The application of the integral equation theory to study the hydrophobic interaction

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The Wertheim's integral equation theory was tested against newly obtained Monte Carlo computer simulations to describe the potential of mean force between two hydrophobic particles. An excellent agreement was obtained between the theoretical and simulation results. Further, the Wertheim's integral equation theory with polymer Percus-Yevick closure qualitatively correctly (with respect to the experimental data) describes the solvation structure under conditions where the simulation results are difficult to obtain with good enough accuracy. © 2014 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4858398>]

I. INTRODUCTION

Hydrophobic interaction refers to the solvent-mediated attraction between two hydrophobic particles in water.¹ It plays a central role in numerous chemical, physical, and biological phenomena, such as protein folding and various self-assembly processes. The strong dependence of hydrophobic interaction on the external conditions (e.g., temperature, pressure, salt) is reflected in processes such as cold and pressure protein denaturation.

Hydrophobic interaction between a pair of solutes is best described by their potential of mean force (PMF), i.e., the free energy needed to bring two hydrated solutes from infinity to a certain distance. It has been established long ago that PMF between two solute particles exhibits two distinct minima corresponding to contact (CC) and solvent-separated configuration (SSC).^{2–4} The effect of temperature,^{5,6} pressure,^{7–9} solute concentration,¹⁰ solvent polarization,¹¹ and solvent-solvent interactions¹² on the structure of PMF has been reported. A lot can be learned from PMFs accompanying functions, namely, enthalpy, entropy, and heat capacity change for bringing two solutes from infinity to a certain distance.^{13–18} The (anti)cooperativity of hydrophobic interaction due to its many-body nature has been studied by Shimizu,^{19,20} while others examined the effect of temperature, pressure, solute size, and salt on many-body interaction between the hydrophobes.^{21,22}

Most of the above-mentioned work has been done with molecular dynamics simulations of popular water models (SPC, TIP). Southall and Dill²³ took the opposite approach and studied the PMF between two hydrophobes within the simple water model, namely, Ben-Naim's two-dimensional water model often referred to as Mercedes-Benz (2D MB) water model. Urbic *et al.*²⁴ applied the Wertheim integral equation theory (IET) to the same model to obtain the solute-solute pair distribution functions (PDFs), which are directly related to the PMFs via: $\text{PMF}(r) = -k_B T \ln g(r)$. More recently, Dias *et al.*²⁵ used the three-dimensional (3D MB) and slightly modified version of the model, as well as 2D MB and TIP4P water model²⁶ to study the PMF between two hydrophobic solutes.

To extract the correct thermodynamic functions, such as enthalpy, entropy, and heat capacity change, from the PMFs, a high numerical accuracy of the functions is required, which is, especially for more refined models and large solutes, difficult to obtain via computer simulations. Here, we present an alternative approach, the IET, to study the hydrophobic interaction within the simple 3D MB water model, which was shown to capture the essential physics of hydrophobic hydration, namely, the van der Waals interaction and hydrogen bonding.^{27–34} We compared the theoretical PMFs with the exact PMFs obtained through the Monte Carlo (MC) simulations of the same model. The main advantage of such theories like IET is that they are computationally much cheaper than direct simulations, enabling us to explore much wider range of parameters in the same time. We explored the temperature, pressure, and solute size dependence of hydrophobic interaction.

The paper is organized as follows: after above-given introduction we describe the 3D MB water model in Sec. II. Details about the MC protocol are given in Sec. III while in Sec. IV we present IET approach. In Sec. V, we discuss the results from the theory and computer simulations and in Sec. VI we briefly summarize the work.

II. 3D MB WATER MODEL

Although a modified 3D MB water is known to reproduce the properties of the bulk water even better,³⁵ the original 3D MB water model was chosen in this work, mostly due to its simplicity, and for the consistency with previous work.³⁶

The description of the model was in details given in Ref. 36. To avoid unnecessary repetition, only the main features are presented here. A water molecule within the 3D MB model is represented as a Lennard-Jones (LJ) particle with an additional orientationally dependent potential that tries to mimic the hydrogen-bonding of real water.³⁷ The interaction potential between two water molecules is

$$U(\mathbf{X}_i, \mathbf{X}_j) = U_{LJ}^{11}(r_{ij}) + U_{HB}(\mathbf{X}_i, \mathbf{X}_j), \quad (1)$$

where r_{ij} is the distance between the centres of particles i and j and $\mathbf{X}_i$ is vector denoting position and orientation of particle i . U_{LJ}^{mn} is modified Lennard-Jones potential

$$U_{LJ}^{mn}(r_{ij}) = \begin{cases} 4\epsilon_{LJ}^{mn} \left[\left(\frac{\sigma_{LJ}^{mn}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{LJ}^{mn}}{r_{ij}} \right)^6 \right], & \text{if } \sigma_{LJ}^{mn} < 0.85r_{HB} \\ 4\epsilon_{LJ}^{mn} \left[\left(\frac{\sigma_{LJ}^{mn'}}{r_{ij}'} \right)^{12} - \left(\frac{\sigma_{LJ}^{mn'}}{r_{ij}'} \right)^6 \right], & \text{if } \sigma_{LJ}^{mn} \geq 0.85r_{HB} \end{cases}, \quad (2)$$

where ϵ_{LJ}^{mn} denotes the well-depth and σ_{LJ}^{mn} is the contact parameter, m is 1 if i th particle is water or 2 if it is solute and the same applies for n . Using this potential we got rid of artificially exaggerated potential well around big solutes. As the size of the solute increases, the width of the attraction well would grow unreasonably large with standard Lennard-Jones potential. The hydrogen-bonding (HB) term is the sum of interactions over all possible pairs of HB arms

$$U_{HB}(\mathbf{X}_i, \mathbf{X}_j) = \sum_{k,l}^4 U_{HB}^{kl}(r_{ij}, \mathbf{\Omega}_i, \mathbf{\Omega}_j), \quad (3)$$

where $U_{HB}^{k,l}$ is the interaction between HB arms k and l on two particles, and vector $\mathbf{\Omega}_i$ denotes the orientation of particle i . The interaction between two HB arms of different particles is

$$U_{HB}^{kl}(r_{ij}, \mathbf{\Omega}_i, \mathbf{\Omega}_j) = \epsilon_{HB} G(r_{ij} - r_{HB}) G(\mathbf{i}_k \mathbf{u}_{ij} - 1) G(\mathbf{j}_l \mathbf{u}_{ij} + 1). \quad (4)$$

Here, $\mathbf{u}_{ij}$ is the unit vector pointing from particle i to particle j , $\mathbf{i}_k$ is the unit vector representing arm k on particle i , and $G(x)$ is unnormalized Gaussian function

$$G(x) = e^{-x^2/2\sigma^2}. \quad (5)$$

We used the following values for parameters: $\epsilon_{LJ}^{ww} = 0.05|\epsilon_{HB}|$ and $\sigma_{LJ}^{ww} = 0.7r_{HB}$, where $\epsilon_{HB} = -1$, and $r_{HB} = 1$. All thermodynamic quantities were expressed in reduced units normalized to $|\epsilon_{HB}|$ and r_{HB} : $T^* = k_B T / |\epsilon_{HB}|$, $U^{EX*} = U^{EX} / |\epsilon_{HB}|$, $V^* = V / r_{HB}^3$, and $P^* = P r_{HB}^3 / |\epsilon_{HB}|$. All distances were expressed in r_{HB} . The value of parameter σ in Eq. (5) was chosen to be 0.085 as in other studies of this model.^{25,35,37}

The nonpolar solutes are modeled as Lennard-Jones particles without hydrogen-bonding arms, interacting with the water molecule through the potential described by Eq. (2). The parameters for LJ potential were obtained using the standard Lorentz-Berthelot rules. The well-depth was taken to be $\epsilon_{LJ}^{ws} = \epsilon_{LJ}^{ss} = 0.05|\epsilon_{HB}|$ in all cases while contact parameters, σ_{LJ}^{ws} and σ_{LJ}^{ss} , were varying.

III. MONTE CARLO SIMULATION

We performed isothermal-isobaric (NPT) Monte Carlo simulations of $N = 1000$ 3D MB particles and one solute (LJ) particle that was fixed at the centre of the box. The periodic boundary conditions and minimum image convention were applied.³⁹

After equilibration run consisting of 2×10^6 MC cycles ($N + 1$ displacements and rotations) the PMFs were collected in production runs, during which we performed Widom's particle insertion method to compute the solute-solute PMFs.³⁹ Production runs consisted of 1.8×10^6 MC cycles. Every 2

MC cycles we made N Widom's insertions to compute the excess chemical potential, μ_{EX} , and 50 insertions for each hydrophobe-hydrophobe distance from the central solute (to obtain the excess chemical potential at each solute-solute distance, $\mu_{EX}(r)$). Excess chemical potential was computed via standard Widom relation, namely,³⁸

$$\beta\mu_{EX} = -\ln \langle e^{-\beta\epsilon} \rangle, \quad (6)$$

where ϵ is the interaction energy of inserted particle and the averaging is performed over the system containing N 3D MB particles and one fixed hydrophobe, and

$$\beta\mu_{EX}(r) = -\ln \langle e^{-\beta\epsilon(r)} \rangle, \quad (7)$$

where $\epsilon(r)$ is the interaction energy of particle inserted at the distance r from the central hydrophobe. Again the averaging is performed over the system of N 3D MB particles and one fixed hydrophobe. By definition PMF equals

$$\text{PMF}(r) = \mu_{EX}(r) - \mu_{EX}. \quad (8)$$

We ensured that computed PMFs were all well converged. In some cases we were, due to bad statistics of Widom's method, forced to perform direct simulations of solutions, i.e., MC simulations of 10 LJ solutes and 1000 3D MB particles, in order to obtain solute-solute PMFs.

IV. INTEGRAL EQUATION THEORY

To give information about mutual correlations of fluid particles, it is necessary to use the integral equation theory.⁴⁰ In this work, we extend the orientationally averaged version of the Wertheim's multidensity Ornstein-Zernike (WOZ) equation and the polymer Percus-Yevick (PPY) closure⁴⁰⁻⁴² to a mixture of 3D MB water molecules and LJ spheres which is a straightforward matrix generalization to mixtures. In the orientationally averaged version of the WOZ integral equation, the positions of bonding arms of a molecule are not fixed relative to each other. The intramolecular angles can assume random values between the arms. A similar approximation is built into the thermodynamic perturbation theory, where the reference system with spherical symmetry is used.³⁶

The WOZ equation can be written in k space in form

$$\hat{\mathbf{h}}(k) = \hat{\mathbf{c}}(k) + \hat{\mathbf{c}}(k)\boldsymbol{\rho}\hat{\mathbf{h}}(k). \quad (9)$$

$\hat{\mathbf{h}}(k)$ and $\hat{\mathbf{c}}(k)$ are the matrices whose elements are the Fourier transforms of the partial total correlation functions $h_{ij}(r)$ and direct correlation functions $c_{ij}(r)$, respectively. We use partial correlation functions which remain finite upon decrease of the temperature.⁴³ Furthermore, $\boldsymbol{\rho}$ is the matrix containing the partial densities. Here, we restrict ourselves to the so-called "ideal network" approximation.^{41,42} This means that we neglect the component of the correlation that is responsible for the formation of the ring-like structures.⁴² By taking into account the equivalence of the bonding arms, we have

$$\hat{\mathbf{z}}(k) = \begin{bmatrix} \hat{z}_{00}^{11}(k) & \hat{z}_{01}^{11}(k) & \hat{z}_0^{12}(k) \\ \hat{z}_{10}^{11}(k) & \hat{z}_{11}^{11}(k) & \hat{z}_1^{12}(k) \\ \hat{z}_0^{21}(k) & \hat{z}_1^{21}(k) & \hat{z}^{22}(k) \end{bmatrix}, \quad (10)$$

$$\rho = \begin{bmatrix} \rho_1 & 4\rho_1 & 0 \\ 4\rho_1 & 12\rho_1 & 0 \\ 0 & 0 & \rho_2 \end{bmatrix}. \quad (11)$$

Lower indices denote the state of the MB molecules (0 for unbonded, and 1 for bonded), the upper indices denote the molecule (1 for a MB molecule, and 2 for a solute), z stands for either the h or c correlation function, and ρ is the matrix containing the partial densities. The coefficients 4 and 12 in matrix ρ result from the reduction of the dimensionality of the WOZ equation. In order to solve Eq. (9), an appropriate additional (closure) relation between total, h , and direct correlation function, c , is needed. In the present study, the polymer Percus–Yevick closure,⁴⁰ which is good for system with short range association interactions,^{24,43} is used

$$c_{ij}^{11}(r) = f_{LJ}^{11}(r)(t_{ij}^{11}(r) + \delta_{i0}\delta_{j0}) + \delta_{i1}\delta_{j1}x_1^2\bar{f}_{HB}(r)e_{LJ}^{11}(r)[t_{00}^{11}(r) + 1], \quad (12)$$

$$c_i^{12}(r) = f_{LJ}^{12}(r)(t_i^{12}(r) + \delta_{i0}), \quad (13)$$

$$c_i^{21}(r) = f_{LJ}^{21}(r)(t_i^{21}(r) + \delta_{i0}), \quad (14)$$

$$c^{22}(r) = f_{LJ}^{22}(r)(t^{22}(r) + 1), \quad (15)$$

where $t^{kl}(r) = h^{kl}(r) - c^{kl}(r)$, x_1 is the fraction of 3D MB particles not bonded at one arm, $f_{LJ}^{kl}(r) = e_{LJ}^{kl}(r) - 1$, and $e_{LJ}^{kl}(r) = \exp[-\beta U_{LJ}^{kl}(r)]$, and δ_{ij} is Kronecker delta. Furthermore, $\bar{f}_{HB}(r)$ is the orientationally-averaged Mayer function for the hydrogen-bond potential, and x_1 follows from mass-action law

$$x_1 = \frac{1}{1 + 4\rho_1 x_1 \Delta}. \quad (16)$$

ρ_1 is the density of water molecules, and Δ is defined by^{40,44}

$$\Delta = 4\pi \int g_{00}^{11}(r)\bar{f}_{HB}(r)r^2 dr. \quad (17)$$

The pair distribution function $g^{ij}(r)$ is calculated via the relations

$$g^{11}(r) = g_{00}^{11}(r) + 4g_{01}^{11}(r) + 4g_{10}^{11}(r) + 16g_{11}^{11}(r), \quad (18)$$

$$g^{12}(r) = g_0^{12}(r) + 4g_1^{12}(r), \quad (19)$$

where $g_{ij}^{11}(r) = h_{ij}^{11}(r) + \delta_{i0}\delta_{j0}$ and $g_i^{12}(r) = h_i^{12}(r) + \delta_{i0}$.

V. RESULTS AND DISCUSSION

We start our study by comparing the water-water PDFs. The results for different temperatures (a) $T^* = 0.16$, (b) $T^* = 0.20$, and (c) $T^* = 0.30$ are shown in Figure 1. The MC results are shown by symbols, and the lines represent the results of the IET. In all cases studied here, the agreement between the IET and the MC calculations is excellent, indicating that the “ideal network” approximation built into the IET is a good choice for the systems studied. The IET properly describes the water structure development with the decreasing temperature. Only at the lowest temperature studied the IET predicts slightly less structured water at large distances.

FIG. 1. The water-water PDF at (a) $T^* = 0.16$, (b) $T^* = 0.20$, and (c) $T^* = 0.30$. The Monte Carlo results are presented by symbols and the IET results by continuous line. Pressure for all temperatures is $P^* = 0.12$.

Next, we focus on the hydrophobic interaction itself. First, we examined the water structure around hydrophobic particles. It has been shown previously^{25,45} that water molecules around hydrophobic solutes are more ordered than bulk water. We therefore examined the description of the hydration shells as given by the solute-water PDFs. The PDFs for a water-like size solute ($\sigma_{LJ}^{ss*} = 0.7$) are for different temperatures, i.e., (a) $T^* = 0.15$, (b) $T^* = 0.20$, and (c) $T^* = 0.30$, shown in Figure 2 ($P^* = 0.12$). Again, the Monte Carlo results are represented by symbols, and the IET results are shown by lines. As for the water-water PDFs described above, excellent agreement between the theory and simulation is obtained for all the cases studied. The first peak in the solute-water PDF decreases with increasing temperature, indicating weaker hydration shell in hot water. The trend is very well captured by the IET. A similar excellent agreement between the IET and computer simulation results was obtained for somehow larger solute ($\sigma_{LJ}^{ss*} = 1.5$) for which the results are shown in the supplementary material.⁴⁶

The main focus of this work was to examine the potential of mean force between two hydrophobic particles. It has been established previously^{2,23} that the hydrophobic interaction between two small hydrophobic solutes is attractive, and

FIG. 2. The solute-water PDF at (a) $T^* = 0.15$, (b) $T^* = 0.20$, and (c) $T^* = 0.30$. The Monte Carlo results are presented by symbols and the IET results by continuous line. Pressure for all temperatures is $P^* = 0.12$. Size of solute is $\sigma_{LJ}^{ss*} = 0.7$.

their solubility decreases upon increasing temperature due to stronger correlations.^{13,25,47} Figure 3 is showing the potential of mean force between two small solutes ($\sigma_{LJ}^{ss*} = 0.7$) for different temperatures at $P^* = 0.12$. Except in the case of the lowest temperature studied (i.e., 0.15), excellent agreement between the two methods is obtained. One can see that both methods predict very small change in the first minimum in the PMF with temperature, which is in contrast with previous studies, where the depth of the contact minimum pronouncedly increases with increasing temperature.^{13,25,47} The possible reason for this is the relative low pressure.³⁶ Since the phase diagram of the 3D MB water is not known, we cannot directly compare our results with those of more refined models. However, both methods predict the same behavior, indicating the correct application of the theory. Similar good agreement between the two methods was obtained for larger solutes ($\sigma_{LJ}^{ss*} = 1.5$), as well as for other pressures (see the supplementary material⁴⁶).

From previous studies using the IET,^{24,43} it has been established that the theory fails to predict the correct solute-solute pair correlation functions at low temperatures and high density of water. We checked how IET is doing at high pres-

FIG. 3. The solute-solute PMF at (a) $T^* = 0.15$, (b) $T^* = 0.20$, and (c) $T^* = 0.30$. The Monte Carlo results are presented by symbols and the IET results by continuous line. Pressure for all temperatures is $P^* = 0.12$. Size of solute is $\sigma_{LJ}^{ss*} = 0.7$.

ures and at low temperatures for this particular model. This comparison is presented in Figure 4. We can see that IET is doing rather well for small solutes, while for large solutes, the discrepancies at these conditions become rather large: the theory underestimates the correlations between the hydrophobic particles. Similar discrepancies have been previously observed when studying the nonadsorbing polymer liquids by IET method using the PY approximation.^{48,49} We speculate that a possible improvement would be to use the hypernetted-chain (HNC) closure.

As already mentioned in the Introduction, one of the main advantages of the integral equation theory compared to the computer simulations is its numerical accuracy which enables us to use the results for the potential of mean force to calculate the thermodynamics of the hydrophobe-hydrophobe interaction. Following the idea of Dias *et al.*,²⁵ we have calculated the ΔH , ΔS , and Δc_p from the PMFs obtained via IET at different temperatures ($P^* = 0.12$), using the numerical derivation. The results for two small solutes ($\sigma_{LJ}^{ss*} = 0.7$) are shown in Figure 5, and the results for somehow larger solutes ($\sigma_{LJ}^{ss*} = 1.5$) are shown in the supplementary material.⁴⁶ While very little dependence of the ΔH on the

FIG. 4. The solute-solute PMF for different pressures and sizes of solute (a) $P^* = 0.25$, $\sigma_{LJ}^{ss*} = 0.3$, (b) $P^* = 0.25$, $\sigma_{LJ}^{ss*} = 0.7$, (c) $P^* = 0.25$, $\sigma_{LJ}^{ss*} = 1.5$, (d) $P^* = 0.40$, $\sigma_{LJ}^{ss*} = 0.3$, (e) $P^* = 0.40$, $\sigma_{LJ}^{ss*} = 0.7$, and (f) $P^* = 0.40$, $\sigma_{LJ}^{ss*} = 1.5$. The Monte Carlo results are presented by symbols and the IET results by continuous line. Temperature for all pressures is $T^* = 0.15$.

FIG. 5. Dependence of (a) potential of mean force, (b) entropy, (c) enthalpy, and (d) heat capacity on distance at $T^* = 0.14$ (red line), $T^* = 0.15$ (green line), and $T^* = 0.16$ (blue line). Size of solute is $\sigma_{LJ}^{ss*} = 0.7$.

temperature was obtained, the $T\Delta S$ increases with decreasing temperature which is consistent with previous observations,²⁵ suggesting the importance of the entropy contribution for the temperature dependence of the hydrophobic effect.

VI. CONCLUSION

We have applied the statistical-mechanical theory developed for associated fluids by Wertheim,⁴⁰ to study nonpolar solvation in the 3D Mercedes-Benz model of water. We show that the Wertheim approach captures quantitatively the properties of nonpolar solvation in hot, and also cold water. The IET properly describes the structure of the hydration water, as well as the potential of mean force between two hydrophobic particles in a large temperature and pressure range, and it only fails in describing the water structure around large solutes at low temperatures and large pressures. As such, the IET approach, which is analytical, and therefore computationally much more efficient than computer simulations, enables us to extract accurate thermodynamic parameters of hydrophobic interactions, even in the range of parameters, where computer simulations fail to provide reliable statistics.

Further, the IET can be, with appropriate modifications, used to describe properties of more refined water models that are generally used to describe properties of aqueous solutions.

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