

Supplementary Information for:

Pair Interactions among Ternary DPPC/POPC/Cholesterol

Mixtures in Liquid-Ordered and Liquid-Disordered Phases

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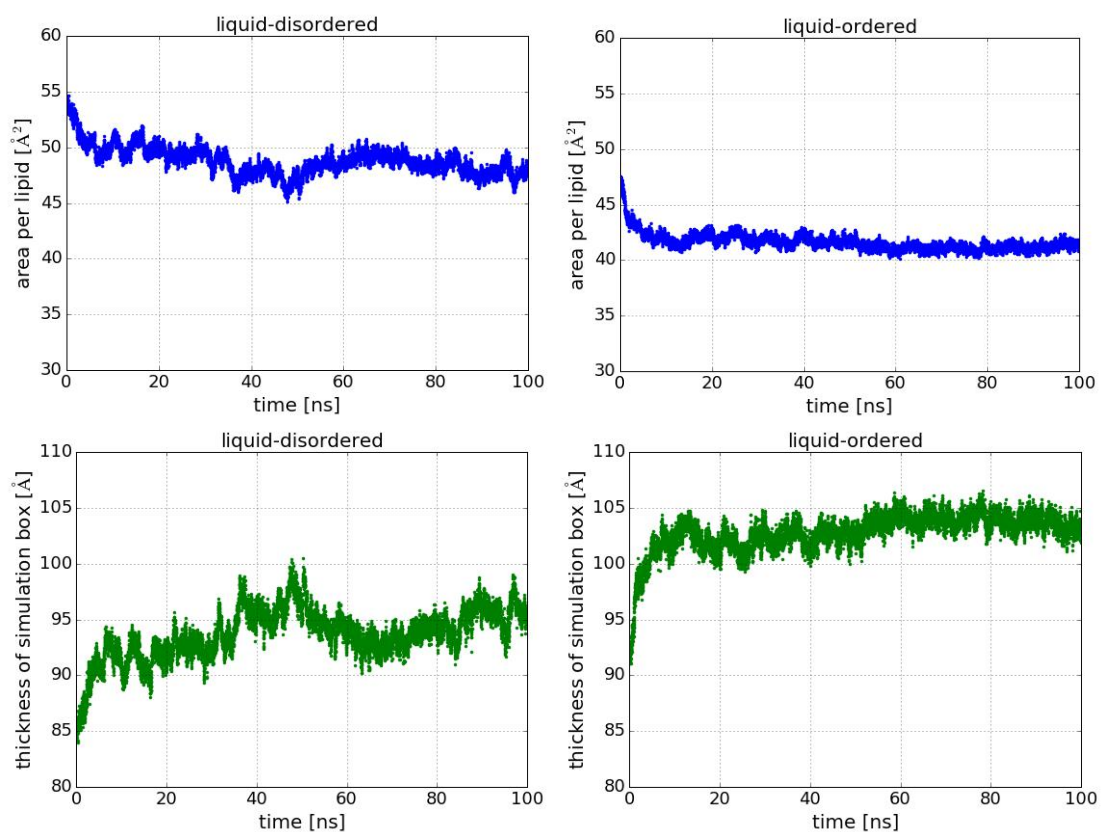


Figure S1: Area per lipid (top figures) and thickness of the simulation box (bottom figures) as a function of time during 100 ns equilibration for systems in the liquid-disordered and liquid-ordered phases.

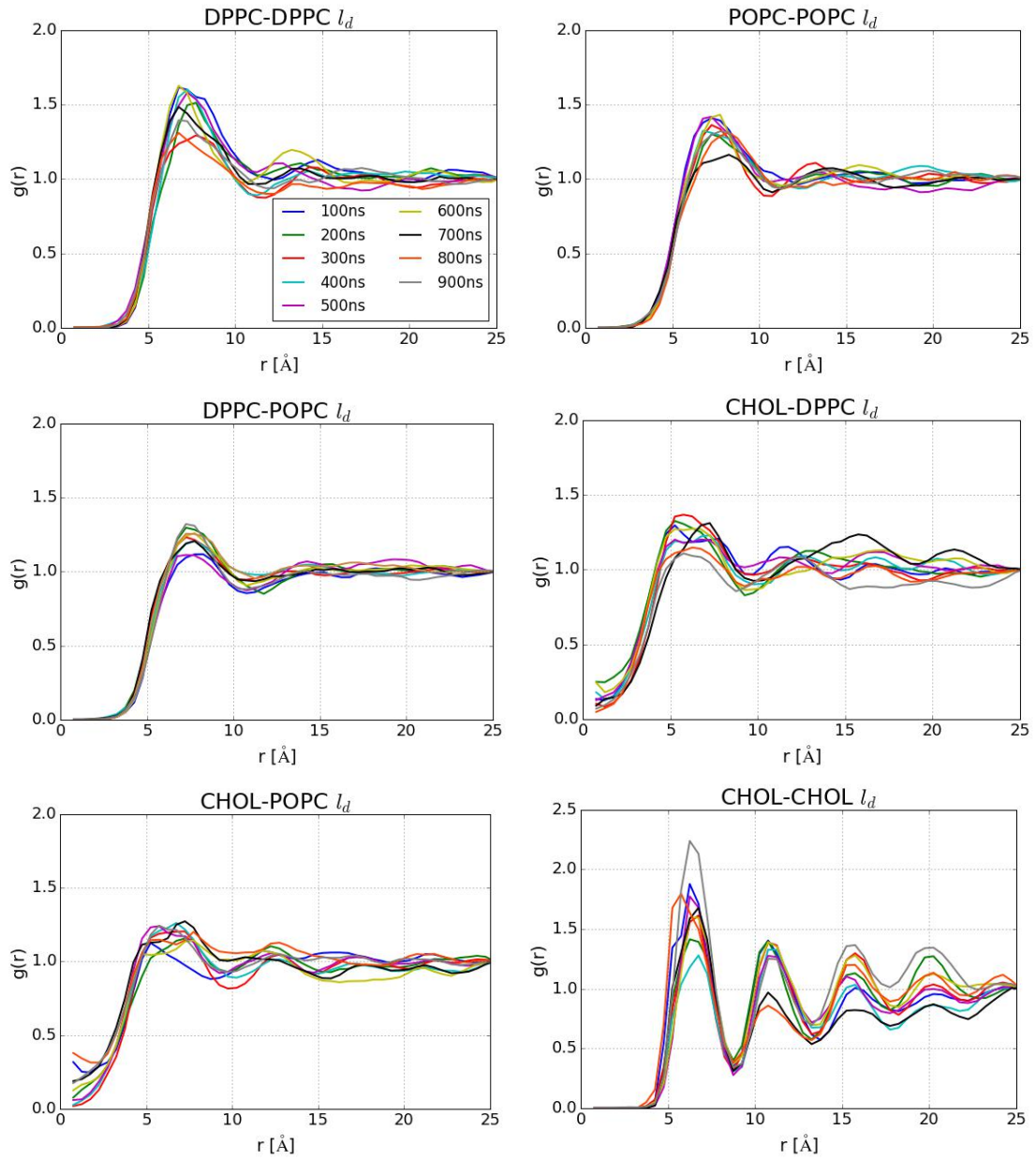


Figure S2: Lateral radial pair distribution function $g(r)$ for DPPC/POPC/CHOL mixtures in the l_d phase calculated from every 100 ns time interval of the 900 ns production run.

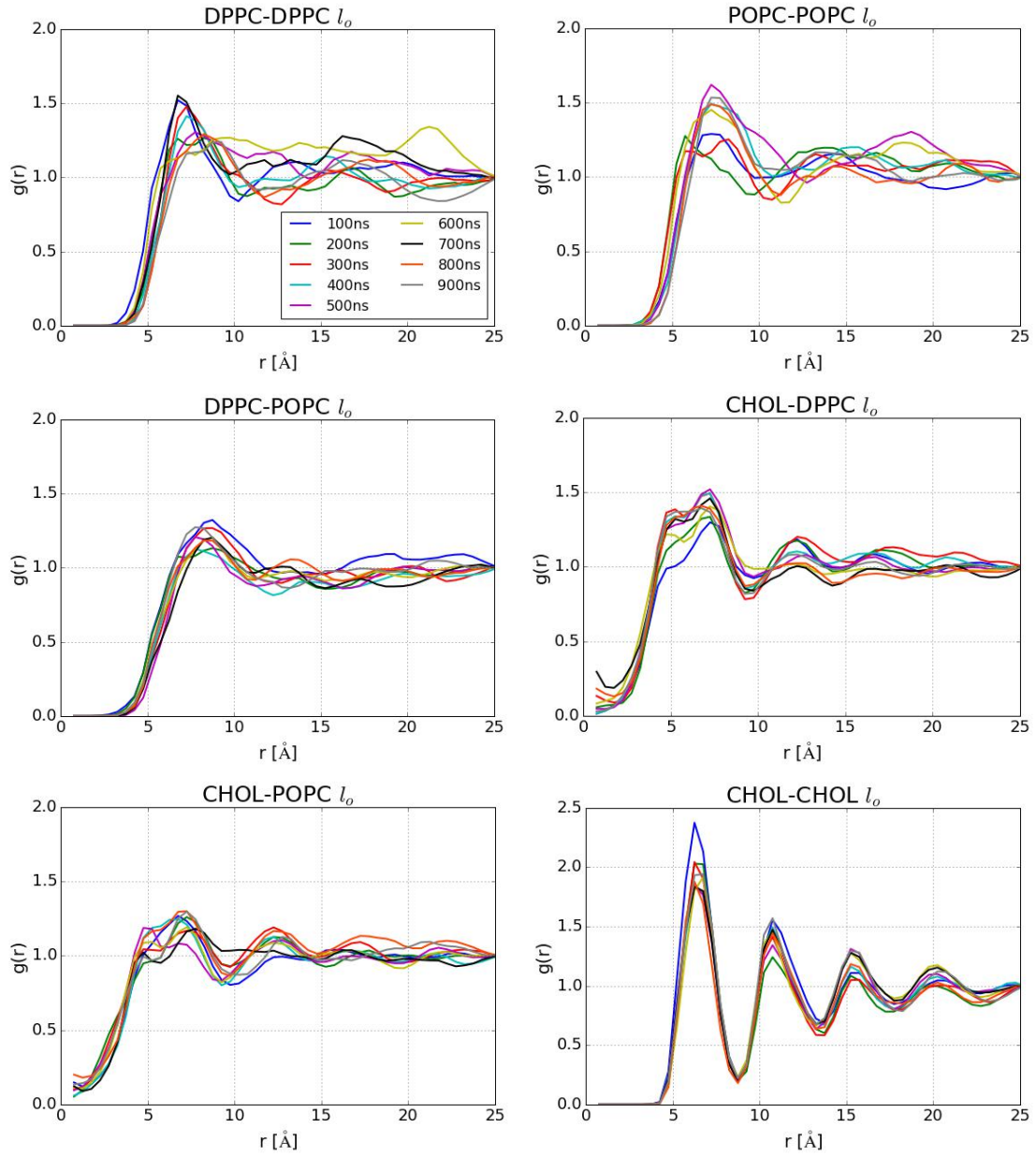


Figure S3: Lateral radial pair distribution function $g(r)$ for DPPC/POPC/CHOL mixtures in the l_o phase calculated from every 100 ns time interval of the 900 ns production run.

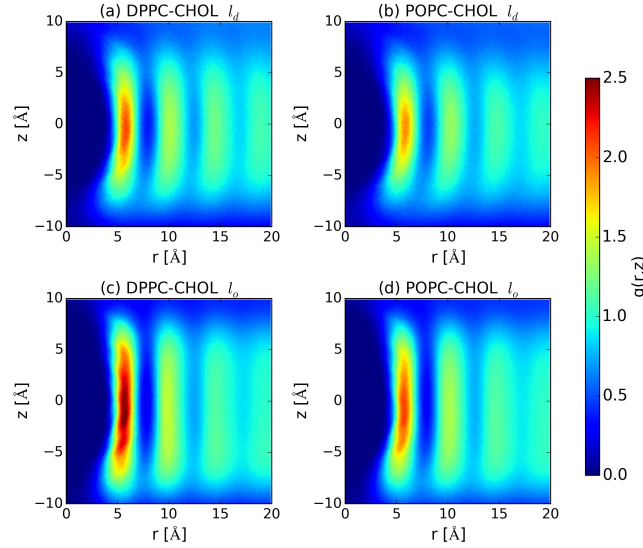


Figure S4: Lateral-vertical radial distribution function $g(r, z)$ between the center of mass of cholesterol and the carbon atoms of lipid tails.

The pull for CHOL-DPPC in the l_o phase and the push for CHOL-POPC (Fig. 3b in the paper) agree well with the experiments by Regen et al.^[1] and indicate that the interactions of cholesterol-saturated phospholipids and those of cholesterol-monounsaturated phospholipids are different. To have a more intuitive understanding of the effect of lipid saturation on cholesterol-lipid interactions, we obtain the lateral-vertical radial distribution function $g(r, z)$ between cholesterol and carbon atoms in lipid tails, where r is the lateral distance between the centers of mass (COM) of cholesterol and a lipid tail carbon, and z is the vertical distance between the COM of cholesterol and a lipid tail carbon. $z=0$ is defined as the COM of cholesterol, and the positive direction of z is towards the membrane-water interface. As shown in Figure S4, DPPC has higher densities around CHOL in the z direction compared with POPC in a given phase. As the phase changes from l_d to l_o , the boundary curves between cholesterol and lipids are straightened for both DPPC and POPC, indicating that the change of lateral radial distribution function $g(r)$ in different phases (Fig.2 in the paper) may be attributed to the change of packing in the vertical direction. This straightening effect is consistent with the condensing effect of cholesterol on saturated and unsaturated lipid chains, which lengthens phospholipid molecules complexed with cholesterol and thickens lipid bilayers^[2]. The vertical packing densities for DPPC-CHOL are enhanced significantly in the l_o phase, corresponding to a favorable pull^[1]. Although the POPC-CHOL interaction is a significant push in the l_d phase, they mix more ideally in the vertical direction as the lipid tails become more ordered in the l_o phase, resulting in neither attractive nor repulsive interactions in l_o phase^[1,3]. Consequently, the lateral-vertical packing property $g(r, z)$ provides a straightforward point of view to examine the interactions of cholesterol-lipid, and explain well the change of lateral packing property $g(r)$ in line with experiments.

[1] C. Wang, M. R. Krause and S. L. Regen, *Journal of the American Chemical Society*, 2015, **137**, 664–666.

[2] W.-C. Hung, M.-T. Lee, F.-Y. Chen and H. W. Huang, *Biophys. J.*, 2007, **92**, 3960–3967.

[3] M. R. Krause, T. a. Daly, P. F. Almeida and S. L. Regen, *Langmuir*, 2014, **30**, 3285–3289.