13° Congresso Nazionale
aifm 2025
VERONA

VERONA • 16-19 Ottobre 2025

INNOVARE PER CURARE:
LA FISICA MEDICA NEL FUTURO DELLA SALUTE

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Monte Carlo Simulation for Medical Physics

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INFN MILANO

Monte Carlo and Medical Physics

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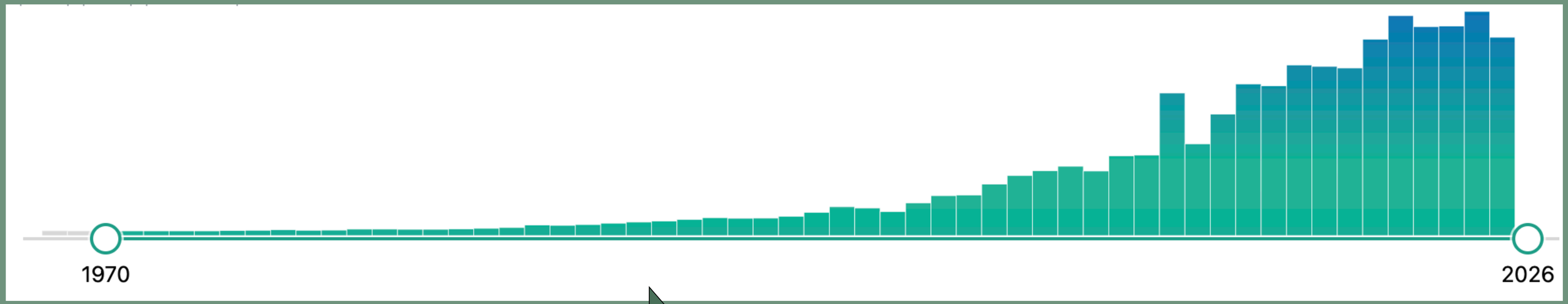
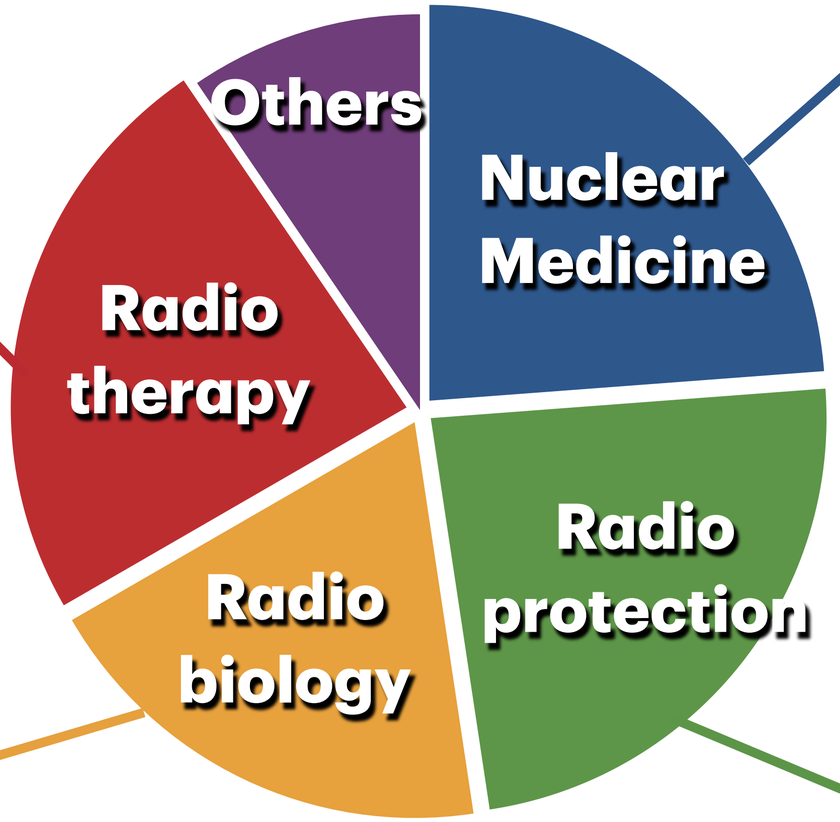


Use of MC is spreading out in medical physics since ‘90s

Monte Carlo and Medical Physics

- External/Internal sources and dosimetry
- Phantom Simulation
- Treatment Planning
- Quality Assurance



- Detector Simulation
- Imaging Correction
- Absorbed Dose Evaluation

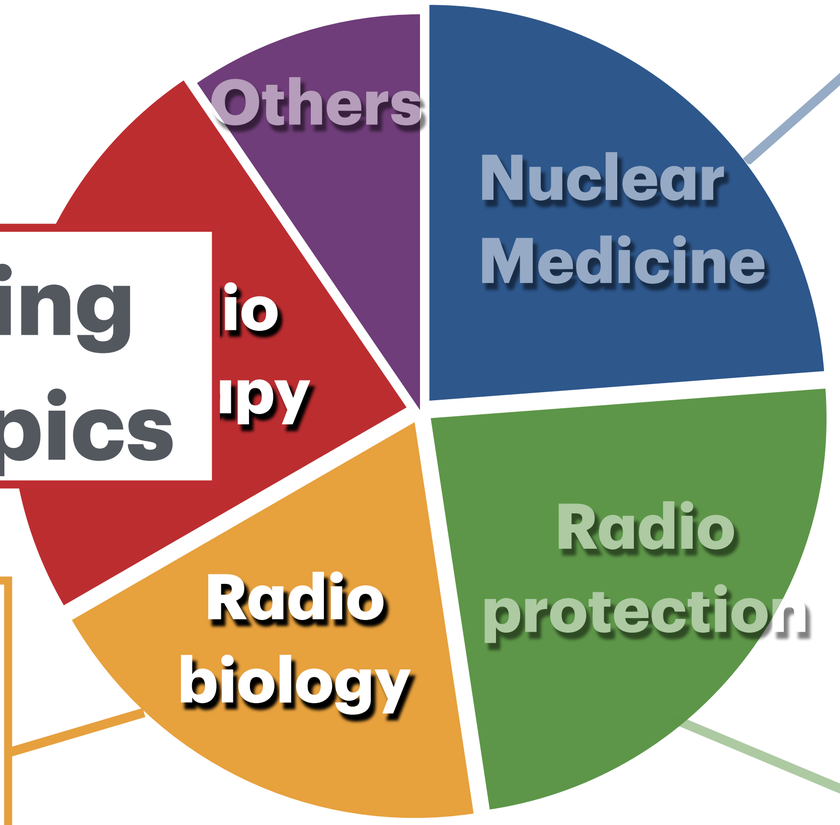
- Biological Dose calculation
- FLASH effect modeling

- Design and commissioning of novel clinical facilities
- Shielding Design of facilities
- Evaluation of ambient dose

Monte Carlo and Medical Physics

- External/Internal sources and dosimetry
- Phantom Simulation

- Treatment Planning in PT + related topics



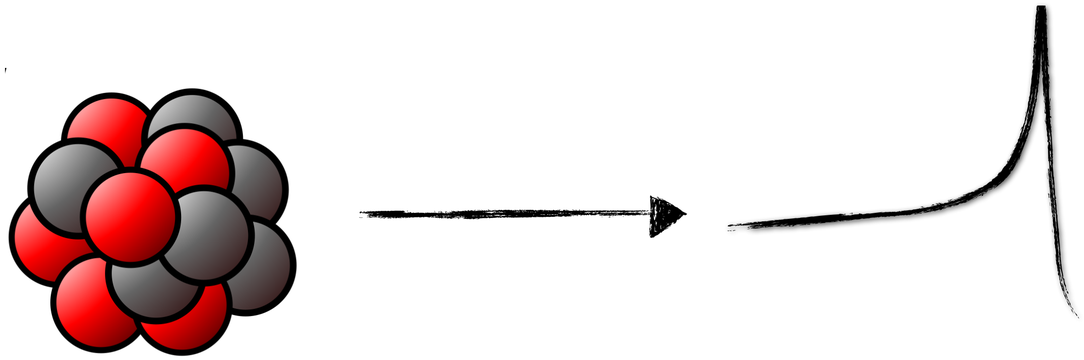
- Detector Simulation
- Imaging Correction
- Absorbed Dose Evaluation

- **Biological Dose calculation**
- **FLASH effect modeling**

- Design and commissioning of novel clinical facilities
- Shielding Design of facilities
- Evaluation of ambient dose

Outlook

1. **Particle Therapy: some background**
2. **Introduction to the radiation transport problem**
3. **The Monte Carlo approach**
4. **Basic ingredients for a Monte Carlo based Treatment Planning in Particle Therapy**
5. **Some Examples**

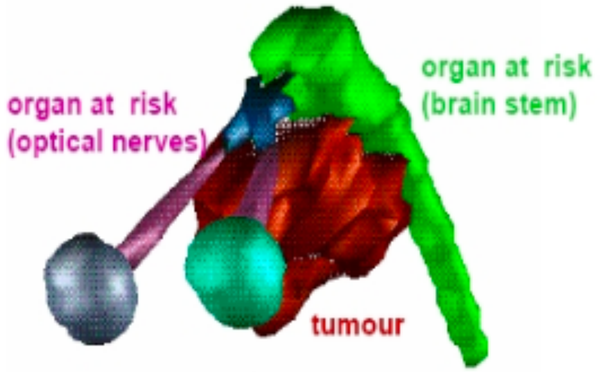


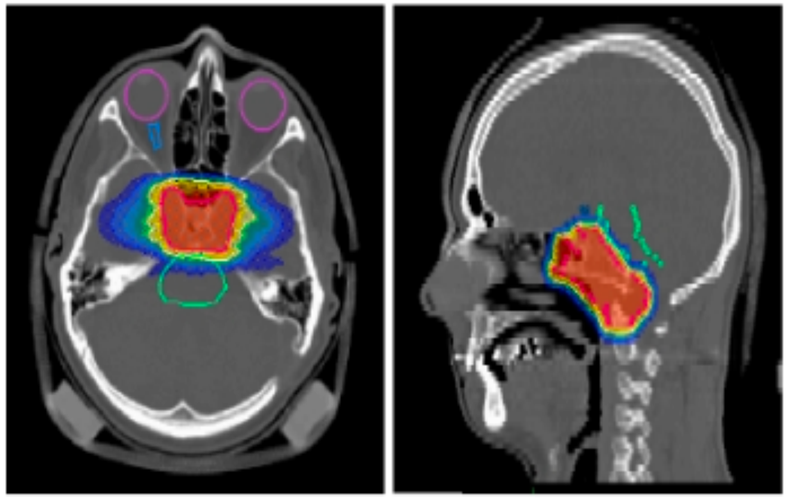
1. Particle Therapy: some background

Radiotherapy: Conventional RT And PT

RADIATIONS

- **Conventional RT:** photons, electrons
- **Particle Therapy:** protons and light ions (^{4}He, ^{12}C, ^{16}O)

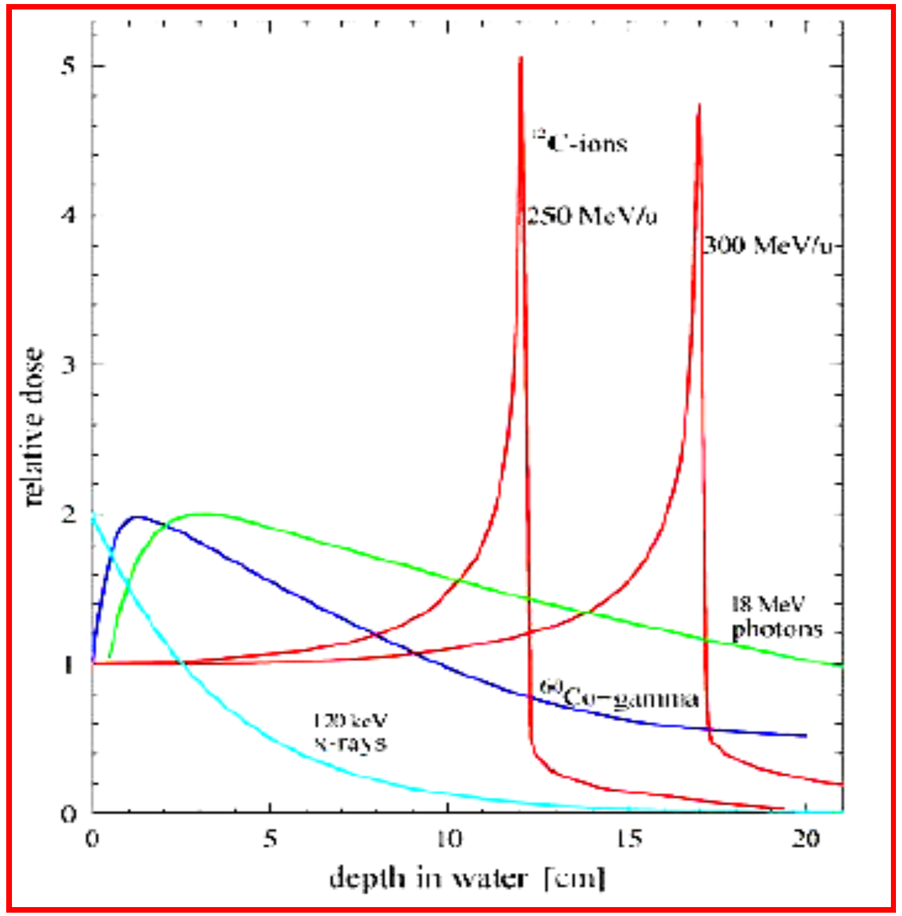




AIMS

- Dose conformity over the tumor
- High Dose to tumor
- Low Dose to normal tissues

Particle Therapy: Motivations



Advantages of PT wrt conv RT:

- Dose Conformity (Bragg peak)
- Healthy tissue sparing
- High LET beam (e.g. ^{12}C ions)
  => high RBE

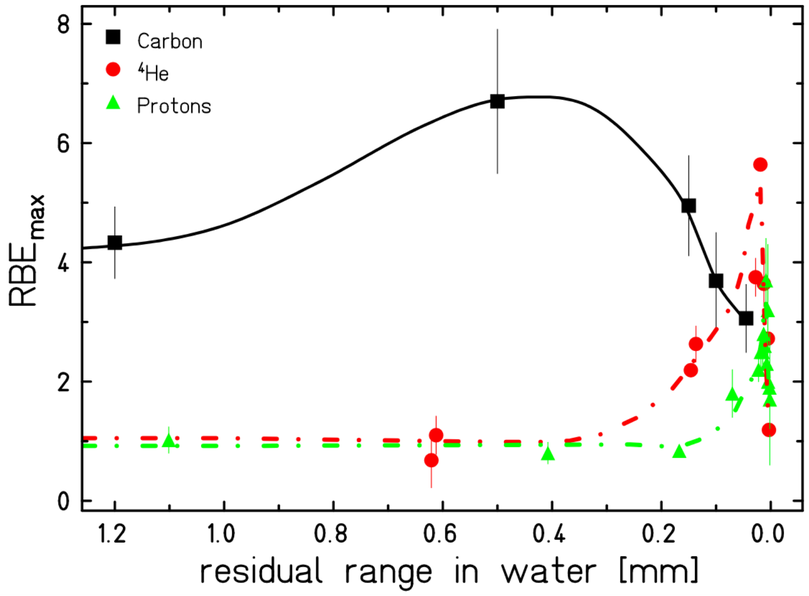
PT good to treat tumors
deep seated, close to organs at risk,
radioresistant

Particle Therapy: Challenges

Using protons:

target fragmentation

=> change in RBE



Using Z > 1 ions: beam fragmentation

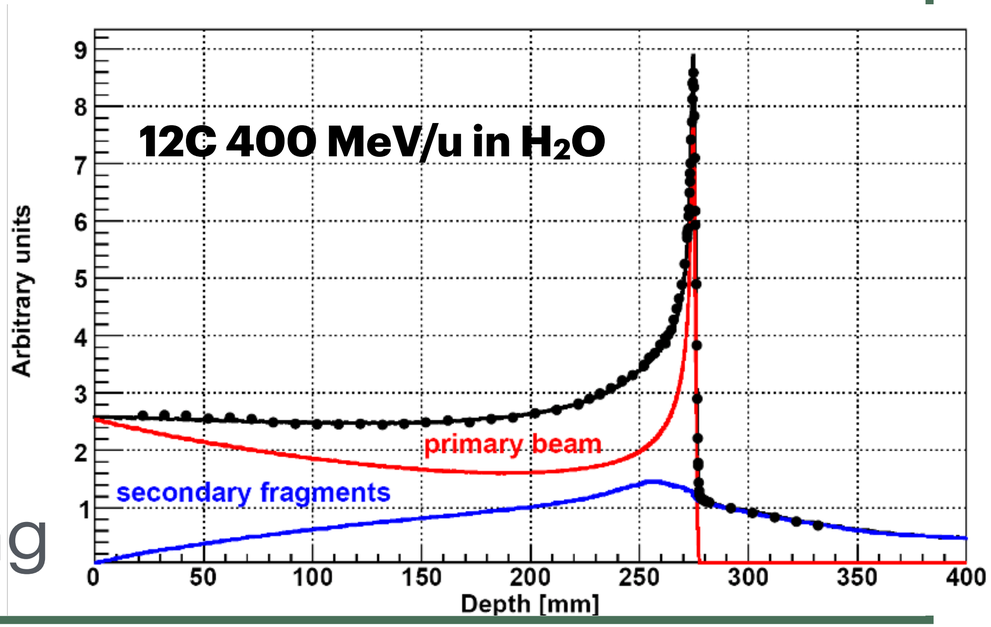
=> beam attenuation

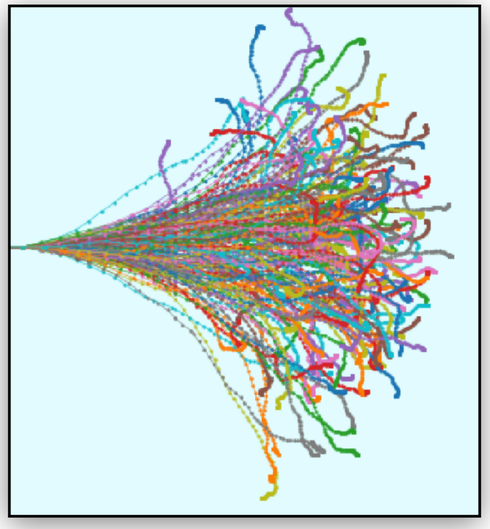
=> longer range of lighter fragments

=> Mixed field dosimetry

=> complex RBE calculation

=> fragments for range monitoring





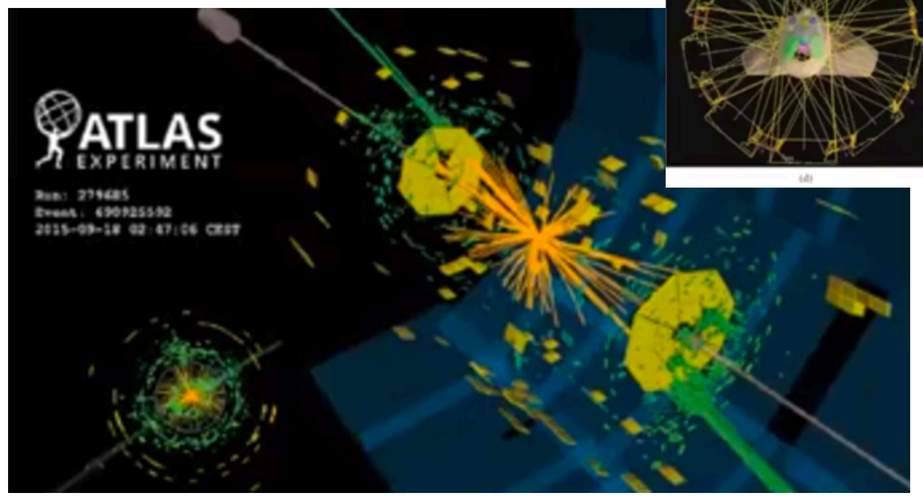
2. Introduction to the radiation transport problem

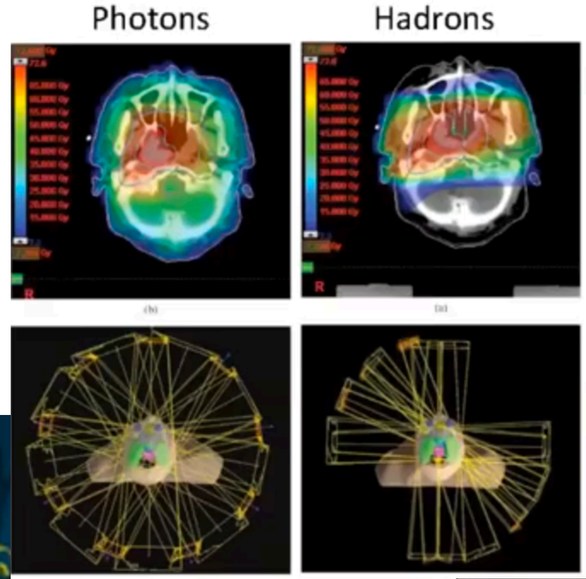
The Radiation Transport problem

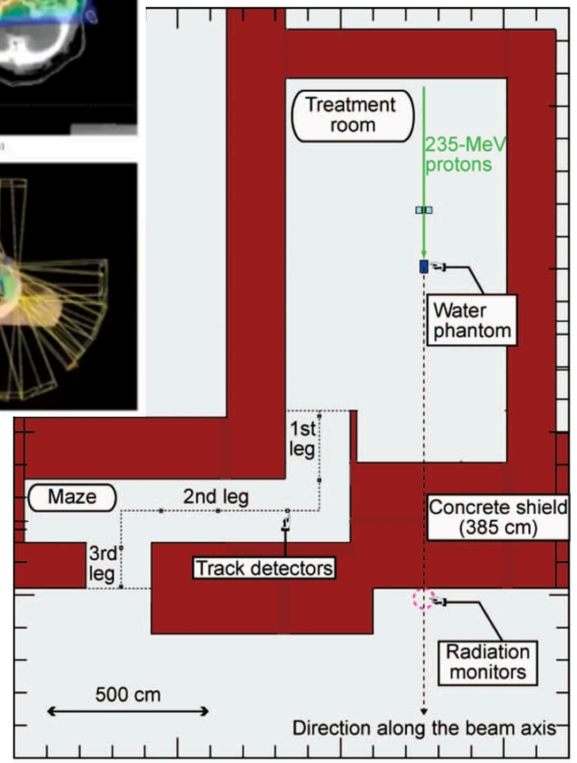
Radiation Source

Propagation in matter

Detection







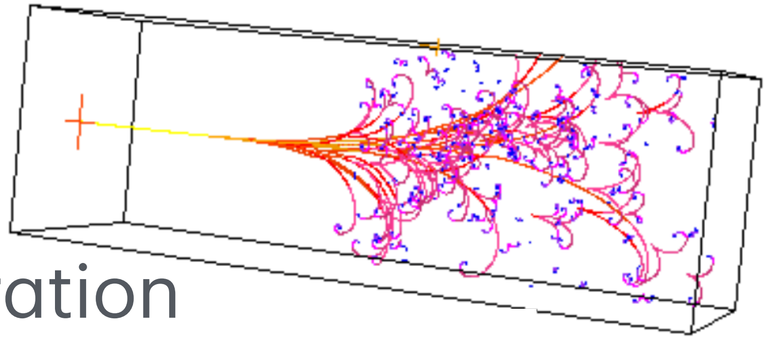
The Radiation Transport problem

Radiation Source

Propagation in matter

Detection

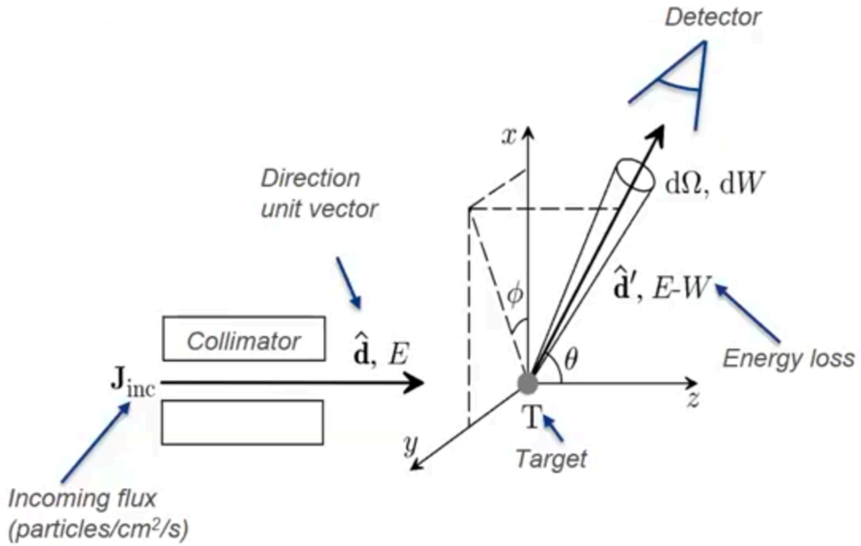
- Ensemble of particles (γ, $e^{\pm}$, $\mu^{\pm}$, n, p, $\pi^{\pm}$, ν_i, ions...)
- Radiation-matter interaction mechanisms:
  - -> angular deflections
  - -> energy losses
  - -> secondary particles generation
  - -> residual nuclei production



- Solution of the Boltzmann equation

Basic Quantities

- **Particle density** $n_i(\mathbf{r},E,\Omega,t)$: number of particles of species i per unit volume, unit energy, unit solid angle, at a given time
- **Cross Section**: probability of interaction per unit length, with the length measured in atoms/cm^2 (the number of atoms contained in a cylinder with a 1 cm^2 base)



Double differential cross section

$$\frac{\mathrm{d}^2\sigma}{\mathrm{d}\Omega\,\mathrm{d}W} \equiv \frac{\dot{N}_{\text{count}}}{|\mathbf{J}_{\text{inc}}|\,\mathrm{d}\Omega\,\mathrm{d}W}$$

Cross section

$$\sigma \equiv \int\int \frac{\mathrm{d}^2\sigma}{\mathrm{d}\Omega\,\mathrm{d}W}\,\mathrm{d}\Omega\,\mathrm{d}W$$

Dimensions: Area
Typical unit: 1 barn (=10^{-24} cm^2)

The Radiation Transport problem

THE TRANSPORT EQUATION

Time evolution of particle density $n_i(\mathbf{r},E,\Omega,t)$ in a small volume V:

$$\int_V \mathrm{d}\boldsymbol{r}\,\frac{\partial n_i(\boldsymbol{r},E,\Omega,t)}{\partial t} = -\oint_S \mathrm{d}A\,\mathbf{j}(\boldsymbol{r},E,\Omega,t)\cdot\hat{\boldsymbol{a}}$$

(unscattered particles)

$$-N\int_V \mathrm{d}\boldsymbol{r}\,n_i(\boldsymbol{r},E,\Omega,t)v(E)\sigma(E)$$

(particles scattered out)

$$+N\int_V \mathrm{d}\boldsymbol{r}\int \mathrm{d}E'\int \mathrm{d}\Omega'\,n_i(\boldsymbol{r},E',\Omega',t)v(E')\frac{\mathrm{d}\sigma}{\mathrm{d}\Omega''\mathrm{d}W''}$$

(particles scattered in)

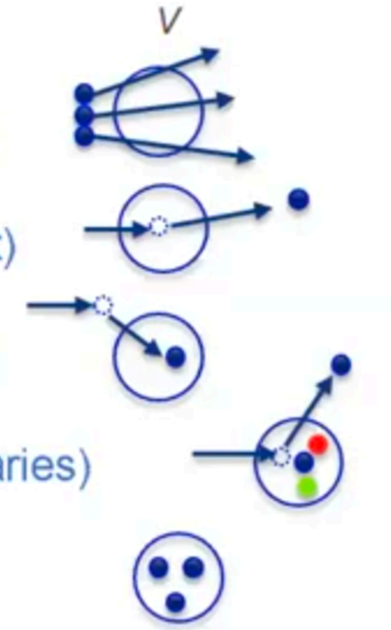
$$+N\int_V \mathrm{d}\boldsymbol{r}\int \mathrm{d}E'\int \mathrm{d}\Omega'\sum_j n_j(\boldsymbol{r},E',\Omega',t)v(E')\frac{\mathrm{d}\sigma_{\mathrm{sec},i}}{\mathrm{d}\Omega''\mathrm{d}W''}$$

(production of secondaries)

$$+\int_V \mathrm{d}\boldsymbol{r}\,Q_{\mathrm{source}}(\boldsymbol{r},E,\Omega,t)$$

(source)

Number of target atoms per unit volume



The Radiation Transport problem

THE TRANSPORT EQUATION

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$$-N\int_V \mathrm{d}\boldsymbol{r}\,n_i(\boldsymbol{r},E,\Omega,t)v(E)\sigma(E$$

$$+N\int_V \mathrm{d}\boldsymbol{r}\int \mathrm{d}E'\int \mathrm{d}\Omega'\,n_i(\boldsymbol{r},E'$$

$$+N\int_V \mathrm{d}\boldsymbol{r}\int \mathrm{d}E'\int \mathrm{d}\Omega'\sum_j n_j($$

$$+\int_V \mathrm{d}\boldsymbol{r}\,Q_{\mathrm{source}}(\boldsymbol{r},E,\Omega,t)$$

Number of target atoms per unit volume

- **Integro-differential equation**
- **Analytical solution only for simplified scenarios (few particle species, few interaction mechanisms…)**

MC approach needed

3. The Monte Carlo approach

The MC Method: Integration or Simulation?

- Originally, the Monte Carlo method was not a simulation method, but a device to solve a multidimensional integro-differential equation by building a stochastic process such that some parameters of the resulting distributions would satisfy the equation
- The equation itself did not necessarily refer to a physical process and, if it did, that process was not necessarily stochastic

The MC Method: Random Numbers

Numerical method based on random sampling of probability distributions

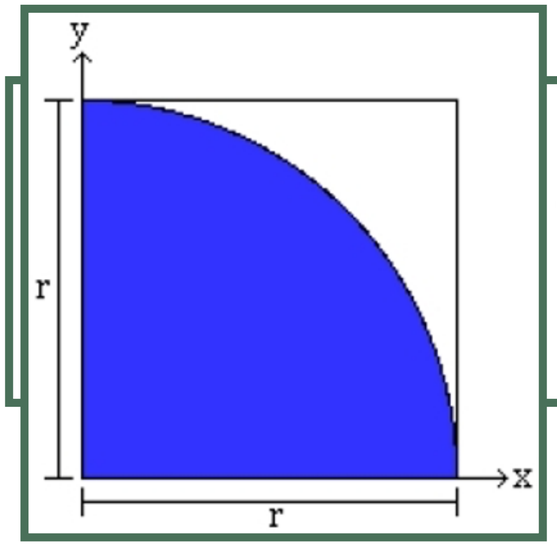
=> based on **RANDOM NUMBERS**:

- sequence of random numbers: set of numbers that have nothing to do with the other numbers of the sequence
- uniform distribution of random numbers: every number has the same chance of turning up

The MC Method: Random Numbers

Π computation using random numbers

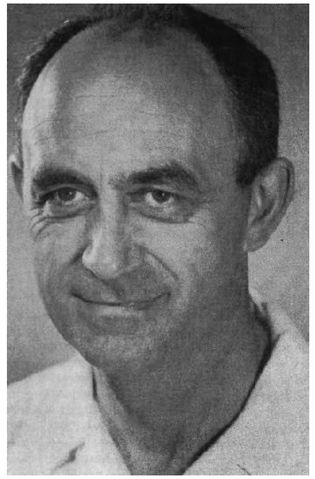
- G. Lecrerc and Compte de Buffon (1777)
  => idea of tossing a needle



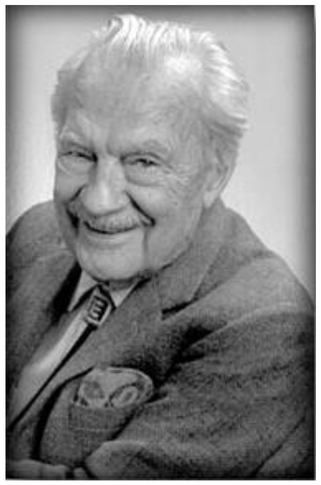
- Laplace (1886) => random points in a square enclosing a circle

The MC Method: Particle Transport

- 1930s: early historical idea by E. Fermi to exploit statistical sampling techniques using random numbers for neutron transport problems
- 1940s: idea developed within the Manhattan project in parallel with the development of the computer ENIAC



E. Fermi



N. Metropolis

S. Ulam

J. von Neumann

The MC Method: Mathematical Foundation

The Central Limit Theorem is the mathematical foundation of the Monte Carlo method:

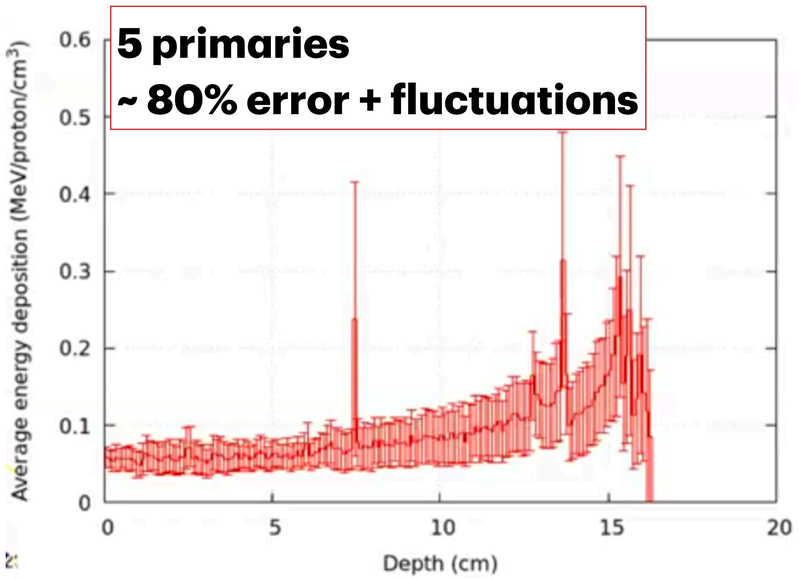
Given any observable A, that can be expressed as the result of a convolution of random processes, the average value of A can be obtained by sampling many values of A according to the probability distributions of the random processes.

The MC Method: Mathematical Foundation

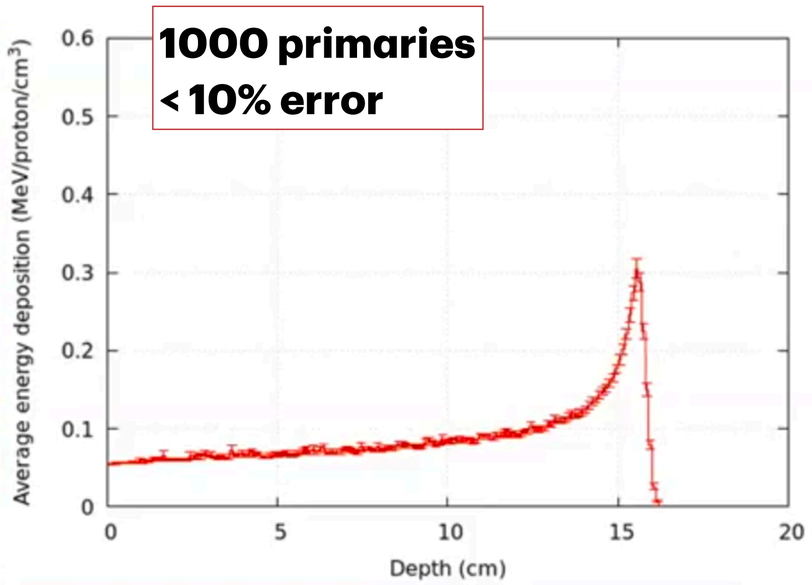
- The accuracy of the MC estimator depends on the number of samples:

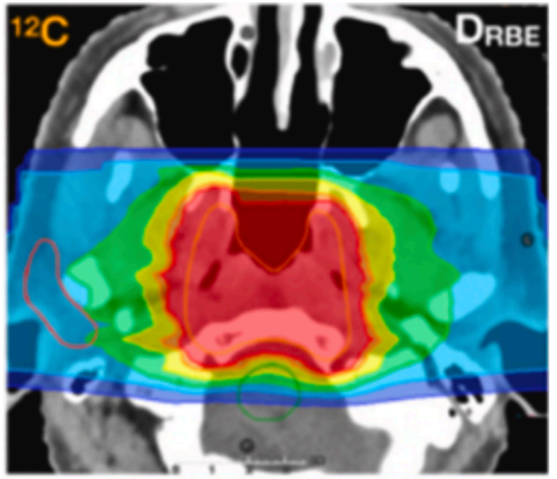
$$\sigma \propto \frac{1}{\sqrt{N}}$$

- From a 150 MeV protons in H_2O target:



Statistical convergence

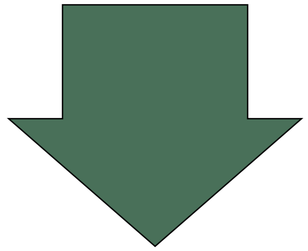




4. Basic ingredients for a Monte Carlo based Treatment Planning in Particle Therapy

The Importance of Dose Accuracy

Accuracy on the total dose released over a tumor volume at 5% max



Accuracy in the dose calculation at 1-2% max

Report 85 AAPM (2004): "***1% accuracy improvement in dose results in 2% increase in cure rate for early stage tumors.***" **(Boyer and Schultheiss, 1988)**

and will require the greatest dosimetric accuracy. At this point, a 5% change in dose may result in a 10% to 20% change in tumor control probability at a TCP of 50%. Similarly, a 5% change in dose may result in a 20% to 30% impact on complication rates in normal tissues. The results mentioned above refer to changes caused by homogeneous dose distributions covering the whole tumor or organ at risk considered, which is characterized by certain D_{50} and γ values. Nevertheless, they demonstrate the potential impact that a certain change in dose to the clinical outcome may have.

A simplified scheme

- Patient modeling
- Beam line modeling
- Radiation transport and particles interactions modeling
- Dose calculation
- Biological evaluation for a given particle beam
- TPS Optimization (Kernel)
- TPS Validation/Control
- Monitoring devices

A simplified scheme

MC based

CT scan (ρ vs Dx,Dy.Dz)

PTV

TPS kernel

Table of DE vs E_{beam}, x,y,z

RBE vs E_{beam}, x,y,z

Fluences for each beam spot

TPS verification and correction

Dosimetry monitoring and correction

Pros and Cons for MC TPS

PROs

- Accurate geometry/inhomogeneity treatment, beyond the water equivalent approximation
- Full 3D treatment of scattering and e.m. and nuclear interaction and mixed fields
- Easy beam line features embedding
- Easy and accurate dose calculation: no convolution, no superimposition, just scoring

CONSs

- Memory demanding
- CPU time needed

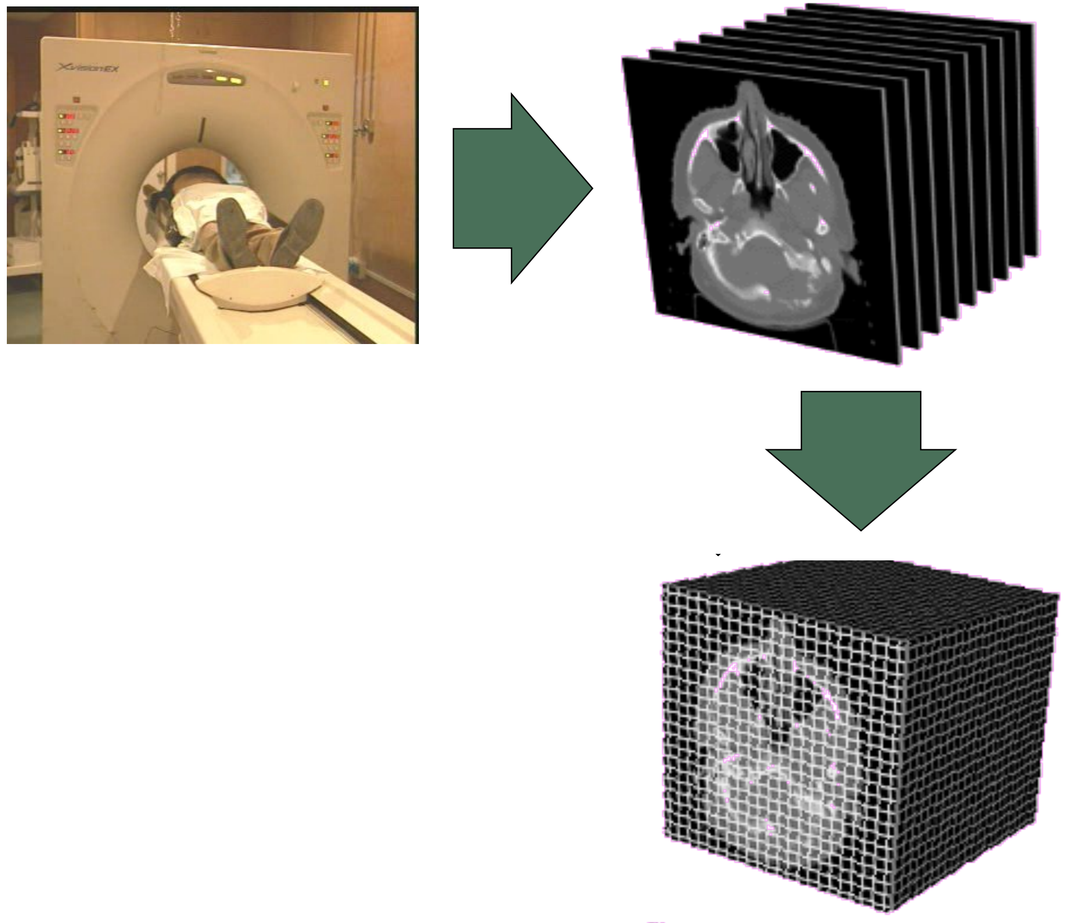
Monte Carlo codes assumptions

- **Static, homogeneous, isotropic, amorphous media and geometry**
  Problems: e.g. moving targets, radioactive decay, atmosphere represented by discrete layers of uniform density
- **Markovian process**: the fate of a particle depends only on its actual present properties, not on previous events or histories
- **Particles do not interact with each other**
- **Particles interact with individual electrons, atoms, nuclei, molecules**
  Problem: invalid at low energy (X-ray mirrors)
- **Material properties are not affected by particle reactions**
  Problem: e.g. burnup

Patient Modeling

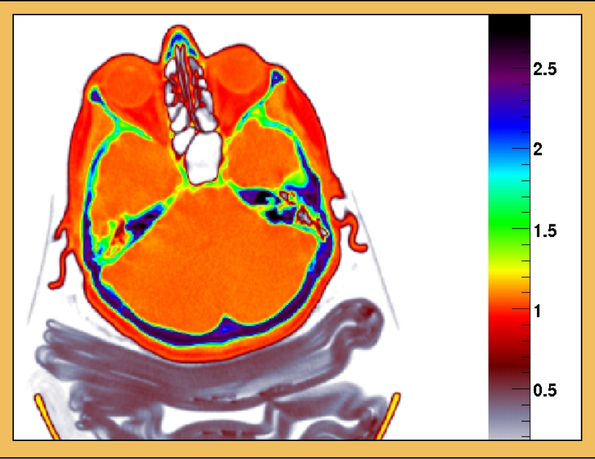
The MC needs the patient modeling for TPS optimization, but **MC for Particle Therapy do not use (hopefully!) the water equivalent approach**

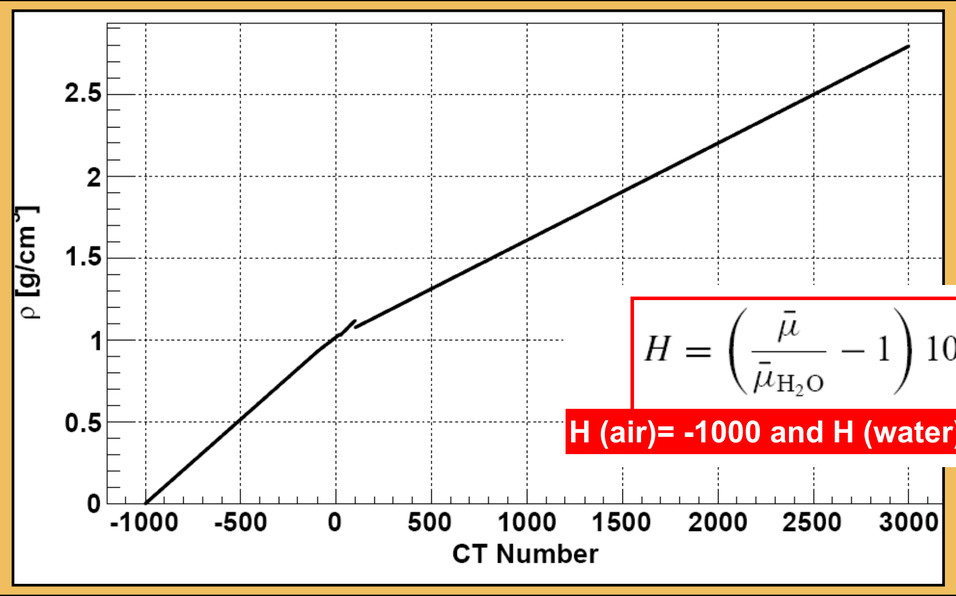
- **Easily imported CT geometry in MC**
  => DICOM info translated in voxel/volumes structure (3D grid of little bricks)
- Contiguous voxels can be grouped to form **organs**



Patient Modeling

- **Stoichiometric calibration from CT** electron density (HU) **to the Z,A,rho** needed by the proton & ^{12}C MC
  => **Nominal mean density for each HU interval**
  (Jiang and Paganetti MP 31, 2004), but real density varies continuously with HU value





$$H = \left(\frac{\bar{\mu}}{\bar{\mu}_{H_2O}} - 1\right) 1000$$

H (air)= -1000 and H (water) = 0

Air, Lung, Adipose tissue

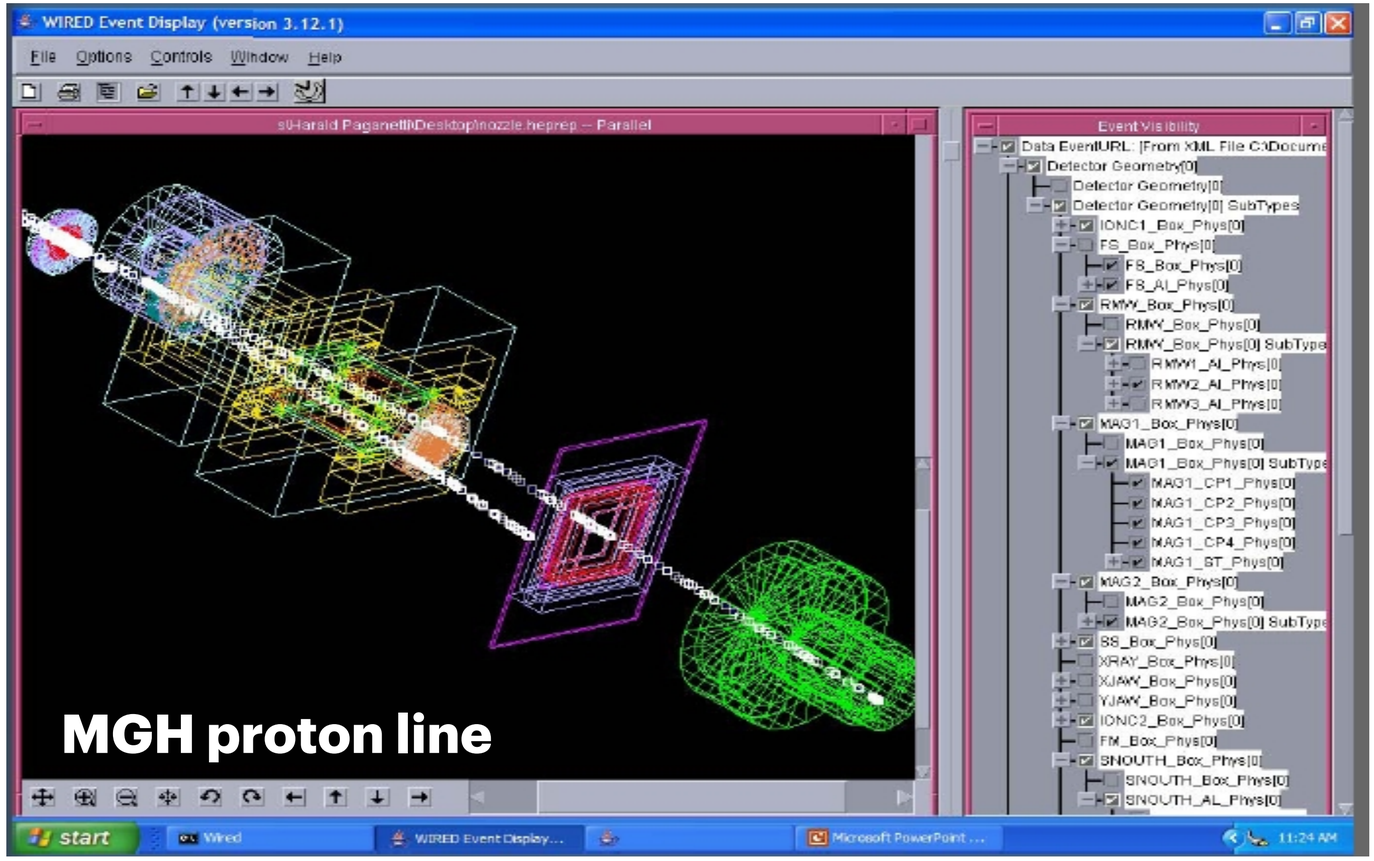
Soft tissue

Skeletal tissue

H	w_i(pp) H	C	N	O	Na	Mg	P	S	Cl	Ar	K	Ca
−1000–−950			75.5	23.2						1.3		
−950–−120	10.3	10.5	3.1	74.9	0.2		0.2	0.3	0.3		0.2	
−120–−83	11.6	68.1	0.2	19.8	0.1			0.1	0.1			
−82–−53	11.3	56.7	0.9	30.8	0.1			0.1	0.1			
−52–−23	11.0	45.8	1.5	41.1	0.1		0.1	0.2	0.2			
−22–7	10.8	35.6	2.2	50.9			0.1	0.2	0.2			
8–18	10.6	28.4	2.6	57.8			0.1	0.2	0.2		0.1	
19–80	10.3	13.4	3.0	72.3	0.2		0.2	0.2	0.2		0.2	
80–120	9.4	20.7	6.2	62.2	0.6			0.6	0.3			
120–200	9.5	45.5	2.5	35.5	0.1		2.1	0.1	0.1		0.1	4.5
200–300	8.9	42.3	2.7	36.3	0.1		3.0	0.1	0.1		0.1	6.4
300–400	8.2	39.1	2.9	37.2	0.1		3.9	0.1	0.1		0.1	8.3
400–500	7.6	36.1	3.0	38.0	0.1	0.1	4.7	0.2	0.1			10.1
500–600	7.1	33.5	3.2	38.7	0.1	0.1	5.4	0.2				11.7
600–700	6.6	31.0	3.3	39.4	0.1	0.1	6.1	0.2				13.2
700–800	6.1	28.7	3.5	40.0	0.1	0.1	6.7	0.2				14.6
800–900	5.6	26.5	3.6	40.5	0.1	0.2	7.3	0.3				15.9
900–1000	5.2	24.6	3.7	41.1	0.1	0.2	7.8	0.3				17.0
1000–1100	4.9	22.7	3.8	41.6	0.1	0.2	8.3	0.3				18.1
1100–1200	4.5	21.0	3.9	42.0	0.1	0.2	8.8	0.3				19.2
1200–1300	4.2	19.4	4.0	42.5	0.1	0.2	9.2	0.3				20.1
1300–1400	3.9	17.9	4.1	42.9	0.1	0.2	9.6	0.3				21.0
1400–1500	3.6	16.5	4.2	43.2	0.1	0.2	10.0	0.3				21.9
1500–1600	3.4	15.5	4.2	43.5	0.1	0.2	10.3	0.3				22.5

Schneider et al PMB 45, 2000

Beam Line Modeling



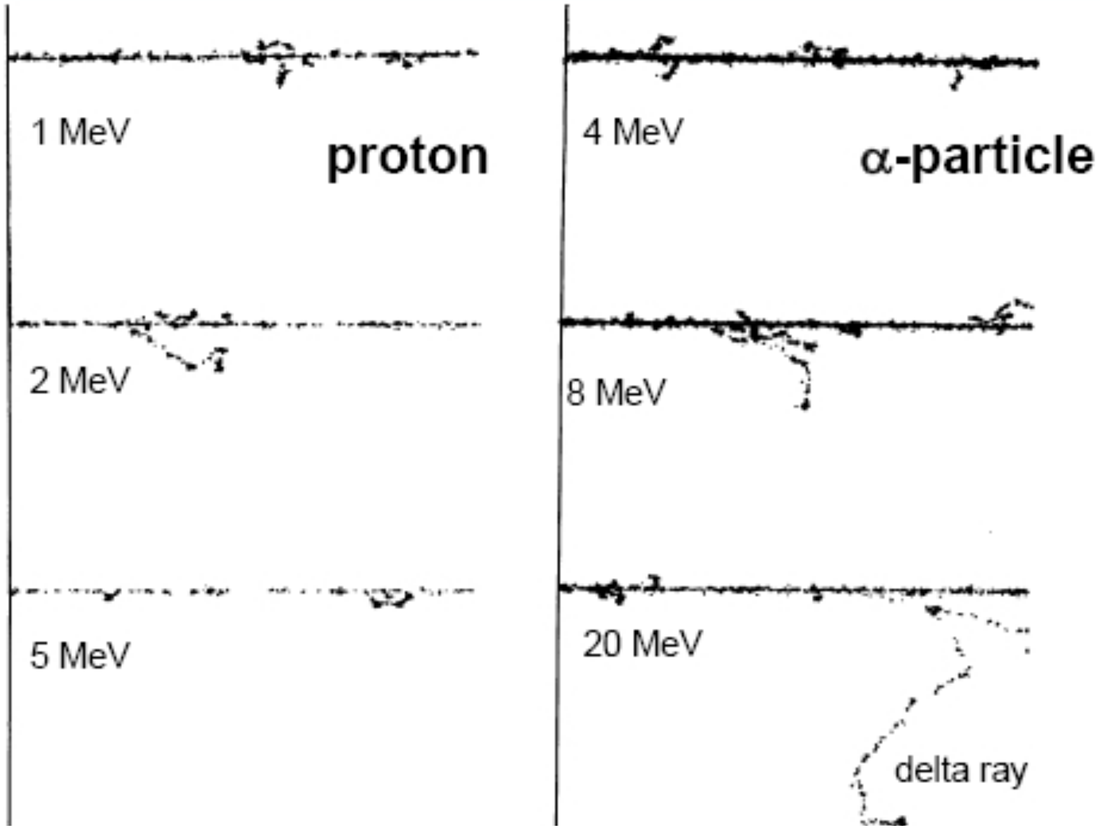
Monte Carlo model of the nozzle (~ 1000 objects)

- Not Patient Specific -

^{12}C narrow beams => need for carefully shaped passive absorbers as ripple filters

- Spread energy
- Multiple Scattering
- Secondary Fragments (!)

Radiation Transport and Interactions



The process of dose deposition is stochastic and can be very complex

=> MC must simulate several concurrent processes to obtain the dose released in tissue

Radiation Transport and Interactions

Consider a particle (radiation = γ, e, p, 12C...) defined by $\mathbf{r}_0$, $\mathbf{p}_0$, E_0.
Oversimplifying the physics involved is given by:

- Energy loss (charged)
- Multiple Scattering (charged)

} **Condensed history: summed up at each step**

- E.M. interactions (γ, charged)
- Nuclear interactions (p, Z>1 ions)

Each interaction has a probability $P_i(\Delta X)$ to occur
=> from $P_i(\Delta X)$ we sample the step length ΔX_i

$$P(\Delta X) = \frac{1}{\lambda} e^{-\frac{\Delta X}{\lambda}}$$

$$\lambda_i = 1/(N\sigma_i)$$

Mean free path for the i-th interaction

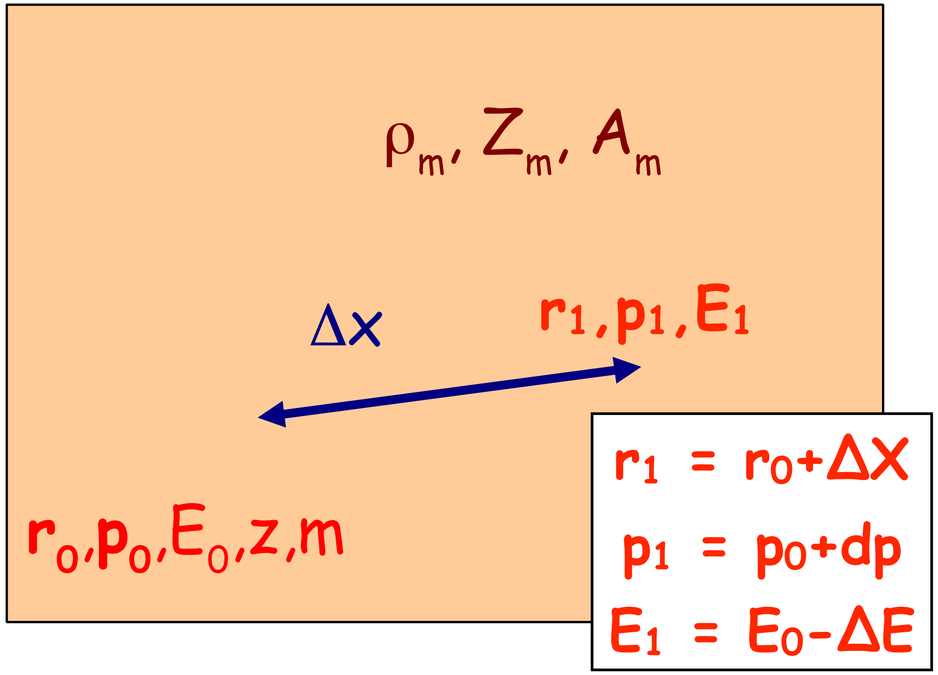
Radiation Transport and Interactions

ΔX_i is sampled for each process, but there are limitation to the step length:

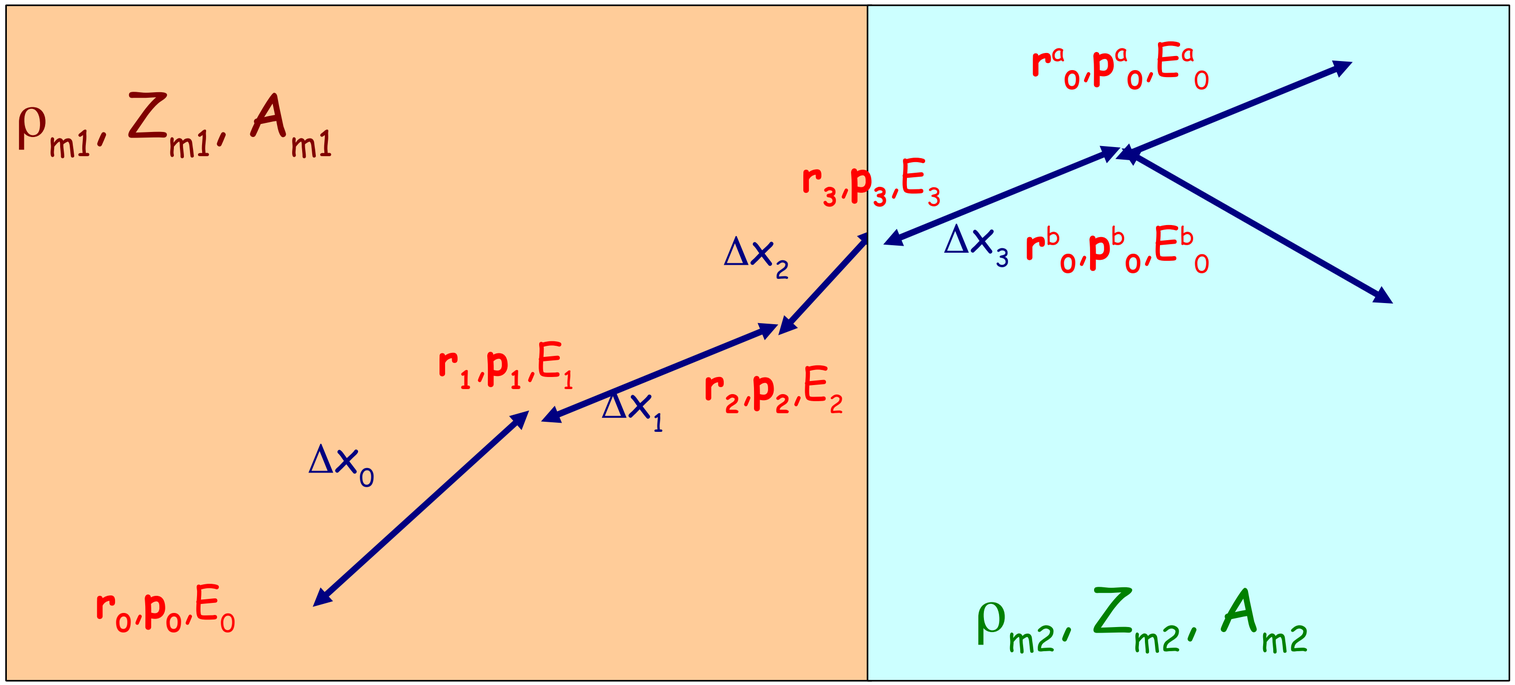
- Δx_{max}(E.L.) → in longer step **p** modulus changes too much
- Δx_{max}(M.S.) → in longer step **p** direction changes too much
- Δx_{max}(Vol.) → longer step takes too near to new region/mat.

The step is then chosen as:
$\Delta X = \min(\Delta X_{max}(E.L.), \Delta X_{max}(M.S.), \Delta X_{max}(Vol.), ...)$

ρ_m, Z_m, A_m = medium parameters



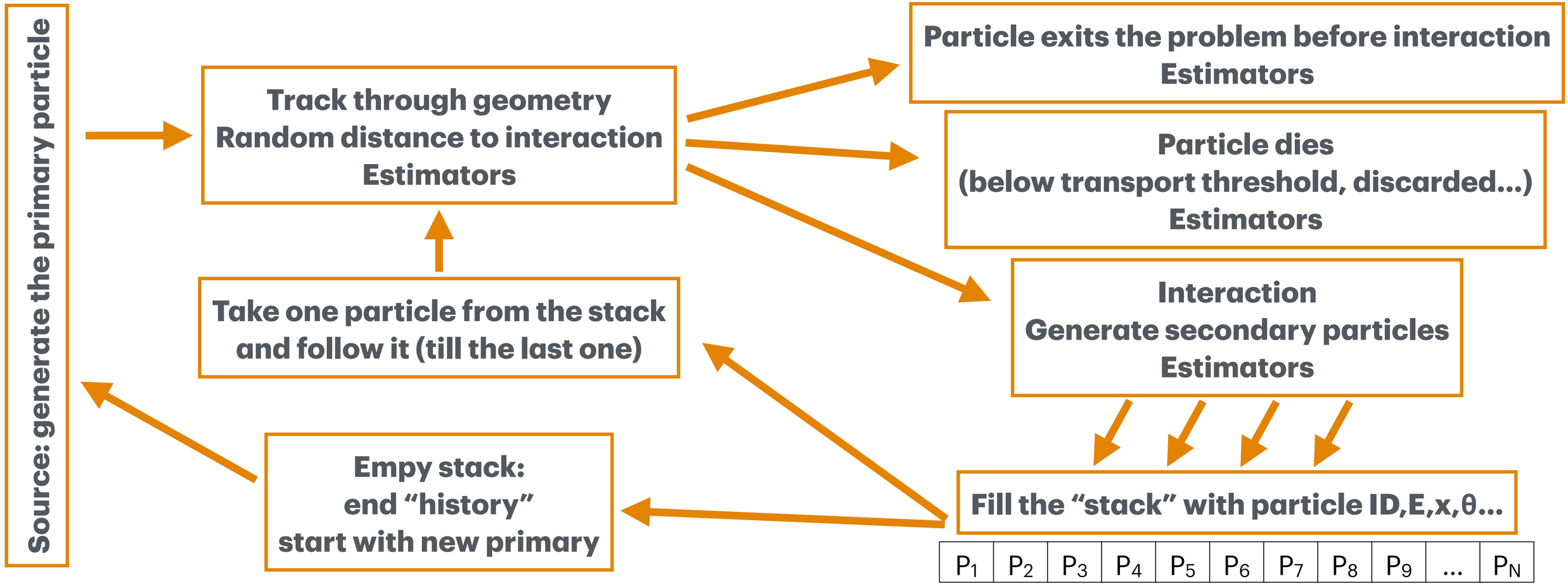
Radiation Transport and Interactions



The step is shortened at the region/material boundaries.

When the process that wins (*i.e.* has a shorter step) creates a new particle (e.*g.* ion fragmentation) a new story is started on the spot.

Radiation Transport and Interactions



Electron and γ

- The e.m. physics underlying is well known and easily calculable and/or parametrizable (Energy loss, Rayleigh & Compton scattering, photo-electric effect, pair production, atomic relaxations, bremsstrahlung, positron annihilation)
- For e.m. physics the water equivalent approach (i.e. The CT electron density info) is a good approximation
- CPU time reduced wrt adrons. (less charged tracks, possible parametrization of the beam features, etc...)
- Exist several commercially available TPS completely based on MC: (for example: Isogray TPS & Pelelope MC)

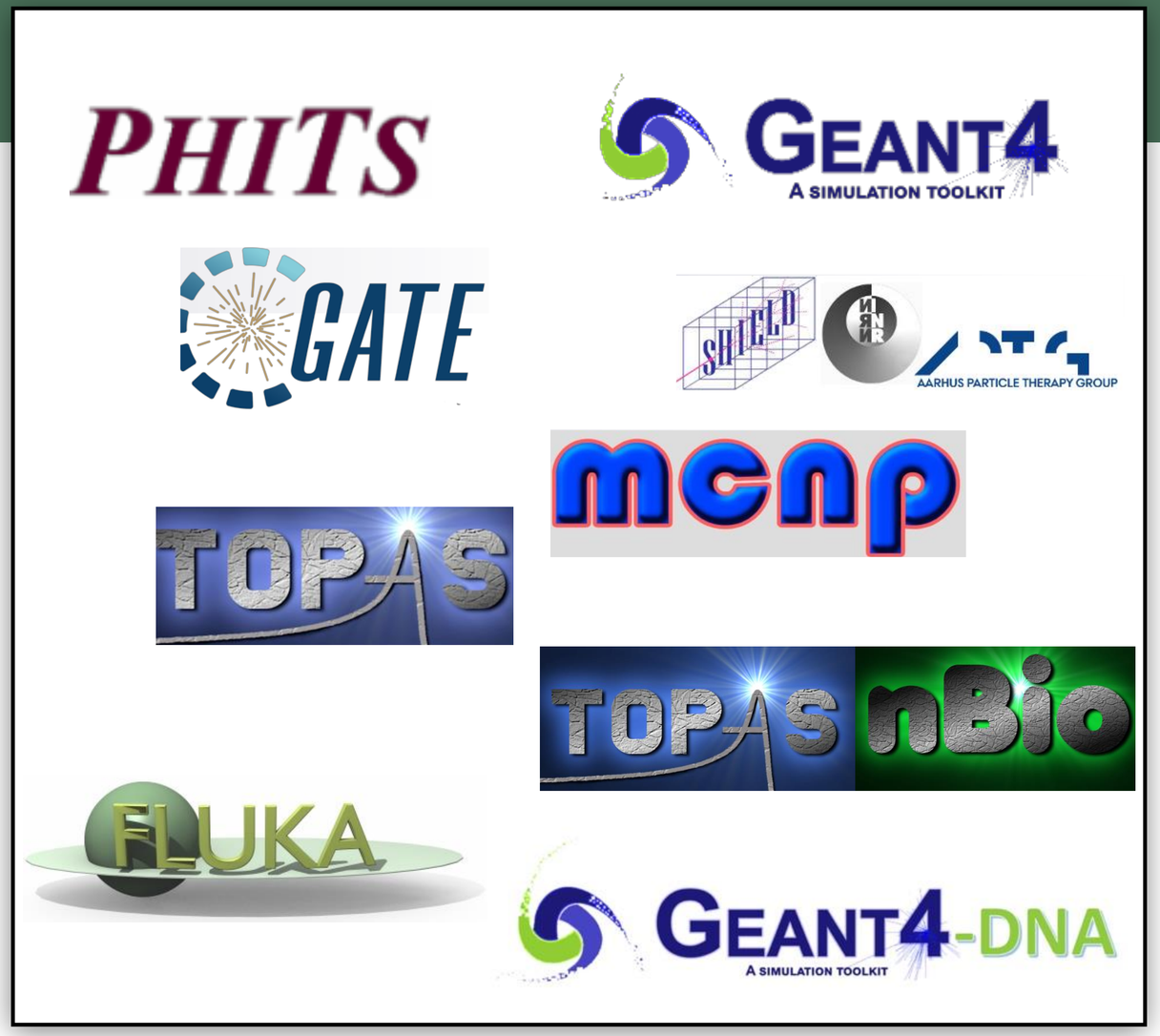
Proton and ^{12}C

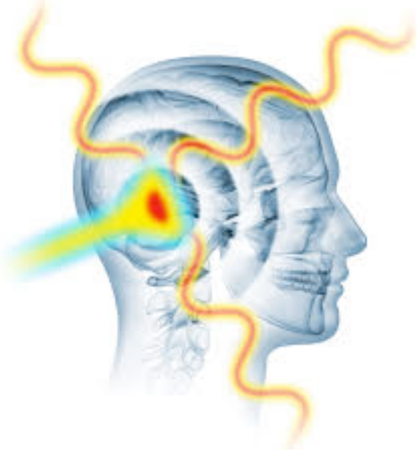
- The nuclear physics underlying is poorly known and not easily calculable and/or parametrizable (Fragmentation, nuclear evaporation)
- The radiobiological effect (RBE) plays a key role →huge dose correction factor, radiobiological database needed
- Nuclear interaction need $A_{mat}, Z_{mat}, \rho_{mat}$ → extrapolation (approximation) of the tissue composition from CT info
- Beam delivery system must be explicitely taken into account (ripple filter) → source of beam spread and fragmentation

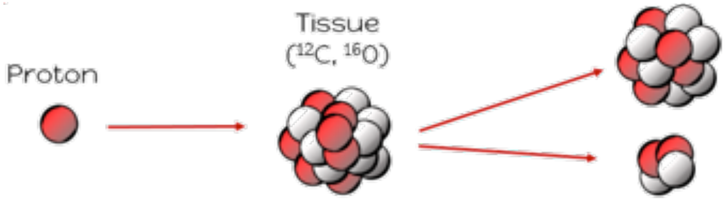
Monte Carlo codes

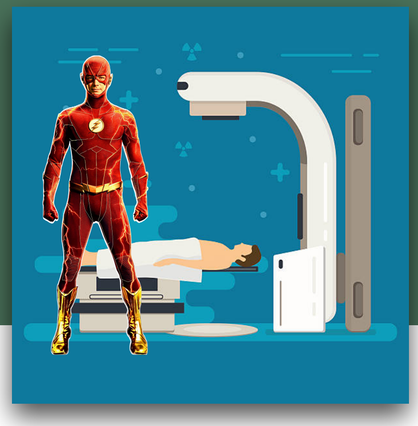
- **EGS4, EGSnrc, ETRAN, PENELOPE**: electron, positron and photon
- **VMCpro, ISTAR**: proton, parametrized nuclear interactions
- **SHIELD-HIT**: protons and heavy ions
- **MCNP, Geant4, PHITS, FLUKA**: general purpose, transport any particle from photon to heavy ion
  => **Geant4**: very large community, optimized version for lo energy, flexible
  => **FLUKA**: very accurate description both f e.m. and light ions interactions

...Not Exhaustive List





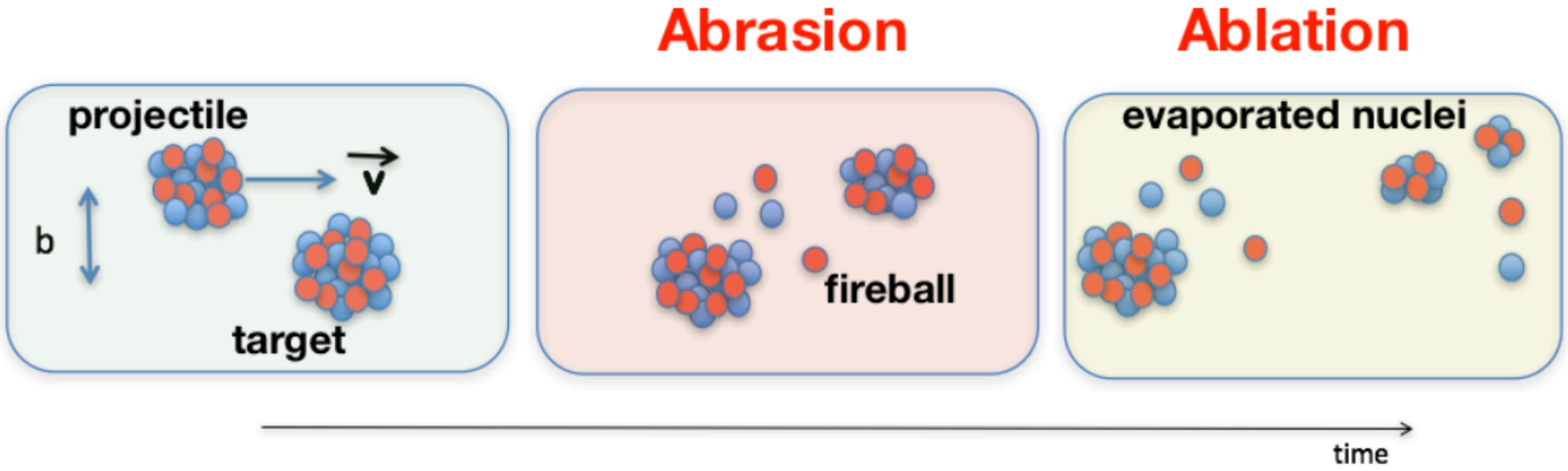




4. Some Examples

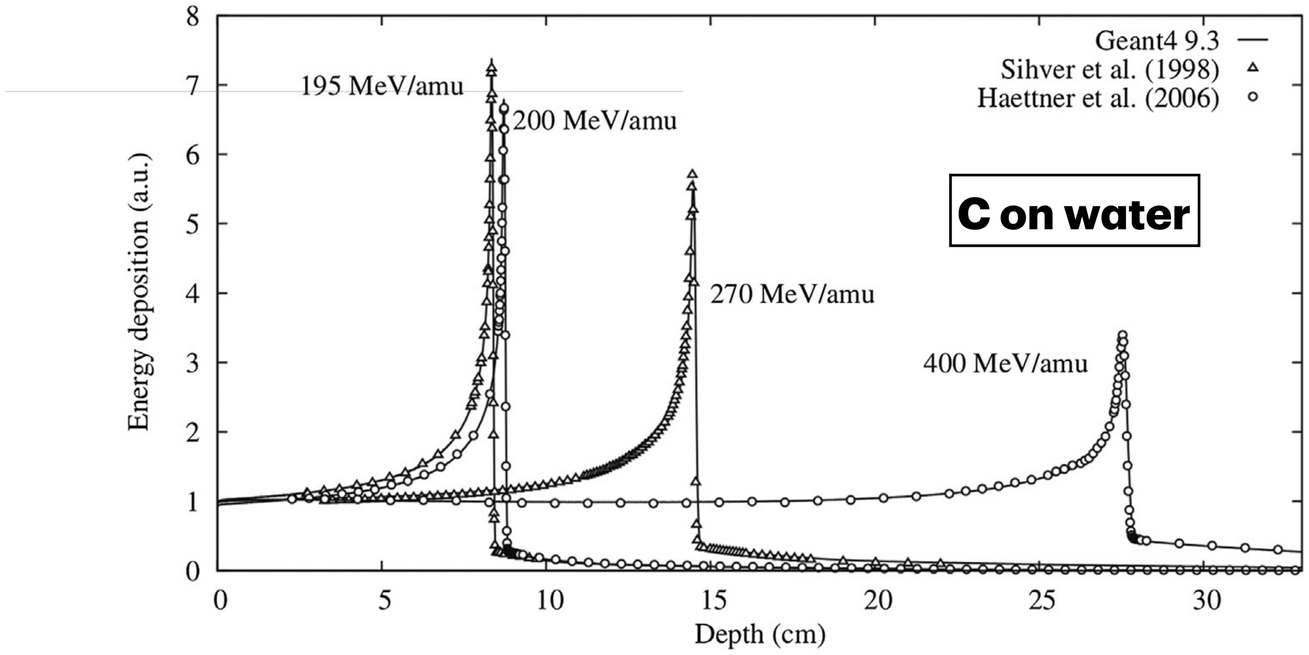
Nuclear Interactions in Monte Carlo

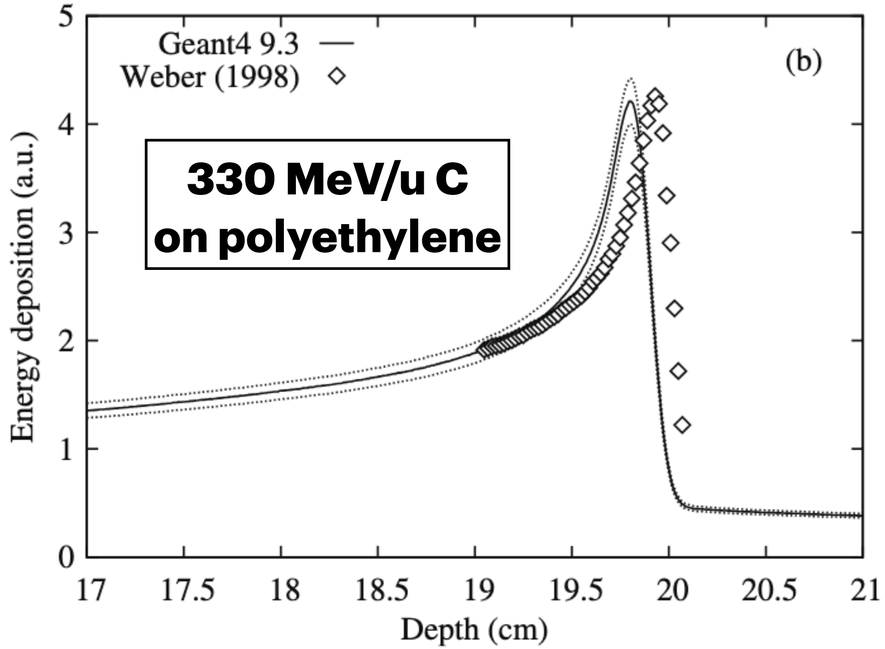
At Ekin ~ (10 MeV/u - 1 GeV/u), peripheral collisions are probably the most frequent reactions, described in MC by the abrasion-ablation model



Nuclear Interactions in Monte Carlo

Accuracy on the **physical dose** calculations reached in Particle Therapy, depending on target, beam species and beam energies.





Lechner et al, 2010, doi:10.1016/j.nimb.2010.04.008

Nuclear Interactions in Monte Carlo

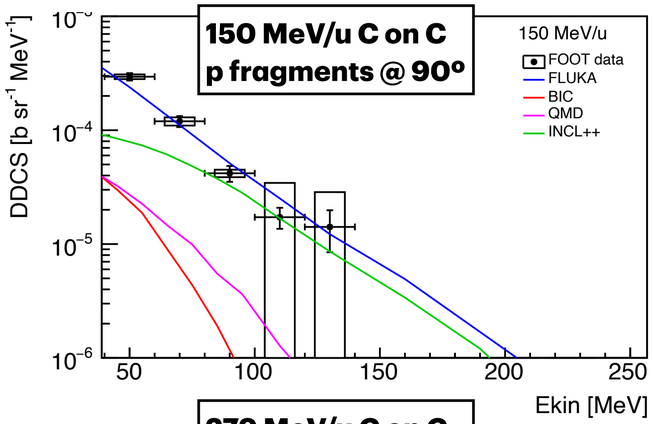
Cross section measurements (better if double differential in Ekin and angle) are needed to benchmark and tune the Monte Carlo codes models.

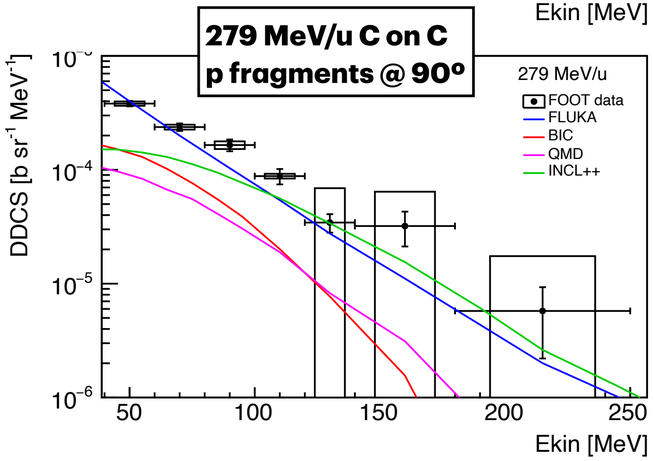
Incident beam	Energy [MeV/u]	Target	Measurement	References
^{4}He	70–220	H, C, O, and Si	Charge and mass changing cross sections	Horst et al. [98, 99]
^{4}He, C	135, 290, and 400	C, Li	Double differential cross section measurements of neutron production	Handbook [97], chapter 3
^{12}C, ^{20}Ne	83, 200, 250, and 300	C, Al, Ca, Fe, Zn, Y, and Ag	Total cross sections	Kox et al. [100, 101]
^{12}C	30 to 400	Be, C, and Al	Total reaction cross section as function of projectile energy	Takechi et al. [102]
^{12}C	200 to 400	Water and polycarbonate	Total and partial charge changing cross sections for production of fragments up to $Z = 4$ at various energies	Toshito et al. [103]
^{12}C	62	C	Double differential cross sections and angular distributions of secondary charged fragments up to 25°	De Napoli et al. [104]
^{12}C	95	C, CH_2, Al, Al_2O_3, and Ti	Double differential cross sections for secondary charged fragment production ranging from protons to carbon isotopes	Dudouet et al. [77]
^{12}C	50	C, CH_2, Al, Al_2O_3, Ti, and PMMA	Double differential cross section for secondary charged fragment production ranging from protons to carbon isotopes	Divay et al. [78]
^{12}C	115, 153, 221, 281, and 353	C, plastic scintillator, and PMMA	Energy differential cross section at 60° and 90° of fragments with $Z = 1$	Mattei et al. [105]

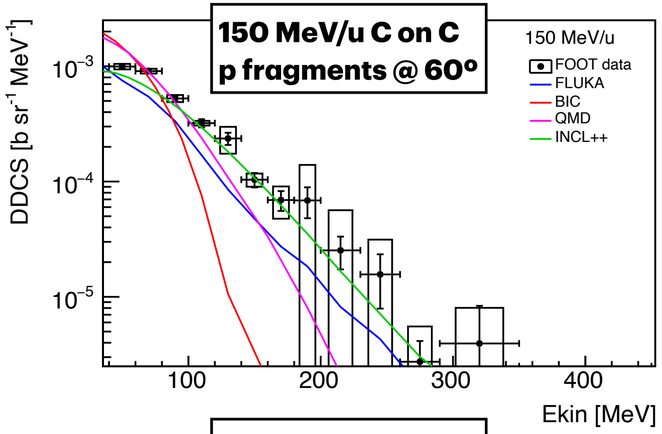
...Not Exhaustive List

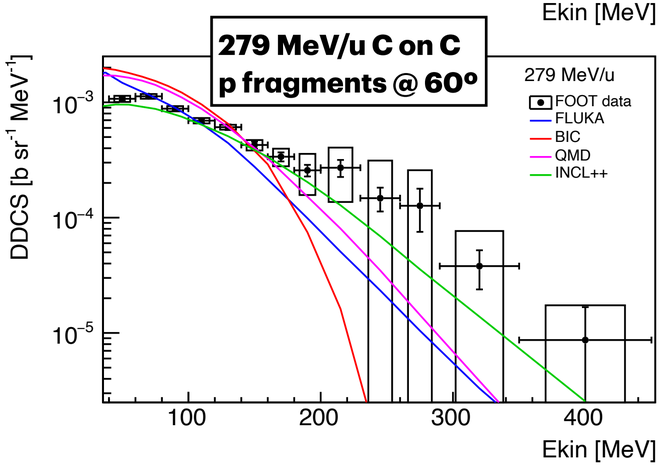
Battistoni, Muraro, Kraan, 2020, doi: 10.3389/fphy.2020.567800

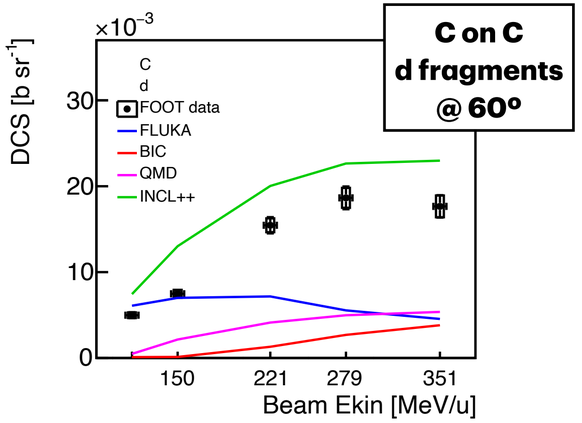
Nuclear Interactions in Monte Carlo

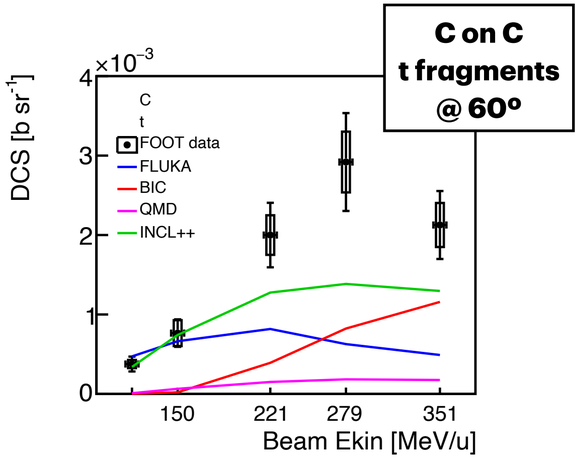












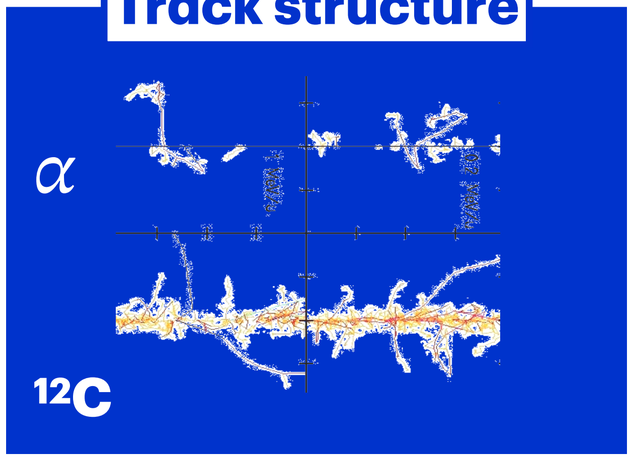
Dong et al, 2025, EPJA, accepted

Further work is needed to improve **double differential cross-section measurements**, thereby enhancing the MC models' ability to describe reality and accurately predict **physical and biological doses**

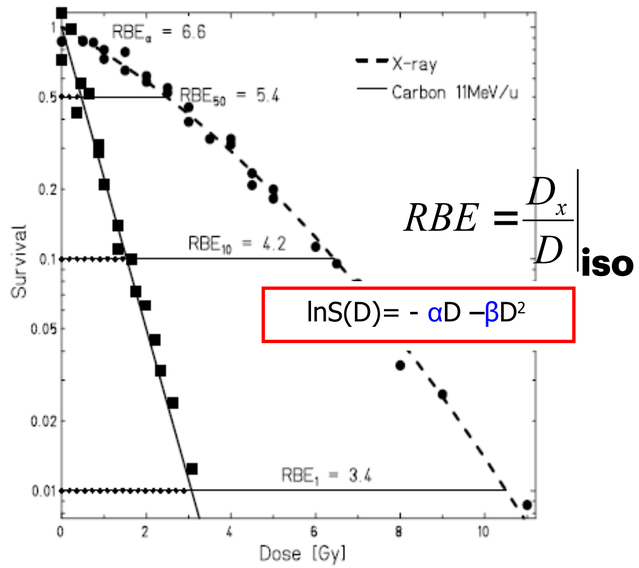
Radiobiological models

Radiobiological models are fundamental especially for high LET particles, having a highly changing RBE along their path in human tissues down to the Bragg peak.

Track structure



The most successful and still-widely used model for cell killing by radiation is the **linear-quadratic (LQ) model**



$$RBE = \frac{D_x}{D}\Big|_{iso}$$

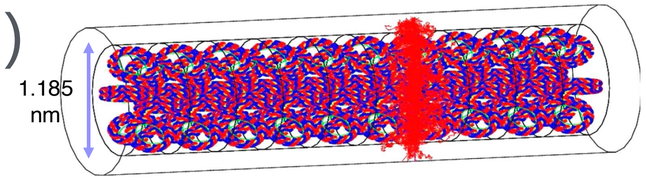
$$\ln S(D) = -\alpha D - \beta D^2$$

LQ model is not predictive on different cell lines.
Impossible to experimentally measure all the Survival Fractions for a TPS (energies, ions, cell lines...)

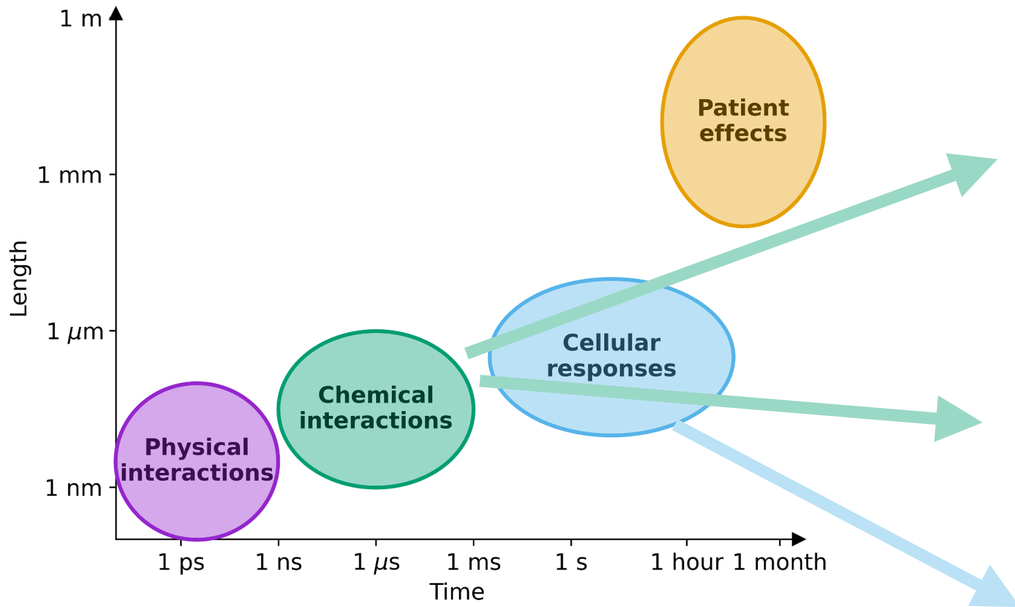
Need of predictive radiobiological model (*e.g.* LEM, MKM, RMF)

Radiobiological models

MC track structure models simulate the radiation interactions at **cellular scale** in liquid water as a surrogate for cellular composition (lack of data!)



Geant4 and Geant4-DNA
TOPAS and TOPAS-nBio
KURBUC
PARTRAC
RITRACKS
TRAX
IONLYS
PHITS
gMicroMC
FLUKA



Gardner et al, 2024, doi 10.1088/1361-6560/ad70f0

development of independent reaction time methods (diffusion rates of reactant pairs, interaction parameters)

more complex initial chemical environments (role of oxygen in hypoxia, FLASH effect)

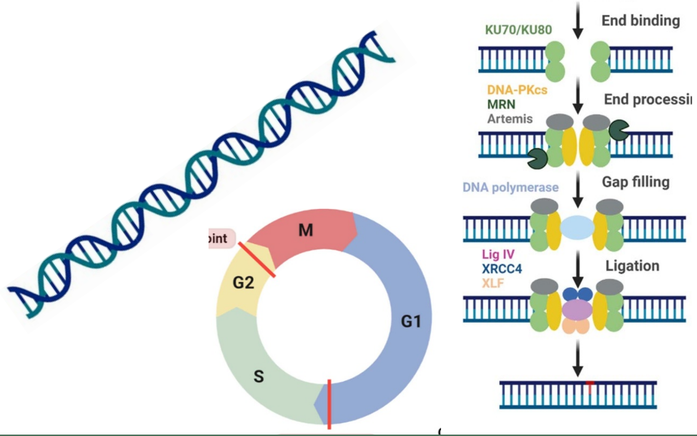
DNA modeling, DNA repair, cell cycle, cell death

Radiobiological models

MC track structure models simulate the radiation interactions at **cellular scale** in liquid

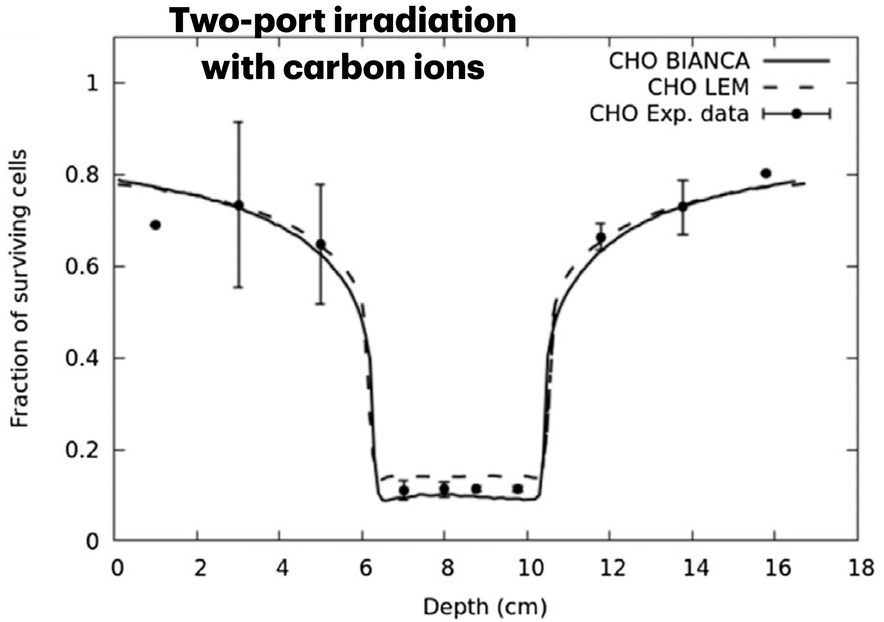
TOPAS and TOPAS-nBio

Need of integrated approaches



and coupling of general-purpose MC codes with radiobiological models (D_{RBE} from precomputed db of the SF coefficients, LEM model, BIANCA...)

Gardner et al, 2024, doi 10.1088/1361-6560/ad70f0

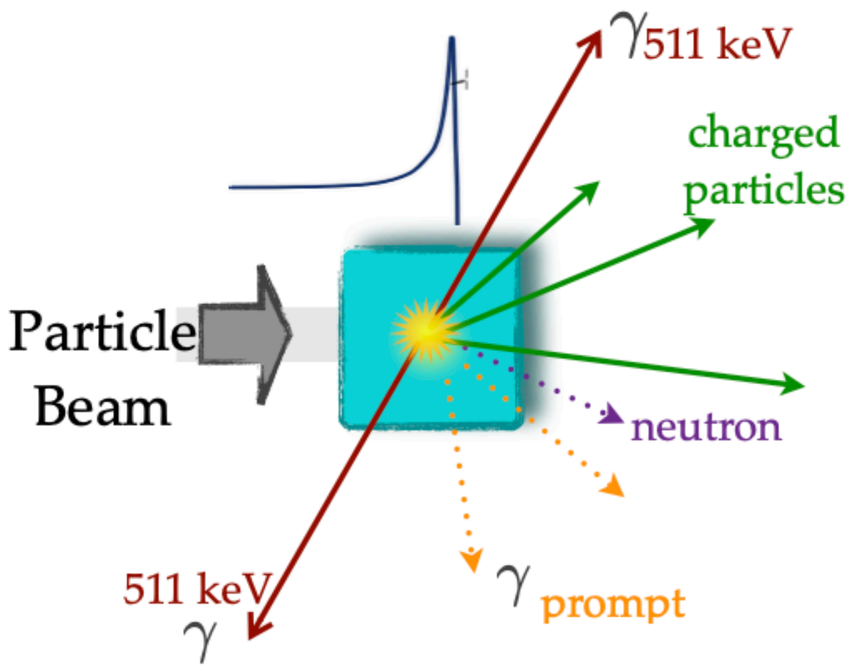


Carante et al, 2019, doi:10.1088/ 1361-6560/ab490f

DNA modeling, DNA repair, cell cycle, cell death

Range Monitoring in PT

Range monitoring techniques in PT are **all based on the detection of secondaries** (charged fragments, photons, neutrons) produced **by nuclear interactions** of beam projectiles with tissue's nuclei

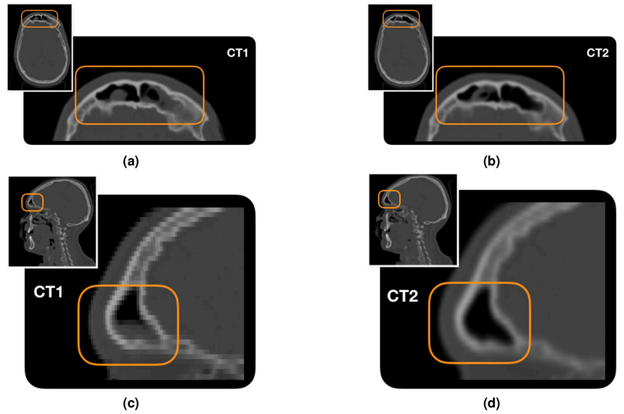


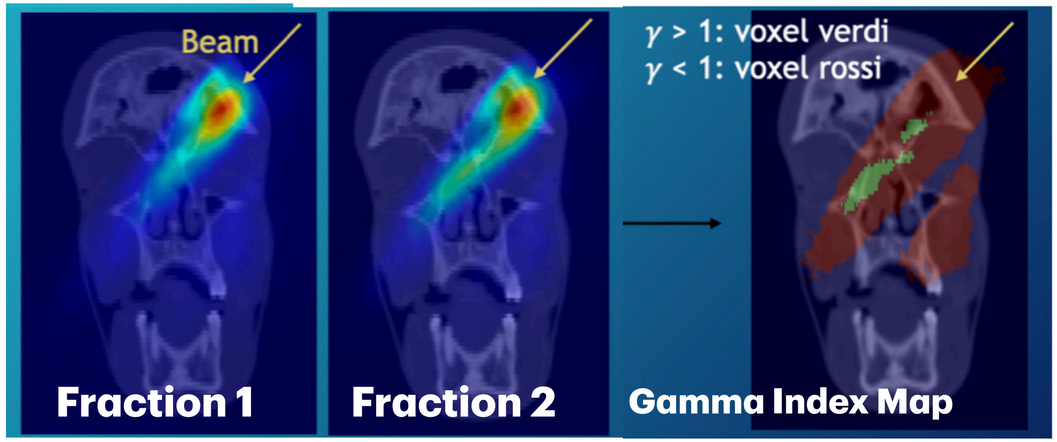
Need of detectors to measure nuclear products

MC prediction of fluxes of secondary particles exiting the patient

Inter-fractional 3D Monitoring in PT

Dose Profiler: check differences between charged secondaries 3D emission point maps between different fractions

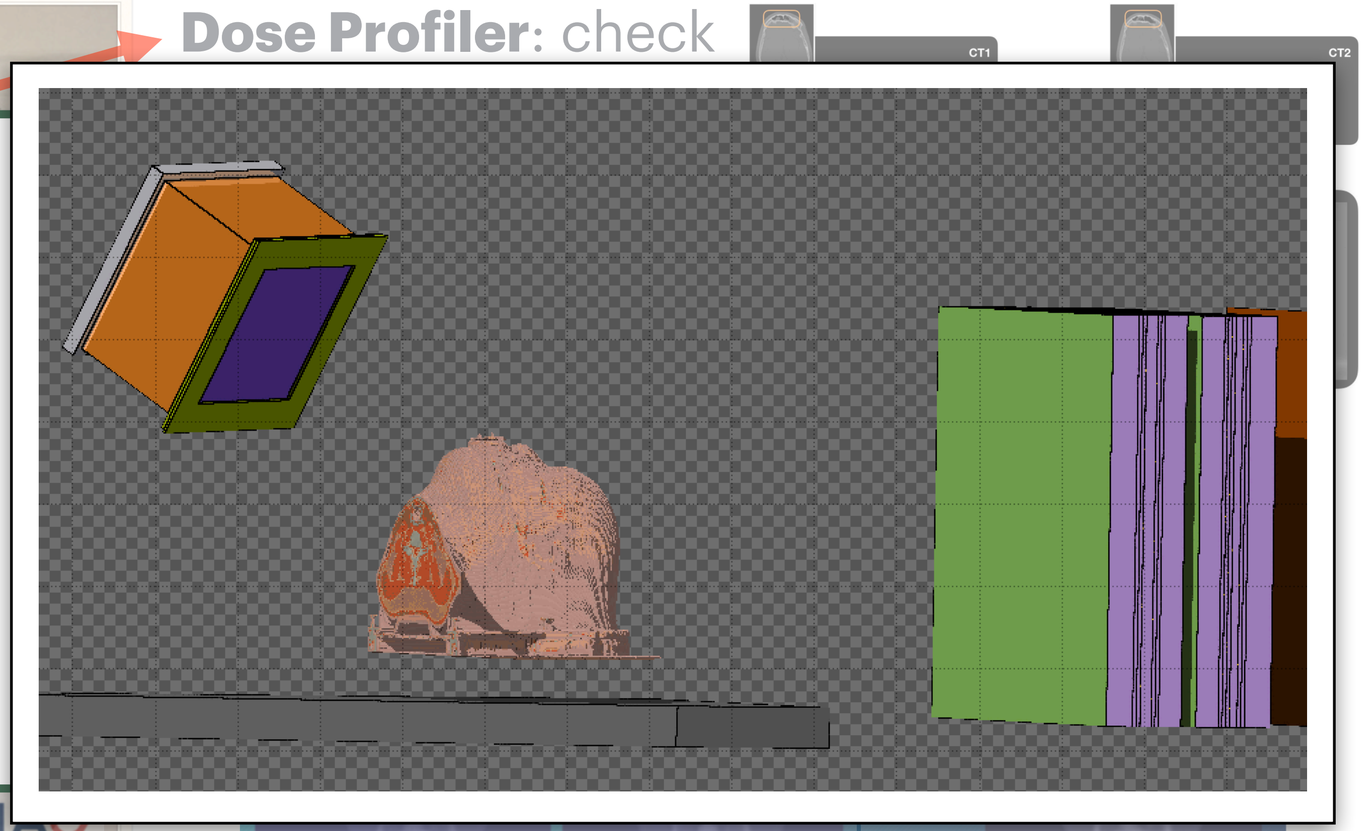




Inter-fractional 3D Monitoring in PT

Example of MC role:
find optimized parameters for gamma index test on experimental data by simulating patient's treatment plan on Planning CT and Control CT

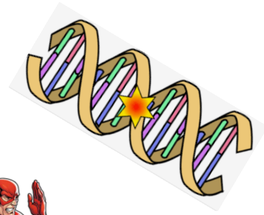
Dose Profiler: check



Fraction 1 | Fraction 2 | Gamma Index Map

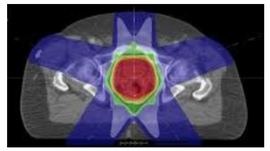
MC role in FLASH Therapy

FLASH therapy could be a promising technique since the FLASH effect has been observed at the end of the '90s. Since then, several aspects are under study:



- **Radiobiology** => understand the mechanisms behind the FLASH effect
- **Accelerators** => develop FLASH beam delivery techniques (photons, electrons, protons, carbon ions...)

- **Dosimetry** => enable accurate measurement of FLASH ultra-high doses and dose rates
- **Treatment Planning** => evaluate clinical implementation and potential benefits over conventional radiotherapy



MC role in FLASH Therapy

FLASH therapy could be a promising technique since the FLASH effect has been observed at the end of the '90s. Since then, several aspects are under study:

- **Radiobiology** => understand the mechanisms behind the FLASH effect
- **Accelerators** => develop new techniques (photons, electrons, protons)
- **Dosimetry** => enable accurate measurements of FLASH beams and dose rates
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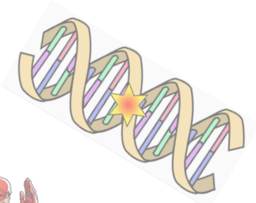
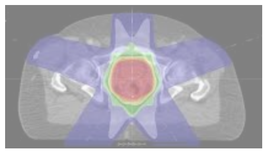
Need Of Monte Carlo Simulations to preliminary investigate and address key aspects related to FLASH therapy





MC TPS for VHEE in FLASH Therapy

For pancreatic tumors it is crucial to minimize radiation-induced toxicity to the nearby duodenum.

PRESCRIPTION

- **PT1**: seven fields were used, with a prescription to the **PTV of 30 Gy** in **5 fractions.**
- **PT2**: five fields were used, with a prescription to the **PTV of 32.5 Gy** in **5 fractions.**
- **PT3**: five fields were used, with a prescription to the **PTV of 30 Gy** in **5 fractions.**

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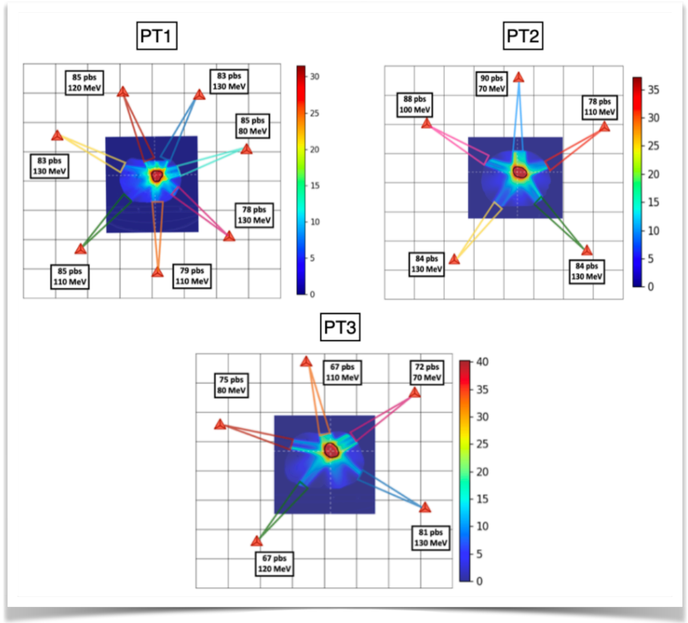
FIELD GEOMETRY



FOR FLASH IRRADIATION TEST!

DOSIMETRIC CONSTRAINTS

ROI	Constraints	Volumes [cc] PT1	PT2	PT3
PTV	$V_{95\%}^{PT1} > 95\%$ $V_{105\%}^{PT1} < 5\%$ $V_{100\%}^{PT2,PT3} > 95\%$ $D_{max}^{PT2} \leq 40.95$ Gy $D_{max}^{PT3} \leq 37.8$ Gy	94.9	81.6	117.9
Duodenum	$V_{35Gy} < 0.1$ cc $V_{25Gy} < 10$ cc	93.5	94.4	101.6
Bowel	$V_{30Gy} < 1$ cc	1035.1	563	1511.4
Stomach	$V_{12Gy} < 50$ cc $V_{33Gy} < 0.1$ cc	173.2	168.6	287.1
Spinal cord	$V_{25.3Gy} < 0.035$ cc	60.3	111	109.2
Liver	$D_{mean} \leq 13$ Gy $V_{15Gy} < 700$ cc	892.5	1202.8	1504
Kidneys	$V_{10Gy}^{p} < 45\%$	256.6	250.3	940.7

MC TPS for VHEE in FLASH Therapy

The Böhlen Model for FLASH effect

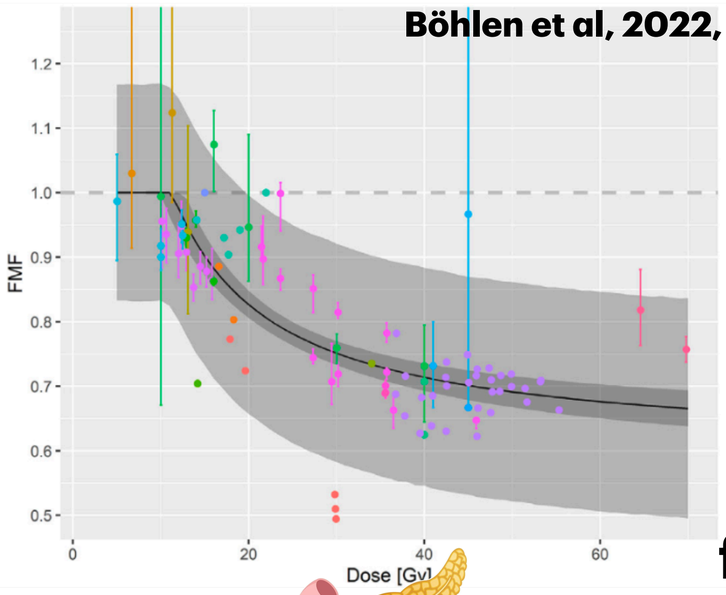
Biological dose $D_{FMF} = FMF \cdot D$ Physical dose

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

FMF → Reduction of radiation effect on healthy tissue

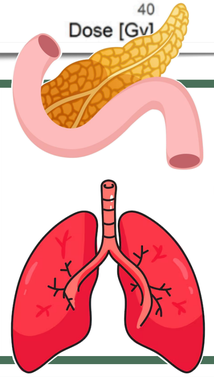
- FLASH effect seems to be triggered on normal tissues beyond high **dose threshold** (>6-8 Gy)
- An hypothetical clinical treatment optimization must include the **phenomenological FMF_{min} and the D_T parameters**

Böhlen et al, 2022, doi: 10.1016/j.ijrobp.2022.05.038

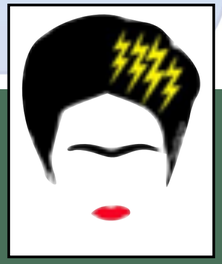


14.1, Mouse lung
17.1, Mouse survival
18.1, Mouse radiation syndrome
18.2, Mouse gastro-intestinal
18.3, Mouse brain
19.2, Mini pig skin
19.3, Mouse brain
20.1, Mouse crypt
20.2, Mouse skin
20.3, Mouse survival
20.4, Mouse survival
21.1, Mouse survival
21.2, Mouse crypt
21.3, Mouse skin
21.4, Mouse survival
22.1, Human skin
22.2, Mouse skin
71.1, Mouse survival
74.1, Rat skin 7-35d
74.2, Rat skin 5-23w
74.3, Rat foot deformity
82.1, Mouse tail necrosis

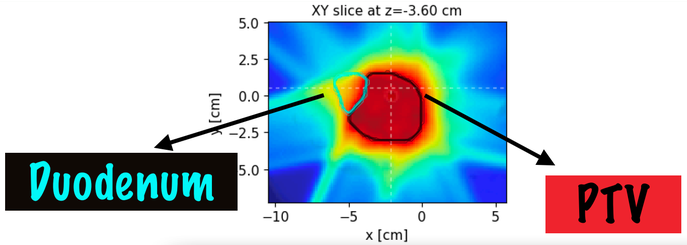
from available data



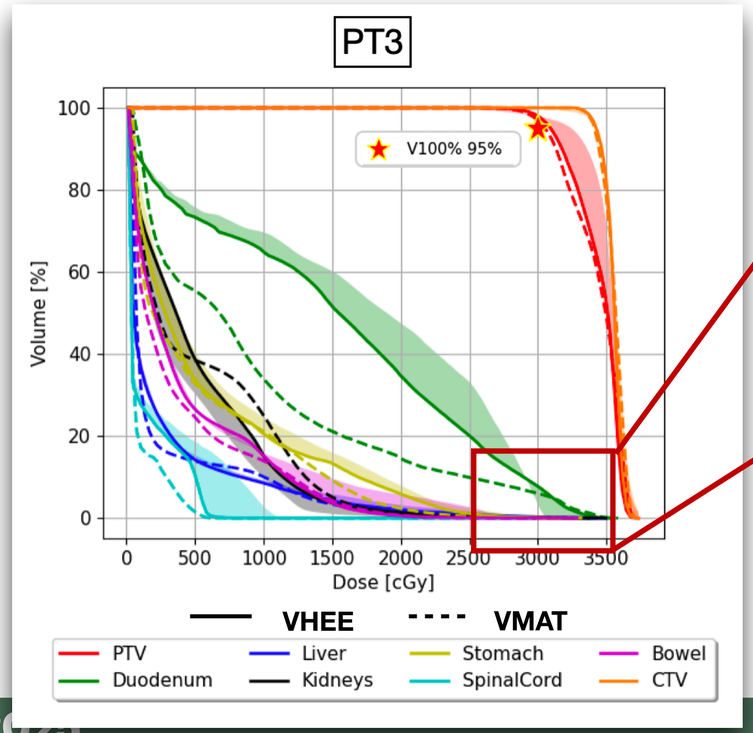
Highly hypofractionated tumors (e.g. pancreas, lung etc) as targets for FLASH treatment due to the high dose threshold

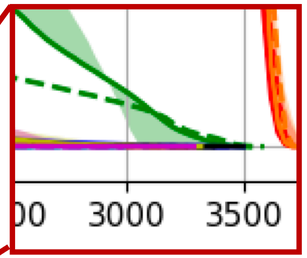


MC TPS for VHEE in FLASH Therapy



Transparent bands: potential improvement if the plan is delivered in UHDR conditions.





	VMAT	VHEE	VHEE-FLASH
PTV	99%	98.32%	98.32%
Duodenum D_{max}	35.88 Gy	35.11 Gy	31.06 Gy
Stomach	31.04 Gy	33.28 Gy	29.97 Gy

• FMFmin = 0.6 to 1 • Dth value of 25 Gy.

The FLASH optimization results in an **increase in the average** dose delivered to the duodenum, while **reducing its maximum absorbed dose** by approximately 4 Gy. This allows to increase the PTV coverage!

MC TPS: FAST MC codes

Fast MC techniques to overcome the large computing power asked by MC based TPS due to full MC calculations (several hours for a multi-field proton therapy treatment plan).

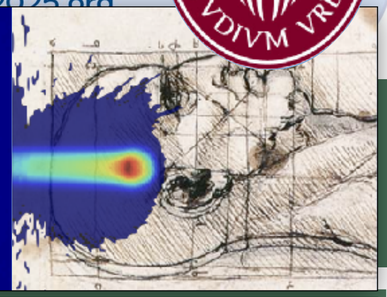
- New technologies in computing hardware
- Simplifying the code structure focusing on dedicated processes

- GPU based MC (FRED)
- Phase-Space Files (not for passive PT)
- Track-repeating algorithms
- Voxel MC algorithms ...

BUT FULL GENERAL PURPOSE MC CODES ARE STILL NEEDED!

FRED: a FAST MC code

Schiavi et al, PMB 62 (2017)



fast MC on GPU

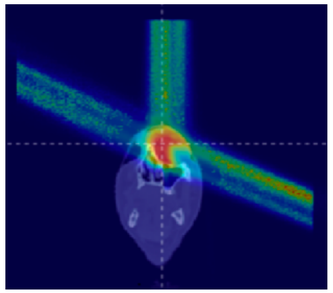
- standard MC algo approach
- full geometry
- full materials
- simplified interaction model

- tracking kernel respectful of GPU hardware constraints
- use FP32 wherever possibile
- LUT for hardware interpolation on Texture units
- explore event-based and history-based kernel solutions

Tracking Performances

	Hardware	primary/s	Patient plan recalculation*
FLUKA/GEANT4	single CPU core	$0{,}75 \times 10^3$	16 days
FRED	single CPU core	15×10^3	19 hours
FRED	single GPU card	1×10^7	**2.3 min**
FRED	cluster of 144 GPU cards	3×10^8	3 s

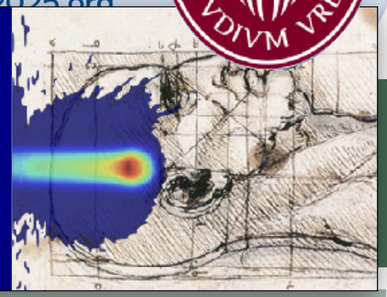
3 fields Head-Neck plan at 1% of total protons (700mln p)



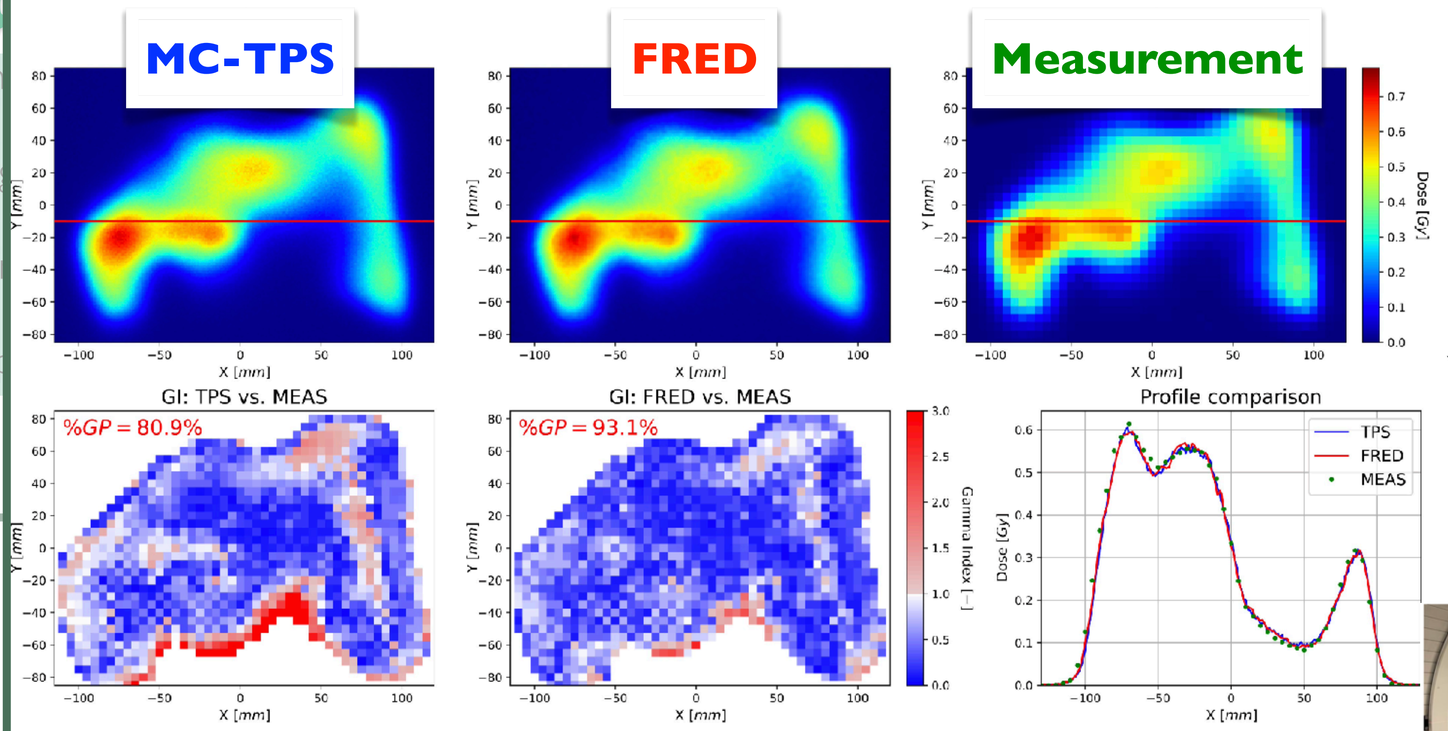
FRED: a FAST MC code

Schiavi et al, PMB 62 (2017)

Fred

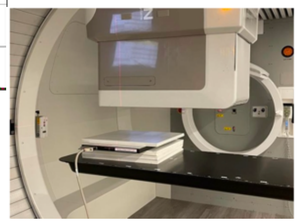


Patient QA @ Maastro



Maastricht

Octavius



Patient plan recalculation*
16 days
19 hours
2.3 min
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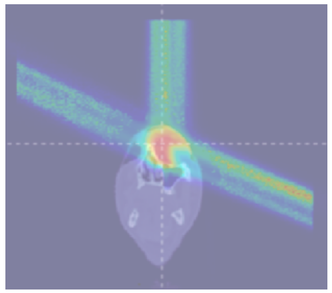

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Schiavi et al, PMB 62 (2017)

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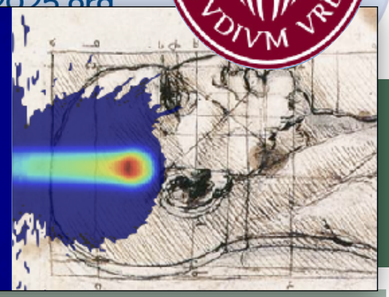
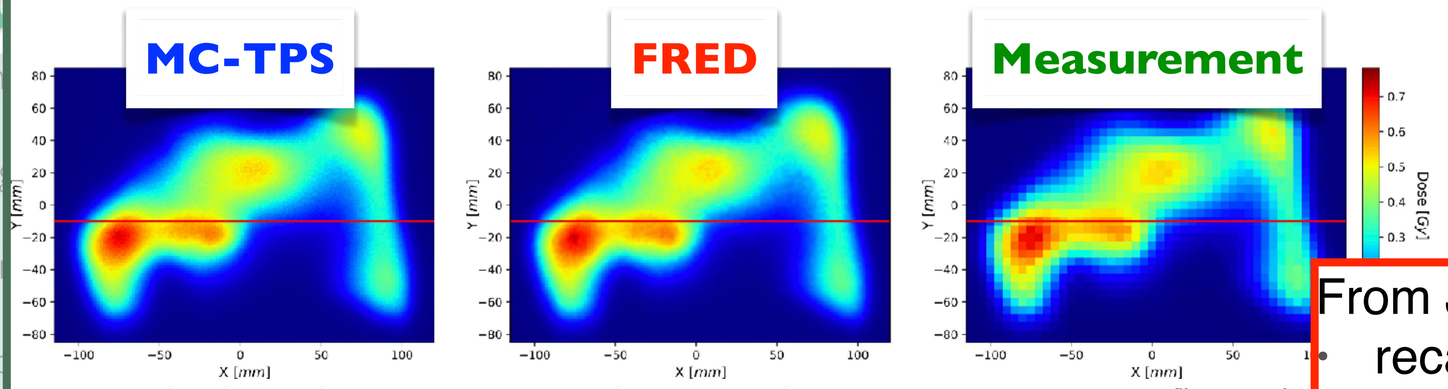
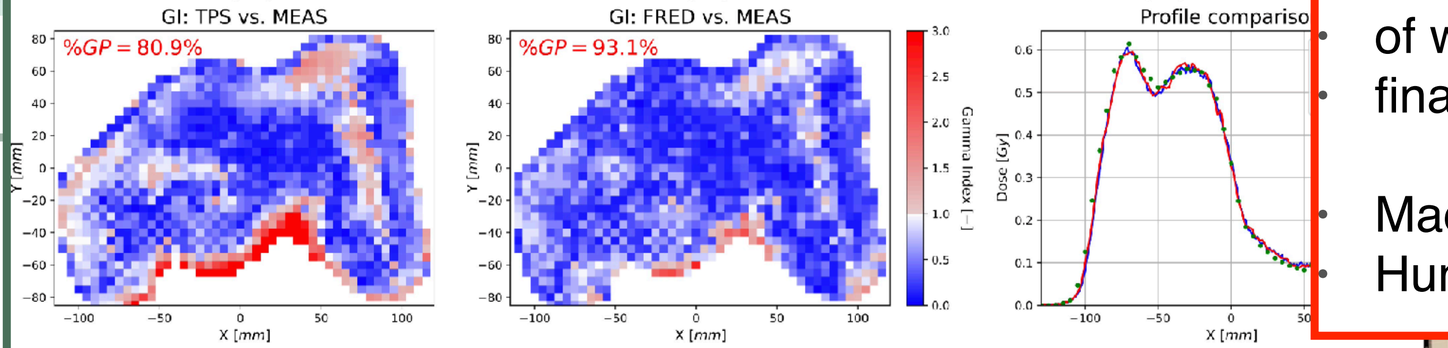


Patient QA @ Maastro





Maastricht

es

Patient plan recalculation*
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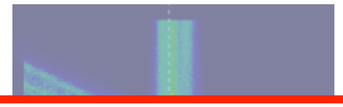


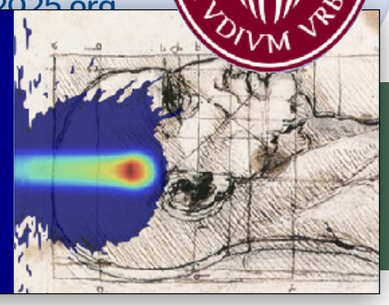
From Jul 2020 to May 2025:

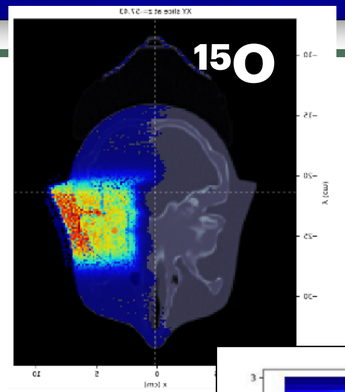
- recalculated plans with FRED: > **6000** plans
- of which **3272** machine log-file based PSQA
- final passing rate: **99.5** %

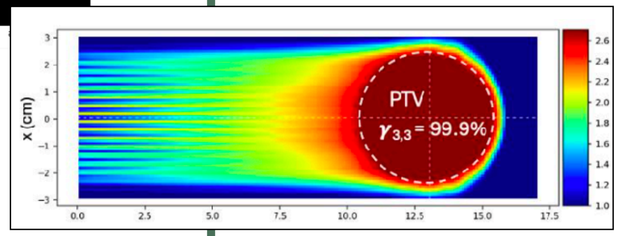
- Machine time saved: **> 3000 h**
- Human time saved: **100-400 working days**

FRED: a FAST MC code

Schiavi et al, PMB 62 (2017)

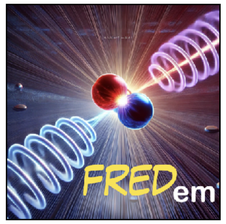


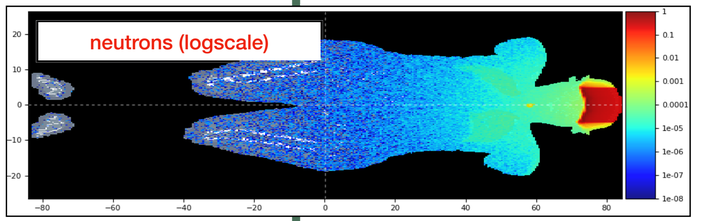




...AND much more...

- Range verification in proton therapy with PET-γs
- Radiation quality in proton therapy
- Fast optimization for 3D range modulators for FLASH proton therapy
- Carbon ions
- VHEE (with FREDem)
- Neutrons for studies for pregnancy in proton therapy





Artificial Intelligence for Medical Physics

Artificial intelligence in medicine uses machine learning to:

- **Medical imaging**: support for disease detection and early diagnosis, reducing errors, predictive analysis of disease progression and therapy outcome
- **Drug discovery**: analysis of molecular structures and genetic data, creating better drug designs and finding promising new drug combinations
- **Treatment planning**: selection and development of treatment plans, dose accuracy

- Personalized medicine enhancing the quality of care
- Improvement of clinical resources reducing inefficiencies and healthcare costs

Artificial Intelligence for Medical Physics

Artificial intelligen… medicine uses machine learning to:

- **Medical imagi…** …e detection and early diagnosis, reducing errors, predictive and… …therapy outcome
- **Drug discove…** …ic data, creating better drug designs and…
- **Treatment pla…** …accuracy

- Person… …quality of care
- Improvement of … …ucing inefficiencies and healthcare…

…and much more!… as seen in this congress: AI-based reconstruction algorithms in imaging techniques, AI to manage and interpret inhomogeneous data on FLASH effect, AI for radiobiology, dosimetry…

Conclusions

- Monte Carlo simulations play a key role in Medical Physics
- In **Particle Therapy,** general purpose MC codes improve the **dose accuracy** with respect to analytical TPSs
- The development of **radiobiological models** MC based is fundamental to address the therapy outcome and effects at a microscopic and macroscopic level
  => important also for **FLASH therapy**
- **Neutron dose calculation is needed** to predict **long-term effects in PT** (but also to design spacecraft shielding for astronauts radioprotection in long missions)
- **FAST-MC codes** are developing to enlarge the use of MC-based treatment plans but also to produce datasets for radiobiological models training

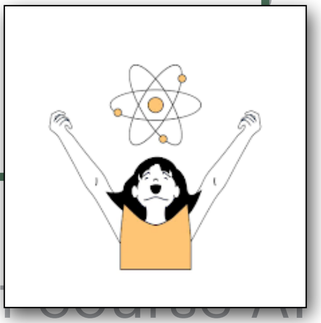
..and of course AI

Conclusions

- Monte Carlo simulations play a key role in Medical Physics
- In **Particle Th**
respect to
- The develop
the therapy o
=> especially
- **Neutron dos**
design space
- **FAST-MC codes** are developing to enlarge the use of MC-based treatmen
but also to produce datasets for radiobiological models training

Expertise and data from nuclear physics experiments are essential to improve radiobiological models of tissue response to particle treatments in Monte Carlo simulations.

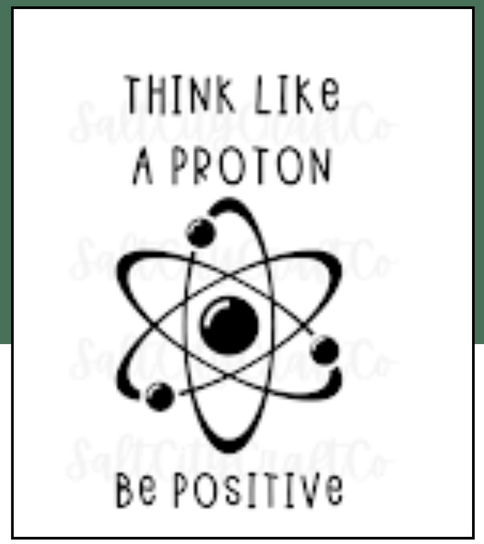
I still am an experimental physicist!



..and o

INFN MILANO

Thank you for the attention



with thanks to Prof.s V. Patera, G. Battistoni and A. Schiavi
for the supporting material

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SPARES

The MC Method: Random Generators

Some RANDOM NUMBERS GENERATORS nowadays

Python

Lista non esaustiva…

random.**random()** _____ Genera pseudorandom in (*0,1*)

random.**uniform(*a, b*)** _____ Genera pseudorandom in (*a,b*)

random.**triangular(*low, high, mode*)**___ Distribuzione triangolare in (*low,hide*)

random.**expovariate(*lambd=1.0*)**_____ Distribuzione esponenziale

random.**gammavariate(*alpha, beta*)**_____ Distribuzione gamma

random.**normalvariate(*mu=0.0, sigma=1.0*)**___ Distribuzione normal gaussiana

random.**gauss(*mu=0.0, sigma=1.0*)**_____ Distribuzione normal gaussiana *(più veloce di normalvariate)*

random.**randint(*a, b*)**_____ Genera pseudorandom intero in (a,b)

random.**binomialvariate(*n=1, p=0.5*)**_____ Distribuzione binomiale

ROOT

Lista non esaustiva…

TRandom class (TRandom1, TRandom2, TRandom3)

Rndm () _____ Genera pseudorandom in (*0,1*)

Integer (UInt_t imax)_____ Genera pseudorandom intero in (*0,imax-1*)

Uniform (Double_t x1, Double_t x2)_____ Genera pseudorandom (*x1,x2*)

Exp (Double_t tau) _____ Distribuzione esponenziale

Gaus (Double_t mean=0, Double_t sigma=1) Distribuzione normal gaussiana

Rannor (Double_t &a, Double_t &b) coppia di pseudorandom normal-gaussiani

Landau (Double_t mean=0, Double_t sigma=1) Distribuzione di Landau

Sphere (Double_t &x, Double_t &y, Double_t &z, Double_t r)
_____ vettore 3d random di lunghezza r

Circle (Double_t &x, Double_t &y, Double_t r)
_____ **vettore 2d random di lunghezza**

Poisson (Double_t mean) _____ Distribuzione di Poisson

Binomial (Int_t ntot, Double_t prob)_____ Distribuzione Binomiale

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The MC Method: Central Limit Theorem

Central limit theorem:

$$\lim_{N\to\infty} P(S_N) = \frac{1}{\sqrt{\frac{2p}{N}}\,s_A} e^{-\frac{(S_N - \bar{A})^2}{2s_A^2/N}}$$

For large values of N, the distribution of averages (normalized sums S_N) of N independent random variables identically distributed (according to any distribution with mean and variance ≠ ∞) tends to a normal distribution with mean $\bar{A}$ and variance σ_A^2/N

$$\lim_{N\to\infty} S_N = \lim_{N\to\infty} \frac{\sum_1^N A(x, y, z,...) f'(x)\, g'(y)\, h'(z) \ldots}{N} = \bar{A}$$

Particle Therapy: TPS

Aspects contributing to the complexity of Treatment Planning in hadron therapy

- Management of interfaces/corrections
- Nuclear composition of materials

Relevant technical aspects

- Integration with local beam delivery systems
- Need for "fast" calculation; possibility of producing alternative plans in due time
- Production of general and flexible analysis tools for the inspection of isodose curves on CT scans and Dose-Volume histograms (DHV), etc

Exploitable benefits

- Production of active nuclides, particle emission
  → possibility of in-beam monitoring
  → possibility of feed-back correction to Planning

Monte Carlo for TPS: How to

- Each medium is characterised by its composition and density.
  Density of atoms (or molecules) per unit volume: $\mathcal{N} = N_{\mathrm{A}}\rho/A_{\mathrm{m}}$

- Each interaction mechanism i is described by means of its differential cross section, differential in the energy loss W and the angular deflection Ω: $d^2\sigma_i/(\mathrm{d}\Omega\,\mathrm{d}W)$
- Total cross section: $\sigma_i = \int \mathrm{d}\Omega \int \mathrm{d}W \frac{\mathrm{d}^2\sigma_i}{\mathrm{d}\Omega\,\mathrm{d}W}, \qquad \sigma_{\mathrm{T}} = \sum_i \sigma_i$
- Mean free path: $\lambda_i = 1/(\mathcal{N}\sigma_i), \qquad \lambda_{\mathrm{T}}^{-1} = \sum_i \lambda_i^{-1}$
- Probability distribution functions:

$$p(s) = \lambda_{\mathrm{T}}^{-1}\exp(-s/\lambda_{\mathrm{T}}), \qquad p(i) = \frac{\sigma_i}{\sigma_{\mathrm{T}}}, \qquad p_i(\Omega, W) = \frac{1}{\sigma_i}\frac{\mathrm{d}^2\sigma_i}{\mathrm{d}\Omega\,\mathrm{d}W}$$

The required information reduces to the atomic DCSs for the relevant interaction mechanisms