AIMS Biophysics

AIMS Biophysics, 10(4): 482–502.
DOI: 10.3934/biophy.2023027
Received: 12 August 2023
Revised: 22 October 2023
Accepted: 01 November 2023
Published: 30 November 2023

http://www.aimspress.com/journal/biophysics

Research article

Cholesterol affected dynamics of lipids in tailor-made vesicles by ArcVes software during multi micro second coarse grained molecular dynamics simulations

Chia-Wen Wang, Meng-Han Lin and Wolfgang B. Fischer*

Institute of Biophotonics, School of Biomedical Science and Engineering, National Yang Ming Chiao Tung University, Taipei, Taiwan

* **Correspondence:** Email: wfischer@nycu.edu.tw; Tel: +886228267394, Fax: +886228235460.

Suppl. Table 1. Values of the area-per-lipid (apl) [nm^2/lipid] are given for the mixed vesicles POPC/CHOL, DOPC/CHOL, and POPC/DOPC, pure vesicles POPC, DOPC, and POPC-5 as well of the respective dry and wet membrane patches. Values are calculated for the equilibrated initial conditions (initial) before the production run as well as the averaged values from the MD simulations (simulation) and presented with standard deviation. "i\o" = number separated for inner (i) and outer leaflet (o). "//" = separating dry and wet Martini systems (dry // wet).

Area per lipid [nm^2/lipid]			
Vesicle	POPC/CHOL	DOPC/CHOL	POPC/DOPC
Initial (i\o)	0.69\0.64	0.68\0.65	0.62\0.62
Simulation (i\o)	0.52 ± 0.0\0.49 ± 0.0	0.49 ± 0.0\0.56 ± 0.01	0.69 ± 0.01\0.67 ± 0.0
Vesicle	POPC	DOPC	POPC-5
Initial (i\o)	0.78\0.81	0.64\0.62	0.67\0.62
Simulation (i\o)	0.66 ± 0.01\0.74 ± 0.0	0.69 ± 0.0\0.68 ± 0.0	0.79 ± 0.01\0.68 ± 0.0
Patch	POPC/CHOL	DOPC/CHOL	POPC/DOPC
Initial (i\o)	0.66\0.66 // 0.53\0.53	0.66\0.66 // 0.56\0.56	0.66\0.67 // 0.68\0.68
Simulation (i\o)	0.66 ± 0.01\0.66 ± 0.01 // 0.52 ± 0.01\0.52 ± 0.01	0.66 ± 0.01\0.66 ± 0.01 // 0.55 ± 0.01\0.55 ± 0.01	0.66 ± 0.0\0.66 ± 0.0 // 0.68 ± 0.01\0.69 ± 0.01
Patch	POPC	DOPC	
Initial (i\o)	0.66\0.66 // 0.67\0.67	0.66\0.66 // 0.70\0.70	
Simulation (i\o)	0.66 ± 0.0\0.66 ± 0.0 // 0.67 ± 0.01\0.67 ± 0.01	0.66 ± 0.0\0.66 ± 0.0 // 0.70 ± 0.01\0.70 ± 0.01	

Suppl. Table 2. Averaged values for radii [nm] of the vesicles POPC, DOPC, and POPC-5, the thickness [nm] of the membranes, the number of lipids [count], as well as their diffusivity [10^{-7} cm^2 s^{-1}]. Values are given for the equilibrated initial conditions (initial) before the production run as well as averaged values from the MD simulations (simulation) and presented with standard deviation. "i\o" = number separated for inner (i) and outer leaflet (o).

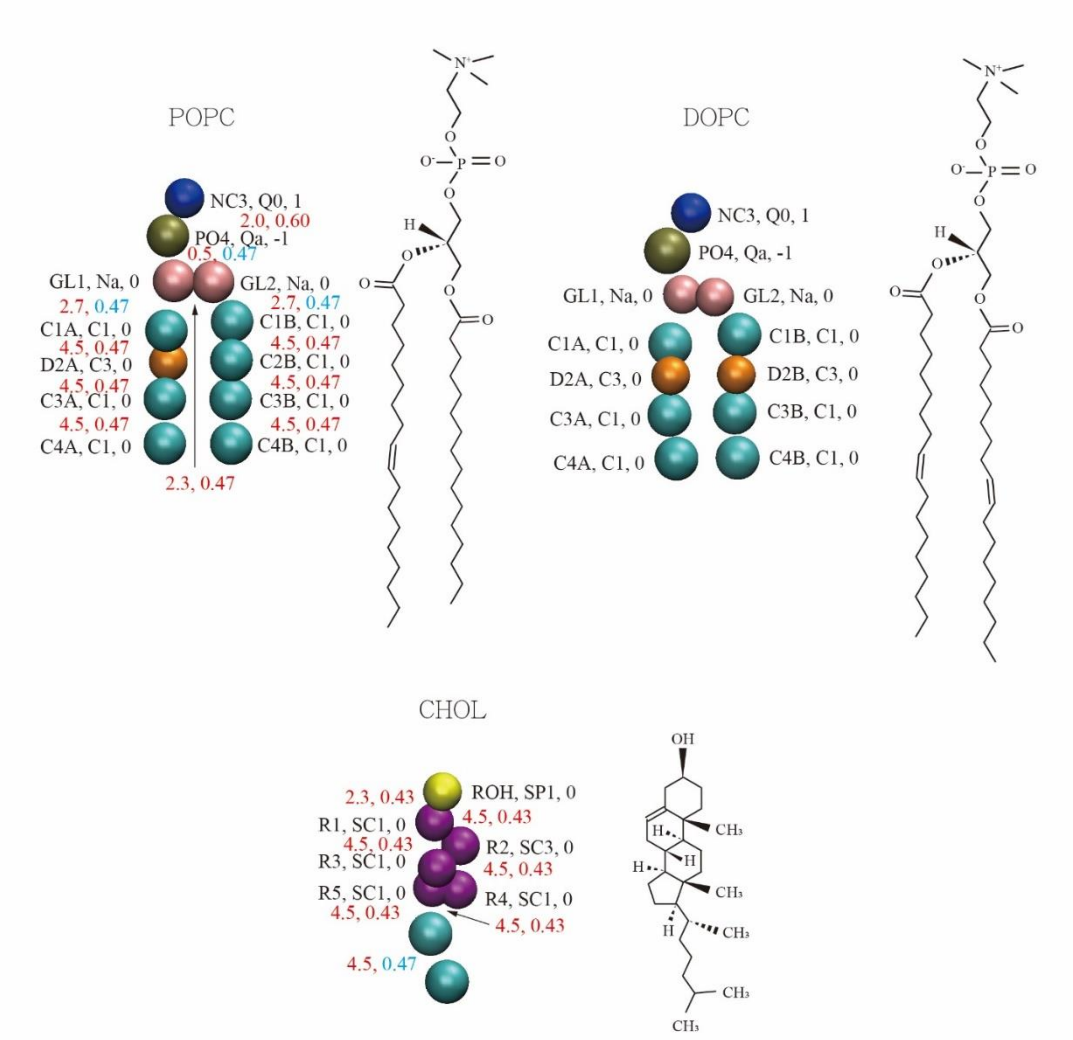
	POPC	DOPC	POPC-5
Radius [nm]			
Initial	10.3 ± 0.8	9.8 ± 0.9	5.1 ± 0.9
Simulation	9.7 ± 0.1	10.2 ± 0.1	5.4 ± 0.0
Δr	0.00 ± 0.03	0.00 ± 0.03	0.00 ± 0.03
Thickness [nm]			
Initial	3.6 ± 0.2	3.9 ± 0.1	3.9 ± 0.2
Simulation	3.9 ± 0.0	3.9 ± 0.0	3.8 ± 0.0
Δnm	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Number of lipids [count]			
Initial (i\o)	1424 \ 1873	1498 \ 2259	262 \ 641
Simulation (i\o)	1426 ± 2 \ 1871 ± 2	1499 ± 2 \ 2258 ± 2	263 ± 1 \ 640 ± 1
Diffusivity [10^{-7} cm^2 s^{-1}]			
i	10.4 ± 0.2	13.2 ± 0.4	8.9 ± 0.6
o	17.5 ± 0.3	18.4 ± 0.5	15.8 ± 0.8

Suppl. Table 3. Averaged values for thickness [nm] of the membrane patches POPC and DOPC, the thickness [nm] of the membranes, the number of lipids [count], as well as their diffusivity [10^{-7} cm^2 s^{-1}]. Values are given for the equilibrated initial conditions (initial) before the production run as well as averaged values from the MD simulations (simulation) and presented with standard deviation. "i\o" = number separated for inner (i) and outer leaflet (o). "//" = separating dry and wet Martini systems (dry // wet).

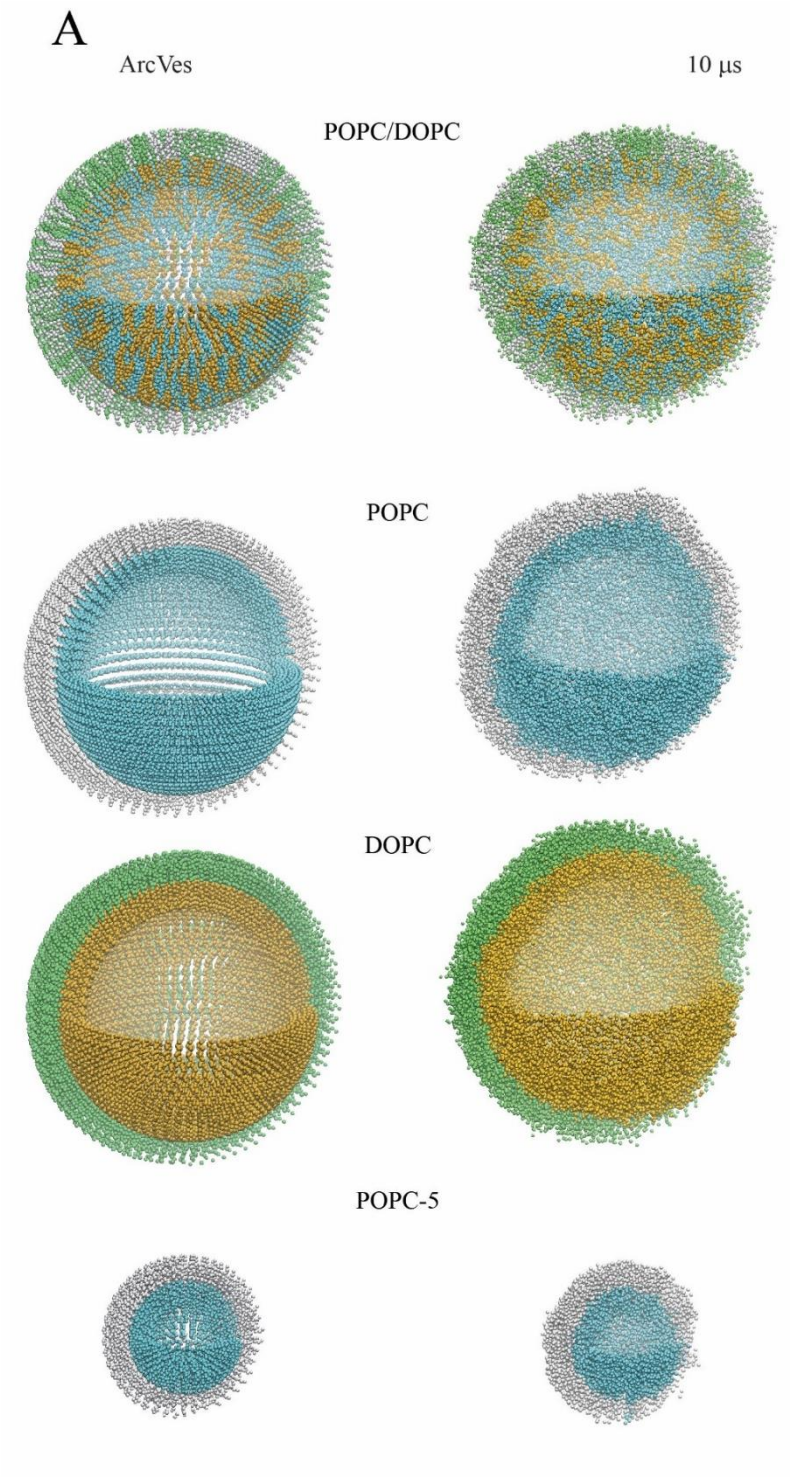
	POPC	DOPC
Thickness [nm]		
Initial	3.5 ± 0.3 // 3.9 ± 0.3	3.6 ± 0.3 // 3.8 ± 0.3
Simulation	3.7 ± 0.0 // 3.9 ± 0.0	3.7 ± 0.0 // 3.8 ± 0.0
Δnm	0.0 ± 0.0 // -0.0 ± 0.0	-0.0 ± 0.0 // -0.0 ± 0.0
Number of lipids [count]		
Initial	256\256	256\256
Simulation (i\o)	256 ± 0\256 ± 0 // 256 ± 0\256 ± 0	255 ± 0\255 ± 0 // 256 ± 0
Diffusivity [10^{-7} cm^2 s^{-1}]		
i	4.1 ± 0.0 // 7.9 ± 0.0	5.1 ± 0.0 // 8.9 ± 0.0
o	4.0 ± 0.0 // 7.7 ± 0.0	5.7 ± 0.0 // 9.0 ± 0.0

Suppl. Table 4. Averaged values for thickness [nm] of the membrane patches POPC/CHOL, DOPC/CHOL and POPC/DOPC, the number of lipids [count], as well as their diffusivity [10^{-7} cm^2 s^{-1}]. Values are given for the equilibrated initial conditions (initial) before the production run as well as averaged values from the MD simulations (simulation) and presented with standard deviation. "/" = different types of lipids or molecules. "i\o" = number separated for inner (i) and outer leaflet (o). "//" = separating dry and wet Martini systems (dry // wet).

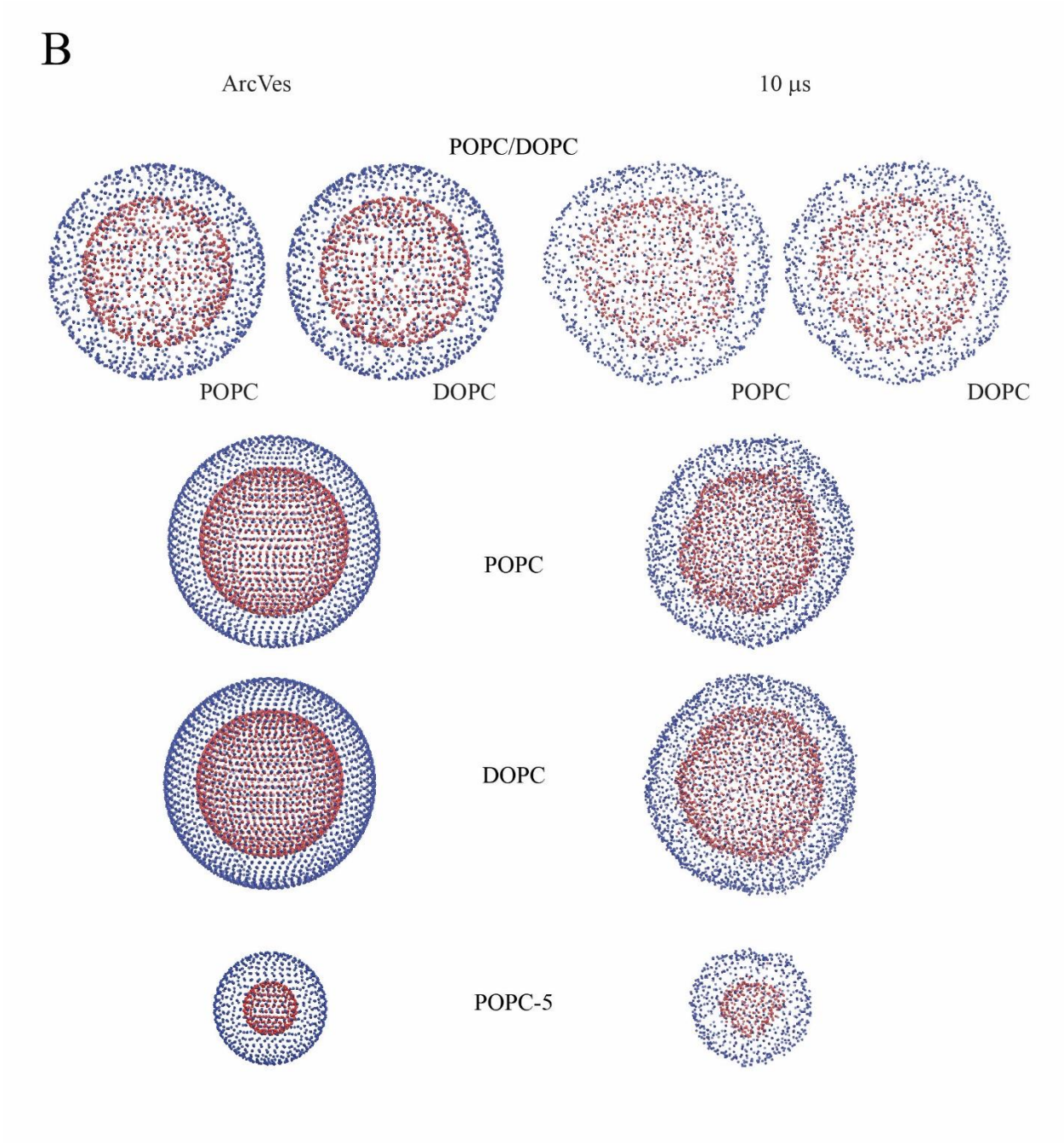
	POPC/CHOL	DOPC/CHOL	POPC/DOPC
Thickness [nm]			
Initial	3.3 ± 0.2 // 4.0 ± 0.3	3.3 ± 0.2 // 3.9 ± 0.3	3.5 ± 0.3 // 3.8 ± 0.3
Simulation	3.3 ± 0.0 // 4.1 ± 0.0	3.2 ± 0.0 // 3.9 ± 0.0	3.7 ± 0.0 // 3.8 ± 0.0
Δnm	0.0 ± 0.0 // 0.0 ± 0.0	0.0 ± 0.0 // 0.0 ± 0.0	0.0 ± 0.0 // 0.0 ± 0.0
Number of lipids [count]			
Initial	179/77	179/77	128/128
Simulation (i\o)	17 ± 1/76 ± 5 \ 179 ± 1/ 78 ± 5 // 179 ± 0/77 ± 3 \ 179 ± 0/ 77 ± 3	179 ± 1/77 ± 5 \ 179 ± 1/77 ± 4.9 // 179.0 ± 0.2/76.7 ± 3.1 \ 179.0 ± 0.2/77.1 ± 3.1	128.2 ± 0.5/128.0 ± 0.2 \ 127.9 ± 0.5/128.0 ± 0.2 // 128.6 ± 1.0/128.0 ± 0.1 \ 127.4 ± 1.0/128.0 ± 0.1
Lipid content [%]			
Initial	70:30	70:30	50:50
i	70.1± 1.4:29.9 ± 1.4 // 70.0 ± 0.8:30.0 ± 0.8	69.9 ± 1.4:30.1 ± 1.4 // 70.0 ± 0.8:30.0 ± 0.8	50.0 ± 0.1:50.0 ± 0.1 // 50.1± 0.2:49.9 ± 0.2
o	69.8 ± 1.4:30.3 ± 1.4 // 69.8 ± 0.8:30.2 ± 0.8	70.0 ± 1.3:30.0 ± 1.3 // 69.9 ± 0.8:30.1 ± 0.8	50.0:50.0 // 49.9 ± 0.2:50.1 ± 0.2
Diffusivity [10^{-7} cm^2 s^{-1}]			
i	2.7 ± 0.0/2.8 ± 0.0 // 5.4 ± 0.0 / 5.3 ± 0.0	2.7 ± 0.0/2.2 ± .0 // 4.1 ± 0.0 / 5.4 ± 0.0	4.8 ± 0.0/5.1 ± 0.0 // 7.5 ± 0.0 / 7.0 ± 0.0
o	2.7 ± 0.0 / 2.7 ± 0.0 // 3.80 ± 0.0 / 5.40 ± 0.0	2.3 ± 0.0 / 2.5 ± 0.0 // 4.5 ± 0.0 / 5.1 ± .02	5.0 ± 0.0 / 4.4 ± 0.0 // 8.0 ± 0.0 / 9.0 ± 0.0



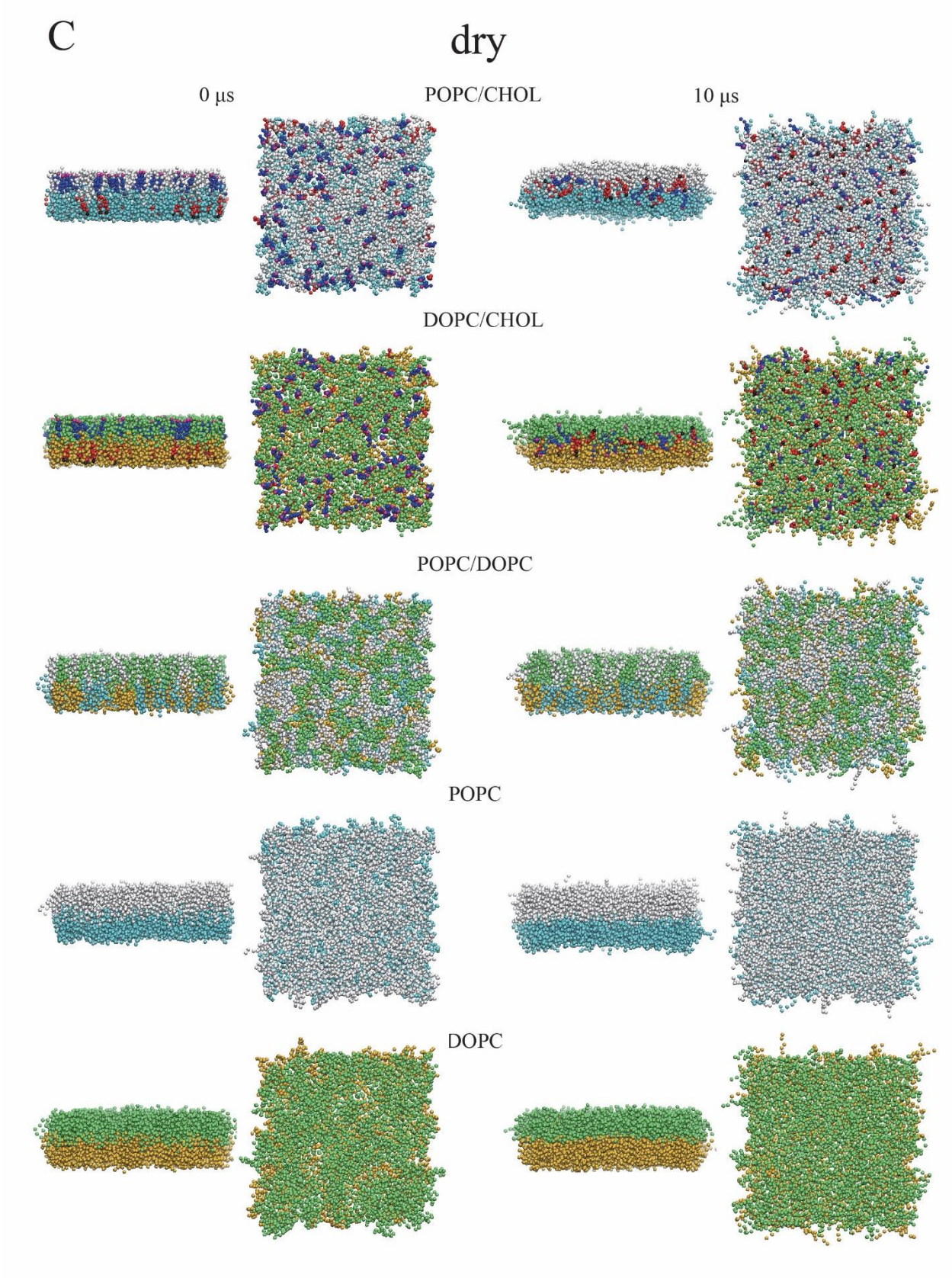
Suppl. Figure 1. Coarse grained (CG) representations of the lipid molecules POPC, DOPC and CHOL [1,2] according to the ff of dry Martini v2.1 [3]. In addition to the spheres, atom/group, bead type and charges are listed. The interaction strength between the spheres ε_{ij} (i, j, denotes different spheres) is given as red numbers (kJ/mol), e.g. 2.0, followed by the value for closest distance of approach between two particles, σ_{ij}, (red numbers) as e.g. 0.60. The σ-numbers in blue are showing the standard distance of 0,47 nm. The numbers are the same for DOPC and therefore not shown. The lipid headgroup region for POPC and DOPC is represented by a blue and tan sphere representing the amino moiety (NC3 (atom/group), Q0 (bead type), 1 charge)) and phosphate (PO4, Qa, -1) moiety, respectively. The glycerol is represented by two pink spheres (GL1, Na, 0, and GL2, Na, 0). The hydrophobic tails for POPC and DOPC are shown as cyan spheres for sp^3 hybridized carbon atoms (C1A/B to C4A/B, C1, 0) and orange spheres for the two $2p^2$ hybridized carbon atoms of the double bonds (D2A, C3, 0). The hydrophobic tail of CHOL is also shown in cyan spheres (C1 to C2, SC1,0). The steroid nucleus is shown in violet spheres with the sp3 carbons as (R1 to R5, SC1, 0, and the sp2 carbons (the double bond system as R2, SC3,0). The hydroxyl group is shown as yellow sphere (ROH, SP1, 0). The 2D model are generated using PubChem Sketcher V2.4 (last used May 2023).



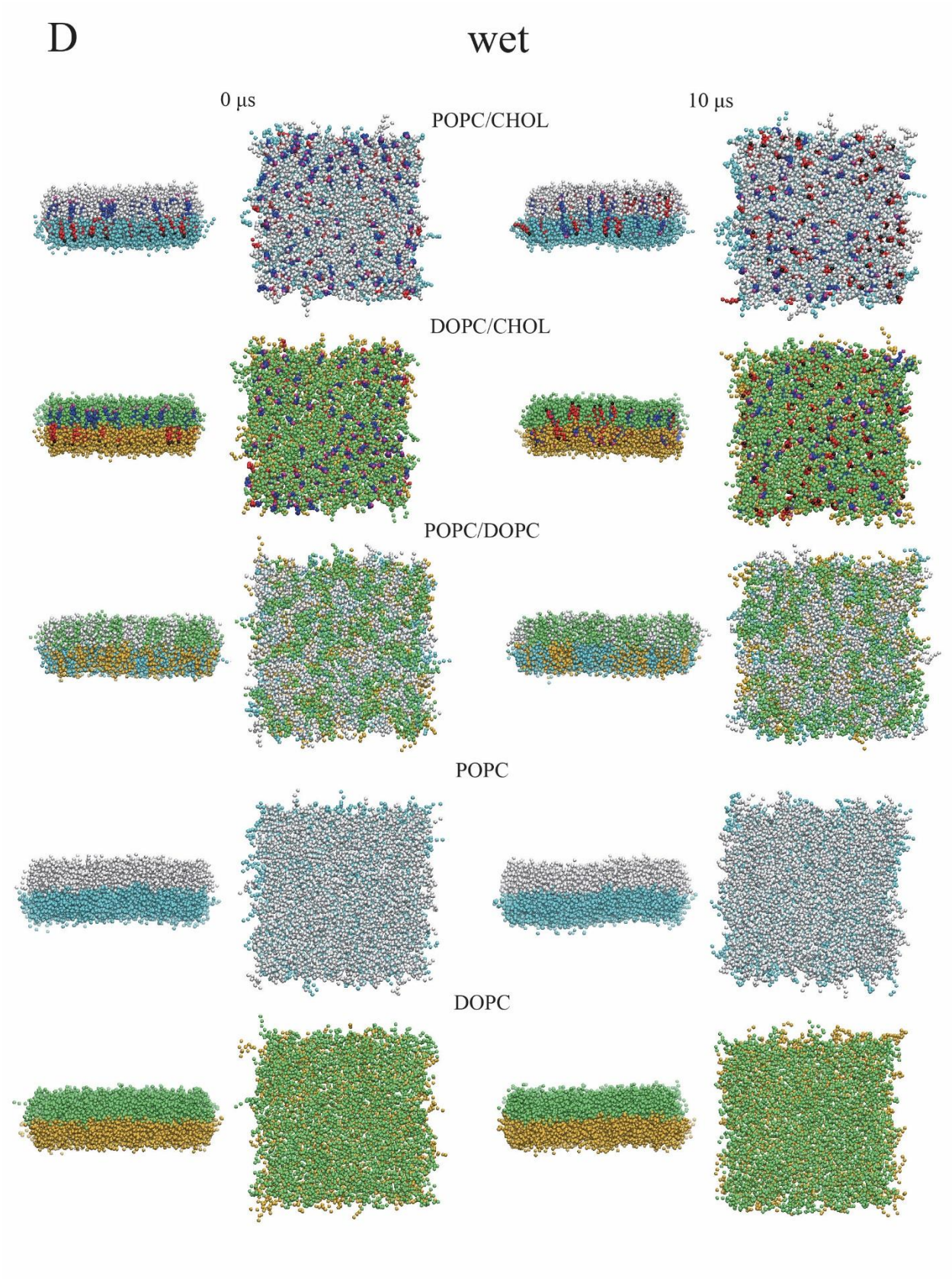
Suppl. Figure 2 (cont.)



Suppl. Figure 2 (cont.)

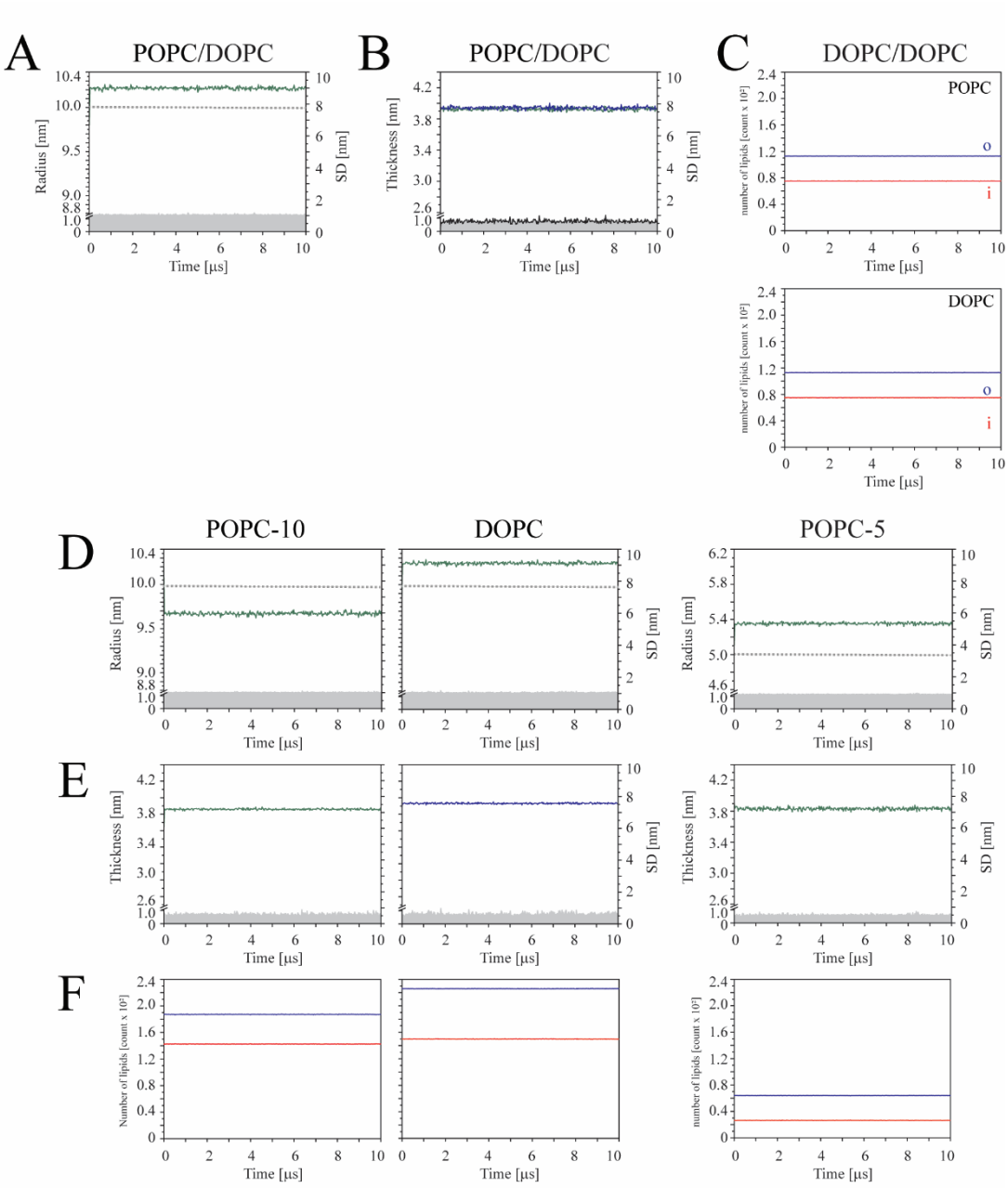


Suppl. Figure 2 (cont.)

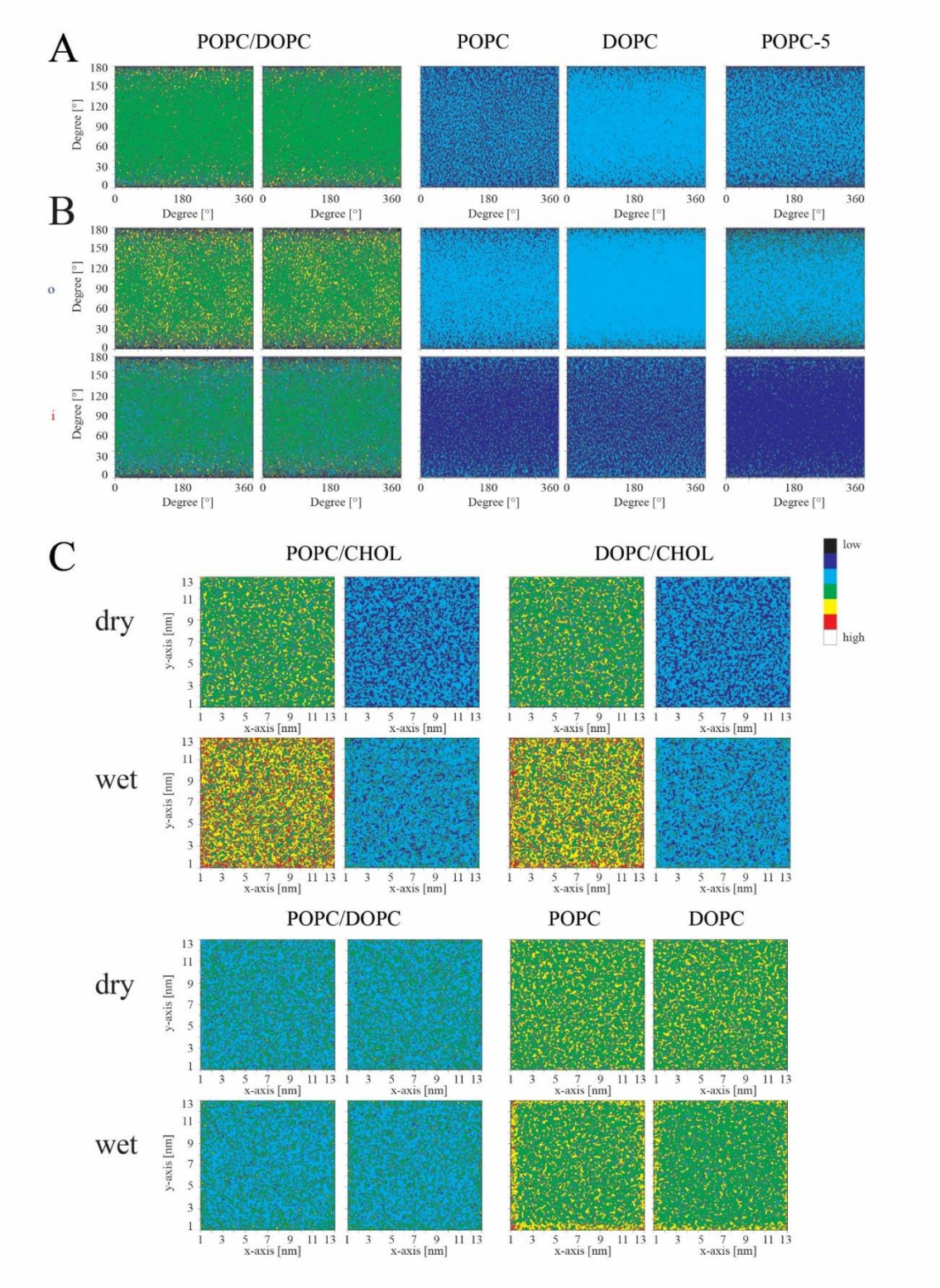


Suppl. Figure 2 (cont.)

Suppl. Figure 2. (A) Coarse grained (CG) models of pure and mixed vesicles from ArcVes (left column) and at 10 μs (right column) of MD simulation using the dry MARTINI v2.2 force field (ff). From top to bottom: mixed vesicles, POPC/DOPC, vesicles of pure POPC molecules (grey spheres for lipid molecules in the outer leaflet, light blue for inner leaflet), and DOPC (green and yellow for outer and inner lipid molecules) all with radii of 10 nm, as well as a vesicle of POPC (color coding as before) with a radius of 5 nm (POPC-5). The vesicles allow insight into the interior by omitting half of the molecules of the outer leaflet and one quarter of the molecules of the inner leaflets. (B) The same mixed vesicles showing the lipids separately for respective POPC and DOPC ('PO4'-spheres in blue for outer and red for inner leaflet) and the respective cholesterol molecules ('ROH'-spheres in blue for outer and red for inner leaflet). (C) Patches of single type of lipids and a binary mixture in side and top view at 0 μs (left column) and 10 μs (right column) using dry MARTINI v2.1 ff (dry). From top to bottom: POPC/CHOL, DOPC/CHOL, POPC/DOPC, POPC and DOPC. (D) Simulations of the similar lipid patches using a hydrated lipid membrane system using MARTINI v2.2 ff (wet). Color coding of the lipid molecules in the patches with cholesterol represented by blue (in one leaflet) and red (in the other leaflet) spheres with the oxygen highlighted in magenta for outer and black for inner leaflet is the same as in (A) and Figure 1A.



Suppl. Figure 3. Time dependent calculate properties from the simulations of vesicle consisting of a lipid mixture of POPC/DOPC and vesicles consisting of single type of lipids POPC, DOPC, and POPC with radius of 5 nm (POPC-5). For the single-type/mixed vesicles, (A/D) radius [nm], (B/E) thickness [nm], and (C/F) number of lipids [count $\times 10^2$]. Thickness values of POPC and DOPC are shown in green and blue lines. Standard deviations (SD [nm]) are shown in grey area representation in radius-plot and for POPC in thickness-plot. The SD for DOPC in thickness-plot is shown by black line. The value for the ArcVes setup-radius is marked as a light grey dashed line. In the plots for the number of lipids, values are all shown in blue and red for outer (o) and inner leaflets (i), respectively.



Suppl. Figure 4

Suppl. Figure 4. 2D projection of the density [count/nm^2] of the vesicles composed of a mixture of POPC/DOPC, as well as of pure POPC, DOPC, and POPC-5 calculated from a 10 μs MD simulation. The density is calculated for both leaflets. (A) Density of both

leaflets. (B) Density of the outer (upper row, o) ad inner leaflet (lower row, i). The calculation is done by flattening the entire vesicles resulting in axis ranging from 0°−180° and to 0°−360°. (C) 2D projection of the density [count/nm^2] of the membrane patches composed of POPC/CHOL, DOPC/CHOL, POPC/DOPC, POPC and DOPC. The upper rows show the density calculated from the simulations using dry MARTINI v2.1 ff, the lower rows show the density for the wet simulations (MARTINI v2.2 ff). The color coding goes from low to high density as black < dark blue < light blue < green < yellow < red < white.

References

1. Marrink, SJ, de Vries AH, Harroun TA, et al. (2008) Cholesterol shows preference for the interior of polyunsaturated lipid membranes. *J Am Chem Soc* 130: 10−11. https://doi.org/10.1021/ja076641c
2. Risselada HJ, Marrink SJ (2008) The molecular face of lipid rafts in model membranes. *Proc Natl Acad Sci USA* 105: 17367−17372. https://doi.org/10.1073/pnas.0807527105
3. Arnarez C, Uusitalo JJ, Masman MF, et al. (2015) Dry Martini, a coarse-grained force field for lipid membrane simulations with implicit solvent. *J Chem Theory Comput* 11: 260−275. https://doi.org/10.1021/ct500477k

AIMS Press