Effect of Pressure on Adsorption Free Energy in Protein Adsorption Simulations

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Introduction

Molecular simulation methods have great potential to be used to understand and control protein adsorption behavior for biomaterials surface design. However, these methods must first be developed to accurately represent molecular behavior for this specific type of system. When performing molecular simulations of a condensed-phase system (e.g., protein folding in aqueous solution), system pressure is often considered to be of relatively minor importance. This, however, may not be the case for the simulation of protein adsorption behavior.

Objective

Conduct molecular dynamics simulations to quantitatively investigate the influence of system pressure on the adsorption behavior of a peptide on a nonpolar surface as characterized by the free energy of adsorption, ΔG_{ads}.

Model System

The model system consists of a TGTG-V-GTGT peptide (T=Threonine, G=Glycine, V=Valine) solvated in explicit TIP3P water over a methyl-terminated self-assembled monolayer (SAM) surface with Na^+ and Cl^- ions approximating a 140 mM physiological saline solution. The system dimensions are 43.30 Å × 45.00 Å × (65.17+Δz) Å, where Δz is varied from -2.00 Å to +2.00 Å.

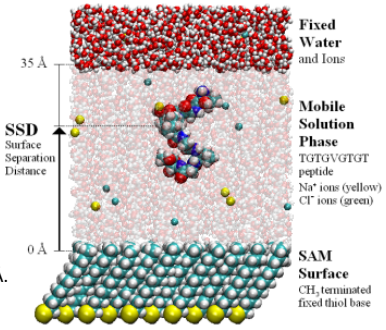


Fig. 1. Snapshot of the model system where the peptide has a surface separation distance (SSD) of 23 Å.

Simulation Details

- **PROGRAM**: Academic CHARMM (34b2) [1]
- **PARAMETERS**: CHARMM22/CMAP [2] for peptide and saline; CGenFF [3] for SAM
- VV2 integrator with Nosé-Hoover thermostat (298K)
- SHAKE algorithm on bonds with hydrogens
- Particle Mesh Ewald electrostatics (≈1 grid point/Å^3)
- Non-bonded cutoff force-switching from 8-12 Å
- **HEATING**: 200 ps (1 fs time step), 100-298K
- **EQULIBRATION**: 400 ps (1 fs) + 600 ps (2 fs), 298 K
- **PRODUCTION**: 5 ns (2 fs), 298 K

Pressure Optimization

- A traditional NPT optimization of the virial-based system pressure cannot be determined using atom coordinate rescaling when fixed atoms are present.

$$P = \frac{1}{3V}\left[\left\langle N_{dof} k_B T\right\rangle - \langle W\rangle\right];\quad W = \sum_{i}^{N}\sum_{j>i}^{N}\left(r_{ij}\cdot f_{ij}\right)$$

Here V = volume, N_{dof} = number of degrees of freedom, k_B = Boltzmann's constant, T = temperature, W = virial of the mobile phase of the system, and r_{ij} and f_{ij} are the position and force vectors between atom pairs, respectively.

- Instead, the virial of a slab of mobile solvent in an NVT simulation is used as a parameter to gauge the pressure. The correct form of the virial for the slab is:

$$W_{slab} = \sum_{i}^{slab}\sum_{j>i}^{slab}\left(r_{ij}\cdot f_{ij}\right) + \sum_{i}^{slab}\sum_{j>i}^{outside}\left(r_{ij}\cdot f_{ij}\right)$$

- CHARMM utilizes a single sum evaluation of the virial based on the position, r_i, and net force, F_i, acting on each atom which we re-program to report an effective (i.e., approximate; not rigorously correct) virial of the slab, W_e:

$$W_e = \sum_{i}^{slab}\left(r_i\cdot F_i\right)$$

- A cross-sectional solvent slab spanning the width of box with height from a SSD of 15-25 Å was used for evaluation of the effective pressure of the system.

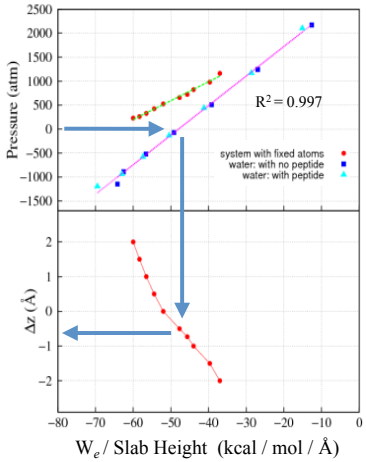


Fig. 2. Two-stage pressure optimization process:
a.) The pressure of a pure water box slab (with or without the peptide) is found as a function of the effective virial, W_e, of the slab.
b.) To choose the correct height (Δz) for the model system the W_e of a water slab taken from the model system is matched to the W_e from a 1 atm pure water box having identical dimensions.

Free Energy Calculation

ΔG_{ads} was calculated from the average probability distribution of the surface separation distance (SSD) between the peptide and the SAM surface over 3 independent 5 ns biased replica-exchange molecular dynamics (REMD) simulations [4].

Results and Discussion

Fig. 3 shows the z-coordinate distribution function (ZDF) profile for the TIP3P water molecules in the system as a function of their SSD from the hydrophobic CH_3-SAM surface for eight distinct perturbations, Δz, of the waterbox height. For comparison, the ZDF of a system having a vacuum layer instead of fixed water layer is also shown to model the ZDF of a 0-1 atm water droplet adsorbed to the SAM. Pressure is seen to strongly effect the density of the TIP3P hydration layers about the SAM surface and, hence, the adsorption behavior of the peptide.

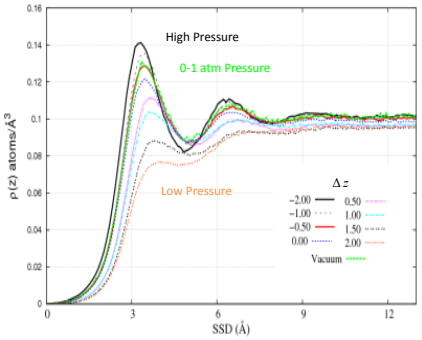
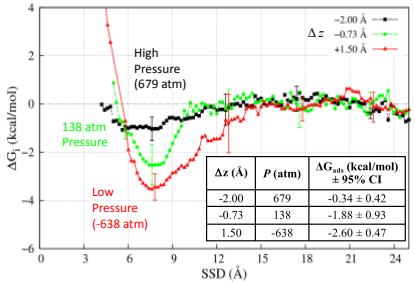


Fig. 3. ZDFs illustrating the evolution of water structure over the SAM surface as a function of the change in water box height (Δz).

Fig. 4 summarizes calculated values of P and ΔG_{ads} for 5 ns of biased-REMD simulation on systems having various waterbox heights. The 'negative' pressures shown indicate a non-equilibrium situation where the system has been adiabatically expanded to the point where excess vacuous space exists between the TIP3P waters near the SAM surface in anticipation of the formation of a vacuum bubble when the system has reached a critical volume.



Δz (Å)	P (atm)	ΔG$_{ads}$ (kcal/mol) ± 95% CI
-2.00	679	-0.34 ± 0.42
-0.73	138	-1.88 ± 0.93
1.50	-638	-2.60 ± 0.47

Fig. 4. PMFs obtained via biased-REMD sampling and used in the calculation of ΔG_{ads}. The inset lists these ΔG_{ads} values and P for each Δz.

Conclusions

- ΔG_{ads} calculated by peptide adsorption simulations is very sensitive to pressure.
- Higher pressure systems exhibit strong hydration layer peaks and higher free energies (i.e., weaker adsorption).
- Lower pressure systems have ill-defined hydration layers and decreased adsorption free energy (i.e., stronger adsorption).
- A difference of a few tenths of an Angstrom in waterbox height can correspond to a pressure shift of hundreds of atmospheres, thus emphasizing the importance of monitoring pressure for the simulation of peptide & protein adsorption behavior.

Acknowledgements

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References

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