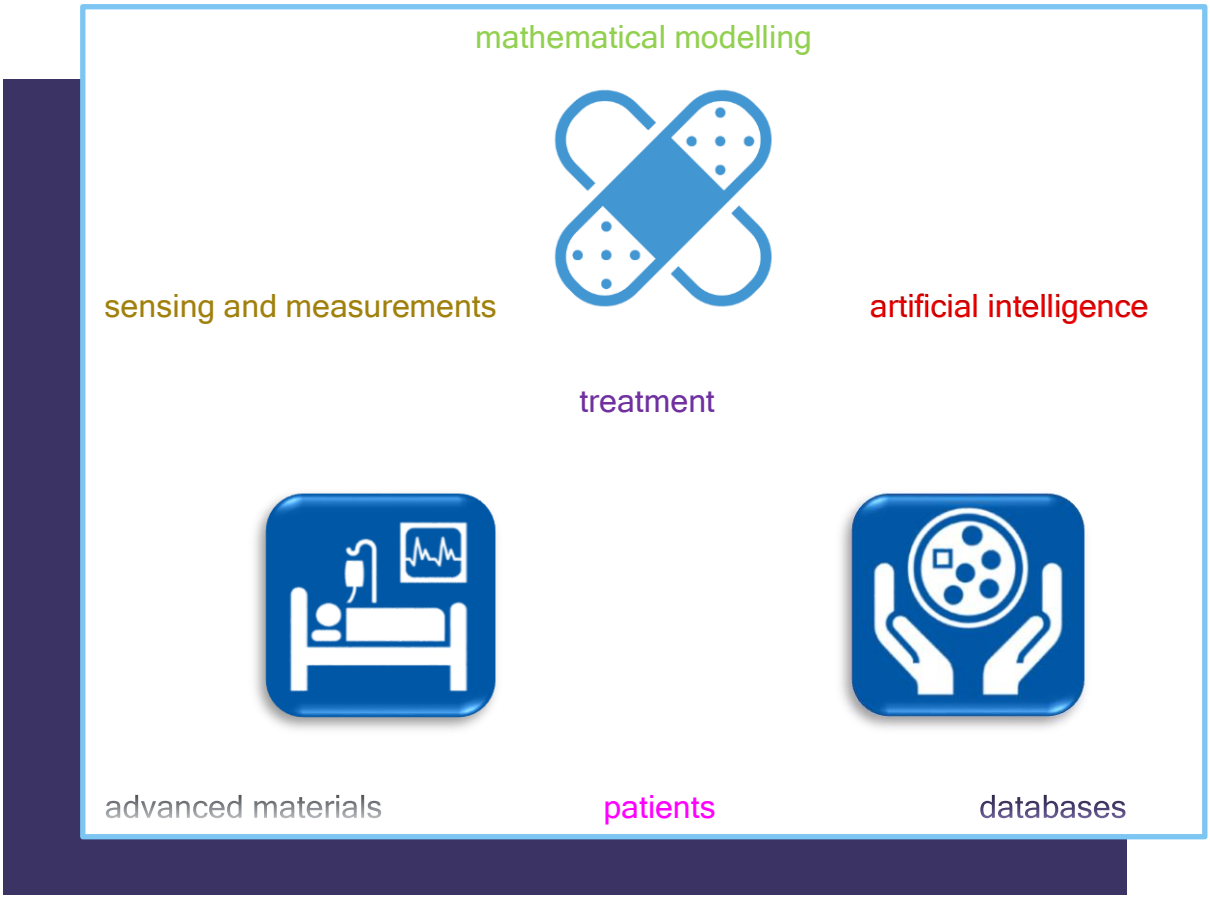
Cyclops Healthcare Network plus



ANNUAL REPORT 2018

Cyclops (Closed loop control systems for optimization treatment) is a multidisciplinary and multi-stakeholder network that aims to use approaches that involve using mathematical models to continuously monitor key clinical parameters to adapt treatment that is personal to the individual patient.

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EPSRC Engineering and Physical Sciences Research Council

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DEAR CYCLOPS' MEMBERS

We are at the end of a stimulating year for the network which has seen the development of new research ideas and the award of further funding for feasibility studies. Highlights include:

Strategic Highlights

- ✓ Increased membership: Membership to network rose from 80 to 120 in the past year, overall adding to existing expertise and the diverse set of skills available.
- ✓ Published Journal and conference papers: Despite projects being in early stages, four publications has been achieved, with others in progress.
- ✓ Increased engagement of early career researchers: Early career researchers are critical to our network as it shows development of researchers. A majority of projects in the network have the involvement of an early career researcher, including one project led by an early career academic.
- ✓ Increased collaborations: Collaborations within the network have increased with more universities working with each other, and with clinicians and industries.

Collaborations within the network have increased with 33 individual research partners from 19 universities, 17 academic departments, 7 clinical organisations, 3 Ltd companies, and one overseas institution

Financial Highlights

- ✓ A further call for proposals was announced in January 2018. Twelve feasibility project applications and one extension were received. Four feasibility projects and one extension were funded at a value of £230,000.

Operating Highlights

- ✓ Grand challenge workshop II: The 2nd Grand challenge workshop took place at the De Vere Jubilee conference centre on 11-12 January 2018. Delegates explored various perspectives in creating closed-loop control solutions for autonomous treatments in healthcare.
- ✓ We have redesigned our website www.cyclops-network.ac.uk to reflect themes in the Cyclops network in Cancer, Chronic Wounds and Critical care.
- ✓ Facilitating collaboration: for those unfunded feasibility study applications we provided feedback and where appropriate suggested additional collaborators from within the network.

Looking Ahead

In the third year of Cyclops, we aim to bring together ideas from our funded projects to support future funding applications. Increased collaborations has enabled us to form multidisciplinary teams that can collectively find solutions to autonomous personalised treatments in Cancer Care, Chronic Wound Care and Critical Care.

Particular thanks to Cyclops Network Manager, Dr Jasmine Harvey over the last year for her efforts in organising meetings, putting in place contracts and assembling this report.

Professor Steve Morgan
Principal Investigator of Cyclops

On behalf of the Leadership Team:

Programme Director:	**Dr Sergiy Korposh, University of Nottingham**
Co-Investigators:	**Prof Declan Bates, University of Warwick**
	Prof Helen Byrne, University of Oxford
	Prof Jon Hardman, University of Nottingham
Network Manager:	**Dr Jasmine Harvey**

GRAND CHALLENGE WORKSHOP II

The 2nd grand challenge workshop took place 12-13th January 2018, at the De Vere Jubilee Conference Centre, University of Nottingham. 55 delegates from 21 universities attended the workshop; including 9 clinicians, a patient representative, industry representatives, and technology adoption and translation service managers. Delegates were diverse on the disciplinary spectrum, ranging from mathematical modellers, data science and machine learning experts to biologists, human scientists, and specialist practitioners of healthcare. There was a high proportion of early-mid career researchers. The workshop enabled the network to grow from approximately 80 to 120 members.

Delegates explored various perspectives in creating closed-loop control solutions for autonomous treatments in healthcare. This year the focus of our grand challenge workshop was led by scientific themes especially: artificial intelligence, cognitive computing and data science, in relation to clinical themes of Cyclops. Over the two days, delegates were challenged to form multi-disciplinary teams to utilise these scientific themes to achieve finely titrate-able autonomous treatments. A call for feasibility study proposals was launched on 12th January 2018.

Call for proposals

Applicants were given 6 weeks to submit their feasibility study proposals. 12 proposals were received in addition to one extension on an existing project. This was a 117% increase in applications from the previous year, and funds applied for total £679k.

Proposals were reviewed and scored by the Cyclops steering panel using criteria set out in Table 1. Scores informed panel decision on awarding funding. The panel awarded funding to four feasibility studies totalling £230K and one extension at £15K. Funding was awarded at 80% full economic cost (FEC). Proposed projects were of high quality, and the panel would have awarded more funding were it possible. The next section details lay summary of the four funded projects.

Table 1: Evaluation criteria for guiding funding decisions of Cyclops projects

Evaluation (Please assign score for each item below out of the % allocated for each criterion)	
Items	**Grade**
Overall evaluation of the project	
1. Quality of the project is excellent in terms of novel ideas, concepts and techniques. (30%)	
2. Project addresses the remit of the Cyclops network: application of closed loop control systems to one or more of the clinical exemplar areas: cancer care, intensive care, chronic wound care. (10%)	
3. Evidence of understanding the clinical problem within the closed loop system framework by demonstrating a clear methodology. (10%)	
4. Project identifies effective activities to engage beneficiaries and collaborators for impact. (10%)	
5. Applicant(s) have good track record, includes early career researchers and show a balanced team. (10%)	
6. Project timeline and outcomes are feasible. (10%)	
7. Costs are properly justified and represent value for money. (10%)	
8. Project has potential to aid the development of a larger funded project and properly outlines next steps, including potential funding sources. (10%)	
❖ Please provide a summary of review	
❖ Strengths of project	
❖ Weaknesses of project	
❖ Suggestions for applicants	

2018 FUNDED PROJECTS

1. Smart Active Footbed for Wound Prevention and Management

Principal investigator:
Professor Paul Stewart,
University of Derby.

Project start year: 2018

Awarded: £57,952

Co-investigators:
Professor Frances Game - Royal Derby Hospital;
Professor Jill Stewart - University of Derby.

Lay summary

This project will establish the feasibility of using an active orthotic device with diabetic patients to manage their risk of developing foot ulcers. Such a device would contain an array of sensors to monitor foot health and possess the ability to alter its shape in response to any changes. These technologies will be enabled by a closed-loop intelligent control system that decides how best to manage an emerging problem. Our approach could potentially reduce both the number of appointments required with healthcare professionals AND advise the patient when referral to a specialist is appropriate. Data collected over time from the footbed would also be available to support diagnosis, prognosis and treatment decisions. There are three aspects to this work:

1. We will evaluate the performance of 'smart' materials in the form of active footbeds (these being materials whose shape can be changed by temperature or electrical signals).
2. We will establish what combination of sensors and intelligent data processing are available and appropriate for monitoring foot health.
3. We will integrate the available data into a closed loop control system that comprises smart sensing, intelligent signal processing, controlled smart materials and decision support.

The outcome of this work will be a novel prototype of an intelligent footbed. We will demonstrate that this device can adapt its shape in response to different footwear, varying patient weight and gait, and the development of minor foot deformations or injuries. We will also specify a roadmap for further research and development.

2. Combining physiological sensing and biomarkers with intelligent support surfaces for closed loop prevention of chronic wounds

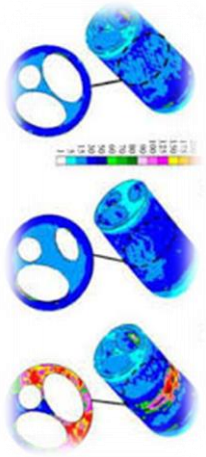
Principal investigator: Professor Dan Bader, University of Southampton

Project start year: 2018

Co-investigators: Dr Peter Worsley, Dr Luciana Bostan.

Awarded: £37,643

Other partners: Professor Steve Morgan - University of Nottingham; Professor Steve Jeffery - Birmingham City University; Mrs Siobhan McCoulough - OSKA Ltd.



Lay summary

The treatment of chronic wounds, such as diabetic foot, leg and pressure ulcers, represent a major burden to both the NHS and those affected with the condition. Indeed its financial burden has been estimated at approximately £5 billion per annum. Therefore the prevention of these chronic wounds via early detection of at risk individuals, represents a major challenge to healthcare organisations. Several monitoring technologies are available to detect changes in skin response to loading, involving an array of physical and biochemical markers, which can inform the effectiveness of intervention strategies for prevention.

The proposed research aims to provide an early detection system allied to an intelligent prevention strategy for pressure ulcer prevention, which will be evaluated with small cohorts of at-risk individuals. New and existing sensing technologies will provide distinct thresholds of physiological parameters, particularly involving CO2 sensing and biomarker concentrations, which could inform the effectiveness of both preventative measures and therapeutic interventions.

An intelligent active control system used in conjunction with the local support surfaces in contact with the skin will provide the platform for a closed-loop intervention. The surface, with for example periodic turning or alternating air pressure capability, will react to the physiological status of the skin and off-load vulnerable sites until complete physiological recovery has been achieved. Continual physiological monitoring and surface adaptation will provide the means for sustained postures, which are typically adopted in the hospital and community settings.

3. Closed-loop control for optimising chemotherapy infusion

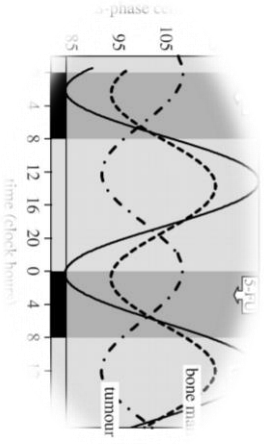
Principal Investigator: Dr Leandro Pecchia, University of Warwick

Project start year: 2018

Co-investigators: Professor Helen Byrne, University of Oxford.

Awarded: £59,876

Other partners: Dr Pasquale Innominato - Warwick Medical School; Prof Stephen Fôn Hughes, BCUHB, North Wales & North West Urological Research Centre; Prof Mike Chappell & Dr Vishwesh Kulkarni - University of Warwick.



Lay summary

"Inner clock adapts our physiology to the dramatically different phases of the day, […] regulating critical functions such as behaviour, hormone levels, sleep, body temperature and metabolism". This phenomenon is known as the biological clock or circadian rhythm and in 2017 its discoverers were awarded the Nobel Prize in medicine. Due to circadian rhythms, the efficacy and side effects of chemotherapy change throughout the day. Chemotherapy in turn alters circadian rhythm. This creates a closed-loop requiring control.

While circadian rhythms can be monitored using blood/salivary/urine hormone tests, such tests are not practical at home and do not provide continuous real-time monitoring. Combining artificial intelligence (machine learning and deep learning) and signal processing with commercial sensors embedded in smartwatches or clothes that measure physiological and behavioural attributes (features/variables) offers unprecedented and as yet unexplored opportunities to monitor circadian rhythms in real time. To the best of our knowledge, this project will be the first to:

Develop models for real time monitoring of circadian rhythms;
Model how circadian rhythms affect response to chemotherapy;
Answer fundamental questions that will pave the way for developing a (personalised) closed-loop control system in which the delivery of chemotherapy is related to a patient's circadian cycle.

This project could revolutionise the administration of chemotherapy, improve patient responses, and reduce side effects and costs.

4. Closed loop infection control using biocompatible wound dressings

Principal investigator: Professor Ipsita Roy, University of Westminster.

Project start year: 2018

Awarded: £59,385

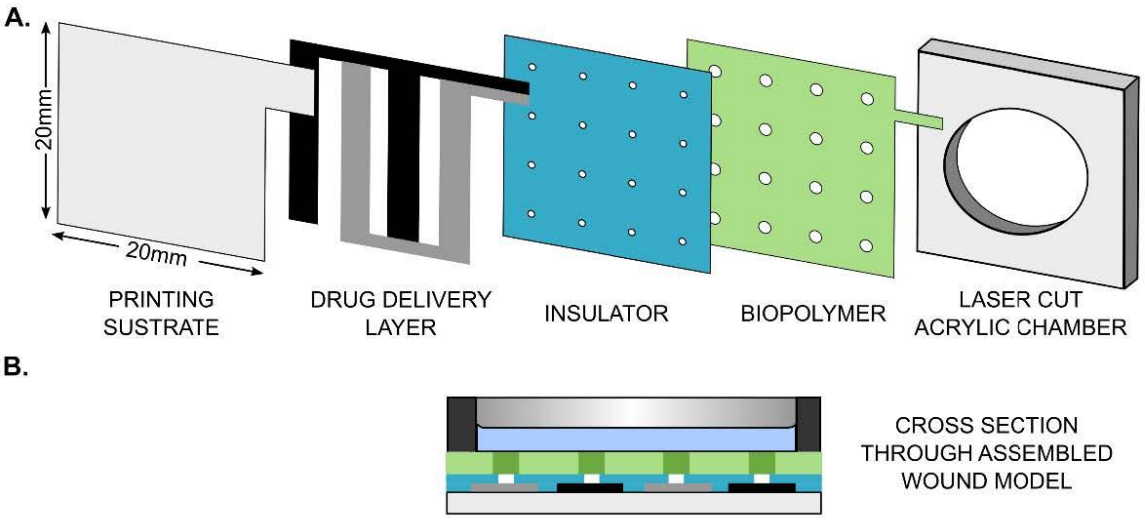
Co-investigators: Dr Damion Corrigan, Professor Patricia Connolly - University of Strathclyde; Dr Jongrae Kim, Dr Samit Chakrabarty - University of Leeds.

Lay summary

Chronic wound infections can have life changing consequences to patients and represent a significant burden to healthcare providers such as the NHS. Infections delay wound healing and can result in a worsening of the patient's condition.

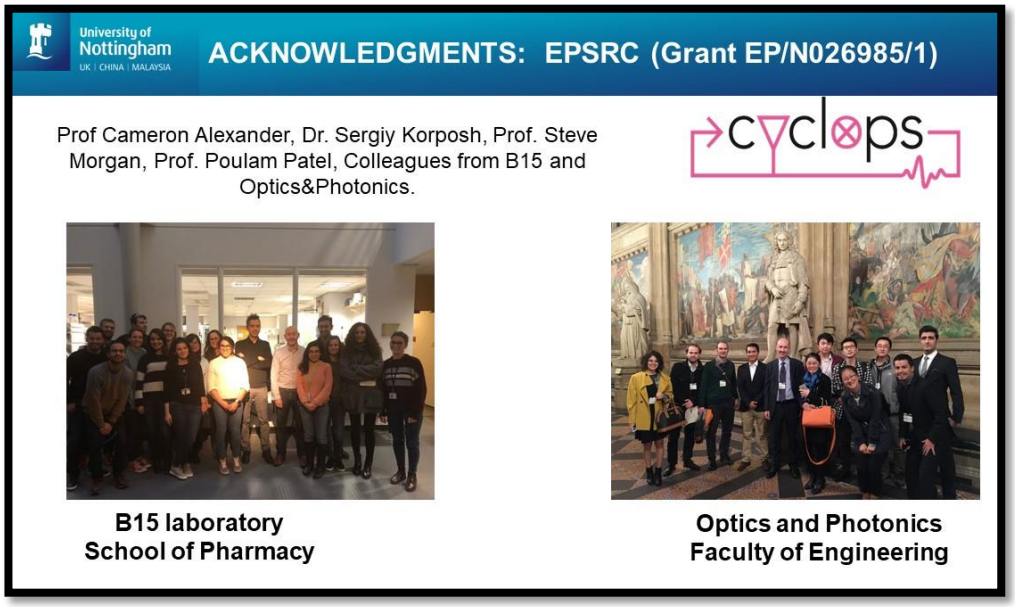
In this feasibility study, we will explore the use of a special polymer that promotes wound healing, whilst continuously checking the wound for infections. When an infection is detected, silver will be automatically released into the wound in order to kill the bacteria and help the wound to heal.

The concentration of silver released into the wound will be carefully controlled in order to ensure that the bacteria are killed, without building to levels of sliver that are toxic to the wound. At this stage, we will explore whether this approach is feasible using a series of laboratory based tests in a study across three separate universities.



PROGRESS REPORT ON EXISTING PROJECTS

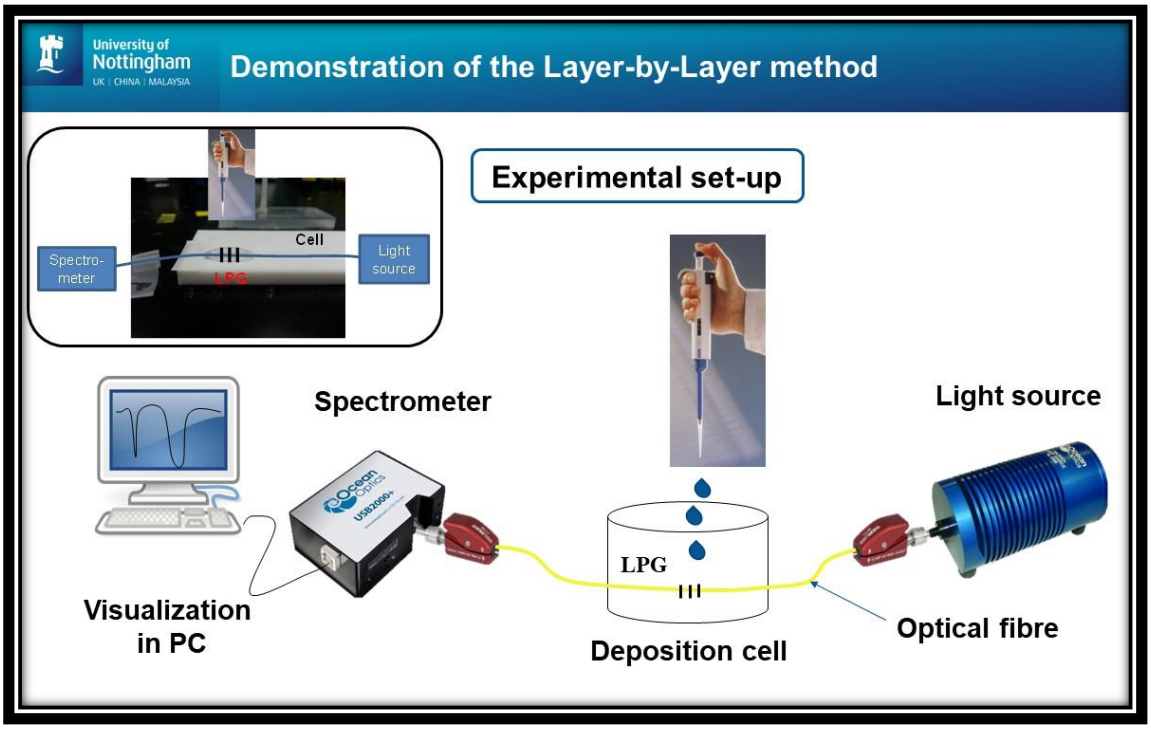
1: "SPI-CLOPS" (Surface Polymer Imprinted Closed Loop Optical Patient Sensors) for Dose Detection and Prevention of Cancer Resistance



The project was awarded £59,796 and is led by Professor Cameron Alexander from the School of Pharmacy, University of Nottingham. Members of the team include Dr Ulises Hernandez (post-doctoral research fellow), Dr Serhiy Korposh and Professor Steve Morgan from the Optics and Photonics group at Faculty of Engineering, University of Nottingham; Professor Poulam Patel from Nottingham University Hospitals NHS Trust; Professor Helen Byrne from the Mathematical Institute, University of Oxford; and Dr Kristofer Thurecht, University of Queensland, Australia.

Status Summary

Key aims of this project are to accurately monitoring of dose and detection of resistance in cancer, and develop an ambitious new healthcare technology, applicable to areas far beyond melanoma. The research currently is focused on the first stage of the project, that is, the development of a polymer-coated fibre long period grating (LPG) to detect dabrafenib in serum. The polymerization is tried onto the surface of optical fibres through photo-polymerization (using UV light), and characterization of the polymers has been performed using spectroscopy techniques (UV-Visible and FTIR) and nano-metric scale microscopy (SEM). All the experiments and results obtained up to date were implemented with 2-Aminoquinoline, which is an analogue of the drug of interest (B-Raf inhibitor dabrafenib).



Overview

The project has three objectives:

a) Develop polymer-coated optical fibre long period gratings to detect dabrafenib in serum.
b) Derive 2D and 3D cultures of B-Raf sensitive cells and validate dabrafanib monitoring in extracellular milieu.
c) Interface recognition polymers with pH sensors in the fibre which can detect local changes in pH, and test readouts from fibres in 3D tumour spheroids.

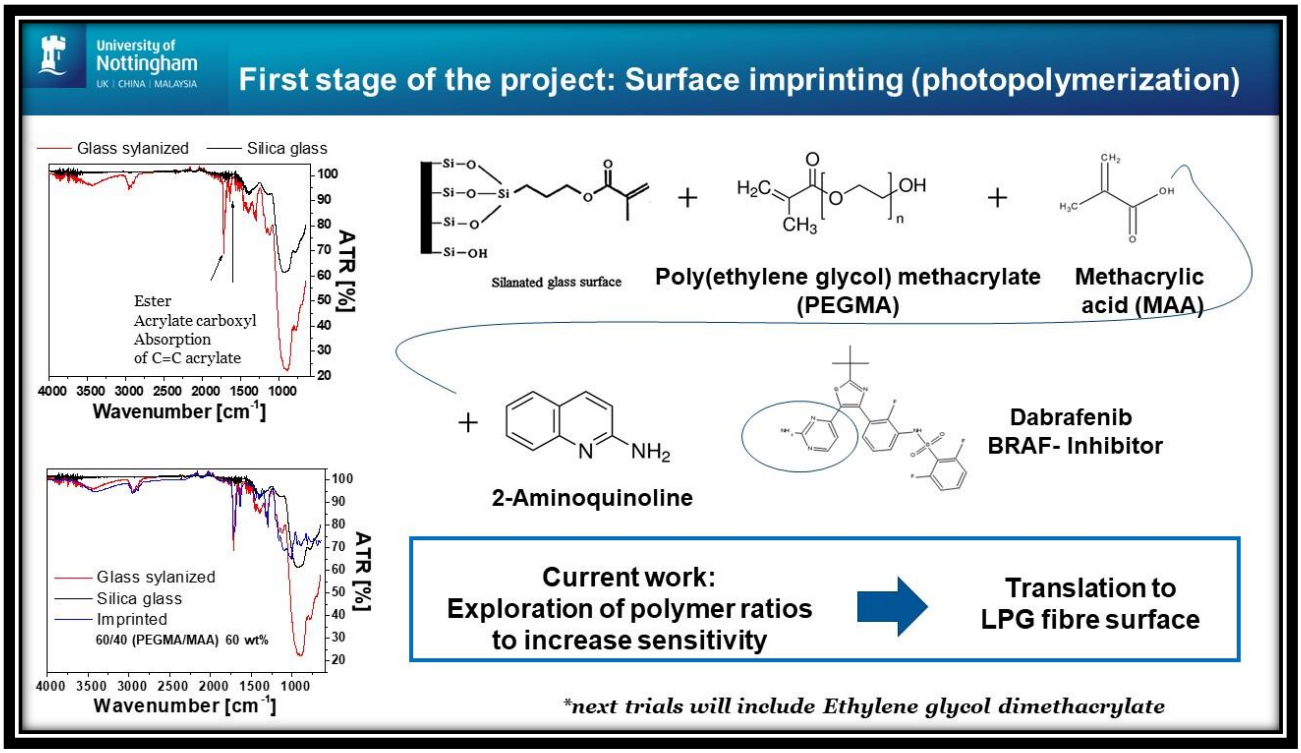
The project is on budget and time. Each objective is being addressed collaboratively by the project investigators with good progress, more than 50% is completed in some cases.

Challenges

Project specific challenges are concerned with demonstrating certain techniques and components of the solutions being created. For example: Demonstration of 2-AQ and dabrafenib binding on polymer-coated LPGs and demonstration and validation of the polymer-coated optical sensors in 2D or 3D cultures of B-Raf.

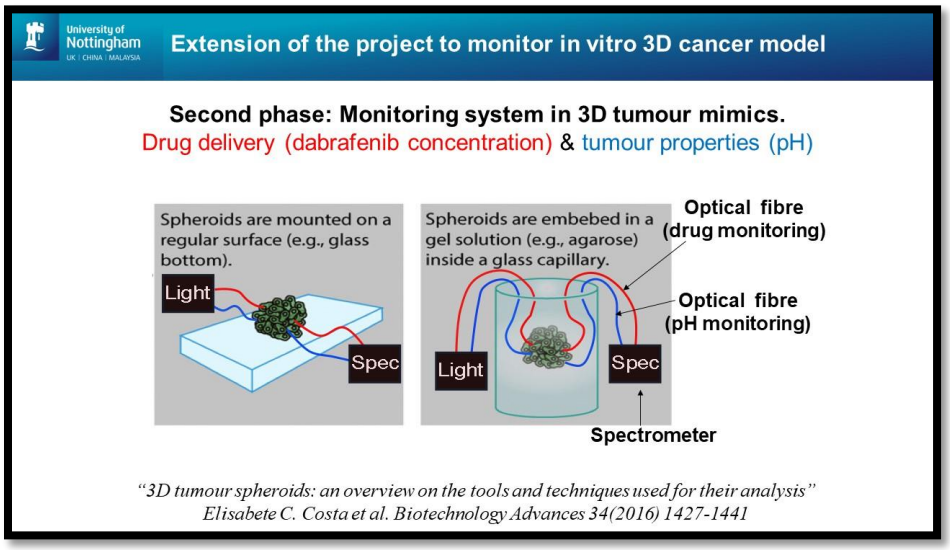
Achievements

These, so far, are project specific and include Dr Hernandez mastering the technique of characterization of photo-polymerization, and being able to translate the technique onto LPGs to make the device more sensitive. A conference paper has been accepted (further details on page 19).



NEXT STEPS

The feasibility of this project will include the best conditions to reproduce photo-polymerization onto LPG sensors and allow detection either of 2-AQ or dabrafenib in serum, water or PBS. Cross-sensitivity with similar compounds will be reported along with detection limits and best sensitivity for analyte detection (as anticipated achievements).



The project's time frame has been extended for a further six months to achieve a validation with 3D spheroids. Development of 3D spheroids started in June 2018 in the cell culture laboratory of Boots Science Building. Validation with skin organ tissue will not be feasible during the next 6 months, but a protocol and ethics application form is being prepared for a second stage of this project.

2: Investigation of closed-loop ventilation strategies for neonatal ICU patients using computational simulation

This project was awarded £59,700.00, and is jointly led by Professor Declan Bates from the School of Engineering, University of Warwick as the Principal Investigator; and Dr Don Sharkey from School of Medicine, University Nottingham. Other members of the groups are Dr Lara Shipley (clinical academic fellow), and Professor Jonathan Hardman, both from the School of Medicine University of Nottingham.

Status Summary

The project is about to enter into the main data collection phase following a period of mandatory NHS approvals. As part of WP1, paperwork for ethics, R&I and HRA approval were prepared and submitted in January 2018. Approvals have been obtained since April 2018, however there has been a significant delay obtaining the required research passports from the hosting NHS Trust as a result of major reconfigurations in their structure. The data collection system has been revised and this is all ready to collect data once all researchers have the required approvals to collect clinical data.

Overview

This project has five work packages, which aims are:

a) WP1: Generation of a comprehensive dataset on the responses of neonatal patients to changes in mechanical ventilator setting.
b) WP2: Additional modelling work to incorporate specific aspects of neonatal physiology into our current simulation platform.
c) WP3: Training, optimisation and validation of the new neonatal patient simulator against extant and prospectively acquired patient data.

d) WP4&5: Development and evaluation using in silico “virtual clinical trials” of algorithms to implement closed-loop ventilation on the neonatal patient simulator. Industrial partnerships.

Despite challenges (outlined under status summary), good progress has been made overall. For example 80% of WP2 is completed. The team has met and reviewed some of the parameters for the modelling based on published measures and clinical databases. Preliminary work looks encouraging and areas to develop the models have been identified.

CHALLENGES

The processes of obtaining Ethics, NHS Research and Innovation, and Health Research Authority (HRA) approvals have been key obstacles. These processes are time consuming for clinical-related projects where human subjects are being studied. In addition, obtaining a research passport from a NHS Trusts for research to be conducted on their premises is another obstacle that needs to be overcome. Devising a new pathway for obtaining research passports from a NHS Trust would contribute greatly to research time.

ACHIEVEMENTS

A logging system for a robust data collection has been established, and preparation work needed for the project to commence is being finalised.

NEXT STEPS

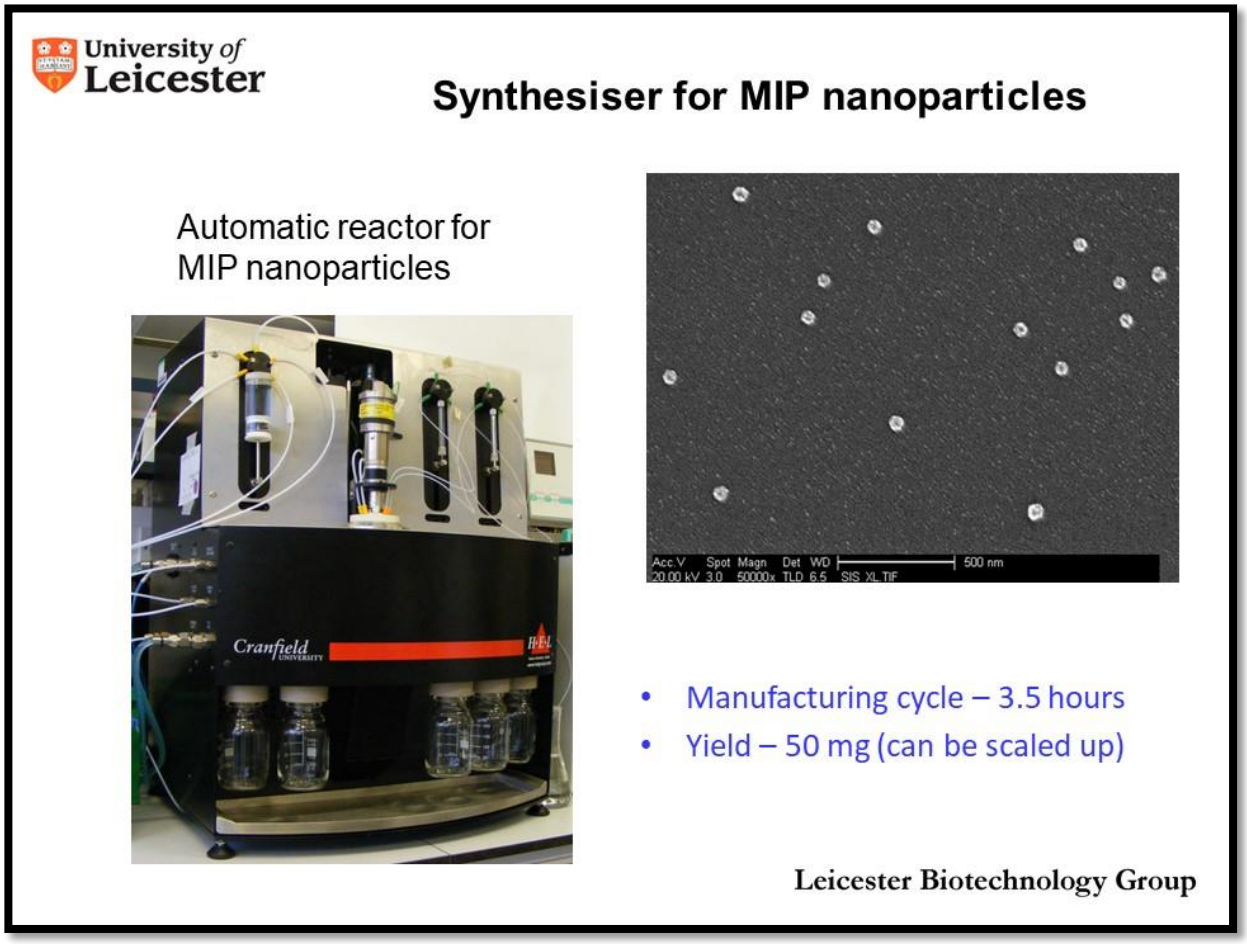
The aim is to begin patient data collection in July and move swiftly through all patients once all approvals in place. Models have already been reviewed and revised to address patient population disease entities. This will provide the feasibility data for the latter work packages and allow the new simulation models to be developed and tested; the team aims to be through a majority of this phase in the next six months now the major approvals challenge is almost complete.

3: Closed loop drug monitoring and delivery in intensive care

This project was awarded £57,210 in 2017, and is led by Dr Andrew Norris, Consultant Anaesthetist, at Nottingham University Hospitals NHS Trust. The team include Professor Sergey Piletsky, Department of Chemistry, University of Leicester, Dr Francesco Canfarotta (senior research scientist) at MIP diagnostics Ltd, Leicester, Mr Liang Liu (PhD candidate), Dr Serhiy Korposh and Professor Steve Morgan from Optics and Photonics group, Faculty of Engineering University of Nottingham.

Status Summary

The group have been successful in developing novel optical sensors to measure sedative and analgesic drugs such as fentanyl and propofol. The sensors comprise molecular imprinted nano-particles (MIPs) deposited onto long period grating optical fibre sensors. Initial proof of concept data demonstrated the high potential of the proposed sensing platform and successfully detected fentanyl at clinically relevant concentrations. A peer-reviewed conference paper has been published, and this work has been presented at Optical Fibre Sensors (OFS'26) conference, Switzerland, 24-28th of September 2018.



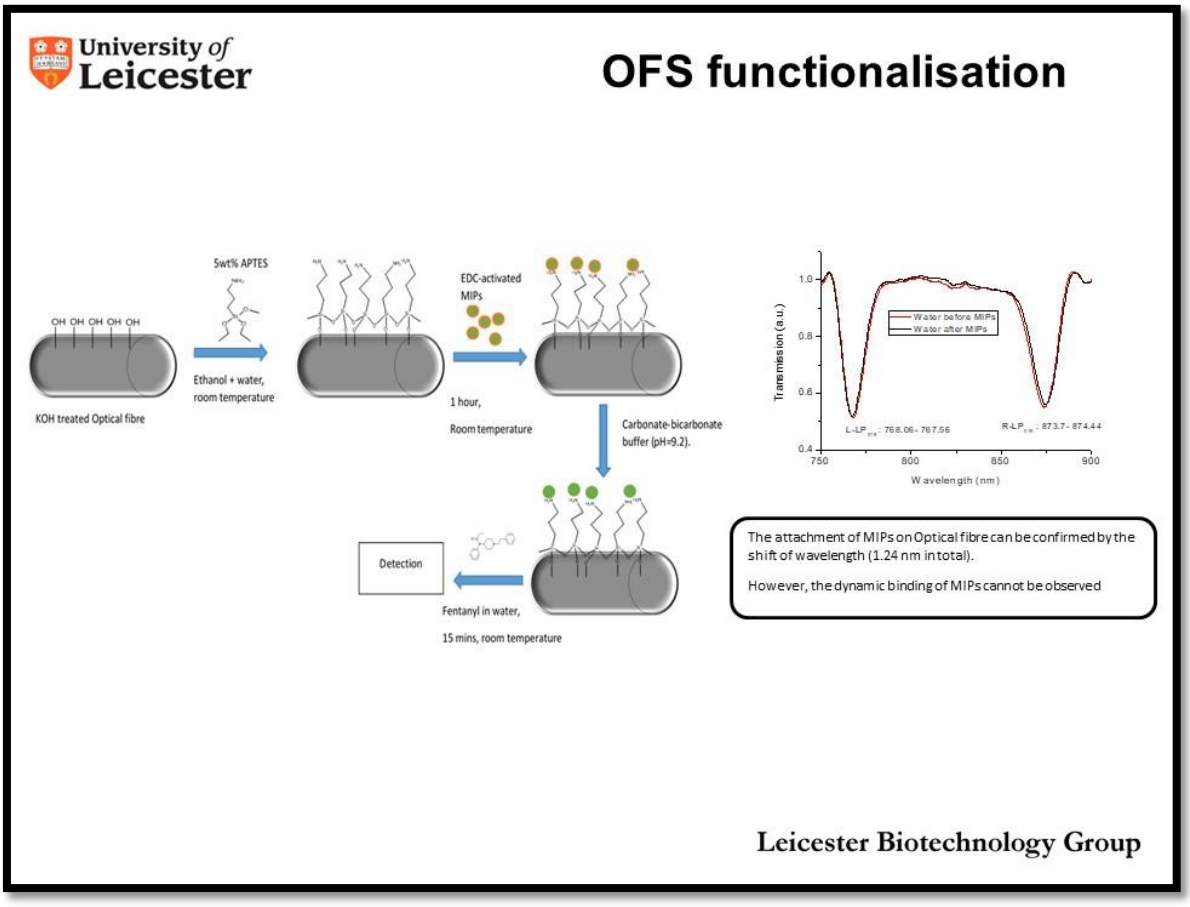
Overview

The aim of this project is to produce a closed loop control system in which key pharmacological and physiological parameters are monitored in real time and the drug dose altered automatically to optimise patient treatment.

Three key objectives of the study are:

1. Synthesise nanoMIP particles (MIPs) for fentanyl and propofol.
2. Integrate of MIPs with optical fibre sensors.
3. Test sensor performance in model samples and blood.

The first objective is completed. MIPs were synthesized for fentanyl and propofol. Three candidate drugs were tested, and two were successful. The suitable binding agent could not be manufactured in the time available for the 3rd drug (midazolam) due to challenging chemistry. The second objective is also completed. NanoMIPs were successfully deposited onto an LPG (see conference paper in publications section for results). The third objective is 50% completed. The sensor was successfully tested with fentanyl and propofol dissolved in the buffer. Next steps will be to conduct these measurements in blood samples. The team has discovered, and would like to explore, novel aspect using fluorescence of the nanoMIPs that can be used to detect fentanyl and propofol.



There has not been a particular challenge identified on this project, however it is hoped that results can lead to optimisation and the creation of more uniform sensors with greater density of binding sites.

Achievements

Project specific achievements are that the LPG sensor responded to fentanyl, the development of fluorescence nanoMIPs where a change in the fluorescence signal was detected, and this can be used to provide a road map for other projects; and the LPG sensor responded to the propofol.

For wider achievements, in addition to the accepted conference publication, a peer-reviewed journal paper was published in Sensors & Actuators: B. Chemical. Further details are discussed on page 19 under Early Impacts.

Next Steps

Objectives set in the proposal were successfully achieved. Novel sensors have been developed and tested. Once further proof of concept data have been obtained, the group plans to apply for funding for further development including clinical trials and regulatory approval towards developing a commercial system.

It is believed that the enhanced patient safety and personalized care aspects of the subsequent proposed study will be attractive to the NHS and international healthcare providers. The more detailed proof of concept data obtained during next few months will be used for the EPSRC funding application.

Due to the success of this project, cyclops panel members awarded a further £15,000 to its investigators to enable further exploration of findings.

EARLY IMPACTS

Journals and conferences

From the three projects funded in 2017, two journal articles have been published in peer review journals. They are:

1. **R. Correia**, S. James, **S. Morgan**, **S-W. Lee**, **S. Korposh**, Biomedical application of optical fibre sensors. Journal of Optics, 2018, 20, 073003.
2. **L. Liu, L**. Marques, **R. Correia**, **S. Morgan**, **S.-W. Lee**, P. Tighe, L. Fairclough, **S. Korposh**, Highly sensitive label-free antibody detection using a long period fibre grating sensor, Sensors & Actuators: B. Chemical, 2018, 2018, 271, 24-32.

In addition, two conference papers were presented at the 26th International Conference on Optical Fibre Sensors (OFS) held from 24-28 September 2018 at SwissTech Convention Center, Lausanne, Switzerland. The conference papers are led by Mr LiangLiang Liu and Dr Francisco Ulises Hernandez, who are both early career researchers. Title of the papers are: '*Molecularly Imprinted Nanoparticles Based on Long Period Grating Sensor for Detection of Fentanyl';* and, '*Propofol Detection Using Optical Fibre Long Period Grating Sensors with Molecularly Imprinted Host-Guest Binding Sites in TiO2 Films'* respectively.

Other outputs

Network PI, Professor Steve Morgan and other investigators have conducted talks concerning Cyclops ambitions at various healthcare events. An example is Prof Morgan's talk at a Centre for Healthcare cross-disciplinary networking event held at Nottingham on 28th March 2018. Also, Cyclops Network funded project, '***Smart shoe insole for monitoring foot health of patients with diabetes***', has been selected as one of the case studies for MEU marketing documents. The novel insole contains an array of sensors to screen feet: full article.

Other activities

Network members describing Cyclops activities including our open calls competitions include blogs by Professor Paul Stewart from University of Derby (http://www.pesri.net/blog/?p=3913); and Professor Dan Bader from the University of Southampton (https://www.southampton.ac.uk/mdvsn/news/2018/06/cyclops.page

"We are learning that the idea behind Cyclops is popular, and researchers are capable of creating autonomous technological solutions that could revolutionise treatment. We are at the early stages but believe we have sown the seeds for exciting new developments"

Dr Serhiy Korposh, Director of Cyclops

Future plans

- Shaping future proposals: In our next annual event, we plan to involve key members in the network who are interested in extending their feasibility studies into further funding applications.
- Special interest group: We are also exploring the possibility of obtaining additional funding to run Special interest group events so ideas and nuances within Cyclops can be explored further.
- Dissemination event: Network funding will end during 2019 and we aim to hold a dissemination event in September 2019.

We will explore with network partners whether there is demand to run the network beyond the funding end date and explore ways of doing this.