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Interaction dynamics and site-specific electronic recognition of DNA-nicks with 2D solid-state nanopores

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Single-stranded breaks in the DNA backbone caused by many endogenous and exogenous agents often lead to double-stranded breaks that are known causes of chromosomal instabilities leading to copious diseases. We describe a label-free detection technique using two-dimensional (2D) solid-state nanopore field-effect transistors (FETs) to sense and map site-specific nicks in the DNA backbone. We use all-atom molecular dynamics simulations coupled with electronic transport modeling to illustrate the 2D membrane device capability to sense minute structural changes of any translocating biomolecules via their in-plane electronic sheet current signatures, whereas Van der Waals analyses explain the distinct hydrophobic interactions between various DNA-nick types with graphene and MoS₂ nanopore membranes. Specifically, we describe the atypical unzipping behavior of DNA strands caused by the biomolecule sticking at nicked site in the graphene nanopore, under the influence of voltage-specific translocations.

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INTRODUCTION

DNA damages in the form of single-stranded breaks (SSBs) and double-stranded breaks (DSBs) occur daily in every cell due to many endogenous and exogenous factors¹. Approximately, 10⁵ such lesions are estimated to occur in every human cell in 1 day^{2–4}, with SSBs accounting for the majority of them. Endogenous factors that induce structural damages to the DNA can arise during the DNA replication process^{1,5} or from exposure to reactive oxygen species and other reactive metabolites that arise during normal cellular metabolic processes^{3,6–8}. In addition, exogenous agents such as ionizing radiation, UV radiation, and other environmental chemical sources are known to induce oxidation of DNA nucleotides leading to SSBs and DSBs⁸.

Various DNA repair pathways subjected to different lesions are activated by the cell to counteract the damages induced to the DNA¹. Though these repair mechanisms efficiently fix the continuously occurring damages, some unrepaired SSBs get converted into DSBs resulting in genomic instabilities that are known to promote cancer and/or cell apoptosis^{9,10}. Alternatively, the defective DNA damage response mechanisms itself can lead to a plethora of diseases such as neurological disorders, immunological defects, infertility, premature aging, cancer, growth defects, type II diabetes, epileptic seizures, cardiovascular disease, and many more^{1,3,4,8–15}. Furthermore, anticancer chemotherapeutic drugs and radiation therapy formulated for the treatment of cancer can act as a double-edged sword: despite evidence of the above-mentioned therapies reducing tumors, they are also known to cause DNA damages^{16–19}.

For many decades, problems pertaining to the structural integrity of the DNA strand due to SSBs, the DNA repair pathways and the enzymatic reactions used in repairing these damages have been well studied^{1,19–24}. However, given the vital role of SSBs on cellular functioning and its impact on human health, detecting these crucial biomarkers for genotoxicity and cytotoxicity, early in the tumorigenesis process, has not yet been addressed in a broad manner. Although the research is still ongoing, it is found that

SSBs, also called *nicks* are known to be formed by breaking the phosphodiester bond often followed by subsequent removal of a combination of atoms in the backbone, thereby leading to a unique conformation of the DNA strand itself^{1,6,9,14,23–32}. One of the common molecular structure of the nicks is the missing phosphodiester bond and phosphate group at 5' end caused by hydroxyl and other DNA damaging radicals²⁴.

Previous detection methodologies implemented to sense DNA lesions are based on bulk measurements that only provide information on the damage frequency, but not their specific site location along the DNA strands^{33,34}. Furthermore, the idea of using high-fidelity sequencing technologies has recently been considered as an additional way to detect DNA-nicks. However, all these techniques require extensive preparation of the samples, prior chemical modifications, and amplification steps to construct a specialized library of protocols to be followed for the detection.

Nanopores have emerged as the third-generation sequencing tool that has the capability to probe biomolecules with single-molecule precision^{35–37}. This sequencing scheme has many advantages such as being label-free, able to handle long read length with high throughput, requiring minimal material input requirements, and enabling direct detection of epigenetic markers^{38–43}. However, commercially available nanopore sequencers are based on biological nanopores that are known to have several innate drawbacks such as limited chemical and mechanical stability, and constant pore size. The emergence of 2D semiconductor materials for nano-electronic applications has offered new opportunities to make solid-state nanopores with the capabilities to overcome those drawbacks. Specifically, electrically active 2D materials i.e. graphene, and transition metal dichalcogenide such as MoS₂, WSe₂, etc. offer two very important advantages for biosensing, which are their excellent spatial resolution due to their atomic thicknesses and their ability to simultaneously detect single molecules via in-plane sheet currents, both of which have the potential to revolutionize nanopore-based sensing/sequencing technologies. For these

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reasons, significant efforts have been placed (both theoretical and experimental) towards the realization of 2D back-gated nanopore field-effect transistors (FETs) for in-plane sheet current detection of genetic and epigenetic moieties^{42–56}.

Here, we show that 2D nanopore sequencing methods are well suited for direct detection and mapping of the precise location of molecular damages along DNA strands (SSBs). Through a comprehensive computational analysis, we establish the different dynamics of hydrophobic interaction between various types of nicks and graphene and MoS₂ membranes, which result in differences in the detection characteristics of the two 2D material nanopore FETs. In doing so, we anticipate the ability of the 2D membrane devices to distinguish amongst nicks created between different pairs of nucleotides at various sites along the DNA backbone. In this context, we describe the anomalous behavior of nicked dsDNA that unlike with MoS₂ membrane unzip in graphene nanopores at voltage-specific nick sites during the dsDNA translocation through the nanopore.

RESULTS AND DISCUSSION

System setup

In Fig. 1, we illustrate the experimental setup for the detection of a single nick created by manually removing the atoms from the backbone of dsDNA (random sequence of 20 bp). The DNA with the 2D nanopore membrane is immersed in a neutral ionic solution of 1 M KCl, separated into two sub-cells by a graphene or MoS₂ membrane. For simulation purpose the nicked-DNA is placed just above a 2.6-nm diameter nanopore in a 9 nm × 9 nm membrane and driven vertically through the nanopore by an external voltage between the *cis*- and *trans*-sub-cells. An electronic current driven by a lateral and uniform electric field along the membrane responds to the conductance variations caused by the DNA translocating through the nanopore to sense the presence of the nick along the double strand. A more detailed description of the simulation setup is provided in the “Methods” section.

Interaction dynamics of nicked-DNA with 2D membranes

Figure 2 depicts a plot of the DNA velocity through a graphene pore as a function of time. As the DNA enters the pore under the influence of the electric field, the DNA translocation velocity (red curve, left axis) increases because the negatively charged DNA is strongly attracted towards the positive electrode. As the nicked backbone approaches the graphene nanopore after around ~5 ns, the velocity decreases to 0 Å ns⁻¹ because the DNA strand is

Fig. 1 System setup for detecting nicked-DNA with 2D solid-state nanopore FETs. Illustration of the system setup for detecting a nick (two bases at the nicked site are uniquely represented to clearly indicate the location of the damage) on a 20 bp dsDNA translocating through graphene nanopore membrane. Ionic and in-plane sheet currents are obtained simultaneously as the molecule translocates through the pore.

immobilized in the pore during 4 ns, then after 8 ns, slowly increases as the DNA strand completes its translocation towards the positive electrode. In order to spatially observe the motion of the nicked-DNA in the pore, we also show the position of the dsDNA center of mass (CoM) during the whole simulation time range (blue curve, right axis). The DNA CoM starts in the *cis*-chamber at ~28 Å above the graphene membrane (situated at 0 Å), and then slowly approaches a temporary stop as the nicked site enters the pore, before continuing its journey towards the *trans*-chamber (~15 Å). In the same figure, we also show the number of transversal nucleotides that have passed through the pore during the entire simulation time (black curve, far right axis). One notices that before 5 ns and after 8 ns, the nucleotides translocate through the pore, continuously, but within the 5–8 ns time window, the nucleotide number fluctuates around 10/11 at the nick position, so no translocation is taking place. Overall, all the fluctuations in the (black) curve indicating the nucleotides in the pore are caused by the DNA conformational variations arising from the interaction between the biomolecule and the graphene membrane.

In Fig. 3a, we display the calculated Van der Waals (VdW) energies (E_{VdW}) arising from the interaction between various DNA-nicked sites and the 2D membrane. Here, we identify a nick in the backbone created between homopolymers such as A–A, C–C, G–G, and T–T. One can see that the nicked site on the DNA is attracted (negative E_{VdW} values) to the graphene membrane regardless of its location between different pairs of the bases. This attraction is due to the absence of the hydrophilic phosphate group at the nick site, which leads to the site becoming hydrophobic and induces a strong interaction with the graphene membrane, which causes the DNA strand to halt at the nicked site during its translocation. One also observes a slightly different behavior between the purines (A–A and G–G) nick types and the pyrimidines (C–C and T–T) nick types, as the former are more strongly attracted to the graphene membrane than the latter. Furthermore, in the case of purines, the dip arising during the interaction of the nick with the membrane is sharp, indicating that the DNA translocates through the pore without much conformational fluctuations of the nicked backbone. On the contrary, for the case of pyrimidines, the E_{VdW} signal is softer, and trails till the end of the translocation time. This is due to the fact that the bases at the nicked sites adhere longer to the graphene membrane until the entire DNA is pulled out of the pore by the applied electric field into the *trans*-chamber. Calculated VdW's energies on various other nick types are showed

Fig. 2 Interaction dynamics of nick translocation. Plot of velocity (left axis, red curve), center of mass (CoM) of the nicked-DNA (right axis, blue curve), and the number of translocated nucleotides (far right axis, black curve) during the entire translocation time of the nicked-DNA. The purple line in the center of the plot indicates the location of the graphene nanopore membrane. One clearly observes the CoM of nicked-DNA starts above and ends below the line. The area marked in green shows the interaction dynamics between nick and graphene: reduction in velocity, stalled CoM of nicked-DNA, and standstill count of the number of translocated nucleotides between 10 and 11 bases of nicked-DNA (location of the nick).

Fig. 3 Nonbonded interaction energies between nicked-DNA and 2D nanopore membranes. Plot of pairwise interaction (Van der Waals) energies (E_{vdW}) calculated between various nick sites and 2D membranes: **a** E_{vdW} calculated between nicks and graphene during the translocation event and **b** E_{vdW} calculated between nicks and MoS_2 during the translocation event.

in Supplementary Fig. 1. It can be seen that the attraction (negative E_{vdW} values) between the different nick types and the graphene membrane holds in all cases. In addition, the A-C nick (between adenine and cytosine nucleotides) shows a stronger attraction (~ -6 kcal mol $^{-1}$) to the graphene membrane compared to other nick types (~ -3 kcal mol $^{-1}$).

Simulations performed on nanopores in MoS_2 membranes show similar behavior as with graphene membranes, albeit with weaker attraction between the nicked site and the membrane (Fig. 3b). This is consistent with the fact that DNA sticks less with MoS_2 than graphene⁴². One notable exception, however, arises for nicks created between A-A nucleotides, which display anomalously stronger attraction to the MoS_2 membrane compared to other nicks, which is confirmed by multiple simulations with different initial conditions. While the VdW energies illustrate the interaction dynamics of the various nick types with graphene and MoS_2 nanopore membranes, a more detailed explanation of these behaviors would require first-principles based energy calculations that will be addressed in a future communication.

Dwell time dependence of nicked-DNA on the driving voltage

In Fig. 4a, we show the dwell time of nicked sites in the pore of a graphene membrane as a function of the voltage applied between the *cis*- and *trans*-chamber. For all four types of nicks, it is seen that the dwelling time shows a strong monotonically decreasing dependence on the applied voltage that forces the translocation. As one expects, the dwell time of any nicked-DNA is longer for a lower applied bias as the DNA translocation itself is slow, facilitating a longer interaction time of the nicks with the graphene membrane. In our simulations, we observe that the dwell time of nick types A-A and T-T are shorter than those of nick types C-C and G-G. This difference in dwell times is strongly dependent on the conformational stochasticity of the translocating dsDNA. In Fig. 4b (i) we display four snapshots of a typical

Fig. 4 Dwell time dependence of nicked-DNA translocations on the applied voltages. **a** Plot of dwell time of the nick in the pore versus the voltage applied across *cis*- and *trans*-membrane to induce translocation of the nicked-DNA through graphene nanopore. Star symbols indicate the threshold voltages at which the nicked-DNA strand detaches for different nick at different sites. **b** Snapshots of the translocation events showing the conformational dynamics of nick translocations: (i) normal translocation event, (ii) unzipping of the nicked-DNA at the site during translocation.

translocation of a nicked-DNA molecule (20-bp long) that halts in the pore for a few nanoseconds because of the high hydrophobic interactions between the nicks and the graphene membrane, followed by the regular translocation of the rest of the DNA. This process mostly occurs at low applied bias. However, as shown in Fig. 4b (ii) for high applied voltages, there is a conformational change of the bases at the nick after the DNA translocation is halted in the pore as the DNA unzips from the nick site. Here, the nucleotide in the *cis*-chamber breaks the hydrogen bonds between its complementary nucleotide, and slides onto the top of the graphene sheet (second and third snapshots) because of the strong hydrophobic interaction between the sliding nucleotide and graphene prevents further translocation of the dsDNA molecule. At this stage, it is the strength of the electric field pulling the DNA towards the *trans*-chamber that unzips the DNA

Fig. 5 Detection of nicks in graphene nanopore FETs. Ionic current and in-plane electronic current signals calculated for translocations of DNA strand with nicks between: **a** A–A, **b** C–C, **c** G–G, and **d** T–T through graphene nanopores. In all the cases, both current signals are averaged over time to show the variations clearly. The green tab in each plot indicates the time frame when the nick resides in the graphene nanopore.

at the nicked site (fourth snapshot). It is seen that DNA unzipping at the nicked site occurs at different applied voltages for different nick types. For instance, for the A–A and G–G nicks, DNA unzipping occurs at 1.25 V, whereas it occurs at 1.75 V for the C–C and T–T nicks. In Supplementary Fig. 2, we display the dwell time dependence of the DNA-nicks on the applied voltages and the corresponding unzipping threshold voltage for other nick types. We could only obtain dwell times of nick types: A–C, A–G, A–T, and C–T for an applied bias of 0.25 V. As for other nick types, the translocation of the dsDNA did not happen at such low voltages after many weeks of running MD simulations. Here, we observe a similar monotonic decrease in dwell time with the increase in applied voltage as in the case of nicks between homopolymers. The unzipping threshold voltage for nick types A–C, A–G, A–T, and T–G was found to be 1.25 V, 1.0 V for C–T nick, and 0.75 V for C–G nick. The same set of simulations were performed with MoS₂ nanopores, without observing DNA unzipping during any of the simulations. We attribute this nonappearance to the fact that MoS₂ membranes are less hydrophobic than graphene, weakening the nucleotide interaction at the nicks with the membrane.

Detection of SSBs via 2D nanopore FETs

In Fig. 5a–d, we show a comparison between the signals obtained by simulating the ionic and the transverse current variations caused by the translocation of DNA molecules affected by the four types of nicks i.e. A–A, C–C, G–G, and T–T, respectively. The ionic current and the transverse electronic sheet current across the graphene membrane were calculated from the DNA trajectories obtained from the MD simulations as detailed in the Methods section. For the transverse electronic sheet current, a carrier Fermi energy of 0.1 eV in the graphene membrane was considered across all simulations, which corresponds to an electron concentration of $\sim 2 \times 10^{12} \text{ cm}^{-2}$, as for instance controlled by a back-gate bias V_G of a membrane FET⁵⁷. The voltage across source and drain, V_{DS} , was kept at 5 mV at $T = 300 \text{ K}$. For the four types of nicks, the ionic currents (blue traces) exhibit the blocking and opening of

the pore induced by the presence and absence of the DNA, respectively. Here, the open-pore current signal magnitude is $\sim 10 \text{ nA}$ that is reduced to $\sim 2.5 \text{ nA}$ during the DNA current blocking, without indicating any distinct change (peak or dip) of the presence of a nick on the DNA backbone. It should be pointed out that the ion flow through the nanopore does not experience any significant increase when the nick is in the pore. This can be explained as follows: because the nick is created by the removal of hydrophilic groups i.e. hydroxyl and phosphate groups in the backbone of the DNA, the site becomes hydrophobic, which makes the DNA stick to the graphene pore. In addition, the strong VdW interactions between the nucleotides on either side of the nick and the graphene membrane (as shown in Fig. 3a) causes the DNA to momentarily reside in the pore. During this time interval, the conformational fluctuations of the DNA inside the pore are minimal due to the VdW interactions. Hence, the number of ions translocating through the pore remains unchanged during the entire translocation event of the DNA.

The situation is however different in the (red) traces of the electronic sheet current signals that display sharp dips over specific translocation time windows for all four nick types. These dips in the transverse sheet current are the result of the electrostatic scattering of charge carriers in the membrane around the pore due to the missing bonds and atoms of the DNA-nick in the pore. This change in the potential profile affects the electron transport in graphene resulting in the dip. The in-plane current for all four nick types drops to $\sim 0.72 \pm 0.02 \text{ nA}$ along the graphene quantum point contact nanopore membrane of dimension $\sim 8 \text{ nm} \times 8 \text{ nm}$ used in our transport calculations. In addition, the width of this dip strongly correlates with the dwell time of the nick in the pore, anticipating the possibility of nick electronic detection via graphene nanopore membranes. Ionic and sheet current simulations performed on other nick configurations translocating through graphene nanopore membranes shown in the Supplementary Information (Supplementary Figs 3–6) confirm this conclusion.

The same kind of simulation was carried out on nicked-DNA translocating through MoS₂ nanopore membrane. Figure 6a

Fig. 6 Detection of nicks in MoS₂ nanopore FETs. **a** Ionic current and in-plane conductance variation signals calculated for translocations of DNA strand with nick between A–A through MoS₂ nanopore membrane. The green part indicates the time period where there is an increase in ionic current and simultaneous decrease in in-plane conductance. It is the same time period when nick dwells in the MoS₂ pore. **b** Scatter plot of normalized data points and corresponding Pearson's correlation coefficient values (shown in the legend) calculated for every 0.5 ns time period of the entire translocation time.

shows the signals for the translocation of a A–A nicked-DNA molecule, where the translocation times are comparatively shorter than for graphene nanopore simulations because we use shorter DNA strands (12 bp compared to 20 bp) with a nick at the center in order to reduce the computational time of MD simulations. Unlike in graphene membranes, where the presence of a nick was solely identified by a dip in the in-plane sheet currents, there is a strong inverse correlation between the ionic and the electronic sheet conductance signals during the same time window when the nick dwells in the MoS₂ nanopore. Figure 6a shows the duration of the DNA translocation through the nanopore from 0 to ~2 ns, during which one observes an increase in the ionic current values to a global maximum of ~0.5 nA around 1 ns, and a corresponding decrease in the electronic sheet conductance values to a global minimum of ~7.15 μS, when the nick dwells in the pore (~0.75–1.1 ns). Here, one observes an increase of the ion drift with the presence of the nick in the pore. As the nicked site in DNA molecule is strongly hydrophobic, and given the fact that MoS₂ is less hydrophobic than graphene⁴², the two nucleotides on each side of the nick are seen to widen and open up, and the entire DNA molecule moves closer to the edge of the membrane making room for ions to drift through the pore during the time interval corresponding to the presence of the nick in the pore. Another consequence of these interactions is a quicker translocation of the entire DNA out of the MoS₂ pore compared to similar translocation events observed in graphene nanopore membranes. Hence, one observes a reduced dwell time of the nicked-DNA in the MoS₂ nanopore membrane (~0.2–0.5 ns) compared to graphene nanopore membrane (>1.5 ns). In order to validate the presence of the inverse correlation between the two currents, we calculated the Pearson's correlation coefficient (*P*) for the normalized signals at every 0.5 ns time frame from 0 to 2 ns (see the “Methods” section). A scatter plot of the data points with the

corresponding *P* values is shown in Fig. 6b. The time frame with the lowest *P* value (indicative of strong inverse correlation between the normalized current signals) i.e. between 0.5 and 1 ns agrees with the observation based on Fig. 6a by identifying the time frame when the nick dwells in the pore. Here, a time step of 0.5 ns was chosen to calculate the correlation coefficient in reference to the nick dwelling time in the MoS₂ nanopore membranes. However, one can select smaller (or larger) time step (e.g. 0.25 or 1 ns) for calculating the *P* values depending on the dsDNA length and the particular dwell time in the pore. Similar results were observed in the analyses performed on the DNA trajectories obtained for nicks between different pairs of nucleotides (Supplementary Fig. 7 and 8). The time period during which the in-plane conductance decreases to a global minimum and the ionic current increases to a global maximum strongly corresponds to the time when nick site is dwelling in the nanopore suggesting that DNA damages (SSBs) can be detected via MoS₂ nanopore FETs as well. In addition to the presence of nicked-DNA in the MoS₂ nanopore, conformational noise of the DNA during translocation might result in similar kind of correlation, but in this case, MD simulations coupled with electronic transport modeling show an in-plane conductance increase coinciding with an ionic current decrease.

In DNA translocation experiments, a transmembrane voltage of ~100–200 mV is usually set up to thread the biomolecule through the nanopore, which results in observed translocation times are of the order of milliseconds with dwell times of the order of a few 100 μs^{49,58}. Higher biases are excluded to avoid membrane damages to the FET device caused by dielectric breakdown. However, in molecular dynamics (MD) for which the time step is below 2 fs to capture the motion of all the atoms in the system, the software can only simulate up to several tens of ns of molecular motion. Longer simulation times are computationally prohibitive. So, in order to apprehend the details of the interaction between the biomolecule and the nanopore, a high transmembrane voltage of 1 V is used to speed-up the translocation of the nicked-DNA strand through graphene or MoS₂ nanopore membranes. In addition, MD simulations are performed for smaller systems (low number of ions, dsDNA length of 30 bp, etc.). In reality, as reported in experimental works^{55,59,60} the bandwidth required for recording the ionic and in-plane current signals is reduced to few megahertz. Furthermore, the dwell time of the nicks can be extended by further slowing down the translocation of the DNA in using a viscosity gradient transmembrane chamber using room temperature ionic liquids as shown by Radenovic et al.⁴⁹

In summary, we describe a sensing scenario for recognizing and mapping SSBs/nicks in the DNA backbone using nanopore-based FETs. Data obtained from MD simulations coupled with electronic transport models, indicate the possibility of direct SSB recognition due to the ability of electrically active 2D nanopore membranes to capture transverse electronic sheet currents. In our analysis, we highlight the interaction dynamics of the nicked-DNA with solid-state nanopore membranes such as graphene and MoS₂ and its unique dependence on the driving voltage. In fact, one can obtain a consensus on the location of the nicks (and bases at the nicked site) created by a particular kind of endogenous and/or exogenous agent by translocating the damaged-DNA strands through 2D nanopores at different voltages and identifying the specific applied voltage that causes the denaturing of the strand. Given the ongoing efforts to reduce the error rates and advance the use of solid-state materials for nanopore devices, we believe that one can further their understanding on site-specific SSBs and its effects on various cell activities. We also envision that site-specific break detection can be used in regulating targeted chemotherapeutic drugs and radiation dosage levels in treatment of cancer. Furthermore, aside from its high impact on medical and pharmaceutical research, this sensing mechanism can strongly

influence other independent applications such as DNA data storage and computation⁶¹.

METHODS

MD Protocol

Each simulated system was built and analyzed using the visual molecular dynamics (VMD) software⁶². In total, 9 nm × 9 nm graphene and MoS₂ membranes were built using plugins in VMD. Carbon atoms in graphene were treated as type CA atoms described by CHARMM27 force fields⁶³ and harmonic restraint with a spring constant of 10 kcal mol^{−1} was applied to the boundaries to prevent the drifting of the membrane. For MoS₂ membrane, Lennard-Jones parameters from Stewart et al.⁶⁴ were incorporated and all the atoms were fixed to their initial positions. Nanopores in each membrane were created by manually removing atoms. The dsDNA structure was obtained from the 3D-DART web server⁶⁵ and was described using CHARMM27 force fields⁶³. Nicks in each dsDNA strand were created by manually removing the phosphodiester bond and phosphate atoms in the backbone²⁴. On a side note, one can obtain uniform/clean nicked sites by extracting the DNA with SSBs caused by endogenous or exogenous agents and using a phosphatase to remove the phosphate group at the nicked termini. For each system setup, the 2D membrane along with the DNA were solvated in a water box with 1 M KCl solution. The MD simulations were performed using NAMD⁶⁶. The systems were maintained at 300 K using a Langevin thermostat. Periodic boundary conditions were employed in all directions. Time steps of 1 or 2 fs (for graphene or MoS₂, respectively) along with particle Mesh Ewald⁶⁷ were used to treat long range electrostatics. All systems were minimized for 5000 steps, followed by a 600 ps equilibration as an NPT ensemble. The systems were further equilibrated as an NVT ensemble for another 2 ns before the electric field was applied. Different electric fields specified by corresponding voltages in NAMD scripts were applied to the systems in the z-direction to enforce the translocation of the nicked-DNA through the nanopore. The trajectories of all atoms in the system were recorded at every 5000 steps until the DNA was completely translocated. These trajectory files were further used to calculate instantaneous ionic current described as by Aksimentiev et al.⁶⁸, and to calculate the electronic transport described below.

For each frame in the trajectory file, VdW energies (E_{VdW}) between the 2D nanopore membrane and the nick site on the backbone of the dsDNA are calculated using the usual expression between two nonbonded atoms

$$E_{VdW} = C_n r^{-n} - C_m r^{-m}, \quad (1)$$

where r is the internuclear separation, C_n and C_m are constants for which the value depends on the equilibrium separation between the two atom nuclei and depth of the energy well of each atom, and m and n are power integers specific to particular atoms.

We use NAMD Energy Plugin available in VMD software package to calculate E_{VdW} where, all the parameters such as cutoff distance (12 Å) and time step (1 fs for graphene and 2 fs for MoS₂) are set to the values similar to the ones used in our MD simulations.

Electronic transport calculations

For each frame in the MD trajectory, electrostatic potential, $\phi(r)$, is calculated using Poisson Boltzmann's equation shown in Eq. (2).

$$\nabla \cdot [\epsilon(r) \nabla \phi(r)] = -e[K^+(r) - Cl^-(r)] - \rho_{DNA}(r), \quad (2)$$

where $\rho_{DNA}(r)$ is the charge due to DNA. The charges due to ions (potassium: $K^+(r)$ and chlorine: $Cl^-(r)$) in the KCl solution are described assuming Boltzmann equilibrium.

For graphene, using the obtained electrical potential, transverse conductance, G , at the source-drain bias (V_{DS}) is calculated by nonequilibrium Green's function formalism as shown in Eq. (3)⁴⁵

$$G = \frac{2e}{V_{DS}h} \int_{-\infty}^{\infty} \bar{T}(E) [f_1(E) - f_2(E)] dE, \quad (3)$$

where $\bar{T}(E)$ is the transmission coefficient between leads 1 and 2, $f_a(E) = f(E - \mu_a)$ is the probability of an electron occupying a state at energy E in the lead $a \in \{1, 2\}$, and $V_{DS} = (\mu_1 - \mu_2)/e$ is the bias across the conductor. All transverse conductance values are obtained at a Fermi energy of 0.1 eV.

For MoS₂, electron transport is formulated as a semiclassical model based on thermionic emission using a two-valley model within the

effective mass approximation⁵¹. Briefly, the conductance variation due to thermionic current flowing from source to drain at a given voltage is calculated using Eq. (4).

$$G_{n1,2} = \frac{2e^2}{h} \frac{1}{1 + \exp\left(\frac{E_{n1,2}^K - E_F^L}{k_B T}\right)} + \frac{2e^2}{h} \frac{1}{1 + \exp\left(\frac{E_{n1,2}^Q - E_F^L}{k_B T}\right)}, \quad (4)$$

where E_F^L is chosen energy level setup on the left side of the membrane, $n_{1,2}$ represents energy modes of particular channel, and $E_{n1,2}^K$ and $E_{n1,2}^Q$ are energy level due to effective masses at K and Q , respectively. The total variation in conductance with respect to open-pore conductance, δG , is the sum of conductance values through all modes in each channel. All conductance values are obtained at fixed Fermi energy corresponding to a carrier concentration of 10^{12} per cm².

The detailed description and the rationale behind the calculations used here for electron transport in graphene and MoS₂ are outlined by Girdhar et al.⁴⁵ and Sarathy et al.⁵¹, respectively.

This study focuses on the resistance variations caused by the DNA translocation through the nanopore, and ignores other sources of resistance such as the contact resistance, but also the resistance of the nanoribbon as well as the effect of the environment such as the electrolyte in contact with the membrane. However, all these contributions are mostly time-independent and related to particular fabrication process, which can be minimized by technological optimization to emphasize the DNA signal. Moreover, the overall conductance is determined by Matthiessen rule, where the contribution to the DNA translocation can be isolated from the other source of resistances, and analyzed independently, as described in our forthcoming publication⁶⁹.

In this context, the authors would like to point out that the channel width and length as well as the nanoribbon geometry will determine the magnitude of the in-plane current. However, the variation amplitude of the conductance/current signal caused by the presence of DNA in the nanopore will remain the same, as described in details in our forthcoming publication⁶⁹. Hence, from an experimental viewpoint, once the baseline in-plane current corresponding to the open pore is identified, the conductance/current variations caused by the translocated nicked-DNA can be extracted and analyzed by the same methodology as described in this paper.

Current signal correlation

In order to establish the correlation between the in-plane sheet and ionic currents, each signal is normalized between 0 and 1 in the time frame when the nicked dsDNA translocates through the 2D nanopore, but not when the DNA is outside the nanopore. The Pearson's correlation coefficient is then calculated as

$$\rho = \frac{\text{cov}(I_{\text{norm}}, S_{\text{norm}})}{\sigma_{I_{\text{norm}}} \sigma_{S_{\text{norm}}}}, \quad (5)$$

where cov is the covariance between the normalized ionic current signal, I_{norm} , and the normalized in-plane current signal, S_{norm} , whereas $\sigma_{I_{\text{norm}}}$ and $\sigma_{S_{\text{norm}}}$ are the standard deviations of I_{norm} and S_{norm} , respectively.

DATA AVAILABILITY

Raw data were generated at the XSEDE and Blue Waters supercomputing facilities. Derived data supporting the findings of this study are available from the corresponding author upon request.

CODE AVAILABILITY

The codes used in this study are available on request from the corresponding author (J-P.L.). The codes are not publicly available due to them containing information that could compromise our research privacy/consent.

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AUTHOR CONTRIBUTIONS

N.A., O.M., and J.-P.L. conceived the presented idea. N.A. designed and performed the computations and analyses with J.-P.L.'s contribution. The paper was written through contributions of all authors. All authors have given approval to the final version of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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