Parameterization of an interfacial force field for accurate representation of peptide adsorption free energy on high-density polyethylene

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(Received 4 February 2015; accepted 17 March 2015; published 27 March 2015)

Interfacial force field (IFF) parameters for use with the CHARMM force field have been developed for interactions between peptides and high-density polyethylene (HDPE). Parameterization of the IFF was performed to achieve agreement between experimental and calculated adsorption free energies of small TGTG-X-GTGT host-guest peptides (T = threonine, G = glycine, and X = variable amino-acid residue) on HDPE, with ± 0.5 kcal/mol agreement. This IFF parameter set consists of tuned nonbonded parameters (i.e., partial charges and Lennard-Jones parameters) for use with an *in-house-modified* CHARMM molecular dynamic program that enables the use of an independent set of force field parameters to control molecular behavior at a solid-liquid interface. The *R* correlation coefficient between the simulated and experimental peptide adsorption free energies increased from 0.00 for the standard CHARMM force field parameters to 0.88 for the tuned IFF parameters. Subsequent studies are planned to apply the tuned IFF parameter set for the simulation of protein adsorption behavior on an HDPE surface for comparison with experimental values of adsorbed protein orientation and conformation.

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I. INTRODUCTION

The interaction of proteins with material surfaces is important in many applications including the biocompatibility of implant biomaterials,¹⁻³ drug delivery systems,^{4,5} biosensors,^{6,7} surfaces for bioseparation,⁸ and biodefense.⁹⁻¹² A fundamental understanding of the molecular-level events accompanying protein-surface interactions is necessary to support the knowledge-based design of material surfaces for these applications. Without this level of understanding, surface design to control protein-surface interactions can essentially only be approached by trial-and-error with low probability of obtaining optimal conditions.

Over the past few decades, all-atom empirical force field molecular dynamics (MD) simulations have played a remarkable role in the study of protein folding and unfolding behavior in aqueous solution. Similarly, MD holds great promise as an important tool to enhance the atomistic-level understanding and prediction of conformational shifts and orientation of proteins when they are adsorbed on, or tethered to, material surfaces. However, it must be recognized that the molecular environment at a liquid-solid interface can be expected to be substantially different from the molecular environment in bulk liquid solution.¹³ Therefore, force field parameters that have been developed and optimized to

represent the behavior of proteins in aqueous solution cannot be expected to also accurately represent protein adsorption behavior on a material surface, especially when the force field does not treat electrostatic polarizability. Instead, interfacial force field (IFF) parameters need to be separately tuned to appropriately represent the interactions between amino-acid residues and a material surface before simulations can be expected to accurately represent protein adsorption behavior.^{14,15} In addition, a molecular simulation program is required that enables the use of IFF parameters to represent interactions at an interface independently of force field parameterization that is used to represent the behavior of the liquid and solid phases of the system. Our group has previously made modifications to the CHARMM molecular simulation program to provide this capability,¹⁶ which we refer to as dual-force-field CHARMM (Dual-FF CHARMM).

The Dual-FF CHARMM program employs two independent sets of nonbonded parameters: one set to represent intraphase interactions (i.e., within the solution or material phases) and another set (i.e., the IFF) for interphase interactions (i.e., between the solution and material phases). Dual-FF CHARMM represents an important development for further proposed protein adsorption studies as it permits the IFF to be separately parameterized based on experimental data to accurately represent protein-surface interactions while the conformational behavior of the protein in solution can be

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separately represented by its own validated protein force field.¹⁶ We are presently developing similar capabilities in the LAMMPS molecular simulation program¹⁷ as well.

In order to tune a set of force field parameters to accurately represent the interactions between amino-acid residues and a material surface, it is necessary to first have designated target property values that can characterize amino-acid adsorption behavior and be calculated from simulation. IFF parameters can then be adjusted until the simulated values match those of the target properties. Ideally, these properties would be obtained from experimental data. In the absence of available experimental data, target values must come from an alternate source, such as from quantum mechanical calculations.

One of the most representative properties for the characterization of interactions between amino-acid residues and material surfaces is adsorption free energy, which can be readily determined experimentally and calculated by molecular simulation. Wei and Latour have developed experimental methods using surface plasmon resonance (SPR)^{18,19} to measure the change in Gibbs free energy ($\Delta G^\circ_{\text{ads}}$) for the adsorption of small host–guest peptides on functionalized self-assembled monolayer (SAM) surfaces. The host–guest peptides had the sequence TGTG–X–GTGT, where T and G (threonine and glycine, respectively) are the “host” amino acids, and X represents the “guest” amino acid, which can be any selected amino acid type. By varying the “X” amino acid type, the general character of the host–guest peptide and its subsequent adsorption affinity for a given surface was changed, providing a sensitive model system to characterize amino acid–surface interactions. Recently, Wei and Latour¹⁹ and Thyparambil *et al.*²⁰ extended these methods using atomic force microscopy (AFM) to characterize the adsorption behavior of a large range of peptide–surface combinations on material surfaces that are not conducive for use with SPR, such as silica glass, poly(methyl methacrylate), and high-density polyethylene (HDPE).^{19,20} In previous studies, Latour and coworkers used these experimental data along with the Dual-FF CHARMM program to tune IFF parameters to represent amino acid adsorption behavior to both SAM surfaces^{16,21} and a silica glass surface²² using CHARMM22/CMAP as the default parameter set for the host–guest peptide and its interactions with these surfaces. For both of these types of surfaces, adsorption free energies using the default CHARMM parameter set were found to deviate substantially from experimental values, thus requiring IFF parameter adjustment.

Other groups have taken similar approaches to represent interactions between amino-acid residues and several different types of inorganic surfaces. Tomásio and Walsh investigated peptide–carbon nanotube and peptide–graphite interactions using an implicit solvent and a polarizable force field for peptide–surface interactions.²³ Another set of studies, by Iori *et al.*²⁴ and Wright *et al.*,²⁵ reports a combined *ab initio*- and experiment-based parameterization of a classical atomistic force field for the simulation of amino-acid residues on gold surfaces in aqueous solution using explicit

solvation. In a study by Schneider and Colombi Ciacchi, a combination of metadynamics and steered MD simulations was performed to study the binding affinity of small peptides to titanium and silicon surfaces.²⁶ As an alternative approach, Heinz *et al.* have presented a quantitative analysis of energy changes as a consequence of conformational changes of several short peptides after adsorbing on palladium, gold, and bimetallic palladium–gold surfaces using MD simulations in explicit water with an efficient computational screening technique.²⁷ By another approach, a specialized MD force field for the interactions of amino acids with metals was introduced in a recent study by Feng *et al.* involving the calculation of the free energy of adsorption of small peptides.²⁸ While many groups have thus reported on simulations of peptide adsorption to various inorganic surfaces relatively few studies have addressed peptide interactions with organic surfaces, which represent an equally important category of surface chemistries.

In this present study, we describe a set of studies similar to those conducted by Snyder *et al.*²² for the evaluation and tuning of IFF parameters to represent amino-acid adsorption on an HDPE surface instead of silica glass. As with Snyder *et al.*, we used CHARMM22/CMAP force field parameters as the default IFF parameter set, which we found to result in substantial deviations between calculated and experimental adsorption free energies. We were then able to adjust IFF parameters to bring the adsorption free energies in close agreement with experimental values to establish a set of IFF parameters that should be suitable for subsequent application for the simulation of protein adsorption to an HDPE surface.

II. METHODS

A. Peptide adsorption free energy on HDPE from experimental studies

In previous studies, we used SPR spectroscopy and AFM to determine the standard-state free energy of adsorption ($\Delta G^\circ_{\text{ads}}$) for a custom-designed host–guest peptide and the force required for peptide desorption (F_{des}), respectively, for a wide range of surface chemistries in different buffer systems and showed that these two parameters were strongly correlated.^{20,29,30} In the present study, we implemented our standardized AFM method to determine the effective adsorption free energy of the same host–guest peptides on an HDPE surface, with specific details of this approach previously published.^{20,29,30} All peptide–surface interactions were investigated in a 10 mM potassium phosphate buffer (PPB) with phosphate salts of potassium (Fisher Scientific) added to provide a pH of 7.4.

The host–guest model peptides, which were synthesized by Biomatik (characterized by analytical HPLC and mass spectral analysis; $\geq 98\%$ purity) were designed with the amino-acid sequence of TGTG–X–GTGT or TGTG–X–GTCT with zwitterionic end groups, where G, T, and C are glycine (–H side-chain), threonine [–CH(CH₃)OH side-chain], and cysteine (–CH₂SH side chain), respectively. Ten different “guest” residues (–X–) were used in the host–guest

TABLE I. List of the ten selected amino acids used for the X residue in the TGTG–X–GTCT and TGTG–X–GTGT host–guest peptides. Each amino acid has the general structure of (–NH–CHR–CO–) with **R** presenting the side chain structure as presented here.

–X– residue	Side chain (R)	Property
Alanine (A)	–CH ₃	Nonpolar
Arginine (R)	–(CH ₂) ₃ –NH–C(NH)–NH ₃ ⁺ (pK = 12.52) (Ref. 31)	Positively charged
Asparagine (N)	–CH ₂ –CO–NH	Neutral polar
Aspartic acid (D)	–CH ₂ COO– (pK = 3.97) (Ref. 31)	Negatively charged
Glycine (G)	–H	Nonchiral
Lysine (K)	–(CH ₂) ₄ –NH ₃ ⁺ (pK = 10.78) (Ref. 31)	Positively charged
Phenylalanine (F)	–CH ₂ –C ₆ H ₅	Aromatic
Threonine (T)	–CH(CH ₃)OH	Neutral polar
Tryptophan (W)	–CH ₂ –indole ring (C ₈ H ₆ N)	Aromatic
Valine (V)	–CH(CH ₃) ₂	Nonpolar

peptides in this study, which were selected to represent each of the primary types of amino acids [i.e., nonpolar (aliphatic and aromatic), polar, positively charged, and negatively charged]. These are presented in Table I, along with their side-chain chemical structure and their characteristic property.

TGTG–X–GTGT was initially used in our previous SPR studies^{18,19} while TGTG–X–GTCT was used in both our SPR and AFM studies, with the cysteine (C) residue specifically required for the AFM studies as the linker to connect our host–guest peptide sequences to the AFM tip via a cross-linker (3.4 kDa pyridyldithio poly(ethylene-glycol) succinimidylpropionate (PDP-PEG-NHS), Creative PEGWorks; polydispersity index = 1.08).³⁰ To address concerns of the effect of the swapping of “G” in TGTG–X–GTGT for “C” in TGTG–X–GTCT on the adsorption behavior, we conducted preliminary studies³⁰ to confirm that cysteine could be incorporated into this host–guest peptide model without significantly changing the free energy of adsorption of the peptide. By confirming this equivalence, our previously determined $\Delta G^\circ_{\text{ads}}$ values¹⁹ measured for the TGTG–X–GTGT peptide model using SPR could then be directly correlated with the AFM results using the modified peptide model, TGTG–X–GTCT.

For the present studies, we formed thin films of HDPE by spin-coating HDPE film on glass. The glass substrates (Chemglass Life Sciences) were cleaned by sonicating in “piranha” solution [7:3 (v/v) H₂SO₄ (EMD Chemicals, SX 1244)/H₂O₂; Ricca Chemicals, 3821] followed by basic solution [1:1:3 (v/v/v) NH₄OH (BDH Chemicals, BDH3016)/H₂O₂/H₂O]; with each wash procedure conducted at 50 °C for 1 min. HDPE (M_w = 125 000 Da, Sigma #181900) was then spin-coated onto the clean glass substrates from dodecalin (Sigma #294772) (0.5% w/w) at 1500 rpm for 60 s. The HDPE surfaces were characterized for their static air–water contact angle (contact-angle goniometer; Kruss, DSA-20E),

atomic composition (x-ray photoelectron spectroscopy; NESCA/BIO, University of Washington), film thickness (variable angle spectroscopic ellipsometer; Sopra Inc., GES-5), and surface roughness (AFM; Asylum Research, MFP-3D, over an area of 5 μm $\times$ 5 μm). The results from these surface characterization studies are presented in Table II.

High-resolution desorption force measurements were done using AFM (MFP-3D instrument, Asylum Research) with DNP-10 silicon nitride cantilever tips (Veeco Nanofabrication Center). The host–guest peptide sequences were then covalently tethered to the silicon nitride AFM tips via the heterobifunctional PDP-PEG-NHS cross-linker. Force measurements were performed using our standardized AFM technique.²⁰ Briefly, all force spectroscopy experiments were performed at room temperature in a fluid cell filled with droplets of PPB, pH 7.4. The functionalized tip with the peptide was brought in contact with a HDPE surface for 1 s of surface delay and then retracted at a constant vertical scanning speed of 0.1 $\mu\text{m/s}$. Tips with PEG-OH (i.e., without peptide) were used as controls. The deflection signals (volts) were converted to force (Newtons) using the settings of: (1) deflection sensitivity in the range of 40–100 nm/V, (2) spring constant of tips of 0.058–0.065 N/m (from the thermal-tune method³²), and (3) applying correction for off-set deflection.

The interaction force trace was then recorded as a function of the tip–sample separation distance, from which F_{des} values were measured. For each of the peptide–surface systems, two different substrate samples from the same material were used, and force measurements were performed at three distinct sites on each substrate. A minimum of ten force-separation curves were recorded at each site. In total more than 60 force-separation curves were used to generate a histogram from which the mean value of F_{des} was determined for each host–guest peptide. Effective values of $\Delta G^\circ_{\text{ads}}$ were

TABLE II. Surface characterization: Atomic composition, surface roughness, static contact angle and film thickness analyses for the HDPE surface. Mean ($\pm 95\%$ C.I.), $N = 3$.

Surface	C (%)	O (%)	Roughness (nm)	Contact angle (deg)	Thickness (nm)
HDPE	96.3 (2.7)	3.4 (2.6)	<8.0	97.0 (5)	100 (10)

then estimated from our previously validated F_{des} vs $\Delta G^{\circ}_{\text{ads}}$ correlation²⁹ for each peptide–surface system in 10 mM PPB for direct comparison with adsorption free energy values calculated from molecular simulation.

B. Molecular model construction and equilibration

All model constructions and MD simulations were carried out with our modified CHARMM Dual-FF molecular simulation program.³³ Similar to our experimental studies for peptide adsorption on an HDPE surface, simulations were performed to calculate the change in Helmholtz free energy ($\Delta A^{\circ}_{\text{ads}}$) for the adsorption of TGTG–X–GTGT host–guest peptides with charged N and C termini, where X represents one of the ten different amino-acid types as shown in Table I. As with our experimental studies, this set of amino acids was selected to represent each of the primary types of amino acids. It should be noted that for a condensed-phase system that undergoes negligible change in volume for a designated process (e.g., peptide adsorption), changes in standard-state Gibbs free energy (ΔG° ; obtained under constant temperature and pressure) and standard-state Helmholtz free energy (ΔA° ; obtained under constant temperature and volume) are equivalent, thus enabling the calculated values of $\Delta A^{\circ}_{\text{ads}}$ from our simulations to be directly compared with our experimentally measured values of $\Delta G^{\circ}_{\text{ads}}$.

The molecular model of HDPE was constructed using the coordinates of the unit cell for a (110) surface plane³⁴ from which a square-shaped unit cell in the x – y plane was generated approximately 45 Å on each side (x and y directions) and 15 Å thick (z direction). The surface had five layers (z direction) with nine polyethylene chains in each of the layers (x – y plane), with each polyethylene chain consisting of 18 repeating units of (–CH₂–CH₂–) monomers with their long-axis oriented in the x direction. Since the simulations were performed using 3D periodic boundary conditions (PBC), CHARMM PATCH commands were applied for creating covalent bonds, bond angles, and dihedral angles crossing the boundary between primary and adjacent image cells to represent an infinite surface.

The CHARMM22 protein force field³⁵ with CMAP correction³⁶ was used for the aqueous solution phase of the system (peptide, water, counterions), the CGenFF parameter set³⁷ was used for the atoms of the HDPE surface phase, and IFF parameters¹⁶ were used to represent interphase behavior between the solution phase and the HDPE surface. Initially, the IFF parameters used the nonbonded CHARMM force field parameters^{35,36} [i.e., partial charge (q_i), well depth (ϵ_i), and radius ($R_{\text{min } i}$)] as the default parameter set for each atom, with CHARMM's standard mixing rules applied for Lennard–Jones (L–J) interactions (i.e., geometric mean for well-depth and arithmetic mean for radii).

Each of the simulation systems consisted of a mobile solution phase of CHARMM TIP3P water³³ (~35 Å thick layer) on top of the HDPE surface and a fixed water layer (~15 Å thick) below the surface, with the peptide placed in the top water layer. The fixed layer of water was used to

prevent the peptide from interacting with the bottom of the HDPE surface when using PBC. A large water box was initially separately equilibrated in the isothermal–isobaric [NPT; constant number of atoms (N), pressure (P), and temperature (T)] ensemble at 298 K and 1 atm for 1.0 ns using the leapfrog integrator. Two water layers (35 Å mobile layer and 15 Å fixed layer) were subsequently created from this equilibrated water box. The fixed water layer was then placed in position with respect to the HDPE surface and equilibrated over the bottom of the material surface for 1.0 ns, following which the atoms in the water layer were fixed in position. The 35 Å mobile layer of water was positioned above the HDPE surface and remained mobile. The host–guest TGTG–X–GTGT peptide was then placed into the mobile water layer above the surface and water molecules within 3 Å from the peptide were deleted to eliminate atom–atom overlaps. One Na⁺ or Cl[−] counterion was then also added to the bulk water solution for the systems with X = K, R, or D for charge neutralization. Our simulation system, thus, represents the environment of the peptide solution used in our experimental studies with 10 mM PPB, which is equivalent to less than one ion each of potassium and phosphate (~0.42 PPB molecules) for the size of our simulation system. In order to stabilize the HDPE layer over the fixed layer of water, the positions of all heavy atoms of each of the HDPE chains on the bottom layer of the material surface slab were harmonically restrained with a very large force constant (2400 kcal/mol Å²). A harmonic force was also applied to a single carbon atom of each of the other chains in order to avoid nonphysical dissolution of the HDPE crystalline structure during the simulations. This peptide–HDPE system was then equilibrated for 1.0 ns. An example representation of our final model system for the TGTG–F–GTGT peptide over the HDPE surface is shown in Fig. 1.

After assembling the molecular system, the height of the simulation cell along the z -axis direction was adjusted using an approach previously developed by our group to provide 1 atm pressure for the mobile solution phase of the system.³⁹ This step is necessary because the total pressure that is reported by CHARMM for a molecular system containing fixed atoms can differ by hundreds of atmospheres from the local pressure in the mobile aqueous solution phase of the system. This misrepresentation of the solution pressure is a serious concern since the adsorption free energy is substantially influenced by the pressure of the solution phase of the system.³⁹ Thus if the size of the system is adjusted based on the value of the total system pressure as opposed to the pressure of the mobile solution over the surface, the resulting free energy values will not be comparable to our experimental values, which were obtained under 1 atm pressure conditions.

Following the pressure optimization procedure, the systems were further equilibrated for 6 ns in conventional MD simulation in the canonical [NVT; constant number of atoms (N), volume (V), and temperature (T)] ensemble using the modified velocity–Verlet integrator (VV2)⁴⁰ and a Nosé–Hoover thermostat.⁴¹ The van der Waals interactions were

FIG. 1. Representative model system for simulations with a TGTG-F-GTGT host-guest peptide on the HDPE surface. The specific system consists of 14 975 atoms. The image was generated using VMD (Ref. 38). The mobile water layer is shown using points for clarity, and the fixed water layer is displayed using a ball-and-stick representation. SSD is the surface separation distance between the center of gravity of the peptide and the top HDPE layer.

represented using the 12-6 L-J potential with a group-based force-switched cutoff starting at 8 Å and ending at 12 Å with a pair-list generation cutoff at 14 Å. Coulombic interactions were represented using a group-based force-shift cutoff with the same cutoff values. Bonds involving hydrogen atoms were constrained with RATTLE/ROLL, a SHAKE algorithm implementation in CHARMM,⁴² which enabled a 2 fs time-step to be used for the MD simulations.

C. Calculation of adsorption free energy by molecular simulation

To calculate $\Delta A^\circ_{\text{ads}}$ for peptide adsorption we use an umbrella sampling approach. The calculation of adsorption free energy requires the conformational behavior of the peptide to be sampled over the full range of surface-separation distance (SSD) values, where SSD represents the distance between the center of mass of the peptide and the defined surface plane to which the peptide is adsorbing.^{21,43} Sampling over the full range of SSD values can be problematic for strongly adsorbing material surfaces, such as HDPE. On such surfaces, peptides tend to adsorb very strongly and conventional MD simulations will only tend to sample states with the peptide trapped on the surface even for relatively long runtimes.⁴⁴ Because the calculation of adsorption free

energy requires the determination of the relative probability of the peptide in its adsorbed and desorbed states over the full range of SSD values, such a simulation cannot be used to calculate adsorption free energy. To overcome this sampling problem, we used umbrella sampling⁴⁵ restraining potentials to sample the full range of SSD values.

For our umbrella sampling simulations, a series of harmonic restraining potentials were applied to force the peptide to sample the full SSD coordinate space between 4 and 24 Å. These potentials had the form

$$V_u = 0.5 k_u (\text{SSD} - \text{SSD}_0)^2, \quad (1)$$

where V_u is the applied biasing energy, k_u is the force constant (2 kcal/mol Å²), and SSD_0 is the reference point on the SSD coordinate about which the center of mass of the peptide is restrained. MD simulations were first performed for 3 ns at 298 K in the NVT ensemble to equilibrate the system with the restraining potential applied prior to conducting production-run simulations from which sampling data were collected for analysis. The trajectories produced from the umbrella sampling simulations were then analyzed using the weighted histogram analysis method⁴⁶ to calculate both the probability (P_i) and potential of mean force (PMF) of the peptide as a function of SSD. $\Delta A^\circ_{\text{ads}}$ was then calculated using the probability ratio method from the sampled distribution of states using the expression^{21,43,47}

$$\Delta A^\circ_{\text{ads}} = -RT \ln \left[\frac{W}{\delta P_b} \sum_{i=1}^N P_i \right]. \quad (2)$$

Here, the subscripts i and b represent the interfacial and bulk solution regions of the system and P_i and P_b are the probabilities of the peptide being at positions SSD_i and SSD_b , respectively, with SSD_b being the distance from the surface for which peptide-surface interactions become negligibly small, which for our systems is typically beyond 18 Å from the surface plane. N is the number of incremental segments spanning the SSD-coordinate space for which $P_i \neq P_b$, δ is the theoretical thickness of the adsorbed layer identical to the value used for the calculation of the experimental value of $\Delta G^\circ_{\text{ads}}$,¹⁹ and W is the bin width used to produce the probability distribution. $\Delta A^\circ_{\text{ads}}$ values for the interaction of each host-guest peptide on each of the surfaces can thus be determined from simulations for comparison with the experimentally determined values of $\Delta G^\circ_{\text{ads}}$ obtained from our SPR and AFM studies for these same systems as a direct means of assessing the accuracy of the force field that is used in the simulations. Differences between the calculated and experimental values of adsorption free energy can then be used to identify situations where IFF parameters need to be adjusted to properly represent peptide adsorption behavior.

In our previous studies, we coupled umbrella sampling with replica-exchange MD (REMD) for the calculation of $\Delta A^\circ_{\text{ads}}$.^{21,43,47} This method first involved the generation of an estimate of the PMF profile from a relatively short (i.e., 3 ns) umbrella sampling simulation, the negative of which

was then used as a biasing-energy profile for a subsequent biased-REMD simulation.^{21,43,47} We previously considered this combined approach to be necessary to obtain adequate sampling over both the SSD and conformational phase space of the system for the accurate calculation of $\Delta A^\circ_{\text{ads}}$. This method, however, is very expensive in both time and computational resources. We therefore sought an alternative, more efficient approach for IFF tuning because of the numerous iterations that are involved in parameter adjustment and reassessment until a satisfactory set of IFF parameters can be obtained.

In the present study, we therefore first sought to determine if longer umbrella sampling simulations alone could be used to provide $\Delta A^\circ_{\text{ads}}$ values that were as accurate as those provided by our previous method combining umbrella sampling with biased-REMD. Details of these preliminary studies are provided in the supplementary material, Sec. S.1.⁴⁸ The results from these comparisons (see Fig. S.1 in supplementary material)⁴⁸ showed no significant difference in calculated $\Delta A^\circ_{\text{ads}}$ values using 15 ns umbrella sampling compared with umbrella sampling combined with biased-REMD, thus supporting the use of 15 ns umbrella-sampling simulations alone for the calculation of adsorption free energies for IFF parameter tuning without the need for biased-REMD simulations.

Additionally, we conducted secondary structure analyses of all host–guest peptides in both their solution and adsorbed states with STRIDE.⁴⁹ These analyses showed similar secondary structures in solution and when adsorbed, with the peptides essentially exhibiting random structure in all cases (i.e., STRIDE analysis showing predominantly random coil structure for each peptide). This is not surprising given the fact that the TGTG–X–GTGT sequence of our host–guest peptides was purposely designed to have random-coil structure (see Sec. S.4 and Fig. S.4 in supplementary material).⁴⁸

D. IFF parameter sensitivity assessment and tuning

After obtaining the free energies of adsorption using the standard CHARMM force field as our default parameter set, we compared the calculated adsorption free energy values with the experimentally determined values to evaluate how well they matched. IFF parameters were then adjusted for peptides with adsorption free energies deviating more than 1.0 kcal/mol from the corresponding experimental result to bring them more closely in agreement with the experimental value. This error tolerance was selected based on the 95% confidence interval (C.I.) of the experimental values, which was estimated to be about 0.9 kcal/mol. Because force field parameter tuning typically involves systems that are highly underdetermined (i.e., there is no unique parameter set, but rather many different combinations of parameters can be used to obtain a desired result), preliminary studies were first conducted to provide guidance regarding which parameters should be adjusted for IFF tuning.

The adsorption free energy between a peptide and a surface essentially reflects the competitive binding affinity

between atoms of the peptide and the water molecules in solution for the functional groups of the surface. These noncovalently linked interactions can be further separated into electrostatic and van der Waals contributions. The CHARMM force field represents these nonbonded terms of the force field by a Coulombic potential (ν_{Coul}) and a 12-6 L-J potential (ν_{LJ}), respectively, with the following expressions:

$$\begin{aligned}\nu_{\text{Coul}}(r_{ij}) &= \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}, \\ \nu_{\text{LJ}}(r_{ij}) &= \epsilon_{ij} \left[\left(\frac{R_{\text{min},ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{\text{min},ij}}{r_{ij}} \right)^6 \right],\end{aligned}\quad (3)$$

where q_i and q_j represent the partial charges between atoms i and j , separated by distance r_{ij} ; ϵ_0 is the permittivity of free space; ϵ_{ij} is the well depth of the L-J potential; and $R_{\text{min},ij}$ is the separation of the atoms when the L-J potential is at its minimum value (i.e., $\nu_{\text{LJ}}(R_{ij}) = -\epsilon_{ij}$). For the calculation of $\nu_{\text{LJ}}(r_{ij})$ between two atoms in CHARMM, each atom is assigned a parameter value of ϵ_i and $R_{\text{min},i}$, with geometric combining rules applied for the calculation of ϵ_{ij} (i.e., $\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$) and arithmetic combining rules for the calculation of $R_{\text{min},ij}$ (i.e., $R_{\text{min},ij} = (R_{\text{min},i} + R_{\text{min},j})/2$). Since our simulation systems consisted of a peptide, material surface, and explicitly represented water, it was important to understand which specific L-J and/or Coulomb force field parameters of the system (i.e., parameters for the atoms in the amino acids or water) most strongly contributed to peptide adsorption behavior, thus providing direction regarding which parameters should be adjusted to correct the differences in adsorption free energy. We did not consider modification of IFF parameters of the HDPE surface itself because changes to these parameters would simply tend to influence the adsorption behavior of both the peptide and the TIP3P water in a similar manner, while what is needed is to strengthen the adsorption affinity of the peptide relative to the water.

To investigate this issue, we first performed a simulation of a water droplet on the HDPE surface and calculated the value of the contact angle (θ) to compare with the experimental value⁵⁰ to separately assess how closely the nonbonded parameters between water and the HDPE surface represented actual behavior. We then conducted a series of umbrella sampling studies to generate PMF profiles as a function of SSD with either the Coulombic or L-J potential contributions to the force field removed, to assess which term most strongly dominated the adsorption behavior of the peptides to the HDPE surface. The methods and results from these preliminary simulations are presented in the supplementary material, Secs. S.2 and S.3, respectively.⁴⁸

The results of these preliminary studies indicated that the regular CHARMM parameters appropriately represented interactions between TIP3P water and the HDPE surface and that peptide adsorption affinities were primarily influenced by the L-J well-depth parameter (ϵ_i) of the force field with little influence of the partial charges (q_i). Based on these results, we subsequently modified the L-J IFF ϵ_i parameters

of individual amino acids with adsorption free energies that differed from their experimental values by more than 1.0 kcal/mol. Parameter adjustments were made, and adsorption free energies were recalculated using an iterative process until all adsorption free energies were well within 1.0 kcal/mol of the experimental values. As with any process involving force field parameterization, because similar atom types are present in several different amino-acid residues, adjustment of L-J parameters for a given atom type to correct the adsorption behavior on one amino-acid residue will subsequently alter the adsorption behavior of any other amino acid that contains the same atom type. This can lead to problems where adjustment of L-J parameters to correct the adsorption behavior of one amino-acid type results in further error in the adsorption behavior of another amino acid. When necessary, new atom types can be created (or shared atom types can be forked) to provide a means to independently tune the adsorption behavior of individual amino acids without influencing the adsorption behavior of other amino acids.

For each round of IFF parameter tuning, we conducted three independent umbrella sampling simulations (i.e., each initiated with a different random number seed) to calculate a mean value and variance for $\Delta A^\circ_{\text{ads}}$. The first 3 ns of each umbrella sampling simulation were used as equilibration and the data from the next 12 ns were collected for analysis. Simulations with the final tuned IFF parameter set were performed for as long as 25 ns (i.e., 75 ns of cumulative data from three seeds) for each of the peptides without resulting in significantly different values of $\Delta A^\circ_{\text{ads}}$, thus indicating that 15 ns of umbrella sampling provided converged results for our systems.

III. RESULTS AND DISCUSSION

A. Experimental measurement of adsorption free energies

Using the correlation between F_{des} vs $\Delta G^\circ_{\text{ads}}$,²⁰ mean F_{des} values for each peptide–surface system measured by our standardized AFM method were translated into effective values of $\Delta G^\circ_{\text{ads}}$. Results from these correlations are presented in Table III.

B. Calculation of adsorption free energy using default CHARMM parameters for the IFF

Values of $\Delta A^\circ_{\text{ads}}$ for the 10 host–guest peptide–HDPE systems obtained from the umbrella sampling simulations using the regular CHARMM22 nonbonded parameters as our default IFF parameter set are presented in Table III. Figure 2(a) shows a scatter plot of the simulated free energies plotted against the experimental free energies (round, red data points). These results indicate numerous deviations in the values of $\Delta A^\circ_{\text{ads}}$ relative to the experimental data, with essentially no correlation being indicated between the simulation and experimental results ($R = 0.00$). From an examination of these deviations, it was found that the adsorption free energies from the simulations underestimated the

TABLE III. Free energies of adsorption for TGTG–X–GTGT peptide from experiment and from simulation using CHARMM nonbonded parameters and the tuned IFF parameter set. Mean ($\pm 95\%$ C.I.).

–X–	Adsorption free energy (kcal/mol)		
	Expt. ^a	CHARMM	Tuned IFF
Ala (A)	–5.2 (0.9)	–3.8 (0.3)	–5.2 (1.7)
Arg (R)	–3.5 (0.9)	–1.4 (0.8)	–3.8 (0.6)
Asn (N)	–3.1 (0.9)	–2.5 (0.3)	–3.0 (0.9)
Asp (D)	–2.7 (0.9)	–3.0 (0.4)	–2.3 (1.9)
Gly (G)	–3.2 (0.9)	–3.6 (2.5)	–3.0 (0.1)
Lys (K)	–4.0 (0.9)	–4.2 (1.9)	–4.1 (0.4)
Phe (F)	–3.5 (0.9)	–5.2 (0.5)	–3.9 (0.7)
Thr (T)	–2.4 (0.9)	–2.2 (0.9)	–3.0 (0.9)
Trp (W)	–2.6 (0.9)	–5.2 (1.5)	–3.3 (0.0)
Val (V)	–4.8 (0.9)	–2.8 (0.5)	–4.1 (0.1)

^aNinety five percent C.I. for the experimental data obtained from confidence intervals about the linear correlation between F_{des} measured by AFM and $\Delta G^\circ_{\text{ads}}$ determined by SPR.

experimental values (i.e., simulated binding affinities were too weak) for guest amino-acid residues that contained only aliphatic carbon atoms in their side chains, such as alanine (A) and valine (V). On the other hand, the adsorption free energies of the peptides with the guest residues that predominantly included aromatic carbon atoms, such as phenylalanine (F) and tryptophan (W), were overestimated (i.e., simulated binding affinities were too strong). As these results show, the use of the CHARMM force field for the simulation of peptide or protein adsorption behavior to a hydrophobic surface can be expected to lead to very unrealistic adsorption behavior as the amino-acid residues would not be interacting with the surface with realistic binding affinities. This underscores the need for a separate set of tuned parameters to represent interfacial interactions for this type of multiphase system.

C. Tuning of the interfacial force field parameters

After determining that the vdW constituent of the nonbonded peptide–surface interactions is the main factor contributing to the errors in the free energy of peptide adsorption (see Sec. S.3 in supplementary material),⁴⁸ we executed a number of iterative umbrella sampling simulations with different modified IFF nonbonded parameter sets in order to either weaken or strengthen the adsorption profile for the peptides as necessary to bring them in closer agreement with the experimental values. To do this we only modified the ϵ_i parameters of the amino-acid residues in the IFF, while no modifications were made to the atomic charges.

Evaluation of the results with the IFF parameters set to the default CHARMM values showed that the adsorption affinity of the host–guest peptides with X = R, V, and A needed to be substantially increased while the adsorption affinity of the F- and W-peptides needed to be substantially decreased. The remaining peptides required only small corrections in their simulated adsorption affinities, if any,

FIG. 2. (a) Comparison of $\Delta G^{\circ}_{\text{ads}}$ values from experiment and $\Delta A^{\circ}_{\text{ads}}$ values from 15 ns umbrella sampling simulations on HDPE based on the initial CHARMM parameter set (red circles) and the tuned IFF parameter set (blue diamonds, all within about 0.5 kcal/mol of the experimental values). The solid blue line represents perfect agreement between the simulated and experimentally measured values. The dashed red lines represent deviations of ± 1.0 kcal/mol around the solid blue line. A linear regression and R value for the default CHARMM and tuned IFF parameter sets are represented. (b) Examples of atom names (highlighted in green) and corresponding atom types (highlighted in red) from CHARMM topology for which the L-J ϵ_{ij} parameter has been tuned in order to fit the simulated $\Delta A^{\circ}_{\text{ads}}$ to experimental $\Delta G^{\circ}_{\text{ads}}$ values for selected amino acids.

although some required adjustments in response to changes in atom types present in other residues. The threonine and glycine residues, for example, affected all of the host–guest peptides. In general, however, the approach was to make changes to atom types in a way that affected as few residues as possible. In some cases, this necessitated the creation of new atom types. For example, although the lysine (K) peptide initially provided adsorption free energy that was very close to the experimental value, modification of IFF parameters for other residues that contained atom types also present in lysine substantially weakened its adsorption behavior, thus requiring that the L-J parameters for the amine group of lysine needed to be strengthened. However, the side-chain amine group of lysine involves the same atom types for the N and H atoms as the amine group of the N-terminus. Therefore adjustment of the L-J parameters for these atom types to adjust the adsorption affinity of the K-containing peptide would affect the adsorption affinity of all of the

peptides via their N-termini. Consequently, new atom types for the side-chain N and H atoms of lysine were created and the ϵ_i parameters of these new atom types were modified. Similarly, the C and H atom types of the methyl groups of valine and alanine in CHARMM also appear in threonine (T), which is present four times in the host sequence in all of our peptides. Therefore new atoms types were created for the C and H atoms of both valine and alanine and their ϵ_i parameters were modified. Five amino acids (G, T, F, W, and R) were adjusted without requiring the creation of new atom types. The default CHARMM parameters for the remaining two peptides (N and D) provided adsorption free energies that remained closely in line with the experimental values, and thus did not require adjustment. The final set of tuned IFF ϵ_i parameters are shown in Table IV. In total, we modified the L-J parameters for 12 atom types (including six new atom types) in fitting the free energies of the ten peptide systems. To simplify this process, we took the approach of

TABLE IV. Summary of the tuned IFF parameters used to bring the simulation adsorption free energy of 10 host–guest peptides into agreement with the experimental values for the HDPE surface and comparison with the default CHARMM values. Atom types not listed in the table use standard CHARMM parameters in the IFF.

Residue	IUPAC ^a name	Atom type	L-J Parameter (ϵ_i)	
			CHARMM	Tuned IFF
Gly (G)	HA1, HA2	HB ^b	−0.022	−0.008
Thr (T)	CG2	CT3	−0.080	−0.088
Lys (K)	NZ	NHT3 ^c	−0.200	−0.400
Ala (A)	HZ1, HZ2, HZ3	HCT ^c	−0.046	−0.092
	CB	CTT ^c	−0.080	−0.560
	HB1, HB2, HB3	HTT ^c	−0.022	−0.154
Val (V)	CG1, CG2	CTV ^c	−0.080	−0.240
	HG11, HG12, HG13, HG21, HG22, HG23	HTV ^c	−0.022	−0.066
Phe (F)	CG, CD1, CE1, CZ, CD2, CE2	CA	−0.070	−0.035
Trp (W)	CE2, CD2	CPT	−0.090	−0.100
	NE1	NY	−0.200	−0.220
Arg (R)	NE, NH1, NH2	NC2	−0.200	−0.380
Asn (N)	No change			
Asp (D)	No change			

^aIUPAC: International union of pure and applied chemistry.^bThe HB atom type is also present in every amino acid type as the hydrogen atom linked to the C_α carbon. The designated L-J parameter changes thus apply to all 20 types of amino acids.^cNew atom type introduced for the IFF parameter set.

scaling all L-J parameters in a target functional group (e.g., the N and H atom types in lysine forming the amine functional group) by the same factor, thus reducing the number of adjustable parameters to only 8 during the fitting process. Figure 2(b) shows examples of atom names and atom types from the CHARMM force field topology file⁵¹ for the amino acid residue structure for Trp (W), Phe (F), and Gly (G) that correspond to the parameters shown in Table IV.

As shown in Fig. 2(a), the set of tuned IFF parameters provided adsorption free energies for each of our ten

peptides that are within about 0.5 kcal/mol of their experimental values. The root mean square deviation (RMSD) between simulated and experimental free energies decreased from 1.2 kcal/mol with the default CHARMM parameters to 0.4 kcal/mol with the IFF parameters, thus providing much closer agreement between the model and experiment. The *R* coefficient between the full set of simulated and experimental free energies increased from *R* = 0.00 with the default CHARMM parameter set to *R* = 0.88 with the tuned IFF parameter set, so the IFF model does a considerably better job

TABLE V. Summary of the tuned IFF parameters for the remaining ten amino acid residues that were not present in our experimental data set. These IFF parameters have been estimated based upon similarity of atom types and amino-acid types (i.e., aliphatic, aromatic, polar, and charged functional groups). Atom types not listed in the table use standard CHARMM parameters in the IFF parameter set.

Residue	IUPAC ^a name	Atom type	L-J Parameter (ϵ_i)	
			CHARMM	Tuned IFF
Leu (L)	CD1, CD2	CTV ^b	−0.080	−0.240
	HD11, HD12, HD13, HD21, HD22, HD23	HTV ^b	−0.022	−0.066
Ile (I)	CG2, CD	CTV ^b	−0.080	−0.240
	HG21, HG22, HG23, HD1, HD2, HD3	HTV ^b	−0.022	−0.066
Met (M)	CE	CTV ^b	−0.080	−0.240
	HE1, HE2, HE3	HTV ^b	−0.022	−0.066
Tyr (Y)	CG, CD1, CE1, CZ, CD2, CE2	CA	−0.070	−0.035
Cys (C)	No change			
Glu (E)	No change			
Gln (Q)	No change			
His (H)	No change			
Pro (P)	No change			
Ser (S)	No change			

^aIUPAC: International union of pure and applied chemistry.^bNew atom type introduced in the IFF parameter set.

than the default CHARMM parameters at representing the differences between the individual peptide adsorption free energies. Through the use of the Dual-FF CHARMM program, implementation of this tuned IFF parameter set influences only the interactions of the amino acid residues with the HDPE surface, whereas amino acid–solvent interactions and peptide conformational behavior are still represented by the standard CHARMM protein force field, thus enabling both the conformational behavior of the peptide in solution and its adsorption behavior on the HDPE surface to both be accurately represented in a simulation.

Subsequent studies are planned to apply the tuned IFF parameters to simulate the adsorption behavior of whole proteins, such as lysozyme and ribonuclease A, to HDPE, for which synergistically matched experimental studies have been conducted to provide a basis to assess the protein-adsorption simulations.^{50,52} Before these simulations can be carried out, however, IFF parameters are needed for the full set of 20 naturally occurring amino acids. As an approach to provide IFF parameters for the remaining ten amino-acid residues that were not present in our experimental data set, we have extended our set of IFF parameters to the remaining amino acids, using adjustments to the L-J well depth comparable to that used for each individual amino-acid type (i.e., aliphatic, aromatic, polar, and charged functional groups) along with atom-type matching in the parameter fitting described above. IFF parameters for this remaining set of ten amino-acid types are presented in Table V.

IV. CONCLUSIONS

Adsorption free energies of ten host–guest peptides on an HDPE surface were calculated using umbrella sampling simulations with the CHARMM force field and compared with the experimental results determined by a combined SPR/AFM method. This comparison revealed substantial differences between the simulation and experimental results. Using the Dual-FF CHARMM program, IFF parameters were subsequently adjusted to reduce these differences. The resulting tuned IFF parameter set provides significant improvement in agreement of the adsorption free energies obtained between simulation and experiment with RMSD in the free energies of 0.4 kcal/mol for the ten peptides examined experimentally. This is a great improvement over the RMSD of 1.2 kcal/mol between CHARMM simulation and experiment. The IFF parameters for our test set of ten guest amino acids were subsequently used to estimate IFF parameters for the remaining set of ten amino acids based on corresponding atom and amino acid types.

Attempts were made to match the experimental and simulation conditions wherever possible, but some differences were unavoidable. For example, in this set of studies, the HDPE surface used for the experimental data set was formed by spin coating HDPE on a glass substrate, which can be expected to form a semicrystalline HDPE surface, while the (110) plane of crystalline HDPE was used as the model surface for the simulations. However, by tuning IFF parameters

to match the experimental values, we effectively provide the model HDPE surface with the peptide adsorption characteristics of the experimental HDPE surface.

Simulations are presently underway to apply this IFF parameter set for simulations of protein adsorption behavior on an HDPE surface using lysozyme and ribonuclease A as model proteins. The results from these subsequent simulations will be compared with adsorbed protein orientation and conformation data sets that we have obtained from experimental studies for these two proteins on a spin-coated HDPE surface.^{50,52,53} These comparisons will then be used to assess the ability of this tuned IFF parameter set for amino acid–HDPE interactions to be extended to accurately predict actual protein adsorption behavior on this type of surface.

ACKNOWLEDGMENTS

This project received support from the Defense Threat Reduction Agency-Joint Science and Technology Office for Chemical and Biological Defense (Grant No. HDTRA1-10-1-0028). Computing resources: Palmetto Linux Cluster, Clemson University. The facilities used were also supported by NIH Grant Nos. 5P20RR021949 and 8P20GM103444. The authors also thank Megan Grobman, Lara Gamble, and David Castner of NESAC/BIO at the University of Washington for assistance with surface characterization with XPS under funding support by NIH Grant No. EB002027.

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