Like-charge attraction

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Abstract

As we learned from mean-field theory, like-chared particles repel. However, in the last decade, like-charge polyelectrolyte attraction was observed in the presence of multivalent ions in a variety of biological systems, including DNA, F-actin, microtubules, and filamentous viruses. Considering the fundermental role DNA played in the life-cycle, we find like-charge attraction is not only physically intriguing, but also of great biological significance. In this paper, the theory based on the short-range electrostatic correlations is reviewed, and we show that it provides a lot of insight to the DNA condensation experiment. Finally, recent experimental progress is discussed.

1 Introduction

The physics of electrostatics in aqueous solution has attracted people's interest for centuries. Mean field theory (1) was established more than 80 years ago by Debye and Hückel. The concept of the Debye-Hückel theory is basically the following. Considering macro-ions bathed in the salt solution, the long-range Coulomb interaction between the macro-ions is mediated by the mobile ions from the solution. The effective charges of the macro-ions are reduced as the result of the charge-screening by the mobile counterions. At long enough distance, the interaction between two macro-ions decays exponentially. As a result of the theory, likely charged macro-ions repel. Mean field theory provides the starting point of the electrostatic correlation, and are still widely used nowadays.

As recent studies of biomolecules are booming, novel phenomena, including like-charge attraction (2), have been observed. Theory has also been driven beyond the mean-field treatment. Many biomolecules of interest, DNA for example, are charged. *In vivo* the Coulomb repulsion prevents them from precipitation at high concentrations. In 0.1M solution of NaCl, a DNA molecule assumes a random coil form with a radius of gyration about 1 μm. When DNA molecules with any lengths approach each other within 1 nm, they feel strong repulsion (3; 4). However, a DNA molecule condenses into a closely packed torus with a radius of about 50 nm as shown in Fig 1(a), when multivalent ions are added in the highly dilute solution prepared *in vitro* (3; 4). The distance between the "threads" in the nearest parallel rounds is only 30% larger than the diameter of DNA. The volume of the condensed form is $1/10^4$ of that in the random coil form. This is typically what happens when DNA of a bacteriophage is released to the solution containing suitable amount of multivalent ions. Moreover, genomes released from several bacteriophages can simultaneously form a much larger torus as shown in Fig 1(b). When multivalent ions are further added to the solution, the DNA condensate re-dissociates.
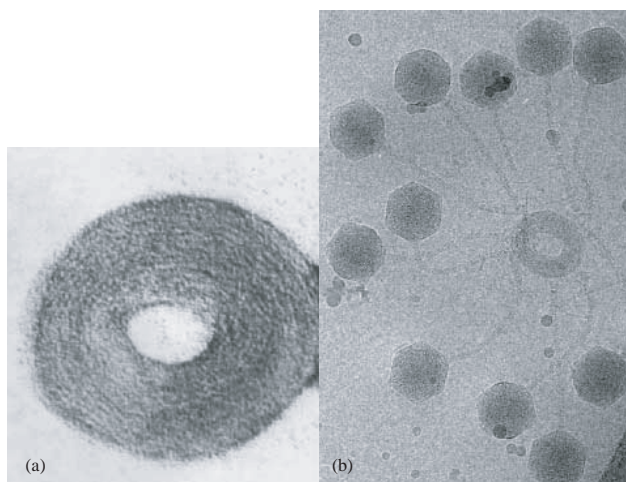

Figure 1: (a) DNA condensates in torus form (4). (b) A much larger torus is being formed simultaneously from the genomes of 11 T5 bacteriophages (5).

Other examples of like-charge attraction are also found in F-actin, microtubules, and filamentous viruses (3; 6; 7). Fig 2(a) shows the condensed form of two F-actin molecules (8).

When more F-actin rods are involved, a liquid crystalline phase emerges under certain conditions. As shown in Fig 2(b), a lamellar phase, i.e. a stacked 2-D network of F-actin cross-linked by counter ions, is formed from either an isotropic or a nematic phase in the multivalent-ion solution (9). The onset of this phase depends on the concentration of the ions. Generally speaking, divalent ions are necessary to condense F-actin and virus. However only several divalent ions are able to achieve DNA condensate.
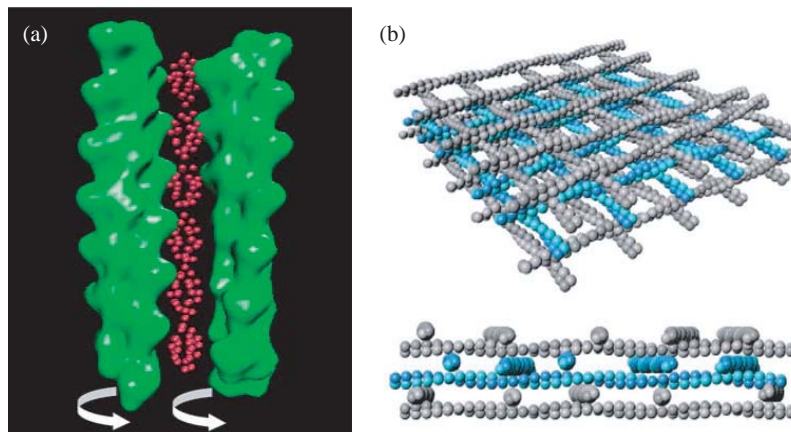

Figure 2: (a) Two actin rods (green) attraction mediated by the barium ions (red spheres) (8). (b) A lamellar phase of F-actin rods formed through like-charge attraction (9).

These observations conflict our common intuition of like-charge repulsion. The physical questions need to be answered include: What is the mechanism of the like-charge attraction? How is the condensate reversed at high multivalent ion concentrations? How is the valence of the ions related to the mechanism? Does the attraction depend on the size of the ions?

2   Biological significance

In the past 30 years, the electrostatics of electrolyte solution is re-examined to resolve the puzzle of like-charge attraction. This is largely driven by the biological significance associated with the structure and function of biomolecules. A detailed understanding may also benefit the fields of biomedical research and gene therapy. Here I briefly describe a cute example of a possible therapeutic application of DNA condensation illustrated in (4).

Bacteriophage T5 is a type of virus that infects *E. coli*. T5's structure can be roughly characterized by a head and a syringe-like tail (10). Its viral DNA is coated in a hard protein shell at the head. The affection takes place when T5 attaches the cell membrane, punctuated it with the tail, and inject the DNA to the cell cytoplasm. The cartoon picture of the DNA injection mechanism is illustrated in Fig. 3. After injection, the T5 bacteriophage takes the advantage of the bio-synthetic machinery of the bacteria, and makes duplicate phages. Eventually the cell bursts, and many offsprings are released. During this procedure, the injection of viral DNA is triggered by the recognition of a unique binding protein, FhuA, locating at the lipid membrane of the cell. The recognition is efficient. Even one FhuA of the entire membrane causes the cell vulnerable to the virus attack.
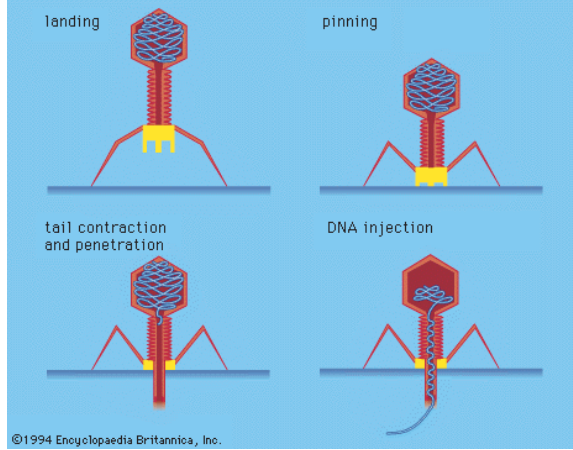
Figure 3: Cartoon picture of T-even phage (a relative of T5) injection (11).

It has been suggested (4) that the injection of T5 can be coaxed into a controlled manner. We can imagine that if FhuA proteins are assembled into the membrane of a liposome, which is a hollow lipid bilayer sphere, T5 virus can then recognize FhuA, bind to it, and inject the DNA into the liposome. By filling the liposome with NaCl solution containing proper amount of spermine^{4+} ions, the viral DNA will condense to a torus. Many T5 viruses can be fooled at the same time to eject their DNA to form a large torus. In this way, the DNA of the virus is isolated, and it can not do any harm.

3   Theory

In this section, we will go over some of the key issues on the electrostatics of polyelectrolyte solutions. As our starting point, the Debye-Hückel model is reviewed. It is followed by the introduction of a very important concept, namely, Manning condensation. Next we will outline a simple model of like-charge attraction. Finally the DNA condensation experiment is explained based on the theory above. Interested readers are referred to (12) for a recent review.

3.1   Debye-Hückel model

Consider a electrolyte solution with dielectric constant ϵ. Positive and negative ions, carrying charge $+q$ and $-q$ respectively, are modeled as spheres with diameter a. The average charge density obeys charge neutrality, hence $\rho_+ = \rho_- = \rho/2$.

The electrostatic potential $\phi(r)$ satisfies the Laplace equation in the region $0 \leq r \leq a$, and obeys Poisson equation outside:

$$\bigtriangledown^2 \phi = \begin{cases} 0, & 0 \leq r \leq a \\ -\frac{4\pi}{\epsilon}\rho(r), & r \geq a. \end{cases} \tag{1}$$

Assume the Boltzmann distribution $\rho(r) = e^{\pm\beta q\phi(r)}$, where $\beta = 1/(k_B T)$. The second equa-

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tion in Eq.1 reduces to the non-linear Poisson-Boltzmann (PB) equation,

$$\nabla^2 \phi = -\frac{4\pi \rho q}{\epsilon} \sinh(\beta q \phi).$$ (2)

When $\beta q \phi(r) \ll 1$, it is usually linearized to yield the Helmholtz equation, $\nabla^2 \phi = \kappa^2 \phi$, where the inverse of the Debye length is defined as $\xi_D^{-1} \equiv \kappa = \sqrt{\frac{4\pi q^2 \rho}{k_B T \epsilon}}$. The solution of the electrostatic potential is

$$\phi_<(r) = \frac{q}{\epsilon r} - \frac{q\kappa}{\epsilon(1+\kappa a)},$$ (3)

$$\phi_>(r) = \frac{q\theta(\kappa a)e^{-\kappa r}}{\epsilon r},$$ (4)

where $\theta(x) = e^x/(1+x)$. The screening takes effect at $r > a$, and the potential falls exponentially.

Consider a fixed colloid particle with radius a, and charge $-Zq$. The argument above implies that the electrostatic potential outside the sphere has the form $\phi_>(r) = -Zq\theta(\kappa a)e^{-\kappa r}/(\epsilon r)$. If we treat $Zq\theta(\kappa a)$ as the effective charge of the colloid, the colloidal pair potential is simply

$$V_{DLVO}(r) = (Zq)^2 \theta^2(\kappa a)\frac{e^{-\kappa r}}{\epsilon r},$$ (5)

which is known in the literature as Derjaguin-Landau-Verwey-Overbeek(DLVO) pair potential. Apparently the DLVO potential has a repulsive nature.

3.2 Charge renormalization and Manning condensation

Polyelectrolytes, DNA for example, are polymers with ionizable groups. Upon hydration, a polyelectrolyte dissociates into charged monomers and counterions. Each monomer carries the same kind of charge. Depending on the sign of charge on the monomer, the polyelectrolyte can be either positively or negatively charged. For instance, DNA in aqueous solution is found to have a high linear charge density of one electron charge per 1.7 Å.

Let us now consider a simple polyelectrolyte solution containing polyions of concentration ρ_p. The solvent is characterized as a uniform electric medium with dielectric constant ϵ. To simply the algebra, we assume that the polyion is a long cylinder with length L and radius a. A polyion has Z ionized groups with a uniform spacing b. The charge carried by each group is $-q$, which gives a linear charge density $\lambda_0 = -q/b$. The counter ion has charge q, and is treated as point charge. The concentration of the counterions is $\rho_c = Z\rho_p$.

The bare electrostatic potential between the polyion and a counterion is

$$\phi = -\frac{2q\lambda_0}{\epsilon} \ln(\frac{r}{r_0}),$$ (6)

where r_0 gives the position of the reference potential. The polyion-counterion's two-body partition function has a analytical form

$$\zeta_1 = L \int_a^R e^{-\beta q \phi(r)} d^2 r = \pi L r_0 \frac{(R/r_0)^{2-2\xi} - (a/r_0)^{2-2\xi}}{1-\xi},$$ (7)

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where R is the cutoff where the pair potential is still valid. The Manning parameter is defined as $\xi = \frac{|q\lambda_0|}{\epsilon k_B T} = \frac{q^2}{\epsilon k_B T b}$.

The partition function in Eq.7 remains finite except that it diverges at $\xi \to 1^-$, if $a = 0$. However $a = 0$ is required for the existence of the limiting laws, which insist the thermo-dynamic functions are independent of the polyion diameter. The divergence indicates that n counterions condense onto the polyion when $\xi > 1$ according to Manning. The effective charge density becomes $\lambda_n = \lambda_0 \frac{Z-n}{Z}$. For $\xi > 1$, the Manning parameter is renormalized,

$$\xi_{eff} = \frac{|q\lambda_n|}{\epsilon k_B T}, \tag{8}$$

and it saturates at 1. The number of condensed counterions can be determined from the above equation as $n^* = Z(1 - \frac{1}{\xi})$. Replace the bare Manning parameter ξ with the renormalized parameter ξ_{eff} in Eq.7. The divergence is eliminated, and limiting laws exist.

Manning's original approach gives a simple picture of counterion condensation, but its underlying logic is flawed. Basically it requires the existence of limiting laws at the first place to derive the limiting law. Although this treatment is not rigorous, Manning condensation can indeed be demonstrated using more complicated methods.

3.3 Like-charge attraction

Mean field theory fails to explain the attraction effect. What is omitted for the counterions could be long-wavelength fluctuation effect (13; 14) and the short-range correlations (15; 16). The first mechanism considers the counterions condensed on the rod-like polyions as clouds of 1-D free electron gas. Similar to the van de Waals interaction originated from the quantum mechanical fluctuation, thermal fluctuation causes an attractive force between rods. The second mechanism resorts to the strong counterion correlation when two polyions come close. It has been proposed that at low temperature counterions condensed on the charged planar surfaces form 2-D Wigner crystal, and the surfaces should attract each other.

Molecular dynamics of model systems shows the long-wavelength fluctuation dominates the high temperature regime, while short-range correlations governs the low temperature regime. Experimental measurement on DNA strands by Cyrus Safinya's group at the University of California, Santa Barbara suggests that the short-range correlations are responsible for the DNA condensation, even though there is no direct evidence of the Wigner crystal yet. In the following, I will only introduce some concepts of short-range correlations mechanism.

The idea of like-charge attraction can be illustrated in a simple model. Consider a pair of polyions similar to those described in Manning condensation. Each polyion has a length L and charge density $-q/b$. The polyions are parallel to each other with a spacing d in the dilute solution containing $\alpha-$valent ions. Again the Manning parameter is $\xi = q^2/(\epsilon k_B T b)$. Following Manning's approach, we find $n = \frac{Z}{\alpha}(1 - \frac{1}{\alpha\xi}) \; \alpha-$ions condensed on each polyions for $\xi > 1/\alpha$. Let us assume that the counterion condensation renormalizes the local monomeric charge from $-q$ to $(-1+\alpha)q$. When $\alpha > 2$, a local charge inversion may appear. Define the occupation probabilities as σ_{ij} with $i = 1, 2, ..., Z$ and $j = 1, 2$. $\sigma_{ij} = 1$ only if a counterion is condensed at the ith monomer of the jth polyion. For other cases, $\sigma_{ij} = 0$. On either of

the polyions,

$$\sum_i \sigma_{ij} = n. \tag{9}$$

The renormalized Coulomb energy of the polyion pair is

$$H = \frac{1}{2\epsilon} \sum_{i,i'=1}^{Z} \sum_{j,j'=1}^{2} \frac{q^2(1-\alpha\sigma_{ij})(1-\alpha\sigma_{i'j'})}{|r_{ij} - r_{i'j'}|}, \tag{10}$$

where the sum is over $(i,j) \neq (j',j')$ pairs. The distance is $|r_{ij}-r_{r'j'}| = b\sqrt{(i-i')^2 + (1-\delta_{jj'})x^2}$, where $x = d/b$. The pairwise partition function is

$$Q = \sum_{\{\sigma_{ij}\}} \exp(-\beta H), \tag{11}$$

where $\{\sigma_{ij}\}$ denotes all the possible configurations satisfying Eq.9. The pairwise force is

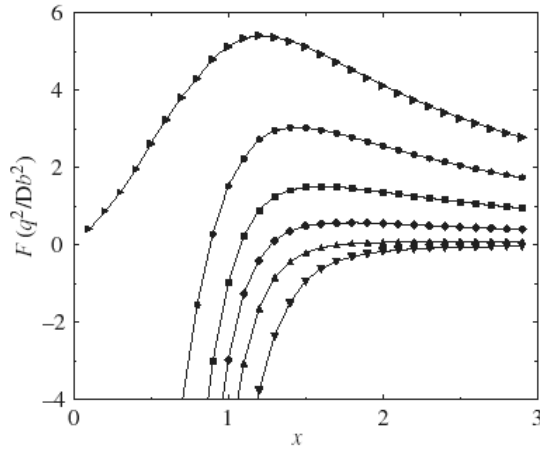$$F = \frac{1}{b\beta} \frac{\partial \ln Q}{\partial x}. \tag{12}$$

Figure 4: Pairwise force between polyions as a function of distance (12). Curves from top to bottom are for $n = 5, ..., 10$ respectively.

At the small separation limit $x \to 0$, the dominant terms in the partition function have such configurations that the condensed counterions in the two polyions are not facing each other. In other words, if $\sigma_{i1} = 1$, then $\sigma_{i2} = 0$. In this way, the positions of the condensed counterions on each polyions are strongly correlated. The Coulomb energy of these configurations is

$$E \approx \frac{2n(1-\alpha)q^2}{\epsilon bx} + \frac{(Z-2n)q^2}{\epsilon bx}. \tag{13}$$

The first term in Eq.13 describes the electrostatic attraction between $2n$ condensed counterions and the bare polyions, and the second term is the Coulomb repulsion between the $Z-2n$

uncompensated charge pairs. From Eq.13, it is evident that the interaction is always repulsive for monovalent counterions. For multivalent counterions, the attraction term dominates at sufficient short separation when $n < Z/(2\alpha)$, whereas the interaction becomes repulsive when $n > Z/(2\alpha)$ at all temperatures. Numerical results of Eq.11-12 for divalent counterions are plotted in Fig. 4. Parameters used are $Z = 20$, $\alpha = 2$, $\xi = 2.283$, and $n = 5, ..., 10$ (from top to bottom). At short distance $x \approx 1$ and high enough condensation $n \geq 6$, the force is negative. This is the demonstration of the existence of like-charge attraction.

Another consequence of strong electrostatic correlation is the so called "overcharging". If the condensed counterions contribute more charges than the bare charges on the polyion, overcharging occurs. As a result, the net charge of the polyion changes sign, When the number of condensed counterions exceeds certain critical value, overcharged polyions repel each other.

3.4   Explanation of experiments

Using the simple models outlined in the previous sections, we can qualitatively understand the DNA condensation experiments. When DNA is solvated in the salt free solution, the counterions condense on the DNA surface. As the counterions are monovalent, DNA has the random coil form and repels each other. Then multivalent α-salt is gradually applied to the solution. Enthalpy and entropy will compete to determine the position of the $\alpha-$ions. When the concentration of $\alpha-$ions are low, they are kept in the solution to maximize the entropy. Until it reaches a critical concentration that the electrostatic interaction with DNA overweighs the loss of the entropy due to the confinement of $\alpha-$ions onto the DNA surface, counterions are released to the solution and $\alpha-$ions condensate onto the surface of DNA. When the number of the condensed $\alpha-$ions becomes sufficient large, like-charge attraction happens. As DNA is a quite stiff molecule with a persistence length of 500 Å, the DNA condensation has a toroidal geometry to minimize bending energy. If we further increase the $\alpha-$ion concentration, overcharging can happen. When the number of condensed $\alpha-$ions reaches a certain limit, the DNA segments repel each other again. Finally the DNA condensate re-dissociates.

4   Discussion

In the previous section, the DNA condensation experiment is quantitatively understood based on the short-range electrostatic correlation argument. The seemingly successful models still leave us many unknowns. For example, what exactly make a multivalent ion different from several monovalent ions? Does the size of the ion have anything to do with the condensation? It is known from experiments that divalent cations such as Mn^{2+} and Cd^{2+} can cause DNA condensation, while Mg^{2+} and Ca^{2+} can not. What is the reason for such specification? The structure of DNA is much more complicated than the model system, i.e. a long cylinder. The geometrical details of DNA can have an impact on ion specification. For instance, Mn^{2+} and Cd^{2+} are preferentially absorbed on the grooves of the DNA, while Mg^{2+} and Ca^{2+} bind to the sugar phosphate backbone of DNA (17). It could cause very different interaction mechanism between the ions and DNA. It has been postulated that supercoiling cooperates

with Mn^{2+} to stabilize helix distortions, and also provides a "pressure" to enhances lateral association (3).

Due to the complexity of the biomolecules and many other effects, such as volume exclusion, in the polyelectrolyte solution, existing models are too simplified to explain all the related phenomena. There at least exist two ways to test and develop the theory. Firstly, one can use computer simulations to investigate the model system. Secondly, one should use simpler structures to eliminate the unknown factors, and tune the variables to yield better statistics. It has been noticed in a recent experiment (17) that the author used a rod-like virus with much smoother charge density distribution. The charge density is variable by applying different PH in the solution. The divalent ions are of the form $H_3N(CH_2)_nNH_3$, where $n = 1, 2, 3, 4$. The advantage of this design is that by varying the number of CH_2 groups in the middle, the separation between the two charge NH_3 group is also tunable. In this sense, the ion can either behave like a single divalent ion at small n or two connected monovalent ions at large n. A phase diagram is constructed upon ion concentration $vs.$ surface charge density. Although the phase diagram is not fully understood based on the existing theory, it provides a good opportunity to establish further understandings.

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