INTERACTION BETWEEN BENDING AND TENSION FORCES IN BILAYER MEMBRANES

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ABSTRACT A theoretical analysis is presented of the bending mechanics of a membrane consisting of two tightly-coupled leaflets, each of which shears and bends readily but strongly resists area changes. Structures of this type have been proposed to model biological membranes such as red blood cell membrane. It is shown that when such a membrane is bent, anisotropic components of resultant membrane tension (shear stresses) are induced, even when the tension in each leaflet is isotropic. The induced shear stresses increase as the square of the membrane curvature, and become significant for moderate curvatures (when the radius of curvature is much larger than the distance between the leaflets). This effect has implications for the analysis of shape and deformation of freely suspended and flowing red blood cells.

INTRODUCTION

The mechanical properties of red blood cell membrane have been extensively studied. Three modes of elastic deformation may be distinguished, and elastic moduli for each have been determined (see Hochmuth and Waugh, 1987). The membrane strongly resists area changes (dilation) resulting from isotropic tension, with a modulus of 450 dyn/cm, and so it deforms at constant area. In-plane shear deformations encounter a much lower elastic resistance, with a modulus of $\sim 6 \times 10^{-3}$ dyn/cm, and the membrane bends easily, with a modulus of 1.8×10^{-12} dyn cm. Based on this information, theoretical analyses have been made of red cell deformation under a variety of conditions (e.g., Zarda et al., 1977; Evans, 1980; Secomb, 1987). Such analyses require constitutive relations giving membrane stresses as functions of strain. However, the constitutive relations are not uniquely determined by the elastic moduli and other experimental data, and can be deduced only with some additional assumptions about the membrane behavior.

Evans and Skalak (1980) provided a rational approach to the development of constitutive relations for multilayer membranes. In their approach, the membrane is considered to be composed of a number of leaflets with fixed spacings between leaflets. Membrane resistance to in-plane deformations resides in the individual leaflets, but the leaflets are considered to have negligible bending resistance, and the membrane-bending resistance is determined by the composite structure.

In previous models of biological membrane mechanics, it has often been implicitly assumed that the in-plane stresses (components of tension) are independent of membrane bending. For many types of thin shells, this is an excellent approximation. However, we show here that when the Evans and Skalak (1980) approach is applied to bilayer membranes such as the red cell membrane, a significant effect of bending on the components of membrane tension is predicted. For example, if a red cell membrane subjected to isotropic tension is bent, according to this theory it will elongate in the direction of curvature.

Recently, Waugh and Hochmuth (1987) analyzed the mechanics of single- and double-layer liquid membrane cylinders. They showed that such a cylinder can support significant axial loads, due to generation of anisotropic resultants of membrane tension in the curved membrane. This is a particular case of the effect mentioned in the previous paragraph. Here, we analyze the effect for a more general class of membrane deformations.

ANALYSIS OF MEMBRANE BENDING

To analyze membrane bending, we consider the configuration shown in Fig. 1. Two leaflets are spaced a uniform distance h apart. We suppose for simplicity that the principal axes of bending and in-plane stretch coincide with each other and with the x and y directions. (This can always be satisfied in the case of axisymmetric shells, for example.) The principal components of curvature are k_x and k_y, and the stretch ratios are λ_x and λ_y. In addition, we assume that corresponding points on the two leaflets remain perpendicularly aligned during membrane bending. It is not known whether this condition is exactly satisfied for red cell membranes, although binding between lipid molecules in the two lipid layers, and/or the presence of protein molecules projecting through both layers, pro-
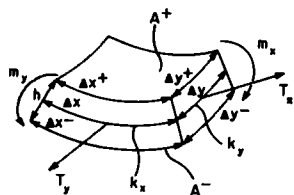
FIGURE 1 Geometry and stress resultants in a small curved membrane element. The upper leaflet has area A^+, and dimensions Δx^+ and Δy^+, and similarly for the lower leaflet. The corresponding element of the midsurface has dimensions Δx and Δy. Principal components are as follows: tension, T_x and T_y; curvature, k_x and k_y, and bending moments, m_x and m_y.

vide mechanisms by which this alignment may be preserved. If this condition is not satisfied, then "nonlocal" bending effects may occur (Evans, 1980). However, we neglect such effects in this discussion.

As already noted, the isotropic modulus of the red cell membrane is much higher than the shear modulus. Therefore, in our initial analysis we neglect the shear resistance of the two leaflets, and assume that the local tension in each leaflet is isotropic and proportional to its local dilation. Also, we assume that each leaflet has the same isotropic modulus $K/2$, where K is the isotropic modulus of the membrane. We restrict our attention to cases in which the radii of curvature, k_x^{-1} and k_y^{-1}, are much larger than h, and the fractional dilation of each leaflet is small.

We consider two small leaflet elements whose boundaries are perpendicularly aligned, as shown in Fig. 1. It is easily shown that the areas A^+ and A^- of the leaflet elements satisfy $A^+ \simeq A^-(1 - k_t h)$, neglecting terms of order $(k_t h)^2$, where k_t is the total curvature, $k_x + k_y$. Suppose that the unstressed areas of the two leaflet elements are A_0^+ and A_0^-. Then the total membrane curvature k_0: in the unstressed state satisfies $A_0^+ \simeq A_0^- (1 - k_0 h)$. The isotropic tensions in the leaflets are given by $T^+ = K(A^+/A_0^+ - 1)/2$ and $T^- = K(A^-/A_0^- - 1)/2$. Because $k_x h$, $k_y h$, and the dilations are all small, it follows that

$$T^+ - T^- \simeq -K(k_t - k_0)h/2. \qquad (1)$$

The tensions in the leaflets generate tension and bending moment resultants in the membrane. It is convenient to refer these resultants to a midsurface lying halfway between the two leaflets, with edges of lengths Δx and Δy. Note that the corresponding edges of the upper leaflet have lengths $\Delta x^+ = \Delta x(1 - k_x h/2)$ and $\Delta y^+ = \Delta y(1 - k_y h/2)$, and similarly for the lower leaflet.

First, we consider bending moments about an edge parallel to the y axis. If m_x is the resultant bending moment per unit length, then

$$m_x \Delta y = (h/2)(T^+ \Delta y^+ - T^- \Delta y^-), \qquad (2)$$

and so

$$m_x \simeq -B(k_t - k_0), \text{ where } B = Kh^2/4. \qquad (3)$$

In this derivation we neglect terms of the form $h^2/4 \; k_y$ $T^+ = Bk_y(A^+/A_0^+ - 1)/2$ because the membrane dilation is assumed small. Similarly,

$$m_y \simeq -B(k_t - k_0). \qquad (4)$$

Therefore, the bending moments are isotropic and proportional to the change in total curvature. This result was given in a more general form by Evans and Skalak (1980, p. 109).

Second, we consider the tensions acting on an edge parallel to the y-axis. It is convenient to define the total mean tension $T_m = T^+ + T^-$ and tension resultants in the x and y directions T_x and T_y. Then, for equilibrium

$$T_x \Delta y = T^+ \Delta y^+ + T^- \Delta y^-, \qquad (5)$$

and so

$$T_x = T^+ + T^- - (k_y h/2)(T^+ - T^-)$$
$$= T_m + Bk_y(k_t - k_0). \qquad (6)$$

Similarly,

$$T_y = T_m + Bk_x(k_t - k_0), \qquad (7)$$

and

$$T_x - T_y = -B(k_x - k_y)(k_t - k_0). \qquad (8)$$

Even though the tensions in each individual leaflet are isotropic, the resultant tension in the membrane is anisotropic, because the leaflet tensions act over slightly different lengths.

These results may be generalized for membrane leaflets of finite thickness. Here, the analysis is summarized for the case of a single anisotropic liquid shell with zero in-plane shear rigidity, as considered by Waugh and Hochmuth (1987). We introduce a coordinate z measured perpendicular to the midsurface, and express surface isotropic stress σ as a function of z. Also, for a given small membrane element, the quantities Δx, Δy, A and A_0 already defined now become functions of z. In the approximation introduced above, neglecting terms of order $(k_t h)^2$, all these functions are easily seen to be linear in z. The right-hand sides of Eqs. 2 and 5 are replaced by integrals over the membrane thickness. Eqs. 4 and 8 are again obtained, but the bending resistance is found to be $Kh^2/12$. For a cylindrical membrane, Eq. 31 of Waugh and Hochmuth (1987) follows as a special case.

The further generalization to a membrane with shear resistance is easily made. If the shear modulus is much smaller than the isotropic modulus, bending generates negligible shear stresses in each leaflet, and the bending moments are independent of membrane shear strain. However, Eq. 5 has to be modified to include the effects of shear resistance. From Evans and Skalak (1980, pp. 76–77), additional terms T_x^s and T_y^s should be included in the principle components of tension, where $T_x^s = (\kappa/2) - $

$\lambda_x^2 - \lambda_y^2 = -T_y^*$ and κ is the shear modulus. According to our assumptions, the principal axes of shear coincide with those of bending-induced tension. The shear resistance may be distributed arbitrarily between the leaflets without affecting the results, because changing the distribution results in negligible changes to bending moment resultants. The large isotropic modulus ensures that $\lambda_x\lambda_y \simeq 1$. Eq. 5 then yields $T_x = T_m - Bk_x(k_t - k_0) + (\kappa/2)(\lambda_x^2 - \lambda_x^{-2})$. Similarly,

$$T_y = T_m - Bk_y(k_t - k_0) - (\kappa/2)(\lambda_x^2 - \lambda_x^{-2})$$

and

$$T_x - T_y = -B(k_x - k_y)(k_t - k_0) + \kappa(\lambda_x^2 - \lambda_x^{-2}). \quad (9)$$

EQUATIONS OF MEMBRANE EQUILIBRIUM

Several theoretical analyses of the shape and deformation of axisymmetric red blood cells have used variational methods, in which the cell configuration is sought which minimizes the elastic energy of membrane deformation (Deuling and Helfrich, 1976; Zarda et al., 1977; Evans, 1980). This approach does not involve the membrane stresses explicitly, and of the three analyses referenced, only that of Zarda et al. (1977) gives expressions for the membrane stresses. However, this analysis uses a different constitutive relation for membrane bending which does not lead to an interaction between bending and tension forces as described earlier. Deuling and Helfrich (1976) and Evans (1980) used essentially the same constitutive assumptions as here.

An alternative approach was developed by Secomb et al. (1986) and Secomb (1987), in which the equations of membrane equilibrium are solved directly. For axisymmetric shells, the equations for equilibrium of normal stress, tangential stress, and bending moments in the membrane are given by Timoshenko (1940):

$$\frac{1}{r}\frac{d(rq_s)}{ds} = \Delta p + k_s t_s + k_\phi t_\phi \quad (10)$$

$$\frac{1}{r}\frac{d(rt_s)}{ds} = t_\phi \frac{\cos\theta}{r} - k_s q_s - \tau \quad (11)$$

$$\frac{1}{r}\frac{d(rm_s)}{ds} = m_\phi \frac{\cos\theta}{r} + q_s, \quad (12)$$

where arc length s, measured along the membrane in a plane containing the axis, is the independent variable and the dependent variables are $r(s)$, distance of a point in the membrane from the axis; $\theta(s)$, angle between the normal to the membrane and the axis; $k_s(s)$ and $k_\phi(s)$, membrane curvatures, taken as positive for convex surfaces; $m_s(s)$ and $m_\phi(s)$, bending moments; $t_s(s)$ and $t_\phi(s)$, components of membrane tension; and $q_s(s)$, shear force per unit length. The subscript s denotes components in a plane containing the axis, whereas ϕ denotes azimuthal components. The loading on the cell consists of hydrostatic pressure differ-

ence $\Delta p(s)$ between external and internal fluids and applied shear stress $\tau(s)$.

The preceding section shows that appropriate constitutive relations are

$$m_s = m_\phi = B(k_t - k_0), \text{ where } k_t = k_s + k_\phi \quad (13)$$

and

$$t_s - t_\phi = \kappa(\lambda_x^2 - \lambda_x^{-2}) - B(k_s - k_\phi)(k_t - k_0). \quad (14)$$

Secomb et al. (1986) and Secomb (1987) used Eq. 13 but omitted the second term in Eq. 14, following Evans and Skalak (1980, pp. 76–77). The consequences of this omission are discussed below. When the second term is included, it is possible to verify rigorously the equivalence of the variational approach with the approach based on the equations of equilibrium. For instance, the equations derived by Deuling and Helfrich (1976) using the variational approach, assuming $\tau = 0$, $\kappa = 0$, and Δp is a constant, can be shown to be equivalent to Eqs. 10–14 with $q_s = r(1 - r^2 k_\phi^2)^{-1/2}\{[B(k_\phi - k_0)^2 - Bk_s^2 + 2C]k_\phi + \Delta p\}/2$ and $t_s = C + B[(k_\phi - k_0)^2 - K_s^2]/2$, where C is a constant. Anisotropic membrane tension is therefore implicit in the Deuling and Helfrich (1976) treatment.

DISCUSSION

To estimate the magnitude of the bending-tension interaction, we consider the effect of bending in the hypothetical case of a membrane with shear resistance, subject to isotropic tension. We assume that the membrane is unstressed when flat ($k_0 = 0$) and curved in the x direction only ($k_y = 0$). Then from Eq. 9,

$$0 = t_x - t_y = \kappa(\lambda_x^2 - \lambda_x^{-2}) - Bk_{x^2}$$

i.e.

$$\lambda_x^2 - \lambda_x^{-2} = Bk_{x^2}/\kappa. \quad (15)$$

The membrane will therefore elongate in the direction of curvature. Taking values for the shear and bending moduli appropriate for red blood cell membrane, we predict that a radius of curvature $k_x^{-1} = 1$ μm will result in a 0.75% extension ($\lambda_x = 1.0075$). The extension increases quite rapidly for smaller radii of curvature, and $\lambda_x = 2$ when the radius of curvature is 0.09 μm. This radius of curvature is much larger than the membrane thickness, which is of the order of 0.005 μm. For membranes with smaller shear moduli, the effect will become significant at even larger radii of curvature.

The calculations of Secomb et al. (1986) and Secomb (1987) neglected the bending-tension interaction. According to the above analysis, the effects of this omission will only become significant when the radius of membrane curvature is much less than 1 μm. Such high curvatures are predicted at the trailing edge of cells in capillaries with diameters 5 μm or less, and the previously predicted cell

shapes and apparent viscosities for these cases are currently being reexamined.

In summary, if the red cell membrane is modeled by two tightly coupled leaflets with large isotropic moduli, then moderate membrane bending is predicted to induce nonisotropic contributions to membrane tension. This effect is significant in red cell membranes because the isotropic modulus is much higher than shear modulus. It is analogous but not equivalent to the "trapezoidal edge" effect discussed by Calladine (1983, pp. 34–35). Although this effect has only recently been recognized, it is implicit in previous variational analyses of red cell shape.

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