Microsecond Molecular Dynamics Simulations of Lipid Mixing

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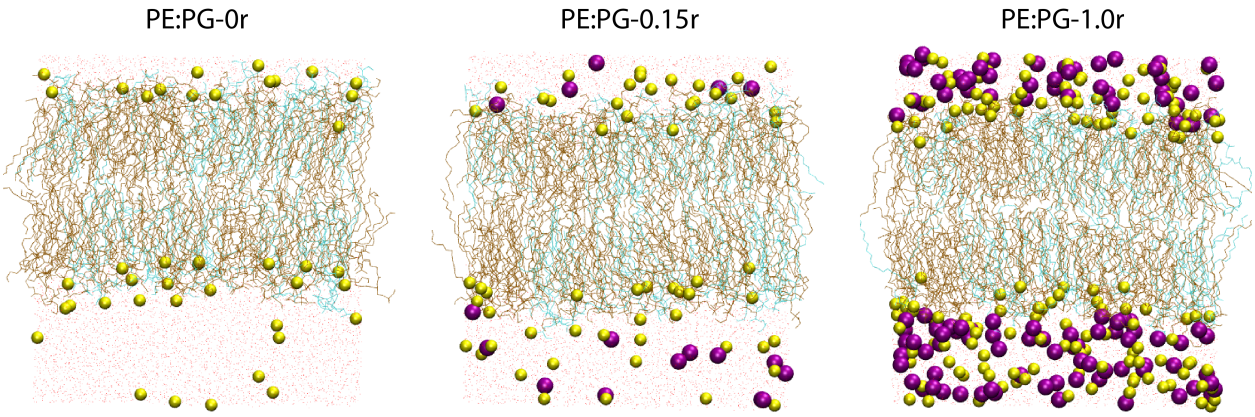

Figure S1: Side views of the PE:PG simulation systems under different salt concentrations. Na^+ and Cl^- ions are colored in yellow and purple, respectively. POPE and POPG lipids are colored in brown and cyan, respectively. Water molecules are shown as red dots. Apart from Na^+ ions needed to neutralize the system, PE:PG-0r has 0 M NaCl, while PE:PG-0.15r and PE:PG-1.0r have 0.15 M and 1.0 M NaCl, respectively.

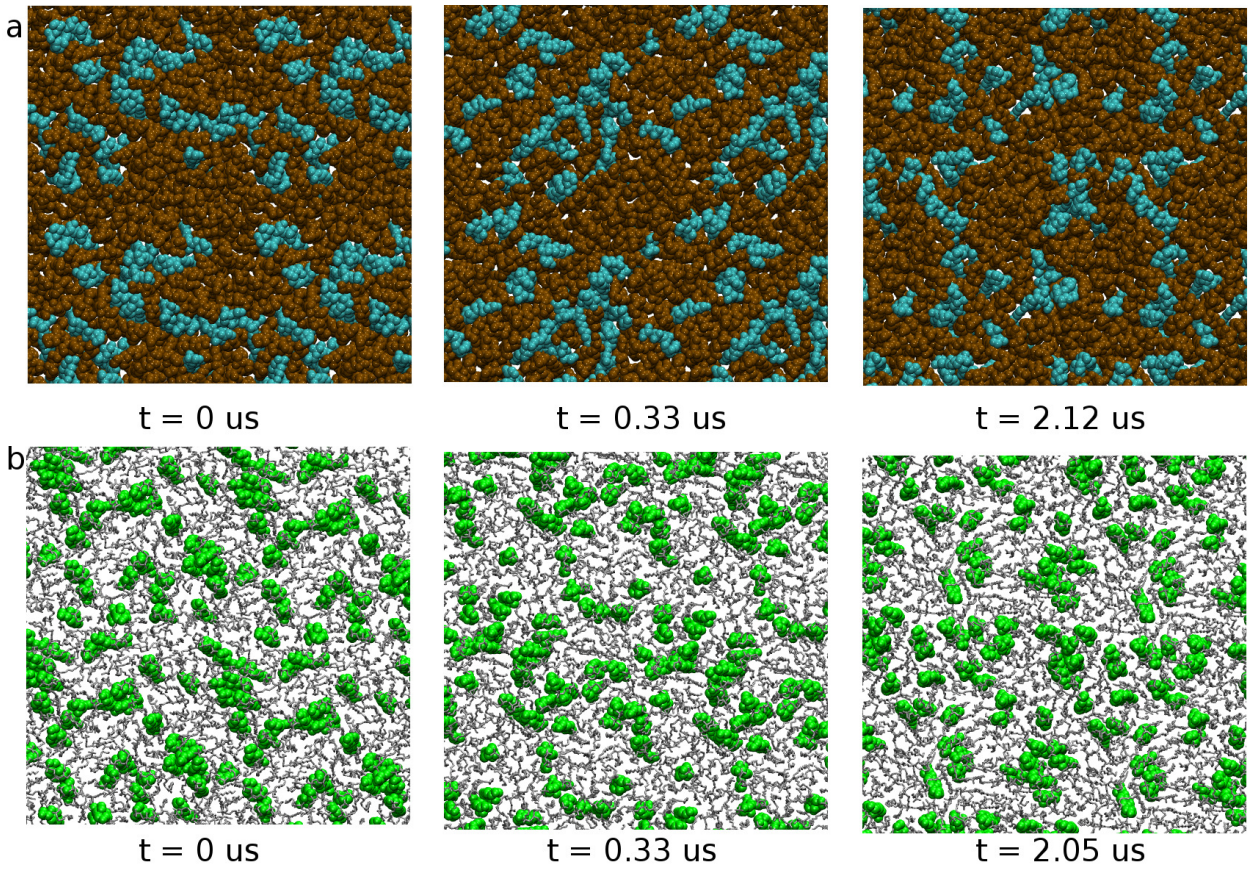

Figure S2: Snapshots of PE:PG-0.15r (a) and PC:CHL-0.15r (b) simulations. Coloring scheme as Fig 1.

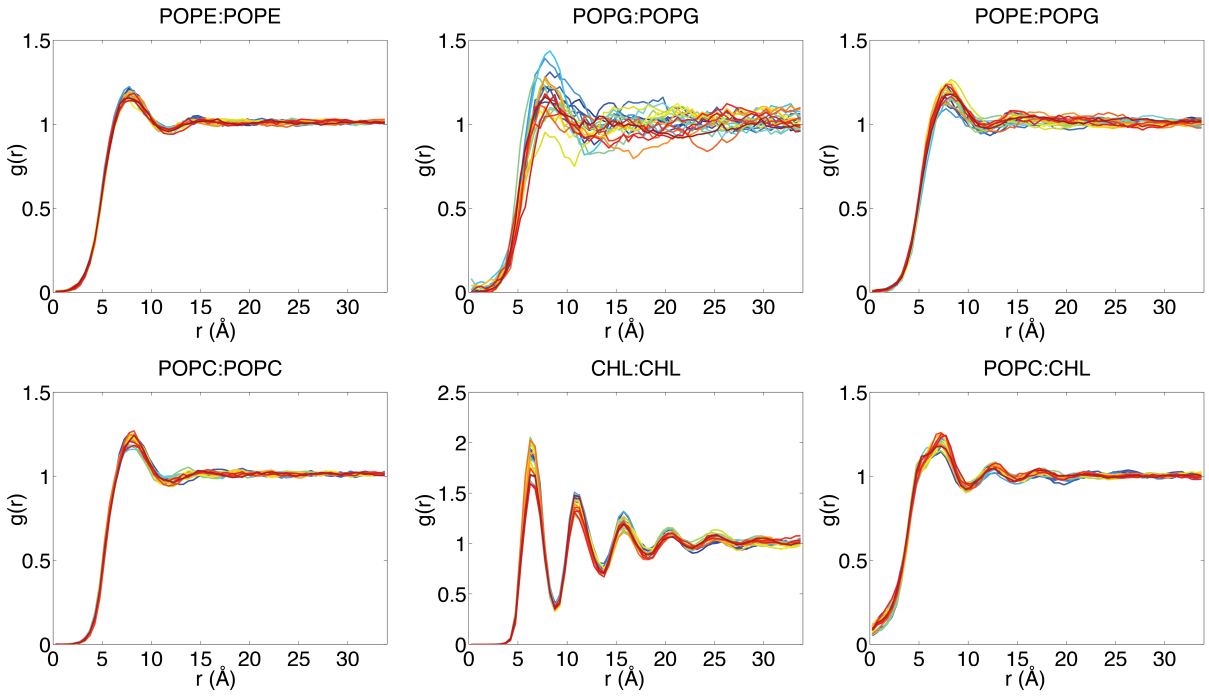

Figure S3: Radial pair distribution functions g(r) calculated using PE:PG-0.15r (top) and PC:CHL-0.15r (bottom) simulations. The lipids were placed randomly at the beginning of both simulations. Coloring scheme as Fig 2.

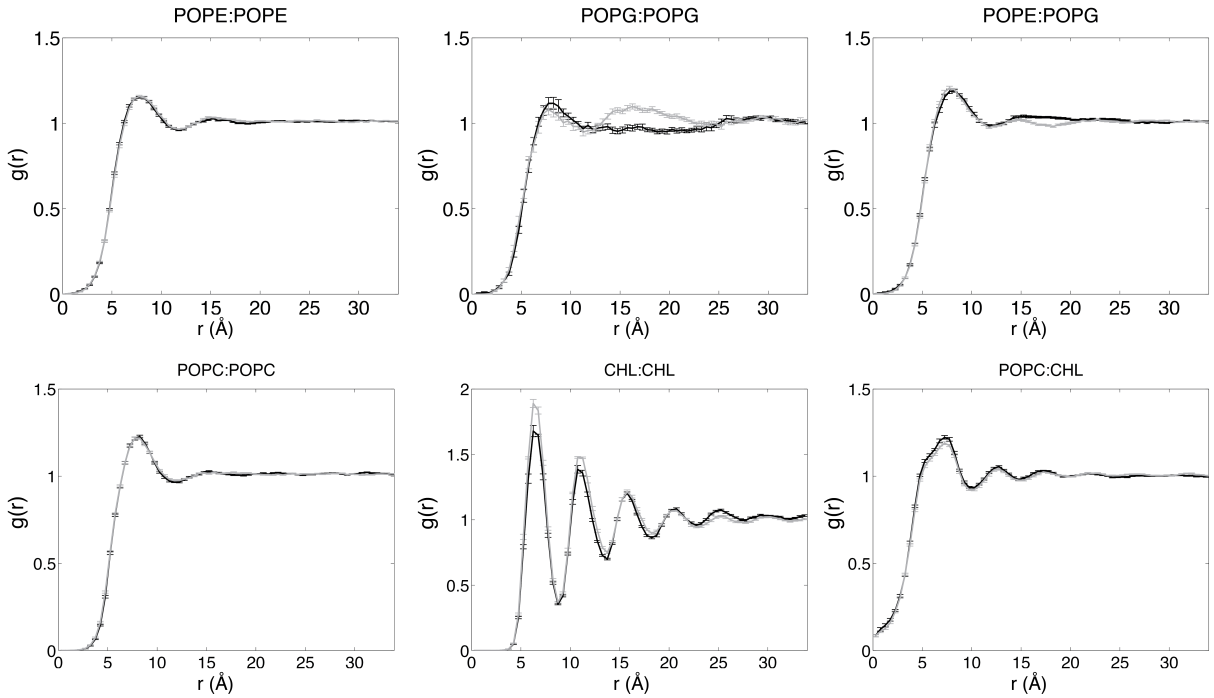

Figure S4: Radial pair distribution functions g(r) calculated using the last 500-ns simulations of the PE:PG (top) and PC:CHL (bottom) mixtures. Results from PE:PG-0.15r and PC:CHL-0.15r simulations are colored in black, while results from PE:PG-0.15c and PC:CHL-0.15c simulations are colored in gray. Error bars were calculated using the standard deviation and the statistical inefficiency obtained from the last 500 ns of each simulation (see Methods for details).

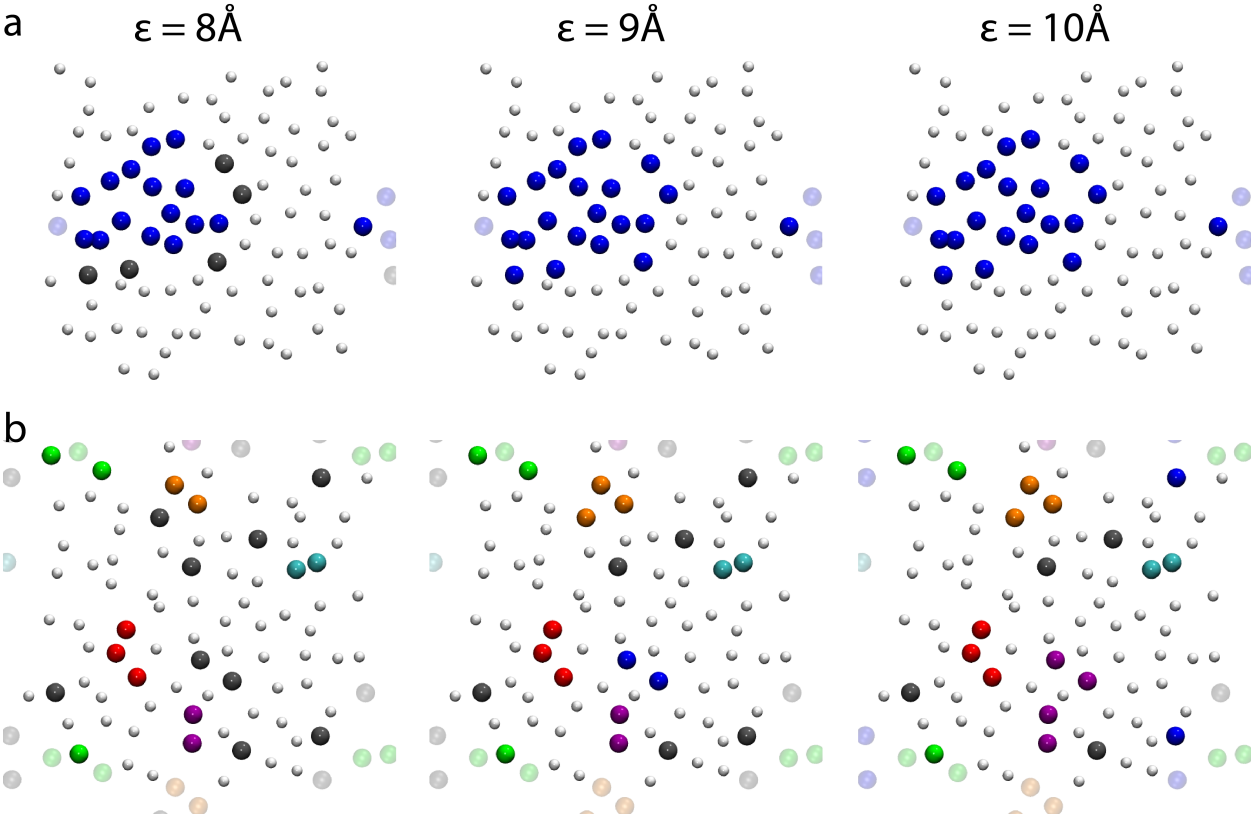

Figure S5: DBSCAN clustering analysis for PE:PG-0.15c at different ϵ. (a) $t = 0$ ns. (b) $t \approx 478$ ns. Coloring scheme as Fig 5.

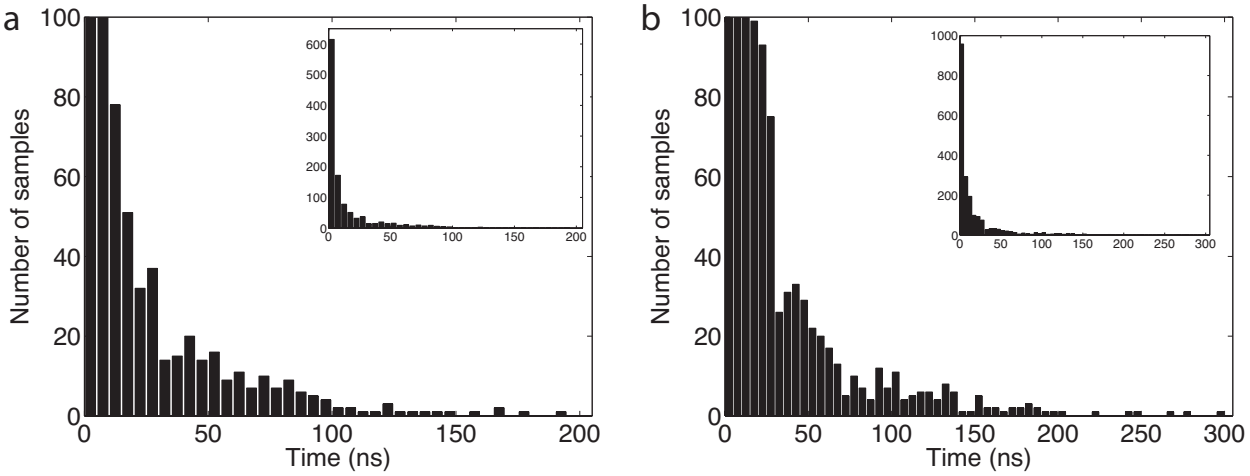

Figure S6: Histograms of the time it takes for two lipids within the same cluster to separate. Calculations were performed for POPG in PE:PG-0.15c (a) and cholesterol in PC:CHL-0.15c (b) using the last 500 ns of the simulations. Two lipids are considered separated once they are no longer within the same cluster for at least 5 ns. The time they spent in the same cluster is recorded and this is considered as one sample. The insets show the same histograms at a larger range of sample numbers.

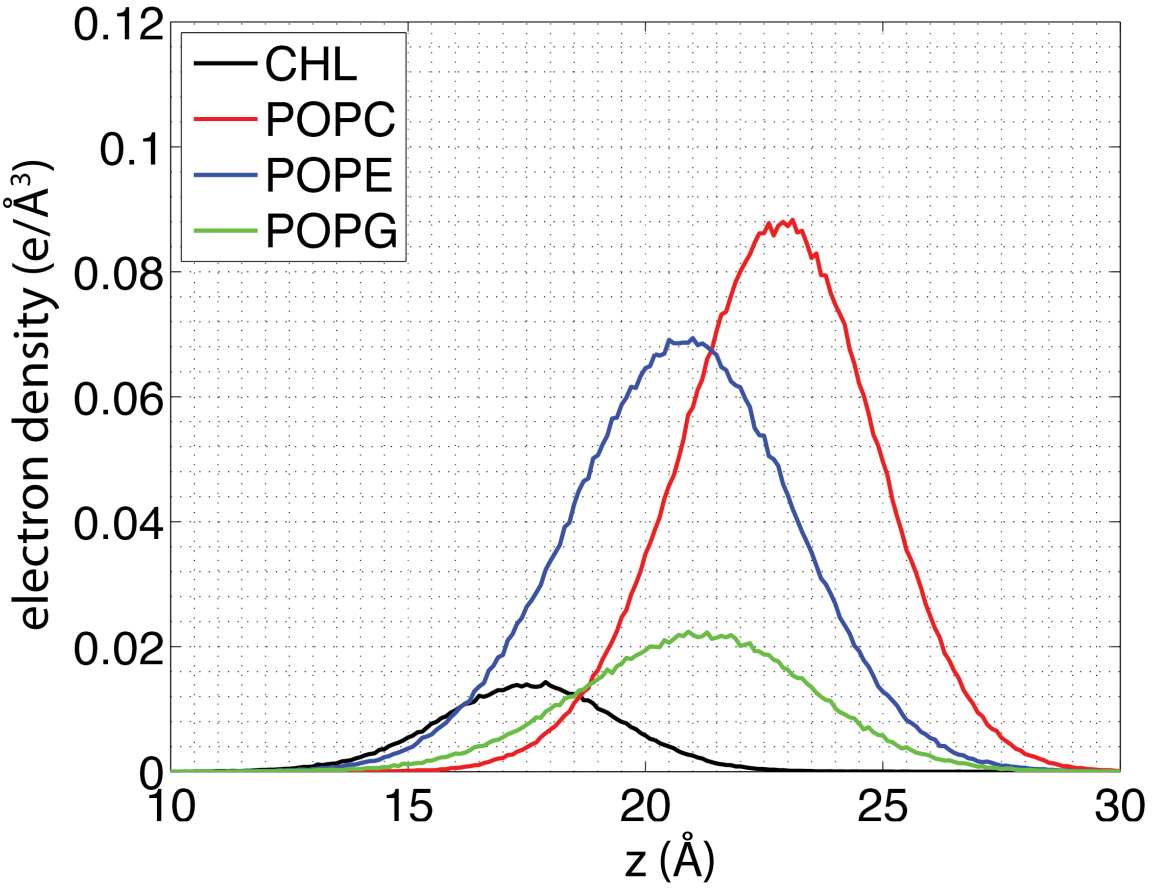

Figure S7: Electron density profiles of phosphate from POPE, POPG, POPC and hydroxyl from cholesterol. The calculation was performed using the last 500 ns of PE:PG-0.15r and PC:CHL-0.15r. For clarity, only results from the upper monolayer are shown. Atoms P, O13 and O14 (CHARMM36 naming convention) are used to calculate the phosphate group.

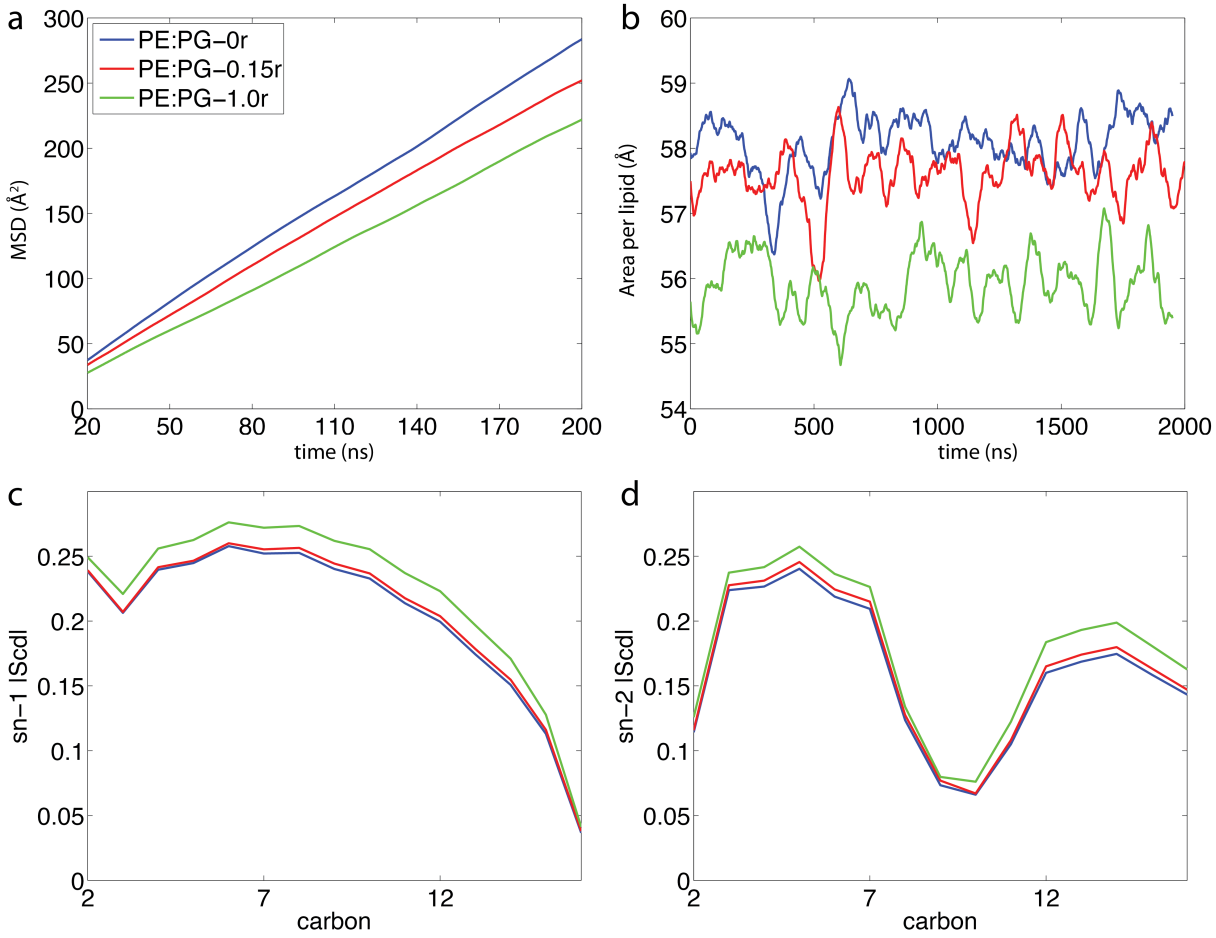

Figure S8: Structural and dynamic properties of PE:PG mixtures under different NaCl concentrations: (a) lateral mean square displacement (MSD) of lipids, (b) area per lipid, (c, d) order parameters ($|S_{CD}|$) of the lipid tails. The area per lipid shown in (b) is the running average with a window size of 500 frames (60 ns).

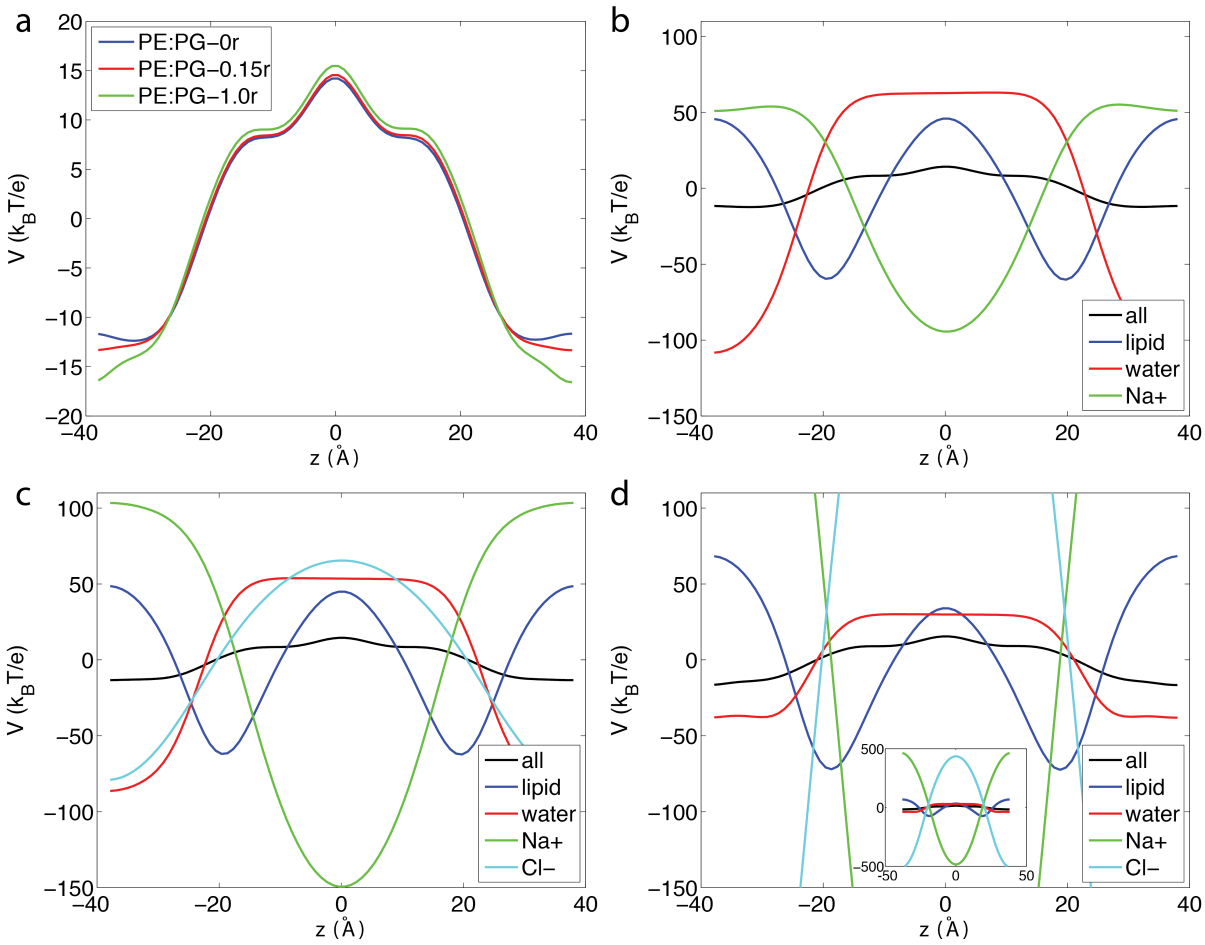

Figure S9: Electrostatic potential in the PE:PG mixtures. (a) Total electrostatic potential. (b-d) Breakdown of the electrostatic potential along membrane normal in PE:PG-0r (b), PE:PG-0.15r (c), and PE:PG-1.0r (d) simulations.

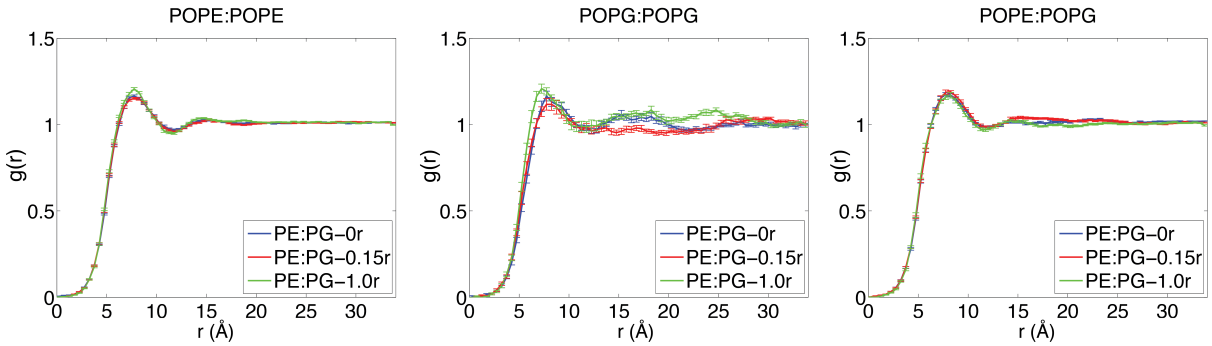

Figure S10: Radial pair distribution functions g(r) calculated using PE:PG-0r, PE:PG-0.15r and PE:PG-1.0r simulations.

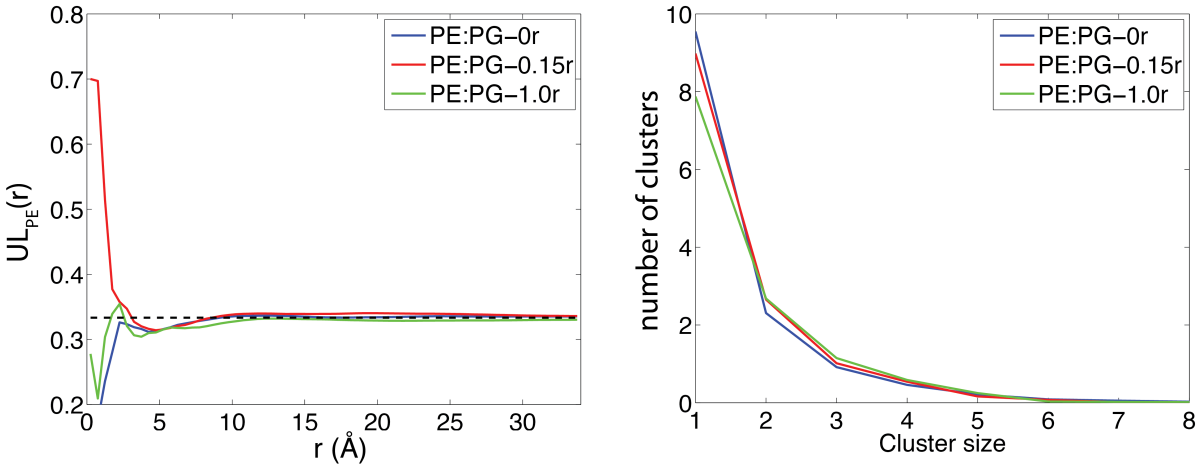

Figure S11: $UL(r)$ and histogram of cluster size calculated using the last 500 ns of PE:PG-0r, PE:PG-0.15r and PE:PG-1.0r simulations.

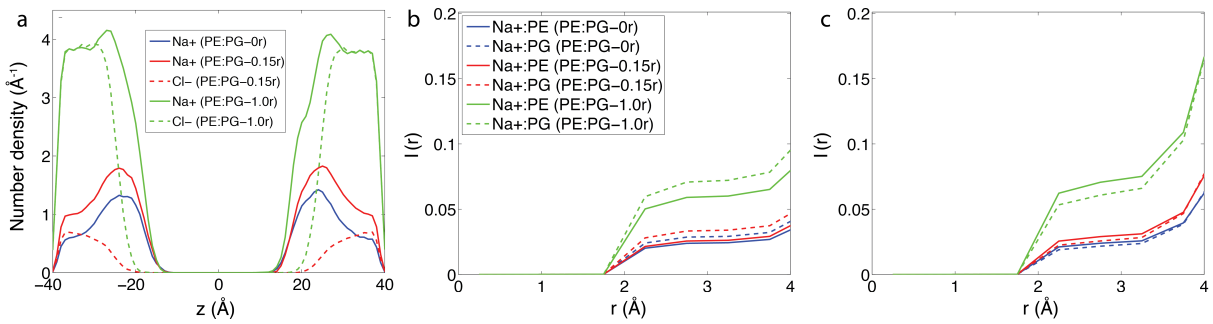

Figure S12: Ion distributions in 100-ns extension runs with NBFIX terms (see Results). (a) The number density of ions in each 1-$\mathring{A}$ slab along the membrane normal. (b, c) The average number of Na^+ ion around an ester oxygen (b) and a phosphdiester oxygen (c) in POPE and POPG.

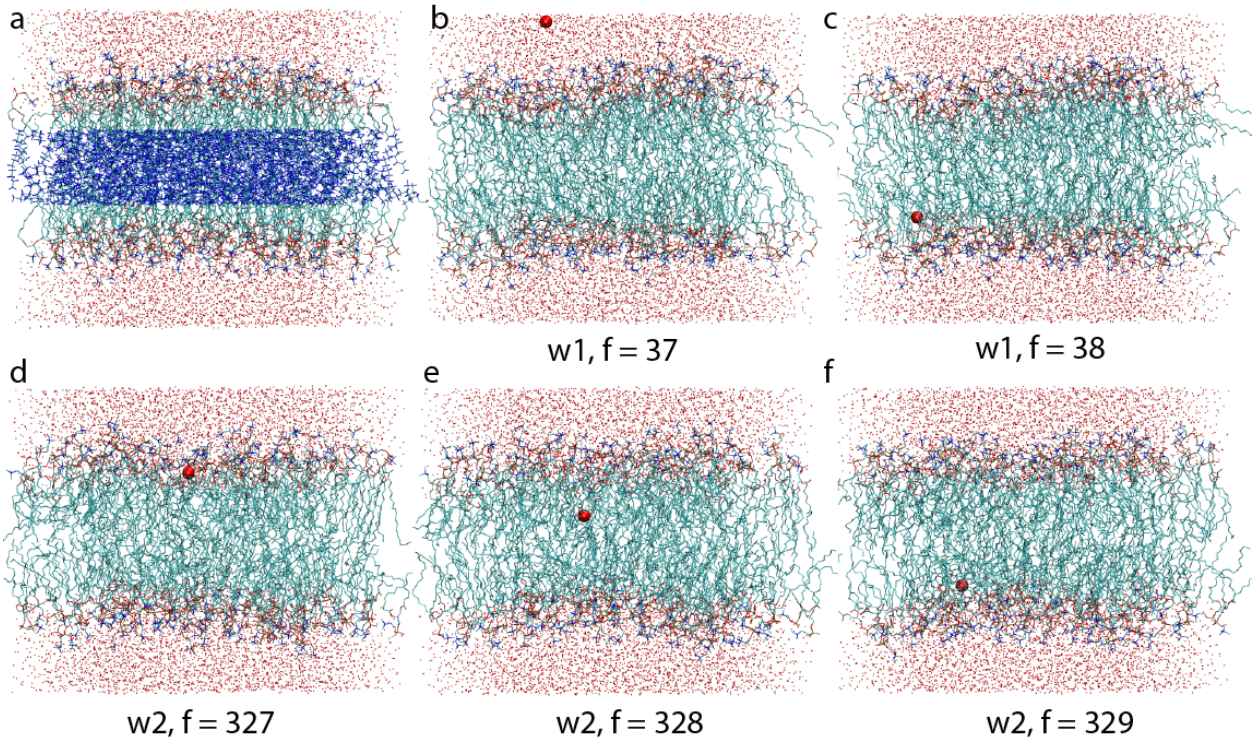

Figure S13: Calculation of water permeation. (a) Definition of the central region (colored in blue) of a bilayer. (b, c) A false permeation event. The water molecule w1 crosses the periodic boundary from frame 37 to 38. (e-f) A true permeation event. The water molecule w2 crosses the central region of the bilayer from frame 327 to 329.