Institution:	**Imperial College London**
Unit of Assessment:	**13A – Electrical & Electronic Engineering**
Title of case study:	**Case 3 – Ultra-Low-Power Electronics for Healthcare Applications**

1. Summary of the impact

Professor Chris Toumazou FRS and his team at Imperial College have developed biomedical technologies based on ultra-low-power CMOS and ISFET electronics to provide the medical community with the means to rapidly diagnose, monitor, and treat diseases with confidence and at low cost. Since 2008, the impact of this research has been to:

- I1) spinout a start-up company DNA Electronics (DNAe) to deliver point-of-care products to quickly recognize genetic diseases and identify potential poor drug interactions;
- I2) enable Life Technologies (formerly Ion Torrent) to develop the Personal Genome Machine (PGM) that have generated $100m in sales (in the 18 months since its launch) using DNAe's core semiconductor sequencing IP;
- I3) save lives by using the PGM in clinical and public health applications;
- I4) spinout a second start-up company (Toumaz) that has released SensiumVitals®, a FDA-approved and CE-marked ultra-low power system for wireless monitoring of patient vital signs;
- I5) provide early warning of adverse physiological events in clinical settings using the SensiumVitals® platform resulting in improved quality of patient care and reduced demand on intensive care provision in hospitals internationally.

2. Underpinning research

Over the last decade we have seen a convergence of semiconductor technology into the world of healthcare, providing new solutions for early detection, diagnosis and therapy of disease. Disruptive semiconductor technology in healthcare relies upon leveraging CMOS technology in novel and unusual ways, for example, designing custom VLSI structures for biosensing, or by exploiting the underlying device physics for energy efficient low precision analogue processing. The biomedical electronics team at Imperial led by Professor Christofer Toumazou has produced key advances in this area as described below.

There are two aspects to the underpinning research for this case study. The first relates to point-of-care diagnostics for the detection of genetic sequences. This field requires biosensing platforms that are sensitive to the target sequence, are fast, can be mass-manufactured, and are disposable. Conventional lab-based methods of detecting DNA sequences rely on optical methods; typically by the addition of fluorescent tags to the target DNA that in turn latches onto a DNA probe sequence only if there is a match between the two. Our research this past decade has developed a pioneering all-electrical approach that does not require tagging of DNA. The principle of **label-free electrochemical DNA detection using an ion-sensitive field effect transistor** (ISFET) was originally described in [R1]. This is now referred to in the industry as "next generation semiconductor sequencing".

A problem with electro-chemical sensors is that they are known to suffer from non-idealities and significant variability in parameters such as drift, offset, sensitivity and lifetime. Fabricating them in CMOS makes them cheap, easy to mass-produce, and allows integration with electronic circuits, but at the same time further degrades their performance. The breakthrough of our research came from the recognition that such on-chip sensors, although inaccurate for absolute measurement, could be harnessed for relative monitoring, i.e. detecting changes rather than absolute values. Specifically, we engineered methods for achieving **robust on-chip relative pH sensing based on the Ion-Sensitive Field Effect Transistor** (ISFET) in a standard CMOS technology. Through a variety of device, circuit and system innovations, a platform that is low cost, easy to manufacture and reliable has been realized [R2, R3].

The second aspect of the underpinning research has been the reduction of transmitted bandwidth from biosensors. Sensory systems acting on real world data typically consist of an analogue sensor interface with signal conditioning, data conversion, and wireless communication, requiring high bandwidth when transmitting raw data. Our research established how to achieve power reduction by placing local intelligence at the front-end, thus reducing communication bandwidth. Using analogue signal processing prior to data conversion, ultra energy-efficient processing could be achieved but at the expense of variability (i.e. drift) and reconfigurability. These limitations were overcome by combining closed-loop digital calibration to ultra low power analogue circuits thus achieving both energy efficiency and precision [R4, R5]. This ultra low power approach has been demonstrated in a number of applications including the world's first totally implantable cochlear prosthesis. This new prosthesis was independently assessed to reduce power consumption by up to two orders of magnitude compared to the state-of-the-art [R6].

3. References to the research (*References that best indicate quality of underpinning research.)

[R1]* S. Purushothaman, **C. Toumazou**, J. Georgiou, "*Towards fast solid state DNA sequencing*", IEEE International Symposium on Circuits and Systems, (2002), 4, pp.169-172. DOI: 10.1109/ISCAS.2002.1010416

[R2]* L. Shepherd, **C. Toumazou**, "*A Biochemical Translinear Principle with Weak Inversion ISFETs*", IEEE Transactions on Circuits and Systems I: Regular Papers, (2005), 52(12), pp. 2614-2619.DOI: 10.1109/TCSI.2005.857919

[R3] L. Shepherd, **P. Georgiou, C. Toumazou**, "*A novel voltage-clamped CMOS ISFET sensor interface*", IEEE International Symposium on Circuits and Systems (ISCAS 2007), 27-30 pg 3331 - 3334 May 2007. DOI: 10.1109/ISCAS.2007.378224

[R4] O. Omeni, **C. Toumazou**, "*A CMOS micro-power wideband data/power transfer system for biomedical implants",* IEEE International Symposium on Circuits and Systems (ISCAS 2003), 25-28 Vol 5, V-61 - V-64 May 2003. DOI: 10.1109/ISCAS.2003.1206184

[R5] O. Omeni, **E. Rodriguez-Villegas**, **C. Toumazou**, "*A micropower CMOS continuous-time filter with on-chip automatic tuning*", IEEE Transactions on Circuits and Systems I: Regular Papers, (2005), 52(4), pp.695-705.DOI: 10.1109/TCSI.2005.844112

[R6]* J. Georgiou, **C. Toumazou**, "*A 126-μW cochlear chip for a totally implantable system*", IEEE Journal of Solid-State Circuits, (2005), 40 (2), pp.430-443.DOI: 10.1109/JSSC.2004.840959

4. Details of the impact

We now provide details of the 5 aforementioned impacts and their links to underpinning research:

I1) **DNA Electronics** (DNAe) is a start-up company founded by Toumazou to exploit the group's breakthrough in semiconductor-based gene sequencing in [R1, R2, R3]. Since 2008, DNAe has developed two genetic analysis platforms: a DNA sequencing platform suited for laboratory use, and a "point-of-care" platform called Genalysis® which is suited for rapid, lab-free testing by non-expert users [E1].

Life Technologies' Personal Genome Machine® (PGM™) – its core semiconductor sequencing technology is licensed from DNAe.

DNAe now employs over 45 full time staff in the UK, brought in revenue of in excess of £25 million through their licensing and collaboration activity, and won six industrial awards. These include: the BBC Focus award for Innovation, the Elektra European Electronics Industry Award for R&D, and e-Legacy Award for Medical Advances (all in 2009); and three IET Awards for Healthcare, for Emerging Technologies and for Electronics (all in 2010).

I2) DNAe's sequencing platform technology with its associated patents (US7888015, US 7649358, US7686929, US8114591), all based on the underpinning research [R1-R3], was licensed to Ion Torrent Systems [E2] and Roche in 2010 [E3]. Ion Torrent Systems was subsequently bought by Life Technologies Inc. for $725 million. Their first DNA sequencing product based on DNAe's technology [E4], the Personal Genome Machine (PGM), was launched in Q1 2011. In the first 18 months since launch in the first quarter of 2011, 1300 units of the PGM were shipped and generated around $100 million in sales revenue for Ion Torrent [E5]. The fact that the PGM is based on DNAe's technology is corroborated in [E4], stating:

> *"Ion semiconductor sequencing is based on the detection of hydrogen ions released during DNA synthesis. Ion Torrent licensed the technology from DNA Electronics in 2010 and incorporated it into products such as the Ion Personal Genome Machine (PGM)."*

I3) Since its release in 2011, the PGM product is being used for clinical and public health applications, and lives have been saved as a result. For instance, the Beery twins' rare genetic disease, dopa-responsive dystonia, was discovered by DNA sequencing using our technology and has since been treated with appropriate medication [E6]. Another example of the impact of our DNA sequencing technology is demonstrated in combating the German E. Coli outbreak of 2011, which was so serious that at least 26 people died and more than 2,700 have been sickened by the outbreak in at least 13 different countries [E7]. Using the PGM, scientists were able to complete rapidly the process of sequencing the 5.4 million letters of the latest bug's genetic code in only three days [E7]. Previous light beam based DNA sequencers would have taken at least a week to read the code of an organism's genome.

I4) **Toumaz** is a second start-up; founded to exploit the group's research in ultra-low power techniques for wireless physiological monitoring. Since 2008, Toumaz developed the SensiumVitals® platform, a wireless system designed to monitor the vital signs of hospital patients. The system, which exploits the underpinning research in [R4, R5 and R6], comprises of a lightweight disposable wireless patch that monitors a patient's vital signs (heart-rate, respiration and axillary temperature) and then wirelessly communicates this data to doctors and nurses via the hospital's patient monitoring IT system. The SensiumVitals® digital plaster is the first product aimed at the general floor population of a hospital to have received FDA (510k) approval in 2011 [E8] and subsequently received the CE mark in 2013.

Toumaz's FDA approved and CE marked SensiumVitals® digital plaster.

Toumaz is now an AIM-listed company (symbol: TMZ) employing 180 people in five countries (of which approximately half are in the UK), with 2012 year-end assets of GBP 51.9 million, and revenue (pro-forma) of GBP 22.3 million. Toumaz has won numerous awards prior to 2008 and the National Microelectronics Institute (NMI) award in 2009.

I5) The Toumaz SensiumVitals® digital plaster has proven to be beneficial in a clinical setting. In a trial at Saint John's Health Centre in Santa Monica, CA, it was demonstrated that the SensiumVitals® system provided early warnings of adverse physiological events to clinical staff. The study showed that the system enables early detection of deterioration, meaning patients can be treated more quickly and safely. In addition, the device was shown to be better than alternatives for patient recovery because it is lightweight, unobtrusive, and comfortable to wear, and so enables patients to walk around. The system was also shown to integrate well with existing clinical workflows. The development of this new technology is widely believed to be part of a new revolution in healthcare technology [E9]. Toumaz has secured an international distribution agreement for its SensiumVitals® digital plaster from NantHealth Group in the US in Oct 2013. Through an initial order of 250,000 units, the SensiumVitals® digital plaster is being fully adopted first in Accident & Emergency at Hurley Medical Center in Flint, Michigan (US) [E10].

Toumaz SensiumVitals® digital plaster in trials at Saint John's Health Centre (Santa Monica, CA) – http://www.youtube.com/watch?v=uVxO4xh_dDs

In recognition of Professor Toumazou's success "*…. in applying semiconductor technology to biomedical and life-science applications, most recently to DNA analysis*", the Royal Society awarded him the 2013 Gabor Medal (http://royalsociety.org/awards/gabor-medal/).

5. Sources to corroborate the impact

E1) "*Powering Preventative Medicine",* Ken Davies, 27 Sept 2011, Bio IT World. http://www.bio-itworld.com/issues/2011/sept-oct/powering-preventative-medicine.html or https://www.imperial.ac.uk/ref/webarchive/8hf (archived on 26/4/13)

E2) "DNA Electronics Licenses IP to Ion Torrent", GenomeWeb Daily News, 3 August 2010. http://www.genomeweb.com/sequencing/dna-electronics-licenses-ip-ion-torrent. Archived here on 23/10/2013.

E3) "Roche, DNA Electronics Partner on Semiconductor-based Sequencing", GenomeWeb Daily News, 1 Nov 2010. http://www.genomeweb.com/sequencing/roche-dna-electronics-partner-semiconductor-based-sequencing . Archived here on 23/10/2013.

E4) "Advances in DNA sequencing lead to patent disputes", Nature Biotechnology, Vol. 30, pp. 1054–1058, 8 Nov. 2012. http://www.nature.com/nbt/journal/v30/n11/full/nbt.2407.html?WT.ec_id=NBT-201211 DOI: 10.1038/nbt.2407

E5) "Analyst: The Better Desktop DNA Sequencer May be Losing The Marketing War", Matthew Herper, 15 Aug 2012, Forbes. http://www.forbes.com/sites/matthewherper/2012/08/15/analyst-the-better-desktop-dna-sequencer-may-be-losing-the-marketing-war/ or https://www.imperial.ac.uk/ref/webarchive/fkf (archived on 29/4/13).

E6) "Twins thank Biotechnology for the Quality of Their Lives", Darleen Hartley, 2 Feb 2012, Bright Side of News. http://www.brightsideofnews.com/news/2012/2/2/twins-thank-biotechnology-for-the-quality-of-their-lives.aspx or https://www.imperial.ac.uk/ref/webarchive/9hf (archived on 26/4/13).

E7) "Gene Probe Yields E. coli Clue", Gautam Naik and Laura Stevens, 9 June 2011, The Wall Street Journal. http://online.wsj.com/article/SB10001424052702304778304576373650243960700.html or https://www.imperial.ac.uk/ref/webarchive/h8f (archived on 18/11/13).

E8) "Toumaz forms joint venture to commercialise its Sensium Digital Plaster", Julien Happich, 12 July 2011, EE Times. http://www.electronics-eetimes.com/en/toumaz-forms-joint-venture-to-commercialise-its-sensium-digital-plaster.html?cmp_id=7&news_id=222908280 or https://www.imperial.ac.uk/ref/webarchive/kjf (archived on 26/4/13).

E9) "Towards the improvement of patients' safety with continuous wireless monitoring: Pilot at Saint John's Health Center", Toumaz Group white paper, 2013. http://www.toumaz.com/sites/default/files/White%20paper%20-%20v1%206%20NL.pdf Archived here on 23/10/2013.

E10) "Distribution agreement: first commercial US orders", Press Release, 15 Oct 2013. http://www.investegate.co.uk/ArticlePrint.aspx?id=201310150700174835Q or https://www.imperial.ac.uk/ref/webarchive/twf (archived on 16/10/13).