

# Fast prediction of hydration free energies for SAMPL4 blind test from a classical density functional theory

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**Abstract** We report the performance of a classical density functional theory (CDFT) in the competition for the solvation free-energy category of the SAMPL4 blind prediction event. The theoretical calculations were carried out with the TIP3P water model and different combinations of solute configurations and molecular force fields. In comparison with the experimental data, the blind test yields an average unsigned error of 2.38 kcal/mol and the root mean square deviation of 2.99 kcal/mol. Whereas these numbers are significantly larger than the best results from explicit-solvent MD simulations, we find that the theoretical performance is sensitive to both the molecular force fields and solute configurations and that a comparable level of accuracy can be achieved by a judicious selection of the solute configurations and the force-field parameters. Most importantly, CDFT reduces the computational cost of MD simulation by almost 3 orders of magnitude, making it very attractive for large-scale hydration free-energy calculations (e.g., screening the aqueous solubility of drug-like molecules).

**Keywords** Solvation · Classical density functional theory · Force fields · Explicit solvent

## Introduction

Hydration free energy plays a key role in solution chemistry but its theoretical prediction often represents a bottleneck in understanding important chemical and biological processes [1, 2]. In particular, solvent–solute interactions in an aqueous environment entail complex microscopic details that make a reliable prediction of solvation properties a serious computational challenge.

While in principle the hydration free energy of any solute can be obtained from quantum–mechanical (QM) calculations, the first principle methods are computationally time consuming and still in the early stage of development for liquid water. The conventional methods for solvation free energy calculations are typically based on either implicit or explicit solvent models. Most implicit-solvent methods are constructed from knowledge-based macroscopic considerations, augmented with the Poisson–Boltzmann (PB) equation for electrostatic interactions [3] or/and QM calculations for the solute charge and configurations (e.g., AMSOL [4]). The implicit models have been popular for practical applications because of their computational efficiency. However, these models provide limited microscopic details that are important for understanding diverse solute properties in a solvent environment [5]. At present, most explicit-solvent models employ a semi-empirical force field to describe solute–solvent interactions [6]. Whereas the computational cost is drastically increased in comparison to the implicit models, solvent-explicit models retain all important microscopic details and are expected to have better capability of predictions. From a practical point of view, the selection of a continuous or solvent-explicit method often reflects a compromise of the computational cost and the scope of microscopic details.

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Classical density functional theory (CDFT) is a statistical-mechanical method that, like molecular simulations, is able to predict the equilibrium properties of thermodynamic systems from a molecular perspective. The mathematical framework is essentially identical to that of electronic DFT except that CDFT is concerned with the distributions of atoms (or coarse-grained segments of polymeric molecules) instead of electrons and that it minimizes the grand potential instead of the ground-state energy. In comparison with molecular simulations, CDFT is computationally much more efficient because it avoids direct sampling of microstates and provides explicit structure–property relationships. Such an analytical approach is particularly desirable for free-energy calculations. The theoretical performance of CDFT has been well established in the past few decades for both simple and complex fluids [7]. In many cases, CDFT is able to reproduce molecular simulation data quantitatively but with significantly less computational time. It is worthwhile mentioning that CDFT is different from conventional integral-equation theories such as the Reference Interaction Site Model (RISM) [8, 9]. While integral-equation methods are built upon heuristic arguments for the closure between various two-body correlation functions, CDFT solves many-body problems based on an exact mathematical framework and systematic ways are available for the development of free-energy functional.

Motivated by the need for high-performance computational methods, we recently developed a three-dimensional CDFT method wherein the free-energy functional was formulated in terms of the site–site intermolecular interactions [10]. It is the intention of this work to test the theoretical performance through participation in the solvation-free-energy category of the SAMPL4 blind prediction challenge [11]. The sample was prepared by Guthrie [12], which includes the hydration free energies of 47 small organic molecules. As a hallmark of SAMPL4 competition,

## Molecular model and Theory

We first recapitulate the main ideas behind the CDFT method for hydration free energy calculations. The mathematical details have been reported in two recent publications [10, 13].

We consider solvation of a solute molecule with  $M$  atomic sites in liquid water at 298 K and 1 atm. The solute is assumed to have a rigid configuration, and the interaction between solute and solvent molecules takes the Lennard-Jones 12–6 plus Columbic potential

$$u_{ij}(r) = 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r} \right)^{12} - \left( \frac{\sigma_{ij}}{r} \right)^6 \right] + \frac{Z_i Z_j e^2}{4\pi\epsilon_0 r} \quad (1)$$

where  $r$  represents the center-to-center distance between atomic sites  $i$  and  $j$ ,  $\epsilon_{ij} = \sqrt{\epsilon_{ii}\epsilon_{jj}}$ ,  $\sigma_{ij} = (\sigma_{ii} + \sigma_{jj})/2$ ,  $\epsilon_{ii}$  and  $\sigma_{ii}$  are the energy and size parameters of the  $i$ th atom (i.e., van der Waals parameters),  $Z_i$  is the (fractional) valence of atom  $i$ ,  $e$  is the elementary charge, and  $\epsilon_0$  is the vacuum permittivity. The hydration free energy, here designated as  $F_s$ , corresponds to the difference between the grand potentials for a large system of water molecules,  $\Omega$ , with and without the solute molecule:

$$F_s[\rho_i(\mathbf{r}); \mu_m, V, T] = \Omega[\rho_i(\mathbf{r}); \mu_m, V, T] - \Omega[\rho_i^b; \mu_m, V, T] \quad (2)$$

In Eq. (2),  $\mu_m$  denotes the water chemical potential,  $T$  stands for the absolute temperature, and  $V$  is the system volume;  $\rho_i(\mathbf{r})$  represents the local densities of hydrogen and oxygen atoms near the solute, and  $\rho_i^b$  is the corresponding atomic densities in the bulk. The system volume is selected such that the properties of water molecules remote from the solute are the same as those corresponding to the bulk.

In essence, the CDFT calculation is based on the minimization of the grand potential as a functional of the local atomic densities. Specifically, we first solve the density profiles of oxygen and hydrogen atoms from

$$\begin{cases} \rho_O(\mathbf{r}_O) = \exp[-\lambda_O(\mathbf{r}_O)] \langle \exp\{-\lambda_H[\mathbf{r}_{H1}(\mathbf{r}_O, \omega)] - \lambda_H[\mathbf{r}_{H2}(\mathbf{r}_O, \omega)]\} \rangle_\omega \\ \rho_{H1}(\mathbf{r}_{H1}) = \exp[-\lambda_H(\mathbf{r}_{H1})] \langle \exp\{-\lambda_O[\mathbf{r}_O(\mathbf{r}_{H1}, \omega)] - \lambda_H[\mathbf{r}_{H2}(\mathbf{r}_{H1}, \omega)]\} \rangle_\omega \\ \rho_{H2}(\mathbf{r}) = \rho_{H1}(\mathbf{r}) \end{cases} \quad (3)$$

we did not have or use any a priori knowledge about the experimental data. In other words, the theoretical predictions reflect a truly blind test of the molecular models and the CDFT approximations.

where  $\lambda_i(\mathbf{r})$  denotes the reduced local potential for atom  $i$ , and  $\langle \cdots \rangle_\omega$  represents average over angular vector  $\omega = (\theta, \phi, \phi')$ . In the CDFT calculations, we use these dipolar and rotational angles instead of the Euler angles

because they are more convenient for numerical operations. As shown in Fig. 1, angles  $(\theta, \phi)$  specify the dipolar direction of a water molecule, and  $\phi'$  is the rotation angle of two H atoms around the dipole axis.

In Eq. (3), the reduced potential for oxygen or hydrogen atoms is defined by their interactions with the solute molecule,  $V_i^{ext}(\mathbf{r})$ , the local correlation energy,  $\beta\mu_i^{ex}(\mathbf{r})$ , and the nominal chemical potential of individual atoms,  $\mu_i$

$$\lambda_i(\mathbf{r}) = \beta V_i^{ext}(\mathbf{r}) + \beta\mu_i^{ex}(\mathbf{r}) - \beta\mu_i \quad (4)$$

The nominal atomic chemical potentials can be determined from the stoichiometric relations and their connection with the molecular chemical potential,  $\sum_i \mu_i = \mu_m$ . The local correlation energy arises from interactions among water molecules and, as discussed below, is related to the correlation functions. This term is also referred to as the local excess chemical potential. Near a solute molecule with fixed configuration, the oxygen and hydrogen atoms experience an external potential due to the water-solute interactions

$$V_i^{ext}(\mathbf{r}) = \sum_{j=1}^M u_{ij}(\mathbf{r} - \mathbf{r}_j) \quad (5)$$

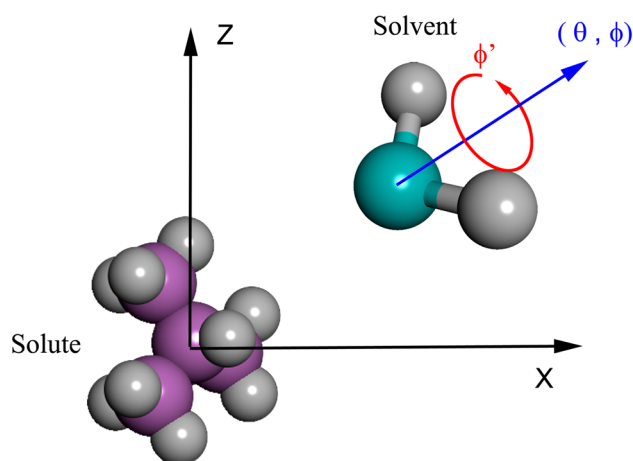
where  $\mathbf{r}_j$  is the coordinate of the  $j$ th atom of the solute molecule.

With an analytical expression for the grand potential and atomic density profiles, we can evaluate the solvation free energy from

$$\begin{aligned} \beta F_s[\rho_i(\mathbf{r})] = & -\Delta N + \frac{1}{2} \sum_{ij} \iint c_{ij}^{(2)}(|\mathbf{r} - \mathbf{r}'|) [\rho_i(\mathbf{r})\rho_j(\mathbf{r}') - \rho_i^b \rho_j^b] d\mathbf{r} d\mathbf{r}' \\ & + \beta F^B[\rho_i(\mathbf{r})] - \sum_i \int \rho_i(\mathbf{r}) B_i(\mathbf{r}) d\mathbf{r} \end{aligned} \quad (6)$$

where  $\beta = 1/(k_B T)$ ,  $\Delta N$  is the change in the number of solvent molecules in the system to accommodate a solute molecule,  $c_{ij}^{(2)}(r)$  represents the site-site direct correlation function of bulk water,  $F^B$  is the bridge functional for water, and  $B_i(\mathbf{r}) = \delta\beta F^B/\delta\rho_i(\mathbf{r})$ . The local correlation energy is given by  $\beta\mu_i^{ex}(\mathbf{r}) = \sum_k \int [\rho_k(\mathbf{r}') - \rho_k^b] c_{ik}^{(2)}(|\mathbf{r} - \mathbf{r}'|) d\mathbf{r}' - B_i(\mathbf{r})$ ,  $\Delta\rho_i(\mathbf{r}) = \rho_i(\mathbf{r}) - \rho_i^b$ . The detail expressions for  $c_{ij}^{(2)}(r)$  and  $F^B$  can be found in our previous publications [10, 13].

In this work, we use the TIP3P model for water [14], and several combinations of van der Waals and charge parameters for the solute-solvent interactions and energy optimization methods for determining the solute structures. The van der Waals parameters are obtained from either GAFF [15] or OPLS-AA [16], two standard force fields from the literature, and the atomic charge fitting is based on either AM1-BCC [17] or ChelpG [18]. While the AM1-BCC charge set is a



**Fig. 1** The molecular frame used in the CDFT calculations. A solute molecule is assumed to have a rigid configuration placed at the origin. The y-axis is perpendicular to the paper and points inward. The location of a neighboring water molecule (solvent) is described by the oxygen atom position  $\mathbf{r} = (x, y, z)$  and angles  $(\theta, \phi, \phi')$  that specify the dipolar orientation and rotation

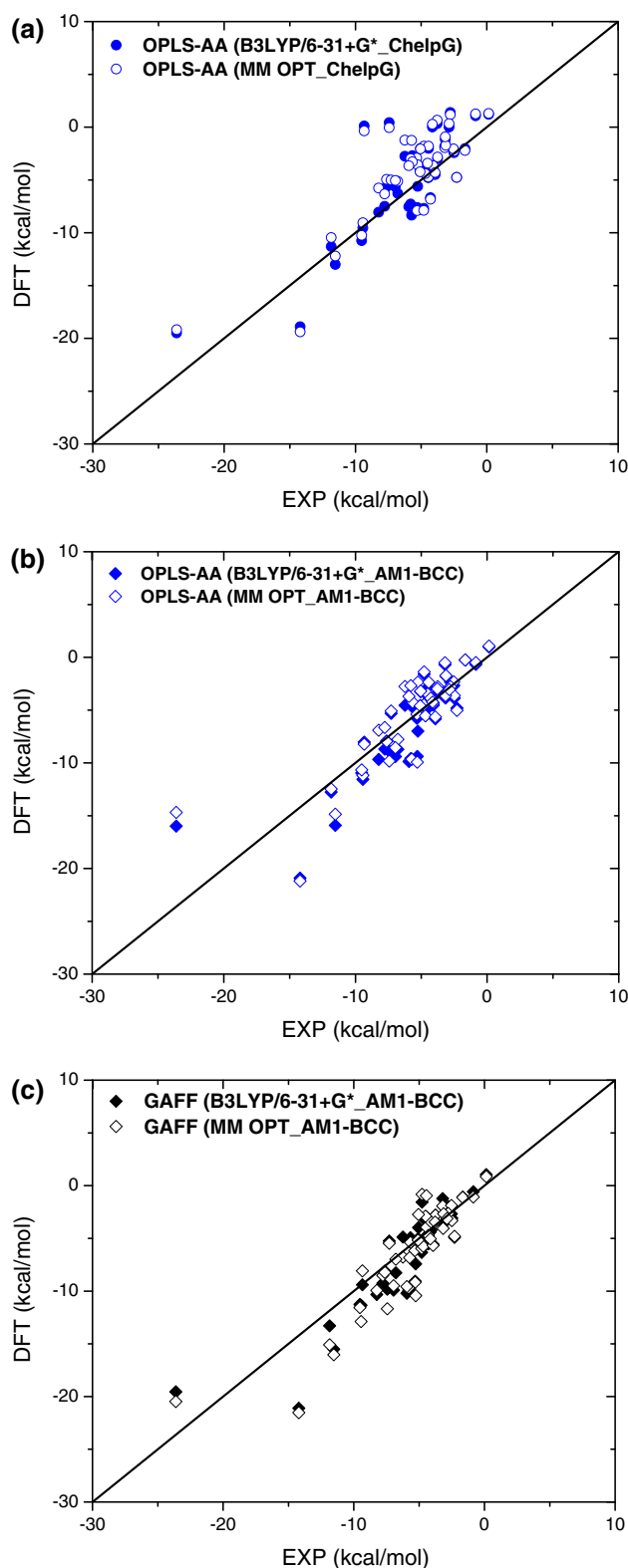
common choice for GAFF, ChelpG has been routinely used in both CHARMM [19] and OPLS-AA force fields.

We assume that each solute takes a rigid configuration, which can be obtained by energy minimization in vacuum or in a dielectric continuum using either quantum mechanical (QM structures) or molecular mechanical (MM structures) methods. The QM calculations are based on several options from Gaussian 09 (HF/B3LYP/MP2) with the 6-31+G\* basis set [20]. These QM structures also allow us to determine the AM1-BCC and ChelpG charge sets. The MM structures can be determined from the conjugated-gradient method (available from GROMACS 4.6.2) [21].

We consider different combinations of solute structures, van der Waals parameters and charge sets in order to examine the theoretical performance more systematically. In the CDFT calculations, we solve the atomic density profiles of water molecules in a cubic box with a solute molecule placed at the center. The box dimension is typically 30–40 Å in each direction, depending on the solute size. The atomic density profiles are discretized into  $128^3$  lattice grids. In comparison to solvent-explicit MD simulations, the CDFT calculations are extremely fast and the numerical results entail no statistical uncertainties (or error bars). For those solute compounds from SAMPL4, the average computational time per solute is less than 30 min on a single CPU core. The detailed numerical procedures can be found in our previous publications [10, 13].

## Results and Discussion

We have performed the CDFT calculations for 47 compounds posted at the SAMPL4 website using many



combinations of solute configurations, van der Waals parameters, and solute charge sets. The numerical outputs for all these calculations are listed in Supporting Information. Because these calculations were still in progress at

**Fig. 2** Comparison of the CDFT hydration free energies with the experimental data. Here the theoretical results are based on **a** OPLS-AA van der Waals parameters with the ChelpG charge set as used in the blind test; **b** OPLS-AA van der Waals parameters with the AM1-BCC charge set; **c** GAFF van der Waals parameters with the AM1-BCC charge set. *Filled symbols* correspond to solute configurations obtained from B3LYP/6–31+G\* QM optimization in vacuum, and *blank symbols* are for solute configurations obtained from MM optimization also in vacuum

the time of the blind test, we submitted only one set of the results from the early stage of this work (submission ID 548).

Our initial stage calculations were based on the solute configurations obtained from either QM or MM energy minimization in vacuum. Figure 2 presents the CDFT predictions for the hydration free energies in comparison with the experimental results. For the SAMPL4 challenge, we submitted the theoretical results only based on the OPLS-AA van der Waals parameters, the ChelpG charge sets, and solute configurations obtained from MM optimization in vacuum. Figure 2a shows the results from both the original submission as well as additional calculations based on the same force field but with the QM optimized solute structures. Our submission yielded an average unsigned error (AUE) of 2.38 kcal/mol, and root mean square (RMS) deviation of 2.99 kcal/mol. Based on these numbers, CDFT was ranked in the middle among 49 total submissions from 19 research groups. A post competition analysis indicates that the CDFT standing could be improved if we had submitted all the results from different combinations of the charge sets, van der Waals parameters, and solute configurations. For example, Fig. 2b shows the CDFT predictions based on the OPLS-AA van der Waals parameters, and Fig. 2c for the GAFF van der Waals parameters, both with the AM1-BCC charge set. For the CDFT results shown in these figures, we have considered the solute configurations from both B3LYP/6–31+G\* QM and MM energy optimizations. The QM structures yield RMS values (2.36 and 2.20 kcal/mol for Fig. 2b, c, respectively), slightly better than those from MM structures (2.46 and 2.40 kcal/mol, correspondingly). All these numbers are noticeably better than that was submitted (2.99 kcal/mol).

Table 1 summarizes the RMS values from our initial CDFT calculations. We see that different structure optimization methods may contribute up to 10 % of RMS. In this work, we determine the solute structures with relatively simple QM methods because our long-term interest is directed at large-scale screening applications (e.g., fast prediction of the aqueous solubility of drug-like molecules). More expensive QM calculations, such as MP2/6–311G(d,p), will increase the computational time by more than two orders of magnitude. Because the CDFT

**Table 1** The root mean square (RMS) deviation of the CDFT results from 6 different combinations of solute configurations, van der Waals parameters, and charge sets

RMS(kcal/mol)	OPLS-AA				GAFF	
	QM		MM		QM	MM
	AM1-BCC	ChelpG	AM1-BCC	ChelpG	AM1-BCC	AM1-BCC
ALL	2.36	2.79	2.46	2.99	2.20	2.40
Fs > -5	1.30	2.17	1.38	2.29	1.27	1.47
-10 < Fs < -5	2.23	3.28	2.24	3.55	2.32	2.52
Fs < -10	5.55	3.22	5.91	3.50	4.53	4.85

Here QM means solute structure obtained by B3LYP/6-31+G\* QM optimization, while MM means by molecular mechanic optimization, both in vacuum

**Table 2** Comparison of CDFT predictions with the experimental data for the hydration free energies of 47 compounds in SAMPL4

RMS(kcal/mol)	GAFF		OPLS-AA	
	AM1-BCC	ChelpG	AM1-BCC	ChelpG
<b>B3LYP</b>				
ALL	2.36	5.51	2.24	5.37
Fs > -5	1.15	3.81	1.18	3.48
-10 < Fs < -5	2.59	4.87	2.47	4.90
Fs < -10	4.80	12.14	4.38	11.92
<b>HF</b>				
ALL	2.15	3.37	2.08	3.09
Fs > -5	1.27	2.51	1.30	2.17
-10 < Fs < -5	2.32	3.15	2.23	3.28
Fs < -10	4.26	6.91	4.03	5.61
<b>MP2</b>				
ALL	2.38	7.93	2.24	7.73
Fs > -5	1.10	5.63	1.11	5.33
-10 < Fs < -5	2.34	6.44	2.29	6.45
Fs < -10	5.28	17.38	4.68	16.90

The CDFT calculations were based on different combinations of van der Waals parameters, charge sets, and solute configurations. Unlike Table 1, here the solute configurations were obtained by energy minimization using the IEFPCM implicit solvent model with various QM methods (B3LYP/HF/MP2 and 6-31+G\* basis set)

calculation relies on a rigid configuration for each solute molecule, more accurate QM calculations in vacuum are probably unnecessary.

We find that the CDFT results are most sensitive to the solute charge set. In general, AM1-BCC yields better results than ChelpG; the difference in RMS can be as large as 20 %. One possible reason is that the ChelpG charge set is highly dependent on the environment, while the AM1-BCC charge set is relatively invariant with different configurations. Because CDFT ignores the solute flexibility, it performs better with AM1-BCC charge set.

Table 1 shows that overall the theoretical predictions agree reasonably well with the experimental data, in particular for those molecules with positive or small hydration free energies (>-5 kcal/mol). With the OPLS-AA van der Waals parameters/AM1-BCC charge set/B3LYP/6-31+G\* QM structure, the CDFT calculation yields an RMS of 1.30 kcal/mol for these compounds, making it comparable to the top tier methods in the hydration free energy challenge. For more hydrophilic solutes ( $F_s < -10$  kcal/mol), however, CDFT gives larger errors. One possible reason lies in the selection of force-field parameters. As suggested by Mobley et al.(submission ID 005) [11], the AUE value could be reduced to 1 kcal/mol by introducing new hydroxyl group parameters, which would represent the best results from MD simulations submitted to the SAMPL4 challenge. The increased discrepancy for hydrophilic compounds may also be attributed to the approximations used in the CDFT functionals. In formulation of the free-energy density functional, we utilized a hard-sphere model to represent the bridge functional for water wherein the hard-sphere diameter of the reference system was calibrated with the solvation free energy for methane [10]. Because the local structure of water molecules is sensitive to the solute hydrophobicity, the effective hard-sphere diameter obtained from a hydrophobic solute may not be applicable to hydrophilic solutes. We expect that the effective hard-sphere diameter for a hydrophilic solute is smaller than that for a hydrophobic solute due to the enhanced solute-solvent attraction.

One major limitation of the CDFT method is that it ignores the flexibility of the solute structures. As demonstrated in our previous work [13], the theoretical results could be significantly improved by sampling the solute flexibility in vacuum and using an ensemble average. Even with a relatively small number of solute configurations, we can improve the results by up to 4 kcal/mol [13]. Regrettably, an explicit consideration of the solute flexibility would drastically increase the computational cost. To avoid repeated CDFT calculations, we have explored different QM



methods (B3LYP/HF/MP2 with 6–31+G\* basis set and the IEFPCM [22] implicit solvent model) to generate the solute configurations. Table 2 summarizes the final results from the CDFT calculations. As expected, the theoretical performance varies with the force field parameters and the solute configurations. In particular, the difference between the results from the AM1-BCC and ChelpG charge sets is noticeably increased with the solute configurations determined from the implicit-solvent QM calculations. We find that overall AM1-BCC remains better than ChelpG for our CDFT calculations. With this charge set, the CDFT predictions are relatively invariant with the solute structures. Table 2 indicates that, with an appropriate combination of the molecular parameters and solute configurations (OPLS-AA van der Waals parameters/AM1-BCC charge set/HF-IEFPCM structure), the best CDFT predictions give AUE = 1.54 kcal/mol and RMS = 2.08 kcal/mol. These numbers are close to those corresponding to MD simulations submitted by Yang's group (submission ID 575, AUE = 1.59 kcal/mol, RMS = 2.10 kcal/mol) and by Gilson's group (submission ID 542, AUE = 1.30 kcal/mol, RMS = 1.89 kcal/mol).

## Conclusions

We have demonstrated that the CDFT provides a valuable alternative to conventional molecular simulations for fast prediction of hydration free energy. For this blind test, the overall error for our initial submission is AUE = 2.38 kcal/mol and RMS = 2.99 kcal/mol in comparison with the experimental data. The theoretical performance is sensitive to the selection of solute configuration, the force-field parameters, in particular the solute charge set. With a proper combination of the force-field parameters and solute structures (OPLS-AA/AM1-BCC/HF-IEFPCM), we could reduce the AUE and RMS values to 1.54 and 2.08 kcal/mol, respectively. The CDFT predictions are most accurate for solutes with slightly positive hydration free energies but become less precise for large hydrophilic solutes.

In comparison to molecular simulations, one key advantage of CDFT is its computational efficiency. For the systems considered in this work, the CDFT calculation for each solute can be readily processed with a single CPU core (Nehalem Xeon 2.67 GHz), within 30 min. The computational cost could be further reduced by optimization of the CDFT programs.

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