Electrostatic Stretching of a Charged Vesicle

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Electrostatic Stretching of a Charged Vesicle

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We present a closed-form solution of electrostatic potential self-induced by a uniformly charged micro/nanovesicle and the corresponding elastic deformation of the vesicle membrane due to Maxwell stress. At equilibrium, the electrostatic force induced on both sides of the membrane is balanced by the elastic force of the stretched membrane. We develop differential and integral solutions of the coupled Poisson−Boltzmann system for a spherical vesicle and demonstrate that the integral solution is relatively flexible in formulating asymmetric configurations. Analytical results are formulated in terms of vesicle size, Debye length, and the surface charge density. The membrane stretching is characterized by the dimensionless group that defines the relative strength of the net electric force with respect to the membrane stiffness. We found that the self-induced electrostatic interaction will lead to a pre-stressed membrane although the small displacement is often negligible compared with the vesicle size. Quantitative analysis also reveals that the electric force can assist the vesicle in recovering its opening pore.

1. Introduction

Synthetic vesicles or liposomes have long been recognized as unique tools in studying membrane biophysics and molecular self-assembly mechanisms. Because of the overwhelming complexity involved in analyzing a real biological membrane and its components, researchers often use a self-assembled lipid bilayer as a model membrane or as an isolated platform to investigate the basic properties of embedded functional proteins. The advantages in utilizing the intercalated proteins and the bilayer membrane with a small dielectric constant have opened up a new way to design membrane-based biosensors and microelectronics.[1] In principle, lipid molecules can be self-assembled into a variety of structures such as a micelle, a planar lipid bilayer, a tubule, and a vesicle. It is also known that the molecular composition and the self-assembly process can be manipulated to control the chemical, mechanical, and transport properties of the membrane. There exists a broad range of scientific interests that are related to giant or small vesicles, and we recommend a concise article[2] and the literature cited therein for an introductory overview.

Electrostatic and electrokinetic properties in an aqueous environment are closely related to many fundamental issues regarding the formation of synthetic and natural membranes. Evidence of lipid swelling and vesicle formation on an electrode has shown that spontaneous vesicle formation is affected by the charge property of lipid molecules, and the formation event can be triggered by an imposed external electric field.[3] Because the electrostatic interaction indeed affects the shape and size of vesicle aggregates,[4] it is necessary to evaluate the electrostatic free energy from the distribution of the electric potential and the interaction with the imposed external electric field. For a liposome-based drug delivery system, although the physical origins are not fully understood at both molecular and continuum levels, experiments have shown that the surface charge indeed affects the liposome−cell binding kinetics, the membrane fusion process, and the uptake of therapeutic agents by the targeted cells.[5] The complexity involved in a liquid electrolyte is further illustrated by many studies such as regulation and saturation of the adsorbed particles on the vesicle membrane due to the rearrangement of the surrounding ionic species,[6] mapping the attractive and repulsive regimes of closely approached planar surfaces,[7] and the equilibrium conformation of a charged colloid wrapped with an oppositely charged membrane.[8] Additional examples include ion-induced lipid vesicle fusion,[9] complex dynamic and kinetic problems occurring in the adhesion and reorganization zone of the membrane,[10] and direct force measurement of a moving membrane modulated by electric polarization.[11]

Early studies of a spherical charged membrane made of ionic amphiphilic molecules were contributed by Mitchell, Evans, and Ninham.[12−14] Mitchell and Ninham provided analytical expressions based on electric double-layer theory to evaluate electrostatic curvature free energy and thus the interfacial tension of a micelle.[12] The oil-like central core of a micelle made of hydrophobic tails has a very low dielectric constant compared with that of the aqueous phase, thus the nonlinear Poisson−Boltzmann equation was applied to the aqueous phase only. The theoretical development of ion binding due to specific ion interaction and physical adsorption has advanced the thermodynamic theory of micellization of an ionic micelle. The electrostatic free energy of a

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charged membrane has also merged with the theoretical development of the bending energy of bilayer fluid membranes based on Helfrich's quadratic approximation.[15] By comparing with the quadratic form, the phenomenological electric contribution to the bending rigidity, the elastic modulus of Gaussian curvature, and the spontaneous curvature were explicitly connected to the Debye screening length and the surface charge density under the framework of the linear[16] and nonlinear[17] Poisson−Boltzmann equations. Helfrich's membrane theory was further explored by investigating the undulation effect of planar ionic lamellar phases.[18,19] In light of these contributions, an analytical approximation of the electrical field across the charged lipid bilayer was proposed by Yuet and Blankschtein,[20] whose analysis has explicitly treated the finite hydrophobic layer made of surfactant tails by mathematically coupling the electric potential inside the layer with the adjacent aqueous compartment and the surrounding electrolyte. A similar system was numerically solved by incorporating a parametrized isotherm to account for the specific ion adsorption at the inner and outer boundaries of the charged membrane.[21] It should be noted that although many fruitful results of physicochemical properties of a charged membrane were built on the classical Debye theory and the Poisson−Boltzmann equation, the extension of these results to biological relevance is not straightforward because the classical double-layer theory is applicable only for a symmetric electrolyte with the charged ionic headgroup that is much smaller than the screening length. This limiting condition is by no means close to a protein solution such as a physiological medium. The validity of double-layer interactions in an asymmetric electrolyte was first discussed by Mitchell and Ninham.[22] The screened Columbic interaction for an asymmetric z:1 electrolyte was characterized by an asymptotic form of the screening length that corrects the classical Debye length. The result, including the multivalent counterion effect, was experimentally verified using a surface force apparatus for a highly asymmetric electrolyte solution in the presence of charged proteins.[23,24]

Indeed, for applications that require solving the potential field from the Poisson−Boltzmann equation, the linear results are limited by the practical conditions and can be used only as reference for very dilute symmetric electrolytes and boundaries with low zeta potentials. However, in analyzing the electric potential across the vesicle membrane, a thin-layer approximation is required in solving the nonlinear Poisson−Boltzmann equation, regardless of whether electrical coupling across the membrane is involved. The perturbation-based analysis can be performed only if the screening length is much smaller than the vesicle's characteristic dimension so that the vanishing electric potential and electric field can be used as far-field boundary conditions for both internal and external domains. If the electric potential at the center point of the vesicle does not vanish, then the analytical approximation for the nonlinear system is unlikely to be successful. After surveying the related literature, what surprised us is that the exact linear solution does not exist for the mutually coupled interior and exterior potentials induced by a charged vesicle. This motivates us to develop a simple differential and integral solution for the electric fields on both sides of the
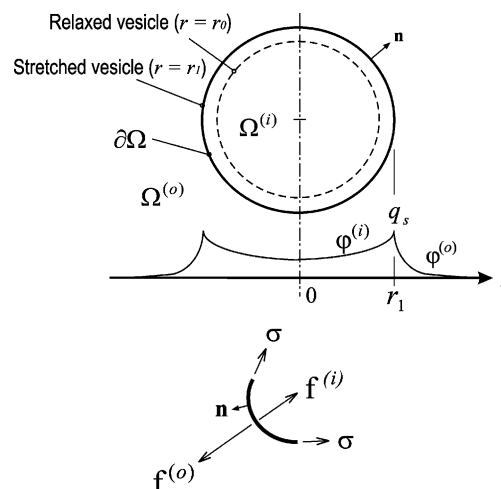

Figure 1. Schematic view of a charged spherical vesicle in unstressed ($r = r_0$) and stretched ($r = r_1$) states. Definition of the interfacial position and the physical domains in solving the coupled electric potentials $\varphi^{(i)}$ and $\varphi^{(o)}$ as functions of radial distance r. The force balance diagram shows a differential segment of the stretched membrane with tension force σ.

membrane. The differential solution is limited to a spherical configuration with uniform surface charge density, whereas the integral solution is applicable in resolving the case with nonuniform surface charge and an asymmetric configuration. Intuitively, we know that a charged vesicle is in a pre-stretched state where the membrane elastic force is balanced by the electrostatic repulsive force. Pre-stretching is known as one of the mechanisms that can induce membrane surface tension,[25] but the phenomenon has not been explicitly quantified. From a modeling point of view, understanding electrostatic stretching is also important in advancing numerical modeling in characterizing the dynamic behaviors of vesicles in a physical medium involving molecular binding, adhesion, and the triggering of a charge-related internalization process. As a starting point, in this article we emphasize the resolving of coupled electric potentials across a thin, charged membrane. The exact solutions for the linear and equilibrium cases are derived by following the classical double-layer theory.

2. Scaling and Formulations

Figure 1 shows an arrangement of the spherical domain with the origin affixed to the center of the vesicle and the surface normal **n** pointing outward along the radial direction. To facilitate the analytical solution, we make the following assumptions: (i) The typical thickness of a lipid membrane h is ~5 nm, which is much smaller than the vesicle size with radius $r \approx 100$ nm to $20\,\mu$m. Therefore, the lipid bilayer membrane is mathematically treated as an infinitesimally thin interface, and the charged molecules are lumped into an apparent surface charge density (the amount of electric charge per unit area) at the thin interface where the potential gradient across the hydrophobic region of the bilayer membrane is neglected. (ii) The average distance between charge molecules is relatively small compared with the double-layer screening length, so the membrane potential distribution is smeared and its electrical properties are ideally represented by a uniformly distributed surface charge density q_s. (iii) The unstressed (undeformed) vesicle has radius r_0 that is equivalent to the radius if the charged molecules are removed or the electric fields are completely screened. (iv) Lipid membranes are rarely permeable to ionic species, but we assume

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that the aqueous solution and ionic species are free to move across the membrane when the lipid molecules self-assemble so that the vesicle can reach a thermodynamic equilibrium state with radius $r \approx r_1$. (v) The symmetric electrolyte solutions inside and outside the vesicle are chemically identical except for the local ionic species concentration that follows the Boltzmann law. (vi) The bending energy of the lipid bilayer does not play a role in the equilibrium system provided $(h/r_0)^2 \ll 1$,[26] thermal fluctuations are negligible, and the self-induced electric forces $\mathbf{f}^{(i)}$ and $\mathbf{f}^{(o)}$ acting on either side of the membrane are solely balanced by the surface tension σ raised by the elastic stretching of the membrane. (vii) There exists no lipid exchange between the bilayer membrane and ionic solution, and the membrane is slightly compressible such that the stretching effect follows the linear elastic theory. (viii) Specific ion interactions, adsorption, and charge regulation are neglected in this model. We present mathematical formulations in dimensionless forms except for those specifically indicated for demonstrating the results. All symbols for the dimensionless parameters and many explicit representation of independent variables are removed to simplify the notation.

2.1. Electric Potentials. The electrostatic force acting on the charged membrane is evaluated at an equilibrium state where the vesicle size is represented by $r = r_1$ (Figure 1). For cases with relatively low zeta potentials, the ionic atmosphere and the electric potential fields at the inner $\Omega^{(i)}$ and outer $\Omega^{(o)}$ domains, induced by the charge density q_s at the interface $\partial\Omega$, are governed by the linearized Poisson–Boltzmann equation.[27] The governing equations for the potential fields in the physical domains separated by the membrane can be written as

$$\nabla^2 \varphi^{(i)}(r) = \lambda^2 \varphi^{(i)}(r) \text{ for } 0 \leq r \leq 1 \tag{1}$$

$$\nabla^2 \varphi^{(o)}(r) = \lambda^2 \varphi^{(o)}(r) \text{ for } 1 \leq r < \infty \tag{2}$$

where $\varphi^{(i)}(r)$ and $\varphi^{(o)}(r)$, the corresponding electric potential fields inside and outside the vesicle, respectively, are functions of r only in the spherically symmetric case (Figure 1). The system is nondimensionalized by scaling the length, potential field, and surface charge density through

$$\text{length} \sim r_1 \qquad \varphi \sim \frac{k_B T}{e} \qquad q_s \sim \frac{\epsilon\epsilon_0 k_B T}{e r_1} \tag{3}$$

where $k_B T$ is the baseline thermal energy, e is the electronic charge, ϵ is the relative permittivity of the electrolyte, and ϵ_0 is the permittivity of a vacuum. The second-order system is complemented by four dimensionless boundary conditions

$$\nabla\varphi^{(i)} = 0 \text{ at } r = 0 \tag{4}$$

$$\varphi^{(o)} \to 0 \text{ as } r \to \infty \tag{5}$$

$$\varphi^{(i)} = \varphi^{(o)} \text{ at } r = 1 \tag{6}$$

$$\mathbf{n}\cdot(\nabla\varphi^{(i)} - \nabla\varphi^{(o)}) = q_s \text{ at } r = 1 \tag{7}$$

where the surface normal $\mathbf{n}$ is equivalent to the radial unit vector $\hat{\mathbf{e}}_r$ so that $\mathbf{n}\cdot\nabla = \partial/\partial n = \partial/\partial r$. Equation 4 at the center point is a symmetric condition. Equation 5 describes the vanishing potential field at infinity. Equations 6 and 7 define the continuity of the potential fields and the jump condition for the normal displacement fields. Equations 1 and 2 are coupled through boundary conditions (eqs 6 and 7), with the given net surface charge density q_s for the thin interface located at $r = 1$. The

dimensionless group λ in the governing system is defined by

$$\lambda = \kappa r_1 \qquad \kappa = \left(\frac{2e^2 n^\infty}{\epsilon\epsilon_0 k_B T}\right)^{1/2} \tag{8}$$

where κ^{-1} is the Debye length related to the bulk ionic strength n^∞. The governing system is complete when the uniform surface charge density q_s is specified.

2.2. Maxwell Stress and Osmotic Pressure. The self-induced electric force can be formulated in terms of the surface traction of the Maxwell stress tensor, expressed in the general form

$$\mathbf{f} = \left(\mathbf{EE} - \frac{1}{2}\mathbf{E}\cdot\mathbf{E}\boldsymbol{\delta}\right)\cdot\mathbf{n} \tag{9}$$

where $\boldsymbol{\delta}$ is the Kronecker delta and the local electric field is defined by $\mathbf{E} = -\nabla\varphi$. For a spherical vesicle with uniform surface charge, the net electric force density reduces to a simple form

$$\mathbf{\Pi} = \mathbf{f}^{(o)} + \mathbf{f}^{(i)} = \frac{1}{2}(E^{(o)^2} - E^{(i)^2})\hat{\mathbf{e}}_r \text{ at } r = 1 \tag{10}$$

where the strengths of the electric fields $E^{(i)} = |\mathbf{E}^{(i)}|$ and $E^{(o)} = |\mathbf{E}^{(o)}|$ acting on both sides of the membrane are function of r only. Once the electric potentials are found, the net electric force density $\Pi = |\mathbf{\Pi}|$ can be calculated with eq 10. The characteristic scales for the electrostatic field and the electric force density are defined by

$$\mathbf{E} \sim \frac{k_B T}{e r_1} \qquad \mathbf{f} \text{ and } \mathbf{\Pi} \sim \frac{\epsilon\epsilon_0 (k_B T/e)^2}{r_1^2} \tag{11}$$

It is important to clarify that the net electric force density Π is equivalent to the so-called disjoining pressure[28−30] caused by the overlapping electric double layers in a confined space. Disjoining pressure is defined as a summation of the Maxwell electric stress and the osmotic pressure raised by the nonuniform ion concentration, which is redistributed by the electrostatic potential based on Boltzmann's law. In our system, the electrochemical equilibrium prevails, thus the distribution of the electrostatic potential and the local ion concentration are continuous across the infinitely thin membrane. Therefore, the disjoining pressure induced by the confined space is equal to the Maxwell stress $\mathbf{f}^{(i)}(r^- = 1)$ plus the osmotic pressure $\mathbf{f}_{os}^{(i)}(r^- = 1)$ with the vanishing external effect from the opposite side of the membrane. This is equivalent to adding electric force densities $\mathbf{f}^{(i)}(r^- = 1)$ and $\mathbf{f}^{(o)}(r^+ = 1)$ from both sides of the membrane. In other words, at the interfacial position, $\mathbf{f}_{os}^{(o)}(r^+ = 1)$ balances $\mathbf{f}^{(o)}(r^+ = 1)$ for the former case and $\mathbf{f}_{os}^{(i)}(r^- = 1)$ for the latter one. To calculate the net repulsive force, one can either cancel the osmotic pressure on both sides of the membrane or consider that the interaction of the force field and the osmotic effect from the external side are vanishing everywhere. This argument is transparent in Parsegian's analysis for the electrostatic interaction of parallel planar layers.[7]

2.3. Membrane Elasticity. The linear elastic behavior of a stretched membrane can be treated as a limiting case of a shell

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(28) Derjaguin, B. V.; Landau, L. D. *Acta Phys. Chem.* **1941**, *14*, 633.

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(30) Israelachvili, J. N. *Intermolecular and Surface Forces*; Academic Press: San Diego, CA, 1991.

material with an infinitesimally thin shell thickness. Following Landau's derivation,[26] the small deformation of a thin-shell hollow sphere driven by the excess pressure inside the sphere is connected to the tension stress through the linear constitutive equation

$$\sigma_{\theta\theta} = \sigma_{\phi\phi} = \frac{Ee}{1-\nu} \tag{12}$$

where E is Young's modulus in units of N/m^2, ν is Poisson's ratio, $e = (r - r_0)/r_0$ is the in-plane longitudinal strain, $r - r_0$ is the small radial displacement, and $\sigma_{\theta\theta}$ (N/m^2) and $\sigma_{\phi\phi}$ are the isotropic tension stresses. The thin-shell theory gives an approximation of the excess pressure p through

$$p \simeq \frac{2h\sigma_{\theta\theta}}{r} \tag{13}$$

By introducing membrane surface tension σ (N/m)

$$\sigma = \frac{hEe}{1-\nu} \tag{14}$$

one can represent the stress balance in an expression analogous to the Laplace equation. For a charged bilayer membrane, we have

$$\Pi = |\mathbf{\Pi}| = \frac{2\sigma}{r} \text{ at } r = 1 \tag{15}$$

where r^{-1} is the dimensionless mean surface curvature. Also

$$\sigma = Y\frac{dA}{A_0} = Y\frac{r^2 - r_0^2}{r_0^2} \simeq \frac{2Y\,dr}{r_0} \tag{16}$$

where $dr = r - r_0$ and an average vesicle size $\bar{r} = (r + r_0)/2 \simeq r_0$ is applied for a small radial displacement. Thus, the constant area modulus Y (N/m) of the vesicle membrane is equivalent to $hE/2(1 - \nu)$. Note that the physical origin of the variable membrane surface tension is fundamentally different from those known for the size-dependent surface tension of small drops.[31,32] Here we assume that the area modulus Y remains constant for a specific vesicle and the membrane tension vanishes in the undeformed state when $r = r_0$. We conclude that

$$\Pi \simeq \frac{4Y\,dr}{rr_0} \text{ at } r = 1 \tag{17}$$

Alternatively, the small deformation can be characterized by the in-plane longitudinal extension ratio

$$\frac{r}{r_0} \simeq 1 + \eta \qquad \eta = \frac{r\Pi}{4Y} \text{ at } r = 1 \tag{18}$$

where the dimensionless group η measures the relative strength of the net electric force as compared to the membrane stiffness. Note that the surface tension σ and the area modulus Y are both scaled as

$$\sigma \text{ and } Y \sim \frac{\epsilon\epsilon_0(k_BT/e)^2}{r_1} \tag{19}$$

(31) Tolman, R. *J. Chem. Phys.* **1949**, *17*, 333.
(32) Tsekov, R.; Stöckelhuber, K. W.; Toshev, B. V. *Langmuir* **2000**, *16*, 3502.

The parameter r at $r = 1$ remains in eqs 15, 17, and 18 to avoid confusion in transforming the parameters back to the dimensional forms.

3. Differential Solution

In the previous section, the electric force and the membrane stretching effect are presented in explicit form. The only question remaining is how to solve the potential fields. By applying the transformation $\varphi = u/r$,[27] the Laplacian of the scalar function φ, $(1/r^2)\,d(r^2 d\varphi/dr)/dr$, reduces to $(1/r)\,d^2u/dr^2$, thus eqs 1 and 2 can be transformed to the following forms

$$\frac{d^2u^{(i)}}{dr^2} = \lambda^2 u^{(i)} \qquad \frac{d^2u^{(o)}}{dr^2} = \lambda^2 u^{(o)} \tag{20}$$

for which the corresponding general solutions are

$$\varphi^{(i)}(r) = \frac{u^{(i)}(r)}{r} = A\frac{\sinh(\lambda r)}{r} + B\frac{\cosh(\lambda r)}{r} \tag{21}$$

and

$$\varphi^{(o)}(r) = \frac{u^{(o)}(r)}{r} = C\frac{e^{-\lambda r}}{r} + D\frac{e^{\lambda r}}{r} \tag{22}$$

where A, B, C, and D are constant coefficients to be determined by the boundary conditions. The hyperbolic functions in eq 21 are introduced to facilitate the implementation of a homogeneous boundary condition (eq 4) because B has to vanish the differentiation of $\cosh(\lambda r)/r$ as $r \to 0$. The constant D also vanishes as a result of the far-field boundary condition (eq 5). Solving coefficients A and C simultaneously by using the coupled boundary conditions (eqs 6 and 7), we obtain

$$A = \frac{q_s}{\lambda e^\lambda} \qquad C = \frac{q_s \sinh(\lambda)}{\lambda} \tag{23}$$

In summary, the exact solutions are

$$\varphi^{(i)}(r) = \frac{q_s}{\lambda e^\lambda}\frac{\sinh(\lambda r)}{r} \text{ for } 0 \le r \le 1 \tag{24}$$

and

$$\varphi^{(o)}(r) = \frac{q_s \sinh(\lambda)}{\lambda}\frac{e^{-\lambda r}}{r} \text{ for } 1 \le r < \infty \tag{25}$$

Thus, the potential at the center point yields

$$\varphi_c = \frac{q_s}{e^\lambda} \text{ at } r = 0 \tag{26}$$

and the membrane potential becomes

$$\varphi_s = \frac{q_s}{\lambda e^\lambda}\sinh(\lambda) \text{ at } r = 1 \tag{27}$$

Both the membrane potential and potential at the center point are proportional to the surface charge density. Taking the normal gradient of the solutions (eqs 24 and 25), the electric field strengths located at $r = 1$ on both sides of the membrane can be expressed by

$$E^{(i)} = \frac{q_s}{\lambda e^\lambda}[\lambda \cosh(\lambda) - \sinh(\lambda)] \tag{28}$$

and

$$E^{(o)} = \frac{q_s(\lambda + 1)}{\lambda e^{\lambda}} \sinh(\lambda) \qquad (29)$$

The corresponding net effect on the membrane is a repulsive electrostatic force, a positive value of Π pointing outward from the center point. By substituting eqs 28 and 29 into eq 10, after simplification we obtain the following compact form:

$$\Pi = \frac{q_s^2}{2\lambda}\left(1 - \frac{\lambda + 1}{e^{2\lambda}}\right) \qquad (30)$$

The net repulsive force is proportional to q_s^2. For a concentrated electrolyte solution with thin Debye length $\kappa^{-1} \to 0$ and $\lambda \to \infty$, the corresponding potential fields and the net electric force vanish accordingly. Combining eqs 15 and 30 gives the membrane tension force, whereas the extension ratio depends on the area modulus through eq 18.

4. Integral Solution

Next, we consider an equivalent integral formulation for the governing system. Although the differential method provides an exact solution for the spherical case, the integral approach is preferred because it can be extended to investigate vesicles with arbitrary configurations with local charge density. Such models are related to a vesicle that has small pore openings, undergoes fusion or budding processes, or deforms in a fluid environment while it interacts with another vesicle or a biological membrane. We present formulations in dimensionless forms by using the same characteristic scales defined in the previous section. The details are as follows. Considering eq 1, the equivalent integral formulation can be derived by setting the residual of the differential equation equal to zero in an integral sense over the volumetric solution domain $\Omega^{(i)}$

$$\int_{\Omega^{(i)}} G(\nabla^2 \varphi^{(i)} - \lambda^2 \varphi^{(i)}) \, dV = 0 \qquad (31)$$

where G is a weighting function. Applying Green's second formula to the Laplacian term above, we have

$$\int_{\Omega^{(i)}} \varphi^{(i)}(\nabla^2 G - \lambda^2 G) \, dV = -\int_{\partial\Omega}\left(G\frac{\partial\varphi^{(i)}}{\partial n} - \varphi^{(i)}\frac{\partial G}{\partial n}\right) dA \qquad (32)$$

with the surface normal $\mathbf{n}$ pointing outward from the solution domain $\Omega^{(i)}$. The notation $\partial\Omega$ presents the interface, and dV and dA denote the volume and area integrals, respectively. Here the weighting function G is defined by the fundamental solution or the free-space Green function of the differential operator $\nabla^2 - \lambda^2$. It satisfies the singularly forced equation

$$\nabla^2 G - \lambda^2 G = -\delta(\mathbf{x} - \boldsymbol{\xi}) \qquad (33)$$

where $\delta(\mathbf{x} - \boldsymbol{\xi})$ is the Dirac delta function, and $\mathbf{x}$ and $\boldsymbol{\xi}$ denote the position vectors of the field and source points, respectively. Equation 33 can be solved by using the standard integral transform technique.[33] The fundamental solution is given by

$$G(\mathbf{x}, \boldsymbol{\xi}) = \frac{1}{4\pi}\frac{e^{-\lambda|\mathbf{x} - \boldsymbol{\xi}|}}{|\mathbf{x} - \boldsymbol{\xi}|} \qquad (34)$$

where the absolute value is the distance between the field and

(33) Kythe, P. K. *Fundamental Solutions for Differential Operators and Applications*; Birkhauser: Boston, 1996.

source points. Combining eqs 32 and 33, the boundary-only integral formulation of eq 1 can be written as

$$\alpha\varphi^{(i)}(\boldsymbol{\xi}) = \int_{\partial\Omega}\left(G\frac{\partial\varphi^{(i)}}{\partial n} - \varphi^{(i)}\frac{\partial G}{\partial n}\right) dA(\mathbf{x}) \qquad (35)$$

where coefficient $\alpha = 1$ for $\boldsymbol{\xi} \in \Omega^{(i)}$, $\alpha = 0$ for $\boldsymbol{\xi} \in \Omega^{(o)}$, and $\alpha = {}^1/_2$ for $\boldsymbol{\xi} \in \partial\Omega$. The first two cases are the direct results from the integral property of the Dirac delta function, and $\alpha = {}^1/_2$ when the source point lies on a sufficiently smooth boundary.[33] The later is derived by a modified contour integral with the source point isolated from the boundary, where the double-layer integral is interpreted in the sense of the Cauchy principal value. Similarly, the integral formulation for eq 2 becomes

$$\alpha\varphi^{(o)}(\boldsymbol{\xi}) = \int_{\partial\Omega}\left(-G\frac{\partial\varphi^{(o)}}{\partial n} + \varphi^{(o)}\frac{\partial G}{\partial n}\right) dA(\mathbf{x}) \qquad (36)$$

with the surface normal $\mathbf{n}$ pointing into the solution domain $\Omega^{(o)}$. The unit normal is consistent with the definition in eq 35. Similarly, coefficient $\alpha = 1$ for $\boldsymbol{\xi} \in \Omega^{(o)}$, $\alpha = 0$ for $\boldsymbol{\xi} \in \Omega^{(i)}$, and $\alpha = {}^1/_2$ for $\boldsymbol{\xi} \in \partial\Omega$.

One of the advantages of using integral formulations is that we can simplify an interfacial problem by combining the integral kernels and representing the result using the coupled boundary condition. In our case, when $\boldsymbol{\xi} \in \Omega^{(i)}$, adding eq 35 ($\alpha = 1$) to eq 36 ($\alpha = 0$) yields

$$\varphi^{(i)} = \int_{\partial\Omega} G\left(\frac{\partial\varphi^{(i)}}{\partial n} - \frac{\partial\varphi^{(o)}}{\partial n}\right) + \frac{\partial G}{\partial n}(\varphi^{(o)} - \varphi^{(i)}) \, dA \qquad (37)$$

By substituting the boundary conditions in eqs 6 and 7 into eq 37, the forcing density of the single-layer potential is replaced by the surface charge density q_s, and the double-layer potential vanishes because of the continuous potential field across the interface. Thus, the closed-form solution for the electric potential inside the vesicle is

$$\varphi^{(i)}(\boldsymbol{\xi}) = \int_{\partial\Omega} G(\mathbf{x}, \boldsymbol{\xi}) \, q_s(\mathbf{x}) \, dA(\mathbf{x}) \text{ for } \boldsymbol{\xi} \in \Omega^{(i)} \qquad (38)$$

Similarly, we can combine eqs 35 and 36 for $\boldsymbol{\xi} \in \Omega^{(o)}$ and $\boldsymbol{\xi} \in \partial\Omega$ and generate explicit solutions for the corresponding domains. The final solution has the same form wherever we place the source point:

$$\varphi(\boldsymbol{\xi}) = \int_{\partial\Omega} Gq_s \, dA(\mathbf{x}) \text{ for } \boldsymbol{\xi} \in \Omega^{(i)} + \Omega^{(o)} + \partial\Omega \qquad (39)$$

Equation 39 is applicable to a vesicle with arbitrary geometry and nonuniform surface charge density. For relatively complicated geometry and charge distribution, the integral equations can be derived with few modifications to facilitate numerical-based analysis.

We now proceed to verify that the solutions obtained from the integral formulation are consistent with those solved by the differential approach. The electric fields on both sides of the interface are defined by the potential gradients along the normal or radial direction. For a given source point located at the interface, the symmetric condition allows us to move out the forcing density functions from the single-layer and double-layer integrals in eqs 35 and 36, expressed as

$$\frac{1}{2}\varphi^{(i)}(\boldsymbol{\xi}) = \frac{\partial\varphi^{(i)}}{\partial n}\int_{\partial\Omega} G \, dA(\mathbf{x}) - \varphi^{(i)}\int_{\partial\Omega}\frac{\partial G}{\partial n} \, dA(\mathbf{x}) \qquad (40)$$

and

$$\frac{1}{2}\varphi^{(o)}(\xi) = -\frac{\partial\varphi^{(0)}}{\partial n}\int_{\partial\Omega} G \, dA(\mathbf{x}) + \varphi^{(o)}\int_{\partial\Omega}\frac{\partial G}{\partial n} \, dA(\mathbf{x}) \tag{41}$$

where both $\mathbf{x}$ and $\xi \in \partial\Omega$. Substituting the symmetric condition for a vesicle with uniform surface charge

$$\varphi^{(i)}(\xi) = \varphi^{(i)}(\mathbf{x}) = q_s\int_{\partial\Omega} G \, dA(\mathbf{x}) = \varphi^{(o)}(\xi) = \varphi^{(o)}(\mathbf{x}) \tag{42}$$

and rearranging eqs 40 and 41, the normal gradients on both sides of the membrane become

$$\frac{\partial\varphi^{(i)}(\mathbf{x})}{\partial n} = q_s\left(\int_{\partial\Omega}\frac{\partial G(\mathbf{x}, \xi)}{\partial n} \, dA(\mathbf{x}) + \frac{1}{2}\right) \tag{43}$$

and

$$\frac{\partial\varphi^{(o)}(\mathbf{x})}{\partial n} = q_s\left(\int_{\partial\Omega}\frac{\partial G(\mathbf{x}, \xi)}{\partial n} \, dA(\mathbf{x}) - \frac{1}{2}\right) \tag{44}$$

with ξ being an arbitrary point selected from the interface. Note that explicit solutions eqs 43 and 44 are applicable only for a spherical vesicle with constant surface charge. For asymmetric geometry with localized surface charge, numerical discretization of the integral equations may be required to solve simultaneously for the local surface potential and the normal gradient along the interface. The integral kernels in the single-layer (eq 39) and double-layer (eqs 43 and 44) integrations can be further expressed by spherical polar coordinates using transformations

$$\mathbf{x} = (x, y, z) = (r\sin\theta\cos\phi, r\sin\theta\sin\phi, r\cos\theta) \tag{45}$$

$$\xi = (\tilde{x}, \tilde{y}, \tilde{z}) = (\tilde{r}\sin\tilde{\theta}\cos\tilde{\phi}, \tilde{r}\sin\tilde{\theta}\sin\tilde{\phi}, \tilde{r}\cos\tilde{\theta})$$

where r, θ, ϕ and $\tilde{r}$, $\tilde{\theta}$, $\tilde{\phi}$ denote the radial, polar, and azimuthal components of the position vectors for the field and source points, respectively. The distance between the field and source points is then determined by the law of cosines

$$|\mathbf{x} - \xi| = (r^2 + \tilde{r}^2 - 2r\tilde{r}\cos\gamma)^{1/2} \tag{46}$$

where γ is the angle between $\mathbf{x}$ and ξ and

$$\cos\gamma = \frac{\mathbf{x}\cdot\xi}{r\tilde{r}} = \cos(\tilde{\theta})\cos(\theta) + \sin(\tilde{\theta})\sin(\theta)\cos(\tilde{\phi} - \phi) \tag{47}$$

Therefore the closed-form solution, eq 39, becomes

$$\varphi(\xi) =$$
$$\frac{q_s}{4\pi}\int_0^{2\pi}\int_0^\pi \frac{\exp[-\lambda(r^2 + \tilde{r}^2 - 2r\tilde{r}\cos\gamma)^{1/2}]}{(r^2 + \tilde{r}^2 - 2r\tilde{r}\cos\gamma)^{1/2}}\sin\theta \, d\theta \, d\phi \tag{48}$$

for $\xi \in \Omega^{(i)} + \Omega^{(o)} + \partial\Omega$. Equation 48 includes a three-dimensional surface integration of an exponentially screened Poisson-like integral kernel. For the spherical case $r = 1$ in a dimensionless form, it is convenient to simplify the integral by locating ξ at the position $(0 \leq \tilde{r} < \infty, \tilde{\theta} = 0, \tilde{\phi} = 0)$ so that $\cos\gamma$ can be simplified to $\cos\theta$. The finite integration in eq 48 therefore gives

$$\varphi(\xi) = \frac{q_s}{2\lambda\tilde{r}}\{\exp[-\lambda(1 + \tilde{r}^2 - 2\tilde{r})^{1/2}] -$$
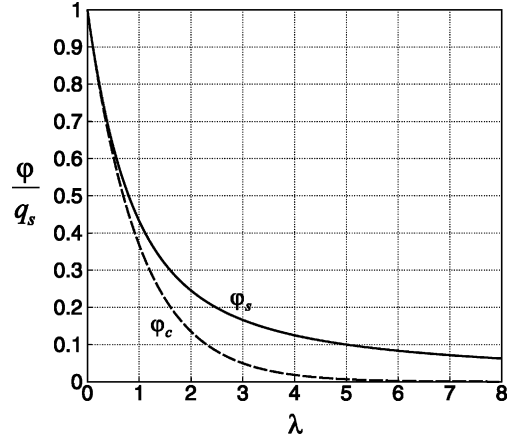$$\exp[-\lambda(1 + \tilde{r}^2 + 2\tilde{r})^{1/2}]\} \tag{49}$$

Figure 2. Membrane surface potential (solid line, obtained by eq 27) and the potential located at the center point (dashed line, from eq 26) vs the inverse of the normalized Debye length ($\lambda = \kappa r_1$).

To satisfy the boundary conditions, we define $(1 + \tilde{r}^2 - 2\tilde{r})^{1/2} = (1 - \tilde{r})$ for $0 \leq \tilde{r} \leq 1$ and $(1 + \tilde{r}^2 - 2\tilde{r})^{1/2} = (\tilde{r} - 1)$ for $1 \leq \tilde{r} < \infty$. Finally, eq 49 reduces to solutions identical to those obtained by the differential approach,

$$\varphi(\xi) = \frac{q_s}{\lambda e^\lambda}\frac{\sinh(\lambda\tilde{r})}{\tilde{r}} \text{ for } 0 \leq \tilde{r} \leq 1 \tag{50}$$

and

$$\varphi(\xi) = \frac{q_s \sinh(\lambda)}{\lambda}\frac{\exp(-\lambda\tilde{r})}{\tilde{r}} \text{ for } 1 \leq \tilde{r} < \infty \tag{51}$$

The resulting electric potentials at the center point ($\tilde{r} = 0$) and the membrane surface ($\tilde{r} = 1$) are consistent with eqs 26 and 27. Considering eqs 43 and 44 again, the double-layer integration can be simplified by letting $\cos\gamma = \cos\theta$, $r = \tilde{r} = 1$, and $\tilde{\theta} = \tilde{\phi} = 0$ to obtain

$$\int_{\partial\Omega}\frac{\partial G(\mathbf{x}, \xi)}{\partial n} \, dA(\mathbf{x}) = \frac{e^{-2\lambda}(\lambda + 1) - 1}{2\lambda} \tag{52}$$

Therefore,

$$\frac{\partial\varphi^{(i)}(\mathbf{x})}{\partial n} = \frac{q_s}{\lambda e^\lambda}[\lambda\cosh(\lambda) - \sinh(\lambda)] \tag{53}$$

and

$$\frac{\partial\varphi^{(o)}(\mathbf{x})}{\partial n} = \frac{-q_s(\lambda + 1)}{\lambda e^\lambda}\sinh(\lambda) \tag{54}$$

where $\mathbf{x} \in \partial\Omega$. The absolute values of eqs 53 and 54 are consistent with the magnitudes of the electric fields, eqs 28 and 29, thus the net electric force is given in eq 30.

5. Results and Discussion

5.1. Symmetric Cases. Figure 2 shows the dimensionless electric potential φ_s at the membrane position and φ_c at the center point of a spherical vesicle with uniform surface charge density. The potential is grouped with the dimensionless charge density q_s and plotted against λ, the inverse of the normalized Debye length. For a very small vesicle or a vesicle in a very dilute solution, λ is small and $\nabla^2\varphi(r) \approx 0$, indicating that the potential at the center point is very close to the membrane potential so that the internal electric field nearly vanishes. When λ increases,
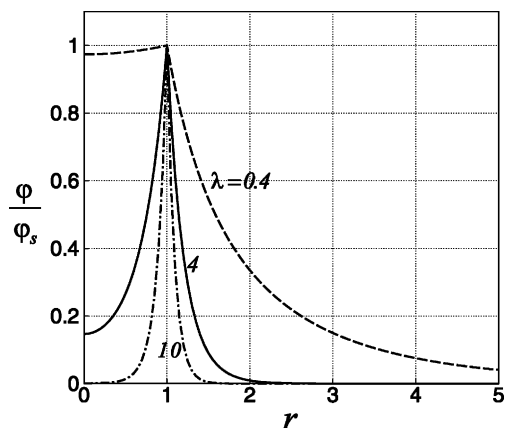
Figure 3. Electric potentials inside and outside the vesicle with the membrane located at the normalized position $r = 1$. Various ionic strengths are represented by $\lambda = 0.4$, 4, and 10.
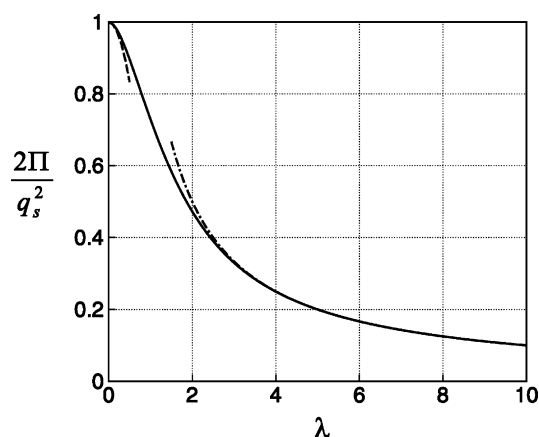

Figure 4. Normalized net electric force density $2\Pi/q_s^2$ as a function of λ (solid line). The dashed ($2\Pi/q_s^2 \approx 1 - (2\lambda^2/3)$) and dashed−dotted ($2\Pi/q_s^2 \approx \lambda^{-1}$) lines are asymptotes for small and large λ, respectively.

the potential away from the membrane is screened by the thin electric double layer so that the potential at the center point vanishes and there exists no double-layer overlapping inside the vesicle. A companion result in Figure 3, the potential profile across the vesicle membrane, shows the classical diffuse behavior for the surrounding ionic atmosphere at equilibrium. The profiles on both sides of the membrane are normalized by the membrane surface potential corresponding to various ionic strengths, $\lambda = 0.4$, 4, and 10. Inside the vesicle, the overlapping region of the electric double layers due to space confinement becomes significant when λ decreases.

The repulsive force density Π (eq 30) is shown in Figure 4 with magnitude normalized by the dimensionless charge density squared. Similar to the electrostatic disjoining pressure of planar parallel surfaces in an electrolyte solution,[28−30] the repulsive force increases when the overlapping region of the electric double layer within the vesicle increases. For a given λ, the repulsive force scales proportionally to q_s^2. In contrast to the planar surfaces, the net force density Π involves the curvature effect such that the repulsive force exists even without the overlapping region. The effect can be seen by inspecting Figures 2 and 4 where the net repulsive force Π remains a finite value when $\lambda \geq 6$ but the center potential φ_c vanishes for similar λ. The asymptotic curves at limiting regimes show that for a given charge density, when $\lambda \gg O(1)$, the repulsive force decreases at the rate of λ^{-1} as λ increases and when $\lambda \to 0$, $\Pi \to q_s^2/2$.

To have a clear picture of these physical variables, we demonstrate a case study in a dimensional form as follows: Given a weakly charged vesicle with radius 1 μm and charge density 10^{-4} Cm^{-2} (equivalent to 7850 single electron charges around the membrane interface) and a dilute 1:1 electrolyte with ionic strength 10^{-6} mol/L and permittivity $\epsilon \approx 78.5$ (relative to the permittivity of free space $\epsilon_0 = 8.854 \times 10^{-12}$ C^2 J^{-1} m^{-1}), the Debye length κ^{-1} is $\sim$304 nm and the thermal energy k_BT/e is $\approx$25.7 mV at room temperature. The dimensionless group $\lambda = 3.29$ and the dimensionless charge density $q_s \approx 5.6$. The electric potentials located at the membrane (eq 27) and at the center point (eq 26) are

$$\varphi_s = \frac{q_s \sinh(\lambda)}{\lambda e^\lambda} \frac{k_BT}{e} \approx 21.8 \text{ mV}$$

and

$$\varphi_c = \frac{q_s}{e^\lambda} \frac{k_BT}{e} \approx 5.4 \text{ mV}$$

respectively. The net electrostatic force density becomes (eq 30)

$$\Pi = \frac{q_s^2(1 - (\lambda + 1)/e^{2\lambda})}{2\lambda} \frac{\epsilon\epsilon_0(k_BT/e)^2}{r_1^2} \approx 2.2 \text{ Pa}$$

The tension force $\sigma = r\Pi/2$, therefore, is around 10^{-3} mN/m, which is about 3 orders of magnitude smaller than the lysis tension of a bilayer membrane. The area modulus Y of a vesicle membrane measured by the micropipet method gives a typical value close to 0.2 N/m,[34] and a similar value of Y was also found in polyelectrolyte vesicles in water (because $E \approx 100$ MPa, $h \approx 10$ nm, and $\nu \approx 0.5$ [35]). From eq 18, the dimensionless group η is around 2.75×10^{-6}, which implies that the weakly charged membrane is fairly stiff. Such an electrostatically induced longitudinal strain is unlikely to be observed under optical microscopy by alternating the ionic environment. The small deformation may be detected by the dynamic light scattering method.[36] Note that the electric force and surface tension are scaled by the squared electric field (eq 10), thus a much higher longitudinal strain is expected as the surface charge density increases. Although in this demonstration case the membrane deformation caused by the electric force is much smaller than that which can be achieved by using osmotically active species,[37] the implication of the small deformation cannot be overlooked. Experimental results have shown that one can increase the surface charge of a self-assembled polyelectrolyte vesicle and reduce its elastic modulus by 1 to 2 orders of magnitude concurrently by varying the pH value of the aqueous solution.[38,39] According to our analysis, this would lead to a large amount of electrostatic stretching, which was recently observed for synthetic polyelectrolyte shells.[40] Significant stretching is anticipated for lipid bilayer vesicles with intercalated proteins showing polyampholyte behavior. Note that the linear result in Figure 4 shows that the repulsive surface force decreases as the ionic strength increases as long as the surface charge density remains fixed. This result

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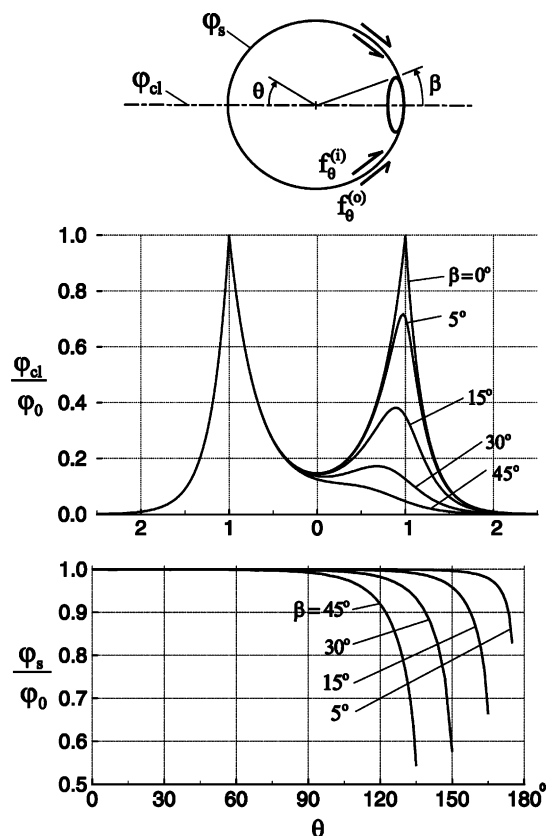(40) Déjugnat, C.; Sukhorukov, G. B. *Langmuir* **2004**, *20*, 7265.

Figure 5. Potential distributions along the axial line φ_{cl} and at the membrane surface φ_s for a vesicle with an opening pore. Both potentials are normalized by φ_0 obtained from the sealed case using the same charge density; the radial distance along the center line is scaled by r_1; and the solvent condition is predetermined by $\lambda = 4$.

is an outcome due to the decaying zeta potential and the relatively symmetric distribution of the Maxwell stresses that are mutually canceled from both sides of the membrane.

5.2. Asymmetric Case. Studies have shown that the direct visualization of the transient dynamics of an opening or closing pore and the liquid leak-out process in a vesicle is fundamentally important to the understanding of transmembrane transport phenomena.[41,42] In these studies, the vesicle configurations are asymmetric, which motivates us to apply the integral technique that can be extend for both analytical and numerical analyses. As an example, we examine a spherical vesicle with an opening pore, shown in Figure 5. The surface charge is uniformly distributed along the membrane, but the potential gradient is no longer perpendicular to the membrane. In dynamic analysis, the electric-field-generated shear force has to be included in force balance for the calculation of line tension, surface tension, Maxwell stress, and the hydrodynamic viscous force. If at equilibrium the membrane is uniformly charged and the pore has an opening angle β, then the integral solution for φ from eq 48 can be written as

$$\varphi(\boldsymbol{\xi}) =$$
$$\frac{q_s}{4\pi}\int_0^{2\pi}\int_0^{\pi-\beta}\frac{\exp[-\lambda(r^2 + \tilde{r}^2 - 2r\tilde{r}\cos\gamma)^{1/2}]}{(r^2 + \tilde{r}^2 - 2r\tilde{r}\cos\gamma)^{1/2}}\sin\theta\,d\theta\,d\phi \tag{55}$$

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for $\boldsymbol{\xi} \in \Omega^{(i)} + \Omega^{(o)} + \partial\Omega$ where the upper limit of integration in the θ direction has been changed to $\pi - \beta$. In Figure 5, the electric potentials along the axial line φ_{cl} and the membrane interface φ_s are compared, and the values are normalized by the surface potential φ_0 for the sealed vesicle ($\beta = 0$) in which the charge density q_s remains fixed. Figure 5 shows asymmetric cases with various degrees of pore opening ($\beta = 5$ to $45°$). With the lack of a small patch of the charged membrane, the induced electric field and the Maxwell stress become asymmetric in both the r and θ directions. It is interesting to see that when pore opens, the decaying potential near the pore region would induce an unbalanced Maxwell stress along the surface close to the pore (Figure 5). Considering $\mathbf{E} = E_r\hat{\mathbf{e}}_r + E_\theta\hat{\mathbf{e}}_\theta$ and the corresponding surface normal, the surface traction given by eq 9 can be simplified to

$$\mathbf{f} = \frac{1}{2}(E_r^2 - E_\theta^2)\hat{\mathbf{e}}_r + E_rE_\theta\hat{\mathbf{e}}_\theta \tag{56}$$

Thus the shear force induced on both sides of the membrane is

$$\Pi_\theta = [\mathbf{f}^{(o)} + \mathbf{f}^{(i)}]\cdot\hat{\mathbf{e}}_\theta = E_r^{(o)}E_\theta^{(o)} - E_r^{(i)}E_\theta^{(i)} \text{ at } r = 1 \tag{57}$$

Also at the interface

$$E_r^{(o)} = -\frac{\partial\varphi^{(o)}}{\partial r} > 0 \qquad E_r^{(i)} = -\frac{\partial\varphi^{(i)}}{\partial r} < 0$$

$$E_\theta^{(o)} = E_\theta^{(i)} = -\frac{1}{r}\frac{\partial\varphi_s}{\partial\theta} > 0 \tag{58}$$

Therefore

$$\Pi_\theta > 0 \text{ at } r = 1 \tag{59}$$

This result is independent of the sign of q_s, indicating that the Maxwell stress self-induced by the charge membrane tends to seal the pore by helping the line tension or the edge energy. Although in general the pore is not in an equilibrium state and the local analysis has to include charge regulation, fluid dynamics, and membrane mechanics, one could still speculate that for a strongly charged vesicle Maxwell stress will play a role in the transmembrane transport phenomena.

Many studies have shown that the tension force involved has a dramatic influence on the fluid−membrane interactions,[43,44] the compression test response,[45,46] and adhesion[47] and fluctuation[48] behaviors. In combining with membrane mechanics, fluid flow interaction, and the mass conservation principle, the integral method is promising for the analysis of the local behavior and transient dynamics of vesicles with arbitrary configurations. In solving the nonlinear Poisson−Boltzmann equation, the Laplacian that deals with diffuse behavior may be formulated separately from the nonlinear density function, which can be treated as a pseudosource term. The resulting nonhomogeneous differential system requires a domain integral after transforming into an equivalent integral formulation. It is possible to involve the lamellar phase and specific ion interactions using integral-based numerical models. We anticipate that the challenges in building these models are not only in the basic understanding of the

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microphysics of the charged membrane in electrolyte solutions but also in the numerical implementation. Finally, the analytical approach in this article might be applicable to the analysis of charged nanodroplets[32] and perhaps nanobubbles.[49,50] Indeed, in many ways the drop or bubble interface acts as a membrane under tension.[51,52] A detailed comparison, however, requires further analysis.

6. Conclusions

We have provided an analytical solution to quantify the charge-induced electrostatic properties of vesicles in an aqueous environment. The coupled linear equilibrium system is solved by both differential and integral solution techniques. Important features of the electric double-layer interactions within a vesicle and the basic electrostatic stretching behavior are formulated in closed forms. The methodology can be extended to studies involving lamellar phases or the phase separation of charged molecules, and the integral technique can be combined with fluid and membrane models for further analysis of vesicle dynamics.

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