Medical applications: a guided example

23rd FLUKA Beginner's Course
Lanzhou University
Lanzhou, China
June 2–7, 2024

History of FLUKA vs hadrontherapy applications

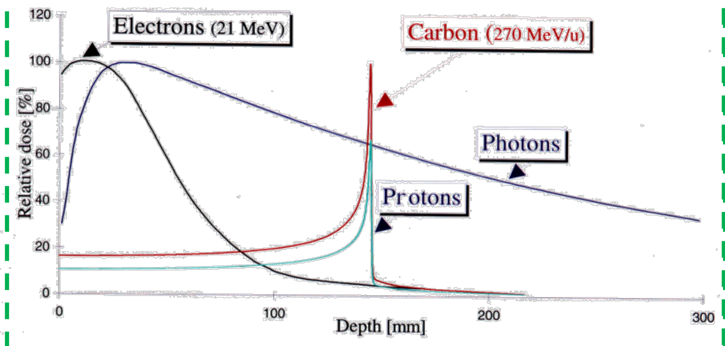
- The very first applications go back to the end of ’90’s *(M. Biaggi et al., NIMB **159** 89 (1999))*
- … in the following years (2000-2008) an **explosion of applications**, many thanks to K. Parodi, now Chair of Medical Physics at the Ludwig-Maximilians-Universität München (LMU) …
- … FLUKA establishes itself as the **standard** for newly created **Heidelberg Ion Therapy** centre (around 2009-2011), and later for **CNAO** …
- … 2011-2019 systematic **progress**, particularly for therapy monitoring, through **several EU programs**, PARTNER, ENVISION, ENTERVISION, and OMA …
- … **Siemens** and later **RaySearch** acquire FLUKA **licenses** for their commercial TPS’s …
- … 2020-now: further progress in the framework of the FLUKA Collaboration mostly with HIT & CNAO
- Too many papers to list, using FLUKA directly or as source of physics data, just a few:

- ✓ P. Lysakovski et al., Med. Phys. 2022, 1-15 (2022)
- ✓ A. Mairani, PMB67, 15TR02 (2022)
- ✓ P. Lysakovski et al., Frontiers in Physics, Rad. Det. and Imaging section, 9, 741453 (2021)
- ✓ S. Mein et al., Physica Medica, 74, 123 (2019)
- ✓ W.S. Kozlowska et al., PMB64, 075012 (2019)
- ✓ S. Mein et al., Scientific Rep., Nature, 8, 14829 (2018)
- ✓ R.S. Augusto et al, PMB63, 215014 (2018)
- ✓ T. Tessonnier et al., Rad. Oncology, 13:2, (2018)
- ✓ T. Tessonnier et al., PMB62, 6784 (2017)
- ✓ T. Tessonnier et al., PMB62, 6579 (2017)
- ✓ G. Magro et al., PMB62, 3814 (2017)
- ✓ G. Battistoni et al., Frontiers in Oncology, Rad. Oncology Sect., 6, 00116 (2016)
- ✓ A. Mairani et al., PMB61, 4283 (2016)
- ✓ T.V.M. Lima et al., Frontiers in Oncology, Rad. Oncology sect., 6, 00062 (8 pages) (2016).

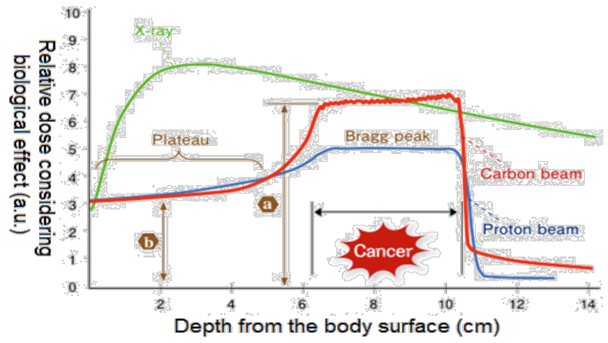
Therapy with hadron beams:

✓ **Rationale** for proton/carbon ion therapy : more convenient depth-dose profile in comparison to photons and electrons, in the case of deep-seated tumors.

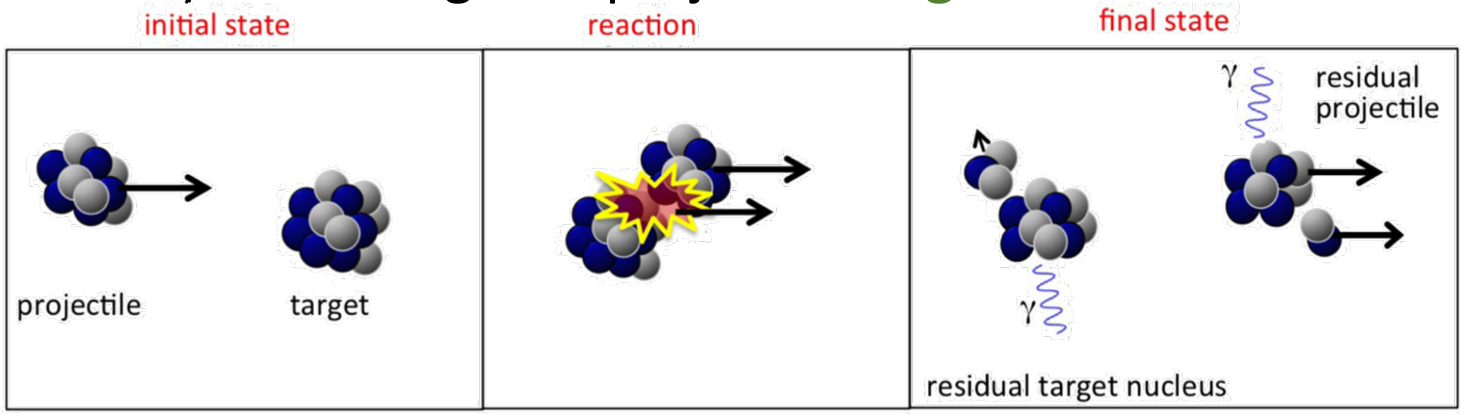
Single Bragg peak



Spread out Bragg peak



✗ However, nuclear interactions between primary ions and patient tissues may cause target or projectile **fragmentation**



Sources:

- Kraan AC 2015 Front. Oncol. 5:150
- Giulia Aricò ND2019 Beijing – China
- http://www.quantumdiaries.org/2012/page/31
- http://www.bestcyclotron.com/particletherapy

Why Monte Carlo for (hadron) therapy?

- In order to be used for patient treatment a calculation must fulfill several criteria beyond the physics model accuracy requirements (next slide):
  - Possibility to be interfaced with **radiobiological models** for biological (GyRBE) dose predictions;
  - Ability to describe in **fine details patient geometries** (possibly acquired directly from CT scans) including in-homogeneities and different materials;
  - Ability to predict **unwanted stray radiation** (neutrons...) important for pediatric patients
  - Ability to predict **detector responses**, for beam and therapy monitoring

✓ Monte Carlo codes are a perfect tool for those purposes, they not only can fulfill the above criteria, but also allow a **deeper understanding** into the complex radiation field generated by hadron (particularly ion) beams

× The only **limitation is speed**, hence general purpose Monte Carlo's are used for

- generation of databases for (commercial) TPS;
- verification/recalculation of TP;
- generation of offline parameterizations for analytical tools (eg Frog, CNAO/HIT), or databases for "fast", GPU-based, Monte Carlo's (eg MonteRay, HIT)

Hadron-Therapy: simulation physics requirements

- ✓ **Very accurate electronic stopping power** for e-, p, and light ions, from sub-MeV/n up to ~ 400 MeV/n (<<1%);
- ✓ **Accurate stopping power fluctuations** (~5%);
- ✓ **Accurate (multiple) Coulomb scattering** (<5%);
- ✓ **Reasonably accurate pA and AA nuclear physics** particularly for ion beams *(nuclear physics is never very accurate…)*;
  - ➢ Interaction cross sections (~5%);
  - ➢ Proton, neutron, and fragments energy and angle distributions (~30%);
  - ➢ De-excitation gammas (~20%) *(for therapy monitoring);*
  - ➢ Residual production, in particular β+ emitters (~20%) *(for therapy monitoring);*

Proton and Ion interactions for HadronTherapy: Dose Estimation, dE/dx and multiple scattering

(Unrestricted) dE/dx for heavy particles:

~ln $\beta^4\gamma^4$ relativistic rise

Spin 0:

$$\left(\frac{dE}{dx}\right)_0 = \frac{2\pi\, n_e r_e^2 m_e c^2 z^2}{\beta^2}\left[\ln\left(\frac{2m_e c^2 \beta^2 T_{\max}}{I^2(1-\beta^2)}\right) - 2\beta^2 + 2zL_1(\beta) + 2z^2 L_2(\beta) - 2\frac{C}{Z} - \delta + G\right]$$

- n_e : target electron density ($\rho N_{Av} Z/P_A$);
- z : $\sqrt{z^2_{eff}}$ "effective" charge of the projectile
- I : mean excitation energy, material-dependent;
- δ : density correction;
- C : shell correction, important at low energies;
- T_{max} : maximum energy transfer to an electron;

Higher order corrections implemented in FLUKA

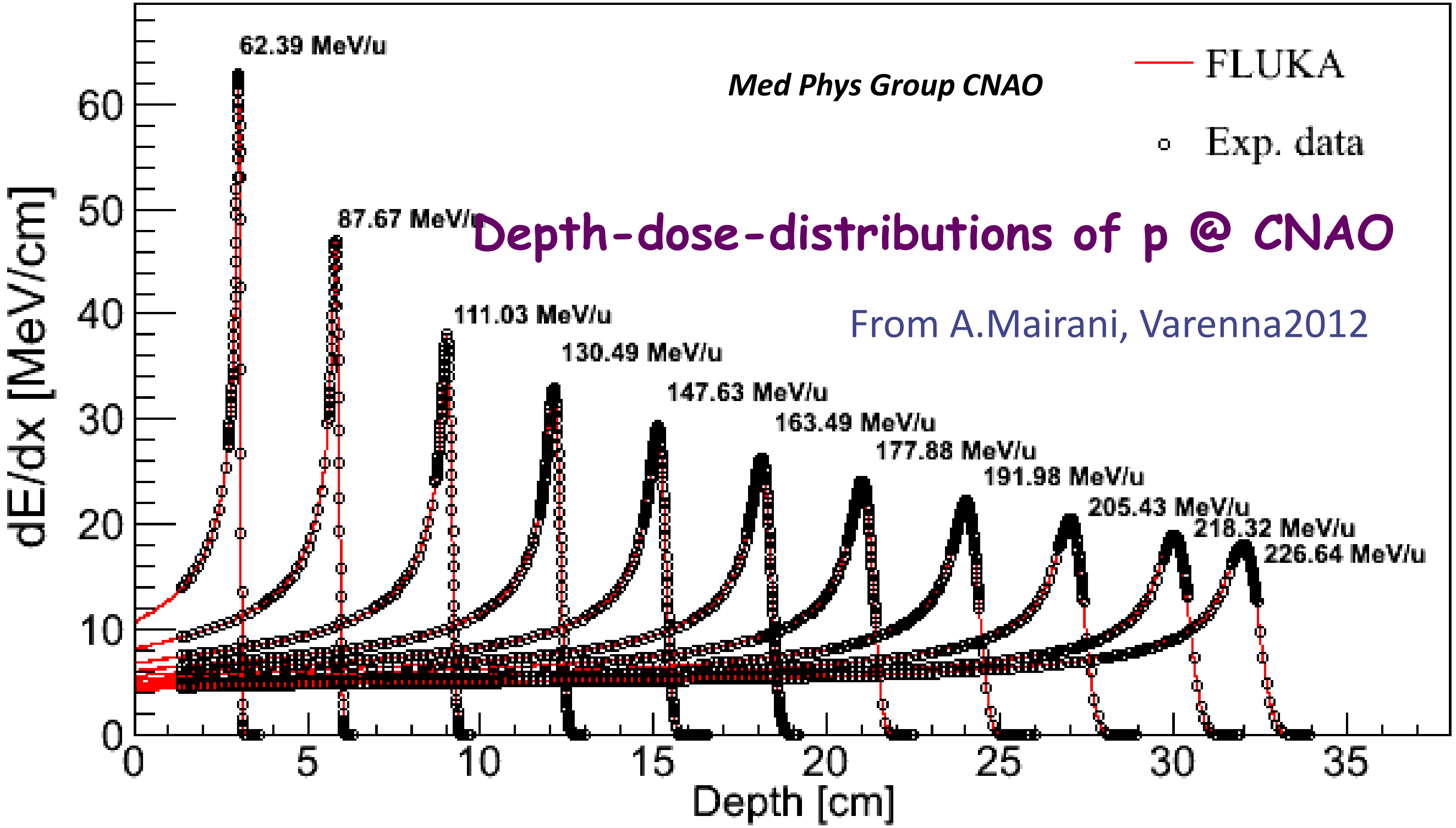
- L_1 : Barkas correction (z^3) $\rightarrow$ difference particles-antiparticles;
- L_2 : Bloch (z^4) correction;
- G : Mott corrections (beyond Born approx. when $\beta\alpha Z$ is no longer << 1)

Mott corrections (maybe the only code)!

- ✓ ***… for the average dE/dx …***
- ✓ ***… for the "Landau" fluctuations"…***
- ✓ ***… for the δ ray production cross section and spectrum***

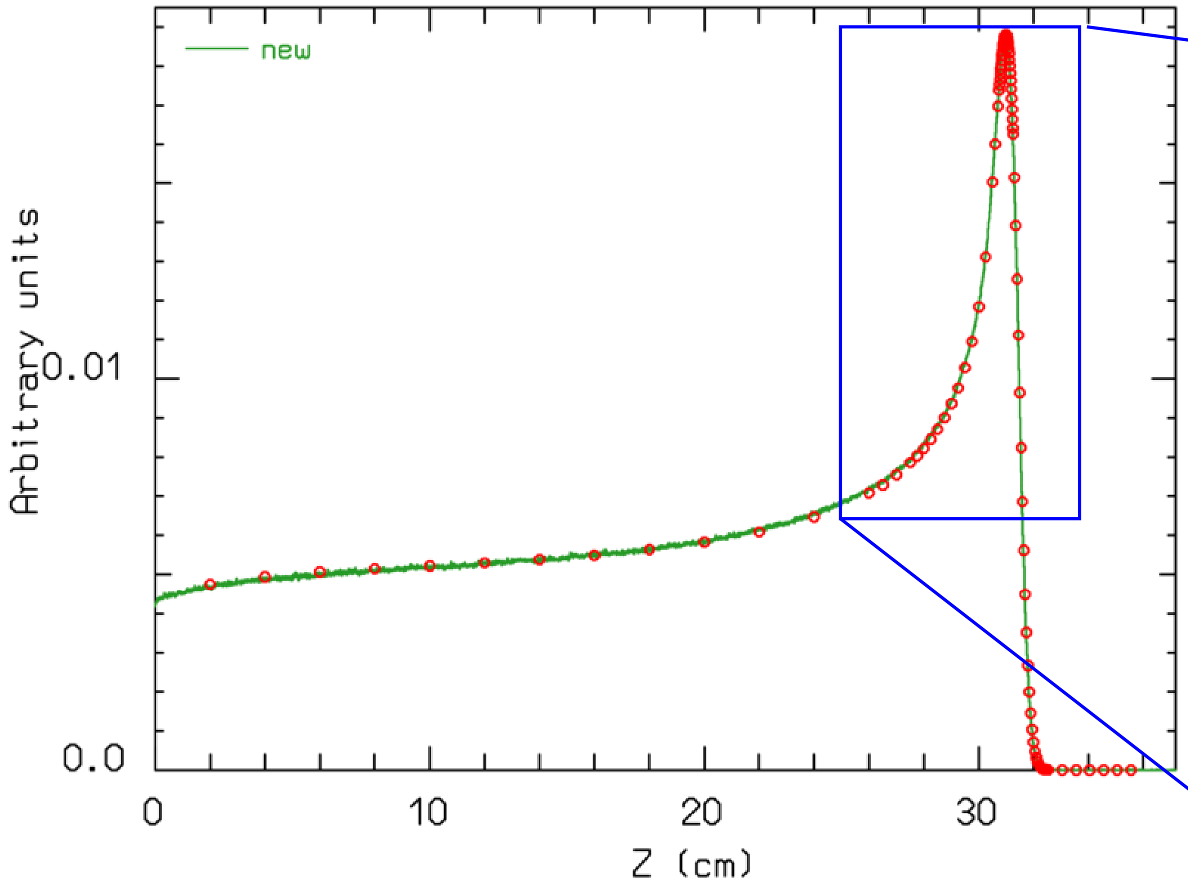
Fluka vs hadrontherapy, protons: HIT, CNAO, …

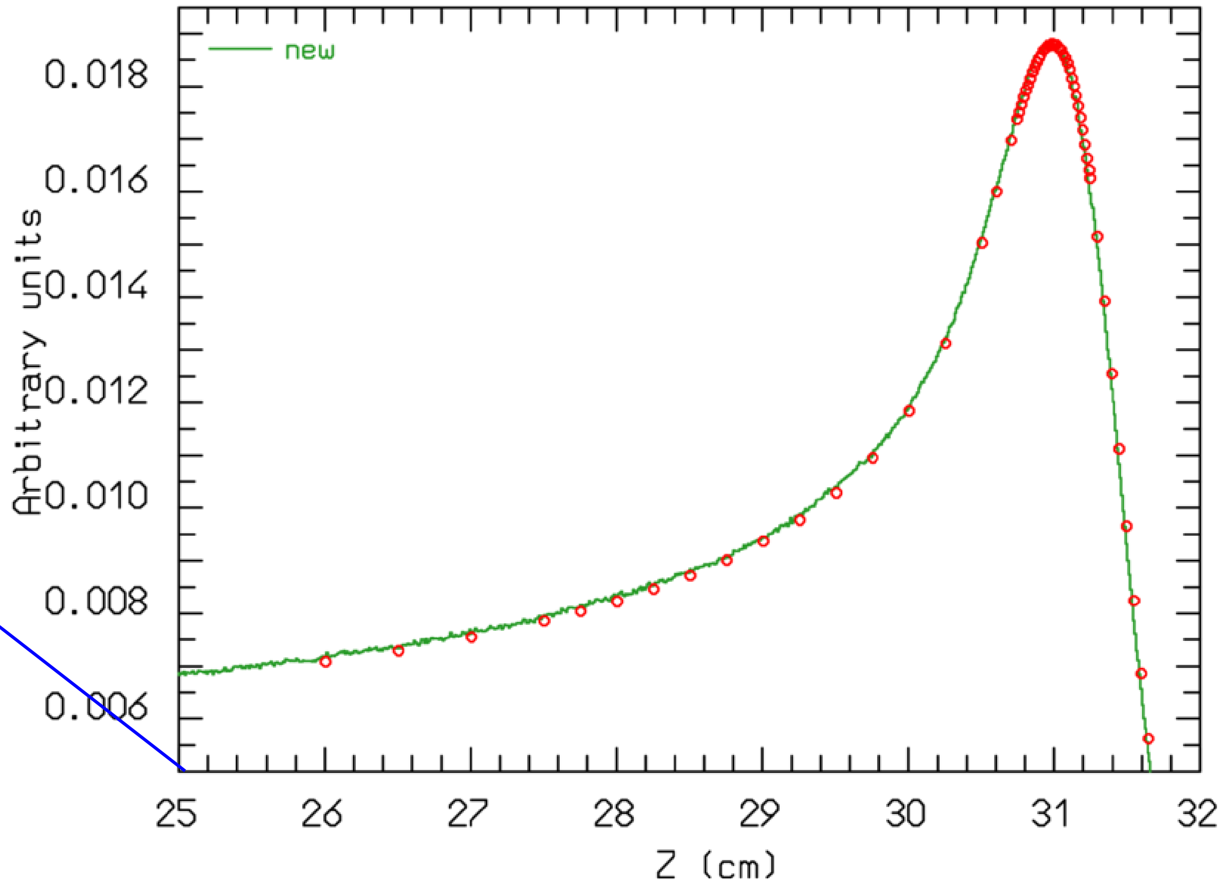
Used for generating dose vs depth databases then used for TP



in water wo/with RiFi for the **147** energies in the initial phase of the operation

221.05 MeV/n p on Water (HIT data):

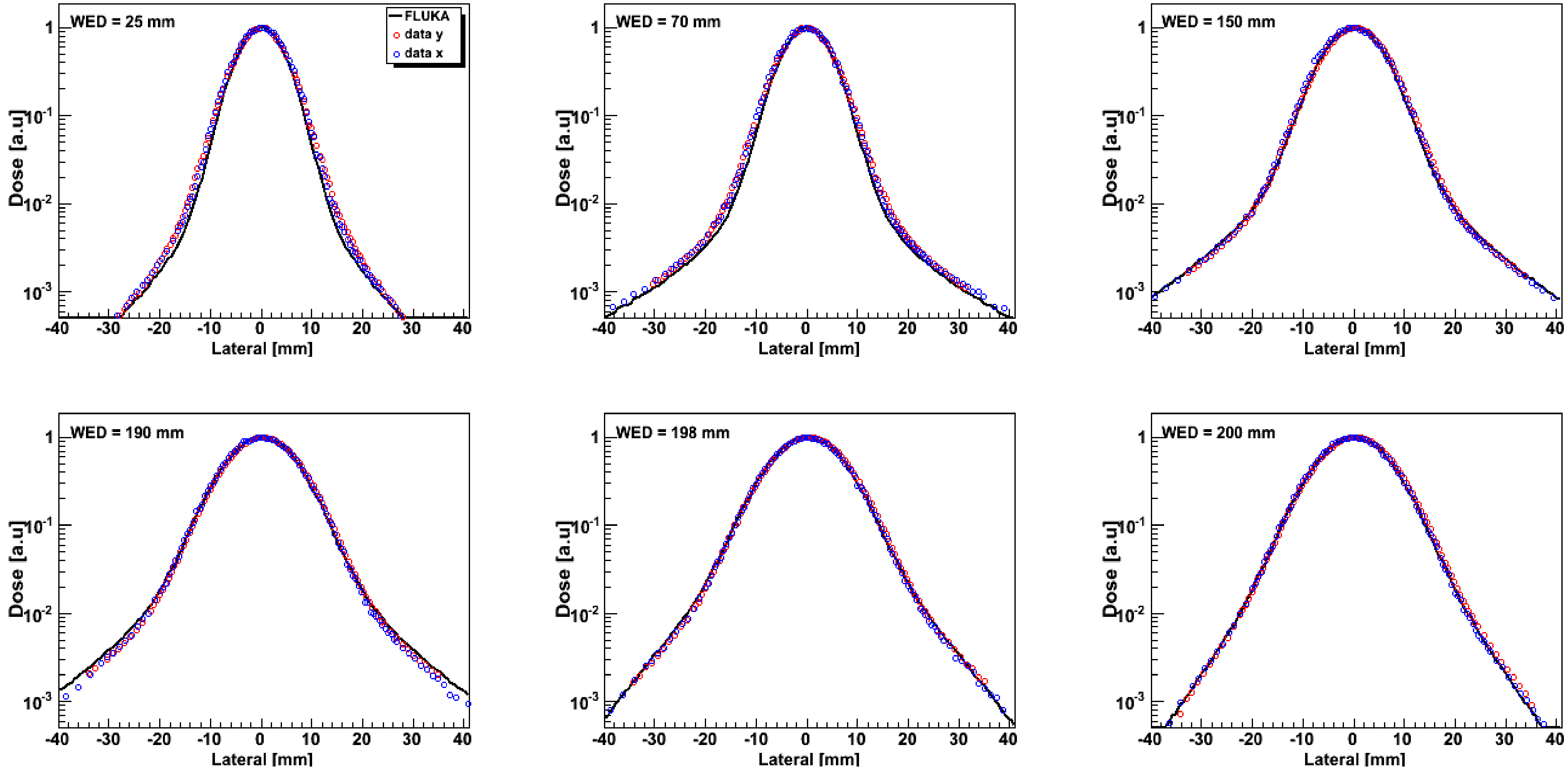




p: Lateral-depth dose distributions @ CNAO

CNAO Med. Physics Group
& Fluka Collaboration

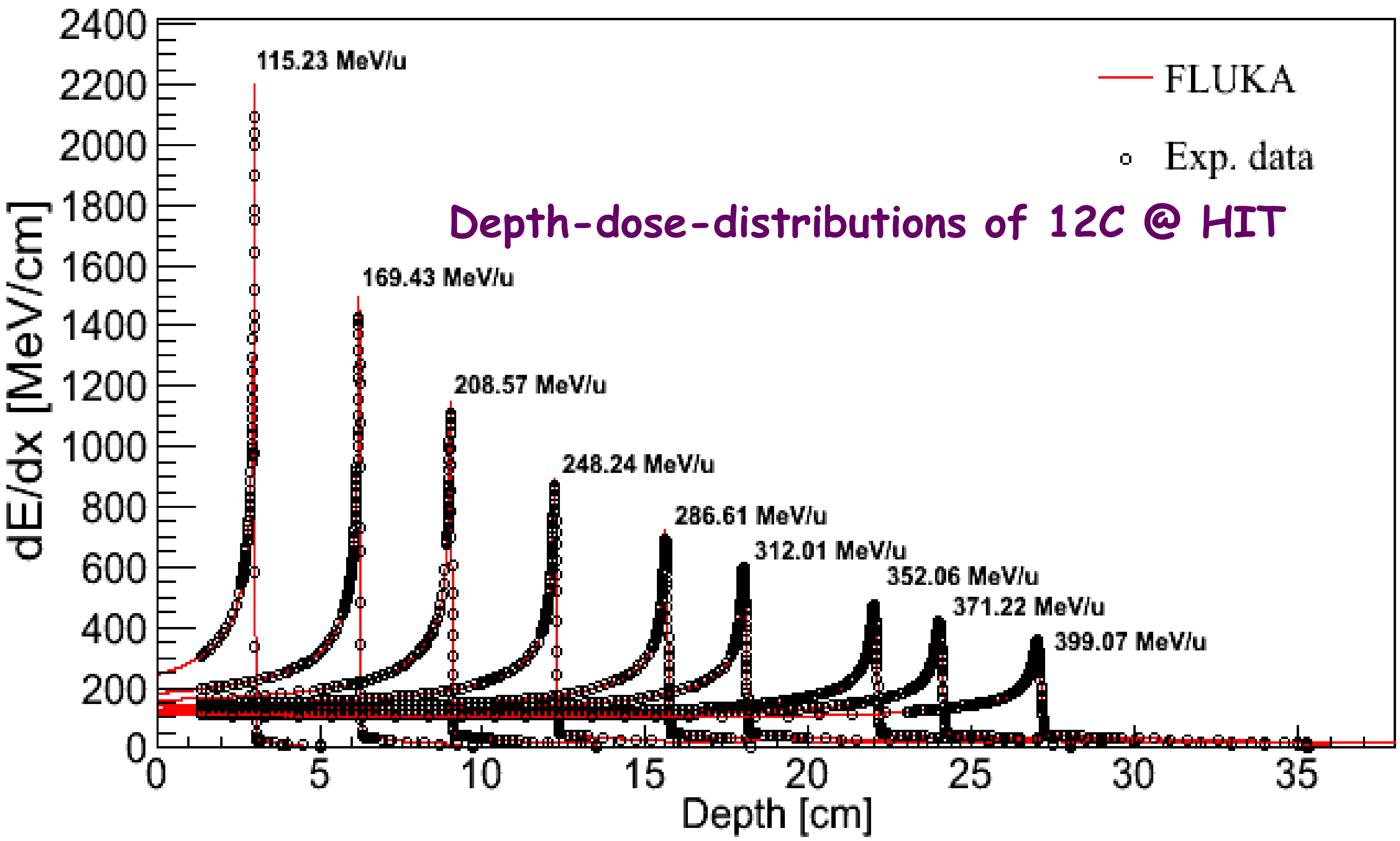
at different water equivalent depths (WED) for p @ 173.12 MeV/u



Both the experimental data and the MC results are renormalized to the maximum at each depth.

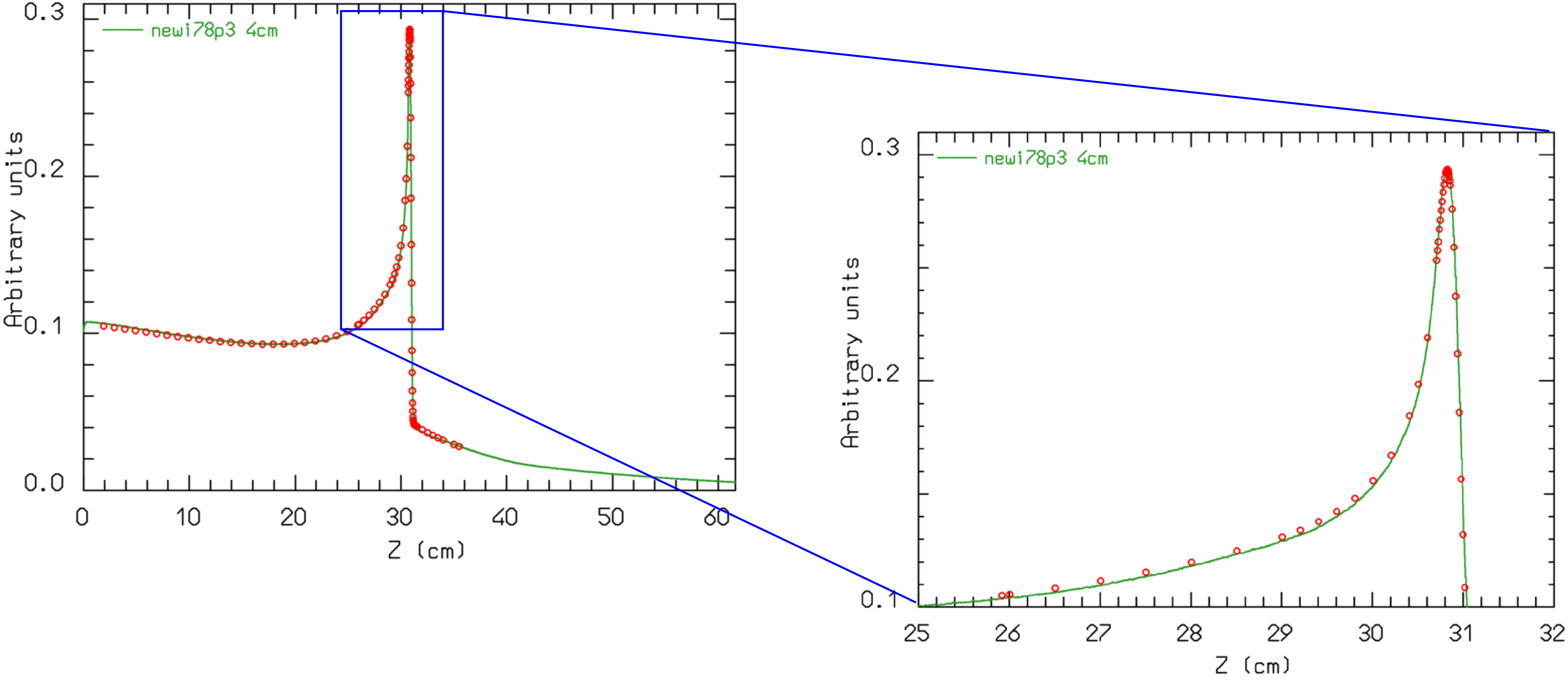
Fluka vs hadrontherapy, ^{12}C: HIT, CNAO, …

Used for generating dose vs depth databases then used for TP



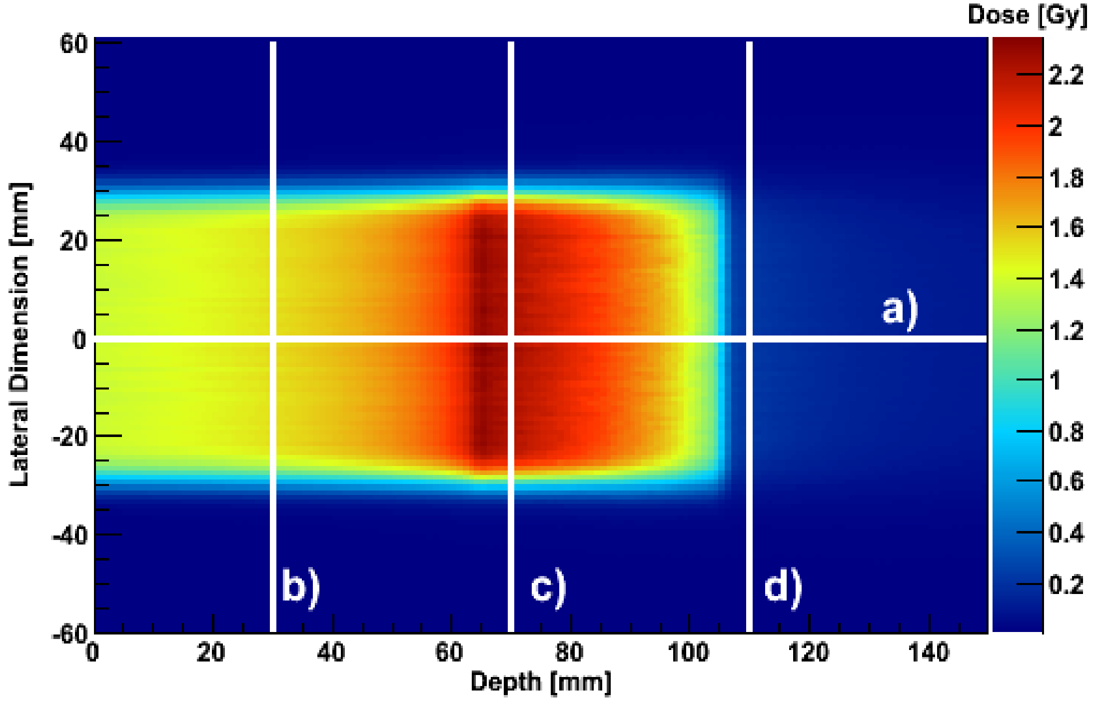
All curves for p, ^{4}He, ^{12}C (and ^{16}O) in water, measured at CNAO or HIT, can be reproduced with the same *I* value +/- < 0.5 eV!

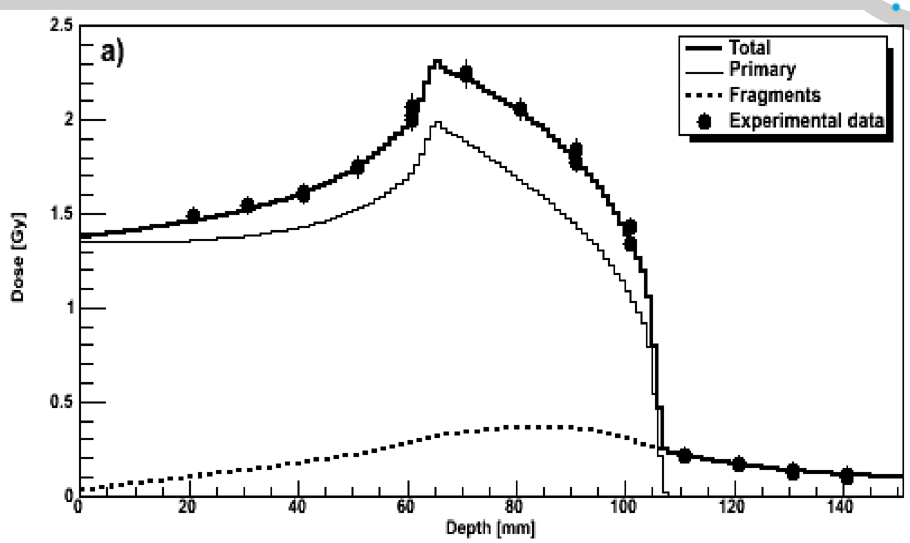
430.1 MeV/n ^{12}C on Water (HIT data):

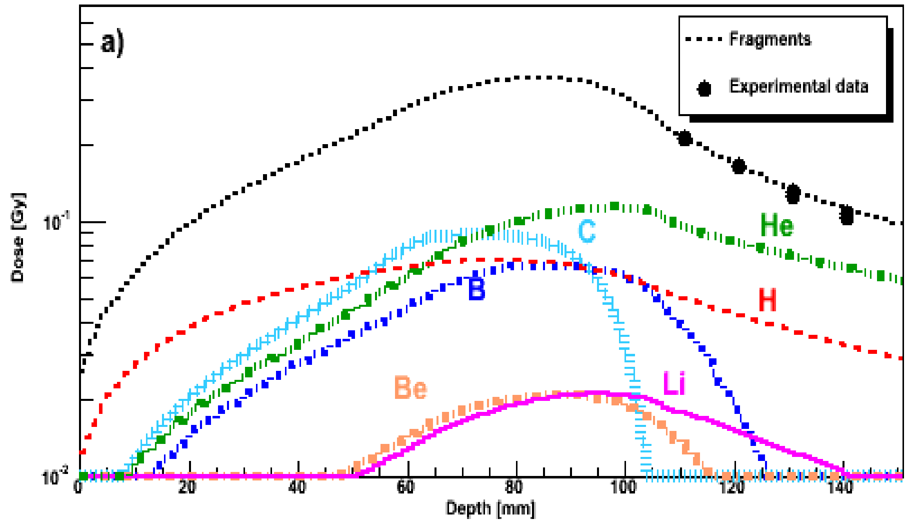


Characterizing a ^{12}C SOBP in water @ HIT I

- Max % difference FLUKA-DATA =1.5%
- At the depths of 3 cm and 7 cm the fragments contribution is 7% and 15% of the total dose.



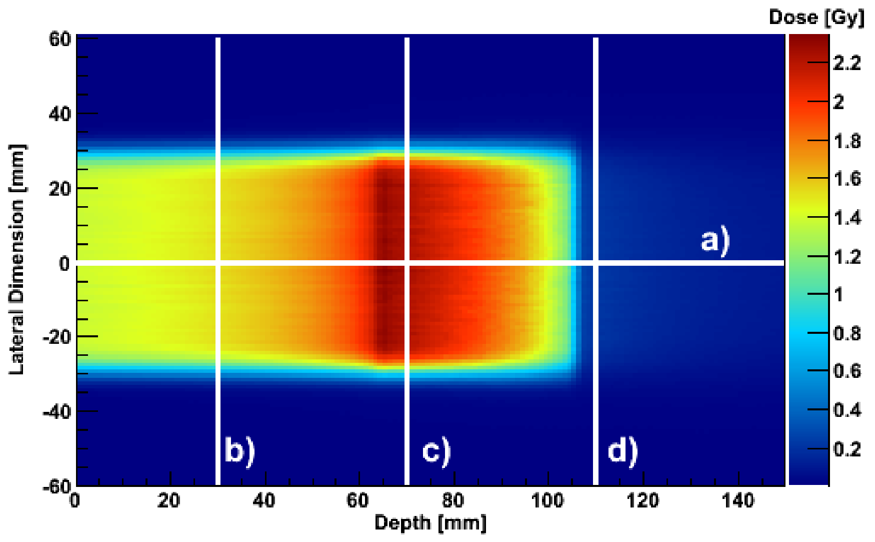


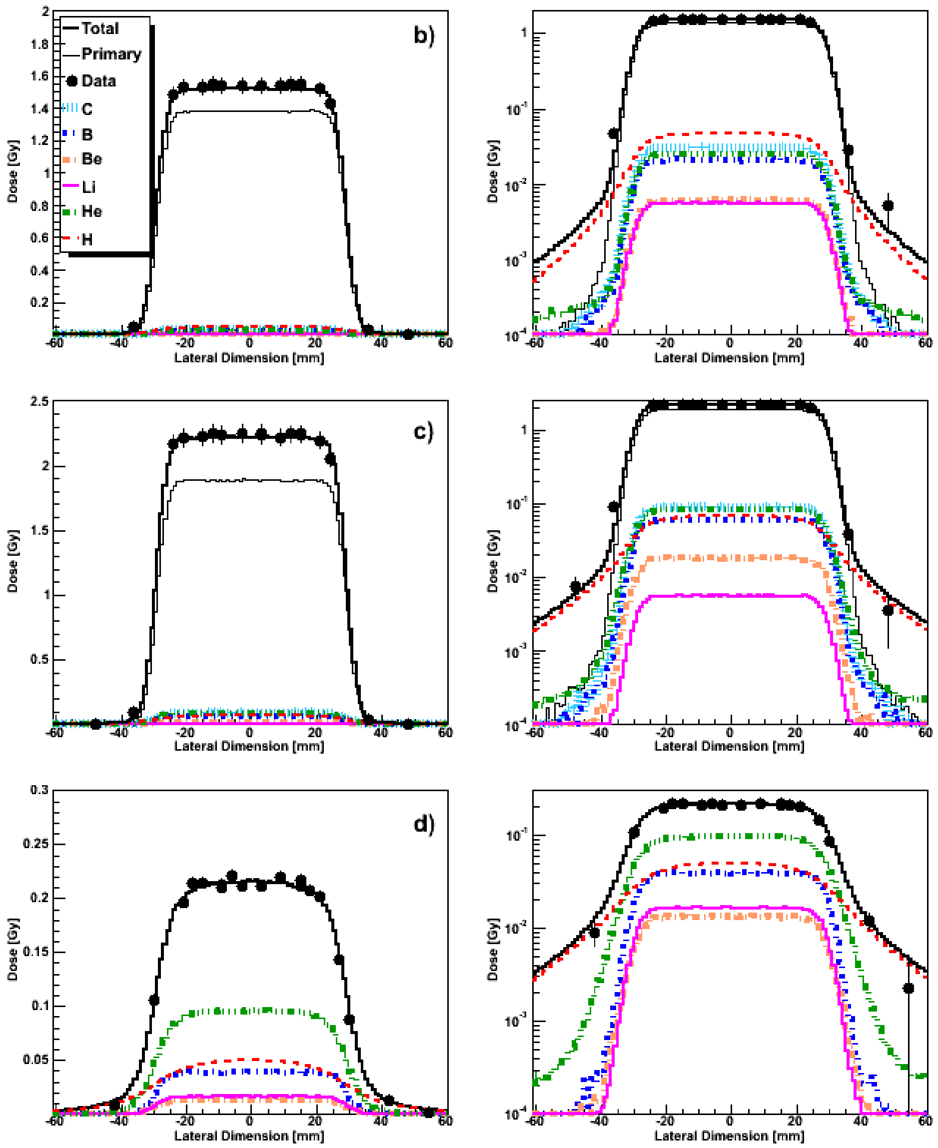


Bauer et al, PMB59, 4635

Characterizing a ^{12}C SOBP in water @ HIT II

- The average CPU time per primary particle history is 10 ms on a 2.133 GHz Intel® Core™ Duo processor.
- CNAO/HIT experience for patient TPS recalculation: simulate 0.5% of the actual ion intensity



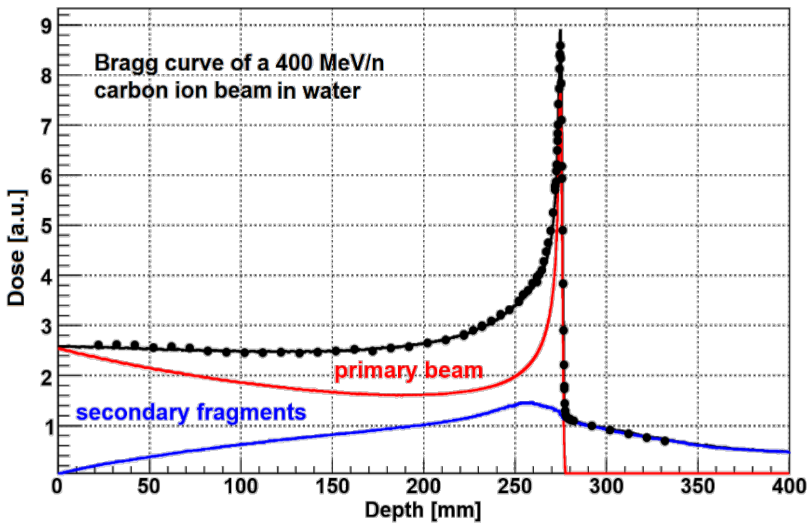


Bauer et al, PMB59, 4635

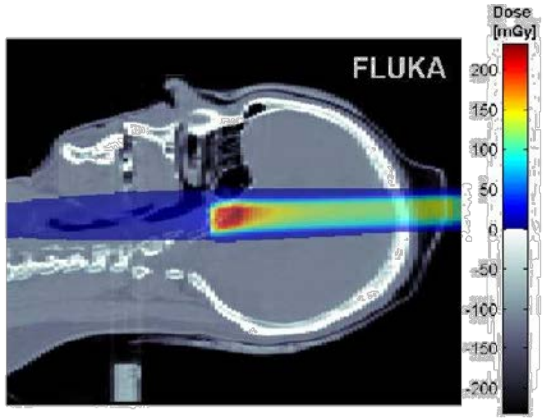
Interactive example:
Basic input example with Flair

Proton and Ion interactions for HadronTherapy: Nuclear fragmentation

✗ However, nuclear interactions between primary ions and patient tissues may cause target or projectile (ion beams only) **fragmentation**



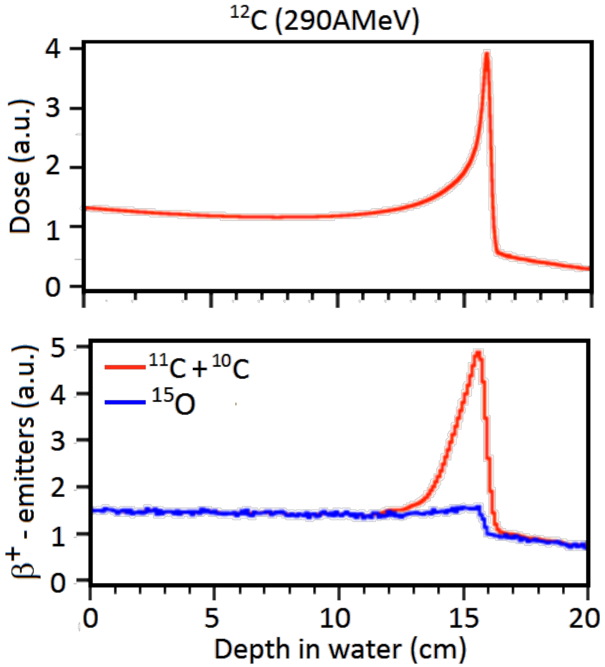
Dose delivered by secondary lighter particles behind the tumor



Sources:
Mairani A 2007,
PhD Thesis, Univ Pavia
Weber and Kraft 2009, the Cancer J **15**(4)

✓… nuclear interaction can be exploited using their products (prompt γ's, charged particles, β^+ emitters) to **monitor from outside the therapeutic beam**

290 MeV/u ^{12}C on water

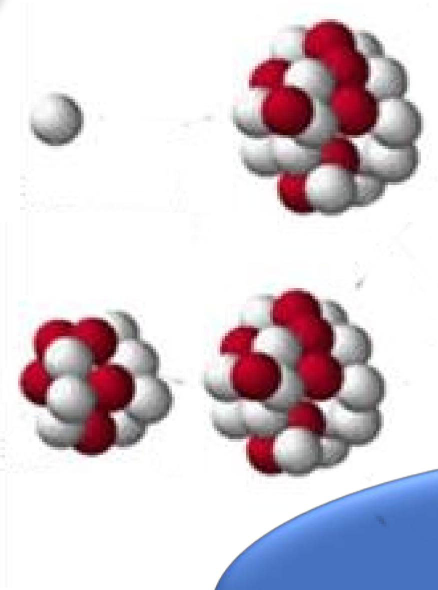


Fluka hA/AA models:

PEANUT
$2{\cdot}10^4 > E > \sim 0.01$ GeV

Photonuclear interactions
ElectroMagneticDissociation
Leptonuclear interactions

10^{-5}eV< Neut <20 MeV
ENDF + EAF
Grpxs and pwxs



DPMJET-3
$10^{11} > E > 2{\cdot}10^4$ GeV
$10^{11} > E/n > 10\text{-}15$ GeV

BME
$100\text{-}150 > E/n > \sim 5$ MeV

Extended rQMD
$10\text{-}15 > E/n > 0.1\text{-}0.15$ GeV

Interactive example:
^{12}C SOBP example with Flair:
1st part, dose, fragments

“Biological” dose

Recent papers:

- Carante, M.P., et al (2019) *“First benchmarking of the BIANCA model for cell survival prediction in a clinical hadron therapy scenario”*, Physics in Medicine and Biology, **64**, 215008.
- Carante, M.P., et al (2021) *“Biological effectiveness of He-3 and He-4 ion beams for cancer hadrontherapy: a study based on the BIANCA biophysical model”*, Phys. Med. Biol., **66**, 195009
- Dahle, T.D., et al (2020) *“The FLUKA Monte Carlo code coupled with an OER model for biologically weighted dose calculations in proton therapy of hypoxic tumors”*, Physica Medica, **76**, 166.
- Magro, G., et al (2017) *“The FLUKA Monte Carlo code coupled with the NIRS approach for clinical dose calculations in carbon ion therapy”*, Physics in Medicine and Biology, **62**, 3814.
- Ramos, R.L., et al (2022) *“Radiobiological damage by space radiation: extension of the BIANCA model to heavy ions up to iron, and pilot application to cosmic ray exposure”*, Journal of Radiological Protection, **42**, 021523
- Rørvik, E., et al (2018) *“Exploration and application of phenomenological RBE models for proton therapy”*, Phys. Med. Biol. **63** 185013.

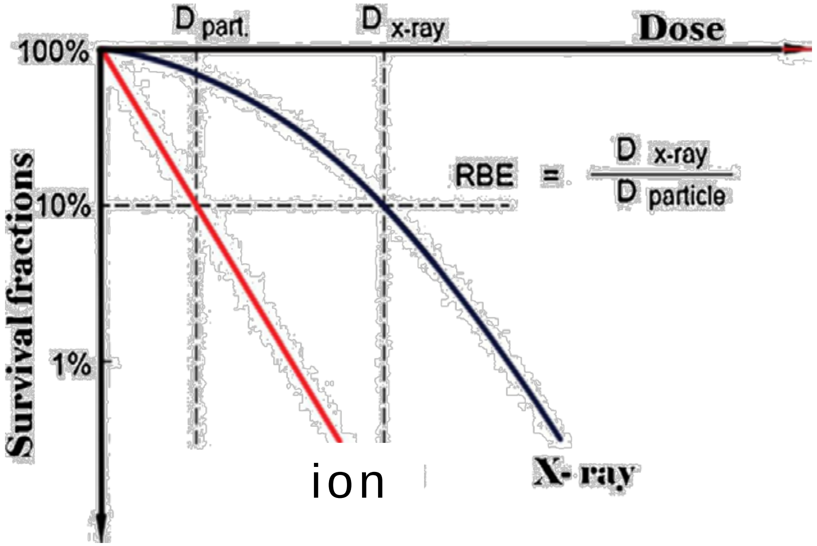
Biological models interfaced to FLUKA

A general Linear-Quadratic model interface for the biological effect has been integrated in FLUKA allowing: MKM, LEM, and most biological clinical or research model calculations:

- **LEM I** (clinical) and LEM IV (research)
- **mMKM** (clinical)
- RMF (research)
- UNIVERSE (research)
- BIANCA (research)

example

Magro et al PMB 62 (2017) 3814



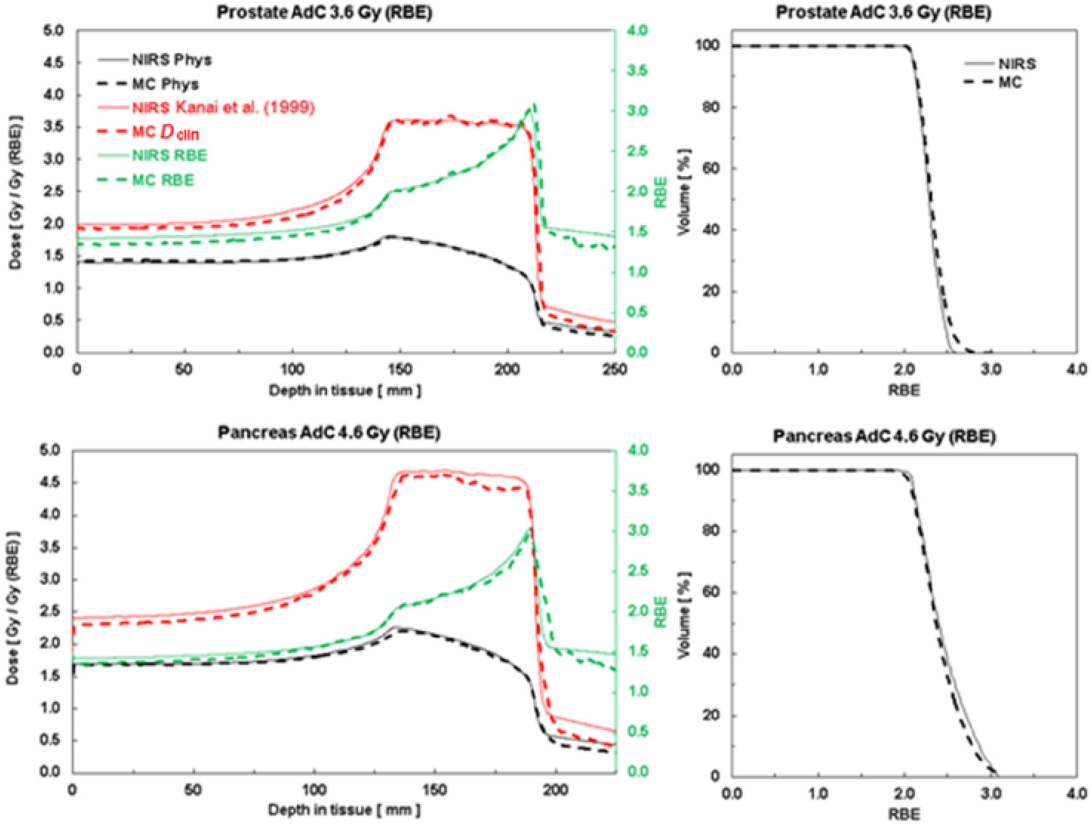


Figure 3. Left panels: comparison of depth physical dose ('Phys') (left y-axis, black lines), effective dose ('Kanai *et al* (1999)' or D_{clin}) (left y-axis, red lines) and RBE (right y-axis, green lines) profiles acquired at the isocenter in the target volume for one prostate AdC and one pancreas AdC case. Right panels: RBE volume histograms for the target structure. In each frame, solid and dashed lines represent original NIRS TPS and MC calculations, respectively.

Biologically Oriented Scoring in FLUKA*: how it works

*PMB55, 4273 (2010)

Under the standard assumption of a linear-quadratic dose-effect relationship, for each **energy deposition i**, FLUKA interpolates from a radiobiological database the **$\alpha_{D,i}$ and $\beta_{D,i}$** parameters for the specific ion with a certain charge at a certain energy.

Then **FLUKA sums up** properly **the mixed radiation effect** applying the Kellerer and Rossi theory of dual radiation action:

$$\sum \alpha_{D,i} D_i \qquad \sum \sqrt{\beta_{D,i}} D_i$$

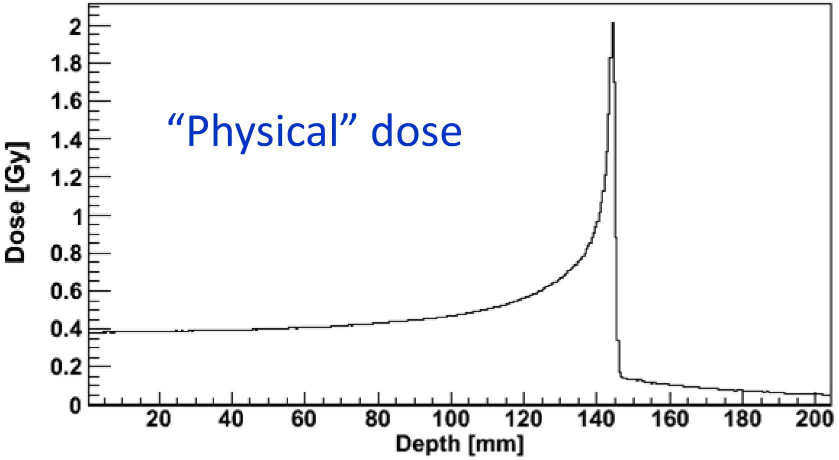
Then the **average biological parameters** can be calculated at the end of the FLUKA run:

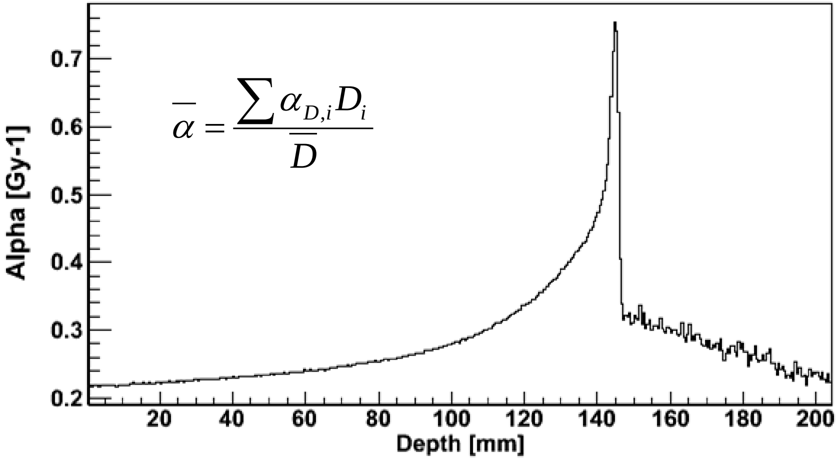
$$\overline{\alpha} = \frac{\sum \alpha_{D,i} D_i}{\overline{D}} \quad \text{and} \quad \overline{\beta} = \left(\frac{\sum \sqrt{\beta_{D,i}} D_i}{\overline{D}} \right)^2 \quad \text{with} \quad \overline{D} = \sum D_i$$

For example the **cell survival** can be calculated:

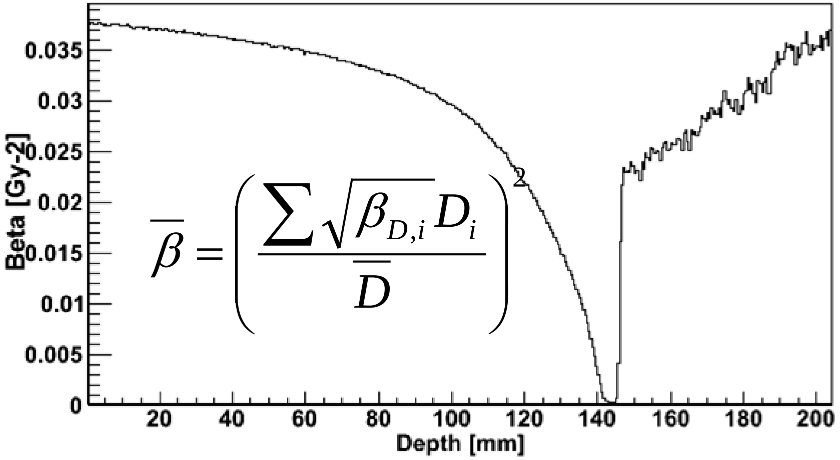
$$S = \exp(-\overline{\alpha}\,\overline{D} - \overline{\beta}\,\overline{D}^2)$$

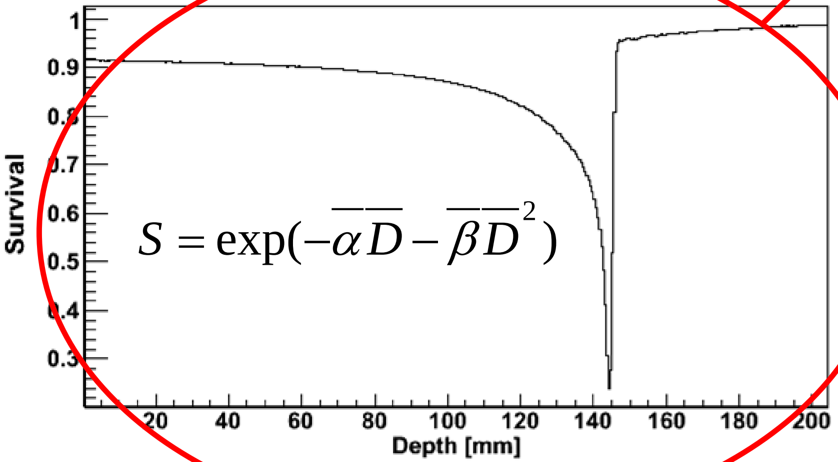
270 MeV/u ^{12}C ions on V79 phantom





Final result: survival curve



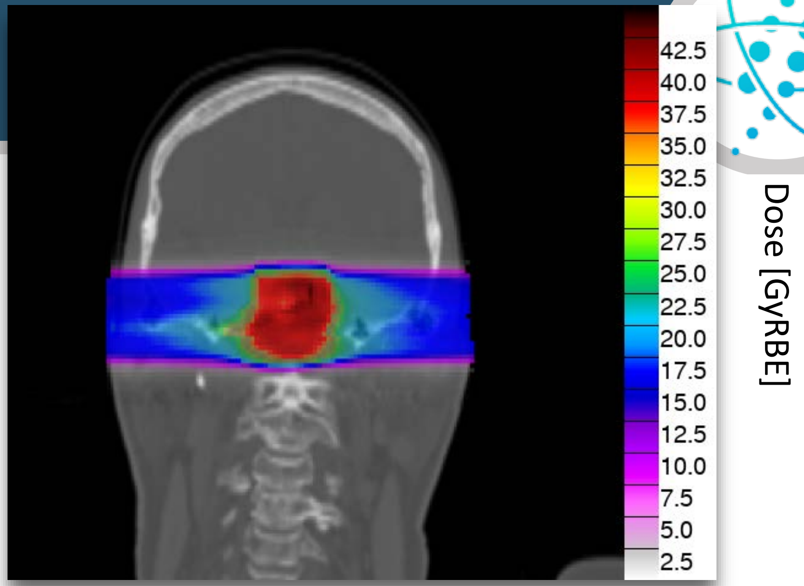


Linear Energy Transfer maps*:

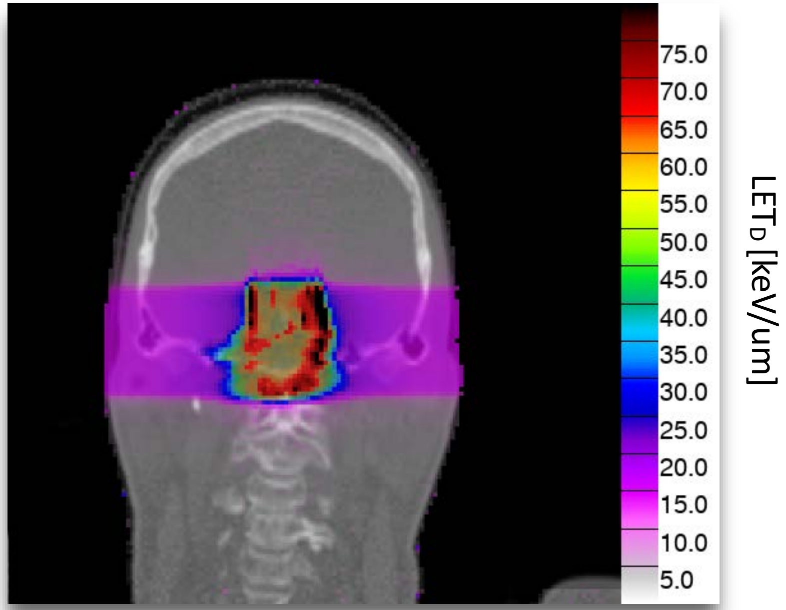
- ❑High-LET particles can improve the treatment outcome for hypoxic - **radioresistant tumors**
- ❑Minimizing LET in the **organs at risk** leads to a potential clinical benefit
- ❑Physical quantity such as **dose-averaged LET** can now be **calculated with FLUKA**
- ❑MC (FLUKA) can better predict contribution in LET_D from secondary particles with respect to analytical tools

$$L_d(z) = \frac{\sum_{i=1}^{N} \int_0^{\infty} S_i^2(E,z)\varphi_i(E,z)dE}{\sum_{i=1}^{N} \int_0^{\infty} S_i(E,z)\varphi_i(E,z)dE}$$

*From W.Kozlowska PhD work, PMB 64, 075012 (2019)

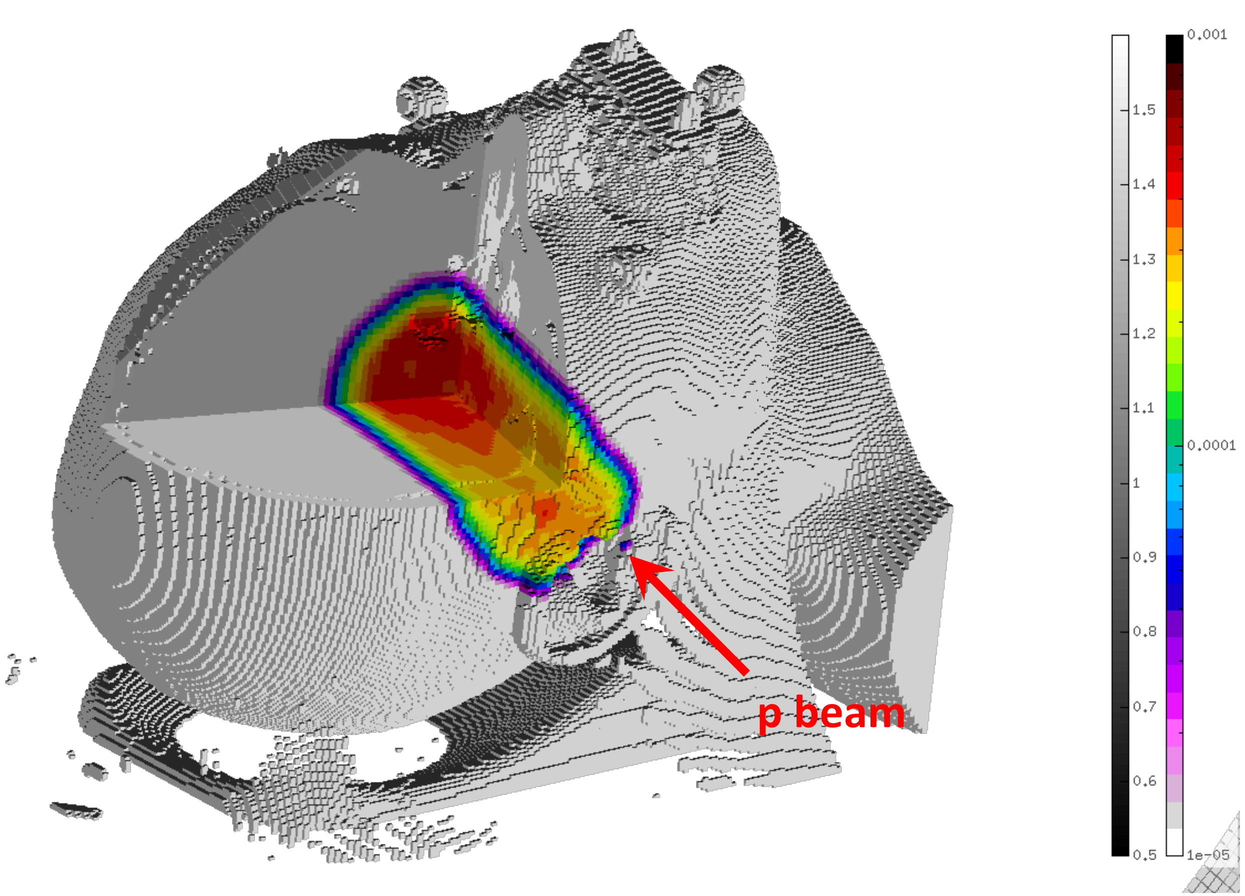


Carbon chordoma patient case (CNAO)

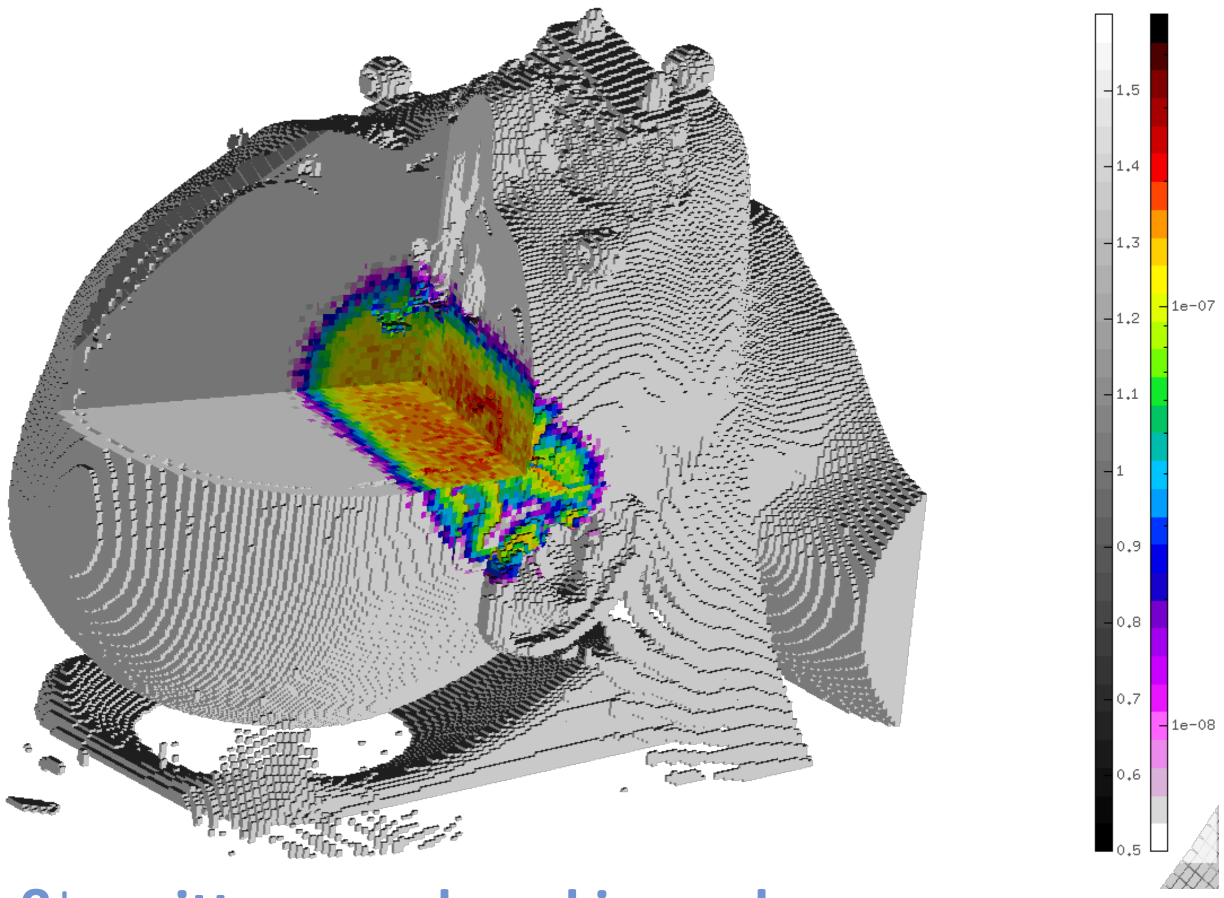


Interactive example:
^{12}C SOBP example with Flair:
2nd part, bio-dose, LET_D

Unwanted nuclear physics turned useful: ß$^+$ isotope prod.



Dose map

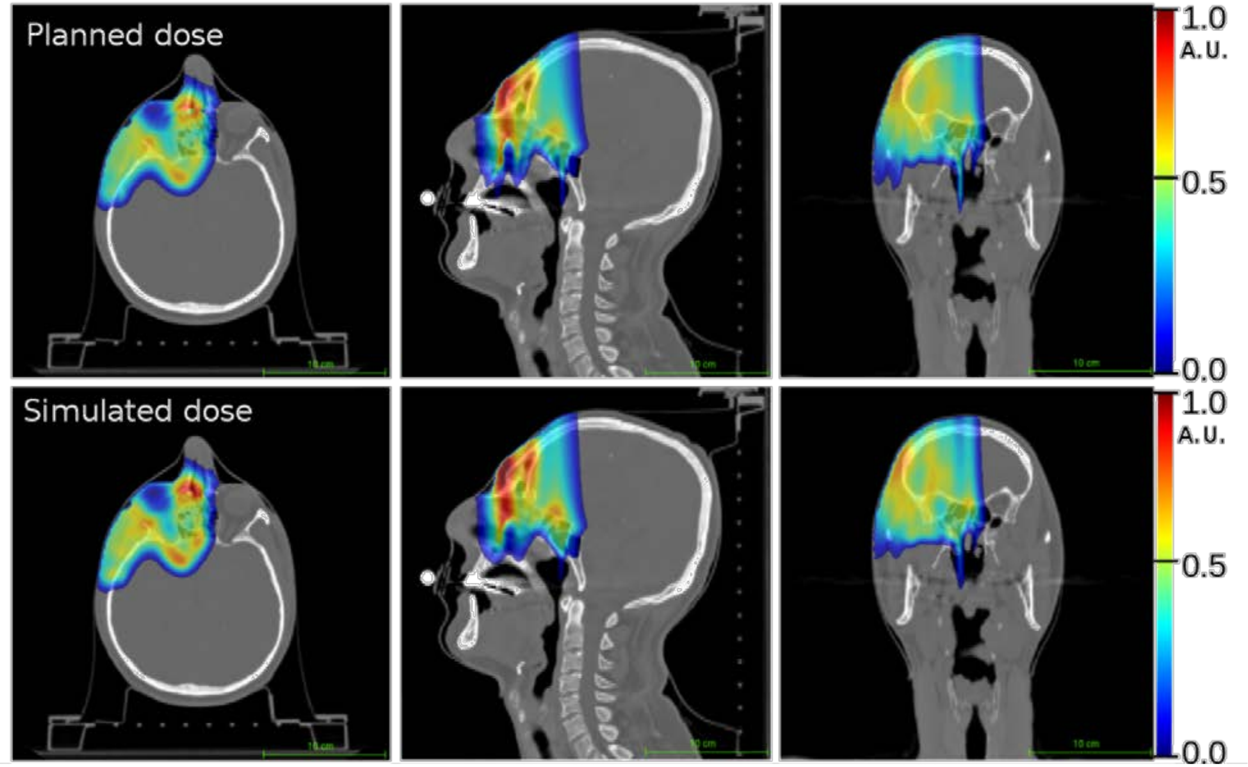


ß$^+$ emitters produced in nuclear interactions map

Positron emitters with FLUKA: proton and carbon beams

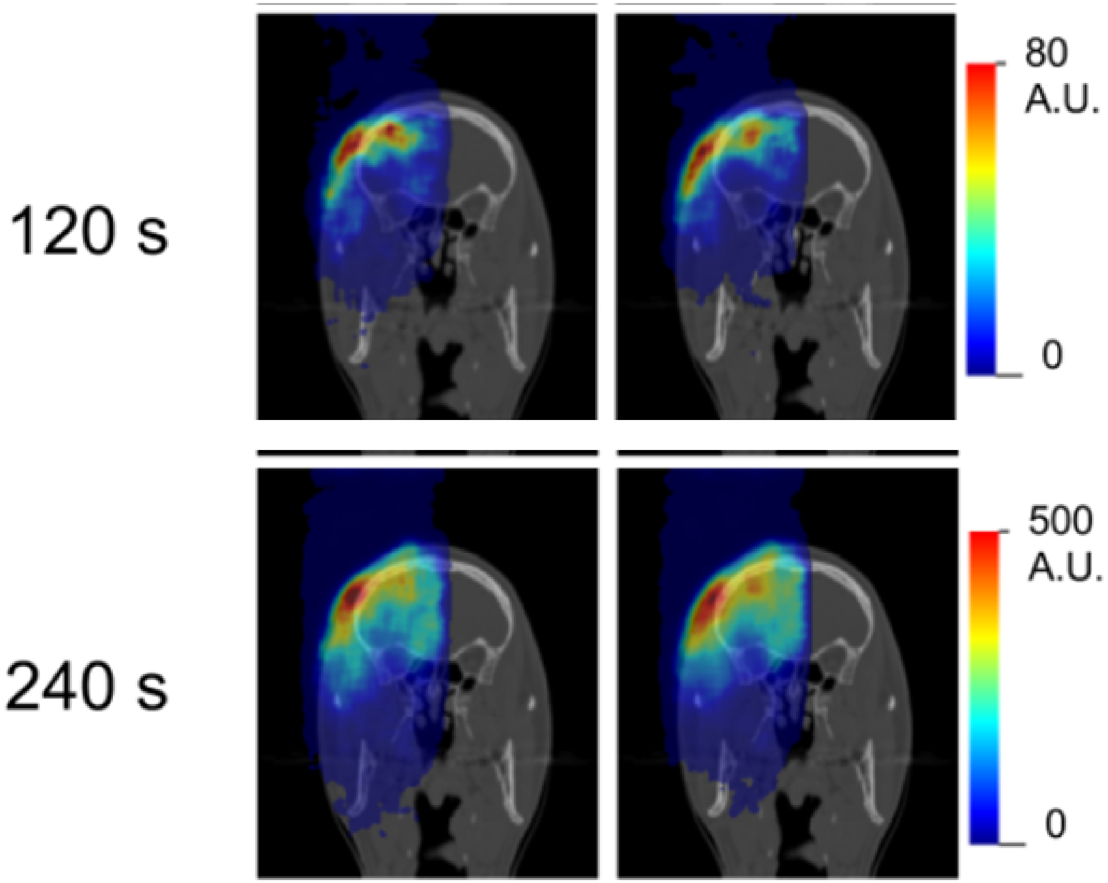
- A.C. Kraan et al., *"Analysis of in-beam PET time-profiles in proton therapy"* Journal of Instrumentation, **14**, C02001 (2019)
- S. Muraro et al., *"Low statistics positron activity reconstruction methods for proton therapy"*, Nuclear Instruments & Methods A, 936, **52** (2019)
- E. Fiorina et al., *"Monte Carlo simulation tool for online treatment monitoring in hadrontherapy with in-beam PET: A patient study"*, Physica Medica, **51**, 71 (2018)
- F. Pennazio et al., *"Carbon ions beam therapy monitoring with the INSIDE*
- *in-beam PET"*, Physics in Medicine and Biology, **63**, 145018 (2018)
- M.G. Bisogni et al., *"INSIDE in-beam positron emission tomography system for particle range monitoring in hadrontherapy"*, Journal of Medical Imaging, 4, 011005 (2017)
- S. Muraro et al., *"Proton therapy treatment monitoring with the DoPET system: activity range, positron emitters evaluation and comparison with Monte Carlo predictions"*, Journal of Instrumentation, 12, C12026 (2017)
- R.S. Augusto et al., *"An overview of recent developments in FLUKA PET tools"*, Physica Medica, 54, 189-199, (2018)
- R.S. Augusto et al., *"Experimental validation of the FLUKA Monte Carlo code for dose and β^+ -emitter predictions of radioactive ion beams"*, Physics in Medicine and Biology, 63, 215014 (2018)

P: Dose/β+ predictions vs TPS/data *(Phys.Medica51, 71,2018)*:



Planned (top) and FLUKA simulated (bottom) dose

Measured (left) PET and simulated (right) PET signal at 120 and 240 s after end of the irradiation



Online evolution and buildup of induced activity

- Arbitrary irradiation/cooling down profiles defined by the user
- … residuals produced during the "prompt" part are processed online
- … time evolution of induced radioactivity calculated analytically

✓ Fully coupled build-up and decay
✓ Resulting isotopes scored for all cooling times ***alltogether***

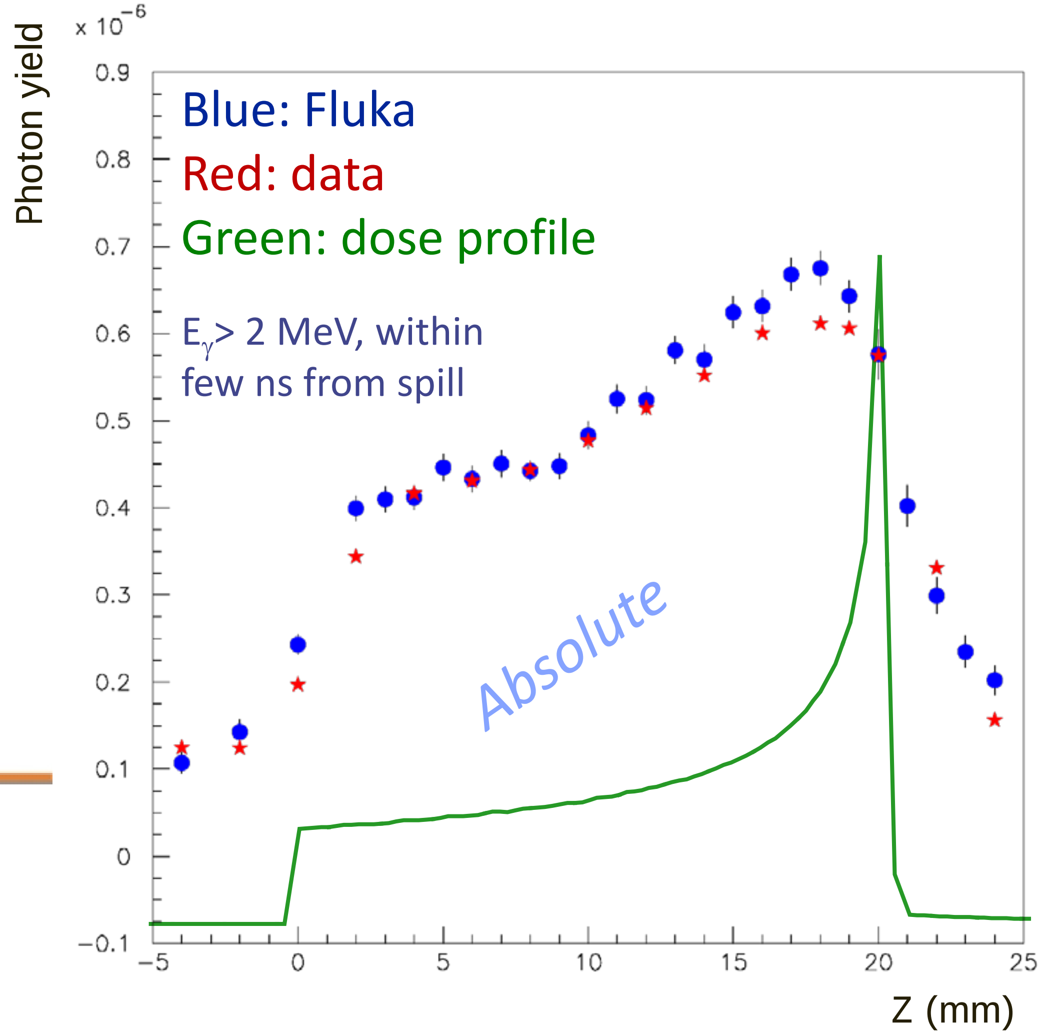
Results available for activities: 2D and 3D spatial distributions, and full inventories/activities at each buildup/cooling time

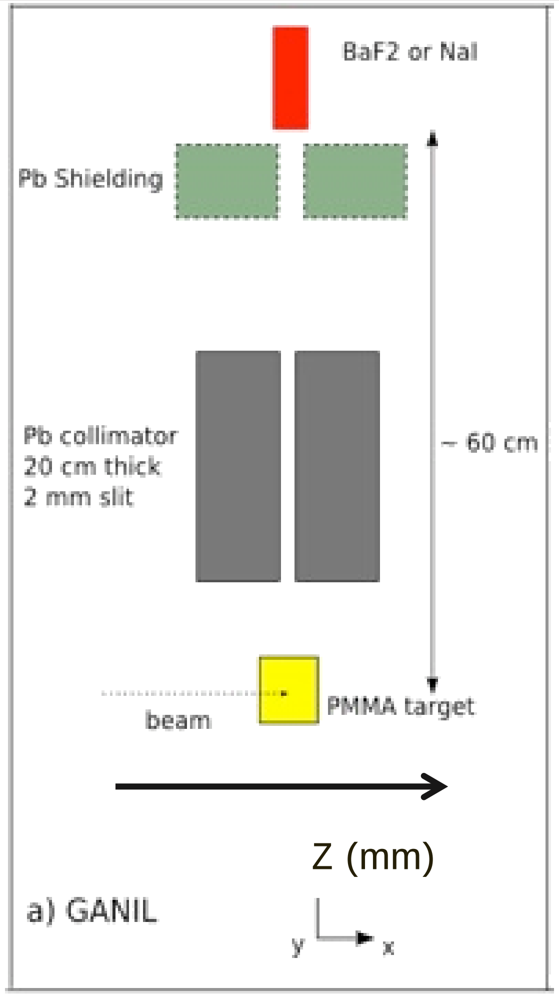
- Decay β+/-'s, γ's, α's, EC electrons, produced according to a database (based on ENSDF, www.nndc.bnl.gov)
- … and transported on-line ***"all cooling times together"***

Results available for energy deposition (dose, decay heat), particle fluences (including dose equivalent with folding online)

The last reaction stages: γ de-excitation (therapy monitoring through prompt γ)

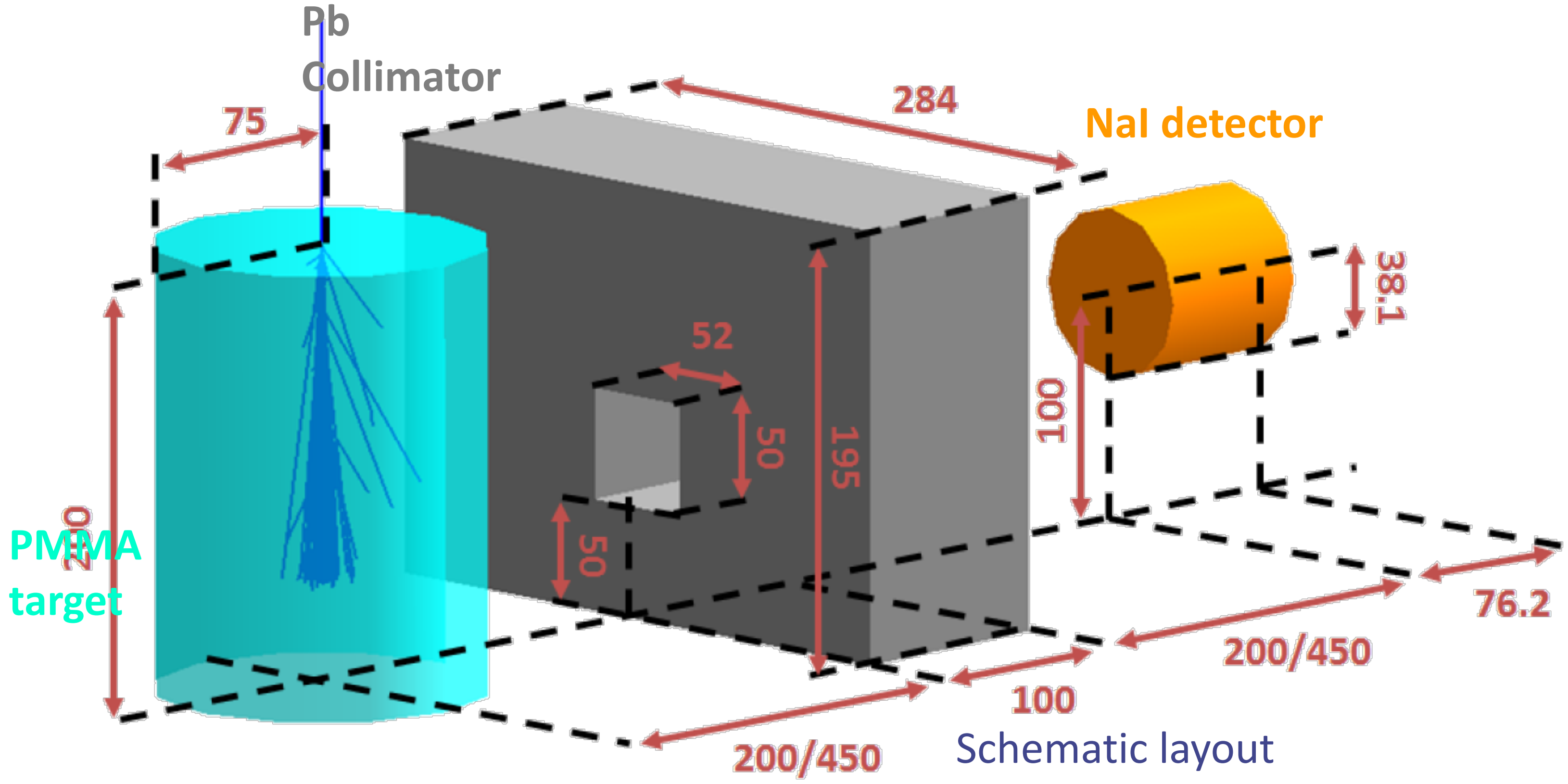
GANIL: 90 deg photon yields by 95 MeV/n ^{12}C in PMMA





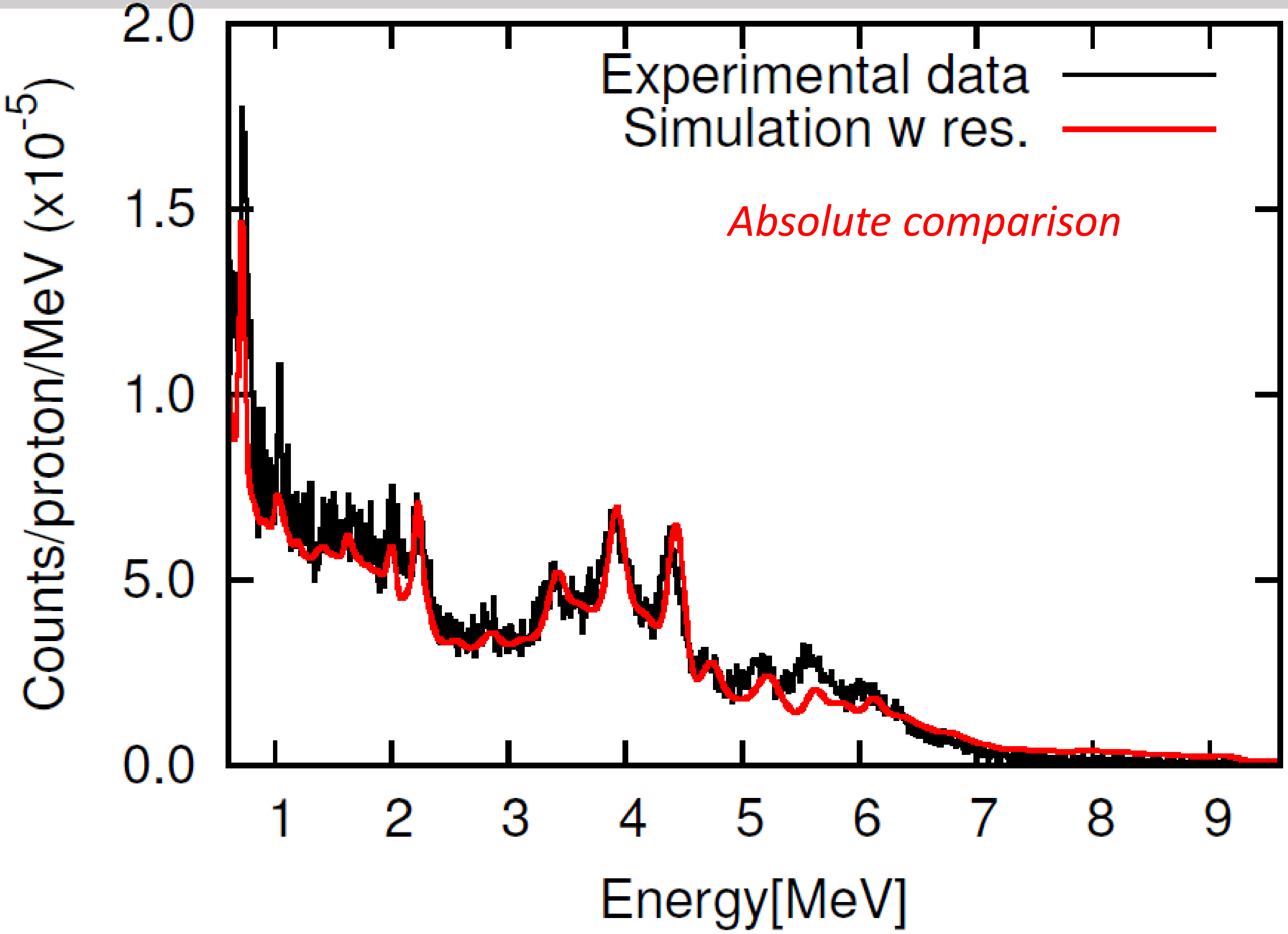
[sketch and exp. data taken from F. Le Foulher et al IEEE TNS 57 (2009), E. Testa et al, NIMB 267 (2009) 993. exp. data have been reevaluated in 2012 with substantial corrections]

Photon yields by 160 MeV p in PMMA



Schematic layout
(dimensions mm)
from J.Smeets et al., IBA

Photon yields by 160 MeV p in PMMA



Energy spectrum of "photons" after background subtraction (collimator open – collimator closed) for 160 MeV p on PMMA. FLUKA **red line**, data **black line** (J.Smeets et al., IBA, ENVISION WP3)

Interactive example:
^{12}C SOBP example with Flair: 3rd part, β^+, prompt γ's

From CT to FLUKA voxel geometry

- Import (read) voxels: elements of the CT scan, defined by the CT granularity
- Group voxels in "organs" == voxels with the same HU value or in a given HU interval
- **User input 1**: provide a "segmentation" of the HU continuous numbering into a set of HU intervals corresponding to tissue compositions. Define corresponding materials: one HU interval == one material . In the FLAIR distribution: example based on Schneider+Parodi (file material.inp)
- Assign to each organ a voxel-region number.
- Assign to each voxel its organ index
- Assign to each organ its material (see above)
- Define a density correction/**calibration** for each HU number within a given HU interval
- **User input 2**: provide the HU vs density calibration curve. In the FLAIR distribution two examples: body.mat and head.mat (courtesy of A.Mairani)
- Code the correction factor information in CORRFACT cards

generate a ".vxl" file embedding all the information

Interactive example:

^{12}C example with Flair + real DICOM

Step-by-step Voxel file generation:

Pre-requirements:

- a directory with a CT example. Example in: Exercises/example_medical/SOBPvxl/CT
- a file with the material definitions: Exercises/example_medical/SOBPvxl/material.inp
- a file with the correspondence HU-material and associated calibration curve (HU related correction factors):
  Exercises/example_medical/SOBPvxl/calib_curve.mat
  !!! BE CAREFUL THIS AN EXAMPLE (BY A.MAIRANI CNAO/HIT), USE THE ONE FOR OUR CT SCANNER/BEAM !!!!
- Then we start from an input, where we want to add the voxel phantom:
  Exercises/example_medical/SOBPvxl/sobp12cvxl.inp
- In order to generate the voxel file:
- Start flair on the input file (sobp12cvxl.inp)
- If there is no Dicom tab, open the menu with the down triangle on the top right and click on it:
- Open the Dicom tab:
  - ✓ In order to read the CT: click on Add (yellow cross): → file browser opens
  - ✓ select the CT directory
  - ✓ click on OPEN → Another window appears with title "select dicom data set":
  - ✓ Select the data set and click "Ok“ (Clicking on Slice one can look at individual slices)
    (Information: patient data, anonymous in this case)

Step-by-step Voxel file generation/plot - 2:

- Click on Voxel (Rubik cube symbol), mandatory: → a new window opens
- Top left: select in the file browser the name of the file with the material definitions (materials.inp)
  select the file with the HU-Material calibration/correction factors (calib_curve.mat)
- Click top right on the red VOXEL button: → the voxel file is generated, give it a name
- Click top right on the black "CARD" button: → the proper VOXEL card is added to the input file
- Save everything

In order to look at the geometry:

- Open the input file with Flair and go to Geometry:
- There is only a grey cube, don't worry...
- Click on "Layers" (just above the region list) and with the arrow change from "Borders" to "Media"
- Click su "Show": in the menu which opens select Voxel and click Apply → The materials appear in a color scale
- In order to change to a gray scale: -> Click su "Show"
  - ✓ Color: change from Material to Density (menu)
  - ✓ In the layer menu, click <add> , choose Palette → the Palette menu opens:
  - ✓ Put a Label (eg GRAY)
  - ✓ Palette: change from FLUKA to Gray (clicking on the menu it opens)
  - ✓ Unselect Log
  - ✓ (Select Invert)
  - ✓ Select Transparent (<min)
  - ✓ Minimum: 0.1
  - ✓ Maximum: 2.0
  - ✓ Apply

Step-by-step Voxel file generation/plot - 3:

In order to superimpose the USRBIN (note the beam is rotated to be along y)

- First make a plot of sobp12cvxl_bin.bnn, using eg 1e-6 .01 as min max
- Inside layer click on add → Palette2
- Select type FLUKA min as per plot (if linear and not log 1e-4 .01)
- … and tick make transparent < min
- Apply
- From Layer: Add → Usrbin
- type the file name
- Use Palette2