Imperial College London

Centre for Bio-Inspired Technology

Annual Report 2014

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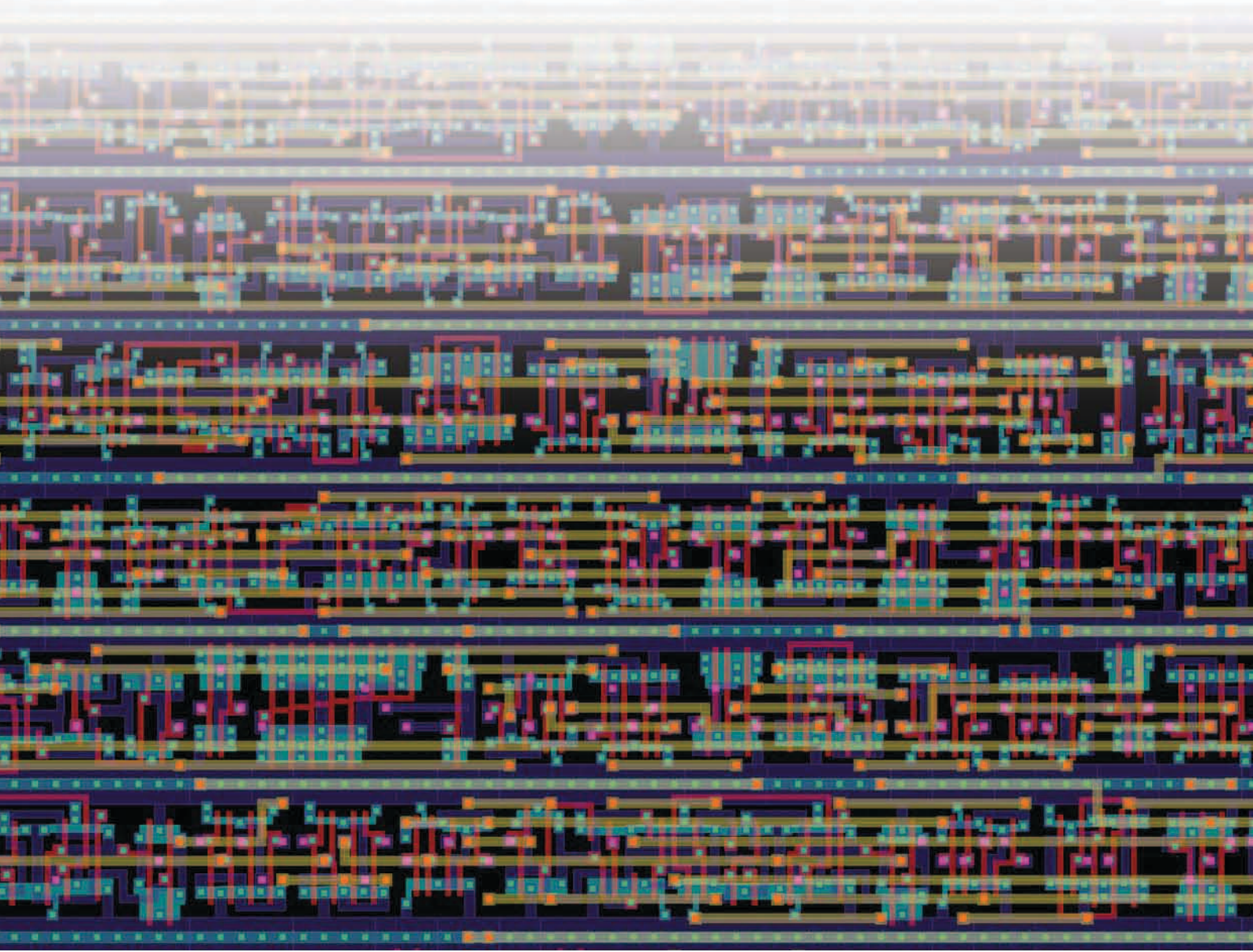

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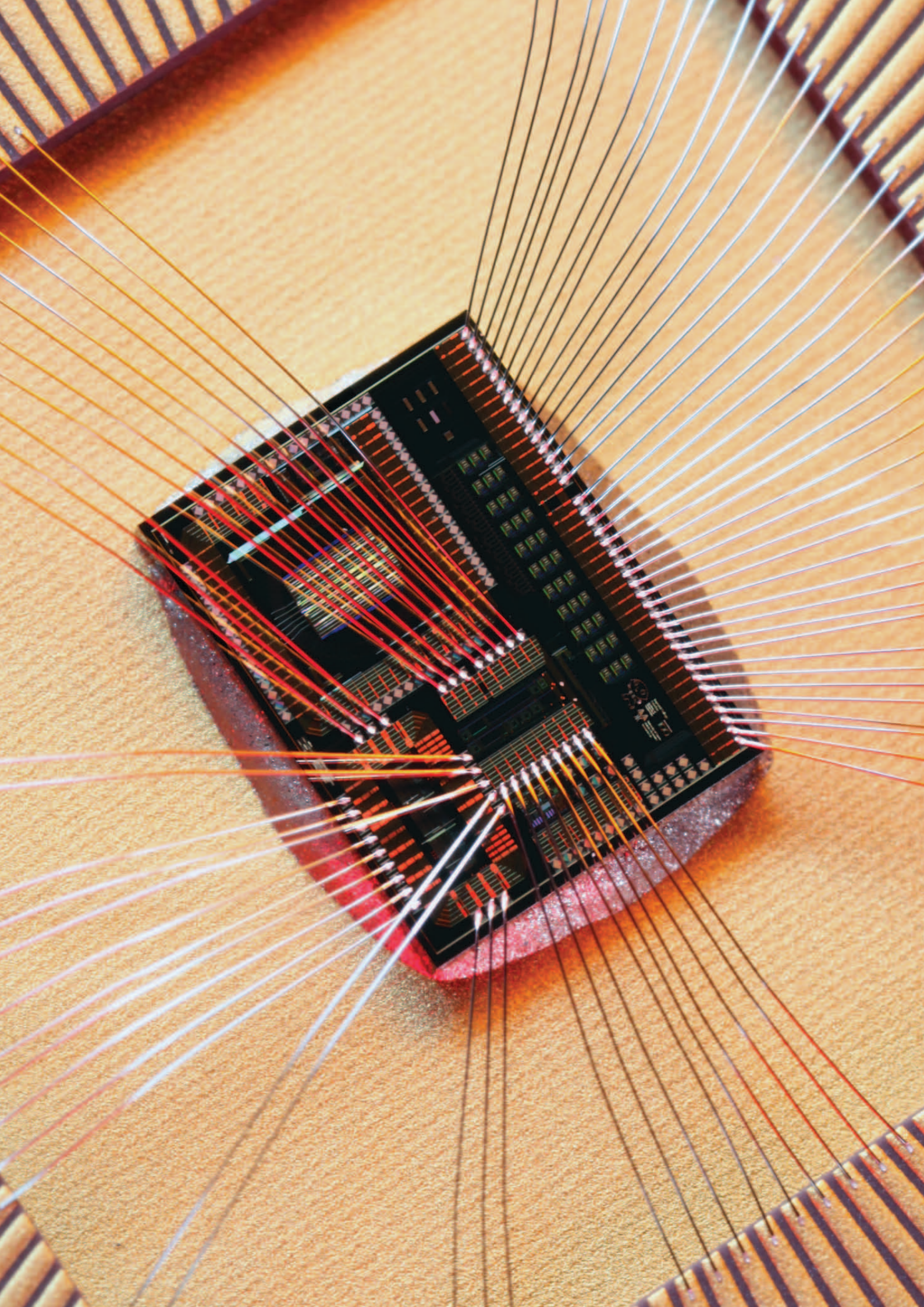


Director's foreword

I am proud to witness yet another year of success for the Centre of Bio-inspired technology. It has been another year of hard work and outstanding research developing state-of-the-art technology with application to fields as diverse as the beauty industry, in addition to biomedical engineering and healthcare.

This year has seen a significant collaboration with Professor Alison Holmes on antimicrobial resistance where the DNA technology is being utilised as a fast rapid detector of bacterial DNA in hospital acquired infections. I am an advocate of the one chip, one drug, one chip, one bug solution.

I am also delighted that we have a number of other new projects just starting. We are a key partner within the CANDO consortium, a new £10m 7-year programme to develop a new type of brain pacemaker and create a first-in-man trial of the device in patients with focal epilepsy. We also have new collaborative projects in monitoring awareness during anaesthesia; sensory feedback for upper-limb prosthetics, wearable electronics for rehabilitation and several others.

Regarding our ongoing projects, results of the group are very encouraging on the bio-inspired artificial pancreas clinical trials at the Hammersmith Hospital are progressing very well. As for the vagus nerve project (I2MOVE), trials are demonstrating the significance of neural stimulation for regulating appetite.

One of the key aims of our Centre is to transfer technology from the laboratory to industry, accelerating the impact of research by making innovation accessible to the greater public. We are passionate at combining electronics with biological processes, as this renders exciting possibilities for healthcare.

One example of this innovation is our pioneering silicon based, chemical sensing technology or CMOS lab-on-chip technology. A small device capable of translating a chemical input to an electrical output, where DNA biochemistry, microchip technology and mechanical engineering are integrated on a single platform. This merge between the electronics industry and healthcare industry will create new innovation that will rival the likes of Apple in the next few decades.

We have implemented this same core semiconductor sensing technology to very different applications: for sepsis, breast cancer and beauty treatments related to skin aging.

Our technology can improve early detection of disease, which when treated in time can change the patient´s outcome – which is a key priority to medicine today. This is particularly relevant to sepsis as every minute matters. This condition, which is triggered by infection, has no major consequences when treated in the first stages, but if detected late it can be mortal. In the UK it is estimated that 37,000 people die of sepsis every year. Our semiconductor technology can help save lives thanks to rapid genetic testing.

We are also applying our technology to finding new strategies for early detections of cancer. Breast cancer, one of the most common cancer types in women, is mainly diagnosed using screening tests such as the mammogram that can not render as to how aggressive the cancer may be, so patients need to go through additional screening as well as having a biopsy. Our preliminary results have shown that we can detect genetic biomarkers that can be directly correlated to breast cancer development using semiconductor technology, aiming to apply these in monitoring the progression and thus the aggressiveness of the disease.

This handheld device for genetic testing can be also used for diagnostic analysis as it helps predict a person's response to given drugs. The physician could then decide which treatment would provide a better result to the patient instead of managing the complications of drug resistance. This silicon-based technology will be core for XXI century medical devices. A new wave of technologies inspired by healthcare, personalisation and well-being.

Our semiconductor based lab-on-chip technology has been recognised the Faraday Medal awarded by the Institute of Engineering and Technology (IET). The highest honour recognising engineering achievement delivered by colleges. The medal recognises our pioneering work in the invention of semiconductor DNA sequencing.

And this June the same technology won the European Invention Award 2014, a distinction for technological innovation, awarded by the European Patent Office (EPO).

I am honoured and deeply moved by these recognitions as they acknowledge the new wave of technology we are producing at the Centre as well as giving our institution visibility worldwide, helping us to secure funding to pursue further research.

Professor Chris Toumazou FRS, FREng, FMedSci, Regius Professor of Engineering

Founding Sponsor's foreword

It is most satisfactory to see another year of research development and innovation at the Centre for Bio-inspired Technology. By securing competitive funding the Centre continues to thrive and is an international hub of multidisciplinary researchers working in pioneering projects.

It was only four years ago that the Centre was created with the idea of transferring knowledge learned at the laboratory to the market. Something that is not trivial as it usually takes years for cutting edge technology to reach the wider public. With this new Centre we wanted to inspire new research and accelerate the pace and bring innovation closer to the consumer.

The Centre is leader in merging electronic and medical industry, by bringing together multidisciplinary teams to find solutions for health care such as satiety control implants, breast cancer detection and insulin intelligent pumps.

Innovation comes from learning how to think outside the box, and by finding new applications to the electronics developed at the Centre we realised that our technology can be even more versatile and that we could do something that nobody from the electronic industry has done before: bringing medical grade technology to the consumer.

The lab-on-chip technology, developed at the Centre, which currently is being applied to health care conditions such as sepsis and breast cancer, could also used for skincare in the cosmetic industry.

Bringing this state-of-the-art technology to the cosmetic and fashion industry is ground breaking. We are bringing the knowledge developed in the laboratory to the high street: the new cosmetic company GENEU.

I am proud to be a major investor and founder of GENEU, as it captures the spirit of the Centre for Bio-inspired Technology, to bring innovation from the laboratory to industry.

We are now embarking into a new entrepreneurial project this time in the cosmetic industry that is a world of its own. GENEU has gathered experts in fashion, design and cosmetics and counts with the invaluable scientific consultancy of Chris Toumazou.

Launching and nurturing GENEU from the early stages to seeing it come to life when opening it´s doors to the public is very exciting. On September of this year GENEU opened its flagship store at one of the most exclusive streets in London, New Bond Street. This is a beautiful retail shop with minimal design where customers can find a new generation of skincare products.

GENEU counts with a dedicated team of experts of the cosmetic industry and pays a great attention to detail and design.

Last September, I was proud to receive, on behalf of the team, the 2014 Luxury Packaging Award for the beautiful airlift pump system created by Toly Products UK for GENEU. These are very prestigious awards organised by Packaging News, the reference publication of the packaging sector. These awards are very prestigious not just nationally but internationally as the UK is world leader in packaging. It is a fantastic recognition to the great efforts and quality products developed at GENEU. It was a celebrated success.

GENEU will bring a revolution to skincare. It is consumer genetics, state of the art technology accessible to the consumer. Bio-inspired technology in the High Street.

Professor Winston Wong BSc, DIC, PhD, DSc

People

Academic & senior research staff

Professor Chris Toumazou FRS, FREng, FMedSci
Regius Professor of Engineering;
Director, Centre for Bio-Inspired Technology;
Chief Scientist, Institute of Biomedical Engineering;
Winston Wong Chair in Biomedical Circuits,
Department of Electrical and Electronic Engineering

Dr Timothy G Constandinou
Senior Lecturer, Department of Electrical and Electronic Engineering
Deputy Director, Centre for Bio-Inspired Technology

Dr Pantelis Georgiou
Lecturer, Department of Electrical and Electronic Engineering
Head of Bio-Inspired Metabolic Technology Laboratory

Professor Chris N McLeod
Principal Research Fellow

Dr Konstantin Nikolic
Senior Research Fellow

Research staff

FELLOWS

Dr Reza Bahmanyar

Dr Andrea Alenda González

Dr Amir Eftekhar

Dr Pau Herrero Vinas

Dr Nishanth Kulasekeram

Dr Yan Liu

Dr Yufei Liu

Dr Belinda Nedjai

Dr Nicoletta Nicolaou (Marie Curie IEF)

Dr Monika Reddy (Clinical)

Dr Nour Shublaq

ASSOCIATES

Dr Benjamin Evans

Dr Melpomeni Kalofonou

Dr Song Luan (appointed November 2014)

Dr Sivylla Paraskevopoulou

Dr William Spinner

Dr Irina Spulber

Dr Huan Wang

Dr Ian Williams (appointed November 2014)

Dr Longfang Zou

Dr Claudio Zuliani

Assistants

Mr Mohamed El-Sharkawy

Mr Bernard Hernandez

Mr Khalid Mirza

Mr Peter Pesl

Mr Satoshi Yoshizaki

Research students

Mr Deren Barsakcioglu

Mr Onur Guven

Mr Dorian Haci

Mr Yuanqi Hu

Mr Ermis Koutsos

Mr Lieuwe Leene

Ms Dora Ma

Mr Nicholaos Miscourides (started October 2014)

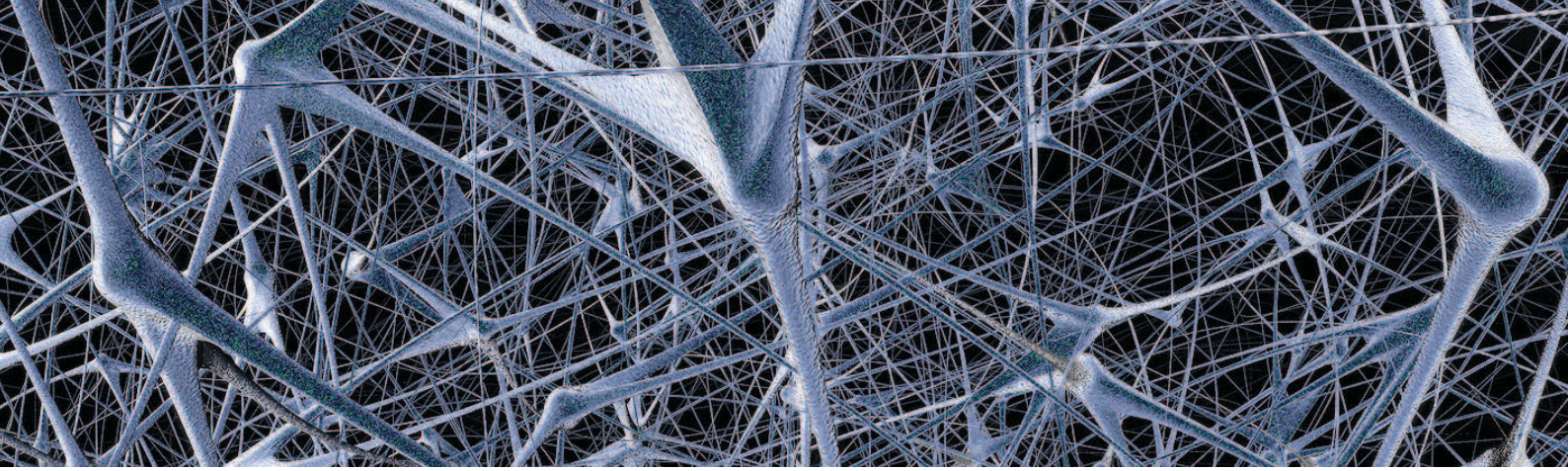
Mr Nicolas Moser (started October 2014)

Mr Adrien Rapeaux (started October 2014)

Mr Mohammadreza Sohbati

Ms Francesca Troiani (started August 2014)

Mr Stephen Woods



Administrative staff

Mrs Wiesia Hsissen
Senior Group Administrator (CAS)

Ms Gifty Kugblenu
PA to Professor Toumazou

Mrs Izabela Wojcicka-Grzesiak
Research Group Administrator (CBIT)

Consultants

Mrs Patricia Chapman
Business Administrator to Professor Toumazou

Mr Raymond Thompson
Rapid Prototyping Design Consultant

Visiting academics

* either currently based at, or frequently visiting the Centre

PROFESSORS

Professor Tor Sverre Lande*
University of Oslo

Professor Bhusana Premanode

Professor David Skellern*
Formerly Macquarie University, Australia

Professor Peter Wells FRS
Cardiff University

Professor Winston Wong
Grace THW, Taiwan

Professor Sir Magdi Yacoub FRS*
National Heart & Lung Institute, Harefield Hospital

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

RESEARCHERS

Dr Alison Burdett
Toumaz Group, UK

Dr Jamil El-Imad
W Investments, UK

Dr Julio Georgiou
University of Cyprus

Professor Gareth Jenkins
Nanjing University of Posts and Telecommunications, China

Dr Kiichi Niitsu
Nagoya University, Japan

Dr Miguel Silveira
Sensium Healthcare Ltd, UK

Dr Themis Prodromakis
University of Southampton

Graduates in 2013–2014

Dr Song Luan
Research Associate, Centre for Bio-Inspired Technology

Dr Tatiana Trantidou
Research Fellow, University of Southampton

Dr Ian Williams
Research Associate, Centre for Bio-Inspired Technology

Researchers who have taken up appointments elsewhere

Dr Alessandro Borghi
Senior Research Associate, Institute of Child Health, UCL

Dr Olive Murphy
RF Silicon Evaluation Engineer, Analog Devices (Limerick, Ireland)

Dr Sanjiv Sharma
Research Fellow, Department of Chemistry, Imperial College London

News: Staff and events

JUNE 2014

Professor Toumazou receives European Inventor Award

Quick DNA test makes preventing illness possible: Chris Toumazou wins European Inventor Award in Research category becoming the first British winner of a prize since 2008.

Announced at the European Inventor Awards ceremony in Berlin on June 17th 2014, Toumazou's win recognises his contribution to medical research with his ground breaking invention. The device, which can show the results of a DNA test within minutes, uses silicon transistors to identify DNA and RNA, offering a simpler, cheaper and more discrete alternative to existing DNA analysis equipment.

The invention involves the amplification and detection of DNA and other biomolecules using pH measurement, providing the ground work for DNA Electronics' molecular diagnostics platform Genalysis®. With the capability of identifying genomic sequences, not only in patients, but also in infectious agents, the company is developing products that will provide clinicians with rapid actionable diagnosis of life-threatening conditions.

Technology has also been licensed to cosmetic company GENEU, enabling customers to personalise skincare products matched to their own DNA. Thus becoming another step towards the consumer culture developed by Toumazou's consumer electronic background.

JULY 2014

Professor Toumazou appointed Honorary Fellow of Cardiff University

In recognition of his outstanding work and contribution to the biomedical engineering industry Professor Toumazou has been made a Honorary Fellow of Cardiff University at The Graduation Ceremony of the Cardiff School of Engineering.

Cardiff University recognises many great figures from a wide and comprehensive range of disciplines, industries and sectors to-date and consider its Fellows to be key ambassadors of the University.

On the receiving of the award, Professor Toumazou spoke about 'lab on a chip technology: "Lab on a chip technology is the idea of taking a whole laboratory and integrating onto a microchip. The laboratory is a DNA lab where all the stages of biochemistry and amplification are integrated onto a small semiconductor microchip".

AUGUST 2014

Dr Timothy Constandinou promoted to Senior Lecturer

The Deputy Director of the Centre has been promoted to Senior Lecturer in the Department of Electrical and Electronic Engineering.

Tim originally joined the department as an undergraduate student in 1998. After completing his PhD in 2005, he then moved to the Institute of Biomedical Engineering where he was appointed research officer for the bionics theme. In 2009, he became deputy director of the Centre for Bio-Inspired Technology and then re-joined the EEE Department as academic faculty in 2010, as a Lecturer in the Circuits & Systems Research group. He continues to maintain his role as deputy director of the Centre and also leads the research theme in Neural Interfaces and Neuroprosthetics.

SEPTEMBER 2014

Professor Toumazou receives IET Faraday Medal

The highest honour of the UK's Institution of Engineering and Technology (IET) presented to Centre's Director for the invention of semiconductor sequencing and pioneering work that has led to disposable semiconductor healthcare.

Professor Toumazou's semiconductor based sequencing technology enables rapid, cheap and even disposable DNA sequencing. As a microchip-based system, unlike optical technologies, it can be scaled down enabling DNA sequencing to be performed on a device the size of a USB stick.

The Faraday Medal is the highest honour presented by the UK's Institution of Engineering and Technology, awarded for his pioneering work leading to disposable semiconductor based healthcare. The IET is one of the largest organisations for engineers and technicians with nearly 160,000 members in 127 countries.

Commenting on the award, Professor Toumazou said: "I am very thankful to the Institution for considering my work for this prestigious award. Being chosen as the 2014 winner is a true honour. For my entire career I have worked to bring electronic inventions to healthcare markets where there is a critical and urgent need. For me, the ability to use semiconductor sequencing to provide a medical diagnosis in just a few hours that once took days is a crucial step in saving the lives of patients. This is particularly significant for the treatment of sepsis where every minute matters."

AUGUST 2014

The Bio-inspired Artificial Pancreas successfully completes clinical trials

We are pleased to announce that the Bio-inspired Artificial Pancreas (BiAP) has completed it's current phase of clinical validation on 20 subjects with type 1 diabetes achieving successful glucose control during fasting, overnight, 24 hours, and fully automated 24-hour trials.

Clinical trials were conducted at the NIHR/Wellcome Trust Sir John McMichael Centre, Hammersmith Hospital, London. The system was proven to safely control blood glucose and successfully completed a total of 821 hours of closed loop control without any adverse effects. An important outcome of the trials was the systems capability to significantly reduce hypoglycaemia when compared with the subjects standard insulin pump therapy. We are now moving forwards over the next year to demonstrate the devices capability in the home environment.

SEPTEMBER 2014

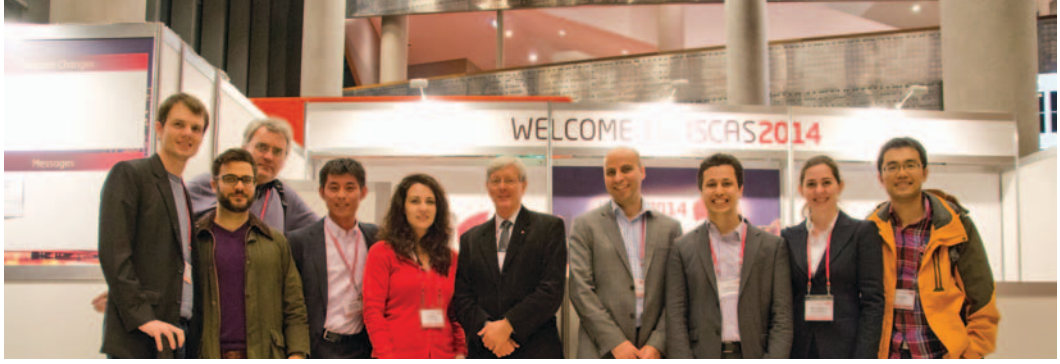
Dr. Wong Accepts Top Luxury Packaging Award for Toly Products on GENEU Packaging

Toly Products has received the 2014 Luxury Packaging Award in the Cosmetics & Personal Care category for the state-of-the-art Airlift Pump System the company designed for GENEU, the cutting-edge 'cosmeceuticals' company Dr. Wong has created.

The Luxury Packaging Awards highlight the best new packaging designs and innovations worldwide and are sponsored by Packaging News, the industry's leading trade publication.

GENEU'S airlift pump system is a refillable pack available in three colors: pearlescent white, gunmetal grey and black. The airlift pump system "houses two personalized refill packs with a magnetic closure and its heavy weight gives the pack that ultra-luxurious feel," according to the packaging designer.

Five criteria were used to judge the entries in the awards competition, including the quality and innovation in graphics, decoration, shape and structure; functionality; how the package stands out on the shelf; how the packaging adds value to the brand; and the luxury feel of the package.



At ISCAS in June (left)

OCTOBER 2013 – SEPTEMBER 2014

Researchers prominent at international conferences

Researchers from the Centre have attended several international conferences this year and delivered papers.

At the annual **Diabetes Technology Meeting (DTM)** on November 2013, held in San Francisco, USA, 1 lecture and 3 posters were presented by Pau Herrero, Peter Pesl, Monika Reddy, Nick Oliver and Pantelis Georgiou *(pictured below)*.

At the **IEEE Biomedical Circuits and Systems (BioCAS) conference** held in Rotterdam, Netherlands in Novemeber 2013, two papers were presented by Mohamedreza Sohbati, Onur Guven, and Lieuwe Leene and Timothy Constandinou.

At the **Advanced Technologies and Treatments for Diabetes (ATTD) Conference** on February 2014, held in Austria Vienna, 1 lecture and 3 posters were presented by Pau Herrero, Peter Pesl, Monika Reddy, Nick Oliver and Pantelis Georgiou.

At the **IEEE International Symposium on Circuits and Systems (ISCAS)** held in Melbourne, Australia in June 2014, 9 papers papers were presented by Satoshi Yoshizaki, Ermis Koutsos, Lieuwe Leene, Yuanqi Hu, Tatiana Trantidou, Melpomeni Kalofonou, Pantelis Georgiou, Tim Constandinou and Konstantin Nikolic.

Pau Herrero and Monika Reddy at ATTD in February (above)

News: 'Spin-out' companies

SEPTEMBER 2013

New international distribution agreement for SensiumVitals®; first commercial orders received

Toumaz Limited has signed a significant new North American distribution agreement with NantHealth Group, 'NantHealth', for SensiumVitals®, its ultra-low power system for wireless monitoring of patient vital signs. This new agreement is structured to accelerate the commercial exploitation of SensiumVitals® technology which has now begun.

Toumaz has also received its first sizable commercial order for SensiumVitals®. The system will be deployed at Hurley Medical Center in Flint, Michigan; where for the first time, a wireless patient vital signs tracking system will be used in Accident & Emergency – thereby assisting physicians with the management of patients after triage.

SensiumVitals® receives CE marking; first UK hospital pilot

Toumaz Limited announces that SensiumVitals®, its ultra-low power system for wireless monitoring of patient vital signs, has received CE marking under the EU Medical Devices Directive.

The CE Mark allows the system to be sold throughout the European Union, and follows the product's US FDA 510k clearance, received in July 2011.

The Group has also secured the first UK pilot deployment of SensiumVitals® with Spire Healthcare ('Spire'), a leading UK provider of private healthcare. The pilot will start in a Spire Healthcare hospital in early 2014. Spire has 38 hospitals across the country and has earned a reputation as a leader in patient care.

JULY 2014

SensiumVitals® deployed in Hurley Medical Centre, Flint, Michigan

Sensium Healthcare›s SensiumVitals® patches monitor vitals signs while patients sit in the waiting room helping Hurley Medical Center to stay ahead of the curve in becoming a fully electronic hospital.

www.mlive.com/news/flint/index.ssf/2014/06/hurley_medical_center_is_front.html

SEPTEMBER 2014

GENEU opens its flagship store in New Bond Street

GENEU opened its doors to the public in September of this year, offering its clients the chance to discover the way their skin ages based on both their genetics and lifestyle choices. Not only is this a breakthrough in the understanding of skin health and ageing, the microchip technology will give an accurate result in 30 minutes – the fastest non-invasive DNA test available.

Whilst other skincare products are only able to match a product to a very broad skin type, GENEU is unique in its ability to provide one-to-one bespoke anti-ageing products matched exclusively to a clients DNA. This ensures your skin receives the suitable actives and concentrations it needs for optimum skin health and protection from environmental damage.

Once the DNA test has been conducted by a PhD qualified scientific advisor, a beauty expert talks the client through their results before providing a bespoke product recommendation that's formulated to target wrinkles, elasticity and fine lines.

Although GENEU is still in its early days, it has received excellent press and praise in *British Vogue*, *Porter* and *Wired* to name a few.

OCTOBER 2013 – SEPTEMBER 2014

SensiumVitals®, Genalysis® and GENEU in the news and Media

FOX – www.foxnews.com/tech/2014/07/22/digital-bandage-checks-vital-signs

CNN – http://edition.cnn.com/video/data/2.0/video/bestoftv/2014/06/12/spc-make-create-innovate-genalysis.cnn.html

BBC – www.bbc.co.uk/news/health-28415753

Marie Claire – www.marieclaire.co.uk/news/beauty/547267/geneu-dna-beautylab-on-a-microchip.html

Design Week – www.designweek.co.uk/news/virgile-and-partners-and-duran-durans-nick-rhodes-work-on-dna-based-anti-aging-brand-designs/3039131.article

Reflections from Alumni

DR TATIANA TRANTIDOU

PhD graduate 2014

Over the past 2.5 years, I had the unique opportunity to work as a PhD student at the Centre for Bio-Inspired Technology in the field of microfabrication and biomedical electronics. The Centre fosters an ideal environment to conduct truly interdisciplinary research.

During my PhD I developed advanced technologies to produce biomimetic cardiac tissue in the laboratory, while in parallel I investigated new materials and technologies to integrate electrical and chemical sensing modalities in the developed cell culture platforms. The long-term application of this effort is to create human-relevant assays in the laboratory for drug screening and disease modelling.

Throughout this programme I interacted with scientists who are leaders in their research field and also networked with science-led global healthcare companies, such as GlaxoSmithKline. This continuous interaction together with the immense support and guidance of my supervisors and the help I received from my colleagues and members of staff, have enabled me to successfully complete my PhD studies within 2.5 years.

Working at Imperial and particularly the Centre was a strategic investment that is best reflected by my academic achievements. Using the Centre's excellent cleanroom and characterisation facilities I gathered extensive expertise in microfabrication technologies, electronics and material science. These skills and qualifications definitely had a positive impact on my personal and professional development. As a result, I am currently a Research Fellow at the University of Southampton, an institute with an outstanding international reputation in nanotechnology and nanoelectronics.

DR ALESSANDRO BORGHI

Research Fellow 2008–2013

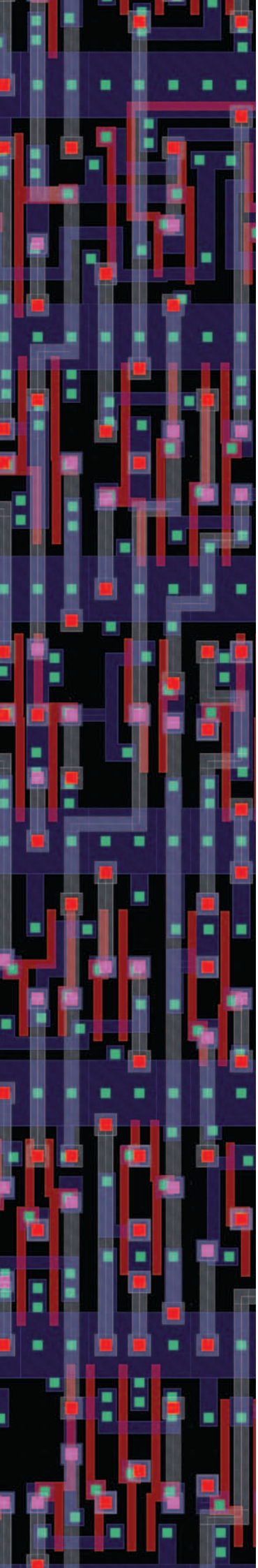
I worked for the Centre for Bio-Inspired Technology for nearly five years, as a research fellow. My research was part of the SAW project, which has been focusing on the design of a novel implantable pressure sensor based on the surface acoustic wave (SAW) technology, previously employed in telecommunication as well as automotive sectors. My role in the project was to design a way to position the pressure sensor inside the body and ensure its mechanical stability and biocompatibility.

What I found great about the Centre of Bio-Inspired Technology was the possibility of working with people of different background and being able to tackle a problem from an extremely multidisciplinary point of view. I have benefited from the access to the state of the art CBIT laboratories as well as other structures within Imperial College.

The centre has a recognised track record of successful project and having worked here opens a wide range of opportunities in academia as well as in the private sector. The experience gathered during my research at CBiT has allowed me to progress further in my career and obtain a post as Senior Research Associate at the Institute of Child Health (UCL) where I am carrying out research on surgical correction of Craniofacial abnormalities, in collaboration with Great Ormond Street Hospital.

Research funding

Project	Sponsor	Start Date	Duration
Enabling technologies for sensory feedback in next-generation assistive devices	EPSRC	March 2015	3 years
Toward Non- invasive Optical Neural Recording Without Molecular Reporters	EPSRC Impact Acceleration Award	December 2014	10 months
Wearable Electronics for smart garments aiding rehabilitation	EPSRC Impact Acceleration Award	November 2014	9 months
Controlling Abnormal Network Dynamics with Optogenetics (CANDO)	Wellcome Trust / EPSRC	August 2014	7 years
"AnaeWARE" Monitoring awareness during anaesthesia	Commission of the European Communities	August 2014	2 years
Multiscale Computational Tools for Optogenetics	Biotechnology and Biological Sciences Research Council	June 2014	15 months
Development of an Easily Deployable Intraocular Wireless Pressure Sensing Implant for Patients with Rapidly Progressing and Blinding Glaucoma	Wellcome Trust ISSF	October 2013	16 months
Iprobe: *in-vivo* Platform for the Real-time Observation of Brain Extracellular Activity	EPSRC	September 2013	3 years
A Bio-Inspired Artificial Pancreas for Control of Type 1 Diabetes in the Home	Wellcome Trust	August 2013	2 years
Real-Time Neural Chemical Sensing in the Peripheral Nervous System	EPSRC	July 2013	3 years
An Intelligent and Implantable Modulator of Vagus Nerve Function Treatment of Obesity	Commission of the European Communities (EU)	April 2013	5 years
Automated Blood Pressure Monitoring	Wellcome Trust	March 2012	3.5 years
Ultra Low Power Biosignal processing	Texas Instruments	May 2011	4 years
'SeeBetter'	Commission of the European Communities	February 2011	4 years
Centre for Bio-Inspired Technology	Winston Wong	October 2009	ongoing



Our mission: 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.

Research strategy

The Centre's research programme involves a strong combination of integrated miniature sensing with biologically inspired, intelligent processing, leveraging on state-of-the-art semiconductor technology. We aim to make small healthcare devices, which combine electronics with biological processes. By applying conventional silicon microchip technology in new ways, we are creating new opportunities for medical device innovation.

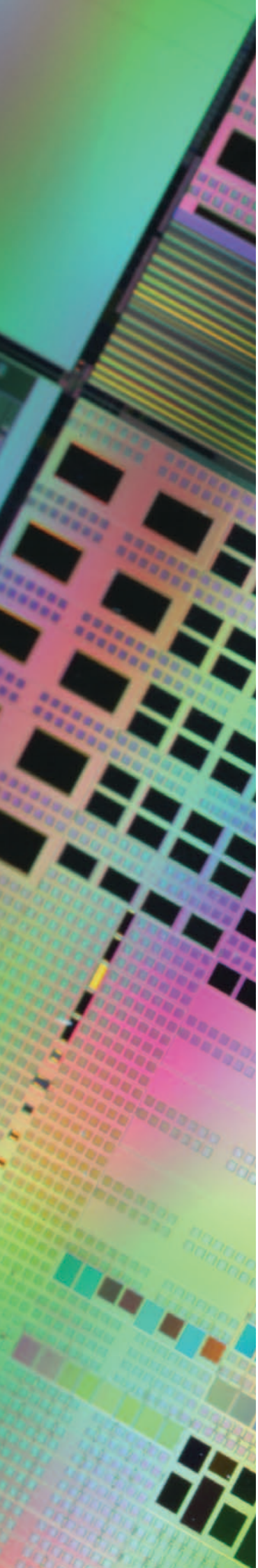
We have pioneered next generation semiconductor sequencing (spun out and licensed internationally), developed and trailed the worlds first bio-inspired artificial pancreas for Type I diabetes, invented and commercialised the disposable digital plaster for healthcare monitoring (now both FDA-approved and CE-marked), and are continuing to push the envelope of how semiconductor technology is being applied to biomedicine.

Such advances mean that there can be a shift in care away from a centralised model that puts the physician at its core to a smarter, more decentralised approach centred on the patient – known as personalised healthcare. They also open up new ways of coping with the huge problems of ageing populations and surges in chronic ailments such as diabetes and heart disease.

We believe this shift in the model will result in a more portable, precise and personal way to deliver healthcare using user-friendly devices such as wearable computing and smart phones. The design of these devices can 'hide' the processes of monitoring physiological conditions but allows data to be displayed in ways that patients can see results and act on the information. We also believe this shift has the potential to reduce the costs of healthcare by removing the need for onsite clinic visits for monitoring and shorter stays in hospital beds because patients can be diagnosed and monitored more quickly and in many cases remotely.

Researchers within the Centre for Bio-Inspired Technology work together with scientists and engineers from across Imperial College as well as in collaboration with partner institutions and industry. Project teams include medical researchers and clinicians to ensure the focus remains on the medical needs we aim to address.

The Centre's Research Strategy is based on applying engineering technologies in innovative ways to provide personalised healthcare devices for chronic disease management. This is organised into four programmes: Metabolic Technology, Cardiovascular Technology, Genetic Technology and Neural Interfaces and Neuroprosthetics.



Genetic technology

Research is focused on the development of semiconductor based genetic and epigenetic detection platforms for early diagnosis and monitoring of disease progression.

HEAD OF RESEARCH

Professor Chris Toumazou FRS, FREng, FMedSci

We are living in an era that has experienced significant technological revolutions as well as advances in medicine and health management, improving our quality of life, giving us the opportunity to be the protagonists of a trend in personalised medicine. Significant advances in the field of genetic technology have been made, with the development of semiconductor based platforms for point-of-need diagnostics, on-the-spot genetic testing and next-generation DNA sequencing to provide lab-free, fast, robust, easy-to-use and cost-effective solutions for healthcare. This realisation has been enabled with the use of CMOS technology, which brings with it the capability of integration of millions of sensors per microchip, enabled by the relentless scaling according to Moore's law.

CMOS based detection systems are expected to revolutionise medical practice, with multiple areas benefiting from these, from genetic analysis of infectious agents and bacterial genome sequencing to early screening of cancer markers and monitoring of chronic disease progression. In addition to genetic changes, epigenetic events play a significant role in multiple stages of disease development. Epigenetic profiles of genes can be used to distinguish diseased from normal cells, and are a powerful tool for risk markers used in early detection strategies.

Our research at the Centre for Bio-Inspired Technology involves the development of 'lab-on-chip' platforms for detection of genetic and epigenetic biomarkers, by integrating CMOS based ISFET sensors with application-specific biochemical assays. Emphasis is given in the areas of genotyping, genetic/epigenetic detection and monitoring of cancer as well as epigenetic monitoring of chronic kidney disease.

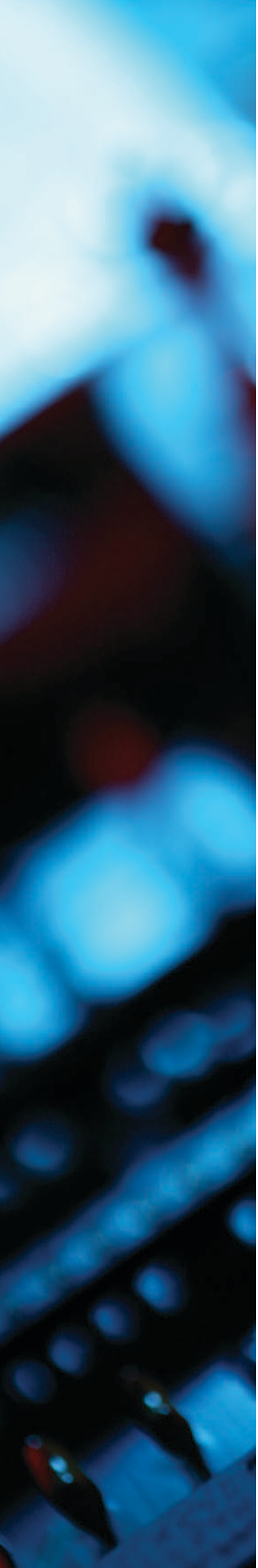
Genetic testing has been conventionally based on complex chemical, lab-based methods to detect DNA sequences. With the use of standard CMOS microchip technology, this can be simplified to a lab-free, sample-to-result answer, a YES or NO output as a result of a 'match' or 'mismatch' of DNA base pairs, translated into an ON or OFF state of a chemically sensitive transistor. Research in the Centre led to the development of the Genalysis® technology platform, a low cost microchip based platform built into a USB-sized device, capable of delivering fast and accurate on-the-spot tests for detection of any target nucleic acid sequence in either DNA or RNA as well as nucleotide insertions. Disposable 'lab-on-chip' cartridges housing biochemical reagents, advanced microfluidics and low-power silicon biosensors are key to this novel technology, with each cartridge to be customised to a variety of applications and markets. Built on the reliability, scalability and processing power of silicon microchip technology, this platform technology is mass-producible and highly portable. The commercialisation of this technology is being undertaken by DNA Electronics Ltd., a spinout company from the Centre.

RESEARCH IN GENETIC TECHNOLOGY CONTINUES IN THE CENTRE WITH A SPECIFIC FOCUS ON:

Epigenetic testing and monitoring of biomarkers involved in the initiation and progression of tumour development could provide valuable information in the clinical monitoring of cancer and the assessment of treatment efficacy. The role of DNA methylation in several stages of tumour development has shown great potential in detection, diagnosis, prognosis and monitoring of disease, through disruptions in gene expression leading to aberrant gene inactivation. We have developed a semiconductor based platform with integrated chemical sensors, able to detect DNA methylation based biomarkers in real-time, avoiding the use of fluorescent dyes or labels. This will be used in cancer risk identification and early diagnosis by measuring simultaneously multiple epigenetic targets on a single microchip.

Epigenetics also plays an important role during the progression of chronic kidney disease (CKD), a condition resulting from chronic kidney damage and prolonged renal dysfunction, often leading to renal replacement therapy. We are applying the same technology to chronic kidney disease monitoring using DNA methylation based biomarkers. The implementation of an efficient detection system aids developments in related epigenetic therapy for typically irreversible kidney damage, preventing the need for dialysis and renal transplantation.

Semiconductor based DNA sequencing has revolutionised the cost of sequencing of the human genome making it more affordable and therefore accessible for healthcare applications where rapid diagnostics is strongly needed for the right treatment to be provided at the right time. This is possible due to pH based DNA detection using Ion-sensitive Field Effect Transistors (patented by our group), which are implemented in CMOS and therefore scale according to Moore's law. This research focuses on creating CMOS based systems with local intelligence, which can efficiently sequence the human genome for a variety of diseases including sepsis, cancer and diabetes.



Metabolic technology

Research is developing technologies for application in early detection, diagnosis and therapy of metabolic disease with the main focus on treating diabetes and its complications.

HEAD OF RESEARCH
Dr Pantelis Georgiou

Recent trends in daily lifestyle and poor diet have led 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, currently the most severe metabolic disease and the leading cause of mortality and morbidity in the developed world, 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 3% of the world's population today is 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.

Clincal studies in subjects with type 1 diabetes have been successfully completed in the Imperial College-Wellcome Trust Sir John McMichael Centre. We studied 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. Results evaluated in fasting, overnight and 24-hours studies confirm the device is safe, good glucose control and reduction in the incidence of hypoglycaemia over night.

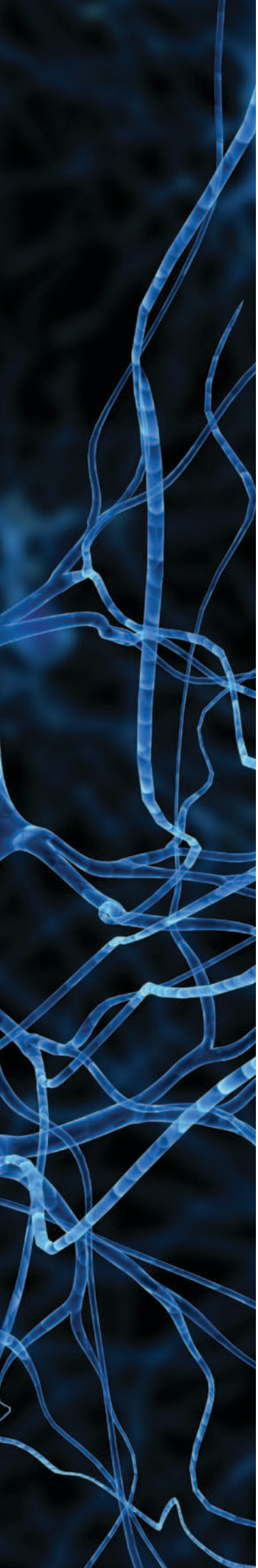
We are delighted to report that the Bio-inspired Artificial Pancreas is currently being funded over the next year by the Wellcome Trust to evaluate it's performance during exercise, mixed meals and in challenging conditions with the objective to conduct the first trials on type 1 diabetic subjects in their home environment.

Diabetes management systems – an integrated system of wireless sensors (glucose, heart rate and motion), decision support systems and smart-phones to create a telemedicine platform capable of continually monitoring, recording vital parameters and providing advice on insulin dosing which is required for treatment of diabetes. Additionally, the smart-phone provides a constant link to a clinicians database to allow constant monitoring from the hospital.

We are delighted to report that our smart-phone based Advanced Bolus Calculator for Diabetes (ABC4D) is currently undergoing clinical trials in people with Type 1 diabetes and results to date are promising.

Sensory systems and lab-on-chips for continuous monitoring and diagnostics – 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 to make reliable and robust continuous glucose snesors and diagnostic systems for screening of type 1 and type 2 diabetes and their associated variants and complications.

Osteoarthritis & antimicrobial resistance – The Group is also part of the Imperial College London Osteoarthritis Centre of Excellence funded by Wellcome Trust and the EPSRC working rehabilitation technology, and the Antimicrobial Resistance (AMR) Collaborative which is using current tools developed for diabetes management to optimise antibiotic prescribing in primary, secondary and intensive care to combat AMR in the NHS.



Neural interfaces and neuroprosthetics

Improvements in medical care and quality of life for individuals with neurological conditions such as epilepsy, spinal cord injury, paralysis and sensory impairment by developing implantable or wearable assistive technologies.

HEAD OF RESEARCH
Dr Timothy Constandinou

We are now entering a tremendously exciting phase in our quest to understand the human brain. With large-scale programmes like the US Presidential BRAIN Initiative and the EU Human Brain Project, there is currently a huge appetite for new neurotechnologies and applications. We have already witnessed the impact made by devices such as cochlear implants and deep brain stimulators, with hundreds of thousands of individuals that have and are benefitting every day. Soon, similar assistive technology will emerge for the blind, those suffering from epilepsy, and many others.

With the current capability in microtechnology, never before have there been so many opportunities to develop devices that effectively interface with the nervous system. Such devices are often referred to as neural interfaces or brain-machine interfaces and range from wearable surface-electrode systems to fully implantable devices. The interface typically uses an electrical connection (i.e. electrodes) to achieve the neural recording and/or stimulation utilising a variety of techniques, including: electroencephalography (EEG), electromyography (EMG), electrocorticography (ECoG) and direct interfacing using cuff electrodes or penetrating microelectrode arrays (MEAs). Neural prostheses use such interfaces to bypass dysfunctional pathways in the nervous system, by applying electronics to replace lost function.

Our research at the Centre for Bio-Inspired Technology is aimed, ultimately at developing such devices to provide neural rehabilitation by exploiting the integration capability and scalability of modern semiconductor technology.

ONGOING NEUROPROSTHETICS RESEARCH

Next Generation Neural Interfaces. Monitoring cortical activity locally using implanted microelectrodes is demonstrating the ability to achieve multi-dimensional motor control. Current devices record from up to 100 channels and typically stream the raw data to an external processor. Our research is developing next generation devices to record from more channels (1000s), extract information locally (spike sorting) and transmit data (transcutaneous) wirelessly directly to output devices (eg. actuators).

Proprioceptive feedback for upper-limb prosthetics. 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.

I2MOVE (Intelligent implantable modulator of Vagus nerve function for treatment of obesity). The vagus nerve is the principal pathway of sensory information passing from gut and other vital organs to brain and spinal cord. Vagus nerve stimulation (VNS) has emerged as an implantable technology to stimulate the pathway and has been used in appetite control, depression and epileptic seizure suppression.

CANDO (Controlling Abnormal Network Dynamics using Optogenetics) is a world-class multi-site cross-disciplinary project to develop a cortical implant for optogenetic neural control. The goal is to create a first-in-man trial of the device in patients with focal epilepsy. Our role in this project is to develop the recording electronics for the implantable device as well as to be a key contributor to the underlying system design.

iPROBE (in-vivo Platform for the Real-time Observation of Brain Extracellular activity) is developing a scalable platform technology to enable the large scale recording in the living brain. This is achieved by using an approach common in computing: a daisy-chain digital serial interface. By allowing simple, robust, and low-noise connection of several multi-electrode arrays, this allows us to monitor thousands of neurons from multiple structures using a single interface.

Thermal Neural Microstimulation. Temperature affects every single physiological process and yet commercially available systems that allow for local change of temperature in physiological studies are difficult if not impossible to be found. The aim of this project is to develop novel devices that will enable direct and individually addressable thermal stimulation of neural circuits in-vitro.

AnaeWARE (Monitoring awareness during anaesthesia – a multi-modal approach). This project proposes a new direction in the field of monitoring awareness during anaesthesia: the combination of various multi-modal signals to obtain a holistic view of anesthetic-induced changes.

Cardiovascular technology

Research is focussed on real time monitoring of vital cardiovascular parameters to enable patients to move out of hospital into 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. In the UK, 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 ageing population and the already burdened health service, the cardiovascular technology research in the Centre is striving to apply cutting edge innovation to help reduce the incidence.

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 clinical 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 requiring no procedure by the patient 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 type of transducer 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.

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.

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 links the sensor data to a wide-area network for remote monitoring – this will be in a computer server in a GP's surgery or hospital clinic where software will generate both patient and clinician messages in the event of abnormal data. The device is designed to improve the diagnostic and progression information available to clinicians to optimise pharmacological therapy for patients living at home with heart failure. The system includes full mHealth connection with means for 24/7 monitoring.

Research is underway to take the implantable pressure sensors through manufacture for regulatory approval and through a Phase 1 safety trial by 2016. The implants and system will be applied to other indications following a successful Phase 1 trial.

GENEU

Professor Chris Toumazou
Chief Scientfic Advisor

Mr Martin Stow
COO

Mr Nick Rhodes
Creative Director

The focus of the Centre for Bio-Inspired Technology has been to revolutionise healthcare towards personalised medicine using semiconductor technology. One of the biggest problems we face today is effective management of chronic diseases. With increasing knowledge in the field of genomics, we understand that each one of us has a unique genetic disposition and that our response to medications may also differ due to these variations. There is without a doubt, a huge incentive for us to tailor medical treatments to better suit individuals towards the future of a more efficient and effective healthcare system.

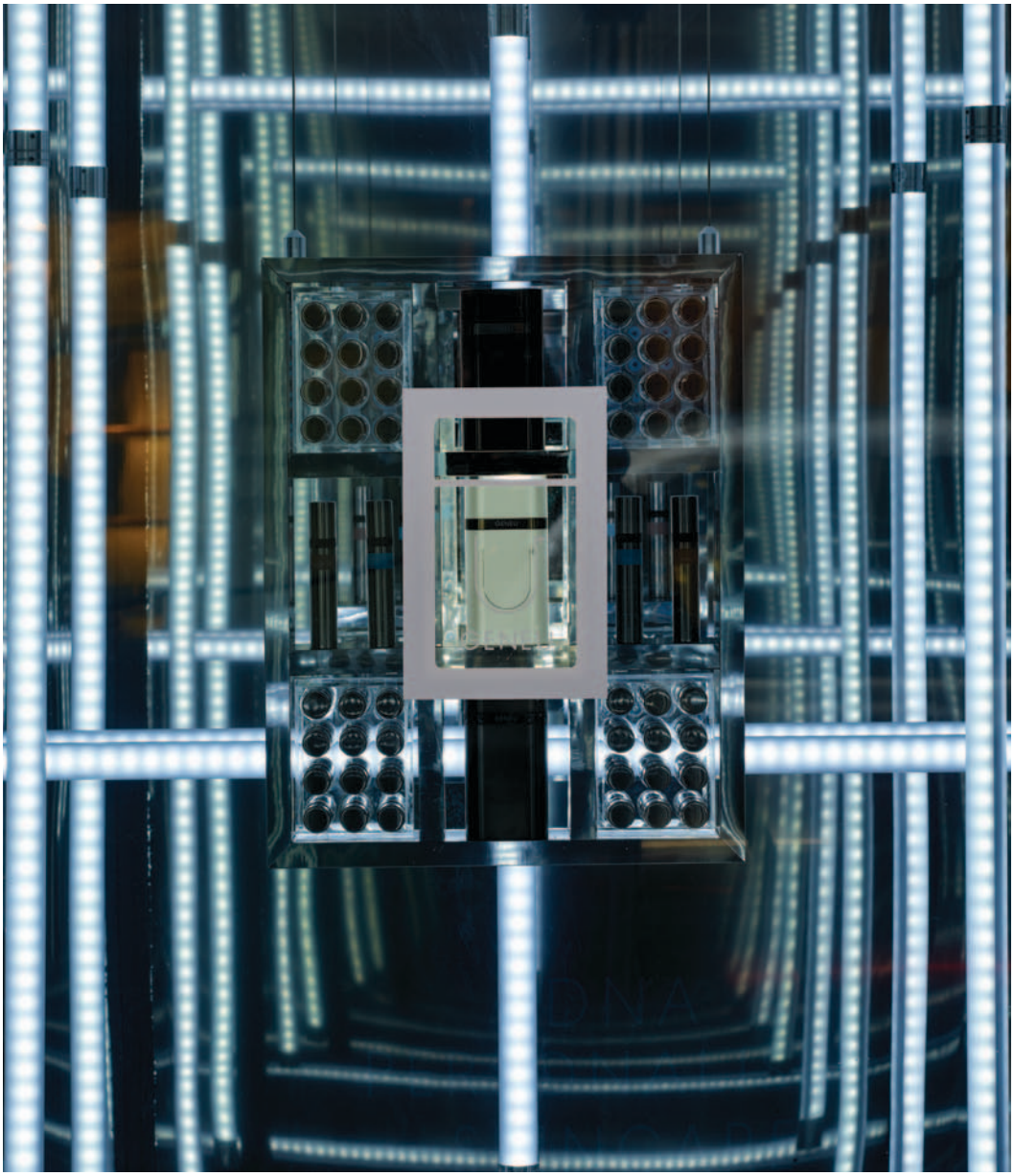
Until recently, the struggle of promoting personlised medicine lies in its restriction to DNA detection methods that can only be carried in resource rich laboratory environments. The invention of semiconductor-based DNA sequencing technology by Prof Toumazou has opened up possibilities for DNA to be analysed within minutes and outside of laboratory. It involves the detection of hydrogen ions released during DNA extensions when a complementary DNA is present with the target DNA. The release of the positively charged hydrogen ions causes a change in pH, which in turn is detected as an electrical signal by the ion semiconductor field effect transistors (ISFETs). The subsequent DNA microchip provides an inexpensive way for doctors to prescribe personalised treatments based on an individual's DNA in a non-intrusive manner.

The skincare industry is one that would benefit exceedingly with personalisation. Aging is a phenomenon that affects all of us and contributes to a majority of diseases. The ageing process is one that is heavily influenced by both genes and environmental factors, making it a valuable area for genetics and epigenetics research. Despite millions of pounds spent every year in skin health research and developing new skincare products, there are no substantial medical guidelines in what treatments to use. The lack of consumer awareness and personalised treatments made the skincare industry very ineffective yet expensive. So there is no better area to commercialise the portable DNA technology for everyday use before applying it in other diseases.

GENEU offers the world's first retail based skin DNA test in a new shop on New Bond street in London. The microchip technology patented by DNA Electronics can test for genetic variations associated with aging and the metabolism of various skincare ingredients in store using an individual's saliva in under 30 minutes. The customers' genetic results are then evaluated in the context of lifestyle choices to create a unique GENEU U+ profile. This GENEU U+ profile is used to produce DNA personalised skincare, tailored to provide daily protection against the individual's daily routine as well as preparing the skin for what it will need in the future.

THE 'DNA BEAUTYLAB ON A MICROCHIP'

Before the opening of GENEU in September 2014, two pilot studies were conducted at Imperial College London to assess human genetic variations in skin



ageing. The aim was to establish the effectiveness of targeted active ingredients that had been selected for an individual's specific genotype and lifestyle factors. The results, obtained from the screening of 120 healthy people, showed that an individual's genotype significantly influences the effectiveness of the cosmetic application, with UV damage being one of the most important mediators of skin ageing due to lifestyle.

The pilot studies provided a platform to test an innovative integrated CMOS microchip for real-time amplification and detection of nucleic acid. This system was invented at Imperial College London and was subsequently developed over the last 10 years by a spin out company DNA Electronics founded by Prof Toumazou. The results delivered in the studies by this semiconductor system were comparable to those obtained by the gold standard Taqman genotyping assays. In 2013, the microchip technology was published in the scientific journal Nature Methods, demonstrating simultaneous DNA amplification and detection using this pH-sensing semiconductor system (Toumazou C. *et al., Nature Methods,* 10, 641–648 (2013)). This semiconductor DNA detection system formed the basis of GENEU's 'DNA BeautyLab on a microchip'.

The GENEU proprietary 'DNA BeautyLab on a microchip' has proven its ability to extract, amplify and detect DNA variations affecting skin ageing from an individual's saliva in just 30 minutes. An entire laboratory technology required to analyse the DNA of an individual has successfully been integrated onto this microchip. The results have proven to be as accurate as traditional fluorescence based methods, which would have normally taken days to complete. The introduction of semiconductor DNA detection has allowed for the user's DNA to be analysed non-invasively and in real time. This breakthrough in point of care DNA testing would undoubtedly revolutionise the personalisation of skin health and other areas of medical research.

The authors would like to thank Maria Zaleska and Dora Ma for their assistance in the preparation of this article.

Monitoring awareness during surgery: a multi-modal approach ('AnaeWare')

Dr Nicoletta Nicolaou

Marie Curie Intra-European Fellow (IEF)

"Suddenly, I was aware something had gone very wrong. I could hear what was going on around me, and I realised with horror that I had woken up in the middle of the operation, but couldn't move a muscle. I heard the banal chatter of the surgeons, and I was aware of many people in the room bustling about, doing their everyday clinical jobs and minding their own business, with absolutely no idea of the cataclysmic event that was unfolding from my point of view. While they fiddled, I lay there, frantically trying to decide whether I was about to die, and what options were open to me."

Patient testimony, as reported in NAP5
www.nationalauditprojects.org.uk/NAP5report

Modern anesthesia is a chemical cocktail of agents, each one targeting a different integral part of anesthesia (unconsciousness, amnesia, analgesia and immobility). Given that there are no strict dosages for these combinations of agents, the anesthetist follows a set of approximate dosage guidelines and adjusts these based on patient characteristics and past experience. However, administering an incorrect dosage could have serious complications. Over-administration leads to unnecessarily deep anesthesia, with dangerous and potentially lethal consequences (e.g. cardiovascular depression). Under-administration leads to light anesthesia, with increased risk of accidental regaining of awareness during surgery.

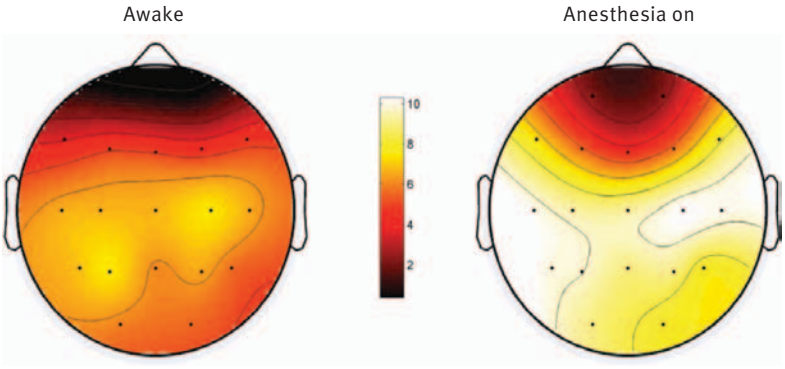
The patient testimony above highlights the severity of accidental regaining of awareness during surgery. Even though intra-operative awareness (IOA) does not happen often, the consequences for patients who do experience it during their surgery are traumatising. Such an experience can lead to long-term psychological problems, including post-traumatic stress disorder and fear of having another surgery. In addition, the majority of surgically-related insurance compensation claims to patients are related to accidental awareness during surgery. The Association of Anesthetists of Great Britain and Ireland has recently published the findings of a comprehensive study (NAP5) of accidental awareness during general anesthesia in the UK and Ireland [1]. The study reports that approximately 300 patients in the UK and Ireland have experienced awareness during their surgery in one year, resulting to an estimated incidence of awareness at 1 patient in 15,000. Other similar studies in the USA report a higher incidence at approximately 0.1% (e.g. [2]). Putting this into perspective, considering that an estimated 234.2 million patients undergo surgery with general anesthesia every year worldwide [3], a conservative estimate of 15,613 patients will experience intra-operative awareness. These estimates are likely to be even higher, as some patients who experience awareness may not remember this due to the amnesic effects of the administered agents and, hence, a number of IOA cases remain unreported.

To address the problem of intra-operative awareness, the state-of-the-art has led to the development of commercial devices that monitor the patient level of hypnosis. Their operation is based on information extracted from the patient's electrical brain activity (electroencephalogram – EEG), as some of the effects of anesthetics cause identifiable changes in EEG activity [4]. The most widely used devices are the BIS® (Aspect Medical Systems, USA) and E-Entropy (GE, Germany). Despite their existence, they failed to become part of routine surgery (reported use in 2.8% of surgeries [1]). This is due to a number of issues related to robustness, inter-subject variability and the large delay between the actual time of awareness and the time of change in the monitoring index [5]. An additional factor is cost of initial purchase, as well as long-term operational cost. The biggest cost is associated with the purchase of consumable sensors, whose prices vary more widely. The NHS cost for the BIS® Vista and the BIS® Vista Bilateral monitoring systems comes to £4,350 and £5,025 respectively, while the BIS® Quatro sensors cost £362.50 per box of 25 and the BIS® bilateral sensors cost £210 per box of 10 [6].

As part of a past project at University of Cyprus, we collected EEG activity from 47 patients undergoing routine surgery at Nicosia General Hospital. This activity was analysed with different methods (e.g. permutation and approximate entropy [7], granger causality [8], synchrony methods [9-10]). Our general findings verified a decrease of EEG complexity during anesthesia and we identified specific changes in brain connectivity and synchrony during anesthetic-induced unconsciousness (an example can be seen in figure 1). Even though the majority of features investigated showed high performance in wakefulness / anesthesia discrimination, our interest focused more on granger causality-based features, as these provided high discriminatory ability (98%) while also capturing general mechanisms of anesthetic-induced changes in brain connectivity. More specifically, we identified a stable and reversible increase in granger causality in the fronto-posterior direction during anesthesia, independently of the particular anesthetic protocol [8].

Based on our previous findings, 'AnaeWARE' (August 2014 – July 2016) challenges the state-of-the-art and

This research has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement no 623767.



Visual representation of (a) wakefulness and (b) anaesthesia, in the form of scalp topographies.

addresses the question whether EEG alone is sufficient for reliable monitoring of anesthetic state. A promising direction for a new generation of monitoring devices is the extension from a single- to a multi-modal approach, utilising additional information that is already available as part of routine monitoring during surgery, e.g. heart rate. This will not impose additional costs to already limited national healthcare funds and could offer a solution for more reliable monitoring. To pursue this direction of research relies, firstly, on the ability to link these multi-modal observations to the underlying mechanisms of anesthetic action; and, secondly, on the ability to take this knowledge and turn it from theory to practice (hardware implementation). The project will involve the collection of anonymous multi-modal signals from patients undergoing elective surgery at Hammersmith Hospital, London. The data will be analysed in order to identify how anesthetic administration affects the relationships between the different modalities and investigate whether such changes provide increased discriminatory power between wakefulness and anesthesia, or even prediction of wakefulness. The latter in particular is highly non-trivial and we envisage to explore this through the aid of theoretical models that describe the effects of anesthetics on neural connectivity. The outcome of the project will be an index of awareness that is robust and takes into account inter-subject variability. A secondary aspect of the project is the 'real-time' estimation of this index of awareness. This will involve the translation of the developed methodologies to hardware form that is capable of performing 'real-time' discrimination of wakefulness and anesthesia.

We believe that the shift to a multi-modal approach will improve performance, allow fast prediction of intraoperative awareness and, thus, provide the necessary push to lead the way for the development of the next generation of devices for monitoring the patient state of hypnosis.

Anesthesia

- Anesthesia is a reversible state comprising of loss of consciousness, amnesia, lack of pain and muscle relaxation.
- Incorrect dosage of anesthetics could result in over-administration (unnecessarily deep anesthesia, potentially dangerous) or under-administration (intra-operative awareness)
- Intra-operative awareness (IOA): accidental or unexpected regaining of consciousness during surgery
- More than 300 people experienced IOA in one year in the UK and Ireland, corresponding to an estimated incidence of awareness of 1:15,000.
- At least 15,613 patients will experience IOA annually worldwide, based on the estimated 234.2 million surgical procedures annually (2008 data).

COLLABORATION

This research is in collaboration with the Hammersmith Hospital and the University of Cyprus (UCY). The respective teams include at CBIT: Dr Nicoletta Nicolaou, Dr Timothy Constandinou, at the Hammersmith: Dr Geoffrey Lockwood, and at UCY: Dr Julius Georgiou.

For more information please visit the project website: **www3.imperial.ac.uk/bioinspiredtechnology/research/anaeware**

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Controlling abnormal network dynamics using optogenetics (CANDO)

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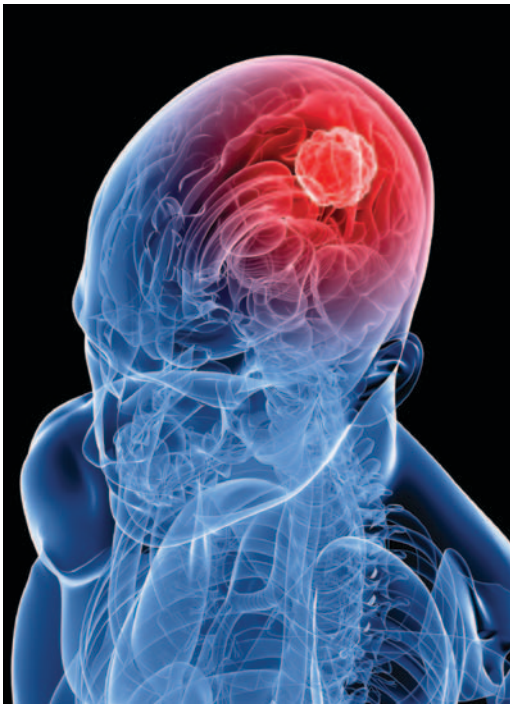
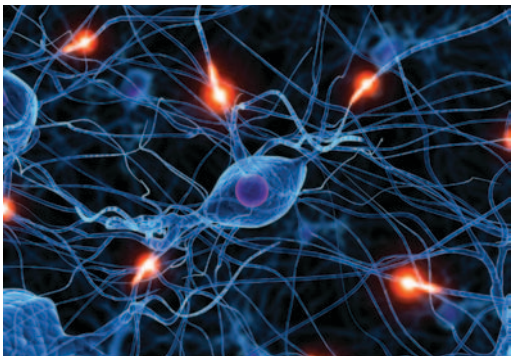
Dr Yan Liu
Research Fellow



CANDO (Controlling Abnormal Network Dynamics using Optogenetics) is a world class multi-site cross-disciplinary project to develop a cortical implant for optogenetic neural control. The goal is to create a first-in-man trial of the device in patients with focal epilepsy. This 7 year, £10m Innovative Engineering for Health Award, funded by the Wellcome Trust and EPSRC involves a team of over 30 neuroscientists, engineers and clinicians based at Newcastle University, Imperial College London, University College London, and Newcastle upon Tyne Hospitals NHS Foundation.

Within the brain nerve cells connect together to generate rhythmic activity visible as brain waves on an EEG. In many neurological diseases this network is disrupted, producing abnormal patterns of activity. In epilepsy, abnormal activity can be localised to a small 'focus', but this can spread across the whole brain as a seizure. Epilepsy affects 600,000 people in the UK alone and uncontrolled seizures have a devastating effect on patients' quality of life. Most cases respond to drugs, but if these are ineffective it may be necessary to surgically remove the 'focus'. However, surgery is not suitable in all patients and can damage cognitive function. This project, led by Dr Andrew Jackson and Professor Anthony O'Neill from Newcastle University, proposes an alternative based on a small implant that continuously records the abnormal activity and provides precisely timed stimulation



to prevent it ever developing into a seizure. This requires that some cells within the focus are genetically altered using a safe virus to become sensitive to light. The implant will monitor their activity and provide pulses of light from tiny LEDs to prevent the build of abnormal activity.

Our role on this project is as a key contributor to the microelectronic design of the implantable electronics. We are leveraging on our past research outcomes and extensive expertise in neural interface design to develop, together with our collaborators, an ultra compact, low power probe for closed loop operation.

COLLABORATION

This is in collaboration with Newcastle University, UCL and the Newcastle upon Tyne Hospitals NHS Foundation. For more details, please see the project website at: **www.cando.ac.uk**

Multiscale computational tools for optogenetics

Dr Konstantin Nikolic

Senior Research Fellow

Optogenetics is a new tool in which light-sensitive ion channels ('opsins') are genetically inserted into cell membranes. This allows for the precise spatial and temporal optical stimulation of excitable cells such as neural ensembles, as well as modulation of signaling cascades, and has numerous applications which are only beginning to be explored.

Apart from becoming a key technology for neuroscience and deconstruction of brain circuits, applications are rapidly emerging throughout biology: e.g. control of cardiac cells, sensing and monitoring cellular activities, optical control of cell signaling pathways, using light to destroy proteins and cells, etc. The field of optogenetics has the potential to be one of the most important new techniques for many years and *Nature Methods* declared it the *Method of the Year for 2010*.

There are several families of opsins, each of which has unique temporal and spectral properties. There is a substantial effort to characterise opsins for each cell population, and a continual drive to improve their efficacy. While the effect of an opsin can be quantified at the level of individual cells (e.g. neurons), it currently remains practically impossible to experimentally test each opsin for each cell type or biological system of interest. This significantly limits the effectiveness of optogenetics as a biological tool.

The aim of this project is to develop multiscale computational tools for optogenetics.

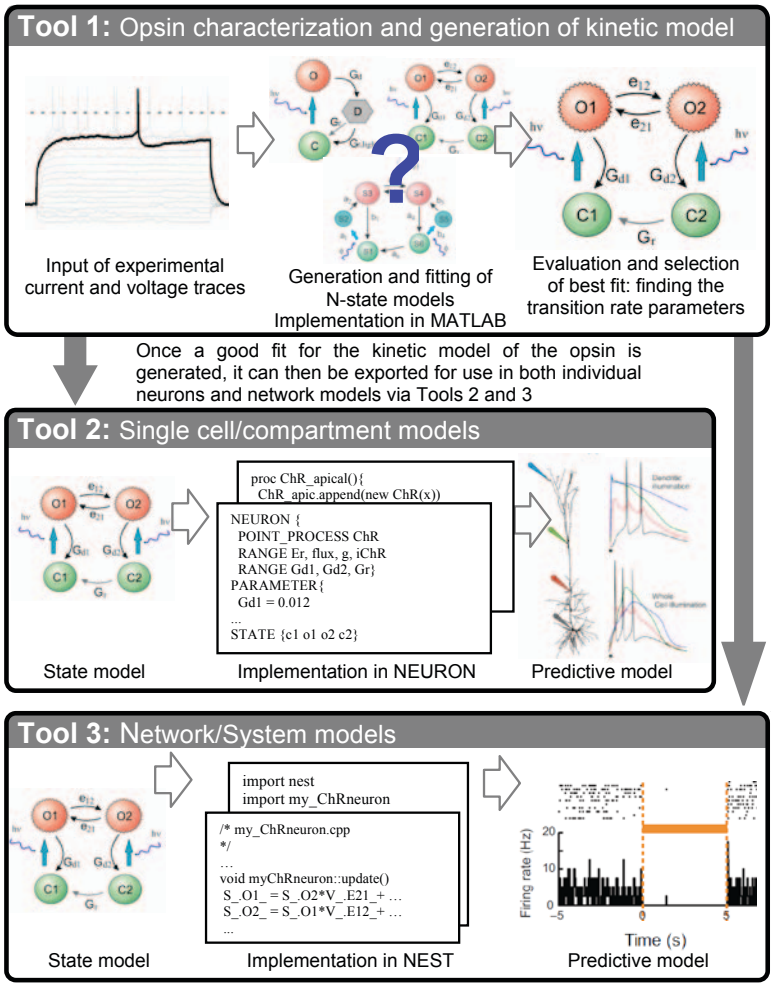
We first develop a tool for characterising opsins, allowing us to link from the underlying biophysical photocycle that defines kinetic model of opsins (molecular-complex scale), see the figure. Consequently this will allow us to obtain a functional understanding of each opsin and hence guide not only opsin choice for a given system, but potentially also guide opsin development.

Secondly, we build software to transform the biophysical model into computational formats for use in commonly used neural simulation tools at the levels of single cell/compartment. From the biophysical model, the corresponding state-model representation will be included into ion-channel representation in NEURON, one of the most commonly used simulation platforms in neuroscience. This will allow the inclusion of opsins within single-compartment and multi-compartment representations of single neurons.

Finally, we will implement opsins within point neurons for inclusion in network level simulations. Using the state-model representation, we will additionally include the biophysical model for several types of 'point neurons', such as Leaky Integrate and Fire (LIF), which are used in network models. Consequently, it will be possible to test realistic effects of optogenetics at the level of neuronal networks and systems to obtain multiscale understandings of optogenetic effects.

The combination of these three parts into a cohesive set of computational tools will facilitate the characterisation and development of opsins as well as assisting the existing and bring new applications of the technology in the field of neurotechnology and prosthetics, as well as cell physiology. The proposed tools will allow the inclusion of realistic models of optogenetics in existing simulations, allowing the use of virtual opsins to identify the correct experimental opsin choice. Together, these tools will improve the use of optogenetics as an effective and refined tool, enabling its potential to transform the biological sciences.

Three sets of tools that we develop in this project



COLLABORATION

This research is in collaboration with the Department of Bioengineering (DoB). The respective teams include at CBIT: Dr Konstantin Nikolic, Dr Benjamin Evans and at DoB: Dr Simon Schultz and Dr Sarah Jarvis.

Biomedical engineering solutions for antimicrobial resistance: a two-pronged attack

Dr Luke Moore

NIHR BRC Clinical Research Fellow

BACKGROUND

Infection is a widespread problem in UK hospitals, with around a third of all patients on normal wards, and two thirds of patients in intensive care on antimicrobials at any one time. Moreover, within hospitals half of those patients on antimicrobials are determined to have healthcare-associated infections, costing the National Health Service over £1billion per annum and representing a major cause of mortality. Superimpose on that the marked, and increasing, prevalence of antimicrobial resistance among the bacteria causing these infections, and the high profile currently attributed to the issue of antimicrobial resistance by the international community can, perhaps, be seen to be warranted.

Strategies to combat this rise in antimicrobial resistance have recently been put forward in international for a by the WHO, but also by the CDC in the US and by the Department of Health here in the UK in their 5 year plan which sets out their policies for this issue through to 2018. Inherent in all these strategies are four key, inter-related policy areas:

- Optimising 'prudent' antimicrobial use
- Improving surveillance
- Improving infection control

DEVELOPING NOVEL THERAPEUTICS

The opportunities for engineering and physical sciences to contribute to this global issue are manifold, from chemical engineering in developing therapeutics, to structural engineers in hospital design, through to computer engineers developing data-warehousing and 'Big Data' analysis techniques to improve surveillance. Perhaps more difficult to achieve, yet no less a valuable target, is use of engineering expertise in pursuit of 'prudent' antimicrobial use. Achieving such prudent use, thereby preserving our current armamentarium of antimicrobials, can be seen to be even more necessary when one considers development of novel therapeutics frequently takes 10 or more years.

Considering this pursuit of 'prudent' antimicrobial use, an engineering solution would have to act to aid each encounter between a doctor and a patient with an infection to achieve a balance between ensuring cure of the patient, buthelp avoid unnecessary biological selective pressure towards antimicrobial resistance.

Getting this balance may be thought to be easy for medical professionals by some, yet perhaps surprisingly, various studies have shown that up to half of all antimicrobial prescriptions are sub-optimal, including in the dose prescribed and the specific antimicrobial chosen. This then creates a research gap in which engineering and physical sciences expertise can generate and develop answers for real world translation.

THE VISION

The last 18 months has seen a strong, evolving, collaboration develop between the Centre for Bio-Inspired Technology headed by Prof Chris Toumazou, and the Centre for Infection Prevention and Management headed by Prof Alison Holmes. Through this cross discipline, cross Faculty, collaboration a vision for engineering solutions for antimicrobial resistance has been developed and is currently pursuing two avenues to aid 'prudent' antimicrobial use.

The first of these is to bring the rapid diagnostic capabilities of lab-on-chip technology developed by the CBIT team led by Prof Chris Toumazou to bear on antimicrobial resistance. Implementing such a diagnostic platform into clinical care would revolutionise diagnostic pathways, which currently rely on culturing bacteria, a process than can take 24–48 hours. The lab-on-chip platform therefore has the potential to improve patient care whilst simultaneously improving antimicrobial use at the societal level by allowing more targeted antimicrobials to be used earlier.

The second avenue being pursued is that of translating the artificial intelligence expertise within the CBIT group (developed around the use of case-based reasoning for decision support in insulin prescribing in diabetes) into the field of antimicrobial prescribing. This further optimises 'prudent' antimicrobial prescribing, where the majority of prescriptions are made by doctors who are not experts in infectious diseases or microbiology, by providing a machine-learning software solution to aid doctors in optimising antimicrobial prescribing for each individual patient.

OUR APPROACH

Close collaborative work between engineering staff in CBIT, clinical researchers in CIPM, and scientific staff from DNAe Ltd has led to the previously developed

lab-on-chip diagnostic platform developed by Prof Chris Toumazou and his team being applied to the field of antimicrobial resistance. Through this collaboration, the genotypic diagnostic platform is being developed to be usable at the point of care to analyse patient samples and provide rapid information of the identification of bacteria causing infections, and moreover give genotypic information on the likely resistance or susceptibility of such organisms to numerous antimicrobial agents. Currently much of the sub-optimal antimicrobial prescription that occurs can be attributed to uncertainty about which specific bacteria is causing the infection and which antimicrobial is likely to be effective – particularly early in the first 24-48 hours of an infection where broad-spectrum antimicrobials frequently need to be used. Using semiconductor technology to provide genotypic information on bacteria in 1-2 hours therefore, can be seen to be hugely beneficial, not only improving the outcome for the patient in question, but also decreasing the amount of broad spectrum antimicrobials that need to be used.

Similar progress has been made in application of machine-learning to decision support for antimicrobial prescribing. CIPM researchers have developed, and had implemented into clinical practice, a rule-based decision support system accessible on mobile devices that has now has over 3,000 users and has been accessed over 105,000 times to improve patient care in West London (the IAPP project). Leading on from that, expertise from CBIT in case-based reasoning has taken this forward, improving upon the initial rule-based model and providing personalised decision support using individual level data specifically for patients in intensive care (the ENIAPP project). This involved 18 months of work including: stakeholder requirements gathering; workflow modelling; medical decision making analysis from critical care and infection specialists; mapping of existing and required information systems; and finally, an adaptive software development process. Clinico-physiological and demographic parameters influencing infection management were categorised and integrated into the case-based reasoning algorithm, and definitions of antimicrobial regime success and failure were developed. The final product has been developed as an mHealth application for use on mobile tablets with information governance assured through use of the App as a thin client, and all communication between the App and the central servers is within secure hospital firewalls. Pilot data on 50 clinical cases showed 100% accurate retrieval of patient demographic, clinical and pathology data from disparate NHS information systems. Clinically the App is in case-accrual phase, and post-implementation data should be available shortly. Leading on from the success of the ENIAPP project, the CIPM/CBIT collaboration has recently been successful in obtaining £650,000 of NIHR funding to develop this case-based reasoning system further, translating the project out from intensive care into other areas of the hospital, to provide personalised decision support to a much wider number of patients. This research (the EPIC IMPOC project) is due to commence in January 2015.

THE FUTURE

2015 will be a busy year; in addition to rolling out the ENIAPP project, starting the EPIC IMPOC development, and progressing the lab-on-chip work, the CIPM/CBIT collaboration have engaged colleagues from other centres across Imperial College and submitted an expression of interest to the current EPSRC call, which focuses specifically on antimicrobial resistance. This bid aims to form the EMBRACE (Engineering and Medicine Bridging Research in Antimicrobial resistance: Collaboration and Exchange) network. Through this collaborative network, we aim to align engineers, mathematicians, molecular scientists, clinical researchers and epidemiologists to meet the EPSRC theme goals of “accelerating diagnostics development” and improving prescribing “behaviour within and beyond the health care setting”. We envisage that this collaboration will promote hybrid cross-disciple research skills, thus building capacity, but also engage an promote novel approaches to engineering solutions for antimicrobial resistance though organisation of various activities including joint seminars, annual conferences, pump-priming competitions and EPSRC Sandpits.

COLLABORATION

This research is in collaboration with the Centre for Infection Prevention and Management (CIPM). The respective teams include at CBIT: Prof Chris Toumazou, Dr Pantelis Georgiou, Dr Pau Herrero, Mr Bernard Hernandez and CIPM: Prof Alison Holmes, Dr Luke Moore, Ms Esmita Charani

PUBLICATIONS

E Charani, Y Kyratsis, W Lawson, H Wickens, ET Brannigan, LSP Moore, AH Holmes. An analysis of the development and implementation of a smartphone application for the delivery of antimicrobial prescribing policy: lessons learnt. *Journal of Antimicrobial Chemotherapy,* Vol. 68, No. 4, pp. 960–7, 2013.

E Charani, E Castro-sánchez, LSP Moore, AH Holmes. Do smartphone applications in healthcare require a governance and legal framework? It depends on the application! *BMC Medicine*. Vol. 12, pp. 29, 2014.

LSP Moore, E Charani, K Murthy, P Herrero, K Hatzaras, P Georgiou, AH Holmes. Infection management in critical care – personalised medicine and antimicrobial stewardship through a point-of-care decision support system. *Proc. 24th ECCMID,* Barcelona, 2014.

M McLeod, M Gharbi, E Charani, E Castro-Sánchez, LSP Moore, M Gilchrist, AH Holmes. Is there a role for using mobile device applications to support antimicrobial stewardship? Preliminary findings from a survey of general practitioners in the United Kingdom. *Int J Pharm Pract*. Vol. 22, No. S2, pp. 71–72, 2014.

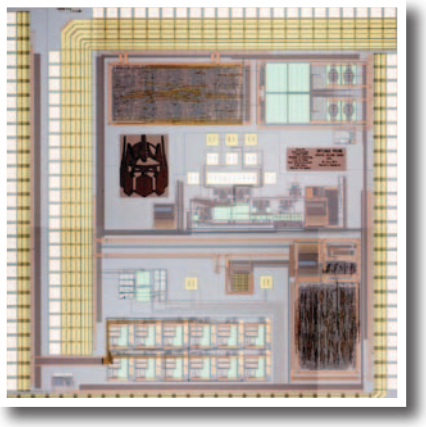
LSP Moore, E Charani, H Bernard, P Herrero, K Hatzaras, P Georgiou, AH Holmes. Case-Based Reasoning for Antimicrobial Prescribing Decision, *Proc. MEC-Bioengineering Conference,* London, 2014.

Chip gallery

The Centre's researchers have produced five new chips this year making a total production so far of 36 chips in a variety of CMOS technologies.

The Centre's focus is primarily the application of modern semiconductor technology to develop new bio-inspired systems and medical devices. This has in part been made possible through the EU-subsidised multi-project wafer (MPW) brokerage service provided by Europractice, which provides our design tools via STFC (UK) and technology access via IMEC (Belgium) and Franhofer (Germany).

The 'Chip Gallery' is also available online at: **www3.imperial.ac.uk/bioinspiredtechnology/research/chips**



IBE14G01 (Optimus Prime) – July 2014

Technology: AMS 0.35µm 2P4M CMOS

Purpose: Multiproject chip including a multi-sensing lab-on-chip platform, silicon beta-cell cluster, EMG fatigue processor.

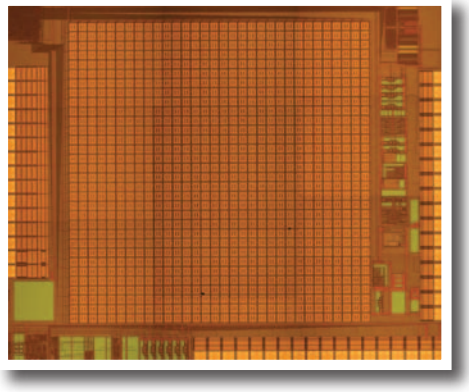
Designers: Ermis Koutsos, Sara Seyedeh Ghoreishizadeh, Mohamed El-Sharakawy, Dora Ma, Nicolas Moser, Vlad Cretu, Pantelis Georgiou

IBE14K01 (Yoda) – November 2014

Technology: AMS 0.35um 2P4M CMOS Technology

Purpose: Optrode for CANDO (Controlling Abnormal Network Dynamics with Optogenetics) project

Designers: Yan Liu, Song Luan, Timothy Constandinou (design in collaboration with Newcastle University: Hubin Zhao, Fahimeh Dehkhoda, Ahmed Ali, Reza Ramezani, Austin Ogweno, Kaung Htet, Patrick Degenaar)

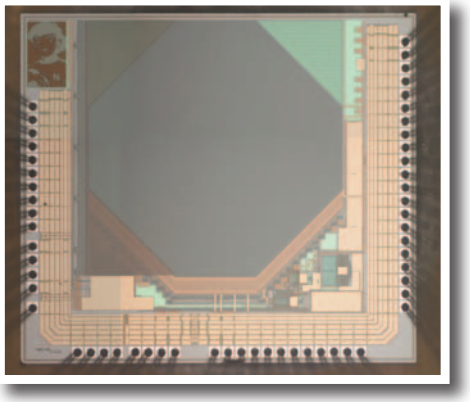


IBE14E01 (Panda) – May 2014

Technology: AMS 0.35µm 2P4M CMOS

Purpose: ISFET based DNA sequencing array, EMG front end.

Designers: Yuanqi Hu, Ermis Koutsos, Pantelis Georgiou

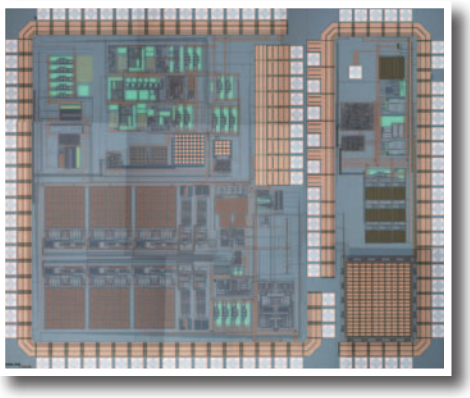


IBE14D01 (Tsubasa) – April 2014

Technology: AMS
0.35µm 2P4M CMOS

Purpose: Octagonal CMOS Image Sensor with Strobed RGB LED Illumination for Wireless Capsule Endoscopy

Designers: Satoshi Yoshizaki, Song Luan, Lieuwe Leene, Yan Liu, Timothy Constandinou

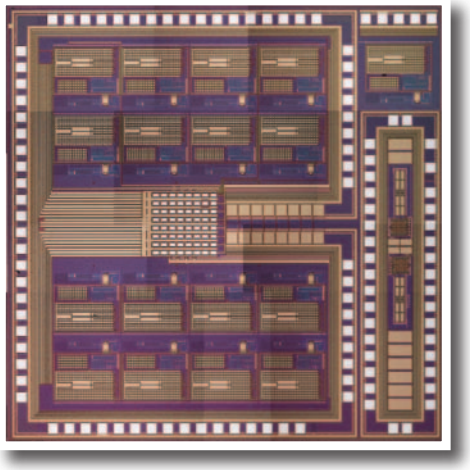


IBE13L01 (Altair) – December 2013

Technology: AMS
0.35µm 2P4M CMOS

Purpose: Multiproject chip including an ISFET autocalibrating array and system for monitoring muscle fatigue

Designers: Ermis Koutsos, Yuanqi Hu, Mohamed El-Sharkawy, Lieuwe Leene, Yan Liu, Pantelis Georgiou



IBE13G03 (Astroboy) – July 2013

Technology: IBM
0.18µm 1P6M CMOS

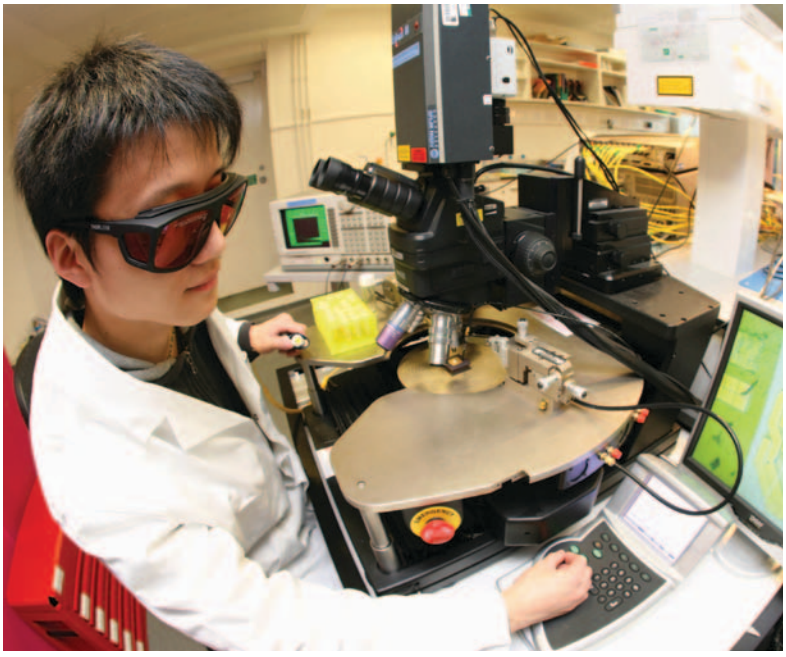
Purpose: Thermal Microstimulation Lab-on-Chip Array

Designers: Kiichi Niichu, Yan Liu, Ferran Reverter, Konstantin Nikolic, Themis Prodromakis, Pantelis Georgiou, Timothy Constandinou

One of the strengths of the Centre, and a significant attraction for researchers, is the 'state-of-the-art' facility. This was made possible through the initial endowment to the Institute of Biomedical Engineering that recognised the importance of the infrastructure, laboratories and equipment needed to make it a Centre of excellence not only in research but in the technology transfer essential to fulfilling the Centre's aims.

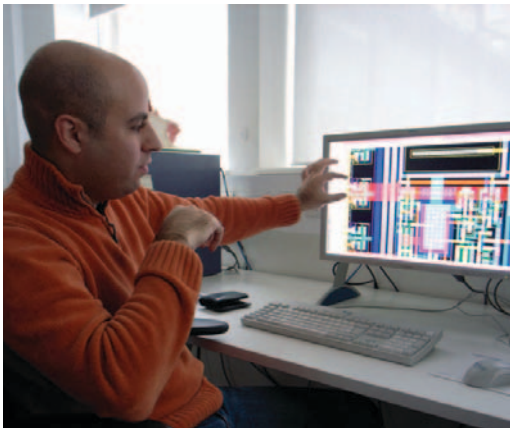
Research facilities

The laboratory areas have been designed to meet the needs of the four main application areas within the Centre's research strategy. Researchers have been able to undertake a large number of high-quality research projects in the Centre by leveraging on the multidisciplinary expertise of their colleagues and collaborators and the employment of the facilities. The main thrust of the research strategy is not to further advance the performance of existing electronic systems but to enable entirely new applications by utilising well-established technologies in new, innovative ways. All members of the Centre have access to the full range of facilities and equipment and some researchers have developed a high level of expertise in specific areas to ensure that these are exploited to the full.

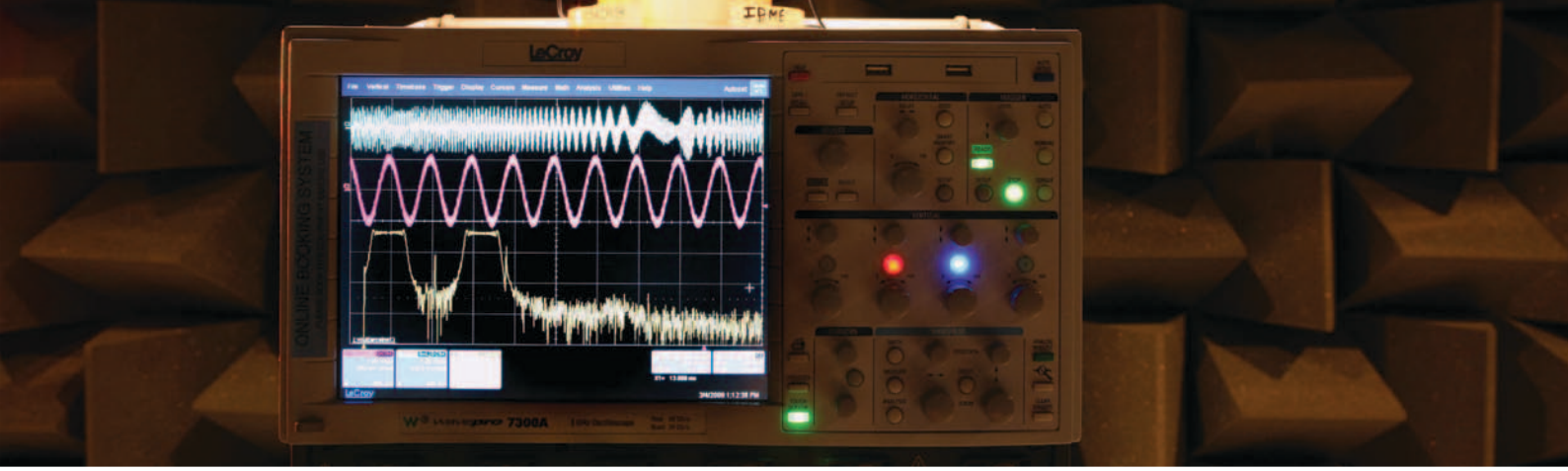


EDA AND CAD LABORATORY

CAD is an indispensable process in any modern engineering design. This laboratory is equipped with high performance workstations and servers to support high-end tools for microelectronic design, microsystems (including MEMS, microfluidics), RF/



microwave devices, mechanical design, etc. For example, researchers here develop application-specific integrated circuits (ASICs) that are then sent for fabrication at CMOS foundries. The facility has licensed all industry standard tools including Cadence, Mentor Graphics, Synopsys, Ansys, Solidworks, and several others, and a range of modern process technologies down to the 45nm node. All servers can be remotely connected from anywhere around the world via the internet enabling designers to work remotely and multiple chip designs can be carried out in parallel.

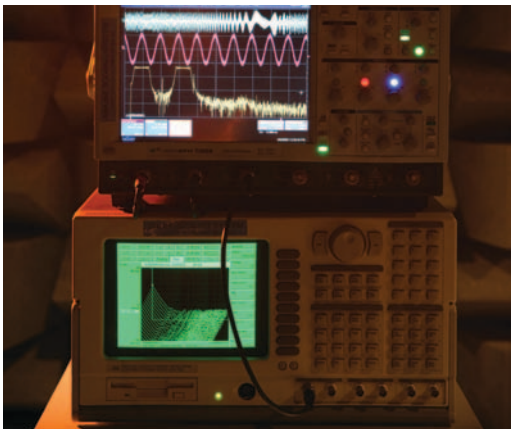


MICROELECTRONICS TEST LABORATORY

This laboratory is comprehensively equipped for the development, testing and measurement of biomedical circuits and systems. Such devices often require low noise instrumentation operating at relatively low frequency and have ultra low power requirements. This facility includes instruments for semiconductor characterisation, equipment for time, frequency and impedance characterisation (e.g. oscilloscopes, spectrum analysers, CV), instruments for low noise transimpedance and voltage amplification, signal generation, a semi-automatic probe station with laser for trimming and failure analysis, a temperature chamber, PCB rapid prototyping facility (LPKF-based), and all standard electronic test & measurement equipment.

ELECTROMAGNETICS TEST LABORATORY

Within this facility is a large, shielded, certified anechoic chamber, valid up to 34GHz, a 67GHz Agilent PNA with Cascade manual probe station and E-CAL automatic calibration for discrete SMA socketed use (up to 26.5GHz), an 8GHz 40Gs/s Agilent oscilloscope and a Picosecond pulse generator, as well as a host of other miscellaneous instruments. It is unique for the Centre to have access to such a chamber and it provides an ideal test facility for any project involving on-body or in-body antennas and indeed the communication between both. This, in conjunction with equipment such as the Agilent PNA and Dielectric Probe facilitates the use of anatomically and electromagnetically correct bio-phantoms to replicate the losses incurred when sensors and antennas are implanted in the body, leading to quicker prototype development and proof of concept.

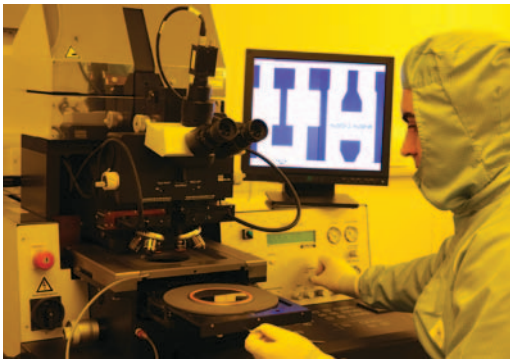


ANECHOIC (RF AND ACOUSTIC) TEST CHAMBERS

State-of-the-art soundproof and electromagnetic radiation proof chambers for ultra-low noise sensing. The acoustic facility includes a large (5m x 5m x 2m) anechoic shielded chamber providing an extremely low-noise environment suitable for all low frequency acoustic, optical and mechanical device/sensor characterisation. The RF facility includes a large (4m x 3m x 2m) anechoic shielded chamber suitable for a wide range of low noise measurements with significantly attenuated electromagnetic levels. This has been calibrated for uninterrupted use between 10MHz and 34GHz.

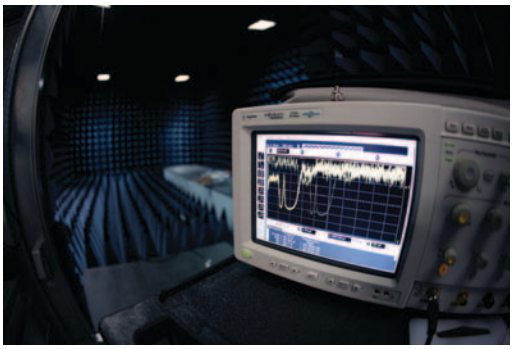
CLEANROOM SUITE

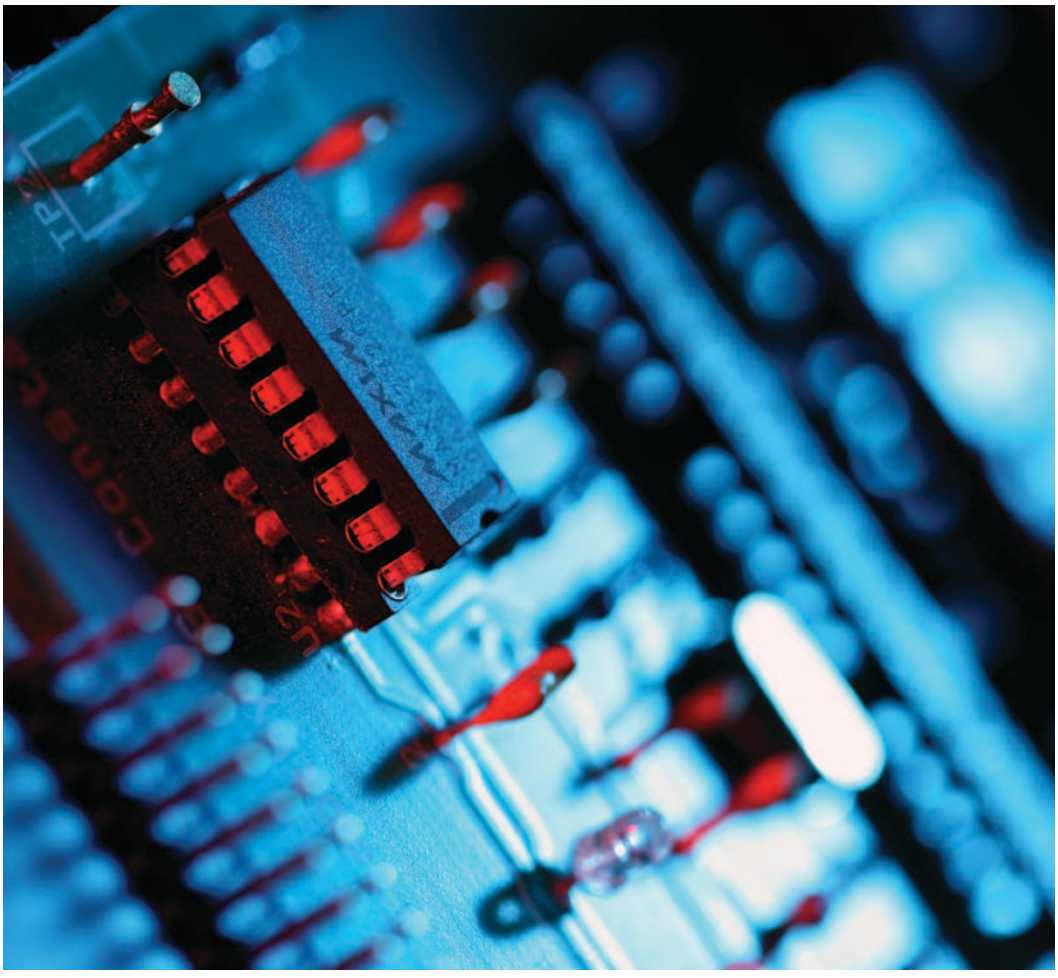
The Centre has a suite of two ISO class 6 cleanrooms (equivalent to US standards class 1000). These have been designed to support CE Marking/FDA approvals, to class 100/1000 to develop biosensor devices, electrode and microfluidic fabrication and packaging/post-processing of CMOS chips. The largest room, the 'yellow' room, houses most of the fabrication tools/processes and all relevant inspection and measurement facilities. This includes photolithography (SUSS MA6/BA6), sputtering/evaporation for film deposition of metals/oxides (BOC Edwards Auto 500), surface characterisation (Veeco Dektak 6M stylus profiler), plasma chamber, wet and dry benches, parylene conformal coating (SCS parylene deposition), microscopy and wirebonding.



APPLICATION SPECIFIC TECHNOLOGY LABORATORIES

In addition to the state-of-the-art “general use” laboratories, the Centre additionally has three specialist laboratories that are application-specific to: Neural interfaces and Neuroprosthetics, Metabolic Technology and Genetic Technology. These laboratories provide application-specific facilities that are research-specific. For example, biosensor characterisation for metabolic technology, low noise biopotential recording for neural interfaces, etc.





Who we are

Professor Chris Toumazou

FRS, FREng, FMedSci, CEng, FIET, FIEEE

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

Toumazou's life work has been dedicated to saving and improving lives through the invention of revolutionary, innovative and disruptive technology and the creation of a leading edge medical research institute and three commercial ventures to commercialize his research.

Toumazou is a Professor of Analog Circuit Design, Chief Scientist and Founder of Imperial's first Institute of Biomedical Engineering, Research Director of the Centre for Bio-inspired Technology, and Winston Wong Chair in Biomedical Circuits at the Electrical and Electronic Engineering Department at Imperial College London. He was made a Professor at Imperial College London at 33, one of the youngest ever to achieve this distinction.

In 2013 he was appointed the first Regius Professor of Engineering, an award made to Imperial College London to celebrate the Diamond Jubilee of Her Majesty The Queen.

In addition to being involved with a number of commercial ventures, Toumazou is Founder and Non-Executive Director of Toumaz Holdings Ltd, UK; Chairman, CEO and Founder of DNA Electronics Ltd, UK; and Chief Scientific Advisor to GENEU Ltd, UK. These technology-based companies have interests spanning ultra-low-power mobile technology, DNA Sequencing and DNA testing to create personalised skin health products.

Toumazou's career began with the invention and development of entirely novel concept of current-mode analogue circuitry for ultra-low-power electronic devices. Since then, he has been involved in inventing, developing and demonstrating new technologies to meet a range of healthcare challenges – mainly applying silicon chip technology to biomedical and life-science applications, most recently to DNA analysis. In particular Toumazou invented and licensed Portable and Rapid Semiconductor Genome Sequencing which has now become a multi-million dollar industry. One of his motivators was the diagnosis of his 13-year old son with end-stage kidney failure through a rare genetic mutation.

In 2003 he raised a total of £26m to create the Institute of Biomedical Engineering at Imperial College London, a multidisciplinary research institute and hub focusing on personalised medicine and bionanotechnology. He became its first Director (2014) and Chief Scientist (2011). His own specialism is in the field of personalised healthcare, providing wearable or implantable devices for early diagnosis and detection of disease.

Toumazou's visionary research and entrepreneurial actions have shown how natural analogue physics of silicon semiconductor technology can be used to mimic and replace biological functions. These include cochlear implants for born-deaf children, a bio-inspired artificial pancreas for type 1 diabetes, wireless heart monitors for personalised ambulatory health monitoring pre- and post- operatively, semiconductor-based DNA sequencing platform with applications in pharmacogenomics and recreational genetics, and an intelligent neural stimulator as a drug alternative to tackle obesity.

He was elected Fellow of the Royal Society (2008), Fellow of the Royal Academy of Engineering (2008) and Fellow of the Academy of Medical Sciences (2013), making him one of a handful in the UK who are fellows of all three premier societies. Toumazou 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 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. He has given numerous public lectures and keynote addresses at a national and international level. In 2011 he was invited to speak at the TEDMED conference in San Diego; his lecture entitled ‹When Will Wireless Medicine Change Healthcare›. Other notable lectures include the G8 Summit (2013) and Royal Society public talk (2011).

In June 2014 Professor Toumazou's technology was also recognised by the European Patent Office when he was awarded the prestigious 2014 European Inventor of the Year Award for Research making him the first British winner since 2008. Toumazou has also been awarded by Cardiff University with Honorary Fellowship in 2014 and later that year – in November 2014 – the Faraday Medal, the highest honour of the UK's Institution of Engineering and Technology (IET) for the invention of semiconductor sequencing and pioneering work that has led to disposable semiconductor healthcare.

To date Chris has published over 750 research papers and holds more than 50 patents in the field of semiconductors and healthcare, for which he has received many awards and honours.

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 Constandinou is currently a Senior Lecturer within the Department of Electrical & Electronic Engineering at Imperial College London and is also the Deputy Director of the Centre for Bio-Inspired Technology. He received both his BEng and PhD degrees in Electrical and Electronic Engineering from Imperial College London, in 2001 and 2005 respectively. He then joined the Institute of Biomedical Engineering as Research Officer until 2009, when he was appointed Deputy Director of the newly formed Centre for Bio-Inspired Technology. In 2010, continuing as Deputy Director, he joined the Department of Electrical & Electronic Engineering, where he currently holds an academic faculty position within the Circuits & Systems research group.

His research utilises integrated circuit and microsystem technologies to develop ultra low power implantable devices, brain-machine interfaces, lab-on-chip/wireless capsule endoscope 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. During his career he has contributed to several projects from concept through to working demonstrator. This includes developing a fully implantable cochlear prosthesis for the profoundly deaf (2001–2), biologically inspired vision chips (2003–5) and an implantable vestibular prosthesis for balance restoration (2006–9). His current research is developing next generation integrated microsystems for neural interfacing and prosthetics.

Ongoing projects include:

- **Ultra Low Power Implantable Platform for Next Generation Neural Interfaces (supported by the EPSRC):** a wireless, multi-channel neural recording interface with on-node spike sorting for real-time motor prosthetic control (in collaboration with Newcastle University and University of Leicester).
- **iPROBE – in-vivo Platform for the Real-time Observation of Brain Extracellular activity (supported by the EPSRC):** a digital 1k+ channel neural recording interface for neuroscience research (in collaboration with UCL and NYU).
- **CANDO – Controlling Abnormal Network Dynamics with Optogenetics (supported by the Wellcome Trust and EPSRC):** a next generation brain pacemaker for the treatment of drug-insensitive epilepsy (in collaboration with Newcastle University and UCL).
- **Thermal Microstimulation of Excitable Cells (supported by the Wellcome Trust):** a lab-on-chip platform for the microscale thermal stimulation of excitable cells in-vitro (in collaboration with National Heart & Lung Institute, University of Southampton, UPC, Nagoya University).
- **AnaeWARE – (supported by EU FP7):** Monitoring awareness during anaesthesia – a multi-modal approach (in collaboration with the Hammersmith Hospital, Imperial College Healthcare NHS Trust).
- **Enabling Technologies for Sensory Feedback in Next Generation Assistive Devices (supported by the EPSRC):** a platform for providing sensory feedback via a PNS interface in upper-limb prosthetics (in collaboration with the Universities of Newcastle, Southampton, Leeds, Keele, and Essex).

Dr. Constandinou is a Senior Member of the IEEE, a Fellow of the IET, a Chartered Engineer and Member of the IoP. He is an associate editor of the IEEE Transactions on Biomedical Circuits & Systems (TBioCAS), serves on the IEEE Sensory Systems Technical Committee (SSTC) and IEEE Biomedical Circuits & Systems Technical Committee (BioCAS-TC). In 2009, he has been named the recipient the IET Mike Sergeant Achievement Award. He was Technical Program Co-Chair of the 2010 and 2011 IEEE BioCAS Conferences, Publications Chair of the 2010 IEEE BioCAS Conference, Technical Program Track Co-Chair (Bioengineering) of the 2012 IEEE ICECS Conference, Technical Program Track Chair (ASICs) of the 2012 BSN Conference. He is currently the chair of the IET Awards and Prizes committee and also serves on the IET Knowledge Services Board (KSB).

Dr Pantelis Georgiou

MEng (Hons), DIC, PhD, CEng, MIET, SMIEEE

Lecturer in Circuits and Systems, Department of Electrical and Electronic Engineering
Head, Bio-Inspired Metabolic Technology Laboratory, Centre for Bio-Inspired Technology

Pantelis Georgiou is a Lecturer within the Department of Electrical and Electronic Engineering and is the head of the Bio-inspired Metabolic Technology Laboratory in the Centre for Bio-Inspired Technology; He received the MEng (Hons) degree in Electrical and Electronic Engineering in 2004 and a PhD degree in 2008 both from Imperial College London.

His current research includes low-power microelectronics, bio-inspired design, integrated sensing systems and development of novel medical devices. One of his key research focuses is on new technologies for treatment of Diabetes such as the artificial pancreas but also develops novel lab-in-chip technology for genetic and microbial screening in addition to wearable technologies for rehabilitation. He has also has been involved in the creation of several commercial technologies such as a point-of-care portable platform technology for genetic detection (DNA Electronics Ltd). In 2004 he was awarded the Imperial College Governors' Prize for Electrical and Electronic Engineering and in 2013 he was awarded the IET Mike Sergeant award for outstanding achievement in engineering and his work on the Bio-inspired Artificial pancreas.

Some of his current research projects include:

- **The bio-inspired artificial pancreas** – Type 1 diabetes results in the inability to produce insulin resulting in extremely high blood sugar. Current methods of control lead to many secondary complications such as blindness, nerve damage and heart disease. This project aims to create a closed-loop system for tight glycaemic control inspired by the biology of the pancreas. The bio-inspired artificial pancreas controls blood sugar continually through intensive insulin infusion improving quality of life and reducing adverse effects of diabetes.
- **Bio-inspired glucose sensing** – This project aims to investigate the sensing mechanisms commonly found in metabolic cells in an effort to engineer more reliable and robust chemical sensing systems in CMOS. Specifically we aim to create glucose-sensing arrays inspired by biological function to improve accuracy and functionality in ambulatory applications for diabetes.
- **Decision support systems for diabetes** – Diabetes, Type 1 & 2 results in extremely high blood sugar. To minimise the adverse effects good control through intensive insulin infusion is required for insulin dependent diabetes and controlled exercise and diet for no-insulin dependent diabetes. This project aims to create a novel decision support system based on artificial intelligence to help guide the control of blood sugar in diabetes through guided supervision in a similar way to what a clinician would recommend. It is capable of factoring in multiple parameters such as blood glucose, exercise, meals and stress, all of which effect outcome.
- **Next generation ISFET arrays for DNA and microbial sequencing** – Semiconductor based DNA sequencing is now becoming an attractive alternative to conventional genome sequencing which uses optical techniques. Due to scaling of Moores law, ISFET based sensors can now be integrated in the millions to create large scale sensing arrays able to decode the human genome cheaply and reliably. This project aims to implement a next generation ISFET based DNA sequencing system capable of real-time genome detection and assembly in CMOS increasing reliability of detection and time to result. Additionally it will be used for microbial screening in a new initiative to combat antimicrobial resistance.
- **Smart clothing for rehabilitation of osteoarthritis–** This project aims to integrate intelligent sensing capability in clothing for smart rehabilitation of osteoarthritis. Through monitoring of joint function through a variety of sensors (flexible impedance, sEMG, motion) and integration of wireless capability a low-power wearable platform will be developed to help guide rehabilitation after intervention such as knee replacement surgery.
- **Real time muscle fatigue detection for smart rehabilitation** – This project will create a real-time method for tracking muscle fatigue for applications in rehabilitation and sport physiotherapy. Through specific continuous time techniques, an energy efficient, miniaturised system will be developed in CMOS that extracts muscle fatigue through monitoring of EMG. More importantly this system will be information driven rather than conventionally data driven, reducing requirements on data transmission and thus saving power.

Dr Georgiou is a member of the IEEE (Institution of Electrical and Electronic Engineers), a member of the IET (The Institution of Engineering and Technology) and a Chartered Engineer (CEng). He serves on the BioCAS (Biomedical Circuits and Systems) and Sensory Systems technical committees of the IEEE CAS Society. He also sits on the IET Awards and Prizes committee.

Professor Chris McLeod

MA, MSc, DPhil, MIPEM

Principal Research Fellow, Centre for Bio-Inspired Technology

Chris graduated from Cambridge University in 1971 with a degree in Engineering and from the University of Strathclyde in 1975 with an MSc in Bioengineering. After working in medical research posts in Oxford for the intervening years, he graduated from the University of Oxford in 1986 with a DPhil in Bioengineering.

He moved to a lecturing post at Oxford Brookes University in 1984, maintaining his research links to clinical departments (Neurophysiology, Anaesthetics and Paediatrics), became an Honorary Research Fellow in Anaesthetics in 1989 and was appointed Professor in Medical Devices in 2002. In 2005 he was appointed Visiting Professor in the new Institute of Biomedical Engineering at Imperial College London, later joining the Institute in 2008 as a Principal Research Fellow.

From 1975–84 he was a Research Associate at Oxford University developing wireless telemetry of physiological data in studies in Cot Death Syndrome (SIDS); novel, minimally invasive monitoring devices for neonatal intensive care and methods and systems for measuring the nutritional intake of breast-fed babies for studies on weaning in regions with low-calorie weaning foods. Between 1984 and 2008 he furthered his research into the non-invasive neonatal monitoring systems which has resulted in the first of a range of new devices coming to the market this year, and instigated a programme to study the mechanisms underlying the depression of breathing by anaesthetic agents. He attracted research funding and published in all of these application areas, particularly on non-invasive, continuous thoracic imaging using electrical impedance tomography and on tissue characterisation using electrical impedance spectroscopy.

Chris instigated and has led the development of implantable pressure sensors for the cardiovascular system since 2004, initially at Oxford Brookes, then at Imperial College London with funding from the Wellcome Trust Technology Translation Fund and then from the Wellcome Trust – Department of Health Healthcare Innovation Challenge Fund. He has published 36 papers on his work.

His current research is to take the implantable pressure sensors through manufacture for regulatory approval and through a Phase 1 ‘first-in-man’ safety trial by 2015 and leading to a Phase 2 efficacy trial. The device is designed to improve the diagnostic and progression information available to clinicians to optimise pharmacological therapy for patients living at home with heart failure. The system includes full mHealth connection with means for 24/7 monitoring. The implants and system will be applied to other CV disease indications following a successful Phase 1 trial. Non-CV pilot studies are also under way where precise pressure information would warrant an implanted device.

Dr Konstantin Nikolic

PhD, DIC, MIEEE, MInstP

Senior Research Fellow, Centre for Bio-Inspired Technology

Konstantin received a DiplEng and Masters from the Department of Electrical Engineering, Belgrade University, Serbia and a PhD in Condensed Matter Physics from Imperial College London. He was a Lecturer and Associate Professor at the Faculty of Electrical Engineering, Belgrade University. He joined the Institute of Biomedical Engineering, Imperial College London in 2005. In 2006 he became Corrigan Research Fellow and in 2012 Senior Research Fellow.

He is a co-author of two very successful physics textbooks for university students, a book about the 3D nanoelectronic computer architecture, 7 book chapters (in the areas of physics, nanoelectronics, and the eye photoreception), and a number of publications in journals and conference proceedings. His papers have 1145 citations, h-index=17, g-index=33 (20/Sep/2014). His current research interests include optogenetics, bio-inspired technologies, systems and computational biology. His work is focused on computational neuroscience, sensory systems neuroscience, enabling technologies for optogenetics and on developing new sensing and information processing paradigms based on molecular biology and neuroscience, and applied to retinal prostheses.

RESEARCH

- **Optogenetics:** Photo-cycle models of channelrhodopsin2 (ChR2), halorhodopsin and archaerhodopsin, modelling of neurons expressing ChR2 mutants/other ion pumps. Manipulation of neural circuits.
- **Mathematical models** of the functional relationship between stimuli and neural response, in particular: characterisation of several recently discovered retinal ganglion cells using the tools developed for nonlinear dynamic systems, such as information theory.
- **Retinal implants** (image processing, stimulator driver algorithms and electronics, etc). Event-based representation of sensory input and its processing.
- **Modulation of neural activity by changing the temperature** (e.g. by using Infrared light or thermal MEAs).
- **Bio-inspired circuits and systems** based on the retina circuitry and cellular signalling and metabolic pathways. Stochastic models of phototransduction and G-protein coupled cascade.

PROJECTS

PI: "SeeBetter – Seeing Better with Hybrid Backside Illuminated Spatio-Temporal Silicon Retina", EU FP7 project. The project is about designing and fabricating a novel type of the retinomorphic vision sensor. Partners: Imec, Leuven Belgium, Institute for Neuroinformatics, Zurich and Friedrich Miescher Institute Basel, Switzerland.

PI: "Multiscale Computational Tools for Optogenetics", BBSRC grant. The project develops three sets of computational tools for the rapidly expanding optogenetic community. Team members: Benjamin Evans, Sarah Jarvis (Bioengineering), Simon Schultz (Bioengineering) and KN.

Co-I: Wellcome Trust Institutional Strategic Support Fund: "Network of Excellence for the Thermal Micro-Stimulation of Excitable Cells". Team members: Tim Constandinou, Pantelis Georgiou, Cesare Terracciano, Yan Liu, Satoshi Yoshizaki, Dorian Haci (visiting from Politecnico di Torino, Italy), and KN.

Patricia Chapman

BA (Hons)

Business Administrator to Professor Chris Toumazou

Patricia joined the newly formed Institute of Biomedical Engineering in 2004 as the first Manager and oversaw the project which created the 'state of the art' laboratory facilities, offices and meeting areas. As a graduate in Biology, she was excited about 'returning' to science after a career in management and customer service.

As Manager of the Institute, she was responsible for appointing the first staff, research assistants and technicians and implementing the scholarship programmes which enabled the Institute to attract well qualified postgraduates to its PhD programmes.

Following its endowment, she assisted Professor Toumazou in establishing the Centre for Bio-Inspired Technology which became a specialist research focus within the Institute.

She also supports Professor Toumazou in his role as Director of the Centre and Chairman and Chief Executive of his 'spin out' companies organising PR and events associated with his commercial activities.

Wiesia Hsissen

Senior Group Administrator, Circuits and Systems Research Group, Department of Electrical and Electronic Engineering

Wiesia is the senior group administrator of the Circuit and Systems (CAS) research group and additionally has the role of PA to the Head of Department. She joined the Department of Electrical and Electronic Engineering in 1990 and has kept a key role in supporting the CAS group ever since.

Her role within the Centre for Bio-Inspired Technology is to support our postgraduate research students from PhD registration and bursaries to thesis submission and examination.

ADMINISTRATIVE STAFF PROFILES

Gifty Kugblenu

PA to Professor Chris Toumazou

Gifty joined the Centre in 2010 as PA to Professor Toumazou. She provides the essential support he needs to fulfil his various roles including as Director of the Centre, Professor of Biomedical Circuits in the Department of Electrical and Electronic Engineering and CEO to Toumaz Ltd and DNA Electronics Ltd.

Izabela Wojcicka-Grzesiak

Research Group Administrator, Centre for Bio-Inspired Technology

Iza is the group administrator for the Centre for Bio-Inspired Technology. She originally joined Imperial in 2006 as an administrator within the Institute of Biomedical Engineering and was appointed group administrator of the Centre in 2009 when it was formed.

Iza now plays a key role within the Centre supporting staff, students, research and facilities. Within her role she deals with all matters relating to finance, HR, proposal development, research projects, health and safety and general administration. Iza is also responsible for compiling and editing our Annual Report.

Fellow

STAFF RESEARCH REPORT

Dr Mohammadreza Bahmanyar

Research focus
Wireless implants and medical devices

Funding
Wellcome Trust and Department of Health

Reza Bahmanyar has been doing research at the interface of engineering and physics with biology for fourteen years. He has developed novel algorithms for ECG feature extraction and pre-processing in his PhD, worked as a research consultant on the design and fabrication of Systems on Chip (SoC) for manipulation and analysis of biological entities, including microfluidic chips for DNA extraction and detection as well as design and prototyping the relevant electronic systems. He joined the Institute of Biomedical Engineering, Imperial College London in 2009 to work on the development of implantable wireless blood pressure sensors and associated RF interrogating systems. These implants were successfully tried in a porcine model in 2011 and currently, he is working on optimization of these devices to meet the regulatory requirements for a phase 1 clinical trial. He is the PI on a Wellcome Trust Institutional Strategic award to develop an Intraocular pressure sensing implant for Glaucoma patients; also collaborating with cardiologists to develop new medical devices.

His main research focus is on development of implants and electronic systems operating at high frequencies. Other interests include developing new medical devices and bio-inspired technologies. The current research projects include:

Implantable SAW Transponder for Acute and Chronic Blood Pressure Monitoring (Supported by Wellcome Trust and the Department of Health): As a research fellow, I specifically work on the design and fabrication of implantable antennas, sensors, RF interrogation system and algorithm development. This includes close collaboration with companies in the US and Europe to develop patient safe medical devices suitable for our planned clinical trial.

Development of an Easily Deployable Intraocular Wireless Pressure Sensing Implant for Patients with Rapidly Progressing and Blinding Glaucoma (Supported by Wellcome ISSF Award): As the PI, I am directing the research; also working on Film Bulk Acoustic Resonator and pressure sensor as well as implanted antenna design, fabrication and characterization.

A pilot study of the diagnostic potential of low frequency sound recorded from cardiac muscle (Supported by Imperial Innovations): I am collaborating with cardiologists at Glenfield hospital in Leicester to assess the diagnostic potential of heart sound. An electronic system for physiological signal acquisition has been built and currently being used in our clinical trial at Glenfield hospital.

PUBLICATIONS

1. Olive H Murphy, Alessandro Borghi, Mohammad Reza Bahmanyar, Christopher N McLeod, Manoraj Navaratnarajah, Magdi Yacoub, Christofer Toumazou, “RF communication with implantable wireless device: effects of beating heart on performance of miniature antenna”; *Healthcare Technology Letters*, Volume 1, Issue 2, June 2014, p. 51 – 55 DOI: 10.1049/htl.2014.0066 , Online ISSN 2053–3713.
2. Zolgharni M, Dhutia N M, Cole GD, Bahmanyar M R, Jones S, Sohaib S M A, Tai S B, Willson K, Finegold J A, Francis D P, “Automated Aortic Doppler Flow Tracing for Reproducible Research and Clinical Measurements,” *Medical Imaging, IEEE Transactions on* , vol.33, no.5, pp.1071,1082, May 2014 doi: 10.1109/TMI.2014.2303782
3. Alessandro Borghi, Olive Murphy, Reza Bahmanyar, Chris McLeod, “Effect of Stent Radial Force on Stress Pattern After Deployment: A Finite Element Study”, February 2014, *Journal of Materials Engineering and Performance*, 10.1007/s11665-014-0913-z.
4. Olive H Murphy, Mohammad Reza Bahmanyar, Alessandro Borghi, Christopher N. McLeod, Manoraj Navaratnarajah, Magdi H. Yacoub, Christofer Toumazou, “Continuous in vivo blood pressure measurements using a fully implantable wireless SAW sensor”, *Biomedical Microdevices*, April 2013; DOI 10.1007/s10544-013-9759-7.

Fellow

STAFF RESEARCH REPORT

Dr Andrea Alenda González

Research focus
Bio-inspired implant to treat obsesity

Funding
European Union ERC Synergy

My name is Andrea Alenda, I am a neuroscientist at the Centre for Bio-Inspired Technology where I work as part of a multidisciplinary team developing a state-of-the-art implant to treat obesity.

Although weight might be regarded merely as a superficial aesthetical concern, it is a serious medical condition. Being overweight or obese can kill. It increases the chances of suffering from health problems and diseases such as stroke, cancer, type 2 diabetes, sleep apnea, high blood pressure, osteoarthritis and depression. Obese people tend to live shorter lives than slim people do. Staying at a healthy weight can extend life spam.

Having a few extra pounds does not come across as being dangerous, specially when everyone around looks a bit large. According to the NHS in England three in five adults are obese or overweight.

Nowadays being obese or overweight is very common not just in England but worldwide. According to the World Health Organization more than 1.4 billion adults and 40 million children under the age of five worldwide are obese or overweight. It is a problem that has reached pandemic proportions.

However obesity related illness is preventable. Even a small percentage of weight loss (sometimes as small as 5%) can reduce the risk of developing a weight-associated disease and hence impact greatly in the quality of life of the patient as well as relieve the economic burden to the healthcare system. Weight reduction treatments are critical for tackling the obesity pandemic.

In the Centre for Bio-Inspired Technology we are working to find a technological solution for obesity. The i2MOVE Project is developing a pioneering weight loss treatment. The objective is to design an implant for appetite modulation, by applying state-of-the-art wireless technology that is able to mimic and reproduce biological signals of satiety to achieve and maintain a healthy weight.

My role as a neuroscientist is to understand the function of the vagus nerve – a nerve that connects the brain with the gut – in relation to appetite.

The vagus is one of the twelve cranial nerves, spreading through the body from the brain stem, thorax to the abdomen. It is a versatile and complex nerve, serving crucial functions in breathing, heart rate and digestive regulation and carrying information from the heart, lungs, liver, stomach, pancreas and intestines to the brain. In relation to digestion it has both sensory and motor functions: sensing when the food is going through the gastrointestinal tract and directing its muscles to move the food through the digestive system. The vagus nerve is key for appetite reduction as it is the main and most direct pathway where satiety signals reach the brain. During a meal it is the vagus nerve that tells the brain when enough is enough.

Understanding vagal satiety signals allows us researchers to imitate the same signals artificially, so the i2MOVE implant can reproduce them in a controlled and timely manner and hence modulate appetite.

Having an implant with such a fine control is key. Just as there are no two identical people, there are no two identical vagus nerves. Current neural stimulators merely produce a fixed stimulation program in a set time frame. However the i2MOVE implant will be able to read the electrochemical signal of the nerve hence adjust its neural stimulation program accordingly. The i2MOVE implant will provide a tailored and adaptable program, capable of evolving with time.

The i2MOVE Project will render ground-breaking technology for appetite regulation.

Fellow

STAFF RESEARCH REPORT

Dr Amir Eftekhar

Research focus
Interfacing with the nervous system

Funding
European Union ERC Synergy

AIMS & OBJECTIVES

To develop the next generation of devices that monitor and regulate your neurological health.

SUMMARY

The nervous system consists of the brain, spinal cord and a large network of nerves that sends information back and forth to your organs and limbs – thus it our vital bodily functions.

My work involves the development and commercialisation of technology for interfacing this central and peripheral nervous system. My primary expertise lies in the use of signal processing techniques applied to real-time neural interfacing applications and the development of the whole interface. Such an interfacing system can take many forms but typically composes off sensors, coupled with front-end electronics, some signal conditioning to eliminate unwanted components, and then digitisation and further processing or transmission.

My main project, is one in which we were fortunate to have been awarded a grant from the ERC in 2012 (ERC Synergy i2MOVE), to tackle Obesity. Obesity is one of the greatest public health challenges of the 21st century. Affecting over half a billion people worldwide, it increases the risk of stroke, heart disease, diabetes, many cancers, depression and complications in pregnancy. Bariatric surgery is currently the only effective treatment available but is has significant risks. We are tackling the problem from the nervous system control of appetite. The gut and stomach are densely innervated by the Vagus nerve, a nerve that connects your brain to your vital organs (heart, lungs, stomach etc.). Our work is to not only identify it's role in appetite, but to also create technology that will allow us to not only record the signaling between stomach and brain, but also regulate it. We have a strong multidisciplinary team in place and have started experiments. For the first time, we are able to capture electro-chemical signatures of the Vagus nerve associated with gut hormones. We also have our first generation of micro-electrode designs in place (necessary for interfacing with the nerve), developing some novel methods for extracting and enhancing the Vagus nerve signals.

This is a snapshot of the type work I am involved in of which all have both clinical and commercial impact that we are realising through commercial development. Other projects include a multi-neuron recording system with on-chip spike sorting (with Leicester university and Newcastle Institute of Neuroscience) and novel methods for ECG processing (with Texas Instruments) and removal of baseline drift in low-power electronics, algorithms for predicting impending epileptic seizures by using language analysis methods on brain signals, analysis of brain abnormalities using brain stimulation (with King's College London) and analysis of neonatal brain activity to automatically detect abnormalities. All of these aim to create novel but practical solutions that utilise our groups unique bio-inspired principles for medical diagnostic and treatment.

RECENT PUBLICATIONS

1. A Eftekhar, C Toumazou, E Drakakis, "Empirical Mode Decomposition: Real-Time Implementation and Applications", Journal of Signal Processing Systems, 2013, *Journal of Signal Processing Systems*, vol 73, 43–58, 2013.
2. S Paraskevopoulou, D Wu, A Eftekhar, T Constandinou, "Hierarchical Adaptive Means (HAM) clustering for hardware-efficient, unsupervised and real-time spike sorting", *Journal of Neuroscience Methods*, vol 235, 145–156, 2014.
3. A Eftekhar, W Juffali, J El-Imad, T Constandinou, C Toumazou, "Ngram-Derived Pattern Recognition for the Detection and Prediction of Epileptic Seizures", *PLOS One*, vol 9, e96235, 2014.
4. D Y Barsakcioglu, Y Liu, P Bhunjun, J Navajas, A Eftekhar, A Jackson, R Quian Quiroga, T G Constandinou, "An Analogue Front-End Model for Developing Neural Spike Sorting Systems", vol 8, 216–227, 2014.
5. J Navajas, D Y Barsakcioglu, A Eftekhar, A Jackson, T G Constandinou, R Quian Quiroga, "Minimum requirements for accurate and efficient real-time on-chip spike sorting", *Journal of Neuroscience Methods*, vol 230, 51–64, 2014.

Fellow

STAFF RESEARCH REPORT

Dr Pau Herrero Vinas

Research focus
Biomedical control

Funding
Wellcome Trust

The main focus of my research has been to apply control engineering and artificial intelligence solutions to biomedical systems, and in particular, in the field of diabetes technology and antimicrobial therapy optimization.

In the field of diabetes technology, I am intensively involved in the development and clinical validation of a Bio-inspired Artificial Pancreas (BiAP) for tight glycemic control in type 1 diabetes. BiAP has already been clinically validated over 20 subjects during 24-hour trials with and without meal announcement. Further clinical trials to test this technology during exercise, mixed meals and real-life conditions are ready to commence.

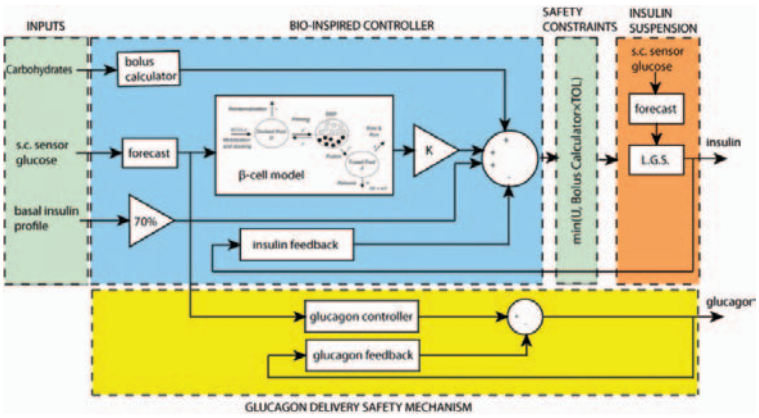
Among the latest software solutions I have developed there are: a web-based telemonitoring solution for the Bio-inspired Artificial Pancreas; a novel technique for robustly identifying the parameters of metabolic models; a mixed meal model library to be incorporated into diabetic subject simulators in order to account for more realistic and varied meals; a novel technique for automatically adjusting the parameters of an insulin bolus calculator; and a robust model-based glucose controller using interval analysis.

Another project I am heavily involved consist of developing an advanced decision support system for insulin dosing using artificial intelligence (i.e. Case-Based Reasoning) and mobile technologies. Such a system is aimed at providing superior glycaemic control with respect to existing insulin bolus calculators embedded in current insulin pumps and glucose meters. This system has been *in silico* validated and is currently being clinically tested over 12 subjects with type 1 diabetes.

Finally, I am also working on a research project that aims to develop a point-of-care decision support system (i.e. mobile app) to optimize antimicrobial therapy in intensive and secondary care settings. The application automatically pulls patient data from NHS servers and uses Case-Based Reasoning to help clinicians to make the right choices for antibiotic therapy from the beginning of the treatment. Such technology is currently being tested at the Imperial College Healthcare NHS Trust.

PUBLICATIONS

1. Herrero P, Pesl P, Reddy M, Oliver N, Georgiou P and Toumazou C. 'Advanced Insulin Bolus Advisor based on Run-To-Run Control and Case-Based Reasoning'. IEEE J Biomed Health Inform. 2014 (ahead of print).
2. Reddy M, Herrero P, El Sharkawy M, Pesl P, Jugnee N, Thomson H, Pavitt D, Toumazou C, D Johnston, Georgiou P and Oliver N. 'Feasibility Study of a Bio-inspired Artificial Pancreas in Adults with Type 1 Diabetes'. Diabetes Technol Ther. 2014; 16(9): 550–557.
3. Pagkalos I, Herrero P, Toumazou C and Georgiou P. 'Bio-Inspired Glucose Control in Diabetes Based on an Analogue Implementation of a Beta-Cell Model'. IEEE Transactions on Biomedical Circuits and Systems. 2014; 8(2):186-195.
4. Moore L S P, Charani E, Murthy K, Herrero P, Hatzaras K, Georgiou P, Holmes A.H. 'Infection management in critical care – personalised medicine and antimicrobial stewardship through a point-of-care decision support system' (oral presentation). *24th European Society of Clinical Microbiology and Infectious Diseases (ECCMID). Barcelona, Spain*. 2014.
5. Herrero P, P Georgiou, Oliver N and Toumazou C. 'A composite model of glucagon-glucose dynamics for *in silico* testing of bihormonal glucose controllers', *J Diabetes Sci Technol*, Vol:7, 941–951, 2013



Block diagram of the Bio-inspired Artificial Pancreas (BiAP) currently being tested in clinic.

Fellow

STAFF RESEARCH REPORT

Dr Nishanth Kulasekeram

Research focus
To develop low-power microelectronics for the development of a full implantable peripheral nerve interface for the monitoring and treatment on Obesity

Funding
European Union ERC Synergy

I have spent 12 years working in the semiconductor industry, contributing to a collection of integrated circuits for various applications. I have mostly worked on CMOS process technologies from TSMC. My experience includes front to back end design of full custom digital, high speed digital, baseband analog, and RF integrated circuits. You are probably interested to know more about my key contributions, and to make it a quick and pleasant article to read, I have provided a break down and referenced it to the companies that employed me in the past.

I worked at Altera, on their Stratix and Cyclone FPGA's and using TSMC (CMOS): 0.18um, 0.13um and 90nm. Circuits designed include DDR Memory, clock trees, LVDS – SERDES architectures, impedance control circuits for differential signalling and LC tank oscillators. The above products were designed 12 years ago and are presently hugely successful, highly profitable and widely known throughout the semiconductor industry.

I then moved onto to Epson where I worked on Large Panel TFT displays, Ferroelectric Random Access Memory and Optical Transceivers. Technology again used TSMC (CMOS) 0.18um. Circuits contributed include sense amplifiers, Giga Hertz trans-impedance amplifiers, laser drivers and post wideband amplifiers Epson was the first to develop large screen printed OLED displays and FERAM memory.

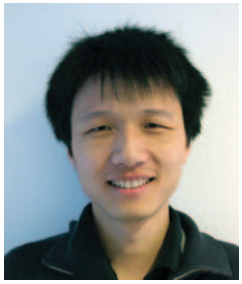
At NXP, I worked on Wireless Bluetooth and DC-DC downconverters in 65nm and 45nm technology. I designed an RF power amplifier for a polar transmitter, which included a semi digital DAC. The latter was patented (EP 2251976 A1). The Bluetooth IP has reached many customers, which includes Samsung, whilst the DC-DC downconverters has been sold to Intel and Apple.

The final leg of my journey before coming to Imperial College was at Cambridge Semiconductors, working on AC/DC Power adapters and Dimmable LED lighting. I used TSMC (High/LOW Voltage CMOS) 0.35um and designed a Logarithmic DAC, Flash ADC, Gm-C, lossy integrator. The AC/DC power adapter products are presently sold via a third party to Nokia.

At this present day, I find myself at Imperial College London, working on a challenging integrated circuits that aims to monitor and regulate nerves in the body responsible for appetite. Thus providing an implantable solution to obesity.

Fellow

STAFF RESEARCH REPORT



Dr Yan Liu

Research focus
Integrated neural microsystems and neural interfaces

Funding
Wellcome Trust/EPSRC

I'm currently a Research Fellow working with Dr Timothy Constandinou in the area of integrated neural microsystems. This work is in part motivated by the current quest to understand the human brain, developing new tools and applying these to create next generation brain machine interfaces. Such devices will need to observe the activity of 1000s of neurons in real time, be chronically stable and be adaptive over time.

There do remain however several challenges in implementing such systems, such as how can they be made to be compact, low power, low noise, high channel count, be suitable for chronic operation and generate high quality, low data rate information. Furthermore the physical embodiment of such microsystems often poses a reliability challenge, for example, how to connect 100 electrodes to a chip in a chronically stable way. Often, device failure is due to wires breaking or ineffective encapsulation.

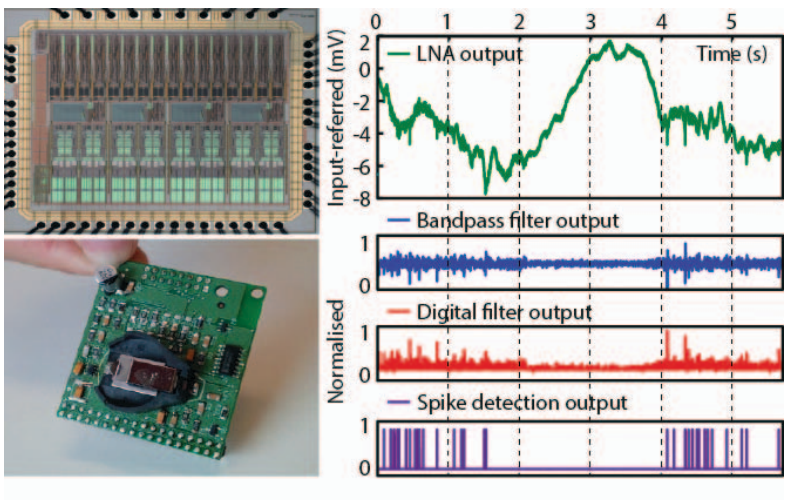
MY WORK

In addressing these challenges, we take a holistic approach, considering the system architecture as a whole, rather than simply scaling existing systems (more channels). One such system we have developed is a 'smart' recording system consisting of a bespoke in-channel DSP and memory to provide local processing. With this system we have showed how both the power consumption and data bandwidth can be reduced without compromising the underlying performance. We have designed and fabricated such a 16-channel smart recording interface in a commercially available CMOS technology (currently under test). Moreover, we have developed a complementary back-end (consisting of an embedded system) for online, on-node spike sorting, which can process the neural signals before external communication and thus can massively save precious bandwidth. We have also individually optimized each component in the signal processing chain to be both effective and efficient.

More recently, I have recently become involved in CANDO – a new multisite, multidisciplinary collaborative project (between Newcastle University, Imperial College London and UCL) to develop a new type of brain pacemaker for drug insensitive focal epilepsy. This is taking an entirely novel approach by developing an optogenetically-enabled closed loop neural probe for regulating network activity. My role on this is as a key contributor on the CMOS design of the neural probe itself and hardware system architecture. We are currently developing a first generation implant that combines optogenetic stimulation with electrical recording, on-probe diagnostics and real-time closed loop control.

RECENT PUBLICATIONS

1. L Zheng, L B Leene, Y Liu, T G Constandinou, "An adaptive 16/64 kHz, 9-bit SAR ADC with peak-aligned sampling for neural spike recording", in *Proc. IEEE International Symposium on Circuits and Systems (ISCAS)*, pp. 2385–2388, 2014.
2. D Y Barsakcioglu, Y Liu, P Bhunjun, J Navajas, A Eftekhar, A Jackson, R Quian Quiroga, T G Constandinou, "An Analogue Front-End Model for Developing Neural Spike Sorting Systems", *IEEE Transactions on Biomedical Circuits and Systems (TBioCAS)*, vol. 8, no. 2, pp. 216–227, 2014.



16-channel 'smart' neural interface chip microphotograph, in-vivo test platform and experimental results.

Fellow

STAFF RESEARCH REPORT

Dr Yufei Liu

Research focus
Advanced micro/nano fabrication, Smart microsystem for point of care application

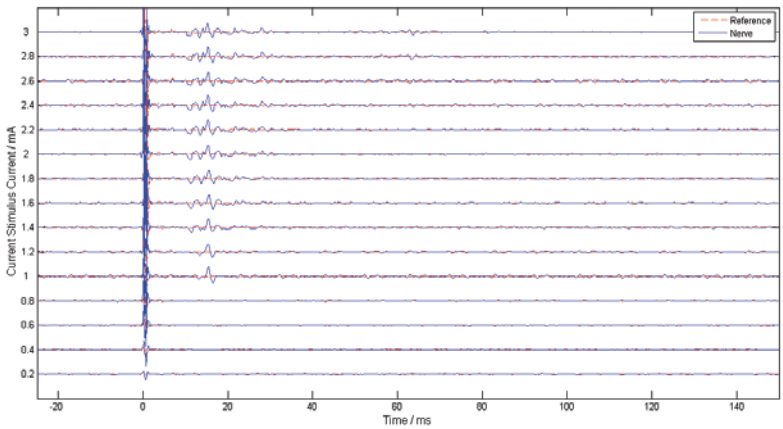
Funding
European Union ERC Synergy

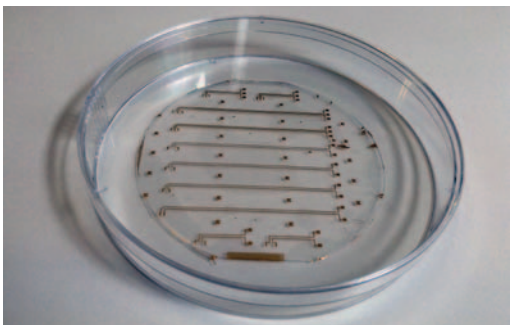
My main research focus lies in the field of Advanced micro/nano fabrication and the Microelectromechanical systems (MEMS) technologies, particularly for smart microsystems in point of care applications and interfaces/monitoring systems for the nervous system. With this ERC Synergy grant, we are developing a joint cuff electrode and microspike array for monitoring the combined electrical and chemical (ion sensitive, such as Na+, K+ and Ca2+) signatures associated with action potential propagation – the nerve signals.

To achieve this I work in a state-of-the-art cleanroom, with advanced micro/nano fabrication facilities which was established in 2006 as part of the Centre for Bio-Inspired Technology. The nerve interface was first developed based on cuff electrode for electrical recording and microspikes for ion selective sensing, respectively. Using UV functionalised polymer, cuff electrodes for this application have been successfully fabricated with photolithography, metal deposition and lift off technologies. We have fabricated bipolar and tripolar electrode arrays made of Chromium-Gold, designed for matching the requirements of impedance and recording signal-to-noise ratio. In-vivo tests have shown that the our cuff electrodes worked successfully for recording nerve signals. I have also fabricated a microspike array, which would subsequently be functionalised to be pH and ion sensitive, using novel organic/inorganic sensing coatings.

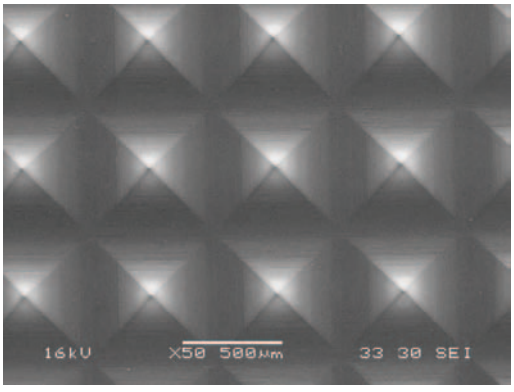
The next step of development would be enhancing the cuff electrodes with a self-wrapping function, which is very helpful for surgeons to implant the device to the nerves. So multi materials of polymers and mechanical self-curling solutions are being investigated.

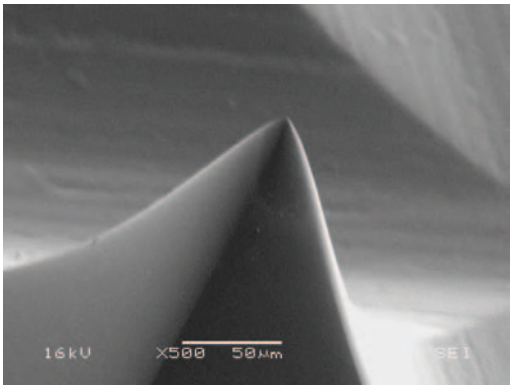
With over 10 years cleanroom working and management experiences, I am also in a management role and students/staffs supervisions, for the cleanroom in the Centre for Bio-inspired Technology.





Recoding signals using the fabricated cuff electrode (right)





Fabricated microspike array (left) and the highlighted 6-mm tip (right)

Fellow

STAFF RESEARCH REPORT

Dr Nedjai Belinda

Research focus
Investigation of the role of human genetic variation in skin ageing and establishment of a correlation between genetic variation and effectiveness of active ingredients used in over the counter (OTC) cosmetic products to slow down ageing.

Funding
Winston Wong Centre for Bio-inspired Technology

The skin care industry spends million in research and development to find product more and more powerful. Each ingredient has the ability to be metabolised by an individual. This ability is based upon the genetic makeup of this person. We have been able to identify the metabolic pathways of many ingredients and create a list of ingredients that either became inactive due to the presence of a SNP or a highly beneficial ingredient.

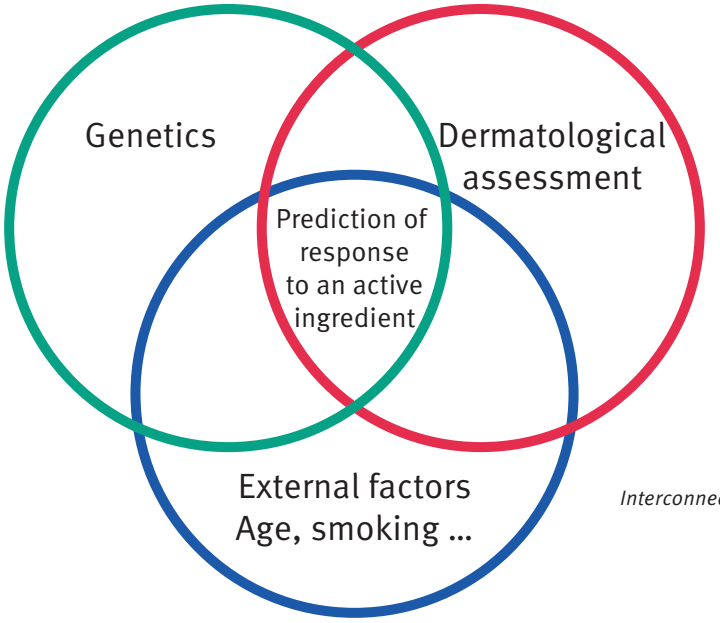
A major feature of aged skin is fragmentation of the dermal collagen matrix. Fragmentation results from actions of specific enzymes (matrix metallo-proteinases) and impairs the structural integrity of the dermis. In aged skin, collapsed fibroblasts produce low levels of collagen and high levels of collagen-degrading enzymes. Matrix metallo-proteinases are responsible for physiologic degradation of various extracellular matrix proteins. Of the 4 collagenases expressed in humans, only interstitial collagenase (MMP-1) is involved in normal turnover of skin collagen. Treatments that stimulate production of new, non-fragmented collagen should provide substantial improvement to the appearance and health of aged skin. In an attempt to dissect out what contributes to skin ageing and photoaging phenotype in the general population, we evaluated the incidence of MMP-1 SNPs. Our hypothesis is that MMP-1 polymorphisms might provide some insight into differential rates of skin ageing. We therefore performed the two subsequent clinical trials:

The first trial (Helen Trial) observed positive changes in aesthetic scores after using an existing over the counter topical day cream, night cream and night serum. Over 7 weeks in 37 subjects, the Helen trial showed an improvement in fine line appearances in all subjects compared to baseline. After cosmeceutical use, we noticed significant differences in the responses of the subjects according to their genotypes (reduction of hyperpigmentation ($p<0.001$) and fine lines ($p<0.01$).

The second trial (Winston Wong trial) observed positive changes in facial aesthetic scores after the application of geneU serum in 86 subjects for 12 weeks. This second trial grouped subjects according to genotype and each group was given a different geneU topical dual serum to apply twice a day.

After 12 weeks, all DNA matched product group show significant improvement in Crows Feet, Meso Labial wrinkles and pigmentation when compared to corresponding genotype placebo or random product group.

The data from both pilot studies may help shape topical strategies for genotype-specific anti-ageing skin care in the future taking into account genetics, dermatological assessment and lifestyle factors to predict which ingredients are more suitable. This work could be applied to photosensitive skin disease, reducing UV triggers and UV-induced skin cancers. In addition, the advent of semiconductor DNA array technology has permitted accurate real time and non-invasive acquisition of an individual's genetic data. UV damage is the most important mediator of skin ageing phenotype, as supported by our baseline data. Innovation in point of care DNA testing, along with recent evidence-based advances in anti-ageing cosmeceuticals, brings skin care personalisation by genotype, a step closer. (Imperial College Research Ethics Committee (ICREC_12_1_112) granted full ethical permission for the study.)



Interconnection between genetic and phenotypic information

Dr Nicoletta Nicolaou

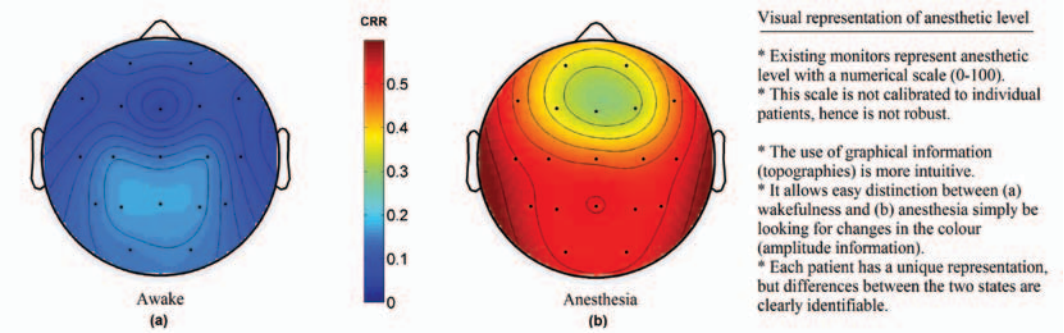
Research focus
AnaeWARE. Monitoring awareness during surgery: a multi-modal approach

Funding
EU FP7 Marie Curie Experienced Researcher IEF

I joined the Centre for Bio-Inspired Technology in August 2014 as a Marie-Curie Research Fellow. I received my BSc. (Hons) in Cybernetics & Control Engineering in 2001, and PhD in Cybernetics (Thesis title: 'Automatic artefact removal from Electroencephalograms') in 2006 from the Department of Cybernetics, University of Reading, UK. After the end of my studies I held a Research Fellow position at the Holistic Electronics Research Lab and KIOS Research Centre (University of Cyprus, 2007-2014). During my appointment there I received a prestigious 3-year award from the Cyprus Research Promotion Foundation on 'Monitoring awareness during surgery' (DIDAKTOR/DISEK/0308/20).

My main research interest is biomedical signal processing. The main signal of interest is electrical brain activity (EEG) and its analysis for a number of applications, disorders and brain states. Investigations include EEG activity during epilepsy, sleep, mental imagery and resting state, but my main area of interest is the study of EEG under anesthetic administration. More specifically, I have been investigating how the patterns of brain connectivity (in terms of causality, synchrony, etc) are affected by anesthetic administration, in order to identify mechanisms of anesthetic-induced unconsciousness for preventing awareness during surgery. My new project, 'AnaeWARE. Monitoring awareness during surgery: a multi-modal approach', extends my previous work to the study of multi-modal signals recorded during surgery (EEG and standard monitoring signals) to identify mechanisms of anesthetic action on the body as a whole and develop more cost-effective solutions for patient monitoring. 'AnaeWARE' is funded by a 2-year Marie-Curie fellowship (FP7/2007-2013; REA grant agreement no. 623767) and you can find more details about the project earlier in this report. My other research interests include the study of EEG activity for various applications (e.g. brain-computer interfaces), mental states (e.g. sleep), and disorders (e.g. epilepsy).

I have served as a Technical Committee member for a number of international conferences in my field and I'm a regular reviewer for a number of international journals and conferences. Throughout my research career I have received a number of awards, including first prize at the international data analysis competition of MLSP 2005 (Artifact reduction in multichannel EEG) and the Best Paper Award at Biodevices 2008 (Nicolaou, Georgiou, Polycarpou, 'Auto-regressive features for a though-to-speech converter'). My work has been published in high impact journals and presented at prestigious international conferences.



Fellow

STAFF RESEARCH REPORT

Dr Monika Reddy

MbChB MRCP

Research focus
The clinical evaluation of the bio-inspired artificial pancreas in adults with type 1 diabetes

Funding
Wellcome Trust

Type 1 Diabetes (T1D) is an autoimmune condition, which leads to destruction of the insulin-producing beta cells of the pancreas by the body's own immune system. This results in an inability of the pancreas to maintain glucose homeostasis, and if left untreated can be fatal. The majority of patients are managed in specialist diabetes clinics and are either on daily multiple subcutaneous insulin injections or continuous subcutaneous infusion of insulin via a pump. Intensive treatment reduces the risk of developing complications but achieving optimal glycaemic control can be very challenging for patients due to the increased risk of hypoglycaemia (low blood glucose) with intensive treatment. Severe or prolonged hypoglycaemia is a major concern and can result in seizures, cardiac arrhythmias and the 'dead-in-bed' syndrome.

A closed-loop insulin delivery system, also known as the artificial pancreas, consists of a subcutaneous glucose sensor, a control algorithm and a subcutaneous insulin pump. It has the potential to improve glycaemic control, reduce the incidence of hypoglycaemia and improve quality of life. The control algorithm used in the Bio-inspired Artificial Pancreas (BiAP) is based on a mathematical model of the beta-cell physiology. It has been implemented on a microchip within a handheld device. The miniaturisation of the system is of great importance for user acceptance.

Clinical evaluation of the BiAP started in May 2012 at the NIHR/Wellcome Trust Imperial Clinical Research Facility.

The aim of the clinical study was to assess the feasibility, safety and efficacy of a novel closed-loop insulin delivery system by applying the technology to adult participants with T1D in a variety of scenarios:

- 6-hour fasting study (n=20)
- 13-hour overnight and post-breakfast study (n=17)
- 24-hour randomised controlled crossover study with three meals (n=12)

The fasting and overnight & post-breakfast studies proved feasibility and safety of the Bio-inspired Artificial Pancreas and the results were published earlier this year (1)

The 24-hour randomised controlled crossover study comparing the Bio-inspired Artificial Pancreas (closed-loop) with standard pump therapy (open-loop) was completed in September 2014.

RESULTS

The BiAP significantly reduced the percentage time spent in hypoglycaemia compared to standard pump therapy (3.0 % vs. 18% respectively, $p<0.01$). The percentage time in the glucose target range (3.9-10mmol/l) did not differ between closed-loop (71%) and open-loop (67%), $p=0.94$.

FUTURE WORK

The next stage of this project includes evaluating the BiAP system with glucagon, exercise and mixed meals in a controlled clinical environment, before testing it in the home environment.

PUBLICATION

Reddy, M, Herrero P, El Sharkawy M *et al*. Feasibility Study of a Bio-inspired Artificial Pancreas in Adults with Type Diabetes. *Diabetes Technol Ther 2014*; 16:10–17

Fellow

STAFF RESEARCH REPORT

Dr Nour Shublaq

Research focus
Technology Transfer and Partnerships

Funding
Winston Wong Centre for Bio-Inspired Technology

Nour is an Electrical Engineer with an M.Sc. and a D. Phil. in Biomedical Engineering from the University of Oxford. After obtaining her doctorate early 2011, Nour joined University College London (UCL) where she was responsible to develop and coordinate major R&D activities/initiatives in the Computational Life and Medical Sciences Domain at UCL/UCL Partners (16 UK NHS Trusts) and beyond, via competitive project proposals aimed at National, European and International funders. She led on industry engagement at SME and large corporation level and looked after collaborations and strategic partnerships in the computational and biomedical domains, e.g. developing a £1M 3-year initiative with Microsoft Research. During her three years at UCL, Nour worked on a range of technology transfer initiatives mainly funded by the EU, and informed the direction of science and e-infrastructure policy at a UK and EU level.

In February 2014, Nour joined Imperial College London and currently provides her technical knowledge and expertise in grant coordination, business organisation and development to drive core activities of the Centre in close collaboration with Imperial Spinouts. To this end, she has spearheaded and managed the application process of various proposals towards the Wellcome Trust (for pre-screening of oesophagus cancer patients based on analysis of exhaled breath, also tackling antimicrobial resistance), Taiwan Ministry of Health (conducting clinical trials for type 1 diabetes) and MRC (point-of-care viral load diagnostic) inter alia. Nour also considers the capture and exploitation of new IP generated from CBIT research including supporting the development and commercialisation of these disruptive technologies.

RESEARCH INTERESTS

A key interest of mine is antimicrobial resistance. This has been publicly recognised as a global threat as important as climate change and international terrorism, mainly owing to the inappropriate or suboptimal use of antibiotics. The prescription of antimicrobials is often a time-pressured clinical-decision, with the potential for the patient to become very unwell, very quickly, if no treatment or an ineffective treatment is administered. One clinical question currently not well answered is whether the patient is presenting with a bacterial infection or some other condition. Then when an antibiotic has been prescribed to work against a particular infection strain or resistance pattern, it is not certain whether the selected therapy has been effective or appropriate to address the cause of a patient's illness. A means of identification, quantification and monitoring of bacterial load that is rapid, reliable and truly deliverable at the point-of-care would contribute to more efficient patient treatment of a range of increasingly 'antibiotic-resistant' pathogenic organisms.

Given my background, my research interests are wide ranging but currently include:

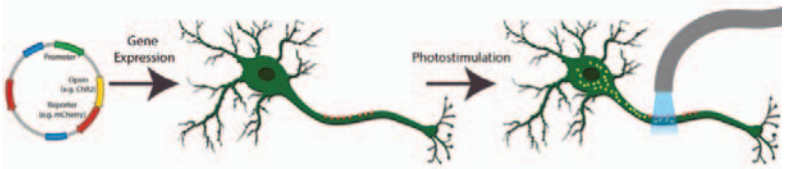
- Bloodstream infection Dxs
- Identification, quantification and monitoring of bacterial load for blood stream infections at the Point of Care:
- Semiconductor Technologies for medical and consumer applications

Dr Benjamin Evans

Research focus
Optogenetics: analysis, modelling and parameterisation

Funding
BBSRC

Optogenetics is a powerful technique for modulating the responses of neurons with millisecond precision, through genetically inserting light-sensitive proteins (known as opsins) into their membranes. Originally proposed as a concept by Francis Crick in 1999, the nascent field became an experimental reality six years later, flourishing to its present state of around 60 customised genes encoding variations of opsins extracted from algae, bacteria and fungi. These opsins have since been used to control activity at multiple scales of neuroscience, from the action potentials of individual neurons, through the activity of neural circuits and brain areas, up to behavioural responses in freely-moving animals. Owing to its temporal and spatial precision and the reversible nature of the manipulations (in contrast to lesion studies for example), this technique provides neuroscientists with an unprecedented tool for advancing our fundamental understanding of brain function.



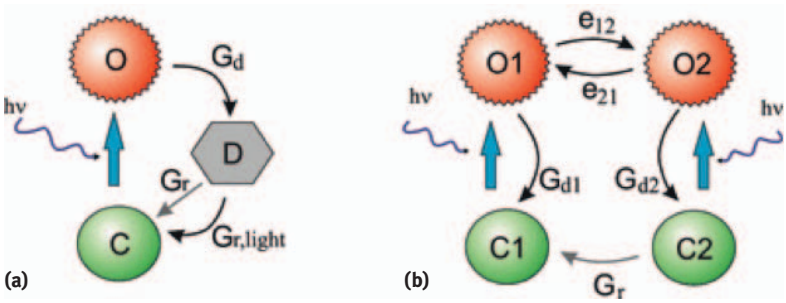
Experimental procedures of Optogenetics leading to neural excitation (or inhibition) (from www.addgene.org)

With so many opsins and types of neuron to partner with, there is a growing need to alleviate the experimental burden of characterising the multitude of combinations. To further develop the field and aid in the design of optogentics protocols, my project aims to model and characterise the photocurrent arising from the optical stimulation of opsins. To this end, software tools will be built (in Python, NEURON and NEST) to automatically select and parameterise an appropriate computational model from limited experimental data, allowing research questions to be more easily addressed *'in silico'*. It is hoped that these tools will help with, not only basic neuroscience research but also eventual medical applications, including deep brain stimulation for Parkinson's disease, neural inhibition for severe epilepsy and sight restoration through sensitising retinal ganglion cells.

I am interested in many areas of science and have enjoyed an unusually multi-disciplinary background, including degrees in Experimental Psychology, Intelligent Systems and a DPhil in Computational Neuroscience. This project is particularly appealing to me, owing to the way in which it draws together a range of skills from these disciplines. In general, I utilise computational simulations of mathematical models in order to understand the complex dynamics of biological systems (ranging from Ant colonies to neural circuits). Prior to Optogenetics, I built self-organising spiking neural networks to model the learning processes of object recognition in the ventral visual system. Having spent my doctorate *reverse engineering* part of the brain, moving from a psychology to an engineering department was a more natural step than it may at first seem. Beyond this, I am also interested in neuromorphic hardware, machine learning and 'Queen's Arms philosophy'.

KEY REFERENCES

1. Boyden E S, F Zhang, E Bamberg, G Nagel and K Deisseroth, 'Millisecond-timescale, genetically targeted optical control of neural activity', *Nature Neuroscience*, 8(9), 1263–1268, 2005.
2. Nikolic K, N Grossman, M S Grubb, J Burrone, C Toumazou and P Degenaar, 'Photocycles of Channelrhodopsin-2', *Photochemistry and Photobiology*, 85, 400–411, 2009.
3. Yizhar O, L E Fenno, T J Davidson, M Mogri and K Deisseroth, 'Optogenetics in Neural Systems', *Neuron*, 71(1), 9–34, 2011.



The two simplest models of the ChR2 photocycle which can qualitatively reproduce the photocurrents in ChR2 transfected neurons. (a) The three-state model: C—closed/ground, O—open and D—closed/desensitized states. (b) Four-state model, with two closed (C1 and C2) and two open states (O1 and O2) (from Nikolic *et al.*, 2009).

Dr Melpomeni Kalofonou

Research focus
Development and translation of semiconductor technologies for analysis of DNA methylation as biomarker for cancer

Funding
Winston Wong Centre for Bio-Inspired Technology

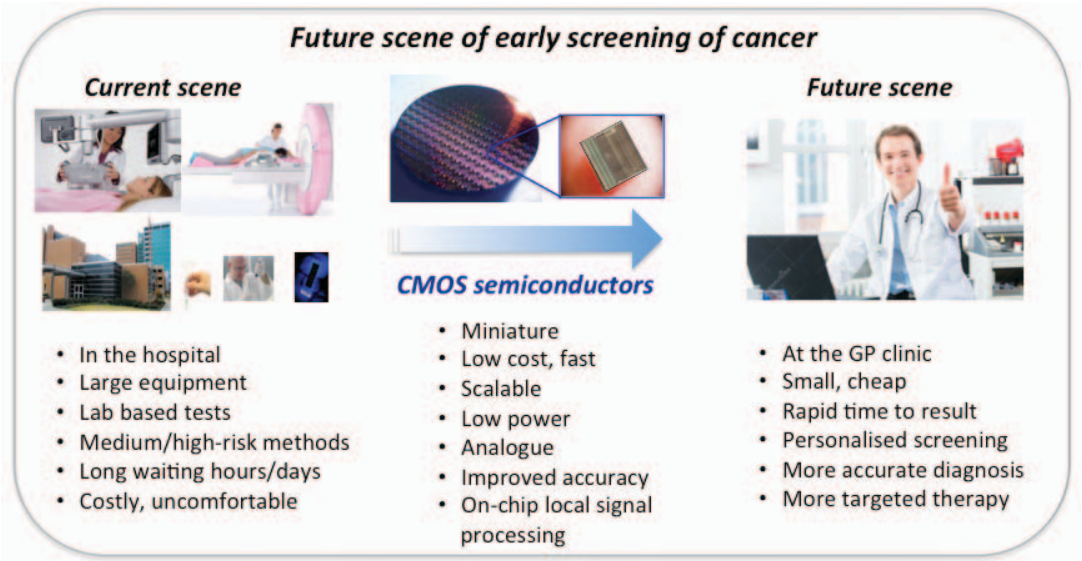
There has been a fast growing interest in the field of epigenetics, with recent advances to change the understanding of biological phenomena and complex diseases, such as cancer, traditionally viewed as genetic in origin. Tumour development has been directly associated with epigenetic changes, participating in mechanisms that may influence the homeostasis of gene expression through a partial or complete gene inactivation. One of the key epigenetic factors, DNA methylation, a dynamic chemical modification that can affect the regulation of gene expression without altering the genetic sequences themselves, has been extensively studied as a biomarker in early detection strategies as well as in cancer prognosis and response to treatment.

Especially in the event of cancer recurrence or metastasis, monitoring tumour-specific DNA methylation based changes could be of great value in stratifying the risk per patient case, contributing in a more individualised clinical assessment, thus providing a better detection efficacy, while reducing the economical burden on the healthcare services. Common types of cancer, such as breast cancer (with a lifetime risk of 1 in 8 women and more than 30% of treated cases to lead most likely to a metastasis) could considerably benefit from a reshaped model of early cancer screening, avoiding the use of imaging methods and the inherent risks of false-positive readings which could result in further unnecessary testing (biopsies/ additional imaging).

Semiconductor technology has been proven to be a very promising approach for rapid and label-free DNA detection using CMOS integrated ISFET sensors, without the need for optics. We have demonstrated that DNA methylation can be detected in real-time using semiconductor technology in a CMOS based System-on-Chip (SoC) platform consisting of fully integrated ISFETs. Based on this foundation, we are currently developing a platform for an epigenetic test, aimed to provide a DNA methylation analysis for identification of cancer risk, early diagnosis and treatment stratification, utilising semiconductor microchip technology.

PUBLICATIONS

1. Kalofonou M and Toumazou C, 'An ISFET based analogue ratiometric method for DNA methylation detection', *IEEE International Symposium on Circuits and Systems (ISCAS)*, 1832–1835, 2014.
2. Kalofonou M and Toumazou C, 'A low power sub-μW Chemical Gilbert Cell for ISFET differential reaction monitoring', *IEEE Transactions on Biomedical Circuits and Systems*, vol. 8, no. 4, 565–574, 2013.
3. Kalofonou M and Toumazou C, 'Semiconductor technology for early detection of DNA methylation for cancer: From concept to practice', *Sensors and Actuators B: Chemical*, vol. 178, 572–580, 2013.



Dr Sivylla-Eleni Paraskevopoulou

Research focus
Real-time neural chemical sensing in the peripheral nervous system

Funding
EPSRC

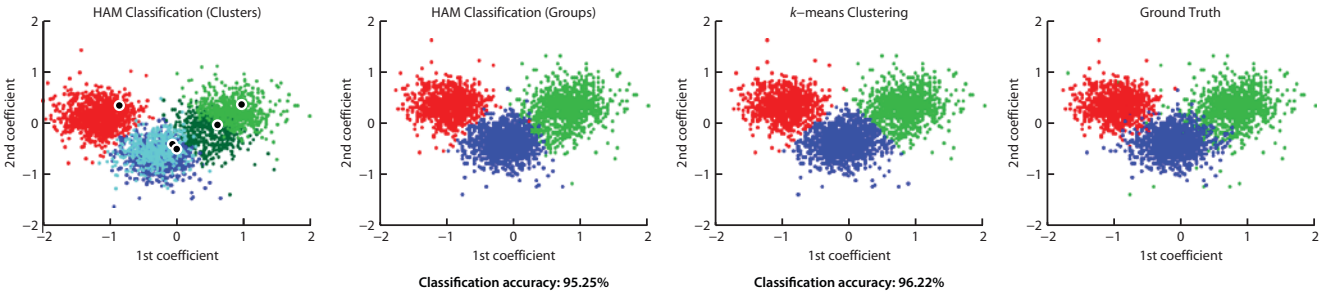
I completed my PhD at Imperial College in 2013. My research has proposed and developed key electronic circuits and algorithms to interface intra-cortical microelectrode arrays. By implementing nano-power circuits and hardware-efficient algorithms, my research has extended current neural recording capabilities by an order of magnitude (100s to 1000s of channels). I am currently a Research Associate at the CBIT developing electro-chemical prosthesis and unsupervised algorithms for interfacing peripheral nerves and working towards a closed-loop system for appetite control. My vision is that next-generation neuroprostheses will be multi-channel, autonomous, adaptive and robust.

Due to close proximity, each microelectrode in intra-cortical arrays can pick up spiking activity from multiple neurons. I have proposed a hardware-efficient classification algorithm that is able to determine the spatial firing pattern of each neuron. The HAM (Hierarchical Adaptive Means) clustering algorithm combines hierarchical clustering (i.e. it is initialised with certain number of clusters and merging occurs when the pre-defined criteria are satisfied), partition-based clustering (i.e. it uses distance metrics to assign data to a section of the clustering space), and density-based clustering (i.e. only clusters that represent small spike population are merged). The main advantages of HAM are that it performs on-line processing, automatically converges to correct number of clusters, requires no calibration training or supervision, introduces novel dual monitoring of cluster evolution, achieves high-accuracy comparable to off-line methods and has low computational complexity and memory requirements.

In the Peripheral Nervous System, one of the first considerations is the small signal amplitude (order of few μVs). This signal is embedded in thermal noise (generated by the electrodes and instrumentation), power-line interference and several other bio-potential sources (e.g. heart rate and muscular signal). Therefore, one of the key elements for recording peripheral nerve activity is the front-end low-noise amplifier. Although there has been a large number of studies on brain neural interfaces, little attention has been given to the Peripheral Nervous System which typically requires stricter noise and higher common mode rejection criteria. To this end, I have designed in commercially available CMOS technology a micro-power ultra-low-noise instrumentation amplifier that achieves high common-mode rejection ratio and dc drift (induced by the electrode-tissue interface) suppression. To further enhance the signal-to-noise ratio of the recorded signal, advanced signal post-processing techniques are employed, such as multi-level wavelet de-noising, rectified bin integration and independent component analysis.

PUBLICATION

S. Paraskevopoulou *et al.*, "Hierarchical Adaptive Means (HAM) clustering for hardware-efficient, unsupervised and real-time spike sorting," *Journal of Neuroscience Methods*, vol. 215, pp. 145–156, 2014.



Clustering results for realistic test dataset using PCA features. Shown are (from left to right): (a) HAM clustering spike assignment (to cluster centroids); (b) HAM clustering output (after grouping); (c) clustering via 10-iterations k-means; (d) ground truth.

Dr William Spinner

Research focus
Genetics and functional genomics

Funding
Winston Wong Centre for Bio-inspired Technology

Our DNA is what makes us unique. We are all unique because of small variations in each of our DNA blueprints. Much of this variation comes as a result of single nucleotide polymorphisms (SNPs) found in our genes. These SNPs can be responsible for functional variations in gene products that can cause differences in our metabolic pathways that can result in differences in our ability to metabolise and respond to chemicals, drugs and products.

The completion of the human genome in 2003[1] paved the way for a wealth of genomic data to form the foundations of future biomedical research. However, with all this knowledge about the human genome, there are very limited opportunities for most people to obtain or discover their own personal genome information.

With the discovery of semi-conductor technology it has now become possible to quantify these variations in an accurate, rapid, non-invasive procedure that until now has not been feasible[2]. After a streamlined sample preparation, a patients DNA sample is analysed in on the semi-conductor microchip and a result is obtained within 15-30 minutes.

How this DNA result is then best translated into a treatment for the patient is the key aim for my research. This aim is to develop a dataset of functional gene single nucleotide polymorphisms that can be used as markers to analyse an individual's genetic predisposition to metabolise a variety of chemical compounds (i.e. drugs/ingredients). Using this information, in conjunction with the rapid DNA sample analysis, we can personalise these optimum chemical compounds according to each individual's genetic make-up to maximise the efficacy of the treatment.

Working closely with DNAe Ltd, an Imperial College London, spin-out company, we have taken these recent advances in semi-conductor technology to transfer this innovative technology from the laboratory to the general public.

Further work is now needed to improve this technology, maximising the sensitivity of detection on the chip whilst minimising both the size and the cost so that the technology can be made accessible to all.

KEY REFERENCES

1. International Human Genome Sequencing Consortium, 'Finishing the euchromatic sequence of the human genome', *Nature*. 2004
2. Toumazou C, *et al.*, 'Simultaneous DNA amplification and detection using a pH-sensing semiconductor system,', *Nature Methods*. 2013

A prototype DNA test kit, incorporating a semi-conductor minilab, that allows live DNA testing

The semi-conductor microchip being inserted into the DNA analyser

Associate

STAFF RESEARCH REPORT

Dr Irina Spulber

Research focus
Wearable electronics for a smart garment aiding functional monitoring and rehabilitation

Funding
Wellcome Trust/EPSRC

Wireless technology has rapidly become an integral component of our lives but its potential is not yet fully realised in the medical and healthcare context. The use of non-invasive wireless sensors has a significant potential for disease prevention, diagnosis and rehabilitation, bringing huge benefits to both patients and clinicians and ultimately having the ability to change the paradigm by which certain medical conditions are presently managed. Miniaturized and integrated onto smart clothing, sensors are more likely to be accepted by patients thus enhancing healthcare in hospital and home environments.

Within the frame of Medical Engineering Solutions in Osteoarthritis Centre, our research focused on the development of a patient-centred, multi-sensing platform for a smart garment (legging) that can support independence and potentially reduce functional decline by guiding the patient in exercising appropriately to manage deteriorating joint function. The garment should be capable of monitoring and assessing a patient's activities in their daily environment, providing clinicians with objective markers of performance and assisting in devising customised rehabilitation strategies.

The first prototype of the wearable electronics platform materialized in the form of a small, light, easy to use, unobtrusive, low power body node capable to run of a 3V battery and remotely send data to a Bluetooth device. The node was tailored as a supportive technology for osteoarthritis (OA) rehabilitation management and embeds miniature triaxial accelerometer and gyroscope for monitoring gait and movement patterns, an EMG front-end to evaluate muscle activity and also provides analogue interface circuitry for a flexible conductive polymer sensor used to measure knee joint angles. The first prototype of the wireless body sensor node was integrated onto a garment that also incorporated a flexible sensor placed anteriorly to the knee, positioned such as to cover the patella. The system was tested on healthy volunteers during real life activities (both indoor and outdoor) and its performance was evaluated in the context of activity discrimination and functional monitoring during activities of daily living.

Further miniaturisation of the wearable electronics, along with hardware and software upgrades were embodied in the development of a second generation of the wireless body sensing node. The new prototype is half the size of the previous one (overall dimensions 3 cm x 5 cm x 2 cm), comes with a rechargeable battery and its charging circuit, allows for remote gain and offset adjustments, and supports an array of four flexible sensors that distributed around the knee joint can provide more robust information about the joint function. The electronics were integrated onto a smart garment and trials are currently conducted at Charing Cross hospital.

Our wireless sensing body node allows simultaneous acquisition and evaluation of multiple parameters for improved accuracy and reliability, and offers a one-system implementation for a multi-sensor data fusion approach for enhanced information extraction.

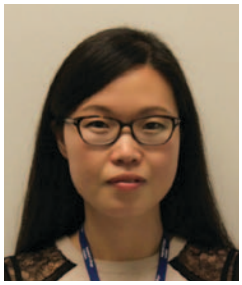
If adopted by NHS as a 'take at home' rehabilitation tool and incorporated into patients daily routines, the smart garment with integrated wearable electronics has a significant potential to improve the OA healthcare long-term outcomes, thus truly generating a positive impact on the quality of life of people with this condition.

PUBLICATIONS

I Spulber, Y M Chen, P Georgiou, E Papi, A McGregor, "Wireless multi-sensor platform for functional rehabilitation", *Medical Engineering Centres Annual Meeting, 3–4 September 2013*, Sunningdale Park, Ascot, UK (Best presentation award in Devices and Biosensors session).

I Spulber, E Papi, Y M Chen, S Anastasova-Ivanova, J Bergmann, P Georgiou, A H McGregor, "Development of a wireless multi-functional body sensing platform for smart garment integration", *IEEE BioCas 2014*.

Y M Chen, I Spulber, E Papi, S Anastasova-Ivanova, J Bergmann, P Georgiou, A H McGregor," An investigation of body worn sensors for lower limb monitoring and rehabilitation management", *MecBioeng14*, London 2014.



Dr Huan Wang

Research focus
Fabrication and characterisation of thin film bulk acoustic wave resonators

Funding
Wellcome Trust

BACKGROUND AND AIMS OF THE PROJECT

Regular eye-pressure monitoring is critical to treat glaucoma, which is a progressive disease and can cause permanent blindness if the eye pressure is not controlled. Globally 60.5 million people suffered glaucoma in 2010 and the number may increase to 80 million by 2020. Since current clinical devices do not provide continuous pressure monitoring, it is a case for developing implantable pressure sensors. Due to the requirement of implantation and operation frequencies at GHz range, traditional sensors are not suitable. Film bulk acoustic wave resonators, based on Hexagonal crystal Aluminium nitride (AIN), have drawn huge attention due to compatibility with silicon and higher bulk acoustic wave velocity; making them suitable for high frequency applications.

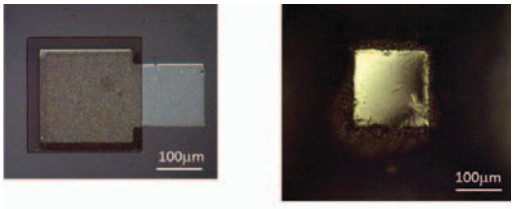
THE PROJECT

The focus of the project I am currently working on is to develop highly sensitive sandwich-structured thin film bulk acoustic wave AIN sensors for pressure sensing. High quality factor is an essential parameter for resonator-based sensors and results in better signal quality, low energy loss and higher pressure sensitivity. My research includes AIN thin film fabrication on silicon using reactive sputtering. In order to produce high quality factor resonators in GHz range, thin films of highly c-axis oriented crystalline of AIN should be grown on silicon substrates. Such films should be characterised by XRD and SEM and AFM to assess crystal quality and the thin film surface roughness. Materials used as the top & bottom electrodes are also important factors for sensor performance. Various materials will be studies to seek best results. At present, Al and gold have been deposited by e-beam evaporation and sputtering, as top and bottom electrodes respectively. Photolithography, dry and wet etching at cleanroom are used to transfer the designed patterns on prepared wafers. So far, we have developed processes for fabrication of AlN sensors at LCN cleanroom facilities and produced preliminary devices as shown in Figures 1 and 2. Figure 1 shows both top and bottom views of one AIN based resonator. Figure 2 shows side views of Al top electrode and AIN membrane.

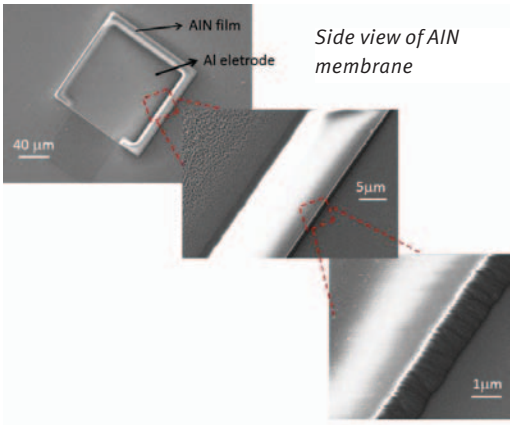
FUTURE WORK

Important parameters of these preliminary devices will be measured including resonator frequency, quality factor and effective electromechanical coefficient. In order to improve the sensitivity of AIN pressure sensors, the effect of various process parameters on the AIN sensitivity will be investigated and cleanroom fabrication processes will be optimised. The AIN devices will be integrated with other parts to form IOP sensors and lab testing will be conducted to characterize these sensors and assess their suitability for continuous monitoring of eye pressure.

Top view *Back view*



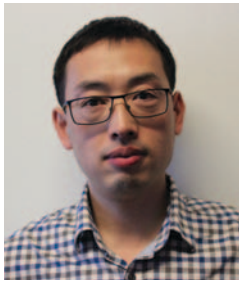
Optical images of the top and bottom views of AIN device (top and bottom views are SEM and optical micrographs, respectively)



SEM image of side views of Al top electrode and AIN membrane

Associate

STAFF RESEARCH REPORT



Dr Longfang Zou

Research focus
Antennas for wireless implanted medical devices

Funding
Wellcome Trust

Wireless implanted medical devices show promising characteristics in continuous monitoring of physiological indicators and possibly raising an alert in case of need, while preserving the mobility and lifestyle of patients. They allow early detection of any degradation in patients' condition, without frequently visiting or remaining in the hospital. In addition to the clear benefits to the patients, it would be advantageous for healthcare provider by reducing recurrent expensive invasive measurements and hospitalization periods.

My role within the wider project is the development of implantable and wearable antennas to provide robust and bidirectional link between the implanted medical devices and external instruments. Along with the mandatory requirements of biocompatibility and electromagnetic compatibility, the research is focused on the design, optimization and in vitro/ in vivo testing of implanted and body worn antennas. In the current blood pressure monitoring project, the implant depth of the passive sensor is larger than 6 cm. The complex, dispersive and highly lossy characteristics of human body put more emphasis on effective energy transfer. The designed antennas have met the necessary standards in phantom testing. The continuing study is devoted to miniaturizing antenna size, improving comfort of patients and preparing animal and human trials. Meanwhile, effective inductive coupling is under investigation to reduce the exposure level of body under electromagnetic for superficially implanted medical devices.

Dr Claudio Zuliani

Research focus
Sensing technology for real-time monitoring of chemicals and bio-markers within neural interfaces

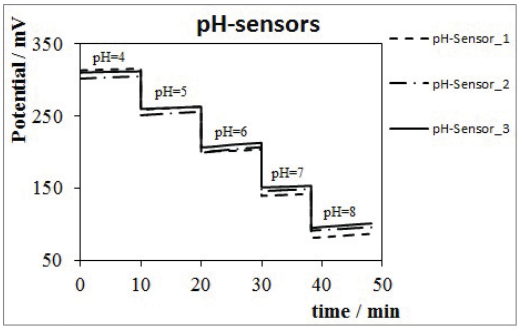
Funding
European Union ERC Synergy

Chemicals are the indispensable letters of the alphabet that our body exploits in order to establish effective and long-range communication at the cellular, tissues and organs levels. The complexity of this network which took millions of years of evolution to refine to such perfection and wonder is still not fully understood. In this regard, new developments in sensing technology combined with progresses in microfabrication and electronics offer the unprecedented opportunity to unravel the dynamics of the underlying biological pathways related to molecular signalling.

Real-time monitoring of these chemical patterns during *in-vivo* studies may allow new avenues for therapeutics of metabolic and neural disorders. In fact, the i2MOVE project proposes tapping into the chemical fingerprints associated with appetite signals in order to engineer a closed-loop neural interface able of modulating intelligently the gut-brain communication. This interface offers novel means of treating obesity and holds the promise of a less-invasive alternative to bariatric surgery.

My role within this project is to engineer suitable sensing devices targeting the changes in the composition of ions such as Na^+, K^+ and Ca^{2+} which occur in the nerve bundle simultaneously to the propagation of the action potentials. In addition, the gut activity triggers the release of specific hormones such as ghrelin and cholecystokinin which act as a secondary neural circuitry between the gut and the brain. Thus, I also deal with the preparation of wearable immunosensors suitable for the low-level detection of these hormones in body fluids such as blood. I leverage my expertise in electrochemistry, wearable sensors, surface chemistry, nano and microfabrication to deliver practical and commercial solutions to these tasks.

Working in the i2MOVE team is extremely exciting since we require a holistic approach to solve all the multidisciplinary challenges of this project, i.e., understanding the physical needs and constraints from an implant point of view, understanding the underlying physiology of the gut-brain system, designing suitable sensing interfaces, tailoring the sensor to the particular microfabrication process and finally combining the electronics into an overall integrated solution.



Visiting Research Fellow

RESEARCH REPORT

Dr Jorge Bondia

Associate Professor, Department of Systems Engineering and Control, Universitat Politècnica de València, Valencia, Spain

I started my academic career in 1995 at the Dep. of Systems Engineering and Control at Universitat Politècnica de València, Spain, reaching my current position of Associate Professor in 2007. During this period I have taught subjects on automation, control engineering and biomedical engineering. I conduct my research at the Institute of Control Systems and Industrial Computing (Institute ai2). I got my PhD in Computer Science in 2002 on the subject of uncertain dynamical systems. In 2004 I started my own research line on diabetes technology and artificial pancreas, to which I am fully devoted nowadays. I currently lead a multidisciplinary team of control engineers, mathematicians and endocrinologists in collaboration with several hospitals in Spain. Our main research lines are modelling of type 1 diabetes pathophysiology, methods for the characterization of intra-patient variability and glucose prediction under uncertainty, tools for insulin therapy optimization, new calibration algorithms for accuracy improvement of continuous glucose monitoring and control algorithms for an efficient and safe artificial pancreas.

Between July and September 2014 I have joined CBIT as visiting researcher under the supervision of Dr. P. Georgiou thanks to a fellowship granted by the Valencian Community regional government Generalitat Valenciana. During this time we have been working on new calibration algorithms for accuracy improvement of continuous glucose monitoring which will enable improved operation of the artificial pancreas and other diabetes management systems. Methods based on clustering techniques and local modelling were used.

As continuous glucose monitors measure interstitial glucose, plasma glucose estimators are needed. This is carried out by characterising local dynamics in interstititum to plasma glucose transport. Local estimators are then combined to yield plasma glucose readings. Methods were evaluated against a new database from closed-loop clinical studies performed at CBIT. Improved accuracy was demonstrated as compared to Medtronic Guardian device.

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Mr Deren Barsakcioglu

Research focus
Resource efficient on-chip spike sorting

Supervisor
Dr Timothy Constandinou
Funding
EPSRC DTA and EP/I000569/1

The ability to interface neurons using electronics is presenting new opportunities for neural rehabilitation with prosthetic devices. Commonly referred as neuroprosthetics, such devices aim to restore the lost sensory and/or motor abilities by tapping into sensory or motor pathways via a neural interface.

Demands from neural analysis and prosthetics have pushed the recording technology to increase the number of recording sites and resulted in an ever increasing number of neurons recorded. However, wireless transcutaneous telemetries that are crucial for both the clinical systems and prosthetic devices have fundamental limitations as to the amount of data that can be transmitted within safe limits for thermal dissipation.

In order to overcome this bandwidth and power consumption bottleneck, the required data compression prior to transmission can be achieved by on-chip spike sorting, which is the identification and grouping of spikes recorded. Hence my research focuses on developing a fully integrated real-time spike sorter with minimal power and area consumption, while maintaining the high sorting performance.

MY WORK

In order to achieve an optimum on-chip spike sorting implementation, one must identify and analyse all parameters that affect spike sorting process[1]. Therefore, one of the main objectives of this research is to identify both the hardware specific and sorting related parameters, and establish their trade-off regarding sorting performance and hardware resources (power and area) utilised[2].

The work to date has dealt with optimisation of the system parameters[1,2]. More specifically, trade-offs of the parameters associated with front-end electronics have been established via both parametric design optimisation and behavioural front-end modelling studies[3]. In addition, parameters related to back-end digital processing have also been investigated. These include (but not limited to) some critical aspects of spike sorting such as alignment, template creation, and window size. Moreover, a new sorting algorithm have been proposed[4].

At the current stage, a novel spike sorting algorithm, which requires minimum hardware resources while maintaining comparable accuracy to counterparts, is being tested and verified on an ultra-low power platform.

RECENT PUBLICATIONS

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3. D Y Barsakcioglu, Y Liu, P Bhunjun, J Navajas, A Eftekhar, A Jackson, R Quian Quiroga, T G Constandinou, “An Analogue Front-End Model for Developing Neural Spike Sorting Systems”, *IEEE Transactions on Biomedical Circuits and Systems (TBioCAS)*, vol. 8, no. 2, pp. 216–227, 2014.
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Mr Bernard Hernández

Research focus
Enhanced, personalized and integrated care for infection management at point of care (EPIC IMPOC)

Supervisors
Dr Pantelis Georgiou and Dr Pau Herrero Viñas

Funding NIHR – i4i Challenge Award

Continuous evolution of microbial organisms and unnecessary antibiotic use, particularly in infection diseases, are a common concern in critical care, infection management and antimicrobial stewardship. Antimicrobial resistance is a growing and significant threat to public health that is compromising the ability to treat infections effectively and is driven by high rates of antibiotic prescribing. Daily reviews of patients in ICU conducted by Microbiology specialists and Infectious Diseases and furthermore guidelines to manage antibiotic prescription are tools to tackle this problem.

OBJECTIVES

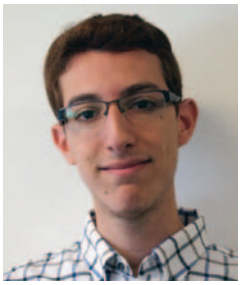
It is critical to reduce unnecessary antibiotic prescription to increase satisfactory patient outcomes. However, there is a lack of information about local resistance patterns and patient records history at point of care (POC). Our aim is to develop a POC application that gathers relevant patient information (i.e. analytics, cultures, allergies) to treat the infection and integrates Decision Support System (DSS) to suggest an optimal solution based on previous similar cases. This application not only attempts to resolve antimicrobial resistance and increase successful treatment rates. It will achieve a potential reduction in infection specialist time spent consulting in critical care and a powerful source of knowledge to educate new specialists.

MY WORK

My work focuses on the development of the DSS and IT infrastructure for validation of the complete POC system. One of the core principles for this project is to evaluate and choose a method to determine the similitudes between two cases. The domain of the problem (infection diseases and antibiotics prescription) is partial and vague. The various outcomes for a same infection disease and treatment and the existence of rare diseases make “experience” the main source of information. We use Case Based Reasoning (CBR), which may provide an engineering solution to meet this need, through adaptive, heuristic algorithms drawn from archived patient cases to inform current medical decision-making.

The server-side Decision Support System (DSS) and the client-side application have been developed and are ready to be used. The web-based nature of the client-side application allows it to be run in any device no matter the operative system. In addition, Responsive Design techniques are used to adapt the interface for any device (mobile or computer) no matter its screen size. The data gathering from the Trust servers is almost complete and we will initiate testing.

We will begin clinical trials this year of the system in the intensive care and secondary care units of hospitals under the Imperial College NHS trust. This will help to evaluate the impact of this system on patient outcomes, antimicrobial usage, antimicrobial resistance and healthcare professional workflow. The number of cases stored in the database will increase substantially and the number of parameters used to model the human body and particularly its behaviour when microbial organisms and drugs are present is huge. It would be an advantage for the system to use of Machine learning techniques to perform dimensionality reduction on the attributes, clustering algorithms to group similar cases and Data Mining to find patterns.



Mr Mohamed El-Sharkawy

Research focus
A bio-inspired glucose sensing system for treatment of diabetes.

Supervisor
Dr Pantelis Georgiou

Funding
Wellcome Trust

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 dollars 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, accurate and have a long lifetime. Currently there are a number of initiatives aimed at fabricating micro-needles which are glucose sensitive and can be worn on the body in the form of a patch. My goal is to design the sensor front end instrumentation for such devices and perform signal processing in a way that mimics the method used by the beta cells in the pancreas to perform bio-inspired sensing which will be used as part of the bio-inspired artificial pancreas.

MY WORK

My work will investigate the method by which the beta cells (insulin producing cells of the pancreas) synchronize their bursting behaviour using gap junction coupling[2] and it's improvement on noise performance and robustness. Using this we will then demonstrate that with an array of coupled beta cells on a CMOS chip and a low power potentiostat as the sensing front end we can improve glucose sensor performance for control of diabetes. This will ultimately be used as part of the Bio-inspired Artificial pancreas and integrated on future micro-needle array sensors.

RESULTS

We have shown through Matlab simulations of coupled beta cells the noise shaping potential of synchronized networks in the context of glucose sensing[3]. Through gap junction coupling of up to 8 cells we can improve sensor performance through a reduction in standard deviation of a glucose sensor signal by 74%. This Matlab model has been implemented on a silicon chip and is currently being tested. It can be seen that a CMOS based system integrating low power glucose sensing and novel signal processing inspired by biology 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.

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Mr Onur Guven

Research focus
Ultra low power microelectronics for robust ECG signal conditioning

Supervisor
Dr Timothy Constandinou

Funding
Texas Instruments and Centre for Bio-Inspired Technology

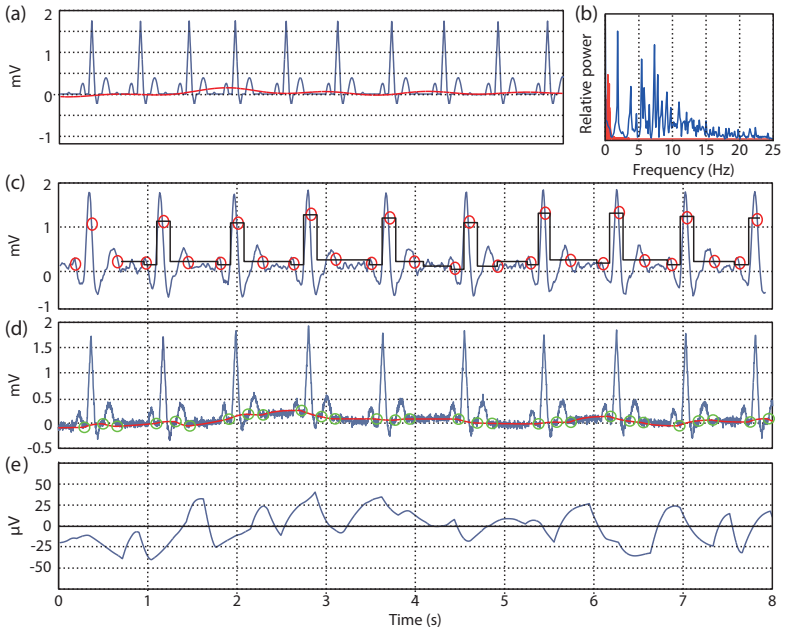
Electrocardiography (ECG) is the recording of the electrical activity of the heart. The ECG signal band is generally defined to be between 50mHz and 150Hz. This is therefore susceptible to interference from other in-band bio-signals, in addition to environmental noise. More specifically, noise sources include electromyograms and respiration signals which both pose a challenge in preserving the ECG signal integrity. Since both these signals' spectral range overlaps with the ECG spectrum, care must be taken in filtering and processing. Various approaches have been reported in the literature to achieve this. However, these often neglect distortion to key features within the ECG signal, for example, the ST segment which crucial in diagnosis of certain conditions like myocardial ischemia. Therefore, it is essential to preserve the signal integrity when applying any filtering to eliminate sources of interference.

MY WORK

I have developed a closed loop approach for maintaining the ECG signal integrity. Conventional systems utilise high resolution converters to digitise the ECG signal together with any noise sources. The ECG signal is then recovered by processing in the digital domain. The approach I have developed however, removes the noise sources at the front end, through a feedback mechanism that estimates the noise. This is beneficial as it relaxes requirements on the data converter (i.e. no longer requiring a high resolution ADC) and therefore has the potential to achieve good power efficiency compared to the state of the art. Furthermore, this provides the opportunity to observe, and act on clinically-relevant (i.e. undistorted signals) in real time.

The proposed closed loop system mitigates requiring a high resolution ADC by instead utilising a high resolution DAC in the feedback loop. This high resolution DAC is generally easier to implement (and considerably lower power) than the equivalent ADC. This resolution is required to ensure noise requirements defined by IEC and AHA standards are met. The system utilises a low gain instrumentation amplifier as the first stage to suppress the high common mode noise, whilst also relaxing the noise performance requirements of the high resolution DAC. The next stage then subtracts an estimated baseline (noise) from the input and then further amplifies the remaining ECG signal to fill the dynamic range of a low resolution ADC. This then then fed to a processor to estimate the baseline drift by using an isoelectric point estimation algorithm.

The algorithm I have proposed has been tested extensively using synthetic signals and also validated with real recordings. The results show a maximum (worst-case ST-segment distortion) error of 34.7µV (mean), 27.8 µV (median) and 21.2 µV (std. dev.) across 50 randomly generated synthetic ECG signals each containing 100 heartbeats. Validation of the algorithm applied to signals from the MIT-BIH arrhythmia databases reveals maximum error per P-T interval with mean, median and std. dev. of 34.4µV, 35.2µV and 9.6µV respectively with suppressed motion artefacts.



Operation of the algorithm using 8 second synthetic ECG and noise artefacts

RECENT PUBLICATION

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Mr Dorian Haci

Research focus
Thermally controlled lab-on-PCB heater array for bio-applications

Supervisors
Dr Pantelis Georgiou and Dr Timothy Constandinou

Funding
Politecnico di Torino and Wellcome Trust Networks of Excellence

Temperature is a highly critical parameter in virtually all biological processes and chemical reactions, such as the Polymerase Chain Reaction (PCR).

Recent research has explored the feasibility of modulating temperature to regulate cellular activity. Lab-on-Chip platforms have introduced the possibility to implement micro-devices, such as actuators and sensors, in a single chip by means of commercially available CMOS technologies. Therefore, the trend for monolithic systems has allowed developing of Thermally Controlled Lab-on-Chip systems. Investigation for low-cost processes and short fabrication time lead our interest towards Printed Circuit Board (PCB) technology.

OBJECTIVES

The aim of the project is to develop such a thermally controlled system using low cost PCB technology. This will first explore the limits of manufacturable features in a variety of commercially available technologies to establish the feasibility and constraints of such an approach.

MY WORK

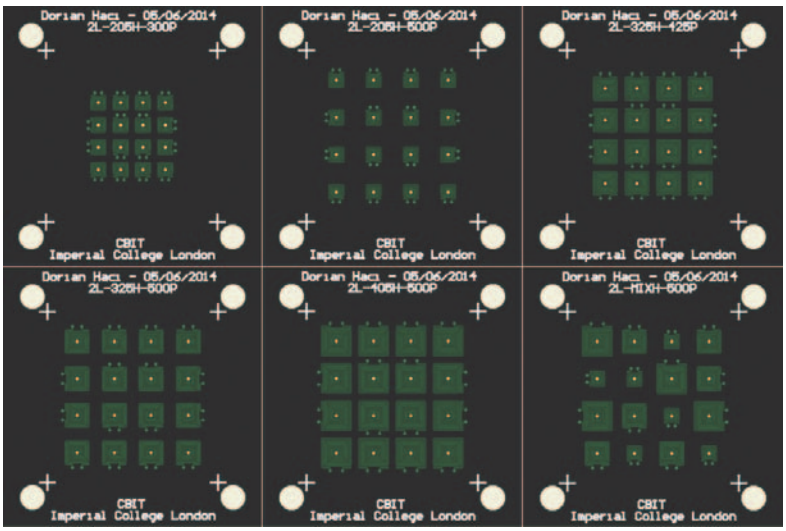
An NxM array of 'pixels' is designed such that each pixel can be independently controlled and monitored. Each pixel of the array consists of three key components:

- Heater, used to vary the temperature;
- Temperature sensor, used to provide the closed loop control the temperature locally;
- Pad/electrode, used to monitor the electrical activity of the solution/tissue in direct contact.

The first prototype structures have been designed and fabricated (see Figure 1) using a 4x4 array of such elements. This has been characterised (both electrically and thermally) through finite element analysis (using COMSOL) and experimental measurement. This has revealed the performance in terms of thermal crosstalk, transient behaviour and reliability.

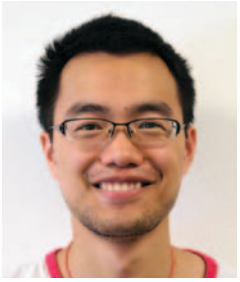
Finally, a control platform incorporating all the required instrumentation and interface electronics has been developed to achieve the required functionality (i.e. independent, rapid temperature control of each pixel and low noise electrical recording). This consists of op-amp based bias and instrumentation circuits, a number of DACs and ADCs and a micro-controller based computer interface.

Prototype PCB-based heater array designs



Visiting Student

RESEARCH STUDENT & ASSISTANT REPORT



Mr Yuanqi Hu

Research focus
Advanced sensing and processing methodologies for ISFET based DNA sequencing

Supervisor
Dr Pantelis Georgiou

Funding
EEE Departmental Scholarship

The integration of DNA detection methods 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, which provides the opportunity of integrating chemical sensing and application specific integrated circuits to improve functionality. This could be hugely beneficial to improve the performance of DNA sequencing systems by making them scalable, reducing the noise, improving robustness and increasing throughput.

MY WORK

My research involves the design complete end-to-end system for DNA sequencing which includes a novel ISFET pH sensing array for DNA sequence detection and a FPGA platform for assembling these detected sequences in real time. The new detection array includes a novel sensor front end[1], which is capable of dealing with some challenges currently faced in ISFET arrays such as trapped charge, drift and capacitive division.

In addition to these factors, process variation is another issue that needs to be addressed. An automatic gain calibration system has been designed to compensate the ISFET sensitivity deviation[2]. We use a sine wave superimposed on the reference electrode, and the output from each sensor pixel is used to examine its in-pixel gain. The amplitude is detected through a rectifier followed by low pass filters. Ultimately this will reduce mismatch in ISFET sensor array to 1%.

I have also designed a DNA assembly platform using an FPGA system that implements a novel comparison algorithm that can be easily run on parallel processing units[3]. This new algorithm has the capability to process the real-time signal coming from the sensor array so that the actual detection time of the sensor can be utilised to do the processing work. This is achieved through a hybrid algorithm that searches the overlap hitting by exact comparison and checks these hitting through dynamic programming. This algorithm can be easily segmented into discrete phases, allowing it to deal with the incomplete data. Additionally, this algorithm has very good scalability so that cluster FPGA system could be realized as long as the parallel architecture is well designed.

The final goal of the PhD is to lay the foundations integrated ISFET based DNA sequencing platforms which will enable an end-to-end system to be realisable. The ultimate aim will be the introduction of the world's first CMOS based DNA microarray capable of sequencing a complete genome on chip in real time.

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Mr Ermis Koutsos

A low-power real-time sEMG fatigue monitoring ASIC for rehabilitation of osteoarthritis

Supervisor
Dr Pantelis Georgiou

Funding
EPSRC DTA

SUMMARY

Electromyography (EMG) is a technique used to evaluate the electrical activity of muscle. Muscle fatigue tracking can be a helpful tool for the rehabilitation of osteoarthritis in the knee, a chronic condition affecting 8.5 million people in the UK causing pain and loss of mobility. Knee rehabilitation focuses on maintaining a balance between the two large muscles that hold the patella (knee cap) in place. Careful tracking of muscle fatigue of these two muscles can provide essential adjustments to the rehabilitation procedure. Furthermore, fatigue monitoring can be applied in the field of spots science, medical research and ergonomics.

OBJECTIVES

The aim of this project is to create a real time method for tracking muscle fatigue for applications in rehabilitation. Through specific continuous time techniques, a compact, energy efficient, wearable device will be developed in CMOS that extracts muscle fatigue through monitoring of surface EMG. Ultimately, this wearable node will be applied to any muscle of the body, thus providing a tool to aid in rehabilitation or muscle research. Processing of the EMG will take place locally, resulting to an information driven system rather than a conventionally data driven system, reducing requirements on data transmission and power.

PROGRESS

Work to date includes the development of novel algorithms for muscle fatigue tracking. Two ICs have been designed and fabricated. Their purpose is to analyse surface EMG signals and estimate either the Median Frequency of the EMG signal or the Muscle Fibre Conduction Velocity. Furthermore, with collaboration from the Motion Laboratory in Charring Cross, Wavelet Transform analysis is explored in an effort to better understand the muscle fatigue manifestations that lead to chronic back pain.

KEY REFERENCES

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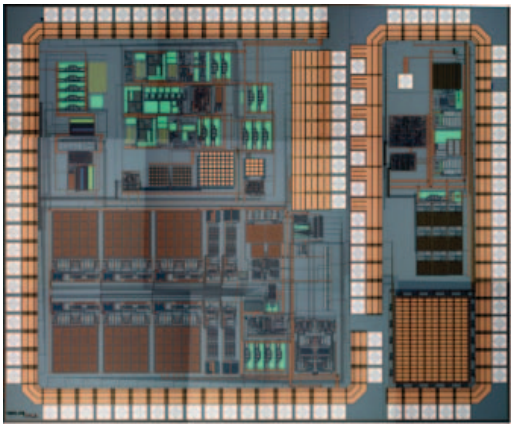
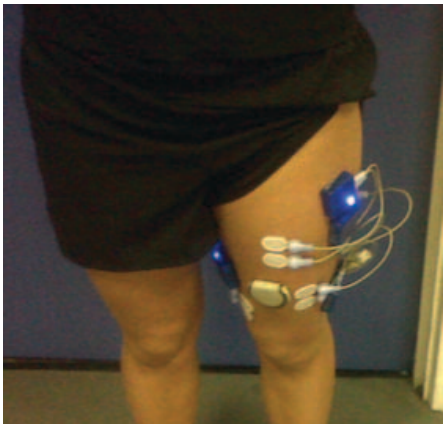
PUBLICATION

Koutsos E, & Georgiou P (2014, June). An analogue instantaneous median frequency tracker for EMG fatigue monitoring. *In Circuits and Systems (ISCAS), 2014 IEEE International Symposium on* (pp. 1388–1391). IEEE.





Mr Lieuwe Leene

Research focus
High-density recording arrays for next generation neural interfaces

Supervisor
Dr Timothy Constandinou

Funding
EPSRC Prize Studentship

The advancement in state-of-the-art neuroscience & neuroengineering are continuously being driven towards improving sustainability and effectiveness in electronic interfaces with the central nervous system for rehabilitation and clinical medication of electrotherapy. The diverse set of challenges faced in this domain has involved many areas in biological and electronic research to achieve the progress of today's systems where it is possible to utilize the neural activity to actively control augmented systems.

The vision for next generation neural interfaces needs to address the growing complexity seen in processing algorithms and instrumentation electronics while meeting the demand for chronic recording of 1000s of neurons in specific brain locations. Such a CMOS based microelectronic bioinstrumentation system will be capable of recording the fine detail of neuronal activity with unparalleled special resolution. The capacity for highly miniaturized integration of such tools will allow multiple chronic implants to be distributed throughout the nervous system with minimal risk factors and promising unprecedented diagnostics.

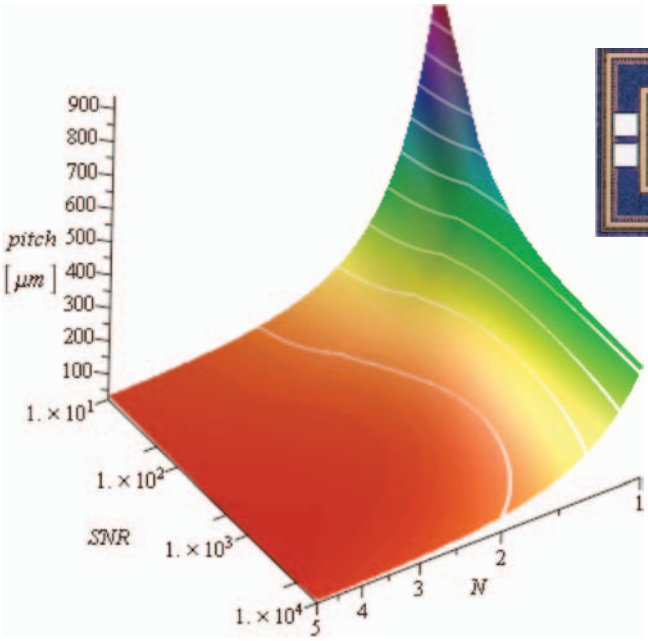
MY WORK

My research targets the full integration of highly compact & distributed neural recording system. Focusing on highly compact topologies and efficient integration strategies will allow on-chip processing that is capable of identifying fine characteristics in each recording. The on-chip processing could allow a single implanted system to selectively test numerous instrumentation algorithms to evaluate real time effectiveness.

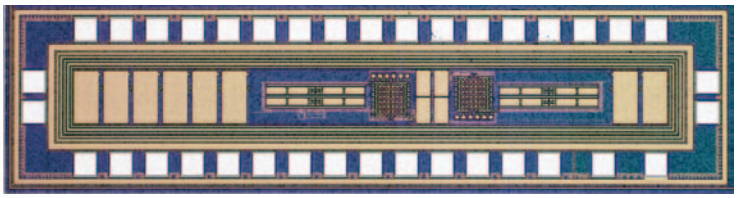
Current work has demonstrated how recording accuracy and complexity affect silicon requirements for different technologies through parameterised models. The resource aware approach enabled targeted innovation towards significant reductions in area in the mixed signal front end of the recording system. Future efforts will explore different approaches to integrate very large channel counts and developing a digital architecture allows data specific distributed processing.

RECENT PUBLICATIONS

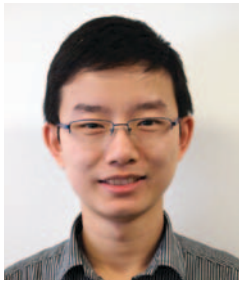
1. L B Leene, Y Liu, T G Constandinou, "A compact recording array for neural interfaces," in *Proc. IEEE Biomedical Circuits and Systems Conference (BioCAS)*, pp. 97–100, 2013.
2. L B Leene, T G Constandinou, "Ultra-low power design strategy for two-stage amplifier topologies", *IET Electronics Letters*, vol. 50, no. 8, pp. 583–585, 2014.
3. L Zheng, L B Leene, Y Liu, T G Constandinou, "An adaptive 16/64 kHz, 9-bit SAR ADC with peak-aligned sampling for neural spike recording", in *Proc. IEEE International Symposium on Circuits and Systems (ISCAS)*, pp. 2385–2388, 2014.



Dependency of the analogue recording channel size on signal to noise ratio and processing complexity



Micrograph of 4 recording channels fabricated in with the C18A6 AMS process



Dr Song Luan

Research focus
Integrated electronics for targeted intraspinal microstimulation

Supervisor
Dr Timothy G. Constandinou

Funding
EPSRC EP/I000569/1

Intraspinal microstimulation (ISMS) is an emerging method that is applied to neuroprosthetics aimed at individuals with spinal cord injury. Compared to traditional spinal stimulation or peripheral nerve stimulation methods, ISMS can activate muscle groups in organised synergies and thus can provide finer control of the generated force also with reduced muscle fatigue.

OBJECTIVES

The fundamental aim of my research has been to develop integrated electronics for achieving safe, energy efficient and selective intraspinal microstimulation.

MY WORK

(1) Exploring the feasibility of developing a fully-integrated charge-mode stimulation circuit for improved stimulation efficiency compared to typical methods for stimulus delivery (i.e. current and voltage mode).

(2) Developing a dynamically reconfigurable (and fully programmable) multichannel stimulator as an investigative tool for enhancing stimulation efficacy.

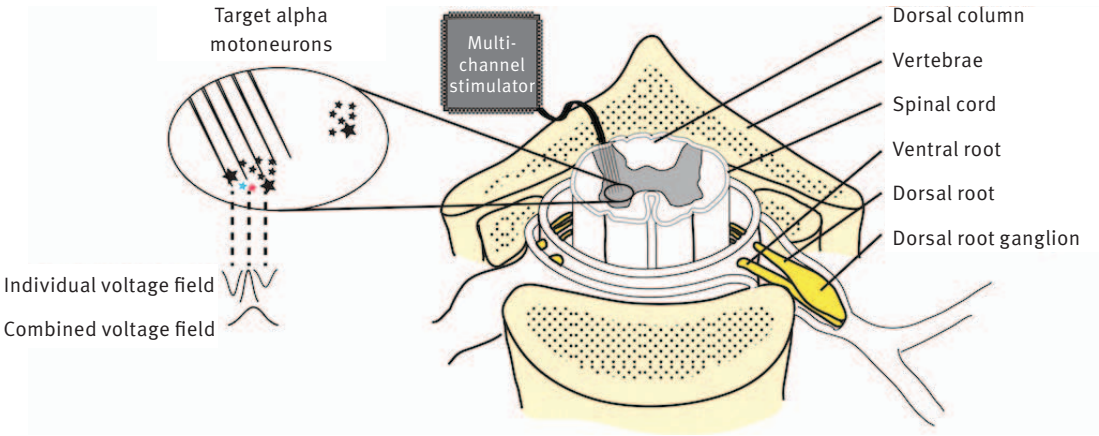
(3) Investigating advanced multipolar stimulation strategies that can confine current spreading thus achieving improved selectivity (spatial resolution).

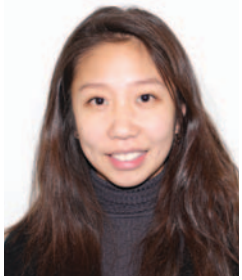
Although I have recently completed my PhD on this topic, this research is very much still ongoing. The circuits and methods I have developed are being further investigated in the Centre, both experimentally and also for application to peripheral nervous system interfaces.

My future work will focus on electronics for extracellular neural recording and combine this with the expertise (in electrical neural stimulation) that I have gained during my PhD.

RECENT PUBLICATION

S Luan, I Williams, K Nikolic, TG Constandinou, "Neuromodulation : present and emerging methods," *Frontiers in Neuroengineering,* vol. 7, no. 27, 2014.





Ms Dora Ma

Research focus
Early detection and monitor progression using DNA methylation based biomarkers for chronic kidney disease

Supervisor
Professor Chris Toumazou

Funding EEE Departmental Scholarship

Chronic kidney disease is the condition used to describe the decline in kidney function over a long period of time. In the UK alone, there are 1.8 million people diagnosed with CKD and a further million is estimated to have the disease but remain undiagnosed. The lack of simple accurate tests and suitable biomarkers has resulted in bad disease management for people suffering from CKD. Over the past 10 years there has been a 63% increase in UK patients requiring renal replacement therapy.

The use of epigenetic markers in diseases is a rapidly growing field. Epigenetics is heritable changes in gene expressions that do not alter the inherent DNA sequence, and are triggered by external factors such as diet and environment. Chronic kidney disease is one of the diseases most affected by lifestyle and therefore subject to many epigenetic changes, namely DNA methylation. DNA methylation is able to affect the number of gene expressions by 'turning on and off' the corresponding sequence. Different gene methylations have been linked to various stages of chronic kidney disease. In particular, it has been shown that high levels of methylation are responsible for distinguishing between a healthy wound repair and scarring of the tissue. The ability to quantify DNA methylation would provide useful information on the type and severity of kidney damage.

MY WORK

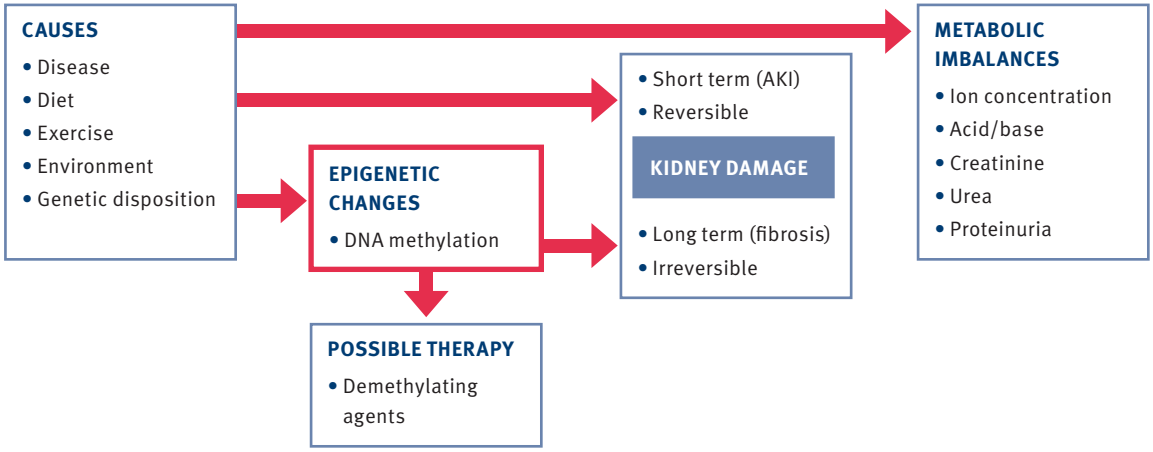
My research aims to develop a Lab-on-chip system to detect and quantify DNA methylation for early diagnosis and monitoring of chronic kidney disease (CKD) progression. Existing methods for chronic kidney disease management rely heavily on the detection of subsequent metabolic imbalances caused by kidney damage. Such techniques suffer from inaccuracy as metabolic markers are also influenced by non-renal related factors. DNA methylation is the mechanism that directly induces permanent kidney damage, thus providing a highly specific and accurate biomarker for CKD management.

Ion sensitive field effect transistors (ISFETs) are used to detect DNA methylations electronically. The adaptation of solid state electrochemical sensor allows for integration of CMOS technology which is fast, cheap, easy to miniaturise and scale. CMOS circuitries also provide the necessary processing power needed to perform quantitative methylation analysis of the target gene.

The ultimate goal is to develop a novel Lab-on-chip technology which uses ISFET sensors to quantify DNA methylation associated with early detection and progression of chronic kidney disease.

KEY REFERENCES

1. L J Smyth, G J McKay, A P Maxwell and A J McKnight, "DNA hypermethylation and DNA hypomethylation is present at different loci in chronic kidney disease.," *Epigenetics*, vol. 9, no. 3, pp. 366–76, Mar. 2014.
2. W Bechtel, S McGoohan, E M Zeisberg, G A Muller, H Kalbacher, D J Salant, C A Muller, R Kalluri, and M Zeisberg, "Methylation determines fibroblast activation and fibrogenesis in the kidney," *Nat Med*, vol. 16, no. 5, pp. 544–550, 2010.
3. T. Sakurait and Y. Husimi, "Real-Time Monitoring of DNA Polymerase Reactions by a Micro ISFET pH Sensor," no. 3, pp. 1996–1997, 1997.



Mr Khalid Mirza

Research focus
The research and development of closed-loop stimulation technology for non-invasive closed-loop obesity management

Supervisors
Professor Chris Toumazou/Dr Amir Eftekhar

Funding EPSRC

The vagus nerve is the longest cranial nerve in the body. It is multifunctional in nature, containing motor and sensory nerve fibers. It has the widest distribution in the body and affects many organs. The nerve fibers in the vagus nerve also transmit responses from the gastric system in a person to the brain. Hence, it plays an important role in controlling the diet of a person. Research suggests that the vagus nerve, regulates the intake of food and can be potentially used to treat obesity.

I am working as part of a multidisciplinary group at the centre aiming to utilize the diet related functionality of the vagus nerve to find a closed-loop solution for obesity management by looking at different methods of Vagus Nerve Stimulation (VNS). Currently, there are two stimulation strategies employed in industry, invasive and non-invasive, which currently aim at providing a cure for epilepsy and depression.

This is because stimulation of the vagus nerve causes release of inhibitory neurotransmitters that reduce the effect of another excitory neurotransmitter glutamate. The first step of my research will be to identify novel methodologies of stimulating the vagus nerve non-invasively that can also have an effect on diet.

An initial system level platform is required to perform validation experiments. In order to close the loop to monitor the effect of VNS, it is also crucial to record the effect of the stimulation using a variety of sensors and low-noise recording system. Currently, a low noise system with less the 1uVrms noise per channel has been developed and is being tested for recording electrical responses and compound action potentials (CAPs) on the vagus nerve using cuff electrodes (electrodes that wrap around the nerve).

REFERENCES

1. El Tahry R, Raedt R, Mollet L, De Herdt V, Wyckuys T, Van Dycke A, & Boon P. (2010). A novel implantable vagus nerve stimulation system (ADNS-300) for combined stimulation and recording of the vagus nerve: pilot trial at Ghent University Hospital. *Epilepsy research*, *92*(2), 231–239.
2. Bugajski A J, Gil K, Ziomber A., Urowski D, Zaraska W, & Thor P J. (2007). Effect of long-term vagal stimulation on food intake. *Journal of physiology and pharmacology*, *58*(1), 5–12.

PUBLICATION

Mirza K B, Luan S, Eftekhar A, & Constandinou T G. (2012, May). Towards a fully-integrated solution for capacitor-based neural stimulation. In*Circuits and Systems (ISCAS), 2012 IEEE International Symposium on* (pp. 2243–2246). IEEE.

Mr Peter Pesl

Research focus
Advanced decision support for diabetes management

Supervisor
Dr Pantelis Georgiou

Funding
Wellcome Trust

OBJECTIVES

For many people with type 1 diabetes (T1DM), achieving optimal glycemic control is a challenge. Insulin bolus calculators have been shown to help diabetics to improve their glucose control but they rely heavily on the tuning of multiple patient specific parameters. Several algorithms to adapt and revise these parameters have been proposed in the literature but have not been implemented in a practical system that reduces the burden for both the diabetic user and the physician. My research focuses on the development of a novel decision support system for personalised insulin therapy which comprises a mobile and user-friendly platform providing real-time insulin bolus advices for people with T1DM and a clinical platform for supervision and revision of bolus calculator tuning parameters.

MY WORK

The decision support system is based on Case-based Reasoning (CBR) as a learning methodology which uses past experience to solve newly encountered problems, whereas problems, solutions and the outcome of solutions are described by cases. While a fully automated system which adapts bolus calculator parameters in real-time might not be accepted by both patients and physicians for safety reasons, we propose a system which separates the functions of CBR into a patient advisory and a clinical supervision platform. The patient platform responsible for providing real-time bolus advices has been implemented into a smart-phone with user-friendly graphical interface based on feedback from a focus group meeting with people with T1DM. The clinical platform, running on a desktop computer, imports data from the patient platform and from a continuous glucose monitor, and is used to monitor and accept adaptations of bolus calculator parameters proposed by a revision algorithm.

RESULTS

A novel decision support platform has been developed which provides enhanced adaptability and flexibility to current bolus calculators for diabetics and an enhanced clinical platform for safety and supervision. In simulations [1] the novel bolus advisor algorithm based on CBR demonstrates improvements by increasing the time of blood glucose levels within target range. The algorithm is now integrated in the patient platform and runs on a smartphone, which enables diabetics to use their own phones for personalised insulin recommendations. At the moment both the patient and the clinical platform are used in clinical trials in order to evaluate their usability and efficacy.

PUBLICATION

Pau Herrero, Peter Pesl, Monika Reddy, Nick Oliver, P Georgiou, and C Toumazou. Advanced insulin bolus advisor based on run-to-run control and case-based reasoning. *IEEE Journal of Biomedical and Health Informatics*, ahead of print, 2014.

Mr Mohammadreza Sohbati

Research focus
Circuits and systems for pH-based DNA detection

Supervisor
Regius Professor Christofer Toumazou

Funding
Winston Wong Centre for Bio-inspired Technology and DNA Electronics

Molecular biology has been remarkably redirecting life sciences by allowing the studying of cellular functions at a molecular level. Understanding the genetic codes and mutations is reshaping the approach to disorders and malfunctions, from diagnostics to prognostics and early detection. However, applying its significant achievements at the point of need and achieving a role to shape human lifestyle requires the companionship of instruments that can accelerate both its progress in the labs and its ease of use. Timliness, accuracy, throughput, and cost are vital in merit of such means. The advent of ion-sensitive transistors has made the semiconductor microchips an exceptional platform in this industry.

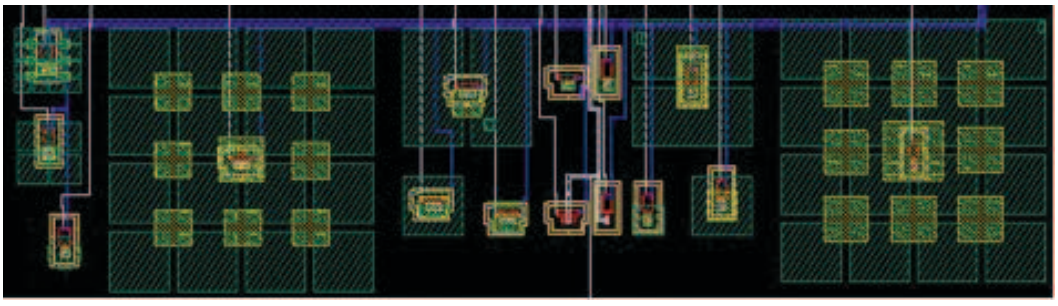
MY WORK

In my research, I have been working on potential methods to enhance the performance and utilisation of ion-sensitive field-effect transistors (ISFETs) in pH-based DNA detection set-ups. In such instruments, scaling for running more tests in parallel affects the signal-to-noise ratio, and consequently the accuracy and throughput. From one side it is the chemistry and kinetics of the reactions, and from another side it is the ISFET geometry and interface circuitry that influence the performance. On the other hand, common background noise in the system and temperature dependency of sensitivity add uncertainty in measurements.

Towards this goal, considerable effort has been dedicated to the ISFET geometry and shape for optimum efficiency, design methodology for suppressing the fabrication non-idealities, and implementation techniques for enhancing its performance. Moreover, novel readout circuits for eliminating the temperature effects, reducing the background noise, and simplifying the readouts for large-scale integration have been developed.

PUBLICATIONS

1. M Sohbati, Y Liu, P Georgiou and C Toumazou, ”An ISFET Design Methodology Incorporating CMOS Passivation,” *Biomedical Circuits and Systems Conference (BioCAS)*, 2012 IEEE
2. M Sohbati, P Georgiou and C Toumazou, “REFET Replication for ISFET-based SNP Detection Arrays,” *International Symposium on Circuits and Systems Conference (ISCAS)*, 2013 IEEE
3. M Sohbati, P Georgiou and C Toumazou, “A Piecewise Linear Approximating ISFET Readout,” *Biomedical Circuits and Systems Conference (BioCAS)*, 2013 IEEE
4. M Sohbati and C Toumazou, “A Temperature Insensitive Continuous Time ΔpH to Digital Converter,” *International Symposium on Circuits and Systems Conference (ISCAS)*, 2014 IEEE
5. M Sohbati and C Toumazou, “Personalised Microchips for Healthcare”, *IEEE Potentials*, 2014



Miss Francesca Troiani

Research focus
Optical neural recording for large scale activity monitoring

Supervisors
Dr Timothy Constandinou and Dr Konstantin Nikolic

Funding
EPSRC DTA and EEE Departmental Scholarship

To better understand how the brain works it is essential to record and analyse its activity. Since Luigi Galvani, in 1791, discovered the existence of a link between electrical activity and the nervous system, electrophysiology has become an extremely important and powerful method to record neural activity, since it is a technique with a very high signal-to-noise ratio (SNR). However, electrophysiology has at least two main challenges:

- This requires the electrode to actually touch the tissue, i.e. it is an invasive technique, and
- This cannot target single neurons, but only detects signal from a cluster of cells.

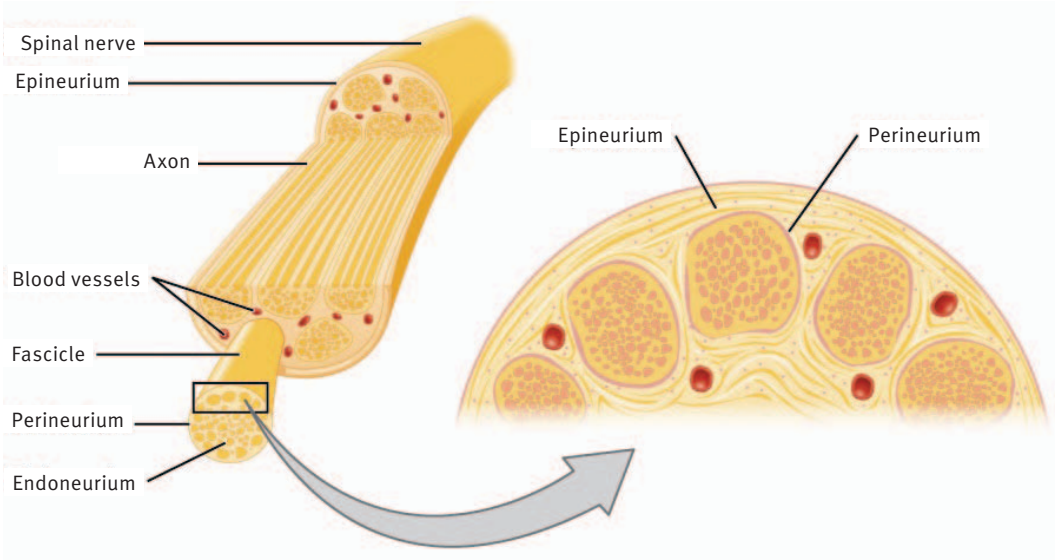
In the late '60s the optical properties of neurons were investigated, and it was discovered that some of them change during neuronal activity. These properties can be divided in two categories: intrinsic (i.e. the ones regarding refractive index and retardation) and extrinsic (i.e. the ones regarding absorption or fluorescence of the stained axons). Since this discovery big efforts have been made to try to detect neural activity using light instead of electricity.

MY WORK

During my PhD I will focus on the changes in the intrinsic optical properties of the neurons during action potentials. After having obtained the samples, I will use a stimulating electrode to obtain the action potential, a laser light source to light the sample and record the optical changes and a recording electrode to be able to study the correlations between the optical and electrical activities.

KEY REFERENCES

1. L B Cohen, "Changes in neuron structure during action potential propagation and synaptic transmission", *Physiological Reviews*, vol. 53, no. 2, 373–418, 1973.
2. M Scanziani, M Häusser, "Electrophysiology in the age of light", *Nature*, vol 461, no. 7266, pp. 930–939, 2009.



Physiology. OpenStax CNX. Jul 30, 2014 http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@6.27

Dr Ian Williams

Research focus
A neural-electronic interface providing proprioceptive feedback for prosthesis control

Supervisor
Dr Timothy Constandinou

Funding
EPSRC DTA

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 lack this proprioceptive feedback and as such struggle to learn to control their artificial limbs and are unlikely to achieve high levels of coordination.

OBJECTIVES

This research will investigate neural stimulation as a method of providing artificial proprioceptive feedback from a prosthetic limb. Our approach makes use of a peripheral neural implant for stimulation and will focus on providing the user with intuitively understood information. As such the research will look at creating neural signals that mimic those naturally found in the body.

MY WORK

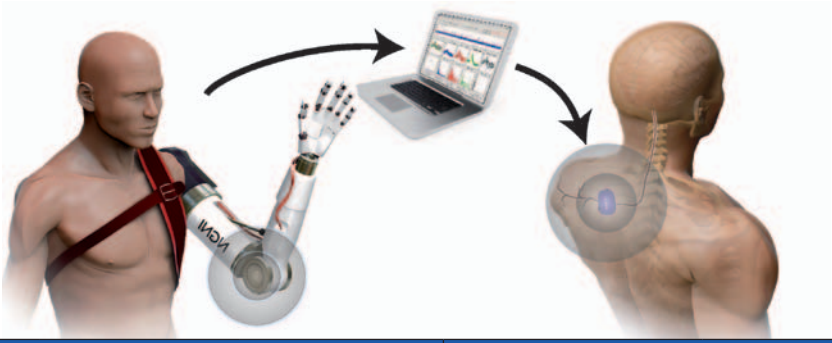
Sensors fitted to a robotic arm measure the joint angles and torques during its motion. The movement and pose of the robotic arm is mapped to a biomechanical model of a human arm and this provides estimates of equivalent muscle lengths and muscle activations in a 17 muscle, 7 degree of freedom model of the human arm. This muscle activation and strain information is then fed into models of 2 key proprioceptive receptors (muscle spindles and Golgi Tendon Organs) producing estimates of the neural signals from these receptors. Finally these neural signals are induced in the user using a low power neural implant that has been developed to safely stimulate the appropriate peripheral nerves.

The neural stimulator has successfully been tested on a frog peripheral nerve and demonstrates good charge balancing and a significant reduction in power consumption. A combined biomechanical and proprioceptive model in C has been developed and tested – results indicate a good match with existing models combined with an orders of magnitude improvement in computational efficiency, as such the model is expected to be suitable for real time operation on a microprocessor.

I am currently assembling collaborative team to deliver a prototype sensory prosthesis with a highly selective neural stimulator. Neural recording will be integrated to improve safety, enable experimentation and to look at the potential for prosthetic limb control using neural rather than muscular signals.

RECENT PUBLICATIONS

1. I Williams, T G Constandinou. "Computationally Efficient Modelling of Proprioceptive Signals in the Upper Limb for Prostheses: a Simulation Study". *Frontiers in Neuroscience*, vol. 8, pp. 181–, 2014.
2. S Luan, I Williams, T G Constandinou, K Nikolic. "Neuromodulation: present and emerging methods". *Frontiers in Neuroengineering*, vol. 7, pp. 27–, 2014.
3. I Williams, T G Constandinou, "An energy-efficient, dynamic voltage scaling neural stimulator for a proprioceptive prosthesis". *IEEE Transactions on Biomedical Circuits and Systems*, vol. 7, 2013.



OUTSIDE BODY			INSIDE BODY	
SENSORS	PROCESSING		PERIPHERAL NERVOUS SYSTEM NEURAL STIMULATOR	
Torque sensor	Muscle activation estimation	GTO signal estimation	Current controlled neural stimulator	Microelectrodes
Angle sensor	Muscle length estimation	Muscle spindle signal estimation		

Mr Stephen Woods

Research focus
Wireless capsule endoscope for targeted drug delivery

Supervisor
Dr Timothy Constandinou

Endoscopes are used routinely by gastroenterologists to diagnose and treat pathologies such as Crohn's disease in the gastrointestinal (GI) tract. However the small intestines pose a problem for these conventional methods as the small intestines are very difficult to access. One method employed to overcome this problem is the use of wireless capsule endoscopes (WCE). These pill-sized cameras take pictures of the intestinal wall which are then used to diagnose pathologies. The problem with this method is that it does not offer the ability to administer therapy to an affected area.

OBJECTIVES

The aim of my research is to design a swallowable microrobot, which is capable of diagnosis and delivering targeted therapy to pathologies of the GI tract, specifically in the small intestine.

MY WORK

I am developing a swallowable microrobotic platform, which has novel functionality that will enable a WCE to deliver targeted therapy. The platform will consist of three highly novel sub-systems: one is a micro-positioning mechanism which can deliver 1 ml of targeted medication through a needle, the second is a holding mechanism which gives the functionality of resisting natural movement from peristalsis and also offers the ability to slow the transit of the microrobot and the third is a system to control the release of the onboard medication.

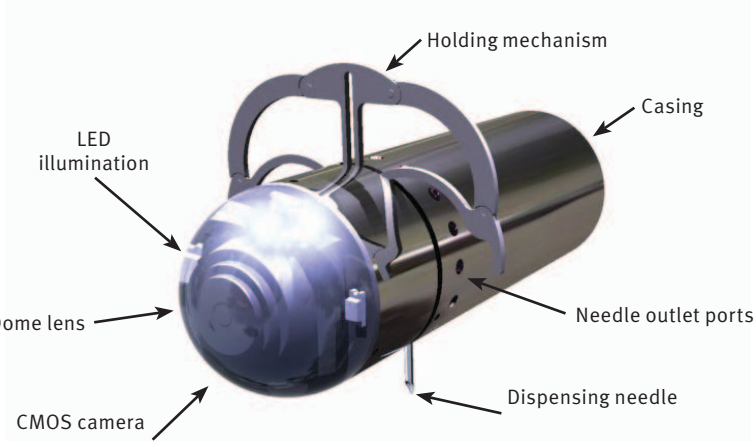
The work I have carried out so far has been the detailed design and analysis of the micro-positioning mechanism and the holding mechanism. A number of manufacturing methods have been explored to produce working prototypes of the micro-mechanical systems. A concept design for the control and release of the onboard medication has also been developed.

Proof of concept prototypes have been produced for the micro-positioning mechanism and the holding mechanism. Figure 1 shows a 3D CAD model of the proposed design. The geometry of the microrobot is based on conventional wireless pill-sized cameras.

The next phase is to develop a 5x scale prototype of the holding mechanism and targeting mechanism. Once the systems have been validated through initial manual testing a specific user interface will be developed which will control the position and deployment of the holding mechanism and also the operation of the dispensing needle.

RECENT PUBLICATIONS

1. S P Woods, T G Constandinou, "Wireless Capsule Endoscope for Targeted Drug Delivery: Mechanics and Design Considerations", *IEEE Transactions on Biomedical Engineering*, vol. 60, no. 4, pp. 945–953, 2013
2. S P Woods, T G 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 (EMBC)*, pp. 7372–7375, 2011



A concept design showing the holding mechanism fully deployed and the dispensing needle deployed diametrically opposite the holding mechanism

Mr Satoshi Yoshizaki

Research focus
Thermal micro-stimulation of excitable cells

Supervisor
Dr Timothy Constandinou

Funding
Wellcome Trust Networks of Excellence

With our quest to understand biological systems, new technologies are being developed to decode genetics, monitor cellular signalling, and interface with the nervous system.

Lab-on-chip (LOC) devices aim to integrate multiple sense and actuation functions on the microscale. Advanced CMOS (microelectronic) technologies are now being applied to develop active large scale LOC devices for variety of fields including genomics, neuroscience, and the biosciences in general. Such technology can allow for the monitoring of biochemical and physical activity at the cellular scale.

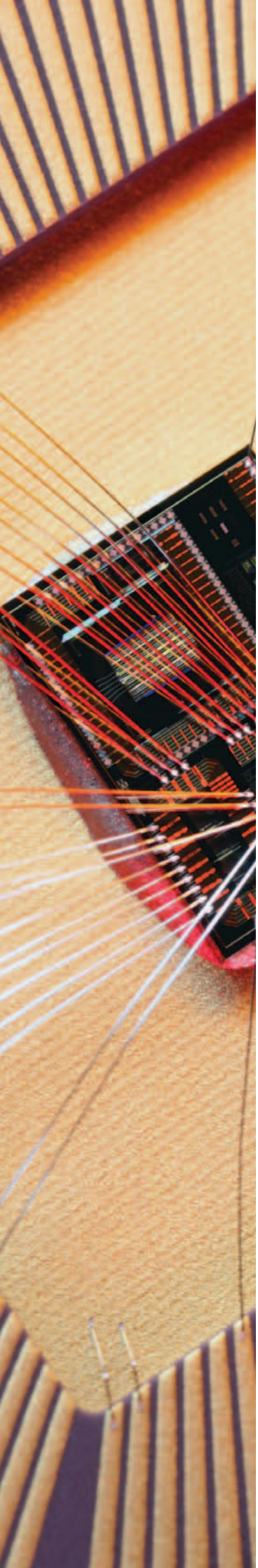
MY WORK

I am currently developing a platform to facilitate in-vitro experiments using a CMOS LOC micro-heater array. The tool is aimed at investigating the thermal stimulation of single, electrically-excitable cells (e.g. neurons) by enabling the precise thermal control of individual cells whilst also monitoring their electrical activity. Specifically, we intend to characterise their thermal properties and explore the feasibility of using rapid thermal control to stimulate or inhibit activity.

A 2-dimensional array has been developed in a 0.18 micron CMOS technology provided by IBM with a 50 micron pitch for fine spatiotemporal control. The complete system platform includes this chip on a removable cartridge, a supporting instrumentation and control PCB and a computer interface with appropriate software. This PC software will include a graphical user interface for monitoring the electrical activity and controlling the thermal dynamics of the array. It is intended this be operated to provide real-time control and feedback.

RECENT PUBLICATIONS

1. F Reverter, T Prodromakis, Y Liu, P Georgiou, K Nikolic, TG Constandinou, “Design considerations for a CMOS Lab-on-Chip microheater array to facilitate the in vitro thermal stimulation of neurons”, in *Proc. IEEE International Symposium on Circuits and Systems (ISCAS)*, pp. 630–633, 2014.
2. S Yoshizaki, A Serb, Y Liu, T G Constandinou, “Octagonal CMOS image sensor with strobed RGB LED illumination for wireless capsule endoscopy”, in *Proc. IEEE International Symposium on Circuits and Systems (ISCAS)*



Research opportunities

We are always seeking talented and highly motivated researchers to join the Centre from a wide range of disciplines in engineering and science. For example, our current researchers span across the following disciplines: electronic engineering, biomedical engineering, mechanical engineering, biology, physics, chemistry, neuroscience, and medicine. Typically, there are opportunities available at several levels, from graduate and exchange students to postdoctoral and senior researchers.

RESEARCH STAFF

This includes research assistants (graduate), research associates (postdoctoral), research fellows (senior postdoctoral). Any currently available opportunities are advertised via the Imperial College employment pages: **www.imperial.ac.uk/employment** (search for: 'Centre for Bio-Inspired Technology'). To enquire about currently-available research positions, please contact the appropriate academic staff member.

VISITING RESEARCHERS

We welcome faculty from other academic/research institutions and industry seeking mutually beneficial research collaboration. We can host sabbaticals, visiting researchers and industry secondments.

RESEARCH STUDENTS (PHD)

We are always receptive to talented and motivated individuals with an engineering/scientific background and a strong interest in medical devices. To be accepted for a PhD, we normally require a 1st class MEng degree (or BEng + MSc with distinction). Funding opportunities are available for UK, EU and overseas students. If you are interested in pursuing a PhD, you should at first instance contact the academic staff member working in your area of interest.

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Neural Interfaces and Prosthetics
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Metabolic and Lab-on-Chip technology
Dr Pantelis Georgiou
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Those wishing to apply for a postgraduate research position will need to complete an online application form. For positions at the Centre for Bio-Inspired Technology, please make your application via the Department of Electrical & Electronic Engineering stating on your application the desired research area and supervisor.

UNDERGRADUATE STUDENTS.

We regularly supervise biomedical electronics/ medical devices/healthcare technology-related research projects for undergraduate (BEng/MEng) final year students, postgraduate (MSc) thesis students and host exchange/erasmus students from other institutions. Any students interested in doing a project in the Centre should contact the relevant staff member. For undergraduate students looking for summer placements, we normally advertise these via the Undergraduate Research Opportunities Programme (UROP) – details at: **www.imperial.ac.uk/urop**

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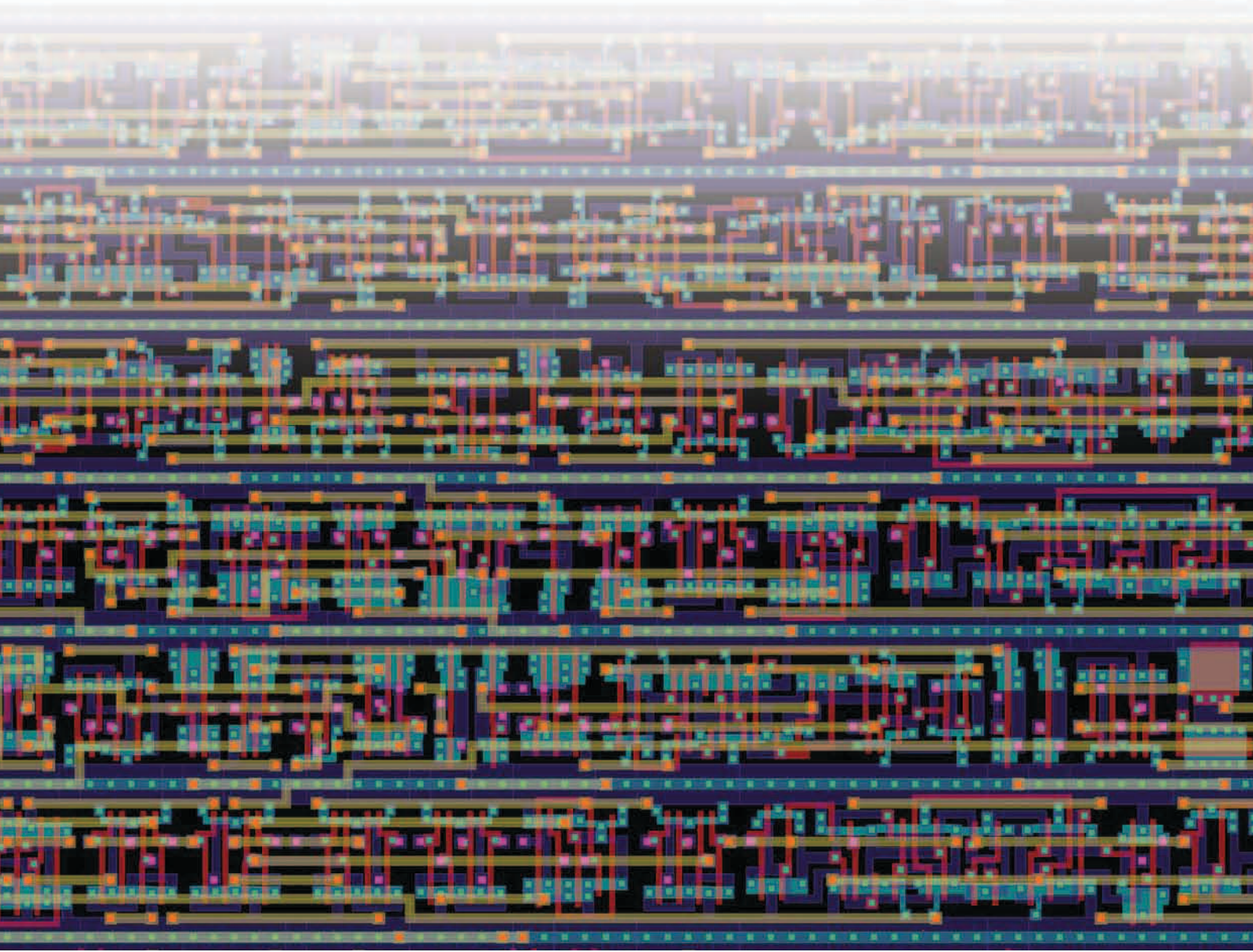

Imperial College London

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