

Development of tools for quality control on therapeutic carbon beams with a fast MC code (FRED)

Candidate: Micol De Simoni

Supervisor: Prof. Vincenzo Patera

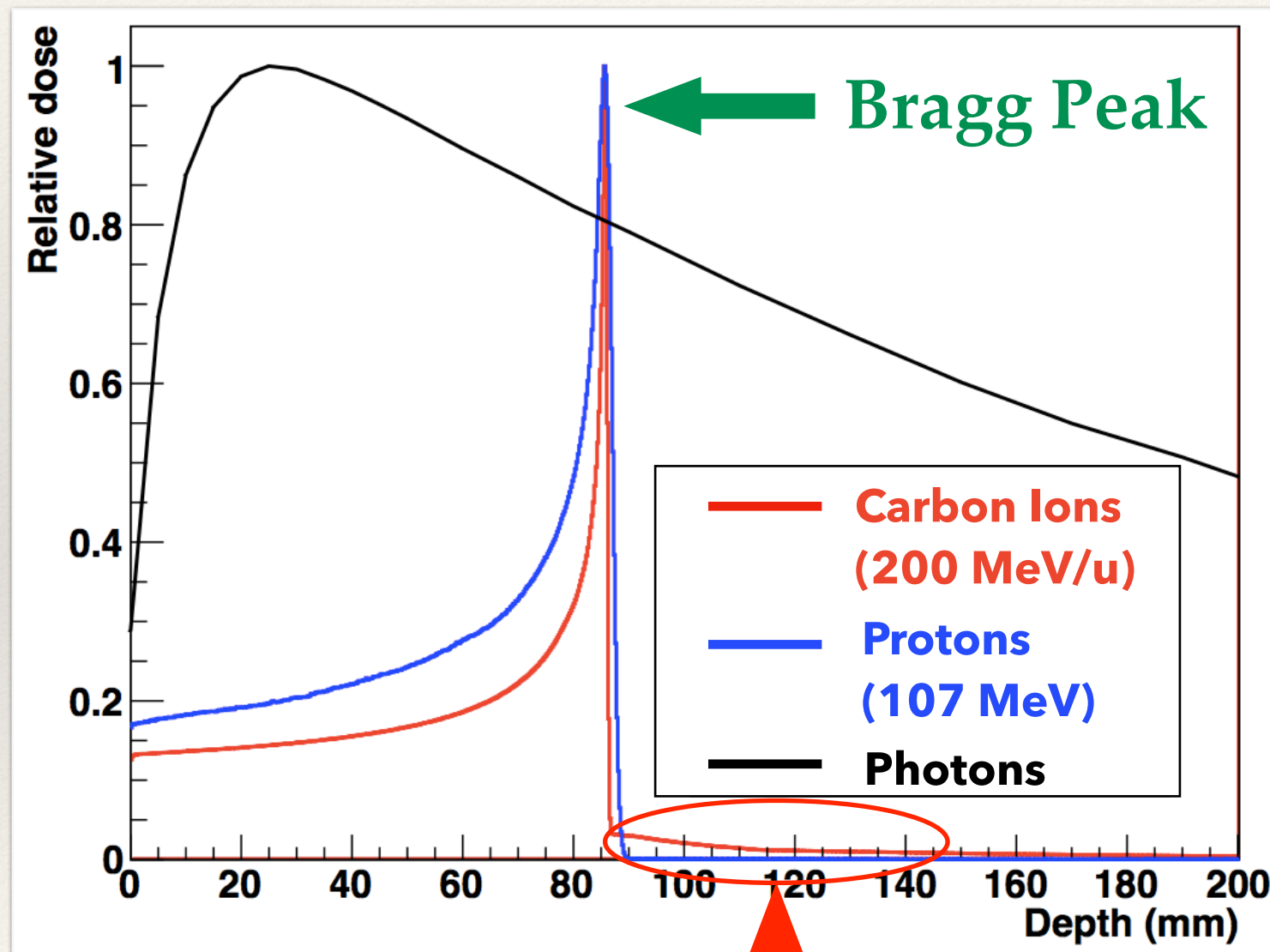
Co-Supervisor: Prof. Angelo Schiavi

PhD “Accelerator Physics”, XXXIII cycle

“Sapienza”, University of Rome

Particle Therapy (PT)

PT is a modern technique of non-invasive radiotherapy mainly devoted to the treatment of tumours untreatable with surgery or conventional radiotherapy. It uses charged particle beams to release energy into the tumour volume causing the apoptosis of tumour cells.



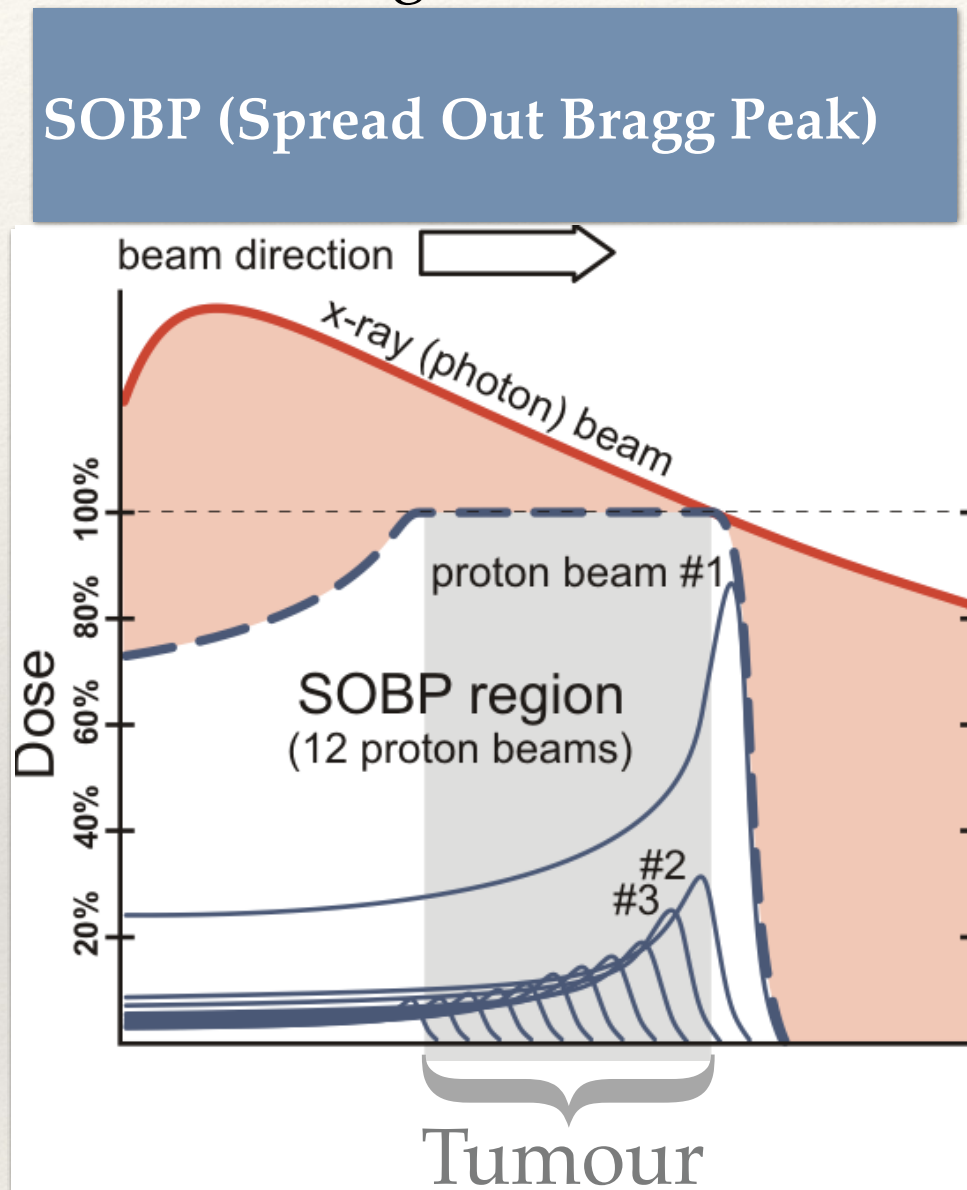
The biological damage is related to the released energy, ionization density and type of projectile used.

$$D = \frac{dE}{dm} \left[1Gy = 1 \frac{J}{kg} \right]$$

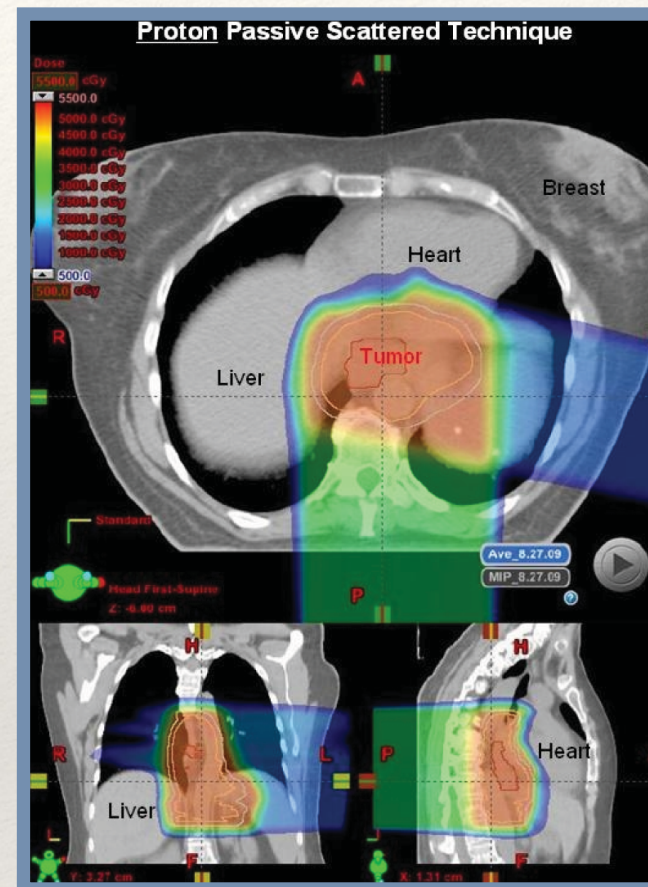


Particle Therapy (PT)

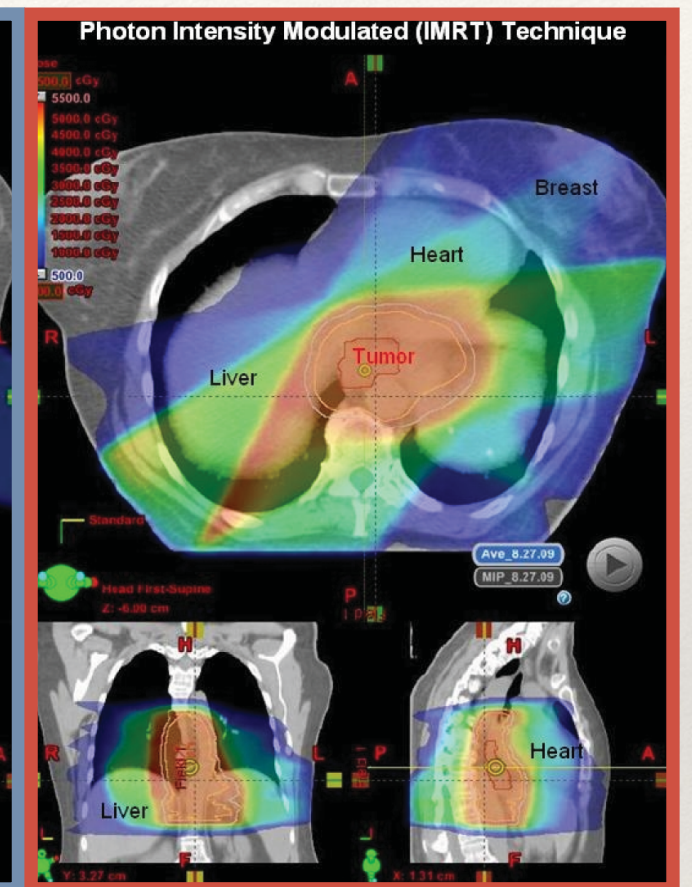
To cover the entire tumor volume, an overlap of beams at different energies is used obtaining a wider irradiation profile:



proton treatment
(2 proton beams)



photon treatment
(5 photon beams)



S. H. Lin, in Cancer, Volume 3 (2011), pp. 490-4101

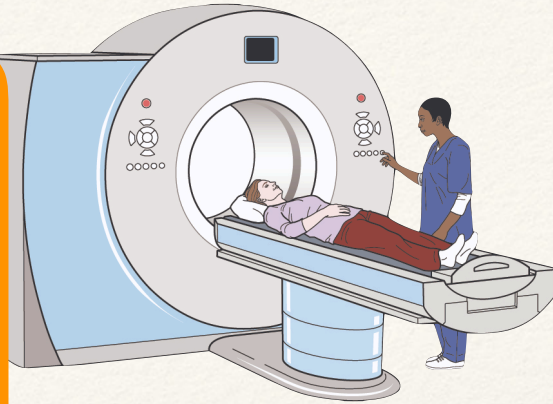
Dose release control at the min level demands for an **accelerator control system of absolute precision and reliability** since benefit for the patient can only be achieved if the treatment is delivered exactly as planned.



Treatment Planning System

Kinetic Energy (MeV)	Stopping Power (MeV cm ² /g)			Range		
	Electronic	Nuclear	Total	CSDA (g/cm ²)	Projected (g/cm ²)	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						
9.000E-03						
1.000E-02						
1.200E-02						
1.400E-02						
1.600E-02						
1.800E-02						
2.000E-02						
2.200E-02						
2.400E-02						
2.600E-02						
2.800E-02						
3.000E-02						
3.200E-02						
3.400E-02						
3.600E-02						
3.800E-02						
4.000E-02						

Patient anatomic data (CT, MRI, PET)



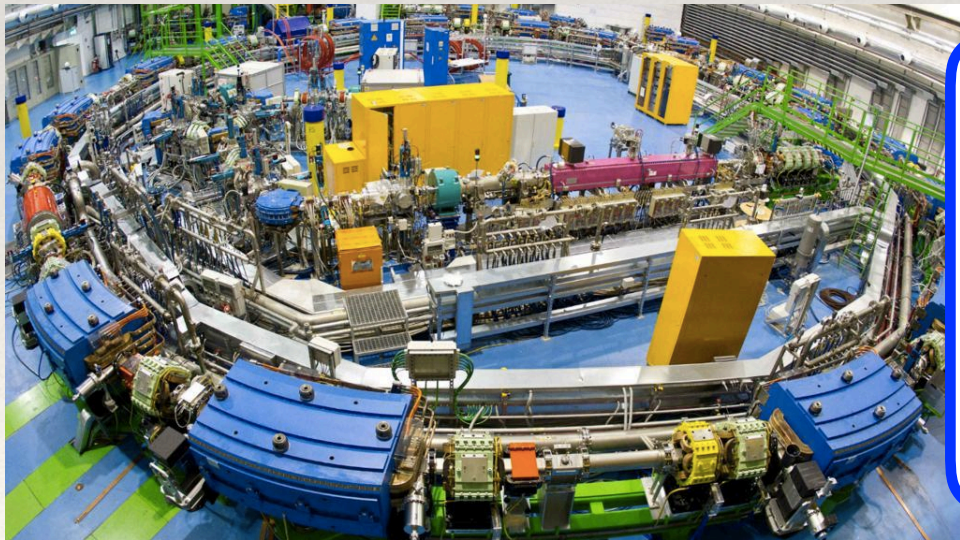
Volume of interest	% of Volume	Prescription/tolerance dose (Gy)	Relative importance
Prostate PTV	100	74.0	1.0
Prostate PTV	5.0	72.0	1.0
Prostate PTV	10.0	76.0	1.0
Rectum	90.0	10.0	0.5
Rectum	50.0	20.0	0.5
		30.0	0.5
		10.0	0.2
		20.0	0.2
		30.0	0.2
		10.0	0.2
		20.0	0.2
		40.0	0.2

Table of:

- ❖ dE vs E_{beam}, x, y, z
- ❖ RBE vs E_{beam}, dE, x, y, z

TPS

Physician Prescription



Accelerators
Parameters:
Fluences for each beam spot

TPS is a sophisticated software tool which provides to the accelerator control system the position, intensity and direction of the beams in order to produce a patient-specific set of particle beams

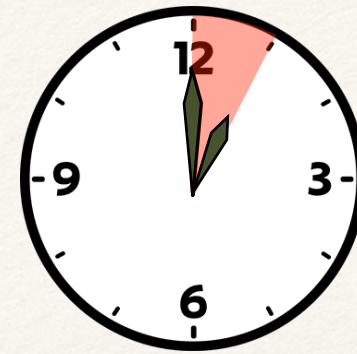


Treatment Planning System

ANALYTIC TPS

- ❖ Fast (~ 1 h/core, minutes on GPU)
- ❖ Simplified beam-body interaction model using a 3D water equivalent representation of the patient morphology

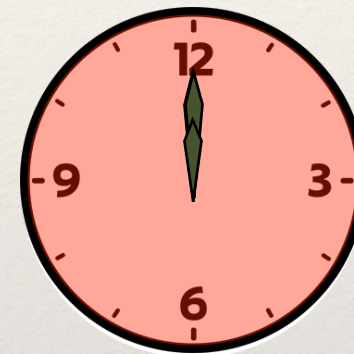
Routinely used in PT treatment



MC TPS (FLUKA and TOPAS/Geant4)

- ❖ Slow (\sim days/core)
- ❖ Explicitly take into account the details in the interaction of particles with human tissues

Only used to check treatment plans for a restricted number of difficult cases



OCTOBER 2020

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	31

www.printable-calendar.com

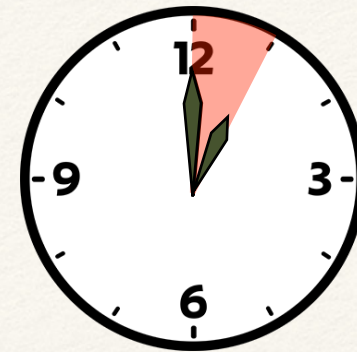


Treatment Planning System

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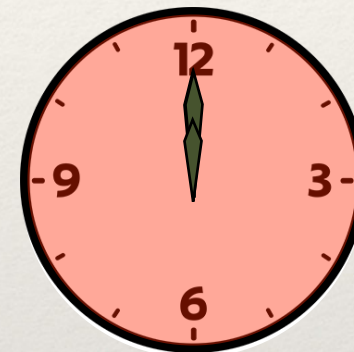
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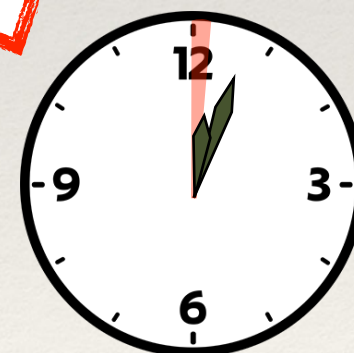


FAST MC: **FRED**

(Fast paRticle thErapy Dose evaluator)

- ❖ Fast (few minutes)
- ❖ Takes into account the details in the interaction of particles with human tissues that are needed for a TPS

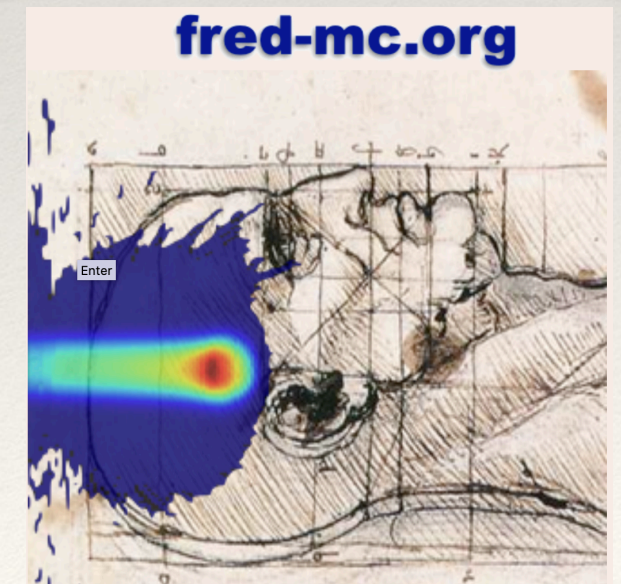
NEW!!



OCTOBER 2020

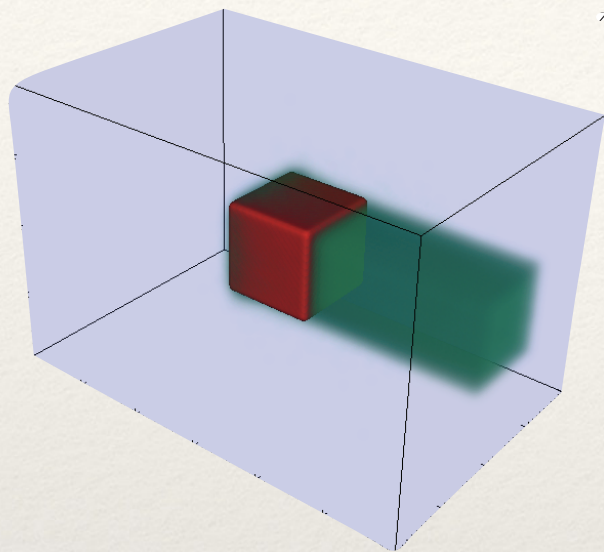
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fred-mc.org



FRED as tool for quality control

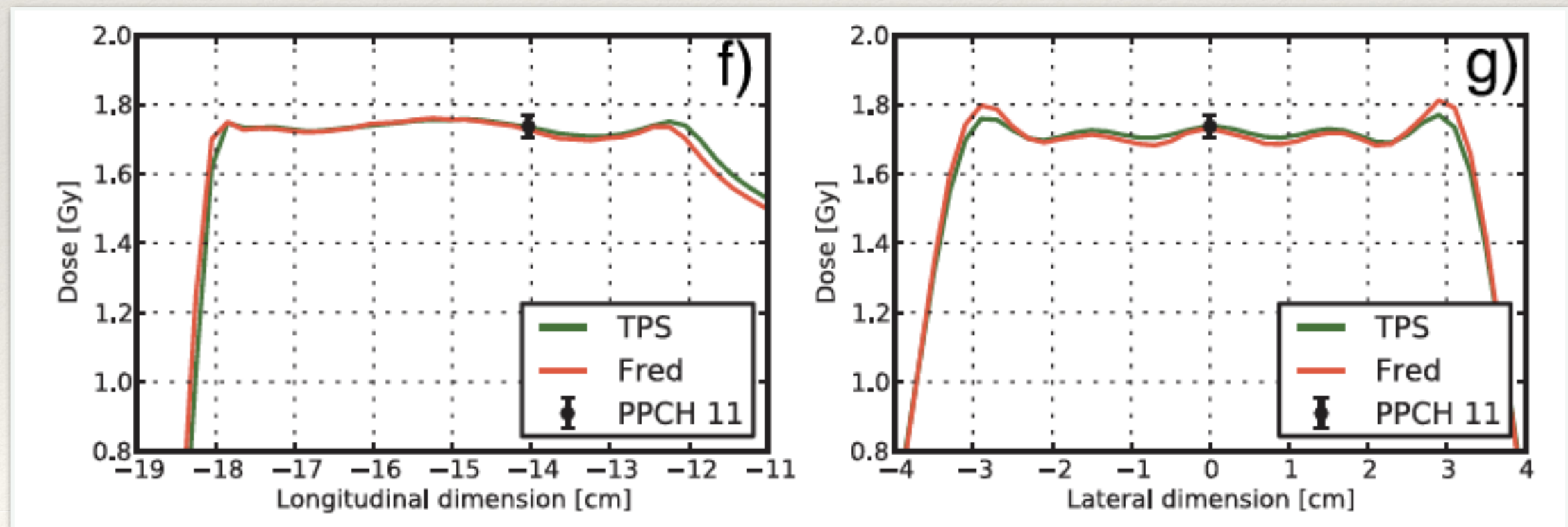
TPS are periodically tested to verify that the accelerators parameters have been calculated correctly for each patient.



The accelerator delivers the beams in a tank full of water following the TPS instructions and the dose is measured in different points of the target with ionization chambers.

FRED can be used to verify that the TPS is correct instead of delivering the beam with the accelerator.

Proton beam



Carbon Therapy

FRED is already used in proton therapy as a quality assurance tool in the clinical center of Maastricht and Krakow and as a research tool at several clinical and research centers in Europe (Krakow, Trento, Maastricht, Lyon and PSI)

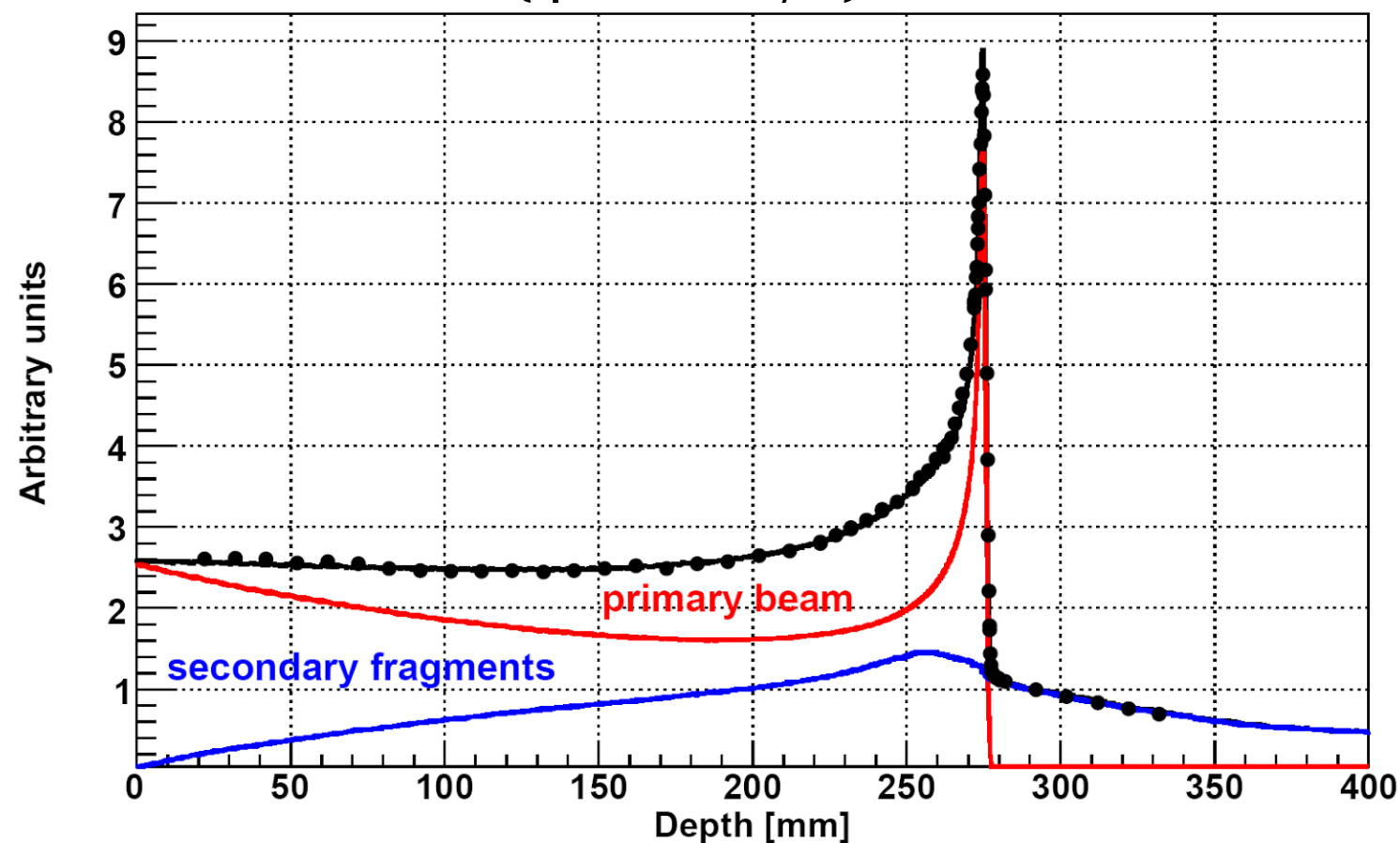
Interest of CNAO and MedAustron for the use of FRED in Carbon Therapy

fondazione
CNAO

MedAustron **N**

Production of different fragments

^{12}C (400 MeV/u) on water



- ❖ Mitigation and attenuation of the primary beam
- ❖ Different biological effectiveness of the fragments wrt the beam
- ❖ Different fragment ranges

Double differential cross section needed: **lack of experimental data** at the energies of interest in medical physics

My PhD work



- ❖ **Ionization energy loss** (Bethe-Bloch, Gaussian approximation, Vavilov and Landau distributions)
- ❖ **Multiple Coulomb Scattering** (theory of Molière adding a scaling factor following Fippel and Soukup approach)



- ❖ **Nuclear Model** (phenomenologic approach based on Ganil measurement at 95 MeV/u):
 - **Coefficient of mass attenuation** to decide when there is an elastic and non-elastic event. Base on data found in literature;
 - **Sampling of the fragments** and their **energy and angle distributions**. Base on Ganil measurement;



- ❖ **Biological Dose and Relative Biological Effectiveness** (LEM I model)

Comparison with :

- ❖ full MC (FLUKA);
- ❖ experiments found in literature.



My PhD work



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- ❖ experiments found in literature.



Coefficient of Mass Attenuation

$$\frac{\mu}{\rho} = \sum_i \frac{N_A w_i \sigma_i}{A_i}$$

Elastic cross-section

Obtained from a fit on data and using the *Ranft* model;

ENDF/B-VII Incident-Proton Data

Non-elastic cross-section

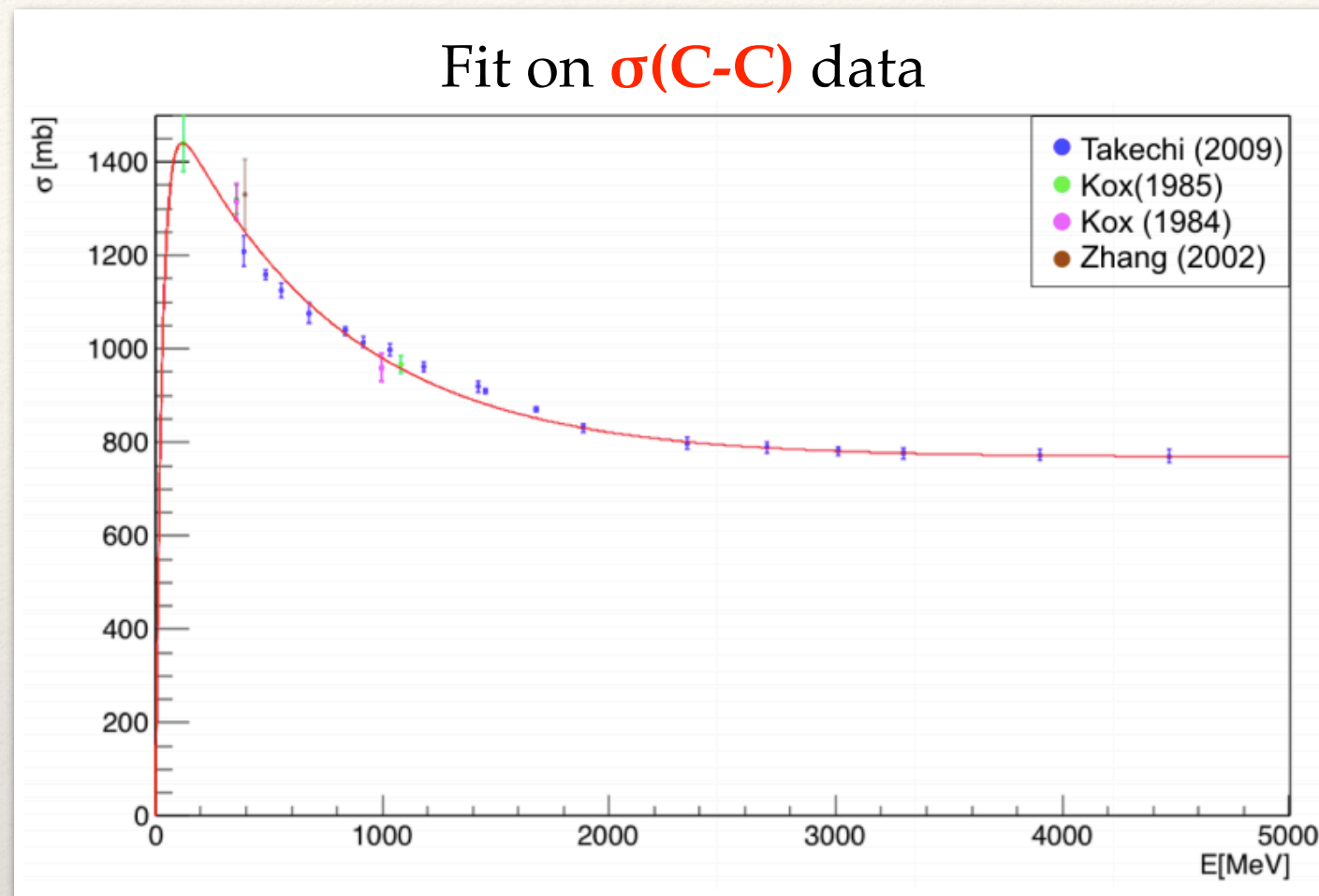
$\sigma(\text{C-C})$ and $\sigma(\text{C-H})$ obtained from a fit on data;

Zhang H. Y. et al. Nucl. Phys. 707 (2002)

Takechi M. et al. Phys. Rev. C 79.6 (2009)

Kox S. et al. Nucl. Phys. 420 (1984), Phys. Letters 159 (1985)

ICRU (International Commission on Radiation Units & Measurements)



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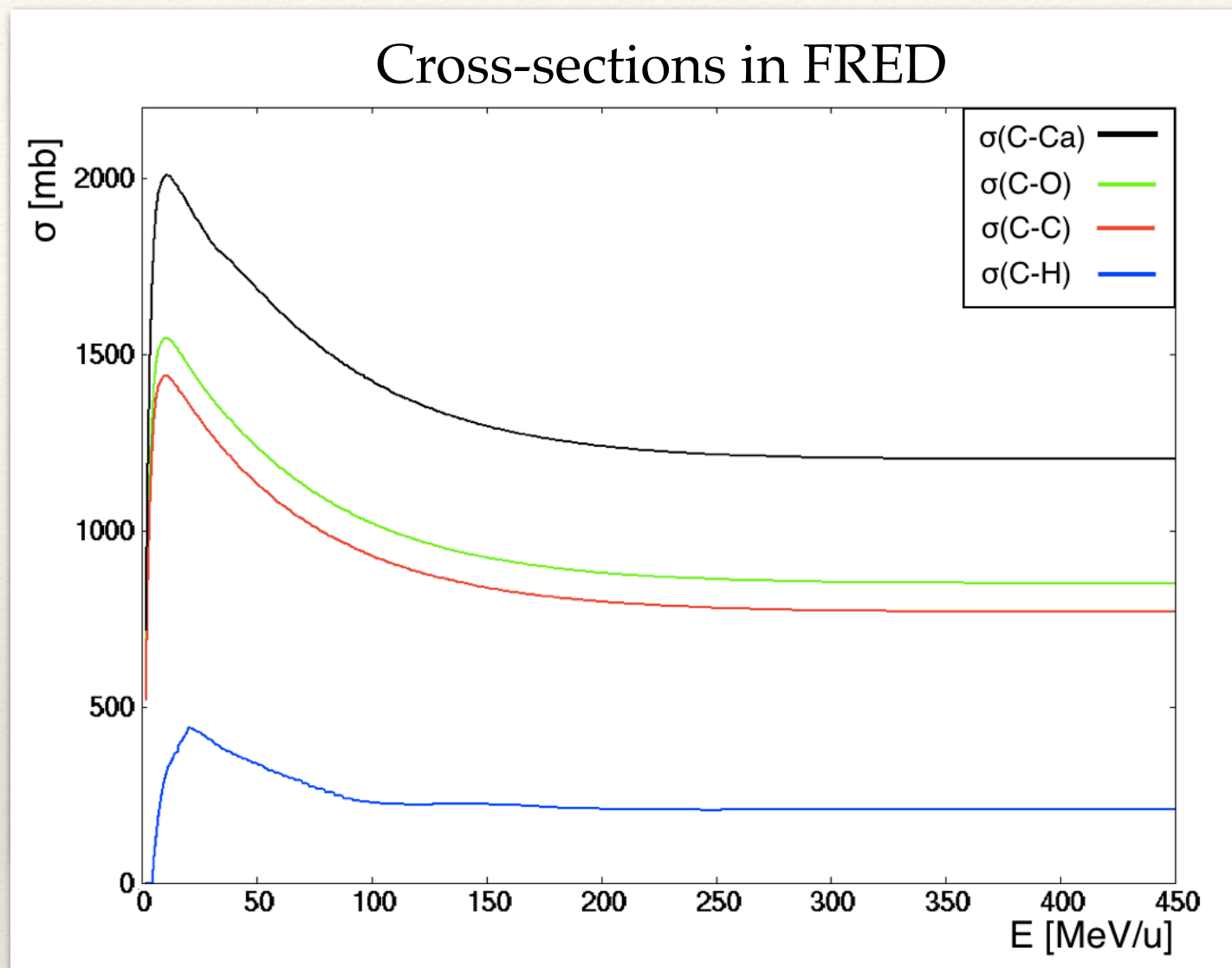
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ICRU (International Commission on Radiation Units & Measurements)

$$K(N_p, N_t, E_{cm}) = \frac{\sigma_K(N_p, N_t, E_{cm})}{\sigma_K(^{12}\text{C}, ^{12}\text{C}, E_{cm})}$$

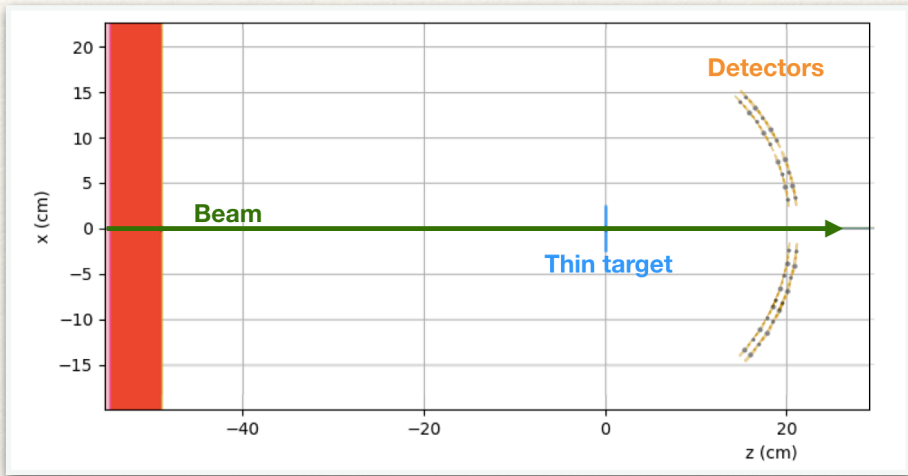
$$\sigma(N_p, N_t, E) = K(N_p, N_t, E) \left(1 - e^{-\frac{E}{E_c}}\right) (p_0 + p_1 E + e^{p_2 - p_3 E})$$



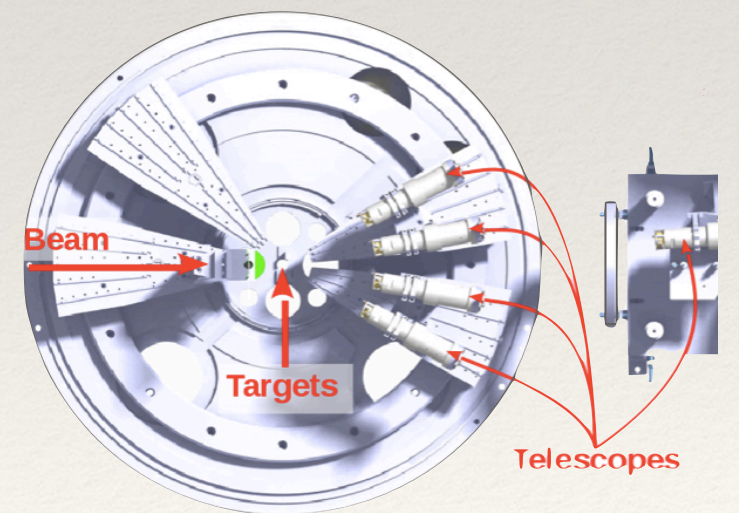
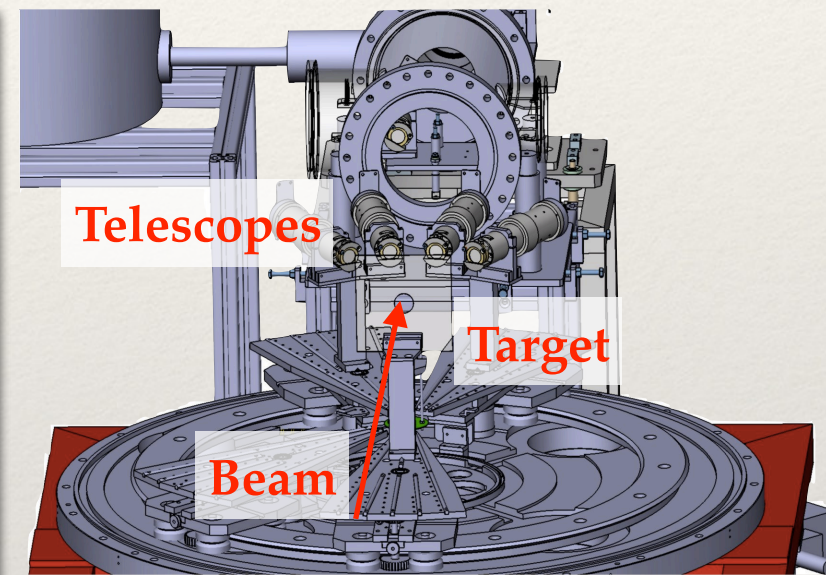
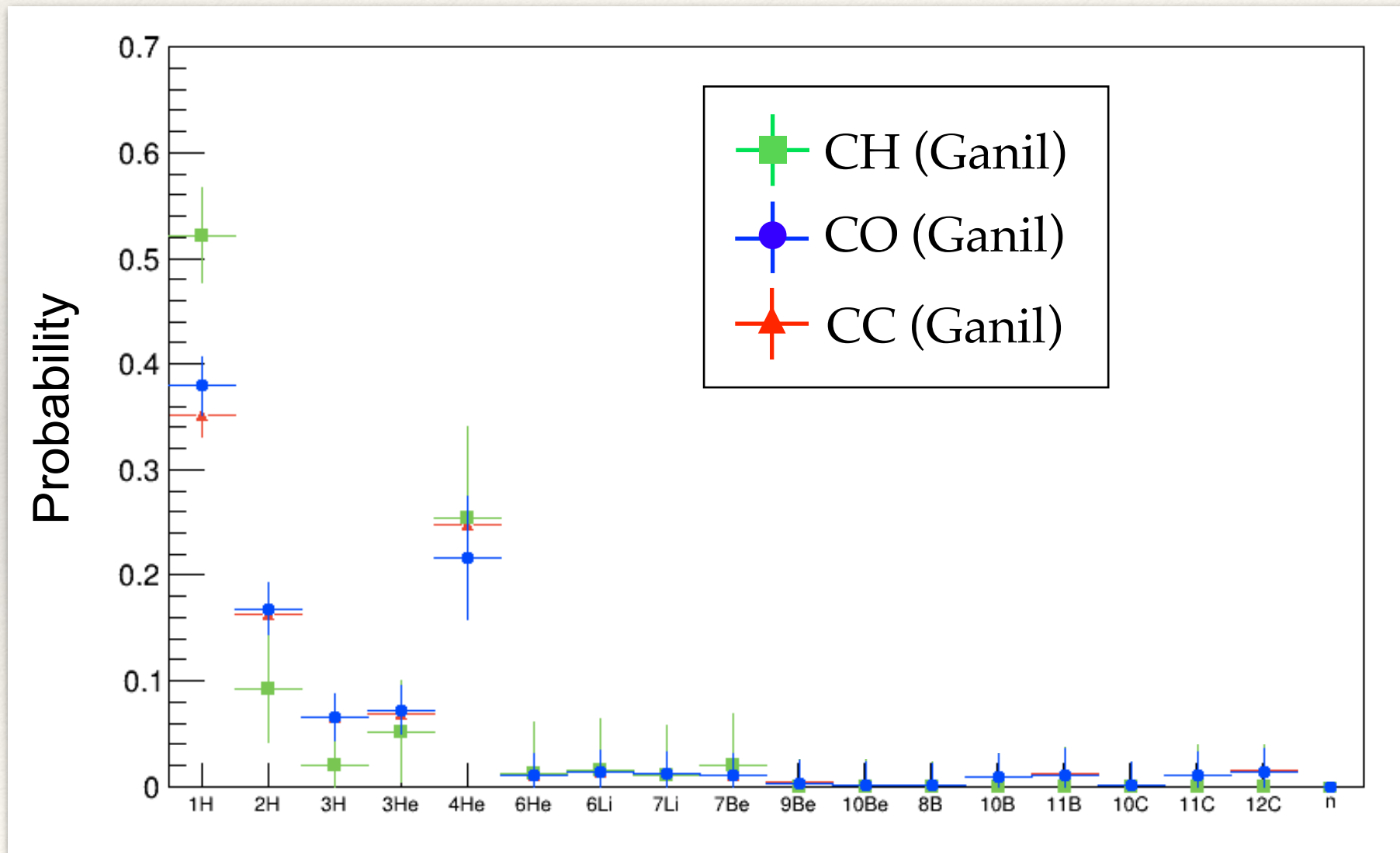
$\sigma(\text{C-Ca})$ and $\sigma(\text{C-O})$ obtained starting from $\sigma(\text{C-C})$ and scaled with the *Kox* formula.

Generating a fragmentation event

simulated with FRED



What do we have? **GANIL's probability of emission** Fragmentation experiment of ^{12}C beam @95MeV/u on different thin targets (O, C, H, Al, Ti). The only experiment which provides double differential cross-section at the energy of interest of PT. *Dudouet. J. et al. Phys Rev C 88 (2013)*

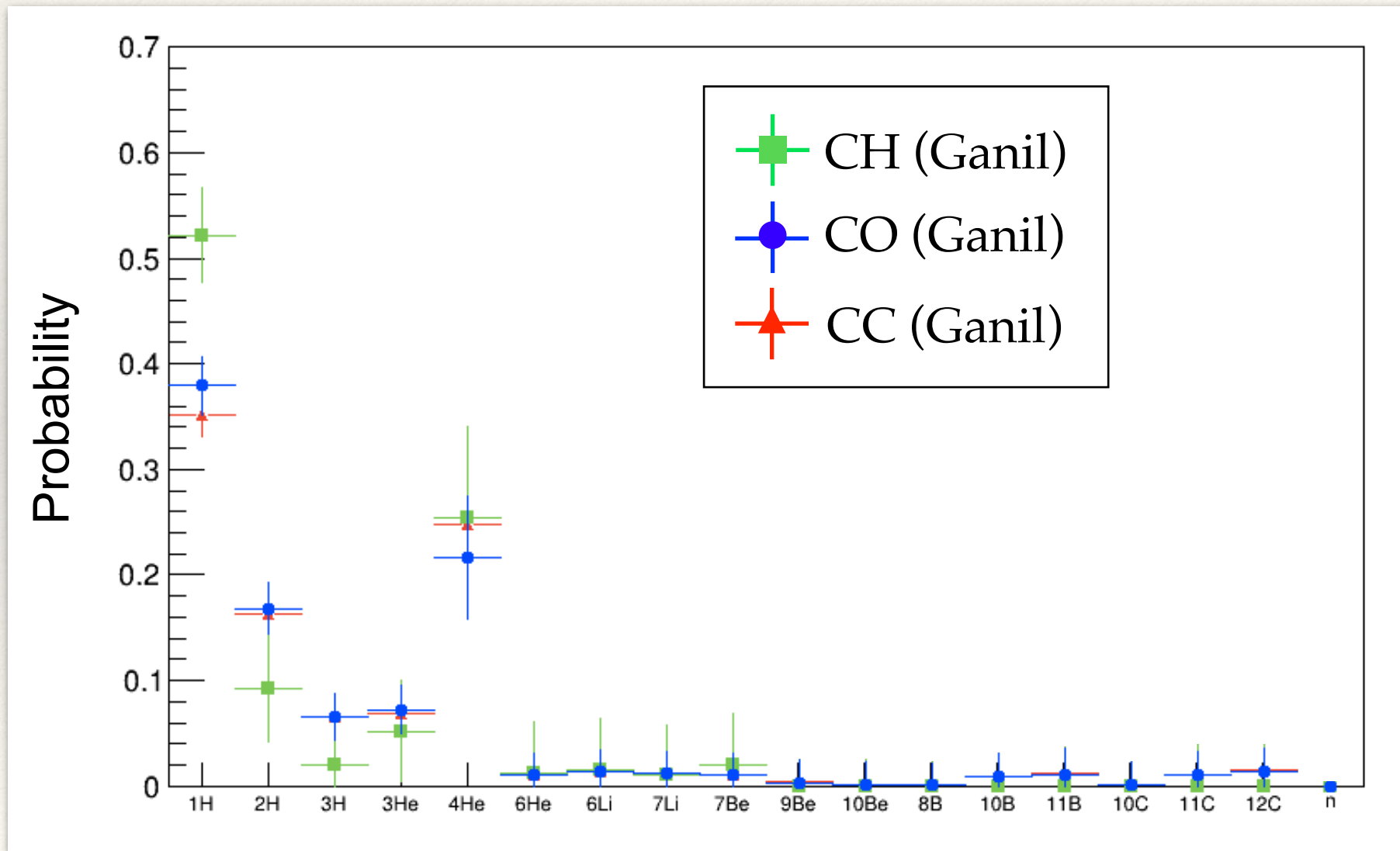


Generating a fragmentation event

simulated with FRED



What do we have? **GANIL's probability of emission**
 If the Ganil probabilities would be used directly for the fragments sampling the final fragments' distribution would be different from that one measured by Ganil due to the sampling procedure.



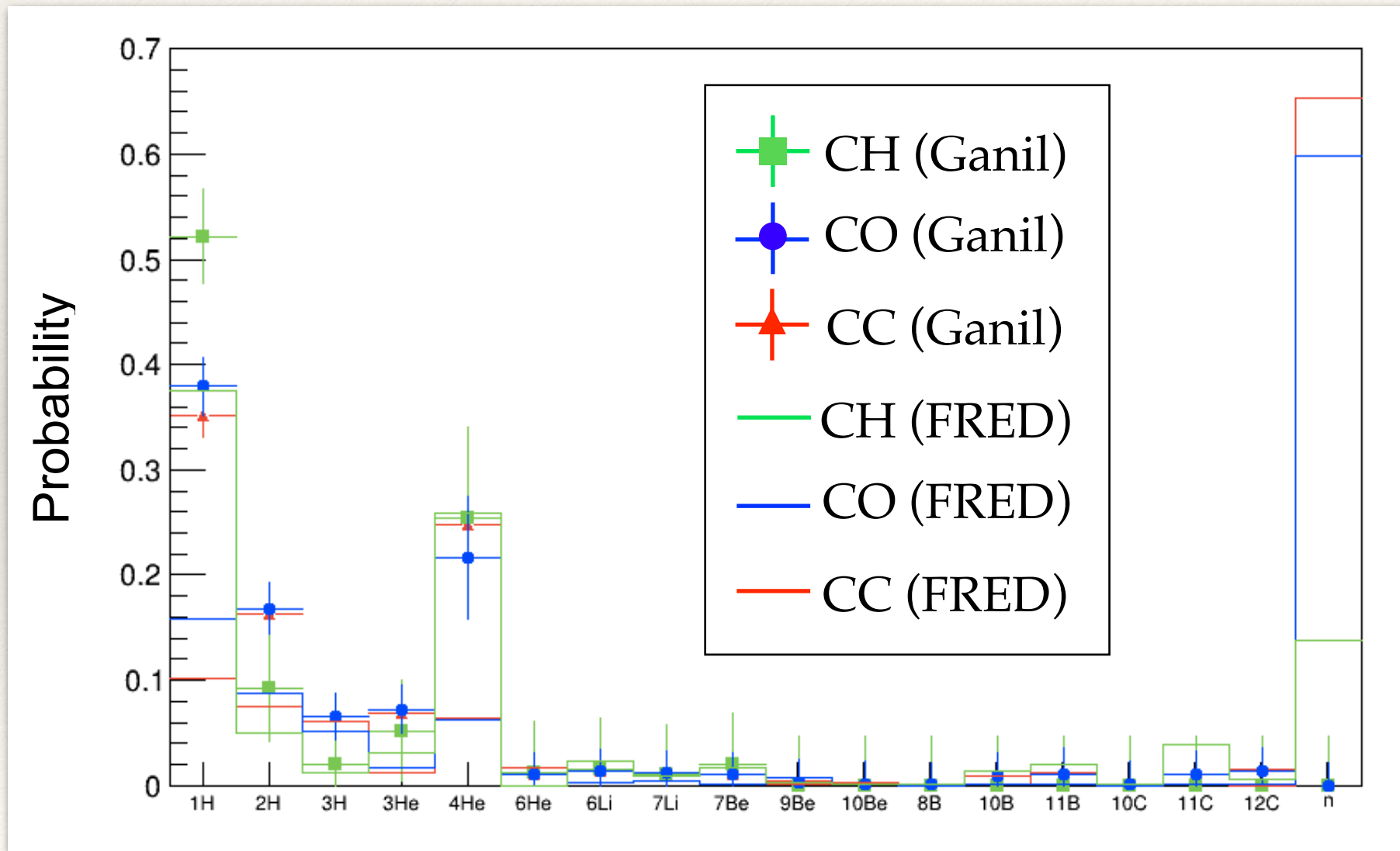
Mass and charge conservation

Generating a fragmentation event

simulated with FRED



What do we have? **GANIL's probability of emission**
 If the Ganil probabilities would be used directly for the fragments sampling the final fragments' distribution would be different from that one measured by Ganil due to the sampling procedure.



Mass and charge conservation

Use of an iterative formalism to have the same generating probability of the Ganil experiment:

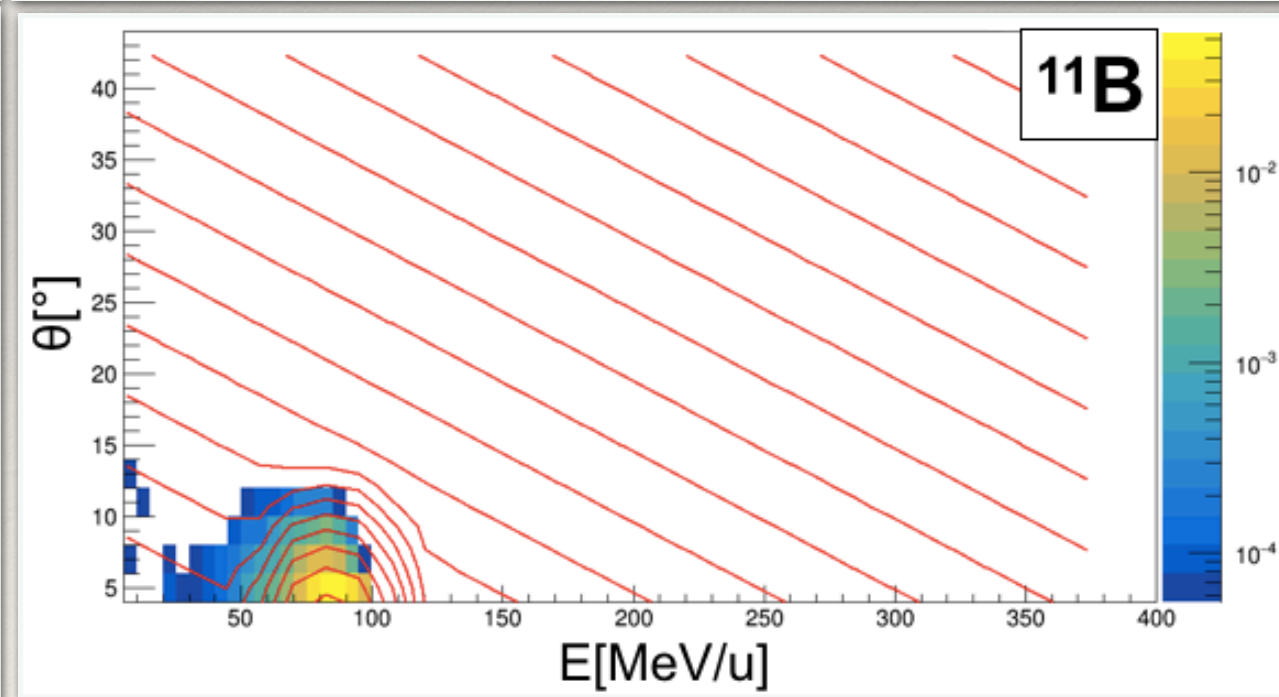
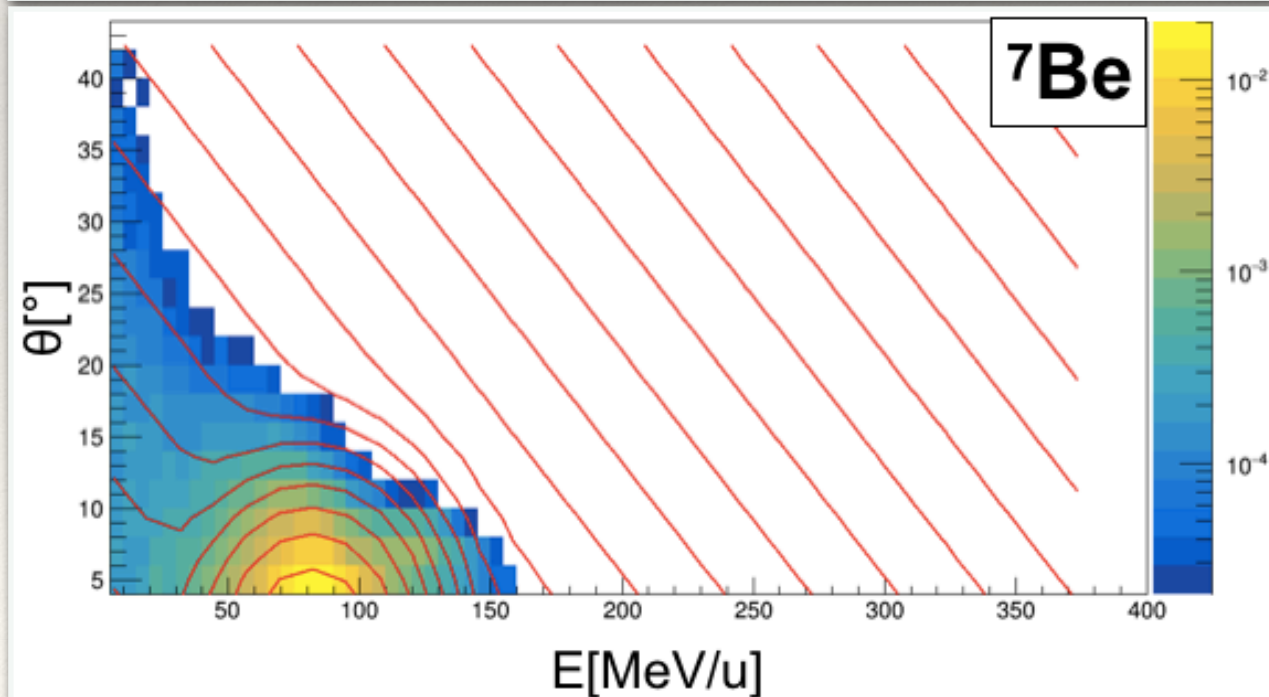
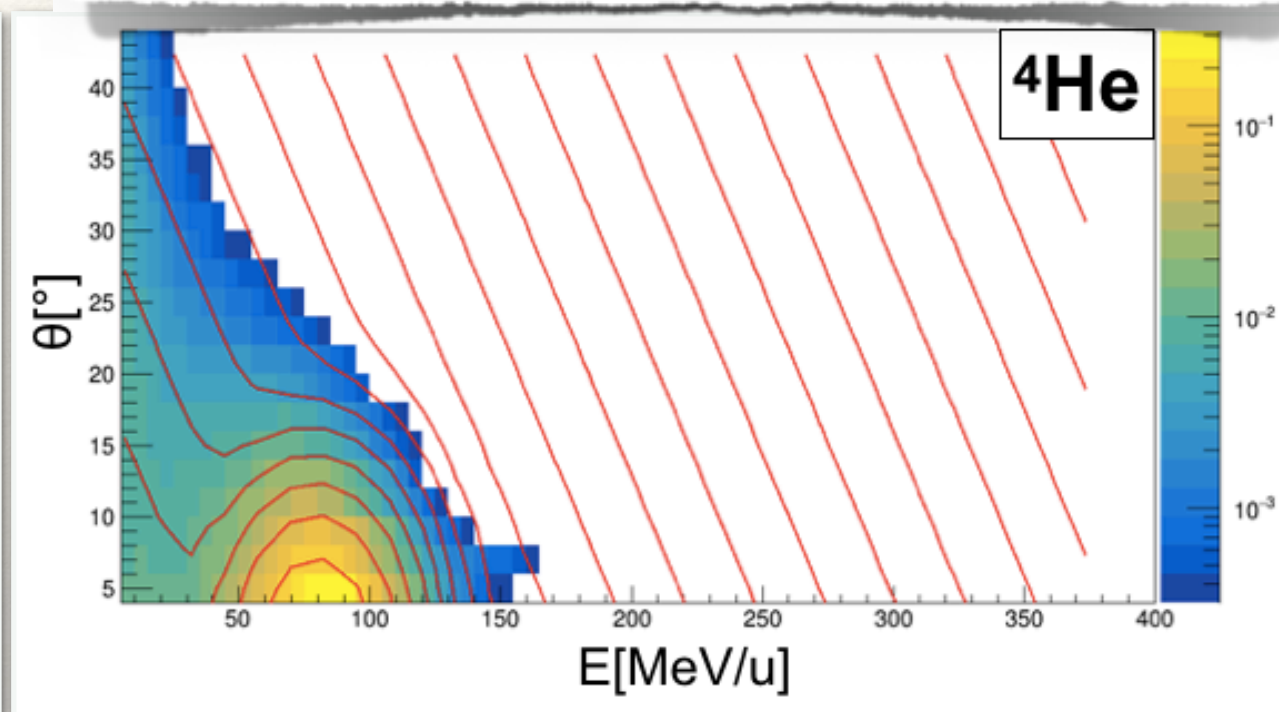
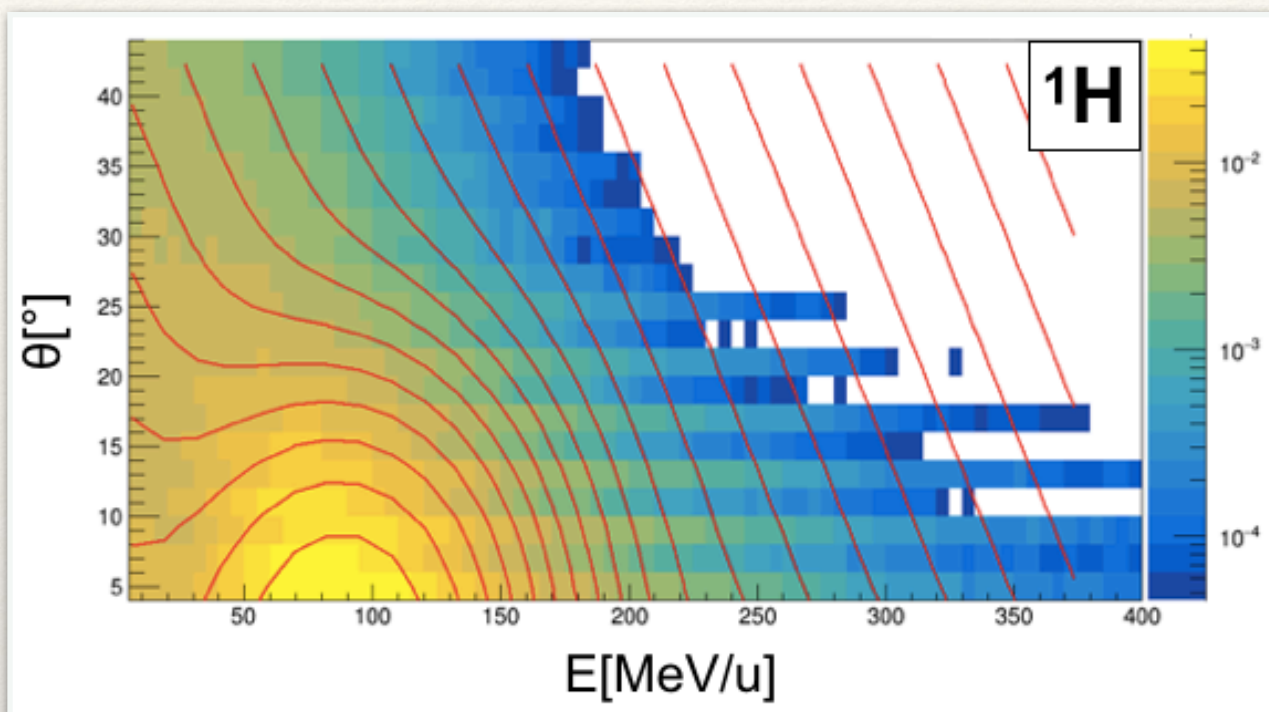
NEW probability of emission

Sampling of energy and angular distribution

Bidimensional fits on GANIL data show that the distribution is composed of:

- ❖ a **gaussian** function (projectile fragmentation) ;
- ❖ an **exponential** function (target fragmentation).

$$f(E, \theta) = A_1 e^{-(\alpha_E E + \alpha_\theta \theta)} + A_2 e^{-\left(\frac{(E - \langle E \rangle)^2}{2\sigma_E} + \frac{(\theta - \langle \theta \rangle)^2}{2\sigma_\theta}\right)}$$



Oxygen target

Sampling of energy and angular distribution

Bidimensional fits on GANIL data show that the distribution is composed of:

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$$f(E, \theta) = A_1 e^{-(\alpha_E E + \alpha_\theta \theta)} + A_2 e^{-\left(\frac{(E - \langle E \rangle)^2}{2\sigma_E} + \frac{(\theta - \langle \theta \rangle)^2}{2\sigma_\theta}\right)}$$

Energy and angular distribution of GANIL correspond at a 95 MeV/u beam.
 Extrapolation of new energy and angle

$$E^i = E_{95\text{MeV/u}}^i \frac{E_{proj} [\text{MeV/u}]}{95} (1 - k)$$

$$\theta^i = \theta_{95\text{MeV/u}}^i \sqrt{\frac{95}{E_{proj} [\text{MeV/u}]}}$$

energy conservation

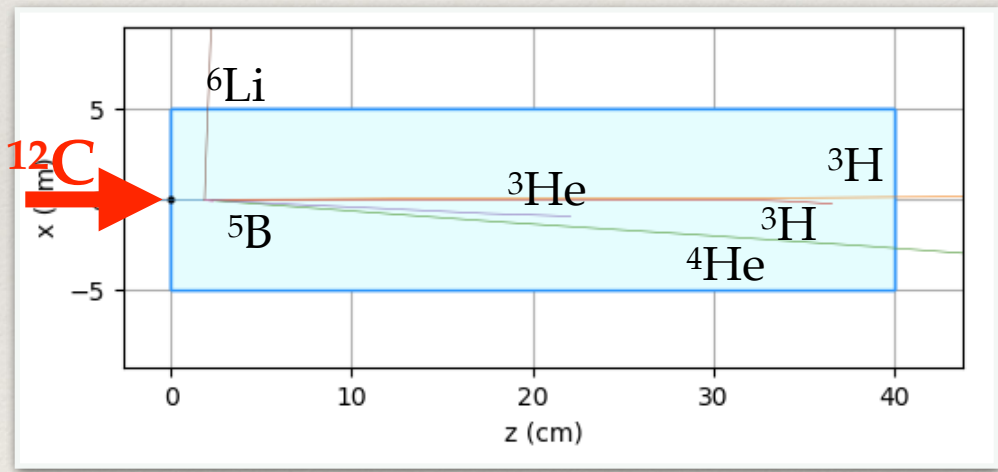
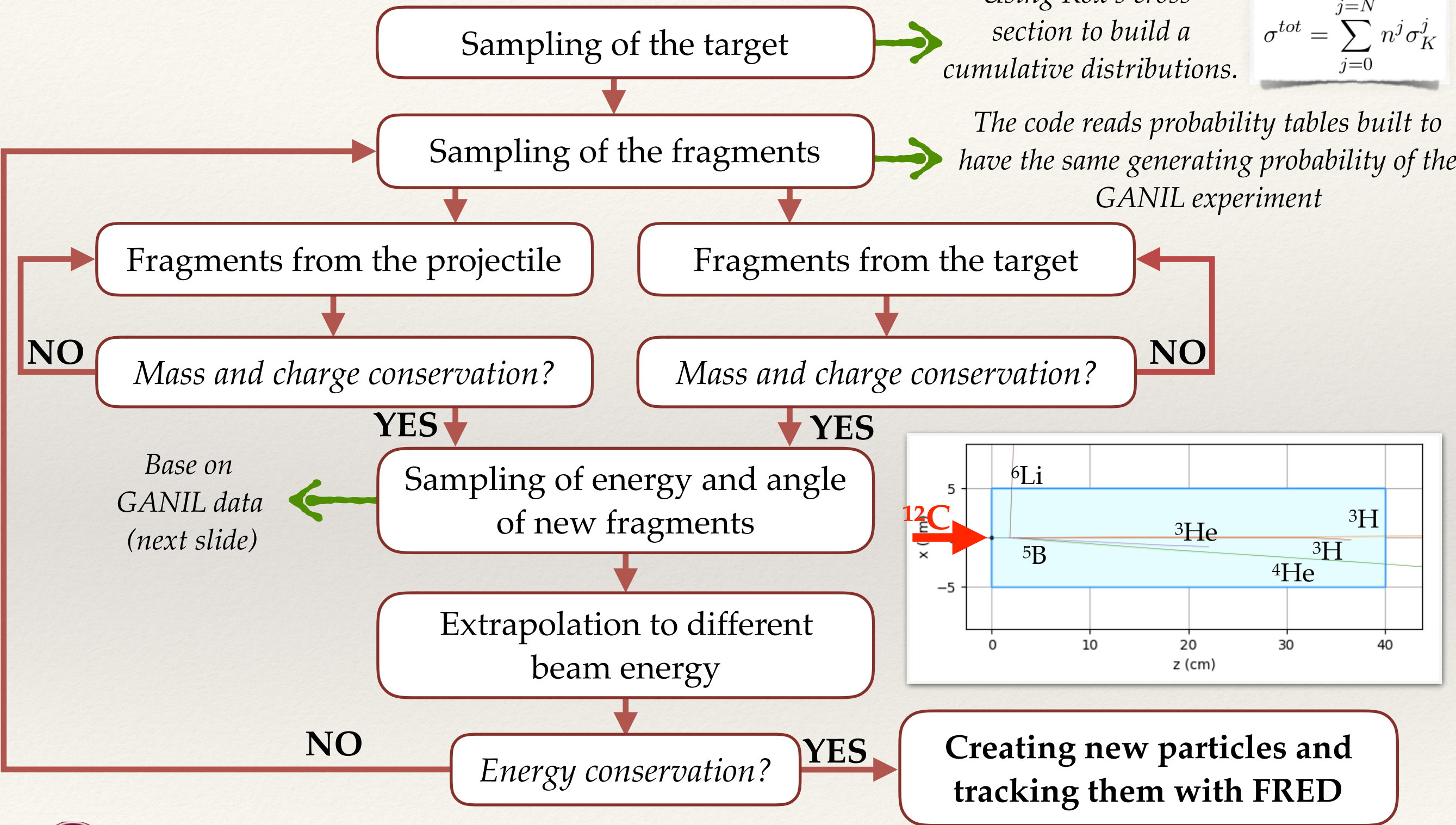


$$P^i = \frac{n^i \sigma_K^i}{\sigma^{tot}}$$

$$\sigma^{tot} = \sum_{j=0}^{j=N} n^j \sigma_K^j$$

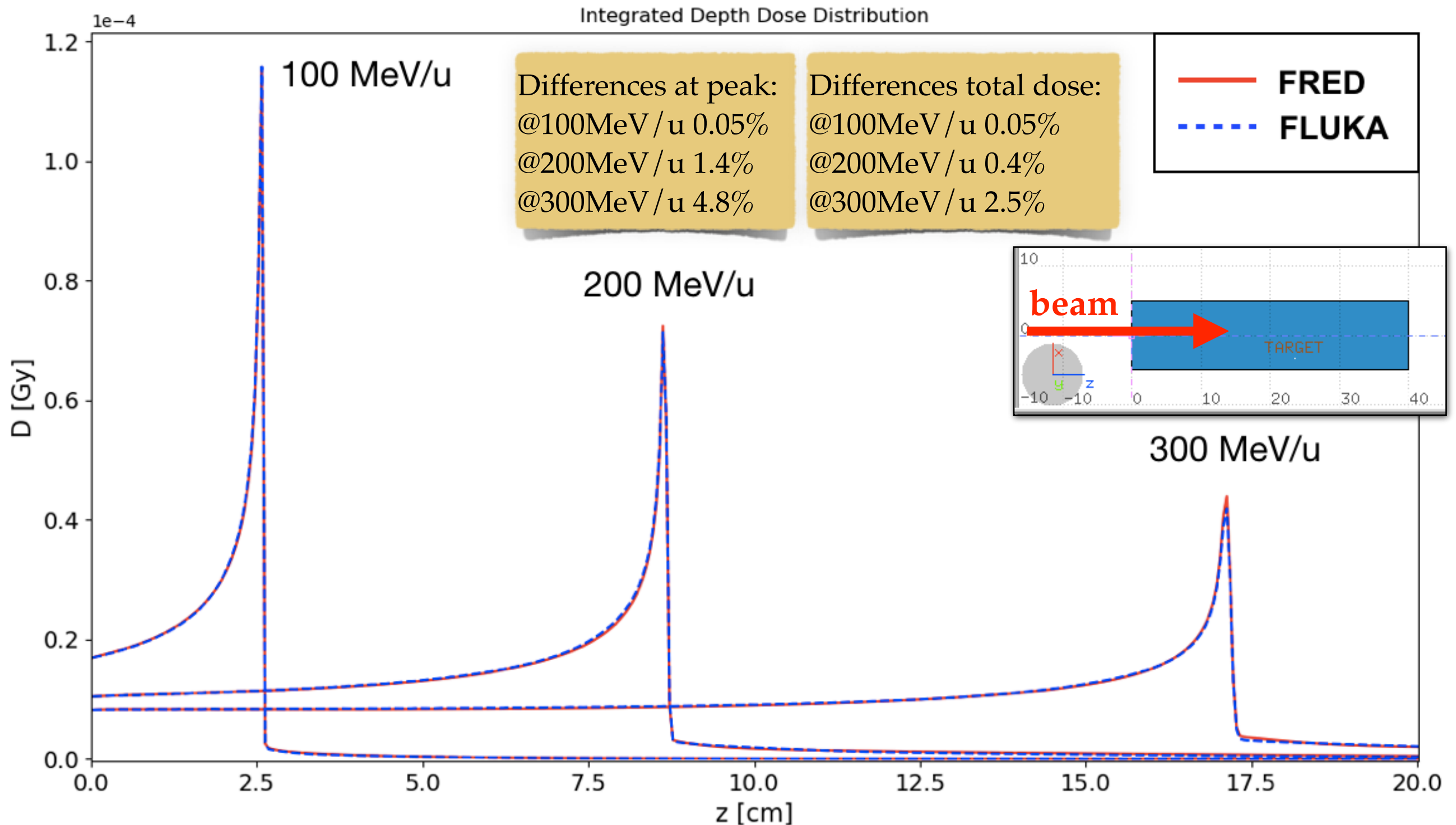
Using Kox's cross-section to build a cumulative distributions.

The code reads probability tables built to have the same generating probability of the GANIL experiment



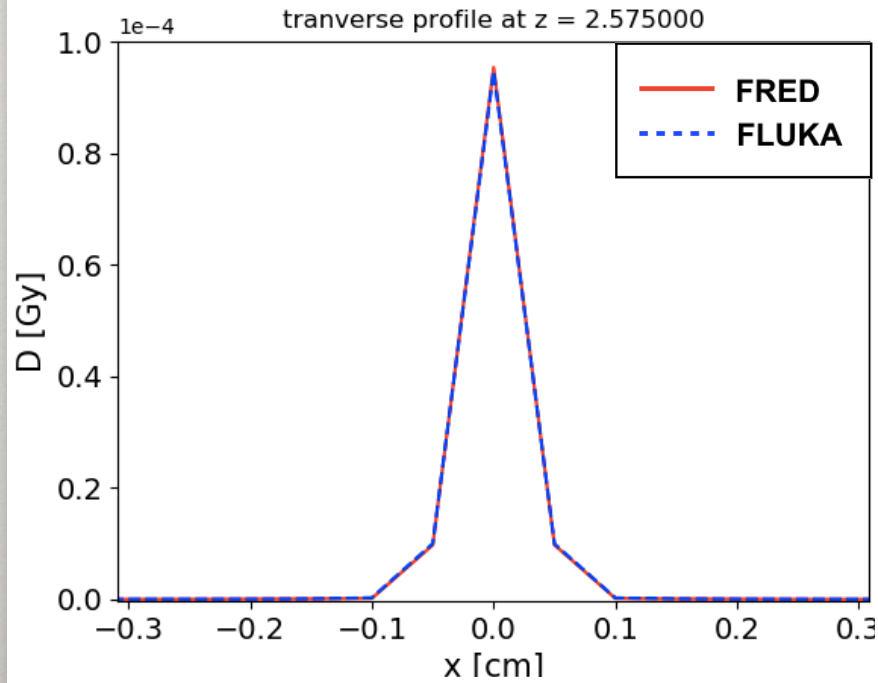
Base on GANIL data (next slide)

Results: DDD of a single PB of ^{12}C in water

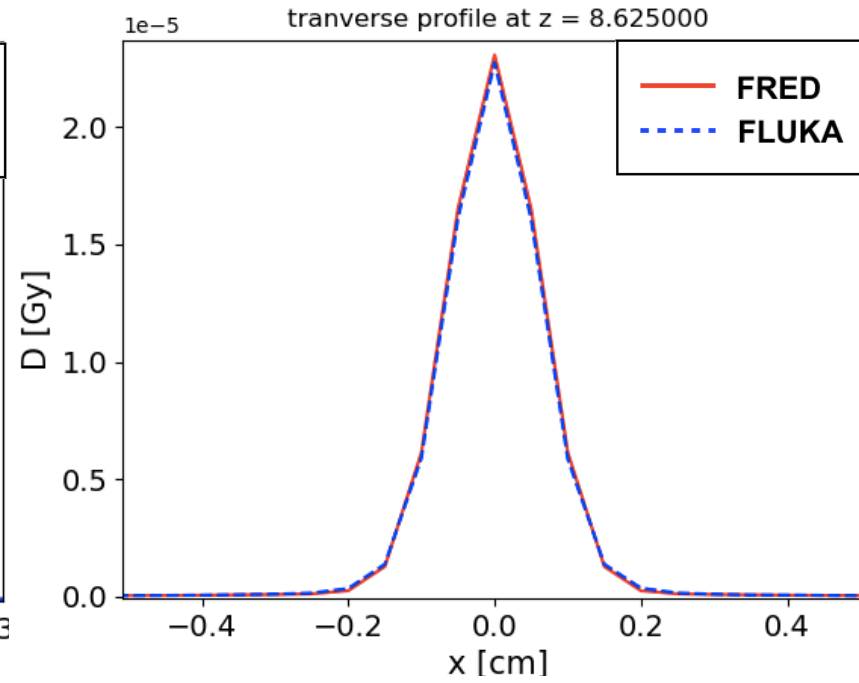


Results: Lateral dose at peak of a single PB of ^{12}C in water

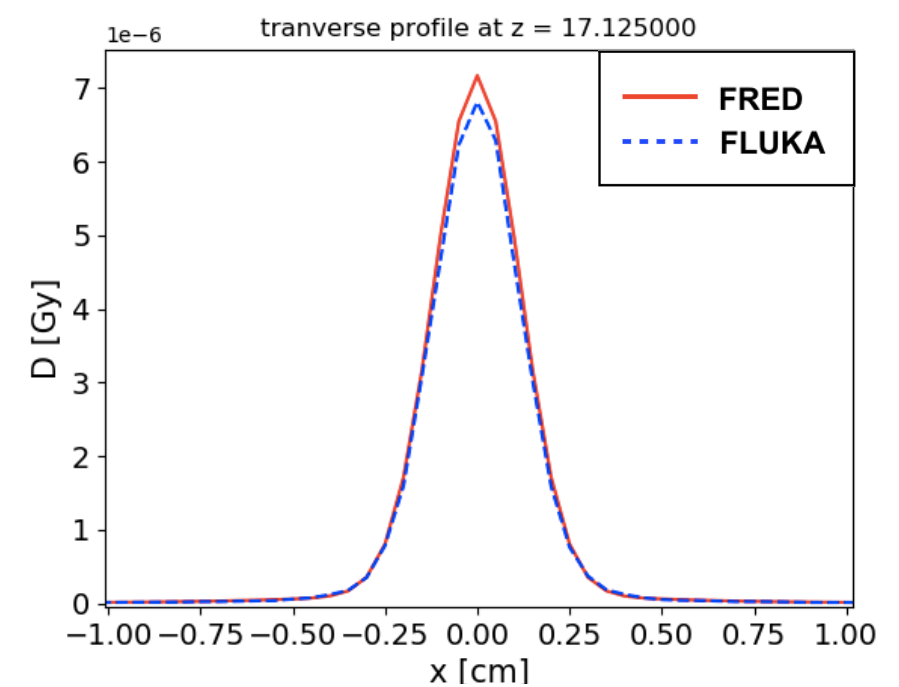
100 MeV/u



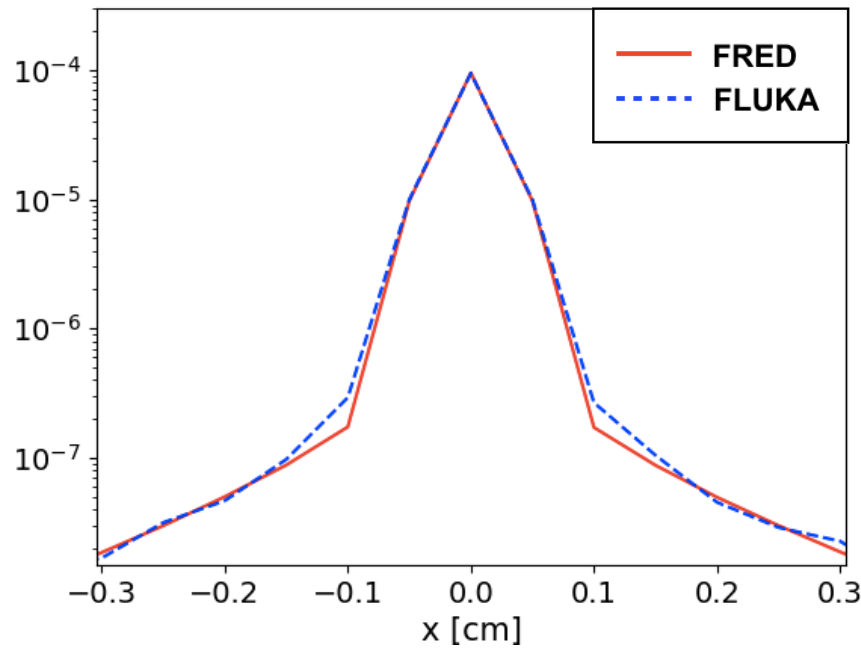
200 MeV/u



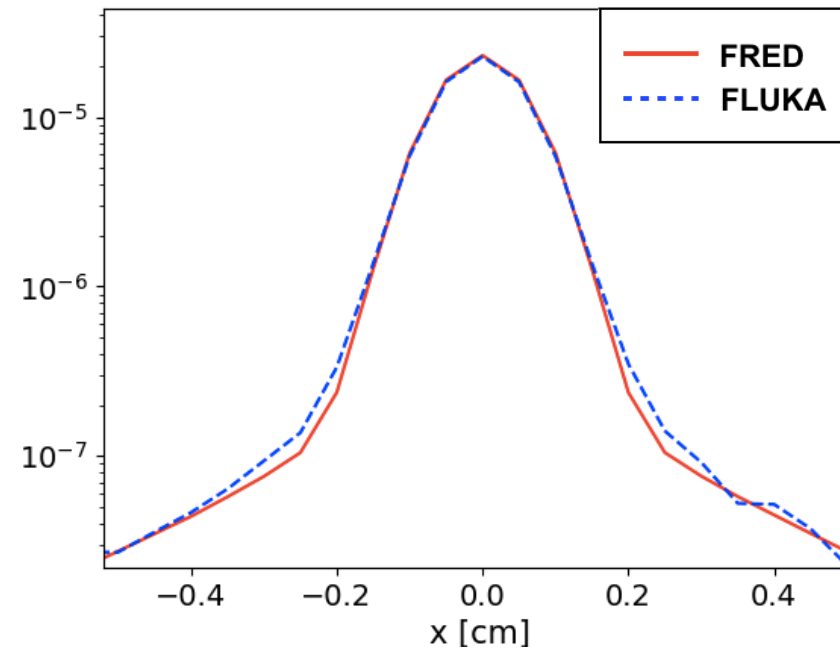
300 MeV/u



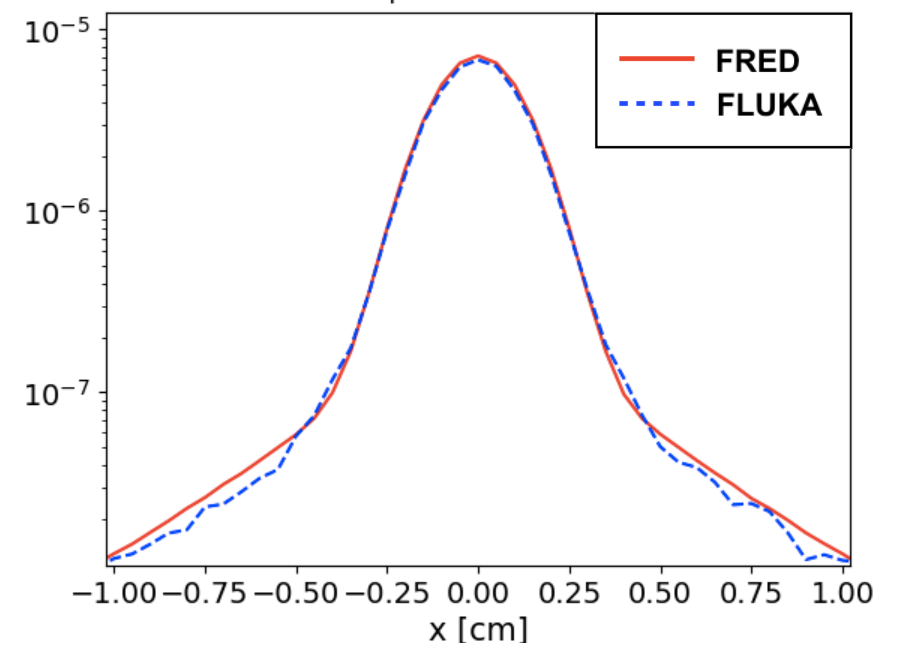
transverse profile at $z = 2.575000$



transverse profile at $z = 8.625000$



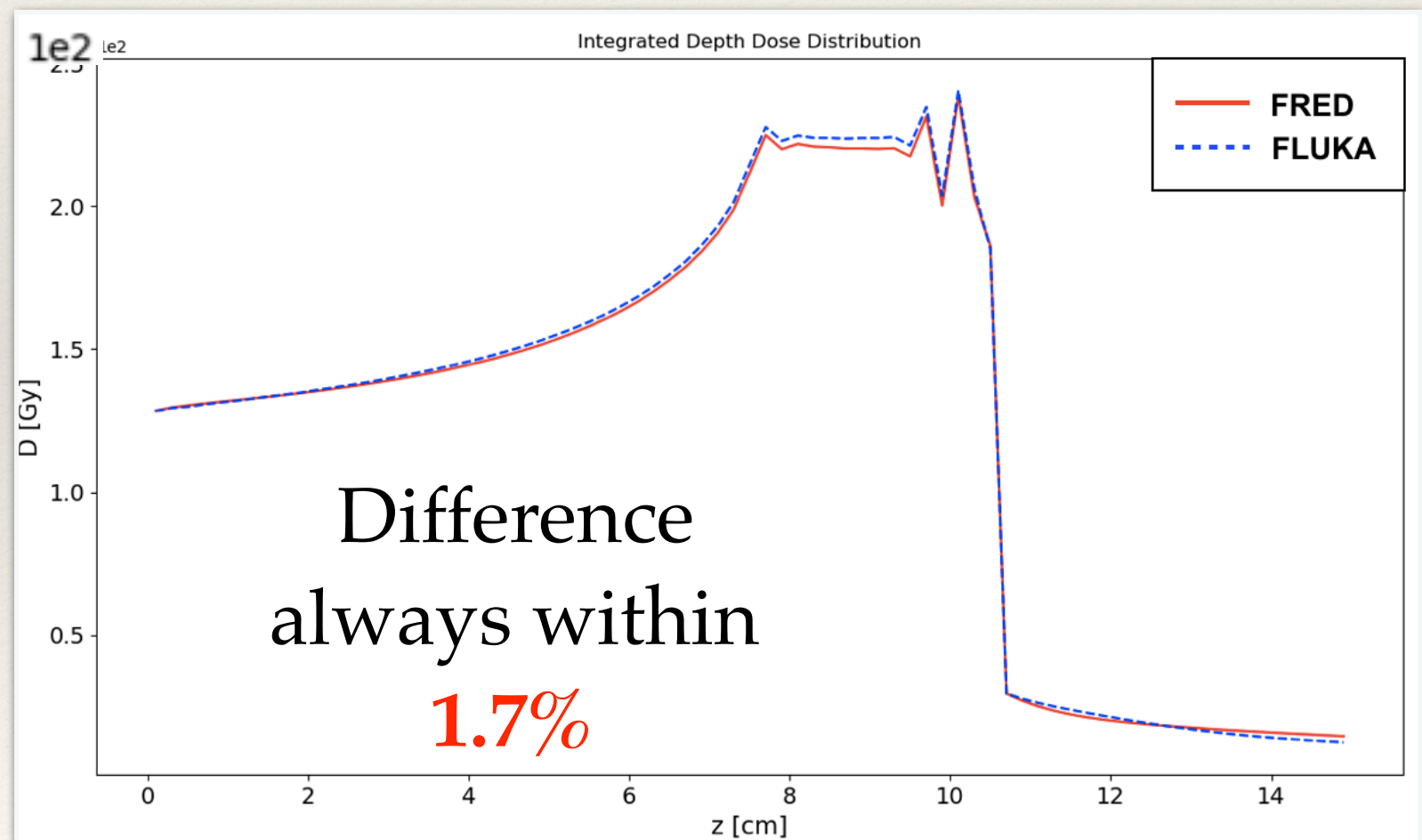
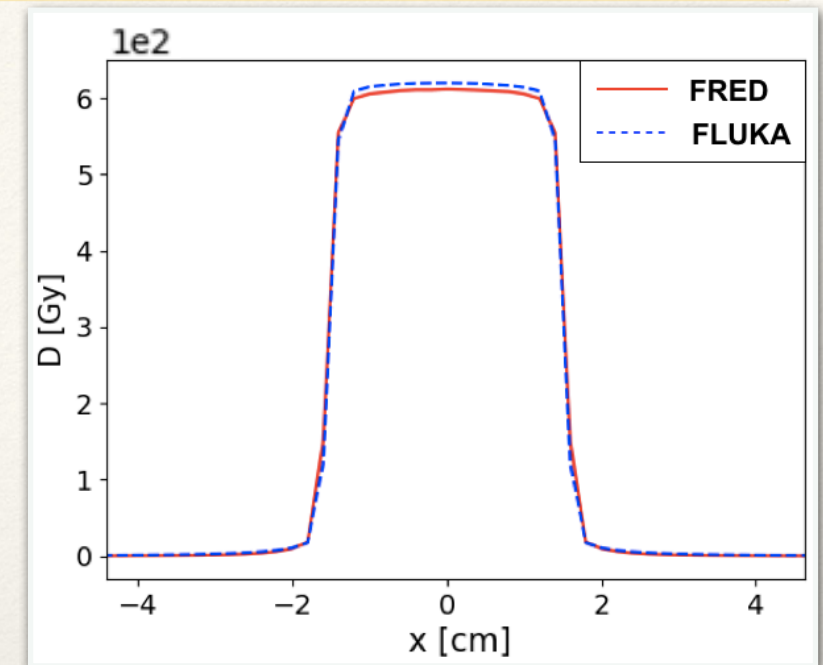
transverse profile at $z = 17.125000$



SOBP from raster file of CNAO

```
patient_id none
machine# 0
projectile 12C
charge 6
mass 12
bolus 0
ripplefilter 0
#submachines 14
#particles 21531.5 333787 2.03959E+08
submachine# 57 186.57 2 6.9
#particles 32280.4 32280.4 7.2631E+06
stepsize 2 2
#points 225
14 14 32280.4
12 14 32280.4
10 14 32280.4
8 14 32280.4
6 14 32280.4
4 14 32280.4
2 14 32280.4
0 14 32280.4
-2 14 32280.4
-4 14 32280.4
-6 14 32280.4
-8 14 32280.4
-10 14 32280.4
-12 14 32280.4
-14 14 32280.4
-14 12 32280.4
-12 12 32280.4
-10 12 32280.4
-8 12 32280.4
-6 12 32280.4
-4 12 32280.4
-2 12 32280.4
0 12 32280.4
2 12 32280.4
4 12 32280.4
6 12 32280.4
```

Combination of:
Beams at 14 different
energies from 186.57 to
223.56 MeV/u,
for each energy
225 beams in different
positions



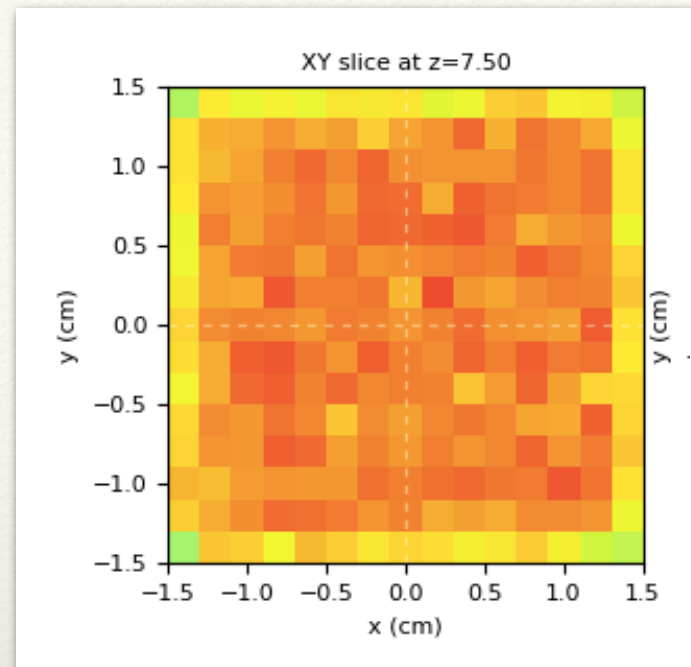
Difference
always within
1.7%



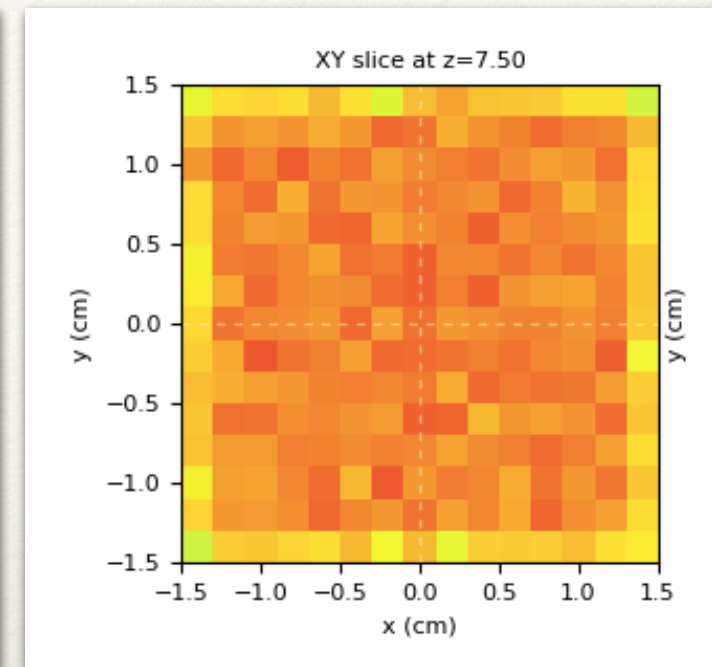
Gamma-index

γ -index 2mm/3%

Reference Map (FLUKA)



Evaluation Map (FRED)



Gamma-index

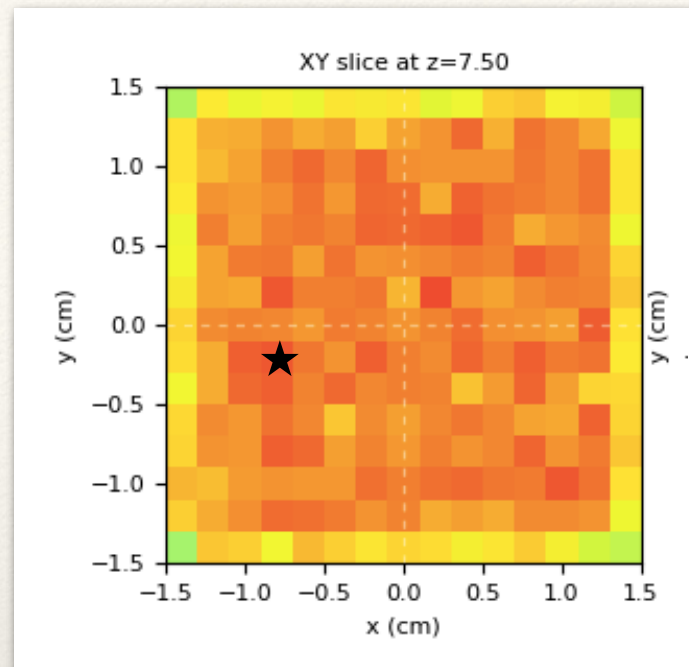
γ -index 2mm/3%

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

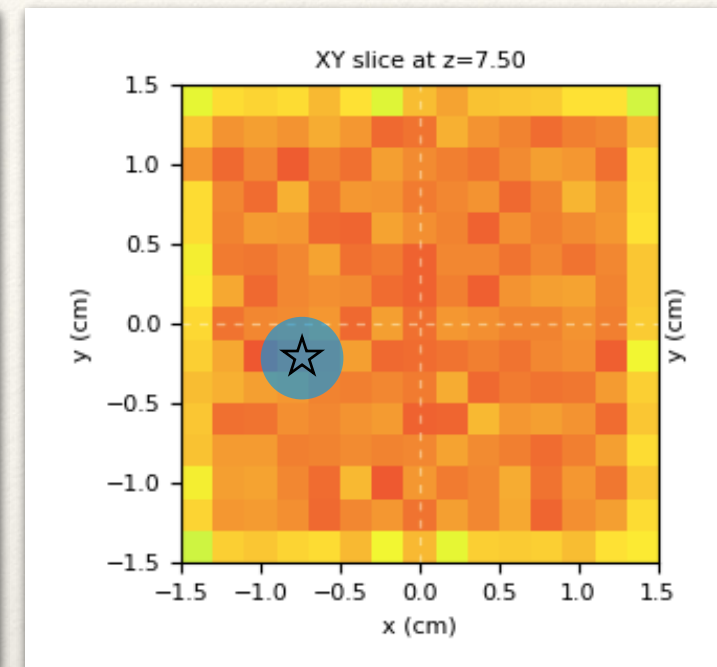
D= dose (D_r of the reference map, D_e of the evaluation map)

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

Reference Map (FLUKA)



Evaluation Map (FRED)



Gamma-index

γ -index **2mm/3%**

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

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

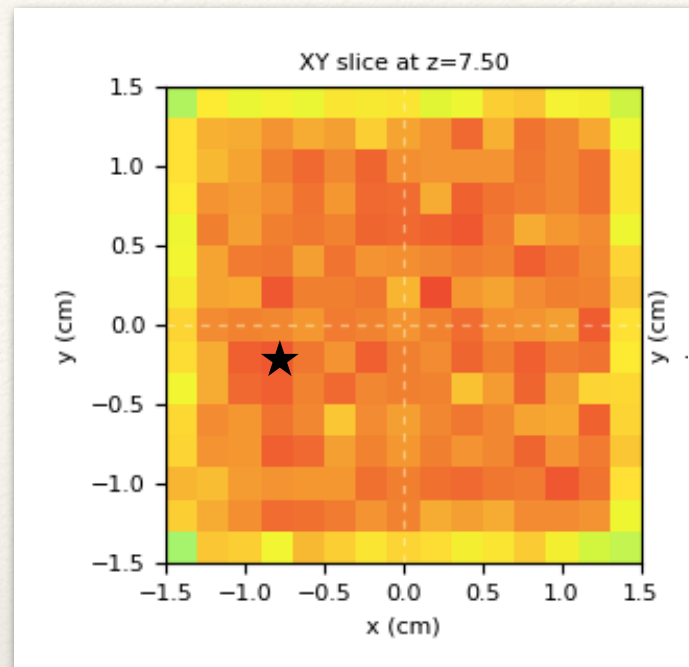
$$\gamma(\vec{r}_r) = \min\{\Gamma(\vec{r}_e, \vec{r}_r)\} \forall \{\vec{r}_e\}$$

$\gamma \leq 1$ = test passed

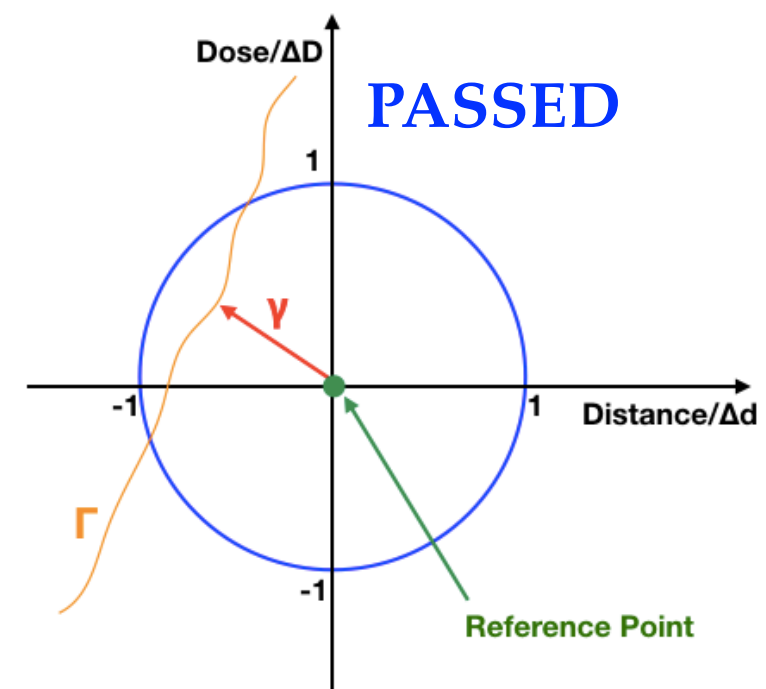
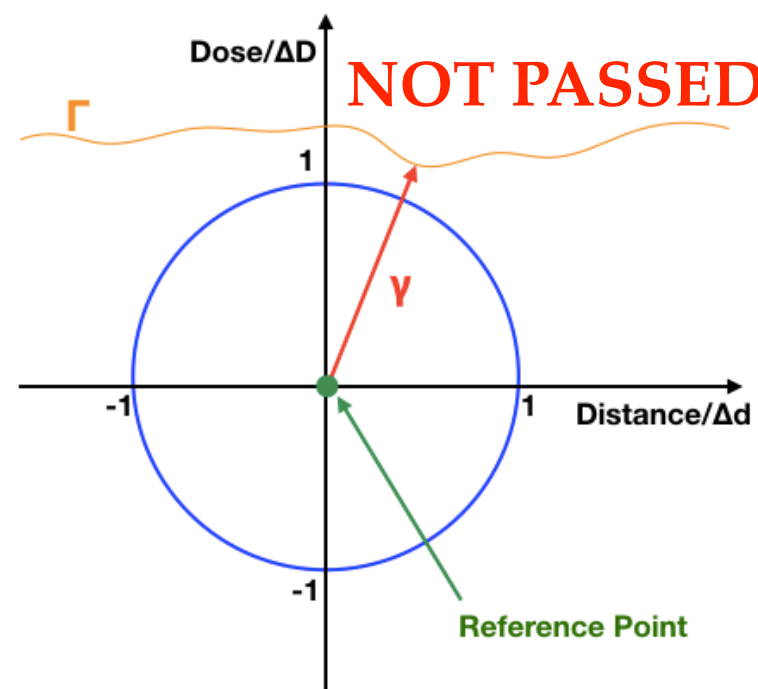
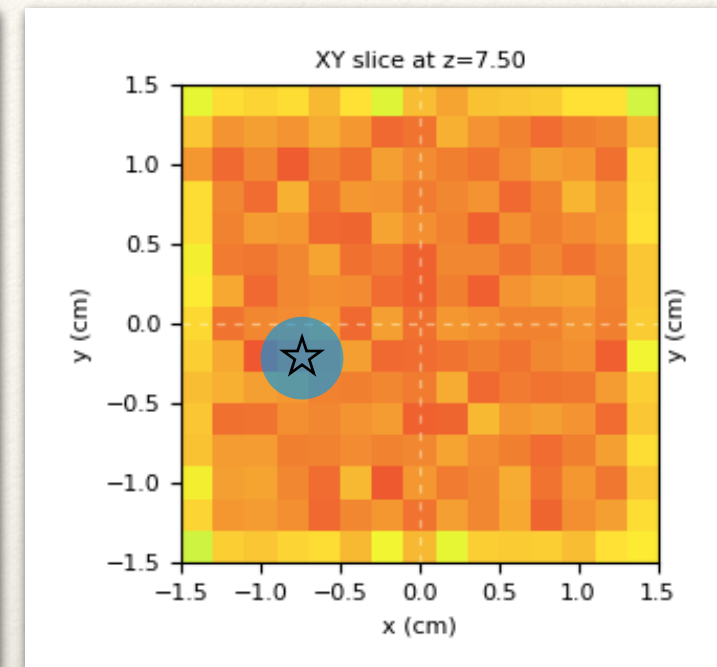
$\gamma > 1$ = test NOT passed

pass rate $\geq 92\%$
clinical acceptance

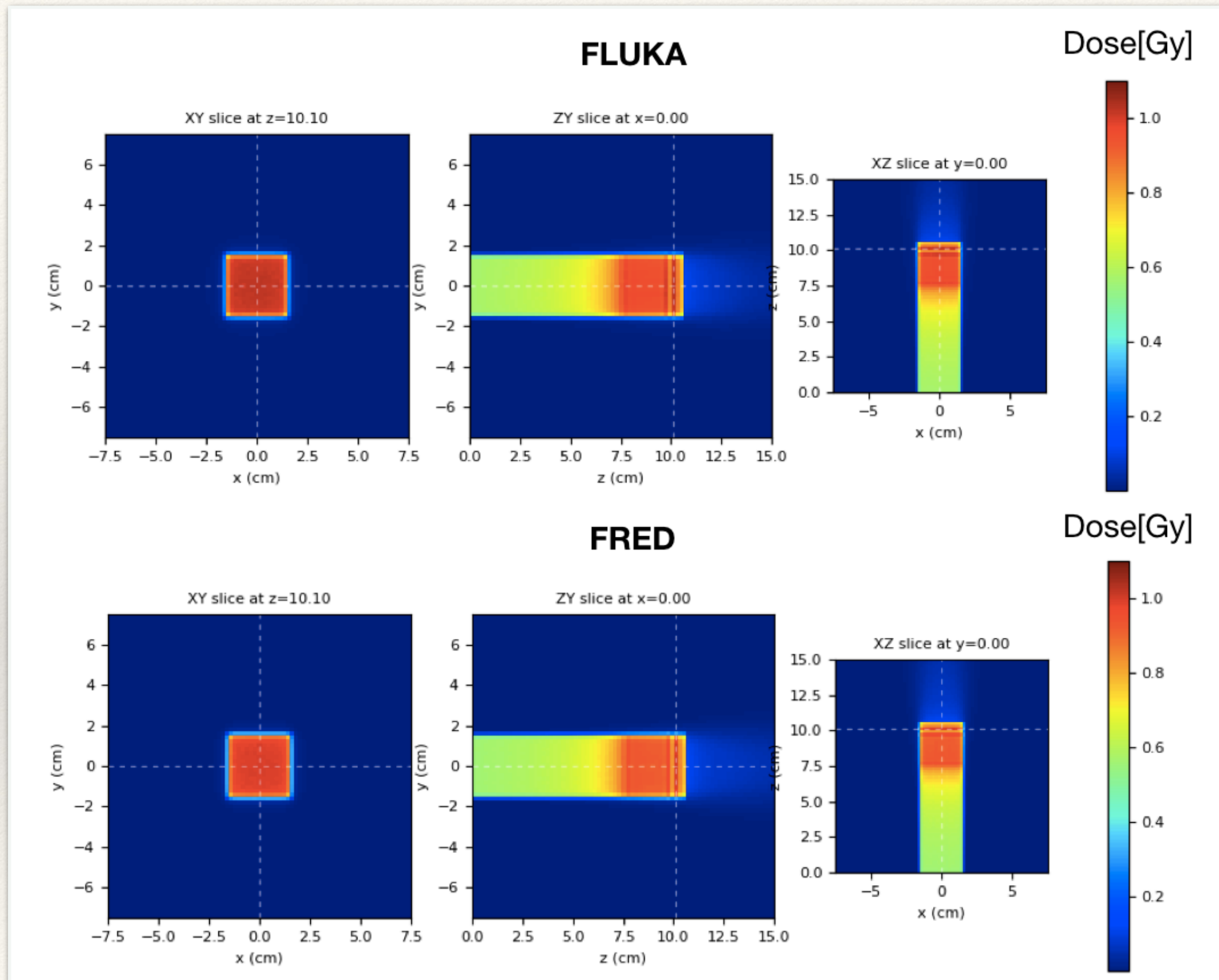
Reference Map (FLUKA)



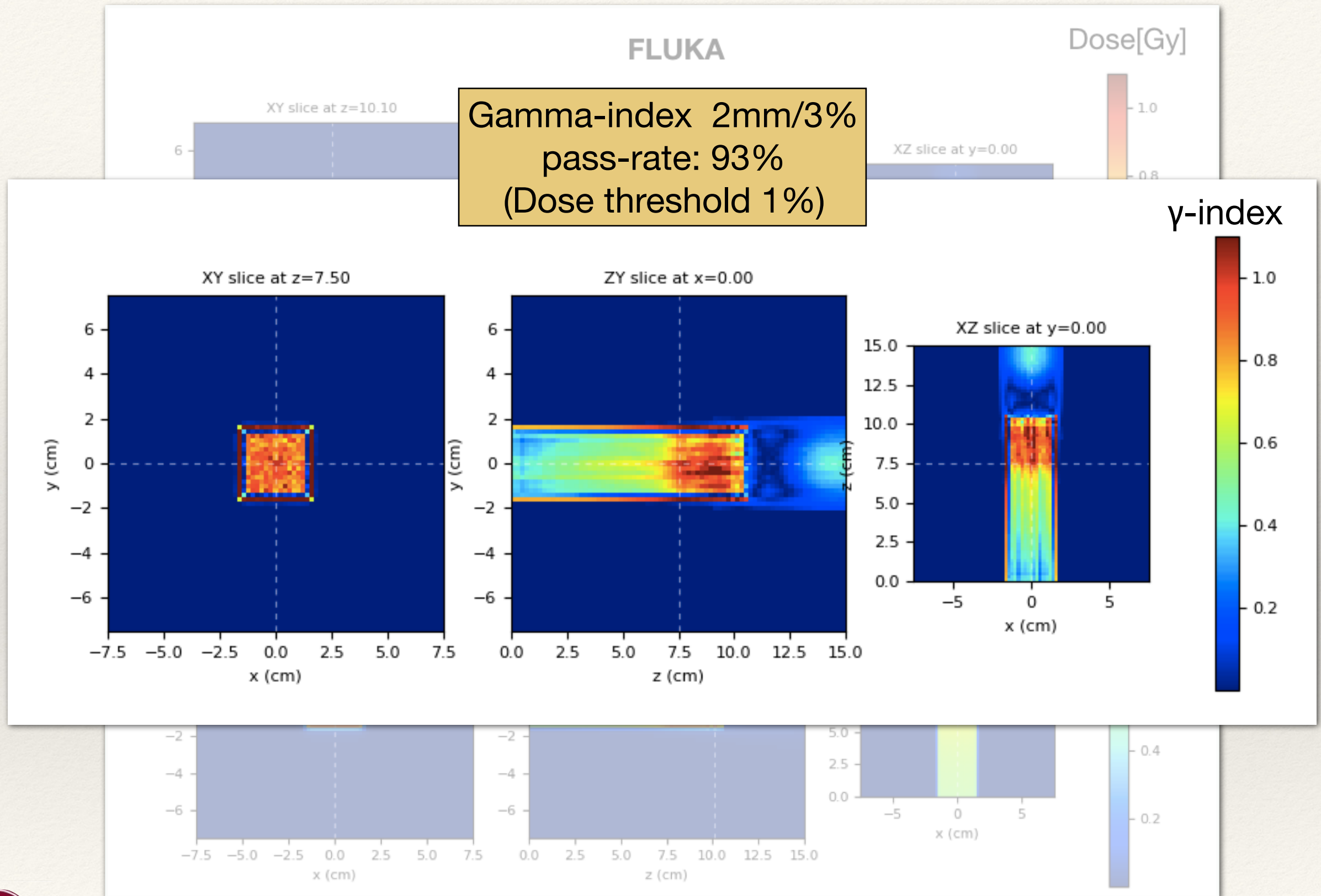
Evaluation Map (FRED)



SOBP from raster file of CNAO

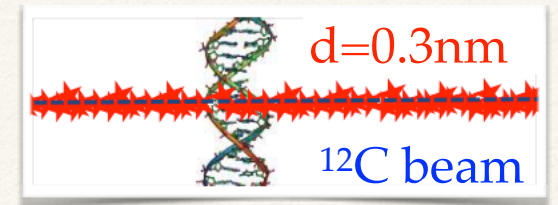
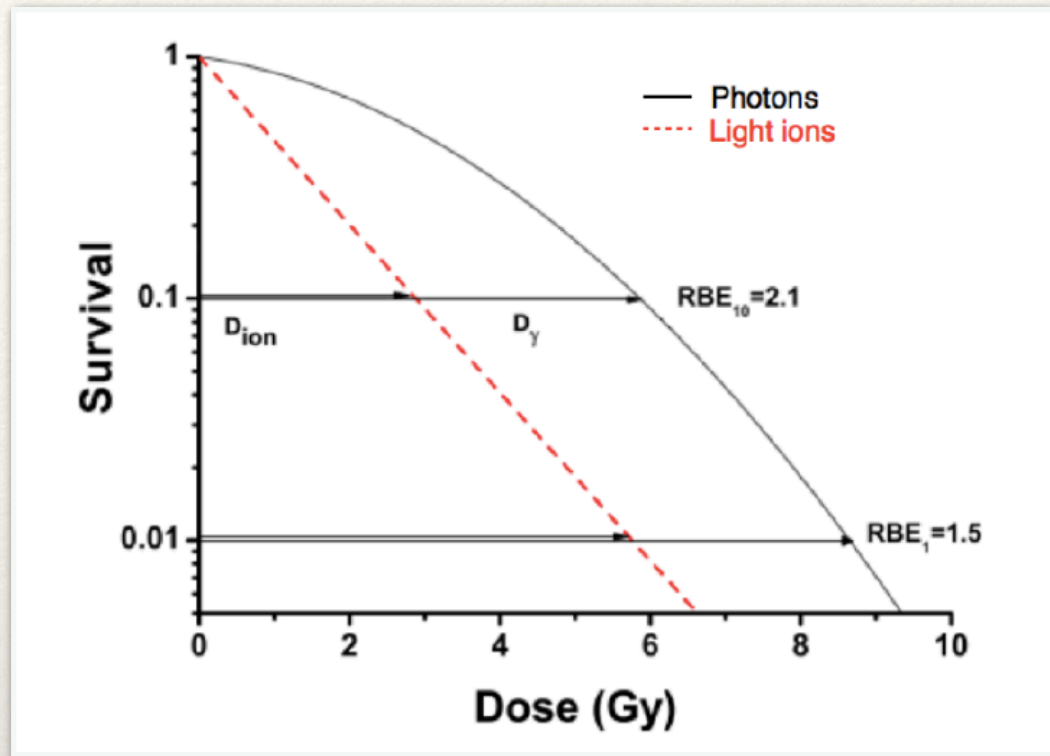


SOBP from raster file of CNAO



Biological Dose & Relative Biological Effectiveness

A given amounts of dose has an effects on the cell that depends on the radiation.

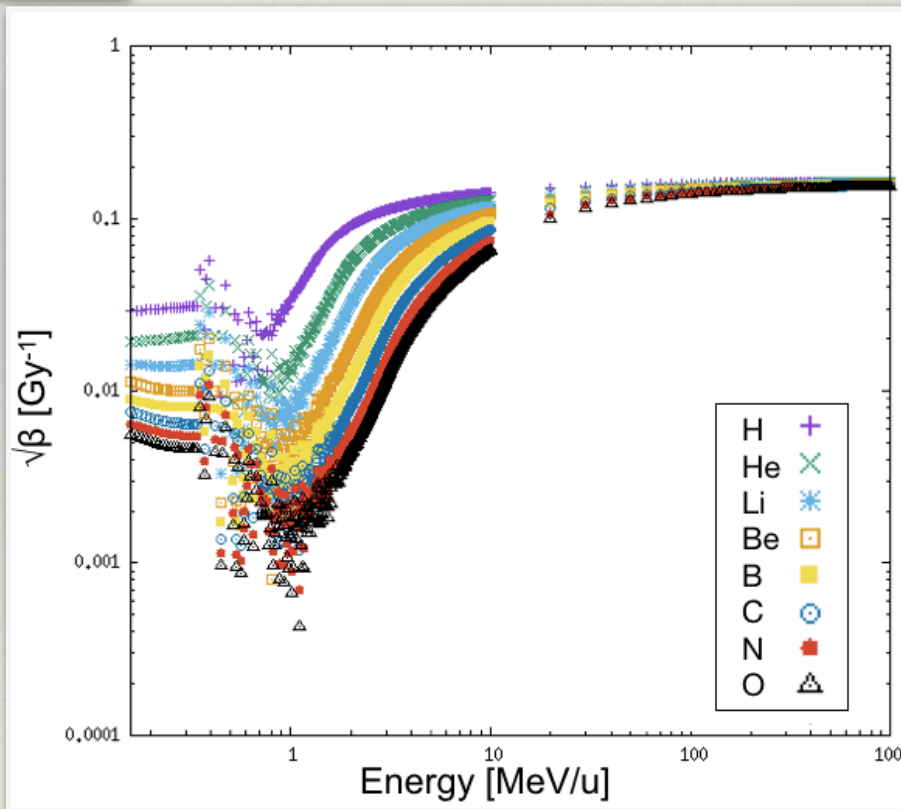
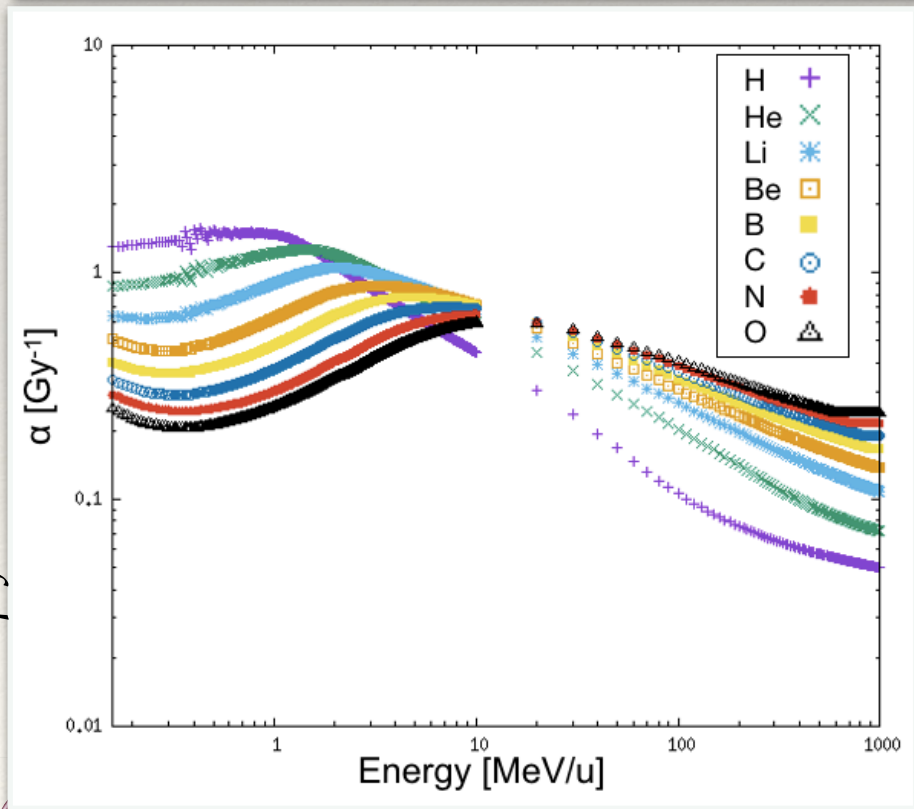


$$S(D) = \frac{N_{survival}}{N_{seed}} = e^{-(\alpha D + \beta D^2)}$$

$$RBE = \frac{D_x}{D_i} \Big|_{Isoeffect}$$

D_x = (or **biological dose**) the dose of a photon radiation to caused the same damage of a ion radiation (D_i).

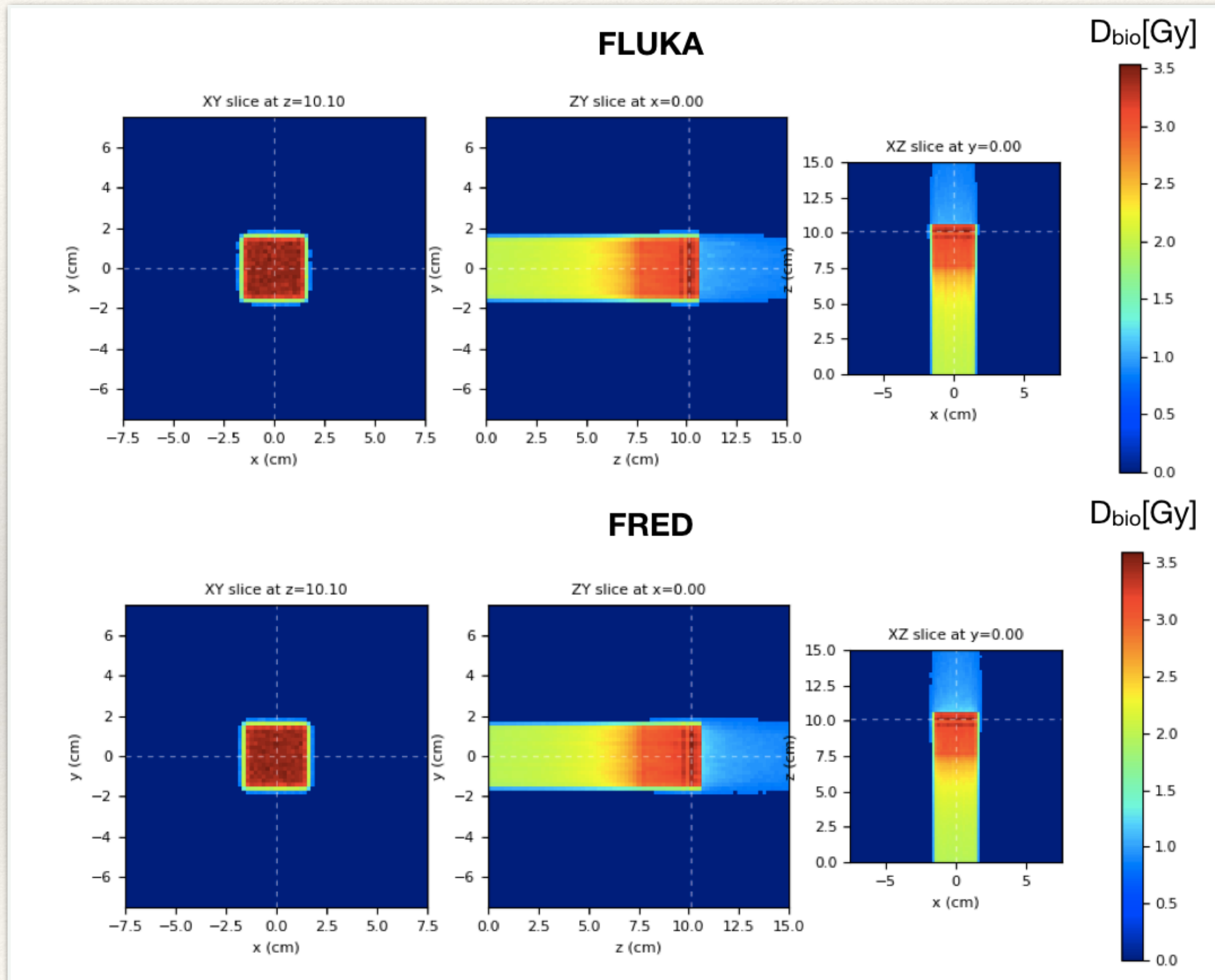
α and β from TOPAS database



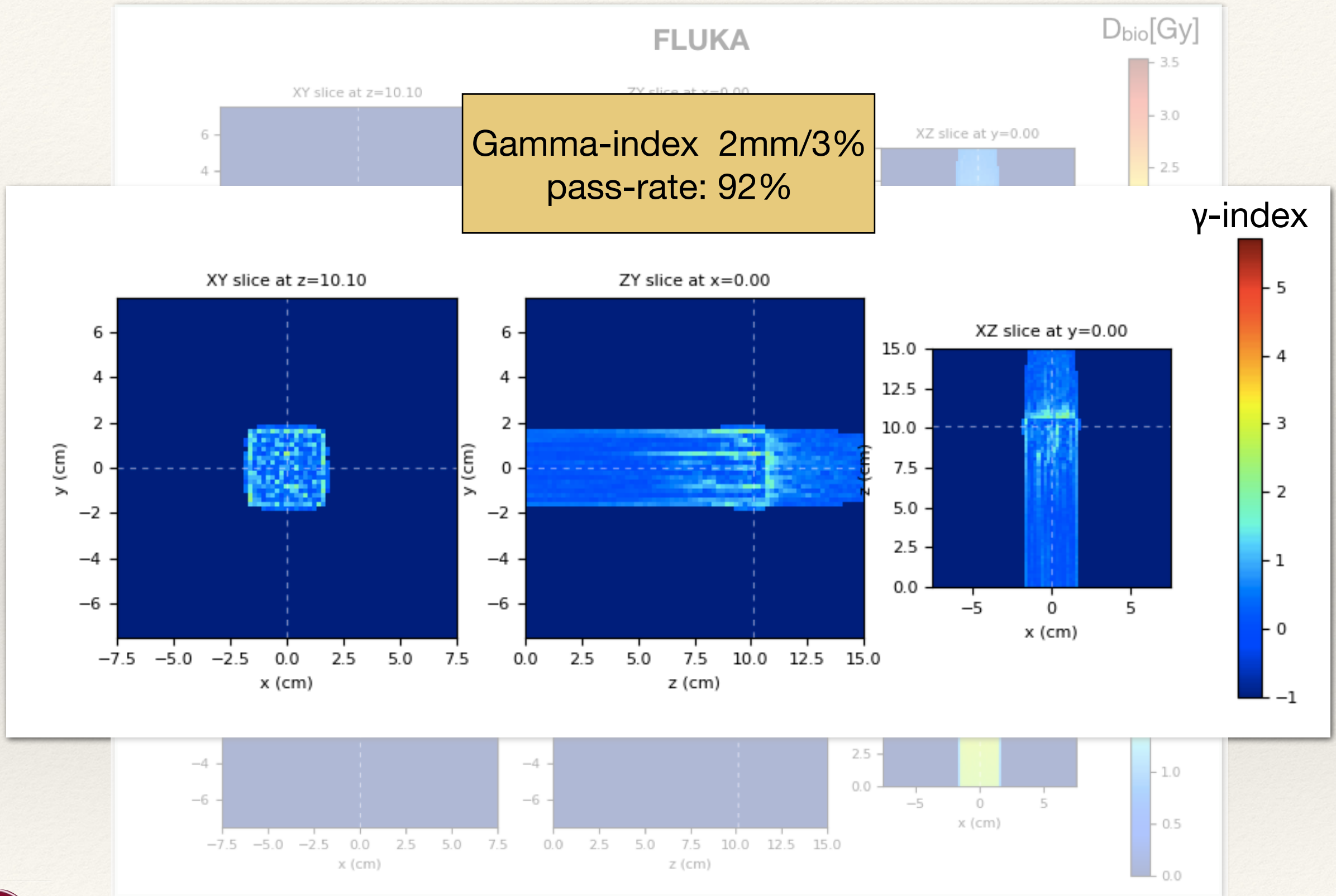
Parameters α and β are strongly correlated to the type of radiation which release dose and its energy.

RBE depends on the fragments and on their energy spectrum.

Biological Dose & Relative Biological Effectiveness



Biological Dose & Relative Biological Effectiveness

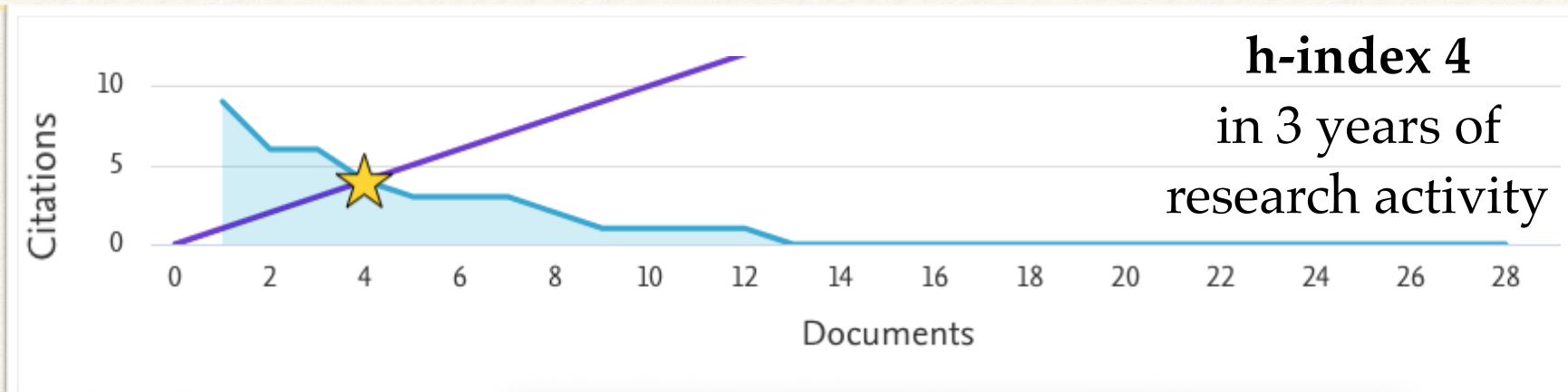


Conclusions

- Implementation of an entirely **new nuclear interaction model** of carbon on light target nuclei in the fast MC FRED.
- Tested of the model against the full-MC code **FLUKA: excellent agreement.**
 - **Single PB:** always within **2.5%** of the total dose deposited in single pencil beams in the 100÷300 MeV / u energy range;
 - **SOBP:** agreement of the dose distribution within **1.7%** and the gamma-index 2mm / 3% pass rate **93.3%**;
 - **Biological dose** and the **RBE** in **good agreement** with FLUKA.
- Comparison with experiments: **good agreement.**
 - **GANIL experiment;**
 - **Haettner experiment.**
- Next steps:
 - Port the model on **GPU**;
 - Comparison of the accuracy of FRED dose recalculation with the CNAO TPS for carbon therapy to achieve **clinical validation.**

Publications

29 publications



- [1] De Simoni M. et al. "FRED: A fast Monte Carlo code on GPU for quality control in Particle Therapy". In: *Journal of Physics: Conference Series* 1548 (2020), p. 012020. DOI: 10.1088/1742-6596/1548/1/012020
- [2] Dong Y. et al. "The Drift Chamber detector of the FOOT experiment: Performance analysis and external calibration". In: *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 986 (2020), DOI: 10.1016/j.nima.2020.164756
- [3] Mattei I. et al. "Charged particles and neutron trackers: Applications to particle therapy". In: *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 954 (2020), DOI: 10.1016/j.nima.2018.09.064
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- [5] Traini G. et al. "Performance of the ToF detectors in the foot experiment". In: *Nuovo Cimento della Societa Italiana di Fisica C* 43 (2020), DOI: 10.1393/ncc/i2020-20016-5
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- [7] Collamati F. et al. "Radioguided surgery with β^- radiation in pancreatic Neuroendocrine Tumors: a feasibility study". In: *Scientific Reports* 10 (2020), p. 4015. DOI:10.1038/s41598-020-61075-2
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- [10] Rucinski A. et al. "Secondary radiation measurements for particle therapy applications: Charged secondaries produced by ^{16}O ion beams in a PMMA target at large angles". In: *Physica Medica* 64 (2019). pp. 45-53. DOI: 10.1016/j.ejmp.2019.06.001
- [11] Gioscio E. et al. "Development of a novel neutron tracker for the characterisation of secondary neutrons emitted in Particle Therapy". In: *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 958 (2019). pp. 162862. DOI: 10.1016/j.nima.2019.162862
- [12] Manuzzato E. et al. "A 16×18 Digital-SiPM Array with Distributed Trigger Generator for Low SNR Particle Tracking". In: *ESSCIRC 2019 - IEEE 45th European Solid State Circuits Conference* (2019). pp. 75-78. DOI:10.1109/ESSCIRC.2019.8902571
- [13] Montesi M. C. et al. "Ion charge separation with new generation of nuclear emulsion films". In: *Open Physics* 17 (2019). pp. 233-240. DOI: 10.1515/phys-2019-0024
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- for the FOOT experiment". In: *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 916 (2019).pp. 116-124. DOI: 10.1016/j.nima.2018.09.086
- [15] Collamati F. et al. "Characterisation of a β detector on positron emitters for medical applications", In: *Physica Medica* 67 (2019). pp. 85-90, DOI: 10.1016/j.ejmp.2019.10.025
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- [17] Fischetti M. et al. "Characterisation of the secondary-neutron production in particle therapy treatments with the MONDO tracking detector". In: *IL NUOVO CIMENTO 41 C* 206 (2018). DOI: 10.1393/ncc/i2018-18206-5
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- [22] Morganti S. et al. "Position sensitive β^- Detector based on p-terphenyl scintillator for medical applications". In: *Journal of Instrumentation* 13 (2018). p. 07001. DOI: 10.1088/1748-0221/13/07/P07001
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- [28] Dong Y. et al. "The Drift Chamber detector of the FOOT experiment: Performance analysis and external calibration". In: *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* (2021). DOI: 10.1016/j.nima.2020.164756
- [29] Toppi M. et al. "The MONDO Tracker: Characterisation and Study of Secondary Ultrafast Neutrons Production in Carbon Ion Radiotherapy". In: *Frontiers in Physics* (2020). DOI: 10.3389/fphy.2020.567990



Conferences

9 presentations at international conferences
(5 oral presentations and 4 poster presentations)

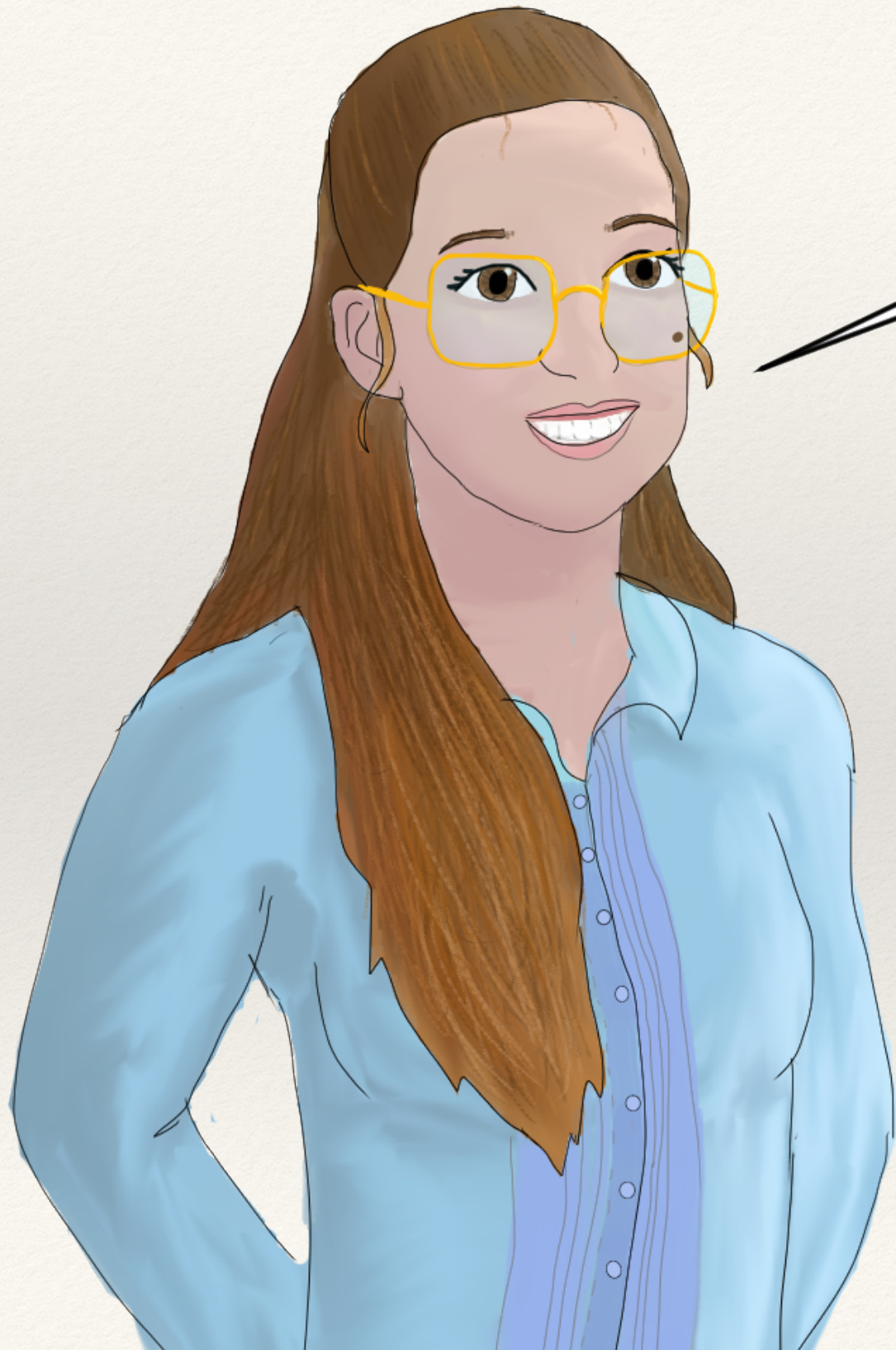
Oral Presentations

- ❖ **Nov. 2020**, *IEEE Nuclear Science Symposium and Medical Imaging Conference* - Online/Virtual, "In vivo verification of carbon ion therapy treatments at CNAO by means of charged fragments detection"
- ❖ **Sept. 2019**, *International Conference on Medical Accelerators and Particle Therapy* - Seville (Spain), "A data-driven nuclear fragmentation model for a fast Monte-Carlo code, FRED, in Particle Therapy with Carbon beams"
- ❖ **Jun. 2019**, *10th Young Researcher Meeting* - Rome (Italy), "FRED: a fast Monte Carlo code on GPU for quality control in Particle Therapy"
- ❖ **Jan. 2019**, *57th International Winter Meeting on Nuclear Physics* - Bormio (Italy), "The Dose Profiler tracker: an online Particle Therapy monitor"
- ❖ **Sept. 2018**, *Società italiana per le ricerche sulle radiazioni* - Roma (Italy), "In-room characterization, using an anthropomorphic phantom, of a novel detector for on-line dose monitoring in light ions cancer therapy")

Posters Presentations

- ❖ **Nov. 2020**, *IEEE Nuclear Science Symposium and Medical Imaging Conference* - Online/Virtual, "Fragmentation model for Treatment Planning System of carbon ions implemented in a fast MC code (FRED)"
- ❖ **Nov. 2020**, *IEEE Nuclear Science Symposium and Medical Imaging Conference* - Online/Virtual, "Study of secondary neutron production in PT treatments using MONDO, an innovative ultra-fast neutrons tracker"
- ❖ **Sept. 2018**, *Società italiana per le ricerche sulle radiazioni* - Roma (Italy), "Applications in Particle Therapy of FRED, a fast Monte Carlo code on GPUs for energy deposition of proton beams in matter"
- ❖ **Sept. 2019**, *International Conference on Medical Accelerators and Particle Therapy* - Seville (Spain), "Spectrum and flux measurements of secondary ultra-fast neutrons produced in Particle Therapy treatments using the innovative MONDO tracker"





Thank you!
Any questions?