**DIFFERENCE VERSUS GAUSSIAN CURVATURE ENERGIES;
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APPLICATIONS TO VESICLE STABILITY**

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DIFFERENCE VERSUS GAUSSIAN CURVATURE ENERGIES; MONOLAYER VERSUS BILAYER CURVATURE ENERGIES APPLICATIONS TO VESICLE STABILITY

HÅKAN WENNERSTRÖM* AND DAVID M. ANDERSON*†

Abstract. The recent discovery that the electrostatic contribution to the curvature free energy G_c of a membrane has, exactly to second order in the principle curvatures c_2 and c_1 , the form $G_c^E = b^E \iint (c_2 - c_1)^2 dA$ [B. Duplantier, *Physica A*, 168, 179–197, eqn. 39] is found to be symptomatic of the group theoretic properties of $G_c(c_1, c_2)$. These properties, together with the need to re-instate stability criteria into a positive-definite expression for G_c and to single out monolayer mean curvature energy as the predominant contribution – rather than writing it as the difference between mean and Gaussian terms of comparable magnitude – all attest that the curvature free energy is most appropriately derived by expanding the free energy density g_c directly in the principal curvatures c_1, c_2 , rather than in the mean and Gaussian curvatures H, K . Using symmetry-adapted expansion coordinates we find to second order $g_c = aH^2 + b\Delta c^2$ (where $2H = c_1 + c_2$; $2\Delta c = c_2 - c_1$) for a system of ground state $D_\infty(D_{\infty h})$ symmetry, i.e. a symmetric bilayer, where the curvatures c_1 and c_2 are measured on the bilayer midsurface. For a system of C_∞ (or $C_{\infty h}$) symmetry, we find $g_c = a(H - c_0)^2 + b\Delta c^2$; this expression applies to both the asymmetric bilayer, in which c_1 and c_2 are measured on the bilayer midsurface, and to the more general case of a (paired or unpaired) surfactant monolayer, where they are registered at the polar-apolar interface. The last formalism most directly incorporates experimental observables.

With this expression, $b \ll a$ inherently, making it clear that not two but **one** rigidity constant is needed to interpret phase progressions which are driven by mean curvature. Indeed, recent work on bicontinuous L_3 phases and on progressions between cubic phases of different symmetries extends the time-tested notion that patterns in phase behavior over ranges of solvents, surfactants, etc. can be simply and quantitatively modeled with one mean curvature energy term. As a further demonstration of the transparency of this approach, using this expansion $g_c(H, \Delta c)$, the value of b is independent of c_0 and non-negative – e.g., it does not change sign as c_0 or H_0 vary – and should be more easily measurable than is a rigidity “constant” which is expected to change (even its sign) with composition and temperature. Furthermore, c_0 ($\neq H_0$ in general) represents the optimal mean curvature in an unconstrained system; this is not the case with the H, K expansion, which is thus once again seen to be distanced from the experimental intuition and interpretation. The expansion of g_c in terms of H and Δc also clearly reveals the presence of two types of bending fluctuation modes.

These expressions are then used to discuss the thermodynamic stability of spherical vesicles from a curvature energy point of view. The expansions to second, and even to fourth, order are greatly simplified compared to the H, K formalism because the “difference curvature” is rigorously zero and cross terms do not enter. It is derived that single-component vesicles can only be stable with a rather special combination of elastic constants and the phenomenon should be observed only rarely. With two or more components in the vesicle there is an extra degree of freedom involving a composition difference between the center and inner monolayers, which makes vesicle stability a much more likely event.

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Introduction. In order to evaluate the curvature free energy of a membrane, we must begin by constructing a mathematical surface and ascribing to it a certain symmetry, which reflects the local symmetry of the membrane. If the membrane is an unpaired monolayer, then this surface is most appropriately drawn at the locus of the bonds linking the polar and apolar portions of the amphiphilic molecules, and there is then an obvious asymmetry with respect to the two sides of the surface. If the membrane is a bilayer, then there are two choices. The bilayer can be viewed as two paired monolayers, and two surfaces drawn, each as in the unpaired monolayer case. Alternatively, the surface can be taken to be the midsurface of the bilayer, which essentially corresponds to the terminal methyl groups on the hydrophobic tails. If the bilayer is inherently symmetric with respect to its two monolayers, then this surface should be described as symmetric with respect to its two sides. This is commonly the case for model bilayers. However, in biological systems, such as cell membranes, additional components such as proteins, glycolipids, and macromolecules effect a natural asymmetry with respect to the two sides of the bilayer, and thus of the mathematical surface.

Given this surface and its ascribed local symmetry, the curvature free energy density is usually expressed¹ in terms of the mean curvature²

$$(1) \quad H = 1/2(c_1 + c_2)$$

and the Gaussian curvature

$$(2) \quad K = c_1 c_2$$

where c_1 and c_2 are the two principal curvatures. For a system of inherent $D_\infty(D_{\infty H})$ symmetry, i.e., in-plane rotational symmetry characteristic of a two-dimensional fluid state and two-fold rotational axis in the membrane plane, as in a symmetric bilayer, the curvature free energy density g_c is written as^{1,3}

$$(3) \quad g_c = \kappa H^2 + \bar{\kappa} K$$

where κ is called the bending rigidity and $\bar{\kappa}$ the saddle splay constant. The total curvature free energy G_c is obtained by integrating g_c over the surface

$$(4) \quad G_c = \int_A g_c dA = \kappa \int_A H^2 dA + \bar{\kappa} \int_A K dA$$

The expression (3) contains all the curvature terms to second order in the given symmetry. However, the choice of H and K as coordinates for characterizing the curvature properties is not unique and other linear combinations of terms second order in c_1 and c_2 could also be used. The rationale for choosing H and K is, to our knowledge, two-fold: i) it confirms

with the elastic free energy expression used for nematic liquid crystals; and ii) it has the virtue of explicitly separating out a Gaussian curvature term, which in the integral of eq. (4) has a remarkably simple property due to the Gauss-Bonnet theorem⁴

$$(5) \quad \int_A K dA = 2\pi\chi_E$$

where χ_E is the Euler characteristic, which only depends on the topology of the surface (we have left out the boundary term for simplicity).

For membranes where there is no perpendicular twofold symmetry axis, like a surfactant monolayer or an asymmetric bilayer, the local symmetry is C_∞ (or $C_{\infty h}$). Due to the lower symmetry an additional parameter is needed in the free energy density expression and conventionally

$$(6) \quad g_c = \kappa(H - H_0)^2 + \bar{\kappa}K$$

where H_0 is called the spontaneous mean curvature.

The description of curvature energies in terms of eqs. (3) and (6) has a long tradition in biological membrane works, particularly for the red blood cell problem⁵. It has also been applied extensively to model membrane problems, particularly by Helfrich and coworkers⁶⁻⁸. In these treatments, the surface on which the curvatures is measured, and over which the area integration is performed, is the midsurface of the bilayer. More recently the same concepts have been used in the description of microemulsions⁹, where the amphiphile is in the form of an unpaired monolayer and the appropriate surface is drawn within the monolayer.

There is also an independent tradition of using basically similar notions in rationalizing the rich phase behaviour of surfactant systems. The basic work in this respect goes back on one hand to Tartar¹⁰, Tanford¹¹ and Israelachvili and coworkers¹²⁻¹⁴, who have stressed the molecular shape and the packing constraints imposed by it. On the other hand Winsor¹⁵ introduced so called R values describing the preferred average radius of an aggregate. Using this concept he was able to rationalize the phase behavior by assuming regular changes in the R -value. In both approaches the focus is on the surfactant monolayer as the natural unit rather than a bilayer.

That monolayer mean curvature, whether expressed in terms of an R -value or v/a_0L_0 or H measured at the polar-apolar interface, is dominant over other curvature energy terms designed to include curvature inhomogeneities is made clear not only by decades of surfactant phase behavior study, but also under more general conditions by more recent experimental and theoretical work. Phase behavior work by Tiddy and coworkers¹⁶, as well as by Auvray et al.¹⁷ has shown that the same patterns of phase behavior seen with water are observed over a wide variety of non-aqueous polar solvents, including aprotic, non-hydrogen bonding solvents such as N -methylsydnone. The phase behavior of bicontinuous

microstructures such as the L_3 phase¹⁸ and bicontinuous cubic phases¹⁹ has been shown to be readily interpreted in terms of monolayer mean curvature. The latter work shows that simple mean curvature arguments can yield quantitative predictions of phase behavior and structural details, including progressions between cubic phases of different microstructure, without the need for Gaussian curvature terms. A cursory examination of phase behavior is enough to reveal that Gaussian curvature is not behaving even remotely monotonic in these systems: the Gaussian curvature in the familiar lamellar to cubic to hexagonal phase progression passes from zero to negative to zero, for example.

In our opinion there is much to be gained by trying to unify the more chemically-oriented approaches with the curvature free energy approach. They rely on basically the same physical effects and one can take advantage of the particular strengths of each of the different approaches. This is one of the main aims of the present paper. We start by examining alternative second order expressions for g_c , which leads to the introduction of a “difference curvature” term. Then we show how the curvature energy of a bilayer is expressed in terms of the monolayer constants. Then we discuss the experience gained from the surfactant systems to obtain qualitative estimates of the elastic constants and to support the notion that curvature energies are from a physical point of view best associated with the polar-apolar interface. The paper is concluded by an investigation of the thermodynamical stability of vesicles demonstrating the usefulness of the conceptual framework developed earlier in the paper.

Curvature Free Energy. The Difference Curvature. Let us derive the curvature free energy in a way slightly different from the usual one based on bulk continuum mechanics concepts. Assume that the total curvature free energy is given as in eq. (4) by an integral of curvature free energy density $g_c(c_1, c_2)$ being a unique function of local principal curvatures. In such an expansion it is convenient to choose symmetry adapted curvature coordinates, and only energy terms that transform as the totally symmetric representation of the particular symmetry group (D_∞ or $D_{\infty h}$) are non-zero. These coordinates are the mean curvature H , and the difference curvature

$$(7) \quad \Delta c = \frac{1}{2}(c_2 - c_1); \quad \Delta c^2 = H^2 - K$$

In $D_\infty(D_{\infty h})$ symmetry, H transform as the σ_- and Δc as the δ irreducible representation and

$$(8) \quad g_c(c_1, c_2) = aH^2 + b\Delta c^2$$

to second order. Both first derivatives and the second order cross term vanish by symmetry. The elastic constants a and b are related to the bending rigidity and the saddle splay constant through

$$(9a,b) \quad \kappa = (a + b)/2; \quad \bar{\kappa} = -b$$

which is obtained by identifying eqs. (3) and (8). Note the mathematically trivial but conceptually nontrivial result that the coefficients κ and a for the mean curvature term are different. κ measures the resistance to bending along one axes leaving the other direction flat, a locally cylindrical deformation, while a measures the resistance to bending which is symmetrical in both directions, i.e., a locally spherical deformation.

In the lower symmetry, C_∞ , H transforms as the totally symmetric representation and the first derivative dg_c/dH is non-zero. It is then natural to expand g_c around a point $\{H = c_0, \Delta c = 0\}$ where the first derivatives are zero. Then, to second order for example

$$(10) \quad g_c = a(H - c_0)^2 + b\Delta c^2$$

analogously to eq. (6). The relation between a and b on one hand and κ and $\bar{\kappa}$ on the other is formally the same as in eq. (9a,b). However, while a and b are obtained as second order derivatives of g_c around a specified point the coefficients in eq. (6) are phenomenological and thus more difficult to relate to a molecular theory of the same system. The preferred mean curvature c_0 is related to the spontaneous curvature through

$$(11) \quad H_0 = c_0 a / (a + b)$$

It is our impression that it is a common misconception to take H_0 as the optimal mean curvature of a topologically unconstrained system. For example, an unconstrained membrane system with $a, b > 0$ would optimally form spheres of radius $|1/c_0|$ rather than $|1/H_0|$. The treatment of ref. 18, as well as other theories which do not include Gaussian curvature terms and focus on the mean curvature, can be viewed in the present context as the expression (10) in which one takes $b \ll a$. Thus in cases where the mean curvature is taken to be the primary effect, the expansion (10) provides the framework to reduce the number of terms from two to one, whereas this cannot be done with expansion (4).

The authors take it as self-evident that there are clear advantages to formulating the curvature free energy expansion in such a way that all terms are non-negative and minimized at $H = c_0, \Delta c = 0$.

Recently Duplantier²⁰ has derived an exact solution of the electrostatic contribution to the curvature free energy expansion (taking the thickness of the bilayer to be negligible). The intent of that work was to write the solution in terms of the conventional H, K expansion. However, in eq. 39 of that paper it shown that the most succinct way to write the result – viz., *with one term instead of two* – is as a **difference** curvature energy. This result holds for his cases a) and b), the conducting membrane and the transparent insulating membrane, resp. For case c), the opaque insulating membrane, the result can be written as the sum of an H^2 term and a difference curvature energy, conforming to our eq. (8).

It is our conclusion that many calculations and discussions using curvature free energy concepts, particularly including the effects of fluctuations, would become more lucid if they were based on the expansion eqs. (8) and (10) rather than on eqs. (3) and (6). The

confusion caused by writing H_0 instead of c_0 provides one example, but probably the most important aspect of eqs. (8) and (10) is that they clearly display the presence of two different types of curvature fluctuation modes; those involving H and those involving Δc . The latter, softer modes have received very little explicit attention in previous work. Implicitly they are responsible for the Talmon-Prager entropy of a bicontinuous microstructure. The simplifications offered by eqs. (8) and (10) are also apparent when one is considering spherical aggregates like microemulsion droplets or vesicles. In that case $\Delta c = 0$ and the inclusion of the second term in eq. (10) is trivial. One case when eq. (3) may be preferred is when there is a physical constraint only allowing variations preserving the topology of the surface, as, for example, in the classical problem of the shape of erythrocytes. In such a case the Gaussian curvature term is a constant when integrated over the surface as shown in eq. (5).

Monolayer Versus Bilayer Curvature Energies. In biological and model membranes as well as in many surfactant systems, two amphiphile monolayers unite to form a bilayer as the local structural unit. However, this local unit can fold in different ways to give rise to various global structures, the most common being planar bilayers, vesicles, cubic bicontinuous phases and the L_3 or anomalous phase. In a recent paper¹⁸ we demonstrated how curvature concepts were very useful for rationalizing the peculiar properties of this latter phase. One key argument in the paper was that the curvature energies are best described in terms of those of the constituent monolayers. The same approach was used in a treatment of curvature free energies in inverted hexagonal phases²¹ and in bicontinuous cubic phases^{19,22}. The physical assumption being, amply supported by the experience gained from surfactant systems in general, that the curvature energies are best associated with the polay-apolar interface.

The surfactant/water inverted hexagonal phase provides one example where the monolayer curvature approach is clearly advantageous. Difficulties arise if the structure is viewed in terms of bilayers, as is commonly done in the closely related lamellar and bicontinuous cubic phases. In the inverted hexagonal phase the midsurface of the bilayer is an **unorientable** surface, a honeycomb arrangement of flat strips which intersect at 120° angles. Mean curvature singularities make approaches using eqn. (3) intractable. On the other hand, the polar-apolar interface of each monolayer is simply a circular (approximately) cylinder, and its mean curvature is uniform and, as is well-known, intermediate between that of the inverted cubic and the inverted micellar solution.

Figure 1 shows a cross section of a bilayer with a midsurface, or “base” surface, at the center and two displaced surfaces assumed to represent the polay-apolar interface. Below we will assume, for simplicity, that the displaced surfaces are parallel to the base surface at a distance L . The argument could equally well be pursued for displaced surfaces of constant mean curvature^{18,22}. For bilayers curving only moderately ($|H| \ll 1/L$) the difference between the two cases is small, while for highly curved cases the distinction becomes important.

Figure 1. Schematic cross section of a bilayer with a midsurface, or “base” surface, at the center and two displaced surfaces assumed to represent the polar-apolar interface. Each point on the displaced surface is at a fixed distance along the normal to a point on the base surface. (Reprinted from ref. 18).

The mean curvatures H_1 and H_2 at the displaced surfaces are related to the mean H_b and Gaussian K_b curvatures of the base surface through

$$(12a,b) \quad H_1 = (-H_b + LK_b)/N_1; \quad H_2 = (H_b + LK_b)/N_2;$$

$$(12c) \quad N_{1,2} = 1 \mp 2H_bL + K_bL^2$$

where it is essential to have a consistent sign convention; the positive normal to the base surface pointing towards displaced surface 2. For the difference curvature we only consider the highest order term so that

$$(13a,b) \quad \Delta c_1 = -\Delta c_b; \quad \Delta c_2 = \Delta c_b$$

Using the expansion eq. (10) and allowing the two monolayers to be different we find for a bilayer

$$(14) \quad g_c = a_1 N_1 [(-H_b + LK_b)/N_1 - c_{01}]^2 + a_2 N_2 [(H_b + LK_b)/N_2 - c_{02}]^2 + (b_1 + b_2)(H_b^2 - K_b)$$

The extra factors N_1 and N_2 in the first two terms take into account the change in area going from the displaced surface to the base surface

$$(15) \quad dA_i = N_i dA_b$$

In the difference curvature term this higher order correction is neglected. Expanding eq. (14) including terms up to second order in the curvatures yields

$$(16) \quad \begin{aligned} g_c = & (a_1 + a_2 + b_1 + b_2 + 2a_1 L^2 c_{01}^2 + 2a_2 L^2 c_{02}^2)(H_b - H_{b0})^2 \\ & - (b_1 + b_2 + 2a_1 c_{01} L + 2a_2 c_{02} L + a_1 c_{01}^2 L^2 + a_2 c_{02}^2 L^2)K_b + a_1 c_{01}^2 + a_2 c_{02}^2 \\ & - (c_{01} a_1 - c_{02} a_2 + c_{10}^2 L a_1 - c_{20}^2 L a_2)H_{b0} + \text{higher order terms} \end{aligned}$$

where the spontaneous **bilayer** mean curvature is

$$(17) \quad H_{0b} = \frac{c_{01} a_1 - c_{02} a_2 + c_{10}^2 L a_1 - c_{20}^2 L a_2}{a_1 + a_2 + b_1 + b_2 + 2a_1 L^2 c_{01}^2 + 2a_2 L^2 c_{02}^2}$$

The spontaneous bilayer mean curvature can thus be nonzero if there is a difference in the two bending constants a_1 and a_2 , or the two spontaneous monolayer mean curvatures, or both. For example, in certain cell membranes there are, e.g., proteins or macromolecules which are incorporated preferentially into one side of the bilayer, making the local symmetry C_∞ rather than D_∞ . An example of this which is particularly pertinent with respect to our discussions of liquid crystals is the prolamellar body (PLB) of certain plant plastids, which are bicontinuous cubic phases in which the “inside”, continuous with the cell cytoplasm, and “outside”, continuous with the exterior of the cell, are not equivalent. Thus there is a nonzero mean curvature to the midsurface of the bilayer, in contrast to binary amphiphile/water cubic phases in which this bilayer mean curvature H_{0b} is zero by symmetry²⁵.

For a symmetric bilayer ($a_1 = a_2 = a$; $b_1 = b_2 = b$; $c_{01} = c_{02} = c_0$) eq. (16) simplifies to (to second order)

$$(18) \quad \begin{aligned} g_c = & 2(a + b + 2aL^2 c_0^2)H_b^2 - 2(b + 2ac_0 L + ac_0^2 L^2)K_b + 2ac_0^2 \\ = & 2a(1 - Lc_0)^2 H_b^2 + 2(b + 2ac_0 L + ac_0^2 L^2)\Delta c_b^2 + 2ac_0^2 \end{aligned}$$

Thus by imposing the bilayer symmetry we regain the form of eqs. (3) and (8) with explicit expressions for the coefficients in terms of those of the constituent monolayer. The bending rigidity κ is found to be slightly larger than the sum over the two monolayer rigidities while the symmetric bending constant

$$(19) \quad a_b = 2a(1 - Lc_0)^2$$

can be either larger or smaller than the sum over the individual layers depending on the sign of c_0 . For the bilayer to be stable relative to other structures $|Lc_0| < 1$ so that a_b cannot reach very low values. Even more significant is that the saddle splay constant

$$(20) \quad \bar{\kappa}_b = -b_b = -2(b + 2ac_0L + ac_0^2L^2)$$

can actually change sign if $a \gg b > 0$ which we will argue in the following section is typically the case. Then when $c_0 < 0$, $\bar{\kappa}_b$ can be positive and b_b consequently negative. This change of sign of $\bar{\kappa}_b$ for negative values of c_0 is viewed in the H_b , K_b approach as the source of the formation of the L_3 phase. Under such circumstances the bilayer prefers to form highly connected structures to achieve a slight curvature towards the solvent¹⁸.

The fact that the conventional saddle splay constant $\bar{\kappa}_b$ depends on the spontaneous monolayer mean curvature c_0 , means that this “constant” is considerably more elusive than is suggested by the simple expression (3). This would plague the interpretation of experiments designed to measure $\bar{\kappa}_b$, and in fact one should expect $\bar{\kappa}_b$ to vary strongly when intensive parameters are changing. Since the whole point of introducing curvatures and associated constants is to attempt to interpret and extrapolate experimental results, the strongly varying nature of $\bar{\kappa}_b$ would seem to limit its usefulness, despite one attractive feature of expression (4) from a theoretical point of view due to the Gauss-Bonnet theorem.

The exception to this would be the case in which the **bilayer** spontaneous mean curvature H_{b0} is significantly nonzero, so that the curvature of the asymmetric bilayer as a whole would dominate the picture. However, even in such a case it might prove more insightful, though computationally more involved, to use the monolayer approach with $c_{01} \neq c_{02}$. Charvolin and Sadoc²³ have shown elegantly that in the case of binary surfactant/water bicontinuous cubic phases, the symmetry of the bilayer leads to zero **bilayer** mean curvature, and indeed minimal surfaces provide models for the base surfaces of these structures.

Equation (12) must be recognized as occupying a central role in the discussion of curvature expressions. We argue herein that it is the mean curvature H_i over the polar-apolar interface that is physically most significant, and in the next section that therefore $b \ll a$ generally and the first term in expression (10) – with the curvatures measured at the polar-apolar interface – is dominant. On the other hand, equation (12) for H_i in terms of the base surface requires **both** the mean **and** the Gaussian curvatures of the base surface, this means that in the bilayer approach, when the bilayer thickness cannot be neglected, using equation (6) both terms are of comparable magnitude. We maintain that the expansion (10) is the unique decomposition of the energies which results in two terms one of which is inherently smaller in magnitude. Furthermore, through eq. (14) for example, c_{01} and c_{02} are emphasized explicitly rather than suppressed. Refs. 18 and 19 show two of several cases where a more profound insight into the behaviour of bilayer systems can be gained by looking at the system in terms of the constituent monolayers. In understanding the relation between molecular properties and elastic constants much can

be gained by referring to the general knowledge about surfactant systems that has been accumulated.

Surfactant Monolayer Free Energies and Curvature. During his extensive studies of surfactant phase equilibria Winsor¹⁵ found that the trends could be rationalized in terms of regular variations in the radius of the surfactant aggregate and he introduced a so scaled R -value. In the notation of this paper the Winsor R -value is simply $1/c_0$ where c_0 is the preferred mean curvature of the surfactant monolayer. Note that R is related to the preferred curvature c_0 rather than the spontaneous curvature H_0 . The usefulness of the Winsor approach shows that c_0 is one of the most basic properties of a monolayer and it determines to a large extent the geometry of the aggregates found in a particular system.

Another approach to understanding the behaviour of surfactant systems was pioneered by Tartar¹⁰, revived by Tanford¹¹, and further developed by Israelachvili and coworkers¹²⁻¹⁴. The basic idea is to relate the packing requirement to fill space with the molecular shape as characterized by volume v , length L_0 and area of polar group a_0 . The crucial dimensionless parameter is then $v/(L_0 a_0)$ and for example when $v/(L_0 a_0) = 1$ a bilayer has optimal stability which is equivalent to $c_0 = H_0 = 0$ in terms of curvature concepts. Note that the crucial area a_0 is that of the polar headgroup, which in the curvature approach translates to claiming that the curvature free energy is best associated with the polar-apolar interface. In terms of the approach to the curvature energies taken in the previous sections the dimensionless $v/(L_0 a_0)$ ratio is related to $L_0 c_0$ through

$$(21a) \quad v/(L_0 a_0) = [1 - L_0 c_0 + (L_0 c_0)^2/3]$$

using spheres and spherical shells and

$$(21b) \quad v/(L_0 a_0) = (1 - L_0 c_0)$$

for cylinders and cylindrical shells. In general the bilayer half-thickness L is close to the preferred value L_0 . In this approach there is no local curvature term that corresponds to a Gaussian or difference curvature energy, although this could in principle be introduced. There are some fundamental differences between the $v/a_0 L_0$ approach and the mean curvature approach making it difficult to compare the two unambiguously and independently of geometry; after all, $v/a_0 L_0$ is dimensionless whereas H has dimensions of inverse length, and even the two relations (21a,b) are sufficient to demonstrate the geometry dependence of the relation between $v/(L_0 a_0)$ and c_0 (or H_0).

Taking a more overall view, however, clearly in both the Winsor argument and in the packing approach, one has found it sufficient as a first approximation to only consider one parameter characterizing the monolayer. Furthermore, in both theories this one parameter is closely related to the preferred curvature c_0 . The conclusion we draw is that the elastic constants $\{\kappa, \bar{\kappa}\}$ or $\{a, b\}$ are of lesser significance for the phase behaviour. The values of

these constants become important in more free energy competitions between, for example, ternary lamellar phases and microemulsions, or between disordered L_3 phases and cubic phases, where detailed arguments involving entropy and interbilayer interactions must be given. Nevertheless experimental observations do allow some qualitative conclusions to be made concerning the signs and relative magnitudes of a and b . For a monolayer in a liquid-like state all experience shows that both a and κ are positive. This is an explicit assumption in the theories presented above, which assumes the existence of an optimal mean curvature. The fact that the one parameter theories do so well indicates that $|b|$ is much smaller than a . It is generally found that hexagonal phases, normal and reversed, occur in a regular way between micellar and lamellar liquid crystalline phases. If $|b|$ were sizable it would have the effect of stabilizing the hexagonal phases, $b \ll 0$, or suppressing them, $b \gg 0$. Thus the difference curvature term seems to give only relatively small contributions to the curvature free energy of a monolayer. Concerning the sign of b , we are not aware of any conclusive evidence, but the intrinsic stability of lamellar phases²⁴ indicates that in fact $b > 0$ for a monolayer. As shown in the previous section the story can be different for a bilayer. That $b > 0$ is also expected on theoretical grounds since it is generally, but not exclusively, the case that all other things being equal the higher the symmetry the lower the free energy in a disordered system.

Only with symmetry-breaking can b , as defined above, be negative. In that case, one has two choices. First, one can take $b < 0$ with the same defining relation, but then higher order terms must of course be taken. The second alternative is to introduce a spontaneous Δc_0 into the difference curvature energy term.

In the case where a higher-order expansion is necessary, terms may be considered which involve the **gradients** of the curvatures. In such a case the Mainardi-Codazzi relations can be used to compute the gradients of the principle curvatures c_1 and c_2 ; see reference 18 for the appropriate formulae. Interestingly, if one is predisposed to the H, K description, one finds that even in the formula for the gradient of the Gaussian curvature of a surface of constant mean curvature the factor $(c_1 - c_2)^2$ appears – once again the fundamental symmetries of the curvatures are evidencing themselves.

Just before the submission of this paper, the authors were made aware of another treatment of curvature free energies by Fogden et. al which is related to, but differs from, the present approach. For now we choose only to say that, through the analysis of microscopic models as well as with stability arguments, those authors also concluded that the traditional expansion in terms of H and K is wrought with inherent difficulties. One common insight appears to be that simple expressions in the principle curvatures, such as the difference curvature which is so intuitively clear and physically meaningful, can only be clumsily written – non-analytically, in fact – in terms of H and K : thus $\Delta c = \sqrt{(H^2 - K)}$, and $c_i = 2H \pm \sqrt{(H^2 - K)}$ for the lowly principle curvatures themselves.

Vesicle Stability. As an illustration of the usefulness of the concepts presented in previous sections of this paper we turn the attention to the question of the thermodynamic stability of unilamellar spherical vesicles. This is a question that has been extensively debated in the literature^{8,14,25,26} and due to the inherent possible metastability of vesicles it is very difficult to unequivocally experimentally establish thermodynamic stability. Such a stability has only been claimed in a few cases^{27–30} and clearly a theoretical analysis of the problem can help to explain why this is a rare event.

In ref. 18 it was shown that under the circumstances when the monolayer preferred curvature is negative, $c_0 < 0$, i.e. curvature towards solvent is preferred, a multiply connected bilayer can be formed. The formation of vesicles represent the opposite trend where the mean curvature $c > 0$ and one could expect spontaneous vesiculation in some regime when monolayer $c_0 > 0$. This is an argument often presented, albeit often expressed in terms of the packing parameter $v/a_0 L_0$ ^{13,14,31}. As we will demonstrate below this reasoning point in the right direction but the problem is more involved. Among other aspects we will demonstrate that when it comes to finer balances a one-parameter theory involving, for example, only $v/a_0 L_0$, is too simplified. This is particularly true when one is dealing with structures that are not locally homogeneous. In the vesicle problem there is an interesting and important inhomogeneity between the inside and the outside monolayers.

Using the decomposition of energies (eqn. (6)) in H and K is cumbersome even in the case of spherical vesicles since $\bar{\kappa} \neq 0$ in general, and the Gaussian curvature energy term *per molecule* depends on the aggregation number in the vesicle – as well as on the value of $\bar{\kappa}$. On the other hand, the decomposition using H and Δc is very straightforward, and is particularly advantageous in the case treated below where a higher order expansion is needed. Thus, if we restrict the discussion to spherical vesicles the difference curvature $\Delta c = 0$ and a straightforward application of eq. (8) gives the curvature free energy to second order as

$$(22) \quad G_c = 4\pi R_2^2 a (1/R_2 - c_0)^2 + 4\pi R_1^2 a (-1/R_1 - c_0)^2$$

where the inner (1) and outer (2) monolayers have been assumed chemically equivalent. If eq. (22) is expanded for $1/R_i \rightarrow 0$ with a bilayer thickness of $2L$ we regain the factor $2a(1 - Lc_0)^2$ of eq. (19). In discussing smaller size vesicles it is important to specify the constraints on area and volume. For an incompressible fluid, molecular volume v , and a constant area per polar group (a_0), the relation between the radii R_2 and R_1 follows from

$$(23a) \quad Nv_0 = (R_2^3 - R_1^3)4\pi/3$$

$$(23b) \quad Na_0 = 4\pi(R_2^2 + R_1^2)$$

where N is the number of molecules in the vesicle. The free energy per unit area is

$$(24) \quad \frac{G}{Na_0} = 2a \frac{[1 - c_0(R_2 - R_1)]}{R_1^2 + R_2^2} + ac_0^2$$

under the constraint

$$(25) \quad R_2^3 - R_1^3 - 3L(R_2^2 + R_1^2) = 0$$

where $L = v/a_0$ is the monolayer thickness in the planar configuration. In this state $R_1 \rightarrow R_2 \rightarrow \infty$; $R_2 - R_1 = 2L$ and $G/Na_0 \rightarrow ac_0^2$. To obtain a lower free energy for vesicles $c_0(R_2 - R_1) > 1$. The constraint eq. (25) implies that $R_2 - R_1$ varies from $2L$ to $3L$ as R_1 decreases to zero. Thus, in the given approximation, vesicles could only be stable relative to a planar state when $c_0L > 1/3$. However, for radii R_2 approaching $3L$ the approximations in the second order curvature analysis are no longer realistic. Furthermore for c_0L as large as $1/3$ a cylindrical aggregate is more favourable than the vesicle, assuming $|b| \ll a$. The conclusion being that within the second order curvature analysis vesicles are unstable. Helfrich and Harbich⁸ have recently presented a regime where vesicles are found unstable. This is when $\kappa - 2\bar{\kappa} < 0$ which in the present notation implies $a_b < 0$. According to eq. (19) combined with the observation that $a > 0$, $a_b \geq 0$ always. Although related to Helfrich and Harbich criterion, the description in eqs. (24) and (25) contains more detail and should be more precise. The analysis supports the qualitative conclusion that vesicles are most likely to be stable $c_0 > 0$ but in contrast to the results of packing arguments the effect does not come out strong enough to actually support the notion of vesicle stability. However, in the second order treatment of curvature energies the vesicles are only marginally unstable, which could indicate that in a more elaborate description relative free energies could shift sufficiently to give stable vesicles.

In a small vesicle the radii of curvature on the inside and the outside are markedly different and one is no longer necessarily dealing with small deviations from the preferred curvature. It is then appropriate to consider higher order terms in the expansion. For spherical vesicles, $\Delta c = 0$, a fourth order expansion of the monolayer free energy density gives

$$(26) \quad g = a_2(H - c_0)^2 + a_3(H - c_0)^3 + a_4(H - c_0)^4$$

Here a_2 and $a_4 > 0$ while the sign of a_3 determines the orientation of the skewness of g versus H . Such higher order terms have been evoked to explain the minimum size of vesicles³². Note the simplicity of obtaining the fourth order expansion when the difference curvature formalism is followed; if the Gaussian curvature formalism were used instead, terms such as $(H - H_0)^2 K$, K^2 , etc. would be encountered.

Using eq. (26) we could follow the same procedure as with the second order expansion and deduce the free energy per unit area which should be minimized under the constraint eq. (25). This is straightforward but tedious and instead we make a stability analysis of the planar state. The mean curvatures of the two monolayers are related to the curvature of the midplane through eqs. (12a-c), where $K_b = H_b^2$ so that $N_{1,2} = (1 + H_b L)^2$. Inserting

this into eq. (26) and correcting for the change in area element gives for the bilayer

$$\begin{aligned}
(27) \quad g = & 2(a_2c_0^2 - a_3c_0^3 + a_4c_0^4) + 2H_b^2 \{a_2(1 - c_0L)^2 - a_3c_0(3 - 3c_0L + c_0^2L^2) \\
& + a_4c_0^2(6 - 4c_0L + c_0^2L^2)\} + \\
& + 2H_b^4 \{a_4(1 - 4c_0L) - a_3L\} + \text{higher order terms}
\end{aligned}$$

The second order term can be negative if, for $c_0 > 0$, a_3 is sufficiently large and positive. A large value of c_0 also make a negative value more likely, provided that the fourth order coefficient is small. The range for a negative value of the H^2 term is approximately given by $3a_3c_0 \geq a_2$ while $2a_4c_0 \ll a_3$. Under these circumstances a bilayer will bend spontaneously to a vesicle of an optimal radius that can be determined by analyzing the complete expression in eq. (27). The instability of the planar configuration arises since the cost of forming the negative curvature inner monolayer is less unfavourable than suggested by the quadratic expansion. However, the conditions under which vesicles would be stable seem rather restricted and it seems unlikely event. A search for a global minimum, rather than the stability analysis given above, would give the same qualitative picture but with somewhat less stringent conditions on the elastic constants for vesicle stability.

Another mechanism that can act to facilitate vesicle stability is operating in a system of mixed amphiphiles. Normally the preferred curvature is a function of composition and at the formation of a vesicle there is a possibility of a partial segregation of the components between the inner and outer monolayers. This effect has been analyzed by Leibler in general terms³³. In a second order analysis the combined curvature and chemical monolayer free energy density can be written

$$(28) \quad g(H_1X) = a\{H - c_0(X)\}^2 + g(X)$$

where $g(X)$ is the bulk free energy per unit area of a binary mixture with mole fraction X of component 2.

Both the entropy of mixing and the molecular interactions contribute to $g(X)$. We will see that the crucial term entering the vesicle stability is the second derivative d^2g/dX^2 , which for a miscible system must be positive. The entropy term gives a contribution $RT[1/X + 1/(1 - X)]$, assuming random mixing. This term can be partly cancelled by an interaction term depending on the detailed chemistry.

For the composition dependence of the preferred curvature we make the simplest possible assumption that it varies linearly with composition

$$(29) \quad c_0(X) = X(c_{20} - c_{10}) + c_{10}$$

where c_{20} and c_{10} are the preferred curvatures for the pure components. When a vesicle is formed the total composition X is given (assuming homogeneity in the system) but the individual monolayers can exchange material so that

$$X_2 = X + \Delta X_2 \text{ and } X_1 = X + \Delta X_1$$

where the indices refer to the two monolayers. If we assume, for simplicity, that the two components have the same volumes v and areas a_0 , and if the expansion is made around $H_b = 0$ then $\Delta X_2 = -\Delta X_1 = \Delta X$. the free energy per unit area of the vesicle is

$$(30) \quad g(H_b, \Delta X) = 2a\{H_b^2(1 - Lc_0(X))^2 + c_0^2(X) - 2H_b\Delta c_0\Delta X + \Delta c_0^2\Delta X^2\} + \Delta X^2 \frac{d^2g}{dX^2}$$

where $\Delta c_0 = c_{20} - c_{10}$. Define $g(H_b)$ through

$$(31) \quad g(H_b, \Delta X); \quad \partial g / \partial \Delta X = 0$$

Minimizing $g(H_b, \Delta X)$ with respect to ΔX yields

$$(32) \quad \Delta X = 2a\Delta c_0 H_b / \left(2a\Delta c_0^2 + \frac{d^2g}{dX^2} \right) = \Delta c_0 H_b / N$$

The coefficient for the second order term is renormalized from $2a(1 - Lc_0)^2$ to

$$2a_2(1 - 2Lc_0 + L^2c_0^2 - 4\Delta c_0^2/N + 2\Delta c_0^4/N^2 + \Delta c_0^2 d^2g/dX^2/N^2)$$

for a stable mixture $d^2g/dX^2 > 0$ and when $d^2g/dX^2 \gg \Delta c_0^2$ the correction terms are negligible, while for $d^2g/dX^2 \ll \Delta c_0^2$ the coefficient reduces to $2a(-2Lc_0 + L^2c_0^2)$. If higher order terms in H_b are included in the relation between ΔX_1 and ΔX_2 the second order term reduces to zero. This shows by way of example how the extra degree of freedom introduced by having two amphiphilic components could greatly facilitate the spontaneous formation of vesicles. This occurs when the decrease in entropy associated with having different concentrations in the inner and outer monolayers is partly compensated by an interaction term reducing the value of d^2g/dX^2 .

In the presentation of the vesicle problem we have left out the role of interbilayer forces such as double layer, van der Waals and hydration forces. Strong forces either attractive or repulsive will favour the most ordered arrangement of the bilayers, which is the lamellar phase. For a non-charged system the attractive van der Waals force will tend to produce stacked bilayers more or less irrespective of concentration. For sugar lipids and phosphatidylethanolamine attractions are stronger than for phosphatidylcholine. For charged amphiphiles, like the dialkyldimethylammonium systems, studied by Evans, Ninham and coworkers²⁷, the repulsive intervesicular force can be diminished by dilution but there is always an intravesicular contribution which tends to destabilize the vesicles. The role of such long range force cannot satisfactorily be incorporated into a curvature free energy due to the additivity assumption inherent in eq. (4). We have furthermore neglected the role of the entropy increase associated with the formation of finite size vesicles from infinite sheets. this entropic effect is partly offset by the entropy of the bending indulations

of the infinite bilayer. A complete analysis of the problem of vesicle stability would have to include these factors, in addition to the bending elastic energies, which we, however, consider to be the most important factor.

During completion of this paper, an analysis of the stability of spherical vesicles by Safran et al.³⁴ appeared. The basic approach to the vesicle stability problem in ref. 34 is much the same as that presented above. These authors have concentrated on the two-component vesicle problem having a more molecular description of the surfactant mixture.

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