Dosimetry in synchrotron microbeam radiation therapy

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DOSIMETRY IN SYNCHROTRON MICROBEAM RADIATION THERAPY

A thesis submitted in fulfilment of the requirements for the award of the degree of

Doctor of Philosophy

from

UNIVERSITY OF WOLLONGONG

by

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School of Physics
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2016
CERTIFICATION

I, Pauline Fournier, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Physics, Faculty of Engineering and Information Sciences, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

________________________
Pauline Fournier
1 October 2016
Microbeam Radiation Therapy (MRT) is a novel radiation therapy modality currently developed at several synchrotron sources around the world. The MRT technique is based on the use of plane parallel arrays of microbeams produced by a multi-slit collimator (MSC). The major benefit of MRT lies in the dose volume effect: a higher radiation tolerance of the normal tissue when using micrometer scale beam size. Moreover, pre-clinical studies highlighted the detrimental effect of MRT on the tumor tissue and demonstrated the presence of a differential effect between normal and tumor tissue. One of the possible applications of MRT is the treatment of inoperable paediatric brain tumors where conventional radiotherapy presents a high level of toxicity on the developing brain. Despite the numerous pre-clinical studies that demonstrated the efficiency of the MRT technique over the last twenty years, efforts are still required for the dosimetry quality assurance (QA) before being able to move from pre-clinical to human clinical stage and are the framework of this study.

Currently, a 3rd generation synchrotron X-ray source is required to perform MRT irradiations. Indeed, the low beam divergence allows the production of plane parallel microbeams, the high dose rates ensure fast irradiation times thus avoiding any blurring of the microbeams with cardiosynchronous motion and the energy spectrum in the range 27-600 keV provides sharp beam penumbra. Quality Assurance (QA) is required for MRT but remains a challenging task due to the high spatial resolution and the radiation resistance properties required from the dosimeter.

In MRT, QA must include reference dosimetry in a reference broadbeam (i.e. no spatial fractionation of the beam) and the dosimetry of the microbeams. Microbeam dosimetry consists in the experimental determination of the dose in the microbeams (i.e. peak dose), of the dose between the microbeams (i.e. valley dose), of the Peak to Valley Dose Ratio (PVDR) and of the scatter factors. Many detectors have been investigated and led to the conclusion that ionisation chambers (IC) and Gafchromic® films currently are the most accurate detectors for broadbeam and microbeam dosimetry respectively. However, due to the high dose rates encountered in MRT, lack in collection efficiency has been observed from the IC leading to significant uncertainties. Moreover, despite their great spatial resolution, Gafchromic® films do not provide sufficient dynamic range to display both peak and valley doses, they are passive detectors and still present too significant reading uncertainties to be used as primary detectors. Within this context, the aim of this study was to improve both broadbeam and microbeam dosimetry at the ID17 biomedical beamline at the ESRF (European Synchrotron Radiation Facility).
Synchrotron Radiation Facility, Grenoble, France) where MRT is developed and to propose the corresponding quality assurance procedures.

First, the lack of collection efficiency of the MRT reference IC was addressed by the development of a new method based on the measurement of the IC response at different dose rates. This method provides correction factors to be applied to the reference IC and results in the determination of the absolute dose with an accuracy better than ± 5%. In the context of MRT veterinary trials on the ID17 biomedical beamline, an absorbed dose to water protocol has been established within this work.

In collaboration with ID17, the Centre for Medical Radiation Physics (University of Wollongong, Australia) developed the X-Tream dosimetry system especially for MRT QA applications. The system relies on a high resolution silicon Single Strip Detector (SSD) for the microbeams acquisition. The X-Tream dosimetry system has been characterised at the ESRF and a particular attention was dedicated to the study of the radiation damage induced into the SSD as well as on the experimental determination of the energy dependence of the device. The ability of the SSD to perform rapid and efficient QA tests prior MRT treatment has been evaluated: in-air measurements of 1D intensity profiles of the synchrotron beam used in MRT were performed in order to assess the alignment of the MSC. The SSD was able to detect small misalignments of the MSC which resulted in changes in the valley shape and on the peak and valley signals. The results obtained by the SSD for the MSC alignment were in agreement with the monitoring IC currently used for this purpose on ID17. An alignment procedure based on the pink-beam imaging modality available at the ESRF has also been developed in order to align the SSD with the MRT beam. The SSD has then been used at the ESRF under reference conditions in order to experimentally determine the PVDRs and scatter factors. For the first time, an active detector has been able to measure both valley and peak signals with the same accuracy leading to a direct determination of the PVDRs in agreement with published results obtained using Gafchromic® films and MC simulations. Finally, preliminary tests have been carried at the Imaging and Medical BeamLine (IMBL) at the Australian Synchrotron (AS) where the microbeam array have been acquired for the first time with an active detector.
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Preamble

This thesis is divided into eight chapters. First, the clinical context under which Microbeam Radiation Therapy (MRT) technique emerged is explained as well as the major outcomes and remaining challenges that motivated this PhD project.

Chapter 1 introduces the Microbeam Radiation Therapy principle and gives a brief history of the technique. The major findings obtained during pre-clinical studies carried to either demonstrate the technique efficiency, investigate the optimisation of the MRT treatment or explain the underlying mechanisms are presented. A special attention is then dedicated to the dosimetry issues encountered in the case of medical applications of a synchrotron X-ray beam. The challenges related to microbeam dosimetry are presented and the main results obtained in previous studies investigated different methods and/or detectors are detailed. The objectives and aims of this PhD project are also exposed in this chapter.

Chapter 2 introduces the facilities where the experiments presented in this study were conducted. The synchrotron principle is first explained before describing in details the instrumentation of both the ID17 biomedical beamline at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France, and the Imaging and Medical Beam Line (IMBL) at the Australian Synchrotron where the MRT technique is developed.

Chapter 3 focusses on reference dosimetry that needs to be performed under broad-beam conditions (i.e. no spatial fractionation of the beam) before MRT irradiation. As this dosimetry procedure uses a cylindrical ionisation chamber (IC), the principle of this detector will be explained as well as the different correction factors that needs to be applied to the IC reading in order to measure an absolute dose. At the ESRF, a reference dosimetry protocol has been established and is especially adapted to the MRT technique. Indeed, due to the high dose rates encountered in MRT, this protocol required the development of a dedicated method for the determination of the saturation correction factor to be applied to the IC reading. This method is fully described in this chapter. A study dealing with the energy spectrum verification for two beam conditions available at the ESRF and based on half value layer measurements is also presented.

Chapter 4 presents the X-Tream dosimetry system especially developed by the Centre for Medical Radiation Physics (CMRP) for microbeam dosimetry. The system
is composed of a silicon Single Strip Detector (SSD), a pre-amplifier module, a central data acquisition system unit (CSU) and a graphical user interface. In this chapter, the dynamic range of the two pre-amplifier modules used for the different experiments, and thus their suitability for MRT applications, was investigated by measuring the output signal from each module as a function of the input current. These measurements also allowed the determination of the current to counts conversion factor for both modules. As silicon-based detectors are known to be quite sensitive to radiation damage and to exhibit a high energy dependence, these two aspects were studied in detail and are presented in this chapter.

Chapter 5 evaluates the ability of the SSD to perform rapid and efficient QA test prior MRT treatment. This study is based on in-air measurements of the horizontal profiles of the microbeams X-ray field in order to determine the relative intensity of each microbeam and assess the alignment of the MSC.

In chapter 6, the SSD has been used for microbeam dosimetry at the ESRF. The Peak to Valley Dose Ratio (an important dosimetric parameter in MRT) was assessed in three different dosimetric phantoms and results were compared to Monte Carlo (MC) simulations. The scatter factors used to convert the dose measured in the MRT reference field (i.e. 20 mm × 20 mm) to the dose in a microbeam have also been measured using the SSD and compared to MC simulation results.

Chapter 7 presents preliminary experiments that have been carried at IMBL at the Australian Synchrotron. These experiments consisted in broadbeam experiments where the SSD behaviour was compared to the IC used for reference dosimetry at IMBL. Intensity profiles of horizontal microbeams have been obtained in the MRT hutch at IMBL (hutch 1B) for two different microbeams widths settings.

Finally, chapter 8 resumes the major findings of this thesis and gives the concluding remarks.
Chapter 1

Introduction

1.1 Context and motivations

In 2012, brain cancer (and other CNS tumours) has been estimated to have caused the death of 189,000 people worldwide [UK Cancer Research Website]. In 2007, brain cancer represented 1.4% of the new cancer cases in Australia [AIHW 2012]. However, over the 2003-2007 period, brain cancer was the leading cause of cancer death for adolescent and young adults (15-29 years old). Indeed, the 5 year relative survival is only of 21.6% for brain cancer and has remained essentially unchanged for the last 30 years [AIHW 2014]. This bears testimony to the limitations of the technologies currently used to cure brain cancer and to the crucial need to develop new treatment modalities.

Within this context, Microbeam Radiation Therapy (MRT) is currently under development. MRT uses a highly brilliant synchrotron X-ray source spatially fractionated into an array of quasi non-diverging microbeams (≈ 25 to 100 µm wide beams spaced by a 100 to 400 µm distance). The major physical benefit of this approach lies in the dose volume effect: a higher radiation tolerance of the normal tissue when using micrometer scale beam size [Curtis 1967; Zeman et al. 1961, 1959]. Such tolerance is not observed for cancer tissue [Bouchet et al. 2010] which leads to a natural differential effect in the MRT approach. Using MRT thus implies an extraordinary sparing
1.2 Microbeam Radiation Therapy

of the normal tissue and one of the possible application of MRT is the treatment of inoperable and very radiation resistant paediatric brain tumors where conventional radiotherapy presents a high level of toxicity on the developing brain [Laissue et al., 2007; Ribi et al., 2005; Slatkin et al., 1992].

Over the last 20 years, many pre-clinical studies have been performed and demonstrated the efficiency of the MRT technique [Bouchet et al., 2012; Dilmanian et al., 2003; Laissue et al., 1998; Le Duc et al., 2011; Miura et al., 2006; Régnard et al., 2008a; Smilowitz et al., 2006]. However, before moving from the pre-clinical to the clinical trial stage, new and novel developments are required from the dosimetry aspect and are the framework of this study.

1.2 Microbeam Radiation Therapy

1.2.1 Dose volume effect

Spatially fractionated beams have been used for a long time in the interest of preserving normal tissues. In 1909, Alban Köhler introduced the use of a grid made of iron wires in order to avoid patients skin necrosis when using medium energy photons [Köehler, 1909; Laissue et al., 2012]. Indeed, by preserving some skin cells from the direct radiation, the skin showed a better ability to recover from the burns induced by the radiations. With the emergence of megavoltage X-rays radiotherapy techniques and their associated sparing of the skin tissue via the dose build up with depth in the patient, the grid is now used occasionally in the case of advanced and/or large tumors in order to enhance the tumor control [Laissue et al., 2012; Mohiuddin et al., 1999; Peñagaricano et al., 2010].

MRT takes advantage of the dose volume effect that occurs when micrometer scale beams are used relying on superior repair mechanism. The dose volume effect was
highlighted in the late 1950’s when Zeman et al. investigated the effect of cosmic radiations on mouses’ brain using deuterium beams of different sizes. The authors observed a much higher tissue tolerance when using smaller beam sizes: for a 1,000 µm beam, a dose of 300 Gy was sufficient to observe a complete tissue destruction while when using a 25 µm beam the dose had to reach 11,000 Gy prior creating a lesion [Zeman et al., 1959].

Figure 1.1: Histological images of a mouse brain irradiated with a 22.5 MeV deuterium beam. On the left image, the mouse brain tissue, irradiated with a 1 mm diameter beam and an entrance dose of 280 Gy (120 days post-irradiation), is completely destroyed while on the right image the tissue irradiated with a 25 µm beam and an entrance dose of 4,000 Gy is preserved (28 days post-irradiation). Reproduced from [Zeman et al., 1961].

A histological study was thus carried out on mouse visual cortex with high energy particles. For a 1000 µm wide beam the dose required to produce the complete destruction of cells within 24 days was 140 Gy whereas, for a 25 µm large beam, a dose of 4000 Gy only introduced the destruction of the cells within the beam path while the tissue remained intact [Curtis, 1967; Zeman et al., 1961]. Indeed, in the case of the larger beam sizes the authors observed tissue necrosis, circulatory disturbances and delayed radiation damage of vessels. At the time, this extraordinary radioresistance of the brain tissue was explained by a fast vessels repair along the microbeams path.
thus allowing the preservation of the vascular network. However, the heavy ions used in this study are attenuated at relatively low depth (1.5 mm depth under the skin) which prevents their use for a radiation therapy application.

In 1992, the emergence of synchrotrons X-rays sources provided the impulse for the development of MRT. Indeed, synchrotron beam divergence is very low (\(\sim 0.5\) mrad and \(\sim 0.02\) mrad in the horizontal and vertical direction respectively at the ESRF) compared to conventional X-ray sources (\(\sim 35\) mrad) thus allowing the production of plane parallel beams. Moreover, fast irradiation times are required in MRT in order to avoid any blurring of the microbeams induced by cardiovascular or pulmonary motions. The highly brilliant X-ray beam produced by a synchrotron source results in large radiation dose rates enabling the dose delivery in very short times. Finally, the kilovoltage energy range of the synchrotron beam limits the range of the secondary electrons leading to sharp beam penumbras and edges.

MRT was first proposed and started being developed in 1992 at the Brookhaven National Laboratory (BNL) in collaboration with the National Synchrotron Light Source (NSLS) in Upton (USA) \cite{Slatkin1992}. In 1994, a patent on the MRT technique was submitted \cite{Slatkin1994} and MRT was implemented on the biomedical beamline (ID17) of the European Synchrotron Radiation Facility (ESRF) in France. Since 2005, MRT experiments have been able to be performed at Spring 8 in Japan. In 2008, the Australian Synchrotron and the Candadian Light Source (CLC) opened their medical beamlines where MRT is also under development. Finally, in November 2013, the first MRT veterinary clinical trials was conducted at the ESRF where a cat patient presenting a spontaneous tumor was treated.
1.2. Microbeam Radiation Therapy

1.2.2 MRT technique

As mentioned previously, the MRT technique relies on the use of highly collimated, quasi-parallell arrays of microbeams produced by a 3rd generation synchrotron source in the kilovoltage energy range.

The spatial fractionation of the synchrotron beam is performed by a multislit collimator (MSC) made of tungsten carbide (WC). The MSC slits aperture can either be fixed or tunable. In this last case, two MSCs of alternating low and high atomic number materials are used (i.e. either aluminium/gold or air/tungsten combination) and the microbeams width is modified by a horizontal translation of one MSC relative to the other MSC as shown in Figure 1.2.

Figure 1.2: Illustration of the synchrotron beam collimation using two MSCs allowing a tunable microbeam width. Reprinted from [Siegbahn et al., 2006].

The microbeam sizes are typically between 25 and 100 µm wide and spaced by a 100 to 400 µm [Bräuer-Krisch et al., 2010b]. Figure 1.3 is a schematic diagram of the typical dose profile observed when irradiating tissue material with an array of microbeams (extracted from [Blattmann et al., 2005]). This profile illustrates the formation of the so-called peak and valley regions. The peak dose corresponds to the
dose deposited in the path of the microbeams and the valley dose originates from
the photons scattered from the peaks. The valley dose is much lower than the peak
dose but remains significant for the tissue. The valley dose depends on the peak
dose, the distance between the microbeams, the microbeams width, the beam energy,
the chemical composition of the target, the number of microbeams in the array, the
irradiation field size and the point in depth of the irradiated target.

Figure 1.3: Schematic representation of a typical dose profile in MRT. Reprinted from [Blattmann et al., 2005].

The Peak to Valley Dose Ratio (PVDR) is an important parameter in MRT. As
its name suggests, the PVDR is equal to the dose deposited in the peak divided by
the dose deposited in the valley. The distance between two microbeams is called
the center-to-center distance (c-t-c). In the context of pre-clinical studies, the term
“peak entrance dose” was introduced and corresponds to the peak dose at 3 mm depth
in tissue/water. Therefore for the pre-clinical studies, the irradiation conditions are
usually defined by the peak entrance dose, the microbeams width and the microbeams
spacing (i.e. the c-t-c distance).
1.2.3 Pre-clinical results

The very first MRT pre-clinical trial was carried out at BNL in 1995 where the brains of healthy rats were irradiated for different microbeams widths, heights and spacings and for skin entrance doses ranging from 312 to 10,000 Gy. Irradiations were performed using a single slit collimator defining either a $20 \mu m \times 4 \text{ mm}$ (MRT 2), $7 \text{ mm} \times 42 \mu m$ (MRT 4) and $37 \mu m \times 4 \text{ mm}$ (MRT 5) (width × height) microbeam. Parallel slices of the rats’ brain were exposed to the microbeam after a $200$ or $75 \mu m$ (MRT 2 and MRT 5) or $200 \mu m$ (MRT 4) lateral translation of the rat. 3 or 20 brain slices were irradiated for the MRT 2 configuration. 20 and 21 slices were irradiated for the MRT 4 and MRT 5 configurations respectively. For MRT 2 and MRT 4 the space between the slices was of $200 \mu m$. For MRT 5, two different spaces between the slices were investigated: either $75$ or $200 \mu m$. The rats were sacrificed two weeks or one month after the irradiation. Two of the four rats that received the maximum skin entrance dose developed brain tissue necrosis. For the two other rats that received an entrance dose of 10,000 Gy, all of the rats that received 5,000 Gy and some of the rats that received an entrance dose of 2,500 or 1,250 (57% and 25% respectively), a loss of nuclei (and their pezikarya) was observed along the microbeams path but without any brain necrosis nor brain damage [Slatkin et al., 1995]. For 312 Gy and 625 Gy entrance doses, the rats’ brain tissue appeared normal histologically.

After these promising results, Laissue et al. investigated the potential of MRT to treat rats bearing cerebral 9L gliosarcomas [Laissue et al., 1998]. They used either one or two arrays of microbeams orthogonally crossed in the tumor volume. Each array contained 101 microbeams, $25 \mu m$ wide and spaced by $100 \mu m$ c-t-c. A peak dose of 625 Gy was delivered for the single array configurations and two different peak doses were investigated for the two orthogonal arrays configuration (312 and 625 Gy). Each configuration gave a higher median survival time than for the unirradiated controls.
1.2. Microbeam Radiation Therapy

As one can see in Figure 1.4 the longest survival time was obtained for the irradiation performed with two orthogonal arrays of microbeams delivering a peak dose of 625 Gy (median survival time of 139 days after tumor implementation compared to 20 days in the case of untreated rats). Moreover, the authors observed a disappearance of the tumor for 61% of the irradiated rats even in the case of an irradiation performed with a single array of microbeams (observed for 4 rats over the 11 treated with a single port using a microbeam array).

![Survival curves obtained for 9L cerebral gliosarcoma bearing rats either unirradiated (Controls), irradiated with one single array of microbeams and 625 Gy peak dose (625-1) or irradiated with two orthogonal arrays of microbeams with a peak dose of either 312 Gy (312-2) or 625 Gy (625-2). Reprinted from Laissue et al. 1998.](image)

This study highlighted for the first time the efficiency of MRT for the tumor control without observing any macroscopic damage on the normal brain tissue. The extraordinary radioresistance of the normal brain tissue was hypothesised to result from a fast repair of the microscopic lesions by adjacent cells in the valley that have received less dose. However, it was important to ensure that the normal brain tissue tolerance to MRT irradiation still remained in the case of immature developing brain. Laissue et al. 1999 thus conducted a long-term study on suckling rats where they performed unidirectional irradiation of the normal brain using peak entrance dose of 50 or 150 Gy.
1.2. Microbeam Radiation Therapy

Gy, a 28 µm microbeam width and a c-t-c spacing of either 105 or 210 µm. 15 months after the irradiation none of the rats had died or needed to be euthanised. An important weight loss coupled to neurological and behaviour anomalies were observed but only in the case of the rats irradiated with the highest dose and the narrowest c-t-c spacing. For the other c-t-c spacing and peak entrance dose combinations, the rats development remained similar to the unirradiated control rats.

It was also necessary to demonstrate that the structure of peak and valley regions was still preserved for larger brains. Indeed, in the tissue, the peak dose is attenuated at a higher rate than the valley dose thus resulting in a decrease of the PVDR with depth (this behaviour will be detailed in Section 1.3.3 and illustrated in Figure 1.17). A long-term study was thus carried out with piglets aged between 40 and 47 days old by Laissue et al. [2001]. This animal model was chosen because piglets neurological development is comparable to human infants. Irradiations were conducted with skin entrance peak doses ranging from 150 to 600 Gy and with a 1.5 cm x 1.5 cm field composed of 25 µm large microbeams spaced by 210 µm. The animals developed normally over at least a year and no neurological changes were observed between the irradiated piglet and the non-irradiated ones. Histological studies performed on a piglet brain 15 months after irradiation and that received a 300 Gy skin entrance dose showed destroyed cells (and their nuclei) in the path of the microbeams but no signs of hemorrhage nor necrosis was found (see Figure 1.5) [Laissue et al., 2007, 2001].

These first trials demonstrated the efficiency of MRT to treat brain tumors but also the sparing of the normal brain tissue and led to the consideration of MRT for the treatment of brain tumors for both adult and pediatric patients. Indeed, the normal tissue sparing of MRT could be very beneficial for pediatric patients for whom conventional treatments can cause neurocognitive dysfunction [Ribi et al., 2005].

The encouraging results obtained by Laissue et al. [2001] were the starting point
of numerous pre-clinical studies carried out in order to optimize the MRT parameters, increase the efficiency and understand the mechanisms responsible for the differential effect observed between normal and tumor tissue.

### 1.2.4 Optimisation of the MRT irradiation parameters

Among different aims of the pre-clinical studies, some of the research was focussed on the determination of the optimum parameters to be used in MRT in order to ensure both tumor control and preservation of the normal tissue and cognitive functions. They mostly relate to the determination of the optimum microbeam size and spacing.

**Microbeams inter-spacing (c-t-c distance)**

Dilmanian *et al.* [2002] implanted fisher rats brains with 9L gliosarcoma. The rats were then irradiated with an array of unidirectional microbeams. The microbeam width was fixed to 27 µm and different microbeam spacings (50, 75 and 100 µm) and
1.2. Microbeam Radiation Therapy

Skin entrance doses (150, 250, 300 and 500 Gy) were investigated. The survival curves obtained for the different irradiation configurations are displayed in Figure 1.6 and compared to the one obtained for the untreated rats.

![Survival curves for different irradiation configurations](image)

Figure 1.6: Survival curves obtained for the treatment of cerebral 9L gliosarcoma bearing rats using different entrance peak doses and microbeams spacings. Reproduced from [Dilmanian et al., 2002].

As one can see, for each configurations, the MRT treatment has contributed to an increase of the survival time when compared to the unirradiated group for which the median survival was 19 days. However, the median survival times vary between 31 and 171 days depending on the beam spacing and peak dose considered. The lowest median survival times were observed for irradiations combining small beam spacing with the highest peak entrance dose (i.e. 50 c-t-c with a 300 Gy peak entrance dose and 75 c-t-c with a 500 Gy peak entrance dose). These results suggest that MRT efficiency highly depends on the valley dose and the authors concluded that, in the normal tissue, the valley dose must remain under the organ dose tolerance in order
to preserve the MRT beneficial effect. Régnard et al. [2008b] treated 9L gliosarcomas bearing rats with an unidirectional array of microbeams. The microbeam width was fixed to 25 µm and the spacing between the microbeams was either 100 or 200 µm. They observed a higher median survival time by using a 100 µm spacing but also normal tissue damages. They concluded that, for the parameters used, the 200 µm spacing was the best compromise between curing the tumor and sparing the healthy tissue. One limitation of this study was the fact that the peak dose (around 615 Gy) was not modified between the 200 µm and the 100 µm wide beams configurations thus introducing a valley dose almost three times higher in the case of the 100 µm wide microbeams than in the case of the 200 µm wide microbeams which explains the normal tissue damages observed.

Microbeams width

Serduc et al. [2009] irradiated both healthy rats and rats implanted with 9L gliosarcoma for different microbeam widths (25, 50 and 75 µm) and a constant beam spacing (211 µm). The peak doses were calculated in order to produce the same valley dose (18 Gy) for each configuration. The 50 µm microbeam width was found as the best compromise between tumor control and normal tissue toxicity. More recently Griffin et al. [2012] investigated the effect of the beam width (50 and 500 µm), beam spacing (200 and 2,000 µm) and peak dose (75 or 150 Gy at 0.5 mm depth) on the tumor control in the case of mouse mammary carcinomas. The authors obtained the best tumor control in the case of the highest peak dose and smallest beam width and spacing. For this configuration, the valley dose was equal to 7.5 Gy at 10 mm depth. In the case of a human U251 glioma cells, Uyama et al. [2011] also observed a better tumor growth suppression with narrow microbeams (20 µm width, 100 µm c-t-c) rather than with wide microbeams (100 µm width, 500 µm c-t-c).
1.2. Microbeam Radiation Therapy

Results from the pre-clinical studies indicate that for a constant ratio between the beam width and the beam spacing, the smallest beam width and spacing is more efficient in tumor control probability. Additionally, in MRT, narrow microbeams are desirable because a larger dose would be tolerated by the normal tissue and a higher peak dose could be delivered to the tumor. Reducing the microbeam spacing would have the advantage of delivering a higher valley dose and increase the direct killing of the tumour cells but such dose prescriptions are limited by the normal tissue tolerance. The valley width thus plays an important role: enlarging the valley width would lower the valley dose and increase the proportion of healthy tissue receiving low doses which is expected to be instrumental for the repair mechanisms.

Multiple irradiation ports

In order to enhance the dose delivered in the tumor while ensuring normal tissue sparing, irradiation configurations using multiple irradiation ports are currently explored. The cross-firing technique consists in the delivery of two perpendicular arrays of microbeams. Usually, this method is performed using two orthogonal irradiation ports as displayed in Figure 1.7 in order to maximise the valley dose in the tumor volume while ensuring the normal tissue sparing in front and behind the target volume.

![Cross-firing technique](image)

Figure 1.7: Cross-firing technique. Reprinted from Serduc et al. 2008a.
1.2. Microbeam Radiation Therapy

The cross-fire irradiation techniques have been applied since the early stage of MRT pre-clinical work. In 1998, Laissue et al. treated 9L gliosarcoma bearing rats with either a single array of microbeams or two orthogonal arrays of microbeams. Both configurations were delivering a peak dose of 625 Gy and the highest survival time was obtained for the rats treated with the two orthogonal arrays (median survival time of 139 days against 24 days in the case of the single array) [Laissue et al., 1998]. Dilmanian et al. [2003] compared the efficiency of MRT cross-fire irradiation, MRT uni-directional irradiation and broadbeam irradiation (delivered in a single fraction) for the treatment of murine EMT-6 mammary carcinoma implanted in the hind leg of mice. When compared to the MRT uni-directional irradiation, the cross-fire technique gave the best compromise between tumor control and toxicity. Their results also suggested a higher therapeutic index of the cross-fire technique than the broadbeam irradiation. Miura et al. [2006] evaluated the efficiency of the cross-firing MRT technique to treat aggressive murine SCCVII squamous cell carcinomas implanted in mouse leg. A better palliation of the carcinoma was achieved when using MRT rather than a broadbeam irradiation performed with a 100 kVp X-ray beam. Since then, the MRT cross-fire technique has been used in many pre-clinical studies [Bouchet et al., 2012, 2013, 2010; Le Duc et al., 2011; Schültke et al., 2008; Serduc et al., 2009].

The interspersed geometry is another irradiation technique using two arrays of microbeams in such way that the spacing between the microbeams can be divided by a factor of 2 in the tumor (see Figure 1.8). The aim here is to keep a low valley dose in the normal tissue surrounding the tumor while increasing it in the tumor in order to enhance the toxicity [Bräuer-Krisch et al., 2005b]. Finally, Serduc et al. [2010b] developed another irradiation modality where 4 microbeam arrays, each composed of 52 µm wide microbeam spaced 200 µm c-t-c, are interlaced with a 45° angle in order to deliver a homogeneous dose distribution in a
1.2. Microbeam Radiation Therapy

Figure 1.8: Illustration of the interspersed irradiation technique. Reprinted from Bräuer-Krisch et al. [2005b].

target volume (see Figure 1.9).

Figure 1.9: Interlaced irradiation technique from Serduc et al. [2010a]. (A-C) Four arrays of microbeams are interlaced in order to create a region where the dose deposition is homogeneous. (D) Gafchromic film exposed under interlaced irradiation geometry. The red line represents the region where the dose is homogeneous and the black line, a region that has only been exposed to one array of microbeams. (E) Comparison of the dose profile obtained either with an unidirectional array of microbeams (black line) or with the interlaced geometry (red line).

The development of new irradiation geometries has optimised the dose delivery and has contributed to increase the median survival times of tumor bearing animals. Another way to enhance the MRT therapeutic effect is to couple the technique with
Combination of MRT with adjuvant therapies

One of the first combinations of MRT with an adjuvant therapy was performed by Smilowitz et al. [2006] who coupled unidirectional MRT irradiation with gene-mediated immunoprophylaxis. In addition to the MRT treatment, 9L gliosarcoma bearing rats received successive subcutaneous inoculations of radiation-disabled 9L gliosarcoma cells transfected with the GMCSF gene (Granulocyte Macrophage Colony Stimulating Factor). One year after therapy, 44% of the rats that received the treatment coupling MRT and gene-mediated immunoprophylaxis were still alive compared to 20% for those that only received the MRT treatment. In 2008, Schültke et al. used the MRT cross-fire technique to treat rats that have been implanted with F98 or C6 gliomas. MRT treatment was delivered alone or coupled with buthionine-SR-sulfoximine (BSO) in order to increase the radiosensitivity of the tumor. When compared to MRT treatment delivered alone, an increase in survival time was obtained for treatment coupling MRT to BSO injections for the F98 gliomas. However, the administration of BSO was followed by memory dysfunctions which improved with time for the tumor bearing animals. The memory dysfunction was much less for the animals that only undertook MRT irradiation Schültke et al., 2008. Bouchet et al. 2012 coupled the MRT cross-fire irradiation with the JAI-51 chemotherapeutic agent for the treatment of 9L gliosarcoma bearing rats. The JAI-51 chemotherapeutic agent was either administered alone or just after the MRT irradiation. The injection was repeated three times per week for a maximum time of 20 weeks after the irradiation. The JAI-51 chemotherapeutic agent delivered alone did not increase the rats survival when compared to the control rats. The median survival time with MRT delivered alone was of 35.5 days after tumor implantation and reached 48 days in the case of MRT coupled
with the injections of the chemotherapy agent. This can be explained by the fact that the 9L glioma has a high permeability limiting the perfusion of the JAI-51 inside the tumor. Delivery of the MRT irradiation previous the JAI-51 injections, contributed to the decrease of the tumor permeability which then enabled the chemotherapy agent to perfuse the tumor resulting in the higher therapeutic effect observed.

[Régnard et al. 2008a] demonstrated the potential advantage of combining the MRT treatment with intracranial injections of gadolinium (Gd). Indeed, due to its high atomic number ($Z = 64$), the Gd is used as a dose enhancer. Rats bearing 9L glioma have thus been treated either with MRT or with MRT combined to intracranial injection of Gd. For the rats receiving only the MRT treatment, an increase lifespan\footnote{Relative difference of the median survival times obtained for the treated and untreated group (relative to the untreated group)} of 60.5% was observed when compared to untreated tumor bearing rats. In the case of the rats that received the MRT treatment combined to intracranial Gd injections the increase life span reached 131.6%. The principle of using a high Z element to enhance the dose deposition in the tumor has been improved by the use of nanoparticles. Indeed, nanoparticles are large enough to prevent their extravasation from normal vessel and small enough to passively accumulate in the tumor. Gd nanoparticles intravenous injections have been coupled to MRT irradiation (delivered either 5 or 20 minutes after the injection) using the cross-fire geometry for the treatment 9L gliosarcoma implanted in rats [Le Duc et al. 2011]. For animals being irradiated 20 minutes after the Gd nanoparticles injection, the median survival time reached 90 days whereas it is was of 34 days for MRT performed 5 minutes after the injection, 47 days for the MRT treatment performed alone and of 19 days for the untreated animals. The survival curves obtained for this study are displayed in Figure 1.10.

Another advantage of high Z material is that they can be clearly distinguished from tissue matter on X-ray or MRI imaging modalities which could lead to the possibility...
Figure 1.10: Survival curves obtained for untreated rats (black dashed), rats treated only with MRT (blue), rats irradiated with MRT 5 minutes (red) and 20 minutes (green) after injection of Gd-based nanoparticles. Exctrated from [Le Duc et al., 2011].

of performing image guided MRT in the future.

Pre-clinical trials showed that the MRT therapeutic effect could be enhanced using different irradiations geometries or the concomitant use of drugs. However the mechanisms that lead to the normal tissue sparing and of the differential effect between the normal and tumor tissue are still not fully understood and are the purpose of ongoing pre-clinical studies.

Normal tissue tolerance

Several authors made the hypothesis that the extraordinary radioresistance of the healthy tissue to MRT irradiation was due to a rapid repair of the microscopic lesions enabled by the migration of the minimally irradiated cells from the valley regions to the peak regions [Blattmann et al., 2005; Laissue et al., 1998; Slatkin et al., 1995, 1992; Zeman et al., 1961]. Blattmann et al., 2005 suggested that the rapid repair of the irradiated normal tissue could also be attributable to two other mechanisms: an increase in the neighboring cells surface (endothelial stitching) or to a local settlement
of circulating stem cells. They also mentioned that the fast repair process could be a combination of the three different mechanisms.

In 2006, a study of the early effect of the microbeam irradiation on the vascular permeability and volume was carried out on normal mice brain [Serduc et al., 2006]. For skin entrance doses of either 312 or 1,000 Gy, the authors did not observe any blood volume nor vascular density change in the normal tissue. In another study carried under the same conditions, the presence of a minor and transient cellular edema in the case of the 312 Gy exposure was observed one day after irradiation. In the case of the 1,000 Gy exposure, the results suggested the presence of cellular and vasogenic edema. Both edema resorbed within a week after exposure which may attest of the normal tissue sparing in MRT [Serduc et al., 2008b]. Van Der Sanden et al. [2010] irradiated the left hind leg of normal mice with an array of 26 microbeams (50 µm width spaced by 400 µm) and investigated the influence of MRT irradiation on arteries for two different peak doses (312 and 2,000 Gy). Despite a slight modification of the walls of the arteries in the path of the microbeams, no occlusion was observed nor damage in the valley region.

The preservation of the vascular network might explain the extraordinary radiore sistance of the normal tissue to MRT irradiation. However, as mentioned before, normal brain sparing is only ensured for a valley dose remaining below the normal tissue tolerance [Dilmanian et al., 2002].

MRT differential effect and mechanisms

In 2011, Sabatasso et al. [2011] highlighted the differential effect that exists between the mature and immature vascular network. They studied the response of chick chorioallantoic membrane (CAM) to a single array of microbeams (25 µm width, 200 µm c-t-c distance) at different stages of maturation and observed that more damage was
induced in the case of the immature CAM. Consequently, the results implied that an immature vasculature, like the tumor one, would be less capable of repairing the lesions induced by MRT irradiation than a mature vasculature like the normal tissue.

In order to understand the mechanisms responsible for the differential effect of MRT between the tumor and the normal tissue, Serduc et al. [2008a] irradiated nude mice brain implanted with 9L gliosarcoma with two orthogonal arrays each made up of 28 microbeams (25 µm width, 211 µm spacing and 500 Gy peak entrance dose) and studied the short-term response of the tumor and its vasculature. As the authors did not observe significant change in both the apparent diffusion coefficient and in the blood volume on the magnetic resonance images, they stated that the increased survival time observed for the MRT irradiated rats bearing 9L gliomas was mostly due to a cytoreduction (i.e. a reduction of the tumor volume) rather than an early effect of the radiations on the blood vessels. Bouchet et al. [2010] investigated the effect of MRT on the normal and tumor tissue. Rats implanted with the 9L tumor model in the brain were irradiated using two orthogonal arrays of microbeams intersecting in the tumor region. In the tumor, a loss of endothelial cells was observed and followed by a decrease of the blood volume and vessel diameter. No damage was reported in the normal tissue thus demonstrating the differential effect of the cross-fire MRT irradiation geometry on tumor and normal tissue. In 2013, Bouchet et al. studied the effect of cross-fire MRT irradiation on the oxygenation of 9L gliosarcomas implanted in rats brain. A significant decrease of oxygenation was observed in the tumor leading to hypoxia. On the contrary, the normal tissue exposed to MRT remained perfused enough to avoid hypoxia [Bouchet et al., 2013].

In 2014, Bouchet et al. tested the expression of 28,000 transcripts before and after unidirectional MRT irradiation. In the tumor, the authors observed changes in the expression of some genes after MRT which were either in favor or disfavor of the
tumor palliation [Bouchet et al., 2014]. The identification of these genes could allow the development of molecular therapy enhancing or reducing these genes expression in order to further improve the MRT therapeutic index.

Pre-clinical studies have demonstrated the existence of a differential effect in MRT between the normal and tumor tissue vasculature and pointed out the influence of vascular network maturity on the tissue damage. However, differential effects have also been observed at the cellular and molecular level and could partially explain the mechanisms responsible for the MRT differential effect.

1.3 Dosimetry

1.3.1 Fundamentals

Reference dosimetry consists in the determination of the absorbed dose to water under reference conditions. The notion of absorbed dose has been introduced in order to predict the effect of radiations on tissue. The absorbed dose corresponds to the quantity of energy deposited by charged particles per unit of mass:

\[ D = \frac{\Delta E}{\Delta m} \]  

The dose SI unit is the gray (Gy) which corresponds to one joule per kilogram (J.kg\(^{-1}\)). As photons are uncharged particles, a photon source is an indirect radiation source. The dose is actually deposited by secondary electrons produced by the interaction of the primary photons with the matter. Once those electrons are created they will lose their energy via inelastic collisions and contribute to the dose. There are three main ways for the primary photons to interact with matter: photoelectric effect, Compton scattering and pair production.

For the photoelectric effect, the incoming photon transfers all its energy to an
electron within the medium of interest. In the case of electrons bound to the atoms making up the medium, if the transferred energy is higher than the binding energy of the electron, the electron is ejected from the bound shell and becomes a photo-electron with kinetic energy \( E_{e^-} \) equal to the energy transferred by the photon \( (h\nu, \text{ with } h \text{ the Planck’s constant and } \nu \text{ the frequency of electromagnetic radiation}) \) minus the binding energy \( (E_b) \) (see equation [1.2]).

\[
E_{e^-} = h\nu - E_b
\]  

(1.2)

In the case of Compton scattering, the incoming photon is scattered from its original direction by an angle \( \theta \) and transfers part of its energy to the electron. The electron thus acquires kinetic energy and is referred to as a recoil electron. The energy of the deflected photon is expressed by:

\[
h\nu' = \frac{h\nu}{1 + \frac{h\nu}{m_0c^2}(1 - \cos \theta)}
\]  

(1.3)

with \( m_0c^2 \) the mass energy of an electron at rest (0.511 MeV).

The pair production process occurs only if the incoming photon energy is higher than twice the rest mass of an electron (1.02 MeV). The photon energy is used to produce an electron-positron pair and the energy is equally shared between the two created particles. The positron will eventually go through an annihilation process with another electron. This will result in the creation of two annihilation photons emitted in two opposite directions (at 180° from each other) if the positron is at rest when it annihilates.

The predominance of one interaction process to another depends on the energy of the incoming photon and on the material atomic number \( (Z) \) (see Figure [1.11]). The photoelectric effect is predominant for low energies and is highly dependent of the \( Z \) number of the material: the probability of observing the photoelectric effect is
proportional to $Z^N$ where $N$ is between 4 and 5. For the Compton scattering, this probability is linear with $Z$. For the pair production interaction the threshold energy of the incoming photon is 1.02 MeV and the probability increases with $Z^2$ and the photon energy.

Due to the photons energy range encountered in MRT, the photons interact with matter primarily through the photoelectric effect and Compton effect.

1.3.2 Dosimetry of homogeneous synchrotron beam dedicated to medical applications

Reference dosimetry is part of the QA to be performed in radiotherapy in order to ensure a correct dose delivery. Instructions are provided by the IAEA TRS 398 protocol [IAEA, 2000] for different sources and beam qualities. However there is currently no code of practice available for radiation therapy modalities using synchrotron sources.

In 2011, Prezado et al. published a dosimetry protocol dedicated to Synchrotron Stereotactic Radiation Therapy (SSRT) in the context of the upcoming clinical trials.
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at the ESRF [Prezado et al., 2011a]. SSRT is an irradiation modality dedicated to the treatment of brain tumors. The technique involves injection of an iodine contrast agent in order to enhance the dose deposition in the tumor followed by a stereotactic irradiation with a monochromatic synchrotron X-ray beam tuned to 80 keV [Adam et al., 2008; Boudou et al., 2005]. The dosimetry protocol developed by Prezado et al. remains as close as possible to the TRS 398 guidelines for medium energy X-rays. However a few reference conditions had to be adapted to the specificities of the synchrotron source. In SSRT, the beam dimensions at the patient stage are limited to 3 mm in height and 150 mm in width. In order to perform irradiation at a clinically relevant height, the patient is scanned through the beam at a constant speed. Prezado et al. demonstrated in their protocol the equivalence of the scanning technique to an uniform irradiation field and showed that the dose measured by an ionisation chamber (IC) centered into the irradiation field (as presented in Figure 1.12) was equal to:

\[ D = \frac{z_{\text{beam}} \cdot \dot{D}}{v_z} = \frac{z_{\text{beam}} \cdot \dot{D}_{\text{scaled}}}{I \cdot v_z} \]  

(1.4)

Where \( D \) is the measured absorbed dose (Gy), \( \dot{D} \) the dose rate (Gy.s\(^{-1}\)) , \( z_{\text{beam}} \) the beam height (mm), \( v \) the scan speed (mm.s\(^{-1}\)), \( I \) the current in the synchrotron storage ring (SR) and \( \dot{D}_{\text{scaled}} \) the dose rate scaled by the SR current (Gy.s\(^{-1}\).mA\(^{-1}\)). \( \dot{D}_{\text{scaled}} \) can then be deduced from the measured dose and allows the determination of the scan speed to be used in order to deliver the correct dose during the irradiation. Indeed, as the SR current is decaying at the ESRF, the scan speed needs to be adapted depending on the desired dose and the current in the machine at the time of the irradiation.

As recommended by the TRS 398 code of practice, the absolute dosimetry in SSRT is performed using a cylindrical ionisation chamber (IC) (Semiﬂex 31010, PTW). Once the uncertainties relative to the IC positioning, calibration factor and correction factors are taken into account, the global uncertainty on the measured dose is as good as 2%
1.3. Dosimetry

Figure 1.12: Schematic illustration of the dosimetry configuration in SSRT. Extracted from [Prezado et al., 2011a].

under the SSRT reference conditions.

At the ESRF, the synchrotron beam dimensions are more limited in MRT as they can only reach a maximum of 2.5 mm in height and 41 mm in width. As in SSRT, a scanning method is employed to reach larger field sizes and the dose given by equation [1.4] is measured with an IC. The Pinpoint 31014 (PTW) IC has been chosen as reference dosimeter for MRT due to its smaller sensitive volume (0.015 cm$^3$) intended to minimize the saturation effect when performing measurements at very high dose rates. Indeed the dose rate in MRT can reach 20 kGy.s$^{-1}$ while the average dose rate in SSRT is around 1 Gy.s$^{-1}$. This is much higher than the dose rates encountered in conventional radiation therapy which remain below 2400 MU.min$^{-1}$ (i.e. $\sim$24 Gy.min$^{-1}$ depending on the monitor chambers calibration). In MRT, a significant lack in collection efficiency is the main challenge to establish an absolute dosimetry protocol and to evaluate the uncertainty on the measured dose.

In order to determine the absolute dose rate at the Imaging and Medical Beamline (IMBL) at the Australian Synchrotron, graphite calorimetry was performed in collaboration with ARPANSA (Australian Radiation Protection And Nuclear Safety Agency) [Harty et al., 2014]. Graphite calorimetry relies on the measurement of the temperature increase induced by the radiations which is directly proportional to the absorbed dose. The ARPANSA graphite calorimeter consists of a core suspended by microbeads inside a 150 $\times$ 150 mm$^2$ piece of graphite (see Figure 1.13). The core consists in a
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disc of graphite including two thermistors. In order to thermally insulate the system from ambient temperature, the graphite assembly is surrounded by 35 mm of polystyrene and thin aluminised Mylar sheet. Thermistors are calibrated in such a way that when performing an irradiation, the change in the measured resistance can be directly converted into a change in temperature. An example of the temperature changes observed at IMBL after (a) one single or (b) multiple exposures of 10 sec is displayed in Figure 1.14.

Figure 1.13: Schematic representation of the ARPANSA graphite calorimeter used for the absolute dose measurements at IMBL. Extracted from [Harty et al., 2014].

The change in temperature $\Delta T$ is then converted into dose rate $\dot{D}$ using the following equation:

$$\dot{D} = \frac{\Delta T c_g}{t} \cdot \frac{A_{\text{core}}}{A_{\text{beam}}}$$  \hspace{1cm} (1.5)

where $c_g$ is the heat capacity of the graphite core, $t$ the irradiation time, $A_{\text{beam}}$ the cross-sectional area of the beam, and $A_{\text{core}}$ the cross-sectional area of the core. Conversion factors calculated by Monte Carlo (MC) simulations are then applied in order to transpose the absorbed dose in the graphite into absorbed dose to water. Measurements were performed at three different depths, two filtering conditions and compared
to the results obtained with a free-air chamber. Measurements performed in depths agreed within 1% while those performed at the surface were within an agreement of 3%. However, these measurements were performed at dose rates much lower (maximum of 50 Gy.s\(^{-1}\)) than those commonly used in MRT. This was a necessary condition in order to avoid the saturation of the free-air chamber. Experiment under MRT dose rate conditions are thus foreseen in the near future at IMBL.
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1.3.3 Microbeam dosimetry

In order to switch from the broadbeam to the microbeams irradiation configuration, a multislit collimator (MSC) is inserted in the synchrotron beam path. Figure 1.15 displays an example of a lateral dose profile at 3 mm depth in water (obtained by the superposition of a single microbeam calculated by Monte Carlo (MC) simulation [Bräuer-Krisch et al., 2005a]).

\[ v_z = \frac{z_{\text{beam}}}{D_{3\text{mm}}} \cdot \dot{D}_{\text{scaled}} \cdot I \cdot f \]  

(1.6)

\( v_z \) is the scan speed of the goniometer, \( z_{\text{beam}} \) the beam height, \( D_{3\text{mm}} \) the desired peak entrance dose at 3 mm depth, \( \dot{D}_{\text{scaled}} \) the dose rate scaled to the beam current (Gy.mA\(^{-1}\).s\(^{-1}\)) obtained from reference dosimetry and \( I \) the current in the machine at the time of the irradiation. \( f \) is the output factor that scales the measured dose.
rate scaled to the beam current to the desired peak entrance dose. This factor takes into account the microbeam width, the field size, the depth and the contribution of the scattering coming laterally from the peaks depending of the c-t-c distance.

In order to predict the peak, valley and PVDR for a MRT irradiation, MC simulations are required and need to be experimentally benchmarked.

Monte Carlo based microbeam dosimetry studies

Many authors have investigated the dose distribution in MRT using MC simulation methods [Orion et al., 2000; Siegbahn et al., 2005, 2006; Slatkin et al., 1992; Stepanek et al., 2000]. Different codes have been investigated such as Geant4 [Bartzsch et al., 2014; Cornelius et al., 2014; Stepanek et al., 2000], EGS4 [De Felici et al., 2007; Orion et al., 2000], EGS5 [Hugtenburg et al., 2010] and PENELOPE [Martínez-Rovira et al., 2012; Siegbahn et al., 2005, 2006]. De Felici et al. [2008] compared five MC codes (EGS4, PENELOPE, GEANT4, EGSnrc, and MCNPX) under identical irradiation conditions and scoring geometries. The authors stated that for simple geometries and material composition, the results given by the different codes agreed together within ± 20%. The differences between the different codes were observed in the regions outside the primary beam and were therefore attributed to the electron transport modeling used in the MC code. The MCNPX code showed the highest disagreement.

Siegbahn et al. [2006] showed that the deposited dose in MRT was mainly coming from the Compton scattering and that the valley dose was due to the lower energy photons scattered out of the primary beams. Consequently when increasing the c-t-c distance, the PVDR increases as the valley dose becomes lower due to a less important contribution of the scattered photons. From their MC calculations, Siegbahn et al. showed that the valley dose was produced by two different types of scattering. Nearby the microbeam, the main contribution to the valley dose is due to the photo-
1.3. Dosimetry

electrons scattered from the primary microbeam field while at larger distances from the microbeam, the valley dose is mainly coming from Compton scattered photons and electrons (see Figure 1.16).

Figure 1.16: Effect of different interaction processes on the lateral dose deposition of a 1 cm × 25 µm microbeam (obtained by MC calculation, by scoring the energy deposition between 7 and 8 cm depth). Diagram extracted from Siegbahn et al. [2006].

Figure 1.17: Peak and valley doses variation with depth in the center of a planar microbeam array for two different microbeam spacings (100 and 200 µm) and calculated for a 3 × 3 cm² array of 25 µm wide microbeams. Reprinted from Siegbahn et al. [2006].

Siegbahn et al. [2006] also simulated the variation of peak and valley doses with depth in a water phantom for a 3 × 3 cm² array of 25 µm wide microbeams and two different microbeam spacings (100 and 200 µm). The results (presented in Figure 1.17) are normalised to the maximum peak dose for the 100 µm spacing. One can observe a dose buildup in the valley which is due to the scattered photons. In the case of the peak dose, the build-up is reached before 1 mm depth and is not visible on the graph. Finally, Siegbahn et al. demonstrated the relevance of Output Factors (OF) as the study showed a dose decrease of 14% within a single 25 µm wide microbeam compared to a 75 µm wide microbeam (dose calculated within a 1 cm slice located at 7-8 cm depth in water for a 1 cm high beam).

The ESRF’s ID17 biomedical beamline has been modeled by Martínez-Rovira et al. [2012] using the PENELOPE MC code and includes the current instrumentation for
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the pre-clinical beam conditions from the wiggler source down to the sample to be irradiated. The state variables of the simulated photons are stored into a phase-space file (PSF) just before the MSC location. The PSF was generated for three different field sizes (1 cm × 1 cm, 2 cm × 2 cm and 3 cm × 3 cm) and used as input to generate the photon beam model. PVDRs have then been calculated for these three field sizes and for the default microbeam width and spacing on ID17 (50 µm width, 400 µm c-t-c). The PSF produced by Martínez-Rovira et al. [2012] was the basis for the development of the MRT treatment planning system (TPS).

The TPS is a software that takes as input the patient medical images (obtained from computed tomography, MRI or positron emission tomography) and simulates the treatment using radiation transport simulations. TPS thus allows the visualisation of the irradiation geometry and the relative dose deposition. TPS using convolution-based algorithms provides much faster computation times than TPS based on MC simulations. For conventional radiation therapy using medium energy X-rays, TPS based on convolution algorithms are usually not able to provide a sufficient accuracy. Indeed, in the case of medium energy photons, a greater focus needs to be dedicated to the photoelectric dose deposition and to the scattered photons energy transport. In order to meet these requirements in the specific case of MRT, Bartzsch and Oelfke [2013] proposed a new method based on analytical dose kernels. The accuracy obtained on the dose calculation using this approach was comparable to MC simulations. This algorithm was implanted in the MRT TPS and can provide a treatment plan within a few minutes while several days are required when running MC simulations. Bartzsch et al. [2014] then developed a simplified version of the MC code allowing faster dose calculations and more accurate dose determination. The main parameters influencing the dose distribution in MRT were first identified by analysing the information of the phase space developed by Martínez-Rovira et al. [2012]. They found that the
important features to consider were the flux profile across the broadbeam, the insufficient absorption of the MSC material, and the geometrical change of the beam width due to inclined incidence outside the beam axis. Thus they developed a source model of parallel microbeams and included the appropriate corrections required for the features identified. The PVDRs obtained with the so-called semiadjoint MC code at different depths and for two different field sizes were compared to those published by Martínez-Rovira et al. [2012] and a good agreement was observed (see Figure 1.18).

As one can see in Figure 1.18, the PVDR first decreases rapidly with depth. This is due the build-up observed in the valley dose. Once the valley dose starts decreasing, the PVDR becomes almost flat since the valley dose decreases at almost the same rate than the peak dose. Bartzsch et al. [2014] also investigated the effect of the synchrotron radiation polarisation on the delivered dose for broadbeam geometry. They showed that the polarisation influence was the most important in the off-field region where
they observed dose differences up to 40%. Nonetheless, the beam polarisation does not have an important impact for MRT dose calculations and could even be neglected for PVDRs and valley dose calculations. [Cornelius et al., 2014] developed a GEANT4 MC model of the ID17 beamline in order to be used for an independent verification of the TPS. Moreover, the code is adapted for the dose calculations under the veterinary clinical trials conditions. The veterinary conditions differ from the pre-clinical conditions by the introduction of a Krypton gas filter and additional monitoring chambers (the instrumentation relative to pre-clinical and veterinary beam configurations will be detailed in section 2.2). In this paper [Cornelius et al., 2014] also assessed the issue of the synchrotron beam polarisation. They showed that ignoring the resulting asymmetry in the out-of-field dose profiles could lead to errors of up to 150% and therefore stated that the effect of beam polarisation on out of field doses should be included in the TPS.

Both [Bartzsch et al., 2014] and [Cornelius et al., 2014] mentioned the lack of more precise experimental dosimetry data. [Bartzsch et al.] stated that due to the limitations of current experimental techniques it was still not feasible to conclude on the influence of the possible photon scattering from the inside surfaces of the MSC on the dose distribution nor on the possible total external reflection that could be induced by photons with an incidence angle below the critical angle. [Cornelius et al.] recommended more precise dosimetry system coupled to refining theoretical models of Compton scattering in order to reach a very high accuracy in the out-of-field dose calculations.

**Experimental dosimetry**

The experimental dosimetry of the microbeams is a challenging task given the requirements that the detector has to satisfy. The detectors should ideally meet the following criteria:
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- Micrometer-scale spatial resolution
- Ability to withstand dose rates up to 20 kGy.s$^{-1}$
- Large dynamic range in order to measure both peak and valley doses with the same accuracy
- Waterproof properties for QA in water
- Real time readout
- Made of water equivalent material

Solid state detectors and in particular MOSFET (metal oxide semiconductor field-effect transistor) were among the first devices investigated for microbeam dosimetry. Indeed MOSFET detectors provide a high spatial resolution because of their very small radiation sensitive area defined by the thickness of the oxide film. The ability of MOSFETs to scan a 200 \( \mu \)m wide microbeam was first demonstrated by Rosenfeld \textit{et al.} [1999] during measurements performed at NSLS, BNL. When used in edge-on, the beam profile obtained with the MOSFET detector was similar to the one obtained with Gafchromic® films [Kaplan \textit{et al.}, 2000; Rosenfeld \textit{et al.}, 1999]. The spatial resolution of the MOSFET was estimated to be 1 \( \mu \)m. Orion \textit{et al.} [2000] compared the relative lateral dose fall-off of a single microbeam measured with a MOSFET detector at BNL to MC simulations and the agreement observed was a very encouraging result at the time of the study (see Figure 1.19).

Vertical profiles of a 30 \( \mu \)m wide microbeam were acquired at the ESRF using the MOSFET detector [Rosenfeld \textit{et al.}, 2001]. The FHWM of the acquired profiles was actually of 35 \( \mu \)m but the analysis of the measurements revealed a misalignment of 5.7°. The MOSFET detector has also been used for the measurement of the absolute
1.3. Dosimetry

Figure 1.19: Microbeam profile obtained experimentally with the MOSFET compared to the absorbed dose simulated using MC calculations. The profiles are compared after normalizing the results to the maximal dose point. Reprinted from Orion et al., 2000.

Peak and valley doses Bräuer-Krisch et al., 2003. The experimental results obtained were approximately 20% less than the MC predicted values.

In 2009, Siegbahn et al. reported PVDRs obtained by MC simulations up to 50% higher than the experimental PVDR measured with a MOSFET detector. These discrepancies were mainly attributed to the energy dependence of the detector Siegbahn et al., 2009. The MOSFET significant energy dependence was also highlighted in the work of Kron et al., 1998, De Felici et al., 2005 and Cheung et al., 2009. Moreover, Rosenfeld et al., 2005 observed a lateral distortion in the microbeam profile measured with the MOSFET detector. This distortion was attributed to a lateral dose enhancement induced by the interaction of the microbeam with substrate adjacent to one side of the sensitive volume. Finally the major drawback of the MOSFET detector relies on its low tolerance to high dose rates. Indeed, Siegbahn et al., 2009 observed that after an approximate accumulated absorbed dose of 1000 Gy, the MOSFET was saturated.
and had to be replaced. This was a major limitation as it prevents the detector from being used under the MRT standard operation mode at the ESRF.

PVDR have also been measured at the ESRF using 2D LiF:Mg,Cu,P (MCP-N)-based thermoluminescence (TL) detectors. Three different beam widths (25, 50 and 75 µm) and two c-t-c distances (200 and 400 µm) were considered. The measured PVDRs were between 11% and 17% smaller than MC predicted values [Ptaszkiewicz et al., 2008].

Very high resolution measurements have been performed at the ESRF using Fluorescence Nuclear Track Detectors based on Al2O3:C,Mg single crystals detectors [Bartz et al., 2011]. Microbeams profiles have been acquired for peak doses of 3, 10, 30, 50 and 100 Gy. For peak doses above 50 Gy, the detector was saturated and the dose was under-estimated. The authors also observed an underestimation of the measured peak dose at 3 and 10 Gy. This was attributed to the combined uncertainty relative to the background substraction and the fluctuation of the detector sensitivity. One major advantage of this detector is that it allows 3D representation of the dose as shown in Figure 1.20. FNTDs could be an interesting tool for the TPS benchmarking once the uncertainties of measurement could be reduced to 5%.

Gafchromic® films currently are the most widely used detectors for microbeam dosimetry in MRT. Indeed, these detectors have a high spatial resolution and do not require the intervention of an external lab or company: storage, calibration and reading can be realised on the beamline. Moreover, Gafchromic® films dedicated to high dose measurements have a dynamic range large enough to obtain the calibration curve for MRT applications (i.e. optical density of films as a function of delivered dose). Indeed, HD-810 and HD-V2 films from ISP (Nuclear Associates) are usually used over a dose range from approximately 10 to 400 Gy and from 10 Gy to 1.0 kGy respectively. Gafchromic® film have thus been used in numerous studies for the determination of the
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Figure 1.20: 3D distribution of fluorescence from an FNTD irradiated with 10 Gy using an array of microbeams. Reprinted from Bartz et al. [2011].

peak dose, valley dose and PVDRs [Bartzsch et al. 2015, Bräuer-Krisch et al. 2009b, Crosbie et al. 2008, Martínez-Rovira et al. 2012, Nariyama et al. 2009]. However, Gafchromic® films dynamic range does not allow to read both peak and valley dose on the same film; either the peak dose saturates the films or the valley dose is too low to be read on Gafchromic® films dedicated to high doses measurements. Therefore, for MRT applications, it is recommended to irradiate two films separately: one for the peak dose and the other one for the valley dose determination in order to remain in the most linear range of the calibration films. To measure the valley dose, the user can either use films dedicated to a lower dose range (EBT films for example) or increase the peak dose by a known factor in order to be able to observe the valley dose on a Gafchromic® film dedicated to high dose measurements (such as HD-810 or HD-V2).

In the study from Crosbie et al. 2008, the authors chose to use films of different sensitivity to measure either peak or valley dose (HD-810 or EBT respectively). An example of a HD-810 films irradiated with an array of 5 microbeams as well as the corresponding relative dose profile are displayed in Figure 1.21. Crosbie et al. compared the experimental PVDRs values obtained to MC results published by different authors
1.3. Dosimetry

Bräuer-Krisch et al. 2005b; De Felici et al. 2005; Siegbahn et al. 2006; Slatkin et al. 1992; Stepanek et al. 2000 who considered the same microbeam width and spacing (25 µm and 200 µm respectively). The PVDRs values reported by Crosbie et al. were higher than those obtained in the different MC studies. Indeed, Crosbie et al. obtained a maximum PVDR of 144 ± 29% at 1 mm depth in water and a minimum PVDR of 60 ± 29% at 50 mm depth while MC studies from Slatkin et al., Stepanek et al., De Felici et al. and Siegbahn et al. report PVDRs closer to 30. The discrepancies observed were attributed to the fact that, in the MC studies considered, the full beam line instrumentation was not included in the simulations especially the MSC.

Figure 1.21: Top: scan of a HD-810 film irradiated with a 5 microbeam array and an entrance peak dose of 160 Gy. Bottom: corresponding relative dose profile. Extracted from Crosbie et al. 2008

In 2009, Nariyama et al. 2009 used HD-810 Gafchromic® films and obtained a good agreement of the measured peak dose with MC simulation while the measured valley was higher than theoretical values. Bräuer-Krisch et al. 2009b compared the
1.3. Dosimetry

valley dose measured using HD-810 Gafchromic® films and obtained a good agreement with the MC simulations within the uncertainty bars.

PVDRs values obtained from the complete simulation of the ID17 beamline performed by Martínez-Rovira et al. [2012] were compared to HD-810 Gafchromic® measurements and a good agreement was obtained.

Bartzsch et al. [2015] investigated the feasibility of performing radiochromic film dosimetry using a microscope to validate peak and valley doses in MRT. In this study, the authors compare the performance of HD-810 and HD-V2 films. Indeed, until now the HD-810 films exhibited the best performance in terms of sensitivity and resolution in MRT but these films are not available any more and have been substituted by HD-V2 films. Peak and valley doses measurements were performed at the ESRF using both HD-810 and HD-V2 films in a solid water phantom for a 20×20 mm² microbeam field. The microbeam width and the c-t-c distance were 50 µm and 400 µm respectively. Results are presented in Figure 1.22 and are compared to MC calculations.

The peak and valley doses measured with the films agree with MC calculations within the uncertainties. Bartzsch et al. reported that the peak dose was determined with an accuracy better than 5% and the valley dose with an accuracy between 10% and 15%. The uncertainties are related to the statistical noise, the film inhomogeneities, and the calibration errors. Despite the good agreement obtained with the MC calculations, a systematic difference between HD-V2 and HD-810 films was observed: valley doses were higher on HD-810 films and peak doses were higher on HD-V2 films. This difference was attributed to the different film sensitivities at low photon energies. Indeed, the performance evaluation of the films showed that the HD-810 films exhibit a higher energy dependence at low photon energies than the HD-V2. However, a higher statistical noise was observed in the case of the HD-V2 films. The authors concluded that both films could be used for dosimetry in MRT.
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Figure 1.22: A. MRT dose profile obtained using Gafchromic® films. In order to remain within the films dynamic range a combination of two measurements was used: the peak regions were measured with a low peak entrance dose and the valley regions with a high peak entrance dose. B. Peak dose as a function of depth in the solid water phantom. C. Valley dose as a function of depth in the solid water phantom. D. Resulting PVDRs. Figures have been extracted from Bartzsch *et al.* [2015].

Gafchromic® films are an interesting tool for MRT applications but still exhibits some limitations. As mentioned before, films dedicated to high dose measurements have a logarithmic response with dose and a limited dynamic range that prevents the reading of peak and valley signal on the same film. Moreover, according to a Task Group report (TG55) by the American Association of Medical Physicists (AAPM) one should wait between 24 to 48 hours after the exposure before reading the films. This time is necessary for the polymerisation process to stabilise [Niroomand-Rad *et al.*, 1998] which makes impossible the dosimetry check before a patient treatment. Finally, results obtained with Gafchromic® films have a significant uncertainty. [Crosbie *et al.*]
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reported an error of $\pm 29\%$ on their experimental PVDR. \cite{brauer-kirsch2009b} mentioned an error of 10\% on the absolute dose measurement and the uncertainty on the experimental PVDR obtained by \cite{martinez-rovira2012} are up to 23\% (at 2 $\sigma$). Finally, the sensitivity of Gafchromic® film is not homogeneous over one sheet of film. \cite{brauer-kirsch2010b} reported that this effect affected the dose reading by 8\%. These uncertainties are higher than the maximum uncertainty tolerated on the dose delivery to the planning target volume (PTV) during the treatment (i.e. 5\%) \cite{thwaites2005}. Gafchromic® films can therefore not be used for reference dosimetry but remain one of the best candidate for relative dosimetry and have been successfully used for the TPS benchmarking at the ESRF \cite{bartzsch2014, bartzsch2015}.

\cite{brauer-kirsch2010a} gave a general overview of the main experimental devices investigated for MRT dosimetry and summarised detectors specifications in a table. This table, reprinted from \cite{brauer-kirsch2010a} is displayed in Figure 1.23.

Other techniques have recently emerged and are currently investigated for absolute and relative dosimetry in MRT such as 3D dosimetry using solid radiochromic plastic PRESAGE® \cite{doran2010, doran2013}, thermoluminescent Ge-doped silica fibres \cite{rahman2010}, erasable samarium doped glass (based on the reduction of Sm$^{3+}$ to Sm$^{2+}$ with irradiation) \cite{martin2013, morrell2014, okada2011, okada2014} and optical fibers \cite{belley2015, sporea2014}.

\cite{ackerly2011} demonstrated the proof-of-concept of a dosimetry method based on reference image topography (RIT) combined with particle image velocimetry. This method consists in the mapping of the rate of change of the water refractive index induced by the temperature increase from which the absolute dose deposition can be determined. However, because of the thermal diffusion, the authors reported than in
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Figure 1.23: High resolution detectors tested for MRT applications. Pinpoint 31014 ionisation chamber and alanine are suitable for broadbeam dosimetry only. Reproduced from [Bräuer-Krisch et al., 2010a].

the case of MRT, the measured PVDR would be equal to 76% of its initial value.

Many detectors and techniques have been investigated for the task of microbeam dosimetry. Some of them such as Gafchromic® films gave very satisfying results but are not suitable for pre-treatment QA mostly due to their lack of real-time readout and accuracy. The Centre for Medical Radiation Physics (CMRP, University of Wollongong, Australia) has developed the X-Tream dosimetry system based on a high resolution silicon strip detector (SSD) especially for MRT applications. The characteristics and properties of the detector will be given in Section 4.1.
1.4 Thesis aims and objectives

MRT is a novel radiation therapy technique allowing the preservation of the normal tissue surrounding the tumor because of the spatial fractionnination of the incoming beam into an array of microbeams. Moreover, pre-clinical studies highlighted the detrimental effect of MRT on the tumor tissue and demonstrated the presence of a differential effect between normal and tumor tissue. MRT therapeutic index could be further enhanced by optimising the irradiation parameters and coupling the MRT treatment to adjuvant therapies.

As for conventional radiation therapy modalities, dosimetry QA is required for MRT and this development is a mandatory step to reach the MRT clinical stage. QA includes reference dosimetry in a reference broadbeam, check of the beam geometry and shape, and accurate experimental determination of the peak and valley dose. Many detectors have been investigated for this purpose and led to the conclusion that IC and Gafchromic® films currently are the most accurate detectors for broadbeam and microbeam dosimetry respectively. However, due to high dose rates encountered in MRT, lack in collection efficiency has been observed from the IC leading to significant uncertainties. Moreover, despite their great spatial resolution, Gafchromic® films do not provide sufficient dynamic range to display both peak and valley doses, they are passive detectors and still present too significant reading uncertainties to be used as primary detectors. Within this context, our aim was to improve both broadbeam and microbeam dosimetry and to propose the corresponding quality assurance procedures.

First, the Pinpoint IC lack of collection efficiency was addressed by the development a new method based on the measurement of the IC response at different dose rates. This method provides correction factors to be applied to Pinpoint IC and results in the determination of the absolute dose with an accuracy better than ± 5%. In the context of MRT veterinary clinical trials on ID17, an absorbed dose to water protocol
1.4. Thesis aims and objectives

has been established within this work.

The X-Tream dosimetry system developed by the Centre for Medical Radiation Physics has been characterised at the ESRF. Particular attention was payed to the evaluation of the radiation damage induced in the SSD as well as on the experimental determination of the energy dependence of the device.

The ability of the SSD to perform rapid and efficient Quality Assurance test prior MRT treatment has been evaluated. In-air measurements of 1D profiles of the synchrotron beam used in MRT were performed in order to assess the alignment of the MSC. The SSD was able to detect small misalignments of the MSC which resulted in changes in the valley shape and on the peak and valley signals. The results obtained by the SSD for the MSC alignment were in agreement with the monitoring IC currently used for this purpose on ID17. Moreover, an alignment procedure based on the pink-beam imaging modality available at the ESRF has been developed in order to align the SSD with the MRT beam within half an hour.

The SSD was used at the ESRF under reference conditions in order to determine experimentally the PVDRs and scatter factors. For the first time, an active detector was able to measure both valley and peak signals with the same accuracy leading to a direct determination of the PVDRs in agreement with published results obtained using Gafchromic® films and MC simulations.

Finally, preliminary tests have been performed at the Imaging and Medical Beam-Line (IMBL) at the Australian Synchrotron (AS).
2.1 Synchrotrons

A synchrotron with an electron storage ring provides an extremely brilliant source of X-rays generated by the change in direction of electrons moving nearly at a relativistic speed. If a charged particle is deviated by a magnetic field from its uniform direction, the particle will loose energy in form of electromagnetic radiation. In the case of non-relativist electrons, the radiation field is displayed in an isotropic way around the particle (Figure 2.1 (A)) but in the case of a relativist electron, the radiation field will take the form of a cone and be emitted tangentially to the electron direction (Figure 2.1 (B)).

Figure 2.1: Distribution of the radiation field emitted by a non-relativistic (A) and relativistic electron (B) following a non-uniform direction.
2.1. Synchrotrons

The work presented in this thesis took place at both the ID17 biomedical beamline at the ESRF and at the Imaging and Medical BeamLine (IMBL) at the AS. Both ESRF and AS are 3rd generation synchrotrons. At such facilities the electrons are generated by a Linac (linear accelerator) by heating a cathode in an electron gun. The electrons are then extracted by a strong electric field before being packed into bunches and accelerated to 200 MeV at the ESRF and to 100 MeV at the AS.

In the booster synchrotron, electrons are accelerated to their final energy (6 GeV at the ESRF and 3 GeV at the AS) before being injected into the storage ring. At the ESRF, the booster is only used a few times a day to refill the storage ring. At the AS, the continuous top-up operation mode is used in order to maintain a constant current in the storage ring (200 ± 0.5 mA). This operation mode consists in a periodical injection of small amounts of currents in the storage ring. The ESRF is planning to switch to the top-up operation mode in the near future.

![Main structures of a synchrotron facility.](image)

In the storage ring electrons circulate under vacuum. Quadrupoles and sextupoles are used as focusing magnets in order to maintain the electron beam orbit. Bending magnets (BM) are dipole magnets that are used to force the circular trajectory of the electrons. BMs can also be used to create synchrotron radiation (see Figure 2.3). 3rd generation synchrotrons such as the ESRF and the AS, use insertion devices (ID) (see Figure 2.4) on top of the BMs to produce synchrotron radiation of higher intensity.
2.1. Synchrotrons

Figure 2.3: Representation of a bending magnet.

Figure 2.4: Representation of an insertion device.

There are two types of IDs: the undulators and the wigglers. They consist of two parallel arrays of magnets between which the electron beam is traversing and periodically deflect the electrons' direction. Depending on the ID used, the electron beam will either undulate or wiggle and create a much more brilliant photon source than the one created by a BM. The gap between the array of magnets (wiggler or undulator gap) can be tuned to adjust both the energy spectrum and the fluence of the created photon source. In the case of the ID17 beamline or the IMBL, the photon source is generated by a wiggler. On the ID17 beamline, the photon source is produced by a 15 cm period wiggler (w150) while IMBL uses a superconducting multipole wiggler (SCMPW). The parameters of both insertion devices are given in Table 2.1.

Table 2.1: Comparison of the wiggler IDs used on ID17 and on IMBL for the generation of the photon source.

<table>
<thead>
<tr>
<th>ID parameters</th>
<th>ID17 (w150)</th>
<th>IMBL (SCMPW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic field period (cm)</td>
<td>15</td>
<td>4.8</td>
</tr>
<tr>
<td>Number of period</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Magnetic field strength (T)</td>
<td>1.592</td>
<td>4.17</td>
</tr>
<tr>
<td>Deflection parameter</td>
<td>22.30</td>
<td>18.7</td>
</tr>
<tr>
<td>Critical energy (keV)</td>
<td>38.6</td>
<td>25</td>
</tr>
<tr>
<td>Total Power (kW)</td>
<td>19.3</td>
<td>29.5</td>
</tr>
</tbody>
</table>

In order to compensate for the energy loss caused by the generation of synchrotron radiation, radiofrequency (RF) cavities are used to re-accelerate the electrons in the
2.2 ESRF ID17 Biomedical Beamline

ID17 is the medical beamline of the ESRF. The main areas of research on ID17 are medical imaging, radiation biology and radiation therapy. MRT and SSRT are the two radiation therapy modalities under development at the beamline. SSRT and MRT are performed in two different experimental hutchies; the MRT hutch is located 40 m from the source in the experimental hall while the SSRT hutch is located 150 m from the source in a satellite building (see Figure 2.5).

![Figure 2.5: ID17 beamline. The optical hutch and the MRT experimental hutch are located in the experimental hall. A tunnel connects the MRT hutch to the satellite building where one can find the Monochromator hutch and the SSRT experimental hutch.](image)

In MRT the photon source is produced by a 15 cm period wiggler (w150). When working in the SSRT hutch, a second wiggler (w125) with a 12.5 cm period can be used in order to further increase the monochromatic photon flux.
MRT optical hutch

A representation of the MRT optical hutch is displayed in Figure 2.6.

From the wiggler, the beam travels inside a long stainless steel pipe under vacuum. Different valves and Beryllium (Be) windows (300 to 500 µm thick) provide isolation between the different vacuum sections. At 21.6 m from the source, a diaphragm limits the beam dimensions to 2.4 cm in the horizontal direction and to 0.5 cm in the vertical direction in order to minimise the heat load of the downstream instrumentation devices. The maximum beam dimensions at the sample stage can therefore not exceed $41 \times 2.5 \text{ mm}^2$. The primary slits, made of oxygen free copper blocks, are situated at 29.3 m from the source and define the so-called primary horizontal and vertical gaps. The photon beam is filtered by a combination of different water cooled attenuators in order to remove energies below 30 keV from the energy spectrum. The typical MRT filter combination is as follows: 1.42 mm of C, 0.28 mm + 1.24 mm of Al and 0.35
mm + 0.69 mm of Cu. In the study of Martínez-Rovira et al. [2012] spectra have been obtained by MC simulations at different locations on the ID17 beamline and are presented in Figure 2.7. At the sample/patient location, the energy spectrum ranges from 27 to 600 keV with a mean energy at 99 keV. The fraction of photons with energies higher than 300 keV is equal to 0.1%.

Figure 2.7: Integrated spectrum obtained by MC simulation at different beamline locations. The primary slits aperture was set in order to produce a 2×0.1 cm$^2$ field size at the patient position. The 500 µm aperture of the vertical slit was used. Extracted from Martínez-Rovira et al. [2012].

Due to the extremely high dose rates encountered in MRT, the exposure time must be accurately controlled. A fast shutter has therefore being developed at the ESRF allowing closing times below 5 ms [Renier et al., 2002]. The fast shutter is composed of two 15 mm thick blades made of tungsten carbide (WC), each coupled to an actuator magnet (see Figure 2.8). In the rest position, the blade (1) (upstream) is under the beam axis and the blade (2) (downstream) is blocking the beam. Before an irradiation, the system is armed, i.e. the blade (2) goes above the beam and the blade (1) goes in the beam by the activation of the electromagnets. When the irradiation starts, the supply of the blade (1) electromagnet is cut which accelerates its motion back to rest...
2.2. ESRF ID17 Biomedical Beamline

position. Once the irradiation is performed, the blade (2) goes back to its rest position also by cutting the supply of its electromagnet. In order to limit the heating of blade (2), a photon absorber made of a 15 mm thick cooled copper block, follows blade (2) motion but with a longer reaction time (around 1 sec). A diagram summarizing the fast shutter and photon absorber sequence is displayed in Figure 2.9 (extracted from Renier et al. 2002).

A Laue type monochromator consisting in a double-Si (111) crystal is available in the optical hutch but is only used for imaging purposes. The MRT slits are former slits that used to define the field size at the patient/sample position and clean up the beam. They are no longer in use. The safety shutter finishes the beamline and is protected from heat load by a photon absorber. A last Be window protected by an Al foil makes the transition between the optical and the MRT experimental hutch, i.e. between the vacuum and in-air section. When entering the MRT experimental hutch, the total thickness of Be attenuators is equal to 2.3 mm.

![Figure 2.8: Mechanical design of the fast shutter. Extracted from Renier et al. 2002](image)

![Figure 2.9: Sequence of the fast shutter and photon absorber. Extracted from Renier et al. 2002](image)
In the context of the veterinary clinical trials, additional elements have been inserted in the beam path for patient safety leading to two different beams filtering conditions: the pre-clinical and the veterinary configurations.

In the optical hutch, the veterinary configuration differs from the pre-clinical configuration by the insertion of an additional gas beam attenuator and of a beam monitoring chamber (IC0). The gas attenuator consists of a 2.2 m long krypton (Kr) gas pipe maintained at an effective pressure of 85 mbar and is inserted upstream the primary slits. This gas filter provides a beam filtration like the downstream mechanical filters cutting the energies below 30 keV [Requardt et al., 2013]. The purpose of the Kr gas filter is twofold. First, it will prevent any patient overexposure in the unlikely event of multiple mechanical filter failure (sudden cracking). Second, as the Kr gas pressure is monitored, any change in the pressure can be detected and such a signal can be used safely to intervene in due time to shut down the beam if necessary.

IC0 has been especially developed by the ESRF to suit the synchrotron intense beam. IC0 consists in two redundant in vacuo Compton counters made of two parallel Al plates. In order to prevent the device from radiation damage, the Al plates are coated with $\sim 100 \mu m$ of Au [Berkvens et al., 2013]. The relative dose measurements provided by IC0 are linked to the MRT Patient Safety System (PASS) and are correlated to the absolute dose measured under reference conditions the day before the patient treatment.

**MRT experimental hutch**

A layout of the MRT experimental hutch is displayed in Figure 2.10. An ionisation chamber (IC1) monitors the beam right after the optical hutch. PMMA attenuators and a rotary shutter are available for imaging purposes. IC1, the PMMA attenuators and the rotary shutter are kept out of the beam for pre-clinical MRT irradiations. In
order to select only the central homogeneous part of the synchrotron beam, vertical slits are used. Four different apertures are available with nominally 50, 100, 500 and 800 $\mu$m. Horizontal slits can be inserted in the beam in order to define beam width below 1 mm. Both the horizontal and vertical slits are made of tungsten carbide (WC).

![Figure 2.10: Technical drawing of the MRT instrumentation in the experimental hutch. (Courtesy of Michel Renier from ID17). Right top: photo of the optical table in MRT.](image)

For the MRT veterinary clinical trials at the ESRF, a dedicated collimator with a fixed beam aperture and spacing has been manufactured in order to ensure treatment reproducibility and more reliability in the Monte-Carlo based treatment planning system [Bräuer-Krisch et al. 2009a]. A microbeam width of 50 $\mu$m was chosen since it was the best compromise between the biological data provided by the pre-clinical studies, the available mechanical performance to manufacture the MSC and an acceptable uncertainty in the Output Factors determination. The microbeam spacing was fixed to 400 $\mu$m in order to ensure a high enough PVDR for potentially therapeutic peak
2.2. ESRF ID17 Biomedical Beamline

entrance dose values. The MSC is made of a 8 mm thick block of WC inside which the slits have been grooved thanks to a high precision wire cutting technique [Bräuer-Krisch et al., 2009a]. A schematic drawing of the MSC is displayed in Figure 2.11.

Figure 2.11: Technical drawing of the MSC with a fixed aperture of 50 µm spaced by 400 µm. Reprinted from Bräuer-Krisch et al. [2009a].

The MSC is embedded in a dedicated Al box and cooled thanks to a nitrogen gas flushing. The nitrogen gas also prevents the MSC carbide surface from oxidation that could arise at the surface of the MSC from the ozone production and the temperature increase induced by the irradiation. The patient, sample or dosimetry phantom is set on the a 3-axis Kappa-type high precision goniometer (Huber, Germany) located at 40.5 m from the wiggler X-ray source center.

For the veterinary trials configuration two additional redundant in-air monitoring ionisation chambers (Bragg Peak ionisation chambers 34070, PTW), with an equivalent PMMA thickness of 19 mm (PTW private communication), are set between the MSC and the goniometer. Those chambers, linked with the MRT PASS, integrate and verify the dose at each 500 µm vertical displacement of the goniometer. If the integrated dose measured exceeds a pre-defined threshold value, the PASS system interrupts the exposure.

At around 4 m from the goniometer stage, an ionisation chamber (IC2) is used
for beam monitoring and beam alignment. Downstream the IC2 chamber, a two dimensional X-ray detector is available for imaging purposes. The detector consists in a Fast-Readout Low-Noise (FReLoN) CCD camera designed and developed at the ESRF [Labiche et al., 2007]. When performing imaging in MRT, the fast shutter and the photon absorber in the optical hutch are fixed opened (i.e. kept out of the beam). The beam delivery is then controlled by the rotary shutter located in the experimental hutch.

**Monochromator hutch**

A 100 m long in vacuo pipe links the MRT experimental hutch to the monochromator hutch in the satellite building. Water cooled attenuators are located just after the long pipe and before the secondary slits defining the beam dimensions. A layout of the monochromator hutch is displayed in Figure 2.12.

There are three different monochromators in the hutch; the multilayer, the computed tomography (CT) monochromator and the angiography monochromator. The multilayer is a fixed exit double multilayer mirror monochromator. The first set of mirrors delivers energies ranging from 30 to 60 keV. The multilayer provides a beam with a broader bandpass than the CT monochromator but with a smaller beam height (∼1 mm). The second set of mirrors is designed to deliver energies ranging from 18 to 35 keV but is currently not in use at the beamline. The CT monochromator consists in two cylindrically bent Si crystals in the Laue geometry and operates at energies between 25 to 150 keV. The angiography monochromator is a K-edge subtraction monochromator that operates at beam energies ranging from 17 to 100 keV. It uses a single Si (111) crystal that is bent to vertically focus the beam on the target. In the case of K-edge subtraction imaging, a contrast agent is injected and two images are simultaneously acquired with two monochromatic beams of different energies: one just
below and one just above the K-edge energy of the contrast agent. This method allows the determination of the contrast agent concentration and is used for a wide range of applications on ID17 (coronary angiography [Bertrand et al., 2005], bronchography [Bayat et al., 2009; Porra et al., 2010; Porra et al., 2011] study of nanoparticles biodistribution [Alric et al., 2008], brain and spinal cord perfusion [Balvay et al., 2009; Kelly et al., 2007; Schültke et al., 2010] etc.). In order to obtain the two monochromatic beams, a tungsten splitter is used to block the central part of the beam and two monochromatic beams at slightly different energies (typically separated by $\sim 300$ eV) can be obtained.

The monochromators are under oxygen free helium flow at atmospheric pressure and are separated from the vacuum section by a 500 $\mu$m thick Be window. Right after the monochromators comes an optic bench supporting Plexiglass attenuator, clean-up slits and beam monitors. This bench can move up and down and be tilted up to
13° in order to align different optical elements with the monochromatic beam. As in the MRT optical hutch, a fast shutter is used in order to obtain fast beam opening and closing times. For imaging purposes, a rotating chopper is also available. The chopper is synchronised with the FReLoN camera located in the SSRT experimental hutch in order to avoid the camera exposure during read out times [Renier et al., 2005].

**SSRT experimental hutch**

At the start of the SSRT experimental hutch, cerrobend masks can be used in order to define the field size at the patient stage. Since the irradiations can be performed from different ports, several masks corresponding to the different ports are individually manufactured. The masks are set on a rail in order to be switched when moving from one irradiation port to another. Two redundant transmission ionisation chambers monitor the beam and as in MRT, are linked to the PASS.

Under SSRT irradiation conditions, the beam height is limited to 2 mm at the patient/sample stage which requires a vertical scanning of the stage through the beam in order to irradiate clinically relevant field sizes. A dedicated patient chair has been developed and allows 5 degrees of freedom (see Figure 2.13). The patient can therefore be accurately positioned, the relevant field sizes can be reached and the chair rotation permits to perform computed tomography (CT) images of the patient before the irradiation for positioning purposes.

Finally, after the patient/sample stage comes the detectors stage where two different imaging detectors are permanently installed: a Germanium (Ge) detector and a FReLoN camera with taper. The Ge detector is 2 mm thick and composed of two lines of 432 parallel strips spaced by 350 µm. This detector is often used for bronchography, in-vivo brain perfusion studies, K-edge subtraction imaging and also to determine the iodine concentration in the brain for SSRT patients. The FReLoN camera has a 93
2.3. Australian Synchrotron Imaging and Medical Beamline (IMBL)

The Australian Synchrotron (AS) is a 3rd generation synchrotron working at an energy of 3 GeV. The storage ring operates under the top-up mode resulting in a more stable beam. Nine different beamlines are available at the AS including the Imaging and Medical Beamline (IMBL) where MRT is currently under development.

Figure 2.13: At the entrance of the SSRT experimental hutch, cerrobend masks define the field size at the patient stage and the beam is then monitored by two redundant plate ionisation chambers.(Courtesy of Michel Renier from ID17).

×93 mm² field of view, a 46 µm pixel size and is principally used for microtomography experiments.
2.3. Australian Synchrotron Imaging and Medical Beamline (IMBL)

The continuous top-up mode confers an advantage for MRT as the irradiation parameters, such as scan speed, would be able to remain identical for dosimetry and patient irradiation. This is also an advantage for dosimetry measurements that don’t need to be normalised to the beam current as it is the case at the ESRF. At the time of the experiments presented in this study, there was no motorised stage able to perform vertical motion during the irradiation. MRT was thus performed in the so-called static mode (i.e. no vertical motion) or in step and shoot mode where the sample is vertically moved between two consecutive static exposures.

IMBL first saw synchrotron light in December 2008 and since then, the beamline has undergone many improvements and some developments are still in progress. A general overview of the current state of the beamline instrumentation is provided here.

At IMBL, a superconducting multipole wiggler is used as a photon source. The wiggler is located at the exit of the storage ring in the front end section and is followed by two different sets of masks, a diamond window that removes low energy components from the beam, and a photon stop (see Figure 2.14). The front end section is terminated by a safety shutter.

![Figure 2.14: Front End section of the IMBL. (Courtesy of Jayde Livingstone from IMBL).](image_url)

After the front end starts the hutch 1A (optical hutch, see Figure 2.15) where all the instrumentation is under vacuum. Water cooled vertical and horizontal tungsten made slits are used to optimise the synchrotron beam size in order to minimise unnecessary
heat load of the downstream elements. Different mechanical filters (C, Al and Cu) are available in the filter vessel. In MRT mode, the filter combination is chosen in order to remove the photons with an energy lower than 30 keV and to protect the downstream components and decrease the skin entrance dose. During normal beamline operation, the first three filters are fixed to 0.45 mm of C + 5 mm of high density C + 10 mm of high density C. A double Laue monochromator is also available but is not used for MRT applications. A diagnostic cross is used for beam monitoring. It consists in measuring signal from a Be foil (white beam intensity monitor), a Be wire (monitoring of white beam vertical position) or a W wire (monitoring of monoenergetic beam vertical position). The MRT shutter is located in vacuum. It is composed of 2 blades used together so that the gradient in the vertical direction resulting from the use of one blade alone is counteracted by the second blade. This shutter allows fast opening and closing time (down to 30 ms as of the writing of this thesis). The beamline finishes with a safety shutter. A photon stop is located upstream the shutters to prevent them from overheating.

Three different operating modes are available on IMBL. Mode 1 takes place in the experimental hutch 1B (20 meters from the source) and is dedicated to high dose rate, step and shoot MRT. At this distance from the source the maximum beam dimensions are limited to $30 \times 2$ mm in horizontal and vertical direction respectively. Beam defining slits are located in vacuum and He flushed Be window protected by an Al foil makes the transition between the vacuum and in-air sections. The MRT table includes two beam monitors (ionisation chambers located before and after the multislit collimator) and a sample stage. The multislit collimator is actually composed of two separated collimators superimposed in order to change the microbeams width by vertically translating the collimators. The two available microbeam widths are 25 and 50 $\mu$m. For both configurations the c-t-c distance is 200 $\mu$m. The collimators
are composed of W plates between which thin sheets of kapton are sandwiched. The incident beam is thus attenuated by the W plates and goes through the thin apertures defined by the kapton areas. A manual mode shutter made of lead ends the hutch.

In hutch 2A, downstream the beam defining slits ("Mamma Bear"), two beam shutters are available: an imaging rotary shutter and a MRT shutter (see Figure 2.16). They are both set on the same rail in order to use one or another depending on the purpose of the irradiation performed in hutch 2B (either imaging or MRT). A beam monitoring ionisation chamber is located right after the MRT shutter. Slits, shutters and beam monitor chamber are positioned within an air path of 0.6 m isolated from the vacuum sections by Be windows.

A new MRT shutter has been installed in hutch 2A in June 2015 and is currently being tested. This shutter is working using the same principle as the MRT shutter located in hutch 1A except it is operating in-air. Depending on the operation mode, i.e. mode 1 or mode 2, this new shutter is meant to be installed in hutch 1B or 1A.
respectively. During our experiment, the new in-air MRT shutter was not in place and only the in-vacuum MRT shutter in hutch 1A was used.

Figure 2.16: Diagram of the optical and experimental hutches in mode 2. In green, the removable components. In red, the components under development. (Courtesy of Jayde Livingstone from IMBL).

In operating mode 2, a long vacuum pipe is going through the entire hutch 1B and imaging and fast computed tomography of small objects are performed in the hutch 2B located at 32 m from the source. Hutch 2B is also currently used for the development of dynamic MRT. Dynamic MRT consists in performing vertical motion of the patient/sample during the irradiation, i.e. as MRT irradiations are delivered at the ESRF since 1995.

The dynamic MRT instrumentation is located on the so-called Dynamic MRT (DynMRT) table. It is composed of beam defining apertures, tungsten-carbide made MSC and a sample stage. The beam defining aperture is a removable component which provides three beam heights (0.5, 1 and 2 mm) all of the same width (30 mm). The MSC generates vertical microbeams with a fixed width (50 µm) and spacing (400 µm c-t-c). Two silicon (Si) diodes, located upstream and downstream the MSC, monitor
the dose rate. If the dose rate appears to be sufficient in hutch 2B to perform MRT, then DynMRT will be performed in this same hutch. Otherwise, the DynMRT setup will be moved to hutch 1B. A computed tomography (CT) table is located after the DynMRT table and holds the sample to be imaged.

Two imaging detectors are available in hutch 2B: Diamond and Ruby2. Diamond is a very high spatial resolution X-ray detector, able to image with sub-micron pixel sizes (image pixel size down to 0.64 µm). Two Ruby detectors are actually available on the IMBL: Ruby is located in hutch 3B and Ruby2 in hutch 2B. Ruby is a custom designed detector based on a photo sensitive device coupled by a bright lens to a suitable X-ray sensitive scintillator. It produces images at a lower resolution than the Diamond detector (minimum image pixel size of 6.35 µm) but provides a larger field of view (up to 70 mm). More detailed information about Diamond and Ruby detectors can be found elsewhere [Hall et al., 2013].

A Manual mode shutter finishes this section of the beamline. After the hutch 2B, the beam leaves the main building and is transported to the two hutches in the satellite building in a long vacuum pipe called “beam transfer line”.

The hutch 3B is located in a satellite building at 140 m from the source and is dedicated to imaging and computed tomography of large objects (Figure 2.17). Indeed, in this hutch, due to the beam divergence, beam dimensions reach 120 × 40 mm [Harty et al., 2014].

In addition to Ruby, the Argus commercial detector (Teledyne Dalsa) is available in hutch 3B. Argus is a CCD imager that provides a lower spatial resolution (27 µm pixel size) but a wider field of view (22 cm) than Ruby. Beam defining slits (“Papa Bear”) and a beam monitoring are located upstream the sample stage. Because of the lower flux and higher field sizes available, the set up can be modified to perform detector characterisation experiments.
At different locations across the beamline several valves and pumps maintain the vacuum.
Chapter 3

Reference dosimetry in MRT

At the ESRF, the MRT irradiation is delivered for a prescribed peak dose. Reference dosimetry is performed using a homogeneous radiation field and an output factor is applied in order to convert the reference dose to the dose within a microbeam at 3 mm depth. The reference dosimetry is therefore a crucial step for the accurate delivery of the treatment dose. Furthermore, the establishment of a reference dosimetry protocol allows the internal calibration of dose monitors within the MRT patient safety system as well as the calibration of high spatial resolution detectors dedicated to the quality assurance of the microbeam field to be used for the actual MRT treatment.

This chapter presents the MRT reference dosimetry protocol to be performed before a MRT irradiation at the ID17 biomedical beamline at the ESRF\(^1\). First the principle of the ionisation chamber based dosimetry is presented. Within the establishment of the MRT dosimetry protocol, a special attention is paid to the determination of the correction factors to be applied to the ionisation chamber reading accounting for the effect of the MRT beam quality and of the ion recombination occuring in the air cavity of the ionisation chamber.

\(^1\)Part of the work presented in this chapter has been published in the journal of Physics in Medicine and Biology \cite{Fourier2016b}.\footnote{Part of the work presented in this chapter has been published in the journal of Physics in Medicine and Biology \cite{Fourier2016b}.}
3.1 Ionisation chambers

3.1.1 Description and Principle

Ionisation Chambers (ICs) are the gold standard dosimeter in conventional radiation therapy. Cylindrical ICs are recommended for medium energy kilovoltage X-ray beam [IAEA, 2000] and are therefore the reference dosimeter for the radiotherapy modalities on ID17 and IMBL. Hereafter the operational principle of ICs is presented as well as the different correction factors to consider when using such detectors. Finally, the Pinpoint 31014 and Semiflex 31010 ionisation chambers used for reference dosimetry in MRT and SSRT respectively are introduced.

Cylindrical ICs consist of an air cavity inside which ions are created from the interaction of incident radiations with the air. The inner conductive wall of the IC cavity serves as the external electrode and the collection electrode is located at the centre of the air cavity. A polarisation voltage in the order of a few hundred volts is applied between the two electrodes in order to induce the motion of charges created after ionisation, collect them so as to avoid their recombination. Electrodes are generally made of low Z material such as Al, C or conductive plastic. When a positive polarisation voltage is applied to the external electrode, the central electrode (i.e. the collecting electrode) detects the positive ions. A guard electrode prevents the signal electrode from detecting leakage current and parasitic signals coming from regions with distorted electric field [Seco et al., 2014]. The IC measures the quantity of charge collected in Coulombs (C) which is directly proportional to the absorbed dose. The IC signal is read with an electrometer. UNIDOS\textsuperscript{webline} Dosemeter electrometers (PTW, Freiburg) are used in MRT and SSRT.
3.1.2 Ionisation chamber based absolute dosimetry

According to the TRS 398 code of practice [IAEA, 2000], the absorbed dose to water $D_{w,Q}$ is given by:

$$D_{w,Q} = M_Q \times N_{D,w,Q_0} \times k_{Q,Q_0}$$  \hspace{1cm} (3.1)

$N_{D,w,Q_0}$ is the IC calibration factor in gray per nano coulomb (Gy.nC$^{-1}$) that is applied to the IC readings in order to convert the measured current into an absorbed dose. $N_{D,w,Q_0}$ is dosimeter specific and is provided by a metrology lab in terms of absorbed dose in water at the reference beam quality $Q_0$.

If the IC is used at a beam quality $Q$ that differs from the reference beam quality $Q_0$, a beam quality correction factor $k_{Q,Q_0}$ needs to be applied. $k_{Q,Q_0}$ is equal to:

$$k_{Q,Q_0} = \frac{N_{D,w,Q}}{N_{D,w,Q_0}}$$  \hspace{1cm} (3.2)

If the path of the secondary electrons is larger than the detector volume, the Bragg-Gray theory [Ma and Nahum, 1991] can be applied and $k_{Q,Q_0}$ can be determined using the following equation:

$$k_{Q,Q_0} = \frac{(s_{w,air})_Q}{(s_{w,air})_{Q_0}} \frac{(W_{air})_Q}{(W_{air})_{Q_0}} p_Q$$  \hspace{1cm} (3.3)

Where $s_{w,air}$ is the Spencer-Attix water/air stopping power ratios, $W_{air}$ the mean energy expended in air per ion pair formed and $p_Q$ the perturbation factors. The $k_{Q,Q_0}$ factors can be obtained by measurements or provided by a metrology lab for a specific beam quality. $M_Q$ is the raw IC reading $M_{raw}$ corrected for different influence quantities $k_i$ (see equation 3.4). These influence quantities are described hereafter in
3.1.3 Correction for influence quantities

In order to measure the absolute dose with an IC, several correction factors, needs to be applied to the IC reading.

Temperature and Pressure

The mass of air contained in the cavity and thus the ionisation current measured is dependent on the atmospheric conditions at the time of the measurement. As atmospheric conditions at the time of the calibration may be different from those during the measurements, a correction factor $k_{T,P}$ accounts for this effect:

$$k_{T,P} = \frac{P_0 T}{T_0 P}$$  \hspace{1cm} (3.5)

$T_0$ and $P_0$ respectively are the temperature and the air pressure at the time of the calibration while $T$ and $P$ are the temperature and the air pressure at the time of the measurement. In the case where the measurement is performed within a water phantom, $T$ has to be the water temperature. Both $T_0$ and $T$ have to be expressed Kelvin.

Polarity effect

$k_{pol}$ corrects for the differences that can occur in the dosimeter reading depending whether the polarisation voltage is positive or negative. The polarity effect can be caused by a parasitic radiation-induced current arising from secondary electrons produced by the Compton effect in the wall and electrodes of the IC. A potential difference
3.1. Ionisation chambers

between the guard and the central electrode can also have an influence on the polarity effect as this could distort the electric field and cause polarity asymmetry [Kim et al., 2005]. Parasitic current can also occur from the irradiation of the IC cable and induce polarisation effects.

\[ k_{\text{pol}} = \frac{|M_+| + |M_-|}{2M} \]  \hspace{1cm} (3.6)

Ion recombination

If the applied voltage of the IC is not high enough, the current measured during an irradiation will be dependent on the applied voltage. Indeed, if the applied voltage is not high enough, the ions created inside the air cavity will recombine before reaching the electrode thus resulting an underestimation of the dose. By increasing the polarisation voltage, the ions are collected more rapidly and the recombination process is reduced. The measured current will stabilise with the applied voltage when the IC will enter the so-called saturation regime where all the charges are collected. ICs therefore need to be used in this regime where the ion recombination is expected to be small. However, the IC readings still need to be corrected for this effect by applying the ion recombination correction factor \( k_s \).

There are two different types of ion recombination processes: the initial and general (or volume) recombination [IAEA, 2000]. The initial recombination is coming from the recombination of one single particle track and is independent on the dose rate. On the other hand, the general recombination is due to the recombination of ions created by different particle tracks and is dependent on the dose rate. Both effects are dependent on the IC geometry and on the voltage applied to the IC. Volume recombination
is considered as the one having the highest influence and the ion recombination correction factor is determined using the so-called ”two-voltage” method. In the case of synchrotrons sources, the beam is pulsed but the frequency is so high (352 MHz at the ESRF), compared to the charge collection process in the ionisation chamber, that it can be considered as a continuous beam. According to the TRS 398 code of practice [IAEA 2000], in the case of a continuous beam, $k_s$ is estimated as follows:

$$k_s = \frac{(V_1/V_2)^2 - 1}{(V_1/V_2)^2 - (M_1/M_2)}$$

(3.7)

Where $M_1$ and $M_2$ are the signals measured by the electrometer at the polarising voltages $V_1$ and $V_2$ respectively with $V_1$ the IC operating voltage and $V_2$ chosen in order to obtained a ratio $V_1/V_2$ ideally equal or larger than 3.

Other correction factor to take into account

Other correction factors need to be applied to the IC reading in order to perform absolute dosimetry. $k_{elec}$ is the correction factor for the electrometer calibration. This factor is determined by the metrology lab when the IC and the electrometer are sent for calibration.

3.1.4 Reference ionisation chambers on ID17 and IMBL

The Semiflex 31010 (PTW) has a sensitive volume of 0.125 cm$^3$ and is the reference chamber for SSRT. This IC has also been considered in a dosimetry protocol published by [Prezado et al. 2011a] in the context of pre-clinical trials in minibeam radiation therapy on the ID17 beamline.

For the purpose of MRT reference dosimetry a PinPoint 31014 IC (sensitive volume
3.1. Ionisation chambers

Figure 3.1: Top: Semiflex 31010 reference ionisation chamber for SSRT. Bottom: PinPoint 31014 reference ionisation chamber for MRT.

Figure 3.2: Top: Technical drawing of the Semiflex 31010. Bottom: Technical drawing of the PinPoint 31014.

of 0.015 cm\(^3\)) from PTW has been chosen because of its suitability for measurements in field sizes down to 2 cm × 2 cm. Furthermore, from theory it is known that the
3.2 Establishment of a dosimetry protocol for reference dosimetry on ID17

recombination in ICs is proportional to the dose rate and to the electrode spacing [Boag, 1966, 1987; Swanson, 1979]. With the PinPoint effective electrode separation (considering both the spherical and cylindrical parts of the sensitive volume) being less than for the Semiflex, the PinPoint can be clearly identified as more appropriate dosimeter for reference dosimetry in MRT. The PinPoint 31014 IC is thus the reference IC for MRT reference broadbeam dosimetry at both ID17 at the ESRF and IMBL at the AS.

3.2 Establishment of a dosimetry protocol for reference dosimetry on ID17

3.2.1 Introduction

The MRT reference dosimetry protocol is intended to be applied in the context of veterinary trials, and therefore requires reference conditions that remain as close as possible to the irradiation conditions used during the MRT treatment. The experimental validation of the energy spectrum in both pre-clinical and veterinary beam filtering conditions helped us to decide under which beam quality the PinPoint had to be calibrated and therefore led to the determination of the $k_{Q,Q_0}$ correction factor to be applied to the PinPoint dose readings. The MRT irradiation conditions also imply that special care needs to be dedicated to the determination of the ion recombination correction factor. Indeed, in the particular case of synchrotron X-ray beam spectrum $k_s$ is by far the most challenging correction factor to determine, due to the very high dose rates involved [Crosbie et al., 2013; Nariyama, 2006]. Since no international recommendations are available for synchrotron medical beam dosimetry at such high dose rates, a storage ring current ramping method was investigated.
3.2.2 MRT irradiation technique and reference dosimetry conditions

The MRT energy spectrum ranges from $\sim 30$ to 600 keV with less than 1% of the photons with energies higher than 300 keV and a mean energy around 100 keV [Crosbie et al., 2015; Martínez-Rovira et al., 2012; Siegbahn et al., 2006]. The dosimetry protocol presented here remains as close as possible to the international recommendations of the TRS 398 code of practice for medium energy kilovoltage X-ray beam whenever technically possible.

Reference dosimetry takes place under broad beam conditions; the MSC is kept out of the beam path so there is no spatial fractionation of the beam. At the ID17 beamline, the maximum synchrotron beam dimensions at the sample stage are 41 mm $\times$ 2.5 mm in the horizontal and vertical directions respectively. The primary horizontal slits and the vertical slits are used to select a part of the synchrotron beam having a homogeneous intensity distribution in both vertical and horizontal directions. At the sample stage, the MRT field is thus reduced to 520 $\mu$m height and 3.5 cm width.

As detailed in subsection 1.3.2, in order to cover treatment field sizes of a clinically relevant height, a scanning method is employed; the target is positioned on a goniometer stage and vertically translated at constant speed (including pre-calculated acceleration and deceleration times). Target irradiation is done via the shutter device that opens and closes at the vertical position of the goniometer to deliver the desired dose over the pre-selected target field size [Renier et al., 2002].

For medium energy kilovoltage X-ray beams the TRS 398 protocol recommends performing the dosimetry at 2 cm depth in water under a $10 \text{ cm} \times 10 \text{ cm}$ field size. Since the synchrotron beam propagates in the horizontal direction, our reference dosimetry uses the MP3-P water tank from PTW (Freiburg, Germany) allowing irradiation from the side. The water tank is thus mounted on the goniometer located 40.5 m down-
3.2. Establishment of a dosimetry protocol for reference dosimetry on ID17

stream of the X-ray source. Because of the high attenuation of the MRT beam in water equivalent material the initial entrance window of 5 mm PMMA was replaced by thin kapton window (around 70 µm thick). The resulting window limits the reference field size to 2 cm × 2 cm. This field size allows a homogeneous irradiation as well as a negligible error in case of small misalignment of the IC with the beam (∼1 mm). Moreover the lateral electronic equilibrium is ensured as the electron CSDA (continuous slowing down approximation) range at 100 keV is around 150 µm in water [Berger, 1992]. Therefore, a 2 cm × 2 cm field size has been adopted for reference dosimetry in MRT.

A 20 mm.s⁻¹ vertical scan speed was chosen as the reference speed because it is close to a typical treatment speed. Reference conditions for reference dosimetry in MRT are summarised in Table 3.1 and compared to those recommended by the TRS 398 protocol for medium energy photons.

<table>
<thead>
<tr>
<th>Parameter of interest</th>
<th>TRS 398</th>
<th>MRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phantom Material</td>
<td>water</td>
<td>water</td>
</tr>
<tr>
<td>Ionisation chamber type</td>
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<td>cylindrical</td>
</tr>
<tr>
<td>Measurement depth (z_{ref})</td>
<td>2 g.cm⁻²</td>
<td>2 g.cm⁻²</td>
</tr>
<tr>
<td>Reference point</td>
<td>Central axis,</td>
<td>Central axis,</td>
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<tr>
<td>of chamber volume</td>
<td>at the centre</td>
<td>at the centre</td>
</tr>
<tr>
<td>Reference position</td>
<td>z_{ref}</td>
<td>z_{ref}</td>
</tr>
<tr>
<td>Field size</td>
<td>10 cm×10 cm</td>
<td>2 cm×2 cm</td>
</tr>
<tr>
<td>Vertical slit size</td>
<td>N.A.</td>
<td>500 µm</td>
</tr>
<tr>
<td>Scan speed</td>
<td>N.A.</td>
<td>20 mm.s⁻¹</td>
</tr>
</tbody>
</table>

3.2.3 Determination of $k_{Q,Q_0}$

As presented in Section 3.1.2, $k_{Q,Q_0}$ is a factor that corrects for the difference between the beam quality $Q_0$ used for the calibration and the beam quality $Q$ under which the
measurements are performed. At the ESRF, the PinPoint 31014 is calibrated in terms of dose to water towards the $^{60}$Co beam quality. The most appropriate beam quality for the PinPoint 31014 calibration in order to perform reference dosimetry in both pre-clinical and veterinary beam filtering conditions thus needs to be determined.

Figure 3.3 represents the dose rate scaled to the storage beam current ($\hat{D}_{\text{scaled}}$) obtained from PinPoint 31014 IC measurements at different depths in water in both pre-clinical and veterinary configurations. Only the $k_{T,P}$ correction factor was applied to the IC readings.

![Figure 3.3: Depth dose measurements performed in water using the PinPoint 31014 IC for both pre-clinical and veterinary beam filtering conditions. Only the $k_{T,P}$ correction factor was applied to the IC readings. Error bars correspond to two standard deviations.](image)

The switch from pre-clinical to veterinary beam filtering configuration introduces a beam intensity attenuation of 41% at 20 mm depth. In order to see if any spectral change occurs between the two configurations, percentage depth dose (PDD) curves has been deduced from results reported in Figure 3.3 and are displayed in Figure 3.4. The introduction of the additional components in the beam doesn’t seem to affect the
energy spectrum as no significant change can be observed on the PDD curves obtained for both configurations.

Figure 3.4: Percentage depth dose obtained from depth dose measurements in both pre-clinical and veterinary beam filtering conditions (Figure 3.3). Depth dose measurements have been performed in water and are normalised to 100% at 20 mm depth. Error bars correspond to two standard deviations.

In order to validate the pre-clinical and veterinary beam spectrum, [Crosbie et al. 2015] calculated them using the SPECTRA program (version 9.0) [Tanaka and Kitamura 2001] and the XOP program (version 2.3) [del Rio and Dejus 2004]. The calculations were validated experimentally by transmission measurements through different thicknesses of high-purity copper sheets (Gammex 116 HVL attenuator set; Gammex Inc., Middleton, WI, USA) in order to determined the first to third half value layer (HVL) of each beam. HVL is defined as the material thickness (Cu or Al) required to attenuate a X-ray beam intensity by 50%. The first, second and third HVL thus correspond to the thickness of copper that attenuates the original beam intensity by 50, 75 and 87.5% respectively. The transmission measurements were performed in air using the PinPoint 31014 IC.
3.2. Establishment of a dosimetry protocol for reference dosimetry on ID17

From the energy spectra calculated by the Spectra program, a MATLAB-based computer program called Dose4IMBL was used to extract information of dosimetric interest such as the HVLs and the mean energy. The HVLs measured for the two different MRT beam configurations were then compared to the calculated ones. In the pre-clinical conditions, the first HVL measured was 1.754 mm and 1.763 mm for the calculated one. In veterinary conditions, a HVL of 1.962 mm was measured compared to 1.984 mm with theoretical calculations. The calculated mean energies were 105 keV and 110 keV for the pre-clinical and veterinary configuration respectively.

Knowing the value of the 1st HVLs the MRT spectra, one can determine the most suitable beam quality toward which calibrate the PinPoint 31014 IC. The filtration and the copper 1st HVL of the two MRT spectra are compared to three beam qualities available at PTW for beam calibration in terms of absorbed dose in water in Table 3.2.

Table 3.2: Comparison of the MRT spectrum mean energy and 1st Cu HVL to those of the closest beam quality available at PTW for calibration.

<table>
<thead>
<tr>
<th>Beam Quality</th>
<th>Mean Energy (keV)</th>
<th>1st Cu HVL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRT pre-clinical</td>
<td>105(^a)</td>
<td>1.754±0.035</td>
</tr>
<tr>
<td>MRT veterinary</td>
<td>110(^a)</td>
<td>1.962±0.039</td>
</tr>
<tr>
<td>TH 140</td>
<td>65.7(^b)</td>
<td>0.43</td>
</tr>
<tr>
<td>TH 200</td>
<td>109(^b)</td>
<td>1.67</td>
</tr>
<tr>
<td>TH 280</td>
<td>163(^b)</td>
<td>3.40</td>
</tr>
</tbody>
</table>

\(^a\) Fluence.
\(^b\) Air kerma.

At PTW, the TH 200 beam quality is obtained from an X-ray generator operating under a 200 kV tube voltage filtrated with 4.0 mm of aluminium and 1.0 mm of copper. This results in an energy spectrum with a mean energy of 109 keV (air kerma). As one can see from Table 3.2, the TH 200 beam quality is the closest to the MRT spectrum for both pre-clinical and veterinary beam filtering conditions. Consequently, when the PinPoint IC is calibrated in terms of absorbed dose to water for the reference \(^{60}\)Co beam quality, PTW now provides us with a \(k_Q\) value for the TH 200 beam quality.
3.2.4 Determination of $k_s$

For medium energy kilovoltage X-ray beams, the TRS 398 protocol recommends to use the Two-Voltage method for the determination of $k_s$. This method is based on the linear dependence of the ion recombination with the polarisation voltage applied to the IC. The $k_s$ value obtained with this method therefore depends on the dose rate and should be determined at the different dose rates available on the machine.

At the ESRF the current in the SR is constantly decreasing with time leading to a significant change in dose rate. This decreasing current prevents to use the conventional Two-Voltage method for MRT reference dosimetry measurement because the dose rate will be different between the measurements performed at the normal IC polarisation voltage and those performed at the lower polarisation voltage. For MRT dosimetry, the $k_s$ correction factor should be determined as a function of the dose rate. The current ramping method is based on the measurement of $\dot{D}_{\text{scaled}}$ at different SR currents.

The initial recombination is generally less than 0.2% for beams except for heavy ions [IAEA, 2000]. Therefore, in the present study, the initial recombination was assumed to be negligible and the study only focussed on the general recombination. Measurements of $\dot{D}_{\text{scaled}}$ using the PinPoint IC at different dose rates were performed in order to observe the effect on the chamber collection efficiency. However, a constant energy spectrum over the range of dose rates investigated was required. As such the use of beam attenuators to modify the dose rate was not possible. Since the dose rate is directly proportional to the beam current in the SR, it represents the only parameter that can be changed without influencing the energy spectrum and dose measurements were performed at SR currents ranging from 20 to 200 mA. The irradiations were done under reference conditions (2 cm depth in water, 2 cm × 2 cm field size, 520 µm beam height, 20 mm.s$^{-1}$ scan speed) and under the pre-clinical filtering conditions.
From the dose measurements performed at the different SR currents, the corresponding dose rates scaled for the SR current ($\dot{D}_{\text{scaled}}$) were determined using equation 1.4. The resulting values of $\dot{D}_{\text{scaled}}$ obtained at the different beam currents under pre-clinical filtering conditions are presented in Figure 3.5. Only the $k_{T,P}$ correction factor was applied to the measurements and five data points were acquired at each ring current. The error bars are equal to one standard deviation ($\sigma$). The uncertainty in the beam current was assumed to be negligible.

As $\dot{D}_{\text{scaled}}$ corresponds to the dose rate divided by the current in the SR, no change should be observed on its value as long as the IC efficiency remains constant. Due to the ion recombination occurring in the air cavity of the PinPoint chamber, $\dot{D}_{\text{scaled}}$ is linearly decreasing with the current from 20 to 200 mA. The experimental data points
were fitted using the following linear equation:

\[ D_{\text{scaled}} = (-1.69 \times 10^{-2} \times I) + 75.81 \quad [\text{Gy. mA}^{-1}. \text{s}^{-1}] \] (3.8)

In this approach, it was assumed that no ion recombination occurs at very low current (i.e. very low dose rate). The dose rate scaled for the SR current for a 100% collection efficiency was thus assumed to correspond to the value obtained for a 0 mA SR current using equation 3.8 i.e., 75.81 Gy.mA\(^{-1}.s\(^{-1}\)). The \(k_s\) factor to be applied to the IC reading as a function of the current in the SR can thus be determined using equation 3.9:

\[ k_s(I) = \frac{\dot{D}_{\text{scaled}}(I = 0 mA)}{\dot{D}_{\text{scaled}}(I)} = \frac{1}{1 - (2.23 \times 10^{-4} \times I)} \] (3.9)

In order to evaluate the error on the determination of \(k_s\) using equation 3.9, the extreme possible fits of the experimental data have been determined using the gradient method. In order to determine those fits the two extreme experimental data points were considered (i.e. those obtained at 20 and 200 mA). The curve with the maximum slope intercepts the points of coordinates (20 mA; \(\dot{D}_{\text{scaled}}(I = 20 mA) + \Delta \dot{D}_{\text{scaled}}(I=20 mA)\)) and (200 mA; \(\dot{D}_{\text{scaled}}(I = 200 mA) - \Delta \dot{D}_{\text{scaled}}(I=200 mA)\)). Conversely the curve with the minimum slope intercepts the points of coordinates (20 mA; \(\dot{D}_{\text{scaled}}(I = 20 mA) - \Delta \dot{D}_{\text{scaled}}(I=20 mA)\)) and (200 mA; \(\dot{D}_{\text{scaled}}(I = 200 mA) + \Delta \dot{D}_{\text{scaled}}(I=200 mA)\)). The resulting curves and their corresponding fitting equations are displayed on Figure 3.6. For each current, the extreme possible values of \(k_s\) (i.e. \(k_{s,\text{min}}\) and \(k_{s,\text{max}}\)) can thus be calculated as follows:

\[ k_{s,\text{min}}(I) = \frac{1}{1 - (1.94 \times 10^{-4} \times I)} \] (3.10)
3.2. Establishment of a dosimetry protocol for reference dosimetry on ID17

\[ k_{s,\text{min}}(I) = \frac{1}{1 - (2.51 \times 10^{-4} \times I)} \]  

(3.11)

\[
\begin{align*}
    y_{\text{min}}\text{ slope} &= -1.47 \times 10^{-3} \times x + 75.65 \\
    y_{\text{max}}\text{ slope} &= -1.91 \times 10^{-3} \times x + 75.95
\end{align*}
\]

Figure 3.6: Determination of the maximum (Red) and minimum (Green) slope fitting curves using the gradient method.

From equation 3.9, \( k_s \) is calculated for the different current values investigated during the experiment and results are displayed in Figure 3.7. The absolute difference between \( k_s \) and \( k_{s,\text{max}} \) is higher than between \( k_s \) and \( k_{s,\text{min}} \). In order to remain conservative, the error on \( k_s \) \( (\text{i.e. } \Delta k_s) \) displayed on Figure 3.7 is equal to the absolute difference between \( k_s \) and \( k_{s,\text{max}} \).

From Figure 3.7 and equation 3.9, the \( k_s \) factor to be applied to the Pinpoint IC reading can be determined as a function of the SR current at the time of the measurement. At the maximum SR current, the \( k_s \) factor was found equal to 1.047 ± 0.006. However, this determination as a function of the SR current is only valid if the filtering conditions are identical to those used in the ramping experiment. If the beam filtering conditions are changed, then the dose rate at a given SR current may need to be modified leading
3.2. Establishment of a dosimetry protocol for reference dosimetry on ID17

Figure 3.7: $k_s$ as a function of the storage ring current in the machine.

to a different $k_s$ factor. For example, under MRT veterinary filtering conditions, the normalised dose rate measured at a SR current of 200 mA decreased to around 40 Gy.mA$^{-1}$.s$^{-1}$. However, as showed in the Material and Method section, the spectral mean energy shift between the pre-clinical and the veterinary beam filtering conditions is only of a few electron volts. Assuming that $k_s$ is proportional to the dose rate, $k_s$ is expected to be around 1.025 at 200 mA under veterinary beam filtering conditions.

3.2.5 Evaluation of the uncertainty in MRT reference dosimetry

The relative uncertainty of our reference dosimetry technique applied to MRT was determined by summing in quadrature, all the uncertainties on all correction factors applied to the PinPoint chamber reading.

On the PinPoint calibration certificate from PTW, the uncertainty on $k_{elec}$ is given
equal to 0.5% and the uncertainty on \( k_Q \), for the TH 200 beam quality, is given equal to 3.7%. The polarisation effect correction factor \( (k_{pol}) \) is reported to be <1.0%. In order to remain conservative, an uncertainty of ±1% was considered for \( k_{pol} \). Our thermometer has an accuracy of ±1% and the barometer ±1.0 hPa + one digit.

The error on the \( k_{T,P} \) will therefore be dependent on the temperature and pressure measured. The uncertainty on \( k_{T,P} \) was evaluated not being higher than ±0.3%.

The calibration certificates provide uncertainties at the 2\( \sigma \) level so we have extended our uncertainty to 2\( \sigma \) for our experimentally determined \( k_s \) values. The relative uncertainty in \( k_s \) increases with the dose rate, so we calculate the uncertainty at the maximum dose rate reached during the ramping experiment (i.e. when the SR current was 200 mA) and this uncertainty is ±1.2%. Finally, an error in the PinPoint ion chamber alignment on the x axis (i.e. beam axis) was introduced. From the measured broad beam depth dose curves, we deduced that for both pre-clinical and veterinary beam spectra, a misalignment of ±1 mm at the reference depth induces a change in the dose reading of ±1.6%.

\[
\frac{\sigma_D}{D} = \sqrt{\left(\frac{\sigma_{k_Q}}{k_Q}\right)^2 + \left(\frac{\sigma_{k_{pol}}}{k_{pol}}\right)^2 + \left(\frac{\sigma_{k_{elec}}}{k_{elec}}\right)^2 + \left(\frac{\sigma_{k_{TP}}}{k_{TP}}\right)^2 + \left(\frac{\sigma_{k_s}}{k_s}\right)^2 + \left(\frac{\sigma_{position}}{D}\right)^2}
\]

\[
\quad = \sqrt{(2.3)^2 + (1)^2 + (0.5)^2 + (0.3)^2 + (1.2)^2 + (1.6)^2}
\]

\[
\quad = 4.4\%
\]

Using the propagation of uncertainties of the independent variables by summing in quadrature, as shown in equation \[3.12\], we obtain an overall percentage uncertainty of ±4.4%.
3.2.6 Conclusion

We have presented a method for MRT reference dosimetry at the ID17 biomedical beamline of the ESRF, Grenoble, France. In developing our new method we have tried to remain as close as possible to the recommendations of the TRS 398 code of practice for medium energy kilovoltage X-ray beams. Some of the reference dosimetry conditions (such as the reference dosimeter and the reference field size) had to be adapted to the ESRF specific synchrotron X-ray source, instrumentation and irradiation technique. Previous work on the MRT beam energy spectra [Crosbie et al. 2015] allowed us to determine the best beam quality for our reference dosimeter calibration.

A limitation of the current ramping technique is that it requires dedicated SR shifts which has a significant impact on all the other beamline stations around the synchrotron facility. Indeed, as a modulation of the SR current impacts all the beamlines at the same time, these experiments can be logistically difficult to organise at a facility such as the ESRF. However, such measurements only need to be performed each time a new reference chamber is purchased or calibrated at a reference beam quality in a metrology laboratory (i.e. every two to three years).

From the measurements presented here we do not expect the change from pre-clinical to veterinary beam filtering conditions to significantly affect the energy spectrum. The major effect observed being a substantial decrease in the average measured dose rate (from $\sim 70 \text{ Gy.mA}^{-1}\text{s}^{-1}$ down to $\sim 40 \text{ Gy.mA}^{-1}\text{s}^{-1}$). For this reason, the estimation of the $k_s$ correction factor from the ramping experiment presented here should be suitable for reference dosimetry in the context of veterinary trials. However, the ramping method should at one point be performed under the veterinary beam filtering conditions which is technically not feasible on ID17 at the moment. Indeed moving from pre-clinical to veterinary beam filtering configuration includes the insertion of a krypton gas filter. The fact of progressively increasing the SR current from 20 to 200
mA induces a strong local temperature and pressure gradient across the krypton gas pipe. The high temperature along the X-ray beam path leads to a local reduction of the gas density which, combined with the partial ionisation of the krypton, decreases the density of electrons available to absorb the beam and causes a decrease of the beam attenuation. This effect thus prevents us to perform dose ramping measurements with the krypton gas filter in place unless such effects can be accurately modelled. This will be the focus of a study in the future.

Calorimetry is another possible technique to be investigated for absolute dosimetry in broadbeam radiation fields with a similar quality to that used in MRT [Harty et al., 2014]. However, for a routine protocol, the use of a small volume IC remains the best compromise between detailed dosimetry measurements incorporating radiation transport Monte Carlo correction factors and a routine clinical dosimetry protocol such as that used in daily quality assurance of clinical radiotherapy. This protocol also provides the basis to correctly scale the dose values from the MRT treatment planning system (TPS) [Bartzsch, 2014] to the spatially fractionated dose distribution in the animal to be treated, based on the previously acquired CT data. Furthermore, such reference dosimetry protocol is of high importance for internal calibration of dose monitors within the MRT patient safety system and for calibration of high spatial resolution solid state detectors used to perform verification of the spatially fractioned beam for the actual MRT treatment [Bräuer-Krisch et al., 2010a; Lerch et al., 2011; Petasecca et al., 2012; Povoli et al., 2015]. In the case of the applied ramping method, the determination of the ion-recombination correction factor may not result in exactly the same values applying a uniform irradiation or a scanning method. However, since the scanning conditions at ID17 are unique, any hypothesis cannot be experimentally verified. The important point remains that the introduction of a reliable dosimetry protocol for MRT at such high dose rates is essential. In the case of the spatially frac-
tionated dose delivery in MRT, the physical dose may not result in the same biological effects when compared with broad beam irradiations and it may be of higher importance to determine a biologically equivalent dose (BED) in MRT. This is the focus of much current research internationally and beyond the scope of the work presented here.

This reference dosimetry protocol demonstrates the ability of performing reference absorbed dose to water measurements in a high dose rate synchrotron-generated X-ray beam with an acceptable precision. This protocol will therefore be used for future MRT pre-clinical studies and veterinary trials at the ID17 beamline. The precision could be further improved in the future by calibrating the MRT reference IC directly at the TH 200 beam quality and by performing the current ramping experiment using this calibration.

The very high dose rates associated with synchrotron X-ray sources requires careful consideration of how to correct IC readings for ion recombination effects. This study therefore provides a method, the current ramping method, dedicated to the determination of the ion recombination correction factor for a small volume ionisation chambers exposed to highly brilliant synchrotron radiation sources. This current ramping method allows the direct determination of the ion recombination correction factor using the reference dosimeter (PinPoint) in the reference dosimetry conditions and in the pre-clinical beam filtering configuration. Using the data presented in Figure 3.7, we are able to predict a value of $k_s$ for a given SR current. The maximum value of $k_s$ factor was found to be $1.047 \pm 0.006$. Under veterinary beam filtering conditions, $k_s$ is expected to be around 1.025. It should be noted that no uncertainty was considered on the SR current as this value is provided with a 0.05% precision at the ESRF.
Chapter 4

X-Tream Dosimetry System Characterisation

4.1 X-Tream dosimetry system

The X-Tream dosimetry unit has been developed by the CMRP in consultation with the ESRF biomedical beamline. The aim was to design a new dosimetry system able to cope with the challenging MRT dosimetry specifications [Lerch et al., 2011; Petasecca et al., 2012]. The system is composed of a silicon Single Strip Detector (SSD), a pre-amplifier module, a central data acquisition system unit (CSU) and a graphical user interface (see Figure 4.1).

Figure 4.1: The different elements composing the X-Tream dosimetry system.
4.1.1 Silicon Strip Detector (SSD)

The SSD consists in a microstrip diode fabricated via ion implantation on a p-type epitaxial substrate. The single strip dimensions are $900 \times 10 \, \mu m^2$. The 100 $\Omega$-cm p-type epitaxial layer is grown on top of a 370 $\mu$m thick substrate of lower resistivity (0.001 $\Omega$-cm) [Lerch et al., 2011; Petasecca et al., 2012]. A silicon oxide (SiO$_2$) layer surrounds the silicon detector in order to protect the bulk silicon (from dust, oil, grit, etc.) and avoid the generation of surface leakage currents that would otherwise degrade the overall performance of the device. The SSD structure also incorporates an n-type guard ring limiting the width of the sensitive area to approximately 30 $\mu$m for an applied bias of -50V [Petasecca et al., 2012]. A cross-sectional view of the detector sensor is displayed in Figure 4.2.

![Cross-sectional view of the SSD chip. Reprinted from Petasecca et al., 2012.](image)

The sensitive volume (SV) of the SSD depends on the applied (reverse) bias. Interaction of the incident radiation within the SV of the SSD leads to the generation of electron-hole (e-h) pairs that separate under the influence of the electric field and induce a photocurrent (proportional to the dose rate) in an external circuit.

The SSD can be either used in passive mode or active mode, i.e. with or without
4.1. X-Tream dosimetry system

Figure 4.3: (A): Waterproof flexible carrier with USB interface connection to pre-amplifier, (B): detail of the SSD chip mounted in the end of the flexible carrier using the CMRP patented “drop-in” technology, (C): detail of the chip mounted in the flexible carrier, (D): Scanning Electron Microscopy (SEM) image of the SSD chip where the 900 \( \mu \text{m} \times 10 \mu \text{m} \) sensitive volume (SV) is indicated.

applying a polarisation voltage. For MRT applications, the SSD is working in active mode by applying a voltage of between -50 and -70 V. Pictures of the SSD for different magnifications as well as an image of the SSD acquired using scanning electron microscopy are displayed in Figure 4.3.

Very high resolution dosimetry can be achieved using the SSD in “edge-on” mode (see Figure 4.4) and in active mode using the above operating voltage range. When using the “edge-on” orientation, the depletion region in the epitaxial growth direction defines the intrinsic width of the SV. Because of the low resistivity of the silicon, this length can be as low as 10-12 \( \mu \text{m} \) at a -30 V polarising voltage [Petasecca et al., 2012].

In addition to this, the effect of the guard ring design allows further reduction in the depletion width as it acts as sucking electrode to collect a proportion of the charge created directly under the strip electrode. Two orientations of the SV are available: so called “90\(^\circ\)” orientation, with the long axis of the SV strip parallel with the beam
4.1. X-Tream dosimetry system

Figure 4.4: Different possible orientations of the SSD.

direction, and so called “straight”, with the long axis orthogonal to the beam in the vertical dimension. Figure 4.4 summarises the different possible orientations of the SSD.

4.1.2 Pre-amplifier module

The pre-amplifier is directly connected to the SSD probe via a USB connector and to the Central data acquisition System Unit (CSU) via a long cable (see Figure 4.1). The pre-amplifier needs to provide a dynamic range sufficiently large to allow the measurements of the peak and valley signals with the same accuracy. A linear sensitivity over the entire dynamic range is also a requirement of the pre-amplifier. For MRT applications, a low-gain amplifier is used and another pre-amplifier called “high-gain” amplifier has been engineered for applications at lower dose rates. A schematic of the pre-amplifier module is displayed in Figure 4.5.
4.1. *X-Tream* dosimetry system

Figure 4.5: Schematic of the pre-amplifier module. (Courtesy of Dr. Marco Petasecca from CMRP).
4.1.3 Central data acquisition system

The CSU provides the voltage bias to the SSD. The system sampled the generated photocurrent at 1 MHz and proceeds to its digital conversion. The CSU also provides a communication between a remote personal computer used to operate the system via a USB cable.

4.1.4 RADPLOT Graphical user interface

The custom software RADPLOT is an user interface that displays the photocurrent generated (in ADC counts) as a function of time. An example of a signal acquired with the X-Tream system on the RADPLOT interface is showed in Figure 4.6.

![Figure 4.6: Signal acquired by the SSD on the ID17 beamline for a 2 cm × 2 cm field size at 2 cm depth in solid water phantom (50 mm.s\(^{-1}\) scan speed)](image)

Cursors are used to select an area of interest under which the integrated counts is measured. A first set of cursors is used to sample a region where the beam is off in order to quantify the baseline counts associated with the dark current of the SSD detector at its operating voltage. A second set of cursors is used afterwards to select
4.2 Characterisation of the X-Tream pre-amplifier modules

The gain of the X-Tream pre-amplifier depends on the capacitor and feedback resistor (referred as C1 and R1 respectively in Figure 4.5). The linearity response of both the high and low pre-amplifier modules as well as their dynamic range have been investigated in order to test their suitability for MRT quality assurance purposes. These measurements also allowed the determination of the current to counts conversion factor for both modules.

Resistances of 200 kΩ, 21.94 MΩ and 101.8 MΩ were used as an input of the considered pre-amplifier and different polarisation voltages were applied across the device in order to generate a current source ranging from 9.82 nA to 154 µA. The output was acquired by the ADC level signal with the Radplot software.

Figure 4.7 shows the high gain pre-amplifier response as a function of the input current. The high-gain pre-amplifier exhibits a linear behaviour between $10^{-7}$ A and $10^{-5}$ A. For larger input currents the ADC count value stabilises because of the saturation of the ADC at 60,000 counts. From these results, the dynamic range of the high gain pre-amplifier can be deduced as being around $10^2$. This dynamic range does not suit the MRT requirements as a dynamic range of at least $10^3$ is desirable. However, this pre-amplifier can be used for experiments performed at lower dose rates.
4.2. Characterisation of the X-Tream pre-amplifier modules

Figure 4.7: Response linearity of X-Tream high gain pre-amplifier module as a function of the input current.

than MRT, like in SSRT for example. From the slope of the linear fit in Figure 4.7, the current to counts conversion factor was found to be 5.332 counts/nA for the high gain pre-amplifier.

The low gain pre-amplifier response as a function of the input current is displayed in Figure 4.8. The low gain pre-amplifier response was found to be linear from $10^{-7}$ A to $10^{-4}$ A. Similarly to the high gain pre-amplifier, for larger input currents, the ADC reaches the 60,000 counts and saturates. The ADC counts to nano-Ampere conversion factor was determined to be 0.606 counts/nA for this amplifier. The dynamic range of the high gain amplifier was found to be equal to $10^3$ which is suitable for MRT applications.

The low level of around 300 and 100 ADC counts observed for the high gain and low gain pre-amplifier respectively depends on the offset of the low pass band filter of the ADC. This level can be adjusted to compensate for the offset generated by the leakage current of the detector. In theory it could be compensated to zero ADC
counts by nulling the input leakage current but, in practice, it is typically set to 100 ADC counts to make sure that there is a baseline to be subtracted. Consequently, if required, the dynamic range could be further increased by adjusting the offset of the low pass band filter and thus by reducing the baseline signal.

4.3 Radiation Damage

4.3.1 SSD pre-irradiation

Silicon-based detectors exposed to radiations are known to experience radiation damages leading to a decrease of their sensitivity [Rikner and Grusell, 1987]. Radiation damages induced by X-rays in silicon-based detectors are generated by the electrons with energy higher than 260 keV and that have enough energy to dislocate an atom (i.e. point defect) from the silicon lattice [Flicker et al., 1962]. This atom vacancy acts as a generation-recombination centre which can trap or release a carrier. Elec-
4.3. Radiation Damage

eutrons mostly generate point defects which define extra energy levels in the forbidden bandgap of the semiconductor band structure. The defects acting as traps are the ones responsible for the decrease of charge collection efficiency [Lindström et al., 1999]. In both n and p type substrates, the carrier lifetime (τ) is inversely proportional to the concentration of deep-level defects and is thus responsible for the deterioration of the sensitivity of the sensor with the accumulated dose [Rosenfeld, 2006].

Silicon-based detectors sensitivity also depends on their resistivity and whether the detector is n-type or p-type. Indeed, p-type radiation detectors are known to be more radiation hard [Lozano et al., 2005]. This is the reason for this material type being chosen for the SSD.

The knowledge of the SSD response behaviour as a function of the accumulated dose is thus of the highest importance as response reproducibility is required from the detector in order to be used for quality assurance in MRT. The SSD response was measured as a function of the pre-irradiation dose at the ESRF and results are reported in Figure 4.9.

![Figure 4.9: SSD response as a function of the accumulated dose.](image)

First, a slight rise in response with pre-irradiation dose is observed which is related
to the generation of an accumulation layer of negative charge in p-Si below the Si-SiO$_2$

due to a buildup of the positive charge in the SiO$_2$ induced by the X-ray radiations.

This effect increases the length of depletion region in the lateral direction and thus the
detector’s SV. The charge collection and hence the signal are increased accordingly.

Then the response of the SSD decreases with the delivered dose before stabilising
at around 40 kGy. At this pre-irradiation dose the initial response of the SSD has been
reduced by 84%. This decrease in response is likely to be coming from the combination
of two effects. First, as explained before, the X-ray radiations induces point defects
in the silicon bulk that lead to a degradation of the carrier lifetime and thus to a
reduction of the response. Moreover the accumulation of trapped charges in the oxide
layer surrounding the silicon detector reduces the electric field slightly which degrades
the effective charge collection efficiency.

Above 40 kGy the reduction in response is $\sim$1% per 1000 Gy. Since the peak en-
trance dose (measured at 3 mm depth) is usually below 1000 Gy, 40 kGy was therefore
chosen as the recommended pre-irradiation dose for normal MRT QA for in-phantom
measurements in order to maximise the useful operational lifetime of the SSD without
too much decrease in overall response with dose.

### 4.3.2 SSD Initial Over-response Mechanisms

After demonstrating the mandatory pre-irradiation of the SSD in order to stabilise its
response, an investigation into the underlying mechanisms responsible for this initial
change in response was required. Several line scans of the synchrotron X-ray broad
beam were performed over a SSD with a straight orientation of the SV oriented face-
on (see schematic drawing in Figure 4.10) in order to look at the detector response
as a function of line position for different accumulated radiation doses. The resulting
recorded photocurrent as a function of the lateral location are displayed in Figure 4.11.
4.3. Radiation Damage

Figure 4.10: Drawing of the SSD chip representing the detector guard ring, the microstrip and its pad and the p+ substrate connector pad.

Figure 4.11: SSD recorded current from the line scans performed for different pre-irradiation doses.

As expected from the pre-irradiation results obtained in subsection 4.3.1, the area below the resulting curves is decreasing with the pre-irradiation dose and stabilises once the accumulated dose reaches 37 kGy. The initial increase in overall SSD response (or charge collection) observed in Figure 4.9 is not directly noticeable in the line scan presented in Figure 4.11 as the increment in dose was too large.

In Figure 4.11 it can be seen that the response in the area under the microstrip stabilises very quickly. This stability is indicated by the flat plateau region in the line scan which is $\sim$900 µm long (corresponding to length of the microstrip) and that does not decrease after 5 kGy of total irradiation dose. This stable component of the response is due to the presence of the n+ junction under the collecting electrode which is able to maintain a strong and constant electric field so as to allow a consistent amount of photogenerated charge drift and collection when the SSD is exposed to the same irradiation conditions. The experimentally observed decrease in overall response of the SSD up to a 37 kGy pre-irradiation dose is therefore primarily due to the decrease
4.3. Radiation Damage

in the otherwise undesired photogenerated charge collection from the area around the wire bonding pad of the SSD and inside the guard ring indicated in Figure 4.10.

On the line scans acquired, from a 2 kGy accumulated dose, the small over-response peak on the left-hand side of the plateau in Figure 4.11 corresponds to a charge collection under the microstrip. This peak continues to decrease in intensity with total irradiation dose and is primary responsible for the associated decrease in the overall radiation response of the SSD observed experimentally. This peak is associated with charge collection from the region located between the detector pad and the microstrip. This finding is an undesired behaviour as the response of the SSD would ideally be constant over all the SV of the detector. A 2D scan of an unirradiated SSD was performed at the ID17 beamline in order to study the charge collection behaviour across the device. The SSD was face-on oriented and irradiated with a 50 µm × 50 µm beam spot at different horizontal and vertical locations via a raster scanning technique. The SSD was reverse biased at -30 V. The resulting response as a function of the vertical and horizontal beam position on the SSD chip was established and is represented in Figure 4.12. In order to ease the interpretation of the results, the map obtained from the SSD 2D scan has been superimposed on the SSD chip technical drawing.

In Figure 4.12 a strong over-response (indicated by the red region associated with large charge collection) is observed in the region between the microstrip and the immediately adjacent wire bonding pad. This is due to the (undesired) charge collection which almost doubles the sensitive area of the detector. This explains the massive broad peak observed in Figure 4.11 when irradiating a non pre-irradiated SSD face-on oriented.

The charge collection region is also present in the area between the guard-ring pad and the microstrip pad. A residual charge collection (i.e. of lower intensity) is also spreading underneath the p+ junction around the guard ring which makes the charge
4.3. Radiation Damage

Figure 4.12: 2D scan of an unirradiated SSD chip using a 50 µm × 50 µm beam spot. The color scale is in ADC counts. An over-response of the device is particularly highlighted in the region between the pad and the microstrip.

collection region very wide. However, after the first two steps of pre-irradiation the charges are exclusively collected from the microstrip and the area delimited by the guard ring and the response of the detector starts stabilising.

In order to improve the SSD charge collection behaviour, a 3D model of the device was developed by Marco Petasecca (CMRP, University of Wollongong) using the Synopsys TCAD simulation software package. The electric field, total current density and electrostatic potential of the SSD were simulated for bias voltages ranging from 0 to -100 V. Simulations showed no breakdown in the electric field meaning that the charge collection efficiency of the SSD increases with the amplitude of the reverse bias voltage applied. A significant increase in both the electrostatic potential and current density in the region between the microstrip and the pad was observed and was seen to increase with the amplitude of the applied bias. It was concluded that the over-response observed in the region between the pad and the microstrip was introduced by the fact that the guard ring is positioned (unavoidably) around the wire bonding pad.
(see Figure 4.10). Indeed, the distance being larger between the guard ring and the pad than between the guard ring and the microstrip, charge collection is allowed from the metal-oxide-semiconductor (MOS) capacitor generated by the Al pad, the silicon oxide layer under the wire bonding pad and the silicon substrate.

The carrier lifetime is constant in the silicon substrate and sufficiently long to allow the electrons to diffuse from under the wire bonding pad (but inside the guard ring) into the drift region of the microstrip where they can be collected. This effect will also contribute to the over-response observed in unirradiated SSDs.

All these contributions to the charge collection efficiency clearly reduce significantly once the detector is pre-irradiated: only a small over-response is observed in the final profile presented in Figure 4.11 and the SSD response remains quite stable above 40 kGy.

4.4 X-Ray Photon Energy Dependence of the SSD

4.4.1 Introduction

Silicon based dosimeters are known to over-respond to low energy X-ray photons compared to water-equivalent dosimeters. This energy dependence is due to the higher atomic number Z of the silicon compared to water which enhances the number of photon interactions in the material and thus the energy deposition. The energy dependence of silicon based detectors therefore strongly depends on the presence of high-Z materials in the dosimeter packaging [Rosenfeld et al., 1995]. The importance of this over-response also depends on the energy spectrum.

For MOSFETs, the over-response introduced by the detector energy dependence has been determined experimentally to be as high as a factor of 3 for an X-ray source of 50 kVp [Cheung et al., 2009]. In MRT, as the photon energy spectrum ranges from
30-300 keV with a mean energy around 100 keV, the over-response of silicon based detectors is expected to be considerable and to vary with depth in water due to beam hardening. This energy dependence could lead to an over-response in valley dose due to the dominance of lower-energy photons scattered out of the primary beam [Siegbahn et al., 2006]. In the study of Siegbahn et al. [2009] the discrepancies observed between the experimental and MC calculated PVDRs were attributed to the energy dependence of the MOSFET detector.

An experimental study was conducted at the ESRF to investigate the energy dependence of the SSD. Measurements were performed at four different beam energies (35.3, 60, 80 and 100 keV) using the SSD. On top of the SSD response behaviour with the beam energy, the SSD linearity with dose was investigated for each beam energy. The influence of both the SSD and SV orientation was studied for both the linearity and energy dependence studies.

### 4.4.2 Material and Methods

The study to experimentally determine the energy dependence of the SSD was performed in the SSRT hutch of the ID17 beamline using monochromatic beams. For these experiments, a Laue monochromator was used, producing monochromatic beams with energies ranging from 25 keV up to 150 keV.

Two SSDs were tested: a first one with a $90^\circ$ orientation of the SV and a second one with a straight orientation of the SV. Each detector was irradiated in both face-on and edge-on orientation. The aim was to study the possible influence of the orientation of both the detector and their SV on the device response.

Before starting measurements at a given energy, one needs to exactly know the amount of dose delivered to the detector. Consequently, dosimetry measurements using a reference dosimeter were required before performing SSD acquisitions at a
4.4. X-Ray Photon Energy Dependence of the SSD

given energy.

During an SSRT irradiation, the delivered dose is monitored by two redundant plane parallel ICs located upstream the sample stage. Before an SSRT treatment, those chambers are calibrated towards the SSRT reference Semiflex 31010 IC fixed at 2 cm depth in a solid water phantom for the different irradiation masks about to be used for the treatment. This calibration allows to correlate the plane parallel ICs recorded signal to the dose delivered at 2 cm depth in the phantom. In the context of the energy dependence experiments, three different masks were used for the calibration. These masks defined squared field size of dimensions 2 cm \( \times \) 2 cm, 3 cm \( \times \) 3 cm and 5 cm \( \times \) 5 cm. The measurements were performed in the Easy Cube cubic solid water phantom produced by Euromechanics.

Once the calibration is performed, a given dose can be delivered at 2 cm depth using one of the available masks via a user graphical interface. The irradiation is then monitored by the two plan parallel ICs and stopped once their signal reach the value corresponding to the desired dose.

For each beam energy investigated, the Semiflex 31010 SSRT reference IC was used for dosimetry. This chamber has a calibration factor for a TH200 beam quality delivered by PTB (Physikalisch-Technische Bundesanstalt) in Germany. \( k_Q \) correction factors are also provided for different beam qualities. The different beam qualities under which the \( k_Q \) correction factor is known for the Semiflex 31010 IC are reported in Table 4.1. In order to have a reference dosimetry as accurate as possible, the aim was to perform our energy dependence study at energies as close as possible to the beam qualities reported in Table 4.1. From the 1\textsuperscript{st} Cu HVL provided by PTB to define each beam quality, it is possible to estimate the closest beam energy to this beam quality. Indeed, as the 1\textsuperscript{st} Cu HVL corresponds the copper thickness required to obtain a photon beam intensity \( I_{1/2} \) equal to half of the intensity of the primary
beam $I_0$, $I_{1/2}$ can be written:

$$I_{1/2}(E) = \frac{I_0(E)}{2} = I_0(E)e^{-\mu_{Cu}(E)x_{1/2}} \quad (4.1)$$

with $E$ the beam energy, $\mu_{Cu}(E)$ the copper energy attenuation coefficient and $x_{1/2}$, the 1st Cu HVL. From Eq. 4.1, it is possible to determine the copper energy attenuation coefficient. Then, by dividing the $\mu_{Cu}(E)$ coefficient by the copper density, the Cu mass energy attenuation coefficient is obtained. From this value, one is able to determine the beam energy by using the NIST database providing the mass energy total attenuation coefficient with coherent scattering as a function of the beam energy [Berger et al. 2010]. The energies obtained using this method for the different beam qualities are reported in Table 4.1.

**Table 4.1: Beam qualities available at PTB for the Semiflex IC calibration. Beam qualities are defined by the 1st Cu HVL. For each of them, the correction factor $k_Q$ is provided in order to perform absolute dosimetry measurements at different beam qualities. From the 1st Cu HVLs, the corresponding beam energy has been calculated using the NIST database providing the energy total attenuation coefficient (with coherent scattering) [Berger et al., 2010].**

<table>
<thead>
<tr>
<th>Beam Quality</th>
<th>1st Cu HVL (mm)</th>
<th>$k_Q$</th>
<th>Calculated Beam Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T70</td>
<td>0.1</td>
<td>0.985</td>
<td>34</td>
</tr>
<tr>
<td>T100</td>
<td>0.18</td>
<td>0.983</td>
<td>42</td>
</tr>
<tr>
<td>T140</td>
<td>0.46</td>
<td>0.986</td>
<td>59</td>
</tr>
<tr>
<td>T150</td>
<td>0.82</td>
<td>0.989</td>
<td>73</td>
</tr>
<tr>
<td>T200</td>
<td>1.59</td>
<td>1</td>
<td>97</td>
</tr>
</tbody>
</table>

The $k_Q$ values provided by PTB are plotted as a function of the calculated energy beam in Figure 4.13. For practical and technical reasons, the experiments had to be performed at the following beam energies: 35.3, 60, 80 and 100 keV. When possible, the $k_Q$ factor was thus estimated using a linear interpolation between the two closest beam energies for which the $k_Q$ factor was known. For the 100 keV beam energy, a $k_Q$ factor equal to 1 was used as this energy is very close to the mean energy of the
4.4. X-Ray Photon Energy Dependence of the SSD

T200 beam quality. The $k_Q$ values finally used for the dosimetry measurements at the different beam energies are displayed in Figure 4.13.

Figure 4.13: $k_Q$ determination for the PTW Semiflex 31010 at different beam energies investigated in the energy dependence study.

As the dosimetry was performed at 2 cm depth in the Easy Cube phantom, the SSD was set at the same depth in the same phantom. The SSD was fixed in a gammex...
plate where a dedicated groove was created to hold the SSD either in face-on or edge-on orientation. Figure 4.14 shows the SSD set up for irradiations performed in edge-on mode. In SSRT, the dose rate under reference conditions (i.e. at 2 cm depth in the Easy Cube phantom and using a 5 cm × 5 cm field size), the dose rate is ranging between 14 and 18 Gy/min [Prezado et al., 2011b]. As the dose rate is much lower than the one encountered in MRT, the high gain amplifier of the X-Tream dosimetry system was used for the experiments in order to maintain a good Signal to Noise Ratio (SNR). Three different doses were delivered to the detectors: 0.25, 0.5 and 1 Gy. During the irradiation, the dose delivery was monitored by the two redundant plane parallel ICs upstream the Easy Cube phantom. All the measurements were performed within a 2 cm × 2 cm field size and the beam height was 2 mm.

4.4.3 Results

Figure 4.15 represents the signal acquired by the SSDs as a function of the delivered dose and for the four different beam energies investigated. The annotations “90°” and “straight” stand for the SSD with a “90°” or “straight” orientation of the SV respectively.

For both detectors, the acquired signal is linear with dose for the different energies investigated in both face-on and edge-on orientations. Experimental results have been fitted with linear curves. Depending on the beam quality, different slopes are observed because of the energy dependence of the SSD. The difference in terms of ADC counts values between both detector is most likely due to the total irradiation dose being significantly different for each detector. This means that the sensitivity of each detector cannot be compared directly.

Using the detector in edge-on or face-on orientation doesn’t seem like having a significant effect on the measurements. The slight difference in terms of recorded counts
4.4. X-Ray Photon Energy Dependence of the SSD

Figure 4.15: Investigation of the SSD linear behaviour with dose at different beam energies. Two orientations of the SSD have been tested (face-on and edge-on), both for the two possible orientations of the SV (straight and 90°).

sometimes observed is most likely coming from a lack in position accuracy of the detector between the different sets of measurements. Also, additional measurements have been performed separately where the response of the "straight" SSD in edge-on mode was compared with the response of the same SSD but rotated by 90 degrees. In this case the response of the SSD varied by less than 10% [Lerch "private communication"].

Currently, the only way to obtain a dose value from the SSD is to calibrate the detector relative to a reference IC and to convert the integrated counts recorded into a dose value. As evident from Figure 4.15, this calibration will depend on the beam quality. Therefore, from the measurements performed, it is difficult to accurately quantify the detector response as a function of the beam energy as only a relative
difference in the SSD response can be extracted from the results. For example, for the results obtained in the “90°, Face-On” detector configuration, one can only state that the SSD response obtained at 35.3 keV is around 4 times higher that the response obtained at 100 keV. The only way to provide a more precise analysis of the SSD response variation as a function of the beam energy is to compare our experimental results to what is expected from theory.

The dose deposited by a monoenergetic photon beam of energy $E$ into a Si medium is equal to:

$$D_{Si} = \Psi(E) \times \frac{\mu_{en}(E)}{\rho} \bigg|_{Si}$$

(4.2)

with $\Psi(E)$ the energetic fluence (J.cm$^{-2}$), $\mu_{en}(E) \bigg|_{Si}$ the mass energy-absorption coefficient of silicon (cm$^2$.g$^{-1}$) at the energy $E$. Conversely, the absorbed dose in water delivered by a monoenergetic photon beam of energy $E$ of similar energetic fluence $\Psi(E)$ is equal to:

$$D_{H_2O} = \Psi(E) \times \frac{\mu_{en}(E)}{\rho} \bigg|_{H_2O}$$

(4.3)

Therefore, the ratio of $D_{Si}$ over $D_{H_2O}$ as a function of the photons energy should have a trend close to the response of the SSD as a function of the beam energy. For an identical energetic fluence, the ratio of $D_{Si}$ over $D_{H_2O}$ becomes:

$$\frac{D_{Si}}{D_{H_2O}} = \frac{\Psi(E) \times \frac{\mu_{en}(E)}{\rho} \bigg|_{Si}}{\Psi(E) \times \frac{\mu_{en}(E)}{\rho} \bigg|_{H_2O}} = \frac{\mu_{en}(E) \bigg|_{Si}}{\mu_{en}(E) \bigg|_{H_2O}}$$

(4.4)

The SSD signal was thus normalised to the ratio of Si to H$_2$O mass energy-absorption coefficients (extracted from the NIST database [Berger et al., 2010]) for a 100 keV energy. Figure 4.16 represents the resulting response of the two different SSDs for
both face-on and edge-on orientations as well as the Si to H\textsubscript{2}O mass energy-absorption coefficients ratio as a function of the beam energy.

Figure 4.16: Experimental determination of the energy dependence of the SSD for two detector orientations (face-on and edge-on) as well as for the two possible orientations of the SV (straight and 90\textdegree). Results have been normalised to the ratio of Si to H\textsubscript{2}O mass energy-absorption coefficients at 100 keV.

Due to time constraints, it was not possible to repeat several times the measurements for each doses. Consequently, for the energy dependence investigation, the signal obtained for the 0.25 and the 0.5 Gy delivery were respectively multiplied by 4 and 2 in order to be compared to the signal obtained for the 1 Gy delivery and to get a higher statistics on the results. The uncertainty bars represent two standard deviations (2 \(\sigma\)). The experimental results are consistent with the variation in the absorption coefficient ratio, with differences most likely associated with the impact of scattered photons from the surrounding phantom material. Detailed MC calculations are now required in order to validate this experimental work but are beyond the scope of this thesis. The results represent a worst case scenario as in reality the photon energy used in MRT at the sample stage is “pink” (see Figure 2.7), not monoener-
getic and with no component in the primary spectrum less than 30 keV. Additional measurements could be performed in the future with different pink beam spectra (i.e. varying peak beam energies) which would provide a more realistic impact of the SSD’s silicon energy dependence on the calculated doses in MRT.

The SSD energy dependence may be critical for the experimental determination of the PVDRs. Indeed, as previously described by Siegbahn et al. [2009], as the valley dose is due to the photons scattered from the microbeams, the energy spectrum in the valley region is softer than in the peak.

Figure 4.17: Peak and Valley energy spectra at 1, 10 and 20 mm depth in water simulated with a Geant4 MC code. Made by Dr. Stefan Bartzsch.

Considering the energy dependence of silicon-based detector, this could introduce an under-estimation of the PVDR. Energy spectrum in both the peak and valley regions at different depths in water have been simulated by Dr. Stefan Bartzsch (postdoctoral training fellow at the Institute of Cancer Research, London) using a Geant4 MC simulation code. The simulation has been run in a 20 mm × 20 mm field size and for 50 μm FWHM microbeams spaced by 400 μm. Figure 4.17 represents the valley and peak spectrum at different depths in water. The variation of the mean
4.4. X-Ray Photon Energy Dependence of the SSD

A 30 keV offset between the peak and valley mean energy is observed at narrow depths and decreases progressively with depth. The main reason for the difference in mean energy is due to the higher contribution of Compton scattered photons at lower energy in the valley. As the valley dose is directly correlated to the peak dose (i.e. generated by the photons scattered out of the microbeams), the valley mean energy increases accordingly. At the reference depth (i.e. 20 mm depth), the mean energy is equal to 97 keV and 77 keV in the peak and in the valley respectively. In addition, the lack of backscattered photons at depth (no scattering medium present beyond 50 mm in the simulations) further adds to the shift of the valley spectrum to high energy.

Considering the energy dependence results obtained for the SSD, one can thus expect this offset to have a significant impact on the PVDRs measurements.

![Variation of both peak and valley energy spectra mean energy with depth in water. Simulations were performed using a Geant4 MC code by Dr. Stefan Bartzsch.](image)
In this chapter experimental measurements have been performed in order to characterise the SSD response to total irradiation dose as part of a radiation damage investigation. First, the SSD response as a function of the accumulated dose was studied. An initial slight rise in response with pre-irradiation dose was observed and has been attributed to the positive charge buildup in SiO$_2$ induced by the X-ray radiations. This effect was already observed in the study of Aldosari et al. [2013] where the authors characterised p-type epitaxial diode used as sensitive elements of the MagicPlate detector [Wong et al., 2012]. Then the SSD response decreased by around 84% before stabilising once a 40 kGy accumulated dose was reached (see Figure 4.9).

Line scans were performed on the SSD for different pre-irradiation doses in an attempt to isolate and therefore better explain the radiation damage mechanisms, and a similar behaviour was observed: the signal stabilises after a pre-irradiation dose of 37 kGy (see Figure 4.11). However, the SSD response with vertical scans exhibited a plateau corresponding to the signal measured from charge collected under the microstrip which remains stable from a 5 kGy accumulated dose. After the 5 kGy pre-irradiation dose, the SSD response reduction is most likely due to the charge accumulation in the oxide layer surrounding the silicon detector which decreases the electric field and the effective charge collection efficiency.

In Figure 4.11 an over-response in the region between the microstrip and its pad was noticed. A 2D response mapping of a non pre-irradiated was thus performed at the ESRF with a 50 $\times$ 50 $\mu$m beam spot. As expected, a strong over-response was observed in the region between the microstrip and the detector pad which is coming from the metal-oxyde-semiconductor (MOS) capacitor generated by the pad and the silicon oxide underneath it which allows charges collection from the pad in unirradiated SSD devices. A charge collection region has also been noticed in the
area between the guard-ring pad and the microstrip pad as well as a residual charge collection spreading underneath the p+ junction around the guard ring thus resulting in a very wide sensitive region. But, as demonstrated by the line scans, after the first two steps of pre-irradiation the charges are exclusively collected from the strip-guard ring area and the response of the detector starts stabilising.

During the pre-irradiation process, once the concentration of the point defects generated reach approximately the same concentration as the generation centres, the carriers recombine before reaching the electrodes. There is then no more signal associated with the charge generated underneath the pad. As the dimension of the pad is around 200 $\mu$m $\times$ 200 $\mu$m, the pre-irradiation process is thus of major importance in order to limit the charge collection to the microstrip and improve the spatial resolution of the detector. After, an accumulated dose of around 40 kGy, the change in SSD response is $\sim$1% per 1000 Gy. As a peak dose of a few hundreds grays are usually delivered for a MRT treatment, the SSD should be quite suitable for MRT as the change in SSD response is acceptable. However for clinical applications one needs to either recalibrate or model the decrease in response with total accumulated dose. Between 70 and 80 kGy the overall response of the device is extremely stable so for very high precision dosimetry (future clinical work for example) a 70 kGy pre-irradiation dose is recommended for such dosimetry conditions.

In the future, it would be ideal to extend the pre-irradiation procedure on different SSDs until an effective deterioration of their response is reached in order to evaluate the SSD lifetime. This would allow the establishment of standard operating procedures in order to ensure the most accurate and reproducible results from the SSD. Additional simulations are also required in order to validate the experimental results obtained. Finally, each batch of detectors should be characterised in order to correct for the slight decrease observed in SSD response above 40 kGy. This will contribute to extend the
effective radiation lifetime of the SSD which may be useful in the clinical application of the SSD.

The energy dependence of the silicon single strip detector was experimentally determined at the ID17 beamline at the ESRF. Measurements were performed in the SSRT experimental hutch at four energies in the range of the MRT energy spectrum. The monoenergetic beams were delivered by a Laue monochromator. Two different SSDs presenting different orientations of the SV (i.e. straight or 90°) were tested in both edge-on and face-on configurations. The SSDs linearity with dose was studied at the different beam qualities by delivering three different known doses to the detectors. For all configurations investigated, the SSDs showed a linear behaviour with the delivered dose. A decrease of the slope of the linear fits with the beam energy was observed due to the over-response of the SSD at low energies. Indeed, as demonstrated in Figure 4.16, all the SSD configurations investigated exhibit a strong energy dependence below 100 keV. The influence of the SV orientation and the SSD setup configuration (i.e. face-on or edge-on configuration) on the SSD response with beam energy needs to be further investigated. The energy dependence is a major limitation of the SSD as it would make absolute dose measurements in MRT a complex task. Indeed, despite the possibility of calibrating the detector under reference conditions, this calibration will be lost as soon as the experimental conditions differ from the reference ones. For example, change of detector depth in a dosimetric phantom will affect the detector response due to the hardening of the energy spectrum with depth. Change in the irradiation geometry may also induce difference in the SSD response as this will modify the amount of scattered radiations.

MC simulation results show a difference of mean energy about 20 keV between the valley and peak energy spectra at 20 mm depth in water. Given the energy dependence of the SSD, this offset could lead to an under-estimation of the PVDR measured with
4.5. Conclusion

the SSD. This issue was assessed in the context of a MOSFET dosimeter by Siegbahn et al. [2009] where the photon energy spectrum in both the valley and peak regions was calculated using MC simulations. From the acquired spectra, Siegbahn et al. [2009] estimated that the PVDRs measured with the MOSFET detector had to be multiplied by a factor of 1.7 in order to compensate for the energy dependence of the detector.

In the near future, additional measurements could be performed at higher energies (at 150, 200 and 250 keV) in order to verify that the SSD energy dependence is stabilising from 200 keV. This would also allow the establishment of an experimental set of data for energies ranging over the entire MRT spectrum. These measurements were not feasible at the time of the experiments as the maximum reachable beam energy was limited to 150 keV. They might though be complicated to perform because of the reduced photon flux at those energies. MC simulations are also required in order to confirm the experimental results. These simulations should also include an investigation of the SSD response in both microbeam and valley spectra in order to predict the influence of the SSD energy dependence on the PVDRs measurements.

In a longer term approach, the design of the SSD could be improved in order to mitigate for the energy dependence effect. To this end, thinning the Si substrate and adding a water equivalent material (PMMA) encapsulation around the device could be considered.
Chapter 5

MRT Beam Quality Assurance at ESRF

The quality of MRT treatment demands reproducible and precise spatial fractionation of the incoming synchrotron beam. The intensity profile of the microbeams must also be quickly and quantitatively characterised prior to each treatment for comparison with that used for input to the dose planning calculations. In this chapter, the ability of the SSD to perform rapid and efficient QA test prior to each MRT treatment is evaluated. This study is based on in-air measurements of the horizontal profile of the intrinsic microbeam X-ray field in order to determine the relative intensity of each microbeam and also assess the alignment of the MSC.

5.1 Methods

5.1.1 Instrumentation

The experiments were performed at the ID17 MRT beamline at the ESRF. The filtering conditions consisted in the pre-clinical configuration with two additional beam modifiers inserted in the beam; the krypton gas filter and the IC0 beam monitoring ionisation chamber as they are both planned to be used in the context of the veterinary clinical trials for patient safety purposes. At a 24.8 mm wiggler gap, insertion of

\[\text{Part of the work presented in this chapter has been published in the Journal of Synchrotron Radiation [Fournier et al., 2016a].}\]
these additional elements shifts the mean energy from 105 to 108 keV. In the current study, the most relevant beamline components are the beam defining vertical slits, horizontal slits, the high-precision multi-slit collimator (MSC), and the goniometer. The horizontal slits were used to limit the horizontal field to 20 mm at the sample stage. The vertical slits aperture was set to the reference height of 500 µm, resulting in a beam height of 520 µm at the patient position due to beam divergence. The MSC was used to produce the 50 µm FWHM microbeams separated by a center-to-center (c-t-c) distance of 400 µm.

5.1.2 Detectors and Readout

A single strip detector was used for this study. For measurements performed in-air, the X-rays interacting in the silicon wafer and device packaging generate secondary electrons which in turn create electron hole (e-h) pairs in the sensitive volume. These e-h pairs, moving under the influence of the electric field in the device, induce a current in an external circuit. This current was sampled and recorded using the X-Tream fast data acquisition system presented in section 4.1. The RADPLOT software was used to configure the data acquisition system, acquire data, and display the ADC counts against time profile. By careful alignment of the device with the central axis of the synchrotron radiation beam, and by scanning the device in the horizontal directions, one is able to measure the energy deposition in silicon in the array of microbeams. To facilitate rapid installation, alignment, and scanning, the device was mounted directly on the goniometer stage (see Figure 5.1).
5.1.3 Rapid detector alignment with pink beam imaging

An imaging modality known as 'pink-beam' imaging [Serduc et al. 2010a] was used to align the device with the beam axis. Currently, the pink-beam is obtained by opening the wiggler gap from 24.8 mm to 100 mm and removing the MSC from the beam path. Under pre-clinical beam filtering conditions, moving from the irradiation to imaging modality decreases the beam intensity by 99.99% and shifts the mean energy from the initial 105 keV to 50 keV. The imaging system is comprised of a two dimensional X-ray detector located at around 4.3 m downstream of the goniometer stage. The detector consists of a fast-readout low-noise CCD camera (FReLoN) developed at the ESRF [Labiche et al. 2007]. A characterisation of the FReLoN camera can be found in [Coan et al. 2006]. The aim is to benefit from the small pixel size (23.26 µm ×
23.26 $\mu$m at the sample stage) of the FReLoN camera to image the SSD chip in order to align it with the beam. When shifting from irradiation to imaging mode, the beam defining slits can be removed from the beam path leading to a beam height around 2 mm at the goniometer stage. For large samples, in order to avoid the limitation of the image dimension in the vertical direction, a vertical scan is performed using the goniometer and images are acquired at different vertical offsets. The acquired frames are piled-up together to obtain a complete image of the sample [Serduc et al., 2010a].

During the beam alignment procedure, the pixel of the FReLoN camera corresponding to the central part of the beam is defined as the central pixel. When the MSC is inserted in the beam, the plane of the resulting X-ray microbeams is parallel with the vertical plane of the FReLoN camera (see Figure 5.2). The clear roll-off of the intensity of the microbeams is clearly visible in the FReLoN image which is a direct result of the wide wiggler gap used. The MSC is aligned in the beam in order to make the centroid of the central microbeam match with the central pixel of the camera.

![Figure 5.2: Image of the 2 cm $\times$ 520 $\mu$m parallel array of microbeams obtained with the FReLoN camera.](image)

To proceed to the SSD imaging, the detector was set-up on the goniometer stage and the MSC removed from the beam path. One frame image of the SSD was acquired by exposing the detector during 0.1 s. On the resulting image, the vertical and horizontal offset between the current position of the centre of the SSD chip and the central pixel position can be quantified. The detector was thus moved to the central position using the goniometer vertical and horizontal motion motors. A second image is usually acquired to verify its correct alignment.
5.1. Methods

5.1.4 Quality Assurance of multi-slit collimator alignment

At the ID17 biomedical beamline at the ESRF, the MSC is aligned by the monitoring of the output of a beam monitor IC whilst rotating the MSC about the vertical axis (z) perpendicular to beam direction (x). The MSC is rotated through small angles, typically ranging from 0.1° to -0.1° in increments of 0.01°. During alignment, the wiggler gap is set to a nominal setting of 40 mm in order to minimise beam fluence and associated ozone accumulation in the experimental hutch. In order to benchmark SSD measurements against the IC, the measurements with the SSD were also performed for a wiggler gap of 40 mm. For the beam filtering conditions considered during the experiments, moving the wiggler gap from 24.8 to 40 mm led to a 62% photon flux decrease and moved the mean energy from 108 to 90 keV.

A SSD with a straight orientation of the SV was used and the detector was edge-on oriented. The straight orientation of the SV was chosen to minimize the misalignment of the SV with the microbeams. The MSC rotation angle was moved between 0.05° and -0.05°. For each angle, the SSD was horizontally scanned through the 2 cm large array of microbeams at a constant speed (2 mm.s⁻¹). As the measurements were performed in-air, the notion of PVDR is irrelevant in the context of the present study. The notion of Peak to Valley Intensity Ratio (PVIR) corresponding to the ratio of peak signal and valley signal measured by the SSD was thus introduced. The effect of the MSC rotation on the peak and valley signal, PVIR and shape of the microbeams was investigated.
5.2 Results

5.2.1 Rapid detector alignment with pink-beam imaging

The images acquired during the alignment process for both face-on and edge-on oriented detector are displayed in Figure 5.3. These images consist in one single frame acquisition (i.e. the SSD was not moved through the beam during the image acquisition, only one image was acquired at a given vertical position of the detector). The pink-beam imaging of the detector is very fast as a 0.1 s exposure per frame was sufficient to acquire the image of the detector with a satisfying image quality. Therefore, the total time to set-up the detector and align it in the centre of the beam was approximately 30 minutes.

Figure 5.3: Images of the detector chip acquired with the FReLoN camera, in (A) face-on and (B) edge-on orientation, with one single frame and 0.1 s exposure. The red area on the image represents the dimensions of the MRT beam used for the experiment (i.e. 520 µm high at the goniometer stage).

In clinical practice a pre-aligned SSD could be mounted permanently in air. The imaging procedure would thus merely confirm that no misalignment of the detector, with respect to the microbeams, had occurred immediately prior to exposing the SSD to the full intensity X-ray microbeams to characterise the intrinsic MRT field profile.

The red area on the image represents the dimensions of the reference MRT beam (i.e. 20 mm × 520 µm) used for the experiments. One can notice that only a part
of the detector is exposed the beam as the sensitive volume of the SSD (900 µm) is longer than the beam height.

### 5.2.2 Quality Control of the multi-slit collimator alignment

The RADPLOT software records the ADC counts as a function of time. Knowing the scan speed of the motor used to perform the acquisition of the microbeams horizontal profile, one is able to convert the time variable into a distance value. The detector response profile of a 2 cm wide array of X-ray microbeams obtained for a 0° angle of the MSC is displayed in Figure 5.4.

*Figure 5.4: 2 cm wide array of microbeams acquired in air with the SSD (after subtraction of the baseline) for a wiggler gap of 40 mm. MSC rotation angle = 0°.*

On this figure, the RADPLOT data have been averaged by a factor equal to 500 and the baseline signal has been subtracted. During the experiment, the baseline noise of X-Tream with the SSD was better than ± 1.3 ADC counts (1 standard deviation) with no averaging applied. On Figure 5.4 one can verify the dimension of the lateral field size and that all the 49 microbeams are present. The peak signal is defined as the
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maximum signal in the microbeam and is represented by the red crosses (Figure 5.4).

Figure 5.5 presents a focus on the five central microbeams of the array presented in Figure 5.4. As a logarithm scale is used on the ordinate axis, one can notice that the valley is not stable and the lowest value is not necessary in the middle of two consecutive microbeams. Therefore, in order to determine the valley signal, the signal has been averaged over a region of interest of 100 µm centered in the middle of two consecutive microbeams. The resulting valley is presented by the blue crosses in Figure 5.4 and Figure 5.5.

Figure 5.5: Focus on the five central microbeams of the 2 cm wide array of microbeams acquired in air with the SSD for a wiggler gap of 40 mm. MSC rotation angle = 0°.

Figure 5.6 represents the central microbeam profile obtained for 0.0°, 0.02° and 0.04° rotation angle of the MSC about the z-axis. One can see that the intensity of the central microbeam is decreasing with the MSC angle because of the reduced aperture resulting from the MSC misalignment.

With the change of the MSC rotation angle, one would expect the Full Width Half Maximum (FWHM) of the central microbeam to decrease as the effective slit
5.2. Results

Figure 5.6: Central microbeam signal for three different rotation angles of the MSC (0°, 0.02° and 0.04°).

aperture is decreasing. Consequently, one possible way to check the MSC alignment would be to measure the FWHM of the central microbeam for the different angles of rotation investigated. The highest FWHM should then be obtained for a rotation angle corresponding to the optimum alignment of the MSC. For the different angles of rotation investigated, the lateral profile of the central microbeam has thus been fitted with a gaussian (not shown here) in order to extract the FWHM and FW10%M (Full Width at 10% Maximum) values from the fitting equation. The resulting FWHM and FW10%M values are reported in Figure 5.11. Only a 1.6% decrease is observed between the highest and lowest FWHM and FW10%M values which highlights the advantage of using an intensity method to determine the optimum MSC rotation angle rather than this method.

At the ESRF, the readings from a monitoring IC are used for MSC alignment purposes by acquiring the IC signal while rotating the MSC. The maximum integrated air kerma (proportional to the total fluence) measured by the IC is considered to
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Figure 5.7: FWHM and FW10%M of the central microbeam as a function of the MSC angle. Only a 1.6% decrease is observed between the highest and lowest FWHM and FW10%M values.

correspond to the optimum MSC alignment with the beam. From the horizontal profiles obtained in-air with the SSD, the integrated counts over the resulting microbeam arrays have been extracted for each MSC rotation angle investigated. Figure 5.8 compares the monitoring IC signal recorded for MSC rotation angles ranging from -0.1° to 0.1° to the integrated counts values extracted from the SSD measurements performed at the different MSC rotation angles investigated. Each set of data is normalised to 1 for their respective maximum recorded value. A good correlation can be established between the two detectors as they both agree on a maximum signal reached for 0°. Of course, such a scan to check the alignment of the MSC immediately prior to a patient treatment would be enough to verify the MSC alignment. However the current MRT treatment protocol demands that power to all such motors is switched off to minimise the risk of accidental and undesired change in MSC angle or position. Therefore such a measurement is impossible immediately prior to a patient treatment.

From Figure 5.7 one can see that for a 0.0° rotation of the MSC, the FWHM of the
5.2. Results

Figure 5.8: Total silicon SSD counts integrated over the microbeam array for the different angles investigated and comparison to the results obtained by the beam monitoring IC.

Central microbeams is around 78 µm. At the goniometer stage, the microbeam FWHM is expected to be equal to 51.5 µm due to the beam divergence. The over-estimation of the microbeam width is due to misalignment of the SV of the detector. Indeed, the SV length should be parallel to the microbeams but, as one can see in Figure 5.3 (B), the SSD chip is slightly tilted in the vertical direction (∼ 7°) which degrades the effective spatial resolution and leads to an overestimate of the microbeam FWHM as seen in the microbeam profile.

A lateral profile containing 49 microbeams has been acquired with the SSD fixed at 2 cm depth in a phantom made of water equivalent material. For these measurements, the krypton gas filter and the two redundant Compton chambers were kept out of the beam leading to an increase of 25% of the beam intensity compared to the previous experiments. The wiggler gap was set to 40 mm. The three central microbeams of the resulting array are displayed in Figure 5.9 and the central microbeam is fitted with a gaussian. As the SSD was rigidly mounted in the edge-on orientation in the phantom,
5.2. Results

Figure 5.9: Central microbeams signal obtained at 2 cm depth in a water equivalent phantom. The krypton gas filter and the two redundant Compton chambers were out of the beam. The wiggler gap was set to 40 mm. It was thus less sensitive to motion and its alignment could be performed with a higher accuracy. Indeed Figure 5.10 shows the pink-beam image acquired during the SSD alignment within the water equivalent phantom and one can clearly notice that the tilt of the SSD chip ($\sim 3^\circ$) has been reduced compared to the in-air configuration.

Figure 5.10: Image of the SSD rigidly fixed in the edge-on orientation within a water equivalent phantom acquired with the FReLoN camera. The red area on the image represents the dimensions of the MRT beam used for the experiments (i.e. $20 \, \text{mm} \times 520 \, \mu\text{m}$ at the goniometer stage).
The spatial resolution has thus been improved accordingly: on Figure 5.9 the FWHM of the central microbeam, deduced from the gaussian fitting equation, is equal to 61 μm. It should be noted that all FWHM values reported in this study include the intrinsic dimensions of the SSD.

Concerning the c-t-c distance, a value of $412 \pm 2 \, \mu m$ was measured in the water equivalent phantom and $413 \pm 2 \, \mu m$ in air. These values are in close agreement with the $412.2 \pm 3.2 \, \mu m$ c-t-c distance reported by Bräuer-Krisch et al. [2009a] from Gafchromic® films measurements.

5.2.3 Effect of the MSC rotation angle on the intensity distribution of microbeams

When performing measurements for the QA of the MSC alignment, satellite peaks were observed on the edge of the microbeams array for small rotation angles of the MSC. Figure 5.12 and 5.11 compare the SSD response profile on the field edge for 3 different angles: $0.0^\circ$, $-0.02^\circ$ and $-0.04^\circ$; satellites peak only appear on the right edge of the microbeams array when the MSC is misaligned. Conversely, for positive rotation angles (Figure 5.13 and 5.14), satellite peaks only appear on the left edge of the microbeams array (see Figure 5.10). As the satellite peaks are only observed on one side of the array and as this side is dependent on the rotation direction of the MSC, they are likely to be related to total external reflection of the photons on the side walls of the MSC. This represents an important finding, as the detection of satellite peaks suggests a dose deposition outside of the irradiation field and must be minimised.

As the effect of the misalignment of the MSC was observed on the edges of the microbeams array, Figure 5.15 shows the effect induced on the central microbeams for the following MSC rotation angles: $-0.02^\circ$, $0^\circ$ and $0.02^\circ$. One can see that the
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MSC rotation angle has a strong influence on the valley signal. Once again, photon reflections may occur on the side walls of the MSC and modify the valley signal.

Figure 5.16 displays the average of the 48 peaks and 48 valleys signals measured over the microbeams array as a function of the MSC angle. The uncertainty bars
5.2. Results

Figure 5.15: Central microbeams obtained for three different rotation angles of the MSC (-0.02°, 0° and 0.02°).

represent the standard deviation of the mean $\sigma_{\text{mean}}$ defined as:

$$\sigma_{\text{mean}} = \frac{\sigma}{\sqrt{N}} = \frac{1}{\sqrt{N}} \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (x_i - \bar{x})^2}$$

(5.1)

where $N$ is the number of peaks or valleys measured in one array of microbeams (48 in the present case) and $\bar{x}$ either is the peak or valley mean value over the array of microbeams. The valley signal first increases with rotation angle of the MSC, from 15 counts at 0° to around 17 counts at ± 0.02°. For larger angles, the signal in the valley decreases due to the higher effective thickness of the MSC with misalignment thus attenuating even more the primary beam. For the peaks, the signal decreases constantly with the MSC angle as previously observed in Figure 5.6.

As measurements were performed in-air, the SSD should ideally only be sensitive to the photon flux. At the centre of the microbeam the flux is not expected to change significantly for such small MRT collimator angles since the air-scatter contribution to the photon flux here is negligible. The immediate decrease in response with angle
5.2. Results

Figure 5.16: Average peak and valley signals obtained for the full range of angles investigated.

demonstrates that the SSD is sampling the intensity across a significant proportion of the width of the microbeam. This result is consistent with the SSD effective spatial resolution degradation observed when the SSD is misaligned.

The 48 PVIR values deduced from the peak and valley signals measurements over the microbeam array have been averaged and are presented in Figure 5.17 as a function of the MSC rotation angle. The error bars represent the standard deviation of the mean. For rotation angles between 0 and $\pm 0.02\, ^\circ$, the PVIR decreases as the peak signal is decreasing while the valley signal is increasing. For larger angles, the PVIR increases again as the valley signal decreases at a higher rate than the peak signal.

The QA results presented here highlight the importance of precise alignment of the MSC relative to the X-ray beam. Even in what may be considered a worst case scenario for the SSD (poorly aligned), the system is still able to confirm that the MSC is aligned appropriately. However in order to precisely determine the relative peak intensity of each microbeam for input into the dose planning system the SSD should
be optimally aligned.

### 5.3 Discussion and Conclusion

A single silicon based strip detector was used for the acquisition of 1D profiles of the synchrotron beam used in MRT. The SSD was used to measure the horizontal profiles of a 2 cm wide microbeam array. The detector was able to detect small misalignments of the MSC which resulted in changes in the valley shape but also in modifications of the peak, valley and PVIR values. The rotation of the MSC did not have a significant impact on the FWHM and FW10%M values extracted from the gaussian fit of the central microbeam of the array under the measurements conditions presently used. The significance may increase if the detector had a spatial resolution of 1 µm and was perfectly aligned with the X-ray microbeams. Such a detector is under development and will therefore be investigated in the future. Consequently, the MSC alignment was performed by calculating the integrated counts recorded over the array of microbeams.
by the SSD for the different rotation angles of the MSC. The results were in agreement with the monitoring IC currently used for the MSC alignment on ID17.

The SSD provided a complete view of the microbeam array enabling rapid verification of the lateral field size as well as the correct shape and number of microbeams. Similar measurements using ionisation chambers or films is impossible. As the alignment of such a small device can be tedious, an alignment procedure based on the pink-beam imaging modality available at the ESRF was developed, allowing an alignment of the SSD within half an hour for a completely dismantled SSD.

Using the SSD, satellite peaks have been detected outside of the defined irradiation field for a misalignment angle of the MSC as small as -0.02°. The presence of such peaks suggests a dose deposition outside of the irradiation field. These satellite peaks may originate from photons that have undergone total external reflection from the inner surface of the MSC. Future Monte Carlo studies interfaced with a ray-tracing and X-ray optics code (Cornelius et al., 2014) should be conducted in order to validate this hypothesis. If this is the case, one way to alleviate this problem would be to adapt the MSC aperture to the beam divergence in order to have an angle of incidence greater than the critical angle to prevent total external reflection to occur. Pre-treatment QA using the SSD could thus be performed to ensure that the MSC is accurately aligned and that the treatment beam profile is cleared from any satellite peaks.

The valley dose is very sensitive to any changes in the irradiation set-up, in particular to the alignment of the MSC. Since an increased valley dose would compromise the sparing of the normal tissue, QA dedicated measurements to ensure patient safety should additionally be performed with the SSD. It should be noted that the increase in valley dose has a well defined upper limit which can be characterised as a function of MSC alignment angle. In addition, any measured change in the intensity profile due to slight MSC misalignment can be easily accounted for by the dose planning
system. According to the theory the spectrum of photons in the satellite is the same as the primary spectrum which minimises any correction required due to the energy dependence of the SSD identified in the previous chapter.

On the horizontal scan of the 2 cm wide microbeam array acquired, the measured c-t-c distance was in very good agreement with the values previously reported by Bräuer-Krisch et al. [2009a]. However, an over-estimation of the microbeam width was observed and attributed to a slight misalignment of the detector.

Indeed, the greatest limitation highlighted in this study is the degradation of spatial resolution when the SV is not perfectly aligned with the beam axis. The angular misalignment of the detector could be mitigated using additional positioning motor available on the goniometer. However, using such motors requires the SSD to be precisely positioned at the centre of rotation of the goniometer coordinate frame of reference. Adding the alignment of the SSD on the rotation axis of the goniometer as a step within the detector set-up would lead to a much more time-consuming task which is not compatible with a QA procedure. A decrease in the SV length could be considered to mitigate for the detector sensitivity to slight misalignments. However, the dimensions of the SSD are designed to ensure that an adequate photocurrent is able to be generated in all MRT dosimetry and QA conditions (microbeam peak and valley regions, beam filtering, depth in water or water equivalent materials etc.). In addition, for ideal QA measurements one need to minimise any partial volume effects related to the sensitive volume. Therefore a trade-off exists between SSD sensitivity and spatial resolution. A permanently mounted SSD in air, pre-aligned with the MRT beam, would consequently be the most suitable alternative. This solution will mean that the alignment will only need to be checked using the FReLoN imaging technique. In the future, it could be envisaged to perform a 1D scan of the beam using a high resolution 1D array of silicon microstrip detectors which could provide
an instantaneous 1D fluence profile \cite{Povoli2015}. Another possible technical improvement would be to include a modality within the RADPLOT software taking the motor scanning speed as an input and thus allowing the SSD signal to be displayed as a function of the distance. This would considerably facilitate and accelerate MRT QA procedures performed using the X-Tream system.

MRT represents important challenges in QA because of the strong influence in biological outcome from possible misalignment directly influencing the quality of the microbeams. This also especially important in MRT which is inherently a hypofractionation technique (i.e. the number of treatment fractions is minimal). QA in radiotherapy is required to ensure effective treatment and patient safety and an interest is rising in conventional radiotherapy to pursue fluence-based pre-treatment plan verification over in-phantom dosimetry measurements \cite{Boggula2010}. The SSD, or similar technology, could be a potential candidate in the field of MRT to ensure that fluence profiles assumed by the TPS are consistent with response profiles experimentally acquired. Finally, one can consider to extend the SSD use to MRT pre-clinical experiments where an accurate knowledge of the beam properties would contribute to reduce experimental uncertainties between two sets of experiments.
Chapter 6

MRT Dosimetry at ESRF

Numerous pre-clinical experiments have demonstrated the efficiency of the MRT technique to treat brain tumors in small animals while preserving the non-tumourous tissue as well as the cognitive functions. However, the MRT beneficial effect highly depends on the delivered dose. Dilmanian et al. [2002] showed that in order to preserve the sparing effect of MRT, the valley dose should be kept below the non-tumourous tissue dose tolerance. On the other hand, a large peak dose is preferred in order to enhance the tumor control. Consequently, a maximisation of the Peak to Valley Dose Ratio (PVDR) is desired. The accurate knowledge of the PVDRs is therefore very important and should be experimentally measured before the MRT treatment in the context of a MRT dosimetry QA.

Up to now, PVDRs values for square fields sizes have been obtained by Monte Carlo simulations at different depths in a solid water phantom and compared to those obtained using HD-810 Gafchromic® films Martínez-Rovira et al. [2012]. The Treatment Planning System (TPS) especially developed for MRT is based on analytical dose kernels and has also been benchmarked against Gafchromic® films Bartzsch 2014. Indeed, Gafchromic® film dosimetry currently is the most widely used means to acquire the PVDRs because this technique exhibits high enough resolution to access the dose within the microbeams (i.e. the peak dose). Despite their great resolution, Gafchromic® films have some drawbacks for applications in MRT. First, the film
6.1. Material and Methods

reading is not direct; the recommended time between the exposure and the reading is between 24 to 48 hours \cite{Niroomand-Rad et al., 1998} which does not allow the use of such detector for QA purposes right before the patient treatment. Second, the dynamic range of films is not sufficient to display both peak and valley doses at the same time; either the valley dose is too low to be precisely read on the films or the peak signal is saturated the film if the valley dose is high enough to be seen on the films. For these reasons, a real time dosimetry allowing simultaneous acquisition of the peak and valley signal is required.

For MRT irradiations, Output Factors (O.F) are used in order to correlate the dose measured under reference dosimetry conditions ($20 \times 20$ mm$^2$ field size, at 2 cm depth) to the so-called peak entrance dose (at 3 mm depth). An intermediate step towards the output factor determination is the assessment of the scatter factors which quantify the dose in a single microbeam at 2 cm depth compared to the dose measured under reference conditions. Scatter and output factors are obtained from Monte Carlo simulations. An experimental verification of those factors is therefore required as a part of the MRT QA process.

In this chapter the X-Tream dosimetry system is used for the experimental validation of the PVDRs in clinically relevant field sizes and for the determination of the scatter factors.

\section{6.1 Material and Methods}

For all experiments presented here, SSDs with a straight orientation of the SV were used and set in the edge-on configuration in order to optimise the spatial resolution. The SSD was set at 2 cm depth in a phantom and aligned within the central microbeams using the pink beam imaging modality available on ID17.
6.1.1 Assessment of PVDRs

For the PVDR measurements, the MSC producing 50 µm FHWM microbeams spaced by 400 µm c-t-c was inserted in the beam path in order to create the microbeams array. The vertical slits aperture was set to 500 µm leading to a 520 µm beam height at the goniometer stage. The phantom was vertically moved through the beam, at a scan speed of 50 mm.s$^{-1}$, in order to define squared shape irradiation fields. Three different field sizes were investigated for the experiment: 1 cm $\times$ 1 cm, 2 cm $\times$ 2 cm and 3 cm $\times$ 3 cm. The horizontal and vertical dimensions of the field were defined by the primary slits located in the MRT optical hutch and by the vertical motion of the goniometer respectively. For each field size, irradiations were done for different horizontal locations of the SSD in order to acquire the signal across the central microbeam and deduce the peak and valley signal (i.e. step and shoot mode). The peak signal was considered as the maximum signal measured with the SSD. Conversely, the valley signal was considered as the minimum recorded signal.

6.1.2 Assessment of scatter factors

When performing MRT irradiations, a Graphical User Interface (GUI) scales the goniometer speed ($v_z$) to the desired peak entrance dose at 3 mm depth ($D_{\text{peak}}$). The scan speed is calculated using Eq. (6.1) which takes into account the current value in the storage ring at the moment of the irradiation ($I$), the scaled dose rate measured from the reference dosimetry ($\dot{D}_{\text{scaled}}$), the vertical slit size selected ($z_{\text{beam}}$) and the output factor ($K_0$) corresponding to irradiation geometry.

$$v_z = \frac{\dot{D}_{\text{scaled}} z_{\text{beam}} I}{D} K_0$$

(6.1)

$K_0$ values used are extracted from a Monte Carlo based library. In order to obtain
this factor, one also needs to calculate the so-called scatter factors \((S)\) which correlates the dose at 2 cm depth in a given beam width and height \((D_{beam})\) to the dose at 2 cm depth in the reference 2 cm × 2 cm field size \((D_{reference})\). The scatter factors \((S)\) are therefore determined using the following equation:

\[
S = \frac{D_{beam}}{D_{reference}}
\]  

(6.2)

The scatter factors were measured at 2 cm depth in a solid water phantom (defined as Phantom C hereafter) for horizontal field sizes varying from 50 to 30 000 \(\mu\)m and for three different vertical field sizes: 10, 20 and 30 mm. The vertical field sizes were defined by scanning the phantom through the beam via the vertical motion of the goniometer. Horizontal beam sizes between 30 and 5 mm were defined by the primary horizontal slits located in the optical hutch. For horizontal beam sizes lower than 5 mm, the horizontal slits located in the MRT hutch were used on top of the primary slits.

### 6.1.3 Phantoms

PVDR measurements were performed at the reference depth (i.e. 2 cm) into three different phantoms. The first phantom was a MP3-P water tank from PTW (Freiburg, Germany) (see Figure 6.1) as water phantom remains the gold standard for dosimetry experiments. This phantom will be referred as “Phantom A” in the rest of this chapter. In order to perform measurements at different horizontal positions, the SSD was mounted on a high resolution motor allowing horizontal motions with a resolution of 5 \(\mu\)m. This motor was set on two parallel aluminium rails where a series of holes were grooved with a step of 1 cm in order to enable the mounting of the high resolution motor at different locations along the beam axis (i.e. x axis). Consequently the detector had to be moved manually in order to change the depth of the measurements
and this position could only be changed with a resolution of 1 cm. For the PVDRs measurements, the detector was positioned at an approximate depth between 2.2 and 2.3 cm. To ensure that the SSD would remain straight in water, the detector was taped against a gammex support.

Figure 6.1: SSD installed in the water tank for PVDRs measurements (Phantom A).

Since full installation of the SSD within the water tank is quite a tedious time-consuming task, two other possible configurations, without significantly compromising the set-up, were investigated. Both of them were based on the use of a RW3 solid water slab phantom from PTW of dimensions $30 \times 12 \times 30 \text{ cm}^3$. In the first configuration (referred to as "Phantom B" hereafter), a $28 \times 2 \times 29 \text{ cm}^3$ gammex plate was machined into three different pieces which, once put back together, hold the SSD in the edge-on orientation (see Figure 6.2). A 1 cm and a 0.5 cm thick RW3 slabs were put in front of the detector in order to have the SV of the SSD located at 2 cm depth. The rest of
the RW3 slabs were used as backscatter material.

Figure 6.2: SSD fixed within three gammex plates for PVDRs measurements (Phantom B).

Figure 6.3: SSD installed in the IC insert within the RW3 slab phantom.

Figure 6.4: The phantom is then closed and the insert is filled up with water. This configuration (Phantom C) was used for both the PVDRs and scatter factors acquisition.
The last phantom consisted in the complete RW3 solid-water slab phantom where the SSD was fixed edge-on in the insert dedicated to a Farmer-type IC (see Figure 6.3 and 6.4). As the insert was larger than the detector, the empty area was filled up with water. This phantom, referred as “Phantom C”, was used for both PVDRs and scatter factors measurements.

In the case of Phantom B and Phantom C, as the detector was not able to move within the phantom, the entire phantom was moved at different horizontal locations using the goniometer motion motors.

For each phantom configuration, pink beam images of the SSD have been acquired in order to align the detector with the beam (see Figure 6.5-6.8). On Figure 6.5 the SSD is installed in Phantom A and one is able to distinguish the SSD edge-on oriented taped against the gammex support. Figure 6.6 represents the SSD within the 3 gammex plates (Phantom B). Despite the effort carried to tailor the gammex plates to the SSD dimensions, tight air-gaps are noticable at the junction between the different plates. In Figure 6.7 the SSD is inside the RW3 solid-water slab phantom (Phantom C) and the IC dedicated insert is clearly visible on this image. The insert was then filled up with water in order to homogenise the medium. The resulting pink beam imaging for Phantom C is presented in Figure 6.8.
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Figure 6.5: Pink beam image of the SSD taped against a gammex support and set in the water phantom (Phantom A).

Figure 6.6: Pink beam image of the SSD in the dedicated gammex plate (Phantom B).

Figure 6.7: Pink beam image of the SSD in the IC dedicated insert of the solid water phantom (Phantom C).

Figure 6.8: Pink beam image of the SSD in the IC dedicated insert of the solid water phantom filled with water (Phantom C).
6.2 Results

6.2.1 PVDRs

The SSD signal was recorded at different horizontal (y) locations across the microbeams array in order to measure the energy deposition in the SSD in both the valley and peak regions and to assess the PVDRs in the three different square fields. At each horizontal location investigated the integrated counts resulting from the acquired signal was calculated using the RADPLOT software. As the SR current is constantly decreasing at the ESRF, the integrated counts have been normalised by the current value in the storage ring at the time of the acquisition. Figure 6.9 presents an example of the central microbeam profile thus obtained.

![Microbeam profile](image)

Figure 6.9: Example of the microbeam profile obtained with the SSD with the step and shoot method in Phantom B for a 1 cm × 1 cm field size. The data have been normalised by the SR current and then to 100% at the maximum value and fitted by a Gaussian. The FHWM resulting from the Gauss fit is equal to 66 µm.

This profile was achieved in a 1 cm × 1 cm field in the Phantom B. The integrated counts measured by the SSD and normalised by the SR current have been normalised to
100% at the maximum value. The data have then been fitted by a Gaussian exhibited a FWHM of $66 \, \mu m$. As for the in-air study presented in the previous section, the difference between the measured FWHM and the $50 \, \mu m$ expected value is most likely coming from a slight misalignment of the SSD sensitive volume with the beam.

The ADC counts recorded by the SSD as a function of the vertical position (as opposed to horizontal position in previous chapters when characterising the intrinsic MRT irradiation field which is only $520 \, \mu m$ high typically) of the detector during the irradiation are displayed, for the three different field sizes, in Figures 6.10-6.15. Figure 6.10 and Figure 6.11 represent the signal acquire in the valley and the peak respectively when exposed in a 1cm x 1cm microbeam irradiation field. Similarly, Figure 6.12 and Figure 6.13 represent the signal acquire in the valley and the peak when exposed in a 2cm x 2cm microbeam irradiation field and Figure 6.14 and Figure 6.15 the signal acquire in the valley and the peak when exposed in a 3cm x 3cm microbeam irradiation field. The horizontal location of the SSD was either at 0 mm (i.e. in the peak, see Figure 6.9) or at 0.2 mm (i.e. in the valley). As expected, the change of field size is more noticeable in the valley region than in the peak because of the scattering enhancement with the field size.

From the acquisitions presented in Figures 6.10-6.15 the integrated counts in the peak and in the valley regions can be assessed in order to calculate the PVDR. This has been done for the three field sizes and the three phantoms investigated. The resulting PVDRs are reported in Table 6.1 where they are compared to the PVDR values reported in the study of Martínez-Rovira et al. [2012]. In this study, the PVDRs were obtained using both Gafchromic® HD-810 films within the RW3 solid water slab phantom and MC simulations. The PVDRs presented in Table 6.1 for the SSD are not corrected for the energy dependence of the detector.

The PVDR obtained in Phantom A and Phantom C are in close agreements with
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Figure 6.10: Signal acquired in a valley with the SSD for a 1 cm \(\times\) 1 cm field (\(y = 0.02\) mm in Phantom B).

Figure 6.11: Signal acquired in a peak with the SSD for a 1 cm \(\times\) 1 cm field (\(y = 0\) mm in Phantom B).

Figure 6.12: Signal acquired in a valley with the SSD for a 2 cm \(\times\) 2 cm field (\(y = 0.02\) mm in Phantom B).

Figure 6.13: Signal acquired in a peak with the SSD for a 2 cm \(\times\) 2 cm field (\(y = 0\) mm in Phantom B).

Figure 6.14: Signal acquired in a valley with the SSD for a 3 cm \(\times\) 3 cm field (\(y = 0.02\) mm in Phantom B).

Figure 6.15: Signal acquired in a peak with the SSD for a 3 cm \(\times\) 3 cm field (\(y = 0\) mm in Phantom B).
6.2. Results

Table 6.1: PVDR values obtained at 2 cm depth in three different phantoms and for three field sizes. These results are compared to those reported by Martínez-Rovira et al. [2012] obtained using both MC simulations and Gafchromic® films measurements.

<table>
<thead>
<tr>
<th>Field Size</th>
<th>Phantom A</th>
<th>Phantom B</th>
<th>Phantom C</th>
<th>MC simulations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Films&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 × 10 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>53±3</td>
<td>68±5</td>
<td>54±2</td>
<td>51±3</td>
<td>47±7</td>
</tr>
<tr>
<td>20 × 20 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>31±1</td>
<td>35±2</td>
<td>26±3</td>
<td>28±2</td>
<td>28±4</td>
</tr>
<tr>
<td>30 × 30 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>21±1</td>
<td>25±2</td>
<td>20±2</td>
<td>20±2</td>
<td>18±3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Simulated for the RW3 solid-water slab phantom.
<sup>b</sup> Obtained in the RW3 solid-water slab phantom.

The MC simulations results reported by Martínez-Rovira et al. [2012]. For the 10 mm × 10 mm field size, the PVDRs measured in Phantom A and in Phantom C with the SSD are even closer to the MC calculations than the values recorded with Gafchromic® HD-810 films. However, the PVDRs obtained in Phantom B are higher than expected. For the 30 mm × 30 mm and 20 mm × 20 mm field sizes, the PVDRs measured in Phantom B are 25% higher than expected from the MC and for the 10 mm × 10 mm field size the difference reaches 33%. These discrepancies might be coming from the small but significant air-gap present between the gammex plates of Phantom B noticable on the pink-beam image acquired during the alignment of the SSD (see Figure 6.6). The presence of such air-gaps around the SSD could modify the beam attenuation (photon streaming) and directly impact the peak and valley intensity and thus the PVDR.

However, it is important to consider the difference in terms of composition between the different phantom investigated as they may also play a role on the measured PVDRs. Hill et al. [2010] observed that for low energy photon beams (below 280 kVp), some of the so-called water equivalent materials could exhibit a behaviour different than water. In this study, the PENELOPE MC code was used to calculate depth doses within a 2 cm diameter field size in different phantom materials (including gammex and RW3 phantoms). The resulting doses were compared to the corresponding doses
6.2. Results

They observed that, for a primary photon beam energy less than or equal to 180 kVp, in the case of a RW3 phantom, the calculated dose was lower than the dose calculated in the water while the doses calculated in gammex material were very close to the dose calculated in water. In the 280 kVp photon beam energy, the depth dose in the RW3, gammex or water phantom were equivalent. A Geant4 MC code was developed by Dr. Iwan Cornelius (former PostDoctoral fellow at the CMRP, University of Wollongong) in order to simulate the dose deposition in a homogeneous phantom irradiated by the 20 mm $\times$ 20 mm pre-clinical MRT broadbeam; for water, RW3, and PMMA phantom materials commonly used in MRT. The results are presented in Figure 6.16.

Figure 6.16: Geant 4 MC simulations of the dose deposition in a homogeneous phantom irradiated by the 20 mm $\times$ 20 mm pre-clinical MRT broadbeam for three different compositions: water, RW3, and PMMA. The second y-axis represents the relative difference to water profiles for the RW3 (red) and PMMA (blue). Made by Dr. Iwan Cornelius.

The second y-axis in Figure 6.16 represents the relative difference to water profiles for the RW3 (red) and PMMA (blue) phantom materials. No significant difference is expected between measurements performed at 2 cm depth in water or in RW3 for the
MRT pre-clinical beam. Following the results published by Hill et al. [2010] and the MC simulation results obtained by Iwan Cornelius, the differences observed in terms of PVDR in the Phantom B are more likely to be coming from the air-gaps observed around the SSD.

Prior the measurements performed in Phantom C, dosimetry was performed with the PinPoint 31014 reference IC at 2 cm depth in the RW3 solid water phantom in a 2 cm × 2 cm broadbeam. The SSD was irradiated at the same depth and under the same irradiation field size in order to have the detector calibrated. This calibration allowed the conversion of the integrated ADC counts recorded in the peak and in the valley into doses. The estimated peak and valley doses from the SSD measurements are reported in Table 6.2.

Table 6.2: Estimation of the peak and valley doses at 2 cm depth in the Phantom C from the integrated ADC counts recorded by the SSD.

<table>
<thead>
<tr>
<th>Field Size (mm)</th>
<th>Scaled integrated counts in peak, ADC counts/mA</th>
<th>Scaled integrated counts in valley, ADC counts/mA</th>
<th>Estimated peak dose, Gy</th>
<th>Estimated valley dose, Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 × 10</td>
<td>1.83×10^6</td>
<td>3.37×10^4</td>
<td>72.7</td>
<td>1.34</td>
</tr>
<tr>
<td>20 × 20</td>
<td>1.89×10^6</td>
<td>7.23×10^4</td>
<td>75.5</td>
<td>2.89</td>
</tr>
<tr>
<td>30 × 30</td>
<td>1.85×10^6</td>
<td>9.19×10^4</td>
<td>72.7</td>
<td>3.62</td>
</tr>
</tbody>
</table>

6.2.2 Scatter factors

The assessment of the scatter factors have been performed in Phantom C as this phantom allows an easier and quicker set-up of the SSD as well as a more precise alignment of the SSD than in Phantom A. The experimental scatter factors obtained are presented in Figure 6.17 (dot markers) and compared to Geant4 MC simulation results (solid line) obtained by Stefan Bartzsch (Postdoctoral training fellow at the Institute of Cancer Research, London). The data are given with respect to a 20 × 20 mm² reference field at 20 mm depth.
Figure 6.17: Scatter factors measured at 2 cm depth in a solid water phantom compared to MC simulations results. Exp$_{10 \, \text{mm}}$, Exp$_{20 \, \text{mm}}$ and Exp$_{30 \, \text{mm}}$ represent the experimental data acquired with the SSD in a 10, 20 and 30 mm high beam respectively. Conversely, MC$_{10 \, \text{mm}}$, MC$_{20 \, \text{mm}}$ and MC$_{30 \, \text{mm}}$ stand for the MC simulation results obtained in a 10, 20 and 30 mm high beam respectively.

For a beam aperture lower than \(\sim 300 \, \mu\text{m}\) the maximum dose reached is dominated by electron scattering. Decreasing the beam aperture even more leads to a larger proportion of electrons that scatter out of the beam which results in a lower dose in the beam. For larger beam widths, the maximum dose is dominated by photon scattering [Bartzsch, 2014].

For beam widths between 100 \(\mu\text{m}\) and 30 mm, scatter factors obtained with the SSD are in very close agreement with the simulation results as the maximum relative difference observed in reference to the MC simulation results is equal to 3.2\%. However, for a horizontal beam aperture of 50 \(\mu\text{m}\), while the scatter factors are expected to be similar for the three beam heights, the SSD reports different scatter factors values which are up to 15\% below the expected value (i.e. 0.73). Reason for this behaviour
could probably be attributed to a slight misalignment of the detector that would introduce partial volume effects and lead to a higher reduction in signal than expected at very small fields. The energy dependence of the SSD may also influence the scatter factor measurements. Indeed, the broad-beam is made up of a large scattered photon component, while a single 50 µm wide beam has little contribution from scattered photons. This will lead to an underestimated signal in the 50 µm beam and thus an under-estimated scattered factor with the effect less prominent at larger apertures.

Due to time constraints, scatter factors measurements have only been performed once during the experiment, resulting in a lack of statistics. These measurements should be repeated several times under identical conditions in order to quantify the uncertainty bars and see if a better agreement can be reached between the experimental and simulation results.

6.3 Discussion and Conclusion

The SSD was used for the experimental determination of the PVDR and the scatter factors at 2 cm depth. For the PVDR, three different phantoms were considered for the experiment; a water-based phantom (Phantom A), a RW3 solid water slab phantom including a Gammex slab especially engineered for the SSD (Phantom B) and the RW3 solid water slab phantom with the SSD located in the IC dedicated insert filled up with water (Phantom C). For the three field sizes investigated, PVDR values measured in both Phantom A and Phantom C were in close agreement with published PVDR values obtained using both MC simulations and Gafchromic® films measurements [Martínez-Rovira et al., 2012]. Because of the small air-gaps present in the Phantom B, higher PVDRs were measured than in the two other phantoms. Scatter factors were measured in Phantom C and compared to MC simulation results. A close agreement was obtained with the two techniques down to a beam horizontal
aperture of 100 $\mu m$.

For the first time, an active detector has been able to measure both valley and peak signals with the same accuracy leading to a direct determination of the PVDR in agreement with published values. However, the limitations raised in the chapter concerning the averaging effect in the 50 $\mu m$ beam (and the corresponding under-estimation) as well as the SSD energy dependence observed for broad beam irradiation that leads to over-estimation of the measured signal should both be addressed in order to validate those promising results. A complete Monte Carlo model of the SSD should help us understand and quantify these effects and propose the necessary technical improvements.

Until now, the only reliable detectors allowing PVDR measurements were Gafchromic® films. However, for PVDR measurements, their limited dynamic range prevents the reading of peak and valley dose on the same film. Also, the 24h time delay required between the irradiation and the film reading [Butson et al., 2003] prevents this detector to be used for the MRT QA tests to be performed just before the delivery of an MRT treatment. The SSD could therefore be a dosimeter of interest for MRT applications, especially for PVDR verification.

The scatter factor for a 50 $\mu m$ large and 20 mm height beam has already been experimentally assessed in the study of Prezado et al. [2012] using Gafchromic® films and a PTW 34070 large area chamber (LAC). Values of 0.72 $\pm$ 0.07 and of 0.72 $\pm$ 0.10 were obtained with the films and the LAC respectively. The scatter factor value obtained with the SSD for this beam dimensions is 0.64, which is actually within the uncertainty bars reported by Prezado et al. In this study, the authors also compared the scatter factors experimentally assessed to MC simulation results using either the PENelope or GEANT4 MC codes. A value of 0.68 $\pm$ 0.04 was reported with the PENelope code and of 0.75 $\pm$ 0.04 with the GEANT4 code. The scatter factor
measured with the SSD thus sits within the uncertainty bars of the scatter factor obtained with the PENELOPE MC code. The differences in the scatter factors presented in the study of [Prezado et al.] depending on the method or MC simulation code used perfectly illustrates the complexity of determining this quantity. In the PhD work of Stefan Bartzsch [Bartzsch, 2014], scatter factors were also experimentally determined using Gafchromic® films for a 20 mm beam height and a beam aperture ranging from 20 µm to 20 mm. Experimental results were compared to MC simulations and a good agreement was obtained between the two techniques. However, measurements exhibited uncertainties in the order of 10% thus requiring further repetitions of the measurements in order to show that computations and measurements agree with smaller uncertainties.

The lack of statistics for the SSD measurements also limits the interpretation of the results. Measurements of the scatter factors should thus be repeated under identical conditions in order to establish error bars and see if MC simulation results and SSD experimental results agree within the uncertainties down to a beam width of 50 µm.

The PVDRs measured with the SSD have not been corrected for the energy dependence of the detector. In order to determine if the difference of energy spectrum between the valley and peak regions impacts the experimental determination of the PVDRs using the SSD, MC simulations of the detector response in both spectra are required. Finally, PVDR measurements using the SSD should be performed at larger depths in order to check if the agreement observed between the SSD, MC simulations and Gafchromic® films remains with depth.

Despite the remaining improvements and investigations required, the SSD is the first active device that had been able to measure PVDRs values in such a close agreement with Gafchromic® films and MC simulation results and could therefore be considered as a potential candidate to perform dosimetry QA in MRT.
Application of the SSD at the Imaging and Medical Beamline at the Australian Synchrotron

The MRT technique is also under development at the Imaging and Medical Beam Line (IMBL) at the Australian Synchrotron. Therefore, preliminary experiments were performed at IMBL using the SSD. These experiments consisted in broadbeam dosimetry (i.e. without any spatial fractionation of the primary beam) and in the acquisition of the horizontal microbeams.

Broadbeam measurements performed with the SSD were compared to those obtained using a PinPoint 31014 IC as this detector is also the reference dosimeter at IMBL. The SSD was then used to measure intensity profiles of horizontal microbeams in hutch 1B for two MSC configurations (25 µm or 50 µm FWHM microbeams spaced by 200 µm) at different depth in a solid water phantom.

The broadbeam measurements highlighted the high spatial resolution of the SSD compared to the PinPoint. An over-response of the SSD compared to the PinPoint was observed when performing measurements in a broad beam at different depths in water. This effect was attributed to the energy dependence of the SSD. For the horizontal microbeams intensity profiles obtained at different depths, different region of interests

\[\text{Part of the work presented in this chapter has been published in Radiation Measurements Fournier et al. 2017.}\]
(ROI) were investigated to define the valley region in order to observe its impact on the PVDR.

7.1 Broadbeam experiments conducted in hutch 1B

7.1.1 Material and Methods

Broadbeam experiments were conducted in the MRT hutch at the Australian Synchrotron also known as hutch 1B. Figure 7.1 shows the hutch 1B and the instrumentation used during the experiments. The MRT dedicated hutch is located as close as possible to the wiggler source thus maximising the dose rate [Lewis 2005].

![Instrumentation in Hutch 1B at IMBL](image)

Figure 7.1: Instrumentation in Hutch 1B at IMBL where the measurements of the horizontal microbeams were performed.

The clean-up slits are positioned upstream the sample stage which is located at around 20 m from the beam source. The vertical slits can define two different beam heights: 1 mm and 2 mm. In the lateral direction, the maximum lateral field size is limited (by application of an acceptable beam intensity roll-off) to 30 mm at the sample stage.

The energy spectrum used during the experiment has been calculated using the SPECTRA program for the parameters presented in Table 7.1. In order to distribute the heat load over a larger area, the in vacuo filters were tilted by 45° in regard to the
incident synchrotron beam [Crosbie et al., 2013]. The resulting effective thickness of each filter are also given in Table 7.1 and the resulting energy spectrum is displayed in Figure 7.2.

Table 7.1: Parameters used for the spectra calculation.

<table>
<thead>
<tr>
<th>Parameter of interest</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electron energy in the storage ring</td>
<td>3.032 GeV</td>
</tr>
<tr>
<td>Storage ring current</td>
<td>200 mA</td>
</tr>
<tr>
<td>Peak magnetic field</td>
<td>3 T</td>
</tr>
<tr>
<td>Clean up slits aperture</td>
<td>1 mm × 1 mm</td>
</tr>
<tr>
<td>Distance from the source</td>
<td>22 m</td>
</tr>
<tr>
<td>Filtration in hutch 1A</td>
<td>1 m air</td>
</tr>
<tr>
<td></td>
<td>+ 0.35 mm Be</td>
</tr>
<tr>
<td></td>
<td>+ 10 mm C at 45° (Effective thickness = 14.14 mm)</td>
</tr>
<tr>
<td></td>
<td>+ 1 mm Al at 45° (Effective thickness = 1.41 mm)</td>
</tr>
<tr>
<td></td>
<td>+ 2 mm Cu at 45° (Effective thickness = 2.83 mm)</td>
</tr>
<tr>
<td>Filtration in hutch 1B</td>
<td>1 m air</td>
</tr>
</tbody>
</table>

Figure 7.2: Photon energy spectra used during the experiments performed in hutch 1B (Calculated by Andrew Stevenson from IMBL using the SPECTRA program).

At IMBL, as at the ESRF, a Pinpoint 31014 IC is used to perform the reference dosimetry of the homogeneous beam before MRT experiments. Broadbeam experiments were thus performed with both the SSD and the PinPoint.
First, the detectors were aligned with the beam by performing horizontal and vertical scans using a step and shoot technique; irradiations were performed at different locations across either a 1 mm high beam for the vertical alignment or across a 1 mm wide beam for the horizontal alignment. The detectors were centred at the location resulting in the maximum recorded signal.

Measurements were performed with both detectors at different depths in a water phantom (see Figure 7.3) and for the following field sizes (horizontal \times vertical): 1 mm \times 5 mm, 1 mm \times 10 mm, 1 mm \times 20 mm, 2 mm \times 5 mm, 2 mm \times 10 mm and 2 mm \times 20 mm.

![Figure 7.3: Water tank used for in-water measurements.](image)

Additional broadbeam measurements were performed with the PinPoint at different depths within a solid water Gammex phantom (see Figure 7.5).

During the measurements, both detectors were oriented perpendicularly to the incoming horizontal synchrotron X-ray beam. The SSD was set edge-on with a 90° orientation of its sensitive volume.
7.1. Broadbeam experiments conducted in hutch 1B

7.1.2 Results

The vertical profiles obtained in a 1 mm high beam by the PinPoint and the SSD are displayed in Figure 7.6 and Figure 7.7 respectively. For the SSD, the profiles were obtained at 2 cm depth in water and for the PinPoint at 2 cm depth in the solid water phantom. For both detectors, the data are normalised to 100% for the maximum recorded signal.

In Figure 7.6, the vertical profiles measured by the PinPoint are affected by the spatial resolution of the PinPoint limited by the dimensions of the sensitive volume (1 mm radius and a length of 5 mm). In Figure 7.7, the high spatial resolution of the SSD is especially highlighted. For both detectors, the lateral field size does not look as having a strong influence on the signal recorded at the centre of the field. However when enlarging the lateral field sizes, a higher penumbra is observed due to the increased photon scattering.

The PinPoint signal recorded at different depths in water and for different field sizes is displayed in Figure 7.8. The data are normalised to 100% at the maximum recorded signal. One can see that the PinPoint is very sensitive to the beam height...
7.1. Broadbeam experiments conducted in hutch 1B

Figure 7.6: Vertical alignment of the PinPoint chamber with a 1 mm high beam of three lateral sizes (5, 10 and 20 mm). Data are normalised to 100% at the maximum value obtained.

Figure 7.7: Vertical alignment of the SSD within a 1 mm high beam of three lateral sizes (5, 10 and 20 mm). Data are normalised to 100% at the maximum value obtained.

as for a beam height switch from 2 mm to 1 mm, the PinPoint signal is divided by a factor of 2. This is due to the fact that the PinPoint sensitive volume is larger than the vertical beam size: volume averaging effects cause the signal to be smaller than it should be i.e. the absolute dose rate measured by the IC will be smaller than reality when measured under these conditions. The PinPoint is also sensitive to the lateral scattering as when the horizontal beam size is reduced, the PinPoint signal decreases due to the reduction of the Compton photon scattering. It should be noted that the PinPoint IC is not recommended to be operated in such field sizes (20 mm × 20 mm is the smallest field recommended by PTW) so such effects are expected.

Figure 7.9 represents the SSD integrated signal (normalised to 100% at the maximum recorded signal) obtained with the SSD for the different field sizes investigated and at different depths in water. On the contrary to the PinPoint, the SSD is much less sensitive to the beam dimensions as the detector sensitive volume is much smaller (10 µm in the vertical direction) than the incident beam. However, the SSD still remains sensitive to the Compton photon scattering as the amount of integrated counts recorded with the SSD decreases when the beam area is reduced. The observed change
7.1. Broadbeam experiments conducted in hutch 1B

Figure 7.8: PinPoint signal obtained for 1 second exposure at different depths in water for different broadbeam field sizes (data are normalised to 100% at the maximum recorded signal).

Figure 7.9: SSD integrated signal (normalised to 100% at the maximum recorded signal) obtained for 1 second exposure at different depths in water and for the different broadbeam field sizes available in hutch 1B at IMBL.

in SSD response with beam height is consistent with the definition of the dose rate for MRT [Fournier et al. 2016b] where to a first approximation, the vertical dose profile of
7.1. Broadbeam experiments conducted in hutch 1B

the beam is assumed to be a top-hat function. This profile is a result of the low energy photon spectrum in MRT and of the short range of associated secondary electrons.

SSD and PinPoint measured signals at different depths in water for a 20 mm × 2 mm beam are compared in Figure 7.9. For both detectors, the signal is normalised to 100% at the reference depth of 2 cm [Fournier et al., 2016b]. The relative difference of the SSD resulting signal relative to the PinPoint is defined as:

$$
\Delta = 100 \times \frac{SSD(x) - PinPoint(x)}{PinPoint(x)}
$$

where $SSD(x)$ and $PinPoint(x)$ respectively are the SSD and the PinPoint normalised signal at the depth $x$. $\Delta$ is represented by the black dots in Figure 7.9. At shallow depths, the SSD signal is lower than the PinPoint but the relative difference remains below -2%. From 70 mm depth, the amplitude relative difference is increasing with depth and reaches -36.3% at 250 mm depth.

Figure 7.10: Variation of both PinPoint and SSD signals with depth for a normalisation to 100% at 20 mm depth. The second y-axis represents the relative difference of the SSD data to the PinPoint (black dots).
7.1. Broadbeam experiments conducted in hutch 1B

As demonstrated in Section 4.4, the SSD has a strong energy dependence for photon beam energies below 150 keV. As a result, the SSD is expected to be more water equivalent at deep depths where the contribution of low energy photons is less (i.e. where the energy spectrum is harder). Since the MRT reference depth is 20 mm, so SSD measurements at depths where significant beam hardening occurs (i.e. deeper than 50 mm) therefore appear in Figure 7.10 to under-respond compared to the PinPoint IC. In Figure 7.11 the SSD and PinPoint signals are normalised to 100% at the deepest depth (i.e 250 mm) in order to better highlight the impact of the SSD energy dependence.

![Graph showing variation of PinPoint and SSD signals with depth](image)

**Figure 7.11:** Variation of both PinPoint and SSD signals with depth for a normalisation to 100% at 250 mm depth. The second y-axis represents the relative difference of the SSD data to the PinPoint (black dots).

From 250 mm depth to 70 mm, the SSD over-response goes from 0 to 47.8%. For shallower depths, the difference remains around 55%. The constant over response, while not ideal, implies that only a single calibration factor is required for depths between 10 and 50 mm for QA of the MRT treatment planning.

Depth dose measurements were also performed with the PinPoint within the solid water phantom using a 20 mm × 2 mm field size. The aim was to check if a similar dose
was measured under similar irradiation conditions between the two phantoms and thus if the solid water phantom could be used instead of the water tank to perform reference dosimetry before MRT experiments. This would facilitate the reference dosimetry as the solid water phantom is easier to handle and enable quick measurements to be performed.

In order to compare measured dose between the two phantoms, correction factors have been applied to the PinPoint readings and are summarised in Table 7.2. At the time of the experiments, the IMBL PinPoint was only calibrated with reference to a $^{60}$Co source, therefore a $k_Q$ factor equal to 1 was applied. Correction factors accounting for the pressure and temperature conditions, the polarisation effect and the chamber saturation were determined using the formulas described in Section 3.1.3. The two voltage method for continuous beam was applied using polarisation voltages equal to 400 V and 100 V.

Table 7.2: Correction factors to be applied to the PinPoint Chamber readings in both water and solid water phantoms

<table>
<thead>
<tr>
<th>Correction factor</th>
<th>Water Phantom</th>
<th>Solid Water Phantom</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{T,P}$</td>
<td>1.026</td>
<td>1.028</td>
</tr>
<tr>
<td>$k_Q\ (^{60}\text{Co})$</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>$k_{pol}$</td>
<td>0.999</td>
<td>1.000</td>
</tr>
<tr>
<td>$k_s$</td>
<td>1.003</td>
<td>1.003</td>
</tr>
<tr>
<td>$k_{elec}$</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>General Correction Factor</td>
<td>1.028</td>
<td>1.031</td>
</tr>
</tbody>
</table>

Figure 7.12 presents the depth dose curves obtained with the PinPoint in both the water and the solid water phantoms. In solid water, measurements were only performed down to a depth of 100 mm due to the limitation of gammex plates available. The measurements performed at 100 mm depth included a backscatter of 50 mm of solid water.

For measurements that have been performed at the same depth in both phantom,
7.1. Broadbeam experiments conducted in hutch 1B

Figure 7.12: Comparison of the signal recorded by the PinPoint in either water or solid water phantom. In both case, the detector was exposed for 1 second within a 20 mm × 2 mm field size. The second y-axis represents the relative difference of measurements performed in solid water to those performed in water which is represented by the black dots on the graph.

The relative difference of the measurement performed in the solid water in regards to those performed in water has been determined and is represented by the black dots in Figure 7.12. For depths shallower than 50 mm, the dose measured in the solid water phantom remains close to the dose measured in the water phantom as the relative difference remains below -2%. For larger depths, the amplitude of the relative difference rises constantly until reaching -3.9% at 90 mm depth. According to these results, it should be feasible to perform quality assurance procedures in the solid water phantom rather than in the water tank phantom which would allow such procedures to be carried out more quickly. However, the increasing dose differences measured from 50 mm depth requires further investigations. These studies are currently underway by CMRP PhD student Matthew Cameron using Monte Carlo radiation transport simulations.
7.1.3 Conclusions

Broadbeam experiments were performed in the MRT hutch (hutch 1B) at the IMBL at the Australian Synchrotron. In this study the results obtained with the reference dosimeter at IMBL (i.e. the PinPoint 31014 IC) have been compared to the SSD. The detectors were aligned with the beam by performing horizontal and vertical scans using a step and shoot technique. The detectors were centred at location corresponding to the maximum recorded signal. Broadbeam measurements were performed at different depths in a water phantom for different field sizes. Additional broadbeam measurements were performed with the PinPoint at different depths within a solid water Gammex phantom.

The PinPoint exhibited a high sensitivity to the beam height since for a beam height switch from 2 mm to 1 mm, the recorded signal was seen to reduce by a factor of 2. This effect was attributed to the PinPoint’s larger sensitive volume (i.e. 5 mm long) compared to the beam height. The PinPoint was also sensitive to the lateral scattering. As the SSD sensitive volume was fully covered by the incident beam, the detector was much less sensitive to the beam dimensions but remained sensitive to the Compton photon scattering as a decrease of the ADC integrated counts was observed with the reduction of the beam area.

The SSD energy dependence was highlighted in the measurements performed at different depths in water when compared to the PinPoint results.

Depth dose curves were obtained with the PinPoint in both water and solid water phantoms. Measurements in the solid water were lower than in the water phantom but the difference seems to increase with depths from 50 to 90 mm. One possible explanation for these discrepancies could be the solid water phantom misalignment that can occur when switching from one depth to another as the phantom has to be completely dismantled. Such misalignment would introduce a change in the effective
thickness in front of the detector and thus affect the dose readings. Additional measurements should be performed in both phantoms at larger depths in order to obtain a more accurate interpretation of the results. For these measurements, a special care should be dedicated on securing the water phantom alignment with the incident beam. Finally, the water equivalence of Gammex at different depths and for the IMBL energy spectrum should be checked using MC simulations.

7.2 Horizontal microbeams acquisition in hutch 1B

7.2.1 Material and Methods

The MSC available in hutch 1B creates horizontal microbeams. The MSC is made of several tungsten plates separated to each other by kapton foils of different thicknesses which define the microbeam apertures and thus the microbeam width. This MSC permits two microbeams setting configurations named hereafter as 25-200 and 50-200. The 25-200 MSC configuration generates 25 $\mu$m FWHM microbeams separated by a 200 $\mu$m c-t-c distance. Accordingly, the 50-200 configuration of the MSC generates 50 $\mu$m FWHM microbeams separated by a 200 $\mu$m c-t-c distance.

The experiments consisted in the acquisition of the microbeams profiles for both MSC configurations using the SSD. The SSD was fixed in a dedicated Gammex plate (see Figure 7.13) and vertical profiles were acquired at different depths within the solid water phantom.

A 10 mm $\times$ 1 mm field size was used and the vertical profiles were acquired with 5 mm.s$^{-1}$ vertical scan speed. A bias of -70V was set across the SSD.
7.2.2 Results

The vertical profile obtained with the SSD at 20 mm in the solid water phantom for the 25-200 MSC configuration is displayed in Figure 7.14. As the beam height was limited to 1 mm, the scan results in an array of four microbeams. A FWHM of 59 µm was found instead of the 25 µm expected value.

This difference is most likely to be coming from the misalignment of the SSD. Indeed, at the time of experiments, the positioning motors of the sample stage did not allow such a high precise alignment of the detector and no imaging modality was available to image and align the SSD. The peak of smaller amplitude observed on the right side of the array corresponds to the start of a fifth microbeam cut by the beam defining slits.

Figure 7.15 shows the array using a logarithmic scale for the y-axis in order to better illustrate the valley region. On this figure, the peak value is represented by red crosses. As one can see, the valley dose is not flat between two microbeams. It is thus
7.2. Horizontal microbeams acquisition in hutch 1B

Figure 7.14: Horizontal microbeams measured with the SSD for the 25-200 configuration.

Figure 7.15: Horizontal microbeams measured with the SSD for the 25-200 configuration using semilog scale on the y-axis. Red crosses represent the peak signal. The valley signal is presented either as the minimum value between two consecutive peak (pink crosses) or as an average over an ROI of 25 µm (blue crosses) or 50 µm (green crosses).
difficult to evaluate the length of the region of interest (ROI) over which the valley needs to be sampled. Indeed, considering only the minimum value could lead to an under-estimation of the valley which can be critical for the MRT treatment efficiency. Therefore, three different ROIs have been investigated to determine the valley signal: by considering only the minimum value between two peaks (pink crosses on the figure), by averaging the signal over a 25 \( \mu \text{m} \) ROI (blue crosses) and by averaging the signal over a 50 \( \mu \text{m} \) ROI (green crosses). On Figure 7.15 the ROIs are delimited by dashed lines: in blue for the 25 \( \mu \text{m} \) ROI and in green for the 50 \( \mu \text{m} \) ROI.

Similar graphs than those presented in Figure 7.14 and Figure 7.15 have been obtained for the 50-200 MSC configuration and are presented in Figure 7.16 and Figure 7.17.

![Figure 7.16: Horizontal microbeams measured with the SSD for the 50-200 configuration.](image)

Because of the larger beam aperture, the peak signal is higher for the 50-200 MSC configuration. As the c-t-c distance is the same for the two MSC configurations, the valley signal is also higher for the 50-200 MSC configuration. At each depth...
investigated the four peaks values have been averaged as well as the three valley values and the resulting data are presented as a function of depth in Figure 7.18 and Figure 7.19.

From the peak and valley values reported in Figure 7.18 and Figure 7.19 the PV-DRs have been determined and are presented in Figure 7.20 and Figure 7.21 for the 25-200 and 50-200 MSC configurations respectively. For both configurations the resulting PV-DRs remain stable with depth as the peak and valley signals decreases with depth as the same rate. As detailed in Section 1.3.3 for squared field sizes, PV-DRs are first expected to decrease with depth before reaching a plateau and stabilise. As the field size was 10 mm × 1 mm, and as the PV-DRs are extracted from a 1D vertical scans through the four horizontal microbeams, it is not relevant to compare the PV-DRs behaviour obtain in this particular configuration to the expected behaviour. As expected though, the PV-DRs are higher for the 25-200 MSC configuration as the
7.2. Horizontal microbeams acquisition in hutch 1B

Figure 7.18: Peak (left y-axis) and valley signals (right y-axis) measured at different depths in the solid water phantom for the 25-200 configuration.

Figure 7.19: Peak (left y-axis) and valley signals (right y-axis) measured at different depths in the solid water phantom for the 50-200 configuration.

valley signal is around 7.2 times lower than in the 50-200 MSC configuration while the peak is only 2.5 lower.

For both MSC configurations, the PVDRs are displayed in Figure 7.20 and in
7.2. Horizontal microbeams acquisition in hutch 1B

Figure 7.20: PVDRs obtained in the 25-200 configuration for a valley either equal to the minimum value between two consecutive peak (blue crosses) or equal to the average signal over an ROI of 25 $\mu$m (green crosses) or 50 $\mu$m (red crosses) centred between two consecutive peaks.

Figure 7.21: PVDRs obtained in the 50-200 configuration for a valley either equal to the minimum value between two consecutive peak (blue crosses) or equal to the average signal over an ROI of 25 $\mu$m (green crosses) or 50 $\mu$m (red crosses) centred between two consecutive peaks.
Figure 7.21 for the different ROIs investigated for the valley signal determination. At 90 mm depth, considering a ROI of 50 µm for the valley determination instead of the minimal value between two consecutive microbeams leads to a PVDR reduction of 22.3% for the 25-200 MSC configuration and to a PVDR reduction of 14.5% for the 50-200 MSC configuration.
7.2.3 Conclusions

Horizontal microbeams intensity profiles have been measured at different depths within a solid water phantom for both the 25-200 and 50-200 MSC configurations. For the first time at IMBL, the array of microbeams have been measured with an active detector. Due to the lack of SSD alignment possibilities at the IMBL beam line at the Australian Synchrotron, the measured FWHM of the microbeams were higher than expected (59 µm and 73 µm measured FWHM instead of the 25 µm and 50 µm expected values). However, the c-t-c distances measured (207 µm and 205 µm for the 25-200 and 50-200 MSC configuration respectively) were in agreement with the 200 µm expected value. Nevertheless, it is difficult to be sure of the expected FWHM value as this parameter will also being influenced by volume averaging effect and electron diffusion.

From the acquired intensity profiles, peak and valley signals were assessed and the PVDR were deduced from the resulting values. Different ROIs were considered for the valley definition and the effect on the resulting PVDRs was investigated. The results showed that the valley was not uniform even in small regions right between two consecutive peaks. Consequently, it would be important for future studies to agree on the way to define the valley region depending on the microbeams width and their spacing as this can have a significant effect on the PVDR and therefore on the expected normal tissue tolerance to MRT treatment. In particular, the 25-200 and 50-200 MSC configurations will be interesting cases to consider as electrons from the microbeams should have a significant contribution to the valley.

Finally, the presence of several tungsten plates in the IMBL MSC, one can expect this MSC to introduce photon reflections and potential dose deposition outside of the MRT field. However, one must consider the fact that kapton is used to separate the plates as this will have a significant impact on the scattering conditions. An experiment
similar to the in-air experiment performed at the ESRF and presented in chapter 5 could be performed at IMBL in order to investigate this effect.
Chapter 8

Summary and Conclusions

Microbeam Radiation Therapy (MRT) is an exciting development in the field of radiation oncology. It involves the treatment of tumours using planar arrays of highly collimated, low divergent X-ray microbeams. The underlying principle of MRT is a fascinating radiobiological effect known as the dose-volume effect, whereby healthy tissue demonstrates a remarkable resistance to ionising radiation when spatial fractionation of the primary beam into microscopic beams is employed. Many pre-clinical studies demonstrated the efficacy of MRT in treating gliomas and paved the way to veterinary trials that are currently conducted at the ESRF. However, because of the synchrotron source properties and the MRT beam geometry, dosimetry remains a challenging task. This thesis aimed to provide some solutions for both reference and microbeam dosimetry.

Most of the results presented in this thesis have been performed at the ID17 biomedical beamline at the ESRF and preliminary measurements were carried at the Imaging and Medical beamline (IMBL) at the Australian Synchrotron. Both beamlines instrumentation have been described in details in chapter 2.

Reference dosimetry is a crucial step for the accurate delivery of the treatment as the prescribed peak dose is scaled on the reference dose. To palliate the current lack of method and recommendations for the determination of the ion recombination correction factor \( k_s \) in the specific case of high photon flux from a synchrotron X-ray...
source, a new method was developed at the ESRF for this purpose and was presented in chapter 3. This method allows the direct determination of the ion recombination correction factor using the reference dosimeter (PinPoint 31014) in the reference dosimetry conditions. A dosimetry protocol has been established for reference dosimetry to be performed prior to MRT irradiation. This protocol permits a determination of the absolute dose with an accuracy better than ± 5% and will therefore be used for future MRT pre-clinical studies and veterinary trials at the ID17 beamline. A verification of the MRT spectrum based on Cu half value layer (HVL) measurements in both clinical and pre-clinical conditions led to the conclusion that the TH 200 beam quality was the closest to the MRT spectrum for both filtering configurations and therefore the most appropriate for the MRT reference IC calibration. Having the MRT reference IC directly calibrated at the TH 200 beam quality and performing the current ramping experiment using this calibration should further improve the reference dosimetry precision. In the future, it is crucial to validate the current ramping method under full veterinary beam conditions. Indeed, the current ramping method is currently limited to filtering configurations that do not include the krypton gas filter used under the clinical conditions as the filtration provided by the krypton is affected by the storage ring current. Calorimetry is another independent and reliable technique that should be investigated for absolute dosimetry in broad beam radiation fields in MRT and for validation of the ramping method.

The dosimetry system (X-Tream) based on a high spatial resolution silicon strip detector (SSD) was especially developed by Centre for Medical Radiation Physics (CMRP) for MRT applications. A full description of the system was given in chapter 4 as well as the characterisation of the high and low gain X-Tream pre-amplifiers over their full dynamic range. The low gain pre-amplifier exhibited a dynamic range of $10^3$ which suits the MRT requirements. The conversion between counts obtained by
the system and input current was also established. In section 4.3, a study of the SSD radiation damage was carried out. Vertical scans of the SSD sensitive volume in straight orientation for different accumulated doses combined to 2D response mapping of the detector highlighted an over-response of the SSD at the junction between the pad and the microstrip. This over-response is mainly coming from the metal-oxide-semiconductor (MOS) capacitor generated by the pad and the silicon oxide allowing charges collection from the pad in not pre-irradiated SSD devices. The SSD pre-irradiation process should therefore mitigate for the SSD over-response as irradiation damage induces a decrease in the carrier lifetime. By studying the effect of the SSD response with accumulated dose, it was determined that pre-irradiation dose around 40 kGy had to be delivered to the SSD in order to stabilise its response (change in SSD response is lower than 1% per 1000 Gy). For very high precision dosimetry a 70 kGy pre-irradiation dose could be recommended in order to ensure a very stable response from the device. However, re-calibration of pre-irradiated SSD should be performed regularly in order to verify the constancy of the SSD response with the accumulated dose. Similarly, a model of the SSD response with total accumulated dose should be developed in the future. Also, a study of the SSD energy dependence was carried out in the SSRT hutch at the ESRF using monochromatic beams of different energies. Two different SSDs presenting different orientations of the sensitive volume (i.e. straight or 90°) were tested in both edge-on and face-on configurations. The SSD linearity with dose was studied at the different beam qualities by delivering three different doses to the detectors. For all the configurations investigated, the SSDs showed a linear behaviour with the delivered dose. A decrease of the slope of the linear fits of the experimental data with the beam energy was observed due to the over-response of the SSD at low energies. MC simulations should be performed to validate the experimental results. In a longer term approach, the design of the SSD could be improved in order
to mitigate the energy dependence effect. To this end, thinning the Si substrate and adding a water equivalent material (PMMA) encapsulation around the device could be considered. As additional characterisation tests, further measurements are required to evaluate the SSD response linearity with the dose rate at ranges currently used in MRT.

The ability of the SSD to detect minute misalignment of the MRT MSC, and its potential use for rapid pre-treatment quality assurance in MRT was investigated in chapter 5. This study was based on in-air measurements of the horizontal profiles of the X-ray microbeams in order to determine the relative intensity of each microbeam and assess the alignment of the MSC. The results showed that the SSD was able to resolve individual microbeams which therefore provides invaluable QA of the horizontal field size and microbeams number and shape. They also demonstrated that the SSD was very sensitive to any small misalignment of the MSC. In order to allow as rapid QA as possible, a fast alignment procedure of the SSD based on X-ray imaging with a low intensity, low energy beam was developed. One of the major limitations of the SSD highlighted in this study was the degradation of the spatial resolution of the SSD as soon as the detector is slightly misaligned. In clinical practice a pre-aligned SSD could be mounted permanently in air and the imaging procedure would thus confirm that no misalignment of the detector had occurred. To even more decrease the duration of QA procedures, one could consider including a manual entering of the scan speed as an input in the RADPLOT software in order to directly display the microbeam intensity as a function of distance.

The SSD has then been used for the assessment of PVDR and scatter factors at 2 cm depth and results were presented in chapter 6. Three different phantoms were considered for the PVDR measurements; a water-based phantom (Phantom A), a RW3 solid-water slab phantom including a gammex phantom, specially engineered for the
SSD (Phantom B) and the RW3 solid-water slab phantom with the SSD located in the IC dedicated holder filled up with water (Phantom C). For the three field sizes investigated, PVDRs values measured in both Phantom A and Phantom C were in close agreement with PVDR published values obtained by both MC simulations and Gafchromic® films measurements [Martínez-Rovira et al., 2012]. Because of small air-gaps present in the phantom B configuration, higher PVDRs were measured than in the two other phantoms. Scatter factors were measured in Phantom C and compared to MC simulation results. A close agreement was obtained with the two techniques down to a beam horizontal aperture of 100 µm. For the first time, an active detector has been able to measure both valley and peak signals with the same accuracy leading to a direct determination of the PVDRs in agreement with published values. Due to time constraints, the scatter factors acquired with the SSD have only been performed once, leading to a lack of statistics. These measurements should thus be repeated under identical conditions in order to establish error bars and see if MC simulation results and experimental results agree within the uncertainties down to a beam width of 50 µm. The PVDRs measured with the SSD have not been corrected for the energy dependence of the detector. In order to determine if the difference in terms of energy spectrum between the valley and peak regions impacts the experimental determination of the PVDRs using the SSD, MC simulations of the detector response in both spectra is required. Also, PVDR measurements using the SSD should be performed at larger depths to see if results still agree with published MC and Gafchromic® films results from Martínez-Rovira et al. [2012].

Preliminary measurements performed at the Imaging and Medical Beamline at the Australian Synchrotron were described in chapter 7. Broadbeam experiments were performed in the MRT hutch (hutch 1B) and compared the results obtained with to the reference PinPoint 31014 IC used at IMBL. Measurements were performed
at different depths and an over-response of the SSD was observed compared to the PinPoint which was attributed to the energy dependence of the SSD. For the first time vertical intensity profiles of the horizontal microbeams were acquired with an active detector (the SSD) in the IMBL MRT hutch. From these measurements, peak, valley and PVDRs values have been extracted. Different ROIs were investigated to define the valley signal. The length of the valley ROI has been proven as being a very important parameter as it has a direct influence on the PVDR (and thus on the expected normal tissue tolerance to MRT treatment) especially for a c-t-c distance of 200 $\mu$m. Consequently, an agreement should be sought in order to establish the way the valley region should be defined depending on the microbeams width and their spacing.

As a conclusion, despite the remaining improvements and investigations required, the ability of the SSD to perform in-air QA tests has been demonstrated. Moreover, this is the first active device that has been able to measure PVDRs values in such a close agreement with Gafchromic® films and MC simulation results. Therefore the SSD, or similar technologies, should be considered as potential candidates to perform QA tests in MRT in the future.
Appendix A

Characterisation of beam monitoring chambers at the ESRF

In the context of veterinary trials at the ESRF, the characterisation of the beam monitors intended to be used for the patient safety was required. The ramping method was used to determine the linearity of both IC0 and IC0bis monitoring chambers with the SR current.

In Figure A.2, one can see that the response of the IC0 remains quite flat with the storage ring current. The average response of IC01 is $1.27 \times 10^{-8} \pm 1.13 \times 10^{-10}$ (2σ) and is thus suitable for MRT beam monitoring applications.

The same characterisation was performed for the IC0bis monitoring chamber. The
chamber response as a function of the SR current was obtained for two different beam heights: 520 and 51 µm.

The signal recorded by the IC0bis chamber (IC0bis1+IC0bis2) as a function of the current in the storage ring for a 51 µm beam height is displayed in Figure A.3. IC0bis exhibits a linear behaviour with the SR current. IC0bis recorded signal has then been divided by the SR current and normalised to 100% at the maximum value in order to observe the IC0bis response with the SR current (see Figure A.4).

![Figure A.3: Signal recorded by the IC0bis chamber (IC0bis1+IC0bis2) as a function of the current in the storage ring for a 51 µm beam height.](image1)

![Figure A.4: IC0bis response as a function of the storage ring current for a 51 µm beam height.](image2)

For the 51 µm beam height, the IC0bis response remains quite stable over the full range of current investigated (within ±2.5%).

The signal recorded by the IC0bis chamber as a function of the current in the storage ring for a 520 µm beam height is displayed in Figure A.5. The response is first linear with the beam current then, from 70 mA, the chamber signal saturates which results in a decrease in the IC0bis response from 100% down to 31% (see Figure A.6).

The results presented for IC0bis have been obtained with the chamber fixed in the beam. For the purpose of the veterinary trials, the IC0bis chamber will be set-up on a dedicated support that will vertically move the chamber through the beam. This support will be synchronised with the goniometer vertical motion. A characterisation
of the IC0bis chamber behaviour when scanned through the beam was thus perform.

The IC0bis chamber was taped against the water tank positioned on the goniometer stage and was scanned through the beam at four different scan speed (2, 5, 20 and 100 mm/s). Measurements have been performed within a 2 cm × 2 cm field at SR current ranging from 20 to 200 mA and two different beam heights have been investigated (51 and 520 µm). Results are presented in Figure A.7 and Figure A.8 for the 51 µm and the 520 µm beam height respectively.

For the 51 µm beam height, IC0bis exhibits a linear behaviour over the entire range of SR current investigated and the measured signal is proportional to the scan speed. For the 520 µm beam height, as previously observed in the case of IC0bis fixed in the beam, saturation occurs when the SR current reaches 75 mA. At scan speed of 100 mm/s, as the dose rate perceived by the chamber is the lower, IC0bis starts to saturate at a beam current of 100 mA.

IC0bis can therefore not be used under broadbeam conditions if the beam height is higher than 51 µm. However, when introducing the MSC in the beam, the effective dose rate seen by the chamber is reduced by a factor of 8. The IC0bis chamber could thus be suitable for microbeam monitoring when using the reference beam height of
Figure A.7: Signal measured by the IC0bis in 2 cm × 2 cm broadbeam (using a the 50 µm vertical slits) as a function of the SR current. Four different scan speeds were investigated.

Figure A.8: Signal measured by the IC0bis in 2 cm × 2 cm broadbeam (using the 500 µm vertical slits) as a function of the SR current. Four different scan speeds were investigated.

520 µm. The experiment with IC0bis taped on the water tank was thus repeated at different SR currents with the MSC in the beam for three different scan speeds (5, 20 and 100 mm/s). The results are displayed in Figure A.9.

Figure A.9: Signal measured by the IC0bis in 2 cm × 2 cm microbeam field (using the 500 µm vertical slits) as a function of the SR current. Three different scan speeds were investigated.
As expected, since the effective dose rate seen by IC0bis is much reduced when the MSC is inserted in the beam, IC0bis exhibits a linear behaviour with the SR current and the IC0bis recorded signal is proportional with the scanning speed. Therefore the IC0bis has been evaluated as a suitable monitoring device for the MRT veterinary trials.
Appendix B

MRT broadbeam profiles obtained with the PinPoint 31014 and the Semiflex 31010 ionisation chambers

As a part of the investigation of the most suitable detector to perform MRT reference dosimetry (c.f. chapter 3), vertical and horizontal beam profiles have been performed at 2 cm depth in a RW3 solid water slab phantom using both the PinPoint 31014 IC and the Semiflex 31010 IC. The profiles presented have been obtained with a 520 µm high beam and a scan speed of 20 mm.s\(^{-1}\).

Three different squared field sizes were considered: 10 mm × 10 mm, 20 mm × 20 mm and 30 mm × 30 mm. For the lateral beam profiles (i.e. horizontal (y) profiles), the all phantom was horizontally moved through the beam using the goniometer lateral motion motor. For the vertical beam profiles (z direction), as the phantom and the IC are vertically scanned through the beam, the irradiation start and stop positions were modified in order to simulate a vertical beam profile. For example, if the IC is centred in the beam at a z position equal to 50 mm, the goniometer start and stop position to be used to irradiate the chamber in the centre of a 2 cm × 2 cm field size are 40 and 60 mm respectively. In order to simulate the vertical profile, defining the goniometer start and stop position at 20 and 40 mm will be equivalent to moving the IC 20 mm away from the field centre.

The horizontal and vertical beam profiles obtained with the PinPoint IC are dis-
played in Figure B.1 and Figure B.2 respectively.

Figure B.1: MRT broadbeam horizontal profiles measured with the PinPoint 31014 IC for three different field sizes (10 mm × 10 mm, 20 mm × 20 mm, 30 mm × 30 mm).

Figure B.2: MRT broadbeam vertical profiles measured with the PinPoint 31014 IC for three different field sizes (10 mm × 10 mm, 20 mm × 20 mm, 30 mm × 30 mm).

Figure B.3: Comparison of the horizontal and vertical profiles obtained with the PinPoint IC for the MRT reference broadbeam field size (i.e. 20 mm × 20 mm). Data have been normalised at 100% at the maximum measured value.

The vertical broadbeam profiles give a wider penumbra than the horizontal one. For comparison they are both displayed Figure B.3 for the reference MRT broadbeam
(i.e. 20 mm × 20 mm). The data have been normalised to the highest recorded signal which corresponds to the readings obtained at the position y=0 when performing the horizontal beam profile.

An asymmetry in the out-of-field dose profiles is observed due to polarization effects. As the polarisation is predominant in the electron orbital plane of the synchrotron, the photons undergoing Compton interactions in the phantom/patient will be preferentially scattered in the vertical direction. As a result, the out-of-field dose is greater in the vertical direction than in the horizontal direction [Hugtenburg et al. 2010]. This asymmetry on the out-of-field was previously highlighted in the work of [Cornelius et al., 2014] and [Bartzsch et al., 2014].

The horizontal and vertical profiles obtained with the Semiflex 31010 are displayed in Figure B.4 and Figure B.5 respectively.

![Figure B.4](image1.png)  ![Figure B.5](image2.png)

Figure B.4: MRT broadbeam horizontal profiles measured with the Semiflex 31010 IC for three different field sizes (10 mm × 10 mm, 20 mm × 20 mm, 30 mm × 30 mm).

Figure B.5: MRT broadbeam vertical profiles measured with the Semiflex 31010 IC for three different field sizes (10 mm × 10 mm, 20 mm × 20 mm, 30 mm × 30 mm).

Again, when comparing the horizontal and vertical profiles in the MRT reference broadbeam field (see Figure B.6), the asymmetry in the out-of-field dose can also be observed.

Figure B.7 and Figure B.8 respectively compare the horizontal and vertical MRT
Figure B.6: Comparison of the horizontal and vertical profiles obtained with the PinPoint IC for the MRT reference broadbeam field size (i.e. 20 mm × 20 mm). Data have been normalised at 100% at the maximum measured value.

Figure B.7: Comparison of the horizontal profiles measured by either the PinPoint 31014 IC or the Semiflex 31010 IC in the MRT broadbeam reference field size (i.e. 20 mm × 20 mm).

Figure B.8: Comparison of the vertical profiles measured by either the PinPoint 31014 IC or the Semiflex 31010 IC in the MRT broadbeam reference field size (i.e. 20 mm × 20 mm).

reference beam profiles obtained with both the PinPoint and the Semiflex chambers. In the centre of the beam, the scaled dose rate measured by the semiflex is around 29% lower than the scaled dose rate measured by the PinPoint IC. This is attributed
the ion recombination effect expected to be much higher in the Semiflex IC because of the higher effective separation between electrodes in the Semiflex design compared to the PinPoint (as detailed in subsection 3.1.4).


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