

Electrokinetic-flow-induced viscous drag on a tethered DNA inside a nanopore

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Recent work has shown that the resistive force arising from viscous effects within the pore region could explain observed translocation times in certain experiments involving voltage-driven translocations of DNA through nanopores [Ghosal, Phys. Rev. E **71**, 051904 (2006); Phys. Rev. Lett. **98**, 238104 (2007)]. The electrokinetic flow inside the pore and the accompanying viscous effects also play a crucial role in the interpretation of experiments where the DNA is immobilized inside a nanopore [Keyser *et al.*, Nat. Phys. **2**, 473 (2006)]. In this paper the viscous force is explicitly calculated for a nanopore of cylindrical geometry. It is found that the reductions of the tether force due to viscous drag and due to charge reduction by Manning condensation are of similar size. The result is of importance in the interpretation of experimental data on tethered DNA.

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The interaction of charged polymers such as DNA with nanometer-sized natural and artificial pores has received considerable attention recently [1–7]. Such studies are partly motivated by the desire to understand how polymers cross internal membranes of cells [8]. The possibility of developing devices capable of detecting properties of biopolymers at the single-molecule level for applications such as rapid DNA sequencing [9] is also a motivating factor for such studies.

In a recent paper [10] Keyser *et al.* reported experimental measurements in which a single molecule of double-stranded DNA was immobilized while threaded inside a nanopore by the application of a pulling force to counteract the electrical force on the DNA. This was achieved by attaching one end of the DNA strand to a Streptavidin-coated polystyrene bead and holding the bead in a laser optical trap. The displacement of the bead from its equilibrium position could be detected and used to measure the pulling force on the DNA. The measured value was found to be about 75% of the maximum electric force on the DNA within the pore based on its bare charge, irrespective of the electrolyte (KCl) concentration. This pulling force is, however, determined by a complex interplay between electric forces and hydrodynamics, as noted by Keyser *et al.* [10]. The point of this calculation on an idealized physical model is to understand the relative importance of hydrodynamics and the reduction of effective charge on the DNA due to Manning condensation in determining the observed pulling force. Since the DNA as well as the internal walls of the pore are charged, the pore region has a cylindrically symmetric distribution of oppositely charged counterions. In the presence of a strong electric field an electro-osmotic flow [11] is therefore generated in this region that flows in a direction opposite to the direction in which the DNA would move if it were not immobilized (Fig. 1). This flow produces a hydrodynamic drag on the DNA, partially balancing the applied electrical force. In this paper, a simplified geometry of the pore region is used to calculate the viscous drag explicitly. It is shown that the drag is a significant fraction of the total force acting on the DNA and needs to be taken into account for a proper interpretation of experimental data on DNA-nanopore interactions.

A simplified model is adopted in which the nanopore is regarded as a cylinder of radius R (5.0 nm) and length L (60 nm). The part of the DNA inside the nanopore is regarded as a uniformly charged cylinder of radius a (1.1 nm) along the axis of the pore. The DNA has a linear charge density λ (two electron charges every 0.34 nm—the distance between adjacent bases) and a lower “effective” charge density of $\lambda_e = \lambda/q_B$ due to the Oosawa-Manning [12,13] phenomenon of counterion condensation on its surface. The factor q_B is the Oosawa-Manning factor; it has the value of $q_B = 4.2$ for an ideal model of an infinite line charge in an unbounded electrolyte. Referring to the system sketched in Fig. 1, the fluid velocity in the pore is axially directed and is described by some function $u(r)$ where r is the distance from the central axis. The electric potential is $-E_0z + \phi(r)$, where the first term is due to the externally applied axial electric field E_0 along the pore (the z direction). The functions u and ϕ are governed by the Stokes equation for viscous flow (with zero pressure gradient and an electric body force term) and the Poisson equation of electrostatics, respectively.

$$\mu \frac{1}{r} \frac{d}{dr} \left(r \frac{du}{dr} \right) + \rho_e(r) E_0 = 0, \quad (1)$$

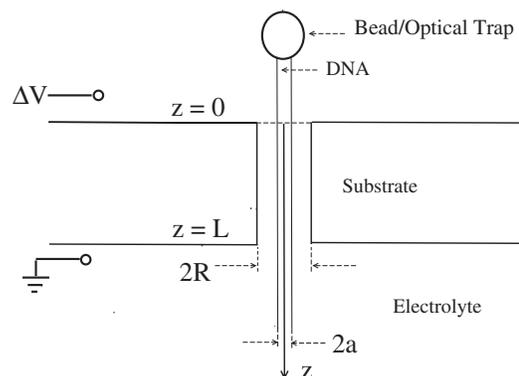


FIG. 1. Sketch illustrating the tethered nanopore experiment with a cylindrical pore.

$$\epsilon \frac{1}{r} \frac{d}{dr} \left(r \frac{d\phi}{dr} \right) = -\rho_e, \quad (2)$$

where ϵ is the permittivity of the electrolyte and ρ_e is the electric charge density due to ions. The classical boundary conditions of no slip are assumed for the velocity:

$$u(a) = u(R) = 0. \quad (3)$$

Eliminating ρ_e from the pair of equations (1) and (2) and using (3) determines $u(r)$ in terms of the potential $\phi(r)$:

$$u(r) = \frac{\epsilon E_0}{\mu} \left(\phi(r) - \phi(R) + \Delta\phi \frac{\ln(r/R)}{\ln(a/R)} \right), \quad (4)$$

where $\Delta\phi = \phi(R) - \phi(a)$. The viscous force (along the z axis) on the DNA is then

$$F_v = 2\pi a L \mu u'(a) = 2\pi a \epsilon E_0 L \left(\phi'(a) + \frac{\Delta\phi}{a \ln(a/R)} \right). \quad (5)$$

If S is the surface charge density on the channel wall, then by Gauss's law,

$$-2\pi a \epsilon \phi'(a) = \lambda_e, \quad (6)$$

$$\epsilon \phi'(R) = S. \quad (7)$$

Using the first of these equations to eliminate $\phi'(a)$ and noting that the electrical force on the DNA is $F_e = \lambda_e L E_0$, Eq. (5) may be written as

$$-\frac{F_t}{F_e} = \frac{F_e + F_v}{F_e} = \frac{2\pi\epsilon\Delta\phi}{\lambda_e \ln(a/R)}, \quad (8)$$

where $F_t = -F_v - F_e$ is the tether force.

In order to calculate the ratio F_v/F_e from Eq. (8), all that remains to be done is to calculate the quantity $\Delta\phi$. If the potential ϕ anywhere in the gap does not greatly exceed $k_B T/e$ (about 30 mV at room temperature; k_B is the Boltzmann factor, T the absolute temperature, and e the magnitude of the electric charge) then ϕ may be computed from the Debye-Hückel model (λ_D is the Debye length):

$$\frac{1}{r} \frac{d}{dr} \left(r \frac{d\phi}{dr} \right) = \frac{\phi}{\lambda_D^2}, \quad (9)$$

with the boundary conditions (6) and (7). The solution to that problem is

$$\phi(r) = \frac{\lambda_e}{2\pi\epsilon} \left[A I_0 \left(\frac{r}{\lambda_D} \right) + B K_0 \left(\frac{r}{\lambda_D} \right) \right], \quad (10)$$

where the constants A and B may be compactly expressed in terms of the dimensionless variables $a^* = a/\lambda_D$, $R^* = R/\lambda_D$, and $S^* = (2\pi a S)/\lambda_e$. Thus,

$$A = \frac{S^* K_1(a^*) + K_1(R^*)}{a^* [I_1(R^*) K_1(a^*) - I_1(a^*) K_1(R^*)]}, \quad (11)$$

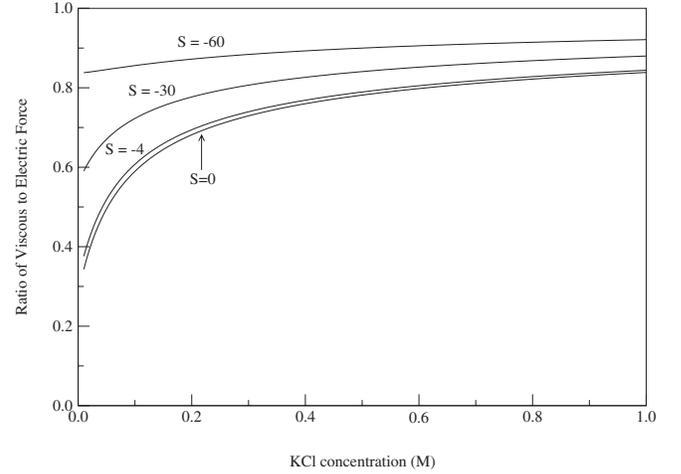


FIG. 2. Ratio of viscous to electric force on DNA ($-F_v/F_e$) plotted as a function of KCl concentration assuming a charge of two electrons per base pair on the DNA (Manning factor of unity) and a constant surface charge on the pore wall parametrized by the surface charge density S (in mC/m^2).

$$B = \frac{S^* I_1(a^*) + I_1(R^*)}{a^* [I_1(R^*) K_1(a^*) - I_1(a^*) K_1(R^*)]}, \quad (12)$$

where K_n and I_n (n is a non-negative integer) are modified Bessel functions of integral order. The potential drop $\Delta\phi$ in Eq. (8) is now easily found from Eq. (10):

$$\Delta\phi = \frac{\lambda_e}{2\pi\epsilon} (A \Delta I_0 + B \Delta K_0),$$

where $\Delta I_0 = I_0(R^*) - I_0(a^*)$ and $\Delta K_0 = K_0(R^*) - K_0(a^*)$.

The result of the calculation as described above is shown in Fig. 2. The figure shows the magnitude of the viscous to the electric force ($-F_v/F_e$) evaluated from Eq. (8) using the value of λ_D appropriate for a symmetric binary electrolyte [11]. The effective charge of the DNA is assumed to be the same as the bare charge ($\lambda_e = \lambda$) of $-2e$ per base pair and the applied voltage is $\Delta V = -120$ mV. The surface charge concentration on the substrate S has been assumed independent of the KCl concentration. From measurements of conductance and streaming potentials, it has been shown [14,15] that in Si/SiO₂ nanopores $S \approx -60$ mC/m^2 for KCl concentrations greater than about 0.1M. However, for low concentrations, the surface charge density drops substantially and needs to be calculated from a more elaborate model that takes into account the equilibrium of surface reactions at the interface. For very low concentrations, $S \approx -4$ mC/m^2 . Due to the approximate nature of our model it does not seem worthwhile to attempt to incorporate the proper dependence of S on KCl concentration. Instead, it suffices to show how $-F_v/F_e$ varies with salt concentration for several fixed values of S between -4 and -60 mC/m^2 as shown in Fig. 2. The important feature that these curves illustrate is that $-F_v/F_e$ is essentially constant for most of the KCl concentration range at a value of around 0.7–0.8. Thus, the viscous force is not small, and, furthermore, if the viscous force were neglected and the reduction in the electrical pulling force were attrib-

uted to counterion condensation, it would appear that the DNA effective charge is lowered by about 75% (just the right amount to lead one to conclude that charge reduction by the Manning factor of $q_B=4.2$ is being validated). Figure 2 shows an increase in the hydrodynamic drag with increase in the magnitude of S , because the surface charge on the pore walls enhance the electro-osmotic flow due to the DNA charge. A model that properly accounts for the variation of S with KCl concentration is expected to follow the $S = -4 \text{ mC/m}^2$ curve closely for low concentrations (below about $0.1M$) and asymptote to the $S = -60 \text{ mC/m}^2$ curve at high concentrations. The distribution of counterions in the calculations presented here was treated by means of the equilibrium Debye-Hückel theory and one may question whether that corresponds to the experimental conditions. Taking the ratio $-F_v/F_e \approx 0.75$, Eq. (8) gives $\Delta\phi \approx 80 \text{ mV}$ if for λ_e one assumes the DNA bare charge of two electronic charges per base pair. If this is reduced by the Manning factor of $q_B = 4.2$, then $\Delta\phi \approx 19 \text{ mV}$. Though the formal requirement for the Debye-Hückel linearization is $|\phi| \ll k_B T/e \approx 33 \text{ mV}$, in practice the double-layer structure calculated from the Debye-Hückel theory does not deviate substantially from the more accurate Poisson-Boltzmann calculation as long as the maximum value of $|\phi|$ is not substantially larger than $2k_B T/e \approx 66 \text{ mV}$ [16]. Therefore the Debye-Hückel theory certainly suffices for our present purpose. For the cylindrical geometry considered here, the applied potential does not disturb the equilibrium Debye layer structure, since the applied field is always along the isoconcentration surfaces of the ions. However, for the real nanopore, the applied electric field may have a radial component, and one may ask if this is strong enough to distort the equilibrium Debye layer. Since $|\Delta V| = 120 \text{ mV}$ and $L = 60 \text{ nm}$, this imposed field is $E_{ext} = |\Delta V|/L \approx 2 \times 10^6 \text{ V/m}$. The radial field within the Debye layer may be estimated as $E_{int} = |\Delta\phi|/(R-a) \approx 5 \times 10^6 \text{ V/m}$ with Manning condensation and $E_{int} \approx 20 \times 10^6 \text{ V/m}$ with

the DNA bare charge. Thus, though the distortion of the double layer can be neglected for the purpose of obtaining a rough estimate, it should be accounted for if one desires an accurate calculation of the viscous force. In order to do so, the cross-sectional shape of the nanopore must be known.

Analysis of this simplified model suggests that a more careful modeling is needed in order to properly interpret the Keyser *et al.* experiments [10]. Such a model should account for hydrodynamic drag while taking into account the proper pore shape, the variation of substrate charge with KCl, possible departures of the equilibrium potential from the Debye-Hückel model, and other relevant conditions of the experimental set up. Numerical simulation on a more elaborate model incorporating these details used in conjunction with the experimental data could provide a more complete picture of the effective charge on DNA inside a nanopore. One may be tempted to question the use of classical continuum hydrodynamics for flows on the nanometer scale. However, the classical approach has already been shown to give results in reasonable agreement with experiments on DNA translocation through solid state nanopores [7,17]. Molecular dynamic simulations, such as those presented by Aksimentiev *et al.* [18], could be used to further refine these calculations and to show that the effects described here persist even if continuum hydrodynamics is replaced by a discrete molecular model. In situations where the length of the DNA polymer is much greater than the length of the nanopore, entropic forces due to random coiling of the polymer become significant. Such entropic effects have been considered by Muthukumar [19–21]. In the limit $R \gg a$, the hydrodynamic friction with the pore walls becomes unimportant and the problem becomes one of determining the electric field that would immobilize a polyelectrolyte acted upon by given nonelectrical forces in the presence of Brownian fluctuations. This problem has been studied in its general form by Long *et al.* [22,23].

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