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Validation of the analytical irradiator model and Monte Carlo dose engine in the small animal irradiation treatment planning system *μ*-RayStation 8B

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Abstract

Dose calculation in preclinical context with a clinical level of accuracy is a challenge due to the small animal scale and the medium photon energy range. In this work, we evaluate the effectiveness and accuracy of an analytical irradiator model combined with Monte Carlo (MC) calculations in the irradiated volume to calculate the dose delivered by a modern small animal irradiator.

A model of the XRAD225Cx was created in μ-RayStation 8B, a preclinical treatment planning system, allowing arc and static beams for seven cylindrical collimators. Calculations with the μ-RayStation MC dose engine were compared with EBT3 measurements in water for all static beams and with a validated GATE model in water, heterogeneous media and a mouse CT. The GATE model is a complete MC representation of the XRAD225Cx.

In water, μ-RayStation calculations, compared to GATE calculations and EBT3 measurements, agreed within a maximal error of 3.2% (mean absolute error of 0.6% and 0.8% respectively) and maximal distance-to-agreement (DTA) was 0.2 mm at 50% of the central dose. For a 5 mm static beam in heterogeneous media, the maximal absolute error between μ-RayStation and GATE calculations was below 1.3% in each medium and DTA was 0.1 mm at interfaces. For calculations on a mouse CT, μ-RayStation and GATE calculations agreed well for both static and arc beams. The 2D local gamma passing rate was >98.9% for 1%/0.3 mm criteria and >92.9% for 1%/0.2 mm criteria. Moreover, μ-RayStation reduces calculation time significantly comparing with GATE (speed-up factor between 120 and 680).

These findings show that the analytical irradiator model presented in this work combined with the μ-RayStation MC dose engine accurately computes dose for the XRAD225Cx irradiator. The improvements in calculation time and availability of functionality and tools for managing, planning and evaluating the irradiation makes this platform very useful for pre-clinical irradiation research.

1. Introduction

Over the past few years, technological developments in the field of preclinical irradiators have reduced the gap between machines dedicated to patients and those designed for small animals (Verhaegen *et al* 2011, 2018, Delpon *et al* 2016). Modern preclinical radiotherapy allows mimicking of 3D image-guided clinical radiotherapy, taking the small animal and target size constraints into account. The smallest beam sizes are reduced down to roughly 1 mm in diameter. Consequently, a sub-millimeter targeting accuracy is needed, which is ensured by low mechanical tolerances and good quality images. Image pixel size is scaled down from ~2 mm to ~0.2 mm. Due to small thicknesses and small beam sizes, the beam energy is reduced from MV to kV.

Once these technological issues have been overcome, the challenge is to mimic the classic clinical radiotherapy workflow including the following steps (Verhaegen *et al* 2018): planning CT acquisition, segmentation of

planning CT in tissues (elemental composition and density), registration with additional imaging (CT, MRI, PET/SPECT/BLI, etc), contouring of target and organs at risk, plans creation (isocenter, beams size and angles, etc), accurate dose calculation, plan analysis (isodoses, dose-volume histogram, comparison tools, etc) and dose delivery. Generally, treatment planning and dose administration are performed in one session while animal is under anesthesia. Sometime, biological studies require various treatment fractions, in which case tools for dose accumulation, such as deformable image registration (DIR), can be useful. Absorbed dose must be determined as accurately as possible given that many preclinical studies aim at identifying the relationship between the delivered dose and the biological effects observed in the animal. The accuracy level of dose calculation for preclinical studies should be comparable to the clinical practice accuracy defined in the AAPM Task Group 65 (Papanikolaou *et al* 2004). However, modelling of a small animal irradiator, combining medium energy and field sizes smaller than the focal spot size of the x-ray tube, remains a challenge. The use of Monte Carlo (MC) simulations represents an interesting opportunity in this complex radiation transport problem (Chetty *et al* 2007, Granton *et al* 2012, Verhaegen *et al* 2018). Considering all of this, modern preclinical radiotherapy requires a comprehensive treatment planning system (TPS), similar to clinical systems, which provides all the tools necessary and ensures the required accuracy level for dose calculation.

In our institution, the XRAD225Cx μ-irradiator is used for preclinical studies. A MC model (GATEv7) was previously created and validated for dose calculation in small animals (Smekens *et al* 2014, Noblet *et al* 2016). However, on one hand, typical MC environments do not provide the same tools, that are available in a clinical TPS, to manage patient workflow and irradiation. On the other hand, clinical TPSs are not adapted for preclinical requirements and cannot be used directly. To overcome this limitation, the clinical TPS RayStation, has been adapted for preclinical requirements, and the resulting software is called μ-RayStation (RaySearch Laboratories, Stockholm, Sweden). The GATE model is a complete MC model, including irradiator and irradiated volume when μ-RayStation combines an analytical model of the irradiator with a MC calculation in the irradiated volume.

In this work, we study the capability of such hybrid system, implemented in μ-RayStation 8B, to model the XRAD225Cx preclinical irradiator, assessing its dose calculation accuracy in small animals. The analytical model was first developed and validated comparing calculations with EBT3 measurements and GATE calculations in water. Secondly, μ-RayStation and GATE dose distributions in heterogeneous media and in mouse were compared.
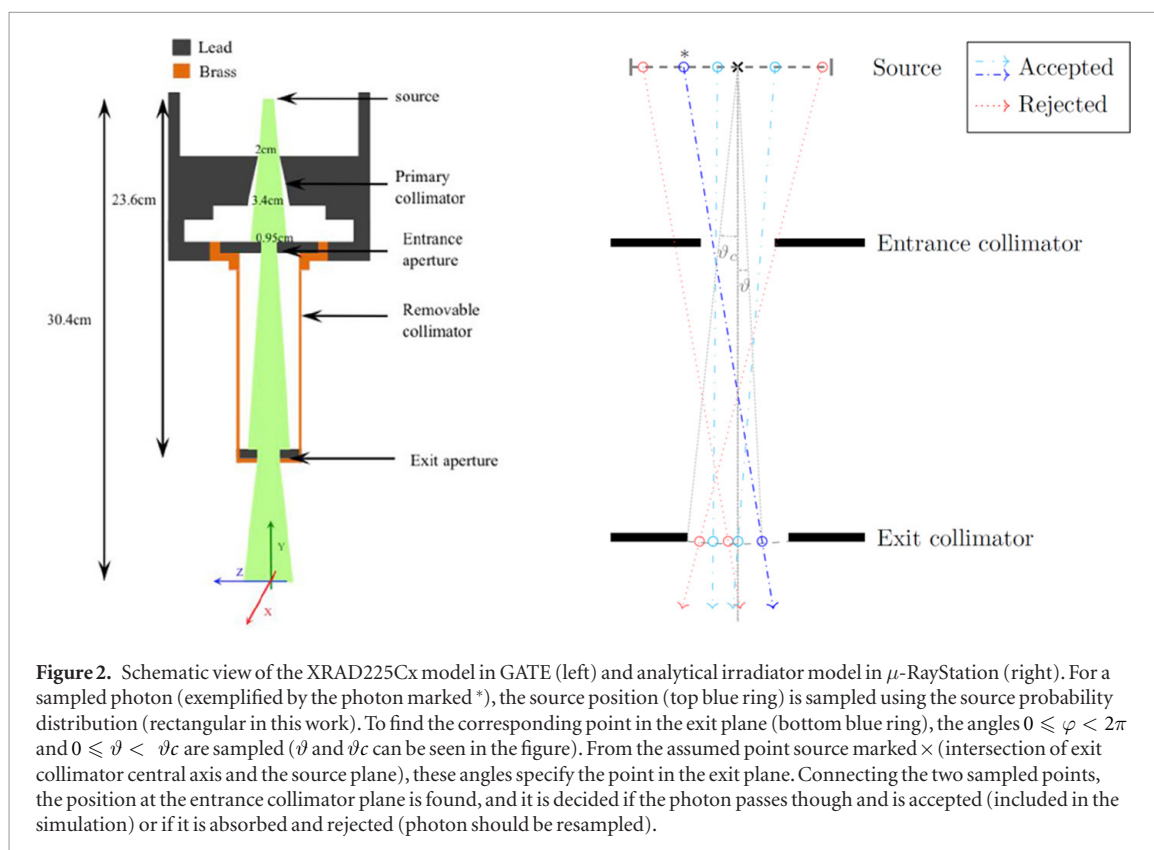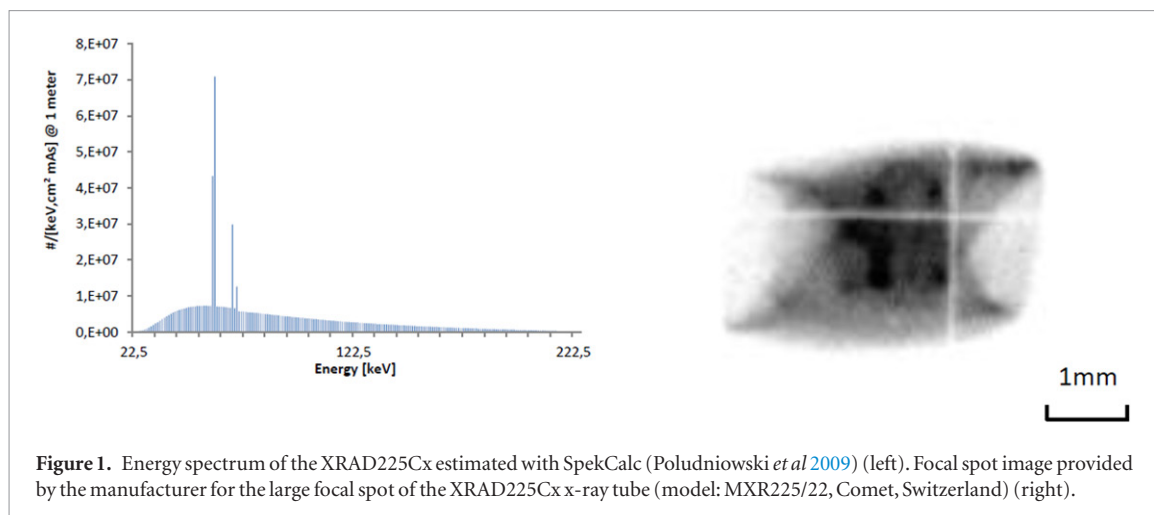
2. Materials and methods

2.1. XRAD225Cx
The XRAD225Cx (Precision XRay Inc.) is a modern small animal irradiator (Clarkson *et al* 2011) allowing image-guided radiotherapy (IGRT). It consists of a kilovolt x-ray radiation source combined with high-resolution cone beam CT (CBCT) imaging equipment for image guidance. The dual focus x-ray tube (model: MXR225/22, Comet, Switzerland) and the digital imaging panel (model: XRD 0820 AN3 ES, Perkin-Elmer, Germany) are mounted face to face on a rotating arm. A set of cylindrical collimators provides circular beams with diameters from 20 mm down to 1 mm at the isocenter. Due to the collimation, the heel effect is negligible. The specimen couch is computer-controlled so that X–Y–Z motion can be performed with an accuracy better than 0.1 mm. Fluoroscopy or CBCT are typically performed at 40 kVp and 2.5 mA using the small focal spot (~1 mm in diameter). Irradiations are performed at 225 kVp and 13 mA using the large focal spot (~5 mm in diameter) with static beams or arcs. The large focal spot used for irradiation allows to increase beam intensity providing a dose rate suited for radiotherapy application (few Gy/min). However, the size of this focal spot is not negligible, particularly for the smallest beams with diameter of less than 5 mm. Moreover, it presents an irregular shape, a heterogeneous fluence and a lateral shift (figure 1, right).

2.2. GATE/GEANT4 XRAD225Cx model
A MC model (GATEv7) was previously created for dose calculation in small animals (Smekens *et al* 2014, Noblet *et al* 2016). GATE is a MC platform based on the GEANT4 toolkit specifically dedicated to medical physics applications (Jan *et al* 2011, Sarrut *et al* 2014). The model consists in a photon source placed at the same position as the focal spot. The XRAD225Cx energy spectrum was computed with SpekCalc (Poludniowski *et al* 2009) with the following optimized parameters: beam angle 60°, beryllium thickness 0.8 mm and copper thickness 0.29 mm (figure 1, left). The size, shape and non-uniform spatial distribution of the focal spot influence the dose distribution, particularly for beam smaller than the focal spot size. These parameters were included in the MC model using the focal spot image of the x-ray tube provided by the manufacturer (figure 1, right), to create a spatial-varying fluence source. To save calculation time, the beam angle was adapted at each collimator aperture. All the components of the XRAD225Cx tube and collimators were modelled in GATE (figure 2 left).

In order to reduce calculation time, particle tracking was optimized using the split exponential track length estimator (seTLE) method (Smekens *et al* 2014). This kerma-based method combines MC splitting, ray casting

Figure 1. Energy spectrum of the XRAD225Cx estimated with SpekCalc (Poludniowski *et al* 2009) (left). Focal spot image provided by the manufacturer for the large focal spot of the XRAD225Cx x-ray tube (model: MXR225/22, Comet, Switzerland) (right).

Figure 2. Schematic view of the XRAD225Cx model in GATE (left) and analytical irradiator model in μ-RayStation (right). For a sampled photon (exemplified by the photon marked *), the source position (top blue ring) is sampled using the source probability distribution (rectangular in this work). To find the corresponding point in the exit plane (bottom blue ring), the angles $0 \leqslant \varphi < 2\pi$ and $0 \leqslant \vartheta < \vartheta c$ are sampled (ϑ and ϑc can be seen in the figure). From the assumed point source marked $\times$ (intersection of exit collimator central axis and the source plane), these angles specify the point in the exit plane. Connecting the two sampled points, the position at the entrance collimator plane is found, and it is decided if the photon passes though and is accepted (included in the simulation) or if it is absorbed and rejected (photon should be resampled).

and deterministic dose calculation. It extends the splitting procedure to all photon sources, primary (x-ray generator) and secondary (interaction sites) with respectively Mp and Ms multiplicities. According to the sensitivity study made by Smekens *et al* (2014) Mp and Ms were fixed to 100 and 400 in the model. Inside the voxelised volume, the ray casting technique is used to perform the dose calculation during photon transportation between production/interaction sites by using attenuation and energy absorption coefficients. GEANT4 provides low-energy electromagnetic radiation physics models (Poon *et al* 2005). The emlivermore physics list, effective from 250 eV, was used for photon interactions (Photoelectric effect, Compton and Rayleigh scattering) with a cut-off distance of 5 μm below which no secondary particles were generated. As a result of the use of seTLE method, the energy transferred to the electrons was assumed to be deposited locally.

The use of the seTLE method in the context of small animal radiotherapy was validated comparing with full MC calculations (Smekens *et al* 2014). In parallel, our GATE MC model of XRAD225Cx, based on the seTLE variance reduction technique (VRT), was extensively validated by comparing simulation results with measurements in homogeneous media (Noblet *et al* 2016) and in small animals (Noblet *et al* 2018).

2.3. μ-RayStation: an adaptation of RayStation

In the clinical TPS RayStation 8B (RaySearch Laboratories, Stockholm, Sweden), dose calculation for photon beams is typically performed by an analytical collapsed cone (CC) algorithm (Mackie *et al* 1987). For electron dose calculation, the VMC++ MC dose engine (Kawrakow *et al* 2000a, Chetty *et al* 2007) is used.

In RayStation 8B, all tools and dose calculation algorithms are intended for patients and thereby not suitable for the sub-millimeter dimensions and low energy found in small animal irradiation. For this reason, μ-RayStation 8B (RaySearch Laboratories, Stockholm, Sweden) was developed. The VMC++ MC code is used for the low energy photon dose calculations. VMC++ has previously been validated for photon beams in the energy range from 20 keV to 1000 keV (Terribilini *et al* 2010), on a typical human patient scale (~40 cm simulation geometries). The MC transport parameters used for VMC++ in μ-RayStation are the same as the more exact of the parameter sets used by Terribilini *et al* (AP = AE = Ecut = 10 keV, no KERMA approximation, ESTEPE = 0.15 and XIMAX = 0.5). These parameters were selected to provide accurate doses for low energies and small voxels.

VMC++ uses a Class II condensed history (CH) scheme for the simulation of charged particle transport. It is optimized for 3D dose calculations in voxel-geometries and employs a variety of VRT such as photon splitting, Russian Roulette, use of quasi-random numbers, simultaneous simulation of sets of particles, and KERMA approximation for scattered photons with energy below a user-defined threshold (not used in μ-RayStation). Since VMC++ is an MC algorithm, the accuracy of the computed dose will depend on the number of simulated histories. In μ-RayStation, this is controlled by the user-selected number of MC histories per beam area unit. The inherent statistical uncertainty is reported using the combined relative statistical uncertainty (RSU) (introduced by Kawrakow *et al* (2000b)). The RSU is the average statistical uncertainty (one standard deviation) in all voxels with a dose larger than 50% of the maximum dose, relative to the maximal dose. This is the same measure as is used for the clinical electron dose calculations in RayStation 8B. In this work, dose to medium is considered both for VMC++ and GATE calculations (Chetty *et al* 2007, Vaniqui *et al* 2019).

2.4. Analytical modelling of the irradiation device in μ-RayStation

Since μ-RayStation uses a MC dose engine, dose calculations require the input of initial incident particles, a phase space. The irradiation device can either be modelled explicitly in the simulation (as in the GATE model), pre-computed phase space files can be used, or the fluence resulting from the irradiator can be modelled analytically. μ-RayStation uses an analytical model of the irradiator, from which photons exiting the irradiator can be sampled for use in the MC simulation.

2.4.1. Components

The μ-RayStation irradiator model consists of three basic components: a source (the x-ray tube target), an entrance collimator and an exit collimator (see figure 2, right). In principle the shapes of these three objects can be any geometry that can be described analytically, but in μ-RayStation 8B the source is either rectangular, elliptical or elliptically Gaussian. In this work, the source shape has been chosen to be rectangular after some initial comparisons for calculated dose distributions. Further, for the cylindrical collimators considered in this work, both the entrance and exit collimators are circular.

2.4.2. Assumptions

In using the model described in this work, there are some assumptions that are being made. Firstly, the collimators are assumed to be perfect absorbers, meaning that if a photon intersects any of them it is completely absorbed. Secondly, the model assumes that any scatter generated in the irradiator is negligible, and hence that only primary photons are needed in the modelling. Thirdly, it is assumed that the energy and fluence is independent of the direction from the source, in other words, the heel effect, commonly seen in x-ray tubes, is neglected. All these assumptions, and their validity, have been investigated in closer detail by Granton *et al* (2013).

2.4.3. Sampling

When a photon is to be sampled from the irradiator model, it needs an energy, a position and a direction. Since the collimators are assumed to be perfect absorbers and that there is no scatter, only photons that pass through the exit collimator will reach the simulated geometry. Because of this, the point at which the photon exits the exit collimator can be sampled. Assuming an isotropic point source aligned with the center of the exit collimator, the direction of a photon passing through a circular exit collimator can be described by two angles; $0 \leqslant \varphi < 2\pi$ and $0 \leqslant \vartheta < \vartheta c$, where φ is the azimuthal angle, ϑ is the polar angle, and ϑc the maximal polar angle for which photons still passes through the exit collimator. These two angles are sampled (Bielajew 2001);

$$\vartheta = \arccos\left(1 - r_1\left(1 - \cos\left(\vartheta c\right)\right)\right),$$
$$\varphi = 2\pi r_2.$$

Where $0 \leqslant r_1, r_2 < 1$ are uniformly distributed random variables. Given these angles, the position of the photon when passing the exit collimator plane is found assuming it originated in the point source location. If the exit collimator is not circular, the angles would be resampled if the photon is not inside the collimator shape.

The photon originates in the source, which in reality is not a point (figure 1, right), and so, its positions there is sampled according to the source distribution (as mentioned; rectangular, elliptical or elliptically Gaussian). The center of the source distribution is allowed to be shifted relative to the beam central axis. Since the source shape in this work is decided to be rectangular, the source distribution is a uniform distribution over a rectangular area. The photon position in the source plane in combination with the photon position in the exit collimator plane provides two points that give the direction of the sampled photon (and a starting position). In addition to this information, the energy is needed. This is sampled using a provided energy spectrum (figure 1, left).

To include the entrance collimator in the sampling process, the position of the photon when crossing the entrance collimation plane is found using its direction and starting position. If the photon at this plane happens to not be within the opening of the entrance collimator, the photon is disregarded, and another photon sampling is performed. This process is performed until the path of the generated photon is open (see figure 2, right).

For arc beams the position of the irradiator relative to the irradiated object is not fixed, and thus, to generate photons from all the directions that the beam covers, for each photon an angle within the arc is sampled uniformly and the irradiator assumed to be at this angle for this photon.

2.5. μ-Raystation validation

2.5.1. Calculation in water

Measurement used for beam commissioning and GATE validation were used to create and validate the μ-RayStation model (Noblet *et al* 2016). Reference absorbed dose was measured in water with a cylindrical ionization chamber (F65-P, PTW-Freiburg GmbH, Germany) following the TRS 398 dosimetry protocol (Andreo *et al* 2000), based on an in-water calibration (Perichon *et al* 2013). Relative measurements—off-axis profiles (OAP), percent depth dose (PDD) and output factors (OF)—were performed with EBT3 films (International Specialty Products, Wayne, NJ, USA) in $30 \times 11 \times 30$ cm^3 RW3 stack (PTWFreiburg, Freiburg, Germany). Water equivalence of the RW3 solid material at 225 kVp was previously assessed for relative dosimetry (Chiavassa *et al* 2013). Measurement and calculation conditions are summarized in table 1. The overall accuracy of EBT3 film measurements was estimated to 3.2%. EBT3 management is described in detail in Noblet *et al* (2016). Corresponding calculations were performed in water, in μ-RayStation and GATE, for the seven circular collimators (field diameter 20, 15, 10, 8, 5, 2.5 and 1 mm).

2.5.2. Calculation in heterogeneous phantom

A virtual heterogeneous phantom was created in μ-RayStation and GATE, composed with four slabs of known materials: Water (1 g cm^{-3}), Bones (1.85 g cm^{-3} from ICRP 23 (ICRP 1975)), Lung (0.26 g cm^{-3} from ICRU report 44 (ICRU 1989)) and Water. A 5 mm beam was applied perpendicularly to the slabs with an exposure of 780 mAs (13 mA during 60 s). A calculation grid size of $0.1 \times 0.1 \times 0.1$ mm^3 was defined in both GATE and μ-RayStation. GATE provides statistical uncertainty on each voxel. In order to compare statistical uncertainty of the two systems, the definition of RSU used in μ-RayStation was applied to GATE simulation through a python script. RSU was 0.87% in GATE and 0.20% in μ-RayStation.

2.5.3. Calculation in mouse

Two mouse CBCTs (abdominal and thoracic) have been acquired on the XRAD225Cx (40 kVp, 2.5 mA, small focal spot) and imported in μ-RayStation in the DICOM format. Images were segmented by automatic thresholding (Air/Lung = −568 HU, Lung/Soft tissues = −150 HU, Soft tissues/Bones = 821 HU) and following known materials were applied: Air (0.001 g cm^{-3}), Lung (0.26 g cm^{-3} from ICRU report 44 (ICRU 1989)), Muscle (1.05 g cm^{-3}) and Bones (1.85 g cm^{-3} from ICRP 23 (ICRP 1975)). This very simple method of material assignment is not adapted for accurate dose calculation in preclinical context, particularly for bone materials (Bazalova *et al* 2011, Noblet *et al* 2018). However, the use of the densest bone in this study allows considering the most critical situation for dose comparison. A target volume was delineated in the spine of the abdominal CBCT. In a first plan (figure 3, left) 3 static 5 mm beams were centered on the target volume (beam angles 0°, 50° and 140°). In a second plan (figure 3, middle) a full-arc beam (1° to 359°) was applied with the collimator of 5 mm. A common calculation grid size of $0.2 \times 0.2 \times 0.2$ mm^3 was used for these two plans. A target volume was delineated in the lung of the thoracic CBCT. 6 static 1 mm beams (beam angles 0°, 30°, 195°, 240°, 270° and 320°) were centered on the target volume (figure 3, right). Grid size was reduced to $0.1 \times 0.1 \times 0.1$ mm^3 according to the beam size. The same set of geometries and beams were simulated in GATE using similar grid sizes. Maximal RSU was 0.98% for each beam in μ-RayStation, 1.45% in GATE for the arc plan and 0.65% and 0.87% for the 5 mm and 1 mm 3D-conformational plans respectively. An identical exposure of 780 mAs (13 mA during 60 s) was chosen for all simulations. A local gamma analysis was performed (Verisoft®) between μ-RayStation and GATE calculations

Table 1. Studied parameters for the measurement, GATE and μ-RayStation comparison. The simulated geometry is restricted the parts close to the film measurements, and hence smaller that the experimental setup.

Parameter	Experimental setup	Calculation (μ-RayStation and GATE) setup
OAP & OF	EBT3 films placed at the isocenter, 2 cm depth in a $30 \times 11 \times 30\,cm^3$ RW3 stack. Profiles extracted in the anode/cathode direction (in-plane) and parallel direction (cross-plane)	Water tank $3 \times 3 \times 4\,cm^3$. SSD = 28.4 cm Calculation grid $0.1 \times 0.1 \times 0.1\,mm^3$ for 2.5 and 1 mm collimators; $0.2 \times 0.2 \times 0.2\,mm^3$ for greater collimators
	SSD = 28.4 cm	RSU < 0.5% for μ-RS8 and Gate mean statistical uncertainty <0.5%
PDD	EBT3 films inserted perpendicularly to the beam axis at different depths along the beam axis in a $30 \times 11 \times 30\,cm^3$ RW3 stack	Water tank $3 \times 3 \times 8\,cm$. SSD = 30.4 cm Calculation grid $0.2 \times 0.2 \times 0.2\,mm^3$ for 2.5 and 1 mm collimators; $1 \times 1 \times 1\,mm^3$ for greater collimators
	SSD = 30.4 cm	RSU < 0.4% for μ-RS8 and Gate mean statistical uncertainty <1%

SSD = source-surface distance; RSU = relative statistical uncertainty.

for the axial, coronal and sagittal plans crossing the isocenter, inside the isodose 20%. Gamma criteria were set to 1%/0.3 mm and 1%/0.2 mm.

3. Results

3.1. Measurement in water

Comparison of in-plane and cross-plane OAP for all beams is presented in figure 4. The two smallest beams (2.5 and 1 mm in diameters) present irregular shape and position due to the focal spot size. In GATE, the focal spot image was added to the simulation. In the model defined in μ-RayStation 8B, the source shape was chosen rectangular and offsets of 0.35 mm and 0.15 mm were added to simulate the influence of the focal spot shape and shift, providing satisfying agreement compared to both GATE calculation and EBT3 measurements (figure 4). The complete list of geometrical irradiator model parameters can be seen in table 2. The maximal distance-to-agreement (DTA) between μ-Raystation 8B and both EBT3 measurements and GATE was 0.2 mm for all beams.

Comparison of PDDs for all beams is presented in figure 5. Relative comparison between μ-RayStation 8B and measurement on the one hand, and μ-RayStation 8B and GATE on the other hand, was made considering respectively measurement and GATE calculation at 1 cm depth as reference. Between μ-RayStation 8B and measurement, mean absolute error were 1.1%, 0.7%, 0.8%, 1.0%, 0.8%, 0.6% and 0.6% for collimators with a field diameter of 20, 15, 10, 8, 5, 2.5 and 1 mm respectively (global mean error 0.8%). Corresponding comparison between μ-RayStation 8B and GATE were 0.5%, 0.4%, 1.0%, 0.8%, 0.6% and 0.6% (global mean error 0.6%). In all cases, the maximal absolute error was 3.2%. Measured reference dose in water and relative OF were used to determine collimator specific dose scaling adjustments for the model.

3.2. MC comparison in heterogeneous phantom

Absolute dose rate (Gy/min) was extracted from GATE and μ-RayStation in the central axis of the heterogeneous phantom, perpendicularly to the slabs (figure 6). Impact of heterogeneities is clearly visible in both dose distributions, particularly in the bone slab which increases absorbed dose by a factor 3 (figure 6). Indeed, the dosimetric impact of material composition and density is critical here due to predominance of photoelectric effect at medium energy range. GATE and μ-RayStation provide closely matching dose distributions, with a mean absolute error of 0.8%, 0.8%, 1.3% and 1.3% for slabs of water, bone, lung and water respectively. Interfaces present slight deviations with a DTA of 0.1 mm, corresponding to one voxel. Figure 7 presents absolute dose rate (Gy/min) profiles extracted from GATE and μ-RayStation in the cathode/anode (in-plane) direction, in the center of each slab. The depth was respectively 0.5 cm (water slab), 1.5 cm (bone slab), 2.5 cm (lung slab) and 3.5 cm (water slab). DTA between GATE and μ-RayStation at 50% of the central dose are 0.11 mm, 0.15 mm, 0.19 mm and 0.22 mm on the anode side and 0.03 mm, 0.07 mm, 0.09 mm and 0.13 mm on the cathode side for depths 0.5 cm, 1.5 cm, 2.5 cm and 3.5 cm respectively. DTA obtained for the same collimator in water at 2 cm depth were 0.07 mm and 0.1 mm (figure 4).

3.3. MC comparison in mouse

Dose distributions in mouse calculated with μ-RayStation and GATE are very close. Table 3 presents gamma passing rate, inside the isodose 20%, for the planes crossing the isocenter, for the different plans. For the 1%/0.3 mm criteria, the mean and minimal gamma passing rates (from table 3) are 99.4% and 98.9%, respectively. For the 1%/0.2 mm criteria the mean and minimal gamma passing rates are 96.9% and 92.9%, respectively.
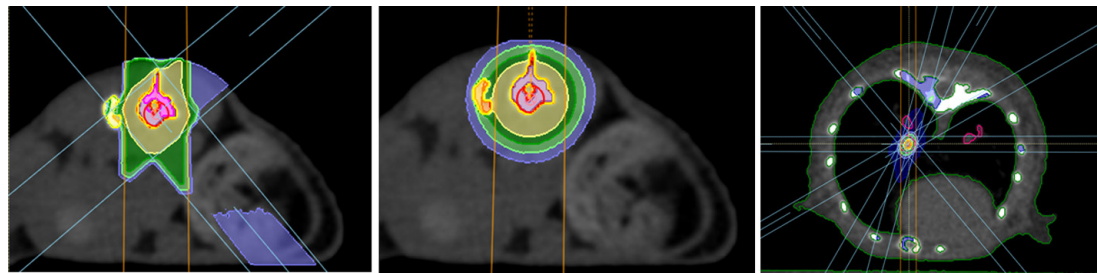
Figure 3. The three plans calculated in mouse CBCT with μ-Raystation 8B: three 5 mm static beams centered on the spine (left), 5 mm arc beam centered on the spine (middle) and six 1 mm static beams centered on the lung target (right).

Figure 8 shows dose-volume histogram comparison for the lung target. Relative difference for average and maximal doses in tumor calculated by μ-RayStation and GATE were 1% and 2% respectively. No significant dose difference was found in right and left lungs. Figure 9 compares two doses profiles extracted from μ-Raystation and GATE calculation for the lung target treatment. The two profiles in mouse are close. But, in the air outside the mouse, dose calculated with GATE (~0.36 Gy) is significantly higher that dose calculated with μ-RayStation (~0.09 Gy). Calculation in air is a limitation of the seTLE method applied in our GATE model, since the energy transferred to the electrons is assumed to be deposited locally. In preclinical conditions (medium energy range and submillimeter spatial resolution), this assumption has no impact in tissues, even in low densities such as lung, but has significant impact in air due to the electrons path lengths (Smekens *et al* 2014). However, dose in air has no impact on preclinical studies.

3.4. Calculation time comparison

μ-RayStation uses an analytical irradiator model (and thus only performs MC transport in the specimen geometry) while our model in GATE includes all the components of the irradiator. This (in addition to the high performance of VMC++) leads to significant difference in calculation time. For example, a 5 mm anterior beam in water ($3 \times 3 \times 4\,cm^3$ geometry, calculation grid resolution of $0.2 \times 0.2 \times 0.2\,mm^3$, 20×10^6 histories per mm² and RSU of 0.3%) requires 302 min with GATE against 5.0 min with μ-RayStation. A typical 3D-conformal treatment (three 5 mm static beams) for the mouse case used in this work (calculation grid resolution of $0.2 \times 0.2 \times 0.2\,mm^3$, 8×10^6 histories per mm² and RSU of 0.7%) requires 690 min with GATE against 3.7 min with μ-RayStation. In the same way, a complete arc (5 mm beam) for the mouse (calculation grid resolution of $0.2 \times 0.2 \times 0.2\,mm^3$, 10^6 histories per mm² and RSU of 1.0%) requires 733 min with GATE against 1.0 min in μ-RayStation. The resulting speed-up factors are 60, 180 and 680, respectively. Obviously, computing power must be taken into account: GATE calculations were performed on a CPU 8 Core not parallelized (2.3 GHz Intel Core i7) and μ-RayStation on a CPU 8 Core parallelized (Intel Xeon E5-2667 V3). The short calculation time of μ-RayStation is well-suited to preclinical studies allowing higher throughput or testing of various treatment possibilities.

4. Discussion

The two outstanding features of preclinical irradiation studies are the millimeter beam and target sizes, requiring a submillimeter resolution, and the medium energy range used for irradiation. These characteristics require tracking photons of medium and low energies in very small structures. Moreover, due to the predominance of the photoelectric effect at this energy range, the impact of heterogeneities is very high and must be considered accurately.

The μ-RayStation model created for the XRAD225Cx is accurate and provides dose distribution in water very close to EBT3 measurements. The impact of focal spot shape, size and misalignment has successfully been taken into account, providing a good agreement between measured and calculated OAP (including for the two smallest and irregular beams). Previous low energy VMC++ validation (Terribilini *et al* 2010) has only been performed on a typical human patient scale (40 cm large simulation geometries with a millimetric resolution) but not on a typical preclinical scale (few cm large geometries with a sub-millimetric resolution). In this study, comparisons were made between μ-RayStation 8B and GATE calculations in heterogeneous phantom and in mouse for typical preclinical irradiations (static beams and arc). The typical clinical gamma criteria (3%/3 mm) were adapted to the preclinical constraints. RSU of both μ-RayStation and GATE calculations were very low (about 1%) allowing the use of a dosimetric criterion of 1%. The DTA was first scaled down to 0.3 mm to be in adequacy with small beam and target sizes. The resulting gamma passing rate inside the isodose 20% was very high (>98.9%). The DTA criterion was then reduced to 0.2 mm with a satisfying gamma passing rate (>92.9%). These results show
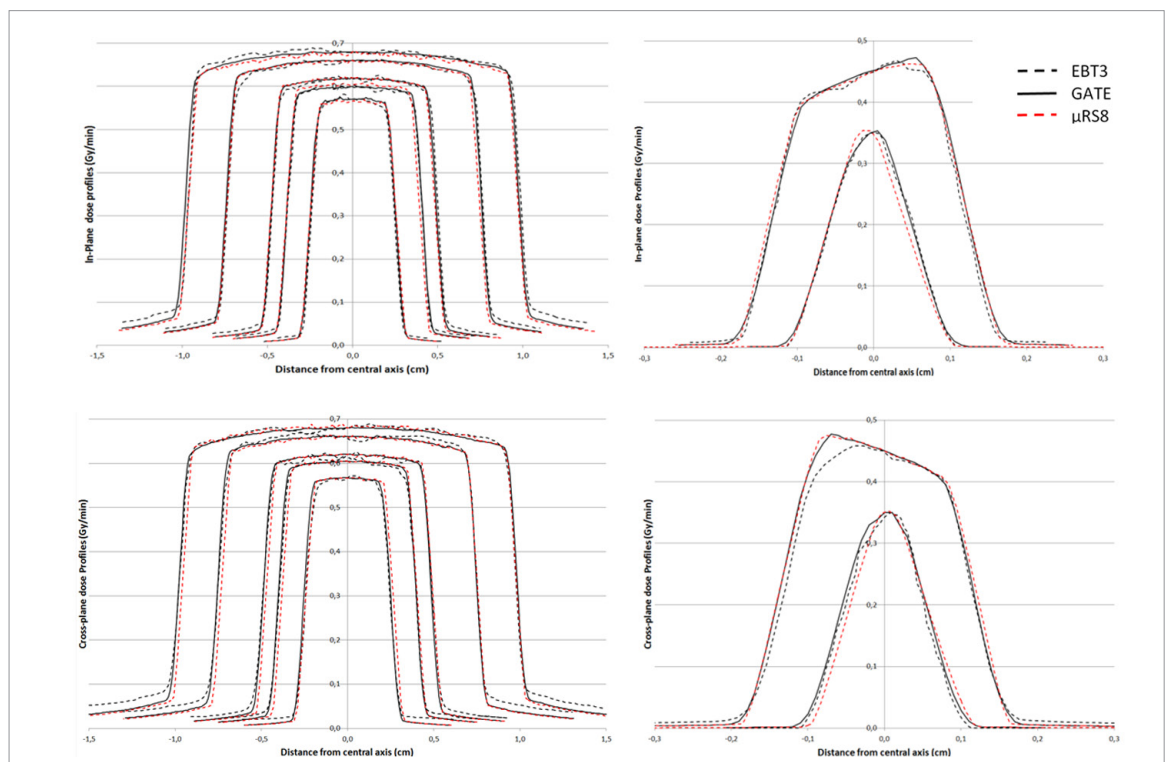
Figure 4. Measured (EBT3) and calculated (μ-RayStation 8B and GATE) In-plane (top) and Cross-plane (bottom) OAP for (left) the five collimators with a diameter greater than the focal spot size (5, 8, 10, 15 and 20 mm in diameters) and (right) the two collimators with a diameter smaller than the focal spot (2.5 and 1 mm in diameters). EBT3 uncertainty was 3.2%. RSU was below 0.5% for both MC simulations. Data were normalized at the central axis.

Table 2. Parameters of the XRAD225Cx irradiator model in μ-RayStation. Offsets are displayed as cathode–anode direction/lateral direction. The parameters marked with * are the ones that have been tuned from irradiator measures (or estimates) to give a good match to measurements in water.

Parameter	Irradiator model value
Exit collimator diameters	1.5, 1.15, 0.75, 0.61, 0.40, 0.19, 0.09 cm
(2.0, 1.5, 1.0, 0.8, 0.5, 0.25, 0.1 cm fields)	
Effective distance between source and entrance collimator	9.2 cm
Effective distance between source and exit collimator	23.6 cm
Effective distance between source and iso-center	30.4 cm
Source shape model*	Rectangular
Source size*	0.35×0.35 cm^2
Source offset*	0.015/0.035 cm
Entrance collimator offset*	0.03/0.0 cm
Exit collimator offset	0.0/0.0 cm
Entrance collimator diameter*	0.8 cm (0.1, 0.25 cm collimators)
	Not used (other collimators)

the capability of VMC++ to track medium and low energy photons in small animals. This work thus validates the combined analytical irradiator model and MC dose engine used in μ-RayStation 8B. This hybrid approach is efficient in term of calculation time. These characteristics combined with a graphical user interface make μ-RayStation 8B adapted to easily manage a large number of preclinical studies. GATE based on a complete MC approach, although more calculation time-consuming and less easy to use, presents the advantage to be free and fully configurable. Moreover, it provides a lot of information in addition to dose distribution, such as particle energy, position or interaction in all modeled areas, allowing extensive investigations.

In this study, the same materials were considered in GATE and μ-RayStation. However, for absorbed dose calculation in preclinical practice, tissue classification is a primordial parameter to reach reliable dose distributions due to the major dosimetric impact of heterogeneities. To validate the full accuracy of the dose calculation for real pre-clinical cases, the material assignment methods and their impact on the dose calculation needs to be thoroughly evaluated. Recently, a new tissue segmentation method was developed and applied to GATE calcul-
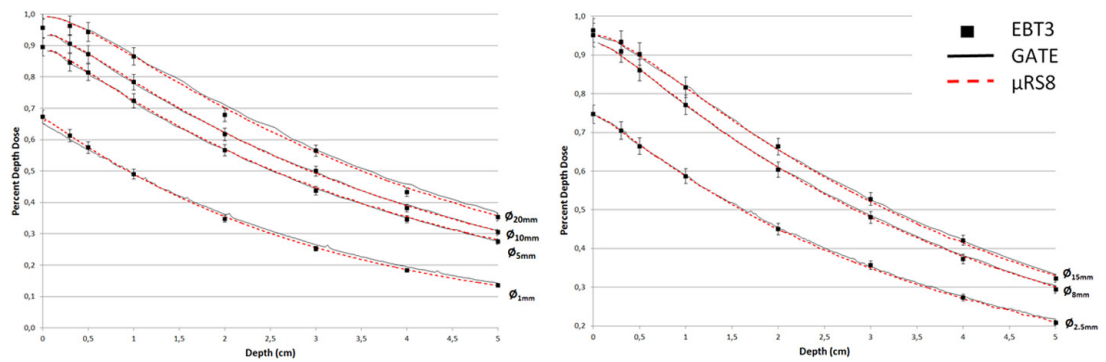
Figure 5. Measured (EBT3) and calculated (μ-RayStation 8B and GATE) PDD for collimators of diameters 1, 5, 10 and 20 mm (left), and 2.5, 8 and 15 mm (right). PDD are weighted by OF. EBT3 uncertainty was 3.2%. μ-RayStation RSU was below 0.4%. GATE mean statistical uncertainties were below 1%.
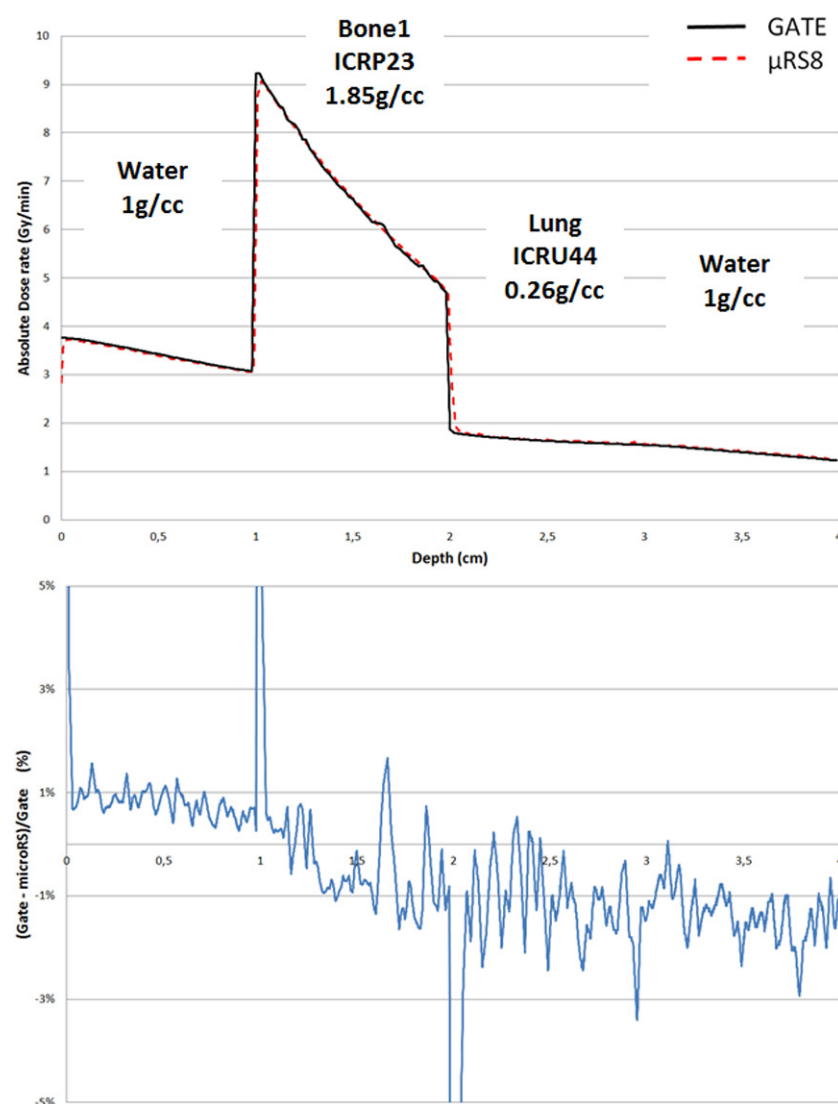

Figure 6. Absolute dose rate (Gy/min) in depth in calculated heterogeneous slabs with GATE and μ-Raystation 8B (top). Relative error (%) between GATE and μ-RayStation in depth (bottom). RSU was 0.87% in GATE and 0.20% in μ-RayStation.

ation to automatically assign materials (Noblet *et al* 2018). This method, called 'ρZeff' method, improves dose calculation accuracy by automatically assigning 125 'dose-equivalent' tissue. In μ-RayStation, tissue assignment can be performed manually by delineating regions, by CBCT thresholding or by using a HU to density table as in the clinical RayStation (with 55 interpolated human tissues). Moreover, the 'ρZeff' method could be added in
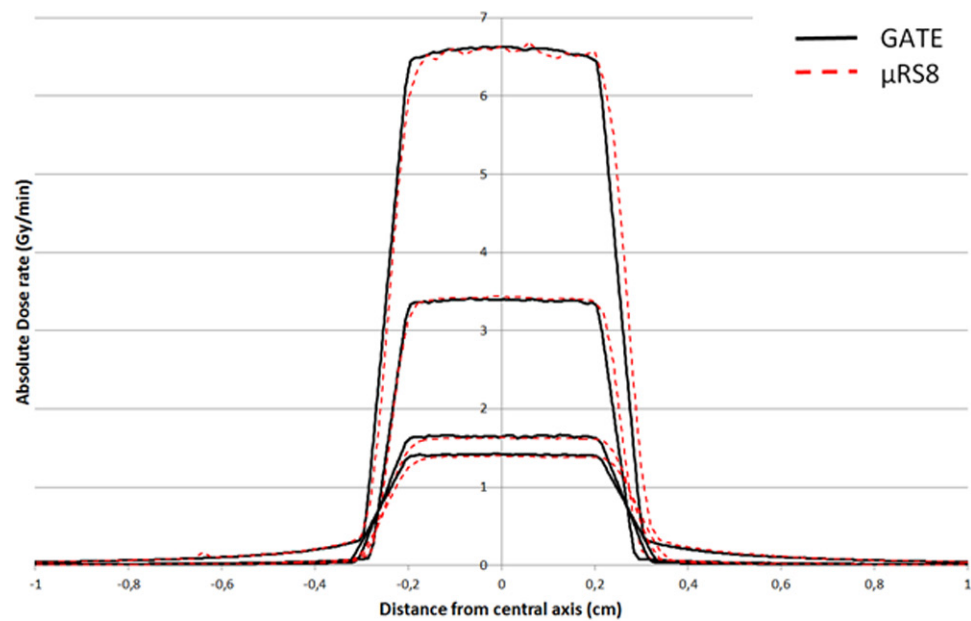
Figure 7. Dose rate profiles in anode/cathode direction calculated with GATE and μ-RayStation 8B in the heterogeneous phantom. Profiles are extracted at depth 0.5cm (water), 1.5cm (bone), 2.5cm (lung) and 3.5cm (water).

Table 3. 2D Gamma-local analysis between μ-RayStation and GATE calculation in mouse. The axial, coronal and sagittal planes intersect the beam isocenter.

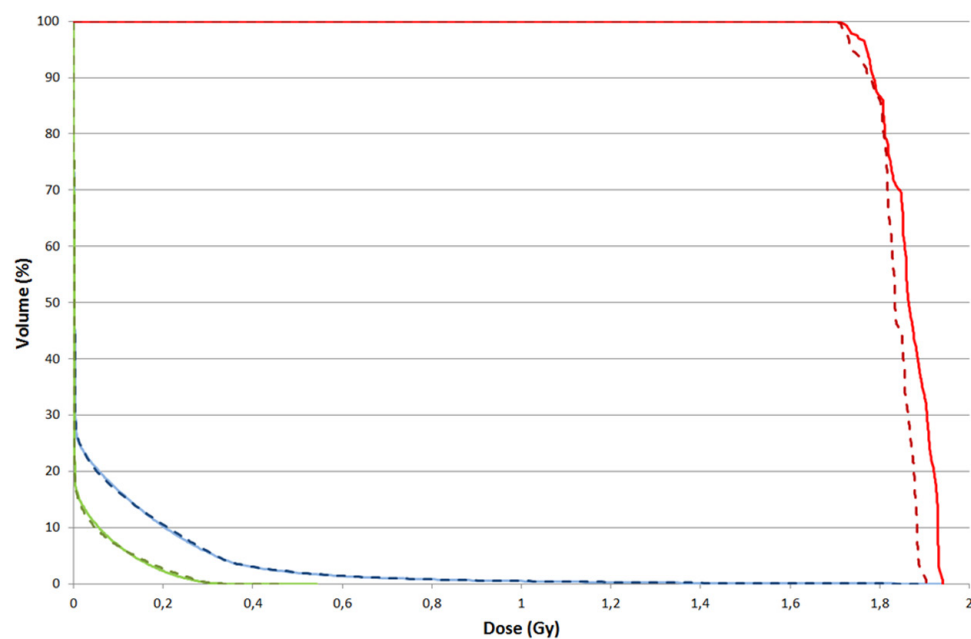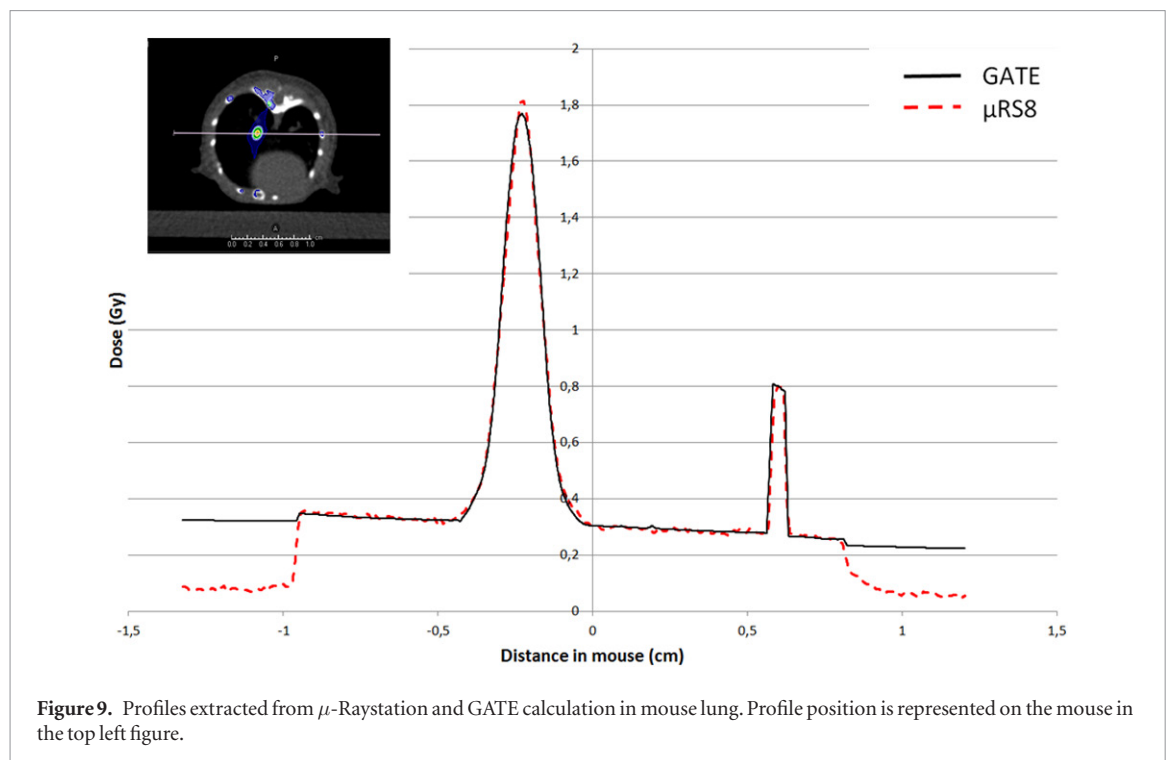| % pixels local-γ passed criteria	3 static beams—spine 5 mm collimator			Arc plan—spine 5 mm collimator			6 static beams—lung 1 mm collimator		
	Axial	Coronal	Sagittal	Axial	Coronal	Sagittal	Axial	Coronal	Sagittal
1%/0.3 mm	99.8	99.6	99.5	99.0	99.3	99.7	99.1	99.5	98.9
1%/0.2 mm	92.9	94.3	98.1	95.3	97.7	98.0	97.9	99.5	98.3

Figure 8. Dose-volume histogram of left lung (green), right lung (blue) and tumor (red) calculated in μ-Raystation from μ-Raystation calculation (solid lines) and GATE (dotted lines).

Figure 9. Profiles extracted from μ-Raystation and GATE calculation in mouse lung. Profile position is represented on the mouse in the top left figure.

μ-RayStation through a python script. Dosimetric impact of tissue assignment in μ-RayStation will be investigated by comparing with measurements in a future work.

5. Conclusion

Using an analytical model of the XRAD225Cx, in combination with MC simulation, μ-RayStation 8B provides accurate dose calculations in small animals in a few minutes. Similar small animal irradiation research platforms could be modelled in the same way using the analytical irradiator model described in this work, used in μ-RayStation. With accurate and fast dose calculation and various tools for management, contouring, planning and evaluation (borrowed from the clinical RayStation), μ-RayStation has the potential to be a very useful tool in pre-clinical irradiation research. Full MC simulations, such as GATE, although less adapted to manage a large number of preclinical studies, remain a powerful complementary tool.

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