Theory of DNA translocation through narrow ion channels and nanopores with charged walls

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Translocation of a single-stranded DNA molecule through genetically engineered α-hemolysin channels with positively charged walls is studied. It is predicted that transport properties of such channels are dramatically different from neutral wild-type α-hemolysin channels. We assume that the wall charges compensate a fraction x of the bare charge q_b of the DNA piece residing in the channel. Our predictions are as follows. (i) At small concentration of salt the blocked ion current decreases with x. (ii) The effective charge q_s of the DNA piece, which is very small at $x=0$ (neutral channel) grows with x and at $x=1$ reaches q_b. (iii) The rate of DNA capture by the channel grows exponentially with x. Our theory is also applicable to translocation of a double-stranded DNA molecular in narrow solid state nanopores with positively charged walls.

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I. INTRODUCTION

A DNA molecule in a water solution carries negative charge. With the help of an applied voltage V, it can translocate through an ion channel located in a lipid membrane or through a solid state nanopore in a semiconductor film. In this paper we are interested in the cases when the DNA barely fits into a narrow pore, leaving only a small gap for water with the width $d<l_B$, where $l_B=e^2/\kappa k_B T$ is the Bjerrum length and κ is the dielectric constant of water. An intensively studied example is the translocation of a single-stranded DNA (ssDNA) molecule through an α-hemolysin (α-HL) channel [1–9]. With an average internal diameter $\sim$1.7 nm the channel can accommodate a ssDNA molecule with $\sim$1 nm diameter. In this case, $d=0.35$ nm$<l_B=0.7$ nm.

Our theory also should be applicable to a double-stranded DNA (dsDNA) with $\sim$2 nm diameter translocating through a narrow solid state nanopore with $2a\sim3$ nm diameter [10,11]. On one hand, no experimental data are available for nanopores so narrow. On the other hand, there is impressive progress in making and studying wider nanopores [10–14].

The peculiarity of narrow channels is related to the fact that the dielectric constants of the channel stem and lipids and the dielectric constant of the body of DNA are much smaller than the dielectric constant of water. When the water-filled gap between DNA and the channel wall is narrow ($d<l_B$), the electric field of small ions is squeezed in the gap. The potential for interaction of charges becomes logarithmic. This creates an electrostatic barrier for the ion current similar to the one that was intensively studied for ion transport through narrow DNA-free channels [15–17].

Previous discussion of the role of this barrier for ion transport in the case of DNA translocation [18] was narrowly focused on neutral channels, because the wild-type α-HL channel can be considered practically neutral. A good measure of neutrality of a channel is its cation or anion selectivity, measured by the ratio of cation to anion currents. For the wild-type α-HL channel, this ratio is 1.1, while it is equal to unity for an exactly neutral channel. It is known that at pH 7 the α-HL channel is neutral in the body of the stem, but has a ring of seven negative charges near the bottom of the narrow cylindrical part of the channel (stem) [19]. These charges are screened by the salt in the water outside the stem and, therefore, do not determine the transport through the channel, which remains weakly selective. Solid state nanopores can be neutral, too. For a neutral narrow channel Ref. [18] addressed several challenging problems posed by the experimental data [1–9].

First, Ref. [18] explained how the electrostatic barrier makes the current when the channel is blocked by DNA, I_b, at least ten times smaller than the open-channel current I_0. Second, the effective stall charge q_s of the piece of DNA residing in the channel was calculated. This charge determines the force $F_s=q_sV/L$ stalling DNA against the voltage V (L is the length of the channel). It was shown that for a neutral channel with small I_b/I_0 the charge $q_s\simeq q_bI_b/I_0$, where q_b is the bare charge of the piece of DNA occupying the channel (for the α-HL channel $q_b=-12e$). In agreement with experiments, this results in a very small absolute value of the stall charge, namely, $q_s\sim-1e$. Third, the origin of the exponentially small DNA capture rate, growing with the salt concentration, was elucidated.

Recently, genetically modified α-HL channels became available [20–22]. In this paper we concentrate on those that have amino acids with positive residues on the internal wall of the narrow cylindrical part of the channel (stem). Internal walls of solid state nanopores may also be charged. The charge density of these walls can be tuned by different chemical treatments or just by a change of the solution pH. Thus, our theory for charged α-HL channels simultaneously addresses narrow charged nanopores used for dsDNA translocation experiments [10].

We assume below that the fraction x of the bare charge q_b of the DNA piece fitting into the channel is compensated by positive internal wall charges, which are, roughly speaking, randomly distributed on the internal wall of the channel (Fig. 1). We predict below that this simple assumption leads to a number of dramatic changes of DNA translocation in comparison with a neutral channel. Let us list these predictions.

(i) The blocked ion current I_b becomes even smaller than in the neutral channel, particularly at small concentrations of salt.

(ii) The effective charge q_s of the piece of DNA residing in the channel grows with x as $q_s\simeq xq_b$. At $x=1$ the stall and

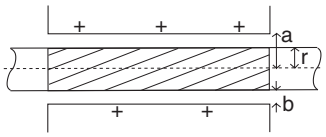

FIG. 1. Cross section of the membrane and channel with radius a. The positive charges of the internal wall of the channel are shown schematically. The captured DNA is shown as a cylinder with radius r. The piece of DNA fitting into the channel is shaded. The DNA phosphates of this piece have the total charge $q_b=-12e$. They are neutralized by the wall charges $x|q_b|$ and the charge of mobile cations $(1-x)|q_b|$.

bare charges of DNA are almost equal. The large effective charge will make possible DNA manipulation with the help of small voltages.

(iii) The barrier for DNA capture decreases with increasing x. As a result the DNA capture rate grows exponentially with x, and the number of translocation events observed in a given experiment increases. This should lead to much more effective averaging of the noise and may prove helpful in attempts at DNA sequencing. At some $x=x_c$, the capture barrier vanishes. At $x_c<x\leqslant 1$, DNA is attracted to the channel. The capture rate then is only diffusion limited and independent of x. On the other hand, for a captured DNA the probability to escape from the channel becomes activated. The escape barrier grows with x at $x>x_c$.

The structure of our paper is simple. It consists of three sections leading to conclusions (i), (ii), and (iii), respectively.

II. RELEASE OF COUNTERIONS AND BLOCKED ION CURRENT

In the case of the α-HL channel we assume the ssDNA molecule is a rigid cylinder coaxial with the channel. The inner radius of the α-HL channel is $a\simeq 0.85$ nm, and the radius of the ssDNA molecule is $r\simeq 0.5$ nm. Salt ions are located in the water-filled gap between them, with thickness $b\simeq 0.35$ nm. The length of the channel is $L\simeq 5$ nm. This kind of model is even more appropriate for double-helix DNA in a wider (say 3 nm in diameter) cylindrical solid state nanopore [10,11].

The dielectric constant of the channel or the ssDNA molecule ($\kappa'\sim 2$) is much smaller than that of water ($\kappa\simeq 80$). So if ssDNA is neutralized by cations and there is an extra charge e in the thin water-filled gap between the channel internal wall and ssDNA, the electric field lines starting from this charge are squeezed in the gap. This results in a high self-energy of the charge [15,16,18]. According to the estimate of Ref. [18] for the case of ssDNA in an α-HL channel, the self-energy of the charge in the middle of the channel is $\sim 5k_BT$. Here and everywhere in this paper, T is room temperature.

Because of the large self-energy of a charge in the narrow water gap, the piece of ssDNA inside a wild-type neutral α-HL channel is neutralized by counterions, say K^+ in KCl solution [18]. ssDNA covered by cations presents a conducting DNA backbone wire responsible for the blocked ion current I_b at small concentration of salt $c<1M$. In this range of concentrations, I_b is practically c independent [9]. At larger concentration $c\geqslant 1M$, additional pairs of anions and cations in the channel provide a mechanism of conductivity parallel to the DNA backbone wire. (Recall that the DNA backbone wire occupies only a small fraction of the water-filled gap.) The linear growth of I_b with c at $c\geqslant 1M$ is experimental evidence for the second mechanism of conductivity [9].

In a mutated, positively charged channel, the situation is rather different. Let us consider a channel with 12 uniformly distributed positive charges ($x=1$). We argue that in this case both the ssDNA and internal wall charges release their counterions into the surrounding salt solution. The net charge of the channel is still zero and, thus, there is practically no price in the Coulomb energy. On the other hand, counterion release leads to a large gain in entropy. As a result, the DNA backbone wire loses its carriers and becomes an insulator. Therefore, I_b is determined only by the contribution of additional pairs of salt ions. This should lead to a linear dependence of I_b on c in the whole range of salt concentrations. In other words, I_b becomes much smaller than in the wild-type channel at small $c<1M$, but is not much changed at larger concentrations of salt.

So far we talked about wall charges totally compensating the bare charge of DNA ($x=1$). At $x<1$ DNA counterions are only partially released and the conductance of the DNA backbone wire is only partially depleted. Although the number of counterions on the DNA wire is proportional to x, their mobility may grow somewhat with decreasing x, due to the increase of the number of empty sites.

III. EFFECTIVE CHARGE OF DNA

As we mentioned above, for the wild-type channel the stall charge of DNA, q_s, is much smaller than the bare charge of DNA, q_b. Let us recall why this happens. Counterions neutralizing DNA in the channel receive from electric field momentum with the same absolute value as for DNA, but in the opposite direction. Most of the time, the counterions are bound to DNA charges and transfer all their received momentum to DNA. During this time, the net electric field force acting on DNA vanishes. At rare moments when counterions get free and move along the channel, contributing to I_b, they transfer half of their momentum to the internal channel wall. This deficit of momentum transfer to DNA results in a small net average force on DNA and its small effective charge q_s [18].

In a channel where positively charged walls compensate the bare charge of DNA, the balance of forces is completely different. When counterions of DNA and the walls are released, the electric field provides opposite momenta to DNA and to the wall charges. The latter are static and, therefore, transfer all their momentum to the wall. Thus, the DNA gets its momentum only directly from the electric field. This means that $q_s=q_b$.

So far we have talked about a channel that totally compensates the charges of DNA ($x=1$). Similar logic leads to the result $q_s=xq_b$ for any $x<1$.

IV. DNA CAPTURE AND ESCAPE RATES

In addition to the blocked current and the stall charge, one can measure the average time between the two successive

translocation events, τ, or the capture rate $R_c=1/\tau$ of a DNA molecule into the channel. It is natural to compare the observed value of R_c with the diffusion-limited rate R_D of ssDNA capture. For the wild-type neutral α-HL channel, this comparison shows that $R_c \ll R_D$. The capture rate at zero voltage, $R_c(0)$, is so small that all experiments are actually done with a large applied voltage $V=50-200$ mV. Apparently there is a large barrier for DNA capture. A large part of this barrier is due to the loss of the conformational entropy of ssDNA. The capture barrier, however, depends on the salt concentration, what means that a part of it has an electrostatic origin. The reason for such an electrostatic barrier is as follows [18]. When a DNA molecule enters the channel, the DNA counterions are squeezed in the narrow water-filled space surrounding the DNA. Due to this compression the total free energy of the DNA and ions is higher for DNA in the channel than for DNA in the bulk. In agreement with experiment, this barrier decreases with growing c, because the entropy of counterions in the bulk solution decreases and, therefore, the price for compression is smaller.

In the case of a channel with positively charged walls the ssDNA does not need to bring all its counterions into the channel, because there are already some positive charges. Thus, the charge xq_b is released by DNA to the bulk of the solution, making the electrostatic barrier for DNA smaller. An additional, roughly speaking, equal gain is provided by release of the counterions of the wall charges, which screen the walls in the absence of DNA. Thus, due to the counterion release the electrostatic barrier becomes $1-2x$ times smaller. At $x=1/2$ the electrostatic barrier vanishes, but the conformation barrier remains intact and the capture rate is still activated. At $x>1/2$ the electrostatic contribution to the total barrier becomes negative and, at small enough concentration of salt, when $x=x_c<1$, it eventually compensates the conformation barrier, so that $R_c=R_D$. At $x>x_c$ the capture rate saturates at R_D, but the escape rate has an activation energy. The linear dependence of the barrier on x can be measured.

To summarize, in this paper we studied DNA translocation through narrow channels with positively charged walls. Our predictions for the stall effective charge and capture rate are dramatically different from the case of neutral channels. Interpretation of the stall effective charge theory also becomes much simpler. This paper extends the theory of narrow channels started in Ref. [18]. Meanwhile, a detailed, theoretical description of wider channels became available [12]. Therefore, one can ask when our theory crosses over to the results of [12]. The crossover happens when the width of the water gap, d, becomes larger than l_B. For double-helix DNA this happens for nanopores with diameter 3.5 nm or larger.

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