

Opinion piece



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Authors for correspondence:

Christofer Toumazou

e-mail: c.toumazou@imperial.ac.uk

Pantelis Georgiou

e-mail: pantelis@imperial.ac.uk

A new era of semiconductor genetics using ion-sensitive field-effect transistors: the gene-sensitive integrated cell

Christofer Toumazou¹, Tan Sri Lim Kok Thay² and Pantelis Georgiou¹

¹Centre for Bio-inspired Technology, Department of Electrical and Electronic Engineering, Imperial College, London, UK

²Genting Group, Jalan Sultan Ismail, 50250 Kuala Lumpur, Malaysia

Semiconductor genetics is now disrupting the field of healthcare owing to the rapid parallelization and scaling of DNA sensing using ion-sensitive field-effect transistors (ISFETs) fabricated using commercial complementary metal-oxide semiconductor technology. The enabling concept of DNA reaction monitoring introduced by Toumazou has made this a reality and we are now seeing relentless scaling with Moore's law ultimately achieving the \$100 genome. In this paper, we present the next evolution of this technology through the creation of the gene-sensitive integrated cell (GSIC) for label-free real-time analysis based on ISFETs. This device is derived from the traditional metal-oxide semiconductor field-effect transistor (MOSFET) and has electrical performance identical to that of a MOSFET in a standard semiconductor process, yet is capable of incorporating DNA reaction chemistries for applications in single nucleotide polymorphism microarrays and DNA sequencing. Just as application-specific integrated circuits, which are developed in much the same way, have shaped our consumer electronics industry and modern communications and memory technology, so, too, do GSICs based on a single underlying technology principle have the capacity to transform the life science and healthcare industries.

1. Introduction

The ion-sensitive field-effect transistor (ISFET) was first proposed in the 1970s as a device for neurophysiological monitoring [1], just over a decade after the introduction

of integrated circuit technologies by Jack Kilby of Texas Instruments in 1959 and complementary metal-oxide semiconductor (CMOS) logic by Frank Wanlass of Fairchild Semiconductor in 1963. Since those early circuits of just a handful of transistors, CMOS technology has seen exponential growth, doubling the number of devices that can be integrated onto a silicon wafer according to Moore's 1965 law [2], and has led to the large-scale integrated semiconductor microchips which shape our modern world. Yet, the ISFET has had limited commercial success beyond its use as a glass-free stand-alone pH meter for industrial and environmental applications, partly owing to its widely reported sensor drift and sensitivity to temperature, meaning that regular calibration is required, and partly owing to the fact that the ISFET system spans two phases, both solid state and liquid, which makes experimental and theoretical work very demanding and requires a convergence of knowledge and techniques in electrochemistry, materials, semiconductor device physics and electronics.

The work of Toumazou & Purushothaman [3] introduced the perfect application to overcome the ISFET's first challenge of sensor drift and temperature sensitivity, and that was to apply the device to the measurement of discrete changes of signal which arise from the result of a specific chemical reaction. The work described the detection of nucleotide incorporations using ISFETs, applied both to DNA sequencing, where the time and magnitude of the pH change can be used to identify sequential DNA insertions, and to single nucleotide polymorphism (SNP) detection.

CMOS-based technology has clear advantages for implementing systems required for portable, low-cost, high-density systems, which will have a huge impact on healthcare in the years to come [4]. Particularly so for the area of genomics, whereby we are already seeing mainstream technology developed for point-of-care diagnostics as well as DNA sequencing offering huge potential in the areas of drug development, medical diagnosis and genomic research.

In this paper, we present an overview of ISFET technology and its implementation in CMOSs, which through Moore's law scaling is now paving the way for next-generation DNA sequencing technology. We introduce the new concept of the gene-sensitive integrated cell (GSIC), which can now allow integrated design of these systems, combining semiconductor devices and DNA chemical reactions for both detection and sequencing.

2. Moore's law and DNA sequencing

The National Human Genome Research Institute has tracked the costs of sequencing the human genome ever since it was first decoded in 2001 [5]. As in electronics, where we relate Moore's law with a doubling of transistors per chip every year, and therefore computing power, a similar association has been followed in genetics, showing that the cost of sequencing the human genome was halving every year [5] (figure 1). This trend was being followed until 2008, when DNA-sequencing methods shifted from conventional Sanger-based (dideoxy chain termination sequencing) to next-generation sequencing methods which would allow the detection of DNA and sequencing to occur in parallel. This has caused a rapid decrease in the cost of sequencing that is ultimately being pushed towards the \$1000 genome, which would allow affordable and rapid sequencing to be applied in healthcare.

Next-generation sequencing platforms are all based on the parallel detection of DNA hybridization. The first-generation machines, which came into being in 2008 from companies such as Illumina and Roche 454, used sequencing chemistries, which were optically based on fluorescence and therefore difficult to scale. In 2011, however, there was the introduction of semiconductor sequencing, which used a non-optical CMOS-based method for DNA reaction detection based on a technology invented by Toumazou and co-workers [3,6] using ISFET sensors by monitoring of a pH-derived reaction as a result of DNA chain extension using triphosphate nucleotides. A semiconductor sequencing chip was presented [7] with 1.2 million sensors capable of sequencing up to 25 million bases in a 2 h run. The performance and scalability of this method

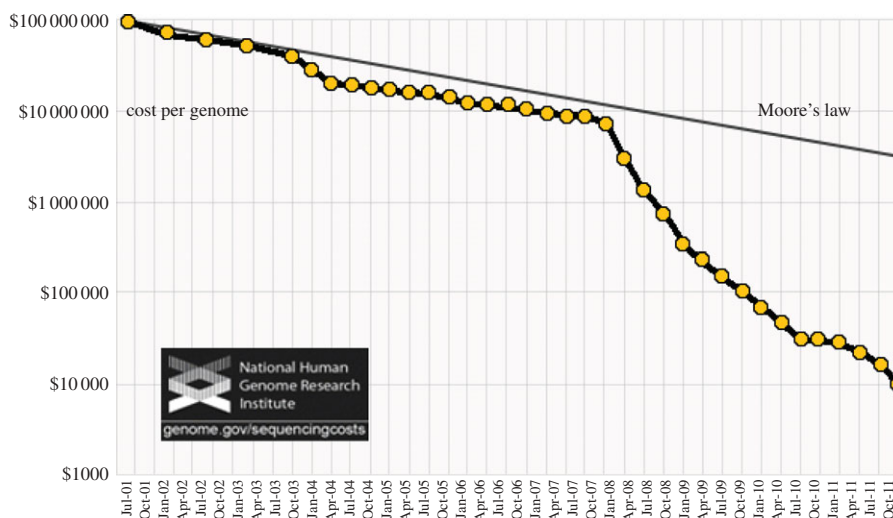


Figure 1. Cost of sequencing the human genome [5]. (Online version in colour.)

was demonstrated by sequencing three bacterial genomes and one human genome with results comparable to current state-of-the-art optical methods.

The ultimate potential of semiconductor sequencing, however, lies in the ability for ISFET sensors to scale with the semiconductor roadmap according to Moore's law [2]. Given that ISFETs are derived from standard metal-oxide semiconductor field-effect transistors (MOSFETs), we are now seeing this trend increase the number of sensors per microchip, ultimately allowing more DNA fragments to be detected and decreasing the cost of sequencing. As Moore's law for DNA sequencing originally dictated the reduction in cost, with ISFET technology it is now dictating the number of sensors per chip, which is in line with its original definition. This convergence will now push forward sensor density and ultimately realize the \$100 genome. We now proceed to give an overview of ISFET sensing technology and its application to sensing arrays over the last decade as a result of this scaling.

3. Ion-sensitive field-effect transistor-based technology

In the early 1970s, Piet Bergveld had the insight to customize a silicon transistor, which at the time was used for the creation of radios and amplifiers, into something which could sense chemical changes owing to release of hydrogen ions [1]. This was called the ISFET. The ISFET was implemented using a standard MOSFET, simply by removing the gate metal oxide and exposing the polysilicon to a solution (figure 2). The result was that the threshold voltage of this device was directly related to the pH of the solution owing to the binding of hydrogen ions arising from the site binding of ions on the insulator surface combined with the formation of a double layer capacitance owing to the Helmholtz plane and Gouy–Chapman layer [8],

$$V_{\text{th(ISFET)}} = \gamma + \frac{2.3\alpha kT}{q} \text{pH} + V_{\text{th(MOSFET)}}. \quad (3.1)$$

Although the ISFET was mainly designed for pH sensing, it has been customized to be able to sense various other analytes, opening it up to a wide range of applications in the life sciences industry. The two most popular derivations from ISFETs are the CHEMFETs (chemical-FETs), which have been used to sense ions in the blood, such as potassium and sodium [9], and the EnFETs (enzyme-FETs), used in diabetes and renal applications by sensing glucose [10] and urea [11].

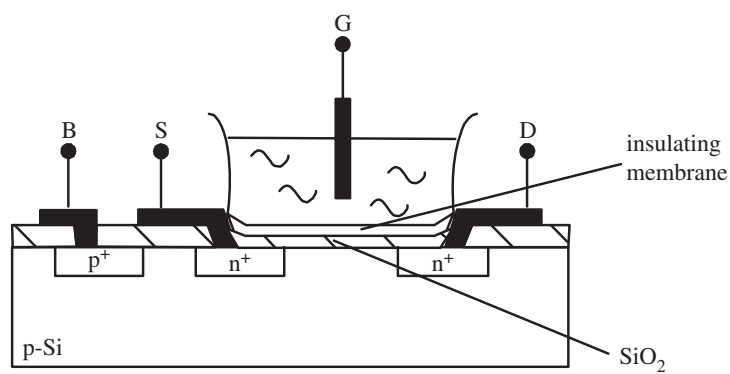


Figure 2. The ion-sensitive field-effect transistor.

Table 1. Comparison of CMOS ISFET arrays over the last decade.

year	tech. (μm)	array size	pixel size (μm)	application	group	ref.
2001	1.2	6 (6×1)	—	blood gas	Leuven	[14]
2004	0.35	4 (2×2)	2.9×6.2	cell culturing	Glasgow	[15]
2005	0.35	256 (16×16)	12.8×12.8	extracellular imaging	Glasgow	[16]
2006	0.18	50 (5×10)	50×50	DNA detection	Stanford	[17]
2008	0.35	33 (3×11)	57.5×57.5	electrolyte imaging	Imperial	[18]
2008	0.35	256 (16×16)	12.8×12.8	extracellular imaging	Glasgow	[19]
2008	0.35	4 (2×2)	12.8×12.8	electrolyte imaging	Glasgow	[20]
2009	0.18	64 (8×8)	20×2	handheld inst.	Imperial	[21]
2009	1.2	256 (16×16)	105.3×81.4	DNA detection	Nagoya	[22]
2010	0.35	40 (40×1)	—	DNA detection	DNAe/IC ^a	[23]
2010	0.35	64 (8×8)	50×50	opto-chemical imaging	Imperial	[24]
2010	0.35	8 (8×1)	30×100	—	Imperial	[25]
2011	0.35	1.5 M	5.1×5.1	DNA detection	Ion Torrent	[7]
2012	0.18	9 (3×3)	10×10	DNA detection	Imperial	[26]
2012	0.35	256 (16×16)	14×14	electrolyte imaging	Glasgow	[27]
2012	0.35	4096 (64×64)	10.2×10.2	electrolyte imaging	Glasgow	[28]
2013	0.35	40 (40×1)	104×34	DNA amplification	DNAe/IC ^a	[29]

^aImperial College London.

Following on from the initial success of the ISFET as a discrete pH sensor, its implementation was demonstrated in a CMOS in 1988 by Wong & White [12] and in 1999 in an unmodified CMOS by Baussels *et al.* [13], paving the way for a new area of biomedical systems, whereby the ISFET could be combined in a single chip with integrated circuits allowing intelligent signal processing in addition to advantages such as scalability, low cost of manufacture and miniaturization by leveraging on the economies of scale of the semiconductor industry. This was made possible by the extension of the polysilicon gate of the device to the top metal, which contacts a pH-sensitive insulating membrane. This development has paved the way for a decade of tremendous integration of ISFETs in CMOSs, creating arrays for a variety of applications ranging from blood analysis, extracellular imaging and DNA detection, the works of which are summarized in table 1 for the leading research groups around the world.

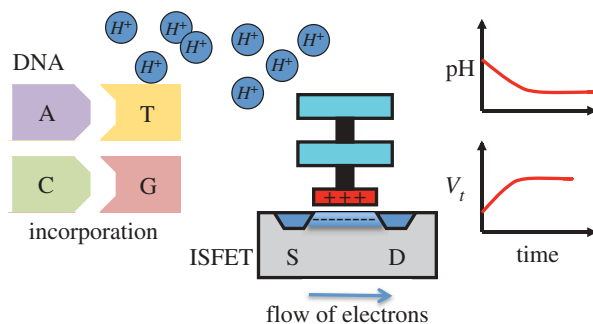


Figure 3. ISFET used for reaction monitoring of a DNA base pair incorporation. (Online version in colour.)

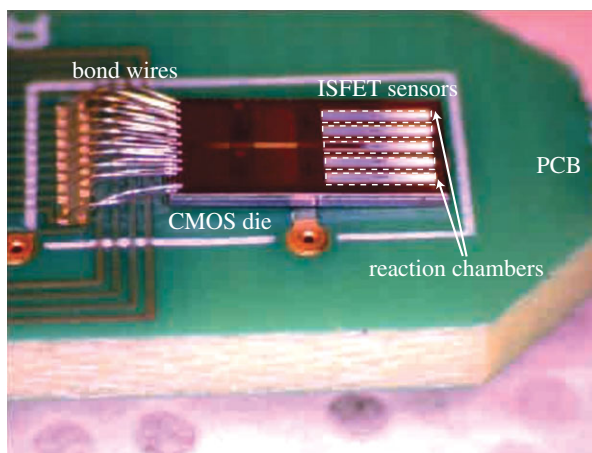


Figure 4. An ISFET-based CMOS microchip used for the detection of SNPs. PCB, printed circuit board. (Online version in colour.)

Implementation in CMOSs, however, leads to many technical challenges for sensor function, primarily owing to drift and threshold voltage mismatch, making the use of CMOS ISFETs as stand-alone sensors very challenging [8]. It was apparent that this technology was more tailored to monitoring a change rather than an absolute reaction, and in 2001 the ideal application for this in DNA detection was introduced [6,30].

DNA base pair incorporation, which is the fundamental procedure used for DNA combination and has therefore inspired sensing technologies for DNA sequencing and SNP detection, is by nature a discrete Boolean event which causes a reaction change when there is a match between a nucleotide and its complementary base pair (A matches with T, and C with G), as shown in figure 3. The combination of bases in the presence of an enzyme called DNA polymerase releases protons and pyrophosphate, causing changes in pH. pH change owing to the incorporation can thus be monitored, giving a positive or negative indication of base pair incorporation just by observing whether a reaction change has occurred or not [31].

This pH releasing method has now paved the way for new-wave genomic technology, which until recently relied on large optical instruments to do the detection through fluorescent labelling. Implementation of such systems using CMOS-based ISFET technology with separable reaction chambers, shown in figure 4, allows label-free, portable, real-time detection to be realized using scalable, cost-effective solutions, which are ideally suited for point-of-care diagnostics as well as DNA sequencing.

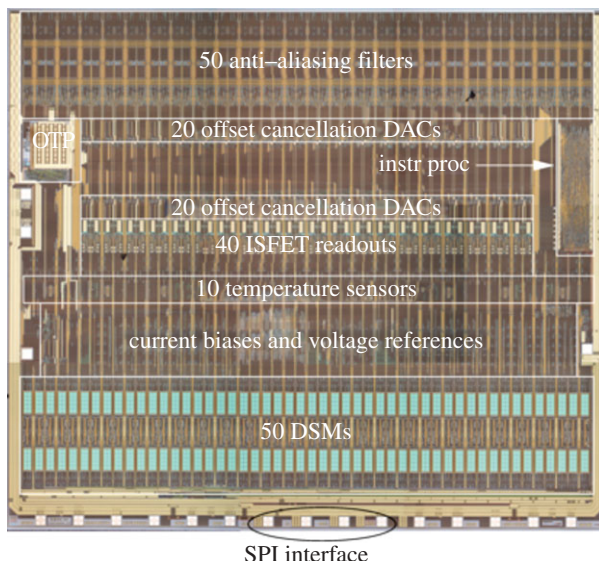


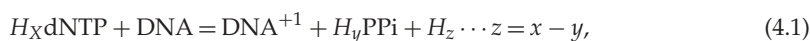
Figure 5. A complete DNA system-on-chip [23]. DAC, digital to analogue converter; instr proc, instruction processor; DSM, delta sigma modulator; SPI, serial peripheral interface. (Online version in colour.)

As an example, in [23] a full system on a chip in a CMOS measuring 5.5×4.7 mm (shown in figure 5) was presented comprising an array of 40 ISFETs capable of identifying up to 19 SNPs. What is more, the combination of sensors and integrated circuits in a CMOS allowed the implementation of integrated readouts to increase the dynamic range as well as temperature sensors and heaters for actuation of the system, used to control conditions in the reaction chambers where the DNA samples were placed (figure 5). This was shown to be the first system capable of real-time concurrent DNA amplification and detection, a process termed pH polymerase chain reaction (PCR) [29].

4. The gene-sensitive integrated cell

Detection of single or multiple DNA insertions is possible by nucleotide binding using deoxynucleotide triphosphates (dNTPs) and DNA polymerase. Sequencing of individual base pairs in a strand of DNA owing to nucleotide incorporation may cause a change in pH owing to proton production from the hydrolysis of dNTP during the DNA extension. Detecting this change in reaction serves as a positive marker for that nucleotide, therefore confirming its presence in that strand of DNA. This unique reaction chemistry can be applied for single-base detection in applications such as SNP detection or DNA sequencing, multi-base detection in applications such as homopolymerism detection in sequencing or genotyping and clonal amplification such as PCR.

The single base pair incorporation may be described by the following reaction, which is also shown pictorially in figure 6:



whereby DNA represents the target stranded DNA and $H_X \text{dNTP}$ represents the triphosphate nucleotide, which can be any of the four bases (dATP, dCTP, dTTP and dGTP). After binding of the dNTP, the DNA strand is extended by one nucleotide, represented as DNA^{+1} and the release of pyrophosphate $H_Y \text{PPi}$ and hydrogen ions H_Z . This reaction is in a unique dynamic equilibrium whereby the number of hydrogen ions released, z , is a function of those bound to the original dNTP, x , and those consumed by the pyrophosphate, y [29].

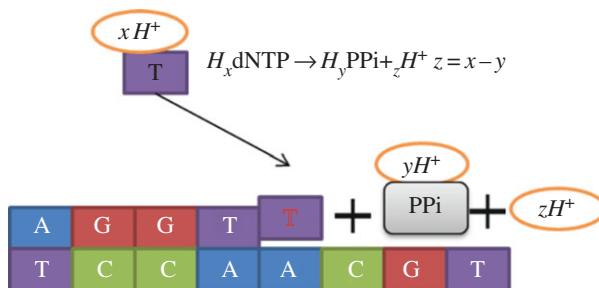


Figure 6. DNA extension chain releasing protons. (Online version in colour.)

Considering now that a change in pH is a function of the protons generated and the buffer capacity, which in itself is a function of pH, we may generalize that a change in solution pH in the reaction chamber may be given by

$$\Delta \text{pH} = \frac{H_z}{\beta}. \quad (4.2)$$

There are two potential mechanisms for increasing the amount of protons given from a DNA base pair incorporation. This can be through either multiple base incorporation on consecutive bases in a single strand, which we have defined as an increase in A_1 , or incorporation on multiple copies of DNA through clonal amplification, which we have defined as an increase in A_2 , or even a combination of the two. This allows us now to define a unified equation for the pH change which takes into account both the number of insertions and the number of copies,

$$\Delta \text{pH} = A_1 \cdot A_2 \frac{H_z}{\beta}. \quad (4.3)$$

This generic equation can now define the pH change in a variety of DNA detection processes ranging from sequencing through to SNP detection. For example, a sequencing by synthesis approach, which would require sequential insertions of one base at a time on a single strand, can have $A_1 = 1$ and $A_2 = 1$. Alternatively for a SNP detection, we can have a single insertion on a strand of DNA, $A_1 = 1$, but multiple copies of this to boost the signal, $A_2 \gg 1$.

With such a unique discrete chemistry in place, we can now define an integrated cell capable of sensing genetic chemistries which we shall call the GSIC. Transduction of the pH signal from the chemical reaction to an electronic system is possible in the GSIC owing to the realization of ISFET chemical sensors in CMOSs [13]. ISFETs are ideal candidates for implementing GSICs because they may be created using standard MOSFETs, offering a unique relationship between the chemical reaction and the electrical characteristics of the device. Therefore, they can become part of any integrated circuit.

The cross section of a GSIC is shown in figure 7. In this arrangement, a CMOS microchip, with an integrated microfluidic assembly on the top for containing a chemical sample, contains embedded ISFET sensors to detect a pH change in addition to integrated circuits for instrumentation and feedback through the actuation layer [29]. The ISFETs in this implementation are created using a standard MOSFET from a given CMOS technology, with the gate oxide of the device extended to the top metal passivation which acts as the sensing layer. The protons then modulate the charge distribution in the channel of the ISFET, changing the threshold voltage of the device. A change in ionic concentration can thus be measured by observing the threshold voltage of the transistor.

(a) A gene-sensitive integrated cell macromodel

When the ISFET is biased with a stable reference electrode (typically Ag/AgCl), ions in solution bind to the passivation causing an accumulation of charge, which in turn modulates the threshold

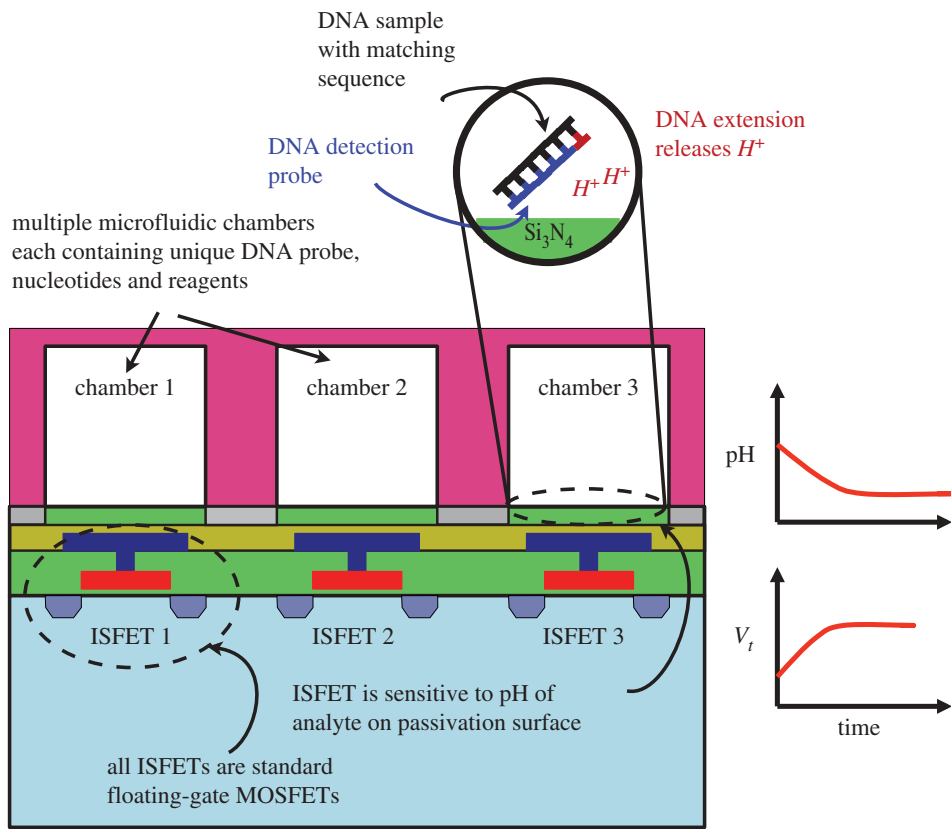


Figure 7. Gene-sensitive integrated cell. (Online version in colour.)

voltage of the device [1]. This results in a dependence of the ISFET threshold voltage to pH, which can be observed as a shift in the threshold voltage of the device. The expression for the threshold voltage is typically defined as

$$V_{\text{th(ISFET)}} = V_{\text{chem}} + V_{\text{th(MOSFET)}} \quad (4.4)$$

and

$$V_{\text{chem}} = \gamma + 2.3\alpha U_t \text{pH}, \quad (4.5)$$

where $V_{\text{th(MOSFET)}}$ is the threshold voltage of the intrinsic MOSFET from which the ISFET is made and V_{chem} (4.5) is a grouping of the chemically related terms, including pH [8], where U_t is the thermal voltage of the device, γ is a grouping of non-chemically related potentials and α is a number ranging from 0 to 1, describing the reduction in sensitivity from the Nernstian response, typically 59 mV/pH. This allows for a more intuitive description of the ISFET characteristics as it contains a term relating to the pH of the electrolyte.

We can now unify the equation of threshold voltage of the ISFET with the DNA base pair reaction by combining equations (4.6) and (4.3) and taking the first derivative to calculate the change in pH,

$$\Delta V_{\text{th(ISFET)}} = \frac{2.3\alpha kT}{q} \Delta \text{pH} \quad (4.6)$$

and

$$\Delta V_{\text{th(ISFET)}} = A_1 \cdot A_2 \frac{2.3\alpha kT}{q} \frac{H_z}{\beta}. \quad (4.7)$$

The implementation of the GSIC, whose generic equation is now defined by equation (4.7), can now be represented by the macromodel shown in figure 8. This combines both the ISFET

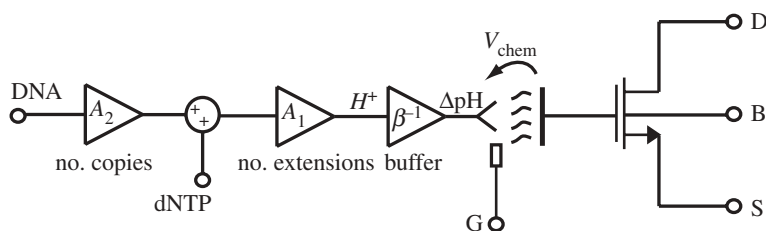


Figure 8. Gene-sensitive integrated cell macromodel.

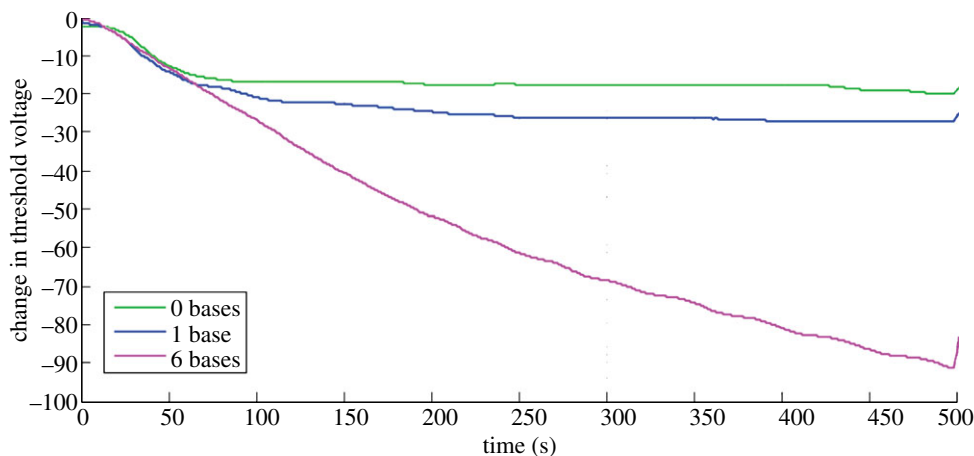


Figure 9. DNA base pair incorporation reaction for 0 bases, 1 base and 6 bases. (Online version in colour.)

characteristics, taking as an input the gate voltage G , and the reaction chemistry of DNA, taking as inputs the target DNA and dNTP used for incorporation, and through a change in pH giving as an output a change in the threshold voltage of the transistor, while combining the tuneable gain terms, A_1 and A_2 , and the buffer capacity, β , making it applicable to a wide cohort of genetic applications.

We now proceed in explaining how the GSIC can be used to realize both the multi-base extension in DNA and clonal amplification.

(b) Multi-base extension

Multi-base extension in DNA may occur when we have multiple successive identical nucleotides such that the dNTP will cause multiple incorporation. This can be seen by the reaction amplitude shown in figure 9 for 0, 1 and 6 consecutive base pair incorporations. Multi-base incorporations can cause an increase in the hydrogen ion production through the multiple insertions.

In this experiment, a 0.03 pH change was detected for one base insertion with about a fourfold increase when six bases were incorporated. This can be viewed as an amplification of the pH signal through a gain which relates to the number of insertions. Six insertions in this case would result in $A_1 = 4$, with $A_2 = 1$ in equation (4.3) as we have a single strand of DNA.

(c) DNA amplification

In most clinical applications, the starting quantity of DNA is relatively low, and it is desirable to amplify the DNA before adequate detection or quantification can be accomplished. To do so, one

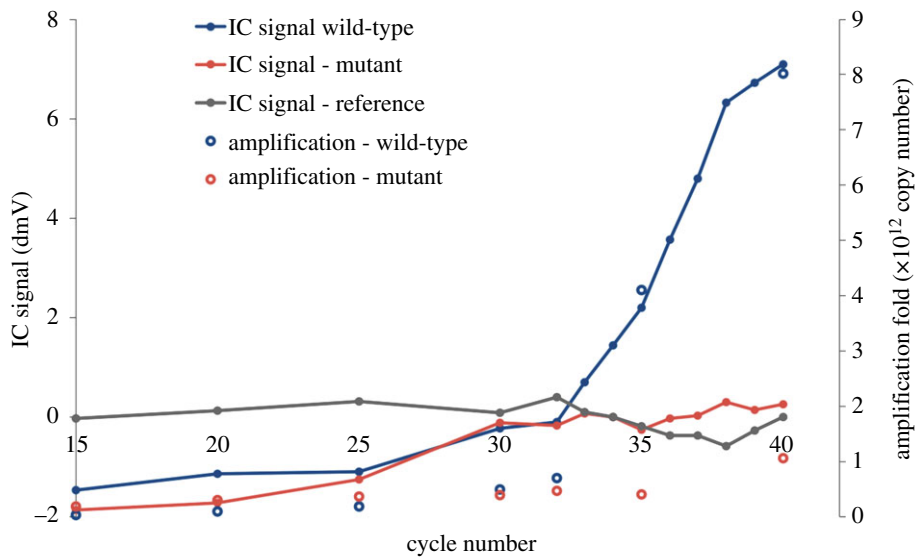


Figure 10. pH amplification through multiple copies of DNA. IC, integrated circuit. (Online version in colour.)

Table 2. Input parameters to tailor the GSIC to a variety of applications.

application	A_1 no. insertions	A_2 no. copies
single-base insertion (sequencing, SNP detection)	1	1
multi-base detection (sequencing, genotyping)	4 (six bases)	1
real-time amplification (all of the above)	1	13.63

possible mechanism is to pre-prepare and amplify the DNA first, which entails running a PCR creating multiple copies of the same DNA, and subsequently detecting the genetic information at the endpoint in a separate process.

Figure 10 shows an example of this, whereby multiple PCR thermocycles produce multiple copies of DNA, which incidentally cause an amplification of hydrogen ions produced, owing to dNTP incorporations on the multiple DNA strands which increase exponentially after each cycle. This was conducted using a CMOS-based Si_3N_4 ISFET pH sensor causing about a 14-fold increase in hydrogen ion production over 40 cycles [29]. In a similar fashion to multi-base extension, we can now define this procedure as something which amplifies the hydrogen ion production, through a gain, A_2 , which is related to the number of copies of DNA produced by the number of PCR cycles it has undergone. In the specific experiment of figure 10, this may be defined as $A_2 = 13.63$ for 40 cycles and one insertion, $A_1 = 1$.

A summary of the potential utilization of the GSIC for single-base extension, multi-base extension and DNA amplification is shown in table 2.

With the GSIC we can now accurately describe, simulate and build circuits and systems which implement the detection of single-base, multiple base and multiple copy nucleotide insertions. This now allows the formulation of next-generation DNA sensing technology for both point of care and sequencing. This will enable, for the first time, real-time targeted sequencing with

a rapid time to results that has the potential to focus on clinically relevant genes of a specific condition or disease, decreasing time to diagnosis in a cost-efficient way which can impact on disease treatment and cost of healthcare.

5. Conclusion

Moore's law has successfully set a trend for the microelectronics industry to increase the number of transistors per silicon microchip, leading to a revolution not just in computational power but also in life sciences by driving down the costs of DNA sequencing, through semiconductor-based platforms using ISFET sensors. We have shown that we can now begin to think of the ISFET as a more versatile device that combines both DNA sensing capability and electrical functionality, which is known as a GSIC. GSICs are shown to capture chemical reaction monitoring scenarios for single-base, multiple base and multiple copies of DNA. This versatile device can now be used to design next-generation semiconductor genetic platforms. Just as application-specific integrated circuits have shaped our consumer electronics industry and modern communications and memory technology, so, too, do GSICs have the capacity to transform the life science and healthcare industries. With this, we shall be able to carry out rapid targeted genetic sequencing potentially impacting on healthcare for years to come.

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