leftrightarrow}{\mathbf{I}}$, where $\overset{\leftrightarrow}{\mathbf{I}}$ is the $m \times m$ identity matrix. With the further identification of $\overset{\leftrightarrow}{\rho} [W; 1]$ as the diagonal matrix whose (i, j) elements are $\delta_{ij}\rho_i[W; 1]$, and \star as a matrix multiplication with an integration^q over the summed variable, for example

$$(\overset{\leftrightarrow}{\mathbf{c}} [W; 1, 3] \star \overset{\leftrightarrow}{\mathbf{h}} [W; 3, 2])_{ij} \equiv \sum_{k=1}^m \int dx^{(k)} (\overset{\leftrightarrow}{\mathbf{c}} [W; 1, 3])_{ik} (\overset{\leftrightarrow}{\mathbf{h}} [W; 3, 2])_{kj}, \quad (\text{B.68})$$

then the OZE can be written in the matrix form

$$\overset{\leftrightarrow}{\mathbf{h}} [W; 1, 2] = \overset{\leftrightarrow}{\mathbf{c}} [W; 1, 2] + \overset{\leftrightarrow}{\mathbf{c}} [W; 1, 3] \star (\overset{\leftrightarrow}{\rho} [W; 3] \cdot \overset{\leftrightarrow}{\mathbf{h}} [W; 3, 2]). \quad (\text{B.69})$$

This equation can be repeatedly substituted into itself to obtain an solution for $\overset{\leftrightarrow}{\mathbf{h}}$ in terms of a power series in $\overset{\leftrightarrow}{\rho}$

$$\begin{aligned} \overset{\leftrightarrow}{\mathbf{h}} [W; 1, 2] &= \overset{\leftrightarrow}{\mathbf{c}} [W; 1, 2] + \overset{\leftrightarrow}{\mathbf{c}} [W; 1, 3] \star (\overset{\leftrightarrow}{\rho} [W; 3] \cdot \overset{\leftrightarrow}{\mathbf{c}} [W; 3, 2]) + \\ &\quad \overset{\leftrightarrow}{\mathbf{c}} [W; 1, 4] \star (\overset{\leftrightarrow}{\rho} [W; 4] \cdot \overset{\leftrightarrow}{\mathbf{c}} [W; 4, 3]) \star (\overset{\leftrightarrow}{\rho} [W; 3] \cdot \overset{\leftrightarrow}{\mathbf{c}} [W; 3, 2]) + \dots \\ \overset{\leftrightarrow}{\mathbf{h}} [W; 1, 2] &= \overset{\leftrightarrow}{\rho} [W; 1]^{-1} \cdot \mathcal{C} \left\{ \overset{\leftrightarrow}{\mathbf{c}} [W; 1, 2], \overset{\leftrightarrow}{\rho} [W; 3] \right\} \cdot \overset{\leftrightarrow}{\rho} [W; 3]^{-1}. \end{aligned} \quad (\text{B.70})$$

The second equation exhibits the OZE as a *chain sum*.^{156, 157} The chain sum is really a diagrammatic expansion for $\overset{\leftrightarrow}{\mathbf{h}}$. The free energy, GCF, HCF and CCF can all be expressed as diagrammatic expansions of various functions.^{28, 158, 159} This methodology provides an alternate path to the derivation of the OZE and related equations; however, the simple chain sum is the only expansion that shall be needed in our derivations.

Any chain sum of functions like $\overset{\leftrightarrow}{\mathbf{A}} = \overset{\leftrightarrow}{\mathbf{A}}(\mathbf{r})$ can be solved analytically through the use of Fourier transforms and the convolution theorem.^f For example, consider the general chain sum matrix equation

$$\begin{aligned} \overset{\leftrightarrow}{\mathbf{F}} &= \mathcal{C} \left\{ \overset{\leftrightarrow}{\mathbf{A}}, \overset{\leftrightarrow}{\mathbf{B}} \right\} \\ &= \overset{\leftrightarrow}{\mathbf{B}} \star \overset{\leftrightarrow}{\mathbf{A}} \star \overset{\leftrightarrow}{\mathbf{B}} + \overset{\leftrightarrow}{\mathbf{B}} \star \overset{\leftrightarrow}{\mathbf{A}} \star \overset{\leftrightarrow}{\mathbf{B}} \star \overset{\leftrightarrow}{\mathbf{A}} \star \overset{\leftrightarrow}{\mathbf{B}} + \dots \\ &= \overset{\leftrightarrow}{\mathbf{B}} \star \overset{\leftrightarrow}{\mathbf{A}} \star \overset{\leftrightarrow}{\mathbf{B}} + \overset{\leftrightarrow}{\mathbf{B}} \star \overset{\leftrightarrow}{\mathbf{A}} \star \overset{\leftrightarrow}{\mathbf{F}}. \end{aligned} \quad (\text{B.71})$$

Fourier transforming both sides of the equation converts the real space matrix product and convolution (\star) to a Fourier space matrix product. The equation can then be solved algebraically

$$\begin{aligned} \overset{\leftrightarrow}{\mathbf{F}}(\mathbf{k}) &= \overset{\leftrightarrow}{\mathbf{B}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\mathbf{A}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\mathbf{B}}(\mathbf{k}) + \overset{\leftrightarrow}{\mathbf{B}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\mathbf{A}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\mathbf{F}}(\mathbf{k}) \\ \overset{\leftrightarrow}{\mathbf{F}}(\mathbf{k}) &= \left[\overset{\leftrightarrow}{\mathbf{I}} - \overset{\leftrightarrow}{\mathbf{B}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\mathbf{A}}(\mathbf{k}) \right]^{-1} \cdot \overset{\leftrightarrow}{\mathbf{B}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\mathbf{A}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\mathbf{B}}(\mathbf{k}). \end{aligned} \quad (\text{B.72})$$

^qThis integration will be a convolution when the functions involved depend only on the difference between their arguments, eg. $A(\mathbf{x}, \mathbf{y}) \equiv A(\mathbf{x} - \mathbf{y})$. For the OZ equation this will be a convolution for $W = 0$.

^fThe convolution theorem applies *only* to convolutions of the form $\int_{-\infty}^{\infty} dx A(x)B(y-x)$, it does not apply to angular convolutions in more than one dimension. Therefore, the angular part of the OZE cannot be solved by the convolution theorem—the integrations must be explicitly performed.

Applying Eq. B.72 to the OZE with $W = 0$ (and an angularly independent intermolecular potential)

$$\overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{h}}(\mathbf{x}_1 - \mathbf{x}_2) \cdot \overset{\leftrightarrow}{\rho} = \mathcal{C} \left\{ \overset{\leftrightarrow}{\mathbf{c}}(\mathbf{x}_1 - \mathbf{x}_2), \overset{\leftrightarrow}{\rho} \right\}, \quad (\text{B.73})$$

one obtains, after a little simplification,

$$\overset{\leftrightarrow}{\mathbf{h}}(\mathbf{k}) = (\overset{\leftrightarrow}{\mathbf{I}} - \overset{\leftrightarrow}{\mathbf{c}}(\mathbf{k}) \cdot \overset{\leftrightarrow}{\rho})^{-1} \cdot \overset{\leftrightarrow}{\mathbf{c}}(\mathbf{k}). \quad (\text{B.74})$$

The single particle configurational density in Eq. B.74 is, once more, a constant matrix $(\overset{\leftrightarrow}{\rho})_{ij} = \delta_{ij} \rho_i / \Omega_i$. The HCF, GCF and CCF are no longer functionals and $\mathbf{x}_1 - \mathbf{x}_2$ is the difference in the positional configuration of the two particles (their species depends on the matrix element).

In the more general case of angularly dependent functions, the OZE has one other important property that simplifies solution. In the $W = 0$ case, where molecular species number 1 is the solute with $N_1 = 1$ and $\rho_1 \rightarrow 0$, the OZE written in matrix form

$$\overset{\leftrightarrow}{\mathbf{h}}(1, 2) = \overset{\leftrightarrow}{\mathbf{c}}(1, 2) + \overset{\leftrightarrow}{\mathbf{c}}(1, 3) \star (\overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{h}}(3, 2)) \quad (\text{B.75})$$

separates into three equations, one for solvent-solvent interactions, one for solute-solvent interactions, and one for solute-solute interactions. To see this, one divides the $\overset{\leftrightarrow}{\mathbf{h}}$, $\overset{\leftrightarrow}{\mathbf{c}}$ and $\overset{\leftrightarrow}{\rho}$ matrices into submatrices

$$\begin{aligned} \overset{\leftrightarrow}{\mathbf{h}} &= \begin{pmatrix} \overset{\leftrightarrow}{\mathbf{h}}^{vv} & \overset{\leftrightarrow}{\mathbf{h}}^{vu} \\ \overset{\leftrightarrow}{\mathbf{h}}^{uv} & \overset{\leftrightarrow}{\mathbf{h}}^{uu} \end{pmatrix} \\ \overset{\leftrightarrow}{\mathbf{c}} &= \begin{pmatrix} \overset{\leftrightarrow}{\mathbf{c}}^{vv} & \overset{\leftrightarrow}{\mathbf{c}}^{vu} \\ \overset{\leftrightarrow}{\mathbf{c}}^{uv} & \overset{\leftrightarrow}{\mathbf{c}}^{uu} \end{pmatrix} \\ \overset{\leftrightarrow}{\rho} &= \begin{pmatrix} \overset{\leftrightarrow}{\rho}^v & 0 \\ 0 & 0 \end{pmatrix}, \end{aligned} \quad (\text{B.76})$$

where, for example, $\overset{\leftrightarrow}{\mathbf{h}}^{vv}$ is the matrix of solvent-solvent direct correlation functions, $\overset{\leftrightarrow}{\mathbf{h}}^{uv}$ is the matrix of solute-solvent direct correlation functions, and $\overset{\leftrightarrow}{\mathbf{h}}^{uu}$ is the matrix of solute-solute direct correlation functions. Substituting these into Eq. B.75

$$\begin{pmatrix} \overset{\leftrightarrow}{\mathbf{h}}^{vv} & \overset{\leftrightarrow}{\mathbf{h}}^{vu} \\ \overset{\leftrightarrow}{\mathbf{h}}^{uv} & \overset{\leftrightarrow}{\mathbf{h}}^{uu} \end{pmatrix} = \begin{pmatrix} \overset{\leftrightarrow}{\mathbf{c}}^{vv} & \overset{\leftrightarrow}{\mathbf{c}}^{vu} \\ \overset{\leftrightarrow}{\mathbf{c}}^{uv} & \overset{\leftrightarrow}{\mathbf{c}}^{uu} \end{pmatrix} + \begin{pmatrix} \overset{\leftrightarrow}{\mathbf{c}}^{vv} & \overset{\leftrightarrow}{\mathbf{c}}^{vu} \\ \overset{\leftrightarrow}{\mathbf{c}}^{uv} & \overset{\leftrightarrow}{\mathbf{c}}^{uu} \end{pmatrix} \star \left[\begin{pmatrix} \overset{\leftrightarrow}{\rho}^v & 0 \\ 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} \overset{\leftrightarrow}{\mathbf{h}}^{vv} & \overset{\leftrightarrow}{\mathbf{h}}^{vu} \\ \overset{\leftrightarrow}{\mathbf{h}}^{uv} & \overset{\leftrightarrow}{\mathbf{h}}^{uu} \end{pmatrix} \right] \quad (\text{B.77})$$

and performing the matrix multiplication, one obtains

$$\begin{pmatrix} \overset{\leftrightarrow}{\mathbf{h}}^{vv} & \overset{\leftrightarrow}{\mathbf{h}}^{vu} \\ \overset{\leftrightarrow}{\mathbf{h}}^{uv} & \overset{\leftrightarrow}{\mathbf{h}}^{uu} \end{pmatrix} = \begin{pmatrix} \overset{\leftrightarrow}{\mathbf{c}}^{vv} + \overset{\leftrightarrow}{\mathbf{c}}^{vv} \star (\overset{\leftrightarrow}{\rho}^v \cdot \overset{\leftrightarrow}{\mathbf{h}}^{vv}) & \overset{\leftrightarrow}{\mathbf{c}}^{vu} + \overset{\leftrightarrow}{\mathbf{c}}^{vv} \star (\overset{\leftrightarrow}{\rho}^v \cdot \overset{\leftrightarrow}{\mathbf{h}}^{vu}) \\ \overset{\leftrightarrow}{\mathbf{c}}^{uv} + \overset{\leftrightarrow}{\mathbf{c}}^{uv} \star (\overset{\leftrightarrow}{\rho}^v \cdot \overset{\leftrightarrow}{\mathbf{h}}^{uv}) & \overset{\leftrightarrow}{\mathbf{c}}^{uu} + \overset{\leftrightarrow}{\mathbf{c}}^{uv} \star (\overset{\leftrightarrow}{\rho}^v \cdot \overset{\leftrightarrow}{\mathbf{h}}^{uu}) \end{pmatrix}. \quad (\text{B.78})$$

The important result of Eq. B.78 is that the bulk solvent correlation functions, $\overset{\leftrightarrow}{\mathbf{h}}^{vv}$ and $\overset{\leftrightarrow}{\mathbf{c}}^{vv}$, are given by the standard solvent-only OZE. They are *independent* of the solute and thus, once calculated, can be used with any solute. The solute-solvent correlation functions needed to compute the free energy, are not given by a standard OZE. The total correlation functions appearing on the right hand side of the equation are the “known” solvent-solvent functions. This reduces the equation for the

solute–solvent correlation functions from a non-linear integral equation to an essentially algebraic equation where the total correlation functions can be easily computed once the direct correlations are known.

Given the functional form of the CCF, the HCF and the GCF can be analytically obtained through the use of Eq. B.67, Eq. B.74, or Eq. B.78. While the OZE is exact (it does not even assume a pairwise potential), and describes the correlation functions in an intuitively simple fashion, it essentially defines a new unknown function, the CCF. Before, there was only one unknown, the HCF. Now there are two unknowns and one non-linear equation linking them. In order to analytically compute the GCF, another independent equation must be derived which links the HCF to the CCF. While another exact equation that one can computationally implement cannot be obtained, various good approximate relations are derived in the next section.

B.4.3 Approximate Closure Relations

Thus far, the only major approximations that have been made are that the molecules are rigid and that the intermolecular potential energy is pair-wise additive. In order to make progress solving for the GCF, other much more significant approximations must be made. In light of the quest for the solution to Eq. B.37, the field free ($W = 0$) ensemble of Section B.3.2 shall be used. In this ensemble of m molecular species, species 1 is the solute molecule with $N_1 = 1$. Because there is no external field, the position and orientation of the solute molecule can be integrated out of the configurational partition function as in Eq. B.14

$$\mathcal{Z}_{N_1, \dots, N_m} = \frac{V\Omega_1}{\sigma_1} \int \left(\prod_{i=2}^m \frac{d\mathbf{X}^{(i)}_{1\dots N_i}}{\sigma_i^{N_i}} \right) \exp(-\beta\mathcal{V}(\mathbf{X}^{(2)}_{1\dots N_2}, \dots, \mathbf{X}^{(m)}_{1\dots N_m})), \quad (\text{B.79})$$

where $\mathbf{X}^{(i)}_j \equiv \mathbf{x}^{(i)}_j - \mathbf{x}^{(1)}_1$. Since the value of $\mathbf{x}^{(1)}_1$ is now arbitrary, it can be fixed such that the solute is at the origin of the coordinate system in some particular orientation.

The solvent–solute potential energy, Eq. B.33, can be factored out of the total potential energy, Eq. B.32

$$\mathcal{Z}_{N_1, \dots, N_m} = \frac{V\Omega_1}{\sigma_1} \int \left(\prod_{i=2}^m \prod_{j=1}^{N_i} \frac{d\mathbf{x}^{(i)}_j}{\sigma_i} \exp(-\beta\lambda U_i(\mathbf{X}^{(i)}_j)) \right) \exp(-\beta\mathcal{V}'(\mathbf{X}^{(2)}_{1\dots N_2}, \dots, \mathbf{X}^{(m)}_{1\dots N_m})), \quad (\text{B.80})$$

where \mathcal{V}' is the total potential energy without the solute-solvent part, Eq. B.33 — the intermolecular interaction between all molecules of species 2 through m . Comparing Eq. B.80 to Eq. B.55 one can see that, with the identification of $W^{(i)}(j) = \exp(-\beta\lambda U_i(\mathbf{x}^{(i)}_j - \mathbf{x}^{(1)}_1))$, Eq. B.80 is just $V\Omega_1/\sigma_1$ times the partition function for the other $m - 1$ species of molecules in the external field $W(\lambda)$,^s

$$\mathcal{Z}_{N_1, \dots, N_m} = \frac{V\Omega_1}{\sigma_1} \int \left(\prod_{i=2}^m \prod_{j=1}^{N_i} \frac{d\mathbf{x}^{(i)}_j}{\sigma_i} W^{(i)}(j) \right) \exp(-\beta\mathcal{V}'(\mathbf{X}^{(2)}_{1\dots N_2}, \dots, \mathbf{X}^{(m)}_{1\dots N_m}))$$

^sThe potential energy function \mathcal{V}' is pair-wise additive over all pairs of molecules that do not include the solute. Therefore, each energy function depends on a difference like $\mathbf{X}^{(i)}_j - \mathbf{X}^{(k)}_t \equiv \mathbf{x}^{(i)}_j - \mathbf{x}^{(k)}_t$. These differences are all independent of $\mathbf{x}^{(1)}_1$, so variables can be changed back to $\mathbf{x}^{(i)}_j$.

$$= Z_1^{\text{ig}} Z_{N_2, \dots, N_m}[W]. \quad (\text{B.81})$$

The constant Z_1^{ig} will cancel in the calculation of all correlation and distribution functions because they all involve logarithmic derivatives of the partition function. The solvent single-particle configurational density in the presence of this external field, $\rho_i[W; 1]$, is thus proportional to the 2-particle solute–solvent configurational density when the solute is fixed at the origin, $W = 0$. By confining the solute to the origin, one has only “lost” the orientational and positional freedom of the solute (effectively setting $Z_1^{\text{ig}} = 1$). Thus the proportionality constant is $\rho_1[W = 0; 1]$ and the relation is

$$\rho_i[W; 1] = \frac{\rho_{1i}[W = 0; 1, 2]}{\rho_1[W = 0; 1]}. \quad (\text{B.82})$$

The solvation of a solute in a mixture of molecular fluids can be treated as the effect of perturbing the bulk solvent by an effective external field, $W(\lambda)$. In fact, if the size of this perturbation is small, the single particle density can be expanded in a functional Taylor series about zero potential. However, most solutes of interest have hard core centers which make such an approximation inadequate.^{20, 28} A better approximation involves expanding various functions of the density in terms of the deviation from bulk density, $\Delta\rho_k[1] = \rho_k[W; 1] - \rho_k[W = 0; 1]$.^t Expanding the functional $\rho_i[W; 1]/W^{(i)}(1)$ results in the Percus–Yevick (PY) equation.^{160, 161} With the definition of the functional Taylor series, Eq. B.53, one has to first order

$$\begin{aligned} \frac{\rho_i[W; 2]}{W^{(i)}(2)} &\approx \rho_i[W = 0; 2] + \\ &\sum_{j=2}^m \int d\mathbf{x}^{(j)} {}_3 \left(\frac{\delta}{\delta\rho_j[W; 3]} \frac{\rho_i[W; 2]}{W^{(i)}(2)} \right)_{W=0} (\rho_j[W; 3] - \rho_j[W = 0; 3]). \end{aligned} \quad (\text{B.83})$$

Using $\rho_j[W = 0, 3] = \rho_j/\Omega_j$ and taking advantage of Eqs. B.82 and B.59 to write $\rho_j[W; 3] - \rho_j[W = 0; 3] = \rho_j[W = 0; 3]h_{j1}(3, 1)$, Eq. B.83 becomes

$$\frac{\rho_i[W; 2]}{W^{(i)}(2)} \approx \frac{\rho_i}{\Omega_i} + \sum_{j=2}^m \frac{\rho_j}{\Omega_j} \int d\mathbf{x}^{(j)} {}_3 \left(\frac{\rho_i[W; 2]}{W^{(i)}(2)} \frac{\delta}{\delta\rho_j[W; 3]} \ln \frac{\rho_i[W; 2]}{W^{(i)}(2)} \right)_{W=0} h_{j1}(3, 1). \quad (\text{B.84})$$

The definition of the direct correlation function Eq. B.60 provides the simplification

$$\frac{\rho_i[W; 2]}{W^{(i)}(2)} \approx \frac{\rho_i}{\Omega_i} + \sum_{j=2}^m \frac{\rho_j \rho_i}{\Omega_i \Omega_j} \int d\mathbf{x}^{(j)} {}_3 c_{ij}(2, 3) h_{j1}(3, 1). \quad (\text{B.85})$$

Finally, taking into account a definition of the GCF from Eqs. B.82 and B.59,

$$g_{i1}(2, 1) = \frac{\Omega_i \rho_i[W; 1]}{\rho_i}, \quad (\text{B.86})$$

the value of $W^{(i)}(2)$, and the OZE,^u for $W = 0$, Eq. B.85 becomes

$$g_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) = e^{-\beta\lambda U_i(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1)} \left(g_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) - c_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) \right), \quad (\text{B.87})$$

^tThere are many possibilities, all of varying usefulness. One could also expand to different orders in $\Delta\rho_k[1]$.

^uThe sum in Eq. B.85 is from 2 to m but in the OZE Eq. B.67 it is from 1 to m . This is acceptable because in the present case, $N_1 = 1$ and this particle is already fixed at the origin. There are no more molecules of species 1 to interact with, so the $m = 1$ terms are all zero.

or

$$h_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) = e^{-\beta\lambda U_i(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1)} \left(1 + h_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) - c_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) \right) - 1, \quad (\text{B.88})$$

which is the Percus–Yevick closure equation.

The Percus–Yevick equation, Eq. B.87, can be combined with the OZE, Eq. B.67, resulting in two coupled nonlinear equations for the GCF and the CCF that can be solved numerically. In fact, PY depends *only* on the GCF, CCF and interaction energy of the single molecular species involved. This is unlike the OZE which mixes the effects of all the various species through matrix products. This PY approximation has been very successful for short ranged potentials, e.g., fluids of non-polar molecules.²⁸

An expansion that works much better for long ranged potentials, e.g., Coulombic, produces the Hypernetted Chain (HNC) closure equation.^{28,159} To achieve this, one expands the functional $\ln(\rho_i[W; 1]/W^{(i)}(1))$ to first order

$$\ln \left(\frac{\rho_i[W; 2]}{W^{(i)}(2)} \right) \approx \ln(\rho_i[W = 0; 2]) + \sum_{j=2}^m \int d\mathbf{x}^{(j)}_3 \left(\frac{\delta}{\delta\rho_j[W; 3]} \ln \left(\frac{\rho_i[W; 2]}{W^{(i)}(2)} \right) \right)_{W=0} (\rho_j[W; 3] - \rho_j[W = 0; 3]). \quad (\text{B.89})$$

Here, we can immediately substitute the definition of the direct correlation function, Eq. B.60, and take into account the identities used in the derivation of the PY equation

$$\ln \left(\frac{\rho_i[W; 2]}{W^{(i)}(2)} \right) \approx \ln \left(\frac{\rho_i}{\Omega_i} \right) + \sum_{j=2}^m \frac{\rho_j}{\Omega_j} \int d\mathbf{x}^{(j)}_3 c_{ij}(2, 3) h_{j1}(3, 1). \quad (\text{B.90})$$

Now, using the OZE and rearranging terms, one obtains

$$\ln \left(\frac{\rho_i[W; 2]\Omega_i}{\rho_i W^{(i)}(2)} \right) \approx h_{1i}(1, 2) - c_{1i}(1, 2) \quad (\text{B.91})$$

Substituting the value of $W^{(i)}(2)$ and Eq. B.86, the HNC equation is

$$g_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) = e^{-\beta\lambda U_i(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1)} e^{(h_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) - c_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1))}, \quad (\text{B.92})$$

or

$$h_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) = e^{-\beta\lambda U_i(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1)} e^{(h_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1) - c_{1i}(\mathbf{x}^{(i)} - \mathbf{x}^{(1)}_1))} - 1. \quad (\text{B.93})$$

One can readily see that the PY equation Eq. B.88 can be obtained from the HNC equation Eq. B.93 by expanding the exponential $\exp(h_{1j}(1, 2) - c_{1j}(1, 2)) \approx (1 + h_{1j}(1, 2) - c_{1j}(1, 2))$, so the PY closure is a linearization of the HNC closure. However, the large \mathbf{r} limits of these closures are different. For ionic fluids, the HNC closure reduces to a Debye–Hückel approximation.²⁸ The HNC closure has also been shown to approach continuum electrostatics in the limit of weak fields and slowly varying potentials¹⁶² for general systems. In comparison, the PY closure does not have such behavior. In this sense, one expects the HNC equation to be more accurate.

B.5 Extended Reference Interaction Site Method (XRISM)

So far, a method for computing the GCF has been developed. However, it requires the solution of coupled non-linear integral equations in up to four dimensions. Such solutions, while they have been attempted,^{162–166} are computationally expensive. In addition, considering the fact that to evaluate the free energy of solvation, Eq. B.37, the value of the GCF for *many* values of λ must be computed, it seems very difficult to employ the theory just developed. The solution of the OZE for atomic fluids or fluids with spherically symmetric correlation functions is, however, relatively straight forward. All of the angular integrations are trivial and the remaining convolutions can be evaluated with one-dimensional Fourier transforms. Transforming the full GCF theory to a spherically symmetric theory would, then, greatly simplify computation.

The assumptions of pair-wise additive potentials and rigid molecules allow one to compute the angularly dependent intermolecular potential energy function from a sum over pairs of atomic potential energy functions. Let each molecular species i be composed of a_i atoms at positions $\mathbf{l}^{(i)}(\omega^{(i)})$ relative to the center of mass of the molecule. Then, the energy of interaction between two such molecules is

$$w_{ij}(\mathbf{x}^{(i)}, \mathbf{x}^{(j)}) = \sum_{s=1}^{a_i} \sum_{t=1}^{a_j} u_{ij}^{(st)} (|\mathbf{r}^{(i)} + \mathbf{l}_s^{(i)}(\omega^{(i)}) - \mathbf{r}^{(j)} - \mathbf{l}_t^{(j)}(\omega^{(j)})|), \quad (\text{B.94})$$

where $u_{ij}^{(st)}$ is the *spherically symmetric* interaction energy between atomic sites s and t of molecular species i and j , respectively. Then, any function of the intermolecular energy, such as the average potential energy of solvation, Eq. B.39, or the free energy of solution, Eq. B.37, can be written as a sum over atomic site-site radial distribution functions (RDFs). To see this, examine the integral

$$I = \int \frac{d\mathbf{x}^{(i)} d\mathbf{x}^{(j)}}{\Omega_i \Omega_j} w_{ij}(\mathbf{x}^{(i)}, \mathbf{x}^{(j)}) g_{ij}(\mathbf{x}^{(i)}, \mathbf{x}^{(j)}). \quad (\text{B.95})$$

Inserting the expression for the molecular interaction energy, Eq. B.94, and the fact that the GCF only depends on the difference between its arguments, I becomes

$$I = \sum_{s=1}^{a_i} \sum_{t=1}^{a_j} \int \frac{d\mathbf{x}^{(i)} d\mathbf{x}^{(j)}}{\Omega_i \Omega_j} u_{ij}^{(st)} (|\mathbf{r}^{(i)} + \mathbf{l}_s^{(i)}(\omega^{(i)}) - \mathbf{r}^{(j)} - \mathbf{l}_t^{(j)}(\omega^{(j)})|) g_{ij}(\mathbf{r}^{(i)} - \mathbf{r}^{(j)}, \omega^{(i)} - \omega^{(j)}). \quad (\text{B.96})$$

Now, instead of integrating over all positions of the centers of mass of the molecules and over all orientations about these centers of mass, one can change variables and integrate over all positions of site s on molecule i and of site t on molecule j and over all orientations of the molecules about these positions

$$I = \sum_{s=1}^{a_i} \sum_{t=1}^{a_j} \int d\mathbf{r}_s^{(i)} d\mathbf{r}_t^{(j)} u_{ij}^{(st)} (|\mathbf{r}_s^{(i)} - \mathbf{r}_t^{(j)}|) \int \frac{d\omega^{(i)} d\omega^{(j)}}{\Omega_i \Omega_j} g_{ij}(\mathbf{r}_s^{(i)} - \mathbf{l}_s^{(i)}(\omega^{(i)}) - \mathbf{r}_t^{(j)} + \mathbf{l}_t^{(j)}(\omega^{(j)}), \omega^{(i)} - \omega^{(j)}). \quad (\text{B.97})$$

Comparing this with Eq. B.21, one sees that

$$g_{ij}^{(st)}(r = |\mathbf{r}_s^{(i)} - \mathbf{r}_t^{(j)}|) = \int \frac{d\omega^{(i)} d\omega^{(j)}}{\Omega_i \Omega_j} g_{ij}(\mathbf{r}_s^{(i)} - \mathbf{l}_s^{(i)}(\omega^{(i)}) - \mathbf{r}_t^{(j)} + \mathbf{l}_t^{(j)}(\omega^{(j)}), \omega^{(i)} - \omega^{(j)}) \quad (\text{B.98})$$

is the atomic site-site RDF describing the spatial structure of the density of atoms of type t in molecules of species j around atoms of type s in molecules of species i . This equation can also be written in operator form¹⁵⁶

$$\begin{aligned} g_{ij}^{(st)}(r) &= \hat{R}_{ij}^{(st)} [g_{ij}(\mathbf{x}^{(i)} - \mathbf{x}^{(j)})] \\ &= \int \frac{d\mathbf{x}^{(i)} d\mathbf{x}^{(j)}}{\Omega_i \Omega_j} g_{ij}(\mathbf{x}^{(i)} - \mathbf{x}^{(j)}) \delta(\mathbf{r}^{(i)} + \mathbf{l}_s^{(i)}(\omega^{(i)})) \delta(\mathbf{r}^{(j)} + \mathbf{l}_t^{(j)}(\omega^{(j)}) - \mathbf{r}). \end{aligned} \quad (\text{B.99})$$

These RDFs are spherically symmetric and easier to compute than their six-dimensional counterparts. The method of describing fluid properties in terms of individual interaction sites located at the positions of the atoms is called the Interaction Site Method (ISM).¹⁵⁶ In terms of the RDFs, the solvation free energy and average solute–solvent interaction energy are given respectively by

$$\Delta\mu^{\text{solv}} = \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \rho_k \int_0^1 d\lambda \int_0^\infty 4\pi r^2 dr U_k^{(st)}(r) g_{1k}^{(st)}(r; \lambda) \quad (\text{B.100})$$

$$\Delta U(\lambda) = \lambda \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \rho_k \int_0^\infty 4\pi r^2 dr U_k^{(st)}(r) g_{1k}^{(st)}(r; \lambda) \quad (\text{B.101})$$

The immediate drawback of using RDFs is that the detailed three-dimensional solvent structure about the solute is lost. One cannot reconstruct the angularly dependent GCF from the RDFs. Therefore, one cannot compute the induced polarization of the solvent for non-spherical solutes either. Accepting these drawbacks in the face of the potential computational benefit of using one-dimensional instead of six-dimensional functions, one must generalize the OZE to describe them. To obtain the generalized OZE, one simply applies the operator $\hat{R}_{ij}^{(st)}$ to both sides of Eq. B.67 arriving at

$$\begin{aligned} h_{ij}^{(st)}(r) &= c_{ij}^{(st)}(r) + \sum_{k=1}^m \frac{\rho_k}{\Omega_i \Omega_j \Omega_k} \int d\mathbf{x}_3^{(k)} d\mathbf{x}_1^{(i)} d\mathbf{x}_2^{(j)} c_{ik}(\mathbf{x}_1^{(i)} - \mathbf{x}_3^{(k)}) h_{kj}(\mathbf{x}_3^{(k)} - \mathbf{x}_2^{(j)}) \times \\ &\quad \delta(\mathbf{r}_1^{(i)} + \mathbf{l}_s^{(i)}(\omega_1^{(i)})) \delta(\mathbf{r}_2^{(j)} + \mathbf{l}_t^{(j)}(\omega_2^{(j)}) - \mathbf{r}). \end{aligned} \quad (\text{B.102})$$

Some manipulation, or the application of the theory of diagrams, allows this to be simplified to¹⁵⁶

$$h_{ij}^{(st)}(r) = c_{ij}^{(st)}(r) + \sum_{k=1}^m \sum_{u=1}^{a_k} \sum_{l=1}^m \sum_{v=1}^{a_l} \rho_k \int d\mathbf{r}_0 d\mathbf{r}_1 s_{ik}^{(su)}(|\mathbf{r}_0|) c_{kl}^{(uv)}(|\mathbf{r}_0 - \mathbf{r}_1|) h_{lj}^{(vt)}(|\mathbf{r}_1 - \mathbf{r}|), \quad (\text{B.103})$$

which is known as the site–site Ornstein Zernike equation (SSOZE). The new function $s_{ik}^{(su)}$ is the intramolecular correlation matrix. It provides for the propagation of correlations along sites rigidly connected in the same molecule. It has the form^v

$$s_{ij}^{(uv)}(\mathbf{r}) = \delta_{ij} \frac{\delta(|\mathbf{r}| - |\mathbf{l}_{uv}^{(i)}|)}{4\pi |\mathbf{l}_{uv}^{(i)}|^2}, \quad (\text{B.104})$$

where $|\mathbf{l}_{uv}^{(i)}|$ is the bond length between sites u and v on a molecule of species i .

^vOne can deviate from the rigid molecule assumption here and allow bond vibrations, since this is essentially a two-body term. The form for the intramolecular correlation matrix in this case can be found in ref. 167.

Generalizing the matrix form of the OZE, Eq. B.69, to the SSOZE, Eq. B.103, each matrix element $(\overset{\leftrightarrow}{\mathbf{h}})_{ij}$ now represents an $a_i \times a_j$ matrix of site–site correlation functions. From now on $\overset{\leftrightarrow}{\mathbf{h}}$, $\overset{\leftrightarrow}{\mathbf{c}}$, $\overset{\leftrightarrow}{\mathbf{g}}$, $\overset{\leftrightarrow}{\rho}$ and $\overset{\leftrightarrow}{\mathbf{s}}$ will represent these larger site–site matrices. In this notation, the SSOZE is compactly written as

$$\overset{\leftrightarrow}{\mathbf{h}}(r) = \overset{\leftrightarrow}{\mathbf{c}}(r) + \overset{\leftrightarrow}{\mathbf{s}}(r) \star \overset{\leftrightarrow}{\mathbf{c}}(r) \star (\overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{h}}(r)). \quad (\text{B.105})$$

Substituting the identity

$$\overset{\leftrightarrow}{\mathbf{c}}(r) = \overset{\leftrightarrow}{\mathbf{s}}(r) \star \overset{\leftrightarrow}{\mathbf{c}}(r) \star \overset{\leftrightarrow}{\mathbf{s}}(r) \quad (\text{B.106})$$

into the SSOZE, Eq. B.105, and multiplying from the left and right by $\overset{\leftrightarrow}{\rho}$ (while noting that $\overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{s}}(r) = \overset{\leftrightarrow}{\mathbf{s}}(r) \cdot \overset{\leftrightarrow}{\rho} \equiv \overset{\leftrightarrow}{\mathbf{S}}(r)$), the SSOZ is expressible in terms of a new chain sum

$$\begin{aligned} \overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{h}}(r) \cdot \overset{\leftrightarrow}{\rho} &= \overset{\leftrightarrow}{\mathbf{S}}(r) \star \overset{\leftrightarrow}{\mathbf{c}}(r) \star \overset{\leftrightarrow}{\mathbf{S}}(r) + \overset{\leftrightarrow}{\mathbf{S}}(r) \star \overset{\leftrightarrow}{\mathbf{c}}(r) \star (\overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{h}}(r) \cdot \overset{\leftrightarrow}{\rho}) \\ &= \mathcal{C}[c(r), \overset{\leftrightarrow}{\mathbf{S}}(r)]. \end{aligned} \quad (\text{B.107})$$

Eq. B.107 has a solution in Fourier space

$$\begin{aligned} \overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{h}}(k) \cdot \overset{\leftrightarrow}{\rho} &= \left[\overset{\leftrightarrow}{\mathbf{I}} - \overset{\leftrightarrow}{\mathbf{S}}(k) \cdot \overset{\leftrightarrow}{\mathbf{c}}(k) \right]^{-1} \cdot \overset{\leftrightarrow}{\mathbf{S}}(k) \cdot \overset{\leftrightarrow}{\mathbf{c}}(k) \cdot \overset{\leftrightarrow}{\mathbf{S}}(k) \\ \overset{\leftrightarrow}{\mathbf{h}}(k) &= \left[\overset{\leftrightarrow}{\mathbf{I}} - \overset{\leftrightarrow}{\mathbf{s}}(k) \cdot \overset{\leftrightarrow}{\mathbf{c}}(k) \cdot \overset{\leftrightarrow}{\rho} \right]^{-1} \cdot \overset{\leftrightarrow}{\mathbf{s}}(k) \cdot \overset{\leftrightarrow}{\mathbf{c}}(k) \cdot \overset{\leftrightarrow}{\mathbf{s}}(k). \end{aligned} \quad (\text{B.108})$$

Unlike the full OZE, the correlation functions in the SSOZE depend only on the absolute value of the distances between the sites. Thus the convolution theorem holds and the derivation of Eq. B.108 is valid. The discussion leading to the reduction of the OZE into three separate equations for the solvent–solvent, solute–solvent and solute–solute correlation functions Eq. B.78 is also valid for the SSOZE in matrix form.

To obtain a closure equation for the SSOZE, one can perform the same functional Taylor series expansion as that leading to Eqs. B.88 and B.93, but with site labels decorating the potential energy and density functions as well as molecular type labels. The derivations go through exactly the same and result in the site–site PY closure

$$h_{ij}^{(st)}(r) = e^{-\beta \lambda u_{ij}^{(st)}(r)} \left(1 + h_{ij}^{(st)}(r) - c_{ij}^{(st)}(r) \right) - 1, \quad (\text{B.109})$$

and the site-site HNC closure

$$h_{ij}^{(st)}(r) = e^{-\beta \lambda u_{ij}^{(st)}(r)} e^{h_{ij}^{(st)}(r) - c_{ij}^{(st)}(r)} - 1. \quad (\text{B.110})$$

Now, using the SSOZE equation, Eq. B.107, and its solution, Eq. B.108, in combination with the PY or HNC closures, one can computationally obtain the GCFs for any system of molecular fluids and thus compute the free energy of solvation. Actually, use of the HNC closure allows a very simple computation of the free energy of solvation because the thermodynamic integration can be done *analytically*,¹⁶⁸ so that the GCF's need only be obtained for $\lambda = 1$. To see this, consider the equation for the solvation free energy Eq. B.100. Using the Mayer f -function^{20, 28, 159}

$f_{ij}^{(ab)}(r) = \exp(-\beta u_{ij}^{(ab)}(r)) - 1$ and an auxiliary function $y_{ij}^{(ab)}(r) = [1 + f_{ij}^{(ab)}(r)]^{-1} g_{ij}^{(ab)}(r)$, the free energy of solvation can be written as

$$\Delta\mu^{\text{solv}} = \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \rho_k \int_0^1 d\lambda \int_0^\infty 4\pi r^2 dr \frac{df_{1k}^{(st)}(r, \lambda)}{d\lambda} y_{1k}^{(st)}(r, \lambda). \quad (\text{B.111})$$

Now, HNC closure implies that $y_{ij}^{(ab)} = \exp(h_{ij}^{(ab)}(r) - c_{ij}^{(ab)}(r))$ and from the relationship between g and y , one can compute (dropping indices for now due to their redundancy)

$$\frac{dh}{d\lambda} = \frac{d}{d\lambda} [(1 + f)e^{h-c}], \quad (\text{B.112})$$

which yields, after differentiation and re-arrangement,

$$y \frac{df}{d\lambda} = \frac{d}{d\lambda} (c - \frac{1}{2}h^2) + h \frac{dc}{d\lambda}. \quad (\text{B.113})$$

Half of this expression is a pure differential, which is easily evaluated when plugged into Eq. B.111. The other half, after summing over the indices, as in Eq. B.111, and substituting in the SSOZE, Eq. B.103, yields

$$\begin{aligned} \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} h_{1k}^{(st)}(r, \lambda) \frac{dc_{1k}^{(st)}(r, \lambda)}{d\lambda} &= \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \left[c_{1k}^{(st)}(r, \lambda) + \right. \\ &\left. \sum_{l=1}^m \sum_{p=1}^m \sum_{u=1}^{a_l} \sum_{v=1}^{a_p} s_{1l}^{(su)}(r) \star c_{lp}^{(uv)}(r, \lambda) \star \rho_p h_{pk}^{(vt)}(r) \right] \frac{dc_{1k}^{(st)}(r, \lambda)}{d\lambda}. \end{aligned} \quad (\text{B.114})$$

This, in Fourier space, looks like

$$\begin{aligned} \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} h_{1k}^{(st)}(\mathbf{k}, \lambda) \frac{dc_{1k}^{(st)}(\mathbf{k}, \lambda)}{d\lambda} &= \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \left[c_{1k}^{(st)}(\mathbf{k}, \lambda) + \right. \\ &\left. \sum_{l=1}^m \sum_{p=1}^m \sum_{u=1}^{a_l} \sum_{v=1}^{a_p} s_{1l}^{(su)}(\mathbf{k}) c_{lp}^{(uv)}(\mathbf{k}, \lambda) \rho_p h_{pk}^{(vt)}(\mathbf{k}) \right] \frac{dc_{1k}^{(st)}(\mathbf{k}, \lambda)}{d\lambda}. \end{aligned} \quad (\text{B.115})$$

The total correlation functions, $h_{pk}^{(vt)}$, do not depend on λ because the solute density, ρ_1 , is zero; so the only total correlation functions that could depend on λ are eliminated by the density factor. Using the property that the intramolecular correlation function $s_{1l}^{(su)}$ is proportional to δ_{1l} , one can see that, other than the fact that one direct correlation function is a derivative, there is really nothing asymmetric about the direct correlation functions appearing in the equation. Therefore, one can pull the derivative through the sums and multiply by a factor 1/2 to account for the product rule to obtain

$$\begin{aligned} \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} h_{1k}^{(st)}(\mathbf{k}, \lambda) \frac{dc_{1k}^{(st)}(\mathbf{k}, \lambda)}{d\lambda} &= \frac{d}{2d\lambda} \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \left[c_{1k}^{(st)}(\mathbf{k}, \lambda) + \right. \\ &\left. \sum_{l=1}^m \sum_{p=1}^m \sum_{u=1}^{a_l} \sum_{v=1}^{a_p} s_{1l}^{(su)}(\mathbf{k}) c_{lp}^{(uv)}(\mathbf{k}, \lambda) \rho_p h_{pk}^{(vt)}(\mathbf{k}) \right] c_{1k}^{(st)}(\mathbf{k}, \lambda). \end{aligned} \quad (\text{B.116})$$

This gives, in real space,

$$\sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} h_{1k}^{(st)}(r, \lambda) \frac{dc_{1k}^{(st)}(r, \lambda)}{d\lambda} = \frac{d}{2d\lambda} \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} h_{1k}^{(st)}(r, \lambda) c_{1k}^{(st)}(r, \lambda), \quad (\text{B.117})$$

which is a perfect differential in λ . Using Eqs. B.117 and B.113 in the free energy Eq. B.111, one obtains an analytic expression for the free energy of solvation under the SSOZE and the HNC closure

$$\begin{aligned} \Delta\mu^{\text{solv}} = & \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \rho_k \int_0^\infty 4\pi r^2 dr \left[c_{1k}^{(st)}(r, \lambda = 1) - \frac{1}{2} h_{1k}^{(st)}(r, \lambda = 1)^2 \right. \\ & \left. + \frac{1}{2} h_{1k}^{(st)}(r, \lambda = 1) c_{1k}^{(st)}(r, \lambda = 1) \right] \end{aligned} \quad (\text{B.118})$$

Such an expression is very useful, for now one does not have to worry about numerically integrating the GCFs over λ and only has to compute the GCFs for a single value of λ , namely $\lambda = 1$.

When one wishes to actually solve these equations, one assumes the total and direct correlation functions go to zero rapidly after a few molecular diameters, i.e. they are short ranged. With this assumption, one can truncate these functions after only 20 Å or so, and expect to get the same answers for the interaction energy and the free energy, as if they were truncated after 100 or 1000 Å. However, for Coulombic potentials, this assumption breaks down since, at least for atomic liquids, it can be shown that $c(r) \approx -\beta u(r)$ for large r . One way to eliminate this long range behavior is to renormalize the SSOZE.^{167,169} If one denotes the dimensionless long range part of the potential by $\overleftrightarrow{\phi}(r) = -\beta \overleftrightarrow{\mathbf{u}}_{\text{coul}}(r)$, then one can write the chain sum OZE, Eq. B.107, as

$$\overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{h}}(r) \cdot \overleftrightarrow{\rho} = \mathcal{C}[\overleftrightarrow{\mathbf{c}}(r) - \overleftrightarrow{\phi}(r) + \overleftrightarrow{\phi}(r), \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(r)]. \quad (\text{B.119})$$

It is easy to show,¹⁵⁷ by writing out the first several terms in the chain sum, that this sum is equal to

$$\overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{h}}(r) \cdot \overleftrightarrow{\rho} = \mathcal{C}[\overleftrightarrow{\phi}, \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(r)] + \mathcal{C}[\overleftrightarrow{\mathbf{c}}^*(r), \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(r) + \mathcal{C}[\overleftrightarrow{\phi}, \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(r)]], \quad (\text{B.120})$$

where $\overleftrightarrow{\mathbf{c}}^*(r) = \overleftrightarrow{\mathbf{c}}(r) - \overleftrightarrow{\phi}$ is the renormalized direct correlation function.

One can define the function $\overleftrightarrow{\mathbf{Q}}(r) = \mathcal{C}[\overleftrightarrow{\phi}, \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(r)]$, which is easily computed using Eq. B.72. In fact, $\overleftrightarrow{\mathbf{Q}}(r)$ only depends on the long range potential, the density of the molecules, and the structure of the molecules. These are known independently of the GCF, i.e. $\overleftrightarrow{\mathbf{Q}}(r)$ can be determined quickly and easily before attempting to solve for the GCF. In certain circumstances, the renormalized long range potential, $\overleftrightarrow{\mathbf{Q}}$, can be associated with the Debye–Hückel potential.¹⁵⁹ Now, applying Eq. B.72 to Eq. B.120, one obtains the renormalized solution to the SSOZE

$$\begin{aligned} \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{h}}(r) \cdot \overleftrightarrow{\rho} - \overleftrightarrow{\mathbf{Q}}(r) &= \mathcal{C}[\overleftrightarrow{\mathbf{c}}^*(r), \overleftrightarrow{\mathbf{Q}}(r) + \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(r)] \\ \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{h}}(k) \cdot \overleftrightarrow{\rho} &= \overleftrightarrow{\mathbf{Q}}(k) + \left[\overleftrightarrow{\mathbf{I}} - (\overleftrightarrow{\mathbf{Q}}(k) + \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(k)) \cdot \overleftrightarrow{\mathbf{c}}^*(k) \right]^{-1} \cdot \\ & (\overleftrightarrow{\mathbf{Q}}(k) + \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(k)) \cdot \overleftrightarrow{\mathbf{c}}^*(k) \cdot (\overleftrightarrow{\mathbf{Q}}(k) + \overleftrightarrow{\rho} \cdot \overleftrightarrow{\mathbf{s}}(k)), \end{aligned} \quad (\text{B.121})$$

where explicit dependence on the long range potential has been removed and the renormalized potential decays much faster than $1/r$.^{167,169}

A discrepancy that one immediately finds when computing the solvent correlation functions is that they produce an incorrect value for the bulk dielectric constant. It can be shown^{170,171} that when combining the HNC closure and the second moment expression for the dielectric constant,

ϵ , the SSOZE yields $\epsilon = 1 + 3y$, where $y = \sum_{i=1}^m 4\pi\rho_i\beta\mu_i^2/9$ and μ_i is the mean molecular dipole moment of molecular species i . For actual water-like molecules, this effective dielectric constant is around 18, as opposed to the expected value of about 80. This is a big discrepancy and, essentially, it says that in the SSOZE the solvent does not screen the Coulombic interactions properly.

As an ad-hoc remedy to this problem, it has been proposed that to account for screening one can multiply the Coulombic interactions by some constant. If we call this constant A , so that $u_{\text{eff}}(r) = Au_{\text{coul}}(r)$, then the same procedure can be followed and one obtains

$$\epsilon = \frac{1 + 3Ay}{1 + 3(A - 1)y}. \quad (\text{B.122})$$

From this equation, one can define the parameter A such that one obtains any desired dielectric constant. In practice, this method is used to obtain the bulk solvent correlation functions. Then, to obtain the solute–solvent correlation functions, an unmodified ($A = 1$) solute–solvent interaction is used. This method has been shown to give better agreement with experimental results than using only the unmodified Coulombic potential.¹⁷²

The expression for the free energy of solvation given in Eq. B.118 can be improved by assuming that the solvent interacts with the solute statistically with a Gaussian probability distribution function and that the solute is coupled to the solvent bath linearly in the density field.^{173,174} The revised formula, which essentially results in removing the $h^2(r)$ term from the integrand, is

$$\Delta\mu^{\text{solv}} = \sum_{k=2}^m \sum_{s=1}^{a_1} \sum_{t=1}^{a_k} \rho_k \int_0^\infty 4\pi r^2 dr \left[c_{1k}^{(st)}(r, \lambda = 1) + \frac{1}{2} h_{1k}^{(st)}(r, \lambda = 1) c_{1k}^{(st)}(r, \lambda = 1) \right]. \quad (\text{B.123})$$

This form for the free energy of solution has also been shown to yield free energies in much better agreement with experiment, Monte Carlo and molecular dynamics simulations.^{172,175}

B.6 Numerical Computation of the GCFs

The theory developed in the previous sections can now be put to use in computing the radial site–site correlation functions, the GCFs. The first consideration is to obtain the point at which one can truncate the numerical histograms of the correlation functions. It has been found that one can truncate at 20 Å without loss of accuracy.¹⁷⁶ Second, one must determine how finely to bin this range. A fine grid allows very accurate sampling, but costs computation time. A sampling of 512 bins per 20 Å has been shown to provide accurate sampling.¹⁷⁶ Third, one must determine the species of molecules in the fluid and their respective densities. Using this information and Eq. B.104, one can compute the matrices $\overleftrightarrow{\rho}$ and $\overleftrightarrow{\mathbf{s}}(r)$. One can also compute the Coulombic screening constant A from Eq. B.122.

Next, one must determine the site–site potential energy functions. This is typically done by assuming that the intermolecular energetics can be adequately described by van der Waals (modeled by a Leonard–Jones potential) and Coulombic terms. The potential between sites a and b on two different molecules would be

$$u_{ab}(r) = -4\epsilon_{ab} \left(\left(\frac{\sigma_{ab}}{r} \right)^6 - \left(\frac{\sigma_{ab}}{r} \right)^{12} \right) + A_{ab} \frac{Z_a Z_b}{r}, \quad (\text{B.124})$$

where the interatomic van der Waals parameters are obtained by the Lorentz–Berthelot rules $\sigma_{ab} = (\sigma_a + \sigma_b)/2$ and $\epsilon_{ab} = \sqrt{\epsilon_a \epsilon_b}$. The partial atomic charge on each site is denoted by Z and the ad-hoc screening constant introduced to correct the bulk dielectric constant is denoted by A_{ab} .

With the knowledge of the Coulombic interaction terms, $(\overset{\leftrightarrow}{\phi})_{ab} = A_{ab} Z_a Z_b / r$, and the intramolecular correlation matrices, one computes the screened Coulombic potential $\overset{\leftrightarrow}{\mathbf{Q}}(r) = \mathcal{C}[\overset{\leftrightarrow}{\phi}, \overset{\leftrightarrow}{\rho} \cdot \overset{\leftrightarrow}{\mathbf{s}}(r)]$ using Eq. B.72. Then, one is ready to solve the coupled renormalized nonlinear SSOZE, Eq. B.121, and HNC, Eq. B.110, for the correlations functions.

These equations are solved by making an initial guess for the CCF, plugging this guess into the SSOZE to get a new guess for the HCF and then plugging this into the HNC closure to get a new guess for the CCF. The Fourier transforms required for this process can be performed one-dimensionally because the functions in question are spherically symmetric.¹⁷⁷ If the integrated difference between the new and old guesses for the HCF is sufficiently small, i.e.

$$\sqrt{\int_0^\infty dr (h_{\text{old}}(r) - h_{\text{new}}(r))^2} \leq 0.0001, \quad (\text{B.125})$$

for every site–site correlation function, then the functions have “converged” and one has obtained a solution. If the integrated difference is large, then the new guess is combined with the old guess to obtain a revised guess and the process is repeated.^w

There are two commonly used methods used to mix old and new guesses and hasten convergence. The first, the Picard method, mixes them together linearly.¹⁷⁸ This method has the advantage of being very fast, but it takes many iterations (thousands) to converge. The other method, based on a mixture of Newton–Raphson interpolation and Picard iteration, converges very quickly, but is much slower to implement.^{179–181}

The initial guess often determines how quickly, or even if, one can obtain convergent solutions to the OZSSE and HNC equations. One method of guessing that works well is to use the hard-sphere correlation functions. The CCFs for hard spheres can be computed analytically under the PY closure.²⁸ The solution is

$$c(x) = \begin{cases} -\frac{(1+2\eta)^2}{(1-\eta)^4} \left(1 + \frac{\eta x^3}{2}\right) + 6\eta x \frac{(1+\frac{1}{2}\eta)^2}{(1-\eta)^4} & r < d \\ 0 & r \geq d \end{cases}, \quad (\text{B.126})$$

where $x = r/d$, $\eta = \pi d^3/6$ is the packing fraction, and d is the hard sphere radius. Using the suggestion of Monson, one chooses $d_{ab} = 0.9\sigma_{ab}$ and sets $c(r) = 0$ for $d \leq r \leq 1.5d$ to obtain good convergence.¹⁸⁰

Once the equations have been solved and the GCFs are available, the free energy of solvation and the energetic and entropic contributions can be obtained from Eqs. B.123 and B.101.

^wThis allows one to achieve faster, more stable convergence than by simply using the new results.