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Abstract Booklet
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Dosimetry and Radiobiological Research on the Birmingham MC40 Cyclotron

Stuart Green – University Hospital Birmingham

The Scanditronix MC40 variable energy cyclotron at the University of Birmingham is perhaps the most flexible research cyclotron in the country. Its extracted beam facilities are well used for isotope production, surface activation / wear and materials damage studies. Over the least 5 years a capability for radiobiology and dosimetry studies has been developed which enables use of the available proton and ion beams.

The majority of work to-date has made use of proton beams at typical nominal energies of 36, 29 and 15MeV although the cyclotron can produce other energies. This talk will describe the facility and use two published studies to illustrate its capabilities

- The work of Kirby et al on the proton energy response of various types of radio-chromic film has been published and highly cited. The excellent energy resolution of the cyclotron beams enabled detailed work to be undertaken to define the "relative effectiveness" of EBT and MD-55 films at low proton energies and to pick-out the differences between them. For other low energy sources (such as those produced by laser accelerators) use of this energy response is critical in correctly characterising both the spectrum and the total yield of protons.
- In collaboration with Mark Hill and colleagues at the Gray Institute, we have undertaken proof of principle irradiations to illustrate the proton energy (ie the LET) dependence of the biological effect of radiation dose modifiers. In particular work on an experimental compound which acts as an inhibitor of the PI3K pathway has been published.

Dosimetric Characterisation of Glass Bead TLDs in Proton Beams

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Purpose: To investigate the feasibility of using glass beads as a novel thermoluminescence dosimeter (TLD) in proton radiotherapy. The glass beads have several physical characteristics which suggest their use as TLDs in this area: a spherical physical shape with a hole in the middle that facilitate their use in 2D and 3D arrangements; chemically inert nature; small size of 1.5 mm diameter and 1 mm thickness; inexpensive and readily available; reusable; and importantly their TL light transparency with negligible self-attenuation which is very important for high LET beams. Proton beams have high LET and therefore can deposit dose nonuniformly across a detector. Readout of TL detectors can be influenced if any opacity is present causing self-attenuation of TL light [1], [2]. The transparency of glass beads to TL light means the beads have the potential to avoid such issues.

Material and Methods: Commercially available glass beads were investigated for their response in a 62 MeV clinical ocular proton beam (fig. 1). A novel thin window phantom was designed to position the glass beads in water and avoid attenuation from neighbouring detectors. The beads were irradiated with doses ranging from 0.5 to 100 Gy to investigate their linearity. A typical ocular treatment fraction of 12 Gy was used with dose rates of 5, 10, 20, 30, 50, and 100 Gy/min to investigate the dose rate dependency. The glass beads were threaded together using thin elastic plastic yarns and measurements were performed in a water tank to assess the profiles and linearity and a perspex phantom to measure depth dose curve. A HARSHAW 4500 model TL system was employed for read out.

Results: A linear dose response was observed in the investigated range, 0.5–100 Gy, with a correlation coefficient of $R2 > 0.999$. The dose rate response was within ≤ 1% for dose-rates from 5 Gy/min to 100 Gy/min. The ability of detector to assess the high gradient region of penumbra was investigated by assessing the beam profiles obtained with the glass beads, the results demonstrate high sensitivity of glass bead TLDs to proton beams having a high yield of TL light with a minimum detection limit of 50 mGy, which demonstrated the beads ability to measure beam profiles. The readout was found to be independent of bead orientation on the readout planchet thus confirming insignificant self-attenuation of TL light.

Conclusion: The dose linearity and dose rate independency shown suggest that glass beads have potential as TLDs for verification measurement in proton therapy.

A focused scanning vertical beam for charged particle irradiation of living cells with single counted particles

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The Surrey Vertical beam is a facility for targeted irradiation of cells in medium with singly counted ions. A duo-plasmatron ion source and a 2 MV Tandem accelerator supply a range of ions from protons to calcium for this beamline and fluorescence microscope end-station, with energy ranges from 0.5 to 12 MeV. We present the design and capabilities of this beamline, showing the capability to count single ions with 98% certainty demonstrated on CR-39 track etch. We also show that the beam targeting accuracy is within 3 microns and selectively target human fibroblasts with a <3 μm proton beam, using γH2AX immunofluorescence to demonstrate which cell nuclei were irradiated.

The Surrey Vertical Beam also has the capability to irradiate cells in a "broadbeam" mode. We have used this capability to investigate the influence of the cell nucleus area distribution on the survival fraction after charged particle broad beam irradiation. More specifically, this work aims to explain the deviation or tail which might be observed in the survival fraction at high irradiation doses. For this purpose, the nucleus area distribution was added to the beam Poisson statistics and the Linear-Quadratic model in order to fit the experimental data generated by broad beam irradiation with high energy heavy ions. As shown in this study, the nucleus size variation and the associated Poisson statistics can lead to an upward bending in the survival fraction after broad beam irradiation.

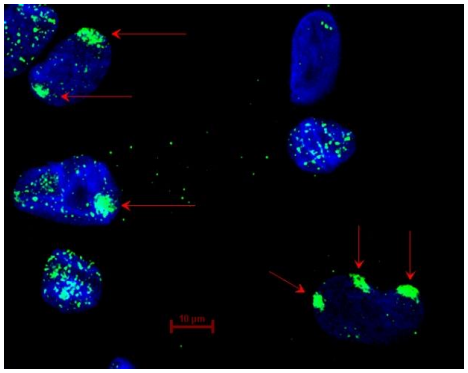

Figure 1. Targeted irradiations of single AGO1522 human fibroblast cells using 3.8 MeV protons: A γ-H2AX stain (green) is used to show double strand breaks induced by a 1 Gy irradiation of targeted 3.8 MeV protons within a 5 μm diameter beam focus, at the locations indicated, The cell nuclei are stained with Hoescht 33258 (blue). Additional γ-H2AX foci on non-targeted cells are due to double strand breaks associated with mitosis.

Graphite Calorimetry in Scanned Proton Beams

Lauren Petrie – National Physical Laboratory

In order to facilitate accurate dosimetry, especially in preparation for the new proton centres in the UK, the NPL proton graphite calorimeter is being characterised in scanned proton beams.

This work compares models made in COMSOL Multiphysics with experiments done at Clatterbridge Cancer Centre (a fixed beam line). In order to simulate a scanned beam, the calorimeter was attached to a carriage which could be remotely controlled, in order to "scan" the calorimeter across the beam.

Also described are the measurements taken in a recent visit to Prague.

First direct comparison between a graphite calorimeter and a water calorimeter in a 60 MeV proton beam

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Background: Absorbed dose to water is the quantity of interest in clinical reference dosimetry. The most common primary method to determine absorbed dose is calorimetry. To avoid applying a dose conversion from non-water calorimeters, some laboratories developed water calorimeters (WCal). However, due to their advantages in terms of physical and chemical material properties and the precision and the ease of the manufacturing process, solid calorimeters have been maintained as primary absorbed dose standards. Direct comparisons between these two independent technologies are very rare. This work describes the first direct comparison between a WCal and a graphite calorimeter (GCal), performed in modulated and non-modulated, low-energy passive scattered clinical proton beams at the Clatterbridge Cancer Centre (UK).

Method: In the quasi-adiabatic mode of calorimeter operation, the absorbed dose is calculated as the product of the measured radiation-induced temperature rise and the specific heat capacity of the medium. The technological challenge consists of the measurement of temperature increases of 0.25 mK and 1.4 mK per gray for WCal and GCal, respectively. The GCal can also be used in isothermal mode. In this case, the absorbed dose is derived from electrical energy substitution, which is used to maintain the calorimeter at a constant temperature, divided by the core mass.

Preliminary results presented here include all corrections, except that for the heat transfer within the WCal. This requires a detailed modelling of the detection vessel non-water materials and dose distribution and their effect on the heat transferred to the point of measurement. Using hydrogen saturated high purity water in the water calorimeter, the heat defect can be assumed to be zero, provided the system is free of trace oxygen. For the GCal, the heat transfer correction is zero in the isothermal operation mode and less than 0.5% for the quasi-adiabatic operation mode. The dose conversion in the latter system results from the water-to-graphite stopping power ratio (1.118 ± 0.010 based on data from ICRU Report 49) and a fluence correction factor accounting for the different nuclear interaction cross sections of water and graphite (1.000 ± 0.002 and 0.998 ± 0.002 for the modulated and non-modulated beam, respectively). Ionization chambers were used to monitor and correct for beam instability and output variation. Differences in the positioning of both calorimeters (depth, distance) are accounted for, based on measured dose gradients.

Results/Conclusions: The preliminary ratios of the graphite to water calorimetry dose are 0.995 and 0.987 for the modulated and non-modulated beam, respectively, with an uncertainty of 1.2%. The main contributions to this uncertainty are: the dose conversion for the GCal (1.1%) and the chemical heat defect of the WCal (0.3%). If we remove the uncertainty on the dose conversion for the GCal, we obtain the experimental uncertainty with which we can measure the dose conversion factor, i.e., 0.4%.
These results are encouraging and confirm the accuracy of the dose conversion procedure for the GCal to determine the dose-to-water in proton-therapy. Further work is required to determine the heat loss correction for the WCal system and the overall uncertainty on absorbed dose to water determined using each system.

Cherenkov light production during proton therapy: simulation and experiment

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Motivation: Eye cancer patients frequently report a visual sensation during proton therapy. We investigated the possibility of Cerenkov emissions being behind it and explored using Cerenkov light for dosimetry and dose localisation in proton therapy.

Approach: A Monte Carlo simulation using GEANT4 was used to explore the different sources of Cerenkov emissions in proton therapy, and to predict the deposited energy and Cerenkov light production in a water phantom. By measuring the light distribution emanating from the phantom, the relationships between the deposited energy, Cerenkov light production and the depth distribution of different radionuclides were investigated. A PMT was used to measure the time scale of the Cerenkov emissions from a clinical proton beam penetrate a water phantom, and to explore the dose linearity.

Results: We found that the Cerenkov light emissions in proton therapy can be divided into two distinct mechanisms: a fast component due to prompt gamma interactions (99.13%) and neutron interactions (0.87%), and a slow component due to radioactive decay. The simulated depth distribution of the Cerenkov emission shows a strong relation with the positron activity induced. The fast component was found to be linear with dose, while the slow component increases non-linearity with dose.

Conclusions: The fast component of the Cerenkov emission could result in the observed visual sensation. The simulated depth profile of Cerenkov emission confirms the possibility of using the slow component to verify the range of the proton beam mainly from ^{15}O radionuclides. While as the fast

component depends on gamma rays, which may interact far from their point of origin, therefor no spatial information could be retrieved from the fast component. The experimental data of the dose linearity with Cerenkov emission suggest the possibility of using the fast component of Cerenkov emission to verify the dose, while the slow component is less linear with dose.

Developing an Accurate Beam Model for a Proton Therapy Spot Scanning Monte-Carlo Verification System

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The Christie NHS Foundation Trust is one of two centres nominated to provide a Proton Beam Therapy (PBT) service to the UK and is commencing developmental work in preparation. It is crucial that a highly accurate model of a spot-scanning proton beam is developed such that the spatial distribution of energy deposition can be precisely predicted. I will report on the progress of a project using GATE, a Geant4 based MC simulation code (e.g. Jan et al. 2011), to parameterize a clinical spot-scanning proton beam in terms of the energy distribution and optical parameters at the nozzle exit based on data from Gantry 2 of PSI. The parameterization of the relevant variables for both integral depth dose and lateral profiles will be discussed.

The overall objective of the project is to integrate the resulting beam model into an automated MC verification system to save on machine-based verification time. The greater the capacity to treat patients, combined with the freeing up of physicists for other work, will be cost effective for the radiotherapy department.

Water and tissue equivalent phantom materials for clinical proton beam dosimetry

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Purpose/Objective: The aim of this work is to find ideal and realistic atomic compositions of water and tissue equivalent phantom materials for clinical proton beam dosimetry.

Methods: In proton therapy, for treatment planning proposes, it is crucial to know the delivered dose and range of a proton beam in the patient accurately. Currently, these are measured in liquid water, which has similar radiation absorption properties to tissue for determining the absorbed dose. In order to simplify the experimental set-up, water equivalent plastic phantoms are frequently used in the
measurements. These materials are well developed for conventional radiotherapy such as high-energy photon and electron beam, but for proton therapy this is not the case due to the difference between non-elastic nuclear interactions for different elements (oxygen and other nuclei). Therefore different rates of secondary particles are produced, which leads to a difference in the particle fluence present in
water or tissue compared to the target material at an equivalent depth. This difference is corrected by using the fluence correction factor, which is determined by the differences of the charged particle fluence distribution in water as compared with that at the scaled depth in the plastic phantom.

An analytical model was implemented in MATLAB to make an approximate estimate (ignoring transport of secondary particles) of the fluence correction factors between water or tissue and any other material in order to find atomic compositions equivalent to water or tissue.

Results: In the work done up to now, various compositions for water equivalent phantom materials for protons were tested and promising results were found.

Conclusions/Future work: Monte Carlo simulations using the FLUKA code will be performed to test the water equivalence of the proposed material. Combined with the constraints imposed by the production process, optimal compositions for water and tissue equivalent plastics will be proposed and produced. These will then be evaluated experimentally in low and high energy clinical proton beams.

Proton-counting imaging for proton radiotherapy using CMOS APS detectors

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In the early 1960s, the potential for proton imaging to assist proton radiotherapy was recognized by Allan Cormack (Cormack 1963 *J. Appl. Phys.* **34** 2722). However, over fifty years later the modality is still removed from clinical practice. This may soon change with technological advancements and as remarked in a recent keynote speech: "*In 10 years, we should aim for low-dose, daily isocentric proton CT for dose recalculation"* (Martijn Engelsman, Delft University of Technology, PTCOG 13). Various approaches to proton radiography are in development. Here we propose the use of radiation-hard CMOS Active Pixel Sensors (APS). The capability for such sensors to resolve the passage of individual therapy protons is demonstrated using a 36 MeV beam (University of Birmingham Cyclotron, Birmingham, UK) and a 200 MeV radiotherapy beam (iThemba LABS, Cape Town, SA). A proof-of-principle for the tracking individual protons through multiple detector layers is also provided using a two-layer stack of sensors. Thus, the feasibility of constructing a proton range telescope using CMOS APS technology is demonstrated. Possible advantages of this technology are the spatial discrimination of events inherent to pixelated detectors, in combination with information on both the range and residual energy of a proton.

Proton Gantry Mounted CBCT Development at Massachusetts General Hospital

Brian Winey, Yang Kyun Park, Mingyao Zhu, Hsiao-Ming Lu, Maryam Moteabbed, and Gregory Sharp

Purpose: To develop a proton gantry mounted CBCT system for accurate patient position monitoring and proton dose calculations.

Methods: Procedures were developed to generate accurate geometric and reconstruction calibration parameters for the CBCT images. Proton gantry wobble was characterized using 13 months of clinical and physics test images to determine the physical crosshair position and reproducibility. In addition to precise flexmap corrections, CBCT images suffer from image artifacts. CBCT projection images were acquired with photon gantry mounted imaging systems for testing of artefact reduction methods including scatter, beam hardening, and lag. Pelvis and cranial anthropomorphic phantoms were reconstructed with CBCT and proton dose calculations were performed to compare to a reference CT dose calculation.

Results: The gantry isocentricity can wobble up to 5 mm during a rotation. The wobble is reproducible to within 0.5 mm. The gantry sag is currently corrected using physical crosshairs. Scatter is the dominant effect in image quality loss for CBCT and an *a priori* model using the planning CT reduced the effects of scatter. Dose calculations demonstrated range variations of up to 1 cm when compared to reference CT calculations. The range variations were due to the CBCT HU calibration error in addition to the residual CBCT artifacts. Conclusions: The gantry sag can be corrected using a flexmap calibration. CBCT artifacts in reconstructions can be reduced by accounting for scatter, beam hardening and lag. Optimal absolute calibration of Hounsfield Units and Stopping Power Ratios is a continuing project.

Investigation on dual energy CT tissue characterization methods for particle beam dose calculation

Hugo Bouchard – National Physical Laboratory

The goal of this study is to compare two methods for extracting radiotherapy-relevant tissue information from DECT images. The first method is an extension of the stoichiometric method of Schneider et al. (1996) being widely used with conventional CT scanners. The second method is an extension of the formalism of Alvarez and Macovski (1976) and consists of modelling photon transmission sinograms in terms of tissue-information sonograms, such as electron density and effective atomic number. Although the latter method shows the advantage of removing most beam hardening effects, the DECT stoichiometric calibration method seems significantly less sensitive to noise and spectral information. Although preliminary results suggest that the first method is more reliable for clinical implementation, a rigorous sensitivity study on dose calculation is yet to be performed.

Effects of Patient Setup Uncertainty on Proton SRS Treatment Planning

Brian Winey, Jakob Liebl, Harald Paganetti

Purpose: To quantify the effects of patient setup uncertainty on target and organ dosimetry and develop safe treatment planning protocols for proton radiosurgery.

Methods: A retrospective analysis was conducted to determine the setup uncertainties of cranial patient treatments at the Massachusetts General Hospital proton therapy center. Treatment plans for eight patients with cranial lesions treated with double scattered stereotactic proton therapy were simulated with Monte Carlo to include setup displacements. The clinical treatment plans for the 38 fields included range margins and smeared range compensators. Doses to the target and organs at risk (OARs) were compared to the expected doses.

Results: Anatomy based setup was less accurate than fiducial based patient positioning. The increased setup error resulted in an increase of patient positioning mean range error of 2.8 mm (6.6 mm vs 3.8 mm) at the 50% distal falloff. The 90% falloff was more sensitive to setup errors. The maximum range errors always occurred for beams passing alongside high contrast tissue boundaries. Target coverage was not significantly affected due to the current clinical practice of including a range margin in planning. OAR doses were generally not significantly affected. The largest clinically significant OAR dose difference occurred for the sella target located adjacent to the optic chiasm.

Conclusions: With proper treatment planning techniques including range margins, beam angle selections and use of three or more fields, the effects of setup uncertainties are minimal in many patients. When OARs are located in close proximity to the target, a planning risk volume is recommended. Tools to assist in beam angle selection are being developed to indicate the tissue heterogeneity across the beam's eye view.

Incorporating and managing range uncertainties in proton beam therapy.

Stacy McGowen – University of Cambridge

An optimised treatment plan will not only meet the aims of the planner, but will meet them at each and every fraction, therefore, ensuring both sufficient plan dosimetry and plan robustness.

The finite range of protons and their high electron density dependence leads to uncertainties in the proton range due to both discrepancies between planned and delivered dose and at dose calculation. Therefore it is required that range uncertainties be taken into account in proton therapy planning. Understanding the origin and magnitude of range uncertainties and incorporating them into the planning process is essential for ensuring adequate plan robustness. Additional problems lie in not only assessing and managing uncertainties, but in establishing site-specific robustness criteria.
We will present here both an understanding of the characteristics of range uncertainties and the practical solutions to these challenges, including robust planning criteria.

Dose remapping and summation for head and neck adaptive radiotherapy applications

Catarina Veiga, Ana M. Lourenço, Gary Royle, Jamie McClelland

Purpose/Objective: In this work we study the effect that different approaches for pCT-CBCT deformable image registration (DIR) have in dose remapping and summation in adaptive radiotherapy applications for head and neck patients (HN).

Methods: NiftyReg is an open-source implementation of the B-Splines DIR algorithm, implemented in our institution. Two DIR implementations are available: a typical unidirectional algorithm (non-symmetric) and a symmetric approach. Symmetric registrations should produce more realistic, robust and physically plausible deformation fields since they are not biased towards the registration direction, but they are more computationally expensive. Accurate point-to-point matching is particularly important when handling dose remapping and summation. However, the symmetric approach is a time consuming process with potential practical drawbacks for its implementation in the GPU (unlike the non-symmetric), which increases the computation time from a few minutes to a couple of hours.

We registered a planning CT (pCT) to multiple following CBCTs acquired throughout the treatment for one HN patient. This patient had been closely monitored during radiotherapy due to visible weight loss that was of concern to the treatment efficiency. Dose calculations were performed on deformed pCTs (instead of directly on the CBCTs due to its poor quality image) using the treatment IMRT plan, and they were mapped back for dose summation using 3 different methods: (i) non-symmetric registration on both directions, (ii) symmetric registration on both directions, and (iii) non-symmetric registration in the forward direction and numerical estimation of its inverse transformation. The cumulative dose distributions were displayed on the planning CT dose space, and compared using dose differences (DD), gamma analysis and dose volume histograms (DVHs).

Results: The results were found to be consistent between different inverse transforms. The DD was smaller than 2% of the prescribed dose on over 94% of the body's voxels and they passed a 3% and 3 mm gamma-test criterion on over 99.5% of the voxels. The DVHs overlapped considerably and maximum values of absolute dose differences in organs at risk were found to be less than 0.8 Gy.

Conclusions: We have presented a feasibility study on using different registration approaches to obtain cumulative dose distributions. Standard unidirectional registrations and numerically estimating the inverse gave similar results to more complex and computationally expensive inverse consistent approach, therefore they are more feasible to clinical use. Future work will focus on IMPT plans.

Collimation of spot scanned proton therapy beams to sharpen the lateral edge of uniform dose volumes

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Purpose/Objective: In general In general, the lateral edge (termed penumbra) of a pencil beam scanning (PBS) system is worse than that of a double scattered divergent beam at shallow depths in the patient. This is predominantly due to the in-air scattering associated with the spot scanned beam. Depending on the minimum accelerator energy output, the beam may need to be degraded through Perspex beyond the nozzle, further blurring the penumbra. Here, Monte Carlo simulations have shown that the penumbra is significantly improved by the use of a short source-surface distance (SSD) and/or collimation. To date, there have been few studies of the factors affecting the lateral penumbra of homogeneous dose volumes.

Materials and Methods: The GATE (Jan et al., PMB 2011) Monte Carlo software was used to simulate double scattered and pencil beams, with results validated against those of Safai et al. (PMB 2008). Key parameters such as SSD, collimator-surface distance, collimator thickness and diameter, use of range shifter, spot properties and optimisation were separately investigated to assess the conformity of treatment. Additionally the delivery of homogeneous dose volumes using spot scanning was simulated to ensure that the penumbra can be sharpened throughout the whole volume. For spherical volumes, the use of a MLC was simulated in attempt to improve the penumbra.

Results: For the collimated divergent and uncollimated single pencil beams, GATE results agreed with the analytical model of Safai et al. (PMB 2008) to within 1-2mm, validating the Monte Carlo model. Reducing the SSD of a

pencil beam array has a greater effect at lower energies due to the reduction of in-air scattering. Collimation of a monoenergetic pencil beam array reduces the entrance penumbra from 0.4-1.2cm to 0.1-0.2cm, depending on SSD and initial energy. Beams 'pulled back' through a Perspex range shifter suffer penumbral blurring; placing a collimator beyond the range shifter sharpens the penumbra to approximately that of an uncollimated PBS. Collimation of homogeneous volumes is shown in Figure 1.

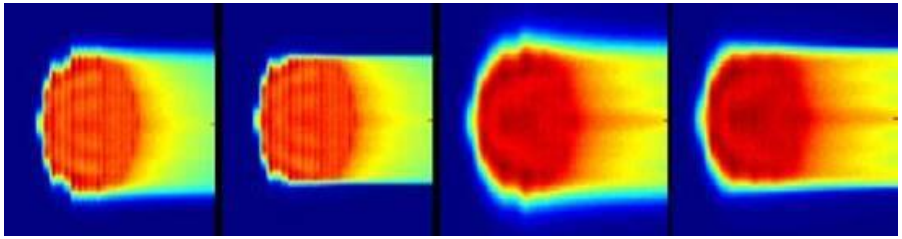

Figure 1: 2D profiles in a 20x20x20cm3 water tank for a (L-R) uncollimated, singly collimated, uncollimated pullback and collimated pullback pencil beam array using a square grid of spots. The latter 2 beams have been pulled back through 10cm Perspex. The beams have been weighted to ensure a homogeneous dose in the spherical volume.

Conclusions: Positioning the nozzle of a spot scanned beam at short SSD produces penumbra comparable to that of a double scattered system. For very superficial tumours and for beams which have to be degraded through Perspex, use of a collimator significantly improves the lateral penumbra; this is seen both for single energy layers and for doses to homogeneous volumes.

Fluence correction factors for graphite calorimetry in clinical proton beams using Geant4

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The conversion of absorbed dose-to-graphite in a graphite phantom to absorbed dose-to-water in a water phantom is performed by water to graphite stopping power ratios. If, however, the charged particle fluence is not equal at equivalent depths in graphite and water, a fluence correction factor, k_{Φ}, is required as well. This is particularly relevant to the derivation of absorbed dose-to-water, the quantity of interest in radiotherapy, from a measurement of absorbed dose-to graphite obtained with a graphite calorimeter.
In this work, fluence correction factors for the conversion from dose-to-graphite in a graphite phantom to dose-to-water in a water phantom in a 60 and 200 MeV mono-energetic protons were calculated using Geant4. The methodology for determining these factors will be described as well as some of the issues encountered and the results are compared with similar calculations performed with other Monte Carlo codes (FLUKA, MCNPX, SHIELD-HIT and McPTRAN.MEDIA).

In general the fluence correction factors for 60 MeV protons were found to be close to unity at the surface when only protons are considered and ~0.5% less than unity at shallow depths when all charged particles are considered (due to the contribution from alpha particles). The correction then increases by ~1.0-1.5% with depth up to the Bragg peak region. For 200 MeV, the fluence correction was found to vary more substantially being ~2% below unity near the surface and up to ~6% above unity around the Bragg peak.

RBE variation along monoenergetic and modulated Bragg peaks of a 62 MeV therapeutic proton beams

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Background: Biological optimization of proton therapy critically depends upon the accurate mapping of RBE variations along the full Bragg Curve. The routinely utilized clinical RBE value of 1.1 represents a broad average and oversimplification, which disregards the steep rise of Linear Energy Transfer (LET) at the distal end of the Spread-Out Bragg Peak (SOBP). With particular attention to key endpoint of cell survival we analyzed comparative cell killing RBE variations along monoenergetic and modulated (SOBP) proton beams using human normal and radioresistant cells with the aim to investigate RBE dependence on LET and intrinsic radiosensitvity.

Material and Methods: We irradiated human fibroblasts (AG01522) and glioma (U87) cells at six depth positions along pristine and modulated 62 MeV proton beams at the INFN-LNS (Catania, Italy). Cell killing RBE variations were measured using standard clonogenic assays and were further validated using Monte Carlo simulations and the Local Effect Model (LEM).

Results & Conclusions: We observed significant cell killing RBE variations along the protons beam path, particularly in the distal region showing strong dose dependence. Experimental RBE values were in excellent agreement with the LEM predicted values indicating dose averaged LET as a suitable predictor of proton biological effectiveness. Data were also used to validate a parameterized RBE model. The predicted biological dose delivered to a tumor region based on the variable RBE inferred from the data, varies significantly from clinically used generic RBE of 1.1 and lead to about 18% excess biological dose deposition in the SOBP region and a marked increase of ≈79% in the distal dose fall off region. This significant RBE increase at the distal end suggests potential to enhance optimization of other treatment modalities such as LET painting of hypoxic tumors. Our study highlights the limitation of adoption of a generic fixed RBE for proton therapy and suggests approaches for fast implementation of RBE models in treatment planning.

Developing a fluorescence microscopy method of cell cycle phase determination, compatible with targeted irradiation protocols.

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When investigating low dose effects on cells after particle irradiation, targeted irradiation protocols must be used to ensure accurate dosimetry. The vertical beam line at Surrey Ion Beam Centre is capable of such irradiations. Cells, attached to a substrate, are initially detected using a fluorescence microscope in conjunction with a moveable stage, on which the cell dish is positioned. The imaging system as a whole, named the end-station, is located above the beam exit nozzle. Using cell detection software, cells are identified and then irradiated. If investigations into phase effects are also required then this irradiation protocol is incompatible with gold standard synchronisation methods that would be required. It was therefore proposed that the fluorescence signal collected and analysed by the microscope/software could be used to determine cell cycle phase. This is possible due to the use of a nuclear stain whose uptake into the cell nucleus is proportional to the DNA content and also the resulting fluorescence signal detected. Because the end-station was to be used as a cytometry device, cell data was collected from the end-station and DNA histograms were produced that could be compared to flow cytometry histograms collected for the same cell line. This was performed for both asynchronous and synchronised cells. A number of other tests were also carried out to validate the use of the end-station as a cytometry device. To compliment the protocol devised, a mathematical model called FloCytUS (Flow Cytometry University of Surrey) was developed. This model was based on an existing cell cycle model, CelCyMUS, both of which were written in Fortran. This model allows simulated populations of cells to be passed through either a virtual flow cytometer or a virtual end-station. The resulting data could then be fitted to real data to provide a measure of the likelihood that a cell is in a particular phase given its fluorescence signal detected. The initial tests showed that using the end-station as a cytometry device was valid. Initially this protocol was used in conjunction with survival and γ-H2AX experiments using 250 kV_p X-rays and was shown to be successful.

Radiosensitisation by nanoparticles in Proton therapy

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Background: The use of nanoparticles (NPs) with a high atomic number for radiosensitisation has been studied by different groups in x-ray radiotherapy. A radiosensitisation effect was seen by these groups, however there has been a debate as to the optimum conditions and mechanisms (both physical and biological) for this effect. We propose to look at applying NP dose enhancement to proton therapy and investigating the hypothesis that a similar radiosensitisation effect can be observed to x-ray radiotherapy.

Materials and methods: A wide literature review was performed to ascertain reasons for the vast differences in reported NP dose enhancement, particularly at clinical energies. Preliminary information was obtained for x-rays and protons using Geant4 to carry out Monte Carlo simulations. The work involved using Geant4 to simulate a single NP, of a specified material, and then irradiating the particle using an x-ray or proton beam. From this simulation we were able to investigate the nanoscale effects: the different secondary particles produced, their energies and ranges. As our work focuses on the use of protons, our model also incorporated Linear Energy Transfer (LET), as protons promote a denser ionisation effect; NP presence would further increase this ionisation effect. We also considered proximity of NPs to the nucleus to investigate ability to damage DNA. We looked at the secondary electrons produced and found an average distance travelled to determine where in the cell would be most suitable for locating the NPs.

Results: We used our simulation code to verify x-ray dose enhancement results found in the literature. Preliminary simulation results highlighted physical factors that greatly affect the level of radiosensitisation observed, such as the incident energy and the size and material of the particle. We present characteristics of secondary particles produced with NP-proton interactions, and put forward optimum cellular locations for NPs to instigate greatest DNA damage.

Conclusions: From this study we plan to determine the primary physical factor that contributes to radiosensitisation and further our investigation by optimising that factor through NP design. In the future, we then plan to use our optimised NP as part of a bio-phantom, in the form of a 3D *in vitro* biomimetic cancer model ('tumouroid'). Using the tumouroid we will then be able to form an investigation looking into the biological mechanisms that contribute to NP dose enhancement.