Electrostatic effects in DNA stretching

Alexei V. Tkachenko (alexei@umich.edu)
Department of Physics and Michigan Center for Theoretical Physics
University of Michigan, 450 Church Str., Ann Arbor, 48109 MI, USA

The response of a semiflexible polyelectrolyte chain to stretching in the regimes of moderate and weak screening is studied theoretically, with a special focus on DNA experiments. By using the nonlinear Poisson–Boltzmann description of electrostatic self-interactions of the chain, we explicitly demonstrate the applicability of the concept of effective charge to certain aspects of the problem. This charge can be extracted from the far-field asymptotic behavior of the electrostatic potential of the fully aligned chain. Surprisingly, in terms of the effective charge, the electrostatically renormalized persistence length can be formally described by the classical Odijk-Skolnick-Fixman (OSF) formula, whose domain of applicability is normally limited to linearized Debye-Huckel (DH) approximation. However, the short scale behavior of the chain in the nonlinear regime deviates from the DH-based result, even upon the charge renormalization. This difference is revealed in the calculated stretching curves for strongly charged DNA. These results are in good agreement with the recent experiments. In the limit of weak screening we predict the elastic response to have a distinctive two-stage character, with a peculiar intermediate "unstretchable" regime.

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I. INTRODUCTION

Single molecular micromechanical experiments are among the major tools of modern biophysics. Pioneered by the studies of double-stranded DNA (dsDNA)[1], these techniques are now applied to a wide range of biologically relevant problems [2]-[4]. Theoretically, it has been demonstrated that the observed response of dsDNA to stretching (i.e. elongation vs. pulling force) can be successfully described by semiflexible Worm-Like Chain (WLC) model [5][6], over a considerable range of applied forces. Within this model, the molecule is viewed as a rigid rod subjected to thermal fluctuations, and the only free parameter is its persistence length $l_p$, which is proportional to the bending modulus of the rod.

Since DNA is strongly charged, the effects of the electrostatic interactions should in principle play a significant role in its elastic response. However, they are typically suppressed due to the strong screening under physiological conditions. In addition, it is implicitly assumed that the electrostatic effects can be incorporated by renormalization of the parameters of the effective models, e.g. persistence length $l_p$ in WLC. This is indeed a valid assumption in certain regimes, as was shown in works of Odijk, and Skolnick and Fixman (OSF) [7]. They have demonstrated that within linearized Debye-Huckel (DH) approximation, there is an additive electrostatic correction to the persistence length of a semi-flexible WLC, and this term scales quadratically with Debye screening length $\kappa_s$. However, the classical result has to be significantly revised in the regime of highly flexible chains, which was in focus of numerous studies over the last two decades [8]-[11].

Another limitation of OSF picture is that it is only valid on the length scales larger than $\kappa_s$. When the chain is strongly stretched, its properties on shorter scales are being probed. Within DH theory, this regime can be described in terms scale-dependent electrostatic rigidity [12][6]. Finally, OSF result is known to be inadequate outside of DH approximation, i.e. in strongly nonlinear regime. Compared to other aspects of the problem, its non-linear generalization has attracted only a limited attention since the early works back in '80s [13][14]. In this paper, we study the electrostatic effects on the elastic response of strongly charged WLC, in the regimes of moderate and weak screening. In these regimes, DH approximation may no longer be applicable, and the analysis of the non-linear Poisson-Boltzmann equation is necessary. While stated as a generic problem, our study is especially important in the context of DNA stretching experiments.

The plan of the paper is as follows. In Section II, we formulate the problem and review the results obtained within DH theory. We revisit the problem of scale-dependent rigidity, and demonstrate that in the limit of weak screening, the chain exhibits a two-stage response. These two stages are characterized by the renormalized and bare persistence lengths, respectively, and they are separated by a peculiar "unstretchable" regime. In Section III, we study the problem beyond the linearized DH approximation. Our central result is that the effective rigidity in the non-linear regime can be described by classical OSF formula, in terms of effective linear charge density determined by the far-field asymptotic of chain's electrostatic potential. This is the first explicit demonstration of the applicability of the concept of renormalized charge in the context of the non-linear problem. While the notion of the effective charge is not new, in the past it was introduced in a purely heuristic manner. As follows from our results, the effective charge approach has significant limitations and it is not valid on the length scale comparable to $\kappa_s$. As a result, the extension curve for strongly charged chains is different from the result of linearized DH theory, even upon the charge renormalization. Finally, in Section IV we discuss applications of the theory both to ds- and single stranded (ss-)DNA, and...
II. RESULTS OF LINEARIZED THEORY

In the presence of monovalent ions of concentration $n$, the electrostatic potential in water is well described by Poisson-Boltzmann (PB) equation:

$$\Delta \Psi (x) - r_s^{-2} \sinh \Psi (x) = -4\pi l_B^{-1} \rho (x) / e$$  \hspace{1cm} (1)$$

Here, reduced potential $\Psi$ is expressed in units of $kT/e$; $D$ is the dielectric constant of water; $l_B = e^2 / DK = 7\AA$ is Bjerrum length, and $r_s = 1 / \sqrt{4\pi l_B n}$ is Debye screening length. For low value of $\Psi$, the above nonlinear equation can be linearized, which corresponds to the well known DH approximation. In particular, one can obtain Yukawa-type pair potential acting between two point charges $e$:

$$V(r) = l_B / r \exp (-r / r_s).$$  \hspace{1cm} (2)$$

The effective Hamiltonian of an electrostatically neutral WLC stretched by an external mechanical force is given by [6]:

$$H_0 = \int_0^L \left[ \frac{kT l_p}{2} \left( \frac{\partial^2 x}{\partial s^2} \right)^2 - f \frac{\partial x}{\partial s} \right] ds$$  \hspace{1cm} (3)$$

Here $f$ is the stretching force applied at $s = L$. Function $x(s)$ determines the chain conformation in space, and it is subjected to constrain $|\partial x / \partial s| = 1$ (i.e. the chain is not extendable). Within DH approximation, the electrostatic self-interactions of uniformly charged chain give rise to the following new term in Hamiltonian

$$H_{el} = \frac{e^2 \alpha^2}{2 D l_B^2} \int_0^L \int_0^L \exp \left( - |x(s) - x(s')| / r_s \right) / |x(s) - x(s')| ds ds'$$  \hspace{1cm} (4)$$

Here $\alpha e / l_B$ is the linear charge density of the chain. Manning parameter $\alpha$ has the physical meaning of the number of electron charges per Bjerrum length.

According to OSF theory [7] developed within DH approximation, the electrostatic interactions lead to a higher effective bending modulus of a semirigid chain. This results in renormalization of its persistence length:

$$l_p' = l_p + \alpha^2 r_s^2 / 4 l_B.$$  \hspace{1cm} (5)$$

For the case of flexible chain, OSF approach has been revised by Khokhlov and Khachaturian, who have introduced the concept of electrostatic blobs [8]. On the length scales smaller than blob size, $\xi_e = (l_p'^2 / \alpha^2)^{1/3}$, the electrostatic effects may be neglected. On the larger scales, a flexible polyelectrolyte can be viewed as a stretched chain of blobs, and OSF picture can be recovered upon proper renormalization of its parameters. For a semiflexible chains, we can introduce a characteristic length which would play the same role as the size of electrostatic blobs $\xi_e$ in flexible case: $l_c = DK T / (e r_s^2) = l_B / \alpha^2$. This length defines the minimal scale at which electrostatic effects become relevant, and the semiflexible regime itself is determined by condition $l_c < l_p'$.

When the chain is strongly stretched, one may keep only terms quadratic in the transverse components of displacement, $u_s = x(s) - f (f \cdot x(s)) / f^2$. After going to Fourier representation, $u_s = L^{-1/2} \sum q u_q \exp (i q s)$, the overall effective Hamiltonian $H = H_0 + H_{el}$ can be written as:

$$H [u_q] = \text{const} + \sum_q \frac{q^2 u_q u_{-q}}{2} \left[ l_p q^2 + \Lambda_{el} (q) + f / kT \right]$$  \hspace{1cm} (6)$$

Here, all the electrostatic effects are collected within the term $\Lambda_{el} (q)$, which has the physical meaning of scale-dependent electrostatic tension:

$$\Lambda_{el} (q) = \frac{\alpha^2}{4 l_B} \left[ \left( 1 + \frac{1}{q^4 r_s^2} \right) \log (1 + q^2 r_s^2) - 1 \right]$$  \hspace{1cm} (7)$$

This electrostatic term was originally introduced by Barrat and Joanny [12], and later adopted to the case dsDNA in the classical paper of Marko and Siggia [6]. By using the Equipartition Theorem, they have calculated the difference between the end-to-end distance $R$ and the length of the fully–stretched chain, $L$.

$$\frac{L - R}{L} = - \frac{\langle \dot{u}^2 \rangle}{2} = \int_{-\infty}^{+\infty} \frac{1}{l_p q^2 + \Lambda_{el} (q) + f / kT} dq - \frac{1}{2\pi}$$  \hspace{1cm} (8)$$

The calculated stretching curves are shown in Figure 1. Interesting observations can be made by further analysis of the above result in the limit of weak enough screening, $r_s \gg l_c \equiv \alpha^{-2} l_B$. In this case, the overall mechanical response has a striking two–stage character. For large forces, $f >> kT / 4 l_c$ we recover well–known result for a neutral WLC [6]:

$$\frac{L - R}{L} \sim \int_{-\infty}^{+\infty} \frac{1}{l_p q^2 + f / kT} \frac{dq}{2\pi} = \frac{1}{2} \sqrt{\frac{kT}{f l_p}}$$  \hspace{1cm} (9)$$

In addition, one can identify a new moderate force regime, $kT l_e / 4 r_s^2 \ll f \ll kT / 4 l_c$. In this case, Eq. (8) has two distinct contributions which correspond to the integration over wave numbers $q$ much smaller and much larger than $r_s^{-1}$, respectively:

$$\frac{L - R}{L} \approx \frac{1}{2} \sqrt{\frac{kT}{f l_p + \alpha^2 r_s^2 / 4 l_B}} + \frac{1}{\alpha} \sqrt{\frac{l_B}{l_p}} g \left( \frac{\alpha r_s}{\sqrt{l_B l_p}} \right)$$  \hspace{1cm} (10)$$
nearly static interactions. In other words, the chain becomes unstretchable when the end-to-end distance reaches a certain value $R_e$. Following Oosawa [18], the idea of separating condensed and free counter-ion components, has been widely used in literature. Nevertheless, it is hard to justify its applicability for our problem. First, there is an ambiguity in defining the "near" and "far" region of the cylinder with a finite aspect ratio, and therefore the effective charge is not well defined. Furthermore, the electrostatic interactions are strongest on lengths scales shorter than $r_s$, exactly where DH approximation is invalid (for $\alpha \gtrsim 1$).

The leading corrections to the free energy due to small fluctuation of the chain can be evaluated without any model assumptions. Namely, one can linearize PB equation near its solution for a static cylinder $(\psi(\Phi))$, and couple the perturbations of potential $\phi(x) = \psi(x) - \psi(0)(x)$, to the conformational fluctuations $\mathbf{u}_s$. The displacements of the charged cylinder can be described by the local perturbations to the in-plane electrostatic moments. In particular, the monopole, dipole and quadrupole moments have the following forms, respectively:

$$\tau_s = \frac{\tilde{\alpha} e}{2l_B} \left( \frac{\partial \mathbf{u}_s}{\partial s} \right)^2;$$

$$\mathbf{d}_s = \frac{\tilde{\alpha} e}{l_B} \mathbf{u}_s;$$

III. NONLINEAR THEORY AND EFFECTIVE CHARGE

Strictly speaking, the linearization of Eq. (1) is only possible for weakly charged chains or very strong screening. In a more general case, one has to study the complete non-linear equation. In order to apply our results for the case of strongly-charged polymers like ds- or ss-DNA, one has to go beyond the linearized DH approximation. Early attempts of such a generalization go back to early 80s [13] [14]. At that time, it was shown by the numerical studies that effective rigidity clearly deviates from the linear OSF theory. However, no alternative model had been proposed.

Various aspects of PB equation in cylindrical geometry have been studied for several decades. Among other important advances, was the discovery of the counter-ions condensation by Manning [17]. It was shown that when the linear charge density on a thin rod exceeds certain critical value, a finite fraction of the counter-ions get localized within a near region of the rod, thus effectively reducing its overall charge. This phenomenon occurs at critical Manning parameter $\alpha_c \approx 1$. Upon the condensation, the residual effective charge of the rod saturates at its critical value, $\alpha_c/l_B \approx 1/l_B$. For a strongly-charged cylinder with a finite radius $r_0$, a similar phenomenon occurs with the effective charge becoming a function of aspect ratio, $r_0/r_s$. Following Oosawa [18], the idea of separating condensed and free counter-ion components, has been widely used in literature. Nevertheless, it is hard to justify its applicability for our problem. First, there is an ambiguity in defining the "near" and "far" region of the cylinder with a finite aspect ratio, and therefore the effective charge is not well defined. Furthermore, the electrostatic interactions are strongest on lengths scales shorter than $r_s$, exactly where DH approximation is invalid (for $\alpha \gtrsim 1$).

The force regime (9), occurs.
Here we have switch to Fourier representation, and expressed the result in terms of the dipolar field \( \phi_q^{(1)}(r) \). The latter satisfies the inhomogeneous linearized PB equation:

\[
\left[ \partial_r^2 + \frac{1}{r} \partial_r - \left( q^2 + \frac{1}{r^2} + \frac{1}{r_s^2} \cosh \Psi^{(0)}(r) \right) \right] \phi_q^{(1)} = 0,
\]

subject to boundary condition:

\[
\left. \left( \frac{1}{r} - \partial_r \right) \phi_q^{(1)} \right|_{r = r_0} = 1.
\]

Thus,

\[
\delta H_{el}[\mathbf{u}_q] = \sum_q \left[ 2\alpha^2 \frac{2}{l_B} \left( \phi_q^{(1)}(r_0) - \phi_0^{(1)}(r_0) \right) \mathbf{u}_q \mathbf{u}_{-q} + C q^2 \mathbf{u}_q \mathbf{u}_{-q} \right]
\]

Here the we have used the fact that the first two terms in Eq. (15) are local in \( \partial \mathbf{u}_q / \partial s \):

\[
\text{const} \cdot \int (\partial \mathbf{u}_q / \partial s)^2 ds = \sum_q C q^2 \mathbf{u}_q \mathbf{u}_{-q}
\]

We can determine coefficient \( C \) by noting that the low-\( q \) behavior of the electrostatic correction to the Hamiltonian, \( H_{el}[\mathbf{u}_q] \) should still be dominated by bending modes, \( q^2 \mathbf{u}_q \mathbf{u}_{-q} \), and therefore all the terms containing \( q^2 \mathbf{u}_q \mathbf{u}_{-q} \) must cancel in that limit:

\[
C = -\alpha^2 \frac{2}{l_B} \left( \frac{\partial^2 \phi_q^{(1)}(r_0)}{\partial q^2} \right)_{q=0}
\]

After substitution of this value of \( C \) into Eq. (19), we obtain a nonlinear generalization of the electrostatic tension term \( \Lambda_{el}(q) \) which enters the earlier results, Eqs. (6) and (8):

\[
\Lambda_{el}^{(nonlin)}(q) = \frac{4\alpha^2}{l_B} \left( \frac{\phi_q^{(1)}(r_0) - \phi_0^{(1)}(r_0) - \partial^2 \phi_q^{(1)}(r_0)}{2q^2} \right)_{q=0}
\]

By solving Eqs. (1) and (17) numerically, we found function \( \Lambda_{el}^{(nonlin)}(q) \) for various regimes. Its low-\( q \) asymptotic may significantly deviate from classical OSF result, which is consistent with the earlier studies [13] [14]. One could interpret this deviation in terms of renormalized effective charge, by defining the effective Manning parameter \( \alpha^{(eff)} \) so that in the limit \( qr_s \ll 1 \),

\[
\Lambda_{el}^{(nonlin)}(q) \simeq \frac{\left( \alpha^{(eff)} r_s q \right)^2}{4l_B}
\]

Surprisingly, this effective effective charge appear to have a clear physical meaning. With an excellent accuracy, \( \alpha^{(eff)} \) has the same value as effective Manning parameter \( \alpha_\infty \), which can be extracted from the far-field behavior of potential \( \Psi^{(0)}(r) \), i. e.

\[
\Psi^{(0)}(r) \simeq 2\alpha_\infty K_0(r/r_s)
\]

for \( r \gtrsim r_s \) [16]. Here \( K_0 \) is the modified Bessel function which is the solution to DH equation in cylindrical geometry.

Figure 2(a) demonstrates a striking correlation between \( \alpha^{(eff)} / \alpha_0 \) and \( \alpha_\infty / \alpha_0 \), in a wide range of parameters. Each curve there corresponds to the fixed value of \( \alpha_\infty \). The solid and dashed lines represent \( \alpha^{(eff)} / \alpha_0 \) and \( \alpha_\infty / \alpha_0 \) respectively, as functions of the aspect ratio \( r_0 / r_s \). The close agreement between the two types
of data shows that \( \alpha^{(eff)} \) and \( \alpha_\infty \) nearly coincide for an arbitrary value of the bare linear charge, as long as the aspect ratio \( r_0/r_s \) remains small. Figure 2(b) illustrates the dependence of \( \alpha^{(eff)} \) on the aspect ratio for the values of the bare charge close to those of dsDNA and ssDNA (\( \alpha_0 = 4 \) and \( \alpha_0 = 1 \), respectively). One can see that for the practical purposes, \( \alpha^{(eff)} \) of ssDNA is close to .7, while its value for dsDNA follows the saturation curve (corresponding to infinitely–charged cylinder with the same radius). Note that the far-field definition of the effective charge is unambiguous, and it does deviate from Oosawa–Manning result, even for zero aspect ratio (see Figure 2(c)). Furthermore, one can modify Oosawa–Manning approach to evaluate the effective charge as a function of \( r_0/r_s \), as demonstrated in Ref. [19]. The result of that calculation is also shown in Figures 2(b)-(c), and it clearly deviates from our far-field based definition of \( \alpha^{(eff)} \).

We have explicitly demonstrated that OSF result is formally applicable even outside of DH approximation, given that the effective charge is properly defined. While similar effective charge descriptions have been previously utilized in several works [16][15], they were all introduced as purely empirical assumption. In fact, our result is rather non–trivial since the electrostatic interactions are strongest in the vicinity of the chain, where the effective description is not valid. The effective charge picture works only because the bending of the chain affects the far region much stronger than the near one. Indeed, \( q^2 \) term in Eq. (17) is most relevant for \( r \gtrsim r_s \).

Furthermore, for \( q \gtrsim 1/r_s \) the effective charge description breaks down, and deviations from DH approximation become considerable, as shown in Figure 3.
The above results can be applied to the experiments on both ds- an ssDNA. The two cases are characterized by rather different values of the physical parameters. In particular, the persistence length of ds-DNA, $l_p^{(ds)} \simeq 50\text{nm} \simeq 70\lambda_B$ significantly exceeds that of ss-DNA chain, $l_p^{(ss)} \sim 1\text{nm} \sim \lambda_B$. In addition, their linear charge density differ approximately by factor of 4. Finally, while WLC model is well established as a standard description of ds-DNA, the situation with elasticity of ss-DNA is not as settled: the extensible version of WLC is among several proposed models all of which are in reasonable agreement with the existing experimental data [20]. Plots in Figures 1(a) and (b) roughly correspond to the parameters of ds- and ss-DNA, respectively. As one can see from the Figure, the two-stage behavior and the intermediate ”unstretchable” regime becomes pronounced when $r_s$ substantially exceeds the persistence length. Note however that this regime is unlikely to be accessible in the case of ds-DNA, since the double helix would become unstable at such a week screening due to the electrostatic repulsion between the strands. For ss-DNA, the two-stage stretching must be observable at $r_s \gtrsim 100\text{nm}$.

While Figure 1 gives only a general idea about the mechanical response of semiflexible chain with electrostatic interactions, a more detailed comparison of our results with experiments is presented in Figure 4. The plot shows the stretching curves of ss-DNA taken at various screening conditions, as reported in Refs. [2] and [4]. These experimental data are fitted by our theory with the Debye screening length calculated for each salt concentration. As a result, the only fitting parameter was the bare persistence length $l_p$, and the best fit is achieved at $l_p = 5.5\text{\AA}$. This value is somewhat smaller that the earlier estimates of the effective persistence length $l_p^* \simeq 8\text{\AA}$, which difference is due to our explicit account for the electrostatic corrections to chain rigidity. Unlike the plots in Figure 1 which for the sake of simplicity were calculated by assuming $r_0/r_s = 0$, in Figure 4 the non zero diameter of ss-DNA chain is taken into account. Based on the known structure of the molecule, we have assumed $r_0 = 5\text{\AA}$, and this parameter was not used for fitting.

Even though the theoretical stretching curves were calculated with WLC model, our approach can be also applied to alternative descriptions of ss-DNA, such as Extensible Freely-Joint Chain model (EFJC). However, this modification is unlikely to produce any significant change since within the force range of interest, the competing models (WLC, EFJC, and discreet version of WLC) are known to give nearly identical fitting to the electrostatics–free stretching behavior of ss-DNA [20]. Indirectly, this model independence is supported by the fact that the above experimental data were also successfully fitted with numerical simulations based on EFJC model [4]. In that work, in addition to electrostatic interactions described within linear DH approximation with renormalized charges, the effects of excluded volume and hairpin formation were included [15]. Since these additional effects are only important for relative small chain extension, they were neglected in the context of our work.

**V. CONCLUSIONS**

In conclusion, we have studied the effects of electrostatic self-interactions on elastic properties of strongly-stretched WLC, with application to ds- and ss-DNA at moderate and weak screening conditions. By revisiting the earlier studied problem of scale–dependent electrostatic rigidity we have demonstrated that in the limit of weak screening, the mechanical response of the chain has a distinctive two-stage character. The two modes are characterized by the bare and the renormalized persistence length, respectively, and they separated by intermediate ”unstretchable” regime.
The central theme of our work is the effect of non-linearity of PB equation on the classical results obtained within DH approximation. Consistently with previous studies of the problem [13] [14], the OSF result for the electrostatic renormalization of the persistence length is not applicable in the nonlinear regime, and in particular the scaling $l_p^* - l_p \sim r_s^2$ is not valid. However, we have explicitly demonstrated that the OSF formula is formally correct if the actual line charge density is replaced with the effective one. The latter is determined from the far-field asymptotic of the electrostatic potential of the strongly stretched chain. In the light of this result, the deviation from OSF scaling is due to the non-trivial dependence of the effective charge on the aspect ratio $r_0/r_s$.

The renormalized OSF description is however only partially adequate since the electrostatic corrections to the chain rigidity do not follow the result of DH theory on scales shorter that $r_s$, even upon the charge renormalization. This deviation is due to the fact that the effective charge itself is a scale-dependent concept. Our solution to the complete nonlinear problem is shown to give an adequate description to the experimentally observed stretching behavior of ssDNA at various salt conditions.

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