Commissioning of GPU-accelerated Monte Carlo code Fred for clinical applications in proton therapy

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Abstract. We present commissioning and validation of Fred, a GPU-accelerated Monte Carlo (MC) code, for two proton beam therapy facilities of different beam line design: CCB (Krakow, IBA) and EMORY (Atlanta, Varian). We followed clinical acceptance tests required to admit the certified treatment planning system for clinical use.

We implemented an automated and efficient procedure to build a parameter library characterizing the clinical proton pencil beam. Beam energy, energy spread, lateral propagation model, and a dosimetric calibration factor were parametrized based on measurements performed during the facility start-up. The Fred beam model was validated against commissioning and supplementary measurements performed with and without range shifter.

We obtained (i) sub-millimeter agreement of Bragg peak shapes in water and lateral beam profiles in air and slab phantoms, (ii) <2% dose agreement for spread out Bragg peaks of different ranges (iii) average gamma index (2%/2mm) passing rate >95% for >1000 patient verification measurements using a 2D array of ionization chambers, (iv) GI passing rate >99% for 3D dose distributions computed with Fred and measured with an array of ionization chambers behind an anthropomorphic phantom. The results of example treatment planning study on >100 patients demonstrate that Fred simulations in patient CT enable an accurate prediction of dose distribution in patient and application of Fred as second patient QA tool. Computation of a patient treatment in a CT using $10^4$ protons per pencil beam took on average 2’30 min with tracking rate of $2.9\times10^5$ p/s.

Fred was successfully commissioned and validated against the clinical beam model showing that it could potentially be used in clinical routine. Thanks to high computational performance due to GPU-acceleration and an automated beam model implementation method, the application of Fred is possible for research or quality assurance purposes in most of the proton facilities.
1. Introduction

In proton radiation therapy Monte Carlo (MC) methods offer more accurate modeling of proton interactions with heterogeneous media and improved dose calculation accuracy in complex geometries with respect to analytical pencil beam algorithms (Paganetti et al. 2008; Saini et al. 2017; Widesott et al. 2018; Tommasino et al. 2018). The application of MC algorithms in treatment planning can eventually lead to a reduction of the target volume safety margins by about 2% and more accurate prediction of the treatment outcomes (Paganetti 2012). The state-of-the-art commercial proton beam therapy (PBT) treatment planning systems (TPS) employ MC methods for treatment plan optimization and dose calculation (Langner et al. 2018; Chang et al. 2020), but they are still not the standard treatment planning tools in all clinically operating PBT facilities. Many proton facilities still use analytical pencil beam algorithms of limited accuracy in heterogeneous media. Further, the time performance of the MC-based TPS remains to be an issue, especially when applying robust optimization algorithms that require to compute several dose distributions for one Computed Tomography (CT) image or in treatments of moving targets where 4D-CT consisting of series of CT images of several motion phases of one patient are employed in treatment plan optimization (Trnková et al. 2018). In addition, proton radiation therapy Quality Assurance (QA) procedures are time consuming and require manpower for experimental measurements of dose distributions in phantoms, typically performed at few depths in water for each treatment field. In fact, time needed for patient QA could be dedicated for the actual patient treatment. Therefore, reduction of the number of measurements is widely discussed among medical physicists. Supplementing or replacing patient QA measurements with dose distribution recalculation using a second, independent dose calculation engines can be beneficial for PBT facilities.

In several PBT facilities, general purpose MC simulation toolkits e.g. FLUKA (Battistoni et al. 2015), Geant4 (Allison et al. 2006; Jarlskog and Paganetti 2008) or Shield-HIT (Henkner et al. 2009) as well as more user-friendly environments built on Geant4 like GATE/GATE-RTion (Jan, Santin, et al. 2004; Jan, Benoit, et al. 2011; Sarrut et al. 2014) and TOPAS (Perl et al. 2012; Testa et al. 2013) are used to support research activities and/or simulations for patient QA. The clinical application of general purpose MC tools is limited, mainly due to the time required to recalculate a complete plan ranging from tens of minutes to even a few hours. For this reason, the parallelization of the particle tracking on several Central Processing Units (CPU) or general purpose Graphical Processing Units (GPU) is of interest for radiotherapy. The PBT dedicated GPU-based MC code gPMC was implemented by Jia et al. (2012), further developed (Qin et al. 2016) and validated using clinical patient data (Giantsoudi et al. 2015). Following the gPMC development, Wan Chen Tseung and colleagues presented a high performance GPU-accelerated MC code which is used for routine clinical QA and as the dose calculation engine in a clinical MC-based Intensity Modulated Particle Therapy (IMPT) treatment planning system (Wan Chan Tseung, J. Ma, and Beltran...
Commissioning of Fred MC for clinical applications in proton therapy

2. Materials and Methods

2.1. GPU-accelerated MC code Fred

The great benefit of Fred with respect to general purpose MC codes is its computation performance achievable on a variety of different hardware without compromising the
Commissioning of Fred MC for clinical applications in proton therapy

dose computation accuracy. The typical tracking rates range from 10-100 thousand
protons per second using a single CPU, to about million particles per second using
GPU cards. Fred is equipped with an interface to convert phantom/patient geometries
stored in DICOM CT images to a voxelised geometry of the patient containing the
atomic tissue composition using a conversion table based on stoichiometric calibration
(Schneider, Pedroni, and Antony Lomax 1996). In addition to patient geometry, user
defined geometries of specific material composition can be included enabling simulations
of proton transport in passive elements like range shifter.

The physical interaction models implemented in Fred are trimmed-down with
respect to general purpose MC codes, such as Geant4/FLUKA within the regime
that is relevant for particle therapy, in order to speed up the execution time without
compromising the accuracy of dose deposition calculations. In particular, the physics
processes contributing to the dose deposited by protons in a patient tissue, i.e.: mean
energy loss, energy fluctuations, nuclear elastic and inelastic interactions with target
nuclei as well as the trajectory deflection via a multiple Coulomb scattering are
implemented in Fred (Schiavi et al. 2017). Moreover, Fred offers linear energy transfer
(LET) and radiobiological effectiveness (RBE) weighted dose calculations by means of
different RBE models, providing further information, which is not available in the state-
of-the-art commercial TPS. The LET and RBE computations in Fred are out of the
scope of this manuscript.

2.2. Commissioning measurements and Fred simulations

Fred commissioning was performed for one gantry room of two PBT facilities of
different beam-line design equipped with scanned proton beams that are in clinical
operation since 2016 and 2018, respectively. Krakow facility is an IBA design based
on Proteus C-235 cyclotron equipped with two rotational gantries, an eye treatment
room, and an experimental hall. The TPS Eclipse from Varian, version 13.6, is used
for treatment planning in CCB. EMORY PBT center in Atlanta is a ProBeam system
designed by Varian and equipped with three rotational gantries and two horizontal
beam lines. The TPS RayStation from RaySearch laboratories, version 8A, is used
for treatment planning in EMORY. The properties of proton beams and the measurement
methods used for acquisition of clinical beam model commissioning data at both facilities
are listed in table 1.

The commissioning measurements that include depth dose distribution measure-
ments in water phantom, measurements of the lateral profiles (without range shifter) in
air and absolute dose measurements in a water phantom were used to build parameter
libraries characterizing the Fred beam model for Krakow and Atlanta facilities. The
water phantom and in-air setup used for commissioning measurements is schematically
illustrated in figures 1a and 1b, respectively. The figure indicates how the proton beam
is transported from the nozzle towards the detector/phantom. During irradiation, the
beam is deflected vertically and horizontally by scanning magnets and crosses a posi-
Table 1. Selected properties of CCB and EMORY PBT centers and measurement methods used for the proton beam model commissioning. RS - range shifter, SM - scanning magnet, meas. - measurement, IDD - integrated depth dose, Abs. - absolute.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CCB</th>
<th>EMORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy range [MeV]</td>
<td>70-226.1</td>
<td>70-242</td>
</tr>
<tr>
<td>Measurement step [MeV]</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>RS thicknesses [mm] (density [g/cm³])</td>
<td>36.7 (1.168)</td>
<td>20, 30, 50 (1.202, 1.191, 1.191)</td>
</tr>
<tr>
<td>RS material</td>
<td>PMMA</td>
<td>Lexan</td>
</tr>
<tr>
<td>Snout position [cm]</td>
<td>fixed: 36.9</td>
<td>variable: 5-15</td>
</tr>
<tr>
<td>SM distance (X/Y) [cm]</td>
<td>221.5/184.6</td>
<td>200/256</td>
</tr>
<tr>
<td>Lateral profile meas. method (air)</td>
<td>Lynx (IBA)</td>
<td>Lynx (IBA)</td>
</tr>
<tr>
<td>Detector position relative to isocentre [cm]</td>
<td>-20, -10, 0, +10, +20</td>
<td>-30, -20, -10, 0, +5</td>
</tr>
<tr>
<td>Water phantom</td>
<td>Blue Phantom² (IBA)</td>
<td>Blue Phantom² (IBA)</td>
</tr>
<tr>
<td>IDD meas. method (water)</td>
<td>Bragg Peak chamber (PTW)</td>
<td>StingRay (IBA Dosimetry)</td>
</tr>
<tr>
<td>IDD meas. acceptance correction</td>
<td>Yes (FLUKA)</td>
<td>No</td>
</tr>
<tr>
<td>Abs. dosimetry meas. method (water)</td>
<td>Markus (PTW) at 2 cm</td>
<td>PPC-40 (IBA) at 2 cm</td>
</tr>
<tr>
<td>Monoenergetic field size</td>
<td>10×10 cm²</td>
<td>10×10 cm²</td>
</tr>
</tbody>
</table>

The Fred simulation setup mimics the commissioning measurements setup shown in figures 1a and 1b. The virtual beam source is located at the position of the scanning magnet located closer to the isocentre because the at this position the deflection of the beam, in both X and Y directions is defined. The different position of the X and Y scanning magnets is taken into account, while calculating the direction of a single pencil beam. The beam propagation in the IC23 is omitted in the simulations and is taken into account by adjusting beam source parameters, in such a way that the beam size fits the results of beam size measurements in air performed with scintillating screen (Lynx). The proton beam was propagated without and with range shifter. Fred simulations in water were performed in 40×40×40 cm³ virtual phantoms of 1×1×1 mm³ voxel size (figure 1a). The ionization potential of water was set to 80 eV (ICRU 2016). Fred simulations of the in-air setup used for beam model validation were performed in a virtual air phantom. The total time of Fred MC simulations includes tracking time, time needed for memory allocation and the file writing. The tracking rate of simulation is given as the number of protons tracked per second (p⁺/s).
Figure 1. Experimental and simulation setups for water phantom (a) and in-air scintillating screen measurements (b). On the left, beam nozzle elements (scanning magnets and position sensitive beam monitor (BM) chambers), not taken into account in MC simulations, are shown (gray scale). In MC simulations the primaries are generated in Monte Carlo virtual source and transported through range shifter (RS) to phantoms/detectors (blue). The figure is not to scale.

2.3. Beam model parameters

The beam model parameters characterize longitudinal and lateral pencil beam profiles as well as dosimetric calibration. Two parameters, energy (E) and energy spread (Eσ), characterize proton pencil beam depth dose distribution (longitudinal) profile. One further parameter, Monitor Units (MU) to number of particles conversion factor (SF_{MU}), characterizes IDD dosimetrically. The lateral propagation of the proton pencil beam can be characterized by a quadratic model by means of modeling beam emittance or bilinear model by defining virtual point source. In fact, the bilinear model is an approximation of a quadratic model in a limited range. The virtual point source approach can be applied, when the waist of the quadratic function of emittance model is far enough from the isocentre to approximate lateral beam propagation behind the nozzle exit by a bilinear function. Fred is capable of handling lateral beam propagation using both, virtual point source or emittance approaches.

For characterizing the lateral propagation, the lateral beam profiles measured during facility commissioning in air at different Z positions (cf. figure 1b) were fitted using the Gaussian fit and its σ(z) was calculated. Fitting σ(z) to commissioning data from both facilities at different distances from the isocentre using bilinear and quadratic functions indicated that the emittance model is appropriate for Krakow facility, whereas the virtual point source model can be used for EMORY.

For characterizing the beam lateral propagation in Krakow the total number of six
emittance model parameters \((\epsilon, \alpha, \beta)\), three in \(X\) and three in \(Y\) direction were used. The Twiss parameters \(\epsilon, \alpha, \beta\) were obtained according to the following formula (Twiss and Frank 1949):

\[
\sigma^2(z) = \epsilon \cdot \left( \beta - 2 \cdot \alpha \cdot z + \frac{1 + \alpha^2}{\beta} \cdot z^2 \right),
\]

where the emittance \(\epsilon\) corresponds to the area in the \(X/Y\)-position-velocity phase space, and is assumed to be constant over the beam propagation in air. The Twiss parameter \(\alpha\) is related to the focusing/defocusing of the beam, whereas \(\beta\) characterizes the length over which the beam changes its transverse shape.

For characterizing the beam lateral propagation in Atlanta, the total number of four parameters, two in \(X\) and two in \(Y\) direction, specific for a bilinear approximation were used. The parameters were obtained according to the following formula:

\[
\sigma(z) = S \cdot z - VSD,
\]

where the \(S\) is the function slope and corresponds to the rate of the spot size variation and \(VSD\) stands for virtual source distance and corresponds to the distance from the virtual source to the isocentre. Note that for both approaches, virtual point source and emittance model of lateral beam propagation, particles are transported starting from the position of the scanning magnets regardless of the position the emittance waist and \(VSD\).

For TPS exploiting analytical pencil beam algorithm, the emittance model is defined for configurations with and without range shifter, whereas in MC-based TPS and in Fred only the configuration without range shifter is defined and proton transport in range shifter is simulated according to its model parameters (material composition, density, physical thickness).

2.4. Generation of beam model parameter library

We implemented a set of software tools that calculate beam model parameters in three automated steps (see figure 2). The beam model parameter libraries were generated in the entire proton beam energy range in 10 MeV steps (table 1) for both facilities. Figure 2 schematically illustrates how the Fred MC commissioning procedure uses the facility commissioning measurements as the input to obtain beam model parameters per nominal energy, i.e.: beam energy \(E\), energy spread \(E_\sigma\), MU scaling factor \(SF_{MU}\) and six emittance or four virtual point source parameters. The procedure is automated and does not require any interaction with the user, except preparation of the measurement data. Fred simulations of single pencil beams were performed using \(10^8\) primary protons.
**Step 1.** In the first step (figure 2: Step 1), the emittance or virtual point source model (Eq. 1 and 2) was fitted to the measured beam spot size ($\sigma_{x/y}$) as a function of the position along the beam (see sec. 2.3). For Krakow beam model, in addition to the beam size measurements performed with Lynx, the beam size measurements performed during irradiation with IC23 installed close to the nozzle exit were used to fit the emittance model (see sec. 2.3). In this way, emittance model parameters ($\epsilon, \alpha, \beta$) or virtual point source parameters ($S, VSD$) were obtained for $X$ and $Y$ directions and each energy.

**Step 2.** In the second step (figure 2: Step 2) beam energy ($E$) and energy spread ($E_\sigma$) were obtained. The measured and simulated integrated depth dose (IDD) profiles were fitted using a formalism proposed by Bortfeld (1997) (Gajewski 2017). Using the fit and semi-empirical relations proposed by Bortfeld (1997), the initial energy and energy spread of protons producing an IDD distribution were computed. The Bragg peak range ($R_{80\%}$) defined as 80% of the maximal value at the distal fall-off and the Bragg peak Full Width at Half Maximum (FWHM) were numerically calculated from the fitted curve. The $E$, $E_\sigma$, $R_{80\%}$, FWHM parameters were calculated for both, experimental data and each Fred simulation. An automated iterative optimization procedure was developed to find such $E$ and $E_\sigma$ values in Fred, which minimize the absolute difference of Bragg peak range ($|\Delta R_{80\%}|$) and FWHM ($|\Delta \text{FWHM}|$) between simulation and measurement. The dependence of $|\Delta R_{80\%}|$ and $|\Delta \text{FWHM}|$ on $E$ and $E_\sigma$ is a continuous function with a single global minimum. The optimization procedure was implemented in Python exploiting the Nelder-Mead simplex algorithm (Nelder and Mead 1965). The initial guess of energy and energy spread was estimated from the Bortfeld curve fitted to measured data. Each consecutive step of the optimization algorithm included: (i) new simulation of a depth dose distribution in water with energy and energy spread computed by the optimization
Commissioning of Fred MC for clinical applications in proton therapy

algorithm, (ii) Bortfeld curve fit and estimation of $R_{80\%}$ and FWHM for the simulated curve, and (iii) estimation of $|\Delta R_{80\%}|$ and $|\Delta \text{FWHM}|$ comparing measurement and new simulation. The Fred beam energy ($E$) and energy spread ($E_{\sigma}$) are considered optimal when $|\Delta R_{80\%}|$ and $|\Delta \text{FWHM}|$ are less or equal 0.05 mm.

**Step 3.** In the third step (figure 2: Step 3), the dosimetric calibration from TPS MU to the number of particles ($SF_{MU}$) was obtained for each nominal energy, mimicking the measurement setup. For this purpose, a monoenergetic $10 \times 10 \text{cm}^2$ field in water was simulated with spot spacing 2.5 mm, 1 MU per spot and unitary MU scaling factor. The dose in the uniform field center at 2 cm depth in water, $D_{2\text{cm}}$, was derived from the simulation. The MU scaling factor ($SF_{MU}$) was obtained as the ratio between $D_{2\text{cm}}$ obtained from commissioning measurement and Fred MC simulation.

The output of the characterization procedure is a list of beam model parameters per nominal energy and is stored in a text file. We developed a software tool that converts clinical TPS treatment plan into Fred input files using the beam model library (cf. figure 2: Conversion and calculation of treatment plans). The parameters in between nominal energies are linearly interpolated mimicking the procedures applied by TPS and beam line control system.

### 2.5. Validation in homogeneous media

This section describes how the beam model library was validated by comparing Fred simulations to measurements performed at each facility. We compared (i) lateral propagation of proton pencil beams, (ii) treatment plans of dose cubes and (iii) patient QA treatment plans. The beam model validation steps are schematically illustrated in figure 2 (lower row). The treatment plans were exported from TPS and converted from DICOM to Fred input file format. The QA treatment plans were simulated in Fred using $10^5$ protons per pencil beam. After simulation, the dose from each spot was scaled to the actual number of particles optimized in the treatment plan using dosimetric calibration ($SF_{MU}$).

**Lateral propagation of proton pencil beams.** The measurements of lateral profiles of proton pencil beam were performed using the Lynx scintillating screen (IBA Dosimetry) in air (i) for CCB and EMORY at five positions behind the range shifter for proton beams at 100, 150 and 200 MeV and (ii) for CCB at several positions in slab phantoms consisting of RW3 for proton beams at 100, 150 and 200 MeV and for EMORY in PMMA for proton beams at 130, 180 and 240 MeV. Fred simulations for pencil beams were performed at the corresponding positions behind the range shifter in air and in solid phantoms. The transverse shape of the beam in $X$ and $Y$ direction was fitted with a single Gaussian fit and the $\sigma$ obtained from measurements and simulations was compared.

**Spread Out Bragg Peak (SOBP).** The longitudinal profiles of dose cubes (SOBPs) were measured at (i) CCB using a dosimetrically calibrated plane-parallel
Markus chamber placed in a water phantom (sensitive volume $0.055 \text{ cm}^3$) with variable 0.1-1 cm step length and (ii) at EMORY using the Zebra detector (IBA Dosimetry) without dosimetric calibration. The QA treatment plans of dose cubes were optimized in clinical TPS aiming at achieving homogeneous biological dose of 1 Gy(RBE) and 4 Gy(RBE) at CCB and EMORY, respectively. All cubes had a lateral size of $10 \times 10 \text{ cm}^2$. At CCB, dose cubes of 5 cm length (modulation) and variable range of 10, 15, 20, 25, 30 cm without range shifter were optimized and evaluated. At EMORY, dose cubes of 10 cm length (modulation) and constant range of 15 cm without and with three range shifters of different thickness were investigated. Simulations of the SOBP plans were performed in a virtual water phantom. The measured SOBP dose profiles were compared with the profile extracted from 3D dose calculation obtained from Fred MC simulations. Absolute dose comparison was performed for Markus chamber measurements conducted at CCB, whereas relative dose comparison was performed for Zebra measurements conducted at EMORY.

Patient QA. To evaluate the accuracy of Fred simulations, patient QA treatment plans were simulated in a virtual water phantom and compared to patient QA measurements routinely performed in the clinic. The comparison of TPS versus measurement is also shown.

In CCB and EMORY, the MatriXX PT (IBA Dosimetry) is currently in use for patient QA. MatriXX is a 2D array of 1020 plane-parallel ion chambers of 4 mm diameter arranged in a $32 \times 32$ grid with the distance between chambers of 7.62 mm. In both facilities, the MatriXX detector was calibrated to dose in water according to protocol proposed by the manufacturer. Patient QA measurements are typically performed at 3-5 depths at CCB and at 1-2 depths at EMORY. The measurement layers are selected individually for each patient. The patient QA treatment plans of 74 patients (1077 measured layers, 967 without and 110 with range shifter) treated in Krakow and 13 patients (56 measured layers) treated in EMORY were evaluated. The dose distributions obtained from TPS and Fred calculations were compared to measured data by means of dose profile and Gamma Index (GI) analysis (Low et al. 1998). GI calculation tools implemented PyMedPhys Python package (Biggs and Jennings 2019) were used for evaluation. The three-dimensional (3D) GI test (2%/2mm criteria) was used to compare 2D slice of dose field measurement (reference) with 3D Fred dose distribution calculation (evaluation).

2.6. Validation in heterogeneous media

The end-to-end experimental validation of Fred physics models, beam model and CT calibration using a heterogeneous CIRS head-and-neck phantom (model 731-HN) (Albertini et al. 2011) was performed in Krakow. The experimental setup is shown in figure 3. The CIRS phantom consists of five tissue equivalent materials: brain, bone, larynx, trachea, sinus, teeth and nasal cavities. One half of the phantom consists of single piece and the other is sliced into three segments as shown in figure 3a. The CIRS
phantom was positioned in the treatment room using orthogonal X-ray imaging system and the phantom CT scan, following the clinical patient positioning procedure applied in Krakow. The irradiation plans of $10 \times 10 \text{cm}^2$ monoenergetic fields at nominal energies 100, 150 and 200 MeV were prepared in clinical TPS with and without range shifter. The dose distribution downstream from the CIRS phantom was measured using the MatriXX detector placed in the DigiPhant water phantom (IBA Dosimetry, see sec.2.5). Data were acquired in 5 mm water-equivalent steps yielding 3D dose distribution with lateral resolution of 7.62 mm and longitudinal resolution of 5 mm. Dose distributions were measured behind half CIRS head in water for nominal energies 150 and 200 MeV (cf. figure 3b). The dose distribution was measured behind 1/6 slice of CIRS head in water-equivalent RW3 slab phantom using 100 MeV proton beam (IBA Dosimetry; cf. figure 3c), since 100 MeV protons have insufficient range to traverse the half-head phantom to acquire dose distribution in water using MatriXX (with and without range shifter).

The measurements were compared to Fred simulations of the experimental setup performed in the CT image of the CIRS and water phantoms. The CT image of CIRS phantom was acquired using the CT scanner (Siemens SOMATOM) calibrated for treatment planning in Krakow. The comparison of measured and simulated 3D dose distributions was performed using a 3D GI method.

2.7. Patient data

A retrospective patient study was performed to investigate time performance of Fred as an independent MC-based proton dose computation tool and demonstrate its applicability for patient QA in the clinic. For this purpose we referred our results to the TPS computations.

The 122 treatment plans (including boost plans) of 90 head and neck as well as brain patients treated at CCB from 2016 to 2018 and an example treatment plan of a patient treated in EMORY in 2019 were simulated in Fred on CT geometries. The clinical CT
Commissioning of Fred MC for clinical applications in proton therapy

Images were sampled down to 1.5×1.5×1.5 mm³ voxel size. The facility specific clinical CT calibration curve obtained from stoichiometric calibration (Schneider, Pedroni, and Antony Lomax 1996) was implemented in Fred. The CT calibration curve used in Fred contains information on the composition, relative stopping power (RSP) of protons, radiation length and density of 93 materials. The density and RSP of CT numbers between 93 predefined points are linearly interpolated. The CT images of the patient anatomy and delineated contours were used for optimization of the plans in clinical TPS using an analytical intensity modulated proton therapy (IMPT) optimization algorithm. Depending on the target size and the number of fields, the number of pencil beams in a treatment plan varied from 1378 to 32290 with the median value 10989. 10⁴ protons per pencil beam were simulated for each patient treatment plan recalculated in Fred and the obtained dose was scaled to the actual number of particles optimized in the treatment plan.

An example treatment planning study on 122 plans included a comparison of dose distributions obtained from Fred and from clinical TPS. We evaluated three parameters based on dose volume histogram (DVH) that characterize the quality of dose distribution. (i) The mean dose (D_mean) is related to the prescribed dose (D_p). (ii) The Homogeneity Index (HI) characterizes the slope of the DVH, hence the uniformity of the dose distribution in the PTV. The HI is defined as HI = (D_2% − D_98%) / D_p, where D_2% and D_98% are the doses received by 2% and 98% of the PTV, respectively (ICRU 2010). (iii) The Conformity Index (CI) describes how much dose prescribed to the planning target volume (PTV) is delivered outside the PTV, possibly to organs at risk. The CI is defined as CI = V_{body, 95%} / V_{PTV, 95%}, where V_{body, 95%} and V_{PTV, 95%} are the volumes of the body PTV, which receive at least 95% of the prescribed dose D_p (Pathak and Vashisht 2013).
3. Results

3.1. Generation of the beam model parameter library

The beam model parameter libraries characterizing the proton beam model for CCB and EMORY facilities was generated using an automated procedure (cf. sec. 2.3) and are illustrated as a function of nominal proton beam energy in figure 4. Using the beam model library, the nominal primary proton beam energy for each pencil beam from the treatment plan is used to define the initial parameters of the pencil beams used by Fred simulations. Figure 4 (top-left panel) shows a linear relation between the nominal proton beam energy used by TPS and FRED. The energy spread values fluctuate within 1 MeV and are slightly smaller for Krakow than for Atlanta proton center. Figure 4 (top-right panel) shows the dosimetric scaling factors used to convert
MU to number of primary particles per pencil beam spot. The bottom panels of figure 4 show the six parameters of emittance model used for Krakow (bottom-left panel) and the four parameters of VPS model used for Atlanta facility, characterizing the lateral beam propagation (bottom-right panel). The lateral asymmetry of the pencil beams in $X$ (filled circles) and $Y$ (empty circles) directions is taken into account in the beam model characterization.

The IDD profiles of single proton beams in water for three nominal energies: 100, 150, and 200 MeV are given in figures 5a and 5b for the Krakow and Atlanta facilities.

**Figure 5.** Examples of longitudinal proton beam propagation in water (top panels) and lateral proton beam propagation ($\sigma$) in $X$ and $Y$ directions in air (bottom panels) for CCB (left) and EMORY (right) facilities at three proton beam energies: 100, 150 and 200 MeV. Depth dose distribution profiles of proton pencil beams simulated with beam model parameters in FRED (FRED Bragg peak) and obtained experimentally during the facility commissioning (measured Bragg peak) for CCB (panel a) and EMORY (panel b). The transverse shape and velocity evolution of the proton beam represented by means of the emittance model for CCB (panel c) and VPS model for EMORY (panel d).
The profiles are in agreement with the commissioning measurements: the range ($R_{80\%}$) of the pencil beams agrees within 0.02 mm, the relative dose difference along the pencil beam profile is below 4\%, the FWHM of the Bragg peak agrees within 0.05 mm, the distal fall-off width between 80\% and 20\% Bragg peak dose agrees within 0.04 mm, the peak-to-plateau ratio agrees within 0.11.

The fitted single beam sizes in air obtained in commissioning measurements,

![Figure 6. Spot sizes in air in X (blue) and Y (red) directions for CCB and EMORY without range shifter and behind the range shifters used at facility (single range shifter (RS) of thickness 36.7 mm for CCB and RS2, RS3 and RS5 of thicknesses 20, 30 and 50 mm, respectively, for EMORY). The measured spot sizes are shown as points with error bars ($\pm 0.1$ mm) and the solid lines show the simulation results.]
Commissioning of Fred MC for clinical applications in proton therapy

described by $\sigma_{x/y}$ of lateral pencil beam profiles is shown in the figure 5c and 5d for three nominal energies: 100, 150, and 200 MeV for the Krakow and Atlanta facilities, respectively. The maximum absolute difference between fitted and measured beam sizes in range from -20 to 20 cm (CCB) and -30 to 5 cm (EMORY) around the isocentre is smaller than 0.05 mm. We deem this sufficiently accurate to model lateral beam propagation in clinical applications. The quadratic and linear shape of the fit justifies the use of the emittance (figure 5c) and VPS (figure 5d) model for the Krakow and Atlanta facilities, respectively.

Dose computation time for a single pencil beam at 100, 150, and 200 MeV simulated with $10^8$ primary protons was 36 s, 44 s and 53 s respectively. The corresponding tracking rate is $10.1 \times 10^6$, $5.7 \times 10^6$ and $3.6 \times 10^6 \text{ p}^+/\text{s}$. The tracking rate decreases with the beam range as more interactions must be processed.

The total computation time needed to determine the beam model parameters for all reference energies following the automated procedure described in sec. 2.3 was approximately 12 hours. Within this time (i) the parameters characterizing beam lateral propagation were fitted (figure 2 step 1; total time: few seconds), (ii) simulations required for E and $E_\sigma$ optimization were performed and the optimization procedure itself was executed (figure 2 step 2; total time: approx. 10 hours), as well as (iii) simulations of monoenergetic $10 \times 10 \text{ cm}^2$ fields required for SF$_{MU}$ calculation were performed (figure 2 step 3; total time: approx. 2 hours). For CCB, full beam model characterization required a total of 303 Fred MC simulations, including 286 simulations for E and $E_\sigma$ optimization and 17 simulations for SF$_{MU}$ calculation (average time of single simulation was approximately 2 min and 7 min, respectively).

![Figure 7. The transverse shape evolution ($\sigma$) of proton pencil beam measured and simulated in water equivalent slab phantom.](image-url)
3.2. Validation in homogeneous media

**Lateral propagation of proton pencil beams.** The lateral propagation of pencil beams in air behind range shifter of different thickness (figure 6) and in slab phantoms (figure 7) was simulated in Fred and compared to the beam size $\sigma_{x/y}$ of lateral pencil beam profiles obtained experimentally. Note that the comparison was performed at different positions/depths and for different primary proton beam energies at CCB and EMORY facilities.

The lateral propagation of the beam in range shifter as well as in slab phantom is modeled in Fred very accurately. The values of $\sigma_{x/y}$ obtained from measurements agrees with simulated values mostly within 100 $\mu$m, as indicated by error bars in figures 6 and 7. The results in air and in slab phantom are within the spot size QA acceptance criterion of $\pm 0.6$ mm used by CCB therapy center.

**Spread Out Bragg Peak (SOBP).** Depth dose distribution profiles of cubic volumes obtained from measurements and Fred simulations are shown in figure 8 for CCB in the top panels and for EMORY in the bottom panels. The results obtained for CCB are absolute dose, whereas they are relative normalized to the dose value in the middle of the SOBP for EMORY. Since the treatment plans were optimized in clinical TPS, the obtained physical dose differs from the prescribed biological dose by the RBE factor of 10%.

Good agreement between Fred MC simulations and dose measurements along the SOBP profiles was obtained. The maximum relative dose difference is 2% for most of the measurement points. The largest relative dose differences are observed at the distal fall-off, i.e. a high dose gradient region, and result from the detector positioning uncertainties, estimated to be about $\pm 0.3$ mm. Small variations between the measurements and simulations are present at the beginning of the plateau and in the SOBP of cubes with range of 25 cm and 30 cm. They are potentially related to the implementation of the nuclear interaction model in Fred for the highest beam energies. This accuracy is acceptable for the scope of the presented clinical application.

The tracking rate of the dose cube simulation ranged from $4.5 \times 10^6$ p/s to $2.0 \times 10^6$ p/s and the complete dose computation time for a single dose cube was up to 10 minutes, with the statistics $10^5$ primaries per pencil beam.

**Patient QA.** 2D transversal dose maps obtained from measurements performed with the MatriXX detector in water phantom were compared to Fred and TPS simulations of patient treatment plans using the GI method. Data from 1077 measurements performed at CCB and 52 measurements performed at EMORY were investigated and are summarized in table 2. The average GI passing rate obtained comparing all simulated and measured layers was 97.83 (4.94)% (1σ) for CCB and 95.51 (3.88)% (1σ) for EMORY. 1022 out of 1077 layers evaluated for CCB fulfill the requirement of the GI passing rate (%GP) to be greater than 90%. For EMORY, 47 out of 52 investigated layers fulfill this requirement. Figure 9 shows an example of a transversal dose field layer extracted from Fred MC simulation and the corresponding dose distribution measured
Figure 8. Dose profiles of cubic volumes of SOBP obtained from Fred MC calculations (solid line) and measurements (dots) for CCB (top panel) and EMORY (bottom panel) facilities. The relative dose difference between the measurement and simulation is illustrated by crosses.

with MatriXX at the same depth in water, as well as the GI map.

For a patient verification treatment plan, the average tracking rate and complete dose computation time was $3.4(0.4) \times 10^6 \text{p/s (1}\sigma)$ and $2.34(1.38) \text{min (1}\sigma)$, respectively.

Table 2. Summary of patient QA evaluation. RS - range shifter, \%GP - Gamma Index passing rate. The values in brackets for \%GP denote standard deviations.

<table>
<thead>
<tr>
<th></th>
<th>FRED vs Measurement</th>
<th>TPS vs Measurement</th>
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<tr>
<td></td>
<td>All</td>
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<tr>
<td>CCB</td>
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<tr>
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</tr>
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<td>%GP</td>
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<td>97.99(4.61)</td>
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<tr>
<td>passed</td>
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<td>923</td>
</tr>
<tr>
<td>EMORY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>52</td>
<td>16</td>
</tr>
<tr>
<td>%GP</td>
<td>95.51(3.88)</td>
<td>98.20(2.68)</td>
</tr>
<tr>
<td>passed</td>
<td>47</td>
<td>16</td>
</tr>
</tbody>
</table>
Figure 9. A transversal 2D dose distribution layer measured with an array of ionization chambers in water phantom (left panel), obtained from FRED MC simulations (middle panel) and a GI map computed comparing FRED simulation and measurement using GI (2%/2 mm) method (right panel). GI passing rate is 99.53% for the CCB case shown in the top panels and 95.95% for EMORY case shown in bottom panel.

3.3. Validation in heterogeneous media

The experimental validation of FRED accuracy was performed by comparing 3D dose distributions behind the heterogeneous phantom obtained experimentally and from FRED simulations (cf. sec. 2.6). An example of the comparison of FRED simulation against the experimentally acquired data is shown in figure 10. Two 3D dose measurements, one with and other without range shifter, were performed for each of the investigated energies (100, 150, 200 MeV). An excellent agreement between FRED simulations and measurements was achieved. For all the investigated cases, the 3D GI (2%/2 mm) is greater than 99%. Comparing the clinical (analytical) TPS simulation and the measurements, the GI passing rate is $93.2\,^{98.0\%}\pm8.4\%$ ($\sigma=8.4\%$). See the supplementary material of the manuscript for detailed results of other measurements performed at 100 and 200 MeV, with and without range shifter.
3.4. Example clinical application of Fred

As an example, dose distributions, dose profiles and DVHs recalculated with Fred and clinical TPS, for one patient case from CCB and one from EMORY are shown in figure 11. For CCB patient case (figure 11 top panels), dose distributions computed with Fred are less uniform compared to the analytical TPS calculations. This is also observed analyzing the dose profiles and the DVH for PTV, and results in the reduction of the mean dose in PTV and organ at risk. For EMORY patient case (figure 11 bottom panels), the differences in dose distributions are less visible as MC-based TPS was used for the dose optimization and calculation. The observed differences between Fred and RayStation MC-based TPS are similar to the results obtained comparing RayStation to ECLIPSE MC algorithm reported by Chang et al. (2020).

Analysis of 122 treatment plans of patients treated at CCB was performed to quantify the time performance and demonstrate the clinical applicability of Fred dose computations for patient QA. Comparing dose distributions in PTV we observed that the ratio $D_{mean}/D_p$ obtained with Fred is more dispersed than the one obtained with analytical TPS (median values are -1.20% and -0.02%, respectively), as shown in figure 12 (left panel). The analysis of HI in PTV is shown in figure 12 (middle panel), where the median HI is 0.11 and 0.16 for clinical TPS and Fred, respectively. Figure 12 (right panel) shows the CI distributions, which present no substantial difference between both, Fred and TPS calculations (median CI is 1.26 and 1.23 for TPS and Fred, respectively).

For a treatment plan, the total simulation time varied depending on the complexity of the plan i.e. total number of pencil beams and presence of range shifter in the plan. For the simulations in CT geometry rescaled to $1.5 \times 1.5 \times 1.5 \text{ cm}^3$ voxels the computation time ranged from 21 s to 6’26 min (average value 2.28 (1’25) min (1σ)) with the average tracking rate $2.9 (1.1) \times 10^5 \text{ p/s} (1\sigma)$. 

**Figure 10.** The experimental validation of Fred simulations in heterogeneous CIRS phantom. Panel (a): measurement of 3D dose distribution in water phantom performed using MatriXX. Panel (b): Fred simulation of 3D dose distribution. Panel (c): 2D GI map (2%/2 mm) obtained comforting experiment to Fred simulations. The color maps on panels a-c are overlaid on CT scan of CIRS and water phantom. Panels (d) and (e) show respectively longitudinal and lateral profiles obtained from measurements (dots) and simulations (solid line). See supplementary material for the complete report of the validation.
Commissioning of Fred MC for clinical applications in proton therapy

4. Discussion

We have built a proton beam model libraries for Fred MC code according to the QA protocols and we accomplished acceptance tests required for beam model validation in a

Figure 11. The evaluation of the treatment plan of patient treated at CCB (top panels) and at EMORY (bottom panels). On the left panels, dose distributions computed with clinical TPS and Fred are shown. PTV (black solid line) and 95% isodose (blue dashed line) are delineated. The corresponding dose profiles and DVHs are shown in top-right and bottom-right panels, respectively.
Commissioning of Fred MC for clinical applications in proton therapy

Figure 12. The parameters characterizing the quality of 122 dose distribution obtained from patient treatment plans computed with clinical TPS (blue) and Fred (red). The left panel shows the ratio $D_{\text{mean}}/D_p$, the middle panel shows the Homogeneity Index (HI) and the right panel the Conformity Index (CI).

commercial TPS at proton therapy facilities. We performed MC commissioning avoiding the nozzle geometry modeling similar to work presented by other groups (Grevillot et al. 2011; Fracchiolla et al. 2015; Grassberger, Anthony Lomax, and Paganetti 2015). The beam model library parameters containing the information on initial proton energy and energy spread, lateral beam propagation, as well as dosimetric calibration were identified in 10 MeV energy steps in the therapeutic energy range to best fit the commissioning measurements of proton pencil beams (cf. sec. 3.1). A submillimeter agreement between simulated and measured Bragg peaks shape and range in water and lateral beam sizes in air and in solid phantoms was obtained with and without range shifter for beam model of two facilities of different beam-line design.

In the study we assumed the uncertainty of single pencil beam and SOBP depth dose profile measurements to be ±3%. The uncertainty of positioning of the ionization chamber in the water phantom is about 0.3 mm. The uncertainty of the lateral pencil beam size measurement performed with scintillating screen (Lynx detector) in air as well as in the RW3/PMMA slab phantom is ±0.1 mm, whereas the measurement with IC23 has 0.5 mm uncertainty (Grevillot et al. 2011). We estimate the uncertainty of the slab phantom positioning at 1 mm, but it has negligible impact on the beam lateral profile measurements. The statistical uncertainty of Fred calculations in water phantoms of resolution of $1 \times 1 \times 1 \text{ mm}^3$ is negligible. The statistical uncertainty of Fred calculations in patient CT geometry resampled to $1.5 \times 1.5 \times 1.5 \text{ mm}^3$ resolution is below 2%.

Comparison of experimental results in homogeneous media and anthropomorphic phantom to Fred simulations (cf. sec. 3.2-3.3 and supplementary materials) indicates that fast dose recalculations in patient CT performed with Fred (cf. sec. 3.4) is a very accurate simulation of proton treatment. A retrospective treatment planning study and the statistical evaluation of DVH parameters is an example of routine clinical application of Fred for patient QA. The dose nonuniformities in PTV shown in an example CCB patient case recalculated with Fred (figure 11) are also observed in analysis of $D_{\text{mean}}/D_p$. 
Commissioning of Fred MC for clinical applications in proton therapy

and HI for 122 patient cases summarized in figure 12. Fred calculations predict dose nonuniformity which cannot be calculated with analytical TPS used in Krakow. Note that these clinical results, both from TPS and Fred, include uncertainties related to acquisition of commissioning data, beam model implementation, CT calibration, etc. On the other hand, the distribution of $D_{\text{mean}}/D_p$, HI and CI indicate that, overall, the dose distribution calculations performed with both, clinical TPS and Fred are within the clinically relevant acceptance. In clinical practice, additional information about dose, LET and RBE-weighted dose distributions calculated with Fred can be an indication for medical physicists to revise the treatment plan optimization or to perform additional experimental validation, when the results deviate from the predictions of TPS exceeding acceptance criteria. The time performance of Fred enables to obtain this information within about 2.5 minutes. Fred is currently adapted to be executed as a stand-alone library which will enable its easy integration with commercial TPS, e.g. Eclipse or RayStation, as well as dedicated software tools for patient QA, e.g. MyQAion.

Schiavi et al. (2017) reported that simulation of dose deposition in a water phantom induced by $10^6$ primary protons can be reduced from 22 minutes required by FLUKA MC code to 0.5 second when employing Fred running on two GPU modules (ibid.). Regarding dose distribution simulation in patients, Grassberger, Anthony Lomax, and Paganetti (2015) reported that the patient simulation for the head and neck patient took 371 min ($10^6$ primaries simulated) on single CPU using TOPAS (Geant4), which corresponds to a tracking rate of $45 \frac{p^+}{s}$, whereas the average tracking rate obtained with Fred is $2.9 \times 10^5 \frac{p^+}{s}$ in patient CT rescaled to $1.5 \times 1.5 \times 1.5 \text{mm}^3$ using two GPUs. The time performance results presented in this manuscript can be linearly scaled as a function of the number of GPU cards applied (Schiavi et al. 2017). Note that the simulation time depends on number of primaries simulated per pencil beam, tumor depth (i.e. the beam energy) and scoring resolution used for the simulation. The most accurate dose calculations in tissue heterogeneities can be obtained performing the simulation in original CT grid. In order to achieve the statistical uncertainty below 1% on CT grid used at CCB ($0.7 \times 0.7 \times 1.2 \text{mm}^3$), $10^5$ primaries per pencil beam should be simulated. The average simulation time for the patient group investigated in sec. 3.4 in original CT resolution is $31.8^{+61.8}_{-5.5} (\sigma=23.8)$ min.

The clinical application of proton therapy and development of new treatment protocols, for example studies on the reduction of safety margins accounting for treatment plan robustness, require treatment planning studies that can be only performed analyzing several treatment planning approaches. The total simulation time of all 122 patient cases shown in sec. 3.4 was about 5 hours. An example study of 10 possible treatment planning approaches on our patient group could be performed using Fred within about two days simulation. Another application is robust optimization of treatment plans, that is particularly relevant for treatment planning of moving targets, when several dose distribution must be computed on 4D CT. Performing such studies without the time performance offered by Fred would not be possible with any general purpose MC code in reasonable time.
In addition to its clinical applications, the time performance of FRED enables preparation of the proton beam model faster with respect to a general purpose MC codes. This is particularly useful when due to technical modifications or maintenance at accelerator a new beam model must be implemented in the clinical routine. When the facility beam commissioning measurements are available, the GPU acceleration offered by FRED allows to parametrize the beam model within about 12 hours requiring minimal manual intervention. This potentially enables easy and quick use of FRED for research and patient QA purposes in most of the proton facilities with little experimental efforts.

5. Conclusion

In this manuscript, we share our experience from commissioning and validation of GPU-accelerated MC code FRED based on commissioning measurements of two proton beam therapy facilities of different beam-line design: CCB (Krakow) from IBA and EMORY (Atlanta) from Varian. FRED passed acceptance tests required to admit TPS for clinical use. The approach we used combines application of a new GPU-accelerated MC code, implementation of two proton beam lateral beam propagation models, automated beam model optimization method, experimental validation of beam model parameters in an anthropomorphic phantom with and without range shifter and comparison of patient treatment plans computed with FRED and clinical TPS in patient CT. Our commissioning and validation results demonstrate the universal and accurate implementation of the physics models in FRED allowing its flexible applications for medical physics and research purposes. The application of FRED as a secondary MC engine for patient QA in clinical routine is foreseen in Krakow proton facility. FRED is currently used for treatment planning studies evaluating radiobiologically effective dose using variable RBE.

Acknowledgments

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Author contribution

JG, MG, AS, ASc, and AR developed the beam model for CCB. JG developed automated beam model library implementation method and performed data analysis to validate the
model. JG, MG and ASc developed the emittance and virtual point source models for Fred. JG, NM and AR designed, while JG, MG, NM, AR, MR performed validation experiments with proton beams at CCB. JG performed data analysis of experiments. KC, NK and MPN supported data analysis. RK provided access to beam model commissioning and validation data from CCB. JG participated in commissioning measurements is CCB. CC and LL provided commissioning, validation and patient data from EMORY. JG implemented beam model for EMORY and performed analysis of validation and patient data. RK and EP provided access to patient data from CCB; KK and MR exported the patient data from clinical TPS. MG and JG performed simulations and analysis of patient data. ASc and VP developed and made substantial improvements in Fred source code required to enable presented studies. MD, IR, ES and FT provided expertise in beam modeling and medical physics. JG prepared all figures. JG and AR drafted the manuscript. AR designed the project and acquired funding. All the authors reviewed and approved the manuscript.

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Widesott, Lamberto et al. (2018). “Improvements in pencil beam scanning proton therapy dose calculation accuracy in brain tumor cases with a commercial

The end-to-end experimental validation of Fred physics models, beam model and CT calibration using heterogeneous CIRS head-and-neck phantom performed in Krakow. Treatment plans of $10 \times 10 \text{cm}^2$ monoenergetic fields at nominal energies 100, 150 and 200 MeV were irradiated with and without RS. The dose distribution downstream from the CIRS phantom was measured using MatriXX detector placed in DigiPhant water phantom (IBA Dosimetry GmbH). For nominal energies 150 and 200 MeV the dose distributions were measured behind half CIRS head in water. For nominal energy 100 MeV proton beam the dose distribution was measured behind 1/6 slice of CIRS head in water-equivalent RW3 slab phantom.

The experimental data are compared to Fred MC simulations and Eclipse TPS calculations performed in the CT scan of the CIRS and water phantoms. The comparison of measured and simulated 3D dose distributions was performed using a 3D GI method. See the GI pass rate results in table 1 and corresponding 1D and 2D dose profiles as well as GI maps in figures 1-6.

Table 1: 3D GI passing rate (%GP) comparing the 3D dose distributions (reference) measured with MatriXX detector behind heterogeneous head phantom to the dose calculated by TPS and Fred MC (evaluation). The notation in form DD/DTA/DCO describes the GI criteria, where DD is the dose difference, DTA is the distance to agreement and DCO is dose cutoff in percent of the maximum dose. RS stands for range shifter.

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<th>%GP (TPS vs MatriXX)</th>
<th>%GP (Fred vs MatriXX)</th>
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<td>1%/1 mm/2% 2%/2 mm/2%</td>
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Figure 1: Comparison of TPS, Fred and MatriXX planes and profiles for 100 MeV without RS.
Figure 2: Comparison of TPS, FRED and MatriXX planes and profiles for 100 MeV with RS
Figure 3: Comparison of TPS, FRED and MatriXX planes and profiles for 150 MeV without RS
Figure 4: Comparison of TPS, FRED and MatriXX planes and profiles for 150 MeV with RS
Figure 5: Comparison of TPS, FRED and MatriXX planes and profiles for 200 MeV without RS
Figure 6: Comparison of TPS, Fred and MatriXX planes and profiles for 200 MeV with RS.