

The Composition-Dependence of Water Permeation Across Multicomponent Gel-Phase Bilayers

SUPPORTING MATERIAL

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Implementation of the z-constraint method

Constraint forces on water molecules are calculated in windows separated by 2 Å. The number of windows is chosen to cover a range beyond the bilayer height, but smaller than the height of the simulation box. To account for the differences in bilayer height and box height, between 35 and 48 windows are used. Sampling in each window cannot be simultaneously performed, since strong interaction between water molecules in neighboring windows would affect the calculation. On the other hand, sampling only a single window per simulation is computationally inefficient. The total number of windows is chosen such that sampling of the windows can be evenly

distributed among 5 or 6 simulations. 7 or 8 windows are thus simultaneously sampled in each simulation, with the sampled windows separated in z by 1 or 1.2 Å (i.e., 5 or 6 windows apart, respectively). Figure S1 shows a snapshot of a (7:1) DSPC-C12 bilayer with 8 tracer molecules.

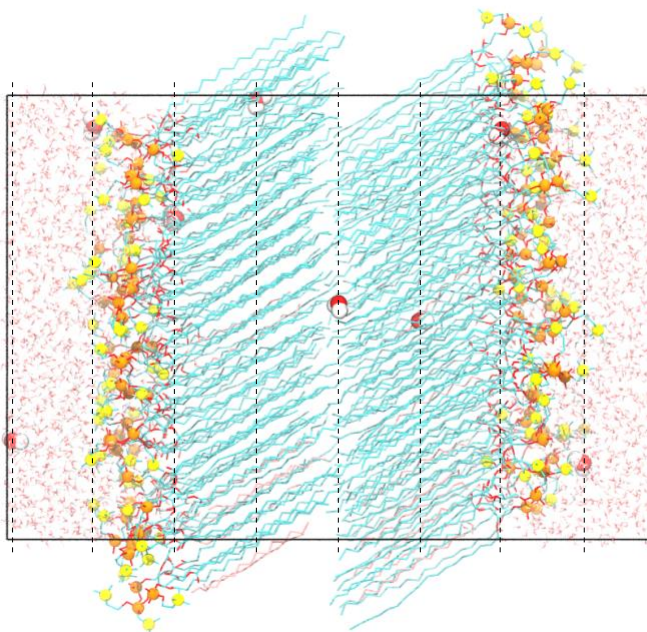


Figure S1: A (7:1) DSPC-C12 bilayer with 8 constrained water molecules at different z -positions.

The permeability simulations were initialized by first randomly selecting 7 or 8 tracer molecules from the aqueous phase. The center of mass of each of these tracer molecules was then connected to a weak harmonic spring (2.8×10^6 N/m) with the other end of the spring at a z -position corresponding to a window. These tracer molecules were free to move in x and y . After 20 ps the weak spring was replaced by a stronger spring (3.5×10^7 N/m) and the simulation was continued for an additional 20 ps to ensure that the tracer molecules are close to their corresponding window position. The spring was then removed and the z -position of the tracer molecule fixed at the z -position of the window, after which the system was equilibrated for 500 ps. The resulting configuration (Figure S1) served as the starting point for the first of the 5 or 6 permeability simulations needed to sample all windows. The starting configurations for the other simulations were created by moving each of the tracer molecules simultaneously at a constant

speed of 10 m/s in the z -direction and storing the configuration after each 20 ps (i.e., 2 Å). These configurations were again equilibrated for 500 ps.

Data was collected for 1.3 ns after equilibration. This sampling time is short compared to the slow motion of the lipids, but it is longer than the relaxation time of the water molecules in the headgroup region (where the smallest diffusion coefficients for water are observed), which is similar to the hydrogen bonding life time (up to 300 ps). Additional data is collected by repeating the sampling multiple times, with water molecules at different lateral positions in the bilayer. The repeated sampling of each window is referred to by ‘sweeps’, which were at least 35 (for more permeable bilayers) and maximum 75 (for most the most occlusive bilayer). Sweeps were performed until the maximum relative uncertainty in the excess free energy reached below 5%. The total amount of sampling per window is thus between 46 ns (i.e., 35 times 1.3 ns) and 98 ns. We note that Das *et al.*,¹ followed the same approach, but performed 15 sweeps and used a sampling time of 2 ns, thus effectively sampling each window for 30 ns. Table S1 shows an overview of the bilayer heights, number of windows, number of tracers, number of parallel simulations needed to complete a single sweep, and the number of sweeps performed for each of the bilayers considered.

Additional data

Table S1: Summary of the permeability simulations. Reported are the bilayer height \AA , the number of windows (each 2 \AA wide), the number of simulations per sweep, and the number of tracer molecules per simulation. The numbers in parentheses are the standard deviation.

	H [\AA]	Windows	Sim / sweep	Tracers	Sweeps
DSPC	48.2 (2.1)	35	5	7	50
(7:1) DSPC-ISIS	53.1 (2.1)	40	5	8	40
(1:1) DSPC-ISIS	54.8 (1.7)	40	5	8	40
(7:1) DSPC-C12	50.8 (1.8)	40	5	8	75
(3:1) DSPC-C12	53.7 (1.8)	40	5	8	35
(1:1) DSPC-C12	54.1 (1.8)	42	6	7	40
(1:2) DSPC-C12	52.0 (1.8)	40	5	8	35
(1:1) DSPC-C18	56.4 (1.4)	42	6	7	35
(1:1) DSPC-C24	63.0 (1.6)	48	6	8	35

Table S2: Summary of the excess free energy barrier and permeability coefficient for each of the bilayers studied. The numbers in parentheses are the standard deviation.

	$\Delta G(z)$ [kJ/mol]	P [cm/s]
DSPC	13.1 (0.5)	1.4e-8 (3.6e-9)
(7:1) DSPC-ISIS	15.1 (0.7)	8.2e-10 (2.5e-10)
(1:1) DSPC-ISIS	11.5 (0.4)	1.4e-7 (2.4e-8)
(7:1) DSPC-C12	15.4 (0.5)	3.3e-10 (8.7e-11)
(3:1) DSPC-C12	14.4 (0.8)	1.9e-9 (6.8e-10)
(1:1) DSPC-C12	14.2 (0.5)	1.7e-9 (5.2e-10)
(1:2) DSPC-C12	14.5 (0.6)	1.0e-9 (2.6e-10)
(1:1) DSPC-C18	12.7 (0.6)	3.1e-8 (6.3e-9)
(1:1) DSPC-C24	12.8 (0.6)	1.0e-8 (2.9e-9)

Mass density profiles

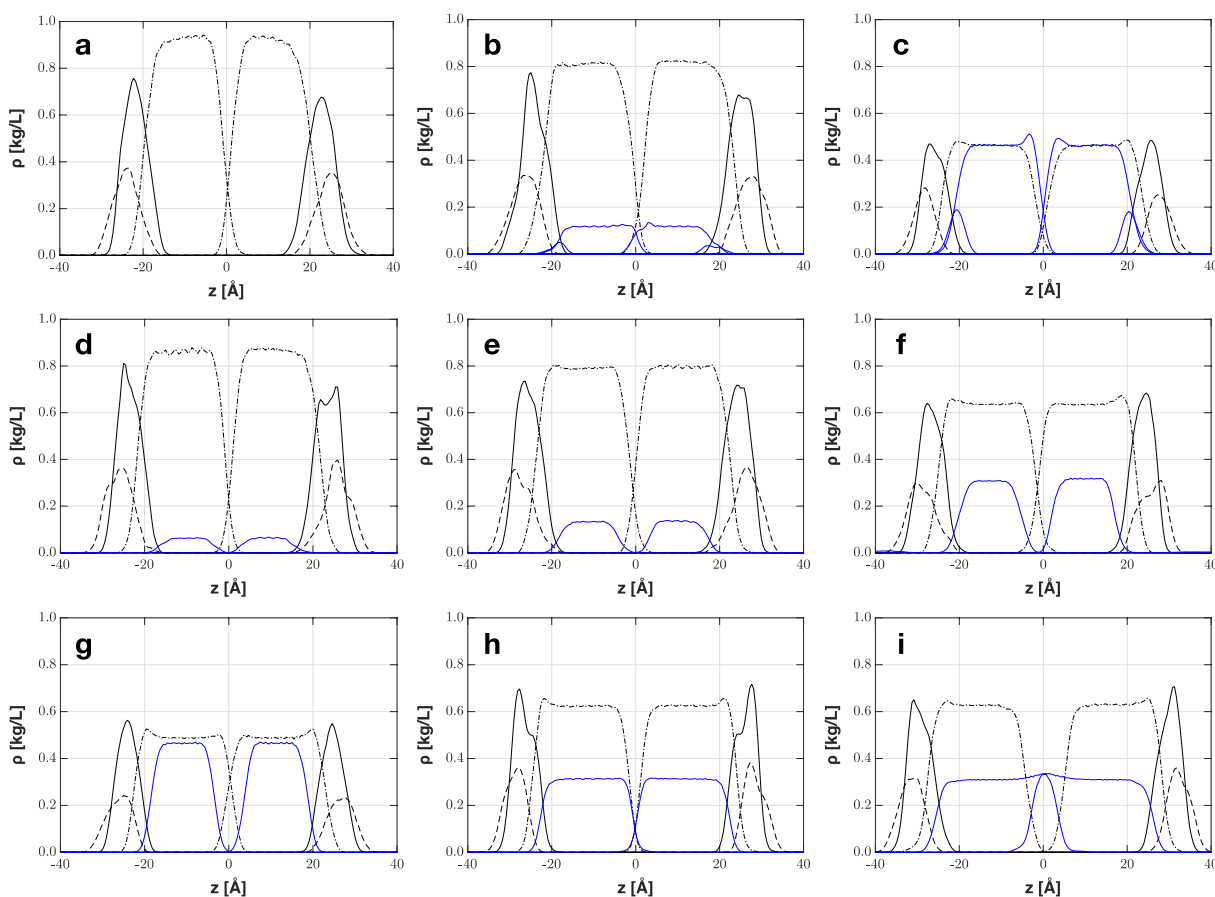


Figure S2: Mass density profiles of (a) pure DSPC, (b) 7:1 DSPC-ISIS, (c) 1:1 DPSC-ISIS, (d) 7:1 DSPC-C12, (e) 3:1 DSPC-C12, (f) 1:1 DSPC-C12, (g) 1:2 DSPC-C12, (h) 1:1 DSCP-C18, and (i) 1:1 DSPC-C24. The DSPC density is shown in black, with choline in dashed lines, phosphate/glycerol in solid lines, and tails in dash-dotted lines. The blue lines represent the alcohol or ISIS molecules, with the ISIS ester headgroup and tails drawn separately.

References

1. Das, C., Olmsted, P. D. & Noro, M. G. Water permeation through stratum corneum lipid bilayers from atomistic simulations. *Soft Matter* **5**, 4549–4555 (2009).
2. Hartkamp, R. *et al.* Structural Properties of Phospholipid-based Bilayers with Long-Chain Alcohol Molecules in the Gel Phase. *J. Phys. Chem. B* **120**, 12863–12871 (2016).