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COMMENTARY

Dreams, themes and particle beams—an oncologist's perspective on technology trickle-down from the LHC

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ABSTRACT

11 years ago, the European Network for Light Ion Therapy (ENLIGHT) was established as a multidisciplinary network of engineers, physicists and clinicians with a common interest in the development of hadron therapy in Europe. ENLIGHT is coordinated from the European Centre for Nuclear Research (CERN), the home of the Large Hadron Collider. The network has evolved into a mature platform for research, with more than 100 researchers working in CERN and its allied research centres. One of the benefits of hosting this network at CERN is the ability to translate hardware and software developments, originally developed in the High Energy Physics domain, into clinical applications. From the perspective of a clinical radiation oncologist within the network, this commentary reviews the ways in which leading edge technological developments in detectors and solid state physics, Monte-Carlo simulation, grid computing and accelerator design have trickled down into real-world clinical applications.

In March 2013, scientists at the European Centre for Nuclear Research (CERN) confirmed the discovery of Higgs Boson amidst a wash of international publicity. The effort represents the culmination of decades of effort in accelerator and detector design, and represents a huge contribution to mankind's knowledge and understanding of the physical world. However, the development of the Large Hadron Collider (LHC), A Toroidal LHC Apparatus (ATLAS) and the Compact Muon Solenoid (CMS) have driven numerous other developments in a range of domains, including those of imaging and radiation therapy. The following account is a description of some of these technologies, from the personal perspective of a clinical radiation oncologist.

THE ENLIGHT NETWORK

Established in February 2002 as a European Union funded project from the European Society of Therapeutic Radiology and Oncology, ENLIGHT is a contraction of the term "European Network for Light Ion Therapy". The ENLIGHT network is coordinated by Professor Manjit Dosanjh from CERN. At its inaugural meeting, it included 70 members from the fields of radiation biology, medical physics, engineering, accelerator physics and radiation oncology, sharing a common interest in the implementation of hadron therapy (HT) in Europe. 11 years on, the network has matured considerably. Over 100 researchers belong to the network, which has accrued over €26 million in funding across four

Framework 7 grants (Box 1). The research output of the network focusses on a range of biomedical applications in fields coherent to CERN's main areas of research. At the outset, the consortium also included research representatives from two companies with interest in the HT market, namely Siemens (Erlangen, Germany) and IBA (Louvain-La-Neuve, Belgium). Siemens have since withdrawn from the HT field, but IBA remains a committed partner to our research endeavours. Within the consortium, I am one of three radiation oncologists, and although we are small in number, our contribution to discussions and strategic planning is always highly welcomed. The clinicians in the consortium share an interest in clinical radiation biology and have advised on the design of experiments investigating cellular response to hadron irradiation and novel drug and radiation combinations. We have provided input into tumour modelling projects and also provided clinical relevance to the data and informatics projects undertaken by the consortium.

DETECTORS AND IMAGING

A significant part of the research effort for the creation of ATLAS and CMS has been the development of fast, high-sensitivity detectors to map collision events. Exactly the same requirements apply in the medical imaging domain for gamma cameras, specifically for positron emission tomography (PET) imaging. The "Crystal Clear" collaboration

Box 1.

CERN is derived from the acronym for “Conseil Européen pour la Recherche Nucléaire” or European Council for Nuclear Research. It was founded in 1952 with the mandate of establishing a world-class fundamental physics research organization in Europe. For more details, see <http://home.web.cern.ch/>

ENLIGHT is derived from the term for “European Network for Light Ion Therapy”. It was founded in 2002 and consists of four major research programmes:

PARTNER (Particle Training Network for European Radiotherapy). PARTNER is a Framework 7 Marie Curie initial training network in particle therapy, which was established in 2008. For more details, see <http://partner.web.cern.ch/>

ULICE (Union of Light Ion Centres in Europe): established in 2009, ULICE is an European Union infrastructure project for the provision of beam time and informatics for hadron therapy research. For more details, see <http://ulice.web.cern.ch/>

ENVISION (European Novel Imaging Systems for Ion Therapy): ENVISION is a second Framework 7 research project to develop digital imaging for hadron therapy. It was established in 2010. For more details, see <http://envision.web.cern.ch/>

ENTERVISION (European Training Network in Digital Medical Imaging for Radiotherapy): established in 2011, ENTERVISION research training network for three-dimensional digital imaging, following on from the research collaborations that were established in ENVISION. For more details, see <http://envision.web.cern.ch/>

is a community of 70 physicists from 15 institutes, with interests in solid state physics and condensed matter. The members span commercial, industrial and academic domains, with a common goal of sourcing the highest quality crystals for use in calorimeters or gamma cameras. The same group also exchanges knowledge in photodetector design and readout electronics. ClearPEM® (Supersonic Imagine, Aix-en-Provence, France) is an example of such a technology arising from the Crystal Clear collaboration. The device is a high-sensitivity PET imaging device designed specifically for breast screening. The entire device, including readout electronics, is small enough to fit in the palm of my hand. Combined with ultrasound elastography, the device allows for simultaneous structural and physiological imaging of the breast, whilst keeping radiation dose exposures down in the safe range for a screening technology. Another application that is being actively developed in the European Novel Imaging Systems for Ion Therapy and European Training Network in Digital Medical Imaging for Radiotherapy programmes is the use of time-of-flight PET detection for in-beam PET auto-activation that occurs with exposure to high-energy hadrons. Whilst steep gradients of physical and biologically effective dose make HT an attractive treatment technique for radiation oncologists, the lack of exit dose makes it difficult to ascertain whether or not the planned dose distribution has been delivered to the correct location within the patient. Reconstruction of dose from PET auto-activation represents an exciting opportunity for *in vivo* dosimetry, but represents a challenge

owing to the very-low counting statistics, which are several orders of magnitude lower than those observed in diagnostic PET. As a result, sophisticated time-of-flight PET detectors and extremely fast electronics with high temporal resolution are required to maximize the sensitivity, specificity and spatial resolution of the PET signal. Many of our early-stage researchers are engaged in this problem and are working on the development of crystal and resistive plate chamber sensors, fast programmable gate array electronics designs and Monte-Carlo simulations of the PET imaging devices. The same technologies have now been applied to conventional diagnostic PET-CT systems. Siemens was the first company to integrate time-of-flight PET into a commercial device with their Biograph™ Truepoint™ HD PET unit. The improvements in resolution and signal-to-noise ratio translate immediately into clinical benefit, particularly in the imaging of small intra-abdominal lymph nodes that were difficult to resolve using conventional PET-CT.¹

MODELLING AND SIMULATION

Development of in-beam PET solutions has relied heavily on Monte Carlo simulation of particle-matter interaction and positron emission within the patient. This was made possible by the use of particle tracking code, which had been developed for high energy physics applications. GEANT, a portmanteau from GEometry AND Tracking, was developed in CERN in 1974 and originally written in FORTRAN. FLUKA (portmanteau of FLUktuierende KAskade) was developed jointly by the Istituto Nazionale di Fisica Nucleare and CERN. It is the second particle transport code that is being used extensively in the medical domain. Increases in computing power allow for more sophisticated simulations to be conducted using these techniques. PARTRAC (PARTicle Tracking) is a separate package specifically designed to investigate particle-matter interaction at the cellular component scale, such as the interphase spread of a mammalian cell, which contains 6 billion DNA base pairs on a phosphate backbone. The package has been utilized to investigate the genotoxic effects of hadron beams of varying linear energy transfer and radiation-induced DNA fragmentation.²

At the opposite end of the length scale, the Geant Human Oncology Simulator is a full Monte Carlo simulation of the megavoltage imaging system within the TomoTherapy® (Accuray, Inc., Sunnyvale, CA) image-guided radiotherapy (IGRT) treatment unit. It has been used to estimate the risk of radiation-induced malignancy associated with the additional imaging dose used in daily IGRT treatment. In the PARTNER (Particle Training Network for European Radiotherapy) research project, large-scale simulations of treatment hardware have been created to verify dose calculation algorithms used in proton and carbon ion planning at the recently opened HT facility at the National Centre for Oncological Hadron Therapy (CNAO) in Pavia, Italy.

INFORMATICS AND GRID COMPUTING

When offloading data from the ATLAS detector, the global high-energy physics grid infrastructure can consume up to 10% of the global bandwidth for internet connectivity. Medical applications are dwarfed by such endeavours, but one of the benefits of the ENLIGHT platform has been the engagement with the European grid community. As European centres started to make plans for

HT treatment facilities, it became apparent that transnational access to highly specialized HT facilities would create its own challenges for the flow of patient data. The Hadron Therapy Information Sharing Portal (HISP) is a component of the informatics research within the PARTNER project (Figure 1). HISP provides a framework for transnational access to patient data for HT referral, treatment and follow-up, allowing diagnostic data to follow the patient as they journey to receive treatment. Furthermore, once the patient returns to his/her home clinic for follow-up, the platform provides a mechanism for staff at the treatment centre to obtain information on the outcome of treatment and for researchers to obtain censored information on treatment outcomes. I was fascinated by the way in which open-source technologies from the Grid community could be applied to problems we face in the sharing of medical data. Many web-based tools for information security, user access control, and joining of databases in different institutions, were directly applicable to the HISP project.

ACCELERATOR DEVELOPMENT AND BIOMEDICAL APPLICATIONS

From time to time, the clinical community receive requests to consider challenges and technologies that may be of importance over the next 5–10 years. Although this is difficult for medical doctors, it is a necessity for accelerator scientists. In 2005, 3 years before the first useable beam time on the LHC, researchers from the International Committee for Future Accelerators had already established proposals for the High Luminosity LHC to come online in 2018. Following the same paradigm, the Proton-Ion Medical Machine Study project (PIMMS) was established in 1996 by Philip Bryant from CERN. The project was a collaboration to develop a novel synchrotron design for cancer therapy

and produced a design plan for a mixed proton and carbon ion treatment centre. Two European centres formed part of the collaboration, Med-AUSTRON in Wiener Neustadt, Austria, and the TERA Foundation in Novara, Italy.³ 12 years after the completion of the PIMMS project, the design has been implemented at the HT Centre for Cancer Treatment (CNAO) in Pavia, Italy, which treated its first patient with carbon ions on 13 November 2012. EBG MedAustron, as it is now known, is the second centre to be built to the same basic design. Construction started in March 2011 and is scheduled to start treating patients in 2015.

There are also plans to utilize existing hardware at CERN for biomedical applications. The Low Energy Ion Ring (LEIR) is normally used to accelerate lead ions for filling into the LHC. LEIR is capable of producing ion species from protons to neon ions with an energy spectrum that is suitable for biomedical applications. Although CERN statutes prevent experiments on whole animals, such a facility could be used for cell irradiation, tissue scaffolds, microdosimetry, radiation detector development and proton tomography. Similar biomedical end stations exist in a number of treatment facilities, but competition for beam time against clinical applications and service commitments means that experimental beam time is limited and must often be conducted overnight. LEIR could easily be adapted to operate in “time-sharing” mode during LHC operations, to provide beam time for biomedical applications during normal working hours. As an organization, CERN is extremely effective at brokering international collaboration, and in June 2012, a brainstorming meeting was held in CERN to discuss plans for a biomedical endstation for LEIR. Despite the timing and relatively short notice, the meeting was attended by >200 scientists from 26

Figure 1. Hadron therapy (HT) Information Sharing Platform is a web-based infrastructure that would allow secure access to clinical data, as a patient is referred to a HT treatment centre and returns home for their follow-up. It works by using well-established technologies for distributed data storage and access that were developed by the grid community.

Box 2.

“CERN’s role is not to build future machines for medical applications but to co-ordinate and catalyse feasibility studies for future developments of a cost-effective accelerator facility”. Steve Myers, CERN Life Sciences Meeting, Geneva, 25th June 2012.

countries, including Australia, Canada, Colombia, Russia and India (Box 2).

CONCLUDING THOUGHTS

The potential health impact of the technologies mentioned in this commentary lie in areas of cancer screening and curative radiotherapy treatment. As life expectancy rises and cardiovascular mortality falls throughout Europe, the lifetime risk of developing cancer may rise beyond the current estimate of one person in three. The UK breast cancer screening programme has resulted in an 8% reduction in mortality from breast cancer since 1990, using X-ray based imaging techniques.⁴ The ClearPEM device, with its improved sensitivity and specificity for early tumour detection, seems attractive as a new screening technology providing the cost of implementation and radiation exposure can be minimized.

Radiotherapy is an effective anticancer therapy and is used in the treatment of >40% of patients who are cured of cancer. My own work in Monte Carlo simulation of radiotherapy demand has shown that according to published evidence, 40.6% of patients developing cancer should receive radiotherapy treatment at some point in their cancer journey, and that a 22% rise in the number of radiotherapy treatments is projected for 2020.⁵ I believe that HT has the potential to deliver a high-throughput radiotherapy service for specific clinical indications, and that the lower integral doses and higher biological effectiveness might facilitate hypofractionated treatment regimens. Curative radiotherapy treatment could be delivered in 3–5 instead of 35 treatments. Advances in in-beam dosimetry and radiation biology made by our group will facilitate clinical trials of such treatment strategies in existing centres over next 10 years. However, the prohibitive capital investment costs for HT remain the biggest obstacle to widespread implementation of this technology. I look to the high-energy physics community to prototype novel particle acceleration technologies, which will be smaller and cheaper by perhaps one to two orders of magnitude.

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