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Calculation of PMF from the WHAM and FEP molecular dynamics simulations: Case study of the methane dimer in water

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Abstract

Combined use of the weighted histogram analysis method (WHAM) and the free energy perturbation (FEP) method for the calculation of potential of mean force (PMF) from the molecular dynamics simulations is examined for the methane–methane association in TIP3P water with the SCAAS-model spherical boundary. The linear square fit of the informative free-energy profile from the WHAM, but with an uncertain baseline, to the discrete absolute free energies of binding from the FEP calculations yields the PMF with an accurate zero level. Such a procedure may be particularly useful in PMF simulations of biochemical systems when only a short part of the entire reaction pathways is considered.

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1. Introduction

Calculation of free energies is a challenging and important problem in computational chemistry. In many cases, a particular interest may present evaluation of the free-energy profile along the reaction pathway. Such a free-energy profiles, also known as the potential of mean force (PMF), are expressed as a function of the reaction coordinate, ξ, by Eq. (1) [1]:

$$W(\xi) = W_0 - \frac{1}{\beta} \ln P(\xi) \tag{1}$$

The distribution function $P(\xi)$ in Eq. (1) is an ensemble average $P(\xi) = \langle \delta(\xi - \xi(\mathbf{X})) \rangle$ over the phase-space configurations $\mathbf{X}$ with a particular value of ξ, $\beta = 1/k_B\mathrm{T}$, and W_0 is a constant. The uniform sampling of all points in a phase space, implicitly required in the PMF calculations, can be attained by using the umbrella sampling approach [2,3], where the frequency of accessing the region of a phase space (e.g., near a high-energy activation barrier) is augmented via biasing the Boltzmann distribution probability by a factor of $\rho(\mathbf{X})$. The umbrella sampling techniques allow, in this case, recover the unbiased PMF from the equilibrium ensembles with the biased Boltzmann distributions (e.g., [2–6]).

The aim of this work is to explore the performance of the weighted histogram analysis method (WHAM) [7,8] and the free energy perturbation (FEP) method [9–11] in the calculations of the PMF for methane–methane pair in water solution from the molecular dynamics (MD) simulations. Both methods are widely used in the free energy microscopic MD simulations but produce somewhat different type of data. The FEP/MD calculations render the free-energy difference between the two states and, in special cases, provide the absolute free energies of a process [10,11]. The WHAM simulations produce a smooth PMF profiles but with an uncertain baseline level. Correction of zero-energy level of the WHAM results using the absolute free energies from the FEP simulations may allow then obtain the accurate and unbiased PMF. The considered prototypic case of the PMF of hydrophobic association of the methane-size particles in water was thoroughly explored in computational studies on a different level (e.g., [5,12–22] and the references therein), including separate evaluation of the PMF baseline [13,20,21]. In this

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study we examine how one can compute the PMF by combining results from the WHAM and the FEP method. The MD simulations are carried out using a spherical solvent model with multiple harmonic restraints, which confine the coordinate space sampled by the solutes. This makes them somewhat different from the previous PMF studies performed for the rectangular cells. The free-energy contribution from the solute restraints is evaluated using a rigorous unbiasing umbrella-sampling procedure.

2. Methods

Molecular dynamics of methane molecules was explored in water spheres with the radii of 16, 20, and 25 Å, and in a periodic cubic box of 28 Å. Van der Waals parameters for methane (united-atom C: $\sigma = 3.73$ Å, $\varepsilon = 1.23$ kJ mol^{-1}, and $q = 0$ [23]) and TIP3P water (OW: $\sigma = 3.15$ Å, $\varepsilon = 0.636$ kJ mol^{-1}, and $q = -0.834$ eu; HW: $\sigma = 0$, $\varepsilon = 0$, and $q = 0.417$ eu, [24]) are combined using geometric mixing rule. In the simulations of the water spheres the non-bonded cut-off for the water–water interactions was 9.5 Å, while beyond this distance the local reaction field was approximated by the first four terms in a multipole expansion of the solvent electrostatic effect [25]. No cut-offs were used for the methane–methane and methane–water non-bonded interactions. The surface-constrained all-atom solvent (SCAAS) model [26,27] was employed for describing water boundary conditions. The MD simulations of the periodic box were performed at constant volume using the cut-off of 9.5 Å for all non-bonded interactions (the non-bonded interactions beyond 9.5 Å were neglected). All MD simulations were carried out at $T = 300$ K with a temperature coupling constant of $\tau_T = 0.2$ ps and a time step of 2 fs. The water molecules were kept rigid using SHAKE [28]. The frequency of updating the list of non-bonded pair interactions was 20 fs. All systems were in the beginning equilibrated for 1 ns prior to producing molecular dynamics trajectories used for the free-energy calculations. The software for MD simulations was that of Ref. [27], whereas program of the WHAM was prepared by the author.

The first approach for the free-energy calculations in this work was the Weighted Histogram Analysis method described elsewhere [7,8,20,29]. The WHAM calculates $W(\xi)$ self-consistently from the umbrella sampling simulations in a set of sampling windows. The corresponding distribution functions are produced using the bias of $\rho(\mathbf{X}) = e^{-\beta w(\xi)}$, associated with the harmonic restraints at the points on ξ. The biased MD simulations were performed in the sampling windows $i = 1,\ldots,21$, where ξ was restrained to the values of $\delta_i = 3.5 + (i{-}1)\,{}^{*}0.5$ Å using a harmonic potential

$$w_i(\xi) = 0.5k_{\mathrm{hr}}(\xi(\mathbf{X}) - \delta_i)^2 \tag{2}$$

with k_{hr} of 8.368 kJ mol^{-1} Å^{-2}. The PMF was quantified along the reaction coordinate in narrow bins of 0.1 Å (for the purpose of comparison the overall WHAM/MD simulation setup is taken similar to the one from Ref. [21]). The length of molecular simulations in each window varied from 50 ps to 1 ns. The simulation data, used in the WHAM calculations, was collected every 2 fs after equilibration. In the simulations of spherical models the coordinates of one of the two methanes were additionally restrained to the center of the water sphere with a harmonic restraint

$$V(r_{\mathrm{mc}}) = 0.5k_{\mathrm{chr}}r_{\mathrm{mc}}^2 \tag{3}$$

using a default value of 4.184 kJ mol^{-1} Å^{-2} for the force constant k_{chr}. In Eq. (3) r_{mc} is the distance from the restrained methane to the sphere center. Instantaneous configurations of the solute-solvent system are not symmetric for such a setup. However, the overall effect of the harmonic restraints of Eqs. (2) and (3) is that the MD trajectories of the second methane form concentric spherical layers around the center of the water sphere and in this way follow the symmetry of the model system.

The second approach, employed in this work for calculation of the PMF, was the Free Energy Perturbation method described elsewhere [10,11,30]. This approach, in general, only allows calculate a relative free energy $\Delta G_{\mathrm{II,I}}$ between the two states II and I. The transformation (mutation) from state I to state II is usually performed in a number of small steps, where the potentials of the intermediate states may be calculated from a linear combination of the initial and final potentials:

$$U(\mathbf{R}) = (1 - \lambda)U_{\mathrm{I}}(\mathbf{R}) + \lambda U_{\mathrm{II}}(\mathbf{R}) \tag{4}$$

The mapping parameter λ changes from 0 to 1. Further arrangement of the *inter*-state mutations into closed cycles [31] provides a useful way for estimating relative free energies of molecular and protein-ligand complexes (Scheme 1).

In addressing the PMF calculations, the relative binding free energy of the complexes $[AA]$ and $[AB]$ can be expressed then as a function of ξ:

$$\begin{aligned}\Delta\Delta G_{\mathrm{bind}}(AB - AA, \xi) &\equiv \Delta G_{\mathrm{bind}}(AB, \xi) - \Delta G_{\mathrm{bind}}(AA, \xi)\\ &= \Delta G_{\mathrm{mut}}(AA \to AB, \xi) - \Delta G_{\mathrm{mut}}(A \to B)\end{aligned} \tag{5}$$

In a special case of mutation to a ‘dummy’ molecule B, i.e. annihilation of one of the two molecules A, ΔG_{bind} (AB, ξ) in Eq. (5) is 0 for all ξ, and therefore

$$\Delta G_{\mathrm{bind}}(AA, \xi) = \Delta G_{\mathrm{mut}}(A \to 0) - \Delta G_{\mathrm{mut}}(AA \to A0, \xi) \tag{6}$$

Eq. (6) yields the absolute free energy of molecular association, or *pari passu* PMF, using the free energies, which are

$$\begin{tikzcd}
A + A,\ \textit{separated} \arrow[r, "\Delta G\mathit{bind}(AA)"] \arrow[d, shift right=4] \arrow[d, "\Delta G\mathit{mut}(A\to B)"] & {[AA]} \arrow[d, "\Delta G\mathit{mut}(AA\to AB)"] \\
A + B,\ \textit{separated} \arrow[r, "\Delta G\mathit{bind}(AB)"'] & {[AB]}
\end{tikzcd}$$

Scheme 1.