

# Calculation of adsorption free energy for peptide interactions with a crystalline polylactide polymer surface

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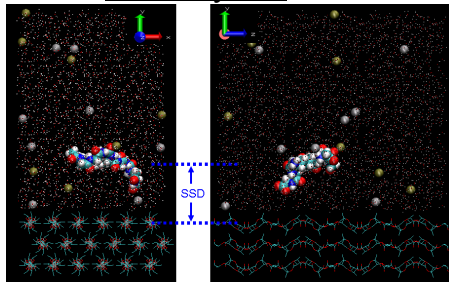
## Introduction

- Cellular interaction with implanted biomaterials is mediated by a layer of proteins that adsorb rapidly to the surface of the implant.
- A fundamental understanding of the interaction between this adsorbed layer and the polymer surface is crucial in guiding the design of biocompatible devices for biomedical applications.

## Objectives

- Develop molecular simulation capabilities for the accurate simulation of protein adsorption behavior that address existing sampling limitations.
- Examine interactions between model host-guest peptides and polylactide (PLA) surfaces under physiological conditions (Figure 1).

## Model System



**Fig. 1.** GGGG-K-GGGG peptide (G = glycine; K = lysine) solvated in explicit TIP3P water over a crystalline PLA surface with Na<sup>+</sup> (tan) and Cl<sup>-</sup> (silver) ions approximating a 140-mM physiological saline solution. (Note: PLA hydrogen atoms have been omitted for clarity. Nominal system dimension: 36.9 × 66.0 × 57.8 Å. Peptide is shown with an SSD value of 15 Å.)

## General Simulation Details

- Academic CHARMM (31b1); VV2 integrator
- Nosé-Hoover thermostat; Particle Mesh Ewald
- SHAKE algorithm on hydrogen atoms; 2-fs time step

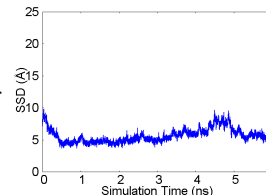
## Free Energy of Adsorption

- Characterize and quantify the interaction between the peptide and the surface as a function of Surface Separation Distance (SSD), calculated as the distance between the peptide's center of mass and the surface.
- The change in free energy of adsorption,  $\Delta G_a$ , depends upon the positional probability ( $P_i$ ) of the peptide in SSD space compared to the probability of a defined reference position ( $P_0$ ).

$$\text{Eqn. 1} \quad \propto \frac{RT}{P_i} \ln \frac{P_i}{P_0}$$

## MD Simulation

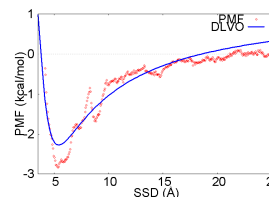
- Eqn. 1 needs finite  $P_i$  values for the entire range of SSD space of the system.
- Strongly interacting systems sample only the region of SSD space adjacent to the surface (see Figure 2) within a reasonable time frame.



**Fig. 2.** Trajectory from a conventional MD simulation reveals that the peptide “sticks” to the surface - the sampling problem.

## Windowed Umbrella Sampling

- 44 windows (independent simulations) spanning an SSD range of 3.5 – 25 Å in 0.5-Å increments.
- Harmonic constraint potential applied to peptide to ensure thorough sampling of a small region of SSD space per window.
- Iteratively solve Eqn. 1 with Weighted Histogram Analysis Methods (WHAM) to obtain an estimate of the Potential of Mean Force (PMF, Figure 3).



**Fig. 3.** Estimate of the PMF for the peptide-PLA system obtained from windowed umbrella sampling (points) and best-fit DLVO-type potential (line) to be used as a biasing potential (Eqn. 2).

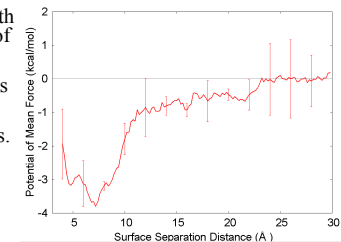
## Biased Replica Exchange Molecular Dynamics (REMD)

- The DLVO (Derjaguin and Landau; Verwey and Overbeek) potential shown in Eqn. 2 was used to model the PMF obtained from umbrella sampling.

$$\text{Eqn. 2} \quad V_{DLVO} = \frac{abc}{SSD^2 SSD_0^2 e^{-\frac{SSD}{\tau}}}$$

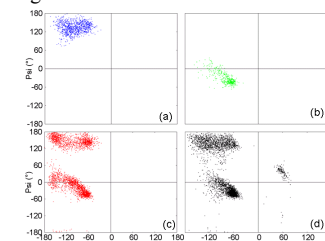
- An applied bias potential – as the negative of the DLVO fit in Fig. 3 – was added to the force field to encourage the peptide to more uniformly sample SSD space, enabling

biased REMD simulations to be performed with **Fig. 4.** Estimate of the PMF as a function of SSD for the peptide-PLA system obtained from biased REMD simulations. Error bars represent 95% confidence intervals based upon three independent REMD simulations. (The grey line at PMF = 0 is shown as a guide for the eye.)



## Conformational Sampling

- Previous work has indicated that neither umbrella sampling nor unbiased REMD simulation alone are adequate to fully capture the behavior of protein adsorption. It is hypothesized that enhanced conformational sampling explains the difference in PMFs calculated from the umbrella and biased REMD simulations.
- Phi/Psi dihedral angle distributions for the guest residue (lysine) are presented in Figure 5 as a measure of conformational sampling.



**Fig. 5.** Ramachandran plots for the lysine residue from three simulations: (a) and (b) independent biased MD, (c) Biased REMD compared to (d) 4153 lysine residues from the 500-structure, high-resolution database of Lovell et al.

## Conclusion & Future Work

- A fairly strong adsorption response was predicted between the GGGG-K-GGGG peptide and the PLA surface, with an adsorption free energy of  $-2.5 \pm 0.6$  kcal/mol. This response is primarily driven by hydrophobic interactions between non-polar groups of the peptide and the PLA surface (a relatively hydrophobic polymer).
- The results from these simulations will be used to develop simulations in which a PLA chain has been hydrolyzed, a physically realistic and important phenomenon.

**Acknowledgements:** This work was supported by the ERC program of the National Science Foundation under Award Number EEC-9731680.

