Supplementary Information for "Curvature-mediated cooperative wrapping of multiple nanoparticles at the same and opposite membrane sides"

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Note 1: Dissipative particle dynamics simulation method

In our DPD simulations, the dynamics of elementary units obeys Newton's law of motion. Typically, beads *i* and *j* interact with one another via a pairwise additive force consisting of the conservative force F_{ij}^{C} , dissipative force F_{ij}^{D} , and random force F_{ij}^{R} . The total force exerted on bead *i* can thus be expressed as

$$F_{i} = \sum_{i \neq j} (F_{ij}^{\rm C} + F_{ij}^{\rm D} + F_{ij}^{\rm R}).$$

The conservative force F_{ij}^{C} between beads *i* and *j* is of a soft repulsion acting along the line connecting the bead centers and has the form

$$F_{ij}^{\rm C} = a_{ij} P_{ij} \max\{1 - r_{ij} / r_{\rm c}, 0\},\$$

where a_{ij} is the maximum repulsive strength between beads *i* and *j*, $r_{ij}=r_j - r_i$ (r_i and r_j are their positions), $P'_{ij}=r_{ij}/|r_{ij}|$, and r_c is the cut off radius and taken as $r_c=0.646$ nm. In the simulations, physical quantities are scaled with the cutoff radius r_c , bead mass *m*, and thermal energy k_BT with k_B as the Boltzmann constant. All simulations were performed with the timestep of $\Delta t = 16$ ps, with the periodic boundary conditions adopted in all three directions.

According to previous studies,^{1,2} the values of interaction parameters a_{ij} between beads of the same type in the pure membrane system were set to $a_{WW} = a_{HH} = a_{R_HR_H} = 25$ and $a_{TT} = a_{R_TR_T} = 15$, and those between beads of different types were $a_{TW} = a_{R_TW} = 80$, $a_{HT} = a_{HR_T} = a_{R_HR_T} = a_{R_HR_T} = 50$, and $a_{TR_T} = 15$. Detailed values of the interaction parameters are summarized in Table S1.

The dissipative force is determined by the equation

$$F_{ij}^{\rm D} = -\Gamma (1 - r_{ij} / r_{\rm c})^2 (r_{ij}^{\prime \prime} v_{ij}) r_{ij}^{\prime \prime},$$

where Γ is the friction coefficient, $v_{ij} = v_i - v_j$ (v_i and v_j are their velocities). This expression conserves the momentum of each pair of interacting beads, and consequently the total momentum of the system is conserved.

The random force between beads *i* and *j* is calculated by

$$F_{ij}^{\mathrm{R}} = -\Sigma (1 - r_{ij} / r_{\mathrm{c}})^2 \theta_{ij} r_{jj}^{\mathrm{R}}$$

where Σ represents the noise amplitude and θ_{ij} is an uncorrelated random variable with zero mean and unit variance.

For lipid molecules, the interaction between neighboring beads in the same molecule is described by a harmonic spring force, which is given by

$$F_{\rm S} = K_{\rm S} (r_{ij} - r_{\rm eq}) r_{ij}^{\prime}$$

where $K_{\rm S} = 128$ is the spring constant and $r_{\rm eq} = 0.7$ is the equilibrium bond length.

In order to maintain the bending rigidity of lipids, the force constraining the variation of the bond angle is calculated by

$$F_{\varphi} = -\nabla U_{\varphi}$$
 and $U_{\varphi} = K_{\varphi} [1 - \cos(\varphi - \varphi_0)]$,

where $\varphi_0 = \pi$ is the equilibrium bond angle, φ is the real bond angle, and K = 10.0 is the bond bending force constant.

In addition, to represent specific interactions between ligands coating on the NPs and active points of receptors embedded in the membrane, a modified truncated LJ potential was applied and defined by

$$U_{\rm LJ} = 4\varepsilon \left[(\lambda / r_{ij})^{12} - (\lambda / r_{ij})^{6} \right] + 0.22\varepsilon ,$$

where $r_{ij} < r_c$, $\lambda = 0.624r_c$, and ε represents the strength of the ligand-receptor interaction. The largest repulsive force is set to be $10k_BT/r_c$, aiming to ensure the propel running of DPD simulations.³⁻⁵

	Н	Т	R_{H}	R _T	Р	L	W
Н	25	50	25	50	25	25	25
Т	50	15	50	15	80	80	80
R _H	25	50	25	50	25	25	25
R _T	50	15	50	15	80	80	80
Р	25	80	25	80	25	25	25
L	25	80	25	80	25	25	25
W	25	80	25	80	25	25	25

Table S1 Interaction parameters (a) used in our simulations

Note 2: N-varied DPD method

In this work, a specific variant of the DPD method, named the *N*-varied DPD simulation method, was applied to simulate the membrane interaction with NPs. In this method, the targeted membrane tension can be maintained constant by adjusting the lipid number per area (LNPA) in the membrane boundary region serving as a lipid reservoir.⁶⁻⁸ By adding and removing lipids, the value of LNPA in the boundary region is kept within a desired range ($\rho_{\text{LNPA}}^{\text{min}} < \rho_{\text{LNPA}}^{\text{max}}$). To keep the overall average density of beads in the simulation box constant, water beads are added into or deleted from the box correspondingly. Each addition or deletion move is performed every 1500 steps to leave enough time for the propagation of the membrane tension to the whole membrane.

Note 3: Determination of the membrane configurations in theoretical model

In our theoretical modeling, the membrane configuration is fully characterized by the tangent angle ψ with geometrical relations $dr / ds = \cos \psi$ and $dz / ds = \sin \psi$, and the minimum energy state of the vesicle at each given wrapping degree *f* and NP distance *d* can be expressed as $E = E(\psi_1, \psi_2, \alpha)$. Here we further introduce two new variables $t_i = s_i / l_i$ ($t_i \in [0,1]$, i = 1, 2) with l_1 and l_2 as the total lengths of the inner and outer free membranes, respectively, and reparametrize the unknown variables $\psi_i(s_i)$ as $\psi_i(t_i) = \sum a_j^{(i)} N_j^{(i)}(t_i)$ ($j = 0,1,...,n_i$) based on cubic B-spline approximation. Here the control points $a_j^{(i)}$ are the coefficients of the basic functions $N_j^{(i)}(s_i)$.

We employ the interior point optimization technique to numerically determine the minimum state of the membrane elastic energy at given f and d. The required boundary conditions are as follows. In the case of two cylindrical NPs adhering on the same side of the membrane, we have r = z = 0 and $\psi_1 = 0$ at $t_1 = 0$ due to the symmetric membrane configuration; while in the case of two cylindrical NPs adhering on the opposite membrane sides, we have r = z = 0 and zero membrane curvature ($\psi_{e_1}^R = 0$) at $t_1 = 0$ (point O) due to the antisymmetric membrane configuration. At the remote boundary ($t_2 = 1$), we have z = 0 and $\psi_2 = 0$. Other mandatory conditions are continuities of the *r*-coordinate and tangent angle ψ at two contact edges. To approximate the remote condition $l_2 \rightarrow \infty$, the total length l_2 of the outer membrane region is determined by a large prescribed length of the membrane projection of 20*a*. Under these conditions, the system free energy *E* at given *f* and *d* is minimized with respect to $a_j^{(i)}$, l_i , and α , and the corresponding membrane configuration could be determined.



Note 4: Supplementary simulation results

Fig. S1 Time sequences of typical snapshots and evolutions of the NP distance for two identical NPs of diameter D = 6.5 nm at an initial distance of 13 nm but different receptor-ligand interaction strength ε .



Fig. S2 Equilibrium wrapping configurations as functions of the NP distance and receptor-ligand binding strength. (A-C) Typical snapshots from top and side views showing three representative membrane wrapping states. (D, E) Phase diagrams of wrapping states for two NPs of diameter D = 6.5 nm (D) and 3.5 nm (E) at different NP distances and receptor-ligand binding strengths. Symbols representing the wrapping states are illustrated in A-C. The density of ligands on the NP surface is decreased to 25% of that in Fig. 2 in the main text.

Fig. S3 Time evolution of the distance between two identical NPs weakly adhering on the membrane. The NP diameter is D = 3.5 nm and the receptor-ligand interaction parameter is $\varepsilon = 3.5 k_{\rm B}T$. Four typical snapshots at different time are presented in the right panel to demonstrate the NP movement on the membrane.

Fig. S4 Time evolutions of the wrapping degree for two NPs of D = 6.5 nm at $\varepsilon = 5.0$ $k_{\rm B}T$ and two different initial NP distances (d = 9.4 nm and 17.2 nm). Insets show representative snapshots and the evolution of the NP distance in the time range between 2.5 µs and 4.0 µs.

Fig. S5 The effect of adhesion strength on the wrapping process of two NPs at opposite sides of the membrane. (A-D) Time sequences of typical snapshots of the membrane wrapping processes at $\varepsilon = 3.0 \ k_{\rm B}T$ (A), 4.0 $k_{\rm B}T$ (B), 5.0 $k_{\rm B}T$ (C) and 8.0 $k_{\rm B}T$ (D). Corresponding time evolutions of the average membrane wrapping degree (E) and NP distance (F). The initial NP distance was set to be 20.7 nm.

Fig. S6 The effect of the initial NP distance on the membrane wrapping of two NPs with diameter D = 6.5 nm at opposite membrane sides. (A-C) Time sequences of typical wrapping snapshots with initial NP distances as 0 nm, 13.8 nm, and 20.7 nm, respectively. (D) Time evolutions of the degree of membrane wrapping around each NP. NPs at shorter initial distances are wrapped by the membrane with a higher extent due to the cooperative effect. (E) Time evolutions of the NP distance. The receptor-ligand interaction strength was set as $\varepsilon = 3.0 k_{\rm B}T$.

Fig. S7 Effect of the membrane tension on the membrane wrapping of two NPs from opposite sides of the membrane at $\varepsilon = 5.0 \ k_{\rm B}T$. (A-C) Time sequences of typical snapshots at fixed lipid surface densities of 1.7 (A), 1.65 (B) and 1.60 (C). Time evolutions of the average membrane wrapping degree (D) and NP distance (E) at different lipid densities. The NP diameter and initial NP distance are D = 6.5 nm and d = 20.7 nm, respectively.

Fig. S8 Effect of membrane tension on the membrane wrapping of two NPs from opposite sides of the membrane at $\varepsilon = 8.0 \ k_{\rm B}T$. (A-C) Time sequences of typical snapshots at fixed lipid surface densities of 1.7 (A), 1.65 (B) and 1.60 (C). Time evolutions of the average membrane wrapping degree (D) and NP distance (E) at different lipid densities. The NP diameter and initial NP distance are D = 6.5 nm and d = 20.7 nm, respectively.

Fig. S9 Equilibrium NP arrangements at different initial NP distances and NPmembrane adhesion strengths. Under each condition five independent simulations were performed.

Note 5: Supplementary theoretical results

Membrane wrapping of two cylindrical NPs at the opposite membrane sides

Fig. S10 Energy and force profiles for the membrane wrapping of two cylindrical NPs at the opposite membrane sides. (A) The system elastic deformation energy ED/κ (at $\gamma = 0$) and (B) difference of local membrane force $\Delta F^r D^2/\kappa$ between the inner free and outer free membranes in the *r*-direction as functions of the wrapping degree *f* and NP distance d/D. Insets: corresponding contour plots. The membrane tension $\sigma = 0.2 \kappa / D^2$ is considered here.

Fig. S11 The system elastic deformation energy ED/κ at zero adhesion energy as functions of the wrapping degree *f* at $\sigma = 6\kappa/D^2$ and different NP distance d/D in the case of the wrapping of two cylindrical NPs at the opposite membrane sides. Symbols on the curves represent the full wrapping states.

Fig. S12 Wrapping degree f at different adhesion energy γ in the cases of $\sigma = 0.2\kappa/D^2$ (A) and $6\kappa/D^2$ (B) for the wrapping of two cylindrical NPs at the opposite membrane sides. Here $\overline{\sigma} = \sigma D^2/\kappa$ and $\overline{\gamma} = \gamma D^2/\kappa$.

Membrane wrapping of two cylindrical NPs at the same membrane side

For the wrapping of two identical cylindrical NPs of diameter D at the same membrane side, the system energy and interaction force are basically the same as these used for the wrapping of NPs at the opposite membrane sides (see subsection 2.2 in the main text). At d > D, the elastic deformation energy decreases slowly as d increases at a given f (Fig. S13A). The local membrane force ΔF^r is negative and drives NPs away from each other (Fig. S13B), indicating a repulsive NP interaction.

Fig. S13 (A) The system elastic deformation energy ED/κ ($\gamma = 0$) and (B) difference of local membrane force between the inner free and outer free membrane in the *r*-direction $\Delta F^r D^2/\kappa$ as functions of the wrapping degree *f* and NP distance *d/D*. Insets: corresponding contour plots. Here $\sigma = 6\kappa / D^2$ is considered.

Selected membrane configurations at $\sigma = 6\kappa / D^2$ are shown in Fig. S14. In the case of $d / D \in (1, 2)$, the wrapping of two separated NPs is smooth in the early wrapping stage, followed by a discontinuous configurational transition with the shallow wrapping state abruptly jumping to a deep wrapping state (as demonstrated in Fig. S14A from f = 0.3 to f = 0.6). This discontinuous configurational transition occurs around f = 0.5 and is reflected by the kinked red line in Fig. S15. Eventually two NPs reach a full wrapping state around f = 0.9 in which the outer free membranes touch the inner free membrane. The smooth blue short dash line in Fig. S15 means that the wrapping process is continuous at d/D = 2.

Fig. S14 Selected membrane configurations at different f and d in the cases of $\sigma = 6\kappa / D^2$. Arrows at the NP centers represent the interaction force ΔF^r due to the membrane deformation with the force values listed on the right sides. A negative ΔF^r indicates repulsive NP interaction.

Fig. S15 The system elastic deformation energy ED/κ at $\gamma = 0$ as functions of the wrapping degree *f* at $\sigma = 6\kappa/D^2$ and different NP distance *d/D*. Symbols on the curves represent the full wrapping states.

Fig. S16 Total free energy E(A) and wrapping degree f(B) at $\overline{\sigma} = 6$ and different $\overline{\gamma}$.

At a given adhesion energy γ , the total free energy *E* decreases as the NP distance d/D increases (Fig. S16A), indicating a repulsive NP interaction. The evolution of the wrapping degree *f* as a function of d/D is shown in Fig. S16B.

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