BLUE WATERS
SUSTAINED PETASCALE COMPUTING

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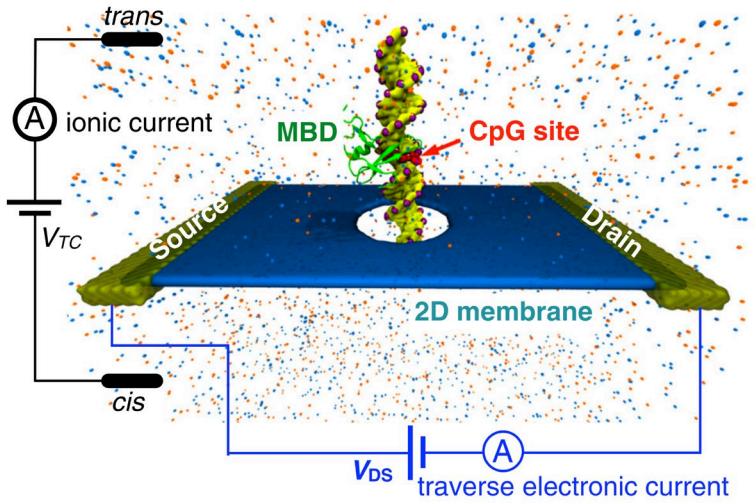
EPIGENETIC IDENTIFICATION AND MAPPING USING SOLID-STATE 2D NANOPORES

Research Challenge

Aside from sequencing DNA molecules, the identification of traits of the human genome such as methylation is crucial for diagnosis of epigenetic diseases. Recent experimental evidence of DNA methylation alterations linked to tumorigenesis suggests that DNA methylation plays a major role in causing cancer by silencing key cancer-related genes. Until now, detection and mapping of such DNA methylation patterns using solid-state nanopores have been unsuccessful due to rapid conformational variations generated by thermal fluctuations that result in low signal to noise ratio.



Schematic of the simulated nanopore device. A mDNA-MBD1 complex is being threaded through a nanopore in a 2D material membrane (e.g., graphene or MoS2) embedded in an electrolyte solution. A voltage, VTC, was applied across the membrane to move the mDNA–MBD1 complex, and meanwhile, to induce an ionic current through the pore. Another voltage, VDS, was applied between a source electrode and a drain electrode connecting the 2D material, inducing the flow of a electronic sheet current in the membrane

Methods & Codes

Two-step process that first uses molecular dynamics (MD) simulations with the latest NAMD version and then exploits the MD data to calculate the current variations due to DNA translocation through the nanopore via electronic transport modeling. The system is built, visualized, and analyzed using VMD. The protein and DNA are described by the CHARMM22 force field with CMAP corrections and the CHARMM27 force field ,respectively. In the second step, electrostatic and the electronic transport code are written and maintained by the Leburton Group at the University of Illinois at Urbana-Champaign.

Results & Impact

"Noise-free" electronic currents were calculated for all biomarkers. These signatures were compiled into a set of dictionary signals for each of the marker proteins. When a target noisy signal includes the stochastic conformational fluctuations obtained from MD simulations and electronic transport calculations whose marker protein is unknown is fed into the matched filter, it is correlated with the different dictionary signals to identify the marker-protein type. We anticipate that this algorithm can be extended to the detection of multiple markers attached to the same DNA molecule.

Why Blue Waters

Investigation of the interactions of biomolecules with solid-state materials and acquisition of the electronic response using all-atom MD simulations coupled with electronic transport calculations are only possible with petascale computing resources such as Blue Waters. Our systems are about 500K atoms in size, 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 our research needs.