4MD
Multi-Modal Manufacturing of Medical Devices

UKRI
Engineering and Physical Sciences Research Council

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A PLATFORM FOR **SUCCESS** FINAL REPORT

JULY 2017-MARCH 2023

HERIOT WATT UNIVERSITY

4MD delivered high quality and internationally leading research which supports medical device manufacturing.

MULTI-MODAL MANUFACTURING OF MEDICAL DEVICES

4MD worked to develop and translate cutting edge manufacturing capabilities in order to enhance their fabrication, function and uptake of innovative medical devices in modern clinical practice.

Our multidisciplinary team enabled research focused on the intelligent combination of precision modification; additive and subtractive manufacturing techniques across a wide range of materials; tolerances; and dimensions and complexity to address challenges in the manufacture of medical devices, driven by clinical need for efficient and cost-effective solution.

A PLATFORM FOR SUCCESS

CONTENTS

Josh Gammie and Femi Johnson explaining development of ProstaPalp(R) cancer-screening device to Gordon Ford of Innovate UK

REPORT ON ACTIVITIES

INTRODUCTION

The overarching objective of the 4MD Platform was to develop and exploit manufacturing technologies to provide medical device manufacture that is both practical and commercially viable, and hence to enable new and improved healthcare solutions.

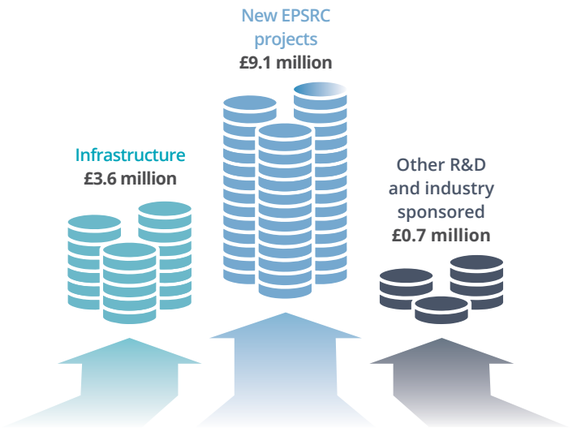
This was achieved by flexibly resourcing our multidisciplinary team to enable a research programme focused on the intelligent combination of precision additive and subtractive manufacturing techniques for the manufacture of novel medical devices.

Subsidiary objectives were to:

- Provide flexible customisation of medical devices tailored to address specific requirements and modalities.
- Drive the impact of our research and to enhance the success of future research bids (e.g., to EPSRC, industry, Innovate) by providing critical proof-of-principle studies.
- Build on our current collaborator base to develop additional research partnerships with both clinicians and relevant industry.
- Provide career development opportunities for our experienced PDRAs for future roles in academia and industry.

Over the period of the grant, the area of medical device manufacture, allied with related research in biomedical and healthcare engineering, has grown to become of strategic importance in the University, forming the focus of its third strategic theme (along with Robotics and Energy).

Highlights of new research and impact totalling £13.4 million directly attributable to the Platform include:



£1.3M ALLOCATED TO 4MD PROJECTS

- Total follow-on funding raised by PIs on the pilot projects of ca. £11.3M, a gearing of a factor of around 10 with many projects yet to develop to a stage where an application can be made.
- Two significant successes (ca. £1.2M each) in EPSRC Healthcare Impact Partnerships
- A major grant (£6.1M) led by HWU to investigate deep ultraviolet light therapies (pages 10/11)
- Establishment of the £3.6M Medical Device Manufacturing Centre at Heriot-Watt, involving 4 Scottish universities, funded by the Advanced Manufacturing Challenge Fund (AMCF) and the Edinburgh City Deal, to enable small and medium sized companies to undertake first-in-patient studies
- The winning of a Royal Academy of Engineering Enterprise Fellowship and around £200k of follow-on funding for a University spin-out company

Growing our research base

The original named **7 academic staff formed a Management Group**, which met approximately monthly, and the collaborators (along with the Management Group) formed an advisory group, which met approximately once every six months. The named RAs had rolling membership of the Management Group. The Management Group was charged with raising and reviewing proposals for new projects which were then ratified by the Advisory Group. Three workshops were held; one specifically to widen the clinical participation and two aimed directly at introducing new members of academic staff to the area.

7
Management Group

20
Final Investigators

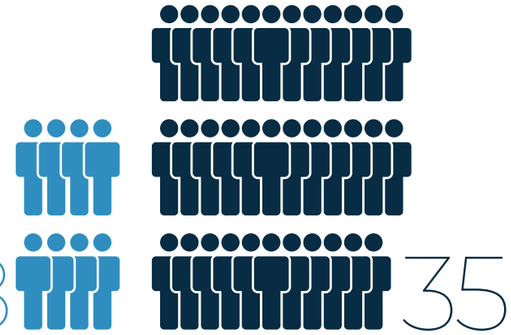
In all, the Platform has funded 19 projects in 3 categories

- **INVESTIGATOR-LED**
  Typically of duration 9 person-months of RA time, led by one of the original investigators
- **SEEDCORN**
  Typically of 6 months duration, led by one of the associated RAs
- **NEW-ACADEMIC**
  Typically of around 4 person-months of RA time (although some were extended for a second period), open to academic staff from outside the investigator group

Growing our networks

The distribution of the projects is: 7 investigator-led, 6 seedcorn and 6 new academic (including 2 led by Carter who transitioned from RA to academic staff during the funded period)

The collaborative network has grown over the period of the grant. The original 7 **investigators have been complemented by 10 new members of academic staff**. 1 new member joined the Advisory Group, and **23 new clinical collaborators and 4 new industrial collaborators** have been involved in 4MD projects.



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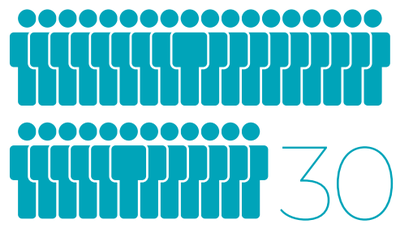
Advisory Group

35
Final list of collaborators

Developing careers



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Final number of researchers engaged in 4MD projects

Of the 8 originally named RAs,

- one (Carter) has become a member of academic staff at Heriot-Watt winning two significant EPSRC manufacturing projects in 2019 and being promoted in 2020,
- one (Cummins) has become a member of academic staff at Birmingham university,
- two (Beck and Pavuluri) are running seedcorn projects and are associated with further EPSRC funding,
- one (Gora) has moved to a permanent role with one of the industrial collaborators (Renishaw), one (Wlodarczyk) is an optical design engineer at Intel Corporation in the laser-based manufacturing group at Heriot-Watt,
- one (Choudhury) is a research and development engineer at Optoscribe
- one (Hammer) has moved to a teaching-based role at Heriot-Watt University

In addition, 19 new RAs have received exposure to relevant research, many of them going onto other RA roles.

GROWTH OF COLLABORATIVE NETWORK, PER PROJECT

THOSE NEWLY INVOLVED HIGHLIGHTED AT FIRST MENTION

Project	Investigators	Partners	RA(s) and assoc. PhDs
GENERIC MANUFACTURING TECHNOLOGIES			
Laser PBF Process Fundamentals	Moore, Thomson, Shephard	**Jones**, Weston (Renishaw), Dhaliwal, **McCafferty** (QMRI)	**Bitharas**
"Laser manufacturing distal-end microsystems for fibre-optic medical instruments"	Thomson, Hand, Shephard, **MacPherson**	Renishaw, UoE, UoBath	**Ross**, **Benoit**
ViTAlink - Custom Ti6Al4V structures with 3D multiscale controlled porosity	Reuben, Chen, **White**, **Wolfram**	**Bhattia**, **Walls** (EPGDI), **Mehendale** (UoE, NHSL), **Williamson** (IMET Alloys)	**Majidi**
ENHANCING EFFECTIVENESS OF MEDICAL PROCEDURES			
Safe Target (Epidural anaesthesia)	Desmulliez, Hand	Denison (QMRI), McLeod (Dundee SoM)	**Pavuluri**
Endoscopically deployable optics for picosecond laser surgery	Shephard, Thomson	Jayne, **West** (Leeds)	Beck, **Risbridger**
Ultrashort pulsed laser resection for brain cancer treatment	Beck (seedcorn), Bitharas, Moore, Shephard	**Mathew**, Jayne (Leeds)	
A Platform for Electrical, Optical and Mechanical Sensing (POEMS)	**Crichton**, Desmulliez, Hand, **Marques-Hueso**	**Elliot** (NHSL)	**Dzipalski**, **Gamal**
Pressure Resolution by Optical Sensing Enhancement (PROSE)	Crichton, Hand, Marques-Hueso	McLeod (Dundee)	Dzipalski, **Jomaa**, **Turnbull**
Post-transplant Drug Dosage Detection – (Tacrolimus)	**Carter**, MacPherson	**Knight** (UoE/NHSL), **Clancy** (UoG/NHSGG&C), **Vendrell** (UoE)	Dzipalski
TACROSENSE (Post-transplant Drug Dosage Detection)	Carter, MacPherson, **Kersaudy-Kerhaus**	Knight (UoE/NHSL), Clancy (UoG/NHSGG&C), Vendrell (UoE)	**Chandrasekharan**, **Haque**
REHAB-SENSE (Novel metrics for rehabilitation)	Desmulliez	Knight, **Lyons**, **Harrison** (UoE/NHSL)	Pavuluri, **Rodriguez**
RF-COVID (Microwave Induced Inactivation of SARS-CoV-2)	Pavuluri (seedcorn), Desmulliez	**Haas**, **Griffiths** (UoE, EMS)	

new clinical collaborators new industrial collaborators new academic staff new RAs

Project	Investigators	Partners	RA(s) and assoc. PhDs
MEDICAL DEVICES			
DynoClaw: A dynamic palpation device with two points of tissue contact	Reuben, Hand, **Chen**	McNeill, **Paterson**, **Noble** (WGH)	**Balmer**, Gora
Fibre optic probes for endoscopic measurement of uterine hypoxia	**Tanner new acad**	**Maybin** (QMRI)	**Ehrlich**, **Green**
Wearable piezoresistive fibre sensors for mobility and gait analysis of people with lipoedema	**Amjadi (new academic)**, Chen, **Macintyre**	**Williams** (QMU)	**Siwicki**, **Anderson**
PressureCap, a novel ingestible motility capsule (IMC)	Pavuluri (seedcorn), Desmulliez	**Potter** (WGH), **Clutton** (UoE, RSVS), **Mitrakos** (Touchlab)	
Surgical margin delineation probe: Towards in-vivo mid-infrared ATR spectroscopy	**Ehrlich (seedcorn)**, **Reid**, **Ross**, **Castro**	Dhaliwal, **Nixon** (QMRI)	
Electromagnetic actuators for anterior magnetic stimulation of human body	**Purushothama (seedcorn)**, **Ding**	**Pemberton** (Stimulate Medical)	
TRANSLATION INTO CLINICAL SETTINGS			
ProstaPalp	**Johnson (seedcorn)**, Reuben, Hand, Chen, Gora, **Novo**	McNeill, **Good**, **Davie** (NHSL)	

new clinical collaborators new industrial collaborators new academic staff new RAs

GENERIC MANUFACTURING TECHNOLOGIES

LASER PBF PROCESS FUNDAMENTALS

Project Type
Investigator-led

PI
Moore

Co-Is
Thomson, Shephard

Partners
Jones, Weston (Renishaw), Dhaliwal, McCafferty (QMRI)

Researcher
Bitharas

Aim

Laser powder bed fusion (PBF) is an additive manufacture (or 3D printing) process that can make complex components from metal powder. The primary aim of this project was to generate fundamental understanding of the PBF process for materials used in healthcare applications.

Outcomes

- New understanding of the effect of crossflow of inert gas on the laser PBF process, including the range of stochastic collisions between powder particles and refractive index gradients produced by the vapour jet ejected from the melt pool, which can both affect the build consistency negatively;
- First simultaneous in-situ synchrotron x-ray and schlieren imaging of the laser PBF process, demonstrating that the melt pool stability can be inferred from a previously unreported threshold in the input energy density, measured from instabilities in the laser plume produced by the vapour jet.

The improved process understanding will enable laser PBF to manufacture new medical devices and implants and can of course be applied to improve existing devices. Renishaw have submitted a patent based on these key outputs.

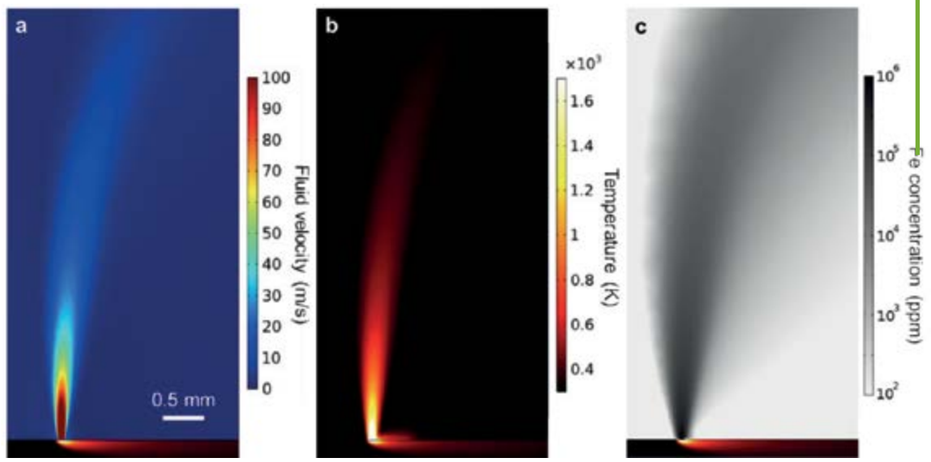


Figure: (a) Calculated velocity, (b) temperature and (c) metal concentration of the vapour jet ejected from the melt pool in laser PBF. It is unaffected by the cross-flow close to the laser-material interaction area.

Associated funding

£234,737 Renishaw, 2019–2021, "Renishaw support for open-architecture PBF research", Principal investigator: A.J. Moore

£197,721 Renishaw, "Research to support PBF process improvements for LAMBDA", 2021–2022, Principal investigator: A.J. Moore

LASER MANUFACTURING DISTAL-END-MICROSYSTEMS FOR FIBRE-OPTIC MEDICAL INSTRUMENTS

Project Type
Investigator-led

PI
Thomson

Co-Is
Hand, Shephard, MacPherson, RCo-I Calum Ross

Partners
Renishaw, Edinburgh University, University of Bath

Researcher
Benoit

Aim

To investigate the feasibility of using advanced laser manufacturing techniques, primarily ultrafast laser modification in combination with selective chemical etching, to develop novel distal end microsystems for minimally invasive medical devices.

Outcomes

- Through this project, we have developed new micro-optic systems for applications in minimally invasive precision microsurgery using ultrafast laser pulses delivered by hollow core fibres developed by the U. of Bath, and new microsystems that allow selective plane illumination when imaging using low-cost polymer imaging fibres currently being tested at the University of Edinburgh College of Medicine and Veterinary Medicine.
- A major manufacturing advance we have made is in the development of beam shaping techniques that enable control of the shape of the focal volume, and therefore more efficient use of the available laser pulse energy, see Fig. 1. This reduces fabrication times by nearly two orders of magnitude, overcoming a major drawback of using ultrafast laser inscription for manufacturing distal-end-microsystems for fibre-optic medical instruments.

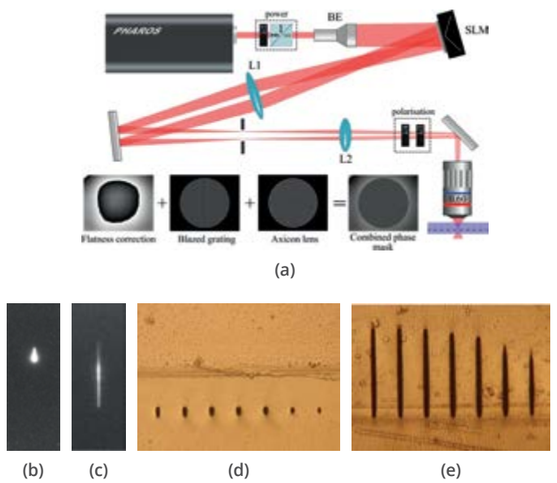


Figure 1: Schematic of the laser fabrication system which was developed to incorporate a spatial light modulator (SLM) for controlling the phase profile of the ultrafast laser beam. (b) and (c) are micrographs of partial free electron plasma emission from the focal region inside fused silica under irradiation for a Gaussian and vortex focus respectively. (d) and (e) are micrographs showing sets of channel cross-sections written with increasing translation speeds for Gaussian and vortex foci.

- Through this project, we are also in the process of developing new ways to polish surfaces that are created using ultrafast laser assisted etching. One approach we are in the process of developing is the use of CO_2 laser polishing to achieve ultra-smooth micro-optic surfaces for imaging and sensing (e.g., Figure 2).

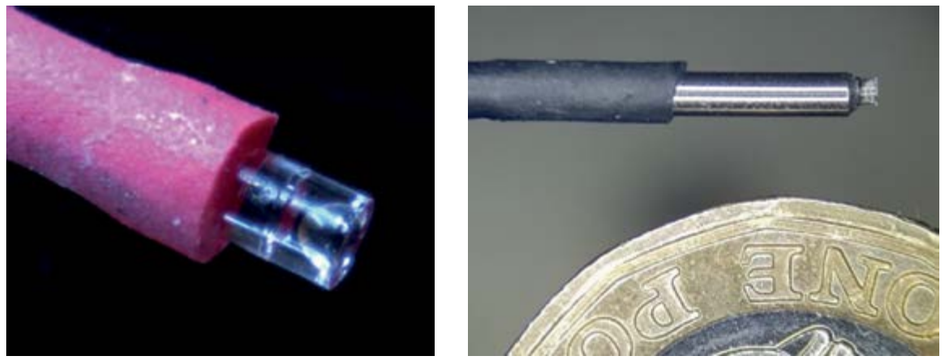


Figure 2: (Left) Microscope image of the ultrafast laser fabricated Raman-based optical biopsy end-probe. (Right) Photograph of assembled Raman probe next to coin for scale.

Associated projects

"A fluorescence guided steerable laser tool for precision resection of early-stage cancers" EPSRC EP/N02494X/1 £0.6M

"U-care: Deep ultraviolet light therapies" EPSRC £6.1M EP/T020903/1

VITALINK: CUSTOM TI6AL4V STRUCTURES WITH 3D MULTISCALE CONTROLLED POROSITY

Project Type
Investigator-led

PI
Reuben

Co-Is
Chen, White, Wolfram

Partners
Krish Bhattia, Angus Walls, Felicity Mehendale (UoE/EDH)

Researcher
Majidi

Aim

This project involved the building of structurally efficient assemblies of Ti6Al4V with controlled porosity, but the method is generic and plays into a circular economy / building back greener agenda of re-use of high value alloys which are highly energy intensive to manufacture as raw materials.

There are a number of critical biomedical applications ranging from cranial plates, spinal fusion (and other bone compatible prostheses) to leave-in-place scaffolds where control of the modulus of implanted metal is vital to avoid localized bone growth to compensate for stiffness discontinuities.

The work was a feasibility study based on a demonstrator with porosity controlled from 1 mm to 200 µm pore size with densities from 100% to 20%. We built structures onto Ti cantilevers of overall size in the order of 1 cm^3 and determined the effective modulus (Figure 1) using an established model for composite beams.

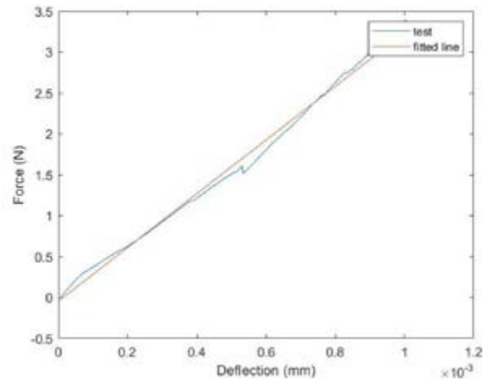


Figure 1: Example cantilever bend test for 3-layer sinter built onto titanium foil substrate.

The key manufacturing challenge was to devise a generic method of preparing and consolidating the bed to produce a predetermined distribution of porosity in 3 dimensions. The method is a variation on the SLS approach but with layers of the bed being initially packed with controlled local distributions of particles and with the minimum heat input into the bed to achieve the surface migration of material characteristic of pre-melting sintering. Within the project, we have sintered in place up to 3 layers of particles onto the substrate (Figure 2).

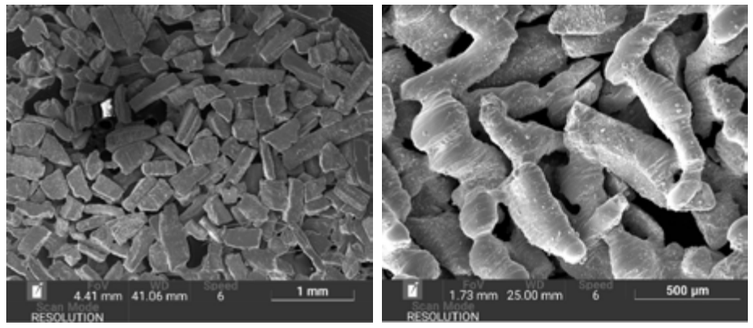


Figure 2: Single-layer particle bed before (left) and after (right) sintering.

To determine the porosity and contiguity we have used serial section along with includes 3D µCT imaging of the final product so that structure and function can be related to the manufacturing processes.

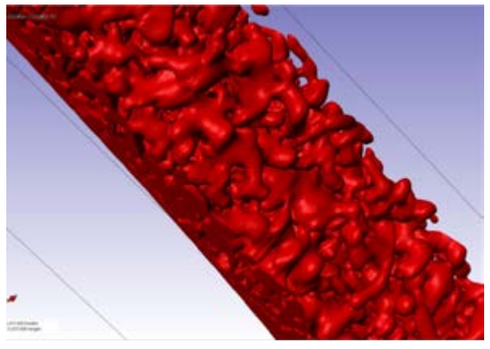


Figure 3: Reconstruction of 3D µCT image of 3-lyer structure. (Reconstruction by Calum Anderson, PhD student in Biomedical Engineering).

Outcomes

The **final output** was:

- An approach for optimal design of Ti6Al4V controlled porosity structures of high structural integrity
- A method for manufacture of such structures without wholescale melting and without pressure

Follow on funding

Some further feasibility research is required which, if successful, IMET Alloys / R2P Powders will seek funding to develop a pilot-scale process for high value-added recycled alloys. Funding for this will probably be through one of the Innovate UK Schemes for which the University would be research provider.

If feasible, the demonstration will lead to one or more major research proposals. The fabrication of controlled porosity structures for medical applications is one potential area, which could be used as tissue engineering scaffolds such as those for the bone-tendon interface (gradient porosity and pore size are required – this is being investigated by Chen and his Medical Research Scotland project in collaboration with UoE) and patient-specific design of surface-textured spine implants. The other potential application could be the combination of the technology with the ability of lasers to 'weld' highly dissimilar materials such as glasses and metal. Here patient-specific partial arthroplasties are of interest which require gradient porosity and pore sizes for a bone surrogate connected to cartilage surrogate akin to an endplate. Finally, the recycling and re-use of high-value titanium alloys is of high generic interest.

Associated projects

KTP Partnership Number: KTP010710 £309,477.26 (Reuben, White, IMET Alloys)

KTP Partnership Number: KTP012449 £242,379.32 (White, Reuben, IMET Alloys)

EP/P005756/1 Identifying the Irreversible Mechanical Behaviour of Individual Mineralised Collagen Fibril Assemblies 95,775 (Wolfram)

EP/N006089/1 Design Optimisation of Tissue Scaffolds Using Patient-specific and In Vivo Criteria 99,733 (Chen)

EP/K036939/1 A Novel Diagnostic Tool: from Structural Health Monitoring to Tissue Quality Prediction 1,024,165 (Chen, with University of Liverpool and University of Edinburgh)

ENHANCING EFFECTIVENESS OF MEDICAL PROCEDURES

SAFE TARGET (EPIDURAL ANAESTHESIA)

Project Type
Investigator-led

PI
Desmulliez

Co-I
Hand

Partners
McLeod (School of Medicine, Dundee University), Denison (QMRI)

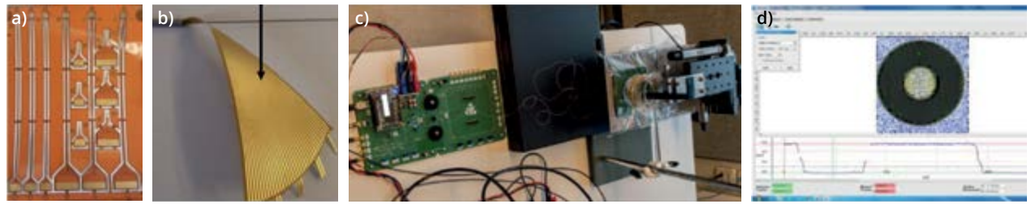
Researcher
Pavuluri

Aims and objectives

Epidural anaesthesia is used in over 25% of labouring women with various degrees of success. The failure rate to deliver the effective analgesia in the right place first time is up to 42% in morbidly obese patients. There is therefore an unmet clinical need to design, manufacture and characterise a needle that allows “to see” the spine as the needle is being inserted into the patient.

The objectives were

- To design an 8-element ultrasound transducer array with flexible substrate, bonding of the transducer onto the substrate and impedance and ultrasound performance tests (figure 1a, 1b).
- To test a 64 element ASIC based ultrasound transducer array bonded onto a flexible substrate (figure 1c). For this test a laser machining technique for laser cutting the ASIC into circular chips needed to be developed (figure 1d).
- To test both devices in ex vivo test at the University of Dundee.



Figures from left to right: a) Flexible substrate with metal tracks, b) flexible substrate with transducer inserted into epidural needle, c) testing of the 64-element transducer using electronic circuitry, d) Successful picosecond laser machining of a 295 mm thick silicon substrate.

Outcomes

- The transducer array was bonded onto flexible substrates, but the yield was rather poor. This was due to the movement of the chip during anisotropic bonding of the die onto the substrate. A new bonding method is required. Electrical impedance measurements were successful. Time was too short to carry out acoustic impedance measurements.
- The 64 element ASIC was successfully tested but the transducer was not bonded onto the flexible substrate. Laser cutting onto a piece of silicon was proven to be successful but was not implemented onto the ASIC due to lack of time.

Associated funding

A pre-outline programme grant proposal is being prepared in order to continue this very ambitious project as the unmet clinical needs are still there for epidural anaesthesia and other types of anaesthesia.

ENDOSCOPICALLY DEPLOYABLE OPTICS FOR PICOSECOND LASER SURGERY

Project Type
Investigator-led

PI
Shephard

Co-I
Thomson

Partners
Jayne, West (University of Leeds and Leeds Teaching Hospitals NHS Trust)

Researchers
Beck, Risbridger

Aim

The ultimate aim of the work was to prove concepts for practically deployable optical elements for the endoscopic delivery of ps laser light via novel hollow core fibres. This followed directly on from an EPSRC project aimed at developing new laser surgical techniques for early-stage colorectal tumour surgery (A fluorescence guided steerable laser tool for precision resection of early-stage cancers EPSRC EP/N02494X/1 £0.6M). The overall concept that ps laser light can be used to precisely resect tumours tissue with virtually no collateral damage to surrounding healthy tissue has been proven by the investigator team. This 1-year 4MD project allowed the team to build on those excellent results and helped address existing technological barriers (out with the scope of the previous funding) that needed to be overcome in order to move towards practical deployment in a clinical environment.

Outcomes

- A range of previously unexplored optical functions including Bessel beams were investigated to assess the effect on the ablation process.
- Bulk optical arrangements were optimised for improved surgical efficacy on clinically relevant tissue models supported by histological analysis (figure 1).
- Novel demonstrator miniaturised optical components were fabricated (figure 2).

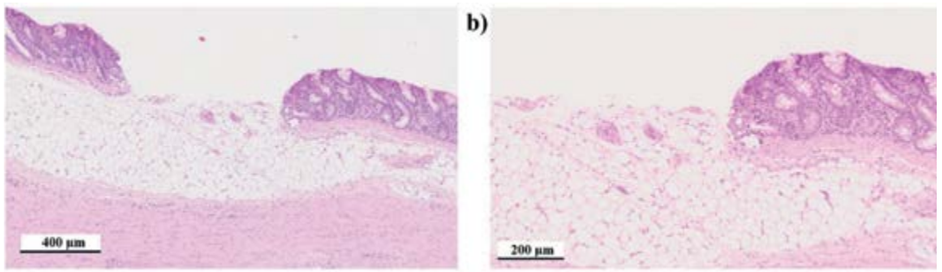


Figure 1: Histology cross-sections of laser resected cavity in porcine intestine with minimal collateral damage at different magnifications.

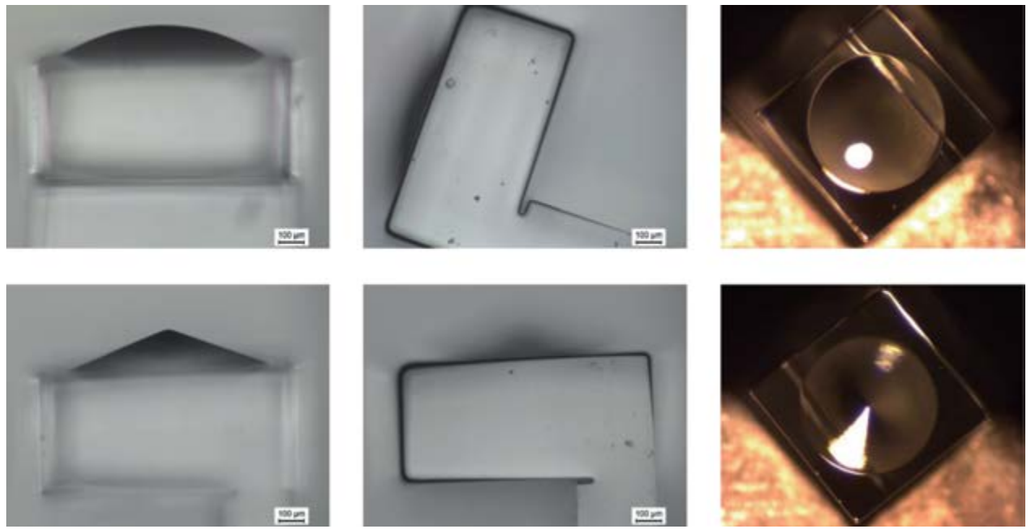


Figure 2: End probes for fibre delivered laser ablation fabricated by ultrafast laser inscription and subsequent flame polishing for a spherical lens (top row) to generate a Gaussian beam and an Axicon lens (bottom row) to generate a Bessel beam.

Associated funding

Project funded under EPSRC Healthcare Impact Partnerships: "PreCisE: A Precision laser scalpel for Cancer diagnostics and Eradication" EPSRC EP/V006185/1 £1.2M, Investigators: Shephard (PI), Hand, Thomson, Beck (RCo-I) (HWU) Jayne, Mathew, and Moor (Leeds, School of Medicine) Project Partners: Coherent Scotland Ltd., Renishaw

ULTRASHORT PULSED LASER RESECTION FOR BRAIN CANCER TREATMENT (SEEDCORN)

Theme
Effectiveness of medical procedures

Project Type
Seedcorn

PI
RA Beck

Co-Is
Bitharas, Moore, Shephard

Partners
Mathew, Jayne (Leeds institute of Medical Research)

Researcher
Beck

Aim

To develop proof-of-concept results for the high precision laser ablation of brain tissue by means of ultrashort laser pulses. This has the potential to overcome existing limitations of conventional neurosurgery for cleaning cancer margins.

Outcomes

All the relevant protocols to carry out laser-based experiments with ex-vivo cancerous human tissue have been established, including the implementation of standard operating procedures, ethics approvals, risk assessments and a tissue transfer agreement. This is a new capability within the Institute and will support a range of research activities going forward on directly clinically relevant, and more readily available tissue samples. Due to restrictions imposed by the COVID-19-pandemic, the development and optimisation of the ultrashort pulsed laser-resection process had to be based on animal tissue models, rather than ex-vivo human brain cancer. The successful laser ablation of brain tissue with similar dimensions to residual cancer in neurosurgery has been demonstrated. The process dynamics including the cavitation effect have been studied by means of high-speed imaging.

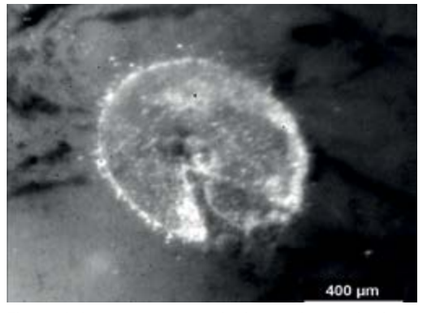


Figure 1: Laser ablated cavity in porcine brain tissue.

Associated funding

"PreCisE: A Precision laser scalpel for Cancer diagnostics and Eradication",
Principal Investigator: Jon Shephard
Co-Investigators: David Jayne, James Moor, Ryan Mathew, Robert Thomson, Duncan Hand
Researcher Co-Investigator: Rainer Beck
EPSRC Reference: EP/V006185/1; Value: £1231581; Start date: 1st January 2021

A PLATFORM FOR ELECTRICAL, OPTICAL AND MECHANICAL SENSING (POEMS)

Project Type
Investigator-led

PI
Crichton

Co-Is
Hand, Desmulliez, Marques-Hueso

Partners
Elliott (NHS)

Researcher
Dzipalski, Gamal

Aim

Within the first POEMS project we proposed the development of a novel electrical, optical, and mechanical sensing microneedle which could be used to detect nerve function changes.

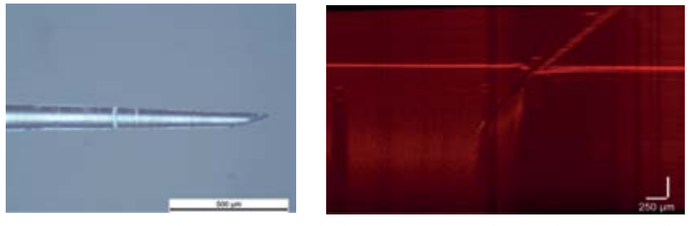
Outcomes

The work that has been done on this project has been very successful in creating a range of microneedles, with a level of mechanical and electrical integration. The manufacturing approach has led to new avenues for pressure cavity development. These advancements in manufacturing continue to develop with a goal to improve the resolution on the pressure cavity. Remarkably, it does demonstrate the potential for optical fibre-based microneedle sensing of mechanical force. We have also made progress in the deposition of electrical contacts on these microneedles, but this work is still in an early stage. The outputs of this work include a conference presentation and clinical discussions with potential collaborators towards specific medical applications.

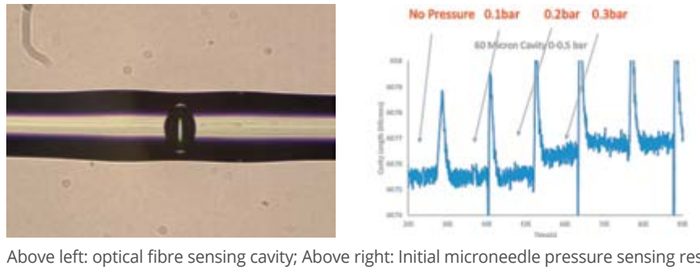
Associated funding

4MD follow-on project PROS

Conference presentation: Adrian Dzipalski, Michael Crichton, Jose Hueso Marques, Duncan Hand "Functional Microneedles: A multimodal sensory platform", ILAS 2021



Above left: microneedle manufactured by laser machining; Above right: Microneedle inserted into tissue phantom.



Above left: optical fibre sensing cavity; Above right: Initial microneedle pressure sensing results using machined optical fibres.

PRESSURE RESOLUTION BY OPTICAL SENSING ENHANCEMENT (PROSE)

Project Type
Investigator-led

PI
Crichton

Co-Is
Hand, Desmulliez, Marques-Hueso

Partners
McLeod (School of medicine, Dundee University)

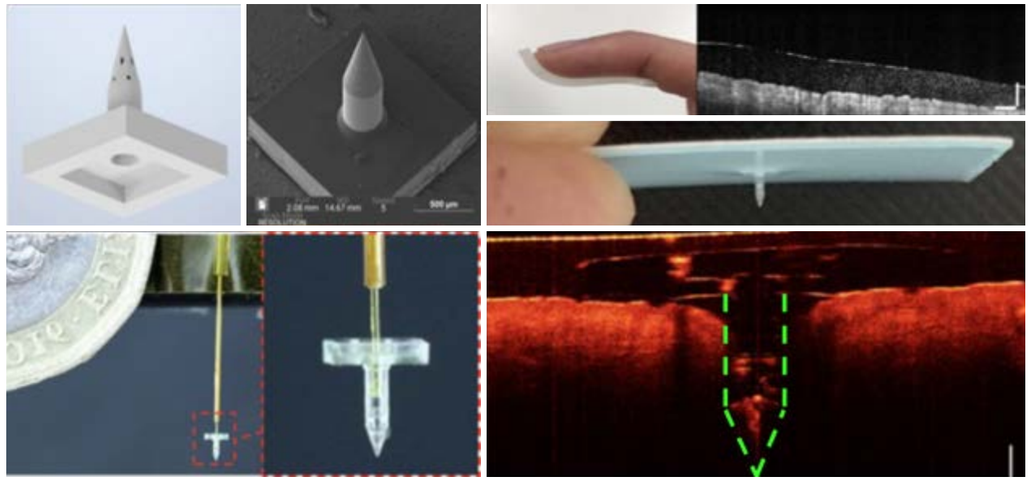
Researcher
Dzipalski, Jomaa, Turnbull

Aim

The changes that happen in the body over time were the key focus of the POEMS project, and the simplicity of microneedles opened a minimally invasive sensing method. Looking beyond initial force and electrical methods, we turned our approach to the mechanical changes that occur within tissues due to biological health or disease. For example, the physical pressure variation that occurs in the body during wounding, inflammation, or vascular damage (either short or long term. Measuring these pressures over time provides a window to track changes in the body and is where PROSE focused its activities.

Outcomes

First, we manufactured optical fibre-based microneedles to measure clinically relevant hydrostatic pressures at a range of depths simultaneously in tissue. To develop these, we required our microneedle sensors to be incorporated into a flexible wearable interface for long term patient monitoring. This work built upon the POEMS project with the goal to create a platform for novel clinical measurement but extended the many medical possibilities arising from it. We then made use of Heriot-Watt's Medical Device Manufacturing Centre (mdmc.hw.ac.uk) equipment (the Nanoscribe system) to fabricate microneedles for pressure sensing in skin. These were mounted on flexible substrates for attachment and monitoring of skin pressure. We are now in a position to test these and although as yet unfunded, we did reach the second stage of Wellcome Leaps SAVE surgical monitoring programme with this device as a core technology. We are currently pursuing additional funding for in-vivo testing and further refinement of the technology.



POST-TRANSPLANT DRUG DOSAGE DETECTION – (TACROLIMUS)

Project Type
Investigator-led

PI
Carter

Co-Is
MacPherson

Partners
Knight (University of Edinburgh/NHS Lothian), Clancy (Glasgow University/ NHS GG&C), Vendrell (Chair of translation chemistry and biomedical imaging University of Edinburgh)

Researcher
Dzipalski

Aim

Organ rejection occurs in 60% of transplant patients and carries a significant clinical, economic, and social burden. Tacrolimus is an immunosuppressant agent and the mainstay of anti-rejection medication for solid organ transplantation. However, Tacrolimus therapy is complicated by intra- and inter- patient variability in its absorption combined with a very narrow therapeutic window (5-10 ng/mL). Correct treatment is therefore highly dependent on fast accurate, testing for Tacrolimus concentration in patients' blood.

Currently detection relies on taking daily whole venous blood samples (which requires a clinical visit by the patient). This blood then undergoes a series of separation and purification steps before final mass spectrometry is used to determine the concentration. The process is both time consuming and expensive. Doctors are therefore left in the position of making delectate dosage adjustments based on information which is anything from 12-24 hrs old and leaves a real risk that dosage is out of phase with clinical requirements.

Outcomes

Previous research has demonstrated that fingerprick tests can be used for Tacrolimus detection, but the detection technique still requires laboratory processing and equipment.

This seedcorn project aimed to investigate a range of rapid optical diagnostic tests (FTIR, Raman, UV/absorption spectroscopy etc.) to determine whether these are suitable in principle for the detection of Tacrolimus in laboratory conditions.

The results of the study indicated that both Raman and FTIR are able to detect Tacrolimus albeit in relatively large concentrations suggesting that a combination of optical detection and microfluidic sample concentration techniques may well provide the possibility of rapid, point of care detection.

Associated funding

12-month project funded by 4MD - Tacrosense

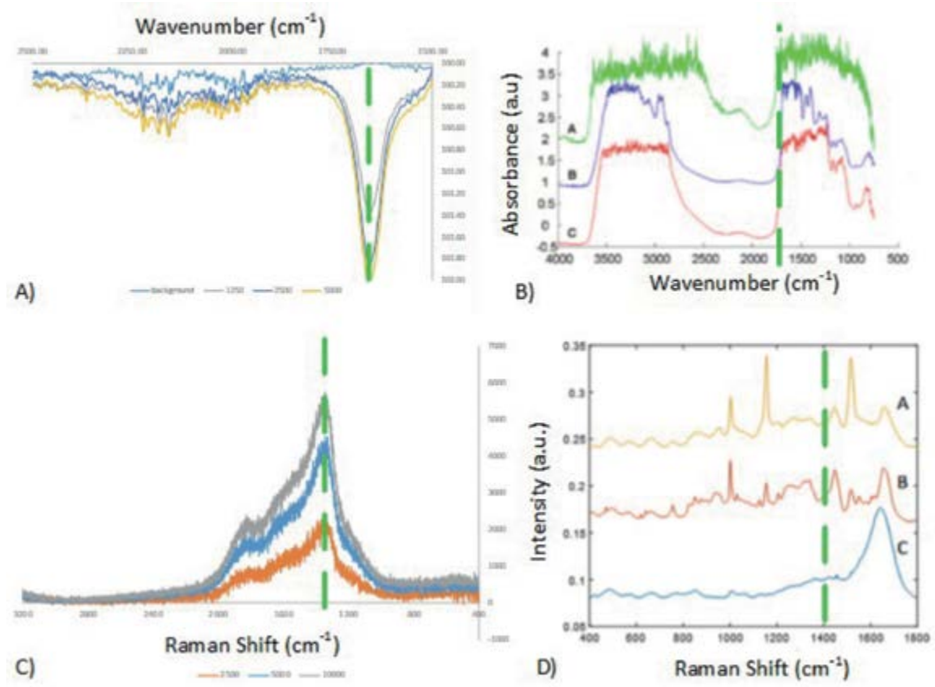


Figure 1: Comparative results of seed corn project: FTIR results for A) Tacrolimus in DI water and B) reference results of human blood [1]. Raman spectroscopy C) Tacrolimus in DI water and D) reference results of human blood [1]. Green lines indicate approximate positions of target wavenumbers on each.

TACROSENSE (POST-RANSPLANT DRUG DOSAGE DETECTION)

Project Type
Investigator-led

PI
Carter

Co-Is
MacPherson, Kersaudy-Kerhoas

Partners
Knight (University of Edinburgh/NHS Lothian), Clancy (Glasgow University/NHS GG&C), Vendrell (Chair of translation chemistry and biomedical imaging University of Edinburgh)

Researcher
Haque

Aim

Tacrolimus is a mainstay of immunosuppressant therapy for post-transplant patients, particularly for soft organ transplants. However the therapeutic range of this drug is narrow and thus there is a requirement to regularly monitor the concentration of tacrolimus from patient blood samples. The current process produces good data but it is complex, time consuming, expensive and requires daily blood draws in a clinical environment. This project aimed to investigate the options for a low cost, point of care, or at home, test for tacrolimus using an inexpensive optical detection technique.

This was split into two work streams. The first investigated the optical metrology techniques and the second developed a modular, inexpensive blood handing and processing system.

Outcomes

In the first research stream optical metrology techniques (Raman, FTIR, spectroscopy and fluorescence) were all investigated. Results demonstrated that a fluorescent protein marker could provide a signal for tacrolimus with a bespoke marker developed by Prof Vendrell's group. This demonstrated a response to tacrolimus in absorption and in fluorescence albeit at concentrations much higher than typical therapeutic ranges; a concentration mechanism is also required.

The second research stream developed a modular microfluidic chip combining a series of elements to meter, lyse, filter and present a blood sample to an optical detection chamber where concentration of the marker would be performed. The system was published (Lab Chip, 23, 62-71, 2023 (10.1039/d2lc00968d), video: https://tinyurl.com/4wtd59nz) and has garnered significant interest for a range of applications in only a short time and will be the basis for a proposal for follow on funding.

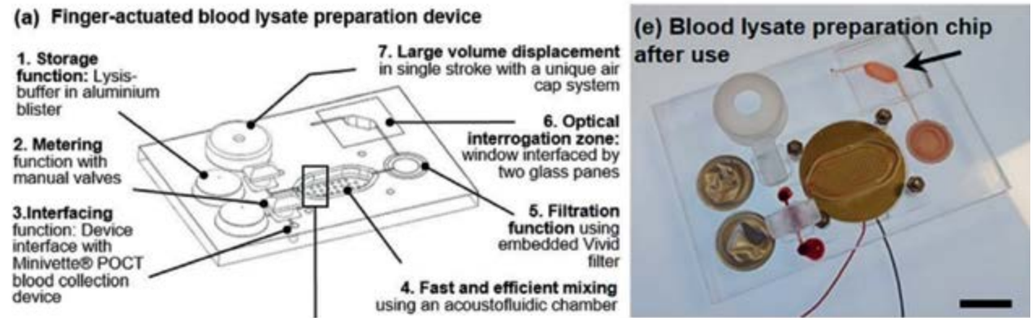


Figure 1: Left, schematic of demonstrator blood sampling chip, Right, photograph of chip after use. Taken from Lab on a Chip 23(1), 62-71, 2023.

Associated funding
Post-transplant Drug Dosage Detection – (Tacrolimus)

REHAB-SENSE (NOVEL METRICS FOR REHABILITATION)

Project Type
Investigator-led

PI
Desmulliez

Partners
Knight, Lyons, Harrison (Edinburgh University/NHS)

Researcher
Pavuluri

Aim

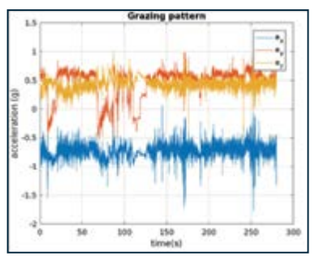
This 6-month project proposed to manufacture a new type of wireless medical sensor system capable of novel recovery metrics and personalized feedback to aid rehabilitation of patients undergoing major invasive surgery. After discharge following cancer surgery, patients currently assume primary responsibility for monitoring their own recovery. More than 10% of patients over 45 years old experience a major postoperative complication, often following discharge, which typically prompts readmission and is associated with increased postoperative mortality across a range of surgical populations.

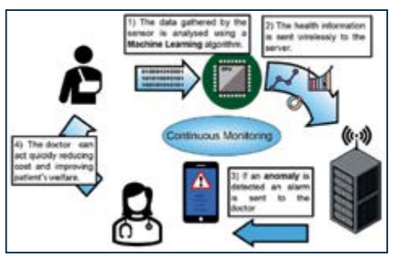
Accelerometer activity data has been shown to identify postoperative complications at an earlier stage and correlate with validated surgical complication severity scoring systems. Despite the potential of smartphones and accelerometer-based devices, which often require synchronization to smartphone devices, the majority of older patients do not own a suitable mobile device and data is frequently not available in real-time for clinician review. A suitable biotelemetry system was therefore proposed here.

Aims and Objectives:

The key questions that this short research proposal aimed to address were:

- Can the data obtained encourage pre-rehabilitation of patients prior to their operation and monitor postoperative recovery?
- Can the physical activity levels captured from the accelerometer-based sensor system be used to describe and quantify postoperative recovery among patients?
- Can the data obtained by recording such physical activity levels be used to discriminate between postoperative trends in physical activity?





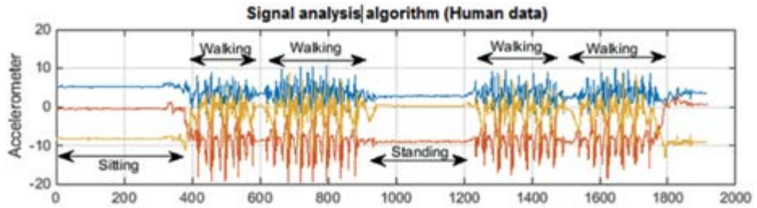
Figures Left: Results obtained for the detection of the grazing pattern of a sheep using the 3-axis accelerometer sensor (only) system. Middle: Early version of the sensor system prototype for the sheep (collar configuration). Right: A LoRaWan based model for patient activity monitoring.

Outcomes

The team previously successfully detected scabbing in sheep by designing and building a proof-of-concept demonstrator along with sophisticated algorithm to distinguish 6 different types of behaviour (coughing, grazing, laying, running, standing, walking)

The following work has been successfully achieved for REHAB-SENSE:

- Reduction in physical volume of the sensor system electronics as a wearable device to monitor human activity.
- Successful development of a wireless sensor system that has
    a. Inertial sensor device with Gyro + Accelerometer + Compass
    b. An LCD screen for display to patient and a micro-LoRa wireless trans receiver
    c. A micro phone and an additional Wi-Fi trans receiver
- LoRaWan has been developed to allow 10 to 15 km range transmission and reception capability.
- The sensor system was ergonomically packaged in a form that is acceptable to the patient.
- An algorithm uncertain-order multivariate autoregressive stick breaking hidden Markov Model (UOmAR-SBHMM) was tested. This algorithm achieved 94.57% accuracy.
- A node-red based user interface developed to retrieve data from the LoRaWan cloud automatically and display data in real time followed by saving data automatically (in final testing phase) in the local database of a pc/laptop.
- Patient accelerated activity test scenarios have been compiled with the help of Dr. Knight.
- Device testing and initial activities monitoring trial are completed with further activities and trials planned for March/April. The developed algorithms have been tested on the initial patient's data recorded.



Figures Top: Compact wearable electronics developed for LoRaWan network-based patient activity monitoring.
Bottom: Sample accelerometer data for detection of human activity using the 3-axis accelerometer sensor (only) system.

Follow on funding

A medical Journal paper is targeted as an outcome of this project. Post-processing of the data for simulated patient activities still need to be completed. Continuation of funding is needed for this. This could be done using the HWU Impact Acceleration Award.

RF-COVID (MICROWAVE INDUCED INACTIVATION OF SARS-COV-2) (SEEDCORN)

Project Type
Seedcorn

PI
RA Pavuluri

Co-Is
Desmulliez

Partners
Haas (Edinburgh Medical School), Griffiths (Edinburgh Medical School/ University of Edinburgh)

Researcher
Pavuluri

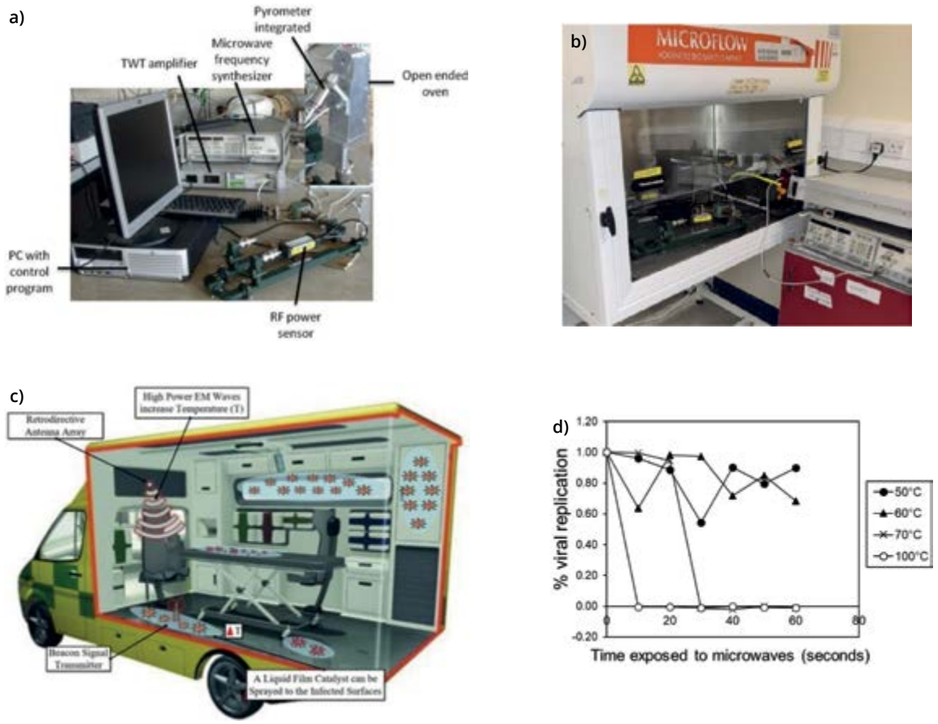
Aim

Demand for protection against COVID by personnel from hospitals and care homes has never been more topical and urgent today as the UK is currently battling against the very infectious strain of the corona virus. UV Germicidal Irradiation (UVGI) is limited by inherent shadow effects of a light source, variability in dosages due to bulb age and different platform constructions and also damages plastic surfaces. There is therefore an unmet clinical need to design, manufacture and characterise a needle that allows “to see” the spine as the needle is being inserted into the patient.

Outcomes

The key deliverables for this short RF-COVID project were:

- A test setup for inactivation of viruses
- Determination of microwave input parameters for heat assisted inactivation of viruses using materials and surfaces that mimic the real-life environments
- Trial of the method for types of surfaces and materials at Royal infirmary (Edinburgh) with the Coronavirus (non-COVID-19)
- A proposal for further funding in order to manufacture and test the device in medical settings



Figures from left to right: a) Microwave assisted test equipment for inactivation experiments b) Experiments conducted in Bio-safety cabinet, c) Concept for deactivation of viruses in ambulances, d) Survival rates of virus when exposed from the tests for 10-60 seconds at four different temperatures: 50, 60, 70 and 100°C.

Results achieved are

- We partnered with virologists at the University of Edinburgh (Royal Infirmary) and new tests were performed at virus certified labs with Prof. Jürgen Haas group.
- We partnered with the EM group at the University of Edinburgh to benefit from their expertise in retrodirective antenna rays.
- Feasibility tests with egg white and live viruses (coronavirus strain CoV-229E-GFP) were completed on plastic materials. Virus inactivation on plastic has been demonstrated. We did not have the time and resources to perform the inactivation of the virus on other surfaces.

An EPSRC grant proposal was submitted in November 2021 in partnership with University of Greenwich and Loughborough University to continue this project for neutralising viruses in blood-like environments. Unfortunately, the proposal was not successful.

Dissemination of the results include

- an IEEE journal: *A methodology for remote microwave sterilisation applicable to the coronavirous and other pathogens using retrodirective antenna rays*. K. Kossenas, S.K. Podilchak, D. Comite, P.D. Hilario Re, G. Goussetis, **S.K. Pavuluri**, S.J. Griffiths, R.J. Chadwick, C. guo, N. Bruns, C. Tait-Burkard, J.H. Haas, **M.P.Y. Desmulliez**, IEEE Journal of electromagnetics, RF and microwaves in medicine and biology, Vol. 6, N.1, pp 41-51 (2022) DOI: 10.1109/JERM.2021.3077110. (number of citations: 5).
- 17 printed journal news articles, over 200 online news including BBC Good Morning Scotland, STV news, The Times, Independent, The Sun, Scotsman Yahoo News including international threads etc, based on the article.
- A conference proceeding article: Remote microwave sterilization applicable to coronaviruses using a Van-Atta retrodirective antenna array with 2-D tracking capability, M. Kuznetcov, K. Kossenas, S.K. Podilchak, D. comite, P.H. Hilario Re, G. Goussetis, **S.K. Pavuluri**, S. Griffiths, R.J. Chadwick, C. Guo, N. Bruns, C. Tait-burkard, J.G. Haas, **M.P.Y. Desmulliez**, Proc. Of the 51st European Microwave Conference (EuMA), pp. 841-844, (2021) DOI:978-2-87487-063-7.

MEDICAL DEVICES

FIBRE OPTIC PROBES FOR ENDOSCOPIC MEASUREMENT OF UTERINE HYPOXIA

Project Type
Investigator-led

PI
Tanner

Partners
Maybin (MRC Centre for reproductive health, QMRI, University of Edinburgh

Researcher
Ehrlich, Green

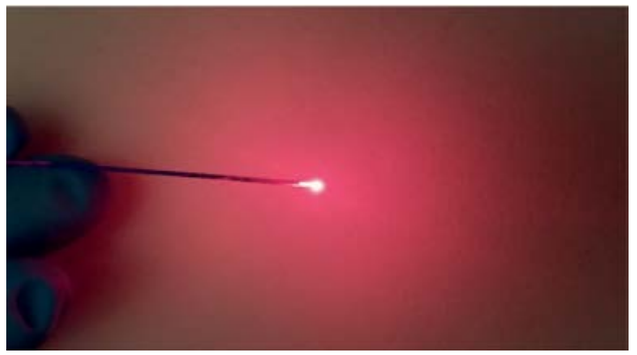
Aim

We manufactured a miniature fibre probe for endoscopic assessment of oxygenation / hypoxia in the uterus. Heavy menstrual bleeding (HMB) affects a quarter of women of reproductive age in the UK, negatively impacting quality of life and with a huge socio-economic burden for women and society. Endometrial physiology and the aberrations that contribute to HMB must be delineated to allow development of personalised medical therapies, specifically the transient hypoxic episode in the endometrium during shedding and subsequent repair. We measured hypoxia via an optical fibre-based probe that can be delivered through the working channel of an endoscope during hysteroscopic assessment. The principle is similar to a digit pulse oximeter, but with a sub-millimetre multi-point emission sensing fibre and external control module. This allows diagnosis of a lack of hypoxia at menstruation during hysteroscopy, facilitating correction of this specific defect with precision medicines.

Outcomes

Key project outputs include: production of fibre optic sub-millimetre oxygen measurement probe; demonstration in tissue models; observation of real time human oxygen variation; assessment of utility for uterine measurement.

Follow on impact targets include: measurement of hypoxia sensing during hysteroscopy; better understand hypoxia processes in the human endometrium and causes of HMB; enabling targeted treatment of HMB.



DYNOCLAW: A DYNAMIC PALPATION DEVICE WITH TWO POINTS OF TISSUE CONTACT

Project Type
Investigator-led

PI
Reuben

Co-Is
Hand, Chen, Shephard, Erden, Crichton

Partners
McNeill, Paterson, Noble (University of Edinburgh/Western General Hospital)

Researchers
Balmer, Gora

This project involved the re-design of a device which uses dynamic instrumented palpation for tissue identification and cancer detection. The adaptation is from a relatively large trans-rectal probe to one that can be used intra-operatively during Robot-Assisted Surgery (RAS). The technique involves applying an oscillating force and measuring the resulting deformation of the tissue at a range of frequencies. The starting point for the new design was a meso-scale gripper, modified to be driven by a hydraulic actuator whose pressure could be controlled to give a range of amplitude and frequency of oscillation.

The object was to explore the limits of miniaturisation available using precision laser cutting and ablation, the target being to fit inside the working channel of a colonoscope.

The final output of the pilot was a layered design (Figure 1), an exemplar of which was built and operated.

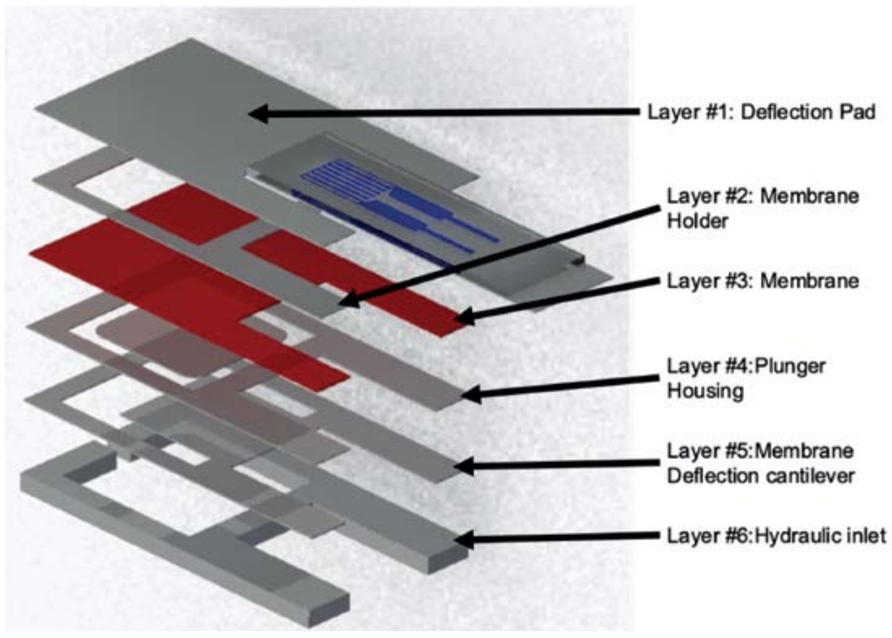


Figure 1: Final DynoClaw output showing layered design fitting within target envelope

However, the assembly was extremely difficult and was at the limits of what can reasonably be achieved with the use of conventional strain-sensitive elements. Further miniaturisation and bulk manufacture would require a different sensing approach and a less intensive assembly process.

Further funding: The project led directly to a proposal to EPSRC under its Healthcare Impact Partnership Scheme to develop model-informed measurement interpretation ("mechanical intelligence") and a multi-scale probing technique, replacing the strain sensitive elements with optical fibre sensors addressing various points on compliant probe elements (Figure 5). This has brought together a new collaboration at HWU: Chen (PI and mechanical modelling), McPherson (optical fibre sensing), Hand (laser-based manufacture) and Reuben (in vivo mechanical measurements). The project has 2 clinical Co-Is: Paterson and Good – Western General Hospital / University of Edinburgh (UoE) and is supported by the Large Animal Research and Imaging Facility (LARIF), Clutton, Greenhalgh (UoE). The project also has 2 industrial partners: **CMR Surgical Ltd and Intellipalp Dx Ltd.** The project, valued at £1,245,293, is due to commence in early 2022.

Associated projects

The original research leading to the concept of DIP was carried out under two linked EPSRC grants: EP/I019472 (PI Reuben) EP/I020101 (PI McNeill): ***E-finger: a tactile diagnostic device with microscale resolution, valued at*** *£402,246 and £399,137, respectively. The work has been further supported by the HWU EPSRC IAA (£84871), the UoE MRC CinC (£69,000), The Urology Foundation (£249,998) and CENSIS (£101,147), all of which has helped to establish the spin-out company Intellipalp Dx.*

PRESSURECAP, A NOVEL INGESTIBLE MOTILITY CAPSULE (IMC) (SEEDCORN)

Project Type
Seedcorn

PI
RA Pavuluri

Co-Is
Desmulliez

Partners
Potter (Colorectal Unit, Western General Hospital, Edinburgh),
Clutton (The Royal (Dick) School of Veterinary Studies),
Mitrakos (Senior Electronic Skin Engineer at Touchlab Limited)

Researcher
Pavuluri

Aim

Motility disorders are disorders that affect the way the GI tract muscles contract. Dysmotility of the small intestine may lead to symptoms such as bloating, pain, vomiting and cramps and may act as an indication to a number of severe conditions such as irritable bowel syndrome, gastroparesis, chronic idiopathic constipation, chronic abdominal pain, dyspepsia, chronic intestinal pseudo-obstruction, bacterial overgrowth, and ileus, amongst others.

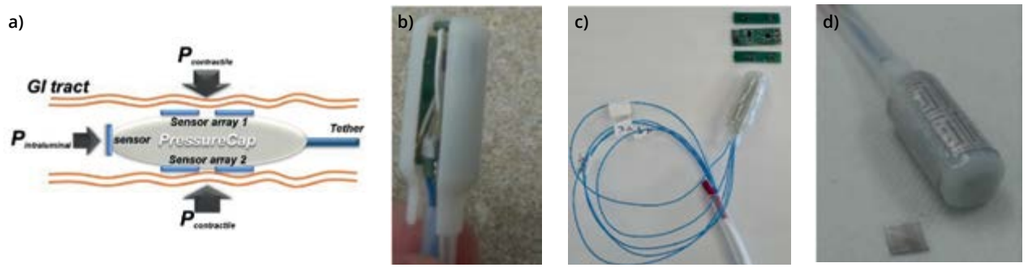
Obtaining the contractile information of the gastrointestinal tract (GI tract) would help to better diagnose motility disorders, providing for example a direct method to assess irregular small intestine motions. Ingestible Motility Capsules (IMCs) offer an attractive alternative to conventional manometry, as these systems are designed to be ingestible and act as a lab-in-a-capsule where the physiological parameters of the GI tract are captured with minimal patient discomfort and potentially advanced diagnostic capabilities. In addition, assessing the contractile information may potentially provide an effective method to localise the capsule, as it travels within the GI tract.

The team has developed successfully flexible thin-film LC pressure sensors and readout system that paved the way to design and develop PressureCap, a novel ingestible motility capsule (IMC), with the potential to monitor simultaneously multiple sites of the GI tract. This capability, to the best of the authors' knowledge, has not been explored in current IMCs.

Outcomes

The key deliverables that this short research project aimed to address were:

- Electronics PCB's development and integration for the PressureCap
- Development and integration of flexible thin-film LC pressure sensors for PressureCap
- PressureCap assembly with the tether, electronic PCBs, and thin film pressure sensors
- Perform *In vivo* live porcine testing at in Dryden Farms, UK, and perform trial with established clinical safety protocol and general experimental configuration and in accordance with the Animal (Scientific Procedures) Act 1986



Figures from left to right: a) General concept design and functionality of PressureCap b) Integrated electronics in 3D printed capsule for PressureCap (c) Integrated electronics and 3D printed capsule for PressureCap with tether before tether integration– PCB's shown in the background (d) A close up image of the integrated PressureCap with thin-film LC pressure sensors affixed.

Work achieved

- The team have successfully developed and integrated the electronics PCB's, thin film pressure sensors to date. Additional pressure capsules (Pressure-Cap) were manufactured, and their performance was characterised on the bench.
- A new algorithm for detecting the natural electrical resonance of the sensor was created which allowed quicker processing of the information.
- *In vivo* testing of pigs was carried out. Results from the measurements are still being processed.
- Tests of the capsule were also performed using an artificial gut manufactured in collaboration with the University of Freiburg. Data obtained with the artificial gut need still to be post-processed.
- One patent in the USA and one GB patent are being filed with Heriot-Watt University and the University of Edinburgh as assignees.

Output

- One US patent. Flexible devices incorporating electronically conductive layers, including flexible wireless LC sensors, V. Mitrakos, **M.P.Y. Desmulliez**, LM Macintyre, P. Hands, Patent *submitted to the USA* P209006.US.01.
- One UK patent. Flexible devices incorporating electrically conductive layers, including flexible wireless LC sensors, V. Mitrakos, P. Hands, L. Macintyre, **M.P.Y. Desmulliez**, Appl. P2002869.2. Filing date: 28 February 2020.O209006.GB.01/TEC4167
- One article was written: "Construction of an endoscopic capsule for the diagnosis of dysmotilities in the gastro-intestinal track", **M. Desmulliez**, Published in circuits and systems for Biomedical Applications, pp.31-48 (2022). River Publishers.

Follow on funding

Post-processing of the data for the animal models and artificial gut needs to be completed. Continuation of funding is needed for this. This could be done using the HWU Impact Acceleration Award.

WEARABLE PIEZORESISTIVE FIBER SENSORS FOR MOBILITY AND GAIT ANALYSIS OF PEOPLE WITH LIPOEDEMA (SEEDCORN)

Project Type
Investigator-led

PI
Amjadi

Co-Is
Chen, Macintyre

Partners
Williams (QMU, clinical advisor)

Researcher
Anderson; McMahon

Aim

Lipoedema is a debilitating progressive medical condition leading to abnormally shaped limbs, painful tissues, excessive bruising, reduced mobility, frequently depression and low quality of life. A common conservative treatment involves wearing compression garments designed for other conditions. No customised compression garments designed for lipoedema patients exist. Therefore, there is an unmet clinical need for an evidence based, ultimately patient-specific, garment therapy to manage lipoedema.

The project team aimed to develop skin-mountable strain sensors for objectively measuring changes in the mobility and gait of people suffering from Lipoedema. In parallel to that, a camera-based digital health tool was developed to quantitatively assess the mobility and level of gait asymmetry (left and right) of the 'patients' affected by lipoedema. Critically, the tool is developed with the affordability in mind, with the ultimate application in self-diagnosis and management for the patients.

Outcomes

In the first part of the project, we formulated a biomechanical human model to identify the key areas in legs and gait cycles where soft sensors would provide the most sensitive and reliable data. The independent working of the camera-based digital tool was also assessed with a promising level of reliability and robustness, where the tool has the capability in detecting abnormal gait and assessing the potential biomechanical impact on simplified musculoskeletal components. The second part of the project focussed on the design of wearable strain sensors using highly stretchable nanomaterial-coated fibres. When the sensors are attached onto the skin or the textile fabric, the localised strain values can be readily measured through changes in the electrical resistance of the s/20ensing materials.

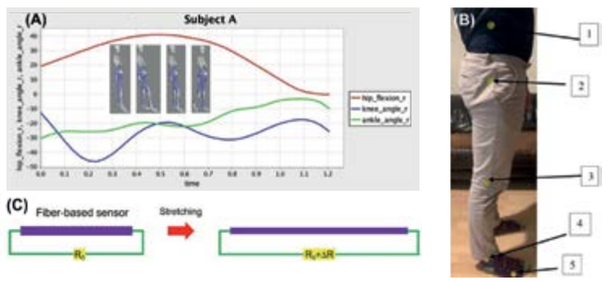


Figure 1. (A) Monitoring of key motion indices and reconstructed biomechanical model through marker-based gait tracking; (B) Locations of markers on the subject; Marker-less tracking with phone camera was also achieved but not shown here; (C) Schematic demonstration of the working principle of the resistance-fibre based strain sensors.

Further collaboration and funding

- Digital Health – a pilot project funded by The Urology Foundation (in collaboration with NHS Lothian) and an EPSRC IAA project funded for further development towards commercialisation, based on the concept of camera-based assessment.

Associated projects

PhD project on camera-based intraoperative tissue condition assessment for robot-assisted surgery, in collaboration with CMR Surgical (2023-2027)

The Urology Foundation Pilot Project: Camera Uroflowmetry: a pilot study (in collaboration with NHS Lothian) (2021-2023)

EPSRC Impact Acceleration Account (IAA): Digital Health Solution for early diagnosis of urological conditions (2022-2024)

SURGICAL MARGIN DELINEATION PROBE: TOWARDS IN-VIVO MID-INFRARED ATR SPECTROSCOPY (SEEDCORN)

Project Type
Seedcorn

PI
RA Ehrlich RA

Co-Is
RA Ross, RA Castro, Reid

Researcher
Ehrlich

Aim

Attenuated-total-reflectance (ATR) spectroscopy is an absorption spectroscopy technique which utilises molecular absorption of an evanescent wave at a high-index interface in contact with a sample surface, such as tissue. ATR spectroscopy is widely used for material sensing, but translation towards clinical applications is inhibited by challenges associated with manufacturing fibre-optic based sensing devices.

The aim of this seedcorn project was to develop a novel fibre-based ATR device, deployable down the instrument channel of a standard endoscope, with potential future applications in cancer margin delineation. ATR is often performed in the mid-infrared (MIR) portion of the spectrum, for which tissue absorption spectra is information rich. For this project, we combined our own experience in laser-based glass microfabrication with the MIR spectroscopy expertise from the Ultrafast Optics group at HWU, to collaborate on the development of a half-ball ATR probe for efficient spectral acquisition in hard-to-reach regions of the body.

Outcomes

The seedcorn funding facilitated the development of novel fibre-optic ATR devices, designed for use in either the near-IR or MIR spectral regions. The development included the optical design, laser-based fabrication and characterisation of the devices. The devices were demonstrated at showcase events for both 4MD and other MedTech related workshops.

The project also enabled new collaborations both internally and externally and complimented research undertaken within the Ultrafast Optics group at Heriot-Watt University.

Preliminary results from the work were presented at "Photon2022", a leading photonics conference in the UK.

Once the projected is completed, we expect that the results will form the basis of a research article. Follow-on funding will be pursued in order to facilitate clinically relevant validation.

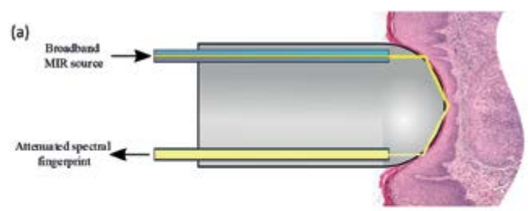


Figure 1: (a) Schematic of the ATR probe tip. (b) Distal-end ATR probe consisting of a ULEA manufactured sleeve that allows for passive alignment of the half ball lens and the optical fibre. (c) The ATR probe packaged within the bore of a hypodermic needle.

Follow on funding

SULSA ECR Development Fund, £4K consumables

INVESTIGATION OF ELECTROMAGNETIC ACTUATORS FOR ANTERIOR MAGNETIC STIMULATION OF HUMAN BODY (SEEDCORN)

Project Type
Seedcorn

PI
Dr. Jayakrishnan, M. Purushothama

Co-I
Dr. Yuan Ding

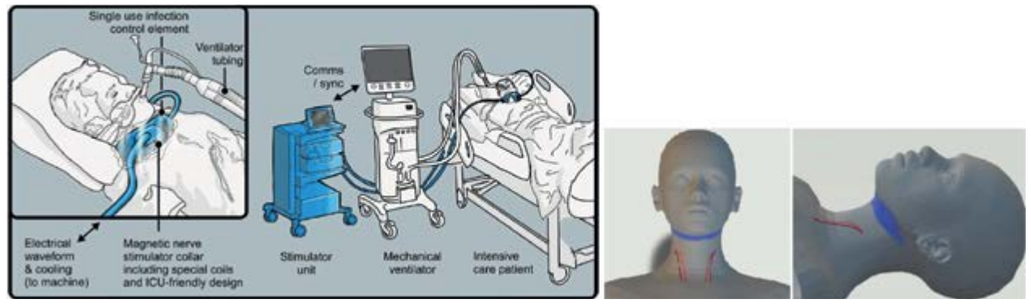
Partners
Dr. Philip Pemberton, Stimulate Medical

Researcher
Dr. Jayakrishnan M. Purushothama

Mentors
Prof. Duncan Hand, Prof. George Goussetis, Dr. Philip Pemberton

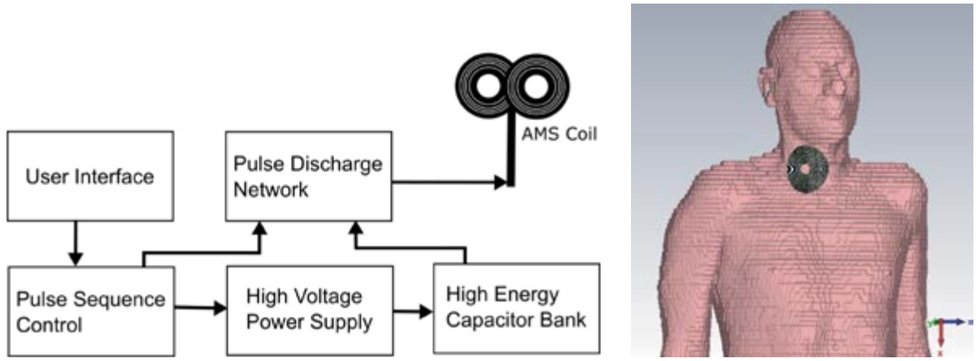
Aim and objective

This 5-month research programme involved initial investigative studies towards development of compact and high efficiency electromagnetic coils for anterior magnetic stimulation (AMS), targeting the human body. Such AMS systems are sought towards non-invasive clinical interventions, to stimulate the phrenic nerves of the human body, to exercise the diaphragm whilst patients are under ventilator care to prevent muscular atrophy.



(a) (b)

Fig.1. (a) Proposed scheme of administration of AMS to human body. (b) Location of phrenic nerves in the cervical (neck) region of human body.



(a) (b)

Fig.2. (a) A simplified functional block diagram of proposed AMS system. (b) Example of a human body voxel model in CST studio suite, along with the AMS coil placed in the cervical region, mimicking an actual application scenario.

Outcomes

The key deliverables of this project were achieved through the following outcomes:

- Extensive literature survey and identification of techniques for coil simulation and modelling, and thermal-electric co-simulation.
- Model definition of different conventional and adapted coil geometries suitable for AMS in a mathematical modelling software (Matlab) and 3D modelling in a CAD based low frequency transient quasi-magnetostatic solver (CST-MQS).
- Analysis of different performance/functionality parameters of modelled coils like inductance, maximum magnetic field produced for a given excitation, magnetic field gradient for a given excitation, full width half maximum (FWHM) calculation of magnetic field distribution, and the comparison of these factors among the modelled coils and against commercial systems.
- Analysis of the factors mentioned in point no. 3, in a scenario where the coils are placed on a human tissue model.
- Technique for thermal co-simulation to study the joule heating effects in the coil for a given electrical excitation.

Future perspectives

Future research directions which could be pursued to follow-up this research include:

- Further optimisation of developed coil geometries and real-life modelling/analysis including with human tissue models.
- Detailed thermal-electric co-simulation to understand the heating effects and adoption of techniques to mitigate the same.
- Development of a fully functional AMS system.

The proposed AMS system (with adequate TRL) would be of great use to medical agencies, like the NHS, and could benefit in cost cutting leading to reducing the number of days a patient should continue in an intensive care after being administered with artificial mechanical ventilation, due to reduced weaning time. The primary end user and industrial partner to help commercialization of this technology, at present is Stimulate Medical Ltd., Coventry, United Kingdom.

TRANSLATION INTO CLINICAL SETTINGS

SECONDMENT TO NHSL FOR PROSTAPALP DEVELOPMENT (SEEDCORN)

Project Type
Seedcorn

PI
RA Johnson

Co-Is
Reuben, Hand, Chen, Gora, Novo

Partners
McNeil, Good (University of Edinburgh/Western General Hospital),
Davie (Medical physics/NHS Lothian)

Researcher
Johnson

Aim

This 3-month project was associated with the commercialisation of a trans-rectal probe, trade-marked ProstaPalp®, for the early detection of prostate cancer. The University has spun out a company, IntelliPalp Dx in which the proposer is a co-Founder and will have a central technical role.

The work involved improving the build quality, sensitivity, reliability and yield of the probes used in the current prototype of ProstaPalp® and liaison with NHS Lothian on regulatory and practical clinical matters. One significant constraint was that the improvements need to be made without any changes to the overall design envelope and protocols approved by NHS Lothian Medical Physics.

Outcomes

Figures 1 and 2 illustrate the work with clinicians towards understanding the constraints of the probe in use with a view to improving the clinical protocols for best quality measurements.

Figure 1: Research nurse Jan Blaikie testing ability to "blind" locate probe at 12 different positions on a model prostate gland

Figure 2: Consultant urological surgeon, Professor Alan McNeill discussing issues with probe deployment under surgical glove prior to in vivo measurements.

continues over

Figure 3 shows an example of the **final output** of the project, one of the mechanical maps taken in vivo on a patient using the improved build and protocols. These maps are correlated with biopsy results to assess the sensitivity and specificity of the test for pre-biopsy cancer screening.

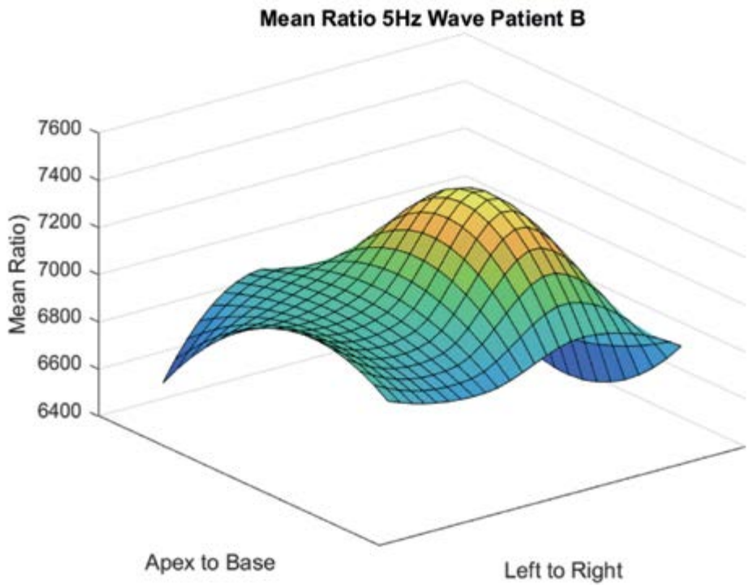


Figure 3: Sample mechanical map of one of 15 mechanical features measured at 12 points on a patient about to undergo biopsy. (Graph by MEng student Joe Bennett from data pre-processed by RA Mahta Majidi)

Further funding: Ms Johnson has been instrumental in bringing further funding both to the University and to IntelliPalp Dx both during and following this seedcorn project, including:

- 'Truly Tactile Mechanical iDRE'. A CENSIS collaborative R&D project bringing **£101,147** to HWU, used to fund part of her salary and the salary of another RA (Mahta Majidi) in 2020/21.
- Scottish Enterprise pre-seed award of **£46,000** for consultants to assist with IP, commercialisation, market strategy, regulatory requirements and various technical issues
- Scottish Enterprise BSE Award of **£15,000** for product mock-up and graphical material for investors
- Scottish Edge Competition Winners of **£75,000** for redesign of actuator/probe/controller assembly
- Royal Academy of Engineering Enterprise Fellowship. Personal award of **£60,000** for salary (£45k) and incidentals (£15k)

Associated projects

The original research leading to the concept of DIP was carried out under two linked EPSRC grants: EP/I019472 (PI Reuben) EP/I020101 (PI McNeill): ***E-finger: a tactile diagnostic device with microscale resolution, valued at*** *£402,246 and £399,137, respectively. The work has been further supported by the HWU EPSRC IAA (£84871), the UoE MRC CinC (£69,000), The Urology Foundation (£249,998)*

4MD

Multi-Modal Manufacturing of Medical Devices

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