Transverse conductance of DNA nucleotides in a graphene nanogap from first principles

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Abstract

The fabrication of nanopores in atomically-thin graphene has recently been achieved and translocation of DNA has been demonstrated. Taken together with an earlier proposal to use graphene nanogaps for the purpose of DNA sequencing, this approach can resolve the technical problem of achieving single-base resolution in electronic nucleobase detection. We have theoretically evaluated the performance of a graphene nanogap setup for the purpose of whole-genome sequencing, by employing density functional theory and the non-equilibrium Green’s function method to investigate the transverse conductance properties of nucleotides inside the gap. In particular, we determined the electrical tunneling current variation at finite bias due to changes in the nucleotides orientation and lateral position. Although the resulting tunneling current is found to fluctuate over several orders of magnitudes, a distinction between the four
DNA bases appears possible, thus ranking the approach promising for rapid whole-genome sequencing applications.

The prospect of finding an improved method for whole-genome analysis is driving significant research efforts to reach that goal. Over the past decade, the traditionally used Sanger method has been increasingly transformed into a highly parallelized and automated process, enabling the rapid rise in decoded DNA sequences seen today. Effectively, the $10,000-genome has been reached through this next-generation sequencing technology. However, for a truly widespread deployment of DNA sequencing (e.g., in clinical trials and eventually even for so-called personal medicine), cost and complexity of the sequencing process will have to be reduced even further, in order to arrive at a cost of $1,000 or less per genome.

In an attempt to realize such third-generation sequencing technology,\textsuperscript{1} nanopores have been at the center of the research focus. Initially, only the monitoring of the ionic current through biological pores was considered, and the merits of this approach continue to be actively investigated.\textsuperscript{2} However, solid-state nanopores have become more and more attractive for the purpose of DNA sequencing,\textsuperscript{3–7} since they generally provide better stability and can be more easily controlled\textsuperscript{8} than biological pores. Furthermore, instead of measuring the ionic current, it was suggested to outfit solid-state nanopores with embedded electrodes and instead monitor the transverse tunneling current induced by them. This possibility was at first only explored theoretically,\textsuperscript{9–12} because the technical challenges to outfit the nanopore with sufficiently thin embedded electrodes had prevented its actual fabrication until very recently.\textsuperscript{13}

About a year ago, a new suggestion was put forward\textsuperscript{14} to use graphene nanogaps in a double function as both separating membrane and electrodes, solving the problem of alignment and making the electrodes atomically thin\textsuperscript{15,16} for optimal single-base resolution. Even more recently, it was experimentally demonstrated for graphene nanopores\textsuperscript{17,18} that it is possible to detect translocation events of DNA.\textsuperscript{19–21} Furthermore, at least one density-functional-theory-based study explored the capabilities of a graphene nanopore setup for the purpose of distinguishing between nucleotides.\textsuperscript{22} In our investigations, we have used state-of-the-art first-principles methods to study
the transport properties of nucleotides inside a graphene nanogap, to assess whether or not this setup could be useful for the purpose of DNA sequencing.

To this end, we investigated the tunneling transport properties of the four nucleotides deoxyadenosine monophosphate (dAMP), deoxythymidine monophosphate (dTMP), deoxyguanosine monophosphate (dGMP), and deoxycytidine monophosphate (dCMP) when located between graphene electrodes with armchair edges chemically passivated by hydrogen. The system is divided into three regions: the left and right electrodes, and the central region, containing a portion of the semi-infinite electrodes on either side of the junction.

To construct the graphene-nucleotide-graphene system, we first optimized the isolated nucleotide and graphene electrodes separately, and then proceeded to place each nucleotide between the hydrogenated armchair edges of the semi-infinite graphene sheets. An electrode-electrode spacing of 14.7 Å (measured from H to H) is maintained throughout the calculations, which allows each of the four nucleotides to be accommodated within the gap in every possible orientation. The central region included graphene electrode edges on either side of the junction together with 8.65 Å of each (left and right) graphene sheet in order to ensure that the perturbation effect from the nucleotides is sufficiently screened. The left and right lead regions are constructed of periodically repeated graphene unit cells 15.62 Å wide. Periodic boundary conditions along the electrode edges effectively create repeated images of the nucleotides separated by ∼10 Å, which was found to be sufficiently large to avoid any unphysical interaction. The combined graphene-nucleotide-graphene system was then optimized again, allowing all atoms in the central region to relax.

Each nucleotide was positioned so as to lie in the plane of the graphene electrodes. We considered the effect of rotation and translation of the DNA nucleotides on the transmission (see figure 1). In our investigation, the nucleotides are rotated around the y-axis from 0 to 180° in steps of 30° (Supporting Information), and translated along the z-axis by ± 0.5 Å for dGMP and dAMP and by ±1 Å for dTMP and dCMP.

All optimizations were performed by using density functional theory (DFT) as implemented in
the SIESTA package. For the exchange and correlation functional, we employed GGA. In the choice of the basis size, we follow Refs. and , adapting them for the Green’s function type simulation: we found that a reduction from double- to single- basis on C (and N) atoms does not affect the relaxed structure of the nucleotides placed between the graphene electrodes. Additional polarization functions were used in the case of P and H atoms. The atomic core electrons are modeled with Troullier-Martins norm-conserving pseudopotentials. The real-space integration was performed using a 170 Ry cutoff, and due to the large cell size, only the -point was considered for Brillouin zone sampling.

Transport calculations were carried out in the framework of the Landauer approach. We used the non-equilibrium Green’s function (NEGF) technique based on DFT as implemented in the SMEAGOL package. The basis sets and the real-space integrations employed in the transport calculation are identical to those described above for the geometrical optimization part. The obtained transmission spectrum corresponds well with the test calculation performed with all double- basis. The electric current was then obtained from integration of the transmission spectrum,

\[ I(V_b) = \frac{2e}{\hbar} \int_{\mu_L}^{\mu_R} T(E, V_b) [f(E - \mu_L) - f(E - \mu_R)] dE, \]  

where \( T(E, V_b) \) is the transmission probability of electrons incident at an energy \( E \) from the left to the right electrode under an applied bias voltage \( V_b \), and \( f(E - \mu_{L,R}) \) is the Fermi-Dirac distribution of electrons in the left (L) and right (R) electrode with the respective chemical potential \( \mu_L = E_F + V_b/2 \) and \( \mu_R = E_F - V_b/2 \) shifted respectively up or down relative to the Fermi energy \( E_F \). Further details of the method are described in Ref. 31.

During the translocation process of a DNA strand through the graphene nanogap, many different orientations of the nucleotides are possible with respect to the graphene electrodes. It is therefore crucial to consider how the transmission function depends on the orientation of a given nucleotide. As seen in figure 1 for all nucleotides, the Fermi level is aligned near the HOMO. The isosurface plots of the molecular orbital corresponding to the first transmission peak below
the Fermi energy are found to be associated with the HOMO of isolated bases, localized on the pyrimidine and imidazole rings, as shown in the respective insets. Consequently, the position of the resonance peak and transmission values are significantly correlated with the base orientation. When a nucleotide is rotated, the peak position shifts upward or downward relative to the Fermi energy, and the transmission changes its magnitude. This is a result of the nucleotide-to-electrode coupling change. The transmission drops exponentially when the nucleotide-graphene coupling is weakened due an increasing distance of a nucleotide from the graphene edge. Zero transmission occurs in the case when a nucleotide is so far removed from the graphene leads that virtually no overlap between the states localized on the nucleotides and the states on the graphene lead exists, as it can be seen from the absence of transmission curves in [figure][1] for certain orientations of dCMP and dTMP.

Let us first discuss how the zero-bias transmission function \( T(E,V=0) \) is influenced by the different base types. There are two groups of nucleotides: one containing purine bases (A and G), and the other containing pyrimidine bases (C and T). The main distinctive physical property between these two groups is the base size: purines are larger than pyrimidines. This leads to smaller separation and stronger coupling of dGMP and dAMP with the electrodes. For all orientations considered here, \( T(-1 \text{ eV} \leq E \leq 1 \text{ eV}, V = 0) \) of dGMP and dAMP ranges from \( 10^{-20} \) to \( 10^{-6} \) \( G_0 \), while the corresponding transmission function of dCMP and dTMP can range from 0 to \( 10^{-8} \) \( G_0 \). The case of zero transmission for dCMP and dTMP is obtained at certain orientations when no coupling exists between the nucleotides and the leads.

Different molecule-electrode separations, and especially effective localization of the HOMO in the middle or at one side of the inter-electrode gap have an immediate effect on the width of the HOMO resonance. The peak widths of the HOMO resonance exhibit a variation due to different base orientations, where the peak widths of dGMP and dAMP are \( \sim 0.10-0.20 \text{ eV} \), while those of dTMP and dCMP are \( \sim 0.05-0.10 \text{ eV} \). This narrowing of the HOMO peak width is a result of weaker coupling between bases and leads for dTMP and dCMP as compared to dGMP and dAMP, caused by narrowing of the transmission cone and by increased localization (and lifetime) of the
electron in the HOMO coupled to the electrodes. Together with the molecule-electrode separation, the nucleotide chemistry and corresponding HOMO symmetry and rotation plays an important role in this coupling and localization of the state.

Comparing the results for dGMP and dAMP, we note that the Fermi level is aligned very closely to the HOMO peak of dGMP \((E \leq -0.5 \text{ eV})\), while that of dAMP appears at \(E \geq -0.5 \text{ eV}\). This circumstance gives rise to a significant difference in conductivity between dGMP and dAMP, which enables electrical distinction between them at low bias voltages.

Upon comparison of the transmission functions of dCMP and dTMP, we see that there is not much difference in the magnitude and position of the resonance peaks (at \(E \leq -0.6 \text{ eV}\)) for a wide range of orientations, and thus it would seem at first that these two nucleotides cannot be easily distinguished. However, as we shall see below, it is in fact possible to achieve an unambiguous distinction once the effects due to finite bias are considered.

To understand how the transmission is affected not only by rotation but also by lateral translation of the nucleotides, we tested effects of a shift in position within the \(x\)-\(z\)-plane. Figure 2 presents the resulting change in the transmission function with translations of dGMP in steps of \(\pm 0.5 \, \text{Å}\) along the \(z\)-axis. Note, that the rotation of the nucleotide alone is coupled to the effective localized HOMO translation between the electrodes. We find that the width of the HOMO resonance peak increases when the base part of the nucleotide is moved closer to the lead due to a broadened transmission cone and decreased lifetime of the coupled state. The broadening of the transmission peak width results from a stronger coupling between base and graphene electrode.

A shift of the HOMO peak position is observed both for rotation and translation of the nucleotide relative to the graphene edges. This is due to Pauli repulsion of the states on the nucleotide and the electrode edge, however charging of the phosphate moiety’s (known to act as an electron acceptor) may play a role as well. An increased accumulation of electrons on the phosphate-group leads to an overall charging of the nucleotide, slightly shifting the molecular energy levels towards lower energies. For all nucleobases, the behavior of the shift and the peak width was found to be qualitatively the same, however, for the smaller pyrimidine bases dCMP and dTMP, the resonance
peak can shift by up to 0.2 eV.

From the zero-bias transmission functions, we conclude that the difference of chemical and physical structures between the purine bases (dAMP, dGMP) and pyrimidine bases (dCMP, dTMP) affect the coupling strength of the DNA bases with the graphene electrodes, thus leading to the possibility to distinguish the two groups of DNA nucleotides under applied bias.

[figure][3][3] shows the range of possible current values for a bias voltage of 1 V when the nucleotides are rotated and translated again in the manner discussed above. The large fluctuations in the current are caused by the large variation of nucleotide-graphene coupling strength. It is important to emphasize that not too much attention should be paid to the absolute value of the current, which is provided in [figure][3][3]; rather, the ratio of the currents may be regarded as more relevant. The absolute current value is largely influenced by our simulation settings, where we use truncated nucleotides instead of extended DNA chains. In fact, we found from a test that when further parts of the sugar-phosphate backbone are included in the simulation, the current does in fact increase. Also, the current could potentially be increased by more than one order of magnitude through the creation of a low concentration of impurities in the graphene electrodes; such a conductivity-raising effect was recently demonstrated from both experiment and theory.32,33

The magnitude of the currents is seen to be ordered in the following hierarchy: $I_{dGMP} > I_{dAMP} > I_{dCMP} > I_{dTMP}$. Thus, dGMP can be distinguished from the other nucleotides due to its strong broad current signal which results from the Fermi energy of the graphene electrodes being close to the wide HOMO peak of dGMP. The other three nucleotides (dAMP, dCMP, and dTMP), which possess HOMO peaks further away from the graphene electrodes Fermi energy, exhibit different characteristic current magnitudes, showing rather little overlap with each other. In our analysis, we neglected very low current values below $I < 10^{-11}$ nA, which are expected to disappear into the electrical background noise in experimental measurements.

From the viewpoint of DNA sequencing applications, it is on the one hand encouraging to see that dAMP and dCMP exhibit a relatively narrow current range which should make them easier to identify. On the other hand, dGMP and dTMP have relatively broad current ranges, covering
several orders of magnitude. However, for dGMP, the current is always at the higher end, while for dTMP, the current is always at the lower end of the scale. Thus, based on our results, it should be in principle possible to distinguish between all for nucleotides in the graphene nanogaps setup.

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Figure 1: The four central panels show the zero-bias transmission function plotted on a semi-logarithmic scale for the four nucleotides, dCMP, dTMP, dAMP, and dGMP. The respective colors of the transmission curves indicate the angle by which the nucleotide has been rotated in a counterclockwise direction around the \( y \)-axis as per the legend at the bottom. The insets show isosurface plots of the molecular orbitals responsible for those transmission peaks marked by an arrow. The four vertically arranged panels to the right display the nucleotide orientations corresponding to 0°.

Supporting Information Available

Figures showing the different orientations of the four nucleotides in the graphene nanogap.

This material is available free of charge via the Internet at [http://pubs.acs.org/](http://pubs.acs.org/).
Figure 2: The change in transmission function of dGMP (with an orientation corresponding to a 30° rotation, as defined in [figure 1]) due to translation in steps of ±0.5 Å along the z-axis.

Figure 3: Current variation due to nucleotide rotation about the y-axis and translation along the z-axis at a bias of 1 V.