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GRAPHENE NANOPORE TRANSISTOR FOR DNA-NICK DETECTION

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EXECUTIVE SUMMARY

Significant effort has been placed on advancing new generations of single-molecule detection technologies. Unlike other existing platforms, solid-state nanopores have the versatility to perform tasks that go beyond DNA sequencing, such as detecting epigenetic modifications, RNA and protein sequencing, and folding patterns. In such settings, it is crucial to develop computational tools that enable the identification of optimal solid-state membranes and pore geometries for the problems at hand. In this regard, the research team studies the implementation of innovative 2D solid-state nanopore devices to detect and map minute structural damages in the backbone of the double-strand DNA molecule, which have been suggested as a cause of cancer. The team's two-step objectives will be achieved through, first, understanding the physics behind the interactions of damaged DNA with 2D solid-state membranes and, second, detecting the variations in ionic current through the pore and the transverse electronic current across the membrane caused by such interactions.

RESEARCH CHALLENGE

A normal human cell is subjected to approximately 70,000 lesions per day. Of these, single-strand DNA (ssDNA) breaks, which are often converted into double-strand DNA (dsDNA) breaks, are a vast majority [1]. A single break in a critical gene can cause the cell to undergo apoptosis (programmed cell death). If the repair mechanism fails, the dsDNA break can cause chromosomal instability, leading to tumorigenesis.

Existing genome sequencing techniques are not suitable for detecting such changes directly. The only known means for ssDNA breakage positioning is to use immunoprecipitation followed by sequencing, which leads to highly limited resolution and low accuracy. Hence, as an alternative methodology, the research team has shown that graphene quantum point contact (g-QPC) nanopore transistors can be used efficiently to detect and map defects in the DNA backbone as miniscule as ssDNA breaks using electronic sheet currents obtained across the membrane.

METHODS & CODES

This research consists of a two-step process that first includes molecular dynamics (MD) simulations with the latest NAMD version and, second, the exploitation of MD data to calculate the current variations owing to DNA translocation through the nanopore via electronic transport modeling. The system is built, visualized, and analyzed using VMD [2]. The DNA is described by the CHARMM27 force field [3]. An external electric field is applied to the system to drive the DNA nicks through nanopores.

For each frame of the trajectory files obtained from the MD simulations, the ionic current blockade is calculated instantaneously [4]. Further, the electrostatic potential induced by the biomolecule around the pore is obtained by using the self-consistent Poisson–Boltzmann equation (PBE) formalism. The PBE

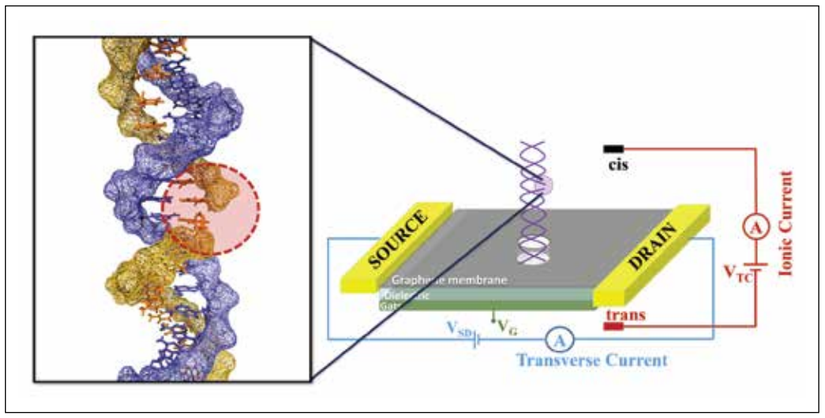

Figure 1: Schematic illustration of the system setup for obtaining ionic and transverse sheet current signals of the damaged DNA (shown on the left) translocating through a graphene nanopore.

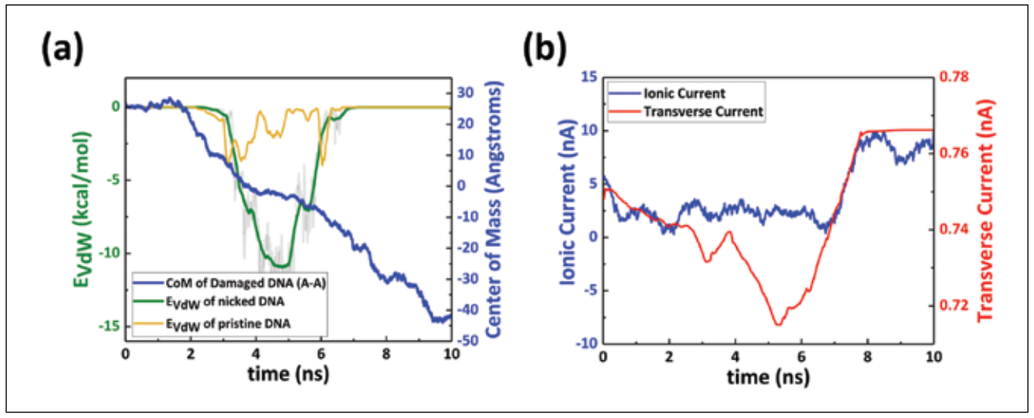

Figure 2: (a) Plot of van der Waals energies calculated between graphene membrane and nicked-/normal-DNA site showing strong attraction at the nicked site of damaged DNA. (b) Plot showing the ionic current and transverse sheet current indicating the detection of the nicked site by sheet currents (dip at -5 ns).

is solved numerically using the multigrid method until the convergence criterion is met. Once the electrostatic potential coplanar to the membrane is obtained, the transverse conductance across the 2D nanopore, graphene, or MoS_2 membrane is computed by using the nonequilibrium Green's function formalism [5] or a semiclassical thermionic emission technique [6], respectively. The Leburton Group at the University of Illinois at Urbana–Champaign wrote and maintains the PBE and electronic transport code.

RESULTS & IMPACT

Real-time detection of damaged-DNA strands is nearly impossible and has not been reported by anyone using existing technologies. Fig. 1 illustrates the nanopore setup used for simultaneous calculation of the ionic and transverse sheet currents. Resolving the duration and magnitude of each dip of the ionic current signal gives an insight into the structure of part of the biomolecule inside the pore. Simultaneously, the variations in the electronic sheet current flowing from source to drain across the 2D membrane detect the change of the electric potential induced on the ridge of the nanopore by the translocating DNA, revealing the position of the damaged backbone.

The results obtained using this methodology are highly encouraging: In all the simulation runs, the molecule is halted in the pore at the nicked site owing to strong attraction between the graphene membrane and the damaged backbone. This behavior can be explained by the fact that the cleaved backbone of the dsDNA molecule is arrested in the pore owing to higher hydrophobic interactions between the DNA and the graphene membrane.

To validate this theory, the research team calculated the van der Waals energies between the normal DNA with graphene and the damaged DNA with graphene (Fig. 2a). It is clear that there is higher attraction at the nicked-site with the graphene atoms resulting in the molecule being arrested in the pore. The ionic currents calculated for the translocation of 20 base-pair dsDNA with a break in the backbone show no distinct feature contributed by the nicked site on the signal. However, a clear dip is seen in the transverse sheet current signal corresponding to the location of the breakage, enabling the electronic detection of damages (Fig. 2b).

The research team has validated the methodology outlined above by detecting other sequence-specific dsDNA breaks along a randomly sequenced strand. This technique can be easily scaled to have a dense array of multiple g-QPC nanopores implemented on a complementary metal–oxide–semiconductor chip to detect multiple damaged DNA strands in a massively parallel scheme [7]. The researchers strongly believe such a detection mechanism can enable the development of versatile semiconductor electronics for early cancer detection caused by structural modification of the genome.

WHY BLUE WATERS

It is only possible to investigate the interactions of biomolecules with solid-state materials, to characterize the stochastic structural fluctuations of the DNA with nicks translocating through solid-state nanopores, and to further obtain the electronic response using all-atom MD simulations coupled with electronic transport calculations with petascale computing resources such as Blue Waters. The research team's systems consist of about 500,000 atoms, each requiring multiple MD simulation (NAMD) runs. With NAMD code efficiently deployed on XE/XK nodes to run highly parallel simulations of large biomolecular systems, Blue Waters is well-suited for the requirements of this research.

PUBLICATIONS & DATA SETS

N. Athreya, O. Milenkovic, and J.-P. Leburton, "Site-specific detection of DNA-nicks using ultra-thin nanopore membranes," in progress, 2019.