# Comparison of Solvation-Effect Methods for the Simulation of Peptide-Hydrophobic Surface Interactions

[#]Yu Sun, [†]Brian N. Dominy, and [#]Robert A. Latour
[#]Department of Bioengineering and [†]Department of Chemistry, Clemson University, Clemson, SC, USA

**Purpose:** At a fundamental level, the adsorption behavior of a protein to a surface is governed by the relative strengths of the interactions between the individual amino acid residues making up the protein and the functional groups presented by the surface within an aqueous environment. The parameter that best characterizes these types of interactions is the adsorption free energy for amino acid-surface interactions. This molecular behavior can be readily investigated using molecular simulation methods by the calculation of the potential of mean force (PMF) acting on a peptide over a surface as a function of its surface separation distance (SSD). The accurate representation of solvation effects is extremely important for these types of simulations, especially for adsorption to a hydrophobic surface. While the explicit representation of water in MD simulations is considered to provide the most accurate results, this comes with substantially increased computational cost. Implicit solvation methods, which calculate solvation effects with a mean-field theory without actually representing individual water molecules, are thus desirable to minimize such costs. In this study, we employed molecular dynamics (MD) simulations using CHARMM[1] (C) to characterize and compare the adsorption behavior of peptides to a hydrophobic surface using three progressively more complex methods of representing solvation effects: A united atom force field (C19) combined with implicit solvation (ACE[2]), an all-atom force field (C22) combined with implicit solvation (GBMV[3]), and C22 with explicit water (TIP3P[4]).

**Methods:** Molecular models were constructed for three different types of amino acid residues placed between two Gly (G) residues to form a series of three-residue peptides in zwitterionic form. The resulting peptides are denoted as GXG, where X = V (valine, nonpolar), S (serine, polar), and D (aspartic acid, neg. charged). The surface was represented by a $CH_3$-terminated alkanethiol self-assembled monolayer ($CH_3$-SAM) on a gold (111) substrate. Fig. 1 shows a typical model for the GVG/$CH_3$-SAM-TIP3P water system. The PMF vs. SSD profiles were calculated for each system using a windowed umbrella sampling method[5] combined with weighted-histogram analysis[6] (WHAM). 20 windows were used to span an *SSD* range from 4.5 to 14.0 Å. For each window, a conventional MD simulation was performed for 600 ps following 100 ps of equilibration under NVT conditions. The time-step was 2 fs and covalent bonds with hydrogen atoms were constrained by the SHAKE algorithm. Nonbonded interactions were switched off from 10 to 12 Å for both van der Waals and electrostatic interactions. The resulting PMF values were determined relative to the PMFs at *SSD* = 14 Å (i.e., PMF defined as zero at 14 Å).

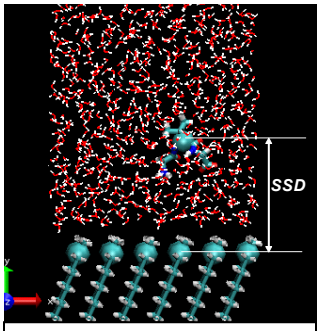


**Fig. 1.** Molecular model of a GVG peptide over a $CH_3$-SAM in TIP3P water.

**Results/Discussion:** The results for these simulations are presented in Fig. 2. As shown, each type of force field-solvation method combination predicts a similar trend for each type of peptide over the $CH_3$-SAM surface, especially for the polar GSG peptide. Quantitatively, however, the implicit solvation methods tend to over-predict both the desolvation benefit for the nonpolar GVG pepide and the desolvation penalty for the negatively-charged GDG peptide relative to the explicitly represent-ed TIP3P water model. These results document the importance of valid-ating each type of force field and solvation method prior to their application to simulate the adsorption behavior of more complex poly-peptides and proteins to a hydrophobic surface.

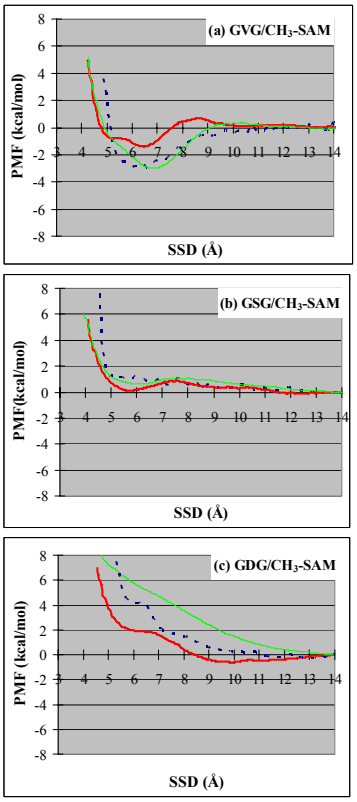


**Fig. 2.** PMF vs. SSD for each solvation method: TIP3P (thick red lines), GBMV (thin green lines), ACE (dotted blue lines).

**Conclusions:** MD simulation provides an excellent method to theoretically investigate peptide adsorption behavior to function-alized surfaces at an atomistic level. Comparisons between implicit and explicit solvation methods provide a basis for the assessment and tuning of the implicit solvent method to provide close agreement with more rigorous explicit solvation simulations to substantially decrease the computational costs of the simulations.

**Acknowledgement:** Funding provided by NIH grant P41 EB001046 through RESBIO at Rutgers University.

**References:** 1) Brooks et al., J. Comput. Chem. 1983, 4:187; 2) Schaefer et al., J. Phys. Chem. 1996, 100:1578; 3) Lee et al., J. Chem. Phys. 2002, 116:10606; 4) Jorgensen et al., J. Chem. Phys. 1983, 79:926; 5) Torrie et al., J. Comput. Phys. 1977, 23: 187; 6) Masunov et al., J. Am. Chem. Soc. 2003, 125:1722.