Research

Estimation of Direct Interaction between Membrane Inclusions

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Abstract:
Within the statistical mechanical description or the phospholipid bilayer membrane, each monolayer is described as composed of patches containing very many inclusions that are characterized by intrinsic curvatures. A patch is subjected to local membrane curvature whereas summing up the free energies of the patches yields the free energy of the membrane. The origin of the single inclusion energy is the mismatch between the intrinsic curvature of the inclusion and the local curvature of the membrane, however, also direct interactions between inclusions contribute to the free energy. Here we upgrade the description by elaborating direct interactions between inclusions. We assume that the direct interactions are subject to van der Waals forces acting on the interfaces between the inclusion and its nearest neighbours. The expression for the interaction depends on the geometry of the inclusions, distance between them and Hamaker constant. The estimated direct interaction between inclusions of the size of small membrane rafts (20 nm) distanced for 0.2 nm with Hamaker constant 7×10^{-21}J is $W \approx 1800\ kT$.

Keywords: Membrane free energy; Membrane curvature; Membrane shape; Shape of the phospholipid membrane; Membrane biophysics; Hamaker constant

1. Introduction

Theoretical description of biological membranes provides an important link between physical laws and features, observed experimentally in complex systems. Previous studies have shown, that the observable shape of the membrane-enclosed structures can be explained by minimization of the membrane free energy at relevant constraints (e.g. prescribed membrane area, enclosed volume, average mean curvature, average mean curvature deviator) (Kralj-Iglič et al., 2020 with included references). The derivation of the free energy is based on the mismatch of the curvature tensor of an infinitesimal membrane element and the curvature tensor of this element in its intrinsic state (Kralj-Iglič et al., 2020). For anisotropic constituents there may be also contribution of the orientation of the inclusion with respect to the principal axes system of the membrane (Kralj-Iglič et al., 2020). The fluid crystal mosaic model (Kralj-Iglič, 2012) emphasizes the effect of orientational ordering of membrane constituents which becomes important in highly anisotropically curved regions such as in the narrow necks (Kralj-Iglič et al., 2006). **Figure 1** shows that considering the orientational ordering of phospholipid molecules becomes noticable in the neck (Panes B) which may considerable impact the equilibrium free energy of the entire vesicle and therefore indicate the direction of spontaneous change of the shape (Kralj-Iglič et al., 2006). In the calculation of the results presented in **Figure 1** the direct interactions between membrane constituents were taken into account as estimated by the van der Waals interaction between phospholipid molecules. It was shown that the direct interactions acted synergistically with the curvature mismatch and that their contributions were of the same order of magnitude (kT) where k in the Boltzmann constant and T is the temperature (Kralj-Iglič et al., 2006).
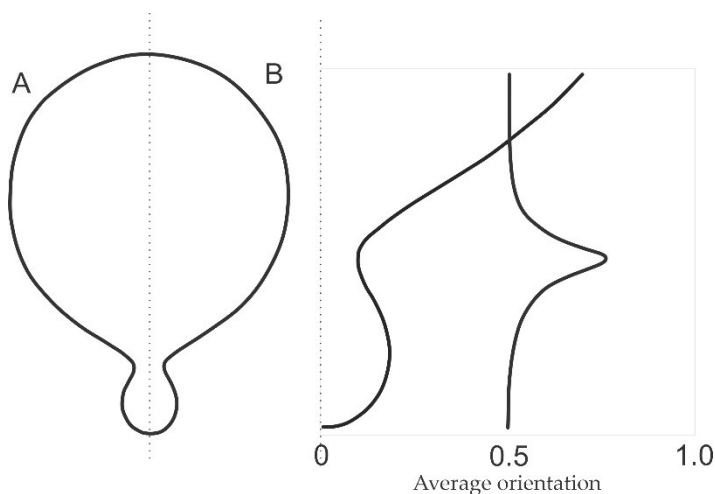

Figure 1. A: Equilibrium shape (shape of minimal free energy of the membrane) of a vesicle enclosed by a phospholipi bilayer membrane as calculated by taking into account orientational ordering of phospholipid molecules. B: The corresponding average orientation of the molecules in the neck (detail from Panel A). The model assumes two possible orientations (with minimal and maximal energy) and value 0.5 indicates that half of the constituents are in each of these two states; value 1 indicates that all of the constituents are in the energetically more favourable state. Adapted from (Kralj-Iglič et al., 2006).

However, in (Kralj-Iglič et al., 2006) the focus was on the orientational ordering and curvature mismatch of lipid molecules. The model should be further developed. Here it is taken into account that the membrane may be viewed as composed of inclusions (complexes of molecules). We focus on the estimation of the direct interactions between the membrane inclusions based on the van der Waals interaction. The derivation of the interaction between two walls, of them one with infinitely extending surface and the other with finite surface area is implemented to estimate the energy of direct interaction of the membrane inclusion with its nearest neighbors.

2.1. Interaction between a small entity and an infinitely extending wall

To calculate potential of the interaction between a small entity and an infinitely extending wall separated by a perpendicular distance D (**Figure 2A**), the entity is represented by a black dot and the wall is imagined to be composed of thin slices of thickness dx. Further, the slice is imagined to be composed of rings of the area d$S = 2\pi r$ dr, their radii extending from 0 to $\propto$ (**Figure 2**).
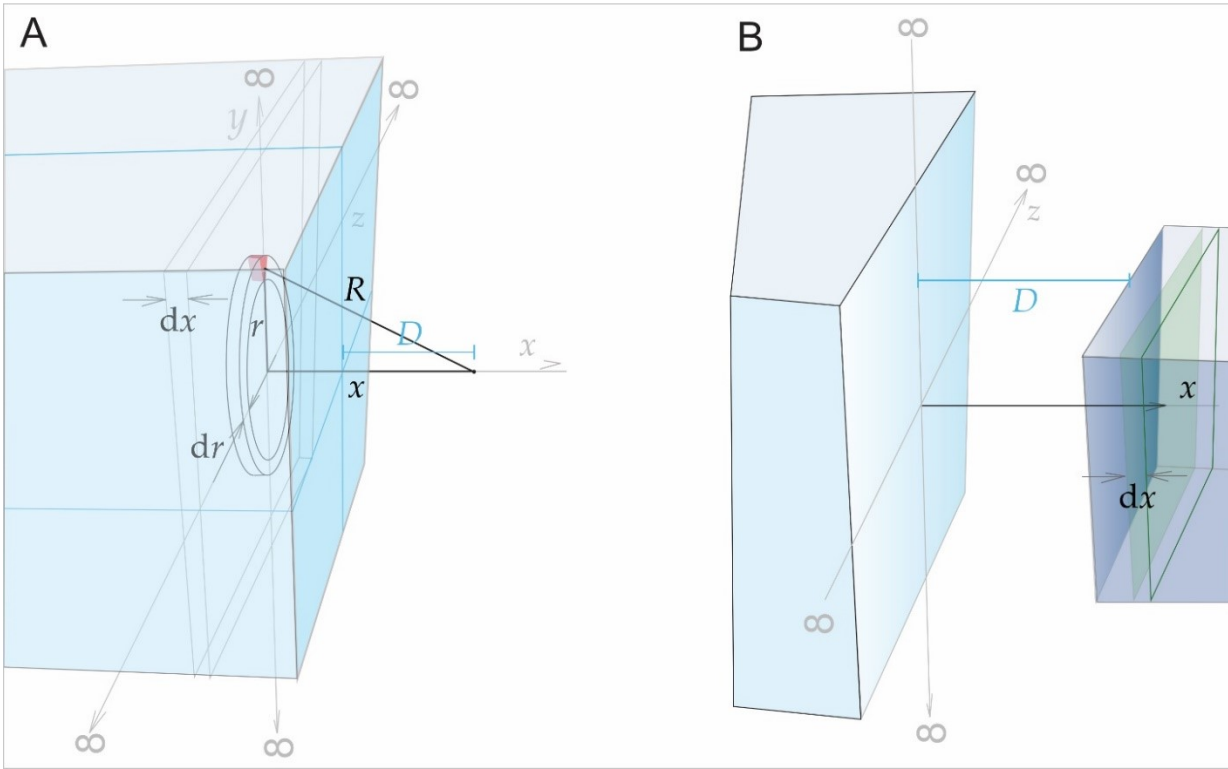
Figure 2. Illustration of the derivation of A: the van der Waals interaction between a wall and a small entity, B: the van der Waals interaction between an infinitely extending wall and a wall with finite surface and infinite length.

The entities within the ring are equally distanced from the chosen x. Following Israelaschvili (2011), it is taken that the potential V at point $(x,0,0)$ created by a small patch within the ring of the plate with radius r (**Figure 1**, red spot) containing dN entities is,

$$dV = - C_{vdW} R^{-6} dN , \tag{1}$$

where (**Figure 1**)

$$R^2 = r^2 + x^2 \tag{2}$$

and C_{vdW} is a constant. Considering Eqs. (1) and (2),

$$dV = - C_{vdW} (r^2 + x^2)^{-3} dN . \tag{3}$$

To include the contributions of the entire wall, the potentials of all thin rings composing the plate are summed and then the contributions of all the slices are summed,

$$V(D) = -\int_x dx \int_r C_{vdW} (r^2 + x^2)^{-3} dN \tag{4}$$

with

$$dN = n\, 2\pi r dr, \tag{5}$$

and n the number density of the entities composing the wall. Integration is performed from $r = 0$ to $r = \propto$ and from $x = -\propto$ to D.

Inserting Eq.(5) into Eq.(4) yields

$$V(D) = - \int_x \mathrm{d}x \int_r C_{\mathrm{vdW}} \, (r^2 + x^2)^{-3} \, n \, 2\pi r \, \mathrm{d}r \; . \tag{6}$$

We introduce a new variable

$$u = r^2 + x^2 \tag{7}$$

and the corresponding differential

$$\mathrm{d}u = 2r \, \mathrm{d}r \tag{8}$$

with the boundaries

$$u(r = 0) = x^2 \tag{9}$$

and

$$u(r = \infty) = \infty \tag{10}$$

to obtain

$$V(D) = - \int_x \mathrm{d}x \, (1/2) \, \pi \, n \, C_{\mathrm{vdW}} \, x^{-4} \; . \tag{11}$$

Integration over x within the boundaries $x = -\infty$ to D gives the energy of the interaction between a small entity and a wall,

$$V(D) = - C_{\mathrm{vdW}} \, n \, \pi \, D^{-3}/6 \; . \tag{12}$$

2.3. Interaction between a wall with a finite surface and a wall with an infinite surface

One of the walls extends infinitely in the y and z directions and the other is parallel to it, but of finite dimensions in the y and z directions, attaining the surface area S. It is imagined that the wall with the finite surface is composed of thin slices with thickness $\mathrm{d}x$. The number of the entities composing a slice is

$$\mathrm{d}N = n \, S \, \mathrm{d}x \; , \tag{13}$$

where it is taken that the number density of the entities of the wall with the finite surface is the same as the number density of the entities of the wall with the infinite surface. Any point within the wall that is at the perpendicular distance D from the wall with infinite surface contributes the same to the energy of interaction. The contributions to the potential of the interaction are summed over the slices from $x = D$ to $x = \infty$,

$$V_{\mathrm{wall\text{-}wall}}(D) = \int_x n \, V(x) \, S \, \mathrm{d}x \; . \tag{14}$$

Insertion of Eq.(12) into Eq.(14) yields

$$V_{\mathrm{wall\text{-}wall}}(D) = - \int_x (1/6) \, C_{\mathrm{vdW}} \, n^2 \, \pi \, S \, x^{-3} \, \mathrm{d}x \quad . \tag{15}$$

The integration is performed from $x = \infty$ to $x = D$ to yield the energy of the interaction between a wall with finite surface area and a wall with infinite surface area (Israelaschvili, 2011),

$$V_{\mathrm{vdW}}(D) = - C_{\mathrm{vdW}} \, n^2 \, \pi \, S \, D^{-2}/12 \; . \tag{16}$$

2.4. Interaction between two membrane inclusions

Within the model, membrane can be considered as composed of inclusions with given principal curvatures $C_1 = 1/R_1$ and $C_2 = 1/R_2$ (**Figure 3A**). Each inclusion shares interfaces with 4 nearest neighbors (**Figure 3B**). In the model, the direct interaction between inclusions is described by the van der Waals interaction between two surfaces. The surfaces of the walls are taken to be parallel (**Figure 2**). The surface areas of the interfaces are finite, however, as the van der Waals interaction falls off with 6ᵗʰ order of the distance between two entities, the smaller surface of the two interacting surfaces in the potential $V_{\mathrm{vdW}}(D)$ for small D largely determines the potential, therefore Eq.(16) is applied. The potential of the interaction of the inclusion with its 4 nearest neighbors is

$$W = 4 \, V_{\mathrm{wall\text{-}wall}}(D) \quad . \tag{17}$$
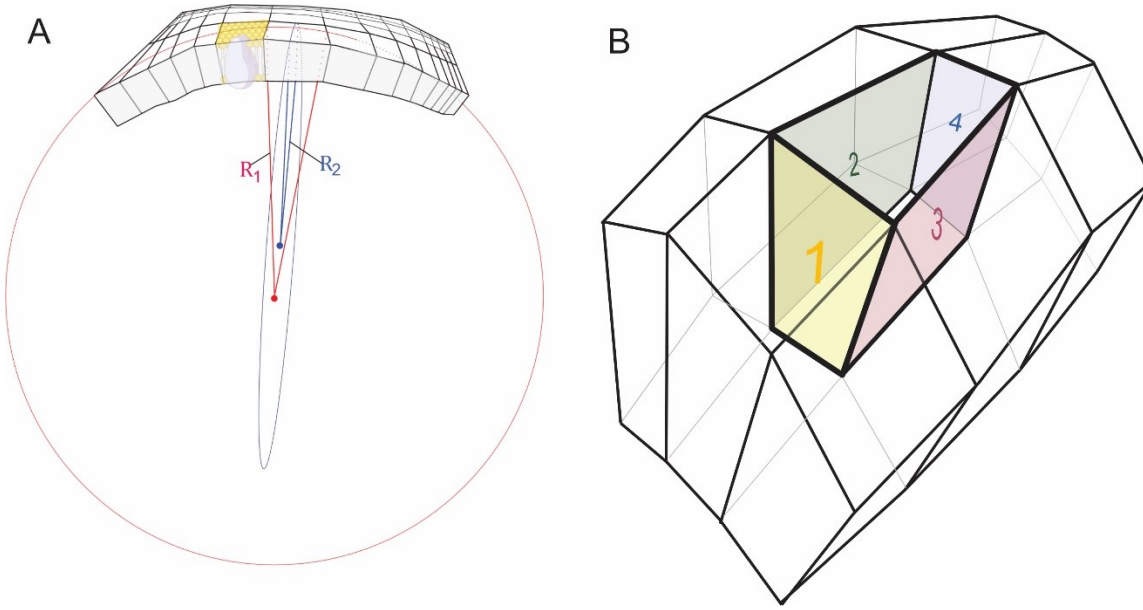
Considering Eq. (16),

$$W = - C_{vdW} \, n^2 \, \pi \, S \, D^{-2}/3 \quad . \tag{18}$$

The product $C_{vdW} \, n^2 \, \pi^2$ is Hamaker constant A (Hamaker, 1938),

$$A = C_{vdW} \, n^2 \, \pi^2 . \tag{19}$$

Considering Eqs.(18) and (19), we get

$$W = ASD^{-2}/3\pi . \tag{20}$$

Figure 3. A: Within the model, the membrane patch is composed of inclusions with certain principal curvatures $C_1 = 1/R_1$ and $C_2 = 1/R_2$. B: Interfaces between inclusions are subjected to inter-surface interactions. The inclusion is viewed as composed of molecules. Each inclusion interacts with its four nearest neighbours.

Hamaker constant for lipid bilayer composed of DPPC was estimated as $A = 6.9 \times 10^{-21}$J while for DPPE it was 7.5×10^{-21}J (Kienle et al., 2014). The size of the inclusion is estimated by the size of the lipid raft (20-200 nm) (Pile, 2008). The distance between the inclusions is estimated by the void between the phospholipid tails. Roughly, the C-C bond attains length below $d = 0.2$ nm (Ishigaki et al., 2018), so the distance D was estimated to be smaller than 0.2 nm.

The estimated direct interaction between inclusions in the lipid bilayer membrane is calculated by using Eq.(20) subject to the above data ($A = 7 \times 10^{-21}$J, $S = 400$ nm^2 (for lower limit of the rafts of the size 20 nm) and $D = 0.2$ nm),

$$W \approx 7500 \times 10^{-21} \text{J} \tag{21}$$

which is at $T = 300$ K

$$W \approx 1800 \, kT \quad . \tag{22}$$

The effect of the van der Waals interactions on the membrane shape was previously estimated by considering the phospholipid molecules as inclusions (Kralj-Iglič et al., 2006). It was assumed that the molecules were distributed in a quadratic lattice. The nearest tails of the neighbouring molecules were described as cylinders were taken into account. The estimated energy of the interaction was $W \approx 1 \, kT$ (Kralj-Iglič et al., 2006). Although already the estimation by phospholipid molecules showed that the direct interactions contributed noticeable to the orientational ordering (Kralj-Iglič et al., 2006), it follows from the above that describing the membrane as composed of inclusions with intrinsic principal curvatures gives the effect of the direct interactions that may be 3 orders of magnitude higher. These estimations suggest a possibility of the major contribution of the van der Waals forces within the hydrocarbon region of the membrane to the membrane free energy. This is in accordance with estimation of energy contributions of dipole-dipole interaction of the headgroups by

Garcia et al. (2019) who found the dipole-dipole energy of around 0.15 kJ mol^{-1} while the experimentally determined total enthalpy change for a gel-to-liquid-crystalline phase transition of dimyristoyl phosphatidyl choline of 23–29 kJ mol^{-1} suggesting that dipole–dipole interactions between phosphatidyl choline dipoles of the head group in the plane of the membrane are likely to play only minor role in the energetics of the gel-to-liquid crystal phase transition (Garcia et al., 2019).

The term "membrane inclusion" was previously used to describe large molecules embedded in the lipid bilayer membranes (Marcelja, 1976; Owicki & McConnell, 1979; Aranda-Espinoza et al., 1996). Here, the complexes of molecules that compose the membrane patch are taken as the inclusions. Such model was developed based on previous theoretical results considering statistical physical description of membrane (Kralj-Iglič et al., 1996; Kralj-Iglič et al., 1999) and of the electric double layer (Kralj-Iglič & Iglič, 1996).

Conflicts of Interest: The authors declare no conflict of interest.

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