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Review

Chemistry

Development of solid-state nanopore fabrication technologies

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Abstract As the key components of nanopore-based nucleic acid sequencing systems, nanopores have drawn more and more scientific interests over these years. Although most of the early nanopore-based sequencers adopted biological nanopores, solid-state nanopores have been gradually growing in popularity due to their increased robustness and durability, control over pore geometry and surface properties, as well as compatibility with the existing semiconductor and microfluidics fabrication techniques. Besides acting as a platform for biomolecular analysis, solid-state nanopores also have great potential in many other fields such as near-field optics, nanostencil lithography and ionic logic circuitry, due to the possibility of parallel massive production. Therefore, many approaches for the fabrication of solid-state nanopores have been developed. This paper reviews the typical solid-state nanopore fabrication techniques reported to date and compares their advantages and disadvantages. The specific applications of each kind of solid-state nanopores are also summarized based on the carefully analysis of their unique morphologies and properties such as the feature size, inner structure and possibility of massive production.

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SPECIAL TOPIC: Nanopore for DNA Sequencing

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1 Introduction

Since the first demonstration of employing a nanopore for biological studies dates to 1996 [1], nanopore-based sensing has attracted more and more interests all over the world [2, 3]. Especially, nanopore-based DNA sequencing, which is considered to be one of the most promising next-generation sequencing technologies [4, 5], has been named as one of the "10 breakthrough technologies" by MIT Technology Review in 2012 (http://www2.technologyreview.com/article/427677/nanopore-sequencing). Its basic idea is that a DNA molecule passing through a nanopore will block the ionic current in a sequence-specific fashion [1]. Compared with the conventional Sanger chain termination methods, nanopore-based sequencing is theoretically cheaper and faster, because it is label-free and amplification-free, and can read long sections of DNA at once [6–9].

As the key components of any nanopore-based sensors, nanopores may be broadly categorized into two types, biological and solid state. Although the early nanopore-based sensors always adopted biological nanopores, solid-state nanopores have been gradually growing in popularity due to their robustness and durability, control over pore geometry and surface properties, as well as compatibility with the existing semiconductor and microfluidics fabrication techniques [2, 10–12]. These remarkable properties significantly expand the versatility and feasibilities of solid-state nanopores. For example, not only acting through the matured mechanism of ionic current blockage, the solid-state nanopore-based sequencing can also act through the new tunneling current change mechanism [13] and capacitive change mechanism [14], as shown in Fig. 1a. In fact, as high-density arrays of solid-state nanopores can be easily fabricated, they have also been widely used in many other fields such as ion-selective field-effect transistors (ISFETs) [15], nanostencil lithography [16, 17] as well as near-field optics [18], as shown in Fig. 1b–d.

There are many techniques to fabricate solid-state nanopores, nanopore arrays and nanoporous materials. In this paper, the development of several typical nanopore fabrication techniques and the most recent advancements were carefully reviewed. The actual and potential applications of different nanopores fabricated with different techniques were concluded and recommended, based on the careful analysis of their unique fabrication processes and nanopore geometries.

2 Ion and electron beams drilling and sculpting of nanopores

Directly "drilling" nanopores to the desired size with focused ion or electron beam is conceptually the most straightforward nanopore fabrication method. However, practical realization of controlled nanometer-scale drilling has been challenging, especially for focused ion beam (FIB). The discovery of controllable nanopore shrinking and enlarging under the exposure of defocused ion beam, namely the ion beam sculpting, made it possible to fabricate solid-state nanopores with nanometer control for the first time. Then, similar effects were found with the defocused electron beam, which was defined as electron beam sculpting. With the improvement of equipment and operation techniques, as well as introduction of new materials such as graphene and molybdenum disulfide (MoS_2), focused electron beam drilling has grown to be the predominant method to prepare sub-10-nm solid-state nanopores.

2.1 Focused ion beam drilling of nanopores

The history of using FIB to drill sub-100-nm solid-state nanopores can date back to two decades ago. Over these years, lots of nanopores with different shapes (e.g., circular and rectangular) have been directly drilled in various membranes, from insulating materials to conductive and semi-conductive materials [19–21]. For example, we have drilled nanopores in suspended graphene membranes with a FIB, as shown in Fig. 2a. However, the typical feature dimensions of such FIB-drilled pores are always above 10 nm, even if an in situ back-face detector for endpointing is added to the FIB system [25]. Fine-tuning of the pore size by FIB drilling is difficult, and the resolution that can be achieved is limited by the beam diameter, beam shape and re-deposition, especially for thick membranes [22].

With the help of a specific and dedicated FIB nanowriter, Gierak et al. [22] firstly drilled sub-10-nm nanopores in 20-nm-thick SiC membranes, as shown in Fig. 2b. Recently, they have expanded the nanopore materials to Si, SiN and SiO_2, as well as in graphene and hexagonal boron nitride (BN) [26]. Another interesting progress of FIB-drilled nanopores is the use of a helium ion microscope

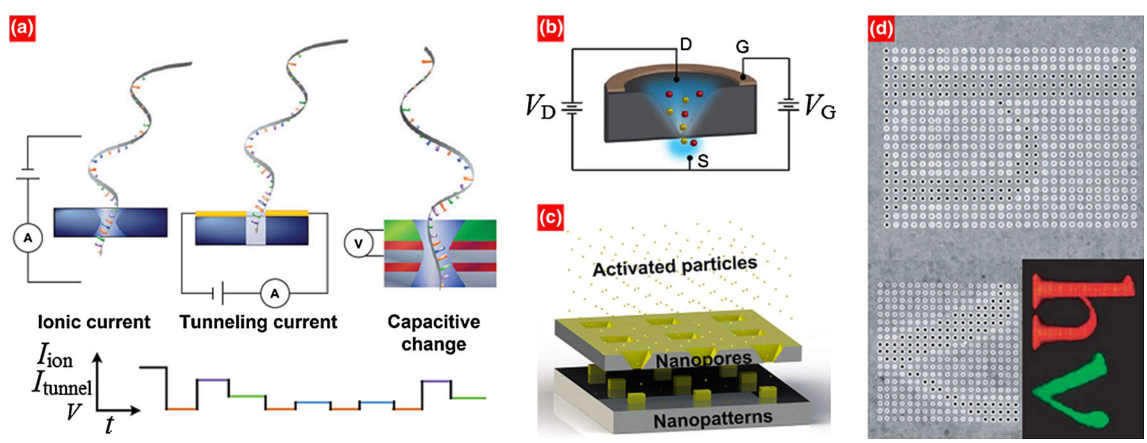

Fig. 1 (Color online) Several typical applications of solid-state nanopores. **a** DNA sequencing based on different schemes. Top, from left to right: direct DNA sequence readout via measurements of ionic current [1], tunneling current [13] and voltage differences [14]. Bottom: highly simplified cartoon illustration of how each of the four different bases of DNA might produce characteristic time series recordings in each of the above schemes. **b** Schematic of a conical nanopore-based ion-selective field-effect transistor. Reprinted with permission from [15], Copyright 2012, American Chemical Society. **c** Schematic of the nanostencil lithography (surface patterning) using pyramidal nanopore arrays as nanostencils (nanotemplates). Reprinted with permission from [16], Copyright 2014, American Chemical Society. **d** Nanopores in a dimple array generating the letters "hv" in light transmission. Reprinted with permission from [18], Copyright 2007, Nature Publishing Group