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Dynamics of Ion Migration in Nanopores and the Effect of DNA-ion Interaction

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Abstract

We have carried out Brownian Dynamics calculations to investigate the effect of DNA-ion interaction on ion transport in a nanopore. We calculated the self-diffusion coefficient of monovalent ions in the presence of DNA in a nanopore and compared with that through an open pore, i.e., without the presence of DNA. We find that the self-diffusion coefficient of the coions is essentially unaffected by the DNA. The self-diffusion coefficient of the counterions, on the other hand, is significantly reduced depending on the ion concentration. At high ion concentration, around 1 M, the effect of DNA on counterion diffusion is relatively small, causing a slight reduction in counterion diffusion coefficient. At low concentration of a few mM, the effect is much larger, resulting in a reduction in counterion diffusion coefficient by about a factor 2.5. The variation in the self-diffusion of the counterion is well described by accounting for the contributions from two components: the adsorbed counterions; and the free counterions. Detailed dynamics of the DNA-counterion interaction is characterized by the varying length of the transient adsorption time of the counterions to the DNA charge sites and the exchange rate with the environment. This variation in counterion adsorption time is attributed to ionic electric screening effect, which is in turn determined by the ion concentration.

Keywords

DNA; nanopore; counterions; coions; diffusion; migration; electric screening; counterion condensation; migration

I. Introduction

Detection on DNA-induced ionic current blockade has attracted considerable recent research interest^{1–9} as nanopores with diameter on the scale of ~10 nm and smaller have been constructed. A number of recent works have reported experiments measuring the effect of DNA on ionic current through nanopores and the variation of such current with ion concentration.^{6–9} A blockade current cross over from negative to positive has been observed as ion concentration is decreased and the mechanisms of counterion condensation and volume exclusion have been invoked to describe the phenomenon with considerable success.^{6–16} Fundamentally, the ionic flow involves two quantities, the ion concentration, and the migration velocity of the ions. The physics of counterion condensation has been reasonably well understood, and the concept of volume exclusion can be intuitively understood. In comparison, our understanding to the dynamic process of ion migration in

nanopore is still very limited when DNA is present. A complicating factor in quantitative analysis of the ion migration is that the counterions are only transiently adsorbed to the DNA (at the charge sites) with an adsorption time on the order of nanoseconds.¹⁷ On a macroscopic time scale, numerous association-dissociation events take place, and the counterions adsorbed to the DNA cannot be treated as static. Thus, there is no straightforward way to account for the effect of the transiently adsorbed counterion. In addition, there is a lack of knowledge to the detailed dynamics on how an initially free counterion becomes adsorbed to DNA and the associated exchange process between an adsorbed and a free counterion. Furthermore, the DNA-ion interaction is attenuated by the presence of background ions. Classical theory has suggested the important effect of the background ions, through electric screening, as characterized by the well-known Debye length, which is determined by the ion concentration.^{18–20} It is thus expected that counterion migration in the presence of DNA should significantly depend on the ion concentration. Therefore, a good understanding to the mechanism of the DNA-counterion interaction in nanopores, its effect on the ion migration, and the dynamics of the counterion dissociation-association is needed for future practical effort in the field.

Theoretical and modeling study of DNA has been performed using a variety of approaches including analytical theory, coarse grained approaches such as Poisson-Boltzmann (PB) calculations and Brownian dynamics (BD), and fully detailed atomistic molecular dynamics simulations. The DNA counterion condensation theory originated with Manning's theoretical analysis on a simple line charge model. It predicts a critical line charge density above which the system becomes unstable and counterions condense to the line charge to reduce the line charge density to stable value.^{10,21} Electrostatics approach, in which the solvent is treated as a continuum, has been used in the study of DNA packaging in viruses, bacteria, and chromosomes, and to investigate the underlying mechanisms – counterion induced DNA-DNA attraction.^{22–25} Similarly, electrostatic approaches have been used to study protein structure and protein-protein interaction.²⁶ In recent years, molecular dynamics has increasingly been used to study DNA. A number of studies have investigated the DNA-ion interaction in bulk aqueous solution.^{27–30} Due to the important potential in nanopore based DNA sequence detection, behaviors of DNA within nanopore environment are being intensely investigated^{31–35} (readers are referred to ref. 35 for a recent review on the subject). These investigations have significantly advanced our understanding of the DNA-ion interaction.

In this study, we carried out a Brownian Dynamics simulation study to obtain a detailed understanding to the microscopic mechanisms for ion migration in nanopores in the presence of DNA. We investigated the diffusive migration of monovalent counterions and coions and the dynamics of counterion adsorption to the DNA, as characterized by the residence time correlation functions (RTCF) of the counterions to the charge sites of the DNA. We further analyzed the effect of the adsorption dynamics on the diffusion of the counterions and the role of the electric screening in modulating DNA-ion interaction, hence its migration. In the following, we present our methods and results. We discuss and analyze the results to elucidate our understanding of the microscopic mechanisms of ion transport in nanopore.

II. Models and Methods

We carried out a Brownian dynamics study of dsDNA in nanopores with K^+ and Cl^- ions for a range of ion concentrations. In our system, the dsDNA is fixed in space. Only ions undergo Brownian motion. The equation of motion for the ions is given by,^{36,37}

$$m_i \frac{d\mathbf{v}_i}{dt} = \mathbf{f}_i - \zeta_i \mathbf{v}_i + \mathbf{f}_i^R \quad (1)$$

where m_i is the mass of the ion (labeled with index i), $\mathbf{v}_i$ is the instantaneous velocity vector, $\zeta_i = k_B T / m_i D_i$ is the friction coefficient with D_i the self-diffusion coefficient in bulk fluid at infinite dilution, k_B the Boltzmann constant, and T the temperature. $\mathbf{f}_i$ is the force due to other ions, DNA, and the pore, and $\mathbf{f}_i^R$ is the random Brownian force representing the effect of the solvent. The position and velocity are updated using the standard algorithm.³⁸ DNA is treated as immobile as its thermal velocity is negligible compared to the ions.¹⁶

In our calculations, the DNA is modeled as a straight cylinder, with an exclusive core radius of 0.80 nm. Negative charges of $-e$ each are placed 0.3 nm out from the core surface in double-helical arrangement. The DNA is capped with hemispherical caps of 0.80 nm at both ends.²⁵ The total length of the pore is 21.76 nm in length and 10 nm in diameter. The DNA is placed at the center of the pore and is parallel to the axis of the pore. The DNA length considered here is less than the persistence length of the double-stranded DNA (~ 50 nm), and is intended to represent a short segment of a long dsDNA, which should be reasonably straight. The total length of the DNA (including the hemispherical caps) is equal to the nanopore length with the cylindrical portion carrying 114 units of electric charges. The K^+ and Cl^- interact with the DNA and with each other through a soft sphere potential and electrostatic interaction.³⁹ The soft sphere interaction potentials and relevant parameters used in this study are summarized in Table I. The dielectric constant of the media far from the DNA in the radial direction is 78.4, modeling an aqueous environment. Close to the surface of the DNA, it has been recognized that the dielectric constant varies with the distance from the DNA.^{40–42} We have thus used a distance dependent dielectric constant within 1 nm from the surface of the DNA, derived based on a fitting to local dielectric constant obtained from molecular dynamics simulation.²⁶ It is given in mathematical form

as $\varepsilon_e(r) = \varepsilon_0 - \left[\left(\frac{\varepsilon_0 - \varepsilon_i}{2} \right) (\alpha^2 + 2\alpha + 2) e^{-\alpha} \right]$, where $\alpha = sr$; $s = 1.2 \text{ \AA}^{-1}$, $\varepsilon_0 = 78.4$, $\varepsilon_i = 1.76$, and r is the distance from the DNA surface. For $r > 1$ nm, $\varepsilon_e(r)$ is indistinguishable from ε_0 . Since the focus of the study is to investigate the effect of the DNA-ion interaction on the diffusion of the ions, we have chosen to model the nanopore wall as neutral, so that there is no electric effect on the diffusion of the ions from the wall, and all the effects are solely due to the DNA. In many experimental situations, the nanopore wall may be charged. We have shown in a previous study that the major effect of such electrically charged wall is the enhancement of the electric double layer overlap when DNA enters the pore, causing the ionic concentration in the pore to deviate from that without DNA. For simplicity in this study, we are using a neutral wall in order to isolate the effect of the DNA from that of the wall on the ion diffusion. For cases of electrically charged wall, the ion concentration used

here should be considered an equivalent concentration (after taking into account the electric double layer overlap effect).

Our main interest is in the system where the nanopores are sufficiently large so that a continuum picture for the solvent is applicable. Thus, we have chosen a pore size of 10 nm in diameter (except Sec. III. 4 where we study the effect of pore size), which is about 30 time larger than the size of water molecules, ~ 0.3 nm. In addition, we have neglected the desolvation effect due to the molecular nature of the water molecules, which has been found to be important for small pores ~ 2 nm.^{43,44}

The electrostatic long-range interaction is treated as in our previous publication.⁴⁵ Because of the one-dimension nature of the system at large distance and the electric neutrality of the system, the long-range correction to the electrostatic interaction can be integrated to give an analytic expression in the line-charge method approach.⁴⁶

Total number of ions in our systems ranges from 116 to 2430. The time step used for updating the position and velocity of the ions is 0.0252 ps. Typical calculations run for 5 to 30 million time steps, depending on the ion concentration. In an extreme case at low concentration, we have run the calculation as long as 200 million time steps.

III. Results

III. 1. Dependence of Counterion Self-Diffusion on Ion Concentration

The diffusion coefficients for K^+ and Cl^- in the axial direction are calculated using the Einstein relation, $\langle [r_{||}(t) - r_{||}(0)]^2 \rangle = 2D_{||}t$, where the symbol $||$ is used to denote the direction parallel to the pore axis. We note that the diffusion coefficient obtained here does not include the effect of hydrodynamic interaction. In general, the calculation of dynamic properties should take into account the hydrodynamic interaction.⁴⁷ For self-diffusion coefficient of small ions, however, it has been shown⁴⁸⁻⁵⁰ that the effect of the hydrodynamic interaction is less than about $\sim 3\%$ at the highest ion concentration studied here and negligible below 300 mM, therefore, the hydrodynamic interaction would not affect the discussion below.

The calculated diffusion coefficients vs. ion concentration (in this work, the ion concentration in the nanopore is defined as the concentration of the coions) are plotted in Figure 1. The most striking feature is that in the presence of DNA, the diffusion coefficient for the counterion decreases with the decreasing ion concentration, approaching essentially a plateau at very low ion concentration. At the lowest concentration studied, where the Cl^- concentration is 1 mM, the K^+ diffusion coefficient has decreased to about 40% of the value at the highest concentration studied, about 1.125 M. On the other hand, the variation in co-ion diffusion coefficient is much smaller, increasing slightly with the decreasing ion concentration and tending to the dilute solution limit, $2.032 \times 10^{-5} \text{ cm}^2/\text{s}$.⁵¹ This slight increase is obviously due to the less frequent collisions among ions at lower concentration. For comparison, we also plot the results for ion diffusion in an open pore where there is no effect caused by DNA. It is seen clearly that for open pore both the counterion and the coion diffusion coefficients show similar trend with a slight increase with decreasing ion

concentration. The horizontal dashed line in Figure 1 shows the experimental K^+ diffusion coefficient at infinite dilution, $1.957 \times 10^{-5} \text{ cm}^2/\text{s}$, as a reference.³¹ The presence of the DNA clearly has an important effect on the dynamics of the counterion transport in the nanopore. Similar effect has been found in NMR measurement of Li^+ and Cs^+ diffusion in humidified DNA fibers, where a reduced counterion diffusion coefficient compared to bulk fluid, as well as a decrease with decreasing salt concentration, were observed.⁵²

Physically, we understand that at the few lowest ion concentrations studied here, there are very few coions. The vast majority of ions are counterions, which are necessarily present to electrically neutralize the charges of the DNA so that the system as a whole is electrically neutral. In the extreme case, the coion concentration is so low that the ratio of the total DNA charge and total counterion charge is nearly unity; the attractive interaction between the counterions and the DNA reaches maximum strength absent of the mediating effect of the coions, so the diffusion coefficient approaches a plateau. On the other hand, at the highest ion concentration studied here, the ratio of the number of DNA charges to the total number of counterions is about 9%, so the counterion diffusion is largely dominated by the contribution from the free counterions.

Note that the diffusion coefficient is calculated as an average over all the counterions or coions, because it is impossible to separate the adsorbed and free counterions as the same ion can dynamically change role from being adsorbed to being free and vice versa (see Secs. III. 2 and III. 3 below for more details). To better quantitatively understand the counterion diffusion slowing down by the DNA, we decompose the contribution to the average diffusion coefficient into the components due to adsorbed and free counterions.

$$D_{eff} = \frac{1}{N^+} \left[D_{ads} \bullet N_{DNA} + D_{free} \bullet (N^+ - N_{DNA}) \right] \quad (2a)$$

Where D_{eff} ($D_{eff} = D_{||}$ of the Einstein relation) is the effective average diffusion coefficient over all counterions in the nanopore, D_{ads} corresponds to the plateau diffusion coefficient of the adsorbed counterions at very dilute ion concentration ($D_{ads} = 0.693 \text{ cm}^2/\text{s}$ is the counterion diffusion coefficient at 1 mM. Inset of Figure 1), D_{free} is the diffusion coefficient of the free counterions ($D_{free} = 1.715 \text{ cm}^2/\text{s}$, derived by extrapolation to high concentration based on the simulation data), N^+ is the total number of counterions, and N_{DNA} is the number of charge sites on the DNA. Note that $N^+ = N^- + N_{DNA}$, where N^- is the number of coions. And since ionic number appears both in the denominator and numerator, Eq. 2(a) is a nonlinear function of the ionic numbers. The physical significance of a non-zero D_{ads} is that although we need N_{DNA} counterions to completely neutralize the DNA charge in the nanopore, there is always a fraction of counterions at any instance of time which remain free due to the incomplete physical adsorption of the counterions to the DNA, unlike in the stronger chemical adsorption. The adsorbed counterions can occasionally dissociate from the DNA and become free and vice versa. The result is plotted as short-dashed line in Figure 1. It is seen that this simple two-component analysis describes very well the concentration dependence of the diffusion coefficient for the counterions in nanopore in the presence of DNA. Thus, for conceptual convenience, the diffusion of the counterions in the presence of

DNA can be attributed to two contributions, one from adsorbed counterions with reduced diffusion coefficient, and the other from free diffusing counterions.

For practical purpose, it is useful to recast Eq. (2a) in terms of concentrations instead of the number of ions and charge sites. This can be done by dividing both the numerator and denominator by the volume, resulting in,

$$D_{eff} = \frac{1}{C^+} \left[D_{ads} \bullet C_{DNA} + D_{free} \bullet (C^+ - C_{DNA}) \right] \quad (2b)$$

Where C^+ and C_{DNA} are the concentration of the counterions and the DNA charge sites in the nanopore. Note that the ion concentration appears in Eq. 2(b) implicitly through the relation $C^+ = C + C_{DNA}$ due to the charge neutrality in the nanopore.

III. 2. Dynamics of Counterion Dissociation from DNA

To gain a deeper understanding to the effect of DNA-ion attraction on the mobility of the counterions, we calculated the continuous residence time correlation function (RTCF) of the counterions around a DNA charge site, defined as,^{53,54}

$$F_c(R, t) = \frac{\sum_{i,j} \langle \theta_{ij}(R, 0) \theta_{ij}(R, t) \rangle}{\sum_{i,j} \langle \theta_{ij}(R, 0) \theta_{ij}(R, 0) \rangle} \quad (3)$$

where the double summation is over all charge sites of the DNA, i , and all the counterions, j . $\theta_{ij}(R, t)$ is the Heaviside step function which is 1 if a counterion remains continuously within a radial distance R of a DNA charge site, taken to be twice the Van der Waals diameter of the potassium ion and DNA interaction, $R = (R_i + R_{DNA}) = 7.332 \text{ \AA}$, from time 0 to t , and 0 otherwise, where $R_i = 2^{1/6} \sigma_i$, and $R_{DNA} = 2^{1/6} \sigma_{DNA}$ are the Van der Waals diameters of the ion and DNA charge site, respectively (see Table 1). The angular brackets represent a time average from the BD simulation. Eq. (3) defines a correlation function at time t for the fraction of counterions which were within the radial distance R of a DNA charge at time 0 that have never left the spherical volume within R in the time interval $[0, t]$. It can be reasoned that if a counterion spends considerable amount of time around a DNA charge site, its migration would then be substantially delayed, resulting in a lower mobility.

The results are shown in Figure 2 for a range of ion concentration. It is seen that the RTCF closely follow an exponential form with characteristic times depending on the ion concentration. By fitting the RTCF to the exponential function we derive a characteristic residence time corresponding to each ion concentration, obtaining values for the residence time, $t_R = 811, 716, 500, 356, 252$, and 191 ps for ion concentration $1, 15, 67, 294, 548$, and 787 mM , respectively. The results show that the residence time strongly depends on the ionic concentration, decreasing with increasing ion concentration. At the lowest concentration, 1 mM , coion population is less than 1% of counterion population in the nanopore that is needed to neutralize the negative charges on the DNA. As a result, the

interactions between the counterions and the DNA charge are essentially the unscreened bare interactions, so the counterions experience the strongest attraction by the DNA. It is thus more difficult for them to escape from the DNA, resulting in a long residence time. Inversely, as the ion concentration increases, there are a large proportion of background ions that are not directly adsorbed to DNA charge sites, but rather spread throughout the nanopore at all radial distance. These ions are more or less free to move about in the pore in response to the local electric field to reduce the interaction strength, such as that between the DNA and the counterions. Furthermore, due to the abundant presence of the background ions, exchange of the free counterions with the adsorbed counterions are more readily possible, so the exchange events occurs more often; this in effect also contributes to the shortening of the residence time of the adsorbed ions.

In the theory of ionic solutions,^{18–20} the electric potential from a charge Q is given, apart from a constant pre-factor, by $\frac{Qe^{-r/\lambda_D}}{r}$, where r is the distance from the charge, λ_D is the

Debye length, given (in SI units) by $\lambda_D = \left(\frac{k_B T \epsilon_e}{e^2 c_s} \right)^{1/2}$ for monovalent ionic solution, where k_B is the Boltzmann constant, T is temperature, ϵ_e is the dielectric constant, e is the magnitude of electron charge, and c_s is the total number density of the ions. Beyond the distance λ_D , the effect of the charged object is largely neutralized by the opposite charged ions. Thus an effective manifestation of the electric screening is the charge neutralization around the DNA by the small mobile ions. This we show in Figure 3 where the net electric charge within a certain distance r in the radial direction, Q_N , including K^+ , Cl^- , and those of DNA ($\Delta Q_N = \sum_i q_i^+ + \sum_j q_j^- + Q_{DNA}$) are plotted. Clearly, the electric neutrality varies with the ion concentration. At the two lowest ion concentrations shown, 1 and 15 mM, the charge neutrality is not reached until the nanopore wall. As the ion concentration increases, DNA charges are increasingly better screened. At 294 mM, DNA charges are essentially completely screened by 2 nm from the DNA surface (which is at $r \approx 1$ nm). At 1125 mM, the DNA charge is completely screened by the counterions about 1 nm from the DNA surface. The rapid initial rise of the plots near $r = 1$ nm in the figure is due to the counterions directly bound to the DNA. At intermediate distance from the DNA (between 1.2 – 1.5 nm), the net charge also increases faster with the ion concentration. The net effect of this concentration-dependent electric screening (or the lack of) is the weaker DNA-counterion attraction at high ion concentration, or inversely, stronger DNA-counterion interaction at low ion concentration. This results in longer residence time for the counterions, which in turn leads to slower migration.

III. 3. Dynamics of Free Counterion Adsorption to DNA

Similar to the function $F_c(R, t)$, we can define a correlation function $G_c(\underline{R}, t)$, which describes a counterion initially in the region $\underline{R}$ complementary to the region R in the nanopore (here R is a combination of spherical volumes within a specified distance R for all DNA charge sites; and $\underline{R}$ spans the whole region in the nanopore exclusive of R) and continuously stay in region $\underline{R}$ until it enters into a local spherical volume associated with one of the DNA charge

sites. In Figure 4, we show correlation function $G_c(\underline{R}, t)$ for a range of concentrations from 1 mM to 787 mM.

It is seen that as the ion concentration increases, the residence time for the ions to stay away from the DNA becomes longer, ranging from 1852 to 3786 ps for the range of ion concentrated studied. The increase of free ion residence time with ion concentration is mainly due to two factors. One is that as the ion concentration increases, the electric screening causes the attractive interaction between the DNA charges and the counterions to weaken so that the counterions are less likely to be attracted to the DNA. The other is that as the ion concentration increases, the free counterions are more abundant. So that on average, the probability is smaller for each counterion to come into close encounter with a charge site of the DNA. Comparing with the residence time of the counterions to remain adsorbed to the DNA, the time duration for the counterions to stay free is significantly larger. At the highest ion concentration calculated for $G_c(\underline{R}, t)$, 787 mM, the duration of counterion to stay free is more than an order of magnitude larger than the bound counterion residence time, which suggests that at high ion concentration a counterion initially unbound to the DNA can migrate freely with relatively little interference from the DNA. Thus, at high concentration, the counterion diffusion coefficient eventually tends to the open pore limit.

It is also noted that the residence time for adsorbed and free counterions vary with ion concentration with opposite trend, which is shown in Figure 5. The difference between the adsorbed and the free counterion residence time narrows as ion concentration decreases. At 1 mM ion concentration, the difference is only about a factor of 2 between the free and the bound counterion, so the counterion transport at low ion concentration is characterized by an intermittent process in which the free counterion migration is frequently interrupted by DNA charges that momentarily trap the counterions to a particular charge site. At very low ion concentration, the residence times of both the adsorbed and free counterions approach plateaus, consistent with the same behavior for the diffusion coefficient.

The results in Figure 5 show that for the nanopore size studied here the free counterion residence time is always larger than the bound counterion residence time. It is possible, however, that as the nanopore diameter decreases, the free counterion residence time may decrease and becomes similar to or even smaller than the bound counterion residence time. As a result, the counterion migration through the nanopore will be more severely reduced.

III. 4. Effect of Pore Size on Counterion Residence Time

To further elucidate the exchange dynamics between free and adsorbed counterions, we investigate the dependence of residence times on the diameter of the pore. For simplicity in comparison, we keep the ion concentration constant while varying the pore diameter. In Figure 6, we plot the residence time of the adsorbed and free counterions as a function of pore diameter for ion concentration 67 mM. It is seen that in the range of pore size studied, the residence time of the bound counterions varies only slightly, except for the smallest diameter where a large drop is observed; whereas that of the free counterion residence time varies by an order of magnitude. In the plot, the data labeled “estimate” for the free counterion residence time are obtained from the following scaling equation, using the calculated value of the residence time for the 10 nm pore as a reference point.

$$\tau_d^f = (V_d^f / V_{10}^f) \bullet \left(\frac{N_d^+}{N_{DNA}} / \frac{N_{10}^+}{N_{DNA}} \right) \tau_{10}^f = (V_d^f / V_{10}^f) \bullet (N_d^+ / N_{10}^+) \tau_{10}^f \quad (4)$$

where τ_d^f , V_d^f , and N_d^+ are the residence time, the spatial volume of free counterions in the nanopore excluding the volume of the DNA, and the total number of counterions in a nanopore of diameter d . The subscript 10 implies that d is set equal to 10 nm, which is the reference pore size for the scaling. N_{DNA} is the number of charge sites on the DNA as before.

For the bound counterions, the behavior of the residence time is relatively easy to understand as it is largely determined by the local interaction between the DNA charge site and counterion. For the free counterions, there are two dominant determining factors. One is the available spatial volume for the free counterions, which varies quadratically with pore diameter. This translates into a phase space volume for the free counterions to explore. The second is that there are more counterions than can be adsorbed by the DNA, so there is a permutation process for different counterions to be adsorbed to DNA through adsorbed-free counterion exchange. The more the counterions, the longer the permutation takes. This prolongs the time for the rest of the counterions to remain free. The fact that the estimated free counterion residence time using Eq. (4) gives values in close agreement with those from simulation for an order of magnitude variation suggests the correctness of the suggested mechanism here.

The reason for the steep drop at smallest pore diameter is that as the free counterions' phase volume decreases, they not only have a small phase volume, but are also closer to the DNA due to the confinement, thus are more strongly attracted by the DNA. As a result, the time duration for them to remain free is shortened more than described by Eq. 4 as seen in Figure 6. This also leads to more frequent exchange with the bound counterions to reduce the bound counterion residence time. However, the total cumulative time that the counterions stay bound to the DNA is longer so this should have an effect of reducing the diffusion rate of the counterions through the nanopore. We caution that for the smallest pore of 6 nm in diameter there might be some explicit solvent effect thus a full atomistic simulation may be needed to more accurately quantify the process. Though on physical ground, we can easily understand the qualitative trend. Another effect for small nanopore is the strong co-ion depletion by DNA which has been discussed in a prior work.¹⁷

III. 5. Counterion Condensation to DNA in Nanopore

To better understand counterion transport, it is also useful to have some knowledge about the amount of counterions attracted to the DNA, commonly referred to as the counterion condensation. In this study, we characterize it by f_q , the fraction of DNA charge which is counter balanced by the adsorbed counterions. For this purpose, we calculated the excess number of counterions around the DNA as a fraction of charge on the DNA. This is obtained by subtracting the background contribution in the region sufficiently far away from the DNA in the radial direction (at 3 nm). In Figure 7, we show such excess charge as a fraction of the total DNA charge, which fall between about 0.60 and 0.82, with small variation between the

radial distance 1.1 and 2.0 nm. For $1.05 < r < 1.15$ nm, f_q quickly rises to about 0.60, a value which is fairly insensitive to the ion concentration. This rise at short distance is obviously due to the counterions which are more tightly bound to the DNA charge sites and are relatively immobile. They neutralize about 60% of the charges on DNA. Further away, there is a gradual slow rise to values between about 0.68 to 0.82. These account for the counterions which are weakly attracted to the DNA, and their motion is relatively more mobile than the tightly bound counterions. Molecular dynamics simulations have been performed to study ion distribution around DNA,^{27,29,33} from which the fraction of DNA charge neutralized was determined. Values between 0.72–0.75,³³ and 0.76^{27,29} have been obtained, with some variation in the Manning radius used. The results obtained here are comparable to these studies. Early experiments based on NMR and electrophoresis measurements reported values for the fractional counterion condensation in a range of 0.53–0.85.^{10–14} A recent optical tweezers experiment reported a value of 0.75.¹⁵ However, the result has been reinterpreted by theoretical analyses,^{55,56} and a molecular dynamics study by Aksimentiev et al.³³ has provided detailed mechanism and interpretation on the forces experienced by DNA. Continued strong interest in accurately determining counterion condensation has led to new techniques. A recent buffer equilibration-atomic emission spectroscopy experiment (BE-AES)⁵⁷ reported charge neutralization values 76–87% for ion concentration between 0.005 – 1.0 M, and an anomalous small-angle X-ray scattering (ASAXS) experiment gave a value of 68%.⁵⁸

III. 6. Effect of Counterion Association on Migration

To illustrate the effect of the counterion association with DNA and the implication of the residence time on diffusion, we plot in Figure 8 the mean square displacement (MSD) for counterions in 10 nm open pore at ion concentration 548 mM, which represents free counterion diffusion without association with the DNA. The MSD corresponds to a diffusion coefficient of 1.756×10^{-5} cm²/s which is fairly representative of ion diffusion in open pore, as the concentration dependence of the diffusion coefficient is weak in the absence of DNA (see Figure 1). The horizontal dashed line at 0.54 nm² in the figure indicates the maximum MSD that a counterion bound to a DNA charge can migrate. The dotted line marked with $\tau_R = 191$ ps, and the long-short dashed line marked with $\tau_R = 811$ ps indicate the MSD a free counterion would have migrated in the time duration the counterion is being adsorbed at 787 mM and 1 mM, respectively. The differences in MSD between the dotted line and the dashed line, and between the long-short dashed line and dashed line represent the delaying effect of the DNA. Thus, at high ion concentration, $C = 787$ mM, for example, when the residence time of the counterion is relatively short ($\tau_R = 191$ ps), a free counterion would migrate a mean square distance about 0.70 nm², whereas a counterion adsorbed to DNA could migrate a maximum mean square distance of $R^2 = 0.54$ nm². The free and the bound counterion MSD are not significantly different so the effect of the DNA-counterion association on the ion mobility is relatively minor. On the other hand, when the residence time is much longer, such as for a counterion at very low ion concentration 1 mM ($\tau_R = 811$ ps), a free counterion would have migrated a mean square distance about 2.9 nm² in the time duration, corresponding to a much higher mobility. While in the same time duration a bound counterion can only migrate a maximum MSD 0.54 nm².

As a demonstration of the concept discussed above, we give a rough estimate of the counterion diffusion coefficient at 1 mM in nanopore in the presence of DNA. A MSD of 0.54 nm^2 in a time duration $\tau_R = 811 \text{ ps}$ would yield an effective diffusion coefficient $3.33 \times 10^{-6} \text{ cm}^2/\text{s}$ which is significantly smaller than the calculated diffusion coefficient of $6.93 \times 10^{-6} \text{ cm}^2/\text{s}$ from simulation, the reason being that there is also a contribution from the counterions which are not adsorbed to the DNA and which can remain free for quite a long time. Based on the discussion on counterion condensation in Sec. III. 4, if we assume 25% of the counterions are free at any moment with a diffusion coefficient of $1.957 \times 10^{-5} \text{ cm}^2/\text{s}$ (bulk experimental value,³¹ then the effective diffusion coefficient at 1 mM ion concentration would be $(3.33 \times 10^{-6} \times 75\% + 1.957 \times 10^{-5} \times 25\%) = 0.739 \times 10^{-5} \text{ cm}^2/\text{s}$, which is somewhat larger than the value obtained from the simulation, but not entirely unreasonable. Thus, based on the knowledge we gained on the dynamics of DNA-counterion interaction, we can reasonably estimate the plateau value D_{ads} in Eq. (2). The high concentration value D_{free} in Eqs. (2) can be taken as the open pore diffusion coefficient. This would then allow us to estimate the counterion diffusion coefficient in the entire concentration range.

IV. Conclusions

We have investigated the dynamics of the ion self-diffusion in a nanopore in the presence of DNA. We find that the diffusion coefficient of the coions is essentially unaffected by the DNA, whereas that of the counterions is strongly reduced by the DNA through the charge-charge interaction between the counterions and the DNA. Such reduction is dependent on the ion concentration, resulting in significantly reduced diffusion coefficient at low concentration, eventually reaching a plateau in the near absence of coions. The variation of self-diffusion coefficient of the counterions can be quantitatively described by considering two contributions, one by the free diffusing counterions; and the other by the transiently adsorbed counterions.

We examined in detail the dynamics of the transient counterion adsorption to and desorption from DNA over a range of ion concentration, which are characterized by concentration dependent residence times that provide characteristic time scales for the process of ion exchange between the DNA and the environment. It is found that the residence time for the counterions to remain adsorbed to the DNA decreases with the ion concentration, whereas that for the counterions to remain free of DNA influence increases with the ion concentration. This is consistent with a physical mechanism that increased ion concentration provides stronger electric screening, which weakens DNA-counterion interaction so that the counterions are less attracted to the DNA. The residence time for the free counterions, i.e., the time duration to migrate freely without the hindrance by DNA, besides the ion concentration, is largely determined by the pore volume and the ratio between the number of counterions and the DNA charge sites.

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Figure 1.

Diffusion coefficient for ions in nanopore in the presence and absence of DNA as a function of ion concentration. The horizontal dashed line denotes the infinite dilution limit for K⁺ in bulk solution. Solid circles, K⁺ in the presence of DNA; solid Squares, Cl⁻ in the presence of DNA; open circles, K⁺ in open pore; open diamonds, Cl⁻ in open pore; up triangles, K⁺ in the presence of hardcore cylinder; inverted triangles, Cl⁻ in the presence of hardcore cylinder; and dashed line, Eq. 2b (with $D_{ads} = 0.693 \text{ cm}^2/\text{s}$, and $D_{free} = 1.715 \text{ cm}^2/\text{s}$). The inset displays the same plots on a logarithmic scale in ion concentration to show the approach to a plateau at low ion concentration.

Figure 2. Continuous residence time correlation function (RTCF) for various ion concentrations. The curves correspond to: red (1 mM), blue (15 mM), green (67 mM), purple (294 mM), black (548 mM), and pink (787 mM). The decrease of the residence time implies faster decay of the RTCF with time as ion concentration increases from 1 to 787 mM.

Figure 3.

Total charge around the DNA in the nanopore within cylindrical volume of radial distance

less than r , $\Delta Q_N = \sum_i q_i^+ + \sum_j q_j^- + Q_{DNA}$ as a function of r . The deviation of Q_N from zero signifies a deviation from charge neutrality within the volume.

Figure 4.

Continuous residence time correlation function (RTCF) for a counterion to stay outside the influence sphere of the DNA charges, i.e., during which the counterions undergo uninterrupted free diffusion without being transiently adsorbed to the DNA. The color code of the curves is the same as Figure 2.

Figure 5.
Concentration dependence of the residence time for the adsorbed counterions and free counterions.

Figure 6.

Counterion residence time as a function of pore diameter. Solid symbols are from simulation and open square are estimate based on scaling Eq. 4.

Figure 7.
Fractional counterion condensation to the DNA as a ratio between the excess number of counterions to the total number of DNA charge sites as a function of radial distance.

Figure 8.

An illustration of the effect of counterion association with DNA on the migration slowing down of a counterion. The dashed line denotes the maximum MSD that a transiently adsorbed counterion can migrate. The dotted and long-short dashed lines denoted by $t = 191$ and 811 ps represent the MSD a free counterion would have migrated in the corresponding time durations, respectively. The longer the adsorption time, the larger the difference between adsorbed counterion and the free counterion, consequently the larger effect.

Table I

Potential models and parameters used in the simulation. ϵ and σ are the Lennard-Jones energy and size parameters, q is electric charge, and D and μ are self-diffusion coefficient and mobility at infinite dilution, respectively.

Interaction Pair	ϵ (kCal mol ⁻¹)	σ (Å)	q (e)	D (10 ⁻⁵ cm ² /s)	μ (10 ⁻⁴ cm ² /Vs)
K ⁺ ^a	0.1000	3.332	+1	1.957	7.616
Cl ^{-a}	0.1000	4.400	-1	2.032	7.909
K ⁺ -Wall ^b	0.1520	3.166			
Cl ⁻ -Wall ^b	0.1520	3.700			
DNA Charge Sites ^c	0.1520	3.200			
DNA Core ^{d,e}	0.1520	3.200			

^a Ion-ion interaction: WCA potential: $V(r) = 4\epsilon \left\{ \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] - \left[\left(\frac{\sigma}{rcut} \right)^{12} - \left(\frac{\sigma}{rcut} \right)^6 \right] \right\}$; Lorentz-Berthelot combining rule is used for cross interaction.

^b Ion-wall interaction: $V(r) = 4\epsilon \left(\frac{\sigma}{r} \right)^{12}$, $r = (R - \rho)$, R is pore radius, ρ is radial distance of the ion.

^c Ion-DNA charge site interaction: WCA potential; Lorentz-Berthelot combining rule for the interaction.

^d Ion-DNA core interaction (cylindrical portion): $V(r) = \epsilon \left(\frac{\sigma}{r} \right)^{12}$, $r = \rho - r_0$, ρ is radial distance of the ions from the DNA center axis, and $r_0 = 8$ Å is the core radius of the DNA.

^e Ion-DNA core interaction (caps): $V(\rho) = \epsilon \left(\frac{\sigma}{\rho} \right)^{12}$, $\rho = |\mathbf{r}| - r_0$, $\mathbf{r} = \mathbf{r}' - \mathbf{r}_{\pm}$, $\mathbf{r}'$ and $\mathbf{r}_{\pm}$ are the position of the ion and the centers of the semispherical end-caps of the DNA, respectively, and ρ is the distance from the cap surface to the ion.