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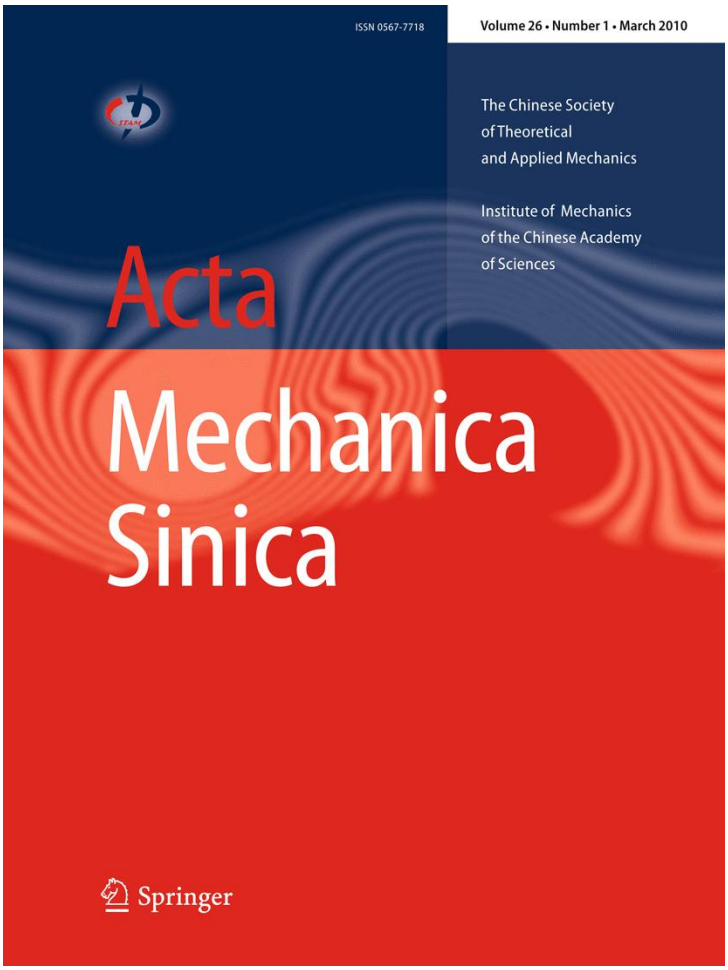

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RESEARCH PAPER

Morphological stability analysis of vesicles with mechanical–electrical coupling effects

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Abstract Using a recently established liquid crystal model for vesicles, we present a theoretical method to analyze the morphological stability of liquid crystal vesicles in an electric field. The coupled mechanical–electrical effects associated with elastic bending, osmotic pressure, surface tension, Maxwell pressure, as well as flexoelectric and dielectric properties of the membrane are taken into account. The first and second variations of the free energy are derived in a compact form by virtue of the surface variational principle. The former leads to the shape equation of a vesicle embedded in an electric field, and the latter allows us to examine the stability of a given vesicle morphology. As an illustrative example, we analyze the stability of a spherical vesicle under a uniform electric field. This study is helpful for understanding and revealing the morphological evolution mechanisms of vesicles in electric fields and some associated phenomena of cells.

Keywords Vesicle · Cell membrane · Stability · Mechanical–electrical coupling

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1 Introduction

Living cells can adapt to variations in their micro-environment by continuously altering their shapes and internal structures. The shape transitions of cell membranes under electric fields are crucial for a wide range of critical physiological functions (e.g., directed migration, adhesion, and differentiation) and manipulation techniques (e.g., electroporation, electrofusion, electrophoresis, electro-deformation and rotation) of cells [1–8]. As a result, considerable attention has been paid in the past decades to the critical conditions and physical mechanisms underlying these phenomena and to the processes of biomembranes associated with electric effects. Full understanding of these issues will be not only of theoretical but also clinical importance for various biomedical engineering applications (e.g., wound healing, cell repair of bones, muscles and nerves) and other micro- and nano-biotechniques (e.g., separation, hybridization, delivery of molecules or drugs into cells).

Vesicles have been widely utilized as a representative model of cells, both in experimental observations and theoretical analysis. Recent experiments have demonstrated that vesicles in an electric field can undergo shape transitions among sphere, prolate, and oblate, depending on the conductivity of the surrounding medium and the electric field frequency [9–11]. For example, Riske and Dimova [11] observed that when subjected to a strong electric pulse a vesicle assume have a disc-, square-, or tube-like shape or other unusual morphologies. Rey [12] derived a membrane shape equation that includes tension, bending, pressure, and flexoelectric effects. However, there is still a lack of investigation on the critical stability conditions of vesicles or cell membranes that can predict such shape transitions.

Theoretically, the stability condition of a vesicle in an electric field can be derived from the electromechanical collapse

model, electrohydrodynamic instability model, or wave instability model [13]. Mitov et al. [14] theoretically investigated the influence of an alternating electric field on the shape and thermal fluctuations of giant vesicles. Their experiments showed that at high frequencies vesicles deform into oblate ellipsoids with the symmetry axis parallel to the electric field, while at low frequencies they deform into prolate ones. Accounting for the dielectric anisotropy of phospholipid vesicles, Peterlin et al. [15] analyzed the prolate-to-oblate transition of vesicle shape with the increase in the electric field frequency. However, these established models have certain restrictions in practical application due to various assumptions. In particular, they cannot interpret some important experimental phenomena [10,11]. Very recently, Gao et al. [16] proposed a more generic liquid crystal model for vesicles under an arbitrary electric field. Their study revealed that although the flexoelectric energy is only a small portion of the total free energy, it plays a significant role in the morphology transition of vesicles. On the basis of this model, they developed an energetic phase field method to simulate vesicle shape transitions under an electric field [17]. The formation of several typical morphologies observed in experiments was theoretically interpreted by analyzing the vanishing first variation of the free energy functional. However, they did not address the morphological stability of a vesicle exposed to an electric field.

To predict the stability behavior of a vesicle shape, the second variation of the energy functional must be considered. Ou-Yang et al. [18] derived a second variation formulation of the Helfrich free energy to investigate the stability of a spherical bilayer under mechanical loading. Using a two-dimensional model, Rosso et al. [19] computed the second variation of the energy functional of a lipid vesicle adhering to a rigid curved substrate, and studied the efficiency of adhesion of a tubular vesicle with an extroverted bump or an introverted groove. Brinkmann et al. [20] gave a stability criterion for the wetting morphology of a droplet on a solid substrate by deriving the second variation of the free energy of the system. Most of these previous investigations are based on the classical theory of differential geometry, which is quite complex and case-dependent. Recently, Tu and Ou-Yang [21,22] developed a more general and canonical geometric framework to deal with such problems. Their surface variational approach is based on the exterior differential form in modern differential geometry theory [23]. One of its advantages is that the derivations of shape equations and second variations are general, without the restriction of a specific coordinate system.

The present work aims to study the morphological stability of vesicles in an electric field. The stability analysis is based on a newly developed electromechanical liquid crystal model of vesicles [16] combined with the theoretical framework of Tu and Ou-Yang [21,22]. We account for such effects as elastic bending, osmotic pressure, surface tension, flexoelectricity, dielectricity, and Maxwell electric pressure. Both the shape equation and stability conditions of vesicles are obtained by way of the liquid crystal model. The stability of a spherical vesicle under a uniform electric field is considered as an illustrative example and analyzed in detail.

2 Free energy

According to the recently established electromechanical model by Gao et al. [16], the Helmholtz free energy of a vesicle is written as

$$F_0 = F_{\rm bm} + F_{\rm fm} + F_{\rm dm} + F_{\rm de} + \lambda_1(V - V_0) + \lambda_2(A - A_0), \tag{1}$$

where $F_{\rm bm}$ is the elastic energy due to bending, $F_{\rm fm}$ the flexoelectric energy of the membrane, $F_{\rm dm}$ the dielectric energy of the membrane, and $F_{\rm de}$ the dielectric energy of the electrolyte. The two Lagrange multipliers λ_1 and λ_2 correspond to the osmotic pressure Δp and the surface energy γ, respectively. V and A are the volume and surface area of the evolutionary vesicle, with V_0 and A_0 being their pre-specified or initial values, respectively.

The elastic bending energy is given by [24]

$$F_{\rm bm} = \int_\Gamma \left[\frac{1}{2}k(2H + c_0)^2 + k_{\rm k}K\right] {\rm d}A, \tag{2}$$

where Γ denotes the surface of the vesicle, k and $k_{\rm k}$ are elastic constants, H the mean curvature, K the Gauss curvature, and c_0 the spontaneous curvature.

The flexoelectric energy $F_{\rm fm}$ associated with the electroelastic coupling effects of the lipid membrane is written as [25]

$$F_{\rm fm} = -\int_\Gamma \int_0^d \boldsymbol{P}^{\rm fm} \cdot \boldsymbol{E} {\rm d}r {\rm d}A, \tag{3}$$

where d is the membrane thickness and $\boldsymbol{E}$ is the electric field intensity. The polarization $\boldsymbol{P}^{\rm fm}$ caused by bending is expressed as

$$\boldsymbol{P}^{\rm fm} = -e_{11}(\nabla \cdot \boldsymbol{n})\boldsymbol{n}, \tag{4}$$

where e_{11} is the flexoelectric coefficient and $\boldsymbol{n}$ is the outward unit normal vector to the membrane surface.

The dielectric energy reads

$$F_{\rm dm} = -\frac{1}{2}\int_\Gamma \int_0^d \boldsymbol{D}^{\rm e} \cdot \boldsymbol{E} {\rm d}r {\rm d}A, \tag{5}$$

where the electric displacement $\boldsymbol{D}^{\rm e}$ can be decomposed as

$$\boldsymbol{D}^{\rm e} = (\varepsilon_\perp + \varepsilon_\parallel)E_n\boldsymbol{n} + \varepsilon_\perp E_u \boldsymbol{Y}_{,u} + \varepsilon_\perp E_v \boldsymbol{Y}_{,v}, \tag{6}$$

where $\varepsilon_{\parallel}$ and $\varepsilon_{\perp}$ denote the anisotropic dielectric constants parallel and normal to the $\boldsymbol{n}$ direction [25], respectively, E_u and E_v are the intensities of the electric field in the $\boldsymbol{Y}_{,u}$ and $\boldsymbol{Y}_{,v}$ directions. The parameterized function $\boldsymbol{Y} = \boldsymbol{Y}(u, v)$ describes the membrane surface shape in terms of two variables u and v, as shown in Fig. 1, which may have different forms in different coordinates. The normal vector $\boldsymbol{n}$ and the two tangential vectors $\boldsymbol{Y}_{,u}$ and $\boldsymbol{Y}_{,v}$ form a local orthogonal coordinate system. We also denote $g_{uu} = \boldsymbol{Y}_{,u} \cdot \boldsymbol{Y}_{,u}$ and $g_{vv} = \boldsymbol{Y}_{,v} \cdot \boldsymbol{Y}_{,v}$.

The dielectric energy of an electrolyte is expressed as

$$F_{\mathrm{de}} = -\int_{\Omega} \frac{1}{2}\varepsilon_{\mathrm{r}}\left|\nabla\phi\right|^2 \mathrm{d}V, \tag{7}$$

where ε_{r} denotes the dielectric constant of the electrolyte and ϕ the electric potential.

3 Variation of free energy

3.1 Surface variational method

The free energy defined in Eq. (1), which involves both surface and volume integrals, is rewritten in the following general form [21]

$$F = \int_{M} \Psi(2H, K)\mathrm{d}A + \lambda_1 \int_{V} \mathrm{d}V, \tag{8}$$

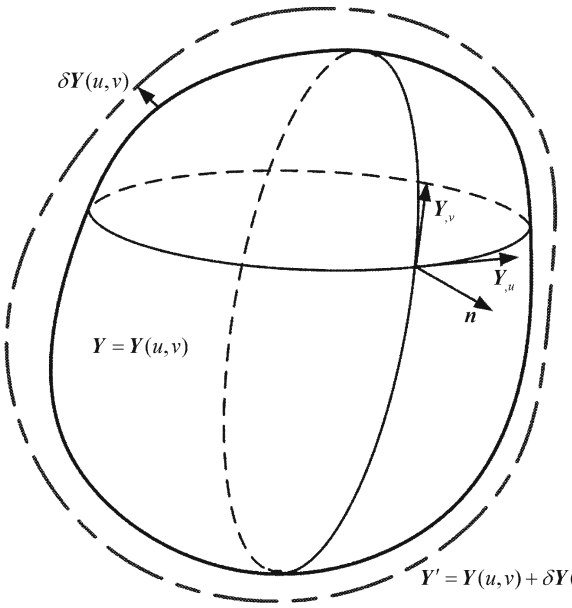

Fig. 1 Schematic of a vesicle described by a parameterized shape function $\boldsymbol{Y} = \boldsymbol{Y}(u, v)$ subjected to a small disturbance $\delta Y(u, v)\boldsymbol{n}$

where M stands for the vesicle surface. The first surface variation of the free energy of Eq. (8) can be derived as

$$\begin{aligned}\delta F = \int_{M} \Bigg\{ & \frac{\partial \Psi}{\partial (2H)}\left[2(2H^2 - K)\Omega_3 \mathrm{d}A + \mathrm{d} * \mathrm{d}\Omega_3\right] \\ & + \frac{\partial \Psi}{\partial K}(2KH\Omega_3 \mathrm{d}A + \mathrm{d}\tilde{*}\tilde{\mathrm{d}}\Omega_3) \\ & - (2H)\Psi \mathrm{d}A + \lambda_1 \Omega_3 \mathrm{d}A \Bigg\}. \end{aligned} \tag{9}$$

Here, $\Omega_3 = \delta Y(u, v)$ denotes a small variation of the surface in the normal direction, as illustrated in Fig. 1, $\mathrm{d} * \mathrm{d}\Omega_3 = \nabla^2\Omega_3 \mathrm{d}A$, $\mathrm{d}\tilde{*}\tilde{\mathrm{d}}\Omega_3 = \nabla \cdot \tilde{\nabla}\Omega_3 \mathrm{d}A$, with d being the exterior differential operator, $*$ the Hodge star, and $\tilde{*}$ the Gauss mapping of the Hodge star. Moreover, the second variation is

$$\begin{aligned}\delta^2 F = \int_{M} \Bigg\{ & \frac{\partial^2 \Psi}{\partial (2H)^2}\left[2(2H^2 - K)\Omega_3 \mathrm{d}A + \mathrm{d} * \mathrm{d}\Omega_3\right] \\ & + \frac{\partial \Psi}{\partial K} K\Omega_3 \mathrm{d}A + \frac{\partial^2 \Psi}{\partial K \partial (2H)}(2KH\Omega_3 \mathrm{d}A + \mathrm{d}\tilde{*}\tilde{\mathrm{d}}\Omega_3) \\ & - \left[2H\frac{\partial \Psi}{\partial (2H)} + \Psi\right]\Omega_3 \mathrm{d}A \Bigg\} \delta_3(2H) \\ & + \Bigg\{ -2\frac{\partial \Psi}{\partial (2H)}\Omega_3 \mathrm{d}A + \frac{\partial^2 \Psi}{\partial K \partial (2H)} \\ & \times \left[2(2H^2 - K)\Omega_3 \mathrm{d}A + \mathrm{d} * \mathrm{d}\Omega_3\right] \\ & + \frac{\partial^2 \Psi}{\partial K^2}(2KH\Omega_3 \mathrm{d}A + \mathrm{d}\tilde{*}\tilde{\mathrm{d}}\Omega_3) \Bigg\} \delta_3(K) \\ & + \Bigg[2\frac{\partial \Psi}{\partial (2H)}(2H^2 - K) + 2\frac{\partial \Psi}{\partial K} KH \\ & + (-2H\Psi + \lambda_1) \Bigg] \Omega_3 \delta_3(\mathrm{d}A) \\ & + \frac{\partial \Psi}{\partial (2H)}\delta_3(\mathrm{d} * \mathrm{d}\Omega_3) + \frac{\partial \Psi}{\partial K}\delta_3(\mathrm{d}\tilde{*}\tilde{\mathrm{d}}\Omega_3), \end{aligned} \tag{10}$$

where

$$\begin{aligned} & \delta_3(2H) = 2(2H^2 - K)\Omega_3 + \nabla^2\Omega_3, \\ & \delta_3(K) = 2KH\Omega_3 + \nabla \cdot \tilde{\nabla}\Omega_3, \\ & \delta_3(\mathrm{d} * \mathrm{d}\Omega_3) = [\nabla(2H\Omega_3) \cdot \nabla\Omega_3 + 2H\Omega_3\nabla^2\Omega_3 \\ & \qquad - 2\nabla\Omega_3 \cdot \tilde{\nabla}\Omega_3 - 2\Omega_3\nabla \cdot \tilde{\nabla}\Omega_3]\mathrm{d}A, \\ & \delta_3(\mathrm{d}\tilde{*}\tilde{\mathrm{d}}\Omega_3) = [\nabla(8H^2\Omega_3 + \nabla^2\Omega_3) \cdot \nabla\Omega_3 \\ & \qquad + (8H^2\Omega_3 + \nabla^2\Omega_3)\nabla^2\Omega_3 - \nabla(4H\Omega_3) \cdot \tilde{\nabla}\Omega_3 \\ & \qquad - 4H\Omega_3\nabla \cdot \tilde{\nabla}\Omega_3 - \nabla(2H\Omega_3) \cdot \tilde{\nabla}\Omega_3 \\ & \qquad - 2H\Omega_3\nabla \cdot \tilde{\nabla}\Omega_3]\mathrm{d}A, \\ & \nabla = g^{\alpha\beta}\boldsymbol{Y}_{,\alpha}\frac{\partial}{\partial \beta}, \quad \tilde{\nabla} = K\bar{L}_{\alpha\beta}\boldsymbol{g}_{\alpha}\frac{\partial}{\partial \beta}, \\ & \nabla^2 = \frac{1}{\sqrt{g}}\frac{\partial}{\partial \alpha}\left(\sqrt{g}g^{\alpha\beta}\frac{\partial}{\partial \beta}\right), \\ & (g^{\alpha\beta}) = (g_{\alpha\beta})^{-1}, \quad (\alpha, \beta) = (u, v). \end{aligned}$$

Equations (9) and (10) simplify the differential geometry approaches in the derivation of the first and second variations of the free energy with surface effects, and hence the formulations in Refs. [18–20] can be easily derived by using the present scheme. In what follows, we will give the first and second variations of a vesicle in an electric field.

3.2 First and second variations

Substituting Eq. (1) into Eq. (9), the first variation of a vesicle with coupled mechanical–electrical effects is derived as

$$\begin{aligned}\delta F_0 = \oint [&k(2H+c_0)(2H^2-c_0H-2K)+\lambda_1-2\lambda_2 H\\ &+f_\mathrm{i}-f_\mathrm{o}+U_{\mathrm{int\,Em}}H+2e_{11}E_{\mathrm{int\,Emn}}K]\Omega_3 \mathrm{d}A\\ &+\oint (2kH+kc_0-e_{11}E_{\mathrm{int\,Emn}})\mathrm{d}*\mathrm{d}\Omega_3. \end{aligned} \tag{11}$$

From the condition $\delta F_0 = 0$, the Euler-Lagrange equation for the shape for a vesicle under mechanical and electric fields is obtained as

$$\begin{aligned}&k(2H+c_0)(2H^2-c_0H-2K)+\lambda_1-2\lambda_2 H\\ &+\nabla^2(2kH+kc_0)+f_\mathrm{i}-f_\mathrm{o}+U_{\mathrm{int\,Em}}H\\ &+2e_{11}E_{\mathrm{int\,Emn}}K-e_{11}\nabla^2 E_{\mathrm{int\,Emn}}=0, \end{aligned} \tag{12}$$

where

$$U_{\mathrm{int\,Em}}=\int_0^d \left[(\varepsilon_\perp+\varepsilon_\parallel)E_n^2+\varepsilon_\perp g_{uu}E_u^2+\varepsilon_\perp g_{vv}E_v^2\right]\mathrm{d}r,$$

$$E_{\mathrm{int\,Emn}}=\int_0^d E_n \mathrm{d}r=\Delta\phi_n,\quad f_\mathrm{i}=\varepsilon_\mathrm{i}\left(E_{in}^2-\frac{1}{2}\boldsymbol{E}_\mathrm{i}^2\right),$$

$$f_\mathrm{o}=\varepsilon_\mathrm{o}\left(E_{on}^2-\frac{1}{2}\boldsymbol{E}_\mathrm{o}^2\right),$$

ε_i and ε_o are the dielectric constants of the inner and outer electrolytes, $\boldsymbol{E}_\mathrm{i}$ and $\boldsymbol{E}_\mathrm{o}$ are the electric field intensities in the inner and outer electrolytes, $E_{in}=\boldsymbol{E}_\mathrm{i}\cdot\boldsymbol{n}$ and $E_{on}=\boldsymbol{E}_\mathrm{o}\cdot\boldsymbol{n}$ are the normal components of the electric field on the inner and outer surfaces, respectively.

Substituting Eq. (1) into Eq. (10) and eliminating λ_2 by using the shape equation (12), the second variation is obtained as

$$\begin{aligned}\delta^2 F_0=\oint \{&[2k(-c_0K^2-8H^3K+8H^5)+2e_{11}E_{\mathrm{int\,Emn}}K^2\\ &+(f_\mathrm{i}-f_\mathrm{o}+\lambda_1+\nabla^2 G)K\\ &-2(f_\mathrm{i}-f_\mathrm{o}+\lambda_1)H^2]\Omega_3^2/H\\ &+[(-2KH+c_0K+12H^3+2c_0H^2)k\\ &-e_{11}E_{\mathrm{int\,Emn}}(K+2H^2)\\ &-\frac{1}{2}(f_\mathrm{i}-f_\mathrm{o}+\lambda_1+\nabla^2 G)]\Omega_3\nabla^2\Omega_3/H\\ &-4G\Omega_3\nabla\cdot\tilde{\nabla}\Omega_3+k(\nabla^2\Omega_3)^2+G\nabla(2H\Omega_3)\cdot\nabla\Omega_3\\ &-2G\nabla\Omega_3\cdot\tilde{\nabla}\Omega_3\}\mathrm{d}A, \end{aligned} \tag{13}$$

where $G=2kH+kc_0-e_{11}E_{\mathrm{int\,Emn}}$. The stability condition of a vesicle with a specific morphology under an arbitrary electric field requires that $\delta^2 F_0>0$. In what follows, a spherical vesicle under a uniform steady electric field is considered as an example to show the application of the proposed formulation to stability analysis.

4 Stability of a spherical vesicle in an electric field

4.1 First and second variations

For a spherical vesicle surrounded by a steady electric field (Fig. 2), one has

$$\nabla\cdot(\sigma\nabla\phi)=0, \tag{14}$$

where the conductivity σ takes the value σ_o in the outer electrolyte, σ_i in the inner electrolyte, and σ_m in the membrane, respectively. The electric boundary conditions are

$$\begin{aligned}&\phi_\mathrm{m}=\phi_\mathrm{o},\quad \sigma_\mathrm{m}\frac{\partial\phi_\mathrm{m}}{\partial n}=\sigma_\mathrm{o}\frac{\partial\phi_\mathrm{o}}{\partial n},\quad \text{on } \Gamma_{\mathrm{om}},\\ &\phi_\mathrm{m}=\phi_\mathrm{i},\quad \sigma_\mathrm{m}\frac{\partial\phi_\mathrm{m}}{\partial n}=\sigma_\mathrm{i}\frac{\partial\phi_\mathrm{i}}{\partial n},\quad \text{on } \Gamma_{\mathrm{im}},\\ &\phi_\mathrm{o}|_{r\to\infty}=-E_0 z,\\ &\phi_\mathrm{o}|_{r\to 0}=0, \end{aligned} \tag{15}$$

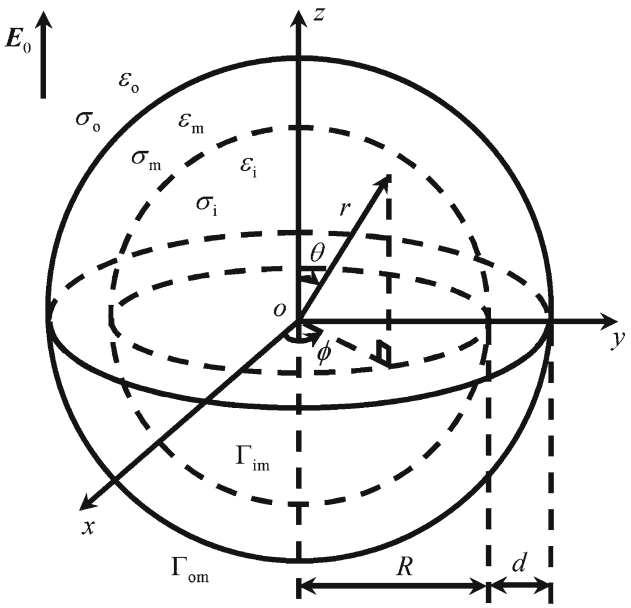

Fig. 2 An initially spherical vesicle subjected to a uniform electric field in the z direction

where Γ_{om} and Γ_{im} denote the outer and inner boundaries of the membrane, respectively. Moreover, R is the radius of the vesicle, and d the thickness of the membrane. $\varepsilon_{\parallel} = 0$ and $\varepsilon_{\perp} = \varepsilon_m$ are the dielectric constants of the vesicle membrane parallel and normal to the $\boldsymbol{n}$ direction, and $\varepsilon_r = \varepsilon_o$ and $\varepsilon_r = \varepsilon_i$ are the dielectric constants of the outer and inner electrolytes, respectively.

The electric potential solutions of the problem have the form [26]

$$\begin{aligned}\phi_o^R &= \left(-E_0 r + \frac{B_o}{r^2}\right)\cos\theta,\\ \phi_i^R &= A_i r\cos\theta,\\ \phi_m^R &= \left(A_m r + \frac{B_m}{r^2}\right)\cos\theta.\end{aligned} \tag{16}$$

Thus we can derive the following analytical solutions:

$$\begin{aligned}U_{\text{int m}}^R = \varepsilon_m\Bigg[&dA_m^2 - \frac{(3\cos^2\theta-1)(d+2R))dB_mA_m}{R^2(R+d)^2}\\ &+\frac{1}{5}\frac{d(3\cos^2\theta+1)(d^4+10R^2d^2+10R^3d+5R^4+5Rd^3)B_m^2}{R^5(R+d)^5}\Bigg],\end{aligned} \tag{17}$$

$$f_i^R = \frac{1}{2}\varepsilon_i A_i^2(2\cos^2\theta-1), \tag{18}$$

$$\begin{aligned}f_o^R = \varepsilon_o\Bigg[&\left(\frac{1}{2}E_0^2 + \frac{2B_oE_0}{(R+d)^3} + \frac{2B_o^2}{(R+d)^6}\right)\cos^2\theta\\ &+\left(-\frac{1}{2}E_0^2 + \frac{B_oE_0}{(R+d)^3} - \frac{1}{2}\frac{E_o^2}{(R+d)^6}\right)\sin^2\theta\Bigg],\end{aligned} \tag{19}$$

$$E_{\text{int Emn}}^R = d\left[-A_m + \frac{(2R+d)B_m}{R^2(R+d)^2}\right]\cos\theta, \tag{20}$$

where

$$\begin{aligned}A_i &= -9\sigma_o\sigma_m E_0/\sigma_D,\\ A_m &= -3\sigma_o E_0(\sigma_i+2\sigma_m)/\sigma_D,\\ B_m &= 3\sigma_o E_0(\sigma_i-\sigma_m)R^3/\sigma_D,\\ B_o &= -[(R+d)^3(\sigma_i+2\sigma_m)(\sigma_o-\sigma_m)\\ &\quad + R^3(\sigma_o+2\sigma_m)(\sigma_m-\sigma_i)]E_0/\sigma_D,\\ \sigma_D &= (2\sigma_o+\sigma_m)(2\sigma_m+\sigma_i)\\ &\quad + 2(\sigma_m-\sigma_o)(\sigma_i-\sigma_m)R^3/(R+d)^3.\end{aligned} \tag{21}$$

For a spherical configuration, we also have the following relations:

$$\begin{aligned}&H = -\frac{1}{R},\quad K = \frac{1}{R^2},\\ &\tilde{\nabla} = \bar{\nabla} = -\frac{1}{R}\nabla,\quad \nabla\cdot\tilde{\nabla} = -\frac{1}{R}\nabla^2,\\ &\nabla(2H\Omega_3)\cdot\nabla\Omega_3 = -\frac{2}{R}\nabla\Omega_3\cdot\nabla\Omega_3,\\ &\nabla\Omega_3\cdot\tilde{\nabla}\Omega_3 = -\frac{1}{R}\nabla\Omega_3\cdot\nabla\Omega_3,\\ &\nabla^2 = \frac{1}{R^2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial}{\partial\theta}\right) + \frac{1}{R^2\sin^2\theta}\frac{\partial^2}{\partial^2\varphi}.\end{aligned} \tag{22}$$

Substituting Eqs. (17)–(20) and (22) into Eq. (12) and letting $d \to 0$, the shape equation of the spherical vesicle is arrived at [16]

$$\begin{aligned}&\Delta p + \frac{2\lambda_2}{R} + \frac{kc_0^2}{R} - \frac{2kc_0}{R^2} + \frac{6e_{11}E_0}{R}\cos\theta\\ &-\Bigg\{\Bigg[-\frac{9\sigma_o^2\cos^2\theta}{(2\sigma_o+\sigma_i)^2} + \frac{9}{2}\frac{\sigma_o^2}{(2\sigma_o+\sigma_i)^2}\Bigg]\varepsilon_i\\ &+\Bigg[\frac{9}{2}\frac{(\sigma_i^2+\sigma_o^2)}{(2\sigma_o+\sigma_i)^2}\cos^2\theta - \frac{9}{2}\frac{\sigma_o^2}{(2\sigma_o+\sigma_i)^2}\Bigg]\varepsilon_o\\ &+\frac{9}{4}\frac{\varepsilon_m R}{d}\cos^2\theta\Bigg\}E_0^2 = 0.\end{aligned} \tag{23}$$

Similarly, substituting Eqs. (17)–(20) and (22) into Eq. (13) leads to the second variation as

$$\begin{aligned}\delta^2F_0 = \oint[&(C_{11}\cos^2\theta + C_{12}\cos\theta + C_{13})\Omega_3^2\\ &+(C_{21}\cos^2\theta + C_{22})\Omega_3\nabla^2\Omega_3 + C_{31}(\nabla^2\Omega_3)^2]\mathrm{d}A,\end{aligned} \tag{24}$$

where

$$\begin{aligned}C_{11} &= \varepsilon_i\frac{A_i^2}{R} - \varepsilon_o\left[\frac{E_0^2}{R} + \frac{B_oE_0}{R(R+d)^3} + \frac{5}{2}\frac{B_o^2}{R(R+d)^6}\right],\\ C_{12} &= \frac{4e_{11}d(A_mR^4 + 2A_mR^3d - 2B_mR - B_md + R^2A_md^2)}{R^5(R+d)^2},\\ C_{13} &= \frac{1}{2}\frac{\varepsilon_oE_0^2}{R} - \frac{B_o\varepsilon_oE_0}{R(R+d)^3} + \frac{\lambda_1}{R} + \frac{2c_0k}{R^3}\\ &\quad - \frac{1}{2}\frac{A_i^2\varepsilon_i}{R} + \frac{1}{2}\frac{\varepsilon_oB_o^2}{R(R+d)^6},\\ C_{21} &= -\frac{1}{2}R\varepsilon_oE_0^2 - \frac{1}{2}\frac{RB_o\varepsilon_oE_0}{(R+d)^3} + \frac{1}{2}A_i^2R\varepsilon_i - \frac{5}{4}\frac{R\varepsilon_oB_o^2}{(R+d)^6},\\ C_{22} &= \frac{1}{4}R\varepsilon_oE_0^2 - \frac{1}{2}\frac{RB_o\varepsilon_oE_0}{(R+d)^3} + \frac{R\lambda_1}{2} + \frac{(c_0R+2)k}{R^2}\\ &\quad - \frac{1}{4}A_i^2R\varepsilon_i + \frac{1}{4}\frac{R\varepsilon_oB_o^2}{(R+d)^6},\\ C_{31} &= k.\end{aligned}$$

4.2 Stability criterion for a spherical vesicle under a uniform steady electric field

We have already derived the shape equation for a spherical vesicle from the variational principle of free energy, as given in Eq. (23). Firstly, the spherical morphology exists in a uniform electric field only when Eq. (23) has a nontrivial solution independent of the angular coordinate θ. Clearly, the existence of such a solution requires that the material parameters fulfill the condition:

$$e_{11} = 0,\quad \varepsilon_m = \frac{2d(\varepsilon_o\sigma_i^2 + \varepsilon_o\sigma_o^2 - 2\sigma_o^2\varepsilon_i)}{(\sigma_i+2\sigma_o)^2R}. \tag{25}$$

Since $\varepsilon_m \geq 0$, the following condition must also be met:

$$\varepsilon_o(\sigma_i^2 + \sigma_o^2) - 2\varepsilon_i\sigma_o^2 \geq 0. \tag{26}$$

Secondly, a stable morphology requires that the second variation of the free energy functional with respect to any small disturbance must be positive. For an axisymmetric configuration, a small disturbance to the surface Ω_3 can be expanded into a Legendre polynomial as

$$\Omega_3 = \sum_{l=1}^{\infty} g_l P_l(\cos\theta), \tag{27}$$

where $P_l(x)$ is the lth-order term of the Legendre polynomial, and g_l is the corresponding coefficient. Then we have

$$\nabla^2\Omega_3 = -\sum_{l=1}^{\infty} \frac{l(l+1)}{R^2} P_l(\cos\theta) g_l. \tag{28}$$

Applying the recursive relation of Legendre polynomials:

$$P_{n+1}(x) = \frac{(2n+1)}{n+1} x P_n(x) - \frac{n}{n+1} P_{n-1}(x), \tag{29}$$

the following relation holds

$$\begin{aligned}\Omega_3 \cos\theta &= \sum_{l=1}^{\infty} \left[\frac{l+1}{2l+1} P_{l+1}(\cos\theta) \right. \\ &\quad \left. + \frac{l}{2l+1} P_{l-1}(\cos\theta) \right] g_l \\ &= \sum_{l=0}^{\infty} \bar{g}_l P_l(\cos\theta),\end{aligned} \tag{30}$$

where $\bar{g}_l = \frac{l}{2l-1} g_{l-1} + \frac{l+1}{2l+3} g_{l+1}$, $g_{-1} = 0$, and $g_0 = 0$. Using Eqs. (27)–(30), in conjunction with the orthogonal integral property of Legendre polynomials, and letting $d \to 0$ and $e_{11} = 0$ according to Eq. (25), the second variation of Eq. (24) is derived as

$$\delta^2 F_0 = \sum_{l=0}^{\infty} (A g_l^2 + B \bar{g}_l^2), \tag{31}$$

where

$$\begin{aligned}A = \frac{(l+2)(l-1)\pi}{(2l+1)} &\left[\frac{9R\sigma_o^2(\varepsilon_i - \varepsilon_o)E_0^2}{(\sigma_i + 2\sigma_o)^2} \right. \\ &\left. + \frac{2(2kl^2 + 2lk - R^3\lambda_1 - 2kRc_0)}{R^2} \right],\end{aligned} \tag{32}$$

$$B = \frac{9\pi R(l+2)(l-1)(\varepsilon_o\sigma_i^2 + \varepsilon_o\sigma_o^2 - 2\sigma_o^2\varepsilon_i)E_0^2}{(2l+1)(\sigma_i + 2\sigma_o)^2}. \tag{33}$$

In the absence of an electric field (i.e., $E_0 = 0$), the stability condition can be obtained by setting $A > 0$ as

$$\lambda_1 < \lambda_{1c} = \frac{2k}{R^3}(6 - Rc_0), \tag{34}$$

where λ_{1c} is the critical pressure for the stable vesicle. If condition (34) is fulfilled, $\delta^2 F_0$ will be always positive for any g_l; otherwise, $\delta^2 F_0$ can be negative for some values of g_l. This result is identical with that of Ou-Yang et al. [18], who did not consider electric effects.

If $E_0 \neq 0$, satisfaction of $\delta^2 F_0 > 0$ requires that $A g_l^2 + B\bar{g}_l^2 > 0$ for all l. The above inequality requires that $A > 0$ and $B > 0$. Thus, the critical electric field should be

$$E_{0c}^2 = \frac{2}{9} \frac{(\sigma_i + 2\sigma_o)^2(R^3\lambda_1 + 2kRc_0 - 12k)}{R^3\sigma_o^2(\varepsilon_i - \varepsilon_o)}. \tag{35}$$

Thus the stability conditions are written as

$$E_0^2 > \frac{2}{9} \frac{(\sigma_i + 2\sigma_o)^2(R^3\lambda_1 + 2kRc_0 - 12k)}{R^3\sigma_o^2(\varepsilon_i - \varepsilon_o)}, \quad \text{if } \varepsilon_i > \varepsilon_o; \tag{36}$$

$$E_0^2 < \frac{2}{9} \frac{(\sigma_i + 2\sigma_o)^2(R^3\lambda_1 + 2kRc_0 - 12k)}{R^3\sigma_o^2(\varepsilon_i - \varepsilon_o)}, \quad \text{if } \varepsilon_i < \varepsilon_o; \tag{37}$$

$$\lambda_1 < \frac{2k}{R^3}(6 - Rc_0), \quad \text{if } \varepsilon_i = \varepsilon_o. \tag{38}$$

For an originally stationary spherical vesicle subjected to a uniform electric field (Fig. 2), the condition in Eq. (36) can be automatically fulfilled by considering (34). This means that when $\varepsilon_i \geq \varepsilon_o$ the spherical vesicle is always stable except when the electric field is so strong as to break the integrity of the vesicle (e.g., electroporation). When $\varepsilon_i < \varepsilon_o$, on the other hand, the vesicle can retain its spherical shape only when the electric field is lower than the threshold value:

$$E_{0c} = \sqrt{\frac{2}{9} \frac{(\sigma_i + 2\sigma_o)^2(R^3\lambda_1 + 2kRc_0 - 12k)}{R^3\sigma_o^2(\varepsilon_i - \varepsilon_o)}}. \tag{39}$$

If the electric field is higher than E_{0c}, the spherical vesicle will deform into an oblate, a prolate or another shape, as has been observed in experiments and simulations [10,16,17].

The above analysis shows that although a spherical vesicle subjected to a uniform electric field generally evolves into a prolate or oblate shape, it can also be stable under certain conditions. The existence of a stable spherical vesicle in a uniform electric field requires simultaneous satisfaction of Eq. (25) and anyone of Eqs. (36)–(38). If Eq. (25) and $\varepsilon_o - \varepsilon_i \leq 0$ are satisfied, the spherical shape is always stable except when the electric field is higher than the critical breaking electric field E_{th}, which corresponds to onset of electroporation. If Eq. (25) and $\varepsilon_o - \varepsilon_i > 0$ hold, the spherical shape will be stable only when $|E_0| < E_{0c}$.

For clearer illustration, we take the following representative values measured from vesicles [11,17]: $\sigma_i = 6 \times 10^{-4}$ Sm^{-1}, $\sigma_o = 1.2 \times 10^{-2}$ Sm^{-1}, $c_0 = -1.36 \times 10^5$ m, $k = 10^{19}$ J, $\lambda_1 = \frac{1}{2}\lambda_{1c}$, and $E_{th} = 45000$ V/m. Then the stability condition of a spherical vesicle under a uniform electric field is plotted in Fig. 3 for three different values of

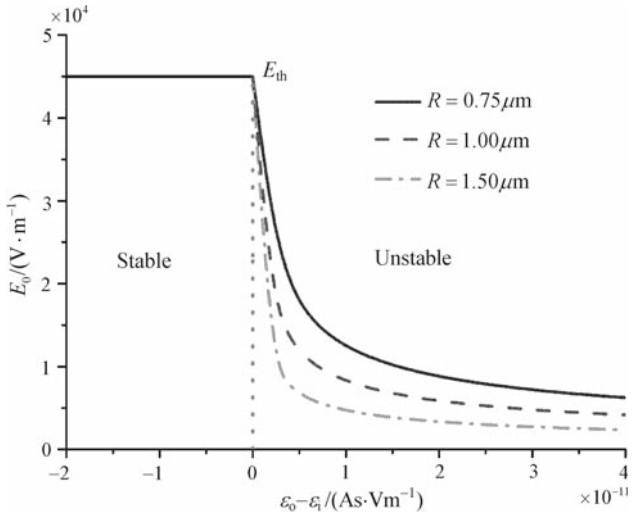

Fig. 3 Stability condition of a spherical vesicle under a uniform electric field

radius R. It is seen that the critical electric field E_{0c} decreases with increasing R. In other words, a smaller spherical vesicle is more stable than a bigger one. The above discussion also shows that the dielectric properties of the inner and outer electrolytes significantly affect the deformation and stability behavior of vesicles under the action of an electric field.

5 Conclusions

The first and second variations of the free energy functional of a vesicle subjected to mechanical and electrical loadings have been derived in a general and compact form. The formulation is based on a liquid crystal model of vesicles accounting for the mechanical–electrical coupling nature of biomembranes. The first variation of the free energy functional determines the existence of the specific morphology of a vesicle, and the second variation allows us to judge whether a possible shape will be stable or not. As a representative example, the stability condition of a spherical vesicle under a uniform electric field has been discussed in detail. Its stability depends not only on such mechanical and geometric parameters as electric bending constant, osmotic pressure, spontaneous curvature and size of the vesicle but also on some electric parameters, e.g., the dielectric coefficient of the membrane and the conductivities of the inner and outer electrolytes.

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