Molecular Dynamics Simulations of Peptide Interactions with a Poly-L-Lactic Acid Surface

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Statement of Purpose: The biocompatibility of a material implanted into the human body is mediated by the adsorbed protein layer that rapidly forms over its surface following implantation. Interactions between cells in the body and the implant then occur, not directly with the material of the implant itself, but rather with this adsorbed layer of protein. Thus, an understanding of protein-surface interactions is a key component in the development of materials with tailored bio-responses. At a fundamental level, protein adsorption behavior is governed by the free energy of adsorption (ΔG_{ads}) between amino acid residues and the functional groups presented by a biomaterial's surface [1].

In this study, molecular dynamics simulations were performed to calculate ΔG_{ads} for the nine-residue peptide GGGGKGGGG (G_4-K-G_4, in which G and K are glycine and lysine, respectively), as a model system to probe the interactions between a positively-charged peptide and a poly(L-lactic acid) (PLA) surface. ΔG_{ads} was calculated by defining the surface separation distance (SSD) as the reaction coordinate for this system and performing a series of windowed umbrella sampling simulations [2]. The SSD measures the height of the peptide's center of mass above the polymer surface. In these simulations, a series of systems were built that differed only in the SSD value to which the peptide was harmonically constrained. The free energy was then extracted from the normalized probability distribution using a standard weighted histogram analysis method (WHAM) [3].

Methods: The molecular simulation program CHARMM (version 31b1) [4] was used for all system construction and molecular dynamics simulations. As shown in Figure 1, the investigated system comprises four components: (1) a G_4-K-G_4 peptide in zwitterionic form solvated in (2) TIP3P water with (3) 140 mM Na^+ and Cl^- ions over (4) a layer of crystalline-phase PLA. The PLA surface was constructed using parameters adapted from molecular models of bulk crystalline PLA [5].

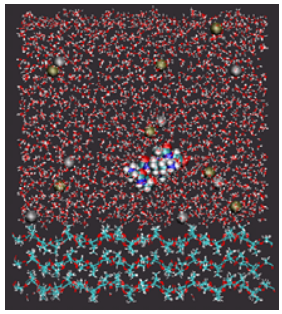

Figure 1. Molecular model of a G_4-K-G_4 peptide over a crystalline PLA surface in 140-mM TIP3P saline.

A parallel series of 42 systems was constructed by positioning identical copies of the peptide over a crystalline PLA surface at values of the SSD spanning from 5.0 to 25.0 Å in 0.5-Å increments. After construction, each system was equilibrated at constant temperature (300 K) and pressure (1 atm) for 250,000 steps using a 2-fs time step with the SHAKE algorithm applied to constrain covalent bonds involving a hydrogen atom.

Upon equilibration, a 1-ns molecular dynamics simulation was performed in the canonical ensemble (300 K; 2-fs time step with SHAKE constraints on H-bonds). Free energy values for each simulation were plotted on a common diagram to confirm an appropriate degree of overlap between adjacent sampling windows, and then a WHAM analysis was performed to extract the adsorption free energy profile over the entire range of the SSD.

Results/Discussion: Figure 2 presents the adsorption free energy as a function of the SSD for the simulated system. Interactions between the peptide and the PLA surface occur primarily through hydrophobic interactions between extended PLA methyl groups and aliphatic regions in the glycine and lysine residues.

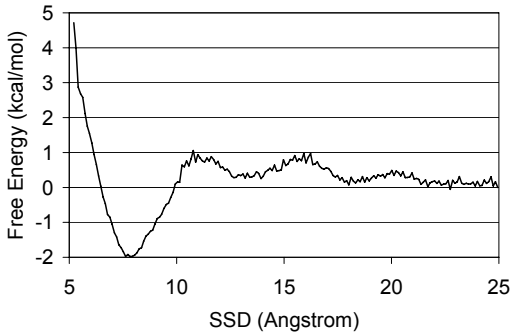

Figure 2. Free energy profile for adsorption of the G_4-K-G_4 peptide over a crystalline poly-L-lactide surface in 140-mM saline.

Conclusions: Molecular dynamics simulations combining windowed umbrella sampling with WHAM analysis provide an excellent means of probing and quantifying the interaction between a peptide and a PLA surface. These simulations can also be readily used to address more complex issues, such as the question of how PLA-chain hydrolysis may influence peptide adsorption behavior. The methodology can also be readily extended to other peptide-polymer systems to provide a molecular-level understanding of protein adsorption behavior.

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References: [1] Raut et al., Langmuir 2005, 2: 1629. [2] Torrie et al., J. Comput. Phys. 1977, 23: 187. [3] Kumar et al., J. Comb. Chem. 1992, 13:1011. [4] Brooks, B.R. et al., J. Comp. Chem., 1983, 4: 187. [5] O'Brien, C.P., Ph.D. dissertation, Dept. of Chem. Eng., Clemson University, 2005.