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Supplemental Information

Lipid Bilayer Composition Influences the Activity of the Antimicrobial Peptide Dermcidin Channel

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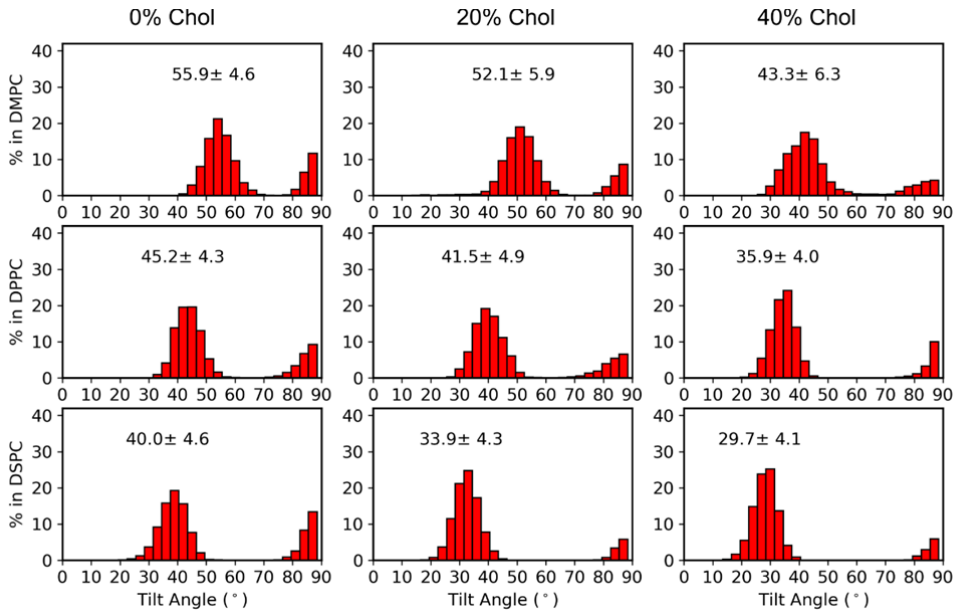
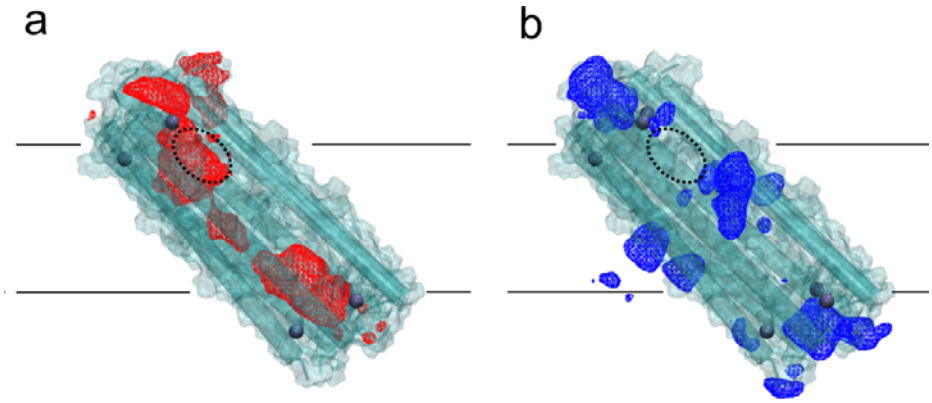
Song et al., SI Fig. S1



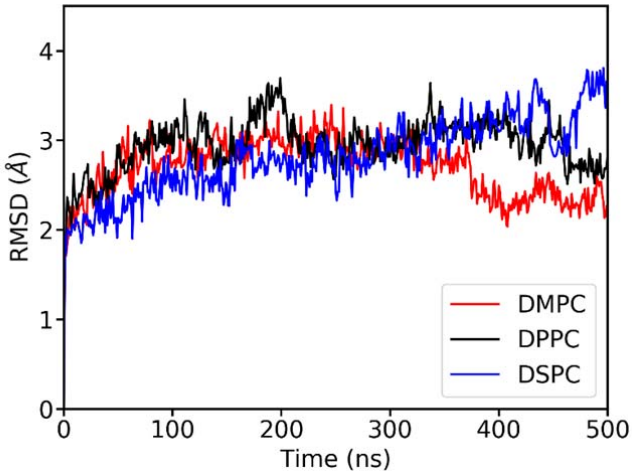
SI Figure S1: Tilt angle distributions of the DCD oligomer relative to the bilayer normal in DMPC (upper row), DPPC (middle row) and DSPC (lower row) lipids, with 0%, 20% and 40% cholesterol in the coarse grain simulations. This analysis was on the 200 ns to 500 ns segments of each trajectory. The mean values and standard deviations of the tilt angles were calculated for the hexamer population in a transbilayer orientation (i.e. with a tilt angle of less than 70°).

Song et al., SI Fig. S2



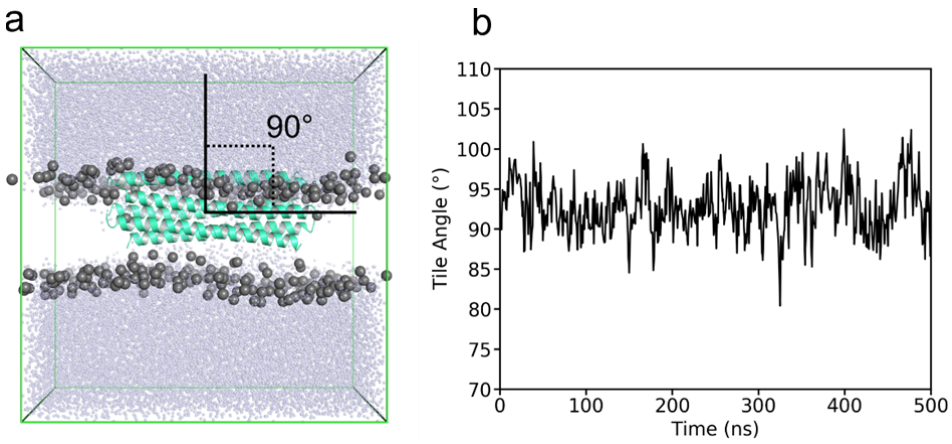
SI Figure S2: The ion number density isosurface around the DCD channel, for the (a) Cl^- and (b) Na^+ ions respectively. The density was calculated from a computational electrophysiology simulation of the DCD in a DMPC bilayer, with a transmembrane potential corresponding to an asymmetric ion distribution across the lipid bilayer (illustrated with the straight black lines). The density isosurface was calculated and rendered with VMD with the same value of 0.0005 $Å^{-3}$ (equivalent to ca. 0.8 M) for both types of ions. The dashed ellipses indicate the rate-limiting entrance to the channel interior along the ion permeation pathway, which is more accessible to Cl^- ions.

Song et al., SI Fig. S3



SI Figure S3: The root mean squared deviation (RMSD) of the Cα atoms of the DCD hexamer in the single-layer DMPC, DPPC and DSPC atomistic simulations. The calculations were done for the alpha carbon atoms. The conformation of DCD was relatively stable, and did not show correlation with its tilt angle in the bilayers. Unlike the RMSD shown here, the tilt angle did not reach a steady value until about 350 ns, as shown in Fig. 4a.

Song et al., SI Fig. S4



SI Figure S4: The parallel orientation of the DCD to the lipid bilayer is (meta)stable. (a) The initial configuration of the atomistic system transformed from the CG result by using the Martini 'backward' tool. (b) The tilt angle evolution of the DCD channel in the atomistic MD simulation, showing that the parallel orientation (tilt angle 90°) was (meta)stable.

Song et al., SI Table S1

	Mean Value of the Tilt Angle (°)	STD of the Tilt Angle (°)	SEM of the Tilt Angle (°)
100%DMPC	55.9	4.6	0.7
80%DMPC+20%CHOL	52.1	5.9	0.9
60%DMPC+40%CHOL	43.3	6.3	1.1
100%DPPC	45.2	4.3	0.5
80%DPPC+20%CHOL	41.5	4.9	1.2
60%DPPC+40%CHOL	35.9	4.0	0.5
100%DSPC	40.0	4.6	0.8
80%DSPC+20%CHOL	33.9	4.3	0.4
60%DSPC+40%CHOL	29.7	4.1	0.5

SI Table S1: The mean tilt angles of the DCD channel in various lipid bilayers, as well as the standard deviation (STD) and standard error of means (SEM). The analysis was on the 200 ns to 500 ns segments of 20 trajectories for each case, and the configurations were saved every 1 ns for the analysis. The mean values and standard deviations of the tilt angles were calculated for the hexamer in a transbilayer orientation (i.e. with a tilt angle of less than 70° as shown in Fig. S1).

Song et al., SI Table S2

	Mean Value of the Bilayer Thickness (Å)	STD of the Bilayer Thickness (Å)	SEM of the Bilayer Thickness (Å)
100%DMPC	33.1	1.6	0.35
80%DMPC+20%CHOL	34.4	0.3	0.04
60%DMPC+40%CHOL	36.8	0.7	0.12
100%DPPC	38.6	0.4	0.11
80%DPPC+20%CHOL	40.3	0.5	0.15
60%DPPC+40%CHOL	42.5	0.6	0.08
100%DSPC	44.5	0.5	0.17
80%DSPC+20%CHOL	46.3	0.4	0.07
60%DSPC+40%CHOL	47.9	0.6	0.09

SI Table S2: The mean bilayer thickness of various lipid bilayers in the CG simulations, as well as the standard deviation (STD) and standard error of means (SEM). The analysis was on the 200 ns to 500 ns segments of 20 trajectories for each case, and the configurations were saved every 1 ns for the analysis. The bilayer thicknesses were calculated by measuring the distance of the two maxima of the P atom densities along the bilayer normal direction.

Song et al., SI Table S3

	Tilt Angle in the Single-layer MD	Tilt Angle in the Double-layer MD 1	Tilt Angle in the Double-layer MD 2
DMPC	51.4±2.3	49.2±2.8	47.2±3.1
DPPC	41.1±2.9	42.0±2.7	43.3±2.7
DSPC	38.2±2.7	40.0±2.5	37.8±2.4

SI Table S3: The mean values and the standard deviations of the DCD tilt angle in various lipid bilayers, calculated for the all-atom MD simulations. We analyzed the last 100-ns of the trajectories for both the single-layer and double-layer simulations, as shown in Fig. 4. The values are in agreement with the CG simulations results, standard deviation taken into account.

Song et al., SI Table S4

	CG	cMD	CE MD
DCD in DMPC	20×500 ns	1×500 ns	2×200 ns
DCD in DMPC+CHOL(20%)	20×500 ns	1×500 ns	3×200 ns
DCD in DMPC+CHOL(40%)	20×500 ns	N/A	N/A
DCD in DPPC	20×500 ns	1×500 ns	2×200 ns
DCD in DPPC+CHOL(20%)	20×500 ns	N/A	N/A
DCD in DPPC+CHOL(40%)	20×500 ns	N/A	N/A
DCD in DSPC	20×500 ns	1×500 ns	2×200 ns
DCD in DSPC+CHOL(20%)	20×500 ns	N/A	N/A
DCD in DSPC+CHOL(40%)	20×500 ns	N/A	N/A
DCD parallel to DMPC bilayer	N/A	1×500 ns	N/A

SI Table S4: All the simulations performed in this work, including the Coarse-Grained (CG), conventional single-layer MD (cMD) and computational electrophysiology MD (CE MD).

Song et al., SI Table S5

System	Tilt Angle	Conductance (pS)	SEM (pS)
DMPC_lower	48.1	114.6	19.0
DMPC_upper	47.4	138.5	33.0
DMPC2_lower	47.2	228.7	22.4
DMPC2_upper	52.7	330.2	58.1
DPPC_lower	42.8	358.2	45.8
DPPC_upper	43.6	124.3	12.3
DPPC2_lower	39.6	270.0	57.0
DPPC2_upper	42.6	141.1	18.1
DSPC_lower	38.3	252.9	24.8
DSPC_upper	36.9	295.9	72.8
DSPC2_lower	37.0	200.2	48.6
DSPC2_upper	37.3	219.0	47.1
DMPC_CHL1_lower	43.7	209.7	35.4
DMPC_CHL1_upper	54.3	343.4	42.2
DMPC_CHL2_lower	22.6	220.9	19.9
DMPC_CHL2_upper	11.4	28.3	5.8
DMPC_CHL3_lower	30.9	125.3	35.2
DMPC_CHL3_upper	35.4	247.4	80.2

SI Table S5: The average tilt angle and conductance of the DCD channel obtained from each 200-ns all-atom computational electrophysiology simulation. The standard error of mean of conductance was calculated by block averaging, with 50-ns trajectories as blocks. The block size was chosen considering that the correlation time of the tilt angle is on the scale of tens of ns. The word ‘lower’ and ‘upper’ indicate the channel embedded in either the lower or the upper patch of the computational electrophysiology simulations.