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Coexistent Fluid-Phase Equilibria in Biomembranes with Bending Elasticity

Ashutosh Agrawal · David J. Steigmann

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Abstract The theory of fluid surfaces with elastic resistance to bending is applied to coexistent phase equilibria in biomembranes composed of lipid bilayers. A simplified version of the model is used to simulate the necking and budding of closed vesicles.

Keywords Biomembranes · Bending elasticity · Phase transitions

Mathematics Subject Classification (2000) 74A50 · 74K25 · 74G65 · 76A15

1 Introduction

Biological cell membranes may be regarded as two-dimensional liquid crystals. The crystalline structure is conferred by lipid molecules consisting of hydrophilic head groups and hydrophobic tail groups. These molecules arrange themselves in opposing orientations that effectively shield the tail groups from the surrounding aqueous solution (Fig. 1). This in turn generates the well known bilayer structure that is characteristic of biological membranes. The creation of an edge entails the rapid reversal of lipid orientation as required to shield the tail groups. This occurs over length scales on the order of molecular dimensions, and is accompanied by an energetic cost attending the displacement of the head groups from their optimal relative alignment. For this reason closed surfaces are relevant in most applications. Accordingly, attention is restricted here to closed membranes.

Continuum theory for biological membranes is typically based at the outset on some variant of the Cosserat theory of elastic surfaces. This is due to the fact that the thickness of the

A. Agrawal
Department of Civil and Environmental Engineering, University of California, Berkeley, CA 94720, USA

D.J. Steigmann (✉)
Department of Mechanical Engineering, University of California, Berkeley, CA 94720, USA
e-mail: steigman@me.berkeley.edu

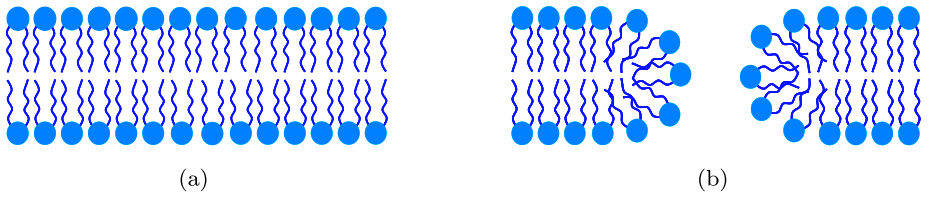

Fig. 1 **a** Bilayer composed of lipid molecules, and **b** Lipid distortion at free edges

bilayer is on the order of molecular dimensions, implying that there is no associated three-dimensional continuum which can serve as the foundation for the derivation of an appropriate two-dimensional theory. The Cosserat theory is based on two vector fields. These are the position field, characterizing the differential geometry of the surface, and a director field that characterizes the configurations of the lipid molecules [1–7]. Local interactions among the lipids favor alignment in the direction of the surface normal if the areal density of lipids is sufficiently high. Further, the molecular lengths are sensibly constant. This phenomenology calls for a constrained theory in which the director field is everywhere identified with the surface normal. Thus, the relevant theoretical framework is nonlinear Kirchhoff-Love shell theory. This has been obtained [8] directly from the balance and constitutive equations of the Cosserat theory by introducing local constraints and using the finite-dimensional version of the Lagrange multiplier rule.

Under typical conditions the lipid molecules diffuse freely on the surface in the manner of a conventional fluid in two dimensions. This behavior may be incorporated into the theory by requiring the relevant free-energy density to satisfy a material symmetry restriction appropriate for fluids, in a manner similar to Noll's treatment of simple fluids as special elastic materials. Here, however, the analysis is complicated by the sensitivity to curvature conferred by the resistance of lipids to changes in their relative alignment. The issue of material symmetry for elastic surfaces with curvature energy received definitive treatment in Murdoch and Cohen's [9] extension of Noll's theory. This work was adapted in [6] to derive a general theory for fluid bilayers as a special case of that for elastic surfaces. An alternative approach, in which the free-energy function is proposed on its own merits and the relevant equations derived from stationary-energy considerations, is summarized in [10], which includes a comprehensive discussion of solutions and applications.

In the present work we use the general theory to describe the necking and budding of vesicles, which in turn facilitate a wide variety of essential cellular functions [11]. These and related phenomena are associated with coexistent membrane domains that are organized by surface curvature [11–13]. In [12] and [13] this is modelled by using conventional theory based on a quadratic free energy, augmented by line tension that accommodates the transition from one domain to another. This approach is similar in spirit to models of phase transitions based on local quadratic approximations of the energy near its minima, together with surface energies attributed to phase interfaces. In biomembranes, line tension is simply the interfacial energy per unit length. This approach has yielded quantitative predictions in certain circumstances [12, 13], but suffers from the drawback, inherent in such models, that the location of the interface is neither known in advance nor predicted by the model.

We consider here an alternative framework in which coexisting domains are described by a model based on a non-convex energy density. Thus, we extend to the theory of biomembranes a classical framework for treating phase equilibria [14]. Much of the preliminary work required for the extension of these ideas to elastic surfaces has already been done [15, 16]. Accordingly, we need only specialize the relevant results to the present setting. This is

discussed in Sect. 3, following a summary of the basic theory for fluid bilayers in Sect. 2. The resulting model, simplified for the sake of illustration and tractability, furnishes predictions that are seen to possess many of the qualitative features observed in experiments [12]. These are discussed in Sect. 5, following the specialization of the differential equations and jump conditions to axisymmetric states in Sect. 4. Solutions to the simplified model are used to illustrate what can be achieved with a minimum of analysis. These lead us to expect that quantitative predictions are within the reach of the general theory discussed in Sects. 2 and 3.

2 Basic Equations

Position on the membrane surface ω, relative to a specified origin, is described in parametric form by the function $\mathbf{r}(\theta^\mu)$, where θ^μ; $\mu = 1, 2$, are surface coordinates. Here and henceforth Greek indices range over $\{1, 2\}$ and, if repeated, are summed over that range. Subscripts preceded by commas indicate partial derivatives with respect to the coordinates, while those preceded by semicolons indicate covariant derivatives. The surface parametrization induces the basis $\mathbf{a}_\alpha = \mathbf{r}_{,\alpha}$ for the tangent plane to ω at the point with coordinates θ^μ. The induced metric is $a_{\alpha\beta} = \mathbf{a}_\alpha \cdot \mathbf{a}_\beta$, and is assumed to be positive definite. A dual basis on the tangent plane is then given by $\mathbf{a}^\alpha = a^{\alpha\beta}\mathbf{a}_\beta$, where $(a^{\alpha\beta}) = (a_{\alpha\beta})^{-1}$. The orientation of the surface is defined locally by the unit-normal field $\mathbf{n} = \mathbf{a}_1 \times \mathbf{a}_2/|\mathbf{a}_1 \times \mathbf{a}_2|$, and its local curvature by the tensor field

$$\mathbf{b} = b_{\alpha\beta}\mathbf{a}^\alpha \otimes \mathbf{a}^\beta, \tag{1}$$

where

$$b_{\alpha\beta} = \mathbf{n} \cdot \mathbf{r}_{,\alpha\beta} = -\mathbf{a}_\alpha \cdot \mathbf{n}_{,\beta}. \tag{2}$$

If $\boldsymbol{\nu}$ and $\boldsymbol{\tau}$ are orthonormal vectors on the tangent plane, then

$$\mathbf{b} = \kappa_\nu \boldsymbol{\nu} \otimes \boldsymbol{\nu} + \kappa_\tau \boldsymbol{\tau} \otimes \boldsymbol{\tau} + \tau(\boldsymbol{\nu} \otimes \boldsymbol{\tau} + \boldsymbol{\tau} \otimes \boldsymbol{\nu}), \tag{3}$$

where κ_ν and κ_τ are the normal curvatures on these axes and τ is the twist.

The equations of equilibrium of the membrane, holding in regions of sufficient continuity, are the well-known shape equation [10] and an equation restricting the variation of the surface tension with respect to surface coordinates. These are respectively the normal and tangential components of the vectorial equilibrium equation [6, 8]

$$\mathbf{T}^\alpha_{;\alpha} + p\mathbf{n} = \mathbf{0}, \tag{4}$$

where p, the difference between the internal and external pressures acting on the membrane, is the osmotic pressure, and $\mathbf{T}^\alpha$ are stress vectors defined by [6]

$$\mathbf{T}^\alpha = \mathbf{N}^\alpha + S^\alpha \mathbf{n}, \tag{5}$$

where

$$\mathbf{N}^\alpha = N^{\beta\alpha}\mathbf{a}_\beta, \qquad N^{\beta\alpha} = \sigma^{\beta\alpha} + b^\beta_\mu M^{\mu\alpha} \quad \text{and} \quad S^\alpha = -M^{\alpha\beta}_{;\beta}, \tag{6}$$

with

$$\sigma^{\beta\alpha} = \rho\left(\frac{\partial\Psi}{\partial a_{\alpha\beta}} + \frac{\partial\Psi}{\partial a_{\beta\alpha}}\right) \quad \text{and} \quad M^{\beta\alpha} = \frac{\rho}{2}\left(\frac{\partial\Psi}{\partial b_{\alpha\beta}} + \frac{\partial\Psi}{\partial b_{\beta\alpha}}\right). \tag{7}$$

Here, $\Psi(a_{\alpha\beta}, b_{\alpha\beta}; \theta^\mu)$ is the free energy per unit mass in the purely mechanical theory, and ρ is the areal mass density; i.e., the mass per unit surface area. Further, the divergence in (4) may be written in the simple form $\mathbf{T}^\alpha_{;\alpha} = a^{-1/2}(a^{1/2}\mathbf{T}^\alpha)_{,\alpha}$, where $a = \det(a_{\alpha\beta})$.

The force and moment, per unit length, transmitted across a smooth curve with unit normal $\boldsymbol{\nu} = \nu_\alpha \mathbf{a}^\alpha$, exerted by the part of the film lying on the side of the curve into which $\boldsymbol{\nu}$ is directed, are [6]

$$\mathbf{f} = \mathbf{T}^\alpha \nu_\alpha - (M^{\beta\alpha}\nu_\alpha \tau_\beta \mathbf{n})' \quad \text{and} \quad \mathbf{m} = \mathbf{r} \times \mathbf{f} - M\boldsymbol{\tau}, \tag{8}$$

respectively. Here, $\boldsymbol{\tau} = \mathbf{n} \times \boldsymbol{\nu} = \mathbf{r}'(s)$, with components $\tau^\alpha = d\theta^\alpha/ds$, is the unit tangent to the curve parametrized by $\theta^\alpha(s)$, s is arclength, $(\cdot)' = d(\cdot)/ds$, and

$$M = M^{\alpha\beta}\nu_\alpha \nu_\beta. \tag{9}$$

It follows from $(8)_2$ that M is a bending couple along the edge. From $(8)_1$, the twisting couple $M^{\beta\alpha}\nu_\alpha\tau_\beta$ is seen to contribute to the force on a curve. This term has come to be well known in principle through Kirchhoff's [17] resolution of the natural boundary conditions arising in classical plate theory (see also [8]).

For *fluid* films, the energy density is a function F of ρ and the invariants [6, 18, 19]

$$H = \frac{1}{2}\operatorname{tr}\mathbf{b}, \qquad K = \det \mathbf{b} \tag{10}$$

of the curvature tensor. These are the mean and Gaussian curvatures of the membrane, respectively. Thus,

$$\Psi(a_{\alpha\beta}, b_{\alpha\beta}; \theta^\mu) = F(\rho, H, K; \theta^\mu), \tag{11}$$

in which the explicit dependence on coordinates θ^μ occurs if the film has non-uniform properties. Equations (6) and (7) specialize to [6]

$$\begin{aligned}
\sigma^{\beta\alpha} &= -\rho(\rho F_\rho + 2K F_K + 2H F_H)a^{\beta\alpha} + \rho F_H \tilde{b}^{\beta\alpha},\\
M^{\beta\alpha} &= \rho\left(\frac{1}{2}F_H a^{\beta\alpha} + F_K \tilde{b}^{\beta\alpha}\right),\\
N^{\beta\alpha} &= -\rho(\rho F_\rho + K F_K + H F_H)a^{\beta\alpha} + \frac{1}{2}\rho F_H \tilde{b}^{\beta\alpha},\\
-S^\alpha &= \left(\frac{1}{2}\rho F_H\right)_{,\mu} a^{\alpha\mu} + (\rho F_K)_{,\mu}\tilde{b}^{\alpha\mu},
\end{aligned} \tag{12}$$

where

$$\tilde{b}^{\alpha\beta} = 2Ha^{\alpha\beta} - b^{\alpha\beta} \tag{13}$$

is the cofactor of the curvature.

Substituting these expressions into (4), and projecting the resulting vector equation onto the normal $\mathbf{n}$ and the tangent plane of the surface at the point with coordinates θ^μ, we obtain [6]

$$p = \Delta\left(\frac{1}{2}\rho F_H\right) + (\rho F_K)_{;\alpha\beta}\tilde{b}^{\alpha\beta} + 2H\rho(\rho F_\rho + K F_K) + \rho(2H^2 - K)F_H \tag{14}$$

and

$$(\rho^2 F_\rho)_{,\alpha} + \rho(F_K K_{,\alpha} + F_H H_{,\alpha}) = 0, \tag{15}$$

respectively, in which $\Delta(\cdot) = [a^{\alpha\beta}(\cdot)_{;\alpha}]_{;\beta}$ is the surface Laplacian. The first of these is the generalization of the well known *shape equation* [10]. Its derivation relies on the Mainardi-Codazzi compatibility equations in the form [6]

$$\tilde{b}^{\alpha\beta}_{;\alpha} = 0. \tag{16}$$

Typical phenomenology suggests that the membrane conserves surface area as it deforms. Assuming the mass to be conserved, this entails the constraint $\rho = \rho_0(\theta^\mu)$, where ρ_0 is the density distribution in some particular configuration of the film. Accordingly, we replace F by

$$F(\rho, H, K; \theta^\mu) = \bar{F}(H, K; \theta^\mu) - \gamma(\theta^\mu)/\rho, \tag{17}$$

where $\bar{F}$ is a constitutive function for the particular film considered and γ is a constitutively-indeterminate Lagrange multiplier. This satisfies $\gamma = \rho^2 F_\rho$ and thus plays the role of surface pressure; $-\gamma$ is the surface tension. Bilayer films are distinguished by the absence of a natural orientation. This imposes the further restriction that $\bar{F}$ be an even function of H [18]:

$$\bar{F}(H, K; \theta^\mu) = \bar{F}(-H, K; \theta^\mu). \tag{18}$$

To obtain a formulation more closely resembling that commonly appearing in the literature, we introduce the areal free energy density

$$W = \rho \bar{F}. \tag{19}$$

We assume the existence of a configuration of the film in which ρ_0 is uniform; i.e., independent of the coordinates θ^μ. Regarding the latter as being convected with the points of the film, we then have that ρ is uniform, by virtue of the constraint. We further assume the constitutive properties of the film to be uniform in the sense that $\bar{F}$ does not depend explicitly on the coordinates. In this case (15) may be integrated to obtain $\lambda = const.$, where

$$-\lambda = \gamma + W, \tag{20}$$

and the shape equation (14) reduces to

$$p = \Delta\left(\frac{1}{2} W_H\right) + (W_K)_{;\alpha\beta}\tilde{b}^{\alpha\beta} + W_H(2H^2 - K) + 2H(K W_K - W) - 2\lambda H, \tag{21}$$

where

$$W(H, K) = \rho \bar{F}(H, K); \quad \rho = const. \tag{22}$$

Thus, the constant factor ρ serves merely to convert the units of the energy density. It is a common conceptual error to interpret (20), in which λ is constant, as implying that the surface tension is constant. In general, this is true only if the bending invariants are constant.

Equation (21) has been obtained by variational arguments [5, 7, 20] in which the film is tacitly assumed to be uniform at the outset. In particular, (21) emerges as the Euler equation associated with normal variations (variations in position parallel to **n**) of the energy functional

$$E = \int_\omega W(H, K) da, \tag{23}$$

where ω is the surface occupied by the film. Further, a formula equivalent to (20) follows from purely tangential variations. In [20] it was also shown that local and global constraints on the surface area are equivalent provided that the distributed load on the film has no tangential components; the former constraint is essentially that adopted here (see also [2]), and the qualifying condition on the distributed loading is satisfied in the present case of loading by osmotic pressure. In [20] the pressure p is a Lagrange multiplier enforcing a global constraint on the volume enclosed by the film. Here, we are concerned with circumstances in which the area-to-volume ratio adjusts in response to changes in temperature or osmotic pressure (see [12]). Given that area is approximately conserved, it follows that volume is not, implying that p is a property of the system and thus not a Lagrange multiplier. In such circumstances (20) and (21) remain valid, but an associated energy functional may not exist.

3 Weak and Strong Relative Minimizers. Nonconvex Energy Densities

In the absence of osmotic pressure it is appropriate to regard equilibria as minimizers of the energy functional (23). Accordingly, it is necessary to specify the class of functions that are allowed to compete for the minimum. We consider equilibria of two types that are well known in the Calculus of Variations: the weak and strong relative minimizers [21]. In both cases we consider equilibria for which the position field $\mathbf{r}(\theta^\mu)$ is piecewise smooth in the sense that the right-hand side of (21) is continuous except at curves where the second derivatives $\mathbf{r}_{,\alpha\beta}$ may suffer discontinuities. These are necessarily of the form [15]

$$[\mathbf{r}_{,\alpha\beta}] = \mathbf{u}\nu_\alpha\nu_\beta, \tag{24}$$

where ν_α are the components of a unit normal to the curve lying in the (continuous) tangent plane, $\mathbf{u}$ is a 3-vector, and the notation $[\cdot]$ is used to denote the jump of the enclosed quantity across the curve. This type of discontinuity supports jumps in curvature and is henceforth called a *phase boundary*. The (continuous) curvatures on either side of a phase boundary characterize the local states of the fluid phases. We remark that the version of (24) given in [15] involves the normal to the image of the curve in some fixed reference placement of the surface. In a convected system of coordinates, the covariant components of this normal are proportional to the ν_α. Here, the scalar factor has been absorbed into $\mathbf{u}$.

In the present setting, strong relative minimizers are those configurations that minimize the energy with respect to perturbations in $\mathbf{r}$ and $\mathbf{r}_{,\alpha}$ that are bounded at all points of the membrane. The minimum is weak if, in addition, perturbations in $\mathbf{r}_{,\alpha\beta}$ are also bounded. Because the latter entails a more stringent requirement, strong minima are also weak. However, weak minima need not be strong. In this work we are concerned with strong relative minimizers. Granted existence, these necessarily achieve values of the energy that bound those attained by weak minima from below.

The locations of phase boundaries are determined in part by jump conditions which depend on the type of minimizer considered. The relevant conditions have been worked out in [15] for a general theory of elastic surfaces which subsumes that considered here (see also [16]). In particular, for both strong and weak minimizers it is necessary that the force and moment be continuous across a phase boundary. Accordingly, (8) furnishes

$$[\mathbf{f}] = \mathbf{0} \quad \text{and} \quad [M] = 0. \tag{25}$$

Strong minimizers satisfy a further jump condition involving the free energy. This is known in the Calculus of Variations as a Weierstrass-Erdmann condition. It may be derived

from a related inequality known as the Weierstrass-Graves convexity condition [22], which is also necessary for strong minimizers. In the present context, the latter condition, which holds pointwise except on phase boundaries, is [15]

$$U(\mathbf{r}_{,\alpha};\, \mathbf{r}_{,\alpha\beta} + \mathbf{a}b_\alpha b_\beta) - U(\mathbf{r}_{,\alpha};\, \mathbf{r}_{,\alpha\beta}) \geq \mathbf{a}\cdot \partial U/\partial \mathbf{r}_{,\alpha\beta} b_\alpha b_\beta, \tag{26}$$

for all 3-vectors $\mathbf{a}$ and for all b_α. Here, $U(\mathbf{r}_{,\alpha};\, \mathbf{r}_{,\alpha\beta}) = F(\rho, H, K)$ is the free energy per unit mass, expressed in terms of the first and second derivatives of the position field, and the derivative on the right-hand side is evaluated at the energy-minimizing position field $\mathbf{r}(\theta^\mu)$. We remark that the derivation of this condition presented in [15] relies on the construction of a variation of the position field that violates the present constraint on surface area. Thus, (26) has not been rigorously shown to apply in the present circumstances. However, the construction given in [15] involves passage to a limit, at which compatibility with the constraint is restored. This leads us to offer the conjecture that (26) is applicable in the present circumstances.

To motivate this conjecture, we note that the function $\bar{F}(H, K)$ used in (17) may be regarded as an extension [8] of the energy from a constraint manifold defined by $\rho = \rho_0$ to an enveloping three-dimensional space parametrized by triplets $\{\rho, H, K\}$. The extended function is well defined for deformations that violate the constraint. Its restriction to the constraint manifold is the actual energy density. Accordingly, we may introduce an auxiliary minimization problem based on the extended energy. The construction given in [15] may be applied to the auxiliary problem to derive (26), in which U is the extended energy density. The values of $\mathbf{r}_{,\alpha}$, and hence that of the mass density, are the same in all terms of this inequality. Allowing only those values of $\mathbf{r}_{,\alpha}$ that satisfy the constraint, inequality (26) then applies with U equal to the restriction of the extended energy density to the constraint manifold, and thus to the actual energy density. Accordingly, inequality (26) then also applies with $U(\mathbf{r}_{,\alpha};\, \mathbf{r}_{,\alpha\beta}) = W(H, K)$.

To interpret (26) for biomembranes, we fix $\mathbf{r}_{,\alpha}$ as indicated, and compute the derivative

$$\partial U/\partial \mathbf{r}_{,\alpha\beta}\cdot \dot{\mathbf{r}}_{,\alpha\beta} = \dot{U} = \dot{W} = W_H \dot{H} + W_K \dot{K}, \tag{27}$$

where $\dot{\mathbf{r}}$ is a *variation* of $\mathbf{r}$, the derivative with respect to a parameter that labels configurations; $\dot{H}$ and $\dot{K}$ are the induced variations of H and K. With $\dot{\mathbf{r}}_{,\alpha} = \mathbf{0}$, $(10)_{1,2}$ imply that (see [20], eq. (12))

$$\dot{H} = \frac{1}{2} a^{\alpha\beta}\mathbf{n}\cdot \dot{\mathbf{r}}_{,\alpha\beta} \quad \text{and} \quad \dot{K} = \tilde{b}^{\alpha\beta}\mathbf{n}\cdot \dot{\mathbf{r}}_{,\alpha\beta}. \tag{28}$$

Thus,

$$\partial U/\partial \mathbf{r}_{,\alpha\beta} = M^{\alpha\beta}\mathbf{n}, \tag{29}$$

where (cf. (9) and $(12)_2$)

$$M^{\alpha\beta} = \frac{1}{2} W_H a^{\alpha\beta} + W_K \tilde{b}^{\alpha\beta}. \tag{30}$$

It follows that

$$\mathbf{a}\cdot \partial U/\partial \mathbf{r}_{,\alpha\beta} b_\alpha b_\beta = \left(\frac{1}{2} W_H + \varsigma W_K\right)\mathbf{n}\cdot \mathbf{a}, \tag{31}$$

where

$$\varsigma = \tilde{b}^{\alpha\beta} b_\alpha b_\beta \tag{32}$$

and the normalization condition $a^{\alpha\beta}b_\alpha b_\beta = 1$ has been imposed without loss of generality.

Let superscripts $+$ and $-$ denote the limiting values of variables as a phase boundary is approached from either side. We apply (26) twice: First, with $\mathbf{a} = \mathbf{u}$, $b_\alpha = \nu_\alpha$, and $\mathbf{r}_{,\alpha\beta} = \mathbf{r}^-_{,\alpha\beta}$; and second, with $\mathbf{a} = -\mathbf{u}$, $b_\alpha = \nu_\alpha$, and $\mathbf{r}_{,\alpha\beta} = \mathbf{r}^+_{,\alpha\beta}$. Invoking (24), $(25)_2$ and (29), we find that $[W]$ is simultaneously not less, and not greater, than $M^\pm\mathbf{u}\cdot\mathbf{n}$, where $M^\pm$ is the common value of the limits of M. Accordingly, $[W] = M^\pm\mathbf{u}\cdot\mathbf{n}$. For $b_\alpha = \nu_\alpha$, we use (3) and (13) to conclude that $\varsigma = \kappa_\tau = b_{\alpha\beta}\tau^\alpha\tau^\beta$. Equation (24) furnishes $[\kappa_\tau] = (\boldsymbol{\nu}\cdot\boldsymbol{\tau})^2\mathbf{n}\cdot\mathbf{u}$. This vanishes, implying that the normal curvature of a phase boundary is continuous. Further, (10) and (24) may be used to derive $[H] = 1/2\mathbf{n}\cdot\mathbf{u}$ and $[K] = \kappa_\tau\mathbf{n}\cdot\mathbf{u}$. Combining these results with (9) and (30), we arrive at the jump condition

$$[W] = W_H^\pm[H] + W_K^\pm[K], \tag{33}$$

in which the same superscript ($+$ or $-$) must be used in both terms on the right-hand side. This is the Weierstrass-Erdmann condition in the present context.

To reduce (26) we first evaluate the finite perturbations of H and K induced by $\mathbf{r}_{,\alpha\beta} \to \mathbf{r}_{,\alpha\beta} + \mathbf{a}b_\alpha b_\beta$ with $\mathbf{r}_{,\alpha}$ fixed. To this end we use (2) to derive $b_{\alpha\beta} \to b_{\alpha\beta} + \mathbf{n}\cdot\mathbf{a}b_\alpha b_\beta$. Consequently, $(10)_{1,2}$ yield $H \to H + \Delta H$ and $K \to K + \Delta K$, where $\Delta H = 1/2\mathbf{n}\cdot\mathbf{a}$ and $\Delta K = \varsigma\mathbf{n}\cdot\mathbf{a} = 2\varsigma\Delta H$. Using (29), we then find that (26) reduces to

$$W(H + \Delta H,\ K + \Delta K) - W(H, K) \geq (\Delta H)W_H(H, K) + (\Delta K)W_K(H, K). \tag{34}$$

This is the Weierstrass-Graves inequality for biomembranes. It requires that the values of H and K associated with an energy minimizer belong to a domain of convexity of the function W almost everywhere on the membrane surface. However, the condition is somewhat nonstandard in the sense that ΔH and ΔK cannot be assigned independently.

A weaker form of the inequality—the Legendre-Hadamard condition—is necessary for weak relative minimizers. This follows by linearizing (34) with respect to $\theta = \mathbf{n}\cdot\mathbf{a}$. To this end we fix H, K and ς and set $G(\theta) = W(H + \theta/2,\ K + \varsigma\theta)$. Then, $G'(\theta) = 1/2W_H + \varsigma W_K$ and (34) is seen to be equivalent to the convexity of $G(\theta)$ at $\theta = 0$; i.e., $G(\theta) \geq G(0) + \theta G'(0)$. This in turn implies that $\theta^2[G''(0) + o(\theta^2)/\theta^2] \geq 0$. Dividing by θ^2 and passing to the limit, we obtain the Legendre-Hadamard condition $G''(0) \geq 0$, which is equivalent to

$$\frac{1}{4}W_{HH} + \varsigma W_{HK} + \varsigma^2 W_{KK} \geq 0, \tag{35}$$

in which the derivatives are evaluated at H and K. This corrects inequality (7.16) of [6] and inequality (56) of [20]. Here, ς is bounded between the largest and smallest eigenvalues of the cofactor of the curvature of the equilibrium surface at the (arbitrary) point in question.

To summarize, (25) and (35) are necessary for both weak and strong relative minimizers. The Weierstrass-Erdmann condition (33) and Weierstrass-Graves condition (34) are necessary for strong relative minimizers. For weak minimizers the former condition is not applicable, whereas the latter is replaced by (35).

In the remainder of this work we consider special free energies that are independent of K. These may depend parametrically on a dimensionless scalar μ, to be discussed, and are denoted by $W(H; \mu)$. Equilibria are regarded as being associated with spatially uniform values of the parameter. In particular, the formulation based on minimum energy considerations remains valid in the presence of the parameter. For example, in some circumstances it may be appropriate to identify μ with a uniform temperature ratio. The various jump conditions and convexity conditions simplify accordingly. Thus, $(25)_2$, (33), (34) and (35) reduce

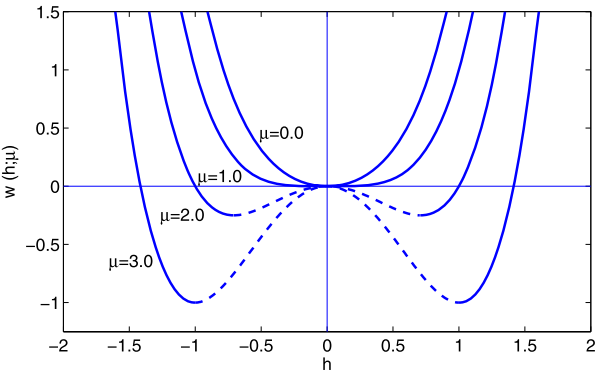

Fig. 2 Energy density as a function of mean curvature

respectively to

$$W_H(H^+) = W_H(H^-), \qquad [W(H)] = W_H(H^\pm)[H], \\ W(H + \Delta H) - W(H) \geq (\Delta H) W_H(H) \tag{36}$$

and

$$W_{HH} \geq 0, \tag{37}$$

in which the parameter μ has been suppressed for clarity.

In the examples to follow, states satisfying these conditions are constructed from the model free-energy function defined by

$$W(H;\mu) = (k^2/\bar{k}) w(h;\mu); \qquad w(h;\mu) = (1-\mu)h^2 + h^4, \quad \text{where } h = \sqrt{\bar{k}/k}H. \tag{38}$$

Here k and $\bar{k}$ are positive material constants, w is the dimensionless energy density, and h is the dimensionless mean curvature. This satisfies the symmetry restriction (18) for bilayers. It is convex as a function of H if $\mu < 1$, and non-convex if $\mu > 1$ (Fig. 2). Accordingly, we regard $\mu = 1$ as a transition value above which phase coexistence is possible. Points on the dotted portions of the curves violate inequality $(36)_3$ and are not admissible as states associated with strong relative minimizers. Admissibility is restored if the membrane has phase boundaries at which the phase equilibrium conditions $(36)_{1,2}$ are satisfied. These entail jumps in H which effectively connect the states at the endpoints of the dotted portions of the curves. For $\mu \geq 1$, the minimizing values of H are $\pm H_0$, where

$$H_0 = \sqrt{k/\bar{k}}\, h_0; \quad h_0 = \sqrt{(\mu-1)/2}. \tag{39}$$

The idea of two minimizing values of H may be motivated by a model of the geometry of lipid molecules inspired by their chemistry. For example, it is known (see Fig. 3 of [11]) that certain types of lipids favor cone-shaped configurations in which the tail groups are splayed rather than parallel. Further, certain enzymes affect head-group size [11], altering the surface area occupied by lipids at one lateral surface relative to that occupied at the other. Both mechanisms cause the surface ω associated with the membrane to bend locally, resulting in minimum-energy states that are curved at the local scale. In a bilayer without any natural orientation, these effects are expected to occur with equal likelihood in either orientation, producing energy wells that are invariant under reversal of the sign of $\mathbf{n}$, and hence that

of H. Judging by the data reported in [12] and their correlation with the solutions discussed in Sect. 5 below, it is appropriate to conclude that the natural bending induced by chemistry may be temperature dependent, and that the effect is more pronounced at higher temperatures. For example, we conjecture that low temperatures suppress the tendency of splayed tail groups to induce natural surface curvature, this then being insufficient to overcome the head-group interactions that favor parallel lipid alignment. This would manifest itself as a phenomenological surface energy with a single minimum at $H = 0$. As temperature is increased, the splayed tail groups presumably traverse a larger domain in their phase space, thus promoting the effect and overcoming the resistance to natural bending. In this picture it is natural to interpret the parameter μ as a monotonically increasing function of temperature over some interval. In the simplest case this would be the ratio of actual temperature to a fixed transition temperature.

To reduce the jump condition $(25)_1$ for free energies of the form $W(H)$ we use (5), $(8)_1$, (12) and the orthogonality of $\boldsymbol{\nu}$ and $\boldsymbol{\tau}$, together with the consequent result $M^{\alpha\beta}\nu_\alpha\tau_\beta = 0$, obtaining

$$[N^{\beta\alpha}\nu_\alpha]\mathbf{a}_\beta + [S^\alpha\nu_\alpha]\mathbf{n} = \mathbf{0}, \tag{40}$$

where

$$S^\alpha\nu_\alpha = -\frac{1}{2}\{W_H(H)\}_{,\alpha}\nu^\alpha, \tag{41}$$

and, from $(12)_3$,

$$N^{\beta\alpha}\nu_\alpha = -\gamma\nu^\beta - \frac{1}{2}W_H(H)b^{\beta\alpha}\nu_\alpha. \tag{42}$$

Using (3), we have $b^{\beta\alpha}\nu_\alpha = \kappa_\nu\nu^\beta + \tau\tau^\beta$. In the examples considered here, $\tau = 0$, identically. Further, from (10) we have $[\kappa_\nu] = 2[H]$, which combines with $(36)_1$ to give

$$[N^{\beta\alpha}\nu_\alpha]\mathbf{a}_\beta = -[\gamma]\boldsymbol{\nu} - W_H(H^\pm)[H]\boldsymbol{\nu} = -[\gamma + W]\boldsymbol{\nu}, \tag{43}$$

where the right-most equality applies to strong relative minimizers. The orthogonality of the terms in (40), together with (20), then yields the force jump conditions

$$[\lambda] = 0 \quad \text{and} \quad [\{W_H(H)\}_{,\alpha}]\nu^\alpha = 0. \tag{44}$$

4 Axisymmetric Surfaces

We consider axisymmetric surfaces parametrized by meridional arclength s and azimuthal angle θ. Thus,

$$\mathbf{r}(s,\theta) = r(s)\mathbf{e}_r(\theta) + z(s)\mathbf{k}, \tag{45}$$

where $r(s)$ is the radius from the axis of symmetry, $z(s)$ is the elevation above a base plane, and $\{\mathbf{e}_r, \mathbf{e}_\theta, \mathbf{k}\}$ is the standard orthonormal basis in a system of cylindrical polar coordinates $\{r, \theta, z\}$. Meridians and parallels of latitude are the curves on which θ and s, respectively, are constant. Phase boundaries are curves of the latter type. Therefore, $\boldsymbol{\nu}$ is a unit tangent to a meridian. Further, because s measures arclength along meridians, we have

$$(r')^2 + (z')^2 = 1. \tag{46}$$

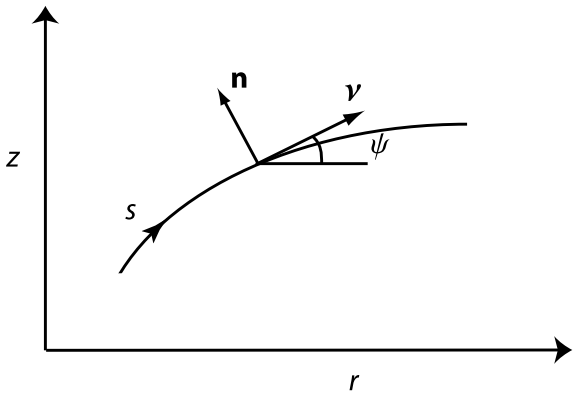

Fig. 3 Meridian of an axisymmetric surface

We select surface coordinates $\theta^1 = s$ and $\theta^2 = \theta$. The induced tangent vectors are

$$\mathbf{a}_1 = r'\mathbf{e}_r + z'\mathbf{k} \quad \text{and} \quad \mathbf{a}_2 = r\mathbf{e}_\theta, \tag{47}$$

and it follows from (46) that there is $\psi(s)$ such that (see Fig. 3)

$$r'(s) = \cos\psi \quad \text{and} \quad z'(s) = \sin\psi. \tag{48}$$

Because $\mathbf{a}_1$ is orthogonal to a parallel of latitude, we identify it with $\boldsymbol{\nu}$. Accordingly,

$$\boldsymbol{\nu} = \cos\psi\mathbf{e}_r + \sin\psi\mathbf{k}, \qquad \boldsymbol{\tau} = \mathbf{e}_\theta \quad \text{and} \quad \mathbf{n} = \cos\psi\mathbf{k} - \sin\psi\mathbf{e}_r. \tag{49}$$

The metric and dual metric are $(a_{\alpha\beta}) = diag(1,\, r^2)$ and $(a^{\alpha\beta}) = diag(1,\, r^{-2})$, respectively, and the latter may be used to compute

$$\mathbf{a}^1 = \boldsymbol{\nu} \quad \text{and} \quad \mathbf{a}^2 = r^{-1}\mathbf{e}_\theta. \tag{50}$$

To obtain the components of curvature we use (2) with

$$\mathbf{r}_{,11} = \psi'\mathbf{n}, \qquad \mathbf{r}_{,12} = \mathbf{r}_{,21} = \cos\psi\mathbf{e}_\theta \quad \text{and} \quad \mathbf{r}_{,22} = -r\mathbf{e}_r, \tag{51}$$

obtaining $(b_{\alpha\beta}) = diag(\psi',\, r\sin\psi)$. Combining this with (1) and (3), we derive

$$\kappa_\nu = \psi', \qquad \kappa_\tau = r^{-1}\sin\psi \quad \text{and} \quad \tau = 0. \tag{52}$$

The sum of the normal curvatures is twice the mean curvature $H(s)$. This furnishes the differential equation

$$r\psi' = 2rH - \sin\psi. \tag{53}$$

Their product yields the Gaussian curvature $K(s)$, which is thus given by

$$K = H^2 - (H - r^{-1}\sin\psi)^2. \tag{54}$$

For free energy functions of the form $W(H)$, the shape equation (21) simplifies to

$$p = \frac{1}{2}\Delta(W_H) + W_H(2H^2 - K) - 2H(W + \lambda), \tag{55}$$

where

$$\frac{1}{2}\Delta(W_H) = r^{-1}L', \tag{56}$$

with

$$L = \frac{1}{2}r(W_H)'. \tag{57}$$

With the aid of (54), this may be recast as

$$L' = r\{p + 2H(W + \lambda) - W_H[H^2 + (H - r^{-1}\sin\psi)^2]\}. \tag{58}$$

Further, for the class (38) of free energies, admissible states of the membrane satisfy inequality (37) in the strict sense. This allows us to write (57) in the form

$$rH' = 2L/W_{HH}. \tag{59}$$

The system to be solved thus consists of $(48)_{1,2}$, (53), (58) and (59), and the unknowns are r, z, ψ, H and L. We are concerned with problems having reflection symmetry with respect to the equatorial plane defined by $z = 0$, where $s = s_e$. The north pole corresponds to $s = 0$. Thus, the geometric boundary conditions are

$$r(0) = 0, \qquad \psi(0) = 0, \qquad z(s_e) = 0 \quad \text{and} \quad \psi(s_e) = -\pi/2, \tag{60}$$

the last of these being equivalent to $\boldsymbol{\nu}|_{s_e} = -\mathbf{k}$. We append two additional boundary conditions based on equilibrium considerations. To render the number of equations consistent with the total number of side conditions, we add [3]

$$\lambda' = 0 \tag{61}$$

to the system of differential equations, to account for the fact that λ, defined by (20), is (piecewise) constant. The jump condition $(44)_1$ implies that this has the same value almost everywhere on the membrane.

One of the additional boundary conditions follows from the equilibrium of a subsurface $\bar{\omega} = \{(s, \theta) : 0 \le s \le \bar{s},\ 0 \le \theta < 2\pi\}$, containing the pole. This is expressed by

$$\int_{\bar{\omega}} p\mathbf{n}\, da + \int_{\partial\bar{\omega}} \mathbf{f}\, dt = \mathbf{0}, \tag{62}$$

where $t = r(\bar{s})\theta$ measures arclength around the perimeter of the parallel defined by $s = \bar{s}$. Here,

$$\mathbf{f} = (N^{\beta\alpha}\nu_\alpha)\mathbf{a}_\beta + (S^\alpha\nu_\alpha)\mathbf{n}, \tag{63}$$

where (cf. (41), (42))

$$(N^{\beta\alpha}\nu_\alpha)\mathbf{a}_\beta = -\left(\gamma + \frac{1}{2}\kappa_\nu W_H\right)\boldsymbol{\nu} \quad \text{and} \quad S^\alpha\nu_\alpha = -\frac{1}{2}(W_H)'. \tag{64}$$

Combining these with $(49)_{1,3}$ yields

$$\begin{aligned}\mathbf{f} = &\left[-\left(\gamma + \frac{1}{2}\kappa_\nu W_H\right)\cos\psi + \frac{1}{2}(W_H)'\sin\psi\right]\mathbf{e}_r \\ &+ \left[-\left(\gamma + \frac{1}{2}\kappa_\nu W_H\right)\sin\psi - \frac{1}{2}(W_H)'\cos\psi\right]\mathbf{k}.\end{aligned} \tag{65}$$

The periodicity of $\mathbf{e}_r(\theta)$ then results in

$$\int_{\partial\bar{\omega}} \mathbf{f}\,dt = -2\pi r(\bar{s})\left[\left(\gamma + \frac{1}{2}\kappa_v W_H\right)\sin\psi + \frac{1}{2}(W_H)'\cos\psi\right]\mathbf{k}. \tag{66}$$

Assuming the osmotic pressure p to be bounded, and invoking the boundary condition $(60)_2$, we then have

$$\frac{1}{2}\lim_{\bar{s}\to 0}\{r(W_H)'\} = 0, \quad \text{yielding } L(0) = 0, \tag{67}$$

where $L(s)$ is defined by (57).

The remaining boundary condition arises from the fact that there can be no transverse shear force at the equator if the membrane is to have reflection symmetry with respect to the equatorial plane. For, if there were a non-zero force transmitted by the material below the equator to that above, then equilibrium would require that it be balanced by an equal and opposite force exerted by the part of the membrane above the equator on that below. This in turn would destroy the reflection symmetry. Accordingly, we require that $\mathbf{e}_r \cdot \mathbf{f}$ vanish at $s = s_e$, which, with $(60)_4$, implies that $(W_H)'$ vanishes at $s = s_e$. This in turn yields

$$L(s_e) = 0. \tag{68}$$

Finally, we note that the continuity of position and slope on the meridian implies that the jump condition $(44)_2$ is equivalent to

$$[L] = 0. \tag{69}$$

5 Simple Solutions for Budding Vesicles and Biconcave Discoids

We illustrate the foregoing model by applying it to the description of vesicle budding under vanishing osmotic pressure. The same basic solution may be used to describe biconcave discoids. The use of a nonconvex energy, together with the operative jump relations, facilitates the nearly trivial construction of solutions. Moreover, these are all global minimizers of the energy. For vesicles and biconcave discoids, we construct two-phase equilibria from the double-well energy defined by (38). For these the mean curvature of the surface is piecewise constant and equal to the optimum values $\pm H_0$.

It is easy to see that locally constant values of H are admissible. In particular, (59) then yields $L = 0$; Equation (58) reduces to an algebraic relation, and $(67)_2$, (68) and (69) are satisfied. For $|H| = H_0$ we have $W_H = 0$ and (58) simplifies further to

$$H(W_m + \lambda) = 0, \tag{70}$$

where W_m is the common minimum value of the energy in the two phases (Fig. 2). Imposing this with $H = \pm H_0$ yields

$$\lambda = -W_m, \tag{71}$$

which satisfies (61) and the jump condition $(44)_1$ for strong relative minimizers. All equilibrium conditions are satisfied, and the problem is thus reduced to differential geometry.

To obtain the shape of the membrane we use $(48)_1$ to write (53) as

$$\frac{d}{dr}(\sin\psi) + \frac{1}{r}\sin\psi = 2H, \tag{72}$$

yielding, in the case of constant H,

$$\sin\psi = rH + C/r, \tag{73}$$

where C is a constant. This result is due to Delaunay [10].

(i) Vesicle budding

Vesicle budding is associated with necking of the surface in a region that includes the equator. Thus, we seek a solution with

$$H(s) = \begin{cases} -H_0; & 0 < s < s_p \\ H_0; & s_p < s < s_e \end{cases} \tag{74}$$

where s_p is the arclength location of the phase boundary. This and s_e are determined in the course of the solution procedure. The radius of the phase boundary is $r_p = r(s_p)$, and that of the equator is $r_e = r(s_e)$. To satisfy the boundary conditions $(60)_{1,2}$, we have

$$\sin\psi(s) = \begin{cases} -rH_0; & 0 < s < s_p \\ rH_0 + D/r; & s_p < s < s_e \end{cases} \tag{75}$$

where D is a constant. The continuity conditions require that this be continuous at s_p. This and the boundary condition $(60)_4$ yield

$$-r_pH_0 = r_pH_0 + D/r_p \quad \text{and} \quad D = -r_e(1 + H_0r_e), \tag{76}$$

which combine to give

$$2x_p^2 = x_e(1 + x_e), \tag{77}$$

where

$$x = rH_0 \tag{78}$$

is the dimensionless radius and x_p, x_e are its values at the phase boundary and equator, respectively. The relevant root is

$$x_e = \frac{1}{2}\left(-1 + \sqrt{1 + 8x_p^2}\right). \tag{79}$$

We note that $x_e = x_p$ if $x_p = 1$ or $x_p = 0$. These extremes correspond respectively to a spherical configuration and a pinched configuration. In the latter the equatorial radius vanishes and the vesicle consists of two adjoining spherical buds. In both cases the arclength measure of the second branch of (74) vanishes and $H = -H_0$ almost everywhere. In intermediate cases we have $x_e < x_p$, corresponding to necking.

To determine x_p in intermediate cases we derive an expression for the total surface area A as a function of x_p. We then obtain those values of x_p that yield an assigned value of area. First, we observe from $(52)_2$ that the normal curvature of a parallel of latitude is $\kappa_\tau = -H_0$ on the first branch of (75). It follows from $(10)_1$ that this is also the normal curvature of the meridian on the same branch; i.e., $\kappa_\nu = -H_0$. The membrane is spherical on this branch. Further, from (76) $\sin\psi$ is seen to increase monotonically (from -1) with r on the second branch. For necking to occur it is thus necessary that $x_p < 1$. Accordingly, $r(s)$ is non-monotone in the interval $(0, s_p)$, first increasing from zero to the maximum value H_0^{-1}, then

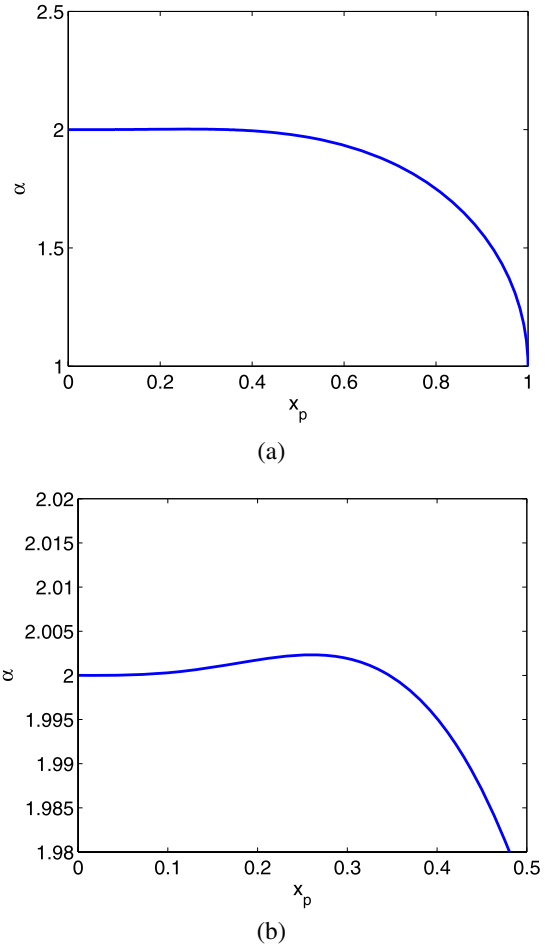

Fig. 4 Surface area vs. phase boundary radius for vesicles. (**a**) Global behavior, and (**b**) Non-monotonicity for small phase boundary radii

decreasing to r_p. On the second branch of (75), $r(s)$ decreases monotonically from r_p to r_e. Using $da = 2\pi[r/r'(s)]dr$ and $\cos\psi = \pm\sqrt{1-\sin^2\psi}$, with the sign chosen in accordance with the foregoing discussion, we compute the dimensionless membrane surface area

$$\alpha = 1 + \sqrt{1-x_p^2} + \int_{x_e}^{x_p} \frac{udu}{\sqrt{1-(u-2x_p^2/u)^2}}, \tag{80}$$

where x_e is given by (79), and

$$\alpha = AH_0^2/2\pi = (Ak/4\pi\bar{k})(\mu - 1). \tag{81}$$

The solution is completed by specifying the membrane area; hence α, and determining $x_p \in (0, 1)$. The restriction on the values of x_p limits the areas that can be assigned if a two-phase solution of this kind is to exist. The graph of α vs. x_p is depicted in Fig. 4. Equation (80) is universal in the sense that the α–x_p relation is independent of the pa-

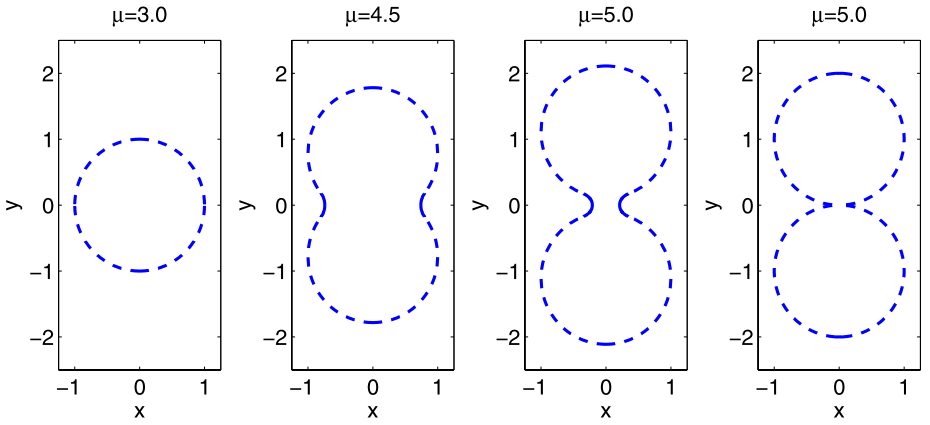

Fig. 5 Sequence of necked configurations. *Dashed curves* correspond to $H = -H_0$; *solid curves* to $H = H_0$. For $\mu = 5.0$, two states (necked and pinched) are shown

rameter μ. On the other hand, the curvature H_0 that minimizes the free-energy function (38) is controlled by μ. If the actual surface area remains fixed, as we assume, then α adjusts accordingly, as indicated, producing a corresponding adjustment of x_p. The shape of the membrane is thus predicted to be dependent on μ and hence on temperature, according to the conjecture offered in Sect. 3. This is reflected in Fig. 5, which illustrates the emergence and progression of necking with increasing μ. This has been generated using $\alpha = (\mu - 1)/2 = h_0^2$, corresponding to $Ak/\bar{k} = 2\pi$. The sequence of necked states begins with the entire membrane in the spherical phase ($H = -H_0$) at $\mu = 3$. The response predicted by this simple solution is in qualitative agreement with the phenomenology described in [12].

Two values of x_p are found for α between 2.0000 and 2.0023 (i.e. μ between 5.0000 and 5.0046), yielding necks with different radii. In [12] it is noted that the neck radius is sometimes observed to collapse abruptly when a certain temperature is reached, resulting in spherical buds that adhere to each other. Further, the process is accompanied by fission, or rupture, of the vesicle. This observation may indicate the emergence of two necked equilibria at a critical temperature, as suggested by the present solution. The authors of [12] express the view that the dynamical process attending collapse may point to the presence of an energy barrier associated with fission. The foregoing analysis, which does not take fission into account, pertains solely to equilibria and predicts that necked states with different radii have the same energy. In particular, fission entails the creation of an edge and an attendant expenditure of energy, as indicated in the Introduction. This may account for the energy barrier discussed in [12]. Within the limitations of the present model, our solution is compatible with the interpretation offered in [12], but a more sophisticated study accounting for membrane dynamics and fission is needed to fully address the issue. The shape shown in the figure is obtained by numerical integration of

$$dy/dx = \tan\psi; \quad y = zH_0, \quad y(x_e) = 0. \tag{82}$$

The actual shape; i.e., the graph of z against r, is obtained by scaling the graph of y against x by the constant H_0, which may then be obtained by fitting some selected feature of the predicted shape to empirical data at a particular value of μ (or temperature).

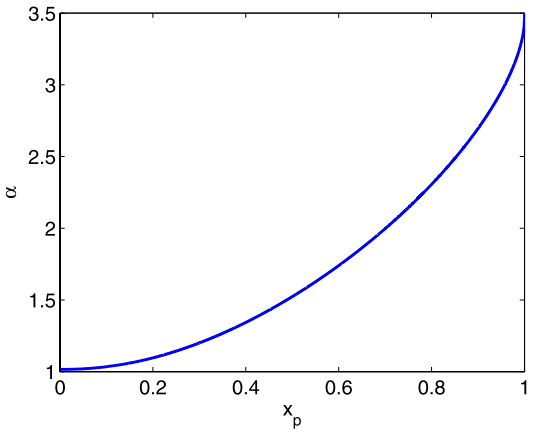

Fig. 6 Surface area vs. phase boundary radius for biconcave discoids

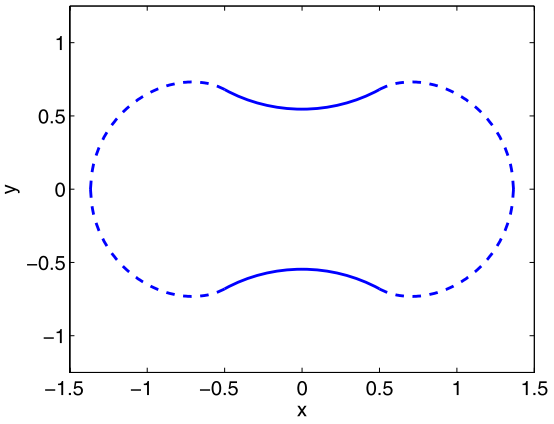

Fig. 7 Biconcave discoid at $\alpha = 1.52$. *Dashed curves* correspond to $H = -H_0$; *solid curves* to $H = H_0$

(ii) Biconcave discoid

The biconcave discoid resembles the equilibrium shape of a healthy red blood cell. It has been the subject of a number of investigations based on convex, quadratic energy densities (e.g. [10]). However, to our knowledge none of the solutions obtained to date, with the exception of that discussed in [3], satisfies the full set of boundary conditions (60), $(67)_2$ and (68).

To describe biconcave discoids we simply interchange $\pm H_0$ in (74). The continuity condition at r_p now yields

$$x_e = \frac{1}{2}\left(1 + \sqrt{1 + 8x_p^2}\right) \tag{83}$$

in place of (79). Using the fact that the function $r(s)$ is now monotonically increasing at all points of the membrane, we find

$$\alpha = 1 - \sqrt{1 - x_p^2} + \int_{x_p}^{x_e} \frac{u\,du}{\sqrt{1 - (u - 2x_p^2/u)^2}} \tag{84}$$

in place of (80). This is a monotone function of x_p (Fig. 6), implying that the problem of assigned surface area has a unique solution. Figure 7 illustrates the shape $y(x)$ obtained by integrating (82) for $\alpha = 1.52$.

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