Supplementary Information

Changes in lipid density induce membrane curvature

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Methods

1. Modeled Membrane Bilayer Systems

We have investigated a series of hydrated lipid bilayer systems containing varying amounts of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylcholine (POPC) and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphatidylserine (POPS). The amount of POPS was varied as follows: 0% PS, 5% PS, 10% PS, 15% PS and 20% PS. Two independent systems for each POPS concentration were simulated for a total of ten model bilayers. The Membrane Builder module in CHARMM-GUI[1] was used to construct the systems that are composed of a lipid bilayer, water and ions. Each system was composed of 250 lipids per leaflet and ~29,000 waters. Each simulation system contained on average ~150000 atoms. A 0.25-M concentration of KCl was used for all simulations. The system characteristics are summarized in Supplementary Table S1.

These ten systems were initially simulated as flat bilayers. Rectangular periodic boundary conditions were imposed with a variable box height of ~90 Å and xy-translation lengths of ~130 Å. The latter dimension was based on 68.3-Å^2 and 62-Å^2 area/lipid ratios for POPC and POPS, respectively[1]. The method used in building these systems also ensured that the correct density of water was used. During the scaling of the *x*- and *y*-coordinates to increase the lipid density, the box size along the *z*-direction was increased accordingly so that the volume of the simulation box was preserved and the water density was maintained.

2. Molecular Dynamics Procedure

The CHemistry at HARvard Macromolecular Mechanics (CHARMM) program[2] was used for this study making use of the CHARMM36 lipid force field[3] and the TIP3P model for water[4] with bonds to hydrogen atoms fixed with the SHAKE algorithm[5]. The particle-mesh Ewald (PME) method[6] was employed to calculate the electrostatics using a mesh size of ~1 Å for fast Fourier transformation, κ = 0.34/Å and a sixth-order B-spline interpolation. Non-bond pair lists were constructed using a 16-Å cutoff

distance and the Lennard-Jones potential was smoothly switched off at 10-12 Å using a force-switching function. Simulations were performed under constant temperature (330 K) and normal pressure (1.0 atm) with a fixed lateral area using Nosé-Hoover methods[7, 8] and the Langevin piston[9].

3. Bilayer Characterization

The radius of curvature of each bilayer system was computed based on the coordinates of the phosphorus atoms of the lipids. These coordinates of the phosphorus atoms were collected at regular intervals and a distribution of its *z*-coordinates across the *x*-*y* simulation box was calculated. From this distribution, the maximum point of the curvature was located and the surface was translated such that the maximum was centered on the origin. Periodic boundaries were used during the centering and translation. This distribution was fitted to a sphere to obtain the radius of curvature of the bilayer.

The solvent accessible surface area (SASA) of the bilayer surface was obtained via the coordinate manipulation facility of CHARMM. It uses the Lee and Richards method[10] for computing the SASA of the selected atoms.

Supplementary References

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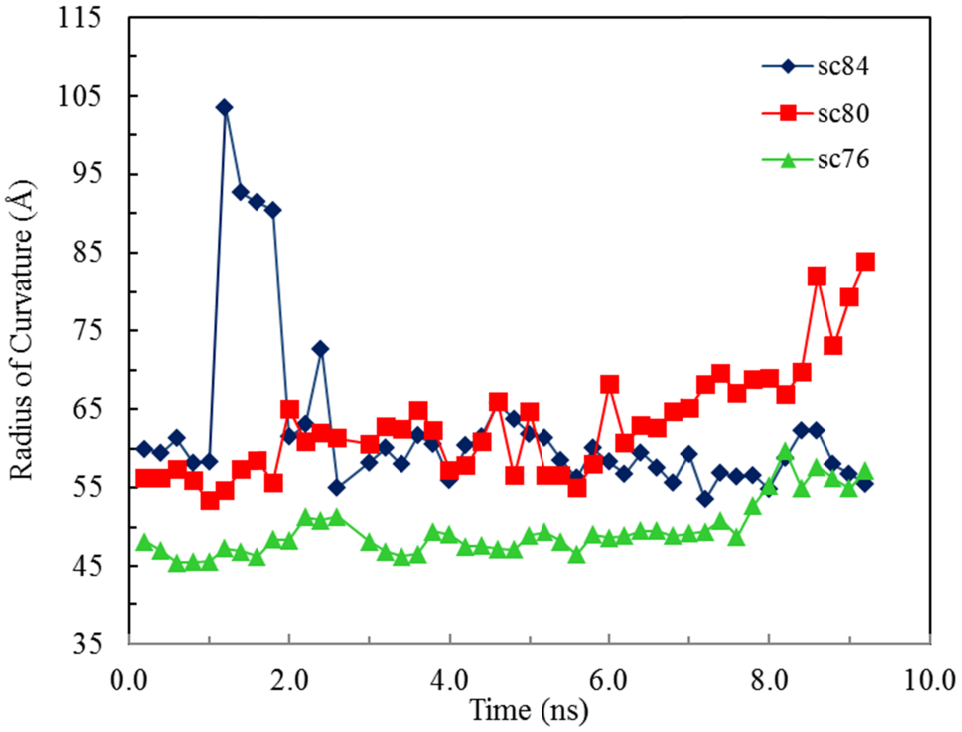
Supplementary Table S1. Characteristics of the simulated membrane systems. The POPS concentration refers to the percentage of POPS molecules in each individual simulation.

System 1			
POPS Concentration	**No. of POPS per leaflet**	**No. of waters**	**Total No. of atoms**
0% PS	0	28877	153889
5% PS	13	28842	153600
10% PS	25	28715	153051
15% PS	38	28549	152369
20% PS	50	28649	152501

System 2			
POPS Concentration	**No. of POPS per leaflet**	**No. of waters**	**Total No. of atoms**
0% PS	0	28961	154141
5% PS	13	28848	153618
10% PS	25	28651	152859
15% PS	38	28550	152372
20% PS	50	28394	151736

Supplementary Figure S1. Time series of the radius of curvature for the simulation systems with 15% PS.



Supplementary Figure S2. Time series of the radius of curvature from the beginning of bilayer compression for the simulation systems with 15% PS. The insets show the radius of curvature during the early stages of compression.