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Simple parameter-free bridge functionals for molecular density functional theory. Application to hydrophobic solvation

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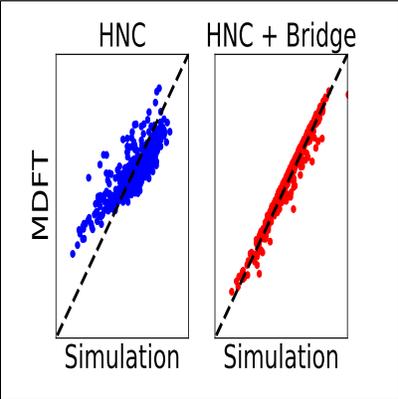
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Abstract

Computer simulations have been substantial in understanding the fine details of hydrophobic solvation and hydrophobic interactions. Alternative approaches based on liquid-state theories have been proposed, but are not yet at the same degree of completeness and accuracy. In this vein, a classical, molecular density functional theory approach to hydrophobic solvation is introduced. The lowest, second-order approximation of the theory, equivalent to the hypernetted chain approximation in integral equations, fails in describing correctly cavitation free-energies. It is corrected here by two simple, angular-independent, so-called bridge functionals; they are parameter-free in the sense that all variables can be fixed unambiguously from the water bulk properties, including pressure, isothermal compressibility, and liquid-gas surface tension. A hard-sphere bridge functional, based on the known functional of a reference hard fluid system, turns out to face strong limitations for water. A simpler weighted density approximation is shown to properly reproduce the solvation free energy of hydrophobes of various sizes, from microscopic ones to the nanoscale, and predicting the solvation free-energy of a dataset of more than 600 model hydrophobic molecules having a variety of shapes and sizes with an accuracy of a quarter of $k_B T$ compared to Monte-Carlo simulations values. It constitutes an excellent starting point for a general functional describing accurately both hydrophobic and hydrophilic solvation, and making it possible to study non-idealized hydrophobic interactions.

Graphical TOC Entry



1 Introduction

Much of the physical chemistry of hydrophobic solvation has been understood from early statistical mechanics theories such as scaled-particle theory, and from the advent of molecular simulations in the 1980's¹⁻³, and its subsequent developments⁴⁻¹⁰. In particular, those simulations have contributed to show that for small hydrophobic solutes, hydration is characterized by a clathrate-like geometry for the solvent, driven by the large enthalpic penalties which would follow from a less ordered solvation layer². The molecular structure of liquid water around larger, nanoscale hydrophobic entities appears governed by the same principle that determines the hydration structure of small hydrophobic solutes, namely the optimization of hydrogen bonding interactions. Substantial structural reorganization occurs at the surface, where the sacrifice of possible H-bonds is required to maximize the total interaction. The resulting orientational structure is inverted from that found for small solutes and the solvation free energy is dominated by enthalpic rather than entropic effects.¹ It was shown further that the structure and free energy of hydrophobic hydration is strongly influenced by the detailed topography of the biomolecule surfaces that contain convex patches, deep or shallow concave grooves and roughly planar area.^{4,5} Indeed, it has been thought for long that the hydrophobic effect plays a key role in the stability of protein structures, in the protein folding process, or in the aggregation of self-assemblies. The proteins contain hydrophobic regions which associate due to the favorable solvent-mediated free energy of aggregation of nonpolar moieties in an aqueous environment. This globally accepted picture has nevertheless given rise to hot debates at the turn of the 21st century and during its first decade as to ascertain the details of the process. Be it a concerted scenario in which water is gradually reduced between the associating regions when the moieties approach each other, or a sequential one where a thermodynamic liquid-gas phase transition occurs in the interstitial region, leading to instantaneous hydrophobic collapse to contact¹¹. Simulations of water next or in between realistic hydrophobic surfaces patched with hydrophilic sites were substantial to show that the conditions for an ideal dewetting transition scenario is hard to achieve in real

systems and that water density next to nanoscale hydrophobic patches can be influenced substantially by nearby hydrophilic motifs.⁶⁻⁸

On the theoretical side, the Gaussian field theory of hydrophobicity initiated by the 1999 paper of Lum, Weeks and Chandler¹², and further developed in subsequent articles^{11,13-15}, has driven the view that nanoscale hydrophobic attraction is induced by a local gas-liquid phase transition. This theory is based on the fluctuations of the density field $n(\mathbf{r})$ and, to our knowledge, was never fully developed to include its coupling to the electrostatic polarisation field¹⁶. A unified field theoretical approach of this sort would be able to describe both hydrophobic and hydrophilic interactions and could be applied to the hydrophobic/hydrophilic patchy surfaces described above.

Another possible theoretical approach is 3D-RISM, a method that has emerged from a consistent formulation of integral equation theory for molecular liquids and solutions¹⁷⁻²¹. That approach is gaining nowadays considerable momentum to describe the solvation properties of complex molecular entities at a numerical cost far below that of molecular simulations, giving access to properties that are as hardly accessible by direct simulations²¹⁻²⁹. The method, however, was shown recently to face strong limitations when describing the hydration properties of nanosized hydrophobic solutes³⁰.

The purpose of this work is to propose an alternative approach to either 3D-RISM²¹⁻²⁹, or Gaussian field theory, namely classical density functional theory in its molecular version, MDFT³¹⁻³⁶. Shortly, MDFT allows to compute the solvation free-energy and the equilibrium solvent structure around a given solute by minimizing a functional of the solvent density $\rho(\mathbf{r}, \omega)$. In the most general case, the solvent density depends on the space coordinates \mathbf{r} and on the orientational ones ω . In this paper, we consider only pure hydrophobes, described by Lennard-Jones potentials and no partial charges, so that it is possible to stay at the level of the current Lum-Weeks-Chandler theory and its extensions and consider the orientationally averaged density field $n(\mathbf{r}) = \int d\omega \rho(\mathbf{r}, \omega)$. We know how to extend the theory to the polarisation field, and in fact to the whole orientational density field $\rho(\mathbf{r}, \omega)$ in

a numerically efficient way³⁵, but this will be put in a future work.

The question raised here is how to go beyond the so-called HNC approximation which we have studied thoroughly in a recent article³⁶. The weaknesses of the HNC approximation have been known for long³⁷: it suffers from the original sin of being a quadratic theory around the liquid bulk density. The homogeneous free energy as a function of density presents a single instead of a double well; it cannot accommodate for the liquid-gas transition and consequently it largely overestimates the cost of creation of an empty cavity (a gas bubble in the bulk). This has to be cured by pushing the theory beyond second order and introducing the so-called bridge functional which, by definition, starts at cubic order in density perturbation³⁸⁻⁴¹. We will explore here what we refer to as parameter-free approaches, in the sense that all the parameters appearing in the expression of the bridge functional are determined unambiguously from the properties of the bulk solvent (pressure, isothermal compressibility, liquid-gas surface tension). The resulting functional is approximate but universal, that is independent of the solute; no parameter has to be subsequently fitted on the dataset or part of the dataset that is studied.

The outline of the paper is as follows. Section 2 exposes the theoretical background. In section 2.1 we start by a general consideration about MDFT and the properties of the bridge functional which need to be fulfilled. In section 2.2, we examine a hard-sphere bridge (HSB) functional that has been proposed as a "universal" bridge functional in the past. In section 2.3, inspired by our previous works, we propose a simple bridge functional based on a weighted density approximation (WDA) which appears more flexible than HSB or than a previous WDA version of ours³⁹. In section 3, as application, we depart from idealized spherical solutes and we compute the hydration free energies of a database of 642 hydrophobic molecules of arbitrary shape using the WDA bridge.

2 Theory

2.1 General considerations

We recall briefly the well-established results of molecular density functional theory: the free energy of solvation of a molecule can be written as

$$\Delta G_{sol} = \min (\mathcal{F}_{id}[\rho] + \mathcal{F}_{ext}[\rho] + \mathcal{F}_{exc}[\rho]), \quad (1)$$

where \mathcal{F}_{id} , \mathcal{F}_{ext} , and \mathcal{F}_{exc} are the ideal, external and excess functionals of the solvent position and orientation density, $\rho(\mathbf{r}, \omega)$. The notation ω stands for the three Euler angles that describe the orientation of a rigid body in three dimensions. The whole MDFT procedure can be summarized as how to find the spatial and angular density that minimizes the sum of the three contributions. Knowing the functionals, the density at minimum, by virtue of the theorems derived by Mermin⁴² and Evans⁴³, is also the thermodynamic equilibrium density of the solvent around the solute $\rho(\mathbf{r}, \omega)$. As far as the various contributions are concerned, we have (i) the ideal contribution, that is known exactly, (ii) the external contribution that is the direct cost of the interaction of the solute with the solvent density. The interaction energy $\phi(\mathbf{r}, \omega)$ is typically given by classical force fields like SPC/E water for the solvent and, *e.g.*, OPLS for the solute. (iii) the excess contribution which, as usual in liquid state theories, is known analytically as an infinite diagrammatic resummation of virial diagrams, but is not tractable numerically. It can be approximated by a Taylor expansion around the homogeneous bulk solvent density, $\rho_b \equiv n_b/8\pi^2$ with n_b the number density. Truncation at second order in $\Delta\rho(\mathbf{r}, \omega) = \rho(\mathbf{r}, \omega) - \rho_b$ yields the so-called hyper-netted chain (HNC) approximation and higher orders are gently put into the so-called bridge functional, \mathcal{F}_B . More explicitly:

$$\mathcal{F}_{id}[\rho] = k_B T \int d\mathbf{r} d\omega \left[\rho(\mathbf{r}, \omega) \log \left(\frac{\rho(\mathbf{r}, \omega)}{\rho_0} \right) - \rho(\mathbf{r}, \omega) + \rho_0 \right], \quad (2)$$

$$\mathcal{F}_{ext}[\rho] = \int d\mathbf{r}d\omega \rho(\mathbf{r}, \omega) \phi(\mathbf{r}, \omega), \quad (3)$$

$$\mathcal{F}_{exc}[\rho] = \mathcal{F}_{HNC}[\rho] + \mathcal{F}_B[\rho] \quad (4)$$

$$= -\frac{k_B T}{2} \int d\mathbf{r}d\omega \Delta\rho(\mathbf{r}, \omega) \int d\mathbf{r}'d\omega' c(|\mathbf{r} - \mathbf{r}'|, \omega, \omega') \Delta\rho(\mathbf{r}', \omega') + \mathcal{F}_B[\rho], \quad (5)$$

where k_B is the Boltzmann constant, T is the temperature. c is the direct correlation function of the bulk solvent, which depends upon the relative position of two solvent molecules and their respective orientations. It is an input of the theory that needs to be calculated once per solvent and thermodynamic condition. We use the ones obtained by Belloni for either the transferable intermolecular potential 3-points (TIP3P) or the extended simple point charge (SPC/E⁴⁴) models of water, using a mixture of MC calculations and integral equations to invert the simulation data and make the asymptotic behaviours well-defined.⁴⁵ Even in its simplest HNC form, the efficient calculation of the excess term is a numerical challenge because of the spatial and angular convolution. For this we use expansions of both the density and the direct correlation function onto generalized spherical harmonics; all technicalities are described in Ref.³⁵ $\mathcal{F}_B[\rho]$ involves by definition terms of order $\Delta\rho^3$ and higher.

The purpose of this paper is to explore the simplest, conceivable approximations for the bridge functional, which amount to neglect the angular dependence and suppose that \mathcal{F}_B depends only on the number density $n(\mathbf{r}) = \int d\omega \rho(\mathbf{r}, \omega)$, that is to say $\mathcal{F}_B[\rho] = \mathcal{F}_B[n]$. Various bridge functionals of this sort have been proposed in the past, built in particular from the fundamental measure theory of hard-sphere fluids^{46–49} The criteria that make it challenging to build a bridge functional for molecular fluids are: (i) to predict correct solvation free energies and structures, and (ii) to remain thermodynamically consistent, i.e., describe correctly the solvation thermodynamic properties of the solvent, in particular its pressure acting on solutes, its compressibility, and its liquid-gas surface tension. As of today, no bridge functional designed for water, including ours^{38–41}, has proved to fulfil thoroughly and convincingly those two criteria.

We will focus in this paper on hydrophobic solutes described as a distribution of atomic

sites with no partial charges, so that for water models such as TIP3P or SPC/E, built with a single Lennard-Jones center on oxygen, the angular dependence of \mathcal{F}_{ext} in eqn. 3 disappears. We will furthermore neglect the orientational couplings in the excess functional and consider a simplified angular-independent functional

$$\begin{aligned} \mathcal{F}[n] &= k_B T \int d\mathbf{r} \left[n(\mathbf{r}) \log \left(\frac{n(\mathbf{r})}{n_b} \right) - n(\mathbf{r}) + n_b \right] + \int d\mathbf{r} \Phi_{LJ}(\mathbf{r}) n(\mathbf{r}) \\ &- \frac{k_B T}{2} \int d\mathbf{r} d\mathbf{r}' \Delta n(\mathbf{r}) c_s(|\mathbf{r} - \mathbf{r}'|) \Delta n(\mathbf{r}') + \mathcal{F}_B[n(\mathbf{r})], \end{aligned} \quad (6)$$

where $c_s(r)$ is the spherically-symmetric direct correlation function. We define that function from the bulk water-water isotropic pair-correlation function, $h_s(r)$, or equivalently from the density-density structure factor $\chi_s(r)$ by the following relation in Fourier space:

$$1 - n_b \hat{c}_s(q) = (1 + n_b \hat{h}_s(q))^{-1} = \hat{\chi}_s(q)^{-1}. \quad (7)$$

For an homogeneous fluid of volume V with no external constraints, this functional becomes a function of the bulk density n which can be written, per molecule, as

$$\beta F(n)/N = f(x) = f_{HNC}(x) + f_B(x) \quad (8)$$

$$= x \log x - x + 1 - \frac{1}{2} n_b \hat{c}_s(0) \Delta x^2 + f_B(x), \quad (9)$$

with $x = n/n_b$ and $\hat{c}_s(0)$ the zeroth-order spherical Hankel transform of $c_s(r)$ taken at $q = 0$. $f_B(x)$ is now a dimensionless bridge function of order at least Δx^3 . As we noted several times, this simple expression already imposes strong restrictions on the possible forms of f_B . Indeed for an empty macroscopic volume V , $n = x = 0$, one should have $F[n] = PV$, P the pressure of the fluid, 1 atm at ambient conditions, *i.e.*, virtually $P = 0$ for since $PV \simeq 0$ for volumes below micrometer sizes. The HNC approximation, corresponding to a $f(x)$ that is an almost quadratic function centered at $x = 1$ as depicted in Fig. 1-a, yields a largely

overestimated value at $x = 0$, related to the pressure

$$\beta P_{HNC}/n_b = f_{HNC}(0) = 1 - \frac{1}{2}n_b\hat{c}_s(0). \quad (10)$$

This overestimation is largely responsible for the deficiencies of HNC in predicting solvation free energies, and lead to the definition of so-called a posteriori pressure corrections^{28,50,51}.

This deficiency has to be compensated by the bridge term, through the condition

$$f_B(0) = -f_{HNC}(0) = -1 + \frac{1}{2}n_b\hat{c}_s(0). \quad (11)$$

This leads to an overall function $f(x)$ depicted in Fig. 1-a and presenting a double-well, with equal minima at $x = 0$ and $x = 1$. Such picture is indeed at the heart of the Gaussian Field theory of hydrophobicity developed along the years by Chandler and collaborators^{12,13,15}.

Note that the condition above can be related to the value of bulk liquid isothermal compressibility χ_T . Using $n_b k_B T \chi_T = 1/(1 - n_b \hat{c}_s(0))$ ⁵², we get

$$f_B(0) = -\frac{1}{2} (1 + 1/n_b k_B T \chi_T). \quad (12)$$

With these conditions in hand, we turn now to the examination of several suggestions reported in the literature for approximating $\mathcal{F}_B[\Delta n]$, including our own proposals. The different approximations will be tested below for three systems for which reference simulation results are available: 1) The solvation of a hydrophobic sphere of increasing radius going from microscopic to macroscopic dimensions; this is the paradigmatic system for either the standard scaled particle theory^{53,54} or the more recent advances in the theory of hydrophobicity and hydrophobic interactions^{55,56}. 2) The solvation of a spherical Lennard-Jones particle of increasing diameter up to nanoscale sizes. 3) The hydration free energies of a dataset of more than 600 realistic although virtual hydrophobic molecules of various shapes and sizes, going up to 40 atomic sites.

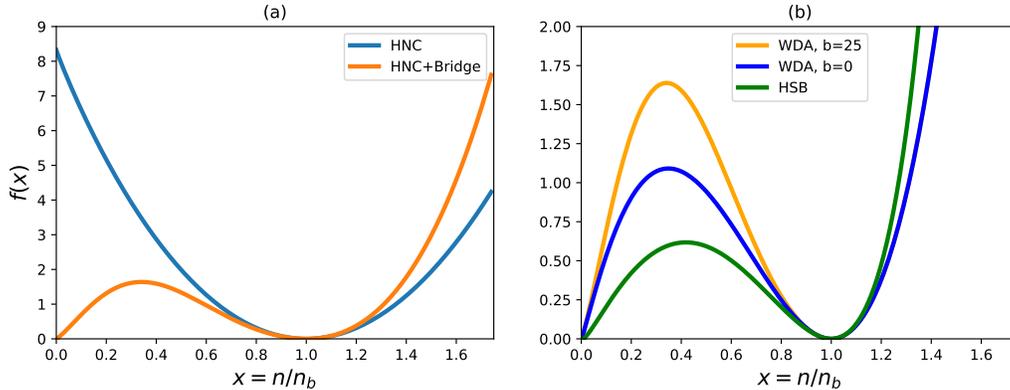


Figure 1: a) Free-energy per particle for the homogeneous solvent, $f(x) = \beta F(n)/N$, as function of the dimensionless density $x = n/n_b$, in the second-order HNC approximation or with a bridge function correcting the pressure and restoring the near coexistence of gas and liquid according to eqn 11. (b) The function $f(x)$ obtained for SPC/E water using the hard-sphere bridge functional of eqn. 13 with $r_{hs} = 1.4576 \text{ \AA}$, or using the WDA expression of eqn. 19 with different values of the barrier control parameter b .

2.2 Hard-sphere bridge functional

Following the recommendation of Rosenfeld that the fundamental measure theory of hard-sphere fluids should provide a "universal" hard-sphere bridge (HSB) functional applicable for general fluids^{57–59}, Wu and collaborators^{60–64}, and later ourselves³⁸, proposed to use such bridge functional for water. It has the form

$$\begin{aligned} \mathcal{F}_B[n] &= \mathcal{F}_{exc}^{HS}[n] - \mathcal{F}_{exc}^{HS}[n_b] - \mu_{exc}^{HS}(n_b) \int d\mathbf{r} \Delta n(\mathbf{r}) \\ &+ \frac{k_B T}{2} \int d\mathbf{r} d\mathbf{r}' \Delta n(\mathbf{r}) \Delta n(\mathbf{r}') c_s^{HS}(|\mathbf{r} - \mathbf{r}'|; n_b). \end{aligned} \quad (13)$$

The first two terms correspond to the fundamental measure theory (FMT) hard sphere functional taken at the inhomogeneous density $n(\mathbf{r})$ and homogeneous density n_b , respectively. We considered the scalar version of FMT derived by Kierlik and Rosinberg⁴⁷, which was shown to be equivalent to the earlier vectorial version of Rosenfeld^{46,65}, but presents supplementary numerical advantages³⁸. We use it in either its Percus-Yevick (PY) or Carnahan-Starling (CS) formulation, relying on the PY or CS hard-sphere equation of state.

Other authors use the modified FMT version⁴⁸, or the white-bear versions⁴⁹. $\mu_{exc}^{HS}(n_b)$ and $c_s^{HS}(|\mathbf{r} - \mathbf{r}'|; n_b)$ represent the corresponding chemical potential and direct correlation functions of the HS fluid at the homogeneous density n_b , by definition minus the first and second derivative of $\mathcal{F}_{exc}^{HS}[n(\mathbf{r})]$ at $n(\mathbf{r}) = n_b$. This expression amounts to subtract from the exact hard-sphere functional all terms of order 0, 1, 2 in the expansion in $\Delta n(\mathbf{r})$ around $n(\mathbf{r}) = n_b$, leaving only terms of order $\Delta n(\mathbf{r})^3$ and higher. The unknown bridge is thus mimicked by that of an equivalent hard-sphere system at the same density. There is one single adjustable parameter to play with: the hard-sphere radius r_{hs} . According to our discussion above, it has to be determined by the condition in eq.11, which leads, according to our criteria, to a parameter-free theory.

Writing the equivalent of eq. 13 for the homogeneous fluid, and using the textbook results⁵²

$$f_{exc}^{HS}(x) = \log(1 - \eta) + \frac{3\eta}{1 - \eta} + \frac{3\eta^2}{2(1 - \eta)^2} \text{ (PY)} \quad (14)$$

$$= \frac{\eta(4 - 3\eta)}{(1 - \eta)^2} \text{ (CS)} \quad (15)$$

for $f_{exc}^{HS}(x) = \beta\mathcal{F}_{exc}^{HS}(n)/N$ in either the PY or CS approximation (here $\eta = \eta_b x$ and $\eta_b = 4\pi r_{hs}^3 n_b/3$), it is a matter of simple algebra to derive the expression of $f_B^{HS}(x)$ from eqn. 13, and get the resulting $f(x)$, eq. 9. One can then plot the dimensionless pressure $\beta P/n_b = f(0)$ as a function of the reference hard-sphere fluid radius in order to identify the value of r_{hs} for which the pressure vanishes. This is represented in Fig. 2 for SPC/E water for which our data give $n_b \hat{c}_s(0) = -14.65$ (corresponding to a dimensionless isothermal compressibility $n_b k_B T \chi_T = 0.064$ instead of 0.063 in Ref.⁶⁶). We find $r_{hs} = 1.4576 \text{ \AA}$ for the PY equation of state, and $r_{hs} = 1.4695 \text{ \AA}$ for the CS one, which leads to a rather high packing fractions $\eta_b = 0.43$ and 0.44 , respectively. It is seen that the variation of pressure is very steep around those values: a small variation of hard-sphere radius involves large variation in pressure. It is satisfactory to find values falling close to 1.4 \AA , a value that can be guessed from the first

peak position of the oxygen-oxygen pair distribution function. Nevertheless, playing around that magic value turns out to have great consequences.

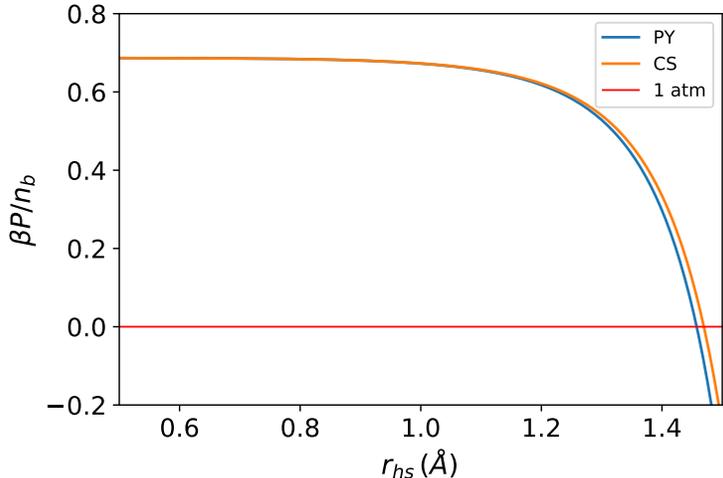


Figure 2: Dimensionless pressure as a function of reference hard-sphere fluid radius r_{hs} taken in the hard-sphere functional of eqn 11, either in the Percus-Yevick or Carnahan-Starling approximation. The red line indicates a pressure of 1 atm, virtually 0 at the scale that matters in the figure.

We computed the solvation free-energy of hard-spheres of different radius R using the HS bridge functional. For microscopic spheres, of radii up to $\approx 5 \text{ \AA}$, results are compared to MC simulations obtained by Hummer *et al* when they tested their information theory of hydrophobicity⁶⁷ as displayed in Figure 3. In Figure 4, results are compared to MD simulations of Huang and Chandler⁵⁵ for spheres up to $R = 14 \text{ \AA}$, reaching the nanoscale.

For the value $r_{hs} = 1.4576 \text{ \AA}$ that yields correct pressure, the hydrophobic solvation free-energy appears considerably underestimated on the whole microscopic to nanoscopic range. In Fig. 4 it can be seen that the solvation free energy per surface area, $\Delta G_{solv}/4\pi R^2$, correctly reaches a plateau for large R 's, giving a value for the liquid-vapor surface tension γ (since $\Delta G_{solv} = \gamma A + PV$ in the macroscopic limit, the volumetric term being negligible for $P = 1$ atm and volumes of nanoscale sizes). The measured value is around 22.5 mJ/m^2 , thus far below the value of 63.6 mJ/m^2 quoted for SPC/E water⁶⁸. One can indeed fit the correct solvation free energy at small R by taking a slightly smaller parameter $r_{hs} = 1.42 \text{ \AA}$; see

Fig. 3. But doing so one gets a considerable overestimation at larger radii above 5 Å, and, as can be seen in Fig. 4, the solvation free energy per surface area does not reach a plateau, as it should. It behaves asymptotically as $PR/3$ with a pressure that is already far from 0, as can be estimated from Fig. 2.

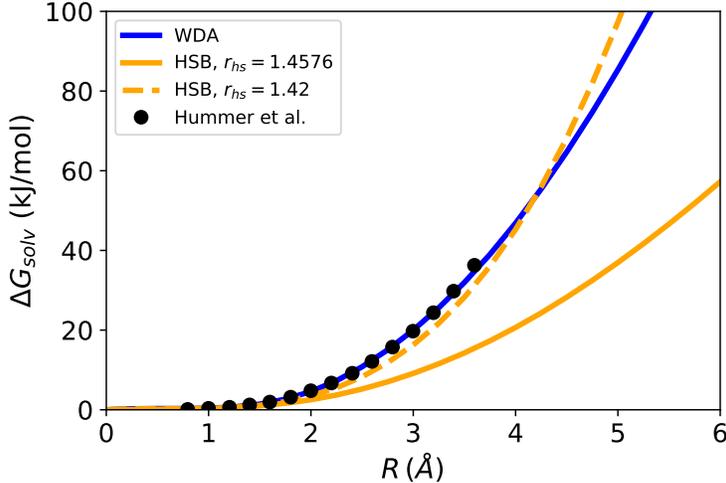


Figure 3: Hydration free-energy of a hard-sphere solute as a function of its radius R . The bullets points are the simulation results of Hummer *et al*⁶⁷. The MDFT results concerns the hard-sphere bridge functional of eqn. 13 in its parameter-free version with $r_{hs} = 1.4576$ Å, or with a slightly smaller radius $r_{hs} = 1.42$ Å that matches the simulation results at small R , or the parameter-free WDA bridge functional of eqn. 16 adjusted on pressure, isothermal compressibility, and liquid-gas surface tension of the bulk solvent.

This deficiency observed for hard cavities extends to solute presenting attractive forces. In Fig. 5, we compare the MDFT-HSB results to the simulation results obtained by Fujita *et al*³⁰ for a Lennard-Jones sphere of diameter σ increasing up to $\sigma = 18$ Å (ϵ is constant and taken equal to 0.5 kJ/mol). Again the hard-sphere parameter r_{hs} that yields the correct pressure leads to a strong underestimation over the whole range of σ , whereas the smaller parameter $r_{hs} = 1.42$ Å determined above does improve the results for small spheres, but leads to a diverging curve afterwards. Beside the fact that playing with the hard-sphere radius r_{hs} contradicts the parameter-free strategy announced in the title, we found no convincing results when trying to fix r_{hs} between the two preceding bounds.

We conclude that section by the ascertainment that a hard-sphere bridge functional,

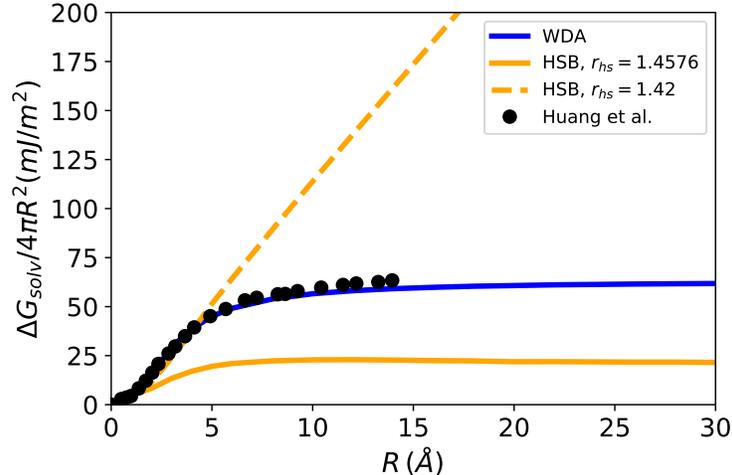


Figure 4: Same as Fig. 3 for the hydration free-energy per unit area, $\Delta G_{soliv}/4\pi R^2$, as a function of the hard-sphere radius R . Here the bullet points are the simulation results of Huang and Chandler⁵⁵.

although being quite appropriate in the case of Lennard-Jones fluids, has limitations when extended to water. This is at least the case in our MDFT approach, here limited to an angular independent functional, and where the second order is fixed by the exact direct correlation function of the bulk fluid, yielding the correct isothermal compressibility. We thus have to turn to another approach.

2.3 Weighted density bridge functional

The well-founded fundamental measure theory of hard-sphere fluids is rooted in the so-called weighted density approximations (WDA) that go back to the foundations of classical DFT⁶⁹⁻⁷¹. In a recent contribution⁴¹, we have proposed to use a more empirical, but more flexible version of WDA than FMT that is able to fulfil more physical conditions than only equation 11. and we have introduced a bridge functional in the form

$$\mathcal{F}_B[n] = k_B T n_b \int d\mathbf{r} f_B(\bar{n}(\mathbf{r})/n_b), \quad (16)$$

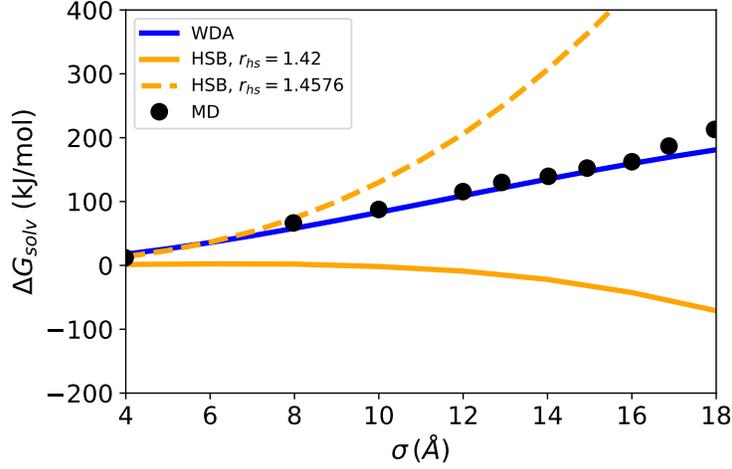


Figure 5: Same as Fig. 3 for the hydration free energy of a Lennard-Jones solute of increasing diameter σ and constant well-depth $\epsilon = 0.5$ kJ/mol. The bullet points are the simulation results of Fujita *et al*³⁰. Both the simulation and MD results have been corrected by the $1/r^6$ long-range contributions beyond cut-off distance.

where $\bar{n}(\mathbf{r})$ is a weighted density using a Gaussian weighting function

$$\bar{n}(\mathbf{r}) = \int d\mathbf{r}' w(|\mathbf{r} - \mathbf{r}'|) n(\mathbf{r}') \quad (17)$$

$$w(r) = (2\pi\sigma_w^2)^{-3/2} \exp(-r^2/2\sigma_w^2). \quad (18)$$

The bridge function f_B is defined again as a function of $x = n/n_b$ and $\Delta x = x - 1$

$$\begin{aligned} f_B(x) &= a \Delta x^3 + b x^2 \Delta x^4 \quad 0 < x < 1 \\ &= a \Delta x^3 \quad x > 1, \end{aligned} \quad (19)$$

where the second condition prevents spurious behaviours of the function at large x . Note that the preceding formulas are reminiscent of those employed by Chandler and collaborators in their Gaussian field approach of hydrophobicity. They are also of similar essence as a WDA approach that we proposed previously, based on a more complex, three-body expression of $\mathcal{F}_B[n]$ ⁴⁰. The approach here has the merit of simplicity. In the expression of $f_B(x)$, the value of a is fixed by the condition of eqn. 11 at $x = 0$, yielding $a = 1 - \frac{1}{2}n_b\hat{c}_s(0)$. The role of

the parameter b is to control the height of the double-well barrier of the total free energy function $f(x)$ (eq. 9) without altering the well-depth equality condition. This is depicted in Fig. 1-b. There are thus two parameters to be fixed, the coarse-graining length σ_w and b . In regard to the hard-sphere bridge parametrisation above, σ_w should roughly correspond to a coarse-graining over the size of a water molecule, with an associated radius $r_{hs} \simeq 1.4 \text{ \AA}$. Equating Gaussian and hard sphere volumes leads to $\sigma_w \simeq (2/3\sqrt{2\pi})^{1/3}r_{hs} = 0.9 \text{ \AA}$. The second parameter b can then be determined to yield the correct liquid-vapor surface tension for the selected water model. This is done by adjusting the asymptotic value obtained for the solvation free energy per surface area of a hard sphere to the correct surface tension, i.e. $\gamma = 63.6 \text{ mJ/m}^2$ for SPC/E water, and $\gamma = 52.3 \text{ mJ/m}^2$ for TIP3P; see Fig. 4. This lead us to $\sigma_w = 0.91 \text{ \AA}$ and $b = 25$ and $b = 12$ for SPC/E and TIP3P respectively; those models differ by the value of the compressibility and surface tension, hence requiring different parameter adjustments.

Note that we have 2 parameters, b and σ_w to reproduce a sole physical property, the surface tension γ . This leaves some flexibility that somehow contradicts the parameter-free claim of the title. Actually, we find that varying σ_w around the above value while readjusting b to reproduce the correct surface tension has very little effect on the computed solvent structure and only small consequences on the hydration free energies. It cannot be denied, however, that even with this procedure, σ_w remains as a fine adjustment cursor.

As seen in Figs. 3 and 4 for SPC/E, not only the asymptotic, macroscopic behaviour of the HS solvation is reproduced properly this way, but also the whole microscopic to nanoscopic range where the 'exact' simulation results of Hummer *et al*⁶⁷ and Huang and Chandler⁵⁵ apply. This excellent and almost miraculous agreement extends to the solvation of the Lennard-Jones sphere of microscopic to nanoscopic size in Fig. 5. Other important features of hydrophobic solvation have been shown to be correctly reproduced, be it with our previous WDA version in Ref.⁴⁰ or with the present one in Ref.⁴¹ This applies to the solvent pair-distribution function around spherical hydrophobic solutes or to the decreasing

contact values of the pair distribution function around hydrophobic spheres as a function of sphere radius, leading to depletion at very large R . For those two cases, the present weighted density bridge functional yields equivalently good results and does considerably improve the HNC ones.

3 Results

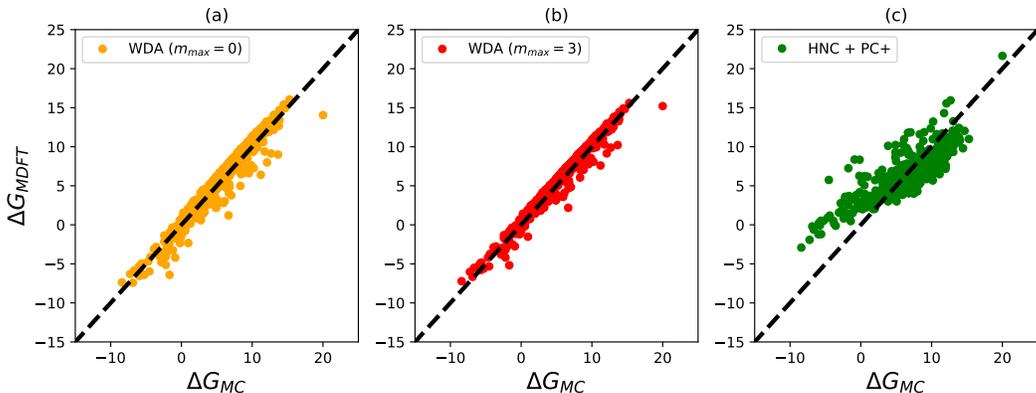


Figure 6: Comparison of the hydrophobic hydration free energies obtained by Monte-Carlo or MDFT (in kJ/mol) for the whole Mobley’s dataset of drug-like molecules (all charges set to zero). (a) Angular-independent free-energy functional of eqn. 6 ($m_{max} = 0$), complemented by the parameters-free WDA functional defined in the text. (b) Same using the full angular-dependent functional of eqs. 2-5 with 84 orientations per spatial grid point ($m_{max} = 3$). (c) Same in the HNC approximation with an a-posteriori pressure correction; Results taken from Ref.³⁶ The mean absolute error is 0.35, 0.25, and 0.7 $k_B T$ in panels (a) to (c), respectively.

We depart here from idealized spherical entities and turn to a more realistic problem: the hydration properties of hydrophobic solutes of arbitrary 3D-shapes. As a model to this, we consider the calculation of the non-electrostatic contribution to the hydration free-energy of drug-like molecules, a quantity that is systematically computed in free-energy perturbation methods (growing slowly the Lennard-Jones potential before introducing the charges), and that is a main source of error when using MDFT-HNC. We refer to the Mobley’s dataset, containing 642 drug-like molecules for which the experimental solvation free-energies, and

more importantly here, the solvation free-energies computed by simulation and decomposed into their non-electrostatic and electrostatic contributions, are available^{72,73}. We have generated ourselves our own reference data with the same force-field parameters as in Mobley’s FEP calculations but with fixed solute geometries in order to compare directly with MDFT. This was done using an original MC/4D-hybrid method and associated code developed by one of us⁷⁴. This amounts to test our approach on a dataset of virtual hydrophobic molecular solutes with a large variety of shapes and sizes. In Fig. 6-a we compare the MC results obtained for the non-electrostatic contribution to the solvation free-energy (all partial charges put to zero) to the same quantities obtained with MDFT in its angular-independent version, eqn. 6, and using the WDA bridge functional defined above. Anticipating future developments, we have also tested the angular-dependent version, eqs. 2-5, which accounts for the density/polarisation couplings that exists even for non-polar solutes, even though they are small. We have used an angular grid of 84 orientations per spatial point, corresponding to a maximum order $m_{max} = 3$ in a generalized spherical harmonics expansion³⁵. A single minimization using a box length of 24 Å and a resolution of 0.3 Å takes a few seconds on a single CPU for the angular-independent case, $m_{max} = 0$, and a few minutes for $m_{max} = 3$. The correlation between simulation and MDFT is already found excellent in the angular-independent case with a mean slope very close to 1 and an overall mean absolute error (MAE) of 0.35 $k_B T$ (Fig. 6-a). The MAE is decreased to 0.25 $k_B T$ when using the full angular-dependent functional (with a slight re-adjustment of the parameter b to stick to the correct value of the surface tension γ); see Fig. 6-b. This is much better than that was obtained previously using the HNC approximation and the best so-called pressure corrections to date. As seen in Fig. 6-c, this lead to a mean slope of 0.55 and an overall MAE of 0.7 $k_B T$, which is already satisfactory compared to the non-corrected HNC approximation³⁶. The pressure correction just mentioned amounts to correct the HNC free energies by an optimized term $-0.86P_{HNC}\Delta V$, where P_{HNC} is the pressure defined in eqn. 10 and ΔV is the measured partial molar volume of the solute. This correction turns out to be very close to the so-called

parameter-free PC+ correction which we have introduced some time ago for MDFT⁵⁰ and 3D-RISM⁵¹, and which is now used routinely in 3D-RISM free-energy calculations^{28,75}. It should be noted that such simple correction formula applies only in a limited range of ΔV values and cannot be true at the nanoscale, where the solvation free energy should go as the surface and not as the volume³⁶. In any case, it is rewarding to find that, at least in the hydrophobic case, a parameter-free bridge functional approach bypasses the need for such a-posteriori corrections while yielding more accurate results.

4 Conclusions

Going further than above, i.e. computing also the electrostatic contribution when the charges are switched on, will require to consider the angular-dependent functional of eqs. 2-5. This bypasses the goal of the present paper which was intended to show that even a simpler and computationally much more efficient angular-independent functional as in eqn. 6, combined with the proper angular-independent bridge functional $\mathcal{F}_B[n]$, is able to capture the main physical features of hydrophobic solvation, at the same time as it provides estimates of hydrophobic solvation free energies with chemical accuracy, a fraction of $k_B T$, compared to state-of-the-art simulation methods. This is made possible using a rather simple weighted density bridge functional yielding liquid-gas coexistence and built from bulk solvent properties such as isothermal compressibility and liquid-gas surface tension. We found that the reputed hard sphere bridge functional proposed by Rosenfeld for general fluids^{58,59} turns out to be a dead end in our case. The value of the hard-sphere parameter which matches the correct pressure and liquid-gas coexistence yields a poor value of the surface tension, and systematically underestimates the solvation free energy of hydrophobes at all length scales. Adjusting this value to reproduce the solvation free-energies of microscopic solutes, as we did in the past³⁸, leads to an overestimated pressure and diverging values of the solvation free-energy at the nanoscale. The model is thus lacking here some flexibility. It proved per-

fectly legitimate in other approaches with different formalism and different water properties requirements⁶⁰⁻⁶⁴

Extending the proposed angular-independent bridge functional to the angular-dependent functional of eqs. 2-5, in order to ascertain all the results obtained here and systematically improve the HNC results of Ref.³⁶ by circumventing a-posteriori pressure/surface tension corrections, will be the subject of a following work. We take our new bridge functional as an important step towards a general density functional for water, describing accurately both hydrophobic and hydrophilic interactions, and making it possible to study hydrophobic interactions in biologically relevant, non-idealized systems, such as those characterized along the years using statistical theories and simulations.¹⁻¹⁰

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This work has been supported by the Agence Nationale de la Recherche, projet ANR BRIDGE AAP CE29. There are obviously two meetings of the present work with pioneering contributions of Peter Rossky in the field of theoretical physical chemistry and biochemistry. The first one concerns his early and more recent elucidation by computer simulation of hydrophobic solvation and hydrophobic interactions. The second one is his invention in the 1980's of a consistent formulation of integral equation theories for molecular liquids and solutions, the extended reference interaction site model, which has given rise later to 3D-RISM. This contribution is faithfully dedicated to him.

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