DNA sequencing is an important tool in the research and medicine fields, which can have a profound impact in areas such as caner, human genetics, infections diseases and personal genomics. There is currently a desire to lower the cost of DNA sequencing while simultaneously decreasing the time required for sequencing. The current state of DNA sequencing is largely based on imaging technology. This technology requires the interaction of light or x-rays with specialized nucleotides or other reagents. These requirements limit the advancement of sequencing, as light source machines are often bulky and expensive while specialize nucleotides and dyes deviate from nature.

One technology that consistently decreases in size and cost per unit area is CMOS technology, but how can a CMOS based chip be used? When a nucleotide is added to a fragment of DNA there is a release in hydrogen atoms, causing a shift in the pH of the surrounding fluid. If the change in pH was able to be detected then the event of a nucleotide being incorporated into a DNA strand could also be detected. A device known as an ion-sensitive field-effect transistor (ISFET) does exactly this [2].

An early version ISFET was composed of an oxide sensing layer along with a heavily doped drain and source located beneath. As hydrogen ions are released, interactions with the oxide-sensing layer causes protonation and deprotonation of the OH groups.

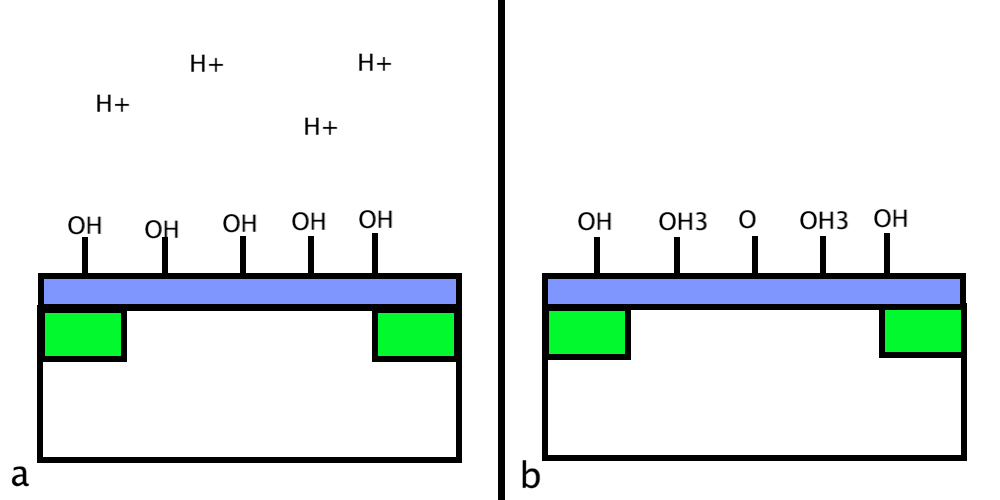


Figure 1 | Oxide Sensing Layer. a. Arrangement of OH groups on oxide-sensing layer before interaction with hydrogen ions. b. Charge accumulation on the oxide-sensing layer after protonation and deprotonation of OH groups.

After the hydrogen bonds interact with the OH groups there is a build up of charge on the oxide-sensing layer. This build up of charge acts similar to the gate voltage of a MOSFET device, enabling a conductive band to be formed between the drain and source allowing current to flow.

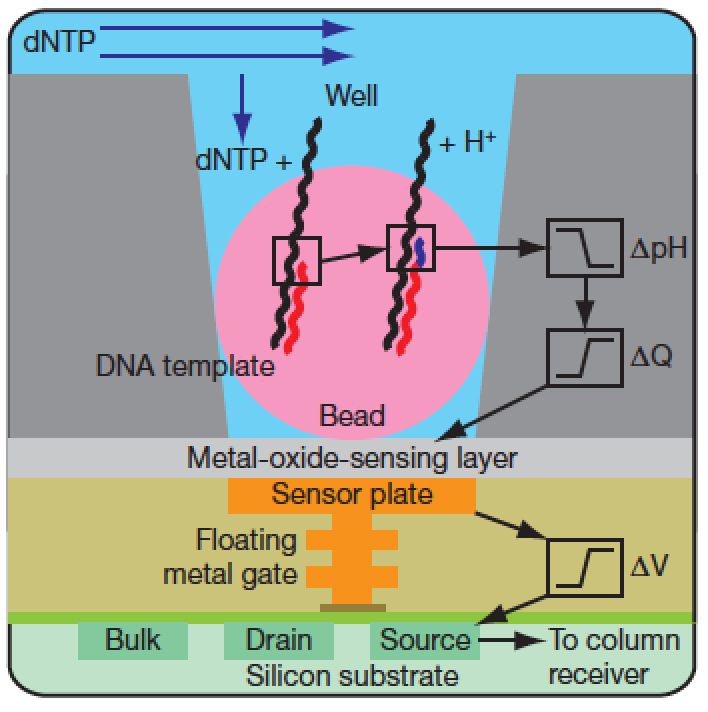


Figure 2 | ISFET device layout. Simplified drawing of a well, a bead containing DNA and the underlying sensor.

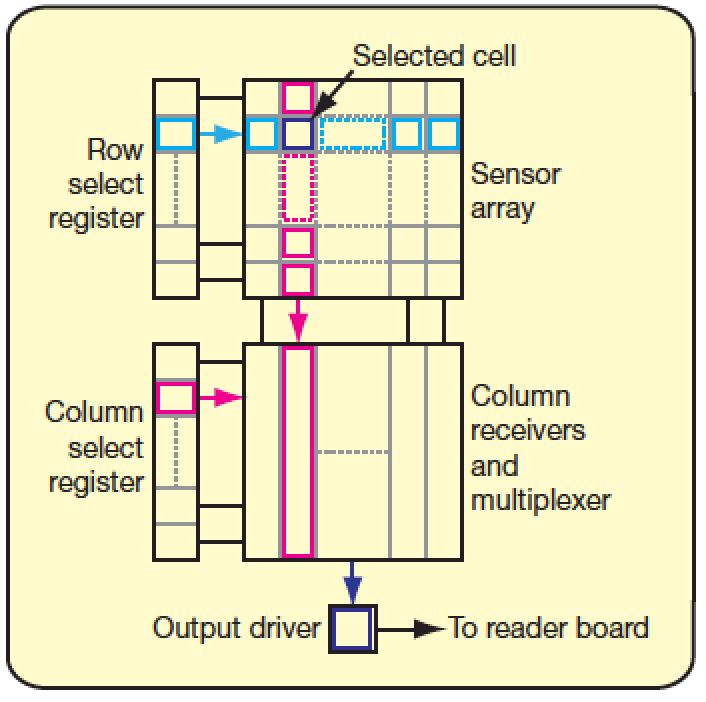
The device presented in this paper is a very large array of ISFETs (Fig. 2) arranged in a two dimensional x andy y pattern. Individual sensors are read with a technique similar to CMOS imagers. Samples are kept stationary by trapping the bead containing the DNA template in a 3.5um-diameter well. At the bottom of each well tantalum oxide provides the sensing surface to detect hydrogen ions. Unlike imaging technology, which gathers many small bits of information to reconstruct the whole picture, each sensor is capable of detecting the nucleotide incorporation event.

Figure 3 | Sensor layout. Each sensor is indexed through a row select register followed by a column select register.

Although not stated specifically the technology used to address each of the sensors is most likely a charge-coupled device which is able to shift charge from one location to another. These devices are very well studied and compatible with CMOS fabrication so their implementation would not have been an issue. One alternative to reading the sensor values independently would be to “collect” all the charge present on the device and use this total charge to identify nucleotide incorporation. This would average out the results from all the sensors and reduce the amount of computation required.

One limitation that is evident is the size of the sensor is constrained to the size of the 3.5um bead. An ISFET can be fabricated with a smaller footprint that the bead so if there was a way to eliminate the need for the bead these devices could become more dense. One possible improvement would be to use a smaller bead with a smaller well however there would be a limit as the beads must remain in the well during each flow cycle of nucleotides. As the bead size decreases the well depth would have to decrease to ensure only one bead enters the well at a time. When the well depth becomes to shallow the bead would be flushed out.