

NANOPORES

Tiny holes with great promise

Sensors that combine solid-state nanopores and nanowire field-effect transistors can be used to detect single DNA molecules quickly and with high sensitivity.

Dario Anselmetti

Nanopores have potential applications in biosensing, diagnostics and separation, and are based on a remarkably simple concept — threading single molecules through a nanometre-sized hole in a solid-state, biological or biomimetic membrane. The nanopore sensing approach can be traced back to a device called the Coulter counter, which was originally used to detect cells and particles. This device consists of two chambers that are filled with electrolyte solutions and are separated by a membrane that contains one or more nanochannels: when a voltage is applied across the membrane, an ionic current through the membrane can be detected. However, when electrically charged molecules are present, they temporarily modulate the ionic current as they pass through the membrane, which allows them to be detected. The advantages of this nanopore technology are single-molecule sensitivity at low cost and label-free detection without molecular amplification. It is no surprise, therefore, that nanopore-based approaches to single-molecule biosensing, and in particular DNA sequencing, have been explored by many research groups over the past decade, and that proof of principle experiments have recently demonstrated single-base resolution and differentiation^{1–3}.

In the race for the '\$1,000 genome'^{4,5} — a point at which sequencing could become an essential part of an individual's medical care (personalized medicine) — nanopore sequencing techniques compete with fluorescent-based approaches, such as advanced capillary electrophoresis and zero-mode waveguide devices^{6,7}. In nanopore sequencing two approaches have been primarily followed: the use of genetically engineered membrane-bound pore proteins^{8–10} and the use of solid-state nanopores¹¹ with integrated molecule detection^{12,13}. However, reaching the goal of the \$1,000 genome with the solid-state nanopore approach will require significant improvements in our ability to measure the fast translocation of molecules through the nanopores. In the Coulter set-up, the ionic currents through nanopores are typically very small (picoamperes), which

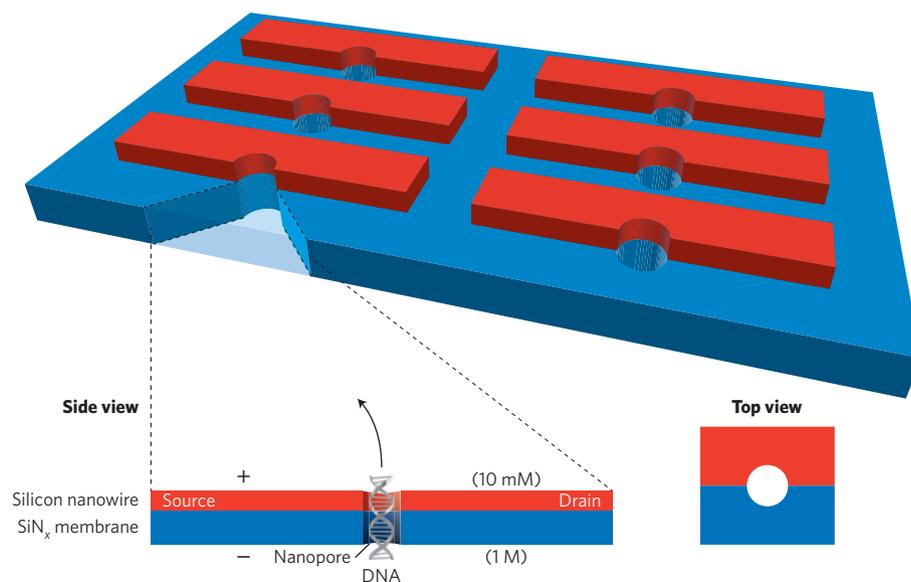


Figure 1 | Detection of DNA translocation with a nanowire-nanopore sensor. The schematic shows an array of six nanowire-nanopore sensors in a single membrane, including a side and top view of an individual sensor. A short silicon nanowire (shown in red) — nanofabricated on top of the membrane (blue) — connects the source and drain terminals of an individual nanowire field-effect transistor (FET). A nanopore located at the edge of the nanowire connects the fluid compartments on either side of the membrane (which are held at different salt concentrations) and acts as the FET gate terminal. The translocation of the DNA molecules through the nanopore causes changes in the potential around the nanopores, which modulates the conductivity of the nanowire. (DNA image: © istockphoto.com/thinkstock)

limits the bandwidth of state-of-the-art current-voltage amplifiers (kilohertz range). However, to analyse a genome quickly, and ideally in less than one day, the translocation speed of a single DNA molecule through a nanopore should be so fast that detection bandwidths above the megahertz range are required. Writing in *Nature Nanotechnology*, Charles Lieber and colleagues at Harvard University, Nanyang Technological University and the National Center for Nanoscience and Technology, China show that highly parallelized solid-state nanopores with integrated sensors could potentially address these issues¹⁴.

Lieber and colleagues have combined solid-state nanopores with silicon-nanowire field-effect transistors (FETs) to create

devices that are capable of sensing single-molecule DNA translocation events with a sensitivity similar to that of ionic-current sensing. However, because the FET signal generated by the device is due to localized electrical potential changes, the bandwidth is potentially up to the gigahertz regime.

The nanowire-nanopore device is composed of a thin silicon nitride membrane separating two fluid compartments (Fig. 1). A 200-nm-long and 50-nm-wide p-type silicon nanowire — nanofabricated on top of the membrane — connects the source and drain terminals of the FET. An approximately 10-nm-wide nanopore located at the edge of the nanowire connects the fluid compartments across the membrane and acts as the gate terminal of the FET.

In a typical experiment, DNA molecules are injected into one of the fluid compartments and a transmembrane voltage of around 2–3 V is applied. The ionic current through the nanopore and the conductance of the nanowire FET are both measured. In contrast to well-established ionic current measurements, which work in all salt concentration ranges (typically 1 M), distinct FET signals could only be detected when the salt concentrations in the two compartments were different (for example, 1 M on one side of the membrane, and 10 mM on the other). However, the experimental bandwidth is directly related to the associated current, and the variations in the current of the FET are ten times larger than those in the ionic current. This suggests that the FET signal can provide higher bandwidth recordings, which could potentially be increased by orders of magnitude by optimizing the dimensions of the nanowire–nanopore devices.

A further important aspect of future biosensing and sequencing applications is the parallel integration of devices into multichannel nanopore arrays¹⁵. To this end, Lieber and colleagues were able to simultaneously record DNA translocation events in an array of three nanowire–nanopore devices. The three FET channels were found to function independently and it should be possible to fabricate working devices in higher numbers and densities. This highlights the other key advantage of the nanowire–nanopore device: namely, operation of a multiplexed nanopore array within a relatively simple and straightforward microfluidic platform.

Although we do not yet have the \$1,000 genome, the nanowire–nanopore approach of Lieber and colleagues has the potential to run in a highly parallel way and with a high intrinsic bandwidth — 1,000 nanopores at 1 MHz, for example. As a result, the technique provides exciting possibilities

for future biosensing and diagnostic applications. □

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References

- Zwolak, M. & Di Ventra, M. *Rev. Mod. Phys.* **80**, 141–165 (2008).
- Branton, D. *et al. Nature Biotech.* **26**, 1146–1153 (2008).
- Venkatesan, B. M. & Bashir, R. *Nature Nanotech.* **6**, 615–624 (2011).
- Service, R. F. *Science* **311**, 1544–1546 (2006).
- <http://www-03.ibm.com/press/us/en/pressrelease/32037.wss>
- Levene, M. J. *et al. Science* **299**, 682–686 (2003).
- Eid, J. *et al. Science* **323**, 133–138 (2009).
- Kasianowicz, J. J. *et al. Proc. Natl Acad. Sci. USA* **93**, 13770–13773 (1996).
- Meller, A. *et al. Proc. Natl Acad. Sci. USA* **97**, 1079–1084 (2000).
- Derrington, I. M. *et al. Proc. Natl Acad. Sci. USA* **107**, 16060–16065 (2010).
- Dekker, C. *Nature Nanotech.* **2**, 209–215 (2007).
- Zwolak, M. & Di Ventra, M. *Nano Lett.* **5**, 421–424 (2005).
- Luan, B. *et al. Phys. Rev. Lett.* **104**, 238103 (2010).
- Xie, P., Xiong, Q., Fang, Y., Qing, Q. & Lieber, C. M. *Nature Nanotech.* **7**, 119–125 (2012).
- Osaki, T., Suzuki, H., Le Piuouf, B. & Takeuchi, S. *Anal. Chem.* **81**, 9866–9870 (2009).

THERMAL MATERIALS

Pulling together to control heat flow

The thermal conductivity of pairs of boron nanoribbons can be switched between high and low values by wetting the interface between the nanoribbons with various solutions.

Chris Dames

The basic challenges involved in understanding and controlling thermal transport at the nanoscale are similar to those in electrical transport: engineering the contact resistance, using nanoscale effects to push the conductivity to extremes (both high and low), and creating nonlinear behaviour such as rectification or switching. Writing in *Nature Nanotechnology*, an interdisciplinary team of researchers led by Deyu Li of Vanderbilt University brings these three threads together by describing a nanoscale thermal switch made from pairs of boron nanoribbons¹. Although various thermal switching mechanisms are known at the macroscale, experimental demonstrations at the micrometre scale and below are rare and often restricted to temperatures of around 1 K (refs 2,3). An effective microscale thermal switch that works at room temperature could prove useful in applications such as device-scale thermal management, thermoelectric energy scavenging or, possibly, information processing⁴.

Li and co-workers¹ used microfabricated thermal stages⁵ to measure the thermal conductivities of three groups of

nanoribbons. First, they found that various samples that contained only single nanoribbons all showed essentially the same thermal conductivity, regardless of how they were made (Fig. 1a). Because these nanoribbons were only 20 nm thick, the extra phonon scattering at the surface reduced the thermal conductivity compared with the value that would be expected in a macroscopic sample.

The second group of samples contained nanoribbons that had been prepared in isopropyl alcohol (IPA), and had then stuck together to form pairs as they dried (Fig. 1b). The thermal conductivity of these double nanoribbons was virtually indistinguishable from that of the single nanoribbons. Therefore, despite the intimate mechanical contact between the nanoribbons in the pairs, the thermal coupling between them was relatively weak, which is typical of interfaces formed by joining two initially distinct structures. Any phonons passing through the interface between the nanoribbons were therefore strongly scattered in all directions.

The third group of samples comprised double nanoribbons prepared in a mixture

of reagent alcohol and deionized water and, surprisingly, they had a higher thermal conductivity than the other two groups of samples (by 45% at room temperature and increasing to 70% at 60 K; Fig. 1c). Using reagent alcohol as the solvent, rather than IPA, resulted in much cleaner interfaces that increased the coupling between the nanoribbons to the extent that many of the phonons were not scattered at the interface and, instead, maintained their momentum along the direction of the temperature gradient. Such strong thermal coupling is normally only seen for atomically intimate interfaces, for example, those prepared by epitaxial growth or evaporated metal contacts, but Li and co-workers argue that van der Waals interfaces (rather than a much stronger covalent or ionic bond) can also result in such large increases in the phonon transmission.

Perhaps the most exciting feature of this work is the evidence that the strength of the coupling between the nanoribbons can be reversibly switched between high and low values (Fig. 1d). Li and co-workers — who are based at Vanderbilt, Southeast