Free Energetics of Arginine Permeation into Model DMPC Lipid Bilayers: Coupling of Effective Counterion Concentration and Lateral Bilayer Dimensions

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S1. SIMULATION TIME

The duration of the simulated trajectory for the free energy profile in each window (including replicates, excluding first 4ns) are summarized in Table S1.

	small membrane system (64 lipids) (ns)	large membrane system(288 lipids) (ns)
[-1.5: 1.5]	118	122
[1:4]	126	128
[3.5:6.5]	126	129
[6:9]	124	118
[8.5:11.5]	124	123
[11:14]	132	123
[13.5:16.5]	130	117
[16:19]	134	108
[18.5:21.5]	134	98
[21:24]	137	105
[23.5:26.5]	134	104
[26:29]	118	100
[28.5:31.5]	140	103
[31:34]	110	77
[33.5:36.5]	124	71
[31:40]	−−	80

TABLE S1: duration of each window

Total simulation time for arg1 small membrane system is 1911ns, arg1 large membrane system is 1706ns.

S2. PMF CONVERGENCE

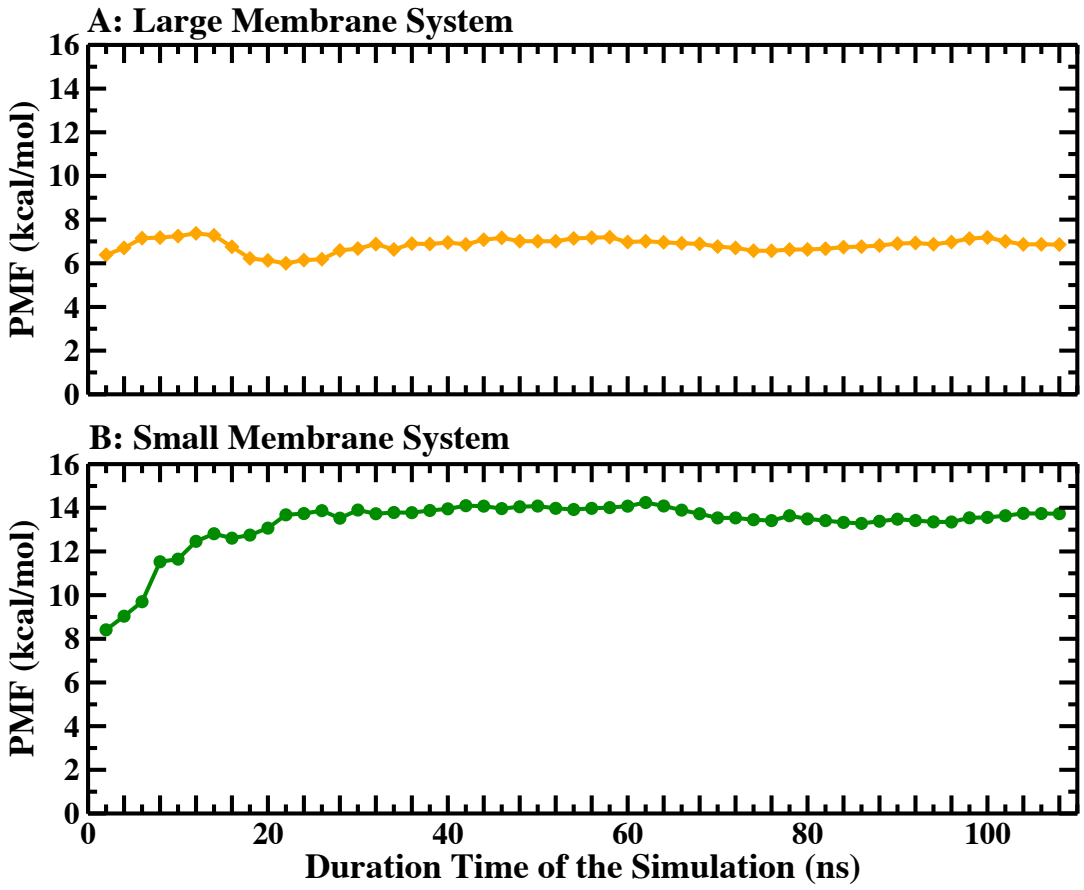

FIG. S1: PMF convergence over 110 ns. The difference in PMF between bulk and bilayer center (y-axis) versus time for: (A) Large membrane system; (B) Small membrane system.

S3. NUMBER OF SAMPLES

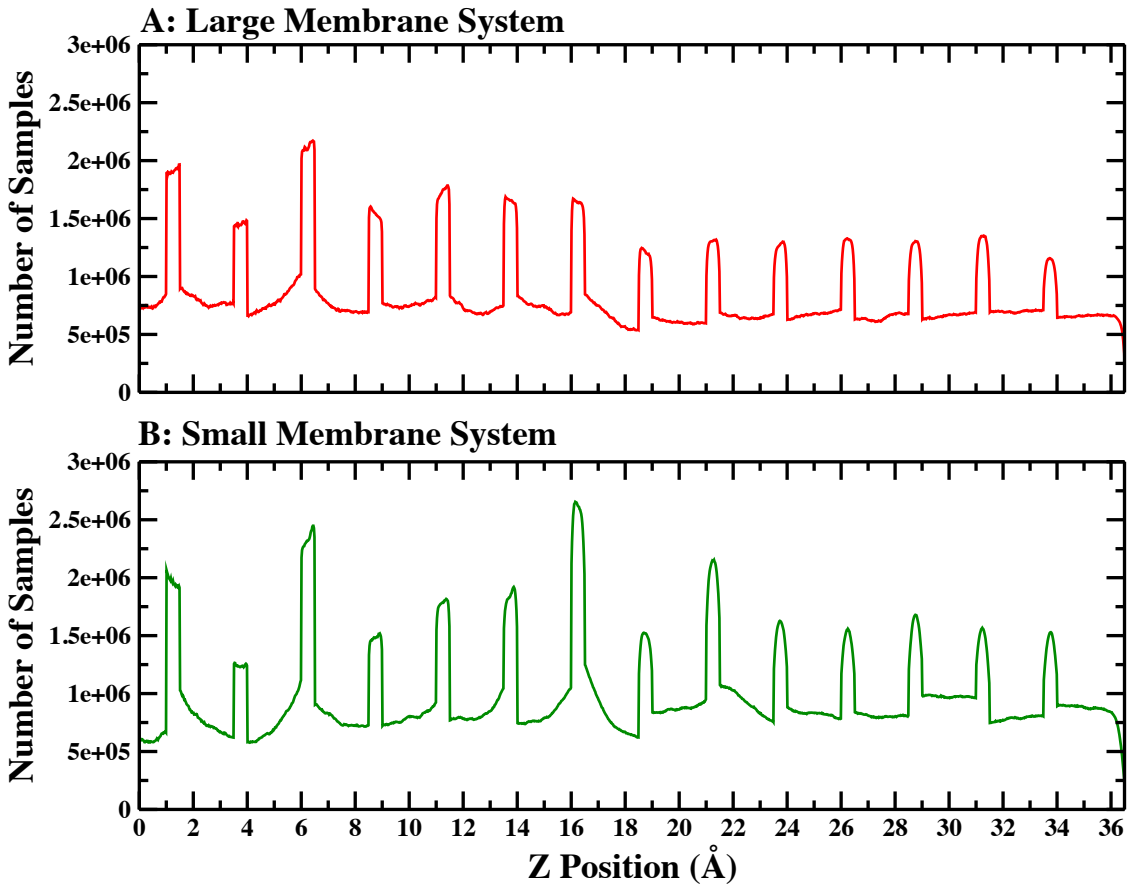

FIG. S2: number of samples in each bin along the reaction coordinate, (A) is 288 lipids system; (B) 64 lipids system.

The number of samples in each bin is showed in figure S2. The peaks show that more data are collected in the overlap region of neighboring windows.

S4. FLUCTUATION OF ARGININE Z POSITION

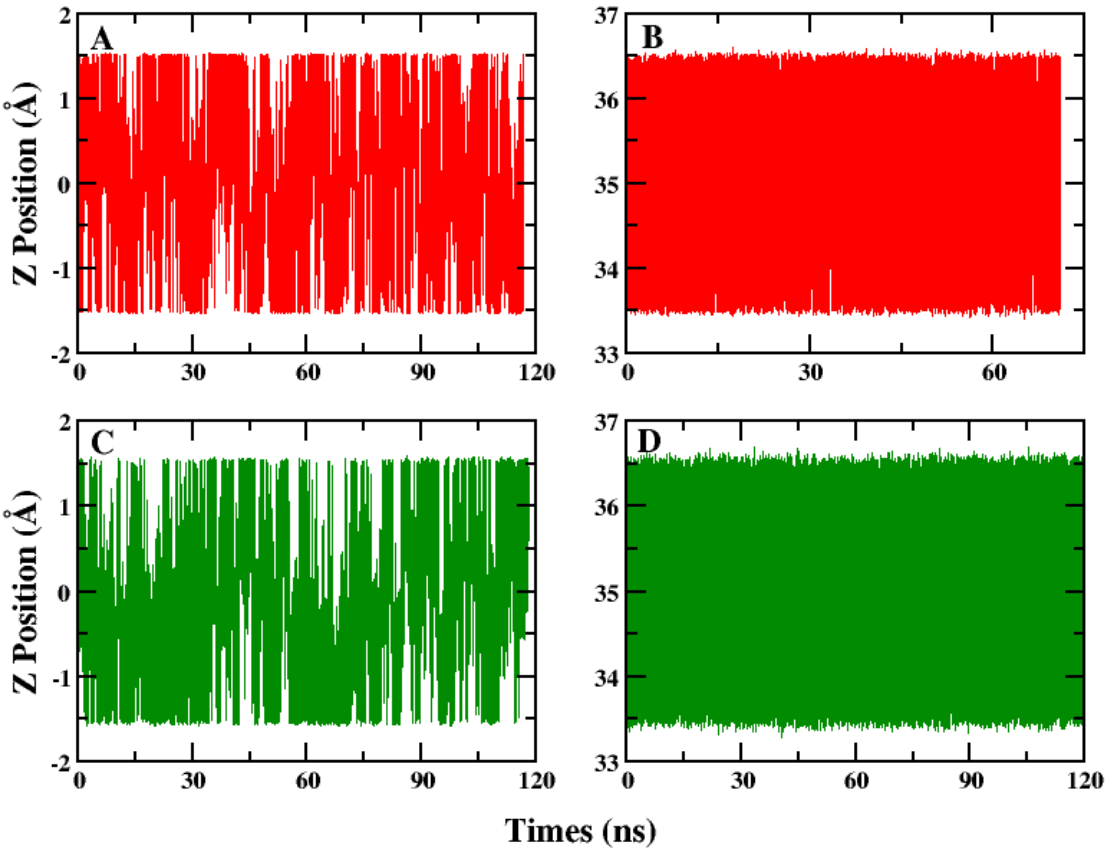

FIG. S3: fluctuation of arginine z position as a function of time. Figures A and B are the large membrane systems; C and D are the small membrane systems; A and C represent the center of bilayers window [-1.5:1.5] Å; B and D represent the bulk water window [33.5:36.5] Å.

S5. FORCE FLUCTUATION AND DISTRIBUTION

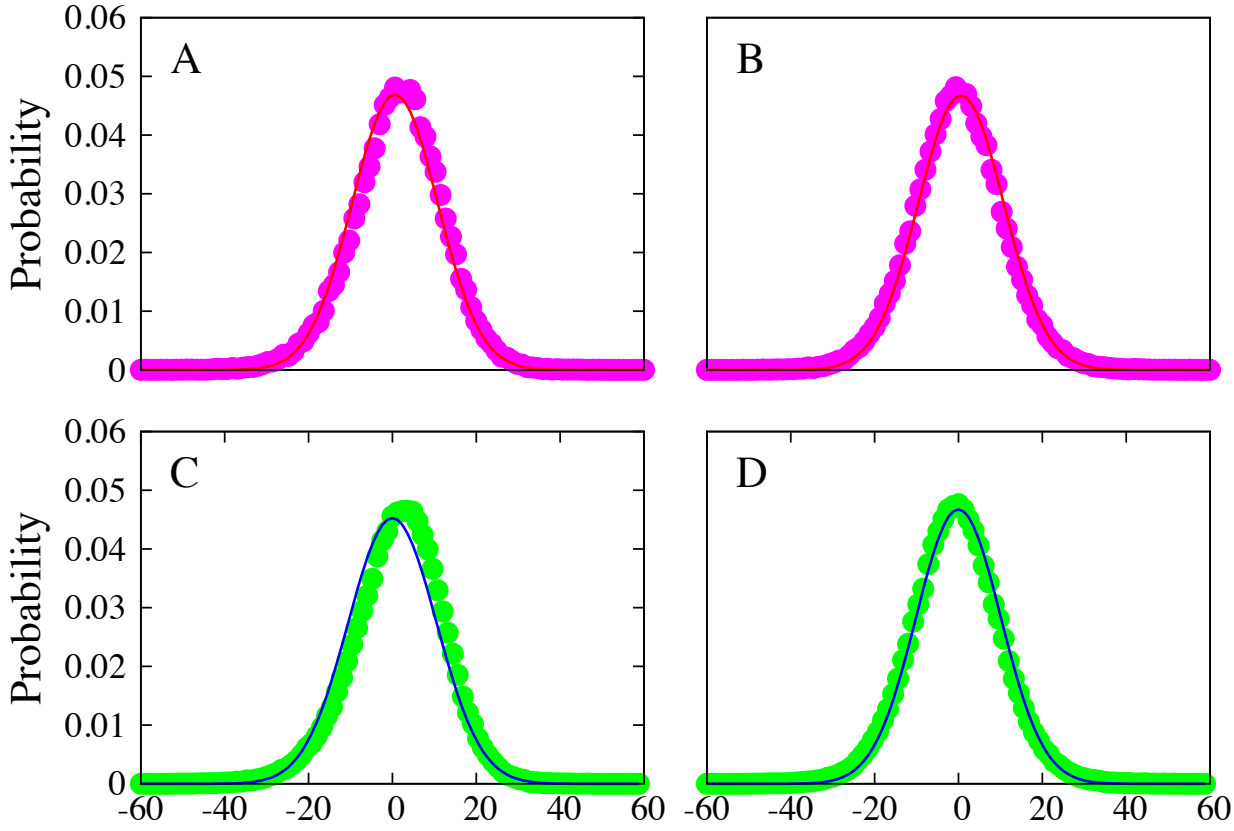

FIG. S4: Distribution of system force in a bin of width 0.02 Å. Solid lines are fitting curves with Gaussian function. Figures A and B are the large membrane systems; C and D are the small membrane systems. Panels A and C represent force distributions in center bin 0.00-0.02 Å, B and D represent force distribution in bulk water region bin 36-36.02 Å.

S6. PMF OF TWO INDEPENDENT SIMULATION OF SMALL SYSTEM

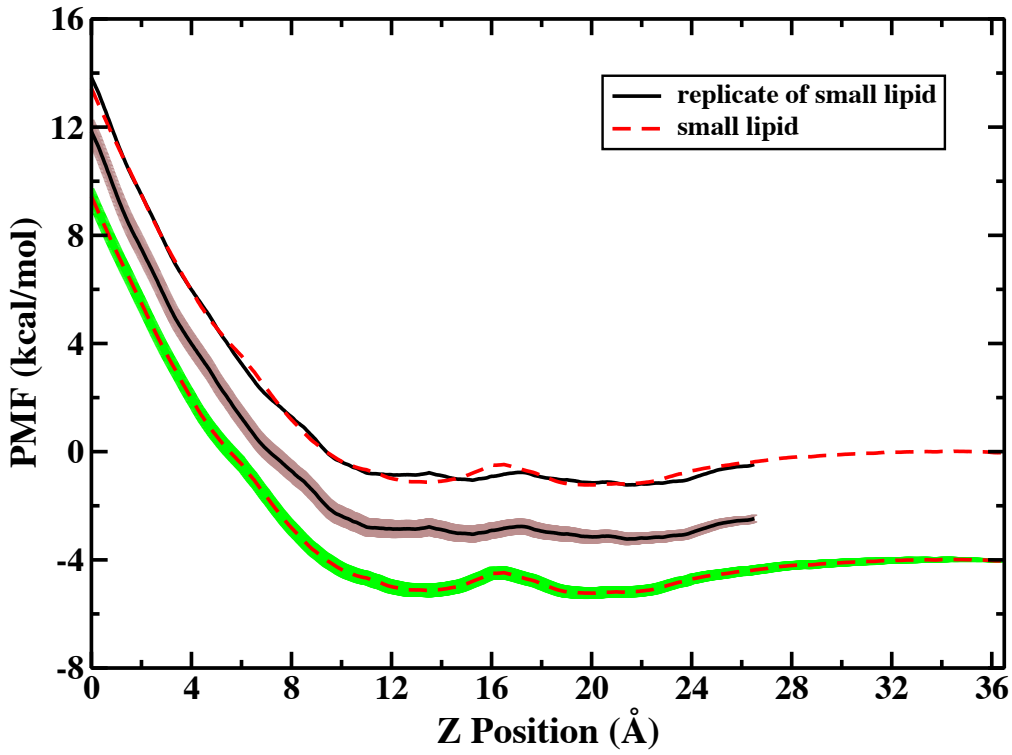

FIG. S5: PMF of the small membrane system, and an independent replicate of the small membrane system. Shadow indicates the PMF uncertainty. PMF of the solid line with shadow is shifted by -2 kcal/mol, and the dash line with shadow is shifted by -4 kcal/mol for clarity.

A. Density profiles

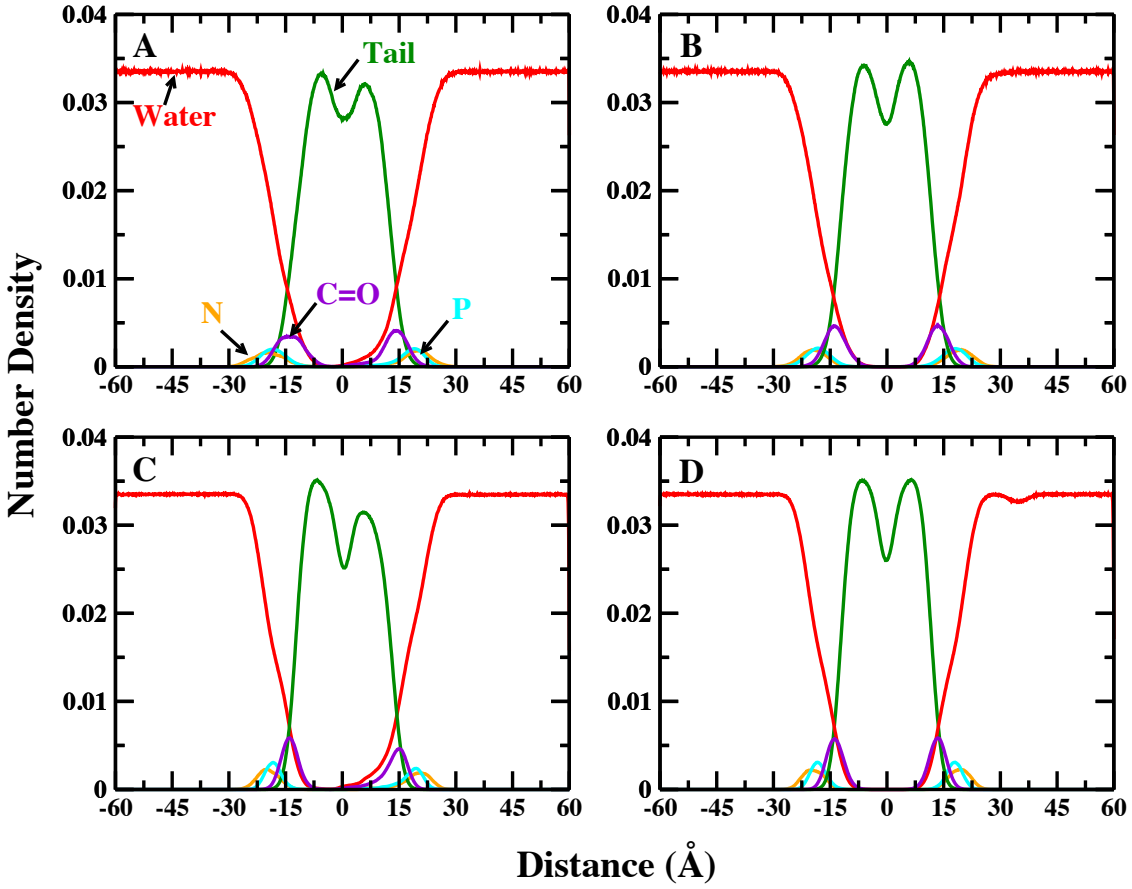

FIG. S6: Number density profiles of water oxygen, lipid nitrogen, phosphorous, carbonyl oxygen and acyl tail carbon groups. (A) and (C) show the center of bilayer window [-1.5:1.5] Å; (B) and (D) show the bulk water window [33.5:36.5] Å.

Due to the deformation of membrane, the lipid tails density is asymmetry in the center of the bilayers, and the water density is slightly higher at the Z > 0 region. A small minimum in figure D around 32 Å shows the affection of arginine to the water density profile in the small membrane system.

S7. CORE WATER FREE ENERGY CONTRIBUTION

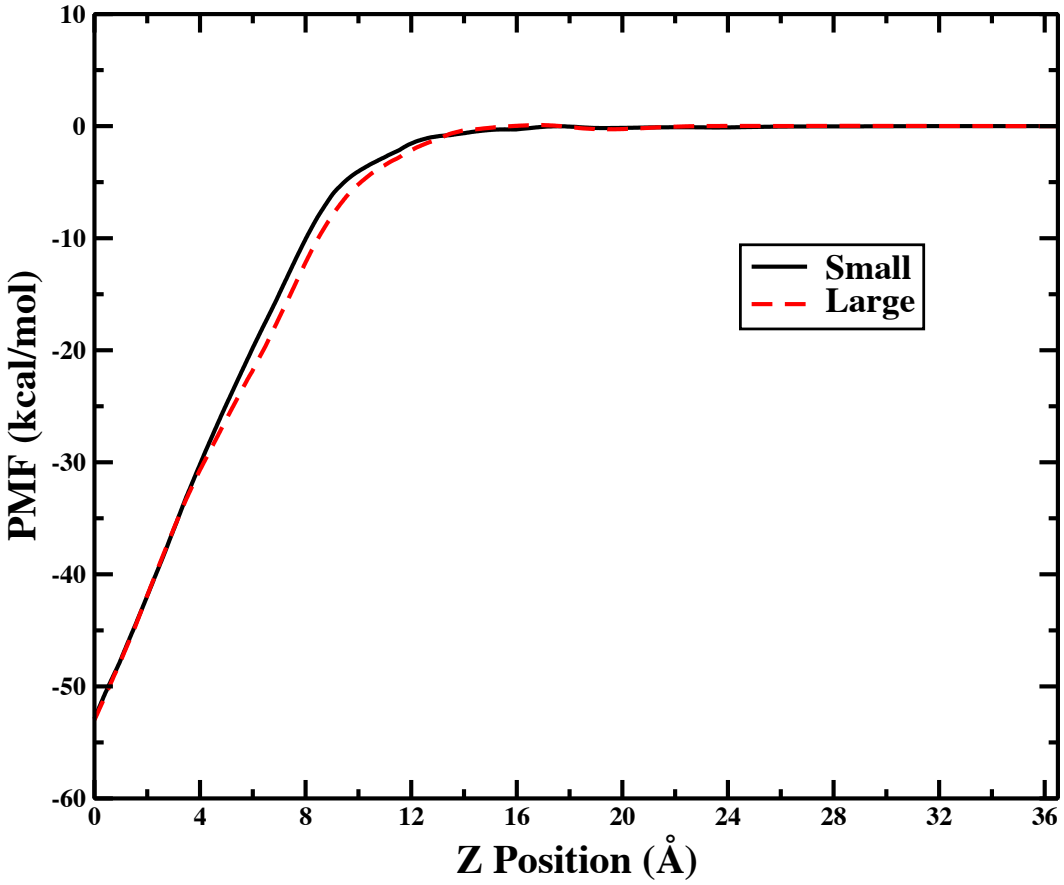

FIG. S7: Free energy contributions from core-located water in both large and small membrane systems. we consider water molecules as core water, when the water oxygen atoms enter the region within 13 Å of the center of the bilayers.

S8. WATER NUMBER IN THE FIRST SOLVATION SHELL

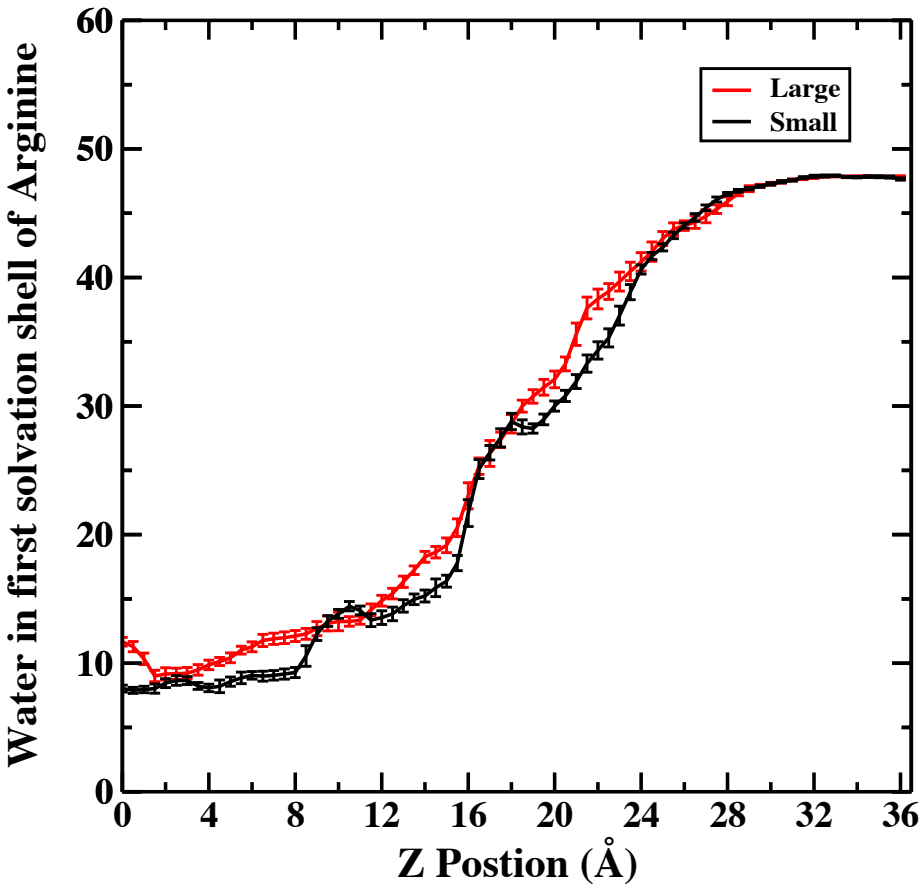

FIG. S8: water number in the first-shell of arginine. Solvation water numbers are the average number of water oxygen within the first solvation shells defined by radii 4.85 Å, relative to the center of mass of arginine.

S9. HYDROGEN BONDING

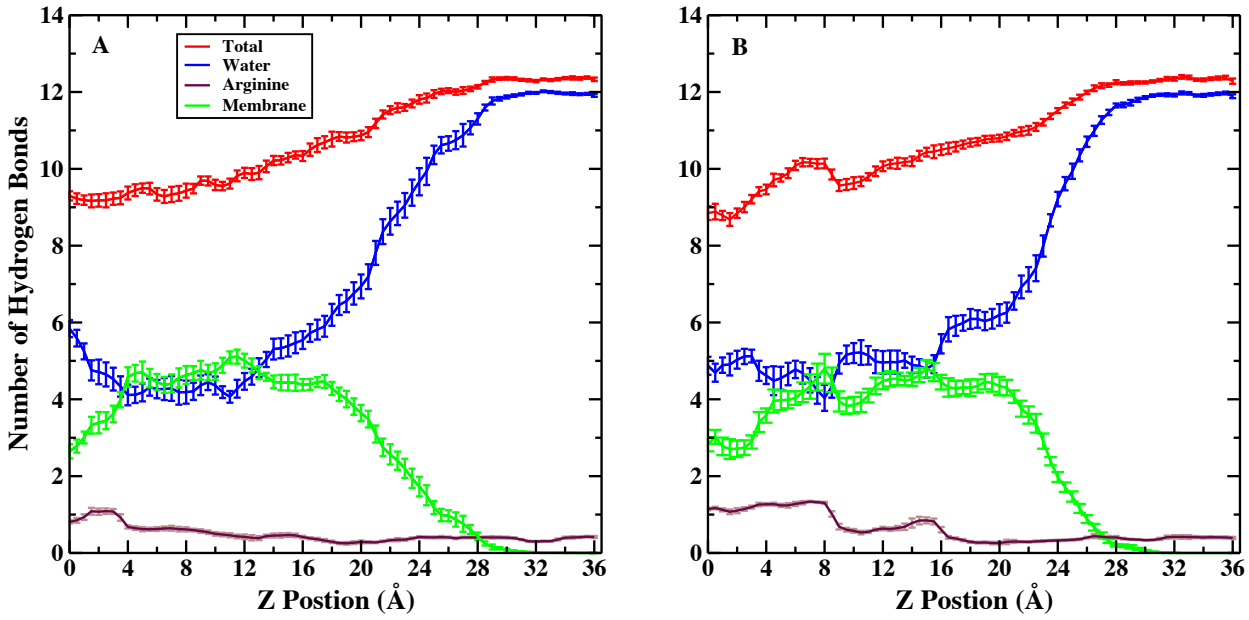

FIG. S9: Total number of hydrogen Bond formation to arginine, and the number contribution from membrane, water and arginine itself. A: large membrane system; B: small membrane system. H-bond geometric criteria[1]: Donor-acceptor distance is less or equal to 3.6 Å, hydrogen-acceptor distance is less or equal to 2.6 Å, and donor-hydrogen-acceptor angle is between 90 and 180 degree.

S10. DEFORMATION

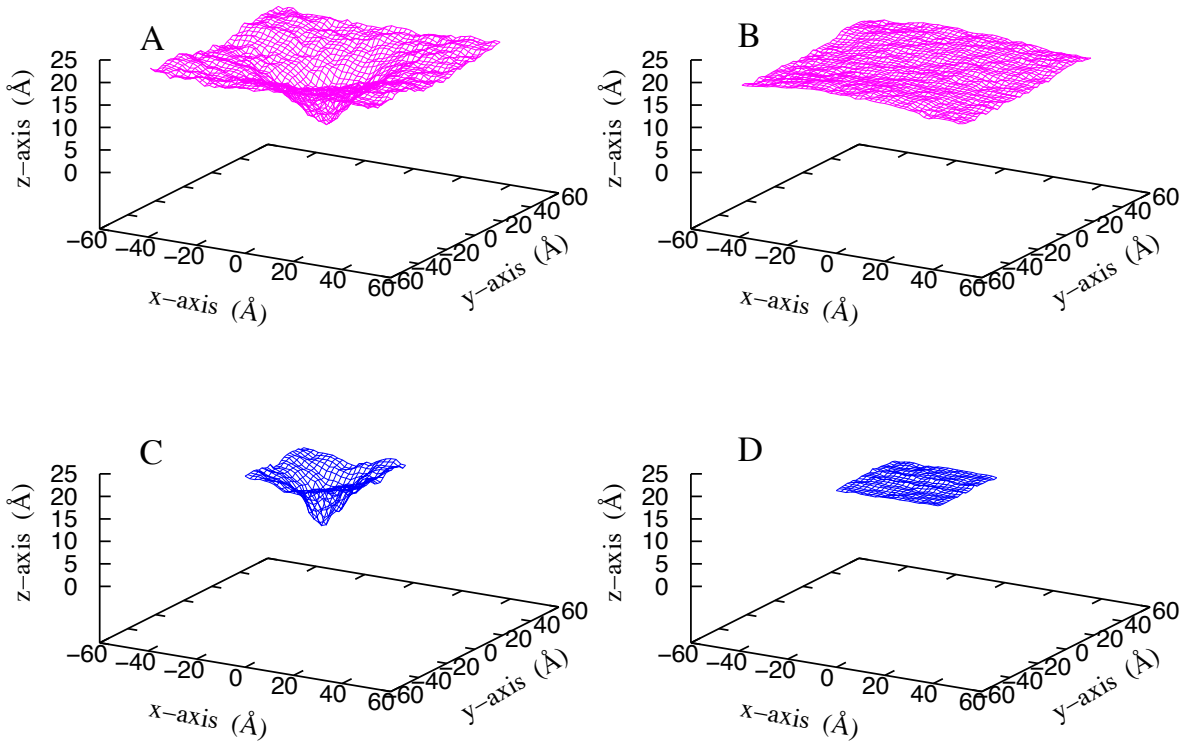

FIG. S10: Deformation profile of lipid nitrogen layer. (A) and (B) large membrane systems; (C) and (D) small membrane systems; (A) and (C) the center of bilayer window [-1.5:1.5] Å ; (B) and (D) the bulk water window [33.5:36.5] Å.

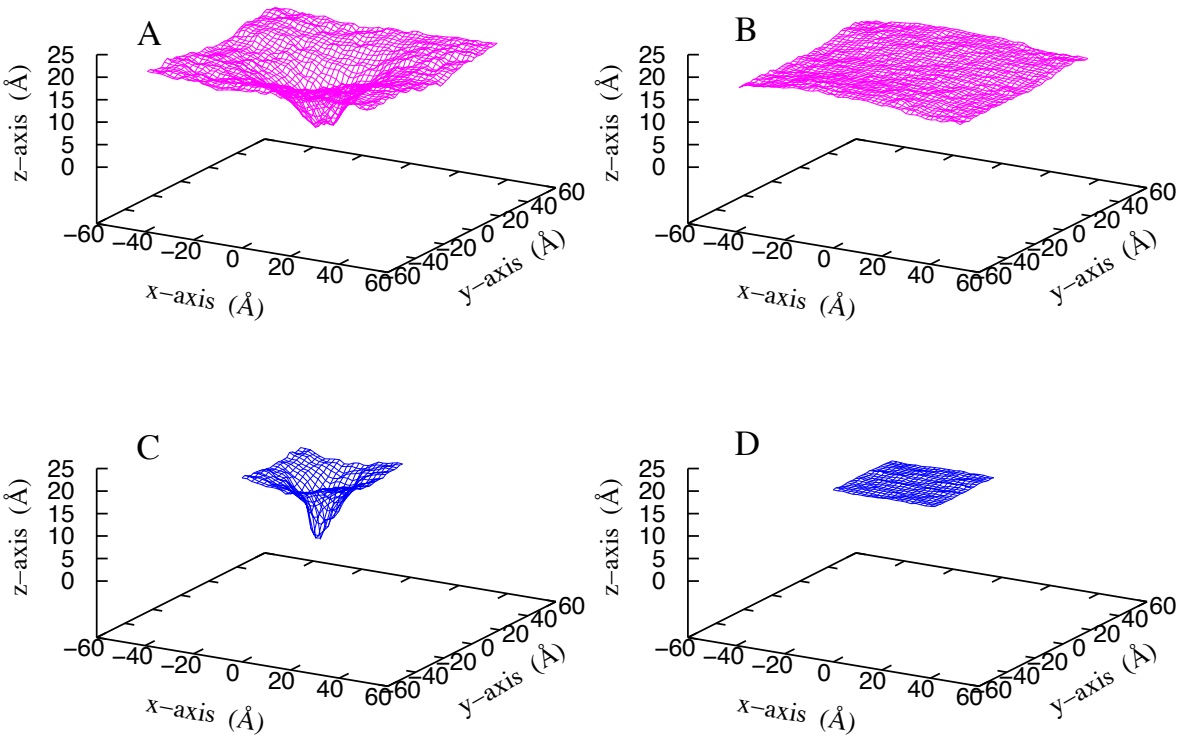

FIG. S11: Deformation profile of lipid phosphorous layer. (A) and (B) large membrane systems; (C) and (D) small membrane systems; (A) and (C) the center of bilayer window [-1.5:1.5] Å ; (B) and (D) the bulk water window [33.5:36.5] Å.

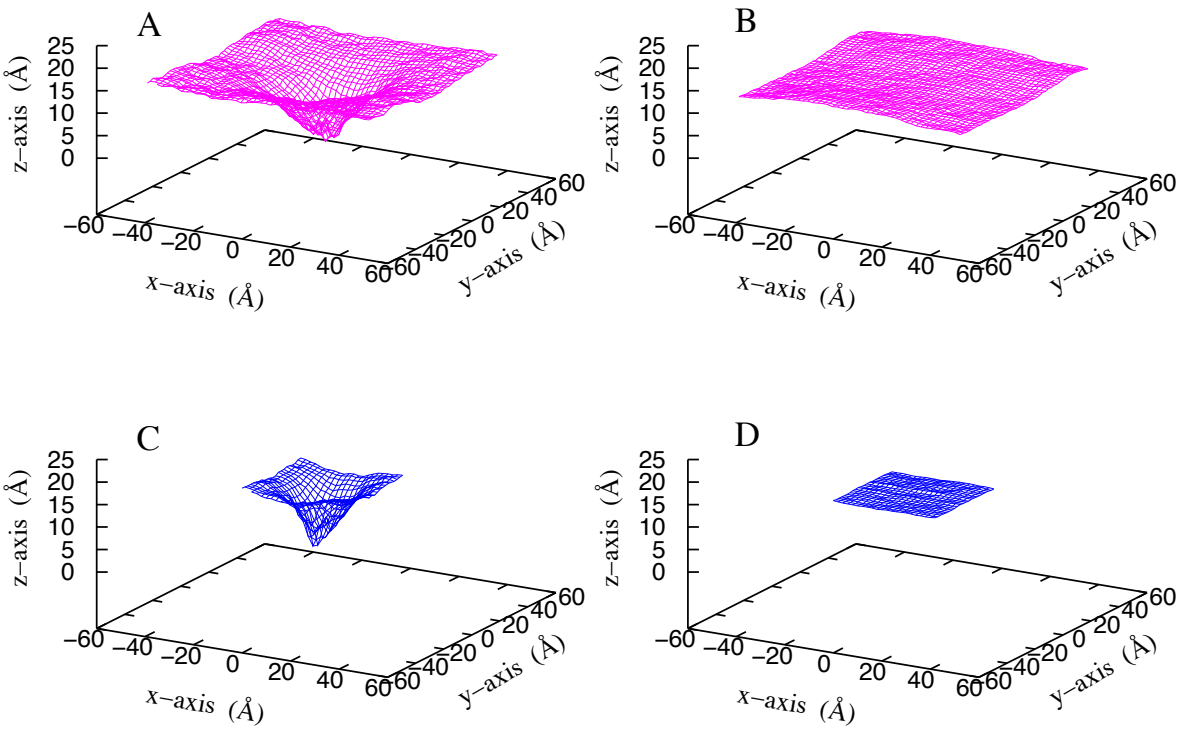

FIG. S12: Deformation profile of lipid carbonyl layer. (A) and (B) large membrane systems; (C) and (D) small membrane systems; (A) and (C) the center of bilayer window [-1.5:1.5] Å ; (B) and (D) the bulk water window [33.5:36.5] Å.

A. Two dimensional Density profiles

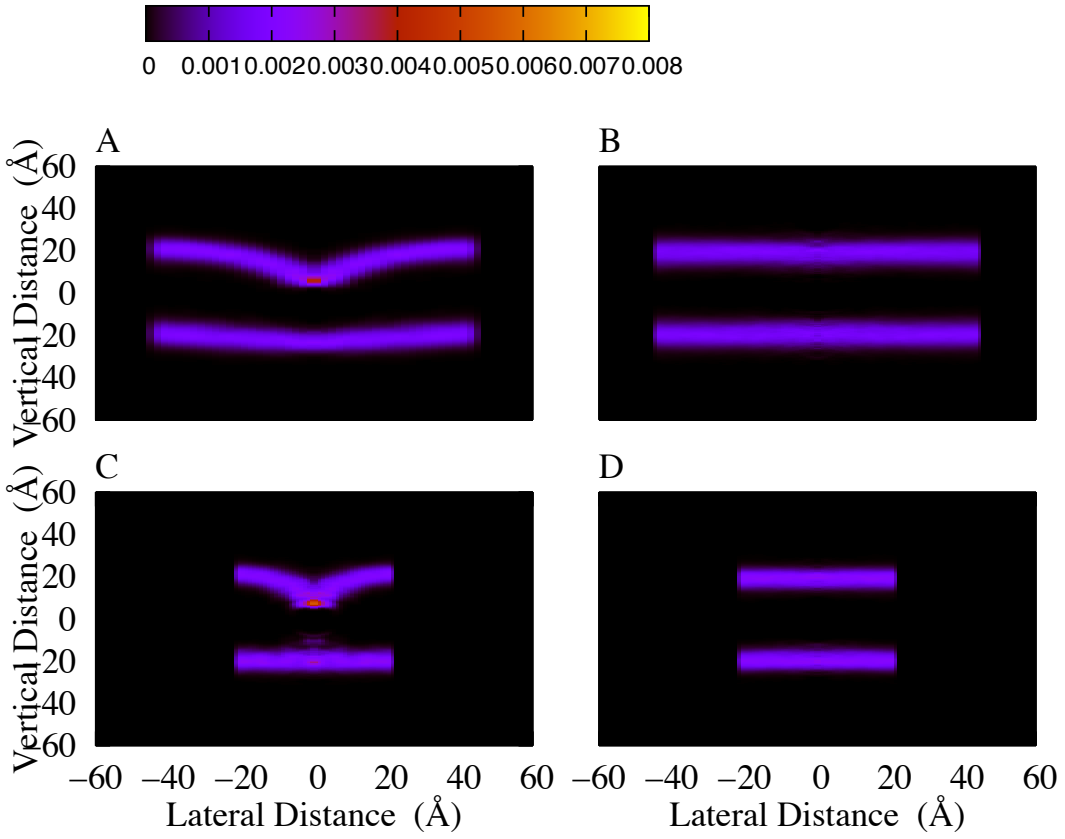

FIG. S13: Two dimensional number density profiles of lipid nitrogen atoms. (A) and (B) large membrane systems; (C) and (D) small membrane systems; (A) and (C) the center of bilayer window [-1.5:1.5] Å ; (B) and (D) the bulk water window [33.5:36.5] Å.

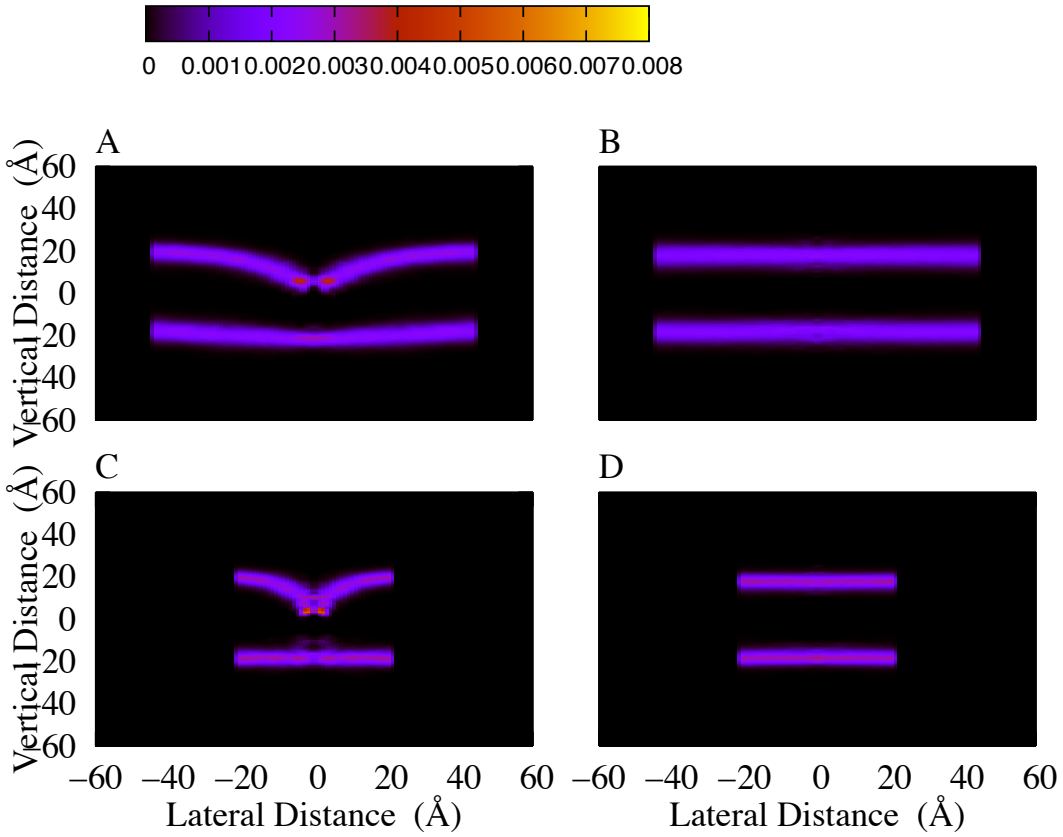

FIG. S14: Two dimensional number density profiles of lipid phosphorous atoms. (A) and (B) large membrane systems; (C) and (D) small membrane systems; (A) and (C) the center of bilayer window [-1.5:1.5] Å ; (B) and (D) the bulk water window [33.5:36.5] Å.

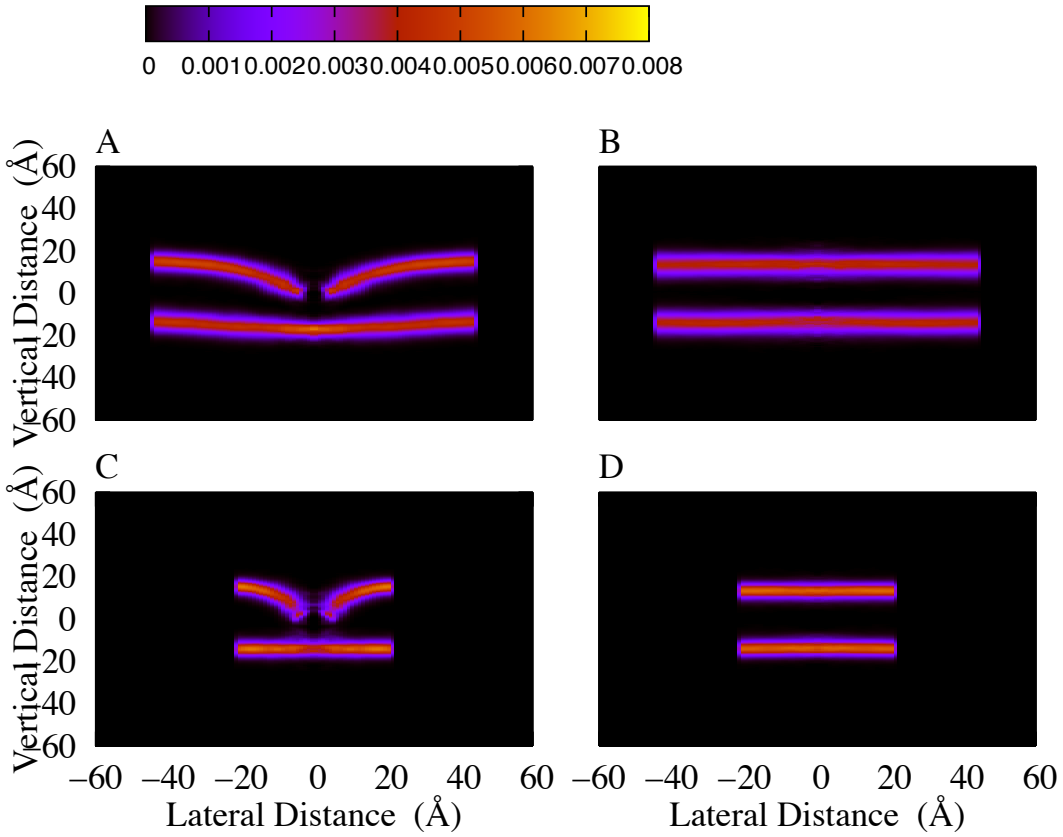

FIG. S15: Two dimensional number density profiles of oxygen atoms in lipid carbonyl groups. (A) and (B) large membrane systems; (C) and (D) small membrane systems; (A) and (C) the center of bilayer window [-1.5:1.5] Å ; (B) and (D) the bulk water window [33.5:36.5] Å.

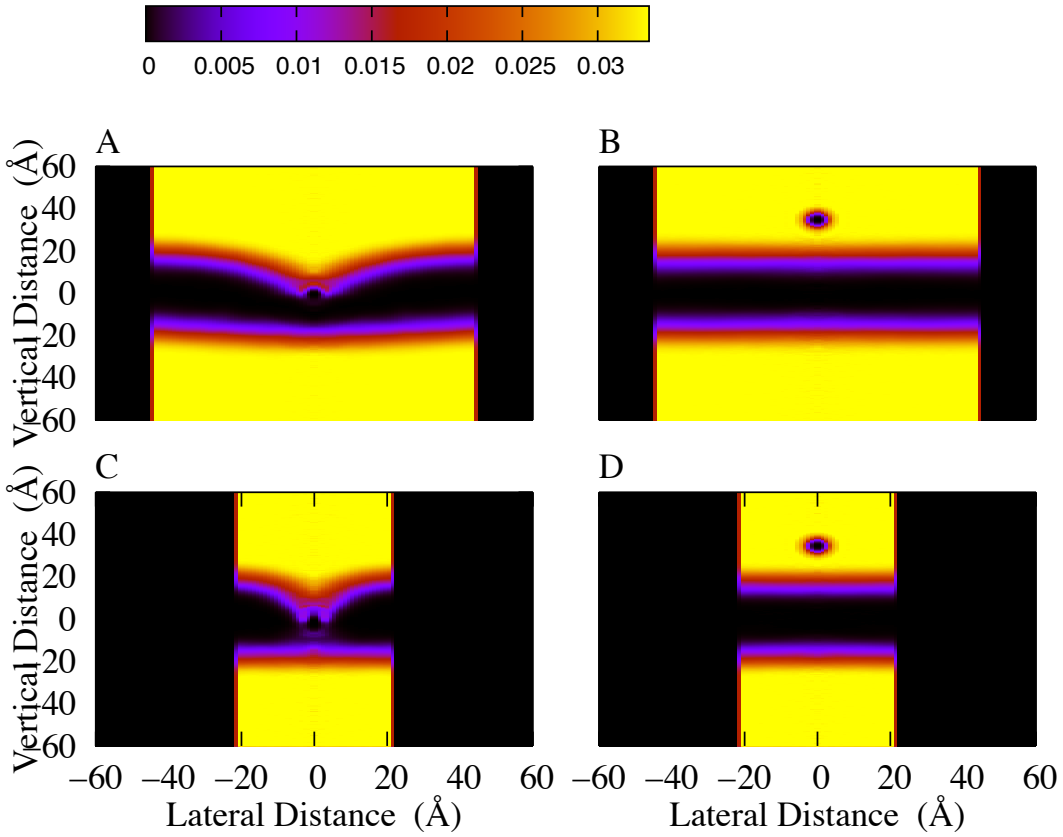

FIG. S16: Two dimensional number density profiles of oxygen atoms of water. (A) and (B) large membrane systems; (C) and (D) small membrane systems; (A) and (C) the center of bilayer window [-1.5:1.5] Å ; (B) and (D) the bulk water window [33.5:36.5] Å.

B. P2 Order Parameter

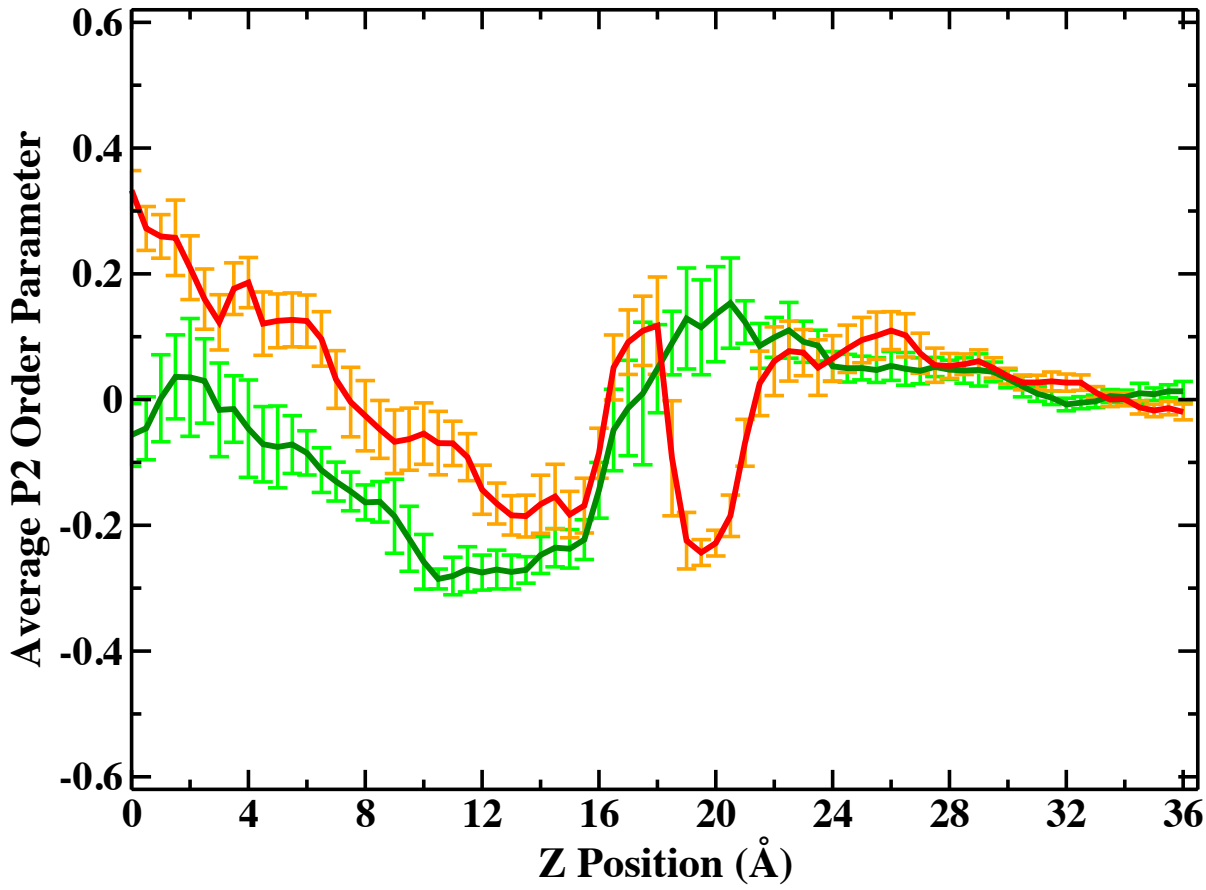

FIG. S17: Average value of the second Legendre polynomial order parameter $P_2 =< 1/2(3cos^2\theta - 1) >$. Red curve shows the large membrane system and green curve shows the small membrane system.

S11. PMF CONTRIBUTION OF COUNTERION

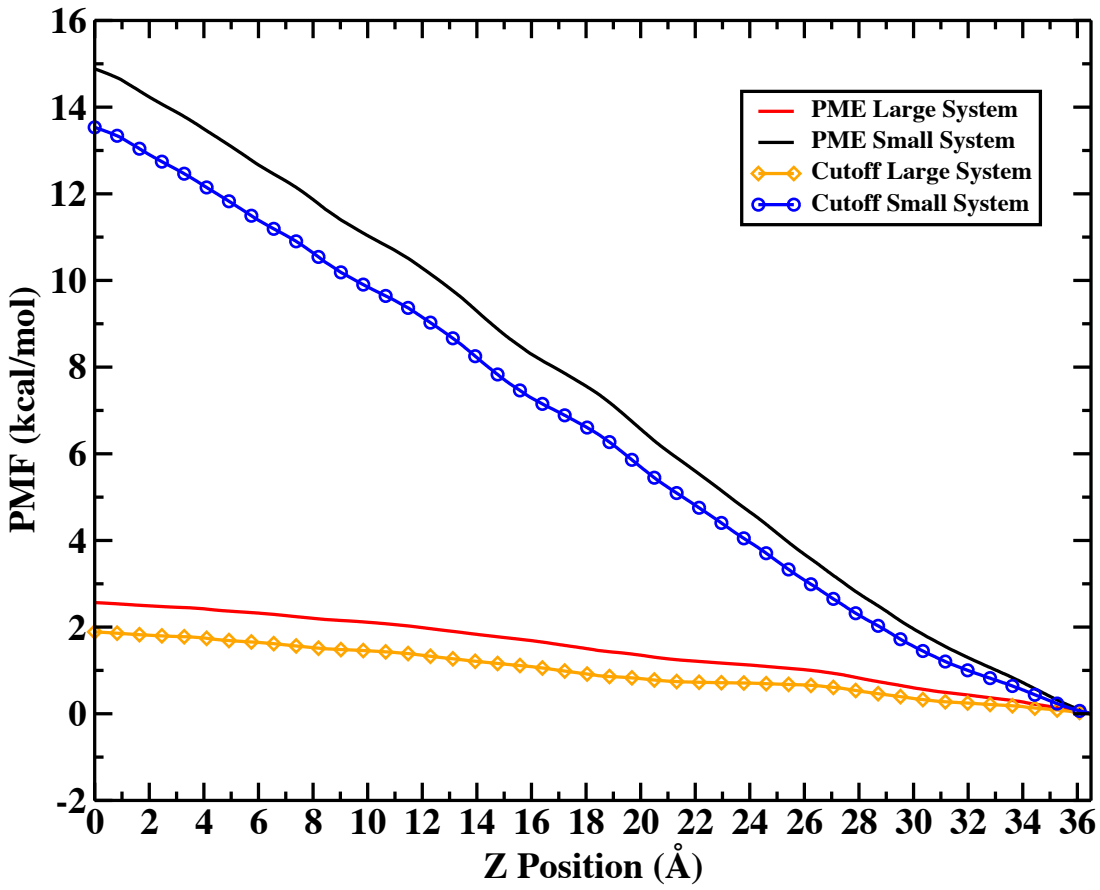

FIG. S18: Counterion Chloride contributions calcuated by using PME or large cutoff (no PME) for small and large systems.

We computed the PMF contributions from counterion Chloride by using PME or large cutoff (no PME). We used a grid of 64 x 64 x 128 points for the small membrane system and 128 x 128 x 128 points for the large membrane system for the PME calculation, and we use a sufficient large cutoff 99999.0 for both systems for the no PME calculation. The difference of the ion contributions between small and large systems is about 11.6 kcal/mol with PME, and 12.3 kcal/mol with large cutoff. They both show that the contribution from the small system is overestimated more than 11 kcal/mol, comparing to the large membrane system.

[1] Habermann, S. M.; Murphy, K. P. Energetics of Hydrogen Bonding in Proteins: A Model Compound Study. *Protein Sci.* **1996**, *5*, 1229–1239.