Development of a Treatment Control System for IOeRT FLASH beams

PhD in *Accelerator Physics*, XXXV cycle
Sapienza University of Rome

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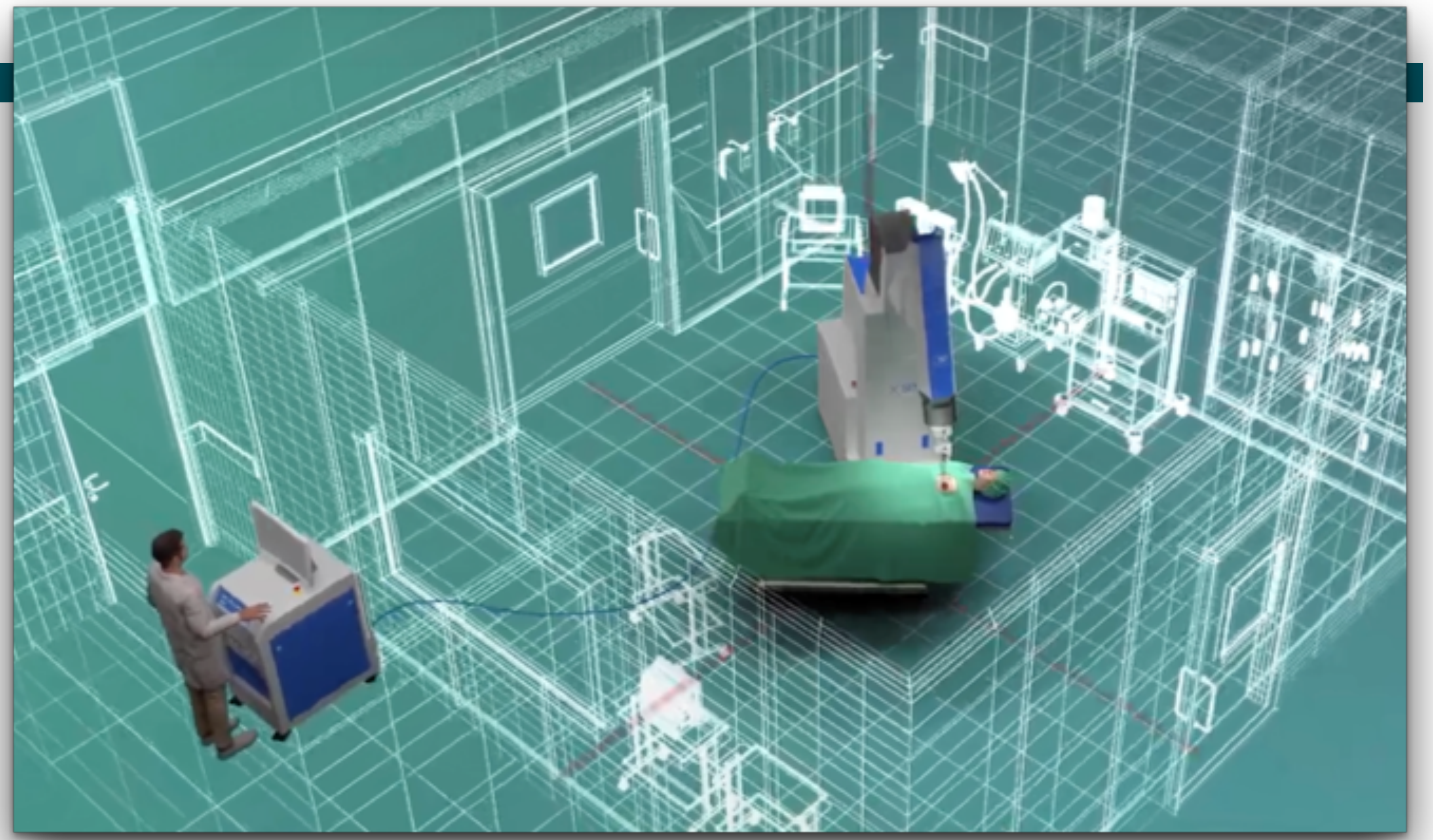
Thesis Advisor: Vincenzo Patera
Co-Advisor: Angelo Schiavi

Rome 18/01/2023

The IOeRT technique



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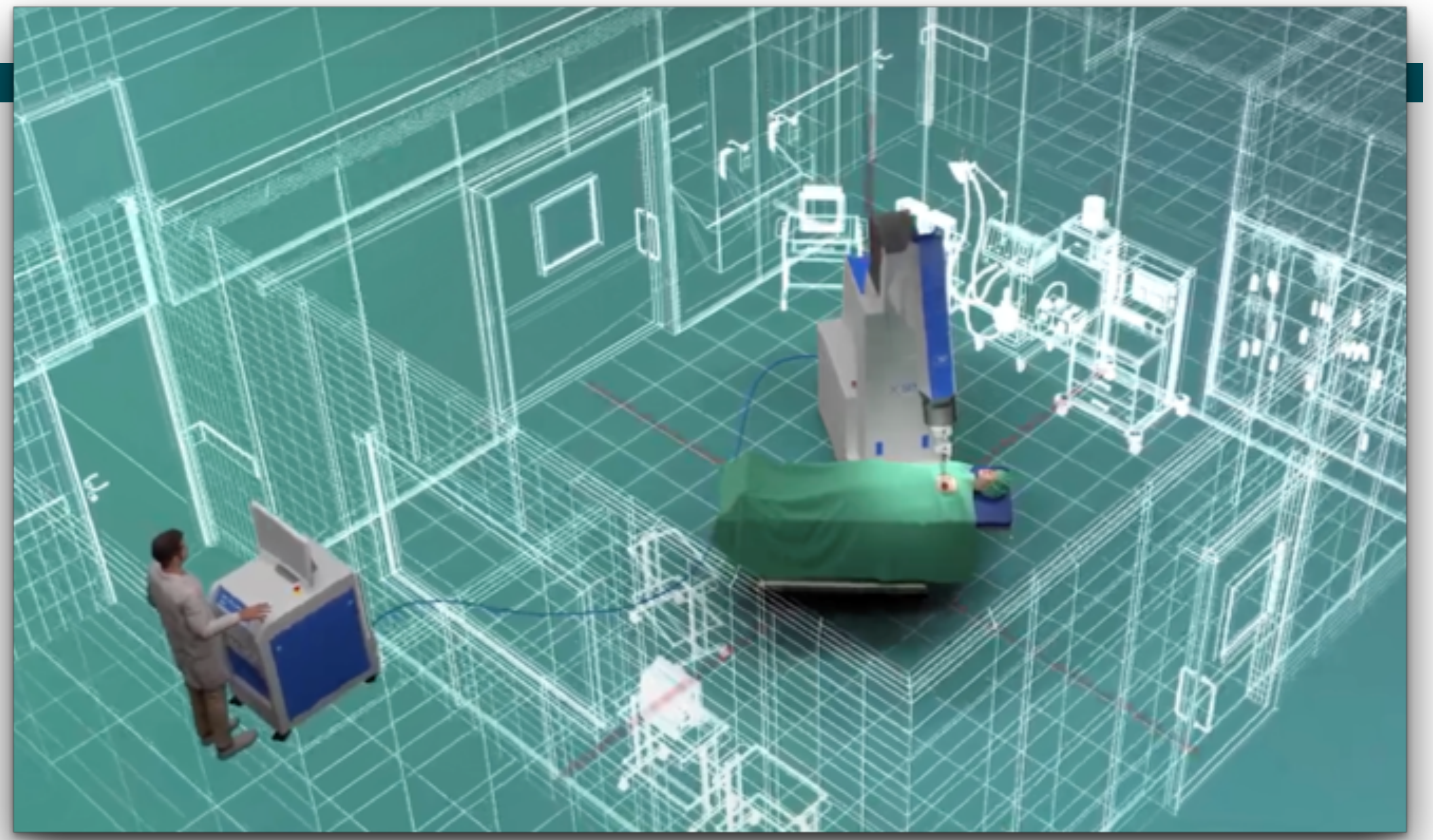

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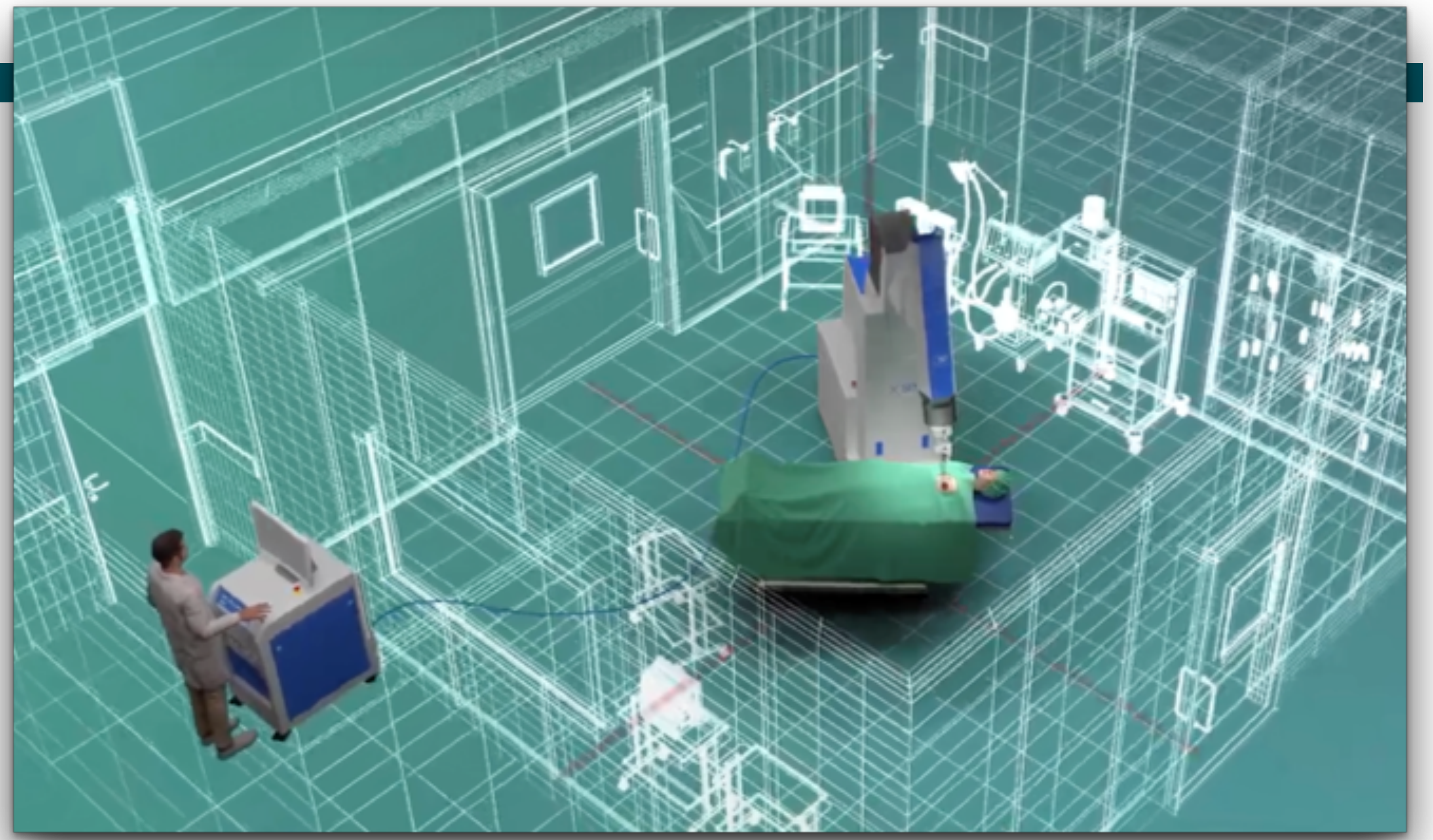

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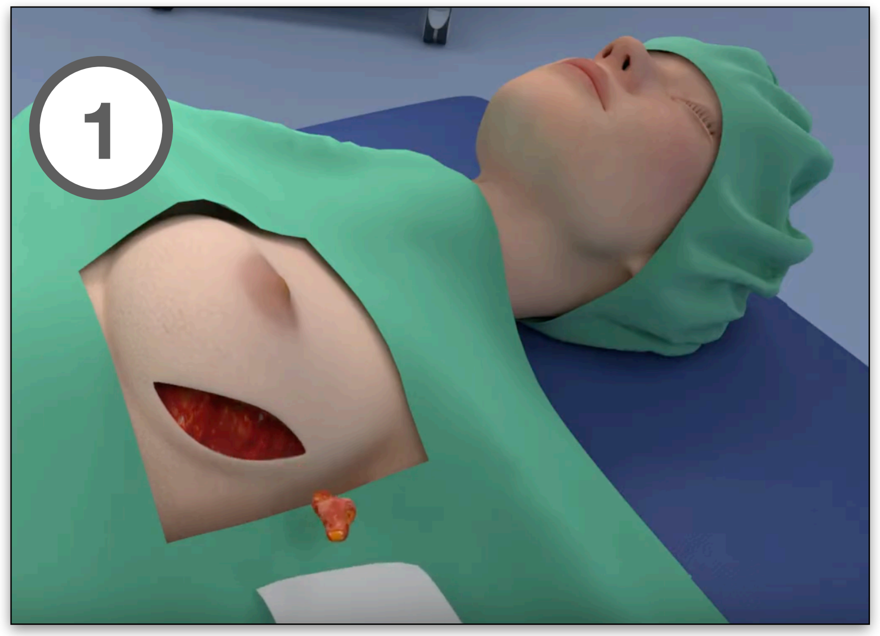

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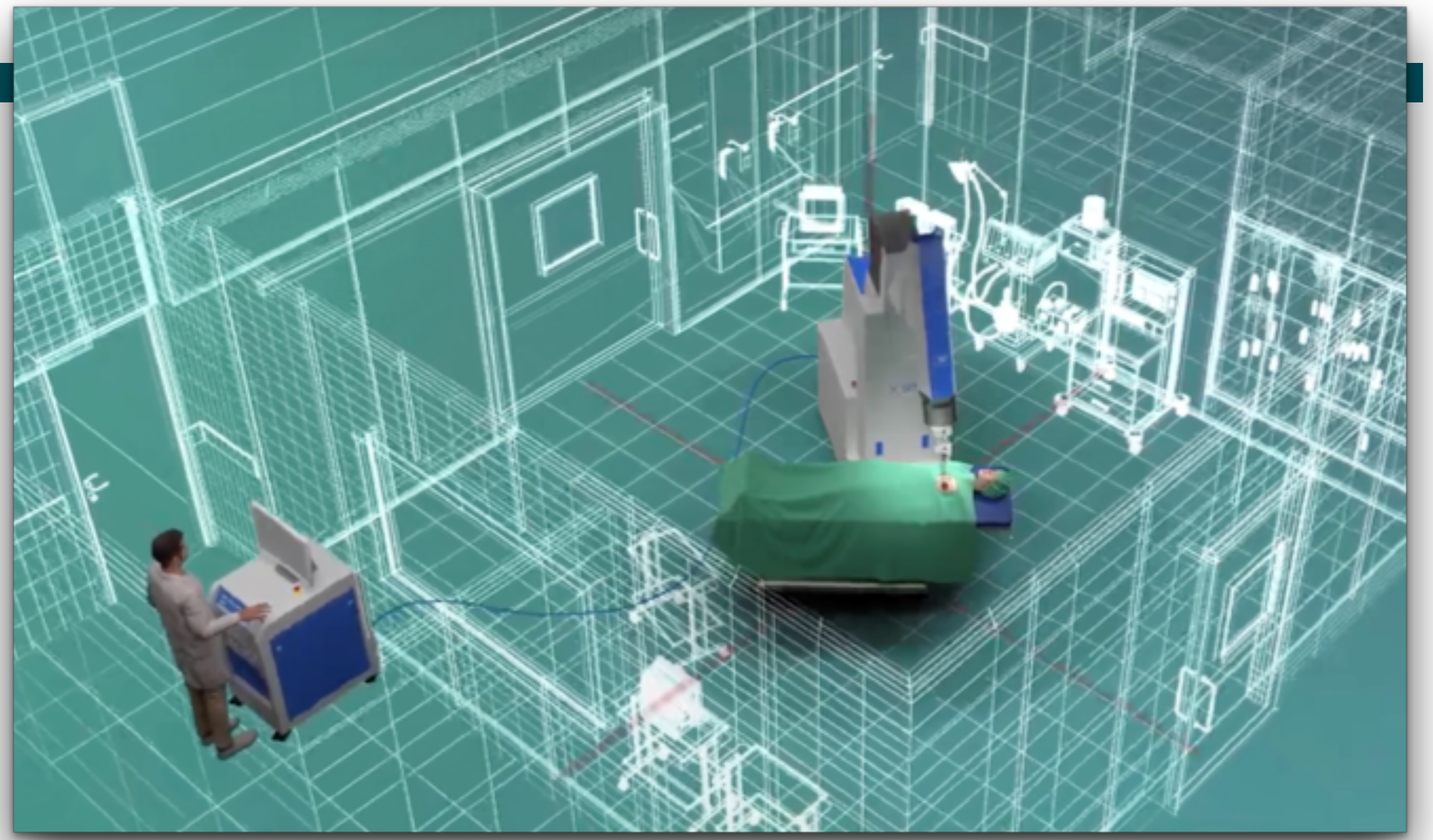

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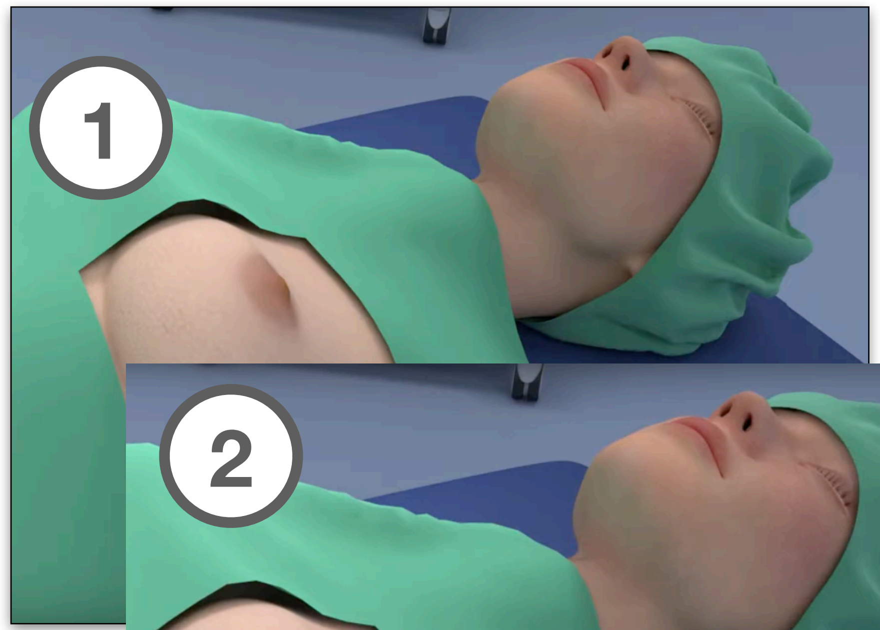

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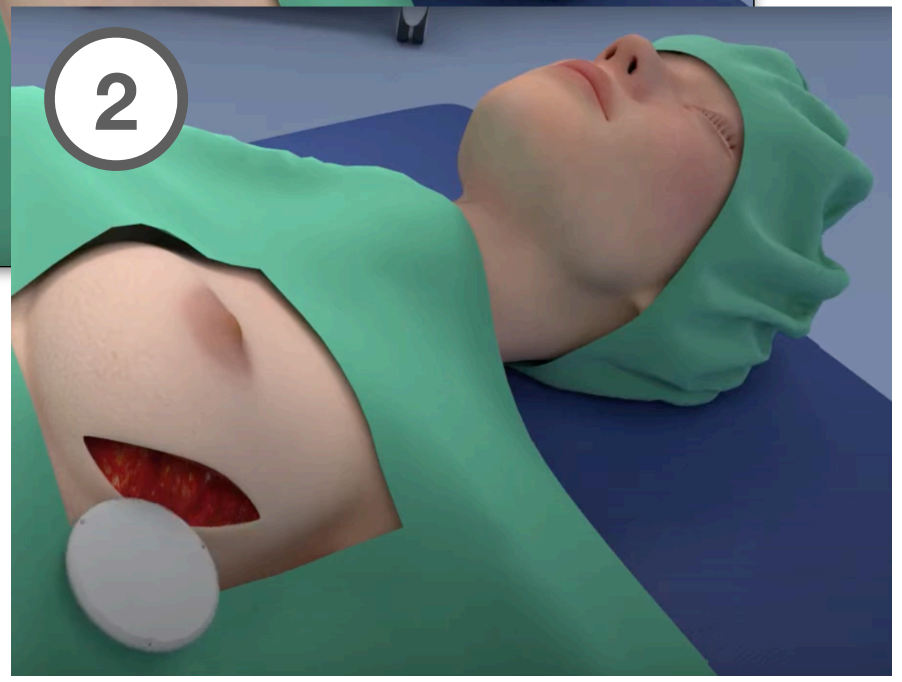

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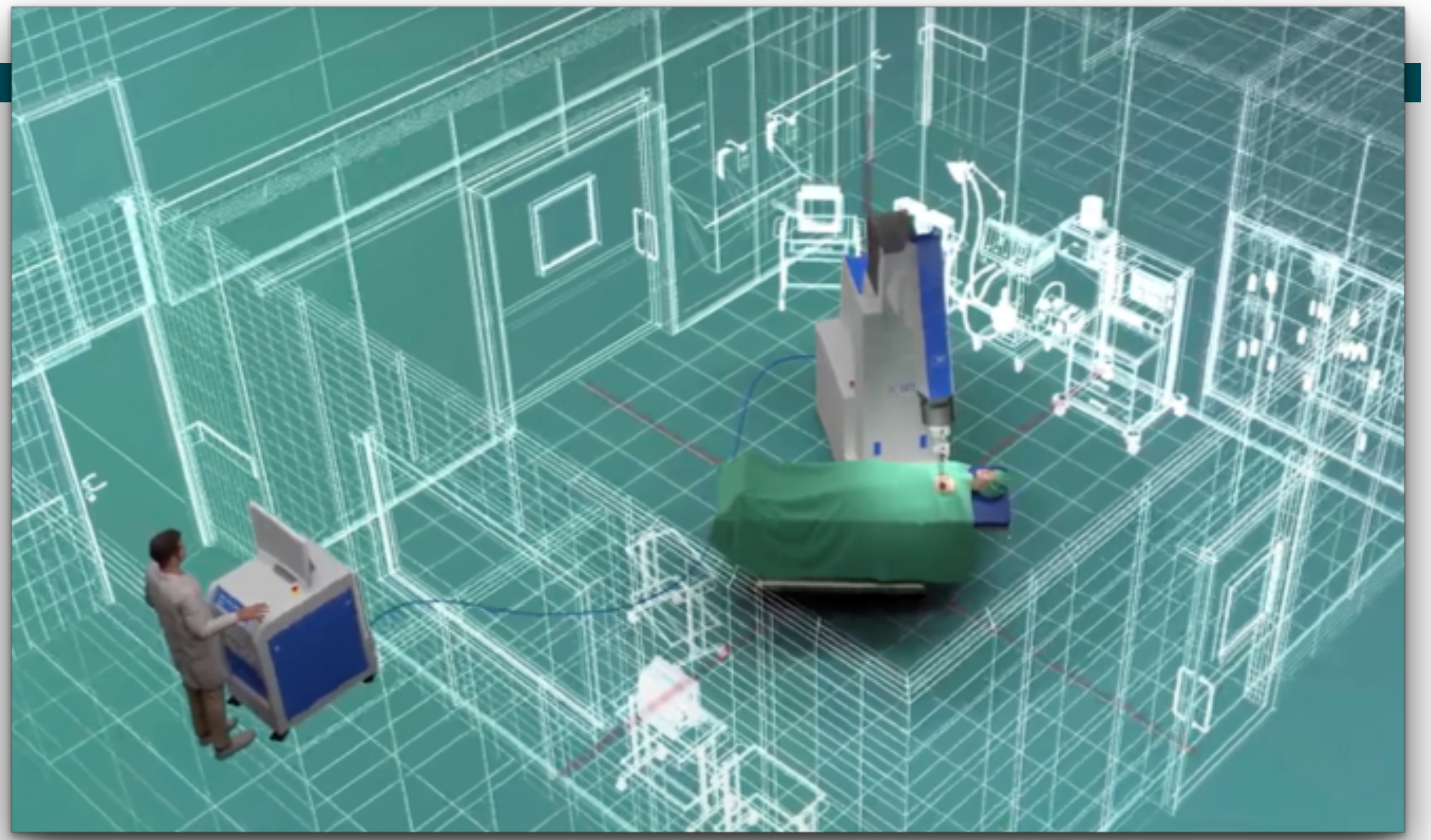

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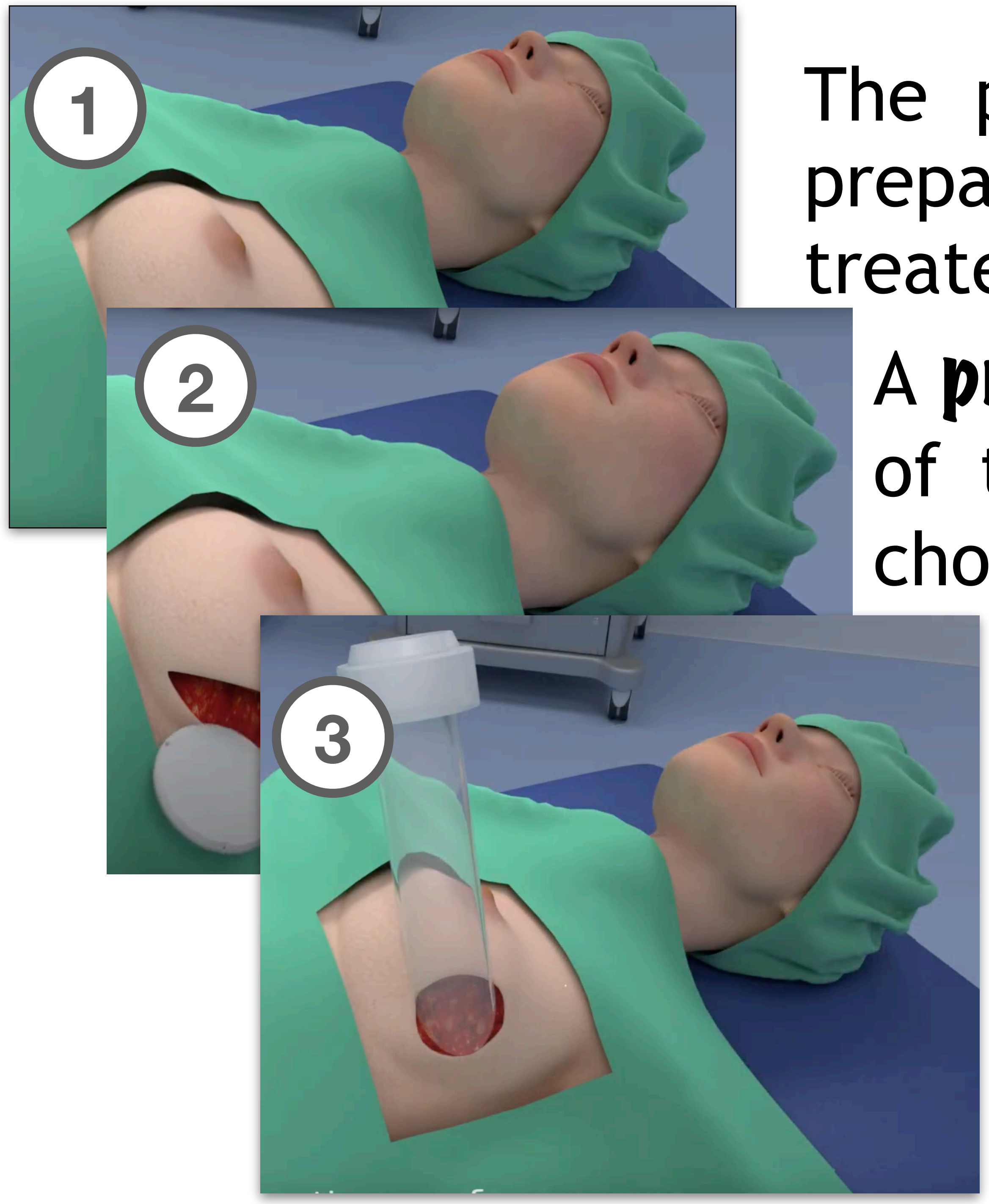

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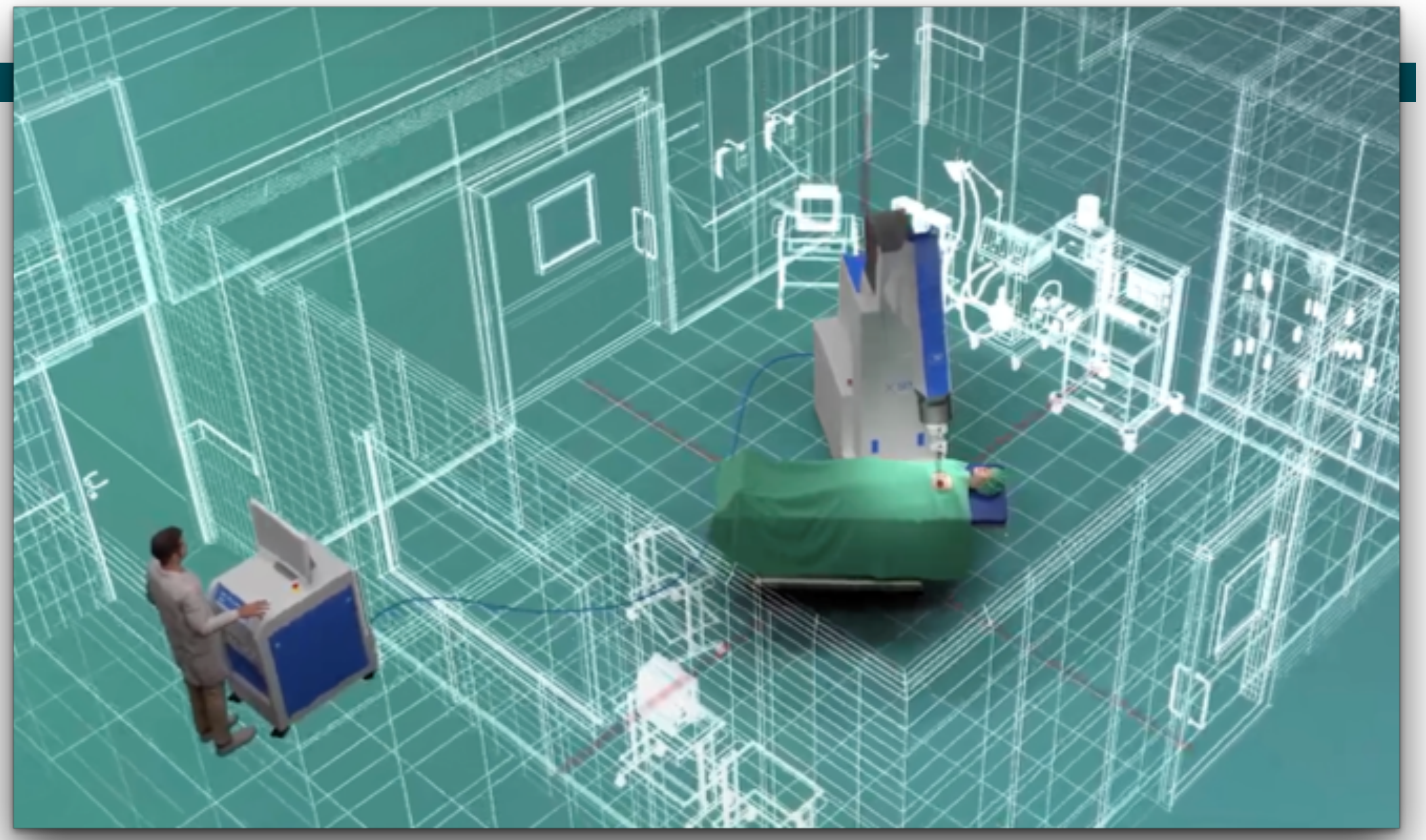

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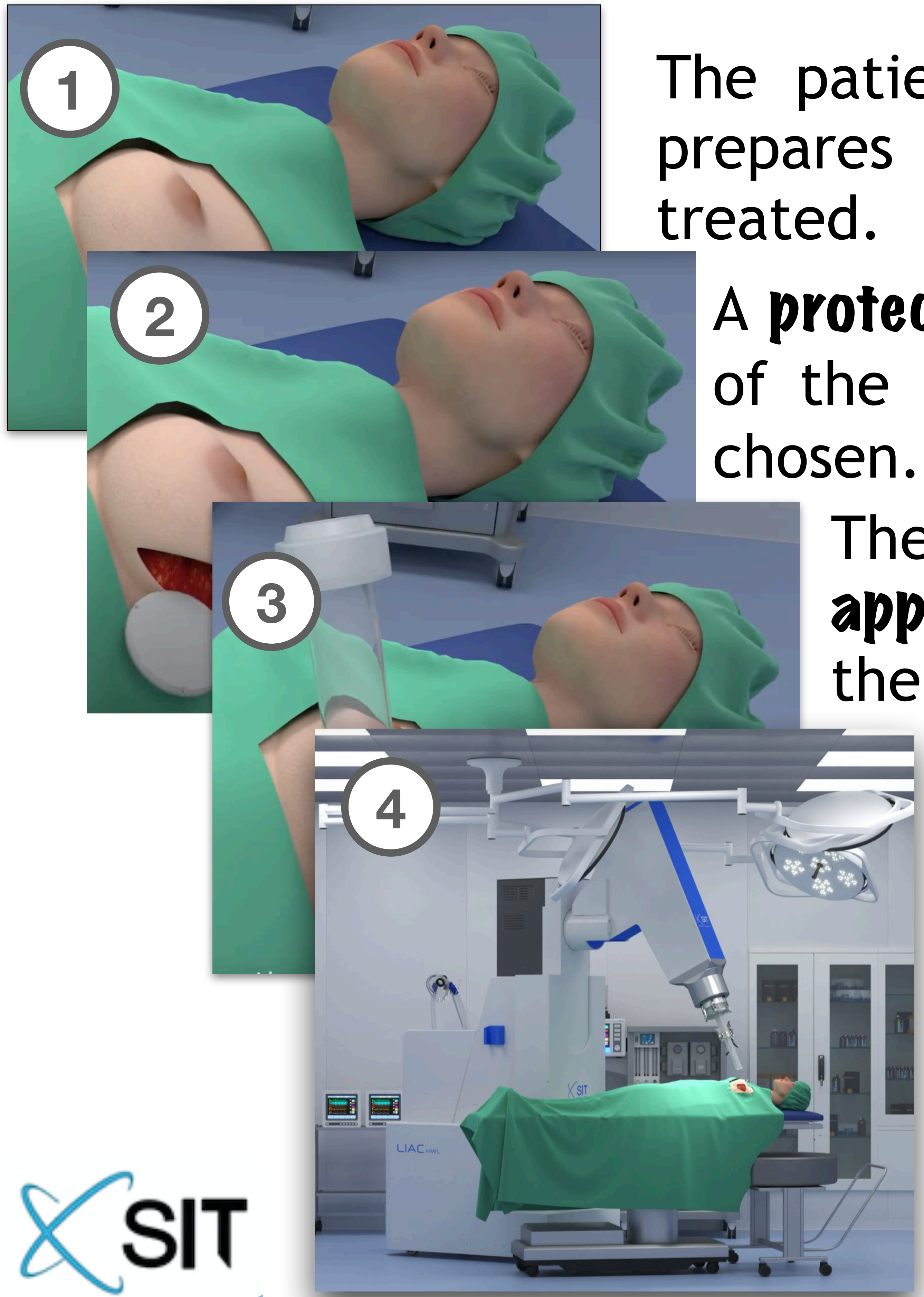

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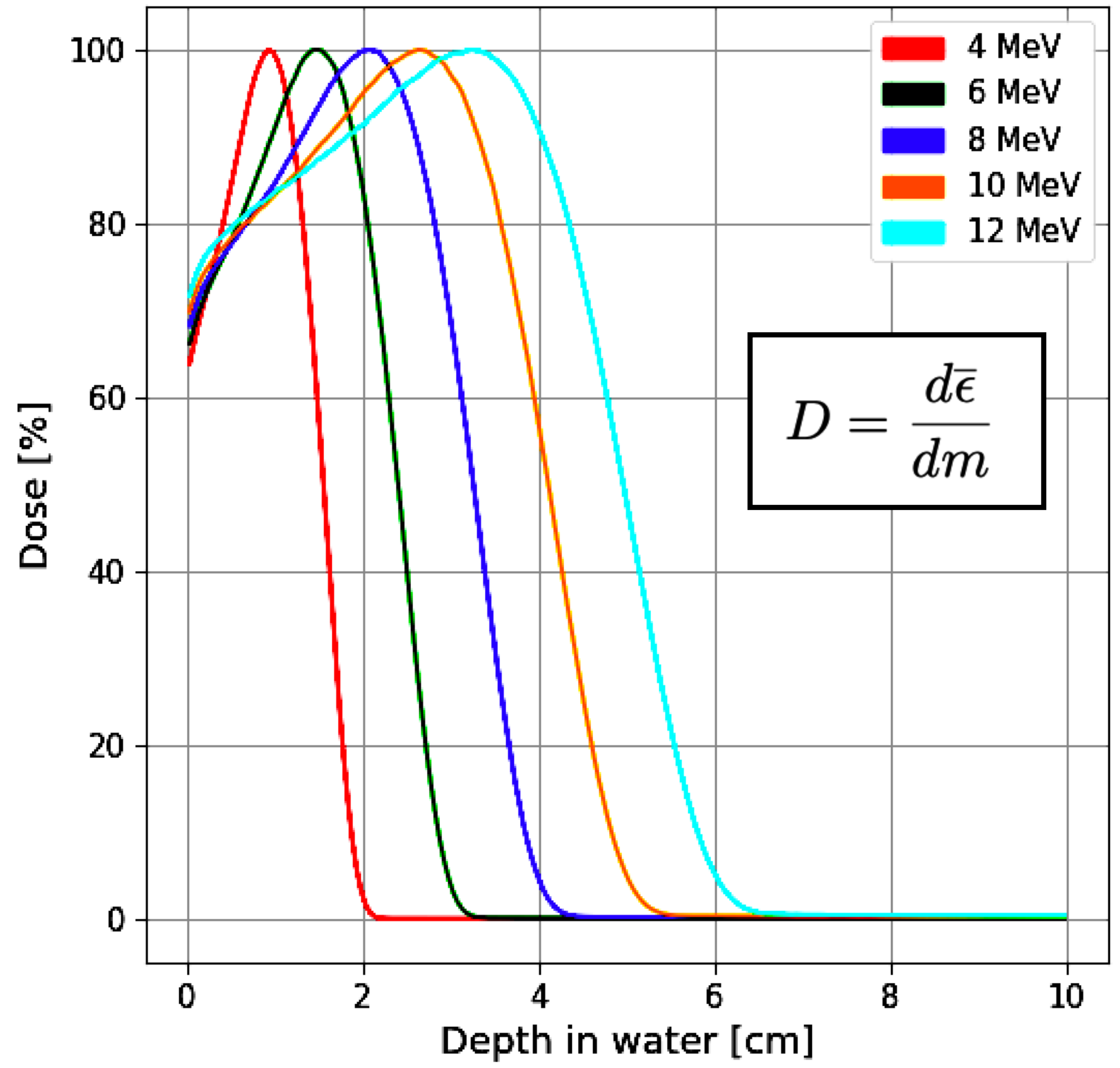
The **dose** is provided by a **uniform electron beam** produced by a miniaturized LINAC accelerator with energy between 4 and 12 MeV.



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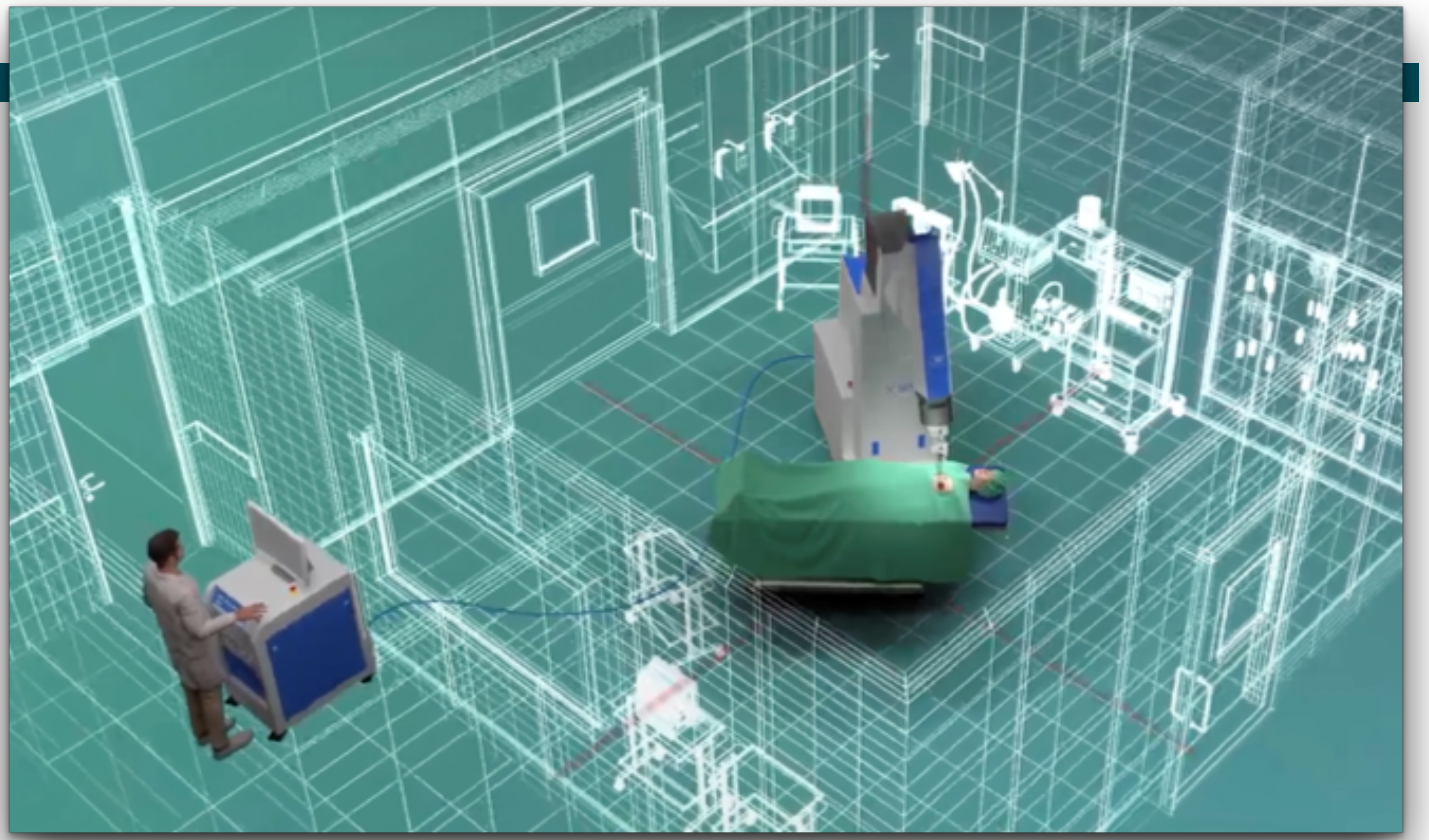

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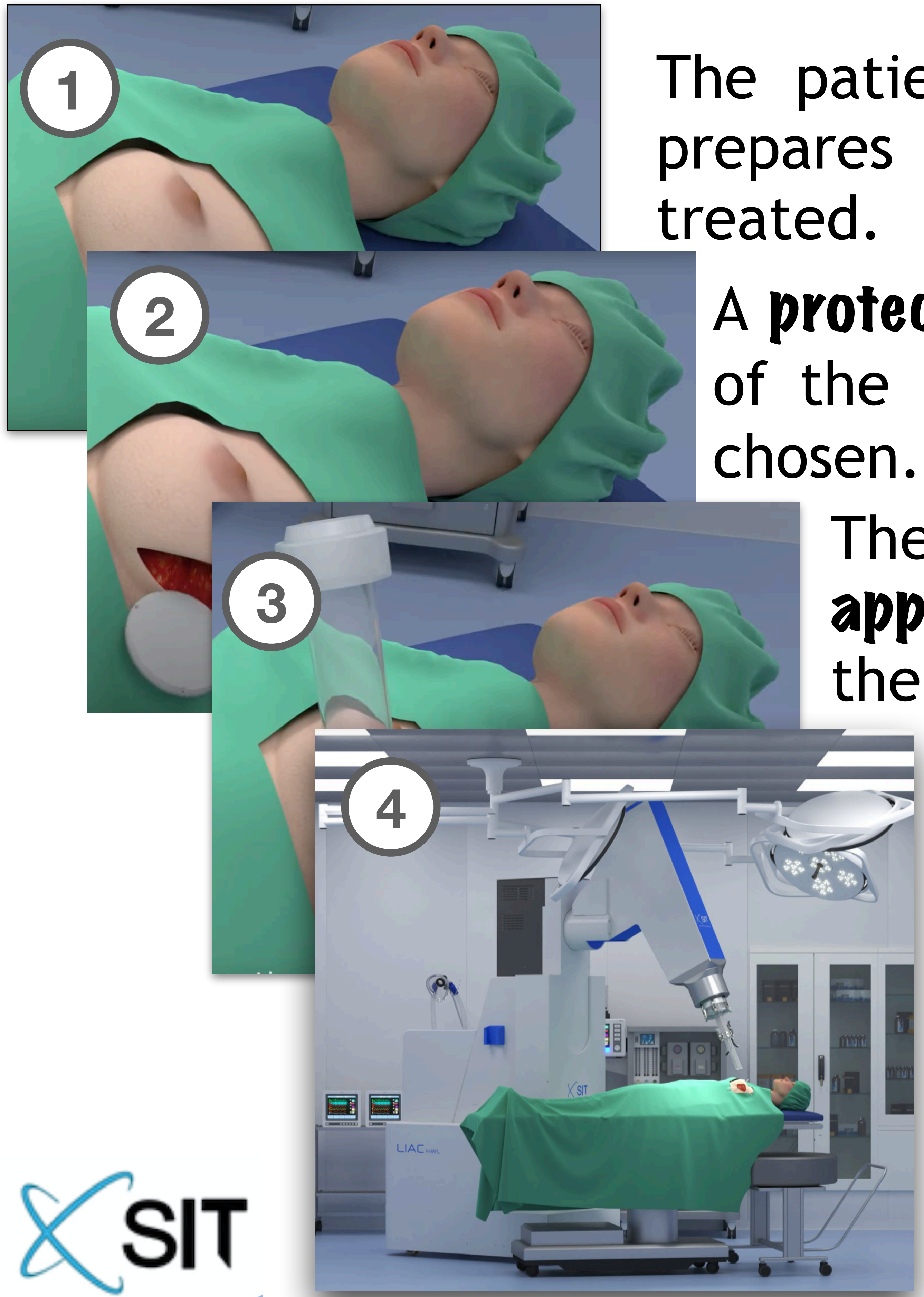

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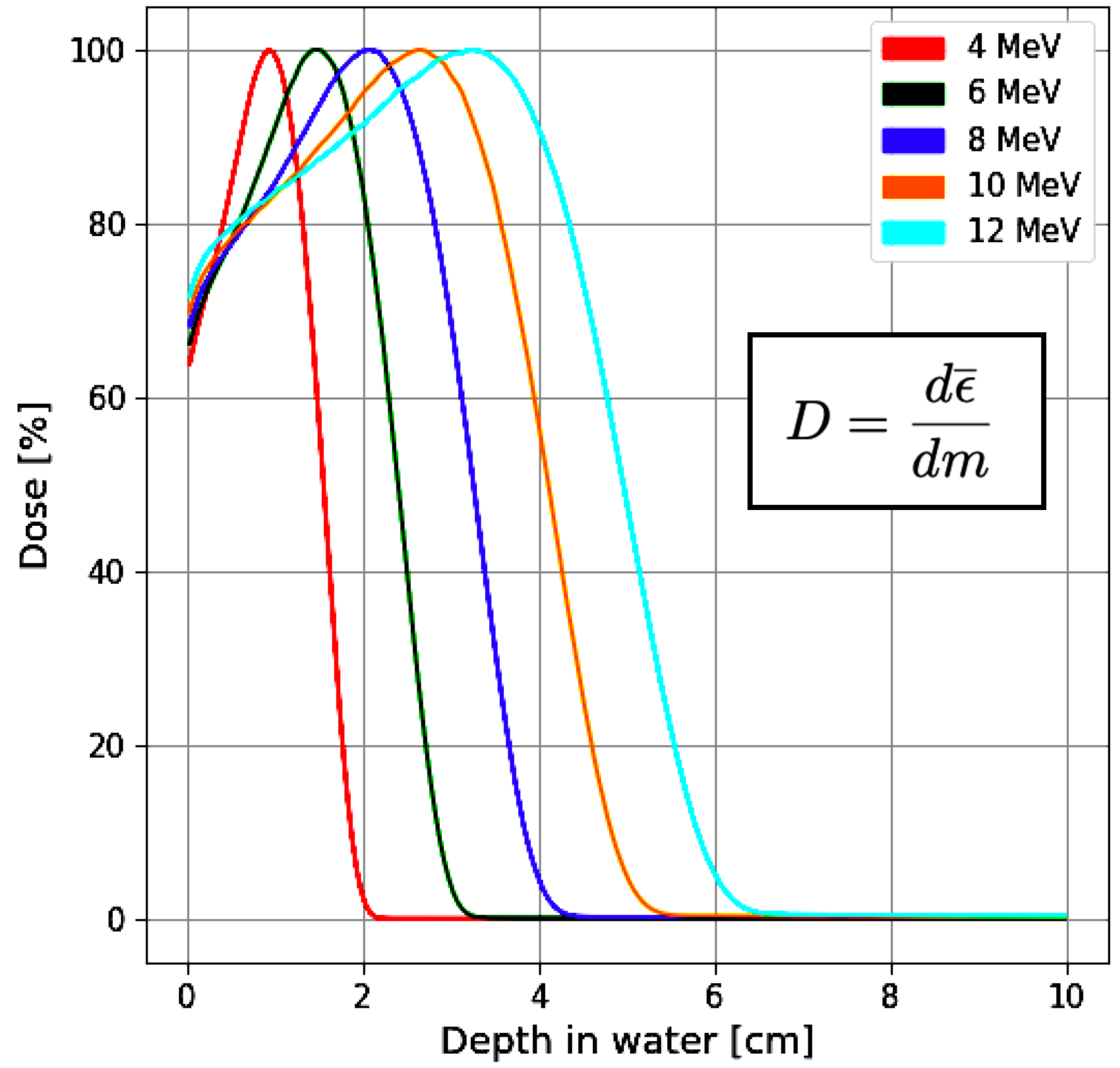
No time to perform a new patient imaging and go through the Treatment Planning System



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Treatment Planning System

The Treatment Planning System (**TPS**) combines the characteristics of the particles at the energies of interest with the accelerator machine parameters to be applied in order to optimize the dose distribution to the patient. In particle therapy it can be analytic or Monte Carlo driven.

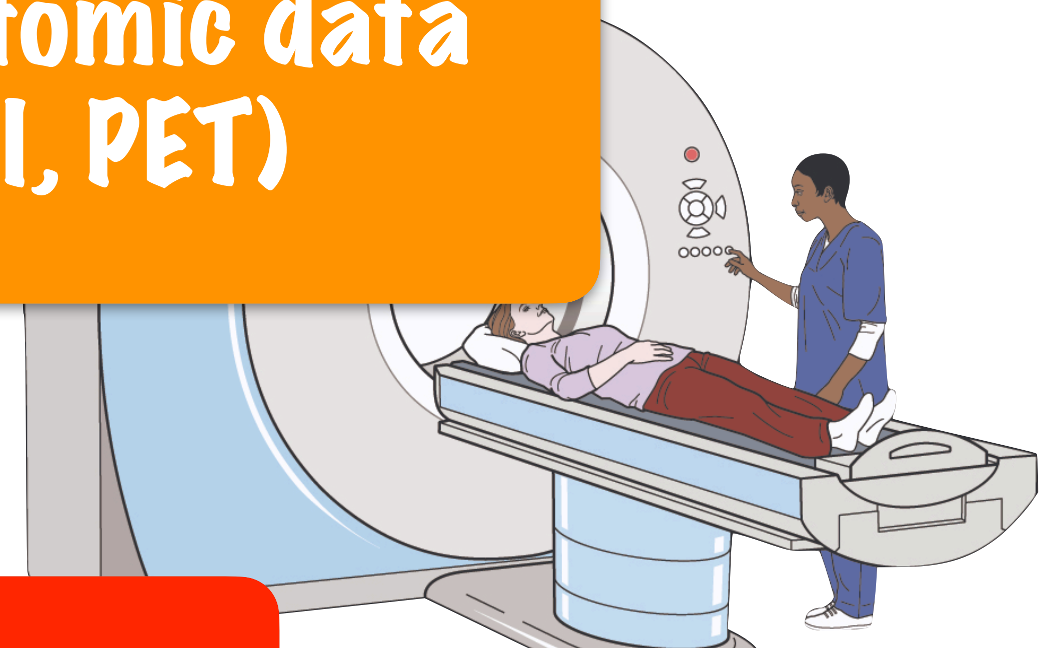
The **TPS** provides information to the beam control system:

- **Position**
- **Intensity**
- **Direction**

(required) Kinetic Energy (MeV)	Stopping Power (MeV cm²/g)			Range		
	Electronic	Nuclear	Total	CSDA (g/cm²)	Projected (g/cm²)	Detour Factor Projected / CSDA
1.000E-03	1.337E+02	4.315E+01	1.769E+02	6.319E-06	2.878E-06	0.4555
1.500E-03	1.638E+02	3.460E+01	1.984E+02	8.969E-06	4.400E-06	0.4906
2.000E-03	1.891E+02	2.927E+01	2.184E+02	1.137E-05	5.909E-06	0.5197
2.500E-03	2.114E+02	2.557E+01	2.370E+02	1.357E-05	7.380E-06	0.5440
3.000E-03	2.316E+02	2.281E+01	2.544E+02	1.560E-05	8.811E-06	0.5647
4.000E-03	2.675E+02	1.894E+01	2.864E+02	1.930E-05	1.155E-05	0.5986
5.000E-03	2.990E+02	1.631E+01	3.153E+02	2.262E-05	1.415E-05	0.6254
6.000E-03	3.276E+02	1.439E+01	3.420E+02	2.567E-05	1.661E-05	0.6473
7.000E-03	3.538E+02	1.292E+01	3.667E+02	2.849E-05	1.896E-05	0.6656
8.000E-03	3.782E+02	1.175E+01	3.900E+02	3.113E-05	2.121E-05	0.6813
9.000E-03	4.012E+02	1.080E+01	4.120E+02	3.363E-05	2.337E-05	0.6950
1.000E-02	4.229E+02	1.000E+01	4.329E+02	3.599E-05	2.545E-05	0.7070
1.250E-02	4.660E+02	8.485E+00	4.745E+02	4.150E-05	3.037E-05	0.7318
1.500E-02	5.036E+02	7.400E+00	5.110E+02	4.657E-05	3.499E-05	0.7514
1.750E-02	5.372E+02	6.581E+00	5.437E+02	5.131E-05	3.938E-05	0.7674
2.000E-02						
2.250E-02						
2.500E-02						
2.750E-02						
3.000E-02						
3.500E-02						
4.000E-02						
4.500E-02						

Table of:
- **dE vs E_{beam}, x, y, z**
- **RBE vs E_{beam}, dE, x, y, z**

Patient anatomic data (CT, MRI, PET)



TPS

Dosimetric Prescription

... interest	Volume	... dose (Gy)	...ve importance
Prostate PTV	100	74.0	1.0
Prostate PTV	5.0	72.0	1.0
Prostate PTV	10.0	76.0	1.0
Rectum	90.0	10.0	0.5
Rectum	50.0	20.0	0.5
Rectum	10.0	30.0	0.5
Bladder	90.0	10.0	0.2
Bladder	50.0	20.0	0.2
Bladder	10.0	30.0	0.2
Femoral heads	90.0	10.0	0.2
Femoral heads	50.0	20.0	0.2
Femoral heads	10.0	40.0	0.2

Accelerators Parameters: Fluences for each beam spot

My Ph.D. thesis challenge

Even if the IOeRT has demonstrated its **great anti-tumor efficacy**, the **outdated planning technology** has slowed down over the time its clinical adaption. The goal of my Ph.D. thesis was to address the technology gap between IOeRT and other radiotherapy techniques, by developing the **first-ever, complete TPS** dedicated to **IOeRT** treatments.

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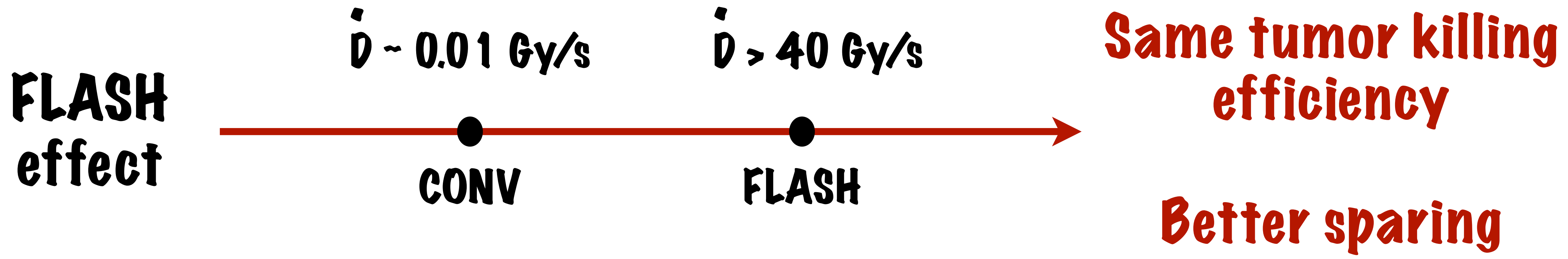
FLASH EFFECT

Toxicity in healthy tissues significantly reduced (from 80% down to 60%), while keeping the same efficacy in cancer killing, if the dose rate is radically increased with respect to conventional treatments!!



DOI: 10.1016/j.radonc.2019.06.019

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How we can do it ?

Since timing is an issue, I needed:

- **Quick imaging** after surgery;
- **Quick and accurate planning tool:** an help for the radio-therapist to choose the position, angle of the applicator and beam energy and # electrons to deliver perceived dose, to ensure a proper OARs sparing

To this aim, I collaborated with the **S.I.T. Sordina IORT Technologies S.p.A.** company

The future TPS operation

The S.I.T. company has solved the problem of providing an **online intra-operative image** by means of the ECHO imaging system, a new **3D real-time ultrasound** imaging acquisition with limited precision (capable of discriminating only large differences in density - air, water, metal)

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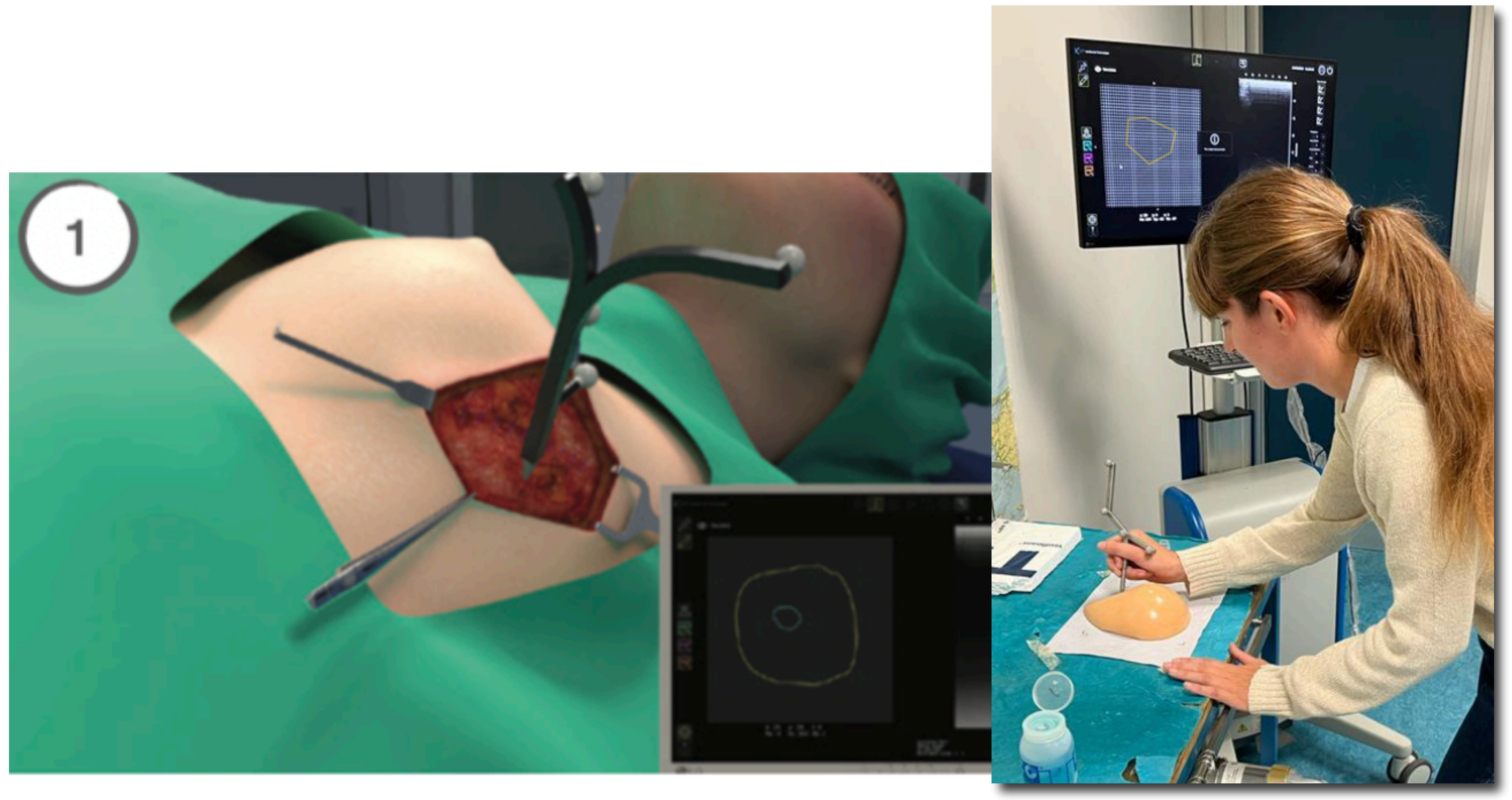

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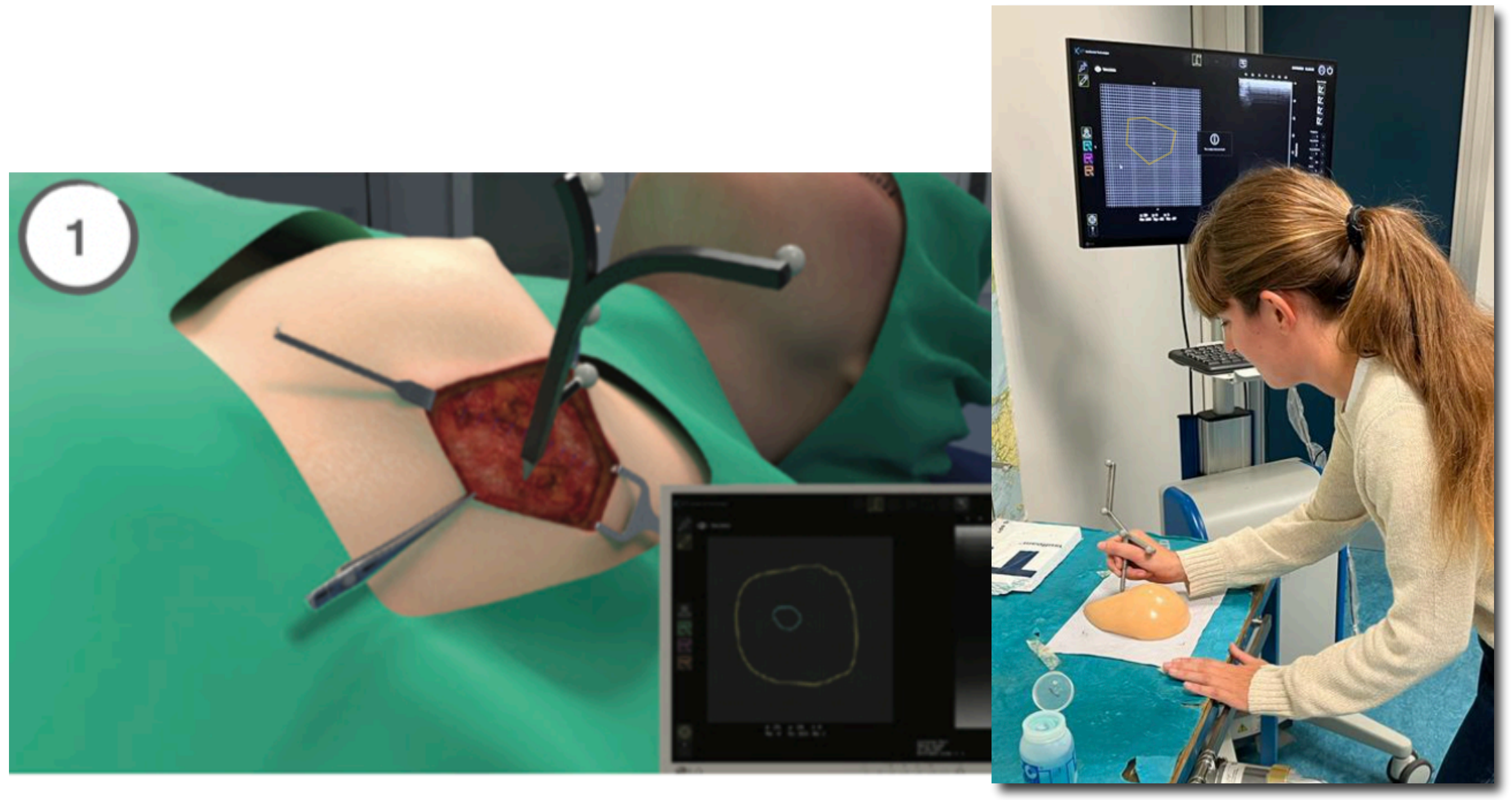

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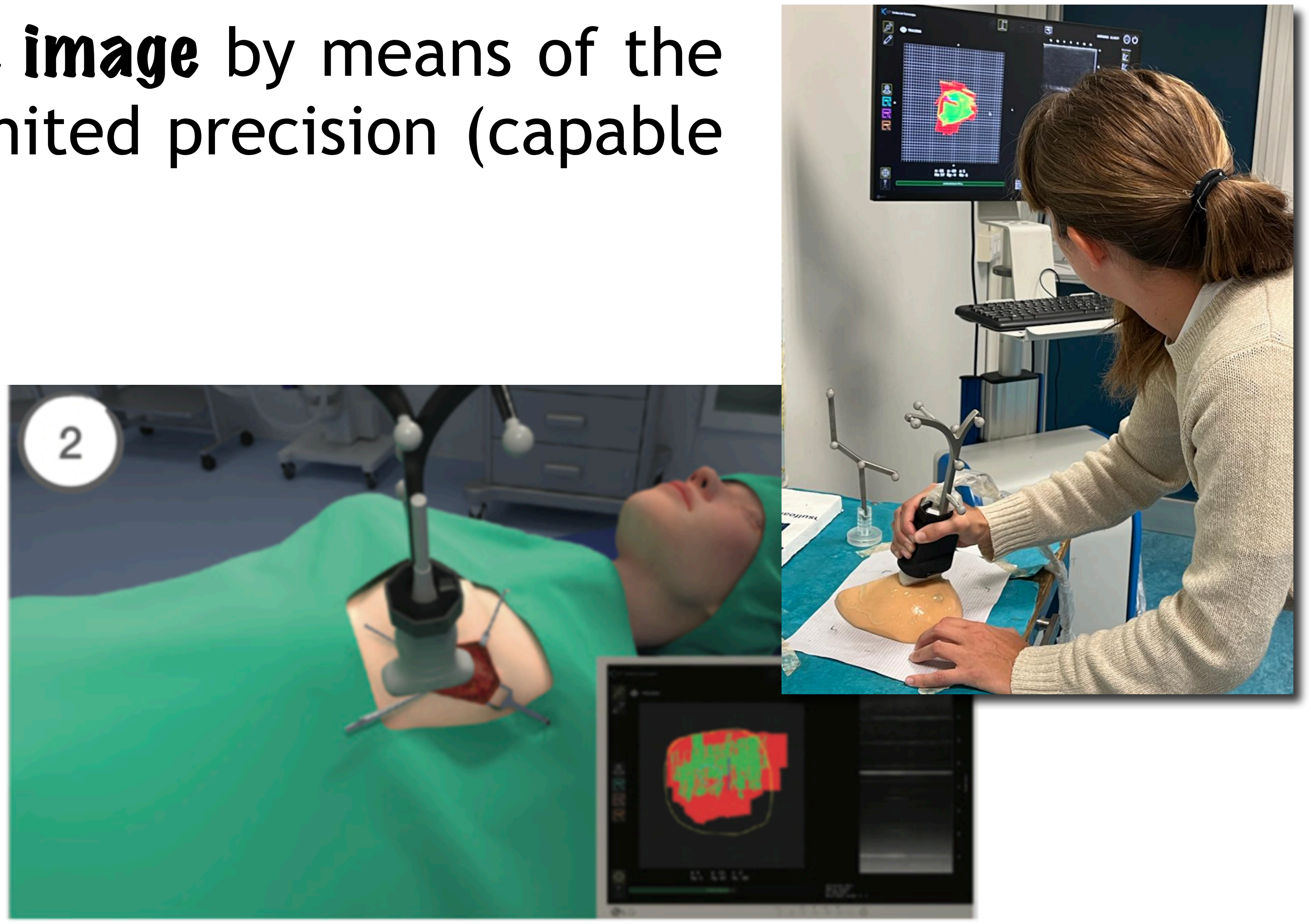

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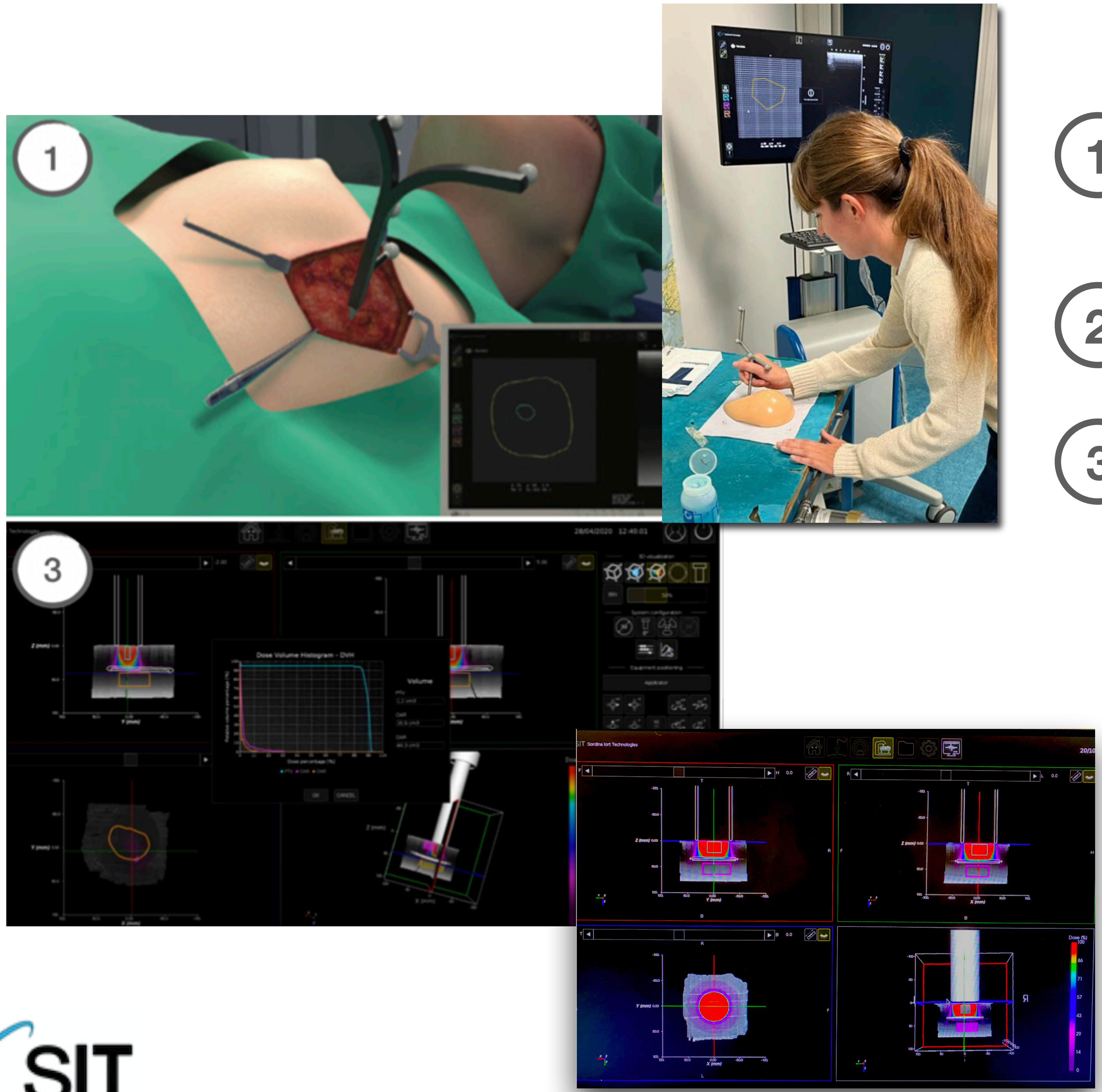

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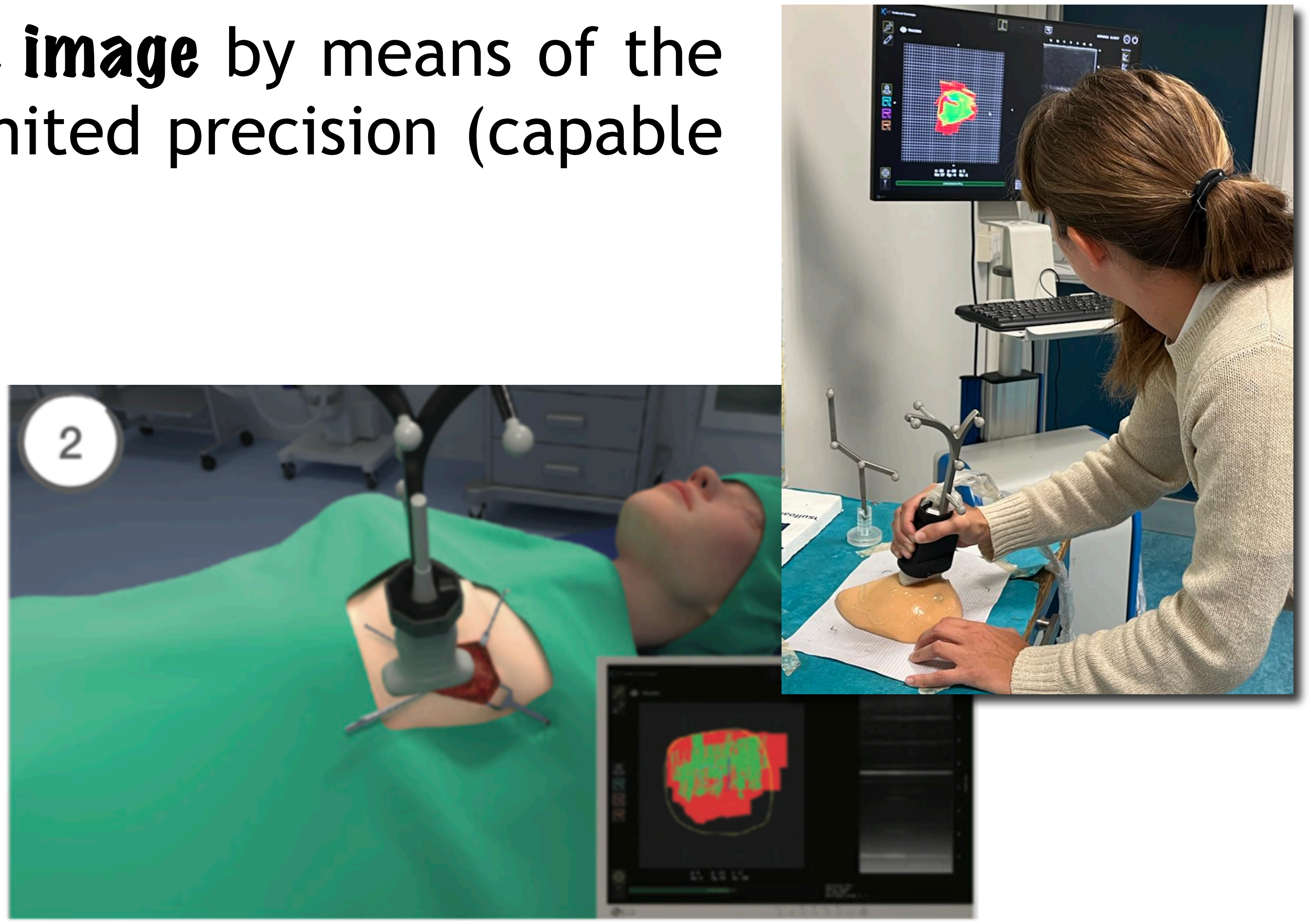

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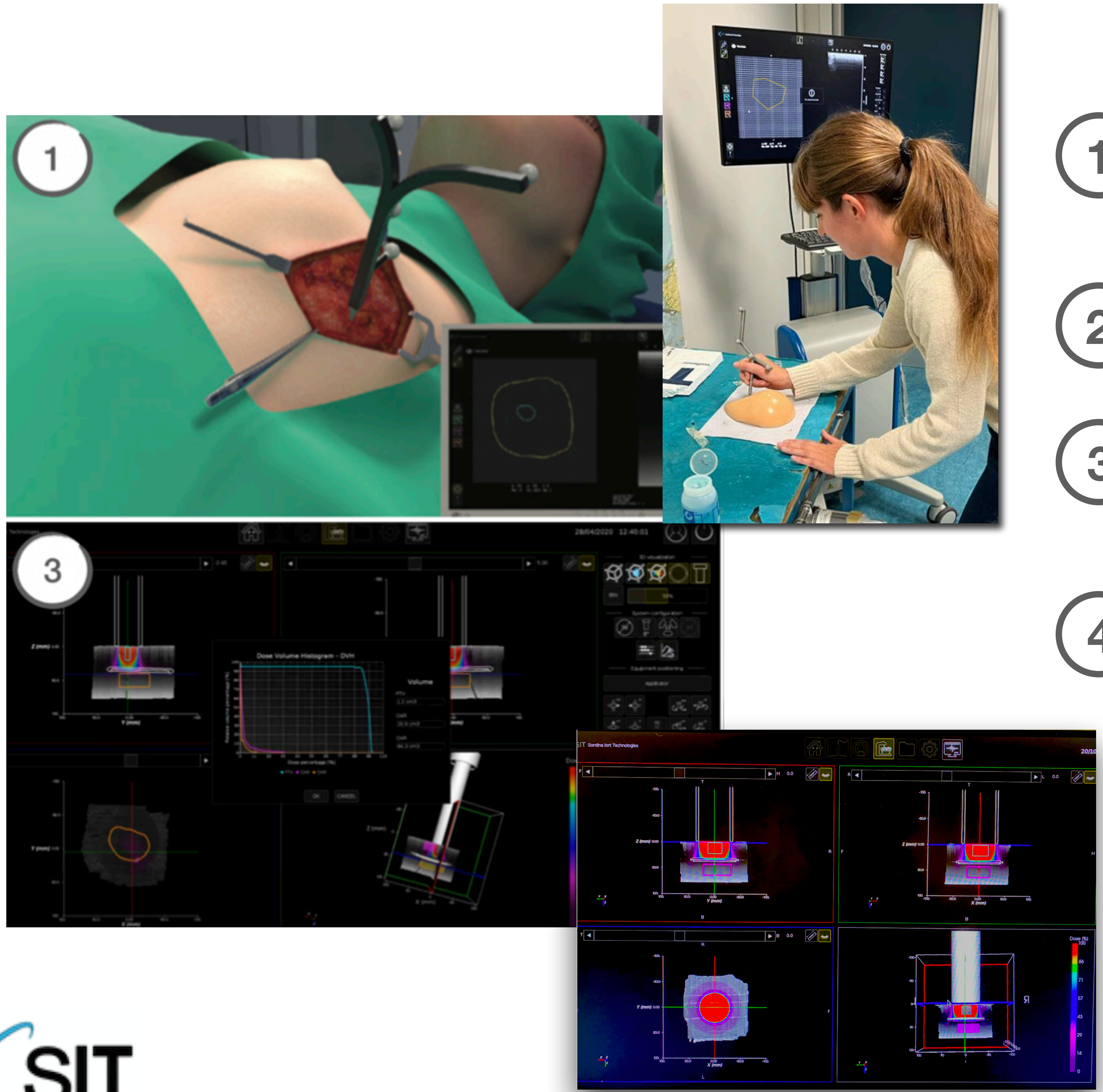

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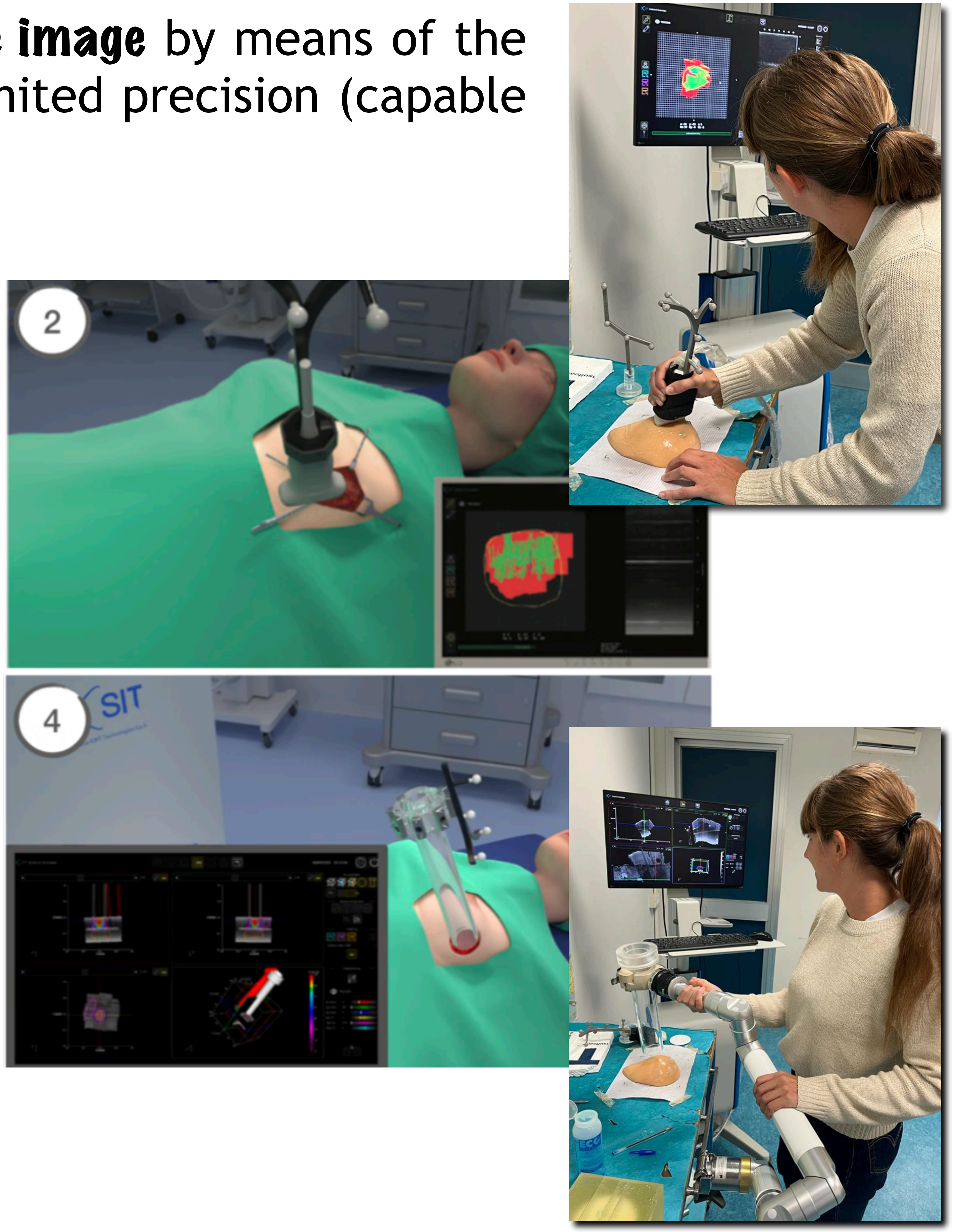

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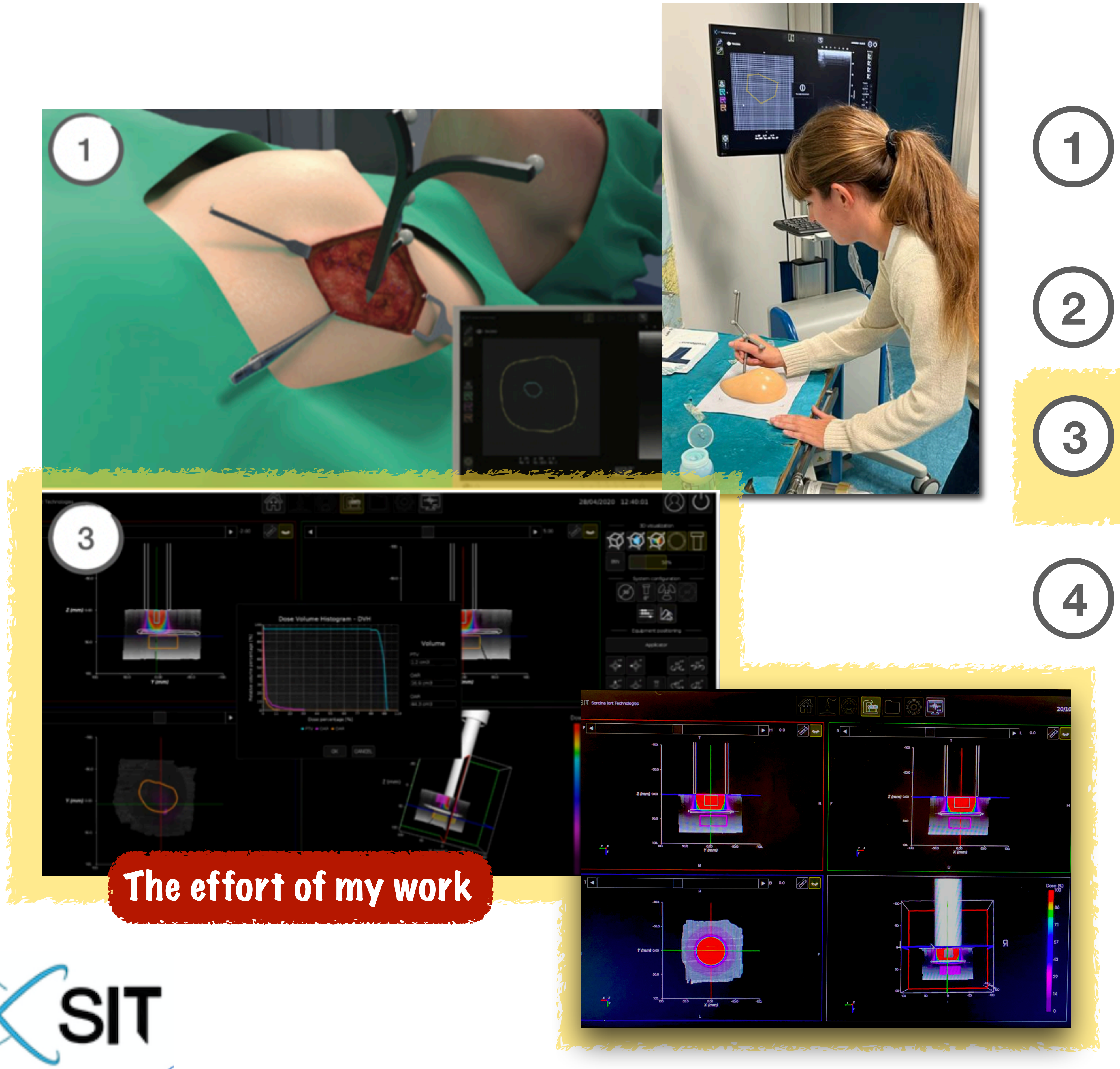

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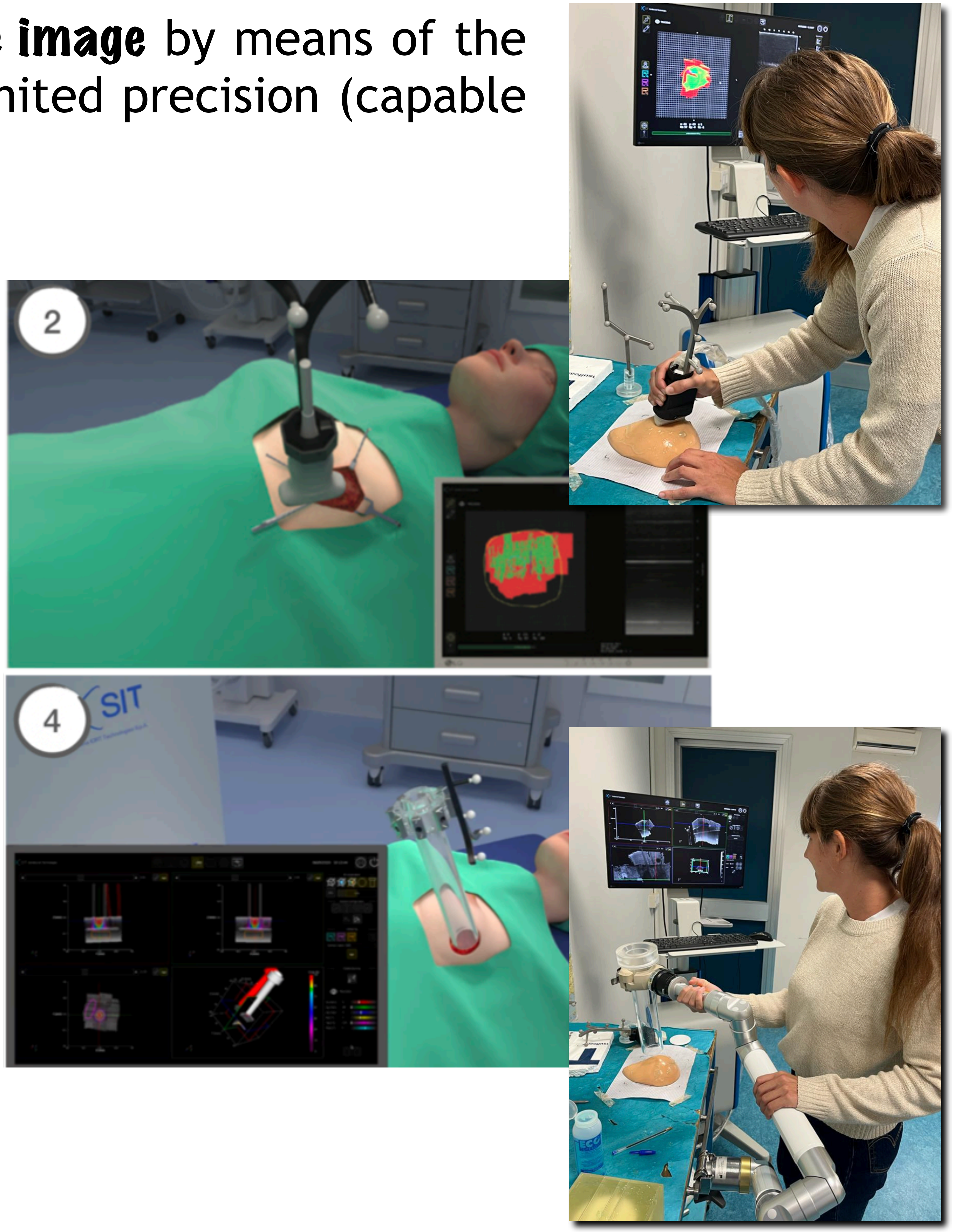

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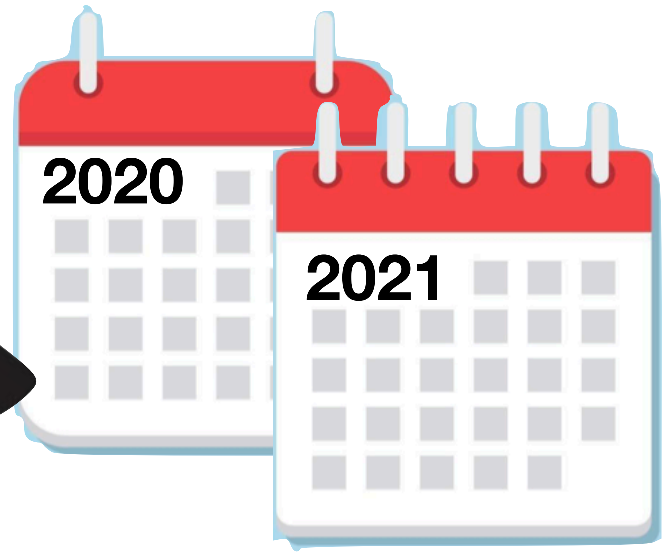
Planning tool: FRED

FRED (Fast paRticle thErapy Dose evaluator) is a fast dose engine based on MC for the transport of particles in heterogeneous media that allows for a quick evaluation of the deposited dose. It has been developed in the context of **Particle Therapy** [4].

FRED has been developed to run on **GPU** (**Graphics Processing Unit**) and reduces the simulation time by a factor of **1000** for proton treatments compared to a standard MC.

For the excellent results achieved with **protons** [4] and **carbon ions** [5] in terms of **tracking performance** and **dose accuracy**, we decided to develop the **electromagnetic** FRED model [6] to extend the use of this MC-on-GPU-based dose engine to other radiotherapy techniques where the **time-factor is crucial**, i.e. the **IOeRT**.

My Ph.D. work thus includes both the complete **development** and test of the FRED electromagnetic model and its first **clinical application** in the context of **IOeRT**.



[4] A. Schiavi et al. "FRED: a GPU-accelerated fast-Monte Carlo code for rapid treatment plan recalculation in ion beam therapy" DOI:10.1088/1361-6560/aa8134
[5] M. De Simoni et al. "A Data-Driven Fragmentation Model for Carbon Therapy GPU-Accelerated Monte- Carlo Dose Recalculation" DOI: 10.3389/fonc.2022.780784
[6] G. Franciosini et al. "GPU-accelerated Monte Carlo simulation of electron and photon interactions for radiotherapy applications" DOI 10.1088/1361-6560/aca1f2

Electromagnetic FRED model

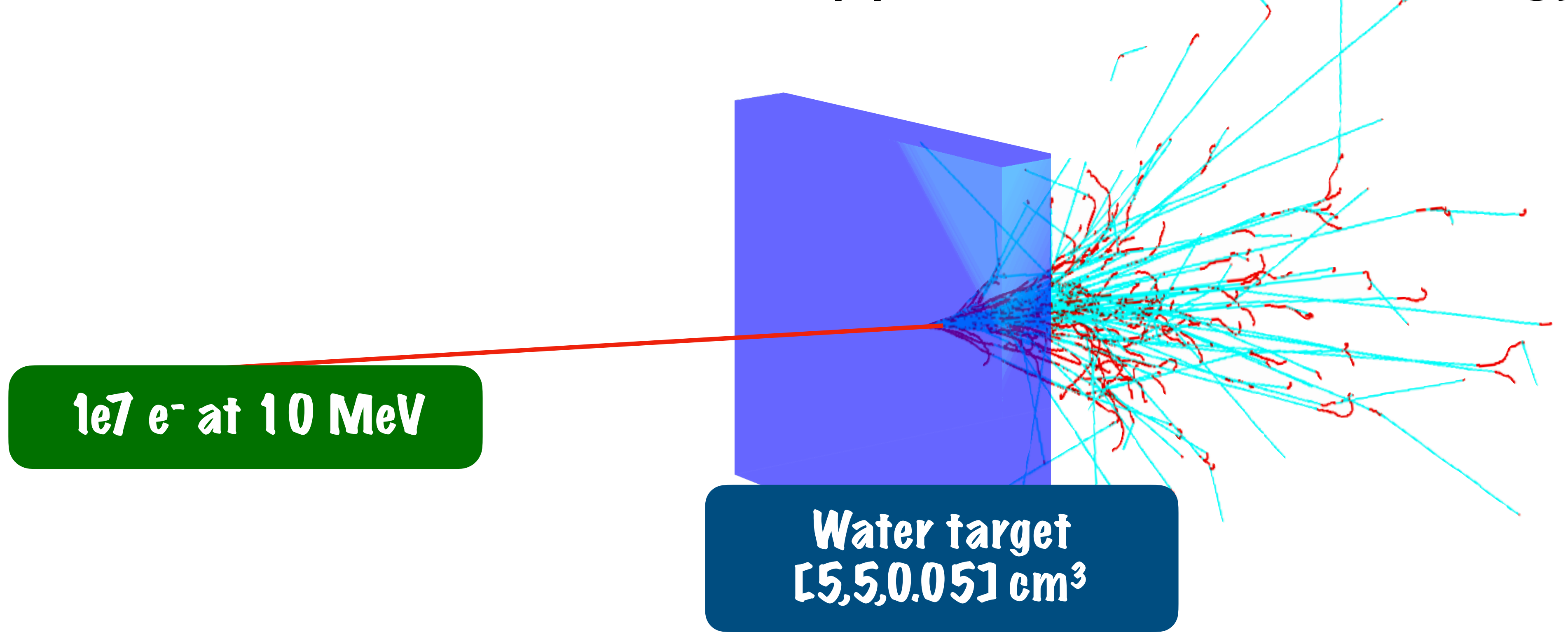
The first step was the implementation of all the electromagnetic processes relevant for medical application in the energy range of 1-200 MeV (from IOeRT to Very High Energy Electron treatments).

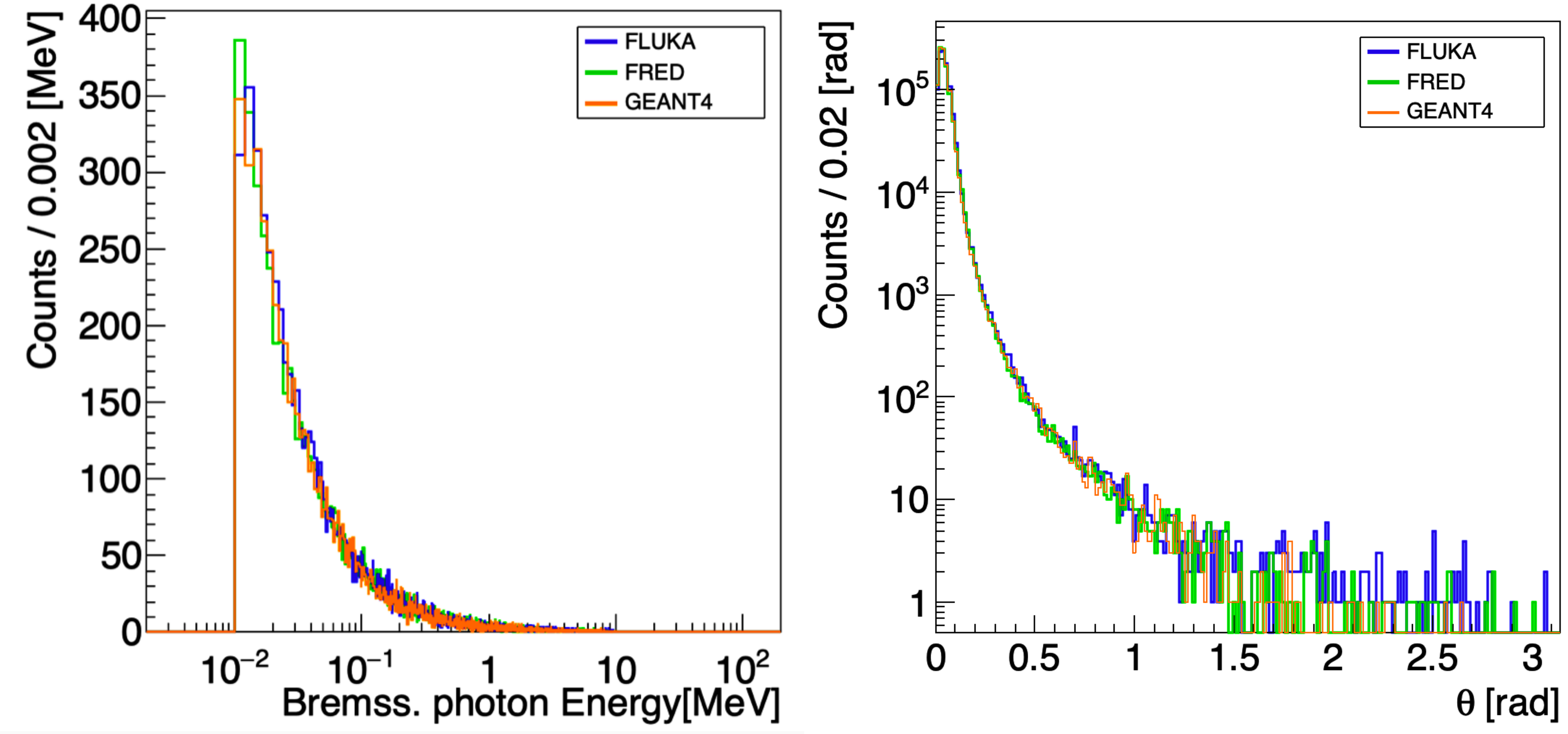
Continuous processes ($e^- e^+$):

- **dE/dx** from NIST eSTAR database + **straggling** (GEANT4)
- **Multiple scattering** (doi: 10.1118/1596230).

Discrete interactions (e^-, e^+, γ):

- **Bremsstrahlung** (Custom code with dσ/dk from doi:10.1016/0092-640X(86)90014-8)
- **Moller/Bhabha** scattering (GEANT4)
- **Coherent scattering** (custom code with XCOM NIST database)
- **Photoelectric** (custom code with XCOM NIST database)
- **Compton** (custom code with XCOM NIST database)
- **Pair production** (XCOM NIST database and GEANT4)
- **Positron annihilation** at rest/ in flight (GEANT4)

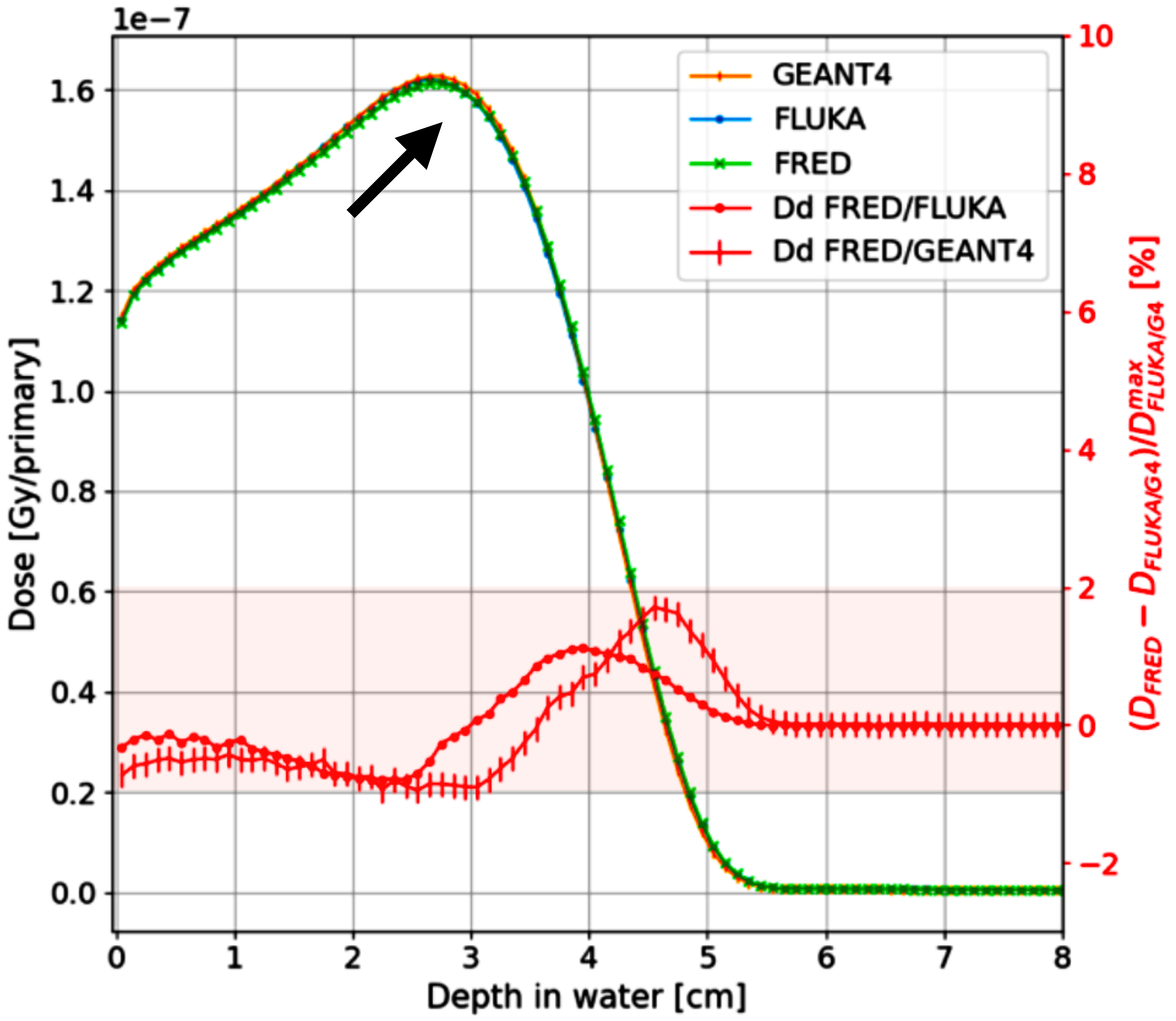


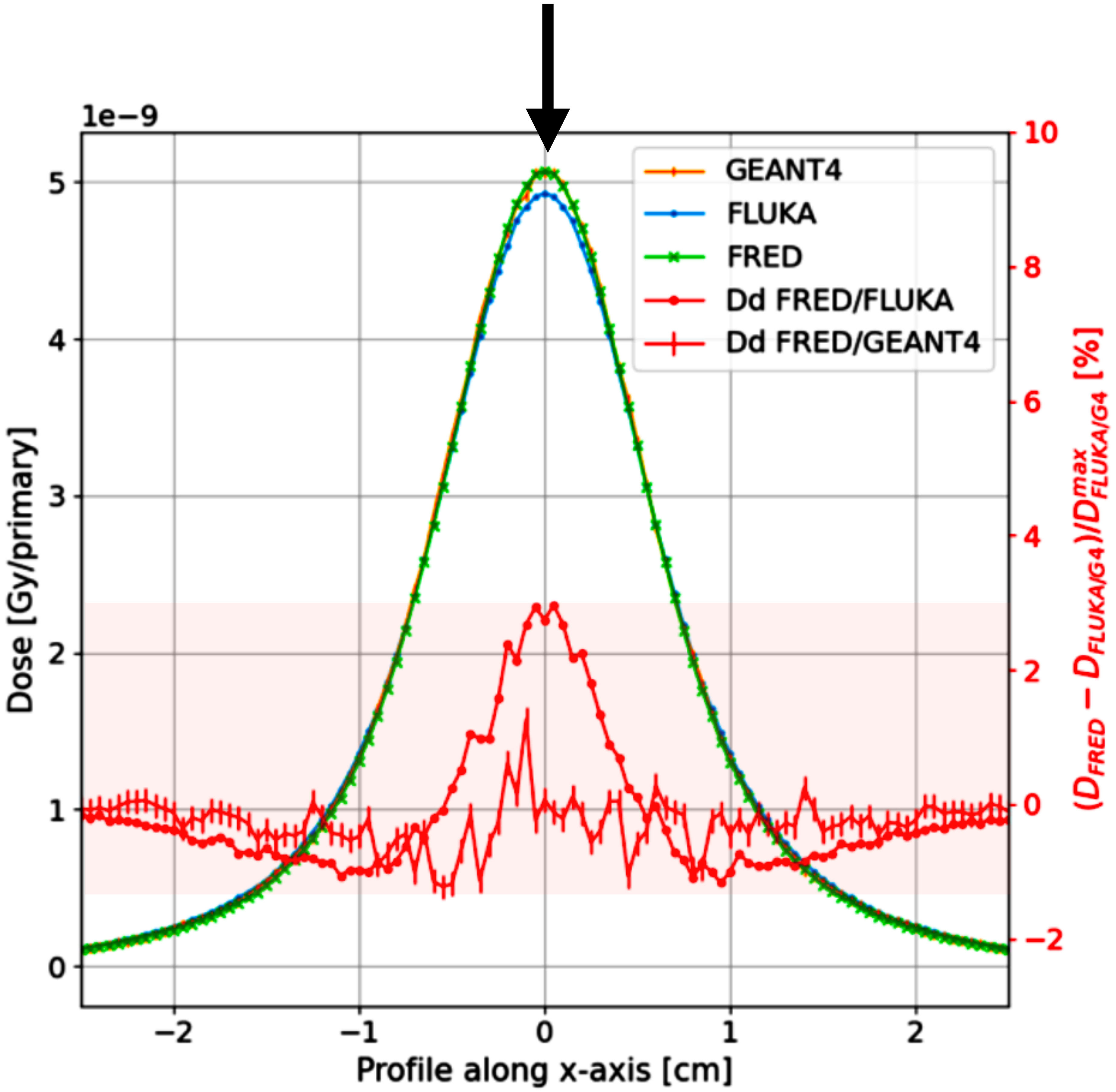


Efficiency and timing performance

Then the **FRED** accuracy and timing performance were tested against state-of-art full MCs, such as **FLUKA** and **GEANT4**, in homogenous and heterogenous phantom and against experimental data (IOeRT LINAC) .

10 MeV e⁻ on water phantom





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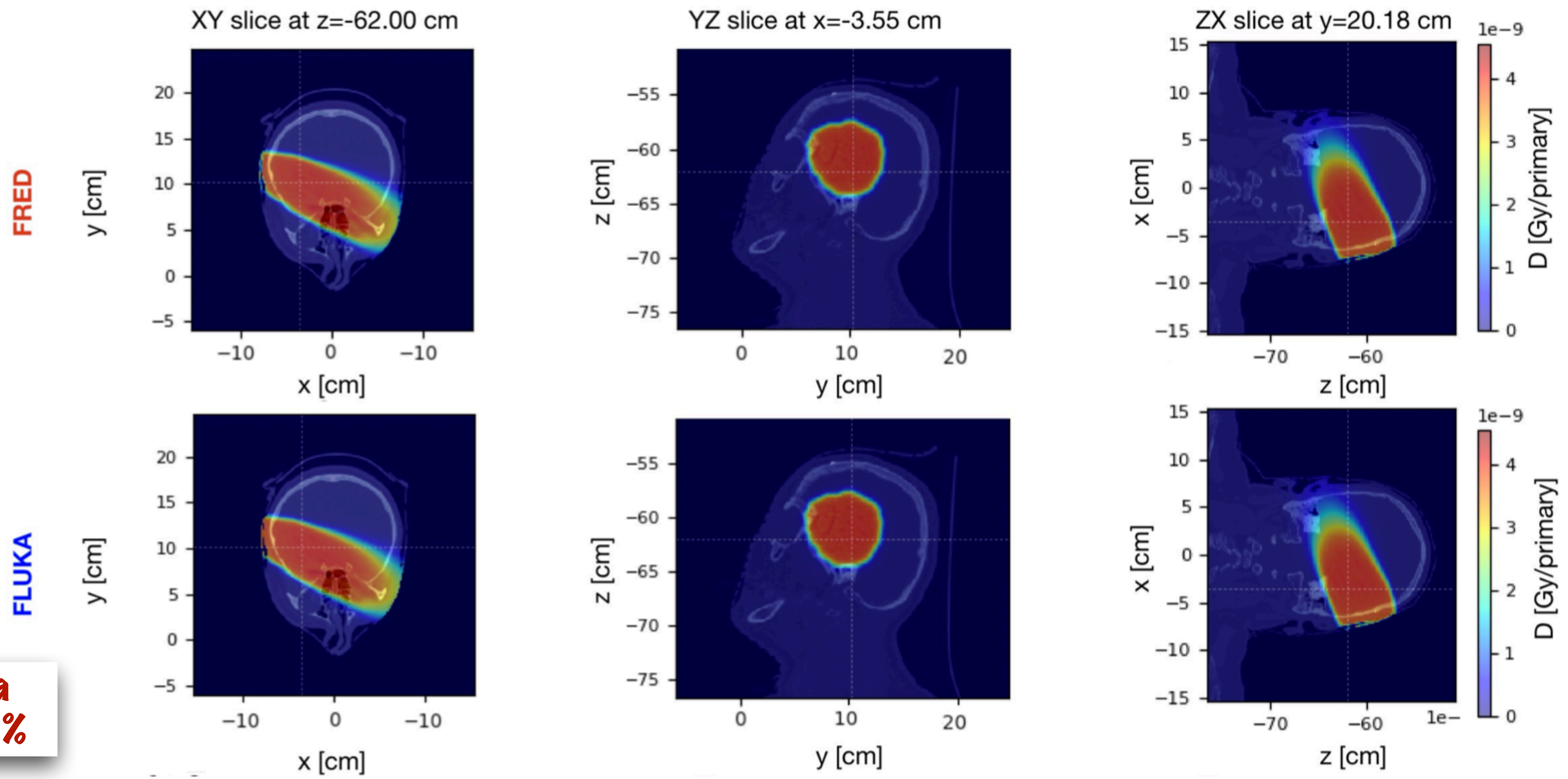
110 MeV e⁻ on Head&Neck CT scan



2mm / 3% gamma index pass rate 99 %

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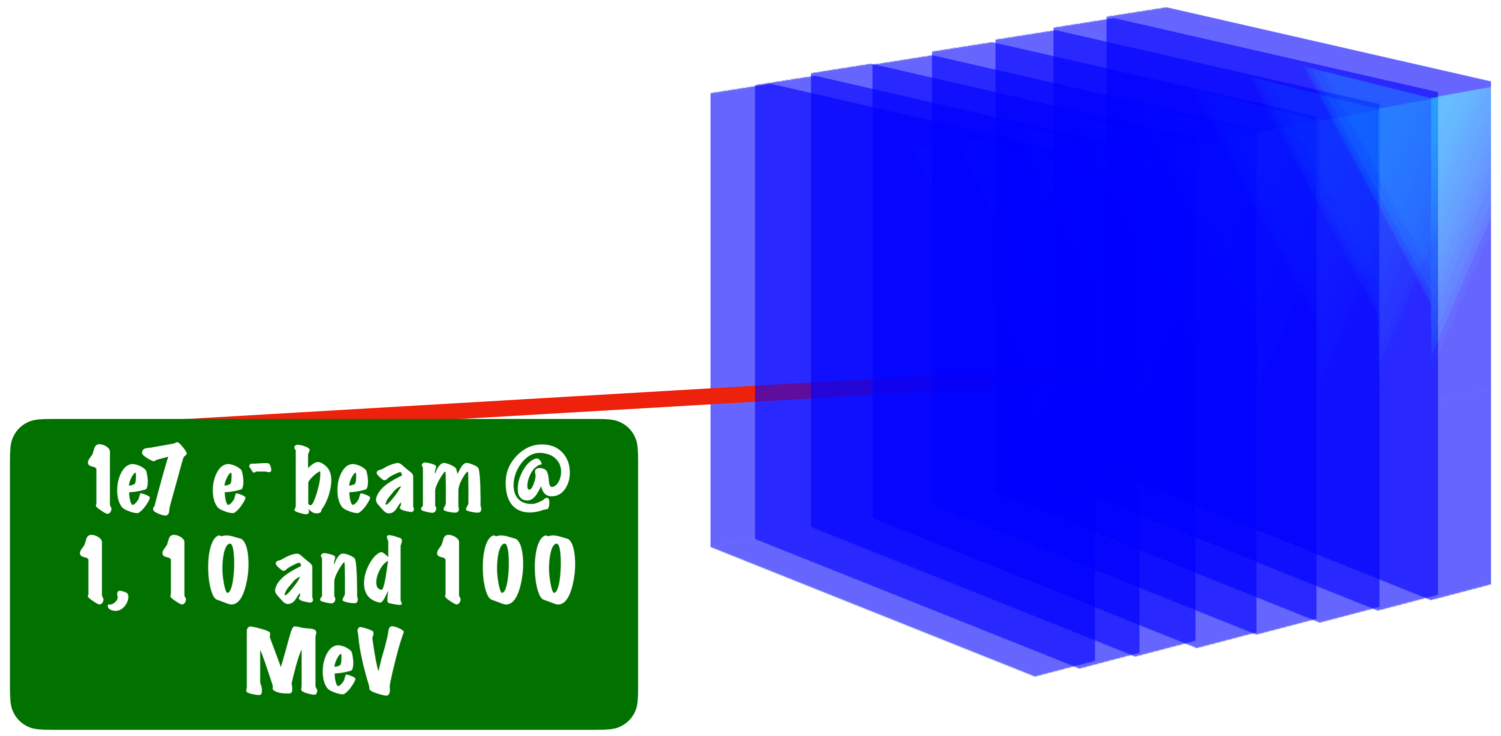
Timing performance

~ x1000

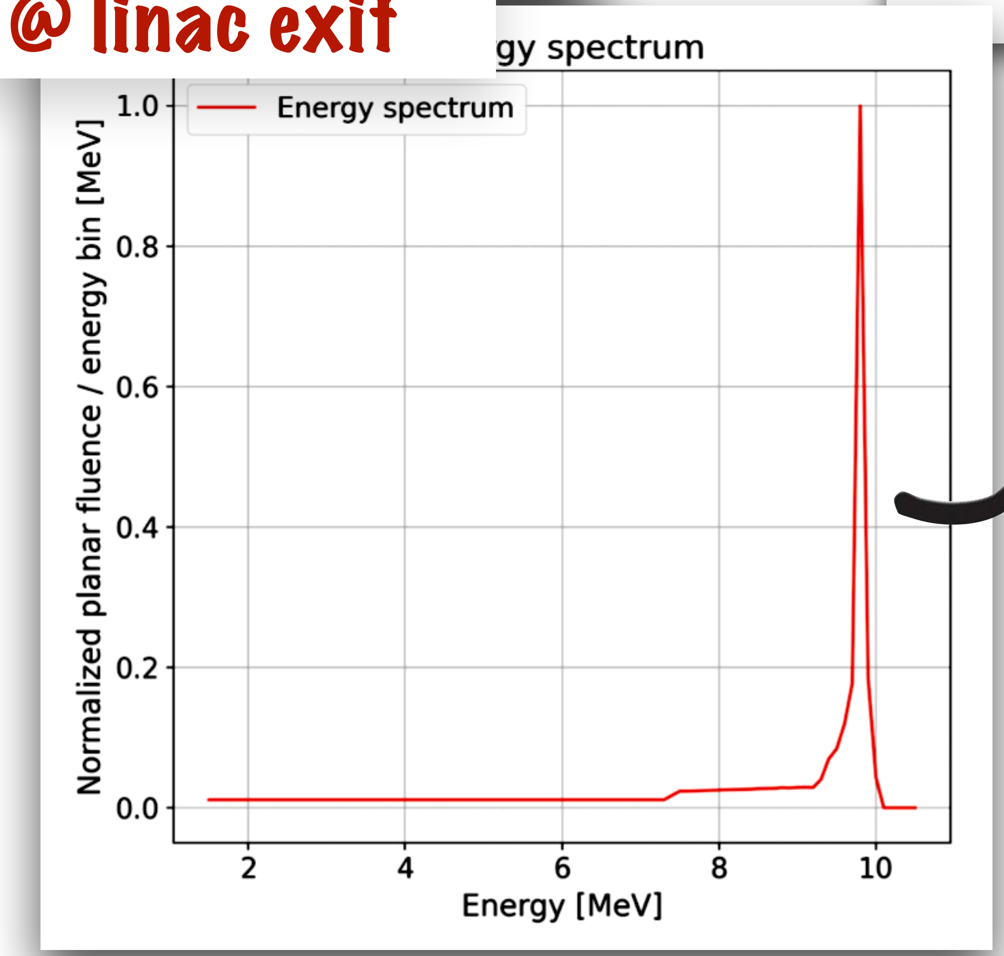
Timing Performance in water	FLUKA 1 CORE	GEANT4 1 CORE	FRED 1 GPU
e^- @ 1 MeV	1.6e4 prim/s	1.3e3 prim/s	3.0e6 prim/s
e^- @ 10 MeV	4.4e3 prim/s	2.2e2 prim/s	4.0e5 prim/s
e^- @ 100 MeV	1.1e3 prim/s	4.8e1 prim/s	7.2e4 prim/s



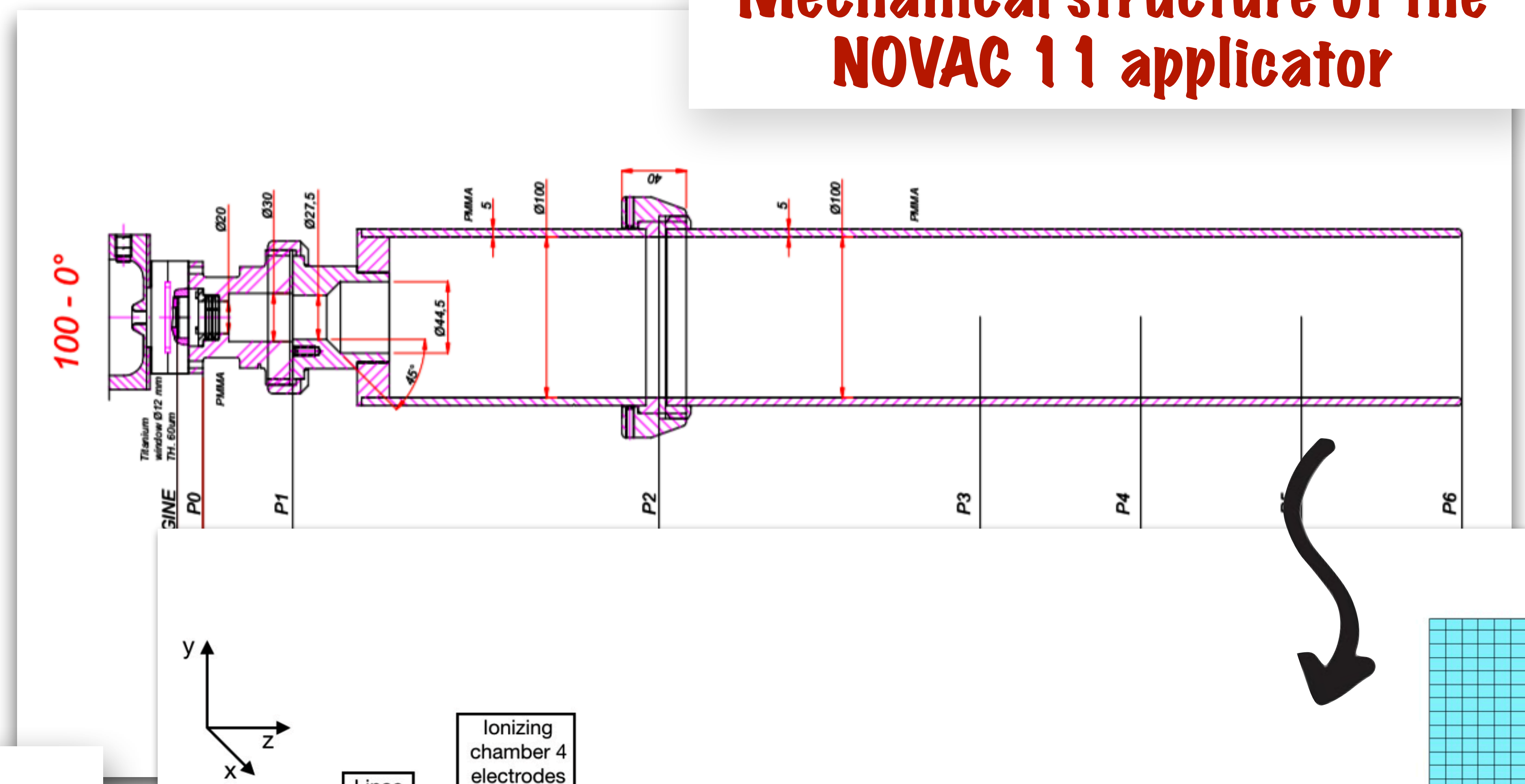
IOeRT application

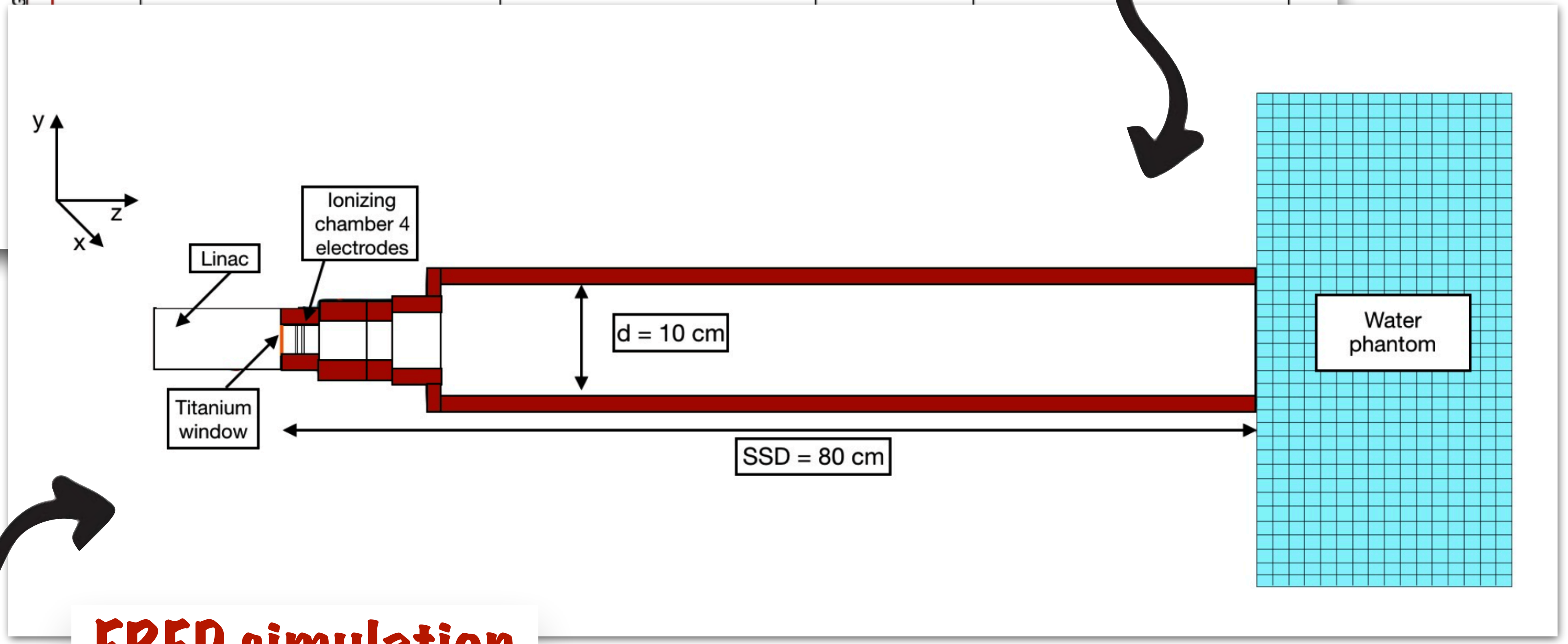
To test the FRED accuracy against experimental data, I considered the IOeRT application: to reproduce the IOeRT dose distributions I simulated in details the geometry of the applicators typically used during the treatments

Energy spectrum @ linac exit



Mechanical structure of the NOVAC 11 applicator





FRED simulation

Geometry setup:

1. **PMMA cylinders** with different diameters (from 20 to 100 mm)
2. Source-to-Skin Distance **(SSD)=80 cm**
3. **Titanium** window **(55 μm)**
4. **Four steel planes** of the ionizing chamber **(20 μm each)**

Simulation setup

1. **~10 MeV** electrons beam;
2. Gauss section with **FWHM=0.13 cm**;
3. Transport and production energy cut = **10 keV and 50 keV** for photons and electrons respectively

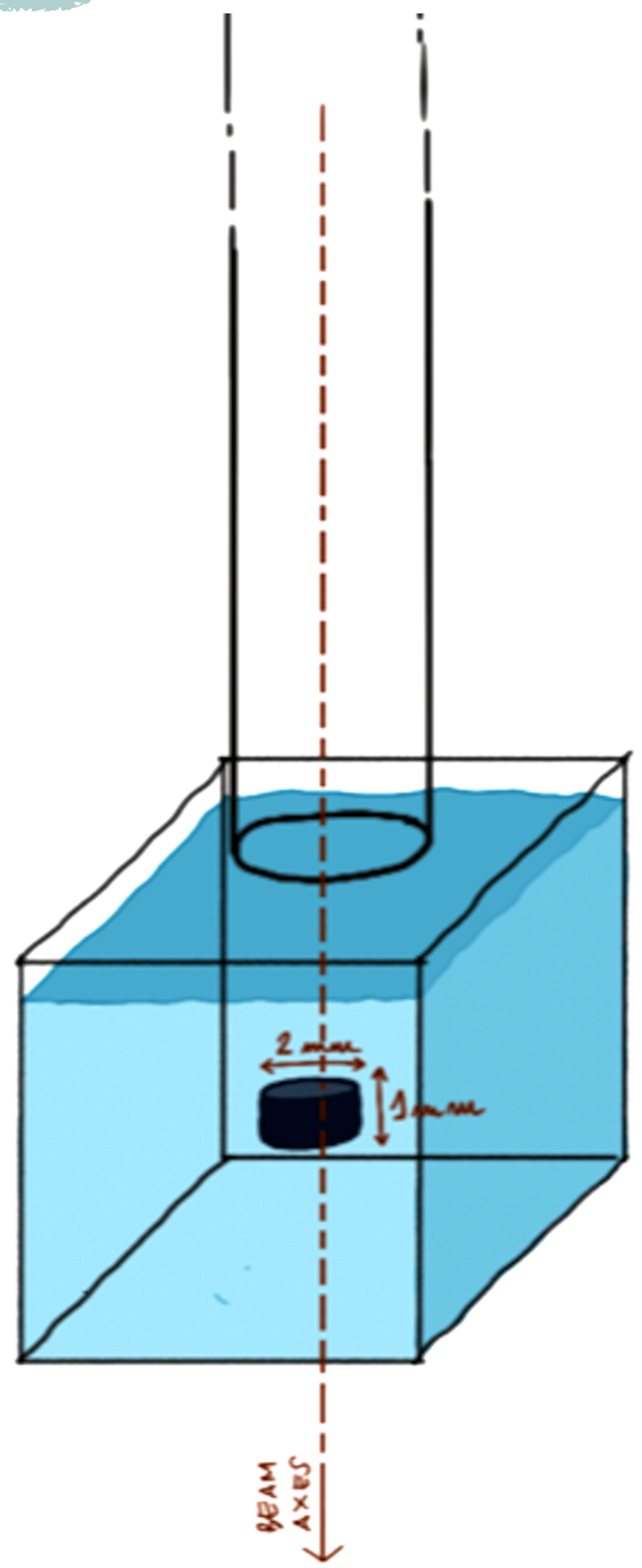
I compared the FRED results against the **experimental data** of the Percentage Depth Doses (PDDs) and off-axis profiles measured in a water phantom.

IOeRT application: experimental setup

Test performed on CPU

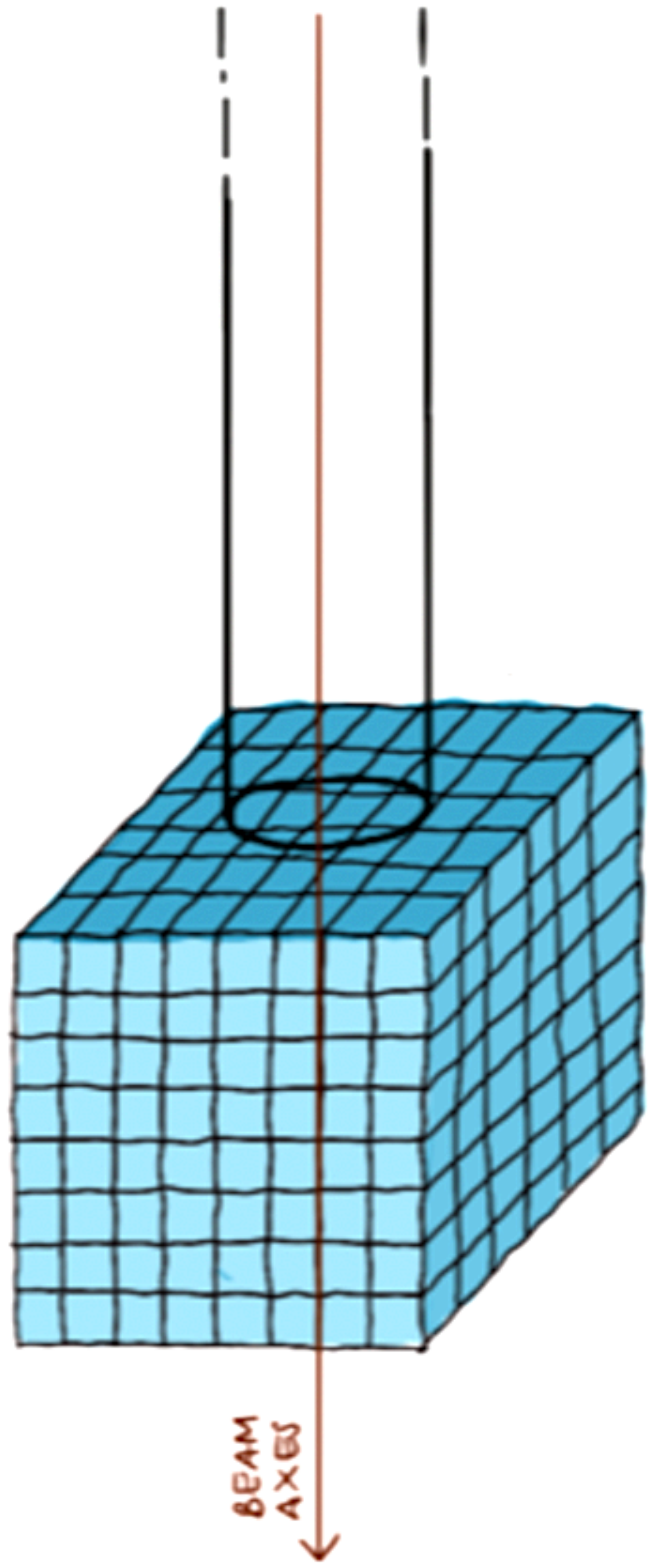
Experimental setup

The experimental setup for relative dosimetry, i.e. PDDs and off-axis profiles measurements consisted of a 3D motorized water phantom equipped with an unshielded diode.



MC setup

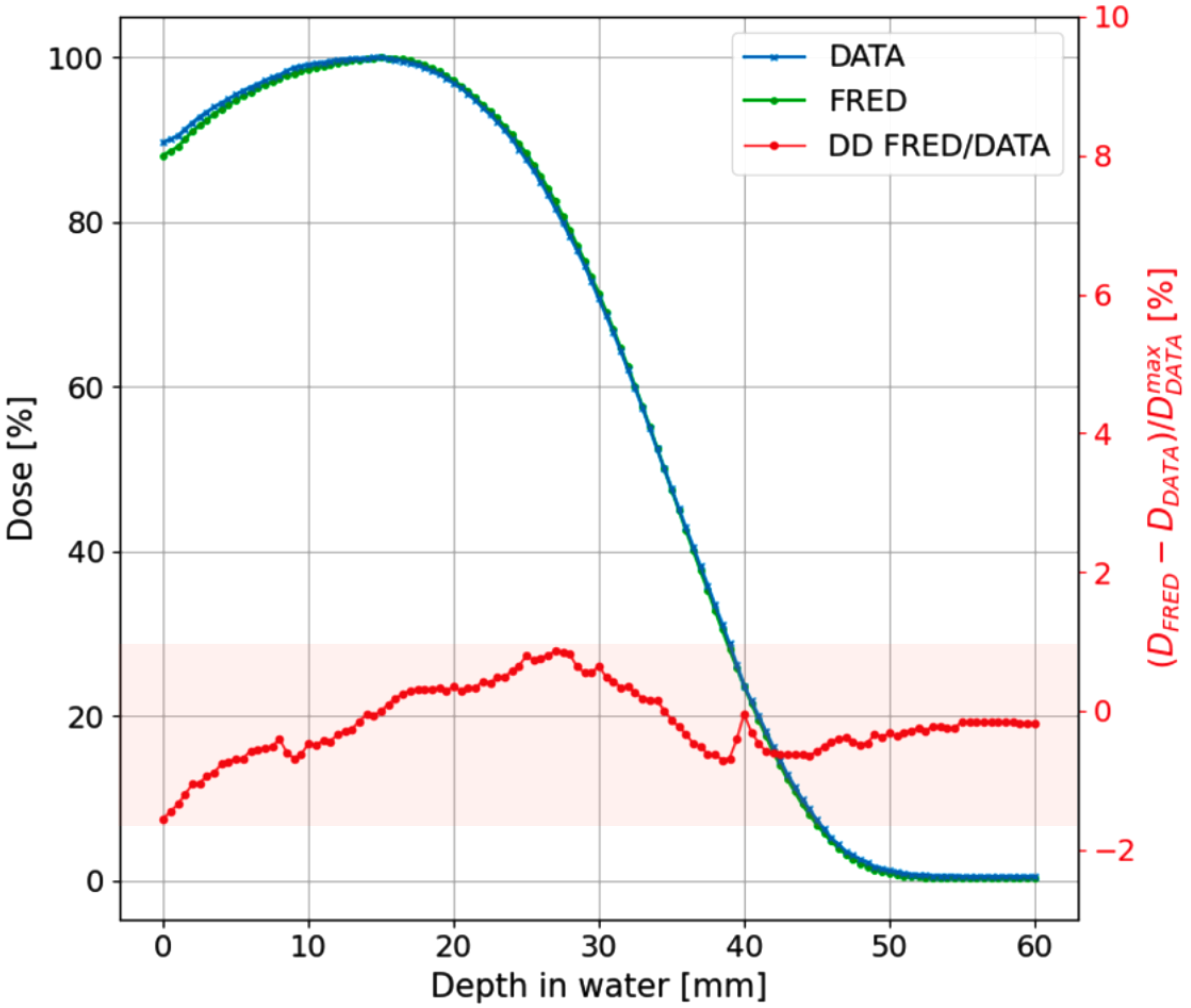
For the MC simulation the absorbed dose was evaluated on a water target with a transverse area of 2×2 mm^2, corresponding to the sensitive are of the adopted diode

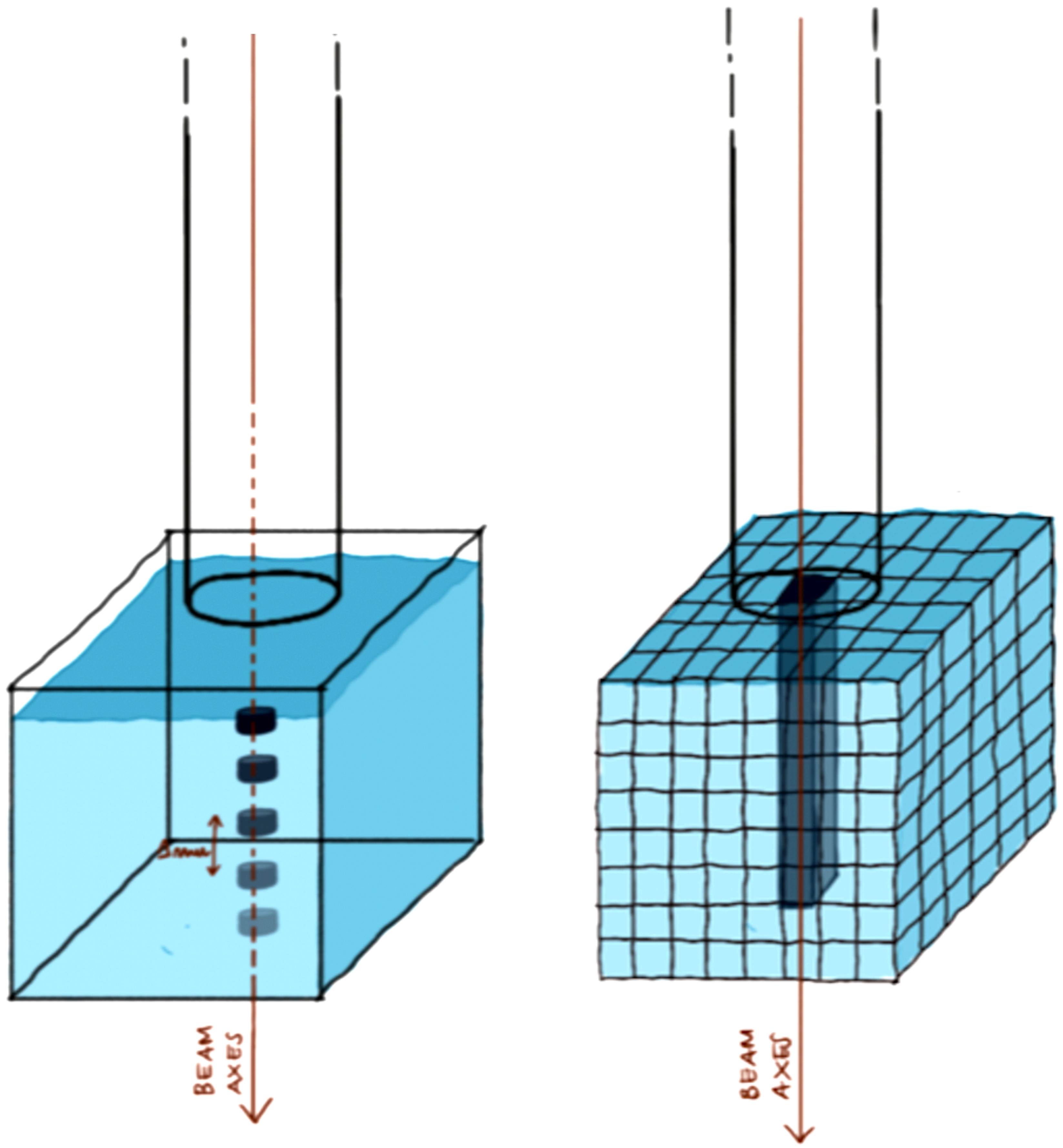


IOeRT application: FRED results

Test performed on CPU

Longitudinal profile

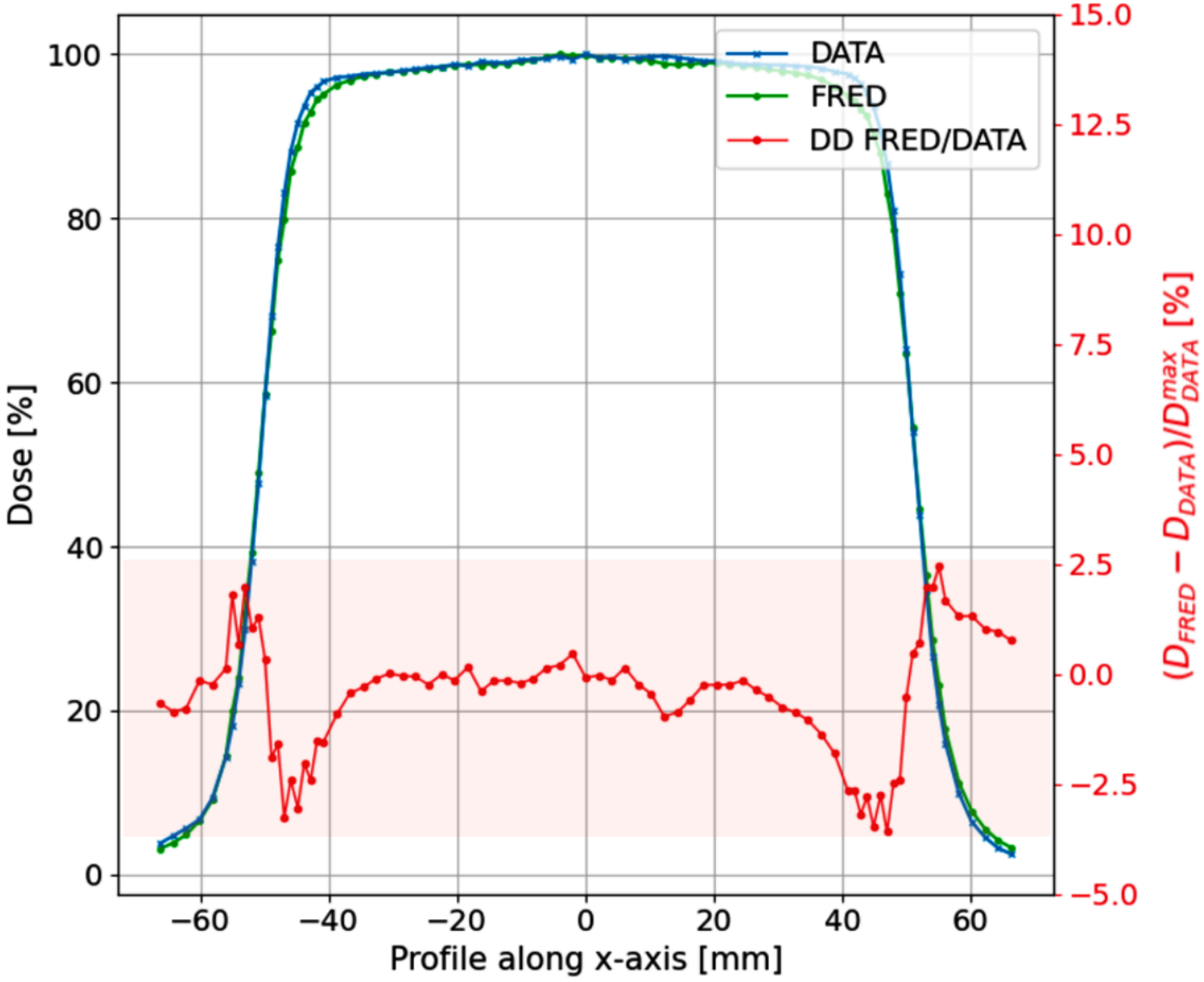


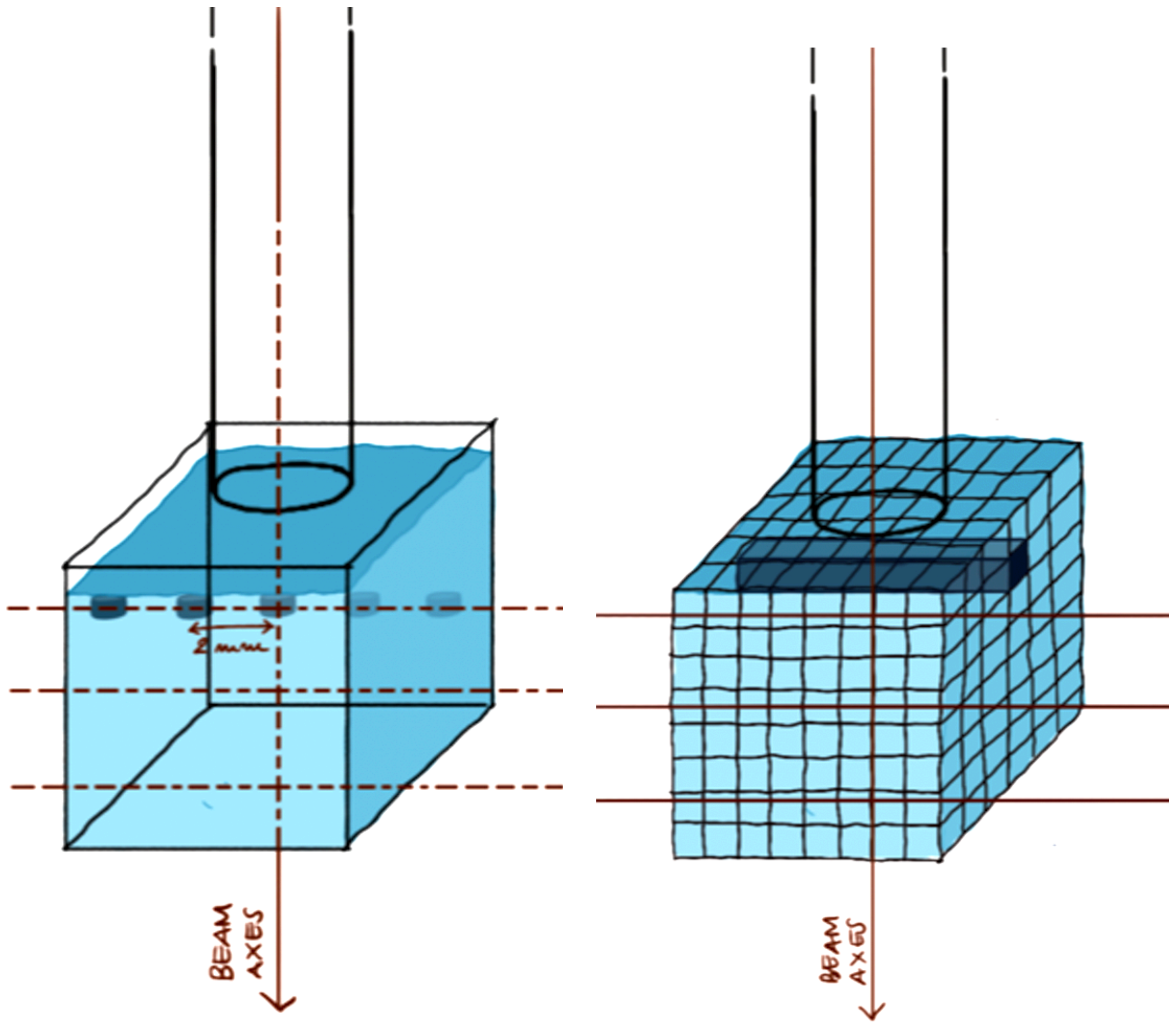


IOeRT application: FRED results

Test performed on CPU

Off-axis profile at Dmax



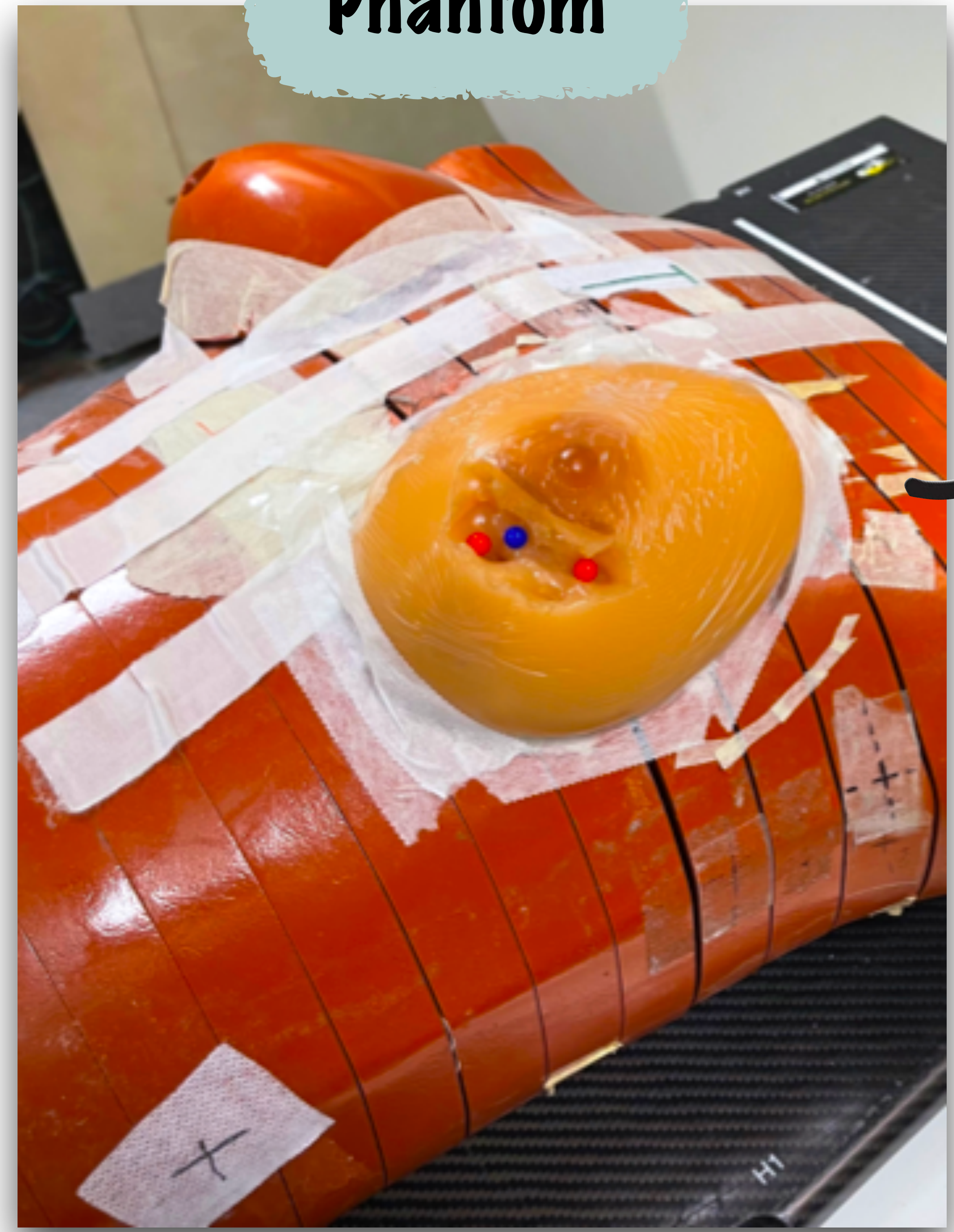


Breast cancer IOeRT TPS

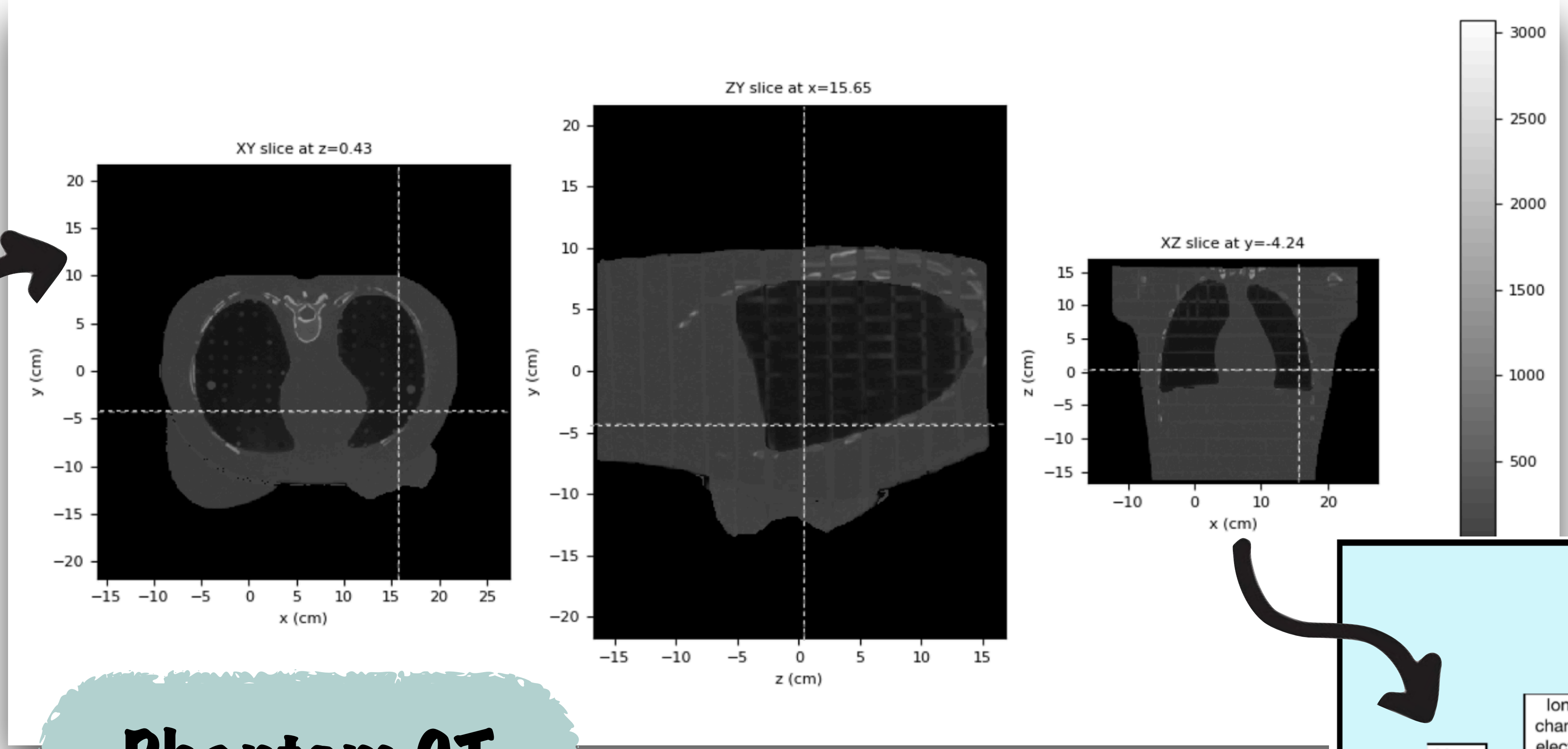
Once I validated the FRED dose engine, in terms of dose accuracy and tracking performance, I started working on its clinical application as a tool for treatment planning and optimization.

Since the US imaging system is today under optimization, to simulate the breast IOeRT treatment, I used a **CT** of a phantom with a **breast prosthesis** used to simulate a breast surgery attached onto it and I tried to **approximate a realistic case**.

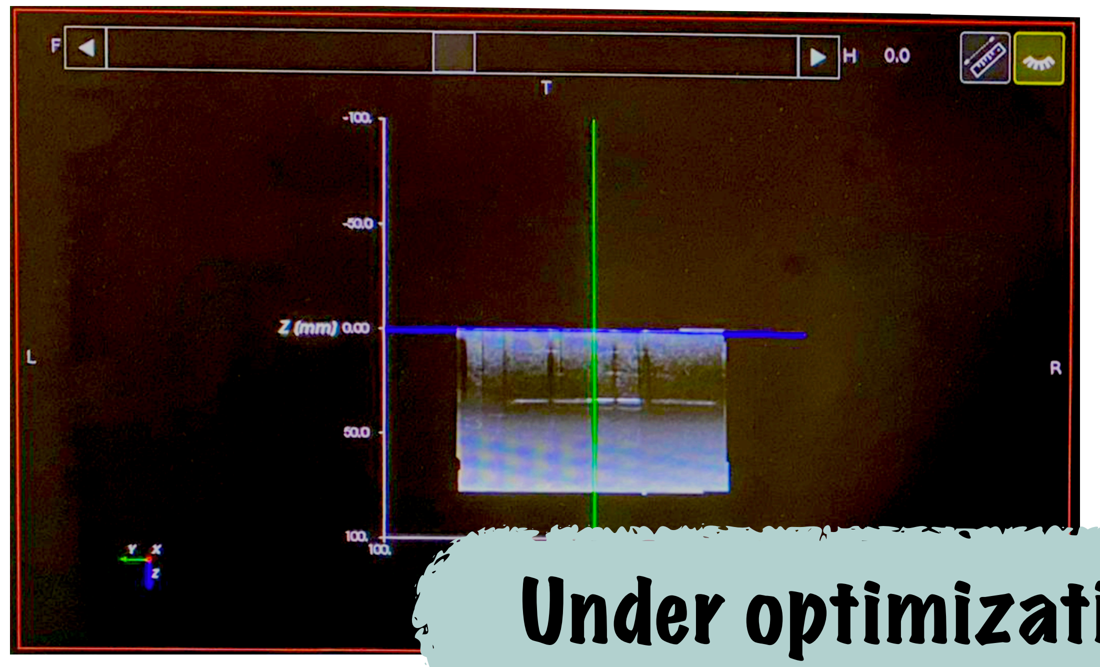
Phantom



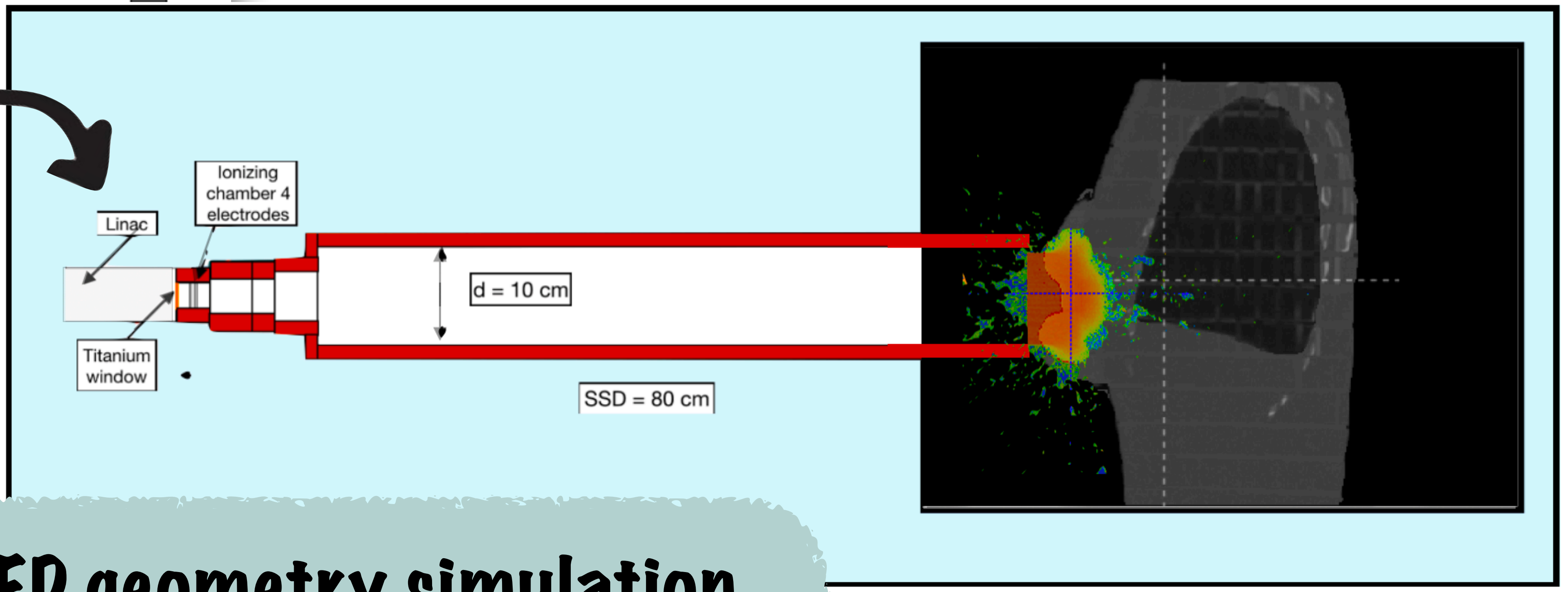
Phantom CT



Under optimization



FRED geometry simulation

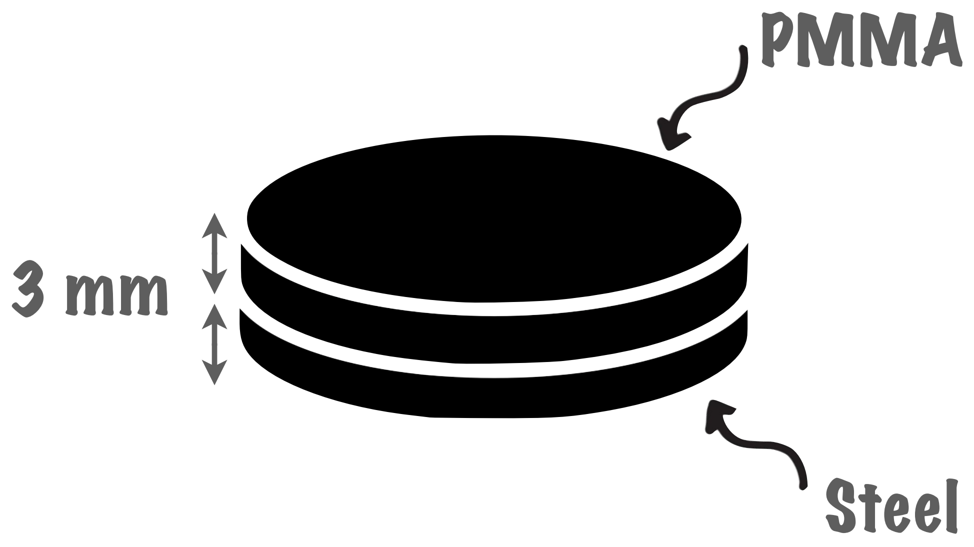


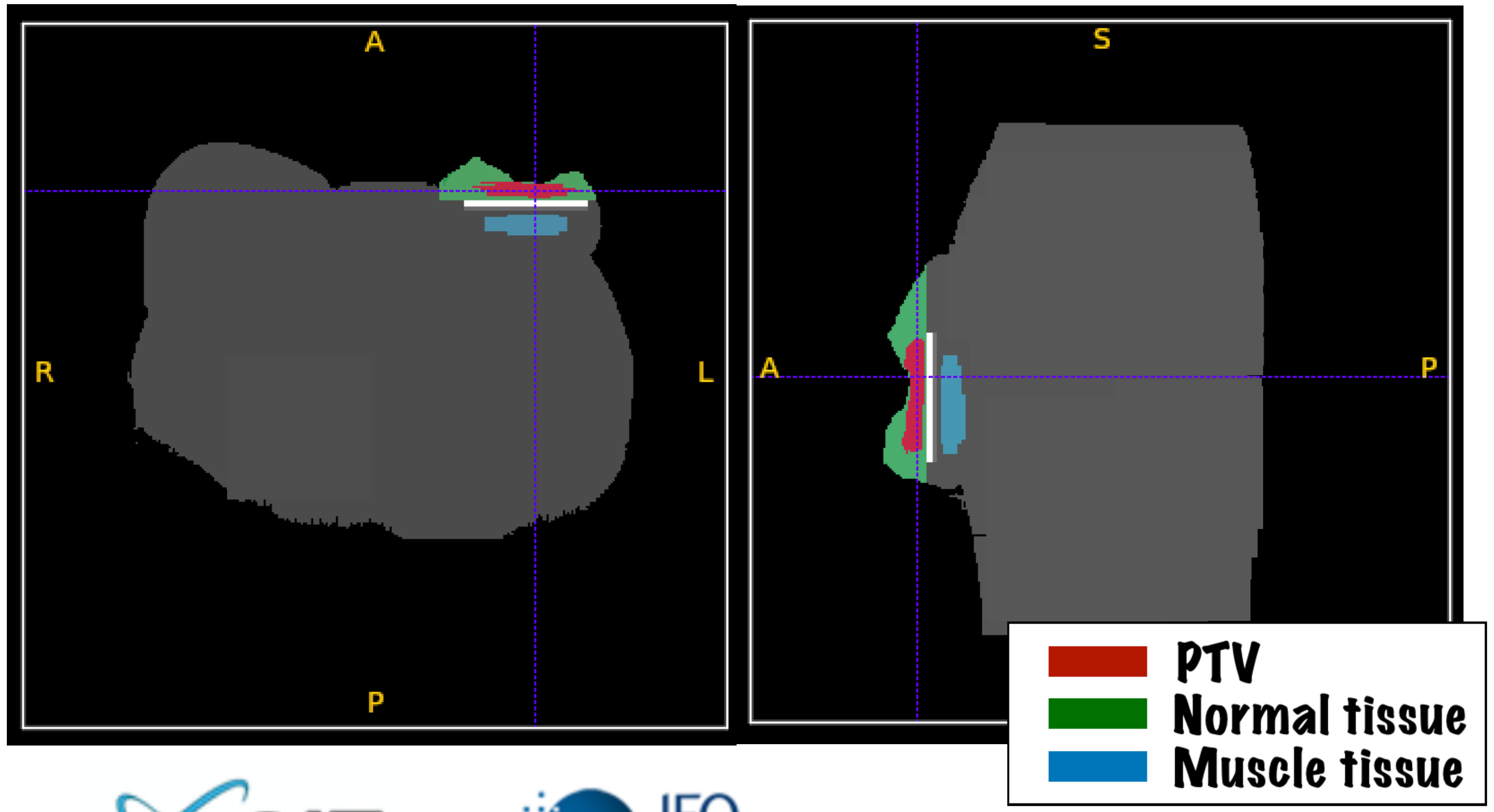
Regions of Interest (ROIs)

I then modified the CT image to meet the future US imagining resolution and identified the treatment ROIs:

- I replaced all the voxels belonging to the patient with the **water** HU value (HU=0) and the ones outside with the **air** HU value (HU=-1000);

- I inserted the radio protection disk;





- According to the US optimal viewing, I defined a reasonable **PTV** (d~6÷7cm, 1cm thick), a **Normal Tissue** region and a volume under the disk (**Muscle Tissue**) at a depth of no more than 7 cm;

Then I tried to optimize the treatment looking for the configuration that maximizes the PTV coverage and sparing of the OARs: I simulated **$5 \cdot 10^5$ electrons*** (several orders of magnitude below a full treatment ~ 3.2e12), of whatever energy, beam size and position, and I analyzed the **resulting Dose Volume Histograms.**

*** Robust results and dose calculation time ~ 7.6 s**

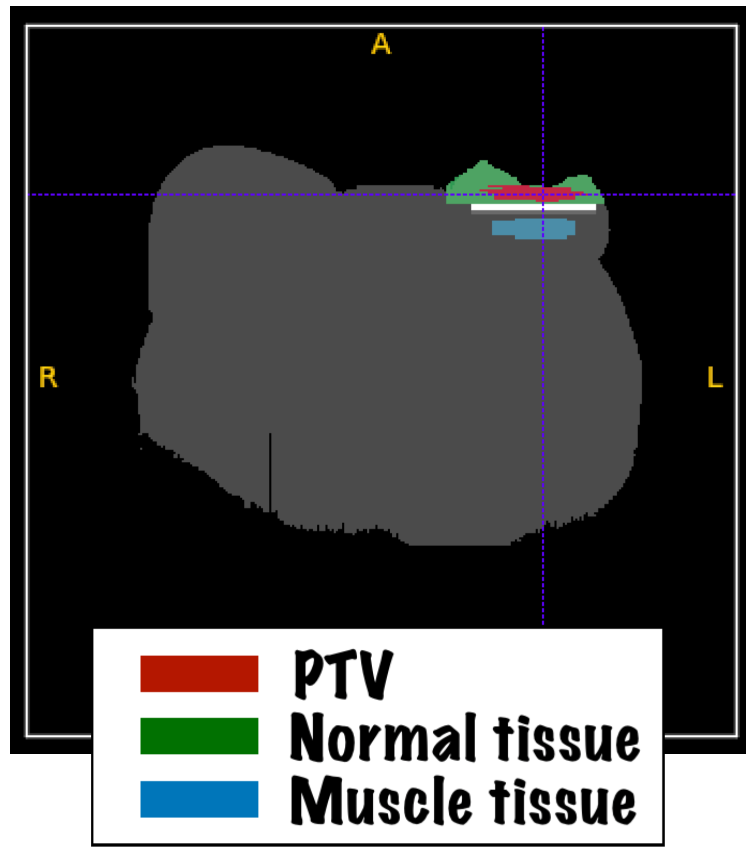
Beam energy scan

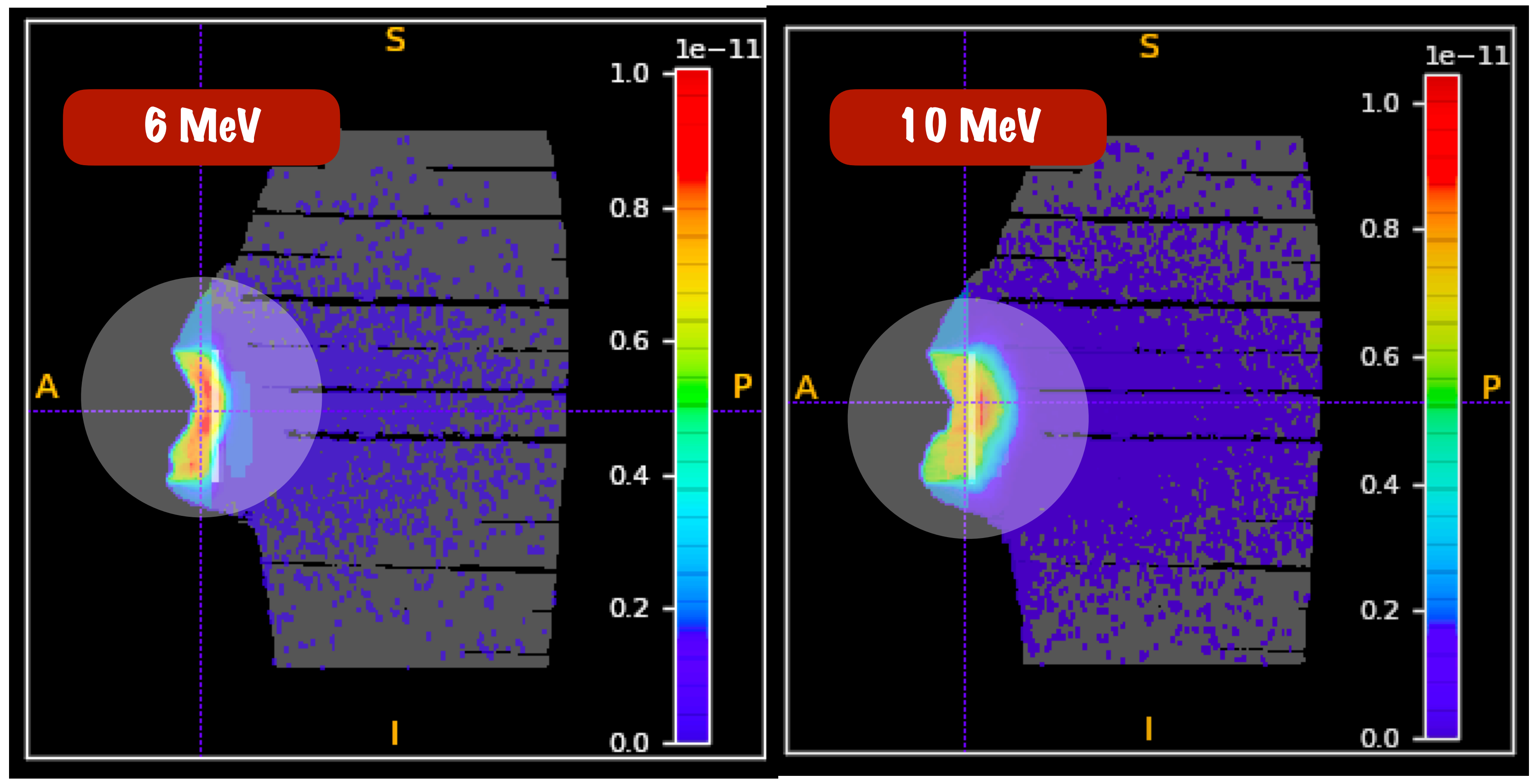
T = 23.1 s

The diameter was fixed at 80 mm and I changed only the beam energy: 6, 8 and 10 MeV were selected according to the PTV thickness.

Dose prescription: ★ **20 Gy @ 90% PTV volume**

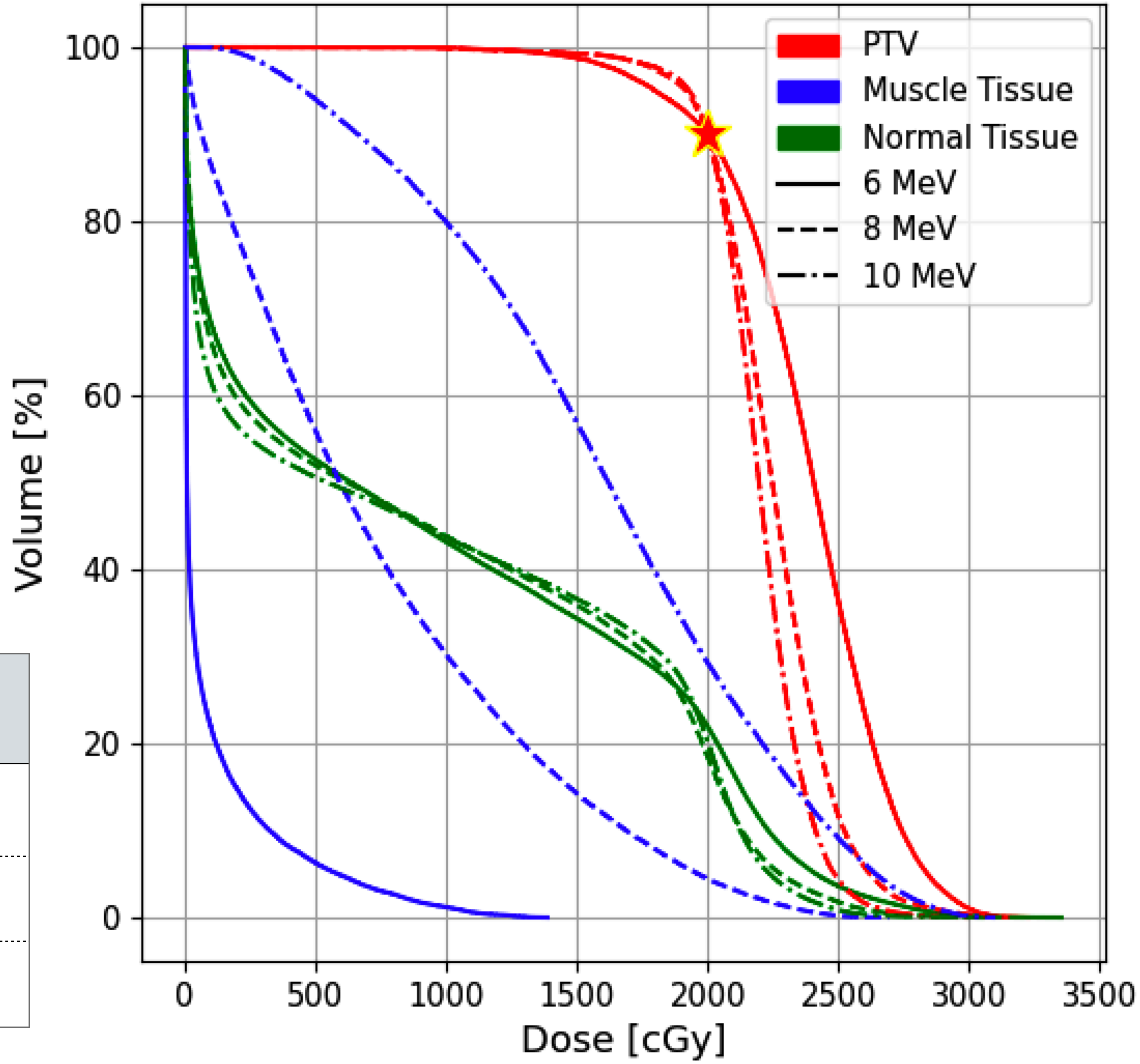
OSS: The FRED dose maps in Gy/primary units were multiplied by the **number** of **electrons** needed to **fulfill** the dose prescription: $3.26 \cdot 10^{12}$, $3.20 \cdot 10^{12}$ and $3.27 \cdot 10^{12}$ for the 6, 8 and 10 MeV simulation.





Dose mean values

D [Gy]	PTV	Muscle Tissue	Normal Tissue
6 MeV	23.7	0.9	9.6
8 MeV	22.4	7.5	9.3
10 MeV	21.9	15.9	9.1



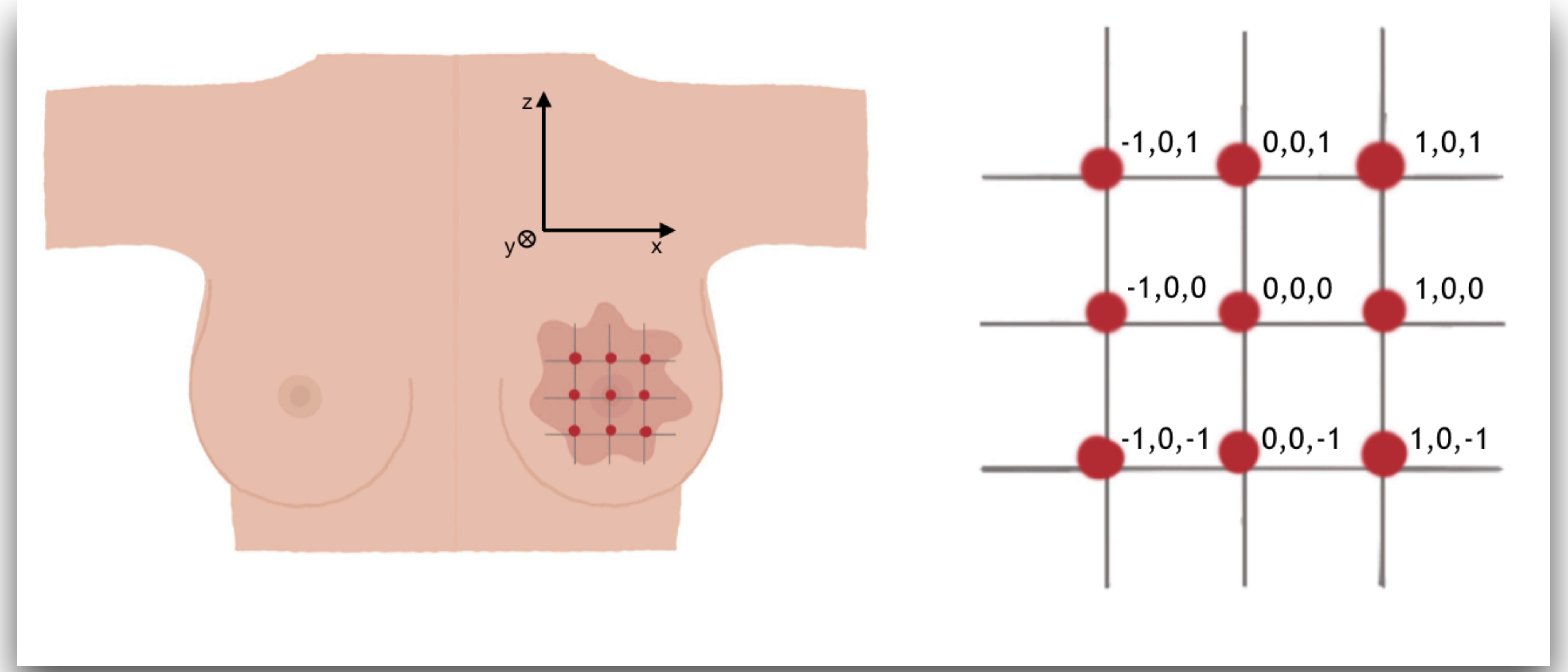
Beam position scan

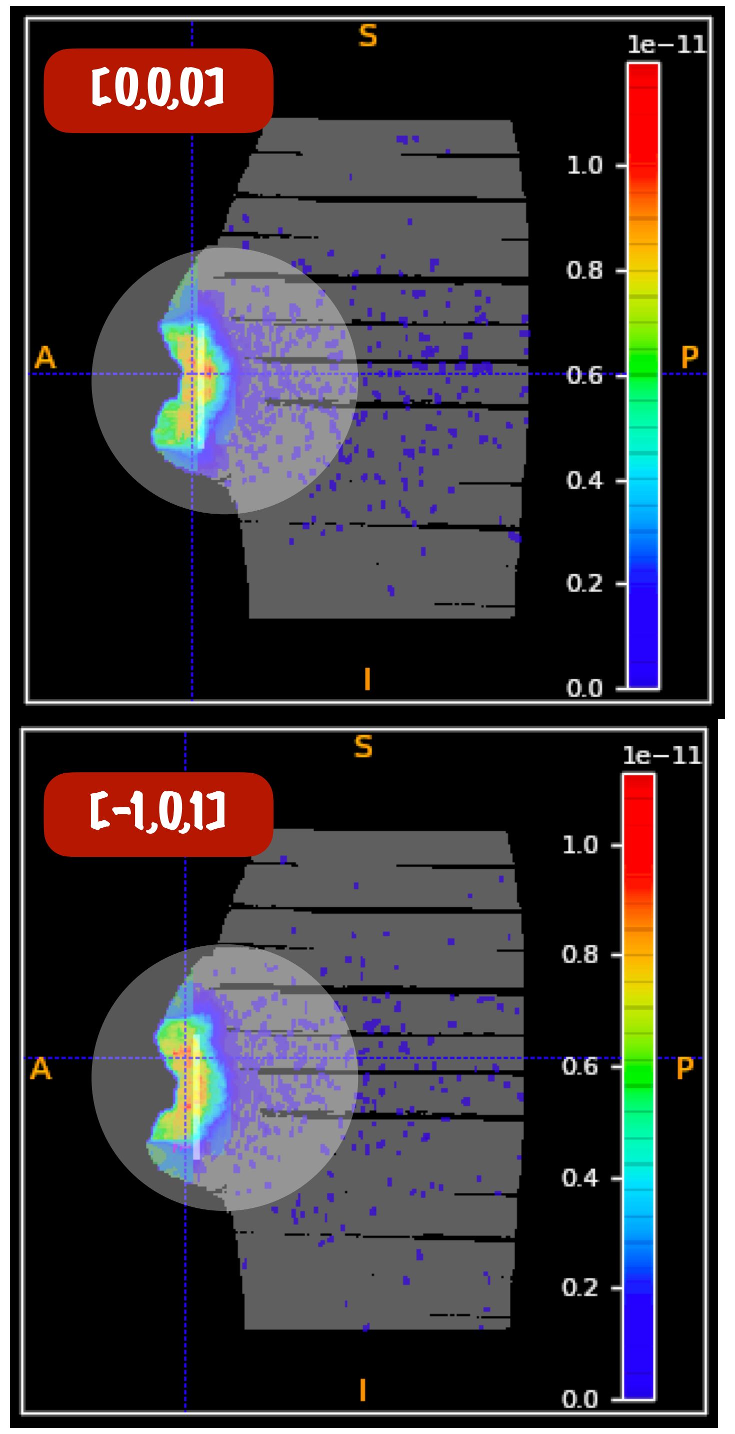
T = 60.3 s

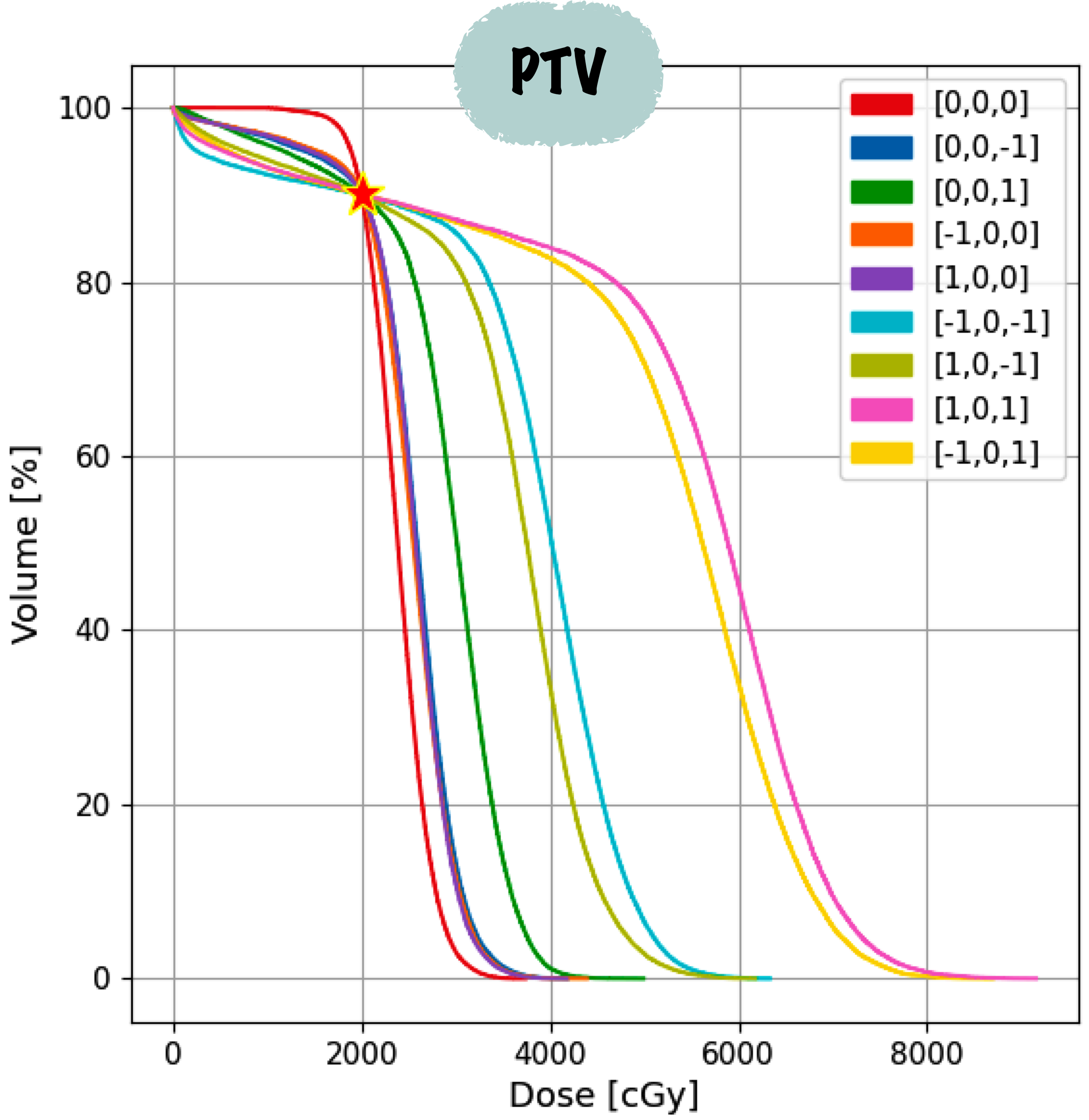
With an 8 MeV circular electrons beam with d=80 mm, I performed a position scan, moving the beam in steps of 10 mm in a **[x,z] grid**

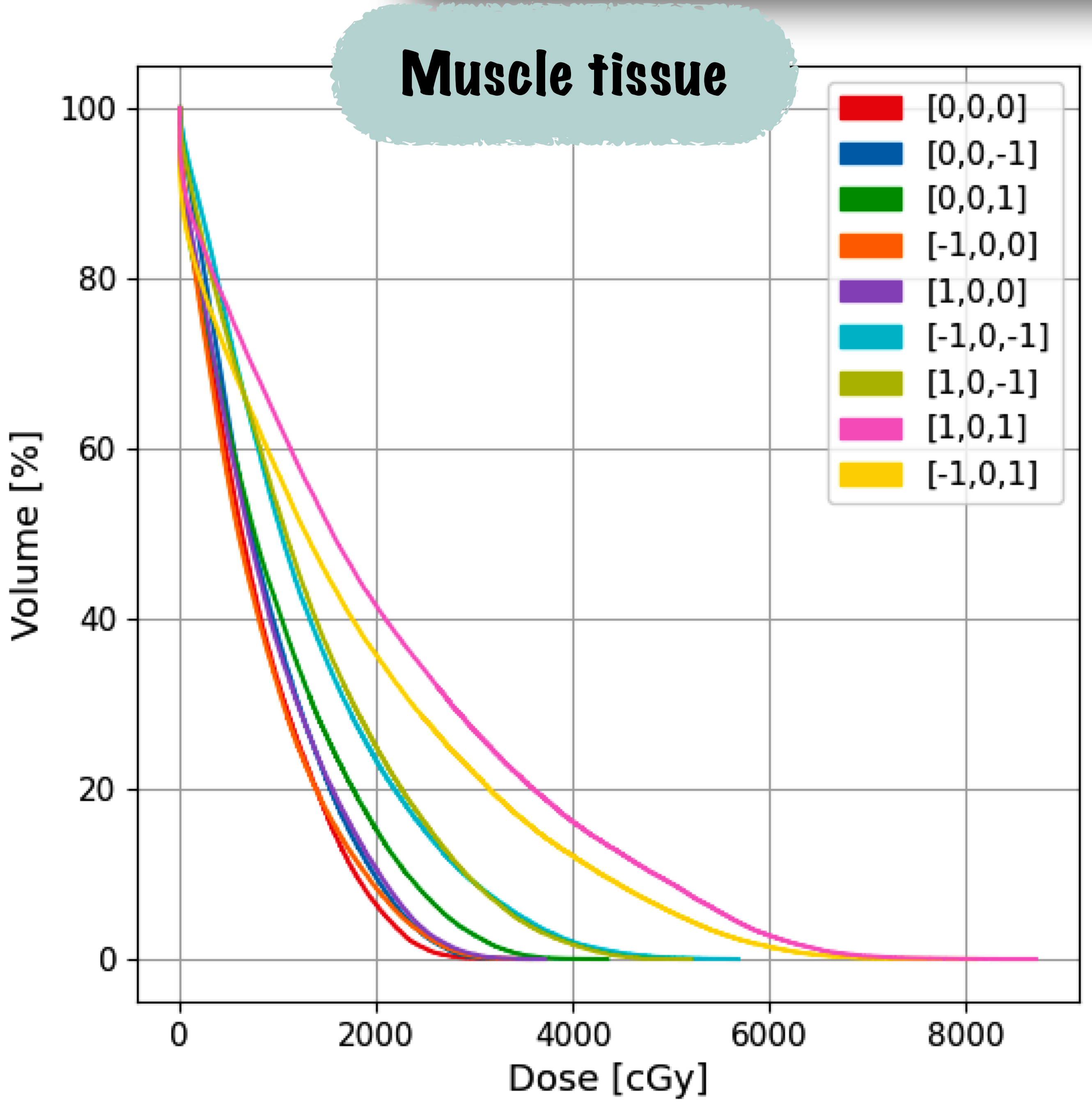
Dose prescription: ★ **20 Gy @ 90% PTV volume**

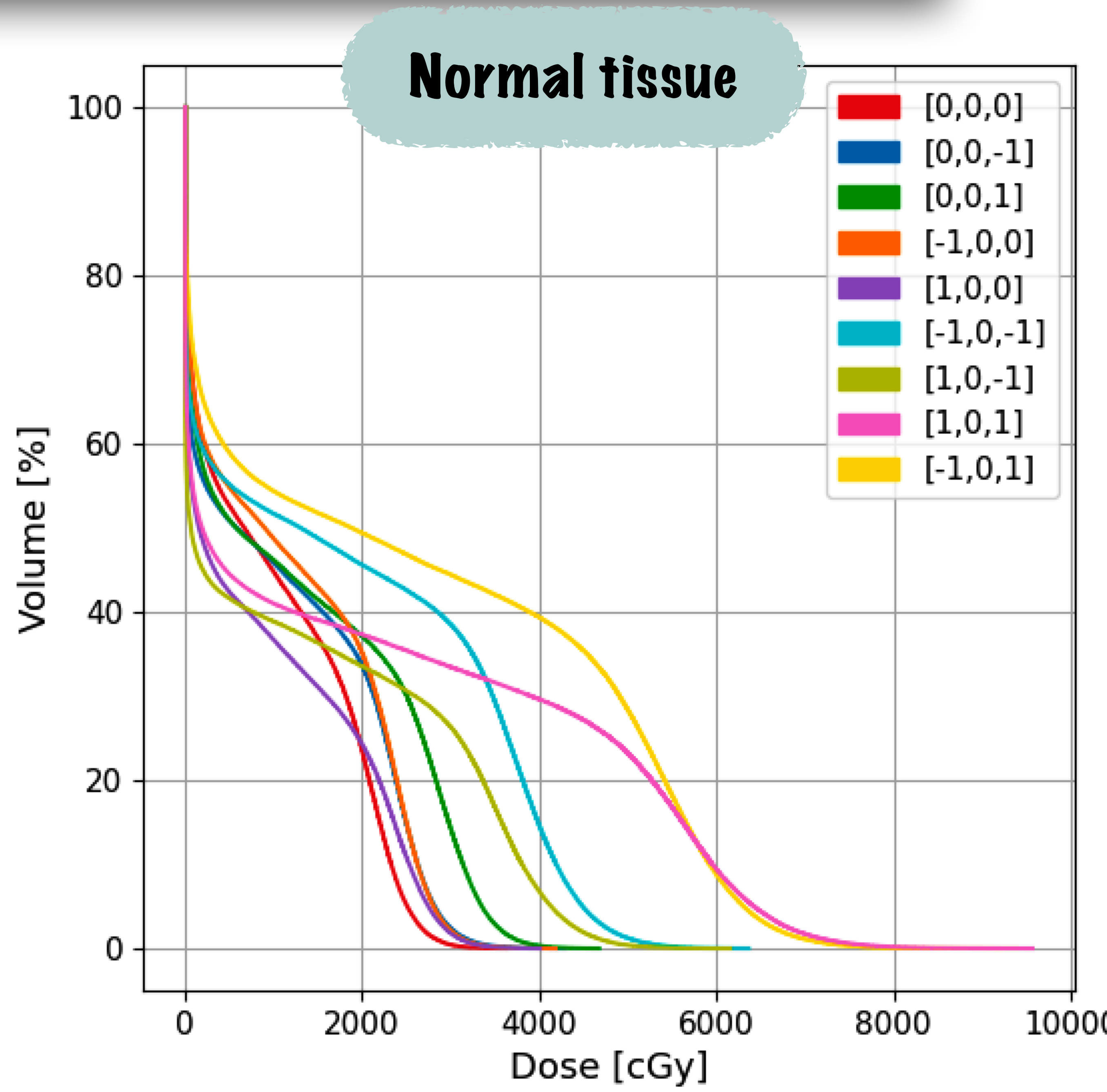
OSS: Also in this case the FRED dose maps in Gy/primary units were multiplied by the **number** of **electrons** needed to **fulfill** the dose prescription ~ 10^{12}









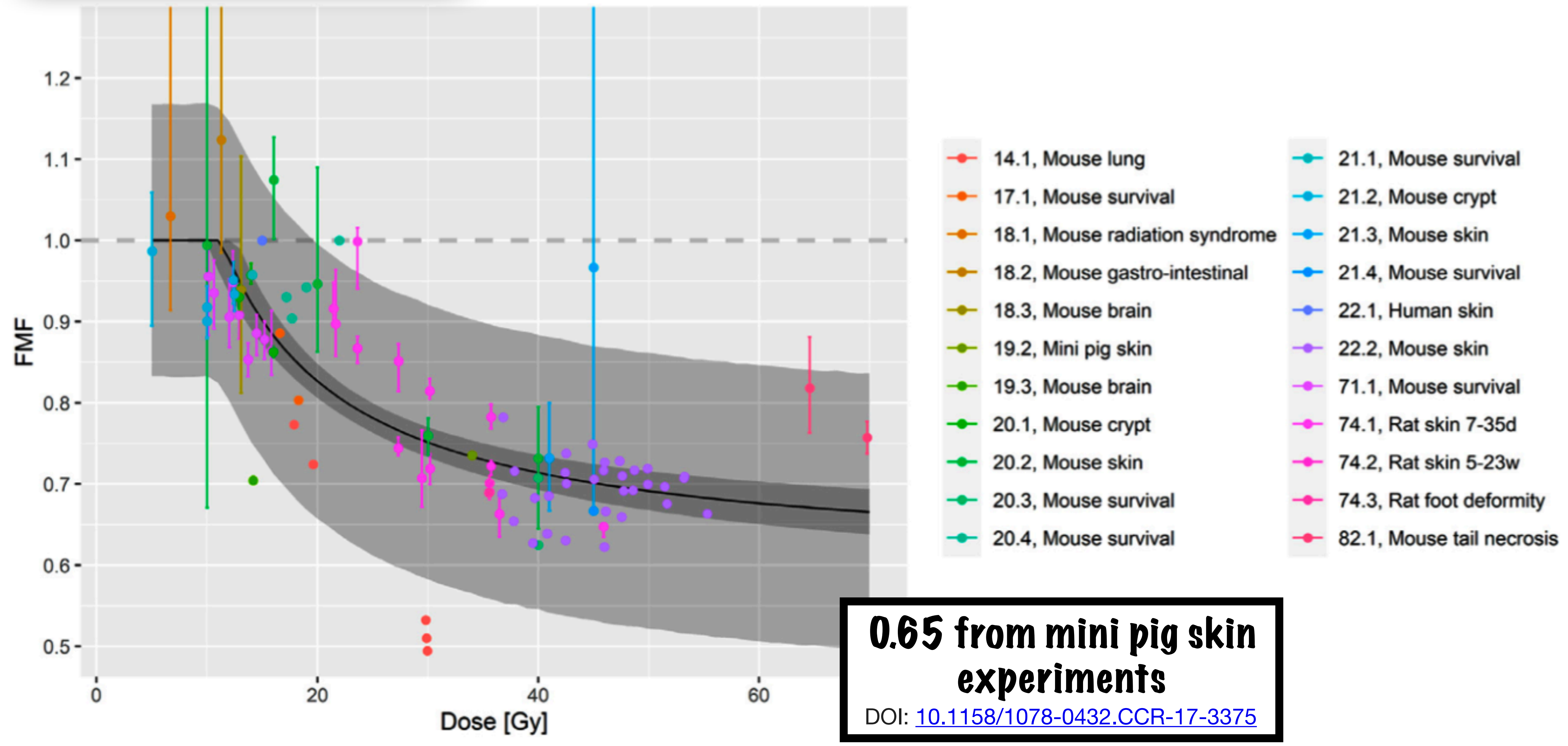


FLASH effect

FLASH irradiation provides the same tumor killing efficiency and a reduced radiation-induced toxicity in normal tissues with respect to conventional one. This effect can be parametrized by the FLASH Modifying Factor (FMF) model.

$$FMF = \frac{D_{CONV}}{D_{UHDR}}\bigg|_{isoeffect}$$

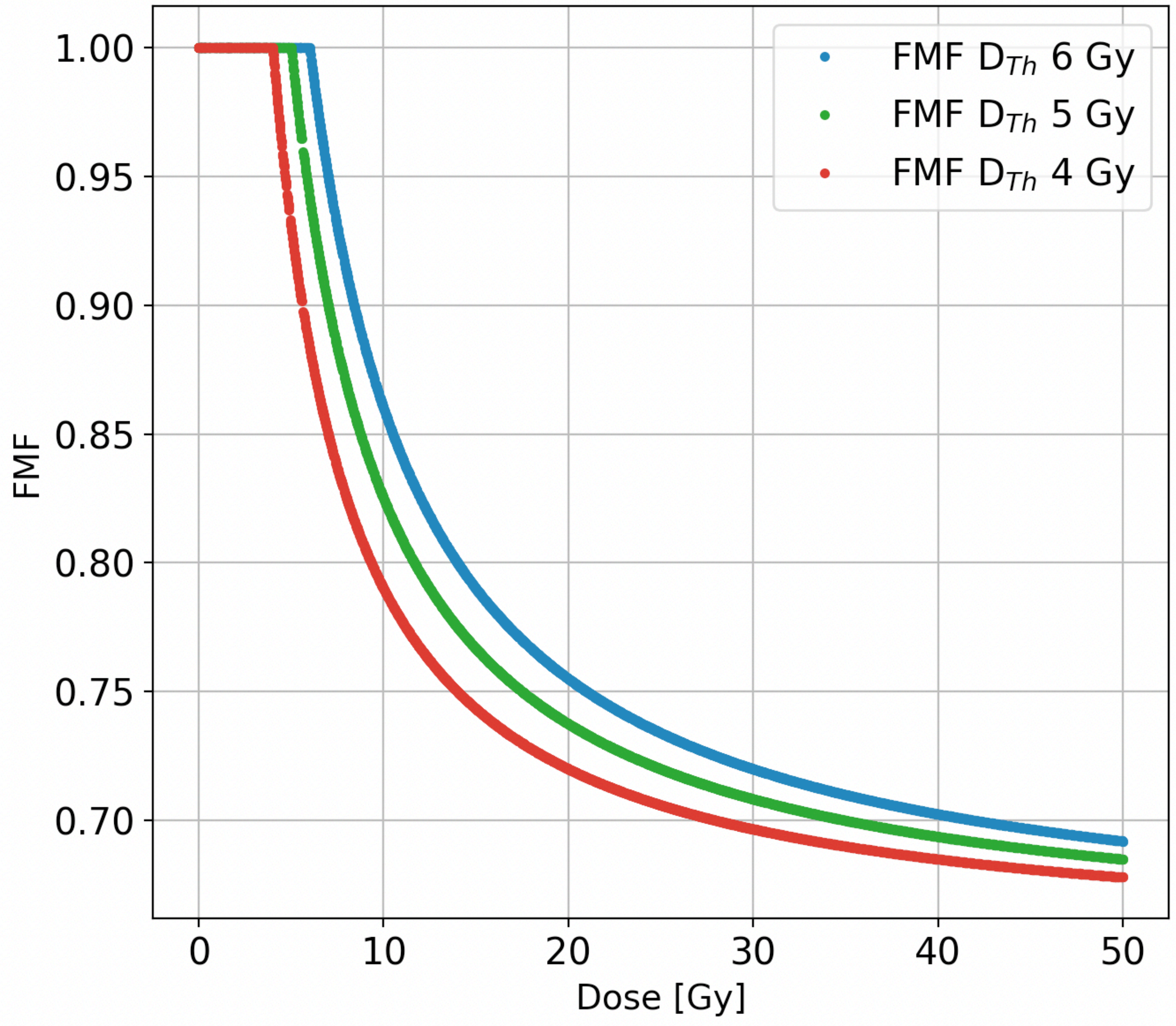
FMF < 1 : greater normal tissue sparing of UHDR compared with CONV irradiation



0.65 from mini pig skin experiments

DOI: 10.1158/1078-0432.CCR-17-3375

$$FMF = \begin{cases} 1 & \text{for } D \leq D_{Th} \\ (1 - FMF^{min})\frac{D_{Th}}{D} + FMF^{min} & \text{for } D > D_{Th} \end{cases}$$



DOI: 10.1016/j.ijrobp.2022.05.038)

IOeRT-FLASH treatment

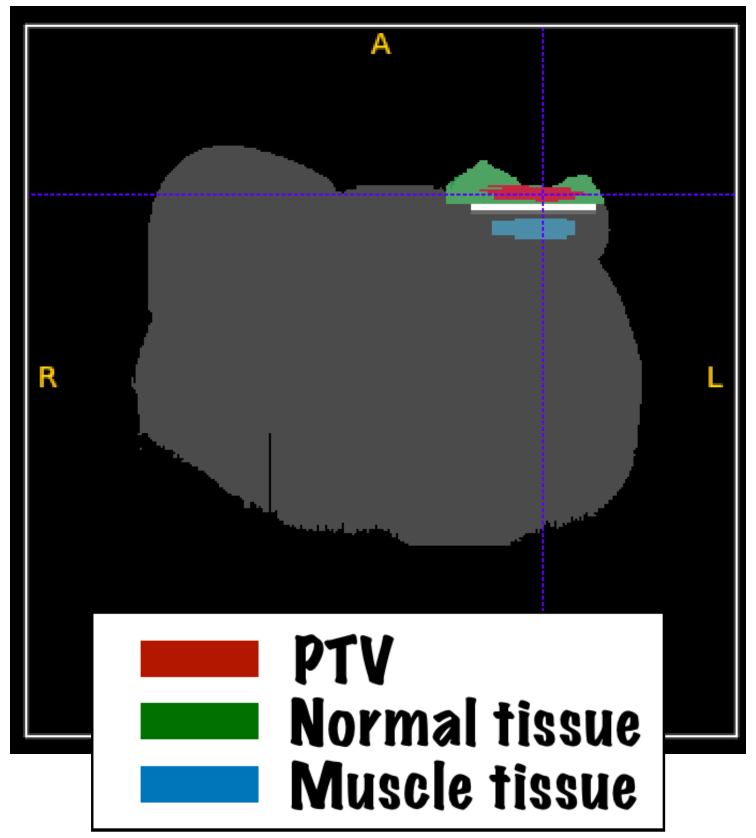
T = 30.8 s

Today the IOeRT presents an high probability of tumor under-dosage, due to the decision to avoid invasive surgery procedure. Therefore, the irradiated area is sometimes smaller than the the effective PTV.

I studied the FLASH effect potential in the sparing of the superficial tissues to asses the possibility to combine **minimally invasive surgery** (small surgical breach) and a **larger electron beam irradiation** delivered at ultrahigh dose rates

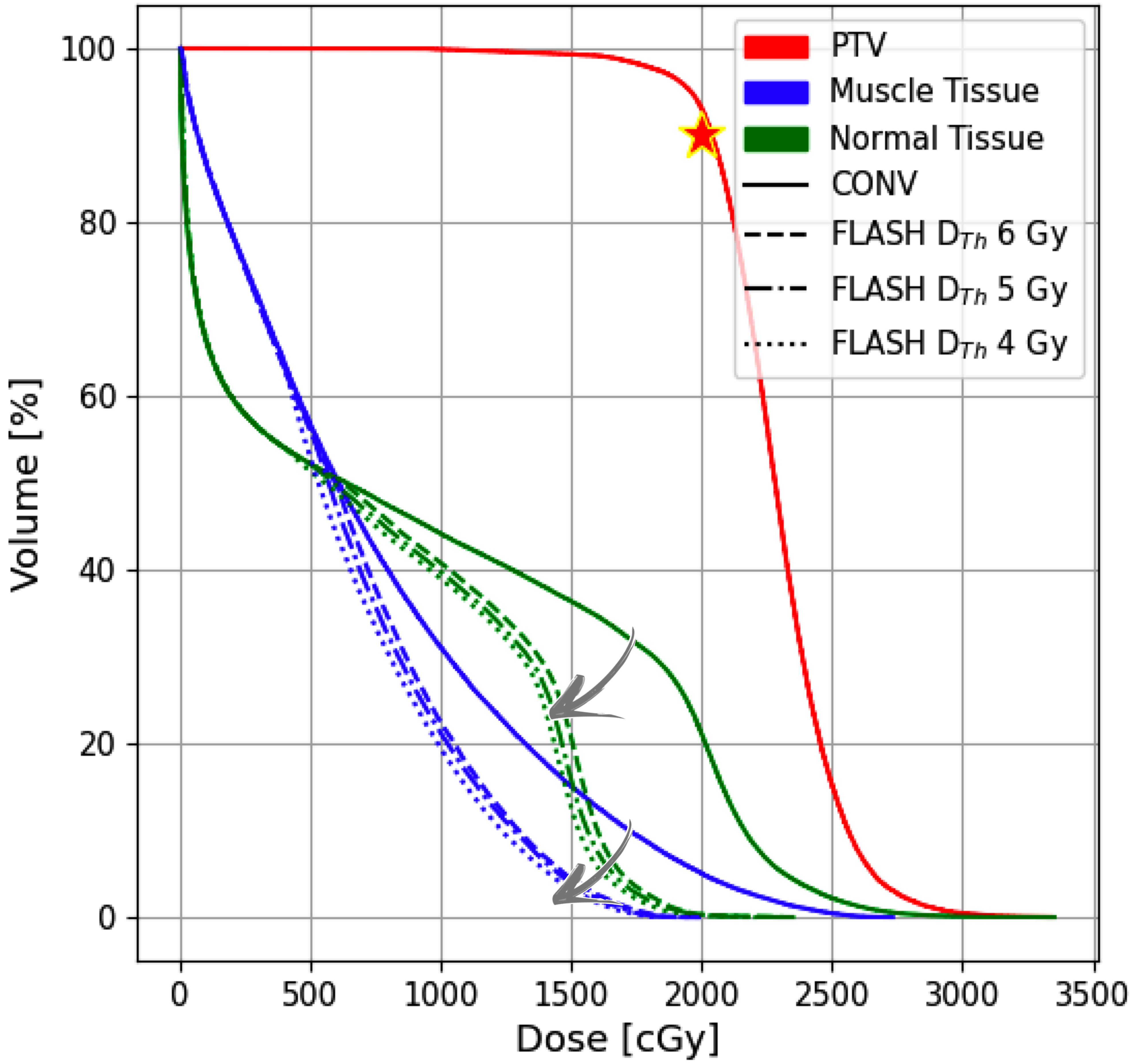
This would allow to improve local tumor control (higher dose) without jeopardizing normal tissue tolerance.

An 8 MeV electrons circular beam with d=80 mm was simulated in **CONVENTIONAL** and **FLASH** regime with D_{Th} = 6, 5 and 4 Gy



Dose mean values

D [Gy]	PTV	Muscle tissue	Normal Tissue
CONV	22.4	7.5	9.5
FLASH D_{Th} = 6 Gy	22.4	6.3	7.3
FLASH D_{Th} = 5 Gy	22.4	6.2	7.1
FLASH D_{Th} = 4 Gy	22.4	5.9	6.9



Conclusion

- In this Ph.D. work I developed from scratch a fast **dose engine based on GPU-MC, crucial for the future IOeRT TPS.** It is capable of reproducing dose distributions in homogeneous and heterogeneous phantoms with an **accuracy** at the level of state-of-art full MCs and with an **impressive gain in processing time**.

- I developed an optimization tool using **FRED** which is able to produce **robust** and **accurate dose distributions** in about **10 seconds** that can be used for **online** treatment optimization.

- Next steps:

- Explore a realistic case of **breast cancer** evaluating the potential of FLASH irradiation, and also **prostate** and **pancreatic applications.**
- **Integration** of the developed treatment planning and optimization tool with **the S.I.T. software** that handles the US imaging acquisition and the graphical interface.
- **TPS validation** against experimental data

GPU-accelerated Monte Carlo simulation of electron and photon interactions for radiotherapy applications

IPEM Institute of Physics and Engineering in Medicine

G. Franciosini[d,a], G. Battistoni[b], A. Cerqua[e], A. De Gregorio[d,a],

Preliminary study on the correlation between accelerated current and dose in water for an electron based linac

G. Franciosini[a,b], S. Muraro[c], A. De Gregorio[a,b], M. De Simoni M.

Submitted

IOeRT conventional and FLASH treatment planning system implementation exploiting fast GPU MonteCarlo: the case of breast cancer

G. Franciosini[a,b], D. Carlotti[g], A. De Gregorio[a], V. De Liso[c], F. De Ro

in writing

Thanks for your attention
Questions are welcome!!

SPARE SLIDES

Conferences and Articles

Conferences

1. **Development of a IORT Treatment Planning System using a GPU-based fast Monte Carlo**, plenary talk, 47th Annual Meeting of the European Radiation Research Society (ERRS 2022), 21^{th}-24^{th} September 2022, Catania, Italy.
2. **A feasibility study of IORT Treatment Planning system using a GPU based fast Monte Carlo**, plenary talk, 4th European Congress of Medical Physics, 17^{th}-20^{th} August 2022, Dublin, Ireland.
3. **A feasibility study of IORT-FLASH using a GPU-based fast Monte Carlo (FRED)**, plenary talk, International Conference on Monte Carlo Techniques for Medical Applications, 11^{th}-13^{th} April 2022, Antwerp, Belgium.
4. **Inter-fractional monitoring in Particle Therapy treatments with ^{12}C ions exploiting the detection of charged secondary particles**, parallel talk, ANPC Applied Nuclear Physics Conference 12^{th}-17^{th} September 2021, Prague, Czech Republic.
5. **Prostate cancer FLASH therapy treatments with electrons of high energy: a feasibility study**, parallel talk, PTCOG 59 Annual Conference of the Particle Therapy Co-operative Group (ONLINE) , 4^{th}-7^{th} June 2021, Rome, Italy.

Articles

1. Pellegrini R. et al, *Novel gamma tracker for rapid radiation direction detection for UAV drone use*. Paper presented at the 2019 IEEE Nuclear Science Symposium and Medical Imaging Conference,
2. G. Traini et al, *Performance of the ToF detectors in the foot experiment* Nuovo Cimento Della Societa Italiana Di Fisica C, 43(1).
3. F. Collamati et al, *Stability and efficiency of a CMOS sensor as detector of low energy β and γ particles* Journal of Instrumentation, 15(11)
4. M. Toppi et al, *The MONDO Tracker: Characterisation and Study of Secondary Ultrafast Neutrons Production in Carbon Ion Radiotherapy*
5. M. Fischetti et al, *Inter-fractional monitoring of ^{12}C ions treatments: results from a clinical trial at the CNAO facility* Scientific Reports, 10(1)
6. G. Galati et al., *Charge identification of fragments with the emulsion spectrometer of the FOOT experiment* Open Physics, 19(1), 383-394.
7. E. Fiorina et al, *Detection of interfractional morphological changes in proton therapy: A simulation and in vivo study with the INSIDE in-beam PET* Frontiers in Physics, 8
8. G. Battistoni E. et al, *Measuring the Impact of Nuclear Interaction in Particle Therapy and in Radio Protection in Space: the FOOT Experiment* Frontiers in Physics, 8.
9. M. Toppi et al, *PAPRICA: The pair production imaging Chamber—Proof of principle* Frontiers in Physics, 9.
10. L. Faillace et al., *Compact S-band Linear Accelerator System for FLASH Radiotherapy* Physical Review Accelerators and Beams (2021)
11. M. Toppi et al., *Monitoring Carbon Ion Beams Transverse Position Detecting Charged Secondary Fragments: Results From Patient Treatment Performed at CNAO* Frontiers in Oncology, 2021, 11, 601784
12. A.C. Kraan et al, *Charge identification of nuclear fragments with the FOOT time-of-flight system* Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, De-
13. G. Calvi et al., *PAPRICA: The PAir PRoduction Imaging ChAmber* Nuovo Cimento della Società Italiana di Fisica C, 2021, 44(4-5),147
14. S. Colombi et al., *Enhancing the understanding of fragmentation processes in hadrontherapy and radioprotection in space with the FOOT experiment* Physica Scripta, 2021, 96(11), 11401
15. Sarti A. et al., *Deep Seated Tumour Treatments With Electrons of High Energy Delivered at FLASH Rates: The Example of Prostate Cancer* Frontiers in Oncology, 2021, 11, 777852.
16. Kraan, A.C. et al., *Localization of anatomical changes in patients during proton therapy with in-beam PET monitoring: A voxel-based morphometry approach exploiting Monte Carlo simulations* Medical Physics, 2022, 49(1), pp. 23–40
17. A. Rahman et al., *FLASH radiotherapy treatment planning and models for electron beams* Radiotherapy and Oncology, 2022, 12, 929949,.
18. M. De Simoni et al., *A Data-Driven Fragmentation Model for Carbon Therapy GPU-Accelerated Monte-Carlo Dose Recalculation* Frontiers in Oncology, 2022, 12, 2234-943X.
19. M. Moglioni et al., *In-vivo range verification analysis with in-beam PET data for patients treated with proton therapy at CNAO* Frontiers in Oncology, 2022, 12, 929949,.
20. A. Trigilio et al., *The FlashDC project: Development of a beam monitor for FLASH radiotherapy* Nuclear Instruments and Methods in Physics Research, Section A, 2022,.
21. M. Toppi et al., *Elemental fragmentation cross sections for a 16O beam of 400 MeV/u kinetic energy interacting with a graphite target using the FOOT ΔE-TOF detectors*
22. A.C. Kraan et al., *Calibration and performance assessment of the TOF-Wall detector of the FOOT experiment*
23. L. Galli et al., *The fragmentation trigger* of the FOOT experiment Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, De-
24. G. Franciosini et al., *GPU-accelerated Monte Carlo simulation of electron and photon interactions for radiotherapy applications* Accepted in Physics in Medicine & Biology

Introduction

From full to fast Monte Carlo

ANALYTICAL ALGORITHMS

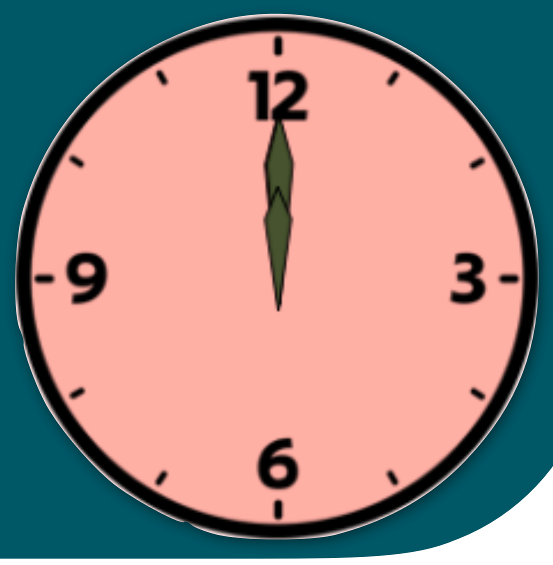
- Reasonable times for calculating the TPS
- Simplified representation of the tissue: the geometry of the patient is represented in an equivalent volume of water, neglecting the real atomic composition of the tissues.
- **Not high accuracy**

Ex. Proton TPS
~ 1 h/core

MONTE CARLO

- Realistic assessment of body composition
- Extracts accuracy in the description of the transport and the interaction of the particles with matter
- **Long times for calculating the TPS**

Ex. Proton TPS
~ days/core



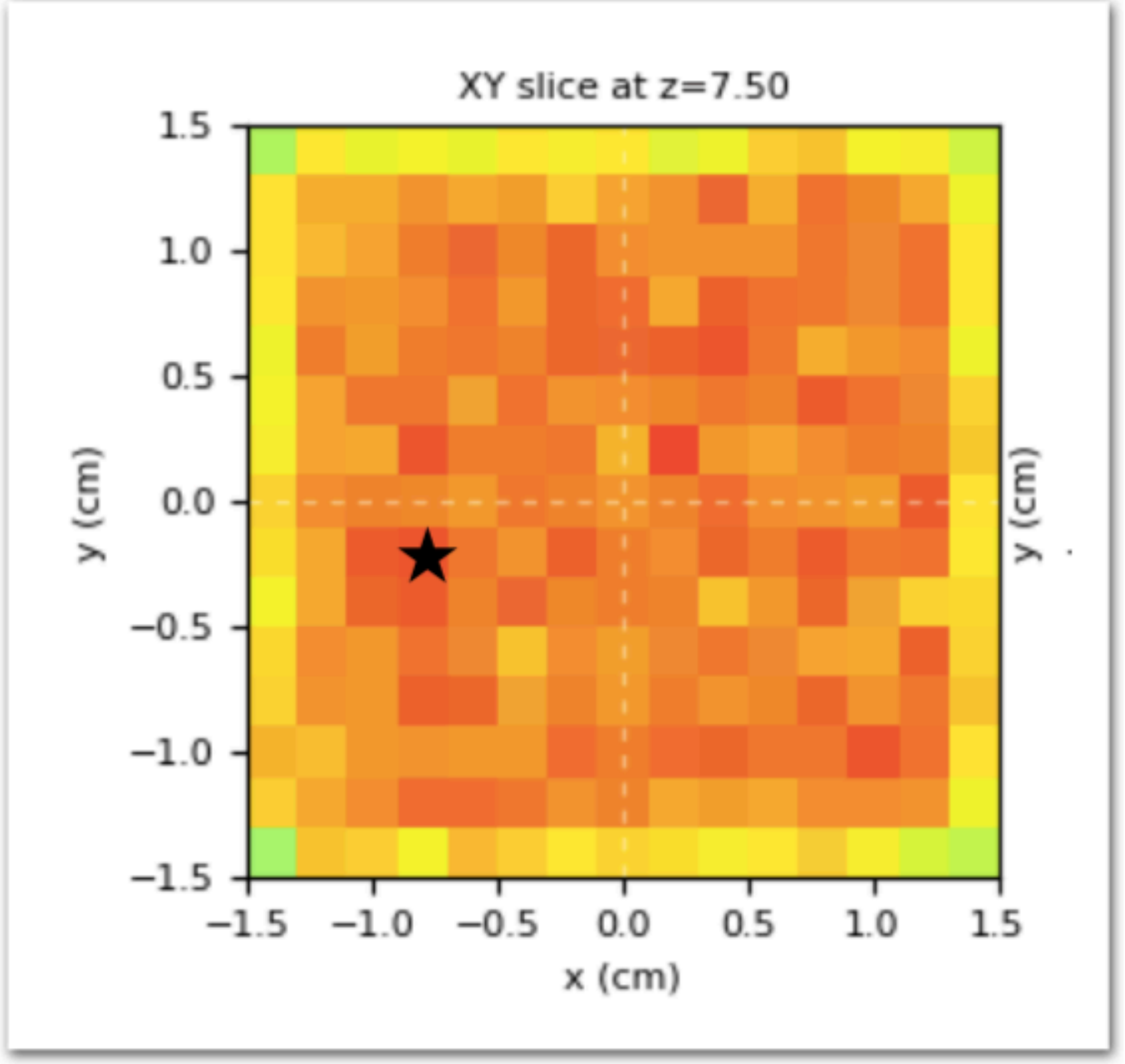
FAST MONTE CARLO

- High accuracy in the description of the transport and of the interaction of particles with matter
- Realistic assessment of body composition
- **Very fast calculation of TPS**

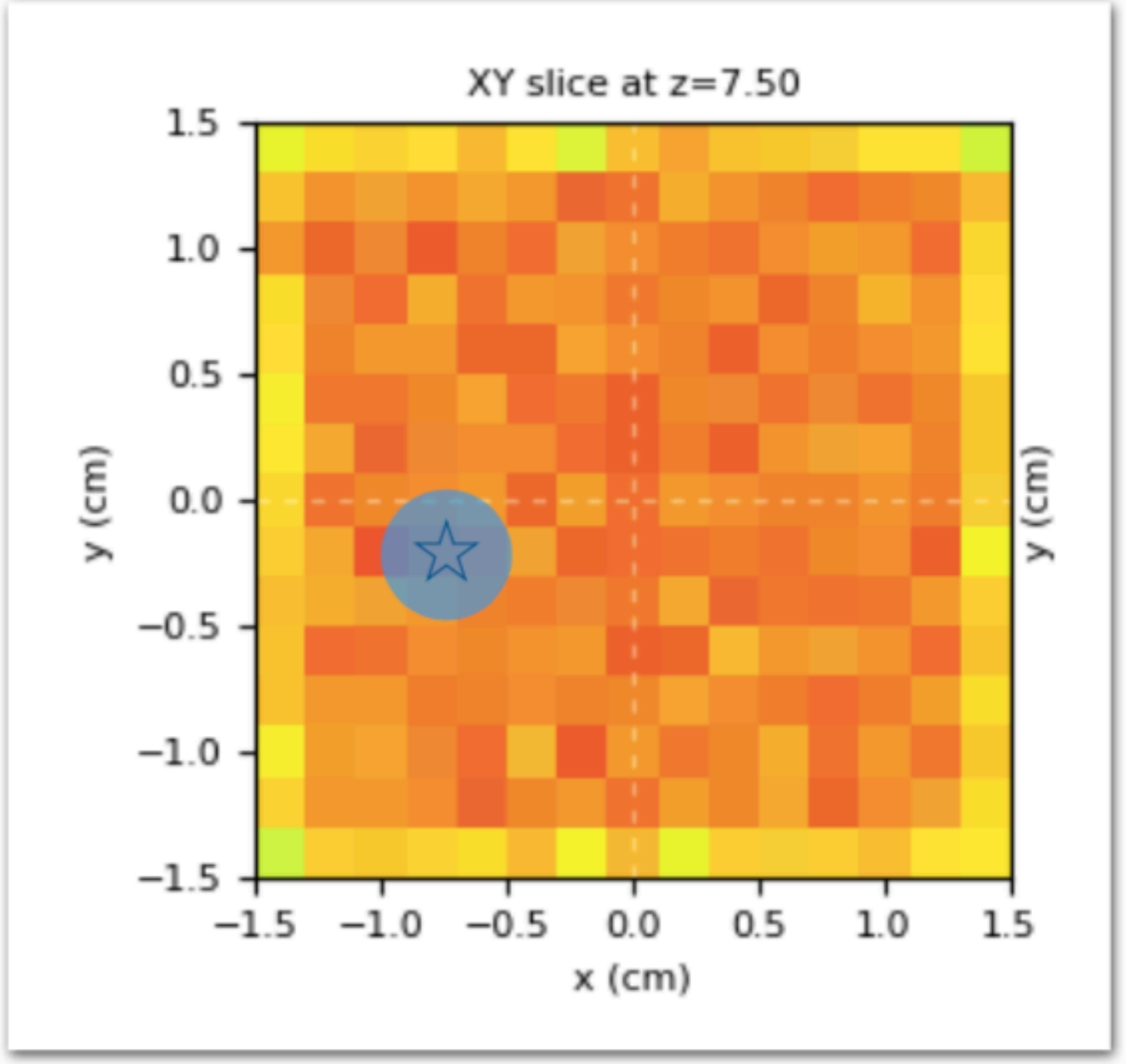
Ex. Proton TPS
~ minutes

Gamma index analysis

Reference Map



Evaluation Map



γ-index 2mm/3%

$$\Gamma(\vec{r_e},\vec{r_r}) = \sqrt{\frac{|\vec{r_e}-\vec{r_r}|^2}{\Delta r^2} + \frac{[D_e(\vec{r_e}) - D_r(\vec{r_r})]^2}{\Delta D^2}}$$

D= dose (D_r of the reference map, D_e of the evaluation map)

r = position of the evaluated point (r_r of the reference map, r_e of the evaluation map)

$$\gamma(\vec{r_r}) = \min\{\Gamma(\vec{r_e},\vec{r_r})\}\forall\{\vec{r_e}\}$$

$\gamma \leq 1$ = test passed

$\gamma > 1$ = test NOT passed

pass rate ≥ 92%
clinical acceptance

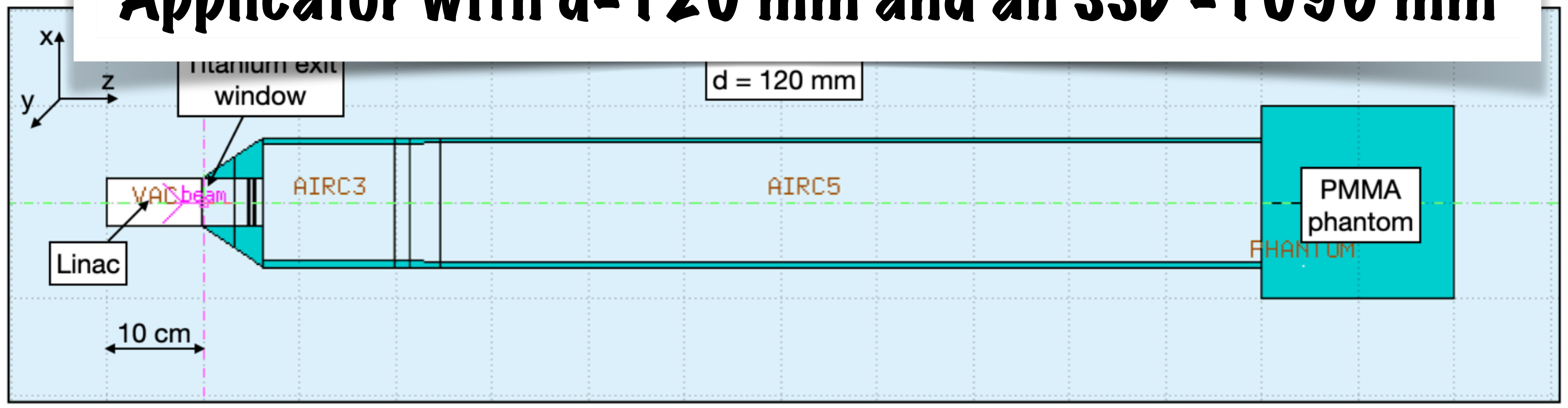
ElectronFlash4000

Characteristics EF4000	Value
Output energy	5 - 7 MeV
Pulse repetition frequency	1 - 250 Hz
Pulse width	0.5 - 4 μs
Maximum peak beam current	120 mA
Dose rate per pulse	$> 10^6$ Gy/s
Mean Dose rate	1000 Gy/s
Max Dose per pulse	30 Gy in a surface of ∅ 10 mm

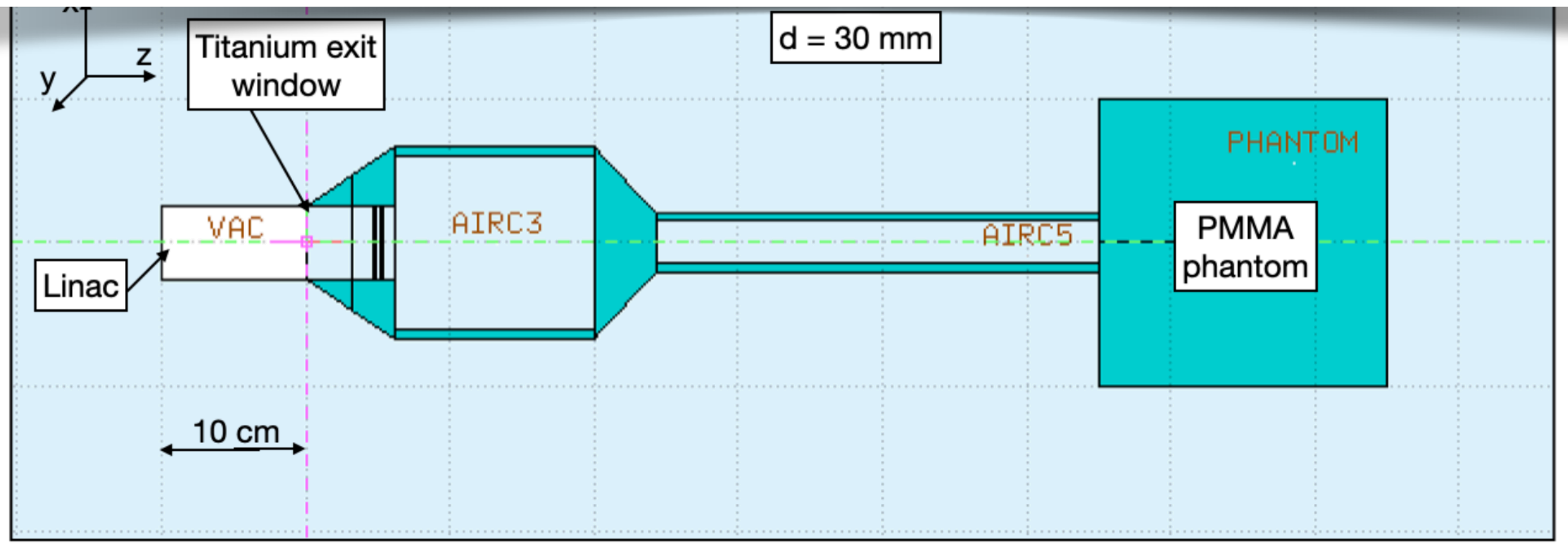
The EF4000 was commissioned by the Curie Institute and it was installed there in August 2020.

I performed the **dosimetric characterization** of the electrons beam produced by the linac by comparing the **experimental data** of the PDD and off-axis profile (Gafchromic EBT-XD films) with the ones obtained with **FLUKA**.

Applicator with d=120 mm and an SSD =1096 mm



Applicator with d=30 mm and an SSD =549 mm



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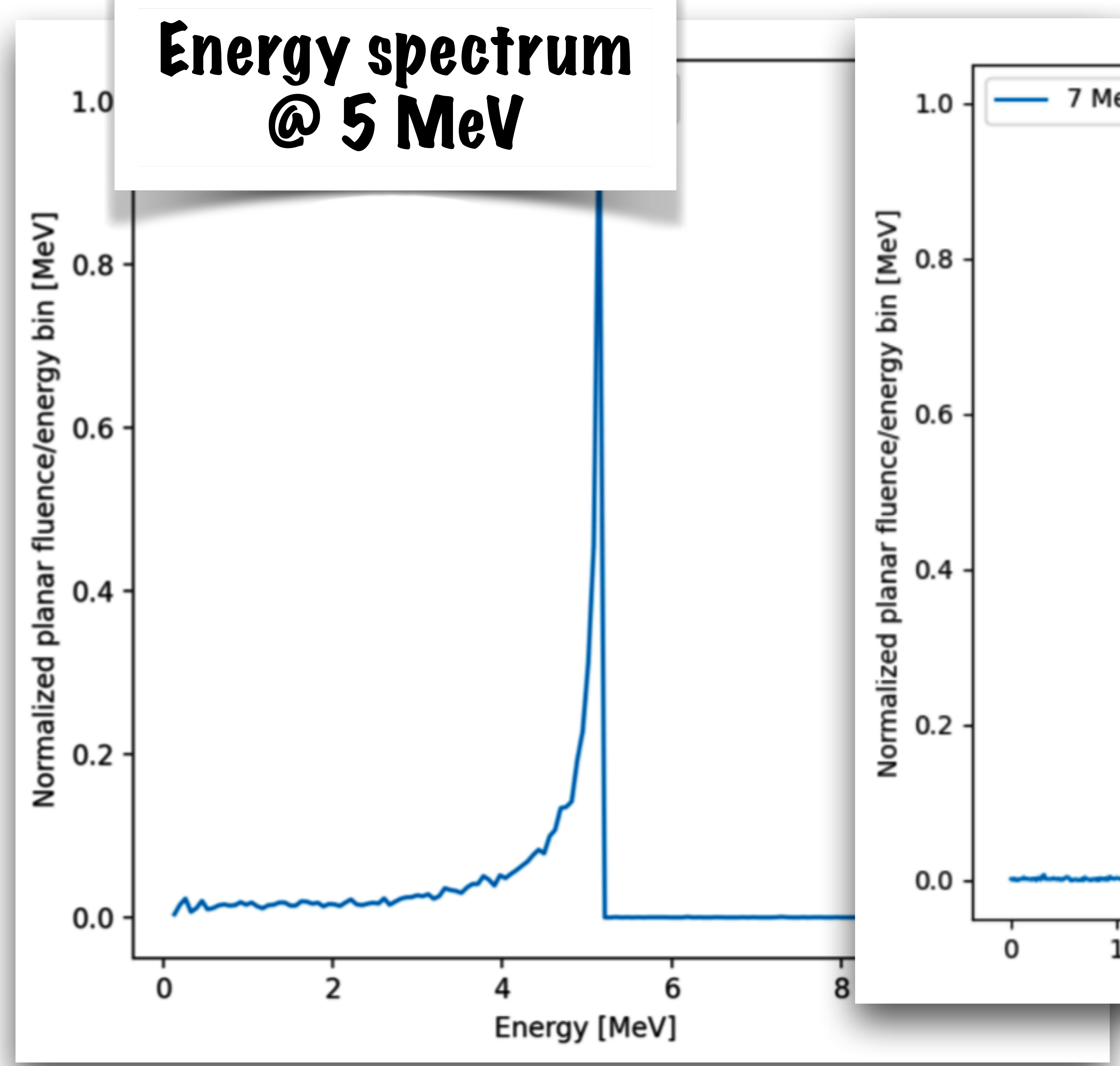
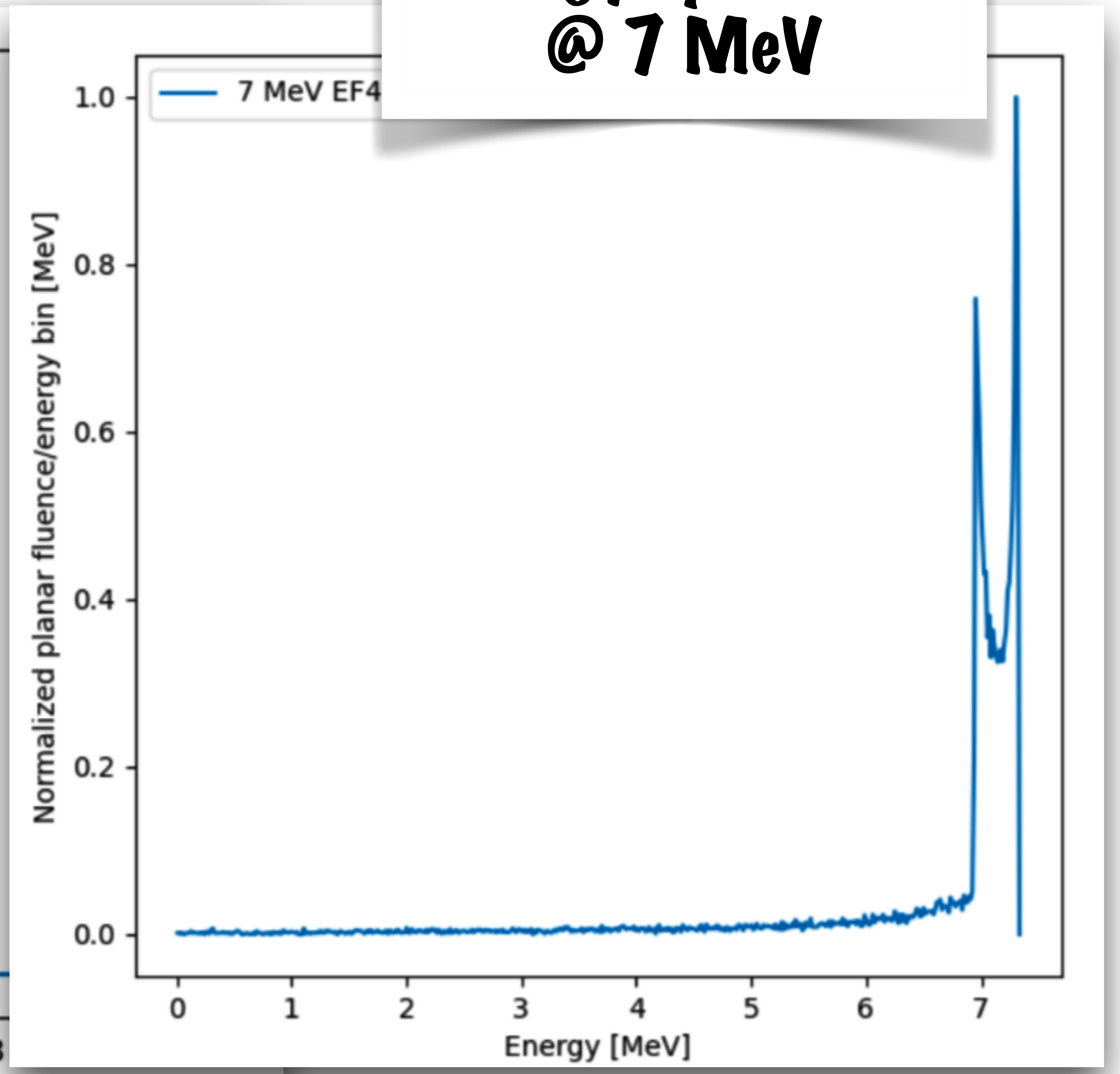
Energy spectrum @ 5 MeV



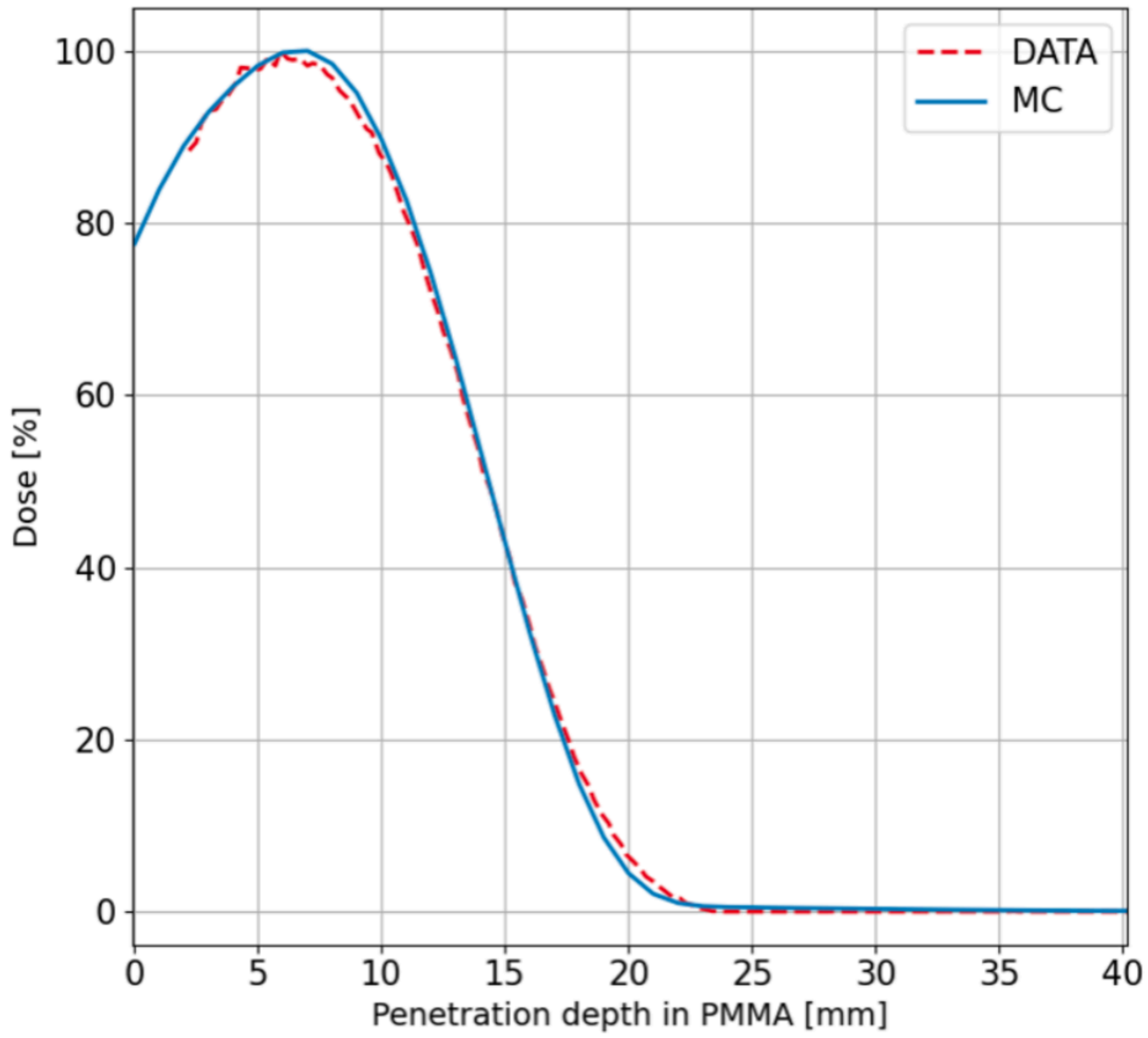
Energy spectrum @ 7 MeV



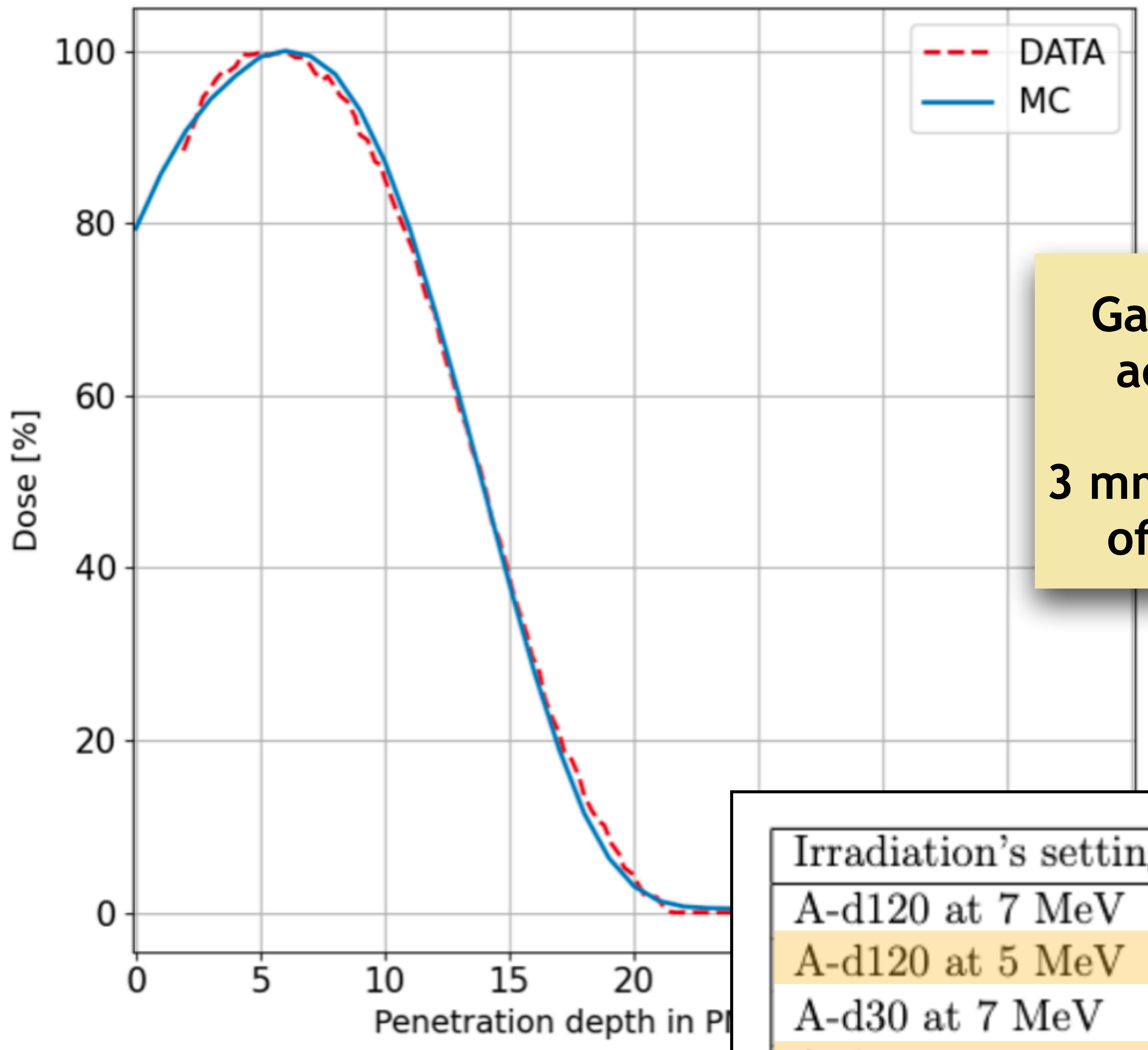
ElectronFlash4000

Example of 5 MeV collimated with the applicator with d=120 mm and 30 mm

d= 30 mm



d= 120 mm



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Gamma index acceptance criteria:
3 mm/3% with 5% of threshold

Irradiation's setting	PDD γ-index
A-d120 at 7 MeV	95.68 %
A-d120 at 5 MeV	99.00 %
A-d30 at 7 MeV	98.67 %
A-d30 at 5 MeV	97.01 %

ElectronFlash4000

Example of 7 MeV collimated with the applicator with d=120 mm and 30 mm

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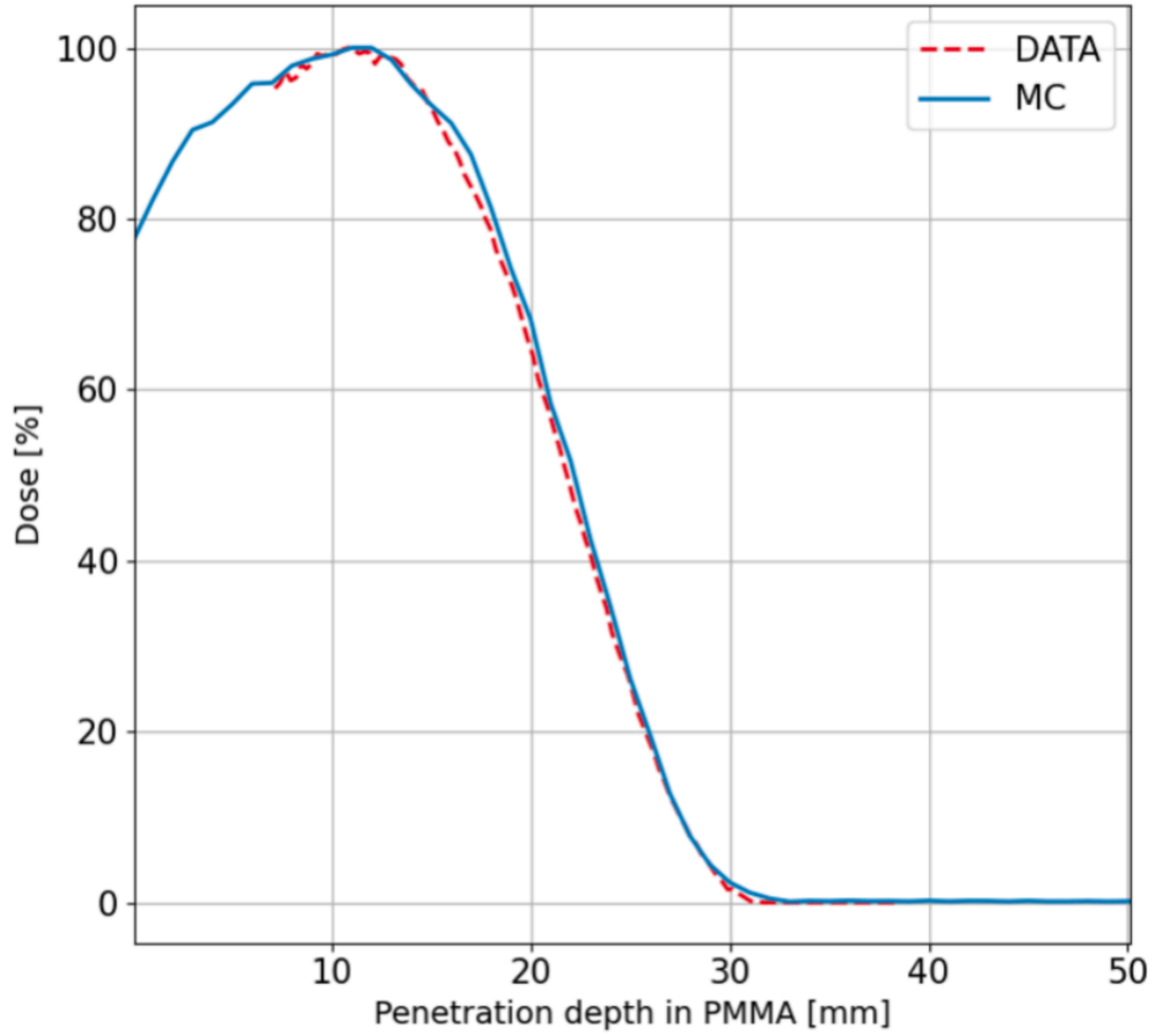
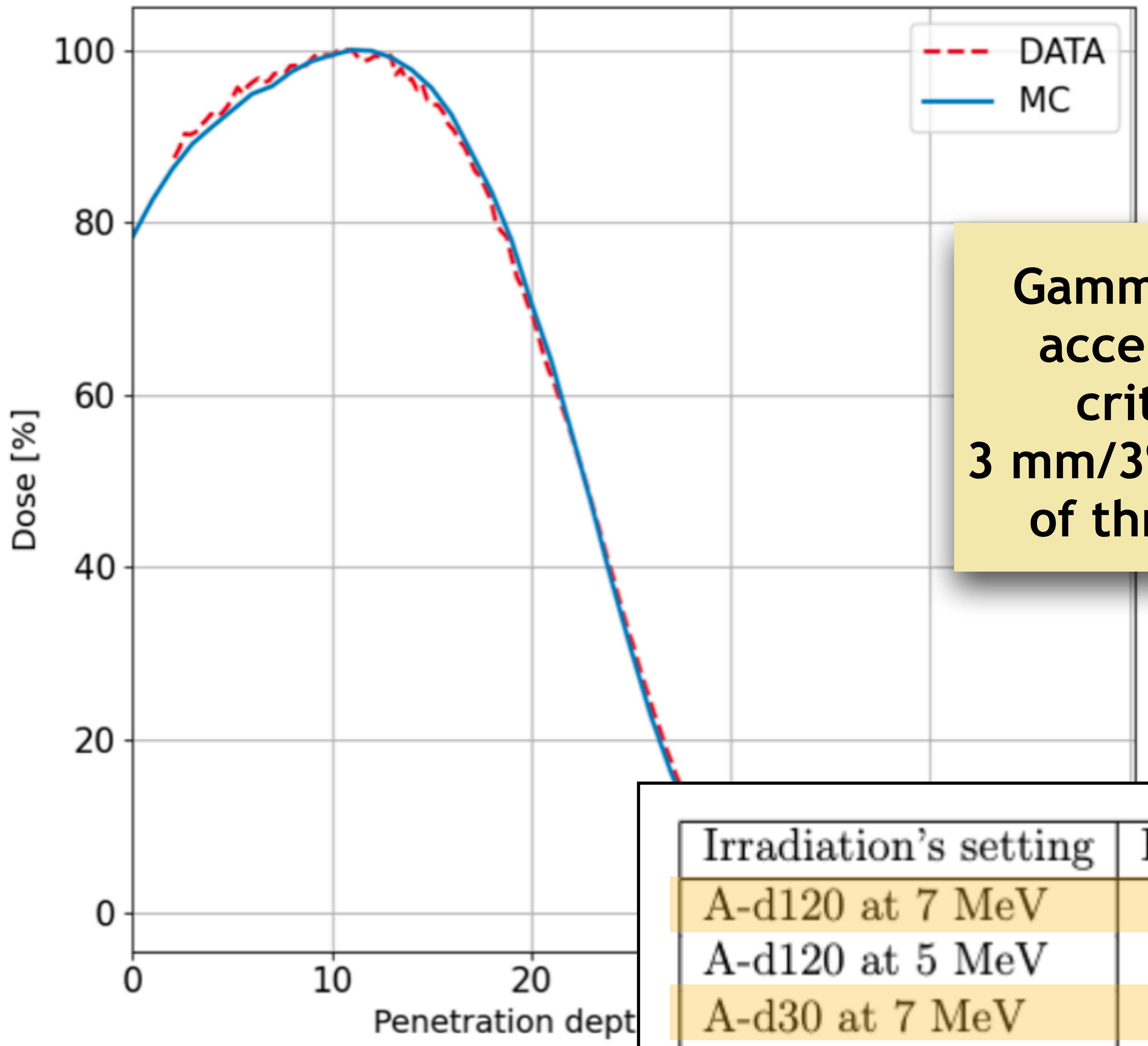
d= 30 mm



d= 120 mm



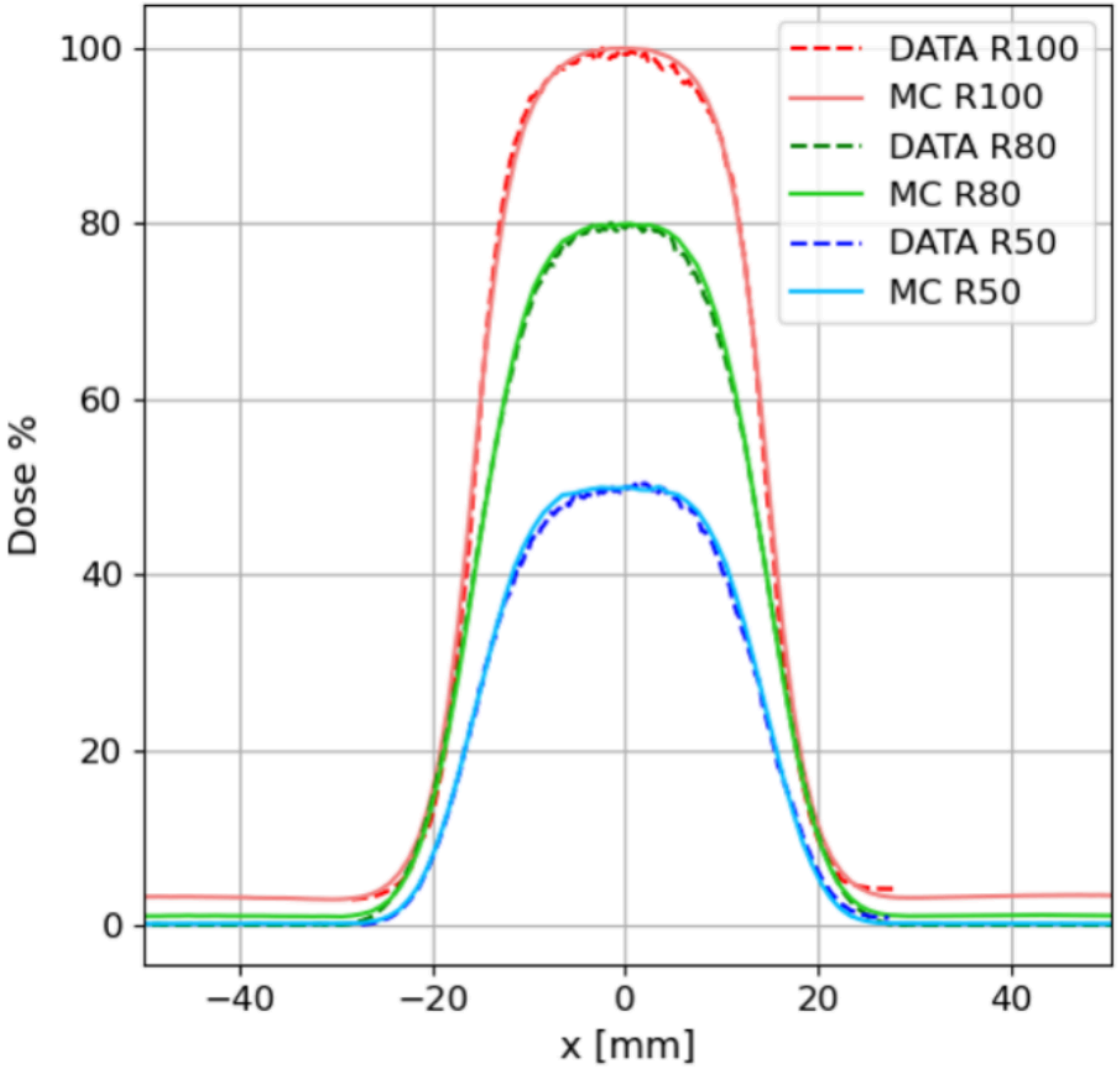
Gamma index acceptance criteria:
3 mm/3% with 5% of threshold

Irradiation's setting	PDD γ-index
A-d120 at 7 MeV	95.68 %
A-d120 at 5 MeV	99.00 %
A-d30 at 7 MeV	98.67 %
A-d30 at 5 MeV	97.01 %

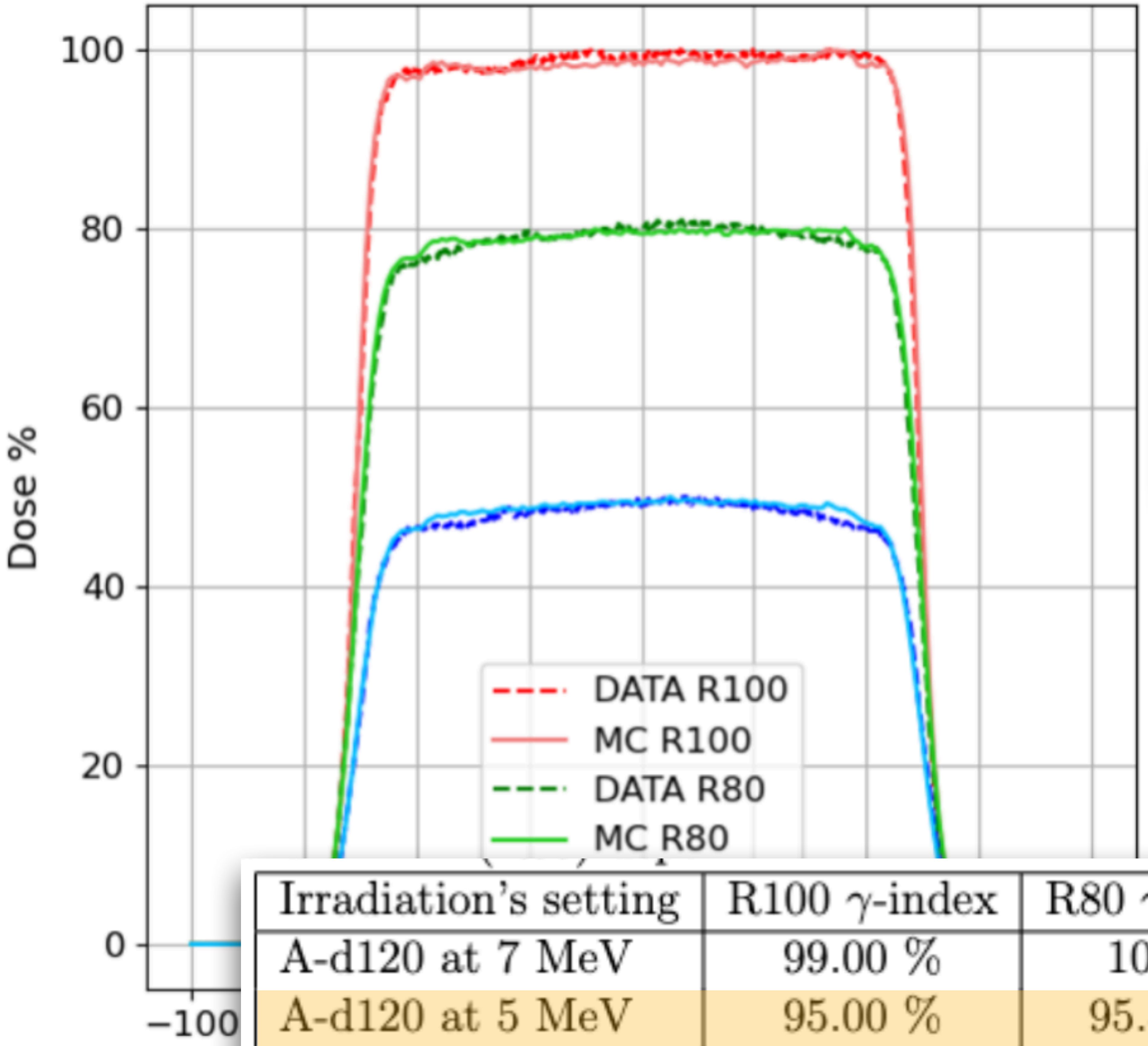
ElectronFlash4000

Example of 5 MeV collimated with the applicator with d=120 mm and 30 mm

d= 30 mm



d= 120 mm



Gamma index acceptance criteria:
3 mm/3% with 5% of threshold

Irradiation's setting	R100 γ-index	R80 γ-index	R50 γ-index
A-d120 at 7 MeV	99.00 %	100 %	96.29 %
A-d120 at 5 MeV	95.00 %	95.57 %	95.00 %
A-d30 at 7 MeV	98.40 %	99.60 %	99.60 %
A-d30 at 5 MeV	96.01 %	100 %	96.41 %

ElectronFlash4000

Example of 7 MeV collimated with the applicator with d=120 mm and 30 mm

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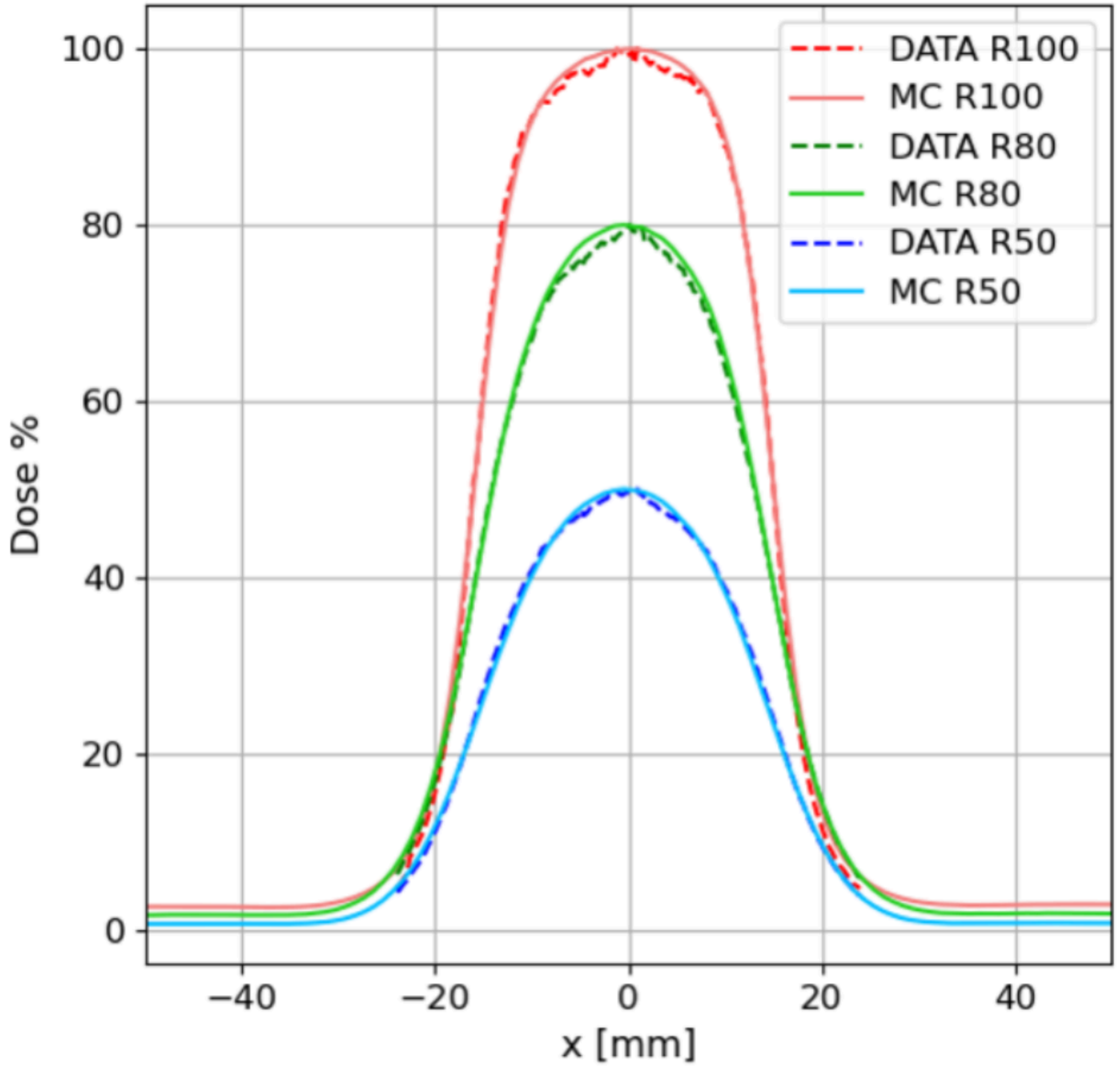
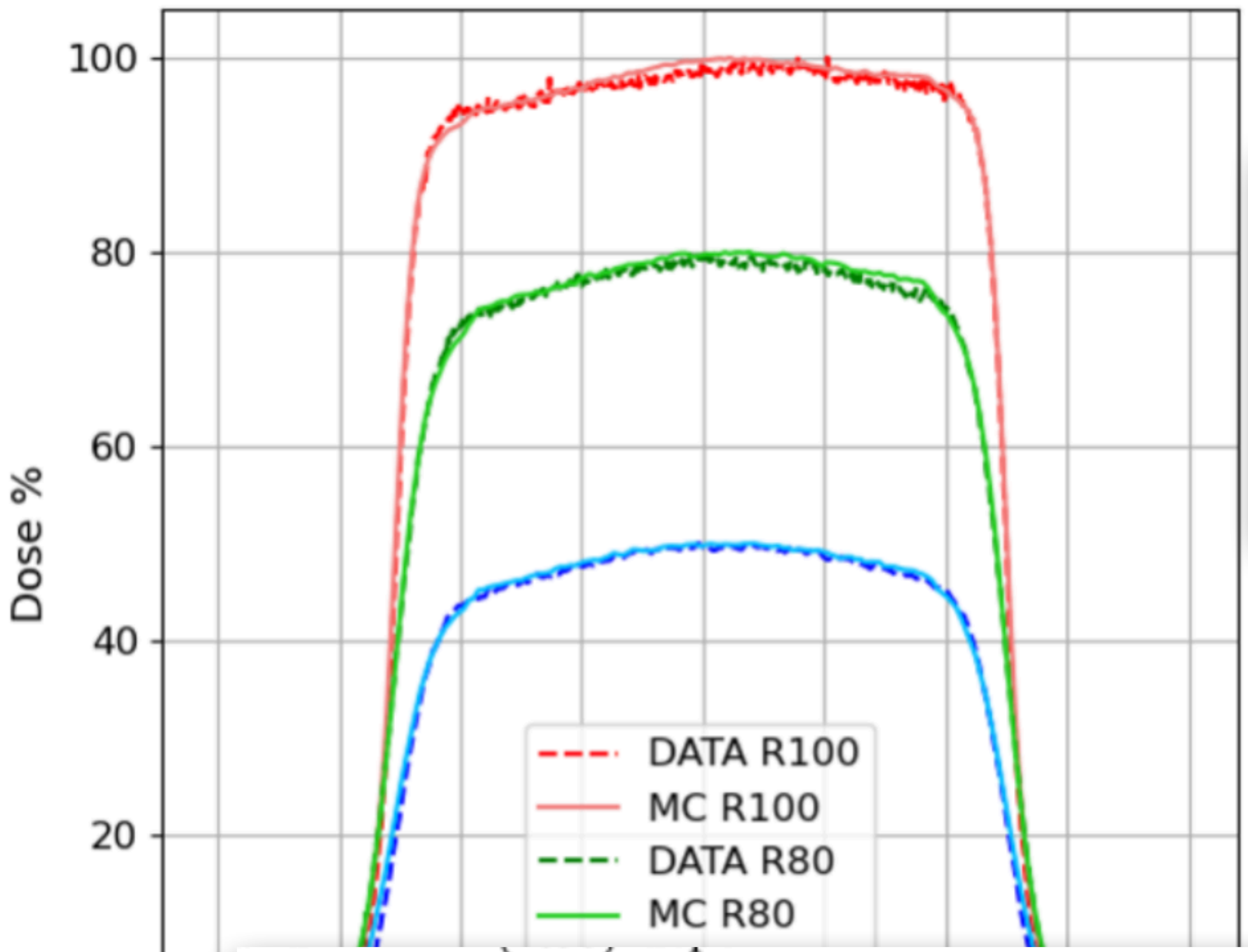
d= 30 mm



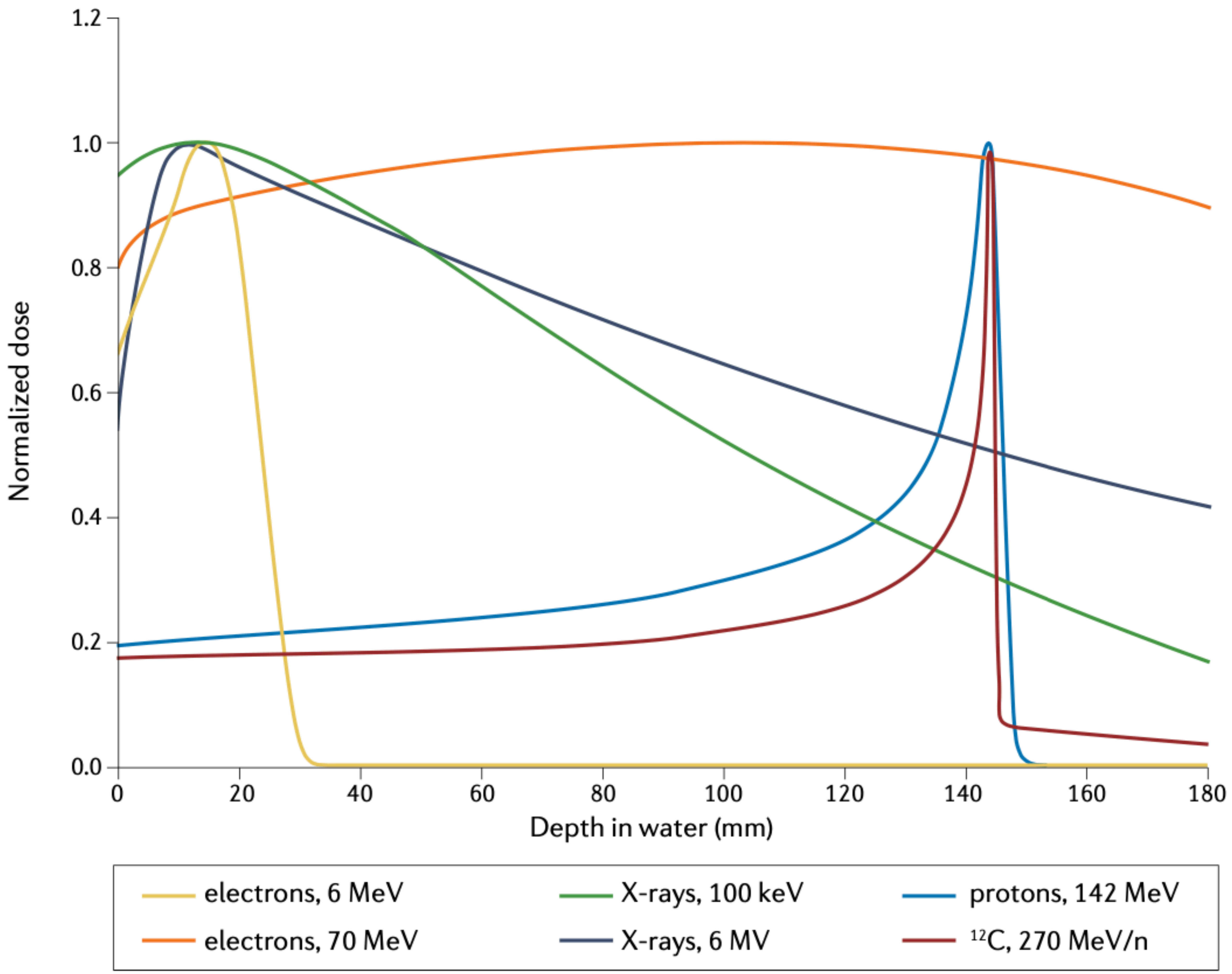
d= 120 mm



Gamma index acceptance criteria:
3 mm/3% with 5% of threshold

Irradiation's setting	R100 γ-index	R80 γ-index	R50 γ-index
A-d120 at 7 MeV	99.00 %	100 %	96.29 %
A-d120 at 5 MeV	95.00 %	95.57 %	95.00 %
A-d30 at 7 MeV	98.40 %	99.60 %	99.60 %
A-d30 at 5 MeV	96.01 %	100 %	96.41 %

PDD e, photon, proton, carbon ion



FLASH

FLASH regime

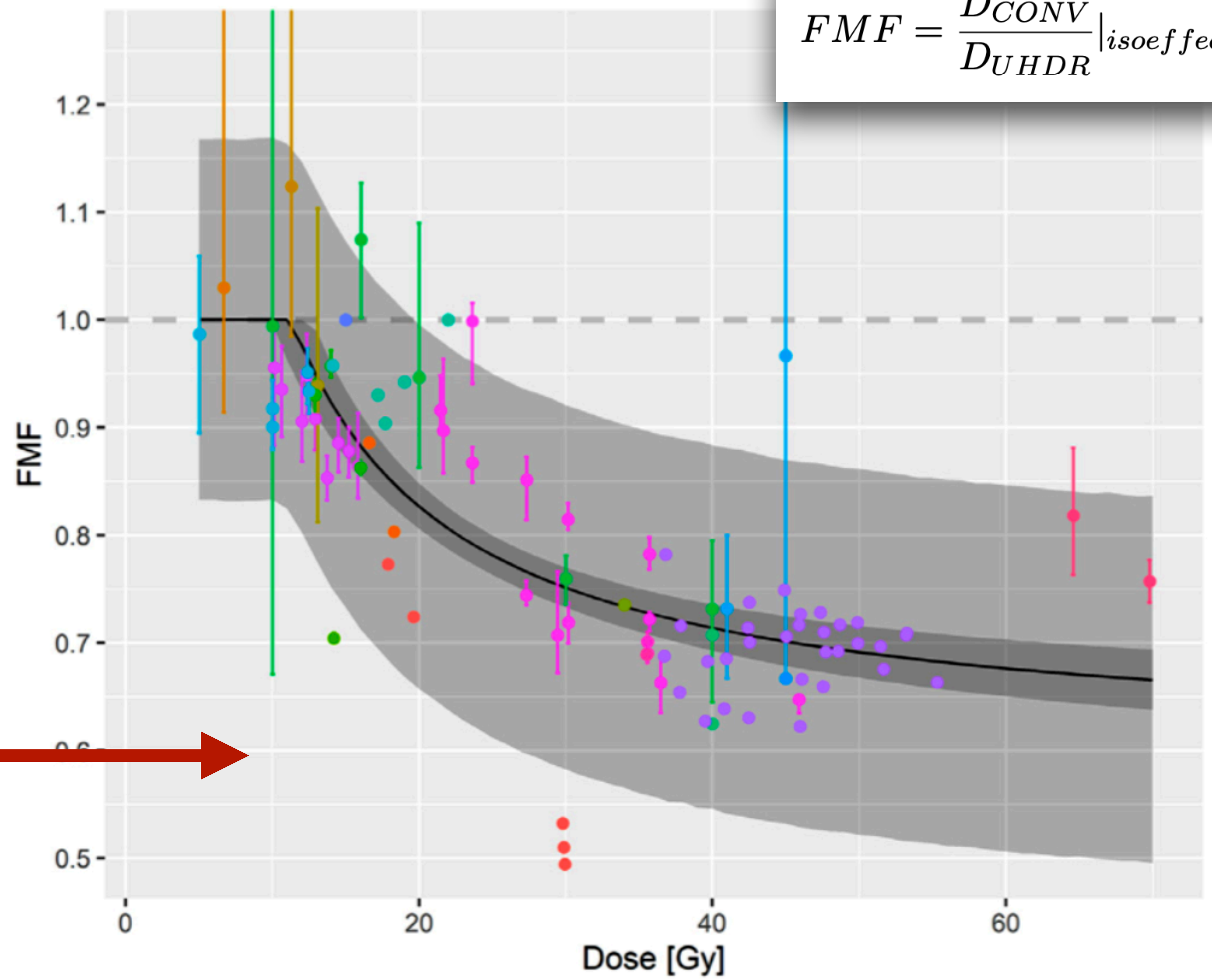
Several pre-clinical studies recently claimed that the toxicity in healthy tissues related to tumour treatments can be significantly reduced (from 80% down to 60%), while keeping the same efficacy in cancer killing, if the dose rate is radically increased (> 40 **Gy/s**, or even more) with respect to conventional treatments (~**0.01 Gy/s**).

Observed with **electrons**, **photons** and **protons** but a combination of different parameters must be reached to work in FLASH regime:

1. Mean dose rate > 40 Gy/s (total dose/total treatment time)
2. Total treatment time ~ 100 ms
3. Pulse width 0.1-4 μs
4. Dose per pulse > 1-2 Gy
5. Instantaneous Dose Rate > 10^6 Gy/s (Dose / pulse width)
6. Dose threshold ~ 4/5 Gy

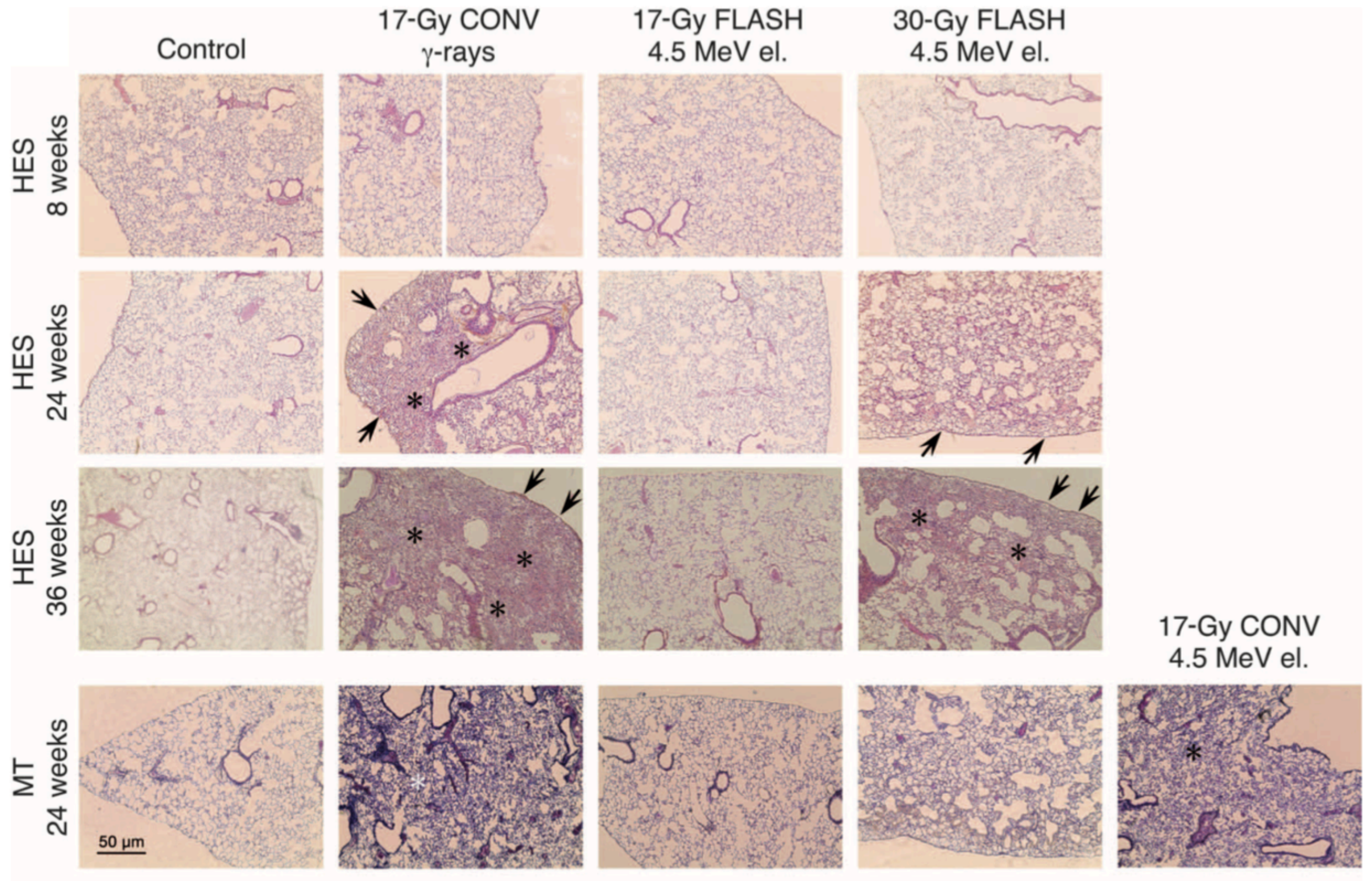
ecc..

$$FMF = \frac{D_{CONV}}{D_{UHDR}}\Big|_{isoeffect}$$



FLASH effect

Mice

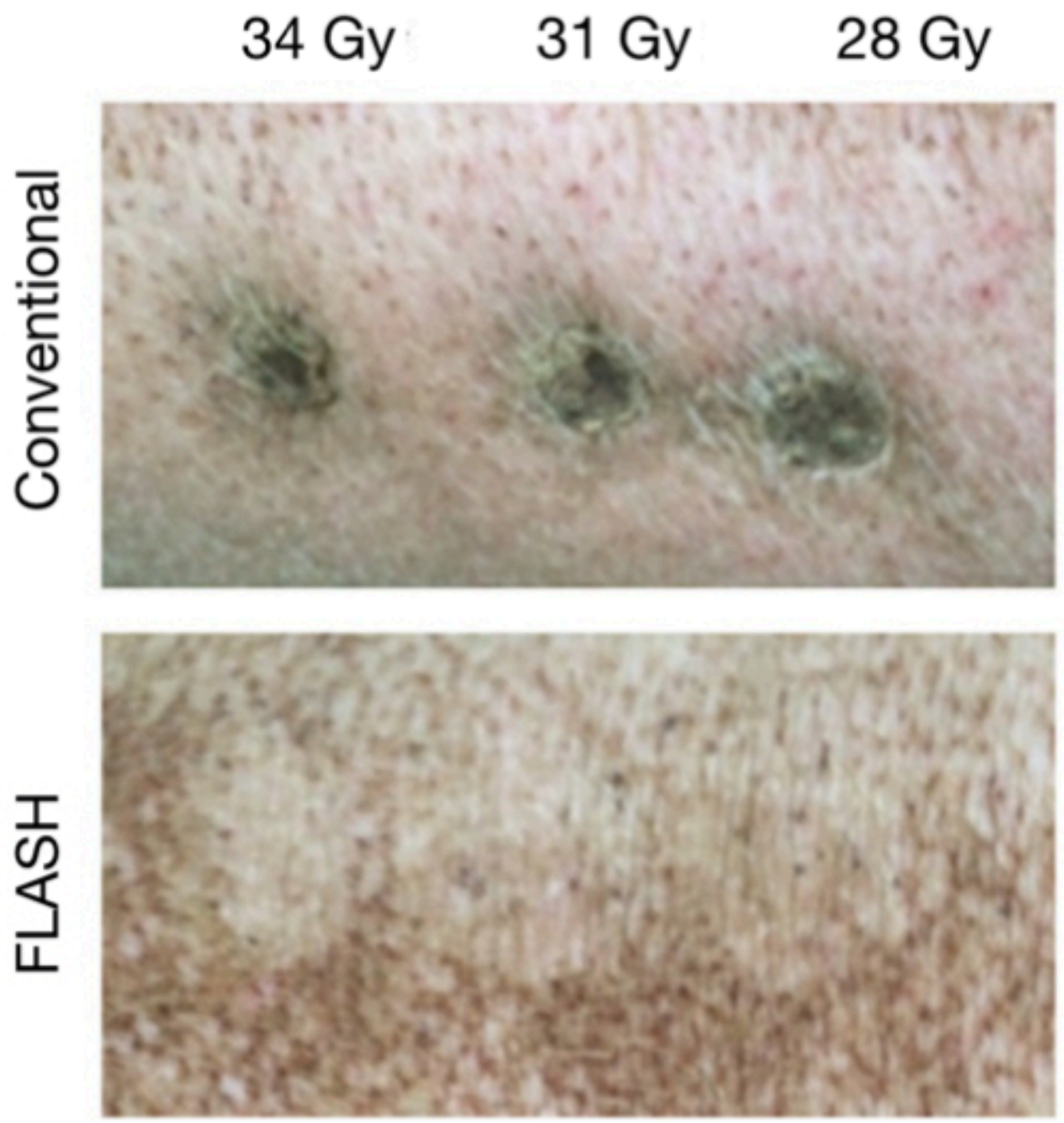


Mice were subjected to thorax exposure to CONV or FLASH irradiation in a single fraction.

Massive fibrotic lesions were observed at 24 weeks after 17-Gy conventional, whereas 30-Gy FLASH irradiation only elicited rare fibrotic patches at this time point.

DOI: 10.1126/scitranslmed.3008973

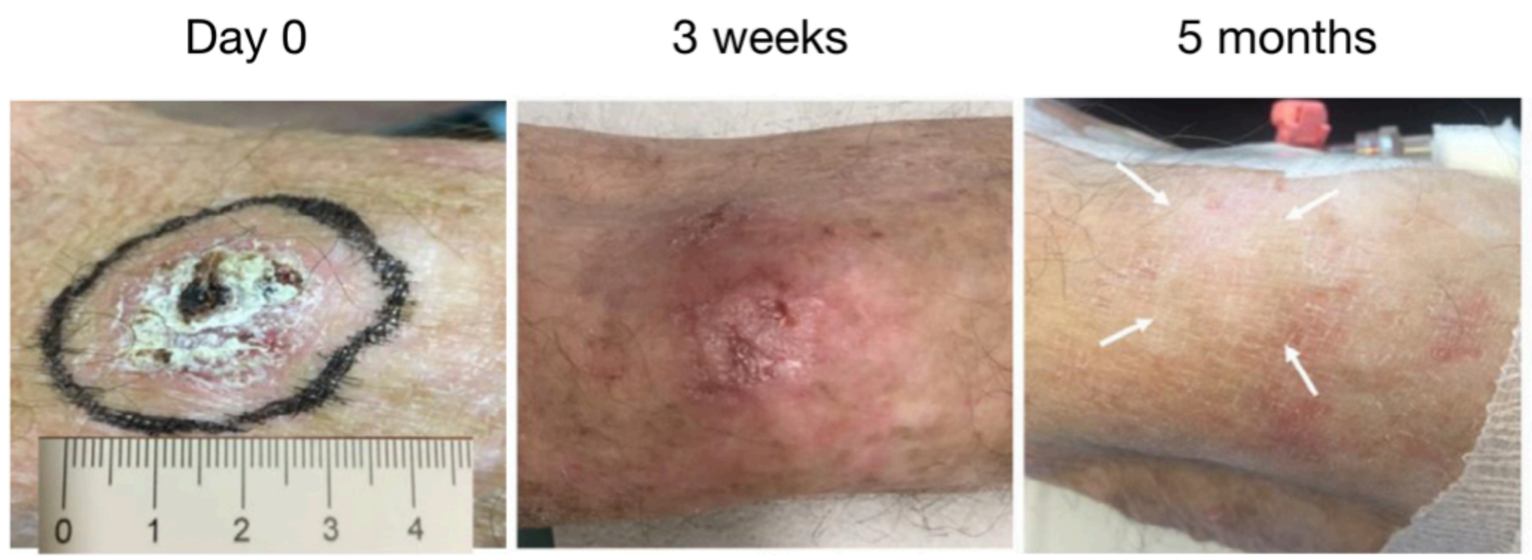
Test on mini-pig skin



No skin reaction in FLASH-RT

DOI: 10.1158/1078-0432.CCR-17-3375

First FLASH therapy patient



The tumor was irradiated with 6 MeV electrons. The dose releases was 15 Gy with a mean dose rate equal to 166 Gy/s

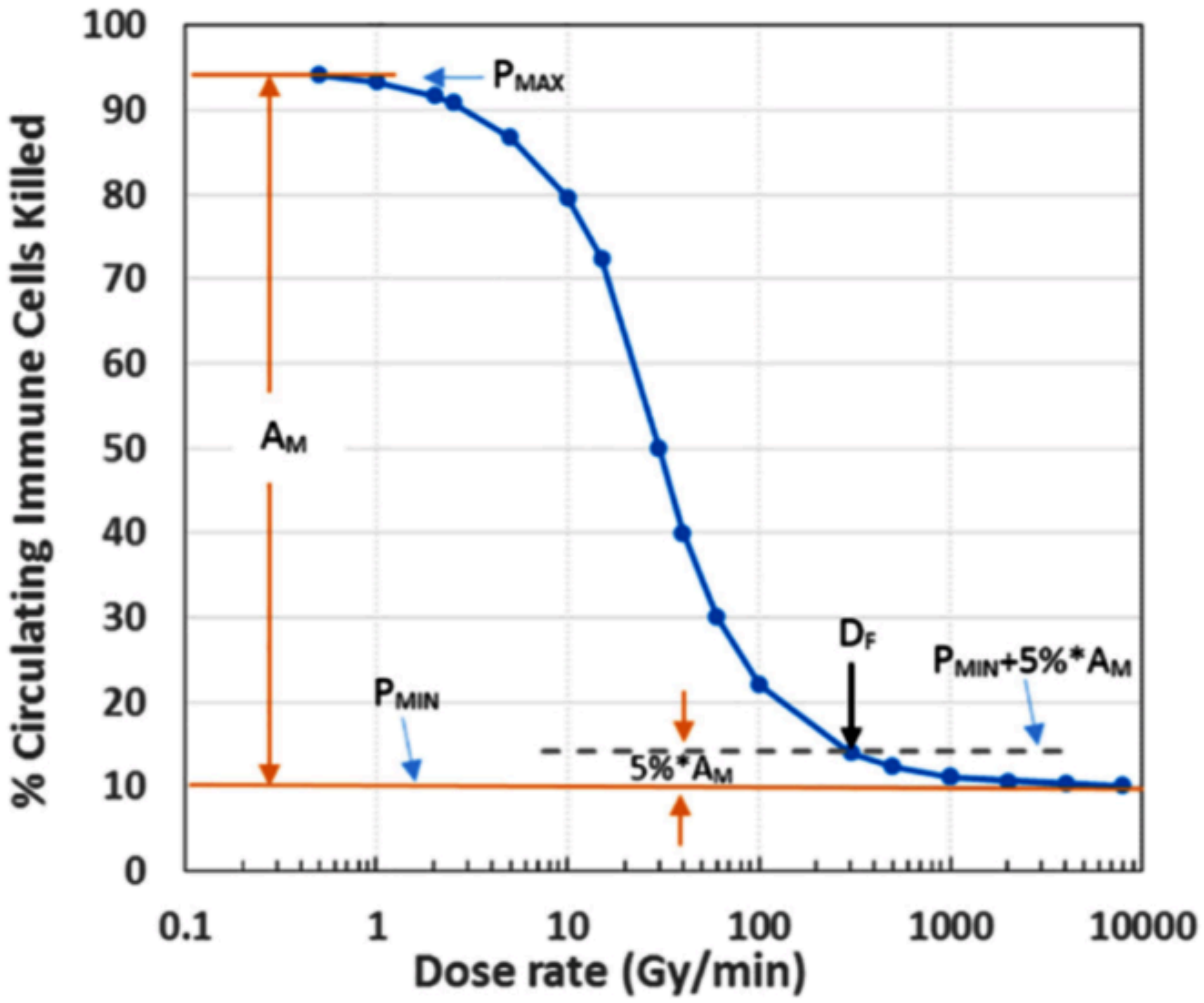
Complete tumor response at 36 days

DOI: 10.1016/j.radonc.2019.06.019

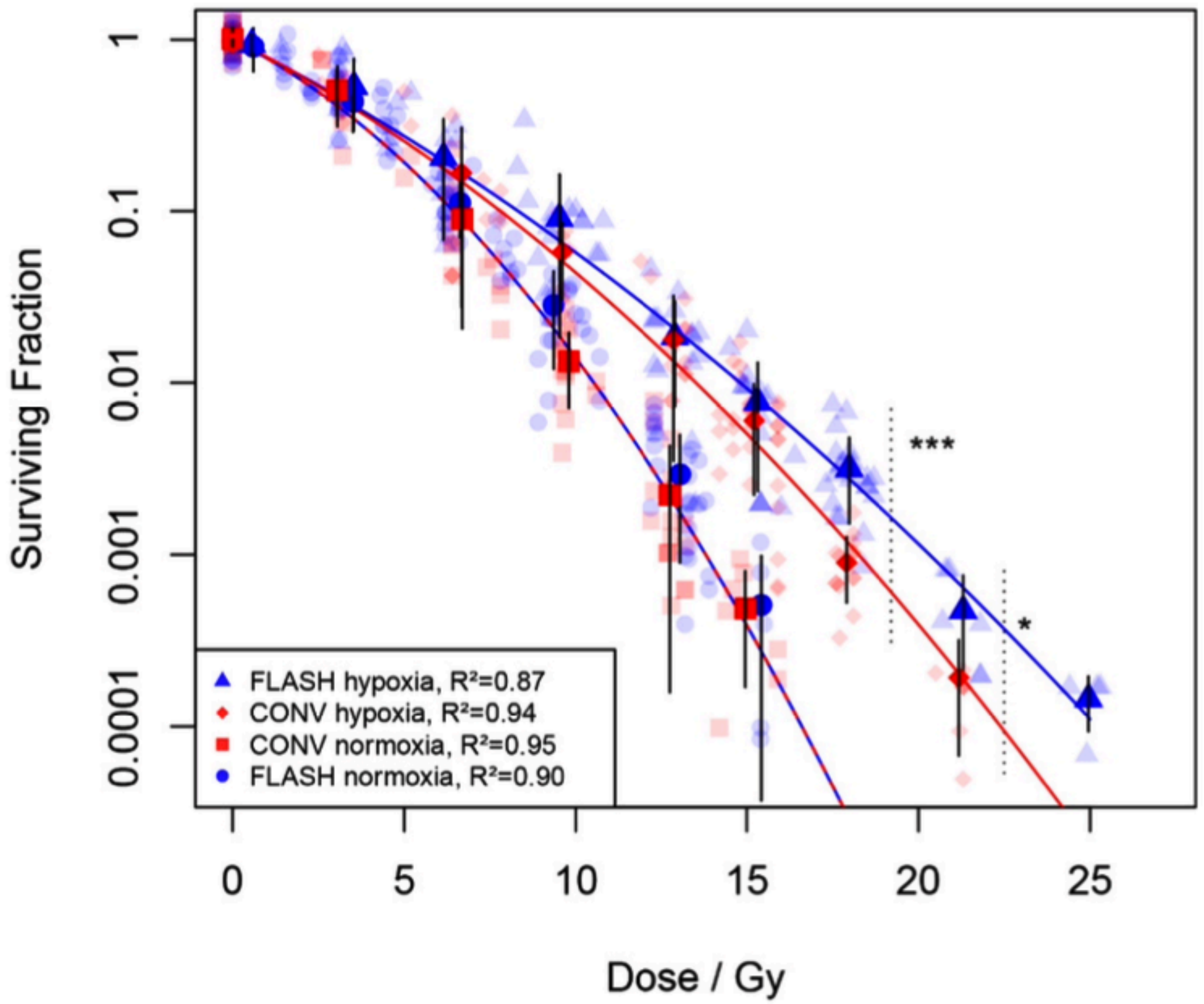
FLASH mechanism

The mechanism responsible for reduced tissue toxicity following FLASH radiotherapy is yet to be clarified

1. Modification of the immune response



2. Oxygen depletion



From CONV to FLASH linac

	LINAC characteristics
Parameter	standard value
Output Energies	3-to-12 MeV in steps
Pulse length	4 μs
Peak current	1.5 mA
Repetition frequency	1-30 Hz
Dose rate	> 4 and < 31 Gy/min

	EF characteristics
EF features	Value
Frequency	2.998 GHz
Magnetron Power	3.1 MW
Number of Cells	11
Linac Length	52 cm
Beam current	> 100 mA
Shunt impedance R	77.5 MΩ/m
Quality factor Q	14877
Electron beam capture	$> 40\%$

ElectronFlash

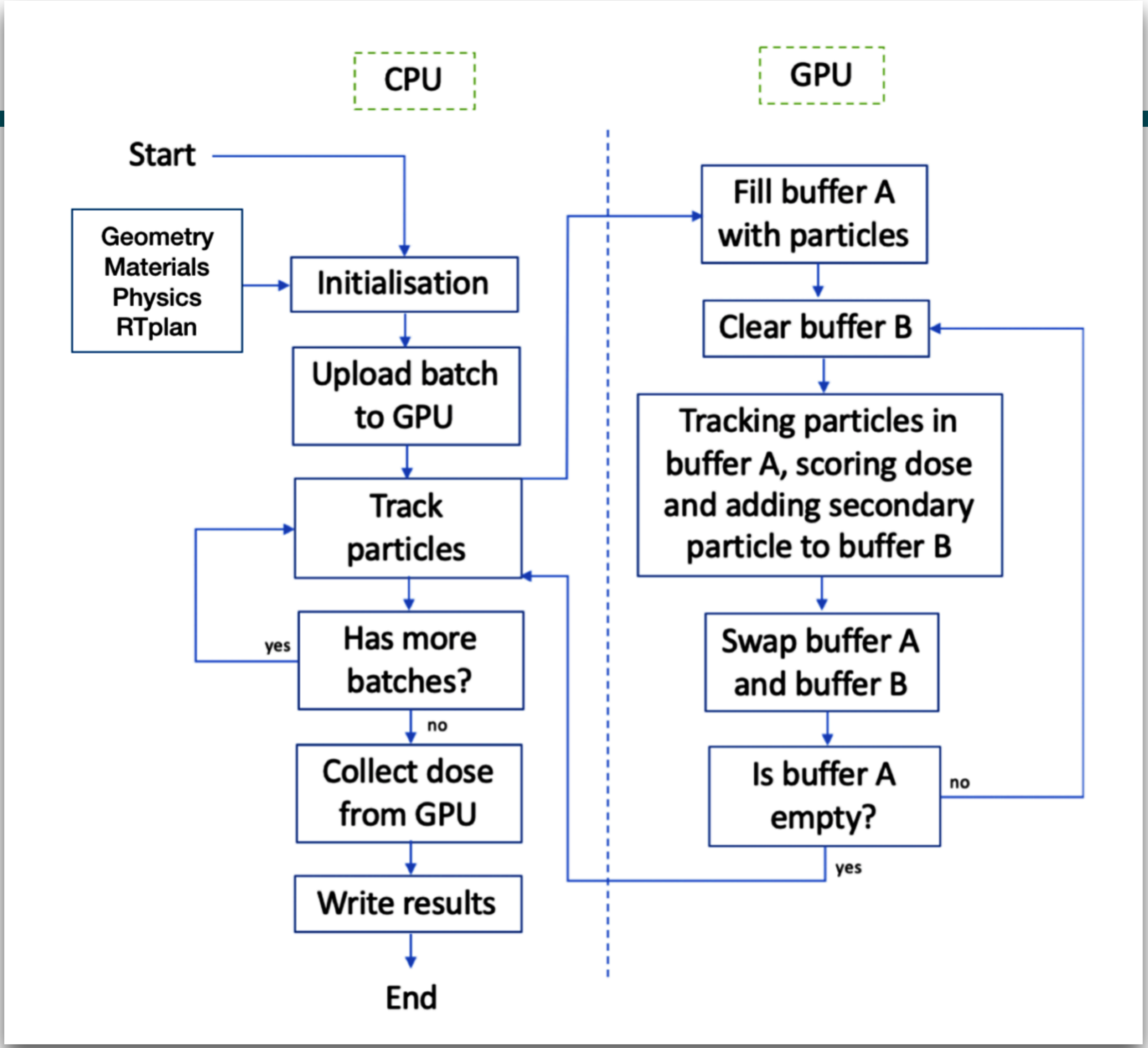
SIT

τ_{pulse}	0.5-4 μs	Beam Intensity	100 mA	Istantaneus Dose rate	7.6×10^6 Gy/s

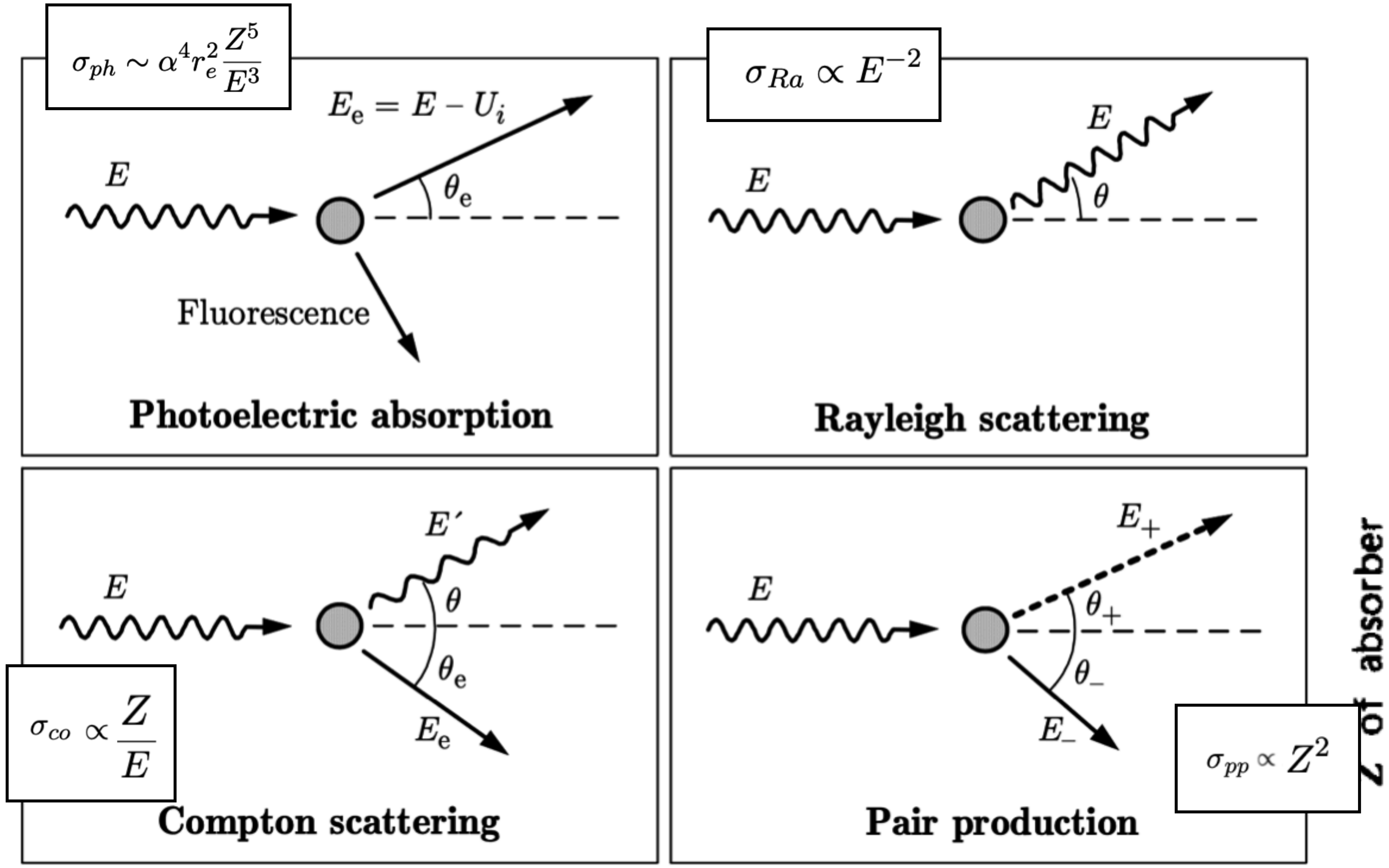
FRED

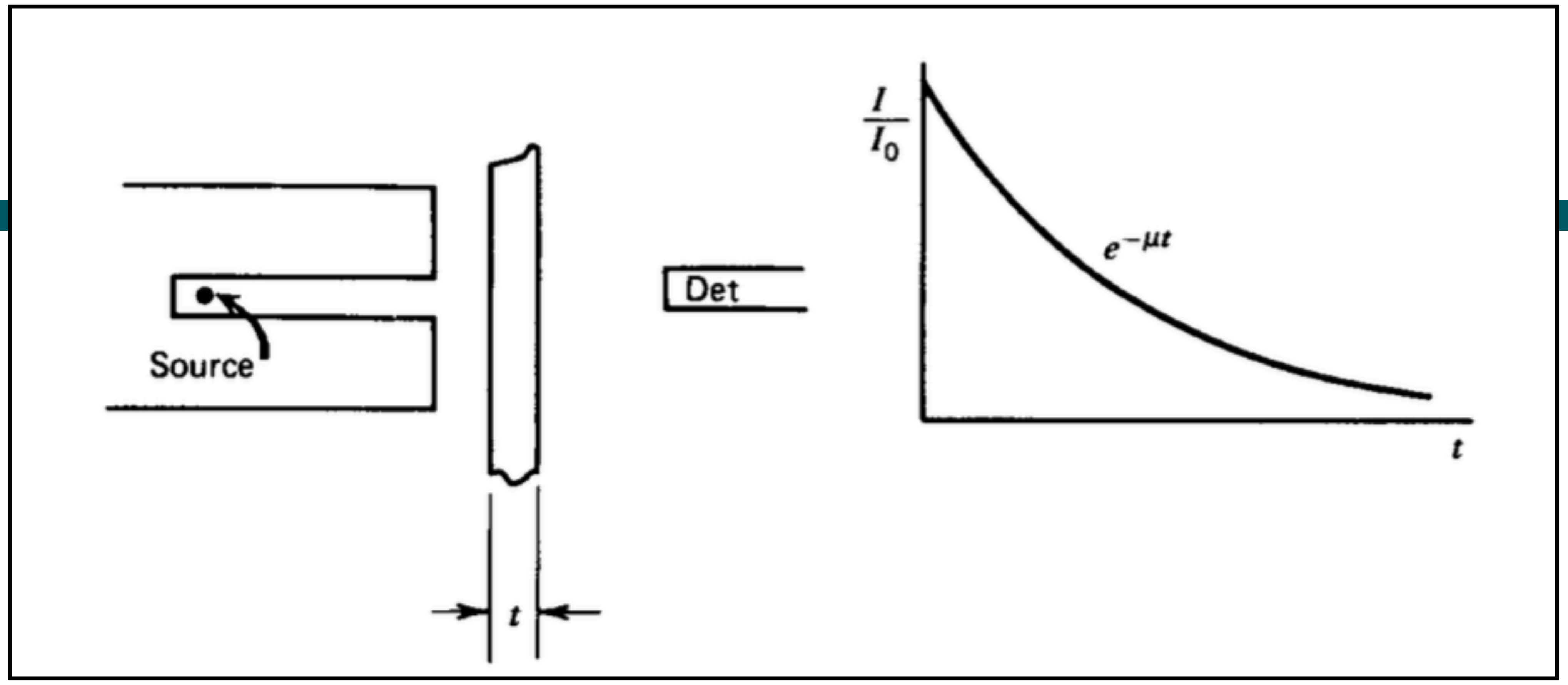
FRED operation

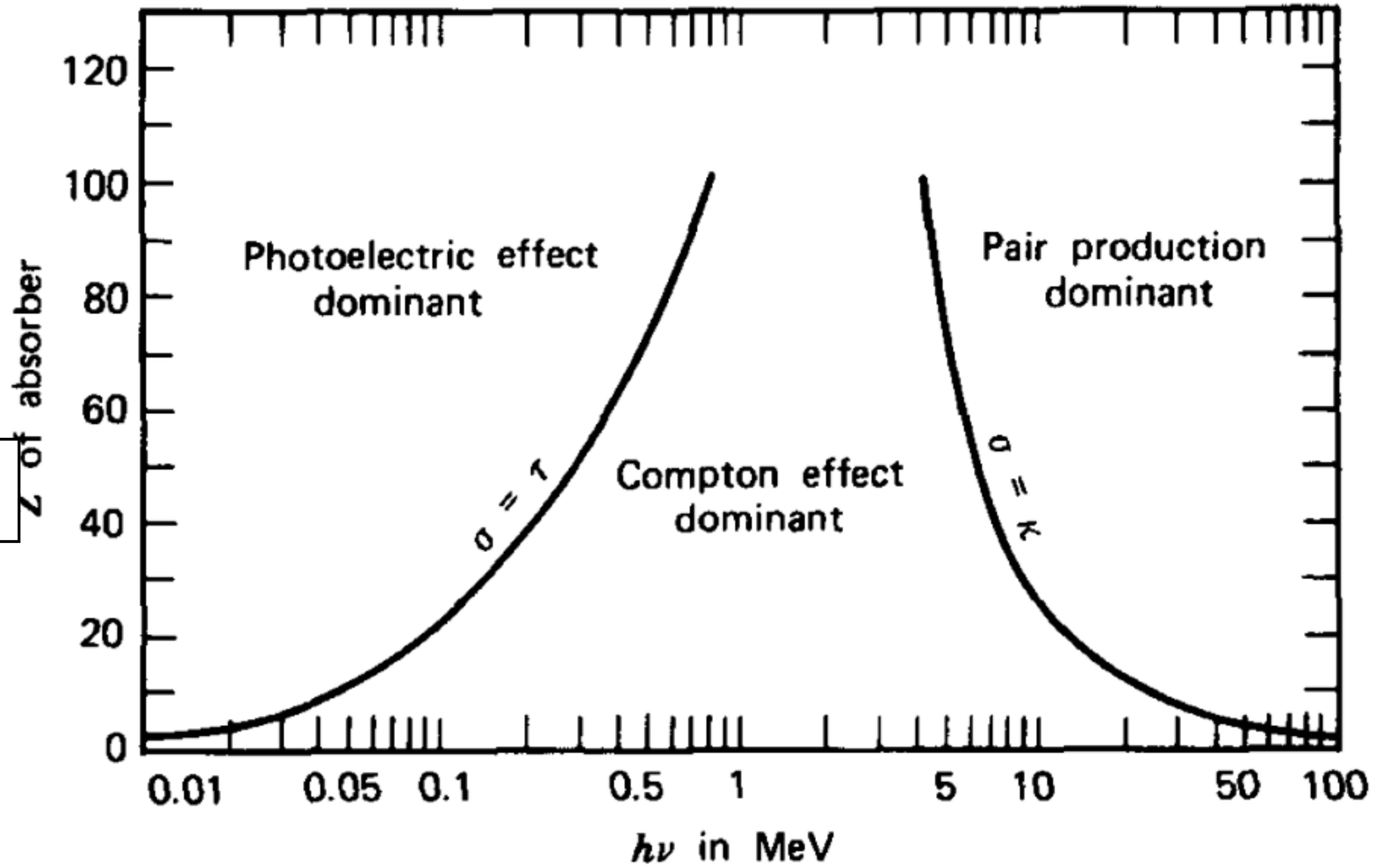
Sketch of the FRED architecture, in which the operation on charge of CPU and GPU are distinguished.



Photon processes







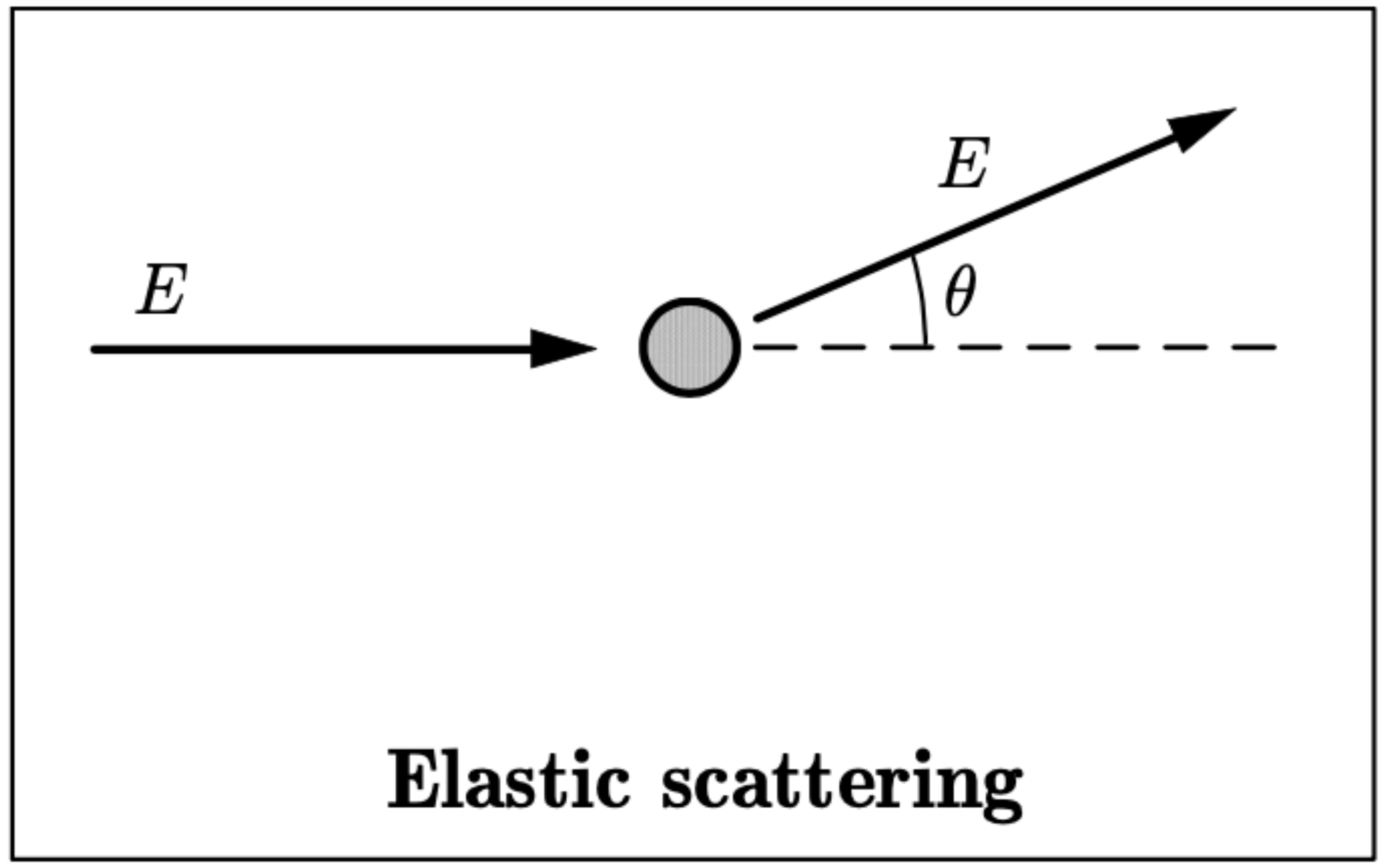
Electron and positron processes

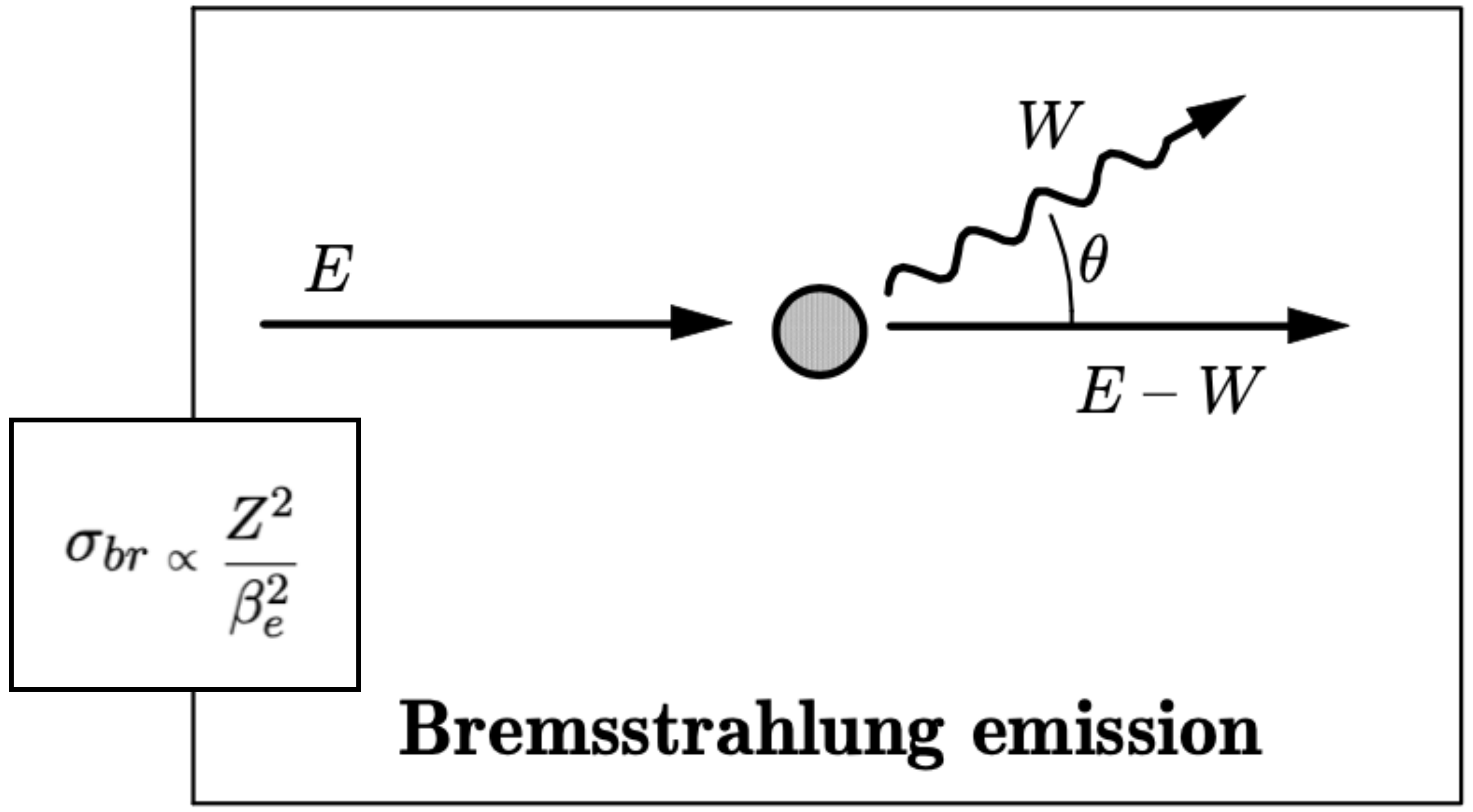
Energy loss

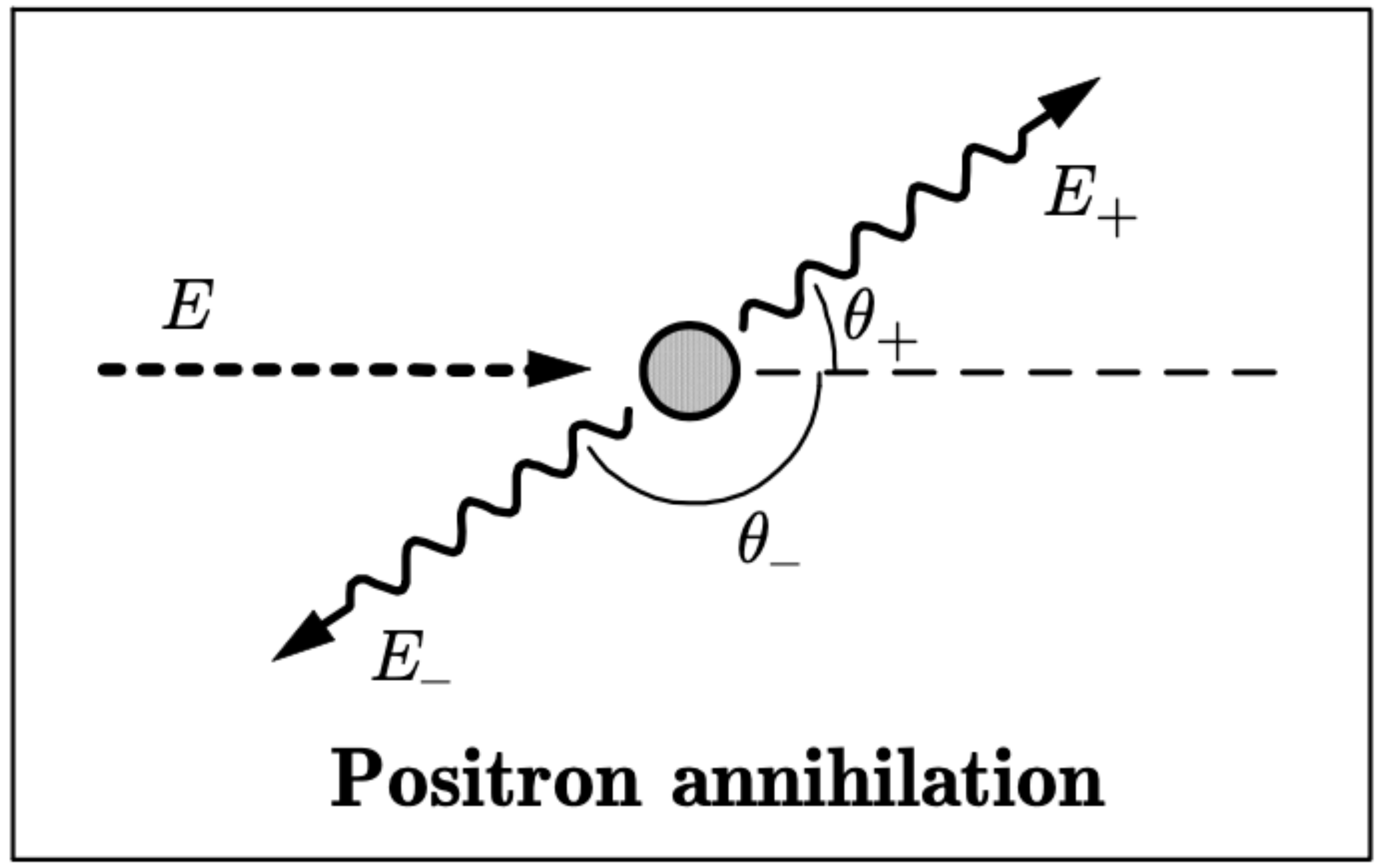
+

delta rays production

+



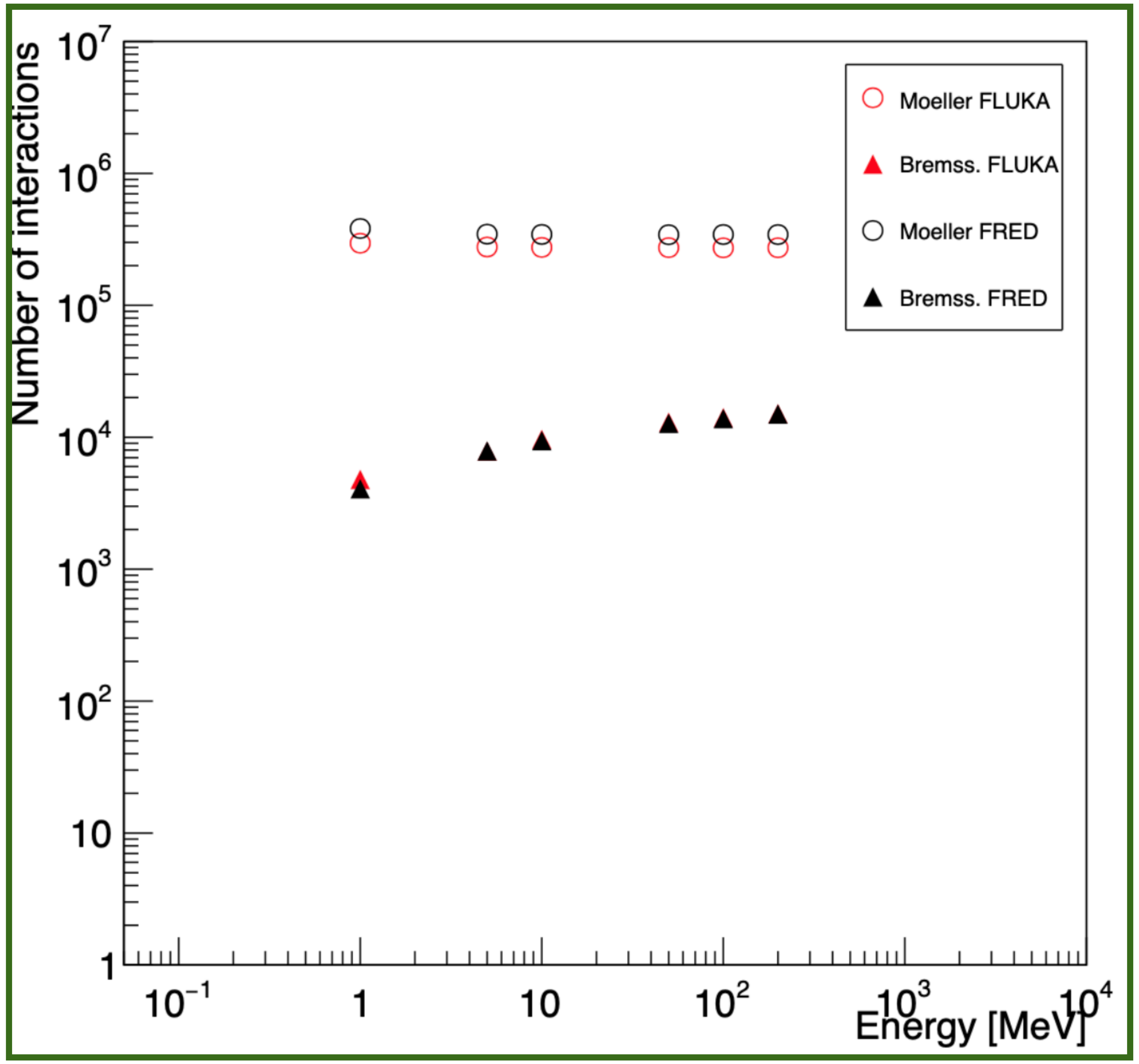


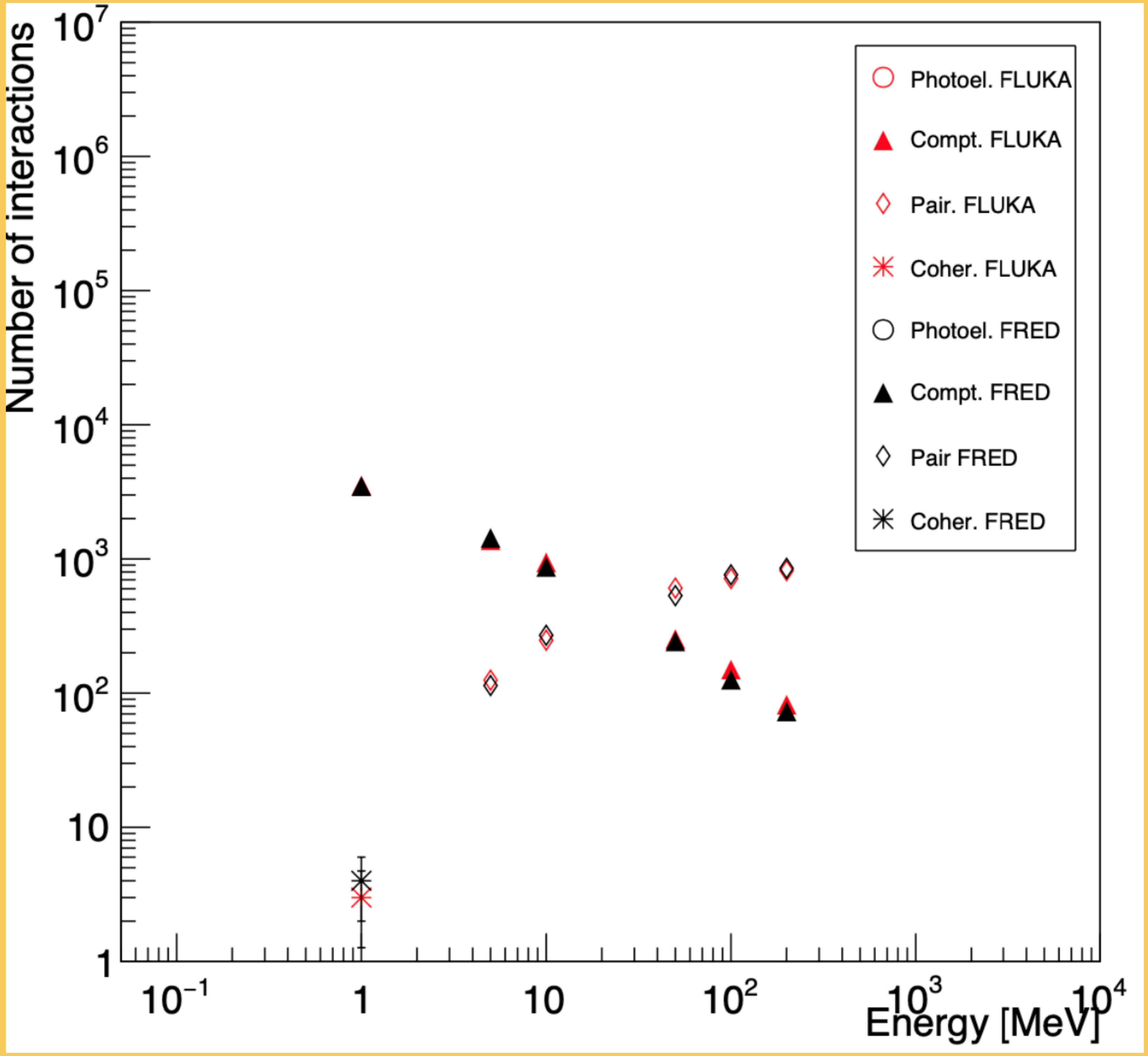


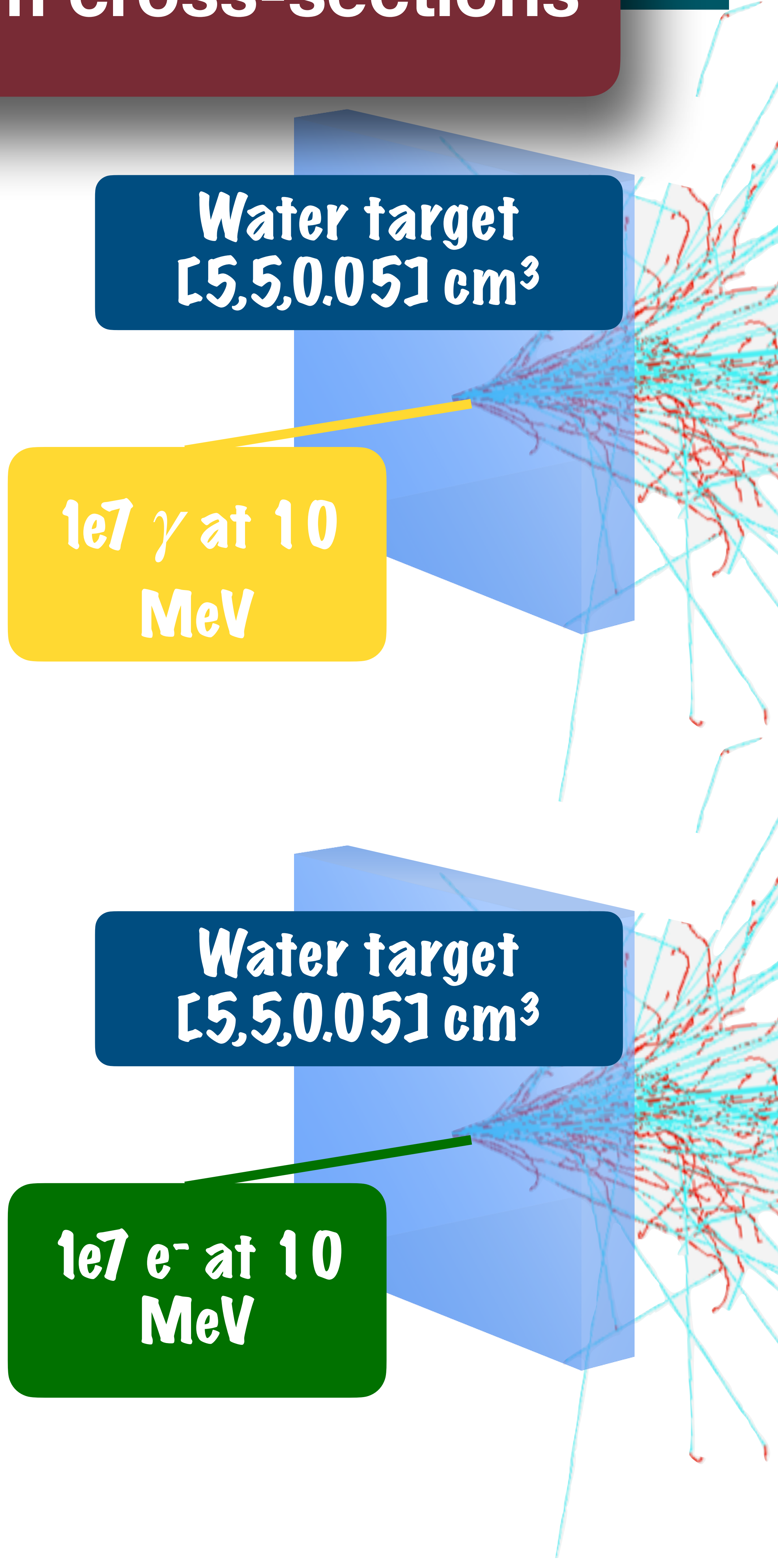
Thin target benchmark

FRED-em cross-sections

I have checked against **FLUKA** the **cross-section models** by counting the number of times a given process took place during the all simulation run.







Thin target benchmark

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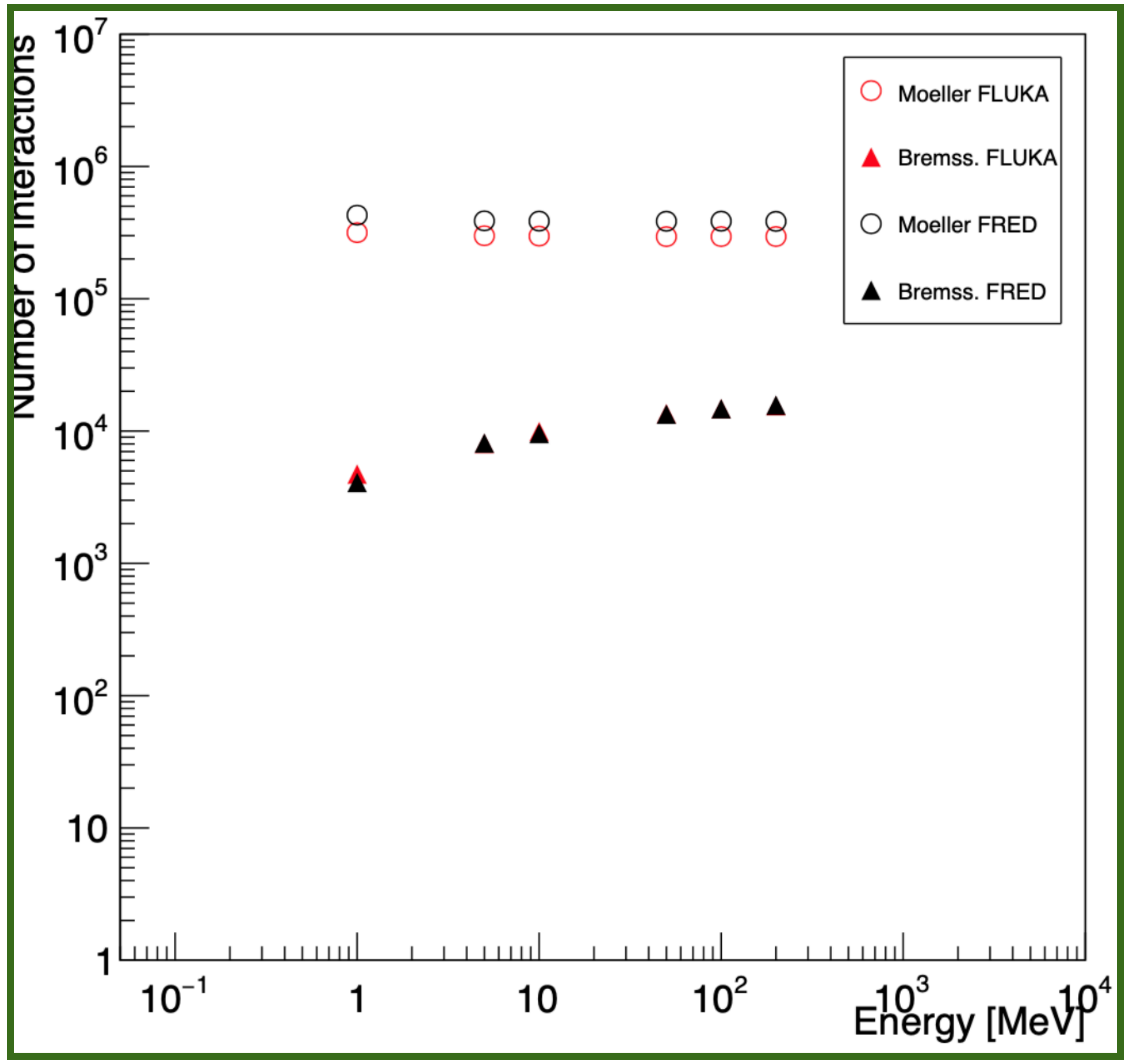
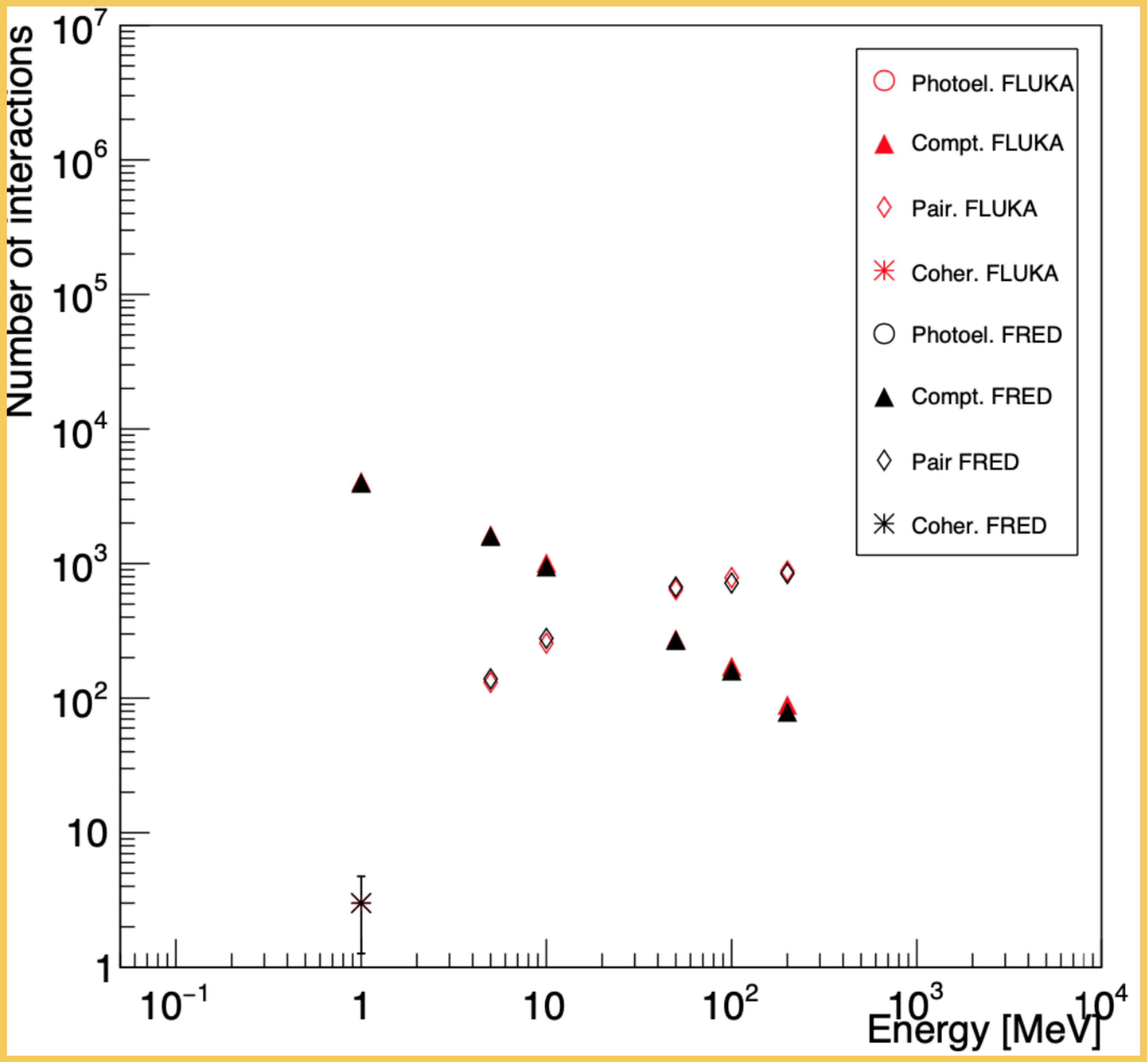
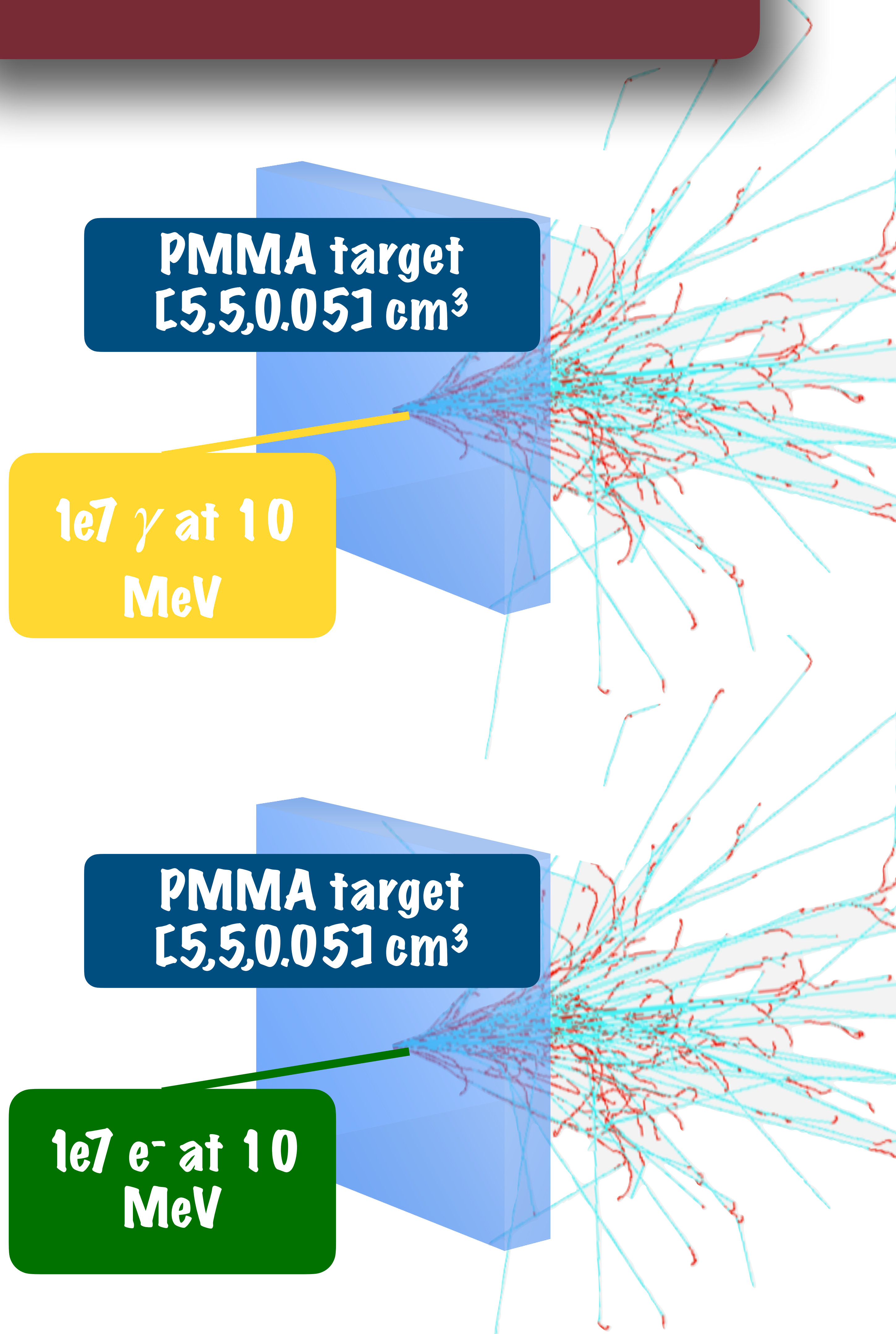
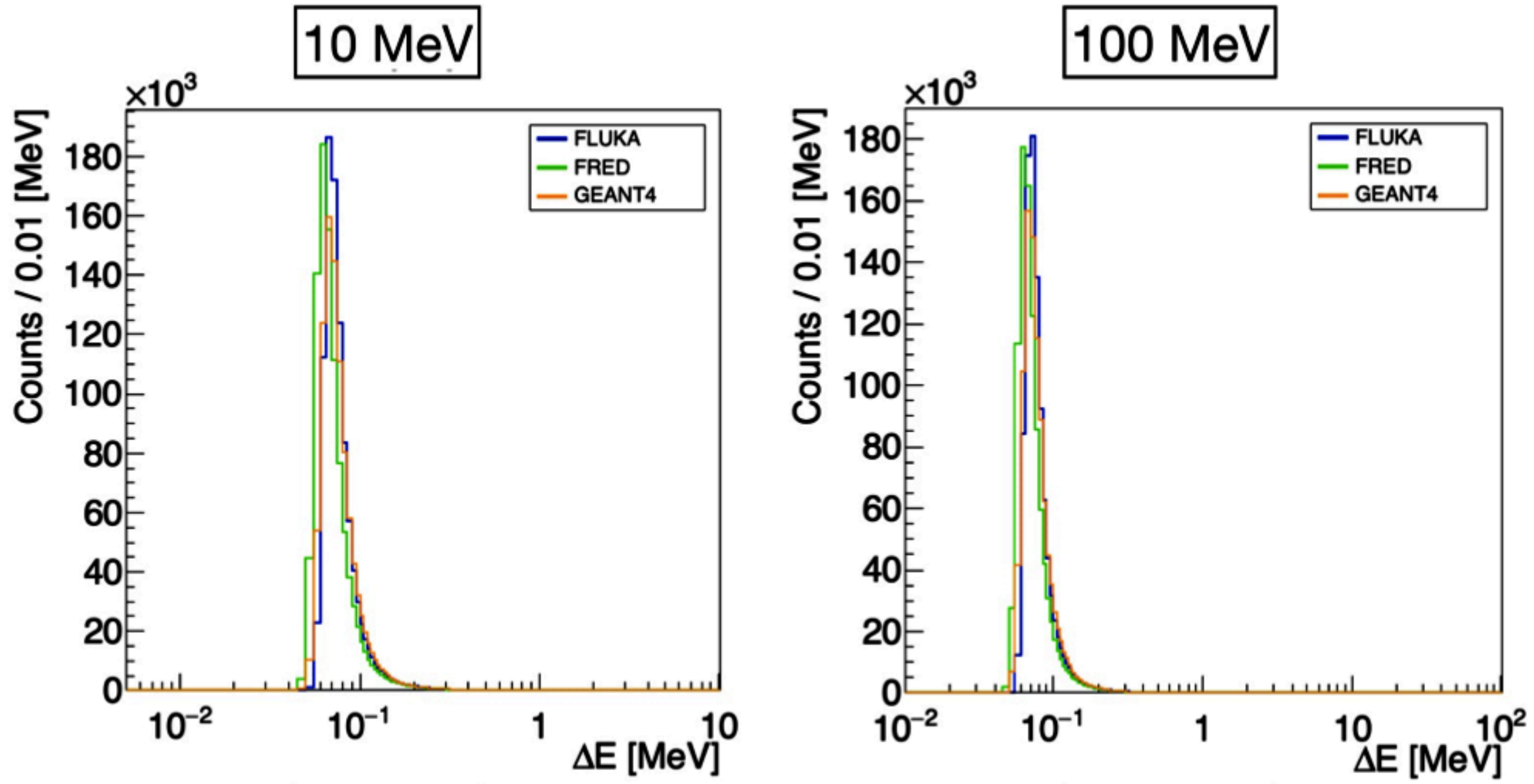


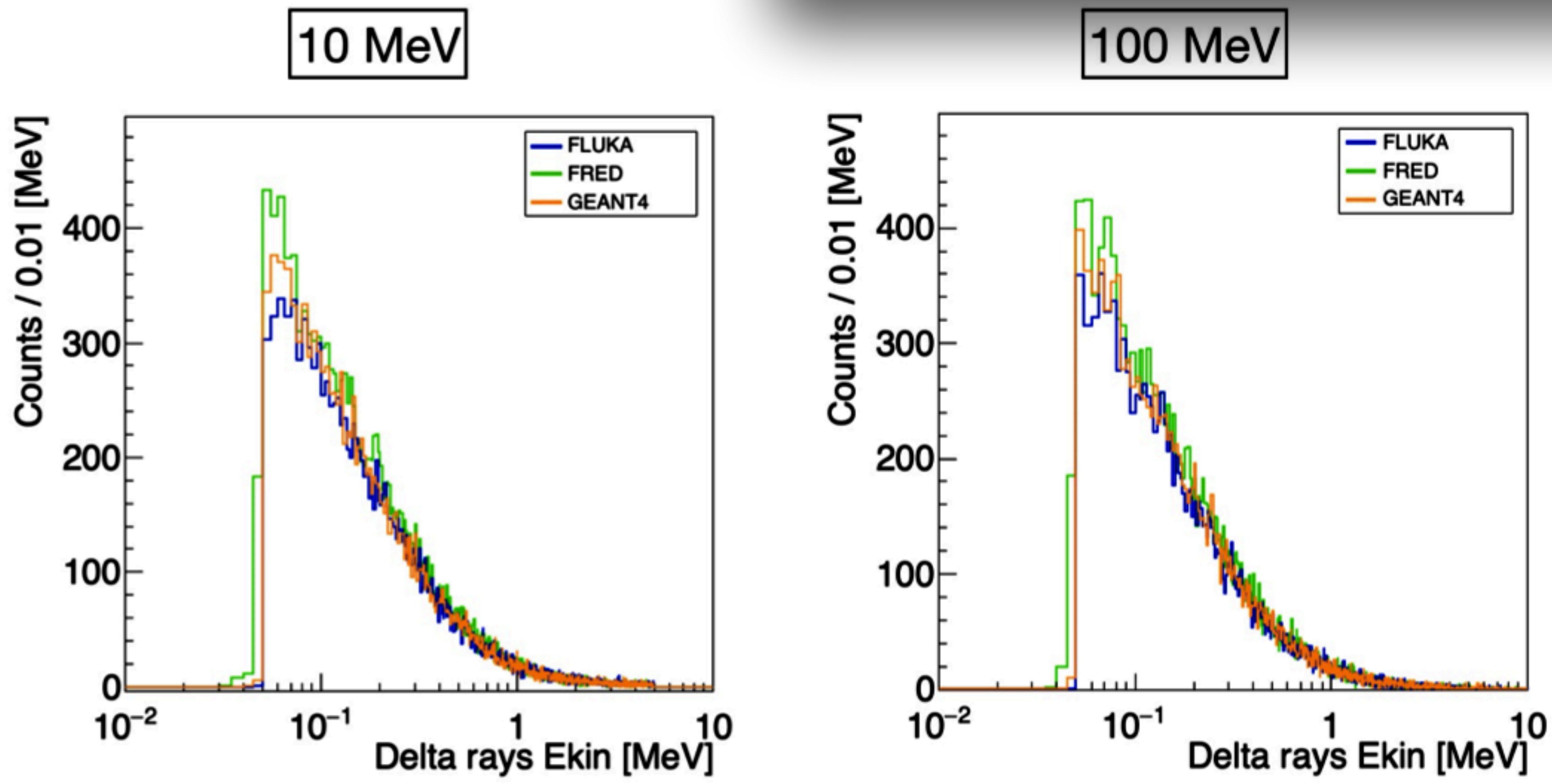


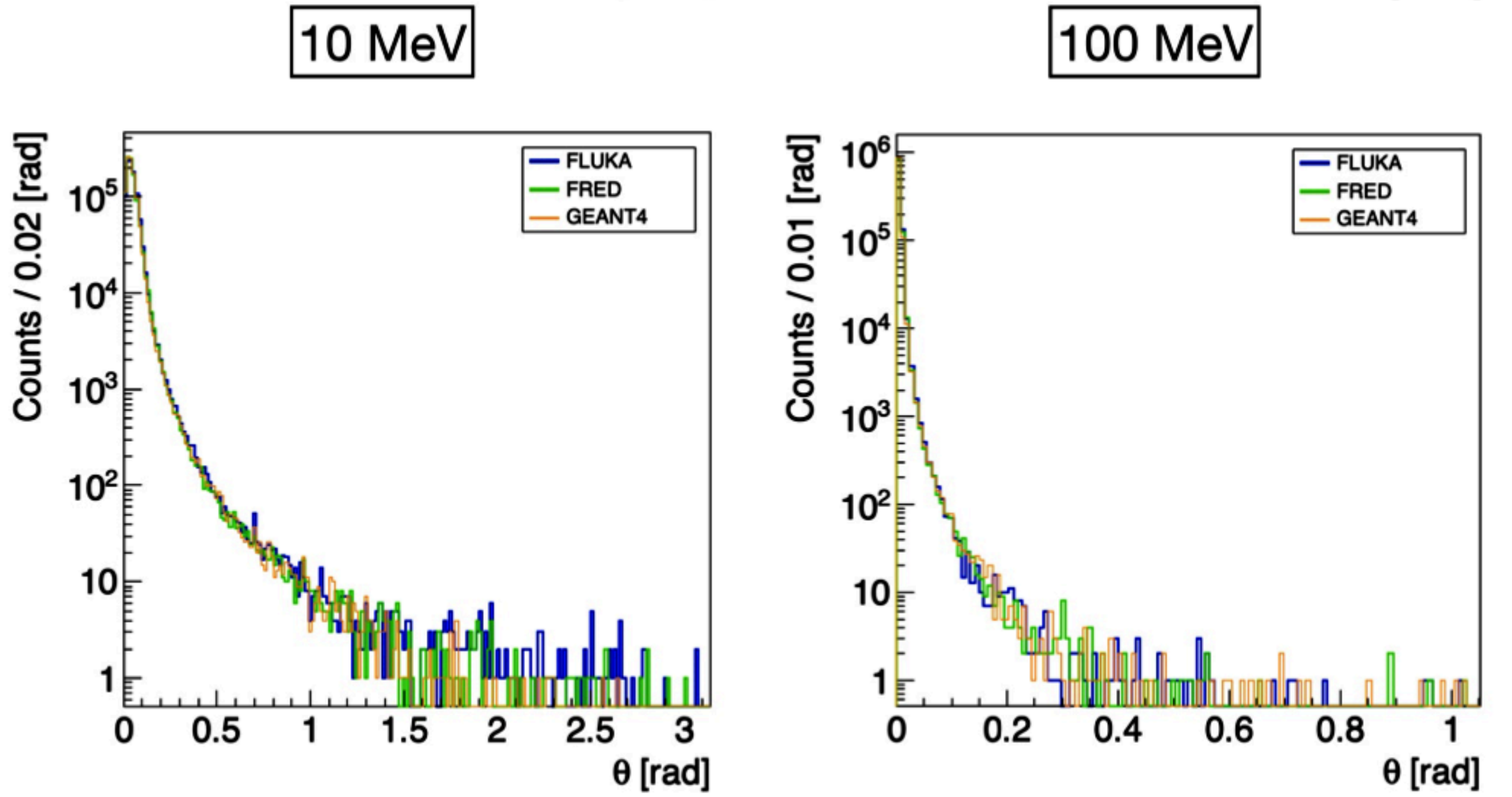


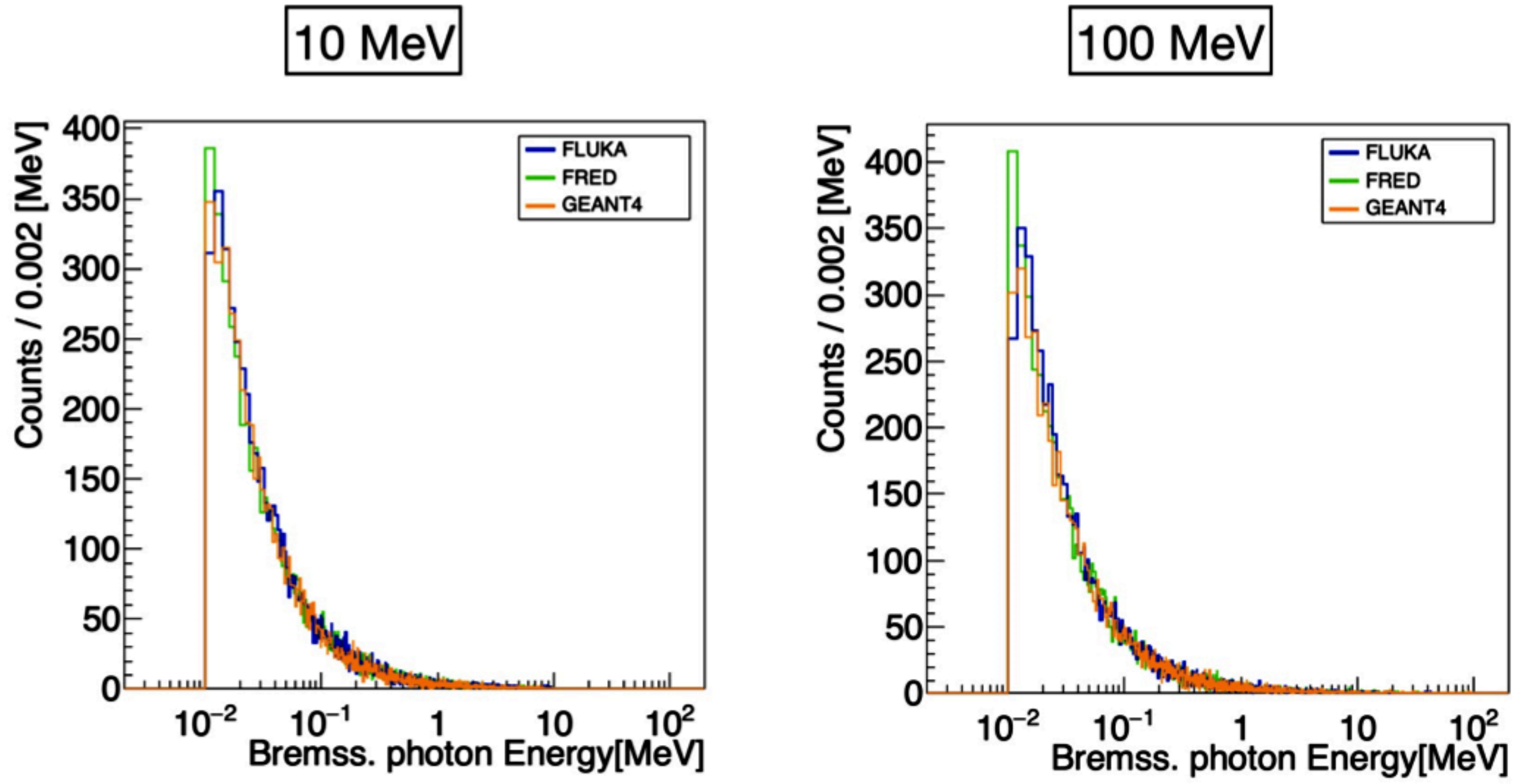
Thin target benchmark

FRED-em cross-sections

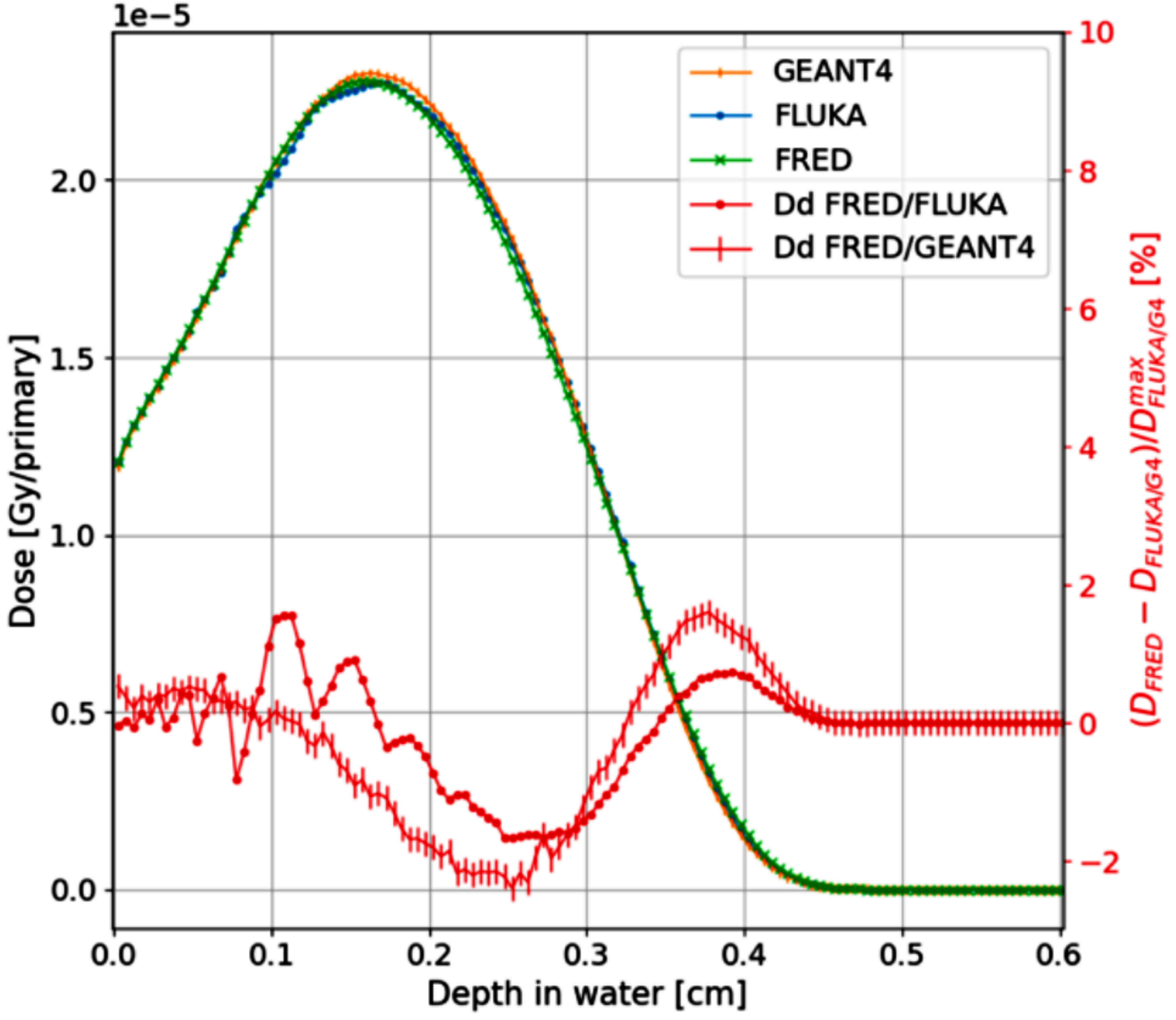


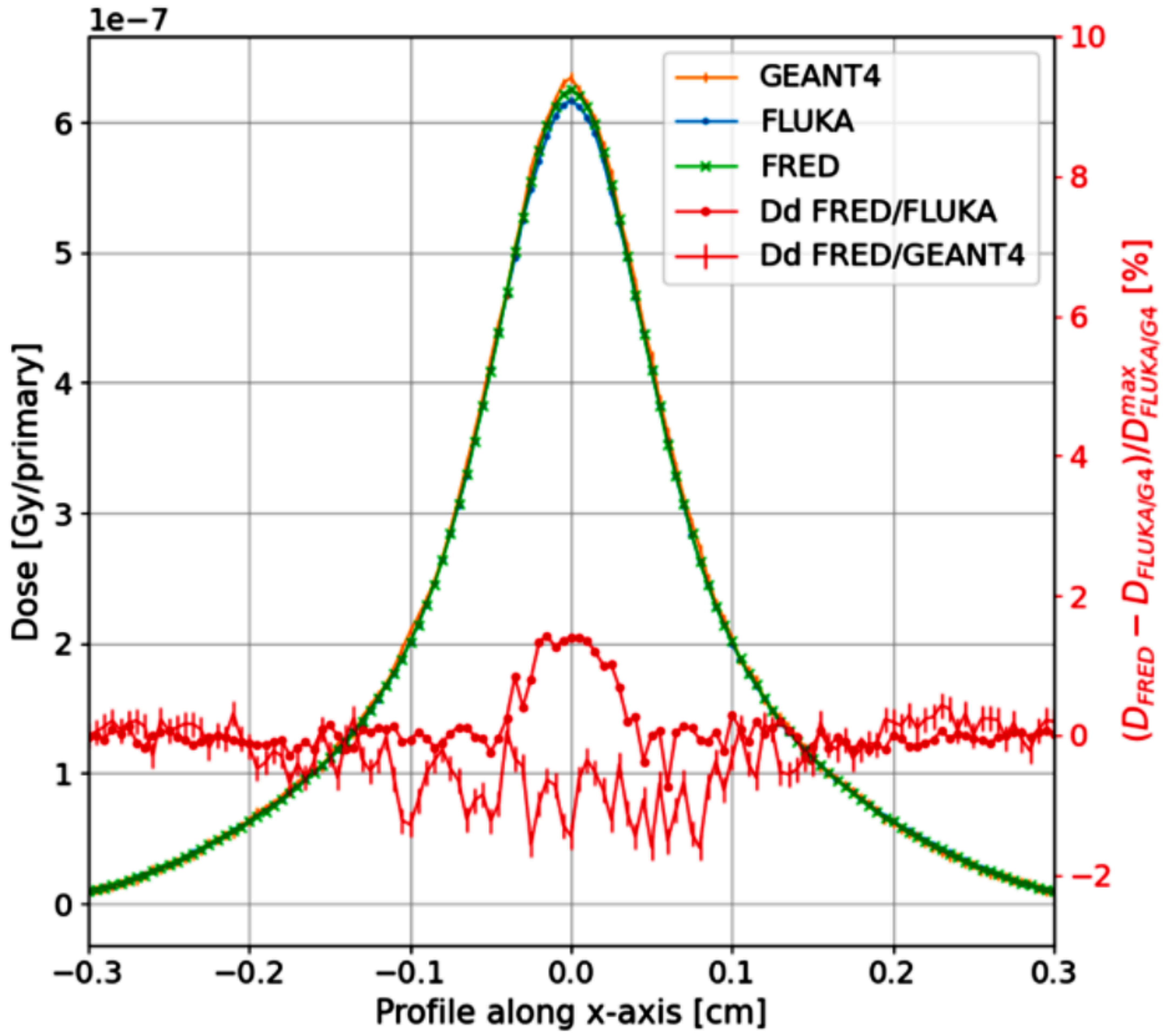




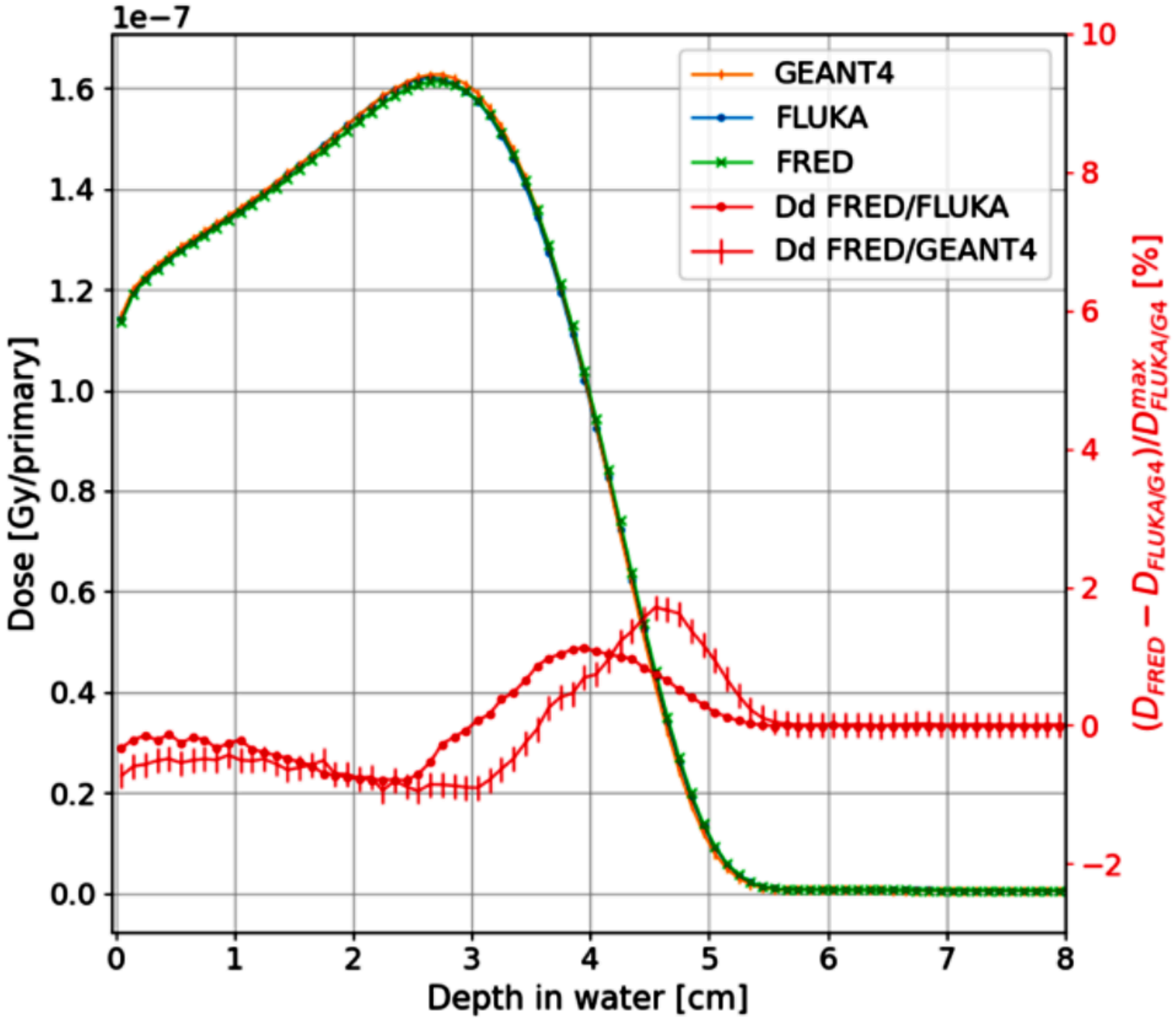


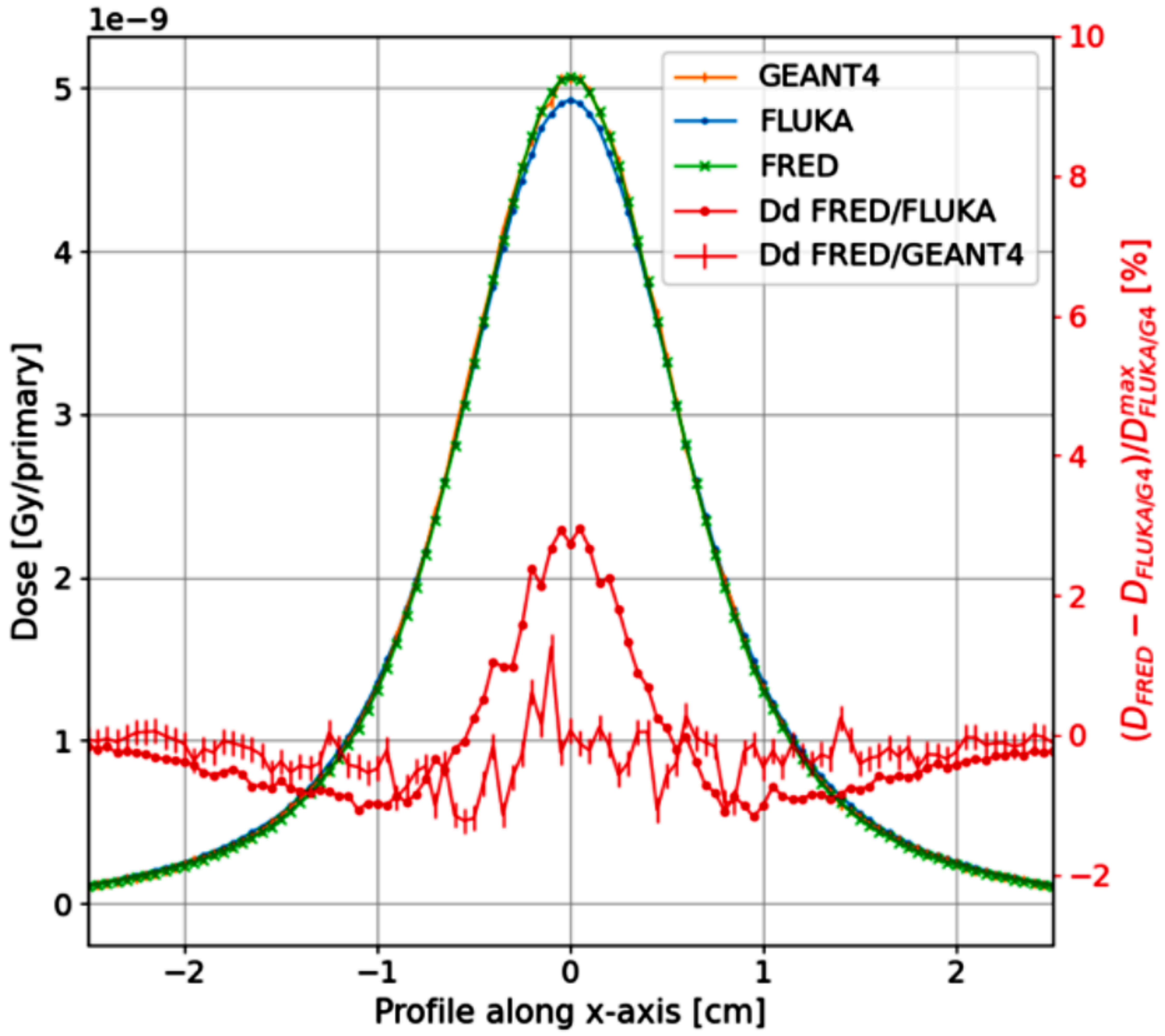
FRED-em: e⁻ @ 1 MeV in water



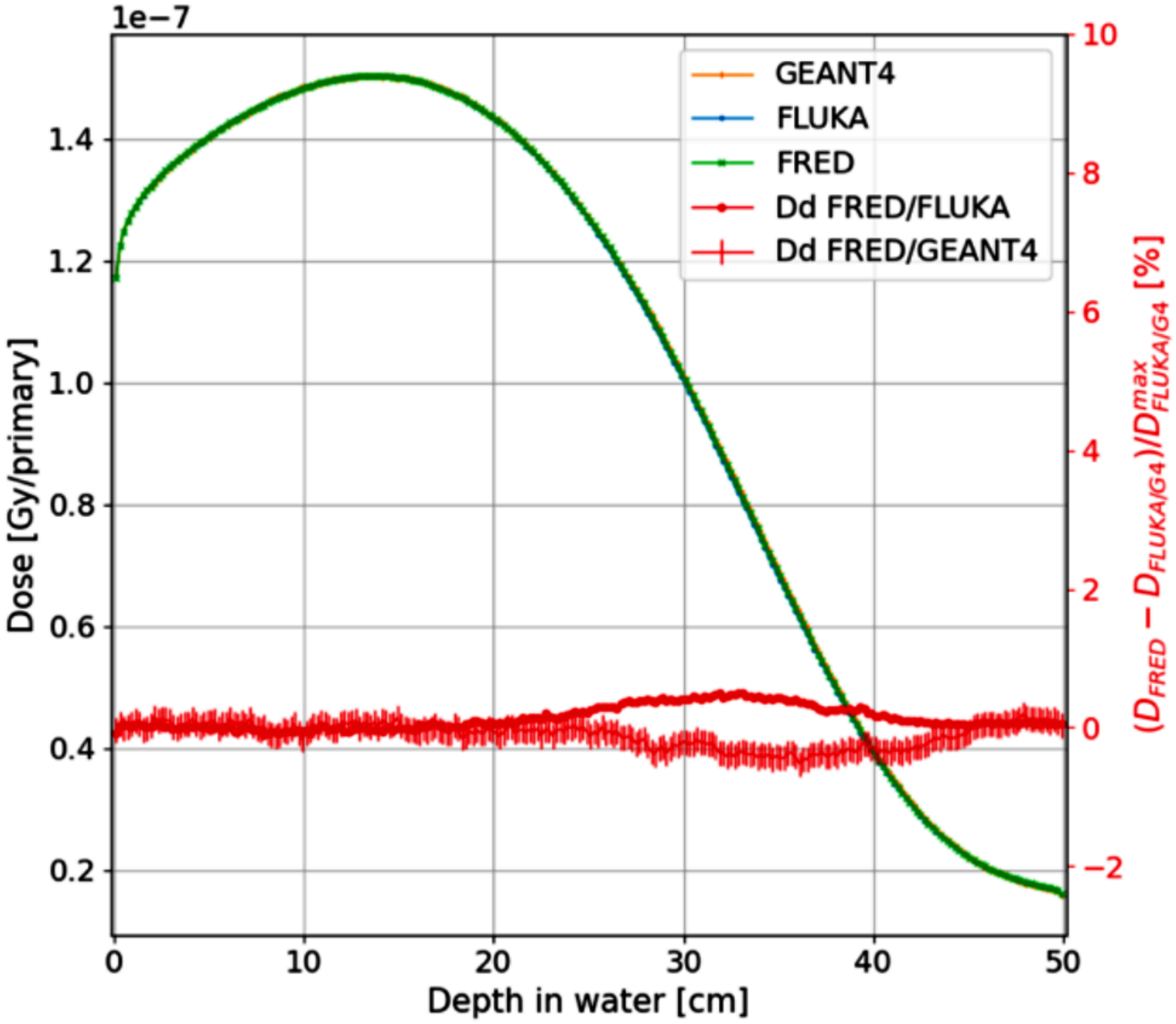


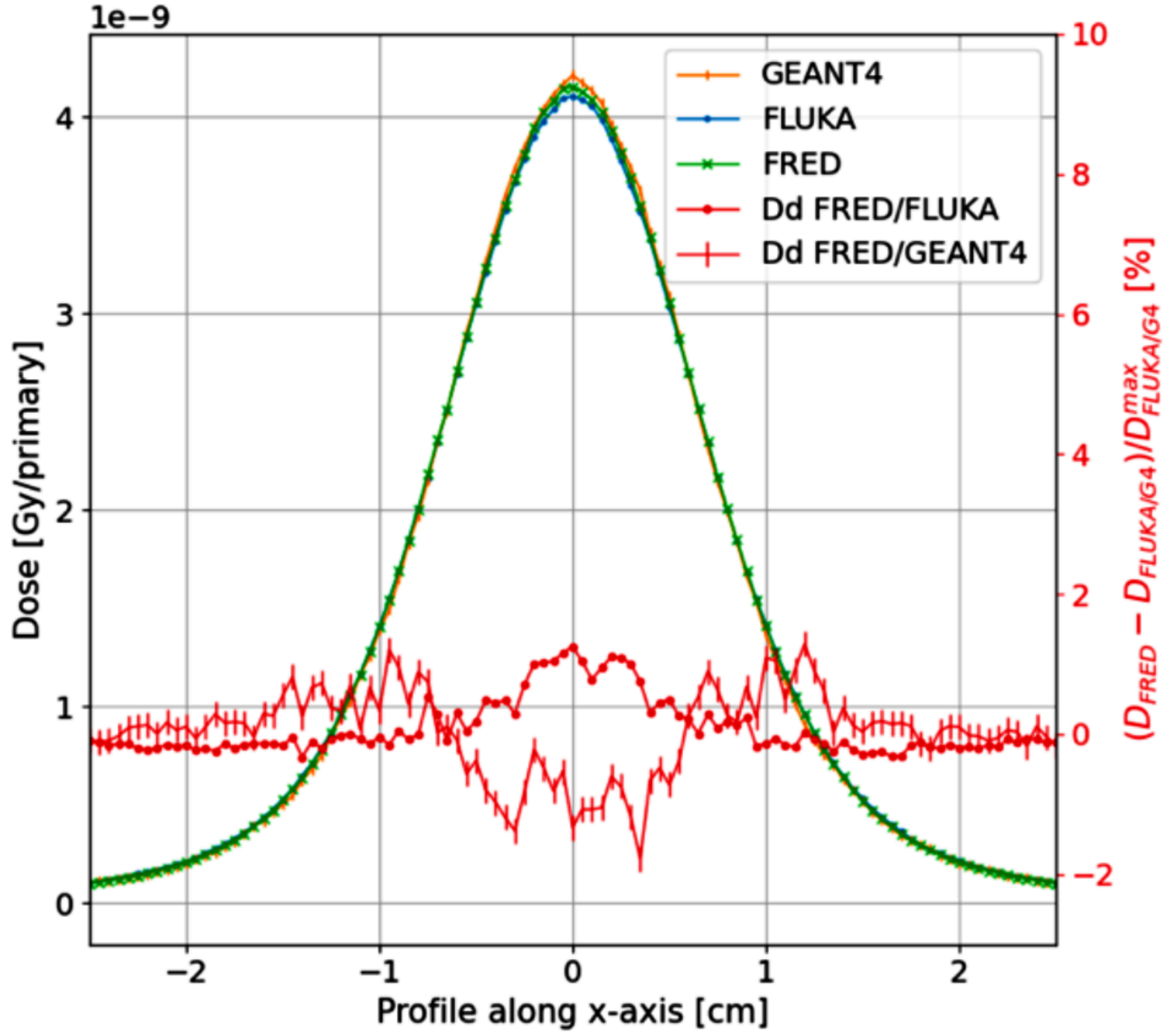
FRED-em: e⁻ @ 10 MeV in water



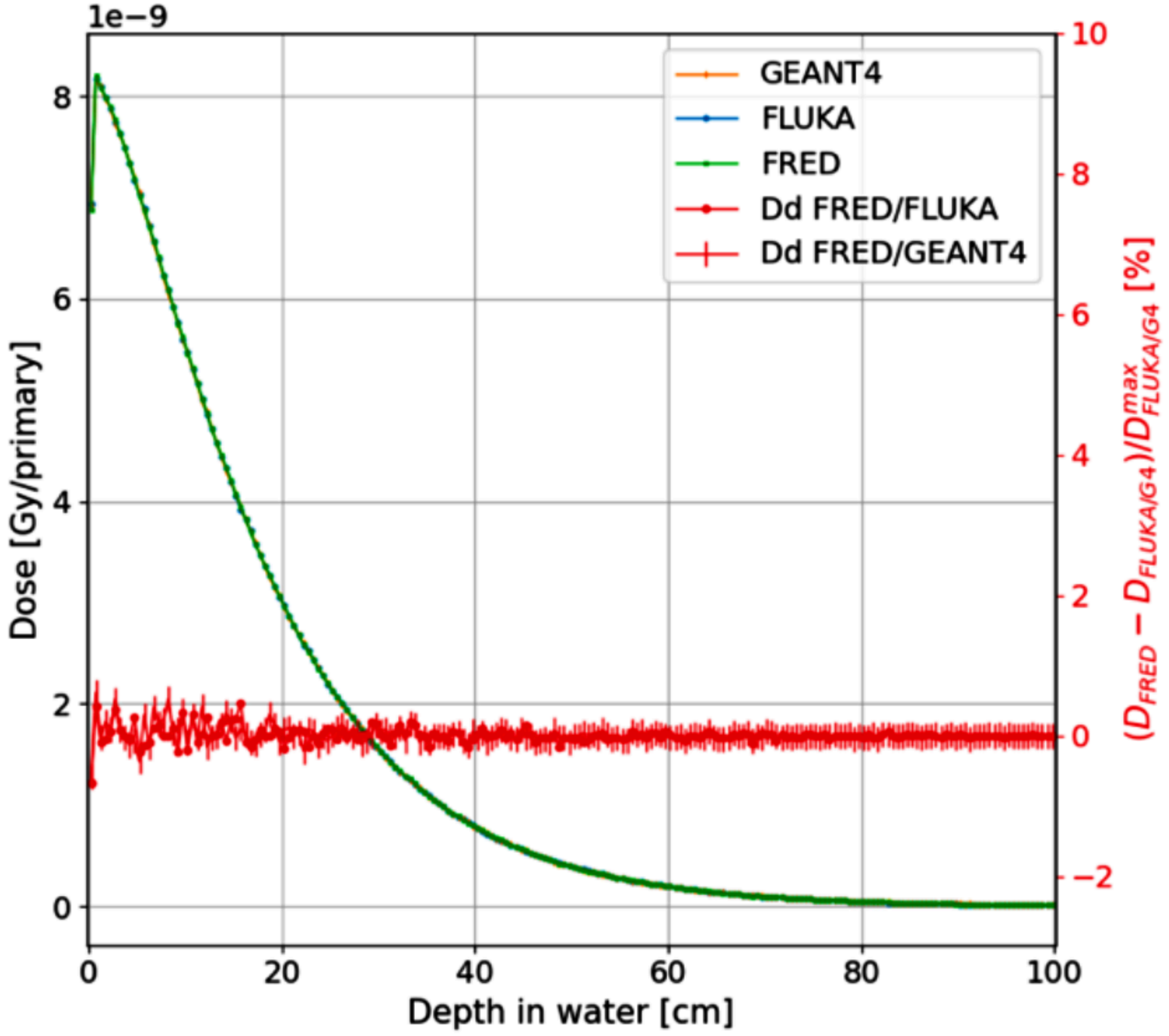


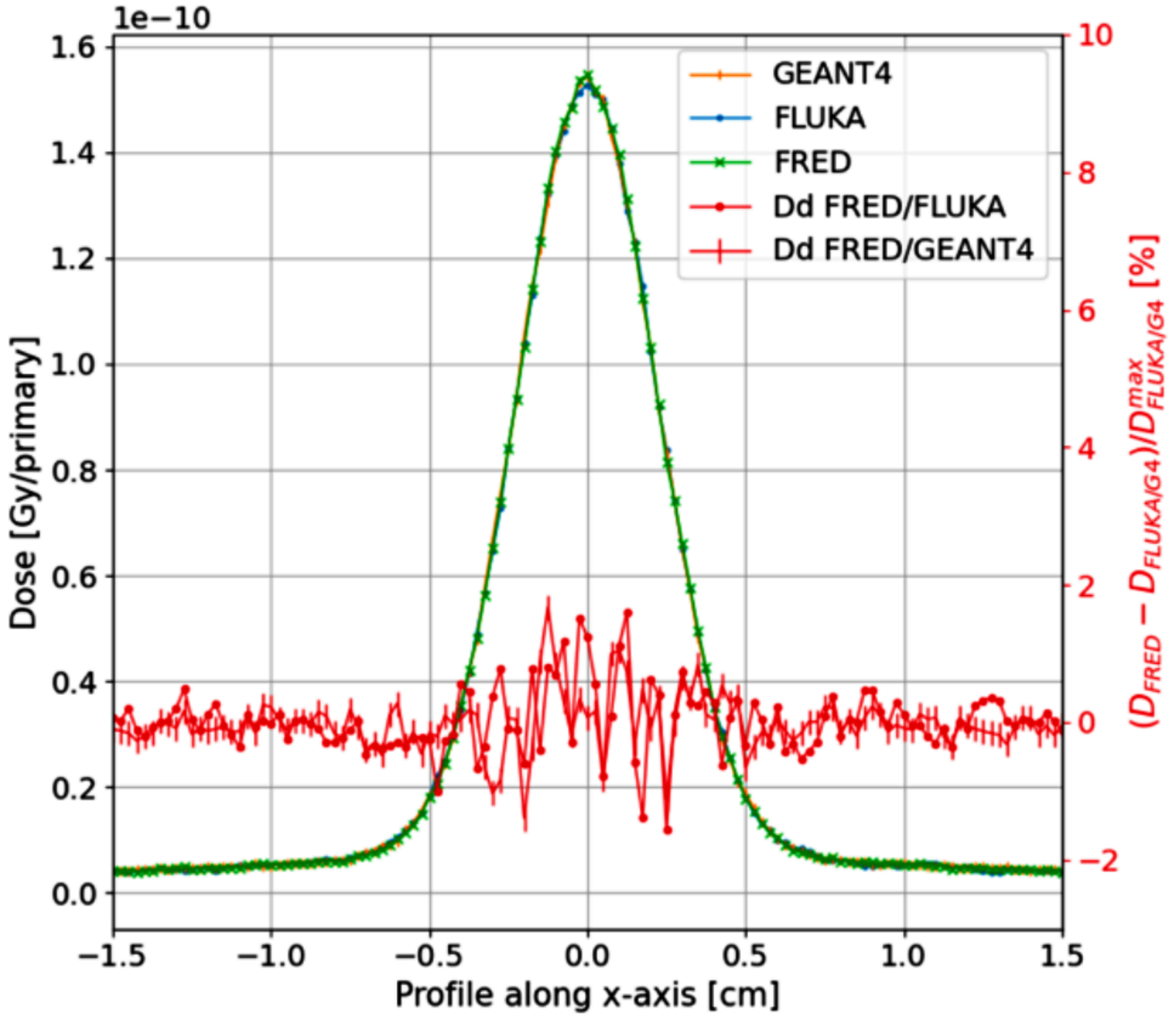
FRED-em: e^- @ 100 MeV in water



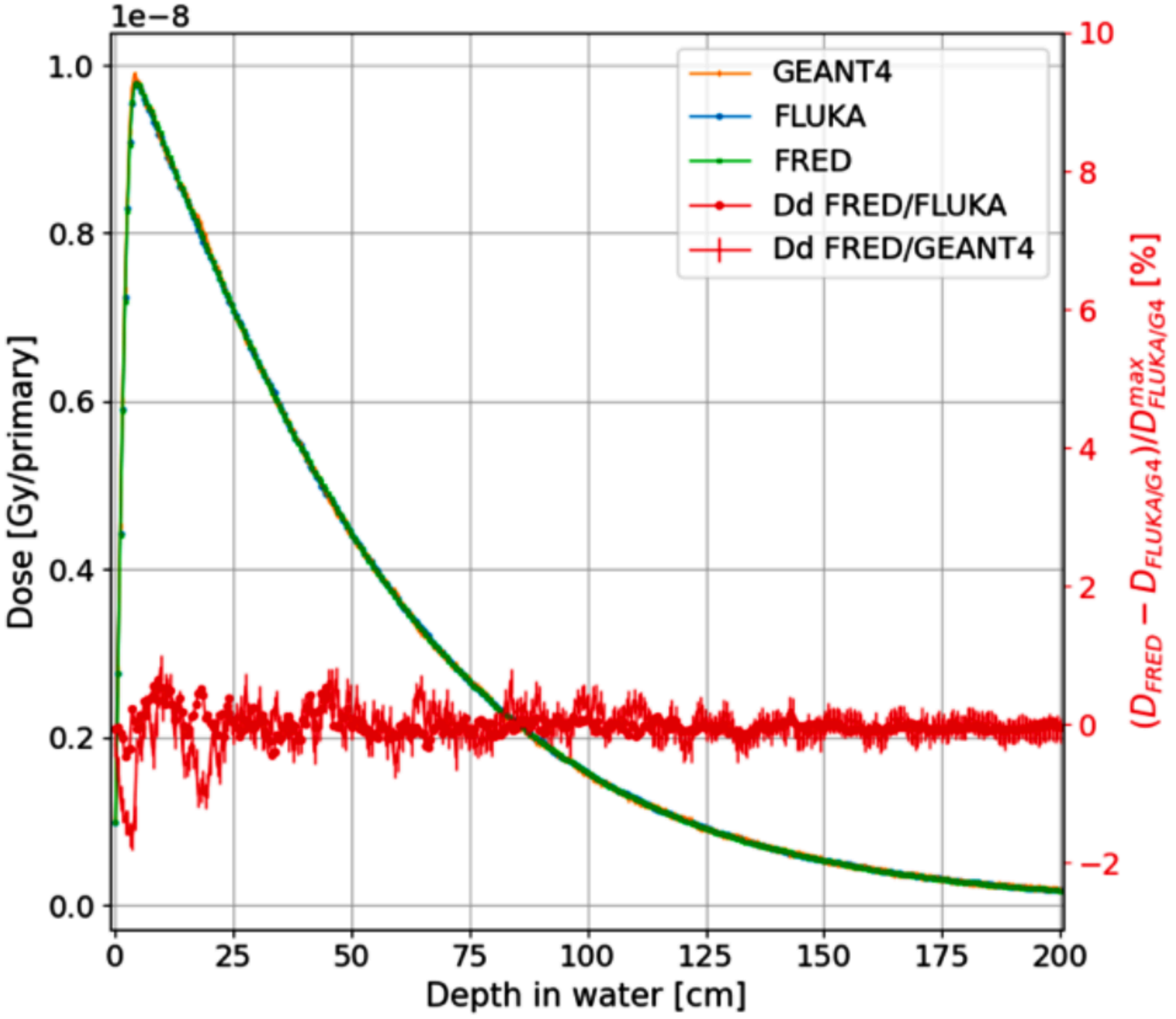


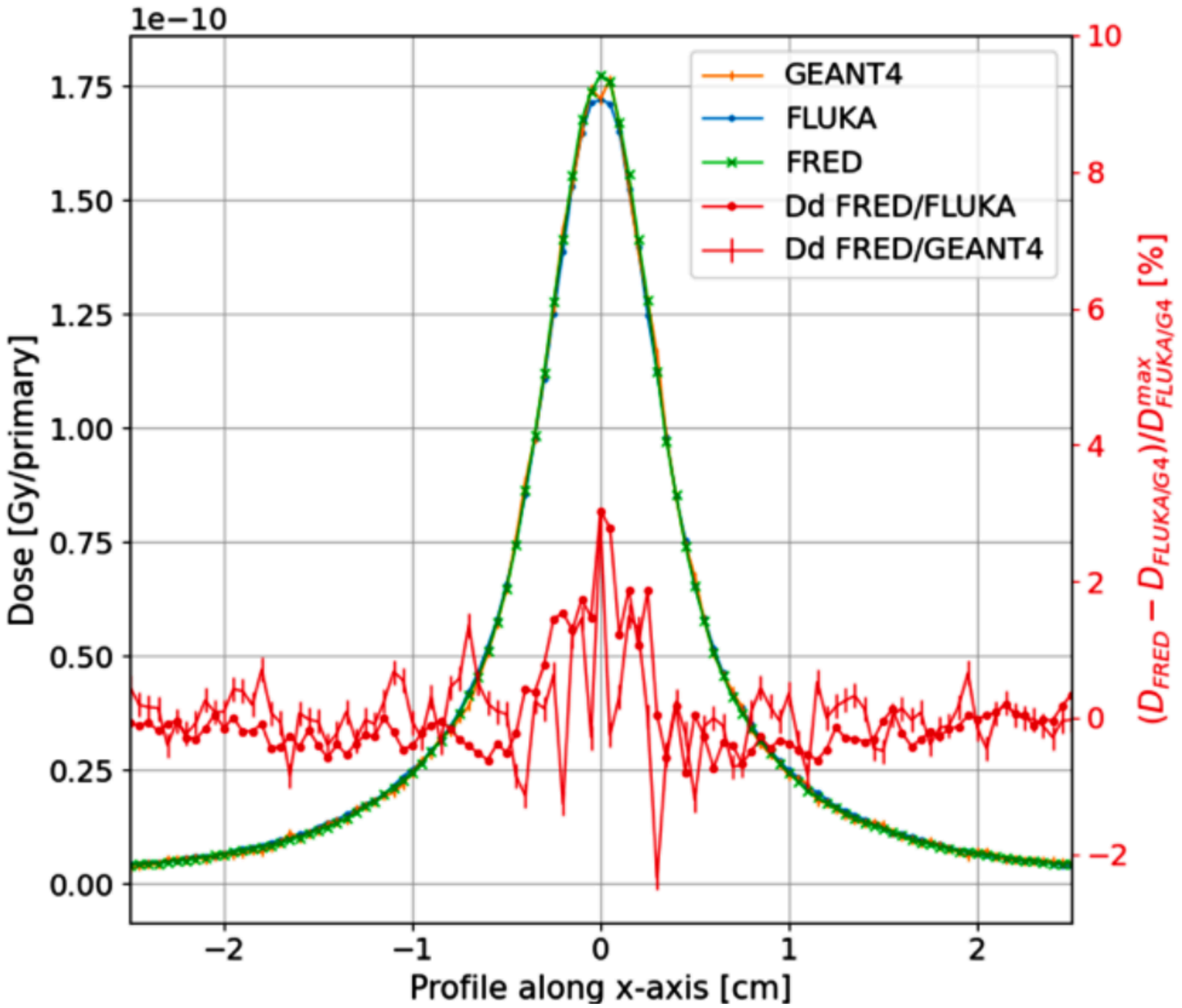
FRED-em: ph @ 1 MeV in water



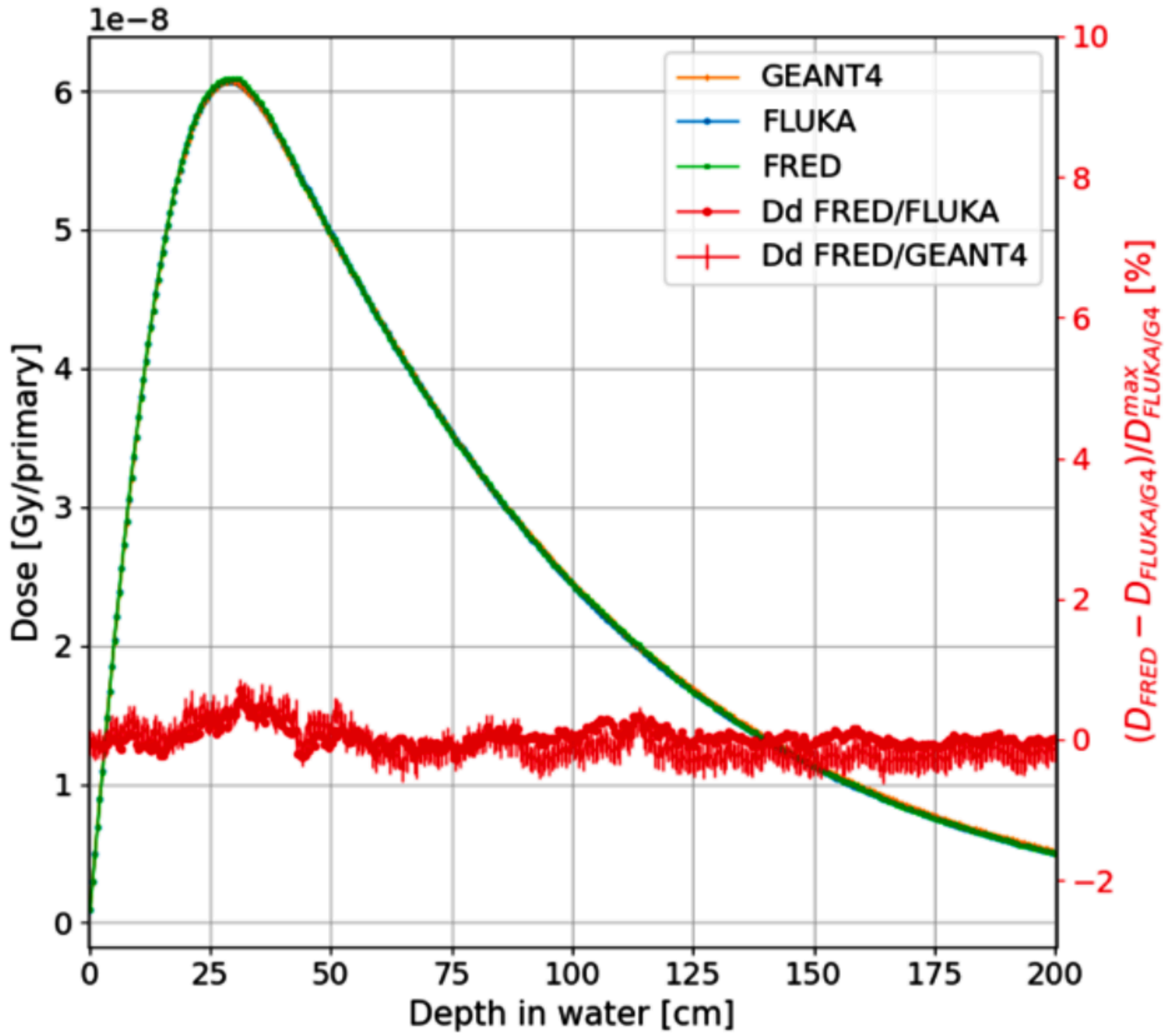


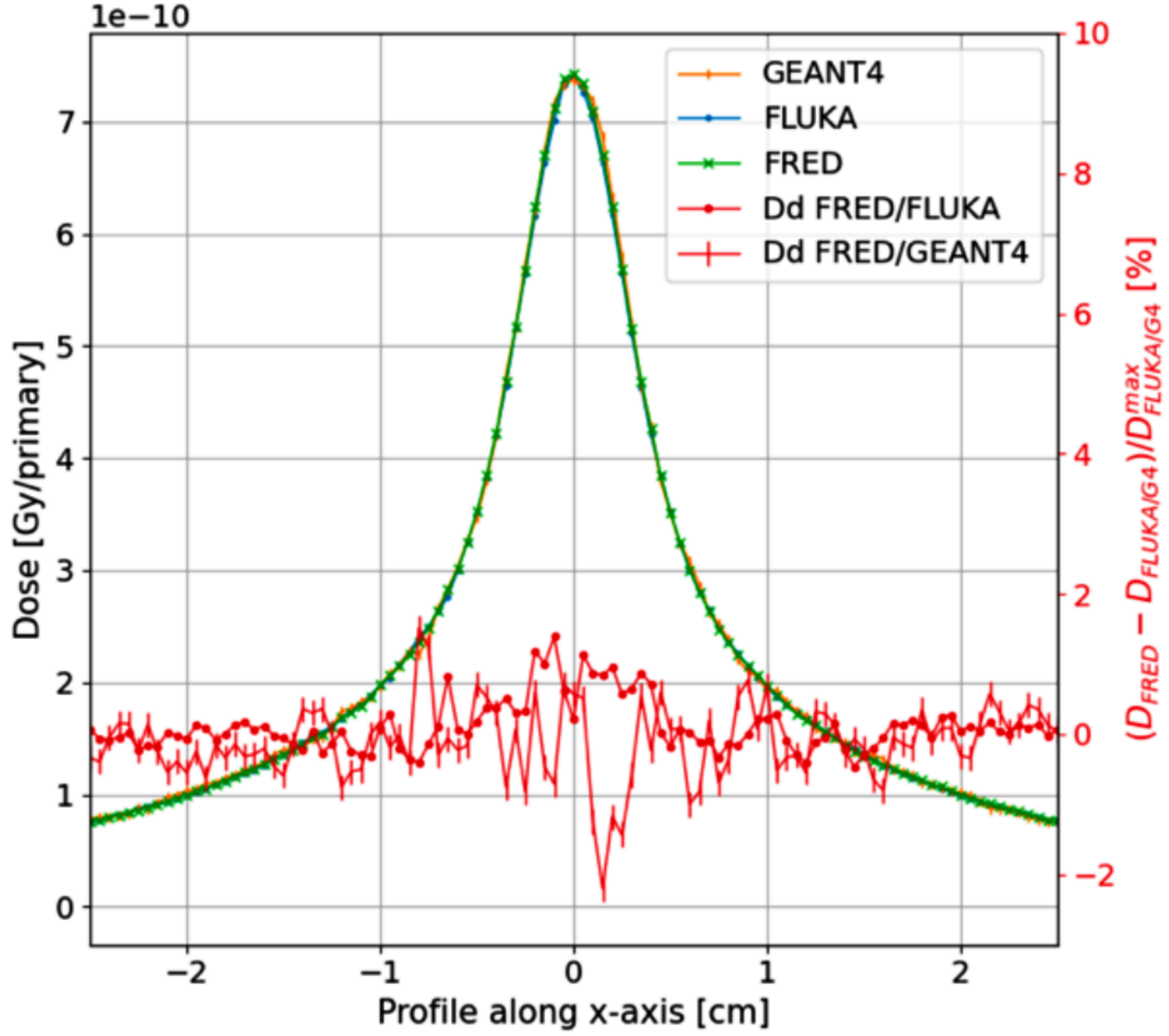
FRED-em: ph @ 10 MeV in water





FRED-em: ph @ 100 MeV in water

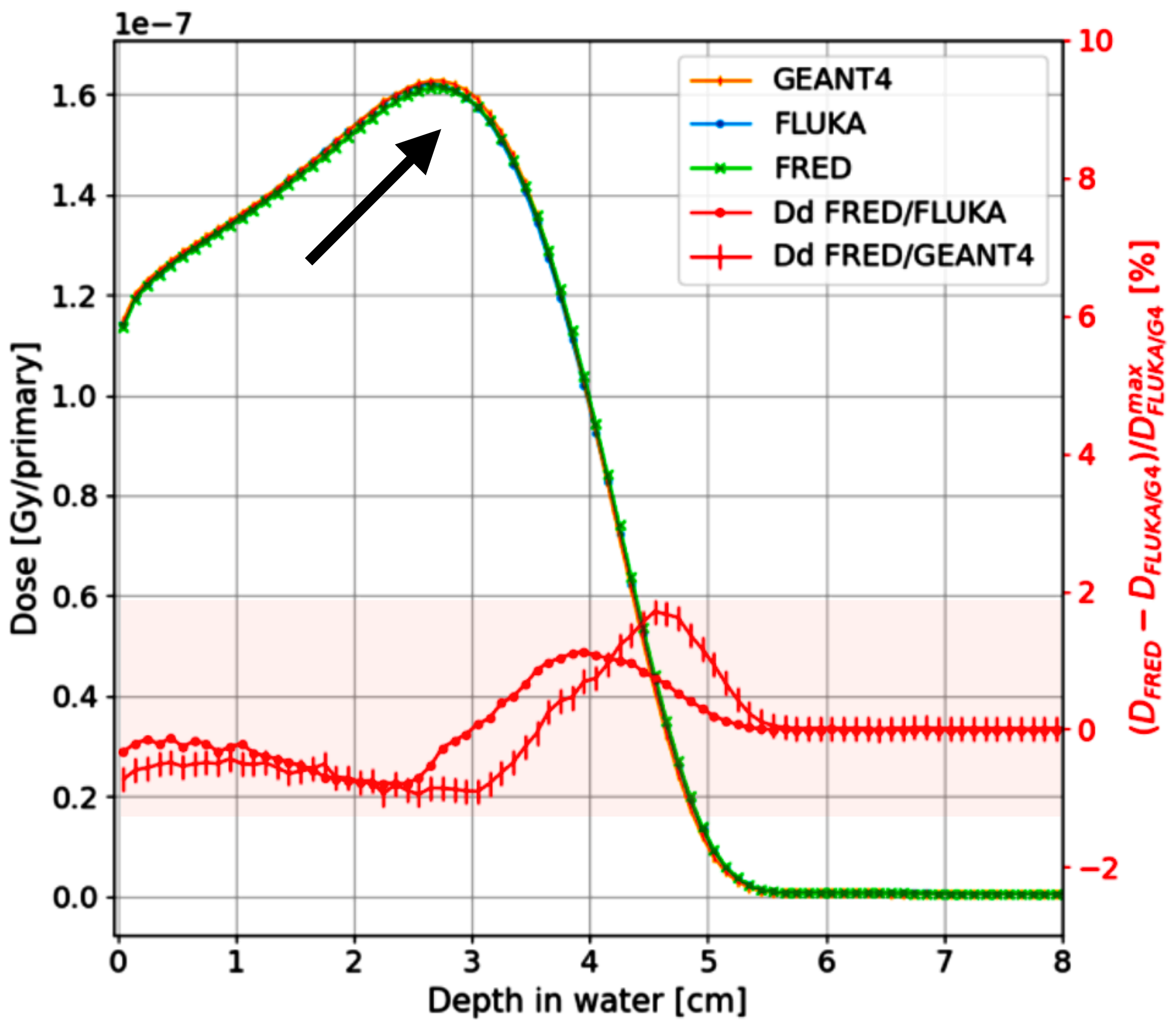


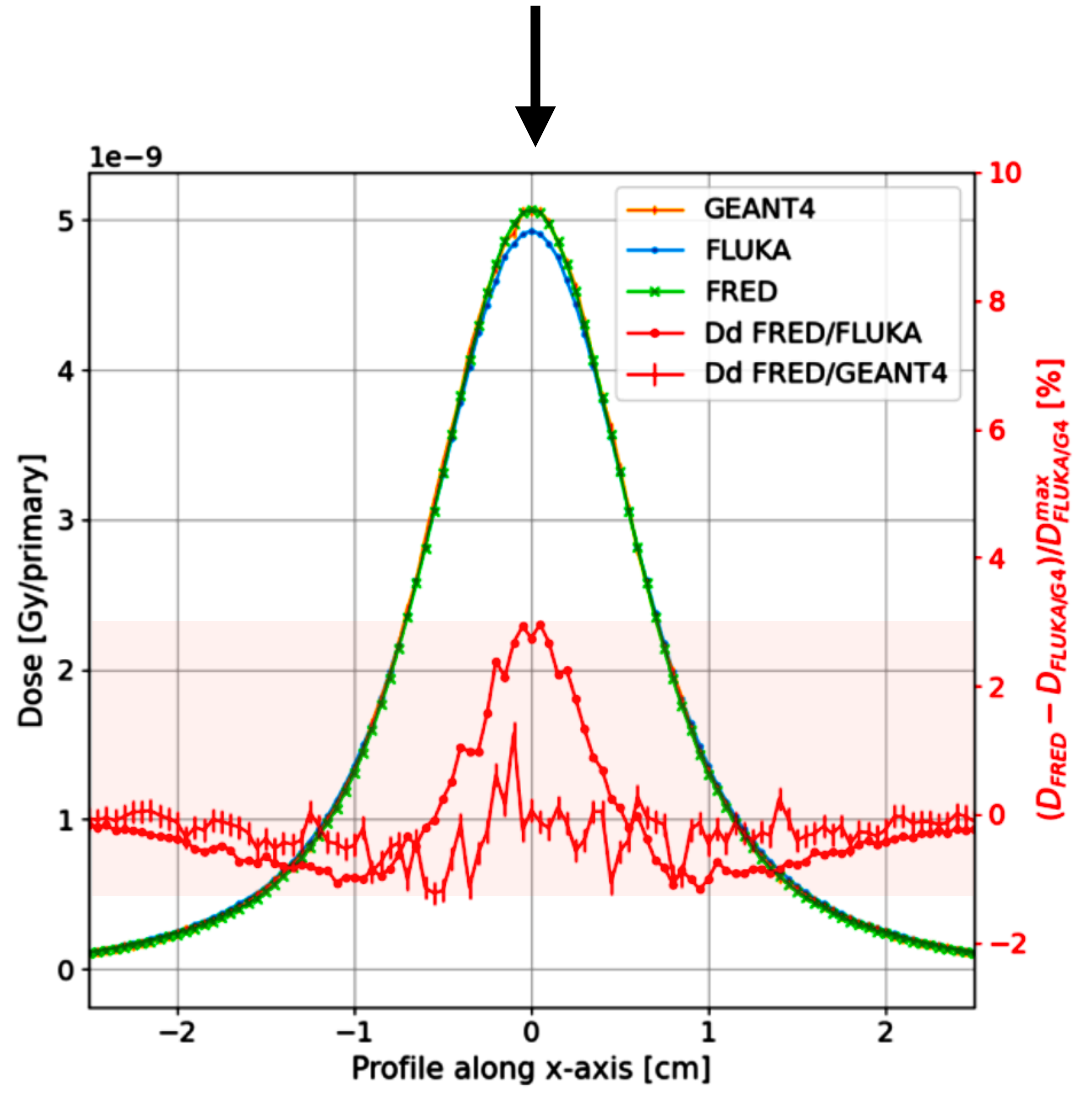


Efficiency and timing performance

Then the **FRED** accuracy and timing performance were tested against state-of-art full MCs, such as **FLUKA** and **GEANT4**, in homogenous and heterogenous phantom and against experimental data (IOeRT LINAC) .

10 MeV e⁻ on water phantom



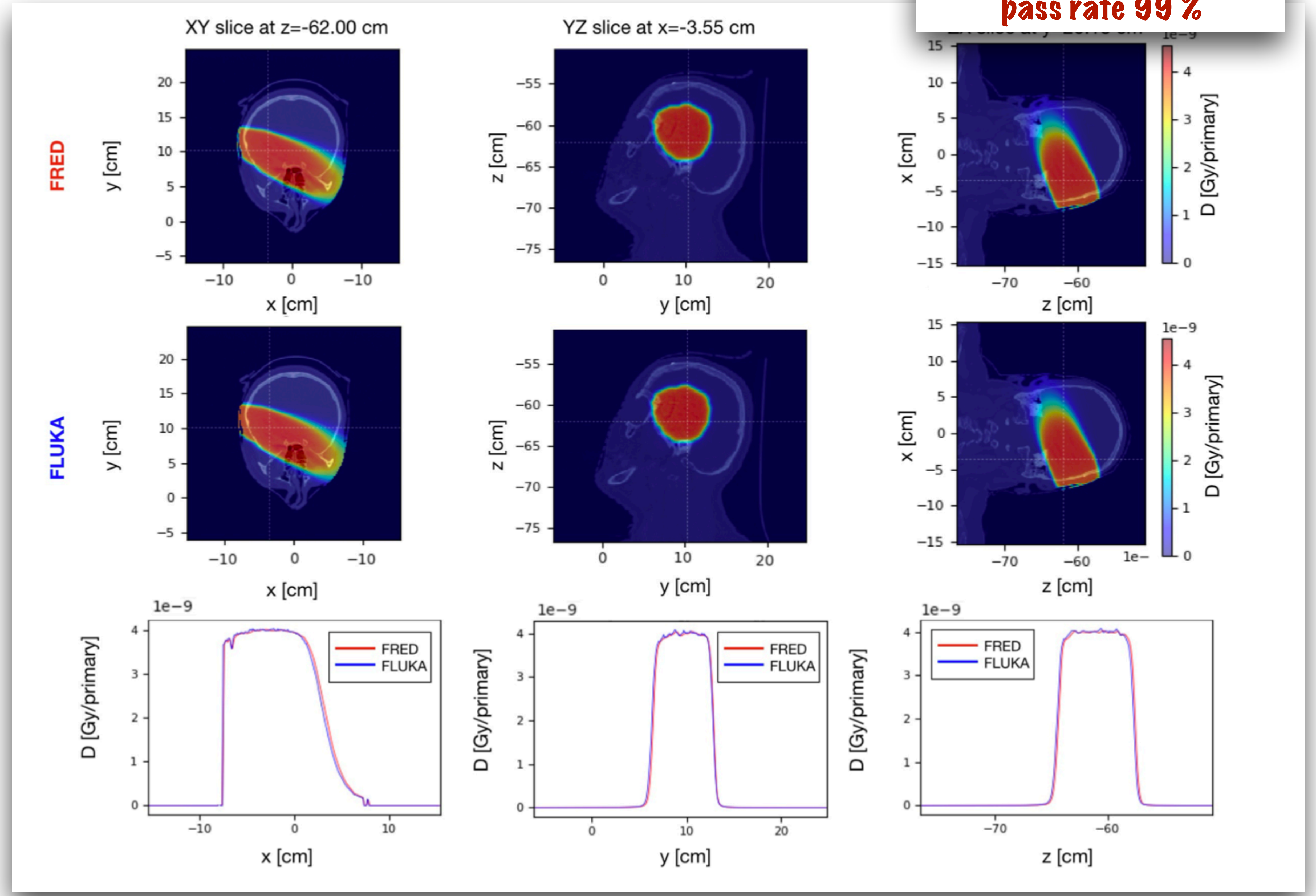


~ x1000

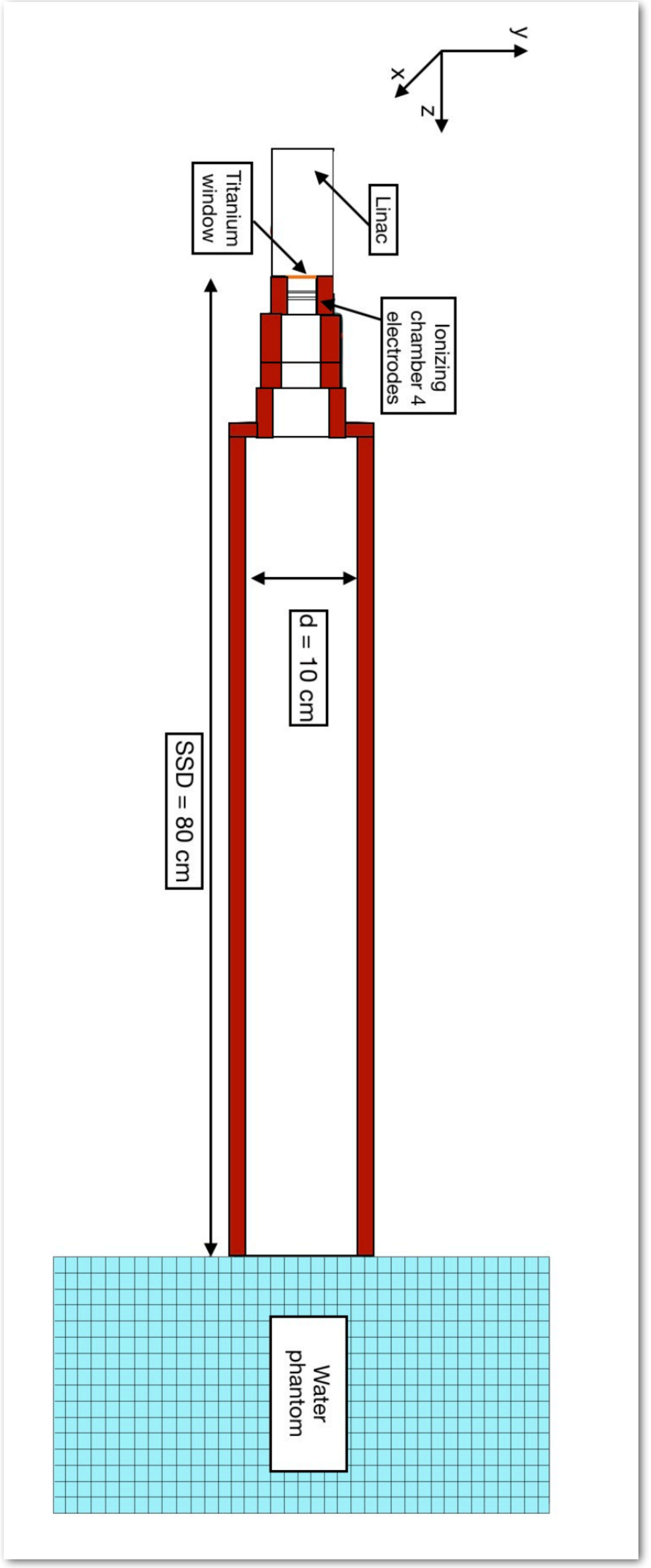
Timing Performance in water	FLUKA	GEANT4	FRED
e⁻ @ 1 MeV	1.6e4 prim/s	1.3e3 prim/s	3.0e6 prim/s
e⁻ @ 10 MeV	4.4e3 prim/s	2.2e2 prim/s	4.0e5 prim/s
e⁻ @ 100 MeV	1.1e3 prims/s	4.8e1 prim/s	7.2e4 prim/s

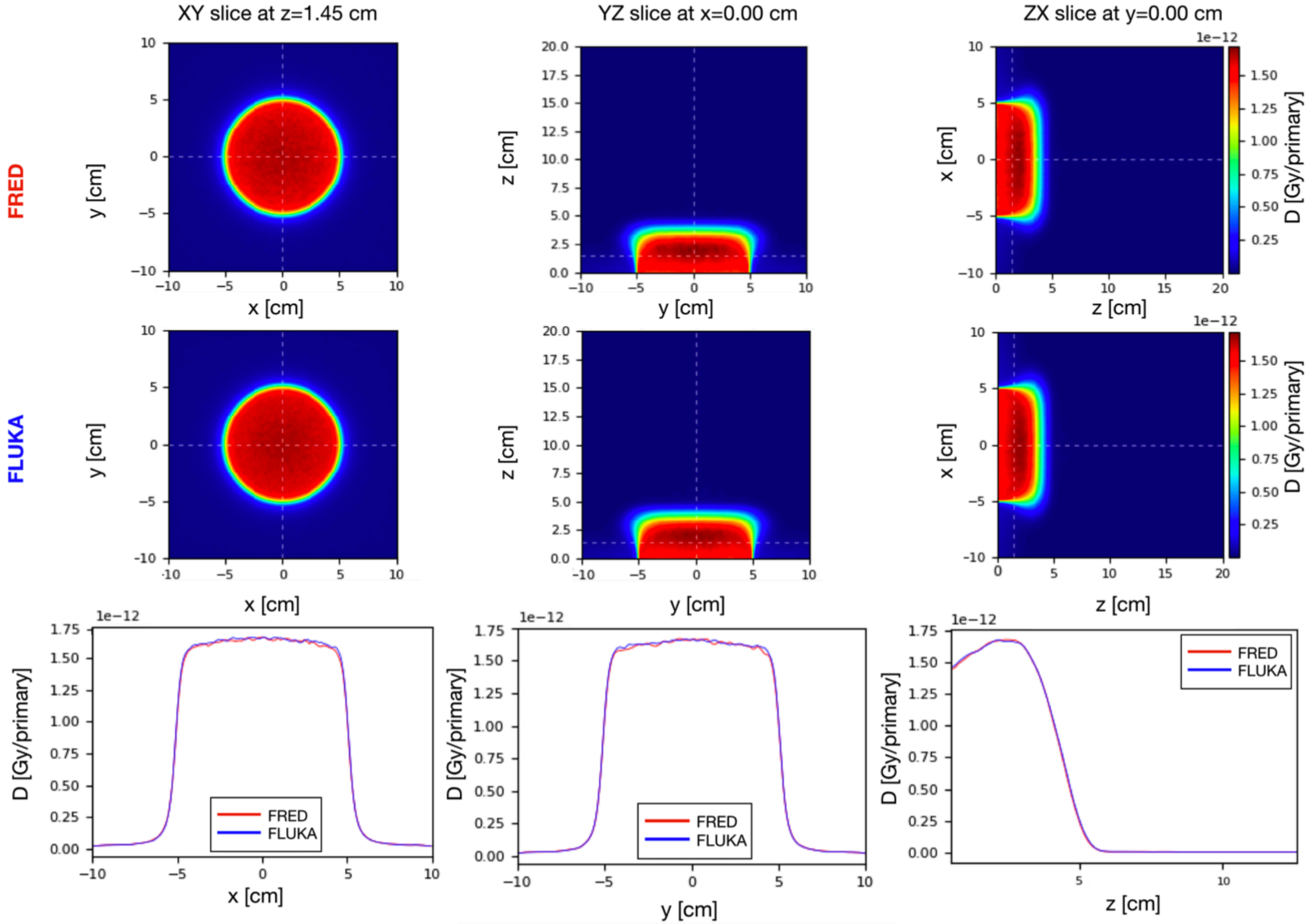
110 MeV e⁻ on Head&Neck CT scan

2mm / 3% gamma index pass rate 99 %



FRED-em: IORT applicator

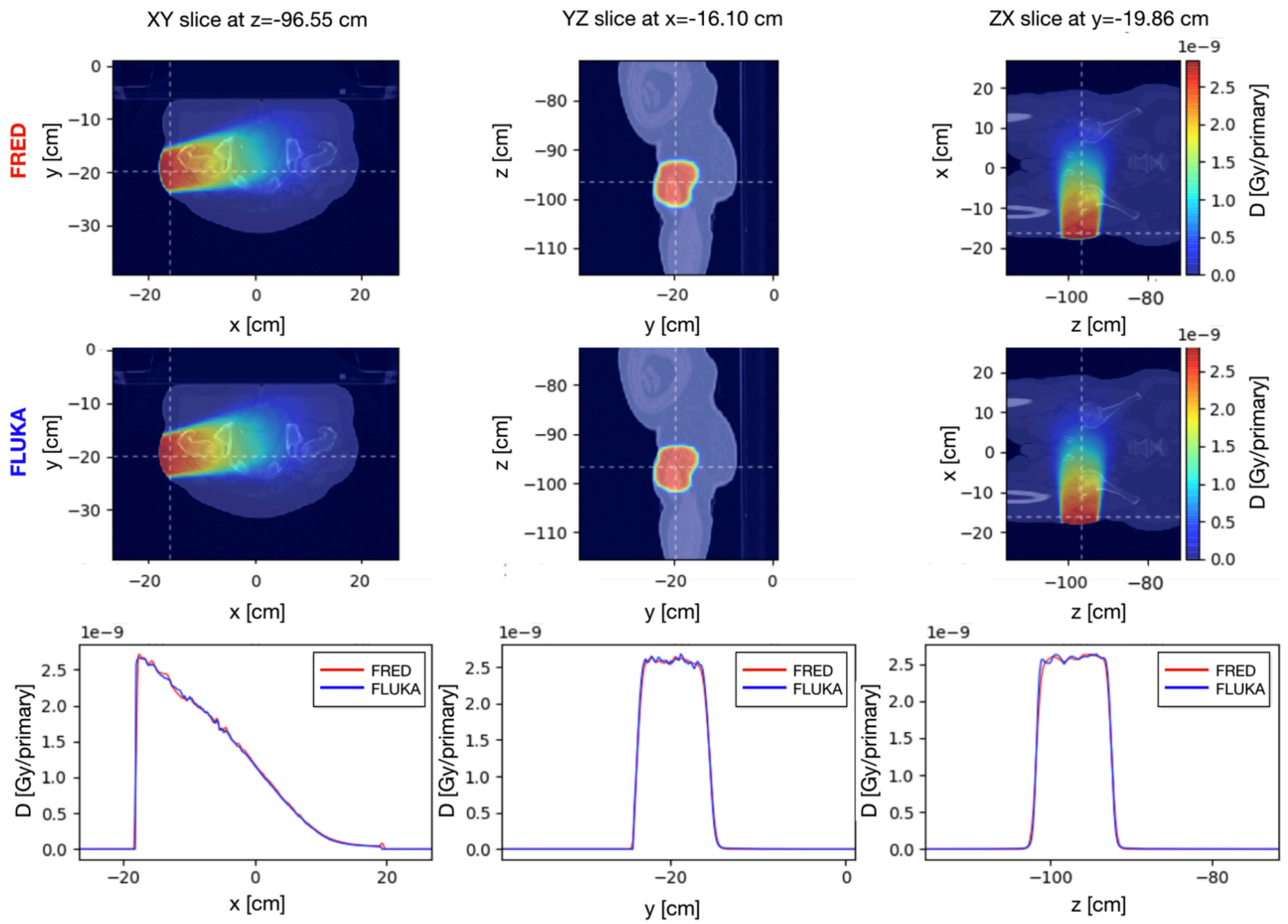




Gamma index acceptance criteria:
2 mm/3% with 5% of threshold

Gamma index pass-rate: 99.80%

FRED-em: VHEE on CT



Gamma index acceptance criteria:
2 mm/3% with 5% of threshold

Gamma index pass-rate: 99%

NOVAC 11

IORT application: NOVAC 11 accelerator

The NOVAC 11 (by Sordina IORT Technologies SpA,Aprilia, Italy) is a linear mobile electron accelerator designed for IORT application:

•Nominal energies: **4, 6, 8** and **10 MeV**;

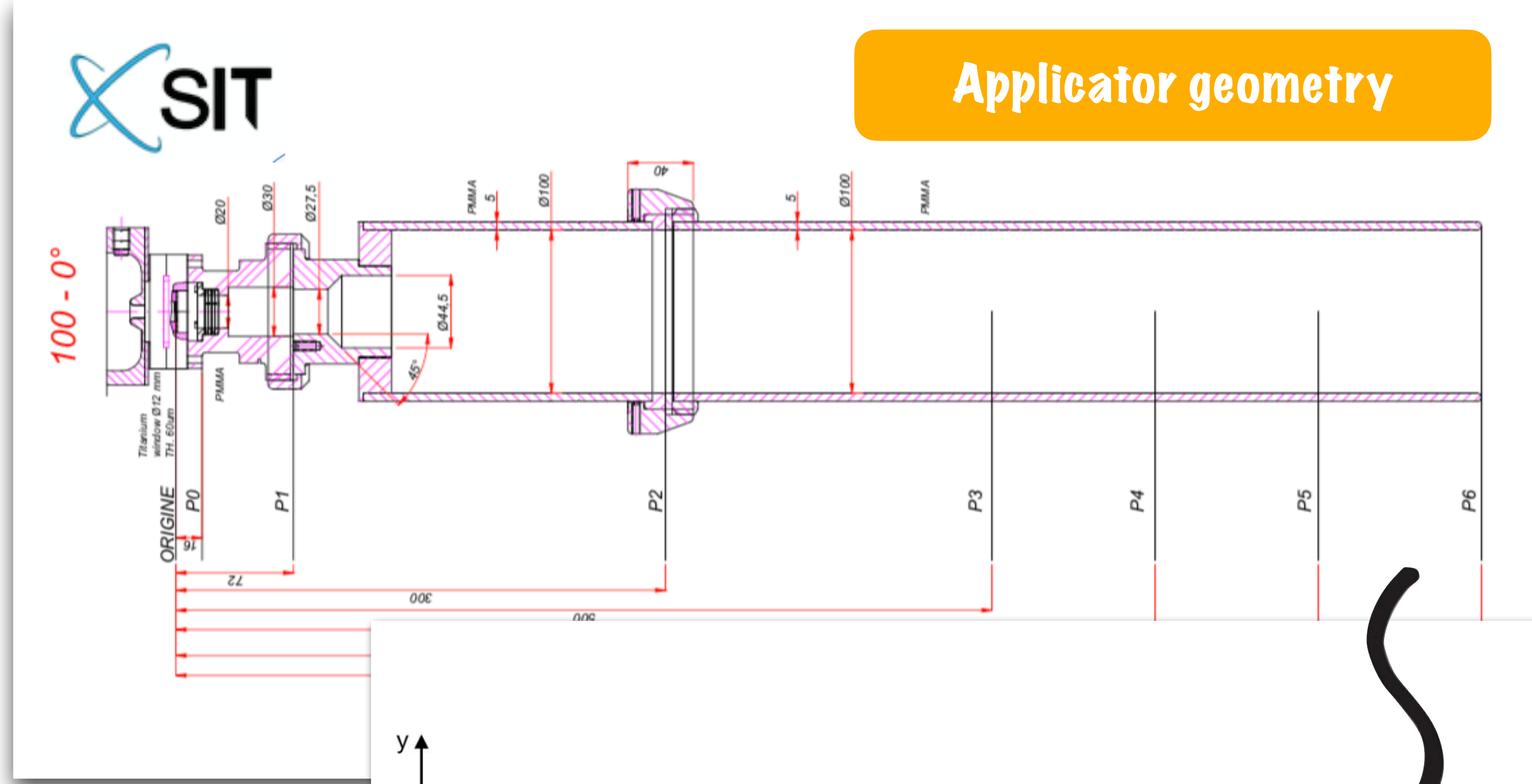
•Able to treat targets volume with a thickness up to **2.6 cm** inside the 90% isodose;

•The device is able to successfully deliver the full treatment in only 100 seconds (up to **21 Gy at 90% isodose**).

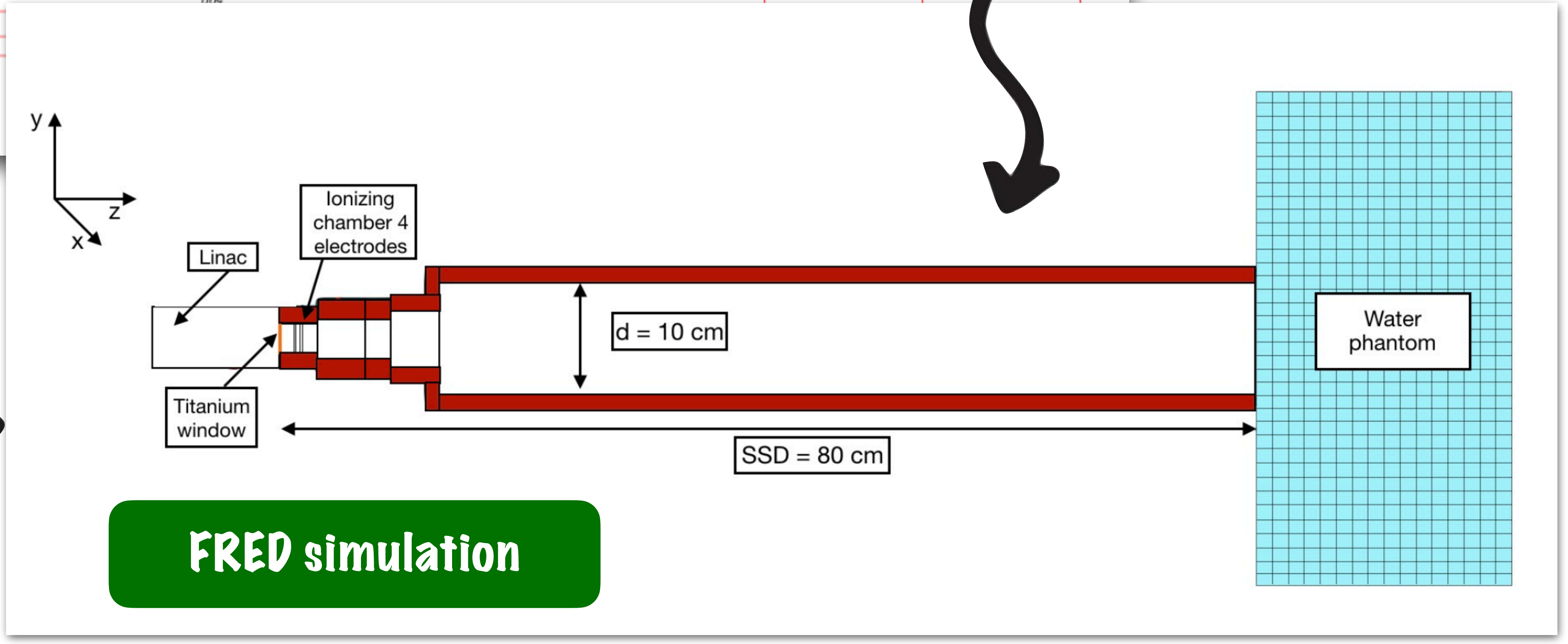
Tpulse	4.5 μs	Beam Intensity	1.5 mA	Dose rate	4-30 Gy/min

IOeRT application

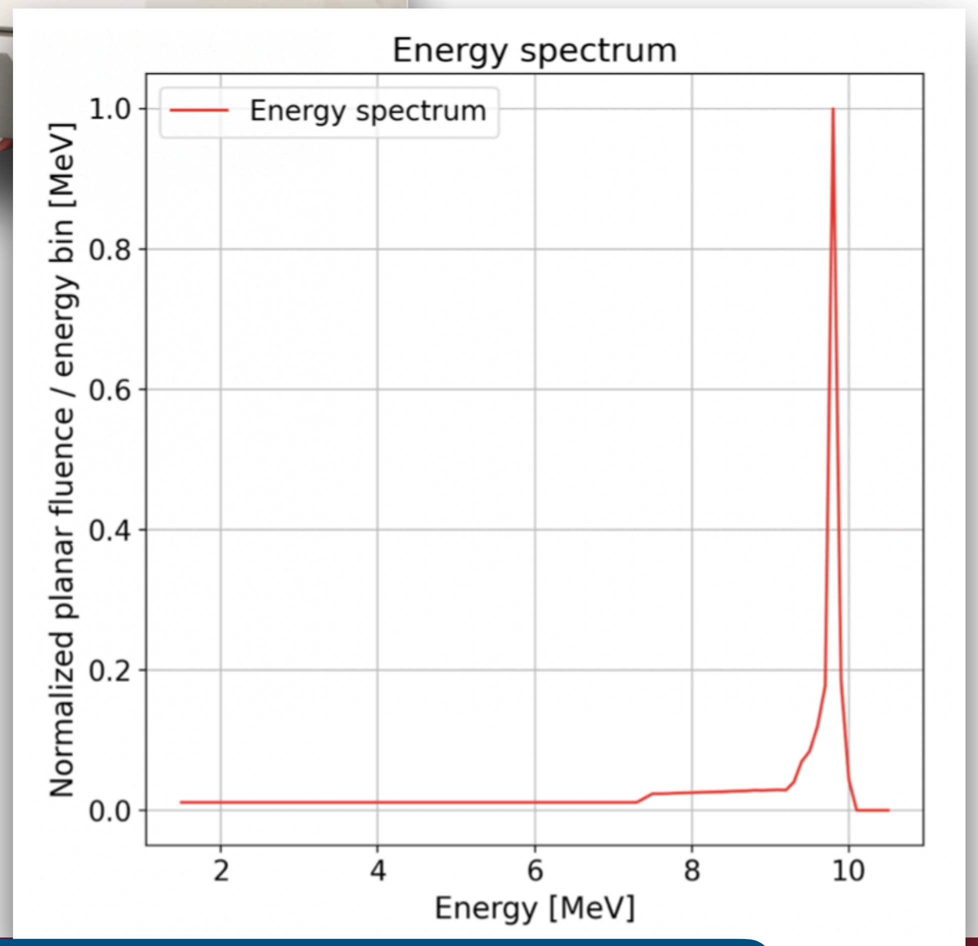
To test the FRED accuracy in reproducing IOeRT dose distributions, I simulated in details the geometry of the applicators typically used during the treatments. To this aim I considered the NOVAC 11 S.I.T. accelerator and its applicators.



Applicator geometry



FRED simulation



Energy spectrum @ linac exit

Geometry setup:

1. **PMMA cylinders** with different diameters (from 20 to 100 mm)
2. Source-to-Skin Distance **(SSD)=80 cm**
3. **Titanium** window **(55 μm)**
4. **Four steel planes** of the ionizing chamber **(20 μm each)**

Simulation setup

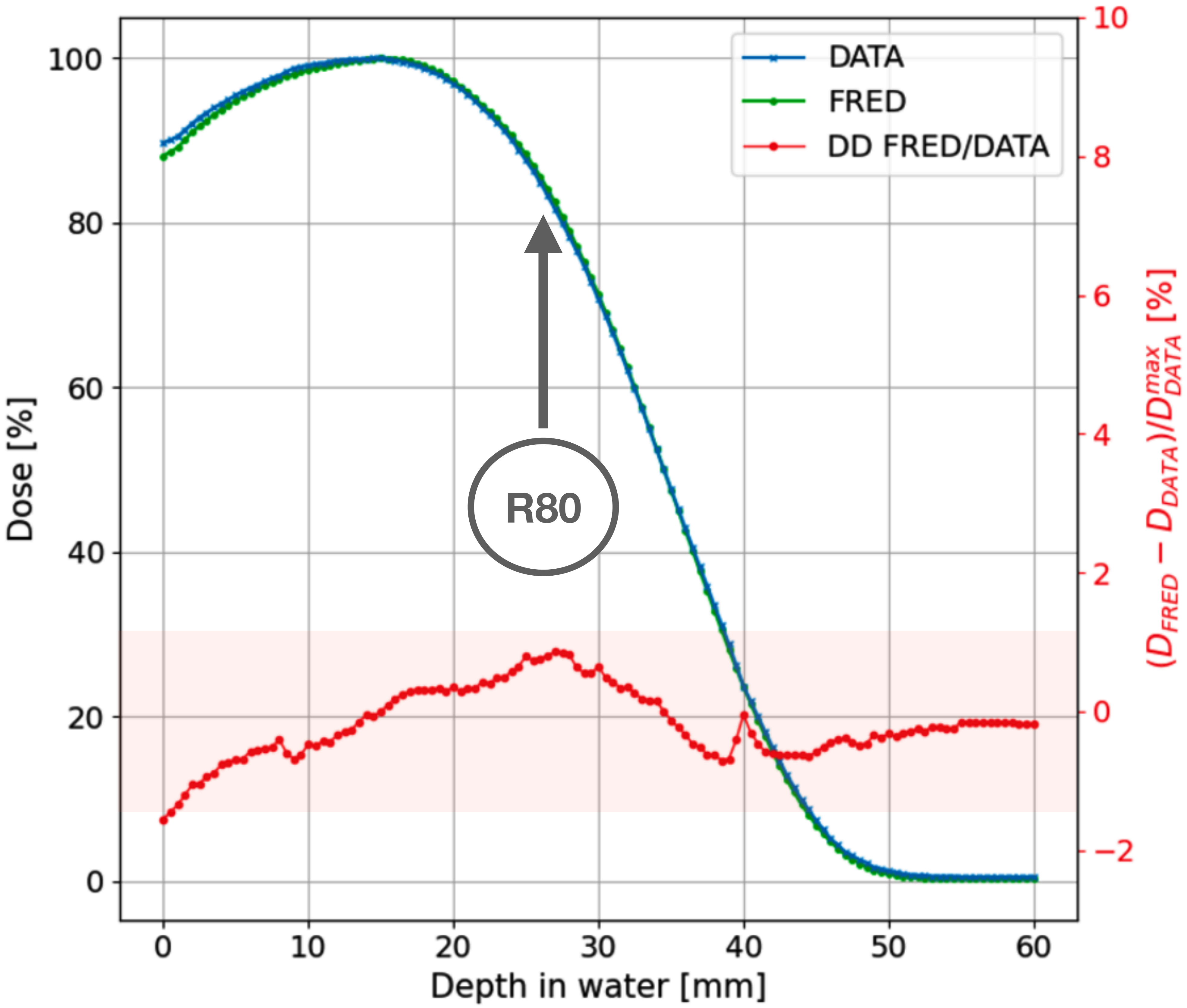
1. **~10 MeV** electrons beam;
2. Gauss section with **FWHM=0.13 cm**;
3. Transport and production energy cut = **10 keV and 50 keV** for photons and electrons respectively

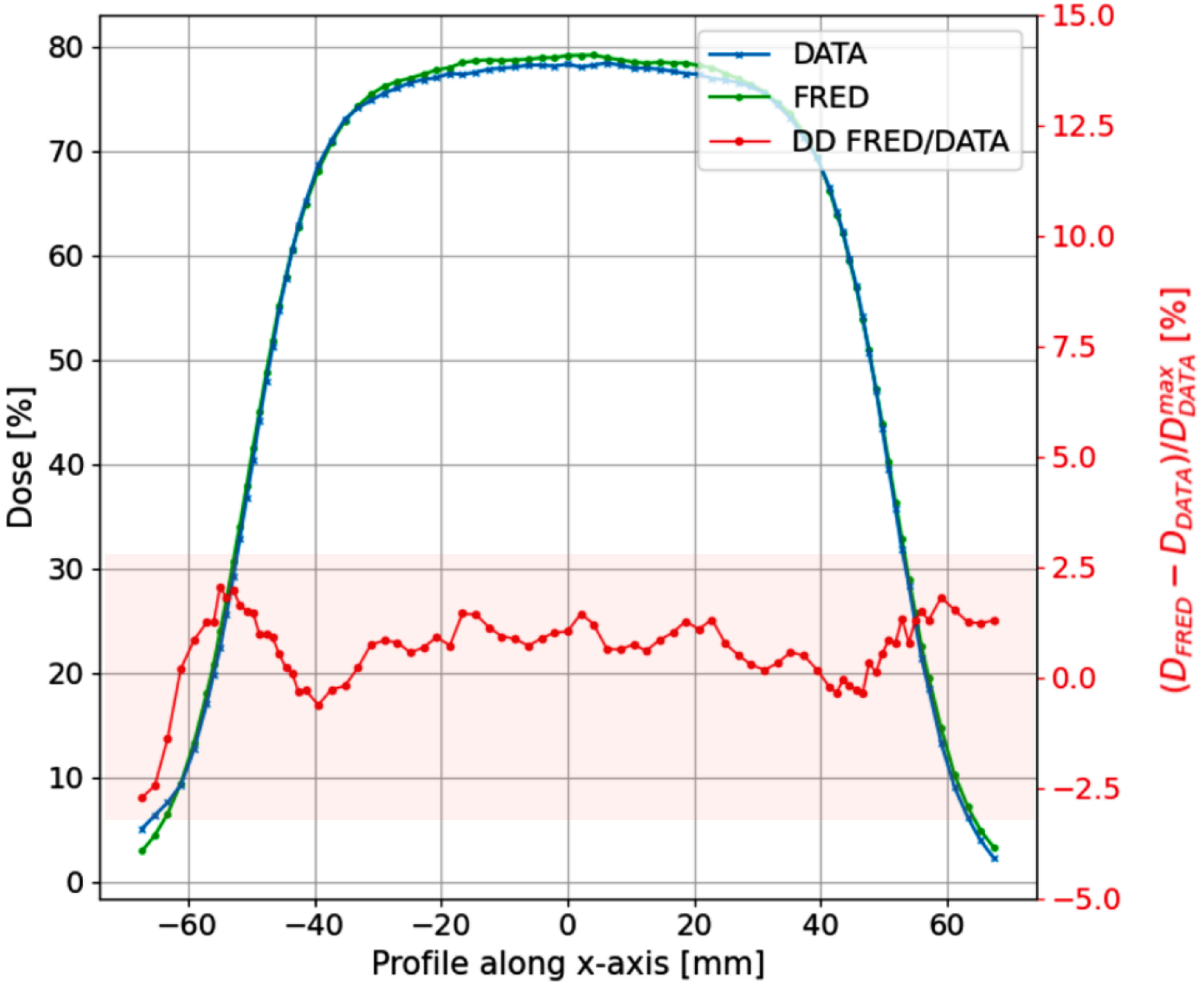
I compared the FRED results against the **experimental data** of the Percentage Depth Doses (PDDs) and off-axis profiles measured in a water phantom.

IOeRT application: FRED results

Test performed on CPU

The experimental setup for relative dosimetry, i.e. PDDs and off-axis profiles measurements consisted of a 3D motorized water phantom equipped with an unshielded diode. For the MC simulation the absorbed dose was evaluated on a water target with a transverse area of 2×2 mm^2, corresponding to the sensitive are of the adopted diode





IOeRT application: FRED results

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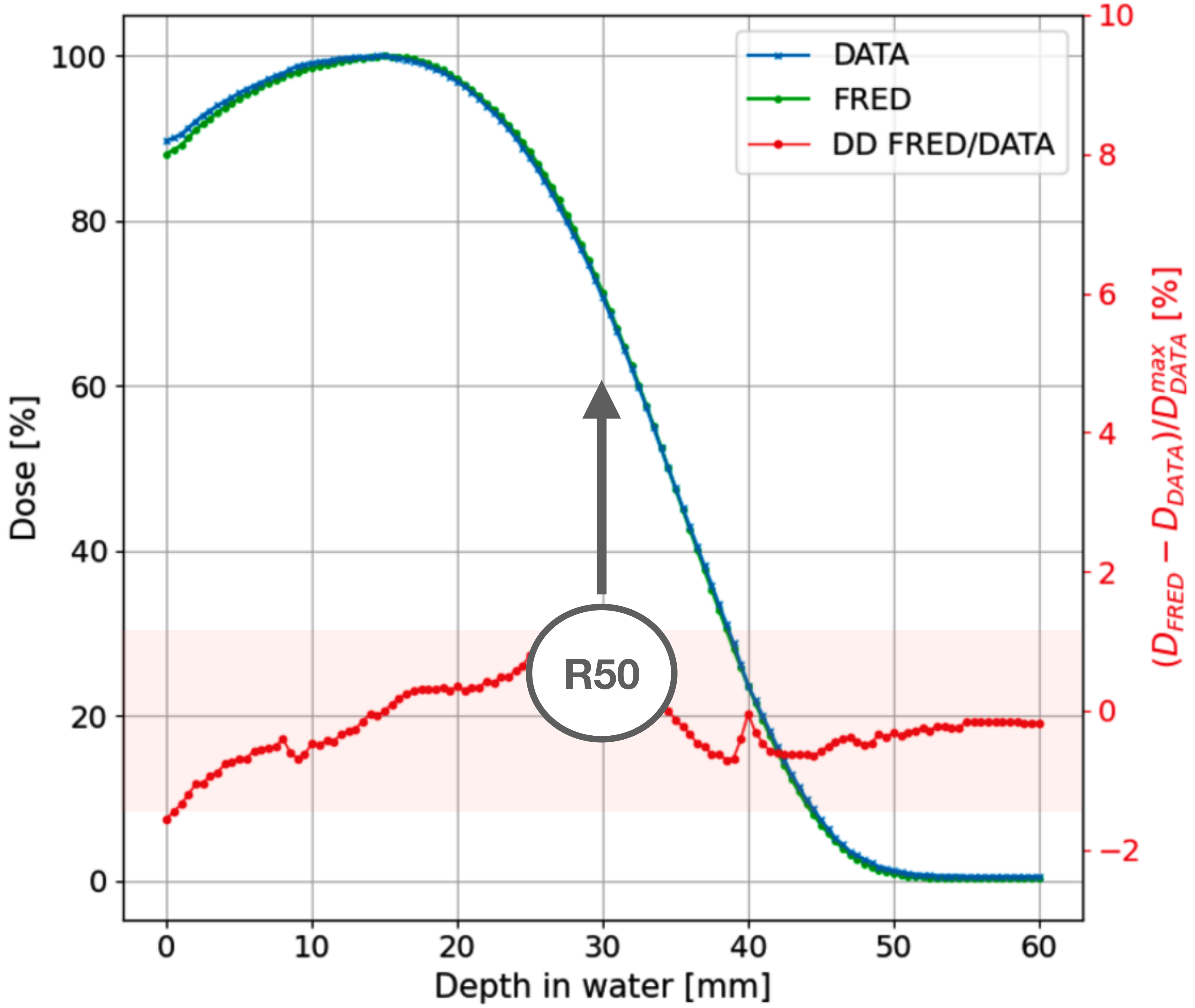
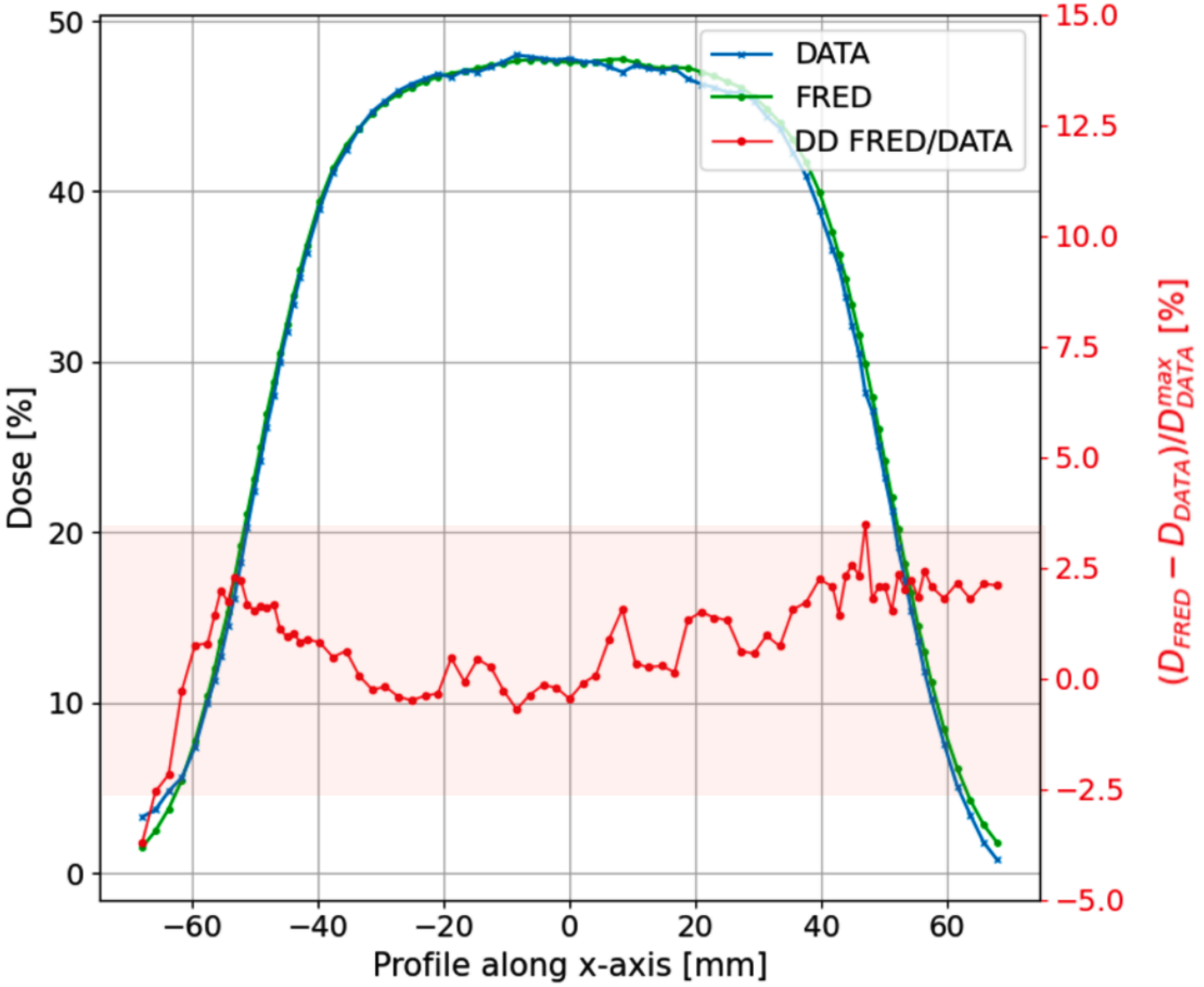


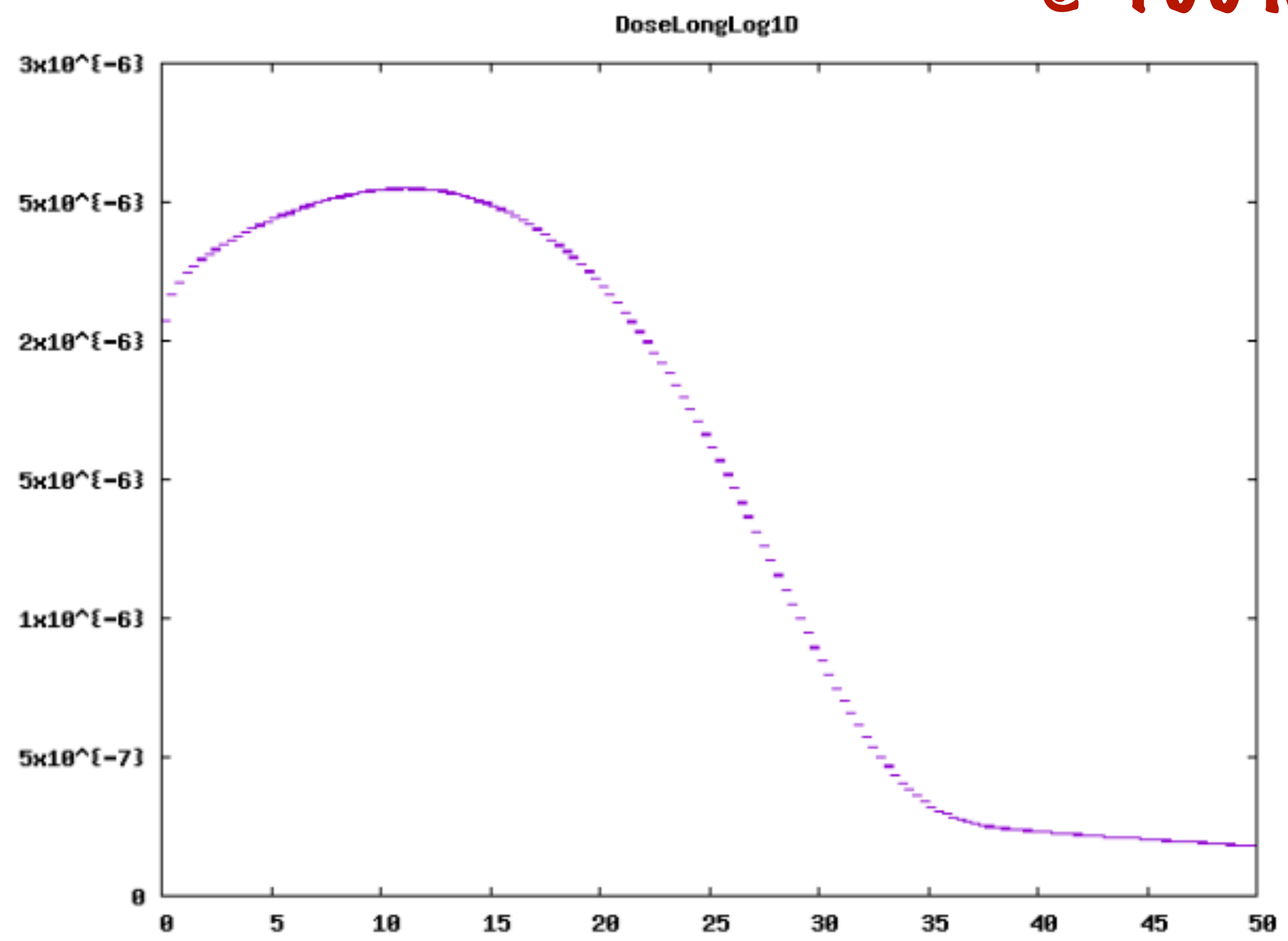


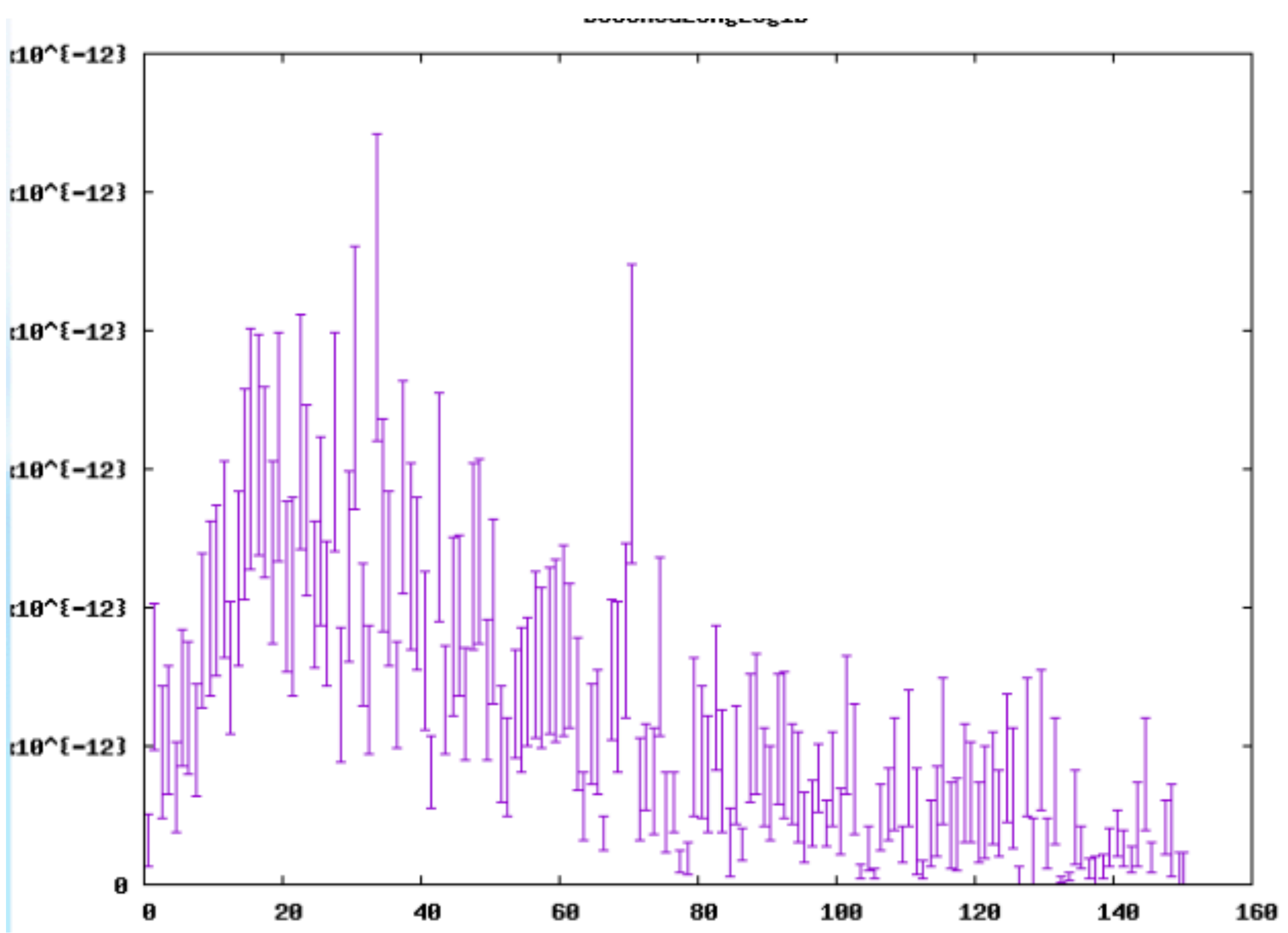
Neutrons contribution

In the medical context we have two main photoneutron production processes by the high-energy bremsstrahlung photons:

1. 10 MeV < E < 30 MeV
GIANT-RESONANCE NEUTRON PRODUCTION
2. 50 MeV < E < 300 MeV
QUASI DEUTERON PRODUCTION AND DECAY

@ 100 MeV in water





IOeRT

We are below the Giant resonance (E < 12 MeV) and thus the photoneutron production is negligible

VHEE therapy

@ 150 MeV in water

Neutron yield : 0.03 n/primary e^-

Increased neutron dose: 0.2%

Increased equivalent neutron dose: 2% (w=10)

Negligible contribution

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Back to the Future: Very High-Energy Electrons (VHEEs) and Their Potential Application in Radiation Therapy

by Maria Grazia Ronga [1,2], Marco Cavallone [1], Annalisa Patriarca [1], Amelia Maia Leite [1,3], Pierre Loap [1], Vincent Favaudon [4], Gilles Créhange [1] and Ludovic De Marzi [1,3,*]

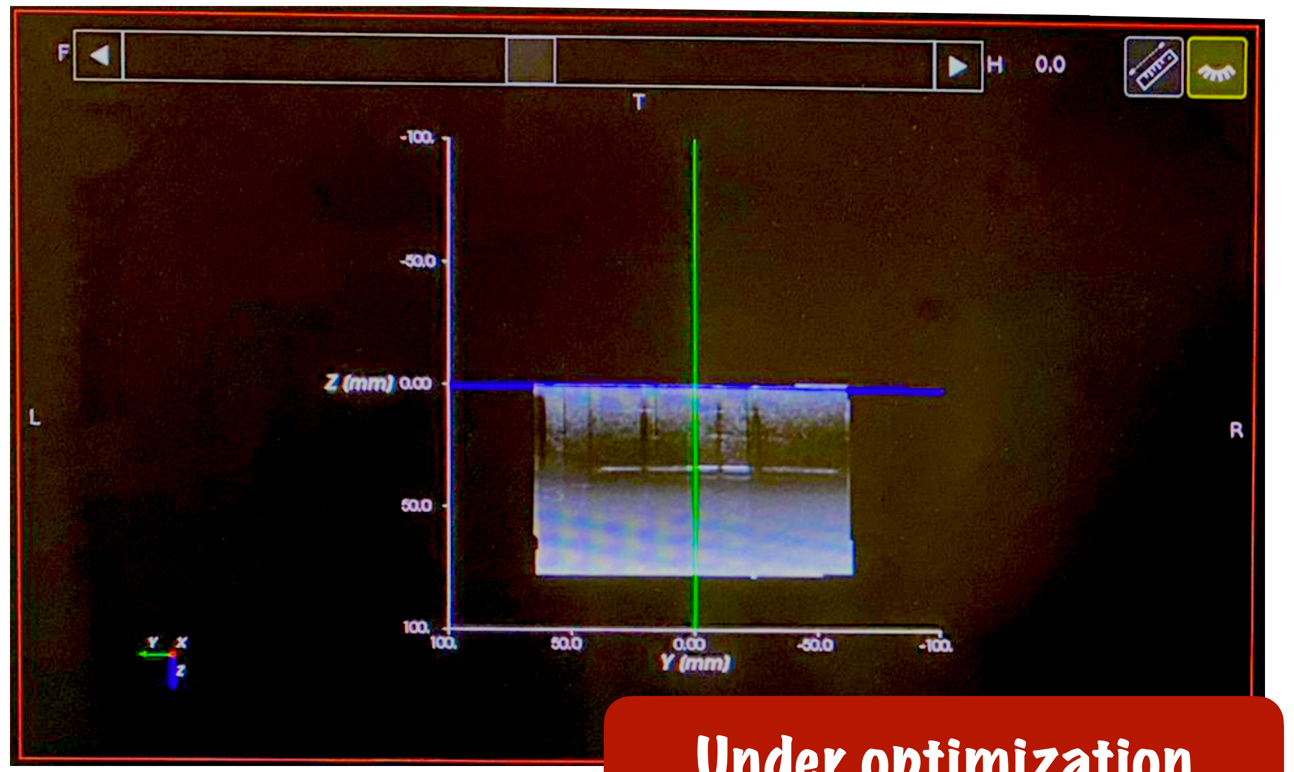
TPS

Treatment planning configuration

To give a reasonable feedback to the operator I need to be capable to 'optimize' the treatment! How can I identify the ideal energy or ideal applicator position/dimension for that **specific treatment**? Answering that question means understanding which are the constraints that have to be respected.

I developed the optimization tools and the relative algorithms, which are based on different inputs:

- ☒ **Ultrasound imaging input with reasonable ROIs (PTV and OAR)**



Currently, the US system is under optimization and thus not yet available. I used **real CT images**, modified to meet the expected US imaging resolution

- ☑ **Dose prescription**

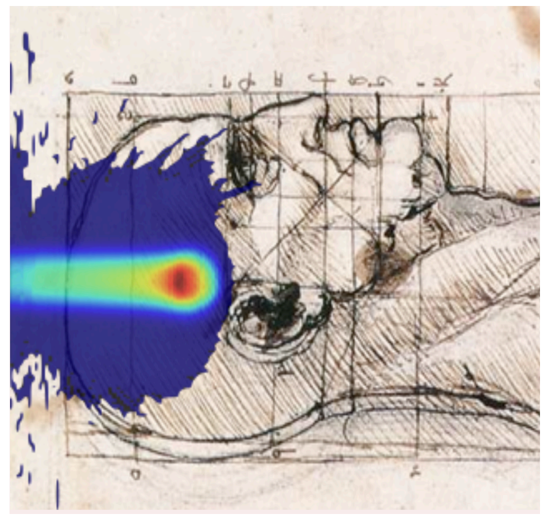
I collaborated with the IOeRT specialists of the European Institute of Oncology (Milan) to define reasonable **dose prescriptions** for the **PTV**.

SIT

IEO Istituto Europeo di Oncologia

- ☑ **Fast simulation tool**

The **FRED** timing performance is highly compatible with the time available during surgery to explore different treatment configurations (order of few minutes).



- ☑ **Phase-space that has to be explored**

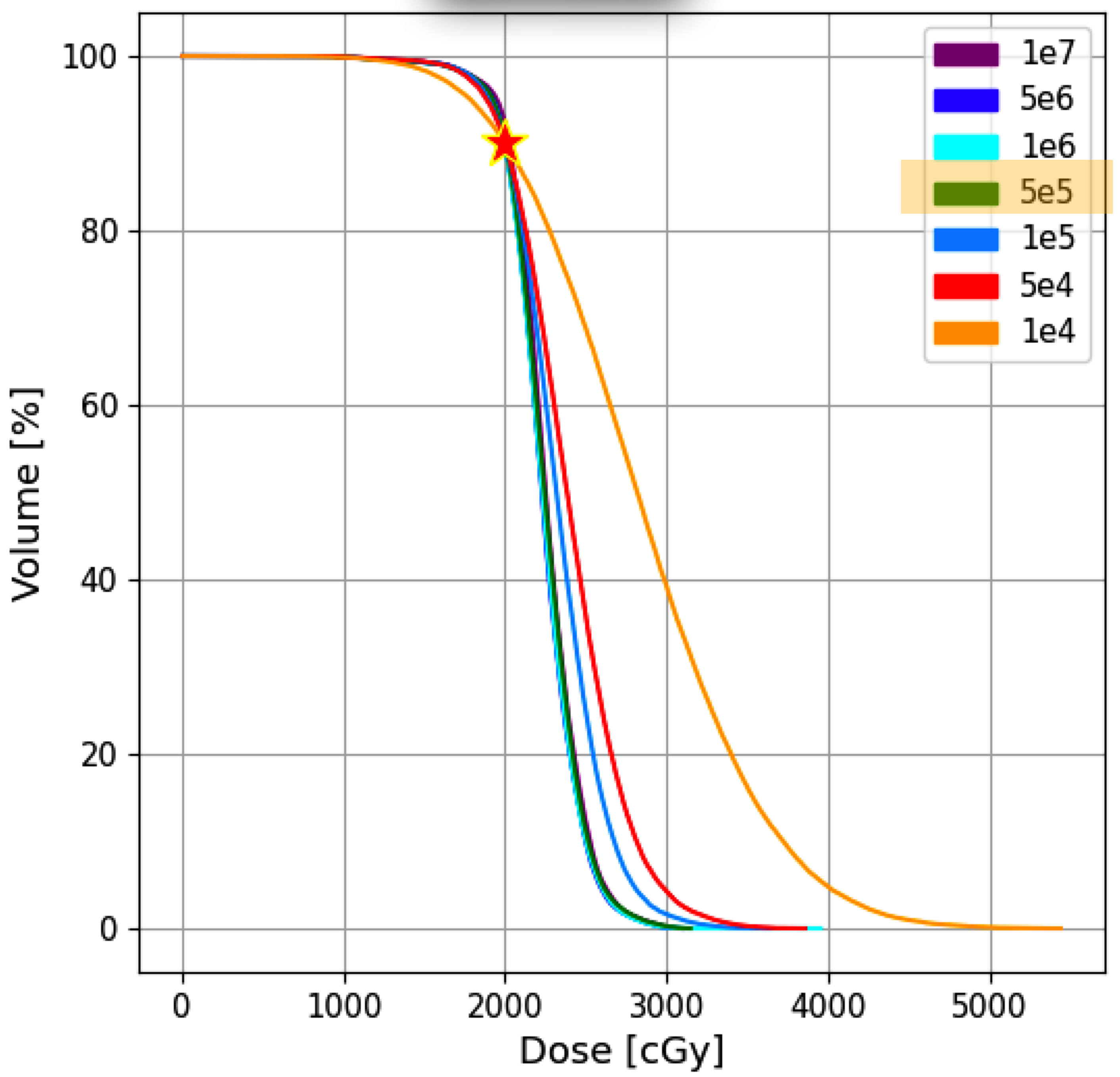
IOeRT specialist helped me to define the energies, and the possibile beam delivery configurations (beam dimension and position)

Needed statistics/GPU time

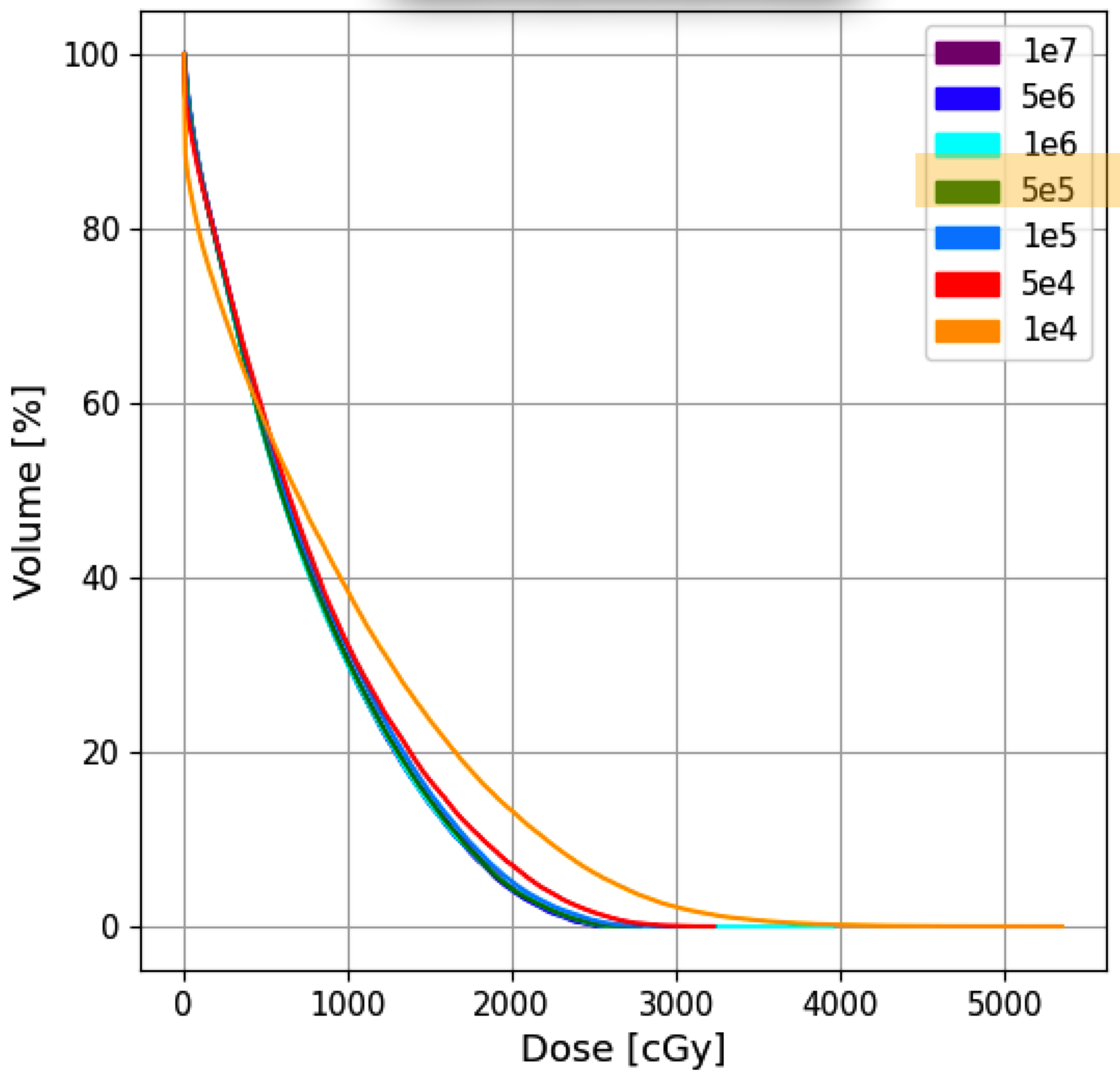
The DVHs depend not only on the "geometry considered", i.e. the volume of the PTV and OARs, but also on the simulation statistics.

I therefore performed a scan simulating different number of primaries with fixed energy and geometry to test the stability of the DVHs.

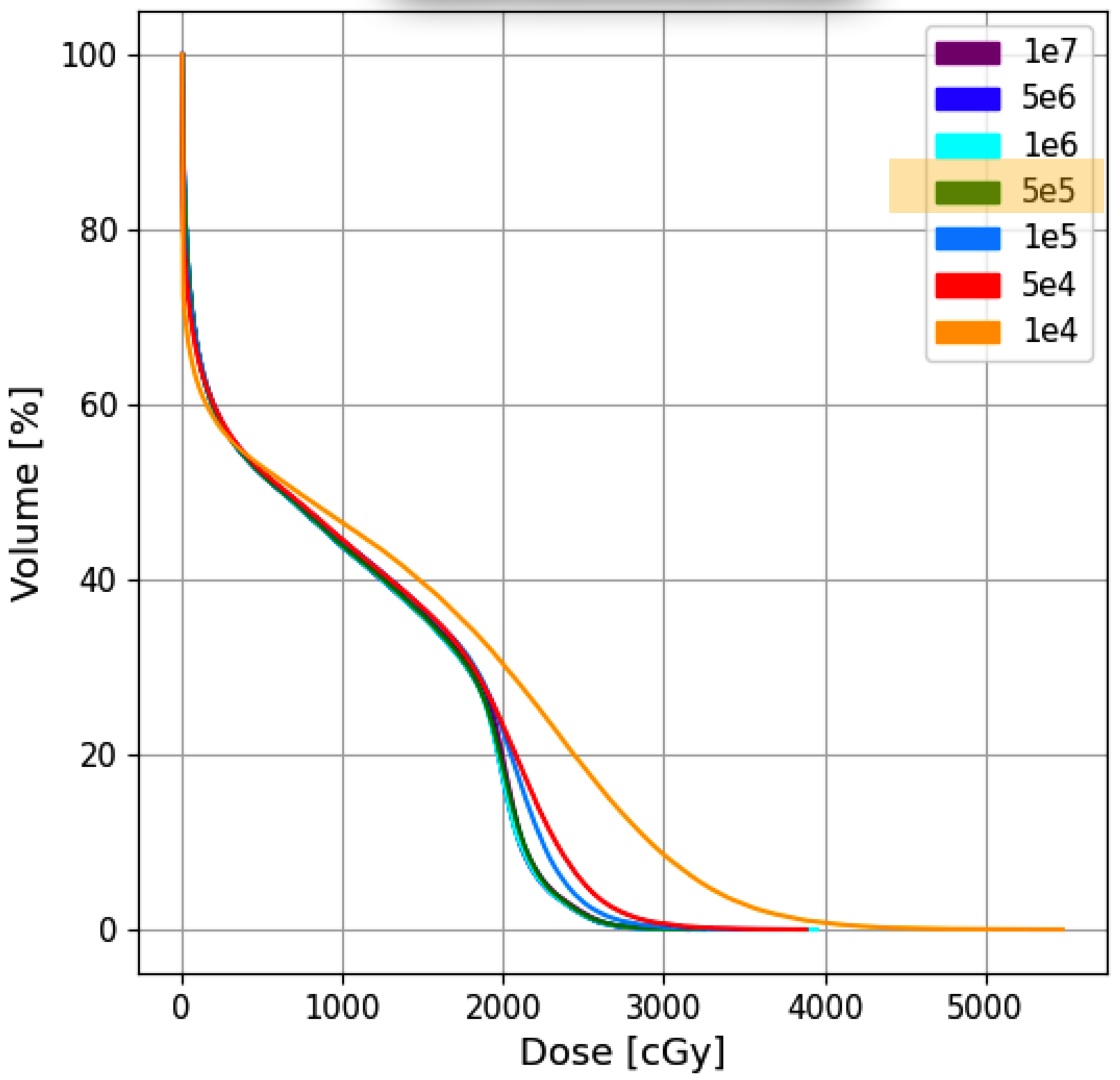
PTV



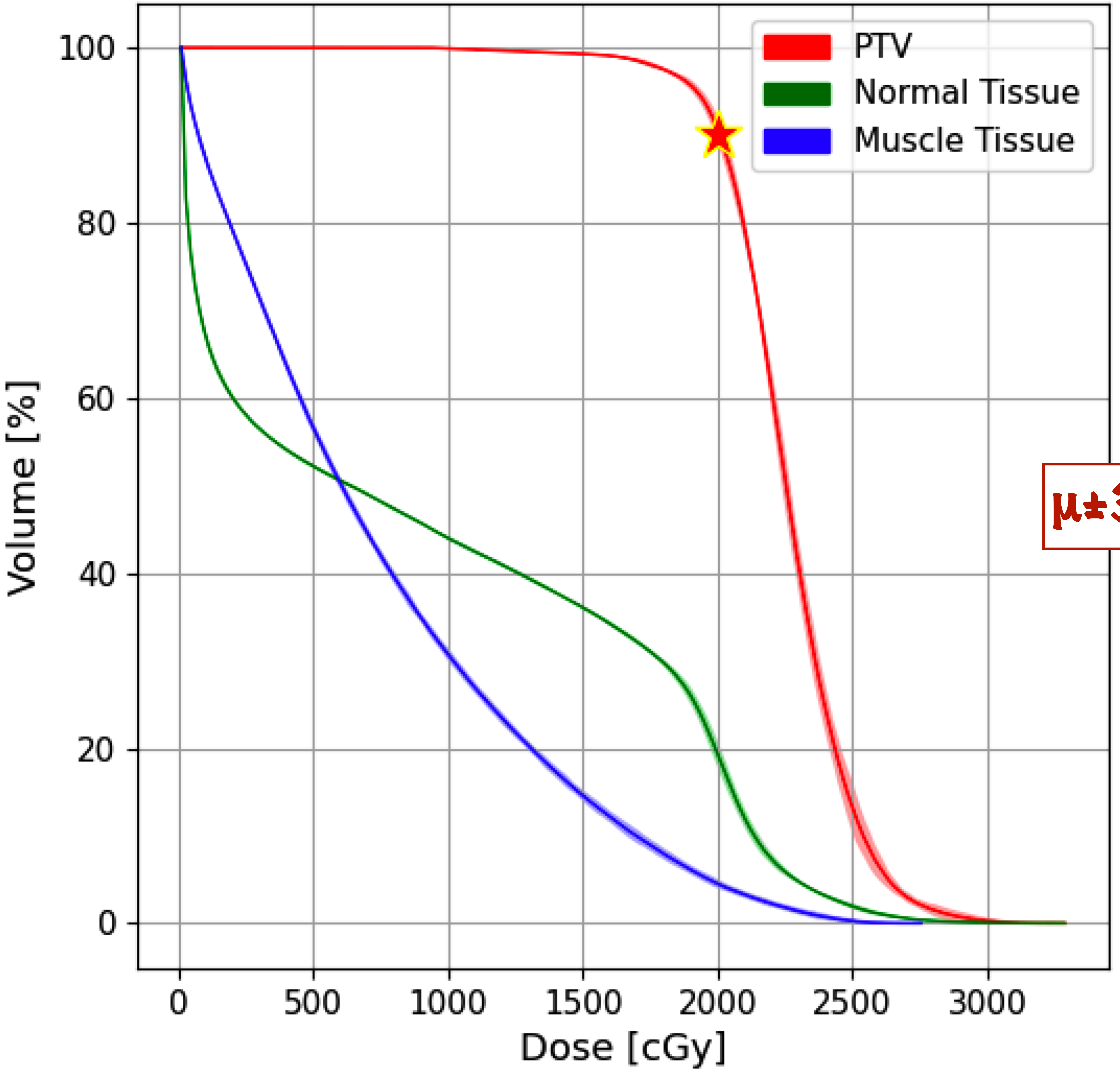
Muscle tissue



Normal tissue



Needed statistics/GPU time



μ±3σ

To test the stability of the FRED outputs, I evaluated the statistical fluctuations of the DVHs and mean dose value absorbed by each ROIs. To this aim, I performed 10 independent equal simulations.

In Fig. the mean DVH, evaluated by calculating for each bin, containing the dose, the average value of the ROI volume absorbing that dose value. The error band, shown in transparency, corresponds to 3σ, with σ the standard deviation of each bin content over 10 simulations.

	$\mu \pm \sigma$
ROIs	D [cGy]
PTV	2256.1 ± 1.3
Muscle Tissue	746.8 ± 2.6
Normal Tissue	927.3 ± 2.8

Beam dimension scan

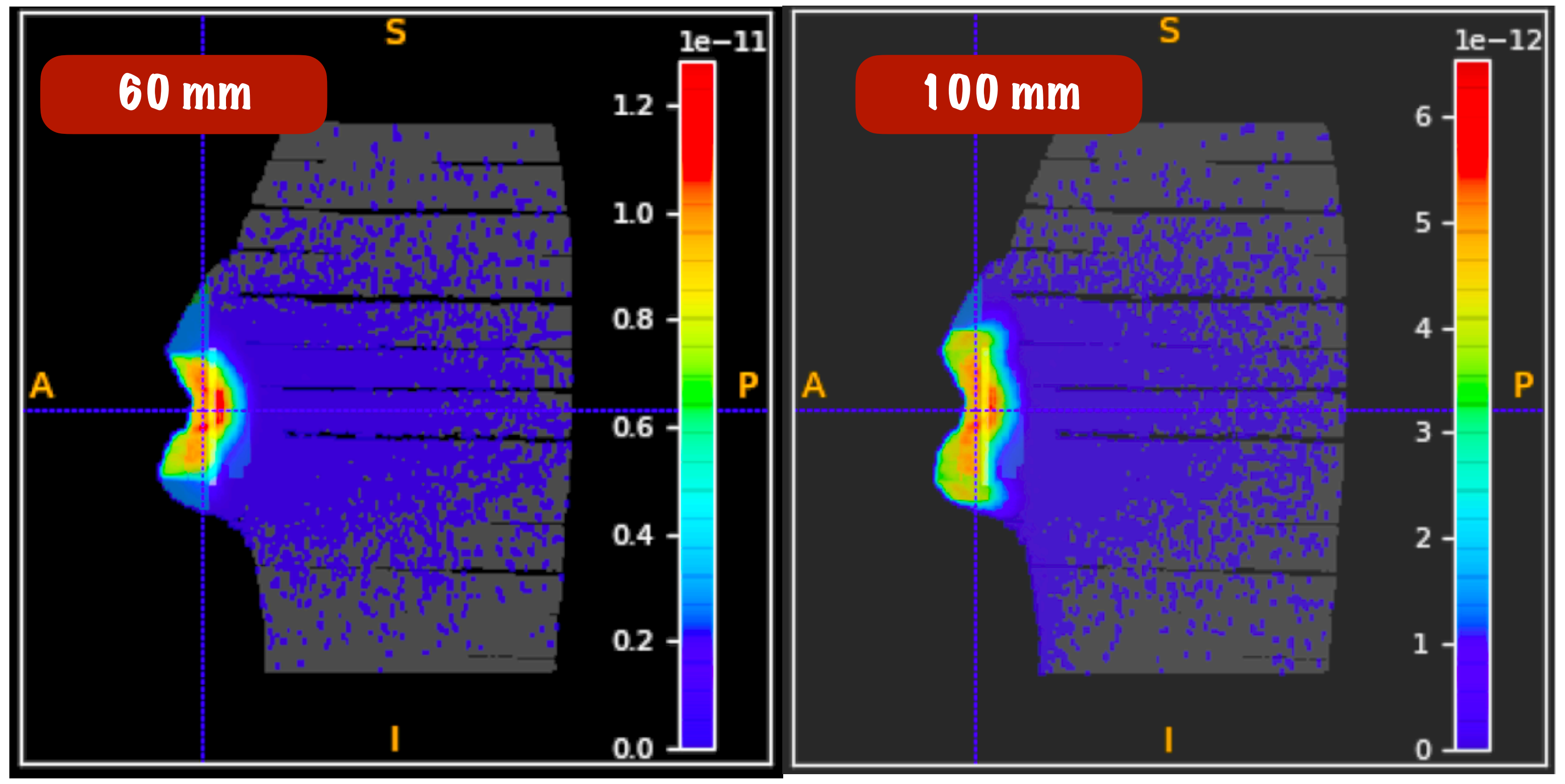
T = 23.8 s

I generated a circular electron beam at ~ 1 cm from the patient skin in a centered position with respect to the PTV.

The beam energy was fixed at 8 MeV and I changed only the beam dimension: 70, 80, 90 and 100 mm were selected according to the PTV dimension.

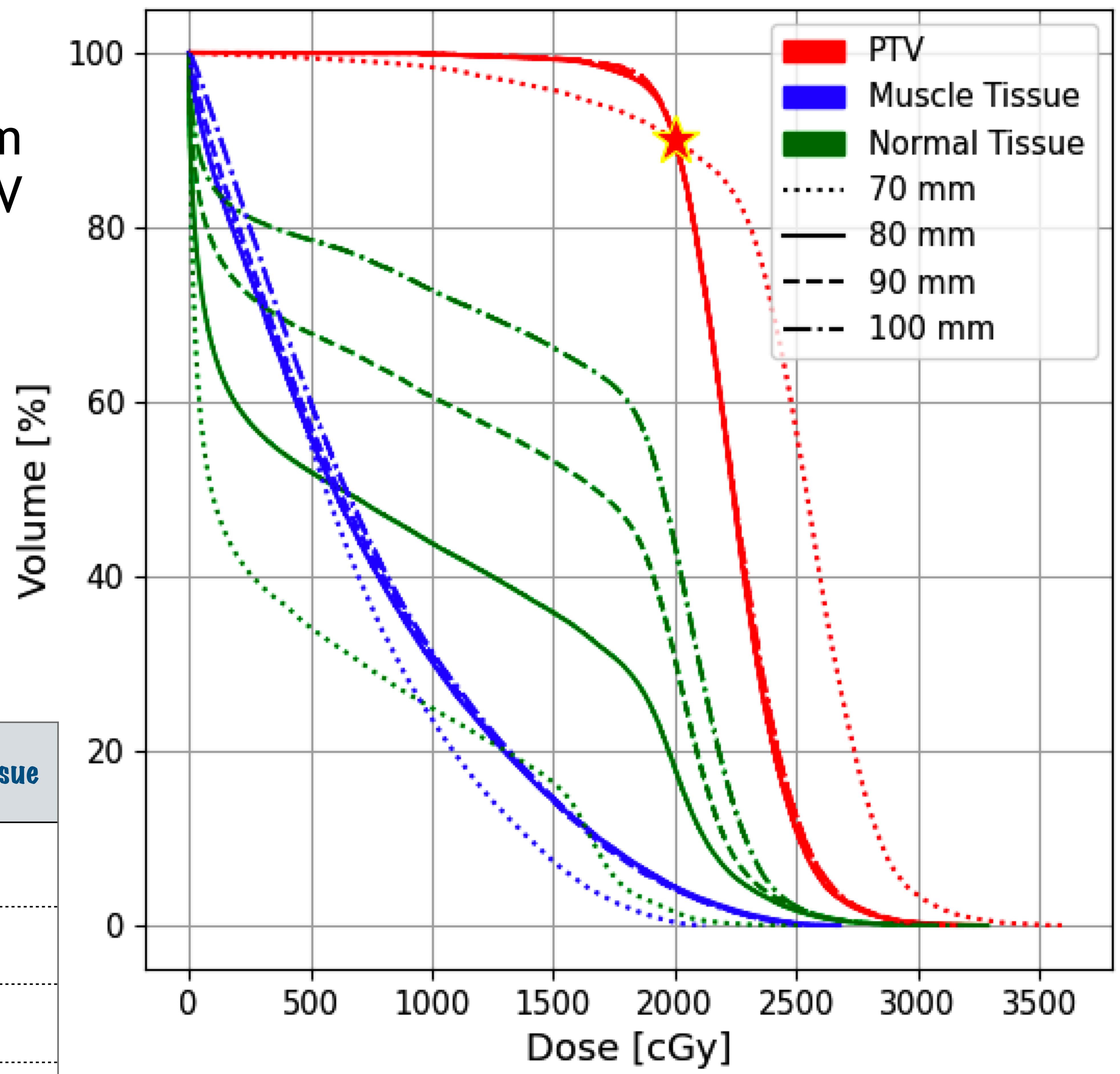
Dose prescription: ★ **20 Gy @ 90%**

OSS: The FRED dose maps in Gy/primary units were multiplied by the **number** of **electrons** needed to **fulfill** the dose prescription: $2.85 \cdot 10^{12}$, $3.20 \cdot 10^{12}$, $4.40 \cdot 10^{12}$ and $5.20 \cdot 10^{12}$ for the 70, 80, 90 and 100 mm simulation.



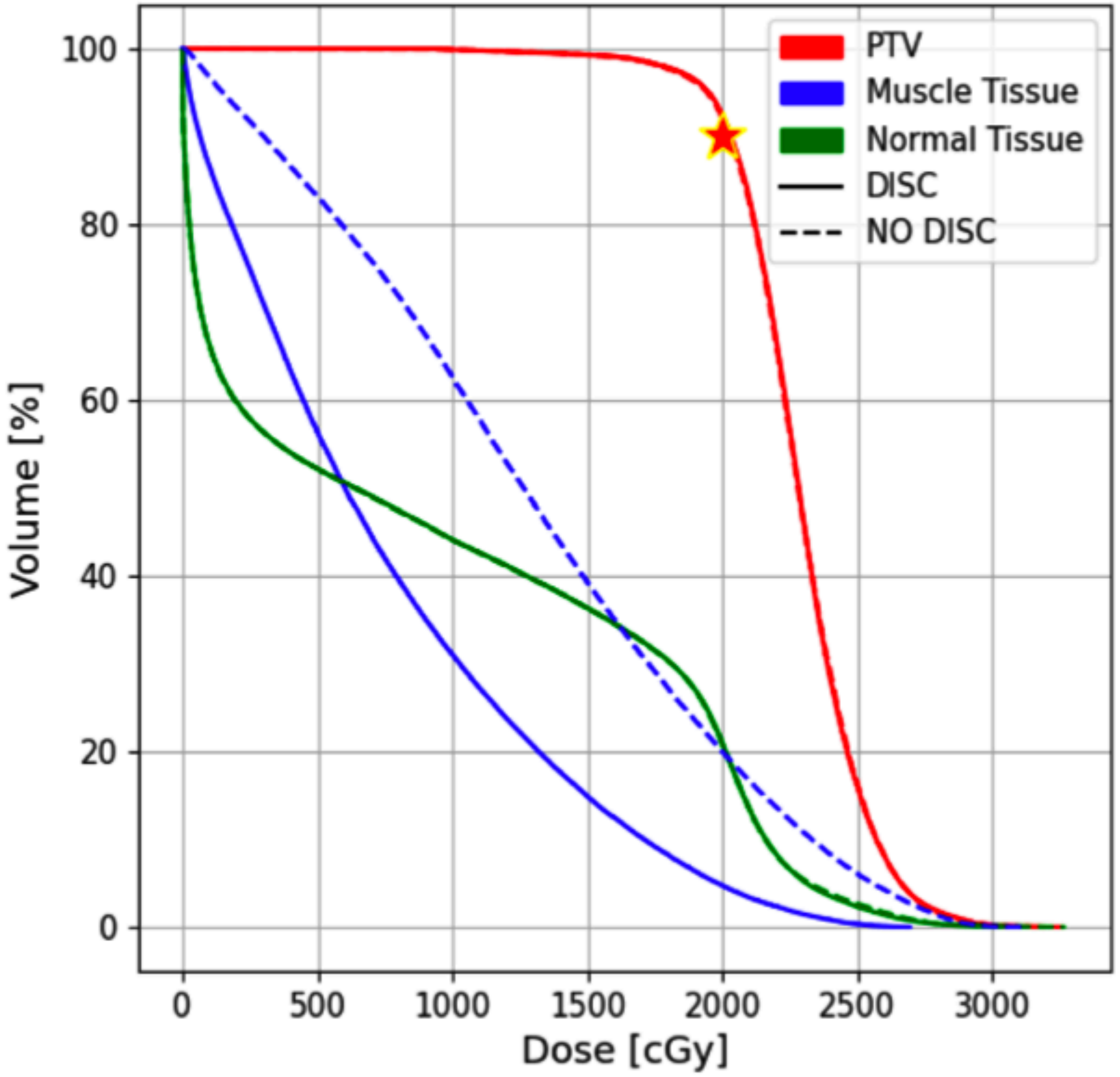
Dose mean values

D [Gy]	PTV	Muscle Tissue	Normal Tissue
70 mm	24.6	6.5	5.1
80 mm	22.4	7.5	9.3
90 mm	22.4	7.6	12.7
100 mm	22.6	7.9	15.3



RP disc impact

The exploitation of the RP disc is not always mandatory but depends on several factors, including the hospital guidelines.



As an example, in Italy, disc insertion under the target volume is the practice, especially if the tumor is located on the left breast, and thus near the heart. In Northern European countries indeed, it is used or not according to patient anatomy.

In order to assess the impact of the RP disc presence or absence, I performed two identical simulations: 8 MeV circular beam with a diameter equal to 80 mm and $5 \cdot 10^5$ primary electrons, impinging on the phantom CT with and without the RP disc inserted

	D [cGy]	
ROIs	RP disc	No RP disc
PTV	2245.3 ± 1.3	2234.2 ± 1.3
Muscle Tissue	747.3 ± 2.9	1269.5 ± 3.4
Normal Tissue	925.3 ± 2.2	928.7 ± 2.3

TPS timing performance

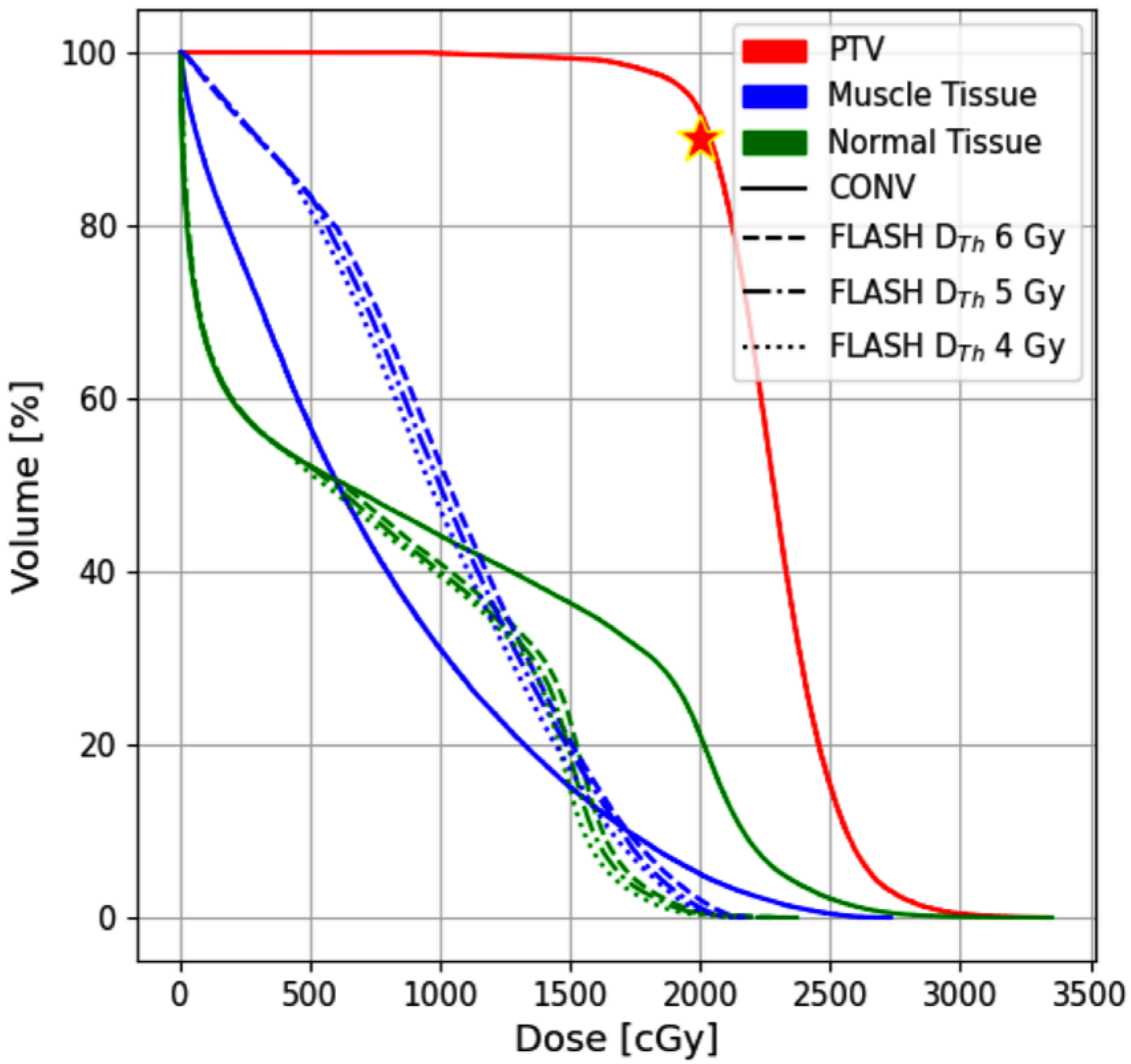
The robustness of the dose maps was one of the two most stringent conditions to be met by the treatment planning and optimization tool. The time factor is in fact crucial for the TPS application in clinical practice.

The timing performance of the developed treatment planning and optimization tool is highly compatible with the time available during the surgery (order of few minutes).

Dose calculation time		
Study	Number of simulations	Time [s]
Energy scan	3	23.1
Beam dimension scan	3	23.8
Beam position scan	9	60.3 s
Impact of the RP	2	15.4

As an example, the simulation time for a preliminary TPS, where three different beam energy and for each energy three different applicator positions are explored, is ~ 1 minute.

Minimally invasive surgery IOeRT-FLASH treatment



To explore the potential of a preliminary combination of minimally invasive surgery and IOeRT FLASH treatment, I evaluated the possibility to remove the RP disc (avoid large surgical breach for RP insertion) during a FLASH IOeRT breast cancer treatment.

	D [cGy]			
ROIs	CONV with RP	FLASH no RP $D_{Th} = 6$Gy	FLASH no RP $D_{Th} = 5$Gy	FLASH no RP $D_{Th} = 4$Gy
PTV	2245.3 ± 1.3	2265.4 ± 1.3	2243.6 ± 1.3	2246.4 ± 1.3
Muscle Tissue	747.3 ± 3.12	1031.1 ± 2.4	1005.6 ± 2.3	975.2 ± 2.3
Normal Tissue	952.3 ± 2.40	739.5 ± 1.7	720.0 ± 1.7	703.4 ± 1.6

Dose report

Beside the unavailability of a dedicated TPS, currently the IOeRT does not have an accurate report of the dose delivered, needed by law from 2020 (European 2013/59/EURATOM Italian D.Lgs 101/2020).

The implemented optimization tool can be used also for dose report: given the treatment parameters it is possible to evaluate the dose absorbed by the patient with great precision.

μ/σ 2D dose maps, with μ average dose and σ standard deviation, obtained from 10 independent simulations performed with an 8 MeV circular beam with a diameter equal to 80 mm and 10^8 primary electrons.

statistical uncertainties < 2%