Supporting Information

Modulating Interactions between Ligand-Coated Nanoparticles and Phase-Separated Lipid Bilayers by Varying the Ligand Density and the Surface Charge

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1. Structural and dynamical properties of the phase-separated bilayer

The lipid bilayer used in this work is composed of DPPC, DFPC (which contains three double bonds per tail), and CHOL with a molar ratio of 4:3:3. The polyunsaturated lipid DFPC ensures the DPPC/DFPC/CHOL lipid bilayer maintains a stable and well-separated structure during the whole simulation as shown in Fig. S1.

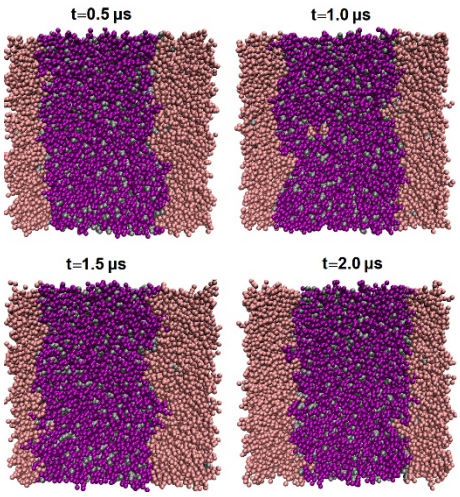

Fig. S1 Representative snapshots of the 2-μs simulation of lipid bilayer composed of DPPC, DFPC, CHOL with a molar ratio of 4:3:3. DPPC, DFPC, and CHOL are shown in color of purple, pink, and silver, respectively.

We also considered a lipid bilayer consisting of DPPC, dilinoleoylphosphatidylcholine (DIPC, which contains two double bonds per tail), and CHOL with the same molar ratio of the DPPC/DFPC/CHOL lipid bilayer. Unfortunately, the structure of this lipid bilayer is not very stable and the boundaries of the Lo and Ld phases are very rough at the simulation temperature of 305 K (see Figure S2). Therefore, we chose the DPPC/DFPC/CHOL lipid bilayer to examine the interactions of the ligand-coated nanoparticle with phase-separated lipid bilayers.

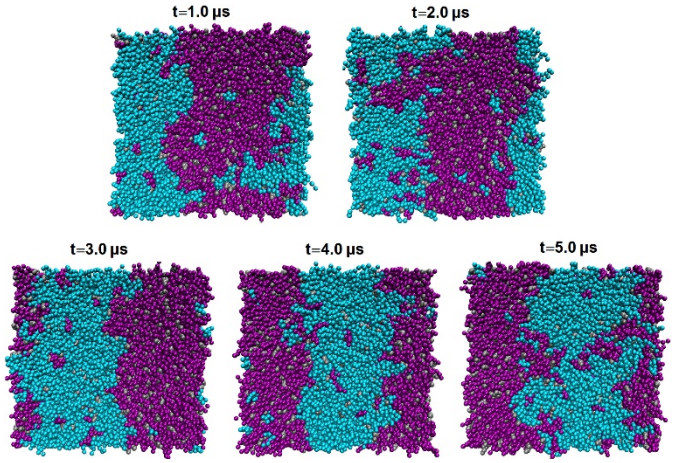

Fig. S2 Representative snapshots of the 5.0-μs simulation of lipid bilayer composed of DPPC, DIPC, CHOL with a molar ratio of 4:3:3. DPPC, DIPC, and CHOL are shown in color of purple, cyan, and silver, respectively.

To characterize the structural properties of the DPPC/DFPC/CHOL lipid bilayer, we calculated the two-dimensional (2D) thickness profile of the lipid domains as shown in Fig. S3(A) using the script GridMAT-MD.[1] Here, the thickness of the lipid domains is defined as the distance between the PO4 beads in the headgroup of DPPC or DFPC lipids in the two leaflets as shown in Fig. S3(A). There is an obvious difference between the thicknesses of Lo and Ld domains. Using the Gromacs tool *gmx density*, we calculated the averaged number densities of PO4 beads of DPPC and DFPC along the normal (*z*) direction of the lipid bilayer (Fig. S3(B)). The densities shown in Fig. S3(B) are averaged using the last 500ns trajectory of the simulation. From the density profiles of DPPC and DFPC shown in Fig. S3(B), we find that the averaged overall thicknesses of Lo and Ld domains, which are the distances between the two peaks of the density profiles, are ~ 4.42 nm and 3.41 nm, respectively. The thickness of the hydrophobic part of each domain is ~ 1nm thinner than the overall thicknesss of the domain, namely, the thicknesses of the hydrophobic parts of Lo and Ld domains are ~3.42 nm and ~2.41 nm, respectively.

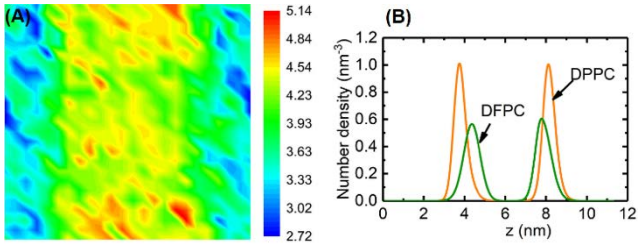

Fig. S3 (A) The 2D thickness profile of the DPPC/DFPC/CHOL lipid bilayer corresponding to the last snapshot shown in Fig. S1. (B) The averaged number density of PO4 beads in DPPC and DFPC along the normal (z) direction of the lipid bilayer.

We also calculated the averaged second-rank order parameter of the PC lipids in Lo and Ld domains, which is defined as

$$P_2 = \frac{1}{2}(3\langle \cos^2\theta \rangle - 1)$$

Here, θ is the angle between the membrane normal and the bond vectors. According to the definition of the order parameter, the lipid chains in the ordered phase have higher order parameters. In our system, the order parameters of DPPC in the Lo phase and DFPC in the Ld phase are 0.85 and 0.19, respectively, which implies the packing of DPPC in Lo domain is much more ordered than the packing of DFPC in Ld domain.

To examine the dynamics of the lipids in Lo and Ld phases, we also calculated the mean square displacement (MSD) of DPPC and DFPC lipids, using the last 1 μs trajectory of the 2-μs simulation of the DPPC/DFPC/CHOL lipid bilayer, removing the overall center of mass motion. Additionally, the lateral diffusion coefficients are fitted from 1.2 μs to 1.8 μs. The MSD curves are shown in Fig. S4. We find that, as expected, the DPPC lipids in Lo domains diffuse much slower than the DFPC in Ld domains and the diffusion coefficients of DPPC and DFPC are 5.2×10^{-7} cm^2/s and 4.0×10^{-6} cm^2/s, respectively.

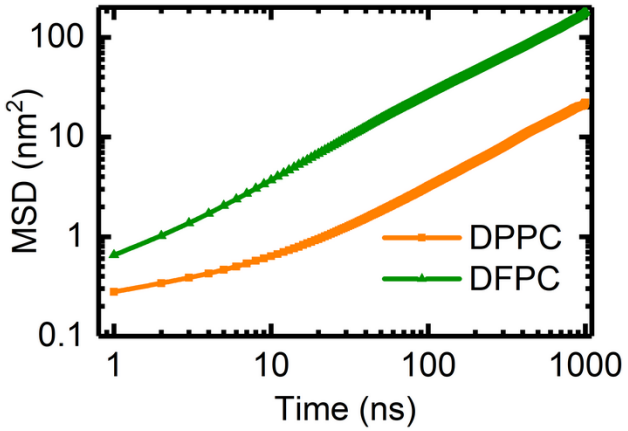

Fig. S4 Lateral mean square displacements (MSDs) of DPPC and DFPC lipids in the DPPC/DFPC/CHOL lipid bilayer.

2. Processes of the penetration of the hydrophobic nanoparticles into the lipid bilayer: Top views

To more clearly illustrate the penetration process of the hydrophobic nanoparticles into the lipid bilayer, we show the top views of the representative snapshots of the MD trajectory as follows. For clarity, we show the lipid with smaller beads and thinner bonds.

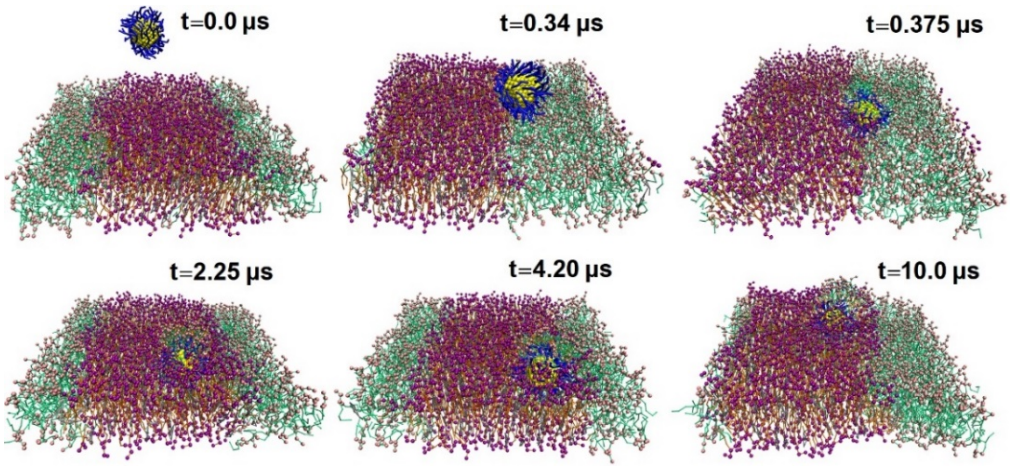

Fig. S5 Top views of representative snapshots of the MD trajectory of the penetration of $NP_{70/0}$ coated with 70 neutral ligands into the phase-separated lipid bilayer. Coloring scheme: DPPC–purple headgroup and orange tail; DFPC– pink headgroup and green tail; CHOL—silver; Nanoparticle–yellow core and blue neutral ligands.

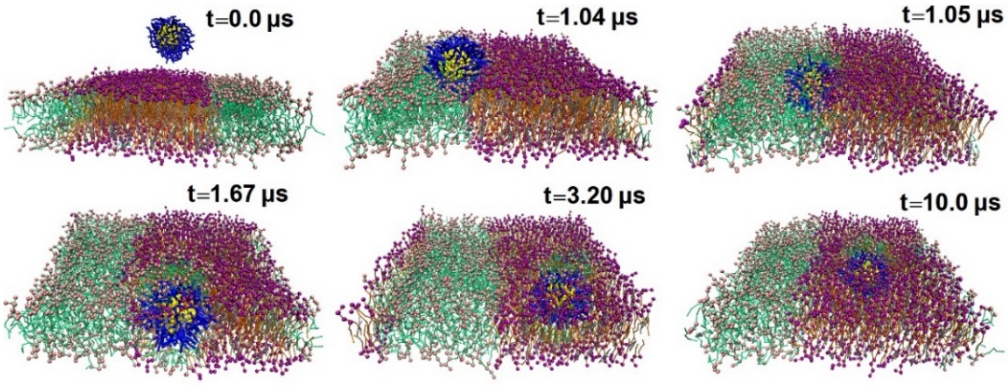

Fig. S6 Top views of representative snapshots of the MD trajectory of the penetration of $NP_{104/0}$ coated with 104 neutral ligands into the phase-separated lipid bilayer. Coloring scheme: DPPC–purple headgroup and orange tail; DFPC– pink headgroup and green tail; CHOL—silver; Nanoparticle–yellow core and blue neutral ligands.

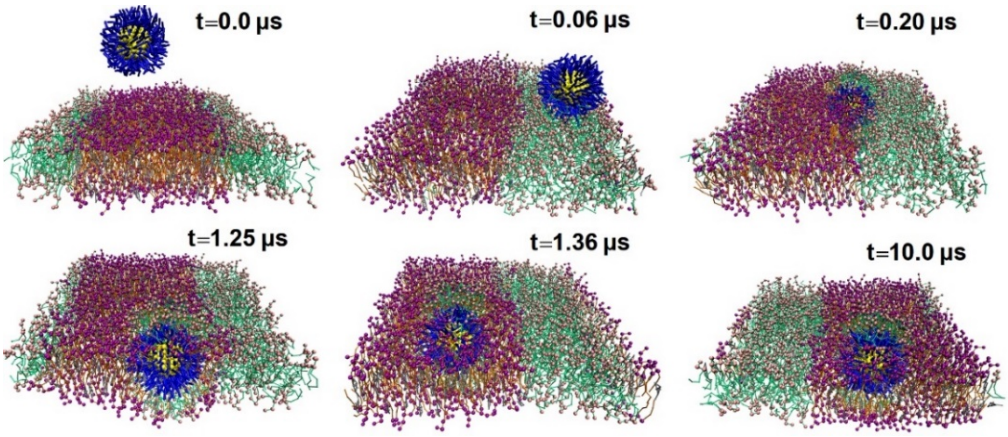

Fig. S7 Top views of representative snapshots of the MD trajectory of the penetration of $NP_{174/0}$ coated with174 neutral ligands into the phase-separated lipid bilayer. Coloring scheme: DPPC–purple headgroup and orange tail; DFPC– pink headgroup and green tail; CHOL—silver; Nanoparticle–yellow core and blue neutral ligands.

3. Radius of gyration of the nanoparticles

In this work, the size of Au core of the nanoparticles is fixed, with a diameter of 2.2 nm. However, with the change of the grafting density of the ligands, the effective size of the nanoparticle is changed. To characterize the effective size of the nanoparticles grafted with different densities, we calculated the radius of gyration (R_g) of the nanoparticles in water using the Gromacs tool *gmx gyrate*. The results are summarized in Table S1. Here, R_g is averaged using the last 200ns trajectory of a 1 us simulation of a nanoparticle in water.

Table S1 The radius of gyration (R_g) of the nanoparticles used in the simulations.

Nanoparticle	$NP_{70/0}$	$NP_{70/70}$	$NP_{104/0}$	$NP_{104/70}$	$NP_{104/104}$	$NP_{174/0}$	$NP_{174/104}$	$NP_{174/174}$
***Rg* (nm)**	1.42	1.44	1.58	1.60	1.62	1.84	1.86	1.89

With the increase of the hydrophilicity of surface of the nanoparticles, R_g slightly increases, which is caused by the hydrophilic interactions between charged ligands and water and by electrostatic repulsion between the positively charged termini of the ligands.

References

1. W. J. Allen, J. A. Lemkul and D. R. Bevan, *J. Comput. Chem.*, 2009, **30**, 1952–1958.