Imperial College
London

Centre for Bio-Inspired Technology

Annual Report 2011

Director's foreword

Professor Toumazou has developed a prototype handheld device that analyses DNA to predict how patients may respond to their prescription medication.

The Centre for Bio-Inspired Technology has just completed its second full year of research and it is my pleasure to introduce the Annual Report for 2011 describing the various research activities on which members of the Group are engaged.

Early diagnosis and therapy for chronic disease remain key challenges for medicine and, through our research projects, we continue to seek inspiration from biological systems to innovate new technologies in response.

I am pleased to announce the first two academic appointments to the Centre. Dr Timothy Constandinou and Dr Pantelis Georgiou have been appointed as lecturers in the Department of Electrical and Electronic Engineering and both are heads of research themes within the Centre.

This year we have undergone some improvements to our laboratories and added additional facilities for microbiological based research.

Last year we featured two research projects funded by Wellcome Trust Technology Transfer Awards. We have continued to make advances in these projects, which is hugely encouraging, in our aim to improve diagnosis and therapy and both have now reached the next stage with acceptance for clinical trials.

A highlight of the year was our association with the Moon Regan TransAntarctic Expedition which was the fastest recorded crossing of the continent. All members of the Expedition wore the Sensium™ plaster under development at Toumaz UK Ltd, a spin out Company from Imperial College London which continues to work closely with the Centre. Ray Thompson, R&D Consultant in the Centre, was a member of the Expedition Team and you can read about his experiences in this Report.

It was a pleasure for me to join the Rector of Imperial College London, Sir Keith O'Nions, and our main sponsor, Professor Winston Wong, in Taiwan this year when the Rector signed an academic partnership with a consortium of universities in Taiwan. Professor Wong and I had both been involved in developing this collaboration which will focus on research activities in the fields of bio-inspired science and technology drawing particularly on the expertise of the Centre for Bio-Inspired Technology.

We continue to be successful in attracting funding for our research and it is particularly satisfying that the research councils and our private funders recognise the contribution which bio-inspired technologies are making towards the challenges facing the health service. I hope you will enjoy reading about our research and the progress we are making in meeting our aims.

Professor Chris Toumazou FRS, FREng

People

Academic staff

Professor Chris Toumazou FRS, FREng
Director
Chief Scientist of the Institute of Biomedical Engineering
Winston Wong Chair in Biomedics Circuits, Department of Electrical and Electronic Engineering

Dr Timothy Constandinou
Lecturer Department of Electrical and Electronic Engineering and Deputy Director CBIT

Dr Pantelis Georgiou
Lecturer Department of Electrical and Electronic Engineering and Head of Metabolic Technology CBIT

Research staff

FELLOWS:

Dr Reza Bahmanyar

Dr Alessandro Borghi

Dr Nir Grossman

Professor Chris McLeod – Principal Research Fellow

Dr Olive Murphy

Dr Belinda Nedjai

Dr Konstantin Nikolic

Dr Themistoklis Prodromakis

ASSOCIATES:

Dr Dylan Banks

Dr Amir Eftekhar

Dr Zhaolei Lang

Dr Herrero-Viñas Pau

Dr Irina Spulber

Dr Thomas Weissensteiner

ASSISTANTS:

Mr Song Luan

Mr Mohamed El-Sharkawy

Mr Matthew Lubelski Katz

Ms Oghenevworhe Omeru

Mr Peter Pesl

Research students

Mr Abdul Al-ahdal

Mr Bård Haaheim

Mr Yuanqi Hu

Mr Walid Juffali

Ms Melpomeni Kalofonou

Mr Jakgrarath Leenutaphong

Mr Yan Liu

Mr Kwoc Lui

Ms Christina Morris

Ms Sivylla Paraskevopoulou

Mr Siavash Saremi-Yarahmadi

Mr Alexander Serb

Mr Ayodele Sanni

Mr Mohammadreza Sohbati

Mr Surachoke Thanapitak

Mr Ian Williams

Mr Stephen Woods

Ms Virginia Woods

Administrative staff and consultants

Mrs Patricia Chapman
Business Administrator to Professor Toumazou

Mrs Wiesia Hsissen
Senior Group Administrator

Ms Gifty Kugblenu
PA to Professor Toumazou

Mr Ray Thompson
Senior R&D Consultant

Mrs Izabela Wojcicka-Grzesiak
Research Group Administrator

Visiting academics

PROFESSORS:

Professor Tor Sverre Lande
University of Oslo

Professor Peter Wells FRS
Cardiff University

Professor Winston Wong
Grace THW, Taiwan

Professor Sir Magdi Yacoub FRS
Imperial College Healthcare NHS Trust

Professor Patrick Soon-Shiong
Chairman of the National Coalition of Health Integration (USA)

Professor Bhusana Premanode

RESEARCH FELLOWS:

Dr Alison Burdett
Toumaz Technology Ltd

Dr Gareth Jenkins

Dr Jamil El-Imad (Honorary Senior Research Fellow)

Graduates in 2010–11

Dr Wai Pan Chan

Dr Panavy Pookaiyaudom

Dr Winston Wong Jr

Researchers who have taken up appointments elsewhere:

Dr Iasonas Triantis
Department of Electronic and Electrical Engineering, UCL

Dr Belinda Garner
Institute of Psychiatry, King's College London

Dr Nick Oliver
Consultant Diabetologist at Imperial College Healthcare NHS Trust and Honorary Senior Clinical Lecturer in the Faculty of Medicine, Imperial College London

Dr Anthony Vilches
Lecturer in Engineering Design, Brunel University

Our news

Honours and awards

JULY 2011

At the 2011 Imperial Biomedical Research Centre (BRC) research festival, the winning poster, as voted by participants, was submitted by Mr Peter Pesl of the Centre for Bio-Inspired Technology. The poster, *'Mobile-Based Architecture of a Decision Support System for Optimal Insulin Dosing'*, described Mr Pesl's research on the development and clinical validation of a smartphone-based decision support system for the management of type 1 diabetes.

Peter Pesl receiving his award from the Rector

The event included a series of 20 speaker presentations, each providing an overview of the BRC-funded areas of study within their respective BRC research theme and a poster exhibition showcasing the ongoing research that is being conducted by BRC-funded researchers. The aim of this initiative was to provide an overview of the translational research programmes supported by the Imperial BRC and the pioneering work that is fostered within the BRC's clinical research facilities.

JANUARY 2011

A paper, originating from research in the Centre for Bio-Inspired Technology, came top of the *Journal of Neural Engineering's* Highlights of 2010 collection. This collection of articles represents a selection of the best work published in the Journal during the previous year. The articles were selected for their presentation of outstanding new research, receipt of the highest praise from international referees and the highest number of downloads last year.

Grossman N, Poher V, Nikolic K et al. 'Multi-site optical excitation using ChR2 and micro-LED array'. *Journal of Neural Engineering*, Vol:7, ISSN:1741–2552, 2010

NOVEMBER 2010

DNA Electronics Limited, a 'spin-out' company from the Centre for Bio-Inspired Technology, won three of the IET's Innovation Awards categories Healthcare, Electronics and Emerging Technologies.

News features

Academic partnership between Imperial College London and universities in Taiwan

Whilst on a visit to China and Taiwan in April, the Rector of Imperial, Sir Keith O'Nions, signed an academic partnership with a consortium of universities in Taiwan. Every year for three years, five Taiwanese students will study at Imperial for their PhDs and 10 academics will undertake research visits. The collaboration will also support joint research projects and research visits to Taiwan by Imperial academics, building on Imperial's strong existing links with the country. The Director of the Centre for Bio-Inspired Technology, Professor Toumazou and the Centre's main sponsor, Professor Winston Wong, who had both been involved in developing this collaboration, were present at the signing.

The initiative, fully funded by Taiwan's Ministry of Education, will focus on research activities in the fields of bio-inspired science and technology, humanities and social sciences, drawing particularly on the expertise of Imperial College Business School and the Centre for Bio-Inspired Technology.

The Memorandum of Understanding is with the Top University Strategic Alliance in Taiwan, represented by National Yang-Ming University, Taipei, and is only the third signed by the Alliance with an overseas partner, following similar agreements with the University of Berkeley, California, and the University of Chicago.

Left to right: The Rector, Sir Keith O'Nions, Professor Winston Wong, Andrew Regan, Expedition Team Leader, with members of the Team at the official launch of the Imperial College London, Moon Regan Expedition partnership.

Crossing Antarctica

Imperial scientists partnered with the Moon Regan Transantarctic team, which crossed the entire continent of Antarctica via the South Pole on a research-led expedition

As well as gathering data in a number of research areas, the team was the first to test biofuel while travelling across this extreme environment.

Researchers demonstrated how a network of mobile wireless sensors, developed at Imperial, continuously monitored the environment, the vehicles and the explorers themselves during the expedition. The team had the opportunity to showcase their technology and vehicles to journalists and the Imperial community before they were packed up and shipped off to Antarctica.

Visiting Professor, alumnus and sponsor of the Centre for Bio-Inspired Technology, Winston Wong, was a major sponsor of the Expedition and the Bio-Inspired Ice Vehicle used in the Expedition bore his name. It is a one-person, biofuelled powered machine that glides on skis, using radar to detect dangerous crevasses in the ice.

« The DNAe team with their IET Awards

Eye inspired imaging chip will extend video capabilities

The Engineer, 12 April 2011

"Researchers are developing a dynamic imaging chip inspired by the human retina that will be capable of capturing high-performance video at low bandwidth and power consumption. The 'silicon retina' is being developed by a European consortium and will have immediate applications for the electronics industry and for machine vision. Charge-coupled devices (CCDs) and complementary metal-oxide-semiconductors (CMOSs) are the most commonly used imaging sensors and have found their way into a variety of devices including mobile phones and laptops. "If you're taking photos that's fine, because you need every single pixel", said project partner Dr Konstantin Nikolic (Centre for Bio-Inspired Technology) of Imperial College London. "But if you're making a continuous film, there is massive redundancy of information. If you're filming at 40fps, each frame consists of millions of pixels, yet there is very little difference from frame to frame."

New diabetes laboratory opened by BBC broadcaster Justin Webb

A new laboratory targeting the development of an artificial pancreas for people with type 1 diabetes has been opened in the Centre for Bio-Inspired Technology. The Metabolic Technology Lab was officially opened by broadcaster and journalist Justin Webb, presenter of the *'Today'* programme on BBC Radio 4.

Scientists working in the lab are developing technology to help people with a range of metabolic and chronic diseases. The opening of the lab also represents a significant step towards the development of a ground-breaking innovation: the world's first bio-inspired artificial pancreas. The new facility provides researchers with a dedicated space in which to carry out their work.

The team is developing a microchip device that takes glucose readings from a monitor and continuously infuses insulin into the body so that people with type 1 diabetes can do away with regular insulin injections.

In 2009, Justin Webb produced a radio documentary, 'Diabetes – The Silent Killer', which explored his family's experience of type 1 diabetes following his young son Sam's diagnosis.

News from the Centre's 'spin-out' companies

JULY 2011

Toumaz Limited announce that the Sensium™ Digital Plaster has been granted 510 (k) FDA approval.

Toumaz Limited has teamed up with Dr Patrick Soon-Shiong to commercialise the Sensium™ Digital Plaster, a disposable wireless body monitoring device.

Toumaz a pioneer in low cost, ultra-low power wireless communications and broadcast technology, has established a new joint venture with Dr Patrick Soon-Shiong's company California Capital Equity LLC ('CCE'), to expand the commercialisation and distribution of the Sensium™ Digital Plaster. The joint venture, which is named 'Toumaz US LLC', will be headquartered in San Diego, California, and will sell and distribute the Sensium™ Digital Plaster in North America and Worldwide.

Nearly all the electronics and firmware for Sensium™ life platform sensor nodes or basestations are integrated onto a system on chip, the TZ1030. This operates at ultra low power and includes a highly flexible sensor interface, digital block with 8051 processor and 64kbyte of RAM and an RF transceiver block. On chip program and data memory permits intelligent local processing of signals at the sensor node extracting information such as heart rate from the raw sensor data. Together with an appropriate external sensor, the TZ1030 can provide ultra low power monitoring of ECG, heart rate, temperature, respiration and physical activity. It also includes the flexibility to interface to sensors with analog or digital outputs. One or more Sensium™ enabled wearable sensor nodes can continuously monitor key physiological parameters on the body and report to a base station Sensium™ plugged into a PDA or Smartphone. The data can be further filtered and processed there by application software.

www.toumaz.com

A version of DNA Electronics Ltd's Genalysis® platform, known as the 'SNP-DR', performed well in a collaborative R&D programme part-funded by the UK's Technology Strategy Board. The goal of the project was to take DNA Electronics' technology for pH-based, label-free detection of DNA and demonstrate a portable DNA detection platform in standard CMOS semiconductor technology. The two-year, £1.2 million project culminated in a pilot study in which DNA Electronics tested the SNP-DR detection module using samples that had been genotyped by Pfizer in a reference lab. The device correctly called 100% of samples tested blindly using the SNP-DR prototype. The company is now progressing towards making the technology totally lab-free.

NOVEMBER 2010

DNA Electronics Ltd, a fabless semiconductor provider of solutions for real-time DNA and RNA analysis, has announced that it has entered a partnership with 454 Life Sciences, a Roche Company. The collaboration will focus on the development of a low-cost, high-throughput, long read, high density DNA sequencing system. As part of the agreement, DNA Electronics has signed a non-exclusive licence to provide relevant IP from its proprietary semiconductor technology portfolio to Roche. This technology which enables sensitive detection of nucleotide incorporation during sequencing will build on 454 Life Sciences' current pyrosequencing-based platform.

The collaboration leverages DNA Electronics' unique knowledge of semiconductor design and expertise in pH-mediated detection of nucleotide insertions with 454 Life Sciences' long read sequencing chemistry to produce a seamless evolution from optical detection to low-cost, highly scalable, electrochemical detection.

www.dnae.co.uk

Crossing Antarctica

In November 2010, the Moon Regan TransAntarctic Expedition started its journey from South America to cross the entire continent of Antarctica, and back. There were four objectives: to complete a successful, safe crossing of the Antarctic, from Union Glacier to McMurdo via the Geographic South Pole; to make the first attempt to reach the South Pole using a bio-fuelled vehicle – the Winston Wong Bio-Inspired Ice Vehicle; to prove the reliability of ground vehicles in this terrain; to bring back significant data for Imperial College London, the Expedition's science partner. The Team hoped to make the first recorded crossing of the continent using wheeled vehicles.

Researchers saw the collaboration with the Expedition as an opportunity to demonstrate how a network of mobile wireless sensors, developed at Imperial, could continuously monitor the environment, the vehicles and the explorers themselves throughout the crossing. The researchers also showcased their technology and vehicles to journalists and the Imperial community before they were packed up and shipped off to Buenos Aires in preparation for the drive to the southern tip of Chile for the flight to Antarctica.

Ray Thompson, from the Centre for Bio-Inspired Technology was a member of the Team and he oversaw the experiments being conducted throughout the Expedition.

Imperial scientists provided a network of mobile wireless sensors, to continuously monitor the health of the explorers and the environment and they equipped the vehicles with solar power technology to provide an independent, renewable power source for the satellite communication system.

The wireless sensors continuously transmitted data to a computer, stored on one of the six-wheeled drive Science Support Vehicles (SSVs). These were mobile laboratories giving the scientists and explorers access to information about the expedition in real time. The computer was connected to a satellite phone, when conditions allowed, so that information from the sensors could be beamed back to the UK for spot analysis by researchers based at Imperial. Further samples, i.e. cortisol tests, were also brought back along with bulk data. These are still undergoing analysis.

One aim of the Expedition was to understand how humans perform in extreme conditions. Scientists from the Winston Wong Centre for Bio-Inspired Technology at Imperial's Institute of Biomedical Engineering provided 'digital plasters', the Sensium™ enabled Life Platform, which expedition members wore at all time, to monitor their vital signs, such as ECG, heart rate, movement and muscle activity. Overnight the sensors monitored sleeping patterns in conjunction with time related cortisol sampling. These disposable digital plasters, the size of a small patch, enabled the team to have their health monitored without being wired up to bulky monitoring machines. The Sensium™ technology was developed by researchers working with Professor Chris Toumazou and are now in development prior to manufacture by Toumaz Ltd, an Imperial College London 'spin out' company. The Sensium™ plasters were granted FDA approval in early 2011.

The Expedition took 22 days to complete. The crossing began on the west coast of Antarctica, leaving from Union Glacier, and travelled via Patriot Hills to the South Pole. This segment of 1150km took six days to complete. After a two day stop at the South Pole station, the Expedition continued, descending Leverett Glacier to the Ross Ice Shelf on the coast seven days and 800km later. The return journey took a further seven days and, in all, the Expedition travelled 3900km across the driest and coldest continent on Earth. The team had to forego the leg of the journey across the Ross Ice Shelf to McMurdo due to time and fuel constraints. They had been delayed in reaching Antarctica by the worst weather conditions in eighteen years which had kept the 3km long 'blue ice runway' at Union Glacier covered by half a metre of snow for 12 days longer than is usual.

Before setting out, Andrew Regan, the Expedition principal, said:

> "The Antarctic is a hostile and punishing environment, with the coldest temperatures on Earth. The terrain is unforgiving and the sastrugi crevasse fields can be treacherous. It is a rare privilege to experience this remarkable continent and to be able to work with our science partner, Imperial College London, to gather important research data. The world has much to learn from Antarctica."

The project, supported by the Faculty of Engineering, the Department of Civil and Environmental Engineering and the Centre for Bio-Inspired Technology, was sponsored by Imperial alumnus and main donor to the Centre, Professor Winston Wong.

Research funding

Project	Sponsor	Start date	Duration
NEUral Memristive Architecture	EPSRC	September 2011	3 years
Automated Blood Pressure Monitoring	Wellcome Trust	August 2011	3 years
Ultra low power Medical Microelectronics	National Semi Conductor Corporation	May 2011	3 years
SeeBetter	Commission of the European Communities	February 2011	3 years
Optimal Insulin Dosing	Imperial College Healthcare NHS Trust-BRC Funding	February 2011	18 months
Advanced Shot Detection	Defence Science and Technology Laboratory	January 2011	1 year
Adaptive Hearing Protection	Defence Science and Technology Laboratory	January 2011	1 year
HIV patents in ICHT	Imperial College Healthcare NHS Trust – BRC Funding	October 2010	18 months
Next Generation Neural Interfaces	EPSRC	October 2010	4 years
Non-invasive Stent Blood Flow	Imperial College Healthcare NHS Trust – BRC Funding	September 2010	2 years
Glucose Monitor – 3	Imperial College Healthcare NHS Trust – BRC Funding	August 2010	2 years
CMOS Electro-Optical Platform	EPSRC	October 2009	3 years
Supercapacitors	EPSRC	October 2009	2 years
Osteoarthritis Medical Engineering Centre	Wellcome Trust/EPSRC	October 2009	5 years
Artificial Pancreas	Wellcome Trust	September 2009	3 years 8 months
Implantable SAW Transponder	Wellcome Trust	September 2008	3 years3 months
3 Tier Sensor Platform	EPSRC	April 2008	3 years 6 months
Centre for Bio-Inspired Technology	Winston Wong	October 2009	10 years
Nanotechnology Research	Wilfrid Corrigan	August 2007	5 years

Research portfolio

SeeBetter Seeing better with hybrid backside illuminated spatio-temporal silicon retina

By developing a silicon chip which incorporates the functionality of the different types of cells present in the retina, this project aims to design an integrated vision sensor. The resulting sensor will also be an ideal retinal prosthetic as it will mimic biological retina information processing and provide an output that mimics functions of the eye's retinal ganglion cells.

Implantable SAW transponder for blood pressure monitoring

Implanted blood pressure sensors offer continuous measurement and monitoring improving the ability to detect events which are almost always missed by traditional once-a-day, or once-a-month, blood pressure checks. The sensor can be used to monitor heart failure, pulmonary arterial hypertension and systemic hypertension when implanted in a major cardiovascular vessel or within the heart.

Artificial pancreas for type-1 diabetes

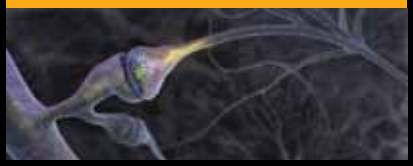
Inspired by the physiology of the pancreas, the artificial pancreas incorporates a clinically approved glucose biosensor, a control algorithm mimicking the function of the alpha and beta cells found inside the pancreas and a dual infusion pump for secreting insulin and glucagon hormones vital for glucose homeostasis.

Next generation neural interfaces

We are developing a system which will provide a key component of future implantable devices for neural interfacing with applications both in basic neuroscience and next-generation approaches to treating neurological disorders.

Memristors: towards autonomous sytems

Conventional computing architectures are great in number crunching but struggle with tasks like face recognition, real-time navigation control, object segmentation and depth perception. We are developing a new type of autonomous computation platform capable of perceiving, learning and adapting like the brain: a memristor which can be used to compute and store information locally, mimicking the way chemical synapses link neurons in our brains.



WiNAM: Neural anomalies monitoring

This technology is being targeted for epileptic seizure detection and prediction. The vision is to develop a system with the capability to forewarn a patient, doctor or nurse of an impending seizure or to use closed-loop stimulation devices to suppress the seizure before it happens.

Point of Care genetic technology

Genetic and epigenetic testing could revolutionize medical practice by allowing early detection of abnormal phenotype as well as by tailoring treatment to individual patients. Using a 'lab-on-chip' system integrating sample preparation, biochemical reactions and sensors, we are testing nucleotide variation using a portable device for 'point-of-care' use. We are also developing CMOS integrated ISFET sensors to detect early signs of cancer.

A directional hearing aid – a helping hand in a crowd

The cocktail party effect: the ability of an individual to distinguish individual conversations within a cluster of people, partake in one, and almost instantly switch to another, is an important aspect of human communication. This is challenging for anyone with normal hearing, for the hearing impaired, it can be an exhausting and frustrating. Established technologies are being applied to provide hearing aids which will overcome some of these difficulties.

Therapeutically aligned research themes

Inspired by life-style aspirations and biological systems, the Centre is inventing, developing and demonstrating devices to meet global challenges in healthcare and well-being, by mimicking living systems effectively and efficiently to create innovative and advanced technologies.

To achieve this mission, we have developed a strategy that brings together three key areas of healthcare: early detection, diagnosis and therapy. Being cross-disciplinary, these areas combine expertise from biologists, engineers and clinicians as well as collaborations from across Imperial College and other organisations to form a world-renowned research team. Together this team leverages on trends in technology to meet the next generation of healthcare needs.

Miniature sensing, biologically inspired, intelligent processing and state-of-the-art semiconductor technology are just some of the key expertise in the Group. These are used to develop novel methods for the continuous, real-time sensing and monitoring of bio-chemicals/biosignals, all with the an application to personalise healthcare in the applications of: Metabolic Technology, Cardiovascular Technology, Genetic Technology and Neural Interfaces and Neuroprosthetics.

METABOLIC TECHNOLOGY

{ projects aim to develop technologies for application in early detection, diagnosis and therapy of metabolic disease the main application area is the treatment of diabetes and its complications }

Head of Research
Dr Pantelis Georgiou

Recent trends in daily lifestyle and poor diet have lead to an increase in metabolic disorders, which are affecting millions of people worldwide. A metabolic disorder develops when organs responsible for regulating metabolism fail to carry out their operation. Diabetes mellitus is currently the most severe metabolic disease of our generation, being the leading cause of mortality and morbidity in the developed world. This is caused by an absolute, or relative, lack of the hormone insulin which is responsible for homeostasis of glucose concentrations. Insulin deficiency leads to elevated glucose concentrations which, in turn, cause organ damage including retinopathy leading to blindness, nephropathy leading to kidney failure and neuropathy which is irreversible nerve damage. At least 150 million people today are diagnosed with diabetes and this number is doubling every 15 years.

Current research includes:

- The bio-inspired artificial pancreas – a fully closed loop system, which mimics the functionality of a healthy pancreas. The core of the system contains a silicon integrated circuit, which behaves in the same way as biological alpha and beta cells of the pancreas. In doing so, it aims to offer more physiological control to type 1 diabetics, using insulin to control hyperglycaemic events and glucagon to prevent hypoglycaemia.

  We are delighted to report that the project has been approved for ethical trials in St Mary's Hospital by the NHRA. We will study 20 subjects with type 1 diabetes aged 18–75 and the trial will assess the safety and efficacy of the bio-inspired artificial pancreas by applying the technology to participants in a variety of scenarios, starting with a fasting test and progressing to overnight control, mealtime control and, finally, an ambulatory test.

- Diabetes management systems – an integrated system of wireless continuous glucose monitors, decision support systems and smart-phone platforms to create a telemedicine system capable of continually monitoring and recording glucose wirelessly and offering advice on insulin dosing. In addition, the smart-phone provides a constant link to a clinicians database to allow constant monitoring from the hospital.

- Diagnostic lab-on-chips for early detection of disease – which includes devices which fully integrate chemical sensors and low power processing algorithms to provide cheap, disposable and intelligent chemical monitoring systems with long battery lifetimes. These are currently being used for the assessment of nephropathy, as kidney failure is a severe complication resulting from poor management of diabetes.

  The bio-inspired control algorithm for our artificial pancreas has already undergone an in silico validation using a commercial simulator (UVa T1DM simulator), approved by the Federal Drug Administration as a substitute to animal trials. The results confirm good control of 200 simulated diabetes patients with 93% time spent in target glycaemia and with no episodes of severe hypoglycaemia.

  The Group is also part of the Imperial College London Osteoarthritis Centre of Excellence funded by Wellcome Trust and the EPSRC working on the diagnostic systems for early detection of the signs of the disease.

CARDIOVASCULAR TECHNOLOGY

{ research is focussed on real time monitoring of vital cardiovascular parameters to enable patients to move out of hospital to the home and provide early warning systems for serious cardiovascular conditions }

Head of Research
Professor Chris McLeod

Recent statistics from the American Heart Association states that over 80 million adults (one in three) have one or more types of cardiovascular disease. The British Heart Foundation states that nearly 200,000 deaths result every year from cardiovascular disease, which accounts for more than one third of all deaths in the UK. Coupling these stark statistics with an aging population and the already burdened health service, the cardiovascular technology research in the Centre is striving to apply cutting edge innovation to help reduce these alarming statistics.

The research involves the design and characterisation of both external and implanted sensors along with the non-trivial issues surrounding wireless communication and bio-signal analysis. The Centre has the capability for *in vitro* experimentation and access to excellent laboratories for *in vivo* verification. These facilities, along with many experienced collaborators, both academic and industrial, provide a closed-loop development cycle for current and future cardiovascular technology projects within the Centre.

Current research includes:

- Implanted blood pressure sensors to measure pressure continuously and with no further procedure necessary will enable doctors to detect 'events' which are almost always missed by traditional once-a-day or once-a-month checks. Using SAW technology, we aim to offer an alternative transducer type measure with inherent characteristics suited to very long-term monitoring. We expect to achieve an implant capable of continuous monitoring for 10 or more years in ambulatory patients.

  Research is continuing to refine the design of the sensor, its delivery to the pulmonary and systemic circulations and the portable reader worn by the patient which will link the sensor data to a wide-area network for remote monitoring – this might be at a GP's surgery or in a hospital clinic.

GENETIC TECHNOLOGY

{ research is focussed on the development of a genetic detection platform and apparatus using bio-inspired technology }

Head of Research

Professor Chris Toumazou FRS, FREng

Genetic information corresponds to a specific region of DNA, which is a biological molecule in the form of chains with millions of base pairs. By investigating this biological code, the gene, early detection of hereditary disease or an allergy can be realized for individual client. The complex chemical detection techniques, such as electrophoresis and fluorescent detection, can be simplified to easy YES and NO questions. An analogue of 'match and mismatch' mechanism of base pairs into 'on' and 'off' states of electronic sensor's output has been made.

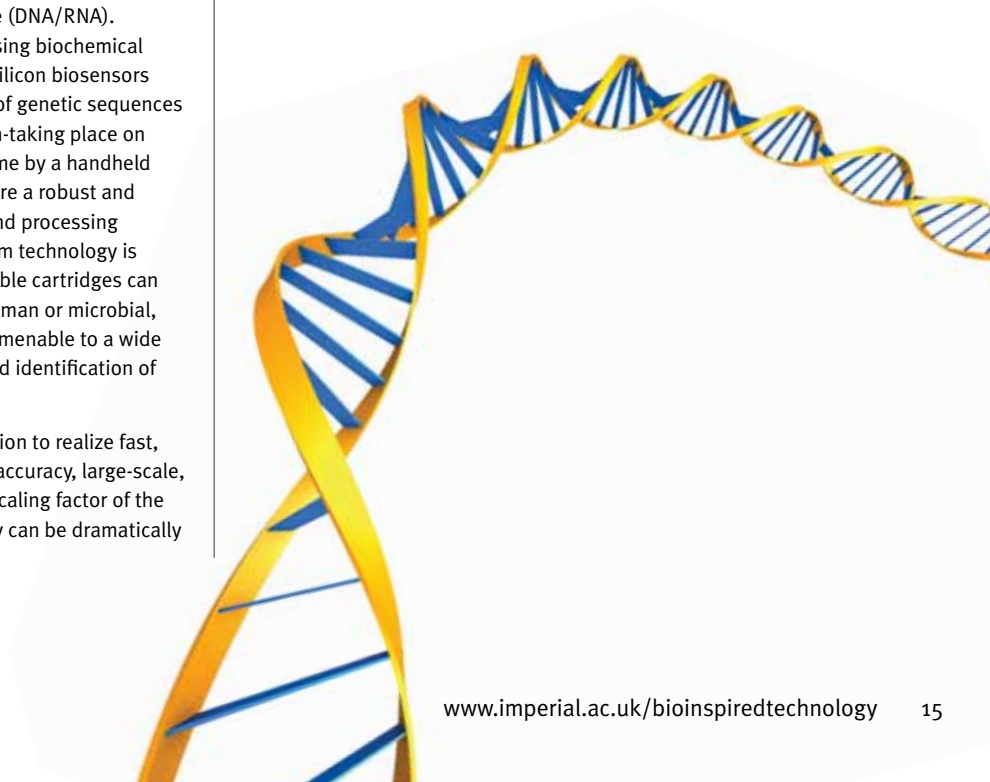
The 'SNP-DR' (silicon system for the prediction of drug response) is a low cost microchip based device which can predict drug efficacy or toxicity at point-of-care. This technology can enable pharmacogenetic testing in personalised medicine, i.e. tailoring drug prescription and dose to the patient's genetic makeup, alongside other factors such as patient history and drug-drug interactions. Predicting drug efficacy will save patient and clinician time, reduce the overall cost of treatment by avoiding the wasteful cycle of trial and error with ineffective prescriptions, and provide improved quality of life for patients.

The SNP-DR platform is capable of delivering fast, accurate on-the-spot tests for any target nucleic acid sequence (DNA/RNA). Disposable, low cost, 'lab-on-chip' cartridges housing biochemical reagents, advanced microfluidics and low-power silicon biosensors are key to this novel technology for the detection of genetic sequences or mutations. The micro-volume gene test reaction-taking place on the fully integrated cartridge is analysed in real-time by a handheld electronic device using custom algorithms to ensure a robust and reliable result. Built on the reliability, scalability and processing power of silicon microchip technology, this platform technology is mass-producible and highly portable. The disposable cartridges can be tailored to any genetic sequence of interest, human or microbial, making this a customisable platform technology amenable to a wide variety of applications and markets, including rapid identification of infections.

In particular, CMOS technology is under investigation to realize fast, robust, biological detection with low-power, high-accuracy, large-scale, integrated processing circuitry. By using the size scaling factor of the semiconductor industry, the detection productivity can be dramatically boosted according to the biological Moore's Law.

Current research includes:

- **Genetic and epigenetic testing** is expected to revolutionize medical practice by allowing early detection of abnormal phenotype as well as by tailoring treatment to individual patients at an unprecedented level. It will require novel devices that are cost-effective, fast, robust and easy to use and we aim to achieve this via a lab-on-chip system integrating sample preparation, biochemical reactions and ISFET based sensors in standard CMOS.
- **HLA B*5701 genotypes** can have a fatal reaction to Abacavir, one of the most widely used drugs in the long-term treatment of HIV. We are addressing an urgent need for rapid and accurate HLA B*5701 typing in the case of an emergency prescription which cannot be provided by current laboratory-based methods.
- **Osteoarthritis** is a degenerative disease affecting the majority of the population over 60, with 1-2% developing clinical signs including severe pain and joint failure. We aim to develop assays for published nucleotide and nucleotide repeat markers that might help to identify individuals at risk, select preventive measures and guide clinical intervention.
- **In addition to genetic changes, epigenetic abnormalities** such as alterations in DNA methylation patterns are highly associated with multiple cancer types and/or stages of tumorigenesis. The aim of this research is to develop arrays of CMOS based ISFET sensors for the detection of DNA methylation in specific gene markers.



NEURAL INTERFACES AND NEUROPROSTHETICS

> we are seeking improvements in medical care and quality of life for patients with neural disorders such as epilepsy, spinal cord injury, paralysis and sensory/sensation loss by developing implantable devices for neural rehabilitation

Head of Research
Dr Timothy Constandinou

Neurotechnology, the application of technology to neuroscience, is a topic that is currently enjoying much interest in the research community. With ever progressing advances in microelectronics and electrode technology, never before have there been so many opportunities to develop devices that effectively interface with neurobiology. Such devices are often referred to as neural interfaces or brain-machine interfaces. Various platforms have been developed both for recording and stimulation, ranging from external surface-electrode systems to fully implantable devices. These include electroencephalography (EEG), electromyography (EMG), electrocorticography (ECoG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), trans/-cutaneous interfacing, direct peripheral nerve interfacing and penetrating electrode interfacing. Typically, different interfacing techniques can be classed by their level of invasiveness, portability and proximity to the nervous system, i.e. Central and Peripheral Nervous System (CNS and PNS respectively). Research in this area at the Centre for Bio-Inspired Technology focus on a number of different platforms that exploit the integration capability and scalability of modern semiconductor technology.

Current research in neural interfacing technology includes the following projects:

- Multi-Electrode Arrays (MEA)
  By integrating standard and custom designed electrode arrays (both for the CNS and PNS) with microelectronics, a variety of techniques are being developed for both recording and stimulation based on signal processing strategies such as beam forming, phased arrays, independent and principal component analysis.
- Targeted PNS Stimulation
  Existing cuff-based systems (for the Vagus nerve and PNS in general) are unable to target specific nerve fibre groups (fascicles) within a nerve bundle. Fascicle selectivity would allow the targeting of specific muscle-groups or organs. To this end, we are currently investigating stimulation strategies for: (1) Fascicle Selectivity – targeting specific organs and/or muscle groups, (2) Fibre-type selectivity and Uni-directionality – targeting either the afferent or efferent pathways, (3) efficient delivery – to improve electrode lifetime, safety and power efficiency.
- Chemical Neural Recording
  As neural conduction is based on ionic current flow, potassium and sodium sensing can be used as part of a neural recording platform offering selectivity with satisfactory SNR, myoelectric interference rejection, and overall minaturization of the interface. Most neural monitoring research so far has focused on the electrical aspect of the signal with very few studies mentioning ionic sensing of this sort. This work focuses on combining chemical sensing together with electrical recording to develop novel, solid-state devices for hybrid monitoring both within the CNS and PNS.
- WiNAM (Epilepsy)
  Modern neural interfaces are able to extract more and more data. However, once extracted, methods of analysis and feature extraction need to be applied to quantify the activity in some way. This project involves the development of an analysis framework for neural signals, including database and interface, for analysing large amounts of data over several cases and data sets.

Past projects include:

- Optogenetic stimulation and optical stimulation
  Neural prostheses are devices that can substitute a motor, sensory or cognitive modality that might have been damaged as a result of an injury or a disease. The potential benefits have already been demonstrated in over 200,000 people with cochlear implants for impaired hearing and 80,000 with DBS devices for Parkinson's, Dystonia and Essential Tremor.

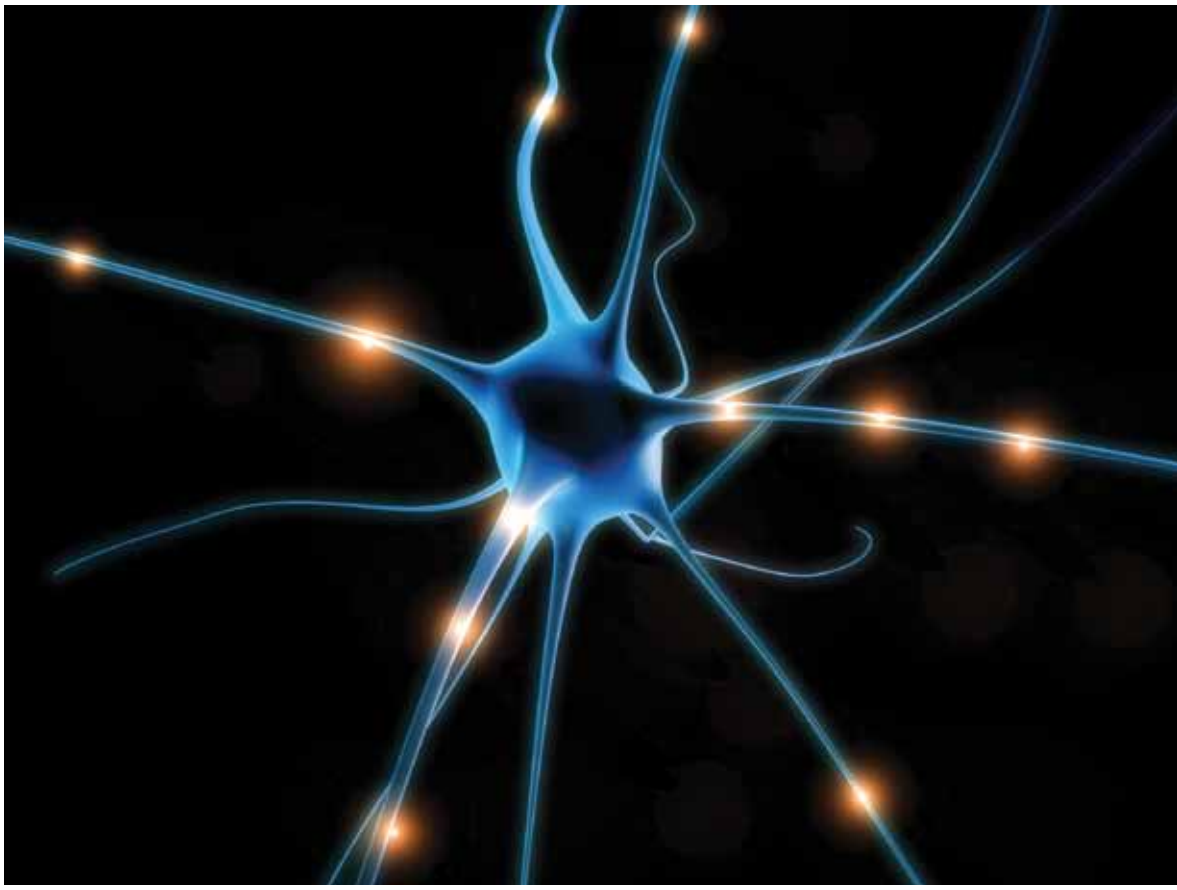
Current research in neural prostheses include:

- Next Generation Neural Interfaces
  The next generation of neural implants will utilise high density microelectrodes to detect the activity of neurons, paving the way for new treatments for conditions that currently weigh a heavy clinical burden. For example, by using the activity of neurons in motor areas of the brain to control electrical stimulation of muscles, it is possible that voluntary movements could be restored to patients paralysed by spinal cord injuries. The aim of this project is to deliver a platform technology that will convert the raw signal from electrodes into a stream of identified spike events, suitable for incorporation into a range of wireless, implantable devices.

- Neural Prosthesis for Proprioception
  Sensory feedback from the body is key to enabling fine motor control, natural (low cognitive load) movement and non-visual awareness of the position of your body. Individuals with prosthetic limbs or suffering from certain types of neural damage lack this proprioceptive feedback in the affected body areas and as such struggle to learn to control them and are unlikely to achieve high levels of coordination. Our research is investigating the provision of artificial proprioceptive feedback from a prosthetic limb by direct electrical stimulation of nerves using a neural implant.

Past projects include:

- A totally-implantable cochlear prosthesis, a vestibular prosthesis for the restoration of balance, a sub-retinal visual prosthesis, and an optogenetic retinal prosthesis.



Featured research

SeeBetter: seeing better with hybrid backside illuminated spatio-temporal silicon retina

Principal investigator
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Research team
Professor Chris Toumazou,
Mr Matthew Katz

Project partners
IMEC (Leuven, Belgium), Institute for Neuroinformatics (ETH and University of Zurich, Switzerland), Novartis Friedrich Miesher Institute (Basel, Switzerland)

Funding
European Union: *SeeBetter* is a focused research project in the work programme 'brain-inspired ICT'.

BACKGROUND

Conventional image sensors are fundamentally limited by comparison with biological retinas because they produce redundant sequences of images at a limited frame rate. By contrast, neuromorphic 'silicon retina' vision sensors mimic the biological retina's information processing capability by computing the salient spatial and temporal aspects of the visual input and encoding this information in a frame-free, data-driven, asynchronous spiking output. The range of application of these silicon retinas remains restricted because of their low quantum efficiency and their inability to combine high quality spatial and temporal processing on the same chip. Solutions to these technical challenges would revolutionize artificial vision by providing fast, low power sensors with biology's superior local gain control and spatiotemporal processing.

Such sensors would find immediate and wide application in industry, and provide natural vision prostheses for the blind. It is the goal of *SeeBetter* to address these limitations by realizing an advanced silicon retina with the superior quantum efficiency and spatiotemporal processing of biological retinas. We will be addressing these problems through a multidisciplinary collaboration of experts in biology, biophysics, biomedical, electrical and semiconductor engineering. Our objectives to achieve our goal are:

- to use genetic and physiological techniques to understand better the functional roles of the six major classes of retinal ganglion cells;
- to model mathematically and computationally retinal vision processing from the viewpoint of biology, machine vision, and future retinal prosthetics;
- to design and build the first high performance silicon retina with a heterogeneous array of pixels specialized for both spatial and temporal visual processing;
- to combine this silicon retina with an optimized photodetector wafer with high quantum efficiency using state of the art back side illumination and hybridization technologies.

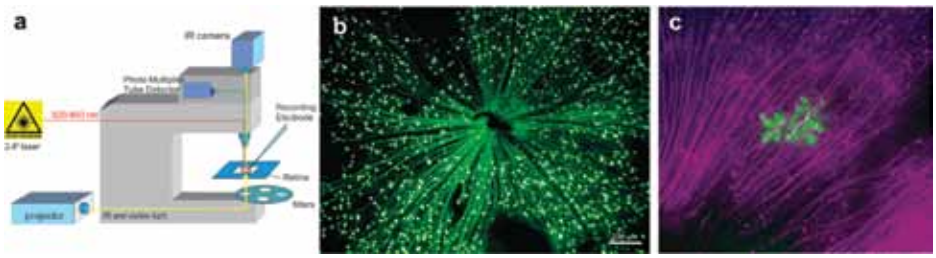
Despite more than 100 years of effort to understand the retina, the function of most of the cells in the retina still remains undetermined. However, recent breakthroughs in genetics, viral transsynaptic tracing and two-photon laser targeted electrophysiology (Figure 1) have made it possible to investigate the functioning of major classes of cells in the brain, and the retina is an ideal substrate in which to apply these techniques [1].

It has also been observed experimentally that the visual system of a wide range of biological creatures from insects to humans, can be partitioned both anatomically and functionally into pathways specialized for spatial and temporal vision [1]. This observation suggests that this specialization is fundamentally important for perception. The output spikes carried on the optic nerve of mammalian retinas are characterized by their asynchronous, event-based, sparse, and informative nature. This representation is vastly superior to the redundant sequences of images generated from conventional cameras for performing perception tasks.

OUR APPROACH

There is a lot of prior art in chips and systems that claim to mimic the vision of different types of animals. Most of these implementations are based on very simple models consisting of an array of identical pixels which implement the photoreceptor element and some basic circuitry that, for instance, mimics the local gain control or spatial filtering properties of biological retinas [2,3]. Recent chips have included event-based readout to mimic the asynchronous spikes carried on the optic nerve and to reduce the amount of output data or to increase the effective frame rate [4,5], Figure 2. Other designs focus on very specific image processing functions which are claimed to be done very efficiently by the eyes of living beings [6].

The range of application of these silicon retinas remains restricted because of their low quantum efficiency and their inability to combine high quality spatial and temporal processing on the same chip. Solutions to these technical challenges would revolutionize artificial vision by providing fast, low power sensors with biology's superior local gain control and spatiotemporal processing. Such sensors would find immediate and wide application in industry, and provide natural vision prostheses for the blind [7,8].



« **Figure 1:** (a) Two-photon microscope with electrophysiology. (b) Live image of a PV retina, each dot is a EYFP labeled ganglion cell, labeled lines are axons. (c) Transsynaptically labeled ganglion cell circuit (green). Red shows a 'turn-key' molecule that allows the transsynaptic tracer to pass one synapse.

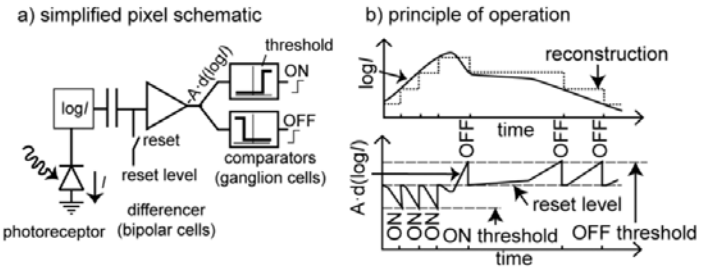


Figure 2: (a) Spike-event based Dynamic Vision Sensor pixel circuit and (b) operation, showing how the ON and OFF events are triggered by fixed-size changes of log intensity [5].

SeeBetter aims to design an integrated vision sensor which takes into account the latest research results in retinal functionality and applies these results in the implementation of an advanced artificial vision sensor. In order to build such a system the different types of cells present in the retina should find their counterpart in the chip.

Since a biological retina is a 3D structure, the area used for phototransduction does not take away from area used for processing. In conventional (front-side illuminated) image sensors, any photodiode area that is used for phototransduction is not available for other circuits. If the fraction available for phototransduction (the fill factor) is small, then there is a fundamental limitation on the achievable signal to noise ratio. This area tradeoff limits the functionality of conventional cameras and is the reason that conventional image sensors have very simple pixels with very limited processing capability. In *SeeBetter* we will build a hybrid vision sensor, where the photo-detection elements modelling the photoreceptors in the retina are fabricated in a different wafer than the rest of 'silicon retinal cells'. The two wafers are then interconnected using bump-bonding techniques.

This hybridization brings about high quantum efficiency (QE), Figure 3, and almost 100% fill factor without taking away from the area available for transduction, amplification, processing, and readout [9]. To achieve high efficiency, the electronics can be fabricated in an advanced CMOS technology without having to worry about the suitability of the technology for photo-detection. This is important, due to the complexity of the retina cell models, and the fact that one would wish to have a large number of photodetectors in order to have high vision resolution.

SeeBetter will address these problems through a multidisciplinary collaboration of experts in biology, biophysics, biomedical, electrical and semiconductor engineering. By succeeding in this effort, we will lay a foundation for future artificial vision systems which is grounded in biology's superior capabilities. The resulting sensor will also be an ideal front end for retinal prosthetics since it attempts to mimics biological retina information processing and provides its output directly in the form of spikes that mimic those carried on the eye's optic nerve. Moreover, it will be useful in a wide variety of practical real-time power-constrained vision applications which have to process scenes that span temporal scales from microseconds to days and illumination conditions from starlight to sunlight.

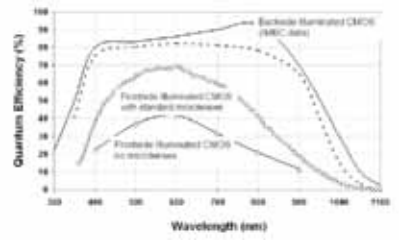


Figure 3: Measured and simulated world record QE of imec's backside illuminated imagers compared to frontside illuminated imagers [9]

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Next generation neural interfaces

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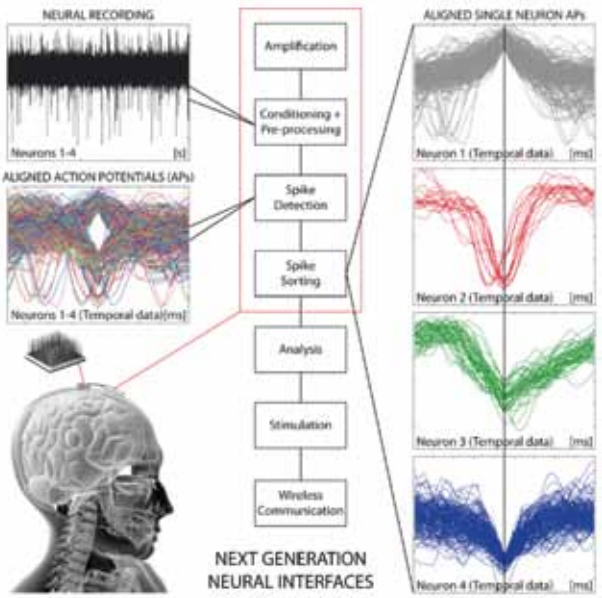
Funding
EPSRC

This project is realising a platform technology for interfacing between the central nervous system and digital microelectronics. We are developing an ultra-low power, implantable system that converts the analogue signals from multiple implanted electrodes (at least 100) into digital streams of sorted spike events. Such a technology will form a key component of next-generation Brain-Machine Interfaces and closed-loop neurostimulation devices.



BACKGROUND

For more than half a century neuroscientists have recorded the characteristic action potentials (spikes) generated by cortical neurons in order to understand how information is represented and transmitted through the nervous system. Until recently, these experiments involved sampling small numbers of neurons over short sessions of a few hours, but with advances in chronic electrode arrays it has become possible to record spikes from large numbers of neurons over many months. As well as providing an unprecedented window into brain function, these techniques are inspiring new translational efforts to develop Brain-Machine Interfaces (BMIs) that communicate directly with the nervous system for therapeutic benefit. For example, neural signals from the motor cortex of paralysed patients have been used to operate assistive devices such as computers and robotic prostheses. Combining data processing capabilities with existing neurostimulation technology will enable a new generation of implanted devices to interact bi-directionally with the nervous system, for example to implement 'closed-loop' protocols where activity sensed at one site in the nervous system determines parameters of stimulation delivered to another site. One such application is closed-loop control of Functional Electrical Stimulation (FES) from spike activity in the motor cortex to restore movement after spinal cord injury, although many other clinical uses of such technology can also be envisaged.

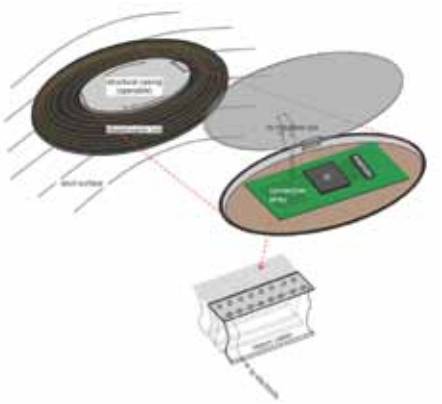
Early implementations of BMIs connected intracortical electrodes to external amplifiers via wires passing through the skin. This breaches the body's natural barrier to bacterial infections, compromising the implant and presenting a serious danger to patients. As channel counts increase, the number of wires that must exit the body and the size of connectors increase accordingly, making this approach impractical, as well as aesthetically unsatisfactory for patients. Several groups have begun developing wireless links for BMI applications to relay neural signals from the brain to an external receiver. However, a major problem is that the brief (~1 ms) spike events can only be detected by sampling at high rates, producing approximately 500 kbit/s of data per neural channel. The number of channels, which can be continuously transmitted wirelessly at this rate, is limited and power consumption is high (~100 µJ/kbit for Bluetooth). Currently, commercial telemetry systems for neural data (e.g. Alpha-Omega Telespike, Neuralynx Sat-Tx, Plexon TBSI) transmit only a small number of channels (e.g. 8-16) and have battery lifetimes limited to a few hours, which is too low for useful BMI applications.

However, given that to a large extent the biological significance of spikes is as indistinguishable all-or-nothing events, the neural code can be represented with a much lower bandwidth than the raw electrode recording (a binary spike train can be encoded with high temporal precision by less than 1kbit/s). The detection and identification of action potentials (spike sorting) is therefore the critical signal-processing bottleneck in neuroprosthetics applications. By converting raw data into binary spike events at source, the data needing to be transmitted from an implant would be compressed by at least three orders of magnitude. Moreover, for many applications such as closed-loop neurostimulation, autonomous spike sorting within an implant would obviate the need for any continuous wireless link at all. Once spike events have been detected and sorted, the binary neural code is ideally suited to processing by conventional low-power digital microprocessors, which could compute relevant features (e.g. the kinematics of intended movements) from neural firing patterns to drive stimulation by a self-contained, implantable unit.

These considerations demonstrate the need for an implantable hardware component that detects and sorts spike waveforms from multiple electrode channels, producing as output a real-time stream of binary spike events. Ideally this would operate with minimal external intervention, powered from a battery that could be recharged wirelessly. Improvements in power consumption and integration density mean that low-power amplification and digitisation of high numbers of neural channels is now feasible. Amplifiers based on the Harrison topology have established themselves as mainstream in the research community and are being deployed in multi-channel neural recording systems. Some systems incorporate rudimentary spike detection based on threshold crossing. However, each electrode detects the spikes of all neurons in its vicinity (see Figure), which may have very different relationships to behaviour. Therefore threshold crossing alone is unable

to provide neural interfacing at the single-cell level. More sophisticated designs have been proposed to extract simple features from the spikes such as peak amplitude or discrete derivatives in an attempt to separate spikes from different neurons, but these methods are insensitive to the subtle differences in waveform that are often observed. Furthermore, the number of neurons and associated waveform parameters must be determined manually, which is subjective, requires specialised expertise and is too time-consuming to be practical for large numbers of electrodes. As yet no implantable system is capable of performing autonomous high-quality spike sorting to the standard required for single-neuron interfacing with the brain. In fact, only recently have any reliable unsupervised spike sorting algorithms become available. The Wave_Clus software developed by Quian Quiroga employs wavelet decomposition and superparamagnetic clustering to determine the number and feature parameters of neurons from the raw continuously recorded data. This software has supplanted manual spike sorting in a number of laboratories worldwide. However, this computationally demanding high-level program runs off-line on desktop computers.

These difficulties are compounded by the technical challenges of developing robust devices that can function in real experimental and ultimately clinical settings. Apart from the risks of infection and other surgical complications, electronic implants must withstand fluid leaks, mechanical stress and motion artefacts while operating reliably on a battery power supply. Jackson and colleagues at University of Washington developed the first fully functional autonomous implant capable of real-time spike sorting (the Neurochip) and used it to deliver closed-loop neurostimulation in freely behaving non-human primates. Despite using off-the-shelf components to implement a simple single-channel time-amplitude window discriminator, this device enabled a number of successful studies during which near continuous neural activity has been recorded in individual animals for periods up to one year. In addition, these experiments helped identify key issues that must be resolved before multi-channel, autonomous spike sorting implants can be realised:



Power consumption – While the use of a conventional architecture to perform spike detection can accelerate the development process, the computational requirements for online spike sorting and required energy budget constrain chronic deployment.

Unsupervised calibration – Spike acceptance criteria are currently being manually set, a process that would be too time-consuming for large numbers of channels. This would require continual expert assistance in any clinical application.

Intelligent spike tracking – Spike waveforms can change over time and neurons can appear or disappear in the recording. Successful scientific and clinical applications of autonomous spike sorting will require the flexibility to track and adapt to slow changes in spike waveform while being robust to the appearance and disappearance of other units in the recording.

OUR APPROACH

Our cross-disciplinary programme takes a multi-level approach to implementing the functionality of sophisticated spike sorting algorithms in custom low power microelectronics. A simple, yet optimal, method to sort spikes on-line is by feature extraction and pattern recognition. However, this approach is only practical if the number of neurons and characteristic features for each neuron are accurately determined. This requires a high-level off-line spike sorting solution. Therefore this project is adapting the Wave_Clus software to automatically calibrate a novel algorithm, which has been optimised for low-power implementation in CMOS technology. During periodic calibration, data will be streamed from the implant to a remote computer that will return feature parameters for each identified neuron. For clinical applications, calibration and charging can be performed during sleep, since cortical neurons are highly active during REM phases. During this period, power will be supplied via an inductive link. At other times the device can run autonomously from a rechargeable battery, to detect and sort spikes on multiple channels in real time. By incorporating intelligent supervision to adapt features sets to slow changes in spike waveform, performance stability between recalibration will be increased.

This methodology provides a step change compared to previous approaches, given that we are proposing an optimal compromise between the very limited algorithms that have been implemented in chip so far and the more sophisticated offline spike sorting algorithms that are too computationally demanding to be implemented in a chip.

The system will provide a key component of future implantable devices for neural interfacing with applications both in basic neuroscience and next-generation approaches to treating neurological disorders. Input spike signals could be sourced from a variety of proven chronic multi-electrode array technologies including microwires, 'Utah' arrays (Blackrock Microsystems), 'Michigan' probes (NeuroNexus Technologies), as well as future improved designs. The output signals consisting of digital spike events could be logged locally or streamed via a low bandwidth telemetry link to external monitoring systems. Alternatively the spike-sorting interface could be integrated with implanted neurostimulation devices to form a bidirectional neural interface. To demonstrate such performance in real-world applications, the technology will be incorporated with existing Neurochip technology to deliver a device capable of multichannel closed-loop neurostimulation to be evaluated *in vivo*.

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Directional hearing aids: a helping hand at a cocktail party

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Funding
Winston Wong Centre for Bio-Inspired Technology

This project involves the development of low-power, low-weight, personal prototype microphone arrays for hearing aid applications.

BACKGROUND

Humans develop the ability to hear before they are born, a 28 week old fetus will respond to sound. Newborn infants can already distinguish different types of speech sound which enables them to identify their carers over others, at a time where their eyesight is severely impaired. During infancy, nerve cells in the superior colliculus develop preferences for specific sound directions and their firing of action potentials indicate which direction a sound is coming from. Throughout childhood, our hearing develops the ability to distinguish between sounds from different directions and in difficult acoustic environments, such as a crowded room with many echoes.

The cocktail party effect: the ability of an individual to distinguish individual conversations within a cluster of people, partake in one, and almost instantly switch to another, is an important aspect of human communication. It can of course, pose challenges for anyone with normal hearing. For the hearing impaired, it can be an exhausting and frustrating process of failure to keep pace with others who can tune out voices and more precisely pick out and stay with one conversation.

TECHNOLOGY PLATFORM

We have developed several MEMS based microphone arrays and processing platforms for military and industrial acoustic location systems, and are building on this platform to develop directional hearing aids.

Several issues are apparent in the tech-transfer from large directional microphone arrays to mobile powered systems: principally, required reductions in size, weight, and power consumption lead to a reduction in the signal-to noise ratio introducing error and requiring a rethink of the processing algorithms. These issues derive from trade-offs that exist between the computational ability of a device in terms of its speed of operation and the complexity of processing required with its relative power consumption and physical size.

Micro-Electro-Mechanical Systems (MEMS) devices cover a broad range of devices, with myriad material and fabrication protocols, ranging from those with commercially available foundry fabrication options integrated with typical integrated circuit (IC) computer chip technologies, to those more exotic in nature that may see commercial viability in the next 10 to 20 years. Typically, they are made up of components between 1 to 100 micrometres in size (i.e. 0.001 to 0.1 mm), and consist of a transistor based processing unit and several components that interact with the outside such as microsensors.

The small physical scale of MEMS devices increases the speed of their operation and allows low power operation. To some this is seen as computationally challenging because the time constants involved

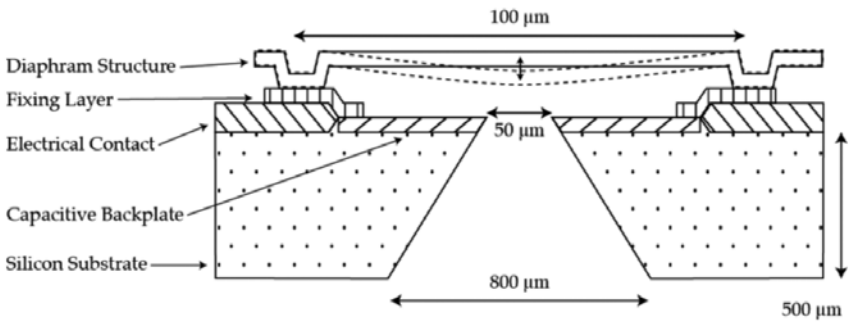

Figure 1: Cross section structure of a MEMS microphone device showing the back etched silicon substrate; the heavily doped capacitive backplate that forms the bottom contact of the capacitor; the electrical contacts that connect the device to the control electronics; the fixing layer that holds in place the diaphragm and the diaphragm structure itself shown in resting and deflected positions (dashed line). The deflection distance indicated by the small vertical arrow between the resting and deflected positions of the diaphragm is equal to x as represented within the equations described above.

are often several orders of magnitude faster than macro-scale devices. From our perspective this is invariably a boon, as it leads to low power small form systems.

A significant advantage of MEMS devices over other larger scale technologies are that they can be incorporated with complementary metal oxide semiconductor CMOS processes, allowing complex integrated devices and structures, incorporated with very low power and size. Further, they are batch processed in the tens of thousands simultaneously, ensuring that they follow similar cost structures to IC devices – the more you make the cheaper they are.

MEMS based sensors, including microphones and accelerometers, are reaching a level of development maturity where they are now ready for rigorous and demanding situations including military specific applications. They are small, low power and lightweight, which makes them ideal for this application.

Where MEMS devices have made commercial breakthroughs they have offered paradigm shifts in terms of size and cost. For example, miniature silicon accelerometers have largely replaced piezoelectric accelerometers, not only because of their size, but principally because the MEMS fabrication process encourages batch manufacture of thousands of devices simultaneously. It is our belief that this area is ripe for a MEMS breakthrough, and that is part of the drive for their exploitation here.

The MEMS microphone is also called a microphone chip or silicon microphone. It is a pressure sensitive diaphragm that is etched directly into a silicon chip, as shown in Figure 1. Most MEMS microphones are variants of the condenser microphone design. MEMS based capacitive microphones offer advantages over other types of microphone for applications such as this because of their small size, relatively high sensitivity, batch fabrication capability, inherently low power consumption and low noise features.

At the acoustic laboratories in the Centre for Bio-Inspired Technology, we have comprehensively tested the dynamic range; frequency response, signal to noise ratio, power consumption, minimum operation voltage, directionality and strength of existing MEMS microphone systems for their suitability to be incorporated within a mobile sound localisation and detection system.

ACOUSTIC CHARACTERISATION OF SPEECH

By measuring the time of arrival of characteristic sound signatures, in addition to their directions of arrival, it is possible to estimate the azimuth, and elevation of their origin. However measuring this is by no means easy. Figure 2 shows a typical spectrogram image of a voice.

ANALYSIS AND FUTURE WORK

Following the tests and results, we confident in saying that the MEMS microphone devices are suitable for sound localisation arrays. We are now incorporating these within 'ready to wear' accessories that can be used in conjunction with hearing aids.

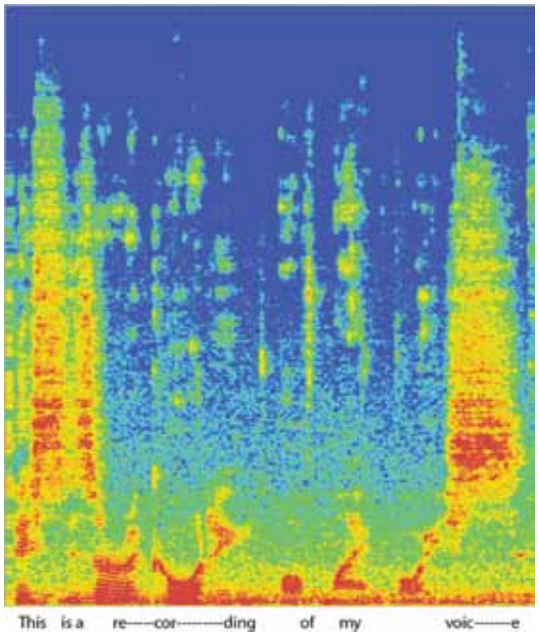

Figure 2: Spectrogram of a recording of my voice with the words illustrated in a time coordinated strip along the bottom. The frequency range is between 50Hz (bottom) and 6kHz (top) the amplitude corresponds to colour, with pressure waves greater than -45dB represented as red and pressure waves greater than -80dB represented as blue.

WiNAM: neural anomalies monitoring

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This project involves the development of a software and hardware platform for real-time neurological monitoring. We are developing an algorithm that analyses patterns within neural signals and extracts information related to brain state and function in the form of pattern counts and ratios. This technology, although broad in its application space, is being targeted for epileptic seizure detection and prediction. Hence, the vision is a system with the capability to forewarn a patient, doctor or nurse of an impending seizure or use closed-loop stimulation devices to suppress the seizure before it happens.

BACKGROUND

The brain (central nervous system, CNS) is a complex network of 100 billion neurons that controls our every function and movement. However, the CNS is affected by hundreds of disorders including diseases and injuries that can have a large impact on quality of life.

One such example is epilepsy. Epilepsy is characterised by seizures, hyper-synchronous neuronal firing, in the brain. It is also the one of the most prevalent conditions of the brain, affecting approximately 450,000 people in the UK and an estimated 0.85% of the world's population. Only 70% of patients can be seizure free with medication, although there are many associated cognitive side effects. Of the remaining, only 3% are eligible for surgery of which there is currently an ever increasing backlog[1].

Diagnostically, epilepsy is assessed via clinical history and electroencephalogram (EEG) recordings. For example, EEG is the initial stage in the procedure to identify focal areas for surgery. It is also coupled with video telemetry to assess clinical significance of electrographic seizures and whether the seizures are in fact of an Epileptic source. Hence, there is a large research community aiming to develop interface technology for real-time seizure detection, prediction and generally understanding underlying seizure mechanisms.

[1] www.jointepilepsycouncil.org.uk

NEURAL INTERFACING TECHNOLOGY

As mentioned epilepsy is one of the cases where a large amount of work is done using neural interface technology to understand, predict and detect seizures. In general, neural interfaces directly interact with neural tissue, for recording or stimulation. In the CNS this involves interacting with a sample of the brain's billions of neurons.

Within the brain, each neuron has up to 10,000 synaptic connections to adjacent neurons with different parts of the brain being associated with different peripheral behaviour. Electrodes interfacing with the brain then either doing so

- at the micro-scale aiming to penetrate the brain, in the extracellular space to record up to several neurons (e.g. single tungsten wires), or extend the micro-scale electrodes in multi-electrode arrays (MEA), which can contain up to 100 penetrating electrodes (e.g. UTAH array) to
- the larger scale grid (electrocortuogram, ECoG) and deep brain electrodes that record (or stimulate) from 10's of thousands of neurons, to
- electroencephalograms (EEGs) which record 100's of thousands of neurons from the scalp surface.

There are other, non-electrical measurement modalities such as fMRI, MEG and PET, but in the context of interfaces for prosthetics and implants, such technology is non-portable and expensive.

These electrodes trade off selectivity with invasiveness. For a specific application the level of invasiveness needs to be justified based on the efficacy of the interfaces treatment or diagnostic capability. For example, deep brain stimulators have recently emerged as a viable technology for conditions such as Parkinson's disease, but they are highly invasive.

However, to first suggest and develop a viable technology for the closed-loop solution for epileptic patients, one needs to consider whether we can in fact extract information from the neurological signals that can predict or detect seizures. Hence, a large research community is involved with analysing brain-based signals.

SEIZURE DETECTION AND PREDICTION

Generally, seizures and EEG-based signals are treated in two different frames of thought: detection and prediction. Prediction has seen work ever since the 1950s applying linear, nonlinear (state-

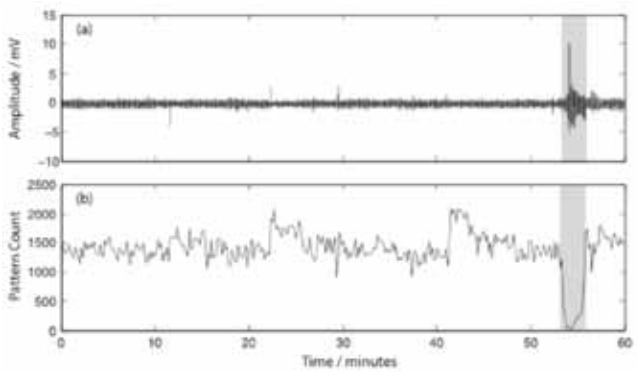

Figure 1: Graphs showing seizure detection

space) or multivariate analysis techniques to the EEG and derivatives of it. The ability to predict a seizure would allow for intervention strategies, such as brain cooling, electrical stimulation or drug delivery to be administered for those patients where medication and surgery has had little or no effect. At present 70% of patients could be seizure free with medication and of the remaining only 3% are eligible for surgery. However there is a large back-log in the UK and these figures are gathered from mainly developed countries. The state of prediction is really best summarised in [1]. In the 1990's up until 2000 there was an optimistic drive towards prediction and the methods and data used varied but all showed optimistic results. Chaotic measures such the Lyapunov Exponent and Correlation Dimension were presented as possible markers.

From 2000 until present a more formal approach emerged to validate results and organise results/data, including more robust statistical validation methods (e.g. surrogate data analysis, sensitivity and specificity quantifies). This quickly showed that all current methods were not much better than chance and that linear methods (energy, entropy etc...) were just as powerful as the more nonlinear and nonstationary methods. Indeed over that last couple of years, the momentum appears to have slowed with still no real answer to whether seizures can be predicted. Currently there are a number of new emerging theories including microseizures, high frequency activity and a high pre-seizure state. There is also an emerging perspective that detection and prediction need to go hand-in-hand, which was discussed in the Freieburg Seizure Prediction Workshop of 2007. However, not much significant work has emerged from this and prediction is still an open question.

Seizure detection in most cases has followed a different path. The majority of literature has focused on neonatal EEG. Seizures in neonates can be indications of neonatal encephalopathy (NE) – the manifestation of abnormal neonatal brain function – and can affect from 0.5-4 neonates per 1000. The incidence of NE can have devastating long-term effects, including cerebral palsy, blindness, deafness, autism and in 10-15% of cases can be fatal. As a result litigation claims for the NHS since 1996 number approximately £3 Billion. One of the issues with neonatal care in the area of seizure detection is that there doesn't exist an automated system for aiding non-expert clinicians from spotting seizure behaviour. Although the initial methods saw value in this observation their results were poor, even when retested with optimisations more recently [4]. State-of-art developments of these approaches have extended to algorithms that include time-frequency methods (wavelet transform), information theory (entropy) and chaotic measures (Lypanov exponent).

Our interpretation of the results shows three main insights, which are key driving points for our approach.

Firstly, the characteristics of rhythmicity, frequency and complexity of the raw EEG signal are the three of the most important factors in quantifying EEG activity. Second is that although frequency pre-processing steps can be used as a primary measure they can also be a valuable step to enhancing other quantification measures. For instance entropy measures are best suited under low-noise conditions; hence denoising methods such as simple filtering to wavelet decomposition have proven to improve these results [10]. Thirdly, complex methods such as chaotic measures do not seem to improve the analysis, at least for seizure detection. These types of methods are computationally expensive and rely on any chaotic nature of the EEG to be related to the seizure activity, which has not been shown [6].

The rhythmicity/frequency is related to spiking activity which can be associated with seizures while the signal complexity suggests quantification of gestational age and expected states of the neonate brain for that age (sleep/wake cycles). Conventional clinical evaluation of seizures in EEG is based on frequency and amplitude changes of particular frequency bands (such as theta and delta) and spiking activity. Spike activity and frequency band information have led to high sensitivity of detection of seizures but with poor specificity, showing false prediction rates (FPR) of 0.66-1.5 per hour [2,3]. The highest sensitivity was based on an optimisation of 40-60 parameters across a neural network (91% sensitivity, 1.17 FDR) [5]. This method was very powerful in optimising relevant features for seizure detection in data sets of different abnormal background activity [5], with one of its successes being the pre-removal of artefacts prior to analysis. Other studies have been positive but have been very specific to the seizure itself and have not considered that it may be of clinical interest to detect and classify any activity that may be seizure related (e.g. inter/post ictal) .

OUR APPROACH

The approach we have taken is to look at the system as whole and not differentiate seizure detect and prediction. In fact it is interesting to consider the psychological implications of predicting seizures. For example, if we consider a person with frequent (10-15) seizures per day. A prediction warning system with a warning window of 1 hour (the prediction community quotes windows of 5 minutes to several hours) then for most of the day the person will be anticipating a seizure. Hence there is a hypothesis that there may be a heightened seizure state in which a person is more susceptible to seizure occurring and not in all cases does the seizure manifest. If this is the case then mechanisms for suppressing such an intermediate state could be the answer – not simply looking at pre-seizure activity.

Firstly, we have developed a novel method for pattern recognition based on an algorithm known as an ngram. Pattern recognition algorithms come in many forms but almost always is made up of three items:

- data acquisition
- data representation
- decision making.

One of the more popular methods of pattern recognition is the statistical approach where features of the data are extracted through methods such as Principal Component Analysis (PCA) or Linear Discriminant Analysis and then selected according to some criteria. Once extracted generally classification methods are used, such as template matching or k-nearest neighbour methods. An excellent review of all these methods and the future perspective on this topic see [6] and references therein.

The ngram model extracts and counts the n sub-sequences from a particular sequence. Traditionally, it is applied in textual and speech recognition programs. Our method of use of the ngram model comes from the work described in the Ngram Statistical Package in Perl. In order to identify patterns from text one first has to break the text into alphanumeric strings delimited usually by a space. Each individual block (between these spaces) is referred to as a token. Once these tokens are established then the ngram generates sequences of tokens (patterns) and a count of their occurrences. These patterns can be directly translated to probabilities of words occurring given the previous n-1 words. For language learning models this is useful as a language can be modelled as the probability of a word occurring given all the previous ones (which reflects the markovian nature of the signal).

In this work we apply the same methodology to neurological signals – EEG and intracranial EEG – to extract patterns associated with seizures. The signals are preprocessed (basic filtering, quantisation etc...) and then analysed using our methodology.

RESULTS AND FUTURE WORK

The results have so far been highly promising. In an initial test on 21 patients we were able to show seizure detection sensitivity of 90% [7] with 100% specificity, an example of which is shown in Figure 1. We also found markers that showed some predictive quality.

After these initial results and the development of an online analysis software (Figure 2) we have now setup collaboration with King's College London's and EPI Zurich's epilepsy groups to take this work further. We plan to carry out a test plan for validating WiNAM as a method for seizure prediction and detection of epileptic seizures as well as explore specific case studies. We will also analyse and develop a hardware system that replicates the WiNAM methodology. This will enable us to look at the optimal implementation solution for integrating such a system in a real-time clinical and personalised healthcare environment.

Figure 2: The graphical interface designed to analyse further data sets – from www.winam.net

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This Centre was funded in recognition of the contribution of Professor Christofer Toumazou FREng FRS

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Centre for Bio-Inspired Technology

Plasticity in NEUral memristive architectures

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SUMMARY

During the past two decades, philosophers, psychologists, cognitive scientists, clinicians and neuroscientists have strived to provide authoritative definitions of consciousness within a neurobiological framework. Engineers have more recently joined this quest by developing neuromorphic VLSI circuits for emulating biological functions. Yet, to date artificial systems have not been able to faithfully recreate natural attributes such as true processing locality (memory and computation) and complexity (10^{10} synapses per cm^2), preventing the achievement of a long-term goal: the creation of autonomous cognitive systems.

This project aspires to develop experimental platforms capable of perceiving, learning and adapting to stimuli by leveraging on the latest developments of five leading European institutions in neuroscience, nanotechnology, modeling and circuit design. The non-linear dynamics as well as the plasticity of the newly discovered memristor are shown to support spike-based- and spike-timing-dependent-plasticity (STDP), making this extremely compact device an excellent candidate for realizing large-scale self-adaptive circuits; a step towards 'autonomous cognitive systems'. The intrinsic properties of real neurons and synapses as well as their organization in forming neural circuits will be exploited for optimizing CMOS-based neurons, memristive grids and the integration of the two into real-time biophysically realistic neuromorphic systems. Finally, the platforms would be tested with conventional as well as abstract methods to evaluate the technology and its autonomous capacity.

BACKGROUND

Our persistent aim for greater computation power has been ascertained by various methods for processing information, the development of ultra-fast switching elements that are continuously scaled down as well as the utilisation of low-power techniques for reducing the overall power consumption. Yet, when compared to simple organisms, programmable machines are still inferior not only by their computational capacity, but also by their incapacity to perform cognitive processing. In contrast, biological neural systems (like the human's brain) make use of primitive elements to autonomously process information in complex environments by perceiving relevant and probabilistically stable features and associations.

In the electrical domain, varying electric currents in an electronic circuit, whether of sound or image, render all types of intelligence. Likewise, biology uses exactly the same process by propagating action potentials between neighbouring neurons. The strength of a synaptic link between two neighbouring neurons depends on its history and more explicitly on the overall amount of neurotransmitters that has been propagated through it (Figure 1a).

Hodgkin and Huxley [1] have described the biophysical characteristics of cell membranes and conductances. A set of time-varying conductances describes the various ionic currents (I_{Na} and I_K) propagating through the membrane due to the neurotransmitter release, as illustrated in Figure 1b. Essentially the synapse is the fundamental biological element in control of memory and intelligence as it serves as the propagating medium, modulates the input according to its previous state (performing analog computation) while at the same time its strength is altered in relation to the propagated signal, therefore demonstrating learning and plasticity. It has been recently shown that synaptic plasticity is strongly dependent on the timing of the pre-synaptic neuron's action potential, and a wide range of learning mechanisms described as spike-time-dependent-plasticity (STDP) have been proposed, extending the traditional Hebbian synaptic learning [2].

The first physical implementation of the Memristor [3] that was postulated in 1971 [4] appeals to be fitting in a variety of applications from non-volatile memory to programmable logic. Particular emphasis is however given to

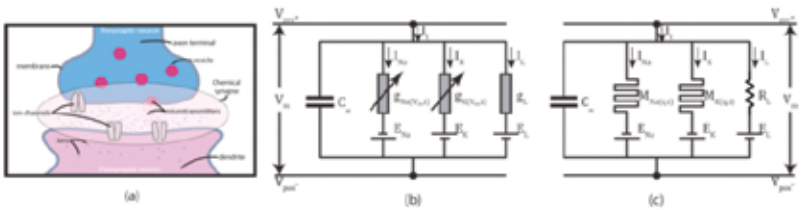


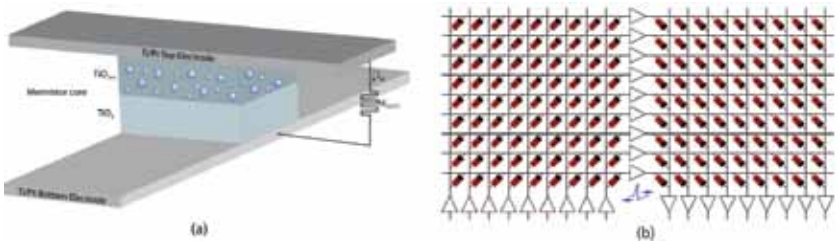
Figure 1: (a) Illustration of synaptic action. Action potentials on the pre-synaptic neuron cause the release of neurotransmitters in the synaptic cleft, which alter the strength of the individual ionic channels. Depending on the amount of neurotransmitter release the ionic channels open and close allowing the flow of ions intobrane circuit model1. Shown are two versions of the equivalent circuit, using: (b) time-varying conductance and (c) Memristors.

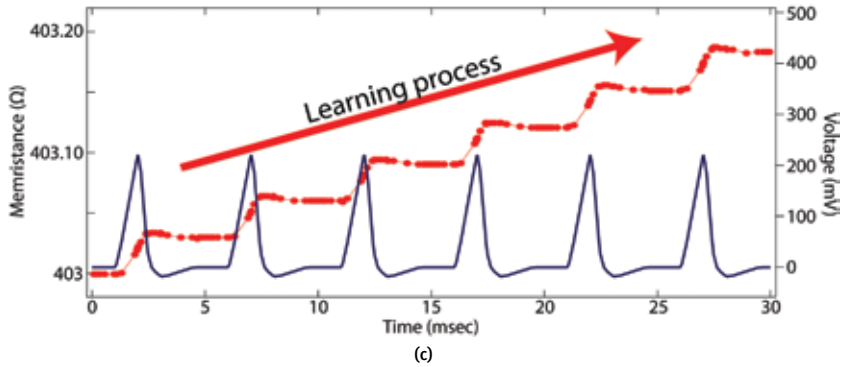
the non-linear nature of the device that resembles the behaviour of neural synapses by emulating the STDP learning rule [5]. In similar fashion with the synapse, the strength of a Memristor M(q) is dictated by the amount of charge q that has flown through it and is defined by a flux-charge (φ-q) slope.

Indoividual memristors, like the one shown in Figure 2a, can be used instead, as demonstrated in Figure 1c, to replicate the strength of different ionic channels, which is a more suitable alternative to CMOS log-domain circuits both in complexity and space. Particularly the latter is a critical parameter for integrating a large number of devices in memristive networks, useful in emulating synaptic networks as shown in Figure 2b. Multiple interconnects between such devices will in principle allow associative indexing by altering the modulation weight of particular trails (Figure 2c), similar to what has been demonstrated for cellular neural networks. The small size of the devices, combined with the employment of novel processing techniques, could facilitate larger scale integration than conventional integrated circuits and consequently further enhance the learning capacity of the system; effectively supporting cognitive functioning/processing.

OUR APPROACH

Throughout this project three emerging scientific fields (neuroscience, electron devices and theory of computation) are effectively coupled to demonstrate experimental platforms with rich internal dynamics that are capable of reproducing the biophysics of biological neural systems. Our approach leverages on the diverse merits arising from the distinct interactions of the individual groups for further developing the supporting scientific foundation, while this project's breakthrough is foreseen to occur through the constructive linking of all three research cores. Essentially, the Holy Grail of the proposed work will be the development of a technological platform that is capable of learning and adapting to different real-world stimuli. This will provide the means to study the processing and encoding of spatio-temporal information in neuro-synaptic networks, to advance the current state-of-the-art in computation and lead to breakthroughs in emerging applications on healthcare and automation.





« **Figure 2:** (a) Cross-section of a memristor core. Intentionally planted deficiencies are introduced in a controlled way, allowing them to be displaced under appropriate biasing for altering the overall conductance of the device. (b) Memristor-neuron interconnection scheme for STDP learning. (c) Spike-based biasing of a single memristor and corresponding conductance modulation.

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Implantable surface acoustic wave (SAW) transponder for chronic blood pressure monitoring

Research team

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Funding

Wellcome Trust

SUMMARY

The value of high-quality blood pressure measurements (BPM) to clinical care was highlighted in the CHAMPION trial[2] of an American implanted sensor, where an almost 40% reduction in the annual rehospitalisation rate was achieved when therapy was guided by direct BPM. SAW technology offers an alternative transducer type with inherent characteristics suited to very long-term monitoring -10 or more years- in ambulatory patients.

BENEFITS/IMPACT

Patients and Health services gain from improved quality of life and reduced healthcare costs respectively when care can be provided outside hospitals in the community. For many cardiovascular diseases, good BPM has been sought as the principal control variable for management of pharmaceutical therapy, often a combination of several active drugs. Good management of BP retards the progression of disease as well as improving the immediate condition.

Implanted BP sensors offer procedureless measurement and, allied to mHealth technology, offer continuous monitoring and the ability to detect events which are almost always missed by traditional once-a-day or once-a-month BP checks.

Heart Failure (HF) patients form the initial group expected to gain from implanted BP sensor technology- there are approximately five million in the US with varying degrees of severity/progression of the disease. The current prognosis is that 60% will not survive five years from first symptoms, so early detection, dietary and lifestyle alteration and optimal pharmaceutical therapy will have major alleviating consequences for a large section of the population.

Similar benefits are anticipated for the even larger numbers of patients with systemic hypertension, but as there are alternative, if inaccurate, measurement systems for BPM the case for implanting a sensor will be made following the risk-benefit analysis of the heart failure group with sensors.

RESEARCH PROGRESS

We are continuing to refine the design of the sensor, its delivery to the pulmonary and systemic circulations and the portable reader worn by the patient which links the sensor data to a wide-area network. We have been successful in attracting funding for the next stage and are very grateful to Wellcome Trust and the Department of Health for their financial support. This stage is intended to take the project through the Phase 1 (safety) trial in a small group of HF patients.

NEXT STEPS

Our aim is to move on from proof-of-concept to approvable medical devices and a clinical trial during the next three years. This will involve engaging with approved medical device manufacturers while continuing to optimise existing designs and to integrate with mHealth systems in a collaborative venture with the Institute of Biomedical Engineering (IBME) at the University of Oxford.

The challenges involved in moving new electronics technology from proof-of-concept, in-house designs to a medium-volume, product manufactured according to strict regulatory requirements for formal CE marking and FDA approval and thence into clinical care, are providing a very rich mix of interdisciplinary interactions. The range of challenges will expand as we seek means to provide a clinical service.

Concept of the system includes a wireless implant, an external reader and onwards communication with a wide-area network. Patient signals will be analysed in real time at the reader and reported in some detail to a hospital-based server for logging, further analysis and feature detection. From there, information for the patient will be sent back to the reader, and reporting or alarms sent to clinical staff. There is a considerable task here in learning what is significant within this previously-unobtainable, detailed information stream and setting appropriate alarm conditions to avoid false alarms or missed alarms. We will also add to the system other independent sensors to provide information on patient activity for better classification of cardiovascular events into normal and abnormal classes.

The project should result in a system suitable for providing an improvement in healthcare provision and, from that perspective, the challenges are not only technical. The cost of the sensor is dwarfed by the cost of surgical implantation and possibly of the infrastructure required to provide connectivity at any moment. The financial viability will impact on the data compression carried out in real time at the reader and the volume of data then forwarded to the server. While these are not the immediate concerns of the team's activity, they form the background for the system design.

DETAILS OF OUR APPROACH

The most distinguishing feature of our approach is the use of SAW transponders. These have been used in non-medical applications – tyre-pressure sensors, for instance, where the same alternatives for wireless sensing based on MEMS devices are also found. MEMS sensors have been produced in the form of passive transponders and also as part of active electronic circuits. We believe that SAW passive transponders offer greater accuracy and long-term stability.

A SAW resonator can be excited by energy picked up from an aerial; when the exciting signal is removed, the energy stored in the resonator is radiated from the same aerial and detected remotely. The information is contained in the natural frequency of the resonator, a function of the pressure applied to the sensor. The sensor therefore requires no local energy, is constructed from chemically inert materials and has an indefinite lifespan. These features are ideal for a chronic implant.

[1] Harefield Heart Centre, National Heart and Lung Institute, Imperial College London.

[2] CHAMPION trial reported at European Society of Cardiology Heart Failure Congress 2010, Berlin, by W. Abraham MD, and in *Lancet* Vol 377, pp. 658–666, Feb 19th 2011.

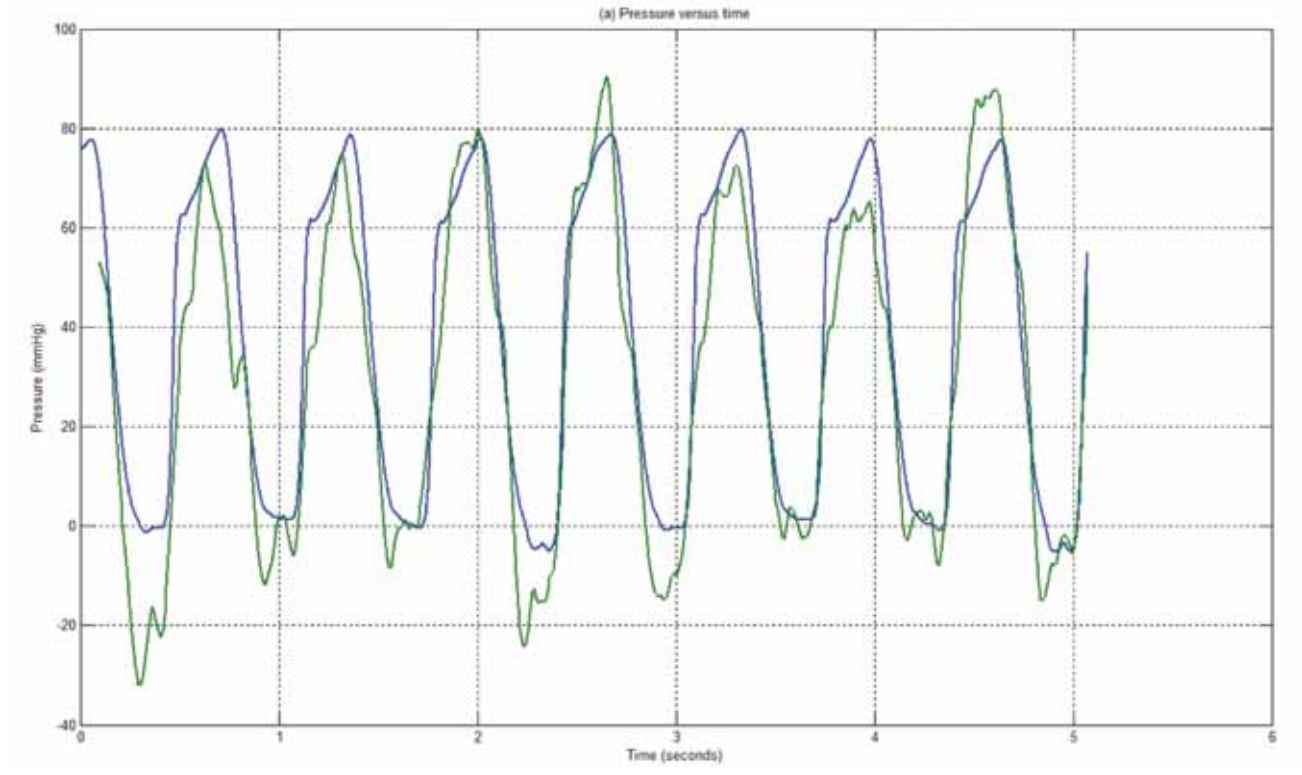

Figure 1: Sample trace of continuous left ventricular pressure recorded wirelessly (green) and from a Millar catheter-tip transducer (blue)

The reader is currently built in conventional laboratory equipment form; the wide availability of powerful computing and wireless communication systems make the translation to a battery-powered, pocket-sized, sophisticated analysis tool with a display for the user (patient) and connection to a remote server a matter of adapting the existing features of a smart phone.

The sensors will be delivered to their site in the cardiovascular system by a catheter similar to existing ones which are used to delivery stents, replacement valves, repair devices or to make measurements within the CV system. Here again, an adaptation of existing techniques will be used or the sensors will be delivered during a planned clinical procedure, minimising the extra risk introduced by implantation. The anatomical features of both the implantation site and the access route have been used to set sensor size, resonant frequency range –determining the aerial dimensions- and retention technique constraints for the design. We are using a license-free ISM band dedicated to short-range wireless applications.

The experimental programme includes optimising the physical design of the sensor and retainer to avoid damaging the endothelium and stimulating tissue reaction which can lead to stenosis at the implantation site. A series of *in vivo* studies is under way to test all aspects of the use of chronically implanted sensors.

Genetic testing using CMOS integrated ISFET sensors

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Project partners
DNA Electronics Ltd.

Funding
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All living things are defined by their genetic code – from the unique identity of a bacteria or virus to the physical and biological traits of humans. Genes determine how a patient will respond to certain drug treatments, the cause of an illness, or a person's genetic predisposition to conditions such as disease, environment or food contamination.

Genetic and epigenetic testing is starting to revolutionize medical practice by allowing early detection of abnormal phenotype as well as by tailoring treatment to individual patients at an unprecedented level. Traditionally however, gene tests can only be carried out in a laboratory by skilled personnel. To be truly effective, a system is required for 'point of care' testing providing a real-time answer which could save time, money and lives. This will require novel genotyping devices that are cost-effective, fast, robust and easy to use. The purpose of the projects described here is to achieve this via a lab-on-chip system which integrates sample preparation, biochemical reactions and ISFET based sensors in standard CMOS.

DNA Electronics, a 'spin-out' company from Imperial led by Professor Chris Toumazou, is creating a suite of electronic microchip-based solutions to enable faster, simpler and more cost-effective DNA analysis. From scalable semiconductor sequencing to rapid, portable molecular diagnostics, the mission is to license the technology enabling licensees to create fast and user-friendly products with wide-reaching and high impact applications in personalised medicine and infection detection. DNA Electronics chips can be tailored to rapidly detect any nucleic acid sequence of interest: human, animal, plant or microbial.

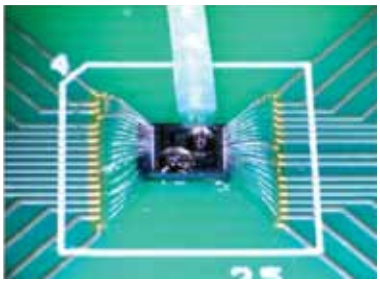
The ability to accurately detect a gene sequence in real-time using a standalone, fully portable, low power unit provides end-users with technology as yet unavailable outside a laboratory. DNA Electronics' silicon-based Genalysis™ platform delivers exactly this.

The key medical applications for this disruptive technology include: infectious disease screening; pharmacogenomic personalised medicine; clinic and home-use diagnostics and hospital bedside screening. Within the Centre we are using the Genalysis™ technology in research to further its application in a range of environments.

Two of these projects focus won optimizing the biochemistry for testing nucleotide variation using a portable point-of-care format of the technology. The third aims to pioneer its use for a different class of DNA modification, DNA methylation, by developing CMOS integrated ISFET sensors, able to detect early signs of cancer.

DIAGNOSTICS FOR OSTEOARTHRITIS

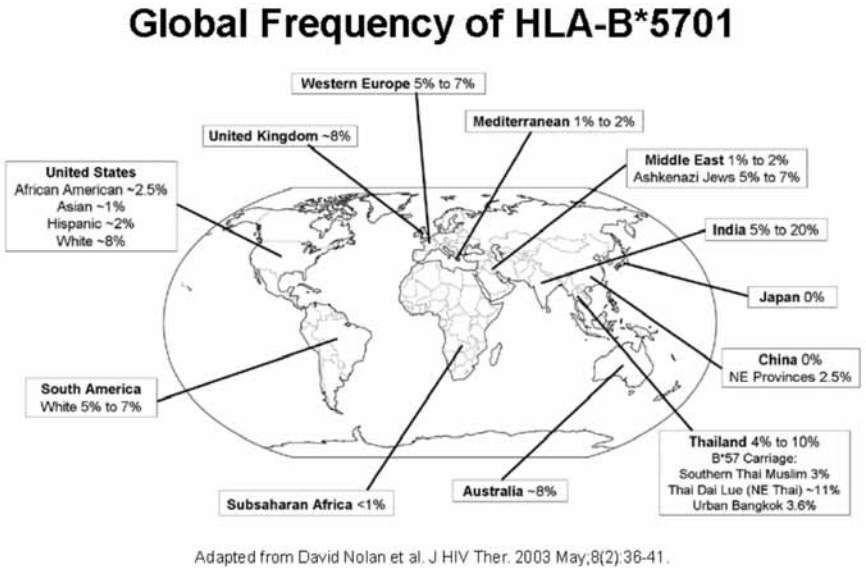
Osteoarthritis is a degenerative disease affecting the majority of the population over 60, with 1-2% developing clinical signs including severe pain and joint failure. The project consists of developing assays for published nucleotide and nucleotide repeat markers that might help to identify individuals at risk, select preventive measures and guide clinical intervention. Almost certainly these tests will involve the generation and interpretation of a genetic profile rather than that of a single marker. Importantly, the lab-on-chip/CMOS approach has the potential for multiplexing and analysing up to 50 markers without additional labour or cost.



HLA B*5701 GENOTYPING

Abacavir (ViiV healthcare) is a preferred first line long-term agent for patients starting HIV treatment in London. It has a well known side effect profile with a potentially fatal hypersensitivity reaction (HSR) during the first six weeks of treatment [1]. Individuals carrying the human leukocyte antigen (HLA) B*5701 allele, are at substantially higher risk than average of developing HSR [2]. The HLA genes encode a highly polymorphic set of cell surface glycoproteins (HLAs) that play a critical role in presenting antigens to T-cell receptors to elicit an immune response. The strong association between abacavir HSR and HLA B*5701 has been demonstrated in both observational and blinded randomized clinical trials in racially diverse populations and represents the best example of clinical utility of pharmacogenetic screening in HIV medicine. Genotyping for HLA B*5701 before prescribing an abacavir containing regimen has been introduced into routine clinical practice as the standard of care for all patients. High resolution HLA testing is needed to identify the HLA B*5701 allele and to differentiate it from closely related alleles, such as HLA-B*5702, HLA-B*5703, and HLA-B*5801/5802, which do not appear to be associated with abacavir hypersensitivity.

Several prospective trials have now demonstrated the efficacy of HLA B*5701 test in significantly reducing and/or eliminating the incidence of hypersensitivity reactions when the test was used prior to administration of abacavir therapy [2,3,4]. Genetic risk stratification based on HLA



B*5701 testing led to a decrease in incidence of HSR from 8%–9% down to 0%–1% in various prospective studies [2,3,4]. Furthermore, for patients who do not carry the HLA-B*5701 allele, the use of the test led to many fewer discontinuations of abacavir therapy for suspected hypersensitivity reactions [3,4]. A cost-effectiveness study demonstrates the test is cost-effective for a screening application prior to administering abacavir [5].

To bring personalised medicine to the bedside in the management of patients infected with HIV within Imperial College Healthcare Trust through the parallel development and validation of novel technologies aimed at point of care (POC) DNA testing to reduce drug toxicity. Current lab-based HLA B*5701 genotyping methods are expensive (c. £50) and slow (two weeks turnaround). This project aims at developing a cost-effective (c. £1), rapid (0.5 hour turnaround) and accurate HLA B*5701 typing device at POC which cannot be provided by current laboratory-based methods. In addition to its timeliness in developing POC testing which will be of immediate benefit to patients, the project will serve as a proof of principle for POC detection of other host genetic polymorphisms and the detection and quantification of infectious organisms which are identified by the NHS and UK Government as high-priority areas.

DNA METHYLATION FOR EARLY DETECTION OF CANCER

Cancer is a result of a multistep process in which genetic errors accumulate and transform a normal cell into an invasive or metastatic tumor cell. However, growing evidence has shown that acquired epigenetic abnormalities participate as well with genetic alterations to cause the dysregulation of gene functions, a key feature of cancer [6]. The growing interest in cancer epigenetics is derived from the fact that epigenetic changes are associated with oncogenesis, either by occurring in the early stages of tumor development and progression or by actually being the initiating events. Such interest has further been augmented by the recent realization that such changes can be exploited as a powerful tool in the clinic and as a novel approach for the early detection and risk assessment of the future development of cancer, opening up an exciting new avenue of research through the development of accurate and sensitive methods to detect the existence of epidemiological epigenetic patterns [7,8].

Epigenetics has evolved as a rapidly developing area of research, referring to heritable and potentially reversible alterations in the gene expression that are not coded in the DNA sequence itself. The epigenome of cancer cells has been most commonly studied at the level of DNA methylation, one of the most frequent alterations that occur in human malignancies.

DNA methylation is one of the most common epigenetic events in the human genome and a highly promising molecular biomarker, playing a critical role in regulating the gene expression. DNA methylation is one of the key epigenetic factors, biologically necessary for the maintenance of many cellular functions widely used throughout the healthy genome. In addition to genetic changes, abnormalities in DNA methylation in particular gene regions, known as ‘CpG islands’, are highly associated with genomic instability and chromosomal aberrations due to inappropriate expression of genes, resulting in epigenetic disease development, in particular cancer [8–10], [11]. Importantly, characteristic DNA methylation patterns have been detected in circulating tumor-derived DNA in the bloodstream of patients, providing a great opportunity for early detection and differentiation of tumour types, as well as monitoring the response to chemotherapeutic agents [12,13].

Over the last decade, the number of studies on the role of DNA methylation in cancer development has grown dramatically, with much effort being put into the development of early-detection strategies. However, the increased complexity together with the additional post-processing steps, the use of labels for detection together with the high cost technologies used to form those methods have been some of their limitations. Consequently, in order to achieve low-cost, biocompatible, massively produced circuitries for detecting DNA methylation with low complexity, at a low power performance, we would use CMOS based ISFET sensors, as a label-free approach, with the ability of being integrated with biochemical processing platforms.

We are developing an early detection system for cancer, in CMOS, consisting of ISFET based sensors, capable of detecting aberrantly methylated DNA of genes of interest that appear as hypermethylated in cancer. The microchip shown in Figure 4 will be capable of detecting methylated DNA markers and distinguish them from unmethylated, giving you indications of whether a specific gene related to cancer is abnormally methylated. This will allow a pro-active rather than re-active approach to treating cancer.

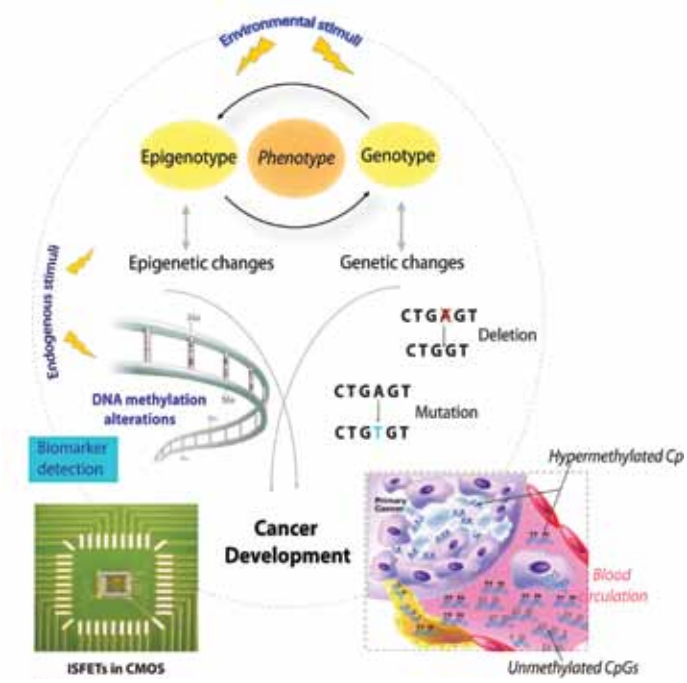


Figure 4: Epigenetic events are affected by both genetic changes and the environment; therefore our phenotype is determined not only by our genotype and the external impact, but also by our epigenotype. In specific, aberrations in DNA methylation patterns may result in cancer, so the identification of DNA methylation-based biomarkers using ISFETs in CMOS may well provide a revolutionized method for early-stage cancer detection.

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Academic staff profiles

Professor Chris Toumazou

FRS, FREng, CEng, FIET, FIEEE

- Director, Centre for Bio-Inspired Technology
- Chief Scientist and Founding Director, Institute of Biomedical Engineering
- Winston Wong Chair in Biomedical Circuits, Department of Electrical and Electronic Engineering

Chris Toumazou has made outstanding contributions to the fields of low power analogue circuit design and current mode circuits and systems for radio frequency and biomedical applications. Through his extensive record of research he has invented innovative electronic devices ranging from dual mode cellular phones to ultra-low power devices for both medical diagnosis and therapy. He has developed a range of innovative electronic devices, utilising analogue mobile phone technology, for use in patient care. This includes the Sensium™ Ultra-Low Power Wireless Body Monitoring System which gives physicians constant access to vital signs including ECG, body temperature, respiration and physical activity of patients with chronic illnesses based at home.

Whilst working on his PhD, he made major advances in the field which led to a radical transformation of analogue signal processing. An insight, which in retrospect may look simple, was to give current rather than voltage the main role in signal processing. Using transistors in the weak inversion regime, the current mode methodology led to markedly superior performance, most dramatically in reduced power consumption. These advances opened up a range of applications, in telecommunications and also in the design of prosthetic implants. In recognition of his outstanding research he was made a Professor at Imperial College London at 33, one of the youngest ever to achieve this distinction.

His pioneering research showed how the natural analogue physics of silicon technology could be used to mimic and replace biological functions. Amongst his many achievements are: the development of one of the world's first implantable cochlear chips, which gave hearing back to the born deaf; the development of an artificial retina using local intelligence to achieve micropower consumption; the development of the silicon pancreas, which mimics the function of the pancreatic beta cell to regulate insulin flow for people with type 1 diabetes and, in collaboration with Professor Sir Magdi Yacoub, the development of a miniature sensor to monitor the hearts of people who have undergone heart operations or who have conditions that could lead to heart failure. In 2001 he invented a silicon chip technology to detect DNA sequences, a fundamental breakthrough in the field of genetics with enormous potential to transform medicine. Moreover, the technology has profound implications for agricultural and food industries, forensics and biosecurity.

In order to realize the enormous potential of these technologies, Professor Toumazou led a campaign to raise £26 million to create a new, postgraduate research institute at Imperial College London and in 2004 established the Institute of Biomedical Engineering, a state-of-the-art facility drawing scientists, medical researchers, clinicians and engineers together to advance medical innovation by applying engineering platform technology to medicine. His own specialism is in the field of personalised healthcare, providing worn or implantable devices for early diagnosis and detection of disease.

He is the founder of four technology based companies with applications spanning intelligent wireless technology for chronic disease management (Toumaz Technology Ltd, UK), biomedical devices (Applied Bionics PTE, Singapore), Digital Audio Broadcasting (Future-Waves Pte Taiwan) and DNA Sequencing (DNA Electronics Ltd, UK). These companies employ over 50 RF and low power engineers worldwide many of whom are former graduate students.

In 2008 he was awarded a Fellowship of both the Royal Society and the Royal Academy of Engineering and he has received numerous awards and prizes for his innovative research including the 2009 World Technology Award for Health and Medicine, the Silver Medal of the Royal Academy of Engineering in 2007 and in 2010 an Honorary DEng from Oxford Brookes University. In 2009 he gave the Keynote Lecture to mark the IEEE 125th Anniversary celebrations in Europe at the Royal Institution. His publications include over 400 research papers in the field of RF and low power electronics and he holds 23 patents in the field many of which are now fully granted.

Dr Timothy Constandinou

BEng(Hons), DIC, PhD, CEng, FIET, SMIEEE

» Lecturer, Department of Electrical and Electronic Engineering

» Deputy Director, Centre for Bio-Inspired Technology

Timothy graduated with a 1st class honours BEng degree in Electrical and Electronic Engineering in 2001 and the PhD degree in 2005 both from Imperial College London. He then joined the Institute of Biomedical Engineering as Research Officer until 2009, when he was appointed Deputy Director, Centre for Bio-Inspired Technology. In 2010, he joined the academic faculty as a lecturer in the Department of Electrical and Electronic Engineering, whilst maintaining his research at the Centre for Bio-Inspired Technology.

His research utilises integrated circuit and microsystem technologies to address challenges in implantable neural prosthetics, brain-machine interfaces, lab-on-chip platforms and medical devices in general. His main focus is to develop microelectronics that interface with neural pathways for restoring lost function in sensory, cognitive and motor impaired patients. In the past he has developed integrated circuits for implantable cochlear and vestibular prostheses as well as for retinal vision processing. His current projects include:

- Next Generation Neural Interfaces: developing the first of its kind, cortical implant for the real-time monitoring of the activity of 100s to 1000s of neurons which will empower the next generation of neural interfaces for motor rehabilitation;
- Neural Prosthesis for Proprioception: investigating the provision of artificial proprioceptive feedback from a prosthetic limb by direct electrical stimulation of nerves using a neural implant;
- CMOS electro-optical lab-on-chip platform: by exploiting the plasma dispersion effect, a CMOS photonics platform is being developed for bondwire-less integrated circuits;
- Wireless Capsule Technology for Targeted Drug Delivery: developing a swallowable microrobotic platform capable of delivering a 1ml payload of medication to a target site within the small intestines.

Other research he has contributed to that has led to commercial ventures includes a disposable intelligent vital signs monitor (Toumaz Technology Ltd) and a point-of-care portable platform technology for genetic detection (DNA Electronics Ltd).

Dr Constandinou is a Senior Member of the IEEE, a Fellow of the IET, a Chartered Engineer and SPIE Member. Since 2005, he has served on both the Biomedical Circuits and Systems (BioCAS) and Sensory Systems Technical Committees (within the IEEE CAS Society). In 2009, he received the IET Mike Sargeant Achievement Award in recognition of his early career achievement. In 2009 he served as Guest Editor for a Special Issue of the IEEE Transactions on Biomedical Circuits and Systems. In 2010, and again in 2011, he was the Technical Program Chair of the IEEE Biomedical Circuits and Systems Conference. In 2011, he was elected the Chair of the IEEE CAS Society, Sensory Systems Technical Committee.

Dr Pantelis Georgiou

MENG(Hons), DIC, PhD, MIET, MIEEE

» Lecturer in Circuits and Systems, Department of Electrical and Electronic Engineering

» Head of Metabolic Technology Laboratory, Centre for Bio-Inspired Technology

Pantelis Georgiou received the MEng degree in Electrical and Electronic Engineering with 1st class honours in 2004 and a PhD degree in 2008 both from Imperial College London. He moved to the Institute of Biomedical Engineering where he was appointed as a research fellow and conducted pioneering work on the silicon beta cell leading towards the development of the first bio-inspired artificial pancreas for type 1 diabetes. In 2011, he joined the academic faculty where he became a lecturer within the Department of Electrical and Electronic Engineering. He is also the Head of the Bio-Inspired Metabolic Technology Laboratory in the Centre for Bio-Inspired Technology and part of the Medical Engineering Solutions in Osteoarthritis Centre of Excellence. He is a member of the IEEE and IET and has been elected a member of the BioCAS Technical Committee of the IEEE Circuits and Systems Society. In 2004 he was awarded the Governors' Prize for Electrical and Electronic Engineering.

His current research within the centre includes:

Bio-inspired design: this involves designing systems by taking inspiration from biology to

- try and understand complex biological behaviours
- replicate bio-inspired processing to make more efficient electronic systems
- make prosthetics to replace biology with something which is more physiological. One of his main focuses of research is the creation of the bio-inspired artificial pancreas.

Integrated sensing systems: this involves integrating sensing modalities within available CMOS technology allowing the design of lab-on-chip devices, which fully integrate chemical sensors and low-power instrumentation and processing algorithms. His key projects in this field are ISFET based chemical sensing, and a DNA sequencing engine.

Medical devices: this involves utilising the knowledge of bio-inspired design and integrated sensing to make novel medical devices in application of early detection, diagnosis and therapy of disease. Additionally, this research theme involves the development of wireless telemedicine platforms to integrate all medical devices. Research projects include rehabilitation technology for osteoarthritis, and wireless telemedicine platforms for diabetes.

Pantelis has also been involved in the development of several commercial technologies such as a disposable intelligent vital signs monitor (Toumaz Technology Ltd) and a point-of-care portable platform technology for genetic detection (DNA Electronics Ltd).

Staff research reports

Dr Reza Bahmanyar

Research focus
Implantable SAW transponder for acute and chronic blood pressure monitoring

Funding
Wellcome Trust

Many cardiovascular and respiratory diseases cause blood pressure changes in the chambers of the heart and the vessels linking the heart and lungs. Measuring such localised pressures has had to rely either on inaccurate external measurements or intermittent data from expensive, and somewhat risky, catheterisations.

Surface acoustic wave (SAW) resonators have been used for wireless pressure measurement in the automotive industry and may be adapted to make implantable sensors for cardiovascular, intra-ocular and intra-cranial blood pressure measurements. Using micro-fabrication techniques, SAW resonators can be made into pressure sensitive sensors. These sensors possess inherent characteristics of SAW devices, namely small size, high stability and very long life. When connected to an antenna, such sensors would form a transponder that can be interrogated for pressure information wirelessly.

Using SAW devices for pressure measurement in the body poses a number of challenges compared to their typical use in tyre pressure monitoring. These include device biocompatibility, delivery system, reliable RF signal transmission and reception, while complying with telecommunication regulations, and signal acquisition and processing.

In order to investigate different aspects of RF interrogation and obtain optimal operating parameters, a portable and flexible system suitable for *in vitro*/*in vivo* animal testing, is required.

The focus of my research within the project is the design and prototyping of the RF interrogating systems, sensor prototyping and characterization, implantable antenna testing as well as signal acquisition and processing. Based on the technical requirements of the project, a number of implants, as well as two RF interrogating systems, have been prototyped and successfully used in animal tests. Currently, different aspects of the project are being optimized in order to achieve approvable medical devices for a clinical trial during the next three years.

Dr Alessandro Borghi

Research focus
Implantable SAW transponder for acute and chronic blood pressure monitoring

Funding
Wellcome Trust

Heart failure is a common, disabling and deadly disease, which affects 1–2% of the population in developed countries, with higher incidence in the elderly population (6–10% of the population over 65 years). It is associated with high health expenditure: in UK the estimated costs have been estimated to be up to 2% of the NHS budget. Heart failure is linked to increased left atrial pressure and, when associated with chronic obstructive pulmonary disease, it can cause pulmonary hypertension (increased pulmonary artery pressure). Hence, the on-going assessment of localized pressures becomes crucial for the monitoring of cardiac failure patients. So far, it has had to rely on inaccurate external measurement or intermittent and invasive and, therefore, partial and risky internal measurements.

This project focuses on the design of a novel pressure sensor based on the surface acoustic wave (SAW) technology, previously employed in telecommunication as well as automotive sectors.

My role in the project is to design a way to position the pressure sensor inside the body and ensure its mechanical stability and biocompatibility, which is the key to maximize the cohort of patients who could benefit from this technology. Materials have been selected to minimize host-tissue reaction and maximize hemocompatibility. After histology tests were performed to ensure body reaction is acceptable, I designed and produced a number of geometrical prototypes which allowed different aerial configurations. A delivery system has been designed and tested in animal model and key issues have been identified to ensure successful deployment. The ongoing work is focusing on the optimization of the device structure and performance and on the scale-up of the production process.

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Dr Nir Grossman

Research focus
Optogenetic Neural Stimulation

Funding
EPSRC, BBSRC, University of London

SUMMARY

Studying neuronal processes such as synaptic summation, dendritic physiology and neural network dynamics requires complex spatiotemporal control over neuronal activities. The recent development of neural photosensitization tools, such as channelrhodopsin-2 (ChR2), offers new opportunities for non-invasive, flexible and cell-specific neuronal stimulation.

METHOD AND RESULTS

First, I developed a novel neural optical stimulator using a matrix of 64 × 64 high-power micro-LEDs. It has optical configurations for both neural network stimulation and for single-cell experimentations. I demonstrated its application *in-vitro* on hippocampal neurons and *ex-vivo* mice retina tissues. The technique provides sophisticated spatiotemporal stimulation patterns for studying neural network dynamics, neuronal disorders and for neural prosthesis applications. The paper presenting this technique [2] was chosen as Top Paper of 2010 by the *Journal of Neural Engineering*.

I then developed a mathematical model, together with Dr Nikolic of CBIT, to represent the response of ChR2-expressing neurons to light stimuli, and then used the model to explore the dynamics of this novel stimulation process. I used the model to examine the effects of using various types of ChR2 mutants. The model and the conclusions presented in this study can help to interpret experimental results, design illumination protocols and seek improvement strategies in the nascent optogenetic field. The major results of this study were published [1,3].

NEXT STEPS

Both the theoretical model and the optical tool will be made available for the neuroscience research community. The model will be expended to incorporate other light sensitive proteins. The optical technology will be further developed to incorporate other neural interfacing.

RECENT PUBLICATIONS

1. Grossman N, K Nikolic, C Toumazou and P Degenaar, 'Modeling Study of the Light Stimulation of a Neuron Cell with Channelrhodopsin-2 Mutants', *IEEE Transactions on Biomedical Engineering*. (Accepted for publication February 2011)

2. Grossman N, V Pohrer, M Grubb, GT Kennedy, K Nikolic, MAA Neil, M D Dawson, J Burrone and P Degenaar, 'Multi-site optical excitation using ChR2 and micro-LED array', *J. Neural Eng*., 7, 16004, 2010.

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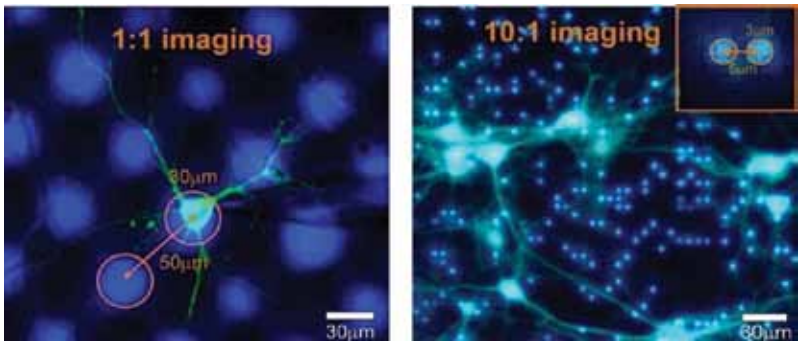
2. Highlights of 2010, *Journal of Neural Engineering*, published online 2011.



« **Figure 1:** Neural cells expressing ChR2 are covered by the 64 × 64 matrix of bright small light spots, with individual control of their intensity and timing.

Professor Chris McLeod

Research focus
Implantable pressure sensor for chronic blood pressure monitoring

Funding
Wellcome Trust

Telecare, Telehealth, eHealth and mHealth are labels applied to systems being developed to improve the care of patients outside conventional clinical settings. The first two usually refer to patients reporting via phone or an internet connection some details of their symptoms and some measurements (weight, temperature, indirect blood pressure measurement, subjective pain, as appropriate to their condition) and receiving advice on medication or lifestyle (exercise, diet) from a clinically qualified respondent. eHealth and mHealth usually refer to the reporting of more objective measurements through electronic communications.

Heart failure is a chronic and progressive condition which can be alleviated and its progression retarded by a combination of drugs, all of which have some side effects, and have therefore to be personalised. This is achieved by making regular clinic visits when weight and blood pressure (BP), in particular, are measured and drug dosages altered. Successful medication reduces blood pressure and improves the patient's ability to walk distances and perform more activities without becoming breathless.

Our research focus is to help health services to achieve successful medication for more of its heart failure patients at a lower staffing, pharmaceutical and financial cost. Recent 'telehealth' trials for heart failure patients[1] have shown no advantage over conventional treatment but use of accurate BP data from an implanted sensor in the pulmonary artery has shown a very significant improvement. Rothwell et al[2] have shown that periodic, accurate blood pressure monitoring (BPM) enables BP variability to be measured; high variability is a better predictor for both the progression of hypertension and the likelihood of stroke.

Our wireless pressure sensor is designed to be implantable in any of the major cardiovascular vessels and to be adaptable for implantation within the heart. The application to heart failure is one example of the intended use of the sensor. Others are for pulmonary arterial hypertension and systemic hypertension.

The capability of continuous BPM enables the development of complex software to extract significant events and to reduce the data to manageable quantities for practical realisations but also to aid research into the effects of treatments by providing hitherto unobtainable measurements.

My roles within the overall project range from research planning and fund-raising to the details of sensor design, data handling and communications in collaboration with the subject experts in the team.

[1]Tele-HF trial, published online November 16, 2010 in *The New England Journal of Medicine*

[2]Rothwell et al. *Lancet*, Vol. 375, pp. 895–905, 2010.

Dr Olive Murphy

Research focus
Implantable SAW transponder for acute and chronic blood pressure monitoring

Funding
Wellcome Trust Technology Transfer Translation Award

The project is based around the development of an implantable surface acoustic wave (SAW) device as an alternative to a wearable blood pressure monitor. The inherent properties of the piezoelectric device with its small size and high stability are exploited and are used to track pressure variations. In addition, the passive sensor is powered from outside the body, producing a reliable and safe method of continuous monitoring.

The on-going assessment of localised pressures has had to rely on inaccurate external measurement or intermittent and invasive and, therefore, partial and risky internal measurements. The difficulties associated with internal direct measurements are device size, power requirements, accuracy, performance degradation, and the risk of infection. Using the SAW pressure sensor, cardiovascular, intra-ocular and intra-cranial pressures can be precisely measured. The traditional difficulties are reduced, and in some cases eliminated, as the SAW transponder is a minute, biocompatible, highly accurate passive device which is now being used to provide continuous pressure monitoring.

My particular areas of research within this project involve sensor characterization and assembly along with the design, optimization and *in vitro/in vivo* testing of deeply implanted antennas. The position and orientation of the implanted antennas are crucial to the efficiency and performance of the whole implanted system. Recent in-vivo experiments have shown excellent results for implanted sensors. The extent of the expertise and data acquired through this research is unique to the Centre and could be easily applied to other deeply implanted sensors.

RECENT PUBLICATION

1. Murphy OH, CN McLeod, M Narvaratnarajah, M Yacoub and C Toumazou, 'A Pseudo-Normal-Mode Helical Antenna for use with Deeply Implanted Wireless Sensors', *IEEE Transactions on Antennas and Propagation*. Accepted for publication 2011.

Dr Belinda Nedjai

Research focus

Clinical applications of neural monitoring technology and development of the next generation in personalised healthcare systems

Funding

Winston Wong Centre for Bio-Inspired Technology

SUMMARY

This research project forms a cross-disciplinary field at the interface between biology, physics, engineering and medicine. The first application of this project is a system to help monitor neural activity and identify, through a processing algorithm, abnormalities in the neural signal. We explore epilepsy and seizure detection as an application case study to show the potential of this method. My role in this project is to contribute to the classification of epileptic predictive marker subgroups (biological markers). For this study we started a Clinical Trial-Stimulation for seizure prediction using our algorithm in collaboration with a research group at King's College London.

The second part of this project will use data from patients involved in the clinical trial. I will explore the link between EEG, genetic information and standard tests (such as blood and urine tests) and how they are linked together to define a personalised benchmark (Figure 1). We aim to create a database to support these results and the information collected will be extremely useful to identify, or confirm, subgroups in epileptic patients in the first instance.

Finally, in the last part of this project, I will investigate the role of the vagus nerve in epilepsy and examine the effect of vagus nerve stimulation on pro-inflammatory cytokine release (Figure 2). Using cuff electrode technology for nerve stimulation and recording, I will investigate mechanisms by which the vagus nerve transmits information to the brain and modulates inflammatory-related processes in the periphery for relevant diseases.

METHOD

The Advanced Neural Interfaces Group at Imperial College London develops innovative custom-designed neural monitoring microelectronics and microsensors that comprise the components of implantable Advanced Neural Monitoring System (ANeMoS). More specifically, we have designed a 56-contact cuff electrode, the so-called 'matrix' cuff, to obtain selective information regarding the direction of the signals as well as the location of the active organ or muscle group.

RESULTS

Our preliminary results show selective, unidirectional activation of A-type nerve fibres using cuff electrode technology. By developing an implantable monitoring and stimulation device for epilepsy management we are seeking improvements in medical care and quality of life for patients.

NEXT STEPS

We are collaborating in the King's College London Clinical Trial-Stimulation-based Seizure Prediction Algorithm. My role will be in the validation of our technique and to develop a hardware system.

KEY PUBLICATIONS

1. Nedjai B et al. 'Differential cytokine secretion results from p65 and c-Rel NF-κB subunit signalling in peripheral blood mononuclear cells of TNF receptor-associated periodic syndrome patients', *Cell Immunol*;268(2):55–9. Epub Mar 1 2011.
2. Nedjai B et al. 'Lessons from anti-TNF biologics: infliximab failure in a TRAPS family with the T50M mutation in TNFRSF1A', *Adv Exp Med Biol* 691:409–19, 2011.
3. Hall SE et al. 'Elucidation of binding sites of dual antagonists in the human chemokine receptors CCR2 and CCR5', *Mol Pharmacol* Jun; 75(6):1325–36. Epub Mar 18 2009.
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2. Juffali W et al. 'The WiNAM Project: Neural Data Analysis with Applications to Epilepsy', *IEEE BioCAS*, 2010.

Dr Konstantin Nikolic

Research focus
Initiatives in neurotechnology

Funding
EPSRC, EU FP7, Corrigan, Imperial Strategic Initiative in Neurotechnology

BACKGROUND

The Faculty of Engineering at Imperial launched the Strategic Initiative in Neurotechnology in 2009. The main aim of the Initiative is to promote collaboration between neuroscientists, engineers and physical scientists, at Imperial and elsewhere, in order to create the next generation of novel technologies for neuroscience experiments, to develop the next generation of therapeutic approaches for brain disorders, and to drive the development of brain-derived technologies for the wider benefit of society.

Neurotechnology encompasses a number of interdisciplinary approaches in neuroscience: using insights and tools from mathematics, the physical sciences and engineering in the investigation of brain function; and using our understanding of neuroscience to aid the design of engineering solutions to real-world problems. Imperial has particular strengths in neural coding, *in vivo* electrophysiological recordings from mammalian and insect brains, the development of novel data analysis algorithms for large-scale neural recordings, novel neuroimaging analysis algorithms, the development of novel biosensors for measuring neurotransmitters and neurometabolytes, multidimensional fluorescence imaging approaches (such as fluorescence lifetime imaging), reversible transgenic gene knockout technologies, the cellular and molecular bases of sleep and anaesthesia, low-power VLSI electronics, robotics, rehabilitation, and human motor control.

My personal research focus is in the fields of mathematical biology, computational neuroscience, retina, optogenetics and optical neural interfacing. I am currently applying these techniques to a range of projects underway in the Centre and directly involved in research in the following areas:

- **Bio-inspired modelling:** modelling and simulations of the experimentally-determined retinal architectures. This research is part of the *SeeBetter* EU project.
- **Thermoelectric extracellular stimulation of myelinated nerves:** the electrical behavior of the Xenopus laevis nerve fibers were studied both theoretically and experimentally, when combined electrical (cuff electrodes) and optical (infrared laser, low power sub-5mW) stimulations are applied. The calculations involve an axial symmetry finite-element model (COMSOL) to calculate electric field distribution along the nerve and imported into a NEURON model, which was built to simulate the electrical behaviour of myelinated nerve fibre. The main result of this study showed that local temperature increase, for the given electric field, can create a transient block of both the generation and propagation of the APs.
- **Light control of neurons:** channelrhodopsin-2 module in NEURON. Optogenetic technology now allows specific, genetically determined and anatomically targeted classes of neurons to be either stimulated or suppressed, by means of a light-activated channel inserted into a cell. Channelrhodopsin (ChR2) and halorhodopsin (NpHR) are examples of such channels. However, their mechanisms of action potential generation and suppression with these channels are still poorly understood. This project aims to incorporate a kinetic model for ChR2 (and also NpHR if possible) into the NEURON environment and then use this tool to investigate the effect of different spatiotemporal illumination patterns on the spiking output. If successful, the project will provide the nascent optogenetic field a powerful tool to selectively stimulate/inhibit neurons in variety of neural networks and configurations for studying functional circuit connectivity and has direct implications in future therapeutic strategies.
- **Stochastic resonance in the human sensory neural pathways:** a pilot study was conducted on 20 subjects in an acoustic anechoic chamber (Figure 1), noting down their gender, age group, first language, musical experience and hearing loss problems. The experiment involved playing noise in one ear and a speech signal in the other ear using the Oldenburg Measurement Applications software. The speech recognition threshold in noise (SRT) was measured on the basis of the English Matrix Sentence Test. The correlation between the noise level and the total signal was established. The expected effect was found only for people where English is not their first language (Figure 1). Another outcome was that the SRT was higher on average for subjects for whom English was not their first language in comparison to those for whom it was. Further research is needed, in particular on subjects with cochlear implants to test for hearing improvements.

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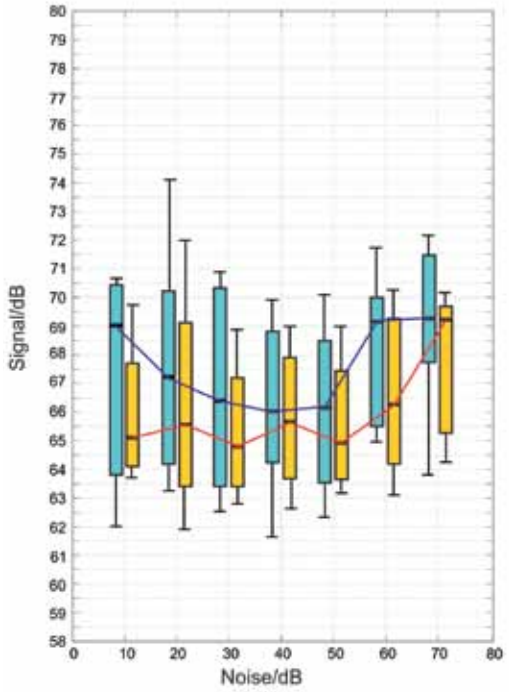

Figure 1. The experiment took place in an anechoic chamber and the test subjects wore noise cancelling headphones. A box plot diagram which shows the distribution of data for subjects for whom English is (red, 10 subjects) or is not (blue, 10 subjects) their first language.

Dr Themis Prodromakis

Research focus
Emerging bio-inspired devices

Funders
WJ Corrigan, EPSRC, The AG Leventis Foundation

SUMMARY

Never has the merger between biology and engineering been so strong, with innovations in medical devices being driven by emerging micro/nano-fabrication techniques. Some of nature's best tricks are conceptually simple and easy to rationalize in physical or engineering terms; but realizing them requires reaching down to the microscopic and ultimately the molecular scale. The advancement of nanotechnologies has provided the means to follow this bottom-up approach by utilising well-established technologies in an innovative way for developing architectures that imitate the functions of biological systems as well as linking their chemical expressions to engineering platforms. Being inspired by the physiology of biological systems, replica devices of the retina, the synapse and the ion-channels with similar functionalities to their biological counterparts can thus be established.

METHODS

Commercially available as well as customised CMOS technologies have been exploited in innovative ways for enhancing the performance of chemical sensors and particularly ISFETs [1]. This work has provided important insights to issues that have challenged engineers within the sensors community such as noise and drift of chemical sensors and has led into a benchmark method for developing low-cost versatile chemical sensing platforms [2–3] and a novel practical approach for the biocompatible encapsulation of integrated sensors [4].

On the other hand, the recent discovery of the memristor has marked a new era for the advancement of neuromorphic applications. Our group has been one of the first within the UK that has made significant research contributions in this field through in-house fabrication [5–6], characterisation [7], modelling [8] and application [9].

NEXT STEPS

Currently I am developing novel nano-scale transducing elements, inspired by biological ion-channels, that can demonstrate an ultra-high detection sensitivity, accuracy and wide dynamic range for significantly enhancing the current state-of-the-art spatio-temporal sensing resolution [10].

The non-linear dynamics as well as the plasticity of the newly discovered memristor are shown to support spike-based and spike-timing-dependent-plasticity (STDP), making this extremely compact device an excellent candidate for realizing large-scale self-adaptive circuits. Our group is particularly exploiting this attribute for developing more efficient nanoscale devices and complex memristive networks that could imitate synaptic networks and essentially the way the human brain functions in processing and storing of information perceived by our body's sensory network.

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Dr Dylan Banks

Research focus
Non-invasive stent blood flow telemetry

Funding
Winston Wong Centre for Bio-Inspired Technology

BACKGROUND

Stenosis is the narrowing of a blood vessel, leading to restricted blood flow, and may be treated by endovascular stenting – the placement of a rigid cuff inside the blood vessel. There is a risk that further narrowing can occur, this is known as restenosis. The risk of restenosis is around 17-18% but this can rise to 25% in diabetic patients. If undetected, restenosis significantly affects morbidity and mortality. As such, the standard protocol is to measure progress at six weeks, three months and twelve months.

Detection of stenosis at present requires contrast angiography in the coronary vessels and a combination of angiography and doppler ultrasound in the peripheral vasculature. I have developed techniques that allow the external measurement of conducting liquids through a stent providing a non-invasive measurement of flow and turbulence within a stent. This provides better, and more timely, judgments of surgical and other interventions.

SCIENTIFIC RATIONALE

I have shown [1] that this technique can be used to measure NaCl concentrations and other analytes within a static fluid. A well known and simple extension to this system yields a quantitative measure of fluid flow [2] and it is a development of this that we are employing within this research.

THE DEVICE

The device is hand held, and slightly larger than a mobile phone which is held to the skin of the patient. The device locates the stents by sending out an electromagnetic beam which detects reflection differences from the beam.

PROGRESS TO DATE

I am working in collaboration with Professor Nick Cheshire, Professor of Vascular Surgery, Department of Surgery and Cancer at Imperial, and have been awarded £560k from the Biomedical Research Council to develop this product towards clinical trials. We expect these trials to commence in early 2012.

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Dr Amir Eftekhar

Research focus
Neural interfacing, acquisition and analysis

Funding
Winston Wong Centre for Bio-Inspired Technology

The primary focus of my work involves interfacing neural tissue in the central and peripheral nervous system. This involves

- electrode technology for interfacing with the central and peripheral nervous system
- front-end electronics for implantable or portable systems to interface with these electrodes
- advanced signal processing methods for extracting and quantifying the dynamical behaviour of the neural signals.

At present, I am largely involved with two main projects. The first is an analysis methodology for extracting detective and predictive markers from brain electrical signals (EEG and intracranial electrodes) related to epilepsy.

Epilepsy affects 450,000 people in the UK and an estimated 0.85% of the world's population. It is characterised by hypersynchronous neural firing in the brain (seizures) that can manifest as brief absences to complete loss of consciousness and motor control. Only 70% of patients can be seizure free with medication, although there are many associated cognitive side effects. However, according to a recent Joint Epilepsy Council briefing, only 52% of patients receive optimal treatment, leaving 69,000 without. In addition 1000 people per year die of epilepsy related causes, of which 400 are avoidable with better treatment and diagnosis. Of the remaining 30% only 3% are eligible for surgery, although with an estimated efficacy of seizure frequency reduction of 20% and a surgery backlog that is predicted will never be cleared. Overall it is estimated £150 million per year needs to be invested to improve and facilitate better epilepsy diagnosis and treatment.

Little is understood as to the mechanisms that lead up to a seizure and as such a wealth of literature has focused on analysing brain signals to predict the onset of them. The ability to define the necessary methods or algorithms for extracting such features as well as translating them into realistic real-time software and hardware implementations is the focus of my work. This will aid in bridging the gap between the sensing front end and treatment or visual back end for any biomedical or personalised healthcare system.

There are many algorithms that achieve this bridge – and the aim is to have a method that has clinical and biological relevance. I am collaborating with a PhD student, Walid Juffali and Dr Jamil El-Imad using novel analysis schemes with the aim of characterizing EEG behavior in a general framework. We are working with King's College London Epilepsy Research Group and EPI epilepsy centre in Zurich to analyse and assess our methods for seizure detection and prediction.

The other aspect of my work is peripheral interfaces for monitoring electrical and chemical signatures associated with action potential propagation. We are developing electrodes that are potassium, calcium and sodium sensitive to monitor intrafascicular activity. This type of information allows us to obtain recordings with less interference from electrical sources and give more detailed information about the underlying neural dynamics for application such as vagus nerve stimulation (VNS).

VNS therapy has emerged over the last 20 years as an effective non-drug treatment. An estimated 50% reduction of seizures can be achieved that increases over time. Now due to longer battery life it has become a feasible cost-effective treatment. However, although estimated to greatly improve quality of life, it has a number of unwanted side effects such as voice alteration, headaches, pain, breathlessness and headaches. These are due to high amplitude and non-selective stimulation that is activated frequently (every 5 minutes) regardless of whether any epileptic activity manifests. The platform we are developing aims to add recording input to the stimulation parameters including amplitude and frequency providing more effective and intelligent stimulation that can potentially increase the efficacy and viability of VNS as a treatment. Initial projects are being formulated in collaboration with King's College London Epilepsy Research Group to develop this technology and to study the use of this technology in improving VNS therapy.

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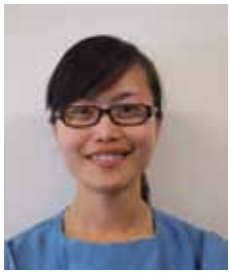

Dr Zhaolei Lang

Research focus
Point of care testing on HLA B*5701 genotyping

Funder
National Institute for Health Research (NIHR); Comprehensive Biomedical Research Centre (BRC)

SUMMARY

Abacavir (ViiV healthcare) is off-patent and one of the most widely used drugs in the long-term treatment of HIV, of which the side effect of hypersensitivity reaction (HSR) is known to be associated with certain genotype. Between 5% and 8% of patients developed HSR, which can be fatal during the first 6 weeks of treatment [1,2]. Individuals carrying the HLA B*5701 allele, an allele of the Human Leukocyte Antigen system, are at substantially higher risk of developing HSR and genotyping is recommended prior to abacavir treatment by the FDA [3]. In the case of emergency prescription, there is an urgent need for rapid and accurate HLA B*5701 genotyping to assist on-site drug description. The need is not filled by the current long turnaround time and usually involves sending samples to a specialized laboratory.

Recently, a label-free electrochemical DNA detection technology using an ion-sensitive field effect transistor (ISFET) has been developed for point-of-care gene detection [4]. My research focus is to develop a portable point-of-care genotyping device, which utilizes de-skilled, cost-effective, disposable and low power system for rapid real-time HLA B*5701 diagnosis. Such technology will benefit both service providers and patients by reducing the risk and time on the treatment, which in turn improve the performance to cost ratio, and eventually improving the understanding of patients' genetic status to assist personalized medication.

METHOD

PCR-based detection assays in micro tubes have been designed for HLA B*5701 genotyping of clinical blood samples and the method is benchmarked to result from sequence-based typing (SBT). The PCR-based assays have also been optimised for ISFET detection using the device. Isothermal genotyping assay is being designed, the result will be used to optimise for the clinical samples and the performance will be compared between isothermal and PCR-based assays.

RESULTS TO DATE

PCR-based assay showed 100% concordance with SBT results, confirming its accuracy. Through optimization, a greatly improved product yield was achieved with a consistent signal from ISFET detection. Further optimization is needed to enhance the output signal. Isothermal assay is under development for evaluation.

NEXT STEPS

My ongoing research includes design and evaluation of allele-specific isothermal assay, benchmarking both PCR-based and isothermal assays by ISFET detection. In further research I will focus on sampling method using salivary extraction for the development of rapid genotyping study. I will validate the sampling method using clinical performance data on PCR and isothermal assays. Eventually, the goal is the integration of the sampling and amplification to the novel lab-on-chip prototype from DNA Electronics Ltd to achieve the realisation of a point-of-care HLA B*5701 genotyping device.

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Dr Herrero Viñas Pau

Research focus
Bio-Inspired artificial pancreas

Funder
Wellcome Trust

The main focus of my research is the design of algorithms for the development of a bio-inspired artificial pancreas (AP) for the management of type 1 diabetes mellitus (T1DM). The final aim of the project is to transfer this technology to initial clinical trials and, ultimately, to a commercially available system.

Algorithms which I have developed as part of this research include: a novel bio-inspired glucose controller based on a model of the β-cell physiology of the pancreas, which has already been validated using an FDA-accepted simulator; a robust fault detection system to detect possible adverse events in an AP; a new technique for estimating the rate of glucose appearance for mixed meal; and a glucagon-extended model for in-silico testing of bi-hormonal glucose controllers.

Another ongoing area of research that is under my focus is the development of an insulin dosing decision support system for T1DM management based on Case Based Reasoning (CBR). The CBR algorithm, together with a telemedicine platform to incorporate this, will be clinically tested.

The final area of research I am involved in is a project which aims to develop a portable and affordable system for safe and effective blood glucose control in hospitalised patients. By using CMOS ASIC technology, this system is intended to integrate a glucose control algorithm and a fault detection and supervision system, together with a commercially available subcutaneous continuous glucose sensor and an intravenous insulin pump.

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Dr Irina Spulber

Research focus
Wireless body sensors system for management of osteoarthritis

Funder
Wellcome Trust, EPSRC

SUMMARY

Osteoarthritis (OA) is a chronic disorder resulting in degenerative changes to the joints that cause pain and loss in mobility. In the UK alone, this condition affects 8.5 million people and is a leading cause of disability and the most common cause of chronic pain, with huge social and economic costs.

To date, there is no cure for osteoarthritis, the condition is mainly managed through lifestyle modifications complemented by pain-killing treatments. Correct regular exercise has been shown to significantly improve function, alleviate pain, and delay the need for surgical intervention. Despite the proven benefits, it is often the case that physiotherapy fails to fulfill its full potential mainly due to poor attendance at sessions, poor compliance to the prescribed regimen or even incorrect execution of exercises due to lack of feedback.

Correct, regular exercise has been shown to significantly improve function, alleviate pain, and delay the need for surgical intervention. The present project embodies one of the research objectives of the Medical Engineering Solutions in Osteoarthritis Centre of Excellence and brings together expertise from Imperial's Musculoskeletal Surgery Department, Centre for Bio-Inspired Technology and Toumaz – a low cost, ultra-low power wireless technology company.

METHOD

Within the frame of this collaborative research, my aim is to develop a dedicated medical sensor system capable of assisting OA patients in their rehabilitation process. The project builds on Toumaz's Sensium™ platform which requires refinement and tailoring for OA monitoring. The wireless sensors will be body-worn and/or embedded into smart clothing to monitor joint motion, muscle activation (EMG) and body movement patterns.

Preliminary tests have been conducted in parallel on Sensium™ and standard gait laboratory equipment in order to evaluate the inertial sensors performance and validate them against the standard optical system. My research will further focus on low-power sensor integration, system development and testing, clinical data collection, data processing, data interpretation and algorithms implementation.

The OA body sensor system will monitor function remotely and provide appropriate feedback to both patient and practitioner, thus assisting the physiotherapists in devising customised rehabilitation strategies to improve therapy outcomes and patient compliance.

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Dr Thomas Weissensteiner

Research focus
Point of care diagnostics for osteoarthritis based on DNA enzymology and CMOS sensors

Funder
Wellcome Trust, EPSRC

SUMMARY

Osteoarthritis is a degenerative disease affecting the majority of the population over 60, with 1-2% developing clinical signs including severe pain and joint failure. Although the disease is poorly understood at present, future molecular diagnostics might help to identify individuals at risk, select preventive measures and guide clinical intervention. My project is the development of biochemical assays for point-of-care genetic testing, using CMOS sensors.

METHOD

Single nucleotide polymorphisms (SNPs) are discriminated by enzymatic extension of allele-specific primers, such as in a polymerase chain reaction. Under appropriate conditions, the different proton affinities of reaction substrates and products lead to a change in free proton concentration which is sensed by an ion-sensitive field effect transistor.

RESULTS

I selected candidate SNPs from the osteoarthritis literature and designed primer sets for typing. A major challenge has been to adapt the PCR reaction to reliably produce pH changes of a suitable magnitude, while retaining allele specificity. A number of factors proved beneficial but their combined effect has so far not led to satisfactory performance. To facilitate optimization and understanding of the reaction, I recently explored the use of fluorescent dyes for real-time, high-throughput pH monitoring.

In addition, I designed an assay for variation in the length of di- and tri-nucleotide repeats. These polymorphisms are widely used in forensic testing, as well as being associated with or directly responsible for some genetic diseases. At the moment however, they cannot be typed with pH-PCR or other simple on-chip methods.

NEXT STEPS

I will continue to improve SNP detection by trying variations of allele-specific pH PCR. I also hope to gain a more fundamental understanding of the reaction by observing the kinetics of pH change and DNA accumulation. Furthermore, I will test a 'digital' tri-nucleotide repeat assay for alleles of the asporin gene which has been reported to be a risk factor for osteoarthritis in Orientals.

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Research Students and Assistants reports

Mr Abdul Al-Ahdal

Thesis topic
ISFET based chemical switch

Supervisor
Professor Chris Toumazou

The Ion Sensitive Field Effect Transistor (ISFET) was first introduced by Bergveld in 1970's [1]. It is composed of a Field Effective Transistor (FET) that has no metal gate. It is replaced by a reference electrode that is immersed in an electrolyte solution which comes into contact with the transistor's gate oxide that acts as an ion sensitive membrane. Therefore, the combination of the electrolyte and the reference electrode play the role of the gate in a normal MOSFET. This makes it sensitive to electrolytes hydrogen ion concentration (pH) [1]. ISFETs have been used as analogue continuous time chemical sensors. A single ISFET, either an n or a p device, forms the sensitive part of the circuit that may condition the signal. Each ISFET has its own ion sensitive membrane as part of it.

My work has shown that, for devices built using a standard CMOS process, it is possible for more than one ISFET to share the same ion sensitive passivation layer. Using floating gate devices concepts, a complementary pair of ISFETs (n and p devices) shared the same ion sensitive membrane forming a fully functioning chemical switch. Its switching threshold voltage shifted with pH change of the electrolyte under test. This forms an electronic switch that is driven by chemical change. It can be built as a single device or in arrays with element separation of a few micro meters.

Successful implementation of this pH driven switch opens the door to build fully digital ISFET arrays that include localized digital signal processing similar to memories. This will radically affect all existing ISFET applications especially those using large arrays like DNA sequencing and lab on chip applications.

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Mr Mohamed El Sharkawy

Thesis topic
A low power potentiostat and sensor fault detection system for continuous glucose sensors

Supervisor
Dr Pantelis Georgiou

Funding
Wellcome Trust

BACKGROUND

The World Health Organization (WHO) estimates that more than 180 million people have diabetes worldwide. It predicts that this number will double by 2030. In the year 2005 almost 1.1 million people died from diabetes. If left uncontrolled, diabetes can lead to a number of serious consequences: these include retinopathy, which can lead to blindness, neuropathy, kidney failure and heart disease, including strokes. Therefore it can be seen that this is a serious disease which cannot be left unchecked. Many health organizations have even described it as a growing epidemic. In addition there are severe economic consequences, for example WHO predicts that from 2006 to 2015 China alone will lose $558 billion in national income to cope with the disease.

However, most of these consequences can be avoided if good blood glucose control is maintained [1]. Consequently there is a need for low power, continuous, glucose monitors (CGMs) which are wearable and have a long lifetime. A key circuit which is needed to bias up the electrochemical sensors is the potentiostat. To date nobody has optimized the power consumption of these circuits. The aim of my research is to develop a low power glucose sensing system incorporating fault detection and self powering.

A CMOS based system integrating low power glucose sensing, fault detection and power management will help diabetics manage their blood glucose levels more effectively and thus help them avoid the short and long term consequences of the disease which arise due to hypo- and hyper-glycaemia.

METHOD

I am investigating the fundamental limits of potentiostat circuits when sensing redox reactions with regards to power consumption and noise. Using this knowledge I aim to design a sub-1V CMOS potentiostat with sufficient gain, bandwidth, low noise and tunable current sensing range for the given application. I will investigate if energy harvesting could be utilized to power up and sustain the designed low power circuit. The idea is to initially power up the circuit inductively in order to bias the sensor so that the redox reactions take place but once that is achieved the current generated by these reactions could power up the circuit [2].

In addition I will investigate and optimize fault detection systems for implementation in hardware. There are two fault detection schemes available, one is model based and the other is based on signal processing. These two approaches will be compared and the trade-off between computational and hardware complexity will be assessed [3].

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Mr Bård Haaheim

Thesis topic
Low power analogue-to-digital converter (ADC) for neural spike recording

Supervisor
Dr Timothy Constandinou

BACKGROUND

Already conducted experiments within neural spike recording have yielded profound insights into brain function and how this complex system is affected by neurological injuries and disease. However, despite considerable advances in electrode technologies, the ability to interface digital microelectronics with the brain at the level of individual neurons is at present severely limited. To be able to mimic complex brain functions like moving limbs or preventing seizures, individual neuron recording and stimulation in numbers of hundreds are required. Researchers are now innovating analytical tools for the *in vivo* measurements of neuron activity and are developing the next generation neural interfaces for totally-implantable devices that use biotelemetry for the transmission of both power and data. This will make new therapeutic avenues available to neurologists battling with, until now, untreatable conditions. However, such links require digitized signals for efficient and reliable data transmission therefore introducing the need for on-chip and ultra low-power analogue-to-digital converters (ADC).

METHOD

The focus of my research is the development of an ultra-low-power 8-bit asynchronous ADC for single channel neuron spike recording. Currently a novel design using a current-mode, successive, approximation topology has been completed and sent for production. This design features easy scalability, enabling a selectable sampling frequency and a tuneable dynamic range in addition to supporting operation voltages down to 1.2V consuming under 500nA. A one-time post-fabrication calibration technique is developed to ensure robust operation through process and mismatch variations. The next step is to create testing equipment for the module and do experimental validations to determine the real performance and stability before an evaluation concerning the use of the ADC in a neural spike recording system can be conducted.

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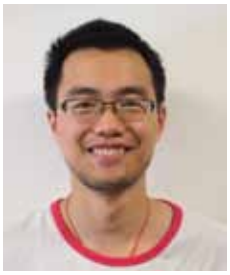

Mr Yuanqi Hu

Thesis topic
A CMOS based DNA sequencing engine

Supervisor
Dr Pantelis Georgiou

Funding
Department of Electrical and Electronic Engineering

The integration of DNA sequencing with semiconductor technology is gaining significant popularity due to the capability of CMOS technology to detect DNA base pair matches with high density and low cost. This is slowly becoming an established platform for DNA sequencing. However, there are still many challenges and technological constraints, which need to be addressed in addition to great potential for novel integration.

This PhD research will involve the design of a novel lab-on-chip array capable of DNA strand detection and recombination. In order for this to be possible, significant research must be conducted to overcome the technological constraints which exist when scaling such devices to deep sub-micron technologies. Additionally, a novel implementation of an algorithm in hardware which is capable of alignment and assembly of DNA in parallel and real time needs to be investigated.

The final goal of the PhD is to lay down significant scientific foundations for design of such systems. The ultimate aim will be the introduction of the world's first CMOS based DNA microarray capable of sequencing a whole genome on chip.

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Miss Melpomeni Kalofonou

Thesis topic
Electrical detection of DNA methylation-based biomarkers in tumours using semiconductor technology

Supervisor
Professor Chris Toumazou

The analysis of DNA methylation-based biomarkers is a rapidly advancing area of research, being actively studied in multiple cancers, with the possibility of the methylation profile to distinguish tumour types and perhaps the response to chemotherapeutic agents. Already, tumour-specific DNA methylation patterns can be detected in tumour-derived free circulating DNA from the bloodstream of cancer patients, coming from DNA, derived from the primary tumour source of the patient. Therefore, the need for detection of aberrancies of DNA methylation appears to be one of the most important assays in early cancer diagnosis.

My research involves the development of the chemical and electrical front-end of a system that will be applied in detecting DNA methylation levels of specific gene markers, by using arrays of ISFET based sensors in standard CMOS, as an early detection tool of identifying warning signs of cancer.

During the course of this research, a principal, multiple-staged method was developed, able to primarily determine and validate the methylation status of a DNA template by using the pH-sensitive ISFET technology, as a sensitive as well as specific method for the basis of DNA methylation detection. Improvements on the instrumentation of the principal prototype led also to the development of an ISFET-based ratiometric circuit and the formulation of the process of using a DNA methylation ratio to determine the level of aberrancies between a pathogenic and a normally methylated gene. Additionally, an ISFET-based readout circuit was proposed based on the 'Gilbert Gain Cell', for differential amplification of current signals originated from PCR oriented biochemical reactions, allowing stable drift reduction, tuneable gain and a low power consumption.

This work is an achieved part of a larger lab-on-chip system, aimed to be developed, forming a strong link between the principal, biochemically processed, DNA methylation based platform and an ISFET based front-end in standard CMOS.

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Mr Jakgrarath Leenutaphong

Thesis topic
Development of an adaptive error correction for a high delay channel

Supervisor
Professor Chris Toumazou

Funding
Royal Thai Scholarship

SUMMARY

My project is focused on the modeling and prediction of the error magnitude of data packets sent through terrestrial digital audio broadcasting (DAB-T) devices and infrastructure. Discrete time-series modeling techniques are used to capture the statistic properties of the sequences of error magnitude, and to produce input data for error magnitude prediction algorithms. The errors are then corrected by either adjusting the parameters of forward error correction, or requesting retransmissions from a sender.

The model's parameter learning algorithm is being developed in order to capture the dynamic nature of the error magnitude in real-time and on-line approach as the amount of memory is limited in practice. Combination of the back tracking information with the model's parameters, providing likelihood values which are used to perform an error magnitude prediction. This prediction is then weighted by the 'cost of transmission' calculated from developed utility function, providing the decision for choosing optimum error control strategy and parameters.

An aim of this development is to integrate these algorithms and functions into a transmission protocol which targets improving the throughput of transmission over the very high delay channel while retaining the integrity of the data sent. It is has been proved that using ordinary transmission on erroneous high delay channel causes a significant reduction on the throughput and quality of service compared to a shorter delay channel. As such erroneous high delay channel can be found on satellite channel and terrestrial digital broadcasting channel. These channels have advantages in very high bandwidth and long transmission range which are considered to be useful in numerous applications.

With the implementation of the developed protocol on DAB-T, the benefit of this protocol is to be able to provide broadband quality and trustworthy communication channel for remote rural areas such as a mobile medical unit. An increasing of data transmission throughput and lower power consumption in an ordinary wireless channel such as Bluetooth or body sensor network are also expected.

METHOD

Similar to adaptive adjustment on volume and speed on human conversation, the adaptive error control algorithm would calculate the appropriate degree of error correction in the same concept by continuously monitoring the condition of a communication channel and transform the condition into a statistical profile, which would result in the improvment in an effective data transfer throughput.

RESULTS TO DATE

The real-time computing in channel condition statistical profiling has been achieved. And the accuracy of the statistical profile has been assessed in term of its predictability. Compared to traditional computing methods, an improvment in predictability accuracy has been gained with a dramatic increase in speed of calculation. Also, the drawback of the Baum-Welch algorithm has been eliminated using the real-time method.

NEXT STEPS

The developed algorithms will be implemented on a DSP platform. Then the existing UDP broadcasting infrastructure on DAB will be modified to accommodate this DSP implemented algorithm. It is expected to have a connection oriented type of communication protocol which has an increasing or effective throughput compared to the naive TCP. This would enable the expansion of the wireless broadband into a rural area or undeveloped countries.

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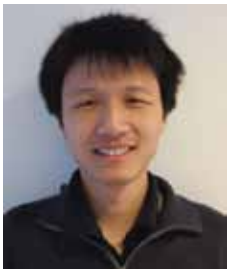

Mr Yan Liu

Thesis topic
Engineering robust CMOS ISFET smart sensor systems

Supervisor
Professor Chris Toumazou

Funding
DNA Electronics Ltd

There is a growing need for portable healthcare devices to integrate intelligent instrumentation with chemical sensors, allowing fast, robust and cheap diagnostics, for applications such as glucose monitoring or DNA sequencing. With the goal of engineering robust chemical sensory systems based on CMOS technology, recent research has focused on the ISFET, a silicon based device capable of translating chemical information to electrical signals.

The focus of my PhD project is to understand the characteristics of the ISFETs, especially non-ideal behaviour, and minimize these by interface circuit techniques and design of an intelligent instrumentation system with low power consumption, hardware complexity and the ability to correct intrinsic non-ideal behaviour. This is intended to simplify the sensor and processing overheads, and ultimately lead to the implementation of large scale sensor arrays for lab-on-chip.

My main project can be divided into three parts: the first, based on experimental results, a compact model for CMOS ISFETs is proposed, incorporating dimension and performance variations. Drift characteristics have been studied intensively and a relationship has been found between drift and the threshold voltage or biasing condition. With properly trimmed threshold voltage or biasing, the drift can be reduced dramatically for CMOS ISFETs. Secondly, two circuits based on Auto-zeroing techniques and PG-ISFETs are designed and fabricated to overcome the threshold mismatch without degrading the chemical sensitivity. Finally, based on Sigma-Delta modulation, a hybrid chemical Sigma-Delta modulation is presented. A chemical measurement system based on this is implemented for both CMOS and custom-made ISFETs. Experimental results demonstrate that it attenuates the low frequency noise by chemically differentiating the drift.

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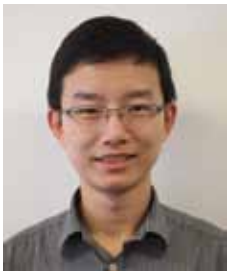

Mr Song Luan

Thesis topic
Implantable microelectronics for advanced neural stimulation

Supervisor
Dr Timothy Constandinou

Funding
EPSRC

SUMMARY

Neural stimulation is a method now used in neural prosthesis to restore the damaged or lost sensory, cognitive and motor modality of an individual. The nerve being stimulated can be part of the central nervous system (CNS), such as the cortex, or the peripheral nervous system (PNS), such as the sciatic nerve. To perform such stimulation, an Implantable Neural Stimulator (INS) is often used in the patient. As part of the Neural Recording Project underway in the Centre, a bi-directional neural interface can be envisioned.

The aim of my PhD is to implement an advanced neural stimulation system that outperforms existing systems. The main contributions are:

- safety monitoring including power, charge and temperature
- power and data telemetry platform with smaller footprint and better efficiency
- multi-site stimulation system with improved stimulation resolution.

METHOD

There are several targets in the design of an advanced INS that surpass the existing systems. Firstly, a precise control scheme is required on the charge delivered to innervate target neurons. Excessive charge delivered will consume more power and thus be less efficient. Secondly, all the charge injected must be recycled. This is much more important than the last aspect because the accumulated DC voltage is highly related to tissue damage. These two targets can be met provided the charge can be monitored. Thirdly, a multi-channel INS is able to increase the bandwidth between the individual and the prosthetic device. It is also beneficial that by sending stimulii through several electrodes simultaneously, better selectivity can be achieved due to the interferences among the stimulii, thus limiting the side effect of stimulation. In developing devices, we aim to enable patients to lead independent lives so our fourth target is to provide power and data telemetry which can perform stimulation without using a battery or restricting the freedom of the individual. A system integrated on a single chip is highly desirable to eliminate any wire connection associated with the implantable device.

NEXT STEPS

At the current stage, a novel, counter-based, charge-metering method for voltage-mode neural stimulation is proposed to improve charge control, charge recycling and power efficiency. Based on a design that aimed to provide a wireless link between a chip and a PCB, the possibility of integrating the whole stimulator (including the antenna) on a single chip is to be evaluated. The feasibility of a multichannel system will depend on the power that can be provided by the wireless link.

KEY PUBLICATION

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Mr Matthew Lubelski Katz

Thesis topic
Bio-inspired modelling of the retina

Supervisor
Dr Konstantin Nikolic

Funding
EU (FEP-Proactive 7 – ICT)

Conventional cameras are fundamentally limited in comparison to biological retinas, because they produce redundant sequences of images at a limited frame rate. By contrast, neuromorphic 'silicon retina' sensors attempt to mimic the biological retina's event-based architecture to provide superior information processing capabilities.

At present, the range of application of these retinas remains restricted because of technical challenges in their design. If these could be overcome it would revolutionize artificial vision by providing fast, low power sensors that would find immediate and wide-spread application in industry, and provide a natural foundation for vision prostheses for the blind.

It is the goal of the *SeeBetter* project to address the technical challenges of producing such silicon retinas and to explore the possible neuromorphic architectures that could be realised in their design. The project is a collaboration between Imperial College London and experts at imec, University of Zurich, and Friedrich Miescher Institute for Biomedical Research.

In the Centre, our work is focused on the mathematical and computational simulation of retinal architectures. I will be modelling the experimentally determined responses of retinal ganglion cells in mice to better understand their excitatory pathways and functional roles. It is hoped that this will provide inspiration for novel architectures that can be incorporated into the silicon retina design. By also producing a behavioural emulation of the proposed silicon retina, we can experiment with these and other neuromorphic architectures and analyse their implications for the information processing capabilities of the final system.

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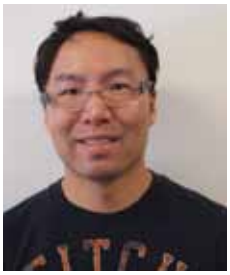

Mr Kwok Wa Lui

Thesis topic
Wirelessly-powered sensor platform using non-traditional antenna

Supervisors
Dr Olive Murphy and Professor Chris Toumazou

The future of medical and environmental technologies is shown to be moving further towards battery-less platforms. This leads to more efficient monitoring of patient's vital signs or remote monitoring in hazardous or toxic environments as battery lifetimes and charging are no longer an issue. To achieve such battery-less platforms, the required energy must be harnessed from the environment, either ambient or directly from a dedicated base-station.

In this project I am developing a wirelessly powered, RF energy harvesting platform to provide power-over-distance for low power applications (low microwatts and low milliwatts). Body-worn devices (e.g. temperature sensor) that typically operate on batteries for months or years can benefit from this RF energy harvesting technology. The cost of wiring or battery replacement can be eliminated in low-power devices through wireless RF power from a base station. This technology is environmentally friendly as it reduces the disposal of batteries and also improves system reliability.

The current results show that it is possible to power up a complete wirelessly-powered temperature sensor within two metres by using 0.05 W RF energy from the base station. This power level is about 20,000 times less than that from a cellular phone. The temperature data can be received at regular intervals from the sensor to the base station. The next goal is to integrate the RF energy harvester into material so that the wirelessly-powered system can be wearable.

KEY PUBLICATIONS

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Miss Christina Morris

Thesis topic
Reverse engineering the pancreatic alpha cell

Supervisor
Professor Chris Toumazou

Funding
Winston Wong Centre for Bio-Inspired Technology

The success of intensive insulin therapies for the treatment of type 1 diabetes is driving the development of novel artificial pancreas systems, consisting of a real-time glucose sensor, feedback control algorithm and insulin pump, that will provide consistent tight glycemic control in an automated manner [1]. Despite the achievements of continuous insulin infusion (CSII) at reducing diabetic complications associated with hyperglycaemic events, clinical studies have highlighted the need to improve control over falling blood glucose levels [2]. Subsequently the study of the physiology of alpha cells and modeling of their glucagon dynamics for potential implementation within an artificial pancreas system has become more significant [3].

The aim of my work is to investigate and model glucagon secretion under different glucose and insulin conditions. We have developed a new biologically-inspired pancreatic alpha cell model based on empirical measurements from *in vivo* and *in vitro* data from the literature. The model incorporates the most significant elements of glucagon and insulin hormone release including influential effector inputs that can be measured and used in artificial pancreas systems or by biologists working in the neuroendocrine field.

Further, I am recording *in vitro* glucagon and insulin data from pancreatic mouse tissue, Islets of Langerhans. The measurement of glucagon dynamics is complicated by a range of factors including low alpha cell numbers and the release of glucagon in concentrations typically three orders of magnitude less than insulin. We have developed a microfluidic cell perifusion system that increases glucagon secretion sample concentrations by up to a factor of 20 compared with standard multi-well plate incubation assays that are used to measure islet cell glucagon release. The device design is simple to manufacture, robust for re-use and it can be maintained in any wet laboratory without the need for advanced fabrication facilities.

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Ms Oghenevworhe Joan Omeru

Thesis topic
Hardware acceleration of retinomorphic algorithms

Supervisor
Dr Dylan Banks

Funding
EPSRC

BACKGROUND

Image processing for artificial vision prosthesis has evolved over the last few decades. Models of the intrinsic layers of the visual pathway have been developed during this time leading to approximate vision processing algorithms. Retinomorphic algorithms which are concerned with models of the retina section are well researched and various silicon hardware processing and digital signal processing methods have been tried and tested. Such algorithms are often computational intensive and limits processing to post simulation verification efforts after initial on-chip signal capture. In a move to achieve real-time vision systems the ability to accelerate these algorithms becomes paramount. An efficient hardware platform that scales with a retina on-chip both in size and performance is the field-programmable gate array (FPGA); this forms the focus of the work.

METHOD

The focus of my research is to accelerate the processing of complex image filtering and processing algorithms by means of FPGA hardware. Such implementation will provide the possibility of achieving complex real-time vision processing for advanced vision prosthesis. This work is determined to exploit existing techniques found in custom circuitry, and implementing them in FPGA fabric, while improving and generating novel methods to further enhance the quality of the outcome. It is expected that multiple parallel computations will be directly implemented such that an additional benefit will see the sensing matrix being further extended beyond those currently reported. This additional feature will explore increased sensing area using micro optical sensors in a densely packed array. It is desired that the increase in complexity of the prosthesis will enable a closer representation of the true complex biological information processing system.

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Miss Sivylla-Eleni Paraskevopoulou

Thesis topic
Ultra low power implantable platform for next generation neural interfaces

Supervisor
Dr Timothy Constandinou

Funding
EPSRC

Next-generation implantable neural interfaces will provide a strong investigative tool for neuroscience research, aiding the understanding of how information is represented in the nervous system. More importantly, a targeted neural interface can be used for therapeutic purposes, for example to aid individuals with severe motor disabilities regain their independence by enabling them to effectively control facilitative appliances, such as computers, speech synthesizers, or neural prosthesis, by feeding back electrical signals into the nervous system.

Implanted recording arrays are used to tap into the single neuron activity of the brain, manifesting as electrical impulses or spikes. To extract useful information from the recorded spikes, signal conditioning and processing is required. The level of processing integrated on chip differs between different implementations, and is mainly dictated by two constraints: stringent power budget and limited communication bandwidth. The power constraint is imposed by the challenge of wirelessly power-supplying the implanted device and the potential damage caused to the surrounding biological tissue by an increase of the chip temperature beyond the limit of 1C, this is a major issue when dealing with valuable brain tissue.

My research is currently focusing on the design of the neural interface's ultra-low power analogue front-end, integrating signal conditioning (amplification and filtering) performed by a two-stage low-power, low-noise amplifier and gm-C filter structures, spike detection, peak detection, peak amplitude extraction, and spike rate encoding.

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Mr Peter Pesl

Thesis topic
Smart-phone based decision support system for optimal insulin dosing

Supervisor
Dr Pantelis Georgiou

Funding
Biomedical Research Centre (BRC)

SUMMARY

Type 1 diabetes affects 250,000 in the United Kingdom and its incidence is increasing rapidly. Poor management of diabetes leads to elevated glucose concentrations, which cause organ damage including irreversible nerve damage, blindness and kidney failure. Hyperglycaemia is also associated with a large increase in cardiovascular risk, leading to heart disease and stroke. Within this project, my aim is to develop and clinically validate a smart-phone based decision support system for management of type 1 diabetes, aiming to improve quality of life for those with this disorder and reduce the secondary complications.

METHOD

The decision support system is based on case-based reasoning (CBR), a consolidated artificial intelligence technique, which has been extensively applied in medicine [1,2,3], and solves newly encountered problems by applying the solutions learned from solving previous problems. These problems are described and stored as cases in a database and include information such as glucose concentration, meal consumption and activity. To date, CBR systems have been PC-based and have not been implemented on portable devices which would allow them to be used by patients leading a mobile lifestyle.

RESULTS

CBR is a viable approach for insulin bolus recommendations, requiring less initial tuning and maintenance than insulin bolus calculators. It is anticipated that by optimal insulin dosing, the subject will have less severe hyper- and hypo-glycaemic episodes. We expect this research to become an integral part of the mobile lifestyle of a person with diabetes.

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Mr Ayodele Sanni

Thesis topic
A 3-tier bio-implantable sensor monitoring platform

Supervisors
Professor Chris Toumazou and Dr Antonio Vitches

Funding
EPSRC

SUMMARY

A generic and reliable bio-implantable interface platform capable of remotely and wirelessly monitoring deeply implanted sensors is proposed. The proposed solution employs a multi-tier approach to transfer power wirelessly to the implant device and consequently transmit captured sensed data by the powered implant to the outside. The inductive coupling sub-system ensures power/data communication through the skin while the ultrasonic sub-system ensures power/data communication in the predominantly liquid medium in a living bio-system.

METHOD/RESULTS

Our CMOS logic gate-based primary inductive coil driver produces a power transfer efficiency of 83% at 2MHz operating frequency and air gap of 1cm. Driving the PZT transducer discs in their lower frequency (200 KHz) radial excitation mode, produces an operating depth of 7cm with an efficiency of 1%. Power consumption for the entire system is 65 mA for a 35 V DC input.

NEXT STEPS

We aim to develop smaller diameter inductor coils with improved inductance and quality factor. We will investigate low input power and high output implant driver circuitry and aim to improve the efficiency of the ultrasonic sub-system by investigating driver circuitry.

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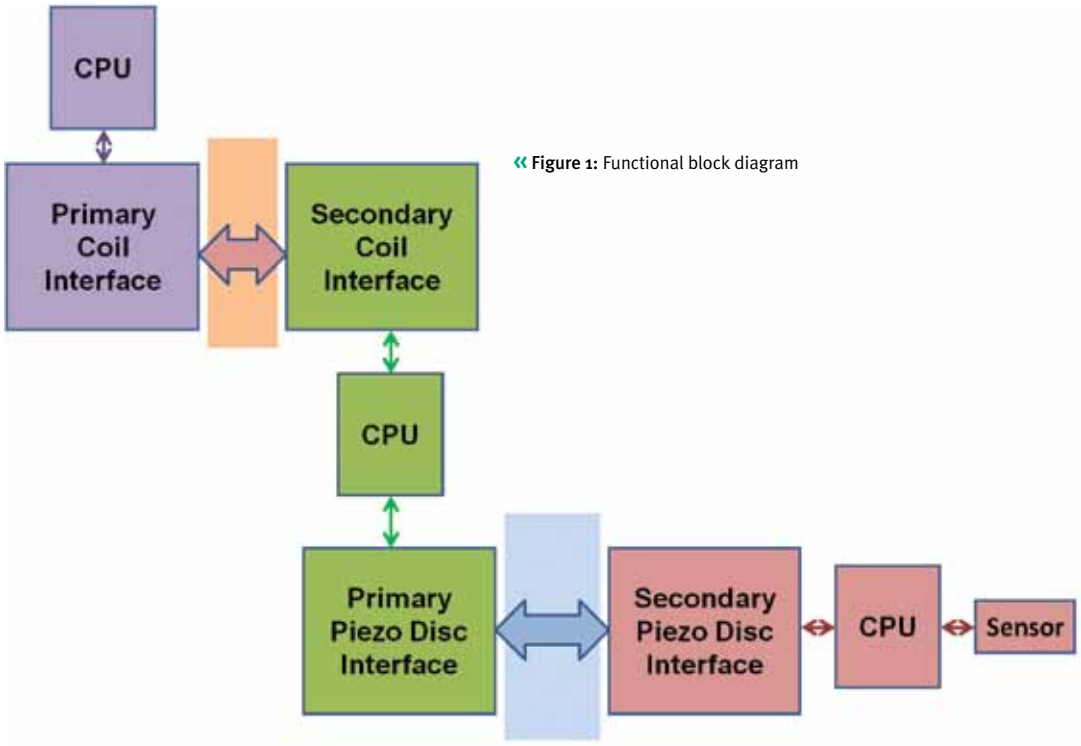

« **Figure 1:** Functional block diagram

Mr Siavash Saremi-Yarahmadi

Thesis topic

RF electrically resonating structures for the monitoring of electrical properties of electrolyte solutions

Supervisors

Dr Kristel Fobelets and Professor Chris Toumazou

SUMMARY

The main aim of my research is to employ planar inductors to perform analysis on electrolyte solutions, or biological samples and systems, with the capability of a wireless data transmission between the sensor and a readout unit. This approach can simplify the packaging process of chemical sensors e.g. replacing bond-wires.

METHOD

The work I have done offers the potential of adapting this sensor with minimum modifications for use as an implantable device e.g. monitoring gastric juice in the oesophagus. It also offers the potential for the use of a near field interface in communicating with implanted sensors inside the human body. The use of finite element analysis and the development of analytical solutions for solving the full wave equation for the system under test are also investigated. A comparison of the results between the two approaches in solving this problem is provided in this research.

The measurement apparatus is divided into two parts; the sensing antenna or the sensor; and the pickup antenna which reads the data from the sensing device. Inductors operating in the RF region of 10 MHz to 1 GHz were fabricated on both FR4 and Rogers 3030 substrates. Variations in the conductivity and the permittivity of a liquid sample were then monitored using these inductors. Sodium dihydrogen phosphate, sodium chloride, hydrochloric acid and samples of onion DNA are used for testing purposes.

RESULTS

The results from this study show that inductors could be employed in designing simple, scalable and integral sensing systems to perform label free analysis without the need for surface activation or perturbing the system being studied. The next step in this research is to design and develop a Helmholtz coil to undertake remote interrogation over an array of electrically resonant structures.

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2. Saremi-Yarahmadi S, K Fobelets and C Toumazou, 'Coupled RF Inductive Sensors for Monitoring the Conductivity of Electrolyte Solutions', *IEEE International Symposium on Medical Information and Communication Technology, Montreux*, March 2011.
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Mr Alexander Serb

Thesis topic
Developing optically coupled, standard CMOS wireless integrated circuits

Supervisor
Dr Timothy Constandinou

Funding
EPSRC

SUMMARY

The aim of my PhD is to develop all the individual, integrated components required to set-up a truly wireless integrated circuit; that is, a chip that requires no wire-bonds in order to communicate data back and forth and receive the necessary power. The project is divided into three sub-sections:

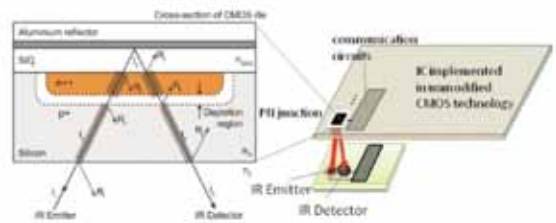
- create the data read-out structures
- design the data read-in structures
- develop a power scavenging system able to operate the data transfer structures and provide extra power for some signal processing.

METHOD

The data read-in structures will be probably the easiest to achieve because photo-receptive elements are well-known and widely used for data read-in. Challenges in this domain are expected to concern noise and the generally very low levels of incoming signal.

The data read-out structures are very challenging to realise, mostly because of the indirect-bandgap nature of silicon which makes it a very low grade optical emitter. As such, building an optical modulator appears to be a far more attractive solution. The fundamental idea is thus to generate IR light off-chip, send it into the modulator and then capture it at an off-chip detector. As such, only the modulator needs to be integrated and the effort involved in coaxing silicon to emit light can be safely circumvented. Once again, extremely low levels of signal (modulation) constitute the main challenge. This section of the project is by far the most innovative one.

The power unit will consist of standard solar cells and a management unit whose task is to up-convert the low incoming photovoltaic cell voltage and stabilise it at a level that is amenable for use by signal processing circuitry and the data read-in/out structures. Many such power management architectures have been created over the years, but real applications always turn out to hide much more detail and many more traps than academic papers usually tend to reveal. As such, the main challenge in this sector concerns gaining an in-depth understanding of the function of power management units and using that to create a system that will ultimately be able to work over a wide range of possible parameters (illumination, loading etc.) and work in even the most simplistic and primitive of CMOS technologies.



Ultimately, a fully functioning, 100% wireless integrated circuit must be produced and demonstrated. It must be able to receive data, process it in some non-trivial way and present the outputs to a read-out system.

RESULTS

So far, the 'first generation' integrated circuit has been constructed. It contained modulator test-structures, which were probed in order to reveal that the concept is sound and robust, and to find the best structure determined to be optimal for the implementation of the modulator. The next stage is to fabricate the demonstrator and operate it successfully.

KEY PUBLICATIONS

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2. Nikolic K, A Serb and TG Constandinou, 'An Optical Modulator in Unmodified, Commercially-Available CMOS Technology', *IEEE Photonics Technology Letters*, 2011

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Mr Mohammadreza Sohbati

Thesis topic
DNA arrays for label-free DNA hybridization detection

Supervisor
Professor Chris Toumazou

Funding
Winston Wong Centre for Bio-Inspired Technology

The focus of my research is to propose a proof-of-concept, generic and reliable bio-implantable, multi-tier, interface platform capable of remotely and wirelessly monitoring deeply implantable sensors without batteries. The proposed solution employs a multi-tier, miniaturized array for genetic tests and DNA hybridization detection and has aroused interest due to the facility and speed they provide in detecting Single Nucleotide Polymorphism (SNP). There have been different methods for reading out biological information either based on optical scanning requiring use of markers (aka labels) or electrochemical sensing protocol. In contrast to the optical methods, label-free electrochemical DNA sensing arrays provide a robust and low cost read out platform.

Several label-free DNA arrays have been introduced which benefit from the CMOS fabrication process. They are mostly based on spectroscopy, measurement of electrode capacitance/impedance or reduction and oxidation on electrodes. They require use of post fabrication processes and use of inert electrodes like gold.

The purpose of my research project is to use CMOS based ion sensitive field effect transistors (ISFETs) to develop low cost, robust, disposable, label free DNA arrays while tackling non-ideal behaviour issues (e.g. drift, noise, cross-coupling, cross-hybridization). Such arrays will contribute to point-of-care diagnosis and test for genetically inherited allergy and susceptibility.

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Mr Surachoke Thanapitak

Thesis topic
Bionics chemical synapse

Supervisor
Professor Chris Toumazou

Funding
Royal Thai Scholarship

My research presents an analogue current mode VLSI circuit which implements four particular receptors of the chemical synapse: AMPA, NMDA, $GABA_A$ and $GABA_B$. The dynamic of postsynaptic receptor is mathematically implemented in the CMOS current mode circuit. The study in sensor which has a capable to sense the fast chemical stimulus is required in this project.

To understand about ISFET fast characteristic, the experiment setup with rapid titration on ISFET is investigated. The technique which is used for fast titration is called iontophoresis. Additionally, the modification of ISFET which has the capability to sense the neurotransmitter (glutamate) is carried out.

This EnFET(enzyme ISFET) is used as a chemical front end for the chemical synapse circuit. The readout circuit of this glutamate ISFET is the current mode CMOS circuit operated in weak inversion region. The advantage of this readout circuit is linearity between current output and concentration of interested analyte and low power consumption.

KEY PUBLICATIONS

1. Thanapitak S and C Toumazou, 'Towards a bionic chemical synapse', *IEEE International Symposium on Circuits and Systems (ISCAS)*, pp. 677-680, 24–27 May 2009.
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Mr Ian Williams

Thesis topic
A neural-electronic interface providing proprioceptive feedback for prosthesis control

Supervisor
Dr Timothy Constandinou

Funding
EPSRC

SUMMARY

Sensory feedback from the body is key to enabling fine motor control, natural (low cognitive load) movement and non-visual awareness of the position of your body. Individuals with prosthetic limbs or suffering from certain types of neural damage lack this proprioceptive feedback in the affected body areas and as such struggle to learn to control them and are unlikely to achieve high levels of coordination.

My research will investigate the provision of artificial proprioceptive feedback from a prosthetic limb by direct electrical stimulation of nerves using a neural implant.

METHOD

My research will focus on providing a user with intuitively understood information. As such, it will include creating software to translate artificial sensor data into signals analogous to those naturally occurring in the human body and will also include creating a neural implant with the performance necessary to safely stimulate the appropriate nerves.

NEXT STEPS

I aim to create a monolithic, low power, neural stimulation chip targeted at stimulating proprioceptive nerves in the peripheral nervous system.

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Mr Stephen Woods

Thesis topic
Swallowable microrobotic platform for microscale diagnosis and targeted therapy

Supervisor
Dr Timothy Constandinou

The diagnosis and treatment of pathologies of the gastrointestinal (GI) tract are performed routinely by gastroenterologists using endoscopes and colonoscopies. However, the small intestinal tract is out of the reach of these conventional systems [1]. Attempts have been made to access the small intestines with wireless pill-sized cameras [2] which take pictures of the intestinal wall and then relay them back for evaluation. This practice enables the detection and diagnosis of pathologies of the GI tract such as Crohn's disease, small intestinal tumours such as lymphoma and small intestinal cancer. The problems with these systems are that they have limited diagnostic capabilities and they do not offer the ability to perform therapy to the affected areas leaving only the options of administering large quantities of drugs or surgical intervention.

The aim of my PhD is to overcome these limitations by developing a swallowable microrobotic platform. The microrobot will have novel functionality such as a targeting system capable of delivering a 1 ml payload of medication to a target site within the small intestines. To achieve this goal the microrobot will also be required to overcome the natural movement from peristalsis.

The work I have carried out so far has been the development of the drug targeting system concept and the stopping mechanism with some preliminary designs proposed for the medication delivery system. Figure 1 shows a 3D CAD model of the proposed design. The geometry of the microrobot is based on conventional wireless pill-sized cameras.

A microrobotic system capable of allowing a surgeon to remotely target and treat a site within the small intestinal tract will be of great clinical benefit as it will allow a lower dose of medication to be delivered to the target site, this in turn could improve the patient's recovery time.

RECENT PUBLICATIONS

1. Woods S and TG Constandinou, 'Towards a Micropositioning System for Targeted Drug Delivery in Wireless Capsule Endoscopy', *Proc. IEEE International Conference of the Engineering in Medicine and Biology Society*, pp. 7372–7375, 2011.

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» Microrobot concept design capable of overcoming peristalsis and delivering targeted therapy to the gastrointestinal tract

Ms Virginia Woods

Thesis topic
The design of optimal stimulation waveforms

Supervisor
Professor Chris Toumazou

Funding
The Whitaker Foundation, Esmee Fairbairn Foundation and Winston Wong Centre for Bio-Inspired Technology

Stimulation with cuff electrodes has been used as a part of several neurorehabilitative applications, such as upper and lower limb prosthetics, diaphragm pacing, bladder control and chronic pain management. Excitation of the nervous tissue relies on the injection of charge from the electrode into the extracellular fluid, where it then diffuses towards the nerve and depolarizes the cellular membranes.

The stimulus signal can be realised either by applying a voltage across the stimulus electrodes ('voltage-mode') or by injecting a current to flow between them ('current-mode'). In many clinical stimulators, waveform specifications are defined in the current mode as current stimulation allows for a controlled amount of charge injection irrespective of changes in electrode-tissue impedance [1]. However, not all of the charge injected during a stimulus pulse is available for neural activation because of the biophysical processes involved in translating the charge carrier [2]. Charge injection is safe and reversible when current flows through a surface capacitance or through the chemical reactions within a material-specific potential range [3]. Irreversible surface reactions while stimulus pulsing alters the surface properties of the electrode resulting in metal dissolution and adverse by-products which can damage to the surrounding tissue [3, 4]. Failure to consider the charge losses at the electrode-electrolyte interface leads to reduced biocompatibility, shorter implant lifespan and ultimately cell death.

Conventionally, the excess charge is minimized by complex hardware solutions, which are often not appropriate for robust long-term implantable solutions. In our recent paper [2], we present a method of waveform design that minimizes irrecoverable charge during continuous pulsing through the use of biphasic waveforms with unequally charged phases. We developed an equivalent electrical model of the electrode–electrolyte impedance based on the electrode's surface chemistry during psuedo-bipolar stimulation conditions. Simulations with the equivalent circuit determined the uncompensated charge to be a function of stimulus parameters. *In vitro* stimulation experiments in saline confirmed that we could preemptively compensate for the excess charge following biphasic stimulus waveforms. As a result, there was a 92% reduction in the pre-pulse potential after a pulse train with this new waveform design when compared to stimulation with conventional biphasic waveforms.

More recently we developed a method for generating stimulus waveforms by considering signal parameters associated with capacitive current flow at a platinum interface and incorporated these features into the design of cathodal pulse shapes. A pulse shape comprising 4 high-frequency 'capacitive' harmonics demonstrated a 40-fold performance benefit compared to a conventional square pulse.

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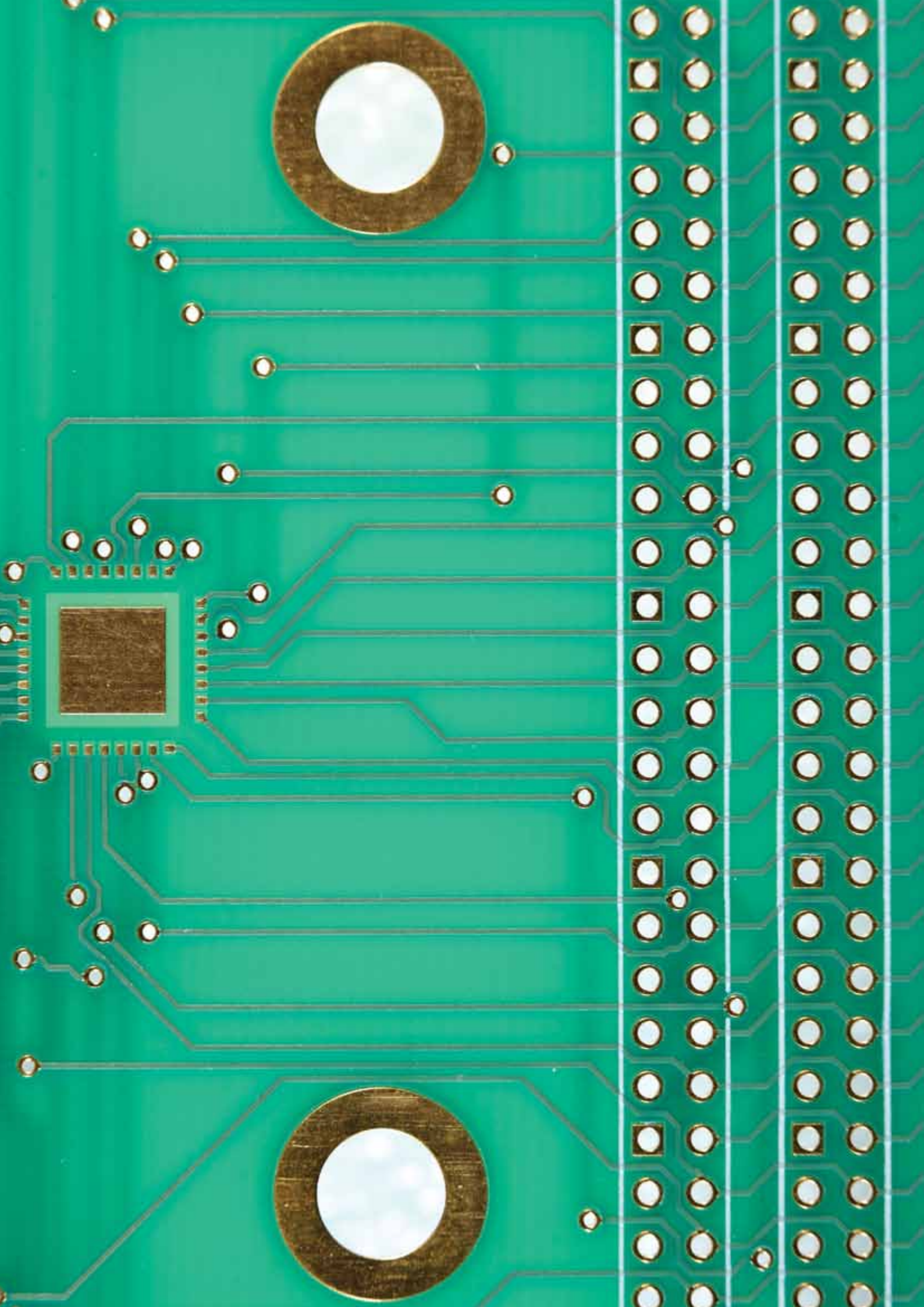

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