Development of data acquisition system for multi channel dosimetry in the quality assurance of microbeam radiation therapy

Sutinder Kumar Khanna

University of Wollongong

Recommended Citation
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Department of Engineering Physics

Development of Data Acquisition System for Multi Channel Dosimetry in the Quality Assurance of Microbeam Radiation Therapy

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2930572

This thesis is presented as part of the requirements for the award of the Degree of Master of Science-Research of the University of Wollongong

August 2011
ABSTRACT
In this research project a DAQ (Data Acquisition) system was developed for use with a new 128 channel, silicon strip detector (SSD) which was designed at the Centre for Medical Radiation Physics (CMRP) University of Wollongong. Software for the data acquisition has been developed using the graphical programming language LabVIEW to readout and display, in real-time, the calibrated and normalised detector response of all 128 channels. In addition to this, was the development of software features, and related hardware that initiate a treatment beam dump should the measured instantaneous dose rate go above a predetermined threshold in any of the 128 channels. Testing of the system was carried out in a clinical setting, a medical LINAC and a research clinical environment, Synchrotron X-ray microbeam radiation therapy. The system was fully characterised and demonstrated excellent performance in both the above clinical treatment settings, and has since been utilized in other clinical settings where high spatial resolution detectors and real-time readout are required for quality assurance in radiotherapy.

PUBLICATIONS

ACKNOWLEDGEMENTS

I am grateful to my supervisor Prof. Anatoly B. Rozenfeld who encouraged me to undertake this research project. He has been a source of inspiration.

I would like to extend special thanks to Dr. Michael Lerch for testing the system at European Synchrotron Radiation Facility (ESRF) in Grenoble, France. It was a moment of immense joy when I received his email confirming that the system has performed as per design.

Big thanks to Mr Peter Ihnat for his unwavering assistance in fabricating RS-232 interface.

Finally I express my heart felt thanks to my colleagues at St George Hospital Department of Medical Physics. Brad Oborn for his valuable input in terms of data analysis, Mr Garry Rule, and Mr Harry Porter for their precision machining skills for fabrication of testing jigs.
# TABLE OF CONTENTS

ABSTRACT .................................................................................................................. i

ACKNOWLEDGEMENTS ......................................................................................... ii

TABLE OF CONTENTS ........................................................................................... iii

LIST OF FIGURES ................................................................................................. v

LIST OF TABLES ................................................................................................... ix

List of Special Names or Abbreviations .................................................................. x

1. INTRODUCTION .............................................................................................. 11

   1.1 Micro-beam Radiation Therapy (MRT) ..................................................... 11

2 Literature review ................................................................................................. 14

   2.1 MRT Radiobiology .................................................................................... 14

   2.2 Microbeam Generation ............................................................................. 28

   2.3 Micro Beam Dosimetry ............................................................................ 34

      2.3.1 Semiconductor Diodes for MRT Dosimetry .................................. 36

3 DAQ system for Multi channel dosimetry Hardware ......................................... 40

   3.1 Strip Detector ............................................................................................ 40

   3.2 Fe4C Front end Board with Tera 03 ......................................................... 44

   3.3 LA TX-RX INTERFACE ........................................................................... 50

   3.4 NI 6534 DIO CARD ............................................................................... 53

4 SOFTWARE ........................................................................................................ 56

   4.1 Data flow programming ............................................................................ 56

   4.2 Graphical User Interface (GUI) ............................................................... 57

   4.3 Software Architecture .............................................................................. 58

   4.4 Hierarchy of VIs ....................................................................................... 60

      4.4.1 Group Config VI: ........................................................................... 61
LIST OF FIGURES

Figure 1.1 This image shows tissue after it has been exposed to a narrow micro-beam of high energy radiation. .......................................................... 12

Figure 2.1 Survival curves using MRT with and without adjuvant therapy for (Left) F98 and (Right) C6 gliomas. .................................................. 25

Figure 2.2 Shows a histopathology slide of a section of the cerebellum of a piglet after being irradiated with microbeams to a dose of 300 Gy in the microbeam peaks. The parallel tracks created are very clearly defined and with no macroscopic ablation of the tissue observed [19]........................................ 26

Figure 2.3 In (a) multislit collimator MSC producing the planar microbeams, and in (b) a collimator producing the cylindrical beams, as shown. Adopted from [34] ........................................................................................................... 29

Figure 2.4 Photograph of the assembled ESRF EMSC that produces micro planar beams adjustable width. Adopted from [34]. .................................................. 31

Figure 2.5 Schematic drawing of one block of the ESRF EMSC with 100 µm slit width and a pitch of 400 µm. Adopted from [34]................................. 31

Figure 2.6 Sketch of the mounted two stacks including the setup used to align the collimators with the beam. Adopted from [34].................................. 32

Figure 2.7 Sketch of the MRT experimental setup with the distance of the elements from the x-ray source. Adopted from [34]. ................................. 33

Figure 3.1 Block diagram of Daq. .................................................................... 40

Figure 3.2 a) Photograph of silicon strip detector under investigation. b) A schematic cross section across two adjacent strips ........................................ 41

Figure 3.3 This picture shows the silicon strip detector used for Daq development. 42

Figure 3.4 Photo of Fe4C Board with 2 Tera03 Chips ........................................ 44
Figure 3.5 Block diagram of Recycling Integrator .................................................45
Figure 3.6 Block diagram of Tera 03 Chip .............................................................46
Figure 3.7 34DIN41651 connector ...........................................................................47
Figure 3.8 16bit mapping of Address lines ..............................................................48
Figure 3.9 Timing sequence of Latch pulse in relations to Address written and Data read ..............................................................................................................48
Figure 3.10 FE4C Front end Board schematic ..........................................................50
Figure 3.11 LA TX RX RS-422 Interface schematic ..................................................51
Figure 3.12 NI PC! 6534 Block Diagram Adopted from [45] ....................................53
Figure 3.13 NI 653X I/O Connector 68-Pin Assignments Adopted from [45]. ..........55
Figure 4.1 Graphical User Interface (GUI) .............................................................58
Figure 4.2 Hierarchy of VIs and data flow ...............................................................60
Figure 4.3 Block diagram of Group Config State VI .............................................62
Figure 4.4 Block diagram of Reset State VI ...........................................................64
Figure 4.5 Block diagram of Write Buffer State VI ...............................................64
Figure 4.6 Block diagram of Buffer Configurations State VI ....................................67
Figure 4.7 Block diagram of Start Buffer VI .........................................................68
Figure 4.8 Block diagram of Read Buffer State VI ..............................................70
Figure 4.9 Block diagram of Read Buffer VI .........................................................71
Figure 4.10 Block diagram of Stop State VI .........................................................72
Figure 4.11 Block diagram of BDA State VI ..........................................................73
Figure 5.1 Resistance vs. Current output of single channel ....................................74
Figure 5.2 Channel response of resistor arrays of various values ............................75
Figure 6.1 Depth dose curve comparing the DAQ system with cc13 ion chamber measurements ..........................................................77
Figure 6.2 Dose linearity of the strip detector..................................................78

Figure 6.3 Detector response before and after uniformity correction..................79

Figure 6.4 Energy response of strip detector, normalized to 1 at 6 MV photon energy. .................................................................80

Figure 6.5 Angular response dependency of the DAQ system. As the angle of the incident beam increased from perpendicular beam (gantry angle 0°) to parallel beam (gantry angle 90°), the strip detector under-responded compared to the planned dose. The maximum deviation of 25.7% was found to be at the parallel incident beam at 90°. ........................................................................................................81

Figure 6.6 Penumbra width _80%–20%_ measured for the 6 MV beam at 1.5 cm depth for the secondary X-jaw and the rounded leaf ends of the MLC using the strip detector and Gafchromic EBT film. The error bars for the EBT profiles represent the 95% CI of the mean of three sets of measurements, while the error bars for the SSD measurements represent the 2% reproducibility uncertainty. .82

Figure 7.1 Set up used at ESRF France. ...............................................................85

Figure 7.2 SSD response for 20 mm wide beam...................................................86

Figure 7.3 Real time snap shot of DAQ software in action during a scan of a single microbeam .................................................................87

Figure 7.4 MRT microbeam + 5 um W slit. In the top figure wings are due to atomic x-ray diffraction. Bottom figure shows realignment........................................89

Figure 7.5 Scan of 10 µm W-slit across SSD # 5. The wiggler gap = 50 mm and it was 10 mm homogenous field size. .................................................................90

Figure 7.6 SSD scan through single SSD MRT ....................................................91

Figure 7.7 SSD5 scan through single MRT on log scale ........................................92

Figure 7.8 System delay of BDA pulse via serial port at 9600 baud rate ...............94
Figure 7.9 Beam dump activation level indicated on the MRT dosimetry system GUI

(red dashed line)............................................................................................................94
LIST OF TABLES

Table 1 .......................................................................................................................... 83
**LIST OF SPECIAL NAMES OR ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DSB</td>
<td>Double Strand Break</td>
</tr>
<tr>
<td>ESRF</td>
<td>European Synchrotron Radiation Facility</td>
</tr>
<tr>
<td>ICA</td>
<td>Iodinated Contrast Agent</td>
</tr>
<tr>
<td>MRT</td>
<td>Micro Beam Radiotherapy</td>
</tr>
<tr>
<td>NHEJ</td>
<td>Non Homologous End Joining</td>
</tr>
<tr>
<td>LINAC</td>
<td>Linear Accelerator</td>
</tr>
<tr>
<td>LV</td>
<td>LabVIEW</td>
</tr>
<tr>
<td>MSC</td>
<td>Multi Slit Collimator</td>
</tr>
<tr>
<td>PVDR</td>
<td>Peak Valley Dose Ratio</td>
</tr>
<tr>
<td>Si</td>
<td>Silicon</td>
</tr>
<tr>
<td>SSD</td>
<td>Silicon Strip Detector</td>
</tr>
<tr>
<td>VI</td>
<td>Virtual Instrument</td>
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1. INTRODUCTION

1.1 Micro-beam Radiation Therapy (MRT)
In Conformal therapy of cancer treatment with radiation, dose from a uniform beam of high energy (3-20 MV) photons produced by linear accelerator and collimated to field sizes ranging from 5 x 5 up to 40 x 40 cm$^2$ is delivered to the patient. In spite of treatment planning done in order to conform the majority of dose to the localized tumour, surrounding healthy tissues still receive a large amount of a dose which often leads to degradation of patient’s quality of life. Thus a method that would avoid the damage to the healthy tissue surrounding tumour site in order to reduce the probability of post treatment tissue complications is required.

Unlike x-ray sources used in clinical radiation therapy, only high-intensity synchrotron sources can be used to confine the beam to the extremely narrow slices with very high dose rates that are needed for MRT.
Scientists at Brookhaven in the USA investigated the use of narrow micro-beams of synchrotron radiation to treat cancer. These x-rays beams are confined to very thin slices of planar beams arranged in parallel arrays with spaces in between - like the parallel panels of open vertical blinds. As a result, the x-rays irradiate only about 1/3 of the tissue, and the areas between the beam slices receive very little radiation.
Figure 1.1 This image shows tissue after it has been exposed to a narrow micro-beam of high energy radiation.

The path of the micro-beam is shown as a dotted line. A functioning blood vessel can be seen in the path of the micro-beam. Normal tissue is highly resistant to radiation damage when micro-beams are used, opening up the possibility of using synchrotron micro-beams to treat cancer.

The main features of highly brilliant Synchrotron sources are an extremely high dose rate and very small beam divergence. High dose rates are necessary to deliver therapeutic doses in microscopic volumes. The minimal beam divergence results in the obvious advantage of steeper dose gradients delivered to a tumour target, thus achieving a higher dose deposition in the target volume in fractions of seconds, with a sharper penumbra than that produced in conventional radiotherapy.

Typically, MRT uses arrays of narrow (~25-75 micron-wide) micro-planar beams separated by wider (100-400 microns centre to centre) micro-planar spaces. Peak entrance doses of several hundreds of Grays (Gy) are surprisingly well tolerated by
normal tissues and at the same time show a preferential damage of malignant tumour tissues.

The scientists hypothesize that, in MRT, some of the endothelial cells (cells that line blood capillaries) survive in the inter beam regions. In normal tissue, these cells appear to replace the neighbouring cells killed by the beam. But in tumours, this replacement process may be impaired, so the blood flow stops and the tumour is destroyed.
2 LITERATURE REVIEW

2.1 MRT Radiobiology

Radiotherapy has always been a standard tool in the treatment of cancer with approximately 50% of cancer patients receiving some form of radiotherapy. Dose escalation to the target volume remains a challenge for radiotherapy as significant dose is received by the surrounding normal tissue. These challenges have led to the advent of new, very successful, forms of radiotherapy. These include stereotactic and intensity modulated radiotherapy and more recently Tomotherapy and Rapid Arc therapy that use static and dynamic multileaf tungsten collimators to spare normal tissue surrounding the target.

Monochromatic synchrotron X-ray beams theoretically permit the enhancement of Photoelectric, Compton and/or Auger effects in high-Z elements [57,58,59] that are contained in drugs injected during irradiation. Photo activation of high-Z elements aims to increase the yield of damage by enhancing energy absorption. The X-ray energies of photo activation that have been used generally correspond to either the absorption edge (K- or L-edge) or to maximizing the relative X-ray absorption of the high-Z element in water. Most imaging contrast agents that are employed in standard radio diagnostics contain iodine atoms. By irradiating iodine-loaded tumours at the appropriate energy, enhanced energy absorption may contribute to increase the therapeutic index. This approach was initially called CT therapy and performed with polychromatic irradiation. More recently, the possibility to photo activated contrast agents containing gadolinium atoms used in nuclear magnetic resonance imaging has been investigated.

Some chemotherapeutic drugs that are used extensively in standard cancer treatments contain high-Z elements. This is notably the case of palatinate agents such as
cisplatinum and carboplatinum. Irradiating platinum loaded tumours at the appropriate energy, contributes to enhanced energy absorption. The micro beam radiation therapy approach is also based on the assumption that microscopic thin planar slices of synchrotron-generated X-rays permit the rapid regeneration of normal micro vessels. Conversely, the accumulation of dose owing to the overlap of micro beams was hypothesized to prevent the recovery of tumour vasculature. In parallel to these recent developments, our understanding in biological effects of ionizing radiation has considerably progressed, notably in the fields of DNA damage repair and stress signalling. In particular, four major features of radiobiology are revolutionizing the evaluation of anti-cancer approaches and must therefore be taken into account for the medical applications of synchrotron radiation. After irradiation of living matter, physical, chemical, biochemical and biological events inter play combined role. Hence, clinical response is the integrated result of molecular, cellular and tissue events whose time scale of occurrence is clearly different. On one hand, theoretical simulations of the radiation dose distribution are useful for predicting the amount of DNA damage induced in the first seconds of irradiation. Conversely, these simulations of physio-chemical events are obviously unable to predict the kinetics of DNA damage repair that occurs in the first hours of irradiation and that is correlated to survival. On the other hand, preclinical trials with animal models, taken separately, are also insufficient to provide mechanistic insights in early events. Hence, the evaluation of an anti-cancer approach requires not only quantitative data about its therapeutic efficacy against tumours but also a better knowledge of all the molecular, cellular and tissue events that it generates. Most of the anti-cancer strategies are based on the concept of depositing dose more efficiently into tumours. However, the amount of induced DNA damage is not predictive of the final response
of tumours to radiation. On the other hand, the amount of un-repaired DNA damage appears to be a more relevant parameter for predicting tumour killing. Furthermore, some tumours possess an impressive capacity for repairing DNA and patients may succumb to dose-dependent side effects. Therefore prediction of its effects on normal tissues rather than its efficacy in killing tumours has to be evaluated.

The absorbed radiation dose appears to date to be an insufficient notion for describing the effects of radiation at the molecular level. The absorbed radiation dose was historically defined as a macroscopic value Joules per Kilogram (J/kg) and is not relevant for describing the distribution of energy and micro depositions in cell nuclei. Furthermore, new observations suggesting bystander effect, i.e., that un irradiated cells are responding to damage induced in irradiated cells and delayed radiation induced effects show that these effects contribute to the formation of DNA damage that are not considered by the radiation dose defined in Gray (Gy).

Radiotherapy notably produces DNA double-strand breaks (DSB) that are generally repaired by a so-called non-homologous end-joining pathway that roughly consists of ligating broken DNA ends. Chemotherapy induced DNA damage is not necessarily DNA breaks but more frequently DNA cross links that activate repair pathways consisting of excising such DNA damage and replacing the missing DNA strand through complex events with strand exchange and polymerization. The interplay of the different DNA repair pathways occurring when a combination of radiotherapy and chemotherapy is administrated which can generate opposing as well as synergistic effects on DNA damage induction and repair.

Historically, the first medical application of photo activation has to be attributed to Norman’s group. In the 1970s, Norman and colleagues observed chromosomal
aberrations and micronuclei in circulating lymphocytes of nine patients submitted to urography and cardiac angiography involving iodinated contrast agents. In these radiodiagnostic sessions a dose of 2 centigray (cGy) was delivered by standard polychromatic X-ray tube (65–75 kVp, 1.3 mA). These cytogenetic findings were similar to those assessed in vitro without iodinated contrast agents at 20 and 30 cGy. Norman’s group hypothesized therefore that such aberrations resulted from a local excess of radiation dose, attributed to an enhanced photoelectric effect owing to the energy absorption by iodine atoms contained in iodinated contrast agents. Their conclusions were confirmed with analysis of ten clinical studies using iodinated contrast agents during angiography or excretory urography.

Norman and colleagues proposed to ‘exploit’ these chromosome-damaging effects by applying them to brain tumours. Hence, the CT therapy approach combined optimized tumour targeting (stereotaxic tomographic irradiation) and differential biological effects owing to the photo activation of iodinated contrast agents present in the tumour during irradiation. X-rays used in CT therapy was initially those used in radiodiagnostic (i.e. high voltage lower than 150 kV, corresponding to a mean energy of roughly 100 keV). This technique presented the considerable advantage of reducing patient displacement during treatment. Although such a strategy did not overcome the problem of chromosomal aberrations in normal tissues, it was applied to animals with limited success and to humans in a unique clinical trial combined with standard radiotherapy sessions. Subsequently, new preclinical trials were performed at the European Synchrotron Radiation Facility (ESRF) by applying monochromatic X-rays to brain tumours of rats that were injected with iodinated contrast agents either intravenously or via the carotid. It is to be noted that iodinated contrast agents were
injected concomitantly with an infusion of hyperosmotic blood-brain barrier opener, the mannitol, which does not make the evaluation of the effect of iodinated contrast agents alone easy. Three X-ray doses (5, 15, 25Gy) and two iodine injection modalities were tested. The maximal median survival time obtained with iodine was 71 days (15Gy; intercarotid injection) while the rats treated with 25Gy without iodine showed a median survival time of 145 days.

In the synchrotron experiments the X-ray energy used was 50 keV, corresponding to the maximal relative X-ray absorption of an iodine solution in water, whereas the K-edge of iodine is 33.17 keV, which corresponds to the local maximum photoelectric cross section. The choice of the energy of 50 keV is based on the evaluation of oncogenic survival after irradiating cells at different X-ray energies in the presence of iodinated contrast agents.

This led the investigators to further explore the following

(1) How are the biological effects of photo actable molecules that contain a given high-Z element can be predicted?

(2) What level of description is needed in a simulation code to predict capabilities for synergistic effects?

Irradiation of cells at 50 keV in the presence of ICAs does not produce any significant excess of the amount of DNA damage as it would be expected if an excess of dose was delivered to the tumour.

However, the toxicity observed in treated cells suggested an impact upon DNA repair pathways. Iodide ions are able to cross membranes and to bind to DNA. Once onto DNA, iodides are capable of inhibiting DNA repair processes. Hence, the irradiation of cells in the presence of iodinated contrast agents may result in an inhibition of
DNA repair owing to the extracellular liberation of iodide ions rather than an extra-production of DNA damage. Unfortunately, photo activation-induced iodides may diffuse through vasculature into normal tissues and also prevent DNA repair of normal cells that were irradiated during treatment. Lastly, further investigations in the early events occurring after a photo activation therapy are also needed to better justify the choice of the X-ray energy applied.

CT therapy opened the wide field of photo activation of other pharmacological compounds containing high-Z elements. Platinum containing drugs like cisplatin, carboplatin and oxaliplatin appeared early to be the best candidates for anti-cancer strategies involving photo activation.

Such drugs bind to DNA by forming DNA adducts and target preferentially proliferating cells. These drugs contain platinum atoms that are theoretically photoactable at 78.4 keV, corresponding to the K-edge of platinum. Photo activation of cisplatin has been particularly developed at ESRF. Recently, Photo activation of platinated agents provided by synchrotron X-rays was applied to rats bearing radioresistant gliomas. After a cisplatin intra tumoral injection, 15 Gy X-rays were delivered by synchrotron radiation into a tumour just above the Pt K-edge (78.8 keV).

Molecular and cellular mechanisms involved in Photo activation of platinated agents have now been identified. DNA double-strand breaks produced by X-rays are generally repaired by the non-homologous end-joining (NHEJ) process that is initiated by the translocation of a protein called Ku up to the site of the breaks.

The presence of cisplatin on DNA prevents the Ku translocation and significantly inhibits non-homologous end-joining (NHEJ) pathway that roughly consists of ligating broken DNA ends. Consequently, association between ionizing radiation and
cisplatin results in irreparable double-strand breaks, as long as the concentration of DNA adducts is sufficient and as long as radiation and cisplatin are used collectively. Interestingly, in the particular case of the photo activation of platinum atoms of cisplatin molecules bound to DNA consists of the production of additional double-strand breaks whose repair is naturally inhibited since they are produced in the close vicinity of DNA adducts that block NHEJ. As a result, the excess of irreparable DSB contributes to increase the therapeutic index of targeted tumours.

The high fluence of synchrotrons also makes possible the production of polychromatic micrometric beams allowing a very precise tumour targeting with extremely high dose rate grid radiotherapy. The accumulation of interlaced micrometric X-ray beams during a single session enables the deliverance of very high radiation doses up to thousands of Grays in a few milliseconds. Threshold doses for complications of radiotherapy increase as the irradiated volume of tissue is made smaller. Normal rat brain tissue displays an unusual radioresistance and therefore permits the application of very high doses into the tumour. An excess of dose into the tumour should result in destruction of the tumour vasculature while lower doses in surrounding tissues should insure a significant repopulation of normal cells. The physical properties of synchrotron X-rays permitted the feasibility of MRT by providing arrays of parallel thin planar micro slices. Furthermore, the use of X-rays in the tens to hundreds of keV range enables higher energy absorption in the tissues.

The MRT technique was initiated at the National Synchrotron Light Source at Brookhaven National Laboratory and was developed at the ESRF. MRT was essentially applied to rat brains, mice and also duck embryos and piglets. MRT irradiation sessions are generally based on a single fraction of radiation dose
delivered either unidirectional or bidirectional (in-planar or cross-planar). The total dose (120–1335 Gy) and the geometry parameters differ depending on the experiments and the research groups. The width of the beam varies between 25 and 90 µm and the space between each beam varies between 50 and 300 µm. Two complementary approaches can be considered about MRT: those that deal with the regeneration of micro vessels after MRT sessions and those that deal with the survival of MRT-treated animals.

With regard to physiological studies of MRT, a dose of thousands of Grays undoubtedly leads to the loss of neuronal cell nuclei inside the peak tracks. Physiopathology and histology observations indicate that rat skin can tolerate a 23-fold higher dose delivered in MRT sessions than in broad beams. However, some peri tumoral necrosis and hyper vascularity phenomena were clearly reported in the peri tumoral zone even if they do not necessarily affect the final survival outcome.

With regard to piglets, the animals have been irradiated with microbeams up to 600 Gy and no late tissue effect has been reported. There is still no available data about the potential tissue effects of the MRT technique to human cells. In addition, no molecular and stress signalling data about MRT effects are yet available. However, a more recent report aimed to investigate the early effects of 312 or 1000 Gy MRT upon the integrity of the normal micro vasculature in mice. A number of questions remain unsolved however, notably with regard to the death pathways that MRT would specifically induce in glial tissue and/or in vasculature. With regard to the survival of animals treated to MRT, the great majority have used 9L glioma as a model, probably for practical reasons (high rate of proliferation, availability of the cell lines in the laboratory etc.). The highest median survival time values provided to date by MRT is 171 days for rats and about 40 days for mice.
Geometric MRT parameters to obtain optimized survival data are as follows:

(1) For a given dose the beam thickness should not exceed a certain width.

(2) For a given thickness the valley dose should be minimized.

(3) The peak dose should be lower than the dose that kills neurons in the direct path of the micro beam.

From theoretical simulations, it appears that the dose delivered in the valleys may represent 1–10% of the dose. For 500–1000 Gy delivered into the peak, these data suggest that a minimum of 5–10 Gy may be delivered in tissues between two peaks and in close vicinity of the tumour. MRT has been essentially applied to rat 9L glioma and modelled from rodent observations. Mammalian and notably rodent cells have long been shown to be much more radioresistant than human cells. The 9L model is one of the most radioresistant rodent cell lines and its survival following X-ray exposure is at the upper limit of radioresistance observed in human cells. As an example, about 20% and less than 1% cell survival is expected after 5 and 10 Gy X-rays (200 kV), respectively, with the same model.

The cell survivals after the same doses are about 5% and negligible for human radioresistant cells, respectively. Further, it is noteworthy that cellular repopulation is not observed after 6 Gy even for the most radioresistant human tumour cells whereas the cell cycle is not totally arrested with 9L cells. Hence, the choice of the total dose inside the tumour will be one of the most important challenges of the clinical transfer
of MRT to humans. What happens in the surrounding normal human tissues after the deliverance of such high radiation doses? In the past 50 years a considerable amount of data have suggested the existence of significant biological effects in cells that are not directly hit by radiation tracks. Even if these effects do not necessarily proceed from a single cause and despite the fact that their molecular bases remain to be explained, radiobiologists describe them under the general term of radiation induced bystander effects.

The most relevant models of radiation induce bystander effects mainly involve calcium ions. The cell can be considered as an electrostatic dipole. Ionizing radiation leads to a depolarization of the cell membrane and a brief release of calcium ions. Such potential oxidative stress can diffuse through a liquid medium and concern cells that were not targeted initially by radiation. This phenomenon occurs also in vivo in tissues and is described as abscopal effects.

Radiation induced bystander effects favour the extension of dose effects to tissue up to tens of micrometres in vitro and up to millimetres in vivo and correspond to the equivalent of 10% of the initial dose. It is still too early to conclude that radiation induce bystander effects may be a source of additional stress for normal tissues in MRT modality but preliminary reports indicate that significant radiation induce bystander effects (as DSB formation and micronuclei) are clearly observed in human fibroblasts after an MRT treatment (dose, 10 Gy; width, 100 µm; space between tracks, 500 µm). These findings suggest that radiation induced bystander effects after MRT may impact significantly upon human cell viability. Certain studies do not include molecular and stress signalling analysis of radiation induced bystander
effects and interprets the repopulation of mammalian cells surrounding those inside tracks as a beneficial bystander effect throughout the effect of very low doses while the beneficial effect of very low doses is still debatable between different investigators.

Quantum of DNA damage in the bystander cells during MRT treatment is under investigation. Lastly, the impact of bystander effects is expected to diminish gradually as far as the distance from the targeted cells increases. Consequently, even if beneficial bystander effects may be observed in bystander cells far from the peak, the question of their toxicity in normal cells in the close vicinity of the targeted tumour tissue remains unsolved. Hence, further bio-chemical investigations and data on human cells are needed to better understand the bystander effects potentially induced by microbeams and particularly whether bystander effects can explain the necrosis and hyper vascularity phenomena observed in the peri-tumoral zones during some MRT treatments. To date, almost all the preclinical assays involving synchrotron X-rays have been performed on gliomas inoculated to rats. Indeed, it was natural that innovative anti-cancer strategies aim to target the most radioresistant tumour types.

Gliomas are the most frequent tumours of the central nervous system. Unfortunately, most gliomas are refractory to standard treatments. The median survival for patients bearing grade IV gliomas (glioblastomas) does not exceed one year even after both aggressive surgery and radiotherapy treatment.
It is well known that the treatment of some cancers (e.g. glioblastoma multiforme) is very challenging. The treatment outcomes of surgery, chemotherapy and/or radiotherapy are not ideal, and for certain variants, the long term prognosis is very poor. Radiosurgery with sub-millimetre X-ray beams (here on in referred to as Microbeam Radiation Therapy (MRT)) was initially proposed as a novel approach to treat such cancers in 1992 [36]. MRT research over the past 20 years has led a vast number of results from preclinical trials on different animal models, including mice, rats, piglets and rabbits [36, 37, 16, 18, 19, 10, 31, and 32] 

Figure 2.1Survival curves using MRT with and without adjuvant therapy for (Left) F98 and (Right) C6 gliomas.

Figure 2.1 shows recent data of survival curves using MRT with, and without, adjuvant therapy buthionine-SR-sulfoximine (BSO or glutamine), for C6 glioma in adult male Wistar rats and F98 glioma in adult male Fischer rats, that were used as animal models for the malignant human brain tumour, glioblastoma multiforme [32]. In 2009 the applicability of MRT was extended at the ESRF, France, through the installation of a dedicated patient treatment room and second wiggler (to provide more flux at higher photon energies) to study the potential of this treatment modality for deep-seated tumours.
Microbeam Radiation Therapy (MRT) is therefore a means of delivering a therapeutic dose to a macroscopic target volume through a high, yet biologically tolerable, dose to several microscopically wide volumes [6].

![Histopathology Slide](image)

Figure 2.2 Shows a histopathology slide of a section of the cerebellum of a piglet after being irradiated with microbeams to a dose of 300 Gy in the microbeam peaks. The parallel tracks created are very clearly defined and with no macroscopic ablation of the tissue observed [19].

The macroscopic dose is delivered to the target volume via secondary particles (electrons) exiting the primary microbeam path and from scattered photon interactions that undergo photoelectric absorption or further Compton interactions [34]. The dose is delivered in either one (unidirectional) fraction or two (orthogonal) fractions, with treatment time of between 100 - 400 ms (depending on field size, microbeam peak dose requirements, etc). MRT therefore requires a highly collimated, parallel array of X-ray microbeams produced by 3rd generation synchrotron sources, such as those at ESRF in France and the Australian Synchrotron, Melbourne [4].
The synchrotron source is necessary as high dose rates are required to deliver the therapeutic dose in minimal time to avoid what is effectively, lateral spreading of the microbeams caused by cardio synchronous movement of the tissues. The synchrotron also provides a very small beam divergence so the microbeam pitch remains constant. The pitch is important in MRT as it strongly correlates with the dose between two microbeams (here on referred to as the valley dose) [32]. The ratio of the peak dose to the valley dose i.e. the dose in the valleys that creates a dose offset in the tissue, has to be below the tolerance threshold dose (PVDR) is therefore an important parameter in MRT. PVDR depends on X-ray energy spectrum, tissue size, tissue composition, microbeam width and center to centre distance and irradiation field and depth. The micro planar X-ray beam arrays are produced by a tungsten multislit collimator positioned ~1 m upstream of the patient, and are typically between 25-100 microns wide with a pitch of 100–400 microns. A filtered white X-ray beam spectrum is provided with an energy range between 30 and 250 keV. This results in the advantage of very steep lateral dose gradients with a sharper penumbra in each microbeam than that produced in conventional radiotherapy, primarily due to the lower energy spectrum, which is a requirement of MRT so as to limit the range of the secondary electrons escaping the primary microbeam path. Such microbeams have shown an unprecedented sparing of normal radiosensitive tissues as well as preferential damage to malignant tumor tissues [11, 6].

A number of critical questions remain unanswered;

(1) What is the optimum in-beam dose for MRT?
(2) What is the optimum peak-to-valley dose ratio for successful MRT (maximal tumor control and minimal normal tissue toxicity)?

(3) Does the optimum ratio vary with the tissue and cell types being irradiated?

(4) What is the optimum energy spectrum for MRT?

(5) What are the threshold doses for damage and death for various cell types as a function of the beam geometries?

(6) What are the optimal dose rates?

2.2 Microbeam Generation
Highly collimated, quasi-parallel arrays of X-ray micro-beams of 50-600 keV, are produced by 3rd generation synchrotron sources for Microbeam Radiation Therapy (MRT). These highly brilliant Synchrotron sources produce beams of extremely high dose rate and very small beam divergence. High dose rates are necessary to deliver therapeutic doses in microscopic volumes, to avoid spreading of the micro-beams by cardio synchronous movement of the tissues. Because of the small beam divergence and the adequate photon spectrum, a Multi Slit Collimator (MSC), inserted into the beam produces a steeper dose gradient that is delivered to a tumour target, thus achieving a higher dose deposition in the target volume in fractions of seconds, with a sharper penumbra than that produced in conventional radiotherapy.

Narrow rectangular beams, also indicated as planar beams, placed close to each other in an array of microbeams have been used as irradiation fields in the preclinical trials until now. A typical array size is 1x1 cm², with a microbeam field size of 1 cm x 25 µm (height x width), where the height and width of the array can be adapted to the tumour size. The center-to-center distance between microbeams determines the
number of microbeams in a given array. A center-to-center distance of 200 µm gives 50 microbeams in a 1x1 cm² microbeam array. The planar microbeams are shaped by either a single slit collimator, moved in front of the target in between two irradiations, or by a multi slit collimator.

The working principle of the MSC is schematically shown in Fig 2.3. The MSC creates an array of microbeams so that the target is irradiated in a single shot. Since the microbeams are closely packed, typically a 0.2-mm center-to-center distance, it is important that the target does not move during the irradiation to avoid the smear out of the dose in between the microbeams. Such motions would jeopardize the tissue sparing effect of the microbeams. An x-ray source which has a high photon flux, suitable for MRT, is a third-generation electron synchrotron like the one at the European Synchrotron Radiation Facility ESRF in Grenoble, France.

Figure 2.3 In (a) multislit collimator MSC producing the planar microbeams, and in (b) a collimator producing the cylindrical beams, as shown. Adopted from [34]

The ESRF has a 6-GeV electron synchrotron with a dedicated medical beam line where x-ray beams are extracted for therapeutic and diagnostic studies. The x-rays
are generated by an insertion device called wiggler which emits photons in a continuous spectrum by “wiggling” electrons through an alternating magnetic field. The x-ray spectrum is then filtered to remove low-energy photons from the beam.

There are two types of variable width MSCs, Archer-type multislit collimator (AMSC) and, the TecometR multislit collimator (TMSC). Experimental data suggests a reduction in the standard deviation from 5.5 to 3.9 µm from the AMSC to the TMSC using a slit scanning method over the entire collimator and width of the microbeams was found to be not uniform. The fluctuation in full width at half maximum (FWHM) values along the microbeam array was far from optimal when measurements on a line across the collimator were compared. These factors did lead to relevant differences in the valley dose. Equally spaced microbeams of identical size will allow simplified Monte Carlo dose simulations, i.e., by calculating the profile for one single microbeam first, then by superimposing copies of this profile to build an array of (identical) microbeams in the calculation. Thus, errors in the dose calculations for multiple planar microbeams can be avoided. The MSC is assembled with two identical 8 mm thick blocks of tungsten carbide, one set in front to the other, presenting 125, three mm high and 100 µm wide equidistant slits to the oncoming seamless x-ray beam, regularly repeated with a uniform pitch of 400 µm centre to centre. A photograph and a schematic drawing of the assembled EMSC, looking downstream from the x-ray source, are shown in Fig 2.4. Fig 2.5 presents a magnified drawing of the upstream face of the first MSC block encountered by the beam.
Figure 2.4 Photograph of the assembled ESRF MSC that produces micro planar beams adjustable width. Adopted from [34].

Figure 2.5 Schematic drawing of one block of the ESRF MSC with 100 μm slit width and a pitch of 400 μm. Adopted from [34].

Two such identical blocks are mounted adjacent and parallel to each other. The upstream block is movable transversely with respect to the downstream block by a precision stepper motor. A perfect parallel alignment of both stacks can be achieved by rotating the downstream stack Fig 2.6. A special alignment procedure to achieve
reproducible results is followed. The procedure involves an iterative adjustment process of the three motors TecomY lateral translation, TecomR rotation of the second stack with respect to the first, and Murot overall rotation of both stacks which allows aligning the whole MSC with the beam.

![Diagram of the mounted two stacks including the setup used to align the collimators with the beam.](image)

Figure 2.6 Sketch of the mounted two stacks including the setup used to align the collimators with the beam. Adopted from [34].

The first step consists in opening the device to produce beams of the maximal 100 µm FWHM (nominal value). In this configuration the artefacts resulting from photons scattering from the inner walls of the MSC should be minimal. By use of an iterative procedure between the three motors, maximum value the intensity of the x-ray beam passing through the MSC is increased. This ensures an optimal parallel alignment of the two stacks as well as the alignment of the entire stack assembly with
the beam. To adjust for experimental parameters, two of the three motor positions remain fixed and only the lateral translation TecomY is adjusted to obtain the desired microbeam FWHM value. The width is measured prior to any MRT experiment using 3–5 µm wide horizontal slits, which are scanned across the microbeams, the intensity of the beams being detected by an ionization chamber located downstream of the MSC. The 125 radiolucent slits are flushed by nitrogen gas to cool the device and, equally important, to protect the tungsten carbide surface from possible oxidation due to the ozone production resulting from the interaction of the high intensity white beam with the temperature increase at the surface of the stacks.

The Synchrotron Radiation X-ray beam is produced in the ID17 wiggler by 6 GeV electron bunches. The collimator is placed in the first experimental hutch of the ID17 beamline 42.0 m from the centre of the wiggler. The MRT program at the ESRF Biomedical Beamline ID17 uses a filtered, white-spectrum SR beam with a critical energy at the source of 38.1 keV. The MRT spectrum has its maximum intensity at 83 keV. A sketch of the setup is shown in Fig 2-7.

![Figure 2.7 Sketch of the MRT experimental setup with the distance of the elements from the x-ray source. Adopted from [34].](image)

After exiting from a beryllium and an aluminium window, the Synchrotron Radiation beam passes from ultrahigh vacuum into air and runs through an ionization chamber and a set of tungsten slits before impinging on the MSC. A 0.75 mm thick aluminium window seals the collimator mounting frame to direct the flow of nitrogen through
the micro slices to allow efficient gas cooling. Horizontal tungsten slits limit the beam width to 38 mm and three adjustable positions offer a choice of different beam heights (50, 100, and 500 µm). Vertical tungsten slits, mounted on a translation stage and positioned upstream, just before the collimator, are aligned with the centre of the beam to allow horizontal scanning of the individual microbeams with 1 µm steps. The signal recorded by an ionization chamber downstream of the MSC gives information about the intensity and FWHM value of each individual microbeam.

2.3 Micro Beam Dosimetry
The geometrical configuration of the microbeams is a crucial factor in the success of MRT but the dose gradients of hundreds of Gray over tens of micron present a significant challenge for dosimetry. Since the microbeams are about 25µm wide and are separated by 200 µm, measuring the peak to valley ratio requires spatial resolution beyond the capabilities of conventional ionisation chamber-based dosimetry. Major work done pertaining to MRT dosimetry employs Monte Carlo computer simulations to model the radiation transport and dose deposition in water. Correct dose measurements of such microbeams also demands excellent, micron size, spatial resolution of a detector system. With the above considerations applied, this presents a challenge as current dosimetry instrumentations do not satisfy the above requirement since the size of the ionization chambers and dosimeter diodes and TLD detectors are physically far too large.

Radiation dosimetry is a significant challenge for MRT due to the combination of high dose rates (typically 16,000 Gy/sec at ESRF) combined with very highly spatially fractionated, sub-millimetre wide X-ray beams. Current dosimetry methods used regularly at ESRF use a combination of ion chamber and Gafchromic film for
the wide X-ray beam configuration (same treatment field size and X-ray spectrum but no microbeams), with only the film dosimetry available for use for microbeam dosimetry. Ion chambers are the “gold standard” in radiotherapy, however, does not have the necessary spatial resolution for X-ray microbeam dosimetry. Gafchromic films have been shown to be a very useful tool in radiotherapy applications, and similarly in MRT e.g. HD-810 [12, 8 and 5]. However, in the case of MRT treatment fields and dose ranges, significant overall absolute dose uncertainty results from known film response fluctuation and reproducibility. This uncertainty can be as high as 8%, due to the intrinsic fluctuation in dose response within a single sheet of film [12]. Moreover, the significant time between exposure and stable dose interpretation via microdensitometry (up to three days for film polymerization process to stabilize), makes film unsuitable for the applications described in this proposal. The dosimetry system to be developed for absolute dose measurements in MRT must have an absolute dose accuracy of 3% to meet the legal requirements of treating human patients [1, 13].

Other dosimetry methods investigated for use in MRT around the world include Edge-on MOSFET dosimetry [25, 26, 3, and 35], flash memory MOSFETs [7], MRI Gel dosimetry [9], fluorescent nuclear track detectors [38], and high resolution TLD dosimetry [23]. Some of these techniques have proven to be suitable for MRT dosimetry, however, they require significant time for post irradiation analysis and will be utilised in the proposed project for comparative studies. None of the above methodologies, however, have the ability to allow fast, online MRT dosimetry as required for the clinical application of MRT. Such ability is essential for MRT development and will be achieved in the course of this proposal.
A new silicon strip detector (SSD) has been designed at the Centre for Medical Radiation Physics (CMRP) University of Wollongong, and has been used in this project to perform fully automatic dosimetry of micro-beam arrays. The doses for each micro-beam and valley within the set time exposure will be presented simultaneously and displayed graphically on a visual display.

2.3.1 Semiconductor Diodes for MRT Dosimetry

2.3.1.1 Theory of p-n Si junction

Crystalline materials have an energy band for electrons which can be separated by gaps or ranges of forbidden energies [40]. The lower band is known as the valence band where the electrons that are bound to specific lattice sites within the crystal. In silicon and germanium these valence band electrons are part of inter atomic forces within the crystal. The second band is known as the conduction band which is the higher lying band on energy scale. Electrons in this band are free to migrate through the crystal and contribute to the electrical conductivity of the material. These two bands are separated by the band gap. The size of this band gap classifies the material as semiconductors. In pure semiconductor, all the electrons in the conduction band and the holes in the valence band are due to thermal excitation, in the absence of any ionizing radiation under these conditions every electron must leave behind a hole thus the number of electrons in the conduction band is equal to number of holes in the valence band. Such material is called intrinsic semiconductor. In real world situation there is always some impurity present in the material and the electrical property of this material is governed by the presence of these impurities. In practice such impurities are injected into the semiconductor during manufacturing process.
These are classified as donor impurities. The measure of impurity level is electrical conductivity or its inverse resistivity. In Silicon a resistivity of about 50,000 $\Omega \text{cm}$ Ohms can be achieved. When a charged particle passes through semiconductor it produces any electron-hole-pairs along the track of the particle and this process may be direct or indirect quantity which is of practical interest for detector applications. The average energy expanded by the primary charged particle to produce one electron-hole pair and is loosely termed as ionization energy is denoted by symbol $\varepsilon$ which is largely independent of energy and type of radiation. The number of electron-hole pairs produced can be interpreted in terms of incident energy of radiation if the particle is stopped completely in the active volume of the detector.

2.3.1.2 Radiation damage of Si diodes by medical LINACS.

The proper operation of semiconductor detectors depends on crystalline lattice structure. Defects in the lattice structure can cause charge carriers being trapped which can lead to incomplete charge collection. If the diode is exposed to radiations for an extensive period of time the exposure can cause these defects in the lattice. The effect of exposure to beta particle or gamma rays tends to be relatively minor as compared to exposure of surface barrier detectors to fission fragments.

The most common type of radiation damage is known as a *Fraenkel defect* which is produced by displacement of an atom from its normal lattice site. This is because of the vacancy that is left behind as the atom is displaced and forms a trapping site. If the number of these sites is significantly increased, carrier lifetime is reduced causing degradation of energy resolution.
In case of gamma radiation and neutrons, damage caused in the diode is distributed. Orientation of detector with respect to incidence of electrons and charged particles plays a significant role in the total depletion of the detectors. Diffused junction diodes are less susceptible to radiation damage as compared to surface barrier diodes.

Diodes are operated in different modes as described below.

### 2.3.1.3 Current and open mode operation of Diode.

A photodiode is a PN junction or PIN structure. When a photon of sufficient energy strikes the diode, it excites an electron, thereby creating a mobile electron and a positively charged electron hole. If the absorption occurs in the junction's depletion region, or one diffusion length away from it, these carriers are swept from the junction by the built-in field of the depletion region. Thus holes move toward the anode, and electrons toward the cathode, and a photocurrent is produced. Following are the modes of operation of diode.

### 2.3.1.4 Photovoltaic zero bias mode operation.

In this mode the diode is often reverse biased. This increases the width of the depletion layer, which decreases the junction's capacitance resulting in faster response times. The reverse bias induces only a small amount of current (known as saturation or back current) along its direction while the photocurrent remains virtually the same. The photocurrent is linearly proportional to the intensity of incident radiation.
Although this mode is faster, the photovoltaic mode tends to exhibit less electronic noise. The leakage current of a good PIN diode is so low (< 1 nA) that the Johnson-Nyquist noise of the load resistance in a typical circuit often dominates.

PIN diodes have good spatial resolution, usually of the order of 1 mm, and a long life span for relative dosimetry. The advantage of Si detectors for radiotherapy on a Linac is in the constancy of the silicon-water electron stopping power ratio over a wide energy range. Silicon detectors have some disadvantages due to their dose rate dependence, angular dependence, energy dependence, and radiation damage. Dose rate dependency can be reduced to 2% by using $p$-Si diodes from low resistivity silicon and pre-irradiation of diodes to reduce the initial carrier lifetime in the base material. Radiation damage effects can be almost eliminated by pre-irradiation of the detector in an electron beam and using low resistivity $p$-type Si diodes which have a much better radiation hardness than $n$-type Si diodes. However, new $n$-type diodes that are heavily doped with platinum have also shown good performance, comparable to $p$-type diodes in their tolerance to radiation damage.
3 DAQ SYSTEM FOR MULTI CHANNEL DOSIMETRY HARDWARE.

Daq system comprises of the following major hardware modules. Each module has been discussed in depth in its respective section.

Strip Detector

Fe4C Front end board with Tera 03 Chips

LA TX-RX Interface

NI 6534 DIO Card

PC with Windows OS

Figure 3.1 Block diagram of Daq.

3.1 Strip Detector

The strip detector has 128 phosphor implanted n+ strips on a p-type silicon wafer. The n+ strips of the detector are 10 µm wide, 5000 µm long, with an inter-strip distance of 200 µm. The strip surface is coated in a 1 µm thick layer of aluminium with a bonding pad at the base for connection to the external circuitry. The surface of the p-type silicon wafer within inter-strip space is coated in a 5 µm thick layer of
silicon dioxide (SiO₂). The bonding pads are insulated from the p-type bulk by a thicker layer of silicon dioxide. Figure 3-2 shows a schematic diagram of the silicon strip detector design.

![Diagram of silicon strip detector](image)

Figure 3.2 a) Photograph of silicon strip detector under investigation. b) A schematic cross section across two adjacent strips
The aluminium bonding pads are connected to wire tracks that allow each $n^+$ strip to be connected to external circuitry as shown in Figure 3.3 below.

![Figure 3.3](image)

Figure 3.3 This picture shows the silicon strip detector used for Daq development.

The silicon wafer is held in place by a ceramic mould. The $n^+$ strips are connected to external circuitry by three levels of wires built into the ceramic mould. Connection to the electronics readout is through SCSI connectors.

The detectors are manufactured with a thin layer of $p^+$ silicon located at the interface of the silicon dioxide layer. This layer of $p^+$ silicon is electrically isolated from the $n^+$ strips and acts as a barrier to charge build-up at the interface.

The device is also designed with a $p^+$ guard ring structure to further assist in the reduction surface leakage current. In these detectors the guard ring also acts as the cathode of the detector which allows the detector to be used as a planar device, causing the electric field in the silicon bulk to expand further laterally away from the
p-n junction. Essentially, this results in more effective charge collection in the region
between the implanted strips.

The detectors were manufactured using p-type silicon of different resistivity. The
resistivity of one type was 10 $\Omega$ cm whilst the other was manufactured using a silicon
wafer with a resistivity of 5k $\Omega$ cm. The resistivity of the p-type silicon bulk has a
significant effect on the sensitivity of the detector due to the difference in diffusion
length for the two different types.
3. 2  **Fe4C Front end Board with Tera 03**  
This board comprises of VLSI Tera 03 chips, decoders, multiplexer and buffers along with glue logic chips and a 5 volts regulator, refer to Fog 3-10.

![Figure 3.4 Photo of Fe4C Board with 2 Tera03 Chips.](image)

Tera 03:

Tera 03 chip design is based on the recycling integrator architecture designed by B.Gottschalk several years ago for an application at the Boston Cyclotron [41, 42, 43].

Block diagram of single channel of recycling integrator is shown below.
Tera 03 is a VLSI CMOS chip containing 64 independent channels and has a total area of 7x4 mm$^2$. Each channel has two main components: analog and a digital. The analog part is basically a current to frequency converter, which converts the input current to a pulse train with a frequency proportional to the current. The charge quantum (charge corresponding to a single pulse) can be set externally by a reference voltage, and can be adjusted in the range from 100 fC through 800 fC. In the present design the pulse period is ~ 250 ns, which limits the maximum output frequency to ~ 4 MHz and maximum input current ~3.2µA. The linearity of the response as a function of the input current is better than 1% in the range 400 pA to 1 µA.

The integrated current, or charge, is reduced by a fixed amount $Q_c$ via a charge subtraction circuit with a “subtraction” capacitance, $C_{sub}=200 \text{ fF}$ (femto farads) when the OTA output voltage (VOTA) reaches a user defined threshold level ($V_{th}$).

The subtraction charge is defined by $Q_c=C_{sub} \times V_{sub}$, where $V_{sub}$ is user defined. This charge subtraction method is far superior to traditional resetting of the integrating capacitor since during the charge subtraction the circuit is still active, i.e.,

![Figure 3.5 Block diagram of Recycling Integrator](image)
the input current continues to be integrated, and therefore there is no associated dead
time. The accuracy of the comparator circuit defines the minimum equivalent $Q_c$
(100 fC) in this case, and hence the lower limit of the dynamic range. The upper limit
of the dynamic range is limited by the maximum voltage of the comparator circuit
(the supply voltage: 5 V), equating to a maximum charge $Q_c$ of 1 pC. The output of
the chip is a 16 bit number that represents the number of times the integrating
capacitor has been discharged. Thus we can measure between 0 and 65536 $Q_c$ charge
units, depending on the level of dark current in the detector, zero in the case of
passive detector that would give rise to a minimum 0 counts. After each counter-
readout clock pulse, the counter is reset to zero. If more than 65536 pulses are
received by the counter with one readout clock cycle, the counter rolls over and start
counting from zero again. The counter output is stored in the output buffer where it is
latched by an external signal (LATCH), and is ready to be sequentially read out as
shown in Figure 3.6.

Figure 3.6 Block diagram of Tera 03 Chip.
The VLSI chips are mounted on printed circuit boards that house voltage sources, data transmission buffers, decoder logic chips and appropriate connectors (SCSI) so that each chip can be easily interfaced to the detector as shown in Figure 3.10

FE4C board is connected to the strip detector with shielded cable having SCSI II sockets on both the ends. The length of the cable has to be of a short length so that least amount of noise is introduced into the DAQ system. This board is housed in a metal cabinet and is kept away from the radiation field to prevent any radiation damage to the electronic components. An external DC power supply of 8-12 volts with 2 amp current capacity is connected to this board. This board is connected to the another electronic interface(outside the LINAC bunker) with 2 ribbon cables each having a set of 34-pin DIN41651 connector on both the ends. Length of the ribbon cable has significance in term of noise and delay introduced into the signal.

Controls signals are sent to the FE4C through a 34-pin DIN41651 connector and are configured and connected according to the following scheme:

```
  33  34  2
```

Figure 3.7 34DIN41651 connector.
Figure 3.8 16bit mapping of Address lines

<table>
<thead>
<tr>
<th>A15</th>
<th>A14</th>
<th>A13</th>
<th>A12</th>
<th>A11</th>
<th>A10</th>
<th>A9</th>
<th>A8</th>
<th>A7</th>
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<th>A4</th>
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<td>Rstd</td>
<td>Rsta</td>
<td>Latch</td>
<td>BA</td>
<td>BA</td>
<td>BA</td>
<td>CS</td>
<td>CS</td>
<td>CA</td>
<td>CA</td>
<td>CA</td>
<td>CA</td>
<td>CA</td>
<td>CA</td>
<td>CA</td>
</tr>
</tbody>
</table>

Std: Data strobe signal

Rstd: Digital reset signal (sets counters to zero), High for at least 100ns..

Rsta: Analog reset signal, (discharges recycling capacitors), High for at least 10 microseconds.

Latch: Signal to latch counter data into internal buffers of Tera03 Chip This input should be high for at least 4 clock cycles.

BA: Board address (Multiple boards can be addressed i.e. 256 channels)

CS: Chip select signal, The bus outputs are enabled at logic HIGH and tri-state at LOW.

CA: Channel Address signals generated by LabVIEW to read the data out of TERA Chip.

Figure 3.9 Timing sequence of Latch pulse in relations to Address written and Data read.
FE4C and LA TX RX boards are connected with two 34-pin DIN41651 connectors.

The data and control signals are connected according to the following pin outs, **OUT0** – **OUT15** are shown below.

<table>
<thead>
<tr>
<th>Pin</th>
<th>Connection</th>
<th>Pin</th>
<th>Connection</th>
<th>Pin</th>
<th>Connection</th>
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<tbody>
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<td>OUT6</td>
<td>25</td>
<td>OUT12</td>
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<td>GND</td>
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<td>GND</td>
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<td>15</td>
<td>OUT7</td>
<td>27</td>
<td>OUT13</td>
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<td>GND</td>
<td>28</td>
<td>GND</td>
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<td>17</td>
<td>OUT8</td>
<td>29</td>
<td>OUT14</td>
</tr>
<tr>
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<td>GND</td>
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<tr>
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<td>OUT3</td>
<td>19</td>
<td>OUT9</td>
<td>31</td>
<td>OUT15</td>
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<td>GND</td>
<td>32</td>
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<td>GND</td>
<td>24</td>
<td>GND</td>
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</tbody>
</table>
3.3 LA TX-RX INTERFACE

This interface is connected between NI 6534 DIO card in the PC and FEC4 front end board in the LINAC bunker. On the PC side this interface is connected with a SCSI connector to the NI card in the PC. Connection between this interface and FEC4
front end card is with 20 meters of ribbon cable passing through the physics port of bunker.

Figure 3.11 LA TX RX RS-422 Interface schematic.
This card is populated with 16 AM26LS32 chips. The AM26LS32A devices are quadruple differential line receivers for balanced and unbalanced digital data transmission. The enable function is common to all four receivers and offers a choice of active-high or active-low input. The 3-state outputs permit connection directly to a bus-organized system. Fail-safe design ensures that, if the inputs are open, the outputs always are high. 8 devices are used for data and another 8 devices are used for control signals. Power for this interface is derived from the PC through the NI 6534 DIO card.
3.4 NI 6534 DIO CARD

Figure 3.12 NI PC! 6534 Block Diagram Adopted from[45].
The NI 6534 DIO (digital input output) card is a high-speed, 32-bit, parallel, digital I/O Interface for PCI bus. This card incorporates the National Instruments DAQ-DIO ASIC, specifically designed to deliver high performance on plug-in DIO devices. The NI 6534 card can perform un-strobed I/O, pattern I/O, and handshaking at speeds up to 20 MHz, or 80Mbytes/s for 32-bit transfers (NI 6534). The NI 6534 delivers digital I/O coupled with large onboard memory for high speed pattern I/O at deterministic rates.

The 32 digital I/O lines are divided into four 8-bit ports. For pattern I/O or handshaking, the ports can be grouped into two 8-bit or 16-bit groups or a single 32-bit group. When configured for output, each data line can sink or source up to 24 mA.

When configured as inputs, the 6534 data lines are diode-terminated to dampen the input signals at TTL levels. When performing static I/O, one can individually configure each of the 32 I/O lines as input or output. In the present setup 16 DIO lines are configured as control/Address lines and another 16 DIO lines are configured as data lines to acquire 16 bit counter data from FE4C front end card.
Figure 3.13 NI 653X I/O Connector 68-Pin Assignments Adopted from [45].
4 SOFTWARE

Software for data acquisition has been developed in graphical programming language LabVIEW (Laboratory virtual instrument engineering workbench).

4.1 Data flow programming

The programming language used is LabVIEW, called G, is a dataflow programming language. Execution is determined by the structure of a graphical block diagram (the LV-source code) on which different function-nodes are connected by drawing wires. These wires propagate variables. In case of multiple nodes variable propagate simultaneously, G is inherently capable of parallel execution. Multi-processing and multi-threading hardware is automatically exploited by the built-in scheduler, which multiplexes multiple OS threads over the nodes ready for execution.

The data-flow (which can be forced, typically by linking inputs and outputs of nodes) completely defines the execution sequence, and that can be fully controlled by the programmer. Thus, the execution sequence of the LabVIEW graphical syntax is well-defined. Furthermore, LabVIEW does not require type definition of the variables; the wire type is defined by the data-supplying node. LabVIEW supports polymorphism in that wires automatically adjust to various types of data.

LabVIEW ties the creation of user interfaces (called front panels) into the development cycle. LabVIEW programs/subroutines are called virtual instruments (VIs). Each VI has three components: a block diagram, a front panel and a connector pane. The latter may represent the VI as a subVI in block diagrams of calling VIs. Controls and indicators on the front panel allow an operator to input data into or extract data from a running virtual instrument. However, the front panel can also serve as a programmatic interface. Thus a virtual instrument can either be run as a program, with the front panel serving as a user interface, or, when dropped as a node
onto the block diagram, the front panel defines the inputs and outputs for the given node through the connector pane. This implies each VI can be easily tested before being embedded as a subroutine into a larger program. In terms of performance, LabVIEW includes a compiler that produces native code for the CPU platform. The graphical code is translated into executable machine code by interpreting the syntax and by compilation. The LabVIEW syntax is strictly enforced during the editing process and compiled into the executable machine code when requested to run or upon saving. In the latter case, the executable and the source code are merged into a single file. The executable runs with the help of the LabVIEW run-time engine, which contains some precompiled code to perform common tasks that are defined by the G language. The run-time engine reduces compile time and also provides a consistent interface to various operating systems, graphic systems, hardware components, etc. The run-time environment makes the code portable across platforms. Generally, LabVIEW code can be slower than equivalent compiled C code, although the differences often lie more with program optimization than inherent execution speed.

4.2 Graphical User Interface (GUI)
When the application is invoked the following GUI (Fig 4.1) appears on the screen. Operator has options to select acquisition time, pulse width and number of channels for which the data has to be acquired. For testing purposes there is a feature to set the continuous acquisition for testing purpose only.

In actual practice single acquisition is selected, after the elapse of the set period the acquisition stops and an LED indicator lights up which informs the operator that acquisition task is over and data is ready for filing. At this time Windows filing
(API) prompt pops up so that operator can select the directory as well as name of the file to record the data in spreadsheet format which can be analysed in MS Excel. Exception handling features have been incorporated in software design so that if error occurs, it gets logged in a file which can be used to debug the source of error.

**Figure 4.1 Graphical User Interface (GUI)**

### 4.3 Software Architecture

Software for DAQ is based on State Machine Architecture. State Machine architecture can be used to implement complex decision-making algorithms represented by state diagrams or flow charts. A state machine implements any algorithm described by a “Moore machine”[48, 49].

State Machines are used in applications where distinguishable states exist. Each state can lead to one or multiple states, and can also end the process flow. A State Machine relies on user input or in-state calculation to determine which state to go to
next. Many applications require an “initialize” state, followed by a default state where many different actions can be performed. The actions performed can depend on previous and current inputs as well as states. A “shutdown” state can then be used to perform shut down action. State Machines are most commonly used when programming user interfaces. When creating a user interface, different user actions send the user interface into different processing segments. Each of these segments will act as states in the State Machine. These segments can either lead to another segment for further processing or wait for another user event.

The software has been designed keeping scalability in mind so that additional features can be incorporated in the future without re-coding the basic code.
4.4 Hierarchy of VIs
Main program is composed of 43 subVIs, a subVI is equivalent to sub routines in conventional textual programming languages. Hierarchy of DAQ for MRT dosimetry is shown in the Fig 4-2.

Figure 4.2 Hierarchy of VIs and data flow.

Main VI (second figure from left hand) calls 6subVIs. For example 6th subVI from top would call 4 subVI, 8th VI would call 4 subVI. This called subVIs would further call other sub VIs as the state machine executes different states as per state execution order.

Order of States:
Group Config State
Reset State
Write Buffer State
Start State
Read Buffer State
Stop State
BDA State

Software has been designed so that it can implement automated execution of a set of VIs using a state machine. The VIs to be executed are placed in a case structure inside a While Loop. The Enum control (outside the loop) specifies the first state (default state/case) to be executed, size of that ring indicates the number of states to be executed. The next state to be executed is determined by the value set in the ring in the current state that has executed. Each execution of VI generates an error status which flows out of the case. This error status is analysed by a function Unbundle by Name. Logical output of this function i.e., Boolean True or False decided execution of the code because this logical output controls Iteration of the While Loop i.e. if Boolean is TRUE then While Loop will stop the execution.

4.4.1 Group Config VI:

First state of the state machine that is executed is Group Config state as shown in Fig 4.3.
Controls on the left of the diagram are for configuration of NI 6534 DIO card.

These controls are described below:

Device #: This corresponds to number of DAQ card used, one in this project.

No of Channels: This control is accessible to the operator to select Number of channels to acquire the data from (maximum 128 channels in the present setup).

Task ID1: This is a software ID generated for the software driver to communicate with NI 6534 card to generate control signals pattern that is written to FE4C card through LA TX -RX card.

Enumerated control: This control defines the different states that the state machine executes during the data acquisition.

Task ID 2 is also a software ID generated for the software driver to communicate with NI 6534 to read data

Write Buffer control is used to set the size of the buffer to read data into. This has been explained in details in the Buffer Config section.
Lastly there is an Error cluster control in red colour outside of While Loop. This cluster is used to display any error that may occur during the execution of the program.

Except for the No of Channels control, all the controls are hidden from the operator in order to make front panel (GUI) user friendly.

Group Config case contains two Group Config VIs and an Error Cluster VI.

NI 6534 card has 32 DIO lines. These individual lines are grouped into ports, comprising of 8 DIO lines. Thus we have 4 ports to use for our application. These ports have been grouped as Port 0 and Port 1 as output ports and Ports 2 and 3 as Input ports.

Thus Group 0 is output group and Group 1 is Input group.

On both the edges of the while Loop there are 4 Shift registers (unique to LabVIEW). These are special local variables available in structures **For and While Loops** that transfer values from completion of one iteration to the beginning of the next.

If an error is generated during execution of these 2 Group Config VIs, that error would be merged by the Merge Error VI. Outside of this case structure the error cluster is unbundled by a (Unbundle by Name) function, True Boolean generated by the Unbundle by name function would stop the execution of the loop and error code would be displayed on front panel to the operator to take necessary action.

### 4.4.2 Reset State

When this state executes then C000 Hex is written to the output channels.

C000 Hex is equivalent to 1100000000000000 in binary, so control lines A15 and A14 (refer Fig 3.8) would go high. This will generate Rstd (Digital Reset) pulse thus zeroing all the counters.
4.4.3 Write Buffer State

This VI passes on the user inputs in terms of integration time (DAQ time), pulse width and Number of channels to acquire data from.

These inputs are passed onto “Buffer Configuration VI”.

Figure 4.4 Bock diagram of Reset State VI

Figure 4.5 Block diagram of Write Buffer State VI
4.4.4 Buffer Configuration State

Buffer Configuration is done in Buffer Configuration VI. This VI comprises of Mode Config VI, Clock Config VI and Buffer Write VI.

The software for Daq (Data Acquisition) has been designed to use Circular Buffer so that data can be written to the FE4C front end card as well as data can be read from FE4C into NI 6534 card simultaneously.

A circular buffer is a data structure of a fixed size which operates as if its ends were connected together to form a ring. The circular buffer is a useful way to buffer data between two operations such as data acquisition and analysis. It allows you to decouple and parallelize different operations which would normally be used in a sequential manner. It is also useful in applications where operations using the same data set are happening at different intervals.

To use the circular buffer, first the size of the buffer must be initialized. The initialize function allocates an array of the desired size for the circular buffer. Once the circular buffer is initialized, data can be written to and read from it. The read and write operations can happen in parallel.

In the VI shown in Fig 4.6, on-board 32 M memory has been configured to be used as circular buffer. Write Buffer size is set to 1000, internal 20 MHz clock is used as clock source. Similarly Read Buffer size has been set to 100000.
This VI generates a pattern of HEX numbers that are sent to 2 output ports (port 2 & port 3) of NI 6534 card. These HEX numbers get transferred to FE4C card through LA TX RX RS-422 interface board.

As discussed and shown in Fig 3.8 and Figure 3.9, in order to acquire data out of FE4C card we need to send Rstd signal followed by Latch signal after some delay. Latch signal in binary representation is 1001000000000000 (9000HEX). Sequential channel addresses i.e. decimal 0-128 is sent out sequentially to read the data stored in onboard buffers of Tera03 chip as shown in Fig 3.6.
Figure 4.6 Block diagram of Buffer Configurations State VI.
4.4.4.1 Start Buffer State

At the conclusion of Buffer Config state the execution is passed onto the next state which is Start Buffer State. This state initiates the execution of Buffer Control subVI. that would commence the generation of pulse pattern in Buffer Config state to be sent out to FEC4 card where by the Rstd pulse, Latch pulse along with Channel Address pulses are transferred to Tera03 chip. 

At this point of program execution, data is ready for reading out of Tera03 chip and is initiated by the next state which is Read Buffer State.

---

**Figure 4.7 Block diagram of Start Buffer VI.**

4.4.5 Read Buffer State

Figure 4.8 shows the read buffer state. During the execution of this state the data is read out of FEC4 board. As mentioned earlier in the explanation of Tera03 chip that recycling integrator is operating continuously so on termination of Rstd pulse which
forces the 16 bit counters to zero, the counters are being updated so initial count is
read out then the program enters the For Loop where the buffer is again read and this
count is subtracted from the first read operation. This count is passed onto shift
register. This register makes the data available on the next iteration of the loop.
Number of iterations performed by the upper For Loop is determined by total time of
integration set at the front panel divide by the pulse width. For example if the total
time of data collection is set for 30 ms and pulse width is set 10 ms then For Loop
would iterate 3 times. Counts thus collected during the following iteration are
subtracted from the previous iteration. This prevents the loss of counts because the
16 bit counter would otherwise over flow to zero after count 65536. Subsequently
counts from individual channels are assembled into an array of having indices
equivalent to the number of channels set at the front panel. Current in individual
channels is calculated as per following equation in the second For Loop.
Current =Count x 200fC x (Vp+ - Vp-)/pulse width
Where (Vp+ - Vp-) = 5.59 volts measured on FE4C board.
When the second For Loop finishes the execution, data is ready for storage.

At this point of program execution operator is prompted to store the data in an existing or new file location.
4.4.6 Read Buffer VI

This VI incorporated in first For Loop of Read Buffer State executes number of times as per the acquisition mode selected at the front panel. Figure 4.9 corresponds to read data subVI that is called by the Read Buffer VI. This VI reads the circular buffer and combines the individual bytes into 16 bit word by the functions shown in the upper right part of the diagram. Data which is being generated is displayed in real time on the front panel as Counts/channel and Current/channel.

![Figure 4.9 Block diagram of Read Buffer VI.](image)

4.4.7 Stop State

On completion of a single scan or a continuous scan circular buffer has to be flushed so that it is ready for the next acquisition. This is achieved by sending a clear command to Clear Buffer Control VI as shown in Fig 4-11. Simultaneously a value True Boolean is passed to the conditional terminal. This would stop the While Loop and the program stops further execution.
During execution of every state the outer While Loop would un-bundle by name the error cluster (shown in red), if error has occurred then true Boolean would be passed onto conditional terminal which terminate the execution of the program and error would be displayed on the front panel (GUI).

4.4.8 BDA State

This system has been designed to work in conjunction with beam dump activator (BDA) of Synchrotron medical beam Line. There is a provision in GUI for the operator to set the maximum level of microbeam intensity desired. When channels are being read, software compares the dataset values to the desired/threshold intensity set in GUI in real-time. In the event of any detector output detected by the Read Buffer State VI to be more than the set value, a string of characters FF(Hex) are sent out through serial port of the PC.
This serial port is interfaced to a microcontroller to generate a pulse to activate BDA (beam Dump Activator) thus shutting down the beamline. BDA State comprises of Serial Config VI and VISA Write VI.

Serial Config VI configures the serial port of the PC in terms of Serial Port number, Baud rate, Parity Bit, Stop Bit. VISA Write VI send hex FF (11111111) to the serial port.

This output of the serial port is decoded by an external hardware comprising of microcontroller PIC16F84 and Max-232 chip. PIC16F84 is programmed to poll one of its dedicated input lines. If this input is read as FF (Hex) then another dedicated output line of PIC16F84 generates a positive pulse that is optically coupled to beam dump activation hardware of Synchrotron.

Figure 4.11 Block diagram of BDA State VI
5 TESTING

Preliminary tests were conducted at St George Hospital prior to sending the system to ESRF France.

Tera03 Chip has 2 volts dc present on all the input channels.

In order to verify the working of the hardware and software, resistors of 1MΩ, 10 MΩ, 100 MΩ, and 1 GΩ were connected to a single channel one at a time and the current was measured by the software.

This was found to be around 2 μA, 0.2 μA, 0.02 μA and 0.002 μA respectively.

Number of data sets was collected and the average data was graphed as shown in Figure 5.1. The error bars indicated represent two standard deviations (i.e. 95% confidence limit) of the mean value.

![Linearity of Channel Response](image)

Figure 5.1 Resistance vs. Current output of single channel.

Subsequently strip detector was mounted on an X-Y stage, controlled by stepper motors. Software was developed in LabVIEW to communicate serially with the X-Y stage so that the strip detector could be moved laterally in fixed increments.
detector was exposed to a fixed red laser source to monitor output of individual detectors. Since the laser beam had fixed crosssectional area, on every increment of lateral displacement of strip detector it was observed that number of peaks seen on the GUI were same through out the complete scan of the detector. This confirmed that all the individual channels are in working order.

Arrays of different combination of 1MegΩ,10MegΩ,100MegΩ,1GΩ of surface mounted resistors were connected to the Tera 03 Chips and current thus produced in the individual resistors was monitored by the Data acquisition system (Daq). Results are shown below in Figure 5.2.

![Channel Response](image)

**Figure 5.2 Channel response of resistor arrays of various values.**

Spikes in the outputs are due to variation in gain of individual channels.
6 RESULTS FROM 6 MV PHOTON BEAM (VARIAN 2100C LINAC)

After the preliminary testing and investigation that were conducted in the Electronics Laboratory, Cancer Care Centre at St George Hospital, the system was tested under the Varian 2100C LINAC.

Following formula was used to estimate charge collection in a single strip

\[
Q = \frac{m \times D}{W/e} \quad \text{(1)}
\]

Where \(m\) is mass of silicon in a single strip

\(D\) is LINAC dose per pulse

\(W\) is energy required to produce a hole pair in Silicone = 3.6 eV

\(e\) = electron charge

Density of Si = 2.33x10\(^3\) kg/m\(^3\)

Assuming sensitive volume \(V\) of charge collecting region of strip to be 100% = 20x5000x300 \(\mu\)m\(^3\)

Then mass of \(m\) = 2.33x10\(^3\) kg/m\(^3\)/20x5000x300 \(\mu\)m\(^3\)

\[= 6.99 \times 10^{-8} \text{ kg}\]

Average dose provided by LINAC = 0.33 mGy/ pulse

\[W/e = 3.6 \text{ eV/}e - h \text{ pair } \times 1.602 \times 10^{-19} \text{ J/eV/1.602 x 10–19 C/e} \]

\[= 3.6 \text{ J/C}\]

Substituting these values in equation (1) gives

\[Q = 6.32 \times 10^{-12} \text{ C (Coulombs)}\]
6.1 Percentage Depth Dose

Fig 6.1 shows the measured percent depth dose profile using the strip detector compared with a CC13 ion chamber measurement, using solid water for a $10 \times 10$ cm field size at source to surface distance of 100 cm. The photon energy was 6 MV (Varian Clinac 2100C). At the depth of 10 cm, $d_{10}$, the difference was 0.1% and at the depth of 20 cm, $d_{20}$, it was 1.2%. This deviation may be due to the lack of scatter with bigger field sizes at greater depth. Due to the fabrication of the detector with its cable connector placed close to the detector, we were not able to place sufficient scattering material at that end of the detector. However the overall results match well to the CC13 results.

Figure 6.1 Depth dose curve comparing the DAQ system with cc13 ion chamber measurements.
6.2 Linearity
The strip detector response is linear with dose range of 3.89 cGy to 311.05 cGy as shown in Figure 6-2. The dose linearity verification was carried out at this range because it was deemed to be within the range of a normal IMRT dose per fraction. This by no means is the dynamic range limit of the detector as the acquisition rate of the detector readout system can be varied to accommodate large counts. The R-squared value, is indicated on the graph, and is a number from 0 to 1 that reveals how closely the estimated values for the trendline correspond to the actual data. A trendline is most reliable when its R-squared value is at or near 1. It is also known as the coefficient of determination.

![Dose Linearity](image)

Figure 6.2 Dose linearity of the strip detector
6.3 Uniformity
Figure 6-3 shows the detector response by each of the detector channels before and after uniformity correction. Before correcting for the detector response, the coefficient of variation is 1.4% whereas after the application of the correction factor, the coefficient of variation is <0.1%. It is essential to perform a broad beam irradiation to obtain the calibration factor of the individual channels.

![Uniformity Correction](image)

Figure 6.3 Detector response before and after uniformity correction.

6.4 Energy Response
The energy response of the strip detector was studied using an Orthovoltage unit and is shown in Fig 6.4. The average photon energy was calculated from the half value layer of the beam. The energy response curve showed an enhanced response at low energies up to six times of the response at 6 MV. The detector showed an over-response at lower photon energies with the maximum dose response at 75 kV nominal photon energy. This is due to the increased of photoelectric effect cross-section in silicon to water at low energies. The energy dependence of the detector was expected as silicon is not tissue equivalent and therefore sensitive to changes in
the energy spectrum. This is in consistent with the literature. The effect of the energy
dependence of silicon in the use of this detector in megavoltage beams such as that
used in radiation therapy may not be as significant as those affecting the
measurements under the Orthovoltage beams.

![Energy Response](image)

Figure 6.4 Energy response of strip detector, normalized to 1 at 6 MV photon energy.

6.5 Angular response dependency

Si detectors are sensitive to the direction of radiation to which they are exposed.

This strip detector along with its ceramic mounting was investigated for its angular
response dependency. For this investigation the detector was mounted in IMRT
phantom and positioned at the Isocentre. It was exposed to 10X10 mm field at 15º
interval over 0º to 90º. These reading were compared to cc13 ion chamber
measurements as shown below in Figure 6-5. Maximum deviation of 25.7 % was
found to be at parallel incident beam at 90º.
Figure 6.5 Angular response dependency of the DAQ system. As the angle of the incident beam increased from perpendicular beam (gantry angle 0°) to parallel beam (gantry angle 90°), the strip detector under-responded compared to the planned dose. The maximum deviation of 25.7% was found to be at the parallel incident beam at 90°.

6.5 Penumbra Measurements
The 80-20% penumbra width of a 10 × 10 cm² field size was measured using the strip detector and comparison was made against measurements from Gafchromic EBT films. The EBT film measurements were done in a water tank. The strip detector and EBT film measured the penumbra at 1.5 cm depth for the secondary jaw to be 2.77 mm and 2.71 mm, respectively. Compared to their measurements, the strip detector seems to be able to resolve a narrower penumbra width. For the multileaf collimator (MLC) rounded leaf end, the strip detector measures a 3.52 mm penumbra width compared to the 4.6 mm MLC penumbra width measured using EBT films [56]. Penumbra was measured at 10.0 cm depth are 3.93 ± 0.2 mm for X-jaw and
5.50 ± 0.2 mm for the rounded left end of the MLC. This is again smaller than the measurement with the EBT films for the X-jaw of 4.5 ± 0.06 mm.[55]. 80-20% penumbra width using thermo luminescent dosimetry extrapolating to infinitesimal small detector found the penumbra width to be 3.2 mm at 1.5 cm depth and 4.2 mm at 10.0 cm depth.

Figure 6.6. Penumbra width _80%–20%_ measured for the 6 MV beam at 1.5 cm depth for the secondary X-jaw and the rounded leaf ends of the MLC using the strip detector and Gafchromic EBT film. The error bars for the EBT profiles represent the 95% CI of the mean of three sets of measurements, while the error bars for the SSD measurements represent the 2% reproducibility uncertainty.
The results are summarized in Table 1 Comparison of the 80-20% penumbra width measurements between the DAQ, Gafchromic EBT films, and other published literatures.

<table>
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<tr>
<th></th>
<th>CMRP (mm)</th>
<th>DMG (mm)</th>
<th>EBT film (mm)</th>
<th>Others (mm)</th>
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<td>X-Jaw (Symmetric) at 1.5 cm depth</td>
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<td>2.71</td>
<td>3.0</td>
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</tr>
<tr>
<td>X-Jaw (Asymmetric) at 1.5 cm depth</td>
<td>2.93</td>
<td></td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>MLC (Symmetric) at 1.5 cm depth</td>
<td>3.52</td>
<td></td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>X-Jaw (Symmetric) at 10.0 cm depth</td>
<td>3.93</td>
<td>4.5</td>
<td>4.2</td>
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<tr>
<td>MLC (Symmetric) at 10.0 cm depth</td>
<td>5.50</td>
<td></td>
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</tbody>
</table>
7 RESULTS FROM BIOMEDICAL BEAMLINE, ESRF FRANCE

After LINAC measurements this system was tested at ESRF France, the results are presented here. The new dosimetry system is to be used to measure the instantaneous micro-beam radiation therapy peak-to-valley dose ratio, which is an important physical parameter in micro-beam radiation therapy that indicates the quality of the micro-beam radiation therapy. In addition to this, the system is able to initiate a fast beam-stop trigger to avoid undesirable dose being delivered to the patient undergoing micro-beam radiation therapy treatment. This is an especially important feature as the MRT treatment time is very short compared to conventional radiotherapy, between 60 ms and 6000 ms depending on the size of the treatment field and desired dose. This system has met the following requirements of MRT dosimetry system:

- On-line capability for MRT beam set up and monitoring ability to make a quick assessment of the PVDR (in less than 100 µs) for all microbeams
- Large dynamic range
- No perturbation of the MRT beam energy spectrum
- No perturbation of the physical MRT array geometry
- Tissue equivalent so as to accurately measure the absolute dose in the microbeam array (PVDR) for correlation with MRT treatment outcomes
- Due to very high dose rates in MRT, detectors were operated in passive mode.
The strip detector was mounted at the surface of a small Perspex and solid water phantom as shown in Figure 7-1. In this way the multi channel detector and readout system could be used in several ways in preparation of MRT experiments. The detector can be exposed to macroscopic or mini beams (indicated in aqua in Figure 7-1) for given times while kept stationary. On the other hand the detector was mounted on a high precision movable translation stage, so the detector could also be scanned at constant speed (as indicated by the yellow arrow in Figure 7-1) through a mini-beam or microbeam for obtaining beam profiles. In addition to obtaining MRT dosimetry related data the multi channel detector and readout system could be used, to provide real-time data, as part of the MRT collimator alignment procedure. Finally, it is also planned to use the detector and readout system as part of the patient safety system, by providing real-time monitoring of each microbeam peak intensity so that the treatment beam could be aborted if necessary.
Figure 7.2. SSD response for 20 mm wide beam.

Figure 7-2 shows the response of a single strip within the detector linear array when exposed synchrotron X-rays for 66 ms. The detector was held stationary and exposed using a fast shutter. The readout system sampling time was 2 ms, which, when multiplied by the total measurement numbers for which a beam response was detected agrees very well with the known exposure time. The right hand axis shows a measured decrease in detector response (indicated as red dots). This decay in response matches that of the synchrotron storage ring current (the X-ray photon flux is directly proportional to the storage ring current) which has a lifetime of 6 hrs in the operational mode (known as 4 bunch) in which these experiments were performed.

To test the full capability of the readout system, all detector channels were readout while a single tungsten slit (slit width was 10 microns and each leaf was 10mm high,
50 mm wide and 10 mm deep) was scanned across the detector. The homogeneous field size was 10 mm wide and 0.5 mm high as set by a separate set of primary and secondary slits (and tertiary slits in the case of the height) upstream of the single tungsten slit.

Figure 7.3 Series of snapshot of the DAQ software operating in realtime during a scan of a single microbeam across the 128 channel detector.

The X-ray photon energy spectrum is determined by the height of the wiggler gap, which corresponds to the separation between the series of wiggler magnets. The minimum gap of 24.8 mm corresponds to the full MRT energy spectrum. It has the maximum intensity at 85 keV and a range from 50 keV to 650 keV. In this test the wiggler gap was increased to 50 mm as the intensity of the beam was such that the current amplifiers in the readout system were otherwise saturated. As such, the
energy spectrum was slightly softer (40 keV – 600 keV) and less intense. In addition to the change in the peak intensity, the intensity profile of the “homogeneous” X-ray beam laterally also decreases significantly across the lateral irradiation field compared to the minimum wiggler gap case. It should be noted that the macroscopic or broad beam X-ray field is referred to as the “homogeneous” field even when the wiggler gap is greater than 24.8 and the radiation field is not actually homogeneous.

Figure 7-3 shows a time lapse series of screen shots of the real-time data acquisition system as the detector is scanned across a single microbeam. As discussed above in the software section the measured instantaneous current in all channels is written to file every 2 ms and displayed on the screen in real-time. Such real-time information was found to be particularly useful during the MRT set-up and alignment process as illustrated in Figure 7-4 using a single, 5 µm wide, tungsten slit. Alignment of the multislit collimator (MSC) is critical to ensure consistent clinical outcomes. Any misalignment of the homogeneous beam with respect to the MSC can result in diffraction wings appearing on each side of every microbeam which have a significant effect on the dosimetric profile of the microbeams.

Normally the alignment procedure is quite complicated (involving a separate 5 micron wide single slit and an additional ionisation chamber) and time consuming as it requires many iterations and scans to optimise the alignment of the beam with the MSC. Using the new multichannel detector and real-time readout system, the additional slit is not required and alignment data is provided on the computer screen in real-time, thus significantly reducing the iterations required for good MSC alignment. Figure 7-4 illustrates what is observed in real-time by showing the response of a single strip within the multichannel silicon detector when the detector
is scanned through a single microbeam and with the slit slightly misaligned (+0.005°). In real-time the same profile as shown in Figure 7-4 is observed because we have 128 individual detectors spatially separated forming a linear array, thus covering the same region of space as that when scanning a single detector.

![Initial measurement](image1.png)

![After realignment](image2.png)

**Figure 7.4** MRT microbeam + 5 um W slit. In the top figure wings are due to atomic x-ray diffraction. Bottom figure shows realignment

Bottom Figure 7-4 shows the same scan as in Figure7-4 but with the MSC misalignment corrected. When the MSC is optimally aligned with respect to the synchrotron X-ray beam no wing structure is observed. In real time the DAQ system displays the wing moving relative to the main peak as the MSC was systematically rotated in (0.001° minimum) steps about its optimal aligned position. Future detectors have been designed with a finer strip detector pitch (current pitch is 100 microns) for higher precision measurements and monitoring of the MSC alignment.
Figure 7.5 Scan of 10 µm tungsten slit across the 128 channel detector. The wiggler gap was 50 mm and the radiation field size was 10 mm wide by 0.8 mm high (homogenous field size upstream of the multislit collimator).

Figure 7-5 shows the measured response in 36 of the detector strips connected to the readout system as the single tungsten slit is stepped across the homogeneous X-ray field, while the detector remained stationary. The four channels show no response and were later traced to bad solder joints in the detector PCB connectors.

As expected, when the slit moves across each strip detector, we observe a maximum in the measured signal current induced in the strip detector. The increase in the intensity of the homogeneous field is clearly observed as an increase in the maximum current induced in each detector, as the tungsten slit moves from the edge of the detector towards the middle. As the slit moved beyond the lateral dimension of the macroscopic field (defined by separate slits upstream) there is a sharp reduction in the measured current induced in the detector.
Of interest, although not directly related to the work described in this thesis, is that careful inspection of the data also shows some wing structure developing as the slit moves towards the edge of the macroscopic field. This is the effect of slight misalignment of the X-ray beam relative to the tungsten slit caused by the finite size of the source and the slight divergence in the synchrotron X-ray beam.

![Figure 7.6 SSD scan through single SSD MRT](image)

The detectors were operated in passive mode in an attempt to minimise the signal current induced by the beam and minimise any radiation damage effects in the detector’s response. In passive mode the charge induced by the irradiation is collected via diffusion of the charge outside the junction region and via drift where the intrinsic electric field exists at the p-n junction. The extent of any charge diffusion is evidenced by cross talk in the current induced in the detector strips. Figure 7-6 shows the response of the SSD array when it is stepped through a single microbeam. In this experimental configuration a 150 µm tungsten slit was placed a 10 cm upstream of the multislit collimator so that only one (central) MSC slit was illuminated with the synchrotron X-ray beam. Unlike the experiment described above
where the slit was stepped through the X-ray field, in these experiments the strip detector was stepped through the single microbeam illuminating from the MSC (as indicated in the inset photograph in Figure 7-6.

In this case the effects of macroscopic radiation field inhomogeneity were negated. Similarly to the above experiments the wiggler gap was set to 50 mm, hence the peak measured current response is the similar to the maximum shown in Figure 7-7. The difference is related to the fact that the synchrotron storage ring current was different for each case.

Figure 7.7 SSD5 scan through single MRT on log scale.

The level of cross talk between the channels is clearly evident in Figure 7.7. The red dashed line in Figure 7-7 indicates that the charge generated at a point on the detector
array and how it is shared between several strip detectors that make up the linear detector array.

Figure 7-7 is the same as Figure 7-6 but displayed on a log scale. The extent of the charge sharing is even clearer than in Figure 7-6. Exponential curve fitting of the data indicates that the diffusion length is consistent with that expected, given the high resistivity of the substrate material (1 kΩ cm). While the charge sharing is of concern with respect to the dosimetry requirements for MRT, the graph does indicate that the data acquisition system has the necessary dynamic range required for precise, clinical dosimetry. It is estimated from Monte Carlo calculations that the ratio of the microbeam peak to adjacent valleys is of the order 100. In order to measure such a ratio experimentally with an uncertainty of <5% a dynamic range of 5 orders of magnitude is necessary Microbeam.

The beam dump activation (BDA) process is one of the most critical features, from the point of view of patient safety, of circuitry to be designed as part of this thesis. If any of the systems fail during a patient irradiation (e.g. one of the in-line filters fail and melt which would lead to an unwanted rapid rise in dose rate) a fast signal is required as soon as such a failure is detected so that the treatment can be aborted immediately. Such a safety system is mandatory in any radiation treatment facility, but particularly in MRT as the treatment dose rates in MRT are very high.

The BDA circuit, as discussed earlier, outputs a trigger pulse generated by the readout software and controlled by threshold level that can be set by the user. If any of the readout channels go above the threshold level as illustrated in Figure 7-8 the BDA circuitry is activated. Such a BDA pulse would be used to immediately shut the
whole synchrotron down, which is the fastest way of stopping the beam, requiring 1-2 ms. The BDA is one of many degenerate beam sensory systems in place, however is only system in place with the ability to monitor the intensity of each microbeam independently.

![Figure 7.8 System delay of BDA pulse via serial port at 9600 baud rate.](image)

Figure 7.8 System delay of BDA pulse via serial port at 9600 baud rate.

![Figure 7.9 Beam dump activation level indicated on the MRT dosimetry system GUI (red dashed line).](image)

Figure 7.9 Beam dump activation level indicated on the MRT dosimetry system GUI (red dashed line).

Figure 7-9 shows the trigger pulse associated with the fast shutter control unit (upper trace) and the BDA trigger pulse (lower trace). The delay between 0.5 ms after the leading edge of the “beam on” trigger pulse (it is 0.5 ms after the pulse before the beam is actually on) and the shutting down of the synchrotron (which occurs 1-2 ms
after the leading edge of the BDA trigger pulse) needs to be minimised to minimise the dose received by the patient.

From the graph there is a 3.4 ms delay between leading edge of the “beam on” trigger pulse and the leading edge of the BDA trigger pulse. Hence there is a maximum total delay time of 4.9 ms. The usual MRT dose rate at the surface of the patient is ~100 Gy/sec/mA, hence at a maximum storage ring current of 200 mA the estimated dose received by the patient before the beam is off is 98 Gy. While 98 Gy is very high by conventional radiotherapy standards the dose volume effect is working in our favour (the beam height is only 500 microns). There is also the possibility to reduce this number substantially as the measured 3.4 ms delay can be significantly reduced by increasing the serial port baud rate from 9600 b/s to 117000 b/s or beyond. This will be the subject of future work.
8 CONCLUSIONS AND RECOMMENDATIONS

In this thesis a DAQ system has been developed for a silicon strip detector array. The system has been used successfully in megavoltage Linac beams, Orthovoltage, and micro beams from a Synchrotron X-ray source.

Potential limitations of the system are minimal. Energy response, linearity, uniformity, angular dependence and response time are sufficient for the majority of quality assurance applications in external beam and microbeam radiotherapy.

The DAQ of a linear array of 128 silicon localized dosimeters strips each of them with an active area 20 5000 m² and pitch of 0.2 mm was characterized and tested in a clinical IMRT delivery.

For a 390-fold variation in the Linac dose per pulse, the detector response changed by 23% compared to the CC13 ion chamber measurement. The percent depth dose profile for the 6 MV photon energy matches closely with the measurement with Farmer ion chamber within 0.8% up to 20 cm depth in solid water. The stem effect of the detector was found to be negligible.

The linearity of the detector with dose is excellent for the dose range of 3 – 300 cGy typical for one fraction of IMRT delivery. The original strip detector had a 2% variation in sensitivity between 128 channels including DAQ electronics that suggests very high reproducibility of the strip detectors with the planar microelectronic technology. The strip detector showed the typical energy dependency intrinsic for silicon at lower photon energies in free air geometry.

Penumbra measurements were performed at the depths of $d_{\text{max}}$ of 1.5 and 10.0 cm for the 6MV photon energy.
The measurements were compared to the measurements of Gafchromic EBT film as well as other data published in literature for the same fields.

The DAQ with its physical spatial resolution of 0.2 mm derived a penumbra 80%–20% width of 2.77 mm at 1.5 cm depth and 3.94 mm at 10.0 cm depth, similar to the EBT film measurements. The dose profile patterns measured by DAQ were comparable to the dose profiles by film measurements. The dose profiles agree fairly well with each other within the uncertainty in the measurements as well as the positioning uncertainty of 1 mm2.

The angular response of the strip detector is within 3.1% 0.1% for the angle of 0°–45°, while for the angle of 90° the response was 28.1% 0.1%. This is associated with the ceramic packaging of the detector as well as the inherent anisotropies in Si.

In addition to high spatial resolution of 0.2 mm, DAQ is capable of providing integral dose profiles for each delivered segment or dose rate measurements at any channel with temporal resolution of 0.1s.

The present design of this DAQ is suitable for beam characterization and measurement of steep gradient dose profiles. The 0.2 mm detector spatial resolution of the DAQ would be suitable as a dosimetry tool for Stereotactic Radiotherapy QA as well. Application of this technology with the same spatial resolution for large radiation fields is limited by the number of readout channels and the detector-to-readout system connection logistic.

In conclusion, TERA ASIC DAQ system, with its high spatial resolution and the accompanying high temporal resolution readout system, is a novel tool for QA in IMRT dose delivery and VMAT dose delivery.
As consequence of this work, the versatility of this system has been well recognized and investigations began into using this system as a QA tool in modern conformal radiotherapy i.e. Stereotactic Radiotherapy, Tomotherapy and IMRT. [61, 62, 63]

The new dosimetry system was also utilized in a new and exciting form of radiotherapy, known as Synchrotron X-ray microbeam radiation therapy. The system demonstrated that it is able to be used to measure the instantaneous micro-beam radiation therapy peak dose, which is an important physical parameter in micro-beam radiation therapy that indicates the uniformity of each microbeam independently in the micro-beam radiation therapy during the treatment of the patient. There is no other system capable of making such multichannel, real-time measurements in the world.

In addition to this, the system is able to initiate a fast beam-stop trigger to avoid undesirable dose being delivered to the patient undergoing micro-beam radiation therapy treatment. This is an especially important feature as the MRT treatment time is very short compared to conventional radiotherapy, between 60 ms and 6000 ms depending on the size of the treatment field and desired dose.

Future work for this system includes:

1. Confirmation of the use of a RS-232 port interface for shutter control at the microbeam facility (France/Melbourne).
2. Cross talk minimization between the adjacent channels
3. Development of DAQ system for Tera-06 chips for measurement of 256 channels simultaneously.
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