ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	The Institute of Cancer Research

Project details

Project title:	**Development of a microbeam-FLASH irradiator for pre-clinical radiation therapy research**

Supervisory team

Primary Supervisor:	Professor Uwe Oelfke
Associate Supervisor(s):	Dr Simeon Nill, Dr Magnus Dillon, Dr Carol Box
Secondary Supervisor:	Professor Kevin Harrington

Divisional affiliation

Primary Division:	Radiotherapy & Imaging
Primary Team:	Radiotherapy Physics Modelling
Site:	Sutton

Project background

Radiotherapy (RT) is one of the mainstay treatment modalities for cancer contributing to 40% of patients cured. The conventional RT paradigm of delivering a homogeneous dose to the whole tumour, conventionally delivered at dose rates of 0.03 Gy/s is challenged by pre-clinical data generated with i) spatially fractionated radiation fields which are periodically modulated on the micrometre scale (microbeam RT (MB RT)), i.e., high dose regions of 50 – 200 microns alternate with low dose regions of 350 to 800 microns and ii) broad beams delivered with dose rates of at least 40 Gy/s (FLASH RT) which is about a factor of 1000 higher compared to conventional RT. The biological mechanisms leading to the observed enhanced therapeutic window for both techniques are still unclear.

Our team at ICR has a long history in developing microbeam and FLASH irradiation technologies for pre-clinical research at international research labs like the European Synchrotron Radiation Facility (ESRF) in Grenoble [1-3] and at ICR [4,5]. This includes the design and implementation of hardware components [4], development of dose algorithms and measurement devices [6,7] as well as treatment planning software. At CCI we have established the first microbeam and FLASH irradiation facilities. While the microbeam irradiator is almost completely developed, we are currently commissioning our FLASH irradiator within a framework of an international SARRP-FLASH consortium (John Hopkins University, U Bern, U Belfast, U Geneva).

The Phd project aims to develop an integrated research platform, which allows to irradiate in-vivo tumour models with advanced microbeam spatial dose patterns which can be delivered at a spectrum of dose rates ranging from 0.05 Gy/s to 100 Gy/s. Starting point will be the FLASH irradiator, whose two axially rotatable x-ray tubes will allow the delivery of 2-dimensional microbeam patterns by irradiating the tumour simultaneously from different angles,

e.g., with an angle of 45 deg between the tubes. The second approach we will pursue is a 'spot-scanning' approach where the animal will be moved by a robotic couch relative to a static spherical microbeam collimator.

Following the design and implementation of the respective hardware and electronics the achievable dose patterns need to be measured and validated. Besides standard film-dosimetry protocols, we will test a novel amorphous ultra-fast silicon detector developed by the University of Wollongong [8,9]. A fast Monte-Carlo dose engine based on our work in ref [2] will be adapted to the phase-space of the novel irradiator to verify the dose measurements such that robust treatment planning can be provided for the ICR teams investigating the relevant cancer biology and immunology (Harrington team, Dillon team, CTI).

Project aims

- Developing cross firing microbeam dose patterns with a dedicated two collimator system (including robust geometric calibrations, hardware planning, implementation)
- Developing robotic spot scanning for minibeams (250 microns), design and implement robotic mouse couch and control software
- Dosimetric validation of 3D-micro/minibeam patterns with gafchromic films and a novel amorphous silicon detector, phantom development, relative dose and absolute dose measurements
- Develop online dose verification for in-vivo studies with entrance and exit dosimetry (Flat panel detectors)
- Develop MC-Carlo dose engine for microbeam/FLASH approach to enable treatment planning, dose prescription

Research proposal

AIM 1: Developing cross-firing microbeams at the FLASH SARRP

The FLASH irradiator at ICR consists of two x-ray tubes (150 kVP, 630 mA) which can be individually rotated allowing a simultaneous tumour irradiation from two different beam angles. This will generate a pattern of cross-fired beams where the tumour tissue is exposed to extremely high dose levels at crossing points of two microbeams, conventional FLASH dose rates for non-overlapping microbeams and low valley doses anywhere else. At 3rd generation synchrotrons (ESRF) these doses patterns were successfully employed to treat larger tumours in dogs [10]. Technically, this approach requires the design of two static microbeam collimators, one mounted to each x-ray tube whose beam entry angles have to be automatically aligned with micro-meter precision. The dose rate can be varied by changing the distance to of the tubes to the isocentre.

AIM 2: Robotic 'spot scanning' to deliver a dose pattern of minibeams

This second technology currently under development at John Hopkins University, uses the ultra-high dose rates of the FLASH SARRP when the focal spots of the two x-ray tubes are perfectly aligned at fixed angles of 0 and 180 Deg. The radiation of both tubes is collimated by two spherical hole collimators, with diameters of 250 – 500 microns. The desired minibeam dose pattern is achieved by moving the mouse bed on a robotic stage in increments of 250 to 1000 micron in two perpendicular directions with respect to the static pencil beam. While the collimator of this design will be simple, considerable effort needs to be made to develop the electronic control system for the robotic stage moving the mouse bed. This dose delivery technique offers to explore a variety of geometric dose patterns with varying peak to valley dose ratios. It is not applicable for smaller microbeams because this technique would lead to extended irradiation times incompatible with the welfare regulations of animal research in the UK.

AIM 3: Dosimetric validation of achieved micro/minibeam patterns

As a starting point for microbeam dosimetry will use our published protocols for film dosimetry of microbeams, which will be audited by the National Physics Laboratory (NPL) in Teddington. The absolute dose will be re-confirmed by alanine dosimetry developed by NPL (A. Subiel, I. Silvestre Patallo). Both methodologies should provide the required accuracy spatial accuracy even at high dose rates, but the required processes (film development and subsequent scanning at our microscope facility) are labour intensive and have to be performed off-line.

We therefore will engage with the group of Prof M. Lerch at the University of Wollongong who has developed a flat-panel detector with a spatial resolution of less than 5 microns and a temporal resolution to measure dose rates up 16.000 Gy/s. Prototypes of this detector were validated at the biomedical beamline ID17 at ESRF [9]. This detector would allow us to measure the radiation dose on-line during the irradiation process.

AIM 4: On-line dose reconstruction verification by entrance and exit dosimetry

Based on this novel detector technology we would be able to measure the entrance fluence delivered from each x-ray tube. These measurements could be used as a first data set which characterizes the phase-space (number of particles emitted per area, photon energy spectrum, distribution of photon emission angles) of the x-ray tubes. This entrance fluence will serve as input for the MC-dose calculation to being developed at AIM 5. The entrance dosimetry approach would be only feasible for the cross-firing dose delivery developed in aim 1.

For the dose delivery of spot scanning described in aim 2 of our proposal, the detectors in front of each x-ray tube would simultaneously detect its entrance fluence and the exit signal (the photons leaving the body of the mouse) from the other oppositely mounted x-ray tube. This superposition of entrance and exit radiation can potentially enhance the accuracy of the on-line dose reconstruction.

AIM 5: Development of a Monte-Carlo dose engine

In a first step we would focus on the calculation of the physical dose within a hybrid approach, i.e., the energy transport of the primary photons and subsequent secondary photons originating from Compton scattering will be modelled by a Monte-Carlo algorithm (GEANT4 from CERN) while the energy transport from electrons can be accounted for density-scaled dose kernels. The characterization of the x-ray source phase space will be taken from the measurements performed in aim 4.

While this dose engine will be established as the 'gold-standard' for any dose calculation in a treatment planning system, it likely will take unacceptably long calculation times to complete, because the dose needs to be calculated with a spatial resolution of a few microns. However, our simplified irradiation geometry should allow to model the cylinder-shaped beam employed for the spot scanning approach with a set of lateral dose profiles multiplied by a density scaled depth dose curve.

Literature references

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[2] Donzelli M, Bräuer-Krisch E, Oelfke U, Wilkens JJ, Bartzsch S. Hybrid dose calculation: a dose calculation algorithm for microbeam radiation therapy. Phys Med Biol. 2018 Feb 13;63(4):045013.

[3] Merrem A, Bartzsch S, Laissue J, Oelfke U. Computational modelling of the cerebral cortical microvasculature: effect of x-ray microbeams versus broad beam irradiation. Phys Med Biol. 2017 May 21;62(10):3902-3922.

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[9] Davis J, Dipuglia A, Cameron M, Paino J, Cullen A, Guatelli S, Petasecca M, Rosenfeld A, Lerch M. Evaluation of silicon strip detectors in transmission mode for online beam monitoring in microbeam radiation therapy at the Australian Synchrotron. J Synchrotron Radiat. 2022 Jan 1;29(Pt 1):125-137.

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Transfer of Microbeam Radiation Therapy: Acute to Subacute Radiotolerance after Brain Tumor Irradiation in Pet Dogs. Cancers (Basel). 2024 Jul 29;16(15):2701.

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants:	BSc or equivalent in either Physics/Engineering (background in biological sciences would be helpful)
Intended learning outcomes:	• Software development • Radiotherapy Physics • Film dosimetry • Monte Carlo dose calculation (Geant4) • Integration of robotic table control with X-ray control system • Basic understanding of Radiobiology

Advertising details

Project suitable for a student with a background in:

- ☐ Biological Sciences
- ☒ Physics or Engineering
- ☐ Chemistry
- ☐ Maths, Statistics or Epidemiology
- ☒ Computer Science