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A generic TG-186 shielded applicator for commissioning model-based dose calculation algorithms for high-dose-rate ^{192}Ir brachytherapy.

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78
79 **Abstract**

80 **Purpose:** A joint working group was created by the American Association of
81 Physicists in Medicine (AAPM), the European Society for Radiotherapy and
82 Oncology (ESTRO), and the Australasian Brachytherapy Group (ABG) with the
83 charge, among others, to develop a set of well-defined test case plans and
84 perform model-based dose calculation algorithms (MBDCA) dose calculations
85 and comparisons. Its main goal is to facilitate a smooth transition from the
86 AAPM Task Group No. 43 (TG-43) dose calculation formalism, widely being used
87 in clinical practice for brachytherapy, to the one proposed by Task Group No.

186 (TG-186) for MBDCAs. To do so, in this work a hypothetical, generic high-dose rate (HDR) ^{192}Ir shielded applicator has been designed and benchmarked.

Methods: A generic HDR ^{192}Ir shielded applicator was designed based on three commercially available gynecological applicators as well as a virtual cubic water phantom that can be imported into any DICOM-RT compatible treatment planning system (TPS). The absorbed dose distribution around the applicator with the TG-186 ^{192}Ir source located at one dwell position at its center was computed using two commercial TPSs incorporating MBDCAs (Oncentra[®] Brachy with Advanced Collapsed-cone Engine, ACE[™], and BrachyVision ACUROS[™]) and state-of-the-art Monte Carlo (MC) codes, including ALGEBRA, BrachyDose, egs_brachy, Geant4, MCNP6, and Penelope2008. TPS-based volumetric dose distributions for the previously reported "source centered in water" and "source displaced" test cases, and the new "source centered in applicator" test case, were analyzed here using the MCNP6 dose distribution as a reference. Volumetric dose comparisons of TPS results against results for the other MC codes were also performed. Distributions of local and global dose difference ratios are reported.

Results: The local dose differences among MC codes are comparable to the statistical uncertainties of the reference datasets for the "source centered in water" and "source displaced" test cases and for the clinically-relevant part of the unshielded volume in the "source centered in applicator" case. Larger local differences appear in the shielded volume or at large distances. Considering clinically-relevant regions, global dose differences are smaller than the local ones. The most disadvantageous case for the MBDCAs is the one including the shielded applicator. In this case, ACUROS agrees with MC within $\pm 4.2\%$, $+4.2\%$ for the majority of voxels (95%) while presenting dose differences within $[-0.12\%, +0.12\%]$ of the dose at a clinically relevant reference point. For ACE, 95% of the total volume presents differences with respect to MC in the range $[-0.5\%, +0.4\%]$ of the dose at the reference point.

Conclusions: The combination of the generic source and generic shielded applicator, together with the previously developed test cases and reference datasets (available in the Brachytherapy Source Registry), lay a

solid foundation in supporting uniform commissioning procedures and direct comparisons among treatment planning systems for HDR ^{192}Ir brachytherapy.

Key words: ^{192}Ir , HDR brachytherapy, Monte Carlo methods, model based dose calculation, TG-186, shielded applicator

1. INTRODUCTION

Conventionally, American Association of Physicists in Medicine (AAPM) Task Group No. 43 formalism^{1,2} (TG-43) based dosimetry marked an improvement over previous dose calculation formalisms for brachytherapy treatment planning by using a source strength quantity traceable to international standards, a one-dimensional (1D) radial dose function, a two-dimensional (2D) source anisotropy. In the past decade, radiotherapy has progressed from the manual dose calculation paradigm to modern three-dimensional (3D) image-based treatment planning systems (TPSs) and dose delivery. The information available multiple modality imaging, however, have not been fully exploited since TG-43 based dose formalisms are based on source-specific data pre-calculated in a standard homogeneous water geometry. Therefore, it disregards patient-specific radiation scatter conditions and the radiological differences of tissue or applicator materials from water.

Unlike TG43, Model-based dose calculation algorithms (MBDCAs)³, representing a new paradigm of Brachytherapy dose calculation, utilize material composition and density information such as that inferred from x-ray computed tomography (CT) to account for (1) patient-specific scattering conditions, which are different from that in the reference geometry of source dosimetric characterization following the TG formalism, (2) patient heterogeneities, as opposed to a homogeneous phantom of water as in TG, and (3) the effect of applicators, which can act as important dose modifiers. For the dosimetric impacts due to taking heterogeneity effects into account, the reader is referred to the in-depth

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review papers by Rivard *et al*^{3,4} and Thomadsen *et al*⁵.

MBDCAs for high-dose-rate (HDR) ¹⁹²Ir brachytherapy (BT) dosimetry have been implemented in two commercial treatment planning systems (TPSs), serving as an alternative to the current dose calculation standard based on the TG-43. MBDCAs of current interest to ¹⁹²Ir BT include the gold standard Monte Carlo (MC) simulation method, the collapsed cone (CC) point kernel superposition algorithm and the grid-based Boltzmann solver (GBBS) of the differential linear Boltzmann transport equation. The latter two algorithms are of interest as they have been adopted by two different TPS vendors.

Early adopters of MBDCAs could experience a departure from the current global uniformity of treatment planning dosimetry practice due to the use of different MBDCA algorithms and implementations, as well as a scarcity of appropriate commissioning and QA procedures. Therefore, the TG-186 report³ recommends maintaining TG-43-based dosimetry and prescription, with MBDCA dose reporting performed in parallel, and proposed the creation of a Registry of quantitative data in electronic format for MBDCA testing by end users according to a well defined workflow. The TG-186 report also identified the necessity to establish an infrastructure consisting of tools and reference datasets available to the BT community for commissioning MBDCAs according to recommended QA guidelines. Based on these considerations, a joint working group was created by the AAPM, the European Society for Radiotherapy and Oncology (ESTRO), and the Australasian Brachytherapy Group (ABG) with charges including:

- to develop a set of well-defined test case plans and perform MBDCA dose calculations and comparisons;
- to identify the best venue for housing reference plans/data, and put in place a collaboration with identified partners of the Registry.

Here, the Registry is the Brachytherapy Source Registry, as managed jointly by the AAPM and the Imaging and Radiation Oncology Core Houston Quality Assurance Center (IROC Houston).

In line with the working group charges, the generic vendor-independent source and the generic shielded applicator presented in this work are indispensable components to create a common DICOM-based test case library for the purpose of verifying the implementation of the MBDCA in a TPS. Together they also allow TPS users to perform an algorithm and/or cross-TPS comparisons when commissioning said TPS. The generic source and its implementation in both Oncentra[®] Brachy v.4.5 and BrachyVision v.13 MBDCAs have been reported in detail in Ballester *et al.*⁶

This study reports the creation of a generic TG-186 HDR ¹⁹²Ir BT shielded applicator, which has been included in the applicator libraries (as “TG-186 applicator”) of the two aforementioned TPSs, and describes the benchmarking of the associated test case designed for the applicator. The benchmarking dataset was created by independent investigators using six different MC codes. The MC codes agreed with each other within 1%. Each TPS MBDCA was benchmarked by comparing its resultant dose distribution with the MC results. Discrepancies were observed in low dose regions and are explained by in-depth analyses in the discussion. The current study represents an independent investigation by the members of the working group, and is not a societal recommendation of the joint AAPM/ESTRO/ABG working group on model-based dose calculation algorithms in BT.

2. METHODS AND MATERIALS

2.A. Generic applicator design

The generic applicator design is based on three commercially available shielded gynecological applicators (see Table I). All three applicators consist of a polymethyl methacrylate (PMMA) body wherein partial (90°, 180°, or 270°) shielding segments of Densimet[®] tungsten alloy can be incorporated and fixed. The diameters and lengths of these commercial applicators are in the range 20–40 mm and 130–140 mm, respectively.

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TABLE I. Dimensions (mm) of shielded applicators available commercially. Applicators are ordered alphabetically with respect to the manufacturer.

Applicator	Manufacturer	Length (mm)	Diameter (mm)
Vaginal/Rectal applicator set variable shielding. SET0025.	Eckert & Ziegler, BEBIG GmbH, Germany	130	22–35
Cylindrical shielded applicator set. #084.320	Elekta AB, Stockholm, Sweden	140	25–40
Shielded applicator set. GM11004380	Varian, Palo Alto, CA.USA.	140	20–35
Generic applicator		140	36

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The generic cylindrical HDR BT applicator design is presented in Fig. 1. It has a total length of 140 mm (a 122 mm body and a 18 mm solid cap). A 180° Densimet[®] tungsten alloy shield has been added with a length of 122 mm and an inner (outer) diameter of 3.2 mm (24 mm). The outer body is made of PMMA with an outer diameter of 36 mm. The cap is made of PMMA with a radius of 18 mm. A stainless steel tube (for catheter insertion) filled with air and with inner (outer) diameter of 1.0 mm (3.2 mm) is inserted along the axis. Note that the stainless steel tube is not closed on the side connecting to the dome. The elemental compositions and densities of the applicator materials are given in Table II.

Fig. 1. The generic cylindrical HDR brachytherapy applicator with 180° shielding (lateral and axial view).
Figure not drawn to scale.

TABLE II. Materials and atomic compositions of the generic applicator.

Component	Material	Elemental composition (chemical formula or % by mass)	Mass Density (g/cm ³)
Cylinder body and Cap	PMMA	C ₅ O ₂ H ₈	1.19
Cylinder stem	Stainless steel 316L	P (0.045%), C (0.08%), Si (1%), Mn (2%), Ni (9.5%), Cr (19%), Fe (68.375%)	8.00
Shield	Densimet (D176) tungsten alloy	Fe (2.5%), Ni (5%), W (92.5%)	17.6
Insertion tube and shield counterpart	Standard 40% humidity air	C (0.0123%), H (0.0732%), Ar (1.2743%), O (23.6077%), N (75.0325%)	1.19×10 ⁻³

2.B. Model-based brachytherapy dose calculation algorithms

2.B.1. Grid-based Boltzmann equation solver (GBBS)

For this study, BrachyVision ACUROS version 13.0 has been used. This version includes a virtual source model as described in Ballester *et al.*⁶ and a virtual applicator configured by the vendors based on geometry and material information given above. In ACUROS GBBS, a Linear Boltzmann Transport Equation (LBTE) is deterministically solved using fine-discretized grid of spatial (via finite element meshes), angular (via discrete ordinates), and energy variables (via the multigroup method), and then the average photon energy-fluence distribution is obtained, which is then converted to a dose distribution. Further details on ACUROS GBBS dose calculation can be found in the literature,⁷⁻¹² and the algorithm reference guide accompanying the system (ACUROS BV Algorithm Reference Guide¹³).

2.B.2. Collapsed-cone superposition/convolution method

The Oncentra[®] Brachy TPS version 4.5 was used. It includes a collapsed-cone (CC) point kernel superposition method suitable for BT under the commercial name ACE. In ACE, dose is computed as a sum of primary, first scatter (dose due to electrons being secondaries to photons that scatter for first time outside the source) and residual scatter (dose due to electrons being secondaries to photons that scatter for the second or higher order) components. The primary component is calculated based on the ray-tracing method. The scatter components are calculated by further transporting energy released to surrounding space by sampling the appropriate dose kernel along directional lines (transport directions). For a detailed description of the CC approximation and how it has been adapted for BT, see Carlsson and Ahnesjö¹⁴⁻¹⁸, Ma¹⁹ and Ahnesjö *et al.*²⁰

2.B.3. Monte Carlo codes

The MC codes ALGEBRA (version 1.0)²¹, BrachyDose^{22,23}, egs_brachy (version 2016.02.01)²⁴, Geant4 (version 9.3)²⁵⁻²⁸, MCNP6 (version 1.0)²⁹, and Penelope2008³⁰ were used in this work. All codes used here simulate only the photon transport histories that yield the energy fluence distribution in space. Then, the collisional kerma is derived for each voxel using the Linear Track Length Estimator (LTLE)³¹, calculating the energy fluence and folding it into the material and energy dependent energy absorption cross-section. Details of the different implementations and use of geometric modeling, physics models, photon spectrum, interaction cross sections, and tracking methods for photon transport have been extensively discussed for each MC code elsewhere.³²⁻³⁴

2.C. Calculation methodology for DICOM water cube phantom tests

The new test case considered in the current study involves a water cube phantom surrounded by air with the applicator (Sec. 2.A) and source (Ballester *et al.*⁶) located at its center. The same voxelized model of a homogeneous water cube (20.1 cm side) surrounded by an air cube (51.1 cm side) created by Ballester *et al.*⁶

was used here for the sake of consistency. Both cubes have a common center and their sides are both parallel to the axes of the Cartesian coordinate system. The dimensions, in-plane resolution, and number of images were chosen so that $(511)^3$ cubic voxels, of size $(1 \text{ mm})^3$ each, fill the space.

The DICOM dataset for the virtual phantom was imported into the MC codes and TPSs. The applicator was positioned with the center of the PMMA cylinder at the origin of coordinates at $(x, y, z) = (0, 0, 0)$. The source was located along the axis of the stainless steel probe, with the center of the active part at the origin of coordinates. The applicator dome and source tip both point towards the positive z direction. This scenario will be denoted in the following as “source centered in applicator”. The rationale to study this particular case is twofold. On the one hand it allows the user to test the influence of the presence of a high-Z shield on the dose distribution. On the other hand, it provides a guide to the user when registering two different objects (applicator and source) at a single point in space in situations where, due to the large dose gradient, positioning accuracy becomes a critical issue.

The two previously created single-source test cases reported in Ballester *et al.*⁶ are re-examined here to evaluate their dose distributions in 3D, and are briefly described here:

- 1) "source centered in water" case uses a 20.1 cm water cube positioned in the center of a 50.1 cm air cube with a single generic ^{192}Ir source positioned in the center of the water cube.
- 2) "source displaced" case uses the same phantom but with the generic source displaced 7 cm along the +x axis.

2.C.1. BrachyVision ACUROS

In BrachyVision, after the test case DICOM dataset had been imported, the "TG-186 Generic Shielded Applicator" was selected in the Solid Applicator library and added to the plan. In the TPS graphical user interface, the applicator was translated and rotated such that its Point Set Editor window reported $(0, 0, 6.05 \text{ cm})$ and $(0, 0, -6.15 \text{ cm})$ and the unshielded half pointed towards the direction. In the Applicator Property window, the source step size was set to 0.5 cm, first source position to 5.7 cm and last source position to 5.875 cm. In the Dwell Control window, the active source dwell position was set to 124.3 cm, which corresponds

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to the center of the cube. The dwell time was set to 50 s, which was chosen to achieve a fixed Total Reference Air Kerma or TRAK for the (10 Ci apparent activity) TG-186 generic source of 36,260 cGy cm²/h. This was stated clearly in the user guide in the Brachy Source Registry.

As with the first two test cases described in Ballester *et al.*⁶, after ACUROS computation, the dose was calculated on a grid of dimension 201×201×201 (1 mm)³ centered at the origin and was then exported.

2.C.2. Oncentra[®] Brachy (OcB) with ACE

The TG-186 applicator (TG-186) was used. It was uniquely positioned by defining coordinates for 3 of 4 anchor points: AP1 (0, 61 mm, 0), AP2 (0, 56 mm, 0) and AP4 (12 mm, 61 mm, 0). The source was placed at the center of the applicator, i.e., the water cube origin, which corresponds to dwell position #244 in the applicator probe for the Flexitron afterloader.

For ACE, OcB provides two predefined calculation modes— Standard and High Resolution. They differ in the voxelization scheme and in the number and setting of the transport directions and hence differences in dose distributions may be expected.

As for the first two cases described in Ballester *et al.*⁶, the dose was calculated using the High Resolution mode (displayed as D_{m,m} TG-186 [H] in OcB). In this mode, 1620 and 320 transport directions were used for the first scatter component and residual scatter component, respectively. Three bounding boxes (10 cm, 20 cm, and 100 cm) were used in this mode, for which the voxel sizes are 1 mm, 2 mm, and 5 mm, respectively. The dwell time was set to 50 s. The same dose grid as for ACUROS was used when exporting the dose.

2.C.3. Monte Carlo calculations

Different MC dose distribution datasets for the “source centered”, “source displaced”, and “source centered in applicator” cases were produced independently by different investigators. For the first two cases, « source centered in water » and « source source displaced », the number of primary photons as taken from the phasespace files for each simulation were 4×10¹⁰ (ALGEBRA), 10¹⁰ (BrachyDose), 4×10¹⁰ (Geant4), 2×10¹⁰ (MCNP5), 10¹¹ (MCNP6), and 2×10¹⁰ (Penelope2008). For the “source centered in applicator” case these

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were: 2×10^{10} (ALGEBRA), 10^{10} (BrachyDose), $9.5 \times 10^9 - 10^{11}$ (egs_brachy), 10^{11} (Geant4), 10^{11} (MCNP6), and 10^{11} (Penelope2008). Collisional kerma was scored in the full water volume using $(201)^3$ 1 mm^3 voxels. In all cases, the large number of photon histories considered yielded statistical uncertainties $< 1\%$. In each case, the number of histories considered was well within the period of the respective random number generator.

A thorough analysis of the total ($k = 1$) uncertainty combining Type A and B components¹ was performed by Ballester *et al.*⁶ The total uncertainty was 0.22% at 1 cm and 0.42% at 5 cm, mainly differing due to volume averaging. Based on this analysis, a total uncertainty of 0.5% ($k = 1$) was estimated for the MC simulations in the current study, being underestimated for those regions under heavy shielding and/or large distances at the volume periphery.

Each MC code constructs the applicator in a different specific way. For the Geant4-based ALGEBRA, the applicator was implemented by parallel world geometry³⁵. With BrachyDose, the applicator was modeled using the multi-geometry approach³⁶ as a superposition of a cylinder, sphere, and rectangular prism; these were embedded in the scoring phantom. In Geant4 the applicator was constructed using Boolean operations on predefined solids. The egs_brachy code modeled the applicator using the egsp C++ class library geometry modules³⁷, with material data sets generated using the PEGS4 data preprocessing code. In the case of Penelope2008 and MCNP6, the applicator was constructed using quadric surfaces and the materials properties were consistently derived using the included material libraries. The geometries generated by all codes are completely equivalent.

2.D. 3D Dose Comparison

Both local and global dose difference ratios were investigated. The local dose difference ratio $\Delta D_{LOCAL} = \frac{D(r) - D_{ref}(r)}{D_{ref}(r)}$ is defined as the difference between TPS/MC dose ($D(r)$) and reference dose ($D_{ref}(r)$) at any point, normalized to the reference dose at the same point. Its purpose is to serve as an indicator of local dose discrepancies. The global dose difference ratio corresponds to the difference between TPS/MC dose and the reference dose at a given point normalized to the dose value at a clinically relevant reference point, $\Delta D_{GLOBAL} = \frac{D(r) - D_{ref}(r)}{D_{ref}(r_{ref})}$ hence emphasizing the relative clinical relevance (if any). The

¹ According to the International Bureau of Weights and Measures (BIMP) if an uncertainty is based on a statistical analysis done by the authors, it is to be treated as a Type A uncertainty, if not it is to be considered a Type B uncertainty.

reference point is located 1 cm away from the source center along the $-x$ direction, $r_{\text{ref}} = (-1 \text{ cm}, 0, 0)$, for the “source centered in water” case, and is located at $r_{\text{ref}} = (6 \text{ cm}, 0, 0)$ for “source displaced”. For the “source centered in applicator” case, the reference point is located 0.5 cm outside of the applicator, at $r_{\text{ref}} = (-2.3 \text{ cm}, 0, 0)$. Based on the above, four different figures of merit have been designed to compare volumetric dose distributions. The first two correspond to 1D histograms of ΔD_{LOCAL} and ΔD_{GLOBAL} to illustrate the 3D behaviour of the dose in the whole volume. The other two are designed to explore the topology of the differences. To do so, 2D histograms correlating ΔD_{LOCAL} and ΔD_{GLOBAL} against the point-to-source distance are presented.

A statistical analysis has also been performed on the ΔD_{LOCAL} and ΔD_{GLOBAL} values. The following metrics were used: *i)* the range of ΔD_{LOCAL} and ΔD_{GLOBAL} values within which 95% of the total number of voxels are located. The value of 95% was chosen following TG-138 recommendations³⁸; *ii)* for the “source centered in water” and “source displaced” cases MC results for ΔD_{LOCAL} present a Gaussian-like distribution, hence they have been fitted to a Gaussian and their mean and root mean square (RMS) values examined to extract any systematic deviations in the data. For the “source centered in applicator” case a two-Gaussian fit was considered more appropriate in order to separate the different contributions of those voxels located in the shielded and unshielded regions.

In all cases, voxels overlapping fully or partially with the source and/or the applicator have been omitted from the analysis.

3. RESULTS.

3.A. Reference dataset

3.A.1. Determination of reference dataset

In order to establish a consistent reference dataset determination strategy, the previous WG test cases were re-examined using the methodology of this work. For the sake of brevity, only select examples of the comparisons performed between the different MC codes are included in the current study. Additional ones can

be found as Supplementary Material ³⁹. The analyses presented are: Fig. 2 (GEANT4 vs. MCNP6) for the “source centered in water” case and Fig. 3 (Penelope vs. MCNP6) for the “source displaced” case.

In Ballester *et al.* ⁶ a different implementation of ΔD_{LOCAL} was used to analyze 2D dose planes for the “source centered in water” and “source displaced” cases. Instead of analyzing the full 2D planes, $10 \times 10 \text{ cm}^2$ and $5 \times 5 \text{ cm}^2$ subsets centered around the source were chosen to focus on clinically relevant regions. Hence, since in the present work a dual $\Delta D_{LOCAL} - \Delta D_{GLOBAL}$ analysis has been performed using the full $20.1 \times 20.1 \times 20.1 \text{ cm}^3$ volume without selecting a particular subvolume, any comparison between the conclusions from both approaches should be done with care.

GEANT4

Fig. 2. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for GEANT4 with respect to MCNP6 for the “source centered in water” case. The reference point is located 1 cm away from the source center along the $-x$ direction: $r_{ref} = (-1 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxels (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the source are

Fig. 3. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for PENELOPE with respect to MCNP6 for the “source displaced” case. The reference point is located 1 cm away from the source center along the $-x$ direction; $r_{ref} = (6 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D

histogram of distance to the source center, $r(cm)$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxels (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the source are removed.

The comparisons above show that all MC results are consistent within calculation uncertainties. For the sake of consistency with the approach in Ballester *et al.*⁶, MCNP6 results were identified as the reference dataset against which other MC results and TPS results were compared, $D_{ref}(r) = D_{MCNP6}(r)$. This choice should not be understood as an endorsement of a particular MC code.

The reference datasets are now available in the Brachytherapy Source Registry⁴⁰.

3.A.2. MC results

To illustrate the results obtained we depict as an example in Fig. 4 the dose distribution comparison for BrachyDose vs. MCNP6 for the “source centered in applicator” case. Figures corresponding to the other MC codes and cases can be found in the Supplementary Material. In these figures, top-left panels contain the 1D ΔD_{LOCAL} histogram (between -5% and +5%), and top-right panels the 1D ΔD_{GLOBAL} histogram (between -0.4% and +0.4%). Bottom panels contain the 2D histograms that correspond to the upper panels with respect to the distance to the center of the active part of the source, from 0 to 18 cm for the “source centered in water” and “source centered in applicator” cases and from 0 to 22 cm for the “source displaced” case. In Fig. 5 (top panel) a color-coded scatter plot is shown where the differences between the shielded (red) and the unshielded (black) regions can be observed. A summary of statistical metrics of MC results can be found in Table III.

BrachyDose

Fig. 4. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for BrachyDose with respect to MCNP6 for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the $-x$ direction; $r_{ref} = (-2.3 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for

ΔD_{GLOBAL} . *Voxels (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the applicator are removed.

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Fig. 5. 2D histogram of distance to the source center, $r(cm)$, vs. local (ΔD_{LOCAL}) dose difference ratios (left)

and global (ΔD_{GLOBAL}) dose difference ratios (right) for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the x direction; $r_{ref} = (-2.3 \text{ cm}, 0, 0)$. The comparisons for BrachyDose (top), ACUROS (middle), and ACE (bottom) with respect to MCNP6 are shown. The red dots correspond to voxels located in the shielded region while the black dots correspond to those located in the unshielded region.

3.B. Benchmarking BrachyVision ACUROS and Oncentra[®] Brachy ACE

The results for ACUROS and ACE for the “source centered in applicator” case are found in Fig. 6 and in Fig. 7. Results for other cases can be found in the Supplementary Material³⁹. The information displayed in the panels is the same as described in Section 3.A.2, the only difference being in the ranges displayed. ΔD_{LOCAL} is displayed in the interval $[-70\%, 70\%]$ and ΔD_{GLOBAL} in the interval $[-3\%, 3\%]$. Fig. 5 contains the color-coded scatter plot discussed above for ACE vs. MCNP6 (middle panel) and ACUROS vs. MCNP6 (bottom panel). A summary of statistical metrics of ACUROS and ACE results can be found in Table III.

ACUROS

Fig. 6. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for ACUROS with respect to MCNP6 for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the $-x$ direction; $r_{ref} = (-2.3 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for

ΔD_{GLOBAL} . Voxels (%) stands for the percentage of the total number of voxels (201^3) once those located inside the applicator are removed.

FIG. 7. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for ACE with respect to MCNP6 for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the $-x$ direction: $r_{ref} = (-2.3$ cm,

0, 0). Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(cm)$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxels (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the applicator are removed.

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TABLE III. Compendium of statistical results for the local $\Delta D_{LOCAL} = \frac{D(r) - D_{ref}(r)}{D_{ref}(r)}$ and global $\Delta D_{GLOBAL} = \frac{D(r) - D_{ref}(r)}{D_{ref}(r_{ref})}$ dose difference ratios, where the reference is the MCNP6 results. In the first and second data columns the ranges (%) of ΔD_{LOCAL} and ΔD_{GLOBAL} values within which 95% of the total number of voxels is located are given. In the third and fourth columns we summarize the parameters (mean and RMS) of Gaussian (“source centered in water” and “source displaced”) and two-Gaussian (“source centered in applicator”) fits. In the case of two-Gaussian fits, individual Gaussians describe shielded and unshielded regions. In those cases where the distribution does not conform to a single or double Gaussian fit, no value (---) has been given.

		ΔD_{LOCAL} range (%)	ΔD_{GLOBAL} range (%)	Mean (%)	RMS (%)
Source centered in water	Penelope	[−0.6,+0.6]	[−0.009,+0.009]	+0.10	0.30
	Geant4 ¹	[−0.5,+0.5]	[−0.006,+0.006]	−0.11	0.23
	ALGEBRA	[−0.4,+0.4]	[−0.006,+0.006]	−0.07	0.21
	egs_brachy	[−0.8,+0.8]	[−0.008,+0.008]	+0.00	0.41
	BrachyDose	[−0.8,+0.8]	[−0.009,+0.009]	−0.06	0.41
	ACE	[−2,+10.5]	[−0.04,+0.06]	---	---
	ACUROS	[−0.5,+2]	[−0.013,+0.0013]	+1.00	0.83

		.5]	13]				
Source displaced in water	Penelope ²	[−0.9,+0 .9]	[−0.009,+0.0 09]	+0.12		0.47	
	Geant4	[−0.6,+0 .6]	[−0.005,+0.0 05]	−0.04		0.31	
	ALGEBRA	[−0.8,+0 .8]	[−0.007,+0.0 07]	−0.06		0.41	
	egs_brachy	[−1.1,+1 .1]	[−0.008,+0.0 08]	+0.00		0.54	
	BrachyDose	[−1.1,+1 .1]	[−0.008,+0.0 08]	−0.02		0.54	
	ACE	[−2,+12]	[−0.04,+0.07]	---		---	
	ACUROS	[−1.0,+3]	[−0.013,+0.0 13]	+1.26		1.16	
		ΔD_{LOCAL} range (%)	ΔD_{GLOBAL} range (%)	Mean (%) (shielded)	RMS (%) (shielded)	Mean (%) (unshielded)	RMS (%) (unshielded)
Source centered in applicator	Penelope	[−1.2,+0 .5]	[−0.04,+0.04]	−0.67	0.37	+0.31	0.14
	Geant4	[−2,+1.5]	[−0.04,+0.04]	−0.33	1.01	+0.16	0.37
	ALGEBRA	[−0.8,+3 .8]	[−0.03,+0.03]	0.31	0.80	−0.07	0.32
	egs_brachy	[−2.1,+1 .5]	[−0.03,+0.04]	−0.51	1.02	+0.11	0.36
	BrachyDose ³	[−2.3,+1 .6]	[−0.04,+0.04]	−0.80	1.05	+0.06	0.35
	ACE	[−8,+15] *	[−1.7,+0.4]	---	---	---	---
	ACUROS	[−4.2,+4 .2]	[−0.12,+0.12]	---	---	---	---

* This range only considers voxels located in the unshielded part of the volume.

¹ See Figure 2.

² See Figure 3.

³ See Figure 4.

4. DISCUSSION

4.A. Reference dataset

For the “source centered in water” and “source displaced” cases it can be observed in ΔD_{LOCAL} (top left panels in Figs. 2 and 3) that some MC codes present systematic deviations smaller than the estimated MC uncertainties. It is important to emphasize though that, as discussed in Section 2.C.3, Type A and B uncertainties are underestimated far from the source or in the shielded regions. This is so for the former because the uncertainty analysis performed by Ballester *et al.*⁶ was limited to a region less than 5 cm from the source center, and for the latter because such analysis did not take into account the low statistics in the water phantom behind the shielding structure in the applicator. In such circumstances, some differences in a reduced subset of voxels far from the source and/or in the shielded volume are to be expected.

These systematic differences are in the range 0.10% (Penelope2008) to -0.11% (Geant4) for the “source centered in water” case and 0.12% (Penelope2008) to -0.06% (Geant4) for the “source displaced” case. The *egs_brachy* code does not present any systematic deviation with respect to MCNP6. For the “source centered in water” case the ranges containing 95% of the voxels for all MC codes vary between [-0.8%, +0.8%] and [-0.4%, +0.4%], therefore being in all cases less than the estimated MC uncertainties. In the “source displaced” case the ranges are slightly wider, the largest being [-1.1%, +1.1%] for BrachyDose and the smallest [-0.6%, +0.6%] for Geant4. Voxels outside these ranges are located more than 8 cm (“source centered in water”) and 6 cm (“source displaced”) away from the source center, the maximum deviations for both cases being located at those voxels bounding the water and air cubes, i.e. mostly at distances around 10 cm. It should be noted that for the “source

displaced” case, because the distance from the source center to the farthest water-filled voxel is 22 cm instead of 17 cm, discrepancies can be found at larger distances than for the “source centered in water” case.

For the “source centered in applicator” case the MC codes analyzed present a systematic ΔD_{LOCAL} deviation of the order 0.5–1% with respect to MCNP6 for those voxels located in the shielded part of the phantom (see Fig. 4). Performing a two-Gaussian fit allows us to obtain the deviations for the voxels in the shielded region: egs_brachy (–0.66% with RMS 0.98%), ALGEBRA (+0.31% with RMS 0.80%), Penelope (–0.67% with RMS 0.37%), Geant4 (–0.33% with RMS 1.01%), and BrachyDose (–0.8% with RMS 1.05%). The source of these systematic deviations can be traced back to different effects: on the one hand, a larger Type A uncertainty due to the reduced statistics in the shielded area; on the other hand, the photon spectrum reaching the shielded region differs greatly from the one radiating into the unshielded parts of the phantom. Type B uncertainties due to differences in the photon spectra, cross section data, scoring scheme, applicator modeling, phasespace simulation implemented in each MC code. And the corresponding impacts have not been considered since they are beyond the scope of the present manuscript. Voxels located in the unshielded region exhibit systematic ΔD_{LOCAL} deviations and RMS values compatible with those observed in the “source centered in water” and “source displaced” cases. With respect to the ΔD_{LOCAL} range where 95% of the voxels fall, within the full water volume it varies from [–2.3%, +1.6%] to [–1.2%, +0.5%] depending on the MC code considered. If the shielded region is removed from the analysis, this range becomes smaller, with an average value of [–1%, +1%]. In both scenarios, voxels outside this range are located mostly more than 6–8 cm away from the source.

With respect to ΔD_{GLOBAL} for the “source centered in water” and “source displaced” cases (Figs. 2 and 3, right panels), it can be observed that 95% of all

voxels have very small differences in the range $[-0.01\%, +0.01\%]$ or smaller. The remaining voxels present maximum deviations of $[-0.4\%, +0.4\%]$ and are located close to the source, less than 1.5 cm away. For the “source centered in applicator” case (Fig. 4, right panels) the situation is similar, with ΔD_{GLOBAL} presenting values in the range $[-0.04\%, +0.04\%]$. The ΔD_{GLOBAL} values outside this interval are not distributed homogeneously in the shielded and unshielded volumes. In the shielded region the larger ΔD_{GLOBAL} values are displaced to negative values, $[-0.4\%, -0.07\%]$, and they are located within 4 cm of the source. This volume, close to the applicator lateral side, is where clinical organs at risk (OAR) might be expected to be located. In the unshielded region the larger ΔD_{GLOBAL} values are more evenly distributed, although along positive values of ΔD_{GLOBAL} , $[+0.07\%, +0.4\%]$. These are located up to 8 cm from the source center and therefore fall within a region that typically encompasses the planning target volume (PTV) for this type of applicator.

In some particular brachytherapy treatments it is required to report dose to tissue directly adjacent to the applicator. That will be for instance where the vaginal mucosa might be compromised. Among the different MC codes, differences in ΔD_{GLOBAL} in the first voxel outside the applicator and perpendicular to the source are in the range $[-0.2\%, +0.06\%]$ in the shielded region and $[+0.5\%, 0.04\%]$ in the unshielded one.

Therefore, it can be concluded that these differences, although concentrated in the area of the OARs and PTV, affect a very small number of voxels and are within estimated uncertainties. Hence, they are not expected to be clinically relevant for any of the cases analyzed.

4.B. Benchmarking BrachyVision ACUROS and Oncentra Brachy ACE

For the comparisons between ACUROS and MCNP6, ΔD_{LOCAL} evaluated for the “source centered in water” (“source displaced”) case shows deviations within $[-0.5\%, +2.5\%]$ ($[-1\%, +3\%]$) in 95% of the volume. The voxels with larger deviations (outside the above ranges) are located in both cases more than 10 cm away from the source. A systematic displacement of 1% (1.25% for the “source displaced” case) can be observed. With respect to ΔD_{GLOBAL} , 95% of the voxels exhibit differences in the range $[-0.013\%, +0.013\%]$ for both cases, which is comparable with that obtained using MC. Voxels presenting

greater global differences outside that range are mostly located closer than 1 cm to the source center.

The results for the comparisons between ACUROS and MCNP6 for the “source centered in applicator” are shown in Fig. 6. In this case, 95% of the voxels have ΔD_{LOCAL} values in the range $\pm 4.2\%$. Those outside this range are located evenly in the whole volume. A very small percentage of voxels located in the shielded region, 0.25%, can reach ΔD_{LOCAL} values up to $\pm 60\%$.

When ΔD_{GLOBAL} is considered, it can be observed that 95% of the voxels present differences with respect to the reference dose in the range $[-0.12\%, +0.12\%]$. The only relevant difference with respect to the location of these voxels comes from those outside that range. Those located in the shielded volume, 0.4%, are displaced to positive values, and hence located in the range $[+0.3\%, +3\%]$ while those in the unshielded volume, 1.6% of the total volume, are in the range $[-3\%, +0.3\%]$. In both regions these voxels are mostly restricted to locations closer than 6 cm to the source and therefore affect in a small way both OAR (0.4%) and PTV (1.6%) volumes.

AcurosBV algorithm parameters such as energy groups (related interaction cross-sections) are fixed to 37 and angular discretization used an adaptive scheme using between 24 and 960 directions, with the higher energy associated with large number of directions. Using a low number of angular directions can lead to significant discretization artefacts or ray effects^{9,41}. User has not control to select the parameters, hence it is hard to make firm conclusions about the specific factors contributing to these systematic deviations found in this work. Papagiannis and colleagues⁴¹ further demonstrated some differences between AcurosBV and MC in the penumbra region around high-Z materials as well as some differences in scatter-dominated regions (e.g. behind bones). However, overall AcurosBV had excellent agreement with MC.

For ACE vs. MCNP6, ΔD_{LOCAL} for the “source centered in water” (“source displaced”) case shows deviations within the range $\pm 2\%$, $\pm 10.5\%$ ($[-2\%, +12\%]$) for 95% of the volume. Those differences are located further than 10 cm away from the source for the “source centered in water” case and further than 8 cm for the “source displaced” case. With respect to ΔD_{GLOBAL} , 95% of all voxels have values in the range $[-0.04\%, +0.06\%]$ for the “source centered in water” ($[-0.04\%, +0.07\%]$ for the “source displaced”) case. Voxels presenting global differences outside this range are located closer than 1.5 cm to the source center.

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The analysis of the “source centered in applicator” (Fig. 7) case shows a distinct asymmetric pattern between the shielded and unshielded volumes. The voxels located in the shielded volume present a systematic ΔD_{LOCAL} deviation of -27% . On the other hand, those located in the unshielded volume of the water phantom only deviate 1.4% , 95% of voxels being in the interval $[-8\%, +15\%]$. With respect to the location of these differences, it can be seen in Fig. 5 (bottom) that the asymmetry also manifests itself in the voxel location. Those in the shielded region are concentrated in voxels mostly between 10–14 cm from the source while those in the unshielded region are located at distances larger than 6 cm where the multiple scatter contribution becomes significant as the contribution of the primary beam diminishes due to attenuation.

When ΔD_{GLOBAL} is considered, it can be observed that 95% of the voxels present differences with respect to the reference dose in the range $[-1.7\%, +0.4\%]$. With respect to location, voxels outside that range in the shielded volume are located closer than 1 cm to the lateral side of the applicator and hence would affect an OAR in the region of maximum shielding. Those in the unshielded part of the water phantom can be found up to 10 cm away from the source, i.e. in the volume where the PTV would reside. Nevertheless, such small deviations in a very small subset of voxels are not expected to affect the outcome in clinical practice.

In low dose region, the systematic deviations of ACE can be attributed to the angular discretization of dose kernels^{4,16,19}. In shielded region, the systematic deviations can be attributed to the fact that the first scatter kernels and residual kernels are determined in water and used for high-Z materials in the generic applicator construction¹⁷. Like ACUROS, ACE is a closed system with few user parameter setting except the predefined standard and high-resolution modes. Hence it is hard to pinpoint further specific factors contributing to these systematic deviations found here for ACE.

When evaluating dose to the tissue directly adjacent to the applicator ΔD_{GLOBAL} values for ACE are -0.9% (unshielded) and -8% (shielded) while those for ACUROS are -0.1% and -1.2% respectively. In Kirisits *et al.*⁴², a literature review on the combined overall uncertainty of different BT procedures was performed. For the particular case of HDR gynecological BT using a shielded

applicator it was concluded that the total dosimetric uncertainty in clinical practice ($k=1$) was approximately 8%, where 1% was due to medium corrections for applicators without shielding. Therefore, the discrepancies observed both in ΔD_{LOCAL} and ΔD_{GLOBAL} are well within this value for ACUROS. In the case of ACE, 87% of the total unshielded volume falls within such an interval for ΔD_{LOCAL} . **For the shielded volume there is a -27% systematic displacement** and differences larger than 8% appear for 85% of these voxels. However, as the largest differences are mainly located at distances larger than 8 cm, the risk of overdosing OARs is very small. Even in such cases, ΔD_{GLOBAL} values show that these differences are well within 8% of the reference dose. Hence, no clinical relevance due to these differences is expected.

In Lymeropoulou *et al.*⁴³ the effect of the internal structure and shielding in the case of a commercial applicator was discussed by comparing MC results against a TG43-based TPS, including corrections for the shielded volume in the form of phenomenological transmission factors which lack information on the change in scatter radiation with distance from the source. For the 180° shield case, differences **up to -8% at 10 cm distance** were found on the unshielded side of the applicator. In the shielded volume, TPS dose results were found to slightly underestimate dose as compared to MC. In our case it can be observed that since both ACUROS and ACE take into account the change in scatter radiation due to the presence of the shield, a different spatial distribution for both ΔD_{LOCAL} and ΔD_{GLOBAL} is obtained.

The dosimetric validation of an ACUROS-based TPS for a shielded applicator was discussed in Petrokonninos *et al.*⁸ for clinical cases. Petrokonninos *et al.* reported that dose differences greater than 2% occur mainly at points in the penumbra region of the shield, observing differences up to $\pm 10\%$ for individual voxels. These differences were experimentally verified. Our results for ACUROS and the generic applicator are in agreement with these findings. As also concluded in Petrokonninos *et al.*, the differences observed between ACUROS and ACE when analysing the case of a shielded applicator are negligible clinically when compared with the very substantial dose overestimation in TG-43-based TPSs.

The results presented here allow us to determine the overall differences observed in 95% of the voxels for both ACUROS and ACE. Upper-values for TPS commissioning global differences are 0.1% and 1.7% for ACUROS and ACE, respectively, over the volume of interest. It is important to emphasize that both results are within the 2% tolerance identified by the AAPM.⁴⁴

4.C. Brachytherapy Source Registry

The Brachytherapy Source Registry contains multiple data identified as “Case” 1-4⁴⁵. It includes the two cases reported in Ballester *et al.*⁶ (**Case 2** "source centered in water" and **Case 3** "source displaced") and the applicator case reported in this work (**Case 4** "source centered in applicator"). One more case (**Case 1**) designed to approximate the TG-43 condition, where the generic source is positioned at the center of a 51.1 cm cube of water (referred to as "Case" see Supplementary material), is also available. Both a MC reference dataset and a baseline TPS dataset are available for each test case, accompanied by detailed user guides for commissioning the MBDCAs in both the Varian BrachyVision and Elekta Oncentra[®] Brachy treatment planning systems.

V. CONCLUSIONS

The 3D evaluation of three of an initial set of four MBDCA commissioning dose distribution datasets has been described. These datasets are based on a previously published generic HDR ¹⁹²Ir source and a virtual DICOM-RT compatible, cubic water phantom, complemented in the current study with a partially shielded cylindrical gynecological applicator. All datasets are available on the Brachytherapy Source Registry website for import into DICOM-RT compatible clinical BT TPSs. The full volumetric dose distributions of the generic source placed at the center of the phantom, placed 7 cm away from the center under reduced scatter conditions, and located at the center of the applicator have been evaluated using two commercially available MBDCAs and compared against state-of-the-art MC codes. All MC codes gave equivalent results within statistical uncertainties. The greatest discrepancy was found in the case of the shielded applicator. In this case, ACUROS agreed with MC reference data within [−4.2%, +4.2%] locally for 95% of voxels presenting dose differences within [−0.12%, +0.12%] of the dose at a clinically relevant reference point. ACE agreed with MC reference data within [−8%, +15%] locally for 95% voxels presenting dose differences within

[-1.7%, +0.4%] of the dose at a clinically relevant reference point. Therefore, as such relatively small differences are not expected to be clinically relevant, the implementations of the ACUROS and ACE dose calculation engines as examined here appear to be suitable for clinical service.

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Figure Captions

Fig. 1. The generic cylindrical HDR brachytherapy applicator with 180° shielding (lateral and axial view). Figure not drawn to scale.

Fig. 2. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for GEANT4 with respect to MCNP6 for the “source centered in water” case. The reference point

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is located 1 cm away from the source center along the $-x$ direction; $r_{\text{ref}} = (-1 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxel (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the source are removed.

Fig. 3. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for PENELOPE with respect to MCNP6 for the “source displaced” case. The reference point is located 1 cm away from the source center along the $-x$ direction; $r_{\text{ref}} = (6 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxel (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the source are removed.

Fig. 4. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for BrachyDose with respect to MCNP6 for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the $-x$ direction; $r_{\text{ref}} = (-2.3 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxel (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the applicator are removed.

Fig. 5. 2D histogram of distance to the source center, $r(\text{cm})$, vs. local (ΔD_{LOCAL}) dose difference ratios (left) and global (ΔD_{GLOBAL}) dose difference ratios (right) for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the $-x$ direction; $r_{\text{ref}} = (-2.3 \text{ cm}, 0, 0)$. The comparisons for BrachyDose (top), ACUROS (middle), and ACE (bottom) with respect to MCNP6 are shown. The red dots correspond to

voxels located in the shielded region while the black dots correspond to those located in the unshielded region.

Fig. 6. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for ACUROS with respect to MCNP6 for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the $-x$ direction: $r_{ref} = (-2.3 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxel (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the applicator are removed.

Fig. 7. Local (ΔD_{LOCAL}) and global (ΔD_{GLOBAL}) dose difference ratios for ACE with respect to MCNP6 for the “source centered in applicator” case. The reference point is located 0.5 cm away from the applicator side along the $-x$ direction: $r_{ref} = (-2.3 \text{ cm}, 0, 0)$. Upper left panel: 1D histogram of ΔD_{LOCAL} . Upper right panel: same for ΔD_{GLOBAL} . Lower left panel: 2D histogram of distance to the source center, $r(\text{cm})$, vs. ΔD_{LOCAL} . Lower right panel: same for ΔD_{GLOBAL} . *Voxel (%)* stands for the percentage of the total number of voxels (201^3) once those located inside the applicator are removed.

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