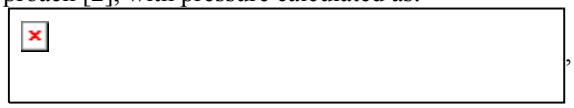
Effect of Pressure on Adsorption Free Energy in Protein Adsorption Simulations

Jeremy A. Yancey*, Nadeem A Vellore*, Steven J. Stuart#, Robert A Latour*
*Dept. of Bioengineering, #Dept. of Chemistry, Clemson University, SC, USA

Statement of Purpose: Molecular simulation methods have great potential to be used to understand and control protein adsorption behavior for biomaterials surface design. However, these methods must first be developed to accurately represent molecular behavior for this specific type of system. When performing molecular simulations of a condensed-phase system (e.g., protein folding in aqueous solution), system pressure is often considered to be of relatively minor importance. This, however, may not be the case for the simulation of protein adsorption behavior. The objective of this study was therefore to conduct molecular dynamics simulations to quantitatively investigate the influence of system pressure on the adsorption behavior of a peptide on a nonpolar surface as characterized by the free energy of peptide adsorption, ΔG_{ads},

Methods: To demonstrate the effect of pressure on ΔG_{ads}, the adsorption of a nonpolar peptide to a hydrophobic CH_3-terminated self-assembled monolayer (SAM) surface was simulated using the CHARMM molecular simulation program and force field [1] for a range of system volumes keeping the number of atoms and temperature fixed, thus changing system pressure. The peptide, with a sequence of TGTGVGTGT (where T, G, and V are the amino acids threonine, glycine and valine, respectively), was chosen for our study and equilibrated using NPT dynamics at 1 atm and 298 K in a 3D periodic box of physiological saline (TIP3P water plus 140 mM Na^+/Cl^- ions). This 'waterbox' had a fixed width of 43.1x45Å^2 and adjustable height Z that was initially set to 35Å. The bottommost side of the NPT equilibrated waterbox was placed approximately 1.2Å directly above the SAM surface to set the initial volume of the system, with this value then varied to adjust the pressure of the system. The resulting models were equilibrated using 100 ps of heating and 300 ps of dynamics at T = 298 K. The instantaneous pressure, P, of the N mobile atoms in each of the equilibrated systems at T = 298 K was calculated using a virial-based approach [2], with pressure calculated as:



where V is the volume, k_B is Boltzmann's constant, W is the virial of the mobile phase of the system, and r_{ij} and f_{ij} are the position and force vectors between atom pairs, respectively. ΔG_{ads} was calculated from the probability distribution of the surface separation distance (SSD) between the peptide and the SAM surface using biased replica-exchange molecular dynamics (REMD) [2] simulations over 3 ns of system sampling.

Results and Discussion: Fig. 1 shows the z-coordinate distribution function (ZDF) profile for the TIP3P water molecules in the system as a function of their SSD from the hydrophobic CH_3-SAM surface for nine distinct perturbations, dZ, of the initial waterbox height. Pressure is seen to strongly effect the density of the TIP3P hydration layers about the SAM surface and, hence, the adsorption behavior of the peptide.

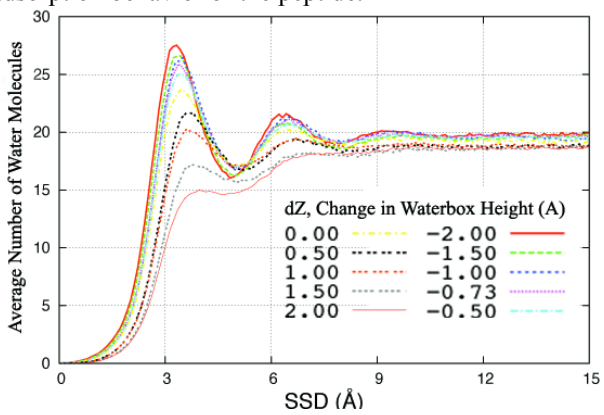


Figure 1. Z-distribution function (ZDF) of water layers over the SAM surfaces as a function of the change in water box height (dZ).

Table 1. ΔG_{ads} values as a function of system pressure

Perturbation in Initial Waterbox Height "dZ" (Å)	Calculated P (atm)	Calculated ΔG_{ads} (kcal/mol) ± 95% CI
-2.00	387.1	-0.34 ± 0.42
-0.73	2.5	-1.88 ± 0.93
1.50	-452.1	-2.60 ± 0.47

Table 1 summarizes calculated values of P and ΔG_{ads} for 3 ns of biased REMD simulation on systems having various waterbox heights. The 'negative' pressure shown in Table 1 corresponds to a non-equilibrium situation where the system has been adiabatically expanded to the point where excess vacuous space exists between the TIP3P waters near the SAM surface in anticipation of the formation of a vacuum bubble when the system has reached a critical volume.

Conclusions: ΔG_{ads} calculated by peptide adsorption simulations is very sensitive to the pressure of the system. Higher pressure exhibit strong hydration layer peaks and higher free energies (i.e., weaker adsorption); lower pressure systems have ill-defined hydration layers and decreased adsorption free energy (i.e., stronger adsorption). A difference of a few tenths of an Angstrom in waterbox height can correspond to a pressure shift of hundreds of atmospheres, thus emphasizing the importance of monitoring system pressure for the simulation of peptide and protein adsorption behavior.

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References: [1] MacKerell et al., J.Phys.Chem B, 1998; [2] Louwerse et al., Chem. Phys. Lett, 2006; [3] O'Brien et al., Langmuir 2008.