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EXECUTIVE SUMMARY OF THE THESIS

Synchrotron x-ray spectra characterization for radiation therapy applications at the ESRF - ID17 Biomedical beamline

LAUREA MAGISTRALE IN PHYSICS ENGINEERING - INGEGNERIA FISICA

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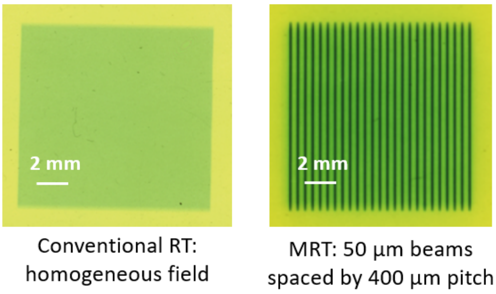
1. Introduction

Microbeam radiation therapy (MRT) is a promising alternative to conventional radiation therapy (RT) with x-rays, where the use of a spatially fractionated irradiating field substitutes the homogeneous broad beam. MRT is based on the dose-volume effect, an unpredictable phenomenon for which a mature biological tissue has a higher tolerance to radiation beams that are few tens of micrometers wide, carrying a dose up to hundreds of Gy, than to wider beams, carrying a dose of only few Gy. MRT showed improved outcome in numerous preclinical studies, thanks to an increased healthy tissue tolerance to the radiation and efficacy in limiting the tumor development [1]. The most common irradiation geometry defined for MRT consists of an array of several beamlets 50 µm wide spaced by 400 µm pitch, for a total field up to some centimeters long, as shown in Figure 1.



Conventional RT: homogeneous field

MRT: 50 µm beams spaced by 400 µm pitch

Figure 1: Radiochromic films irradiated with a homogeneous beam (left) and with an array of microbeams (right).

MRT is currently best performed at synchrotron radiation sources, such as the ID17 Biomedical beamline at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France, where the extreme properties to perform MRT are fulfilled: x-ray energy in the 100-200 keV range to preserve the step dose gradient typical of a microbeams array and to penetrate sufficiently inside the body, a minimal beam divergence to maintain the geometry at microscopic scale, a high dose rate to allow a short irradiation time, needed to mitigate the effect of organic motions on the treatment success. Robust and reliable dosimetry protocols are at the basis of any RT because a high accuracy on the dose delivered during the treatment is mandatory for a successful result. The absorbed dose by the material depends on the depth of penetration of incoming photons and on the mean free path of scattered electrons, hence a precise knowledge of the used x-ray energy spectrum is necessary.

The renovation of the ESRF storage ring in the last years to bring to life the first fourth generation synchrotron in the world combined with the renovation of components of the ID17 beamline in preparation for veterinary trials, generated the need for a new complete characterization of the x-ray spectra used at ID17 for RT studies.

In this work, the spectra characterization has been performed following the Half Value Layer (HVL) method, as already described by [2], but starting from a more recent software for synchrotron experiments simulations and considering correcting factors for measured data never used in the past. The newly defined spectra were used to perform dosimetry validation through the study of the depth dose profiles delivered inside a water-equivalent phantom. The verification that the simulated and measured deposited doses were in agreement is a fundamental step to move towards clinical applications. This study was performed comparing the datasets provided by two independent Monte Carlo (MC) simulations based on different dose calculation algorithms and two different experimental datasets using a PTW PinPoint Ionization Chamber (IC) and radiochromic films. For completeness and accuracy, the study has been performed on different spectra used for RT an MRT studies, resulting from various combinations of the ID17 beamline components.

2. Materials and Methods

2.1. The ID17 beamline

The ID17 beamline is the ESRF biomedical beamline dedicated to biomedical imaging and radiotherapy studies. For brevity, only the main characteristics of the beamline used for MRT study will be presented here.

A wiggler source is used to produce the x-ray beam, made of 10 magnetic field periods spaced by 15 cm, generating an oscillating magnetic field up to 1.62 T at 24.8 mm gap. Before reaching the target, the x-ray beam passes through a combination of five different attenuating filters made of C, Al and Cu, to cut the energy below 50 keV, not effective for MRT. Two ionization chambers can be moved into the beam for monitoring purposes during irradiation: a Compton scattering IC made of two pairs of Al plates covered by a thin layer of Au and a combination of two equivalent PTW Bragg peak chambers. The final beam size used for irradiation is defined by motorized slits that for this study were defining an aperture 20 mm wide and 0.520 mm tall. To obtain larger fields, the sample is positioned on a motorized stage and scanned vertically through the beam after a precise alignment.

Results are reported for the two main spectra used for MRT applications: the one referred to as "conventional" spectrum, the most intense, used for MRT studies, and the more filtered clinical spectrum, intended for future clinical applications, where both monitoring ICs are used.

2.2. X-ray spectra simulation

The raw spectrum generated by the wiggler source was calculated using the OrAnge Synchrotron Suite (OASYS) software. OASYS is a software in-house developed at ESRF that allows to fully model synchrotron virtual experiments, starting from the photon source, the interaction with the beamline optics, until the interaction of the sample with the photon beam [3].

For the study were used the Wiggler widget, to simulate the generation of the x-ray beam from the wiggler source and the Screen- Slit widget, to simulate the passage of the beam through the slits, both taken from the Shadow library that uses a ray tracing approach. For the first time, the measured magnetic field of the wiggler was used as input for the calculation. The simulation output is the raw spectrum in terms of brilliance [ph/s/0.1%BW] over the defined energy range from 0.1 keV to 600 keV.

The obtained raw spectrum was given as an input to a Python code, in-house developed, that calculates the passage of the x-ray beam through the attenuating and monitoring components of the beamline by mean of their attenuation coefficient at each energy. The same was done for the monitoring devices: each of them was divided into the individual composing materials using their exact thickness. The x-ray spectra reaching the target are therefore calculated.

2.3. Half Value Layer method

To validate the calculated spectra, the Half Value Layer (HVL) method was used. Different additional layers of Cu or Al, 99.9% of purity, were placed inside the beam path to decrease the beam intensity. The HVL is the thickness of extra material for which the intensity of the beam is attenuated to half of its initial value. The theoretical HVL for the considered spectra were calculated starting from the same Python code used to simulate the final spectra, by adding the extra thickness of either Cu or Al.

Experimentally, the transmitted signal after the additional metal layers was measured by mean of a PTW PinPoint, the standard dosimeter for reference dosimetry with homogeneous fields. It is a cylindrical IC made of an air cavity of 0.015 cm^3 where ions are generated by the interaction between the incident radiation and the air.

For each configuration of additional layers three measures were taken for statistics. The measured dose was normalized by the current of the storage ring at the moment of the irradiation, obtaining the normalized measured dose D_n [Gy/mA]. The Intensity Ratio (IR) at each data point was calculated dividing the beam intensity measured, D_n, by the beam intensity value measured when no extra layer was inserted, D_{n_0}. The IR curve for each spectrum was obtained by increasing the thickness of additional layers in the beam path.

For the measures obtained with the PinPoint IC, few correcting factor must be carefully considered. These factors include temperature and pressure, beam energy variation and electron recombination corrections. The precise list and origin of these factors can be found on the work of Fournier et al. [4]. For the first time they were all applied for the spectra characterization on the ID17 beamline.

The PinPoint has an active volume that is larger than the x-ray beam, hence during the measurements the IC is vertically scanned inside the beam. The IC measures the D, and the dose rate $\dot{D}$ is then obtained as:

$$\dot{D} = \frac{D \times v}{z_{beam}} \tag{1}$$

where z_{beam} is the beam height and v is the scan speed, set equal to 20 mm/s for the measurements.

2.4. Depth dose profile study

Dosimetry validation with the newly defined spectra have been performed using the depth dose profile method, i.e. measuring the dose delivered at different depth inside a target volume. The phantom used is a cube with a total volume of 18 × 18 × 18 cm^3 made of water-equivalent plastic slabs 1 cm thick. One of the slab has a drilled hole to insert the PinPoint. The cube was placed on the goniometer stage, aligned in order to have the PinPoint centered in the beam and scanned vertically for measurements over the resulting 2 × 2 cm^2 field, as described by Fournier et al. [4].

The measurement have been taken at 1, 2, 4, 6, 8, 10, 12, 14, 16 and 17 cm in deep inside the cube, repeated three times for statistics. The IR curve from the measured dose values was obtained normalizing by the measured value in reference conditions, i.e. 2 cm in deep.

The depth dose profile measurement was performed using also radiosensible detectors, named radiochromic films (RCF). RCFs are made of a thin flexible sheet of plastic, coated with an active material, that once exposed to radiation makes the optical density of the film to change. RCFs are used in general to perform dosimetry with microbeams due to their high spatial resolution. For this study, GAFchromic^{TM} HD-V2 films were used. To perform the measurement with RCFs, they were placed inside the cube attached on the face of the slabs, at the depth chosen for the same experiment with the PinPoint. At each position, three samples were taken for statistics.

Films were digitalized after the irradiation by mean of a flat panel scanner and analyzed by a MatLab program that associated their color to a value on a grey scale [5]. The grey scale gives relative values for the dose, hence, to translate them into absolute values, a calibration curve was obtained by irradiating the films in reference conditions over the 0-400 Gy range useful for depth dose profile measurements. Once the calibration curve was established, the grey value of the film irradiated at different depths were compared to the calibration curve, to obtain the corresponding dose value.

Monte Carlo (MC) simulation of the setup used for the depth dose profile measurement were performed, starting from the computed spectra, to be compared with the experimental profiles. The Geant4 toolkit was used to implement the MC simulations. Two different MC algorithms were used for dose calculation: the conventional algorithm, that treats the interactions of the x-ray beam photons and generated scattered secondary electrons individually and the hybrid algorithm, a new approach developed by Donzelli et al. [6], that uses a kernel to simulate the electrons transport inside the material.

The system simulated is the whole cube, with an inside volume for data scoring of 180 × 30 × 30 mm^3, being x the direction of the beam, and discretized with millimetric resolution for correct dosimetric study. For both simulations, the dose profile was obtained averaging the dose delivered in the center of the irradiation field, over a volume equivalent to the active one of PTW PinPoint.

2.5. Uncertainty budget

The simulated spectra had an uncertainty on the mass attenuation coefficient used of 2%, as taken from the NIST database. For the beamline components a total uncertainty of 4.76% at 2σ was assigned considering an average of 20 layers, including attenuators, monitoring devices and additional layers, starting from the caliper uncertainty of 0.5%, an error on the vertical slits size of 0.19% and an uncertainty on the position of the components of 0.8% [2]. For the PinPoint IC dosimetry, the error on all the correcting factors has been used as explained by Fournier et al. [4], with exception for the k_s factor that has been recalculated later at ID17 obtaining an uncertainty of 0.08%. The total uncertainty at 2σ is hence 3.88% for dosimetry in air (HVL measurements) and 4.16% for dosimetry in reference conditions (depth dose profile measurements). For the radiochromic films the uncertainty at 2σ is 5.02% considering the uniformity as guaranteed from the provider and the uncertainty due to the scanning post irradiation. Regarding Monte Carlo simulations, the uncertainty at 2σ on the conventional algorithm is 0.66% at worst and 1.06% for the hybrid algorithm.

3. Results and Discussion

3.1. Spectra simulation

Figure 2 shows the raw spectrum after passing through the "vertical" slit (VS) of size 20 × 0.52 mm^2, as obtained from the OASYS software, along with the conventional and clinical spectra from the following Python simulation. The spectra are expressed in terms of brilliance [ph/s/0.1%BW] normalized by the maximum storage ring current (200 mA) and the area of the vertical slit, thus [ph/s/0.1%BW/mm^2/mA], as function of the photon energy [keV]. In Table 1, the mean energy in keV, the peak energy in keV and the dose rate in Gy/s of these three spectra are reported.

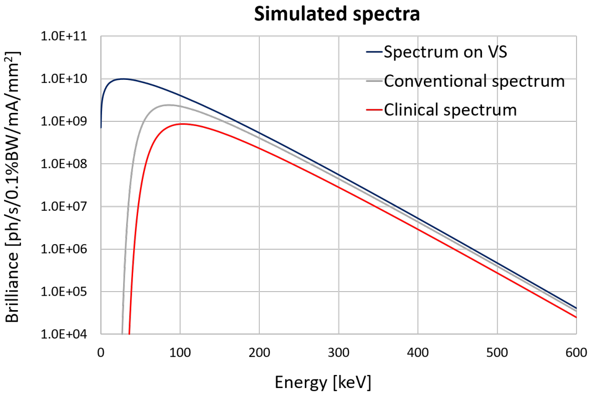


Figure 2: Plot of raw spectrum and spectrum on the VS obtained with OASYS software and three main spectra obtained with Python simulation: conventional, pre-clinical and clinical spectrum.

Spectrum	Mean energy [keV]	Peak energy [keV]	Dose rate [Gy/s]
Conventional	101.8	85.8	15699
Clinical	120.0	102.2	6045

Table 1: Mean energy [keV], peak energy [keV] and measured dose rate [Gy/s] for the conventional and clinical spectra.

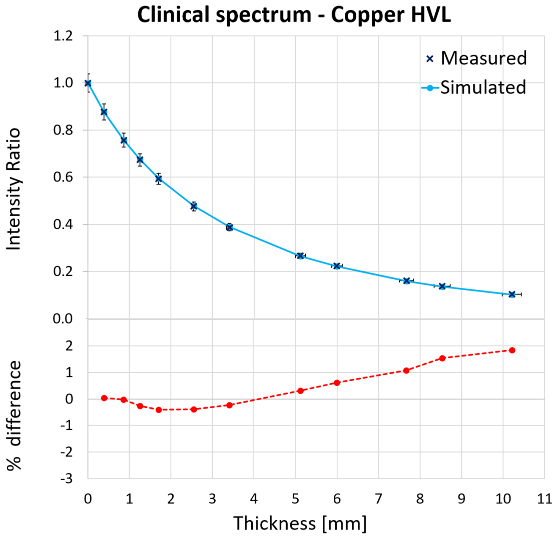
3.2. Half Value Layer results

In Figures 3a and 3b, on the top plot are shown the IR profiles for the clinical spectrum using Cu and Al additional layers, respectively, compared to expected profile from the calculation. On the bottom plot, the % deviation of experimental data with respect to theoretical one can be observed. All the % difference values are below 2% for the shown spectrum; similar results were obtained for all the examined spectral configurations with the % difference below 2% for Al additional layers and below 3% for Cu extra layers.

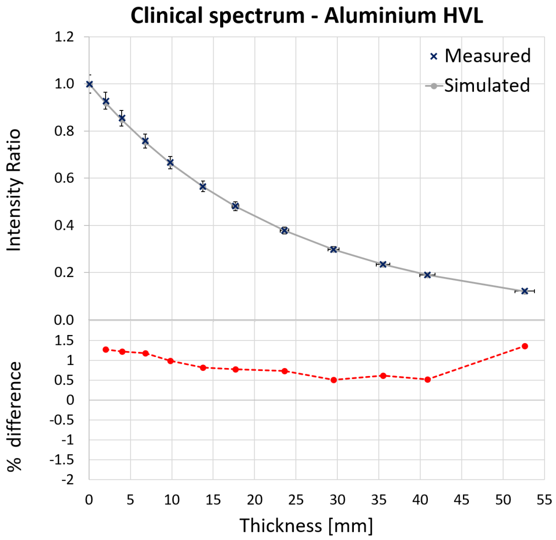
For a further analysis the experimental HVLs were compared with the theoretical ones. They are referred to as HVL1 the thickness for which $IR = 0.5$, HVL2 that for which $IR = 0.25$ and HVL3 that for which $IR = 0.125$. The experimental HVLs are obtained by fitting the measured data curve with a quadratic function, because, being the Lambert-Beer law for a polychromatic beam non exponential, any function that can fit the data could have been chosen.

The resulting HVLs for conventional and clinical spectra are presented in Tables 2 and 3. The % difference between measured and theoretical data is always below 2%. Similar results were obtained

for all the analyzed spectra.
The results obtained with HVL method are validating the calculated spectrum from the OASYS software, being the difference between experimental and theoretical data always below 3%, in most of the cases even below 1%. The spectrum obtained from OASYS is, hence representative of the real spectrum at ID17.



(a)



(b)

Figure 3: Both plots show on top the IR obtained performing HVL measurement for the clinical spectrum using additional Cu in (a), and Al, in (b), layers against the calculated data, as a function of the additional material thickness. On the bottom plot the % deviation of measured data from simulated ones is shown.

3.3. Depth dose profile

The newly validated spectra were given as an input for the MC simulations. To prove the reliability of the new algorithm, results from hybrid MC simulations were compared to those from the conventional ones, obtaining a maximum of 1% deviation. The results were satisfactory and confirmed the goodness of the new algorithm, however an even stronger agreement was expected using a broad beam configuration. The discrepancy is potentially due to different physics library used for the implementation of the algorithms.
The results obtained with conventional algorithm were used as a reference for the values obtained from depth dose profile measurements. In Figure 4, on the top plot, the obtained IR from MC simulation using the clinical spectrum is plotted against the profile obtained from PinPoint IC and RCFs dosimetry. On the bottom plot instead, the % deviation between the two experimental data set and the MC simulation is shown. For the absolute dosimetry, it can be observed that the difference is below 3%; similar values were obtained for all the studied spectra. For the film dosimetry the results were also good, with the most of the values deviating from the computed one for less than 3%, but few outliers were observed, for which the deviation from the theoretical value was up to 5%, which may require further investigation.

4. Conclusions

To move MRT toward a clinical stage, very robust and reliable dosimetric protocols are mandatory: a precise knowledge of the spectrum lies at the foundations. This study aims at the characterization of the x-ray spectra at ID17 Biomedical beamline after the recent renovations of the storage ring and of the beamline.
The spectra at ID17 were calculated using the OASYS software for the first time and successfully validated using the Half Value Layer method. The agreement between the theoretical and experimental data for the HVL was always within 2%, proving that the model used, based on the OASYS software, is reliable in reproducing the spectra at ID17 beamline. In addition, the accurate and complete use of the correcting factors for the IC measurement reinforced the data agreement, improving the results with respect to previous work done [2]. With the obtained spectra, dosimetry validation in a water-equivalent phan-

Conventional with Cu	Experimental [mm]	Theoretical [mm]	% diff
HVL1	1.71 ± 0.10	1.74 ± 0.04	-1.99
HVL2	4.16 ± 0.26	4.24 ± 0.09	-1.88
HVL3	7.36 ± 0.45	1.74 ± 0.15	0.06

(a)

Conventional with Al	Experimental [mm]	Theoretical [mm]	% diff
HVL1	14.99 ± 0.92	14.97 ± 0.30	0.11
HVL2	30.64 ± 1.88	30.76 ± 0.62	-0.41
HVL3	40.94 ± 2.88	47.24 ± 0.95	-0.63

(b)

Table 2: Experimental HVLs of Cu (a) and Al (b) compared to theoretical predictions for conventional spectrum.

Clinical with Cu	Experimental Cu [mm]	Theoretical [mm]	% diff
HVL1	2.37 ± 0.15	2.37 ± 0.05	0.19
HVL2	5.40 ± 0.33	5.4 ± 0.11	0.02
HVL3	9.08 ± 0.56	8.99 ± 0.18	1.01

(a)

Clinical with Al	Experimental Al [mm]	Theoretical [mm]	% diff
HVL1	16.73 ± 1.02	16.69 ± 0.33	0.22
HVL2	33.91 ± 2.08	33.88 ± 0.68	0.08
HVL3	51.54 ± 3.16	51.54 ± 1.03	0.00

(b)

Table 3: Experimental HVLs of Cu (a) and Al (b) compared to theoretical predictions for clinical spectrum.

tom was performed measuring the depth dose profile inside the target volume. Both the PTW PinPoint IC and RCFs were used as detectors and the experimental results were compared to that from MC simulations of the same setup.

The overall agreement between all the four datasets was excellent and within the 3% required in clinical RT to validate and irradiation plan. The few outliers observed for film dosimetry were expected due to the complexity and uncertainties related to this dosimetry protocol.

It can be concluded that the newly characterized spectra are reliable and are a correct starting point for all future works concerning dose calculations and treatment planning necessary for RT applications at the ID17 Biomedical beamline.

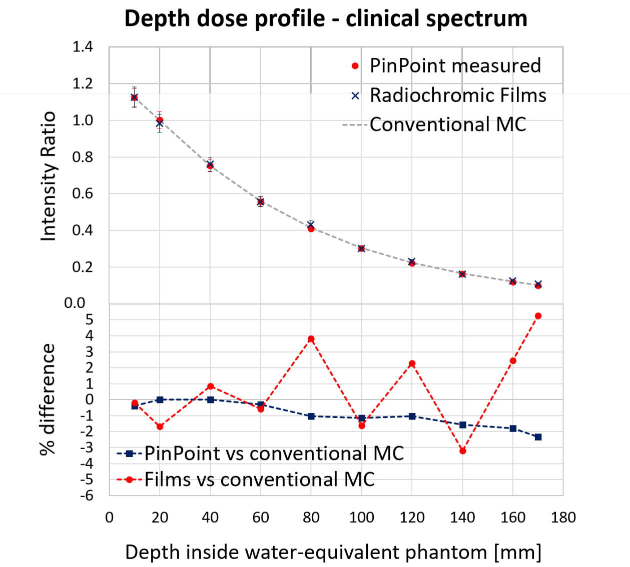


Figure 4: On the top plot the IR measured both with PinPoint and RCFs are plotted against the obtained data using MC simulations as a function of the depth inside the water phantom. On bottom plot the % deviation of the two experimental data sets and the MC simulation are shown.

5. Acknowledgements

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