Structural heterogeneity in transmembrane Amyloid Precursor Protein homodimer is a consequence of environmental selection

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Time evolution of sampling in a POPC bilayer and DPC micelle. All 50 replicas have identical starting states. The structure of each monomer was derived from the experimentally determined left-handed coiled-coil structure.[1] The two monomers were separated and then introduced into the equilibrated POPC bilayer. The simulation of each replica began from independently generated random initial velocities. Following a period of equilibration, peptide monomers were found to diffuse freely throughout the simulation cell with each replica taking between 50 to 700 ns to associate. Time evolution of the dimer trajectories suggested an absence of dependence on initial state of the simulations and a broad sampling of the conformational space represented by the d_{GG}vs. ϕ_{4G}(Fig. 2) and ψ_{Crick} vs. ψ_{Crick} (Fig. 4) order parameter spaces. This point is demonstrated by the example trajectory for one replica see Figure S1.

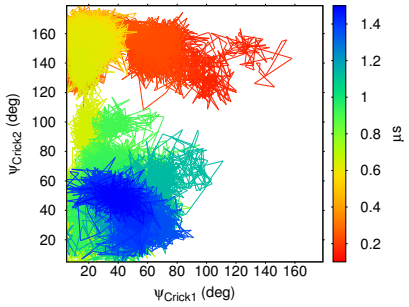

Figure S1. Time evolution of one replica (out of fifty) in POPC projected onto the order parameters ψ_{Crick} colored by time (μs).

Correlation between d_{GG} and ψ_{Crick}. Additional Figure S2 shows the calculated parameters ψ_{Crick1} and ψ_{Crick2} colored by the d_{GG}value. The data demonstrate how smaller ψ_{Crick} angles are correlated with small d_{GG}(Gly-in) values, while large ψ_{Crick} angles are correlated with large d_{GG}(Gly-out) values in simulations in POPC bilayer and DPC micelles.

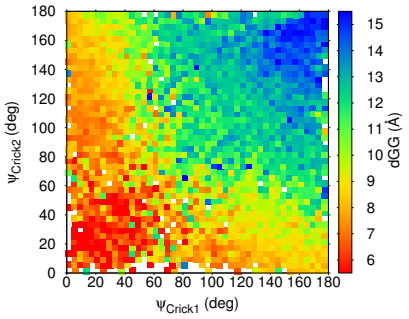

Figure S2. The graph shows the correlation between the calculated parameters ψ_{Crick1}, ψ_{Crick2} and d_{GG} (color scale) of the $C99_{15-55}$ simulations in POPC bilayer and DPC micelles.

Chemical shifts. Chemical shifts were computed for 1000 different structural conformations in the Gly-in and Gly-out all-atom simulations in POPC and DPC environments using SHIFTX2.[2] The average of the calculated chemical shifts for CA (C_α), HA (C_α proton), and amide N and H are presented in Figures S3 and S4. Our results (see Figures S3 and S4) suggest that we observe (1) good agreement with experimentally derived chemical shifts (excluding amide H), (2) little change in the chemical shifts upon dimerization, (2) little difference in the chemical shifts between Gly-in and Gly-out structures outside of amide H, and (4) chemical shifts that are only modestly sensitive to changes in the environment (between DPC micelle or POPC bilayer).

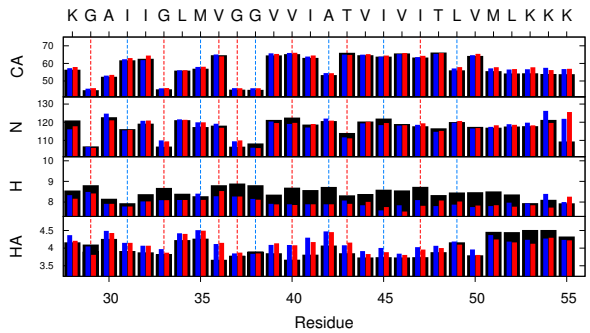

Figure S3. Chemical shifts in (ppm) for each residue of the $C99_{15-55}$ TM helix in POPC bilayer. Results of the calculated chemical shifts in the Gly-in all atom simulations are shown in red and for the Gly-out simulation in blue. The experimentally determined values for the 2LOH experimentally determined structure[1] are presented in black.

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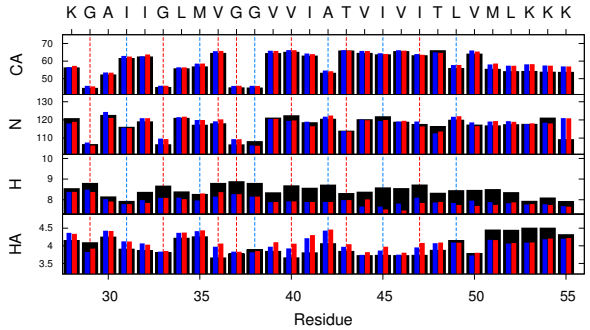

Figure S4. Chemical shifts in (ppm) for each residue of the $C99_{15-55}$ TM helix in DPC micelle. Results of the calculated chemical shifts in the Gly-in all atom simulations are shown in red and for the Gly-out simulation in blue. The experimentally determined values for the 2LOH experimentally determined structure [1] are presented in black.

References

(1) Nadezhdin, K. D.; Bocharova, O. V.; Bocharov, E. V.; Arseniev, A. S. *FEBS Lett.* **2012**, *586*, 1687–1692.
(2) Han, B.; Liu, Y.; Ginzinger, S.; Wishart, D. *Journal of Biomolecular NMR* **2011**, *50*, 43–57.