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Curvature-mediated assembly of Janus nanoparticles on membrane vesicles

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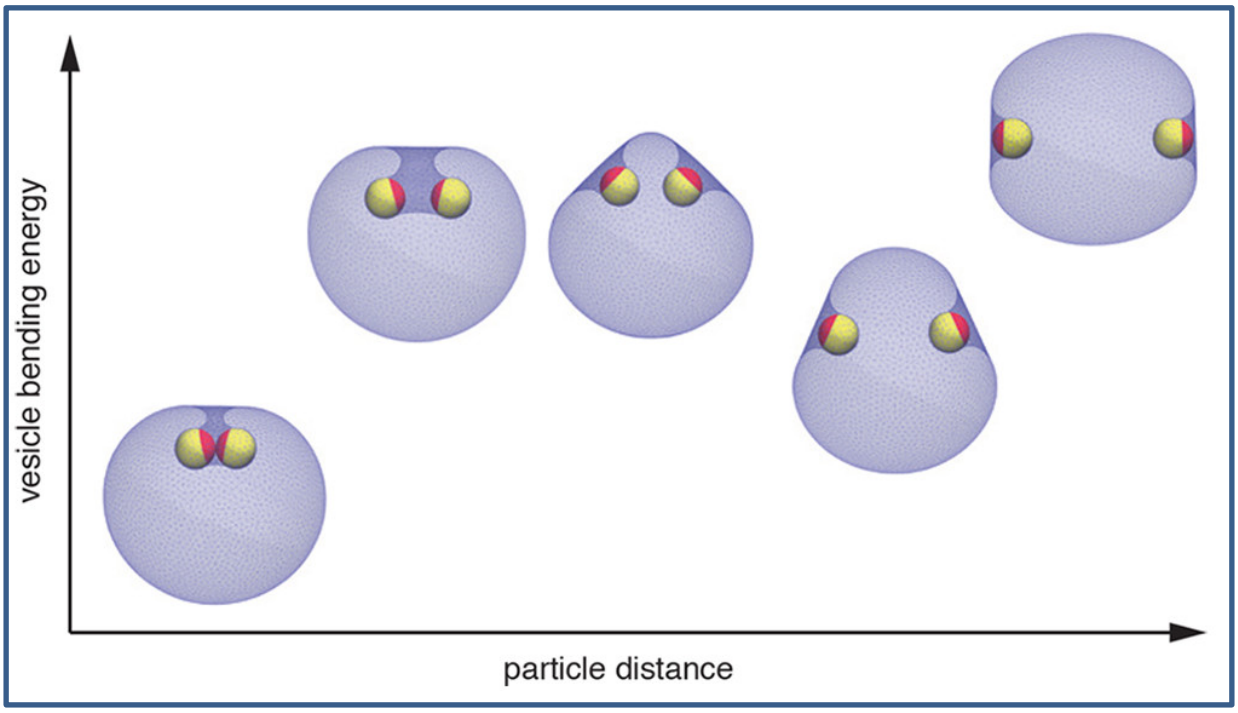

Keywords: bending energy; Biomembranes; Janus particles; membrane-mediated interactions; particle adsorption; vesicles

Curvature-mediated assembly of Janus nanoparticles on membrane vesicles

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Abstract

Besides direct particle-particle interactions, nanoparticles adsorbed to biomembranes experience indirect interactions that are mediated by the membrane curvature arising from particle adsorption. In this letter, we show that the curvature-mediated interactions of adsorbed Janus particles depend on the initial curvature of the membrane prior to adsorption, i.e. on whether the membrane initially bulges towards or away from the particles in our simulations. The curvature-mediated interaction can be strongly attractive for Janus particles adsorbed to the outside of a membrane vesicle, which initially bulges away from the particles. For Janus particles adsorbed to the vesicle inside, in contrast, the curvature-mediated interactions are repulsive. We find that the area fraction of the adhesive Janus particle surface is an important control parameter

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for the curvature-mediated interaction and assembly of the particles, besides the initial membrane curvature.

Keywords: biomembranes, vesicles, Janus particles, particle adsorption, bending energy, membrane-mediated interactions

The assembly of nanoparticles plays an important role in technological applications such as material design.[1,2] In these applications, nanoparticle assembly is typically driven by direct interactions between the particles or by external fields. Additional, indirect driving forces for assembly arise if nanoparticles are confined to liquid-liquid interfaces[3] or adsorbed on biological membranes.[4] The adsorption of nanoparticles on biological membranes is of particular importance for the bioactivity of the particles, which need to be wrapped by membranes before entering the cells and cellular organelles of living organisms.[5] Membrane vesicles with adsorbed or internalized nanoparticles are also promising carriers in drug delivery.[6]

Membrane-adsorbed nanoparticles typically induce a local curvature of the membrane, which leads to indirect, curvature-mediated interactions between adsorbed nanoparticles because the local membrane curvature induced by one nanoparticles is 'felt' by other nanoparticles in the vicinity. More precisely, the curvature-mediated interactions between adsorbed nanoparticles result from the fact that the overall bending energy of the curved membrane[7] depends on the distances and orientations of the nanoparticles. These interactions have been investigated intensively for nanoparticles and proteins that are adsorbed to or embedded in initially planar membranes. The prime example are nanoparticles and proteins with a circularly symmetric boundary line to the membrane: conical transmembrane proteins,[8–12] cap-shaped protein scaffolds,[13] or Janus nanoparticles.[14,15] For initially planar membranes, the curvature-mediated interactions of such nanoparticles and proteins are overall repulsive because the bending energy of the membrane is minimal at large particle distances. At such large particle distances, the nonadhering membrane around a nanoparticle or protein adopts the shape of a catenoidal minimal surface with zero bending energy for typical membrane

tensions that are negligible compared to the membrane bending energy on the relevant length scales up to the order of 100 nm.[16]

In this letter, we demonstrate that the curvature-mediated interactions of adsorbed Janus particles depend on the initial curvature of the membrane, i.e. on whether the membrane initially bulges towards or away from a particle. Biological membranes are often highly curved. Important examples are the curved membranes of vesicles in intracellular trafficking,[17] cell-cell signaling,[18] and drug delivery.[19] As a model system, we consider here the interaction of two Janus particles that are adsorbed either at the inside or outside of a vesicle with freely adjustable volume. For Janus nanoparticles inside a vesicle, the vesicle membrane bulges toward the particles prior to adsorption. For particles outside a vesicle, the membrane initially bulges away from the particles. In our model, the vesicle membrane is described as a triangulated elastic biomembrane,[20] and the surface of the spherical Janus particles is divided into a strongly adhesive cap with area fraction x and a non-adhesive cap with area fraction $1-x$ (see Supporting Information for further information). The strongly adhesive cap of adsorbed Janus particles is fully covered by the vesicle membrane. In experiments, Janus particles with strongly adhesive and non-adhesive surface areas have been realized by partial coating with ligands that bind to receptors anchored in cell membranes.[21,22] Current synthesis methods of Janus particles allow to adjust surface properties such as hydrophobicity, hydrophilicity, and charge[23,24] that affect the adhesiveness to vesicle membranes.[25]

The simulation data of Figure 1 show repulsive curvature-mediated interactions of two Janus particles that are adsorbed at the inside of a vesicle. In our simulated annealing Monte Carlo (MC) simulations, the bending energy of the vesicle is minimized at different, fixed distances of the two particles (see Supporting Information for further information). In this minimization, the adsorbed particles are free to adjust their orientation relative to the membrane and to each other. The minimum bending energy of the vesicle increases at small, contacting distances of the nanoparticles and at large distances at which the vesicle is stretched by the particles. At intermediate distances, the bending energy exhibits a shallow

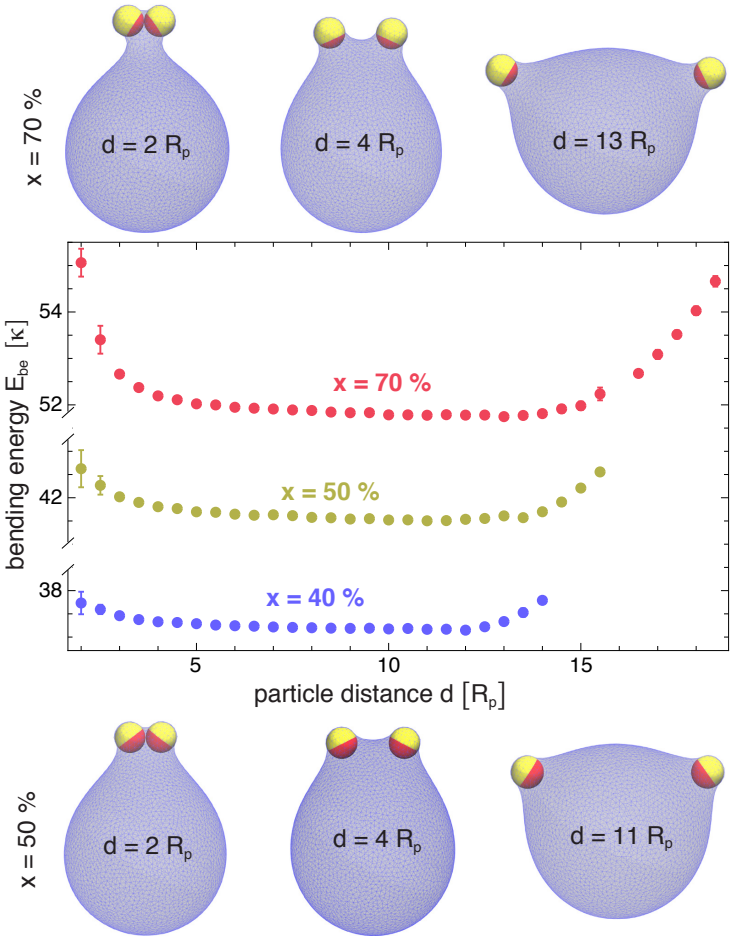

Figure 1: Bending energy $E_{\rm be}$ of a vesicle versus distance d of two Janus particles that are adsorbed at the *inside* of the vesicle. The surface of the spherical Janus particles with radius R_p is divided into a strongly adhesive cap (yellow) with area fraction x and a non-adhesive cap (red). The conformations obtained from our simulated annealing MC simulations illustrate the vesicle shape and particle orientation at different particle distances for the area fractions $x = 70\%$ (top) and $x = 50\%$ (bottom) of the strongly adhesive Janus particle caps. The area fraction of the non-adhesive particle caps is $1 - x$. The area of the vesicle is $A = 4\pi R_v^2$ with $R_v = 5.5R_p$.

minimum with a value that depends on the area fraction x of the strongly adhesive cap of the Janus particles.

The curvature-mediated interaction of two Janus nanoparticles that are adsorbed at the outside of the vesicle, in contrast, is attractive for sufficiently large area fractions x of the strongly adhesive Janus particle caps (see Figure 2). For $x = 70\%$, the bending energy $E_{\rm be}$ is minimal at the distance $d = 2R_p$ at which the particles with radius R_p are in contact. At

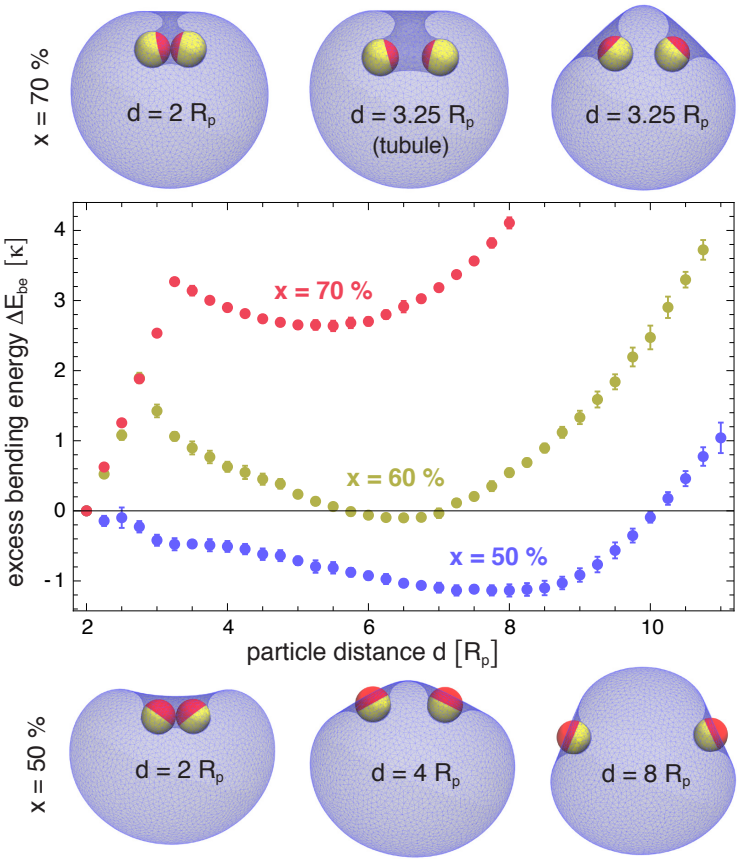

Figure 2: Excess bending energy $\Delta E_{\rm be}$ of a vesicle versus distance d of two Janus particles with radius R_p that are adsorbed at the *outside* of the vesicle. The excess bending energy here is the bending energy difference relative to the distance $d = 2R_p$ at which the particles are in contact. The conformations obtained from our simulated annealing MC simulations illustrate the vesicle shape and particle orientation at different particle distances for the area fractions $x = 70\%$ (top) and $x = 50\%$ (bottom) of the strongly adhesive Janus particle caps. The area fraction of the non-adhesive particle caps is $1 - x$. The area of the vesicle is $A = 4\pi R_v^2$ with $R_v = 5.5R_p$.

a secondary minimum at intermediate particle distances $d \simeq 5.5R_p$, the bending energy of the vesicle is about 2.6 κ larger compared to the contact distance $d = 2R_p$, which indicates strongly attractive curvature-mediated interaction energies of the Janus particles much larger than the thermal energy k_BT for typical values of the bending rigidity κ of lipid membranes between 10 and 40 k_BT.[26,27] For $x = 60\%$, the two minima of the bending energy $E_{\rm be}$ have roughly the same depth. For $x = 50\%$, the bending energy no longer exhibits a minimum at the contact distance $d = 2R_p$, and the curvature-mediated interaction of the membrane-

adsorbed Janus nanoparticles is clearly repulsive. The curvature-mediated interaction of the Janus nanoparticles in Figure 2 thus is attractive for area fractions x of the adhesive Janus particle caps larger than about 60%, and repulsive for smaller values of x.

To understand the attractive curvature-mediated interaction of Janus particles with sufficiently large adhesive area fraction x adsorbed at the vesicle outside, it is instructive to consider the vesicle conformations in Figure 2 for particles with $x = 70\%$ at the distance $d \simeq 3.25R_p$ at which the bending energy exhibits a local maximum. At this particle distance, two different vesicle conformations exhibit the same bending energy within the numerical accuracy of the simulations. In one of these conformations, the two particles are cooperatively wrapped by a membrane tubule that is connected to the vesicle outside by a membrane neck (see Figure 2, top, central conformation). In the other conformation, the particles are individually wrapped by the vesicle membrane (see Figure 2, top, right conformation). The cooperative, tubular wrapping of the particles is energetically favorable for small particle distances $d < 3.25R_p$ and leads to the curvature-mediated attraction of the particles with bending-energy minimum of the vesicle at the contact distance $d = 2R_p$ of the particles. The individual wrapping is favorable at larger distances $d > 3.25R_p$ of the Janus nanoparticles with area fraction $x = 70\%$ of the adhesive cap. The adhesive cap of Janus particles with $x = 50\%$, in contrast, is too small to allow a cooperative, tubular wrapping of the particles at short distances (see Figure 2, bottom, left). The bending energy of the vesicle therefore does not decrease at small distances of these particles, i.e. the curvature-mediated interaction is repulsive.

Figure 3 illustrates how the curvature-mediated attraction of Janus particles with adhesive area fraction $x = 70\%$ adsorbed at the vesicle outside depends on the relative curvature c_r of the particles and the vesicle. The relative curvature is defined as $c_r = \pm R_p/R_v$ where R_p is the radius of the particles and R_v is the initial radius of the vesicle without adsorbed particles. As sign convention, we choose $c_r = +R_p/R_v$ for outside particles and $c_r = -R_p/R_v$ for inside particles. Without particles, the vesicle adopts a spherical conformation with radius

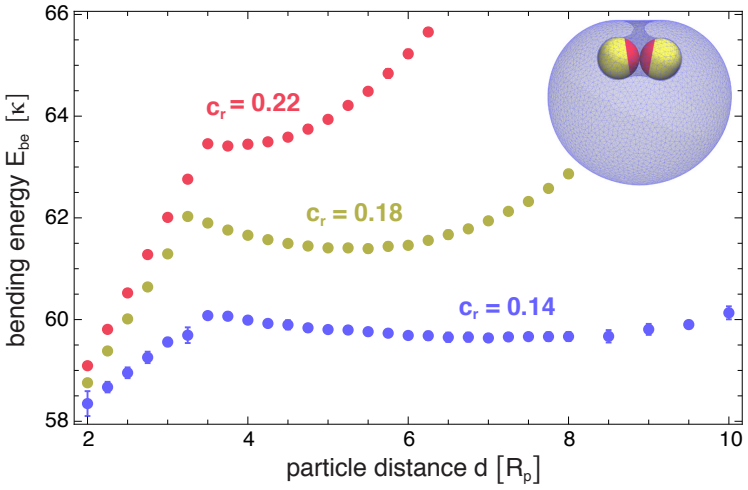

Figure 3: Bending energy of a vesicle versus distance d of two Janus particles adsorbed at the vesicle outside for difference relative curvatures $c_r = R_p/R_v$ of the particles with radius R_p and the vesicle with area $A = 4\pi R_v^2$. The shown conformation from simulations illustrates the vesicle shape for $c_r = 0.22$ at particle contact.

R_v because this conformation minimizes the vesicle bending energy.[28] In our simulations, the relative curvature c_r is varied by varying the vesicle area $A = 4\pi R_v^2$, which is constraint to ensure the near incompressibility of lipid membranes.[29] The curvature-mediated attraction of the outside Janus particles with $x = 70\%$ strongly increases with the relative curvature c_r of the particles and the vesicle.

Figure 4 summarizes the curvature-mediated interaction energies E_{int} of adsorbed Janus particles for different relative curvatures c_r of the particles and the vesicle and different area fractions x of the adhesive Janus particle cap. The indirect, curvature-mediated interaction energy of the adsorbed Janus particles is defined as the difference of (i) the vesicle bending energy at the contact distance $d = 2R_p$ and (ii) the vesicle bending energy at the local or global minimum at larger distances $d > 3.5R_p$. Positive interaction energies E_{int} indicate curvature-mediated repulsion of the adsorbed Janus particles, while negative interaction energies indicate curvature-mediated attraction. The two data points at $c_r = 0$ represent the curvature-mediated interaction energies of two Janus particles with $x = 50\%$ and 70% that are adsorbed to initially planar membranes and have been taken from Ref. 14 (see Supporting Information for further information). All other data points result from the

interaction profiles of Figures 1 to 3. The curvature-mediated interactions of the Janus particles are repulsive if the membrane is initially planar ($c_r = 0$) or bulges towards the particles prior to particle adsorption ($c_r < 0$, particles at vesicle inside), irrespective of the area fraction x of the adhesive Janus particle caps. If the membrane initially bulges away from the particles ($c_r > 0$, particles at vesicle outside), in contrast, the curvature-mediated interaction is attractive for sufficiently large x and c_r. This curvature-mediated attraction results from an energetically favorable cooperative wrapping of the particles by a tubular membrane segment at small particle distances (see shapshot at bottom right). The dashed interpolation lines of Figure 4 indicate a curvature-mediated attraction of Janus particles with $x = 70\%$ for relative curvatures c_r larger than about 0.1, i.e. for initial vesicle radii R_v that are smaller than about 10 times the particle radii. For Janus particles with $x = 60\%$, curvature-mediated attraction occurs for relative curvatures c_r larger than about 0.2. For Janus particles with $x = 50\%$ (snapshots at bottom left and top right), the curvature-mediated interactions are always repulsive and rather independent of the relative curvature c_r of the particles and the vesicle.

For vesicles with many adsorbed Janus particles, the attractive or repulsive curvature-mediated pair interactions investigated here can be expected to determine the overall conformation of the vesicle and assembly of the particles. Janus particles with repulsive curvature-mediated pair interactions can be expected to spread out on the vesicle surface to maximize the distance between neighboring particles, similar to shallow conical membrane inclusions with repulsive indirect pair interactions.[30] Janus particles with attractive curvature-mediated pair interactions, in contrast, are likely to form particle assemblies on the vesicle surface. Depending on the area fraction and adhesion energy of the adsorbed Janus particle caps, we expect conformations in which several particles are cooperatively wrapped in tubular membrane segments, similar to the cooperative wrapping of uniformly adhesive spherical and non-spherical particles by membrane tubes.[15,31–35] Our results identify the area fraction x of the adhesive Janus particle caps and the relative curvature c_r of the particles and vesicles as

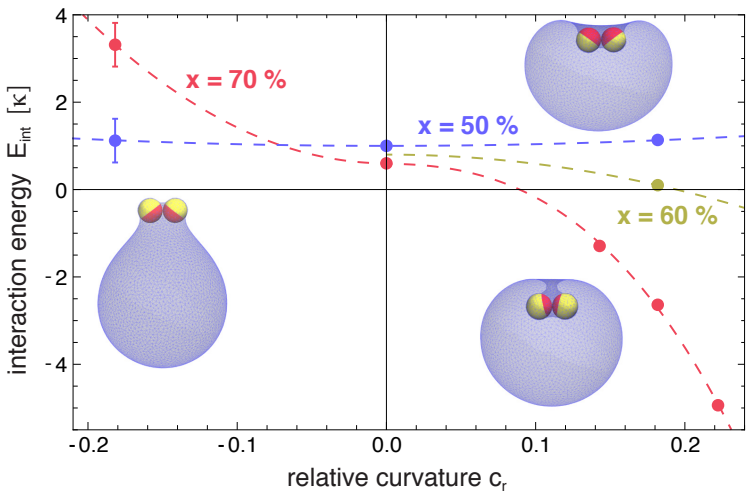

Figure 4: Curvature-mediated interaction energy $E_{\rm int}$ of adsorbed Janus nanoparticles versus relative curvature c_r of the particles and vesicle for different area fractions x of the adhesive Janus particle caps. The interaction energy is the difference in bending energy at particle contact distance $d = 2R_p$ and at the minimum for larger distances $d > 3.5R_p$. The two data points for $c_r = 0$ (initially planar membranes) are from Ref. 14. All other data points are obtained from the interaction profiles of Figures 1 to 3. The dashed interpolation lines are guides for the eye.

experimentally accessible control parameters for the particle assembly. The relative curvature c_r can be adjusted by varying the relative size of the Janus particles and the vesicle, and by confining the particles to the vesicle interior or exterior. The diameter of extracellular membrane vesicles[18,36] and reconstituted lipid vesicles[37] ranges from about 40 nm to 10 μm, while intracellular membrane vesicles have diameters up to about 100 nm.[38] Our results indicate that the curvature-mediated interactions of adsorbed particles depend on the relative curvature c_r for particle diameters that are larger than about 10 percent of the vesicle diameter. Vesicles with freely adjustable volume considered in our simulations correspond to experimental situations without osmotically active particles such as salts or sugars in and around the vesicle.[16] In these situations, the flux of water through the membranes is not constrained by osmotic pressure.

In this letter, we have focused on Janus particles with strongly adhesive spherical caps, which exhibit a circularly symmetric boundary line between the membrane segment that is bound to the adhesive cap and the unbound membrane. The curvature-mediated interactions

of particles and proteins with such circularly symmetric boundary lines are a prime example of indirect interactions mediated by membranes, but have been investigated so far only for initially planar membranes[8–12,14] or for shallow conical inclusions embedded in rather weakly curved membranes.[39] The curvature-mediated pair interactions of circularly symmetric particles and proteins have been found to be repulsive on initially planar or weakly curved membranes. Our results show that these curvature-mediated interactions depend on the initial, background curvature of the membranes and can be attractive for Janus particles with sufficiently large adhesive caps adsorbed to membranes that initially bulge away from the particles with a membrane curvature radius that is smaller than about 10 times the particle radius. Similarly, the pair interactions of particles and proteins without circular symmetry have been investigated only for initially planar membranes,[40–43] but can be expected to depend on membrane curvature, based on our results. An important example is the curvature-mediated interaction of adsorbed crescent-shaped proteins[43–46] such as BAR domains that induce the formation of highly curved membrane tubules with a radius that corresponds to the curvature radius of the crescent-shaped proteins.[47–50]

Supporting Information:

Additional information on the model, the Monte Carlo simulations, and the results of Ref. 14 on curvature-mediated interactions in planar membranes.

Acknowledgement

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