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Simple Physics-Based Analytical Formulas for the Potentials of Mean Force for the Interaction for Amino-Acid Side Chains in Water. Tests with Simple Spherical Systems

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Simple analytical functions consisting of electrostatic, polarization, Lennard-Jones, and cavity terms were proposed to express the potential of mean force of particles interacting in water analytically. A simple analytical approximation based on the integral over the surface-hydration energy density of the interacting sites was derived for the cavity term; the solvation energy density of each site is represented as a difference of two Gaussian terms. This expression can easily be generalized to interaction sites with non-spherical symmetry. The analytical expressions were fitted to the potential of mean force of model systems determined by umbrella-sampling molecular dynamics. The analytical formulas fitted the potentials of mean force very well, and the resulting parameters of the expressions were physically reasonable.

1 Introduction

Effective potentials of amino-acid side chain interactions are a key part of united-residue force fields, because they encode most of sequence specificity. In the UNRES force field developed in our laboratory[1,2] the side chain–side chain interaction potentials are presently assigned arbitrary Gay-Berne[3] functional forms that take into account anisotropy of interactions, and their parameters were determined based on fitting to the correlation functions and side-chain-contact energies determined from the PDB[1]. These potentials have the symmetry of an ellipsoid of revolution[1], which does not capture the amphiphilic feature of side chains such as that of aspartic acid or asparagine, which are composed of a charged/polar "head" and a non-polar "tail" and possess, therefore, a lower symmetry of interactions.

In this communication, we introduce a new model of charged and polar side chains consisting of two centers: non-polar ones and charged/polar ones. The interaction potential consists of three components: a Gay-Berne component to reproduce steric interactions, a solvent-accessible-surface area component to reproduce hydrophobic association and a Generalized Born[4] component to reproduce electrostatic interactions between polar/charged parts. We also introduce an analytical expression for the free energy of hydrophobic solvation, which is based on a Gaussian model of the solvent density around a solute molecule. We fitted the resulting analytical expressions to the potentials of mean force of model systems determined by umbrella-sampling molecular dynamics simulations.

2 Methods

Molecular dynamics simulations for the systems studied were performed with the AMBER 7.0 force filed[5]. The TIP3P[6] model of water was used. The potentials of mean force (PMFs) were determined by using the WHAM method[7]. The detailed computational procedure was described previously[8]. Fitting of analytical formulas to the PMFs was accomplished by minimizing the sum of squares of the differences between the PMF values computed from analytical formulas and determined from MD simulations by using the Marquardt method[9]. We used two expressions for the cavity potential, one derived in this work based on the Gaussian model of solvent energy density and one based on molecular surface area.

3 Results and Discussion

An example of a PMF of the pair of two methane molecules together with curves computed with fitted analytical expressions are shown in Figure 1.

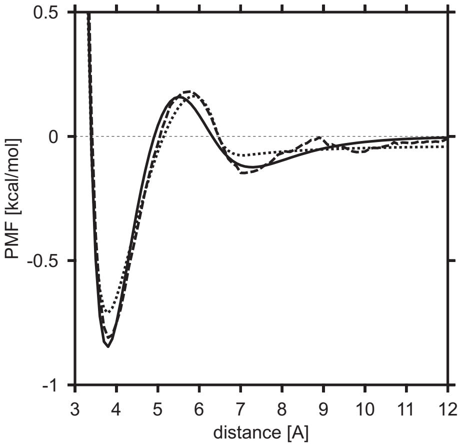

Figure 1. PMF curve of a pair of methane molecules in water determined by simulation (dashed line), the fitted curve with the cavity term expressed by the Gaussian model (solid line) and the fitted curve with the cavity term expressed as molecular surface area (dotted line).

It can be seen from Figure 1 that the Gaussian model of solvent density is able to reproduce both the desolvation maximum and the solvent-separated minimum in the PMF, while the molecular-surface area model can reproduce only the desolvation maximum. Unlike the model based on molecular-surface area, the Gaussian model of hydrophobic solvation can be easily generalized to non-spherical sites and does not produce discontinuities in the energy gradient.

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