FLASH Radiotherapy with hIgh Dose-rate particle beAms

Development of a VHEE accelerator in Sapienza for the treatment of deep seated tumors: planning and radioprotection challenges of a FLASH compact machine.

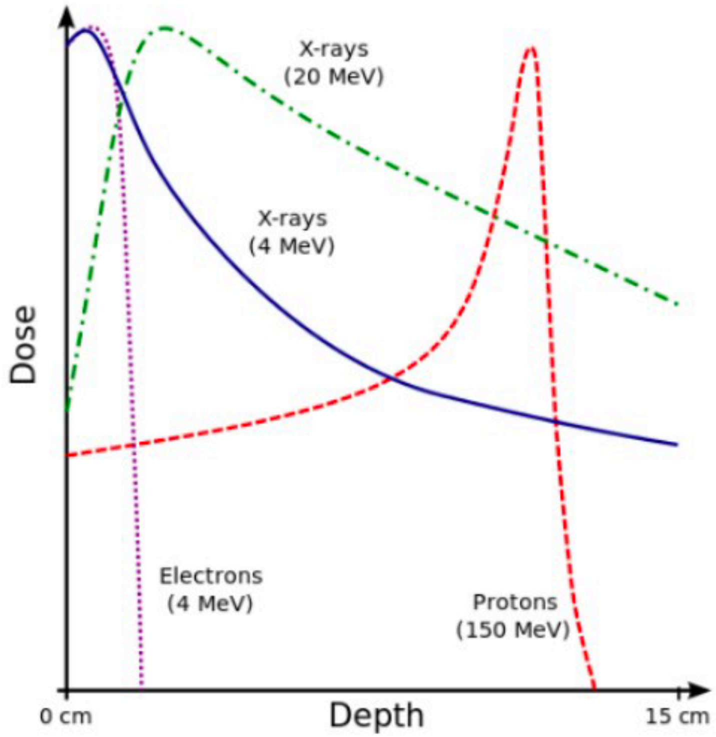
PhD in *Accelerator Physics*, XXXVII cycle
Sapienza University of Rome
Supervisor: Prof. Alessio Sarti

Angelica De Gregorio
Rome, 23 October 2023

Radiation Therapy

Radiation therapy is a medical treatment modality that uses ionizing radiation to destroy or damage cancer cells.

- Different particles can be used: the choice depends on the type and location of the tumor, the stage of cancer, and the patient's overall health.



Photon therapy is the most common form of radiation therapy. It uses X-rays or gamma rays to deliver a focused dose of radiation to the tumor.

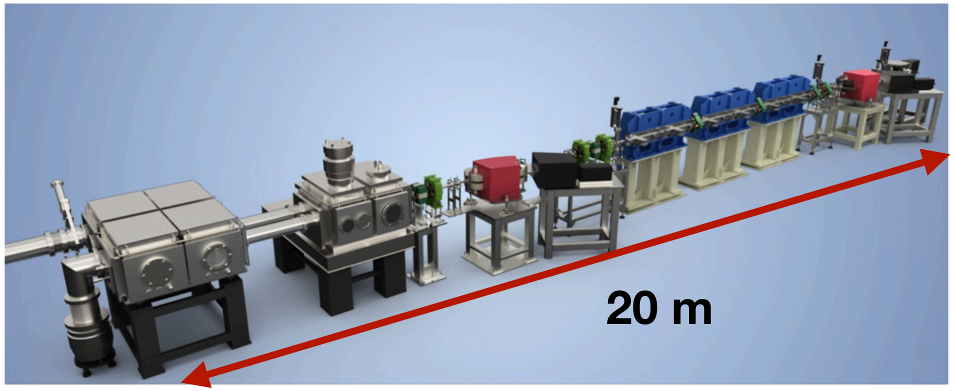
Proton and heavy ion radiation therapy offer a more precise delivery of radiation, minimizing side effects. This makes it useful for tumors located near critical structures.

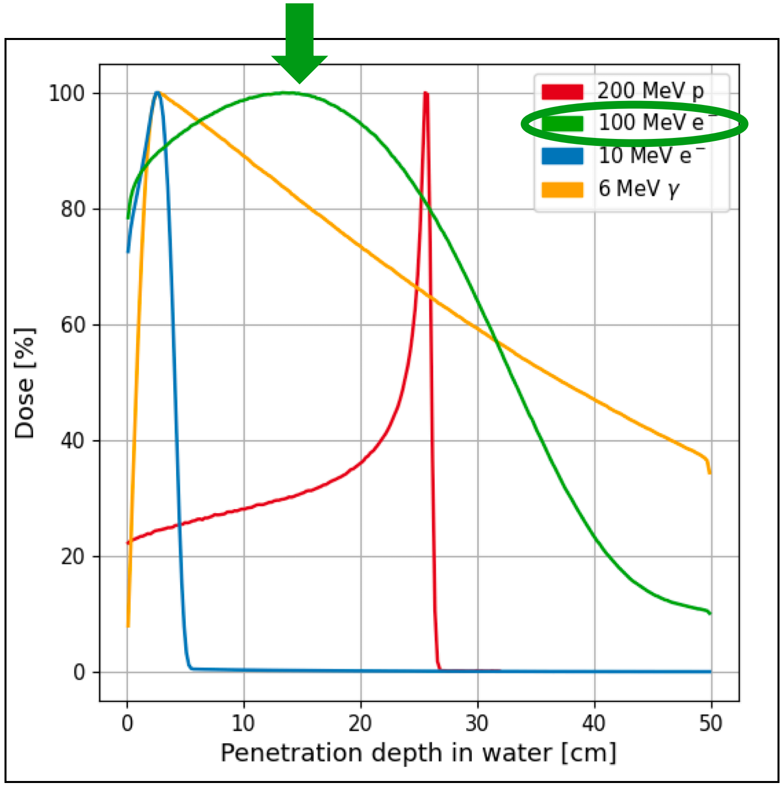
Electron radiation therapy uses low-energy electrons to treat shallow tumors. It has limited penetration, reducing the risk of damaging deeper structures.

VHEE Treatment

Very High Energy Electrons (VHEE) have been considered already in the past as an alternative to protons and photon radiotherapy thanks to their **better longitudinal sparing of Organs at Risks** (OARs) and reduced impact of range uncertainties.

- Their ability to penetrate tissues to varying depths allows for flexibility in treatment planning; ✓
- They have shown performances (comparable with RT or p) only at the cost of having high energies (>150 MeV) and number of fields. ✗





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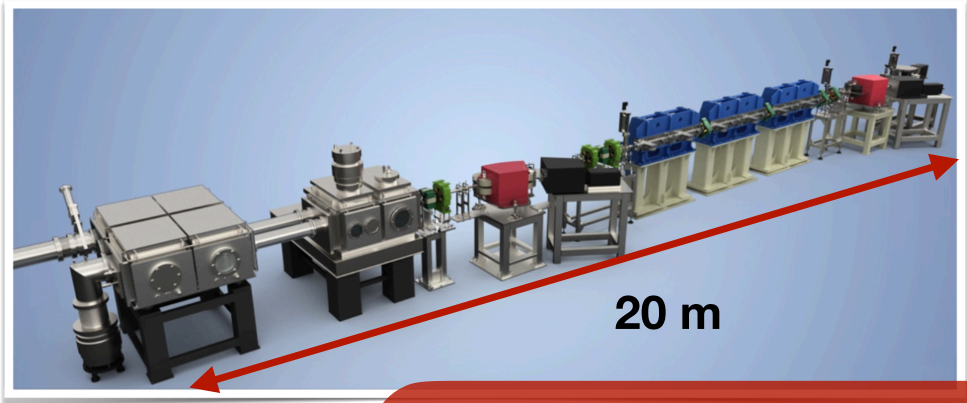
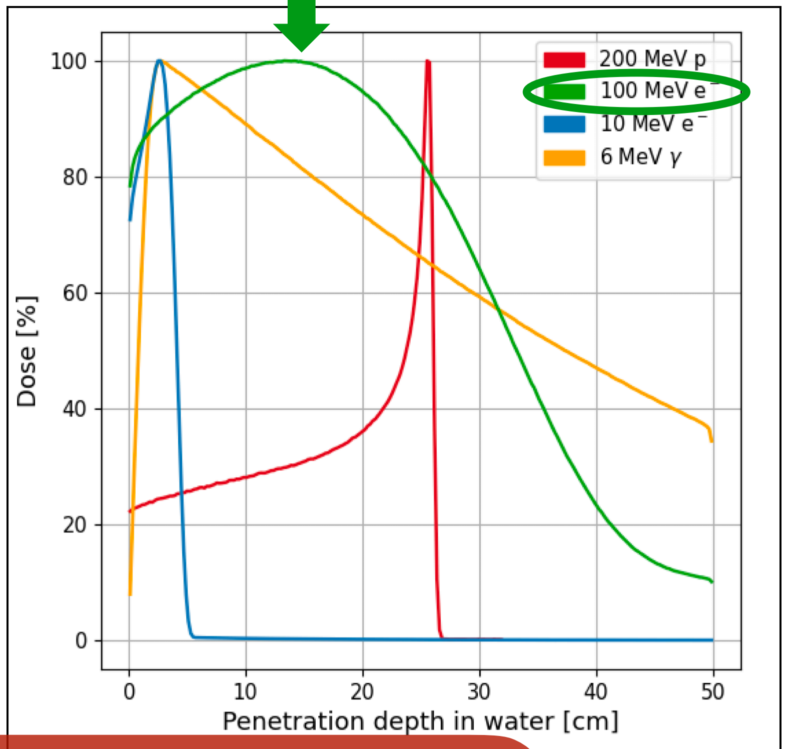




Due to cost, complexity and space (long accelerating system) VHEE have not yet reached the clinical stage.

VHEE Treatment

To date, interest in VHEE has been renewed thanks to two main factors:

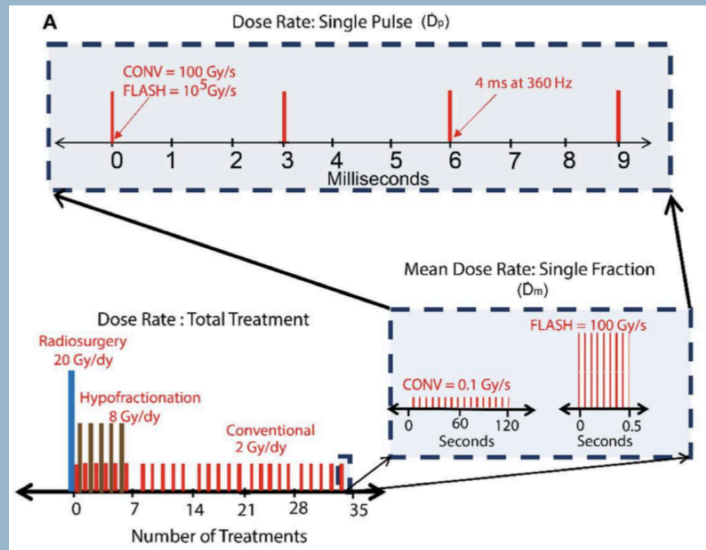
C-Band and X-Band accelerator technology

2.9 GHz	5.7 GHz	12 GHz
S-band	C-band	X-band
G~20 MeV/m	G~50 MeV/m	G~100 MeV/m

- Higher shunt impedance per unit length, shorter filling time, higher breakdown threshold;
- 100% temporal and spatial control of the beam;
- Compact size, used in advanced research facilities and medical applications where space is limited.

FLASH effect

Several pre-clinical studies recently claimed that the toxicity in healthy tissues can be significantly reduced (from 80% down to 60%), while keeping the same efficacy in cancer killing, if the dose rate is radically increased (~**100 Gy/s**, or even more) with respect to conventional treatments (~**0.01 Gy/s**).



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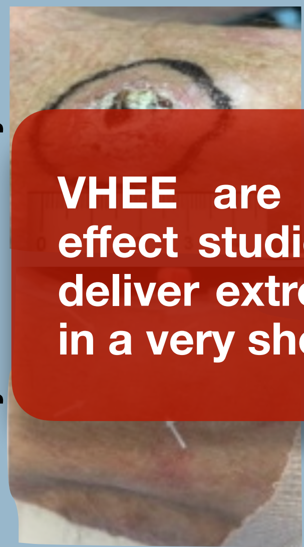
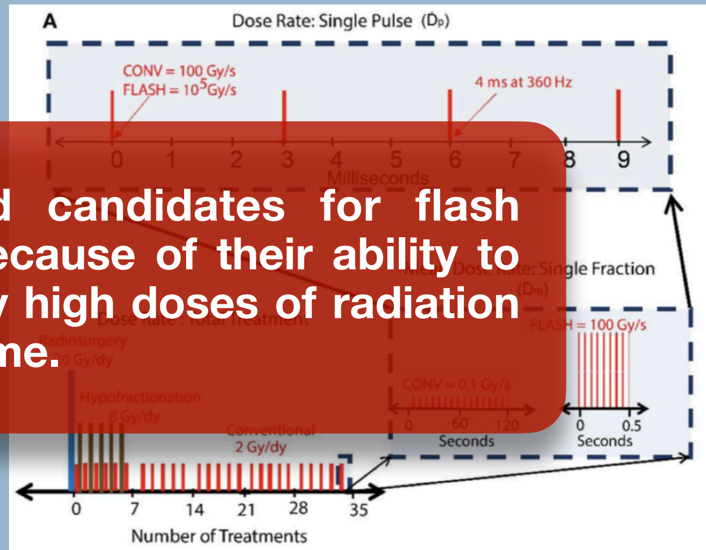
Day 0

Day 150





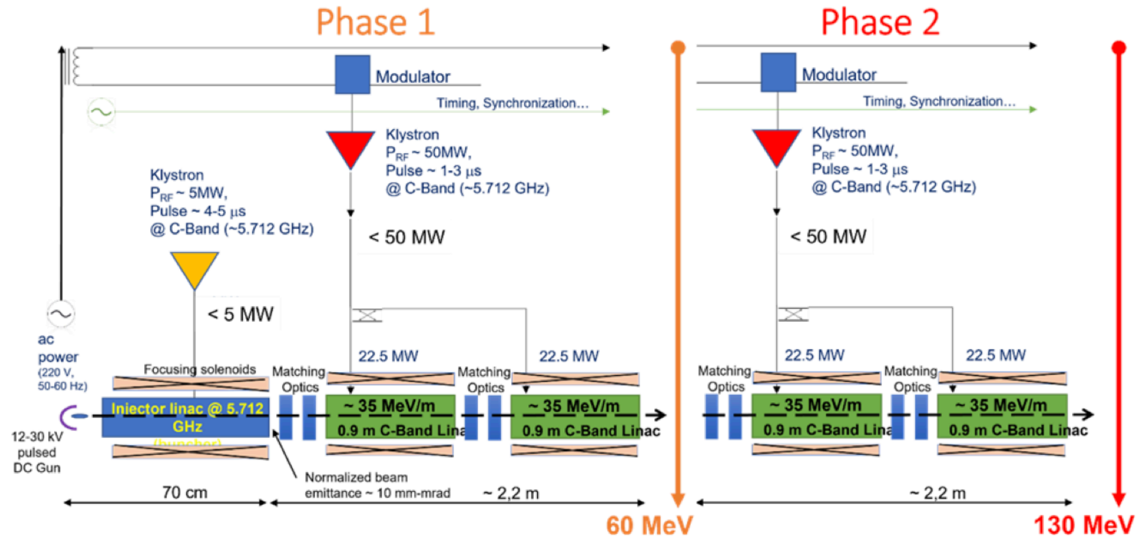
VHEE are good candidates for flash effect studies because of their ability to deliver extremely high doses of radiation in a very short time.

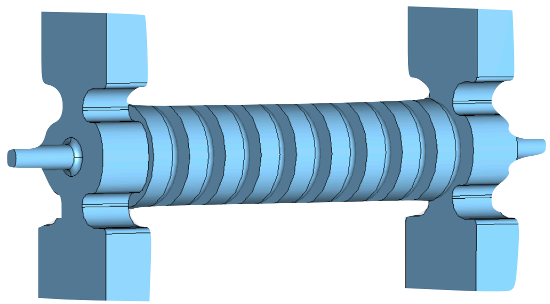
VHEE Accelerator

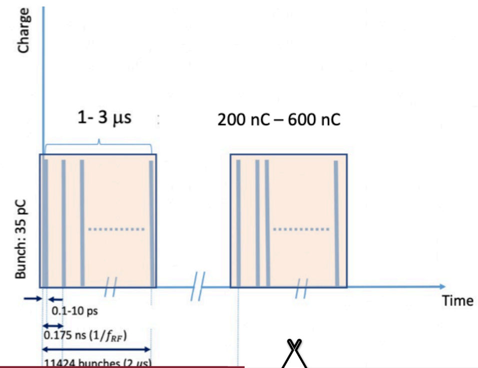
Translation of VHEE radiotherapy in clinical practice requires the development of **accelerators with a compact design** to meet the requirements for a machine suitable for the hospital environment.

SAFEST

- The proposed VHEE source is based on a **C-band LINAC**, working at the frequency of **5.712 GHz**, delivering a high intensity electron beam at FLASH due rates.
- The **high-gradient acceleration** will allow to accelerate electrons up to 130 MeV, maintaining a good transmission efficiency of the particles, necessary to transport the high peak current required for the high dose and dose rate in the FLASH irradiation.

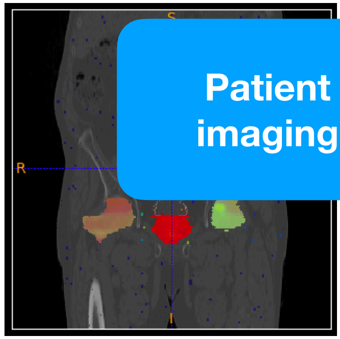


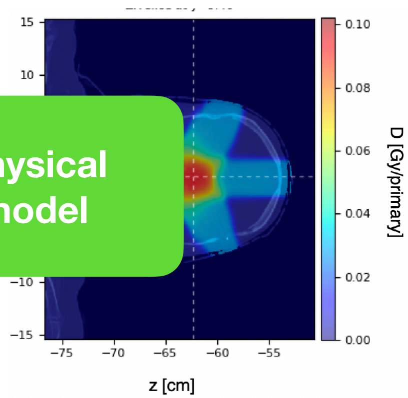




Planning a Treatment: TPS for VHEE

In order to finalize the machine design and to investigate the potential of VHEE based radiotherapy, a **VHEE Treatment Planning System (TPS)** is needed.





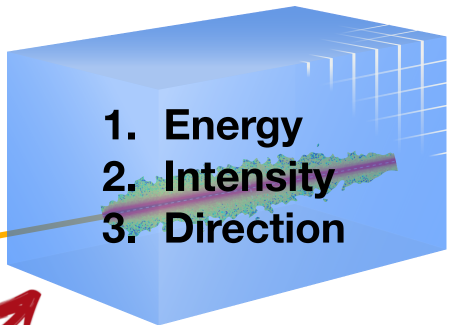
Patient imaging

Dosimetric constraints

Physical model

TPS

Accelerator parameters



TPS aims to **optimize the dose distribution in the patient** with the intent to **maximize tumour control and minimize normal tissue complications.**

The accuracy of the dose distribution calculation should be maximized.

My PhD thesis

In this context the availability of a dedicated facility would allow bridging the gaps in the current knowledge and characterisation of the VHEE based radiotherapy.

The aim of my thesis

1. Radioprotection studies for a VHEE linac

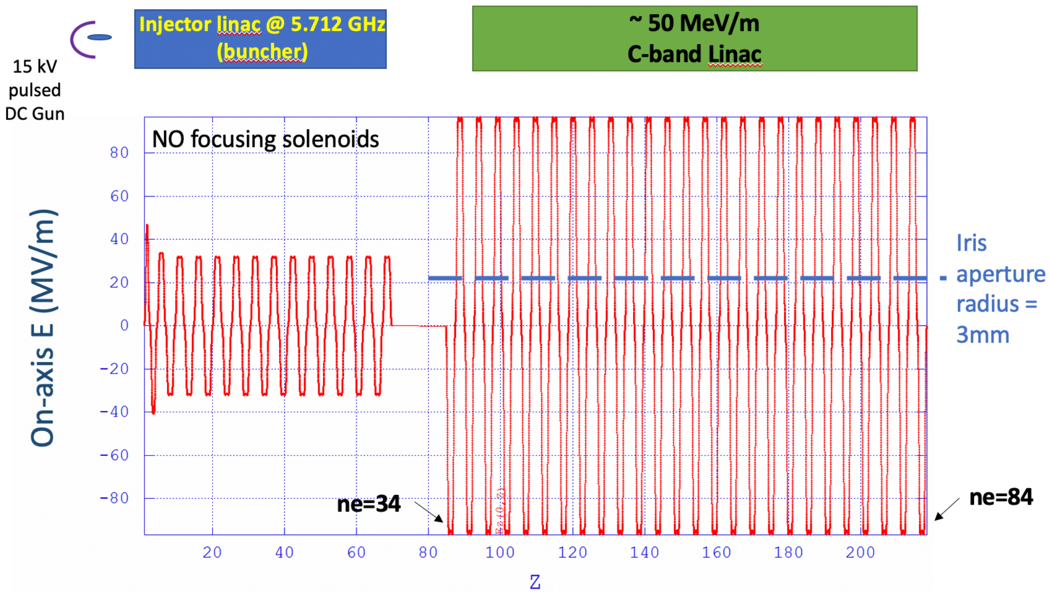
- Implementation of the geometry and **simulation of the physics** with the Monte Carlo tool Fluka;
- Analysis of the simulation and **evaluation of the dispersed flow** in the surrounding environment

2. Development of a VHEE TPS

- Implementation of **Monte Carlo dose evaluation** instead of analytic calculations;
- Implementation of the **Simulated Annealing** and **Quantum Simulated Annealing** algorithms as minimisation methods;
- **Testing and validation** on different type of tumors.

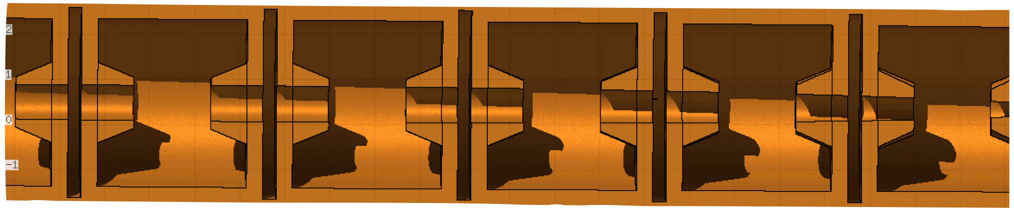
Radioprotection: Geometry

- In the medical field, this kind of accelerator does not exist; for this reason, there is currently no suitable protocol for a 130 MeV machine in a hospital environment.
- The first step was to accurately replicate the geometry and the materials of the accelerator in FLUKA, both for the injector and the accelerating section.



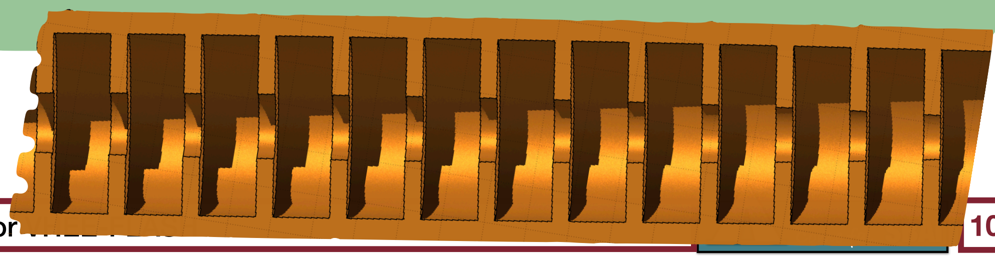
1 Injector

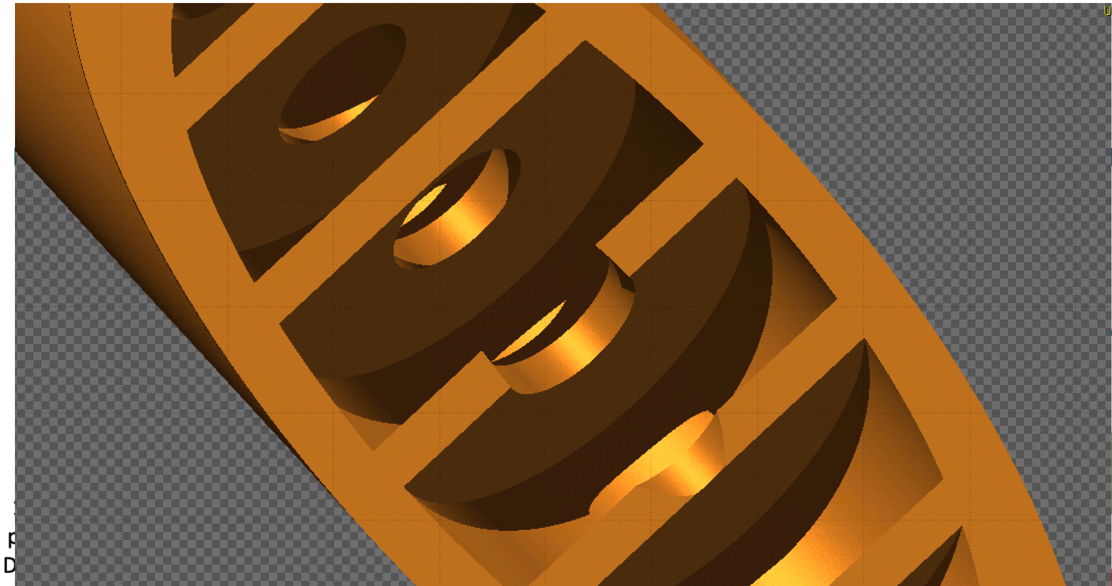
- Standing wave LINAC + 2 traveling wave accelerating structures 90 cm long;
- Accelerates, at an energy of 10 MeV, a current of 200 mA generated by a pulsed DC gun.

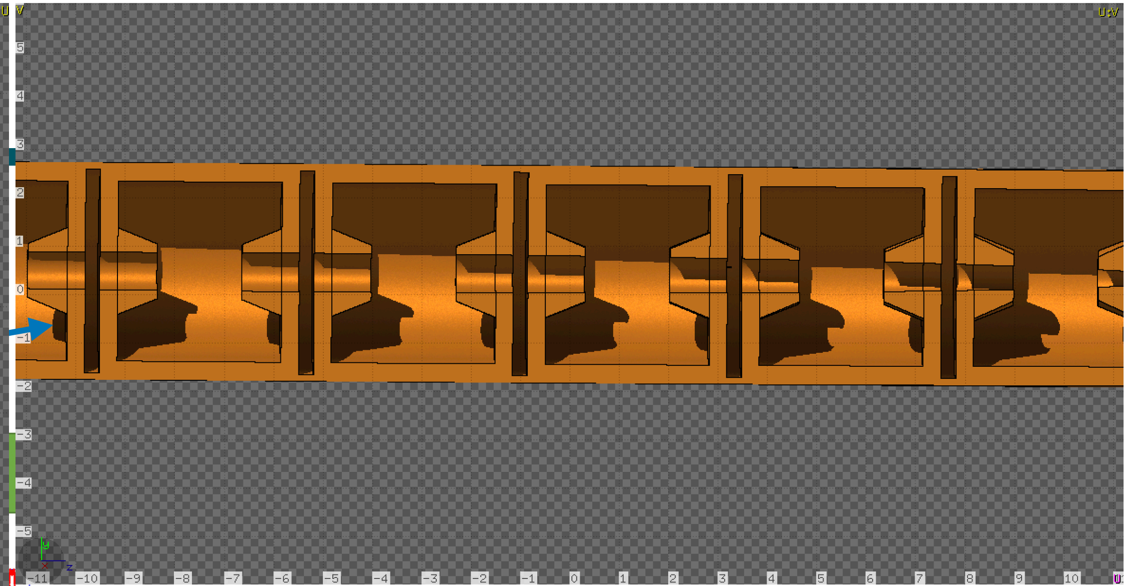


2 C-band LINAC

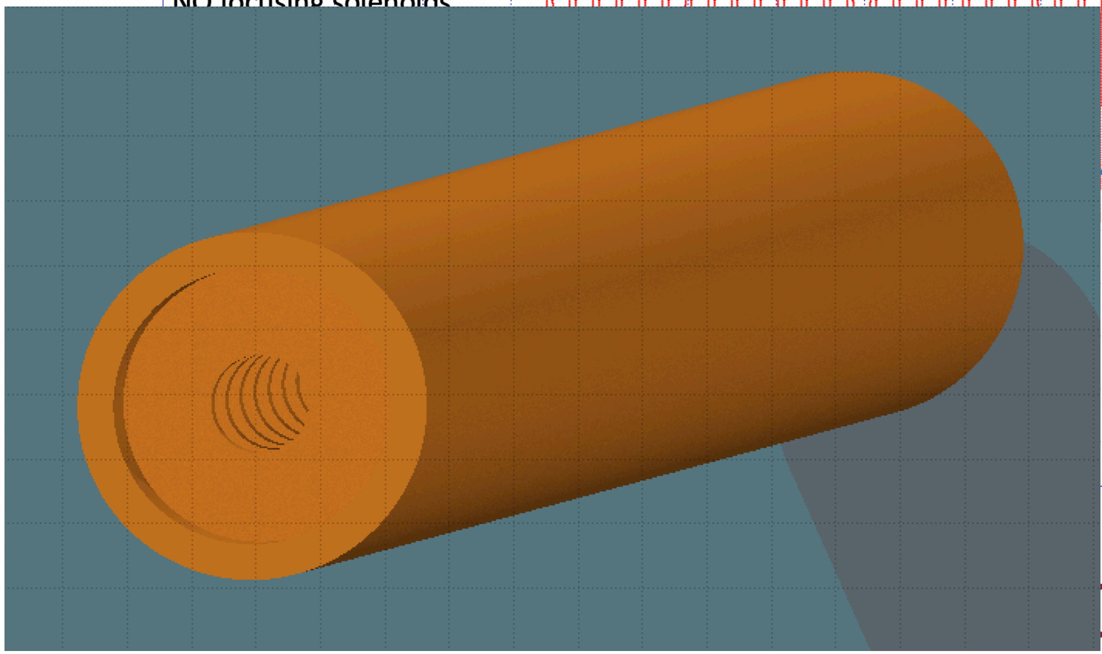
- Compact traveling wave C-band structure with high accelerating gradient (~ 50 MeV/m) able to bring the energy of the electron beam up to about 130 MeV.

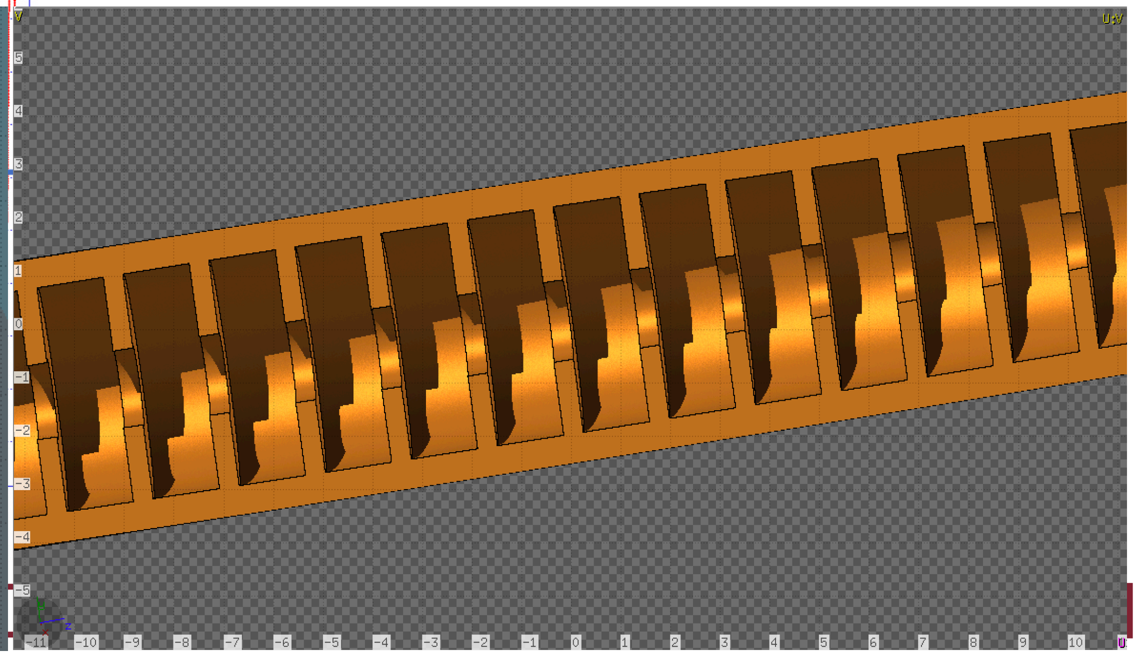






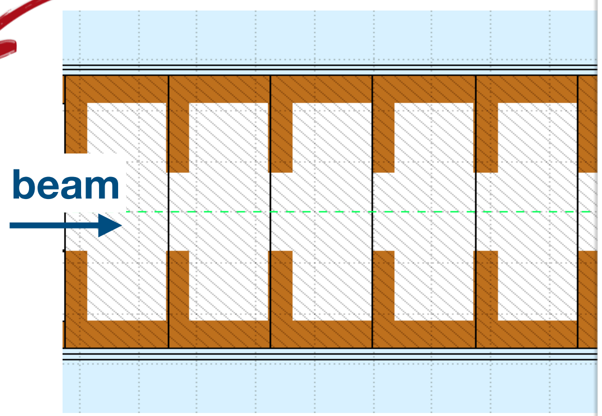
NO focusing solenoids

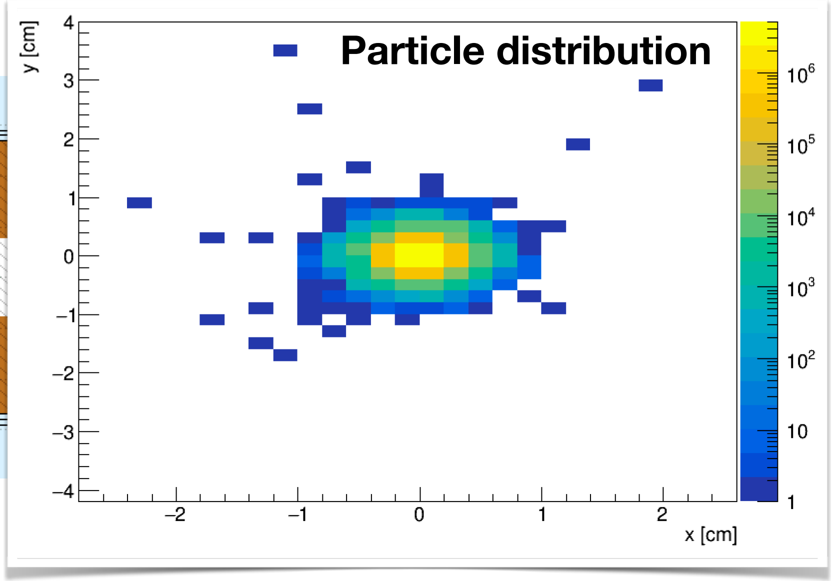




Radioprotection: Interactions simulation

An evaluation of the **radiation background induced by such machine** is needed: starting from the beam dynamics simulations, I extracted all the electrons exiting the beam pipe which interact with the external accelerator material (copper), thereby inducing a stray radiation.





The dose and fluence of each type of particle were retrieved simulating and propagating the outgoing particles (along with their interactions) using the FLUKA Monte Carlo code.

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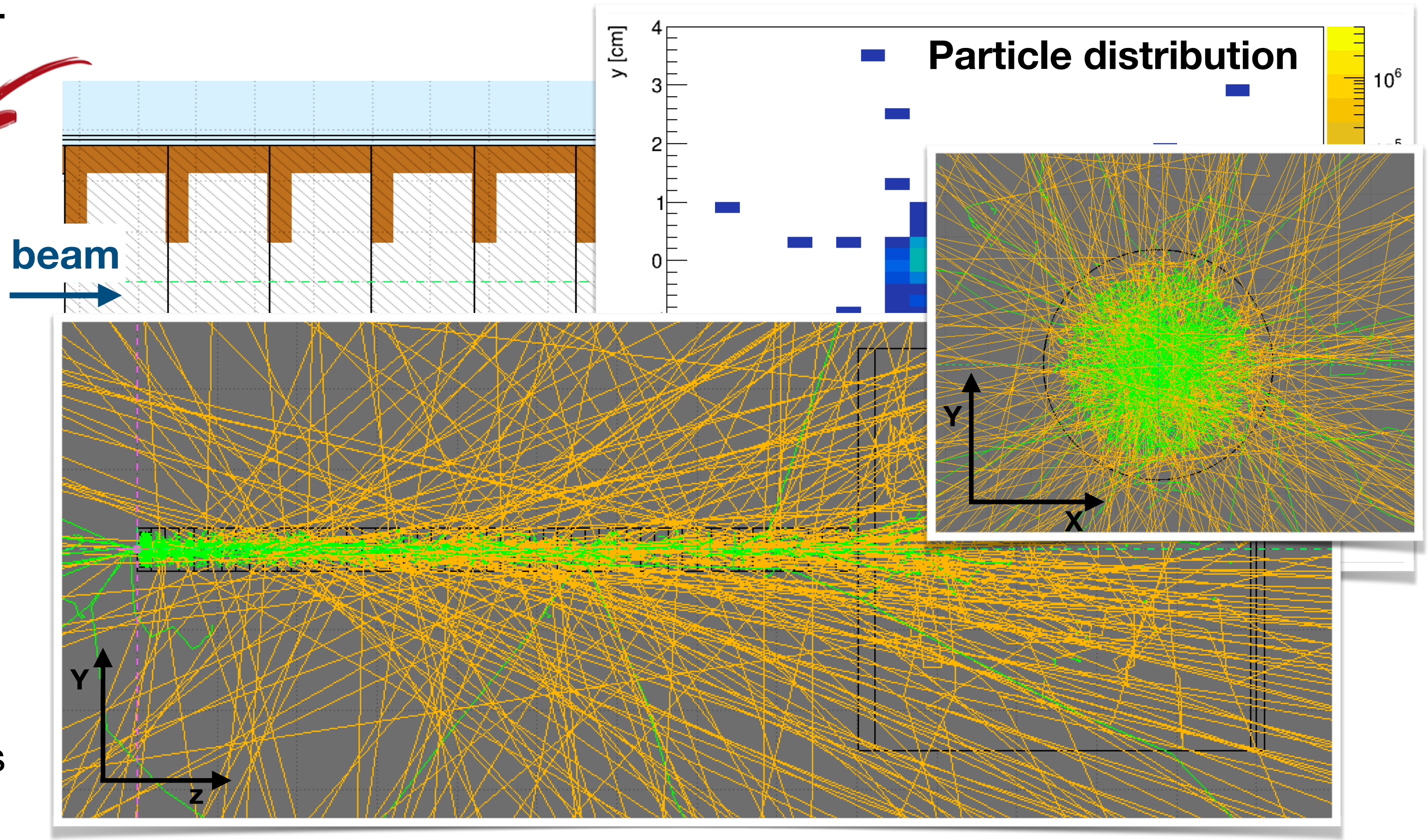

Neutrons
Electrons
Photons

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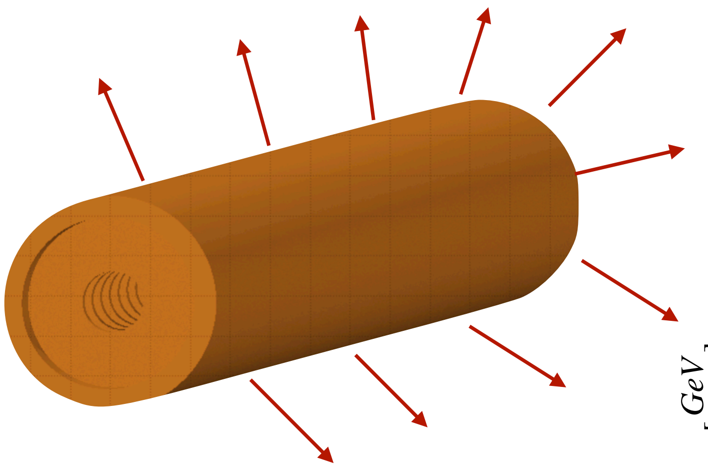
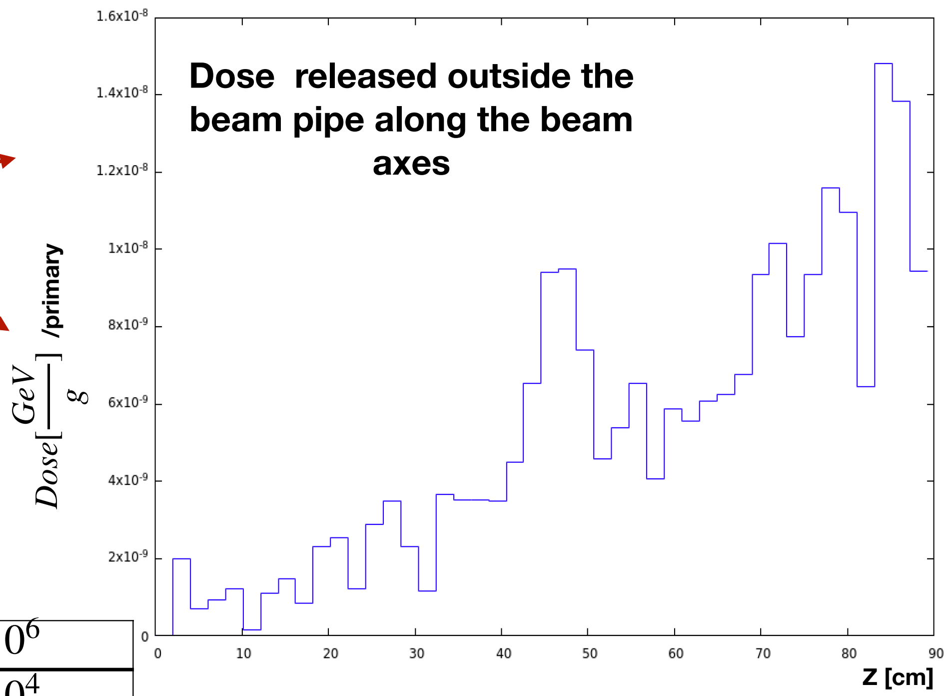


Simulating $3 \cdot 10^{10}$ primary electrons

# photons	$\sim 8{,}1 \cdot 10^6$
# neutrons	$\sim 2{,}7 \cdot 10^4$
# electrons	$\sim 1{,}3 \cdot 10^7$



L. Giuliano et al., Proposal of a VHEE Linac for FLASH radiotherapy. Physics in Medicine and Biology; 2023, DOI: 10.1088/1742-6596/2420/1/012087

$Dose_{AIR} = 1{,}4 \cdot 10^{-3} Gy$

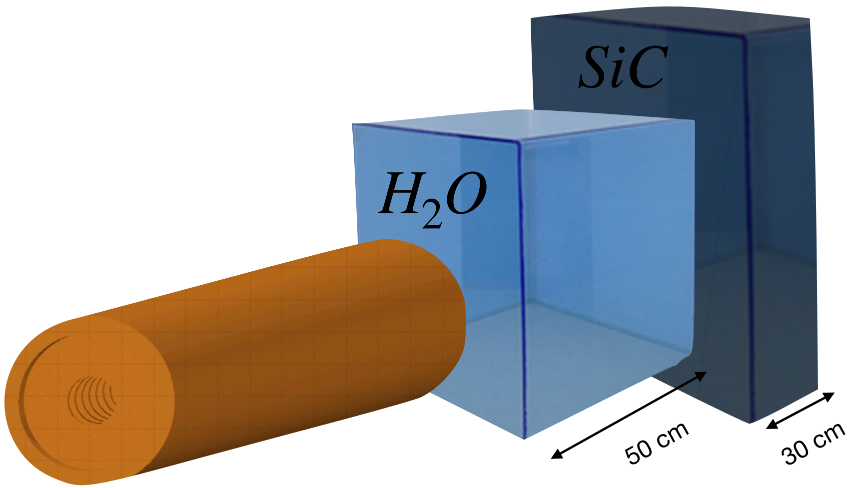
Workload calculation

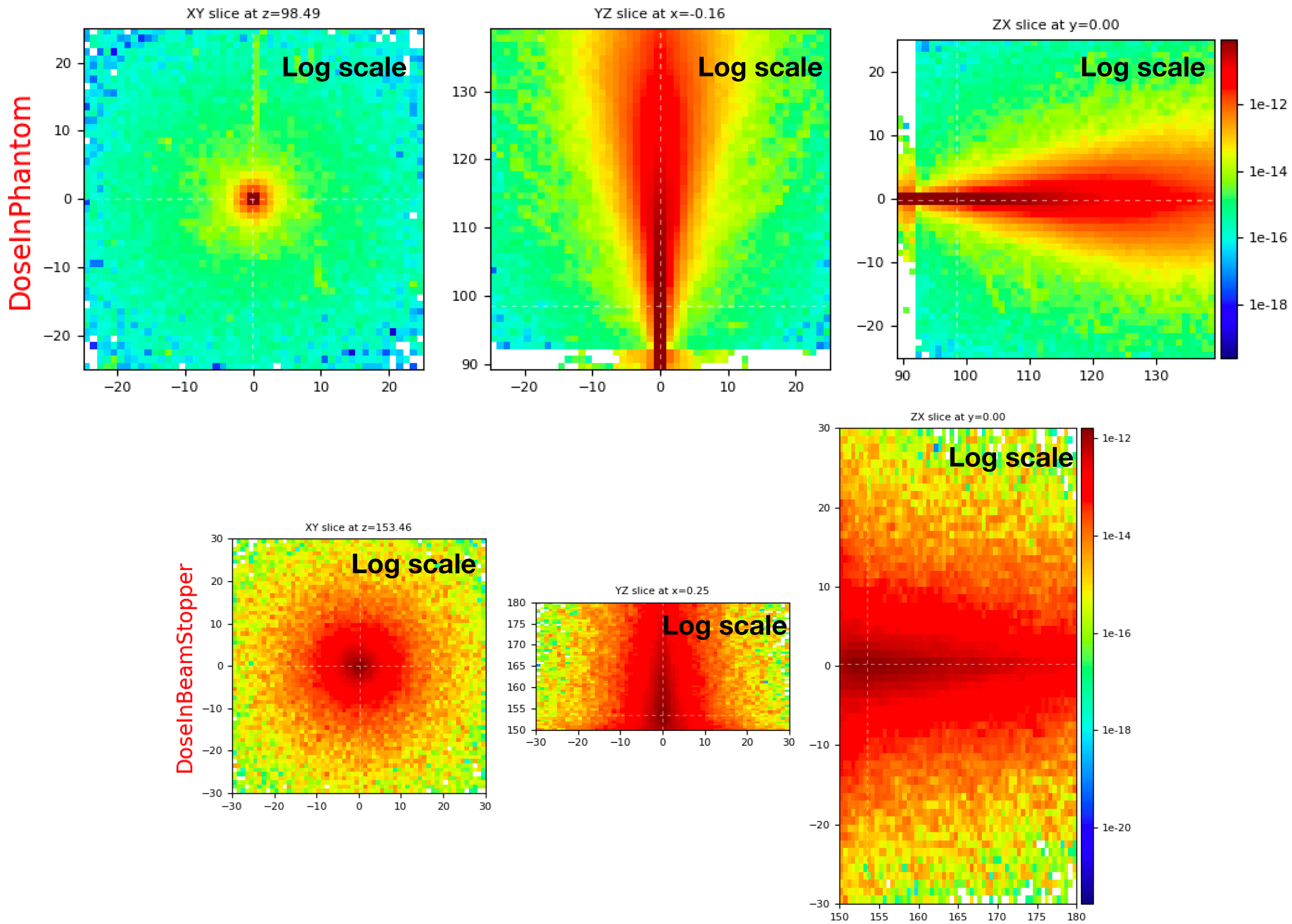
These results will be used for the design/adaptation of the laboratory that will host the accelerator.

WORK IN PROGRESS

Radioprotection: Interactions simulation

- I simulated a **water phantom** placed at the end of the final accelerating section to observe the dose distribution in anticipation of Radiobiology experiments. Then I add a **beam stopper** after the phantom in order to dimension it.





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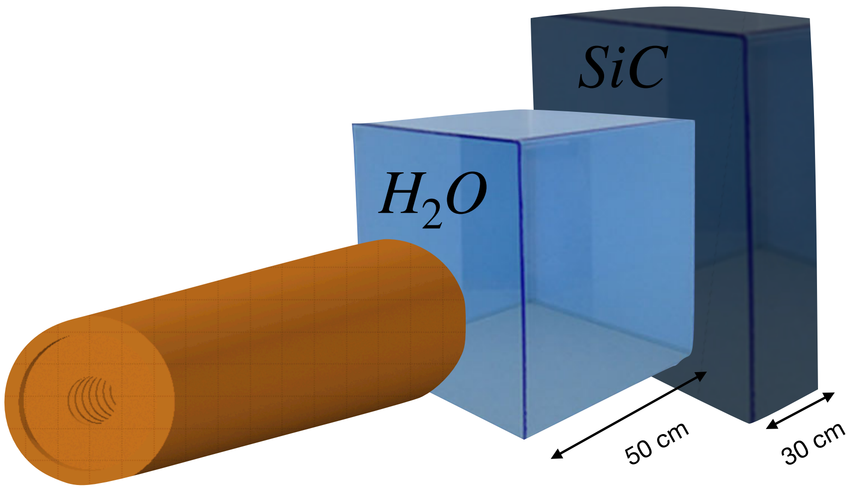
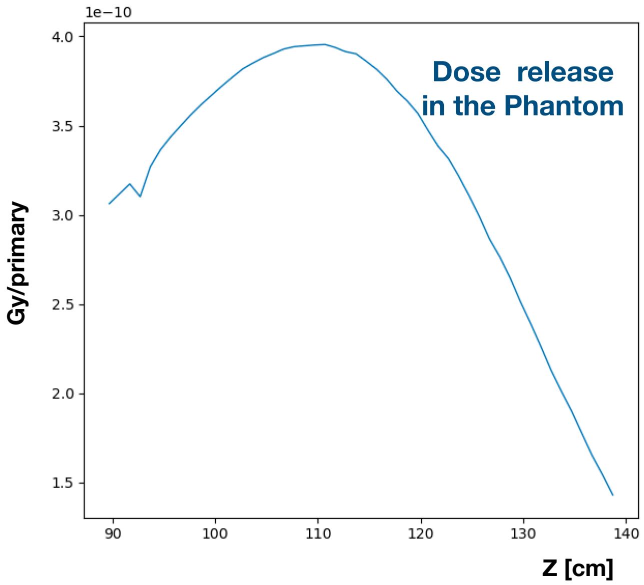
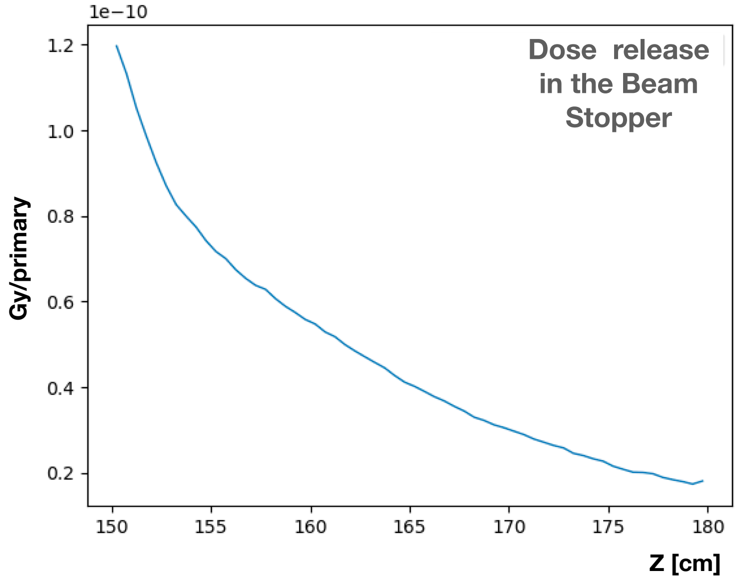




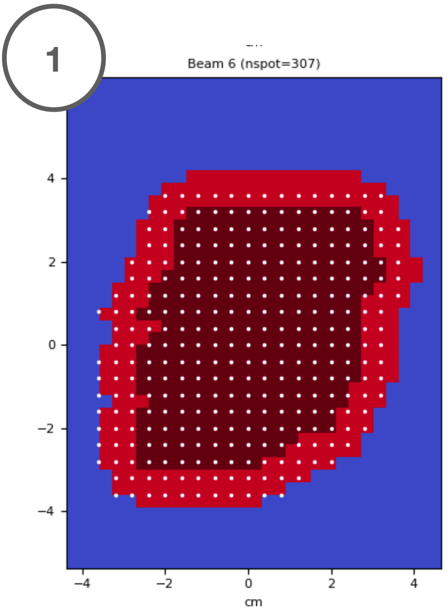


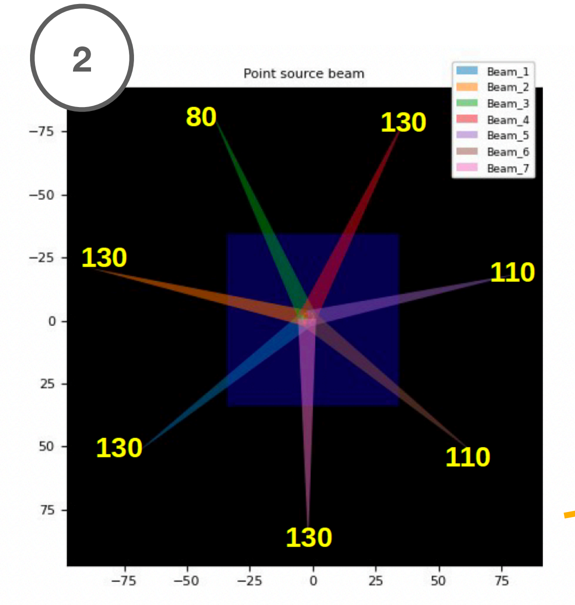
Radiation protection studies are a fundamental aspect as they ensure workers safety, regulatory compliance and ensuring the operability of the facility to enable its utilization.

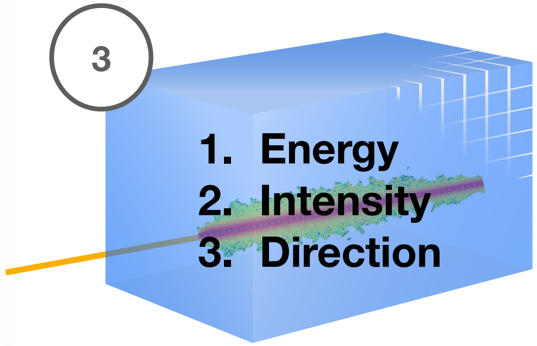
TPS for VHEE: input model

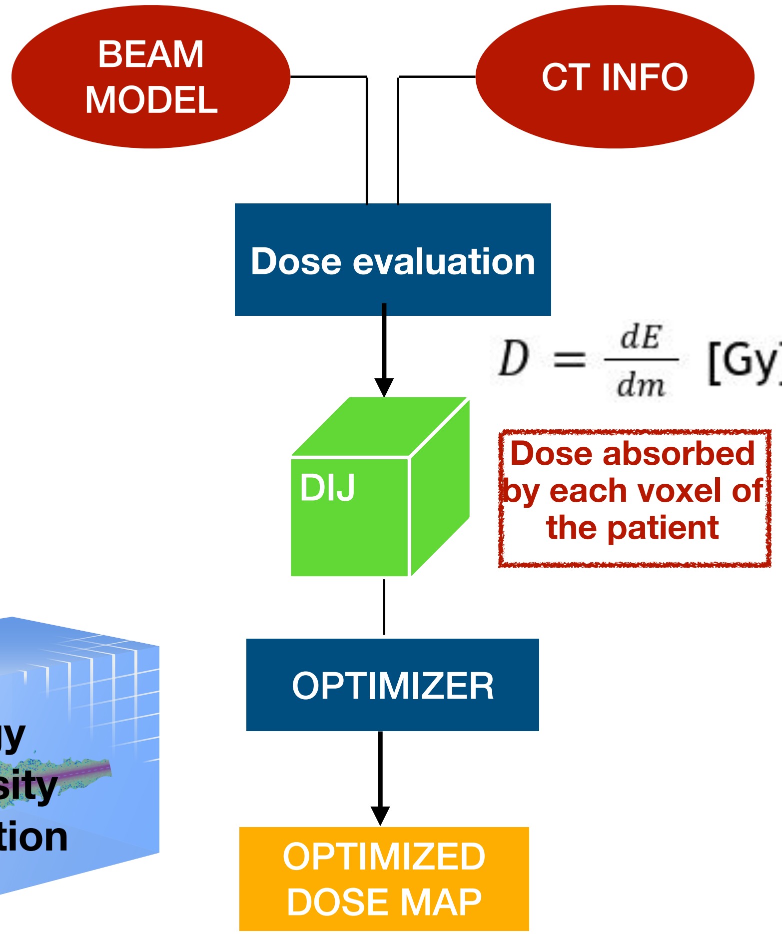
With the current machine design, the primary ingredients for planning are:

1. Active scanning with pencil beams (PB) delivery.
2. Multi field irradiation;
3. Optimisation of the parameters.









$$D = \frac{dE}{dm} \text{ [Gy]}$$

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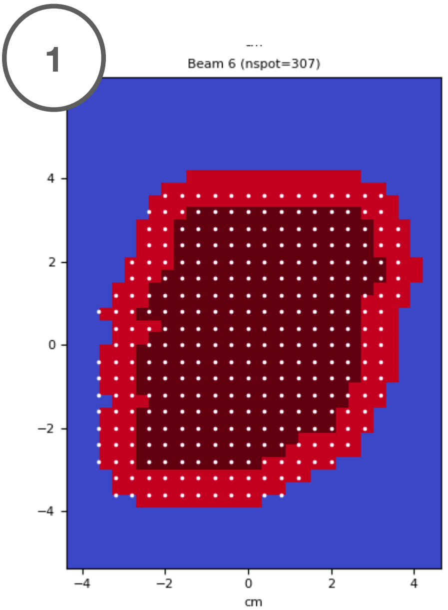
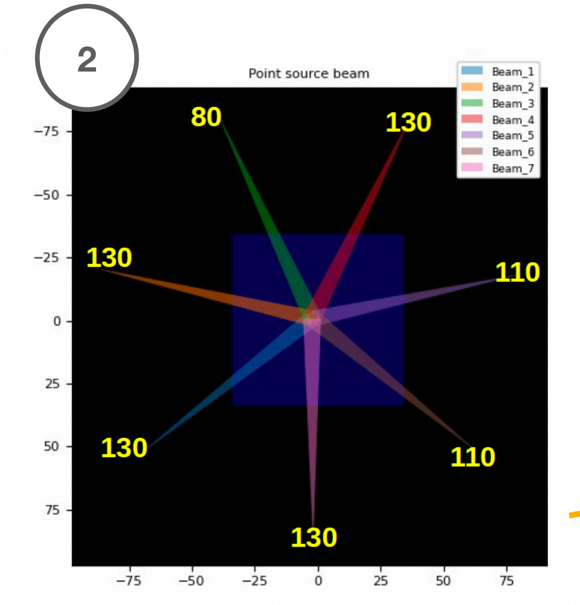
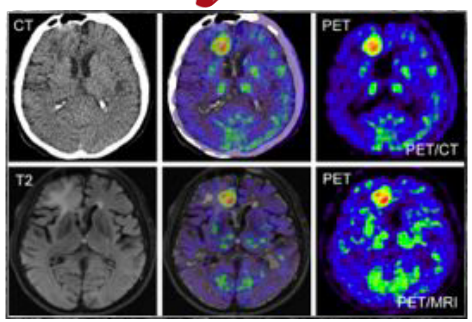
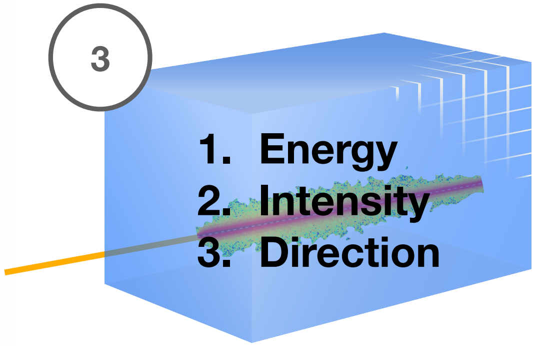
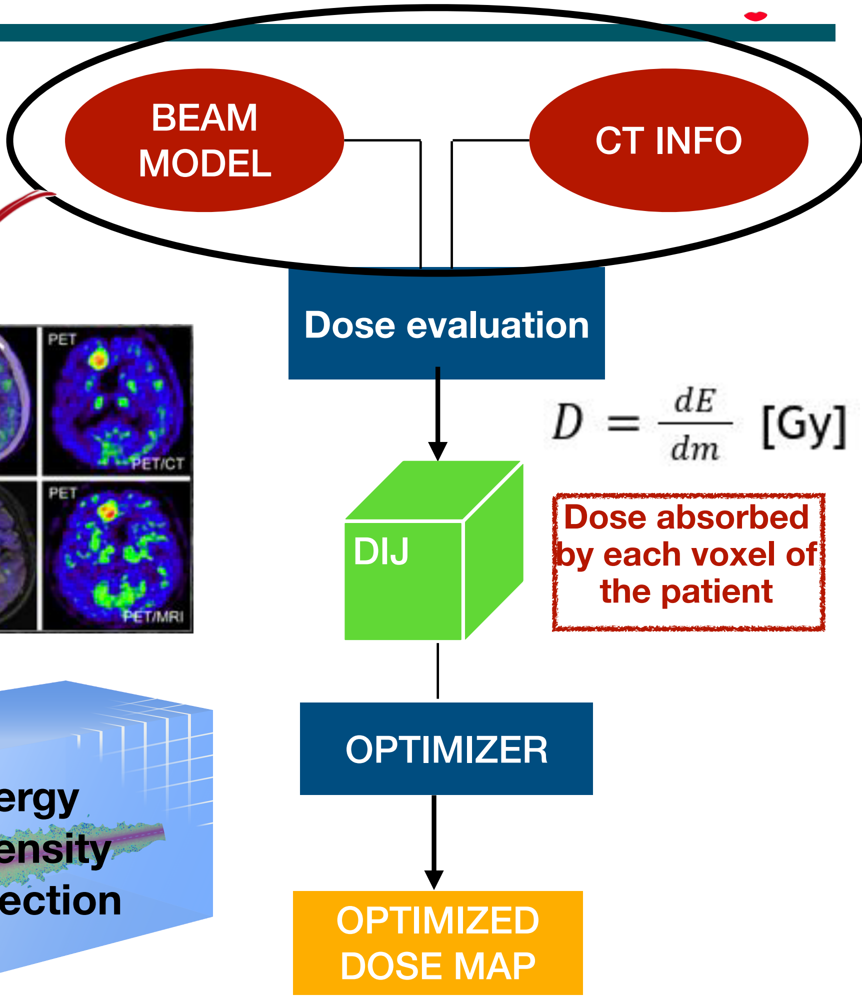




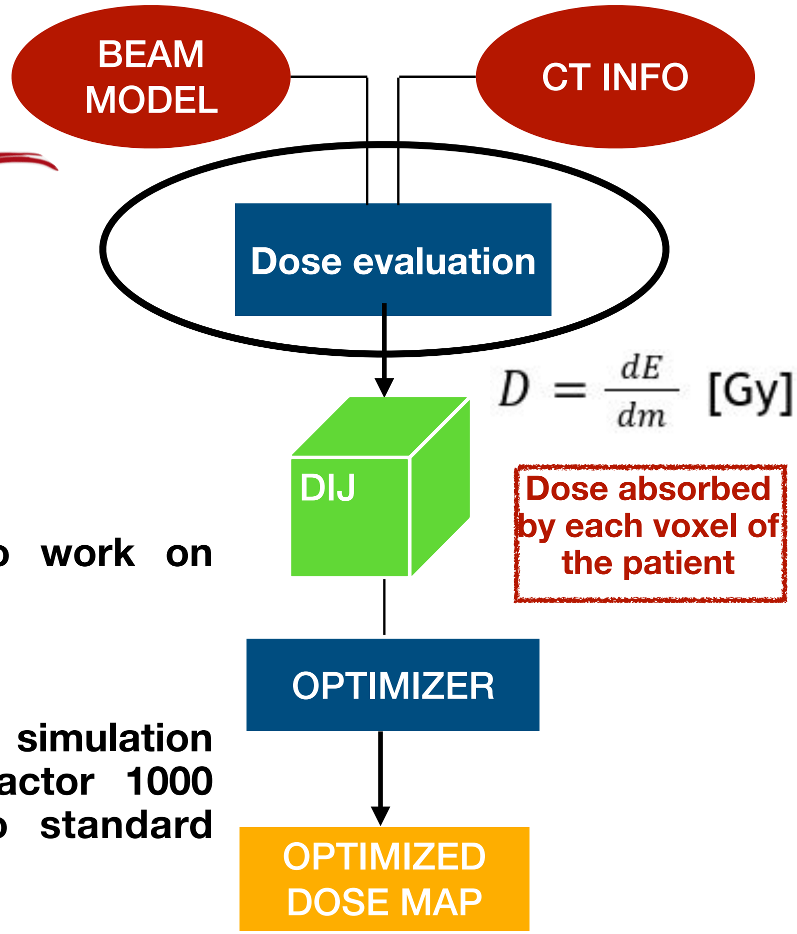






TPS for VHEE: Dose Evaluation

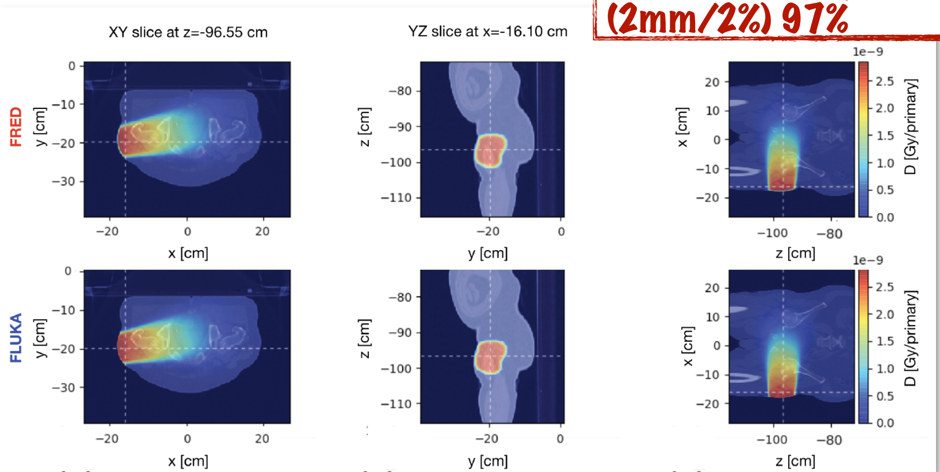
The majority of the TPS softwares use an **analytical** dose evaluation approach, which may be **not so accurate**. So far to make a more precise calculation using a MC simulation was not possibile due to computational cost. Our solution is to use **FRED**.



Dose evaluation with FRED

The FRED MC has been developed to allow a **fast optimization of the TPS** in Particle Therapy, while keeping the dose release accuracy typical of a MC tool.

Gamma-index pass-rate (2mm/2%) 97%



Developed to work on GPU

Reduces the simulation time by a factor 1000 compared to standard MC

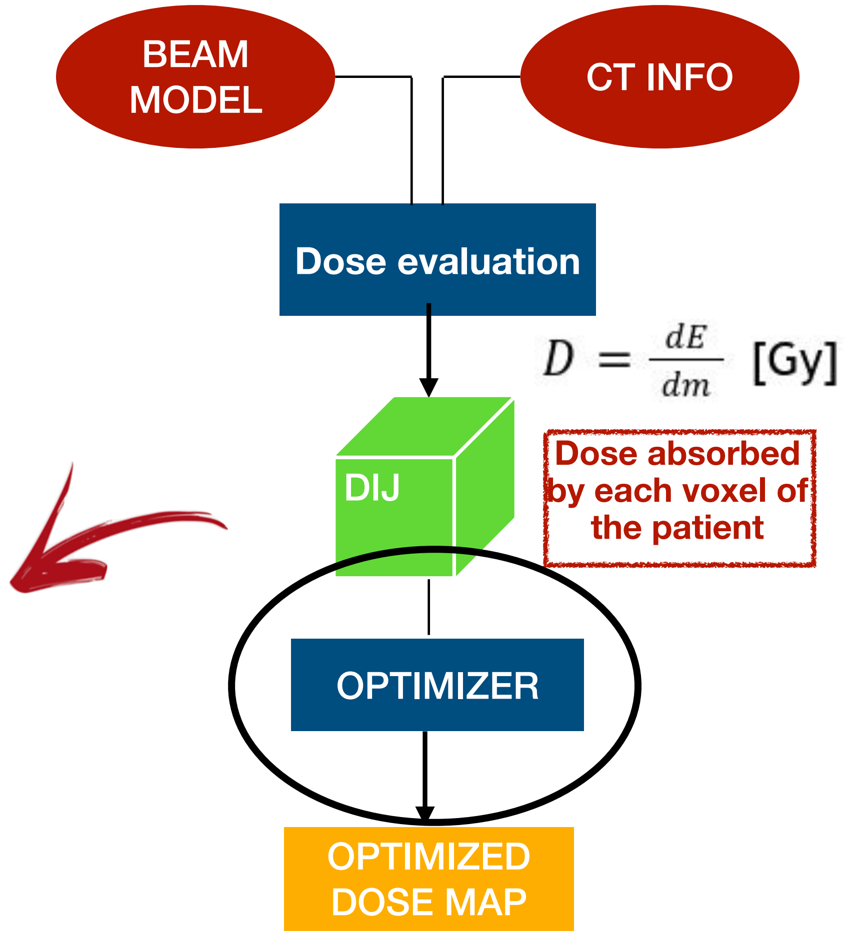
G. Franciosini et al., GPU-accelerated Monte Carlo simulation of electron and photon interactions for radiotherapy applications. Physics in Medicine and Biology; 2023, DOI: 10.1088/1361-6560/aca1f2

TPS for VHEE: Cost Function

The main **goal** is to select:

1. The **Energy** of each field;
2. The **number of particles** of each PB.

1 In order to **maximize tumor coverage** e **minimize the dose delivered to the normal tissue,** the algorithm explore different set of energies and fluences.



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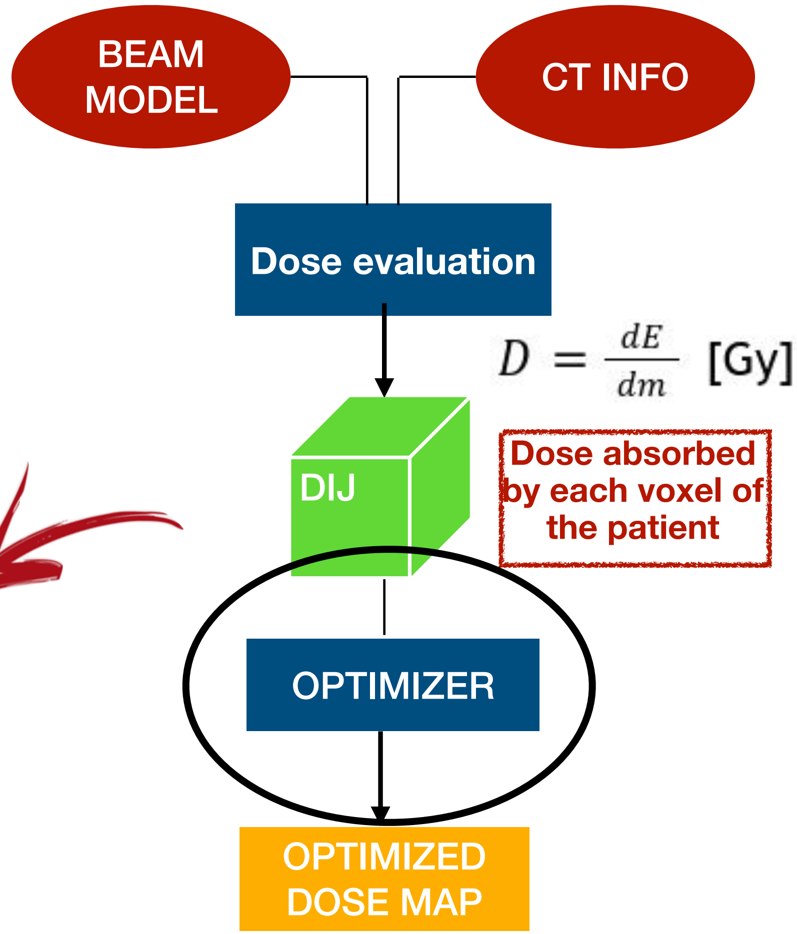

1 In order to **maximize tumor coverage** e **minimize the dose delivered to the normal tissue,** the algorithm explore diff

2 **Calculate the Cost Function for a given configuration**

Dose absorbed by the voxel — Planned dose — Plan factor

Voxel based

$$\chi^2 = \sum_{i \epsilon PTV} \omega_i \frac{(d_i - D_{PTV})^2}{d_i^2} + \sum_{i \epsilon OAR} \omega_i \frac{(d_i - D_{OAR})^2}{d_i^2} * g(d_i - D_{OAR})$$

$$d_i = \sum_{j=1}^{N_j} N_j D_{ij}$$

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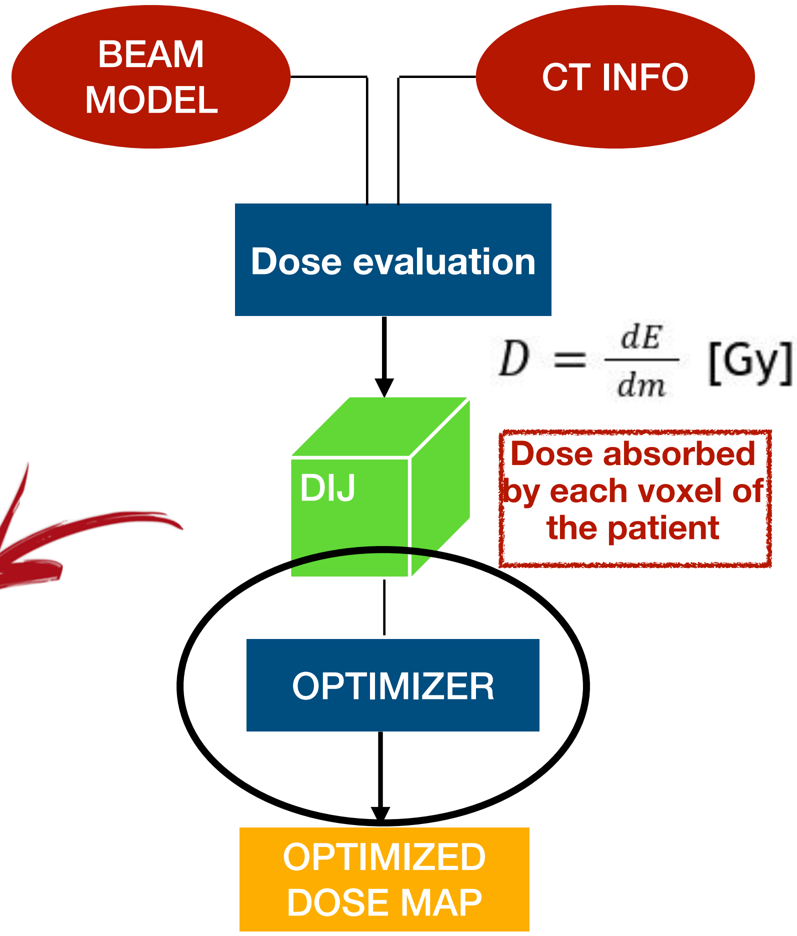


1 In order to **maximize tumor coverage** e **minimize the dose delivered to the normal tissue,** the algorithm explore diff

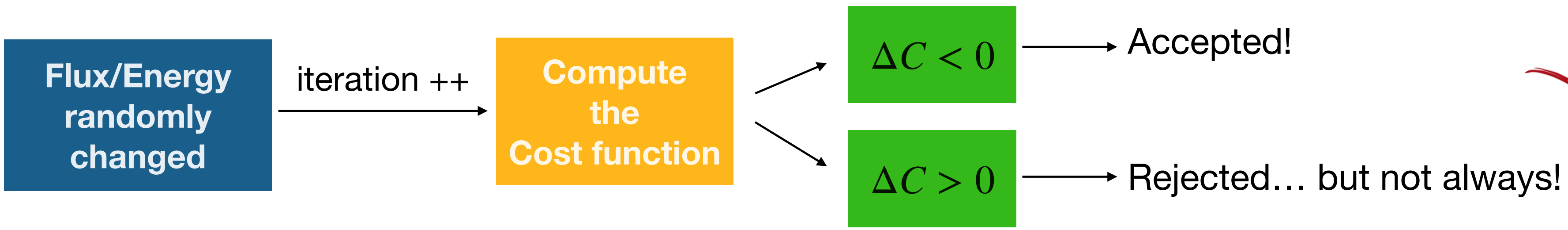
2 **Calculate the Cost Function for a given configuration**

3 **Minimise the Cost Function**

Derivative based minimization methods in current use do not work effectively to select both the energy of the beam and the fluence of the PB.

TPS for VHEE: Minimisation methods

Annealing minimisation algorithms: are a class of probabilistic optimization techniques used to solve search and optimization problems.



$$P = e^{-R(T)}$$

1. The minimization algorithm, **randomly varying the PB fluence and the beam energy**, defines specific configurations.

2. At each iteration, **the change induced in the cost function is evaluated:** if the cost is less than value obtained in the previous iteration then the grain is accepted and the state stored.

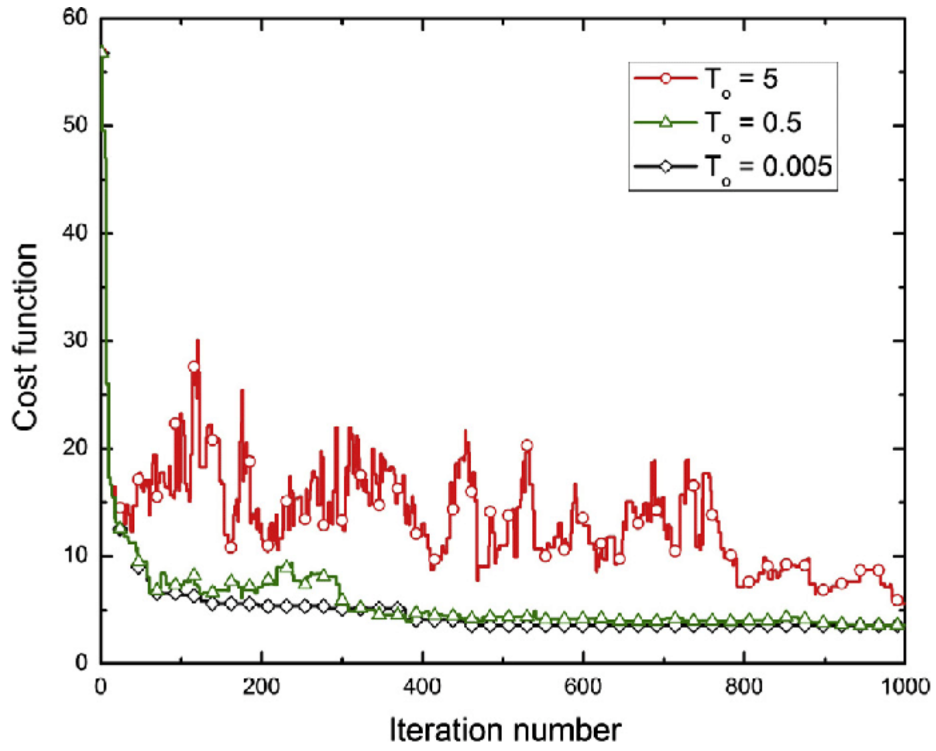
It accepts new solutions if they improve the value of the objective function or with a certain probability, even if they are worse. The probability of acceptance gradually decreases, allowing the algorithm to escape local optima and search for global solutions.

Annealing minimisation algorithms: are a class of probabilistic optimization techniques used to solve search and optimization problems.

$$P = e^{-R(T)}$$

- The algorithm maintains a parameter known as **"temperature"** that controls the probability of accepting worse solutions.

- It **converges** when the algorithm reaches a solution that meets the predefined termination criteria, such as an acceptable objective value or a maximum number of iterations.

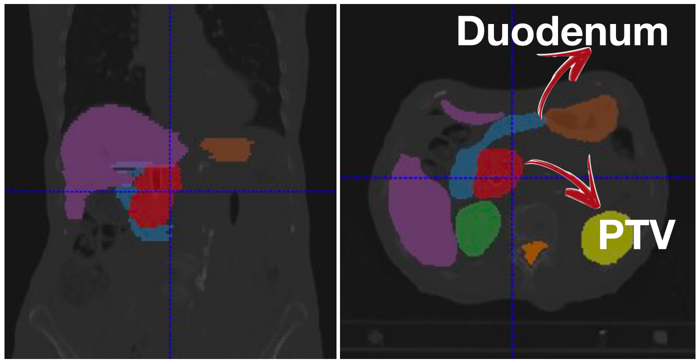


TPS for VHEE: Results

Best candidate for FLASH treatments!

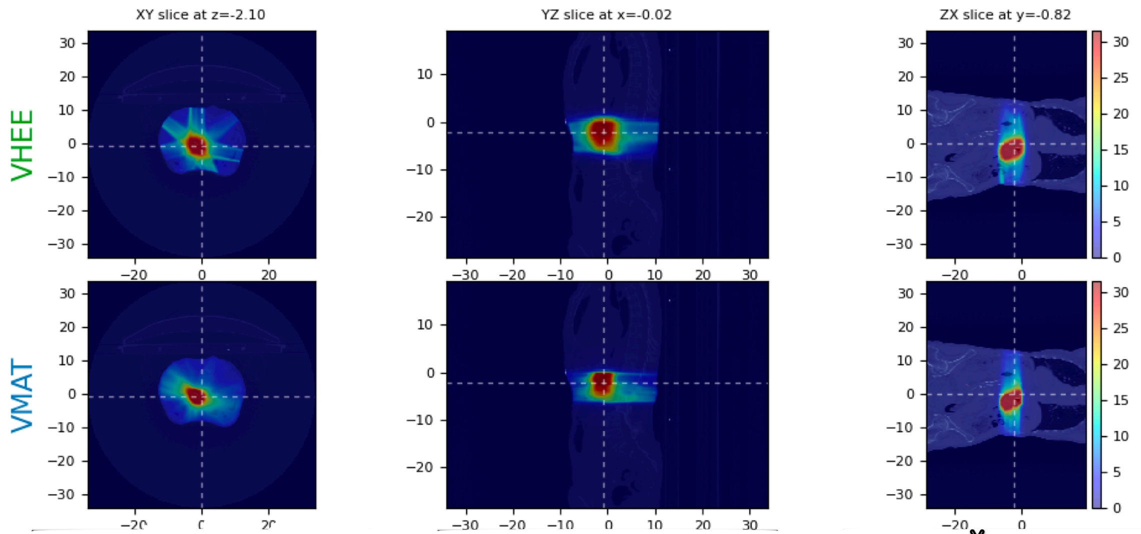
Real pancreatic treatment at Policlinico Universitario Campus Bio-Medico, Rome

The effectiveness of radiotherapy is limited by the toxicity induced in OARs, particularly in the duodenum.



- Patient with pancreatic cancer, was treated with VMAT technique using photons, delivering **30 Gy** in **5 fractions**;

- To simulate the VHEE treatment the dose was evaluated starting from the same number of field and direction used in the actual treatment.



TPS for VHEE: Results

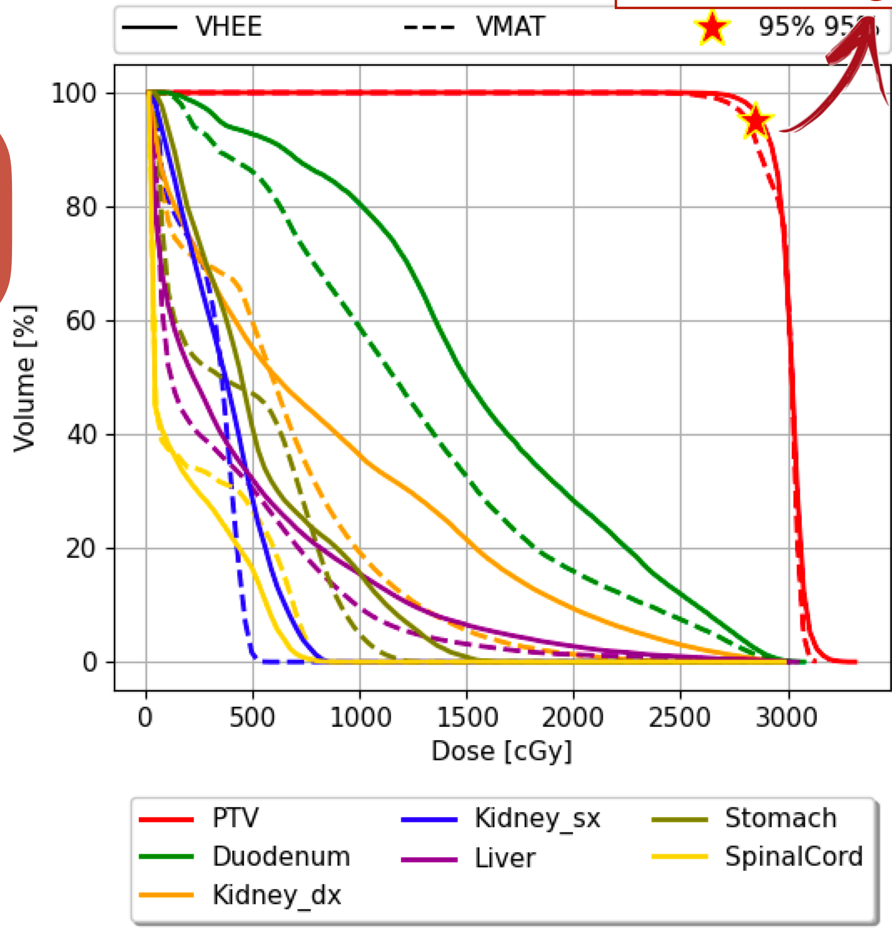
Real pancreatic treatment at Policlinico Universitario Campus Bio-Medico, Rome

GOAL:
PTV coverage
+
Duodenum sparing

DVH quantitatively represents the distribution of radiation dose within a region of interest.

Pancreas case	Constraints	VMAT	VHEE 7 field
PTV Boost	$V_{95\%} \leq 95\%$ $D_{max} \leq 107\%$	99.13 % 83.35 %	98.01 % 71.26 %
Duodenum	$D_{max} \leq 35\ Gy$	29.98 Gy	29.50 Gy
Spinal cord	$D_{max} \leq 18\ Gy$	9.42 Gy	9.09 Gy

PTV coverage!



TPS for VHEE: Results

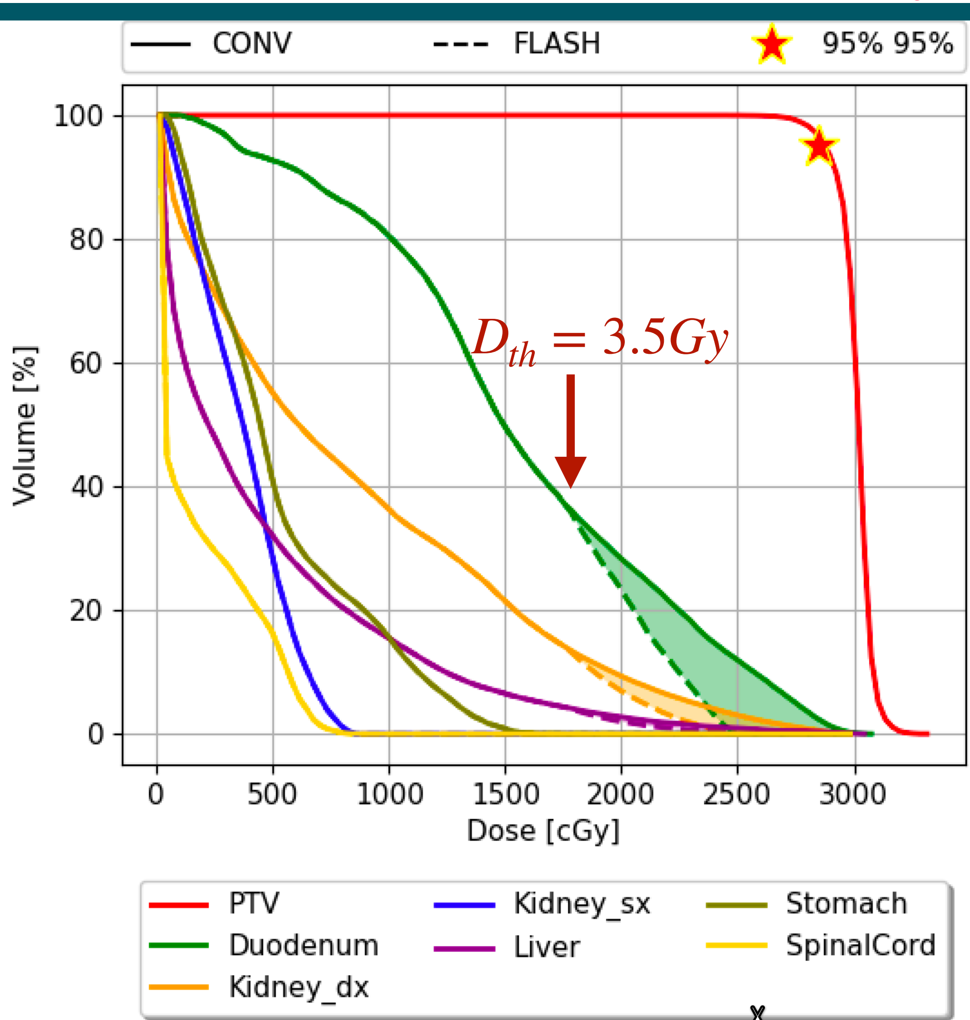
FLASH MODIFYING FACTOR

Used to adapt the dose rate or the amount of radiation delivered to achieve desired effects based on the specific patient's needs and treatment requirements

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

0.6

When a FMF different from 1 is implemented, the organs sparing improve significantly: the dose absorbed by the duodenum is reduced, preventing lesions that could be fatal.



*Bohlen et al. doi:https://doi.org/10.1016/j.ijrobp.2022.05.038

Next steps

Implementation of **volumetric cost function**: volumetric and voxel-based optimizations can be complementary and are often used together to maximize treatment quality. The choice between the two depends on patient characteristics, disease features, and treatment goals.

Flash dose optimization: implementing in the algorithm the model that parameterizes the effect in order to directly optimize the modified dose.

Adapting radiation protection studies to the final machine design to ensure that the laboratories where it will be placed are suitable for its operation.

Thanks for the attention!!!

Publications

- A. De Gregorio et al., Measurements of the 16O cross section on a C target with the FOOT apparatus. Nuovo Cimento della Societa Italiana di Fisica C; 2022,DOI: 10.1393/ncc/i2022-22194-4
- M. De Simoni et al., A Data-Driven Fragmentation Model for Carbon Therapy GPU-Accelerated Monte-Carlo Dose Recalculation. Frontiers in Oncology; 2022,DOI:10.3389/fonc.2022.780784
- 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, DOI:10.3389/fonc.2022.929949
- A. Trigilio et al., The FlashDC project: Development of a beam monitor for FLASH radiotherapy. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2022, DOI: 10.1016/j.nima.2022.167334
- M. Toppi et al., Elemental fragmentation cross sections for a 16 O beam of 400 MeV/nucleon kinetic energy interacting with a graphite target using the FOOT ΔE-TOF detectors. Frontiers in Physics, section Medical Physics and Imaging, 2022, DOI: https://doi.org/10.3389/fphy.2022.979229
- A.C. Kraan et al., Calibration and performance assessment of the TOF-Wall detector of the FOOT experiment. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2023, DOI: 10.1016/j.nima.2022.167615
- L. Galli et al., The fragmentation trigger of the FOOT experiment. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2023, DOI: https://doi.org/10.1016/j.nima.2022.167757
- A. Alexadrov et al., Characterization of 150 μm thick silicon microstrip prototype for the FOOT experiment. Journal of Instrumentation; 2022, DOI: 10.1088/1748-0221/17/12/P12012
- L. Faillace et al., Perspectives in linear accelerator for FLASH VHEE: Study of a compact C-band system. Physica Medica; 2022, DOI: 10.1016/j.ejmp.2022.10.018
- D. Rocco et al., TOPS fast timing plastic scintillators: Time and light output performances. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment; 2023, DOI: 10.1016/j.nima.2023.168277
- G. Franciosini et al., GPU-accelerated Monte Carlo simulation of electron and photon interactions for radiotherapy applications. Physics in Medicine and Biology; 2023, DOI: 10.1088/1361-6560/aca1f2
- L. Giuliano et al., Proposal of a VHEE Linac for FLASH radiotherapy. Physics in Medicine and Biology; 2023, DOI: 10.1088/1742-6596/2420/1/012087
- A. Muscato et al., Treatment planning of intracranial lesions with VHEE: comparing conventional and FLASH irradiation potential with state-of-the-art photon and proton radiotherapy. Frontiers in Physics; 2023, DOI: 10.3389/fphy.2023.1185598

Conferences and Seminars

- iWoRiD: 22nd International Workshop on Radiation Imaging Detectors. Title "The timing detectors of the FOOT experiment: the charge changing cross sections measured using 16O beams of 400 MeV/u energy.", 27 June-1 July 2021; **Oral Presentation**.
- SIF: 107th Congresso Nazionale Società Italiana di Fisica. Title "Measurements of 16O fragmentation cross sections on C target with the FOOT apparatus.", 13-17 September 2021; **Oral Presentation**.
- ECMP: 4th European Congress of Medical Physics. Title "A feasibility study of deep stated tumor treatments combining FLASH effect and Very High Energy Electron beams.", 17-20 August 2022; **Oral Presentation**.
- ICNFP: XII International conference on new frontiers in Physics. Title "Status of the FOOT experiment and first measurements of 16O fragmentation cross sections on C target.", 10-23 July 2023, https://indico.cern.ch/event/1199102/timetable/; **Oral Presentation**.
- IMACS: International association for Mathematics and Computers in Simulation 21st world congress. Title "A new TPS for FLASH VHEE beams: the implementation of quantum based algorithms.", 10-23 July 2023, https://www.imacs2023.eu/index.php/IMACS2023/IMACS2023; **Oral Presentation**.

Award and Scholarships

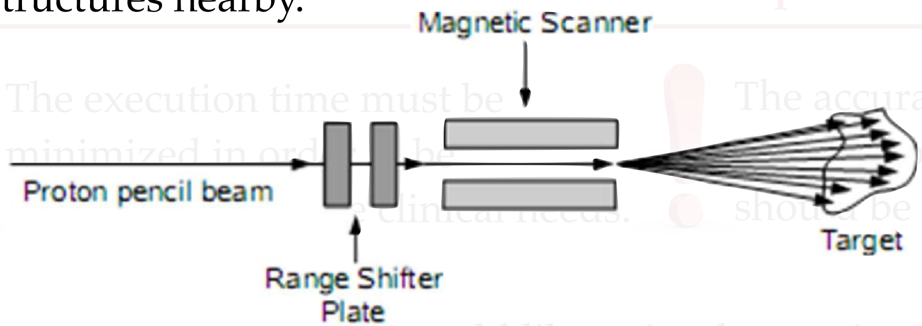
- **Best Oral Communication, SIF 2021**
  "Measurements of ^{16}O fragmentation cross sections on C target with the FOOT apparatus".

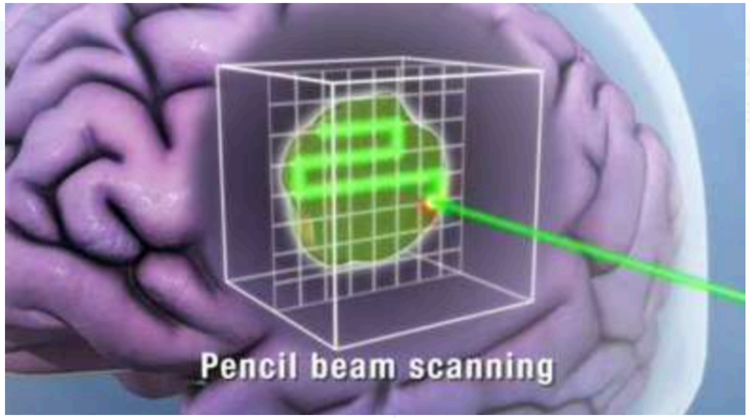
Come fai..SBAI

TPS FOR VHEE

What is a Pencil Beam (PB)

- Pencil beam scanning uses magnets to steer the particle beam, creating a customized, three-dimensional delivery shape. During treatment, radiation is deposited layer by layer, conforming the dose to the specific shape of your tumor and destroying cancer cells while preserving critical structures nearby.





Each beam is divided into fundamental units called **Pencil Beams** (width ~mm)

1. Optimize **field direction**; ✗
2. Field **Energy** and **Pencil Beam flux** optimization **simultaneously**; ✓
3. **Dose-rate** evaluation (in case of FLASH treatments). ✓

Algorithm WORK FLOW

1. Beam Model: how many fields are planned for the treatment and their directions;
2. CT info: the input imaging of the patient (Planned Target Volume, PTV+ Organs at Risk, OARs) discretized in voxels;

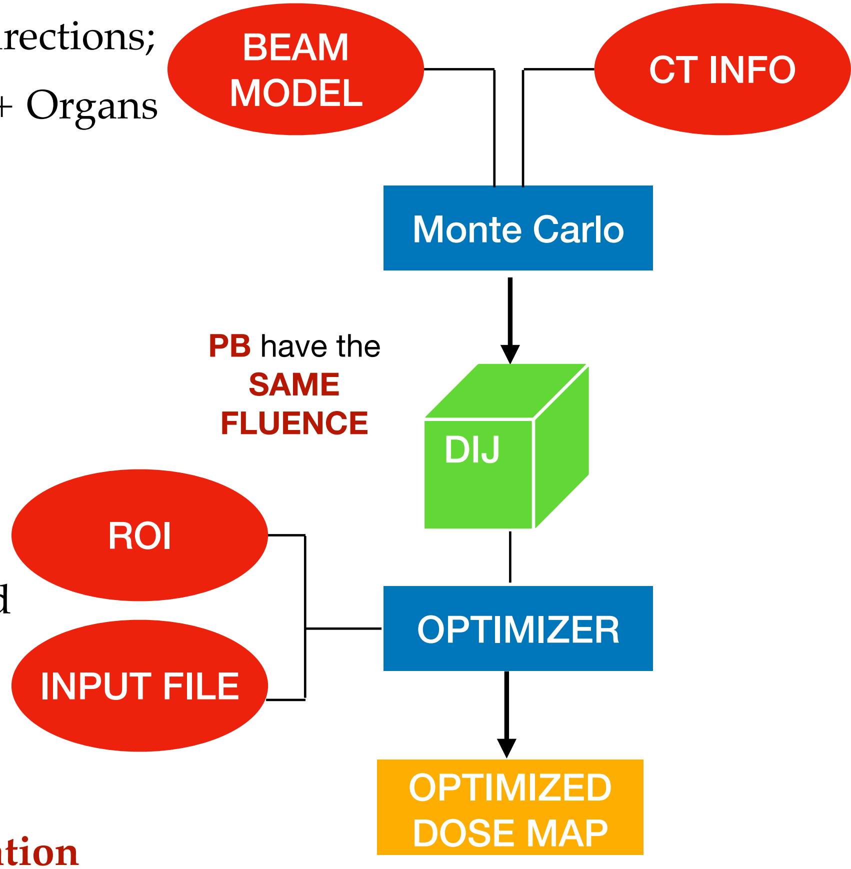
These two inputs are given to a Monte Carlo software: the MC simulate the interaction between the particles of the beam and the patient body and gives as output the **dose map** of the patient, **called Dij.**

$$D = \frac{dE}{dm} \text{ [Gy]}$$

Dose absorbed by each voxel of the patient

1. Dij: the matrix in which we save, for each energy beam, the dose absorbed by the body;
2. ROIs: the geometry of the regions of interest, such as the OARs and PTVs;
3. INPUT FILE: a text file summarizing the dosimetric information and the parameters with which we want the algorithm to work.

These inputs are given to the TPS software which uses **minimization methods** in order to optimize the treatment giving as output the optimized dose map with the **most suitable delivery parameters**.



Spot Spacing of the Pencil Beams

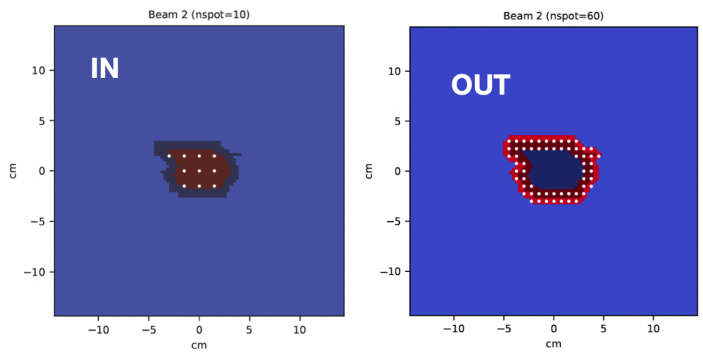
Using FRED we are able to simulate the dose distribution of several beams, the ones planned for the treatment, at different energies.

Doing this, we plan the simulation (using a script called Build Plan) taking into account a **variable Spot Spacing** (SS) between two adjacent PB, depending on where they belong to

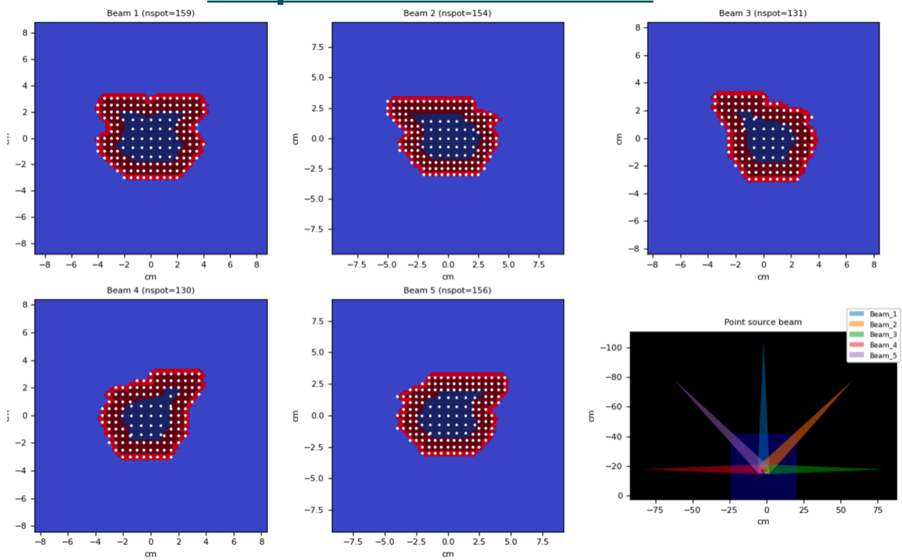
- For each ROI we choose a **margin** within which the pencil beams are densest, with **narrow spot spacing**;
- **Within the region**, on the contrary, pencil beams are simulated with **greater width and spot spacing.**

For example:

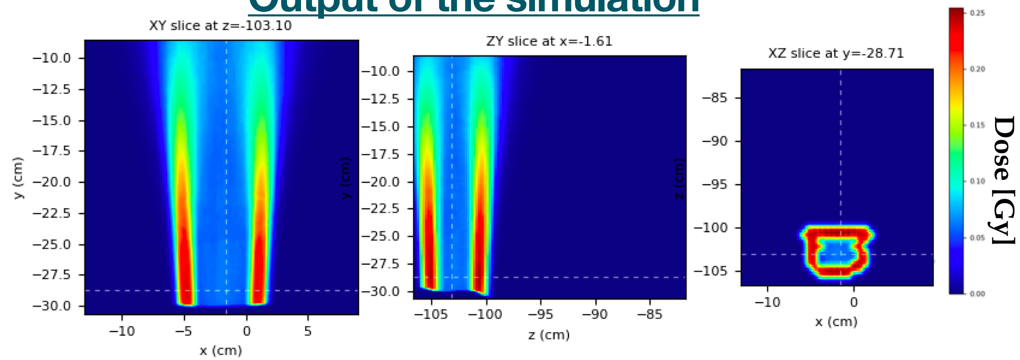
Margin: 1 cm
OUT: ss = 0.75 cm
FWHM = 0.75
IN: ss = 1.5 cm
FWHM = 1.5



Output of the Build Plan



Output of the simulation



Rebinning algorithm

Energy optimization: the problem

- To optimize the energy we have to solve the **dose map problem**: given a PB and a voxel, which is the released dose at energy in the range [70-130]MeV?

Using the current MC approach one could compute the Dij matrix for different energies in the range [70, 130] MeV. Using 3 MeV steps we get **21 Dij matrices**: this means to put in memory the dose matrix that provide for each voxel the dose from each PB at each energy.

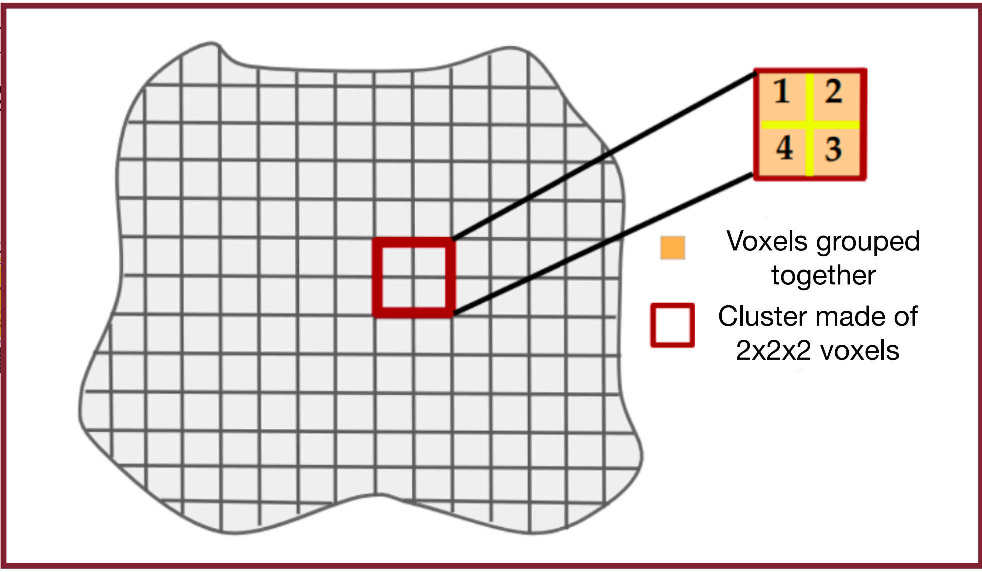
To overcome this limitation a **rebinning algorithm** has been implemented in order to **group voxels** with similar characteristics.

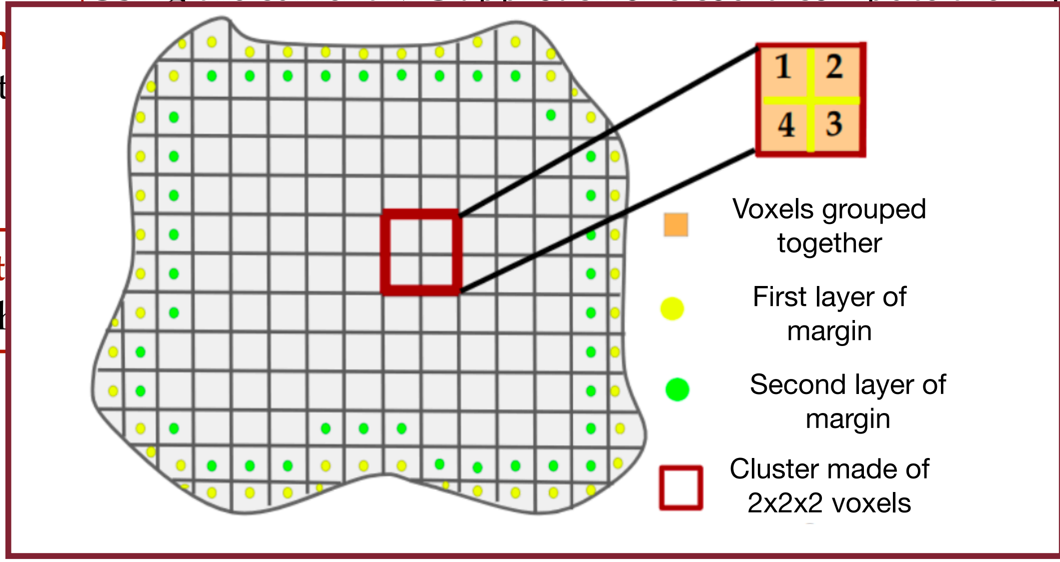
RAM needed $\sim 100 Gbyte$

Rebinning algorithm

Energy optimization: the problem

Using the current MC approach one could compute the Dij





- Voxels belonging to the same region (PTV or OAR) which have **similar density** are **clusterized** together. The cluster size can be adjusted from 8 (2x2x2) to 256 (8x8x8);
- The voxels near the **boundary** of the ROIs are **not grouped**.

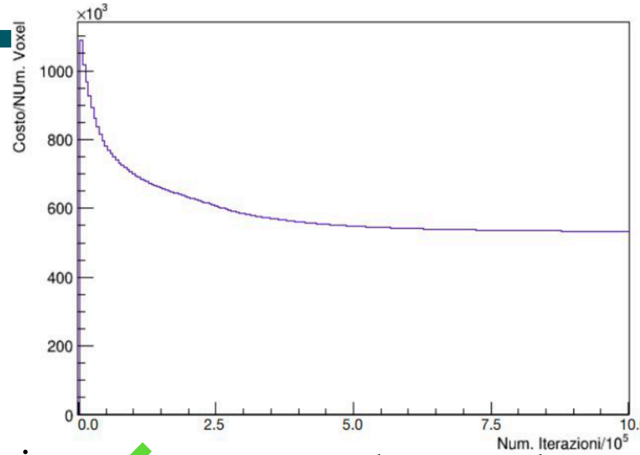
In this way we go from $\sim 2 \cdot 10^5$ to $\sim 4 \cdot 10^4$ voxels (using rebin[4,4,4]) without **any loss of resolution**

Optimization process: Minimization methods

- The algorithm **reach the convergence** and take for good the last configuration when:

1. The maximum number of iterations (set by the user) is reached;
2. A condition on the cost variation is satisfied: $|\frac{\Delta C}{C}| < \epsilon$

Arbitrary parameter

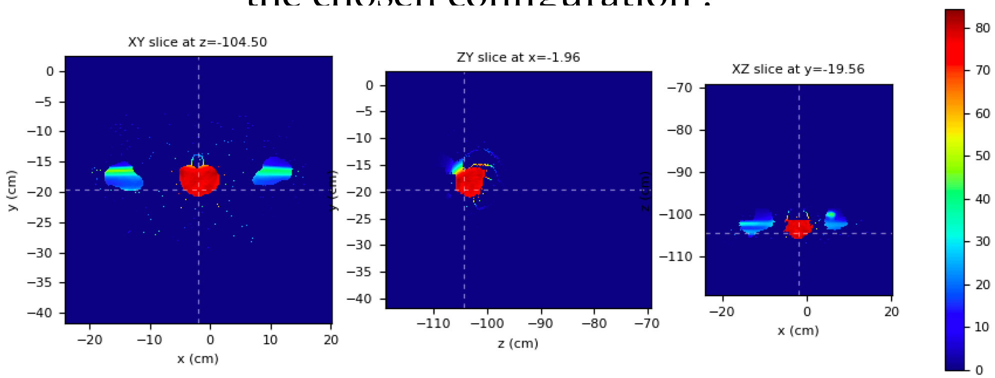


As output the software provides:

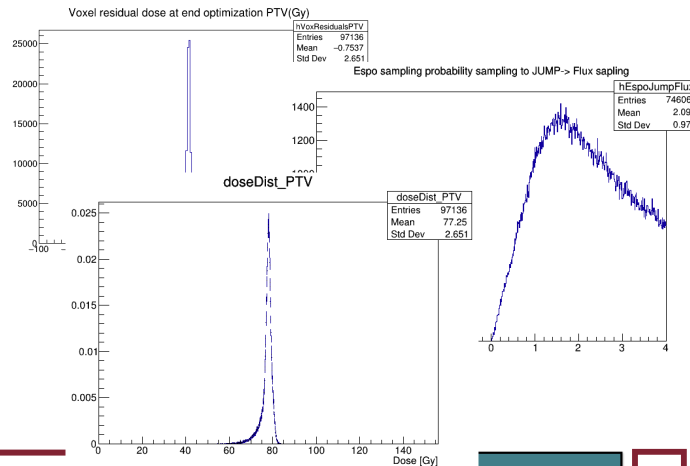
✔ A **file.txt** where the energy for each field and the number of particle for each PB are reported.

```
 5
0  130  70
1  110  70
2  130  57
3  130  58
4  110  68
0  0    513    21706    33617
0  1    306    25686    38791
0  2    828    19949    34031
0  3    0    25812    40644
0  4    0    32028    47888
0  5    0    24089    42379
0  6    442    21539    35315
0  7    125    26100    41419
0  8    216    19958    36403
0  9    0    4442    8616
0  10    769    8685    11262
0  11    319    10349    13475
0  12    396    11077    14876
0  13    0    8816    13270
0  14    0    6885    11186
0  15    0    5045    9192
```

✔ A **file.mhd:** the optimized dose map in which the values of dose absorbed by each voxel of the patient are saved in the chosen configuration .



✔ A **file.root** where all the graphics and plots regarding the process are stored.

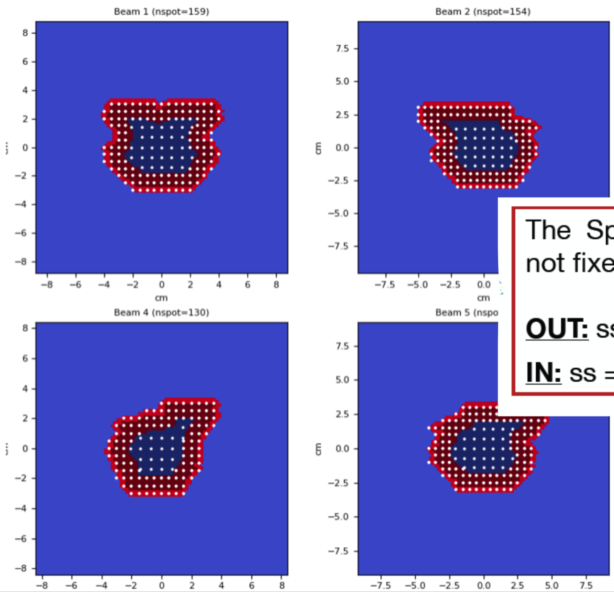


Some results: Prostate Cancer

Real IMRT prostate treatment at Policlinico Umberto I hospital, Rome

- Patient with intermediate-risk prostate cancer, was treated with conventionally fractionated IMRT of **78 Gy** in **39 fractions**;
- Using FRED we have simulated the treatment, planned using 5 fields with energies that go from **70 MeV to 130 MeV** (step of 10 MeV).
- With this choice of SS we obtained:

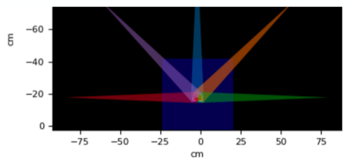
Field	# PB
1	70
2	70
3	57
4	58
5	68

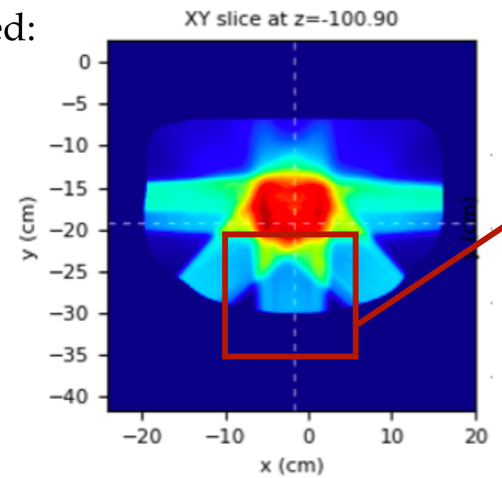


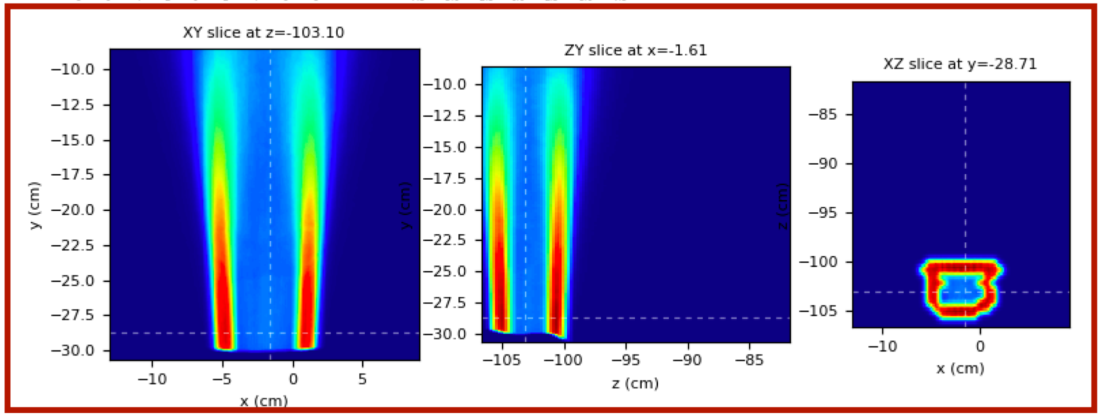
The Spot Spacing between two PB is not fixed. With a 1 cm margin we have:

OUT: ss = 0.75 cm, FWHM = 0.75 cm

IN: ss = 1.5 cm, FWHM = 1.5 cm







Some results: Prostate Cancer

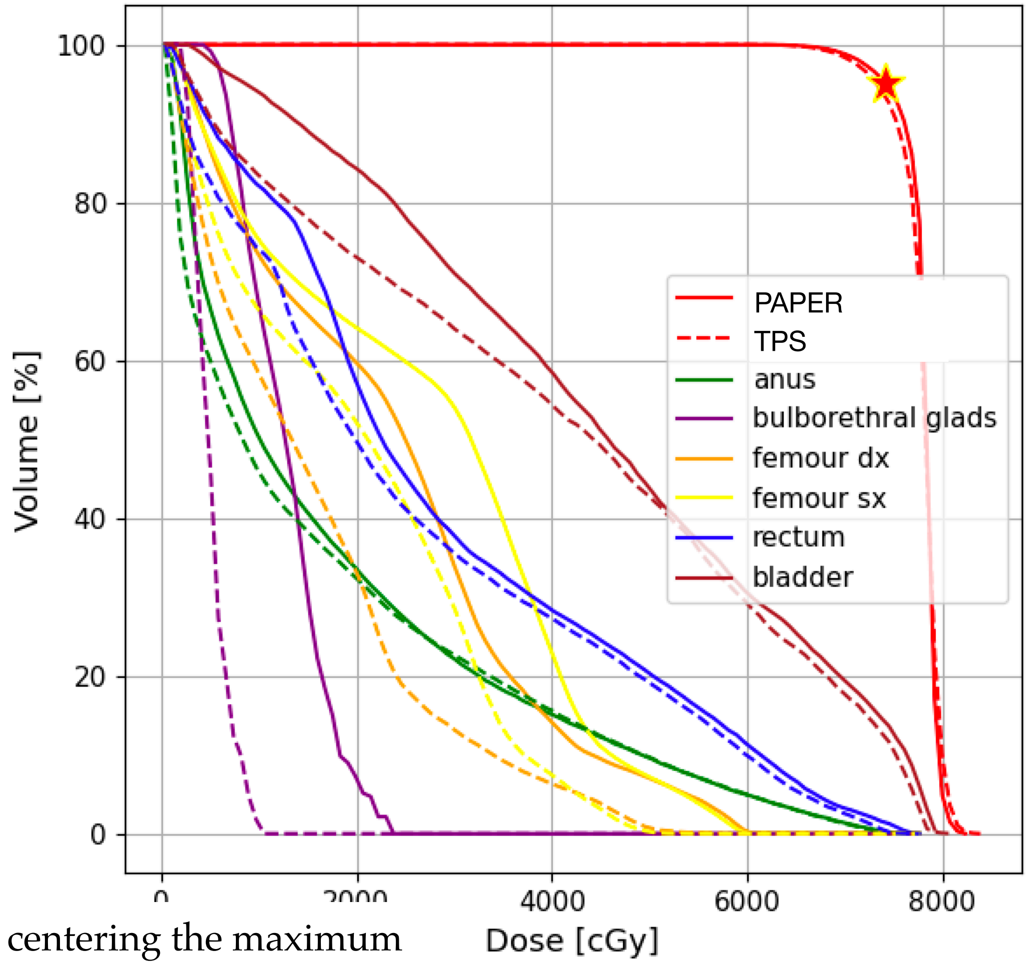
- The first goal was to achieve **at least the result we have obtained with the standard approach** (already published, in which only the number of particle of each PB was optimized) but optimizing the energies of the fields and the PB fluences simultaneously.
- Choosing a proper set of weight for each ROI, we are able to achieve a **better sparing of the Organs at risk** with respect to the standard optimization.
- The energies of the 5 fields chosen by the TPS are:

NEW TPS

Field	E [MeV]
1	120
2	110
3	130
4	130
5	90

OLD (fixed Energies)

Field	E [MeV]
1	70
2	120
3	130
4	130
5	120



The energies were chosen centering the maximum dose release on the isocenter of the PTV.

Some results: Prostate Cancer

- In order to test the rebinning power we also performed an optimization grouping **2x2x1 voxels**.

In this way we obtain **voxels with the dimension of (1.6x1.6x1.6) mm**