Proposal for an INFN Treatment Planning System (TPS) Project

INFN Participants

C.Agodi[a], A.Antoccia[b], F.Attanasi[c], A.Attili[d], G.Battistoni[e], F.Berardinelli[b], F.Bourhaleb[d], R.Cherubini[f], R.Cirio[d], G.A.P.Cirrone[a], G.Cuttone[a], C.D'Ambrosio[g], A.Del Guerra[c], V.De Nadal[f], S.Gerardi[f], F.Marchetto[d], P.Monaco[d], C.Morone[h], A.Mostacci[i,g], S.Muraro[e], V.Patera[i,g], C.Peroni[d], G.Raciti[a], V.Rosso[c,] R.Sacchi[d], P.Sala[e], A.Sgura[b], S.Vecchio[c], C.Tanzarella[b]

a) INFN Laboratori Nazionali del Sud, Catania
b) INFN e Dip. Fisica Univ. Roma 3
c) INFN e Dip. Fisica Univ. di Pisa
d) INFN e Dip. Fisica Univ. di Torino
e) INFN Sezione di Milano
f) INFN Laboratori Nazionali di Legnaro
g) INFN Laboratori Nazionali di Frascati
h) INFN e Dip. Biopatologia e Diagn. per imm. Univ. "Tor Vergata", Roma
i) Dip. di Energetica della Facoltà di Ingegneria Univ. "La Sapienza", Roma

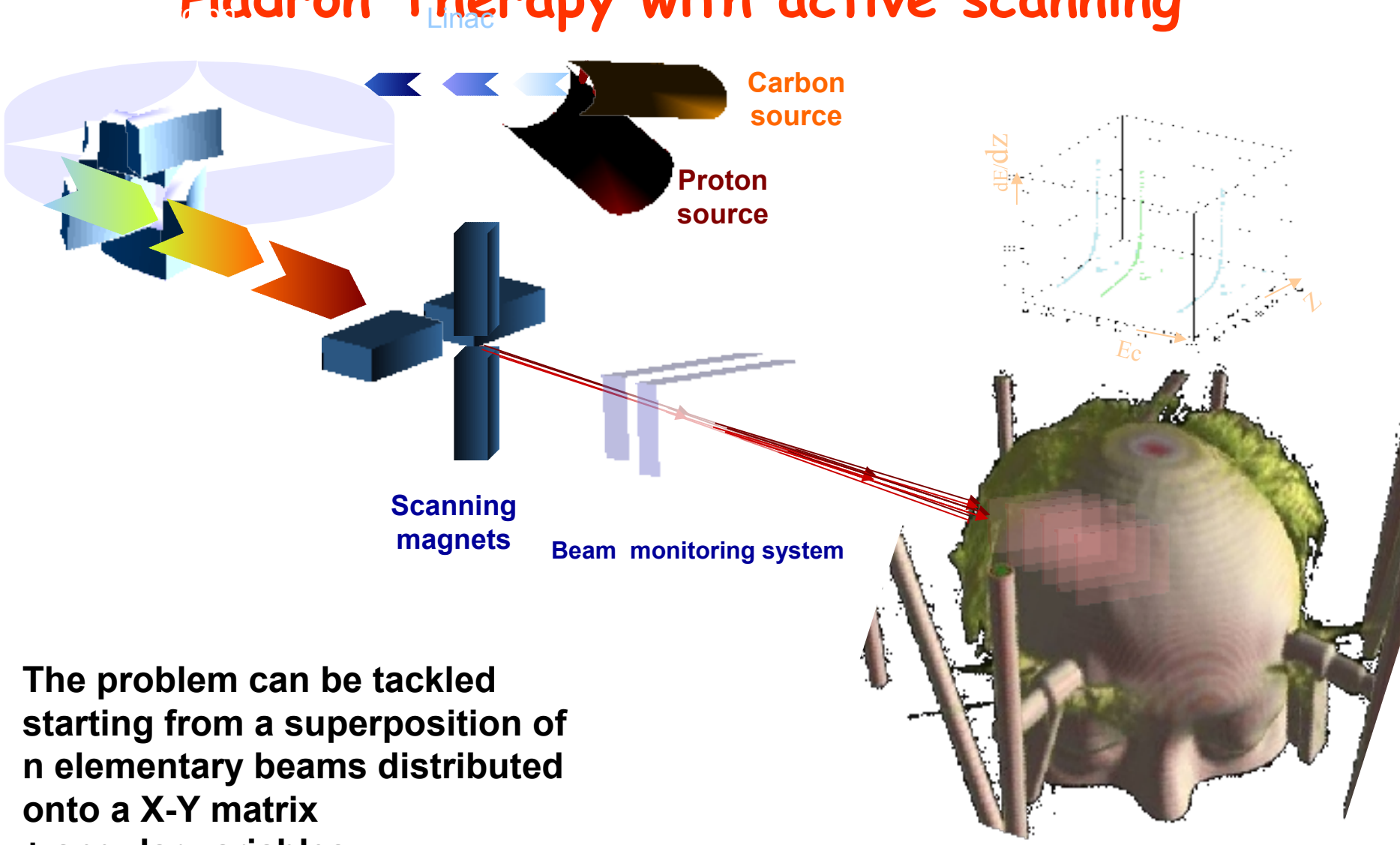
Aim and features of the project

- Contribute to the development of innovative Treatment Planning Systems for therapy with ion beams (in particular ^{12}C, but not exclusively) for active voxel scanning applications

- To produce a well defined, certified and ready-to-use deliverable in collaboration with an industrial partner

- Goals to be achieved within 3 years.

Hadron Therapy with active scanning



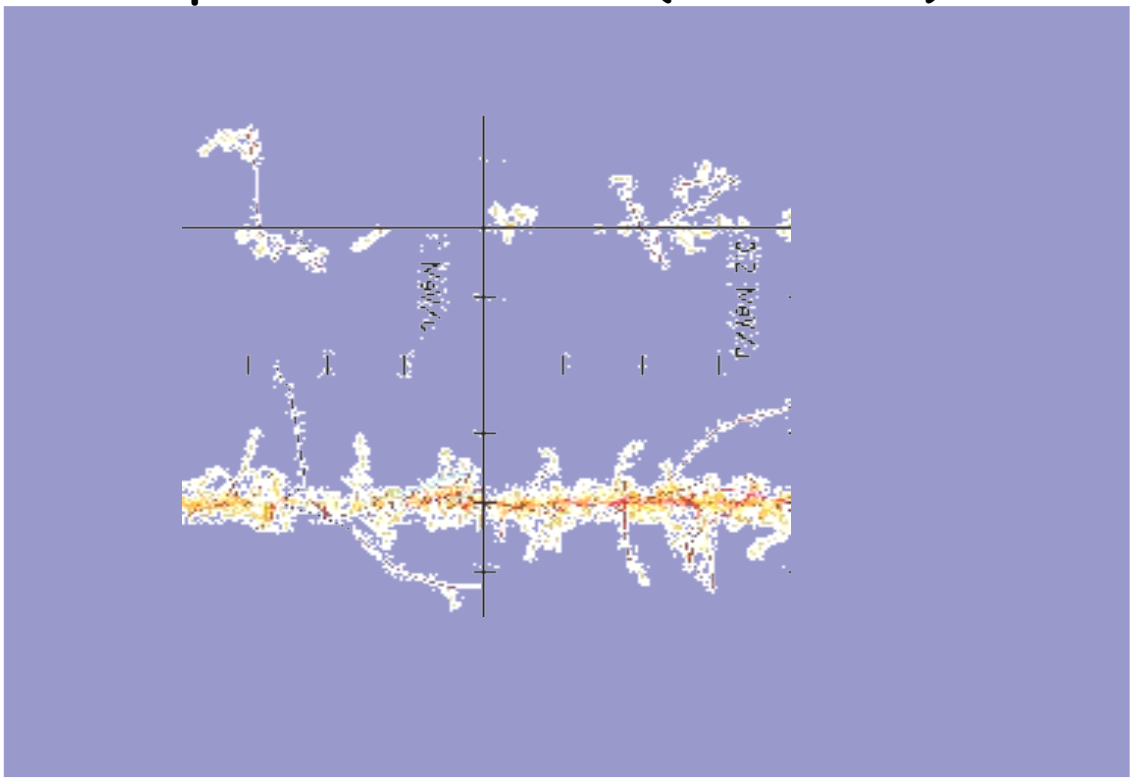
The problem can be tackled starting from a superposition of n elementary beams distributed onto a X-Y matrix + angular variables

The specific case of ion beams - 1

Microscopic track structure (tens of nm)

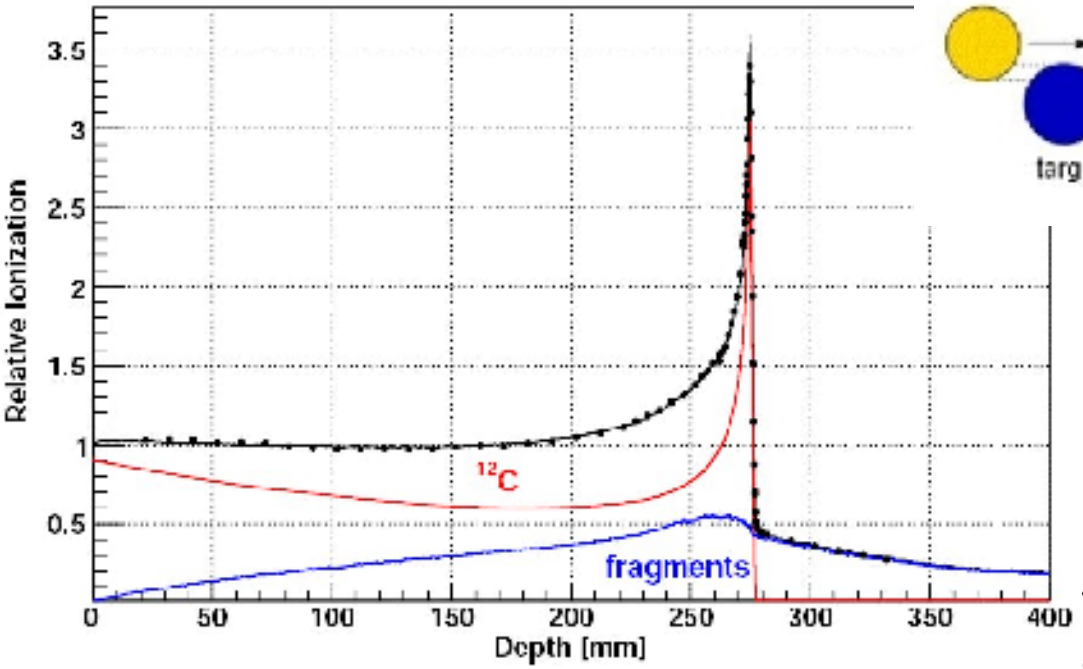
Alpha

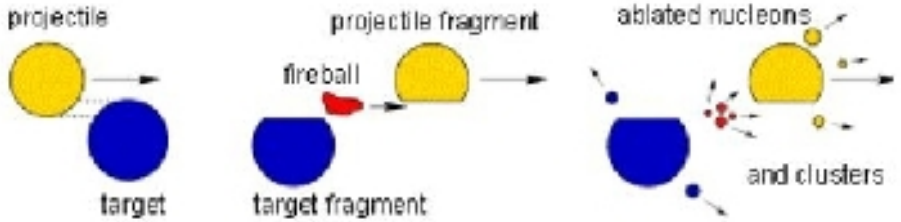
Carbon



Higher deposition density in space regions of size comparable to DNA structures: MORE EFFECTIVE IN CELL KILLING THAN PROTONS AND E.M. RADIATION

The specific case of ion beams - 2

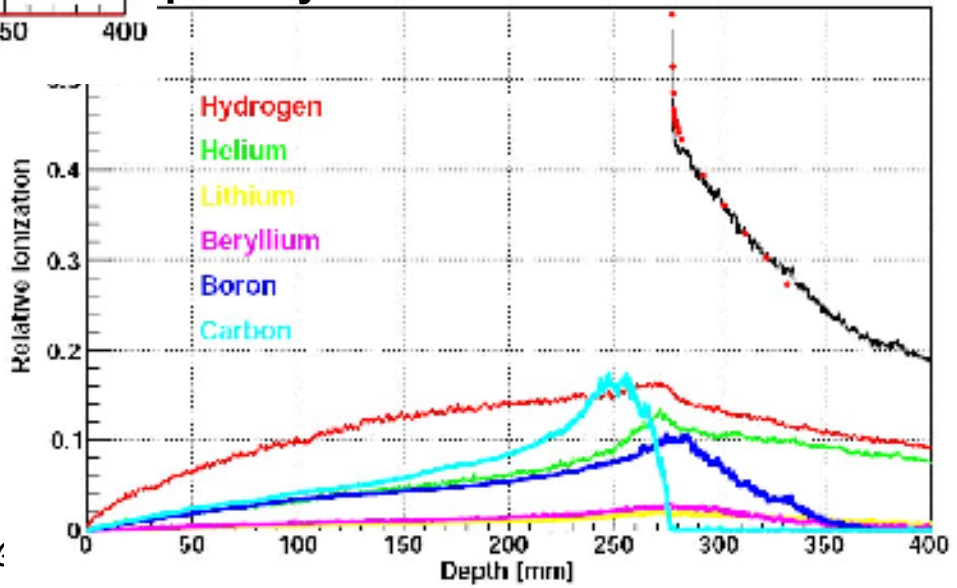




Fragmentation Reactions:

- **Attenuation the primary beam**
- **Buildup pf low-Z reaction products**
- **The lighter fragments give dose beyond the maximum range of primary beam**

Comparison of Exp. Data
to FLUKA MC predictions at GSI



E.Haettner & D.Schardt GSI
K.Parodi & S.Brons, HIT

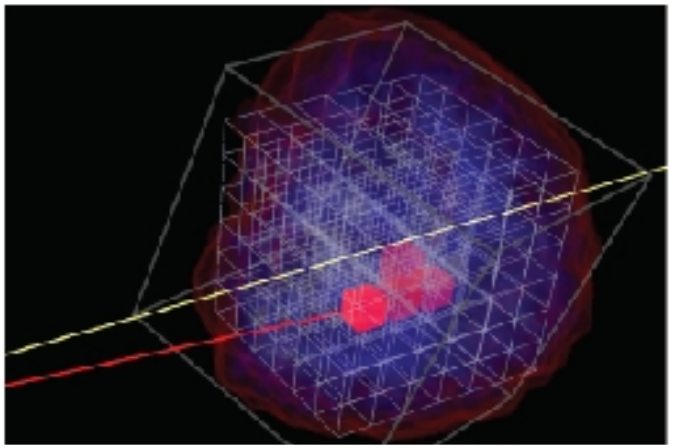
A. Mairani, PhD Thesis

Definition of Treatment Planning 1

- General aim of conformal radiation therapy: deliver as high and uniform dose as possible to cancerous tissues sparing all other parts to avoid/minimize unwanted and unnecessary side effects for the patient.
- The Treatment Planning is the calculation method which allows to determine energy and fluence for each elementary beam in order to achieve the prescribed dose in a well defined volume
- **The optimization has to be done on the basis of biological effect (biological dose)**

Definition of Treatment Planning 2

$i \rightarrow$ *i*-th beam
$\phi_i \rightarrow$ fluence
$E_{Ki} \rightarrow$ kinetic energy
$\theta_i \rightarrow$ direction

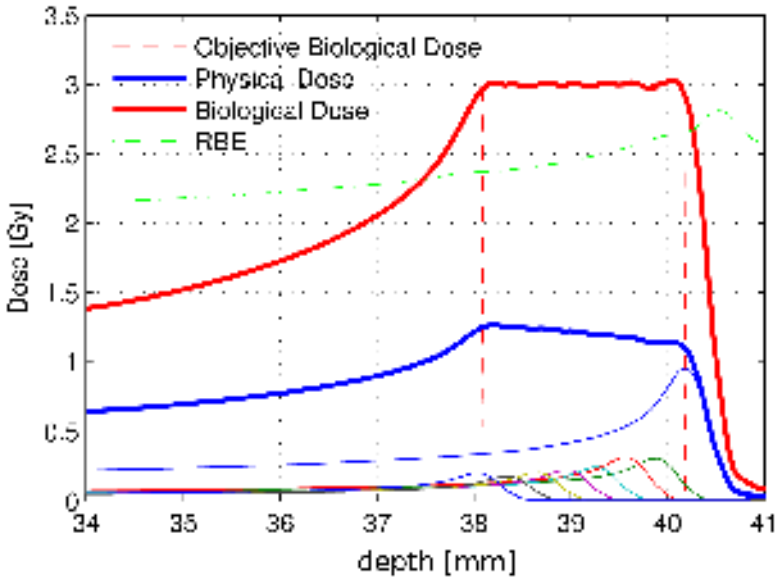


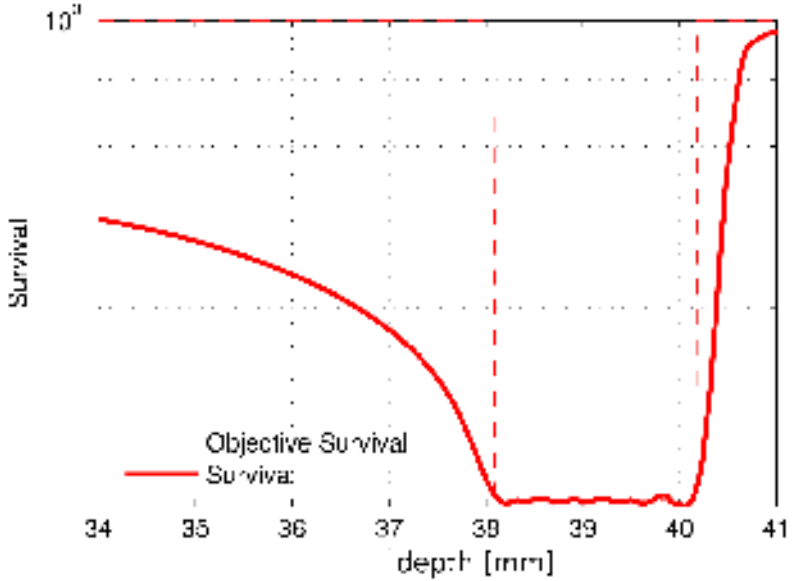
For actual application:

- "Fast" calculation to produce alternative plans

- Production of general and flexible analysis tools for the inspection of isodose curves on CT scans and Dose-Volume histograms (DHV) to check the respect of volume-dose constraints on organs at risk, etc.

One-D example





- Example of "biological" optimization on a depth of 2 mm using 8 beams
- Both RBE calculation and optimization is performed by considering the superposition of all beams

(from INFN Torino)

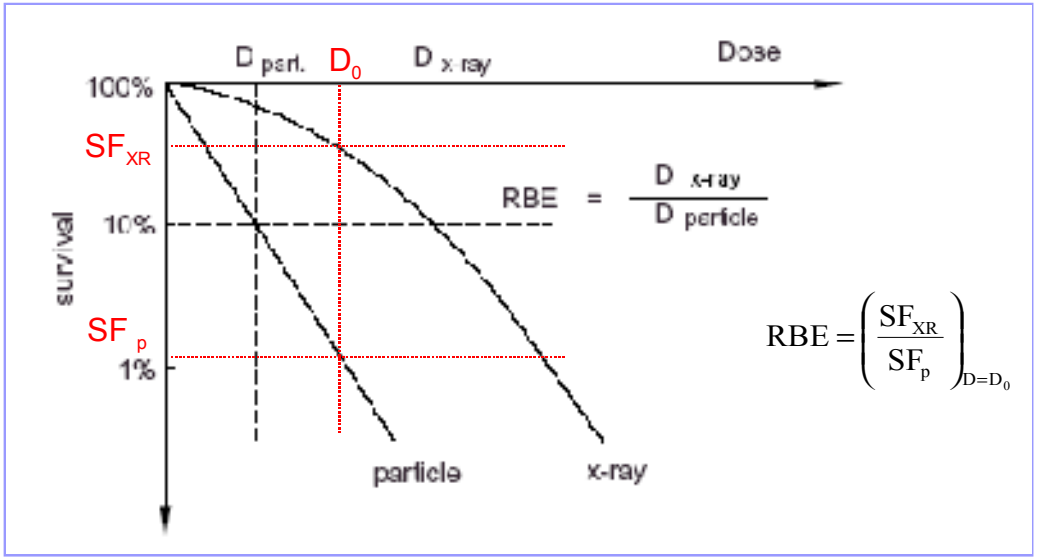
RBE = Relative Biological Effectiveness

The baseline choice for a radiobiological model-1

- The heart of a TPS is the radiobiological model to calculate and take into account the "Relative Biological Effectivness" (RBE)

- RBE: ratio of the dose from a reference radiation (D_{RX}) and the dose for the actual radiation (D_r) needed to achieve the same biological effect under consideration

$$R.B.E. = \left(\frac{D_{RX}}{D_r} \right)_{SF=SF_0}$$



$$RBE = \left(\frac{SF_{XR}}{SF_p} \right)_{D=D_0}$$

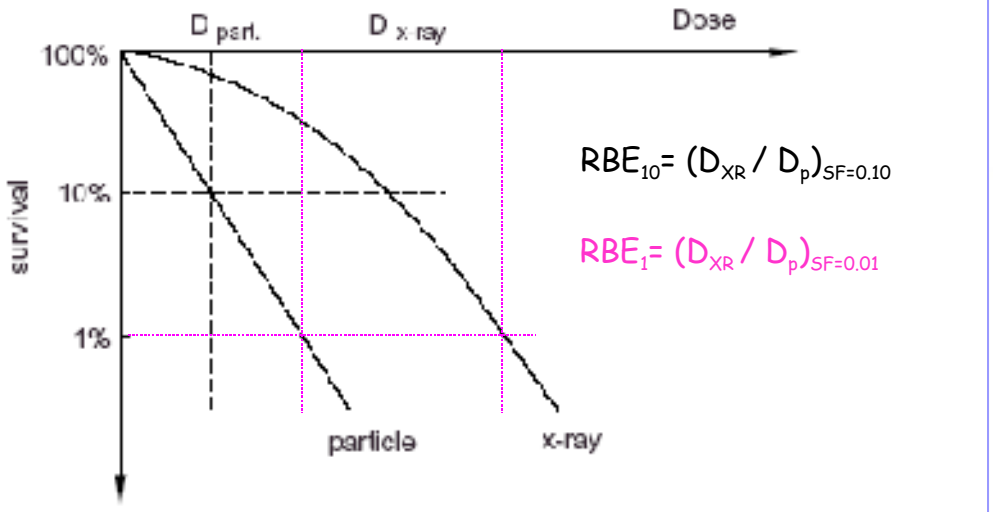
A note about RBE

→ for a given radiation field, RBE is not a univoque quantity

→ … it depends on:

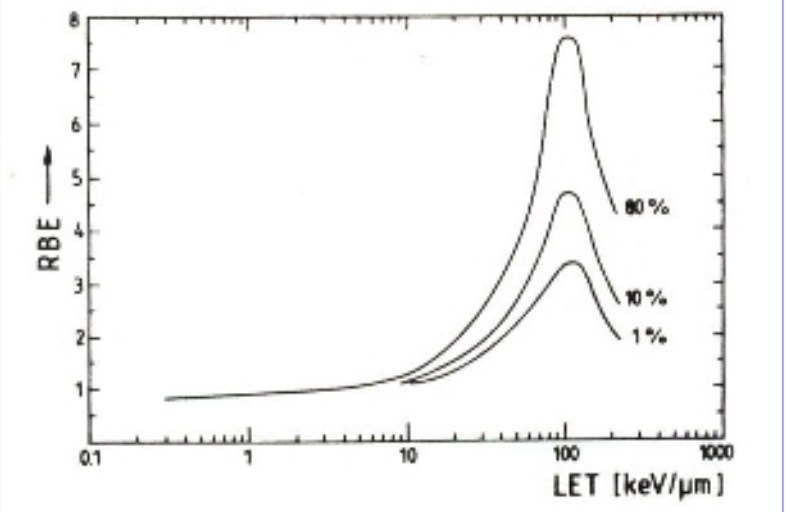
- The definition used in the calculus;
- The considered biological effect (survival, induction of mutations etc.)
- The cell type
- The considered "Level of expression" for a given biological effect

Dependence on the level of expression



$RBE_{10} = (D_{XR} / D_p)_{SF=0.10}$

$RBE_1 = (D_{XR} / D_p)_{SF=0.01}$



The baseline choice for a radiobiological model-2

- models generally used so far have limits and not satisfactory from a conceptual point of view. However they are presently used in the clinic practice with satisfactory results
- From the conceptual point of view the development of "microscopic" radiobiological models would be most appealing approach. However such a solution probably requires a long time with respect to the present needs (years of work).
- A TPS project with the features summarized here has to be based on an already existing model, leaving the possibility of introducing some improvements.
- The **"Local Effect Model" (LEM)** is our baseline (Scholz e Kramer GSI). It can already be technically improved and it is at the base of TRip98, at presents in commerce

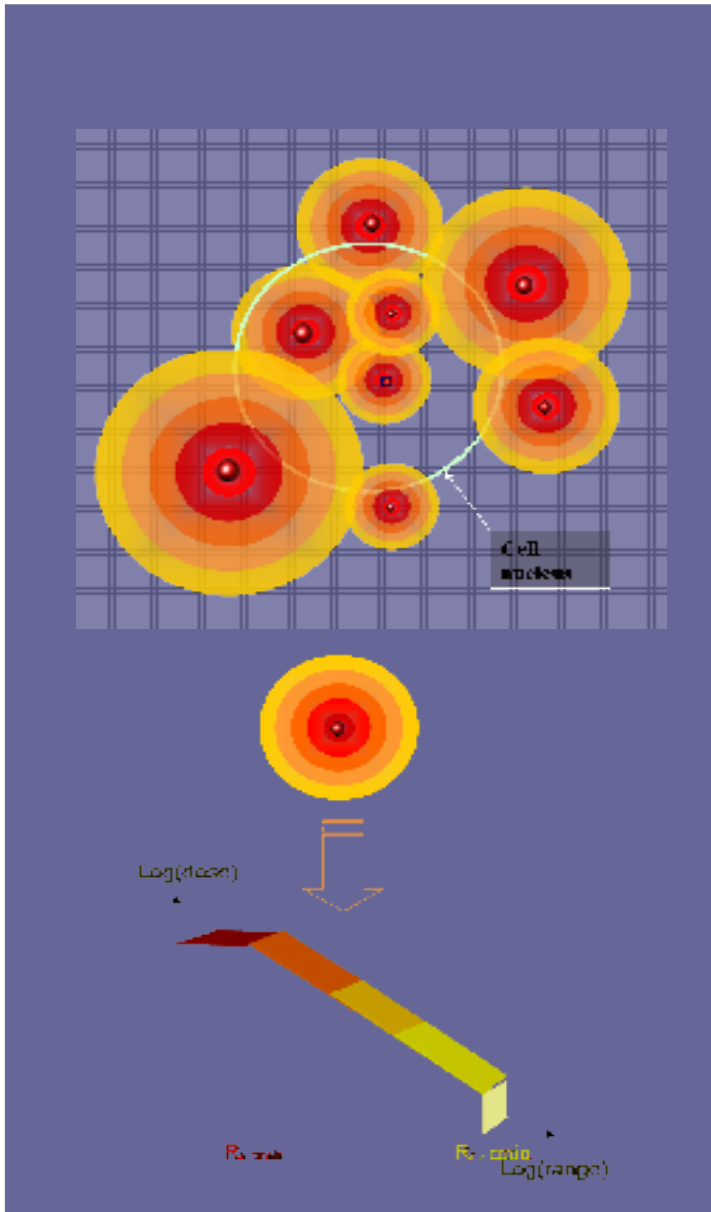
What is LEM

Principles of Local Effect Model (LEM)

- Biological effect completely determined by the local distribution of dose inside the cell nucleus
- Homogeneous cell nucleus with constant density and radiosensitivity
- Locally, the effect of ions can be evaluated using the X-ray Linear Quadratic model:

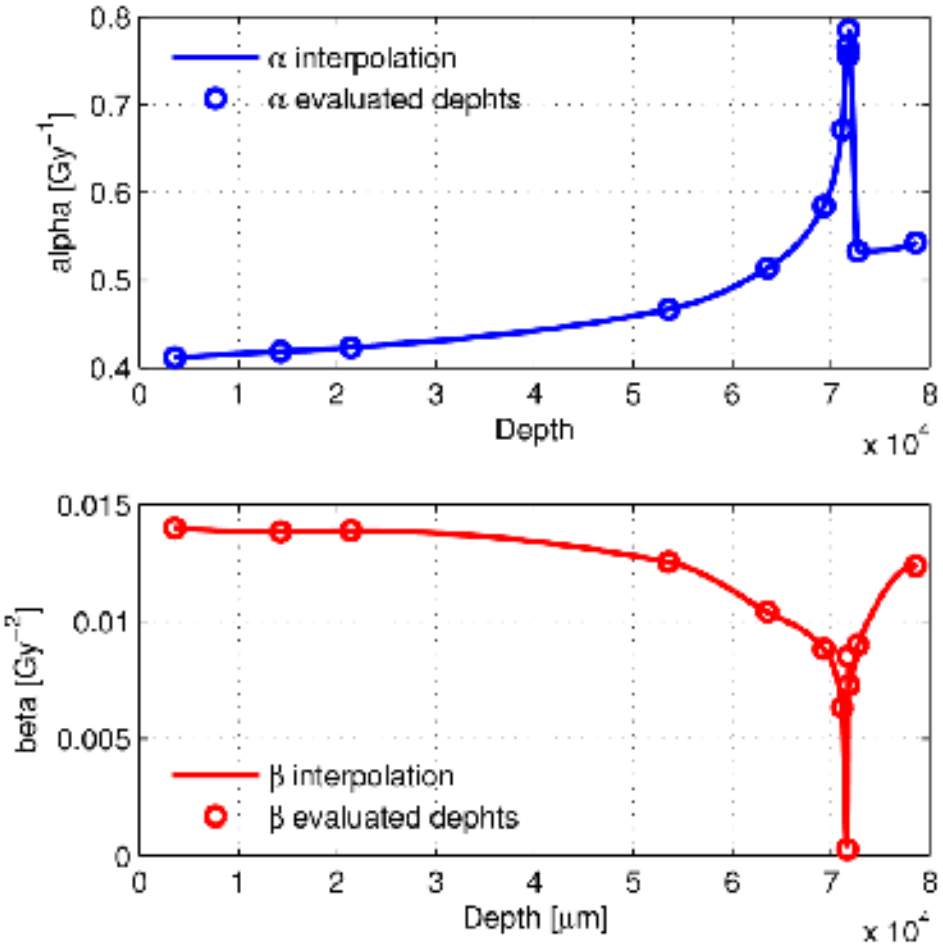
$$S(D) = \begin{cases} e^{-\alpha D - \beta D^2} & D \le D_t \\ S_t \cdot e^{-s(D - D_t)} & D > D_t \end{cases}$$

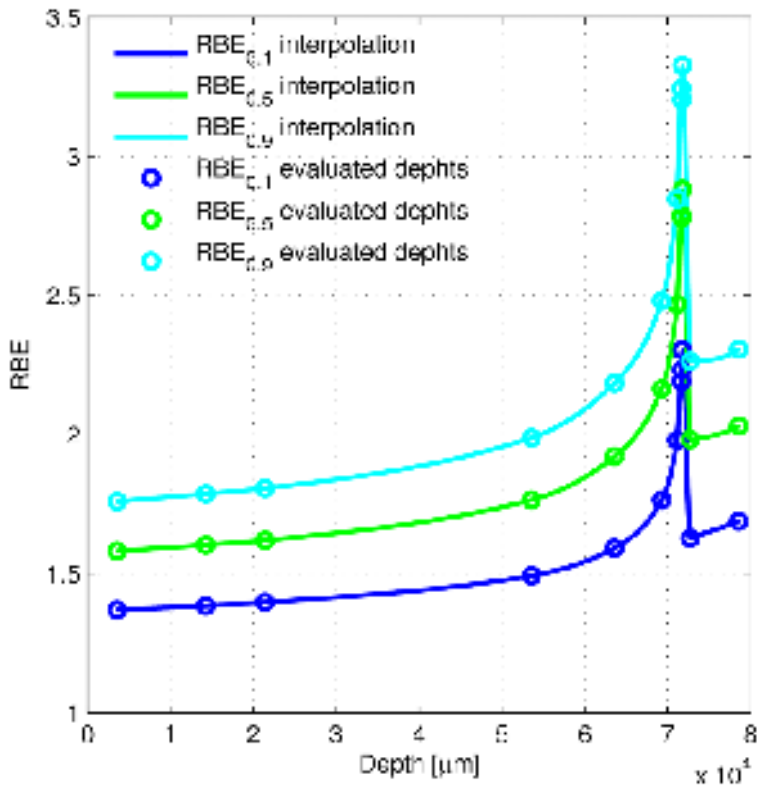
Survival as a function of dose (can be defined in different ways)



Example

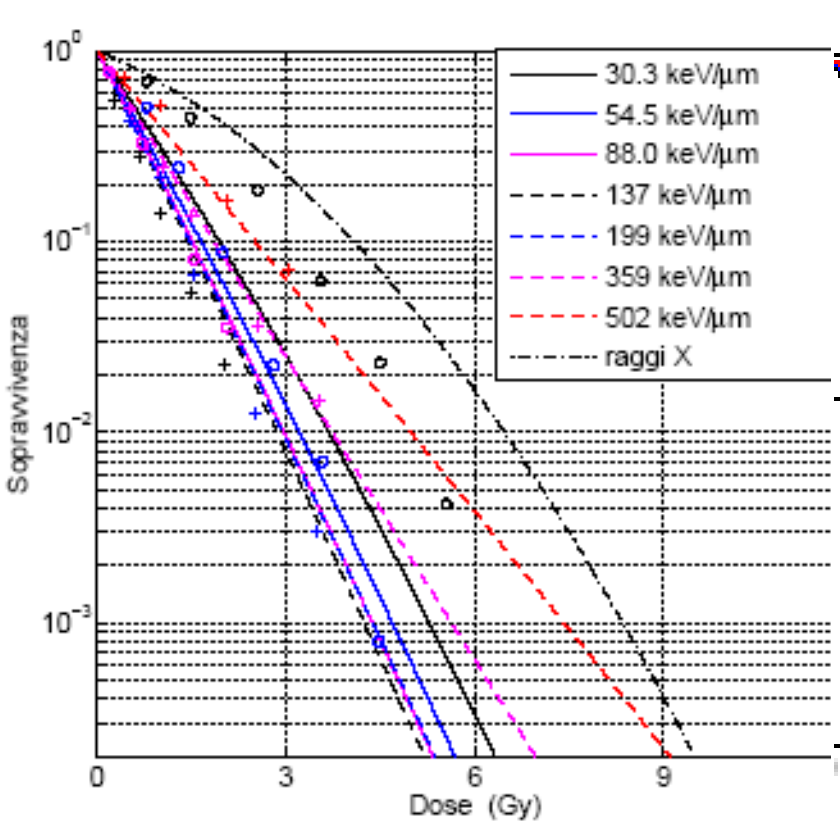
Determination of α and β parameters as a function of depth for a C beam (180 MeV/nucleon). CHO cell type.

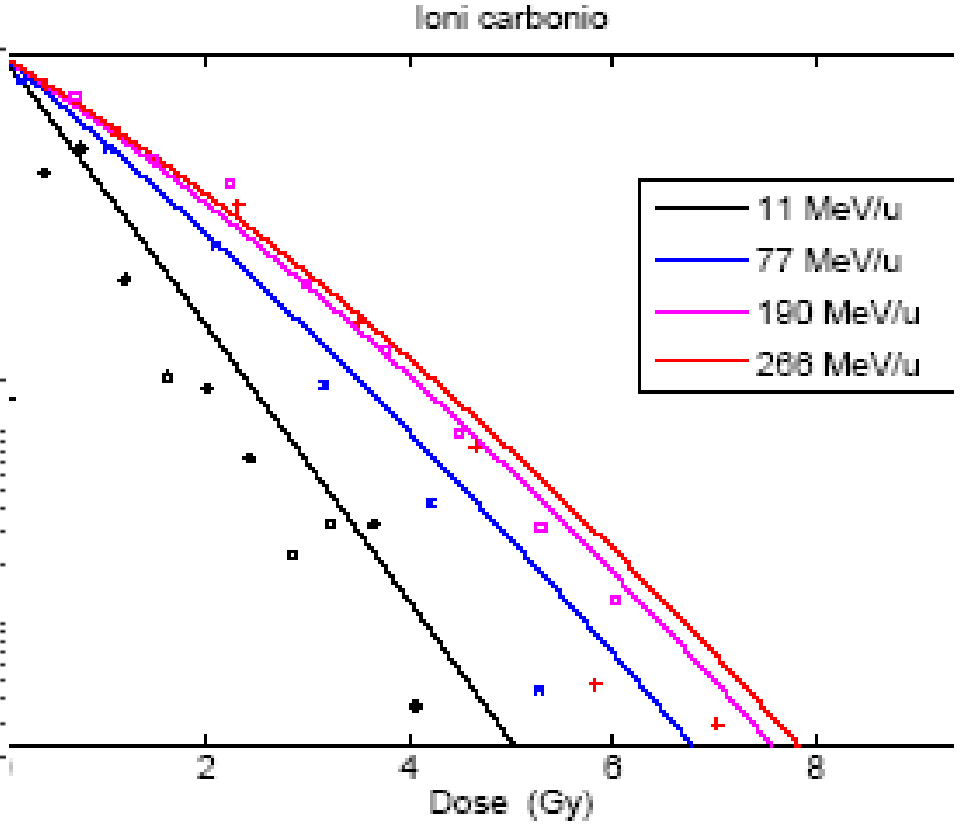




RBE vs depth for different survival thresholds

Examples of comparison of LEM predictions with exp. data





Areas of relevant competences within INFN

- Nuclear Physics
- MC simulation
- Optimization algorithms
- Experimental Radiobiology
- Monitoring "in beam"

these are the 5 tasks of the INFN TPS project

The Nuclear Physics task

- Modelling
- Ion fragmentation measurements (mainly ^{12}C): Up to now there is a lack of data systematic in literature of **12C projectile fragmentation cross sections measurements** at intermediate energies, that is around 20 MeV/A ≤ E/A ≤ 250 MeV/A, range of high interest for hadrontherapy.

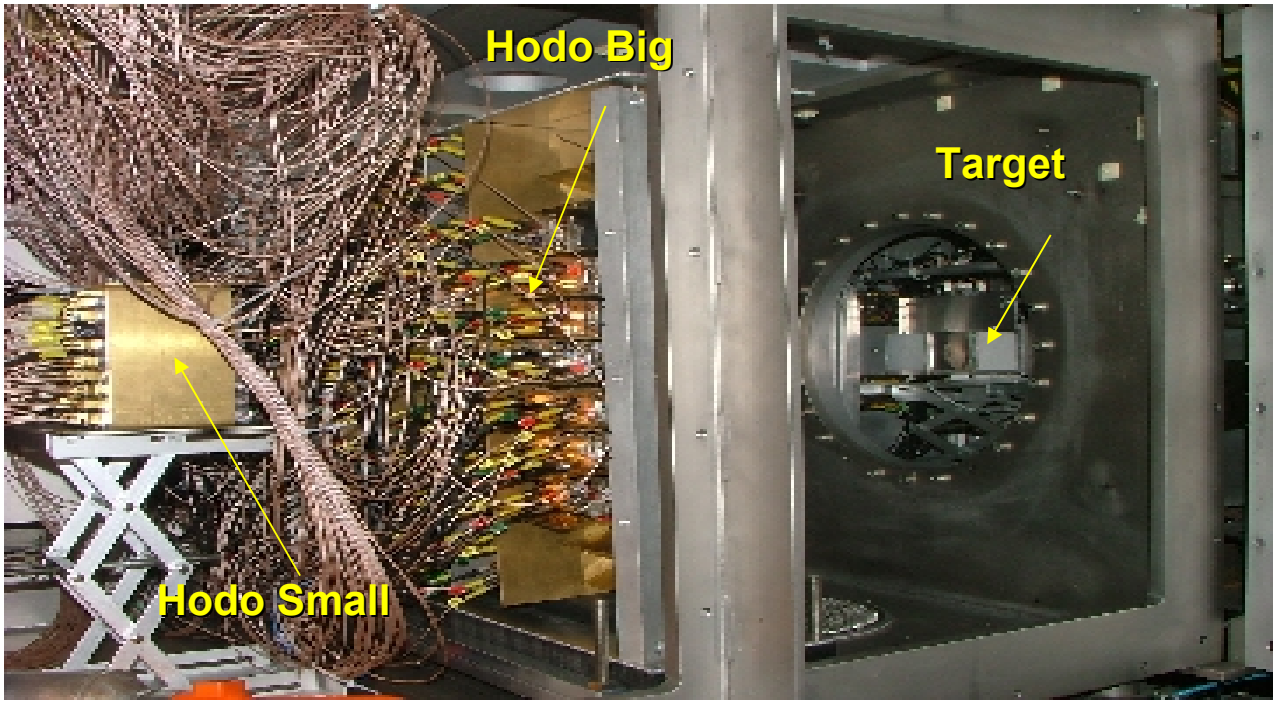
Goals of the task

- Collect new data on ion fragmentation
- Study of radioactive nuclei production
- Measurements at low energy in italian laboratories and at higher energy in other laboratories.
- Collaboration with MC experts to improve and validate nuclear interaction models

Development, assembling and running of a specific detector system

Cross section measurements: activity at LNS

First phase: systematic study of fragmentation cross section of ^{12}C on Au and plastic targets at 60 and 80 MeV/A, @ LNS using the Superconducting Cyclotron.



Hodo-big: **89 three-fold telescopes 50 µm + 300 µm Silicon detectors 3x3 cm² surface followed by a 6 cm long CsI(Tl) *θlab* between ±4.5° and ±16.5°.**

Hodo-small: **81 two-fold telescopes: 300 *µ*m Silicon detectors 1x1 cm² of active area followed by a 10 cm long CsI(Tl) *θlab*=±4.5°.**

The Experimental Radiobiology Task

2 main directions:

1) **Characterization of therapeutic beams:**
   - Study of Survival-Dose correlation in water phantoms
   - Definition of RBE = RBE(x,y) i.e. lateral distr. of RBE
   - Measurement using tissue-like phantoms
   - …

2) **Production of data for TPS validation and to produce the RBE database to build the TPS itself (for instance the set of α and β which are used as parameters in LEM)**
   - LEM validation and integration by means of the widest possible set of experimental data: survival curves for different tissues and cellular lines (both normal and tumoral ones)
   - Use of human cells together with a cellular type considered as a reference biological system.
   - Comparison with results from other hadron therapy centers in the world
   - Study of different end-points such as chromosomic alteration, apoptosys induction, etc.
   - Integration of studies of short and long term effects on non-tumoral tissues
   - ….

The Optimization task

- What is optimization in practice:

•Determination of the weights $w(j)$ for the j-beams on the basis of dose deposition on the i-voxel;

•The physical dose $D_{phys}(i)$ is then modulated by the RBE values;

•Optimization has to be performed by considering the simultaneous contribution of all beams

w(j) := fluence of j-beam
D(i,j) := dose deposited in i-voxel by j-beam

Typical order of magnitude:
N beam (~ N. voxel) $10^4 \div 10^5$

$$D_{phys}(i) = \sum_j w(j) \cdot D(j,i)$$

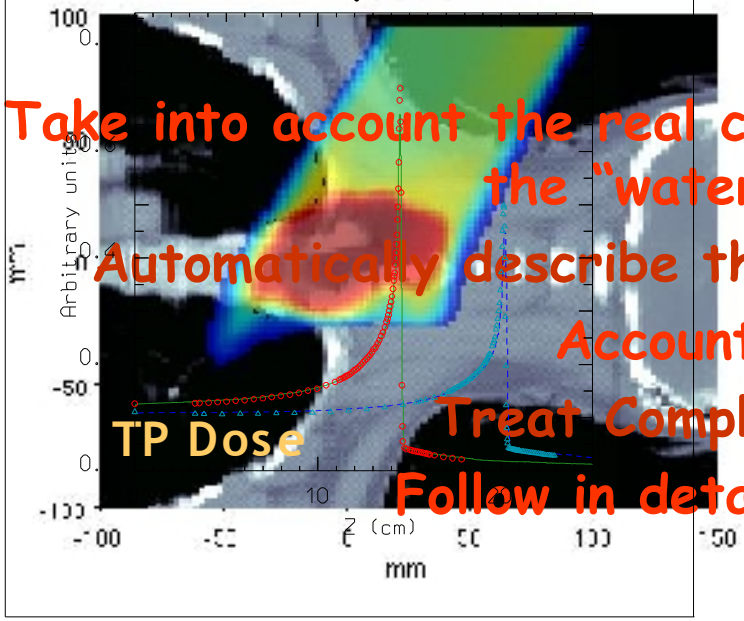
$$D_{bio}(i) = D_{phys}(i)' \; RBE\left(D_{phys}(i), i\right)$$

Specific goals in the present project

- Implementation of physics and LEM models into an optimization algorithm for the specific case of ^{12}C ions.
- Specific optimization procedures for different clinical cases to take into account different tumor types.
- Development of multi-field optimization
- Coupling with the Full MC validation tool (see Monte Carlo task)
- 4D Optimization.
- Direction optimization

The Monte Carlo task

Provide the basic transport and fragmentation data for treatment optimization



Predict the distribution of β^+ emitters for on line PET tomography

Verify the dose distribution predicted by the optimization process on the real patient geometry

MC can

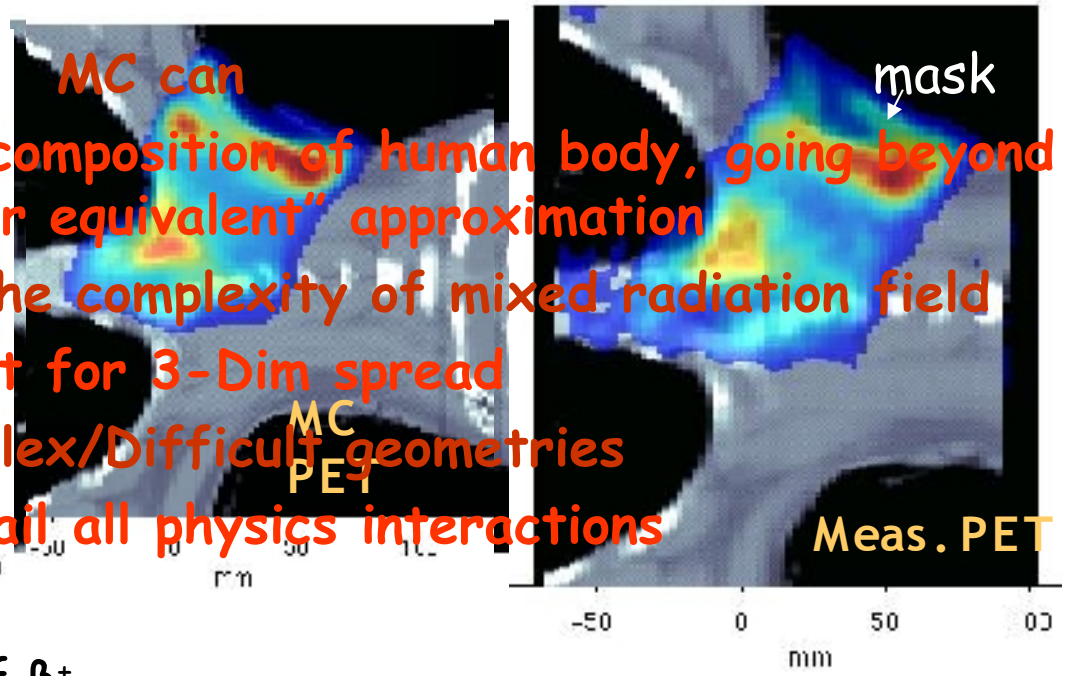
Take into account the real composition of human body, going beyond the "water equivalent" approximation

Automatically describe the complexity of mixed radiation field

Account for 3-Dim spread

Treat Complex/Difficult geometries

Follow in detail all physics interactions



Impossible Dream: perform the full optimization??

Requirements for the MC

- Include sound physical models
- Capability of being coupled to CT scans to import geometry, to import volume/organ definitions
- Possibility to be coupled to the Radiobiological model of TPS

FLUKA (INFN-CERN property) **is the baseline choice for this project**

(http://www.fluka.org)

Work is in progress an all these issues

See the FLUKA2 talk of A.Mairani to understand possibilities of success

Why FLUKA for hadrontherapy

- **Reliable nuclear models. Recent developments:**
  -BME event generator to treat low energy nucleus-nucleus reactions
  (Cerutti et al, Ric. Scient. ed Educ. Perm. S126, Univ. degli Studi di Milano, 2006, 507)
- **Already applied to proton therapy:**
  - Dosimetric/radiobiological studies *(Biaggi et al NIM B 159, 1999)*
- **Import of raw CT scans with optimized algorithms for efficient transport in voxel geometries** *(Andersen et al Radiat. Prot. Dosimetry 116, 2005)*
- **Enormous work in the recent years to include Nucleus-Nucleus interactions**
- **Very promising results in the initial studies of nuclear fragmentation in water**
  (Sommerer et al PMB 51, 2006, Mairani PhD Thesis, Pavia, 2007)
- **First important results in the comparison with analytical TPS for different clinical cases with both protons and C ions**
  (K. Parodi et al JPCS 74, 2007, Mairani PhD Thesis, Pavia, 2007)
- **Recent results obtained for the interface of LEM model (GSI) to calculate biological effects**
  (Mairani PhD Thesis, Pavia, 2007)

CPU time: really a limiting factor?

- Computing time is not a problem for data base production
- Computing time is not a problem for time-to time verifications of TPS
- CPU is a problem for routine validation: **results have to be achieved within ~2 hours**
- CPU is a problem for full MC optimization: **iteration must converge within ~2 hours**

- The dose calculations of a beam port for a clivus chordoma patient recently performed in the patient CT system by means of the FLUKA code have taken about **40 hours of computing time (2.0 GHz machine)**.

- A total number of about **1.7 million primary particles** were sampled
- This simulation has been performed without biasing techniques which could reduce considerably the computing time.

- Routine validation of TPS by MC can be feasible through the use of biasing and multi-CPU clusters
- *Full MC optimization is still a dream…*

The task about PET on line/Monitoring Tool

- We have a specific competence on PET in beam (DOPET exp. in Gr.5)
- It is an almost unique tool to verify on line the release of dose.
  - **Protons:**

    p + ^{16}O, (p,n) + ^{15}O $\quad\quad$ **p + ^{12}C, (p,n) + ^{11}C**

    $\tau_{15\text{-}O}$**=121.8 s** $\quad\quad$ $\tau_{11\text{-}C}$ **=1222.8 s**
  - **Carbon:**

    ^{12}C + p, ^{11}C + (p,n) $\quad$ **^{12}C + p, ^{10}C + (p,2n)** $\tau_{10\text{-}C}$ **=19.3 s**
- The difference in β^+-activation processes and the dominant mechanism of energy deposition, the activity registered by the PET image is not directly proportional to the delivered dose. A proper unfolding algorithm must be used.
- Therapy with ions requires the best possible accuracy in the monitoring of the applied treatment: for this reason the "in vivo" information is extremely useful.
- It is however an indirect method which requires unfolding starting from experimental data
- The work requires the development of a specific hardware integrated to a software tool for prediction and comparison (integration with the MC task)

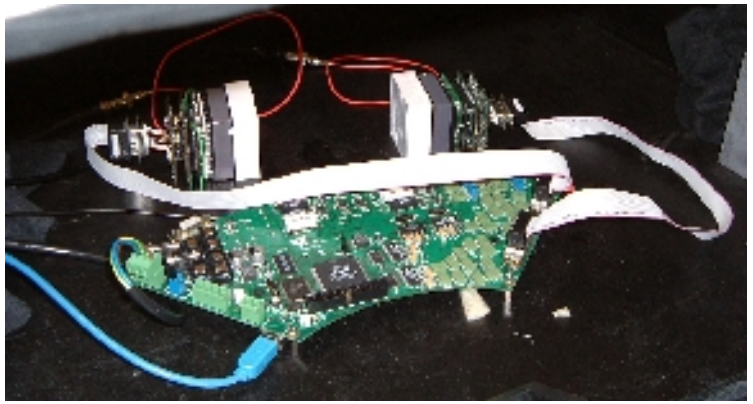
Software goals

- Improvement of the algorithm for the 3D reconstruction of the activity distribution to achieve a better image quality
- Improvement of the system model
- Realization of an unfolding filter to extract the Dose
- Inverse filter to achieve dose localization:

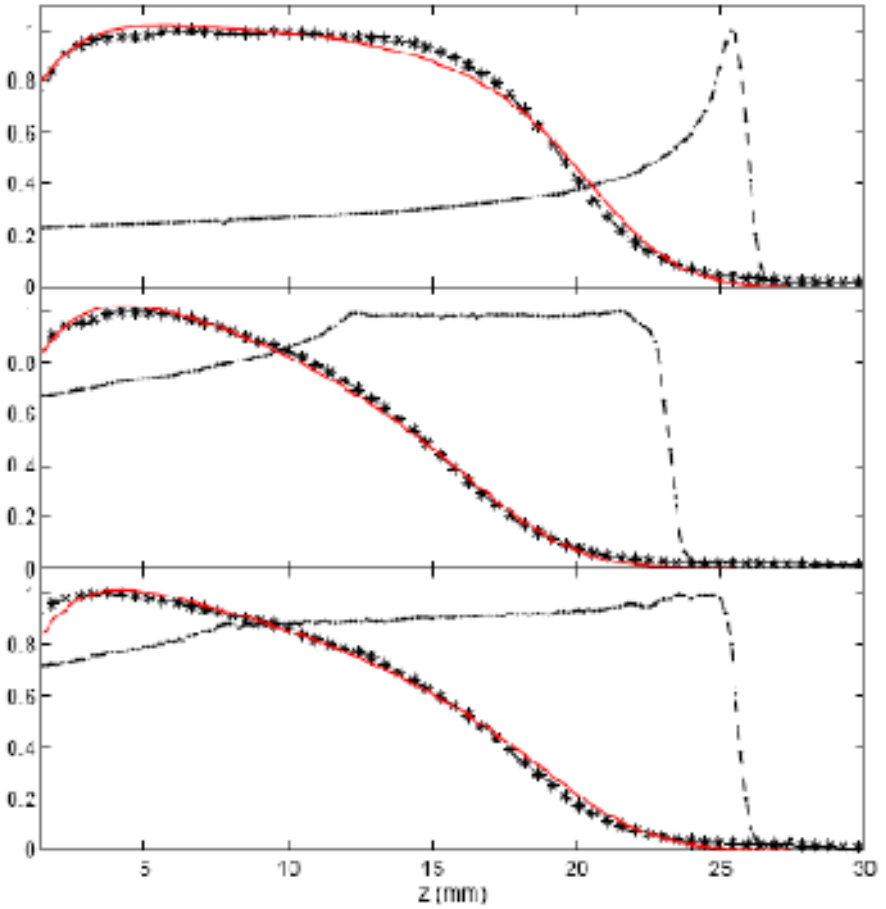
InvFilt * Att = Dose.

Hardware goals

- Design, assembly and test of improved detection modules and readout



Unfolding



DoPET results
F. Attanasi et al.

Fe (62 MeV)

12 mm SOBP

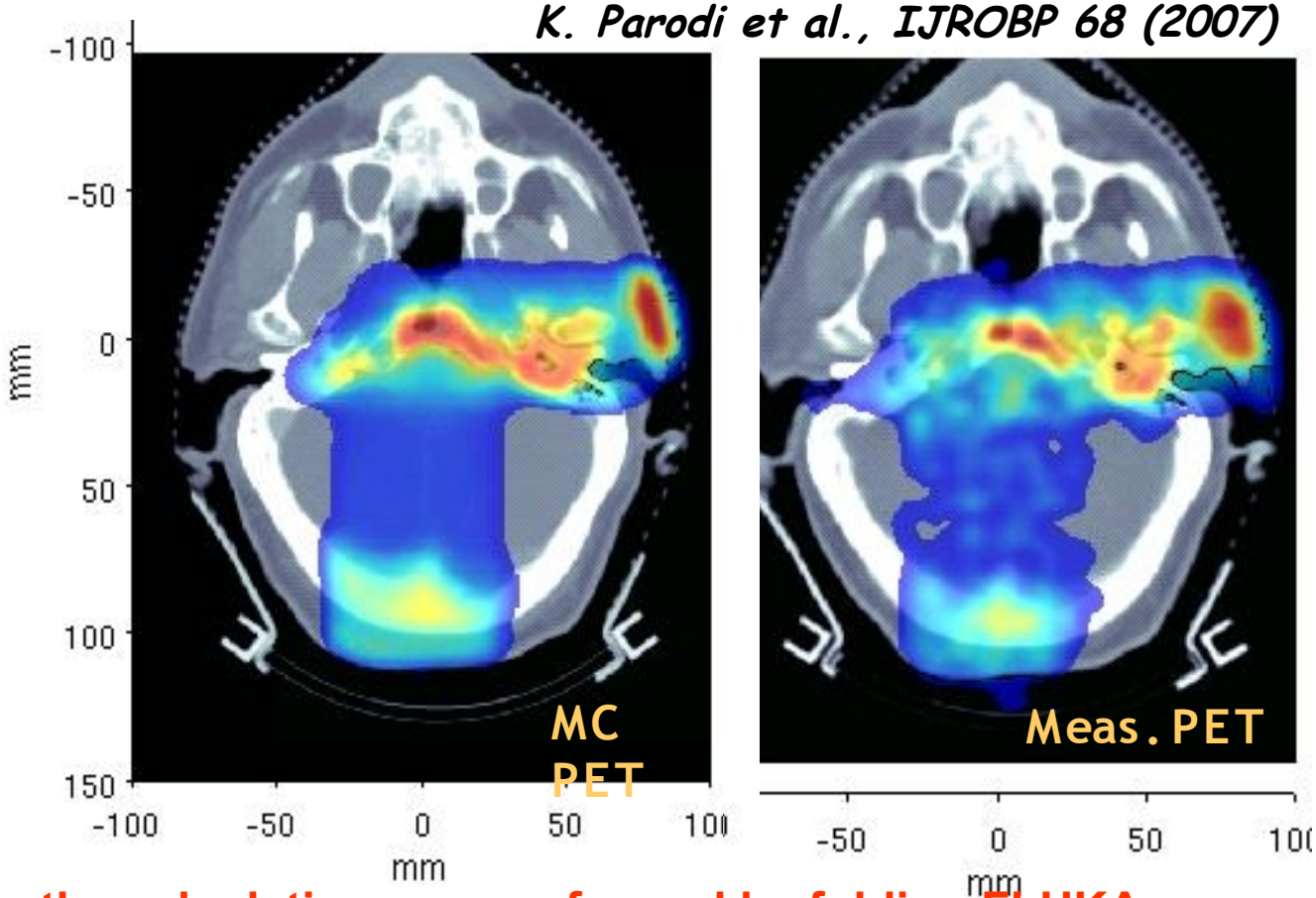
20 mm SOBP

Reconstructed activity (*) in comparison with the dose (dash-dot line) and the filtered dose (solid red line)

Experience at MGH with protons:

livalChordoma, 0.96 GyE /field,

K. Parodi et al., IJROBP 68 (2007)



- In the case of protons the calculation was performed by folding FLUKA with tabulated cross sections for β+ emttier production (fast)
- For C beams: in general cross section not known: full calculation needed!!!

The real challenge

- From basic research to real application
- Integrate all these elements into a tool which can really be used in clinical environment, respecting the needs of actual clinical workflow, passing all certification requirement
- These goals cannot be achieved without an industrial partnership (not yet defined)
- Criterium acceptable by INFN:
  - only a collaboration in which INFN contribution is relevant also at coordination level
  - Scientific material has to be published freely (measurements/ models,…)
  - The actual implementation and its details can remain proprietary

Time schedule: the principal milestones

	First year	Second year	Third year
Nuclear Physics	Measurement of ^{12}C fragmentation at 40-80 MeV	Setup of detector and measurements in the range 80-400 MeV	
Radiobiology	Measurement with ^{12}C beam up to 80 MeV (LNS)	Measurement with ^{12}C beam up to 400 MeV	
Optimization	Implementation of LEM Multi field optimization	Prod. of radiob. database for specific class of a given clinical case Validation with full MC + LEM simulation	Data for several tumors 4D optimization Simulation tools
Monte Carlo	Interface with LEM Study of nuclear models Interface with CT	First prototype of validation tool	Production of validation tool Benchmarking activity
PET Monitoring	Start of inverse filter calculation Proc of components for hardware developments	Assembling of new detector Data taking and inverse filter optimization	Characterization of the complete in-bema PET monitoring and integration with TPS

Production of a first prototipe

Integration into a final TPS