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

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Statement of Purpose: Although cellular response to biomaterial surfaces is recognized to be governed by the bioactivity of adsorbed proteins, the molecular mechanisms that determine adsorbed protein bioactivity are still not well understood. Without this, the design of surfaces to control cellular response can only be approached by trial-and-error. Molecular dynamics (MD) simulation has great potential to be used in conjunction with experimental studies to help elucidate the molecular mechanisms that control protein adsorption. The two primary issues that must be addressed are the accuracy of the force field, which determines how the atoms of the protein interact with the atoms of a surface, and the ability to adequately sample the configurational space of a protein-surface system in order to calculate properties that can be directly compared to experimental values. 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.

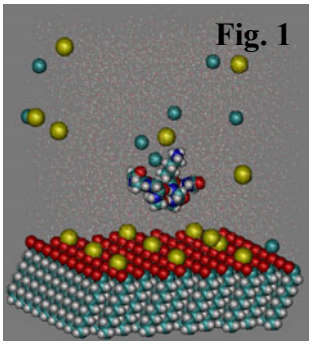
Fig. 1

In previous work, we investigated the application of the standard umbrella sampling (US) algorithm [2] for the calculation of the ΔA vs. separation distance (SD) relationship for a simple ion pair (Na^+/Cl^-) [3], with SD serving as the reaction coordinate (RC) of the system. This study demonstrated the ability of US to enable the MD simulation to escape out of a low-energy well to provide sufficient sampling for the accurate calculation of ΔA vs. SD. While effective, this method requires that either the shape of the free energy surface be known *a priori*, or if not, the system must be divided up into small increments over the range of SD and the results then manually combined to obtain the ΔA profile over the full range of the RC. A much more efficient and automated method of calculation, however, is provided by a method known as "adaptive umbrella sampling" (AUS) [4]. This methods uses non-Boltzmann algorithms combined with the weighted histogram analysis method (WHAM) [5] to generate the free energy surface over the full range of the designated RC in an automated manner. The objective of this present research was therefore to apply the AUS algorithm to the Na+/Cl^- ion system and demonstrate its ability to accurately predict the ΔA vs. SD relationship for this model system over the full range of RC.

Methods: AUS was implemented by the following steps: 1) A conventional MD simulation of the Na^+/Cl^- system was first run followed by a histogram analysis of the trajectory data using the probability ratio method [6] to generate an unbiased potential of mean force (PMF) profile, which was then smoothed and fitted with a polynomial equation. 2) Another simulation was then run with the negative of the previously generated PMF profile equation applied as the umbrella potential to generate a new trajectory. 3) The WHAM algorithm was then applied to combine the statistics from all previous simulations to determine an updated unbiased system PMF profile, which was again smoothed and fitted with a polynomial equation. 4) This process was iterated until the unbiased system PMF profile converged.

Results / Discussion: Fig. 2 presents the results of the AUS simulation for the Na^+/Cl^- system, with the results compared to the analytical solution for this problem. As shown, the results from the AUS simulation provide excellent agreement with the analytical solution over the entire SD range after a series of iterations without reference to any *a priori* knowledge of the system PMF profile.

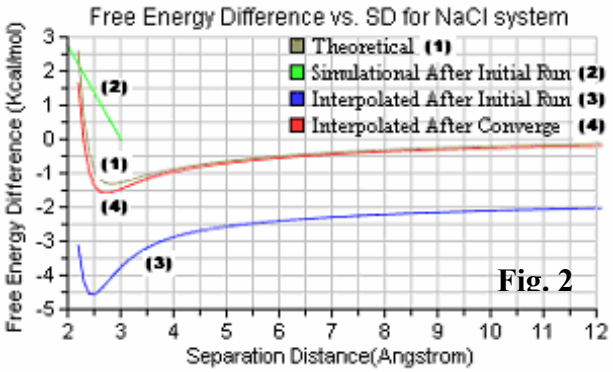

Fig. 2

Conclusions: The AUS algorithm provides an excellent method to calculate ΔA vs. SD relationships for model systems, such as Na^+/Cl^-. This method should similarly provide an excellent method for the calculation of ΔA vs. SD relationships for peptide-surface interactions. This capability provides the means to evaluate and accurately parameterize any selected force field for the simulation of protein-surface interactions by being able to compare simulation results to experimentally determined values of the free energy of peptide adsorption to surfaces [7].

Refs: 1) Raut et al., Langmuir 2005, 21: 1629. 2) Torrie et al., J. Comput. Phys. 1977, 23: 187. 3) Wang et al., Trans. SFB, 2005, pg. 532. 4) Bartels et al., Theor. Chem. Acc. 1999, 101: 62. 5) Kumar et al., J. Comb. Chem. 1992, 13:1011. 6) Mezei et al., Compu. Simu. Chem. Biomol. Sys. 1986, 482:1. 7) Vernekar & Latour, Mater. Res. Innovations. 2005, 9: 337.