Original paper

Monte Carlo-based dose calculation engine for minibeam radiation therapy

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ABSTRACT

Minibeam radiation therapy (MBRT) is an innovative radiotherapy approach based on the well-established tissue sparing effect of arrays of quasi-parallel micrometre-sized beams. In order to guide the preclinical trials in progress at the European Synchrotron Radiation Facility (ESRF), a Monte Carlo-based dose calculation engine has been developed and successfully benchmarked with experimental data in anthropomorphic phantoms. Additionally, a realistic example of treatment plan is presented. Despite the micron scale of the voxels used to tally dose distributions in MBRT, the combination of several efficiency optimisation methods allowed to achieve acceptable computation times for clinical settings (approximately 2 h). The calculation engine can be easily adapted with little or no programming effort to other synchrotron sources or for dose calculations in presence of contrast agents.

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Introduction

Minibeam radiation therapy (MBRT) is a novel radiotherapy (RT) technique based on a distinct dose delivery method which uses submillimetric field sizes (500–700 μm) in combination with the spatial fractionation of the dose. In MBRT, the irradiation is performed with arrays of kilovoltage X-rays beams spaced by around 1.2 mm [1]. The concept was first proposed by Dilmanian et al. (2006) and, since 2008, it has been explored at the ID17 Biomedical Beamline of the European Synchrotron Radiation Facility (ESRF). The resulting biological effects appear to challenge many of the current paradigms in RT. In particular, a remarkable healthy tissue resistance to very high doses in one fraction was observed in several preclinical investigations [2,3]. Additionally, this type of irradiations rendered significant tumour growth delay [3,4].

In contrast with other synchrotron RT techniques like microbeam radiation therapy (MRT) (see Refs. [5–7], among others), MBRT has potential for widespread clinical implementation. Wider beams are used to eliminate the need for extremely short irradiation times (and therefore, high dose rates) in order to prevent beam smearing, as it is the case of MRT. Hence, it is conceptually possible to extend this technique by using modified X-ray equipment, creating an opportunity for its implementation at hospitals [2]. In addition, it is feasible to use higher beam energies (≥ 200 keV), which would lead to lower entrance doses for a given dose to the tumour [8]. Moreover, the interlacing of two orthogonal arrays of minibeam beams that produce a homogeneous dose in the tumour is easier in MBRT [9], while the mechanical precision required in MRT makes such kind of irradiations extremely difficult.

The aforementioned advantages triggered the exploration of MBRT at the ESRF [3,4], where MBRT preclinical trials have started in order to evaluate the tumour and healthy tissue responses. If successful, these preclinical trials would open the way to the future clinical trials in MBRT, similarly to what happened in MRT [10]. Due to the complexity of these techniques, a preliminary step is planned in MRT when moving from the preclinical trials with rodents to the

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clinical trials in humans, which consists in the irradiation of large animals (cats and dogs) [11].

Within this framework, an accurate dose computation software is required to guide the forthcoming MBRT experiments. The peculiar irradiation characteristics, as compared to conventional RT (synchrotron source, beam modifiers, energy spectrum, micrometre-sized fields, etc.), demanded the development of a dedicated dose calculation tool [12,13]. Thus, the aim of this study was the development and experimental benchmarking of a Monte Carlo (MC)-based calculation engine devoted to MBRT. This computation engine includes the complete characterisation and modelling of the synchrotron source and the evaluation of dose distributions in a realistic voxelised model of the patient for one or several (interlaced) arrays.

It is important to note that, despite a previous MBRT dosimetric study has been published including dose calculations in complex structures [14], it does not include neither an accurate source model nor an experimental verification. The dose calculation engine developed in this work, together with the previous developed dosimetry protocol [9] constitute the full set of dosimetry tools required to carry out preclinical and, eventually, clinical trials in MBRT in a reliable and reproducible way. Finally, an estimation of the calculation times in a realistic treatment scenario envisaged in (possible) future clinical trials in MBRT has been evaluated for the first time.

Materials and methods

Radiation source and minibeam generation

The ESRF is a third-generation synchrotron with a 6.04 GeV electron storage ring. Electrons are deflected in devices consisting of a series of magnets, which produce extremely bright X-ray beams. In the particular case of ID17, the device is a wiggler. The generated synchrotron radiation traverses different types of beam modifiers until it reaches the patient position (see Fig. 1), where targets are placed on a high-precision goniometer. The beam characteristics change along its path; the mean energy at the patient position is approximately 100 keV, while the maximum beam dimensions are 2.5 mm in height and 41 mm in width [12]. In order to fill the desired vertical irradiation field size, the target is vertically scanned through the beam [15].

The vertical spatial fractionation of the beam is achieved by using a special device called white-beam chopper, which is

composed by ten 600- μm -wide tungsten carbide blades [16]. This innovative method offers an excellent reproducibility [1].

Source modelling

The ID17 X-ray source (wiggler) was modelled by the synchrotron ray tracing code SHADOW [17] and the MC simulation code PENELOPE [18] was employed to transport the photon beam from the source to the patient position through the beamline. The latter code allows the simulation of the coupled transport of electrons, photons, and positrons in a wide energy range and in arbitrary material systems. The two codes were directly linked by inserting a new source model into the general-purpose main program for PENELOPE named penEasy [19].

The phase-space state variables (energy, position, direction of flight and polarisation state) of the particles were saved in a phase-space file (PSF) at the position marked in Fig. 1. The information contained in this PSF was used as an input to generate an analytical photon beam source model. First, the photon energy was sampled from the MC calculated spectrum, which ranged from 27 to 600 keV with a mean energy of 99 keV. Secondly, a completely linearly polarised beam (along the electron orbital plane) was considered. Finally, the probability distribution of the horizontal coordinate was approximated as a uniform distribution with a width equal to the field size, while the joint distribution for position (x) and divergence (u) was approximated by a straight line obtained by the linear regression $u = ax$, where $a = 0.000256(4) \text{ cm}^{-1}$ is the regression coefficient.

Particles were then transported through the chopper and the vertical slit (see Fig. 1); the vertical scanning of the beam has also been considered. Further details can be found in our previous work [12].

MC simulation tool for dose computations in voxelised phantoms

Dose distributions in several phantoms were computed for a photon beam sampled according to the probability distributions derived from the beam model. The MC code PENELOPE/penEasy was used for dose computation.

Several modifications were performed on the code in order to be able to assess dose distributions at micron scale in a voxelised model of a patient, which is typically obtained from computed tomography (CT) images. For instance, the decoupling of the CT image voxel grid (lateral voxel size in the order of mm) to the dose

Figure 1. Scheme of the ID17 beamline elements from the wiggler to the patient position (not to scale). Adapted from Refs. [12,16].

Figure 2. On the left, photograph of the inner part of the anthropomorphic phantom (CIRS Inc. [22]). On the right, picture of the experimental hutch with the phantom placed on the high-precision goniometer.

bin grid (required lateral bin size in the order of $100\ \mu\text{m}$ in the transversal direction of the minibeam) was performed. Additionally, a program was developed to orientate the CT image along the direction of the minibeam for a given irradiation angle [13].

Typically, the attenuation map represented in the CT images is given in Hounsfield Units (HU). However, most MC codes require knowing the mass density and material index of each voxel. To convert HU to mass density, the calibration curve provided by the hospital where the CT was taken is used. The material index of each voxel was obtained by using a classification approach, that is, defining a mapping between HU intervals and the material index [20].

Several optimisation methods were applied in order to speed up the simulations. In particular, interaction forcing was applied to photon transport [18]. Additionally, simulations were parallelised by using independent random sequences [13,21].

MC calculations and experimental validation in an anthropomorphic phantom

MC calculations were experimentally verified by using radiochromic films (Gafchromic HD-810) analysed with a flat bed scanner (Epson Perfection V750-M Pro Scanner). Dose calculations had already been successfully validated in homogeneous and heterogeneous slab phantoms in the work of Prezado et al. [9]. In this

study, simulations and measurements were performed in a realistic anthropomorphic head phantom [22], which mimics the tissues with approximately 1% accuracy in our energy range (data provided by CIRS Inc. [22]). See Fig. 2. This phantom has already been used in previous dosimetry works [23].

CT images of this phantom were used as an input for the MC calculations. Dose distributions were tallied in voxels of $100\ \mu\text{m}$ along the transversal direction of the minibeam, while the bin size was set to the voxel size in the other two dimensions (CT voxel size: $0.35 \times 1.00 \times 0.35\ \text{mm}^3$). From these distributions, the ratio between the peak dose (dose at the center of one minibeam) and the valley dose (dose in the central flat region of $300\ \mu\text{m}$ between minibeam), also named peak-to-valley dose ratio (PVDR), was assessed. This parameter is one of the most relevant quantities in this type of spatially fractionated synchrotron RT techniques [5].

Table 1

Calculated (MC) versus measured (Film) central PVDR at different depths in an anthropomorphic phantom. MBRT parameters: unidirectional; $570\text{-}\mu\text{m}$ -wide minibeam spaced by $1.2\ \text{mm}$; field sizes: 1×1 , 2×2 and $3 \times 3\ \text{cm}^2$. '(lat)' and '(AP)' denote a lateral and antero–posterior irradiation, respectively. Statistical uncertainties correspond to 2σ .

PVDR						
Depth (cm)	$1 \times 1\ \text{cm}^2$		$2 \times 2\ \text{cm}^2$		$3 \times 3\ \text{cm}^2$	
	MC	Film	MC	Film	MC	Film
4.4 (lat)	12.8 ± 0.2	13 ± 1	6.6 ± 0.1	6.5 ± 0.7	5.2 ± 0.1	5.3 ± 0.5
10.8 (lat)	11.9 ± 0.3	11 ± 1	6.3 ± 0.2	6.5 ± 0.7	4.5 ± 0.1	4.6 ± 0.5
5.6 (AP)	12.9 ± 0.2	12 ± 1	6.6 ± 0.1	6.4 ± 0.6	4.8 ± 0.1	4.2 ± 0.4
7.6 (AP)	12.5 ± 0.3	12 ± 1	6.4 ± 0.2	6.2 ± 0.6	4.4 ± 0.1	5.0 ± 0.5

Figure 3. Coronal, axial and sagittal view of the irradiated dog's head. The arrow represents the beam direction (AP) and the line indicates the central part of the beam in depth. The square in the axial view corresponds to the whole irradiation field size ($2 \times 2\ \text{cm}^2$).

Figure 4. Dose map (arbitrary units, a.u.) at a depth of 9 cm from the dog's head surface. MBRT parameters: AP unidirectional; 570- μ m-wide minibeam spaced by 1.2 mm; field size: 2×2 cm².

PVDR values were evaluated at several depths for different field sizes (1×1 , 2×2 and 3×3 cm²). These field sizes are consistent with previous synchrotron RT dosimetry works [9,12,24,25]. For lateral irradiations, films were placed at the depths of 4.4 and 10.8 cm from the phantom surface and for anterior–posterior (AP) irradiations, at the depths of 5.5 and 7.6 cm. Results are presented in Section *Experimental validation of the MC calculations in an anthropomorphic phantom*.

MC simulations of a realistic treatment plan

An example of a dose calculation in a dog's head will be presented in Section *MC calculations in voxelised structures: an example of a realistic treatment plan*. Voxels of CT image of the dog were classified into three materials: soft tissue, skull, and air. Soft tissue was identified as water with a varying mass density. The skull composition was extracted from the International Commission on Radiation Units and Measurements (ICRU) Report 46 [26].

Two irradiation modalities were evaluated: unidirectional (AP and lateral) and interlaced arrays. In both cases, the MBRT irradiation parameters were fixed to 570- μ m-wide minibeam spaced by 1.2 mm, which showed a perfect interlaced pattern in a homogeneous phantom [9]. The whole irradiation field size was set to 2×2 cm². Dose was tallied in bins of

Figure 6. Dose map (a.u.) at a depth of 9 cm from the dog's head surface for an interlaced irradiation geometry. MBRT parameters: AP and lateral irradiations; 570- μ m-wide minibeam spaced by 1.2 mm; field size: 2×2 cm².

0.74 mm (lateral direction of the minibeam) $\times$ 100 μ m (transversal direction of the minibeam) $\times$ 1.25 mm (depth) (CT voxel size: $0.74 \times 0.74 \times 1.25$ mm³).

Results and discussion

Experimental validation of the MC calculations in an anthropomorphic phantom

Table 1 shows the calculated and measured central PVDR values as a function of depth in an anthropomorphic phantom for several field sizes (see details in Section *MC calculations and experimental validation in an anthropomorphic phantom*). A decrease of PVDR is observed when the field size is increased. Additionally, PVDR values are similar to those found in a homogeneous phantom [15] due to the fact that the radiochromic film positions (limited by the phantom geometry) are far from the bone heterogeneity.

MC calculations reproduce experimental results within uncertainty bars even in such complex phantoms, showing the performance of the developed MC calculation tool for its use in MBRT dose calculations. It is important to note that, for the first time, dose distributions in MBRT were validated in an anthropomorphic phantom.

MC calculations in voxelised structures: an example of a realistic treatment plan

Dose calculations were performed in a voxelised model of a dog's head obtained from a CT scan (see Fig. 3). The minibeam dose pattern is clearly visible in Fig. 4, which shows an axial dose map for an AP unidirectional irradiation (field size of 2×2 cm²).

Figure 5. Vertical dose profile (left) and central PVDR in depth (right) in a dog's head. MBRT parameters: AP unidirectional; 570- μ m-wide minibeam spaced by 1.2 mm; field size: 2×2 cm². Dose was tallied in bins of 0.74 mm (lateral direction of the minibeam) $\times$ 100 μ m (transversal direction of the minibeam) $\times$ 1.25 mm (depth). Statistical uncertainties correspond to 2σ .

Figure 7. Vertical dose profile at a depth of 9 cm from the dog's head surface for an interlaced irradiation geometry. MBRT parameters: AP and lateral irradiations; 570- μm -wide minibeam spaced by 1.2 mm; field size: $2 \times 2 \text{ cm}^2$.

In this type of spatially fractionated RT techniques, quantitative information on peak and valley doses and the corresponding PVDR is needed. The left part of Fig. 5 presents a lateral dose profile (at a depth of 4.5 cm), whereas the right part shows the PVDR values in depth. The enhancement in both the peak and the valley doses (and the corresponding reduction in the PVDR values) is due to the presence of the bone. PVDR values are not uniform in the target volume due to the important tissue heterogeneities encountered by the minibeam in their path.

The calculation time to reach a 2% uncertainty (2σ) in the central valley dose at a depth of 4.5 cm (from the dog's head surface) on a 2.93 GHz Intel Xeon Processor X5670 (Compiler: Intel Fortran v. 10.0, option-O3) is 3.4 days. By parallelising the simulations in 40 cores, the computation time is reduced to 2 h. These values comply with the accuracy of 2–5% in dose delivery that is required to effectively treat certain types of cancers and to reduce complications, as reflected in ICRU Reports 24 and 42 [27,28]. Additionally, these calculation times are perfectly acceptable in such clinical conditions (it is important to note that the flexibility in the timings for clinical trials in synchrotrons is higher than in a clinical environment).

The computation engine also enables the assessment of dose distributions in bidirectional irradiations (or other irradiation modalities). In fact, as it was shown in preclinical trials [2–4], interlacing of two beams is needed in order to increase the valley doses in the target and, thus, achieve a high enough density of lesions in the tumour, while healthy tissues still benefit from the spatial fractionation of the dose. Figure 6 shows the dose map for a bidirectional irradiation interlaced at a depth of 9 cm from the dog's head surface.

Figure 7 shows the vertical dose profile at the centre of the target. One can see that the irradiation parameters that lead to a homogeneous interlaced dose distributions [9] produce hot regions in the target when irradiating realistic geometries. Previous studies revealed that the overlapping parts producing hot spots in the tumour (some tens of microns) should not produce deleterious effects [3,29,30].

Conclusion

MBRT is an innovative spatially fractionated synchrotron RT technique with potential applications using sources other than synchrotrons. To guide the biological studies, an MC-based

computation engine has been developed and successfully benchmarked with experimental data in complex phantoms. An example of treatment planning scenario has been presented, showing the performance of the calculation engine. The final computation time (approximately 2 h) is acceptable for clinical trials in synchrotrons. This calculation engine can be easily adapted with little or no programming effort to other synchrotrons or for dose calculations in presence of contrast agents [31]. The developments performed in this work, along with the previously developed dosimetry protocol [9], constitute the full set of dosimetry tools required to carry out preclinical studies and, eventually, clinical trials in MBRT in a reliable and reproducible way.

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