Charge Regulation with Fixed and Mobile Charges

Yael Avni,1, 2 David Andelman,1 and Rudolf Podgornik2, 3

1 Raymond and Beverly Sackler School of Physics and Astronomy, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel
2 School of Physical Sciences, University of Chinese Academy of Sciences, Beijing 100049, China
3 Kavli Institute for Theoretical Sciences, University of Chinese Academy of Sciences, Beijing 100049, China, and CAS Key Laboratory of Soft Matter Physics, Institute of Physics, Chinese Academy of Sciences, Beijing 100190, China

Uncompensated charges do not occur in Nature and any local charge should be a result of charge separation. Dissociable chemical groups at interfaces in contact with ions in solution, whose chemical equilibrium depends both on short-range non-electrostatic and long-range electrostatic interactions, are the physical basis of this charge separation, known as charge regulation phenomena. The charged groups can be either fixed and immobile, as in the case of solvent-exposed solid substrate and soft bounding surfaces, (e.g., molecularly smooth mica surfaces and soft phospholipid membranes), or free and mobile, as in the case of charged macro-ions, (e.g., protein or other biomolecules). Here, we review the mean-field formalism used to describe both cases, with a focus on recent advances in the modeling of mobile charge-regulated macro-ions in an ionic solution. The general form of the screening length in such a solution is derived, and is shown to combine the concept of intrinsic capacitance, introduced by Lund and Jönsson, and bulk capacitance, resulting from the mobility of small ions and macro-ions. The advantages and disadvantages of different formulations, such as the cell model vs. the collective approach, are discussed, along with several suggestions for future experiments and modeling.

I. INTRODUCTION

The mechanism of ion exchange between dissociable amino acids and their surrounding solution has been proposed already in the 1920’s by Linderstrem-Lang of the Carlsberg Laboratory [1]. Early advances in the dissociation/association equilibria and acid-base properties of polyelectrolytes [2, 3] were introduced in the ground-breaking works of Kirkwood and Schumaker [4]. These, as well as the dissociation equilibria of proteins (Tanford and Kirkwood [5]), have been authoritatively reviewed by Borkovec, Jönsson, and Koper [6].

Another important contribution came in the 1970’s when Ninham and Parsegian [7] introduced the charge regulation (CR) mechanism. In their seminal work, they developed a self-consistent relationship between the local electrostatic potential and the dissociated state of chargeable surface groups. The novelty at that time was to introduce a more special charge-regulated boundary conditions for the Poisson-Boltzmann (PB). The charge association/dissociation process (CR mechanism) couples the local electrostatic field with the local charge, and results in a self-consistent partitioning of dissociated and associated surface states [8, 9].

Charge regulation governs many electrostatic interactions in biological systems, making it fundamental to the understanding of protein complexation [10, 11] and adsorption onto surfaces [12, 13], bacterial adhesion [14], viral capsids assembly [15], translocation of DNA through solid-state nanopores [16] and several other bio-processes [17]. It is also a key ingredient for the design of materials based on polyelectrolytes in solution and polyelectrolyte brushes [18, 20].

The CR formulation can be implemented via the law of mass action [21, 22], and separately, by modifying the surface part of the total free-energy [23, 30]. The latter approach leads to the same results as the law of mass action, but with the advantage that it can be easily generalized to include any non-electrostatic surface interactions [31, 32].

The Poisson-Boltzmann theory with CR surfaces has been studied in the past for uniform charge distributions of dissociable groups, in contact with an electrolyte solution [9, 33, 34]. Other studies involved modeling of a single CR colloid in solution, in the proximity of another charged surface [35]. Most of previous calculations employed linearized CR boundary conditions or a linearized version of the PB equation itself (known as the Debye-Hückel limit) [36, 37]. The assumption of uniform charge distribution was dropped in later works [10, 11], and CR surfaces with patchy chargeable groups were analyzed as well. In some cases, it was found that higher-order electrostatic multipoles may need to be considered in relation to the CR process, in addition to the monopolar ones [42, 43].

A number of models of single protein and protein-protein interactions [44] in aqueous solution have been studied by various simulation techniques [45, 49], and extensively reviewed in Ref. [50]. For proteins, the CR contributes significantly to the fluctuation part of the electrostatic interaction (the Kirkwood-Schumaker interac-
In order to evaluate the importance of charge regulation in protein and polyelectrolyte systems, the standard MC algorithm has to be augmented in order to account for the protonation/deprotonation reaction of the acidic/basic sites. This implies an additional MC step with energy change that follows the Nernst equation, \( \Delta U = \Delta U_{\text{ES}} \pm k_B T \log_{10} (\text{pH} - \text{pK}_0) \), where \( \Delta U_{\text{ES}} \) is the change in the standard electrostatic energy \( [52] \).

Charge regulation was shown to have pronounced effects on the properties of weak polyelectrolytes, such as the pH-dependence of chain conformation and ionization \([19, 25, 26]\). This has been explored for linear \([52]\), star-like \([53]\), and macroscopic networks \([54, 55]\), and microgel architectures \([56]\) of weak polyelectrolytes, and for physically deposited and chemically grafted polyelectrolyte layers \([25, 57]\).

The PB theory of a solution of coupled CR macro-ions was addressed to a much lesser extent, mostly within the context of the cell model \([58]\), for which each macro-ion is placed in the center of a cell whose external boundary mimics the presence of neighboring macro-ions. In this way, the interactions between the macro-ions are taken into account on a simple mean-field level \([6] \). The cell model was later generalized to include charge regulation of macro-ion surfaces \([59]\), which allowed to find the macro-ion effective charge as a function of their concentration \([60]\), and the phase behavior of oppositely charged macro-ion mixtures \([61, 62]\).

While the cell model gives a reasonable approximation for the effective charge of the macro-ions in the homogeneous bulk, it cannot describe the collective effects due to external electric fields, where both the effective charge and macro-ion concentration vary in space, as is depicted in Fig. 1. To account for such effects, one needs to employ a more refined and collective description.

An attempt in that direction was done in a study of the sedimentation of CR colloids \([63]\). However, as the theory was not derive from first principles, its consistency remains uncertain. To that end, a general formalism was introduced in Refs. \([65, 66]\), and account for mobile macro-ion effects in dilute solutions. The macro-ions are treated as point-like particles, similar to small salt ions, while retaining their internal degrees of freedom that determine the macro-ions charge state in a self-consistent way.

In this short review, we discuss some recent developments in the theoretical modeling of CR macro-ions in solution. First, the general free-energy formalism is introduced in section II. Then, we review the cell model (section III) and concentrate on the collective description of mobile macro-ions (section IV), as was set forward in Refs. \([65, 66]\). We end the review (section V) by offering several concluding remarks and future prospects. Throughout this review, we shall employ the mean-field formalism and neglect any fluctuation effects, which are addressed elsewhere \([27, 50, 67]\).

### II. THE GENERAL FREE-ENERGY FORMALISM FOR CHARGE REGULATION

The PB mean-field theory of charge-regulating processes can be formulated as a density functional theory of the free energy. The free-energy functional consists of bulk and surface terms, and the combined free energy assumes the form

\[
\mathcal{F} = \int \! d^3 r \, f_\psi (\psi, \nabla \psi, n_i) + \int \! d^2 r \, f_s (\psi_s, n_s^\pm), \tag{1}
\]

where \( \psi(r) \) is the local electrostatic potential, \( n_i(r) \) is the local concentration of species \( i = 1, 2, \ldots \), and their values on the surface are denoted as \( \psi_s \) and \( n_s^\pm \), respectively. The volume free-energy, \( f_\psi \), contains the electrostatic energy and free-energy terms of an uncharged system. In a dilute solution, these terms represent the ideal-gas entropy of the ions. The surface part, \( f_s \), essentially includes the CR effect via the ion-surface interaction, i.e., charge regulation.

Assuming that the system is composed of monovalent salt, then

\[
f_\psi (\psi, \nabla \psi, n_i) = f_{\psi_0} (\psi, \nabla \psi, n_i^\pm), \tag{2}
\]

is the standard PB free-energy density \([8]\). For simplicity, we further assume that the only ion type that exchanges at the surface is one of the salt species, chosen to be the cation. An additional assumption is that only a single adsorption/desorption mechanism is involved. Consequently, \( f_s \) is a function of the surface potential \( \psi_s \), and of the surface concentration of the adsorbed cations, \( n_s^+ \). Its exact functional form depends on the CR model that is employed \([81]\).

The volume part of the Euler-Lagrange equations is given by

\[
\nabla \cdot \left( \frac{\partial f_\psi}{\partial \nabla \psi} \right) - \frac{\partial f_\psi}{\partial \psi} = 0 \quad \text{and} \quad \frac{\partial f_\psi}{\partial n_i^\pm} = 0, \tag{3}
\]

while the surface part is

\[
\left. n \cdot \frac{\partial f_s}{\partial \nabla \psi} \right|_s + \left. \frac{\partial f_s}{\partial \psi_s} \right|_s = 0 \quad \text{and} \quad \left. \frac{\partial f_s}{\partial n_s^+} \right|_s = 0, \tag{4}
\]

where \( n \) is a unit vector normal to the bounding surface(s). Equation (3) reduces to the PB equation, and Eq. (4) yields the exact CR boundary condition, which was originally derived using chemical equilibrium equation \([7]\). The above formalism can be extended to describe a variety of other geometries, with the only limitation being that the boundaries are taken to be fixed (immobile) in space.
III. THE CELL-MODEL FOR CHARGE-REGULATED MACRO-IONS

As mentioned in the introduction, a viable way to describe charge regulation of immobile macro-ions is the cell-model approach. Each macro-ion occupies the center of an imaginary Wigner-Seitz cell, and is surrounded by solvent molecules and salt ions. Both the cell and the central macro-ion are taken to have a spherical shape for simplicity (although a cylindrical cell is used to model polyelectrolytes in solution).

The macro-ion fixed radius is denoted by \( a \), while the cell radius, \( R \), is determined by the concentration (per unit volume) of macro-ions, \( p \), such that \( R \sim p^{-1/3} \). We can now apply the formalism presented in section II, with the additional demand of electro-neutrality in each cell, separately. For the bulk part, Eq. (3) remain the same, but they are complemented not by Eq. (4), but by two other conditions,

\[
\frac{\partial f_v}{\partial p} = 0 \quad \text{and} \quad \frac{\partial f_v}{\partial Q_p} = 0. 
\]

Solving these equations, one can derive ionic profiles, effective macro-ion charges and electrostatic pressure as function of the macro-ion concentration \( p \), while the interactions between the macro-ions are taken into account in an indirect manner, via the external boundary condition at \( R \).

This single-particle cell-model approach is mostly appropriate at high density of the macro-ions, where their translational entropy is small or even vanishing [55], or when one wants to describe a homogeneous bulk. However, it cannot describe collective effects such as the response of macro-ions in solution to external fields.

IV. THE COLLECTIVE APPROACH FOR CHARGE REGULATED MACRO-IONS

In the collective approach, applicable in the limit of dilute macro-ion solutions, the macro-ions themselves are treated in analogy to point-like salt ions [65, 66]. Assuming a solution containing many point-like CR macro-ions with concentration \( p \), the surface term in Eq. (1) vanishes and is replaced by additional terms in the volume part of the free energy. Equation (2) now reads,

\[
f_v(\psi, \nabla \psi, n_{\pm}, p, Q_p) = f_{PB}(\psi, \nabla \psi, n_{\pm}, p) + p g(\psi, Q_p),
\]

where \( Q_p \) is the overall macro-ion charge, and \( g(\psi, Q_p) \) is the point-like version of the former \( f_v(\psi, n_{\pm}) \), satisfying

\[
g(\mathbf{r}) = \lim_{a \to 0} \int |a^d r f_v(\psi_\mathbf{r}, n_{\pm}(\mathbf{r}))
= g(\psi(\mathbf{r}), Q_p(\mathbf{r})).
\]

The volume part of Eq. (6) is now composed of the PB free energy of the three ionic species, \( n_{\pm} \), and the collective term \( p g(\psi, Q_p) \).

In this formalism, Eq. (3) remain the same, but they are complemented not by Eq. (4), but by two other conditions,

\[
\frac{\partial f_v}{\partial p} = 0 \quad \text{and} \quad \frac{\partial f_v}{\partial Q_p} = 0. 
\]

The macro-ions are now described on the same footing as the solution salt ions, except that their charge, \( Q_p \), is not fixed, but is determined self-consistently.

The most important difference between the cell model and the collective description is the macro-ion translational entropy described by \( f_{PB}(\psi, \nabla \psi, n_{\pm}, p) \). In addition, the CR affects the charge of the macro-ion \( Q_p \), as well as its concentration \( p \) and the corresponding electrostatic potential. The latter is averaged over a local distribution of macro-ions and that of the salt ions around the macro-ions.
The mobility of the macro-ions has several important consequences. In the presence of external fields, both the macro-ionic concentration \( p \) and charge \( Q_p \) vary in space, as is demonstrated in Fig. 2. Some insights on this behavior can be obtained by looking at the effective screening length of the system, \( \lambda_{\text{eff}} \),

\[
\lambda_{\text{eff}}^{-2} = -\frac{1}{\varepsilon_0 \varepsilon} \left. \frac{\partial \rho(\psi)}{\partial \psi} \right|_{\psi=0},
\]

defined in analogy with the Debye screening length, \( \lambda_D \), where \( \rho \) is the local charge density, to be defined below.

We recall that the charge density for an electrolyte solution having \( N \) ion species, each with bulk concentration \( n^b_i \) and with constant charge \( q_i \) on each ionic species \( i \) is:

\[
\rho(\psi) = \sum_i q_i n_i(\psi),
\]

where \( n_i(\psi) = n^b_i \exp(−q_i \psi/k_B T) \), and the Debye screening length is given by:

\[
\lambda_D^{-2} = \sum_i q^2_i n^b_i/(\varepsilon_0 \varepsilon k_B T).
\]

For a monovalent solution, the Debye length reduces to \( \lambda_D = 1/(\sqrt{\varepsilon_0 k_B T b}) \) where \( b \) is the Bjerrum length \( \varepsilon_0 k_B T \).

In the CR case, the screening length depends similarly on \( \rho(\psi) \), the local charge density, but as the macro-ions are charge regulated, the expressions are somewhat different:

\[
\rho(\psi) = n^+ + n^− + Q_p(\psi)p(\psi).
\]

and

\[
\lambda_{\text{eff}}^{-2} = \frac{4\pi \varepsilon_B}{e^2} \left[ e^2 n^+ + e^2 n^− + p_b \left( Q_p^2 + (\Delta Q_p)^2 \right) \right],
\]

where \( Q_p(\psi=0) \) is the average and the fluctuations around the average, due to charge regulation, are given by

\[
(\Delta Q_p)^2 \equiv -k_B T \left. \frac{\partial Q_p(\psi)}{\partial \psi} \right|_{\psi=0}.
\]

The above relations for the average macro-ionic charge and its variance remain the same for all CR models, while the specific form of \( Q_p \) and \( \Delta Q_p \) may vary according to the CR model in mind.

An interesting feature of Eq. (11) is that it allows us to understand the system in terms of the overall capacitance, \( i.e., \) the charge density response to the imposed variation in the electrostatic potential. The capacitance of the system has two contributions: the bulk capacitance, stemming from the spatial redistribution of the charged particles \( (n_\pm + p) \), and the intrinsic capacitance due to the ability of each of the CR particles to adjust its charge, \( Q_p \). Hence, simple ions having a fixed charge, contribute only to the bulk capacitance, whereas the macro-ions contribute to both. Note that the intrinsic capacitance is the same as the capacitance defined by Lund and Jönsson \([52]\) in order to quantify the Kirkwood-Schumaker interaction. Furthermore, Eq. (11) is a generalization of that capacitance for the mobile macro-ion case.

When using a theory that does not take collective effects properly into account, one might derive Eq. (11) without the important \( \Delta Q_p \) term \([68]\). However, this term may modify the screening substantially, especially if the macro-ions are close to the point of zero charge, such that the \( Q_p \) term is small.

Different forms of \( g(\psi) \) depend on the specific model under investigation, and give rise to a rich variation in the screening length, and consequently affect the electrostatic properties. In particular, it is possible to classify CR mechanisms by their asymmetry between the positive and negative ions adsorption \([65]\). In this review, we assumed for simplicity that only cations can be adsorbed on the macro-ions, but the generalization to include a second adsorption process for the anions is straightforward as is presented in Refs. \([9, 65, 66]\). In symmetric CR models, the macro-ions adsorb or release cations and anions in the same amount, resulting in a preference to an overall zero macro-ion charge, \( \overline{Q}_p = 0 \). Asymmetric models, on the other hand, lead to highly charged macro-ions.

The asymmetry is determined by the model parameters, for example the number of positive/negative dissociable groups, and the free energy gain from each dissociation. Symmetric and asymmetric models lead to very different dependence of the screening length on the macro-ion concentration, as was shown in Ref. \([66]\) (see Fig. 3). Apart from the models discussed in Ref. \([66]\), other classification and more complicated CR mechanisms surely exist, their rich behavior awaiting to be uncovered.

V. CONCLUDING REMARKS AND FUTURE PROSPECTS

Our understanding of charge regulation phenomena grew immensely in the passing decades since its discovery \([1]\) and first rigorous formulation \([7]\). Most of the attention has been given to the problem of a single CR macromolecule in solution, or the interaction between two CR macromolecules or between two CR surfaces \([6, 30, 47, 52, 69]\). However, the many-body problem of multiple and coupled CR macromolecules was addressed to a much lesser extent, being mainly analyzed within two frameworks: the cell model \([55, 69]\) and the collective approach \([65, 66]\), each having its own advantages and merits in different situations.

The collective description of mobile CR macro-ions in an electrolyte solution is a simple generalization of the PB paradigm to the case of more complex ionic solutions, composed of macro-ions or nano-particles with non-trivial association/dissociation properties. It is particularly useful in order to understand the screening properties of the bulk solution as well as the inhomogeneous density and electrostatic potential distribution close to an externally imposed charge, as in the case of a bounding charged interface.

Such a collective description provides an explicit generalization of the screening length that consistently takes into account the redistribution of charge density of all the
mobile charged species (just as is done for the standard Debye screening length), combined with specific changes in the macro-ion charge due to the charge regulation process itself. These two properties together determine the screening response of the solution. The understanding of the screening phenomenon in such complex ionic solutions should have repercussions not only conceptually but also practically when decay lengths are extracted from experimental data and compared to theoretical predictions.

The possibly high values of the macro-ion charge ($Q_p$), which can reach up to hundreds of unit charges, make the applicability range of the collective approach difficult to delimit. As the charge of the macro-ions itself varies, a systematic electrostatic coupling constant expansion that defines the strong coupling limit [70] is hard to obtain, and further detailed testing of the collective approach either by new experiments and/or detailed simulations is therefore highly desirable.

The collective approach may see other important applications in the future, particularly in the investigations of inhomogeneous systems subjected to external fields, such as centrifugal sedimentation of colloids [64], proteins near charged membranes, or protein near impermeable membranes that generate electric fields due to the Donnan equilibrium.

On the theoretical side, it would be interesting to study different and perhaps more detailed CR models, including interactions between different dissociable groups, within the collective approach. Such short-range non-electrostatic interactions will generate higher-order terms in the free energy, and may lead to yet unexplored phase separations and phase transitions. Hopefully, these and other unsolved issues will be addressed in the future by experiments and theory.

**Acknowledgement:** This research has been supported by the Naomi Foundation through the Tel Aviv University GRTF Program. One of us (YA) is grateful for the hospitality of the University of the Chinese Academy of Sciences and the Institute of Physics, CAS, where part of this work has been conducted. RP would like to acknowledge the support of the 1000-Talents Program of the Chinese Foreign Experts Bureau, and DA acknowledges partial support from the ISF-NSFC (Israel-China) joint program under Grant No. 885/15.
[1] Linderstrøm-Lang KU: On the ionisation of the proteins. Medd Carlsberg Lab 1924, 15: 1-28.
[2] Marcus RA: Calculation of thermodynamic properties of polyelectrolytes. J Chem Phys 1954, 23: 1057-1068.
[3] Lifson S: Potentiometric titration, association phenomena, and interaction of neighboring groups in polyelectrolytes. J Chem Phys 1957, 26: 727-734.
[4] Kirkwood JG, Shumaker JB: Forces between protein molecules in solution arising from fluctuations in proton charge and configuration. Proc Nat Acad Sci 1952, 38: 863-871.
[5] Tanford C, Kirkwood JG: Theory of protein titration curves. I. General equations for impenetrable spheres. J American Chem Society 1957, 79: 5333-5339.
[6] Borkovec M, Jönsson B, Koper GJ: Ionization processes and proton binding in polyprotic systems: small molecules, proteins, interfaces, and polyelectrolytes. Surface and colloid science, Springer US, 2001. This 2001 review is of great interest as it summarizes the experimental techniques and the different theoretical models used to study ionization processes in small molecules, proteins, interfaces and polyelectrolytes. It thoroughly reviews different approximation levels and different CR models, and compares their predicted pK values and titration curves to experimental data.
[7] Ninham BW, Parsegian VA: Electrostatic potential between surfaces bearing ionizable groups in ionic equilibrium with physiologic saline solution. J Theoretical Biology Chemistry 1971, 31: 405-428.
[8] Markovich T, Andelman D, Podgornik R: Charged Membranes: Poisson-Boltzmann theory, DLVO paradigm and beyond. Chapter 9 in: Handbook of Lipid Membranes, ed. by C. Saffina and J. Raedler, Taylor & Francis, to be published, 2018.
[9] Markovich T, Andelman D, Podgornik R: Charge regulation: A generalized boundary condition? EPL 2016, 113: 26004.
[10] Barroso da Silva FL, Derreumaux P, Pasquali S: Protein-RNA complexation driven by the charge regulation mechanism. Biochemical and biophysical research communications 2018, 498: 264-273.
[11] Barroso da Silva FL, Boström M, Persson C: Effect of charge regulation and ion-dipole interactions on the selectivity of protein-nanoparticle binding. Langmuir 2014, 30: 4078-4083.
[12] Hartvig RA, van de Weet, Østergaard J, Jorgensen L, Jensen H: Protein adsorption at charged surfaces: the role of electrostatic interactions and interfacial charge regulation. Langmuir 2011, 27: 2634-2643.
[13] Hyltegren K, Skepö M: Adsorption of polyelectrolyte-like proteins to silica surfaces and the impact of pH on the response to ionic strength. A Monte Carlo simulation and ellipsometry study. J of col and inter sci 2017: 494: 266-273.
[14] Hong Y, Brown DG: Electrostatic behavior of the charge-regulated bacterial cell surface. Langmuir 2008, 24: 5003-5009.
[15] Nap RJ, Božić AL, Szleifer I, Podgornik R: The role of solution conditions in the bacteriophage PP7 capsid charge regulation. Biophysical J 2014, 107: 1970-1979. This article is based on a coarse-grained model of virus capsids that includes detailed amino acid compositions. It considers the effects of the bathing solution pH and salt on the surface charges of different virus capsids. Based on this model, it is shown that charge regulation of the proteinaceous capsid shell leads to a pronounced buffering action of the inner surface of the capsid, in contact with the genome, but not of the outer one.
[16] Jiang Z, Stein D: Charge regulation in nanopore ionic field-effect transistors. Phys Rev E 2011, 83: 031203.
[17] Perutz MF: Electrostatic effects in proteins. Science 1978, 201: 1187-1191.
[18] Netz RR: Charge regulation of weak polyelectrolytes at low and high-dielectric-constant substrates. J Phys: Condens Matter 2003, 15: S239.
[19] Borkhov I, Andelman D, Borrega R, Cloitre M, Leibler L, Orland H: Polyelectrolyte titration: theory and experiment. J Phys Chem B 2000, 104: 11027-11034.
[20] Kumar R, Sumpner BG, Kilbey SM: Charge regulation and local dielectric function in planar polyelectrolyte brushes. J Chem Phys 2012, 136: 234901.
[21] Pericet-Camara R, Papastavrou G, Behrens SH, Borkovec M: Interaction between charged surfaces on the Poisson-Boltzmann level: The constant regulation approximation. J Phys Chem B 2004, 108: 19467-19475.
[22] Trefalt G, Behrens SH, Borkovec M: Charge regulation in the electrical double layer: ion adsorption and surface interactions. Langmuir 2015, 32: 380-400. This article is quite relevant as it emphasizes the large effect of charge regulation on the electrical double layer and on the force between two interfaces and/or particles. A comparison is made between charge-regulation boundary condition to constant charge and constant potential boundary conditions. Large deviations are shown, especially in asymmetric geometric, where the different boundary conditions may result in different interaction signs.
[23] Podgornik R, Parsegian VA: Forces between CTAB-covered glass surfaces interpreted as an interaction-driven surface instability. J Chem Phys 1995, 99: 9491-9496.
[24] Henle ML, Santangelo CD, Patel DM, Pincus PA: Distribution of counterions near discretely charged planes and rods. Europhys Lett 2004, 66: 284-290.
[25] Longo GS, Olvera de la Cruz M, Szleifer I: Molecular theory of weak polyelectrolyte thin films. Soft Matter 2012, 8: 1344-1354.
[26] Longo GS, Olvera de la Cruz M, Szleifer I: pH-controlled nanoaggregation in amphiphilic polymer co-networks. ACS Nano 2013, 7: 2693-2704.
[27] Adžić N, Podgornik R: Field-theoretic description of charge regulation interaction. Euro Phys J E 2014, 37: 49. This article presents the field-theoretic formalism of the grand-canonical partition function of a system composed of two charge-regulated macroions in a counterion-only ionic solution using. The Saddle-point of the field theory is shown to coincide with the mean-field Poisson-Boltzmann approxima-
tion and the Ninham-Parsegian boundary condition. By calculating the first-order (one loop) correction to the mean-field, the interaction due to the monopolar fluctuation is derived as a generalization of the Kirkwood-Shumaker interaction.

[28] Mags AC, Podgornik R: Electrostatic interactions in the presence of surface charge regulation: Exact results. EPL 2015, 108: 68003.

[29] Diamant H, Andelman D: Kinetics of Surfactant Adsorption at Fluid-Fluid Interfaces. J Phys Chem 1996, 100: 13732-13742.

[30] Ben-Yaakov D, Andelman D, Podgornik R, Harries D: Ion-specific hydration effects: Extending the Poisson-Boltzmann theory. Curr Opin Colloid & Interface Sci 2011, 16: 542-550.

[31] Harries D, Podgornik R, Parsegian VA, Mar-Or E, Andelman D: Ion induced lamellar-lamellar phase transition in charged surfactant systems. J Chem Phys 2006, 124: 224702.

[32] A Majee, Bier M, Podgornik R: Spontaneous symmetry breaking of charge-regulated surfaces. Soft matter 2018, 14: 985-991.

[33] Chan D, Healy TW, White LR: Electrical double layer interactions under regulation by surface ionization equilibria-dissimilar amphoteric surfaces. J Chem Soc Faraday Trans I 1976, 72: 2844-2865.

[34] M Borkovec, Behrens SH: Electrostatic double layer forces in the case of extreme charge regulation. J Phys Chem B 2008, 112: 10795-10799.

[35] Everts JC, Samin S, van Roij R: Tuning colloid-interface interactions by salt partitioning. Phys Rev Lett 2016, 117: 098002.

[36] Behrens SH, Borkovec M: Electrostatic interaction of colloidal surfaces with variable charge. J Phys Chem B 1999, 103: 2918-2928.

[37] Behrens SH, Borkovec M: Electric double layer interaction of ionizable surfaces: Charge regulation for arbitrary potentials. J Chem Phys 1999, 111: 382-385.

[38] Carnie SL, Chan DYC: Interaction free energy between plates with charge regulation: a linearized model. J Colloid Interface Sci 1993, 161: 260-264.

[39] Healy TW, White LR: Ionizable surface group models of aqueous interfaces. Adv Coll Interf Sci 1978, 9: 303-345.

[40] Popa I, Papastavrou G, Borkovec M: Charge regulation effects on electrostatic patch-charge attraction induced by adsorbed dendrimers. Physical Chemistry Chemical Physics 2010, 12: 4863-4871.

[41] Boon N, van Roij R: Charge regulation and ionic screening of patchy surfaces. J Chem Phys 2011, 134: 054706.

[42] Božič AL, Podgornik R: pH dependence of charge multipole moments in proteins. Biophys J 2017, 113: 1454-1465.

[43] Lund M: Anisotropic protein-protein interactions due to ion binding. Colloids and Surfaces B: Biointerfaces 2016, 137: 17-21.

[44] Leckband D, Israelachvili J: Intermolecular forces in biology. Q Rev Biophys 2001, 34: 105-267.

[45] Lund M, Jönsson B: On the Charge Regulation of Proteins. Biochemistry 2005, 44: 5722-5727.

[46] Barroso da Silva FL, Jönsson B: Polyelectrolyte-protein complexation driven by charge regulation. Soft Matter 2009, 5: 2862-2868.

[47] Lund M, Akesson T, Jönsson B: Enhanced protein adsorption due to charge regulation. Langmuir 2005, 21: 8385-8388.

[48] Warshel A, Sharma P, Kato M, Parson W: Modeling electrostatic effects in proteins. Biochim Biophys Acta 2006, 1764: 1647-1676.

[49] Teixeira AAR, Lund M, Barroso da Silva FL: Fast proton titration scheme for multiscale modeling of protein solutions. J chemical theory and computation 2010, 6: 3259-3266.

[50] Lund M: Electrostatic chameleons in biological systems. Q Rev Biophys 2013, 46: 265-281. This review is of great interest as it connects charge-regulation to the concept of intrinsic charge capacitance. The intrinsic capacitance is derived, and it is shown, via free energy arguments, that it can be used to estimate the interaction between two biomolecules. Good agreement between theory and simulations is shown. The relevance of charge-regulation to protein-protein interaction, ligand binding, protein-membrane interactions and protein-polyelectrolyte complexation is examined.

[51] Lund M: Electrostatic chameleons in biological systems. Q Rev Biophys 2013, 46: 265-281. This review is of great interest as it connects charge-regulation to the concept of intrinsic charge capacitance. The intrinsic capacitance is derived, and it is shown, via free energy arguments, that it can be used to estimate the interaction between two biomolecules. Good agreement between theory and simulations is shown. The relevance of charge-regulation to protein-protein interaction, ligand binding, protein-membrane interactions and protein-polyelectrolyte complexation is examined.

[52] Ullner M, Jönsson B, Widmark P: Conformational properties and apparent dissociation constants of titrating polyelectrolytes: Monte Carlo simulation and scaling arguments. J Chem Phys 1994, 100: 3365-3366.

[53] Uhlik F, Kovan P, Limpouchov Z, Prochazka K, Borisov OV, Leermakers FAM: Modeling of ionization and conformations of starlike weak polyelectrolytes. Macromolecules 2014, 47: 4004-4016.

[54] Longo GS, Olvera de la Cruz M, Szleifer I: Molecula rtheory of weak polyelectrolyte gels: the role of pH and salt concentration. Macromolecules 2011, 44: 147-158. This paper studies weak (charge-regulated) polyelectrolyte gels. A theory that combines the configurational entropy of the gel, van der Waals, electrostatic and excluded volume interactions, along with charge-regulation processes is developed, and results are obtained using molecular dynamics simulations. The degree of charge dissociation of the gel as function of the imposed pH and salt concentration is shown to differ from the bulk value. The transition between swelling and collapse of the gel is studied.

[55] Rud O, Richter T, Borisov O, Holm C, Koslov P: A self-consistent mean-field model for polyelectrolyte gels. Soft Matter 2017, 13: 3264-3274.

[56] Hofzumahaus C, Hebbeker P, Schneider S: Monte Carlo simulations of weak polyelectrolyte microgels: pH-dependence of conformation and ionization. Soft Matter 2018, 14: 4087-4100. This article studies the ionization and conformation behavior of weak polyelectrolyte microgels by Metropolis Monte Carlo simulations. A detailed analysis is made by varying the microgel concentration, the content of the acidic groups, and the crosslinking densities. The study shows that when changing the pH, the weak polyelectrolyte microgels changes from an uncharged and unswollen state to a fully ionized and strongly swollen state independent of pH. The titration curve is shifted as compared to the ideal titration curve of a monomer at infinite dilution, and the inhomogeneous radial distribution of the degree
of ionization is determined.

[57] Longo GS, Olvera de la Cruz M, Szleifer I: Non-monotonic swelling of surface grafted hydrogels induced by pH and/or salt concentration. J Chem Phys 2014, 141: 124909.

[58] Alexander S, Chaikin PM, Grant P, Morales GJ, Pincus P, Hone D: Charge renormalization, osmotic pressure, and bulk modulus of colloidal crystals: Theory. J Chem Phys 1984, 80: 5776-5781.

[59] Gisler T, Schulz SF, Borkovec M, Sticher H, Schurtenberger P, D’Aguanno B, Klein R: Understanding colloidal charge renormalization from surface chemistry: Experiment and theory. J Chem Phys 1994, 101: 9924-9936. In this work, highly charged latex particles carrying carboxylic and sulfate groups were studied both experimentally and theoretically. The colloids charge, derived from static light scattering and acid-base titrations techniques, was compared to the charge predicted from a cell-model approach, solved numerically with charge-regulation boundary conditions. A good agreement is achieved by using two-parameter fit.

[60] Boon N, van Roij R: Charge reversal of moisturous porous silica colloids by take-up of protons. J Coll Interf Sci 2012, 385: 66-72.

[61] Allen RJ, Patrick BW: Complexation and phase behavior of oppositely charged polyelectrolyte/macroion systems. Langmuir 2004, 20: 1997-2009.

[62] Biesheuvel PM, Cohen Stuart MA: Cylindrical cell model for the electrostatic free energy of polyelectrolyte/macroion systems. Langmuir 2004, 20: 4764-4770.

[63] Biesheuvel PM, Lindhoud S, Cohen Stuart MA, de Vries R: Phase behavior of mixtures of oppositely charged protein nanoparticles at asymmetric charge ratios. Phys Rev E 2006, 73: 041408.

[64] Biesheuvel PM: Evidence for charge regulation in the sedimentation of charged colloids. J Phys Condens Matter 2004, 16: L499-L504.

[65] Markovich T, Andelman D, Podgornik R: Complex fluids with mobile charge-regulating macro-ions. EPL 2017, 120: 26001. This paper introduces the collective approach to solutions of mobile charge-regulated macro-ions. The general formalism is introduced and implemented on a specific and rather simple CR process. Modifications of the effective screening length and the electric double layer are calculated, along with the positional dependence of the macro-ions effective charge near a charged boundary.

[66] Avni Y, Markovich T, Andelman D, Podgornik R: Charge regulating macro-ions in salt solutions: screening properties and electrostatic interactions. Soft Matter 2018, 14: 6058-6069. This paper is of great interest as it extends the collective approach introduced in Ref. [65] by studying different classes of charge-regulation models, focusing on the solution effective screening length properties. The screening length is shown to exhibit, in some cases, an anomalous non-monotonic behavior which can be quantified in terms of charge-asymmetry of the macro-ions and their donor/acceptor propensity. Modifications to the disjoining pressure between two charged surfaces are calculated.

[67] Adžić N, Podgornik R: Charge regulation in ionic solutions: Thermal fluctuations and Kirkwood-Schumaker interactions. Phys Rev E 2015, 91: 022715.

[68] Hallett JE, Gillespie DAJ, Richardson RM, Bartlett P: Charge regulation of nonpolar colloids. Soft Matter 2018, 14: 331-343.

[69] Borkovec M, Daicic J, Koper GJ: On the difference in ionization properties between planar interfaces and linear polyelectrolytes. Proc Natl Acad Sci 1997, 94, 3499-3503.

[70] Netz RR: Electrostatics of counter-ions at and between planar charged walls: From Poisson-Boltzmann to the strong-coupling theory. Eur Phys J E 2001, 5: 557-574.