Elastic interaction of point defects on biological membranes

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Abstract. The interaction between inclusions mediated by biological membranes undulations is analyzed. The interaction law is interpreted in terms of symmetries associated with inclusions. We show, in particular, that for a C_3 and C_{3v} symmetries the interaction law falls as $1/r^3$. We show that for completely isotropic inclusions, the dominant interaction vanishes to all orders, and the first contribution stems from the induced interaction which behaves as $1/r^4$. The same law holds for any other symmetry which is higher than C_4. We introduce a straightforward method to compute these interactions. We point out important differences with results in the literature and explain the discrepancies.

PACS. 87.16.Dg Membranes, bilayers, and vesicles

1 Introduction

Inclusions which are bound to biological membranes play an essential role in many cell functions. For example, they provide specific receptors for host proteins, act as ionic pumps, or contribute to the integrity of the cytoskeleton, and so on. The so-called peripherical proteins may, under some conditions, undergo an aggregation process in biological membranes [1], pointing to the existence of an effective protein/protein interaction. Besides direct electrostatic and van der Waals interactions, inclusions may interact *via* the membrane modulation [2–6]. An inclusion bends locally the membrane, a bending which can be felt by a second inclusion located elsewhere, and hence an interaction follows. Another source of interaction which is often referred to in the literature is that induced by thermal fluctuations, the so-called entropic interaction. As will be commented in this paper, this interaction is irrelevant for most practical purposes. Finally, interactions between inclusions may directly result from the deformation of the membrane structure (for a review, see [7]), or they can be induced by pressure [8].

As mentioned above, an inclusion bends the membrane, a bending which is characterized by a profile of the membrane modulation (this is the electrostatic analogue of the potential ϕ_1 created by a charge q_1). If a second inclusion is present on the membrane, the two inclusions will interact. The interaction is obtained as a product of the first-inclusion effect (say, its effective potential) and a characteristic of the second inclusion —say, its force quadrupole— (in an electrostatic analogy this means the product $q_2\phi_1$). This interaction may be called *linear interaction*. The origin of this denomination is that (the analogy with electrostatics is quite appealing) it is sufficient to know the potential created by one inclusion, the effective presence of the second one is irrelevant. It will be shown here, however, that when the two inclusions are isotropic, the linear interaction vanishes exactly. This problem is similar to that encountered when studying the interaction of inclusions in 3D solids [9] and 2D thin films [10], and it follows from purely dimensional considerations. This situation is very much like the one encountered in electrostatics [11] for the interaction between an ion and a neutral atom. Indeed the leading atom-ion interaction vanishes after averaging over all directions of the angular momentum of the atom. It is only when one takes the effect of polarizability of the atom that the interaction is nonzero (the induced effect comes from the fact that the atom polarizability is induced by the ion). We shall refer to this interaction as the *induced interaction* or *nonlinear interaction*. In other words, the presence of the second inclusion is necessary and it will be shown here that the interactions are indeed nonadditive. This feature was found in [4,12], but the form of the interaction differs from ours as presented in the discussion.

Several papers [2–6] have dealt with linear and nonlinear interactions between inclusions on a membrane. There are several inconsistencies with our results, and this constitutes the first objective of the present paper. We shall explain the source of inconsistencies. We shall present a

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systematic way for the calculation of the interaction energy. In particular, we shall relate in a general way the interactions (the linear ones) to the inclusion symmetries.

A major discrepancy with previous [2–6] works concerns the induced interaction. A surprising result in the above studies is that, for the interaction to survive, the authors need to introduce a cut-off related to the size of the inclusion. That this cut-off is not necessary to handle the induced interaction in the spirit of [2–6] remains to be shown. Our way of treating the problem does not require any cut-off. An additional result following from [2–6], and which is inconsistent with ours, is that the induced-interaction energy is proportional to the membrane rigidity, while here it will be shown that the rigidity enters the denominator. The origin of this discrepancy will be explained in this paper. It will be shown that this is due to the model used by the authors. That this inconsistency is due to the model spirit itself and not related to the induced character, is corroborated by the calculation of the linear interaction (which is the leading interaction for anisotropic inclusions) in reference [5]. Indeed, theses authors [5] use for linear interaction the same strategy for the evaluation of the induced interaction. That is to say, their results disagree with ours both for linear and nonlinear interactions. However, our result for the linear interaction agrees in principle with that of Park and Lubensky [3]. These authors use a spirit similar to ours regarding this interaction, but not when dealing with the induced interaction (as a consequence, their result differs from ours regarding the induced interaction).

Our method is straightforward and is basically based on the Helfrich energy and symmetries. Our results for the induced interaction (as well as for the linear interaction) agree with those obtained for inclusions in solids where the role of the rigidity modulus is played by the Young modulus. It also agrees with that of Landau and Lifchitz [11] if one draws a parallel between our calculation and that performed in electrostatics.

As shown by Park and Lubensky [3], two anisotropic inclusions (with a group symmetry smaller than C_3) interact with each other as $1/r^2$ with distance r. If the inclusion possesses a symmetry with group C_3 and C_{3v} (say, if the inclusions have a triangular shape), we shall show that the interaction behaves as $1/r^3$. For a higher symmetry (C_4, C_{4v}) the interaction falls as $1/r^4$. It is a simple matter to extend the calculation to a C_n symmetry. The result is that the interaction behaves as $\sim 1/r^n$. However, there is another source of interaction which is of longer range. This is precisely the induced interaction.

The scheme of this paper is as follows. In Section 2 we present the model and the basic ingredients. We then study the linear interaction and compare our results with those obtained by other authors. In Section 3 we study the induced interaction. Section 4 is devoted to discussion and comparison with previous works.

2 Formulation of the problem and linear interaction

Let $h(\mathbf{r})$ denote the membrane profile at position $\mathbf{r}$. In the limit of a small enough deformation, the mean curvature $H \simeq \Delta h$, where Δ is the 2D Laplacian (in the x-y plane). In this limit the Helfrich free energy takes the form

$$E = \frac{\kappa}{2} \int (\Delta h)^2 \mathrm{d}x\mathrm{d}y , \qquad (1)$$

where κ is the membrane rigidity. Note that we have disregarded the contribution involving the Gaussian curvature owing to the topological invariance of the corresponding energy. This is true as long as one disregards inhomogeneities of the rigidity, holes, and boundaries, as will be adopted here (see [4] when a local Gaussian curvature is present). In addition, we neglect tension effects as well as splay-distortion associated with lipid molecules [13], which might become relevant for small enough separation between the inclusions [1]. Let us first consider a single inclusion on the membrane. Due to mechanical equilibrium the total force on the membrane created by the inclusion as well as the total torque must vanish. For a force F located at $\mathbf{r}^{(0)}$ the energy is given by $U = -Fh(\mathbf{r}^{(0)})$. For a set of forces the energy is the sum over different forces; these are generally applied at different points. As in electrostatics, after expansion of h (the potential in electrostatics) in powers of a/r, where a is the distance between two forces associated with the inclusion, one gets to leading order $F_\alpha \partial_\alpha h$ (where repeated indices are to be summed over), where F_α is nothing but the dipole component along the α-axis. This contribution vanishes identically due to equilibrium since it represents the mechanical torque. Thus, the first contribution to the energy originates from the next expansion, which is quadrupolar, and is represented by a rank-two tensor, denoted by $F_{\alpha\beta}$. The mechanical energy associated with a single inclusion takes the form

$$U = \int \delta(\mathbf{r} - \mathbf{r}^{(0)}) F_{\alpha\beta} \partial_\alpha \partial_\beta h(\mathbf{r}) \mathrm{d}x\mathrm{d}y , \qquad (2)$$

where $\mathbf{r}^{(0)}$ refers to the inclusion position. In the presence of an inclusion the total energy consists obviously of the sum [14] of the two contributions (1), and (2). The vanishing of functional derivative of the total energy with respect to the height h yields the equilibrium equation which describes the membrane modulation h,

$$\kappa \Delta^2 h = -F_{\alpha\beta} \partial_\alpha \partial_\beta \delta(\mathbf{r} - \mathbf{r}^{(0)}) . \qquad (3)$$

Note that as in the theory of elasticity [14] the field (here h) obeys an inhomogeneous equation, the r.h.s. is nothing but the source of the deformation. It is important to note at this junction that other authors [2–6] suppose that h obeys a homogeneous equation and that the effect of the inclusion enters *via* a boundary condition at the inclusion (or, alternatively, they introduce a Lagrange

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[1] Note that if the separation becomes too small, the continuum theory of Helfrich type may be called into question.

multiplier [6] to enforce that condition). There is no reason that the inclusion should prescribe the curvature nearby; it is obvious that the presence of an inclusion induces a curvature, but no Lagrange multiplier is introduced to enforce the curvature in the vicinity of the inclusion. This is a completely microscopic problem as to how lipid rearrangements are affected by the inclusion, and this is beyond the scope of a continuum theory. The Helfrich description makes sense only if one is interested to scales which are large enough in comparison to the size of the inclusion. The geometry set by micro-scales can be completely different from that on larger scales where a continuum theory makes sense. Note that here our problem will be solved completely without resorting to any constraint, but only by specifying the forces acting on the membrane (quadrupoles in the present case). This way of reasoning will lead to different results as those found in [2–6] (except in the work of Park and Lubensky [3], where their result for the linear interaction agrees with ours since in that case their spirit is similar to ours, albeit the techniques are different; these authors use, however, another spirit for the induced interaction which will be a source of discrepancy; see section devoted to discussions).

Expression (2) represents the energy of a defect on a membrane. Since the defect position is *a priori* free, one can find, if need be, the most favorable position of the inclusion on the curved membrane. In particular, the defect would move away from flat regions.

As is usually the case in electrodynamics, the determination of the field (here h) is more conveniently obtained by first considering the effect of a charge. In the present problem we consider the response to a localized force,

$$f(\mathbf{r}) = F\delta(\mathbf{r} - \mathbf{r}^{(0)}).\tag{4}$$

The energy due to a single force is simply $U = -Fh(\mathbf{r}^{(0)})$. Variation with respect to h provides us with the following equilibrium equation:

$$\kappa\Delta^2 h = F\delta(\mathbf{r} - \mathbf{r}^{(0)}).\tag{5}$$

All quantities of interest can then be expressed in terms of the Green's function. Let $G(\mathbf{r} - \mathbf{r}^{(0)})$ be the free space (no boundary conditions are to be specified) Green's function. It obeys the following equation:

$$\kappa\Delta^2 G = \delta(\mathbf{r} - \mathbf{r}^{(0)}).\tag{6}$$

The profile h due to the application of a force is given by

$$h(\mathbf{r}) = G(\mathbf{r} - \mathbf{r}^{(0)})F.\tag{7}$$

The Green's function is given by

$$G = \frac{1}{16\pi\kappa}(\mathbf{r} - \mathbf{r}^{(0)})^2\ln(\mathbf{r} - \mathbf{r}^{(0)})^2.\tag{8}$$

The free space Green's function associated with a Laplacian in 2D is classical and is given by $\ln r$. The above Green's function follows directly after simple integrations with respect to r. Note that although the Green's function "diverges" at infinity, the slope of the profile due to

the inclusion goes to zero. Indeed, as stated above, the first contribution of the inclusion stems from a quadrupole (thus we must differentiate G twice, producing $\ln(r)$, and thus a zero slope and zero curvature at infinity).

The response of the membrane to any other force distribution can straightforwardly be obtained by superposing the effects due to individual forces and expanding for large distances. For the quadrupolar distribution (3), the membrane profile reads simply

$$h(\mathbf{r}) = -F_{\alpha\beta}\partial_\alpha\partial_\beta G.\tag{9}$$

This result is obtained from the very definition of the Green's function. This is seen upon differentiating equation (6) with respect to $\partial_\alpha\partial_\beta$ and realizing that $\partial_\alpha\partial_\beta G$ is the response to a source term $\partial_\alpha\partial_\beta\delta$ (see the r.h.s. of (3)). Note the formal analogy with multi-pole expansion in electrodynamics [15].

Let us now consider two inclusions labeled as "1" and "2". Their corresponding quantities will be superscripted accordingly. The total energy is given by

$$E_{\text{tot}} = \frac{\kappa}{2}\int(\Delta h)^2\mathrm{d}x\mathrm{d}y$$
$$+ \int\delta(\mathbf{r} - \mathbf{r}^{(1)})F_{\alpha\beta}^{(1)}\partial_\alpha\partial_\beta h(\mathbf{r})\mathrm{d}x\mathrm{d}y$$
$$+ \int\delta(\mathbf{r} - \mathbf{r}^{(2)})F_{\alpha\beta}^{(2)}\partial_\alpha\partial_\beta h(\mathbf{r})\mathrm{d}x\mathrm{d}y.\tag{10}$$

Integration by parts of the first term yields

$$\frac{\kappa}{2}\int h\Delta^2 h\mathrm{d}x\mathrm{d}y.\tag{11}$$

Note that boundary terms vanish since the membrane extent is illimited on scales of interest.

From minimization of the total energy one obtains (in a very similar manner as with a single inclusion)

$$\kappa\Delta^2 h = -F_{\alpha\beta}^{(1)}\partial_\alpha\partial_\beta\delta(\mathbf{r}-\mathbf{r}^{(1)}) - F_{\alpha\beta}^{(2)}\partial_\alpha\partial_\beta\delta(\mathbf{r}-\mathbf{r}^{(2)}).\tag{12}$$

Substituting in (11) $\kappa\Delta^2 h$ by the above expression, plugging the result into (10), and integrating by parts one obtains

$$E_{\text{tot}} = \frac{1}{2}\int\delta(\mathbf{r} - \mathbf{r}^{(1)})F_{\alpha\beta}^{(1)}\partial_\alpha\partial_\beta h(\mathbf{r})\mathrm{d}x\mathrm{d}y$$
$$+ \frac{1}{2}\int\delta(\mathbf{r} - \mathbf{r}^{(2)})F_{\alpha\beta}^{(2)}\partial_\alpha\partial_\beta h(\mathbf{r})\mathrm{d}x\mathrm{d}y.\tag{13}$$

Let $h = h^{(1)} + h^{(2)}$, where $h^{(1)}$ and $h^{(2)}$ are the displacements caused by each inclusion. Plugging this into the above expression, and subtracting from it the contribution due to each single inclusion (that is subtracting terms like $F_{\alpha\beta}^{(1)}\partial_\alpha\partial_\beta h^{(1)}$ and $F_{\alpha\beta}^{(2)}\partial_\alpha\partial_\beta h^{(2)}$) we obtain the interaction energy

$$U_{\text{int}} = \frac{1}{2}F_{\alpha\beta}^{(1)}\partial_\alpha\partial_\beta h^{(2)} + \frac{1}{2}F_{\alpha\beta}^{(2)}\partial_\alpha\partial_\beta h^{(1)}.\tag{14}$$
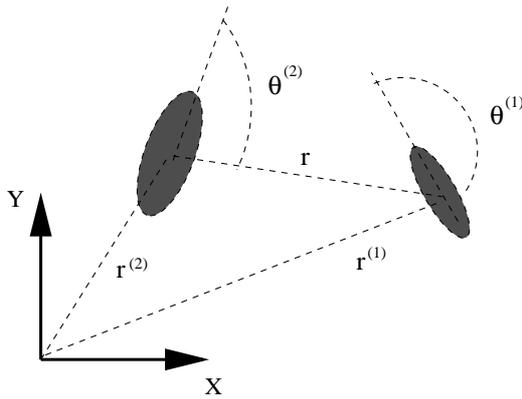
Fig. 1. A schematic view of the system under consideration.

Using (9), the interaction energy becomes

$$U_{\text{int}}(\mathbf{r}) = -F^{(1)}_{\alpha\beta} F^{(2)}_{\gamma\mu} \partial_\alpha \partial_\beta \partial_\gamma \partial_\mu G(\mathbf{r}) \,. \qquad (15)$$

The rank-two tensor can be decomposed as follows:

$$F_{\alpha\beta} = A\delta_{\alpha\beta} + B\left(n_\alpha n_\beta - \frac{1}{2}\delta_{\alpha\beta}\right), \qquad (16)$$

where n_α is the component of a unit vector directed along the inclusion long axis (see Fig. 1), lying in the tangent plane of the membrane. A, B are constants expressing the details of the interaction between the inclusion and the membrane and their precise values depend on the system under consideration. For a symmetry which is higher than C_2, $B = 0$; this case will further be discussed below.

Plugging now the above expressions into (15) we obtain the final result

$$U_{\text{int}}(\mathbf{r}) = -\frac{1}{16\pi\kappa r^2} \Big\{ 2A^{(1)}B^{(2)} \cos 2\theta_2$$
$$+ 2A^{(2)}B^{(1)} \cos 2\theta_1 + B^{(1)}B^{(2)} \cos 2(\theta_1 + \theta_2) \Big\} \,, \quad (17)$$

where θ_1 is the angle between the long axis of the inclusion and the separation vector $\mathbf{r}$. Let us quote few special cases. If both inclusions are identical we have $A^{(1)} = A^{(2)} = A$ and $B^{(1)} = B^{(2)} = B$. In that case we obtain

$$U_{\text{int}}(\mathbf{r}) = -\frac{1}{16\pi\kappa r^2} \{ 2AB(\cos 2\theta_1 + \cos 2\theta_2)$$
$$+ B^2 \cos 2(\theta_1 + \theta_2) \} \,. \qquad (18)$$

If the inclusions possess a higher symmetry (higher than C_2), then $B = 0$ and the interaction vanishes. The interaction vanishes in particular for isotropic inclusions. Thus we must expand the energy to higher orders in the membrane profile, as will be shown in the next section. If one of the two inclusions (say number "1") is completely isotropic, or has a high enough symmetry, then $B^{(1)} = 0$, while if inclusion "2" is anisotropic, then there exists still an interaction

$$U_{\text{int}}(\mathbf{r}) = -\frac{1}{8\pi\kappa r^2} A^{(1)}B^{(2)} \cos 2\theta_2 \,. \qquad (19)$$

We note a difference with the result of Park and Lubensky [3], where this term is absent. However, for the part which is proportional to B^2 in (19) our result agrees with that of Park and Lubensky [3]. That an isotropic inclusion interacts linearly with an anisotropic one was found in [6,12].

Another case which is worthy of mention is the one where the inclusion symmetry is of type D_2, or D_{2d}. This corresponds to the situation where the inclusion is inserted inside the membrane. It follows then that $A = 0$, whereas $B \neq 0$, and the interaction law takes the form

$$U_{\text{int}}(\mathbf{r}) = -\frac{1}{16\pi\kappa r^2} B^2 \cos 2(\theta_1 + \theta_2) \,. \qquad (20)$$

For a defect having a C_3 or C_{3v} symmetry (say triangular), the coefficient B in equation (16) must vanish, and one has to consider higher-order multipolar contributions. This amounts to writing the corresponding inclusions energy as

$$U = \int \delta(\mathbf{r} - \mathbf{r}^{(0)}) \{ A\Delta h(\mathbf{r}) + F_{\alpha\beta\gamma} \partial_\alpha \partial_\beta \partial_\gamma h(\mathbf{r}) \} \, \mathrm{d}x\mathrm{d}y \,.$$
$$(21)$$

We follow now exactly the same strategy as before. After a functional differentiation of the total energy we obtain the equilibrium equation

$$\kappa(\Delta)^2 h = -A\Delta\delta(\mathbf{r} - \mathbf{r}^{(0)})$$
$$+ F_{\alpha\beta\gamma} \partial_\alpha \partial_\beta \partial_\gamma \delta(\mathbf{r} - \mathbf{r}^{(0)}) + \dots \,, \qquad (22)$$

where ... means similar terms related to the second inclusion. The formal solution of the above equation can be expressed in terms of the Green's function

$$h(\mathbf{r}) = -A\Delta G + F_{\alpha\beta\gamma} \partial_\alpha \partial_\beta \partial_\gamma G \,. \qquad (23)$$

In what follows it may be useful to quote the following identity:

$$\Delta G = \frac{1}{2\pi\kappa} \ln r \,. \qquad (24)$$

The interaction energy can be expressed in terms of the Green's function,

$$U_{\text{int}}(\mathbf{r}) = \left\{ A^{(1)} F^{(2)}_{\alpha\beta\gamma} - A^{(2)} F^{(1)}_{\alpha\beta\gamma} \right\} \partial_\alpha \partial_\beta \partial_\gamma \Delta G(\mathbf{r}) \,. \quad (25)$$

One can identify from dimensional considerations the power law $1/r^3$. In order to be more explicit, let us write the tensor in its generic form

$$F_{\alpha\beta\gamma} = C(n_\alpha n_\beta n_\gamma - n_\alpha l_\beta l_\gamma - l_\alpha n_\beta l_\gamma - l_\alpha l_\beta n_\gamma) \,, \quad (26)$$

where $\mathbf{n}$ and $\mathbf{l}$ are two unit vectors which are perpendicular to each other. Note that the tensor is expressed in the coordinate where the mirror of symmetry is perpendicular to $\mathbf{l}$. The interaction energy takes the following form:

$$U_{\text{int}}(\mathbf{r}) = \frac{2}{\pi\kappa r^3} \left\{ A^{(2)}C^{(1)} \cos 3\theta^{(1)} + A^{(1)}C^{(2)} \cos 3\theta^{(2)} \right\} \,.$$
$$(27)$$

This interaction is nonvanishing even in the case where one of the two inclusions is completely isotropic as can easily be seen by setting $C^{(1)} = 0$, in which case the expression becomes

$$U_{\text{int}}(\mathbf{r}) = \frac{2}{\pi\kappa r^3} A^{(1)} C^{(2)} \cos 3\theta^{(2)}. \tag{28}$$

Let us quote a special case which arises when the inclusion has a S_6 symmetry (remember that S_6 stands for rotary reflexion). More precisely, this symmetry corresponds to the product of a rotation of a C_6-axis in the plane oxy per an up-down reflexion. In that case, we have both $B = 0$ and $A = 0$, whereas $C \neq 0$.

For a 4-fold symmetry the same analysis can be performed yielding an interaction falling as $r^{-4} \cos 4\theta^{(1)}$ (one of the two defects is assumed in this expression to be isotropic).

For an n-fold symmetry the interaction behaves as $r^{-n} \cos n\theta^{(1)}$. In fact there is another source of interaction $\sim 1/r^4$. This is the so-called *induced interaction*, which will be analyzed now.

3 Induced interaction

It is clear from equation (17) that if both inclusions are isotropic (or have a high enough symmetry as discussed above) then all-B coefficients vanish. This means that at this order there is no coupling between inclusions. Hitherto, the considered interaction arises from leading order (linear interaction). That is to say, the modulation due to one inclusion suffices to determine the interaction energy. In analogy with electrostatics, if one knows what the field (or potential ϕ_1) created by a charge q_1 is, then there is no need to study the effect of, or on, the second charge in order to determine the interaction; this is simply given by $q_2\phi_1$, where q_2 is the second charge. As is well known, an ion does not interact to leading order with a neutral atom with isotropic charge distribution. However, the ion can induce a polarization of the atom so that the polarization of the atom is proportional to the ion field, and this interaction is known to be nonzero [11]. This is called the *induced or nonlinear interaction*, in a sense that the interaction exists only because the ion induces a charge redistribution of the atom. That the interaction is nonlinear is obvious, since the interaction is proportional to the field created by the ion multiplied by the polarizability of the atom, which itself is proportional to the ion field.

The energy associated with the inclusion must now (for an isotropic inclusion) be written as

$$U = \int \delta(\mathbf{r}-\mathbf{r}^{(0)}) \left\{ A\Delta h(\mathbf{r}) - \frac{D}{2} \partial_\alpha\partial_\beta h(\mathbf{r})\partial_\alpha\partial_\beta h(\mathbf{r}) \right\} \mathrm{d}x\mathrm{d}y. \tag{29}$$

The first term represents the leading order as before (which would be the analogue of the moment of the non-polarized atom), while the second one accounts for an induced effect; this is an expansion of $F_{\alpha\beta}$ in equation (2) in powers of the curvature tensor. Note that we have chosen

a minus sign in front of D for the sake of comparison with the induced interaction in electrostatics (between an ion and a neutral atom). The equilibrium equation for h is simply given by

$$\kappa(\Delta)^2 h = -A\Delta\delta(\mathbf{r} - \mathbf{r}^{(0)})$$
$$+D\partial_\alpha\partial_\beta\delta(\mathbf{r} - \mathbf{r}^{(0)})\partial_\alpha\partial_\beta h + ... \tag{30}$$

Going back to the total energy (that is supplementing U by the Helfrich energy) and making similar operations as before (integration by parts and using the equilibrium equation above), one finds that the interaction energy takes the form

$$U_{\text{int}} = \frac{1}{2}A^{(1)}\Delta h|_{\mathbf{r}=\mathbf{r}^{(1)}} + \frac{1}{2}A^{(2)}\Delta h|_{\mathbf{r}=\mathbf{r}^{(2)}}. \tag{31}$$

We must subtract the self-energy when evaluating the interaction. This expression bears strong similarities with (14). An exact solution [16] of equation (30) can be obtained, and thus we can determine U_{int} exactly. However, in the spirit of the calculation (*i.e.* multipolar expansion) the same result can be obtained in a more direct, albeit perturbative, way. Let $h^{(1)}$ be the displacement due to inclusion "1", and so on. In order to evaluate $h^{(1)}$, for example, we make the following reasoning. $h^{(1)}$ is composed of two contributions. The first one is due to the $A^{(1)}$ term which creates a field $h_0^{(1)}$ exactly as before. The second defect will in its vicinity (and elsewhere as well) change the field. This is nothing but the response of the second defect due to the fact that it feels an "induction" represented by the $D^{(2)}$ term. Thus the next-order contribution to $h^{(1)}$ must involve the product $A^{(1)}D^{(2)}$. This entails that in the second term of the interaction energy (31) we shall have $A^{(1)}A^{(1)}D^{(2)}$. The same reasoning applies to $h^{(2)}$ leading to a contribution in the energy proportional to $A^{(2)}A^{(2)}D^{(1)}$. Formally, we solve equation (30) by perturbation in the induced effect. To leading order, and in the presence of the first inclusion, we must solve

$$\kappa(\Delta)^2 h_0^{(1)} = -A^{(1)}\Delta\delta(\mathbf{r} - \mathbf{r}^{(1)}). \tag{32}$$

Here $h_0^{(1)}$ is the zeroth-order solution (the subscript refers to the order while the superscript labels the inclusion). Let us call $h_0 = A^{(1)}f(|\mathbf{r} - \mathbf{r}^{(1)}|)$ the solution (which is a logarithm as we have seen before; $f = -(2\pi\kappa)^{-1}\ln|\mathbf{r} - \mathbf{r}^{(1)}|$). This field creates on defect "2" an induction $D^{(2)}$ reacting back on the field h. More precisely the next-order equation for h is

$$\kappa(\Delta)^2 h_1^{(1)} = D^{(2)}\partial_\alpha\partial_\beta\{\delta(\mathbf{r}-\mathbf{r}^{(2)})\partial_\alpha\partial_\beta h_0(\mathbf{r}-\mathbf{r}^{(1)})\}. \tag{33}$$

Formally, the solution reads $h_1^{(1)} = D^{(2)}A^{(1)}g(|\mathbf{r} - \mathbf{r}^{(1)}|)$, where g is obtained by inverting the above differential equation. In reality, only Δh is needed and not h alone (as seen in Eq. (31)). Inversion of the Laplacian in equation (33) leads to

$$\Delta g(|\mathbf{r} - \mathbf{r}^{(1)}|) = (2\pi\kappa)^{-1} \int \mathrm{d}\mathbf{r}'\partial_\alpha\partial_\beta\{\delta(\mathbf{r}' - \mathbf{r}^{(2)})$$
$$\times\partial_\alpha\partial_\beta h_0(\mathbf{r}' - \mathbf{r}^{(1)})\}\ln|\mathbf{r} - \mathbf{r}'|, \tag{34}$$

where we have used the fact that the Green's function of the Laplacian is given by the logarithm. Integration by parts leads to

$$\Delta g(|\mathbf{r} - \mathbf{r}^{(1)}|) = (2\pi\kappa)^{-1}\partial_\alpha\partial_\beta \ln|\mathbf{r} - \mathbf{r}^{(2)}|$$
$$\times[\partial_\alpha\partial_\beta h_0(|\mathbf{r} - \mathbf{r}^{(1)}|)]_{\mathbf{r}=\mathbf{r}^{(2)}} . \qquad (35)$$

Since $h_0|\mathbf{r}-\mathbf{r}^{(1)}| = -A^{(1)}(2\pi\kappa)^{-1}\ln|\mathbf{r}-\mathbf{r}^{(1)}|$ we can write at the location of the second defect

$$\Delta g(|\mathbf{r}-\mathbf{r}^{(1)}|)_{\mathbf{r}=\mathbf{r}^{(2)}} = (2\pi\kappa)^{-2}(\partial_\alpha\partial_\beta \ln|\mathbf{r}-\mathbf{r}^{(1)}|)^2|_{\mathbf{r}=\mathbf{r}^{(2)}} . \qquad (36)$$

The field due to the first defect is thus given by $h^{(1)} = A^{(1)}f(|\mathbf{r} - \mathbf{r}^{(1)}|) + D^{(2)}A^{(1)}g(|\mathbf{r} - \mathbf{r}^{(1)}|)$, where now $\Delta h^{(1)}$ is completely determined. The same reasoning applies to the second defect. Using the above result for Δg in (31), and ignoring the self-energy, we obtain finally that the interaction energy is given by

$$U_{\text{int}} = -\frac{1}{4\pi^2\kappa^2 r^4}[(A^{(1)})^2 D^{(2)} + (A^{(2)})^2 D^{(1)}] . \qquad (37)$$

Very much like the induced interaction in electrostatics [11] the interaction behaves as $1/r^4$.

It is worth mentioning that the interaction is not additive and this is easily seen by considering three inclusions (as found also in [4,12]; note that their interaction energy differs from ours as discussed later). Each inclusion is characterized by its constants A, and D. There is an additive part similar to the one presented above, but a nonadditive contribution arises also. For example, inclusion "2" can be "polarized" by inclusion "3", so that the polarization of inclusion "3" is proportional to $A^{(2)}D^{(3)}$. Since "3" is polarized, it can interact with "the charge" of "1", $A^{(1)}$, so that the corresponding interaction energy will be proportional to $A^{(1)}A^{(2)}D^{(3)}$. Of course, all other combinations are possible, but we have not felt it worthwhile to list the full expression, which can be obtained without great deal by following the straightforward method of this paper.

4 Discussion

We first compare our results with previous analyses. The first difference with previous works [3] lies in the angular dependence of the interaction energy when the inclusions are anisotropic. If one compares equation (2.4) of reference [3] with ours (Eq. (17)), one sees that in reference [3] the first two terms (proportional to AD and CB in our expression) are missing. The reason is clear. In [3] their second-rank tensor is taken to be traceless (see Eq. (3.37) in Ref. [3]), and their term Q_2 is the analogue of our B term in the tensor defined here by equation (16). However, in their case the analogue of our A term is taken to be zero. There is no reason at all for A to be zero, except in some special cases quoted in the present paper. The tensor $F_{\alpha\beta}$ accounts for physical properties of interaction between the inclusion and the membrane. Thus if the inclusion turns out to be symmetric, then there is still an effect of the inclusion on the membrane, so that $F_{\alpha\alpha}$ must

be nonzero (compare with liquid crystals where, though the order parameter is traceless, this is not the case for other physical properties, such as the dielectric constants which are nonzero in the isotropic phase!). The fact that the interaction still survives if one inclusion is isotropic was realized in [4,12,5]. However, there is a major difference between their expression and ours (Eq. (17)): their interaction energy is proportional to the rigidity, while here our expression in inversely proportional to the rigidity. It might be thought that since in our expression (Eq. (17)) the constants A and B have the dimension of an energy × a length, then, A and B would be proportional to κ, and that would cure the discrepancy. This is not true. The coupling constant represents the details of interaction with phospholipidic molecules, while the rigidity represents the resistance of the phospholipidic molecules against their bending. One can vary A and B (by changing the nature of the inclusions) without altering κ (by keeping the same phospholipids). The two energies are independent, beyond any doubt.

The discrepancy between the result of references [4, 12,5] and ours (Eq. (17)) originates from their treatment which imposes locally that the inclusion fixes the curvature (they enforce a local condition), which is not consistent with the whole spirit of the model. Indeed, there is no doubt that the inclusion interacts with the membrane molecules, but this is a completely microscopic problem as to how lipid rearrangements are affected by the inclusion, and this is beyond the scope of a continuum theory. The Helfrich description makes sense only if one is interested on scales big enough in comparison to the size of the inclusion. In our treatment we only need to calculate the field created by the first inclusion, and evaluate it at distance r from that inclusion, then multiply this field by the torque of the second inclusion. Note that our way of evaluating the field created by a force (or quadrupole) is precisely along the same line as in elasticity theory of thin plates (a very similar problem). Indeed, as shown by Landau and Lifchitz [14] (formula 12,4), the profile of the plate is entirely determined by the knowledge of the applied forces. As seen in the same paragraph of the same reference (formula 12,5), the field h (noted ζ there) is inversely proportional to κ (the plate rigidity), so that the membrane energy which is proportional to $\kappa\int(\Delta h)^2 \mathrm{d}x\mathrm{d}y$ (or, equivalently, to $\int F_{\alpha\beta}h\mathrm{d}x\mathrm{d}y$; the work of the quadrupole), produces an interaction energy which is inversely proportional to κ, as in our treatment. It is worth pointing out that the fact that the response of the material (here the rigidity) appears in the denominator is a well-known problem (see inclusions interaction in solids —Ref. [17]— and step-step interaction on a vicinal surface [18]). Note that with regard to the dependence with the rigidity our result agrees with that of Park and Lubensky [3]. Their equation (2.4) contains κ in the denominator as our expression (17) does (but their angular dependence is not complete, as we discussed above). The dependence of their expression on κ agrees with ours precisely because their strategy is similar in spirit to ours (though the techniques are different). However, these authors use another spirit when they

evaluate the induced interaction. That spirit is in particular similar to that of [5], on which we have commented above and has pointed out the improper behaviour with κ for the linear interaction. That procedure produces the same dependence with κ for the induced interaction, as discussed again below.

The second serious point of discrepancy with previous analyses lies in the way the induced interaction $1/r^4$ is evaluated in papers [2–4,6], revisited in [19] to show that the Gaussian curvature plays no role in the interaction energy (for a pre-existing local Gauss curvature, see [4]). As shown here, for isotropic inclusions the interaction vanishes to leading order (that interaction is called linear interaction) and there is a need for taking into account the induced effects. The induced-interaction energy is performed in this paper in the same manner as for anisotropic inclusions. Previous works [2–4] have used different spirits than ours, in that they impose that the inclusion fixes the local curvature, but there is no such a constraint in our study (for reasons described above). In addition, their total energy in the presence of the inclusion is written as just the Helfrich energy, but not supplemented with terms like the one in equation (2), which accounts for the work due to the inclusion (this is more visible in papers [2,6]). Our reasoning is similar to that of thin plates in the presence of an external perturbation [14] (formula 12,4). The major discrepancies with [2–4,6] regarding the induced interaction are the following: i) our result (37) contains κ^2 in denominator, while in references [2–4,6] κ enters in denominator; ii) our energy contains explicitly the cross-terms originating from inclusion one and two, as clearly shown by superscripts "1" and "2" in our expression (37). This is precisely how the induced interaction appears in electrodynamics [11] between an ion and an atom: the interaction energy is proportional to the product of the charge of the ion (say the analogue of our constant A) and the polarizability of the atom [15] (our constant D). On the contrary, in references [2,3,6] the interaction is a sum of two effects appearing as if each inclusion were alone. iii) Finally, if one lets the inclusion size go to zero (a point-like defect), then the interaction energy evaluated in references [2–4,6] goes to zero as well! This is clearly nonphysical. It might be that taking this limit is meaningless in the context of their model, but this is a question which is unclear for the present authors, inasmuch as our theory does not need to introduce a cut-off. Of course, our constants A and B have a dimension of an energy times a length scale, simply meaning that both results are dimensionally correct. One could extract a length scale from A and B and both results would have the same dependence with the "molecular" size a. However, unlike the work of [2–4,6], our theory need not specify a spatial extent of the inclusion in the course of calculation. The result according to which a cut-off is needed is linked with the fact that the authors impose that the inclusion fixes the curvature nearby (at $r = a$). As a consequence, the membrane profile created by "2" has a "memory" of the inclusion "1" fixing its own curvature. Another difference which is worth mentioning is that in references [2,3,6] the $1/r^4$ interaction is always repulsive, while in our approach this depends on the signs of the constants D associated with the inclusion (see Eq. (37)). Regarding the dependence of the interaction energy (37) on κ as compared to references [2–6] and [7], the following remark can be made. If one admits that the inclusion fixes the local curvature, one may consider that the constants A and D in equation (37) are proportional to the membrane rigidity. In that case our result (37) agrees with that of references [2–6] and [7] regarding the dependence with respect to κ (but not necessarily the sign of the interaction). In our opinion, care must be taken, however. On the one hand, fixing the curvature at the level of the inclusion is a microscopic question which is beyond the present study. On the other hand, while the constants A and D have a dimension of an energy times a length, they are independent of κ: κ measures the rigidity of the membrane itself (an intrinsic property which is independent of an external action), while A and D account for the interaction of the inclusion with the membrane. One can change the nature of the inclusion (and thus the values of A and D) without changing the membrane (κ remains the same); thus A and D would vary independently of κ.

All the interactions discussed so far occur as long as the inclusions do not preserve the up-down symmetry, otherwise the interaction vanishes. In the latter situation one may evoke the Casimir effect (due to thermal fluctuations) as a possible source of interaction. However, if only one of the two inclusions enjoys the up-down symmetry, then the induced interaction is nonzero.

The (entropic) Casimir effect has been evaluated in [2] and is given by

$$U \sim -k_{\mathrm{B}}T\left(\frac{a}{r}\right)^4, \qquad (38)$$

where $k_{\mathrm{B}}T$ is the thermal energy, and a is the typical linear size of the inclusion. Note that we do not admit that the size of the molecule matters in the geometrical sense, but simply that from dimensional considerations the combinations of energies and energies per unit surface on the scale of the inclusion lead to a length scale which is nothing but a molecular length [2]. It is clear that this effect is always small in comparison to $k_{\mathrm{B}}T$ as soon as r is 2 to 3 molecular distances. That is to say, in most practical purposes the inclusion/inclusion interaction is much smaller than the local thermal excitation, a fact which confers to the Casimir effect in this case only an academic interest.

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[2] Very much like the quadrupole $F_{\alpha\beta}$ which has a dimension of a force multiplied by a distance square, or energy multiplied by a length, the energy represents the details of local interactions, and the length is typically a molecular length; however, in our calculation we never assigned a geometrical extent to the inclusion; it is a point defect.

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