An electro-optical system for improving graphene nanopore DNA Sequencing

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Abstract
I propose a new electro-optical system for sequencing single-stranded DNA molecules. The localized plasmons in graphene combined with the nanopore-based DNA translocation have been suggested for sequencing DNA molecules and decreasing the translocation speed. These localized surface plasmon resonances in the graphene nanopore have three dominant modes. Every-mode peak wavelength is shifted while the DNA nucleobases are presented to the nanopore. The ultraviolet photodiodes with narrow-band filters can separate each mode individually. Then, the electrical-current to voltage convertor, differential pairs based on the bipolar transistors, combine all modes in the effective output voltage. The output voltage level of the circuit is sensitive to the DNA presence and is unique for each DNA nucleobase. Analyzes have been performed for different central wavelengths and spectral width of the light source. Results show that the best sensitivity to the DNA molecule is 6.04, and the best selectivity is 1.1. These factors are directly related to the method's applicability for DNA translocation sensing and DNA sequencing; they are enormously improved. The proposed method and results shed light on a higher selectivity for DNA nucleobases which is the main bottleneck for nanopore DNA sequencing.
1. Introductions

In the growing field of intelligent medicine [1-3], rapid DNA sequencing methods are critical tools that have been targeted in the last decades [4-6]. These developing sequencers utilize any signal due to any changes in the electrical conductivity, ionic current, plasmonic resonances, and surface-enhanced Raman spectroscopy to determine the type of the DNA nucleotides: adenine (A), cytosine (C), guanine (G), and thymine (T) [5-7]. The main limitations of these methods are the need for DNA amplification, fluorescent labeling, and noise effects [8]. In recent years, single-layer materials such as graphene and MoS2 and their physical properties have been considered for rapid DNA sequencing [6]. There are still many other challenges such as low sensitivity, low selectivity, fast translocation speed, and slow sensing mechanisms to achieve errorless sequencing and single-nucleotide resolution [6-8]. Localized and intense plasmons in two-dimensional materials such as graphene and MoS2 are currently considered a candidate for rapid nanopore DNA sequencing [9, 10]. Consequently, plasmonic fields make an enhanced local force that can control DNA translocation speed through the nanopore [11-13].

In this paper, I propose and analyze an electro-optical method for DNA sequencing based on the interband plasmons of the graphene nanopore. At the presence of DNA nucleobase, the absorption spectrum of the graphene nanopore is calculated by employing the hybrid quantum/classical method [10, 14]. Then, the graphene nanopore's transmitted, and reflected rays are filtered and transduced to electrical pulse through ultraviolet (UV) photodiodes. This electrical current is converted to voltage and introduced to the bipolar-transistor amplifiers that can improve the sensitivity and selectivity of the method. Results show a superior capability of this method to improve the graphene nanopore DNA sequencers.
2. Materials and Method

As shown in Figure 1, the first step of the procedure is to consider one-layer graphene with a nano-meter size pore. Due to the more significant amount of molar absorption of DNA molecules at the higher energies, significantly above 5 eV [15], the interband plasmon of the graphene that occurs at the same energy is a promising method to be used in nanopore DNA sequencing devices [9, 10]. The interband plasmon spectrum of the graphene nanopore is strongly affected by the size of the graphene nanosheet and the type of DNA nucleobases [9, 10]. From the optical perspective, reflected, transmitted, and absorbed lights complement the light emitted to the structure. As a result, the transmitted and reflected light spectrums are also affected by the type of DNA nucleobase presented to the nanopore. The type of DNA nucleobases influences the relative intensity and peak wavelength of the main mode of the plasmonic resonances. As shown in Figure 2, four UV photodiodes are used as the detectors, and before each detector, a narrow filter suppresses the incident light spectrum to 10 nm at a specific center wavelength, the total spectral response of the detector and filter assumed to be gaussian. For example, UV photodiode S12742-254 from the Hamamatsu Corporation with customized interference filter for its window [16], the peak sensitivity wavelength is about 254 nm with a highly narrow spectral width at 10 nm. As depicted in Figure 2, detectors number 1 and 3 are designed to be most sensitive to the first mode of the plasmonic resonance, detectors number 2 and 4 are designed to be most sensitive to the second mode of the plasmonic resonance.
It should be noted here that the output of the photodiode is the total integral of the product of the light entering the detector and its frequency response. The frequency response for each detector is shown in Figure 3(a). At this point, part of the light spectrum content is lost and aggregated at the output current of the photodiode. However, part of the spectral content of the light is still preserved by the technique of separating plasmonic modes in specific photodiodes. As shown in Figure 3(b), the output voltage is a four-level pulse. In the UV photodiodes, the output changes if any displacement has occurred for the DNA at the nanopore. For example, consider a single-stranded DNA sequence such as "ATCG". In this case, A is the first nucleobase, and G is the last one to enter the nanopore. Then, each photodiode output current is related to the spectral changes according to the A, T, C, and G nucleobases, respectively. As mentioned, the DNA translocation speed is also affected by the strong plasmonic field applied to the nanopore. The average translocation time for each DNA nucleobase varies from several picoseconds to the case of trapped DNA [11-13]. For rapid human-DNA sequencing in less than ten hours, the maximum acceptable average time to read each DNA nucleobase is 12 us. The UV photodiode S12742-254 rise time is 1 us. Therefore, the pulse duration at each level of the photodiode output voltage will be 12 us, with 1 us rise time, \( t_r \). The maximum frequency, \( f_{\text{max}} \), in a square wave can be related to the inverse value of \( t_r \) and approximated as 500 kHz, as a rule of thumb.

I first try to summarize the signal from the reflected and transmitted light for each plasmon mode. This can be achieved by parallelizing D1 and D3 (also D2 and D4), as shown in Figure 4. The natural output for each detector is an electrical current that should be converted to a voltage by an
operational amplifier with a feedback resistor. The signal received by the base of the transistor Q1 complements the light absorbed by the structure at the spectral range of the first plasmonic mode. Similarly, the signal reaching the base of the transistor Q2 complements the light absorbed by the structure at the spectral range of the second plasmonic mode. Then, the voltage received by the transistors Q1 and Q2 can be simplified as the following equations, Equations 1 and 2.

\[ V_{b1} = V_{d1} + V_{d3} = V_{s} - V_{abs,M1} \]  
\[ V_{b2} = V_{d2} + V_{d4} = V_{s} - V_{abs,M2} \]  

In these equations, \( V_{d1} \) and \( V_{d3} \) are the voltages generated by the detectors D1 and D3 in the first plasmonic mode (M1). Similarly, \( V_{d2} \) and \( V_{d4} \) are the voltages generated by D2 and D4 in the second plasmonic mode (M2). The voltage \( V_s \) is proportional to the light emitted from the light source. The voltages \( V_{abs,M1} \) and \( V_{abs,M2} \) are proportional to the absorbed light by the structure in the first and second plasmonic modes, respectively. That is why we use the differential pair amplifier, where our primary goal is to eliminate the effect of the source light from the output voltage. In the following equations, Equations 3 and 4, differential and common-mode input voltages are calculated.

\[ V_{id} = V_{b1} - V_{b2} = V_{abs,M2} - V_{abs,M1} \]  
\[ V_{ic} = \frac{V_{b1} + V_{b2}}{2} = \frac{2V_s}{2} - \frac{V_{abs,M2} - V_{abs,M1}}{2} \]  

Here \( V_{id} \) is the differential input voltage and \( V_{ic} \) is the input voltage in common mode. Moreover, the active-load stage has a common-mode rejection ratio that is much superior to the resistively-loaded stage. The following equations, Equations 5 to 7, give differential and common-mode output voltage for differential pairs with active load [17].

\[ V_{od} = g_m \left( r_{o2} || r_{o4} \right) V_{id} = g_m V_{abs,M2} - V_{abs,M1} \]
In the above equations, $V_{od}$ is the single-ended output voltage in the differential mode, $V_{oc}$ is the single-ended output voltage in the common mode, $g_m$ is the small-signal transconductance, $P_L$ is the spectral power distribution of the light source, $\alpha_{DNA}$ is the absorbed light spectrum by the graphene nanopore and DNA nucleobases, $F_{D1}$ and $F_{D2}$ are the spectral detections of the filters for D1 and D2, respectively. Note that $K_D$ is the photosensitivity coefficient of the detectors determined in the unit V/W. However, the natural output of the photodiode is an electrical current that should be converted to a voltage by the operational amplifier with the feedback resistor $R_f$, shown in Figure 4. The MAX477 operational amplifier, with $f_{3dB}$ at 300 MHz for unity gain voltage [18], is utilized not to suppress the 500 kHz maximum frequency of the DNA translocation pulse signal. Based on the Hamamatsu datasheet [16], if we choose $R_f$ to be 100Ω, then $K_D$ to be 1.8 V/W and gain of the operational amplifier converter circuit is 100, thus $f_{3dB}$ is 3 MHz which is still much higher than the maximum frequency of the DNA translocation signal (500 kHz).

As shown, the output voltage in the common mode is a fixed small value that does not depend on the common input voltage, and in practice, the output of this mode can be considered zero. Please note that the maximum frequency of the pulse applied to the differential pair is 500 kHz, as calculated previously. At higher frequencies, the coupled-emitter capacitor will be connected to the ground. Despite the resistive-load differential pairs for the active-load pairs, the single-ended common-mode output voltage is still small enough to be neglected. The final amplified voltage contains information about the nucleobases, as shown in Figure 2(b). For example, if 2N3904 bipolar NPN transistor is
utilized, and the bias current of the transistor is assumed to be 1 mA, the minimum value of the small-signal current gain $\beta$ in the active forward region is $100$, $f_T$ higher than 300 MHz, and a typical value for the Early voltage is 75 V [19]. So, the differential gain is almost 1500, and the common-mode output voltage is about 0.01 V.

The proposed setup, including the UV source, the spectral response of the detectors and DNA, plasmonic excitations of the graphene nanosheets, delay response and maximum frequency of the circuit, differential and common mode response of the circuit were modeled in Matlab. The discrete dipole approximation method is utilized to calculate the graphene nanopore's optical extinction efficiency in the presence of DNA [9, 10].

3. Results

As shown in Fig. 5(a), the extinction efficiency of the graphene nanopore has two main modes, M1 and M2, at 260 and 190 nm, respectively [9, 10]. As can be seen, these two modes are strongly affected by the type of DNA nucleobases [9, 10]. The DNA presence in graphene nanopore shows that the peak wavelength of the M1 for A, T, C, and G are 252, 264, 262, and 266 nm, respectively. Also, the peak wavelength of the M2 for A, T, C, and G occurs at 192, 186, 185, and 197 nm, respectively [9, 10]. These results are depicted in Fig. 5(a). So, the central wavelength of D1 and D3, also D2 and D3 detectors should be 258 and 190 nm, respectively. Figure 5(b) indicates each value for output voltage in the differential mode according to the presence of each specific DNA nucleobase for several central wavelengths ($\lambda_C$) and full width at half maximum (FWHM) values of the light source. The power of the light source is assumed to be almost 1000 mW, and it is centered at the peak wavelength ($\lambda_C$) and with the spectral width FWHM. In the horizontal axis of Figure 5(b), the first number indicates central wavelength, and the second number indicates FWHM. These two parameters are related to the light source. The
results are shown for the central wavelengths of 195 and 200 nm and the spectral width of 70, 80, and 90 nm. For each condition of the source light, the output voltage is shown for the following cases. The DNA is absent, and others in which the DNA nucleobases A, T, C, or G are present.

For a more accurate comparison, we define two essential criteria of sensitivity and selectivity. Sensitivity is defined as the average output voltage changes due to all four types of DNA nucleobases. Otherwise, selectivity is defined as the amount of output voltage changes between two different types of DNA nucleobase. If selectivity between A and T nucleobases is the issue, the output voltages are calculated. The more significant the difference between these two voltages, the better the selectivity. To properly compare the results with previous studies, we should define similar criteria for the average sensitivity and minimum selectivity [9, 10], as the following equations, Equations 8 and 9.

\[
Sen = \frac{1}{4} \sum_i \left( \frac{V_{out}^{NoDNA} - V_{out}^i}{V_{out}^{NoDNA}} \right) \quad (8)
\]

\[
Sel = \min \left( \frac{V_{out}^i - V_{out}^j}{V_{out}^{NoDNA}} \right) \quad \forall i, j \in \{A, C, G, T\} \quad (9)
\]

The sensitivity and selectivity factors are indicated by \(Sen\) and \(Sel\) symbols, respectively. Based on the conditions in Figure 5(b) and the definitions for sensitivity and selectivity, the values of these two important parameters are calculated and shown in Figure 6. Further studies show that the sensitivity and selectivity values do not depend on changes in the light source power. This is because the power of the light source leads to changes in the absolute value of the output voltage, but the sensitivity and selectivity values are defined based on the relative changes of these voltages.
As a result, the sensitivity and selectivity factors remain constant. Simulation results show that if the light source power is smaller than 10 mW, the differential-mode output voltage will be comparable to the common-mode output voltage. In this situation, the signal from the presence of DNA will not be distinguishable from the common-mode output relating to the light source power.

The upper limit for the power of the light source is related to the condition in which the differential transistors may be switched off or operate in the saturation region. In the first case, the differential pair is not linear if the differential input voltage is increased. Thus, the small-signal model is not usable. For the latter case, if the common-mode signal increases, the emitter voltage is proportional to the common-mode input voltage. Here, we suggest the 1000 mW power for the light source. However, some practical factors such as environmental conditions, light path, optical instruments, etc., will dramatically affect the practical range of the power of the light source. The best sensitivity is achieved for a gaussian light source with $\lambda_c$ about 200 nm and FWHM about 70 nm. Also, the best selectivity is achieved for a gaussian light source with $\lambda_c$ about 200 nm and FWHM about 80 nm, or $\lambda_c$ about 195 nm and FWHM about 90 nm. Here, the importance of defining two distinct criteria for sensitivity and selectivity is highlighted. The highest sensitivity is obtained for the last case in Figure 6, but the selectivity is zero. The ultimate goal of the proposed method will determine the central wavelength and spectral width of the light source.

Based on the results, the ability to use the plasmonic resonance to detect translocation of the DNA molecule through the graphene nanopore has been improved. By defining similar criteria for the sensitivity to DNA translocation, the highest sensitivity in the previous studies was 0.4 [9-13]. While based on the results of the method proposed in this article, the sensitivity to DNA
translocation is increased to 6, more than one order of magnitude improvement. However, if the main purpose of this method is to achieve a DNA sequencer, then the comparison should be based on the selectivity factor. By defining similar criteria for the selectivity of DNA nucleobases, the highest selectivity in the previous studies was 0.08 [9-13]. While based on the results of the method proposed in this article, the selectivity of DNA nucleobases is increased to 1.1, more than one order of magnitude improvement. This is a significant improvement due to utilizing both transmitted and reflected signals from the graphene nanopore structure. In addition, the differential pair circuit has led to significant amplification for a particular type of input signal. This signal is highly dependent on the DNA absorption spectrum that depends on its nucleobase type. As a result, the optical signal due to the presence of DNA nucleobases in the graphene nanopore will significantly affect the output voltage. The critical point is that the amount of absorbed light is obtained by detectors from reflected and transmitted light. Notably, the differential signal applied to the transistor circuit contains the structure's absorption spectrum and the DNA nucleobase. As a result, the signal amplified in the differential mode of the circuit and has the most significant effect on the output voltage is the same as the DNA absorption spectrum.

Many types of research in the literature proposed experimental setups for biomedical sensing based on plasmonic excitation, transmitted and reflected rays from a graphene-based structure [20]. In the experimental condition, noise effects related to the graphene sheet fluctuations, transistor mismatches, detector mismatches, and time-dependent spectral properties of the UV source may affect the experimentation results. Moreover, the spectral behavior of graphene is related to the size of the sheet [21, 22]. Thus, the size variations may affect the spectral overlap of the UV source, graphene sheet, DNA absorption, and detectors.
The results show that utilizing plasmonic resonance in the graphene nanopore to detect DNA translocation or sequencing is an effective and accurate method that can become one of the future rapid DNA sequencing methods. This paper shows that the combination of electrical and optical methods is one step closer to being practical.

4. Conclusions

In summary, I have studied an electro-optical method for improving plasmonic-based nanopore DNA sequencing methods. The analytical methods showed that the plasmonic resonances in the absorption spectrum for graphene nanopores could be measured through four specific detectors. The simulation results show that there are two main modes in the absorption spectrum of the structure due to plasmonic resonances. However, these modes are strongly influenced by the DNA nucleobase presented to the nanopore. As a result, it is essential to calculate the amount of light absorbed by these plasmonic modes. The best way to separate these modes is to use narrowband UV photodetectors with customized central wavelengths. On each side of the graphene membrane, two detectors (D1 and D2, D3 and D4) are placed to capture these plasmonic modes. The critical point is that DNA sequence information is in the absorption spectrum, but we measured transmitted and reflected light. In the first step, we need to add the amount of light received by detectors D1 and D3 and detectors D2 and D4 for each specific plasmonic mode. An operational amplifier does this with a negative feedback resistor, which simultaneously summarizes the output signal of the two detectors (D1 and D3 or D2 and D4) and converts them from electrical current to voltage. After this,
the differential pair amplifies the differential signal, which contains only the light absorption spectrum generated from the sum of the reflected and transmitted light. Finally, the effects of the changes in central wavelength and spectral width of the light source on the sensitivity and selectivity of the method were investigated. If we want to use this structure to detect DNA translocation, the best central wavelength for the source light is 200 nm, and the best FWHM is 70 nm. However, if the structure sequences DNA molecules, the best central wavelength for the source light is 200 nm, and the best FWHM is 80 nm. Our results indicate that this method is most sensitive to DNA nucleobases' presentation and that each nucleobase has a unique output voltage. Both sensitivity and selectivity factors are improved over one order of magnitude. Despite its technical challenges, using electro-optical mechanisms based on the plasmonic resonances in graphene nanopores is a potential method for rapid DNA sequencing.

References


Bashir Fotouhi was born in Sanandaj, in 1988. He received a B.Sc. degree in Electronic Engineering from the University of Tabriz in 2008. He obtained his M.Sc. and Ph.D. degrees in electrical and electronics engineering from the Tarbiat Modares University. His current interests include nanopore DNA sequencing, graphene plasmonic, quantum computers, and biological photonics.

Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DDA</td>
<td>Discrete Dipole Approximation</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<td>eV</td>
<td>Electron-Volt</td>
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<tr>
<td>FDTD</td>
<td>Finite Difference Time Domain</td>
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<td>Hz</td>
<td>Hertz</td>
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<td>KHz</td>
<td>$10^3$ Hertz</td>
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<td>MHz</td>
<td>$10^6$ Hertz</td>
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<tr>
<td>nm</td>
<td>Nanometer ($10^{-9} m$)</td>
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<tr>
<td>SPR</td>
<td>Surface Plasmon Resonance</td>
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<tr>
<td>UV</td>
<td>Ultraviolet</td>
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<tr>
<td>$\lambda_c$</td>
<td>Peak Wavelength</td>
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<td>FWHM</td>
<td>Full-Width at Half Maximum</td>
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**Figures captions**

**Figure 1.** The proposed method for improving graphene nanopore DNA sequencing. First, a graphene nanopore with a single-stranded DNA molecule, interband plasmons are excited through an ultraviolet light source. Then, the structure's transmitted and reflected optical lights are filtered to separate plasmonic modes at the UV photodiode end. Then, the signal is converted to voltage, and a transistor-based system is designed to detect any small changes in the differential signal received to the photodiodes. The yellow path indicates the optical signal, and the green indicates the electrical signal.

**Figure 2.** The graphene nanopore with a single-stranded DNA molecule is presented to the nanopore. The UV-range light source excites localized plasmons. Each of the transmitted and reflected rays is detected by two UV photodiodes. The light is filtered by the D1 and D3 detectors for the first mode, D2 and D4 detectors for the second mode.

**Figure 3.** The normalized spectral power of the light source and normalized spectral detection range for detectors D1 and D2 (similar for D3 and D4) (a). The circuit's output voltage for each DNA nucleobase presented to the graphene nanopore (b). Please note that the total rise time of the output voltage has been neglected in this figure.

**Figure 4.** The circuit first converts light into electric current by photodiodes, then the operational amplifiers convert the electric current into a suitable voltage to power the base of the transistors. The transistor sections will eventually produce an amplified output by amplifying the differential mode of the input voltage.
**Figure 5.** The extinction efficiency for a graphene nanopore in the presence of DNA nucleobases is shown in (a). The output voltage is shown related to the type of DNA nucleobase (b). The first number indicates the central wavelength in the horizontal axis, and the second number indicates FWHM. These two parameters are related to the light source. The output voltage is shown in the figure belongs to the best results among the various case studies.

**Figure 6.** Sensitivity and selectivity factors, for some central wavelength ($\lambda_c$) and FWHM values of the light source. In the horizontal axis, the first number indicates central wavelength, and the second number indicates FWHM. These two parameters are related to the light source. The sensitivity and selectivity factors showed in the figure belong to the best results among the various case studies.