Supporting Information

Can glucose counterpoise the perturbations in a model lipid bilayer containing ethanol?

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1. Umbrella sampling technique

Umbrella sampling was employed to compute the potential of mean force (PMF) profiles describing the translocation of ethanol across a DMPC bilayer under three conditions: (i) a fully hydrated pure DMPC bilayer containing 256 lipids (128 per leaflet) and 45 water molecules per lipid; (ii) a DMPC bilayer with 9 mol% ethanol; and (iii) a DMPC bilayer with 9 mol% ethanol and 10 wt% glucose molecules. To prepare the initial configurations, a single ethanol molecule was gradually pulled along the membrane normal (z-axis), which served as the reaction coordinate defined by the distance between the solute and the bilayer center of mass. A series of umbrella sampling simulations was then performed using harmonic biasing potentials with a force constant of 2.5 kcal/mol/Å^2, restraining the solute's position relative to the bilayer center. A total of 30 umbrella windows were spaced at 1 Å intervals, covering the range from z = −29 Å to z = +29 Å, thereby encompassing the full permeation pathway from one bulk water phase, across the bilayer, into the opposite bulk phase. Each window was simulated for 20 ns, giving an aggregate simulation time of 600 ns per system. All simulations were carried out using the collective variable module in AMBER20.[1] The biased probability distributions were post-processed with the Weighted Histogram Analysis Method (WHAM)[2-4] to reconstruct unbiased PMF profiles.

Because the lipid bilayer is symmetric, PMF profiles were averaged with respect to the distance from the bilayer center (z = 0 Å), and the free energy in the bulk water phase was normalized to zero. The calculated PMF, *W(z)*, and the local diffusivity profile, *D(z)*, were further used to estimate the permeability coefficient *P*, via the resistivity equation[5]

$$R = \frac{1}{P} = \int_{z_1}^{z_2} \frac{\exp[\beta W(z)]}{D(z)}\, dz$$

where $\beta = 1/k_B T$, T is the temperature, k_B is Boltzmann's constant, and z_1, z_2 are denote positions in the bulk regions on either side of the membrane. To estimate *D(z)* the time series of the solute's position along the z-axis was analyzed using approaches originally developed by Berne and co-workers[6] and later refined by Woolf and Roux.[7] These methods involve the calculation of diffusion coefficients using the velocity autocorrelation function (VACF) and its Laplace transform. However, a more practical method proposed by Hummer[8] was adopted, which allows estimation of *D(z)* from the autocorrelation function (ACF) of the z-position under harmonic restraint:

$$D(z = \langle z \rangle) = \frac{var(z)^2}{\int_0^\infty C_{zz}(t)dt}$$

where ACF, $C_{zz}(t) = \langle \delta z(0)\delta z(t) \rangle$ and $\delta z(t) = z(t) - \langle z \rangle$.[9] This method is advantageous because it is straightforward to implement in typical MD simulations and avoids the complexities of Laplace transformations.

2. Validation of the results

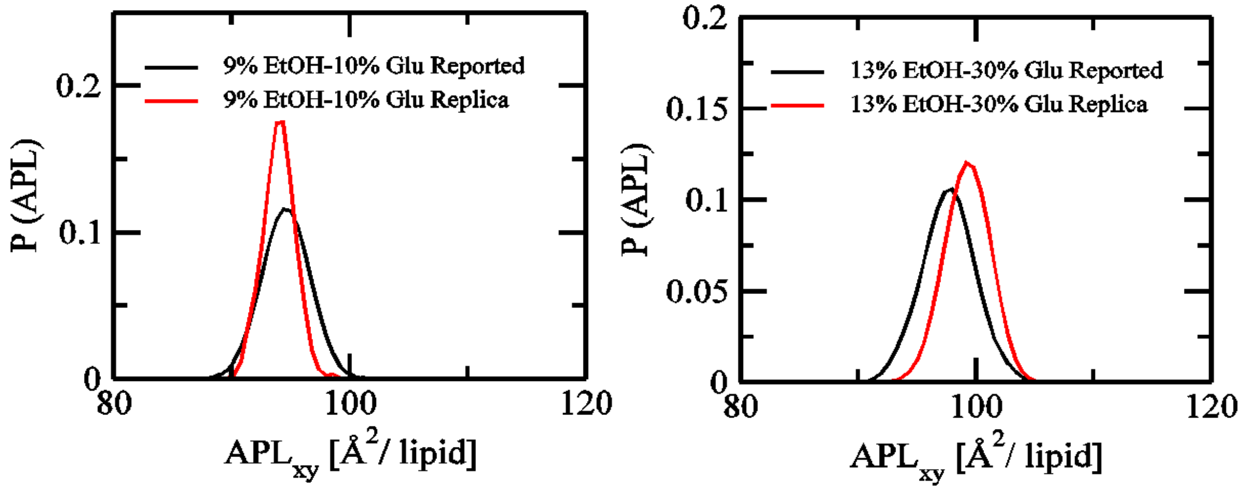

Fig. S1 Distribution of the area per lipid (APL) calculated using $\langle APL \rangle_{xy}$ for both the reported data and the replica simulation.

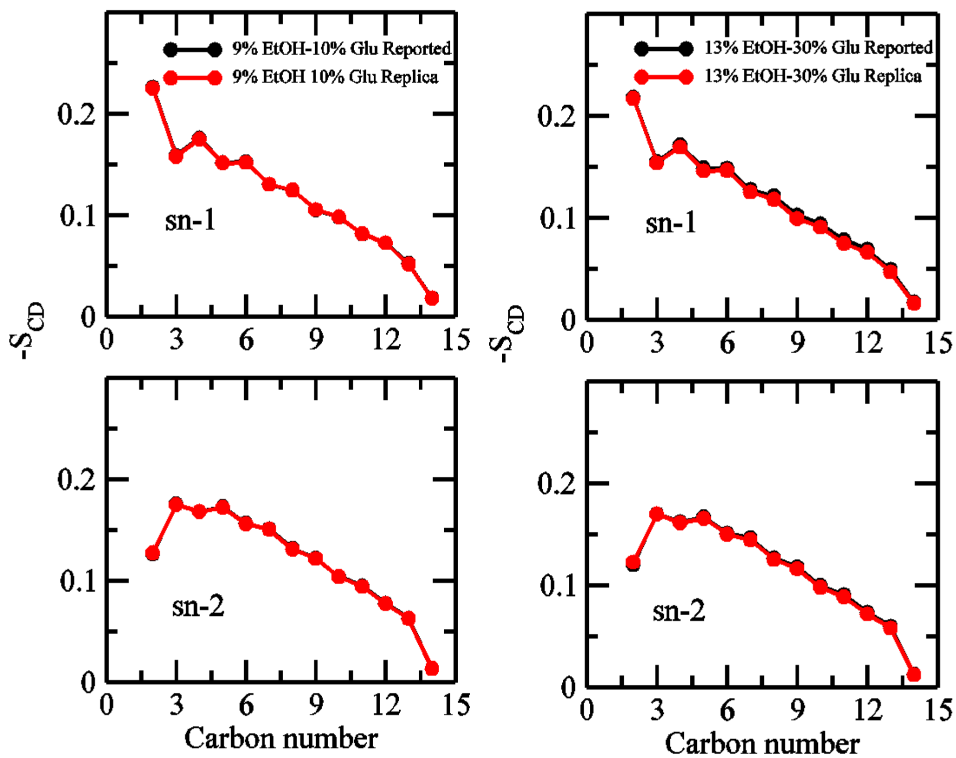

Fig. S2 Average order parameters of the lipid acyl chain carbon atoms in hydrated DMPC bilayers for both the reported data and the replica simulation.

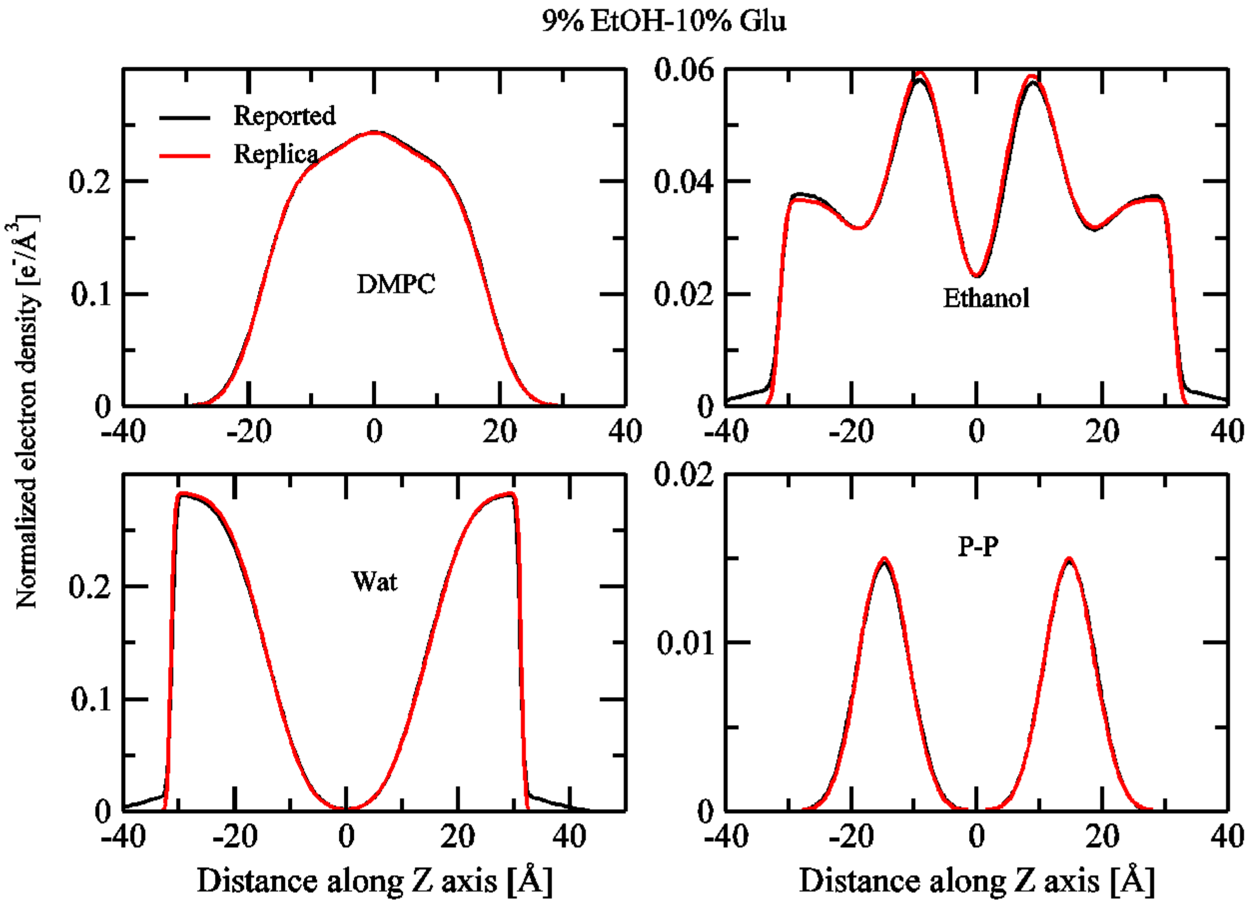

Fig. S3 Electron density profiles showing component-wise contributions from DMPC, water, ethanol, and P-P atoms for both the reported data and the replica simulation.

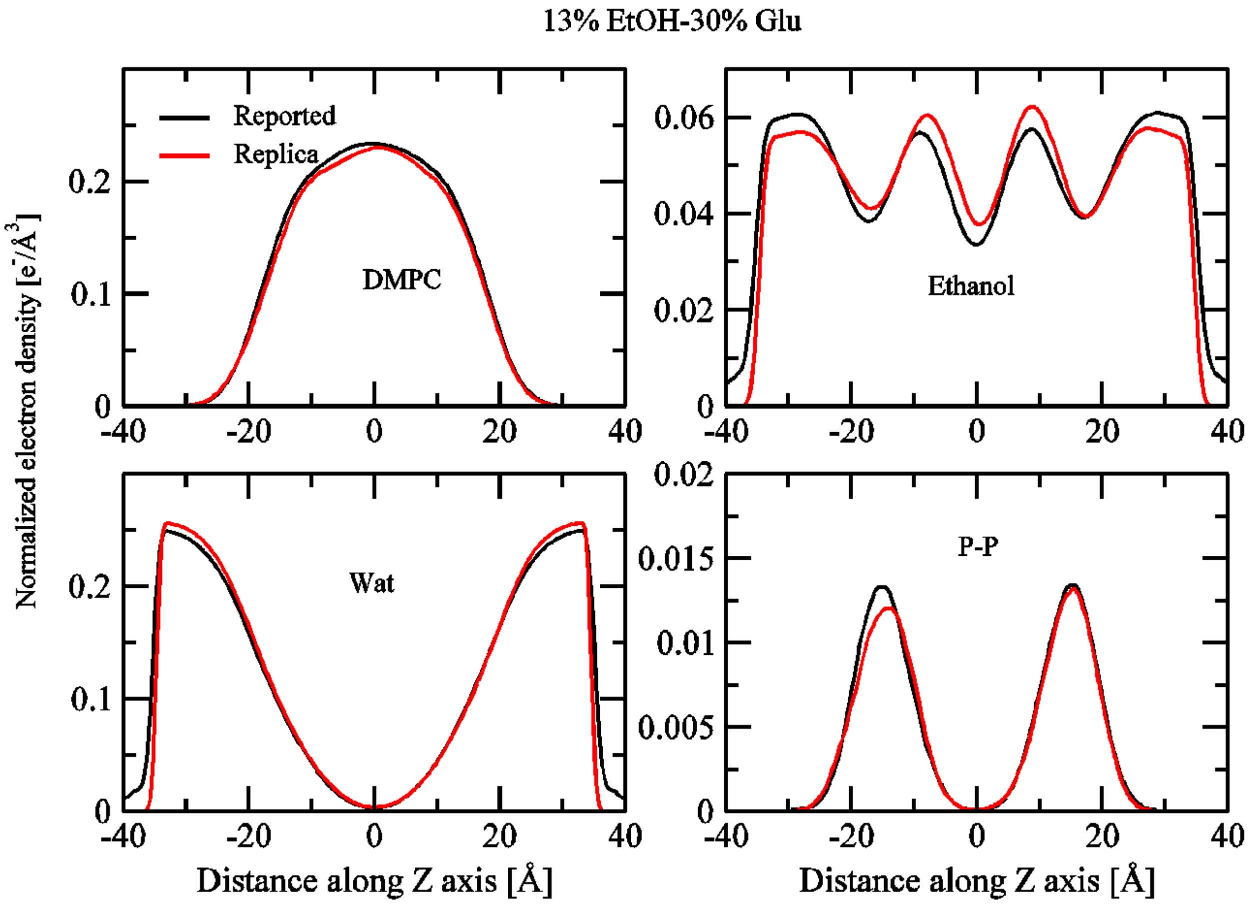

Fig. S4 Electron density profiles showing component-wise contributions from DMPC, water, ethanol, and P-P atoms for both the reported data and the replica simulation.

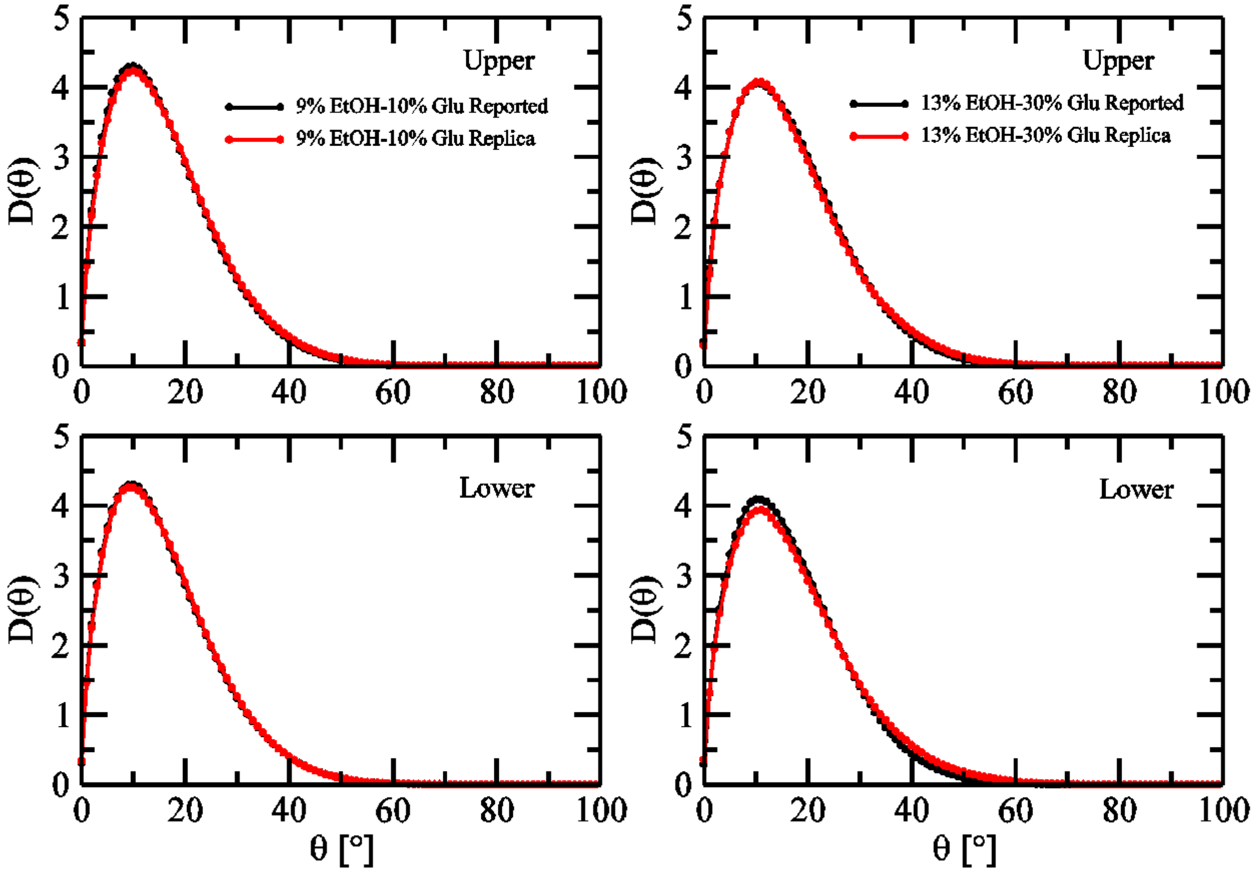

Fig. S5 Surface curvature angle distributions of the upper and lower leaflets of the DMPC bilayer for both the reported data and the replica simulation.

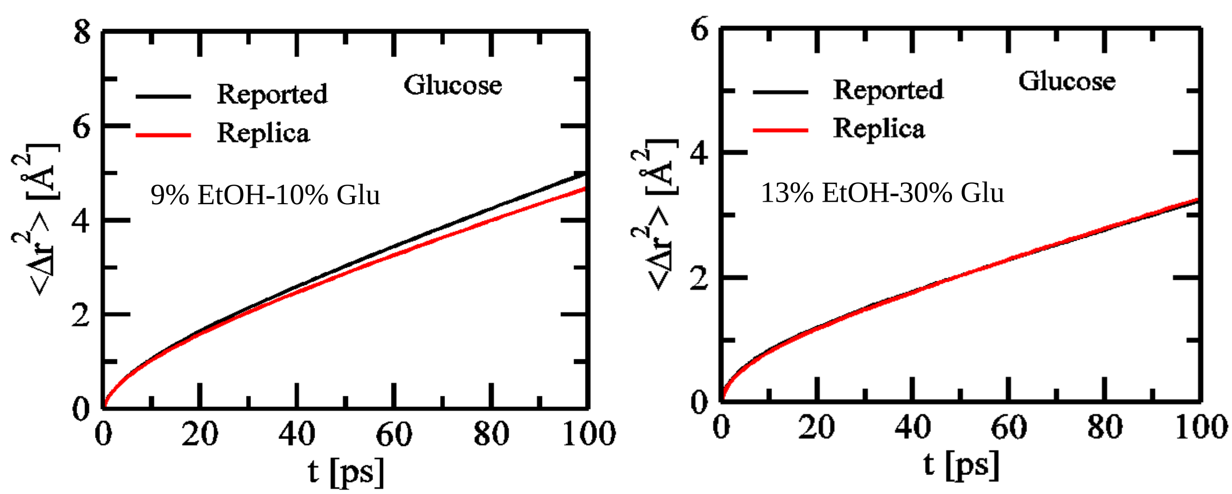

Fig. S6 Mean square displacements (MSDs) of glucose in all three Cartesian directions in hydrated lipid bilayer systems for both the reported data and the replica simulation.

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