Fast DNA Sequencing via Transverse Differential Conductance

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***Abstract*—We propose using characteristic transverse differential conductance for solid-state nanopore-based DNA sequencing and have explored this idea by performing molecular dynamics simulations on the translocation progress of single-stranded DNA molecule through the nanopore, and calculating the associated transverse differential conductance. Our results show that measurement of the transverse differential conductance is suitable to successfully discriminate between the four nucleotide types, and we show that this identification could even withstand electrical noise caused by fluctuations due to changes in the DNA orientation. Our findings demonstrate several compelling advantages of the differential conductance approach, which may lead to important applications in rapid genome sequencing.**

I. INTRODUCTION

The proposal to electrically sequence DNA during its translocation through a nanopore has become the focus of recent research activities, due to its prospect of drastically reducing cost and time required for completion of a whole genome [1-4]. The basic idea is that the different kinds of nucleotides (adenine, thymine, cytosine and guanine, abbreviated as A, T, C and G in the following) have different local densities of states (LDOS), and these differences can be detected electrically and then be used to discriminate between the four nucleotide types [5,6]. Some of the most recent experiments have realized the electrical detection of single isolated nucleotides residing in gaps between nanoelectrodes and identified three nucleotide types (T, C and G) based on statistical distribution curves of associated electrical conductivity [7].

The major challenges to the realization of DNA sequencing using nanopore-embedded electrodes are how to optimize the contrast between electronic signatures of four nucleotide types to provide unique identification for each one, and how to maintain such contrast during the sequencing process where noise caused by polynucleotide structure fluctuation will unavoidably smear them out [2,6]. Here we propose a sequencing technique using transverse differential conductance to address these challenges. Our simulation shows that electrical signatures of four nucleotide types in the transverse differential conductance histograms are sufficiently different for an electronic read-out of the genome sequence and can withstand electrical noise during the sequencing process. The advantageous features of the proposed approach make it very attractive for feasible applications in whole-genome sequencing.

II. DEVICE ARCHITECTURE

Fig.1 shows a schematic view of the setup: a single-stranded (s-s) DNA molecule is being driven electrophoretically through a nanopore under the application of a longitudinal electrical field E_x, while the transverse tunnelling conductance is recorded for the purpose of sequencing. As it can bee seen, first, the inner diameter of the nanopore D_y should be of the dimension of a single nucleotide, *i.e.*, it should be wide enough so that an unfolded s-s DNA molecule can pass through, while also being sufficiently narrow to allow for the measurement of the transverse tunnelling conductance; second, the width of the nanopore-embedded nanoelectrodes W_z should, on the one hand, be of the dimension of single nucleotide, *i.e.*, it should be sufficiently wide to provide enough contacts to the translocating polynucleotide for measurable transverse tunnelling conductance, and on the other hand, it should be sufficiently sharp to achieve the desired single-base resolution. These requirements for the nanopore dimensions represent extreme challenges for the fabrication of nanopore-embedded electrodes.

Fig.2 (a) shows the cross-section of a nanopore in the *y-z* plane. The nanopore is built within a SiN-Au-SiN sandwich structure: a *1-nm* Au layer provides the transverse electrodes, while two *6~8 nm* Si_3N_4 layers at the two ends insulate the electrodes from the solution environment. Here four electrodes are defined to provide more flexibility for conductance measurement. The inner diameter of the nanopore is *1.3 nm*. Fig.2 (b) shows a snapshot of the translocation of an unfolded s-s DNA through the nanopore in KCl solution.

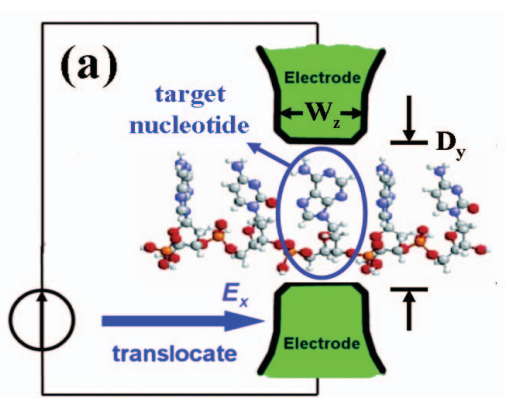

Fig.1 Schematic view of a single-strand DNA translocating through a nanopore under application of an electrical field E_x. The crucial structural parameters of the setup (D_y and W_z) are indicated.

III. Modeling and Simulation Methods

Table 1 presents the simulation flowchart and some key formula along with the software used. First, translocation of homogenous polynucleotides poly(dX)$_{30}$ (X = A, T, C, G) through the nanopore is simulated with NAMD [8], a classical molecular dynamics (MD) package using Amber force-field parameters [9]. Then the real-time atomic configuration is extracted from MD trajectory files, and the corresponding real-time electronic structure of DNA during the DNA translocation is calculated within the extended Hückel model using YAeHMOP [10]. Finally, characteristic resonance levels are picked up for each nucleotide type, and the corresponding transverse differential conductance $g(V_0)$ is calculated within the Landauer-Büttiker formalism and non-equilibrium Green's function technique [11,12]. For the electronic transport simulation the extended molecule method [13] is employed as seen in Fig.3: the system is divided into four electrodes around and the extended molecule in the centre, which is made up by those nucleotides inside the nanopore and Au atoms at the nanopore inner faces contacting to the nucleotides. Gold electrodes are treated as semi-infinite gold nanowires, and self-energies of electrodes are calculated with surface Green's function technique [14].

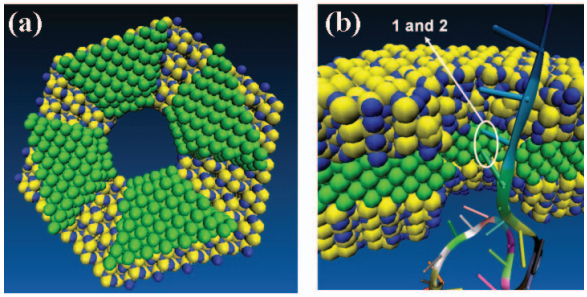

Fig.2 (a): Cross-section view of a bare nanopore with embedded electrodes. (b): A snapshot of the nanopore-based DNA sequencing device taken at working state. Au (green), Si (yellow), N (blue)

IV. Electronic Signatures of Nucleotides During Translocation:

Transverse transmission spectra and densities of states (DOS) projection on base atoms at some moment of the translocation are shown in Fig.4. This figure elucidates our proposal of transverse differential conductance for sequencing: first, DOS near the Fermi surface is made up by base atoms instead of backbone atoms and thus can serve for sequencing; second, the resonance transmission observed in this figure indicates that the transverse electrical properties are determined by resonance levels of nucleotides; last but not least, each nucleotide has its characteristic resonance levels, labeled as α, β, γ, thus enabling unique transmission and conductance spectra for each kind of nucleotide.

Owing to the sampling nature of differential conductance, the associated conductance spectra can reveal directly the characteristic sequence-resolved transmission spectrum built of nucleotide resonance levels:

$$g_{ij}(\mu_F) = (q^2/hk_BT)\int d\varepsilon\ T_{ij}(\varepsilon)\{2+\cosh[(\varepsilon-\mu_F)/\ k_BT]\}^{-1} \quad (1)$$

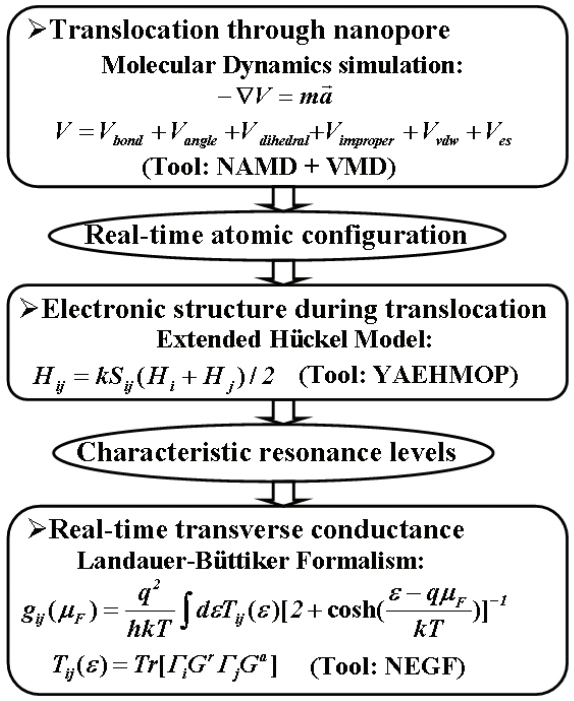

Table I Simulation flowchart

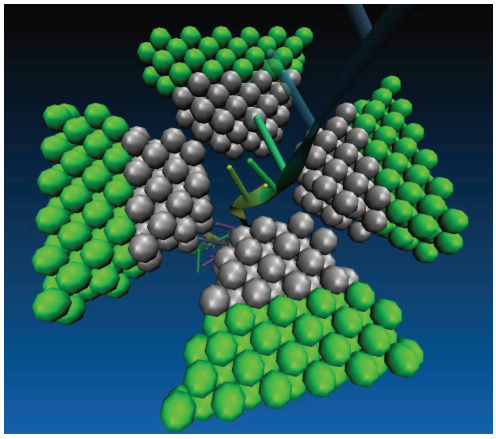

Fig.3 Extended molecule model: the extended molecule includes those nucleotides close enough to the gold nanoelectrodes and gold atoms (grey balls) on the inner surface of nanopore

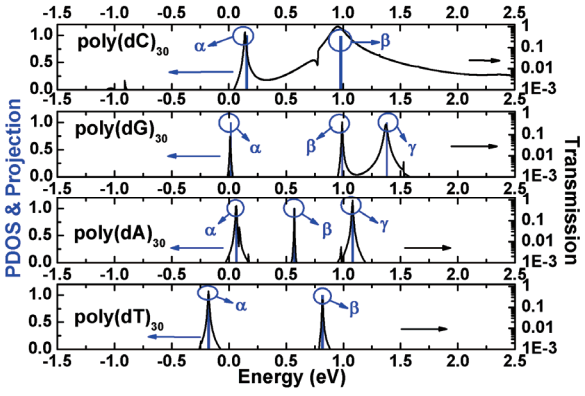

Fig.4 Projected DOS (blue bars) and transmission spectra (black lines) of poly(dX)$_{30}$ at one snapshot during the translocation through nanopore, X=A,T,C,G

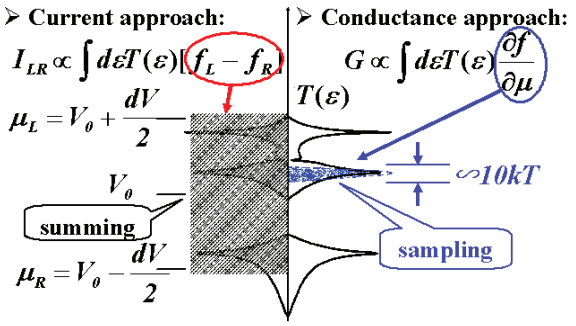

Fig.5 A comparison between electrical current approach and differential conductance approach

In the above equation, g_{ij} is the zero-bias differential conductance between i and j electrodes, T_{ij} is the associated transmission coefficient, μ_F is the Fermi level of the electrodes, and T is the temperature.

The above analysis indicates a potential sequencing approach for DNA transistor: we can utilize transverse differential conductance to characterize electronic signatures of each nucleotide.

It is of interest to draw a comparison between this differential conductance approach and the electrical current approach. The transverse electrical current is expressed as

$$I_{ij}(V) = (2q/h)\int d\varepsilon\, T_{ij}(\varepsilon)[f(\varepsilon-\mu_j) - f(\varepsilon-\mu_i)] \qquad (2)$$

where $V = \mu_i - \mu_j$ is the bias voltage, and $f(\varepsilon-\mu)$ is the Fermi distribution function. Eq.2 shows that the transverse electrical current is proportional to the *sum* of those transmission peaks inside the bias voltage window.

The difference between the *summing* nature of electrical current approach and the *sampling* nature of differential conductance approach is demonstrated in Fig. 5. It demonstrates that for the electrical current approach, an error will occur if the transmission peaks inside the bias voltage window are contributed by two or more nucleotides which are simultaneously close enough to electrodes. Considering the thickness of nanoelectrodes, the case that two or more nucleotides are close enough to the nanoelectrodes and contribute both to the conductivity is expected to be a frequent event. For that reason, the electrical current approach would become invalidated for the goal of sequencing. On the other side, the sampling nature of differential conductance selects no more than one transmission peak each time, and thus circumvents those inevitable miscountings in the electrical current approach.

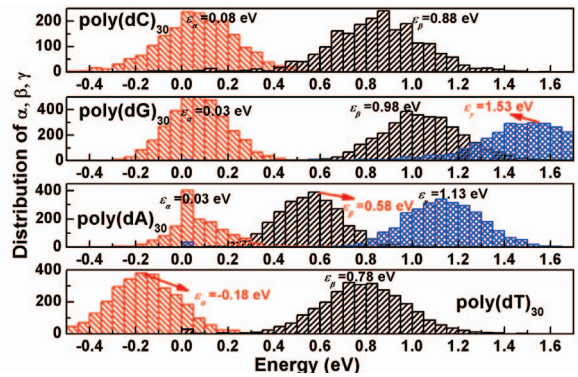

Fig.6 Distributions of characteristic resonance levels of poly(dX)$_{30}$ (X=A, T, C, G) during the translocation through the nanopore.

Now we address the question whether the differential conductance approach can withstand noise caused by structure fluctuations during the translocation of polynucleotide through the nanopore. We keep track of the characteristic resonance levels α, β, γ of poly(dX)$_{30}$ (X = A, T, C, G) on each snapshot during the translocation and plot their distribution diagrams in Fig.6. We can see these resonance levels are still distinguishable during the translocation taking the noise into account. Therefore, this can be regarded as a convincing proof that the transverse differential conductance approach is able to withstand DNA structure fluctuations during the sequencing process and thus is an efficacious sequencing approach.

V. Sequencing via Characteristic Transverse Conductance

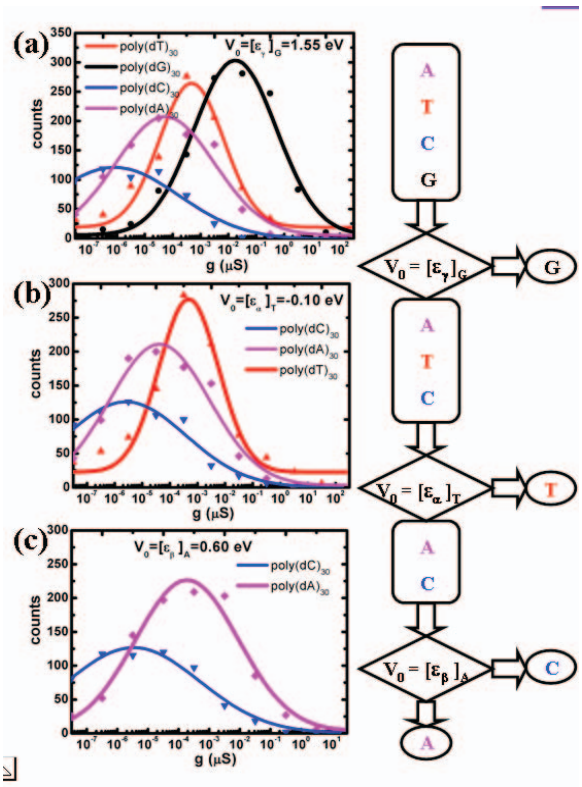

Fig.7 Sequencing step by step: First, V0 is set at εγ of Guanine (1.55 eV), and the normalized conductance distribution $g(V_0)$ of guanine differs from that of other three nucleotides in 2~3 orders, as seen in (a); then, V0 is set at εα of thymine (0.10 eV), and thymine is identified from cytosine and adenine (b); finally, V0 is set at εβ of adenine (0.6 eV), and the remaining two nucleotides are distinguished from each other (c).

Fig. 7 (a-c) show the flowchart of the sequencing approach: at one characteristic resonance level of guanine ($V_0 = V_G \sim 1.45$ *eV*), real-time transverse differential conductance of poly(dG)$_{30}$ is 2~3 orders larger than the other three homogeneous polynucleotides, identifying guanine as seen in Fig. 7(a). In the same way, thymine, adenine and cytosine are detected step by step at their characteristic energies in transverse conductance curves, as plotted in Fig.7 (b) and (c).

Finally, we would like to draw attention to the experimental developments on solid-state nanopore-based DNA sequencing. Although direct experimental setup of nanopore-embedded nanoelectrodes and associated DNA sequencing has not been realized yet, proof-of-principle experiments using scanning tunneling spectroscopy (STM)

has recently been achieved. The latest experiments have revealed that the transverse conductance histograms of different nucleotide types can indeed be used for genome identification [7].

VI. SUMMARY

A novel sequencing approach based on the characteristic transverse differential conductance of single-stranded DNA during its translocation through a nanopore is proposed and theoretically justified. Simulations show that the nucleotide signatures in the transverse differential conductance curves determined by the characteristic resonance levels of each nucleotide are different enough for the sequencing of DNA, and are also sufficiently robust to withstand DNA structure fluctuations during the sequencing process. The achieved results can provide a guide for the rational design of inexpensive and rapid whole-genome sequencing applications.

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