Molecular Dynamics Simulation of Peptide Secondary Structure Adsorption to Functionalized Surfaces

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Statement of Purpose: It is well understood that protein-surface interactions are of fundamental importance for understanding cell-surface interactions, but very little is understood at this time regarding the molecular-level events that govern protein adsorption to surfaces. Molecular dynamics simulations methods have enormous potential for application as a tool to help understand and predict these types of interactions. Due to the large number of atoms that must be represented for the simulation of protein-surface interactions, simulations are usually conducted using an empirical force field method, in which a force field equation is used to calculate the forces that the atoms in the system exert on one another as a function of their position and bonded state. The overall accuracy of a given simulation is thus determined by the accuracy of the empirical parameters that are used to calculate the interatomic interactions using the force field equation. While several force field equations have been previously developed and validated for protein folding behavior in solution, none of these have yet been validated for application to protein adsorption behavior. The objective of our research is therefore to evaluate and assess the accuracy of the protein force fields to assess their suitability for use for the simulation of protein adsorption behavior. To accomplish this, we are conducting a variety of molecular dynamics simulations to predict the adsorption behavior of peptides with secondary structure to functionalized alkanethiol self-assembled monolayer (SAM) surfaces and comparing the results to experimental studies that are being conducted for these same systems.

Methods: Two types of structured peptides are being studied: (1) an α-helix forming peptide with a primary sequence of Ac-L-K-K-L-L-K-L-L-K-K-L-L-K-L-NH_2 (LKα14), where L is leucine (nonpolar amino acid), K is lysine (positively charged amino acid), and Ac represents an acetylated end-group; and (2) a β-sheet forming peptide, Ac–L-K-L-K-L-K-L–NH_2 (LKβ7). Two types of SAM surfaces are represented, (1) a CH_3-SAM (hydrophobic surface) and (2) a 50% deprotonated COOH-SAM surface (negatively charged surface). Simulations are performed with the CHARMM simulation engine using explicitly represented solvent (150 mM Na^+/Cl^- in TIP3P water) with periodic boundary conditions. CHARMM, AMBER, and OPLS force fields are being used in otherwise identical simulations in order to provide a means of evaluating the qualities of each parameter set when used in simulations of peptide-surface interactions. An advanced sampling method, known as replica-exchange molecular dynamics (REMD), is being applied in our simulations to generate Boltzmann-weighted ensembles of states for each peptide-SAM system, with the resulting ensembles providing equilibrated structures of peptide behavior and the surrounding water structure, both in bulk solution and when adsorbed to each type of SAM surface. Simulation results are being compared with NMR, SFG, ToF-SIMS, and SPR experimental studies that are being conducted in a collaborative effort with Professors Castner, Gamble, Stayton, and Drobny at the University of Washington.

Results and Discussion: The simulation results with the CHARMM force field predict that the LKα14 peptide retains its ~~alpha h~~helical structure in solution and when adsorbed to both the CH_3-SAM and the COOH-SAM surfaces in physiological saline, with the peptide orienting in a manner to face its positively charged lysine amino acids towards the surface when adsorbing on the COOH-SAM (Figure 1) and with its nonpolar leucine amino acids facing the surface on the CH_3-SAM.

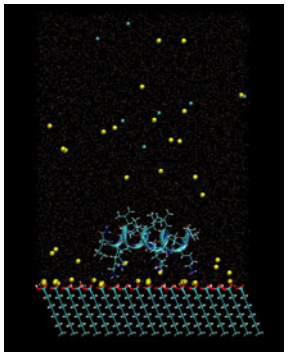
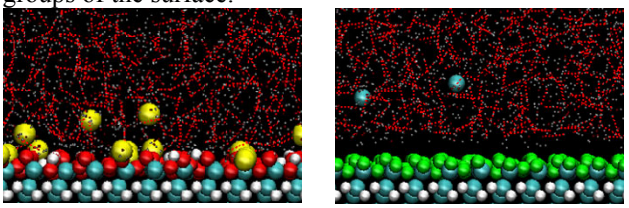


Figure 1. Simulated system of an LKα14 peptide in explicit water with Na^+ (yellow spheres) and Cl^- (blue spheres) ions over a 50% deprotonated COOH-SAM surface.

Results showing the differences in water structure over each of these two SAM surfaces is shown in Figure 2, again using the CHARMM force field. As is clearly evident, the water interacts strongly with the COOH-SAM surface by forming hydrogen bonds with the carboxylic acid groups of the surface, while it interacts minimally with the CH_3-SAM surface because of the lack of the ability to form hydrogen bonds with the nonpolar methyl groups of the surface.



(a) (b)

Figure 2. Hydrogen bonding interactions of explicit water molecules in the presence of Na^+ and Cl^- ions (a) over a 50% deprotonated COOH-SAM surface, and (b) over a nonpolar CH_3-SAM surface. Thus far, these results compare favorably with the experimental studies.

Concluding Remarks: Simulation results with the CHARMM force field are providing simulation results that are appear to closely represent the realistic behavior of this peptide adsorption system. Further simulation studies are underway to evaluate AMBER and OPLS force fields in a similar manner.

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