Institution:	Imperial College London
Unit of Assessment:	12 Engineering
Title of case study:	Bioelectronics, Point-of-Care Diagnostics and their Impact on Healthcare and COVID-19
Period when the underpinning research was undertaken:	2008 - 2020

Details of staff conducting the underpinning research from the submitting unit

Name(s):	Role(s) (e.g. job title):	Period(s) employed:
Prof Chris Toumazou FRS	Regius Professor in Bioelectronics, Department of EEE	1986 – present

Period when the claimed impact occurred: 1 August 2013 – 31 December 2020

Is this case study continued from a case study submitted in 2014? Yes

1. Summary of the impact

Regius Professor Chris Toumazou FRS and his team within the Faculty of Engineering at Imperial College have developed medical device technologies based on ultra-low power CMOS and ISFET electronics and biomedical microsystems. These have provided the medical community with the means to rapidly diagnose, monitor, and treat diseases with confidence and at low cost. Since 2014, and more recently in response to the COVID-19 pandemic in 2020, the impact of this research has been to:

I1) Spinout a startup company (DNAnudge) in 2015 to exploit microsystem integration and bring personalised genetic testing to consumer applications, initially focused on nutrition. Launched a product range and service in partnership with John Lewis and Waitrose;

I2) Repurposed this to enable a 90-minute, lab-free test for COVID-19, rapidly validate this in a clinical trial, and roll out across the UK. The DHSC and NHS has placed a GBP161,000,000 order for 5,800,00 test kits. This is now routinely used in 500 hospitals across the NHS;

I3) Spinout a second startup company (DNA Electronics – DNAe) (founded 2003) to exploit semiconductor-based DNA sequencing and license this core IP to Ion Torrent and subsequently ThermoFisher, contributing to its cumulative revenue totally USD140,000,000,000 (2014 to 2020) via its products based on our core IP;

I4) Since the start of the COVID-19 pandemic, Ion Torrent products have been used internationally for SARS-CoV-2 research, e.g. to study the virus, mutations and track new strains, develop vaccines, and epidemiological investigations. These products are now recommended by the European Centre for Disease Prevention and Control (ECDC);

I5) Use this technology to develop DNAe LiDia-SEQ™, the world's first rapid and direct-from-specimen diagnostic sequencing platform – leading to the acquisition of NanoMR, a new US DNAe facility, and securing up to USD51,900,000 contract with BARDA. This has now been adapted for sequencing and detecting the SARS-CoV-2 virus;

I6) Underpin SensiumVitals®, a CE and FDA approved ultra-low power system for continuous patient vital sign monitoring, by a third startup company (Sensium Healthcare). This has demonstrated impact on quality of care – reducing severity, length of hospital stays and healthcare cost saving. SensiumVitals® is adopted as standard of care across multiple hospitals internationally, several of which are using SensiumVitals® in their care of COVID-19 patient.

2. Underpinning research

Over the past two decades we have seen a convergence of bioelectronics into the world of healthcare, providing new solutions for early detection, diagnosis and therapy of disease. Disruptive 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. Bioelectronics research at Imperial led by Professor Christofer Toumazou has produced key advances in this area as described below.

There are three aspects to the underpinning research for this case study. The first to 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 processing 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** [R1, R2]. This ultra-low power approach has been demonstrated in a number of applications including the world's first totally implantable cochlear prosthesis [R2]. This was independently assessed to reduce power consumption by up to two orders of magnitude compared to the state-of-the-art.

The second aspect of the underpinning research relates to analytical tools and 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 relied on optical methods that required the addition of fluorescent tags to the target DNA to indicate a match. Our research over the past two decades 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 [R3]. This is now referred to in the industry as "next generation semiconductor sequencing". A key challenge however with electro-chemical sensors is they typically suffer from non-ideal characteristics with significant variabilities such as drift, offset, sensitivity and ageing effects. 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 ISFET in a standard CMOS technology [R3, R4].

The third aspect of the underpinning research relates to the miniaturisation of the end-to-end sample preparation and detection platform for point-of-care applications. Applications that analyse biological samples (e.g. blood or saliva) extract miniscule amounts of genetic material that are beyond the limit of detection of most sensing technologies. It is thus essential to amplify the genetic material using a method such as polymerase chain reaction (PCR). This process from sample extraction and amplification to detection typically requires a lab workflow involving a number of reagents and benchtop instruments in a sterile environment. Our research this past decade has enabled lab-free sample-to-result using miniature disposable cartridge technology [R4, R5, R6]. This is made possible through a family of innovations including **simultaneous amplification/detection** [R4], **miniaturised sensor technology** [R4, R6], and **integrated sample handling microsystem** [R5, R6].

3. References to the research

[R1] 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. https://doi.org/10.1109/TCSI.2005.844112

[R2] 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. https://doi.org/10.1109/JSSC.2004.840959

[R3] S. Purushothaman, **C. Toumazou**, J. Georgiou, "Towards fast solid-state DNA sequencing", *IEEE International Symposium on Circuits and Systems,* (2002), 4, pp.169-172. https://doi.org/10.1109/ISCAS.2002.1010416

[R4] **C. Toumazou**, L.M. Shepherd, S.C. Reed, et al, "Simultaneous DNA amplification and detection using a pH-sensing semiconductor system", *Nature Methods,* (2013), 10, pp. 641-646. https://doi.org/10.1038/nmeth.2520

[R5] **C. Toumazou**, S.B. Lowe, S.W. Green, P.S. Harding, G.H. Sanders, N.J. Wooder, N.A. Werdich, M.C. Twisk, R.H. Zander, J. Casey, H.V. Hare, "Method and apparatus for analysing a biological sample", *US patent* (filed 2016, granted 2018). https://patents.google.com/patent/US10093965B2

[R6] M.M. Gibani, **C. Toumazou**, M. Sohbati, R. Sahoo, M. Karvela, et al, "CovidNudge: diagnostic accuracy of a novel lab-free point-of-care diagnostic for SARS-CoV-2", *The Lancet Microbe*, (2020) https://doi.org/10.1101/2020.08.13.20174193

4. Details of the impact

We now provide details of the 7 aforementioned impacts and their links to underpinning research:

I1) **DNAnudge,** an Imperial startup (currently 70 employees, including over 10 Imperial alumni); was founded in 2016 to exploit lab-on-chip integration [R4, R5] and to bring personalised genetic testing to consumer applications. The core platform technology and business model have been protected through a family of 35 patents (15 granted, 20 pending), based on underpinning research [R6]. Initially targeting personalised nutrition, DNAnudge launched a product range, a flagship store in Covent Garden and consumer service in partnership with John Lewis & Waitrose supermarkets in 2019 **[E1]**.

DNAnudge point-of-care platform and test cartridge for rapid, lab-free COVID-19 testing.

I2) Since its emergence in December 2019, SARS-CoV-2 has led to 98,205,841 confirmed cases of COVID-19 and 2,103,068 deaths by the end of January 2021. In response to the SARS-CoV-2 pandemic, the DNAnudge point-of-care (POC) platform was redesigned, from its previous commercial use in human DNA typing, to provide rapid and accurate, true sample-to-answer multiplex RT-PCR diagnosis of SARS-CoV-2 in just over an hour [R5, R6], without the need for any laboratory facilities and trained personnel. This was validated in an initial NHS trial revealing a sensitivity of 98% and specificity of 100% **[E2]**. In April 2020, CovidNudge received the approval from the MHRA for clinical use and has subsequently obtained its CE mark **[E3]**. Following a GBP161,000,000 order of 5,800,000 testing cartridges by the UK Government and the DHSC **[E4]**, the test has been rolled-out UK wide in urgent NHS patient care and elective surgery settings, plus out-of-hospital locations.

For this contribution, Toumazou was awarded one of the President's Special Awards for Pandemic Service by Royal Academy of Engineering "… *recognising exceptional examples of engineering in the service of society in the context of pandemic challenges*" **[E5]**.

I3) **DNA Electronics (DNAe)** is the Imperial startup (currently 102 employees) that invented **next-generation semiconductor sequencing** (**NGS**) based on the group's research in integrated ISFET sensors technology [R3, R4]. DNAe's sequencing platform technology with its associated patents (US7,888,015, US7,649,358, US7,686,929, US8,114,591), all based on the underpinning research [R3, R4], were licensed to **Ion Torrent** in 2010, then immediately acquired by Life Technologies for USD725,000,000 that in turn was acquired by ThermoFisher in 2014 for USD13,600,000,000. Current products including the Ion PGM, Ion GeneStudio and Ion Torrent Genexus™ Integrated Sequencer utilise the same core IP licensed from DNAe. These product sales contributed to Thermo Fisher's USD140,000,000 revenue (cumulative 2014-2020) **[E6]**.

ThermoFisher Ion GeneStudio S5 Series System employing our next-generation sequencing (NGS) IP.

I4) Since the start of the COVID-19 pandemic, Ion Torrent products have been used in more than 34 countries for SARS-CoV-2 research (e.g. viral typing/discovery, host genetics/immune response, vaccine/therapeutics development) and epidemiological investigations **[E7]**. Ion Torrent products are one of the DNA sequencing platforms (inc. Illumina, PacBio and Oxford Nanopore) now recommended by the European Centre for Disease Prevention and Control (ECDC) for transmission patterns, phenotypically relevant mutations, confirmation of reinfection and/or direct transmission and the detection of unknown pathogens or highly divergent strains **[E8]**. Recently, Thermo Fisher announced it will extend its SARS-CoV-2 GlobalAccess Sequencing Program to help the world to identify and track new strains through subsidising Ion Torrent products.

SensiumVitals is now routinely used in several hospitals in Europe and the US.

I5) During the same period, DNAe's sequencing technology has also been applied to diagnostics, creating its own LiDia-SEQ™ platform. This allows low cost, high throughput, rapid detection of bloodstream and viral infection, antimicrobial resistance and liquid biopsy, in a hospital setting. To realise this strategy, DNAe in 2015, acquired nanoMR Inc. for USD24,000,000 bringing in the capability to apply targeted NGS directly to a blood sample for rapid diagnosis. BARDA then (in 2016) awarded DNAe a USD51,900,000 contract to target application of antimicrobial resistant infections and influenza **[E9]**. The LiDia-SEQ™ platform and assay were recently granted *Breakthrough Device designation* by the US FDA and subsequently used to detect and rapidly sequence SARS-CoV2.

LiDia-SEQ™ platform for the direct identification, without the need for culture, the microbial cause of bloodstream infection leading to sepsis.

I6) Sensium Healthcare (integrated within The Surgical Company in 2016), another Imperial College startup (currently 41 employees), was founded to exploit the group's research in ultra-low power techniques [R1, R2] for wireless physiological monitoring. The SensiumVitals® product is a discreet, wearable, wireless system for continuous patient vital sign monitoring. A recent independent study on the health economics based on data gathered through clinical deployment demonstrated the efficacy (early detection of deterioration), utility (added value to healthcare) and economic benefit (cost saving) based on the reduction in length-of-stay **[E10]**.

SensiumVitals® product that is now an approved class-I medical device (both FDA approved and CE-marked).

Since 2014, SensiumVitals® has been adopted as standard of care across hospitals in several countries. Within the UK, it has been deployed as standard of care in King Edward VII (London), Spire Healthcare's Montefiore (Brighton) and Chelsea and Westminster Hospital NHS Foundation Trust. More recently SensiumVitals® is also being used as part of their central role in responding to the COVID-19 outbreak across the community. It has also been used at a quarantine facility near Heathrow for healthcare workers. Internationally, it has and is being used in multiple hospitals in the US, the largest emergency department in France (Bichat University Hospital, Paris), where it has enabled the early diagnosis of atrial fibrillation and acute respiratory failure. Since April 2020, St. Antonius Hospital (Utrecht, Netherlands) is routinely using SensiumVitals® where it has been reported to be particularly helpful with COVID-19 patients **[E11]**.

5. Sources to corroborate the impact

[E1] "Waitrose launches DNA test pop-ups offering shoppers personal genetic health advice", 3 December 2019, Charged. https://www.chargedretail.co.uk/2019/12/03/waitrose-launches-dna-test-pop-ups-offering-shoppers-personal-genetic-health-advice/ Link archived here.

[E2] "One-hour COVID-19 test being trialed at hospitals around London", Reuters May 23, 2020. https://www.reuters.com/article/us-health-coronavirus-britain-test/one-hour-covid-19-test-being-trialed-at-hospitals-around-london-idUSKBN22Z0PI Link archived here.

[E3] "How a DNA Test Machine Mutated to Finding Covid in 90 Minutes", Bloomberg 6 August 2020. https://www.bloomberg.com/news/articles/2020-08-06/ho"w-a-dna-test-machine-mutated-to-find-covid-in-90-minutes Link archived here.

[E4] "Roll out 2 new rapid coronavirus tests ahead of winter" Department of Health and Social Care, 3 August 2020. https://www.gov.uk/government/news/roll-out-of-2-new-rapid-coronavirus-tests-ahead-of-winter Link archived here.

[E5] The President's Award, Royal Academy of Engineering, 2020. https://www.raeng.org.uk/grants-prizes/prizes/prizes-and-medals/awards/presidents-special-awards-pandemic-service/rapid-test Link archived here.

[E6] ThermalFisher Scientific Financial Results 2014 to2020. https://ir.thermofisher.com/investors/financial-information/financial-results/default.aspx Link archived here.

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[E8] "Sequencing of SARS-CoV-2", 23 December 2020, European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/sites/default/files/documents/sequencing-of-SARS-CoV-2.pdf Link archived here.

[E9] "BARDA Awards $51.9 Million Contract to DNAe …", 30 September 2016. https://www.dnae.com/assets/dnae-barda-funding_30sep16_dnae_v"5-clean.pdf Link archived here.

[E10] M. Javanbakht, et al., "Cost utility analysis of continuous and intermittent versus intermittent vital signs monitoring in patients admitted to surgical wards", *J. Medical Economics*, (2020), pp.1-9. https://doi.org/10.1080/13696998.2020.1747474 PDF available here.

[E11] "St Antonius Hospital Starts use of Sensium", 16 April 2020. https://www.sensium.co.uk/news/st-antonius-hospital-starts-use-of-sensium/ Link archived here.