Institution: University of Lincoln		
Unit of Assessment: 9 - Physics		
Title of case study: Optimising Proton Beam Therapy for Cancer Treatment		
Period when the underpinning research was undertaken: 2011 to date		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
ALLINSON Nigel	Distinguished Professor	1 Jan 11 to date
ESPOSITO Michela	Senior Lecturer	1 Jan 18 to date
WALTHAM Chris	Senior Design Engineer	2 Apr 12 to date
Period when the claimed impact occurred: 2011 to date		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

The application of high-energy external proton beams is rapidly gaining clinical application worldwide in the treatment of difficult tumours, for example HMG has invested over £250m in two new NHS Proton Beam Therapy (PBT) centres. Though protons have a finite travel in tissue and deposit most of their energy near the end of this travel, current approaches for treatment planning and monitoring give rise to uncertainties in where the protons will actually deliver their dose. To minimise these uncertainties and so optimise treatments and outcomes, a solution is to use protons to both image and treat. The success of our research, through the Wellcome Trust Translational Grant, PRaVDA, means that we can produce clinical quality proton CT imagery and markedly increase the precision of treatment and plots a route to fully adaptive personalised radiotherapy treatments. Hence, we are currently installing the world's first dedicated proton imaging instrument in an operational PBT clinic, where it is used to refine our understanding of clinical effectiveness, fit with treatment workflows and deliver more accurate quality assurance procedures. We have entered into a partnership with a leading PBT company, *Cosylab*, for coordinated development of proton CT, jointly promote proton imaging and plan entering the market. Furthermore, we have raised public awareness of PBT through major exhibitions and other events – this was at the time of the well-publicised case of 5-year old Ashya King.(https://en.wikipedia.org/wiki/Ashya_King_case).

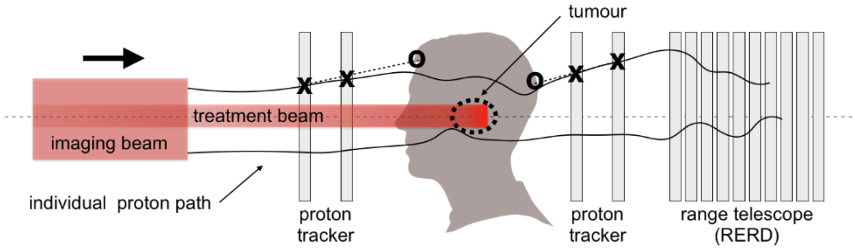
2. Underpinning research (indicative maximum 500 words)

Protons interact with tissue in a very different way to x-rays (main radiation source for conventional radiotherapy); protons deposit most of their energy in a narrow region towards the end of their finite travel so, in principle, allow greater conformity to the target with minimal dose to adjacent healthy tissues. Range uncertainties are due, primarily, to use of x-ray CT for treatment planning are typically ±3.5% (much higher within the skull). Proton CT taken before and during treatment minimises these uncertainties. Attempts have been made for over 20 years to acquire proton CT, however, no clinical quality images had been demonstrated. As protons in matter do not travel in straight lines (due to random scattering), quality images can only be recorded by tracing the paths taken by individual particles – a challenging task that requires very fast sensors and supporting electronics. With our background in scientific and medical imaging using custom CMOS imagers (e.g. EPSRC MI-3 Plus project), we were asked by Prof. Stuart Green, Head of Medical Physics, University Hospitals Birmingham NHS Foundation Trust to consider this challenge.

The first confirmation of proton imaging using CMOS imagers used imagers produced through our Basic Technology Grant, MI-3, at the Massachusetts General Hospital (Seco J, Depauw N. Proof of principle study of the use of a CMOS active pixel sensor for proton radiography. Medical physics. 2011).

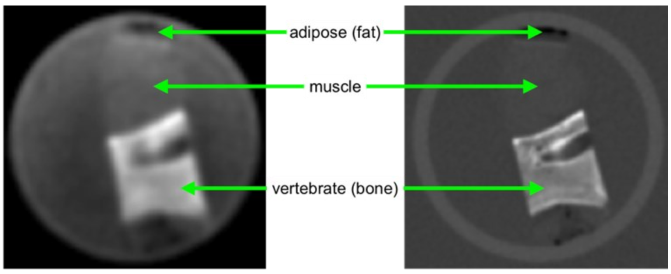
Our preliminary studies confirmed that CMOS imagers were capable of detecting individual proton events over the energy range of interest to PBT. These studies made use of DynAMITe, the world's largest radiation-hard CMOS imager; designed by us at Lincoln under the EPSRC MI-3 Plus award (winner of the IET Innovation Prize for Electronics, 2012). We put together a consortium of engineers, particle physicists, medical physicists and users of PBT, and we were successful in being awarded a Wellcome Trust Translation Grant, PRaVDA. Our partners included the Universities of Birmingham, Liverpool, Surrey, Warwick and Cape Town, iThemba LABS (South Africa), Karolinska University Hospital (Sweden) and four NHS Trusts and Foundation Trusts.

We took a fresh approach to this unresolved challenge by producing the most comprehensive Monte-Carlo simulation (winning the IET Innovation Prize for Model-based Engineering, 2014) to design each element of the system – sets of high-speed proton trackers mounted either side of the phantom (patient) and a fully solid-state residual energy detector (range telescope) – see figure below.



The proton trackers use custom silicon strip sensors, designed by the University of Liverpool Particle Physics group who produce similar sensors for the ATLAS experiment at the Large Hadron Collider. Instead of the conventional x-y crossed strips to give a track position, three equi-angled strips are employed to significantly reduce false hits at high proton flux rates so allowing monitoring of the incident beam during treatment. For imaging, the energy of the protons is increased so that the majority of them pass through the patient and the residual energy of the individual protons recorded by the range telescope. The intensity of the beam is reduced to about a ten-thousandth of the treatment intensity, and the imaging dose is much less than for a conventional diagnostic x-ray CT.

The range telescope was based 21 silicon strip sensors arranged in layers. The range telescope and trackers contain over 2.5 m^2 of processed silicon dies (equivalent to ~7,500 iPhone 10 cameras) and can record ~3 x 10^8 individual proton trajectories and energies per second.



Initial proton CT images were captured using custom calibrated phantoms and biological samples at the iThemba LABS (South Africa) 200 MeV national cyclotron during 2015/6. The most important parameter for treatment planning, and for treatment, is the proton relative stopping power. We recorded this parameter directly from proton CT reconstruction to within ~1% for a range of calibrated tissue substitutes. A comparative proton CT and x-ray CT of the same biological sample was obtained for the first time – see images above.

All work was undertaken by the Wellcome Trust funded PRaVDA programme, and University of Lincoln staff involved were Professor N Allinson (PI and Programme Director), Dr M Esposito (Research Fellow/Lecturer), Dr Grainne Riley (Senior Project Manager) and C Waltham (Senior Design Engineer). PRaVDA was funded from Jan 2013 to July 2017.

Following the success of this work, we were awarded, in 2018, a £3.2m EPSRC grant, OPTIma, to develop a second-generation system for the Research Room at the new NHS Christie Proton Beam Therapy Centre. This next generation system is designed to operate on current scanned pencil-beam delivery systems and match treatment needs and workflows. As well as offering full proton CT, a simpler instrument, the proton probe, will provide detailed planning information (e.g. body fat percentage) and patient positioning. This system can be retro-fitted to existing facilities.

3. References to the research (indicative maximum of six references)

3.1 Poludniowski, N M Allinson, T Anaxagoras, M Esposito, S Green, S Manolopoulos, J Nieto-Camero, D J Parker, T Price and P M Evans (2014), *Proton-counting radiography*

for proton therapy: a proof of principle using CMOS APS technology, 2014 *Phys. Med. Biol.* 59 2569
https://doi.org/10.1088/0031-9155%2F59%2F11%2F2569
3.2 T. Price, M. Esposito, G. Poludniowski, J. Taylor, C. Waltham, D.J. Parker, S. Green, S. Manolopoulos, N.M. Allinson, T. Anaxagoras, P. Evans and J. Nieto-Camero (2015), *Expected proton signal sizes in the PRaVDA Range Telescope for proton Computed Tomography*, *JINST* 10 P05013
https://doi.org/10.1088/1748-0221%2F10%2F05%2FP05013
3.3 J.T. Taylor, P.P. Allport, G.L. Casse, N.A. Smith, I. Tsurin, N.M. Allinson, M. Esposito, A. Kacperek, J. Nieto-Camero, T. Price and C. Waltham (2015), *Proton tracking for medical imaging and dosimetry*, *JINST* 10 C02015
https://doi.org/10.1088/1748-0221%2F10%2F02%2FC02015
3.4 G Poludniowski, N M Allinson and P M Evans (2014), *Proton computed tomography reconstruction using a backprojection-then-filtering approach*, *Phys. Med. Biol.* 59 7905
https://doi.org/10.1088/0031-9155%2F59%2F11%2F2569
3.5 M. Esposito, T. Anaxagoras, P.M. Evans, S. Green, S. Manolopoulos, J. Nieto-Camero, D.J. Parker, G. Poludniowski, T. Price, C. Waltham and N.M. Allinson (2015), *CMOS Active Pixel Sensors as energy- range detectors for proton Computed Tomography*, *JINST* 10 C06001
https://doi.org/10.1088/1748-0221%2F10%2F06%2FC06001
3.6 Taylor, J.T., Poludniowski, G., Price, T., Waltham, C., Allport, P.P., Casse, G.L., Esposito, M., Evans, P.M., Green, S., Manger, S. and Manolopoulos, S., 2016. *An experimental demonstration of a new type of proton computed tomography using a novel silicon tracking detector*, *Medical Physics*, 43*,* pp.6129-6136
https://doi.org/10.1118/1.4965809

4. Details of the impact (indicative maximum 750 words)

Over 370,000 new cancer cases are diagnosed each year in the UK alone. Some 40% of these patients will receive radiotherapy as part of their curative treatment. Most radiotherapy employs high-energy external beams of x-rays. X-rays lose their energy gradually as they pass through tissues. Protons, on the other hand, travel a finite distance depending on their energy and lose most of their energy near their end of travel. Proton beams offer greater conformity to the target tumour with minimal dose to adjacent normal tissues so reduced risk of second cancers developing later and improved quality of life for patients. The advantage of protons is that they stop; the disadvantage is that we cannot predict exactly where. This is rationale for pursuing proton CT.

> *"… the inherent uncertainties in knowing where the proton beam stops in tissue, the proton range, makes it more difficult to utilise proton therapy to its full benefit. The development of Proton CT will help reduce the uncertainty resulting in a greater benefit to the patient".*
> Derek D'Souza, Head of Radiotherapy Physics, UCLH ***[5.1]***.

Ninety-nine PBT facilities worldwide are currently treating patients with PBT (and a further 60 under construction or planned), with nearly 200,000 patients treated to date. The UK alone has five operational centres with another two becoming operational in the next year.

The Christie PBT Centre was the first of the two NHS PBT centres to open and through the generosity of the Christie Charity who raised £5.6m towards the cost of a dedicated research room and a fixed, full PBT delivery system – a unique facility worldwide – this is enabling us to move closer to clinical application.

PRaVDA and OPTIma are providing the solution, and more importantly changed the perception of the potential and possibility of proton CT in the PBT clinic. Though proton CT was first proposed over 30 years ago, it was not until we developed a fully solid-state system capable of very fast data acquisition and clinically relevant imagery, that the radiotherapy community appreciated that proton CT and radiography was possible and would have a critical role in not only treatment planning but also provide personalised adaptive radiotherapy. We have the active involvement of five NHS Trusts and Foundation Trusts, Karolinska University Hospital

(Sweden), iThemba LABS PBT Centre (South Africa) and PSI Center for Proton Therapy (Switzerland) who have contributed staff effort and resources. We have made our experimental data available to the academic research community. We have NDAs with three leading providers of PBT systems (Varian Medical Systems, Inc, Ion Beam Applications SA, Advanced Oncotherapy plc) who actively follow our work. The unique capability of the PRaVDA, and now OPTIma, system is the ability to operate at proton beam currents much higher than other prototype systems around the world. It is the only system able to work within the normal operational envelope of a clinical PBT facility – hence the involvement of The Christie and the commercial interest from the associated industry.

We hold a patent portfolio with five awarded patents relating to the overall instrument concept, the proton trackers and the range telescope, and two on CT reconstruction methods **[5.2]**. The pathway to full clinical acceptance is lengthy as not only does the methodology need confirming that it produces accurate results for a variety of phantoms and biological samples but that it can provide such results within an acceptable time and the use of proton imaging integrates well with treatment workflows. All this needs to be confirmed before any work with patients – initially as an adjunct and then to inform treatment.

We have formed a partnership with Cosylab d. d. (www.cosylab.com) in association with ProtonVDA **[5.3]**. Together, we are jointly promoting the use of proton imaging commercially, assist in the processes to ensure our design meets regulatory requirements, fund research on proton CT reconstruction, and potentially market our system. Cosylab, based in Slovenia, provides over 90% of the control system software for PBT facilities worldwide.

Cancer and its treatment generate considerable public interest, and we firmly believe we should introduce our work and its eventual benefit to patients and the wider public. An interactive display on PRaVDA was exhibited at The Royal Society Summer Exhibition (2014) **[5.4]** – see photos above, GravityFields Festival (2014) and Spark Engineering Festival (2015) as well as in the Wellcome Trust HQ. The display has, in total, been visited by an estimated 25,000 people. These exhibitions and associated talks to diverse groups (e.g. *Women's Institute to cancer* charities) were at a time when the case of Ashya King was much in the public mind (Ashya was "abducted" by his parents from Southampton Hospital, which led to their arrest and subsequent PBT treatment in Prague). There were many misconceptions in the popular media about PBT, so it was very opportune that we were able to explain the scientific and clinical case for PBT to so many members of the public. PRaVDA was also chosen for the Institution of Engineering and Technology's year-long exhibition "100 Objects that Changed the World". The IET described this display as:

> *"The autumn opening at the venue will also unveil a series of 100 engineering ideas that changed the world, as voted for by IET members around the world. The objects are seen as a celebration of the engineering ideas that have had the most impact on humanity and reflect the historic past of the IET. Famous members and well-known faces including T Karl Benz, inventor of the first car powered by an internal combustion engine, and aviation pioneer Amelia Earhart, the first woman to fly solo across the Atlantic, will adorn the interior".* **[5.5]**

At our events, we involved medics who can provide explanations on the clinical issues and then very public controversies. Below is an unsolicited email from a Consultant Clinical Scientist and Radiotherapy Physics Strategy Lead for the University Hospitals Coventry and Warwickshire NHS Trust, who assisted us at the Royal Society event.

> *I got an enormous buzz from talking to all these different people of all ages, genders, ethnicities, backgrounds etc. When this was accompanied by a complementary positive feedback about our work, the marvellous stand, radiotherapy and UK PBT was just wonderful. I definitely feel we promoted our cause and made the public aware of our efforts and there're definitely a few more Londoners aware about the new centre their city and Manchester will be. It was a privilege to been able to participate and less difficult than I thought, mostly thanks to the stand!*
>
> *As NHS professional (this may sound pompous but bear with me) it was a privilege to be able to carry the flag (in an era of adverse publicity for the service) and re-assure the public that they are getting excellent (RT) services, and with the advent of the UK PBT centres, second to none!* **[5.6]**

Against strong competition from industry, we won of the Institution of Engineering and Technology Innovation Prize for Model-based Engineering (2014) **[5.7]** for our simulation of proton imaging and instrumentation; were the runner-up for the Best Design Team in the British Engineering Excellence Awards (2017) **[5.8]** and beating such companies as Jaguar-Land Rover. This last award was particularly pleasing as we were the only academic team to be shortlisted. Prof. Allinson was also awarded the prestigious IET JJ Thomson award 2018 for his pioneering work in the advancement of complex medical imaging instruments for cancer treatment **[5.9]**.Our work was recognised in the Universities UK Nation's Lifesavers – the top 100 individuals or groups based in universities across the country whose work is saving lives and making a life-changing difference to our health and wellbeing **[5.10]**. Professor Dame Janet Beer, President of Universities UK commented on the Lifesavers celebration:

> *"When people think of lifesavers they understandably tend to focus on the dedication and skill of our doctors, nurses, carers, and paramedics – many of whom are trained at universities. Every day, up and down the country, universities are also working on innovations to transform and save lives. Research taking place in universities is finding solutions to so many of the health and wellbeing issues we care about and the causes that matter".*

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Independent views on proton imaging in PBT and our work from Head of Radiotherapy Physics, University College London Hospitals NHS Foundation Trust.

5.2 Current status of awarded patents can be confirmed through [*contact details available*]

5.3 Cosylab minutes of meetings. Details of commercial arrangements can be confirmed though Cosylab Senior Business Development Manager [*contact details available*]

5.4 PRaVDA exhibition (Royal Society Summer Science Exhibition GravityFields, Spark Engineering Festival, Wellcome Trust HQ)

5.5 Institution of Engineering and Technology "100 Objects that Changed the World" Exhibition

5.6 Unsolicited feedback following Royal Society event from Consultant Clinical Scientist and Radiotherapy Physics Strategy Lead

5.7 Institution of Engineering and Technology Innovation Award for Model-based Engineering (2014): https://tv.theiet.org/?videoid=6088

5.8 British Engineering Excellence Award for Best Design Team (2017) – runner-up: https://www.eurekamagazine.co.uk/design-engineering-features/technology/meet-the-winners-of-the-2017-british-engineering-excellence-awards/163440

5.9 Professor Allinson awarded IET JJ Thomson award, 2018

5.10 Universities UK Nation's Lifesavers: http://www.universitiesuk.ac.uk/news/Pages/the-nations-lifesavers.aspx