Electronic Supplementary Material (ESI) for Biomaterials Science

Supplementary Information for: How to Optimize Binding of Coated Nanoparticles: Coupling of Physical Interactions, Molecular Organization and Chemical State

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1 Theory

The system that we describe, schematically presented in Figure S1, consists of a micelle of radius R which has end-tethered N_N neutral polymers (poly ethyleneglycol) (PEG) and N_B polybases (*e.g.*, poly((dimethylamino)ethyl methacrylate) (PDMAEMA)). The degree of polymerization or length of the neutral polymer chain is n_N. The polybase consists of n_B monomer units; each unit is a basic group which can be either protonated (BH^+) or deprotonated (B). The free end of the polybase has a ligand that has specific interactions with the receptors of the lipid membrane. The micelle is positioned a distance D from a surface. The distance is measured from the center of the sphere to the surface. The system is in a solution with fully dissociated salt, $NaCl$, and at a given pH, in most cases both are physiological conditions.

We assume that the system is rotationally invariant along the axis perpendicular to the surface and passing through the poles of the micelle or sphere. This axial symmetry is used explicitly by employing cylindrical coordinates (r, φ, z), enabling the integration of the azimuthal angle φ and consequently reducing the problem from three to two dimensions.

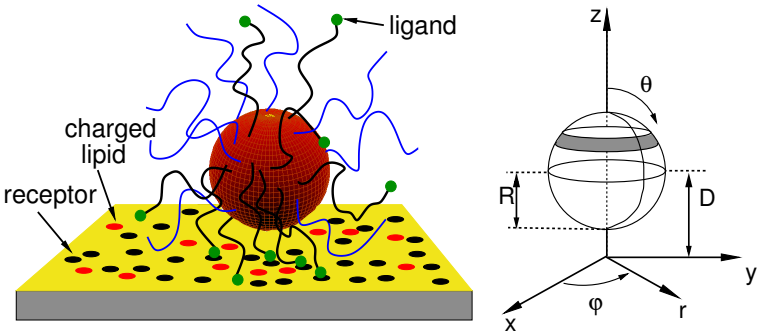

Figure S1: Left: Schematic representation of a nanomicelle with functionalized head-groups. The neutral polymers are represented by blue lines and the polybases (black lines) have a ligand at the free end, (green dot) which interacts with receptors head-group (black) of lipids found in the lipid membrane. The lipid membrane consists of lipids with acidic head -groups, (phosphatidylserine). Right: Representation of the cylindrical coordinate system used. The gray area in the right figure on the sphere represents a surface element with uniform properties.

We describe both end-tethered solid nanoparticles and micelles. For solid nanoparticles the chains are irreversibly end-grafted to the nanoparticle; however, in the case of micelles tethered with polymers, the end-grafted polymer

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chains are able to diffuse on the surface, *i.e.*, have translational entropy [1], since they are part of the surfactant head group. The mobility of the chains implies that we have to allow for an inhomogeneous distribution of the polymers on the micelle. Therefore it is convenient to introduce the local surface of coverage: $\sigma_i(\theta) = N_i(\theta)/A(\theta)$, which corresponds to the number of polymers of type i tethered to a surface sector θ divided by the area of the surface sector. See figure S1. In case of an homogenous polymer distribution the local surface coverage, $\sigma_i(\theta)$, equals the global surface coverage, $\sigma_i = N_i/A_{\rm surf}$. Here $A_{\rm surf}$ is the total surface area of the sphere. Otherwise the total surface coverage is given by the integral $\sigma_i = \int \mathrm{d}A(\theta)N_i(\theta)/A_{\rm surf}$.

The surface consists of a mixture of neutral and charged lipids. The lipids on the membrane are characterized by the areal surface density of their components, which are denoted by $\sigma_N(r)$ and $\sigma_C(r)$, respectively referring to the neutral and negatively charged lipid. The later molecule can be found either in its protonated (AH) or deprotonated (A^-) state; $\sigma_C(r) = \sigma_{A^-}(r) + \sigma_{AH}(r)$. Each, neutral and anionic lipids have an area per lipid of $a_0 = 0.65\ nm^2$. Furthermore, the lipid layer may contain overexpressed receptors. We only consider the case in which the receptors are in large excess and therefore we do not need to consider their density explicitly.

The total free energy describing the system has the following contributions

$$F = -TS_{\rm conf} - TS_{\rm mix,poly} - TS_{\rm mix} + E_{\rm rep} + E_{\rm elec} + F_{\rm chem} + G_{\rm bind} + F_{\rm surf}, \tag{1}$$

where T is the temperature. In the following we describe each of the terms of the free energy in terms of the probability functions and local varying densities. The first term in the free energy represents the conformational entropy of the polymer chains and is given by

$$\begin{aligned} -\frac{S_{\rm conf}(D)}{k_B} &= \int \mathrm{d}\theta\, N_N(\theta) \sum_{\alpha_N} P(\alpha_N,\theta,D)\ln P(\alpha_N,\theta,D) \\ &\quad + \int \mathrm{d}\theta\, N_B(\theta) \sum_{\alpha_B} P(\alpha_B,\theta,D)\ln P(\alpha_B,\theta,D) \end{aligned} \tag{2}$$

The first term denotes the conformation entropy of the neutral chains whereas the second term represent the conformation entropy of the basic polymer chains.

Here, $P(\alpha_i,\theta,D)$ is the probability of finding a type i polymer chain tethered to the surface element θ and micelle lipid membrane distance D in a conformational state α_i. $N_i(\theta)d\theta$ is the number of polymer chains of type i tethered to the surface sector located in the interval $(\theta, \theta + d\theta)$. The micelle and the lipid membrane are a distance D apart. See fig. S1.

The second term in the free energy accounts for the translational entropy of the mobile chains relative to their entropy for a homogeneous surface distribution of the chains; $\sigma_i = N_i/A_{surf}$.

$$-\frac{S_{\rm mix,poly}(D)}{k_B} = \int \mathrm{d}\theta\, N_N(\theta)(\ln \sigma_N(\theta)/\sigma_N - 1) + \int \mathrm{d}\theta\, N_B(\theta)(\ln \sigma_B(\theta)/\sigma_B - 1). \tag{3}$$

In case of immobile tethers the local surface coverage is fixed and this translational entropy contribution to the free energy is constant since $\sigma_B(\theta) = \sigma_B$ and $\sigma_N(\theta) = \sigma_N$.

The third term in the free energy denotes the mixing (translational) entropy of all other species in the system; *i.e.*, water, cations, anions, protons, and hydroxyl ions.

$$\begin{aligned} -\frac{S_{\rm mix}(D)}{k_B} &= \iint \mathrm{d}r\,\mathrm{d}z G(r,z)\rho_w(r,z)(\ln \rho_w(r,z)v_w - 1) \\ &\quad + \iint \mathrm{d}r\,\mathrm{d}z G(r,z)\rho_{Na^+}(r,z)(\ln \rho_{Na^+}(r,z)v_w - 1) \\ &\quad + \iint \mathrm{d}r\,\mathrm{d}z G(r,z)\rho_{Cl^-}(r,z)(\ln \rho_{Cl^+}(r,z)v_w - 1) \\ &\quad + \iint \mathrm{d}r\,\mathrm{d}z G(r,z)\rho_{H^+}(r,z)(\ln \rho_{H^+}(r,z)v_w - 1 + \beta\mu^{\ominus}_{H^+}) \\ &\quad + \iint \mathrm{d}r\,\mathrm{d}z G(r,z)\rho_{OH^-}(r,z)(\ln \rho_{OH^-}(r,z)v_w - 1 + \beta\mu^{\ominus}_{OH^-}). \end{aligned} \tag{4}$$

Here $\rho_j(r,z)$ is the number density of molecular species j at position (r,z) and $G(r,z)drdz$ corresponds to the volume element that in cylindrical coordinates is equal to $2\pi r dr dz$. The terms corresponding to the protons and hydroxyl atoms include also the standard chemical potential ($\mu_i^{\ominus}$) of those species as these terms are necessary for the proper consideration of the chemical equilibrium, see below.

The fourth term, $E_{\rm rep}$, of the free energy describes the intermolecular excluded volume interactions, which are accounted for by assuming that the system is incompressible at every position. Namely, that the sum of the volume fraction of polymers, solvent, and ionic species add up to one at every postition;

$$\langle\phi_N(r,z)\rangle + \langle\phi_B(r,z)\rangle + \rho_w(r,z)v_w + \rho_{Na^+}(r,z)v_{Na^+} + \rho_{Cl^-}(r,z)v_{Cl^-} + \rho_{H^+}(r,z)v_{H^+} + \rho_{OH^-}(r,z)v_{OH^-} + \phi_M(r,z) = 1. \quad (5)$$

These packing constraints are enforced in the minimization of the free energy through the introduction of the Lagrange multipliers $\pi(r,z)$, see below. Here $\langle\phi_N(r,z)\rangle$ and $\langle\phi_B(r,z)\rangle$ correspond to the volume fraction of the neutral polymer and the polybase. These volume fractions are given by :

$$\langle\phi_i(r,z)\rangle = \int \mathrm{d}\theta\, \frac{N_i(\theta)}{G(r,z)} \sum_{\alpha_i} P(\alpha_i,\theta,D) n_i(\alpha_i,\theta;r,z) v_i^p. \quad (6)$$

Here $n_i(\alpha_i,\theta;r,z)\mathrm{d}r\mathrm{d}z$ is the number of segments of polymer type i in the volume element $G(r,z)drdz$ when its conformation α_i is tethered to surface area element $A(\theta)\mathrm{d}\theta$. The area element $A(\theta)$ is given by $A(\theta)d\theta = 2\pi\sin(\theta)R^2 d\theta$. v_i^p denotes the volume of one polymer segment of type i. In the packing constraint Eq. 5, $\phi_M(r,z)$ denotes the volume fraction of the micellar core, which is introduced to allow for solvent and ions to penetrate the micellar core. We assume $\phi_M(r,z) = \phi_M = constant$ for those r,z coordinates inside the micellar core. Throughout the calculation we set $\phi_M = 0.9$. Note that the results are insensitive to the particular choice of ϕ_M.

The hydrophobicity of the polymers, *i.e.*, the solvent quality, can be described by an effective attractive Van der Waals interaction [2]

$$E_{\rm VdW} = \frac{1}{2}\int \mathrm{d}\vec{r} \int \mathrm{d}\vec{r}' \chi_p(|\vec{r}-\vec{r}'|)\langle\phi_p(r,z)\rangle\langle\phi_p(r',z')\rangle. \quad (7)$$

We limit ourself to good-solvent conditions ($\chi_p = 0$) because the polymers we model, PEG and PDMAEMA, are water soluble, *i.e.*, water acts as a good solvent for them.

The fifth term in equation 1 describes the electrostatic energy contribution to the free energy [3]

$$E_{\rm elect}(D) = \beta \iint \mathrm{d}r\,\mathrm{d}z\, G(r,z)\left(\rho_q(r,z)\psi(r,z) - \frac{1}{2}\epsilon(r,z)(\nabla\psi(r,z))^2\right) + \beta\int \mathrm{d}r\, A(r)\sigma_q(r)\psi(r,0), \quad (8)$$

here $\psi(r,z)$ corresponds to the electrostatic potential and $\rho_q(r,z)$ to the charge density. The charge density is the sum of the charge arising form the protonated polybase units and the free ionic species and is given by

$$\rho_q(r,z) = f(r,z)\langle\rho_B(r,z)\rangle e + \rho_{Na^+}(r,z)e - \rho_{Cl^-}(r,z)e + \rho_{H^+}(r,z)e - \rho_{OH^-}(r,z)e, \quad (9)$$

where e is the unit of charge, $\langle\rho_B(r,z)\rangle$ equals the density of polybase monomers, and $f(r,z)$ corresponds to the fraction of polybase segments that are charged at r,z. The surface charge density $\sigma_q(r)$ refers to the amount of charged lipid molecules found on the model cell membrane at r, to be discussed in more detail below.

The free energy associated with the (de)protonation of the base group of the polymer ($B + H^+ \rightleftarrows BH^+$) is represented by [4,5]

$$\beta F_{\rm chem}(D) = \beta \iint \mathrm{d}r\,\mathrm{d}z\langle\rho_B(r,z)\rangle\left(f(r,z)(\ln f(r,z) + \beta\mu^{\ominus}_{BH^+}) + (1-f(r,z))(\ln(1-f(r,z)) + \beta\mu^{\ominus}_{B})\right) \quad (10)$$

The first and third term describe the entropy of mixing between the protonated and deprotonated states at each r,z. The second and fourth term represent the standard chemical potential of forming a protonated and a deprotonated state respectively.

The seventh contribution, $G_{\rm bind}$, to the free energy describes the free energy change associated with the binding of a ligand attached to the end-group of the polybase chain to a receptor located on the lipid membrane. It is assumed that the number of receptor sites on the membrane are in excess corresponding to conditions for which a surface has overexpressed receptors. Then, the free energy contribution of the ligand-receptor binding is given by the number of end-groups ($n_B^e(\alpha_B,\theta;r,0)$) or ligand-receptor pairs at the membrane times the free energy to form one ligand-receptor bond, ΔG_{bind}.

$$\beta G_{\rm bind}(D) = \beta \iint \mathrm{d}r\,\mathrm{d}z\, G(r,z)\int \mathrm{d}\theta\, N_i(\theta) \sum_{\alpha=\alpha_B} P(\alpha_B,\theta,D) n_B^e(\alpha,\theta;r,z)\Delta G_{bind}\delta(z). \quad (11)$$

The free binding energy is expressed in units of k_BT. It is possible to take into consideration with the theory cases where the amount of receptors are not in excess and include within the theoretical framework both the amount of receptors on the surface as well as the fraction of ligand that bind.[6,7]

The last term of the free energy functional labeled $F_{\rm surf}$ represents the free energy contribution arising from the surface lipids[8–11].

$$\beta F_{\rm surf}(D) = \int {\rm d}r\, A(r)\sigma_N(r)(\ln(\sigma_N(r)/\sigma_l)-1) + \sigma_C(r)(\ln(\sigma_C(r)/\sigma_l)-1) + \int {\rm d}r\, A(r)\sigma_C(r)\left[x(r)(\ln x(r)+\beta\mu^{\ominus}_{A^-}) + (1-x(r))(\ln(1-x(r))+\beta\mu^{\ominus}_{AH})\right]. \quad (12)$$

The first two terms in F_{surf} represent the (translational) mixing entropy of the mixture of neutral and charged lipid molecules present on the membrane. Here $\sigma_N(r)$ and $\sigma_C(r)$ are the local areal surface density of the head groups of the neutral and anionic lipids. The lipid membrane is covered with neutral and charged lipids; hence the areal density of both lipids at every position on the membrane add up to the total areal lipid density; $\sigma_l = \sigma_C(r) + \sigma_N(r)$. These constraints are enforced through the introduction of Lagrange multipliers $\pi_s(r)$ in the free energy minimization. The neutral and anionic lipid have the same area per lipid $a_0 = 0.65\,nm^2$. Consequently $\sigma_l = 1/a_0 = 1.54\,nm^2$. The anionic lipid is considered to be a weak acid ($AH \rightleftarrows A^- + H^+$), thus it is either protonated (AH) of deprotonated (A^-) depending on its local environment. The energy and entropic contribution arising from this acid-base chemical equilibruim are accounted for by equation 12. Here $x(r)$ is the fraction of acidic lipids that are charged (deprotonated) at r: $x(r) = \sigma_{A^-}(r)/(\sigma_{A^-}(r)+\sigma_{AH}(r)) = \sigma_{A^-}(r)/\sigma_C(r)$. Following this definition the total surface charge density at position r becomes $\sigma_q(r) = -ex(r)\sigma_C(r)$. The standard chemical potential $\mu^{\ominus}_{AH}$ and $\mu^{\ominus}_{A^+}$ in Eq. 12 denote the free energy of the protonated and deprotonated state respectively and the remaining terms represent the entropy of mixing associated with the protonated and deprotonated state.

The above form of $F_{\rm surf}$ corresponds to a lipid membrane in the liquid-disordered phase, *i.e.*, the lipids are mobile, and the charged lipids are charge regulating (weak acids). Expressions for lipids membranes in a gel phase where the lipids can not move or where the anionic lipids are not charge regulating can be obtained from the above expression by appropriately considering constant lipid areal density or a constant charged lipid fraction. Four different scenarios have been considered, namely the lipid membrane is either in the liquid-disorder or gel phase (mobile or immobile) and the charged lipids are either charge regulating or not.

To establish the thermodynamic equilibrium state, the free energy is minimized with respect to the $P_i(\alpha,\theta)$, $\rho_i(r,z)$, $N_i(\theta)$, $f(r,z)$, $x(r)$, $\sigma_N(r)$, and $\sigma_C(r)$, and varied with respect to the electrostatic potential $\psi(r,z)$ under the constraints of incompressibility, mass balance of the polymer chains, and the fact that the system is in contact with a bath of cations, anions, protons, hydroxyl atoms, and lipids. The proper thermodynamic potential becomes:

$$\begin{aligned}\beta W \;=\;& \beta F + \beta\iint {\rm d}r\,{\rm d}z\, G(r,z)\pi(r,z)\left(\langle\phi_N(r,z)\rangle + \langle\phi_B(r,z)\rangle + \rho_w(r,z)v_w + \rho_{Na^+}(r,z)v_{Na^+}\right.\\ &\left.+\rho_{Cl^-}(r,z)v_{Cl^-} + \rho_{H^+}(r,z)v_{H^+} + \rho_{OH^+}(r,z)v_{OH^-} + \phi_M(r,z) - 1\right)\\ &+\beta\int {\rm d}r\, A(r)\pi_s(r)\left(\sigma_N(r)+\sigma_C(r)-\sigma_l\right)\\ &-\beta\mu_N\int {\rm d}\theta\left(N_N(\theta)-N_N\right) - \beta\mu_B\int {\rm d}\theta\left(N_B(\theta)-N_B\right)\\ &-\sum_{i=Na^+,Cl^-}\beta\mu_i\iint {\rm d}r\,{\rm d}z\, G(r,z)\rho_i(r,z) - \mu_C\int {\rm d}r\, A(r)\sigma_C(r). \end{aligned} \quad (13)$$

The number of independent thermodynamic components is reduced by three, because the system is incompressible, charge neutral, and the water molecules are in chemical equilibrium with the protons and hydroxyls atoms. Due to these constraints, the chemical potentials are exchange chemical potentials. Equivalently, the area constraint reduces the number of independent surface components. Therefore it is unnecessary to explicitly introduce the exchange chemical potential for both the neutral and anionic lipid. For a more extended discussion on the subject of exchange chemical potentials see references[2] and[5]. The total number of polybase and neutral polymer chains are fixed at a value of N_B and N_N respectively; *i.e.*, $\int N_i(\theta){\rm d}\theta = N_i$. The Lagrange multipliers μ_B and μ_N introduced to impose these (mass balance) constraints for the polymers can be identified as the chemical potentials of the polybase and the neutral polymer respectively.

Minimization yields for the probability distribution function of the neutral (PEG) molecule

$$P(\alpha_N,\theta,D) = \frac{1}{q_N(\theta,D)}\exp\left[-\beta\iint n_N(\alpha_N,\theta;r,z)\pi(r,z)v_N^p {\rm d}r{\rm d}z\right], \quad (14)$$

here $q_N(\theta, D)$ is a normalization factor ensuring that the probability distribution function is properly normalized: $\sum_{\alpha_N} P(\alpha_N, \theta, D) = 1$. The term in the exponential results from the repulsive interactions that a neutral polymer in conformation α_N experiences.

Minimization yields for the probability distribution function of a polybase molecule the following equation

$$P(\alpha_B, \theta, D) = \frac{1}{q_B(\theta, D)} \exp\left[-\beta \iint n_B(\alpha_B, \theta; r, z)\pi(r, z)v_B^p \mathrm{d}r\mathrm{d}z - \beta \int n_B^e(\alpha_B, \theta; r, 0)\Delta G_{bind}\mathrm{d}r\right] \times \exp\left[-\iint n_B(\alpha_B, \theta; r, z)\left(\beta\psi(r, z)e + \ln(f(r, z))\right)\mathrm{d}r\mathrm{d}z\right]. \quad (15)$$

The first term in the exponential is identical in meaning to the one appearing in the pdf of the neutral polymer. The second term is an attractive contribution arising from the binding of the functional end-group of the polymer chain when in contact with the surface. This term only contributes to $P(\alpha_B, \theta, D)$ when the end-group of conformation α_B for a given anchor location θ reaches the membrane. The remaining two terms represent contributions arising from the electrostatic interaction and the chemical equilibrium. The probability distribution functions, like other variables such as the densities, also depend on the distance D between the micelle and the lipid membrane.

Minimization of the free energy with respect to the local number of tethered polymers or equivalently the local surface coverage gives

$$\beta\mu_i(D) = -\ln(q_i(\theta, D)) + \ln(\sigma_i(\theta)/\sigma_i). \quad (16)$$

The surface coverage of polymers of type i is

$$\sigma_i(\theta) = \sigma_i e^{\beta\mu_i(D)} q_i(\theta, D) \quad \text{with} \quad e^{\beta\mu_i(D)} = \frac{A_{\text{surf}}}{\int A(\theta)q_i(\theta, D)\mathrm{d}\theta}. \quad (17)$$

The second equation is obtained by integration over the surface of the sphere and using the relations $\int A(\theta)\sigma_i(\theta)\mathrm{d}\theta = N_i$ and $\int A(\theta)\mathrm{d}\theta = A_{\text{surf}}$. The above equations guarantee that the chemical potential, μ_i, of the polymer chains of type i is the same for every position along the micelle's surface, as required by thermodynamic equilibrium. The equations also demonstrate the non-local coupling that exists between the polymer chains tethered at different grafting positions and show that the chemical potential will change with the separation between micelle and lipid membrane. As the distance is reduced, the polymer layer get confined. The confinement results in a change of the probability distribution function of the chains that causes a change of the chemical potential of the polymers.

By minimizing the free energy with respect of degree of dissociation of the polybase we obtain

$$\frac{f(r, z)}{1 - f(r, z)} = K_b^{\ominus} \frac{\phi_{H^+}(r, z)}{\phi_w(r, z)}. \quad (18)$$

Here $K_b^{\ominus} = \exp\left(-\beta\Delta G_b^{\ominus}\right)$ with $\Delta G_b^{\ominus} = \mu_{BH^+}^{\ominus} - \mu_B^{\ominus} - \mu_{H^+}^{\ominus}$ which is equal to the standard free energy of the chemical reaction $(B + H^+ \rightleftarrows BH^+)$. $K_b^{\ominus}$ is the equilibruim constant of the chemical reaction and is related to the equilibrium constant in bulk solution $K_b = [BH^+][OH^-]/[B] = CK_wK_b^{\ominus}$. Here [] denotes the molar concentration and K_w is the water equilibrium constant. The constant C is needed for consistency of units as K_b has the units of molarity whereas $K_b^{\ominus}$ is dimensionless $(C = 1/(N_A v_w))$.

Variation of the free energy functional with respect to the electrostatic potential $\psi(r, z)$ leads to the Poisson equation and its boundary conditions:[3,5]

$$\nabla(\epsilon(r, z)\nabla\psi(r, z)) = -\langle\rho_q(r, z)\rangle \quad \wedge \quad \epsilon\nabla\psi \cdot n_S|_{\partial V} = -\sigma_q(S). \quad (19)$$

Here ∇ corresponds to the gradient or del operator in cylindrical coordinates. The second term represent the boundary conditions with the lipid surface, the micellar core, as well as the boundary conditions with the bulk solution. The explicit electrostatic boundary condition for the lipid surface $(z = 0)$ reads:

$$-\epsilon_w\epsilon_0 \left.\frac{\partial\psi(r, z)}{\partial z}\right|_{z=0} = \sigma_q(r). \quad (20)$$

For $z \to \infty$ we can set $\lim_{z\to\infty}\psi(r, z) = 0$. For general z we need to use $\frac{\partial}{\partial r}\psi(r, z) = 0$ as only when there is no charge on the surface $(\sigma_q(r) = 0)$ does $\lim_{r\to\infty}\psi(r, z) = 0$.

Minimization of the free energy with respect of solvent density yields

$$\phi_w(r, z) = \rho_w(r, z)v_w = \exp\left(-\beta\pi(r, z)v_w\right). \quad (21)$$

The physical meaning of the Lagrange multipliers can be understood from the last expression. They correspond to the position dependent osmotic pressures. One can also view them as the average interaction or potential due to the excluded volume interactions. A more detailed discussion on the physical significance of these quantities can be found elsewhere[2].

The expressions for the densities of the cations and anions are

$$\rho_{Na^+}(r,z)v_w = \exp\left(\beta\mu_{Na^+} - \beta\pi(r,z)v_{Na^+} - \beta\psi(r,z)e\right), \quad (22)$$

$$\rho_{Cl^-}(r,z)v_w = \exp\left(\beta\mu_{Cl^-} - \beta\pi(r,z)v_{Cl^-} + \beta\psi(r,z)e\right), \quad (23)$$

while the density of the proton and hydroxyl ions are given by

$$\rho_{H^+}(r,z)v_w = \exp\left(\beta\mu^{\ominus}_{H^+} - \beta\pi(r,z)v_{H^+} - \beta\psi(r,z)e\right), \quad (24)$$

$$\rho_{OH^-}(r,z)v_w = \exp\left(\beta\mu^{\ominus}_{OH^-} - \beta\pi(r,z)v_{OH^-} + \beta\psi(r,z)e\right). \quad (25)$$

In deriving the above equations we assumed that the system is in contact with a bath of ions. Therefore, as a consequence of thermodynamic equilibrium, the chemical potentials of the ions are constant at every position and their values are determined by the bulk conditions.

By minimizing the free energy with respect of the degree of dissociation of the acidic lipid $x(r)$ we get

$$\frac{x(r)}{1-x(r)} = K_a^{\ominus}\frac{\phi_w(r,0)}{\phi_{H^+}(r,0)} = K_a^{\ominus}\exp(\beta\mu^{\ominus}_{H^+})\exp(\beta\psi(r,0)e). \quad (26)$$

This expression is similar to the equation for the degree of dissociation of the polybase. Here $K_a^{\ominus} = \exp\left(-\beta\Delta G_a^{\ominus}\right)$ with $\Delta G_b^{\ominus} = \mu^{\ominus}_{A^-} + \mu^{\ominus}_{H^+} - \mu^{\ominus}_{AH}$ which is equal to the standard free energy of the chemical reaction. $K_a^{\ominus}$ is the equilibrium constant of the acid-base chemical reaction, $AH \rightleftarrows A^- + H^+$, and is related to the equilibrium constant in bulk solution $K_a = [A^-][H^+]/[AH] = CK_a^{\ominus}$. Observe that the second part of the chemical equilibrium equation is presented to stress the similarity with the chemical equilibrium equation of the polybase. In practice the third equation is used, which depends only on the surface electrostatic potential and $\mu^{\ominus}_{H^+}$ which can be related to the bulk concentration of the protons; *i.e.*, $pH = -\log[H^+]$.

For the density of the neutral and anionic lipids we get

$$\sigma_N(r)/\sigma_l = \exp(-\beta\pi_s(r)), \quad (27)$$

$$\sigma_C(r)/\sigma_l = \exp(-\beta\pi_s(r) - \beta\psi(r,0)(-e) + \ln x(r) - \beta(\mu^{\ominus}_{A^-} + \mu_C)). \quad (28)$$

Compare the above equations with the equations obtained for the ions and the probability distribution functions. They are similar in content and meaning. The value of the chemical potentials can be determined from the bulk composition of the lipid membrane. It turns out to be convenient to introduce the following variable: $f_l(r) = \sigma_C(r)/(\sigma_N(r) + \sigma_C(r) = \sigma_C(r)/\sigma_l$, which is equal to the fraction of acidic lipids in the membrane at position r. Consequently $\sigma_C(r) = f_l(r)\sigma_l$, $\sigma_N(r) = (1 - f_l(r))\sigma_l$ and $f_l(r)$ as a function of $x(r)$ becomes

$$\frac{f_l(r)}{1-f_l(r)} = \frac{e^{-\beta(\mu^{\ominus}_{AH} - \mu_C)}}{1-x(r)} \quad (29)$$

The above equation can be readily solved once the bulk composition f_l^{bulk} and surface potential $\psi(r,0)$ are known.

Having found the equations describing the thermodynamical equilibrium the minimal free energy can be obtained. The effective interaction between the micelle and the surface is given by

$$\begin{aligned}
\beta\Delta W(D) &= \beta W(D) - \beta W(\infty) \\
&= \beta(\mu_N(D) - \mu_N(\infty))N_N + \beta(\mu_B(D) - \mu_B(\infty))N_B \\
&\quad -\frac{1}{2}\beta\iint \mathrm{d}r\mathrm{d}z G(r,z)\left(\langle\rho_q(r,z)\rangle\psi(r,z) - \langle\rho_{q,\infty}(r,z)\rangle\psi_\infty(r,z)\right) \\
&\quad -\beta\iint \mathrm{d}r\mathrm{d}z G(r,z)\left(\pi(r,z)(1-\phi_M(r,z)) - \pi_\infty(r,z)(1-\phi_{M,\infty}(r,z))\right) \\
&\quad -\sum_{i=w,Na^+,Cl^-,H^+,OH^-}\iint \mathrm{d}r\mathrm{d}z G(r,z)(\rho_i(r,z) - \rho_{i,\infty}(r,z)) \\
&\quad -\beta\int \mathrm{d}r A(r)(\pi_s(r) - \pi_{s,\infty}) - \frac{1}{2}\beta\int A(r)\left(\sigma_q(r)\psi(r,0) - \sigma_{q,\infty}\psi_\infty(r,0)\right), \quad (30)
\end{aligned}$$

which corresponds to the difference between the free energy when the micelle and the surface are a distance D apart and when they are infinitely far apart. Equation 30 is obtained by substituting the equations for the densities of the ions, solvent, lipids, the pdfs and local surface coverage of the polymers, the electrostatic potential, and the degree of dissociation of both polybase and acidic lipid into the free energy expression (Eq. 13).

The unknowns in Eqs. 21-29 and 14-18 are the lateral pressures and electrostatic potential.[5,12] Application of the theory requires the determination of these lateral pressures and electrostatic potential. The unknown lateral pressure and electrostatic potential can be obtained by substituting the volume fractions and areal densities of the lipids into the incompressibility constraint, Eq. (5), the Poisson Eq. (19) and the Eq. (29 and 26), the later two equations determine the composition of the lipid membrane. The resulting set of coupled non-linear integrodifferential equations can be discretized and solved numerically. Technical aspects of how to apply and numerically solve the theory are outlined in the next section. The input necessary to solve the equations are the surface coverage of the neutral polymers and polybases, σ_N and σ_B, the binding energy ΔG_{bind} and the radius R of the nanomicelle, the distance D between nanomicelle and surface, and the sets of polymer conformations for the neutral polymer and polybase, α_N and α_B, the pK_b of the polybase, the pK_a of the acidic lipid, the bulk fraction of neutral and acidic lipids, and the salt concentration and pH of the bulk solution.

2 Numerical methodology

A numerical solution for the position dependent lateral pressure $\pi(r,z)$ and electrostatic potential $\psi(r,z)$ is obtained by discretization of the packing constraints, Eq. (5), and the Poisson Eq. (19). The equations are discretized by dividing the rz-plane into a grid of squares of length δ. Functions are assumed to be constant within a grid cell, hence integrations can be replaced by summations. The integral of a general position dependent function $f(r,z)$ then becomes:

$$\int\int \mathrm{d}r\mathrm{d}z\, G(r,z)f(r,z) = \sum_{i,j} \int_{(i-1)\delta}^{i\delta} \mathrm{d}r \int_{(j-1)\delta}^{j\delta} \mathrm{d}z\, G(r,z)f(r,z) \approx \sum_{i,j} f(i,j)\Delta G(i,j), \tag{31}$$

with

$$\Delta G(i,j) = \int_{(i-1)\delta}^{i\delta} \mathrm{d}r \int_{(j-1)\delta}^{j\delta} \mathrm{d}z\, G(r,z). \tag{32}$$

Here $f(i,j)$ denotes the value which function $f(r,z)$ attains within the region located between $(i-1)\delta \leq r < i\delta$ and $(j-1)\delta \leq z < j\delta$, and $G(r,z)drdz = 2\pi r dr dz$ corresponds to a volume element. The geometric factor $\Delta G(i,j)$ is the finite volume of the discrete cell. The calculations can be carried out outside the micelle (sphere with excluded volume interactions) and the derived expressions are strictly valid in that region of space. For discretization of the Poisson equation, to be discussed below, it turns out to be convenient to consider also the inside of the micellar core. This requires a small modification of the discretization of the grid cells. Namely, grid cells (i,j) whose region coincide with the boundary of the micellar core are split in two cells; one that is strictly on the outside and the other that is strictly on the inside. For those grid cells the integration boundary needs to be modified to account for the presence of the boundary of the micellar core. For grid cells (i,j) strictly located outside/inside the sphere: $\Delta G(i,j) = \pi(2j-1)\delta^3$.

Integration of the area of the sphere are discretized as follows,

$$\int \mathrm{d}\theta A(\theta)g(\theta) \approx \sum_k g(k)\Delta A(k), \tag{33}$$

with $\Delta A(k) = \int_{\theta_{k-1}}^{\theta_k} \mathrm{d}\theta\, A(\theta)$. The integration boundaries are determined by the discretization of the grid.

The packing constraint, Eq. (5), in discrete form for grid cell (i,j) read

$$\langle\phi_N(i,j)\rangle + \langle\phi_B(i,j)\rangle + \phi_w(i,j) + \phi_{Na^+}(i,j) + \phi_{Cl^-}(i,j) + \phi_{H^+}(i,j) + \phi_{OH^-}(i,j) + \phi_M(i,j) = 1. \tag{34}$$

Eqs. (21), (6), (14), (15), and (17) in discrete form become

$$\begin{aligned}
\phi_w(i,j) &= \exp(-\beta\pi(i,j)v_w), && (35)\\
\langle\phi_\gamma(i,j)\rangle &= \sum_k \frac{\Delta A(k)\sigma_\gamma(k)}{\Delta G(i,j)} \sum_{\alpha_\gamma} P(\alpha_\gamma,k,D)n(\alpha_\gamma,k;i,j)v_p && (36)\\
n(\alpha_\gamma,k;i,j) &\equiv \int_{(i-1)\delta}^{i\delta} \mathrm{d}r \int_{(j-1)\delta}^{j\delta} \mathrm{d}z\, n(\alpha_\gamma,\theta(k);r,z), && (37)\\
P_N(\alpha_N,k),D &= \frac{1}{q_N(k,D)} \prod_{i,j} \exp[-\beta\pi(i,j)n(\alpha_N,k;i,j)v_N^p], && (38)\\
P_B(\alpha_B,k,D) &= \frac{1}{q_B(k,D)} \prod_{i,j} \exp[-\beta\pi(i,j)n(\alpha_B,k;i,j)v_B^p - \beta\Delta G_{bind}n^e(\alpha_B,k;i,1)] \\
&\quad \times \exp\left[-n(\alpha_B,k;i,j)\left(e\beta\psi(i,j) + \ln(f(i,j))\right)\right], && (39)\\
\sigma_\gamma(k) &= \sigma_\gamma e^{\beta\mu_\gamma} q_\gamma(k,D), && (40)\\
e^{\beta\mu_\gamma(D)} &= A_{surf}/\sum_k q_\gamma(k,D)\Delta A(k). && (41)
\end{aligned}$$

The volume fraction of the counter, co-ions, protons, and hydroxyl ions, (Eqs.(22), (23), (24), and (25)), in discretized space are:

$$\begin{aligned}
\phi_{Na^+}(i,j) &= \phi_{Na^+,bulk} \exp(-\beta(\pi(i,j)-\pi_{bulk})v_{Na^+} - e\beta\psi(i,j)), && (42)\\
\phi_{Cl^-}(i,j) &= \phi_{Cl^-,bulk} \exp(-\beta(\pi(i,j)-\pi_{bulk})v_{Cl^-} + e\beta\psi(i,j)), && (43)\\
\phi_{H^+}(i,j) &= \phi_{H^+,bulk} \exp(-\beta(\pi(i,j)-\pi_{bulk})v_{H^+} - e\beta\psi(i,j)), && (44)\\
\phi_{OH^-}(i,j) &= \phi_{OH^-,bulk} \exp(-\beta(\pi(i,j)-\pi_{bulk})v_{OH^-} + e\beta\psi(i,j)). && (45)
\end{aligned}$$

The above volume fractions depend on the lateral pressure, electrostatic potential and on the bulk volume fractions. The chemical potentials of the ions, protons, and hydroxyl ions are related to their bulk volume fractions.[5] These bulk values are input to the theory.

The discrete form of the degree of dissociation of the acidic lipid is given by

$$\frac{x(i)}{1-x(i)} = K_a^{\ominus} \exp(\beta\mu_{H^+}^{\ominus}) \exp(\beta\psi(i,z=0)e), \quad (46)$$

and the fraction of acidic lipids in the lipid membrane is given by

$$\frac{f_l(i)}{1-f_l(i)} = \frac{e^{-\beta(\mu_{AH}^{\ominus}-\mu_C)}}{1-x(i)}, \quad (47)$$

here $\psi(i,z=0)$ is the surface electrostatic potential of the lipid membrane surface at $(r_i,z) = ((i-1/2)\delta,0)$.

The discretized Poisson equation, in cylindrical coordinates, is

$$\left(1+\frac{\delta}{2r_i}\right)\psi(i+1,j) - 4\psi(i,j) + \left(1-\frac{\delta}{2r_i}\right)\psi(i-1,j) + \psi(i,j+1) + \psi(i,j-1) = -\varepsilon_w\varepsilon_0\delta^2\rho_q(i,j), \quad (48)$$

here $r_i = (i-1/2)\delta$ denotes the middle of the grid cell (i,j) in the radial direction. The above equation only applies for regular grid cells, *i.e.*, those grid cells not at the boundary with the micellar core. For the split "non-regular" grid cells close to the micellar core/NP and the boundary condition of the interface of the micellar core we need to employ a generalized 5-point "stencil" method. Details concerning the constructions of those "stencils" can be found in Ref.[13]. The above scheme is computationally complex and difficult to implement; moreover, overall charge neutrality is not guaranteed. To address this problem and reduce the complexity of the algorithm we applied an approximation of the micellar electrostatic boundary condition. The electrostatic discontinuity of the micellar boundary was "ignored" and we combined the charge density of the "split" non-regular grid cells into one regular cell. Conceptually this means that we "smear" out the charges near the interface of the micellar core. We found that the difference in free energy computed with both approaches is less then 1% at maximum, clearly demonstrating

the relative unimportance of the electrostatic boundary condition near the micellar core. On the other hand, the electrostatic boundary conditions near the lipid membrane are of prime importance as the result presented in the main paper demonstrate. The discretized electrostatic boundary conditions for the surface ($z = 0$) read:

$$\psi(i, 1) - \psi(i, z = 0) = -\delta\epsilon_w\epsilon_0\sigma_q(i). \tag{49}$$

Here $\psi(i, z = 0)$ is the surface electrostatic potential of the lipid membrane surface.

Substituting Eqs. (37), through (45) into the constraint equation (34) and the Poisson Eq. (48) and substituting of Eqs (47) and (46) into the electrostatic boundary condition of the lipid surface (Eq. 49) results in a set of coupled nonlinear equations which can be solved by standard numerical methods. [14]

3 Chain Model

We use the three-state rotational isomeric state (RIS) model of Flory [15] in order to generate a representative sample set of chain conformations. These conformations are generated by a simple sampling procedure that takes into account the self-avoidance of the polymer chain. Through appropriate translational and rotational adjustments, the generated chain conformations are end-tethered to the center of a surface element. In doing so, both the surfaces of the sphere and the external plane are assumed to be non-penetrable by the chain segments. The segment or monomer length of the polymers and the volume of one polymer segment are $l = 0.35\,nm$, $v_N^p = 0.065\,nm^3$ for the neutral PEG polymer and $l = 0.35\,nm$, $v_B^p = 0.113\,nm^3$ for the polybase polymer respectively. The volume of the water molecules is $v_w = 0.03\,nm^3$. The proton and hydroxyl atom have a similar volume; $v_{H^+} = v_{OH^-} = v_w$. The anion and cation have a volume of $v_{Cl^-} = v_{Na^+} = 0.0335\,nm^3$. We used a discretization length $\delta = 0.5\,nm$.

One set of chain conformations is generated for both the neutral and polybase and is used for all calculations reported in this paper. The number of conformations per chain type at each grafting position is 1000000. For a micellar core radius of $R = 2.5\,nm$ this amount to $2.8 * 10^7$ chain conformations. Note that this large number of conformations requires the parallelization of the code.

4 Results

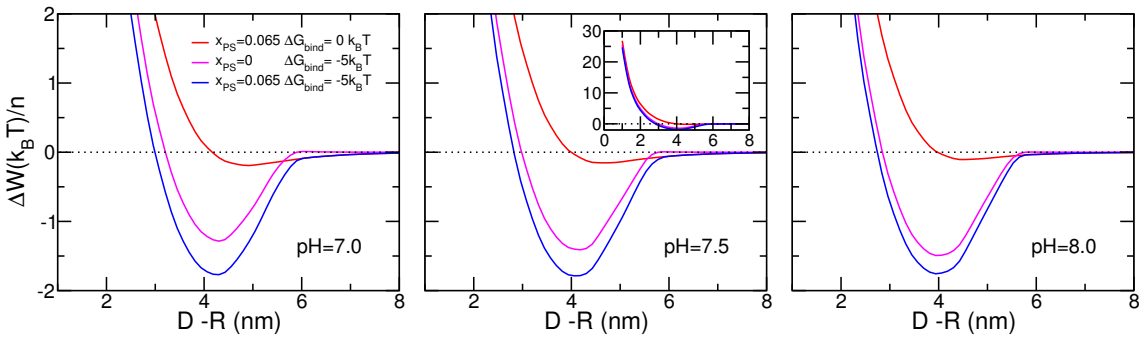

Figure S2: **Free energy** *versus* **separation distance between charged polymer grafted planar surface and membrane** at $pH = 7.0$, 7.5, and 8.0. The condition used for the planar surface are identical to the one used for the coated micelle. The grafted surface has a surface coverage for both PEG and polybase of $\sigma = 0.20\ nm^{-2}$. Both PEG and polybase have $n = 20$ segments. The polybase has a $pK_b = 6.5$. The intrinsic pK_a of the PS lipids is 3.6. The salt concentration is $c_s = 0.10M$. Because of the planar geometry the free energy presented as the free energy per polymer chain. The inset in the middle panel shows the same free energy *versus* distance but on a zoomed out scale, showing the larger (conformation) repulsion (and divergence at short distances) of the interaction between the two planar surfaces. Observe also that the effect of pH is greatly diminished: with decreasing pH the free energy curve only slightly shift to shorter distances.

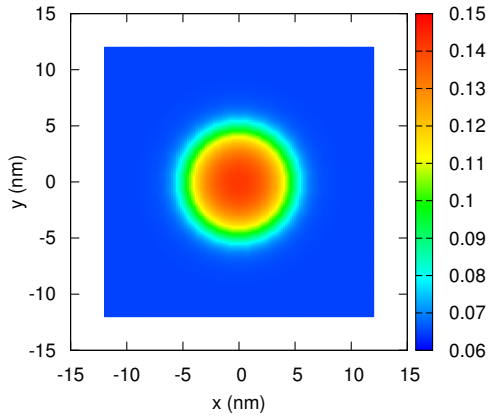

Figure S3: **Contour map of the distribution of the fraction of charged PS head group of the membrane lipids: ($\sigma_C(r)/\sigma_0$).** The center of the micelle is located at $(x, y) = (0, 0)$ and a distance $D - R = 2.0nm$ above the the membrane surface. The core of the micelle has a radius of $R = 2.5\ nm$ and the surface coverage of both PEG and polybase is $\sigma = 0.20\ nm^{-2}$. Both PEG and polybase have $n = 20$ segments. The polybase has a pK_b of 6.5. The salt concentration is $c_s = 0.10M$ and $pH = 7.5$. The intrinsic pK_a of the PS lipids is pK_a of 3.6. The lipids under the adhering micelle are in equilibrium with a bulk lipid membrane that possesses 6.5% of lipids with an acidic headgroup ($x_{PS} = \sigma_C/\sigma_0 = 0.065$).

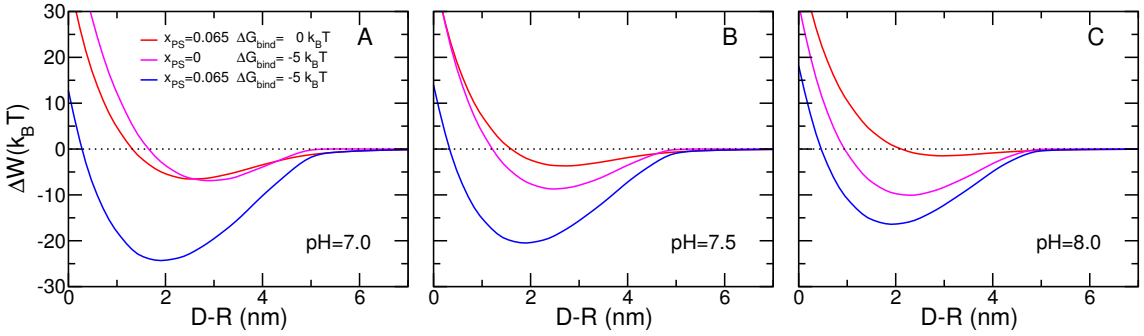

Figure S4: **Free energy *versus* separation distance between charged polymer grafted solid nanoparticle and membrane** at $pH = 7.0$, 7.5, and 8.0. The solid nanoparticle has a radius of $R = 2.5\ nm$ and the surface coverage of both PEG and polybase is $\sigma = 0.20\ nm^{-2}$. Both PEG and polybase have $n = 20$ segments. The polybase has a $pK_b = 6.5$. The intrinsic pK_a of the PS lipids is 3.6. The salt concentration is $c_s = 0.10M$.

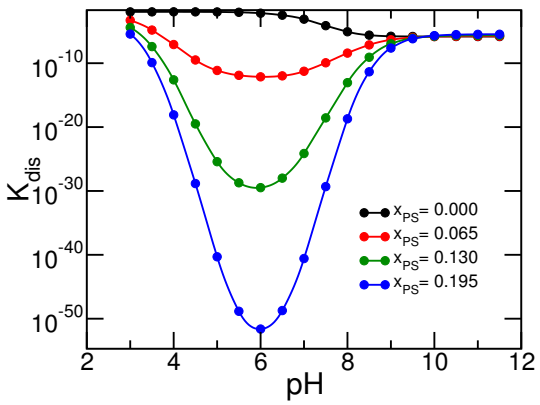

Figure S5: **Dissociation constant** *versus* **pH for a charged micelle interacting with a liquid-like lipid membrane** with different amounts of chargeable PS head-groups. The amount of charge of the PS head-group is determined by an acid-base equilibrium with an intrinsic pK_a of 3.6. All remaining parameters and conditions are identical to the ones presented in Fig S3.

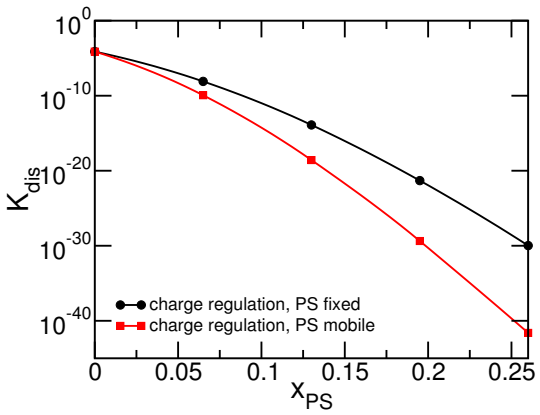

Figure S6: **Dissociation constant** *versus* **amount of chargeable PS head-groups for a charged micelle versus amount interacting with for two different 'types' of lipid membranes.** The black line correspond to a gel like membrane (charges can not move), whereas the red line correspond to a liquid-like membrane (charges are mobile). In both cases the amount of charge is determined by an acid-base equilibrium. All remaining parameters and conditions are identical to the ones presented in Fig S3.

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