Windowed Umbrella Sampling Algorithm for the Calculation of Peptide/Surface Adsorption Free Energy

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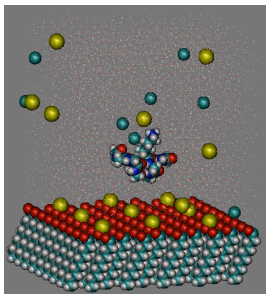
Statement of Purpose: The thermodynamic property that is most important for characterizing the adsorption behavior of a protein on a surface is the change in free energy (ΔA) for the interaction between the peptide residues making up the protein and the functional groups of the surface, as illustrated in Fig. 1. However, due to the complexity of this type of molecular system, conventional MD simulations, which provide Boltzmann sampling, do not sample the configurational space sufficiently for the calculation of ΔA [1]. To address this issue, we are working towards the development and application of non-Boltzmann sampling algorithms that can be efficiently applied to calculate ΔA for peptide-surface interactions. In previous work, we investigated the application of the standard umbrella sampling (SUS) [2] and the adaptive umbrella sampling (AUS) [3] algorithms for the calculation of the ΔA vs. surface separation distance (SSD) relationship. Both of these methods, however, have been found to have intrinsic limitations. The SUS algorithm requires the shape of the free energy profile to be known *a priori*, which is very unlikely for a complicated molecular system such as this. In contrast, AUS uses non-Boltzmann algorithms combined with the weighted histogram analysis method (WHAM) [4] in attempt to generate the ΔA vs. SSD profile over the full range of the designated reaction coordinate (i.e., SSD) in an automated manner starting from a zero biasing potential, and hence requires no *a priori* knowledge. However, while very effective for a simple system such as Na^+/Cl^- interactions in vacuum [5], AUS is not suitable for a peptide/SAM system in explicit solvent because unreasonably long simulation times are needed for each adaptive cycle to allow the peptide to properly diffuse throughout the simulation cell. Preliminary studies have shown that without adequate simulation time per cycle, the AUS method tends to greatly overestimate the free energy barrier as a function of SSD and does not converge to a stable profile. In order to overcome the limitations of the above two methods, the present research investigated another well known variant of umbrella sampling, which is called windowed umbrella sampling (WUS). In this method, the system is simulated with a harmonic constraining potential applied to confine the peptide to stay within a prescribed range about a defined central SSD position (SSD_i), with SSD_i then incrementally varied over the full SSD range to be sampled. This enables the complete SSD range to be sampled at one time using a series of relatively short, parallel, independent simulations. Following completion, the sampling data from each window is combined together using WHAM to calculate the overall ΔA vs. SSD profile.

Methods: The peptide/SAM system (Fig. 1) consisted of a 9-residue peptide, G_4-K-G_4, in zwitterionic form, a COOH-SAM surface with a 9/1 ratio of COOH/COO^- groups in a square solvent box (44.73Å x 43.04Å x 59.46Å) with 0.150 M NaCl in TIP3P water. 26 windows were prepared with the peptide/SAM SSD spanning from 4Å - 29Å. To check for convergence, each window was simulated at 310K for 200–1,000ps in 200ps increments with a harmonic restraining potential by the following formula:

Fig. 1. A G_4-K-G_4 peptide over a COOH-SAM surface in 0.150 M saline.



$$U_i = \frac{1}{2} k_i (\theta - \theta_{i,0})^2$$

with k_i = 3.0 kcal/mol/Å^2 and $\theta_{i,0}$ = SSD_i.

The potential of mean force (PMF) profile (i.e., ΔA vs. SSD) was then generated using the WHAM method [4].

Results / Discussion: Fig. 2 presents the results of the WUS simulations for the model system described above, with the results fitted with a DLVO type potential [7]. As shown, the results converge well when the simulation time goes to 1,000ps as demonstrated by close agreement between the 800ps and 1,000ps results.

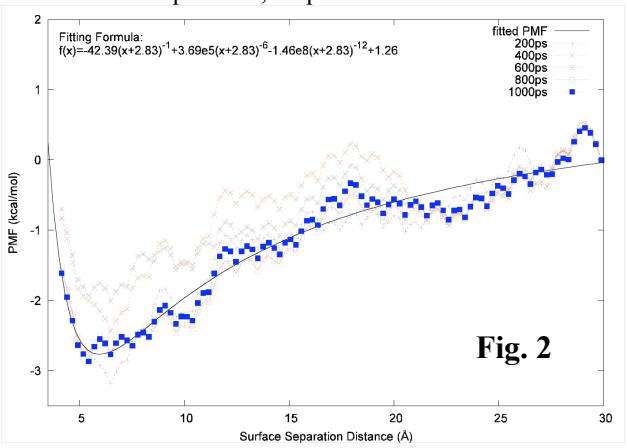


Fig. 2

Conclusions: Our results show that WUS is a superior method for this type of molecular system; it enables a converged PMF vs. SSD profile to be determined from a set of relatively short, parallel simulations without any prior information, and it completely eliminates the diffusion problem that is inherent in the AUS method. This method is currently being further developed in preparation for application to a wide range of peptide/surface systems for comparison with complementary experimental studies.

Refs: 1) Raut et al., Langmuir 2005, 21: 1629. 2) Torrie et al., J. Comput. Phys. 1977, 23: 187. 3) Bartels et al., Theor. Chem. Acc. 1999, 101: 62. 4) Kumar et al., J. Comb. Chem. 1992, 13:1011. 5) Wang et al., Trans. SFB, 2005, pg. 532. 6) Mezei et al., Compu. Simu. Chem. Biomol. Sys. 1986, 482:1. 7) Israelachvili J., Intermolecular & Surface Forces, 2nd Ed., Academic Press, NY, 1992.