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2005 J. Phys.: Condens. Matter 17 S2943

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Charge inversion on membranes induced by multivalent-counterion fluctuations

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Received 22 December 2004

Published 22 July 2005

Online at stacks.iop.org/JPhysCM/17/S2943

Abstract

Based on the two state model, we study the condensation of counterions on oppositely charged membranes in the presence of monovalent salts. Using the Gaussian approximation, we evaluate the contribution of two-dimensional charge fluctuation to the free energy, from which the number of condensed counterions is determined self-consistently. It is shown that charge inversion can occur upon the addition of divalent ions of millimolar range, or of trivalent ions of micromolar range. The driving force for the overcharging mechanism is the charge correlation induced by thermal fluctuation, in which the multivalency of the counterions plays a crucial role.

(Some figures in this article are in colour only in the electronic version)

Counterions in watery solution dominantly distribute near an oppositely charged surface of macroions, forming a diffuse electric double layer. The structure of a double layer of counterions, which has been usually described by the mean-field Poisson–Boltzmann theory, is of great importance in interaction and phase behaviours of macroions [1, 2]. When the macroions are subject to an external electric field, they instantaneously reach a stationary velocity due to the viscous friction from the ambient solution. This is called electrophoresis, and it provides an efficient way to probe the double layer structure and thus to measure the surface potential of charged colloidal systems [3, 4]. The counterions strongly bound to the macroion play an important role in this transport property by renormalizing the electrokinetic charges of the surface [5]. According to the Poisson–Boltzmann theory, the macroion charge is only partially compensated (neutralized) by the counterions so that the sign of the net charge is retained even in the presence of the strongly associated counterions.

It has been however observed that the counterions can further condense on the surface beyond compensation of the macroion charge, leading to reversal of the drift direction in electrophoretic experiments [6]. This phenomenon is called charge inversion, and has been

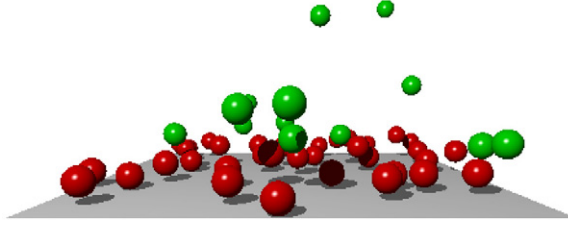


Figure 1. Snapshot for the distribution of multivalent cations near a negatively charged planar surface. For clarification, the monovalent electrolytes that screen the Coulomb interaction among the counterions are not shown. According to the two state model, the counterions are assumed to be either in the bound state (dark sphere), or in the free state (less dark sphere).

appealing for many practical applications such as gene delivery through a similarly charged cell membrane. Therefore, significant theoretical effort has been devoted to study this phenomenon over the last few years [7]. Nguyen *et al* [8] have recently explained the charge inversion with strong structural correlations based on the Wigner crystal picture [9], which is legitimate for a zero temperature limit. The charge inversion, along with the attraction between similarly charged molecules [10, 11], constitutes the apparent evidences for the important role of charge correlations in biological systems.

In this work we investigate the charge inversion from a different point of view from the previous study [8]: based on the Gaussian approximation, thermally induced charge fluctuations are explicitly taken into account, which would be relevant for a finite temperature regime. For this purpose, we consider a charged planar surface or membrane with negative surface charge density $-\sigma_0$, when both multivalent ions and monovalent salts such as NaCl are present in solution. After integrating out the degrees of freedom for all monovalent salts in the bulk, the electrostatic interactions between the remaining (bound) charges are screened. On further integrating out the surface bound charges including the condensed counterions as slow degrees of freedom, we obtain the free energy arising from two-dimensional charge fluctuations, beyond the mean-field theory. The number of condensed counterions is determined self-consistently by considering the phase equilibria between counterions on the surface and in the bulk. It is shown that the effects of correlation and thermal fluctuation can lead to charge inversion, for which the presence of multivalent ions is essential, in consistency with the previous study [8].

Here we employ the two state model (figure 1) in which counterions are divided into two classes, namely, condensed and non-condensed (free) ions [12]: some of counterions can bind to an oppositely charged surface, in spite of entropic penalty, due to the electrostatic attraction being greater than the thermal energy. On the other hand, counterions tend to remain in the bulk to gain entropy. Considering that the ions in solution are either monovalent or multivalent with valency Z , the effective surface charge density of the membrane is reduced due to counterions condensed within the diffusive layer of a finite thickness as

$$\sigma(\mathbf{x}) = -\sigma_0 + \sum_{Z=1} Z e n_Z, \quad (1)$$

where $-\sigma_0$ is the bare membrane charge density, and n_Z is the number density of condensed counterions. The thermal agitation tends to unbind condensed counterions, which, as time goes on, can in turn bind to the surface. In this way, one can expect continuous exchanges between counterions in the two states. Along with lateral diffusion of mobile bare membrane charges, binding–unbinding of counterions gives rise to fluctuations to the surface charge density. The

effective Hamiltonian of membranes with fluctuating field $\sigma(\mathbf{x})$ is given by

$$\mathcal{H} = \frac{1}{2} \int d\mathbf{x} d\mathbf{y} \sigma(\mathbf{x})\sigma(\mathbf{y})v(|\mathbf{x} - \mathbf{y}|, 0) + \frac{\chi}{2} \int d\mathbf{x} (\sigma(\mathbf{x}) - \bar{\sigma})^2 \quad (2)$$

where $v(r) = \exp(-\kappa r)/\epsilon r$ is the screened Coulomb interaction, mostly due to monovalent salts, in a solution with dielectric constant ϵ . The Debye screening length κ^{-1} is mainly determined by the monovalent electrolyte concentration. The second term represents the entropic cost for the density fluctuations in the two-dimensional condensed counterion layer, which is obtained by expanding the ideal gas entropy around the averaged value $\bar{\sigma}$ up to harmonic order. The two-dimensional compressibility χ for density fluctuations is inversely proportional to $\sigma_0/e + \sum_{Z=1} Z^2 \bar{n}_Z$, where $\overline{\dots}$ denotes the average [13].

In order to construct the free energy \mathcal{F} with the charge correlation effects incorporated, we perform the functional integral over $\sigma(\mathbf{x})$:

$$\beta\mathcal{F} = \ln \int \mathcal{D}\sigma(\mathbf{x}) e^{-\beta\mathcal{H}[\sigma(\mathbf{x})]}, \quad (3)$$

where the fluctuation $\delta\sigma = \sigma - \bar{\sigma}$ up to the second order (Gaussian level) is retained, and the self-energy is subtracted following the scheme of Lau and Pincus [14]. This free energy contains two contributions. One is electrostatic attraction arising from the monopole–monopole interaction, which is directly related to the excess surface charge $\bar{\sigma}$ and therefore vanishes when the surface is neutralized by the condensed counterions. The other is the purely charge correlation contribution, corresponding to multipole–multipole interaction, which is particularly important for multivalent ions and is the driving force for charge inversion as will be shown shortly. The electrochemical potential for condensed ions is then determined by variation of the effective free energy with respect to the change of number of condensed counterions, together with the entropic penalty from confinement within the layer, as

$$\mu_Z^{\text{cond}} = \frac{\partial\mathcal{F}}{\partial\bar{n}_Z} + k_B T \ln \left[\frac{\bar{n}_Z v_0}{\ell} \right], \quad (4)$$

where v_0 is the specific volume of a counterion, and ℓ is the thickness of the diffusive layer. On the other hand, for ions in the free state, the chemical potential is assumed to arise mainly from the entropy of mixing [15], as

$$\mu_Z^{\text{free}} = k_B T \ln n_Z^{\text{bulk}} v_0, \quad (5)$$

where n_Z^{bulk} is the bulk concentration of ions with valency Z . The electrostatic contribution to the free energy for the free ions can be estimated using the 3D Debye–Hückel theory as $-k_B T \kappa^3/(12\pi)$ with Debye length κ^{-1} . Then the ratio of contribution from entropy to that from the electrostatic energy to the chemical potential of the free ion is given by

$$\frac{24\pi \ln n_Z^{\text{bulk}} v_0}{3\sqrt{(4\pi \ell_B)^3 n_Z^{\text{bulk}}}}, \quad (6)$$

which is of order of 10, much larger than 1, for both monovalent and divalent ions due to their low densities. Because the free counterions are at low density in the bulk unlike the condensed ones, we assume that the Coulomb energy is negligible for the ions in the free state. In thermal equilibrium, the chemical potential should remain constant throughout the space and thus we use the chemical equilibrium condition as

$$\mu_Z^{\text{cond}} = \mu_Z^{\text{free}} \quad (7)$$

which determines \bar{n}_Z and thus $\bar{\sigma}$ self-consistently.

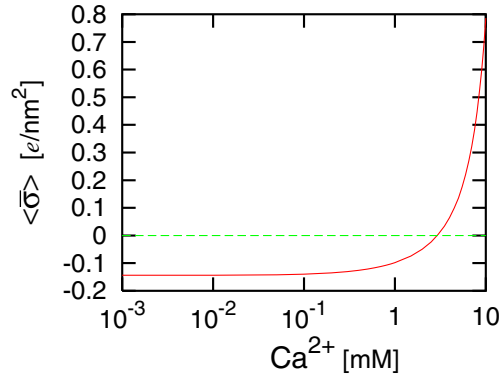


Figure 2. Effective charge density of the surface as a function of calcium (divalent counterion) concentration in the bulk. The bare membrane charge density is given by $-\sigma_0 = -0.3e \text{ nm}^{-2}$ and the thickness of the condensed counterion layer is assumed to be $\ell = 10 \text{ \AA}$. Unless explicitly mentioned, monovalent salts are always assumed to be present with 0.1 M concentration throughout this work, corresponding to the physiological condition. It is shown that the net charge continuously changes its sign upon the influx of Ca^{2+} of millimolar range.

Figure 2 exhibits the effective surface charge density $\bar{\sigma} = -\sigma_0 + \sum Z e \bar{n}_Z$, determined by the above scheme, as a function of bulk concentration of divalent calcium ions. The charged surface is also in contact with a solution of 0.1 M monovalent salts such as NaCl, which corresponds to the physiological conditions and determines the Debye length of the screened electrostatic interaction in equation (2). The thickness of the condensed layer, ℓ , is here assumed to be 10 \AA , and the initial bare membrane charge density is given by $-\sigma_0 = -0.3e \text{ nm}^{-2}$. We find that $\bar{\sigma} = -0.14e \text{ nm}^{-2}$ for the membrane in the solution with NaCl only: the surface charge density is reduced below the bare value due to the condensation of monovalent counterions. However, the contribution of monovalent ions is only possible within a layer thickness ℓ of the order of the Debye length. As will be shown, monovalent ions hardly condense onto the surface if we decrease ℓ to a few angstroms. In the presence of multivalent counterions, we observe the complete compensation of the bare membrane charges with the addition of about 3 mM calcium ions. More interestingly, a continuous sign reversal of the effective surface charge is found upon adding the calcium ions further, indicating overcharging [8].

The charge correlations play a dominant role in the overcharging mechanism. This charge correlation contribution to the chemical potential is shown to have strong dependency on the valency of counterion as

$$\mu_Z^{\text{corr}} = \frac{\partial \mathcal{F}_{\text{corr}}}{\partial \bar{n}_Z} \propto -\frac{Z^2}{\chi}, \quad (8)$$

since χ is inversely proportional to $\sigma_0/e + \sum_Z Z^2 \bar{n}_Z$. Therefore, the charge inversion is observed within our model only for multivalent counterions because the correlation-induced attraction is so weak for monovalent ions. It can also be seen in figure 2: although there are already a lot of monovalent ions corresponding to the concentration of 0.1 M, the charge inversion never happens until divalent ions of millimolar range is added. In order to emphasize the valency dependence, we also consider the injection of trivalent counterions, as shown in figure 3. For the trivalent ions, the charge inversion phenomena is again observed for the range of micromolar trivalent ions, which is considerably lower than that in divalent ions. Recently, this strong charge inversion has been shown to lead to the structural instability

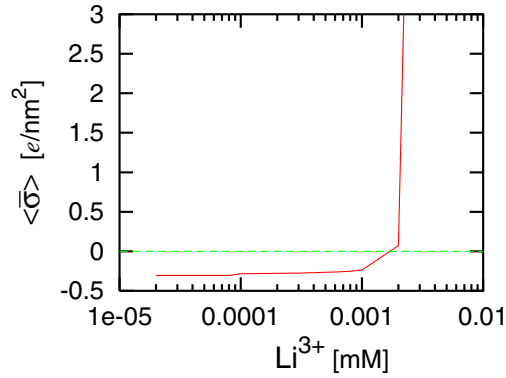


Figure 3. Effective surface charge density as a function of lithium (trivalent counterion) concentration in the bulk. The bare membrane charge density is given by $-\sigma_0 = -0.5e \text{ nm}^{-2}$ and the thickness of the condensed counterion layer is again assumed to be $\ell = 10 \text{ \AA}$. The discontinuous changes of net charge take place when trivalent counterions of micromolar concentrations are added.

of a membrane when it is coupled to thermal undulations, and was thus suggested as a precursor of vesicle fusion [16]. It is interesting to note that the ranges for concentration of multivalent counterions for strong charge inversion agree with fusion thresholds in experiments using Li^{3+} and Tb^{3+} [17]. One also notes that the surface charge for trivalent ions is shown to be discontinuous, which is consistent with the work by Lau *et al* [12]. In their work, they considered the case of counterions only so that the total system is electrically neutral. Accordingly, charge inversion was not studied, but discontinuous counterion condensation was observed as the valency of the counterion increases. The discontinuity of the effective surface charge density shown in figure 3 is a result of a first-order phase transition as in a gas–liquid system: at the transition point, the chemical potential of the high density phase of condensed trivalent ions becomes equal to that of the low density phase, leading to the abrupt jump in $\bar{\sigma}$. Beyond this point of phase coexistence, the effective charge density grows continuously, which is however not shown because the Gaussian approximation we adopted is invalidated in such a highly charged system.

When no electrolyte is added, the counterion density distribution near a surface decays algebraically where the thickness of the condensed-counterion layer is characterized by the Gouy–Chapmann length. On the other hand, in the limit of strong electrolyte, the density profile decays exponentially and the diffusive layer would be rather characterized by the Debye length [18]. In general the thickness should be in between the Debye length and Gouy–Chapmann length. Furthermore, for the surface charge density $-\sigma_0 = -0.3e \text{ nm}^{-2}$ considered in figure 2, the Gouy–Chapmann length $\ell_{GC} = e/(2\pi\ell_B\sigma_0)$ is comparable to the Debye length. So we assumed here that, in the presence of strong electrolytes, ℓ is of order of the Debye screening length. Nevertheless the thickness of the layer is the only arbitrary parameter in this work, so it should be checked with a special attention. For this purpose we investigate the effects of different ℓ on the counterion condensation. In figure 4, we plot the critical concentration of divalent counterions for various ℓ ranging from the order of ionic radius to the order of the Debye length. The critical concentration means the concentration in which complete neutralization, characterized by $\bar{\sigma} = 0$, occurs. It is found that the specific choice of ℓ does not change the qualitative picture of overcharging: the binding energy of a monovalent ion is not much larger compared to $k_B T$. Therefore, if we consider much smaller ℓ , the contribution of monovalent counterions to $\bar{\sigma}$ becomes negligible, due to the large entropic

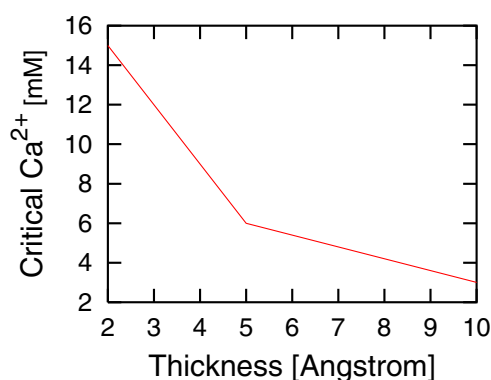


Figure 4. Critical calcium concentration as a function of the thickness of condensed layer ℓ . Critical means the complete compensation of the bare membrane charges by counterions, namely, as defined as $\bar{\sigma}$ in figure 2. The layer thickness varies from the ionic radius to the Debye length. As expected, more calcium ions are required for smaller ℓ due to the enhanced entropic penalty. Nonetheless, the qualitative picture (charge inversion in the presence of millimolar divalent ions) remains the same.

penalty compared to the binding energy. But strong charge inversion is still predicted to occur upon the addition of divalent counterions of millimolar range. It should be noted that, whatever ℓ is, the presence of multivalent ions is essential, as can be inferred by equation (8).

Our model is based on the Gaussian-level theory which is valid when the fluctuation is not so strong. In other words, if the electrostatic interaction energy between surface charges is much larger than the thermal energy, this picture may not be so legitimate that further condensation may be questionable when $\bar{\sigma} \geq$ the order of $1e \text{ nm}^{-2}$. In realistic situations, the counterion distributions near charged macromolecules and surfaces are much more complicated because of various factors. For instance, the discreteness of the surface charges enhances localization of the counterions near the surface. The presence of a Stern layer due to specific chemical adsorption of ions also yields non-trivial modifications to the determination of effective surface charge density through the electrokinetic experiments.

In summary, the over-condensation of counterions can occur as a result of the strong correlation between charges which has a significant valency dependence. Our prediction is grounded on the thermal fluctuation picture, unlike [8] where strong structural charge (Wigner crystal) correlations are taken into account based on a zero temperature picture [9]. At room temperature, our description may therefore be appropriate. However, the physical origins for charge inversion in both cases are common, namely, strong charge correlation leading to inversion. The formulation in this paper is simple, but the obtained results can explain various interesting phenomena, from charge inversion to discontinuous counterion condensation.

Acknowledgments

This work was supported by APCTP (Focus Program), Brain Korea 21 Project, and MOST (KOSEF) through Systems Bio-Dynamics Research Center.

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