Elastic Properties of Lipid Bilayers: Theory and Possible Experiments

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Lipid bilayers, elastic properties

A theory of the elasticity of lipid bilayers is proposed. Three types of strain, *i. e.* stretching, tilt and curvature, are distinguished and the associated stresses are identified. It is argued that in the case of vesicles (= closed bilayer films) the only elasticity controlling nonspherical shapes is that of curvature. Euler-Lagrange equations are derived for the shape in magnetic fields and under excess outside pressure. It is shown that magnetic fields can deform spherical vesicles into ellipsoids of revolution. Under excess outside pressure the spherical shape becomes unstable at a certain threshold pressure. Both effects can be influenced by a spontaneous curvature of the bilayer. Some possible experiments to determine the elastic properties are also discussed.

I. Introduction

Lipid bilayers are a subject of some interest as they appear to be closely related to biological membranes. They are attractive systems to study because, apart from thermal fluctuations, they can be homogeneous down to molecular dimensions. Accordingly, their mechanical properties should permit a continuum-mechanical description. The present article deals with the presumable elasticity of lipid bilayers. It is hoped that the continuum concept is transferable to biological membranes, although this may require averaging over areas involving hundreds of lipid molecules, since the presence of proteins destroys local homogeneity.

Lipid molecules consist of a polar head and one or two hydrocarbon chains. In an aqueous environment they tend to assemble as bimolecular sheets with the hydrophilic heads on the outsides and the hydrophobic chains in the interior of the film. Bilayers can often be prepared in such a way that they close to form vesicles whose diameters range from a few hundred angstroms[1] to some millimeters[2]. We may think of bilayers as solid or fluid, depending on whether the lipid molecules form a two-dimensional lattice or not. The rather smooth contours of biological and bilayers vesicles observed in electron microscopy suggest that the membranes are two-dimensional fluids, at least those capable of forming vesicles. (Bilayers may have two or more phases differing largely by the conformation of the hydrocarbon chains[3]. It seems an open question if some low temperature phases can be regarded as quasi-solid.)

The following description of membrane elasticity is based on the assumption of unrestricted internal fluidity. In addition, we take the "average" direction of the more or less flexible hydrocarbon chains to be normal to the bilayer, thus ruling out a spontaneous collective tilt of the lipid molecules. This assumption may not always be correct. Recent X-ray work revealed the existence of lyotropic smectic liquid crystals consisting of tilted bilayers[4]. On the other hand, a long-range tilt necessitates singularities in closed bilayers which might show as sharp points or ridges, again at variance with most electron micrographs of vesicles.

The elasticity of lipid bilayers may be viewed as a special case of the well-established theory of thin elastic shells[5]. Fluidity amounts to a vanishing shear modulus. For our purpose it appears preferable not to start from a general mathematical apparatus but to base a suitable elastic theory on straightforward physical considerations.

In a preceding note we have already given a formula for the ellipsoidal deformation of spherical vesicles by magnetic fields[6]. It was obtained by minimizing the sum of the curvature-elastic and magnetic energies of the vesicle as a function of its ellipticity. In the present article we discuss the various possible elastic strains and stresses of bilayers and show that curvature should, in general, be the only strain governing the shape of nonspherical vesicles. Euler-Lagrange equations are formulated which permit to rederive the magnetic de-

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formation in a much simpler way, giving at the same time the complete balance of the forces and torques acting on the bilayer. They also serve to show that under excess outside pressure the spherical shape of a vesicle should become unstable above a certain threshold. Some direct experiments on vesicles which offer themselves for determining the curvature-elastic moduli and the spontaneous curvature of bilayers are discussed in detail at the end of the article.

II. Elastic Strains and Stresses

A. Stretching

A lipid bilayer is deformable in more than one way. Let us first consider changes in area due to tension, *i.e.* tangential stress. For weak deformations the elastic energy of stretching per unit area, w_s, must be a quadratic function of $\Delta a/a$, the relative change in area a. We may write

$$w_s = 1/2\, k_s (\Delta a/a)^2, \tag{1}$$

where k_s is the elastic modulus of stretching with the dimensions of energy per unit area. The corresponding stress, a force per length, is

$$\sigma_s = k_s (\Delta a/a) \tag{2}$$

or in vector notation

$$\boldsymbol{\sigma}_s = k_s (\Delta a/a)\, \boldsymbol{e} \ . \tag{3}$$

The dimensionless unit vector $\boldsymbol{e}$ is normal to the imaginary cut on which $\boldsymbol{\sigma}_s$ acts from the side to which $\boldsymbol{e}$ points. Naturally, both $\boldsymbol{e}$ and $\boldsymbol{\sigma}$ are parallel or, in the presence of curvature, tangential to the bilayer. The modulus k_s may be obtained by measuring the swelling of spherical vesicles as a function of internal excess pressure.

A bilayer is capable of exchanging lipid molecules with its aqueous environment. For this reason, the elastic forces upon stretching may last only a limited time. The relaxation is apt to be very slow because of the small solubility of lipids in water. With vesicles it may be further hindered by the need for lipid molecules to flip from one side of the film to the other [7].

A stress which we may ignore here is hydrostatic pressure. It may influence $\Delta a/a$, but we think that in practice this is not an important effect. (An estimate is possible on the basis of the considerations of II E.) Another strain, a change in membrane thickness, is also disregarded. Being only about 50 Å for phospholipid bilayers, the thickness cannot be uniquely defined and measured.

B. Tilt

A straight membrane can be submitted to a torque density, for instance by applying an oblique magnetic field acting on magnetically anisotropic lipid molecules. The counter-balancing elastic torque per unit area, $\boldsymbol{m}_t$, must be provided by a normal force per unit length:

$$\boldsymbol{\sigma}_t = \boldsymbol{m}_t \wedge \boldsymbol{e} \, . \tag{4}$$

The strain underlying $\boldsymbol{m}_t$ and $\boldsymbol{\sigma}_t$ is a tilt of the lipid molecules away from their average normal orientation, as sketched in Fig. 1. Denoting the layer normal by $\boldsymbol{n}$ and the average orientation of the molecules by $\boldsymbol{d}$, both dimensionless unit vectors, we may write for the elastic energy per unit area

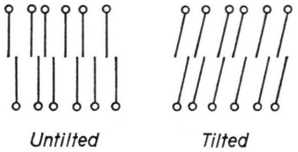

Fig. 1. Highly schematic diagram of untilted and tilted bilayers. Despite their actual flexibility the lipid chains are depicted as straight lines.

$$w_t = 1/2\, k_t (\boldsymbol{n} \wedge \boldsymbol{d})^2, \tag{5}$$

where the dimension of the tilt-elastic modulus is again energy per unit area. Obviously, there are two ways to remove the tilt. One is to rotate the lipid molecules at fixed position, the other is to rotate the piece of bilayer as a whole at fixed molecular orientation. The torque density is given by

$$\boldsymbol{m}_t = -k_t (\boldsymbol{n} \wedge \boldsymbol{d}) \, . \tag{6}$$

Eqn. (4) is, of course, confirmed by the microscopic picture.

An exact expression of w_t as a function of tilt would have to take account of the various parts of the lipid molecule, their average tilts probably being not the same. However, tilt should be minute and its elastic energy negligible in most practical cases (see below), so is appears pointless to develop a detailed molecular therory.

C. Curvature

Finally, we consider curvature of the bilayer. For a convenient description we may use a local right-handed cartesian coordinate system, putting its origin in a given point of the film which is thought to be infinitely thin. The z axis is made parallel to the local layer normal $\boldsymbol{n}$. Regarding $\boldsymbol{n}$ as a function of x and y, we can define the two independent curvatures at the origin

$$c_x = \partial n_x / \partial x\,, \quad c_y = \partial n_y / \partial y\,. \tag{7}$$

The rotation of the vector field $\boldsymbol{n}(x, y)$ must vanish as it is normal to a uniquely defined surface. Therefore, the relation

$$\partial n_x / \partial y - \partial n_y / \partial x = 0 \tag{8}$$

hat to be satisfied by the cross derivatives.

The elastic energy of the curvature is assumed to be a quadratic function of the derivatives of n_x and n_y. The two-dimensional fluid being rotationally symmetric, only those linear and quadratic forms can enter that are independent of the orientation of the x and y axes. They are

$$\partial n_x / \partial x + \partial n_y / \partial y\,, \tag{9}$$

$$(\partial n_x / \partial x + \partial n_y / \partial y)^2, \tag{10}$$

$$\frac{\partial n_x}{\partial x}\frac{\partial n_y}{\partial y} - \frac{\partial n_x}{\partial y}\frac{\partial n_y}{\partial x}\,. \tag{11}$$

The curvature-elastic energy per unit area may be written as

$$w_c = \tfrac{1}{2} k_c \left(\frac{\partial n_x}{\partial x} + \frac{\partial n_y}{\partial y} - c_0 \right)^2 + \bar{k}_c \left(\frac{\partial n_x}{\partial x}\frac{\partial n_y}{\partial y} - \frac{\partial n_x}{\partial y}\frac{\partial n_y}{\partial x} \right). \tag{12}$$

The curvature-elastic moduli k_c and $\bar{k}_c$ have the dimension of energy. The linear term (9) is incorporated through c_0. The spontaneous curvature c_0 allows for bilayers whose two sides are chemically different. The sign of c_0 depends, of course, on the arbitrary polarity of $\boldsymbol{n}$.

The expressions (9) and (11) are analogous to splay and saddle splay as introduced by Frank[8] in dealing with the curvature elasticity of liquid crystals. It may be noted that Eqn. (12) can hold only if tilt in the sense defined above is negligible. (Otherwise $\boldsymbol{n}$ must be replaced by one or more directors $\mathbf{d}$.)

Formulas (7) to (12) remain valid if a single global coordinate system is used instead of the local ones, $\boldsymbol{n}$ still being a function of x and y. The only exception is (8) which becomes

$$\frac{\partial}{\partial x}\frac{n_y}{(1 - n_x^2 - n_y^2)^{1/2}} - \frac{\partial}{\partial y}\frac{n_x}{(1 - n_x^2 - n_y^2)^{1/2}} = 0\,. \tag{13}$$

(A prove may be based on curl grad $z = 0$ where $z(x, y)$ describes the surface.) Here, and in the following, we use $n_z = (1 - n_x^2 - n_y^2)^{1/2}$ to eliminate n_z.

Let us introduce the elastic energy density per unit area in the x, y plane

$$g_c = w_c / (1 - n_x^2 - n_y^2)^{1/2}. \tag{14}$$

It can serve as a starting point to derive Euler-Lagrange equations governing the curvature of bilayers (see below). Here, we only want to show that the total "saddle splay" energy is independent of the size and shape of a membrane with fixed boundary conditions (fixed $\boldsymbol{n}$ on the contour). The energy in question is

$$\int \bar{g}_c \, \mathrm{d}x \, \mathrm{d}y = \int \bar{k}_c \left(\frac{\partial n_x}{\partial x}\frac{\partial n_y}{\partial y} - \frac{\partial n_x}{\partial y}\frac{\partial n_y}{\partial x} \right) \cdot \frac{\mathrm{d}x \, \mathrm{d}y}{(1 - n_x^2 - n_y^2)^{1/2}}\,. \tag{15}$$

It is extreme if $\bar{g}_c$ satisfies the two differential equations

$$\frac{\partial \bar{g}_c}{\partial n_u} - \frac{\partial}{\partial x}\frac{\partial \bar{g}_c}{\partial \dfrac{\partial n_u}{\partial x}} - \frac{\partial}{\partial y}\frac{\partial \bar{g}_c}{\partial \dfrac{\partial n_u}{\partial y}} = 0\,, \tag{16}$$

where $u = x, y$. The left-hand side of the first equation is

$$\bar{k}_c \left(\frac{\partial n_x}{\partial x}\frac{\partial n_y}{\partial y} - \frac{\partial n_x}{\partial y}\frac{\partial n_y}{\partial x} \right) \frac{n_x}{(1 - n_x^2 - n_y^2)^{3/2}} - \bar{k}_c \frac{\partial}{\partial x}\frac{\partial n_y}{\partial y}\frac{1}{(1 - n_x^2 - n_y^2)^{1/2}} + \bar{k}_c \frac{\partial}{\partial y}\frac{\partial n_y}{\partial x}\frac{1}{(1 - n_x^2 - n_y^2)^{1/2}}\,. \tag{17}$$

Inspection shows that the left-hand sides of both equations are identical to zero for any function $\boldsymbol{n}(x, y)$.)

An energy depending solely on boundary conditions, while causing stresses, produces no torque or force densities. As a consequence, the "saddle splay" term can be omitted in many calculations, in agreement with the role of saddle splay in liquid crystals.

The stresses conjugate to curvature are torques per unit length. In order to compute them it is helpful to imagine a small rectangular piece of bilayer which is slightly and (practically) uniformly curved by applying such torques. We employ local coordinates and keep $|n_x|, |n_y| \ll 1$ on the whole piece. Simple energy considerations show that the torque per unit length, $\boldsymbol{\tau}$, may be given the form

$$\begin{aligned}\boldsymbol{\tau} = {} & k_{\mathrm{c}}(c_1+c_2)\cdot(\boldsymbol{n}\wedge\boldsymbol{e})\\ & +\bar{k}_{\mathrm{c}}[c_2(\boldsymbol{n}\wedge\boldsymbol{e}_1)\cdot(\boldsymbol{e}_1\cdot\boldsymbol{e})\\ & +c_1(\boldsymbol{n}\wedge\boldsymbol{e}_2)\cdot(\boldsymbol{e}_2\cdot\boldsymbol{e})]\,.\end{aligned} \tag{18}$$

Here $\boldsymbol{e}_1$ and $\boldsymbol{e}_2$ are orthogonal unit vectors tangential to the bilayer. They represent the principal axes of curvature for which the cross derivatives of $\boldsymbol{n}$ vanish. The principal curvatures along $\boldsymbol{e}_1$ and $\boldsymbol{e}_2$ are c_1 and c_2, respectively. In analogy to other elastic problems, one can obtain the torque density (per unit area) by forming derivatives of $\boldsymbol{\tau}$. Doing this, one finds that the terms containing $\bar{k}_{\mathrm{c}}$ drop out as expected.

D. Nonlinear curvature-elastic stresses

The stresses treated so far are linear functions of the respective strains. However, vesicles possess an inherent curvature even in their undeformed, spherical state. This points to the necessity of including stresses varying as the product of two curvatures.

A first stress quadratic in curvature is an anisotropic tangential stress to be called directed tension. Its existence is quickly demonstrated by means of a tube of bilayer, the radius being R and the length L. The total curvature-elastic energy is, for $c_0=0$,

$$E_{\mathrm{c}}=1/2\,k_{\mathrm{c}}(2\,\pi/R)\,L\,. \tag{19}$$

With constant area

$$A=2\,\pi\,R\,L \tag{20}$$

one has

$$\mathrm{d}E_{\mathrm{c}}/\mathrm{d}R=-k_{\mathrm{c}}(A/R^3)\,. \tag{21}$$

Accordingly, there must be a normal force per unit area which is

$$\boldsymbol{f}_{\mathrm{n}}=k_{\mathrm{c}}(\boldsymbol{n}/R^3)\,, \tag{22}$$

if the layer normal $\boldsymbol{n}$ points outward. The force is linked with a tension parallel to the lines of circumference

$$\sigma_\varphi=-k_{\mathrm{c}}(1/R^2)\,. \tag{23}$$

Both $\boldsymbol{f}_{\mathrm{n}}$ and σ_φ can be balanced by an external force supplied, for instance, by a cylindrical constraint such as a solid tube. In this case, there is no tension along the cylinder axis. The tube may also be stabilized by an isotropic tension offsetting the circumferential tension so that only a tension parallel to the axis is left. This happens naturally if the length of the tube is prescribed by two supporting walls of fixed distance, provided $\boldsymbol{n}\perp$ axis.

Slightly more complex arguments allowing for $c_0=0$ and two non-vanishing principal curvatures result in a complete formula for the directed tension $\sigma_{\mathrm{cc}}^{\mathrm{dir}}$ induced by curvature

$$\begin{aligned}\boldsymbol{\sigma}_{\mathrm{cc}}^{\mathrm{dir}} = {} & -k_{\mathrm{c}}(c_1+c_2-c_0)\;[c_1\,\boldsymbol{e}_1(\boldsymbol{e}_1\cdot\boldsymbol{e})\\ & +c_2\,\boldsymbol{e}_2(\boldsymbol{e}_2\cdot\boldsymbol{e})]-k_{\mathrm{c}}\,c_1\,c_2\,\boldsymbol{e}\,.\end{aligned} \tag{24}$$

The net anisotropy of tension may be expressed by the difference $\sigma_2-\sigma_1$ of the directed tensions along the principal axes of curvature. Naturally, $\boldsymbol{\sigma}_{\mathrm{cc}}^{\mathrm{dir}}$ is equal in all directions on a sphere and thus there is net isotropy. Net anisotropy gives rise to shear stresses along imaginary cuts that are not parallel to the principal axes.

Another stress quadratic in curvature compensates for the tendency of the lipid material to move into regions of lower curvature-elastic energy. This isotropic tension is simply given by

$$\boldsymbol{\sigma}_{\mathrm{cc}}^{\mathrm{iso}}=w_{\mathrm{c}}\,\boldsymbol{e}\,. \tag{25}$$

Other quadratic effects concern the force densities. The normal force produced by the combination of tension and curvature is well known from soap bubbles, etc. Conversely, a normal force per unit length (normal stress) in a curved bilayer causes a tanegntial force per unit area.

E. Estimate of the elastic moduli

It is natural to suppose that the only elasticity influencing the expansion of a spherical vesicle under excess internal pressure is that of stretching. On the other hand, if a vesicle is non-spherical, one may expect its shape to be controlled largely by curvature elasticity. To put these assumptions on a firm basis, we estimate the different elastic moduli. The elastic energy densities can be approximated by a sum of nearest-neighbor contributions. Each of them is roughly the molecular energy of condensation, on the order of 1 eV, times the squared relative change of the intermolecular distance or orientation. In this picture the elastic energy per molecule is about $1\ \mathrm{eV}\approx10^{-12}\,\mathrm{erg}$ if $|\Delta a/a|$, $|\boldsymbol{n}\wedge\boldsymbol{d}|$, and $|c\,d_{\mathrm{i}}|$ are about unity, d_{i} being the intermolecular spacing. With a density of 10^{15} molecules per cm^2 one obtains

$$\begin{aligned}k_{\mathrm{s}}&=10^3\,\mathrm{erg\,cm^{-2}},\\ k_{\mathrm{t}}&=10^3\,\mathrm{erg\,cm^{-2}},\\ k_{\mathrm{c}}&=10^{-12}\,\mathrm{erg}\,.\end{aligned} \tag{26}$$

The smallness of k_{c} is due to the fact that for a curvature of $1\,\mathrm{cm}^{-1}$, *i.e.* a rotation of $\boldsymbol{n}$ by ca.

60° over 1 cm, the average orientations of adjacent molecules differ by only $(10^{-15})^{1/2}$ times this angle. By way of contrast, microscopic and macroscopic deformations are equally strong for stretch and tilt, $\Delta a/a$ and $\boldsymbol{n} \wedge \boldsymbol{d}$ representing the relative change on both scales.

Despite the obvious crudeness of such a model, the estimates for k_s and k_c are not too far from what one would guess on the basis of the known volume elastic moduli of organic liquids ($\approx 10^9$ dyn cm^{-2}) and the curvature elastic moduli of liquid crystals ($\approx 10^{-6}$ dyn). Multiplying those by the thickness of the bilayer (approx. 50 Å), one arrives at $k_s = 5 \cdot 10^2$ dyn cm^{-2} and $k_c = 5 \cdot 10^{-13}$ erg.

An interesting number is the total curvature elastic energy E of a spherical vesicle,

$$E = 8\,\pi\,k_c(1 - r_0\,c_0/2)^2 + 4\,\pi\,\bar{k}_c\,. \tag{27}$$

With $\bar{k}_c = 0$, $k_c = 5 \cdot 10^{-13}$ erg and $c_0 = 0$ one computes the very small value of 8 eV, independently of the radius of the vesicle. Although our estimates may be wrong by a power of ten or more, it appears that the energy E could effect only a minor stretching of the bilayer unless the vesicle comprises just a few tens of molecules. The same energetical reasoning holds for tilt, but in practice tilt is even less likely since any torques produce tilt only locally, while tangential forces may stretch a piece of bilayer.

It is now clear that curvature should be negligible in the swelling of vesicles, apart from special cases. However, curvature will dominate if the volume of a vesicle is reduced below the value characterized by a vanishing total tension in the spherical bilayer. In such cases, one can always find nonspherical vesicle shapes which require no stretching (change in area) or tilt of the bilayer. Curvature being the easiest deformation, it seems permissible to entirely neglect tilt and stretching in any calculus of variation determining the vesicle shape. This approach is used in the following discussion of the deformation of spheres. It is also applied to the small changes in shape which are possible, *e. g.* in a magnetic field, without a significant decrease in volume.

III. Problems of Rotational Symmetry

We are interested in the deformations of spherical bilayer vesicles. In many cases the deformed shape can be expected to be rotationally symmetric. It may then be described by a function $r(\theta)$, r being the distance from some origin within the vesicle and θ the polar angle. However, $r(\theta)$ is not well suited to derive a differential equation for the shape. Since r as well as its first and second derivatives enter the curvatures, a second-order calculus of variation ensues which leads to a fourth-order differential equation. It is preferable to employ another rotationally symmetric function, namely $\psi(x)$, where x is the distance from the polar axis and ψ the angle made by the layer normal with the polar axis. An illustration is given in Fig. 2. As will be seen immediately, $\psi(x)$ permits a standard calculus of variation resulting in a second-order differential equation. The shape of the vesicle is not directly given by $\psi(x)$, but it can be obtained by an integration. For instance, we may introduce a coordinate z along the polar axis, indicated in Fig. 1 b. The integral

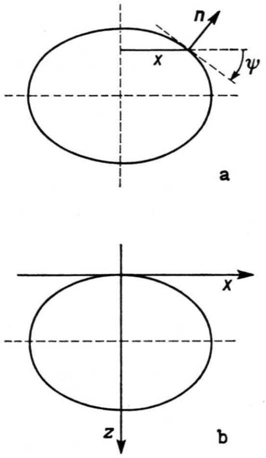

Fig. 2. Coordinates for the description of rotationally symmetric shapes.

$$z(x) = \int_0^x \tan\psi(\zeta)\,\mathrm{d}\zeta \tag{28}$$

renders the contour of the vesicle. Both $\psi(x)$ and $z(x)$ have upper and lower branches which need not be the mirror images of each other.

A. Film between circles

On any rotationally symmetric surface one can define in a unique fashion two sets of orthogonal lines corresponding to the meridians and parallels of a sphere. The principal curvatures of the surface are along these lines and will be designated c_{m} and c_{p}, respectively. For the upper branch of $\psi(x)$ in Fig. 2 they are

$$c_{\mathrm{m}} = \cos\psi\,(\mathrm{d}\psi/\mathrm{d}x)\,, \quad c_{\mathrm{p}} = \sin\psi/x\,, \tag{29}$$

if the layer normal is taken to point outward. It will be sufficient here to explicity consider only the upper branch. Limiting our attetnion to a piece of bilayer between the circles x_1 and x_2, we have for the total curvature-elastic energy

$$\int_{x_1}^{x_2} [\tfrac{1}{2}\,k_{\mathrm{c}}(c_{\mathrm{m}} + c_{\mathrm{p}} - c_0)^2 + \bar{k}_{\mathrm{c}}\,c_{\mathrm{m}}\,c_{\mathrm{p}}]\,\frac{2\,\pi\,x}{\cos\psi}\,\mathrm{d}x\,, \tag{30}$$

the square bracket representing the energy density (per cm^2). To express our assumption that the bilayer is unstretchable, we adopt the auxiliary condition of constant area,

$$\int_{x_1}^{x_2} (2\,\pi\,x/\cos\psi)\,\mathrm{d}x = \text{const.} \tag{31}$$

The auxiliary condition of no tilt is automatically satisfied by our formula for the curvature-elastic energy.

We are now in a position to set up an Euler-Lagrange equation for the shape of rotationally symmetric bilayers. Combining (30) and (31) yields the integrand f of our variational problem,

$$f\left(x, \psi, \frac{\mathrm{d}\psi}{\mathrm{d}x}\right) = \left[\tfrac{1}{2}\,k_{\mathrm{c}}\left(\cos\psi\,\frac{\mathrm{d}\psi}{\mathrm{d}x} + \frac{\sin\psi}{x} - c_0\right)^2 + \bar{k}_{\mathrm{c}}\cos\psi\sin\psi\,\frac{\mathrm{d}\psi}{\mathrm{d}x}\,\frac{1}{x} + \lambda\right]\frac{2\,\pi\,x}{\cos\psi}\,, \tag{32}$$

where λ is a Lagrange multiplier. The integral of f is at an extreme if ψ satisfies

$$\frac{\partial f}{\partial\psi} - \frac{\mathrm{d}}{\mathrm{d}x}\,\frac{\partial f}{\partial(\mathrm{d}\psi/\mathrm{d}x)} = 0\,. \tag{33}$$

Carrying out the differentiations, one finds that the $\bar{k}_{\mathrm{c}}$ terms drop out as anticipated. The Euler-Lagrange equation (33) divided by $2\,\pi\,x/\cos\psi$ can be read as a balance of elastic torque densities. Multiplying (33) by $\cos^2\psi$, one obtains the convenient form

$$\begin{aligned} &-k_{\mathrm{c}}(c_{\mathrm{m}} + c_{\mathrm{p}} - c_0)\,c_{\mathrm{m}}\;2\,\pi\,x\sin\psi \\ &+\tfrac{1}{2}\,k_{\mathrm{c}}(c_{\mathrm{m}} + c_{\mathrm{p}} - c_0)^2\;2\,\pi\,x\sin\psi \\ &+\lambda\,2\,\pi\,x\sin\psi \\ &-k_{\mathrm{c}}\cos\psi\,\frac{\mathrm{d}(c_{\mathrm{m}} + c_{\mathrm{p}})}{\mathrm{d}x}\;2\,\pi\,x\cos\psi + 0\,. \end{aligned} \tag{34}$$

Now we have a balance of the elastic forces in z direction. The first term, without the factor $2\,\pi\,x\sin\psi$, stands for the directed tension $\sigma_{\mathrm{cc}}^{\mathrm{dir}}$, the force being parallel to the local meridian. The second term, without $2\,\pi\,x\sin\psi$, is the isotropic tension $\sigma_{\mathrm{cc}}^{\mathrm{iso}}$. The Lagrange multiplier λ must then be an isotropic tension, *i. e.* a tangential force per unit length, which is uniform throughout the film. The fourth term, without the factor $2\,\pi\,x\cos\psi$, is the normal stress σ_{t}.

Apart from boundary conditions $\psi_1 = \psi(x_1)$ and $\psi_2 = \psi(x_2)$ we may, for instance, prescribe the total surface area. Eqn. (34) allows indeed for three adjustable parameters, one of them being λ. The distance $z(x_2) - z(x_1)$ between the rings assumes the value of minimum energy, *i. e.* of vanishing force F_z.

If the force F_z is non-zero, one has to add to the integrand (32) the terms $-F_z\tan\psi$ which results in the additional term $-F_z$ on the left-hand side of Eqn. (34). (F_z is positive for pull and negative for push.)

B. Deformation of spherical vesicles by a magnetic field

A magnetic field exerts a torque on a magnetically anisotropic film. The effect of a uniform field **H** parallel to the z axis is taken into account by adding the orientational energy per unit area,

$$-(1/2)\,(\chi_{\mathrm{n}} - \chi_{\mathrm{t}})\,b\cos^2\psi\,\mathbf{H}^2, \tag{35}$$

to the square bracket of the integrand (32). We express the susceptibilities per unit area for fields normal and tangential to the bilayer by $\chi_{\mathrm{n}}\,b$ and $\chi_{\mathrm{t}}\,b$, where b is a measure for the thickness of the bilayer. The Euler-Lagrange equation of the problem may be given the form

$$\begin{aligned} &[-k_{\mathrm{c}}(c_{\mathrm{m}} + c_{\mathrm{p}} - c_0)\,c_{\mathrm{m}} + 1/2\,k_{\mathrm{c}}(c_{\mathrm{m}} + c_{\mathrm{p}} - c_0)^2 \\ &\quad - 1/2\,(\chi_{\mathrm{n}} - \chi_{\mathrm{t}})\,b\,\mathbf{H}^2\cos^2\psi + \lambda]\sin\psi \\ &+ \left[(\chi_{\mathrm{n}} - \chi_{\mathrm{t}})\,b\,\mathbf{H}^2\cos\psi\sin\psi - k_{\mathrm{c}}\cos\psi\,\frac{\mathrm{d}(c_{\mathrm{m}} + c_{\mathrm{p}})}{\mathrm{d}x}\right]\cos\psi = 0\,. \end{aligned} \tag{36}$$

The two magnetic terms arising from the variation are left separate in order to display their physical meanings. The first square bracket represents a tangential force per unit length and the second a normal one.

It has been shown previously [6] that a magnetic field may transform a spherical vesicle into an ellipsoid of revolution. The earlier proof was based on energy considerations, here we use the Euler-Lagrange equation (36) for the same purpose. In polar coordinates the ellipsoidal deformation may be described by

$$s = r - r_0 = s_2 P_2(\cos\theta) = s_2 (3/2)(\cos^2\theta - 1/3), \tag{37}$$

where P_2 is the second Legendre polynomial and r_0 the radius of the sphere. In terms of $\psi(x)$ we have

$$\Delta\psi(x) = \psi(x) - \psi_1(x) = \frac{3}{2}\frac{s_2}{r_0}\cos\psi_1(x)\sin\psi_1(x), \tag{38}$$

where the function

$$\sin\psi_1 = x/r_0 \tag{39}$$

represents the original sphere. These formulas are valid only for very small deformations, *i. e.* $|s_2| \ll r_0$. The radius r_0 is used in (39) even though the equatorial radius of the deformed vesicle differs from r_0. The associated change in bilayer area is immaterial in our approximation.

There are two equivalent representations for the curvatures to first order in the deformation. They are

$$\begin{aligned} c_\mathrm{m} &= \frac{1}{r_0} - \frac{s}{r_0^2} - \frac{\mathrm{d}^2 s}{r_0^2\,\mathrm{d}\theta^2}, \\ c_\mathrm{p} &= \frac{1}{r_0} - \frac{s}{r_0^2} - \frac{\cos\theta}{\sin\theta}\frac{\mathrm{d}s}{r_0^2\,\mathrm{d}\theta}, \end{aligned} \tag{40}$$

and

$$\begin{aligned} c_\mathrm{m} &= \frac{1}{r_0} + \frac{\mathrm{d}}{\mathrm{d}x}(\cos\psi\,\Delta\psi), \\ c_\mathrm{p} &= \frac{1}{r_0} + \frac{\cos\psi}{x}\Delta\psi. \end{aligned} \tag{41}$$

Inserting the curvatures in (36), and equating the terms proportional to s_2 and dependent on θ or x, one obtains

$$s_2 = -\frac{r_0^3(\chi_\mathrm{n} - \chi_\mathrm{t})\,b\,\mathbf{H}^2}{3(6 - c_0 r_0)k_\mathrm{c}}. \tag{42}$$

Terms quadratic in s_2 are meaningless in the present approximation. If terms proportional to s_2 are omitted, *i. e.* with $\mathbf{H} = 0$, the stress λ is

$$\lambda = \tfrac{1}{2} k_\mathrm{c} \frac{c_0}{r_0}(2 - c_0 r_0). \tag{43}$$

The ellipsoid is oblate for $\chi_\mathrm{n} - \chi_\mathrm{t} > 0$ and prolate for $\chi_\mathrm{n} - \chi_\mathrm{t} < 0$, provided $c_0 r_0 < 6$. A completely different situation to be discussed below arises for $c_0 r_0 \geqq 6$.

C. Deformation of spherical vesicles by pressure

Another extension of the shape equation (35) includes a difference $\Delta p = p_\mathrm{e} - p_\mathrm{i}$ between external and internal pressure. In this case, the integrand of the variational problem becomes

$$\begin{aligned} f_\mathrm{p}\left(x, \psi, \frac{\mathrm{d}\psi}{\mathrm{d}x}\right) = {} & \left[\tfrac{1}{2} k_\mathrm{c}\left(\cos\psi\frac{\mathrm{d}\psi}{\mathrm{d}x} + \frac{\sin\psi}{x} - c_0\right)^2 \right. \\ & \left. + \bar{k}_\mathrm{c}\cos\psi\sin\psi\,\frac{\mathrm{d}\psi}{\mathrm{d}x}\frac{1}{x} + \lambda\right]\frac{2\pi x}{\cos\psi} \\ & + \Delta p\, x^2 \pi \tan\psi. \end{aligned} \tag{44}$$

The Euler-Lagrange equation determining the shape may be written as

$$\begin{aligned} & - k_\mathrm{c}(c_\mathrm{m} + c_\mathrm{p} - c_0)\,c_\mathrm{m}\, 2\pi x \sin\psi \\ & + \tfrac{1}{2} k_\mathrm{c}(c_\mathrm{m} + c_\mathrm{p} - c_0)^2\, 2\pi x \sin\psi \\ & + \lambda\, 2\pi x \sin\psi \\ & + \Delta p\, x^2 \pi \\ & - k_\mathrm{c}\cos\psi\frac{\mathrm{d}(c_\mathrm{m} + c_\mathrm{p})}{\mathrm{d}x}\, 2\pi x\cos\psi = 0. \end{aligned} \tag{45}$$

Let us study very small deformations, again assuming them to be ellipsoidal. (The first Legendre polynomial describes a translation, not a deformation.) Using (37), one can express x as a function of s_2 and θ and employ representation (40) for the curvatures. Alternatively, one may use representation (41) and write x as function of s_2 and ψ:

$$\begin{aligned} x &= r_0 \sin\left(\psi - \frac{3 s_2}{2 r_0}\cos\psi\sin\psi\right) \\ &= r_0\sin\psi - (3/2)s_2\cos^2\psi\sin\psi. \end{aligned} \tag{46}$$

When the insertions are made in Eqn (45) one obtains

$$\lambda = \tfrac{1}{2} k_\mathrm{c}\frac{c_0}{r_0}(2 - c_0 r_0) - \frac{\Delta p}{2} r_0 \tag{47}$$

from the constant terms, and

$$\Delta p_\mathrm{c} = (2 k_\mathrm{c}/r_0^3)(6 - c_0 r_0) \tag{48}$$

from those proportional to s_2 and varying with θ or x.

At the pressure difference Δp_c the vesicle is in neutral equilibrium with respect to ellipsoidal deformations, the amplitude s_2 being arbitrary in the linear approximation. Obviously, Δp_c in (48) represents a threshold pressure for the deformation of the spherical shape, which is indicated by the subscript *c*. Any infinitesimal deformation corresponding to higher Legendre polynomials than P_2 would require larger pressure differences than Δp_c.

We may infer that weak enough deformations under pressure are indeed ellipsoidal. However, the vesicle shape cannot be expected to be a continuous function of Δp. As the ellipsoid is prolate for $s_0 > 0$ and oblate for $s_2 < 0$, a change in sign of s_2 leads to a physically non-equivalent situation. Consequently, there may be an abrupt deformation when a rising Δp passes Δp_c and an abrupt return to the spherical shape somewhere below Δp_c as Δp is dropping. To make this more plausible, we exploit an analogy of Landau's theory of second-order phase transitions. Regarding s_2 as an order parameter, we think the total free energy E of the vesicle, due to curvature and Δp, to be expanded up to fourth power in s_2. The difference $\Delta p_c - \Delta p$ takes the role of the temperature difference $T - T_c$ in Landau's theory, and we may write

$$E = a(\Delta p_c - \Delta p) s_2^2 + B s_2^3 + C s_2^4 . \qquad (49)$$

Since E is as asymmetric in s_2, the cubic term will, in general, not vanish and the transition will not be of second but of first order. (There can be no linear term since the sphere is an equilibrium state.) Accordingly, the deformation is discontinuous and displays hysteresis, *i. e.* the analogs of superheating and supercooling. In the quadratic approximation the sign of s_2 is free and the ellipsoidal deformation need not be rotationally symmetric. These ambiguities disappear in an abrupt transition (but the deformedshape may be asymmetric with respect to the equatorial plane).

The calculation of the total free energy up to fourth order in s_2 or, equivalently, of the stresses up to third order is tedious and not attempted here. Eqn (49) would give poor results if higher powers of s_2 and higher Legendre polynomials are important. (Associated Legendre functions have to be considered if rotational symmetry is abandoned.) Also, theoretically sharp transitions and hysteresis effects are possibly washed out by thermal fluctuations because of the probable weakness of curvature elasticity (see below). In our approximation, these fluctuations should diverge at the transition.

The deformability (42) of vesicles in a magnetic field goes to infinity and the threshold pressure (48) to zero as c_0 approaches the value of $6/r_0$. Apparently, the spherical shape is in neutral equilibrium at $c_0 r_0 = 6$ without the action of any external forces. For even larger c_0, *i. e.* for spontaneous curvatures at least six times stronger than that of the sphere, the vesicle will be nonspherical. Its shape is likely to be prolate because thus the curvature can assume its large spontaneous value over most of the bilayer area. The deformation caused by spontaneous curvature can, of course, be removed by applying a negative Δp, the critical value again being given by Eqn (48). On the other hand, if c_0 is small or negative, a deformation induced by a positive Δp is likely to result in biconcave-discoid shapes of the type known from red blood cells and their ghosts. Such shapes permit a large decrease in vesicle volume, requiring at the same time comparatively little curvature.

Bilayer vesicles may possess a variety of stable and metastable states. As far as they are caused by spontaneous curvature, a magnetic field, or a pressure difference, they should all be solutions of the above shape equations. It is easy to put up a general relation involving both $\mathbf{H}$ and Δp. The formula for the ellipticity of a weakly deformed vesicle subject to both influences comes out to be

$$s_2 = -\frac{2(\chi_n - \chi_t) b \mathbf{H}^2}{3(\Delta p_c - \Delta p)} . \qquad (50)$$

D. Energies and thermal fluctuations

Sometimes a comparison of energies is more expedient than a balance of forces. A vesicle whose shape is exactly an ellipsoid of revolution has the following curvature-elastic, magnetic, and volume energies in the lowest occurring power of s_2

$$E_c = (8\pi/5)(6 - r_0 c_0) k_c (s_2^2/r_0^2), \qquad (51)$$

$$E_{\mathbf{H}} = (16\pi/15)(\chi_n - \chi_t)\, b\, \mathbf{H}^2 r_0 s_2 , \qquad (52)$$

$$E_V = -(4\pi/5)\Delta p\, r_0 s_2^2 . \qquad (53)$$

Formulas (51) and (52) have been given before[6]. Their calculation is straightforward but fairly cumbersome. The radius r_0 is that of the original sphere. As the surface area is kept constant, r_0 in (37) has to be replaced by the renormalized radius

$$r_0 + \frac{1}{20} \frac{s_2^2}{r_0} + 0(s_2^3) . \qquad (54)$$

Renormalization has been taken into account in Eqn (51). The volume of the renormalized ellipsoid is

$$V = (4\pi/3)\ (r_0^3 - \tfrac{3}{5} r_0 s_2^2) + 0(s_2^3) , \qquad (55)$$

which leads directly to Eqn (53). Knowing that small deformations are ellipsoidal[6], one can use the energy expressions to rederive (42), (48), and (50).

The possible effect of thermal fluctuations of the vesicle shape on the deformation induced by pressure has already been mentioned. According to (51) these fluctuations can be very strong. Their mean square amplitude is deducible from

$$(1/2)\, k_B \mathrm{T} = \langle E_\mathrm{c} \rangle \tag{56}$$

where k_B is Boltzmann's constant and T the absolute temperature. For $k_\mathrm{B} T = 4 \cdot 10^{-14}$ erg. $k_\mathrm{c} = 5 \cdot 10^{-13}$ dyn cm, and $c_0 = 0$, one obtains

$$\left(\left\langle \frac{s_2{}^2}{r_0{}^2} \right\rangle \right)^{-\frac{1}{2}} = 4 \cdot 10^{-2} \, .$$

Bilayer vesicles at room temperature may thus be expected to exhibit, on the average, an appreciable ellipticity. Deformations of higher order will also be excited, so the shape can be rather bumpy. Simple statistical considerations indicate, however, that thermal deformations should not affect a superimposed magnetic deformation too much, unless they distort the original sphere almost beyond recognition.

IV. Possible Experiments

A check of the proposed theory would be experiments aimed at determining the curvature-elastic modulus k_c and the spontaneous curvature c_0. Are measurements of the type outlined above feasible?

A. Magnetic deformation

Let us first deal with the deformation caused by magnetic fields. With $k_\mathrm{c} = 5 \cdot 10^{-13}$ erg, $\chi_\mathrm{n} - \chi_\mathrm{t} = 10^{-7}$, $b = 5 \cdot 10^{-7}$ cm, $\mathbf{H} = 10^4$ oersted, and $c_0 = 0$, one computes from Eqn (42).

$$s_2 = -5 \cdot 10^{-10} \text{ cm} \tag{57}$$

for a vesicle of radius $r_0 = 10^{-5}$ cm. This is a small deformation, but it may be detectable by means of the induced birefrigence of a concentrated solution of vesicles, a formula for which was already been given [6].

We have assumed $\chi_\mathrm{n} - \chi_\mathrm{t} = 10^{-7}$ because this order of magnitude is characteristic of liquid crystals. The magnetic anisotropy of ordinary lipid bilayers is probably smaller. However, the order of 10^{-7} may be reached by lipids with highly unsaturated hydrocarbon chains. Alternatively, it may be achieved with the aid of spin labels. A concentration of roughly 0.1 percent is needed, the bulk susceptibility of paramagnetic organic compounds being typically around 10^{-4}.

Any deformation of a spherical vesicle diminishes its volume if the surface area is fixed. Therefore, a predicted magnetic deformation may be prevented by the hydrostatic elasticity of the enclosed water. To assess the strength of this disturbance, we write down the compressional energy E_w, assuming that without field the vesicle is spherical and $\Delta p = 0$. On the basis of (55) we have

$$E_\mathrm{w} = \frac{2\pi}{3} r_0{}^3 k_\mathrm{w} \left(\frac{3}{5} \frac{s_2{}^2}{r_0{}^2} \right)^2 . \tag{58}$$

The elastic stiffness of water, k_w, is $2 \cdot 10^{10}$ dyn cm^{-2}. E_w varies as the fourth power of s_2, unlike the curvature-elastic energy E_c given by (51). Comparison shows that for $c_0 = 0$

$$E_\mathrm{w} < E_\mathrm{c} \text{ if } s_2{}^2 < 40\,(k_\mathrm{c}/r_0\, k_\mathrm{w}) . \tag{59}$$

For the above vesicle the energy of water compression is negligible if

$$|s_2| < 1 \cdot 10^{-8} \text{ cm} .$$

Clearly, the deformation (57) is well within the limit.

The restriction (59) becomes more stringent for larger vesicles. It seems prohibitive for red blood cells and their ghosts whose radii are about $3 \cdot 10^{-4}$ cm. A certain relief may be provided by permeation which is discussed below. An attractive method for facilitating rapid pressure equalization would be the insertion of pores of tubes, particularly with giant bilayer vesicles [2].

So far, we have neglected the strong thermal fluctuations of the vesicle shape, which, in most cases, are likely to be much stronger than the magnetic deformation. Since the two effects should be essentially independent, as stated earlier, the fluctuations do not prevent meaningful measurements of the induced birefringence. On the contrary, thermal deformation is an advantage whenever magnetic deformation is hindered by slow permeation. Provided the thermal ellipticity is much larger than the induced deformation, one can view magnetic birefringence primarily as a result of the orienting action of the field on preexistent ellipsoids. The additional deformation by the magnetic field is then negligible and there is no need to wait for the end of permeation before measuring the magnetic birefringence.

Of course, the thermal fluctuations have to be fully developed at the time of measurement. In order to get an idea of how fast they form and decay, we consider the relaxation of ellipticity under its own force. The pressure produced by an ellipsoidal deformation is

$$\Delta p = \frac{\mathrm{d}E_{\mathrm{c}}}{\mathrm{d}s_2} \Big/ \frac{\mathrm{d}V}{\mathrm{d}s_2} = \frac{2\,k_{\mathrm{c}}\,(6 - r_0\,c_0)}{r_0^{\,3}}\,. \qquad (60)$$

This is just the critical pressure Δp_{c} and independent of s_2. With $k_{\mathrm{c}} = 5 \cdot 10^{-13}$ erg and $c_0 = 0$ one has

$$\Delta p_{\mathrm{c}} = \begin{cases} 6 \cdot 10^3 \text{ dyn cm}^{-2} \text{ for } r_0 = 10^{-5} \text{ cm} \\ 0.2 \text{ dyn cm}^{-2} \text{ for } r_0 = 3 \cdot 10^{-4} \text{ cm}\,. \end{cases} \qquad (61)$$

The speed of permeation may be expressed by the time derivative of the vesicle volume,

$$\mathrm{d}V/\mathrm{d}t = (P\,M/\varrho\,\alpha)\,\Delta p\,4\,\pi\,r_0^{\,2}\,. \qquad (62)$$

Here P is the permeability, M the molecular weight and ϱ the density of the permeating substance. The ratio α is at room temperature $2.24 \cdot 10^{10}$ dyn cm^{-2} per mole cm^{-3}.

A useful quantity is

$$\frac{\mathrm{d}V}{\mathrm{d}t} \Big/ \frac{4\,\pi}{3}\,r_0^{\,3} = 6\,\frac{P\,M}{\varrho\,\alpha}\,\frac{k_{\mathrm{c}}\,(6 - r_0\,c_0)}{r_0^{\,4}}\,. \qquad (63)$$

The material constants of water are $M = 18$ g mole^{-1} and $\varrho = 1$ g cm^{-3}, the permeability [9] was measured to be 10^{-4} cm sec^{-1} for artificial bilayers and 10^{-3} cm sec^{-1} for red blood cells. With these values, in particular $P = 10^{-4}$ cm sec^{-1}, one computes for the inverse of the right-hand side of (63)

$$\begin{aligned} &5 \cdot 10^4 \text{ sec for } r_0 = 10^{-5} \text{ cm}\,, \\ &5 \cdot 10^{10} \text{ sec for } r_0 = 3 \cdot 10^{-4} \text{ cm}\,. \end{aligned} \qquad (64)$$

These times multiplied by $\langle s_2^{\,2} \rangle / r_0^{\,2}$ should be characteristic of the build-up and decay of thermal shape fluctuations. With $\langle s_2^{\,2} \rangle / r_0^{\,2} \approx 10^{-3}$, the earlier estimate, the relaxation is fairly fast for $r_0 = 10^{-5}$ cm, but unacceptably slow for $r = 3 \cdot 10^{-4}$ cm. However, the very slow permeation of dissolved ions [9] may prevent the establishment of equilibrium in either case.

B. Deformation by pressure

Experimental studies of the deformation caused by pressure differences $\Delta p > 0$ appear to be difficult because of the expected smallness of the critical pressure, as illustrated by (61). For large vesicles such as red blood cells, the theoretical critical pressure is so small that under osmosis the vesicle volume should be simply determined by the relation

$$V \Big/ \frac{4\,\pi}{3}\,r_0^{\,3} = c_{\mathrm{i}}/c_{\mathrm{a}}\,. \qquad (65)$$

Here c_{i} and c_{a} are the initial and actual concentrations of a single nonpermeating solute and it is assumed that from the start the concentration is the same inside and outside the vesicle. The vesicle shape is controlled by curvature elasticity, together with the auxiliary conditions of fixed surface area and volume. Practical experience [9] and estimates like those above indicate that even with red blood cells the permeation of water takes no more than a few minutes under the force of osmosis.

The critical pressure of small vesicles, $r_0 \lesssim 10^{-5}$ cm, is of a more accessible order. However, since the decrease of the vesicle volume by the permeation of water increases the internal solute concentration, Δp is diminished and the deformation stopped befor reaching the shape to be expected with a constant Δp. A sufficiently sensitive method of detection may still reveal the threshold pressure of deformation. Both the intensity and spectrum of scattered light could show the onset of the deformation. Another possibility would be to measure the magnetic birefringence of a vesicle solution. An ellipticity caused by pressure should manifest itself by a dramatic increase of the birefringence.

V. Concluding Remarks

Our discussion of bilayer elasticity and vesicle shapes leaves many open questions, some of which can be answered only by experiment. Of particular interest is the strength of the thermal fluctuations. Where they are very pronounced, curvature elasticity becomes ineffective in controlling the shape of vesicles. The fact that visible vesicles, *e. g.* biconcave-discoid red blood cells, seem to have a constant shape is evidence to the contrary. However, the elastic stiffness of vesicles may vary over a wide range and can be influenced by chemical means, notably through c_0. Another interesting problem is the role of the elastic properties in vesicle fusion and fission. Although in biological systems these processes are probably catalyzed by proteins, it is conceivable that certain elastic conditions must be met to make them possible.

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