Molecular Dynamics Simulations of Protein Interactions with a Hydrophobic Surface

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Statement of Purpose: Hydrophobic interactions are a major driving force for the adsorption of proteins to polymeric biomaterials. Empirical force field-based molecular simulation can provide useful insights to help understand these types of interactions. Sampling and force field accuracy are the two major factors that influence the predictive power of such methods. In a previous study, we evaluated several implicit solvent models with the CHARMM force field, which represent water by a continuum dielectric medium instead of discrete molecules, thus greatly reducing the conformational degrees of freedom that need to be sampled.[1] From this study, ACE[2] was determined as the most reliable overall method for peptide-surface adsorption simulations, although it tended to over-predict hydrophobic interactions. In this present study, we modified ACE to more accurately represent the adsorption free energy for the interactions of short peptides with a hydrophobic surface (CH_3-SAM). Modified ACE was then applied to simulate lysozyme adsorption behavior on a CH_3-SAM surface using an advanced sampling technique called replica-exchange molecular dynamics (REMD),[3] which enables a Boltzmann-weighted ensemble of states to be generated in a non-time-dependent manner.

Methods: Four kinds of peptides with different mid-chain residues were constructed: Gly-X-Gly with X=Phe (F), Val(V), Ser(S) and Asp(D). We evaluated the accuracy of ACE by comparing it with an explicit water model (TIP3P) by computing the potential of mean force (PMF, free energy calculation) between each peptide and the CH_3-SAM by MD simulations. A 2.0 ns REMD simulation of lysozyme/CH_3-SAM interactions was then performed using the MMTSB[5] utility in combination with the CHARMM program. A total of 20 replicas were run in parallel at different temperatures ranging from 310 to 450 K, with configuration exchange between neighboring pairs of replicas attempted every 1.0 ps.

Results / Discussion: We previously found that using ACE with its surface tension parameter set to $\sigma = 15$ cal/mol·Å^2 was suitable for obtaining a reasonable solution structure of lysozyme.[1] However, compared with DFT/SCRF[4] calculations, this condition was found to overestimate the decrease of solvation free energy when GVG or GFG peptides approached the CH_3-SAM from large separation to the contact distance between the hydrophobic side-chain of the mid-chain residue and the surface (Fig. 1). ACE also underestimated the desolvation penalty associated with the approach of polar (S) or charged (D) mid-chain residues to the CH_3-SAM. From the computed PMFs between the four peptides and the CH_3-SAM surface (Fig. 2), it was again found that ACE predicted much stronger attractions between each peptide and the CH_3-SAM than those predicted by the explicit water simulations. ACE parameters were therefore adjusted to tune the peptide/CH_3-SAM interactions in a manner that did not alter the behavior of the peptide residues or the SAM surface themselves. This greatly improved the accuracy of the simulation, as shown in Figs. 1 and 2. The REMD simulation of the lysozyme/CH_3 SAM interactions at 310 K using the adjusted ACE model maintained an exchange acceptance ratio of about 20 % for almost all pairs of replicas. Configurations at 310 K were thus generated by different replicas that visited different temperature space over the course of the 2 ns simulation, thus enhancing system sampling as desired. The resulting ensemble of states at 310 K displayed three dominant orientations of lysozyme on the CH_3-SAM; each which exhibited only moderate conformational change compared with the solution structure of lysozyme (Fig. 3).

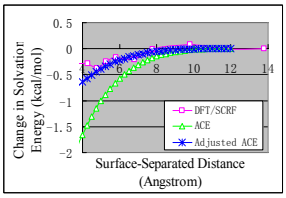
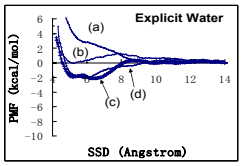
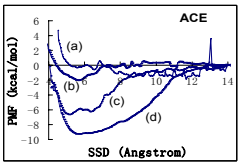


Fig. 1 Comparing ACE with DFT/SCRF for computing the changes in solvation free energies when peptide GVG approaches CH_3 SAM





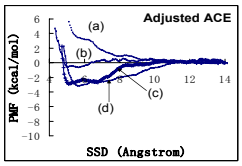


Fig. 2 Comparison of ACE with explicit water simulations for obtaining PMFs between CH_3-SAM and four kinds of peptides: (a) GDG, (b) GSG, (c) GVG and (d) GFG.

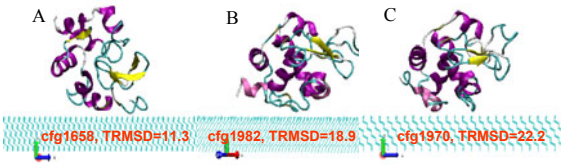


Fig. 3 Three dominant orientations of lysozyme on a CH_3-SAM surface at 310 K determined by a 2 ns REMD simulation. The percentages of configurations in the ensemble taking orientation A, B and C are 21.8 %, 50.1% and 17.8 %, respectively.

Conclusions: The modified ACE model combined with REMD enables protein interactions with functionalized surfaces to closely represent explicit water simulations, but with a much greater degree of sampling efficiency compared with conventional MD simulations. This approach thus provides one of the most accurate and efficient methods of investigating the effects of adsorption on protein orientation and conformation that are available at this time.

Refs: 1) Sun, et al. *SFB Transactions*, 90 (2005). 2) Scheafer & Karplus, *J. Phys. Chem.* 100:1578 (1996). 3) Sugita & Okamoto, Chem. Phys. Lett. 314: 141 (1999). 4) Marten et al. *J. Phys. Chem.* 100: 11775 (1996). 5) Feig et al. *J. Mol. Graph.* 22: 377 (2004).

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