Development of Tuned Interfacial Force Field Parameters in CHARMM for the Accurate Molecular Dynamics Simulation of Peptide Adsorption on Biomaterial Surfaces

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Statement of Purpose

Protein-surface interactions are critically important for a broad range of applications in bioengineering including the biocompatibility of medical devices, the bioactivity of biosensors and bioconjugate systems for tissue engineering and regenerative medicine, and drug delivery, as well as for numerous applications in biotechnology, such as the design of bioactive nanoparticles for sensing, bioassays, and biocatalysis, and the development of detection, filtration, and decontamination systems for biodefense. A fundamental molecular-level understanding of protein-surface interactions (**PSIs**) is crucial for each of these applications if design and optimization is to be undertaken by a knowledge-based approach as opposed to trial-and-error.

All-atom molecular dynamics (**MD**) simulation methods hold great promise as a valuable tool for understanding and predicting PSIs. However, since protein adsorption is very complex by its nature, these methods have to be first properly tuned and validated before they will be able to accurately represent protein adsorption behavior on material surfaces.

Materials and Methods

In this study we used the CHARMM molecular simulation program with available CHARMM force field parameterization to simulate the adsorption behavior for small host-guest peptides (TGTG-X-GTGT: X = N, D, G, K, F, T, W, or V) on high density polyethylene (**HDPE;** (110) crystalline surface plane). Advanced sampling methods (umbrella sampling and biased replica exchange molecular dynamics, biased-REMD) were applied in order to accurately calculate Helmholtz adsorption free energies ($\Delta A°_{ads}$) and compare values with experimentally measured adsorption free energies[1]. The interfacial non-bonded van der Waals (vdW) parameters and atom partial charge parameters were then tuned using our *Dual force field (Dual FF) CHARMM* program[2], to match $\Delta A°_{ads}$ values with experimental values within ±1.0 kcal/mol.

Umbrella sampling simulations were conducted for each host-guest peptide on HDPE using the default CHARMM parameters (Fig. 1), and initial estimates of $\Delta A°_{ads}$ were obtained. Values were found to deviate by up to 2.5 kcal/mol compared to experimental values. Umbrella sampling simulations were then performed to identify the dominant factors controlling peptide adsorption behavior: (*i*) normal CHARMM, (*ii*) vdW interactions only (i.e., partial charges set to zero), and (*iii)* electrostatic interactions only (vdW well depth set to near zero).

PMF profiles from umbrella sampling indicated that vdW effects dominated adsorption while electrostatic contributions were minimal. Interfacial force field (**IFF**) parameters in *Dual FF* CHARMM were then tuned to bring $\Delta A°_{ads}$ from simulation into closer agreement with experimental values (Fig. 3). Final biased-REMD simulations are currently being conducted to further evaluate and tune this IFF parameter set for HDPE.

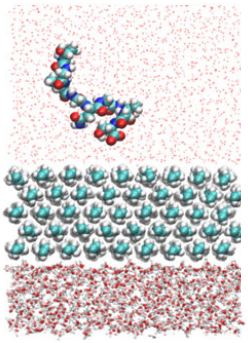

Fig. 1. Representative model of host-guest (TGTG-N-GTGT) peptide in explicitly represented TIP3P water over a HDPE (110) surface for MD simulations. Viewed down long-axis of HDPE chains.

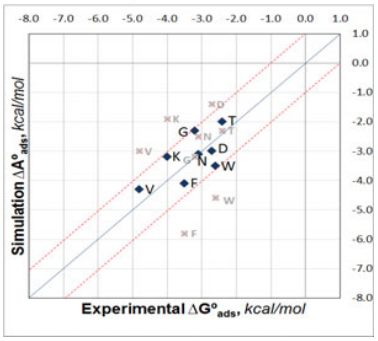

Fig. 2. Correlation between experimental $\Delta G°_{ads}$ values and calculated $\Delta A°_{ads}$ values from simulations using the default CHARMM parameter set (grey points) and the tuned IFF parameter set (blue spots) on an HDPE surface.

Conclusion and Future Work

Final tuning of the IFF parameter set to enable peptide adsorption behavior to closely match experimental results on HDPE is underway. Similar efforts are also in progress to tune IFF parameters for the TGTG-X-GTGT peptides on poly(methy methacrylate) and silica glass[3] surfaces. Subsequent studies are planned to apply the tuned IFF parameter sets to simulate the adsorption behavior of small proteins (lysozyme, PDBID: 1GXV; ribonuclease A, PDBID: 5RSA) to each surface, for which synergistically matched experimental studies are also being conducted. Comparisons will be used to validate the ability of the developed methods to accurately simulate protein-surface interactions.

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