Supplementary Information

Organization and Dynamics of Receptor Proteins in a Plasma Membrane.

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Supplementary Tables

Table S1: Setup the three large simulations

Name	Size	#Lipids	#Proteins	#Particles
PM	135 nm × 135 nm	54,000	none	2.28 M
TMH	146 nm × 146 nm	63,342	576	2.69 M
GPCR	128 nm × 128 nm	59,616	144	2.60 M

Table S2: Area per lipid for upper and lower leaflets from simulations of asymmetric and symmetric 1500 lipid bilayers.

	PM (asymmetric)		**PMUpper (symmetric)**		**PMLower (symmetric)**	
	Upper	***Lower***	***Upper***	***Lower***	***Upper***	***Lower***
All	**0.50 [0.01]**	**0.50 [0.01]**	**0.50 [0.01]**	**0.50 [0.01]**	**0.50 [0.01]**	**0.50 [0.01]**
PC	0.56 [0.01]	0.59 [0.02]	0.56 [0.01]	0.56 [0.01]	0.59 [0.02]	0.59 [0.03]
PE	0.51 [0.02]	0.53 [0.01]	0.51 [0.02]	0.51 [0.02]	0.53 [0.01]	0.53 [0.01]
Sph	0.55 [0.02]	-	0.55 [0.02]	0.55 [0.02]	-	-
GM3	0.44 [0.02]	-	0.44 [0.02]	0.44 [0.02]	-	-
Chol	0.40 [0.01]	0.40 [0.01]	0.40 [0.01]	0.40 [0.01]	0.39 [0.01]	0.39 [0.01]
PS	-	0.54 [0.02]	-	-	0.53 [0.02]	0.53 [0.02]
PIP_2	-	0.51 [0.02]	-	-	0.51 [0.02]	0.51 [0.02]

The average area per lipid over the 5 μs simulation is shown in (nm^2) and standard deviation in square brackets. The area per lipid was calculated using APL@Voronoi (Lukat *et al.* (2013) *J. Chem. Inf. Model*, **53**, 2908-2925) over 5 μs using 2500 frames.

Table S3: Area/Lipid in the Large Membrane Simulations.

System	Leaflet	Lipid	Area (nm^2)
PM (54000 lipids)	upper	PC	0.55
		PE	0.50
		Sph	0.54
		GM3	0.41
		Chol	0.38
	lower	PC	0.57
		PE	0.51
		PS	0.52
		PIP2	0.50
		Chol	0.38
TMH (63000 lipids)	upper	PC	0.55
		PE	0.50
		Sph	0.54
		GM3	0.41
		Chol	0.38
	lower	PC	0.57
		PE	0.52
		PS	0.52
		PIP2	0.46
		Chol	0.38
GPCR (60000 lipids)	upper	PC	0.54
		PE	0.48
		Sph	0.54
		GM3	0.39
		Chol	0.38
	lower	PC	0.58
		PE	0.52
		PS	0.52
		PIP2	0.40
		Chol	0.35
PMUpper (1500 lipids)		PC	0.56
		PE	0.51
		Sph	0.55
		GM3	0.44
		Chol	0.40
PMLower (1500 lipids)		PC	0.59
		PE	0.53
		PS	0.53
		PIP2	0.51
		Chol	0.39

Areas were estimated using APL@Voronoi over the period 1 to 3 μs for each of the three large simulations.

Supplementary Figures

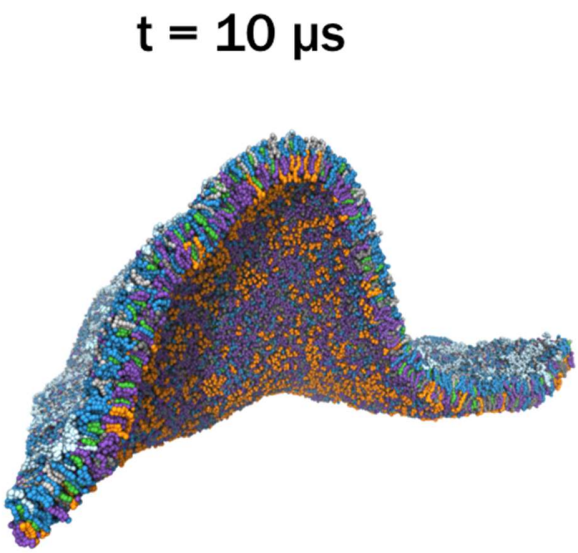

Figure S1. Deformation within the PM system. Large scale deformation of the bilayer in the **PM** simulation shown at 10 μs.

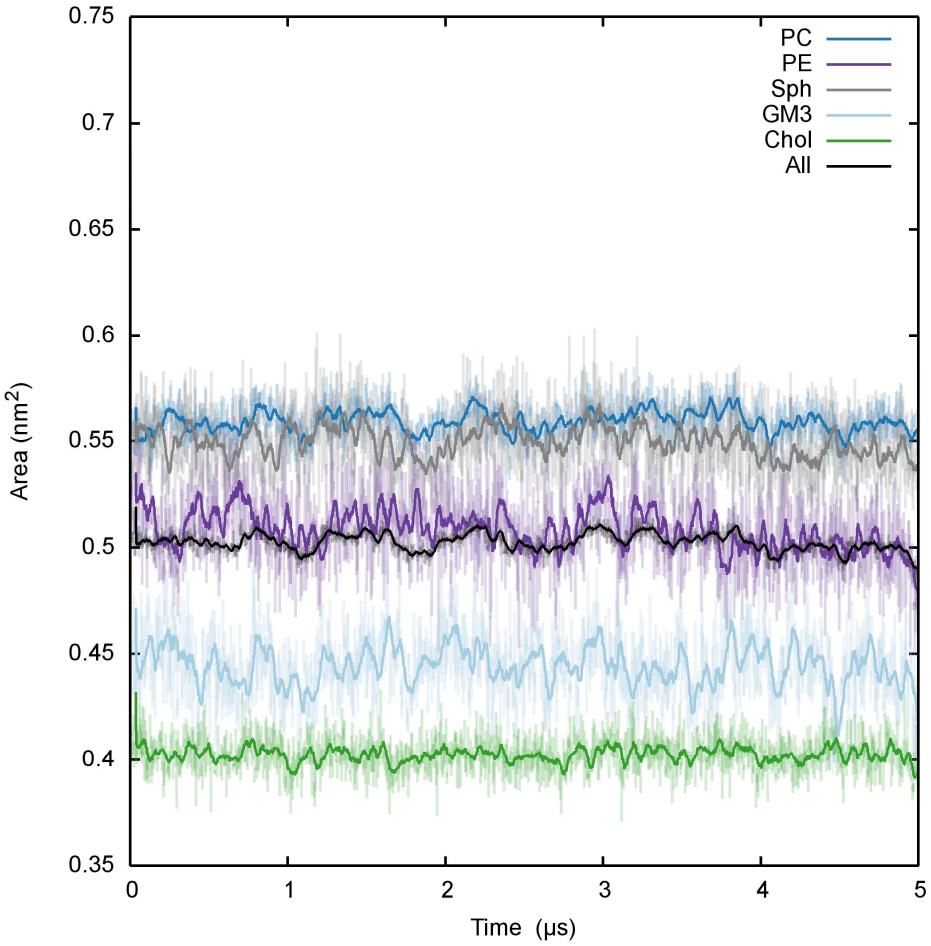

Figure S2. Area per lipid of 1500 lipid PM model. Area per lipid of all lipids and each species within the outer leaflet of an asymmetric PM membrane with a composition in the outer leaflet of PC:PE:Sph:GM3:Chol (40:10:15:10:25) (See Table S2 for further details).

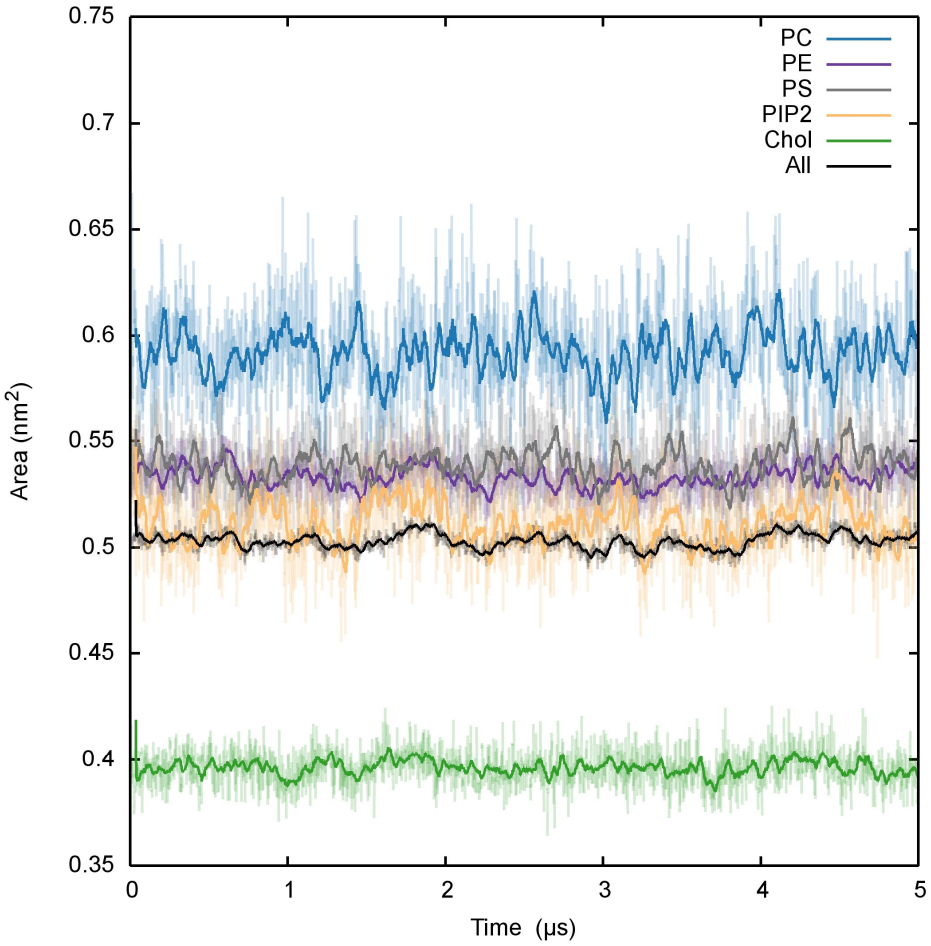

Figure S3. Area per lipid of 1500 lipid PM model. Area per lipid of all lipids and each species within the inner leaflet of an asymmetric PM membrane with a composition in the inner leaflet of PC:PE:PS:PIP_2:Chol (10:40:15:10:25) (See Table S2 for further details).

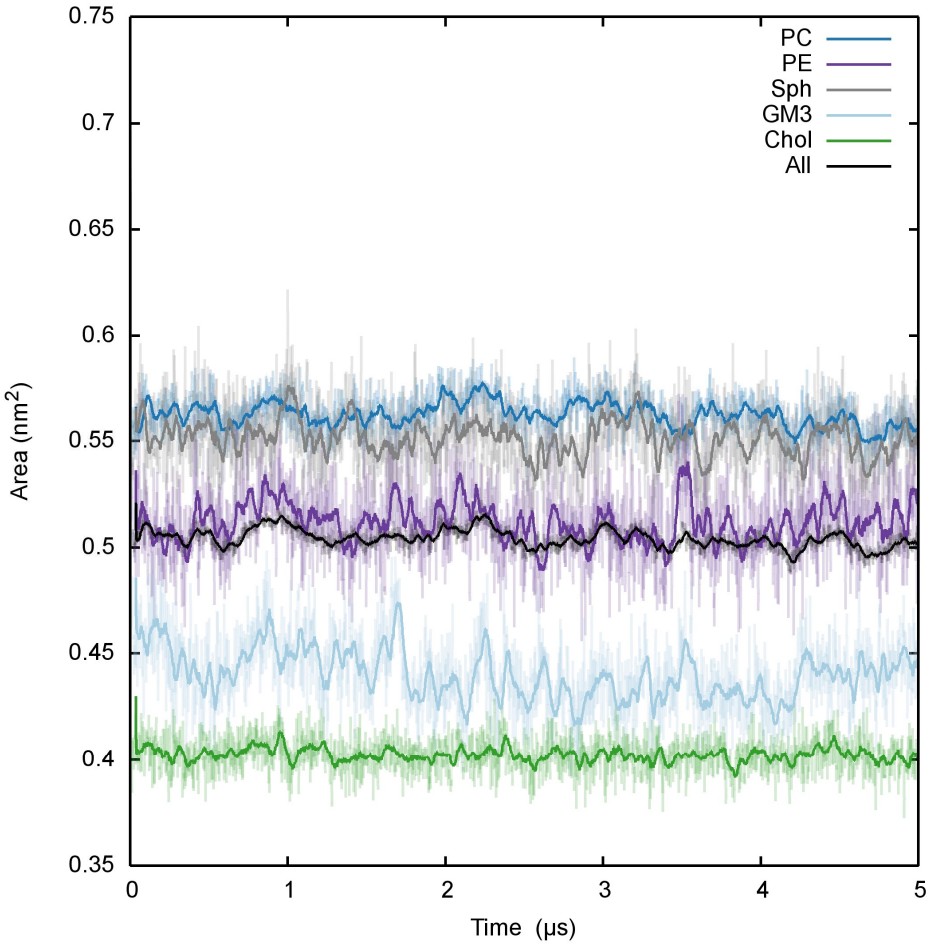

Figure S4. Area per lipid of 1500 lipid symmetric PMUpper model. Area per lipid of all lipids and each species within the outer leaflet of a symmetric membrane with composition of PC:PE:Sph:GM3:Chol (40:10:15:10:25) in both leaflets (See Table S2 for further details).

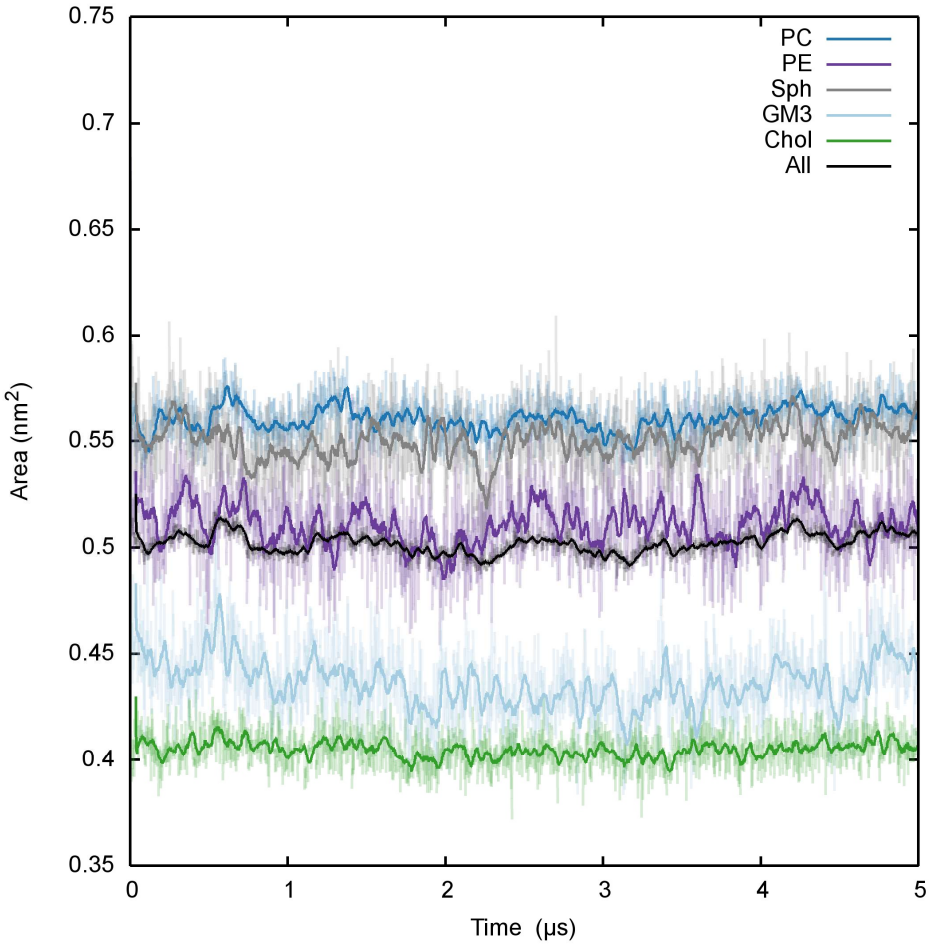

Figure S5. Area per lipid of 1500 lipid symmetric PMUpper model. Area per lipid of all lipids and each species within the inner leaflet of a symmetric membrane with composition of PC:PE:Sph:GM3:Chol (40:10:15:10:25) in both leaflets (See Table S2 for further details).

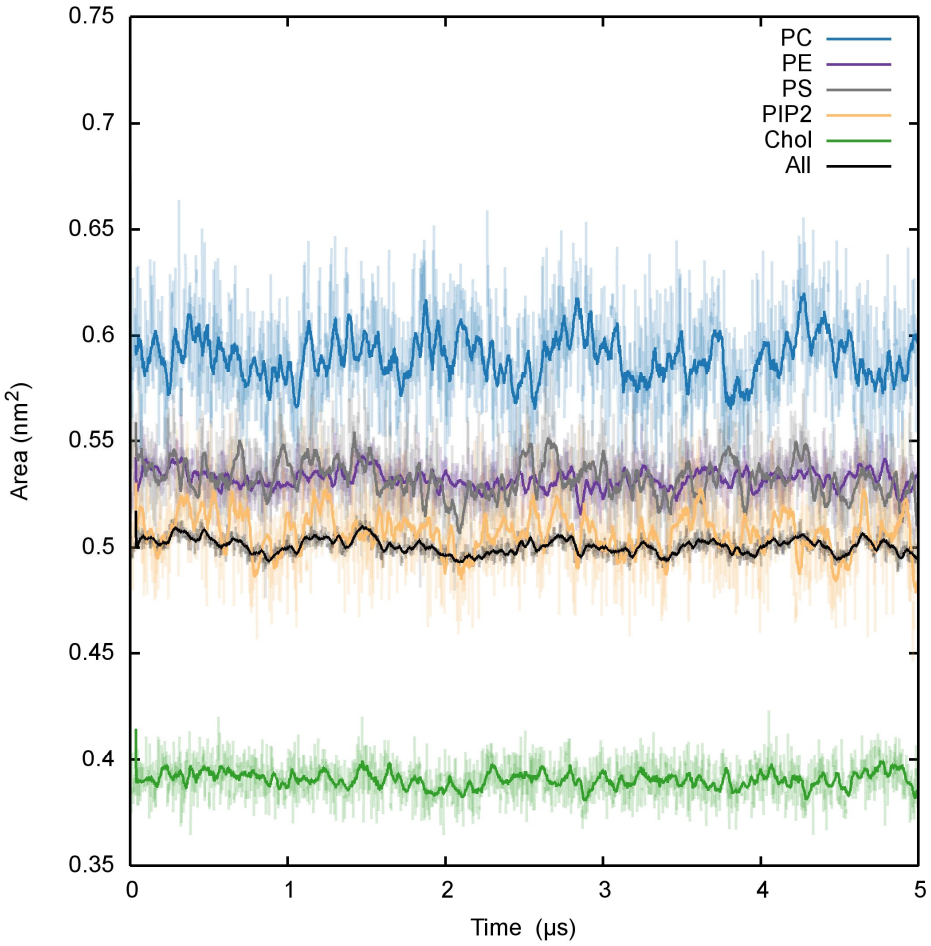

Figure S6. Area per lipid of 1500 lipid PMLower model. Area per lipid of all lipids and each species within the outer leaflet of a symmetric membrane with composition of PC:PE:PS:PIP_2:Chol (10:40:15:10:25) in both leaflets (See Table S2 for further details).

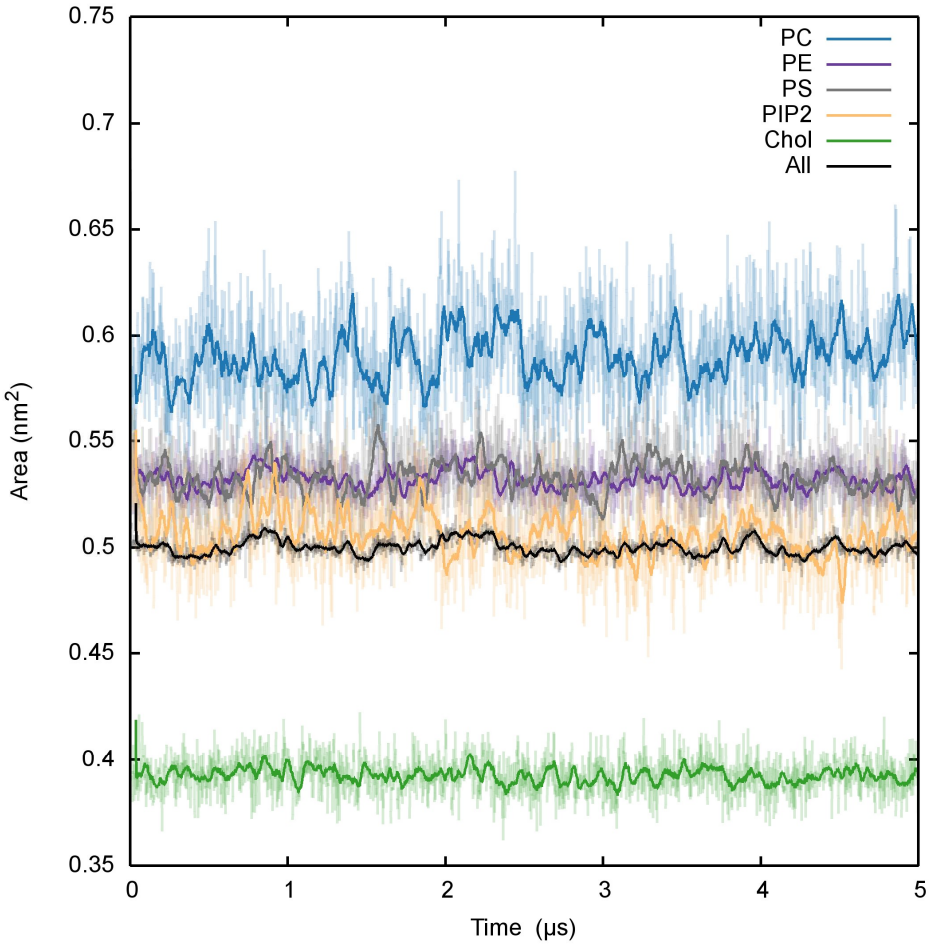

Figure S7. Area per lipid of 1500 lipid PMLower model. Area per lipid of all lipids and each species within the inner leaflet of a symmetric membrane with composition of PC:PE:PS:PIP_2:Chol (10:40:15:10:25) in both leaflets (See Table S2 for further details).

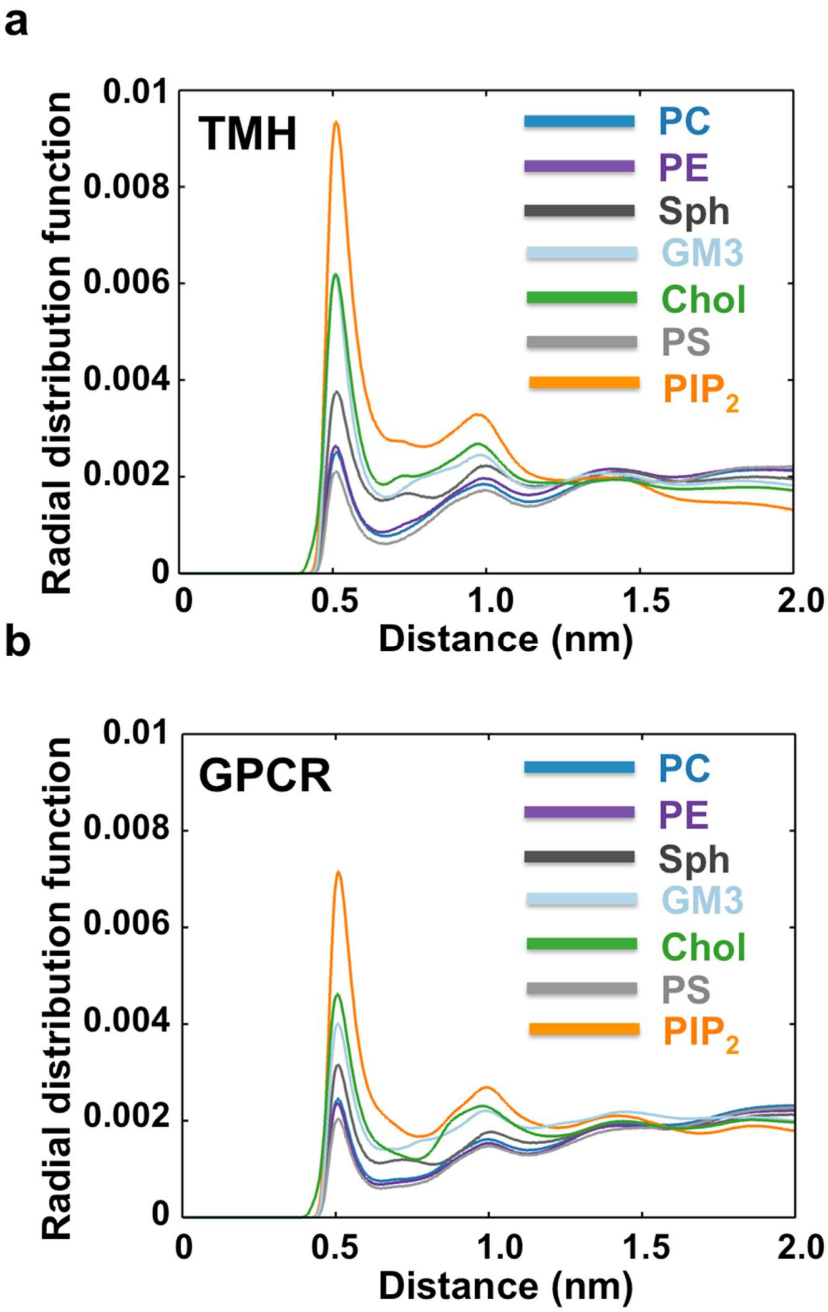

Figure S8. Protein-lipid interactions. Protein-lipid interactions measured by the spherical radial distribution function of lipid species around the protein (blue = PC, purple = PE, dark gray = Sph, light blue= GM3 green = cholesterol, light gray =PS, orange = PIP_2). (**a**) **TMH** system. (**b**) **GPCR** system. The area under the curve of the radial distribution has been normalized to unity to allow for comparison between lipid species.

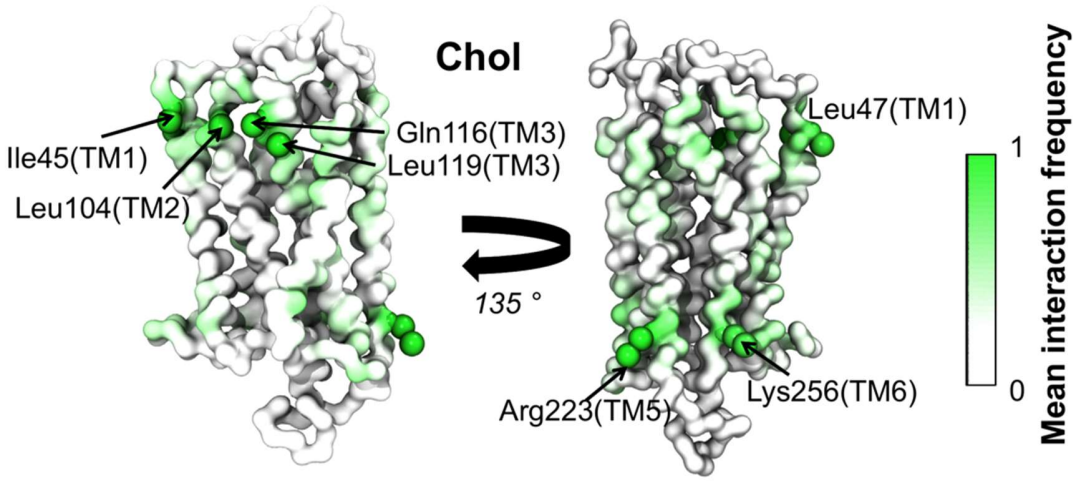

Figure S9. Protein-lipid interactions in the GPCR receptor system. Interactions between cholesterol headgroup have been mapped onto the structure of one of the S1P1 receptors. The colour scale illustrates the mean fraction of time there is an interactions with all 144 repeats of the S1P1 receptor. Thus, a value of 1 indicates a lipid forms a contact with a given residue in all proteins over the entire duration of the simulation. Residues having interactions more than 75% of the time are shown as spheres.

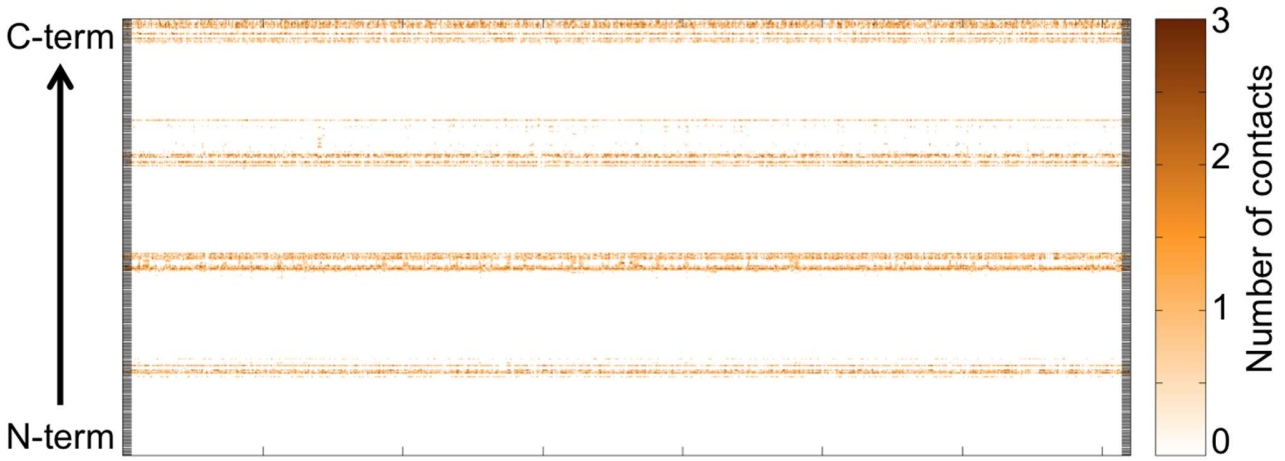

Figure S10. PIP_2 interactions over time. Number of interactions between the head group of PIP_2 and the GPCR over time for each protein (144 in total) with the traces for each protein concatenated together. A cutoff of 6 Å was used to define an interaction.

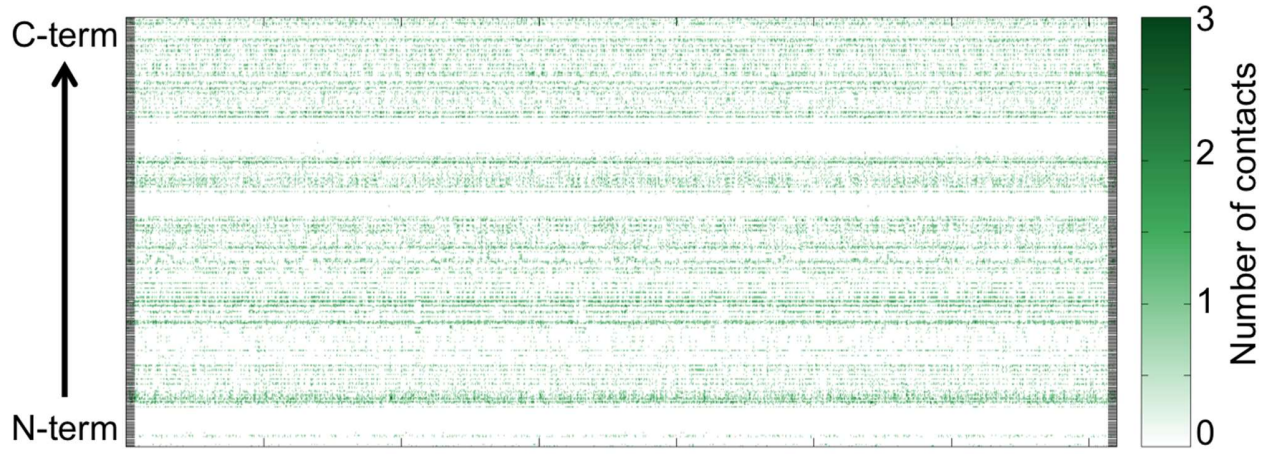

Figure S11. Chol interactions over time. Number of interactions between the head group of Chol and the GPCR over time for each protein (144 in total) with the traces for each protein concatenated together. A cutoff of 6 Å was used to define an interaction.

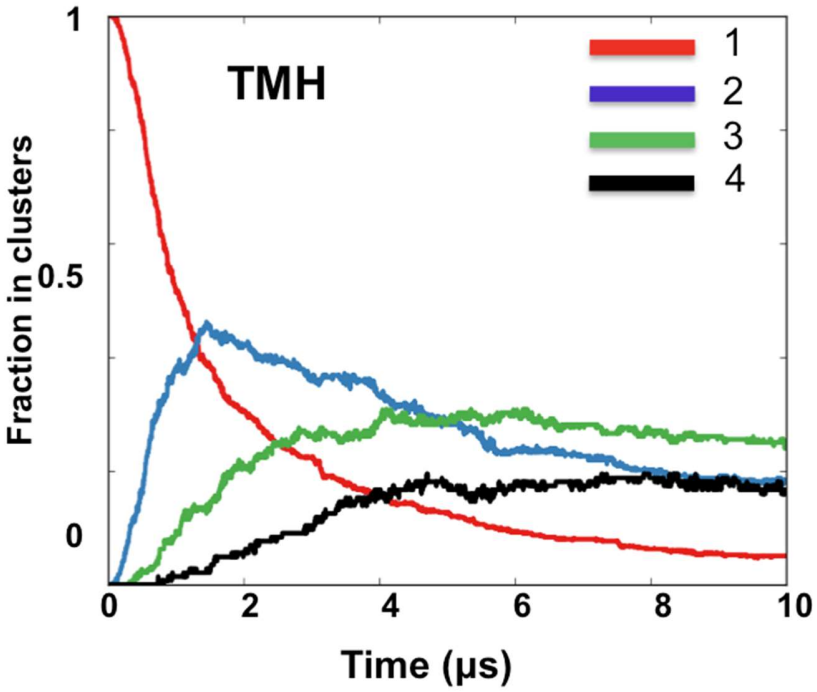

Figure S12. TMH oligomerization. The clustering of the gp130 transmembrane spanning helix model within the **TMH** system over time. Clustering was calculated using a cut-off distance of 1.5 nm between the centres of mass of adjacent proteins.

Supplementary Movies

Movie S1 | 0-10μs simulation of the PM system

Movie S2 | 0-10μs simulation of the TMH system

Movie S3 | 0-10μs simulation of the GPCR system