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Bending stiffness of lipid bilayers. III. Gaussian curvature

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Abstract. — The Gaussian curvature term in the expression for the energy density in bending of a lipid bilayer can be decomposed in two terms one symmetric and the other one antisymmetric in the principal curvatures. The symmetric term is proportional to the square of the mean local curvature. A similar term has exclusively been used to calculate the equilibrium shape of bilayer structures the topology of which does not change. It is suggested that the antisymmetric term which is proportional to the square of the deviator of the local curvature should not be neglected in such calculations.

1. Introduction.

Membranes are ubiquitous in nature. They serve many purposes e.g. compartmentalization, reinforcement, mechanical support. Artificial lipid bilayers preserve a few of the manifold properties of biological membranes. In addition they are themselves pure systems that can be described theoretically. The subject of this paper is their bending stiffness.

The resistance of a bilayer to bending moments can be decomposed into two contributions which have been called bilayer couple bending and single layer bending [1]. Bilayer couple bending arises from the resistance of the two monolayers to a change in surface area and from their fixed interlayer distance. The single layer bending stiffness also called intrinsic bending stiffness arises from the resistance of the molecules making up a monolayer to a change in shape, e.g. from cylindrical to conical. In bilayer couple bending either the local or the global nature or a mixture of both occurs, depending on the time scale of the deformation [1]. In bilayers composed of a single lipid species, single layer bending is local. If more than one lipid species is present, single layer bending can also become global.

In the second paper of this series [2] a modification to the energy density (energy per surface area) for single layer bending was suggested. In symmetric bilayers this modification is relevant for non zero spontaneous curvatures of the monolayers. Here this modification is omitted for clarity; a restriction which has no influence on the conclusions reached.

An expression for the energy density (e_H) stored in local bending of a lipid bilayer has been suggested by Helfrich [3] without specification whether bilayer couple and/or single layer bending was meant. This expression has been used since then by numerous researchers in model calculations. A recent version is given in a publication by Mutz and Helfrich [4]; i.e.

$$e_H = 2 k_c \left(\frac{c_1 + c_2}{2} - \frac{c_0}{2} \right)^2 + \bar{k}_c c_1 c_2, \quad (1)$$

where c_1 and c_2 are the principal curvatures and c_0 is a spontaneous curvature. k_c and \bar{k}_c are the elastic constants (associated with the mean and the Gaussian curvature). The interpretation of k_c in terms of a resistance to deformation can be given (see first paragraph) whereas a direct interpretation for \bar{k}_c is lacking.

The second term on the right hand side of equation (1) has been introduced for mathematical completeness [3]. However, the two measures the mean and the Gaussian curvature are not independent. Indeed, for a symmetric bilayer ($c_0 = 0$), the two terms depend in the same way on the curvature when $c_1 = c_2$.

Usually shape changes of lipid bilayer structures are considered for which the topology of the structure does not change. Then the term with the Gaussian curvature vanishes upon integration over the surface. For this reason little consideration has been devoted to the elastic constant \bar{k}_c . This is the starting point of this work.

2. Analysis.

This chapter deals with local single layer bending only. Bilayer couple bending and global single layer bending will be treated in the discussion.

2.1 DECOMPOSITIONS.

2.1.1 Gaussian curvature. — The second term on the right hand side of equation (1) can be decomposed in a symmetric and an antisymmetric contribution as follows.

$$\bar{k}_c c_1 c_2 = \bar{k}_c \left(\frac{c_1 + c_2}{2} \right)^2 - \bar{k}_c \left(\frac{c_1 - c_2}{2} \right)^2 \quad (2)$$

The first expression enclosed by brackets is recognized as the mean local curvature. The absolute value of the second expression enclosed by brackets we call the deviator of the local curvature, following Evans and Skalak [5, 6].

The dependence on the principal curvatures in the first term on the right hand side of equation (2) is essentially the same as in the first term on the right hand side of equation (1). This is the reason why the mean and the Gaussian curvatures are not independent measures of the actual curvature.

2.1.2 Actual curvature. — The decomposition performed above corresponds to a representation of the actual curvature by a superposition of the curvature of a spherical cap and that of a symmetric saddle. The first has isotropic curvature. The second is characterized by two principal curvatures of the same absolute value. The curvature of the spherical cap and that of the symmetric saddle are called the isotropic and the deviatoric contribution to the actual curvature. They are linearly independent since in a spherical cap there is no deviatoric contribution and *vice versa*.

Each contribution is characterized by a single value ; i.e. the mean and the deviator as defined above.

2.2 GEOMETRY OF ISOTROPIC AND DEVIATORIC BENDING. — In an expression for the bending energy the difference of the actual curvature to the spontaneous curvature must enter. In this section, we interpret c_1 and c_2 as such differences which is equivalent to zero

spontaneous curvature. In this section and the next one (2.3) we consider bending of a single monolayer.

2.2.1 Isotropic plate. — First, we consider the deformation of a plate composed of an isotropic material (Fig. 1A-D). We compare two cases, the deformation to a spherical cap (left column) and to a symmetric saddle (right column). To facilitate the comparison the maximum curvature of the saddle has the same absolute value as the curvature of the spherical cap. A Cartesian coordinate system gives the principal axes (x , y) and the direction of the normal (z). In figure 1A a quadratic section of the plate in the unstrained state is

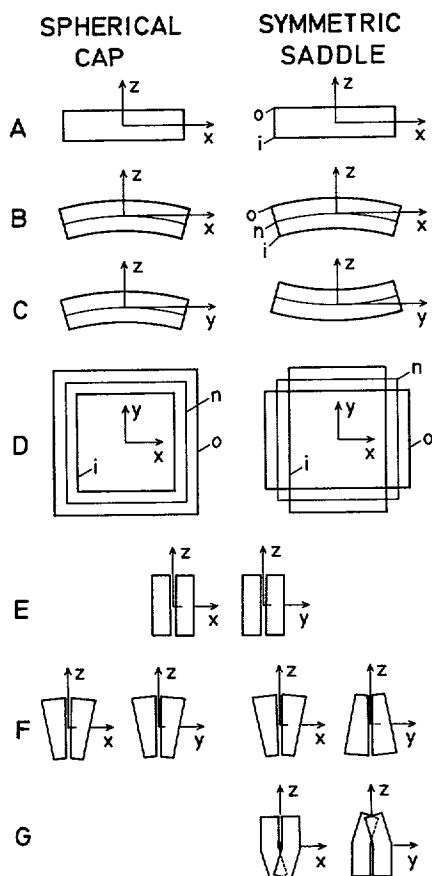


Fig. 1. — Schematical representation of bending a lipid monolayer into a spherical cap (left column) or a symmetric saddle (right column). In lines A-D the monolayer is represented by a plate made of an isotropic material. In lines E-G individual lipid molecules are represented by elastic bodies, packed side by side to form the monolayer. Line A shows in cross section a square plate being flat when unstrained. The origin of a coordinate system is placed in the centre of the plate. The axes x and y are parallel to the corners of the plate and the z -axis is in the thickness direction. Line B and C show the bending of the plate along the x and y direction. Line D shows exaggeratedly how in first order the top (o) and bottom (i) surface of the plate change their shape upon bending with respect to the midsurface (n) the shape of which remains unchanged. Line E corresponds to line A. Two representative molecules of a monolayer are shown. Their unstrained shape is cylindrical. Line F corresponds to line B and C. It shows exaggeratedly how the molecules deform when the layer is bent. For deviatoric bending the molecules can alternatively comply by kinking (line G).

presented in cross section. Figures 1B, 1C show two cross sections after bending. Figure 1D shows exaggeratedly how to first order the top (o) and bottom (i) face of the plate change shape upon bending. The spherical deformation changes the surface area whereas the saddle deformation changes the shape of the faces. This implies that bending to the spherical cap is associated with areal strain in different planes of the plate and bending to the symmetric saddle is associated with in-plane shear.

Please note that changes in the area of the midsurface (n) are not considered here. This is the subject of bilayer couple bending (see 3.3).

2.2.2 Lipid molecules. — We now turn our attention to a lipid monolayer and consider what these deformations mean on a molecular level. Figure 1E shows in cross section two representative molecules which are idealized as two circular cylinders when unstrained. In both kinds of deformation their cross section remains constant in the neutral position which for simplicity is assumed to be in the middle between top and bottom. In the spherical deformation the molecules become cones (Fig. 1F), whereas in the saddle deformation, there are two possibilities. First, the molecules remain straight and change their cross sectional shape (Fig. 1F) from a circle to an ellipse, say. The deformation would be such that the short axes of the elliptical cross sections in the upper and lower half of the layer are oriented at right angles. Second, the molecules keep their circular cross section and are kinked (Fig. 1G) to accomodate the deformation.

2.3 SPONTANEOUS CURVATURE AND WARP. — The same decomposition that was performed with respect to the actual curvature (Sect. 2.1.2) can be done for the spontaneous curvature. An arbitrary spontaneous curvature would then be decomposed in an isotropic and a deviatoric contribution, the first having the shape of a spherical cap the second that of a symmetric saddle. Superposition of the two contributions would give the total spontaneous curvature.

The spontaneous curvature of lipid monolayers has been explained on the basis of the intrinsic shapes of the lipid molecules [7]. Israelachvili [8] has idealized these shapes by rotationally symmetric bodies and characterized them by three parameters. Assembling a lipid monolayer with molecules having all the same parameters results in a total spontaneous curvature which is isotropic. For a non zero deviatoric contribution to the total spontaneous curvature the molecules must not have rotational symmetry. The shape shown in figure 1F (right column) would produce a total spontaneous curvature without an isotropic contribution. This shape is symmetrical with respect to the following operations : (i) reflection with respect to the x, z plane ; (ii) reflection with respect to the y, z plane ; and (iii) reflection with respect to the x, y , plane plus a rotation by $\pi/2$ about the z axis.

The deviatoric contribution to the spontaneous curvature of a lipid monolayer has hitherto not been considered. I suggest that it be called the spontaneous warp. In this way we can retain for the isotropic contribution to the spontaneous curvature its old name : spontaneous curvature.

For a non axisymmetric intrinsic shape of molecules to cause a spontaneous warp the rotational motion of the lipids plays a dual role. First, this motion must be faster than the change in curvature imposed on the layer by the external forces. This is indeed the case since typical time scales of rotational relaxation are many orders of magnitude smaller [9] than typical time scales of deformation. Second, a decrease in entropy is associated with a preferential orientation of molecules. For this reason the net spontaneous warp corresponds to a minimum in the sum of the entropic and the elastic energy contribution. When the layer is composed of more than one molecular species the situation becomes even more complicated because of lateral phase separation [1].

2.4 ALTERNATIVE EXPRESSION FOR THE ENERGY DENSITY. — Having defined the deviatoric contribution to the actual as well as to the spontaneous curvature we are able to formulate a new expression for the energy density (e_s) in single layer bending of a lipid bilayer. We suggest :

$$e_s = 2 B_s \left(\frac{c_1 + c_2}{2} - \xi_s \right)^2 + 2 B_a \left(\left| \frac{c_1 - c_2}{2} \right| - \vartheta \right)^2 \quad (3)$$

The first term on the right hand side is identical to the one in equation (1) except that the definition of the spontaneous curvature (ξ_s) differs by a factor of two with respect to that introduced by Helfrich. The definition of ξ_s was chosen to be in keeping with what one would intuitively call the spontaneous curvature: the mean curvature a small section of the membrane would take on if it was cut out of the closed envelope [1]. The index in e_s and ξ_s indicates that these are quantities in single layer bending as opposed to bilayer couple bending.

The second term is new as it originates from deviatoric bending. The spontaneous warp of the bilayer is called ϑ . 2ϑ is defined as the absolute value of the difference between the two principal curvatures we would observe if we were able to cut a small piece out of a vesicle membrane and let it bend freely. An index is not necessary, since as I will show there is no deviatoric contribution in bilayer couple bending.

Due to the fast rotational motion the net spontaneous warp is always oriented so as to minimize the energy density in deviatoric bending. Therefore the absolute value of the deviatoric contribution to the actual curvature appears in equation (3). For the same reason, ϑ was by definition chosen to be positive.

The spontaneous warp of the bilayer is equal to the weighted sum of the values for the two monolayers, the weight factors being the share of each monolayer in the bending stiffness of the bilayer. It is clear that for a symmetric bilayer ϑ is equal to the spontaneous warp of a monolayer whereas $\xi_s = 0$.

3. Discussion.

Splitting up the Gaussian curvature term and rearranging the new terms in equation (3) takes care of the two points raised in the introduction against equation (1). First, the mean and the deviator are independent measures of the actual curvature. Second, the elastic constant B_a is associated with a clearly defined deformation in contrast to \bar{k}_c the sign of which is not even known. B_a is positive by definition.

According to equation (3) (provided $B_a \neq 0$) the Gaussian curvature is relevant for the shape of a bilayer structure even if its topology does not change. This is in contrast to the notion prevailing to date.

3.1 ELASTIC CONSTANTS. — In equation (3) the elastic constant associated with isotropic bending is called B_s in keeping with an earlier notation [1] where the index s was introduced to indicate single layer bending in contrast to bilayer couple bending. Here the index s is derived from symmetric. B_s is, however, still associated with the same curvature term. It is to be understood that it is an elastic constant in single layer bending. The constant associated with deviatoric bending (B_a) is also an elastic constant in single layer bending.

To get an idea of the value of B_a in relation to B_s we compare the corresponding deformations of the lipid molecules. The changes in cross section parallel to the x, y plane (Fig. 1F) appear to be principally different for cap and saddle deformation. However, the resistance of a phospholipid against volume changes is much larger than the resistance against

shape changes [10]. Therefore the shape change of a lipid molecule can be expected to proceed at constant volume in the cap as well in the saddle deformation. This implies that it is only the orientation of the cross sections (the shape of which is changed) which is different in isotropic compared to deviatoric bending. Without a knowledge of the corresponding elasticities no conclusion can be drawn as to the relation between B_s or B_a . It is, however, likely that their ratio is of the order of unity.

The occurrence of kinks in molecules appears at first sight to offer a smaller resistance to deviatoric bending than the change in cross sectional shape. However, the lateral packing of the lipids might then be compromised. It is therefore questionable whether kinks contribute to the elasticity in deviatoric bending at all.

These considerations make it unlikely that B_a is negligible compared with B_s . Fitting without a deviatoric term may therefore besides other reasons [2] have contributed to the difference in elastic constants that were derived from bilayers of different geometry e.g. spherical, planar, or cylindrical. For an overview see Mutz and Helfrich [4]. Use of equation (3) may allow to determine the value of B_a .

3.2 SPONTANEOUS WARP. — The spontaneous warp ϑ was introduced for completeness. Whether its value is different from zero is an open question.

The molecular structure of phospholipids is characterized by two hydrocarbon chains apposed side by side and a headgroup oriented approximately at right angles to the z -axis. These features make it likely that the cross sections normal to the z -axis are non circular, at least in the gel state. An anisotropy preserved despite the strong segmental motions that prevail in the fluid phase would form the basis of a spontaneous warp of the monolayer. These considerations make a $\vartheta \neq 0$ more likely for lipids with saturated than with unsaturated hydrocarbon chains.

In budding of DMPC vesicles an almost invisible thin neck forms between daughter and mother vesicle [11]. Now, in the neck region, the deviatoric contribution to the actual curvature is dominant. A large value of ϑ would therefore promote the formation of such a geometry. The observation of an instability in budding of DMPC vesicles indicates that ϑ cannot be large. An upper bound can be estimated from the radius of the neck in the last stable configuration before the instability occurred. From the microscopic pictures [11] a value of $1/(4 \mu\text{m})$ is obtained.

If $\vartheta \neq 0$ and $B_a \neq 0$ the equilibrium configuration of the bilayer would not be flat. It can be shown by an approximate analysis that a corrugated surface would have a maximum curvature of about $\vartheta/2$ when $B_a = B_s$. However, no waviness of vesicle contours except for the thermally induced one has been observed in the light microscope. From the microscopic resolution values of ϑ down to $1/200 \text{ nm}$ can be excluded.

Taken together the last two paragraphs indicate that $\vartheta \approx 0$.

3.3 OTHER TYPES OF BENDING STIFFNESS. — Up to now we only considered local single layer bending. We now ask whether for the other cases enumerated in the introduction deviatoric bending is relevant.

The deformation of the monolayers as a whole determines the elasticity in bilayer couple bending. The deformations are visualized in figure 1D when we interpret the plate as a bilayer and the shape changes of its top and bottom surface as shape changes of the outer and inner monolayer, respectively. The area per molecule is changed upon deformation into the cap. The resistance of lipid layers against such a change is enormous [5]. Upon a deformation into a saddle each monolayer is sheared at constant area per molecule. The time scale at which shear stresses relax in lipid layers has been shown to be many orders of magnitude smaller than the time scale of curvature change imposed by external forces [1]. Therefore under

realistic bending deformations there is no shear resistance of the monolayers and consequently no deviatoric contribution in bilayer couple bending.

If a monolayer is composed of more than one molecular species, part of the single layer contribution may relax to the global nature if sufficient time is available for lateral motion of molecules [1]. It has been discussed [1] that this has consequences for the determination of B_s from experiments utilizing the thermally excited shape fluctuations. Provided $\vartheta \neq 0$ these considerations apply in an analogous fashion to a determination of B_a .

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