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Supplementary Information for

Probing molecular forces in multi-component physiological membranes

Arjun Ray[1,2], Frauke Gräter[3,4*], and Lipi Thukral[1,2,4*]

[1]CSIR-Institute of Genomics and Integrative Biology, Mathura Road, New Delhi, 110025, India

[2]Academy of Scientific and Innovative Research (AcSIR), CSIR- Institute of Genomics and Integrative Biology, Mathura Road Campus, New Delhi, 110025, India

[3]Heidelberg Institute for Theoretical Studies, Schlosswolfsbrunnenweg 35, 69118 Heidelberg, Germany

[4]Interdisciplinary Center for Scientific Computing, University of Heidelberg, Im Neuenheimer Feld 205, 69120 Heidelberg, Germany

Corresponding Authors*:

frauke.graeter@h-its.org (F.G);

lipi.thukral@igib.res.in (L.T)

1. Supplementary Tables and Figures

Table S1. No. of lipids in heterogenous membranes. Each membrane is composed of diverse membrane lipids and their ratios are extracted from van Meer et. al., and van Golde et. al.[1, 2]

	POPC	POPE	POPS	POPI	PSM	CARD	Total
ER	360	144	18	60	18	0	600
Golgi	312	132	36	72	48	0	600
Mitochondria	252	210	0	30	0	108	600

Table S2. Simulations Summary. Three membranes are simulated using a standard MD protocol in aqeous envirnment with the following parameters.

	No. of lipids	No. of SOL molecules	Total number of atoms	Temperature [K]	Total production run time [ns]
ER	600	21527	143691	310	700
Golgi	600	21048	142092	310	700
Mitochondria	600	26075	167763	310	700

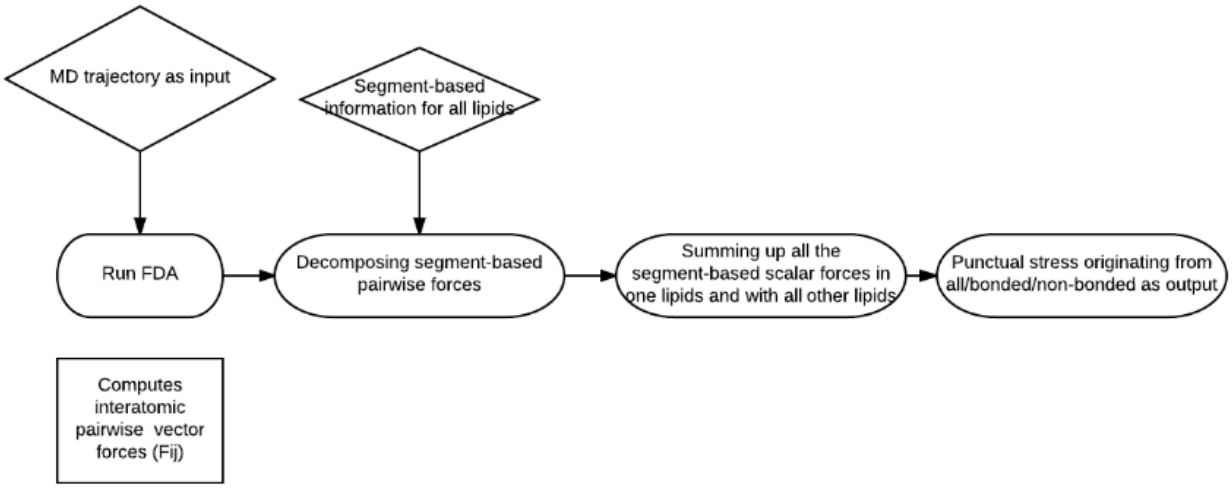

Figure S1: Schematic diagram for the L-FDA scheme. The novel membrane descriptor takes an MD simulation trajectory of a given system as input, in this case the membrane bilayer simulations and calculates segment-based punctual stress as a scalar quantity.

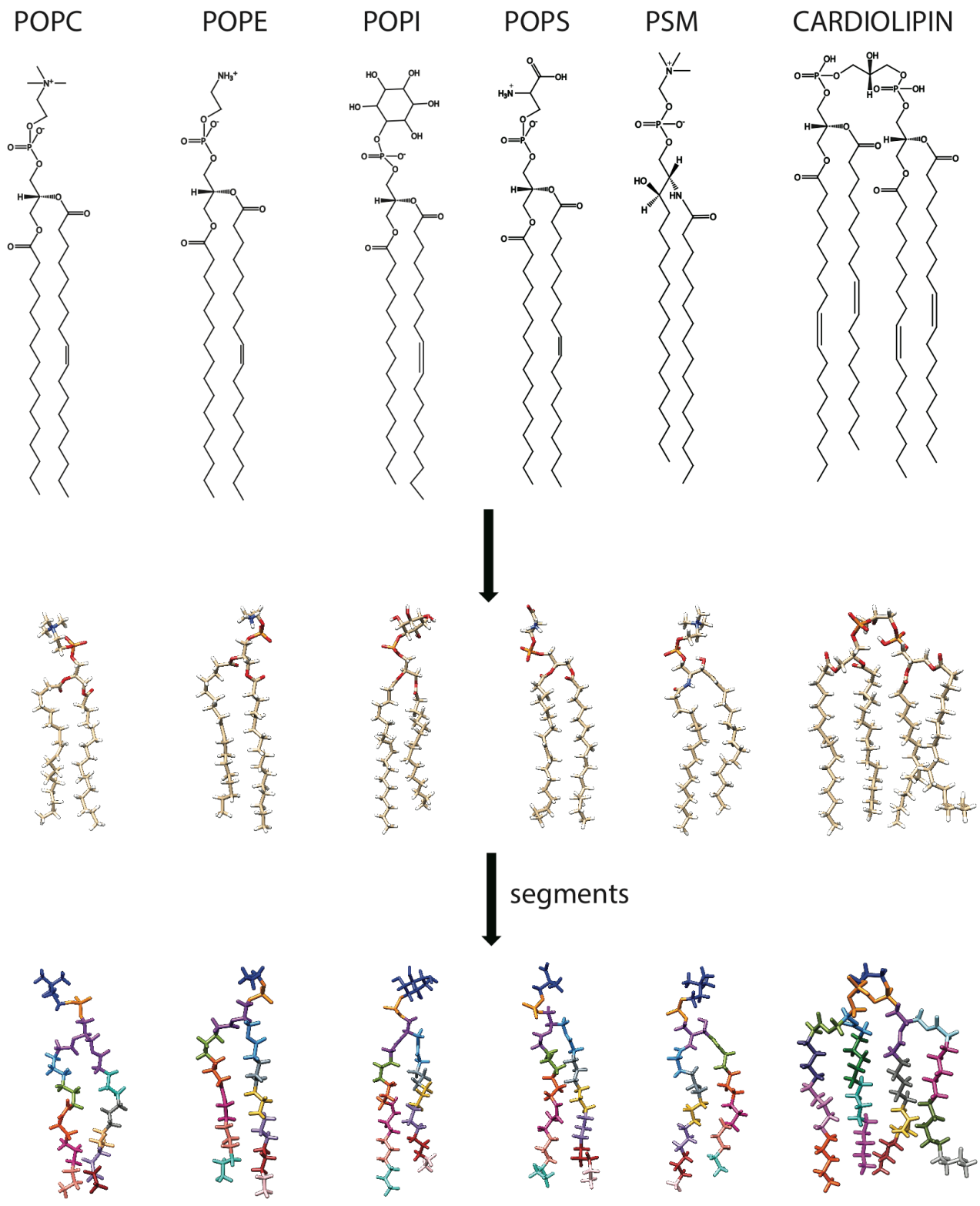

Figure S2 : Segment-wise decomposition of lipids. The lipids were decomposed into 14 segments (except cardiolipin, which has 18 segments). The segment definition (last row) is shown for the bead representation used by the coarse-grained MARTINI scheme. The first and second row show the chemical and structural representation of all lipids,

respectively. Each segment is colored differently in all lipids, as deipted in the last row.

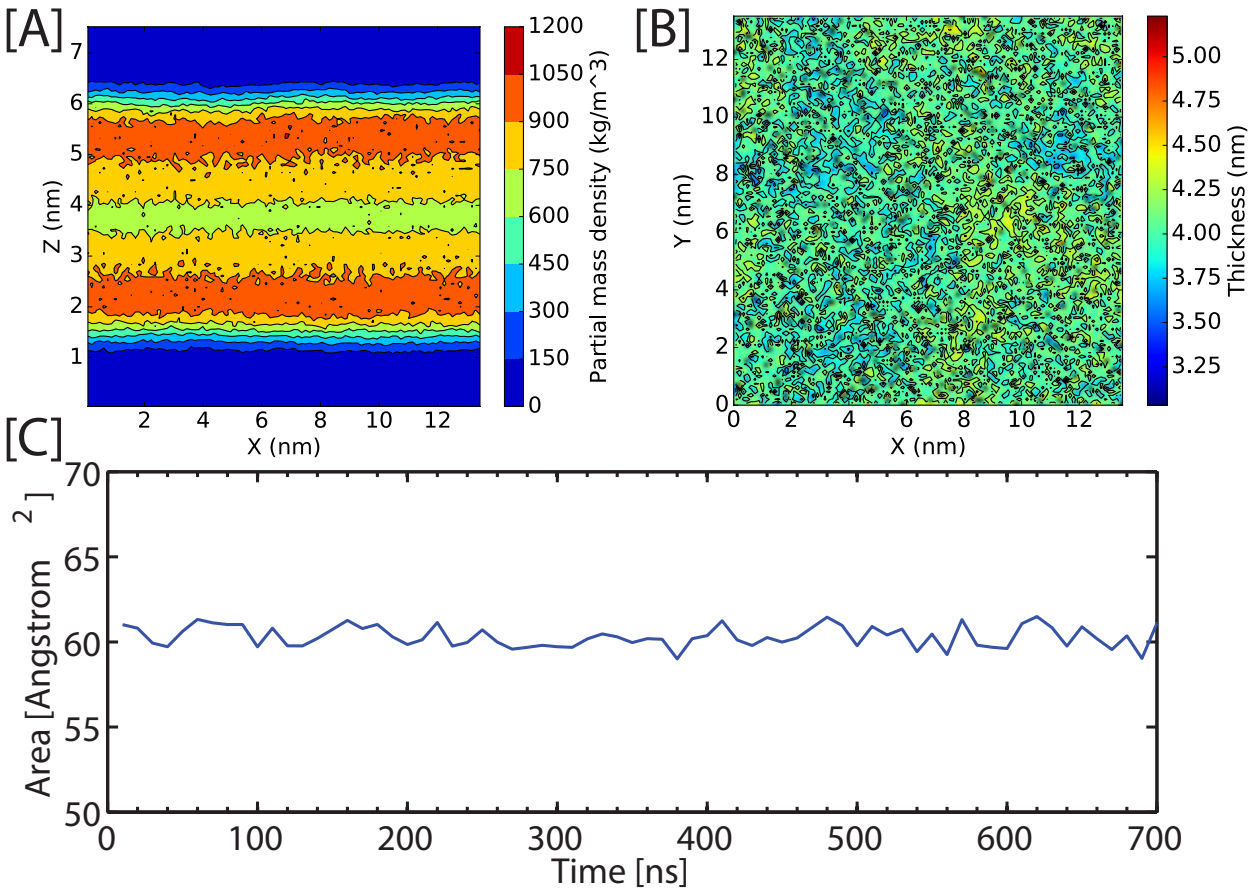

Figure S3. A) Partial density of the acyl chain of all the lipids in the Endoplasmic Reticulum membrane during the last 100 ns of the simulation. The partial densities are calculated along the membrane normal and one of the membrane lateral axis and averaging over the other lateral axis. B) Variation of local membrane thickness over the bilayer at the same last 100 ns of the simulation. For further details, see Methods section. C. Time evolution of total area per lipid calculated for the ER membrane.

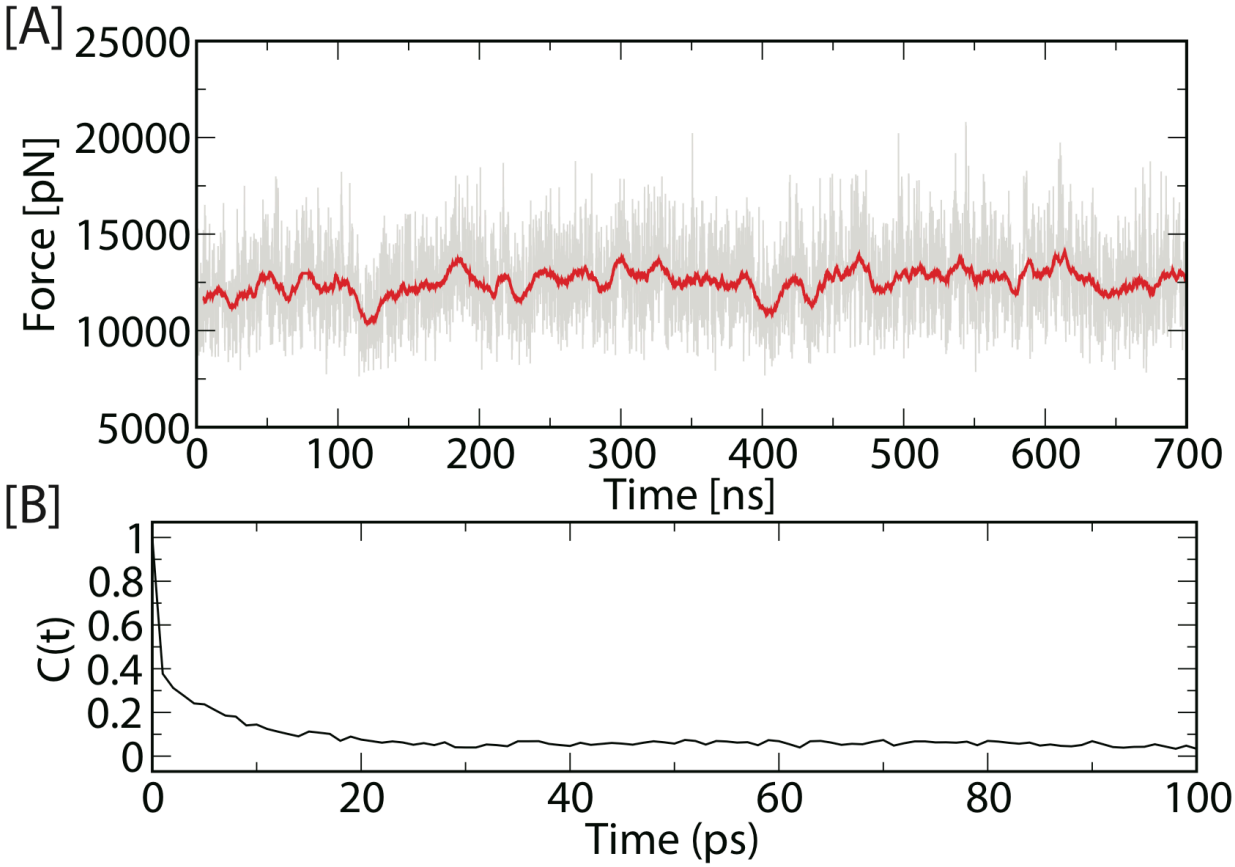

Figure S4. A: Total force acting upon a single P atom for POPC (in the ER) as a function of time (grey) and the running average over 2 ns (red). B: Autocorrelation of the total force F_i^{atomic} acting on the P atom. It decays to zero under equilibrium conditions within ~15ps.

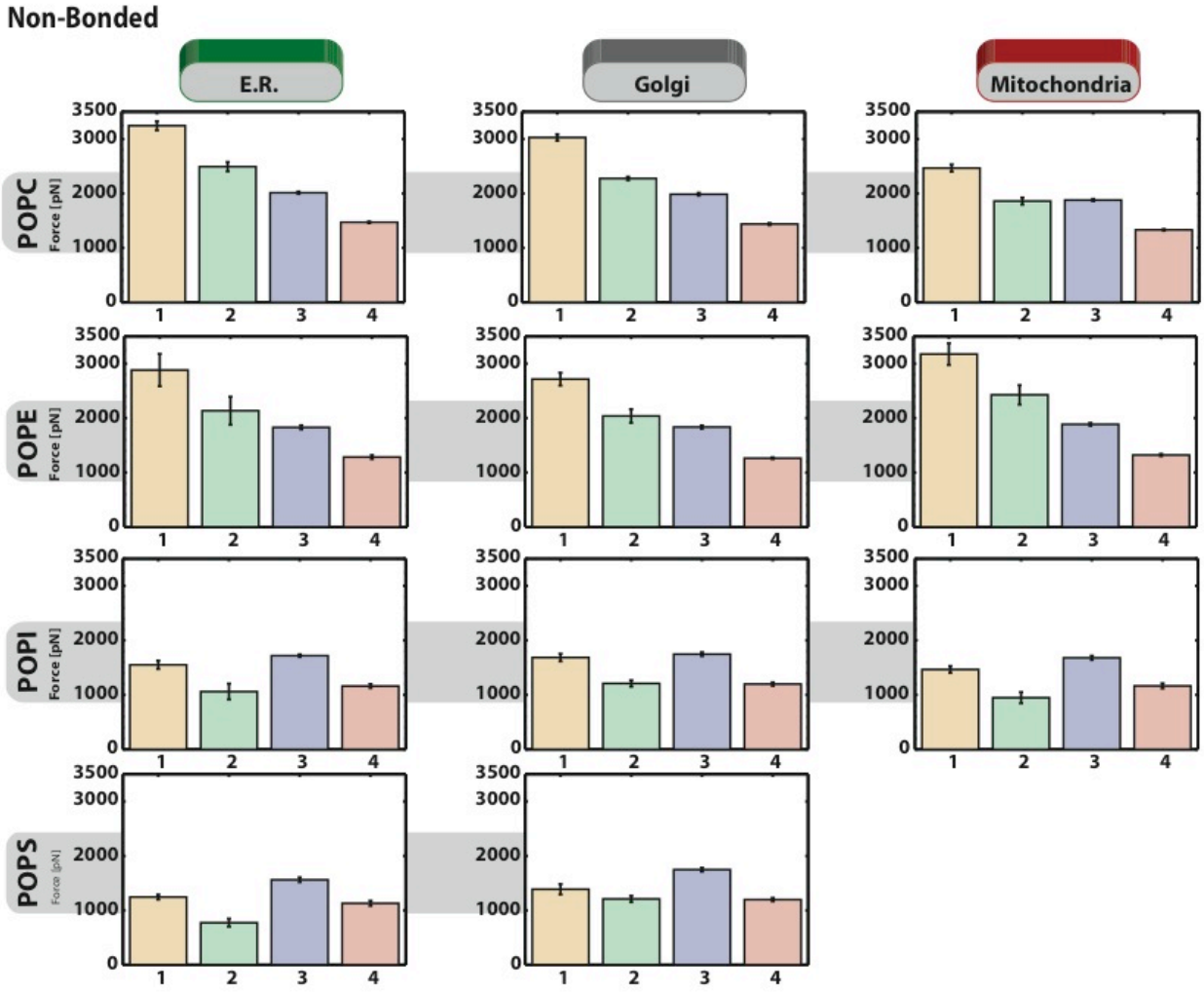

Figure S5. Contribution of non-bonded interactions. High forces are generated within headgroup and phosphate region of zwiterrionic lipids but surprisingly anionic lipids show similar forces in all segments.

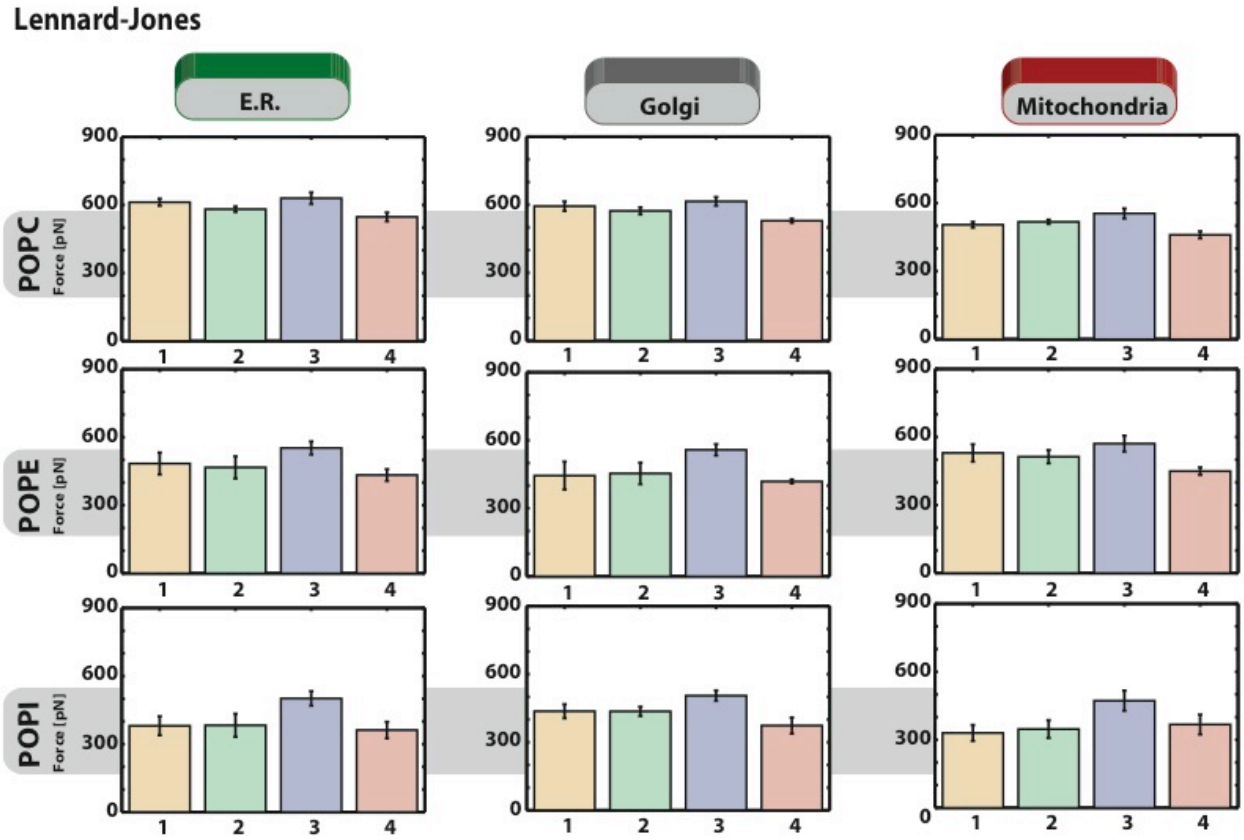

Figure S6. Contribution of LJ non-bonded interactions for all lipids in all membranes. LJ contributed equally to all segments, showing no effect based on segments.

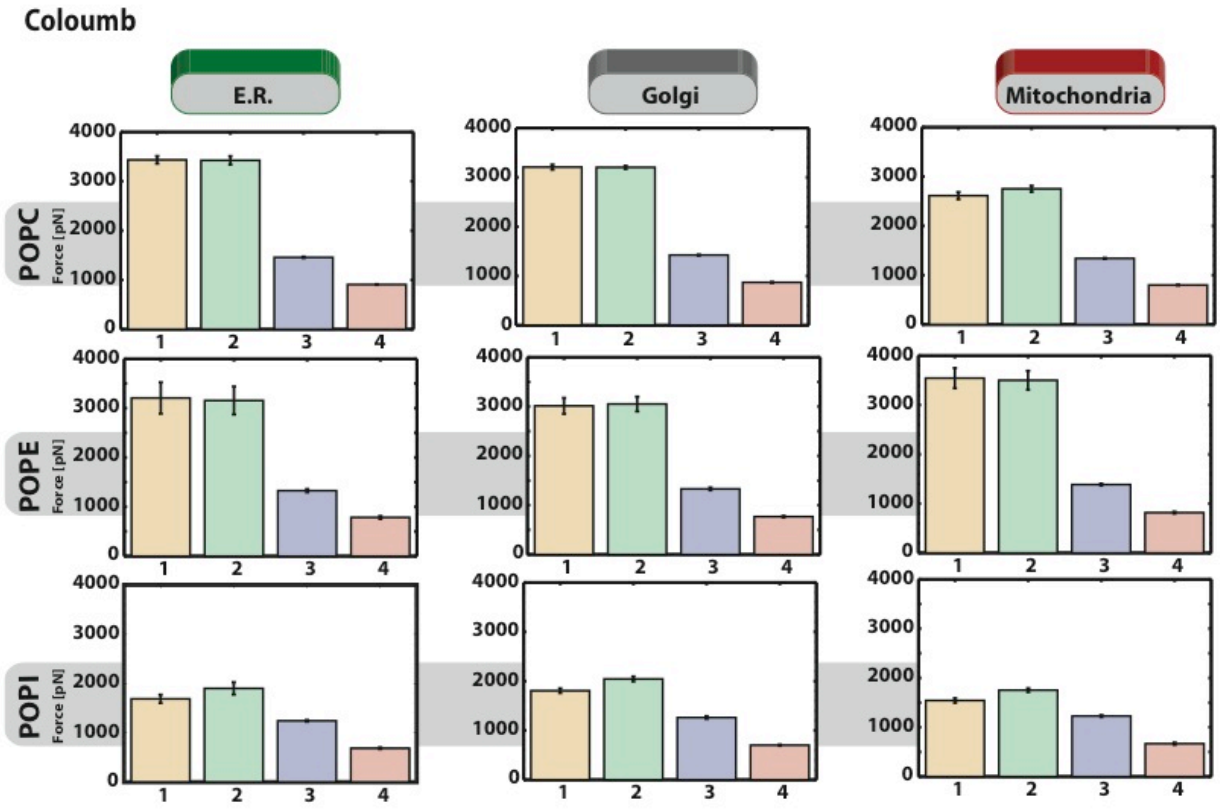

Figure S7. Contribution of Coulombic non-bonded interactions for all lipids in all membranes.

Reference List

1. van Meer, G.; Voelker, D. R.; Feigenson, G. W., Membrane lipids: where they are and how they behave. *Nature reviews. Molecular cell biology* **2008**, 9, 112-24.
2. van Golde, L. M.; Raben, J.; Batenburg, J. J.; Fleischer, B.; Zambrano, F.; Fleischer, S., Biosynthesis of lipids in Golgi complex and other subcellular fractions from rat liver. *Biochimica et biophysica acta* **1974**, 360, 179-92.