Cite this: DOI: 00.0000/xxxxxxxxxx

How Do Salt and Lipids Affect Conformational Dynamics of Aβ42 Monomers in Water?†

Brian Andrews,[a] Thomas Ruggiero,[a] and Brigita Urbanc*[a]

Table S1: Simulation parameters for the six sets of MD trajectories, as described in *Methods*.

Group	Box Type	Aβ42	Na^+	Cl−	DMPC Lipids	Waters
i	Cubic	1 (2.27 mM)	3 (6.83 mM)	0	0	24,328
ii	Cubic	1 (2.27 mM)	3 (6.83 mM)	0	12 (27 mM)	24,193
iii	Cubic	1 (2.27 mM)	3 (6.83 mM)	0	48 (109 mM)	23,193
iv	Cubic	1 (2.27 mM)	69 (157 mM)	66 (150 mM)	0	23,061
vi	Cubic	1 (2.27 mM)	69 (157 mM)	66 (150 mM)	48 (109 mM)	21,566

Table S2: Experimental ^{3}J(H^N, H^{C_α}) constants reported by Roche et al. [1] and MD–derived ^{3}J(H^N, H^{C_α}) constants for an Aβ42 monomer in pure water (W) and water with 150 mM NaCl (S) using four different sets of Karplus parameters reported by: Vuister and Bax [2] (VB), Hu and Bax [3] (HB), Habeck et al. [4] (Habeck), and Vögeli et al. [5]. Errors correspond to SEM values, calculated by assuming statistical independence of the ten MD trajectories considered in each set.

Res	$^3J_{exp}$	$^3J_{VB,W}$	$^3J_{VB,S}$	$^3J_{HB,W}$	$^3J_{HB,S}$	$^3J_{Habeck,W}$	$^3J_{Habeck,S}$	$^3J_{Vögeli,W}$	$^3J_{Vögeli,S}$
D1	0.00 ± 0.00	4.87 ± 0.03	4.85 ± 0.02	5.11 ± 0.03	5.09 ± 0.01	5.23 ± 0.03	5.21 ± 0.01	2.10 ± 0.90	1.65 ± 0.68
A2	0.00 ± 0.00	6.33 ± 0.07	6.21 ± 0.09	6.37 ± 0.07	6.25 ± 0.09	6.42 ± 0.07	6.31 ± 0.09	2.60 ± 1.09	2.03 ± 0.82
E3	6.23 ± 0.03	6.49 ± 0.30	6.53 ± 0.17	6.55 ± 0.31	6.61 ± 0.17	6.60 ± 0.31	6.66 ± 0.17	2.78 ± 1.11	2.21 ± 0.85
F4	7.02 ± 0.05	6.71 ± 0.26	6.48 ± 0.18	6.76 ± 0.27	6.57 ± 0.17	6.81 ± 0.27	6.63 ± 0.17	2.81 ± 1.13	2.20 ± 0.85
R5	7.29 ± 0.06	7.54 ± 0.28	6.93 ± 0.43	7.72 ± 0.26	7.10 ± 0.41	7.79 ± 0.25	7.16 ± 0.40	3.20 ± 1.24	2.45 ± 0.91
H6	0.00 ± 0.00	6.87 ± 0.31	6.55 ± 0.28	6.97 ± 0.31	6.59 ± 0.29	7.03 ± 0.31	6.63 ± 0.29	2.91 ± 1.13	2.26 ± 0.84
D7	6.89 ± 0.13	5.21 ± 0.19	5.95 ± 0.44	5.26 ± 0.21	5.99 ± 0.46	5.32 ± 0.21	6.05 ± 0.46	2.50 ± 0.92	2.03 ± 0.76
S8	6.01 ± 0.14	6.75 ± 0.13	6.66 ± 0.25	6.93 ± 0.14	6.74 ± 0.26	7.01 ± 0.15	6.80 ± 0.26	2.89 ± 1.16	2.25 ± 0.88
G9	6.27 ± 0.20	5.33 ± 0.15	5.79 ± 0.19	5.63 ± 0.17	6.05 ± 0.19	5.76 ± 0.18	6.17 ± 0.20	2.50 ± 1.00	2.01 ± 0.79
Y10	6.39 ± 0.07	6.73 ± 0.36	6.64 ± 0.39	6.78 ± 0.38	6.72 ± 0.41	6.83 ± 0.38	6.77 ± 0.40	2.96 ± 1.11	2.32 ± 0.85
E11	6.27 ± 0.13	6.53 ± 0.31	6.98 ± 0.28	6.61 ± 0.33	7.08 ± 0.26	6.66 ± 0.32	7.13 ± 0.26	2.93 ± 1.15	2.36 ± 0.91
V12	6.77 ± 0.12	7.35 ± 0.51	7.72 ± 0.52	7.44 ± 0.53	7.83 ± 0.53	7.49 ± 0.52	7.86 ± 0.53	3.39 ± 1.24	2.71 ± 0.98
H13	7.14 ± 0.20	7.23 ± 0.54	6.35 ± 0.55	7.38 ± 0.55	6.68 ± 0.55	7.44 ± 0.54	6.79 ± 0.54	3.17 ± 1.14	2.44 ± 0.84
H14	0.00 ± 0.00	6.54 ± 0.24	6.54 ± 0.28	6.83 ± 0.20	6.96 ± 0.18	6.93 ± 0.19	7.10 ± 0.16	2.91 ± 1.18	2.31 ± 0.92
Q15	6.18 ± 0.19	6.30 ± 0.24	6.68 ± 0.37	6.57 ± 0.24	6.96 ± 0.34	6.67 ± 0.24	7.06 ± 0.34	2.93 ± 1.14	2.34 ± 0.90
K16	6.30 ± 0.18	7.07 ± 0.35	6.86 ± 0.33	7.23 ± 0.36	7.03 ± 0.33	7.29 ± 0.36	7.10 ± 0.32	3.08 ± 1.19	2.41 ± 0.90
L17	6.63 ± 0.15	7.12 ± 0.41	7.81 ± 0.26	7.23 ± 0.41	7.92 ± 0.27	7.28 ± 0.41	7.96 ± 0.26	3.24 ± 1.27	2.63 ± 1.02
V18	8.20 ± 0.12	7.85 ± 0.34	7.90 ± 0.32	7.98 ± 0.36	8.02 ± 0.33	8.02 ± 0.36	8.06 ± 0.33	3.42 ± 1.33	2.70 ± 1.03
F19	7.72 ± 0.10	7.70 ± 0.38	7.76 ± 0.44	7.88 ± 0.36	7.96 ± 0.43	7.94 ± 0.35	8.02 ± 0.42	3.43 ± 1.31	2.71 ± 1.02
F20	7.67 ± 0.11	7.14 ± 0.41	7.09 ± 0.45	7.24 ± 0.42	7.25 ± 0.44	7.29 ± 0.42	7.31 ± 0.43	3.18 ± 1.19	2.51 ± 0.92
A21	5.56 ± 0.10	6.45 ± 0.41	6.54 ± 0.34	6.57 ± 0.42	6.60 ± 0.36	6.64 ± 0.41	6.65 ± 0.35	2.88 ± 1.09	2.28 ± 0.84
E22	5.86 ± 0.06	6.68 ± 0.31	6.69 ± 0.27	6.76 ± 0.33	6.74 ± 0.28	6.80 ± 0.32	6.78 ± 0.28	2.89 ± 1.12	2.28 ± 0.86
D23	6.63 ± 0.08	5.66 ± 0.16	5.77 ± 0.13	5.67 ± 0.16	5.87 ± 0.15	5.73 ± 0.16	5.95 ± 0.15	2.43 ± 0.98	1.93 ± 0.77
V24	6.75 ± 0.06	6.75 ± 0.20	7.02 ± 0.22	6.78 ± 0.21	7.15 ± 0.23	6.83 ± 0.21	7.19 ± 0.23	2.94 ± 1.18	2.35 ± 0.92
G25	5.85 ± 0.12	5.53 ± 0.24	5.37 ± 0.21	5.96 ± 0.24	5.75 ± 0.20	6.12 ± 0.23	5.90 ± 0.20	2.53 ± 1.00	1.97 ± 0.76
S26	6.53 ± 0.12	6.50 ± 0.18	6.80 ± 0.24	6.61 ± 0.20	6.96 ± 0.24	6.68 ± 0.21	7.04 ± 0.23	2.88 ± 1.15	2.30 ± 0.90
N27	7.19 ± 0.15	6.65 ± 0.18	6.94 ± 0.23	6.90 ± 0.13	7.21 ± 0.18	7.00 ± 0.12	7.31 ± 0.17	2.96 ± 1.21	2.35 ± 0.95
K28	6.43 ± 0.12	7.48 ± 0.27	7.54 ± 0.15	7.56 ± 0.27	7.64 ± 0.16	7.60 ± 0.27	7.68 ± 0.16	3.17 ± 1.29	2.51 ± 0.99
G29	5.89 ± 0.11	5.81 ± 0.12	5.61 ± 0.08	6.25 ± 0.14	5.95 ± 0.14	6.41 ± 0.15	6.10 ± 0.15	2.59 ± 1.06	2.01 ± 0.79
A30	5.41 ± 0.04	6.72 ± 0.40	6.36 ± 0.27	6.79 ± 0.42	6.40 ± 0.28	6.84 ± 0.42	6.45 ± 0.28	2.86 ± 1.10	2.22 ± 0.82
I31	7.68 ± 0.05	6.92 ± 0.33	6.72 ± 0.26	7.03 ± 0.33	6.80 ± 0.27	7.07 ± 0.33	6.86 ± 0.27	2.96 ± 1.16	2.32 ± 0.87
I32	7.41 ± 0.07	7.44 ± 0.25	6.95 ± 0.31	7.54 ± 0.26	7.01 ± 0.32	7.58 ± 0.26	7.06 ± 0.32	3.11 ± 1.22	2.39 ± 0.90
G33	5.95 ± 0.12	5.39 ± 0.34	5.34 ± 0.17	5.56 ± 0.33	5.52 ± 0.19	5.66 ± 0.32	5.63 ± 0.20	2.40 ± 0.94	1.90 ± 0.72
L34	6.78 ± 0.05	6.72 ± 0.19	6.88 ± 0.23	6.77 ± 0.18	6.94 ± 0.25	6.81 ± 0.18	6.99 ± 0.24	2.89 ± 1.16	2.29 ± 0.90
M35	7.54 ± 0.05	6.55 ± 0.33	6.73 ± 0.11	6.68 ± 0.34	6.84 ± 0.14	6.73 ± 0.34	6.91 ± 0.14	2.85 ± 1.15	2.28 ± 0.89
V36	7.68 ± 0.04	6.56 ± 0.27	6.84 ± 0.16	6.58 ± 0.28	6.90 ± 0.16	6.63 ± 0.28	6.95 ± 0.16	2.84 ± 1.14	2.27 ± 0.89
G37	5.72 ± 0.07	5.76 ± 0.31	5.69 ± 0.08	6.13 ± 0.31	6.05 ± 0.08	6.27 ± 0.30	6.20 ± 0.09	2.59 ± 1.05	2.04 ± 0.80
G38	5.87 ± 0.06	5.67 ± 0.05	5.71 ± 0.05	6.06 ± 0.07	6.06 ± 0.06	6.21 ± 0.08	6.20 ± 0.06	2.52 ± 1.06	1.99 ± 0.81
V39	7.90 ± 0.02	6.69 ± 0.09	6.24 ± 0.11	6.76 ± 0.10	6.35 ± 0.07	6.81 ± 0.10	6.41 ± 0.07	2.69 ± 1.13	2.08 ± 0.84
V40	7.80 ± 0.02	7.16 ± 0.08	6.77 ± 0.30	7.28 ± 0.08	6.92 ± 0.25	7.32 ± 0.08	6.98 ± 0.24	2.97 ± 1.21	2.30 ± 0.90
I41	8.33 ± 0.01	7.10 ± 0.09	7.14 ± 0.13	7.16 ± 0.10	7.19 ± 0.13	7.20 ± 0.10	7.23 ± 0.13	2.96 ± 1.23	2.33 ± 0.94
A42	6.55 ± 0.02	8.28 ± 0.04	7.77 ± 0.47	8.37 ± 0.05	7.89 ± 0.44	8.41 ± 0.05	7.94 ± 0.43	3.45 ± 1.36	2.65 ± 1.02

Table S3: RMSE values of ^{3}J(H^N, H^{C_α}) coupling constants, derived from MD simulations of an Aβ42 monomer in 0 and 150 mM NaCl, relative to experimental values calculated using four sets of Karplus parameters. RMSE values between MD-derived ^{3}J(H^N, H^{C_α}) constants in pure water and water with salt are added for comparison.

Karplus Parameters	Pure Water - Experiment	150 mM Salt - Experiment	Salt - Pure Water
VB [2]	0.75	0.74	0.33
HB [3]	0.76	0.74	0.33
Habeck [4]	0.77	0.75	0.33
Vögeli [5]	0.87	0.75	0.62

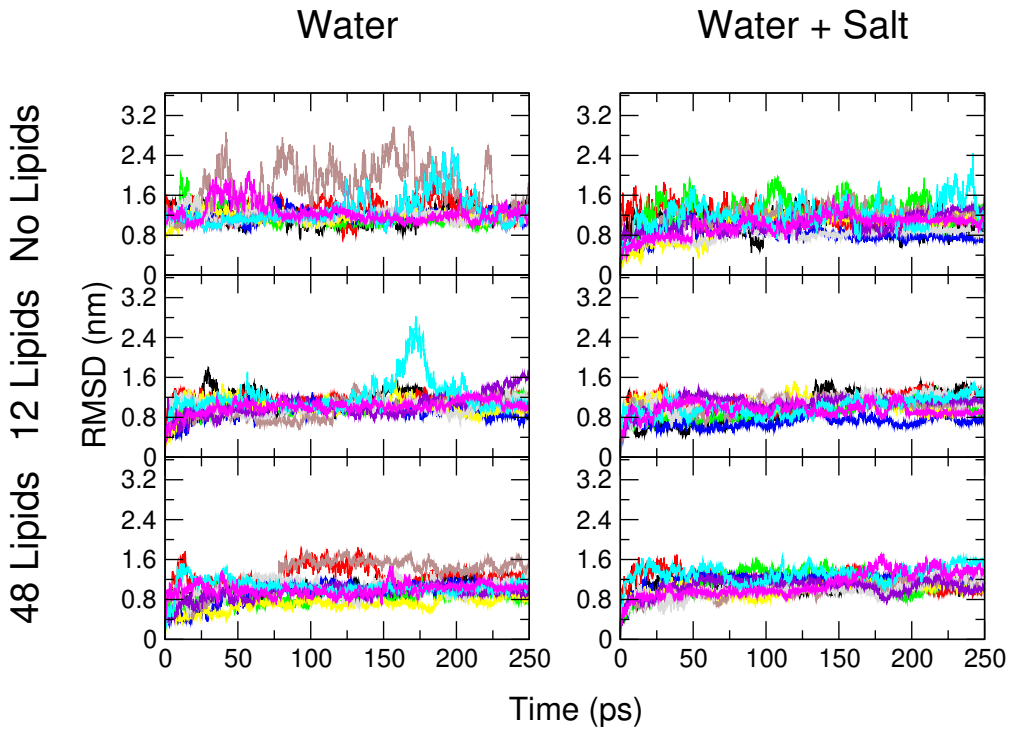

Figure S1: The RMSD of Aβ monomer in pure water or water with 150 mM salt (columns) at three different lipid concentrations (rows) over time for each of the ten trajectories conducted in each set of conditions.

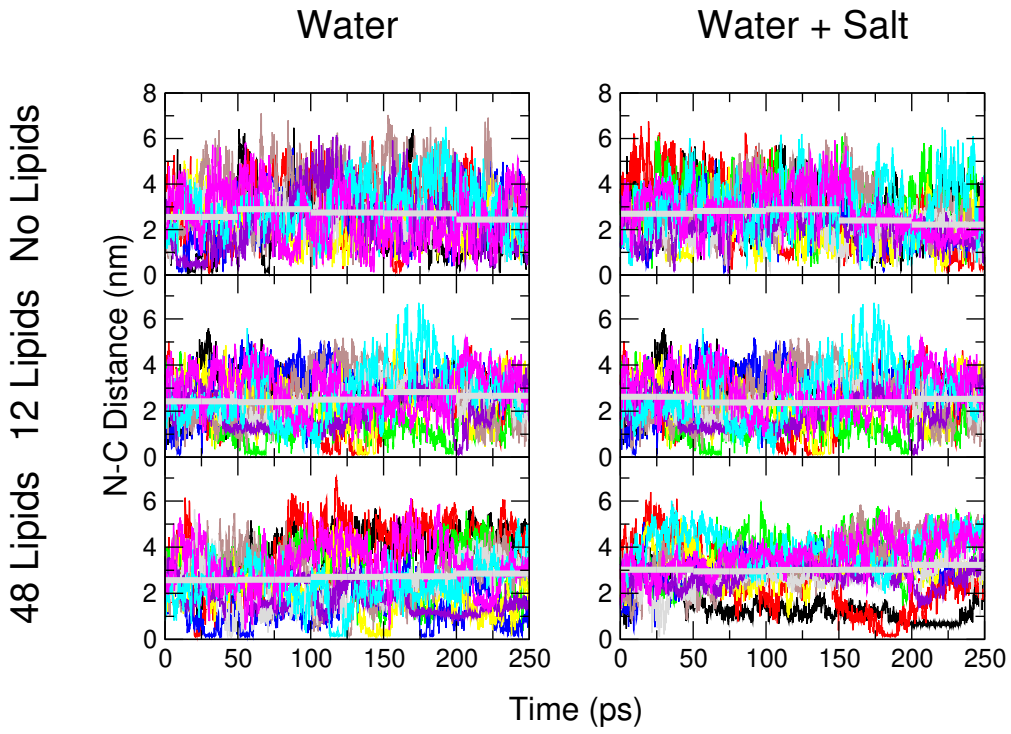

Figure S2: The N2CD of Aβ monomer in pure water or water with 150 mM salt (columns) at three different lipid concentrations (rows) over time for each of the ten trajectories conducted in each set of conditions. Gray lines show 50-ns averages over ten trajectories.

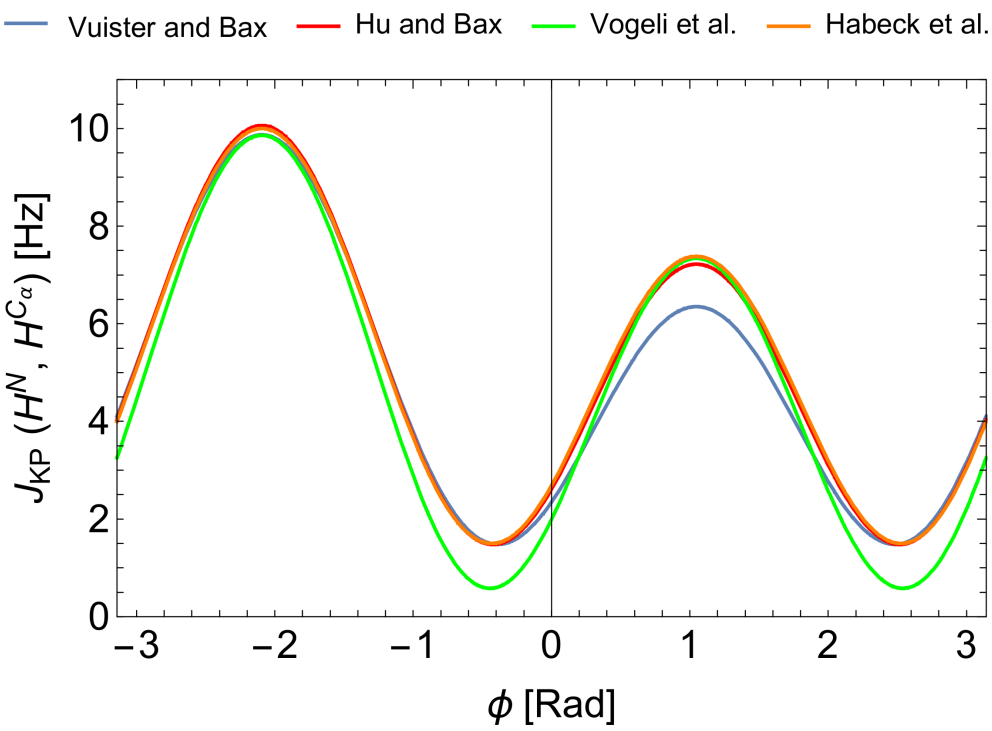

Figure S3: Karplus curves for four sets of Karplus parameters for the ^{3}J(H^N, H^{C_α}) coupling constant, denoted as VB [2], HB [3], Habeck [4], and Vögeli [5].

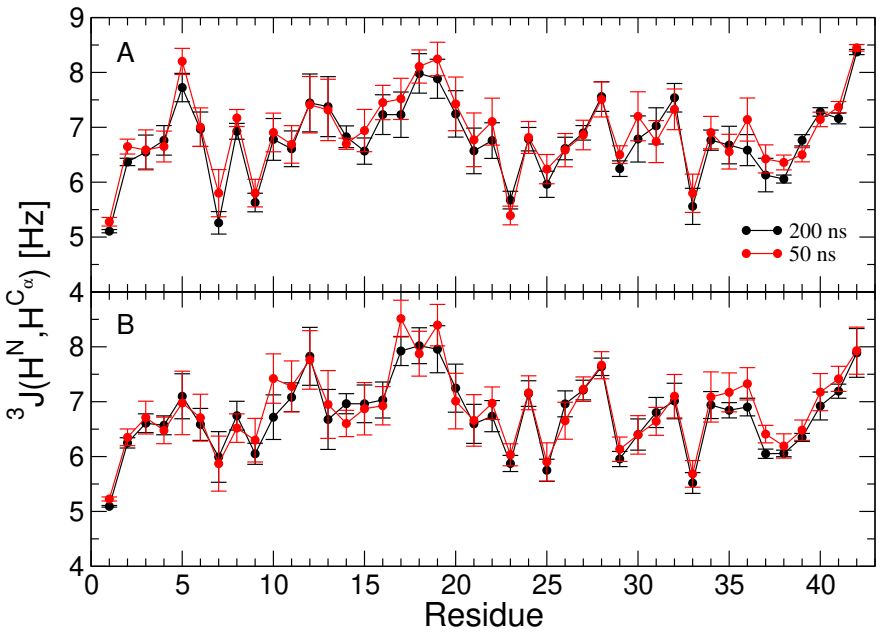

Figure S4: ^{3}J(H^N, H$^{C_\alpha}$) coupling constants calculated from MD trajectories of Aβ42 in (A) water and (B) water/salt using the Kaplus parameter set from Hu and Bax [3] using time frames 50-250 ns (black) and 200-250 ns (red).

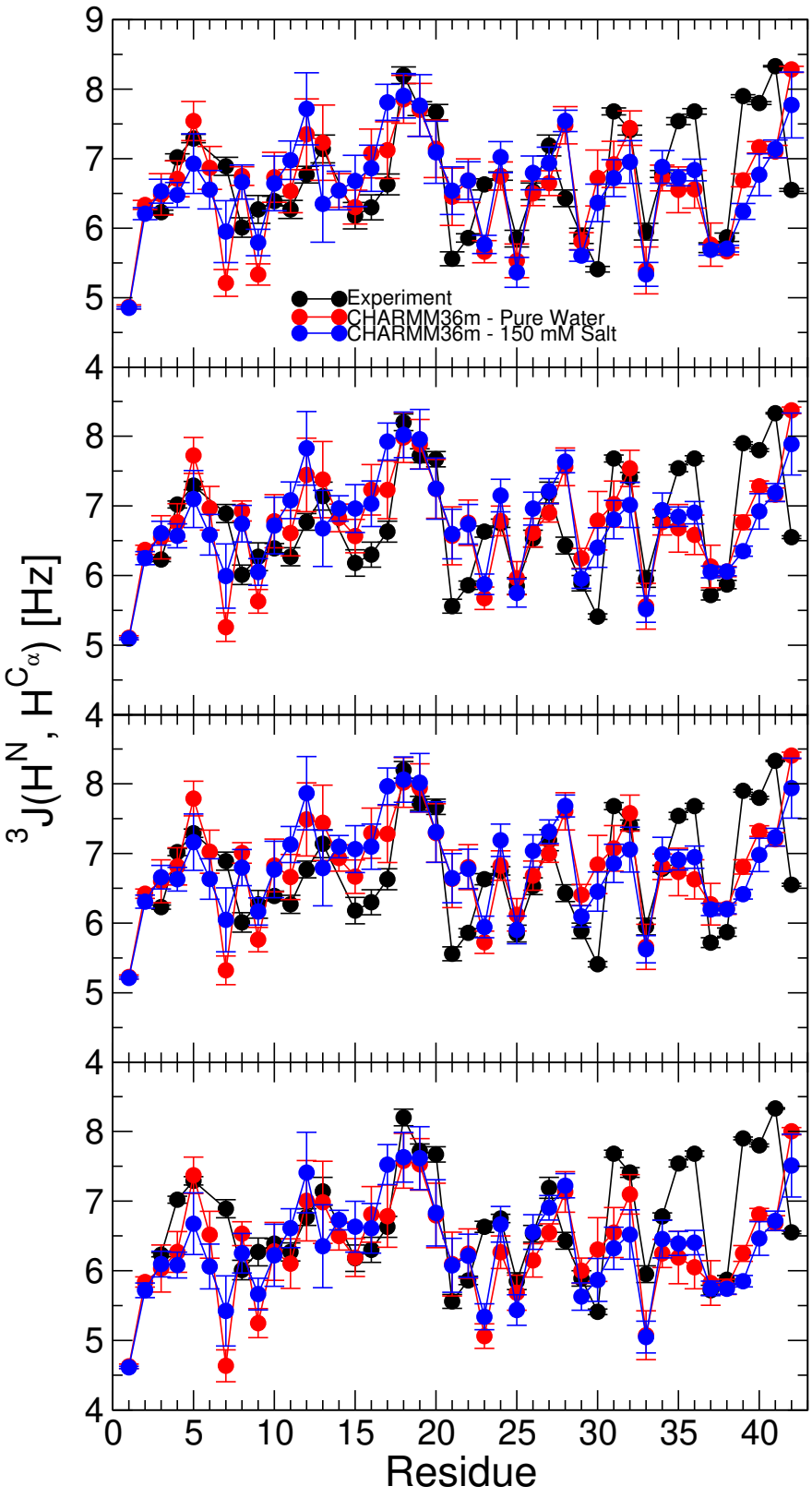

Figure S5: ^{3}J(H^N, H$^{C_\alpha}$) coupling constants calculated from MD trajectories of Aβ42 in water and water/salt using the four Kaplus parameter sets: (A) VB [2], (B) HB [3], (C) Habeck [4], and (D) Vögeli [5]. MD-derived coupling constants are also compared to the experimental values reported by Roche and collaborators [1].

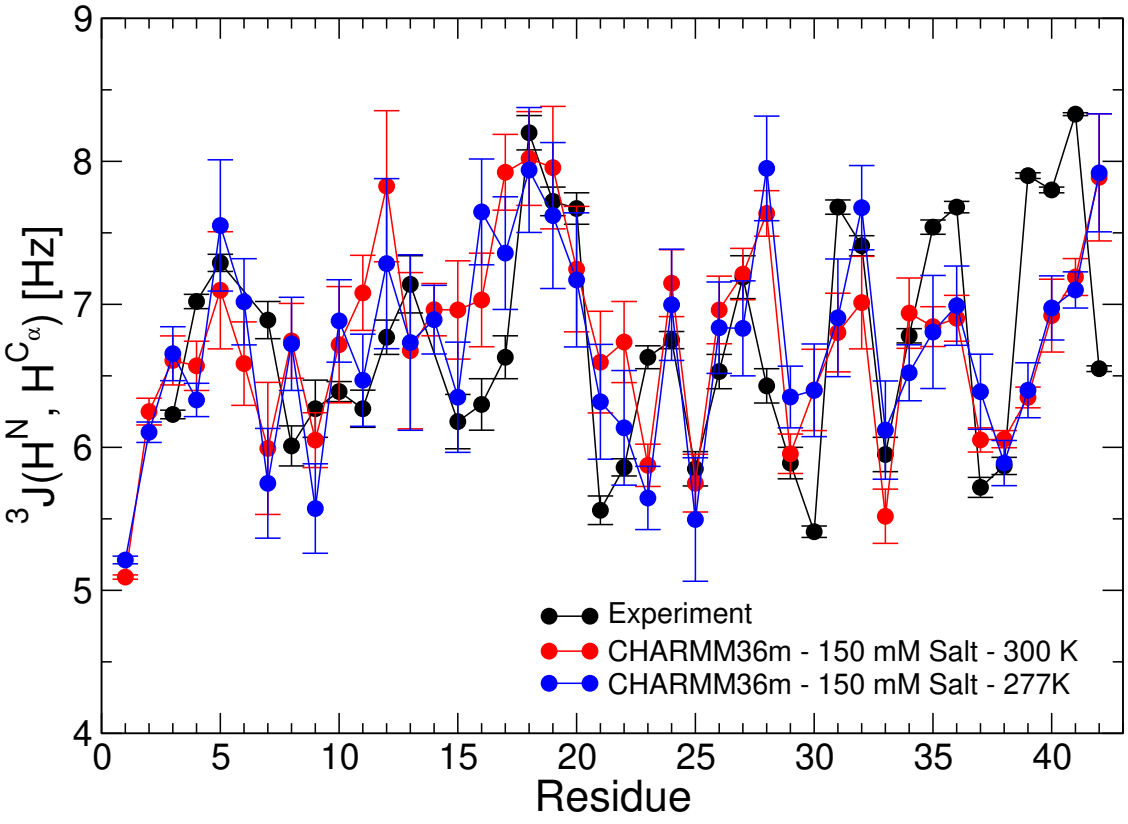

Figure S6: ^{3}J(H^N, H$^{C_\alpha}$) coupling constants calculated from MD trajectories of Aβ42 in water and 150 mM salt using the HB parameter set [3] at 277 K, which is the temperature used to collect experimental values [1].

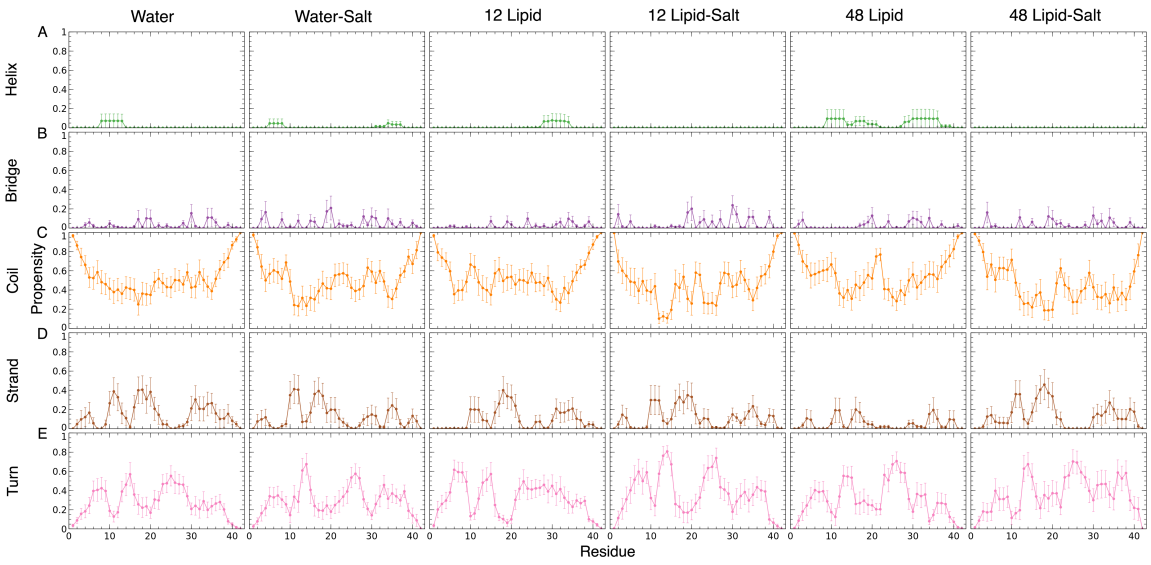

Figure S7: STRIDE-generated (A) helix, (B) bridge, (C) coil, (D) strand, and (E) turn secondary structure propensities for each amino acid residue of monomeric Aβ42 in the following conditions: neutral water, water with 150 mM salt, neutral water with 12 DMPC molecules, water with 12 DMPC and 150 mM salt, neutral water with 48 DMPC molecules, and water with 48 DMPC and 150 mM salt. Data is collected from 10 separate MD trajectories each from times 450-500 ns, sampling every 2 ps, and then averaged. Error bars are calculated as SEM using the averages of individual trajectories to capture trajectory-to-trajectory variability (see *Methods* for more detail).

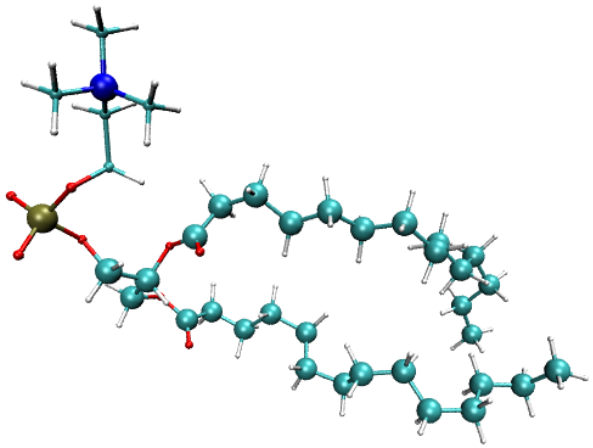

Figure S8: Visualization of a DMPC lipid generated by VMD. The three groups considered for protein-lipid contacts are the head group nitrogen (blue), the phosphorus (gold), and the tail group carbons (cyan), all shown with exaggerated scale compared to hydrogens (white), oxygens (red), and other carbons (cyan) in the molecule.

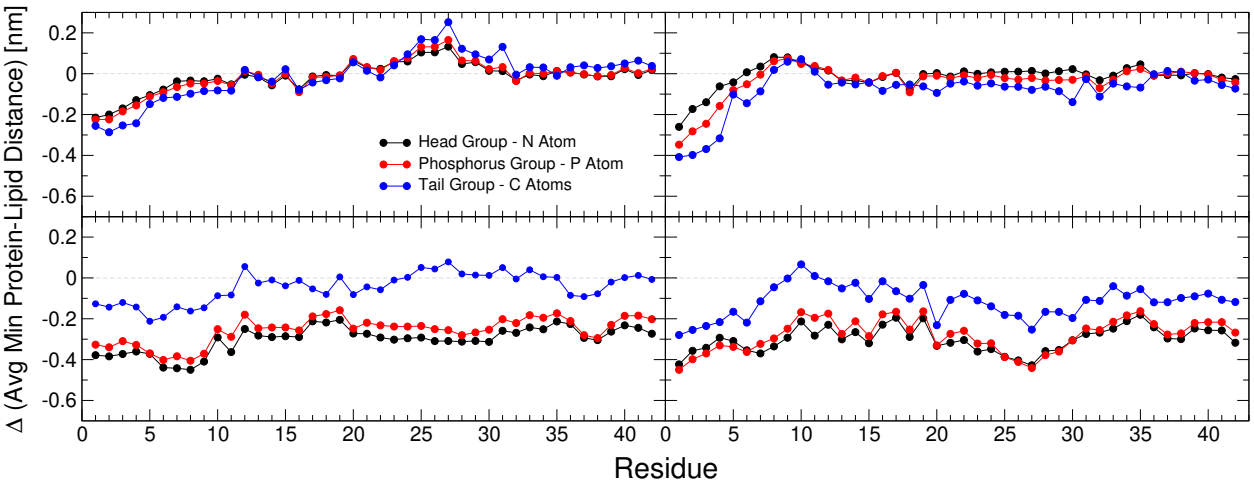

Figure S9: Differences of the average minimum protein-lipid distances calculated by subtracting distances calculated in the following pairs of differing conditions: (A) 150 mM salt and pure water in the presence of 12 lipids, (B) 150 mM salt and pure water in the presence of 48 lipids, (C) 48 lipids and 12 lipids in no-salt conditions, and (D) 48 lipids and 12 lipids in physiological salt conditions.

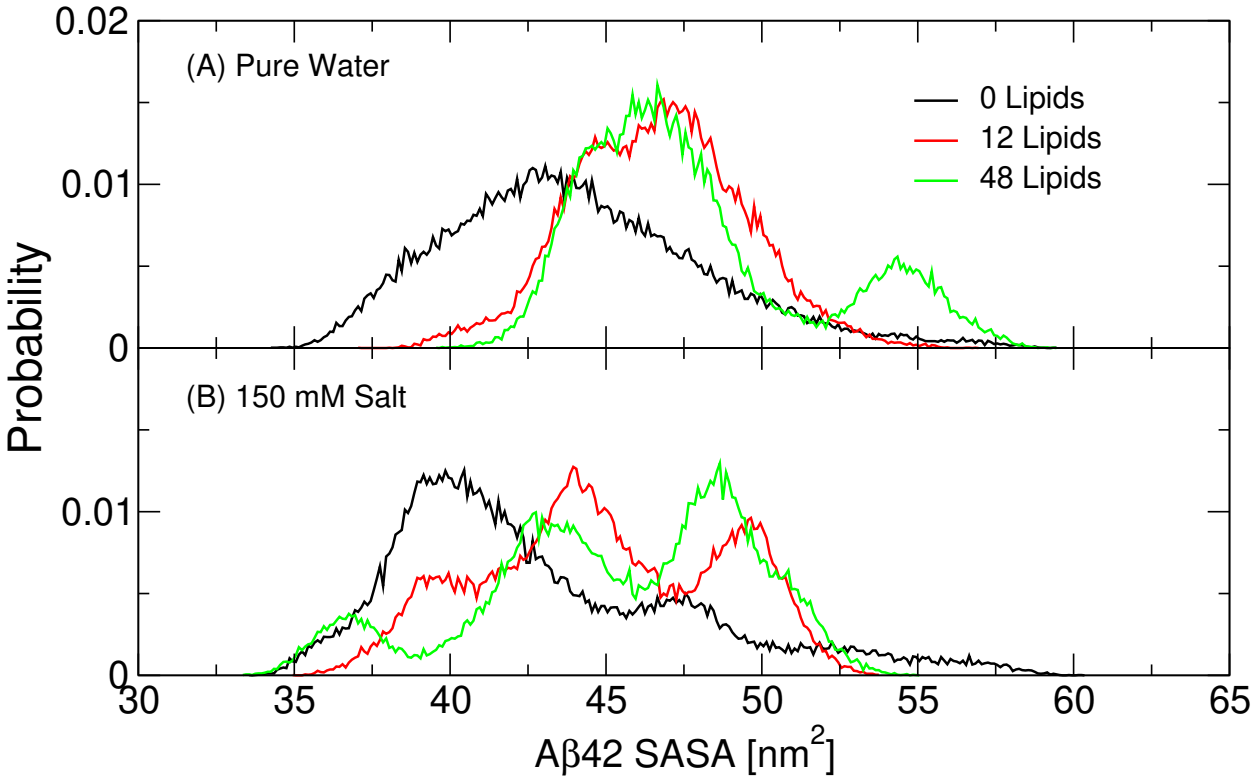

Figure S10: SASA of an Aβ42 monomer in all three lipid concentrations in (A) pure water and (B) 150 mM NaCl. Note that the solvent in these calculations is considered to be the water, lipids, and salt.

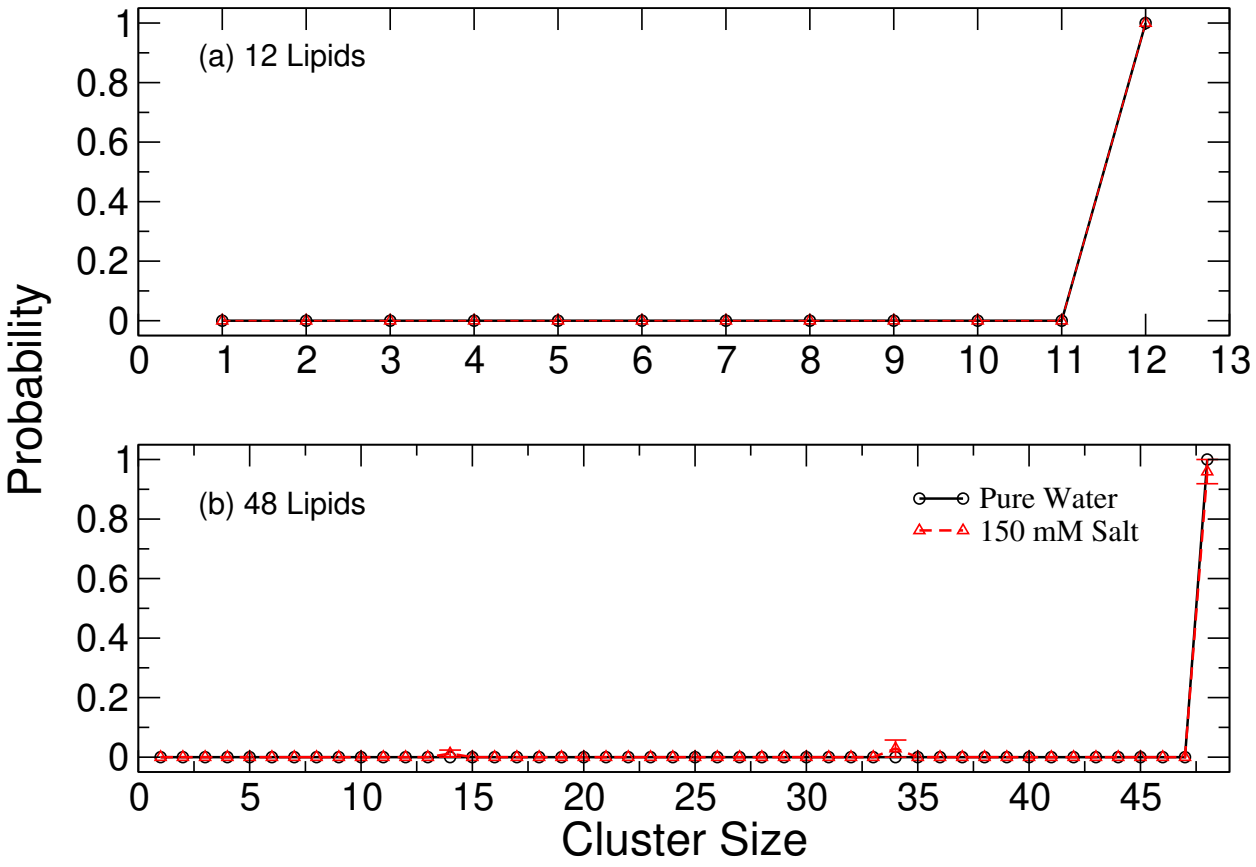

Figure S11: Cluster size distributions for (a) 12 and (b) 48 lipids in pure water (black circles) and 150 mM salt (red triangles). The distributions were calculated as described in *Methods*. Distributions without error bars are associated with average distributions with SEM values of zero.

References

[1] Julien Roche, Yang Shen, Jung Ho Lee, Jinfa Ying, and Ad Bax. Monomeric Aβ^{1-40} and Aβ^{1-42} peptides in solution adopt very similar Ramachandran map distributions that closely resemble random coil. *Biochemistry*, 55(5):762–775, FEB 9 2016.

[2] G. W. Vuister and A. Bax. Quantitative J correlation - A new approach for measuring homonuclear three-bond $J(\mathrm{H}^N\mathrm{H}^\alpha)$ coupling constants in ^{15}N-enriched proteins. *J. Am. Chem. Soc.*, 115(17):7772–7777, AUG 25 1993.

[3] J.-S. Hu and A. Bax. Determination of ϕ and χ_1 angles in proteins from ^{13}C–^{13}C three-bond J couplings measured by three-dimensional heteronuclear NMR. How planar is the peptide bond? *J. Am. Chem. Soc.*, 119(27):6360–6368, JUL 9 1997.

[4] M. Habeck, W. Rieping, and M. Nilges. Bayesian estimation of Karplus parameters and torsion angles from three-bond scalar couplings constants. *J. Magn. Reson.*, 177(1):160–165, NOV 2005.

[5] Beat Vögeli, Jinfa Ying, Alexander Grishaev, and Ad Bax. Limits on variations in protein backbone dynamics from precise measurements of scalar couplings. *J. Am. Chem. Soc.*, 129(30):9377–9385, AUG 1 2007.