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Flexoelectricity and elasticity of asymmetric biomembranes

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In view of the well-established charge and dipolar asymmetry of the two leaflets of a native membrane, the theory of flexoelectricity (and curvature elasticity) is extended to take into account this asymmetry using linear and nonlinear forms of the Poisson-Boltzmann equation. The results are discussed with respect to data from atomic force microscopy studies of electromotility in biomembranes.

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INTRODUCTION

The theory of flexoelectricity has been developed and tested with symmetric lipid bilayers [1,2]. Recent flexoelectric models of electromotility in outer hair cells of the cochlea [3] and atomic force microscopy (AFM) measurements in native membranes [4,5] call for an extension of this theory to the asymmetric situation. It is well established that the composition of outer and inner leaflets are asymmetric [6]. To more fully understand the mechanics, the curvature elasticity also needs to be generalized.

FLEXOELECTRICITY

Flexoelectricity is a mechanoelectric phenomenon known from liquid crystal physics. In the case of a membrane, flexoelectricity refers to the curvature-dependent membrane polarization [1,2],

$$P_S = f(c_1 + c_2), \tag{1}$$

where P_S is the electric polarization per unit area in C/m, c_1 and c_2 are the two principal radii of membrane curvature in m^{-1}, and f is the area flexoelectric coefficient in C (coulombs), typically a few units of electron charge. This effect is manifested in membrane structures where an overall curvature is related to splay deformation of the membrane molecules (lipids, proteins) (cf. [2]). Across a polarized membrane, a potential difference develops according to the Helmholtz equation. Its curvature-dependent part is

$$\Delta U = P_S/\varepsilon_0 = (f/\varepsilon_0)(c_1 + c_2). \tag{2}$$

By measuring simultaneously this potential difference and the curvature, one can determine the flexoelectric coefficient of a given membrane.

A general expression for the flexoelectric coefficient [7] expresses it as an integral of the curvature derivative of the distribution of membrane polarization along the membrane normal ($c_+ = c_1 + c_2$ is the total membrane curvature). A Taylor expansion of the total polarization with respect to total curvature is

$$P_S = \int P(z,c_+)dz = \int \left[P^0(z) + \frac{\partial P}{\partial c_+}\bigg|_0 c_+ + \cdots \right] dz$$
$$= P_S^0 + \left[\int \frac{\partial P(z,c_+)}{\partial c_+}\bigg|_0 dz \right] c_+ + \cdots,$$

i.e., in view of definition (1),

$$f = \int_{-\infty}^{\infty} \frac{dP(z,c_+)}{dc_+}\bigg|_0 dz. \tag{3}$$

Now, consider a membrane (Fig. 1) with an average surface charge density of the outer (inner) monolayer of $\sigma^o(\sigma^i)$, equivalent to a mean degree of ionization per lipid head of β^o (β^i, the sign of β being determined by the sign of σ). $\sigma^i = \beta^i e/A_0^i$, e is the proton charge, A_0^i is the area per lipid head in the *flat* state of the outer monolayer. For convenience, all surface charges are lumped in σ^o. The two membrane surfaces can be bathed by different ionic strength electrolytes, with corresponding Debye lengths λ_D^i (λ_D^o). Let the

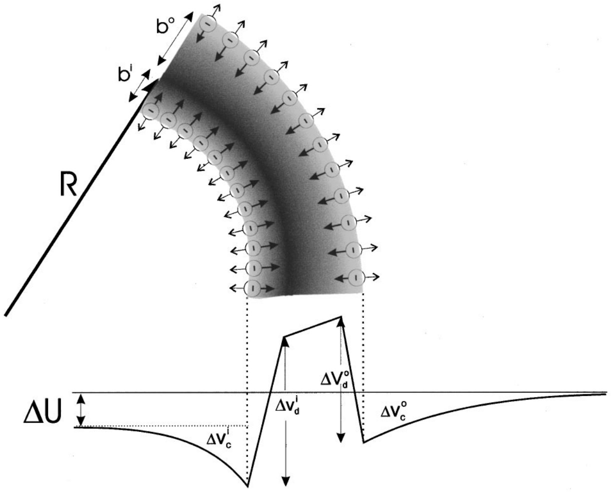

FIG. 1. Cartoon of a curved asymmetric bilayer membrane and its electric potential distribution. Double layer (i.e., charge, $\Delta V_c^{o,i}$) and dipole ($\Delta V_d^{o,i}$) components of the surface potential of each monolayer are indicated. ΔU is flexoelectric voltage, which is proportional to the membrane curvature ($2/R$) (see text) b^o and b^i are the distances between the mechanically neutral surface of the bilayer and the corresponding aqueous interface.

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mean normal component of permanent dipole moment per lipid (polarized water hydration shell included) be μ^o (μ^i) (dipoles are regarded as positive if pointing inward toward the hydrophobic core). Finally, assume that both monolayers have different thickness b^o (b^i) (strictly speaking, b^o and b^i are the distances between the neutral mechanical surface of the *bilayer* and the corresponding membrane interface, Fig. 1). In Fig. 1 the double layer (i.e., charge, $\Delta V_c^{o,i}$) and dipole ($\Delta V_d^{o,i}$) components of the surface potential are indicated. In general, both potentials can be lumped into one: $\Delta V^{o,i} = \Delta V_c^{o,i} + \Delta V_d^{o,i}$. The surface (Volta) potential ΔV is an experimentally measurable quantity in monolayers on water/air or, more representative for half a membrane, on a water/oil interface.

Dipolar contribution

Assume for convenience that polarizations are δ functions peaked at the corresponding interfaces [i.e., for dipoles $P(z,c_+) = P_S^i(c_+)\,\delta(z+b^i) - P_S^o(c_+)\,\delta(z-b^o)$, $P_S^{o,i} = \mu^{o,i}/A_0^{o,i}$, where the direction outward from the center of curvature is regarded as positive]. Observe that $dP_S^{o,i}/dc_+ = (dP_S^{o,i}/dA^{o,i})(dA^{o,i}/dc_+)$. Finally, apply a first-order relationship for parallel surfaces [8], expressing the fact that the outer (inner) interface is expanded (compressed) upon curving the bilayer

$$A^{o,i} = A_0^{o,i}(1 \pm b^{o,i} c_+). \tag{4}$$

The result for the dipolar flexocoefficient in the case of fixed stoichiometry of each interface, i.e., blocked lipid exchange (which in elastic terms means that the membrane bends as a whole around its common neutral surface [2]) will then be

$$f^{\mathrm{DB}} = \left(\frac{\mu^i}{A_0^i} - \left.\frac{d\mu^i}{dA^i}\right|_0 \right) b^i + \left(\frac{\mu^o}{A_0^o} - \left.\frac{d\mu^o}{dA^o}\right|_0 \right) b^o, \tag{5}$$

where the derivatives are taken with respect to the *flat* membrane state.

Another form of f^{DB} can be obtained as follows: Express the potential difference across the membrane via the algebraic sum of the two surface potentials. Furthermore, expand these in a series with respect to the total curvature. Finally, apply the relations $d\Delta V^{o,i}/dc_+ = (d\Delta V^{o,i}/dA)(dA/dc_+)$, Eqs. (4) and (2),

$$f^{\mathrm{DB}} = -\varepsilon_0 \left(A_0^i b^i \frac{d\Delta V_d^i}{dA^i} + A_0^o b^o \frac{d\Delta V_d^o}{dA^o} \right). \tag{6}$$

Equations (5) and (6) are identical in view of the Helmholtz equation $\Delta V_d^{o,i} = P_S^{o,i}/\varepsilon_0 = \mu^{o,i}/\varepsilon_0 A_0^{o,i}$ (ΔV_d is the surface potential of a dipolar lipid monolayer, an experimentally measurable quantity). Equation (6) may also be generalized for other components of the surface potential, where each area derivative is to be multiplied by the corresponding distance to the neutral surface.

In the special case $A_0^i = A_0^o$, $b^i = b^o = d/2$, where d is the bilayer thickness, the dipolar flexocoefficient is conveniently expressed via the mean value of both surface potential derivatives (which can be evaluated from lipid monolayers with matching composition, at their isoelectric points)

$$f^{\mathrm{DB}} = -\varepsilon_0 A_0 \frac{d}{2} \left(\frac{d\Delta V_d^i}{dA} + \frac{d\Delta V_d^o}{dA} \right). \tag{7}$$

To complete the dipolar case, we should note that for free lipid exchange, the corresponding expression is obtained from Eq. (5) by replacing $b^{o,i}$ with $\delta_H^{o,i}$, the corresponding distance from an interface to the neutral surface of its own monolayer [2]. As expected from loss of the constraint, the value of the flexocoefficient is less than that from blocked exchange.

Charge contribution

Calculations of the various charge contributions [2] make a distinction between detailed electric neutrality (a fixed stoichiometry of blocked exchange where each half-space remains neutral upon curving the membrane) and global electric neutrality (unblocked exchange where the two half-spaces become oppositely charged).

Under the detailed electric neutrality condition (in the limit of a linearized Poisson-Boltzmann equation) the charge contribution is easily obtained from Eq. (5) by replacing the permanent dipoles $\mu^{o,i}$ by the effective diffuse double layer dipoles $\beta^{o,i} e \lambda_D^{o,i}/\varepsilon_w$, where $\varepsilon_w \cong 30$ is the dielectric constant of water in the double layer and $\lambda_D^{o,i} = \sqrt{\varepsilon_w \varepsilon_0 kT/2e^2 n^{o,i}}$ are the Debye screening lengths of the outer (inner) 1:1 electrolytes. With lipids having negative surface charges, double layer dipoles are antiparallel to the permanent ones, which is reflected in the negative sign of the mean partial charge per lipid β. Recalling that double layer dipoles are centered at distances $\lambda_D^{o,i}/2$ further away from the corresponding interfaces, we get from Eq. (5),

$$\begin{aligned} f^{\mathrm{CB}} = {} & \frac{e}{\varepsilon_w} \left(\frac{\beta^i}{A_0^i} - \left.\frac{d\beta^i}{dA^i}\right|_0 \right) \lambda_D^i \left(b^i + \frac{\lambda_D^i}{2} \right) \\ & + \frac{e}{\varepsilon_w} \left(\frac{\beta^o}{A_0^o} - \left.\frac{d\beta^o}{dA^o}\right|_0 \right) \lambda_D^o \left(b^o + \frac{\lambda_D^o}{2} \right). \end{aligned} \tag{8}$$

On the other hand, proceeding as per Eq. (6) we get

$$f^{\mathrm{CB}} = -\varepsilon_0 \left[A^i \frac{dV_c^i}{dA^i} \left(b^i + \frac{\lambda_D^i}{2} \right) + A^0 \frac{dV_c^0}{dA^0} \left(b^o + \frac{\lambda_D^o}{2} \right) \right]. \tag{9}$$

This time representation (9) is more general than Eq. (8), since it also holds in the nonlinear case (see below). For lipids that are both charged and dipolar, it is convenient to express the sum of two contributions to the flexocoefficient via the sum of the two components to the surface potential. For the special case used for Eq. (7) and for Debye lengths sufficiently shorter than a half the membrane thickness we can write a simple expression,

$$f^{\mathrm{CB}} + f^{\mathrm{DB}} = -\varepsilon_0 A_0 \frac{d}{2} \left(\frac{d\Delta V^i}{dA^i} + \frac{d\Delta V^o}{dA^o} \right). \tag{9'}$$

Let us now discuss the global neutrality case. The assumption implies that by curving the membrane, the effective displacement of electric charges takes place across the whole membrane thickness (e.g., an excess of negative charges over the expanded outer surface and deficiency over the compressed inner surface, equivalent to an excess positive charge). This will result in a large electric dipole situated in a low polar medium (ε_L), and, consequently, the curvature-induced voltage difference will be large. The result is again obtainable from Eq. (5), this time by replacing the permanent dipole moments $\mu^{i,o}$ with the effective dipole moments of the surface charges with respect to the bilayer's neutral surface: $-\beta^{i,o}eb^{i,o}/\varepsilon_L$. We shall denote the corresponding flexoelectric coefficient by f^M (monopole) in order to distinguish it from the case of detailed electric neutrality,

$$f^{\mathrm{MB}}=-\frac{e}{\varepsilon_L}\left(\frac{\beta^i}{A_0^i}-\left.\frac{d\beta^i}{dA^i}\right|_0\right)(b^i)^2-\frac{e}{\varepsilon_L}\left(\frac{\beta^o}{A_0^o}-\left.\frac{d\beta^o}{dA^o}\right|_0\right)(b^o)^2. \tag{10}$$

The component of the flexocoefficient due to free charges is titratable from the bathing electrolyte, while the dipolar one is not. In the case of high surface charge/low ionic strength, the surface potential of a charged monolayer is given by a solution of the nonlinear Poisson-Boltzmann equation

$$\Delta V_c=\frac{2kT}{e}\,\mathrm{arcsin}\,h\left(\frac{\sigma}{2\sqrt{n\varepsilon_w\varepsilon_0 2kT}}\right). \tag{11}$$

Recalling that $\sigma^{i,o}=\beta^{i,o}e/A_0^{i,o}$, we obtain

$$\frac{d\Delta V_c}{dA}=\frac{e\lambda_D}{\varepsilon_w\varepsilon_0}\,\frac{1}{\sqrt{1+(\sigma/2\sqrt{n\varepsilon_w\varepsilon_0 2kT})^2}}\,\frac{d}{dA}\left(\frac{\beta}{A}\right). \tag{12}$$

Then, in the limit of small σ one can recover from Eq. (9) the result (8). On the other hand, for high σ one gets

$$\frac{d\Delta V_c}{dA}=\frac{2kT}{e}\,\frac{A}{\beta}\,\frac{d}{dA}\left(\frac{\beta}{A}\right), \tag{13}$$

and consequently

$$f^{\mathrm{CB}}=-\frac{2kT\varepsilon_0}{e}\left[\frac{A^i}{\beta^i}\,\frac{d}{dA^i}\left(\frac{\beta^i}{A^i}\right)\left(b^i+\frac{\lambda_D^i}{2}\right)+\frac{A^o}{\beta^o}\,\frac{d}{dA^o}\left(\frac{\beta^o}{A^o}\right)\left(b^o+\frac{\lambda_D^o}{2}\right)\right]. \tag{14}$$

In this limit the flexocoefficient is only weakly sensitive to the surface charge density, since $(I/\beta)(d\beta/dA)=d\ln\beta/dA$. Apart from that, if one (or both) of the Debye lengths diverge because $n^{i,o}\rightarrow 0$, so will the flexocoefficient.

CURVATURE ELASTICITY

For a flaccid membrane (with zero tension) the voltage-induced membrane curvature (converse flexo effect) is obtained from the balance of elastic and flexoelectric torques [2]

$$K(c_1+c_2)=fE, \tag{15}$$

where E is the transmembrane field and K is the curvature elasticity modulus. This equation calls for an expression of K for asymmetric membranes.

In general, curvature elasticity theory is similar to flexoelectricity, in the sense that various elastic moduli can be expressed via integrals across the membrane of the lateral stress distribution $s(z,c_+)$ and its derivatives. In particular [9],

$$K=\int(z-z_0)\,\frac{\partial s}{\partial c_+}\,dz, \tag{16}$$

where z_0 is the position of the neutral surface. Since the hydrophobic core contribution to K is more or less the same regardless the membrane asymmetry [2], we shall discuss the electric contribution (charge or dipole) in more details.

It was shown earlier [10] that the electric contribution to the curvature elastic modulus of a monolayer is given by

$$K^m=\varepsilon\varepsilon_0(\Delta V)^2\left(\frac{p}{3}+b+\frac{b^2}{p}\right). \tag{17}$$

where ΔV is either the dipole or charge (Volta) potential, p is either the length of dipole or the Debye length, ε is either ε_L or ε_w, and b is the distance between the innermost surface of the charges and the dividing surface (the mechanically neutral surface in our case).

Since contributions from both monolayers are additive, one can write for a bilayer of dipolar lipids

$$K^{\mathrm{DB}}=\varepsilon_L\varepsilon_0(\Delta V_d^i)^2\left(\frac{p^i}{3}+b^i+\frac{b^{i^2}}{p^i}\right)+\varepsilon_L\varepsilon_0(\Delta V_d^o)^2\times\left(\frac{p^o}{3}+b^o+\frac{b^{o^2}}{p^o}\right). \tag{18}$$

For a bilayer of charged lipids, respectively,

$$K^{\mathrm{CB}}=\varepsilon_w\varepsilon_0(\Delta V_c^i)^2\left(\frac{\lambda_D^i}{3}+b^i+\frac{b^{i^2}}{\lambda_D^i}\right)+\varepsilon_w\varepsilon_0(\Delta V_c^o)^2\times\left(\frac{\lambda_D^o}{3}+b^o+\frac{b^{o^2}}{\lambda_D^o}\right). \tag{19}$$

In case of both dipolar and charged components of the surface potential, the sum of Eqs. (18) and (19) determines the electric component of the bending stiffness. Again, the charged site is titratable from the bathing electrolyte, while the dipolar one is not.

DISCUSSION

Figure 2 demonstrates the dependence of the total flexocoefficient on the charge and ionic strength asymmetry. For convenience, it is expressed in terms of the direct flexoeffect,

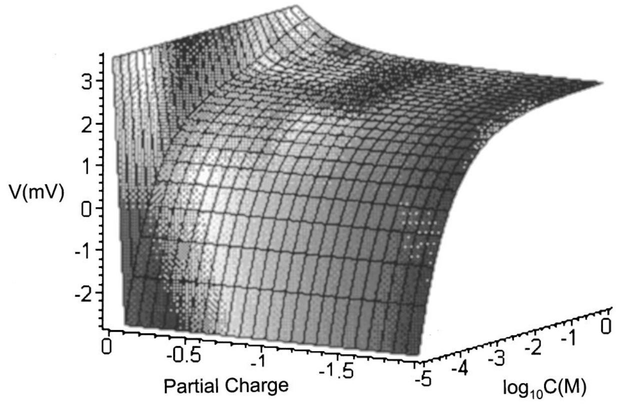

FIG. 2. The flexoelectric voltage (Eq. (2), in mV) across an asymmetric membrane patch with a curvature radius $R=1\ \mu$m. $f=f^{\mathrm{DB}}+f^{\mathrm{CB}}$ is employed, with f^{DB} from Eq. (5) and f^{CB} from Eq. (9). Parameters used: $b^i=4$, $b^o=6$ nm, $A_0^i=0.6$, $A_0^o=0.8\,\mathrm{nm}^2$, $\mu^i=1.5\times10^{-30}$, $\mu^o=1\times10^{-30}$ Cm, $d\mu^{i,o}/dA=d\beta^{i,0}/dA=0$, $\varepsilon_w=30$, $\varepsilon_L=2$; partial charge per head inside was kept fixed at $\beta^i=-0.5$, while outside it was varied from -2.0 to 0; the ionic strength inside was kept fixed at 0.1 M 1:1 electrolyte, while outside it was varied from 10 μM to 1 M.

i.e., the voltage generated across a membrane with 1 μm radius of curvature (as typically of a membrane patch in a pipette). Figure 3 shows the curvature elastic modulus under the same charge conditions, while Fig. 4 refers to the ratio f/K, i.e., to the voltage-induced membrane curvature (converse flexoeffect) according to Eq. (15). We can see that by decreasing the ionic strength of one bath, the original positive sign of the dipole flexocoefficient is reversed, in correspondence to the data in Ref. [5]. An analysis of the flexoelectric motility of membranes measured by AFM is given in the Appendix. The expected nanometer displacements of an indented membrane surface, Eq. (A4), are presented in Fig. 5.

In conclusion, an asymmetric flexoelectric membrane displays a rich variety of direct and converse flexoeffects. These properties may have important implications for understanding the high-frequency motility observed in outer hair cells of the cochlea [3,13].

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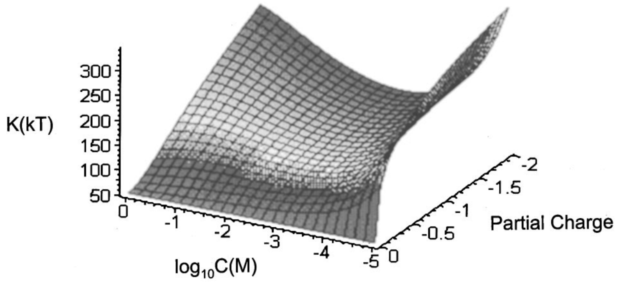

FIG. 3. Total curvature elasticity $K=K^{\mathrm{DB}}+K^{\mathrm{CB}}$ [Eq. (18) + Eq. (19), in kT units] with $p^i=p^o=0.5\,\mathrm{nm}$ and all other parameters as per Fig. 2.

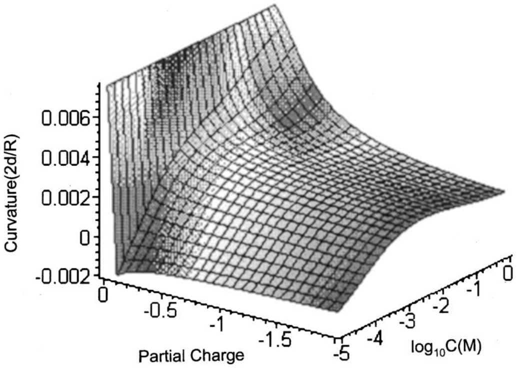

FIG. 4. Electrically induced curvature of a membrane with no constraints. [From Eq. (15) multiplied by d, $K(c_1+c_2)d=f\ Ed$ or, $2d/R=fU/K$]. The ordinate is in dimensionless units of $2d/R$ and $U=E\ d=100$ mV. The ratio f/K is from Figs. 2 and 3 and the other parameters as per Fig. 2.

APPENDIX

Assume that the indentation of an osmotically balanced cell by the AFM tip produces a shape like a logarithmic funnel [11,12] (where at each point $c_1+c_2=0$), and the tip is covered by a spherical cap of radius R and height h (Fig. 6). Producing a logarithmic funnel shape does not cost any curvature energy (apart from the rim matching a finite funnel portion indentation (H) depth to the planar membrane [11]; this term is exponentially small with the indentation H), and it is flexoelectrically insensitive. The only part of the membrane that produces an elastic restoring force is then the spherical segment closing the tip of the funnel; its total energy is

$$W=\frac{1}{2}K\left(\frac{2}{R}\right)^2 2\pi Rh. \tag{A1}$$

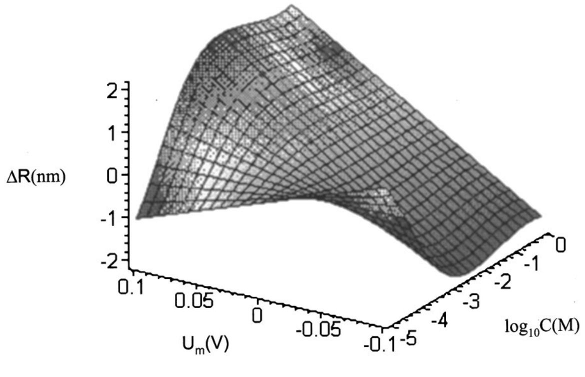

FIG. 5. Displacement [ΔR, Eq. (A4)] of a membrane indented with an AFM tip having a curvature radius $R=100$ nm, as a function of membrane voltage (-100–100 mV) and ionic strength. The outer partial charge per lipid was fixed at $\beta^i=-1$; other parameters as above.

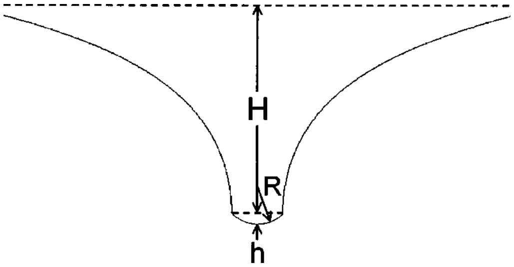

FIG. 6. Cross section of an indented membrane with a spherical cap on a rod approximating an AFM tip.

Taking the derivative with respect to h, one gets the force resultant that opposes an increase of h $(h \ll H)$,

$$q = \frac{dW}{dh} = \frac{4\pi K}{R}. \tag{A2}$$

By increasing the tip load from 0 to q the curvature radius will thus gradually decrease from ∞ down to the AFM tip radius R_0 (ca. 50 nm). For $K = 1 \times 10^{-18}$ J this requires a load of $\sim$250 pN.

Furthermore, in the presence of a transmembrane field $E = U_m/d$, the electrical enthalpy contains (to first order), the flexoelectric term $-2fE/R$ which will modify the radius with respect to the zero-field case. The energy balance now reads

$$q(h+\Delta h) = \left[\frac{K}{2}\left(\frac{2}{R+\Delta R}\right)^2 - \frac{2fE}{R+\Delta R}\right] 2\pi(R+\Delta R) \times (h+\Delta h), \tag{A3}$$

where $\Delta h = \Delta R$ and R is the curvature in the absence of field. For weak fields $(4\pi fE \ll q)$ this yields (in view of (A2)

$$\frac{\Delta R}{R} = \frac{4\pi fE}{q} = \frac{R}{d}\frac{f}{K}U_m. \tag{A4}$$

This predicts that the electromotility response decreases with the mean applied force because the membrane bending becomes energetically costly at small radii. This property may help to distinguish effects due to membrane torque from that due to membrane tension.

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