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DNA sequencing by two-dimensional materials: As theoretical modeling meets experiments

Lijun Liang [a,*], Jia-Wei Shen [b,*], Zhisen Zhang [c], Qi Wang [a,*]

[a] Department of Chemistry and §Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, People's Republic of China
[b] School of Medicine, Hangzhou Normal University, Hangzhou 310016, People's Republic of China
[c] Research Institute for Soft Matter and Biomimetics, Department of Physics, Xiamen University, Xiamen 361005, People' s Republic of China

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ABSTRACT

Owing to their extraordinary electrical, chemical, optical, mechanical and structural properties, two-dimensional (2D) materials (mainly including graphene, boron nitride, MoS_2 etc.) have stimulated exploding interests in sensor applications. 2D-material based nanoscale DNA sequencing is a single-molecule technique with revolutionary potential. In this paper, we review the methodology of DNA sequencing based on the measurements of ionic current, force peak, and transverse electrical currents etc. by 2D materials. The advantages and disadvantages of DNA sequencing by 2D materials are discussed. Besides the recent development of experiments, we will focus on the theoretical calculations of DNA sequencing, which have been played a critical role in the development of this field. Special emphasis will focus on the disagreements between experiments and theoretical calculations, and the explanations for the discrepancy will be highlighted. Finally, some new plausible sequencing methods from computational studies will be discussed, which may be applied in the realistic DNA sequencing experiments in future.

1. Introduction

DNA sequencing does not represent only a fundamental code of life for academic research, but also provides an enormous opportunity to improve the well-being of humankind by ushering in a new era of precision medicine (Mardis, 2011; Shendure and Aiden, 2012). New sequencing technologies developed rapidly under the increasing need for cheap and fast genome sequencing, but the cost of genomic sequencing is still far from the ideal price point of “the $1000 genome” (Porcu et al., 2013). To achieve this purpose, single molecule detection technology especially nanopore sequencing has newly-emerged as the next generation DNA sequencing (Maitra et al., 2012; Rhee and Burns, 2006; Shendure and Ji, 2008). As schematic shown in Fig. 1, the nanopore based single molecule DNA sequencing technology mainly relies on the identification of the ionic current, the characteristic force peak, or transverse electronic currents of different four bases (A=adenine; C=cytosine; G=guanine; T=thymine). Illustrated in Fig. 1a, the basic principle of DNA sequencing on ionic current is that the ionic current could be blocked with the natural negative charged double strands DNA (dsDNA) or single strand DNA (ssDNA) when they were driven to translocate through the nanopore by an applied electric field. The phenomenon was first discovered by Kasianowicz et al. in a study of a DNA molecule translocation through the α-haemolysin membrane pores (Kasianowicz et al., 1996). On the basis of the blockade ionic current difference in different bases, the single base could be identified (Chang et al., 2004). The second DNA sequencing mode has been investigated as a plausible mode in many theoretical works (Zhang et al., 2014b). As shown in Fig. 1b, the DNA was pulled through the nanopore with atomic force microscope (AFM) (Reed et al., 2007) or optical tweezers (Fuller et al., 2006), and four different nucleotides could be distinguished by the characteristic force peak of each type of nucleotide that translocate through the nanopore. The third DNA sequencing mode is schematic in Fig. 1c, where the current flows between nanopore and perturb transverse-direction electronic signals resulting from the DNA translocation through the nanopore (Nicoli et al., 2014).

While the detection by biological nanopore based on the ionic current has achieved in single-nucleotide resolution (Goodwin et al., 2015; Manrao et al., 2012), the application of biological nanopore is still limited by the instability of lipid bilayer membrane in many conditions such as the applied electric field. Solid state nanopore has become promising alternative to biological nanopore for its stability, meanwhile it is easy to fabricate (Dekker, 2007; Fologea et al., 2005; Li et al., 2003). Especially, the nanopores of two-dimensional (2D) materials including graphene

* Corresponding authors.

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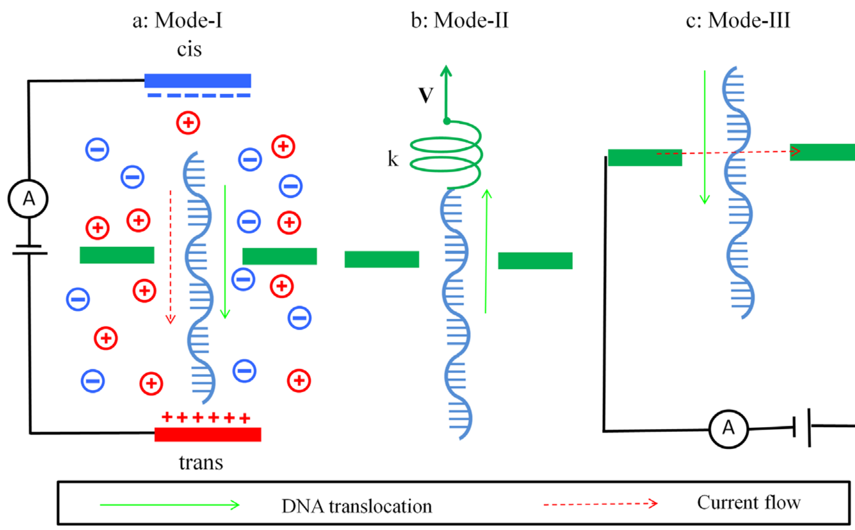

Fig. 1. Schematics of device configurations for the third-generation DNA sequencing based on: (a) ionic current; (b) characteristic force peak; (c) transverse direction electron current.

(Schneider and Dekker, 2012), molybdenum disulfide (MoS_2) (Liu et al., 2014), and hexagonal boron nitride (h-BN) (Liu et al., 2013) fabricated on single atomic layer thick open a new chapter for DNA sequencing. The advantages of such nanopores includes: (1) DNA sequencing using nanopores requires the ability of moving a DNA strand at intervals of ~1 nm and reading sequence information at each position. The single layer atomic thickness of nanopore is close to the interval between two neighbor bases in DNA molecules. It could remain only one DNA base in the nanopore at the same time, and it is also the reason of improving the signal-to-noise ratio (SNR) for DNA sequencing. (2) 2D materials have their extraordinary electrical, chemical, optical, mechanical and structural properties (Mas-Balleste et al., 2011; Novoselov et al., 2005), and have potential advantages in sensor applications. (3) Benefit from the rapid development of nanotechnology, nanopore with different nanoscale and nano-geometry could be fabricated from many methods (Miles et al., 2013). For instance, graphene nanopores with radii as small as 0.3 nm have been synthesized by etching method (Banhart et al., 2010). Thus, DNA sequencing by 2D material nanopore has been extensively studied in experiments (Miles et al., 2013).

Till now, extensive experimental studies on DNA in a solid-state nanopore have been carried out and provide comprehensive understanding of nanopore DNA sequencing. However, these three models for DNA sequencing are challenging because all of them rely on interpreting some indirect measured signal (e.g., current, position, speed, force etc.) into a molecular property. Meanwhile, good resolution of DNA sequencing requires that the critical differences of molecular property in four bases are subtle and the velocity fluctuation of DNA translocation process through a nanopore should be very small. However, the motion of DNA translocation across nanopore is fast and noisy due to the straightforward approach of applying voltage (Carson and Wanunu, 2015). In addition, each solid-state nanopore is unique, and many properties including surface roughness, surface charge densities etc. could be dramatically different from each other, yielding a different translocation behavior of DNA. Therefore, experiments studies alone are not sufficient, and they have certain limitation to understand the mechanism of DNA sequencing by 2D materials, especially under the atom and molecular level, which hinder the design and development of 2D materials for DNA sequencing. Theoretical calculation covers the length scale from the atom to molecule level, and it is important complement for nanopore DNA sequencing experiments (Liang et al., 2014a; Wanunu, 2012). With the development of supercomputer, theoretical calculations have played a significant role in both area of providing atomistic pictures of translocation processes and proposing various novel DNA sequence reading mechanisms.

This review will be dedicated to the DNA sequencing by 2D materials nanopore, presenting the experimental together with the theoretical results with the aim to find a cross point where experiments and theory can meet. We provide an in-depth view on the contribution of biophysical and theoretical calculations to characterize the DNA sequencing dynamics and process by 2D materials nanopore. DNA sequencing by other types of nanopore could be refereed to other reviews (Branton et al., 2008; Haque et al., 2013). The structure of the review is as follows: In Section 2, we introduced and summarized the structure and properties of 2D materials (MoS_2, graphene, and h-BN). In Section 3, the theoretical calculation methods of Mode I, Mode II and Mode III were illustrated. In Section 4, the experiments and theoretical calculation cross points in Mode I, Mode II and Mode III were discussed in detail. The results predicted by theoretical calculation were also described. In Section 5, the future of DNA sequencing by 2D materials nanopore, especially the role of theoretical calculations in this research field in future was discussed.

2. Brief introduction of 2D materials

2D Materials, in which only one dimension restricted, are crystalline materials consisting of a single layer of atoms. 2D crystal was thought to be unstable in nature for a long time until 2004 when graphene, a one-atom-thick honeycomb structure composed of carbon atoms, was successfully prepared (Novoselov et al., 2004). Up to now, as schematic shown in Fig. 2, hundreds of 2D materials have been discovered, and most of them are simple substances from group-IV or binary compounds including metal chalcogenides and complex oxides from group III–V elements (Butler et al., 2013). Due to unique electronic and mechanical properties, 2D materials are expected to have a significant impact on a large variety of applications, ranging from electronics to high performance sensors, gas separation, catalysis, support membranes and so on (Xu et al., 2013). As one atomic layer material with comparable thickness to DNA base pair stacking distance of ~3.4 Å, 2D material nanopore is a promising device for DNA sequencing. However, there are still some disadvantages for DNA sequencing by 2D material, especially the detection accuracy is