Nucleotide Capacitance Calculation for DNA Sequencing

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ABSTRACT Using a first-principles linear response theory, the capacitance of the DNA nucleotides, adenine, cytosine, guanine, and thymine, are calculated. The difference in the capacitance between the nucleotides is studied with respect to conformational distortion. The result suggests that although an alternate current capacitance measurement of a single-stranded DNA chain threaded through a nanogap electrode may not be sufficient to be used as a standalone method for rapid DNA sequencing, the capacitance of the nucleotides should be taken into consideration in any GHz-frequency electric measurements and may also serve as an additional criterion for identifying the DNA sequence.

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Development of low-cost and rapid methods for sequencing DNA, in addition to its obvious medical application, can potentially enable many future breakthroughs in biological and biomedical research. There are several proposed methods based on electric measurement that can directly record the sequence of nucleotides without limiting the length of the DNA fragment to be read in one measurement. Such approaches include recent considerations of measuring the transversal conductance when a single-stranded DNA chain is threaded through a nanogap formed by two gold (Au) nanoelectrodes (1–4), and various nanopore-based methods (5–7). In the conductance approach, the difference in the transverse conductance between DNA nucleotides, adenine (A), cytosine (C), guanine (G), and thymine (T), is exploited for deducing the sequence. But this simple idea may be difficult to realize using a strictly direct current (DC) setup (3,4). The flexibility of the single-stranded DNA chain makes it very difficult to control the geometry of the nucleotides when they are positioned between the nanogap, and this geometrical uncertainty makes the nucleotides indistinguishable. Averaging over geometric configurations with adequate statistics (2), found through independent molecular dynamics simulations, is one of the proposed approaches to overcome the geometric noise. The nanopore approaches essentially attempt to distinguish the nucleotides through their difference in size. Because the strong correlation between the transverse conductance and the size of the nucleotides (3), conductance measurement and the nanopore techniques often share the same weaknesses, i.e., low signal/noise ratio due to the large conformational disorder of the DNA bases. There are proposals of modifications to electrodes (8,9) and the DNA molecule itself (10) to improve the signal/noise ratio in DC measurements.

A more recent work (5) proposed to combine the nanopore technique with an alternate current (AC) capacitor setup and a dynamic measurement to produce sequence-specific responses and to improve the signal/noise ratio. By taking advantage of the conformational distortion during DNA chain translocation through the nanopore, and measuring the related change in the dipole moment using a GHz current, this method can produce differentiating electric signals for DNA strands composed of 25 identical nucleotides. Further refinement of this technique may be needed to be able to produce differentiating signals for DNA sequences that contain a mixture of different nucleotides. The electronic response of the nucleotide molecules to the applied AC field was neglected in the study.

In this study, we focus on the electronic response of the DNA nucleotides to an AC field. We define an effective molecular capacitance that is obtained by measuring the difference in the capacitance between the electrode-molecule-electrode assembly and the electrodes without the molecule. Using a first-principles linear response model, we calculate the effective molecular capacitance for the nucleotide molecules. We find that the capacitance of the nucleotides correlate with their size. We also study the change in the molecular capacitance under conformational distortions. The size of the capacitance of the nucleotides is found to be in the range of 10^{-21} F and would produce a comparable impedance as the transversal conductance in the GHz frequency range. Therefore, the capacitance should be taken into account in GHz-frequency electric measurement techniques, and may be even used as one of the criteria for DNA sequencing.

To define the molecular capacitance, we use the schematic drawing in Fig. 1, which shows two electrodes separated by a nanogap. In Fig. 1 *a*, a molecule is inserted into the gap between the electrodes. In Fig. 1 *b*, there is no molecule. Each electrode has a finite length. This length will be eventually increased in our calculation until convergence is achieved. We divide the space into five regions. Each electrode is divided into two regions (1 and 2 for left electrode, and 4 and 5 for the right electrode) from its midpoint. The molecule (or the vacuum gap) is region 3.

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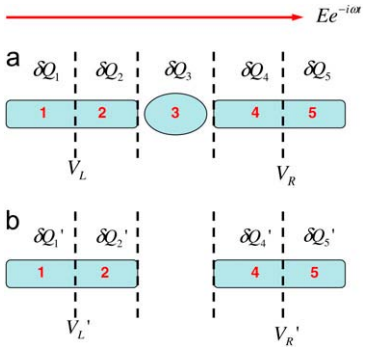

FIGURE 1 Schematic drawing of a nanogap between two electrodes, (*a*) with and (*b*) without a molecule (labeled with number 3) between them. The regions labeled with different numbers are used to define the partial charges in the calculation of the molecular capacitance.

The spatial distribution of the electrostatic potential is essentially constant within the electrodes, even when the size of the electrodes is small (see calculated results presented below). We define the voltage drop ΔV as the difference between the left electrode potential V_L and the right electrode potential V_R as labeled in Fig. 1 *a*, and define the linear-response charge within each region as δQ_i where $i = 1, 2, 3, 4, 5$. The charges δQ_2, δQ_3, and δQ_4 include both the metallic charge response from the electrodes and the dielectric charge response from the molecule. The capacitance should be defined with the metallic charge response but these charges are difficult to separate in a first-principles calculation. Because the system in our calculation is finite and the total net charge is always zero, we can easily use the average of δQ_1 and δQ_5 as the metallic charge response. Therefore, we define the capacitance of segments 2,3,4 in Fig. 1 *a* through

$$C_{2,3,4} = \frac{\delta Q_1 - \delta Q_5}{2\Delta V}. \quad (1)$$

Similarly, the capacitance of segments 2,4 in Fig. 1 *b* can be defined as

$$C_{2,4} = \frac{\delta Q_1' - \delta Q_5'}{2\Delta V'}. \quad (2)$$

Now we define the molecular capacitance as

$$C_3 = C_{2,3,4} - C_{2,4}. \quad (3)$$

We will show below that this definition leads to a converged C_3 with increasing length of the electrodes. The charge response and the electrostatic potential are calculated using the linear response theory (11).

We apply the method to calculate the molecular capacitance of DNA nucleotides. The nucleotide molecules are placed between two Au electrodes as shown in Fig. 2. The Au electrodes are composed of alternating atomic layers in the (111) direction, of seven and three Au atoms, respectively. The width of the nanogap, or the distance between the two Au electrodes, is set at the same value as the previous DC calculations (3,4), at 1.54 nm. The Hamiltonian and the overlap matrices are obtained from the converged self-consistent density-functional theory calculations, using the computational chemistry package NWChem (12). We use the B3LYP exchange-correlation function which is usually believed to work better for organic molecules, and the Gaussian basis based on the CRENBL-effective core potentials, with 16 (4s4p) functions for each atom of N, C, O, and P and 4 (4s) functions for each H, as well as a CRENBS-effective core-potential spherical basis consisting of nine (1s1p1d) functions for each atom was used for Au. Once the Hamiltonian and the overlap matrices are extracted from the density-functional theory calculations, the linear response theory (11) and Eqs. 1–3 are applied to calculate the molecular capacitance. The applied external AC field $Ee^{-i\omega t}$ is along the electrode direction, with a magnitude $E =$ 1 mV/nm and frequency $\omega = 16$ GHz. Since the calculation is within the linear-response regime, the magnitude of the field has no effect on the results. Likewise, the frequency is sufficiently low and far from any resonances so that there is no dependence of the results on the frequency.

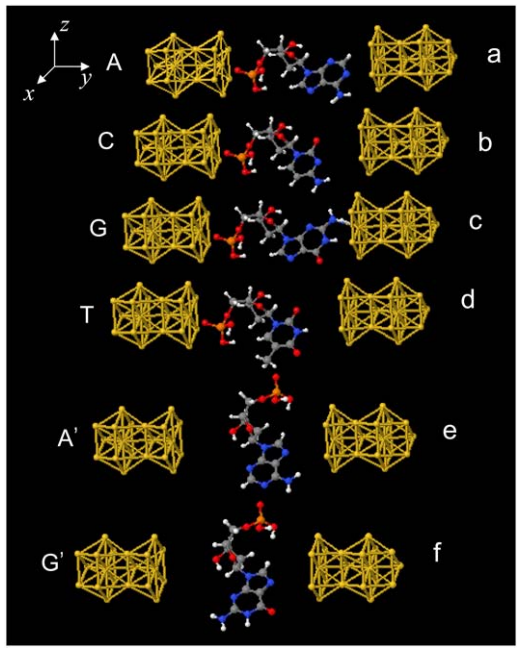

FIGURE 2 Nucleotide molecules (*a*) A, (*b*) C, (*c*) G, (*d*) T, (*e*) A′ (rotated 90° around *x*), and (*f*) G′ (rotated 90° around *x*), between two Au electrodes.

Fig. 3 plots the electrostatic potential profile and charge response of the nanogap system, with the nucleotide molecule A between two electrodes each of 8-Au-layers long. Fig. 3 *a* shows that the electrostatic potential inside the electrodes is essentially flat, despite the small size of the electrodes in this calculation. Most of the voltage drop occurs over the nucleotide molecule. Fig. 3 *b* shows that the charge response occurs mostly at the two ends of both

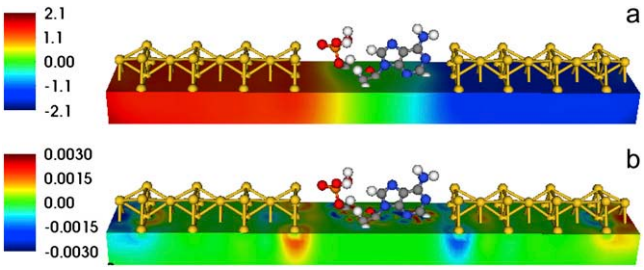

FIGURE 3 (*a*) Voltage profile and (*b*) charge response of the nanogap system with nucleotide A between two electrodes with eight Au layers.

electrodes. There is also a small charge response within the nucleotide A. There is hardly any charge response in the middle sections of both electrodes. It provides justification for our method of dividing each electrode into two half sections and using only the outside charge for calculating the molecular capacitance.

The convergence of the molecular capacitance for all four nucleotide molecules as a function of the length of the two electrodes in terms of the number of atomic Au layers (N_L) in each electrode is shown in Fig. 4. The molecular capacitance is sufficiently converged when the length of the electrodes reaches $N_L = 88$. The converged molecular capacitance for the nucleotide molecules are 1.84×10^{-2} *e/V* for G, 1.41×10^{-2} *e/V* for A, and 0.94×10^{-2} *e/V* for both C and T. (Note that 1 *e/V* is 1.6×10^{-19} F.) Therefore the nucleotides A and G may be distinguished from nucleotides C and T through the molecular capacitance measurement. The values of the capacitance can be compared to the capacitance of a parallel plate capacitor $\epsilon\epsilon_0 A/d$ where A is the cross-section area, d is the width of the gap, $\epsilon_0 = 8.85 \times 10^{-12}$ F/m is the permittivity of the vacuum, and ϵ is the effective dielectric constant. If we use $A = 0.1$ nm^2 and $d = 1.54$ nm, then we find that the effective dielectric constant is approximately between 2 and 5 for these molecules.

Finally, we check the effect of conformational fluctuation on molecular capacitance. For the nucleotides A and G we look at the extreme case when they are rotated by 90° around the x axis, shown as A′ and G′ in Fig. 2, *e* and *f*. This configuration is expected to give the smallest capacitance for the same molecule, since the atoms in the molecule are the farthest away from either electrode. Using $N_L = 88$, the calculated molecular capacitances are 0.59×10^{-2} e/V for A′, and 0.57×10^{-2} e/V for G′.

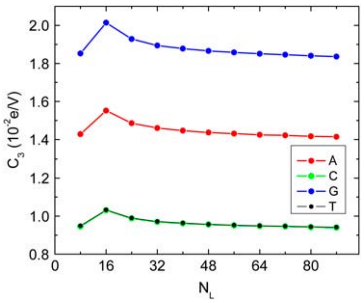

FIGURE 4 Molecular capacitance of the nucleotides A, C, G, and T, as a function of the length of the Au electrodes.

The calculated molecular capacitance distinguishes G and A from C and T. Similar to DC transverse conductance measurements, the molecular capacitance sorts the nucleotides according to their sizes. However, unlike the tunneling conductance, the molecular capacitance is not exponentially sensitive to the conformational disorder. Thus averaging over repeat measurements may provide a better signal/noise ratio than the similar averages in the DC case. The real effect of the statistical approach in the manner of Lagerqvist et al. (2) will be studied in a future work. Therefore, incorporating the capacitance measurement into a DNA sequencing method may help alleviate some of the difficulties faced by the DC electric measurement technique.

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