ROBOTIC TECHNOLOGIES FOR ENHANCED CANCER DIAGNOSTICS

INNOVATION SANDPIT 14–17 JULY 2019

Together we will beat cancer
AIMS

As part of Cancer Research UK’s (CRUK) wider efforts in bolstering early detection of cancer research, we’re bringing together expertise not only from cancer biology, but other disciplines, leveraging the best minds and most novel concepts emerging from chemistry, physics, engineering, mathematics, and computer science. To this end, we are partnering with The Engineering and Physical Sciences Research Council (EPSRC) to develop new multidisciplinary and revolutionary research ideas.

We united research communities from CRUK and EPSRC for the third Early Detection Innovation Workshop from 14–17 July 2019 at The Oxford Belfry, Oxfordshire, focusing on new research to develop robotic technologies for improved cancer diagnostics. Research conducted as a result of this event is relevant to practical challenges in developing new approaches and technologies for diagnostic delivery such as:

- How to apply robotic technology to aid in diagnostic delivery/guidance and accuracy. Can we exploit the potential of micro- and nano-robots?
- How to apply robotics to minimise invasiveness and increase safety of diagnosis (e.g. localised imaging, real-time histopathology/biopsy)

- How to apply robotic technology to improve speed and precision of the diagnostic workstream
- How to develop robotics for both cancer detection and delivery of treatment, if necessary
- How to simplify robotic delivery for lower cost diagnostics that will be robust enough to use within the community
- How can robotics aid in diagnostic decision making and training, including through remote operation?
THE WORKSHOP PROCESS

The Director acts as the leader of the event and guides the process from a scientific content perspective. The Director works closely with the Mentors, guiding them as they interact with the participants and plays a key role in the funding decisions.

The Mentors act as real-time ‘peer reviewers’ but with a much more creative role. At the start of the event, their job is to encourage new ideas by asking questions, highlighting ideas that seem exciting, and making connections between participants and to the wider body of knowledge. The Mentors’ role changes towards the end of the event, when they have to adopt a more critical perspective and assist with the funding decisions.

The sandpit process can be broken down into several stages:

- defining the scope of the challenge;
- sharing understandings of the challenge and expertise brought to the sandpit by participants;
- evolving common languages and terminologies amongst people from a diverse range of backgrounds and disciplines;
- breaking down preconceptions of researchers and stakeholders;
- taking part in break-out sessions focused on challenges, using creative thinking techniques;
- capturing outputs in the form of highly innovative feasibility study proposals;
- a funding decision on those proposals at the sandpit, using “real time” peer-review.

OVERALL: “Very enjoyable. A unique experience and very well managed by the facilitators. Great way to meet other scientists.”

ON REAL-TIME PEER REVIEW: “Excellent. Very, very efficient and effective way to build ideas and troubleshoot.”

MOST VALUABLE LESSON: “This is a very important process to not keep thinking about what is already proven or already in place. A very important process to think about blue sky ideas.”
Professor Pietro Valdastri
Chair in Robotics and Autonomous Systems, University of Leeds

Professor Dan Elson
Imperial College London

Dr Dan Stoyanov
University College London

Professor Sanja Dogramdazi
University of the West of England

Dr Celia Riga
Imperial College London

Professor Simon Leedham
University of Oxford, provided a clinical perspective as an endoscopist and introduced diagnostic challenges where robotics and robotic technologies could make a difference.

Professor Peter Buckle
Imperial College London, spoke about human factors research and considerations to keep in mind when developing new technologies for use in patients.

Professor George Hanna
Imperial College London and member of CRUK’s Early Detection Research Committee. George attended the final pitches and served on the funding panel.
On the final day of the workshop, each group presented their research idea. The Funding Panel, comprising workshop Director, Mentors, and George Hanna, awarded the best proposals up to £100,000 each, to support the subsequent pilot and feasibility studies.

We funded five projects, commencing winter 2019 for a period of 12 months.

**PROJECT 1:**

**Vibr-O-Scope: Human-in-the-loop multimodal early detection of pre-malignant and malignant colonic lesions – Team Vibr-O-Scope**

The team will develop a soft device with vibration and sensing capabilities to be attached to conventional endoscopes to aid in detection of hard to visualise lesions.

**Group members & Institutions:**
George Mylonas (Imperial College London)  
Uriel Martinez-Hernandez (University of Bath)  
Ania Przedlacka (Imperial College Healthcare NHS Trust)  
Watjana Lilaonitkul (University College London)  
Dimitris Tsakiris (University of Aberystwyth)

**Background**
There are 42,000 new cases of colorectal cancer (CRC) diagnosed each year in the UK. Over half of these are diagnosed at a late stage, when more extensive treatment is required. Early cancer detection significantly improves patients’ outcomes. Currently, detection of premalignant and malignant changes is performed by visual inspection of the colonic mucosa during endoscopy, which is less reliable for small pedunculated polyps and for sessile serrated lesions which are not easily visualised. Several changes in the tissue mechanical properties occur from the early stages of malignant transformation, including changes in the tissue matrix geometry, leading to a localised increase in the bowel wall stiffness. This observation could be utilised to distinguish between healthy and abnormal tissues.

**Aims and Methods**
We propose the development of the Vibr-O-Scope, a soft device which can be attached to a conventional endoscope and navigated inside the colon during endoscopy, improving the early detection of lesions which are difficult to visualise. Conceptually, it has two components – an inflatable balloon and an array of sensing elements. The balloon performs gentle controllable and measurable circumferential distension of the colon, as well as induces vibrations to the bowel wall, while the sensing elements register information on the tissue deformity based on the balloon shape changes, and the speed of vibration propagation. The device will also exploit vibrations to assist the endoscope’s movement through the gastrointestinal tract.

The tissue stiffness will be assessed using vibrotactile sensing techniques, similar to established ultrasound elastography (real time elastography, RTE), including two main techniques: strain imaging and shear wave speed measurement. Silicone phantoms and ex vivo porcine colon with simulated lesions will be used for validation of the device. The correlation between the RTE measurements and the histology of malignant lesions will be assessed using freshly excised human bowel tissue.
PROJECT 2:

**Early Detection of cancer in cases of Barrett’s oesophagus using Robotic Endoscopic Image Analysis through Deep Image Retrieval – Team Barrobot**

The team will build an artificial intelligence similarity-detection system to assist clinicians monitoring patients with Barrett’s oesophagus.

Group members & Institutions:
- Lyndon Smith (University of the West of England)
- Alberto Rizzoli (V7 Ltd.)
- Niels van Berkel (University College London)

Background
Barrett’s oesophagus is a condition in which the area between the oesophagus and stomach no longer closes, allowing acidic contents of the stomach to enter the oesophagus and damage its lining. There are around 12,000 registered cases of Barrett’s oesophagus in the UK, with an estimated 1-5% of each case developing into a cancer. Patients require bi-yearly inspection to detect cancer development, a process which is both costly (estimates ranging between $10,000 and $100,000 per Quality-Adjusted Life Year) and faces difficulties in obtaining reliable biopsy outcomes due to the challenges involved in taking both sufficient and a high number of biopsies.

Aims and Methods
This project aims to assist clinicians by offering an informed biopsy process, in which the system presents the operator with clinical outcomes of patients with visually similar GI tracts. Although clinicians already make use of visual indicators to identify (developing) cancers, these are often difficult to detect and may therefore be missed. The project’s goal is therefore to assess the use of an Artificial Intelligence-based similarity-detection system (comparing the current patient to previous patients) to better inform biopsy placement, increasing the reliability of bi-yearly inspections.

The use of AI for similarity analysis between images does not require manual annotation of tongue outlines but instead relies on a ground truth (biopsy result) of a photo taken prior to biopsies. Our proposed process would significantly lower the amount of training data required. Furthermore, this project aims to investigate how best to optimally design the integration of AI-powered technology in day-to-day clinical work - working closely with clinical experts during the design and development of our software.

Using a deep image retrieval network, and including listwise-loss image retrieval we aim to predict:
- The Prague Criteria outcome of a queried case of Barrett’s (quantitative)
- The retrieval of the most similar-looking, ranked images of the case (qualitative)
- If available, the histological outcome of the case via image analysis only (quantitative)

This machine-learning based approach would allow learning Barrett’s visual features with little training data, and predict an outcome by comparing it to, and presenting existing cases, rather than a black-box approach.

Further research would involve the automatic calculation of the Prague Criteria variables via computer vision by measuring within the cylindrical view of the oesophagus.
PROJECT 3:

ARTEMIS – Advanced Robotic Breast Examination Intelligent System – Team ARTEMIS

The team will develop a robotic device for smart sensing of early breast cancer by understanding the techniques clinicians use for breast examinations.

Group members & Institutions:
Fernando Bello (Imperial College London)
Antonia Tzemanaki (University of Bristol)
Amir Masoud Ghalamzan Esfahani (University of Lincoln)
Chris Sutton (University of Bradford)

Background
Early detection has a significant impact on extending breast cancer survival and improving quality of life. Young women (35 years) with breast cancer account for 7% of all breast cancers. Diagnostic delays are common and they present often at an advanced stage, with more aggressive and less responsive disease to hormonal therapy. They experience a poor outcome when compared to cancers of older patients. Screening mammography is not recommended due to the associated X-ray dose, with ultrasound being the first line examination, hampered by a high false positive rate. Hence, there is an unmet clinical need for early detection of breast cancer in young women, where 80% of all breast cancers present with a palpable lump. Equally, high-risk women (~6% of UK 40-73 year olds) may benefit from a safe, convenient, active surveillance of breast health programme for early cancer detection.

Aims and Methods
We propose a complementary approach for detecting the earliest stages of breast cancer in a paradigm shift combining a robotic device for smart sensing, imaging and palpation (SIP), with the possibility of collection and assay of nipple aspirate fluid (NAF) for breast health profiling. Our hypothesis is that multi-modal, timely breast examination will enable detection of the earliest perturbations in breast health and enable treatment with minimal impact on patients or even reverse disease state, thus reducing the need for mastectomy and burden on healthcare systems.

The project will consist of five parallel work packages
- WP1 – User Requirements Specification
- WP2 – Breast Phantom Model and Data Collection
- WP3 – Design and Development of Soft Robotic Palpation Platform
- WP4 – Implementation of Expert Knowledge Transfer (EKT)
- WP5 – Study of NAF Feasibility, Suitability and Acceptability

The ARTEMIS robotic platform will deliver palpation for detection of abnormalities through actuation and sensing, capturing and storing breast compliance and imaging maps. Palpation techniques will be informed by machine learning (e.g. reinforcement learning, learning by demonstration) applied to data derived from a sensorised breast phantom during use by clinical experts. One possible instance of the ARTEMIS platform as a robotic rest chair that could be made available in GP surgeries, pharmacies or mobile breast examination units. A smaller, portable unit for home use will also be explored as part of the longer-term project.
PROJECT 4:

Nanorobots for liquid biopsies in blood – Team Nanorobots

The team will detect early stage lung cancers by combining nanoparticles or nanorobots with photoacoustic technology to capture exosomes in situ.

Group members & Institutions:
James McLaughlan (University of Leeds)
Michael Chen (University of Edinburgh)

Background

Lung cancer is one of the most common forms of cancer with one of the highest mortality rates worldwide. Tackling this problem requires efforts on early diagnosis of the disease as it drastically increases survival rates. An exciting opportunity is to achieve early diagnosis of lung cancer via monitoring exosomes in blood circulation. Exosomes are extracellular vesicles with a size of approximately 30-100nm in diameter. Exosomes excreted from normal cells and cancer cells are substantially different and therefore represent an ideal new type of biomarkers for cancer early diagnosis. In this proposal we aim to use autonomous nanorobots – magnetic gold nanorods with a surface coating of exosome capturing antibodies – in the blood stream to capture these free-flowing cancer exosomes for noninvasive detection using photoacoustics. The exosomes captured nanorobots can be aggregated for detection and quantification when manipulated with an external magnetic field. This approach could be used for patient stratification as a precursor to further diagnostic tests.

Aims and Methods

This proposal will be the first time nanorobots, or even just nanoparticles, have been combined with photoacoustics and cancer exosomes to quantify their presence in situ for a potential early indication of lung cancer. Reflecting the early stage of this research, we aim to manufacture, establish the safety and exosome capture efficiency of these nanorobots in blood mimics. Furthermore, we will quantify the magnetic field strength required for manipulation to assess its feasibility for either clinical applications or in vitro testing. Finally, we aim to demonstrate in vitro photoacoustic sensing of the nanorobots, and validate their detection threshold and its relationship to the exosome population.

The nanorobots will be synthesised with an anti-EGFR functional surface layer with high biocompatibility via chemistry synthesis. Lung cancer exosomes will be extracted from cell culture-conditioned medium via ultracentrifugation and their binding efficiency to the nanorobots will be assessed. Magnetically aggregated nanorobots will be exposed to multi-spectral near-infrared light and due to their surface plasmon resonance (SPR) an ultrasound signal will be generated for quantitative analysis using a high frequency ultrasound detector. Free and exosome captured nanorobots will be differentiated due to their different SPR peak position, thus producing different amplitudes of ultrasound signals to determine the quantity of cancer exosomes.

The results from this project, if shown to be successful, will provide the necessary justification for a comprehensive in vivo validation of this technique.
Project 5:

“MAMMOBOT” – A Flexible Robot for Early Breast Cancer Diagnosis – Team MAMMOBOT

The team will create a flexible, steerable endoscopic robotic system to navigate the mammary ducts and utilise novel sensing technologies to diagnose abnormalities in patients.

Group Members & Institutions:
Daniel Leff (Imperial College London)
Stamatia Giannarou (Imperial College London)
Christos Bergeles (King’s College London)
Ioannis Georgilas (University of Bath)
Moi Hoon Yap (Manchester Metropolitan University)
Animesh Jha (University of Leeds)
Bhagabati Ghimire (King’s College London)
Subramanian Ramamoorthy (University of Edinburgh)

Background
Small invasive and non-invasive cancers such as ductal carcinoma in situ, referred to as “early” breast cancers still require surgery, chemotherapy and radiotherapy at substantial human and financial costs. Reframing what constitutes “early” breast cancer requires a conceptual shift from diagnosing a luminal disease once external stigmata of cancer are evident (e.g. mass, microcalcification) to detecting the disease internally via systematic integration of the mammary duct network. Conventional ductoscopy has failed to penetrate practice as systems are unwieldy and inflexible. However, a flexible robotic system that can safely and reliably navigate the mammary tree has potential to disrupt breast cancer diagnosis and treatment.

Aims and Methods
The aim is to develop the first iteration of “MAMMOBOT”; a flexible steerable endoscopic robotic system that can safely navigate the mammary ducts, and harnesses novel sensors to highlight global duct abnormalities and imaging technologies to make local microscopic diagnoses. The end goal is an integrated platform for a millimetre-scale growing robot and deployed sensor array, with navigation and tissue characterisation capabilities.

To deliver MAMMOBOT we focus on the following methods: a) Robotics: developing a growing robot at 2mm scale that uses hydraulic chambers to enable unfolding and elongation along a desired trajectory; b) Navigation and Localisation: to overcome disorientation due to limited field-of-view and challenges in targeting and retargeting due to tissue motion and changes in topology using a “Surgical GPS”. A 3d computer model of the mammary duct tree will be created and a silicone phantom will be constructed to enable robot navigation to be tested. Localisation will be achieved using matching ductoscopic views with the virtual views from the simulation, and 3D dynamic tracking will provide operator guidance; and finally c) Sensing & Machine Learning: sensing probes such as Optical Coherence Tomography for global duct assessment and Raman Spectroscopy for local diagnosis will be minaturised and navigated on-board the growing robot armed with intelligence acquired from sensing data obtained from histologically validated human breast cancer samples.

Further technological development of MAMMOBOT will enable us to conduct animal trials, with a view to early clinical feasibility testing in the future. Finally, we will seek to develop a robotic system that meets regulatory approval ready for first in women studies.