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REVIEW

Electrostatic field effects on membrane domain segregation and on lateral diffusion

Natalia Wilke · Bruno Maggio

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Abstract Natural membranes are organized structures of neutral and charged molecules bearing dipole moments which generate local non-homogeneous electric fields. When subjected to such fields, the molecules experience net forces that can modify the lipid and protein organization, thus modulating cell activities and influencing (or even dominating) the biological functions. The energetics of electrostatic interactions in membranes is a long-range effect which can vary over distance within r^{-1} to r^{-3}. In the case of a dipole interacting with a plane of dipoles, e.g. a protein interacting with a lipid domain, the interaction is stronger than two punctual dipoles and depends on the size of the domain. In this article, we review several contributions on how electrostatic interactions in the membrane plane can modulate the phase behavior, surface topography and mechanical properties in monolayers and bilayers.

Keywords Electrostatic interactions · Lipid domains · Charged surfactants · 2D diffusion

N. Wilke · B. Maggio
Centro de Investigaciones de Química Bológica de Córdoba (CIQUIBIC-CONICET), Departamento de Química Biológica, Facultad de Ciencias Químicas,
Universidad Nacional de Córdoba,
Córdoba, Argentina

N. Wilke (✉)
CIQUIBIC, Dpto. de Química Biológica, Fac. de Cs. Químicas, UNC, Pabellón Argentina, Ciudad Universitaria,
X5000HUA, Córdoba, Argentina
e-mail: wilke@mail.fcq.unc.edu.ar

Introduction

Biological membranes are the most important electrified interfaces in living systems and can support electrical fields from different origins. Due to the ion concentrations being different between the inside and outside of the cell, a diffusion potential gradient normal to the membrane is generated of about 10^7 V m^{-1} (Clarke 2001). Moreover, when a charged molecule is inserted into the membrane, it creates an electrical double layer which in some cases is equivalent to a layer of permanent dipoles. The intensity of the equivalent dipoles can then be tuned by varying the Debye–Hückel screening length of the double layer trough adjustment of the ionic strength in the aqueous medium. Insertion of a charged protein into the membrane generates local non-homogeneous electrostatic fields of the order of 10^7–10^9 V m^{-1} (Groves et al. 2000; Clarke 2001; Brockman 1994). In membranes with phase coexistence, the presence of domains generates inhomogeneous electrostatic fields both inside and outside the domain, as well as unequal electrostatic interactions between the molecules in each phase and along the lateral interface between the two phases. Furthermore, domains show electrostatic repulsion to each other that extends to inter-domain distances of several micrometers, with electrostatic interactions between macroions and domains having also been observed.

In this review, we will focus on the electrostatic interactions in the membrane plane and how these interactions can modulate the surface topography and phase coexistence in monolayers and bilayers. In biphasic systems, the domains generate an electrostatic field with a geometry that depends on the domain shape and size. The

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effects of such electrostatic fields on the mechanical properties of the membrane are also discussed.

Phase diagrams of lipid mixtures with a charged component

The presence of a charged component in a mixture has a profound influence on lipid mixing. The melting temperatures of charged membranes are typically lower than those of neutral ones, since the charges on the headgroups repel each other, a fluid state with a larger area per lipid is favored. In monolayers, the effect of an electrostatic field on the lipid phase diagram has been clearly shown, and, for binary mixtures with dihydrocholesterol, the application of an electrostatic field gradient at pressures below the critical pressure produces a liquid–liquid phase separation in a monolayer that is otherwise homogenous. However, at pressures slightly above the critical pressure, a field gradient induces a large concentration gradient without phase separation (Lee et al. 1994; Lee and McConnell 1993). In these experiments, although the electrostatic field was created using electrodes, similar potential gradients can be generated when a charged molecule is inserted into the membrane (Groves et al. 2000).

Mixed monolayers and bilayers composed of lipids with a charged component have been studied by different techniques. In general, electrostatic repulsion prevents the formation of large clusters of charged molecules (Huang and Feigenson 1993). It is known that the miscibility depends strongly on pH, and thus on the degree of ionization of the charged molecule (Garidel et al. 1997; Garidel and Blume 1998; Vega Mercado et al. 2011) (Fig. 1). Furthermore, ordered-liquid crystalline phase transitions in bilayers of charged lipids are accompanied by a decrease in the electrostatic free energy, mainly as a result of bilayer expansion. For a uniform charge distribution, the Gouy–Chapman theory in the electrical double layer predicts a decrease of the transition temperature with increasing charge density. For instance, an increase of charge per polar group from one to two elementary charges in phosphatidic acid (PA) lowers the transition temperature by about 20°C, in agreement with this theory. Small changes in pH are sufficient to induce isothermal phase transitions (Träuble and Hansjörg 1973). In addition, the biphasic region of the phase diagram for ternary mixtures with cholesterol is highly reduced when a neutral lipid is replaced by a charged one (Vequi-Suplicy et al. 2010; Shimokawa et al. 2010), with the thermal stability of the two-phase region of mixtures also decreasing.

Inorganic ions and macroions

Even small changes in the ionic environment can induce gross alterations to the bilayer structure. In both monolayers and bilayers, the interaction of lipids with different ions depends on the ion nature, on the lipid headgroups and also on the degree of unsaturation of the lipid hydrocarbon chain (Maggio and Lucy 1976; Mattaij et al. 1989). Divalent cations (Mg^{2+} and Ca^{2+}) generally increase the transition temperature of anionic phospholipids and sphingolipids and condense the membrane by charge neutralization, and thus they can also be used to induce isothermal transitions (Maggio et al. 1987a; Shah and Schulman 1965; Maggio and Lucy 1976). In contrast, monovalent cations (Li^+, Na^+, K^+) usually lower the transition temperature and expand the membrane (Träuble and Hansjörg 1973; Lösche et al. 1985; Sovago et al. 2007; Vega Mercado et al. 2011). This effect has been ascribed to changes of the degree of ionization (Lösche et al. 1985; Grigoriev et al. 1999; Miñones et al. 2002; Benedini et al. 2011) and to the disruption of the hydrogen bonding (Vega Mercado et al. 2011; Wydro 2011), both caused by the presence of ions.

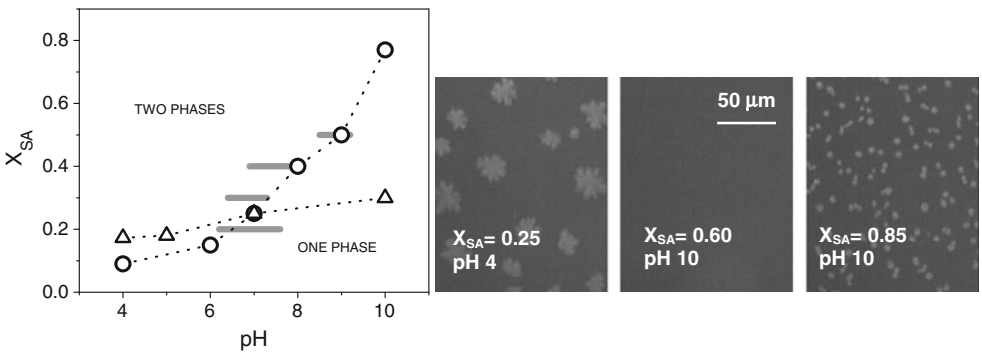

Fig. 1 *Left* Mole fraction of stearic acid at which phase segregation occurs at 17 mN m^{-1} and 20°C on subphases at the indicated pHs. *Gray lines* The phase transition is driven by pH changes at constant surface pressure. *Symbols* The phase transition is driven by compression at constant pH. Suphase composition: NaCl 0.5 M, EDTA 10 mM and TRIS 10 mM (*circles*) or $CaCl_2$ 20 mM and TRIS 10 mM (*triangles*). *Right* Representative images at 17 mN m^{-1} and the indicated conditions. Reproduced from Vega Mercado et al. (2011), with permission

Several examples of phase segregation induced by divalent cations (mainly Ca^{2+}) have been reported (Galla and Sackman 1975; Hartmann et al. 1977; Haverstick and Glaser 1987; Gadella et al. 1990; Flanagan et al. 1997; Rodriguez et al. 2007; Lamberson et al. 2007; Hayden et al. 2009; Vequi-Suplicy et al. 2010; Shimokawa et al. 2010; Vega Mercado et al. 2011) (Fig. 1). The phase separation caused by Ca^{2+} ions is due to the decrease in the Coulombic repulsion, which can be interpreted as a cooperative effect of direct Ca^{2+} binding and an increase in the screening effect. In PA membranes, even charge inversion (a total number of bound counterion charges that exceeds the negative PA charge) may happen at physiological ion concentrations (Faraudo and Travesset 2007).

In a membrane that segregates into two phases, the negatively charged domains can act as recognition patches for positively charged macro-molecules or particles (see references in Murray et al. 1999). A positively charged protein may either adhere to the membrane or insert into the bilayer. In both cases, it may change the phase behavior of multicomponent membranes (Franzin and MacDonald 2001; Roux et al. 1988; Carbone and MacDonald 1996; Maggio et al. 1987b; Gawrisch et al. 1995; Hartmann et al. 1977; Fidelio et al. 1984; Gambhir et al. 2004; Rauch et al. 2002)

The research group of Sasaki (Zendejas et al. 2011) was able to monitor qualitatively the charge on the domain and to analyze the change upon ion and protein binding. These and other authors noted that lipid lateral redistribution leads to an increase in the binding constant of the protein to the membrane and consequently a rise in the affinity (Zendejas et al. 2011; Heimburg et al. 1999; May et al. 2000; Shi and Ma 2007).

Although monolayer systems are not a good model for studying transmembrane proteins, they are able to shed light on membrane–peripheral protein interactions. For example, monolayer experiments have demonstrated that MBP can induce a cholesterol-dependent segregation of phases that can be further regulated by electrolyte concentration of the subphase and by changes in the composition of the non-sterol lipids (Rosetti et al. 2010). Interestingly, it was observed that the presence of low concentrations of amphipatic probes modifies the phase diagram in a charge-dependent manner (Fig. 2).

It has been pointed out that a necessary condition for electrostatically adsorbed proteins to induce lateral phase separation in the membrane is the occurrence of deviation from ideality due to nonelectrostatic interactions between lipids of the same species (May et al. 2000; Rodriguez et al. 2007). Therefore, other effects in addition to those related to electrostatic interactions should also be considered when dealing with macroion–membrane interactions (e.g., curvature effects). Related to this, this type of phenomenon has been reviewed in a very complete work by Marsh (2008).

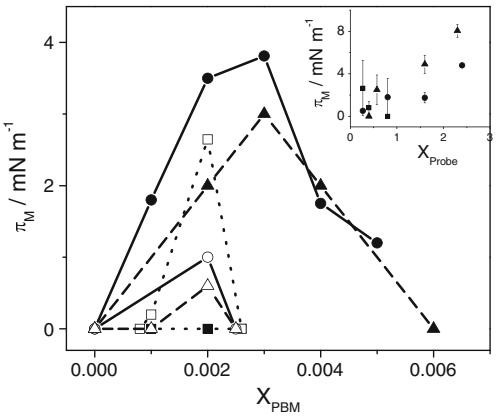

Fig. 2 Mixing/demixing lateral pressure (π_M) as a function of the MBP content for monolayers of myelin lipids with negatively charged (*triangles and circles*) and positively charged (*squares*) amphipatic fluorescent probes at 0.8 mol% (*filled symbols*), 0.27 mol% (*open squares*) and 0.4 mol% (*open triangles and circles*). The *inset* shows the π_M values as a function of the proportion of probe for films with 0.2 mol% of MBP, with the symbols representing the same as those in the main panel. Reproduced from Rosetti et al. (2010), with permission

In summary, all current evidence indicates that the availability of the different species at the membrane in the presence of charged surfactants can be regulated by local changes of pH and of the ionic concentration via phase segregation. In turn, when phase segregation is induced and domains of charged molecules are generated, the presence of these charged patches indirectly regulates the affinity of proteins with the membrane.

Electrostatic fields

The phospholipid polar head group dipole is vectorially oriented, which enables the molecule to act as a surface sensor of the interfacial electrostatic field (Seelig et al. 1987; Bechinger and Seelig 1991). The application of negative potentials to the hydrocarbon side of the interface, with respect to the aqueous subphase, possibly induces stretching of the molecule, and the phospholipid polar head group dipole may bend toward the hydrocarbon phase (Thuren et al. 1987), while the reverse may occur by the application of a positive potential difference. In supported membranes, topological transitions resulting from the application of an electrostatic field have been reported (Wilke et al. 2005). On the other hand, electrostatic fields external and internal to the membrane, have been shown to modulate the interfacial phosphohydrolytic activity (Thuren et al. 1987; Maggio 1999). The electrostatic effect on this activity is inherently coupled to the interactions and location of Ca^{+2} at the interface. These electrostatic perturbations can act as supramolecular transducing factors, which might even favor a better exposure of the acyl ester

bonds to cleavage in the active site of phospholipase A2 (Scott et al. 1990). Furthermore, hyperpolarization or depolarization of the lipid interface by external or local electrostatic fields can affect the phospholipid packing and phase state as well as the effective coordination of Ca^{+2} (which is required for the nucleophilic attack by the enzyme on the phospholipid substrate) (Maggio 1999).

In two-phase monolayers, an applied electrostatic field changes the distribution of domains (Wilke et al. 2006; Wilke and Maggio 2006; Miller et al. 1987; Klinger and McConnell 1993; Mi et al. 1997), with the application of positive potentials above the monolayer inducing domain migration generally away from under the air electrode, while negative potentials cause domain attraction. This can be explained by considering that the dipole moment density of the molecules in the domains is generally higher than that of the molecules in the continuous phase. In addition, charged domains also respond according to the dipole moment rather than to the net charge (Miller et al. 1987). Related to this, the application of electrostatic fields has been demonstrated to be a very convenient tool for modifying the local domain distribution (Wilke and Maggio 2009; Wilke et al. 2010) as well as the domain size (Lee and McConnell 1992), with the variation in the domain density allowing domain–domain interactions and their influence on the membrane mechanical properties to be studied (see below). Moreover, modification of the domain size permits the verification of the theoretical predictions for the domain shape (McConnell 1991). However, domain migration due to the application of an in-homogeneous electrostatic field occurs only until the repulsive force generated by the field on the domains is opposed by the repulsive force exerted by all the domains in the lattice (Wilke et al. 2006)

In contrast with that which occurs in monolayers, the anionic molecules in bilayers are attracted by the anode, as shown in GUVs (Zendejas et al. 2011) and also in supported bilayers (Groves and Boxer 2002) with charged lipid domains or with proteins bound to the domains. However, Groves and Boxer noted that the direction of the electrophoretic drift does not necessarily indicate the net charge of a molecule, since the lateral field induces a bulk electro-osmotic flow which can influence the drift velocity of the proteins and lipids in the membrane (Groves and Boxer 1995; Stelzle et al. 1992). In bilayers, on the other hand, the opposing effect of the dipoles in each hemilayer may erase the dipolar forces present in the lipid monolayers.

In relation to charged surfactants inserted into membranes, Andelman et al. (1986) pointed out that two different behaviors can be identify at high and low ionic strengths. At a high salt concentration, the charged film can be described by effective dipole moments, with the free energy of the system being similar to that of neutral dipolar monolayers. At the other limit, however, the electrostatic interactions are not screened and the system behaves in a Coulomb-like rather than in a dipolar-like fashion (Andelman et al. 1986). Nassoy et al. (1996) treated ionized latex beads as dipoles by considering the subphase counter-ions, and found a good agreement between the theoretically predicted and the experimentally tracked bead motion. The electrostatic field generated by a charge is different from that generated by a dipole (e.g., the interaction energy varies as r^{-1} for charges and r^{-3} for dipoles; r being the distance between charges or dipoles). Also, the effect that an external electrostatic field is different (e.g., a homogeneous field generates a torque on a dipole and a force on a charge). Thus, the electrostatic effects related to a charge are clearly distinguishable from the effects related to a dipole.

In summary, it is important, but also difficult, to predict how a charged molecule would behave as a consequence of its electrostatic properties when inserted into a membrane. Furthermore, it should be considered that the presence of a membrane implies a discontinuity in the dielectric constant and a diffusion barrier for the ionic species.

Effect of electrostatics on membrane rheology

Although not extensively studied, surface electrostatics can also have profound influences on the membrane structural dynamics through variations in elasticity and in the membrane bending rigidity having consequences on the deformability induced by surfactants and peptides (Rowat et al. 2004; Böckmann et al. 2003; Kmetto et al. 2001). Membranes may become unstable from long-wavelength undulations due to Coulomb repulsion between excess charges which affect the membrane bending rigidity. This instability can be suppressed by free ions in solution which screen Coulomb repulsions. Such phenomena appear to be involved in spontaneous vesiculation, and its suppression by added salts was observed in mixtures of ionic amphiphiles (Kim and Sung 2002; Shoemaker and Vanderlick 2003).

In addition to the intrinsic mechanical properties of membranes being affected by electrostatic interactions, apparent diffusional effects related with this type of interactions appear as emergent properties of biphasic systems. In two-phase monolayers, ordered domain lattices due to domain–domain electrostatic repulsion have been observed (McConnell 1991), with the domain Brownian motion being affected by the domain density, since the motion of crowded domains is impaired by their interaction with the other domains in the lattice, as shown in Fig. 3a (Wilke and Maggio 2009). The apparent surface shear viscosity (η_S) can be computed from the domain diffusion coefficient, and it has been shown that it increases sharply with the amount of the condensed phase (Fig. 3b; from

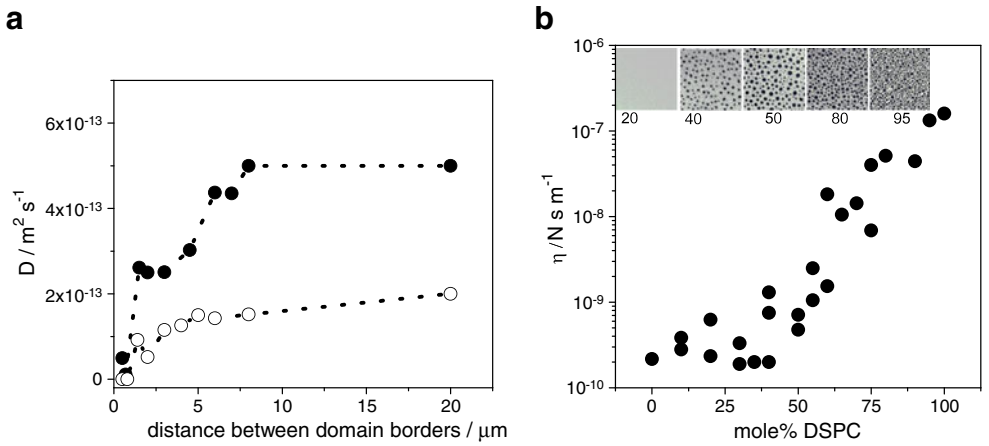

Fig. 3 **a** Domain diffusion coefficients in a lipid monolayer mixture as a function of the distance between neighboring domain–domain borders on 0.15 M NaCl at 5 (*filled symbols*) and 25 (*open symbols*) mN m^{-1}. Taken from Wilke and Maggio (2009), with permission. **b** Shear viscosity for DMPC:DSPC monolayers as a function of their composition calculated from the diffusion coefficients. *Inset* representative images at 10 mNm and the indicated proportions. Taken from Wilke et al. (2010), with permission

Wilke et al. 2010). Furthermore, Ding et al. (2002) determined η_S using a different technique and found that its variation with the percentage of condensed area was analogous to that of the three-dimensional dispersion of spheres in solvent with long-range repulsive interactions.

Nassoy et al. (1996) showed that a partially ionized latex particle inserted into a surfactant monolayer is attracted to the border of domains composed of neutral molecules in a liquid-condensed phase due to dipolar interactions. These authors determined the existence of an electrostatic field of −30 V/cm at the border of the domains, which generated an attractive energy on the bead as high as 300 kT.

In studies of diffusion properties in phase-separated membranes, it was reported that the diffusion coefficients tend to zero as the gel-phase area fraction approaches the percolation threshold (Almeida et al. 1992; Ratto and Longo 2002). Going further into the diffusion processes in membranes, Forstner et al. (2008) modeled systems far from the percolation threshold and found a dramatic slowing down of diffusive propagation, not caused by geometric effects but by the presence of interactions between the domain and the diffusing species. These authors also employed numerical simulations to carry out a systematic study of the diffusion processes in monolayers, and found a sensitive dependence on the interaction strength, with small differences in the potential resulting in orders of magnitude changes of the long-term diffusion coefficient. Related to this, the interaction strength can be easily altered by changing the domain size independent of domain composition (Forstner et al. 2008). This research group also found that there exists an electrostatic potential strength threshold marking the sharp transition from almost unaltered free diffusion to a diffusive process with a drastically reduced diffusion coefficient. In other words, two diffusing species, with only a small difference in their interactions with domains, will have significantly different propagations within the same environment. Thus, the presence of domains can selectively regulate the diffusion of a particle according to the electrostatic properties of the particle and to the size of the domain (Forstner et al. 2008).

In bilayers, unlike in monolayers, domains can often be observed to coalesce over time. However, stable ordered superstructures of stripes and hexagonally ordered domain lattices such as those occurring in monolayers can also be observed (Baumgart et al. 2003; Rozovsky et al. 2005). In addition, it has been shown that dipole–dipole interactions, although still present, are attenuated in lipid bilayers (Liu et al. 2005). Thus, domain–domain repulsion in bilayers contains other non-electrostatic components (Groves 2007).

Not only does the domain size influence the diffusion of a dipole close to a domain but also its shape, since it is known that branched domains generate intense electrostatic

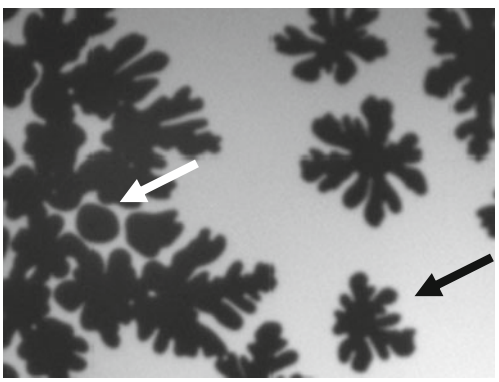

Fig. 4 Mixed monolayers composed of stearic acid and dimyristoyl phosphatidylcholine on subphases at pH 4. Domains were locally crowded and subsequently compressed. Image sizes: 300 × 300 μm^2

field zones in the more curved regions of the domain periphery (Hartel et al. 2005). The domain shape in monolayers has been studied in detail by McConnell (1991), who theoretically predicted that the equilibrium shape of a domain is rounded or flower-like depending on the size of the domain with respect to a critical size, which in turn depends on the ratio of the line tension and the difference in the dipole density, as well as on the percentage of the condensed area.

Although a large number of studies focusing on the shape of neutral domains have been performed, there are few studies related to charged domains. The research group of Janmey formulated a mathematical approach similar to the one presented by the McConnell group, but by considering the net charge on each molecule forming the domain. Compared to a neutral domain, the free energy of the domain has a fourth term that takes into account the effect of charge–charge repulsion on the domain shape. As expected, they found that at a high charge density, a non-circular shape minimizes the domain energy. Furthermore, the critical size at which instability occurs increases with the ionic strength (Foster and Janmey 2001; Cevers and Janmey 2002). Using another approach, Loverde and Olvera de la Cruz (2007) explored the asphericity of charged domains using molecular dynamics simulations, and found that increasing the electrostatic contribution influences the shape of the domains and strongly increases the correlation and ordering between domains. However, no extensive or systematic experimental study oriented toward the analysis of the shape of charged domains has yet been performed.

The size of a domain, which in turn defines its equilibrium shape, is usually distinctive for each given system with the process of domain nucleation defining the amount of nuclei, and thereby the domain size in a given experimental condition. Moreover, the kinetics of phase separation, in relation to the perturbation velocity, is also a key factor in the domain size and domain shape in the case of out-of-equilibrium conditions. The effect of the level of supersaturation on domain shape has been extensively studied by the research group of Castillo (see references in Gutierrez-Campos et al. 2010).

Since the size and shape of the domain determines the geometry of the electrostatic field generated by the domain, it is important to know the physicochemical reasons for the existence and evolution of the composition-dependent domain shape. Then, by knowing the factors that underlie the domain shape and distribution, this allows the surface topography of the system and the electrostatic effect of the domain on the particles inserted into the membrane to be controlled. Domain environment, for example, affects the domain size and shape (Bernchou et al. 2009), which is illustrated in Fig. 4 (unpublished results). In the region of high domain density, domains are small and circular (white arrow), whereas in the regions of low density, flower-like domains occur (black arrow). The circular and small domains influence the motion of particles inserted into the membrane in a different manner than that of the larger and flower-like domains, as mentioned above. This effect may also be amplified to a membrane having different effective mechanical properties due to local electrostatics.

Conclusions

Electrostatic interactions are of paramount importance in defining the phase diagram of a membrane and they modulate the affinity of proteins to the biosurface. In homogeneous membranes, the presence of charges inserted into the membrane or in solution changes the mechanical properties. In two-phase monolayers, the electrostatic field generated by domains greatly influences the motion of the particles inserted into the monolayer. However, in bilayers, this issue is still an open question along with the manner in which a charged surfactant inserted into a membrane will respond to an electrostatic field. Furthermore, it is intriguing that monolayers and bilayers appear to behave differently with respect to these interactions.

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Conflict of interest None.

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