Supporting Information

Tetrameric Aβ40 and Aβ42 β-Barrel Structures by Extensive Atomistic Simulations. II. In Aqueous Solution

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(A) REMD simulations

The GROMACS program was used with periodic boundary conditions, a timestep of 2 fs using SHAKE or LINCS and the velocity Verlet integrator.[1] The peptides at pH 7 have NH_3^+ and CO_2^- termini, deprotonated Glu and Asp, protonated Arg and Lys, and neutral His with a protonated Nepsilon atom. The temperature distributions were determined by using van der Spoel's method.[2]

The perfect barrels of Aβ40 and Aβ42 were centred in truncated octahedron boxes of 519 and 729 nm^3 containing 17000 and 23000 TIP3P water molecules, leading to a peptide concentration of 12.8 and 9.2 mM. The systems were neutralized by Na^+ ions resulting in 52000 and 72000 atoms for Aβ40 and Aβ42, respectively. The first protein force field is the Amber ff99SB-ILDN force field. The velocity-rescaling thermostat was employed, electrostatic interactions were calculated using the particle mesh Ewald method and a cut-off of 1.1 nm, and Van der Waals interactions used a cut-off of 1.2 nm.[3-5] REMD simulations were performed with 64 and 72 replicas for Aβ40 and Aβ42, with a temperature range of 300-400 K. Exchanges between two consecutive replicas were attempted every 2 ps, leading to a mean acceptance ratio of 25%, and each replica ran for 350 ns. The total CPU time is 1.800.000 hours using 1152 cores and 16 cores/replica. Secondary structure was determined using the STRIDE program.[6] CCS values for the β-barrel and non β-barrel states were calculated using the MOBCAL software.[7]

REMD simulations were also repeated with the OPLS/TIP3P force field and the CHARMM36m/TIP3P-modified force field for 150 ns each starting from the most populated cluster Amber ff99SB-ILDN for both Aβ40 and Aβ442 (states S1 see Figure 3). For both systems, we used the same number of replicas as for Amber f99ILDN/TIP3 and the CPU time using OPLS/TIP3P and CHARM36m/TIP3P force fields is 1.500.000 hours.

REMD simulation with Amber99SB-DISP was also performed starting from the S1 state for Aβ42 peptide only. Since DISP is based on the TIP4P force field, we used up to 90 replicas, covering 300 to 400 K and leading to an acceptance ratio of 25%. For this simulation, the CPU time is 810.000 hours using 1800 cores and 20 cores/replica.

(B) Analysis of Aβ40 and Aβ42 by REMD with Amber ff99SB-ILDN/TIP3P

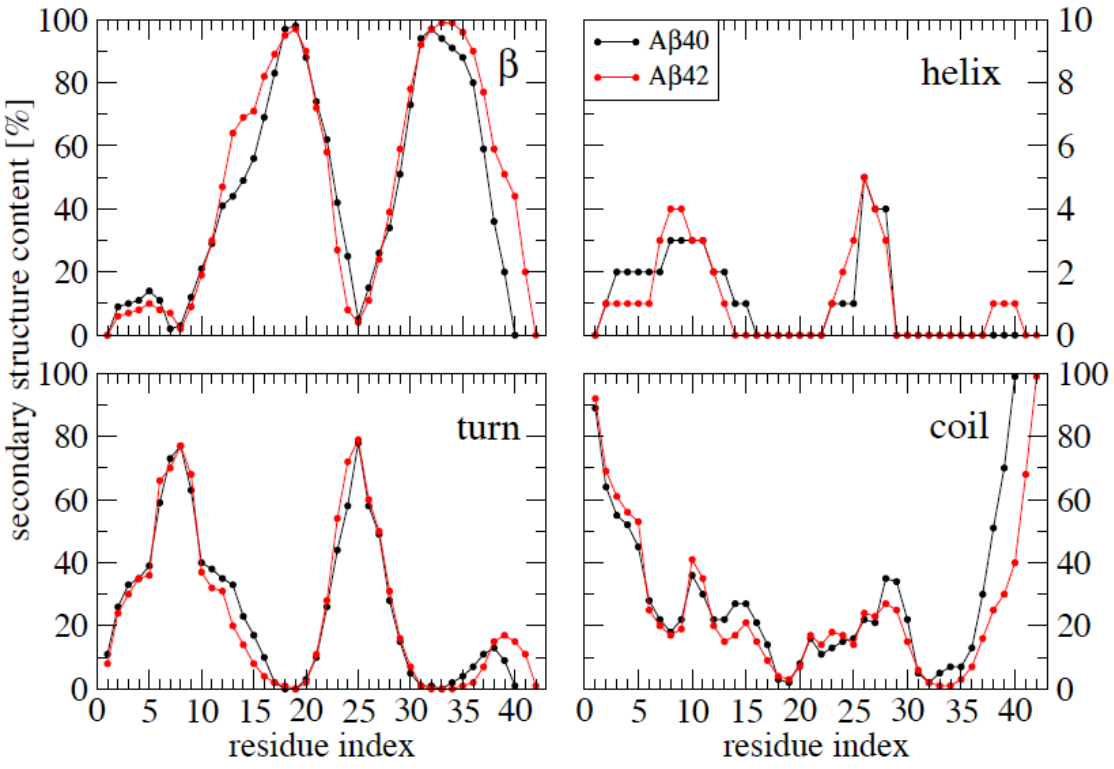

Figure S1. Secondary structure propensities of each amino acid of Aβ40 (black) and Aβ42 (red) peptides at 315 K using the time interval 50-350 ns. Error bars of 2% max are not shown for clarity.

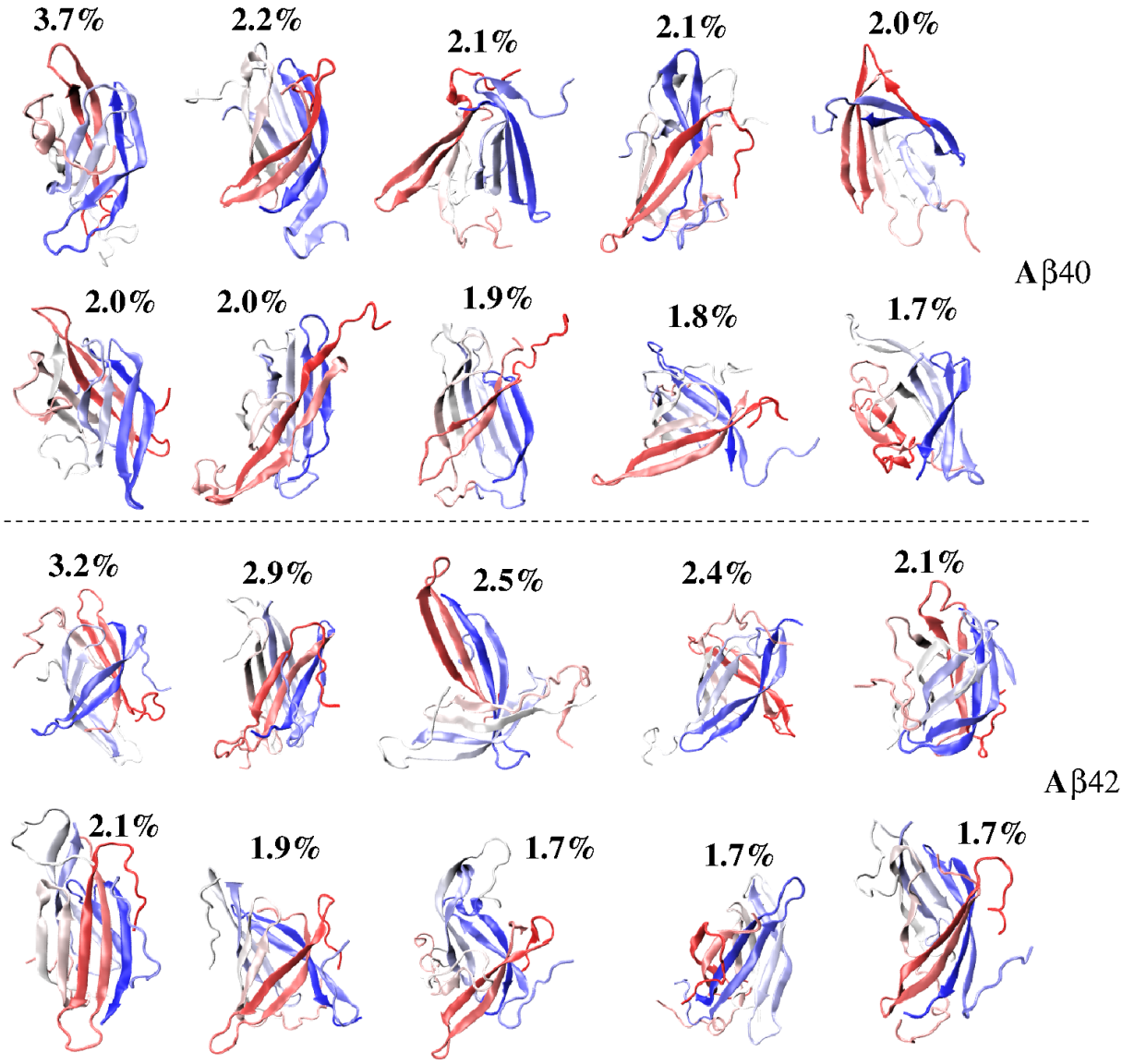

Figure S2. The first ten clusters of Aβ40 and Aβ42 tetramers at 315 K using the time interval 50-350 ns.

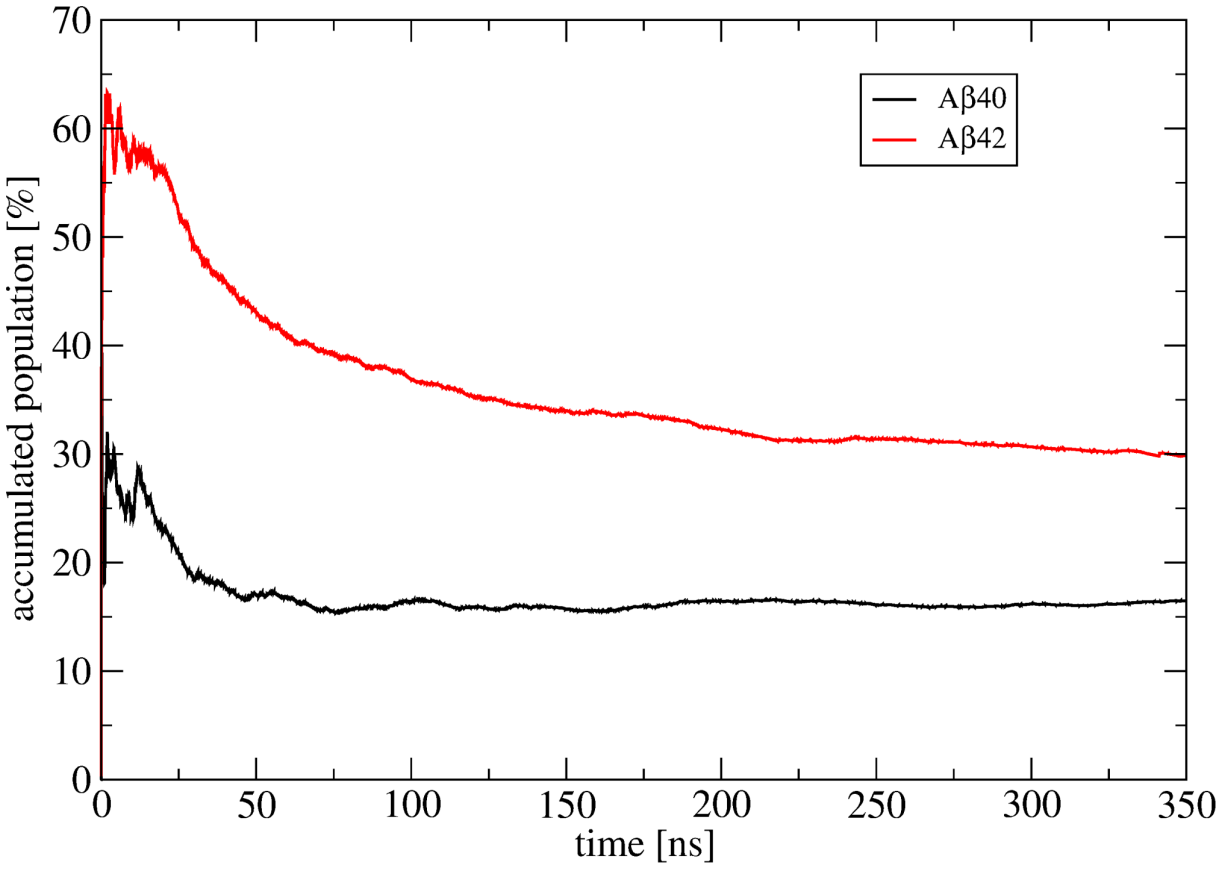

Figure S3. Accumulated population of the barrel structures for $A\beta 40$ (black) and $A\beta 42$ (red) peptides at 315 K. Here, the accumulated population is calculated as: $p_{\mathrm{acc}}(t) = \frac{1}{\tau}\int_0^t p(\tau)$

System	State	P [%]	RMSD [nm]	R_g [nm]	N_{HB}	N_{HB1}	N_{HB2}	N_{HB3}	CCS [A^2]
Aβ40	1	31.43	0.60	1.33	11.02	6.76	3.93	6.33	2197
	2	25.12	0.74	1.36	10.25	7.10	2.87	5.35	1933
	3	19.55	0.48	1.34	11.28	7.71	3.29	5.39	2299
	4	7.32	0.90	1.40	9.54	6.77	2.06	4.24	2342
Aβ42	1	52.68	0.44	1.34	13.10	6.04	6.68	11.32	2030
	2	16.32	0.76	1.51	12.38	4.64	7.65	15.30	2474

Table S1. Aβ40 and Aβ42 non β-barrel characterizations using the time interval 50-350 ns at 315 K.For each state, we give the population P (in %), the tilt angle α (in degrees), the inner diameter of the pore (in nm), the RMSD (in nm) with respect to state 0 and the radius of gyration Rg (in nm) using only residues 11-36, and the total number of interchain H-bonds between residues 11-36 (N_{HB}), interpeptide H-bonds between residues 11-21 and 11-21 (N_{HB1}), between residues 29-36 and 29-36 (N_{HB2}), and between residues 29-40 (N_{HB3}). We also give the collision cross-section surface (CCS). All values are obtained using all conformations belonging to each cluster. Error bars on all CCS values are on the order of 75 $Å^2$

System	Salt-bridge	Population			
		chain 1	chain 2	chain 3	chain 4
	E22-K28	18 ± 1.7	0 ± 0	0 ± 0	14 ± 0.5
Aβ40	D23-K28	8 ± 2.9	4 ± 0.7	5 ± 1.5	3 ± 1.0
Aβ42	E22-K28	15 ± 1.5	1 ± 0.2	0 ± 0	16 ± 0.3
	D23-K28	9 ± 2.0	3 ± 0.3	3 ± 0.5	7 ± 1.8

Table S2. Populations of the intramolecular E22-K28 and D23-K28 salt-bridges in the four chains (or hairpins) using the time intervals 50 to 350 ns. A salt-bridge is considered formed if the distances are between the CG atom of D23 (or CD atom of E22) and the NZ atom of K28 are below a cutoff distance of 0.45 nm.

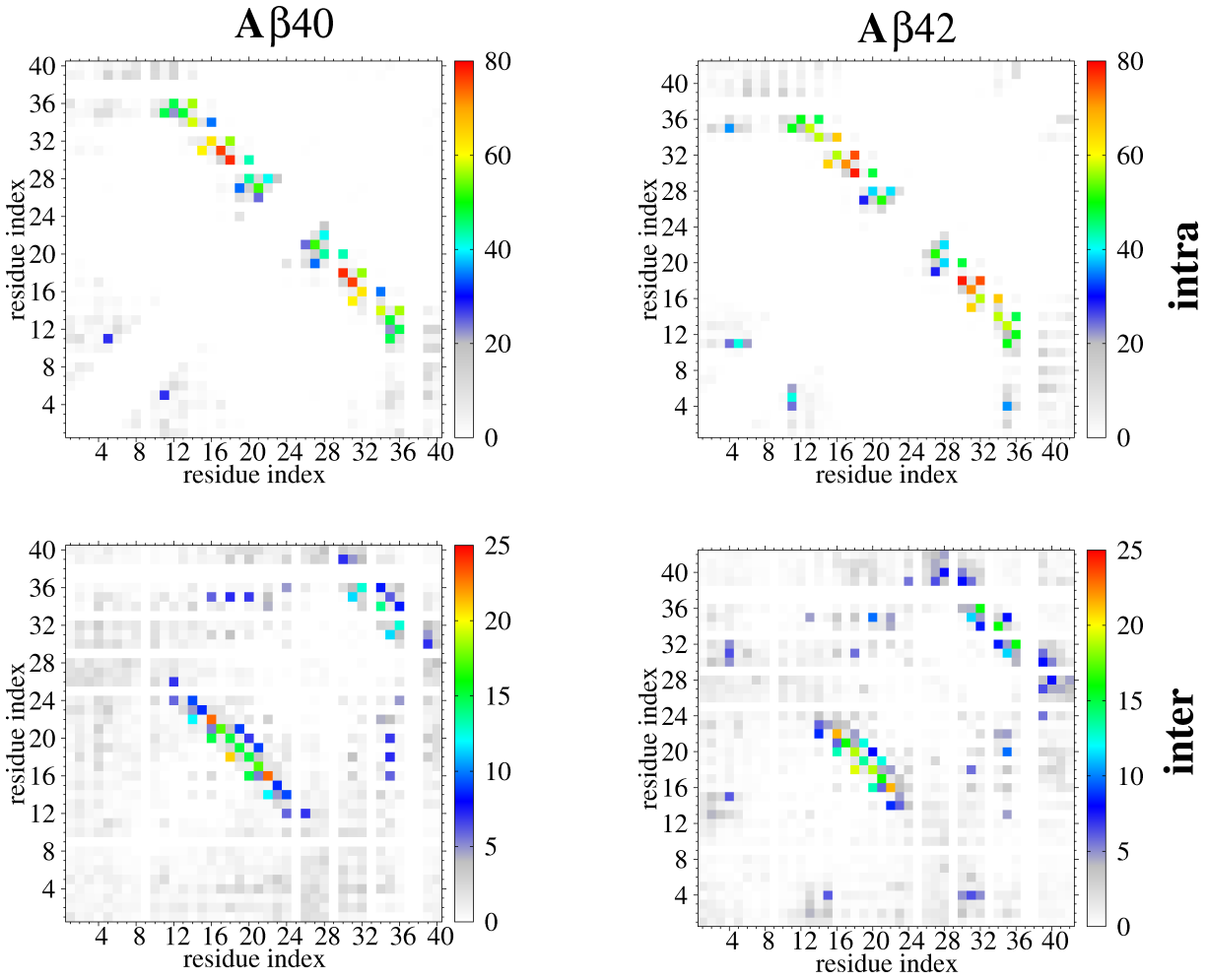

Figure S4. The side-chain – side-chain contact probabilities (in %) of the β-barrel states for the Aβ40 (left) and Aβ42 (right) tetramers at 315 K. The intramolecular maps are averaged over the four chains and the intermolecular maps averaged over the six pairs.

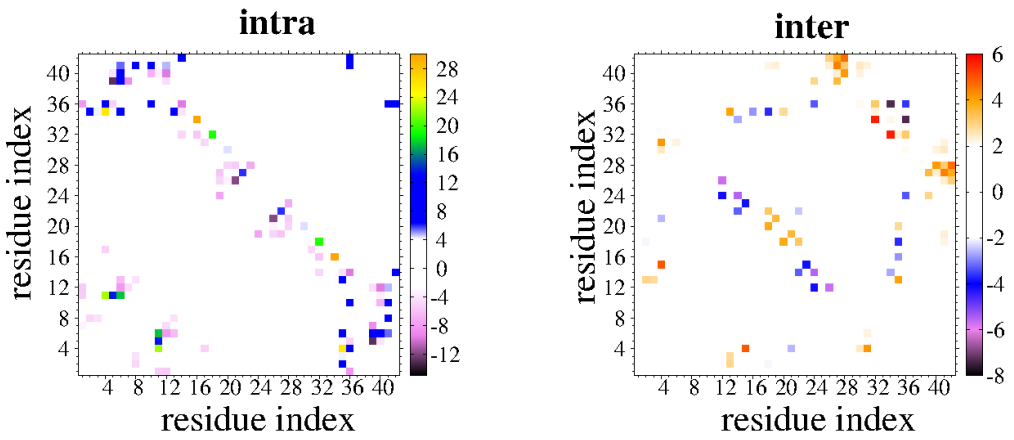

Figure S5. Differences in the contact map probabilities (in %) between the β-barrel states of Aβ42 and Aβ40 at 315 K. Positive values indicate higher probability for Aβ42. For clarity, absolute values between 0 and 4% (intramolecular) and between 0 and 2% (intermolecular) are not shown.

(C) Analysis of Aβ40 and Aβ42 by REMD with OPLS/TIP3P

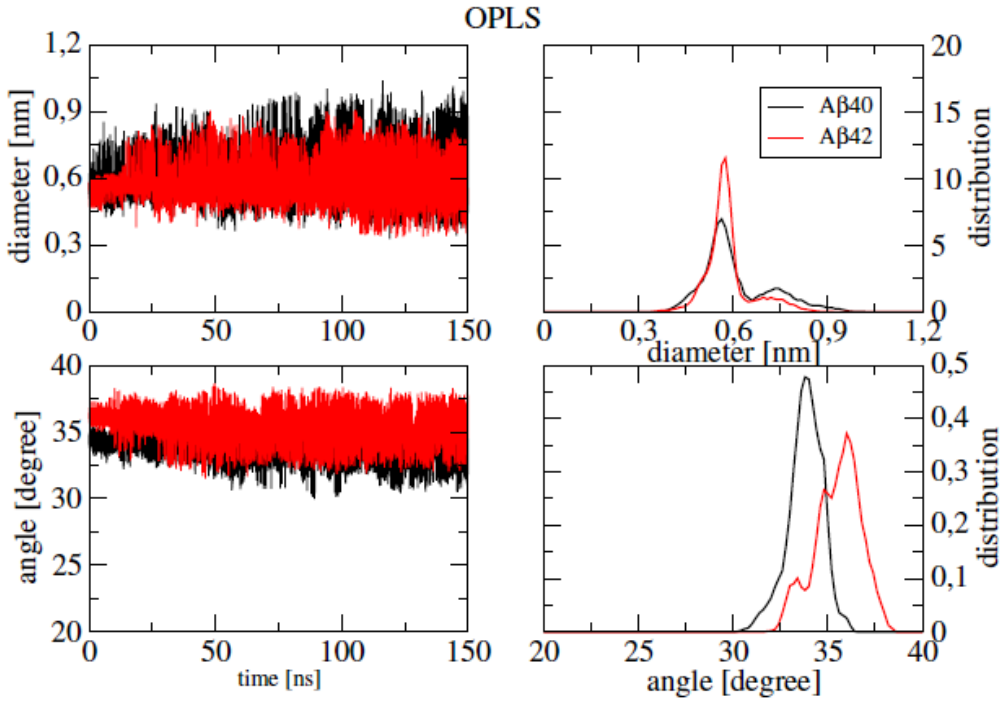

Figure S6. Time evolutions (left panels) and probability distributions (right panels) of the inner pore diameter and tilt angle for the Aβ40 (black) and Aβ42 (red) peptides using the full 150 ns REMD at 315 K with OPLS/TIP3P.

(D) Analysis of Aβ40 and Aβ42 REMD with CHARMM36M/TIP3P-modified

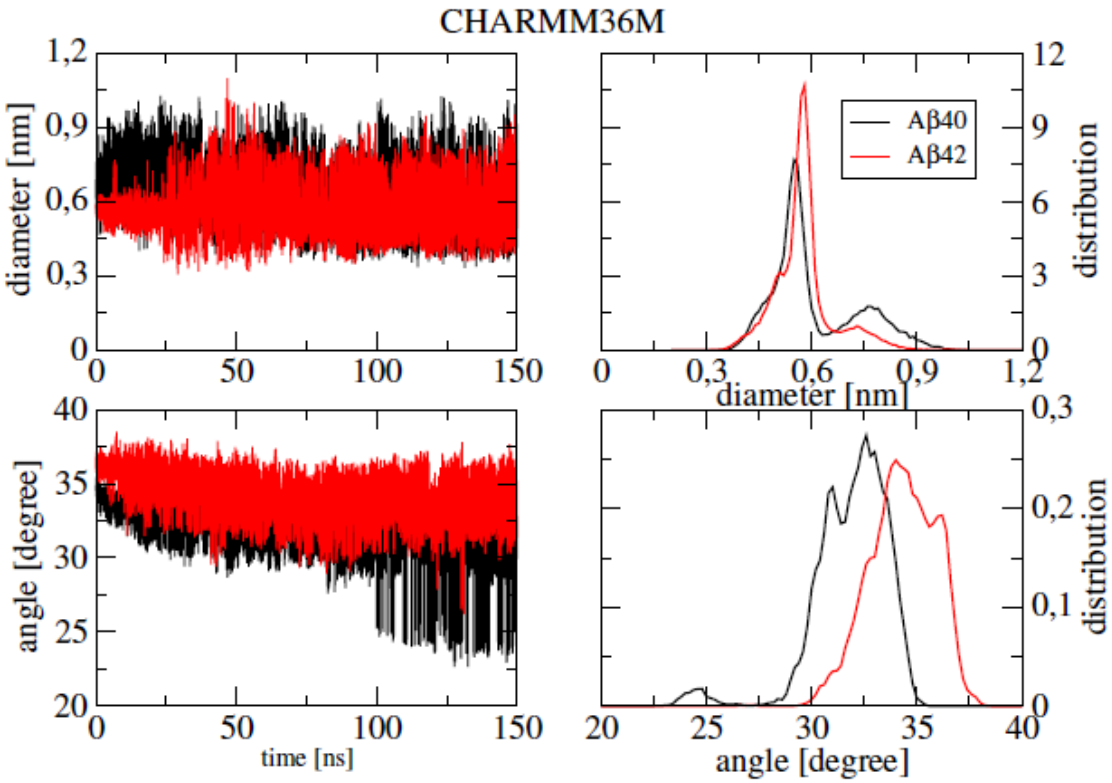

Figure S7. Time evolutions (left panels) and probability distributions (right panels) of the inner pore diameter and tilt angle for the Aβ40 (black) and Aβ42 (red) peptides using the full 150 ns REMD at 315 K with CHARMM36m/TIP3P-modified.

(E) Analysis of Aβ42 by REMD simulations with AMBER99/DISP

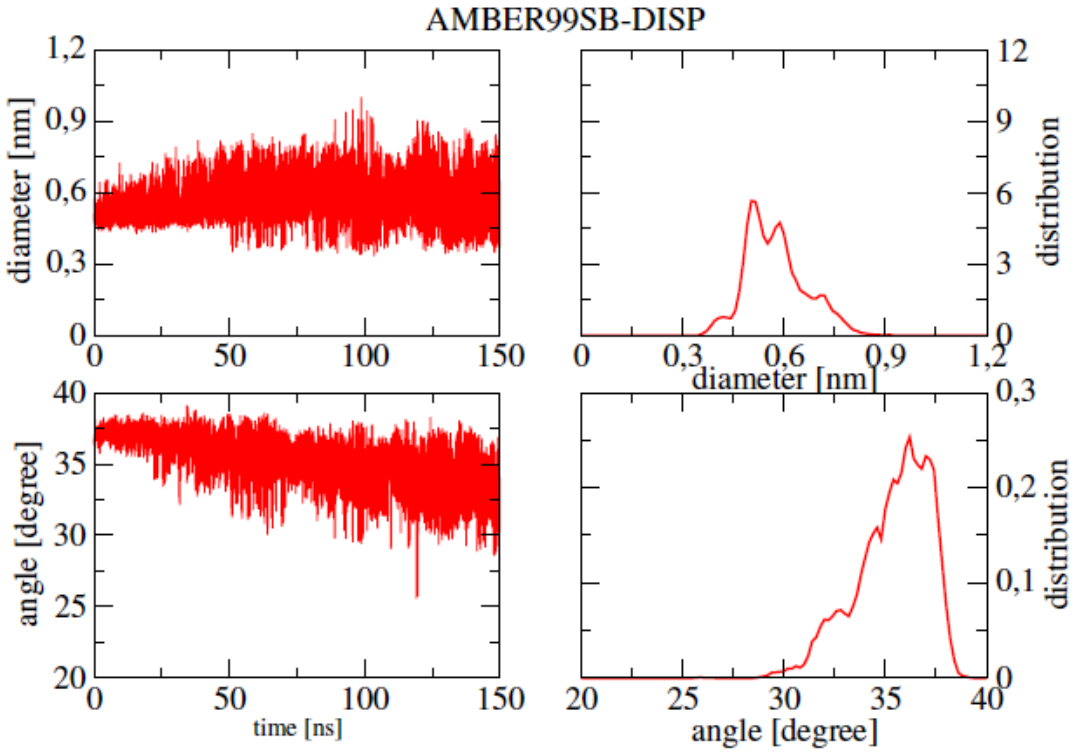

Figure S8. Time evolutions (left panels) and probability distributions (right panels) of the inner pore diameter and tilt angle for the Aβ42 peptides using the full 150 ns REMD at 315 K with AMBER99-DISP.

References

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