# Calculation of Free Energy of Peptide-Surface Interactions Using Biased-Sampling Molecular Dynamics for Force Field Evaluation

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## Introduction

- Implant biomaterials undergo rapid protein adsorption when exposed to soluble proteins in blood.
- This rapid adsorptions coats the surface and subsequent cellular response to the surface is based on their interaction with the adsorbed protein layer, rather than the surface itself.
- Molecular dynamics (MD) simulations of these systems can help us understand these interactions and protein adsorption behavior; which can guide the design of better surfaces to control protein adsorption and cellular response.
- In an MD simulation, the bonded and non-bonded interactions are defined by force-field (FF) equations and parameters.

## Objective

- Use advanced sampling methods to calculate the free energy of adsorption (ΔG) of host-guest model peptides over different functionalized self-assembled monolayer (SAM) surfaces on a Au(111) surface using CHARMM FF.
- Evaluate the accuracy of the FF by comparing ΔG with experimental results obtained by SPR[1].

## Model System:

**Peptide Model :** TGTG-**X**-GTGT
(where X is any of the following guest residue: Val (V), Asp (D), Thr (T), Phe (F) or Lys (K))

**Surface Model :** Alkanethiol SAM over Au(111) lattice (SAM terminal function group : $CH_3$, OH, $NH_2$/$NH_3^+$, COOH/$COO^-$, $COOCH_3$, $NHCOCH_3$, $OC_6H_5$, $OCH_2CF_3$, $EG_3$)

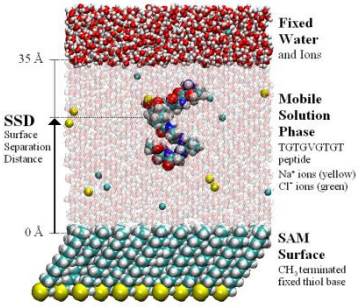


**Fig.1 :** TGTG-**V**-GTGT peptide solvated in explicit TIP3P water over a $CH_3$ SAM with $Na^+$ and $Cl^-$ ions representing a 140 mM physiological saline solution

## Free Energy of Adsorption

The change in free energy of adsorption (ΔG) is calculated using the probability ratio method. ΔG depends upon the positional probability ($P_i$) of the peptide in SSD space compared to the probability of a reference position ($P_0$). For this to be used, the system must be sampled over the entire range of SSD.

$$\Delta G_i = -RT \ln\left(\frac{P_i}{P_0}\right)$$

## Simulation details :

- 45 systems (five peptides over nine surfaces) – TIP3P water
- Velocity-verlet (VV2) integrator (2 fs timestep - NVT)
- Nose'-hoover thermostat : PME for handling electrostatic

### Conventional MD : Sampling issues[2] – 5 ns

- Calculation of ΔG requires sufficient SSD sampling
- Energetic barrier : dihedral sampling of the peptide

### Umbrella sampling of SSD space

- 22 independent simulation of the replica of each system with peptide constrained (harmonic potential) at reference position ranging from 4 – 25 Å in 1 Å increments.
- Combine all windowed simulations using WHAM method to obtain an estimate of the potential of mean force (PMF). The inverse of this potential is defined as the energy needed to escape the surface attraction.

### Biased replica exchange MD (REMD) simulation

- REMD uses high temperature to overcome energetic barriers and provide accelerated dihedral sampling of the peptide.
- 38 of the 45 systems simulated using REMD for 10 ns; (experimental data were not available for 7 systems)
- The inverse fit to PMF generated using umbrella sampling is supplied as biasing energy to enhance SSD sampling
- Temperature range : 298 – 400 K (24 replica for each system)
- Exchange attempt made every 1.0 pico-second (ps).

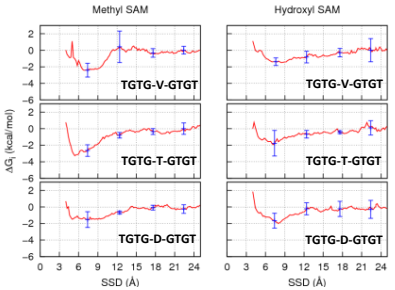


**Fig.2** : Representative free energy profiles from REMD simulation results with error bars representing 95% CI (n=3) about the mean for each peptide.

## Result and Discussion[3]

- Biased REMD simulation enhanced both dihedral sampling and peptide diffusion during the simulation
- ΔG were calculated using the 298 K ensemble from REMD simulation
- On comparing with the experimental results, simulation under-estimated the ΔG for methyl and amine SAM surface
- Simulation predicted ΔG values in agreement with the experimental results within 1 kcal/mol of error margin for most of the systems

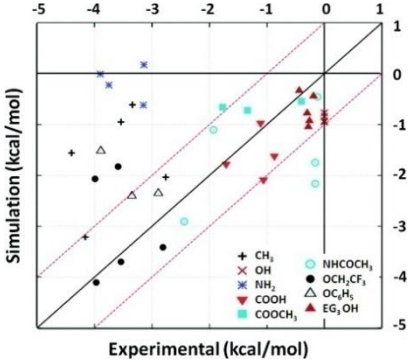


**Fig.3** Comparison of the free energy of adsorption (ΔG) estimated from the biased REMD simulation with the experimental results as obtained by Wei and Latour[1].

## Conclusion & Future

Combination of REMD with biasing potential accelerated the dihedral and SSD coordinate sampling efficiently. The ΔG was calculated for 38 peptide-SAM systems and were compared with the experimental results. These comparisons indicate that the CHARMM FF parameterization does a reasonably good job representing peptide adsorption behavior (within an 1 kcal/mol of the experimental value) for most of the systems, but substantially underestimated the strength of adsorption on surface functionalized by hydrophobic and positively charged amine groups. These results demonstrate that CHARMM FF may not provide an accurate representation of adsorption behavior without modification.

- Additional studies are planned to study and understand the mechanisms of solute-solvent and SAM interaction
- These results provide a basis for the development of an interfacial force field specifically designed for accurately representing protein adsorption behavior.

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**References**

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2. C.P.O'Brein et al., Langmuir (2008)
3. Vellore et al., Langmuir (in press), DOI: 10.1021/la904415d)

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