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Supplemental Information

Molecular Dynamics Simulations of Amyloid β-Peptide (1-42): Tetramer Formation and Membrane Interactions

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Atomistic Molecular Dynamics Simulations of Amyloid β-Peptide (1-42): Tetramer Formation, Rearrangement, and Membrane Interactions

SUPPORTING INFORMATION

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Table S1. Details of Systems and Initial Tetramer Membrane Distances.

Membrane	Membrane Composition	System Dimensions (*x*, *y*, *z*, in nm) after energy minimization	Number of Ions	Minimum Distance between Tetramer and Membrane (nm)
Control POPC	128 POPC	6.34 x 6.31 x 5.8	n/a	n/a
Control Raft	129 POPC 119 PSM 121 Cholesterol	8.75 x 8.75 x 11.8	n/a	n/a
Tetramer + POPC	128 POPC	6.34 x 6.31 x 18	Na^+: 77 Cl^- : 65	Rep 1: 2.5 Rep 2: 2.5 Rep 3: 2.6
Tetramer + Raft	129 POPC 119 PSM 121 Cholesterol	8.75 x 8.75 x 18	Na^+: 136 Cl^- : 124	Rep 1: 3.4 Rep 2: 3.4 Rep 3: 3.5

Table S2. Average percent secondary structure content (shown in %) of key regions of $A\beta_{42}$. [a]

System	Nterm		CHC		Cterm	
	Coil	β-strand	Coil	β-strand	Coil	β-strand
Tetramer Formation	70 ± 20	30 ±10	47 ± 21	53 ± 21	57 ± 9	43 ± 10
Tetramer + POPC	71 ± 20	29 ± 21	46 ± 23	54 ± 23	56 ± 11	42 ± 10
Tetramer + Raft	66 ± 15	34 ± 15	37 ± 14	63 ± 14	51 ± 11	49 ± 11

[a] Percentages represent structural properties of $A\beta_{42}$ tetramers regions, indicating the likelihood of that secondary structure being present in that region, averaged over the final 250 ns of three replicate trajectories for a cumulative sampling time of 750 ns, with corresponding standard deviations. Nterm is defined as residues 1-10; CHC is defined as residues 17-21; Cterm is defined as residues 30-42.

Table S3. Average diffusion coefficients of $A\beta_{42}$ tetramers, with corresponding standard deviation. [a]

System	D (cm^2 s^{-1})
Tetramer Formation	$2.6 \pm 0.8 \times 10^{-6}$
Tetramer + POPC	$1.4 \pm 0.3 \times 10^{-6}$
Tetramer + Raft	$0.6 \pm 0.2 \times 10^{-6}$

[a] Average represents diffusion coefficient of $A\beta_{42}$ tetramers in the indicated simulation, averaged over the final 250 ns of three replicate trajectories for a cumulative sampling time of 750 ns, with corresponding standard deviations.

Table S4. Overview of $A\beta_{42}$ tetramer-membrane hydrogen bonds and total interactions, with corresponding standard deviations. [a]

System	Number of Hydrogen Bonds	Total Number of Interactions	Total Number of Electrostatic Interactions
Tetramer + POPC	22 ± 9	4609 ± 1373	1780 ± 837
Tetramer + Raft	27 ± 4	4985 ± 640	1997 ± 146

[a] Averages represents average number of hydrogen bonds and average number of total interactions (instance when two atoms were within < 0.6 nm) between the $A\beta_{42}$ tetramer and model membrane in the indicated simulation, averaged over the final 250 ns of three replicate trajectories for a cumulative sampling time of 750 ns, with corresponding standard deviations. Interactions were calculated by using index groups to select the side chain atoms of every residue and electrostatic residues were designated as having a net positive (+1) or negative (-1) charged side chain at pH 7.4. Residues included in electrostatic residues were Asp, Glu, Lys, and Arg.

Table S5. Average solvent accessible surface area (SASA) of $A\beta_{42}$ tetramers, with corresponding standard deviations. [a,b,c]

System	Hydrophobic (nm^2)	Hydrophilic (nm^2)	Total SASA (nm^2)
Starting Structure	70 ± 1	58 ± 1	128 ± 1
Tetramer Formation	54 ± 1	46 ± 1	100 ± 2
Tetramer + POPC	56 ± 4	49 ± 3	105 ± 5
Tetramer + Raft	57 ± 1	51 ± 1	108 ± 2

[a] Average represents SASA of $A\beta_{42}$ tetramers in the indicated simulation, averaged over the final 250 ns of three replicate trajectories for a cumulative sampling time of 750 ns, with corresponding standard deviations. [b] Starting structure average was calculated at the onset of MD simulations for the first 20 ns of simulation time. [c] An atom is determined to be hydrophilic if $|q| > 0.2$

Table S6. Average SASA of POPC and raft membranes, with corresponding standard deviation. [a, b,c]

System	Hydrophobic (nm^2)	Hydrophilic (nm^2)	Total SASA (nm^2)
Control POPC	115 ±1	214 ± 1	329 ± 9
Control Raft	208 ± 1	401 ± 2	609 ± 2
Tetramer + POPC	112 ± 2	202 ± 3	314 ± 5
Tetramer + Raft	200 ± 3	400 ± 4	600 ± 7

[a] Average represents SASA of model membranes with $A\beta_{42}$ tetramers bound, averaged over the final 250 ns of three replicate trajectories for a cumulative sampling time of 750 ns, with corresponding standard deviations. [b] The control membrane averages presented represent the average over the last 250 ns of one simulation of the membrane only. [c] An atom is determined to be hydrophilic if $|q| > 0.2$

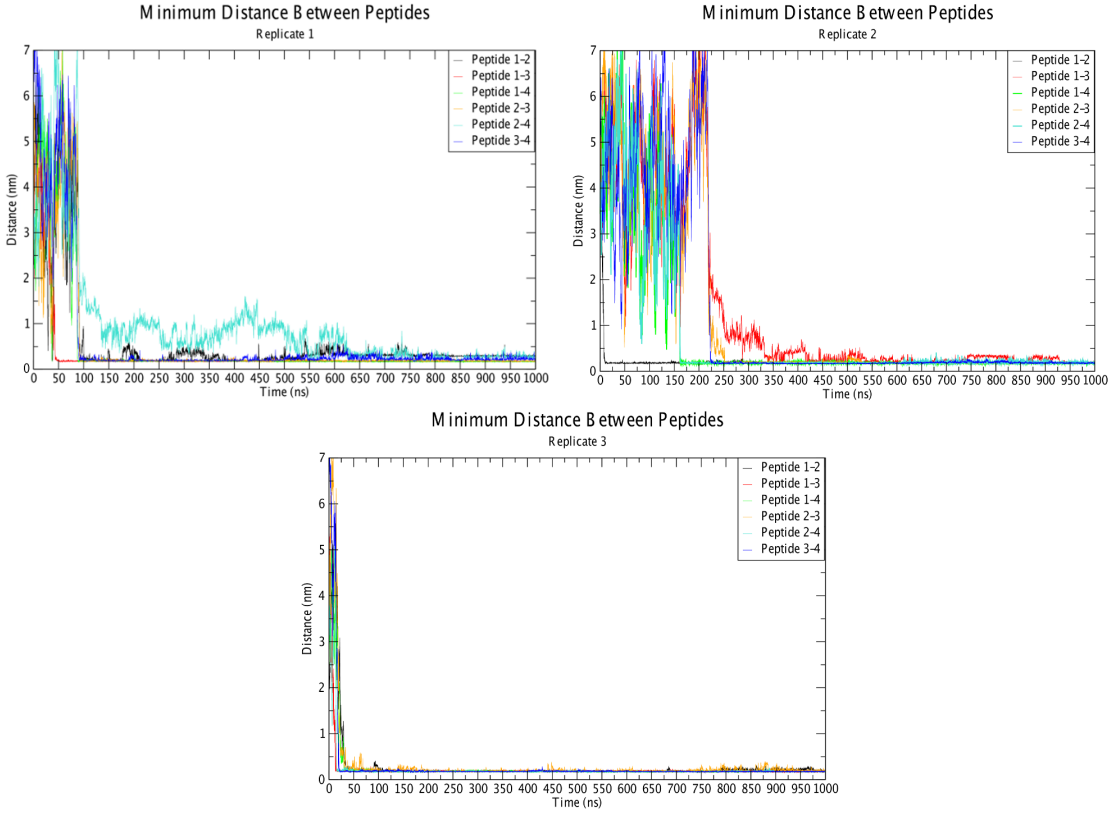

Figure S1. Minimum distance between peptides (denoted as peptides 1, 2, 3, and 4) during tetramer formation. The minimum distance plots show the time and order of events for inter-peptide interaction.

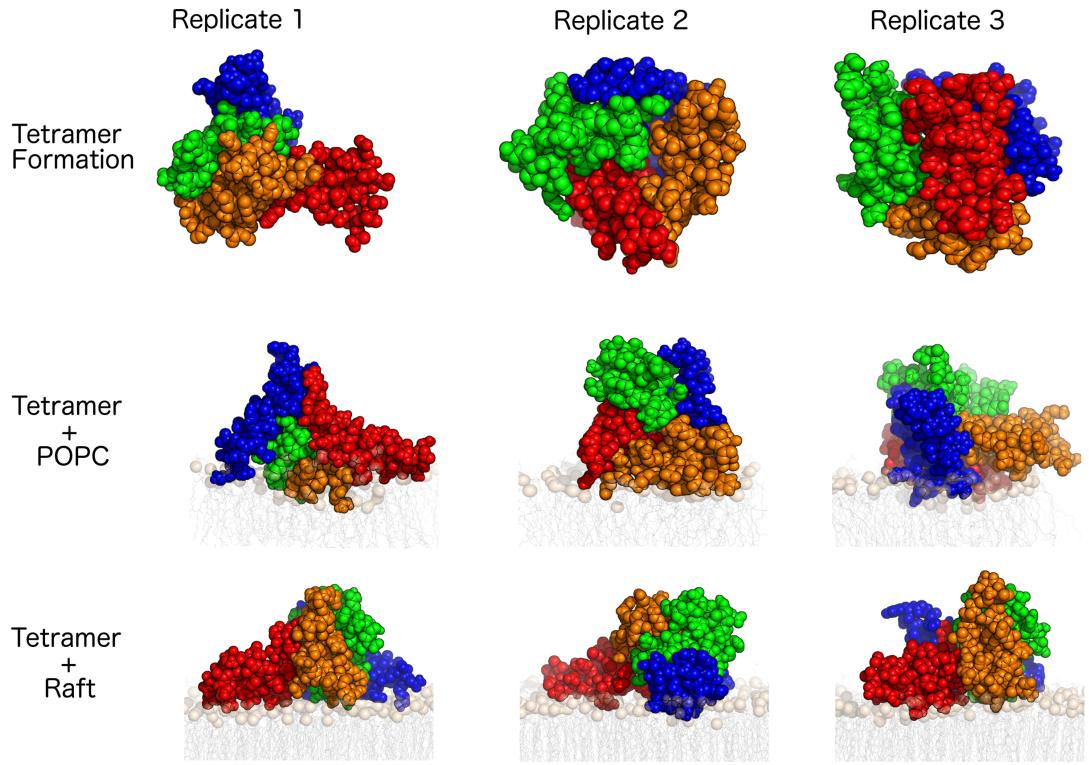

Figure S2. Dominant morphologies of tetramer formation and tetramer-membrane interactions highlighting multimeric state. Representative images from the central structure of the first cluster (for clustering size, see Figure 2), with the peptides shown as spheres and colored orange, green, blue, or red for respective peptide number (1-4). Membranes are shown as grey sticks, with the phosphorus atoms shown as tan spheres for perspective.

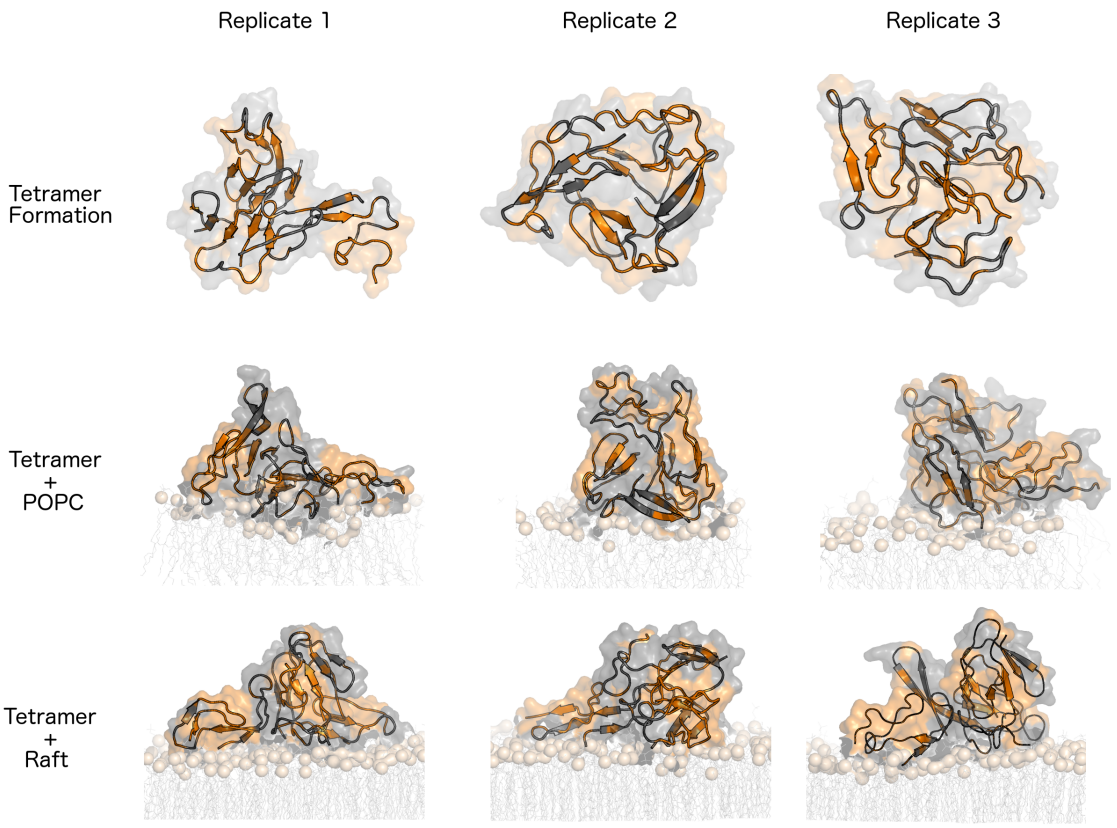

Figure S3. Dominant morphologies of tetramer formation and tetramer-membrane interactions highlighting hydrophobic regions. Representative images from the central structure of the first cluster (for clustering size, see Figure 2), with the peptides shown as cartoon and surface, orange for hydrophobic residues and grey for hydrophilic. Membranes are shown as grey sticks, with the phosphorus atoms shown as tan spheres for perspective.

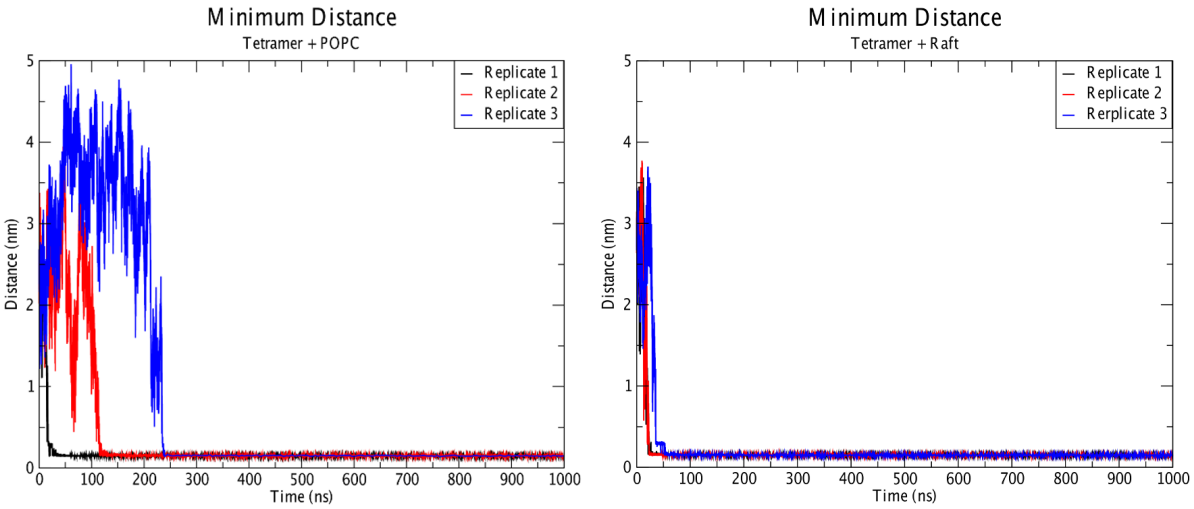

Figure S4. Minimum distance between tetramer and POPC or raft membrane. The minimum distance plots show the time of interaction between the tetramer unit and membrane. For replicate 1 Tetramer + raft simulations, the time of contact is similar to replicate two, and the two lines partially overlay.

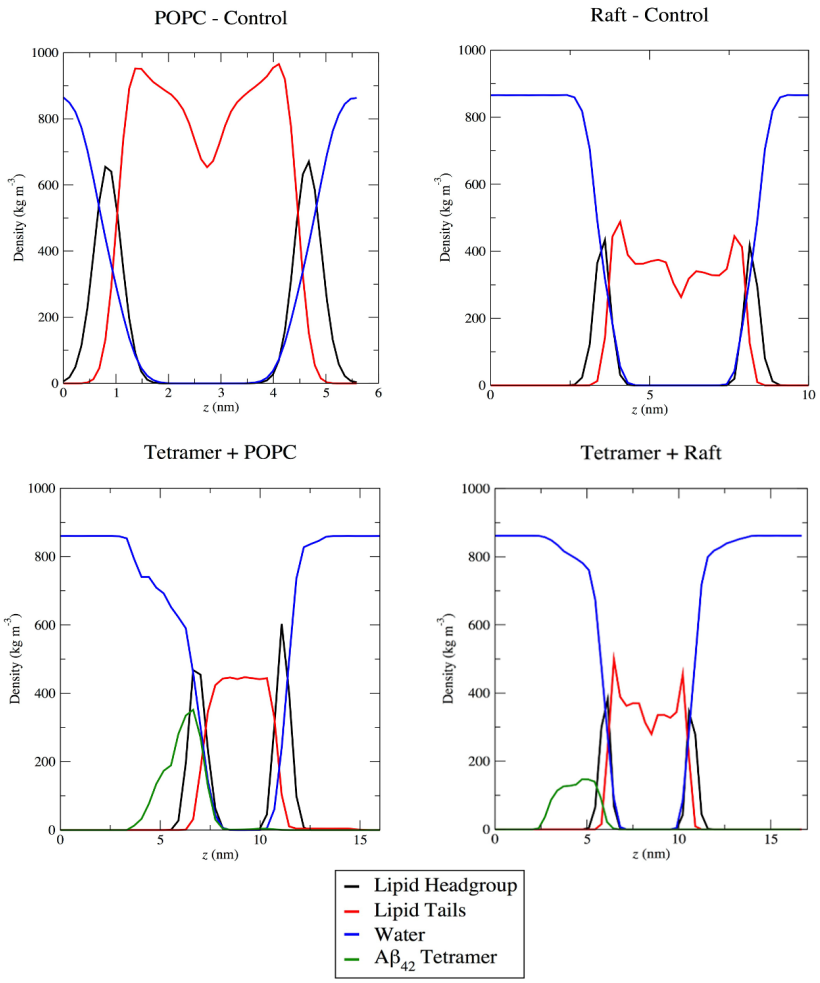

Figure S5. Membrane (PC lipids), water, and protein density profiles for tetramer + POPC and raft membrane simulations. Note the flattening of the density at the core of the Tetramer + POPC profile indicates interdigitation of the PC lipid tails that is not observed in the control POPC membrane. Please note the difference in x-axis plotting is due to the tetramer + membrane simulations utilizing a larger z-axis in their simulation box given the need to place the tetramer ~3 nm away from the membranes as compared to the control.

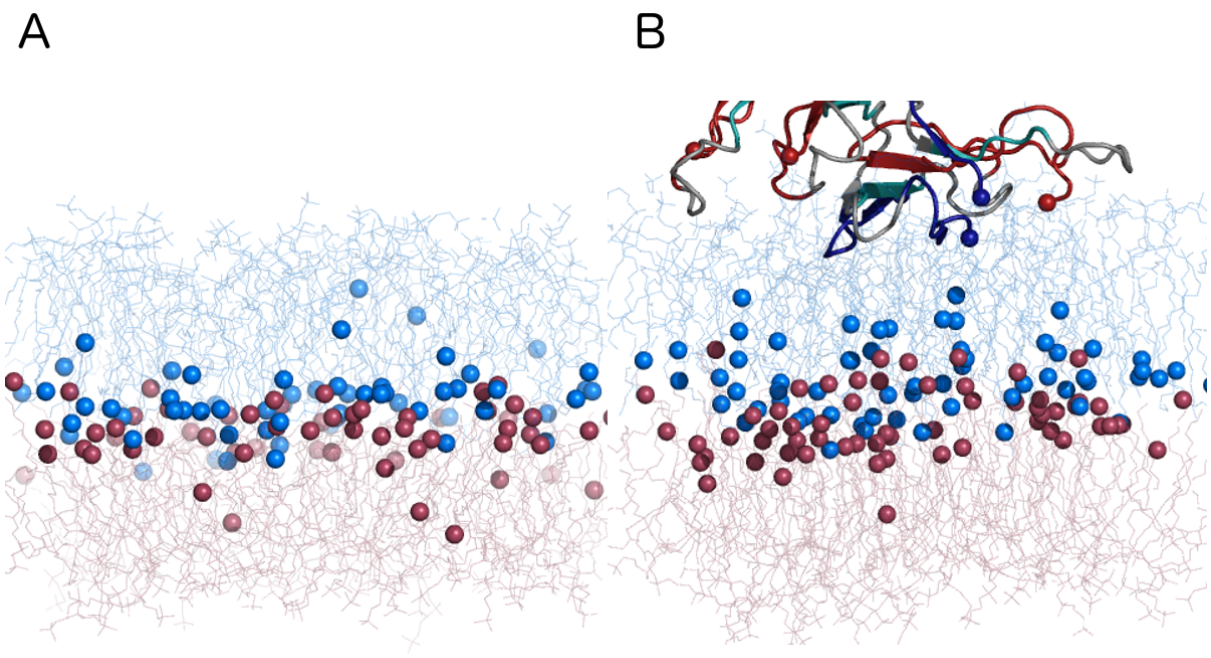

Figure S6. Visual representation of interdigitation at bilayer interface for POPC membrane (A) POPC control and (B) POPC + Tetramer. Lipids are shown as sticks, with the terminal carbon of each chain shown as spheres, colored by leaflet (blue and red). The tetramer is shown for perspective and is rendered as in Figure. 1.

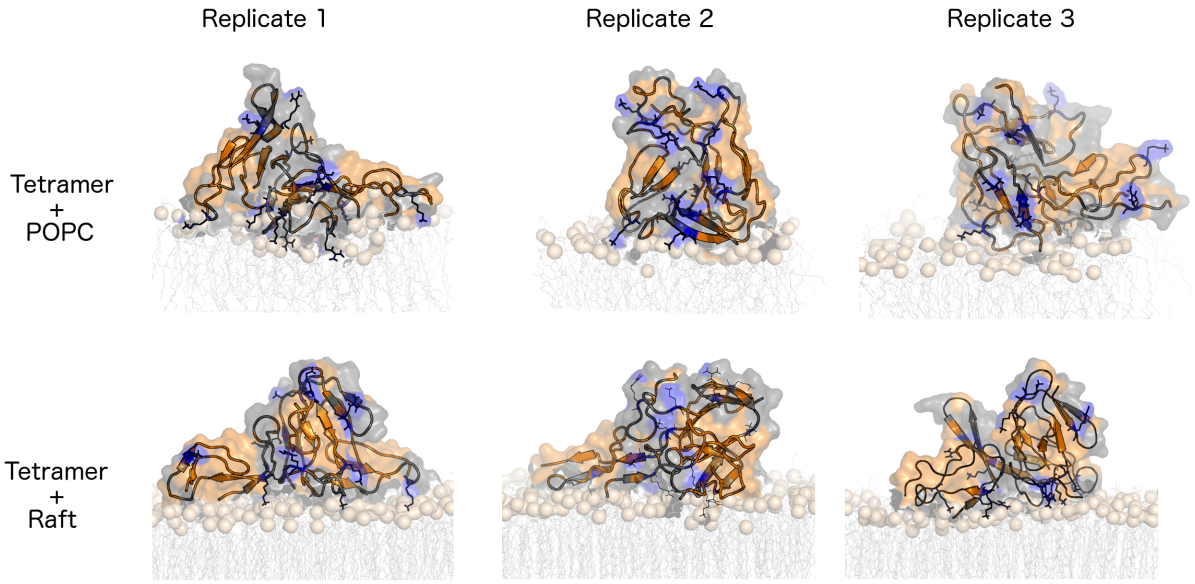

Figure S7. Dominant morphologies of tetramer formation and tetramer-membrane interactions highlighting hydrophobic regions. Representative images from the central structure of the first cluster (for clustering size, see Figure 2), with the peptides shown as cartoon and surface, orange for hydrophobic residues, blue sticks for Arg-5, Lys-16, and Lys-28, and grey for all other hydrophilic residues. Membranes are shown as grey sticks, with the phosphorus atoms shown as tan spheres for perspective.