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Commentary

Inferring the hydrophobic interaction from the properties of neat water

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The present paper by Hummer *et al*. (1), building on previous developments in scaled-particle theory (2) and information theory (3–6) and using molecular simulations to test theoretical ideas, shows how one can predict the free energies of the hydrophobic hydration and the hydrophobic interaction of solutes composed of hard spheres from an analysis of spontaneous cavity formation in neat liquid water. Hummer *et al.* (1) dramatically extend ideas from scaled particle theory and demonstrate a simple, highly efficient approach to computing solution thermodynamic properties from either simulation or theory. This paper is a commentary on the background and the ideas presented in the paper by Hummer *et al*. (1).

The whole field of condensed matter chemistry has been greatly advanced by the power of computer simulation (7). It wasn't until the second half of the 1960s that the first molecular dynamics simulations were performed on simple molecular liquids (8, 9). Molecular simulations provide clear data for theories of liquids, allow direct tests of theoretical approximations, and often point the way to better simplifying approximations to be made in analytical theories. The present paper uses both theory and simulation data to find simple answers to an apparently complicated question. It is difficult to imagine this kind of simplicity without the extensive development of simulation techniques that have gone before.

Water has been studied with simple force fields (10) since the 1970s, and the solubility of inert gases in water has been modeled by treating the inert gas atom as a hard sphere that excludes the center of the water molecule from a region around it (11). Studies of such systems give insight into "hydrophobic hydration," the reorganization of water structure around the hard sphere, as well as the free energy of hydration of the sphere. More realistic solute–solvent interactions can then be treated by statistical perturbation (12) theory using the hard sphere reference system. Such an approach was pioneered by Pratt and Chandler (11). When two hard spheres of type A are dissolved in water, there is a solvent-induced force driving the spheres into association. This is the so-called "hydrophobic interaction." The free energy change, $W(R)$, on bringing the two spheres together from infinity to a separation R, called the potential of mean force (pmf), is related to the radial distribution function of the two spheres, $g_{AA}(R)$, through the relation (12, 13)

$$W(R) = -kT \ln g_{AA}(R).$$

Likewise, the methylene groups in n-butane can be approximated by spheres and one can define a potential of mean force, $W(\phi)$, for changing the torsion angle from the transconformation ($\phi = 0$) to any other angle. In that case, the pmf is related to the probability distribution of the torsion angle $s(\phi)$ through the relation (12, 14, 15)

$$W(\phi) = -kT \ln s(\phi).$$

In 1977, Pratt and Chandler (11) presented a semiempirical theory of hydrophobic hydration and the hydrophobic interaction of hard spheres. From experimental measurements of the oxygen–oxygen radial distribution function, they determined both the free energy of hydration of one hard sphere solute and the pmf of two hard spheres and predicted that the pmf would exhibit two minima: one corresponding to the contact pairing, and the other corresponding to a solvent separated pairing. They also showed that the solvent-separated pair was more probable than the contact pair, a result distinctly at odds with the prevailing intuitive view of that time. Pratt and Chandler (11) also extended the theory to include the more realistic van der Waals interactions between the solute sphere and the water molecules. The theoretical hydration free energies when corrected for the attractive solute–solvent interaction were in good agreement with experiment (11). Based on this, the results for the pmf were thought to be accurate even though there were no measurements of this property at that time.

Shortly after the appearance of the Pratt and Chandler work, Pangali *et al.* (16, 17) performed computer simulations of inert gas atoms in water and corroborated the main findings of the Pratt and Chandler paper (11). This, the first simulation of the full potential of mean force for the solute pair, showed that the solvent-separated pair corresponded to a intersolute distance such that the water could form two fluctuating clathrate cages around the pair with a hydrogen bond in the plane bisecting the intersolute position vector. It also showed that the solvent-separated pair was indeed more probable than the contact pair. Many papers subsequently confirmed and extended these findings (18, 19). The pmf of n-butane was also determined by simulation where it was found that water shifted the conformational equilibrium towards the gauche conformer (15, 20, 21).

The hard sphere model of the solute is a useful model for understanding the essential features of hydrophobicity, as shown by Pratt and Chandler (11). In the hard sphere model, the solute merely excludes water molecules from a region called the "excluded volume." For example, if the solute consists of one hard sphere of radius R_A, the center of no water oxygen atom can get closer to it than $\lambda = R_A + R_W$, where R_W is the radius of the water molecule. The solute thus defines an excluded volume $\Delta v(\lambda) = 4\pi\lambda^3/3$. The reversible work required to introduce this cavity into the solvent, $\Delta\mu^{ex}(\lambda)$, is the excess free energy of hydration of the hard sphere (2). When two hydrated hard spheres are brought from infinite separation $R \to \infty$ to a separation R closer than the correlation length of the spatial correlations in pure water, the solvent begins to reorganize further. For each pair separation, R, the excluded volume $\Delta v(R; \lambda)$ will then depend on R. The reversible work (or potential of mean force), $W(R; \lambda)$, required to bring the spheres from $R \to \infty$ to a distance R can be related to the reversible work to create two spherical cavities separated by R, $W(R; \lambda) = \Delta\mu^{ex}(R; \lambda) - \Delta\mu^{ex}(R \to \infty; \lambda)$. Because each solute sphere orders neighboring water molecules, the two hard spheres will order more water molecules in their first solvent shells when they are distantly separated than when they are in contact. It is thus expected that $W(R)$ will exhibit a global minimum when the hard spheres are in contact. Thus, there should be an entropic driving force that induces the two hard spheres to be in contact. This solvent-induced driving force is the so called hydrophobic interaction.

Similarly, the hard sphere model of butane will have an excluded volume $\Delta v(\phi, \lambda)$, which is a function of the torsion angle ϕ and depends on the exclusion radius λ of the methylene spheres. Then the part of the pmf arising from the solute-solvent interaction will be related to the reversible work required to create a cavity with the shape and excluded volume $\Delta v(\phi, \lambda)$ of the n-butane molecule.

In the simulation literature, the method usually used to compute the hydration free energy is based on thermodynamic perturbation theory. In this method, the solute solvent potential is turned on by small steps and the change is computed in free energy corresponding to each growth step. This method requires one to redo the simulation for each different solute. Pratt and Pohorille (22, 23) showed that there is a much better alternative for hard sphere solutes. The basic approach comes from the scaled particle theory first introduced by Reiss *et al.* (2). One simulation of pure (or neat) water can be analyzed to determine the likelihood, $p_0(\lambda)$, that cavities of size equal to or greater than λ will exist at an arbitrary point in the neat solvent such that a hard sphere solute of radius R_A could be inserted. From this point of view, $p_0(\lambda)$ is the probability that no solvent molecules will be found in cavities equal to the excluded volume. This is accomplished by analyzing each neat water configuration generated in the simulation to determine the distribution function of cavities of all different sizes. Thus, in one simulation one can determine the probabilities of insertion of any kind of cavity, just so long as the volume of the system simulated is sufficiently large compared to the cavities (and thus the hard sphere solutes) of interest. In scaled particle theory, it is shown that

$$p_0(\lambda) = e^{-W(\lambda)/kT}, \qquad \textbf{[1]}$$

where $W(\lambda) = \Delta\mu^{ex}(\lambda)$ is the reversible work required to form the cavity, and

$$W(\lambda) = \Delta\mu^{ex}(\lambda) = -kT \ln p_0(\lambda). \qquad \textbf{[2]}$$

Thus, in principle, an analysis of fluctuations in occupation numbers in regions of size and shape of the excluded volume in neat water can be used to determine free energies of solvation and potentials of mean force for hard spheres in solution.

Pratt and Pohorille (22, 23) were the first to show that, from the study of transient cavity formation in neat water by molecular dynamics, they could determine $p_0(\lambda)$ and $W(\lambda)$. In a set of important papers, they were able to clarify the differences between solubility in water and solubility in non-associated liquids like hexane. They found that the sizes of cavities are more sharply defined in liquid water than in corresponding nonassociated liquids despite the fact that the most probable cavities are about the same size in these two different kinds of liquids.

Another property from scaled particle theory (2) is

$$\rho G(\lambda) = \frac{1}{4\pi\lambda^2 kT}\frac{\partial W(\lambda)}{\partial \lambda}, \qquad \textbf{[3]}$$

where $\rho G(\lambda)$ is the number density of water at the surface of the excluded volume. For small cavities, this density approaches that of liquid water, whereas Stillinger (24) has shown that this density approaches the equilibrium vapor density of water when the cavity becomes much larger than a single water molecule. Water molecules are expelled from a region near the surface of the large cavity. This dewetting is caused by the strain in the hydrogen bonding network for large solutes. Small solutes can neatly fit into a clathrate cage without distorting the network but as the cavity size is increased strain develops. Pratt and Pohorille (22, 23) have shown that the "squeezing force" due to this strain in the hydrogen bond network reaches a maximum near cavity diameters of 2.4 Å.

Scaled particle theory shows (2) that p_0 can also be expressed as

$$p_0(\lambda) = \sum_{j=0}^{\infty}(-1)^j\left\langle\frac{n!}{j!(n-j)!}\right\rangle = 1 - \langle n\rangle + \frac{1}{2!}\langle n(n-1)\rangle + \ldots, \qquad \textbf{[4]}$$

where n is the number of water molecules in neat water that are found in a region of geometry and volume equal to the excluded volume of the solute. These quantities can also be evaluated from the neat solvent configurations.

One can also define the probability p_n that n water molecules can be found in a region of the shape of the excluded volume. The first two binomial moments appearing in Eq. **4** can be obtained from theoretical, experimental, or computer simulated results for the radial distribution function $g_{OO}(r)$,

$$\langle n\rangle = \sum_{n=0}^{\infty} n p_n = \rho\Delta v, \qquad \textbf{[5]}$$

$$\langle n(n-1)\rangle = \sum_{n=0}^{\infty} n(n-1)p_n = \rho^2\int_{\Delta v} d^3r_1 \int_{\Delta v} d^3r_2 g_{OO}(|r_2 - r_1|), \qquad \textbf{[6]}$$

but higher moments like

$$\langle n(n-1)(n-2)\rangle = \sum_{n=0}^{\infty} n(n-1)(n-2)p_n = \rho^3\int_{\Delta v} d^3r_1\int_{\Delta v} d^3r_2\int_{\Delta v} d^3r_3 g^{(3)}_{OO}(r_1, r_2, r_3) \qquad \textbf{[7]}$$

can only be calculated accurately from computer simulations.

No matter how small the cavity it can always accomodate at least the oxygen site of one water molecule but it may be too small to accomodate two water molecules. Then $p_0 = 1 - \langle n\rangle$. As the cavity is made larger, one gets to a volume where no more than two water molecules will fit and $p_0(\lambda)$ will be determined by only the first two moments $\langle n\rangle$ and $\langle n(n-1)\rangle$. Then the only information needed for the determination of $p_0(\lambda)$ and $W(\lambda)$ is ρ and $g_{OO}(R)$. For larger cavities, higher moments and higher order correlation functions will be required (for example, see Eq. **7**). Thus, for small enough cavities, only information about ρ and $g_{OO}(R)$ will be needed. Nevertheless, it was not known how to use this information to determine p_0.

The current paper by Hummer *et al.* (1) presents a very simple information theoretic method for determining $p_0(\lambda)$ and thereby $\Delta\mu_{ex}(\lambda)$ and $W(R)$ for solute molecules made up of hard spheres from information about fluctuations in pure (or neat) liquid water. This paper goes beyond scaled particle theory and provides information about the set of probabilities p_n in neat water defined above. Hummer *et al.* (1) posit a default model of the probabilities $\{\hat{p}_n\}$ and compute the information gained on determining the real probabilities $\{p_n\}$. This information is

$$\eta = -\sum_{n=0}^{\infty} p_n \ln \frac{p_n}{\hat{p}_n}. \qquad \textbf{[8]}$$

To compute the probabilities $\{p_n\}$, one maximizes η subject to normalization and various binomial moments of the probabilities $\{p_n\}$ such as the moments $\langle n \rangle$, $\langle n(n-1) \rangle$, and higher moments that appear in Eq. **4.**

Three default models are suggested but the one that was used is that of uniform probabilities $\hat{p}_n$ = constant. Maximizing η subject to normalization and knowledge of the two moments $\langle n \rangle$ and $\langle n(n-1) \rangle$ then gives

$$p_n = \exp[\lambda_0 + \lambda_1 n + \lambda_2 n^2], \qquad \textbf{[9]}$$

where the constants λ_0, λ_2, and λ_3 are determined from the computed moments. From this the free energies of solvation are determined.

Hummer *et al.* (1) show that this simple information theoretic model gives excellent agreement with computer simulation for the probabilities $\{p_n\}$ and for the free energy and the pmf for hard spheres for spheres smaller than approximately 3.2 Å in diameter. This is a remarkable result for several reasons.

1. It shows how the lower order binomial moments given by Eqs. **5** and **6** can be used to determine p_0 and thereby the free energies of solvation and the pmfs. We saw from Eq. **4** that the information contained in these moments should suffice for the prediction of p_0 for small cavities, but scaled particle theory did not allow us to proceed. Information theory provides the bridge.
2. It implies that the only information required for the calculation and understanding of the hydration of one and two spheres are the first two binomial moments or equivalently the bulk density and radial distribution function of neat water. This is precisely the same information required in the Pratt–Chandler semiempirical theory. For small exclusion volumes, this is expected (see above).
3. The same treatment also works, about as well, for the torsion angle dependence of the potential of mean force of *n*-butane where the methylene groups on *n*-butane are treated as hard spheres. Thus, from scant knowledge about neat water, one can determine the equilibrium constant and the transition state rate constant for gauche $\rightleftharpoons$ trans isomerization. For cavities the size of *n*-butane, one would expect that higher moments would be required, yet from the good agreement for the pmf this appears not to be the case. Why? It would be useful to see if the set of probabilities $\{p_n\}$ for *n*-butane are as accurately given by Eq. **9** as for the small spheres.
4. Since higher binomial moments moments are determined by three, four, and higher order correlation functions of water, we learn that these higher correlations are not important for the hydration of atomic-sized hydrophobic spheres. This should be checked carefully on butane or larger spheres. Stillinger's paper (24) and the papers by Pratt and Pohorille (22, 23) would indicate that for large spheres the hydrogen bond network is strained and one must carefully account for the higher-order correlations.

Hummer *et al.* (1) discuss the interesting connection between the current theory and the earlier Pratt–Chandler theory. As they point out, Chandler (25) has shown that the Pratt–Chandler theory, as well as many of the standard theories of dense fluids, follow from a Gaussian field theory for density fluctuations. The near parabolic behavior of $\{\ln p_n\}$ in figure 1 of Hummer *et al.* (1) appears to be consistent with a Gaussian model. One expects a Gaussian field theory to be good for long wavelength fluctuations but not for small wavelength fluctuations. If one uses the parabolic nature of ln p_n for small spherical regions as a measure of the accuracy of the Gaussian field theory, one would conclude that this theory is good for small wavelength fluctuations as well. This is a remarkable observation. Why should it be so? It is worth making more explicit tests based on simulations of the Gaussian property of the density fields.

Chandler shows that the Gaussian field theory does not account for interfacial phenomena, such as the dewetting of large spheres. The relation of the Pratt–Chandler theory of hydrophobicity and the present two moment information theory to Gaussian field theories suggests that neither predicts the kind of dewetting transition around large spheres noted by Stillinger (24). Wallqvist and Berne (26) have also observed a dramatic dewetting transition as two parallel oblate ellipsoids are brought together. In fact, Hummer *et al.* (1) already detect a deviation from parabolic behavior for spheres of diameter $d > 3.2$ Å. In real systems, there is a dewetting transition in which solvent is excluded from a layer around the surface of the excluded volume. Hummer and colleagues recognize this and probably are thinking of ways of introducing this effect into information theory. Clearly much remains to be done with respect to this problem

The paper of Hummer *et al.* (1) is a very interesting and important paper for it uncovers possible simplifications that could be fundamental in treating the structure and thermodynamics of the hydrophobic interaction. It shows how simulations of spontaneous cavity formation in neat water can be used to generate the solution thermodynamics of small hydrophobic hard sphere solutes. It shows that the only information required for these predictions is the bulk density and oxygen–oxygen radial distribution function of neat water. The big jump here is the demonstration that information theory allows one to compute these thermodynamic properties from only a few binomial moments. It now becomes a simple matter to predict important solution properties of hard sphere hydrophobic solutes.

One attractive byproduct of this paper is that it may lead to the invention of simple efficient methods for determining hydration free energies and pmfs for realistic solute-solvent force fields from computer simulation of neat liquid water, experiments or integral equation theories of the structure of water. For this to happen, it is necessary to show how the results for small hard-sphere solutes can be corrected for realistic soft force fields. In some cases simple corrections, like those in the Pratt–Chandler (11) theory, will suffice. More serious is the need to handle larger solute particles where there is partial dewetting. It may then be necessary to include higher binomial moments (or equivalently many-body correlation functions) as well as building in the kinds of spatial correlations that lead to dewetting.

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