

# Shape Instabilities in Charged Lipid Domains

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A theoretical model describing the formation and shapes of domains in amphiphilic monolayers driven by screened electrostatic interactions is presented. The model is related to previous studies of pattern formation in magnetic systems in Hele–Shaw cells. Using quantitative estimates of line tension, charge density, and ionic strength appropriate for biological systems, this model accounts for the appearance of circular and irregular domains in mixed lipid monolayer systems containing the anionic lipid phosphatidylinositol monophosphate. The results may have implications for pattern formation in both synthetic materials and biological membranes.

## Introduction

Domain formation in lipid bilayers and other thin films formed by amphiphilic molecules is a common feature of many materials including the cell membrane, where lateral demixing of specific lipids into specialized domains is related to several aspects of signal transduction and other cellular functions. The forces governing the formation of such domains are the subject of many studies, and a number of reports have addressed shape instabilities of dipolar domains in amphiphile monolayers.<sup>1–7</sup> These calculations are based on the introduction of a cutoff length representing the distance of closest approach between perpendicularly oriented dipoles. A somewhat different approach has been considered regarding the shape instabilities of magnetic fluid droplets in Hele–Shaw cells,<sup>8</sup> where a natural cutoff length—the thickness of the Hele–Shaw cell—appears. It has been shown that the two models are equivalent.<sup>9</sup> An illustration of the utility of this approach is the description of the undulation instability of a foam in an amphiphile monolayer,<sup>10</sup> which is in good agreement with experimental data and is based on the relation obtained for the analogous instability of a magnetic liquid foam in the limiting case of vanishing thickness in a Hele–Shaw cell. In contrast to the large bibliography of works concerning shape instabilities in amphiphile monolayers governed by steric or dipole–dipole interactions, a model for the shape instability of domains of charged lipids interacting by screened electrostatic interactions in the amphiphile monolayer is not yet developed. This problem has great interest due to the role that charged lipids play in the regulation of cell structure and function<sup>11</sup> and in various biotechnological applications.<sup>12</sup>

## Model and Instability of the Circular Domain

The free energy of a charged lipid domain in the monolayer under the assumption that the Debye–Hückel theory is valid is expressed as<sup>13</sup>

$$E_e = \frac{1}{2} \int \sigma \psi \, dS \quad (1)$$

where  $\sigma$  is the charge density and  $\psi$  is the electrostatic potential.

This free energy accounts for electrostatic interactions as well as entropy of the counterion distribution. Since the dielectric permeability of water is much higher than that of the surrounding air, the one-sided model<sup>14</sup> is assumed in which the electrostatic potential of the planar domain is expressed as follows:

$$\psi(\vec{r}) = \frac{2\sigma}{\epsilon} \int G(|\vec{r} - \vec{r}'|) \, dS' \quad (2)$$

where  $G(|\vec{r}|) = e^{-\chi|\vec{r}|}/|\vec{r}|$  is the fundamental solution of the Helmholtz equation,  $\chi^2 = (4\pi\sum_i z_i^2 e^2 n_{0i})/(\epsilon k_B T)$  is the screening parameter of the surrounding electrolyte solution, and  $\epsilon$  is the dielectric permeability of water. The line energy of the domain boundary will be expressed as

$$E_s = \gamma \int dl \quad (3)$$

where  $\gamma$  is the line tension.

Let us consider the energy of the domain  $E = E_e + E_s$  with the deviation of its shape from circular with radius  $R$  to new shapes given in polar coordinates as  $r = R + \zeta(\varphi)$ . By simple transformations similar to those used before,<sup>8</sup> the electrostatic part of the free energy  $E_e$  up to second-order terms in  $\zeta$  can be written as follows:

$$\begin{aligned} \Delta E_e = E_e - E_e(R) = & \frac{1}{2\pi} \int_0^{2\pi} \frac{dE_e^0}{dR} \zeta(\varphi) \, d\varphi + \\ & \frac{1}{2\pi} \int_0^{2\pi} \frac{1}{2} \frac{d^2 E_e^0}{dR^2} \zeta^2(\varphi) \, d\varphi - \frac{\sigma^2}{2\epsilon} \int_0^{2\pi} d\varphi \int_0^{2\pi} d\varphi' R^2 G_1(\varphi - \\ & \varphi') (\zeta(\varphi') - \zeta(\varphi))^2 \quad (4) \end{aligned}$$

where  $G_1(\varphi - \varphi') = G(R\sqrt{2(1 - \cos(\varphi - \varphi'))})$ , and  $E_e^0$  is the electrostatic free energy of the circular domain with radius  $R$ .

Representing

$$\zeta(\varphi) = \sum_{n=0}^{\infty} a_n \cos n\varphi$$

and expressing  $a_0$  from the condition of the domain area

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conservation as

$$a_0 = -\frac{1}{4R} \sum_{n=1}^{\infty} a_n^2$$

the expression for the electrostatic energy (4) can be rewritten as follows

$$\Delta E_e = \sum_{n=1}^{\infty} \left[ \frac{1}{4} \left( \frac{d^2 E_e^0}{dR^2} - \frac{1}{R} \frac{dE_e^0}{dR} \right) - \frac{2\pi R \sigma^2}{\epsilon} \int_0^\pi dt \frac{\sin^2 nt}{\sin t} e^{-2\chi R \sin t} \right] a_n^2 \quad (5)$$

The first term in the brackets of expression (5) can be rewritten using the expression for the electrostatic energy of the circular domain

$$E_e^0 = \frac{\sigma^2}{\epsilon} \int_0^{2\pi} d\varphi \int_0^R r dr \int_0^{2\pi} d\varphi' \int_0^R r' dr' G(|\vec{r} - \vec{r}'|)$$

and after differentiating and using the Gauss theorem can be expressed as follows

$$\frac{1}{4} \left( \frac{d^2 E_e^0}{dR^2} - \frac{1}{R} \frac{dE_e^0}{dR} \right) = \frac{\sigma^2}{\epsilon} \frac{1}{2} R^2 \int_0^{2\pi} d\varphi \int_0^{2\pi} d\varphi' G_1(\varphi - \varphi') (1 - \vec{n} \vec{n}') \quad (6)$$

where  $\vec{n}$  is the normal to the contour of the circular domain.

Finally, the variation of the electrostatic part of the free energy reads

$$\Delta E_e = -\frac{\sigma^2}{\epsilon} \sum_{n=1}^{\infty} 2\pi R a_n^2 \int_0^\pi dt \frac{(\sin^2 t - \sin^2 nt)}{\sin t} e^{-2\chi R \sin t} \quad (7)$$

We note that expression (7) vanishes at  $n = 1$  as it should be due to translational invariance of the electrostatic free energy.

For the variation of the line energy up to second-order terms we have

$$\Delta E_s = \frac{\gamma\pi}{2R} \sum_{n=1}^{\infty} (n^2 - 1) a_n^2 \quad (8)$$

Instability of the domain deformation takes place if  $\Delta E_e + \Delta E_s < 0$ . This gives the following condition at which the contour of the domain becomes unstable to the  $n$ th mode of the deformation

$$\frac{\sigma^2}{\chi^2 \epsilon \gamma} = \frac{1}{4(\chi R)^2} \frac{(n^2 - 1)}{\int_0^\pi dt \frac{(\sin^2 nt - \sin^2 t)}{\sin t} e^{-2\chi R \sin t}} \quad (9)$$

When the characteristic Debye screening length becomes much smaller than the characteristic domain size the calculated shape instability threshold might be expected to correspond to that obtained in the dipolar approximation.<sup>15</sup> However, this is not the case since the one-sided model based on the expansion with respect to the ratio of dielectric permeabilities of the air and the aqueous subphase is used in the present work, whereas the dipolar term developed in ref 15 is proportional to the ratio of the permeabilities of the air and the water. Thus it is beyond the approximation used in the present work which keeps only

zeroth-order terms. Nevertheless the comparison of the results of the present work with some earlier ones is possible.

The relation (9) for the instability threshold can be compared with the results of the analysis of the effective line tension of a charged semi-infinite membrane in the surrounding electrolyte solution reported.<sup>16</sup> In that case in the framework of the one-sided model for the electrostatic free energy we have

$$\Delta E_e = -\frac{\sigma^2}{\epsilon} \frac{1}{2\pi} \int dk |\zeta(k)|^2 \ln \left( 1 + \frac{k^2}{\chi^2} \right) \quad (10)$$

where  $\zeta(x) = (1)/(2\pi) \int \zeta(k) e^{ikx} dk$  is the perturbation of the edge of the membrane at the position  $y = 0$  in the unperturbed state. Correspondingly the perturbation of the energy of the edge due to the line tension is

$$\Delta E_s = \frac{\gamma}{2} \frac{1}{2\pi} \int k^2 |\zeta(k)|^2 dk \quad (11)$$

For small  $k$ th, the sum of the energies (10) and (11) for the variation of the energy of the membrane due to its edge perturbation gives

$$\Delta E = \frac{\sigma^2}{2\pi\epsilon\chi^2} \int k^2 |\zeta(k)|^2 \left( \frac{\epsilon\chi^2\gamma}{2\sigma^2} - 1 \right) dk \quad (12)$$

which shows that due to the electrostatic interactions the edge has negative line tension if  $(\epsilon\chi^2\gamma)/(\sigma^2) < 2$ .<sup>16</sup> This result is in agreement with the relations (7) and (8) in the limit of large  $R$  when the edge of the circular domain can be considered locally as straight. Since for large  $\chi R$

$$\int_0^\pi dt \frac{\sin^2 t - \sin^2 nt}{\sin t} e^{-2\chi R \sin t} \cong -\frac{2(n^2 - 1)}{4\chi^2 R^2}$$

and the domain edge perturbation  $\zeta = \sum a_n \cos n\varphi$  can be written as  $\zeta = (1)/(2\pi) \int \zeta(k) e^{ikx} dk$  after introducing its wavenumber  $k = n/R$  for large  $n$  and  $R$  where  $\zeta(k) = R\pi a_n$ , resulting in an expression for relation (7) for the electrostatic edge energy as

$$\Delta E_e = -\frac{\sigma^2}{\epsilon\chi^2} \frac{1}{2\pi} \int dk k^2 |\zeta(k)|^2$$

The edge energy due to the line tension can be transformed in the limit of large  $n$  and  $R$  in a similar way as

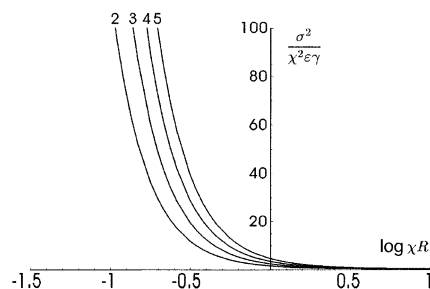
$$\Delta E_s = \frac{\gamma\pi}{2R} \sum_{n=1}^{\infty} (n^2 - 1) a_n^2 \approx \frac{\gamma}{2} \frac{1}{2\pi} \int dk k^2 |\zeta(k)|^2$$

The resulting sum  $\Delta E_e + \Delta E_s$  coincides with the result given by relation (12).

## Results and Discussion

Since the left side of the expression (9) does not depend on domain size, its value determines the critical size of the domain at which instability with respect to the  $n$ -th mode takes place. The right side of expression (9) as a function of  $\chi R$  for several modes is given in Figure 1.

These results can be illustrated by the following numerical example based on the case of a lipid monolayer containing the anionic phospholipid phosphatidylinositol monophosphate (PIP). Let us take for the charge density the value  $q/\Sigma$  where  $q = 2.5e$  and  $\Sigma = 500 \text{ \AA}^2$ , which corresponds to the properties of a monolayer containing 10% PIP and 90% neutral lipid at a



**Figure 1.** Dependence of the critical electric bond number on the size of the domain for the instability of the circular shape with respect to the first four deformation modes in semilogarithmic coordinates.

somewhat compressed but liquid phase.<sup>17</sup> Taking for the line tension a reasonable estimate of  $10^{-7}$  dyne,<sup>18</sup> in the case of 10 mM monovalent electrolyte solution the value on the left side of the expression (9) is approximately 0.66. Thus for those parameters it follows from Figure 1 that instability takes place for domains with a size larger than 100 Å as has been observed experimentally.<sup>17</sup> As the ionic strength increases, the critical size at which instability occurs will also increase. An interesting feature of these phenomena, possibly related to biological structures, is connected with the possible change in surface charge density following the adsorption of peptides or proteins on lipid monolayers and bilayers.<sup>17,19</sup> Compensation of the surface charge density by oppositely charged peptides leads to the restoration of the stability of the circular shape as is observed experimentally in monolayer systems<sup>17</sup> and an analogous event may occur to restructure the domains in cell membranes as cationic protein domains are recruited to sites of high negative charge density at the cell membrane.<sup>19</sup>

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