Development and Validation of an Interfacial Force Field for the Accurate Simulation of Protein-Surface Interactions

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Statement of Purpose: While much has been learned from decades of conducting experimental studies to understand protein adsorption behavior, the experimental methods applied have generally not been able to provide the level of submolecular detail that is necessary to understand and predict it. Molecular modeling methods, on the other hand, are specifically well suited to provide this kind of information. Of the various types of methods available, empirical force field methods are best suited for protein adsorption behavior. Empirical force field methods use an equation to calculate the potential energy of a molecular system by summing up the contributions from each type of chemical bond in the system. The values of these potential energy contributions (e.g., covalent bond stretching) are a function of the set of parameters that are used in the equation (e.g., stiffness of a given type of covalent bond). Accordingly, before accurate simulations of protein adsorption behavior can be conducted, parameters that define the interaction energy between amino acid residues, water, ions, and functional groups of a surface must be properly tuned and balanced to accurately reflect these types of interactions. The objectives of this research were therefore to evaluate an existing empirical force field (CHARMM) for the simulation of protein adsorption behavior by comparing simulations of peptide adsorption behavior with available experimental data, identify systems where the simulation results do not accurately reflect experimentally observed behavior, and then adjust the empirical parameters until satisfactory agreement is achieved.

Methods: Simulations were conducted using the CHARMM molecular simulation program and force field for our initial set of studies. Simulations were conducted using a host-guest peptide in the form of TGTG-X-GTGT (X=guest amino acid), with X varied over amino acid types. Surfaces were modeled as alkanethiol self-assembled monolayers (SAMs) on gold, with surface functional groups varied over a wide-range of functionalities (Fig 1). These molecular systems were selected in order to compare with an available experimental data set generated in which surface plasmon resonance spectroscopy (SPR) was used to determine adsorption free energy (ΔG_{ads}) for a similar set of host-guest peptides and SAM surfaces.[1] Simulations were conducted at 298 K, 1.0 atm pressure using explicit solvation representing physiological saline (TIP3P water in 140 mM Na^+/Cl^-) using periodic boundary conditions. ΔG_{ads} was calculated by molecular simulation using a biased-energy replica-exchange molecular dynamics (biased-REMD) method that we developed for this purpose.[2] By comparing ΔG_{ads} values from the simulations with those obtained experimentally, we were able to identify the types of interfacial adsorption behaviors that the CHARMM force field accurately represents and types of interactions that have substantial error. We then developed a modified version of the

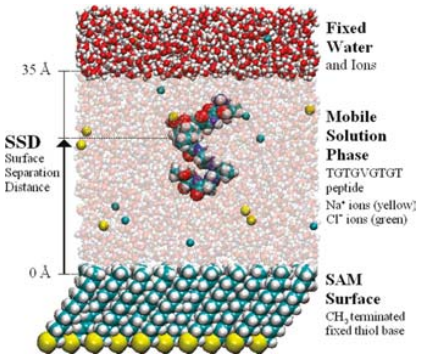

Fig. 1. Molecular model of TGTG-V-GTGT peptide over a CH_3-SAM surface in 140 mM Na^+/Cl^- solution. Yellow spheres = Na^+ ions, blue/green spheres = Cl^- ions.[2]

CHARMM program (which we refer to as dual force field (dual-FF) CHARMM) in which the force field parameters controlling interactions between atoms in the solution phase with those of the surfaces could be adjusted independently of the parameters controlling the behavior of the peptide in solution or the SAM surfaces themselves, thus providing a means of tuning peptide adsorption behavior without altering the behavior of the peptides in solution, for which the conventional CHARMM force field was tuned to represent.

Results: The comparison between the values of ΔG_{ads} calculated using the conventional CHARMM parameters to control interfacial interactions vs. ΔG_{ads} from SPR are

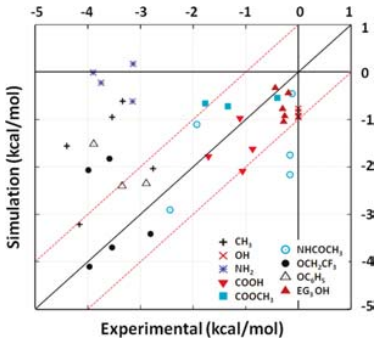

Fig.2. Comparison between ΔG_{ads} values determined by simulation using the conventional CHARMM force field with ΔG_{ads} values obtained using SPR.[2]

shown in Fig. 2. CHARMM substantially underestimates the strength of peptide adsorption for hydrophobic and positively charged surfaces, while slightly over-estimating the strength of adsorption for polar and negatively charged hydrophilic surfaces. These results provide direction for how interfacial force field parameters need to be adjusted to tune the interfacial force field to accurately represent peptide and protein adsorption behavior. We are currently using the Dual-FF program to adjust interfacial parameters to minimize these errors.

Conclusions: Force field parameterization must be specifically tuned and validated to accurately represent protein adsorption behavior.

Acknowledgements: NIH for funding (grant EB006163).

Refs: 1. Wei and Latour, Langmuir 2009, 25:5637.
2. Vellore et al., Langmuir 2010, 26:7396.