cyclops

EPSRC
Engineering and Physical Sciences Research Council

CYCLOPS HEALTH NETWORK PLUS ANNUAL REPORT

2017

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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Executive summary

The closed loop control systems for optimization treatment network (Cyclops) conducted six key activities during the first year of its operation. These activities have grounded the network and laid foundation for its long-term goals:

1. Website creation: a dedicated website was created to increase cyclops visibility and inform network members and external stakeholders at all times.
2. Network creation: A multidisciplinary and multi-stakeholder network was created by invitation to academics, clinicians and industry stakeholders. Institutions which formed part of the EPSRC collaboration bid facilitated in this.
3. Creation of the networks' steering committee: the five co-investigators formed the network's management team, in addition to six members of the advisory board group and a network manager.
4. A grand challenge workshop: A grand challenge workshop was conducted in March 20-21st to bring together all stakeholders so that they could identify opportunities for research within the Cyclops remit in three clinical areas.
5. Feasibility studies: Following a successful call for proposals, three feasibility studies were funded, with the aim to fund five later on.
6. Pathways to impacts: Establishing pathways to impacts on national and international platforms.

HIGHLIGHTS

The effectiveness of these activities enabled Cyclops achieve its first year deliverables, chiefly, the funding of three feasibility projects that could reveal new methods of personalised patient treatment using autonomous clinical decision-making systems; creation of collaborations that could lead to high-level commercial and societal impacts; and, creation of support for earlier career scientists.

LOOKING AHEAD

Looking ahead into year two, we plan to build on the our first year success by funding more feasibility studies that would create further links with clinicians, industry and other organisations and extend interdisciplinary collaborations.

We discuss our six key activities under the following headings.

Professor Steve Morgan (Principal Investigator)

Dr Serhiy Korposh (Director)

November 1, 2017

Network and Website creation

WEBSITE CREATION

Cyclops was initially represented online at the Centre for Healthcare Technologies website. In May 2017, the website was moved to a dedicate space on the web: www.cyclops-network.ac.uk. This helped increase visibility for the network and enabled easier navigation to the site.

NETWORK CREATION

The Cyclops network, which begun in November 2016, is funded by the EPSRC (Engineering and Physical Sciences Research Council, Grant reference EP/N026985/1) as part of their Healthcare Technologies Grand Challenges Networks Plus.

Cyclops stands for closed-loop control systems for optimization treatment. The rationale behind Cyclops is to develop solutions that would enable patients to be treated using a continuous monitoring of clinical parameters informed by mathematic models for autonomous clinical-decision making.

The combination of computer power, sensitive sensors and finely-titratable treatment protocols has the potential to allow closed-loop control approaches to offer a revolutionary leap in medical treatment. Particularly to areas such as the delivery of treatment to cancer patients, moment-to moment management of critical ill (or injured patients) in intensive care, and the accelerated healing of chronic wounds. Challenges and opportunities in these three clinical areas are however yet to be addressed in the closed-loop system.

The rationale behind Cyclops is to bring together multidisciplinary experts comprising academics, clinicians and industrialists as a network, whose aim is to work together to identify clinical and scientific challenges, gaps and new ideas that could impact on society, in relation to autonomous closed-loop control (CLC) systems (Figure 1).

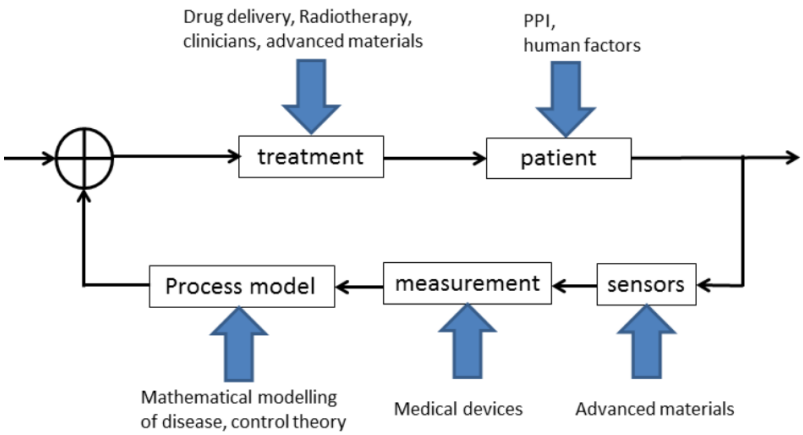
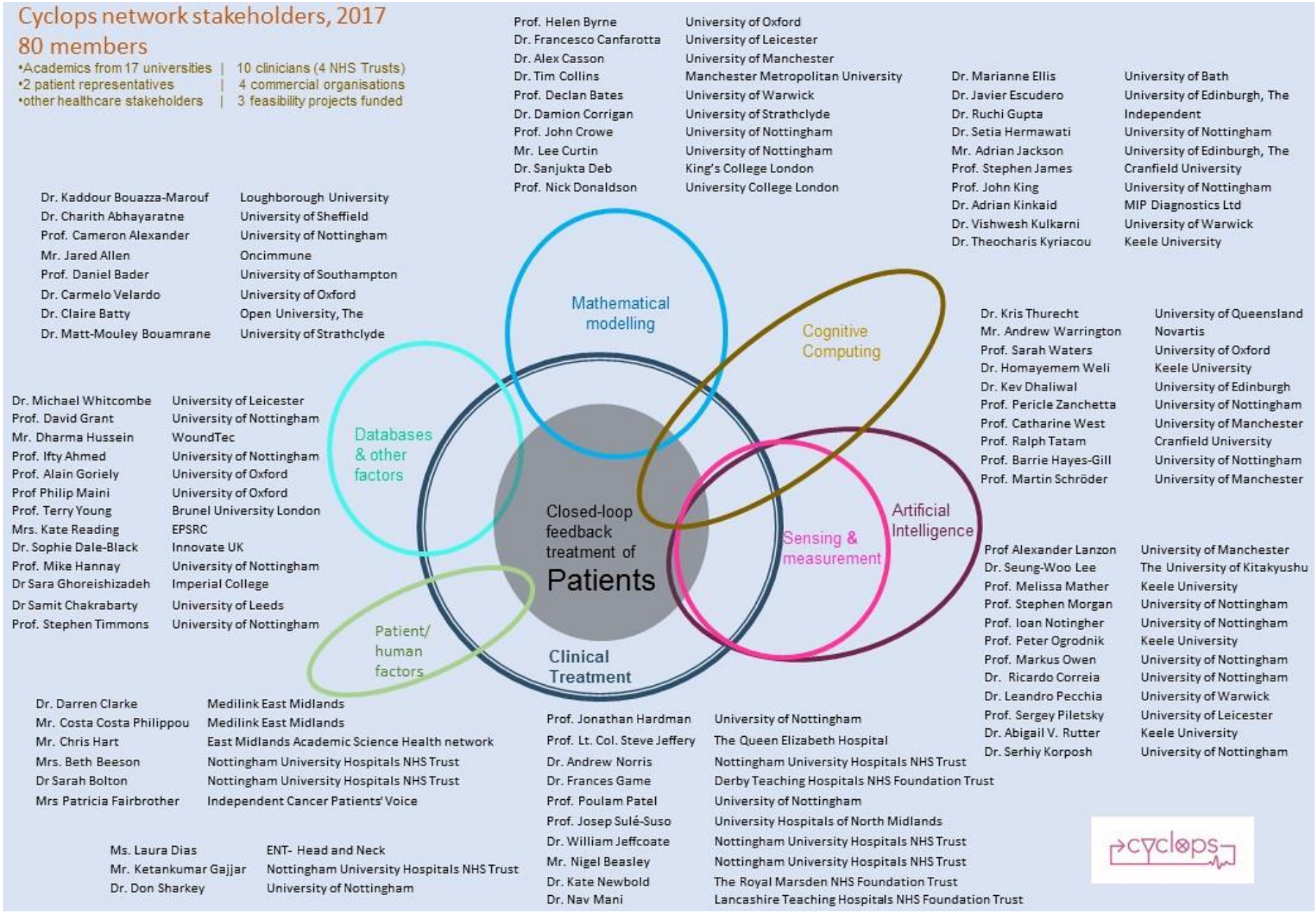


Figure 1: The closed-loop approach to optimising treatment

In year one, the network grew from 40 to 80 members. True to its multi-disciplinary objective, network members consist of academics from 17 universities, patient representations, commercial organisations, NHS organisations and other stakeholders. Figure 2 shows the varied interests of our stakeholders.

Figure 2: Network stakeholders and partnership structure



NETWORK STEERING COMMITTEE

Network steering committee

a. Investigators

Cyclops healthcare network plus is a collaboration between universities of Nottingham, Oxford and Warwick. Short biographies of the investigators are outlined below.

Steve Morgan is Professor of Biomedical Engineering, Faculty of Engineering, at the University of Nottingham His research focuses on the development of novel optical devices to monitor the microcirculation for application in tissue breakdown and wound healing. In Cyclops, he is Principal Investigator and leads the clinical exemplar area of wound care.

Dr Sergiy Korposh is an Associate Professor in Electronics, Nanoscale Bioelectronics and Biophotonics, Faculty of Engineering at the University of Nottingham. His research focuses on the development and fabrication of chemical sensors based on a range of sensing platforms modified with functional nanomaterials. He is Cyclops Co-Investigator and Network Director.

Jonathan Hardman is clinical professor in anaesthesia and critical illness at the University of Nottingham, and a consultant anaesthetist in the NHS. His research focuses on the modelling of human pathophysiology including the application of modelling to anaesthesia and critical care. In Cyclops, he is a Co-Investigator and is co-leading the clinical exemplar area of Intensive Care.

Helen Byrne is Professor of Mathematical Biology at the Mathematical Institute, University of Oxford. Her research focuses on the development and analysis of mathematical and computational models that describe biomedical systems, with particular application to the growth and treatment of solid tumours, wound healing and tissue engineering. She is Cyclops Co-Investigator and leads the clinical exemplar area of cancer care and the pathways to impact activities.

Declan Bates is Professor of Bioengineering, School of Engineering, at University of Warwick. His research focuses on the modelling, analysis, control and design of complex biological systems. He is experienced in the validation and verification of safety-critical systems. He is Co-Investigator and co-leads the clinical exemplar area of Intensive Care.

b. Management

The network is managed by Dr Jasmine Harvey, who is experienced in leading technology-based healthcare projects. She was formerly employed as researcher at Universities of Oxford and Nottingham in Primary Care departments. Jasmine also currently holds an assistant (consultant) professor post at the School of Medicine, University of Nottingham. In Cyclops, she is the Network Manager.

c. Advisory panel

Cyclops advisory panel, together with the management team, steer the network. Six members constitute Cyclops advisory board; their responsibilities are to oversee the award process and ensure fair and transparent distribution of funding to the networks members. Cyclops advisory panel are also tasked to help extend the network and provide advice to the management team. Members were sourced from a variety of disciplinary backgrounds, and constitute:

- Professor Terry Young (Chair) - Professor of Healthcare Systems, Brunel University London.
- Professor Melissa Mather - Professor of Biomedical Engineering, Keele University.
- Mrs Beth Beeson - Consultant Clinical Engineer, Nottingham University Hospitals NHS Trust.
- Mrs Kate Reading - EPSRC representative.
- Professor Mike Hannay - Managing Director - East Midlands Academic Health Sciences Network.
- Dr Carmelo Velardo - Senior Researcher and Departmental Lecturer, the Oxford Institute of Biomedical Engineering.
- Dr Sophie Dale-Black - Communications Manager - Innovation Excellence, Innovate UK (who is currently not active due to change of roles at Innovate UK).

Grand challenge workshop

OVERVIEW

The interdisciplinary workshop took place on 20-21st March at the Nottingham Conference Centre. It was attended by 60 delegates from 18 universities from the UK and internationally. The purpose of the workshop was to facilitate multidisciplinary academics and other stakeholders to create a network, and to identify challenges and gap in the three clinical areas of Cyclops. Gaps identified would then be formed into proposals for feasibility studies that have potential for developing into bigger projects in cyclops clinical areas.

Overall, general consensus among delegates after breakout discussions was that achieving closed-loop solutions in clinical areas such as cancer and wounds would be challenging as a human intervention is necessary. This is unlike intensive care, which leads the innovation in autonomously delivering drug dosages.

A question which arose from the discussion was: what constitutes a closed-loop system? Network members agreed that definition of closed-loops varied in context however, it is generally used to mean when information is fed back and used to change status of the patient to make the loop autonomous.

A call for proposals for launched at the end of the grand challenge workshop to find closed-loop project ideas.

Feasibility studies

Following a call for proposals to create collaborations within the network with the aim of furthering Cyclops objectives, six feasibility study applications were received. The applications reflected some of the challenges discussed at the workshop regarding autonomous solution in areas other than intensive care. Three applications were received on intensive care, two on cancer care and just one on chronic wound care. Although the central messages of the applications aim for closed-loop autonomy, some found it difficult to describe how the closed-loop would be applied in their methodology. Consequently three feasibility studies were funded, two in intensive care, and one on cancer care. This highlighted the problem area of finding autonomous solutions in cancer and wound wounds care. Lay summaries of funded feasibility studies are outlined in the next sub-sections.

FEASIBILITY STUDY 1: INVESTIGATION OF CLOSED-LOOP VENTILATION STRATEGIES FOR NEONATAL ICU PATIENTS USING COMPUTATIONAL SIMULATION

Principal Investigator:	Professor Declan Bates, University of Warwick
Co-Investigators:	Professor Jonathan Hardman, University of Nottingham. Dr Don Sharkey, Nottingham University Hospitals NHS Trust.
Other partners:	Medtronic Research. Philips. Dreager
Cyclops award:	£57,000.00

Lay summary

Ventilated critically ill newborn babies are prone to sudden and large changes in their respiratory state, requiring frequent and rapid interventions by ICU staff. If not acted on promptly, these can increase the risk of brain injury or eye disorders resulting in long-term disabilities and blindness. Closed-loop ventilation control modes have the potential to simultaneously improve patient care and reduce staff workload, by automatically adapting ventilator settings in response to changes in the physiological state of the patient. To date, however, such closed-loop technologies have only been applied to the care of adult ICU patients. We will extend and adapt a computational simulation platform that has been developed by the investigators over the past 10 years, so that it can accurately represent the unique (patho) physiology of mechanically ventilated neonatal patients. Using extant and prospectively acquired date we will validate the capability of our simulator to replicate the responses of individual newborn babies to a variety of changes in mechanical ventilator settings. Once validated, the simulator

will be used to investigate the feasibility of developing closed-loop control algorithms that are tailored to the specific requirements of neonatal patients. Throughout the project, we will engage with our industrial partners (Medtronic, Philips Research, etc) to expedite the transfer of our closed-loop control technologies into the next generation of mechanical ventilators. On completion of the feasibility study, we will write a large-scale EPSRC/MRC grant application that will provide the resources to fully realise the many potential clinical and industrial applications of this work.

FEASIBILITY STUDY 2: CLOSED LOOP DRUG MONITORING AND DELIVERY IN INTENSIVE CARE

Principal Investigator:
Dr Andrew Norris, Nottingham University Hospitals Trust

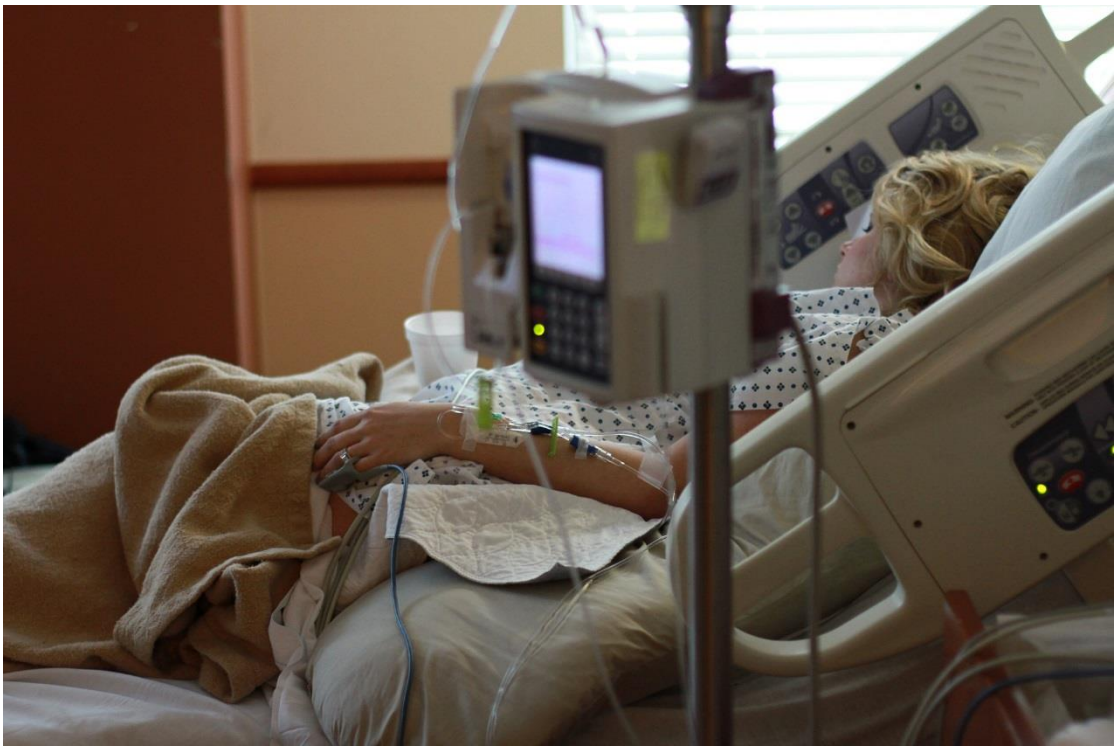
Co-Investigators:
Professor Sergey Piletsky, University of Leicester
Sergiy Korposh, University of Nottingham
Stephen Morgan, University of Nottingham

Other partners:
Prof Alexander Lanson, University of Manchester
Dr Sanjukta Deb, King's College London
Andrew Pritchard (B Braun Ltd)

Cyclops award: £56,710.00

Lay Summary

Survival in intensive care (IC) depends on having a comprehensive picture of a patient's condition. Accurate continuous monitoring of vital parameters such as gas exchange, blood pressures and heart rate, temperature, ventilator mechanics, renal function, nutrition, and metabolism are available. However, continuous monitoring of drug levels is an unmet clinical need, the solving of which would provide a step change in IC practice and enable clinicians to provide optimised and individualized treatment of critically ill patients, with potential for reduced length of stay and of adverse events. Each patient day costs ~£1900. Using novel optical chemical sensors, we propose to



develop real-time blood level monitoring of sedative and analgesic drugs such as fentanyl, midazolam and propofol. This would enable precise and individualized monitoring of infusion rates or other dosing schedules to maintain continuously effective drug levels while minimizing adverse effects due to overdosage and accumulation. This is particularly important in drugs which have a narrow therapeutic window, or those with significant toxic side effects, for example, aminoglycosides and ciclosporin, if not administered correctly, can induce hearing loss and kidney failure.

FEASIBILITY STUDY 3: "SPI-CLOPS" (SURFACE POLYMER IMPRINTED CLOSED LOOP OPTICAL PATIENT SENSORS) FOR DOSE DETECTION AND PREVENTION OF CANCER RESISTANCE

Principal Investigator:
Professor Cameron Alexander, University of Nottingham

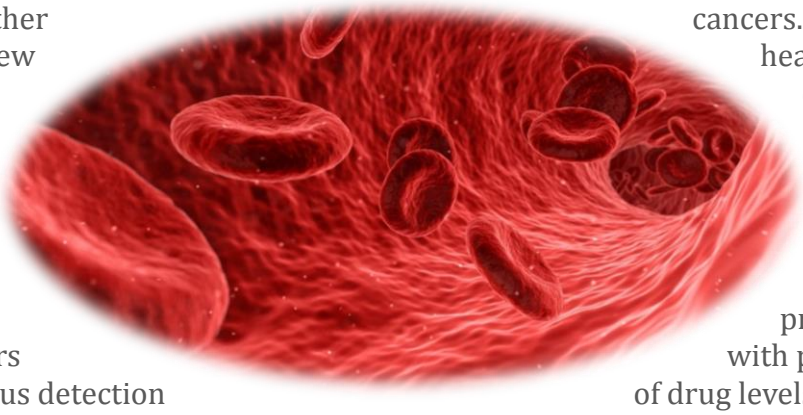
Co-Investigators:
Helen Byrne, University of Oxford).
Ioan Notingher, University of Nottingham
{3} Serhiy Korposh, University of Nottingham
Steve Morgan, University of Nottingham

Other partners:
Kristofer Thurecht, University of Queensland, Australia

Cyclops award: £59,796.00

Lay summary

The treatment of melanoma has improved dramatically since the introduction of drugs that interfere with disease specific pathways. However, the development of resistance to these drugs is a major cause of concern, as it leads to treatment failure and poor patient outcomes. Early stage detection of resistance to cancer drugs could revolutionise therapeutic regimens for melanoma and other cancers. This proposal sets out the first stages in a new healthcare technology which could enable clinicians to monitor the efficacy of cancer drugs in appropriate time scales, and detect the first signs of resistance thus indicating the optimum time to administer combination therapies. Specifically, the project will develop advanced fibre-optic sensors with polymer coatings which allow simultaneous detection of drug levels in a cancer model and the onset of resistance pathways. Our vision is for sensing electronics and polymer materials science to be combined with mathematical modelling and 3D tumour mimics thus providing the critical proof-of-concept data prior to in vivo studies. We have assembled a multi-disciplinary, and international team with expertise linking physical and engineering science to advanced clinical oncology to tackle this vital unmet societal and medical need. Ultimately we envisage a fully automated system in which drug delivery and tumour properties are monitored so that the appropriate dose can be delivered at the appropriate time.



Pathways to impact

Our first year activities show Cyclops is establishing pathways to impact.

A multidisciplinary, multi-stakeholder network was formed and brought together to investigate this approach and its applicability to different clinical conditions in our first all-in-one Grand Challenge Workshop held in March 2017, in which breakout discussion sessions were led by a clinicians and academics. The sessions addressed challenges in intensive care monitoring, wound care and cancer treatment. A summary of discussions can be found at http://www.cyclops-network.ac.uk/documents/notes-from-cyclops-breakout-sessions.pdf.

The first grand challenge workshop was successful in highlighting challenges and gaps, which were converted into feasibility studies. However we learned that certain clinical areas were more popular than others. Our plan therefore is to address the less popular and problematic areas in our next all-in-one Grand Challenge workshop and invite a national leading charity or infrastructure to be an active part of event, For example, Woundtec Healthcare Technology Cooperative.

The Grand Challenge workshop was opened to a wide range of disciplines, industry and other stakeholders. 60 delegates attended, covering academics from 17 universities with expertise in a wide range of disciplines, from monitoring and measuring systems, to human factors to modelling and artificial intelligence. Clinicians (4 NHS Trusts) covering the clinical exemplar areas of wound care, cancer care and intensive care, patient representatives, commercial organisations and other healthcare stakeholders also took part of the workshop. This approach of inviting patient representatives to form part of the Grand Challenge discussions ensured that users were part of the ideas process, which will further motivate researchers to address clinical challenges.

Key international academics were invited speakers of the Grand Challenge workshop and will be invited to speak at future events.

Through the workshop, a shared understanding that facilitated knowledge exchange of the clinical challenges, technology and techniques started to develop within the network, as well as challenges faced by patients to identify the most appropriate monitoring and treatments for closed loop control. We have identified clinical and scientific challenges, and gaps in Cyclops clinical areas and have consequently funded three feasibility studies initially. These studies will form part of a cohort of studies that will be used to produce a roadmap for the development of closed loop control systems for optimising treatment with a view to developing major funding applications.

We have involved medical device translation and adoption experts in our network, whom network members can consult on creating NHS-ready solutions. For example, the director of CHEATA – the Centre for Healthcare Equipment and Technology Adoption (www.cheata.co.uk) is a member of Cyclops advisory

panel and has provided advice on how proposed feasibility studies can use CHEATA services to rapidly translate new devices and technologies into practice. A representative from CHEATA was an invited speaker the Grand Challenge workshop, in which she advised network members about potential regulatory hurdles when introducing closed loop systems. She also highlight CHEATA's ability to support feasibility studies and be involved with downstream projects.

In future we plan to engage with social scientists to support us in eliciting views on the use of automation and artificial intelligence in treating medical conditions.

Lessons learned

A. THINGS THAT HAVE WORKED WELL

- Website creation: a dedicated website was created to interact with and inform network members and external stakeholders at all times.
- Network creation: A multidisciplinary and multi-stakeholder network was created by invitation to academics, clinicians and industry stakeholders. Universities which formed part of the EPSRC collaboration bid facilitated in this.
- Creation of the networks' steering committee: the five co-investigators formed the network's management team, in addition to six members of the advisory board group.
- A transparent grant review and award process was put in place.
- Grand challenge workshop: A grand challenge workshop was held in 20-21st March, 2017 to bring together all stakeholders to identify opportunities for research.
- Feasibility studies: Following a successful call for proposals, three feasibility studies were funded, with the aim to fund five later on.
- Research activity: the development of feasibility studies by network members in the three clinical areas of Cyclops are underway.

In addition, we are continuing to engage with the following with the network

- Ensure diversity (disciplines, stakeholders, region, ECRs, gender).
- Maintain interest in the network (pump priming, follow on funding applications).
- Use facilitators to ensure all engage at network events.
- Good governance by continuing to monitor spend and deliverables on the projects.

Finally, we found that clarifying issues with designated EPSRC representatives have been helpful in smoothing network formation and distribution of awards.

B. THINGS THAT WE WOULD DO DIFFERENTLY

Timeline for network building and call for proposals: Original plan for the first year was to conduct three workshops in each of the three clinical areas identified. However, these were combined into one grand workshop for two main reasons: (i) it was felt that the majority of EPS researchers would want to contribute to all the clinical areas and that clinical attendees would benefit from sharing experiences with clinicians from other disciplines; (ii) we wanted to fairly distribute time for applicants to prepare applications for the pump priming funds. For example, it was deemed that those who attended the first workshop would have enjoyed a longer period to which to submit their proposal than those who attended the last workshop.

A key lesson learned was that, the first workshop did not produce as many applications as anticipated. Many applications that looked promising at the workshop were not received, and just one application was

received in chronic wound care. To address these issues, the PI of Cyclops conducted promotional events in technology touching life (TTL) workshop and other network plus events. Perhaps a longer period should have been allocated to network building to ensure extensive interest in the clinical areas before the workshops began.

A standardised template contracts between universities? Another key lesson is time taken for awards-in-principle to be converted into contracts. It took six weeks for contracts to be produced due to a variety of reasons: a) the number of different personnel involved in the host institution, b) time taken for a contracts officer from the host institution to design bespoke contracts that take into account different institutions involved, and c) liaising with contracts personnel in award institutions. Principal investigators, therefore, could not commence their projects quicker. Perhaps using a standardised contract provided by EPSRC would be more time efficient in distributing funds for quicker commencement of projects.

c. Ethics

Projects funded by Cyclops Network Plus are currently in their first year and therefore have not yet reported on the management of ethics. CHEATA is however able to provide support on obtaining ethics approval for individual projects when required. Using previous projects as examples, Cyclops PI and members of the management team found that employing NHS-approved consulting services such as CHEATA minimises misunderstandings and improves the process of obtaining ethics approval.

2. Next steps

Looking ahead into year two, we plan to build on our first-year success by funding more feasibility studies that would create further links with industry, clinicians and other organisations in the wider innovation landscape in this unique attempt to find autonomous healthcare solutions through a network.

To keep developing the network, the PI is continuing outreach and promotional work through speeches at universities and other EPSRC network events, industry related events around the country, as well as engaging policymakers such as NICE. Co-Investigators are also continuing to contribute to the development of the network by engaging with partners and stakeholders and other promotional work with academics and industries. The network manager is continuing to plan and organise networking activities between investigators and the network. We are, at the time of writing this report, planning a second call for proposals.

One option for sustaining the network is it to become a special interest group of the Medilink Network where Medilink East Midlands can support running events. The most likely way to sustain activity is through follow-on funding to keep developing solutions that could be of great benefit to healthcare from all stakeholder perspectives. Larger future grants (e.g. programme grants) will be able to run stakeholder events which will help to maintain network activity. This is also a good indicator of success of the network. We aim to further widen our engagement with charities, innovation infrastructures, and patient representatives that will broaden the network and its impacts, and help network members disseminate high-level outputs.

3. Future events

Event title:	Cyclops grand challenge workshop II
Date:	January 2018
Event purpose:	To bring together academic, industry and clinical stakeholders to further identify gaps in the three clinical areas of Cyclops
Target audience:	Early career researchers, academics, clinicians and industry
Event title:	Shaping future proposals forum
Date:	January 2019
Event purpose:	To discuss ways in which funded projects can be extended into bigger ones and make impact through adoption and engagement
Target audience:	PPI representatives, government representatives, EPSRC representatives, RCUK representatives, academics, clinicians, and industry
Event title:	Cyclops Dissemination event
Date:	August 2019
Event purpose:	To disseminate findings of cyclops feasibility studies and to discuss best practice and lesson learned.
Target audience:	Policy makers, academics, clinicians and industry

Glossary

CHEATA - Centre for Healthcare Equipment and Technology Adoption

CLC – Closed Loop Control

CHT – Centre for Healthcare Technologies

Cyclops - Closed loop control systems for optimization treatment

EPSRC – Engineering and Physical Sciences Research Council

ICU – Intensive Care Unit

OFS - Optical Fibre Sensors

NHS – National Health Service

CONTACT INFORMATION

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