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Bridge functional for the molecular density functional theory with consistent pressure and surface tension and its importance for solvation in water

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We address the problem of predicting the solvation free energy and equilibrium solvent density profile in few minutes from the molecular density functional theory beyond the usual hypernetted-chain approximation. We introduce a bridge functional of a coarse-grained, weighted solvent density. In few minutes at most, for solutes of sizes ranging from small compounds to large proteins, we produce (i) an estimation of the free energy of solvation within 1 kcal/mol of the experimental data for the hydrophobic solutes presented here, and (ii) the solvent distribution around the solute. Contrary to previous propositions, this bridge functional is thermodynamically consistent in that it produces the correct liquid-vapor coexistence and the experimental surface tension. We show this consistency to be of crucial importance for water at room temperature and pressure. This bridge functional is designed to be simple, local, and thus numerically efficient. Finally, we illustrate this new level of molecular theory of solutions with the study of the hydration shell of a protein.

Molecules in solution, may they be small chemical compounds like drugs or large biomolecules, behave differently from vacuum conditions. How to treat the solvent, the embedding medium, in numerical simulations is challenging. Since solvent molecules are the most abundant species in the system, most of the simulation time is dedicated to computing solvent-solvent interactions. In that sense, they are the limiting constituent of the simulation. To circumvent this problem, implicit models have been proposed, that mimic the solvent as a continuous medium of macroscopic permittivity and local polarizability¹⁻⁴. Implicit models lack the molecular nature of the interactions, like hydrogen bonding or steric effect and impede the rigorous evaluation of entropic contributions. Nevertheless, good parameterizations allowed their rapid and glorious development, sometimes with predicted free energies in good agreement with simulations for a numerical cost reduced to few seconds, orders of magnitude below simulations run-times. Liquid state theories have been another approach, especially the integral equation theory in the molecular picture^{5,6} in the first place. Molecular integral equations, within the so-called Molecular Ornstein-Zernike (MOZ) formalism, are nevertheless difficult, sensible to numerical instabilities and extended only recently to three dimensional systems⁷⁻⁹. They do not seem well suited to arbitrarily complex solutes in 3 dimensions, even if it is still an especially dynamic area of research. An approximation of this method was also developed, the reference interaction site model (RISM)^{10,11}, and then derived and adapted to three-dimensional solutes with 3D-RISM^{8,12,13}. RISM and 3D-RISM are having large successes since they predict solvation energies and profiles with better accuracy than usual continuous methods, as shown recently for small neutral molecules¹⁴⁻¹⁶, large protein-ligand complexes¹⁷ and even ions¹⁸. Nevertheless, they rely on considering molecules as a set of sites correlated together and are thus not diagrammatically consistent. The molecular density functional theory is yet another route. It is diagrammatically consistent, has deep connections with the integral equation theories, but is significantly less sensitive to numerical difficulties since it relies on functional minimization, a comfortable variational problem. Still, finding the perfect functional is difficult, not to say impossible, but nevertheless an ongoing project¹⁹⁻²⁵ that is gaining momentum. Readers interested in the deep roots of liquid state theories and classical density functional theory should refer to²⁶⁻²⁸.

The theoretical work presented therein lies within the classical density functional theory framework, more specifically the molecular density functional theory (MDFT). MDFT consists in minimizing a free energy functional of the solvent density. It is a cousin of the Khon-Sham DFT for electrons²⁹, expressed for a classical molecular solvent density. For atomic fluids, this density, $\rho(\mathbf{r})$, is expressed in number of solvent molecules per volume unit. For molecular solvents like water, the molecular density, $\rho(\mathbf{r}, \omega)$, depends upon the position and upon the molecular orientation. The notation ω refers to the triplet of Euler angles that are necessary and sufficient to describe the orientation of any rigid body in three dimensions. The free energy of solvation of an embedded molecule (the solute) can be written as

$$\Delta G_{\text{solv}} = \min(\mathcal{F}_{\text{exc}} + \mathcal{F}_{\text{ideal}} + \mathcal{F}_{\text{ext}}), \quad (1)$$

where \mathcal{F}_{exc} , $\mathcal{F}_{\text{ideal}}$ and \mathcal{F}_{ext} are the excess, ideal and external functionals of $\rho(\mathbf{r}, \omega)$, respectively. The min is the

variational minimum with respect to $\rho(\mathbf{r}, \omega)$. The whole MDFT procedure can be summarized as how to find the spatial and angular density that minimizes the sum of these three contributions. Knowing the functionals, the "minimizing" density, by virtue of Kohn, Sham and Mermin's theorems, is also the equilibrium density of the solvent around the solute. $\rho_{\text{equ.}}(\mathbf{r}, \omega)$ and ΔG_{solv} are the two natural outputs of MDFT. Of course they can be reduced, like averaged over orientations to produce site-site radial distribution functions $g(r)$. The ideal functional (eq. 2) is known exactly. The external functional (eq. 3) reflects the direct solute-solvent interaction energy $\phi(\mathbf{r}, \omega)$, which is typically given by classical force fields like SPC/E water for the solvent³⁰ and OPLS for the solute^{31,32}. As usual in liquid state theories, the excess contribution (eq. 5) is not tractable numerically. It is often approximated by a second order expansion around a bulk solvent density ρ_b . ρ_b can be any density, even if it is often the density of the liquid phase, ρ_L . Higher orders are gently put into a so-called bridge functional, \mathcal{F}_b .

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

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

$$\mathcal{F}_{\text{exc}} = \mathcal{F}_{\text{hnc}} + \mathcal{F}_b, \quad (4)$$

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

where k_B is the Boltzmann constant, T is the temperature, and $\Delta\rho(\mathbf{r}, \omega) \equiv \rho(\mathbf{r}, \omega) - \rho_b$ is the excess density. c is the direct correlation function of the bulk solvent at a given temperature and pressure. In the following applications, $\rho_b = \rho_L$ of SPC/E water at 298.15 K and 1 atm), calculated exactly by Belloni³³. c is an input of MDFT. Even in the hypernetted-chain approximation, also called homogeneous reference fluid approximation³⁴ or equivalently the Chandler-McCoy-Singer theory^{35,36}, that is without a bridge functional, the calculation of the excess term is a numerical challenge because of the spatial and angular convolutions. We recently reported a solution that relies on projections onto a basis of generalized spherical harmonics and using the optimal frame³⁷. *In what follows, we build a new bridge functional \mathcal{F}_b to go beyond the HNC approximation with unprecedented accuracy and yet numerically simple.* The first paragraphs are dedicated to building a bridge functional that is thermodynamically consistent. Then, we benchmark it on the important case of water, (i) by checking that indeed the important macroscopic thermodynamics are recovered, and (ii) on the hydration structure and hydration free energy of hydrophobic compounds.

Various bridge functionals have been proposed in the past. In particular, bridge functionals built from the fundamental measure theory (FMT) for hard sphere fluids have been shown to significantly improve the predicted solvation free-energies^{23,38-42}. The criteria that make it challenging to build a bridge functional for molecular fluids are : (i) MDFT should predict correct solvation free energies and microscopic structures, and (ii) it should be thermodynamically consistent for nano- macrosized solutes. FMT based bridge functionals do not satisfy this last criteria, as shown by Sergiievskiy et al.⁴². As of today, despite our recent progress²⁵, no bridge functional fulfill completely those two criteria.

To build our functional, we start from the HNC functional. In this approximation, there is no gas phase: as shown in black in figure 1, the free energy per volume unit fluid increases quadratically with the excess fluid density. Consequently, the pressure in the fluid is significantly overestimated^{43,44}. It is typically 10 000 atm for water at room temperature. Said differently, the work required to create a cavity in the fluid is overestimated, while in real water, for instance, the liquid and gas phases are almost at coexistence at room temperature. Recently, we proposed *a-posteriori* pressure corrections to solvation free energies predicted from the HNC approximation. They improve significantly the correlation to reference simulations, but are insufficient since they do not improve the solvent density profile around the solute: They remove the overestimated work needed to create the cavity in which the solute lies. This is not satisfying enough and the first axis to our strategy is to make our functional compatible with the liquid-gas coexistence. This comes back to having no difference in volumic free energy between the gas and liquid phase, as seen in the red curve of figure 1.

What is the physical quantity that should drive our bridge functional ? We borrow ideas at the root of the quasi-exact classical density functional theory for hard spheres : a weighted-density should be able to connect the local, molecular scale, and the longer scales. The successes of these DFTs of hard sphere fluids came with the introduction by Nordholm, Johnson and Freasier⁴⁵ of coarse-grained, weighted densities, and the seminal papers by Tarazona and Rosenfeld⁴⁶⁻⁴⁸ introducing hard-sphere measures (radius, surface, volume). For molecular fluids, we go back to the simplest weighted density

$$\bar{\rho}(\mathbf{r}) = \int d\mathbf{r}' \rho(\mathbf{r}') K(\mathbf{r} - \mathbf{r}'), \quad (6)$$

where the local number density is first averaged over all orientations, $\rho(\mathbf{r}) = \int d\omega \rho(\mathbf{r}, \omega)$, then convoluted with a

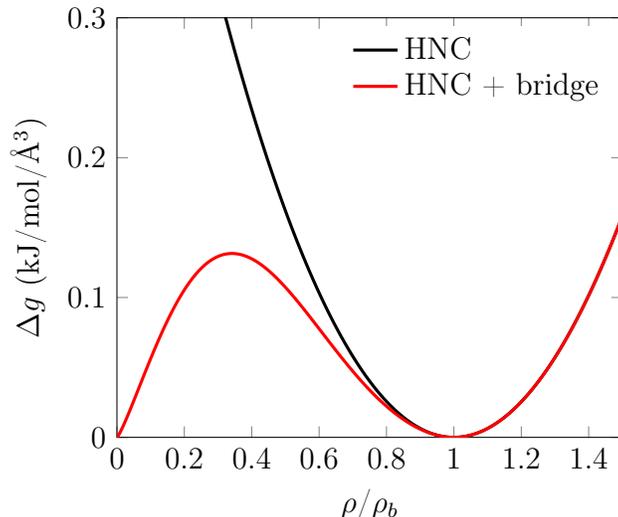


Figure 1. Predicted difference between the grand potential of homogeneous water at a given density ρ and of the grand potential of the bulk solvent at density ρ_b . For water, ρ_b would be $\rho_L = 0.033$ water molecule per \AA^3 ($\equiv 1$ kg/L at 298.15 K and 0.033 water molecule per \AA^3). In black: results from MDFT in the HNC approximation (without bridge). In red, results from MDFT with the coarse grained bridge functional proposed in this work. The narrow left local minimum of the red curve is found at $\rho_G \approx 5 \cdot 10^{-3} \rho_L \approx 0$, as expected for water.

kernel K . The choice of such kernel is mostly technical, and interested readers will find related information in the supplementary material. We end up using a Gaussian kernel with a width of 0.935\AA .

For the expression of the bridge functional, one is already constrained by (i) the liquid-gas coexistence and (ii) the connection to HNC at the homogeneous liquid density. The first condition imposes a double-well for the bulk free-energy as function of ρ , with minima at $\rho_G \simeq 0$ and $\rho_L = \rho_b$. In real water, ρ_G would correspond to a mass density of $3 \cdot 10^{-3}$ kg/L and ρ_L to 1 kg/L. As in many field theories, the height of the barrier is linked to the surface tension γ between the two phases. There is nevertheless no analytic relation between the two for our version of classical DFT, as far as we know. Our bridge was thus constructed in two parts. The first one, of order 3 in $\Delta\rho$, was chosen to impose $\mathcal{F}[\rho_G] \approx \mathcal{F}[0] = \mathcal{F}[\rho_L]$ and so to make liquid-gas coexistence possible. The second part, of order 4 in $\Delta\rho$, should enable allow variations of the height of the double-well without modifying the shape of the wells themselves. Thus we chose:

$$F_b[\bar{\rho}(\mathbf{r})] = A \int \Delta\bar{\rho}(\mathbf{r})^3 d\mathbf{r} + B \int \bar{\rho}(\mathbf{r})^2 \Delta\bar{\rho}(\mathbf{r})^4 d\mathbf{r} \quad (7)$$

where two parameters A and B are enough to sustain all criteria. The value $A = 8\pi^2 k_B T \rho_L^{-2} (1 - \frac{1}{2} \rho_L \hat{c}_{00;0}^{00}(\mathbf{k} = 0))$ is imposed by the coexistence condition, where $\hat{c}_{00;0}^{00}(0)$ is the totally spherically symmetric, mean contribution of c . B is determined using brute force try and error to get the correct surface tension of the solvent, $\gamma = 63.6$ mJ/m² for SPC/E water⁴⁹, leading to $B = 2.37 \cdot 10^{-15} k_B T \rho_L^{-5}$. The determination of A and B is discussed in great details in the supplementary material. With these we do have : the liquid-gas coexistence and incidentally correct pressure and correct surface tension. The resulting free energy curve is shown in red in figure 1. Bridge functionals built from FMT as in^{23,40,41} or from three-body weighted-densities as introduced in⁵⁰ lead to a one-parameter adjustment (the hard sphere radius or cosine prefactor) that could not fill all our requirements. The functional form in equation 7 is furthermore significantly simpler and more efficient numerically. At this point, we have a functional that is built and tuned to be consistent from the point of view of macroscopic thermodynamics. We now want to benchmark it on classical test-cases without any more parameter.

The solvation free energy per surface unit of a simple spherical hard sphere of various radii in SPC/E water is shown in figure 2. The reference all atom simulations by Hummer et al.⁵¹ are shown as black circles. Due to the computational demand of all atom molecular dynamics (or Monte Carlo) simulations, only small spheres of radius less than 4\AA have been considered by the authors. For small radii, the solvation free energy should be proportional to the volume of the sphere⁵², which is the case for both reference simulations and MDFT. MDFT results without and with the bridge functional are shown in black and red lines, respectively. The bridge functional brings a quantitative agreement with the reference simulations. For spheres whose diameter grows to more than 3 to 4\AA , that is when the interface between vacuum and water becomes flat, the solvation free energy is driven by a surface term. Indeed,

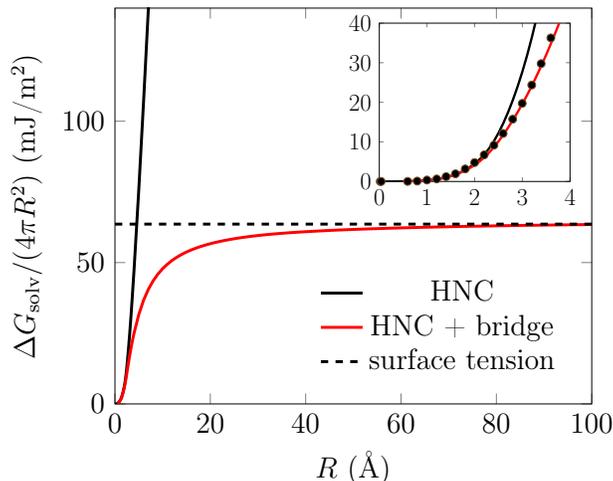


Figure 2. Free energy of hydration of a hard sphere divided by its surface, as a function of its radius. In the insert, we focus on small radii for which reference simulations by Hummer et al.⁵¹ are available (black circles). The reference surface tension of SPC/E water, $63.6 \text{ mJ}\cdot\text{m}^{-2}$, was calculated by means of all-atom simulations by Vega and Miguel⁴⁹.

due to the almost-coexistence, the pressure is almost zero in the system and cancels out the volume contribution. Consequently, the solvation free energy per surface unit of an infinitely large sphere, that is of a hard wall, tends toward the surface tension of the solvent. As described in the introduction, the inconsistent thermodynamics of the HNC approximation leads to a wrong trend, driven by the volume of the sphere. On the contrary, results corrected by the bridge functional show the good trend and the good surface tension of the solvent, that is, the correct limit at infinite radius R in figure 2. Fujita and Yamamoto assessed recently the accuracy of 3D-RISM for nano-sized solutes in water⁵³ and found significantly larger discrepancies than what is showed in figure 2. This is not surprising since 3D-RISM does not include any information about the gas phase, as shown by Sergiievskiy et al.⁵⁴.

We also calculated the solvation free energy of various realistic molecules of spherical symmetry: methane, neon, argon, krypton and xenon. Results are shown in table I. Without the new bridge functional, the solvation free energy is systematically overestimated by large errors. With the new bridge functional, the error gets down to within few kJ/mol of the experimental values. Let us recall here that the parameterization of the functional does not imply any fitting on the solvation free energies of molecules, contrarily to other bridge functionals^{15,24,39-41}. Also, once again, no pressure correction^{42,54} is needed within this new theoretical framework since the pressure of the fluid is correct.

For what concerns the solvation structure, the bridge functional improves also significantly the results, as seen in figure 3 for neon. Especially, the overestimation of the height of the first peak of the radial distribution function (rdf), a usual failure within HNC, is satisfactorily well corrected. This structuration of the water is known to decrease in case of dewetting, that is, the height of the first peak of the rdf must decrease for large hydrophobic solutes. This behaviour is well reproduced by Monte Carlo simulations, like those of Huang and Chandler⁵⁵, as shown in black circles in figure 4. Within the HNC approximation, the height of the first peak grows notably with hard sphere radius. This is also corrected by the proposed bridge functional. To our knowledge, all the bridge functionals in the litterature show spurious prepeaks for large solutes, which is not the case here. More profiles are shown in the supplementary material and lead to the same conclusion.

In the HNC approximation, MDFT overestimates the hydration free energies by dozens of kJ/mol, even for small hydrophobic compounds, as shown in table I. Our new bridge functional also reduces this error to only few kJ/mol, as it does for hard spheres of any sizes, as already shown in figure 2. The numerical cost, that is, the time to solution, is reduced by 4 orders of magnitude between the all atom simulations and the MDFT.

In order to illustrate the performance of this new level of theory on a realistic molecule made of thousands of atoms, we studied the hydration of protein 4m7g. We used both molecular dynamics (MD) and MDFT. In figure 5, we show the isosurface of high densities (precisely 3 times the bulk liquid density) as calculated by MD using a cluster for three days to gather sufficient statistics and by MDFT with our bridge functional using a laptop with sufficient memory in twenty minutes, in blue and red respectively. Simulation details and the whole procedure to extract density maps from the MD trajectories are given in supplementary materials. One sees satisfying agreement between the two density fields. The bridge functional presented here does improve much the results.

In this work, we have addressed the issue of predicting solvation free energies using the molecular density functional theory (MDFT) with a new class of bridge functionals relying on weighted densities. We recover the liquid-gas

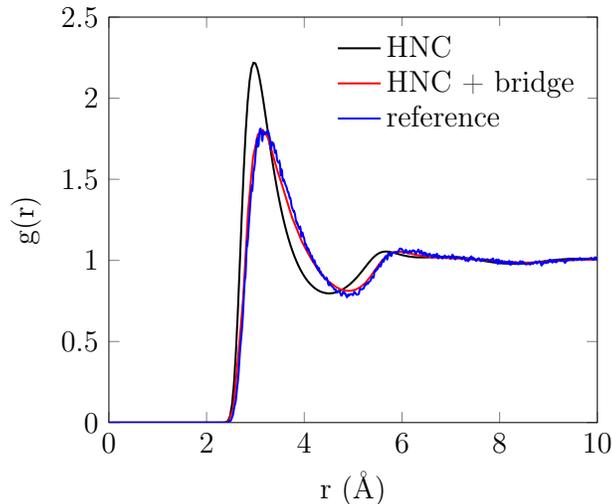


Figure 3. Radial distribution function (rdf) of neon. Those calculated by MDFT-HNC are shown in black and with the new coarse-grained bridge functional in red. The reference calculation shown in blue is done by the authors, as described in supplementary information.

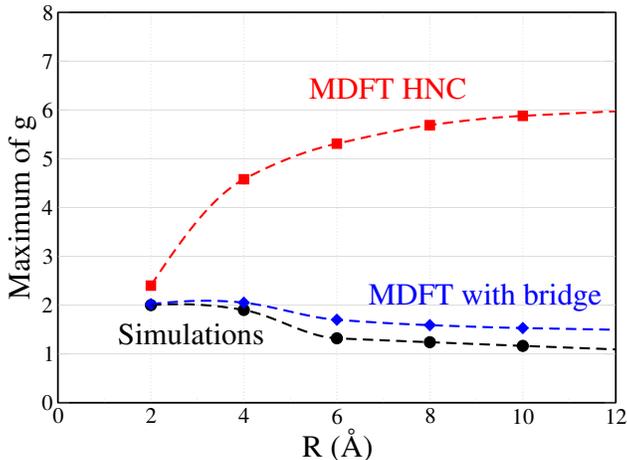


Figure 4. Height of the first peak of the radial distribution function (g) between the oxygen of SPC/E water and a hard spheres of radius 2, 4, 6, 8 or 10 Å. The reference calculations are exact Monte Carlo simulations by Huang and Chandler⁵⁵. The red and blue curves correspond to MDFT in the HNC approximation and with the new coarse-grained bridge, respectively.

	exp.	ref. sim.	HNC	HNC + bridge
Methane	8.08	8.9	27.10	12.25
Neon	10.37	11.6	18.69	11.26
Argon	8.31	8.6	22.25	10.92
Krypton	6.97	7.7	25.41	10.99
Xenon	6.06	7.3	29.72	11.26
MUE	0	2.57	23.61	3.88

Table I. Free energies of hydration in kJ/mol of methane and rare gas at 300 K and 1 atm. Experimental values can be found in Straatsma, Berendsen and Postma⁵⁶ for the noble gas and from Ben-Naim and Marcus⁵⁷ for methane. The bridge functional proposed in this work decreases the mean unsigned error (MUE) from 23.61 kJ/mol to 3.88 kJ/mol. Reference molecular dynamics simulations with thermodynamics integration have been performed by the authors and are described in the supplementary information, with error bars estimated to 0.1 kJ/mol.

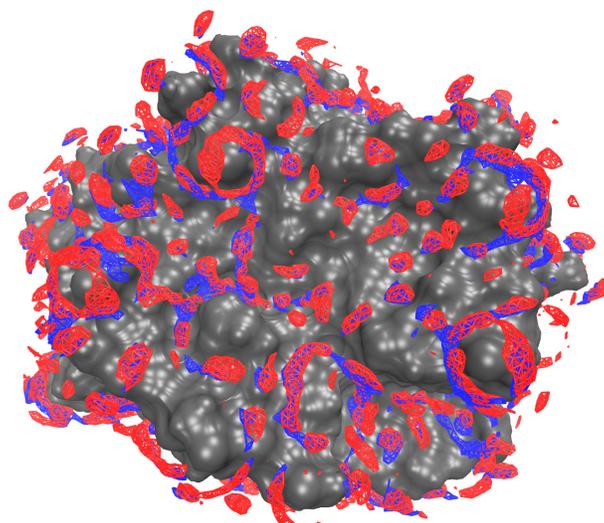


Figure 5. Hydration profile of the protein 4m7g as calculated by molecular dynamics (blue) and MDFT (red). We plot the isosurface of high density where the local water density is 3 times higher than it would be in the bulk liquid, that is, where $g = 3$.

coexistence, the correct pressure of the liquid phase, and the liquid-gas surface tension. These ingredients are critical for the most important case of water at ambient pressure and temperature. The numerical cost of the proposed coarse grained bridge functional is negligible compared to the evaluation of the HNC contribution, since it is made completely local in fourier space thanks to fast Fourier transforms. Finally and importantly, this bridge functional improves significantly the solvation profiles and solvation free energies calculated by the molecular density functional theory, at the microscopic as well as at the mesoscopic scales. This bridge functional will be a basic ingredient for the future developments of the molecular density functional theory. Especially, it will help to upscale to other methods.

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Supplementary information for “Bridge functional for the molecular density functional theory with consistent pressure and surface tension and its importance for solvation in water”

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I. OUR FUNCTIONAL

The free energy molecular density functional we minimize is

$$\mathcal{F} = \mathcal{F}_{\text{id}} + \mathcal{F}_{\text{ext}} + \mathcal{F}_{\text{HNC}} + \mathcal{F}_{\text{b}}, \quad (1)$$

which is the difference between the system made of pure liquid solvent and the system made of the solute in the solvent. In what follows, we illustrate everything in the important case of water. In the main manuscript, we give the following expression for the bridge functional:

$$F_{\text{b}}[\bar{\rho}(\mathbf{r})] = A \int \Delta\bar{\rho}(\mathbf{r})^3 d\mathbf{r} + B \int \bar{\rho}(\mathbf{r})^2 \Delta\bar{\rho}(\mathbf{r})^4 d\mathbf{r}, \quad (2)$$

where

$$\bar{\rho}(\mathbf{r}) \equiv \int d\mathbf{r}' \rho(\mathbf{r}') K(\mathbf{r} - \mathbf{r}') \quad (3)$$

is a weighted density, defined as the convolution between the local solvent density $\rho(\mathbf{r})$ and the convolution kernel K . We note ρ_{G} and ρ_{L} the densities of the homogeneous gas and liquid phases. For water, they translate to $\approx 10^{-3}$ kg/L and ≈ 1 kg/L for the gas and liquid phases, respectively. The excess (with respect to liquid) density is defined as $\Delta\rho(\mathbf{r}) \equiv \rho(\mathbf{r}) - \rho_{\text{L}}$. For what follows, we approximate the gas density to 0, that is $\rho_{\text{G}} \approx 0$. That's a good approximation for water for which the ratio between vapor and liquid density is below 10^{-3} .

A. Imposing the liquid-gas coexistence

If liquid and gas were at coexistence, which is almost the case for water at room pressure and temperature, the difference in grand potential of the two phases would be zero. In the very good approximation that the gas phase has density that tends to zero, this comes to annihilate the grand potential of the zero density limit. For what concerns the ideal part,

$$\lim_{\rho \rightarrow \rho_{\text{G}}} \mathcal{F}_{\text{id}}[\rho] = k_{\text{B}}T\rho_{\text{L}}, \quad (4)$$

where k_{B} is the Boltzmann constant and T is the temperature. There is no external contribution in the bulk fluid. For what concerns the excess part,

$$\lim_{\rho \rightarrow \rho_{\text{G}}} \mathcal{F}_{\text{exc}}[\rho] = -\frac{k_{\text{B}}T}{2} \rho_{\text{L}}^2 \hat{c}_{00;0}^{00}(0), \quad (5)$$

where $\hat{c}_{00;0}^{00}(0)$ is the totally spherically symmetric, mean contribution of the direct, pair correlation function of the bulk fluid. The detailed calculation of this value has been published recently by Belloni for SPC/E water¹. This value is directly linked to the isothermal compressibility². Plugging equations 4, 5 and 2 into 1 and cancelling 1, we have

$$A = k_{\text{B}}T8\pi^2 \frac{1}{\rho_{\text{L}}^2} \left(1 - \frac{\rho_{\text{L}}}{2} \hat{c}_{00;0}^{00}(0)\right). \quad (6)$$

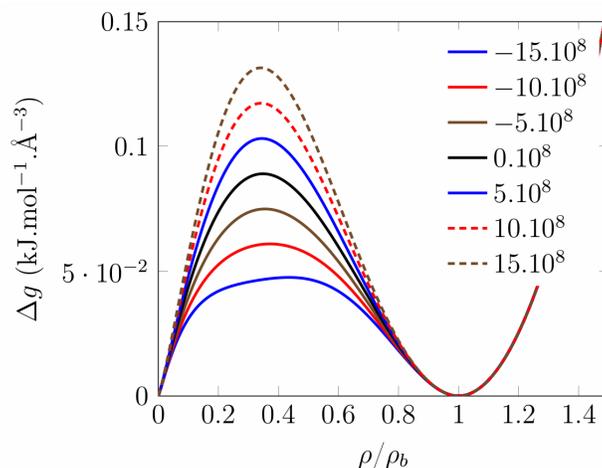


Figure 1. Influence of the parameter B of equation 2 in the difference in grand potential between the gas and liquid phases of SPC/E water. The different values of B are expressed in $\text{kJ}\cdot\text{mol}^{-1}\cdot\text{\AA}^{15}$.

B. Imposing the surface tension

The parameter B in equation 2 controls the height of the barrier between the gas and liquid phases, as illustrated in figure 1. B is chosen so that the correct liquid-gas surface tension γ is recovered. For SPC/E water, the liquid-gas surface tension γ has been measured numerically at 63.6 mJ/m^2 by Vega and Miguel³. We compute the surface tension by measuring the area-dependency of the solvation free energy of larger and larger hard spheres of radius R , that is of

$$\gamma = \lim_{R \rightarrow \infty} \frac{\Delta G_{\text{hydration}}^{\text{hard sphere}}(R)}{4\pi R^2}. \quad (7)$$

At this point, no more “semi-empirical parameters” are free in the model. Nevertheless, in equation 3, we define a weighted density where a convolution appears between the local density and the kernel. We tried heavyside and gaussian kernels. Heavysides led to poor results that are not shown therein. Even if at this point no more parameter is free, one hidden numerical parameter must be set : the gaussian distribution’s width. For each possible value of parameter B , only one gaussian width gives the right surface tension. After brute-force try and error of all possible couples of B and gaussian width, we end-up with a gaussian width $B = 2.37 \cdot 10^{-15} k_B T \rho_L^{-5}$ and a gaussian width of 0.935 \AA which also optimizes the solvation free energies, as shown in the main text.

II. REFERENCE SIMULATIONS AND FORCE FIELD PARAMETERS

In order to have reference results to compare with MDFT, we run molecular dynamics simulations. We use Gromacs⁴. Solutes are solvated in SPC/E water in a simulation box of width 20 \AA . We always follow the same, standard process : we start by minimizing the internal energy of the system. Then, the simulation runs for 1 ns at constant volume and constant temperature of 298.15 K , followed by a constant pressure simulation at 1 atm for about 2 ns . Finally, we start the production run of 100 ns from which we extract the radial distribution function(s). For computing reference solvation free energies, we use the weighted histogram approximation method (WHAM) implemented in Gromacs⁵. It needs 21 steps for a coupling parameter varying from 0 to 1 with a step of 0.05. For this free energy runs, each frame runs for 1 ns . All input files are publicly available on github⁶. The Lennard-Jones parameters used in these simulations are given in table I.

For the special case of the large protein 4m7g presented in figure 5 of the main manuscript, we use the GROMOS97 force field. Also, we froze the coordinates of each site of the protein. The density maps are extracted from snapshots every 10 ps of the 100 ns simulation. This last calculation took 2 days on a high-end workstation with 32 cpu-cores and 2 middle-end GPUs.

	σ (Å)	ϵ (kJ/mol)
methane ⁷	3.730	1.230
neopentane ⁸	6.150	3.496
neon ⁹	3.035	0.154
argon ⁹	3.415	1.039
krypton ⁹	3.675	1.405
xenon ⁹	3.975	1.785

Table I. Lennard-Jones parameters used in the molecular dynamics simulations. These parameters are mixed to SPC/E parameters by usual Lorentz-Berthelot mixing rules.

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