Supporting information

Functional Group Distributions, Partition Coefficients and Resistance Factors in Lipid Bilayers using Site Identification by Ligand Competitive Saturation (SILCS)

Christoffer Lind[1], Poonam Pandey[1], Richard W. Pastor[2] & Alexander D. MacKerell Jr[1,§]

[1] Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, Maryland, 21201, United States

[2] Laboratory of Computational Biology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, United States

[§] To whom correspondence should be addressed. Tel: +1 410-706-7442; Fax: +1 410-706-5017; Email: alex@outerbanks.umaryland.edu

Table S1. Overlap coefficients of selected FragMaps indicating the extent of convergence of the SILCS simulations for the POPC/CHOL and PAMPA systems.

FragMap	POPC/CHOL	PAMPA
MEOO	0.84	0.79
IMIN	0.83	0.78
FORO	0.83	0.79
MAMN	0.83	0.81
ACEO	0.89	0.81
BENC	0.89	0.87
PRPC	0.89	0.87
AALO	0.83	0.78
GEHC	0.89	0.82
TIPO	0.97	0.89

Overlap coefficients (OC) were calculated as previously described[1] between FragMaps calculated from simulation 1-5 and 6-10 from the respective systems. OC values > 0.6 indicate satisfactory convergence. FragMaps are shown for methanol O (MEOO), imidazole acceptor N (IMIN), formamide oxygen (FORO), methylammonium N (MAMN), acetate O (ACEO), benzene C (BENC), propane C (PRPC), acetaldehyde O (AALO), imidazole Cs (GEHC) and water O (TIPO).

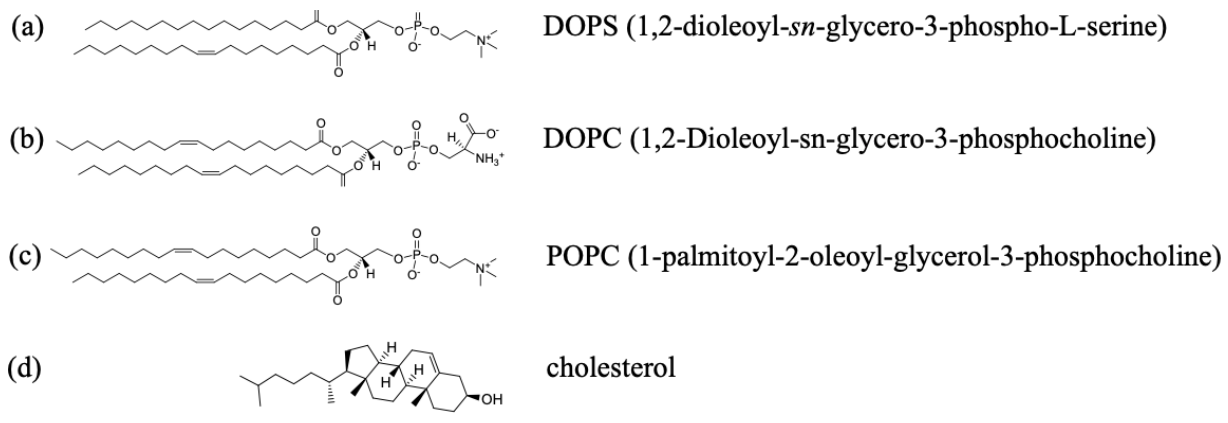

Figure S1. 2D representation of the chemical structures of (a) DOPS, (b) DOPC, and (c) POPC phospholipids; and (d) cholesterol. The PAMPA system is mixture of 0.52:0.18:0.3 DOPS:DOPC:cholesterol.

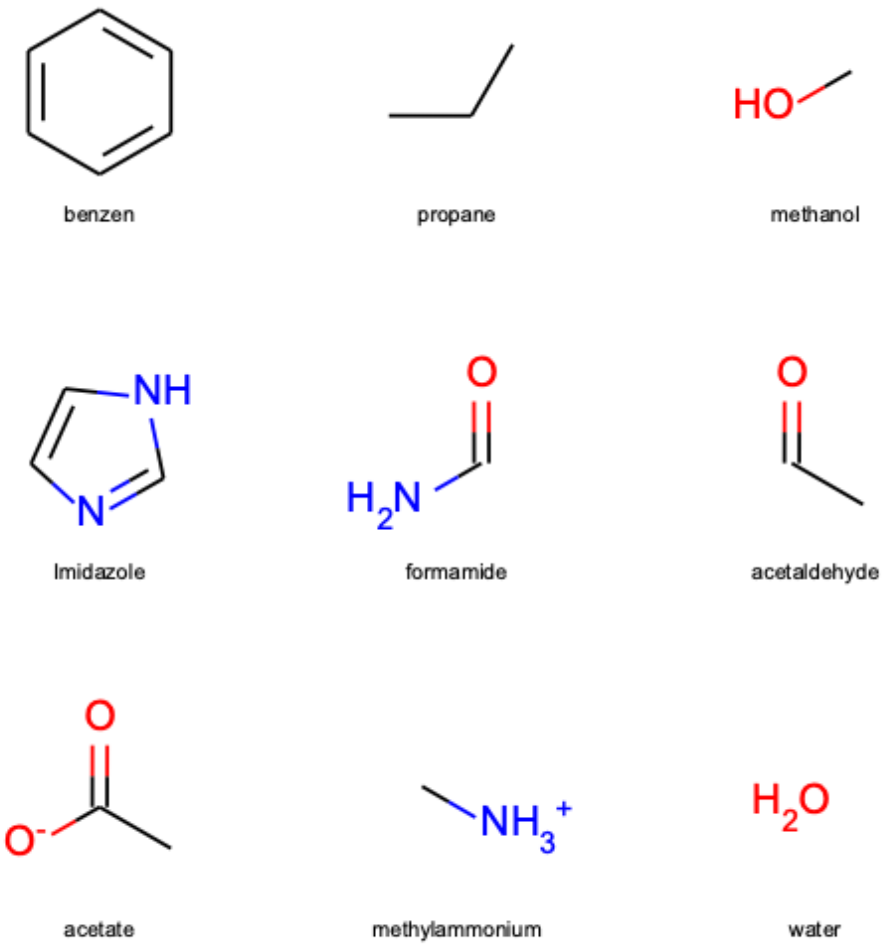

Figure S2. SILCS solutes. Apolar (benzene and propane), polar neutral (methanol, imidazole, formamide and acetaldehyde) and charged (methyl ammonium and acetate) solutes.

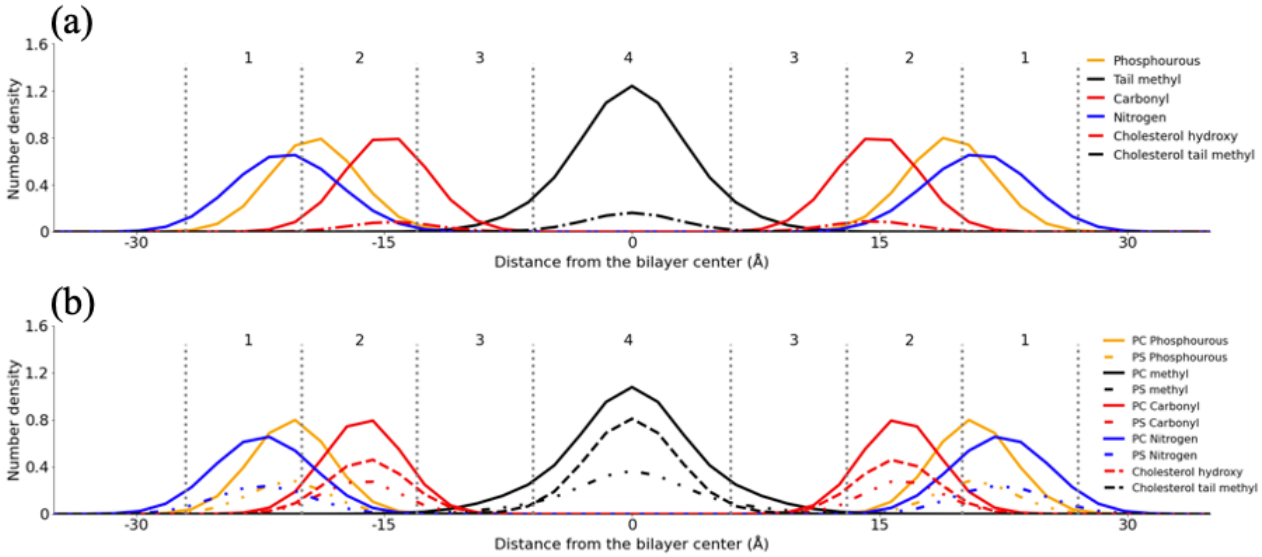

Figure S3. Detailed distribution of the head and tail groups of each lipid type. (a) The POPC bilayers and the leaflets extend to 27-30 Å from the bilayer center as measured from the choline nitrogen head. (b) The PAMPA bilayer is thicker by about 2 Å due to area contraction from the increased concentration of cholesterol.

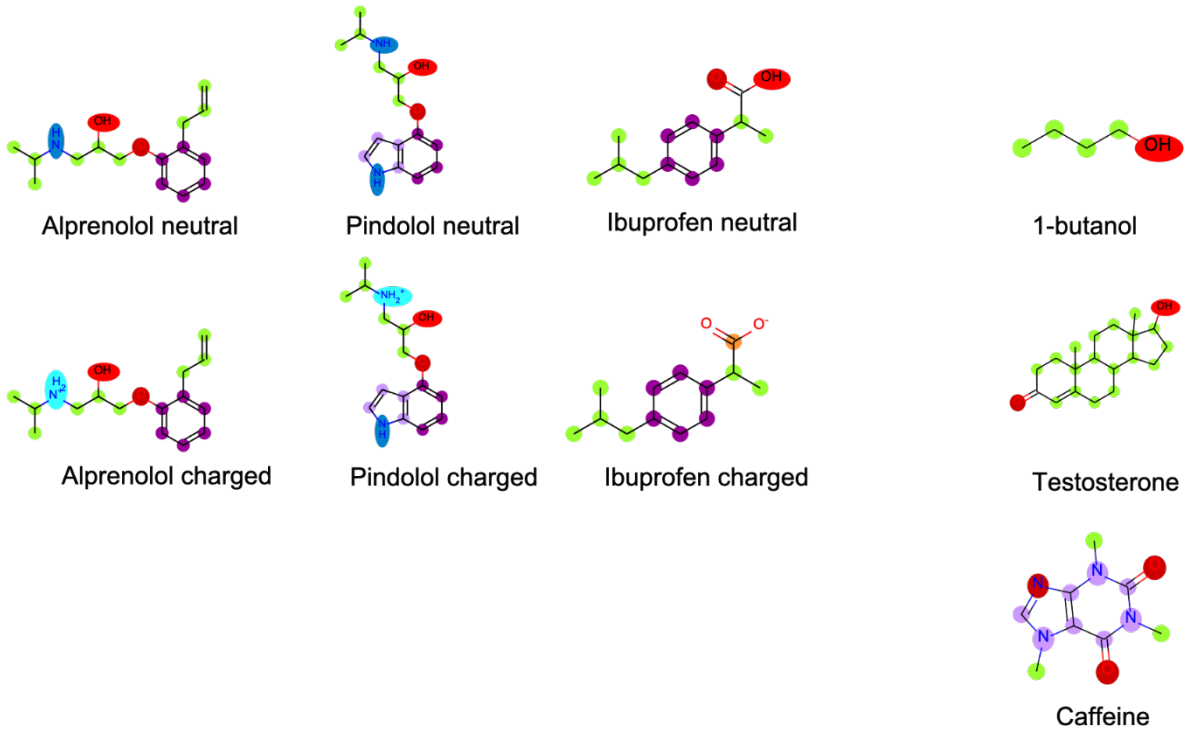

Figure S4. Compounds used to generate the free energy profiles (Figs. 7 and 8 in main text). The 2D representation is highlighted with the respective coloring represented by the conventional coloring of the SILCS FragMaps as follows:green, propane carbon; purple, benzene carbon; dark red, generic acceptor atoms combined of oxygens from formamide and acetaldehyde and unprotonated nitrogen of imidazole; lighter red methanol oxygen; blue protonated nitrogen of imidazole; orange acetate carbon; and cyan charged nitrogen of methylammonium. Coloring and generation of the 2D molecules in-house written python code using RDKit version 2020.03.6.

References

1. Lakkaraju, S. K.; Yu, W.; Raman, E. P.; Hershfeld, A. V.; Fang, L.; Deshpande, D. A.; MacKerell Jr, A. D., Mapping functional group free energy patterns at protein occluded sites: nuclear receptors and G-protein coupled receptors. *Journal of chemical information and modeling* **2015,** *55* (3), 700-708.