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Nanopore in metal-dielectric sandwich for DNA position control

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We present the concept of a nanoelectromechanical device capable of controlling the position of DNA inside a nanopore with a single nucleotide accuracy. The device utilizes the interaction of discrete charges along the backbone of a DNA molecule with the electric field inside the nanopore. In analogy to solid state transistors in which a small voltage controls the current between two electrodes, a voltage strategically located inside the nanopore can control the translocation of a single DNA molecule between a *cis* and a *trans* reservoirs. We propose an immediate application of the device as a replacement of capillary electrophoresis in DNA sequencing. © *2007 American Institute of Physics*. [DOI: 10.1063/1.2798247]

DNA is a strong acid in aqueous solution. The negative charge distribution along DNA molecules is nonuniform and almost pointlike.[1] The maxima of this distribution are located on the phosphate groups of the molecule's helical backbone. The charge localized at this group is close to that of a single electron. The discreteness of the charge distribution along the molecule is a key to the operation of the device we are proposing—the interaction of discrete charges with an external electric potential well leads to the localization of the polymer with a single monomer resolution while a time-oscillating potential well enables translocation of the polymer by one monomer per oscillation. Figure 1 depicts the DNA transistor operating on a single stranded (ss) DNA molecule. The structure of the device is reminiscent of research on DNA translocation through synthetic nanopores.[2] A nanopore of radius r_0 slightly exceeding the radius of ssDNA r_h penetrates through a membrane that separates two reservoirs. The novelty of our design is that the membrane is a "sandwich" of three metal electrodes separated by insulators. The voltage difference between the central and side electrodes is kept at a value V_0.

To estimate the DNA trapping capability of our device, we consider the DNA molecule as an inflexible helix of radius r_h containing single electron point charges q separated by a distance $d=0.34$ nm measured along the helix axis. For the time being, we shall ignore the distortion of the electrical potential inside the nanopore (it will be considered later on) and assume it is a symmetric trapezoidal potential well $V(z)$ of depth V_0 (where z is the axis of the nanopore), characterized by the sidewall thickness S and well length W (see Fig. 1). For a displacement δ in the direction of the axis of the nanopore, the position of ith charge is $id+\delta$. The energy of the polymer,

$$E(\delta) = q \sum_{i=-\infty}^{\infty} V(id+\delta), \tag{1}$$

is a periodic function of δ with period d. We will refer to the difference between maximum and minimum values of $E(\delta)$ as trapping energy ΔE_{TR}. If ΔE_{TR} is sufficiently larger than thermal energy (at 300 K) $E_T=kT/2\approx 13$ meV, the translocation of the polymer between two successive energy minima is unlikely, i.e., the potential V serves as a trap. ΔE_{TR} is very sensitive to the geometry of V. Figure 2(a) shows the dependence of the force acting on the DNA molecule as a function of the displacement δ (measured in units of d) of the charges along the nanopore axis. Grayed rectangles mark two sidewalls—areas with nonzero electric field $\mathcal{E}_{\mathrm{TR}}=|dV/dz|=V_0/S$. Consider the case in which S is a half integer (in units of d) and W differs by a quantity ε $(0\leqslant\varepsilon\leqslant 1/2)$ from being an integer [see Fig. 2(a)]. As the polymer moves rightward in the range $0\leqslant\delta\leqslant\varepsilon$, the force (gray arrows) produced by the electric field on the two charges inside the left sidewall compensates the force due to the two charges on the right sidewall. As δ changes from ε to $1/2$, the net force is a rightward force on the polymer, due to the balance of charges in the left sidewall (which continues to have two charges) and the right sidewall (which for this range of δ has only one charge). For δ between $1/2$ and $1/2+\varepsilon$, a charge is lost in the left sidewall, and, consequently, the rightward force now compensates the leftward force. Finally, as δ changes from $1/2+\varepsilon$ to 1, a second charge enters the right sidewall, creating a net force leftward force on the polymer.

In Fig. 2(b), we represent the force acting on the polymer as a function of δ. The potential corresponding to this force is plotted in Fig. 2(c). It is clear from Figs. 2(b) and 2(c) that the trapping energy is

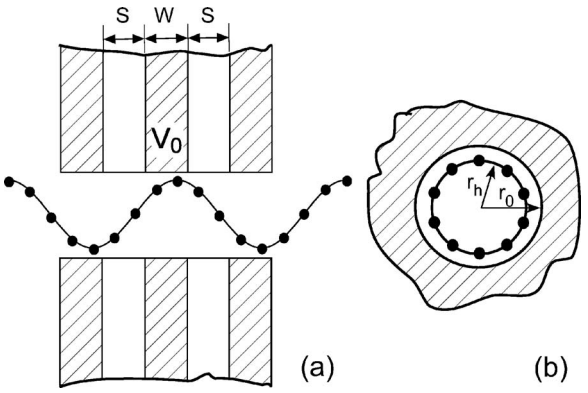

FIG. 1. A schematic of the DNA transistor. The shaded regions in the sketch are conducting, while the nonshaded are insulating. The negative charges of the ssDNA are represented by the solid circles: (a) cross section and (b) top view.

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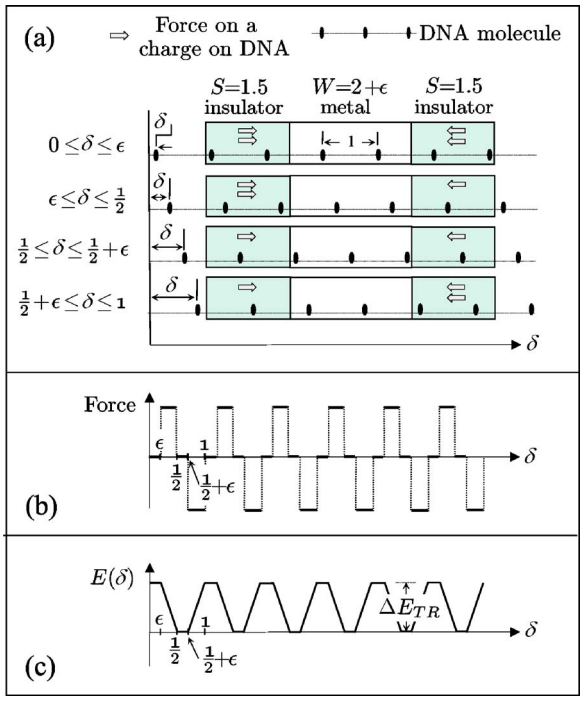

FIG. 2. Trapping potential of the ssDNA: (a) when the sidewall length is a half integer (in units of the intercharge distance d), and the potential well thickness W is slightly larger than integer length, there are displacements δ for which the force of the charges (gray arrows) produces a net force on the polymer, as shown in (b), with displacements for which there is a rightward force, no force, and a leftward force. (c) The poterntial of the force depicted in (b) and the effective trapping barrier ΔE_{TR}. The optimal (maximal) trapping barrier is obtained in the case in which W is integer ($\varepsilon=0$) and S is half integer.

$$\Delta E_{\mathrm{TR}} = q\mathcal{E}_{\mathrm{TR}}\left(\frac{1}{2}-\varepsilon\right)d. \tag{2}$$

Note that the trapping energy is maximum if $\varepsilon=0$, that is, if W is an integer. As an example, let us consider $S=3.5$ d, $V_0=1$ V, and $\varepsilon=0$. In such case, we obtain $\Delta E_{\mathrm{TR}}\approx 11E_T$. Similar considerations allow us to analyze ΔE_{TR} for other sidewall/well geometries leading to different potential wells (V). A slightly larger than integer W [$\varepsilon>0$ in Fig. 2(a)] results in a smaller trapping energy ΔE_{TR}. The trapping energy vanishes ($\Delta E_{\mathrm{TR}}=0$) when both the dimensions of the sidewall S and the potential well thickness W are half integers [$\varepsilon=1/2$ in Fig. 2, see also Eq. (2)]. The same occurs when the sidewall dimension is an integer. In the latter case, the number of charges inside the sidewalls is constant for any δ regardless the value of W, resulting in no charge imbalance and a trapping barrier $\Delta E_{\mathrm{TR}}=0$.

The previous discussion allows us to formulate the requirements for optimal trapping geometry: the sidewall charge imbalance should be nonzero for any displacement δ. Any potential with half-integer sidewalls S and integer well W satisfies this requirement. Thus, Fig. 2 with $\varepsilon=0$ represents the optimal geometry, and from Eq. (2), $\Delta E_{\mathrm{TR}}=q\mathcal{E}_{\mathrm{TR}}d/2$ is the upper estimate on trapping energy. In our simple model, the trapping energy depends only on how close to integer or half-integer values the trap dimensions are, but not on their absolute values. Interestingly, the trapping energy does not depend on the sign of V_0, i.e., whether we have a potential well or a potential barrier. When V_0 changes its sign, local minima swap their positions with maxima, effectively "moving" the local minimum by half

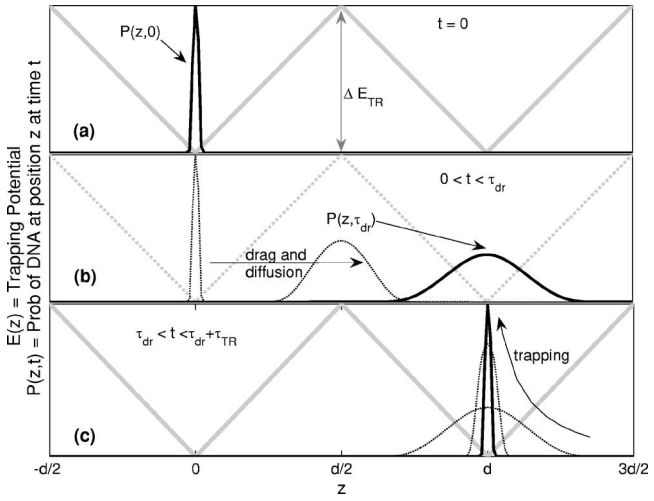

FIG. 3. Time evolution of DNA position distribution during one cycle of digital electrophoresis: The black solid lines correspond to the distribution of positions for a reference nucleotide in the polynucleotide within the nanopore at the latest time indicated in the different subfigures. The black dotted lines indicate the distribution of the reference nucleotide at previous times. The gray lines represent the trapping potential (a) equilibrium: trapping potential is applied (b) drag and diffusion: the trapping potential is removed (indicated by gray line drawn as dotted); (c) retrapping: trapping potential is reapplied.

period. However, this change in the energy profile is irrelevant since it does not have an effect on the trapping properties of the potential. Thus, regardless of the sign of V_0, the ultimate accuracy of molecule position control by the trap is $d/2$.

The discussion so far gives support to the possibility of trapping the DNA within the nanopore. Next, we suggest a mechanism for the controlled translocation of the molecule through the device. Consider a trap in the external "dragging" electric field $\mathcal{E}_{\mathrm{dr}}$. If we switch off the trap ($V_0=0$), the molecule starts to move in the direction of the dragging field. After a time period τ_{dr}, sufficient to translocate it by d, we trap the molecule again by reestablishing V_0. For a trap switching at frequency f, the translocation speed

$$\mathcal{V}=df, \tag{3}$$

is independent on the value $\mathcal{E}_{\mathrm{dr}}$ (with $\mathcal{E}_{\mathrm{dr}}$ only involved in the determination of the maximum frequency $f_{\max}$ of operation of the device). We call this effect *digital electrophoresis*. Digital electrophoresis can be described using Brownian dynamics. Similar to Ref. 3, we use Smoluchowski equation for the position distribution $P(z,t)$ of a reference nucleotide. Leaving the details to another publication, here we illustrate the results using Fig. 3. When the trap is on, the equilibrium distribution $P_{\mathrm{eq}}(z)$ is localized at the minimum of trapping potential ($z=0$) within a spread given by the characteristic length $\xi=(d/2)(kT/\Delta E_{\mathrm{TR}})\ll d$ [Fig. 3(a)]. The rate at which the probability P_{eq} leaks to neighbor minima ($z=\pm d$) is negligible, which justifies the use of the term "equilibrium" distribution for P_{eq}. At $t=0$, the trapping potential is deactivated ($V_0=0$), and $\mathcal{E}_{\mathrm{dr}}$ is turned on, resulting in the drift of the distribution to the right [Fig. 3(b)] with the speed $v_{\mathrm{dr}}=\mu q N_{\mathrm{eff}}\mathcal{E}_{\mathrm{dr}}$, where μ is the mobility and N_{eff} is an effective number of unscreened charges within the nanopore. At the same time, diffusion (characterized by the coefficient D) widens the distribution. At time $\tau_{\mathrm{dr}}=d/v_{\mathrm{dr}}$, the center of the distribution reaches $z=d$ and we remove $\mathcal{E}_{\mathrm{dr}}$ and turn the trap

on [Figure 3(c)]. The drift stops and the distribution begins to contract to its equilibrium form. It takes a trapping time of $\tau_{TR} \approx 5\xi^2/D$ for the system to reach the equilibrium state. Notice that the reference nucleotide, which was close to $z=0$ at $t=0$, has now translocated to $z=d$. After a time $\tau_{dr}+\tau_{TR}$ has elapsed, we are back in the situation depicted in Fig. 3(a), and we have completed a cycle of digital electrophoresis. At this point, another cycle of oscillations start that will translocate the DNA one more nucleotide to the right. We note that a similar process of directed motion by turning on and off a trapping potential well has been previously described in Ref. 4, in the absence of an external drag force but with an asymmetric potential well.

We identify two major characteristics of digital electrophoresis, maximum frequency $f_{max} \equiv 1/(\tau_{dr}+\tau_{tr})$ and accuracy A, which we define as the probability of correct translocation by one monomer per single oscillation of the trapping potential. Referring to Fig. 3(b),

$$A \equiv \int_{d-d/2}^{d+d/2} P(z,\tau_{dr})dz \approx 1 - e^{-[(N_{eff}-2)/2N_{eff}](q\mathcal{E}d/k_BT)}, \quad (4)$$

where the second approximate equality assumes $\mathcal{E}=\mathcal{E}_{TR}=\mathcal{E}_{dr}$. To proceed with numerical estimates for f_{max} and A, we assume $N_{eff}=10$ which corresponds to a 3-nm-long nanopore, $\mathcal{E}_{TR}=\mathcal{E}_{dr}=1$ V/nm, and $D=10^{-12}$ m^2/s. We obtain $\tau_{dr} \approx 1$ ns and $\tau_{TR} \approx 3$ ns, from where $f_{max} \approx 250$ MHz. Such frequencies are well within the capabilities of modern electronics. In practice, f can be decreased by using larger τ_{TR}. For the same parameters, the accuracy is $A=0.995$.

An immediate application of the proposed DNA transistor is in reducing the cost of DNA sequencing.[5] At present, capillary electrophoresis is a major contributor to the cost of sequencing. It is slow (tens of base pairs/s per second) and requires significant amounts of DNA material (femtomoles). The digital electrophoresis application of the DNA transistor appears to be an effective method in determining the length of a single DNA molecule by counting the number of trapping pulses required to translocate the molecule through the nanopore between entry and exit. The presence of the molecule inside the nanopore can be detected, for example, by monitoring the ion current through the nanopore.[6] Taken alone, the single molecule length separation can bring down the amount of reagents by a considerable extent.

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