Membrane-Mediated Interactions between Nanoparticles on a Substrate

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Received: November 15, 2009; Revised Manuscript Received: March 17, 2010

Investigations of the interactions between nanoparticles and lipid bilayer may yield insight into the understanding of the protein−biomembrane interactions and the cytotoxicity of drugs. Here, we theoretically investigate the membrane-mediated interactions between two nanoparticles supported on a substrate. We examine the effects of the packing density of lipids, the direct nanoparticle−lipid interaction, and the direct substrate−lipid interaction on the effective interactions between the nanoparticles and find the effective interactions between the two nanoparticles are mainly dominated by the competition of the deformations of the different parts of the lipid bilayers as well as the stretching of the lipid chains sandwiched between the nanoparticles. By varying the above-mentioned effects, the effective interactions between the two nanoparticles can be efficiently modulated. The results may provide some theoretical insight into experiments on the membrane-mediated nanoparticle organization on a substrate and organization of the membrane proteins or drug nanoparticles on the surfaces of the cellular membranes.

Introduction

Applications of nanoparticles in bionanotechnology, drug design, and other relevant fields have received extensive attention in recent years.[1−3] In these applications, one of the fundamental questions is to reveal the interactions of nanoparticles with cellular membranes. For example, in drug design, the interactions between the drug nanoparticles and the biomembranes are usually relevant to the cytotoxicity of the drugs and may influence the drug efficacy.[4−6] To improve the efficacy of the drugs, many investigations have focused on the understanding of the interactions between drug nanoparticles and cellular membranes.[7−11] On the other hand, for simplicity, the membrane proteins are usually viewed as nanosized rigid inclusions in some theoretical studies of membrane−protein interactions.[12−20] Therefore, through examining the interactions between nanoparticles and membranes, one can reveal both the cytotoxicity of drugs and some microscopic mechanism of protein−membrane interactions.

Because of their flexibility and elasticity, the biomembranes can be easily deformed when proteins or nanoparticles are inserted into them or adsorbed onto their surfaces, and these deformations may induce complex effective interactions between the proteins or nanoparticles. In recent years, considerable theoretical and experimental efforts have been devoted to revealing the membrane-mediated effective interactions between proteins or nanoparticles.[14−33] In most of the previous studies, one mainly focused on the effective interactions between the "embedded inclusions". It was found that the effects that influence the effective interactions between the inclusions include the so-called hydrophobic mismatch effect,[19−22] the bending elasticity and the spontaneous curvature of membranes,[26−28] the chain stretching of the lipids near the inclusions,[28] the lipid packing,[20,27] and so on. Because of the complex interplay of these effects, the membrane-mediated effective interactions between the inclusions are usually nonmonotonic, that is, repulsion and attraction alternately appear in different regimes. In other relevant studies,[16−18,31,32] the effective interactions between the adsorbed proteins (or nanoparticles) mediated by the membranes were also extensively considered. It was found that, when some charged proteins or nanoparticles are adsorbed onto the surfaces of the membranes, not only the membranes will be deformed, but also the lipids in the membranes will be reorganized due to the electrostatic interaction between the proteins (or nanoparticles) and the charged lipids. This deformation of the membranes and the reorganization of the lipids may induce complex and interesting effective interactions between the adsorbed proteins, for example, the attraction between like-charged macroions.[17]

Additionally, the supported membrane, which is an ideal model system for biomembrane study and biosensor design, has attracted more and more interest in recent years.[34,35] Some experiments examined the interactions of the supported membranes with the topologically patterned substrates or nanoparticles.[36−42] It was found that, when a lipid bilayer covers onto some nanoparticles that are placed on a substrate, on one hand the nanoparticles may influence the morphology of the supported lipid bilayers and the lateral organization of the lipids; on the other hand, the deformed lipid bilayers may also induce effective interactions between the nanoparticles and may consequently influence the organization of nanoparticles on the substrate. Thus, one can modulate the assembly of the nanoparticles on the substrate by varying the properties of the supported membranes. However, few theoretical investigations have been carried out to reveal the

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10.1021/jp910852d
Published on Web 04/06/2010

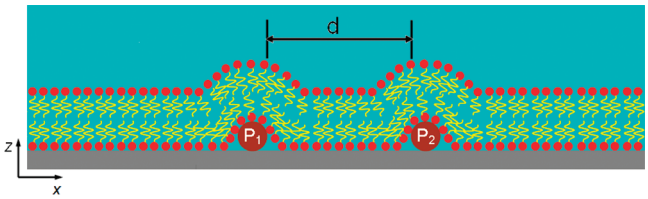

Figure 1. A schematic illustration for the lipid−bilayer-mediated interactions between two spherical nanoparticles supported on a substrate. The size of the nanoparticles P_1 and P_2 is identical and their radius is R, The distance between the two nanoparticle surface is d. The nanoparticle P_1 is assumed to be always placed on the left side of nanoparticle P_2 throughout this paper.

physical mechanism of the effective interactions between the nanoparticles mediated by supported membranes on a substrate.

Motivated by the recent experiments[36−42] and theoretical studies about the interactions between membrane and inclusions,[14−33] we theoretically investigate the effective interactions mediated by the supported membranes between two nanoparticles that are supported on a substrate in this paper. In the present model, the lipids are described by flexible Gaussian chains in the framework of the coarse-grained self-consistent field theory (SCFT).[43−48] Thus, the conformational entropy of the lipids may be excessively estimated, and this model is not suitable to examine the properties of the lipids with gel phase. However, the SCFT results of the lipids with liquid crystalline phases agree very well with the results of experiments and simulations.[45] Here, we mainly focus on the effective interactions between nanoparticles mediated by liquid crystalline lipid bilayers. In previous work, some other excellent molecular mean field theories (e.g., refs 15, 18, and 23−25) and phenomenological models (e.g., refs 26−28) have also been used to examine the membrane-mediated interactions between proteins. Compared to other molecular mean field models (e.g., refs 23−25), SCFT considers fewer molecular details of the lipids, but it can characterize the inhomogeneous distribution of the lipids in the membranes without any assumptions about the chain packing or stretching;[45] compared to the elastic phenomenological model, SCFT can properly consider the chain stretching of the lipids and the strong curvature of the membranes.

With varying the distance between the two nanoparticles while fixing the other parameters, we can obtain the curve of the free energy of the system (F) as a function of the distance between the nanoparticles (d). The $F-d$ curve explicitly demonstrates the effective interactions between the nanoparticles.[49] Through examining the $F-d$ curves with different parameters, we can reveal various effects on the effective interactions between the two nanoparticles. Here, we systematically examine the packing density of the lipids, the direct nanoparticle−lipid interaction, and the direct substrate−lipid interaction on the membrane-mediated effective interactions between nanoparticles. Furthermore, we also analyze the microscopic mechanism of the membrane-mediated interactions between the nanoparticles supported on the substrate. We hope our work can yield some insight into the modulation of the organization of nanoparticles on a substrate and the understanding of the protein−biomembrane and drug−biomembrane interactions.

Model and Method

We consider two spherical nanoparticles (labeled with P_1 and P_2) are laid on a substrate and covered by a lipid bilayer (Figure 1). The size of nanoparticles P_1 and P_2 is identical and their radius is R. The distance between surfaces of the two nanoparticle is d. The lipid bilayer is composed of monocomponent lipids, and each lipid is described by a polymeric chain which has a hydrophilic headgroup.[43,44] The volume of the lipid headgroup is v_h, and the chainlike hydrophobic tail of the lipid consists of N segments with segment volume ρ_0^{-1}. Thus, the volume fraction of the headgroup in each lipid is $f_h = v_h/(v_h + N\rho_0^{-1})$, and the length of the lipid can be characterized by the radius of gyration, $R_g = (N/6)^{1/2}a$, where a is the statistical segment length of the lipid.[50] The nanoparticles and the lipid bilayer are immersed in hydrophilic homopolymeric solvents,[43,45] and each solvent molecule also consists of N segments with segment volume ρ_0^{-1}.

In self-consistent field theory, the free energy of the system (F) can be written as[45−48]

$$\frac{NF}{\rho_0 k_B TV} = -(1-f_h)\phi_l \ln\left[\frac{Q_l}{(1-f_h)\phi_l V}\right] - \phi_s \ln\left(\frac{Q_s}{\phi_s V}\right) + \frac{1}{V}\int d\mathbf{r}\{\chi N[(\varphi_h(\mathbf{r}) + \varphi_s(\mathbf{r}) + \varphi_p(\mathbf{r}))\varphi_t(\mathbf{r}) + (\varphi_h(\mathbf{r}) + \varphi_s(\mathbf{r}))\varphi_p(\mathbf{r})] + H(\mathbf{r})N[\varphi_h(\mathbf{r}) + \varphi_s(\mathbf{r}) + \varphi_p(\mathbf{r}) - \varphi_t(\mathbf{r})] + K(\mathbf{r})N[\varphi_h(\mathbf{r}) + \varphi_s(\mathbf{r}) - \varphi_t(\mathbf{r})] - w_h(\mathbf{r})\rho_h(\mathbf{r}) - w_t(\mathbf{r})\varphi_t(\mathbf{r}) - w_s(\mathbf{r})\varphi_s(\mathbf{r}) - \xi(\mathbf{r})[\Phi_0(\mathbf{r}) - \varphi_h(\mathbf{r}) - \varphi_t(\mathbf{r}) - \varphi_p(\mathbf{r}) - \varphi_s(\mathbf{r})]\} \quad (1)$$

Here, k_B is the Boltzmann constant, and T is the temperature. The effective volume of the system, $V = \int\Phi_0(\mathbf{r})d\mathbf{r}$,[46] where $\Phi_0(\mathbf{r})$ is the total local density of various components at position $\mathbf{r}$, and we choose[43,51]

$$\Phi_0(\mathbf{r}) = \begin{cases} \frac{1}{2}\left[1 - \cos\left(\frac{\pi z}{\varepsilon}\right)\right], & \text{if } z \le \varepsilon \\ 1, & \text{if } z > \varepsilon \end{cases} \quad (2)$$

Here, z-axis is perpendicular to the substrate and $z = 0$ at the substrate surface (Figure 1), ε is a sufficiently small thickness. The variables of ϕ_l and ϕ_s are the respective total volume fractions of the lipids and solvents in the system. Q_l and Q_s are the partition functions of single lipid and solvent, respectively. The functions, $\varphi_h(\mathbf{r})$, $\varphi_t(\mathbf{r})$, and $\varphi_s(\mathbf{r})$, are the respective local density functions of lipid headgroups, lipid tails, and solvents, and $\varphi_p(\mathbf{r})$ is the local nanoparticle density which is fixed in the calculation as[49]

$$\varphi_p(\mathbf{r}) = \begin{cases} 1, & \text{if } |\mathbf{r} - \mathbf{r}_{a(b)}| \le R \\ 0.5, & \text{if } R < |\mathbf{r} - \mathbf{r}_{a(b)}| \le R + \sigma \\ 0, & \text{if } |\mathbf{r} - \mathbf{r}_{a(b)}| > R + \sigma \end{cases} \quad (3)$$

Here, $\mathbf{r}_a$ and $\mathbf{r}_b$ are the respective positions of centers of nanoparticles P_1 and P_2, and σ is the thickness of a very thin depletion shell around the nanoparticle.[49] The total volume fraction of the nanoparticles in the system is $\phi_p = \int\varphi_p(\mathbf{r})d\mathbf{r}/V$, and $\phi_l + \phi_s + \phi_p = 1$.

In addition, $\rho_h(\mathbf{r})$ is the number density of the lipid headgroups, and $\varphi_h(\mathbf{r}) = \gamma\rho_h(\mathbf{r})$, where $\gamma = v_h\rho_0/N$ is the headgroup-to-tail volume ratio of the lipid. The functions, $w_h(\mathbf{r})$, $w_t(\mathbf{r})$, and $w_s(\mathbf{r})$, are the fields acting on the headgroups, the tail segments, and the solvent segments, respectively. The interaction between the hydrophilic components (lipid headgroups or solvents) and the hydrophobic components (lipid tails and bulks of nanopar-

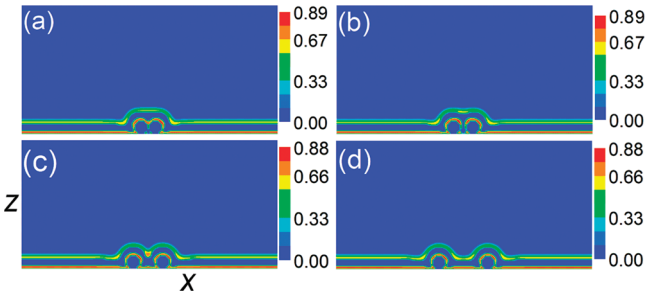

Figure 2. Examples of the density profiles of the lipid headgroups with varying the distance between the nanoparticles. Here, the radius of the nanoparticles is chosen as $R = 4a$, the volume fraction of the lipids is $\phi_l = 0.11$, the surface field strength of the substrate and the nanoparticles are fixed as $\Lambda N = -1$ and $\lambda N = 0$, respectively. (a) $d = 3a$; (b) $d = 7a$; (c) $d = 15a$; (d) $d = 30a$.

ticles) is described by a Flory−Huggins interaction parameter, χ, and the surface field of the substrate is characterized by $H(\mathbf{r})$, and

$$H(\mathbf{r}) = \begin{cases} \frac{\Lambda}{\varepsilon}\left[1 + \cos\left(\frac{\pi z}{\varepsilon}\right)\right], & \text{if } 0 \le z < \varepsilon \\ 0, & \text{if } z \ge \varepsilon \end{cases} \quad (4)$$

Here, Λ is the field strength at the substrate surface.[51,52] Additionally, $K(\mathbf{r})$ is the surface field of the nanoparticles, and

$$K(\mathbf{r}) = \begin{cases} \infty, & \text{if } |\mathbf{r} - \mathbf{r}_{a(b)}| \le R \\ \frac{\lambda}{\sigma}\left\{1 + \cos\left[\frac{\pi(|\mathbf{r} - \mathbf{r}_{a(b)}| - R)}{\sigma}\right]\right\}, & \text{if } R < |\mathbf{r} - \mathbf{r}_{a(b)}| \le R + \sigma \\ 0, & \text{if } |\mathbf{r} - \mathbf{r}_{a(b)}| > R + \sigma \end{cases} \quad (5)$$

Here, λ is the field strength at the nanoparticle surfaces.[51,52] $\xi(\mathbf{r})$ is a field ensuring the incompressibility of the system.

Through minimizing the free energy of the system eq 1 (the detailed formulizm can be found in the Supporting Information), we can obtain the free energy of the equilibrium state of the system with given nanoparticle distance. Then, by varying the distance of the two nanoparticles, we can plot a curve of free energy versus the distance between the nanoparticles through which we can examine the effective interactions between the two nanoparticles. In this paper, we fix the volume fraction of headgroup in each lipid as $f_h = 0.4$, which is close to the volume fraction of headgroup of dioleoylphosphatidylcholine (DOPC).[53] The number of the segments in each lipid is chosen as $N = 50$,[54] thus, the radius of gyration of the lipid is $R_g = (50/6)^{1/2}a \approx 2.9a$. Since the length of lipid is typically 1−2 nm,[55] the statistical segment length $a = 3.5$−7.0 Å. For convenience, all of the lengths involved in this paper are scaled by a. To avoid the finite size effect, we simulate the system in a large enough box with width $200a$ and height $100a$. The interaction parameter is taken as $\chi N = 18$. As an example, we show the morphologies of the lipid bilayer with varying the distance between the nanoparticle and fixing the other parameters in Figure 2. Next, we will reveal the various effects on the effective interactions between nanoparticles mediated by the lipid bilayer.

Results and Discussion

The Effect of the Packing Density of Lipids. The packing density of lipids is tightly related to the bending rigidity of the lipid bilayers. When the packing density of lipids is high, the lipids will be organized compactly and their bonds will be arranged into one identical orientation. Thus, the contact sites between the adjacent lipids will increase, the interaction among the lipids in the bilayer will also be enhanced, and the lipid bilayer will become thicker and relatively rigid. On the contrary, when the packing density of lipids is low, the lipids will be arranged more loosely and the bond orientation of the lipids will become random. Thus, the contact sites between the adjacent lipids will reduce, the interaction among the lipids in the bilayer will be weakened, and the lipid bilayer will become thinner and its rigidity will also be weakened.

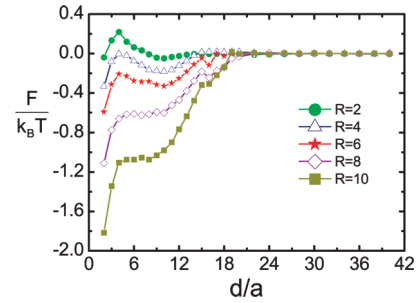

Figure 3. The curves of the reduced free energy (F/k_BT) versus the distance between the two nanoparticle surfaces (d) with varying the nanoparticle sizes. Here, the volume fraction of the lipids is chosen as $\phi_l = 0.11$, the surface field strength of the substrate and the nanoparticles are fixed as $\Lambda N = -1$ and $\lambda N = 0$, respectively.

In our system, the packing density of lipids can be modulated through two different methods. In one method, we fix the system volume and the volume fraction of lipids (i.e., fix the number of lipids in the system) but vary the nanoparticle size to modulate the packing density of lipids. From Figure 2, we find the lipid bilayer covers the most surface area of the nanoparticles. Thus, the total area of the lipid bilayer will increase with the increase of the nanoparticle size. Under the condition of fixed number of lipids, when the size of the nanoparticles is relatively small, the lipids will be organized into a bilayer with relatively small area. Therefore, the packing density of the lipids is relatively high. On the contrary, if the size of the nanoparticles is increased, the lipids will be arranged into one relatively large bilayer. Thus, the packing density of the lipids will reduce. In the other method, we fix the size of nanoparticles and the system volume but vary the number of lipids (n_l) to tune the packing density of lipids.[56] Because the size of the nanoparticles and the system volume are both fixed, the area of the bilayer is also fixed as mentioned above. When the number of the lipids is increased, more lipids will be arranged into a bilayer with fixed area. Therefore, both the packing density of lipids and the thickness of the bilayer will increase. On the other hand, if the number of the lipids is reduced, the packing density of lipids will also reduce. Because the system size in our model is fixed, the volume fraction of the lipids in the system is proportional to the number of the lipids ($\phi_l = n_l(v_h + \rho_0^{-1}N)/V$). For convenience, we modulate the packing density of lipids through varying the parameter of volume fraction of lipids in our model.

Figure 3 shows the curves of the free energy as a function of the distance between the nanoparticles with varying the size of the nanoparticles from $R = 2a$ to $R = 10a$ while fixing the volume fraction of the lipids as $\phi_l = 0.11$, the surface field strength of the substrate and the nanoparticles as $\Lambda N = -1$ and $\lambda N = 0$, respectively. For relatively small nanoparticles (e.g., $R = 2a$−$6a$), we find that when the distance between the nanoparticles is small almost no lipids are sandwiched between the two nanoparticles (Figure 2a). To restore their natural

morphology, the bent parts of the lipid bilayer on the left side of nanoparticle P_1 and the right side of nanoparticle P_2 will produce a force on the nanoparticles to push them to approach each other. Therefore, an effective attraction appears between the two nanoparticles. As the distance between the nanoparticles is increased, some lipids fill in the region between the two nanoparticles (Figure 2b). These lipids are strongly confined by the two nanoparticles and stretched. To restore their natural conformation, the stretched chains will induce a force on the two nanoparticles to push them to separate from each other. In addition, the lower leaflet of the lipid bilayer in the internanoparticle region is also strongly bent. To restore its natural conformations, the bent leaflet of the lipid bilayer between the two nanoparticles will also produce a repulsive force upon the two nanoparticles. On the other hand, the bent parts of the lipid bilayer on the left side of nanoparticle P_1 and the right side of nanoparticle P_2 will push the two nanoparticles to approach each other. However, because the nanoparticles are relatively small, the lipids are arranged compactly, the rigidity of the bilayer is large as mentioned above, and the stretching of the lipids sandwiched between the nanoparticles is also very strong. Consequently, the repulsion induced by the bent leaflet of the bilayer and the stretched lipids sandwiched between the two nanoparticles is very strong, and exceeds the attraction induced by the bent parts of the bilayer on the left side of nanoparticle P_1 and the right side of nanoparticle P_2. Finally, an intermediate-ranged repulsion is produced between the two nanoparticles.

When the distance between the nanoparticles is further increased, the space between the two nanoparticles will become relatively large (Figure 2c). Thus, the nanoparticle-induced conformational perturbation of lipids sandwiched between the two nanoparticles will be weakened. Whereas, the bending of the lipid bilayer on the left side of the nanoparticle P_1 and the right side of nanoparticle P_2 is still strong, and exceeds the effects of the bending of lower leaflet of the bilayer and the stretching of the lipid chains between the nanoparticles. Thus, a long-ranged attraction appears between the nanoparticles. As the distance between the nanoparticles becomes extremely large, the deformations of the lipid bilayer induced by the two nanoparticles are independent, and they do not influence each other. Additionally, the deformations of the bilayer on the right and left sides of each nanoparticle are equivalent (Figure 2d). Therefore, the repulsion and the attraction induced by the bilayer bending and the lipid stretching counteract each other completely, and the effective interaction disappears.

When the size of the nanoparticles becomes relatively large (e.g., $R = 8a-10a$), the short-ranged attraction still exists. However, because the rigidity of the lipid bilayer reduces as mentioned above, when the distance between the two nanoparticles is intermediate-ranged, the repulsion induced by the bending of the lower leaflet of lipid bilayer and the stretching of the lipid chains between the two nanoparticles will be weakened, and can only counteract the attraction induced by the bent parts of the lipid bilayer on the left side of the nanoparticle P_1 and the right side of the nanoparticle P_2. Thus, a platform appears on the free energy curve in the intermediate-ranged distance. As the distance between the nanoparticles is further increased, the repulsion induced by the effects of the bending of internanoparticle part of the lipid bilayer and the stretching of the lipids sandwiched between the two nanoparticles further reduces, thus, the bent parts of the lipid bilayer on the left side of nanoparticle P_1 and the right side of nanoparticle P_2 will push the nanoparticles to approach each other. Thus, a long-ranged attraction again appears. Additionally,

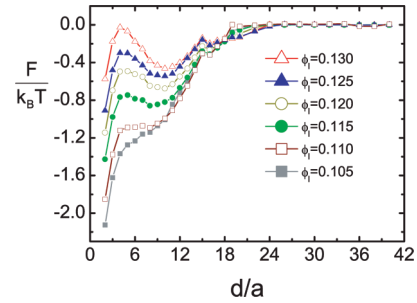

Figure 4. The curves of the reduced free energy (F/k_BT) versus the distance between the two nanoparticles (d) with varying the volume fraction of lipids. Here, the radius of the nanoparticles is chosen as $R = 10a$, the surface field strength of the substrate and the nanoparticles are fixed as $\Lambda N = -1$ and $\lambda N = 0$, respectively.

because the deformation of the lipid bilayer is proportional to the sizes of the nanoparticles, the long-ranged attraction increases with the increase of the sizes of the nanoparticles (Figure 3).

To test the above discussion about the effect of the packing density of lipid bilayer on the effective interactions between the nanoparticles, we further examine the free energy curves with varying the volume fraction of the lipids while fixing the nanoparticle size and other parameters. As shown in Figure 4, just as what we expect with the increase of the volume fraction of the lipids, both the packing density of the lipids and the rigidity of the bilayer is increased, and the platform on the free-energy curve which appears in the case of lower volume fraction of lipids in the intermediate range disappears, and it is replaced by a minimum of the free energy. The free-energy barrier and the intermediate-ranged repulsion that appear in the case of the smaller nanoparticles in Figure 3 are rediscovered. This further confirms our above-mentioned discussion on the effect of packing density of lipids on the effective interactions between the two nanoparticles.

It is notable that Figures 3 and 4 show the change of the effective interactions between nanoparticles mediated by lipid bilayers with different elastic properties. If the elasticity of the lipid bilayer is fixed (i.e., the chain packing density is fixed), the intermediate-ranged repulsion mediated by the bilayer may be proportional to the deformation of the bilayer. Thus, the results of Figure 3 may be opposite, namely, the intermediate-ranged repulsion will increase with the increase of the nanoparticle size.

The Effect of the Direct Nanoparticle−Lipid Interaction. The direct interaction between the nanoparticles and the lipid bilayer can affect the deformation of the lipid bilayer and consequently may influence the effective interactions between the two nanoparticles.

Figure 5 shows the free energy curves with varying the direct interaction strength between nanoparticles and lipids. We find that, as the direct interaction between the nanoparticles and the lipid headgroups is tuned from strong repulsion ($\lambda N = 5$) to strong attraction ($\lambda N = -5$), the free energy barrier becomes higher and higher. This means that the attraction between nanoparticles and lipid headgroups can enhance the intermediate-ranged repulsion between the nanoparticles whereas the repulsion can weaken the intermediate-ranged repulsion between the nanoparticles. This is because that, as the direct interaction between the nanoparticles and the lipid headgroups is changed from strong repulsion to strong attraction, the lipid bilayer between the nanoparticles will be bent more and more strongly to enwrap the nanoparticles due to the attraction, thus, the

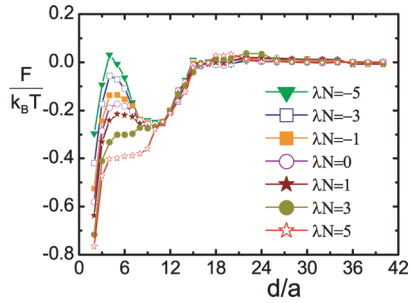

Figure 5. The curves of the reduced free energy (F/k_BT) versus the distance between the two nanoparticles (d) with varying the direct nanoparticle−lipid interaction. Here, the radius of the nanoparticles is chosen as $R = 5a$, the volume fraction of the lipids is fixed as $\phi_l = 0.11$, and the surface field strength of the substrate is set as $\Lambda N = -1$.

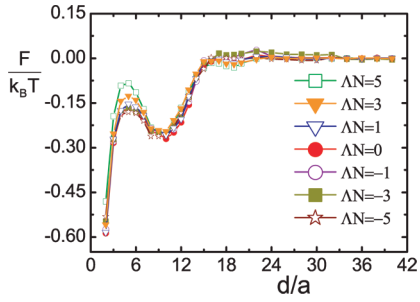

Figure 6. The curves of the reduced free energy (F/k_BT) versus the distance between the two nanoparticles (d) with varying the direct substrate−lipid interaction. Here, the radius of the nanoparticles is chosen as $R = 5a$, the volume fraction of the lipids is fixed as $\phi_l = 0.11$, and the surface field strength between the nanoparticles and lipids is set as $\lambda N = 0$.

intermediate-ranged repulsion which is induced by the bending of the lower leaflet of the internanoparticle lipid bilayer and the stretching of the lipid chains sandwiched between the nanoparticles is enhanced. On the contrary, if the direct interaction between nanoparticles and lipids is repulsive, the deformation of the lipid bilayer will be weakened due to the repulsion. Thus, the intermediate-ranged repulsion between the nanoparticles reduces. When the direct interaction between nanoparticles and lipids is strongly repulsive (e.g., $\lambda N = 3$ or 5), we find the intermediate-ranged repulsion disappears as shown in Figure 5.

The Effect of the Direct Substrate−Lipid Interaction. We also examine the influence of the direct interaction between the substrate and the lipid bilayer on the effective interactions between the nanoparticles. Figure 6 shows the free energy curves with varying the strength of the direct interaction between the substrate and the lipid headgroups from strong repulsion ($\Lambda N = 5$) to strong attraction ($\Lambda N = -5$). Interestingly, just contrary to the effect of the direct nanoparticle−lipid interaction, the free energy barriers become lower and lower as the direct interaction between the substrate and the lipid headgroups is changed from strong repulsion to strong attraction. This implies that the attraction between the substrate and the lipid headgroups can weaken the intermediate-ranged repulsion, whereas the repulsion can enhance the intermediate-ranged repulsion between the nanoparticles. This result can be understood as follows:

If the interaction between the substrate and the lipid headgroups is attractive, to restore its natural morphology the bent lower leaflet of the lipid bilayer in the internanoparticle region must conquer the binding from the substrate, which will reduce the effective repulsive force imposed on the nanoparticles. Additionally, the binding of the substrate can also induce an asymmetric distribution of the lipids in the two leaflet and more lipids will distribute in the lower leaflet of the bilayer. This may induce the lipid bilayer to produce a spontaneous curvature toward the upper leaflet and reduce the bending energy when the lipid bilayer is bent toward the upper leaflet.[55] Thus, the force mediated by the bending of lipid bilayer is weakened, and the free energy barriers and the effective repulsion between the nanoparticles in the intermediate-ranged distance both decrease. On the other hand, if the interaction between the lipid headgroups and the substrate is repulsive, without the binding from the substrate, the deformation of the lipid bilayer induced by the nanoparticles can more easily restore, the lipids may distribute more symmetrically in the two leaflets of the bilayer, and the bilayer has no nonzero spontaneous curvature. Thus, the intermediate-ranged repulsion will be enhanced.

Nevertheless, even if the substrate is attractive with the lipid headgroups, because the sizes of the nanoparticles are relatively small ($R = 5a$), the lipids are arranged compactly and orderly in the bilayer, and the lipids are very difficult to flip-flop from one leaflet of the bilayer to the other.[57] Therefore, the influence of the interaction from the substrate on the bending energy of lipid bilayer is finite, and the change of the shape of the free-energy curves is not very obvious with the increase of the attraction between the substrate and the lipid headgroups as shown in Figure 6.

Conclusion

In summary, we theoretically investigate the lipid−bilayer-mediated effective interactions between two nanoparticles supported on a substrate. We find that the effective interactions between the two nanoparticles are mainly dominated by the competition among the deformation of the different parts of the lipid bilayer as well as the stretching of the lipid chains sandwiched between the two nanoparticles. The deformation of the internanoparticle part of the lipid bilayer and the stretching of the lipid chains sandwiched between the two nanoparticles tend to push the two nanoparticles to separate from each other, while the deformation of the lipid bilayer on the left side of nanoparticle P_1 and the right side of nanoparticle P_2 tends to push the two nanoparticles to approach each other.

By varying the packing density of the lipids in the bilayer, the direct nanoparticle−lipid interaction, and the direct substrate−lipid interaction, the deformation of the lipid bilayer and the stretching of the lipid chains sandwiched between the two nanoparticles can be efficiently modulated, and the effective interactions between the two nanoparticles can consequently be modulated. When the packing density of lipids is high, we find a short-ranged attraction, an intermediate-ranged repulsion, and a long-ranged attraction. On the contrary, when the packing density of lipids is low, the intermediate-ranged repulsion disappears. Furthermore, the direct nanoparticle−lipid interaction and the direct substrate−lipid interaction can influence both the deformation of the lipid bilayer and the distribution of the lipids in the two leaflets of the lipid bilayer and can consequently affect the effective interactions between the two nanoparticles. The attraction between the nanoparticles and the lipid headgroups as well as the repulsion between the substrate and the lipid headgroups can enhance the intermediate-ranged repulsion between the nanoparticles, while the repulsion between the nanoparticles and the lipid headgroups as well as the attraction between the substrate and the lipid headgroups can weaken the intermediate-ranged repulsion between the nanoparticles.

Comparing our results with the widely studied membrane-mediated effective interactions between the embedded inclu-

sions, we find that, the packing density of the lipids and the distribution of the lipids in the two leaflets of the bilayer play important roles in the effective interactions. However, the effects determining the effective interactions between embedded inclusions usually include the mismatch effect, the conformation change of the lipids near the inclusions, and the spontaneous curvature of the lipid bilayer.[19−22,26−28]

Our results provide some microscopic mechanism for the membrane-mediated two-body interactions between nanoparticles and some routes to tune the effective interactions between the nanoparticles induced by the lipid bilayer on a substrate. Although the distribution of the proteins or lipids are mainly dominated by the collective or many-body interactions, the information of the two-body interactions is helpful to understand the many-body interactions (see, for example, ref 33). In the next work, we will further consider the many-body interactions and the organization of an ensemble of nanoparticles or proteins mediated by the lipid bilayers.

Acknowledgment. This work was supported by National Natural Science Foundation of China under Grants 10947136, 10974180, and 10974080, Program for Innovative Research Team in Zhejiang Normal University, Young Scholar Fund in Zhejiang Normal University (Grant KJ20080109), and the Start-up Funding for Doctoral Scholars in Zhejiang Normal University.

Supporting Information Available: The minimizing of free energy of the system. This material is available free of charge via the Internet at http://pubs.acs.org.

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(57) Biomembranes are highly dynamic. The lipids can not only diffuse laterally in the plane of membranes but also flip-flop from one leaflet to another leaflet of the membranes. Although the flip-flop of the lipids is more difficult than the lateral diffusion and depends on various effects such as the lateral pressure imposed on the membranes (Anglin, T. C.; Conboy, J. C. *Biophys. J.* **2008**, *95*, 186), it is ubiquitous in biomembranes and plays important roles in the formation of the internal structures and the reality of some biofunctions of biomembranes (see, for example, Kol, M. A.; de Kroon, A. I. P. M.; Killian, J. A.; de Kruijff, B. *Biochemistry* **2004**, *43*, 2673. Lin, W.-C.; Blanchette, C. D.; Ratto, T. V.; Longo, M. L. *Biophys. J.* **2006**, *90*, 228. Drew Bennett, W. F.; MacCallum, J. L.; Hinner, M. J.; Marrink, S. J.; Tieleman, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 12714).

JP910852D