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Graphene and 2D Materials for Epigenetic Applications

Abstract

The last two decades have experienced rapid technological developments in the search of cheap and high accuracy devices for fast bio-molecular identification. In the realm of DNA and protein sequencing, there has been an increasing interest in the use of nanopores in solid-state materials because of their distinct advantage over biological pores in terms of flexibility in pore design and mechanical strength. Two-dimensional solid state materials such as graphene and Molybdenum di-sulphide (MoS_2) in particular have attracted attention because of their atomically thin layered structure and electrically active characteristics, predisposing them to offer single base resolution and simultaneously multiple modalities of detecting biomolecular translocation. Apart from detecting the individual bases along a DNA in sequencing applications, nanopores have also been sought to identify chemically modified nucleobases for epigenetic applications. One of the most common epigenetic modifications in DNA is the methylation of cytosine, which tends to occur in C-G di-nucleotides (known as CpG sites). Hyper and hypo- methylation of CpG sites in the promoter sequences of genes in DNA are considered to be causes of various cancers. In this presentation, we explore the potential of two-dimensional solid-state nanopores to recognize methylated CpG sites along the DNA by analysis of the blocking ionic current through the pore as well as by the variation of the electronic current along the 2D membrane, when the DNA translocate through the pore. We utilize molecular dynamics coupled to electronic conductance calculations across the two-dimensional nanopore membranes such as graphene [1] and MoS_2 [2]. We show epigenetic detection with graphene and MoS_2 membranes and predict higher detection resolution for DNA methylation than conventional sensing modality by ionic current blocking techniques [3]. Despite intense efforts over recent years, real time base-calling has not be achieved yet by means of solid-state nanopores, mainly because DNA translocation through the pore is too fast and thermal motion of bases is too strong to permit resolving of bases. Hence, the methylated CpG sites along the DNA are complexed by methy-CpG binding domain proteins to enable their indirect detection. Figure 1a shows the presence of methylated sites along the DNA that labeled by MBD1 protein (due to its smaller width) as a biomarker. The measurement setup is shown in Fig. 1b which displays two independent detection methodologies namely, ionic and electronic sheet current, orthogonal to and along the solid state membrane with a 5 nm pore, generated due to voltage biases V_{TC} and V_{DS} respectively embedded in an ionic water solution (1 M). In Figs. 2, we show that the detection sensibility of a 5.2 nm pore MoS_2 membrane, where the ionic current exhibits a characteristic dip corresponding to the protein translocation. Similar features corresponding to deviation peaks in the transverse sheet are also observed showing a one- to-one correspondence between ionic and transverse sheet currents. In Fig.2.d, the latter shows the ability to distinguish between MBD proteins separated by 10 bases.

References

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Figures

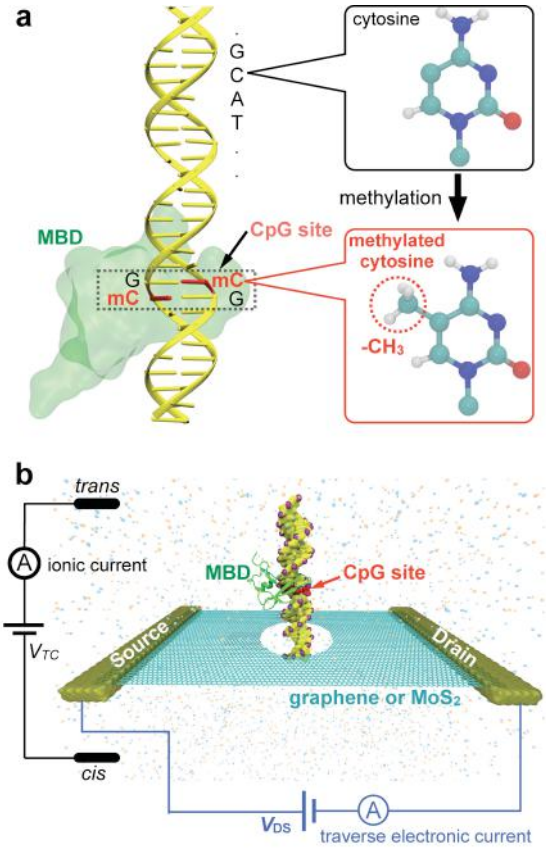

Figure 1: Schematic showing a CpG dinucleotide site in a methylated DNA molecule in complex with MBD1 protein. The right panel shows the chemical structures of a cytosine (top) and methylated cytosine (bottom). b. Schematic of the simulated nanopore device. A DNA-MBD complex is threaded through a 5nm diameter nanopore membrane in an electrolytic solution. Biases are applied across and along the membrane thereby driving an ionic and electronic current respectively

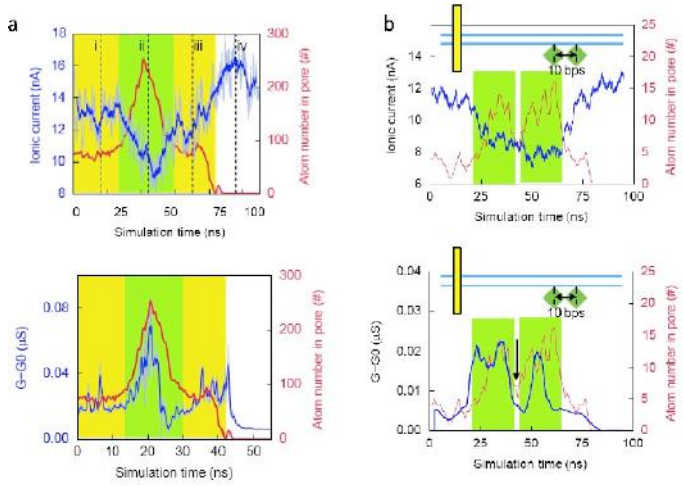

Figure 2: . Detection of DNA methylation with MoS2 nanopores. (a) Top: A typical ionic current trace together with the number of atoms residing in a MoS2 pore when a mDNA-MBD complex translocates through the pore. Bottom: Calculated conductance in the MoS2 layer during the same translo- cation event.(b) Higher resolution of methylation detection using transverse electronic current in MoS2. The differential conductance is shown together with the number of protein or DNA atoms occupying the pore. The arrow marks a dip between two peaks, each corresponding to the permeation of a MBD1 protein bound to a methylation site.