Rewriting nuclear physics textbooks

Nuclear interaction for medicine

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Disclaimer!

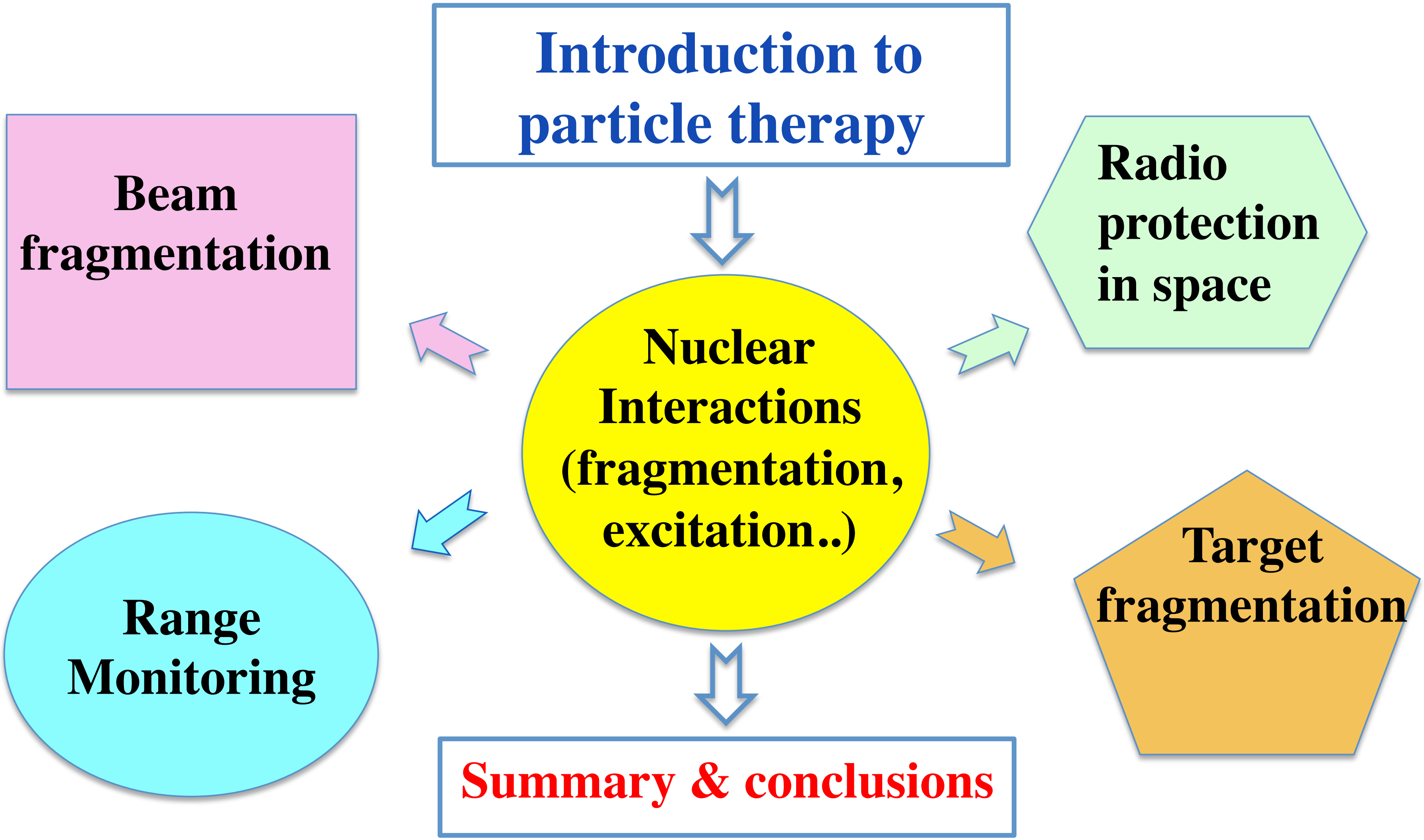
The application of the of the nuclear physics to medicine are almost countless (we have almost "nuclear hospitals" nowadays!!). I just picked up a personal and very small selection focused on tumor therapy using hadron beams.

In particular I will not cover classical items like

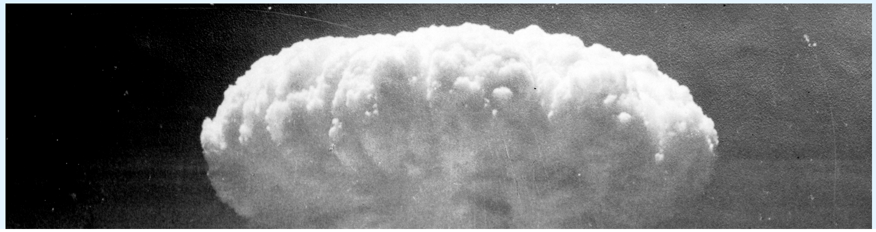
- Positron Emission Tomography (using the positron annihilation in back to back photons of β+ emitters nuclei like ^{18}F, ^{11}C)
- Single Photon Emission Tomography (exploiting the nuclear decay of ^{99}Tc, ^{131}I and many other nuclei)
- Brachitherapy (cancer therapy that exploits the local dose release of α/β nuclear decay)
- Boron Nuclear Capture (exploits a neutron beam capture on boron loaded tumor)
- Etc etc

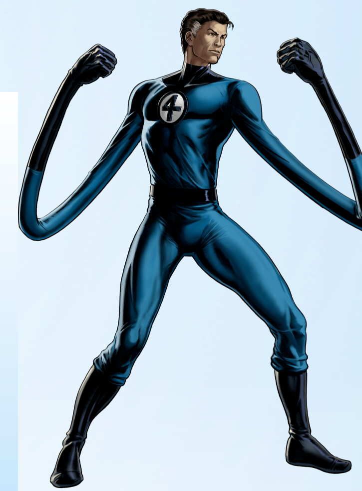
Outline

Bouncing from fundamental physics to applied physics and back…
A spot-like, phenomenological, detector oriented view to the impact of nuclear interactions on particle therapy and radio protection in space



Ma perche' la fisica nucleare… in ospedale?

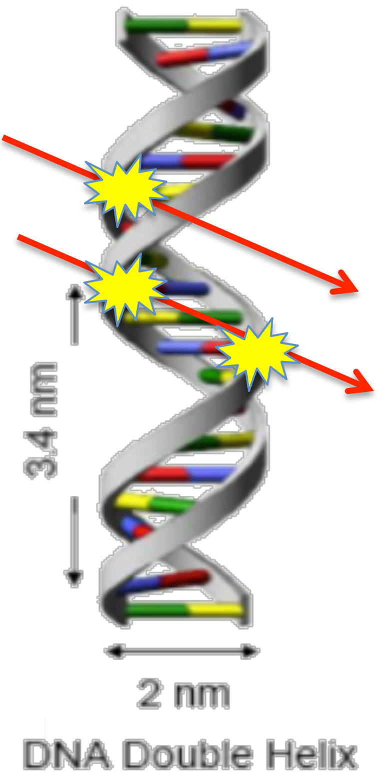




In common sense the word NUCLEAR recall something very scary and dangerous.

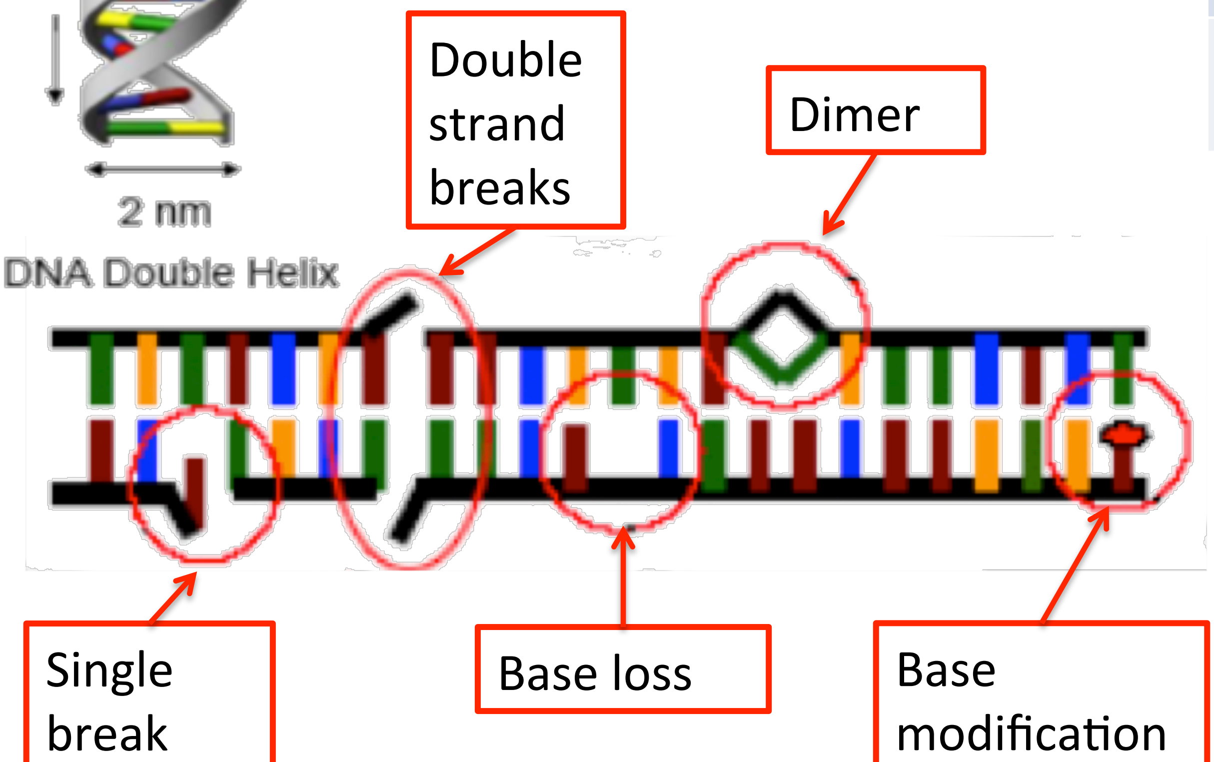
How can be linked this "menace" of nuclear physics with the healthy and careful nature of medicine?

Cells and ionizing radiation



Ionizing radiation can damage the cell DNA.
The DNA helix is very long (~meters) and thin (~nm), and is packed in the 5-10 μm of the cell nucleus

Damage type	frequency (%)
Single break	88
Double break	3
Protein-DNA cross-link	4
Complex damage	5

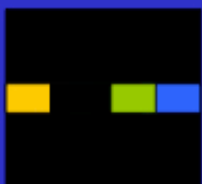


The DNA fix some/all radiation damage in minutes/hour.
Healthy cell are much better at repair DNA then cancer cell

Radiotherapy !!

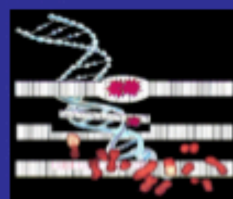
DNA is the most important molecule that can be changed by radiation

- **Effects of DNA Damage**



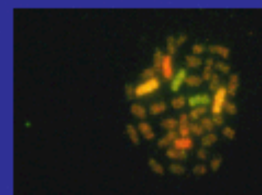
Gene Expression

A gene may respond to the radiation by changing its signal to produce protein. This may be protective or damaging.



Gene Mutation

Sometimes a specific gene is changed so that it is unable to make its corresponding protein properly



Chromosome Aberrations

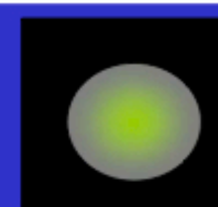
Sometimes the damage effects the entire chromosome, causing it to break or recombine in an abnormal way. Sometimes parts of two different chromosomes may be combined

Side Effects

Genomic Instability

Sometimes DNA damage produces later changes which may contribute to cancer.

RadioTherapy



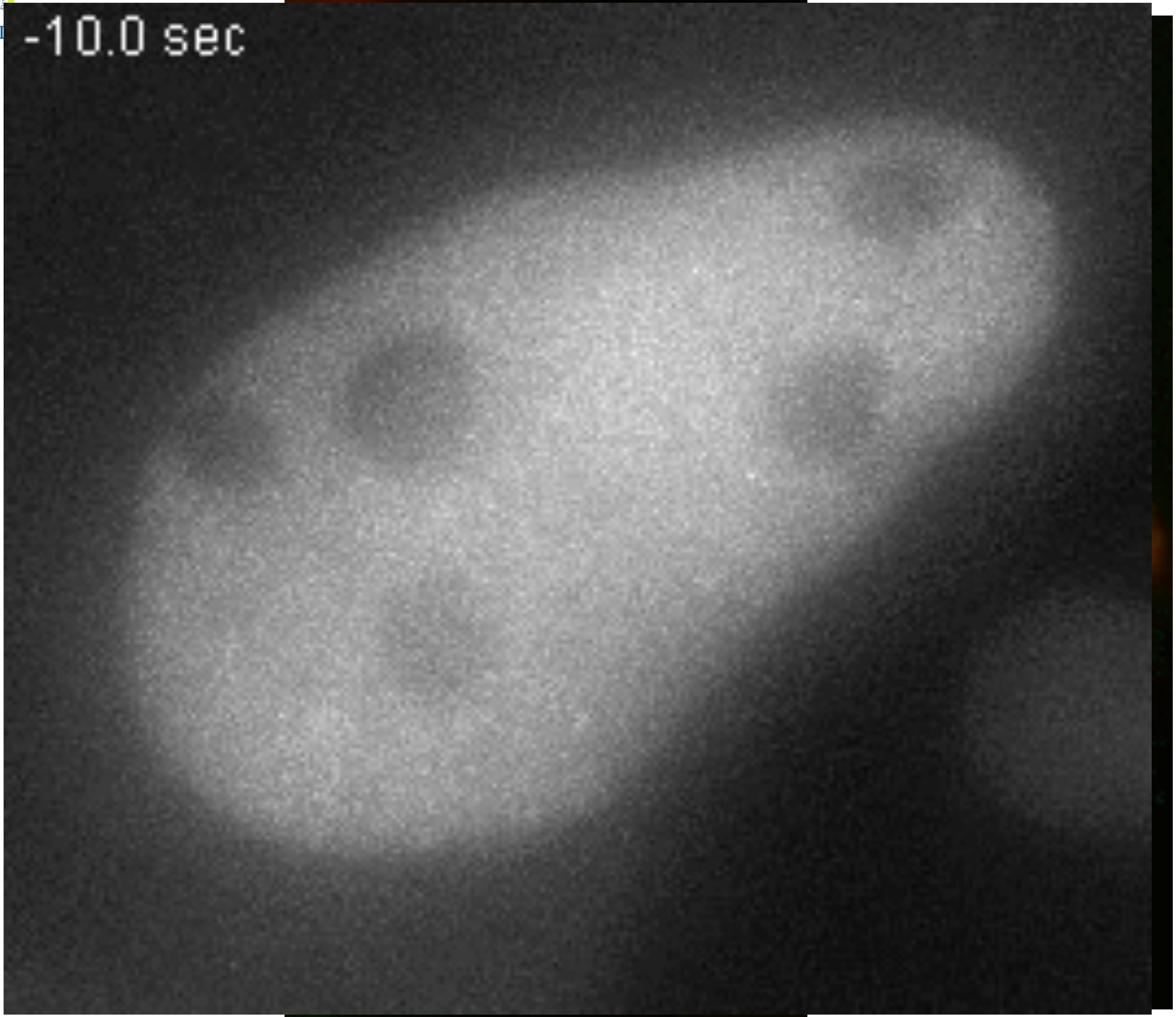
Cell Killing

Damaged DNA may trigger apoptosis, or programmed cell death. If only a few cells are affected, this prevents reproduction of damaged DNA and protects the tissue.

Courtesy of M.Durante

In an adult body ~ 50-70 x 10^9 cells die every day for several reasons. In a year we replace dead cells for the entire mass of our body

Live cell imaging of heavy ion traversals in euchromatin and heterochromatin



Sci. USA 2009; *Nucl. Acids Res*. 2011

The "standard" paradigm

1 Gy γ-rays in one nucleus:

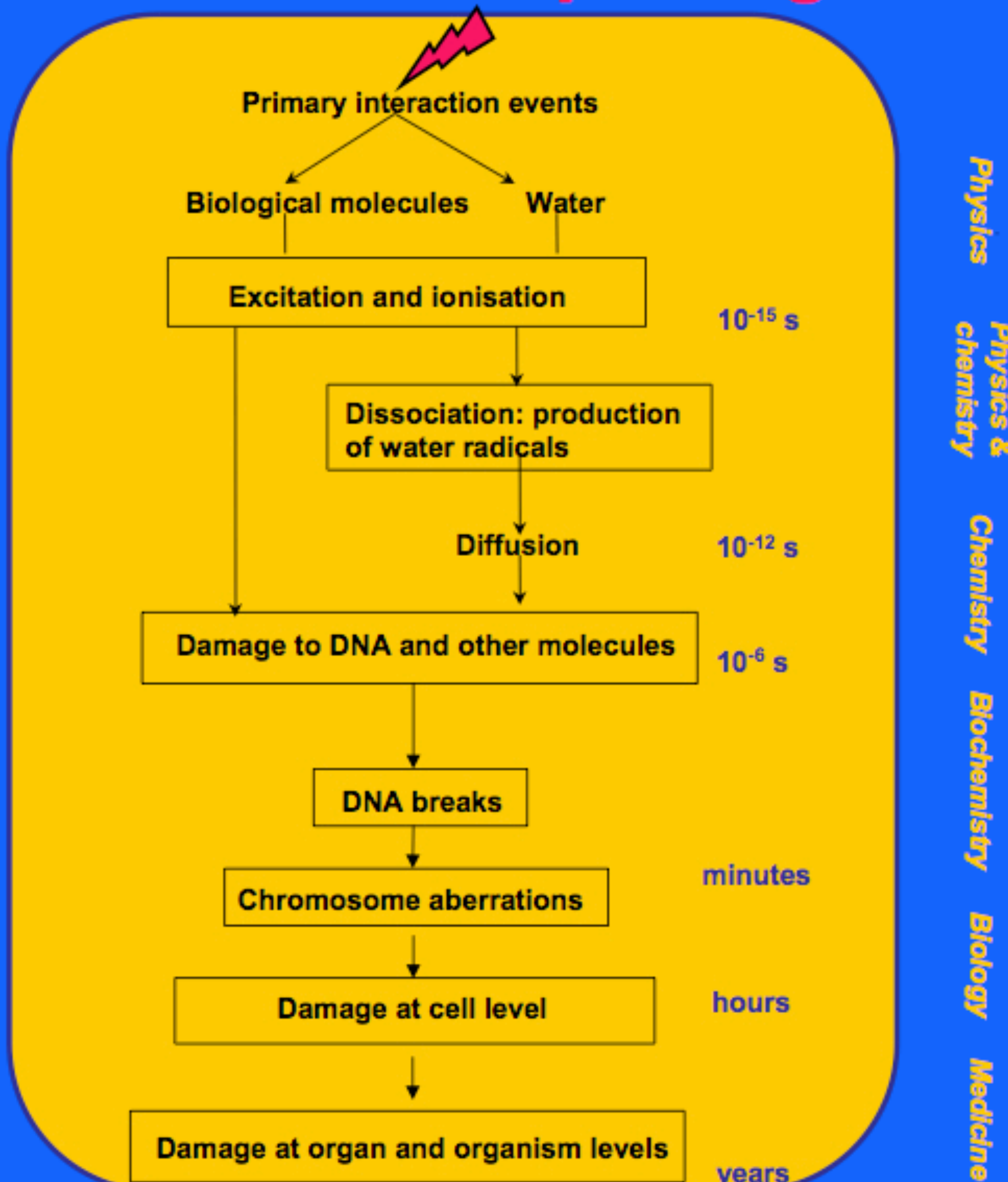
≈ 100,000 ionizations
(≈ 2,000 in the DNA)

≈ 40 DNA DSBs,
≈-1 "complex lesion"

≈ 0.5-1 chromosome aberrations

≈ 0.5-1 lethal lesions
≈ 10^{-5} HPRT mutations
≈ 10^{-5} neoplastic transformations

<< 10^{-5} cancers



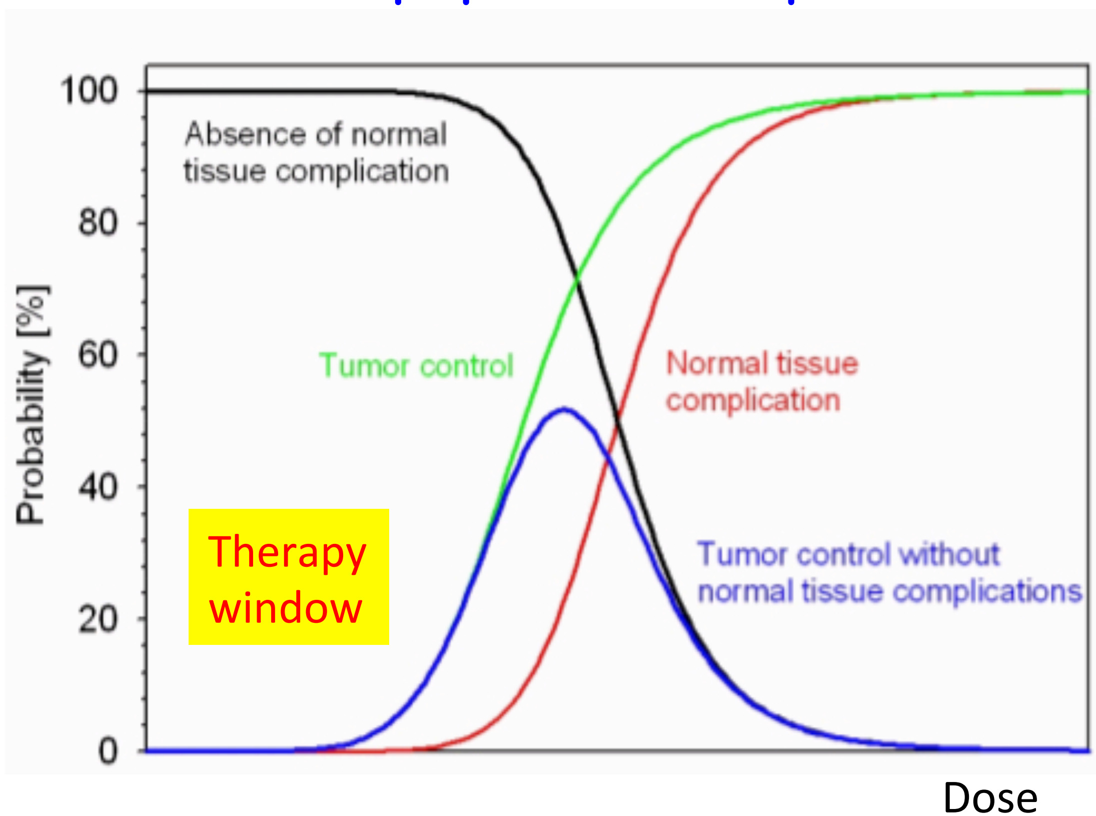
Other Paradigms:
Instabilty;
Bystander;
Micro-environment;
Inflamation;
etc ....

Tumor Control vs Tissue Complication

- Part of multi-disciplinary approach to cancer care
- Used in 50-60% of all cancer patients (also together surgery and/or chemotherapy)
- More of 1/3 of western countries population experiences cancer in lifetime

- Mainly used for loco-regional treatment
- Benefits and side-effects are usually limited to the area(s) being treated

$$Dose = \frac{dE_{abs}}{dm} (Gray)$$

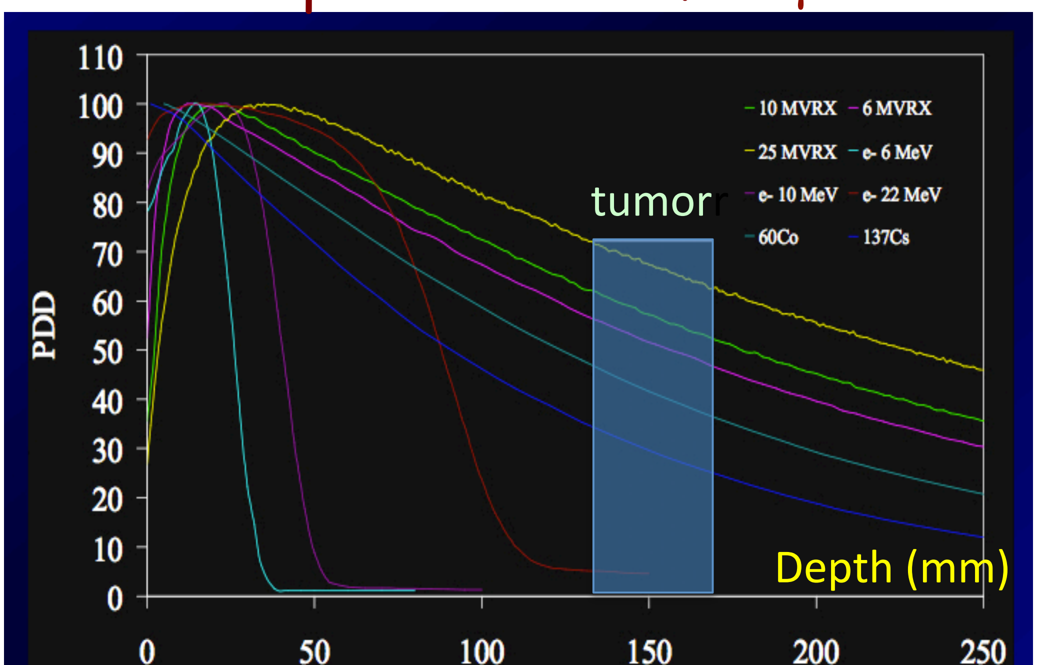


LINAC, Archimede & Radiotherapy

Standard radiotherapy uses γ beam obtained from bremmsthralung in a electron LINAC.

The dose depth relation is not optimal but several beams are concentrated on the tumor to obtain a conformal energy release

Dose-depth relation for γ and e^-



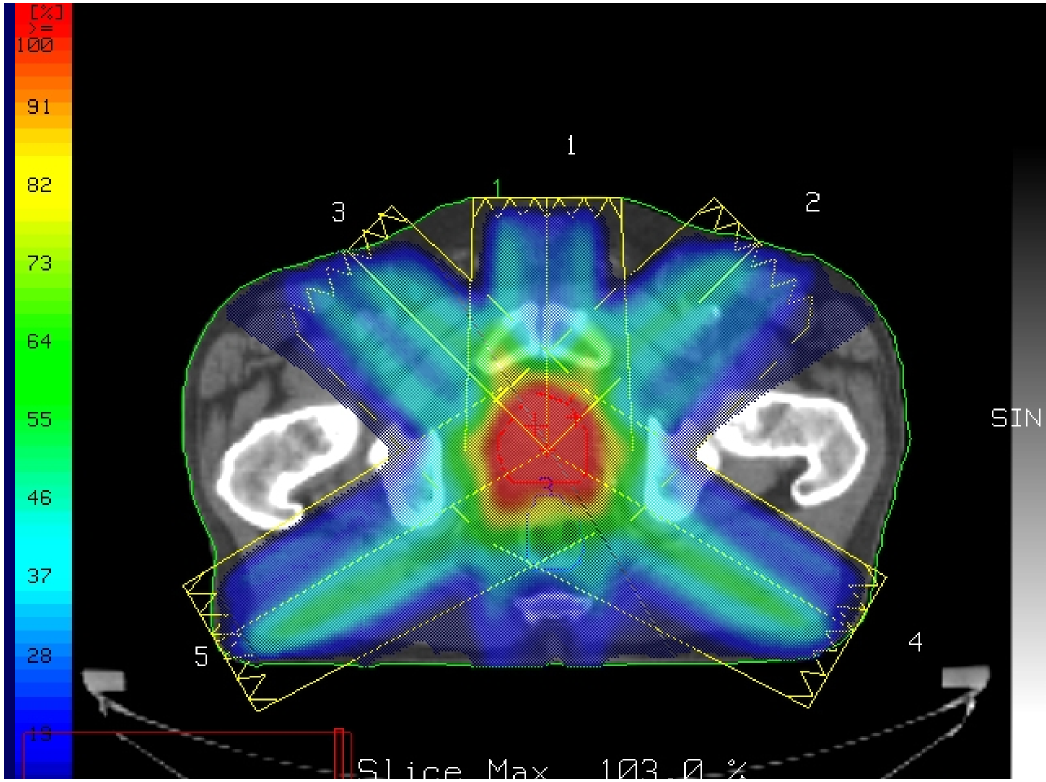
Archimede did it with sun rays

The conventional RT

The photon (and e^-) beams are the most common in RT. Cheap, small, and reliable.

The energy release is not suitable to release dose in a deep tumor.

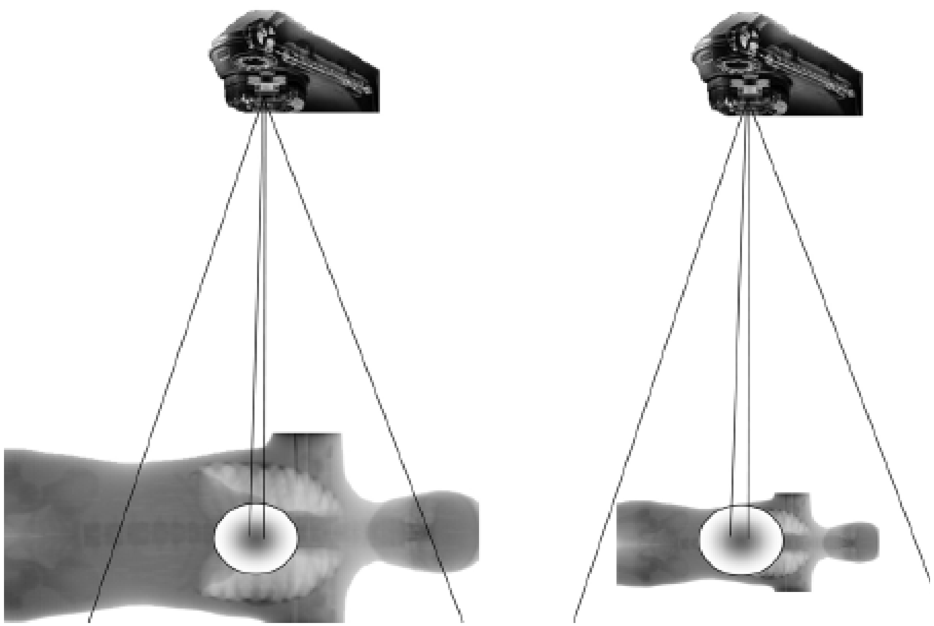
But the use of sophisticated imaging (CT), superposition of several beams, computed optimization, multi-leaves collimators and >40 year of R&D make IMRT effective and widespread

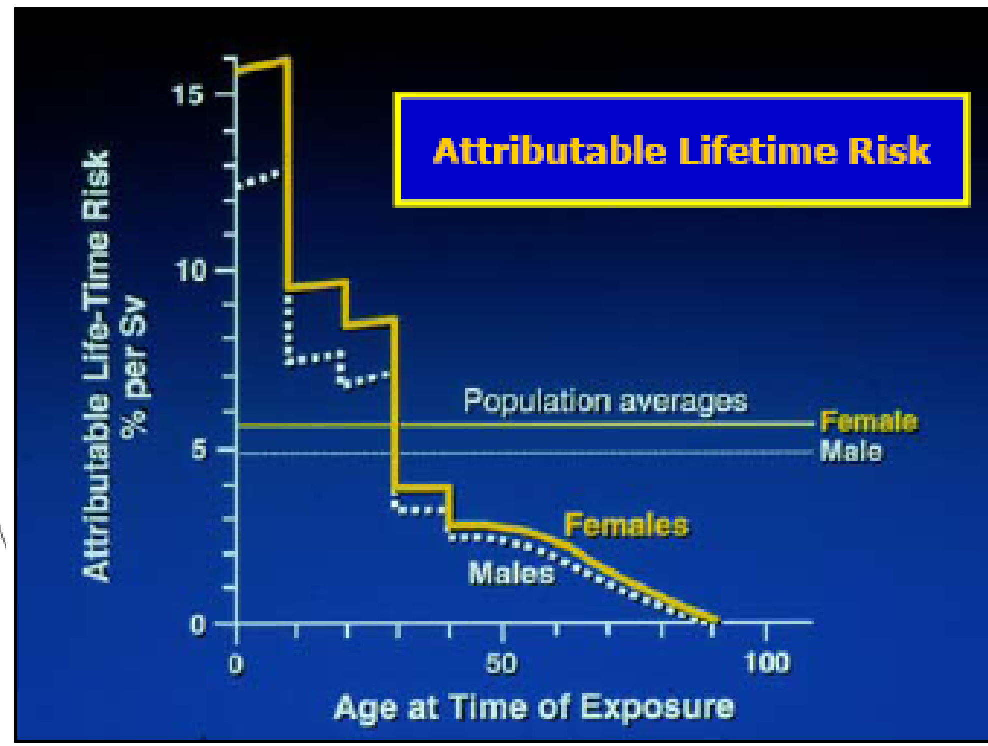


Why not increase the dose release?

Dose escalation in tumor control is limited by probability of secondary cancer in the surrounding healthy tissues , in particular in pediatric patients (photon beams have exponential attenuation..)

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant

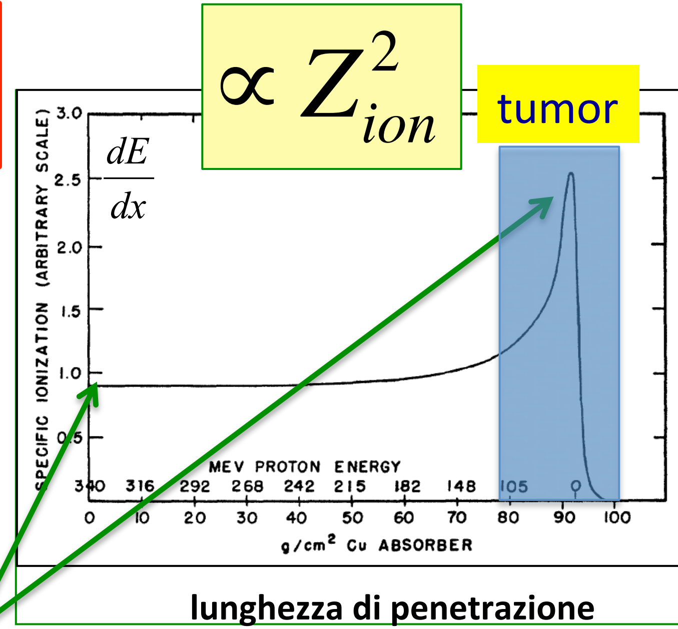


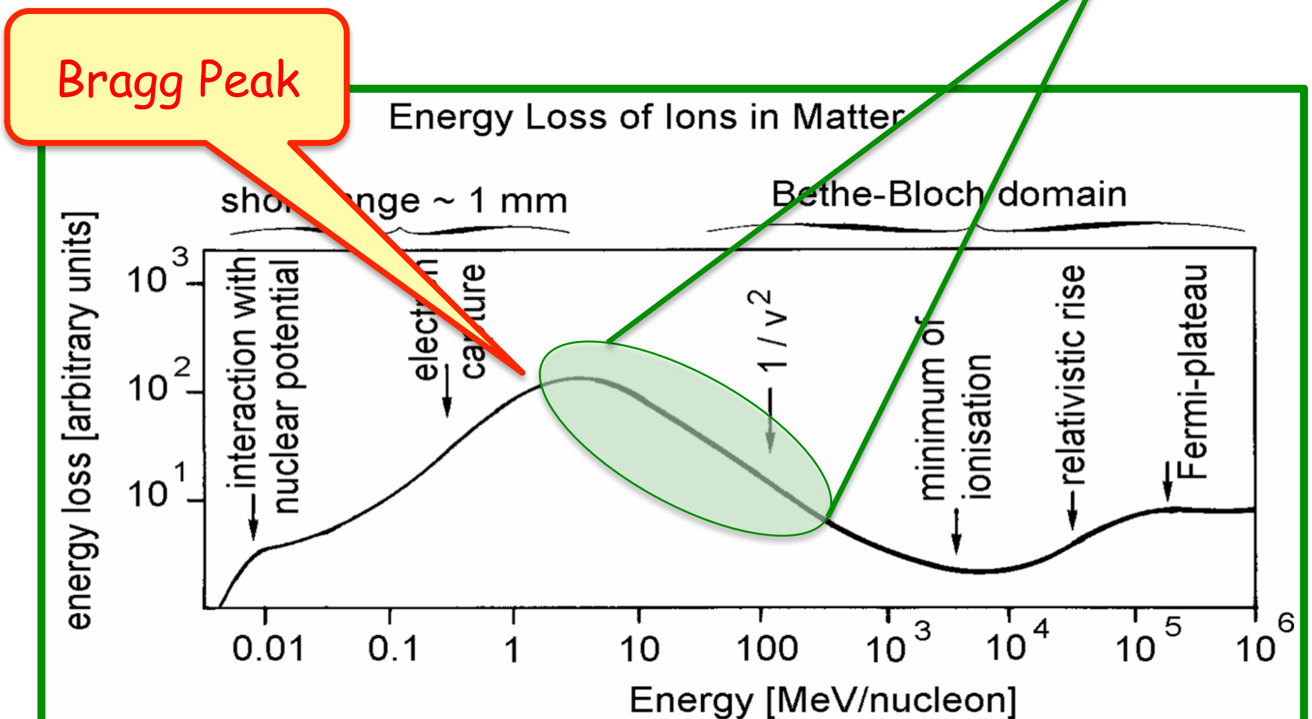


Hall, *IJROBP* 2006

But physics can help…

On the other hand, the release of energy by charge particles has very different, and attractive, features… why not to use them?





Perfect to release energy (dose) in a tumor buried inside the patient, like a depht bomb..

Mostly proton, few ^{12}C beams.

Future ^{4}He, ^{16}O ?

The beginning of the story….

Hadron RT was proposed by Robert Wilson in 1946 but the first HT treatment started in the sixties in USA with protons

R.R. Wilson, "Foreword to the Second International Symposium on Hadrontherapy," in Advances in Hadrontherapy, (U. Amaldi, B. Larsson, Y. Lemoigne, Y., Eds.), Excerpta Medica, Elsevier, International Congress Series 1144: ix-xiii (1997).

Radiological Use of Fast Protons

ROBERT R. WILSON
Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly, used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been ~~applied to medical problems. This has, in ~~e part, been due to the very short ~~ation in tissue of protons, deu~~ ~~particles from prese~~ ~~r-energy mach~~ ~~how~~

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

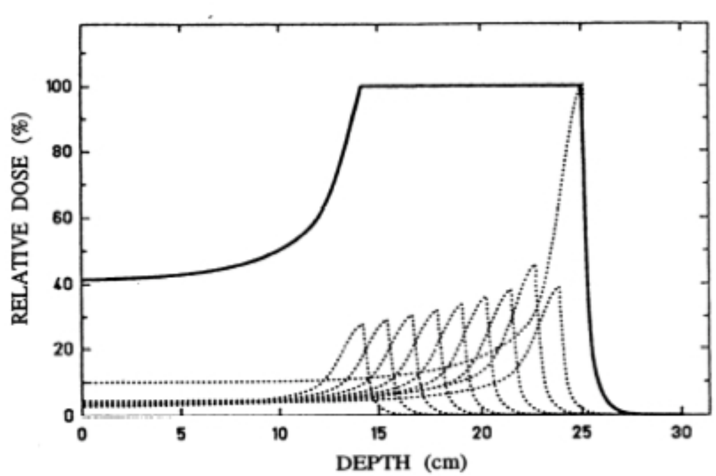
These properties make it possible to irradiate inter~~ly a strictly localized region ~~

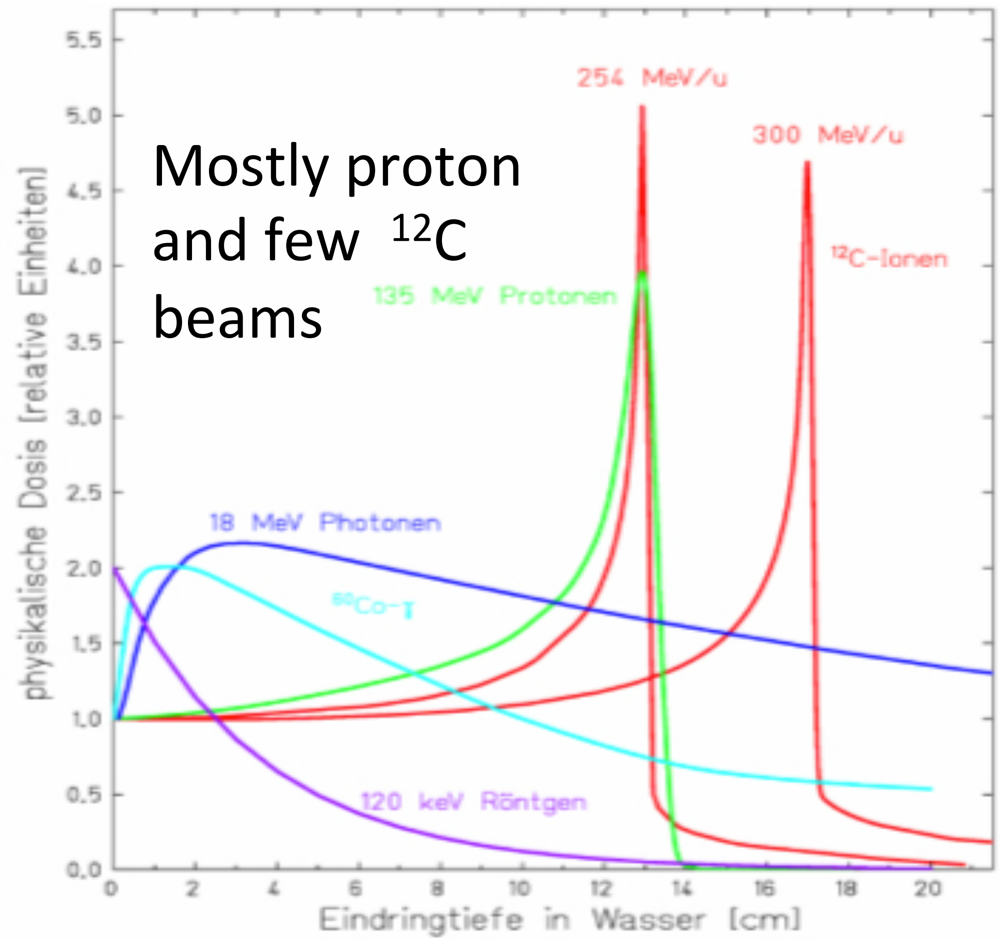
Radiology 47: 487-491, 1946

Particle therapy vs Photon RT

The highest dose released at the end of the track, sparing the normal tissue

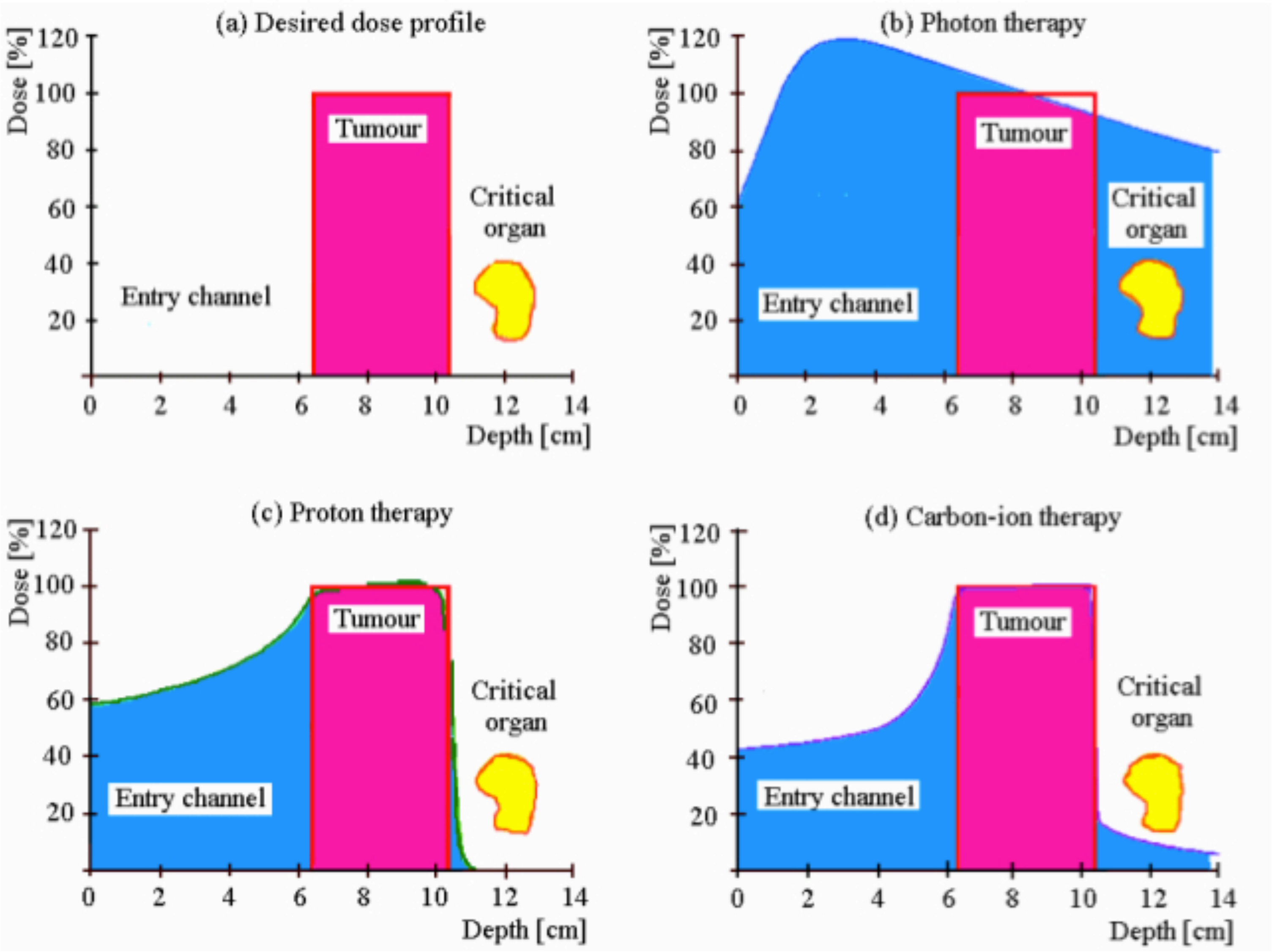
- Beam penetration in tissue function of the beam energy
- Dose decrease rapidly after the BP.
- Accurate conformal dose to tumor with Spread Out Bragg Peak (active scanning!)





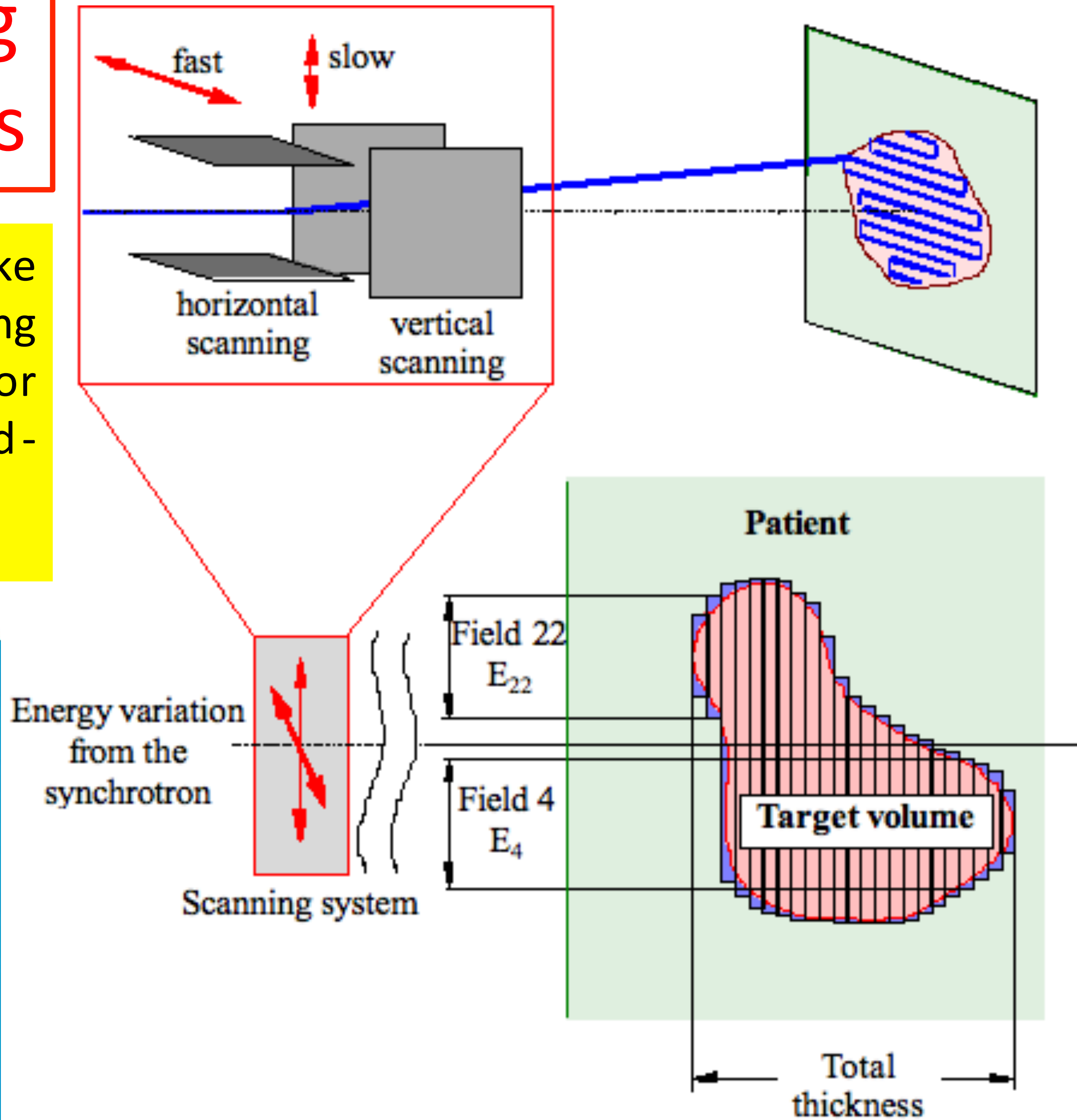
Mostly proton and few ^{12}C beams

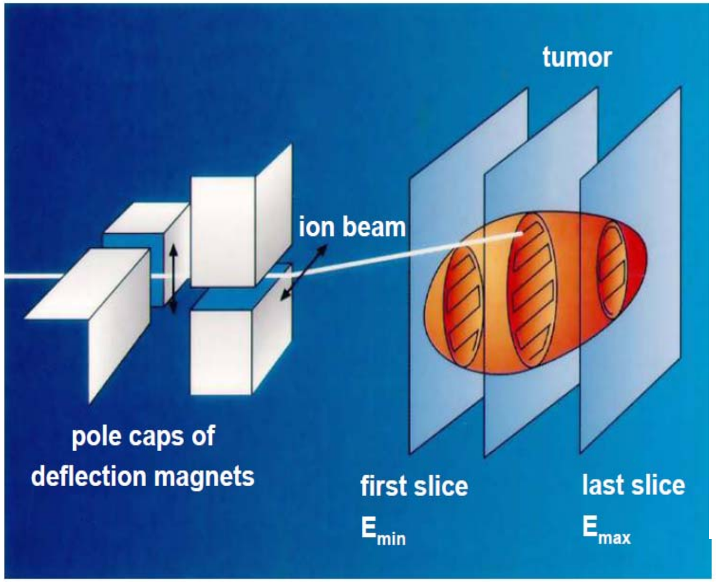
Single Field Dose comparison



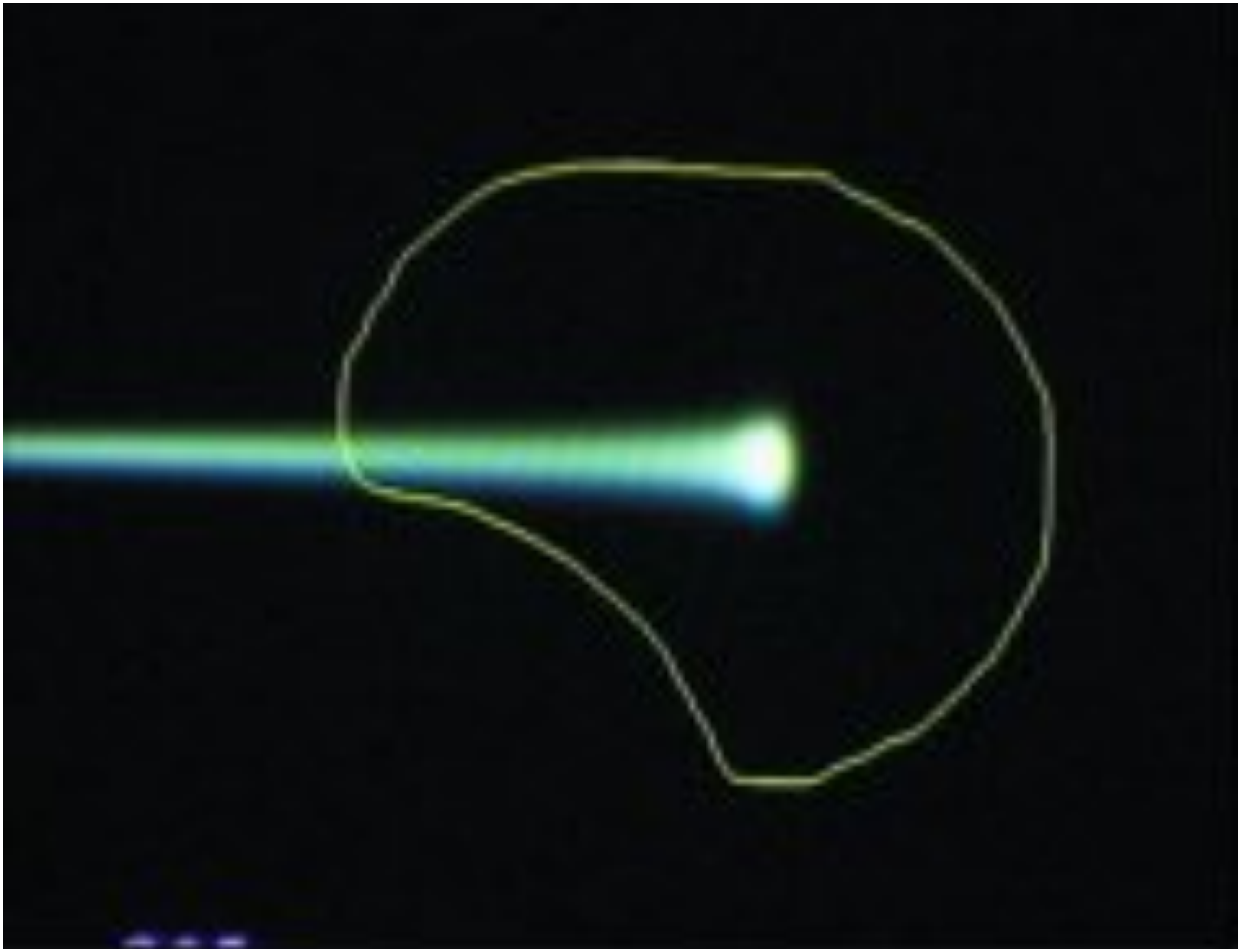
Active Scanning by pencil beams

Moving the hadron beam like in an old TV-set and changing the energy, all the tumor region can be treated->synchrotron





Painting the tumor…



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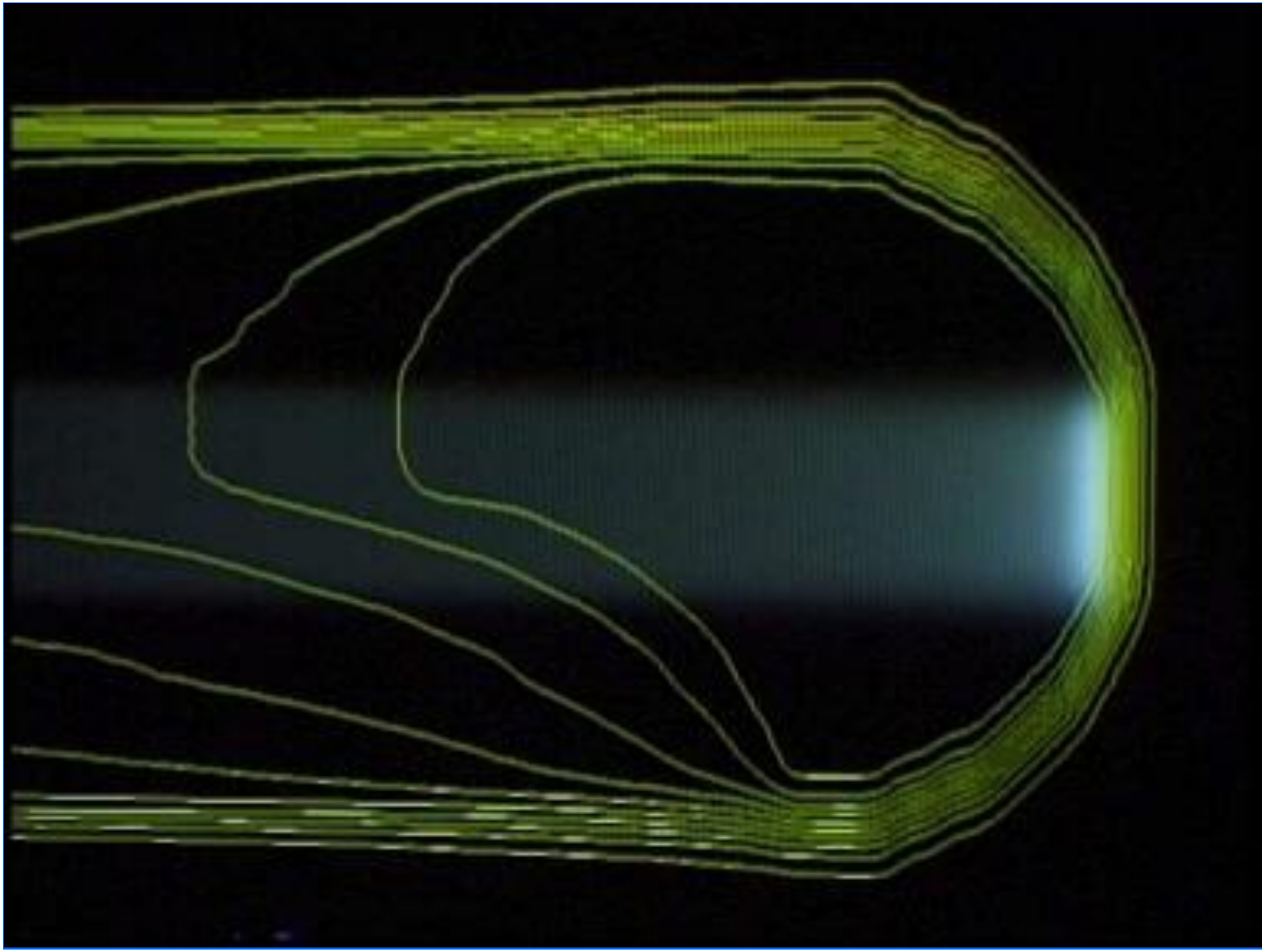

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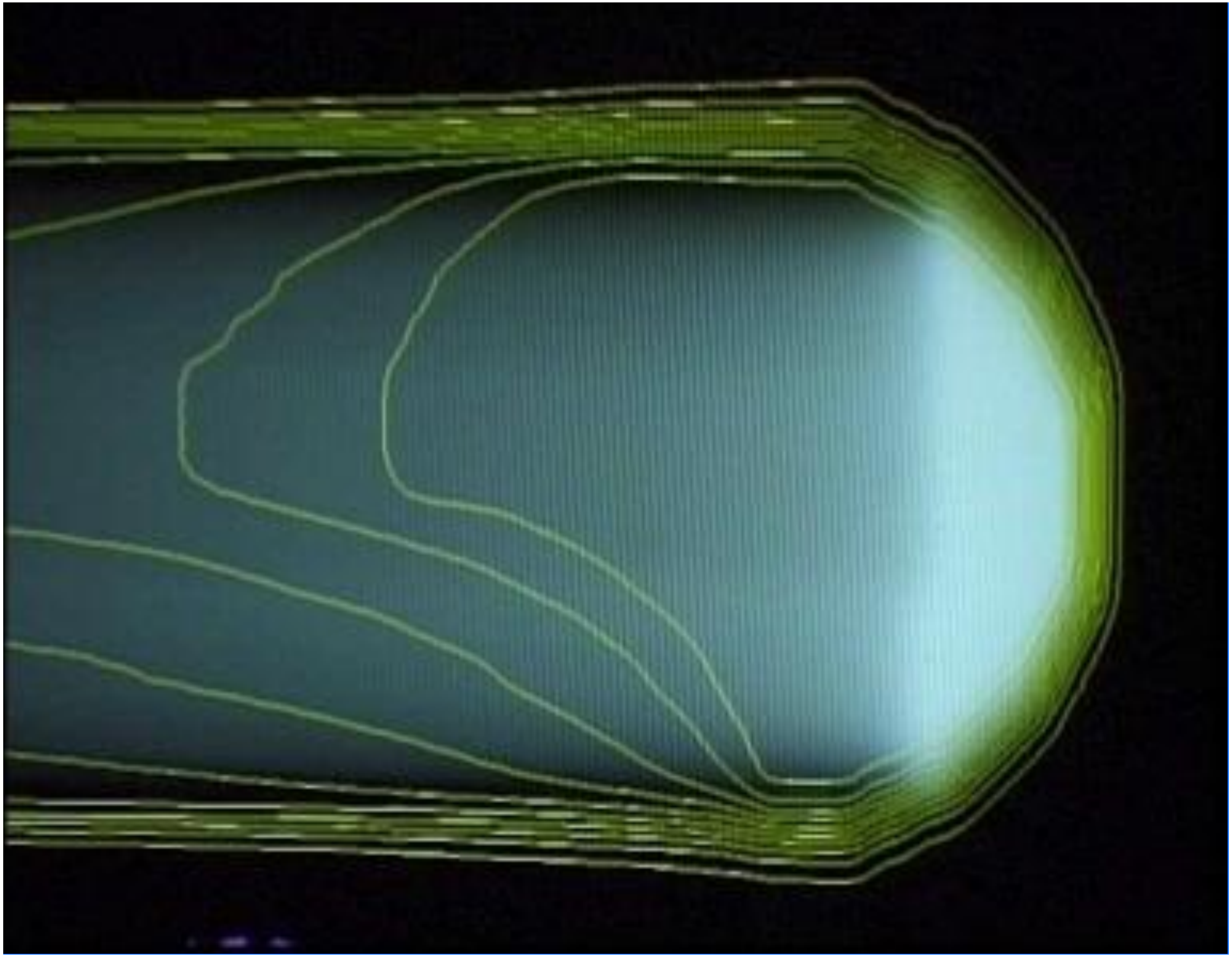
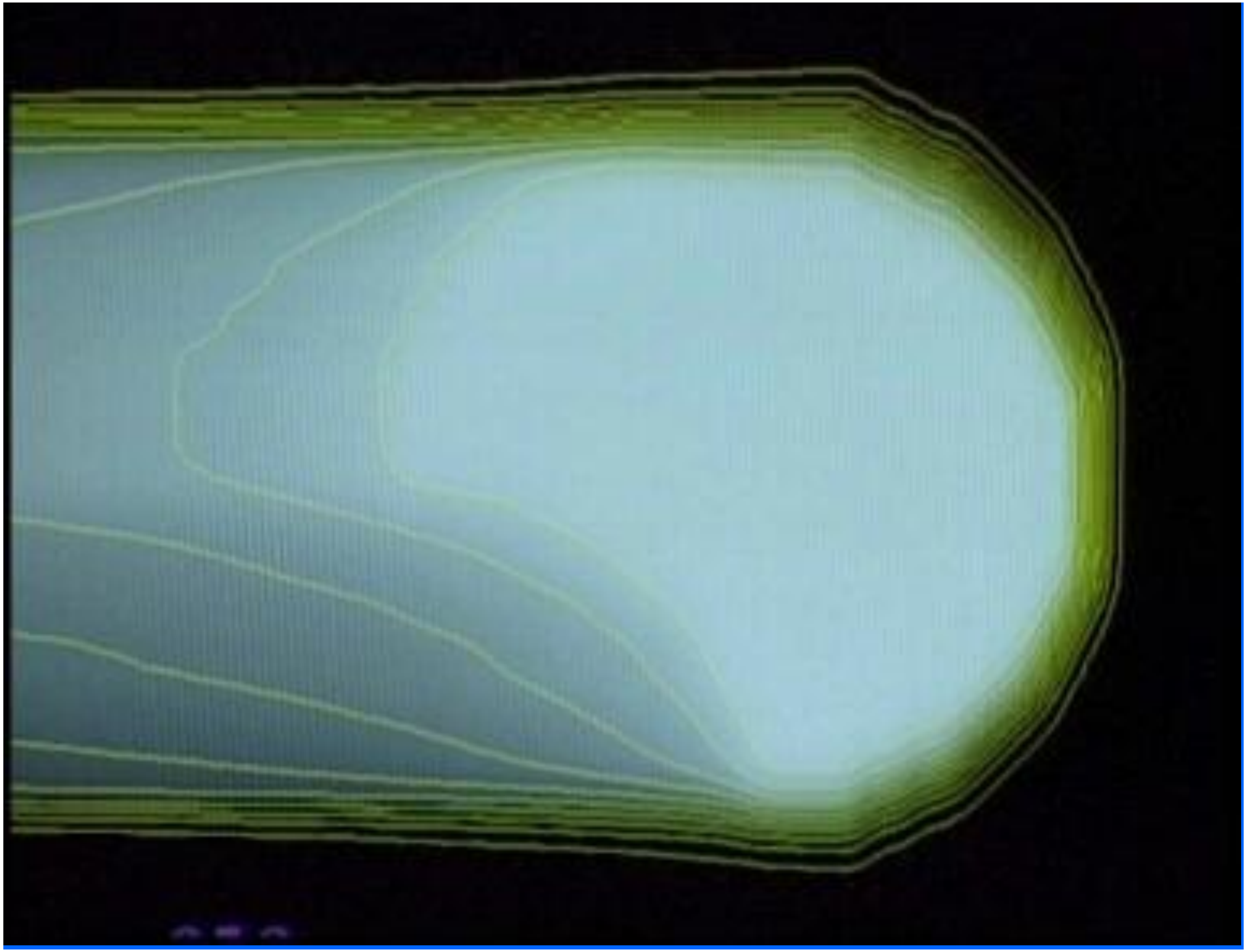
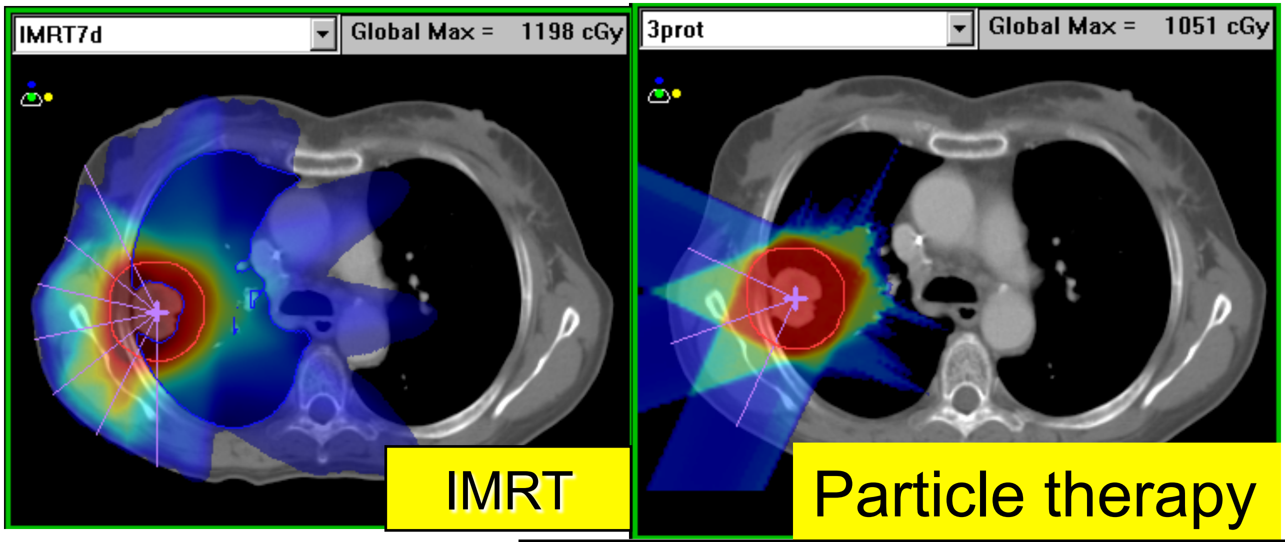


Painting the tumor…

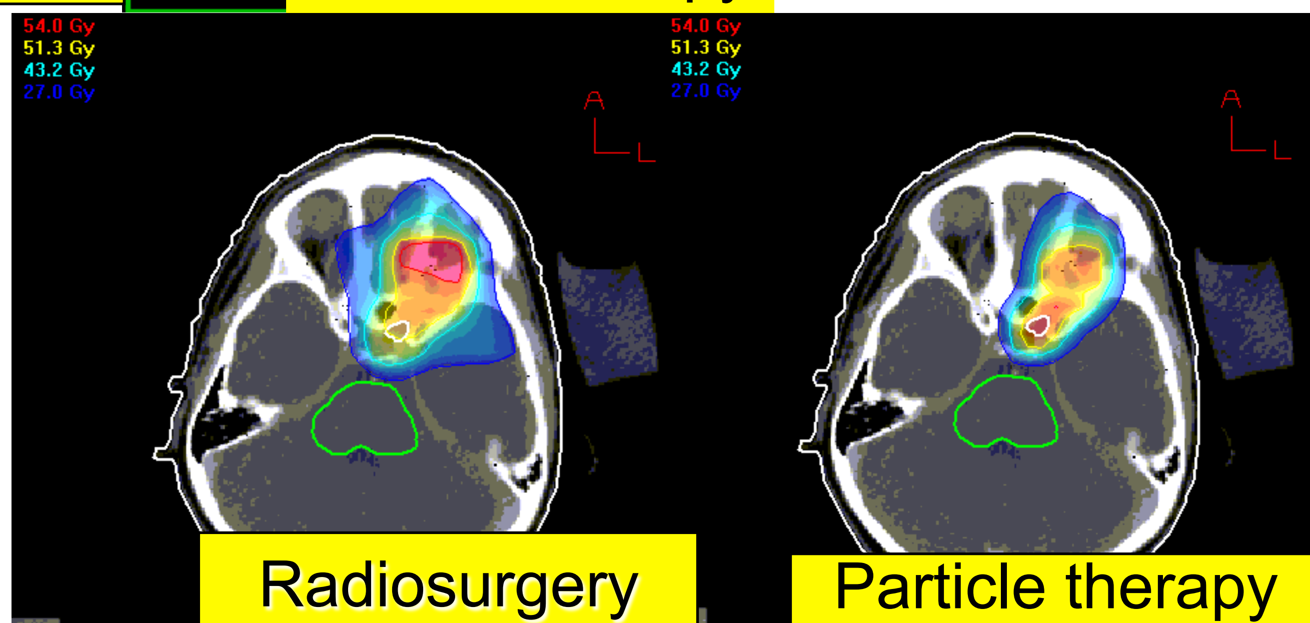


Photons vs Particle saga…



Particle therapy can easily show better selectivity wrt photon techniques…

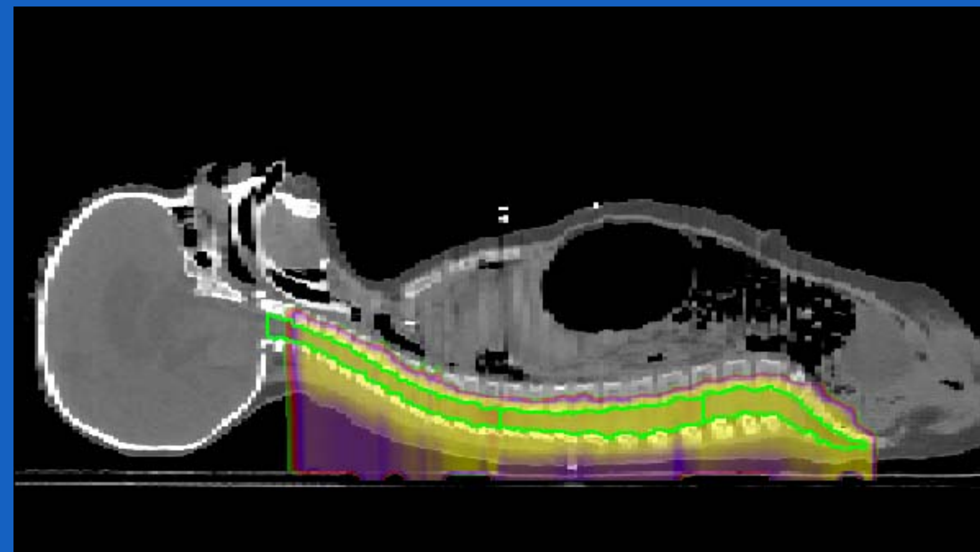
Yet, randomized clinical trials seem the only commonly accepted method to assess eventual superiority of PT technique



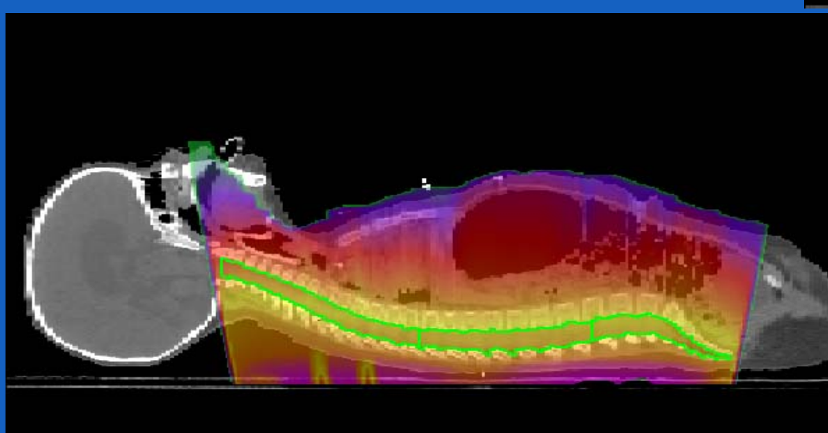
PT and pediatric tumors

Eventual secondary effect of diffuse dose are very relevant for pediatric tumor, where the expected life span is longer.

The neutron contribution is particularly difficult to model and to be taken into account in TPS (environment, reflection, beam halo, etc..



Protons

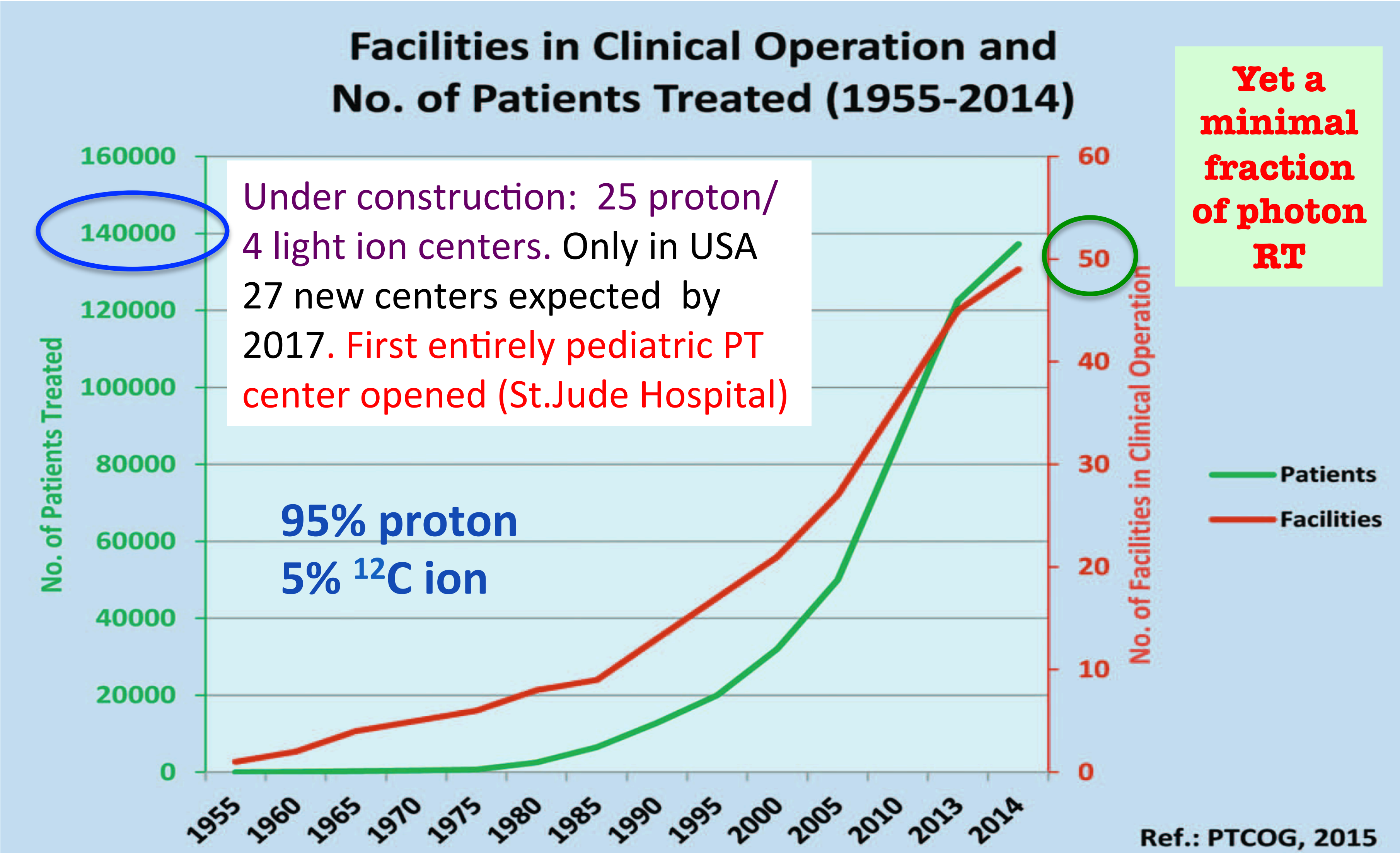


Photons

	X-ray	IMRT	Proton
CTV	90%	90%	90%
Heart	18.2	17.4	0.1
Right lung	3.5	21.9	0.1
Esophagous	11.9	32.1	10.2
Stomach	3.7	20.6	0.1
Right kidney	3.3	29.8	0.1
Transvers colon	2.6	18.0	0.1

Courtesy of R.Orecchia

Charged Particle Therapy in the world



Community looking at ^{4}He – ^{16}O beams: begin to be tested at clinical center

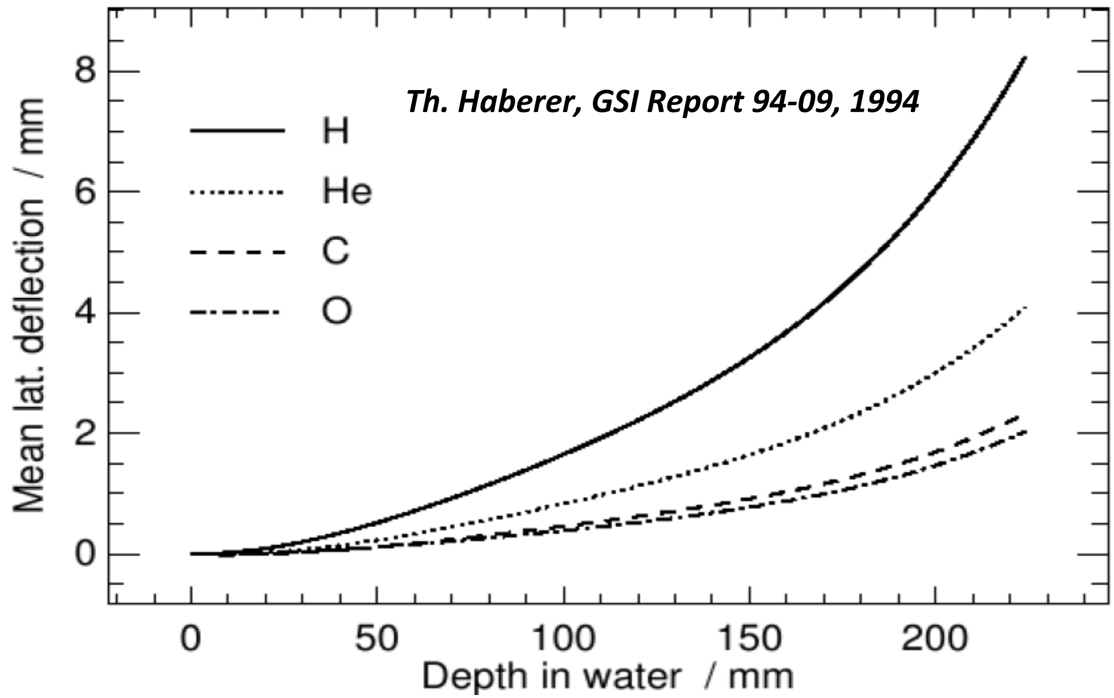
Which is the right beam for therapy?

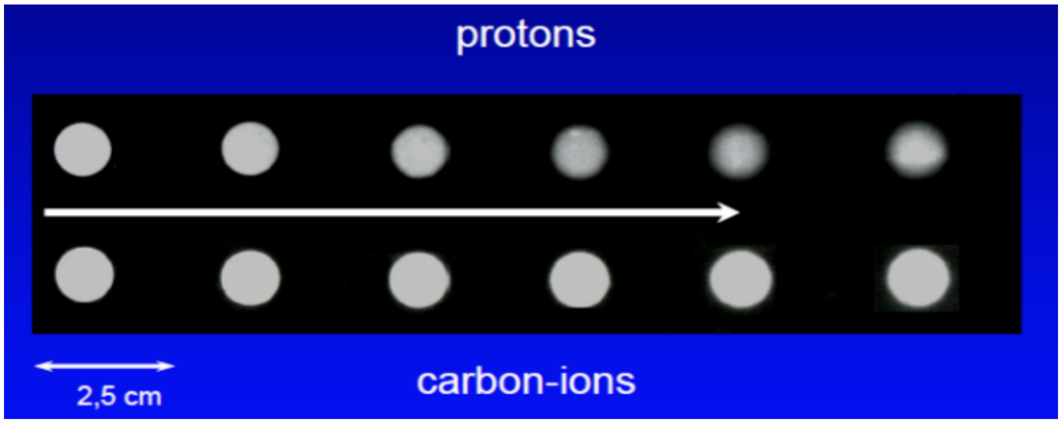
As far as money is the main concern.. protons win easily!

If we come to effectiveness, the landscape can change.

For instance, concerning the beam selectivity, comparing lateral deflection heavier ions have less multiple scattering

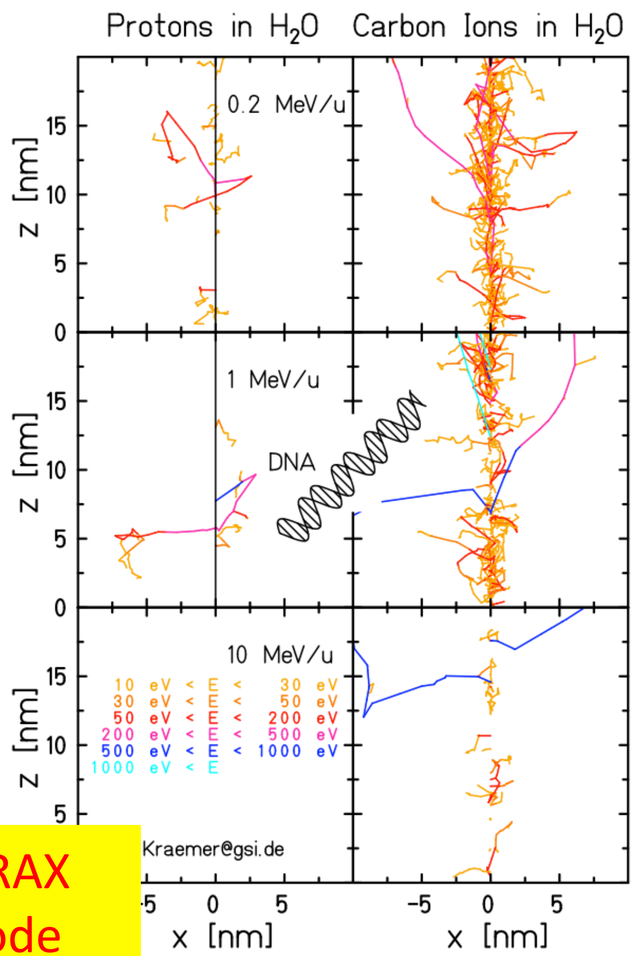
Beam lateral deflection





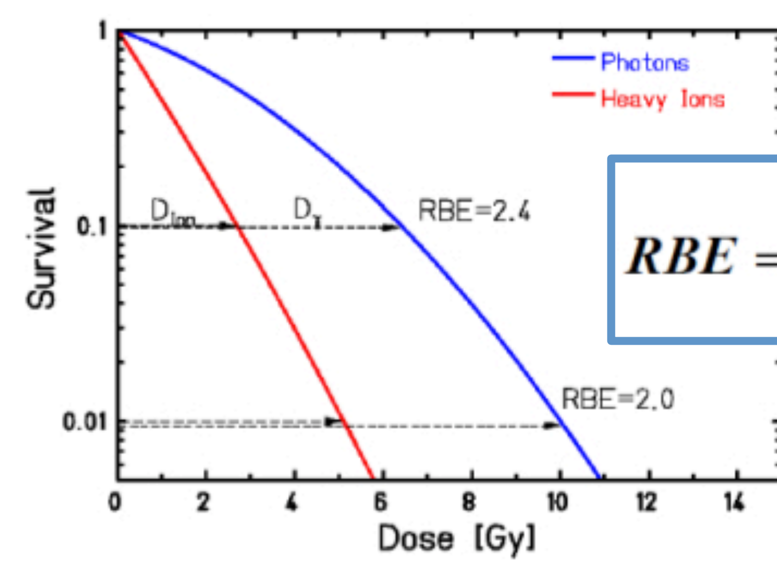
Heavier than proton? Maybe yes (RBE..)

M.Kramer et al. JoP 373 (2012),



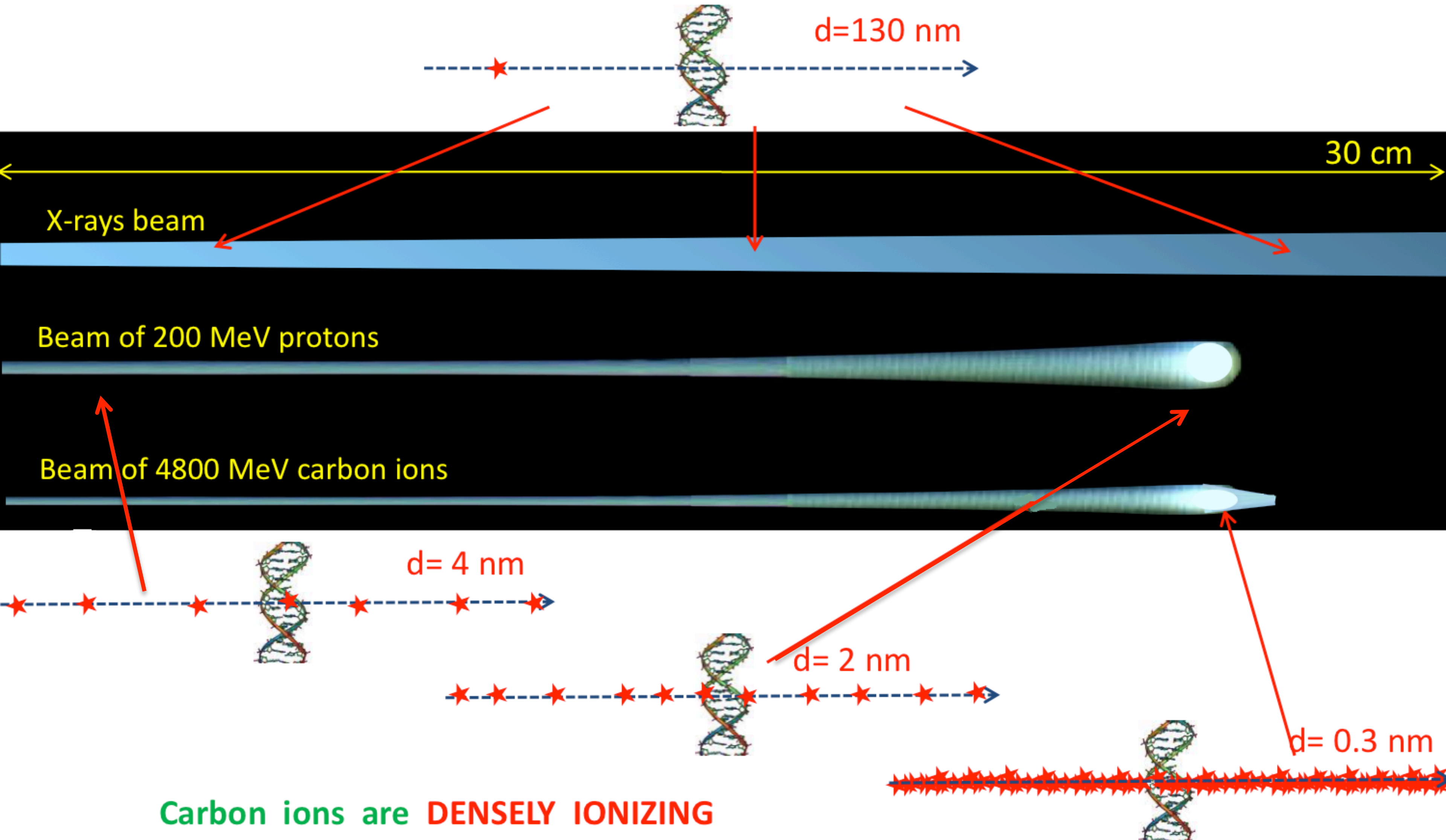
TRAX code

- The heavier ions are much better at killing the tumur cells with respect to the X rays (and p) for a given ➔high RBE
- Heavier ions have better plateau/peak ratio (less dose to the healthy tissue in a treatment) wrt to proton beams



$$RBE = \frac{D_\gamma}{D_{Ion}}\Big|_{Isoeffect}$$

Different bullet, different effects



Carbon ions are DENSELY IONIZING
(higher biological effectiveness)

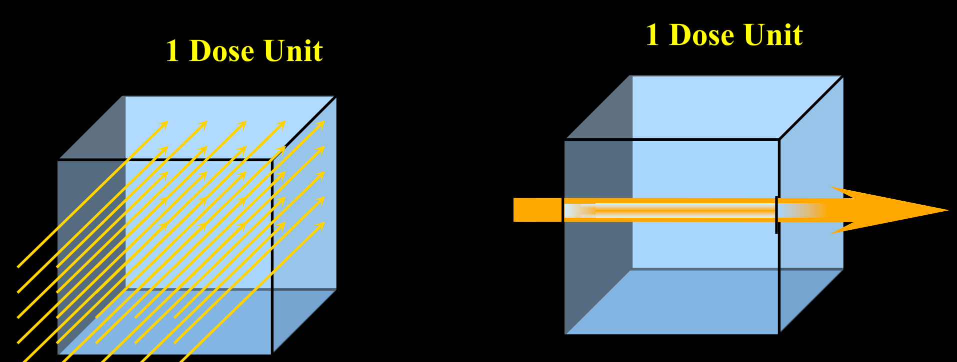
Courtesy U.Amaldi

An Analogy for Structured Energy Deposition and its Consequences

Low LET radiation produces isotropic damage to organized targets.

High LET radiation produces correlated damage to organized targets.

LET: Linear Energy Transfer



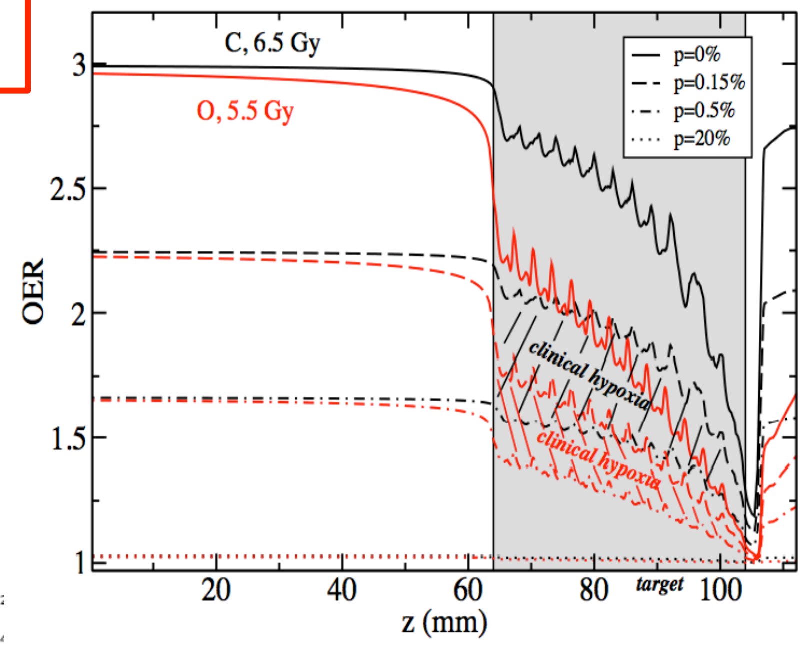
Low LET radiation deposits energy in a uniform pattern

High LET radiation deposits energy in a non-uniform pattern

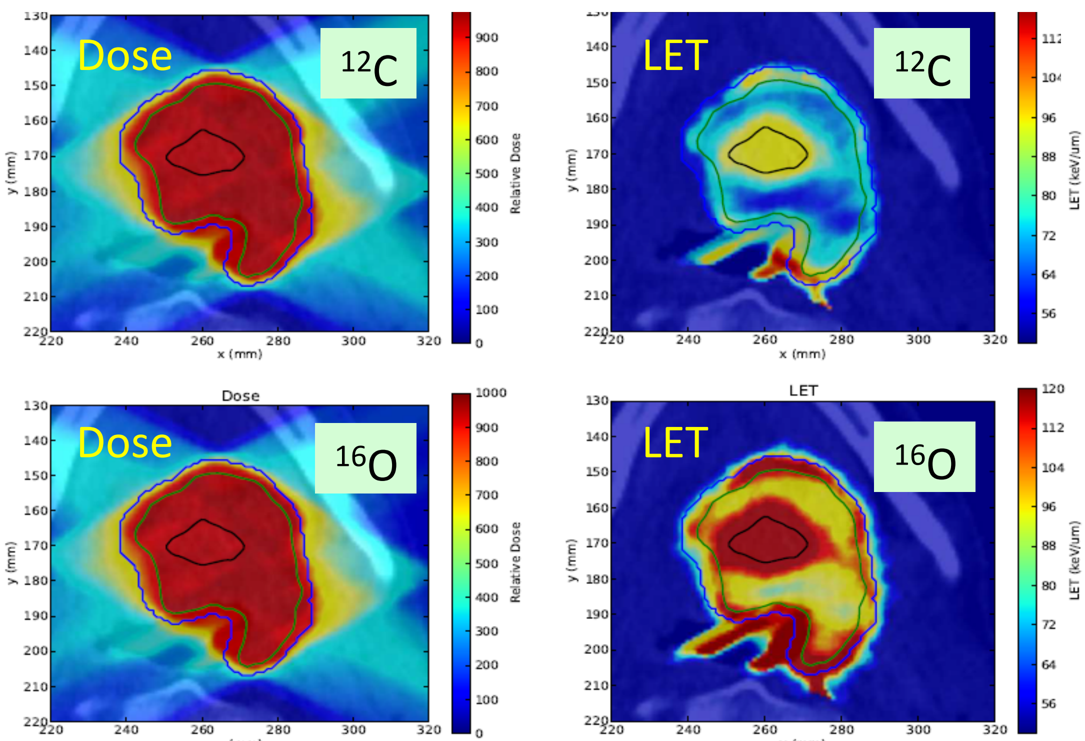
OER and ^{16}O beam

The high LET of the ^{16}O beam is effective against radio-resistant hypoxic tumors (low Oxygen Enhancement Ratio)

M.Kramer et al. JoP 373 (2012),



Bassler et al., Acta Oncol 2013

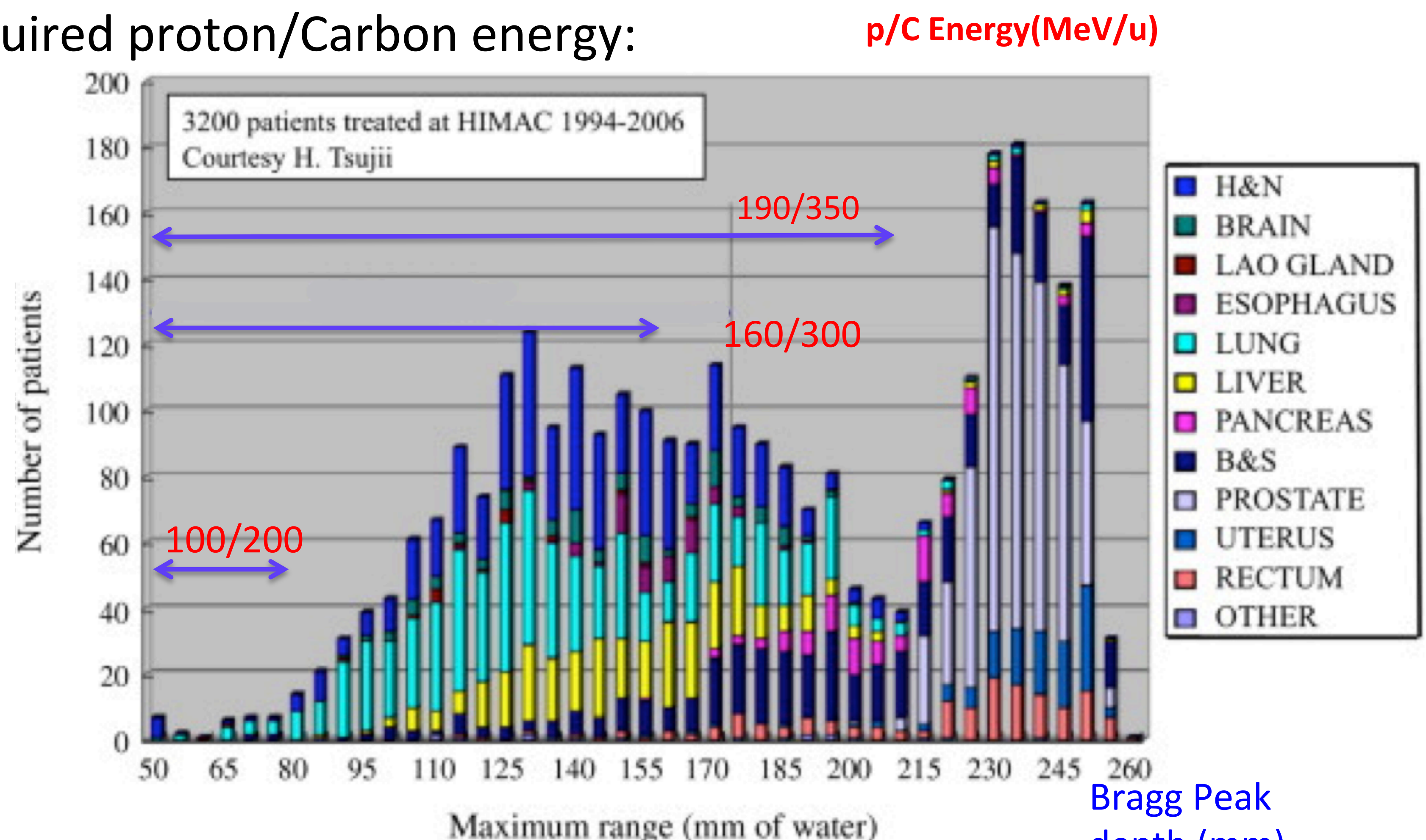


Full treatment or simple boost session with ^{16}O with hypoxic can be a clear improvement with respect to conventional Radiotherapy

Summer School Università di Pisa

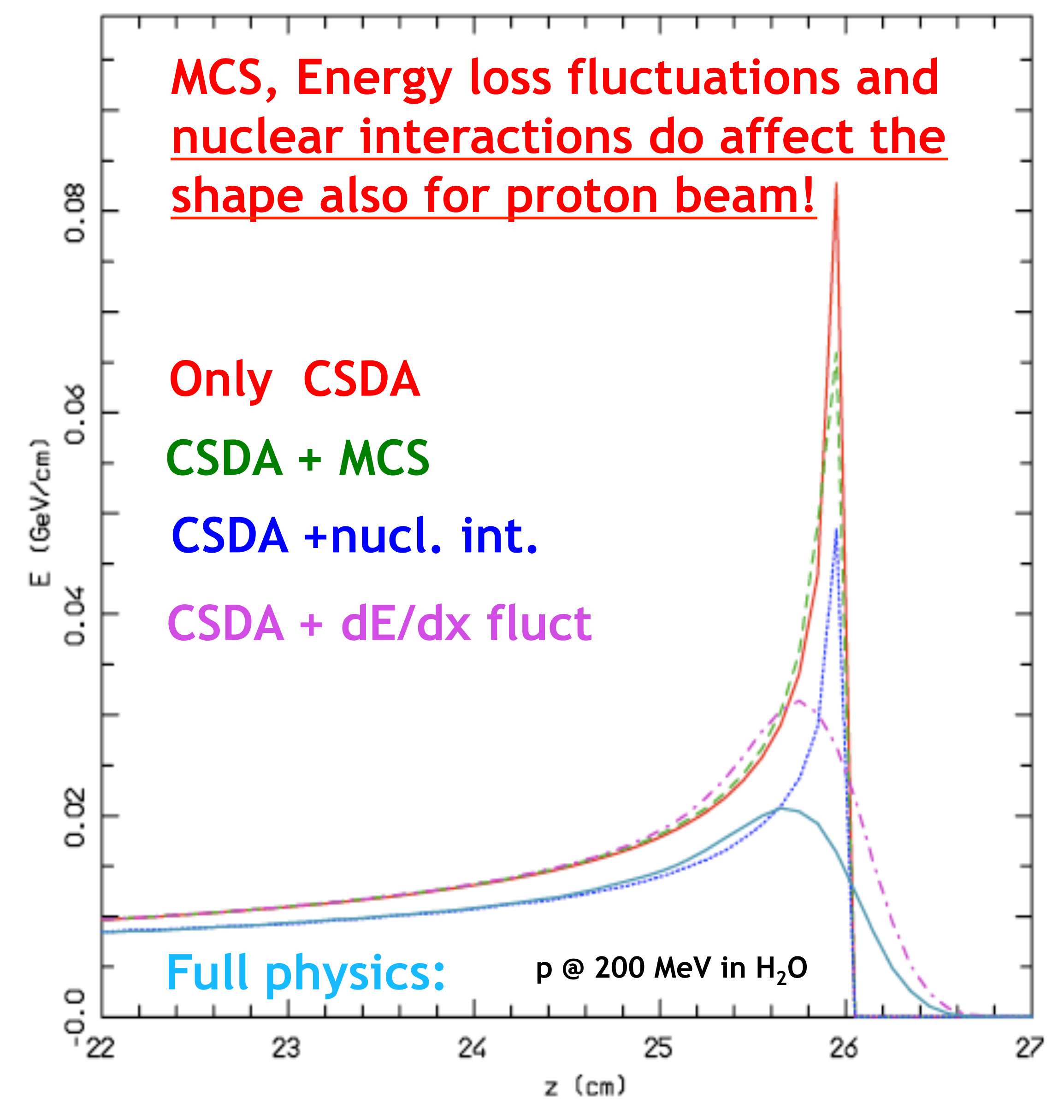
Beam for Particle Therapy

Required proton/Carbon energy:

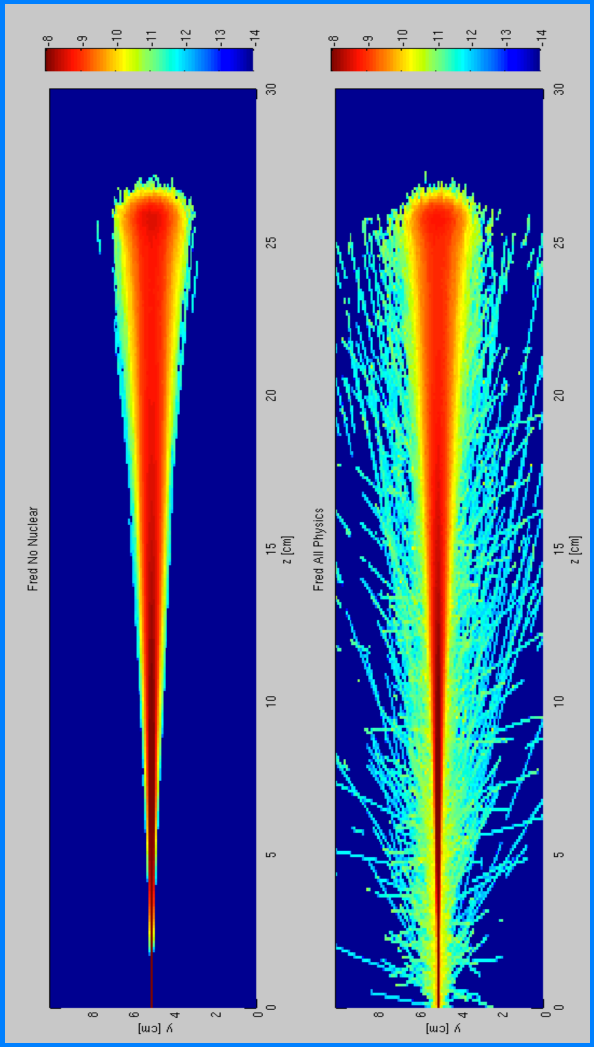


Proton Kinetic Energy between 100-250 MeV
Carbon Kinetic Energy between 200-400 MeV/u

Physics of the Bragg Peak

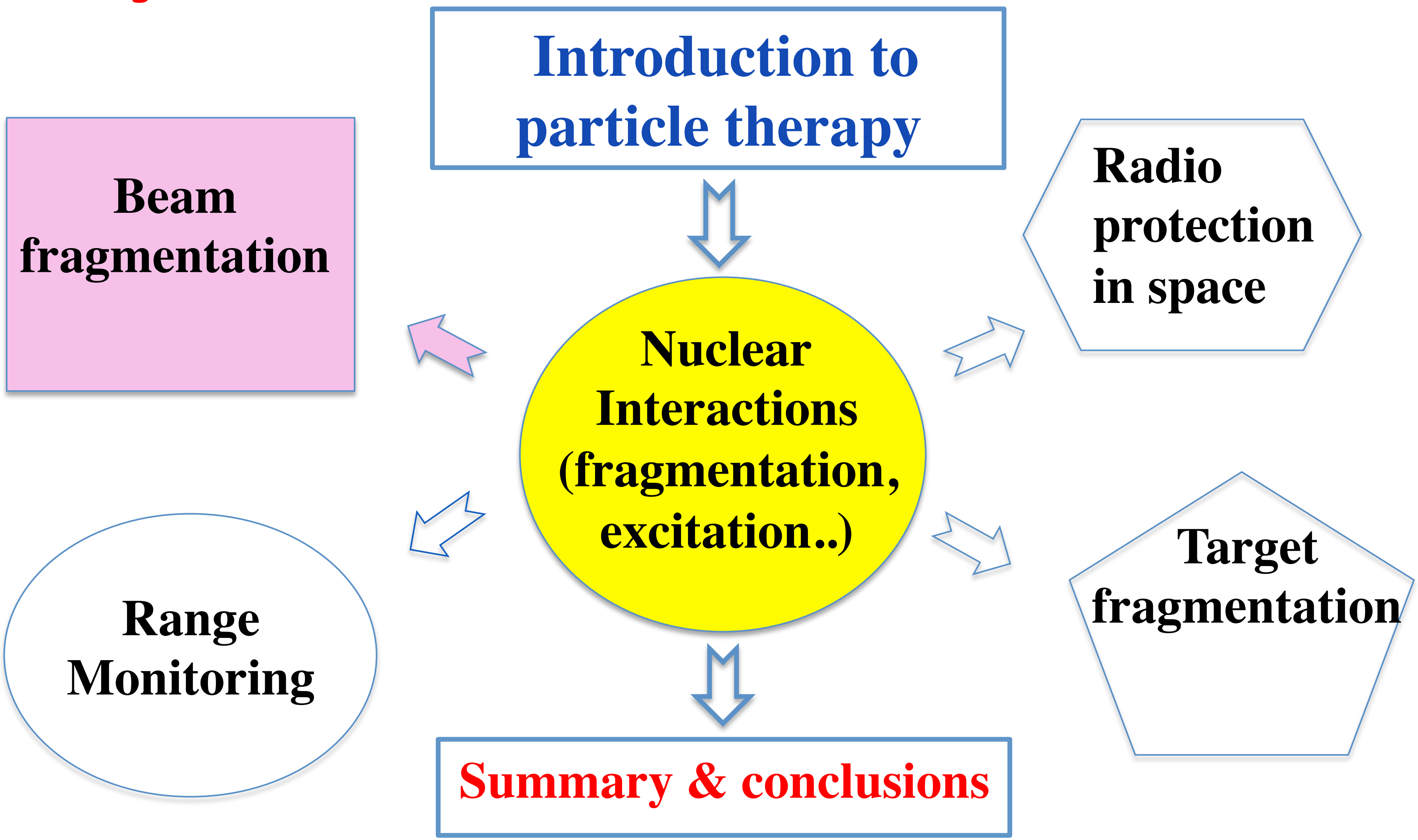


150 MeV proton beam in water with and without nuclear interactions



Outline

Accuracy in the dose release, radio biological effectiveness and effectiveness on radio-resistant hypoxic tumors suggest an escalation to higher Z beam . But the nuclear interaction itself sets a limit …

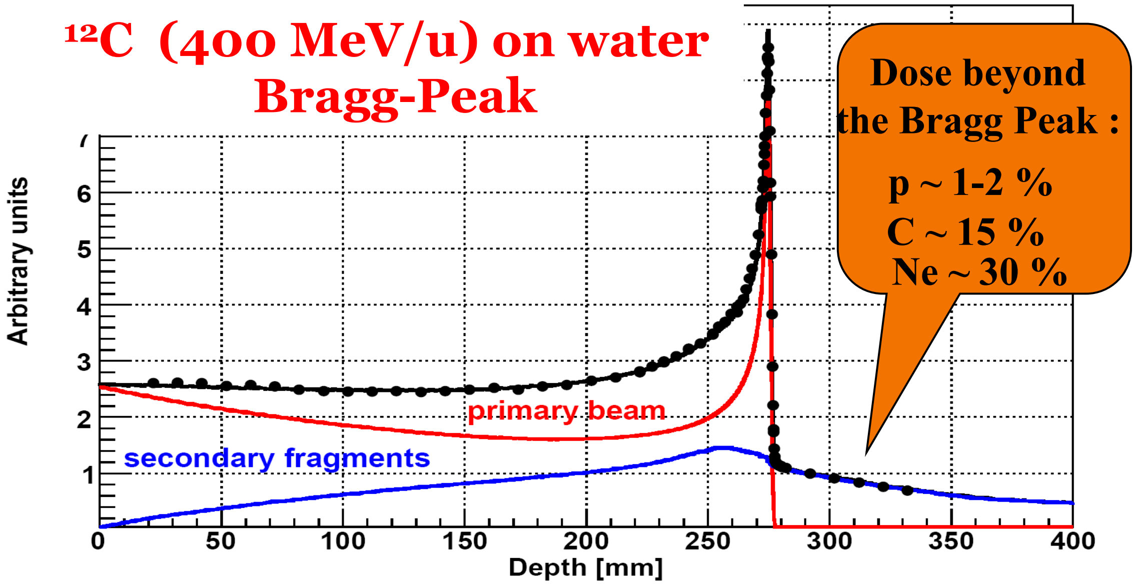


Heavier is better? STOP Fragmentation!

Dose release in healthy tissues with possible long term side effects, in particular in treatment of young patients → must be carefully taken into account in the Treatment Planning System

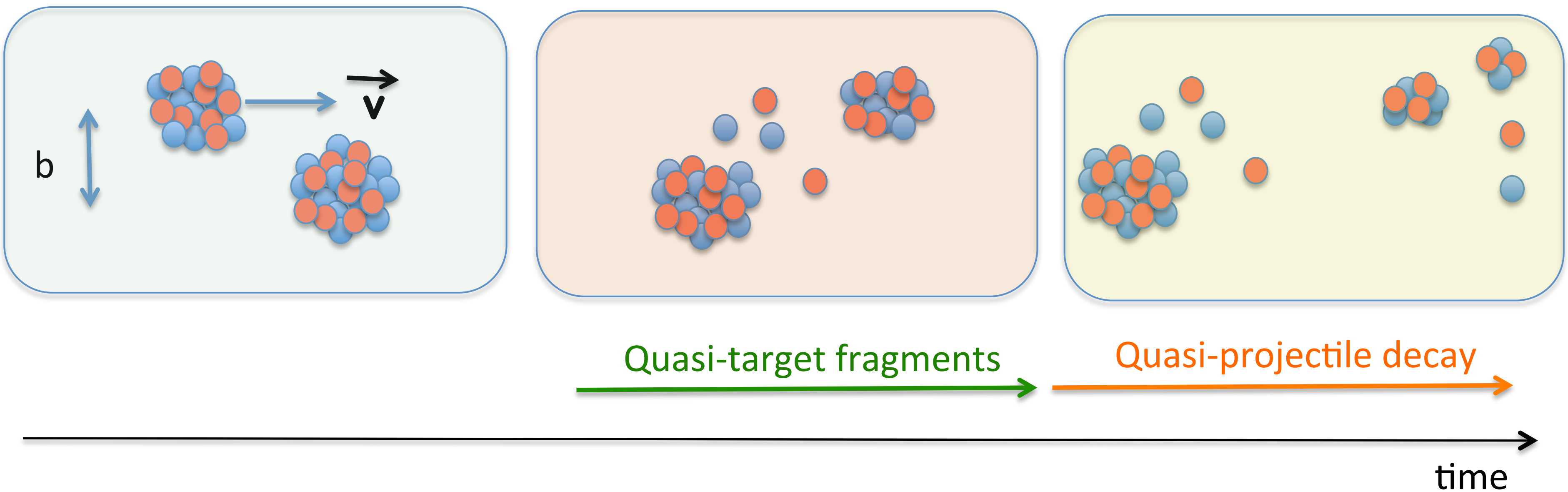
- ✓ Production of fragments with higher range vs primary ions
- ✓ Production of fragment with different direction vs primary ions

- ✓ *Mitigation and attenuation of the primary beam*
- ✓ *Different biological effectiveness of the fragments wrt the beam*



Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006
Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

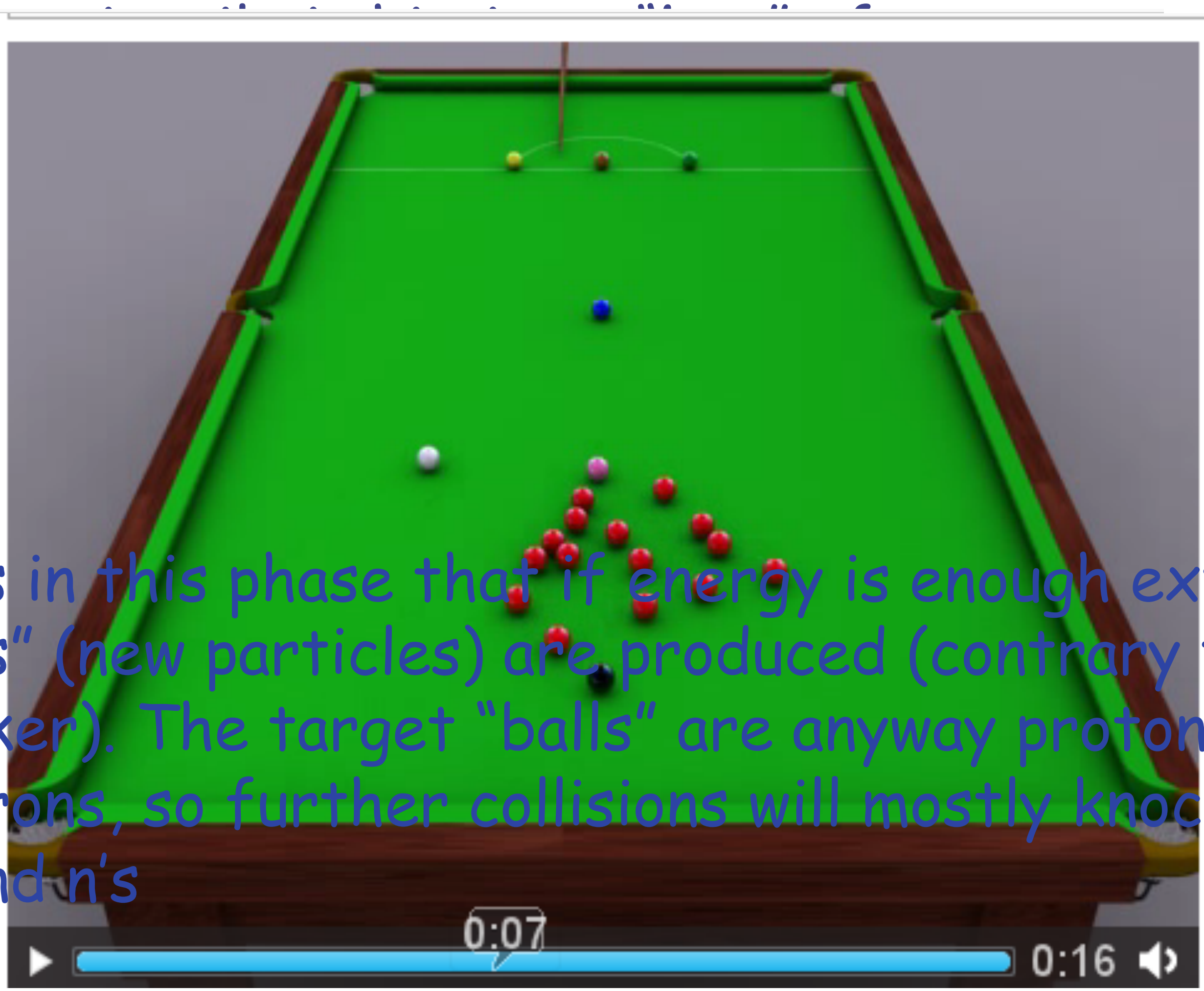
The abrasion-ablation paradigm



- Fragments from quasi-projectile have V_{frag}~V_{beam} and narrow emission angle. Longer range then beam
- The other fragments have wider angular distribution but lower energy. Usually light particles (p,d,He)
- The dose beyond the distal part comes from the quasi projectile contribution. Wide angular halo from the rest of the process

… INC, a bit like snooker…

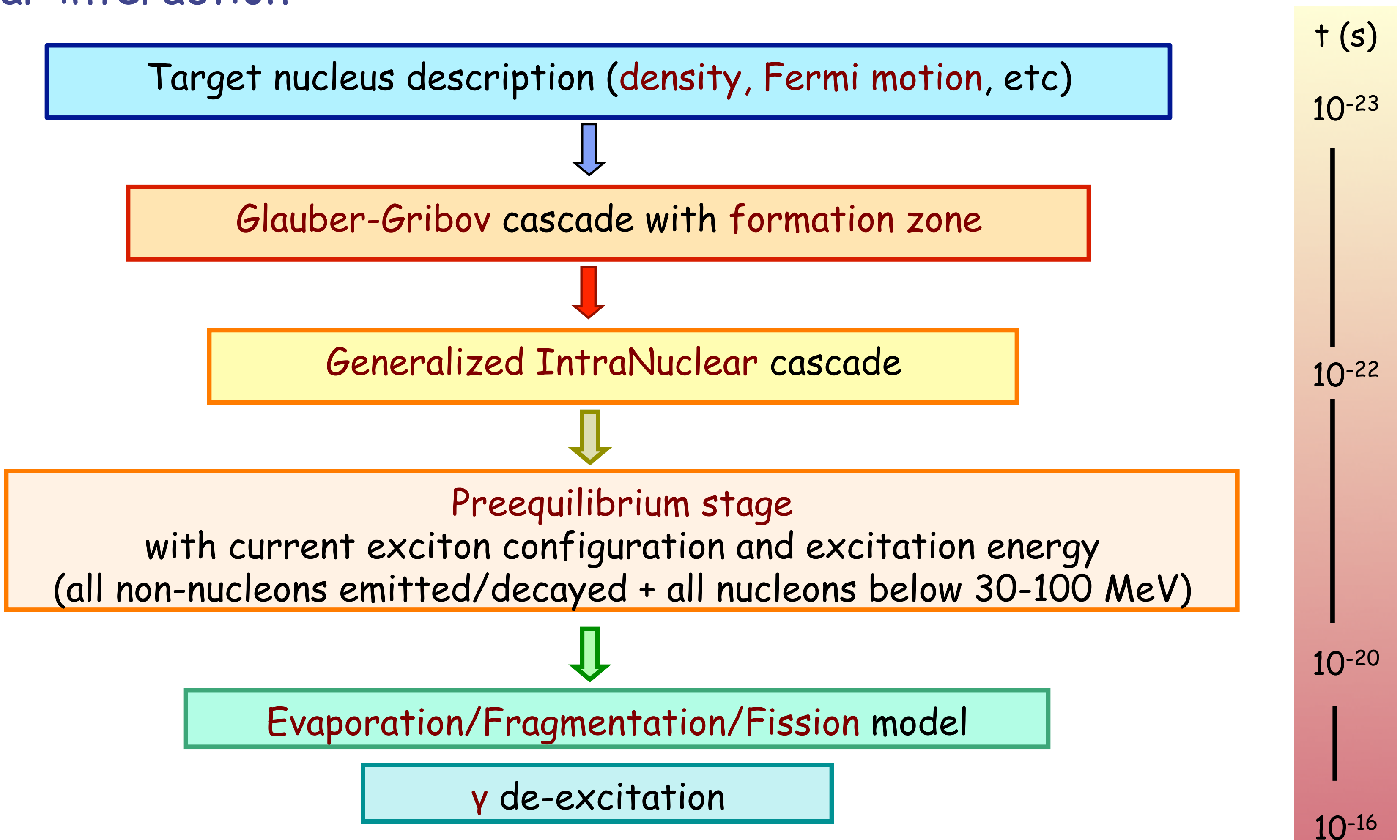
Th d
neu ts of
thi and
pro s, p,n,
π's this
pho



…it is in this phase that if energy is enough extra "balls" (new particles) are produced (contrary to snooker). The target "balls" are anyway protons and neutrons, so further collisions will mostly knock out p's and n's

Nuclear Interactions and MC

The nuclear model embedded in MC try to reproduce the phenomenology of the nuclear interaction. Here we report the FLUKA scheme of the nuclear interaction



Courtesy of A. Ferrari

Fragments from ^{12}C beam (E_{kin}=400 AMeV) on ^{12}C

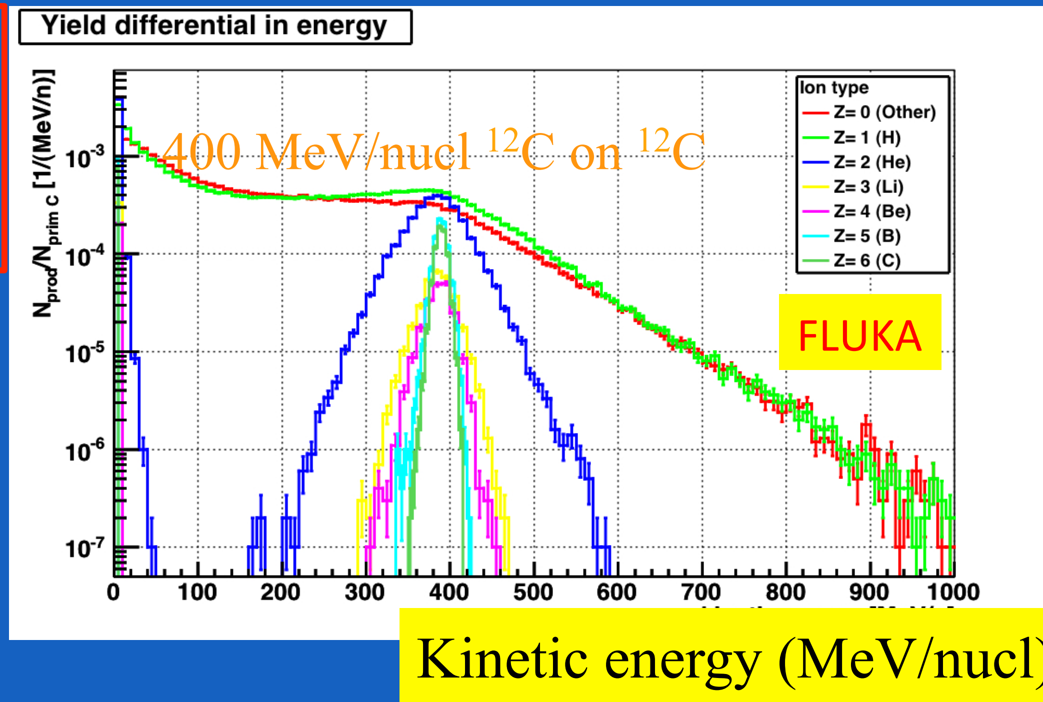
The Z>2 produced fragments approximately have the same velocity of the ^{12}C beam and are collimated in the forward direction

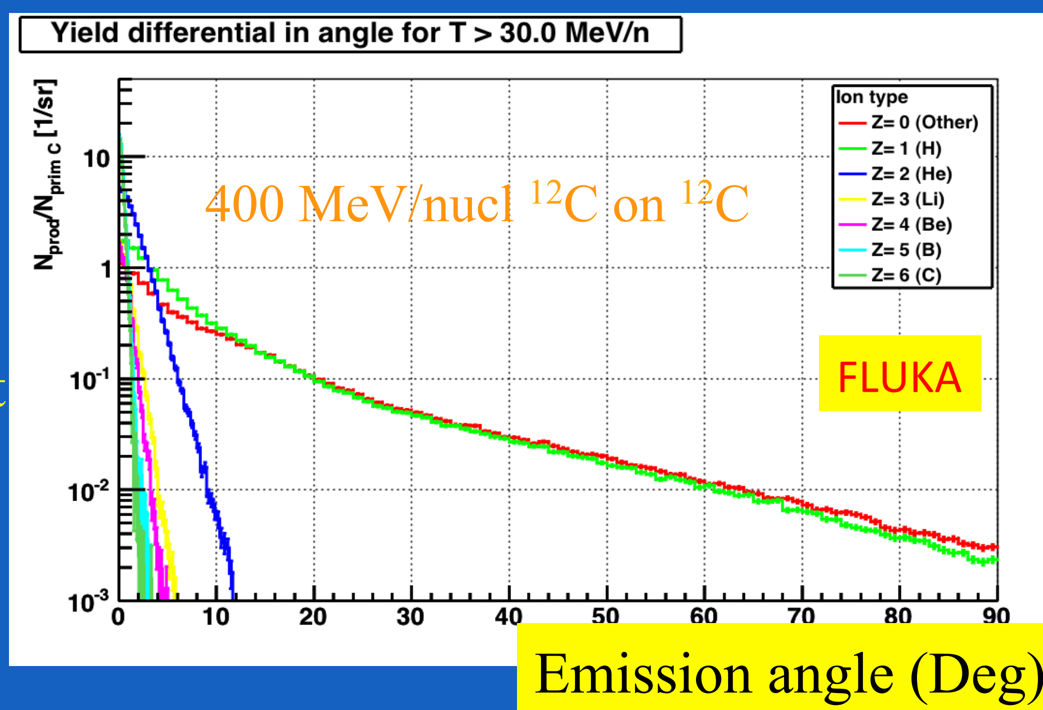
The protons are the most abundant fragments with a wide β spectrum 0<β<0.6 and with a wide angular distribution with long tail

The Z=2 fragment are all emitted within 20^0 of angular aperture

The dE/dx released by the fragment spans from ~2 to ~100 m.i.p.

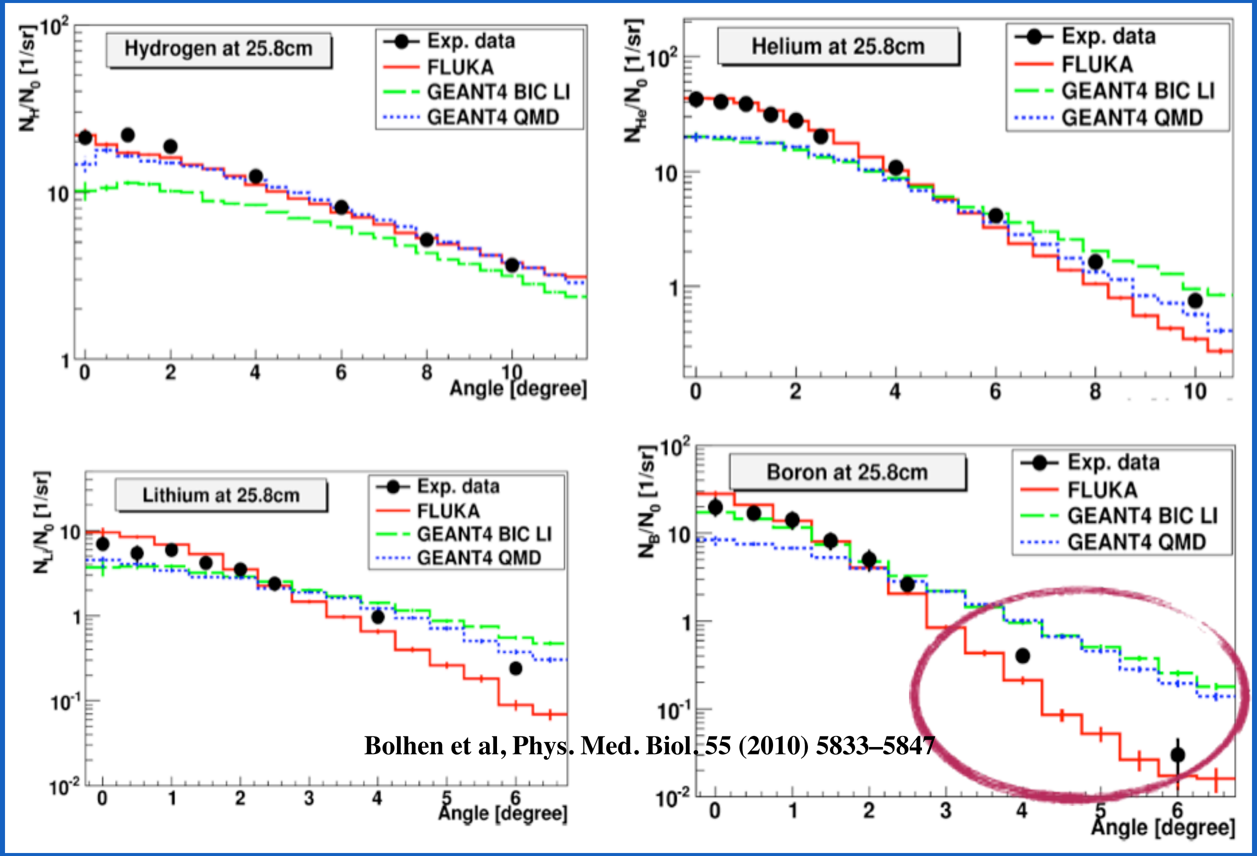
Do not trust MC too much!





Data - MC comparison: ^{12}C ions

Differential/double- differential quantities (vs angle and/or energy) ➔ large discrepancies found!



Bolhen et al, Phys. Med. Biol. 55 (2010) 5833–5847

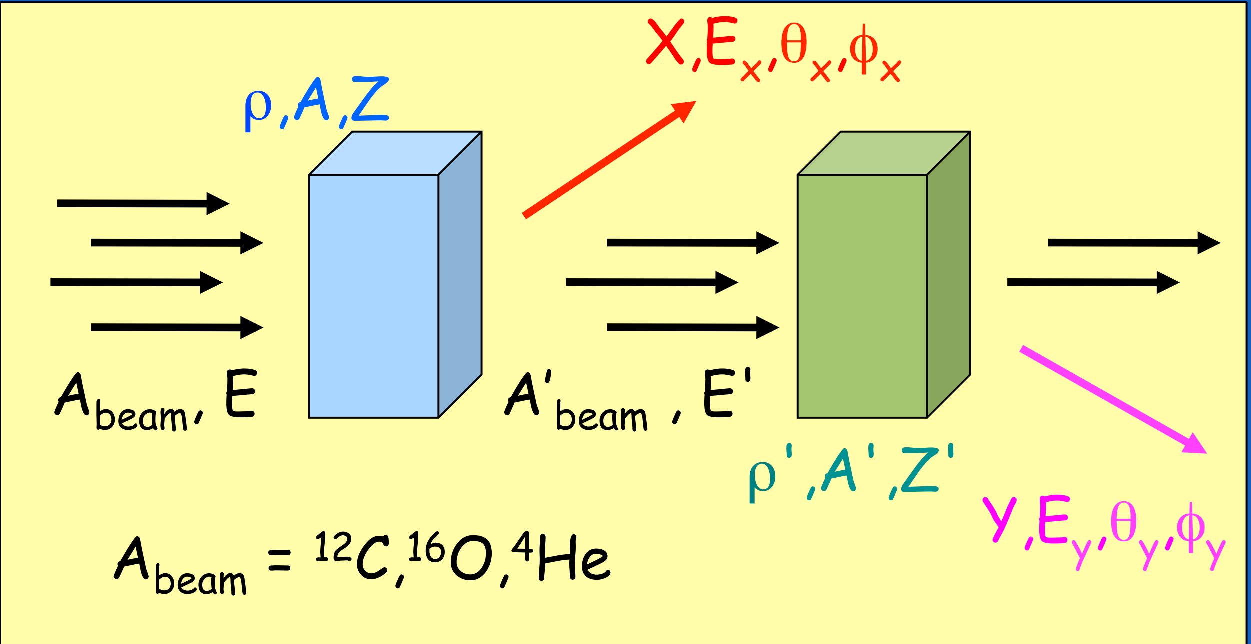
NB: the accuracy on delivered dose MUST be of the order of few %

Some MC benchmarks:
Sommerer et al. 2006, PMB
Garzelli et al. 2006, JoP
Pshenichnov et al. 2005, 2009
Mairani et al. 2010, PMB
Böhlen et al. 2010, PMB
Hansen et al. 2012, PMB

What we still miss to know about light ions fragmentation in 2017?

Data exist at 0^0 or on thick target. But we need to know, for any beam of interest and on thin target:

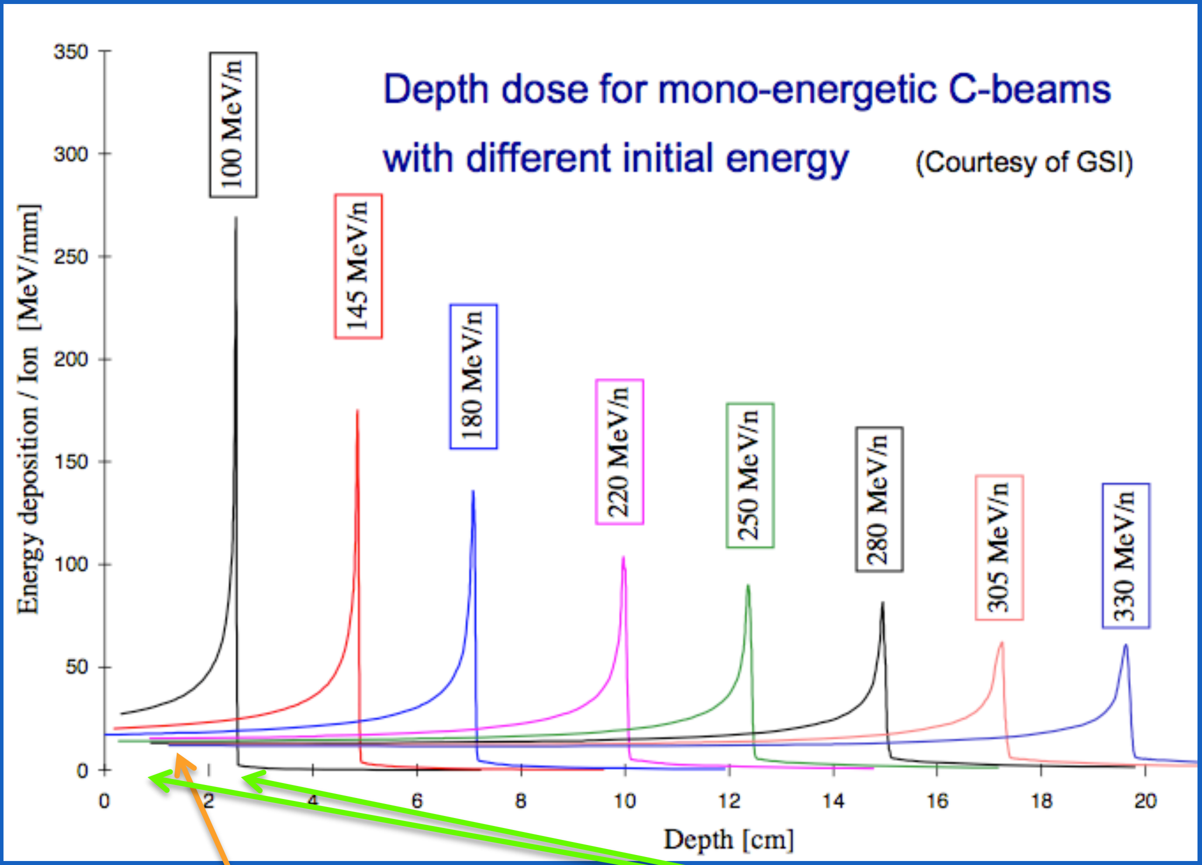
- Production yields of all $Z \leq Z_{beam}$ fragments, if possible of all $A \leq A_{beam}$
- $d^2\sigma/d\theta dE$ wrt angle and energy, with large angular acceptance
- For any beam energy of interest (100-300 AMeV)
- Thin target measurement of all materials crossed by beam



Not possible a complete DB of measurements

We need to train a nuclear interaction model with the measurements!!

Recent thin target, Double Diff Cross Section C-C measurements



LNS 62AMev C beam
See M. De Napoli talk
in this session (2009)

GANIL 50- 95AMev C beam - E600 collaboration (2011)

The community is exploring the interesting region for therapeutic application, in particular for the ^{12}C beam.

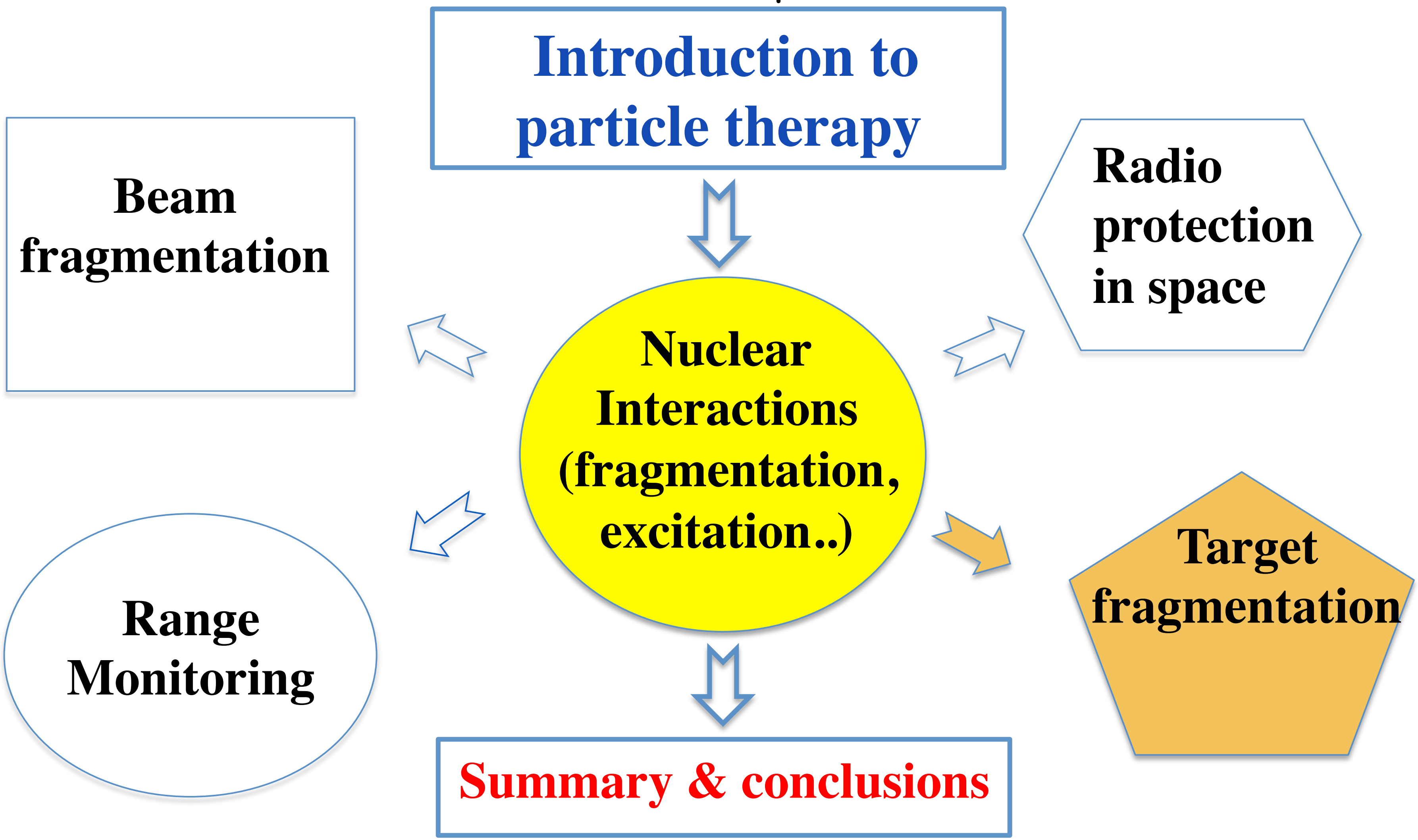
Yet there is a lot of energy range to explore in the range 150-350 AMeV (i.e. 5-22 cm of range…) and need of data also on O, H targets (C,O,H ~ 98% of humen body)

For ^{4}He, ^{16}O beams the need of data is the same

Experiment yet to be made !!!

Outline

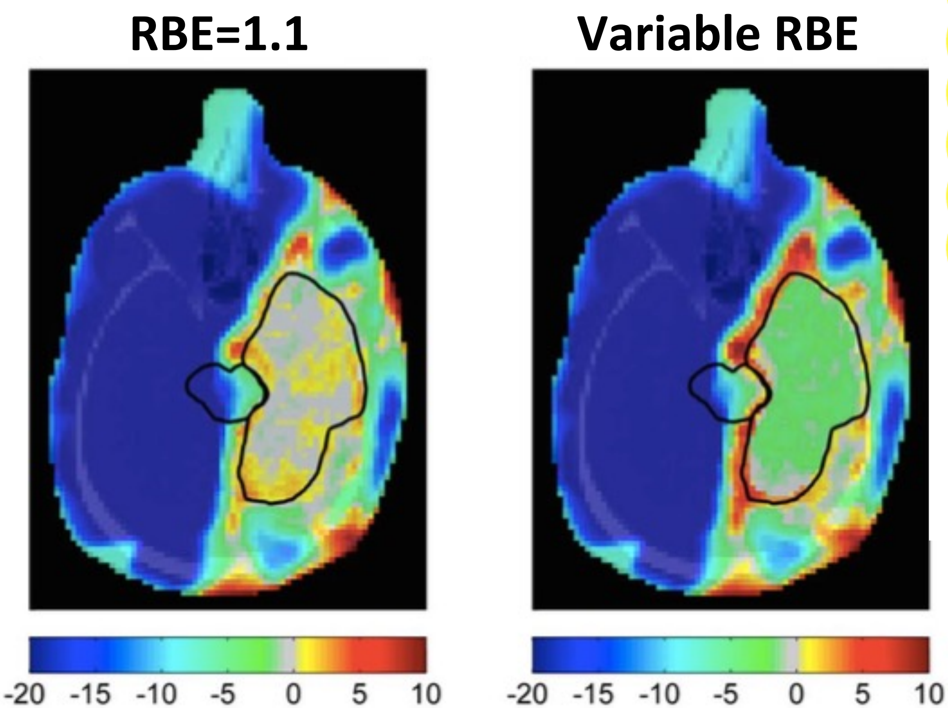
Nuclear fragmentation could affect also the proton therapy. Here the problem could be the patient tissue fragmentation due to the interaction with the proton beam



Target fragmentation & proton RBE

Currently the contribution of target fragments and of the increasing RBE near the PB is implicit (ICRU reccommendation RBE=1.1)

Lately has been pointed out possible impact of variable proton RBE on clinical NTCP values



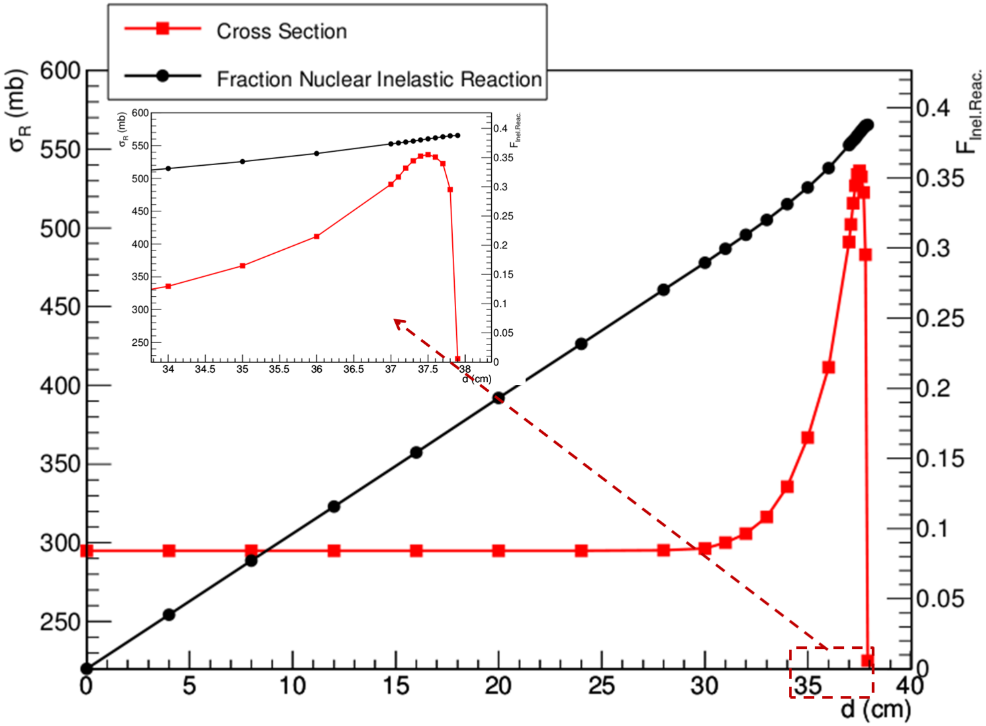
The differences in DVHs and dose distributions are also translated into different NTCP values, shown in Table III. As an example, the probability of necrosis in the brain stem is estimated in case1 to 0.84% for the IMRT plan and 0.57% for the proton plan when assuming a RBE equal to 1.1. However, when assuming a variable RBE the probability increases to 2.13%. Equivalently, the probability for blindness increases from 1.13% (RBE = 1.1) to 4.21% (variable RBE) for protons compared to 1.21% for photons for the optic nerve. The same tendency of estimating a lower NTCP for protons compared to photons when having RBE equal to 1.1, but obtaining a higher NTCP compared to photons when assuming a RBE distribution is also observed for the chiasm and for the other brain cases (see Table III).

Wedenberg 2014 Med Phys

Target fragmentation & PT: is an issue at all?

The target fragmentation could be relevant (only?) for proton beam treatment. The proton inelastic scattering on patient nuclei (C,O,N) produces Z≤8 fragments with low energy -> very high LET and very good at cell killing (very high RBE)

Example : analytic approximation of p -> H_2O @250 MeV



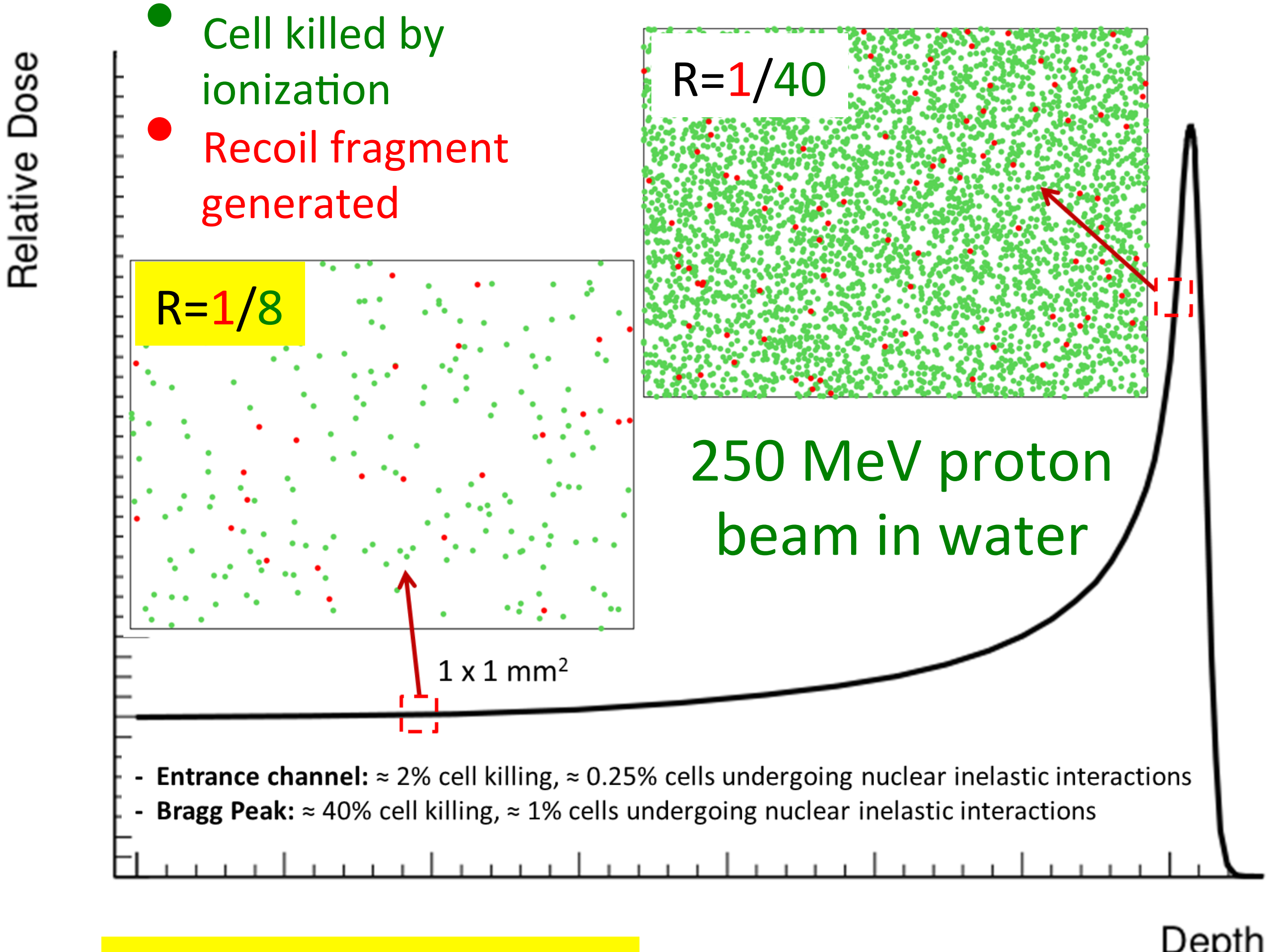
Bradt-Peters formula (Sihver 2009 Radiat Meas)

- In water, **about 1% cm-1** of protons undergo inelastic nuclear interactions
- In a typical treatment, this corresponds to **about 20% of the primary beam**
- 60% of the energy deposited by recoil in charged fragments
- 40% in neutrons and photons out of the field

Courtesy of F.Tommasino

Target fragmentation & PT: there is an issue?

Target fragmentation in proton therapy: gives contribution also outside the tumor region!



Courtesy of F.Tommasino

About 10% of biological effect in the entrance channel due to secondary fragments

Largest contributions of recoil fragments expected from

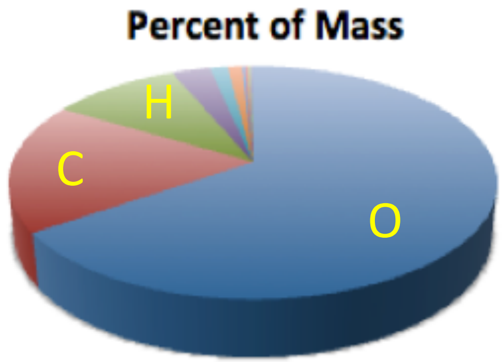
He, C, Be, O, N

See also dedicated MC studies:
- Paganetti 2002 PMB
- Grassberger 2011 PMB

p-> C, p->O scattering @200 MeV

The elastic interaction and the forward Z=1,2 fragment production are quite well known. Uncertainties on large angle Z=1,2 fragments.

Missing data on heavy fragments.



Very low energy-short range fragments, almost isotropic.

MCs confirm this picture but…..

Nuclear model & MC not reliable at the needed level

Needed Z>2 fragment yields and emission energy

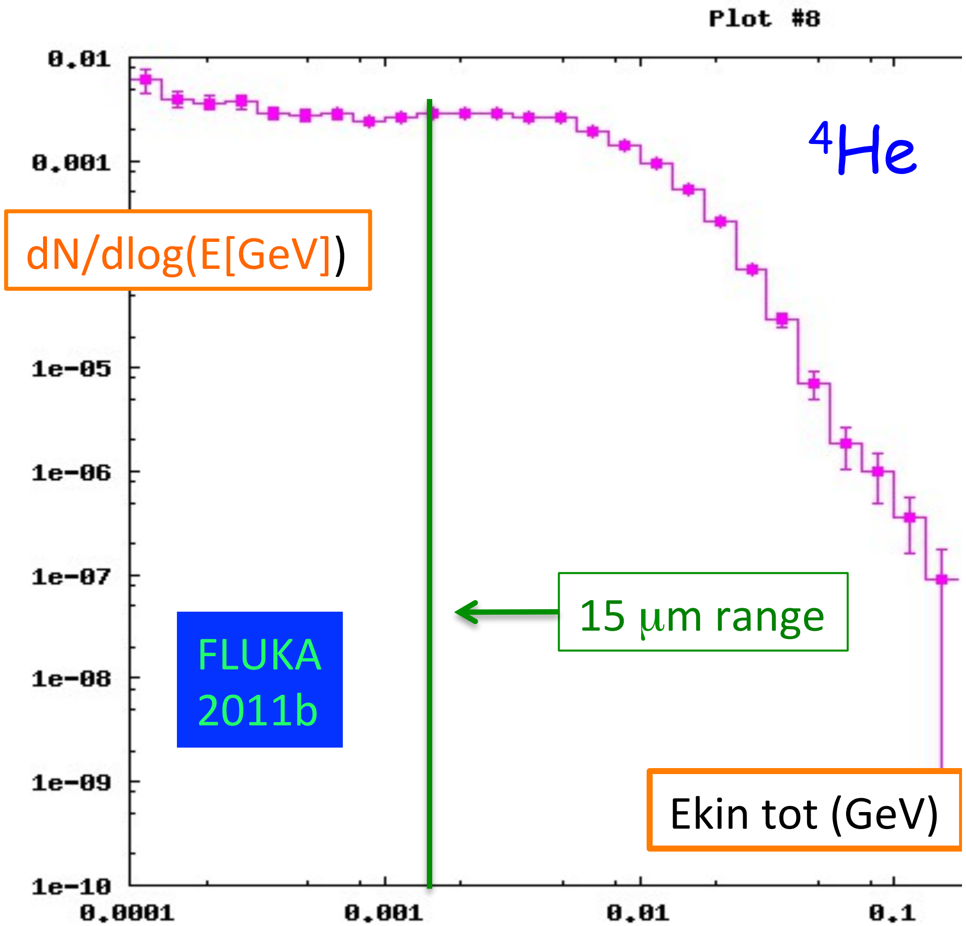
Analytic model results on p->O @200 MeV

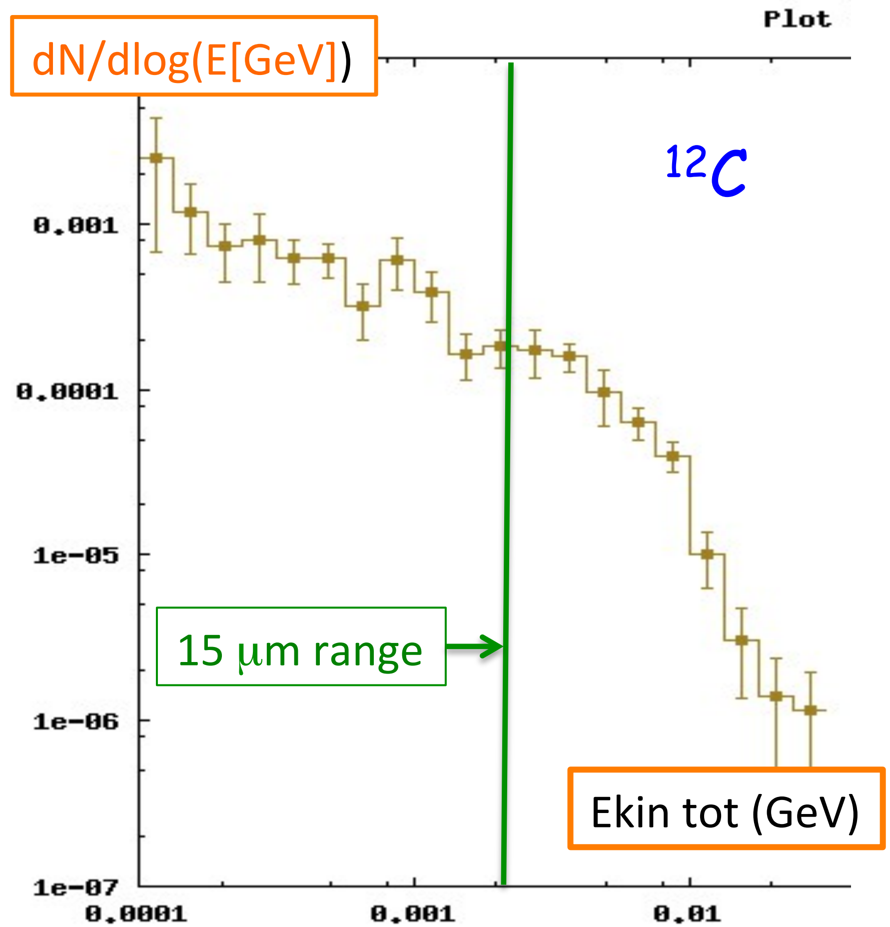
Fragment	E (MeV)	LET (keV/μm)	Range (μm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

Cancers 2015,7 Tommasino & Durante

p-> Brain scattering @200 MeV

Also FLUKA MC suggest a low-energy, short range production of heavy frag: 200 MeV p on “BRAIN” : production of He & C





Radiobiology requests & measurement spec's

To implement sound NTCP models the requirements on the knowledge of the p-> C,O interaction @200 MeV are very strict:

- Heavy fragment (Z>2) production cross section with uncertainty of 5%
- Fragment energy spectrum (i.e. dσ/dE) with 1 MeV/u accuracy
- Not accurate angular measurement in patient frame
- Charge ID at the level of 2-3%
- Isotopic ID at the level of 5%

NTCP modeling (radio biology) activity within INFN: Movit collaboration

Direct measurements : mission impossible

MEMENTO: For RBE exploitation $d\sigma/dE$ is compulsory !!

- The fragments travel few μm in the target-> difficult to directly detect them, even for very thin target (10 μm?)
- The energy loss of the fragment in the target would be substantial and would be a severe systematic to be evaluated
- Such a very thin target produces very few events -> very careful control of the background.
- Possible solution from JET target techniques, where the target is a focused flux of gas crossing the beam in vacuum: difficult and expensive

Physicists & the Lord of the Ring…

A lot of colleagues are fan of the Tolkien masterpiece (myself included), but a particular scene from "The return of the King" explains very well the physics community attitude toward a difficult (or impossible) experiment…

Certainty of death..
Small chance of success..

WHAT ARE WE WAITING FOR???

FramentatiOnOf Target

Inverse kinematic strategy

Since shooting a proton with a given β (Ekin=200 MeV → β=0.6) on a patient (C,O,N nuclei) at rest gives no detection opportunity…

let's shoot a β=0.6 patient (C,O,N nuclei) on a proton at rest and measure how it fragments!!

Then if we measure the X-section, provide we apply an inverse velocity transformation, the result should be the same.

- Use (as patient) beams N, O, C ions with β= 0.6 → Ekin/nucl=200MeV.
- Use a target made of H… but this is difficult! (I will come to this…)

The heavy fragment (all but p,d,t,He) has ~200MeV/nucleon kinetic energy and are forward peaked

Inverse kinematics and the target

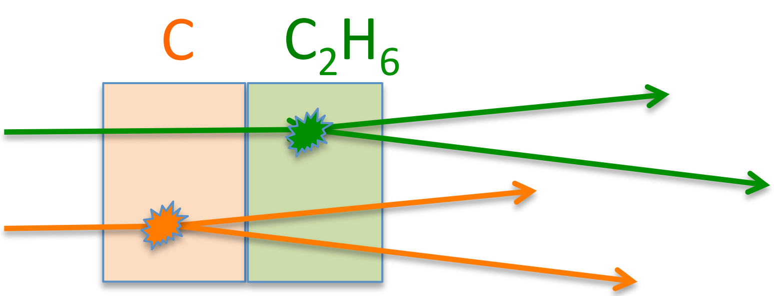
The target can be thick as few mm, since the fragment range is larger than several cm.

The H target could be a Liquid Hydrogen, but with little non H material on the beam path➔criogenics?

A possible solution is to use twin targets: C and hydrocarbons. The fragmentation cross section can be obtained by subtraction.

Simultaneous double target data taking can to minimize systematic, if the setup has good vertexing capability along beam line

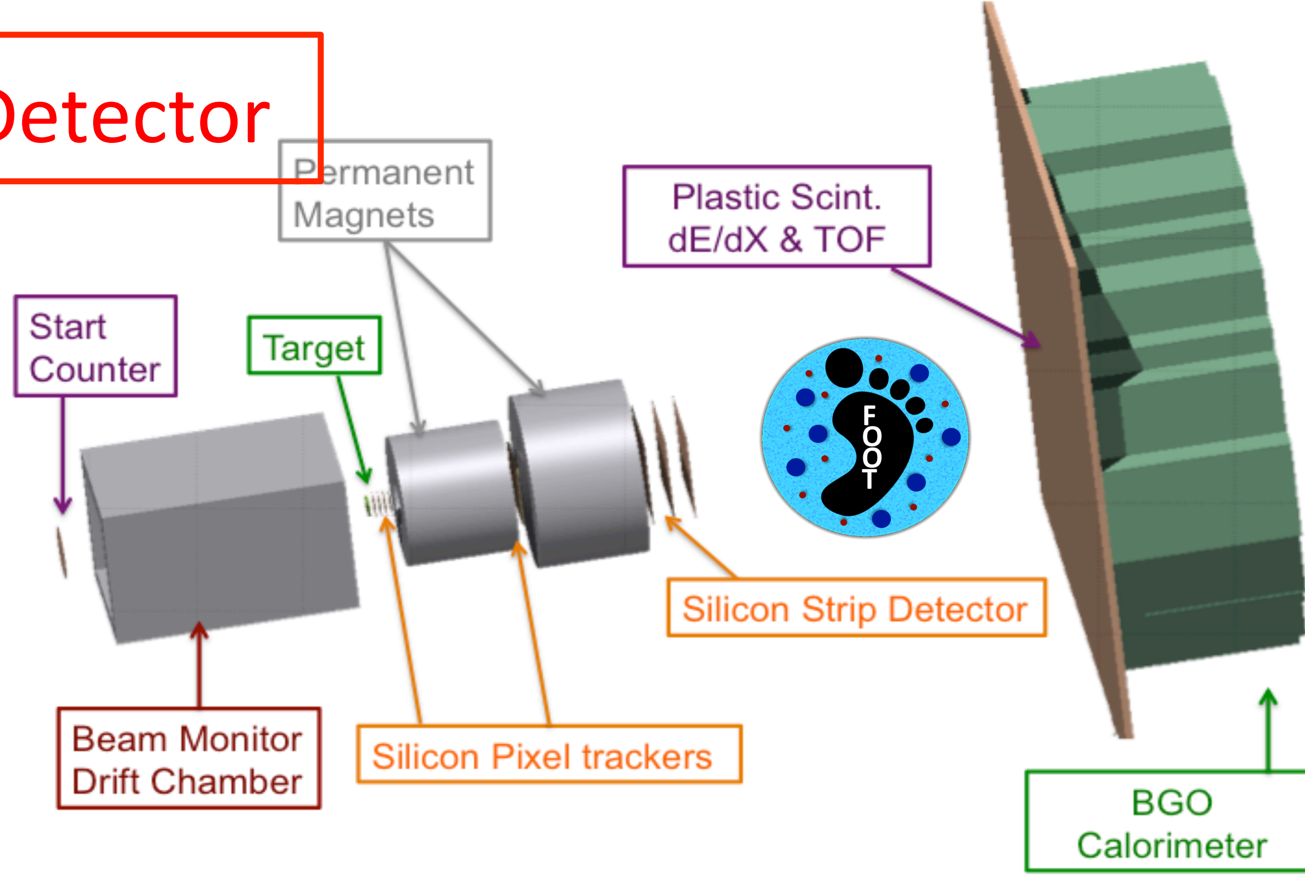
Heavy fragment are forward peaked, must be separated by the beam: very good PID capability



FOOT Detector

For the fragment with Z>2 measurements of TOF, P, Ekin, DE

Maximum 2 meters length



- ✓ Start Counter = thin plastic scintillator
- ✓ Beam Monitor = drift chamber
- ✓ Vertex detector & Intermediate Tracker = monolithic silicon pixel detector
- ✓ Large tracker = silicon strip detector
- ✓ DE/TOF Detector = plastic scontillator
- ✓ Calorimeter = BGO crystal calorimeter

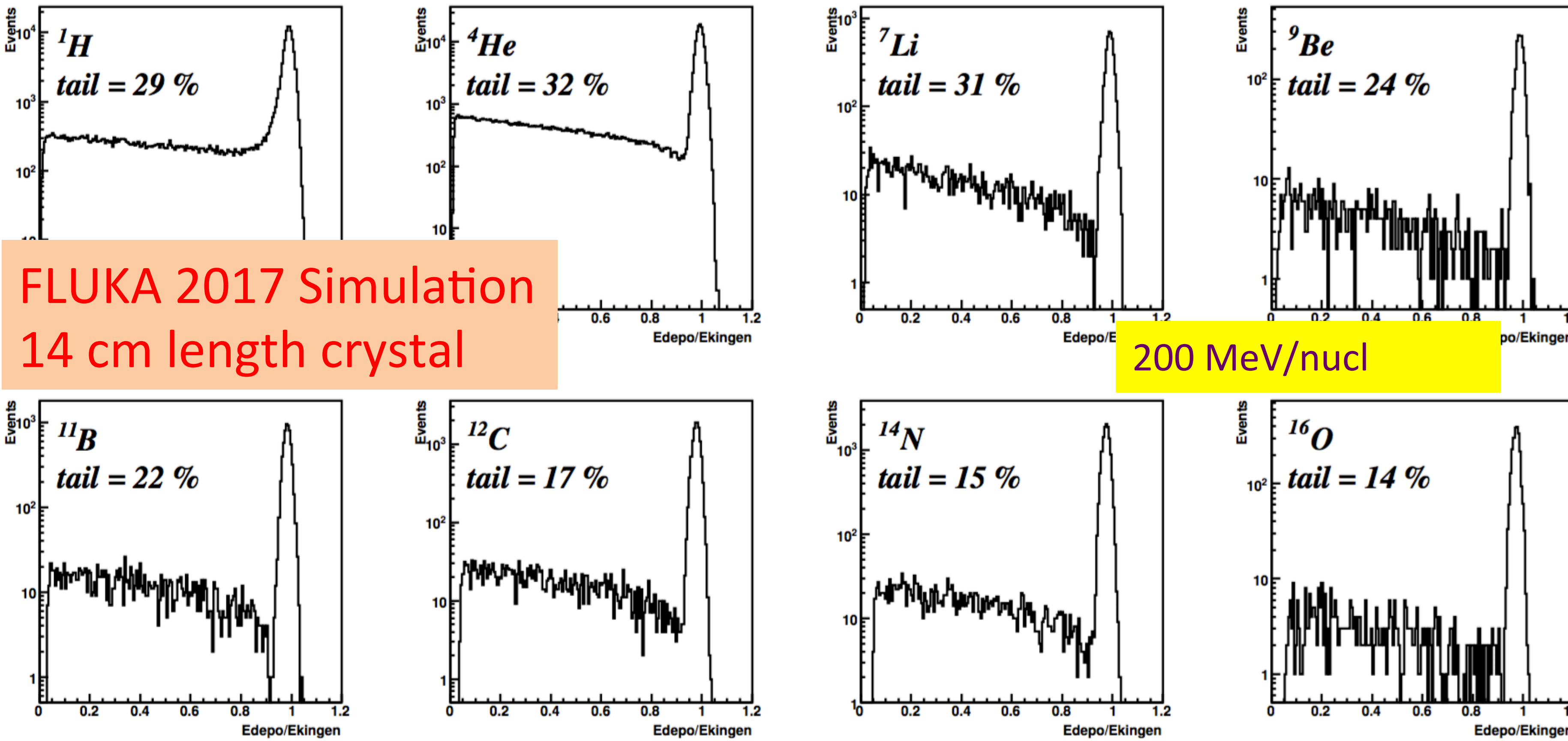
Expected target fragmentation performances:
$\sigma_p/p \sim 5\%$
$\sigma_{TOF} \sim 100$ ps
$\sigma_{Ekin}/Ekin \sim 1\text{-}2\%$
$\sigma_{\Delta E} \sim 2\%$

BGO calo length VS neutron leakage

The neutron leakage in BGO seems to be more and more important for energy higher than 200 MeV/nucl and for light fragments (!)

Even if the fit constrained can tag such events, these must be minimized to keep the systematic under control.

Neutron int. length in BGO at this energy ~ 30-40 cm



Ecalo/Ekin

SUMMER SCHOOL UNIVERSITÀ DI PISA

A Reconstruction / fit

TOF (β) – TRACKER (p)

$$A_1 = \frac{p}{U\beta\gamma}$$

TOF (β)– CALO (T)

$$A_2 = \frac{E_{kin}}{U(\gamma - 1)}$$

TRACKER (p) – CALO (Ekin)

$$A_3 = \frac{p^2 - E_{kin}^2}{2UE_{kin}}$$

RECO QUANTITIES

We used a simplified data set with baseline experimental resolution for the 3 measured quantities. In particular for C @ 200MeV/u:

- Kinetic energy given by $E_{cal} + E_{DE}$: σ_E/E ~ 1-2%
- Tof (β) given by $(T_{DE}-T_{SC})$: σ_{TOF} ~ 100 ps
- Momentum (p) with ~ constant resolution σ_p/p ~ 5%

FIT

- **Standard χ^2 Fit**

$$\chi^2 = \frac{1}{2}\sum_i^{1,3}\left(\frac{A_i - A_{fit}}{\sigma_{Ai}}\right)^2$$

- **Augmented LagrangianFit (ALM)**

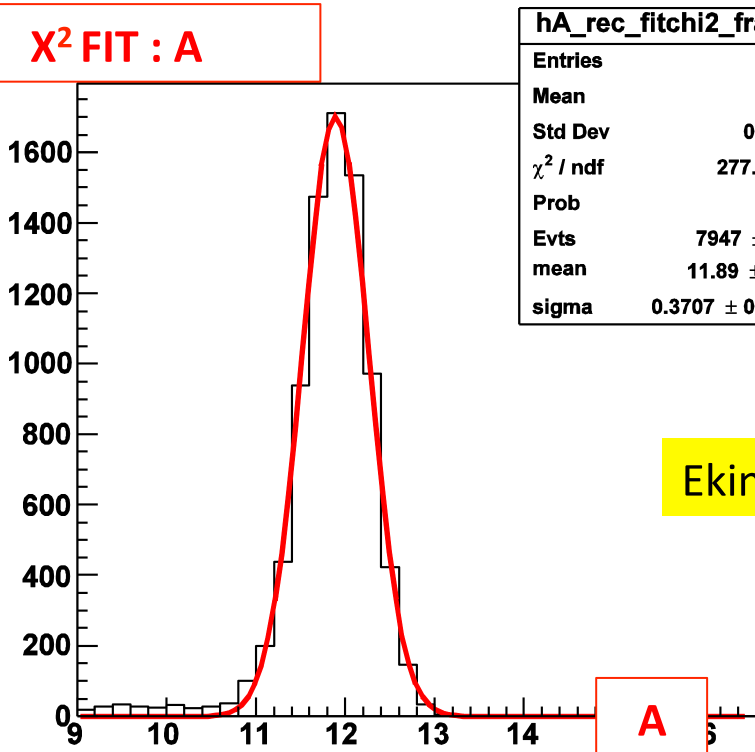
$$C_1 = AU\beta\gamma - p = 0$$

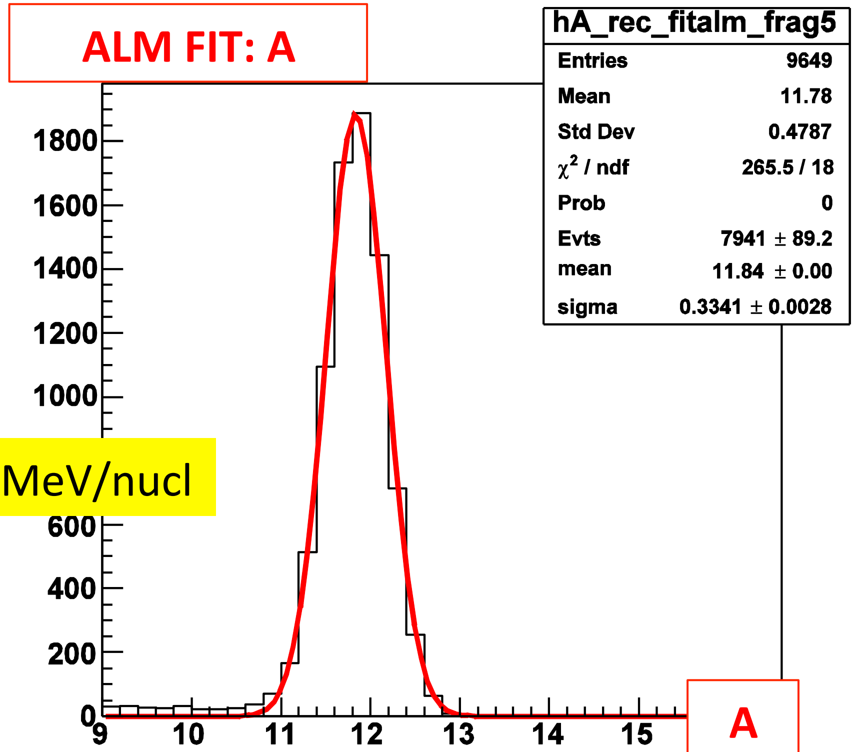
$$C_2 = AU(\gamma - 1) - E_{kin} = 0$$

$$C_3 = 2AUE_{kin} - p^2 - E_{kin}^2 = 0$$

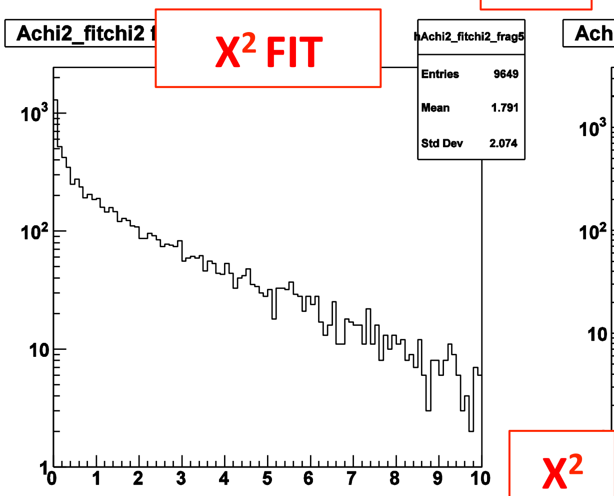
$$L = \frac{(P_{fit} - P_{meas})^2}{\sigma_p^2} + \frac{(TOF_{fit} - TOF_{meas})^2}{\sigma_{TOF}^2} + \frac{(E_{fit} - E_{meas})^2}{\sigma_E^2} - \sum_i^{1,3}\lambda_i C_i(P,TOF,E) + \sum_i^{1,3} C_i^2(P,TOF,E)$$

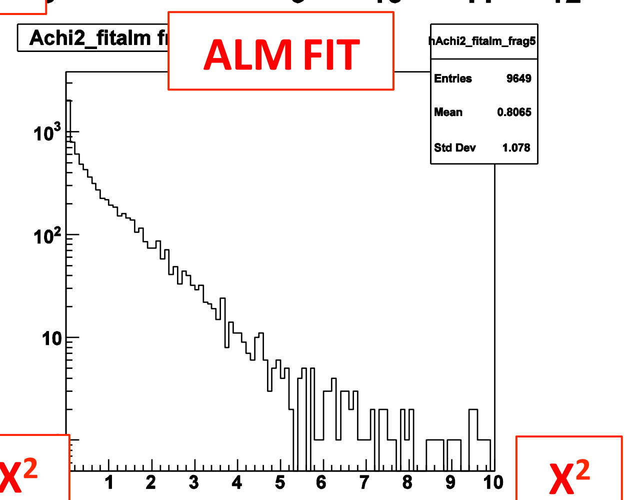
Carbon fragment: FIT results on A





Ekin=200MeV/nucl

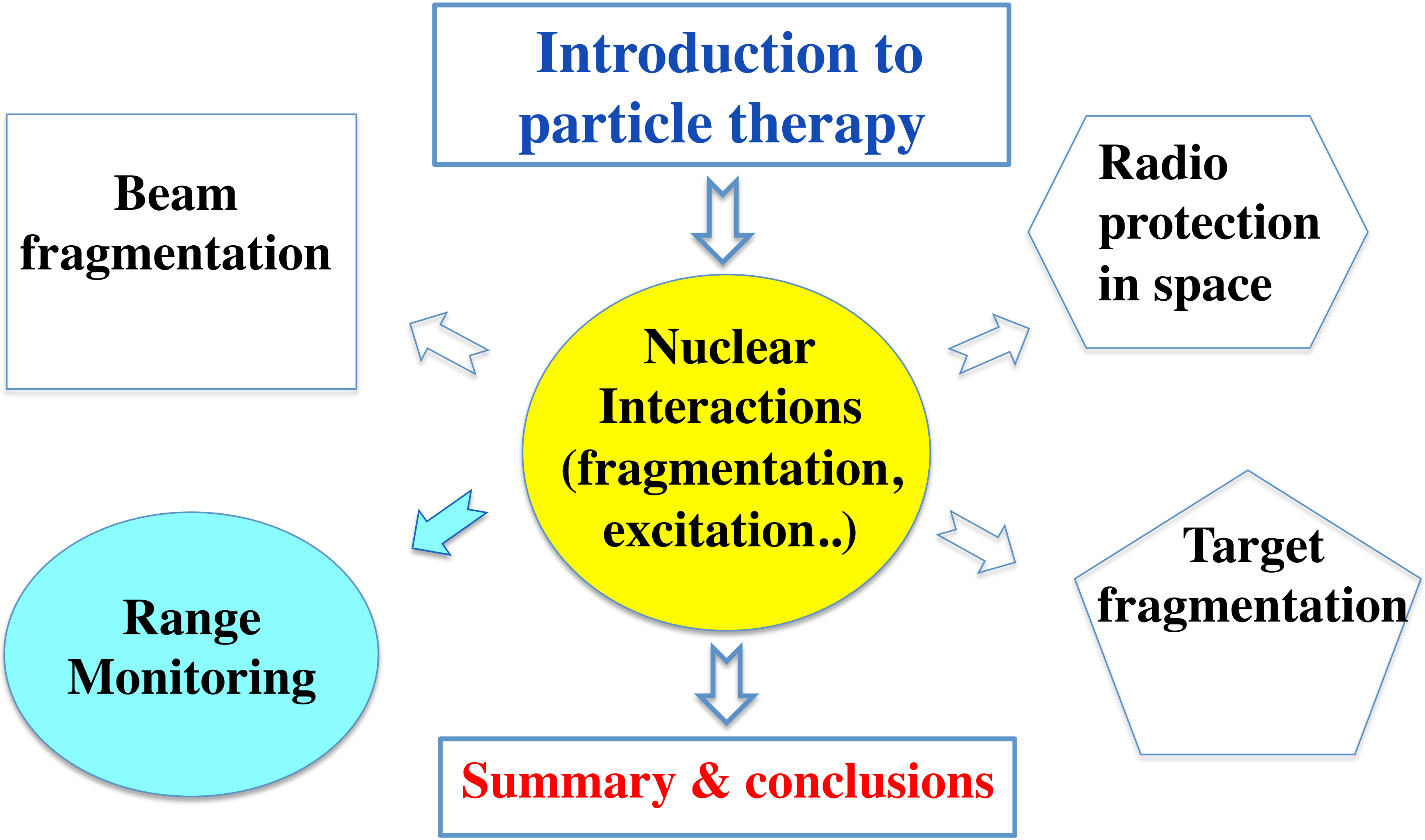




Very Important: This experiment can measure also the beam fragmentation taking data up to 350 AMeV!!!

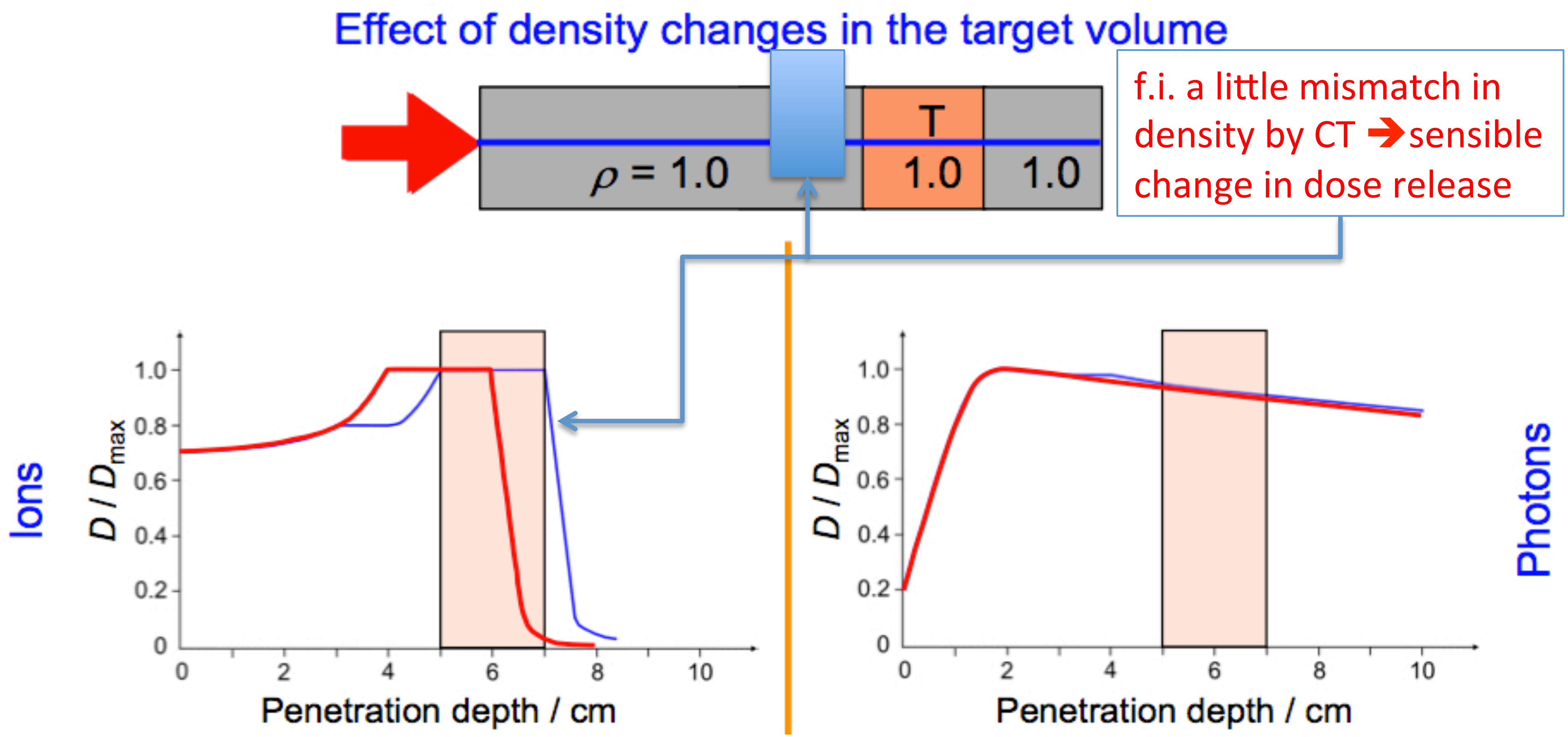
Outline

The nuclear interaction of the beam prevents the use of beam heavier the Oxygen and must be taken into account in TPS.. But can be of help for another crucial aspect of particle therapy: range monitoring



Dose profile in PT

Why is so crucial to monitor the dose in particle therapy with respect to photon RT? It is like firing with machine-gun or using a precision rifle.. Inhomogeneities, metallic implants, CT artifact, HU conversion, inter session anatomical/physiological changes-> range variations



The range verification problem

AAPM, August 2012

Delegates were asked what they considered as the main obstacle to proton therapy becoming mainstream:

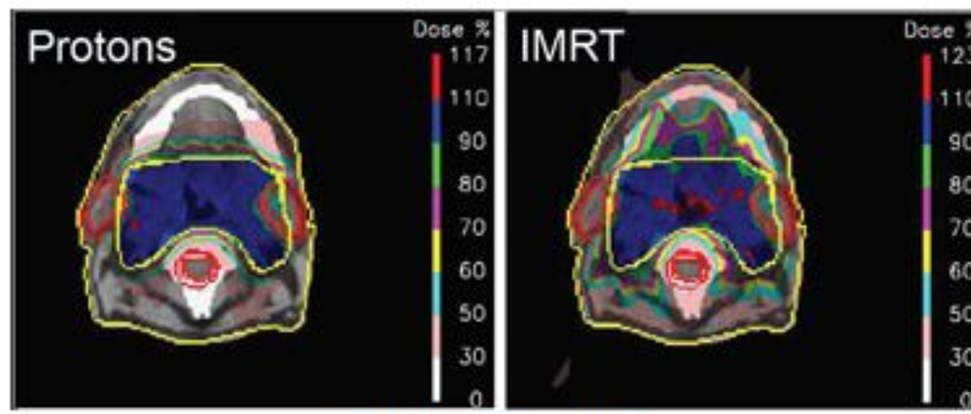
- 35 % unproven clinical advantage of lower integral dose
- 33 % range uncertainties
- 19 % never become a mainstream treatment option

RESEARCH

Aug 22, 2012

Will protons gradually replace photons?

The dose distribution advantages offered by proton therapy, particularly with the introduction of pencil-beam scanning, have stimulated increasing interest in this modality. But is the large capital expenditure required to build a proton therapy facility hindering the widespread implementation of this technique? And how big a problem is range uncertainty, which can prevent proton therapy from meeting its full potential?



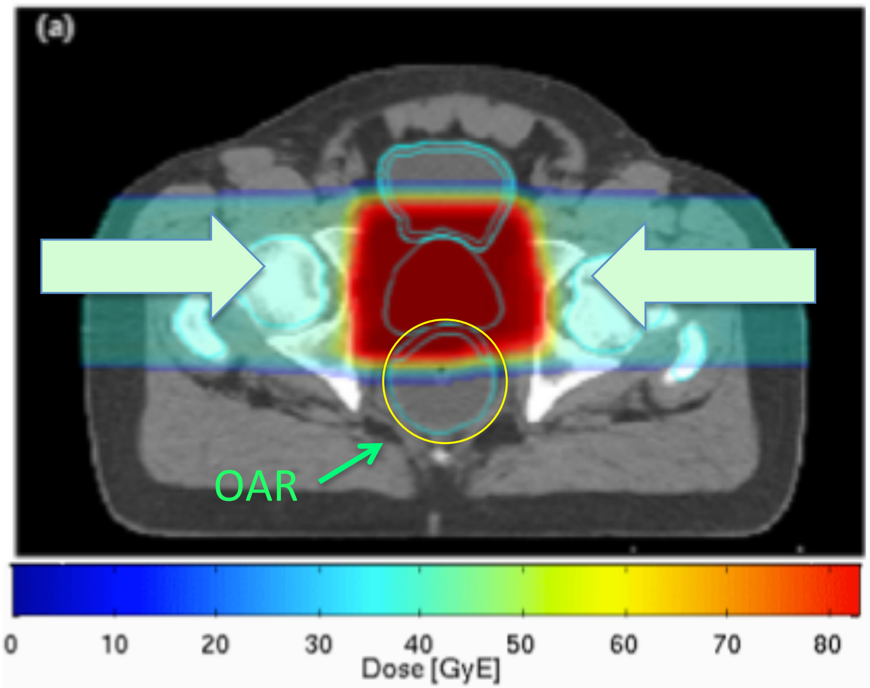
Protons versus IMRT

http://medicalphysicsweb.org/cws/article/research/50584

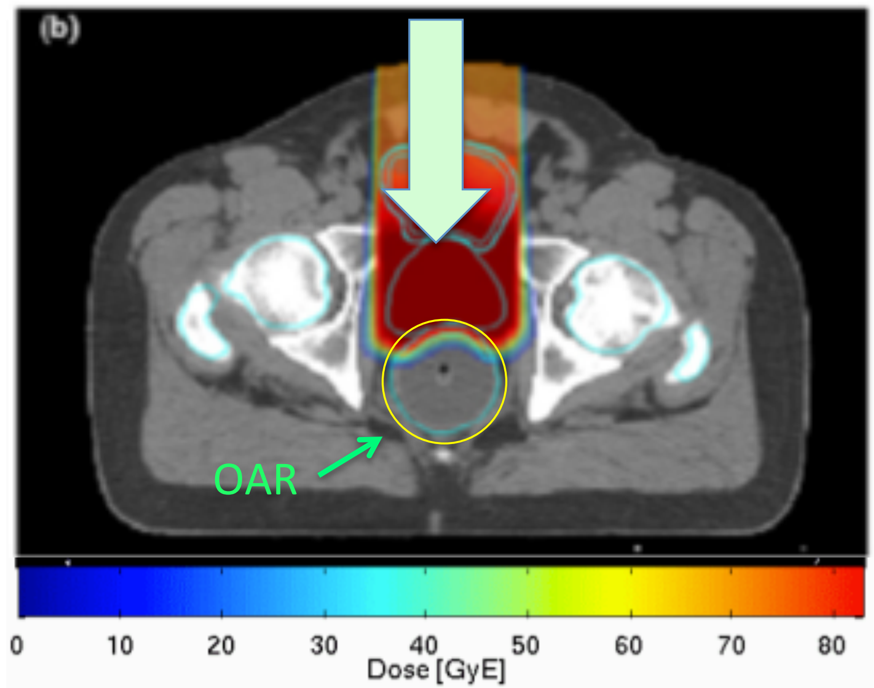
Accounting for uncertainties in the clinical practice

[Tang et al. 2012]

Current approach:
Opposed fields, overshooting



Desirable approach:
Different beam angles and no overshooting



Protons

Spec's of particle therapy monitor

In PT the beam is easily monitored in the transverse direction but longitudinally stops inside the patient.

A PT range monitor should measure the shape and (possibly) the absolute value of dose release with the following spec's:

- ✓ Must relay on the signal by secondary particles, generated by the beam, that comes out from the patient
- ✓ Must deal with the background of the "non signal" secondaries that come out
- ✓ Measurements and feed-back should be provided during the treatment (in-beam). Even better if the monitor response can follow the irradiation scan on line
- ✓ Must be embedded in a treatment room: space, reliability and "easy to run" issues are crucial

Beam secondaries: Background or Signal?

Indicative secondary flux emitted on full solid angle by ~150 MeV p beam

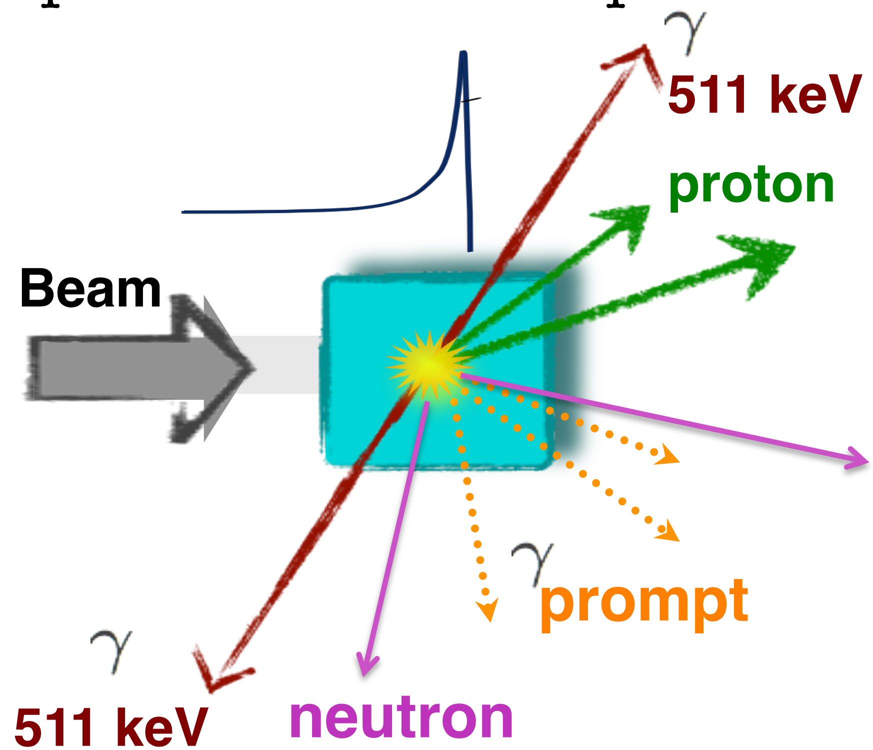
Incident protons:	1.0
Photons	0.3
Neutrons	0.15
Protons	0.005

G4 simulation

How much are the nuclear models reliable? Huge experimental (flux, beam profile) and theoretical development effort ongoing to improve model and update MC

The p, ^{12}C beams generate a huge amount of secondaries: prompt γs from nuclear de-excitation, PET- γs, neutrons and charged particles (in particular ^{12}C beam)

Can be used to **track the tumor path inside the patient**

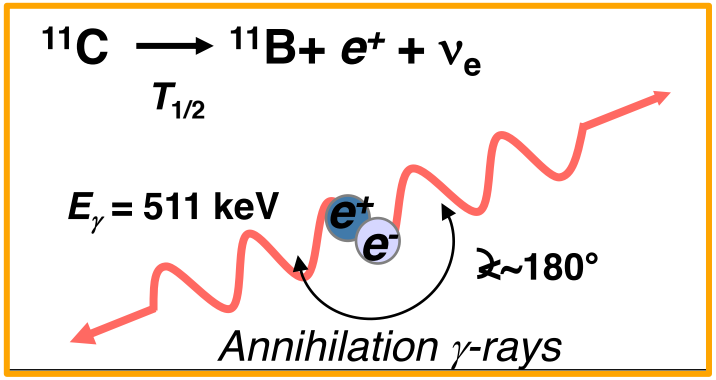


Baseline dose monitoring in PT : PET

Baseline for monitor in PT is PET : autoactivation by hadron beam that creates β^+ emitters and detect back-to-back photons (PET-γ) from e+ annihilation

- Isotopes of short lifetime ^{11}C (20 min), ^{15}O (2 min), ^{10}C (20 s) with respect to conventional PET (hours)
- Low activity in comparison to conventional PET need quite long acquisition time (some minutes at minimum)
- **Metabolic wash-out**, the β^+ emitters are blurred by the patient metabolism

Indirect information => No direct space correlation between β^+ activity and dose release (but can be reliably computed by MC)

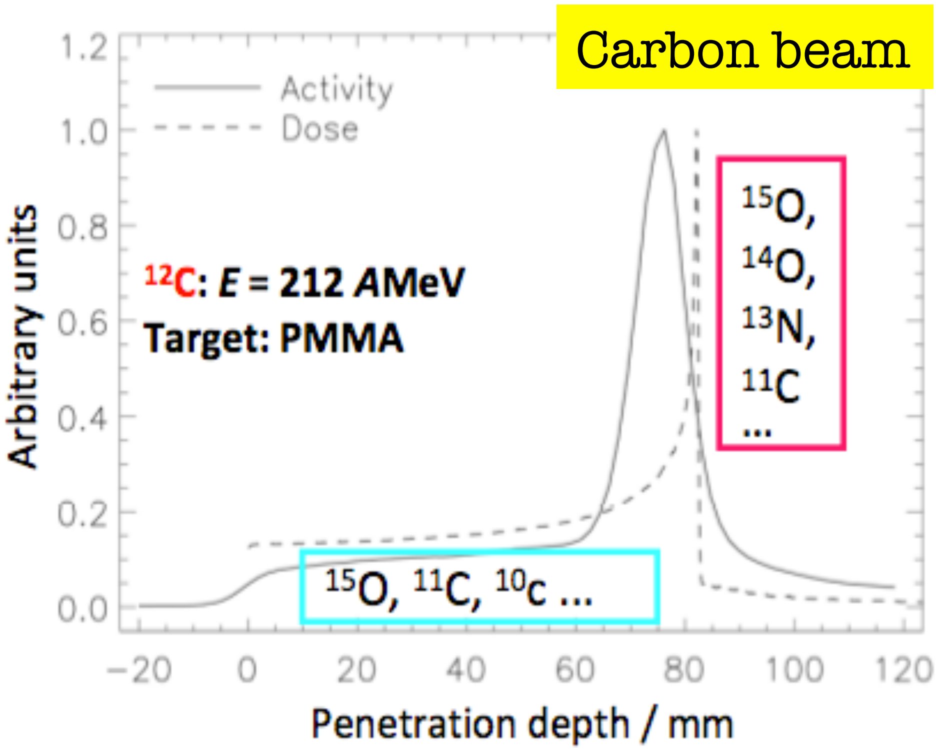


Correlation between β^+ activity and dose

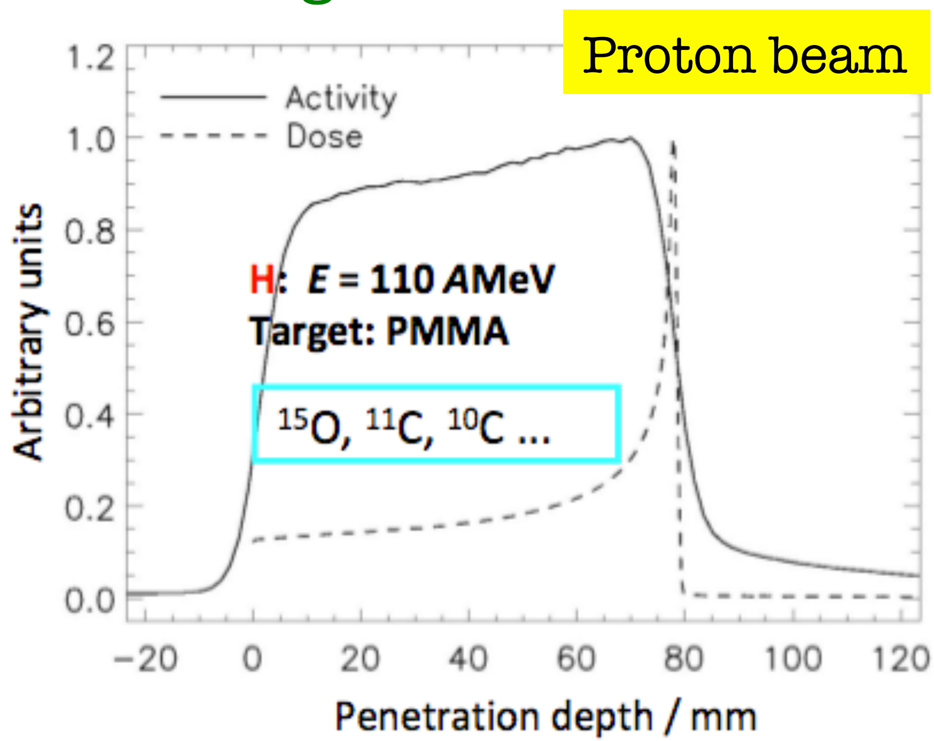
Therapy beam	^{1}H	^{3}He	^{7}Li	^{12}C	^{16}O	Nuclear medicine
Activity density / Bq cm^{-3} Gy^{-1}	6600	5300	3060	1600	1030	$10^4 - 10^5$ Bq cm^{-3}

p treatment uses more particles than ^{12}C treatment (dose ~Z^2)

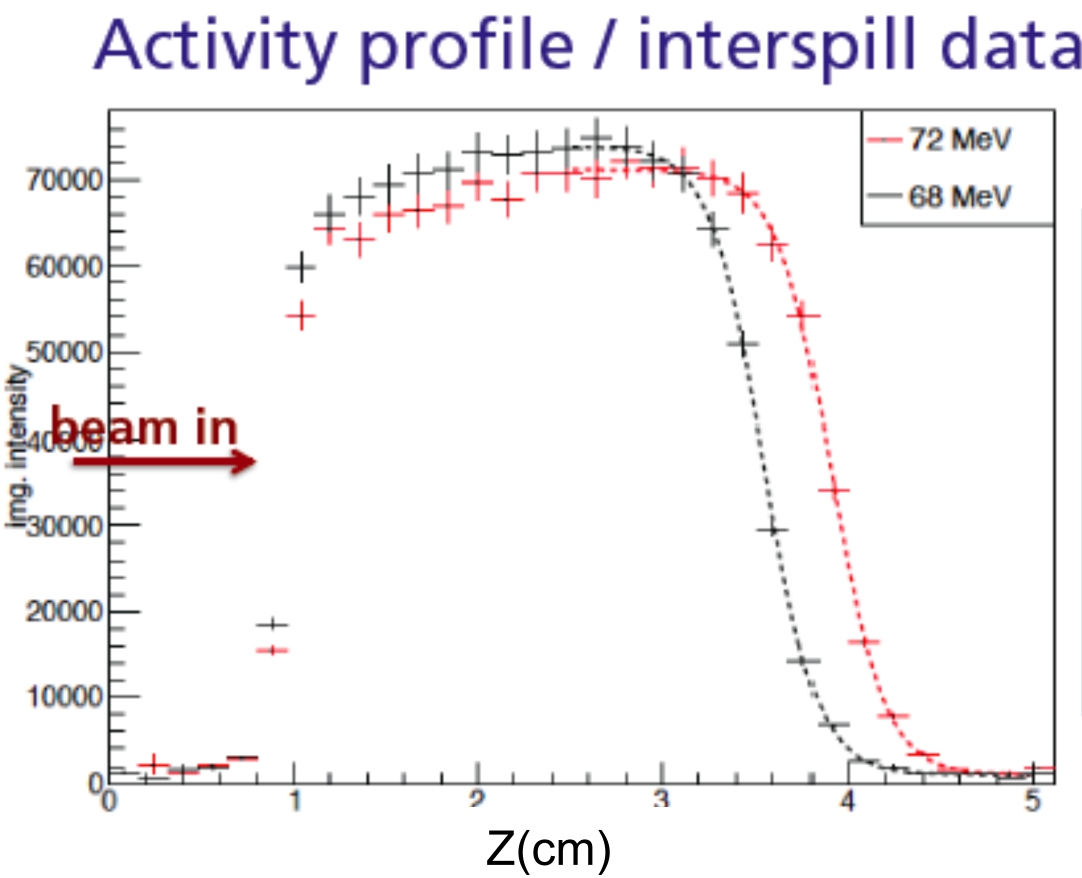
Beam & target activation



Target activation



Proton beams results @CNAO by INSIDE



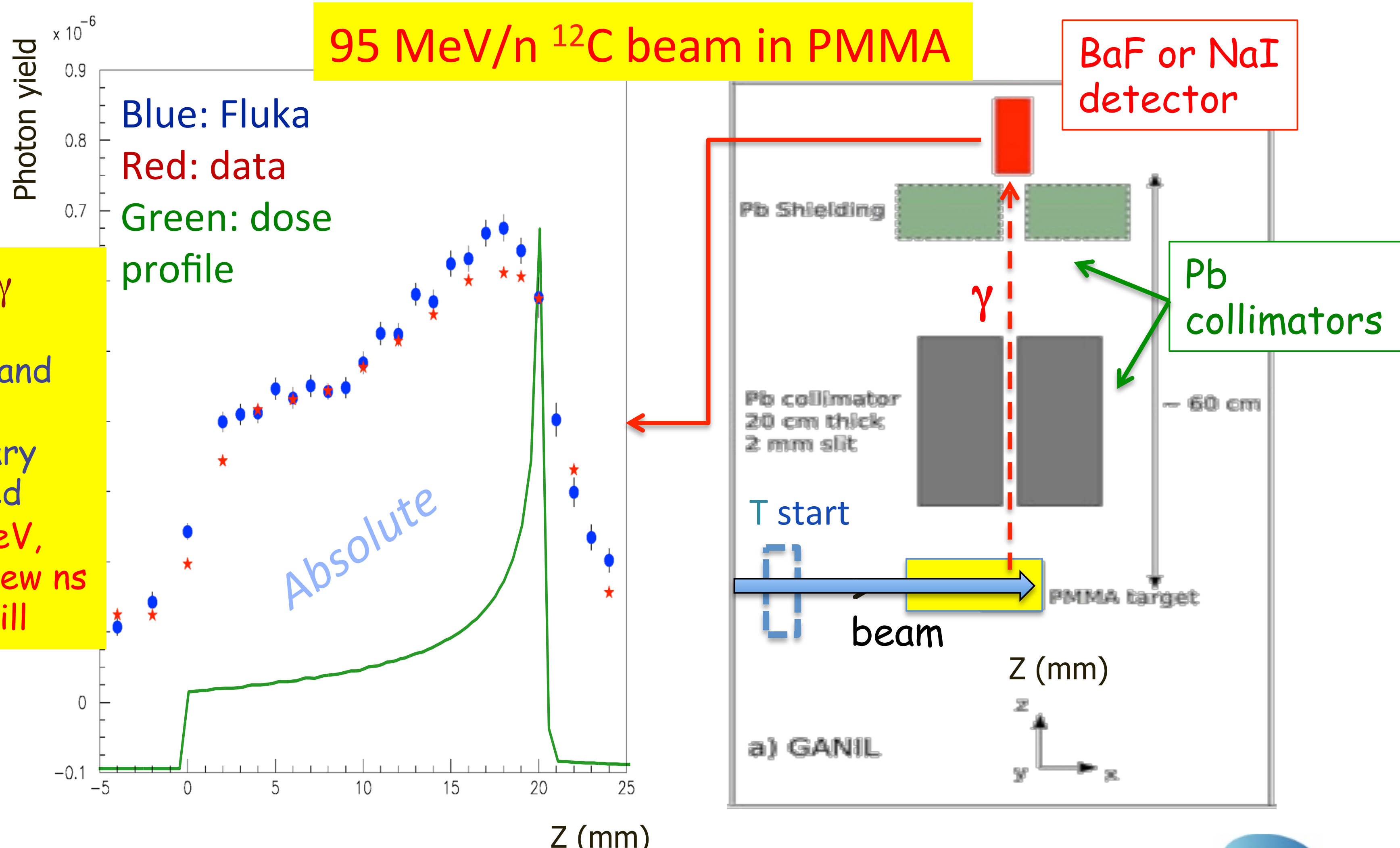
PET data collected during the irradiation time !!! (few minutes)

PMMA phantom
Difference in the distal fall-off

Expected:
3.7 mm
Measured:
(3.6 +/- 0.3) mm

Preliminary !!! Submitted to Scint. Rep

The prompt photon solution



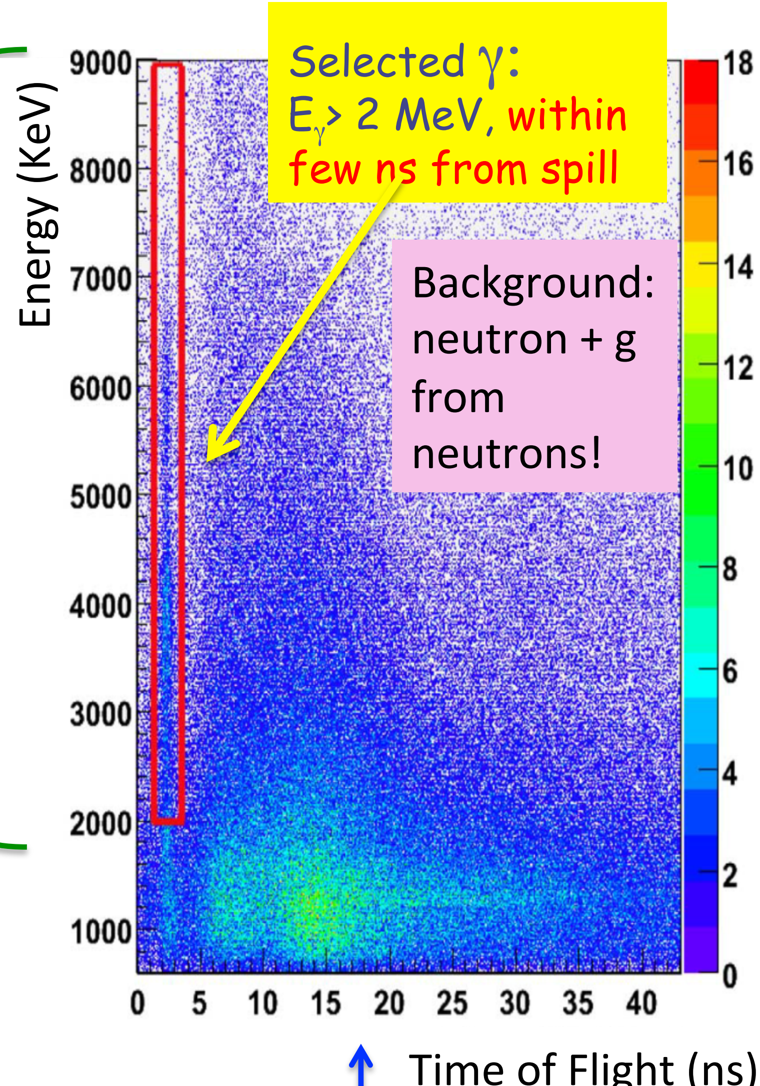
90 deg γ signal
Energy and ToF of secondary recorded
$E_\gamma > 2$ MeV, within few ns from spill

Courtesy of Alfredo Ferrari

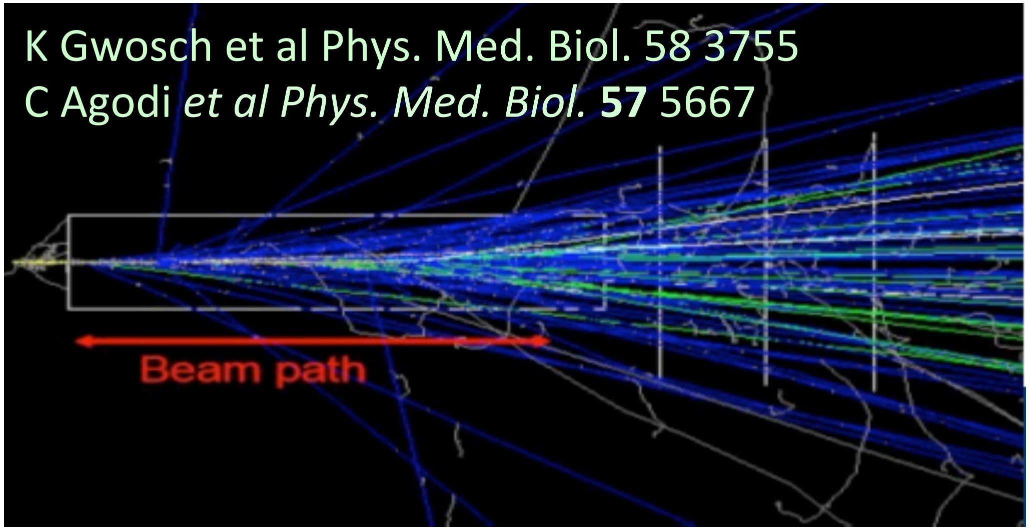
[sketch and exp. data taken from F. Le Foulher et al IEEE TNS 57 (2009), E. Testa et al, NIMB 267 (2009) 993. exp. Data reevaluated in 2012 with substantial corrections

The prompt photon solution

- The gamma are quite copiously produced by proton and ^{12}C beam by nuclear excitation.
- The emission region stretches along all the beam path but has been shown to ends near the Bragg peak for both beams.
- It's not simple backpointing the γ direction: the γ energy is in the 1-10 MeV range-> much more difficult to stop and collimate with respect to ^{99}Tc 144 KeV γ in standard SPECT imaging
- Huge background (beam, energy and site specific) due to neutrons & uncorrelated γs produced by neutrons. TOF not easy to exploit in clinical practice



Something else useful? Charged fragments (protons)



Charged secondaries have several nice features as

- The detection efficiency is almost one
- Can be easily back-tracked to the emission point-> can be correlated to the beam profile & Bragg Peak

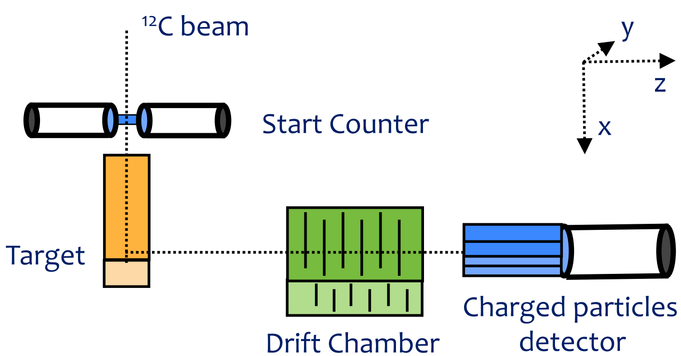
BUT…

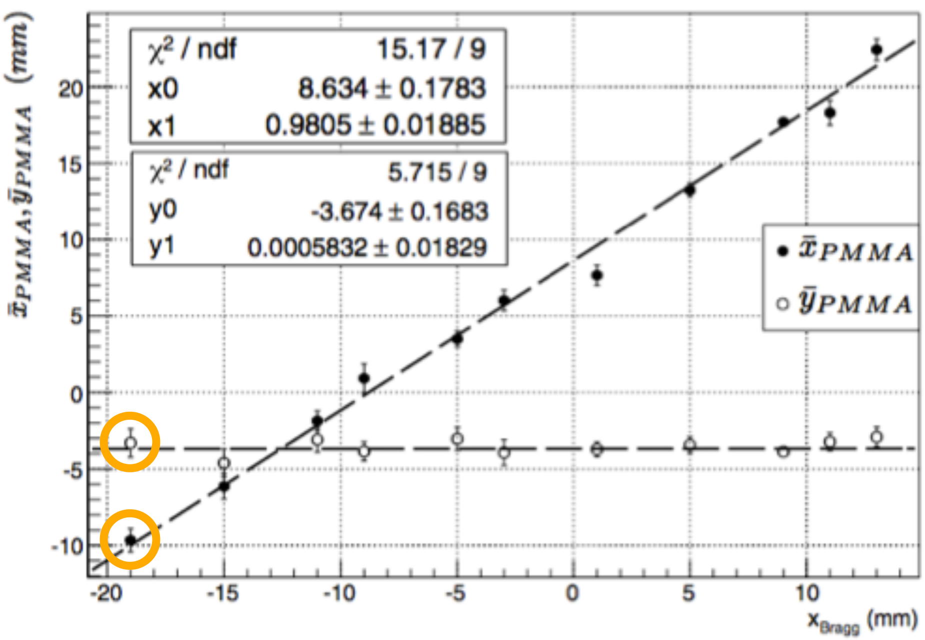
- They are forward peaked
- Energy threshold to escape the patient ~ 80-90 MeV
- They suffer multiple scattering inside the patient -> worsen the back-pointing resolution

MC highly unreliable, probing the very tail of the angular distribution of secondary

Charged secondary emitted from BP ?

- Measurements at LNS (Catania) ^{12}C beam @ 80 MeV/nucleon. Range in PMMA phantom ~ 1 cm.
- Corresponds to the last part of the path in the patient of higher energy, longer range pencil beam -> signal from BP region
- Moving the target the charged signal follows





Agodi et al. PMB 2012

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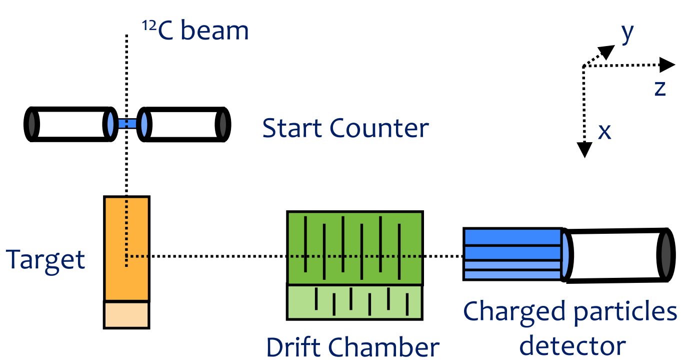
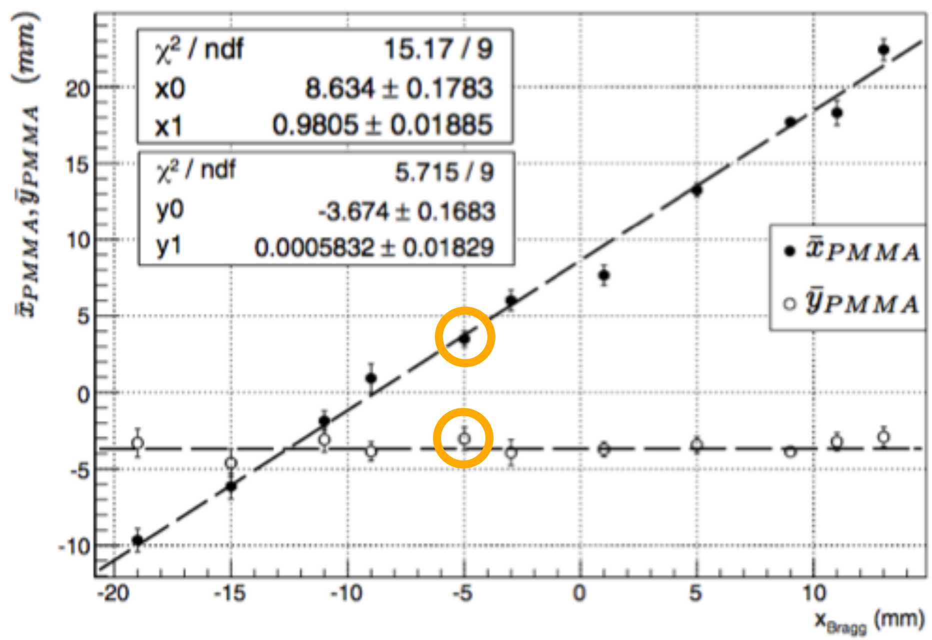
- Moving the target the charged signal follows

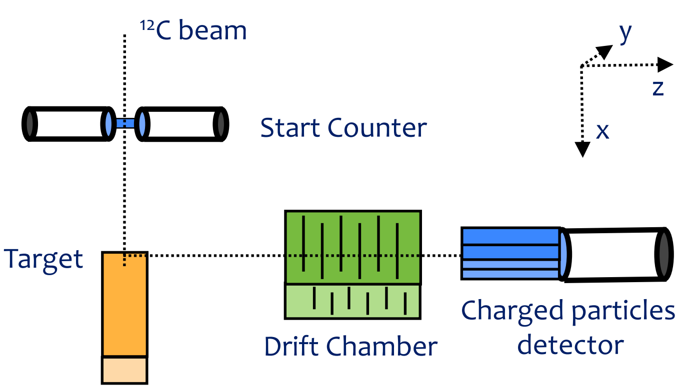


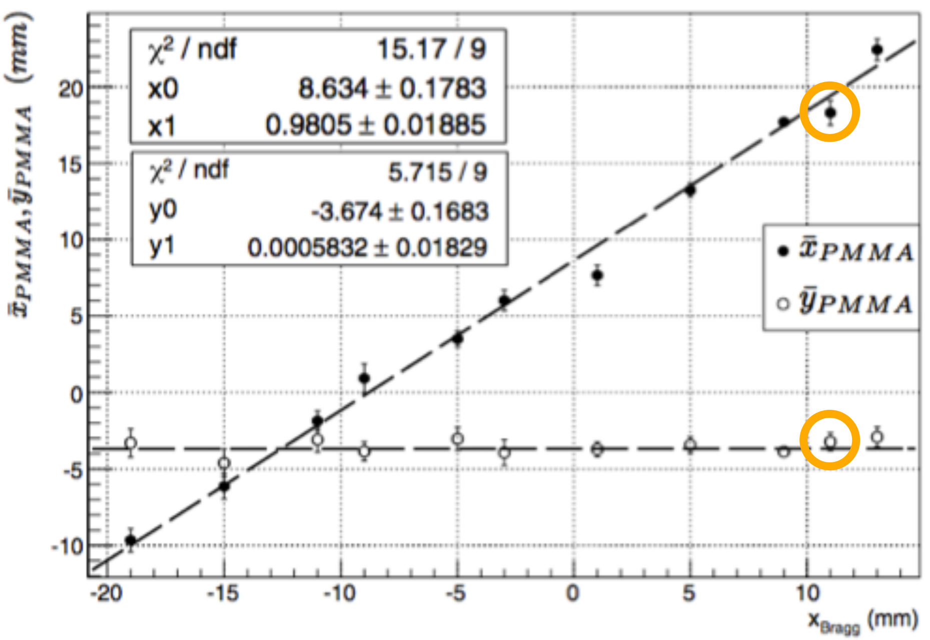


Agodi et al. PMB 2012

Charged secondary emitted from BP ?

- Measurements at LNS (Catania) ^{12}C beam @ 80 MeV/nucleon. Range in PMMA phantom ~ 1 cm.
- Corresponds to the last part of the path in the patient of higher energy, longer range pencil beam -> signal from BP region
- Moving the target the charged signal follows

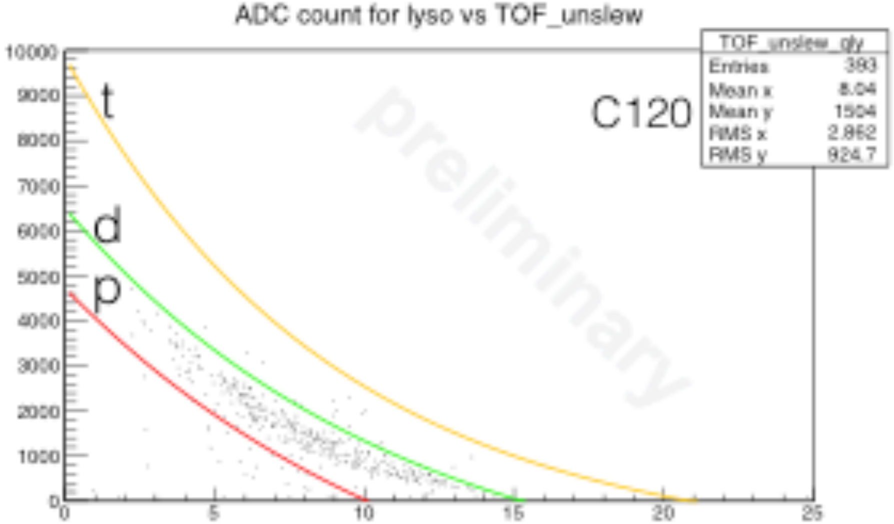


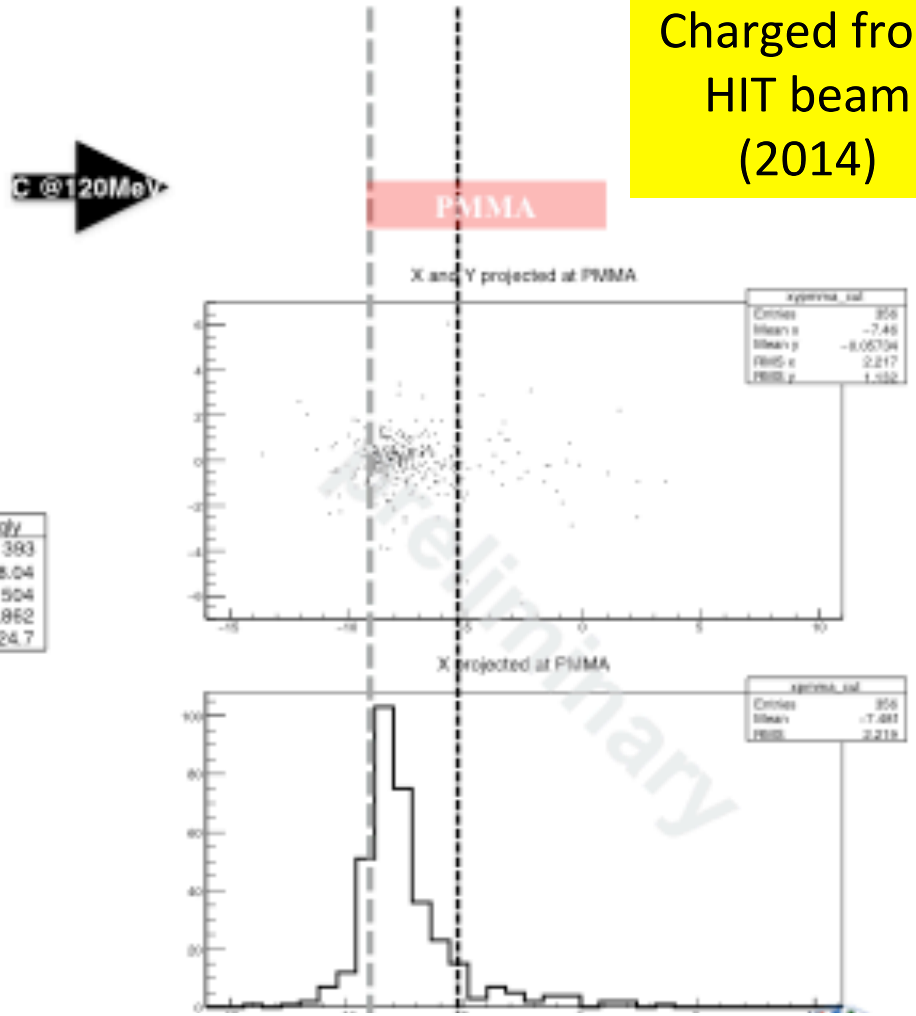


Monitoring charged secondaries

A non negligible production of charged particles at large angles is observed for all beam types.

The emission shape is correlated to the beam entrance face and BP position as already measured with ^{12}C at GSI.
[Piersanti et al. PMB, 59 (2014)]





Charged from HIT beam (2014)

arXiv:1608.04624 Submitted to PMB

Monitoring charged secondaries

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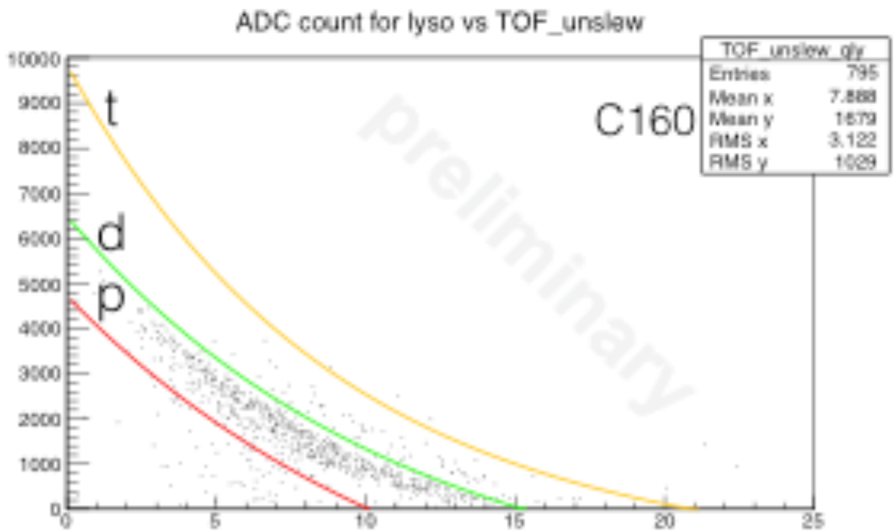
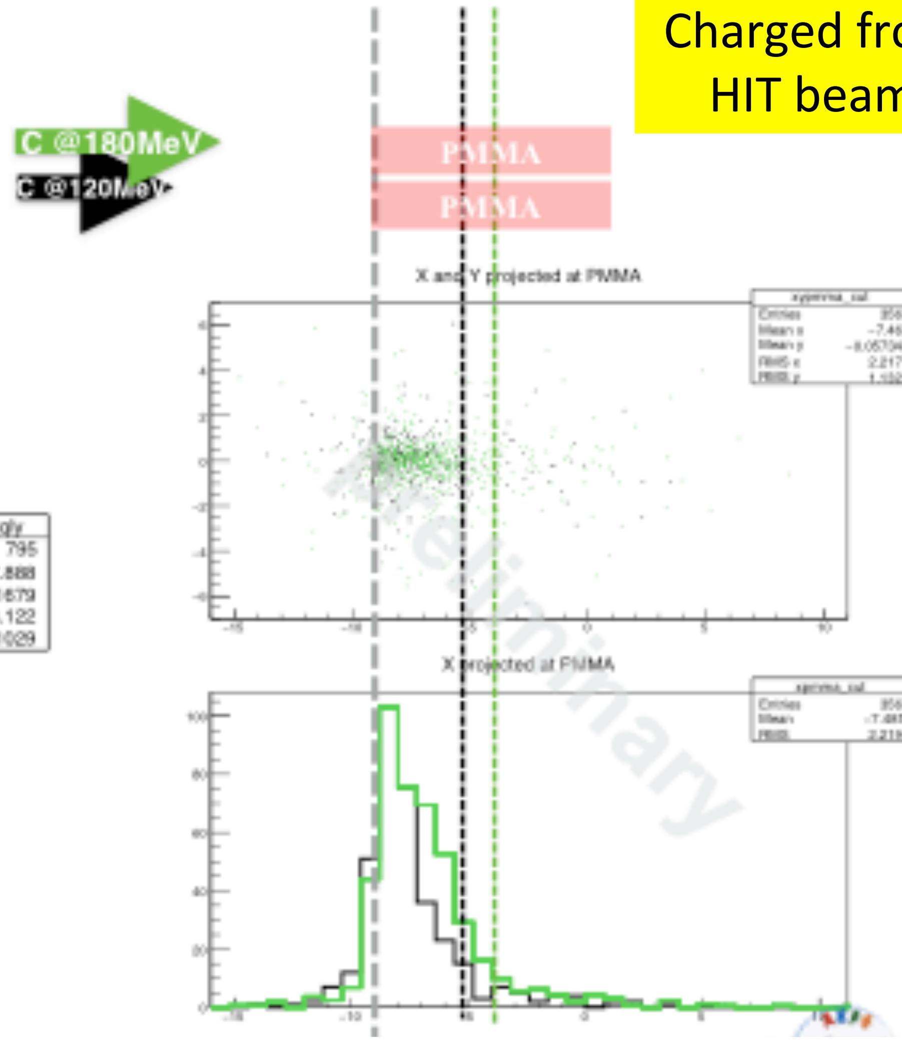


Charged from HIT beam



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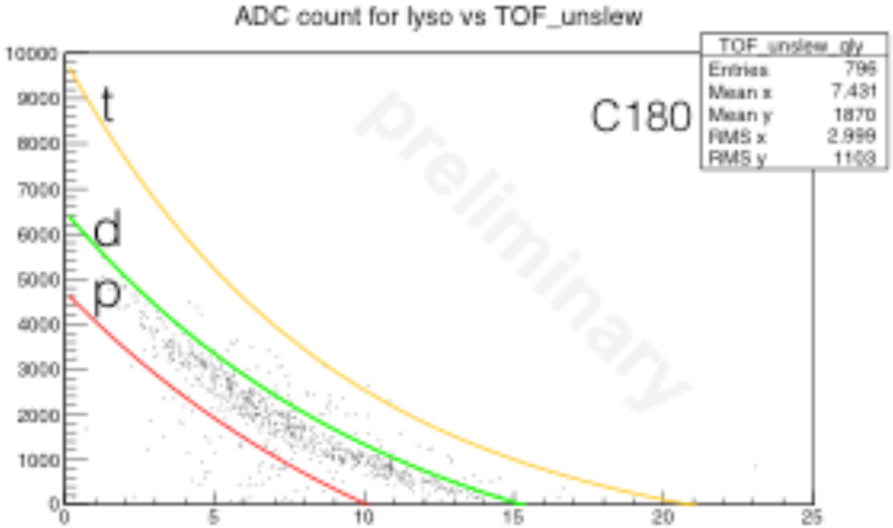

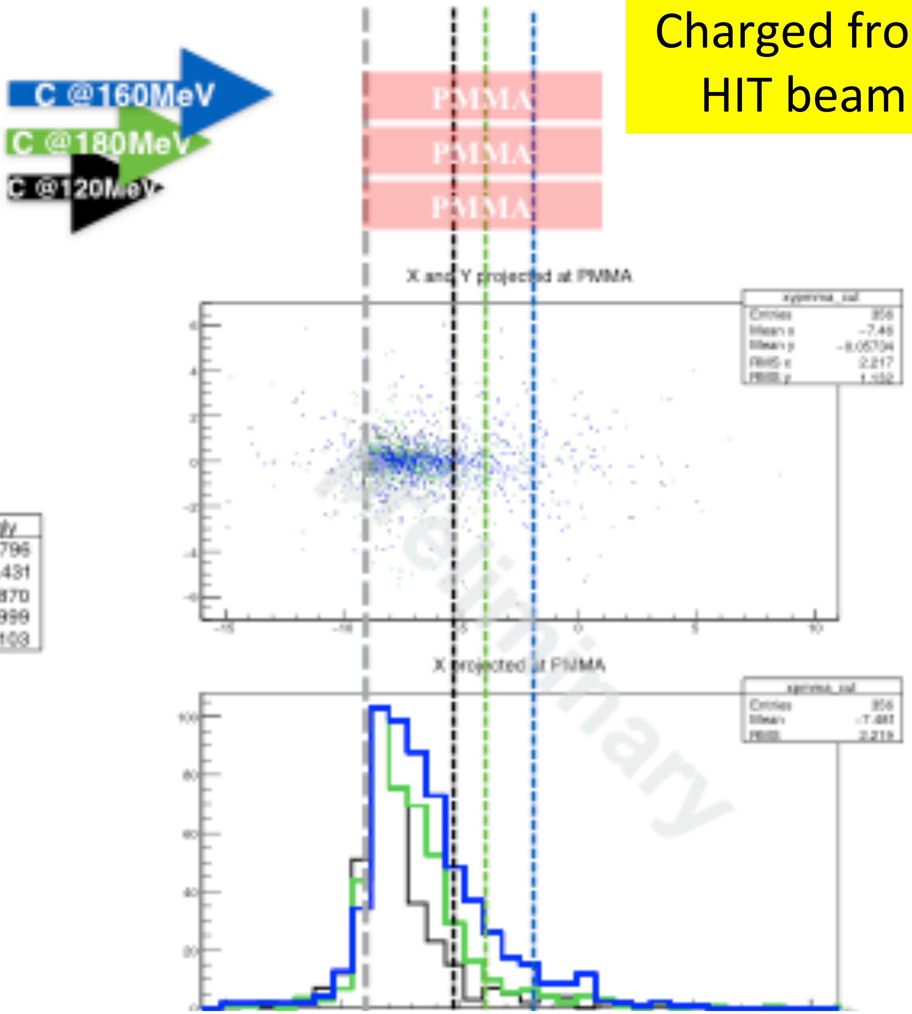

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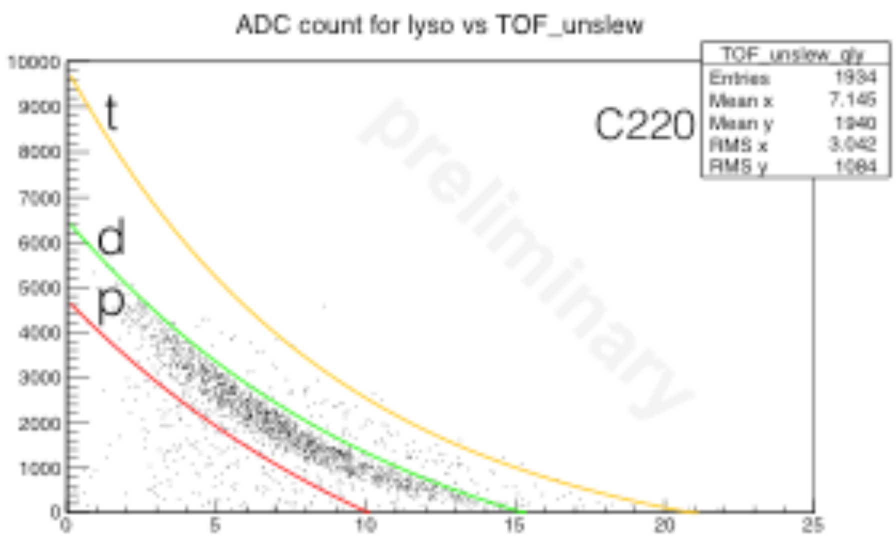
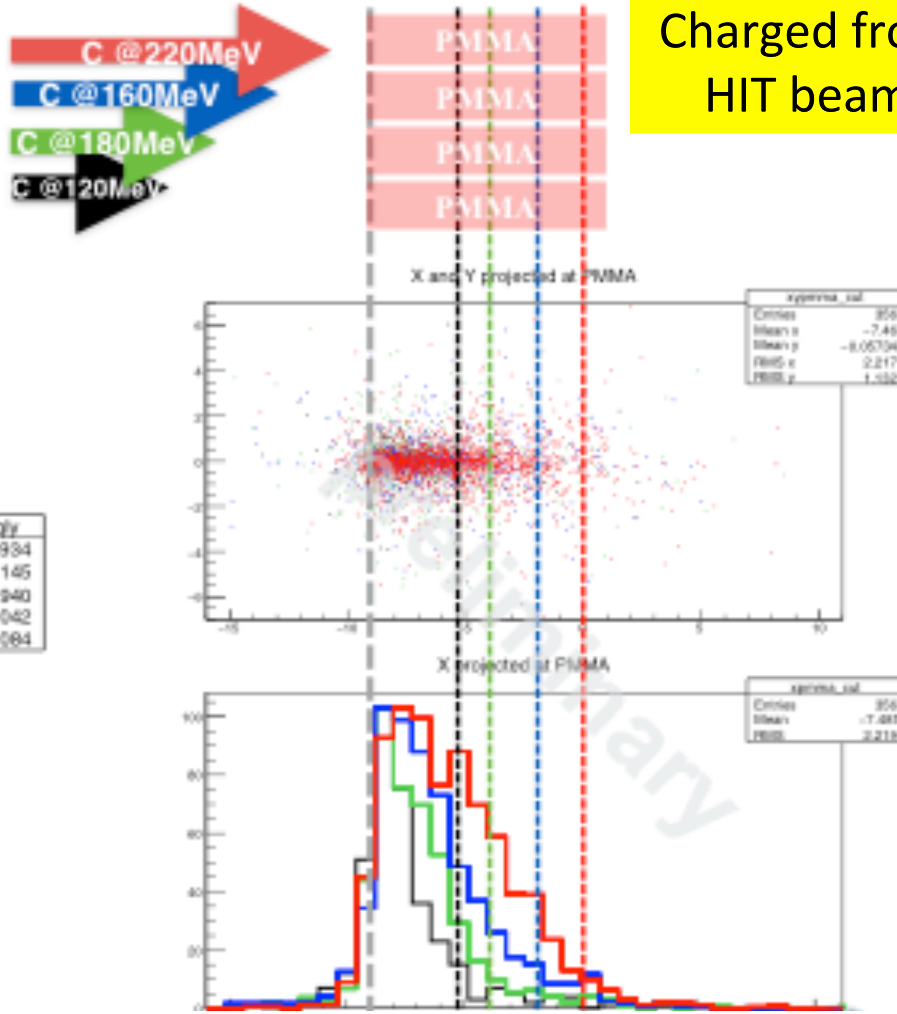




Charged from HIT beam

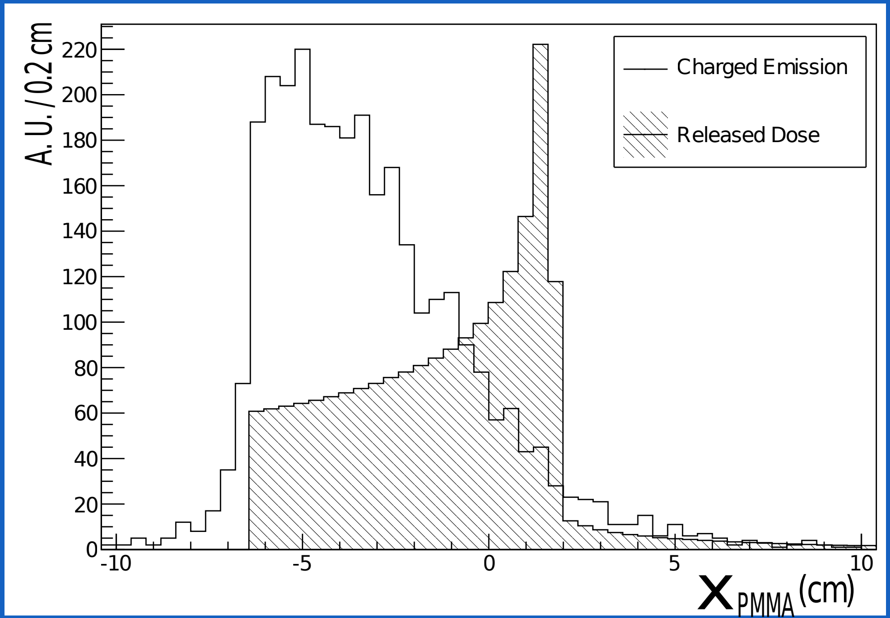
arXiv:1608.04624 Submitted to PMB

Secondary emission point, BP and the patient

The materials crossed to exit from the patient modifies the detected distribution (absorption & MS). Similar approach of PCT needed: exploiting the knowledge of the pencil beam transverse position and the CT deconvolute the emission shape

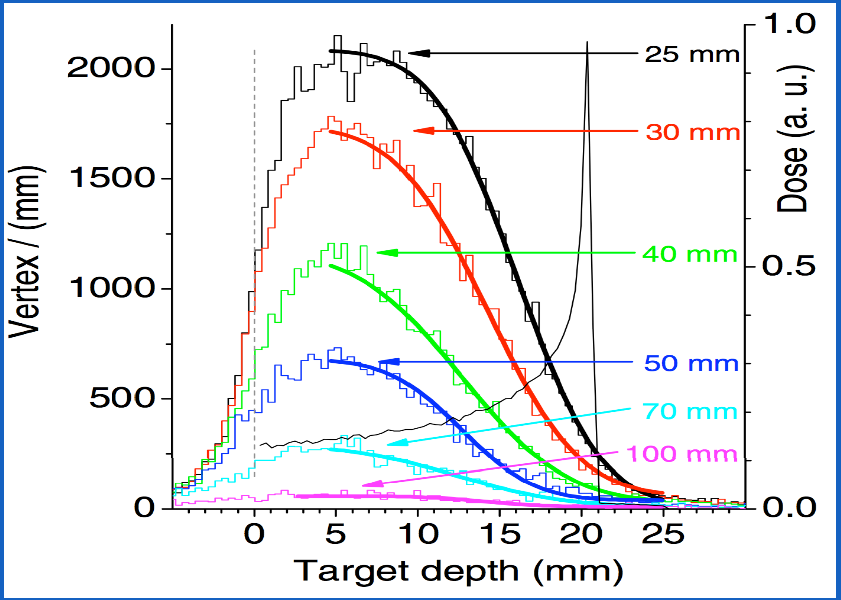
Measured emission shape of protons outside a 5 cm thick PMMA at 90^0 wrt the direction of 220 AMeV ^{12}C beam

L.Piersanti et al. PMB, 2014



Simulated emission distribution shape of protons as detected outside different PMMA thickness at 30^0 wrt the direction of 95 AMeV ^{12}C beam

E. Testa et al Phys. Med. Biol. 57 4655



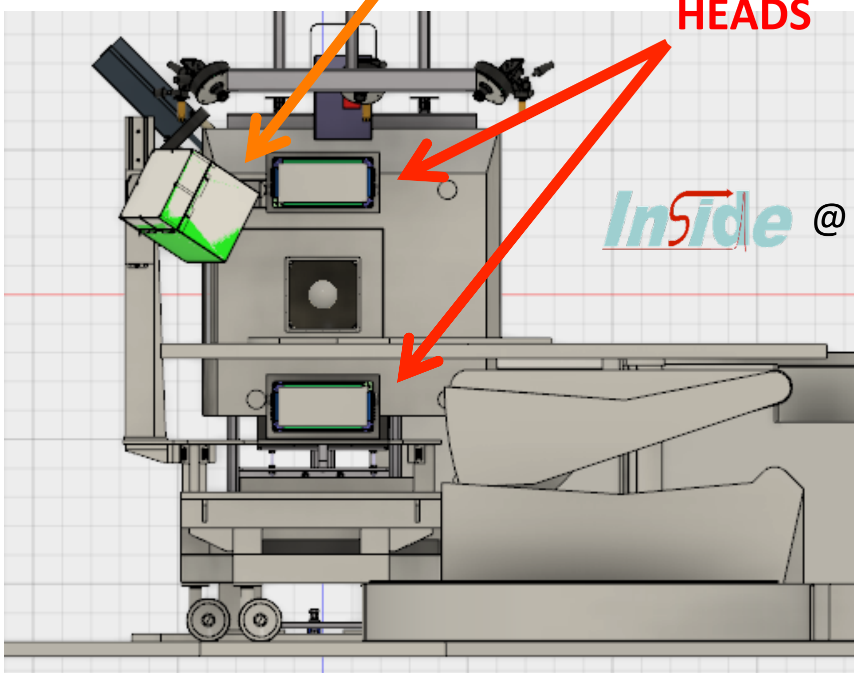
The InSide Project

Prompt charged particles emission

Tracker = DOSE PROFILER

β^+ activity distribution

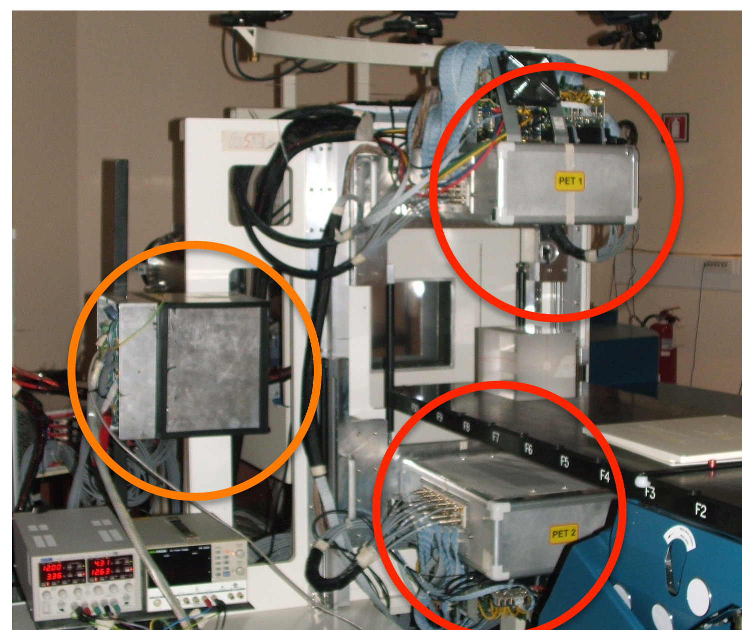
IN-BEAM PET HEADS



InSide @ CNAO

INnovative **S**olutions for In-beam **D**osim**E**try in Hadrontherapy

- integrated in treatment room
- operated in-beam
- **provide an IMMEDIATE feedback on the particle range**



PRIN + Centro Fermi + INFN project

P. Cerello
S. Coli
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G. Sportelli

C. Peroni
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M. Marafini
C. Morone

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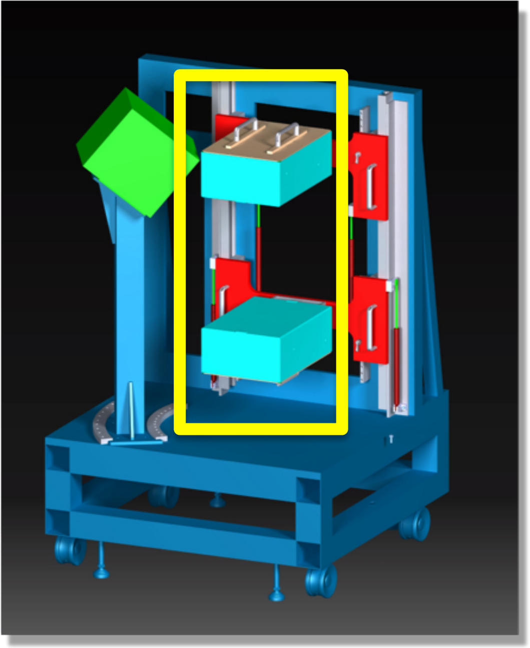
A. Sciubba
C. Voena

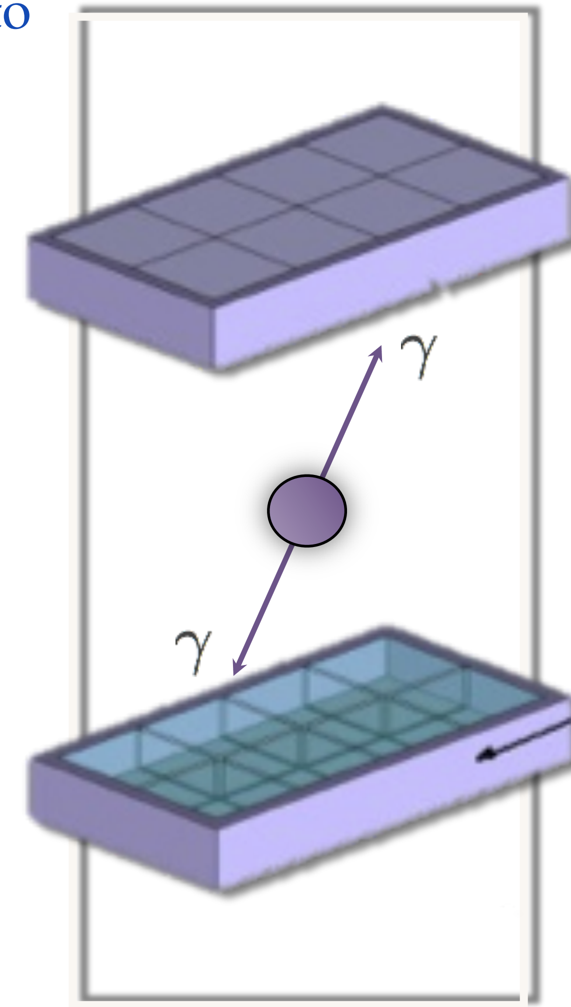
F. Ciciriello
F. Corsi
F. Licciulli
C. Marzocca
G. Matarrese

G. Battiston
S. Muraro
P. Sala

The INSIDE Project: PET system



- Detectors to measure the 511 keV back-to-back photons in order to reconstruct the β^+ activity map;
- Two planar panels: 10 cm x 20 cm wide => 2 x 4 detection modules;

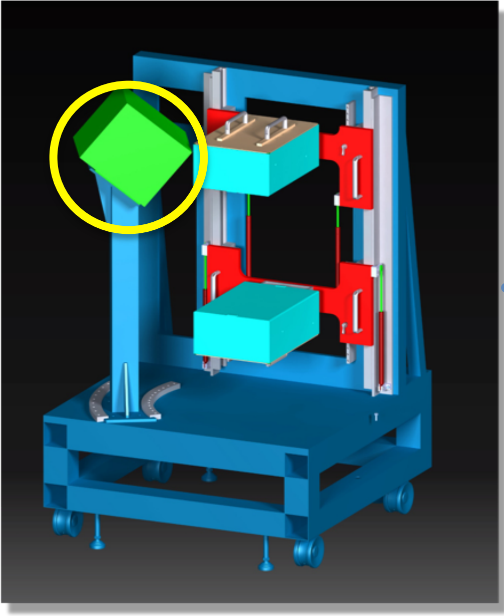


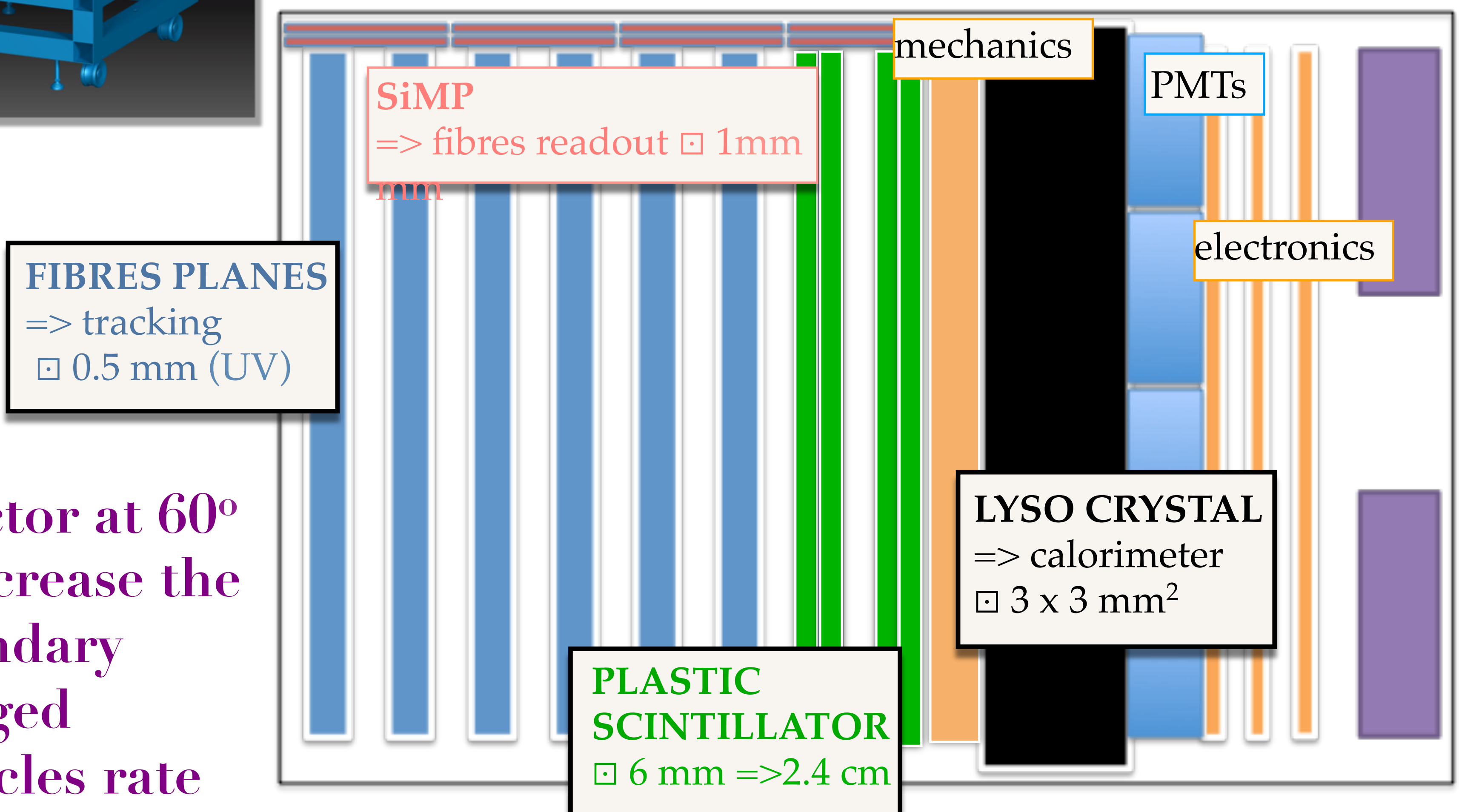
- Each module is composed of a pixelated LYSO matrix 16 x 16 pixels, 3 mm x 3 mm crystals (pitch 3.1mm);
- LYSO matrix readout: array of SiPM (16x16 pixels) coupled one-to-one.

The **resolution** of the two PET heads system in the β^+ activity reconstruction map is expected to be between 1 and **2 mm (FWHM)** in beam direction.

The INSIDE Project: Dose Profiler

- The Dose Profiler aim is to back tracks the secondary particles (p,d,t and prompt photons) and reconstruct their emission point together with their flux.

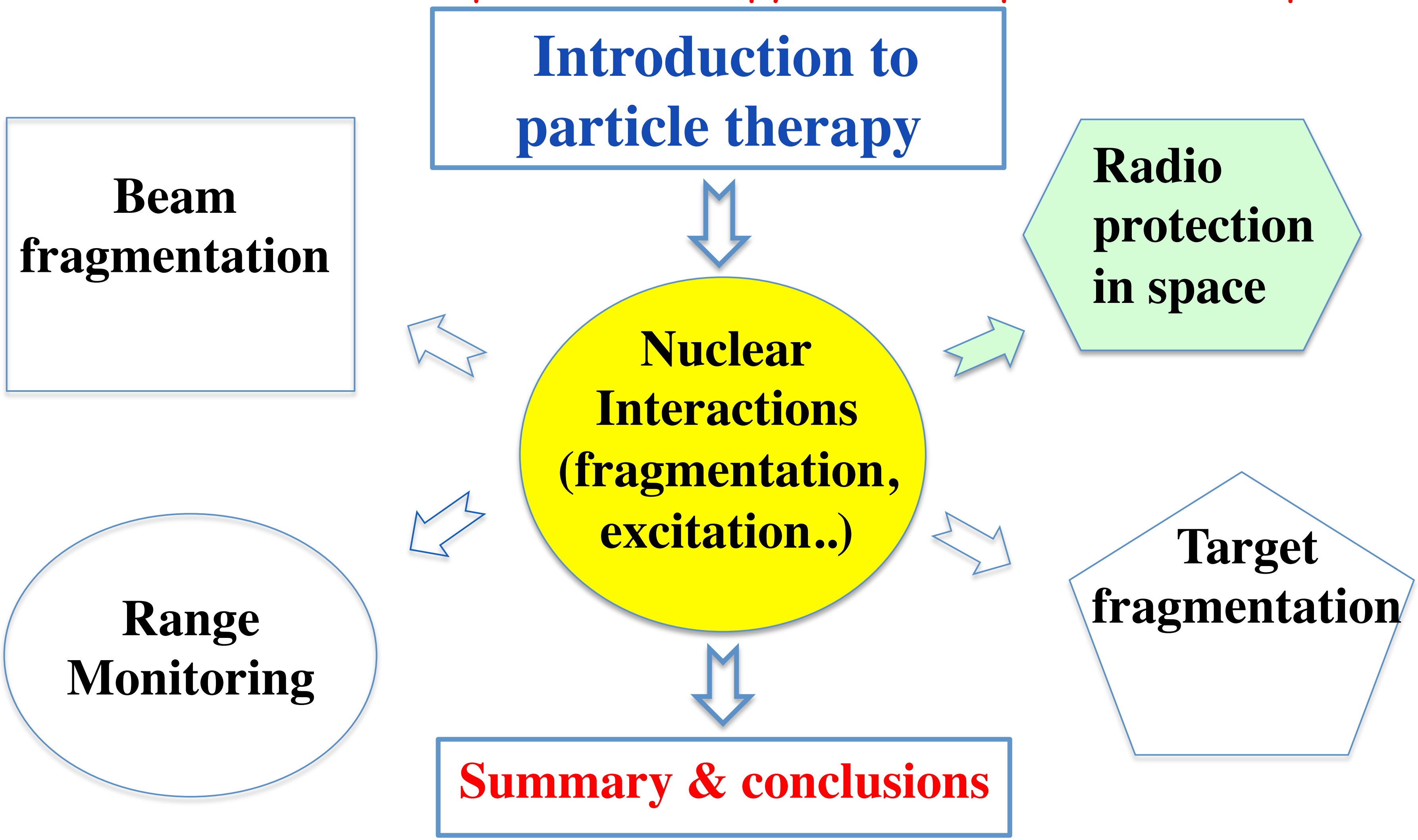




detector at 60° to increase the secondary charged particles rate

Outline

Bouncing from fundamental physics to applied physics and back…
A spot-like, phenomenological, detector oriented view to the impact of nuclear interactions on particle therapy and radio protection in space

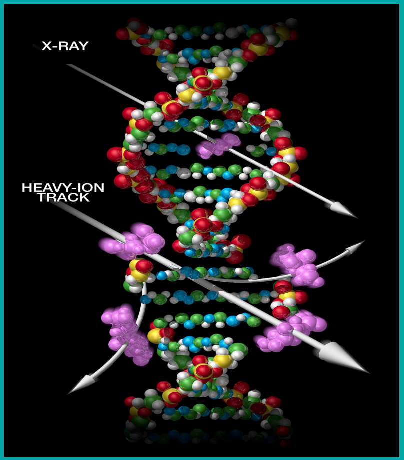


Cosmic Radiation Risks for Human Exploration of the Solar System

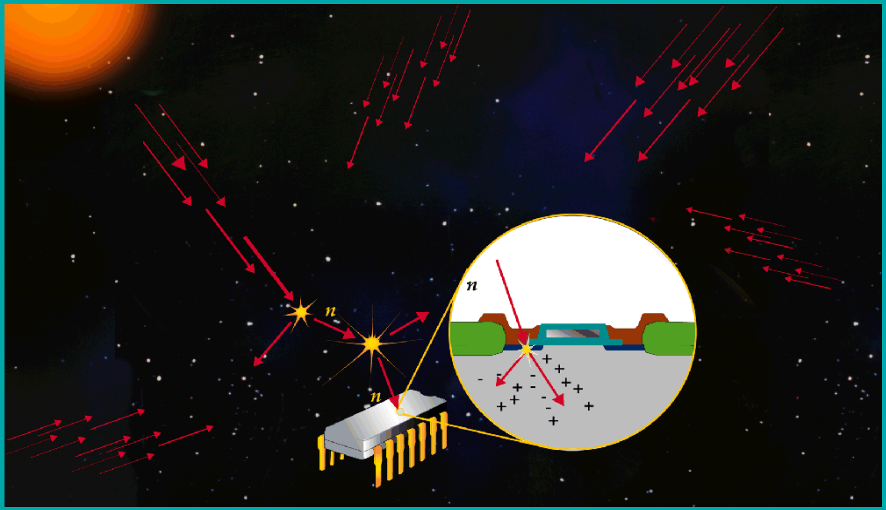
- **Radiation is the main hindrance to safe human space exploration**
- OVERALL OBJECTIVE
  - To allow exploration and colonization of the Solar system with acceptable risk from space radiation exposure

Beyond radiation protection:
Astrobiology
Plant breeding in space

What do we need to know in space radiation for interplanetary spaceflight?



- Risk estimation for humans in space
  - Acute effect
  - Late effects
    - ✓ CNS damage
    - ✓ cataracts
    - ✓ cancer



- Radiation effects on non-biological material
  - Shielding
  - Radiation hardening
  - Single even upsets in [illegible]tronic devices

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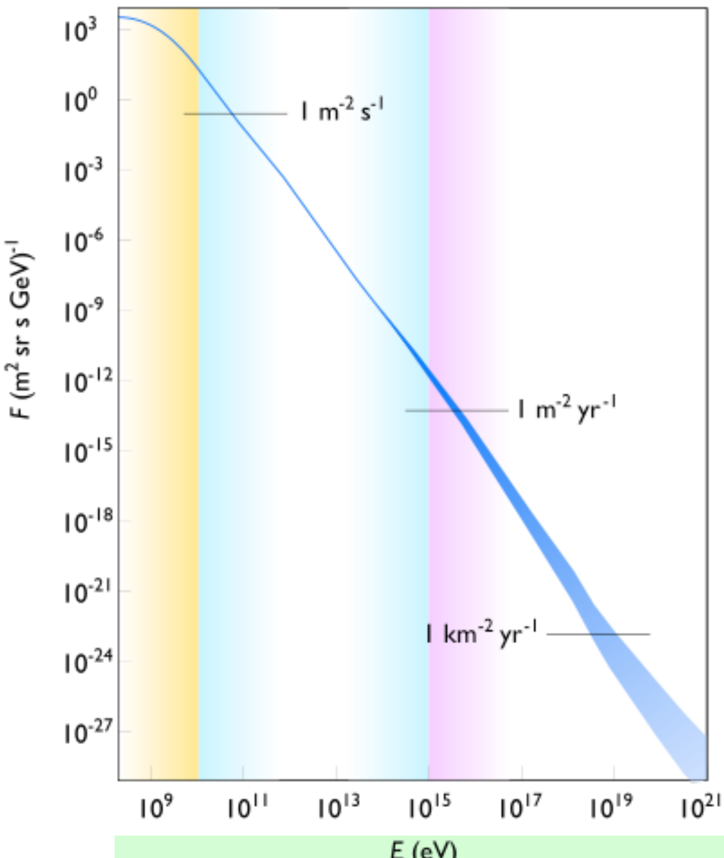
Cosmic Rays

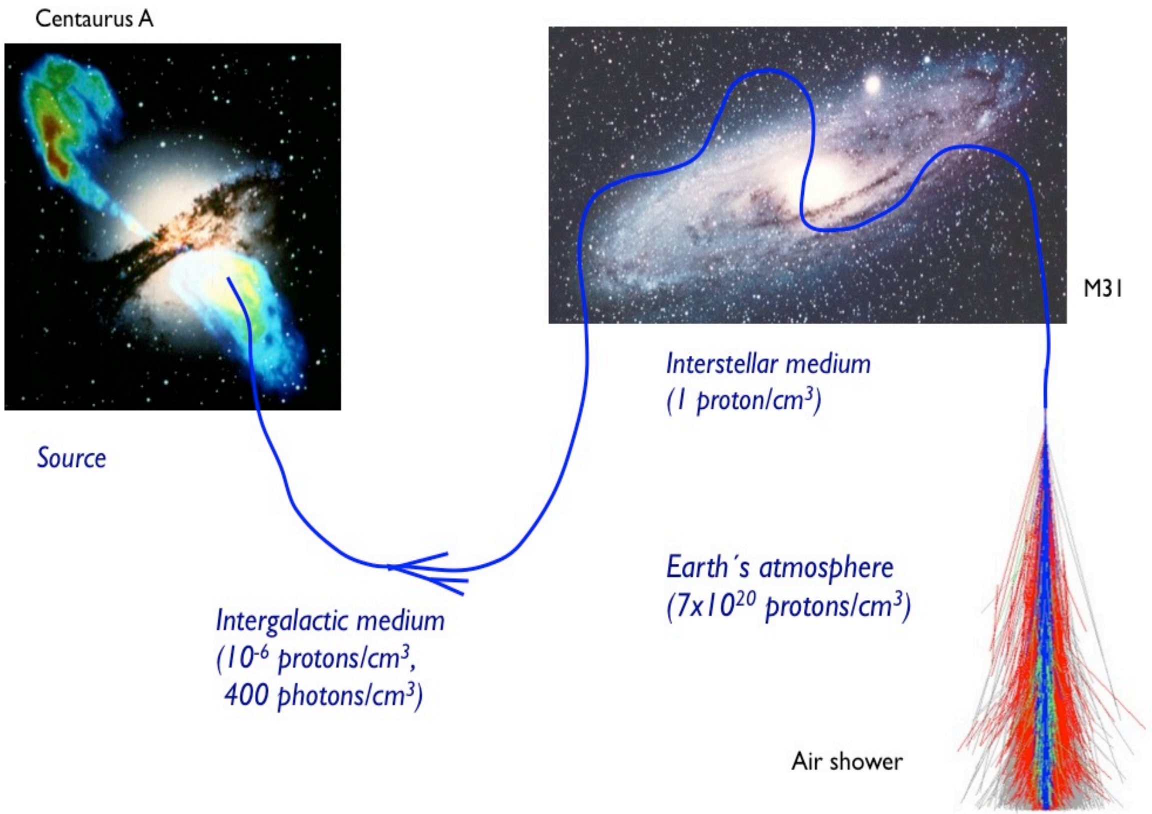
- We are embedded in a continuous bath of particles coming from Sun, galactic sources, extragalactic sources.
- The energy associated to this kind of radiation adds up to 1/3 of the estimated "normal" energy (non dark energy) of the universe
- The source are cosmic objects like active galactic nuclei, supernovae plus other space "monsters"
- The relevant part of CR for radioprotection in near (solar system) space is the charged component originating the Sun and from our Galaxy

From very very far … right to us

Flux of the CR (source: Sven Lafebre)



Watch out: we are X-ed by 100 charged particles from CR per second!!!



NB: deflected by the magnetic field in the galaxy

Relevant Radiation sources in space

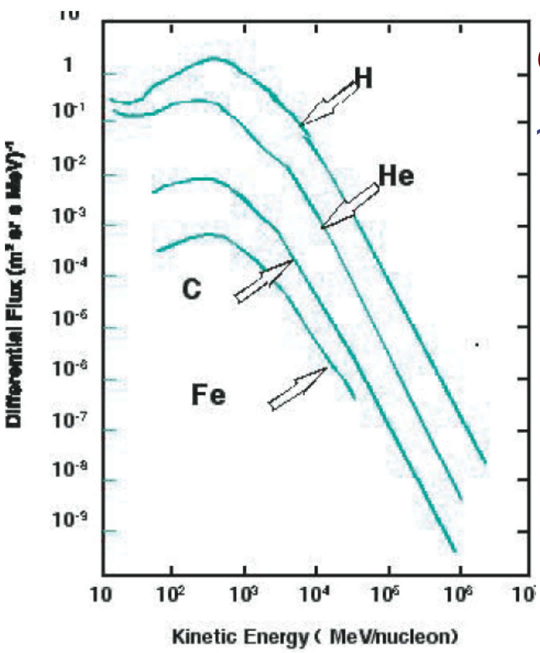
Continuos irradiation!

Very rare (years)

Galactic Cosmic Rays

spectrum: 87% protons, 12% He ions and 1% heavier ions (in fluence) with peaks at 1 GeV/n

flux: 4 particles/(cm^2 s) at solar min.



dose: ~1 mSv/day

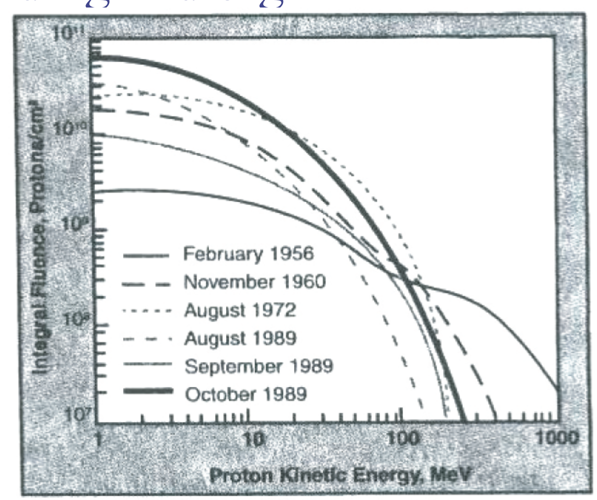
NASA pub. 1998

Solar Particle Events

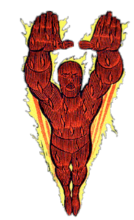
spectrum: 90% protons, 10% heavier ions with energy mainly below ~200 MeV

flux: up to ~10^{10} particles/cm^2 in some hrs.

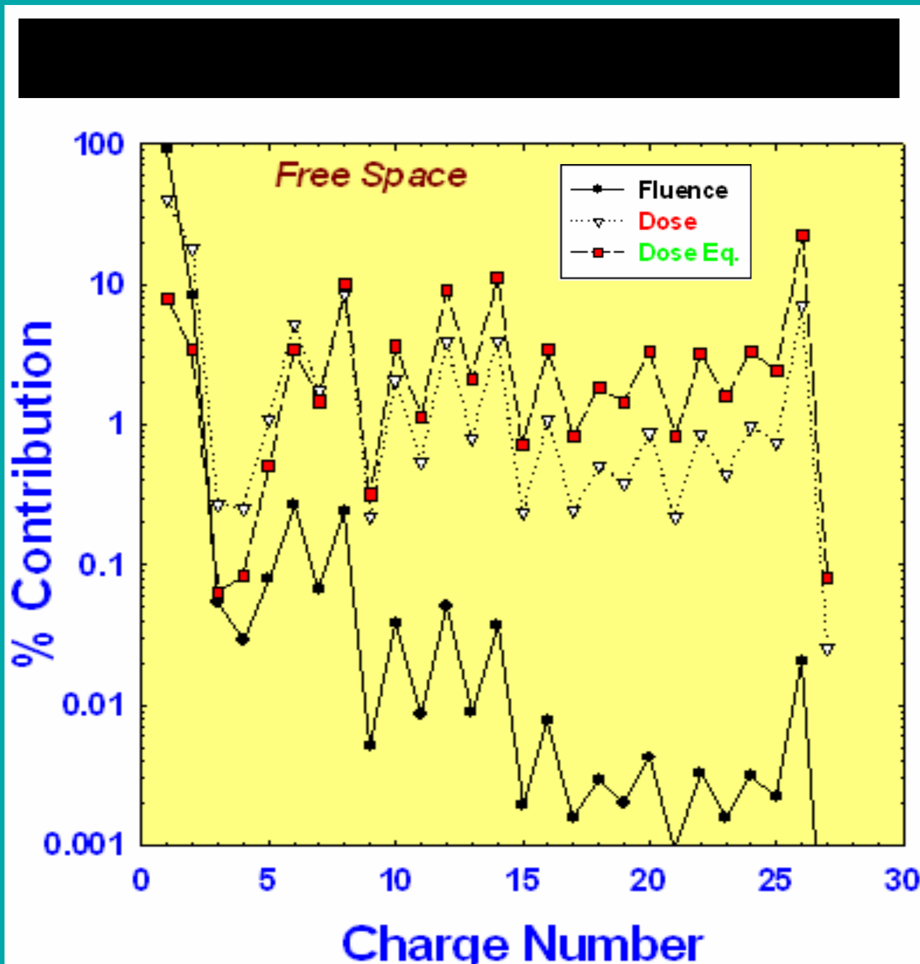
dose: order of Sv, strongly dependent on shielding and organ



NASA pub. 1998



GCR contribution from different particles



Dose (physical) D

D= ΔE/Δm [Gy]=[J]/[kg]

Equivanet Dose = QD [Sv]

The Q constant takes care of the fact that not all particles give the same contribution (remind RBE?)

Dose eq. on **Earth**: 10 μSv/d

Dose eq. on **Mars**: 100-200 μSv/d

Dose eq. on **Moon**: 300-400 μSv/d

Dose eq. Mission to Mars (9 monthes): 1.2 Sv

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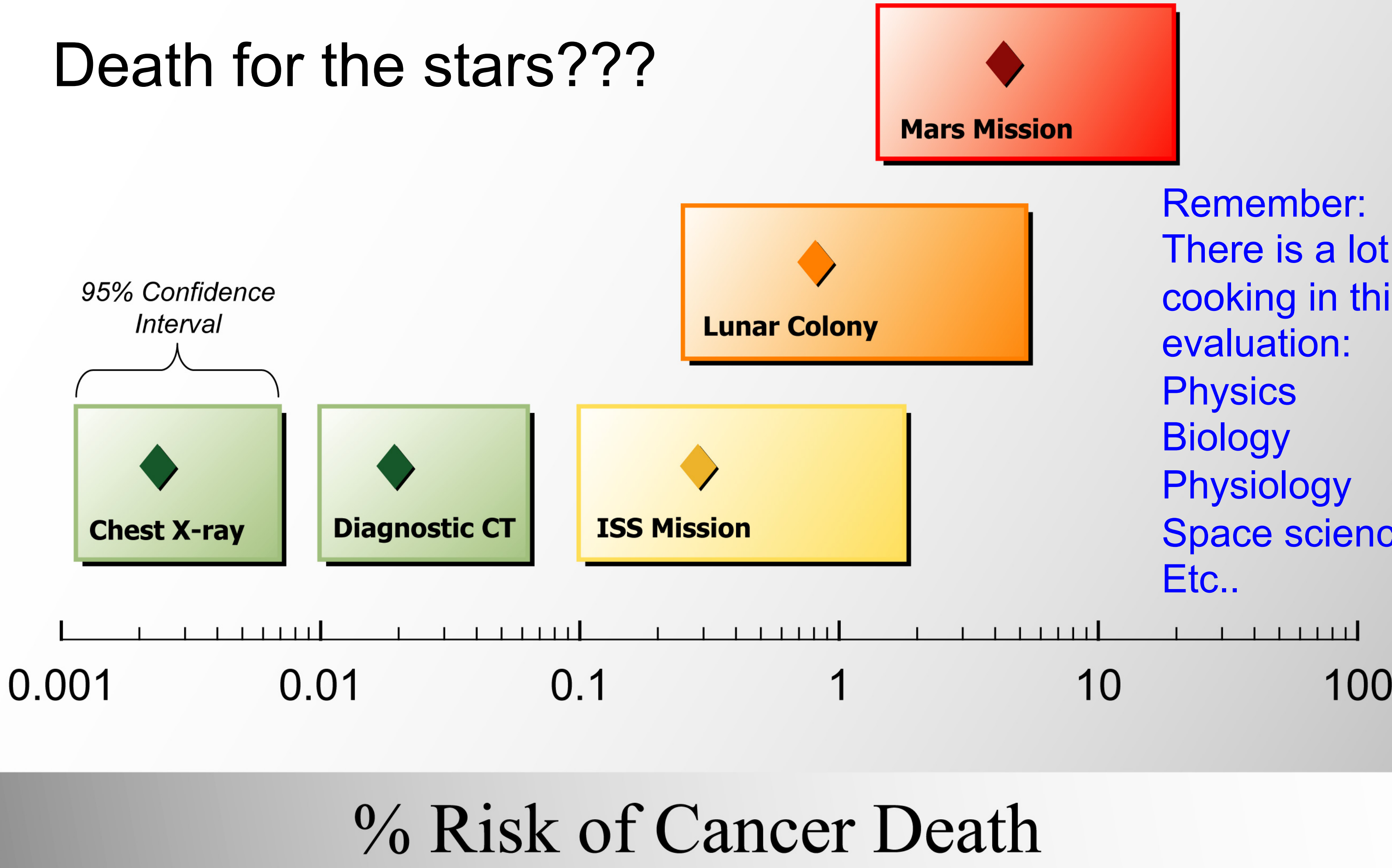
**Francis A. Cucinotta (NASA, Lyndon B. Johnson Space Center), private communication*

Death for the stars???

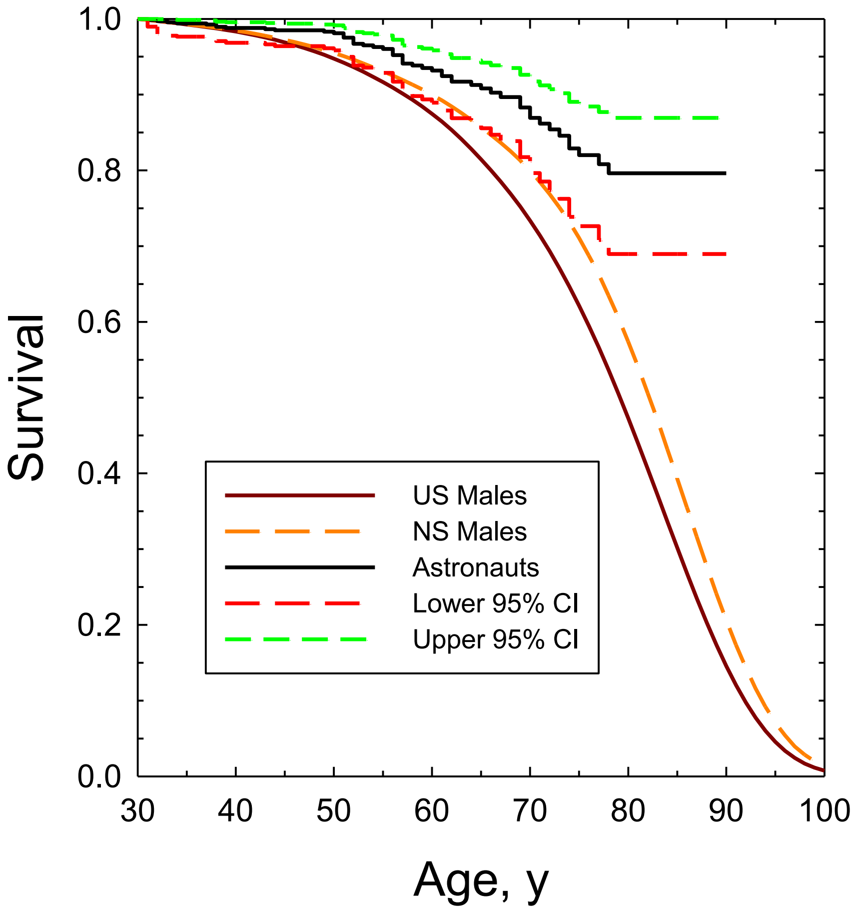


Remember:
There is a lot of cooking in this evaluation:
Physics
Biology
Physiology
Space science
Etc..

Durante & Cucinotta, *Nature Rev. Cancer* (2008)

NASA ASTRONAUTS' CAUSE-SPECIFIC MORTALITY

Astronauts excluding Flight Tragedies

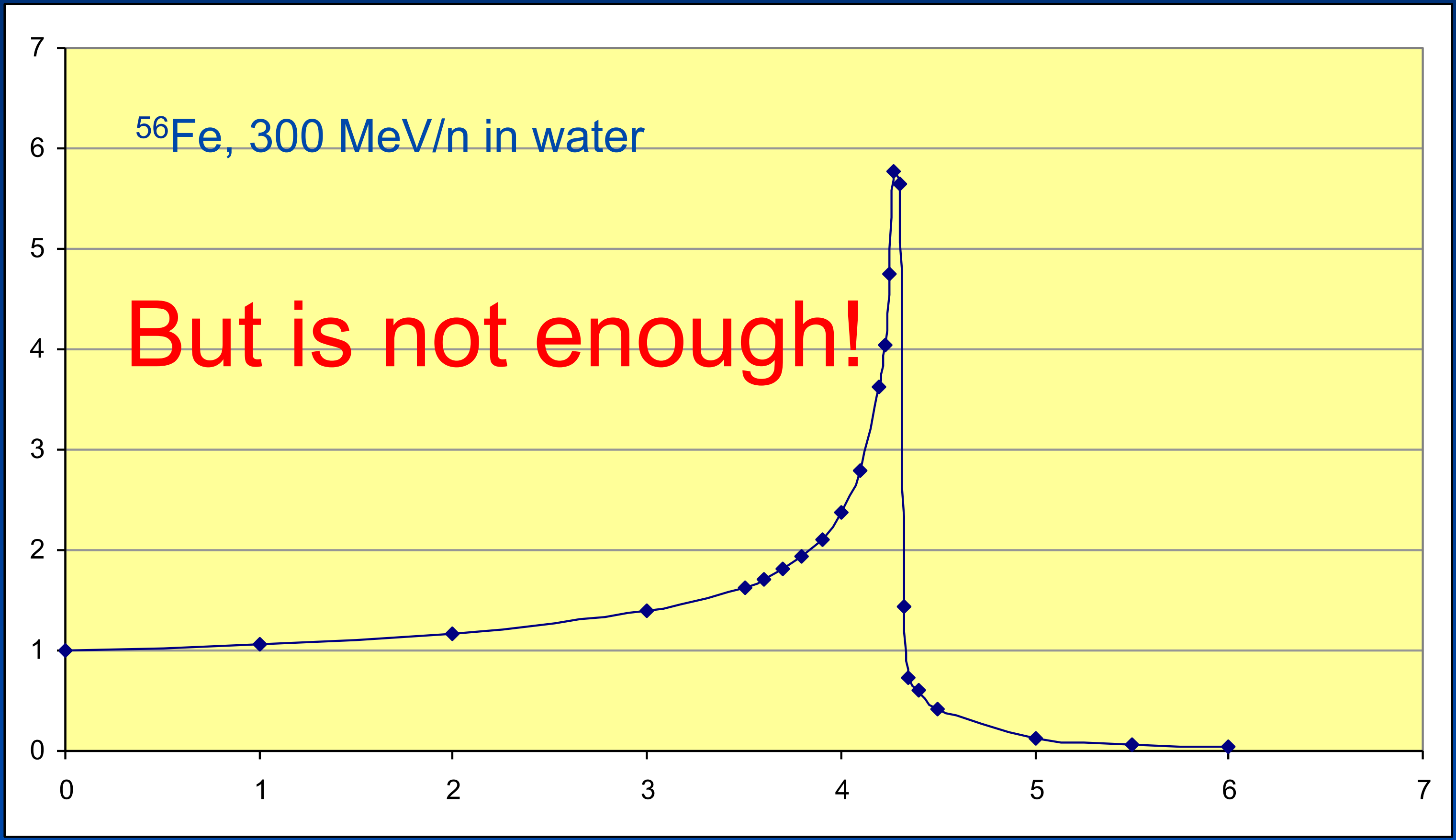


	Total Frequency	Death Frequency
Total	339	45
Male	269	41
Female	40	4
Astronaut	316	44
Payload Specialist	23	1

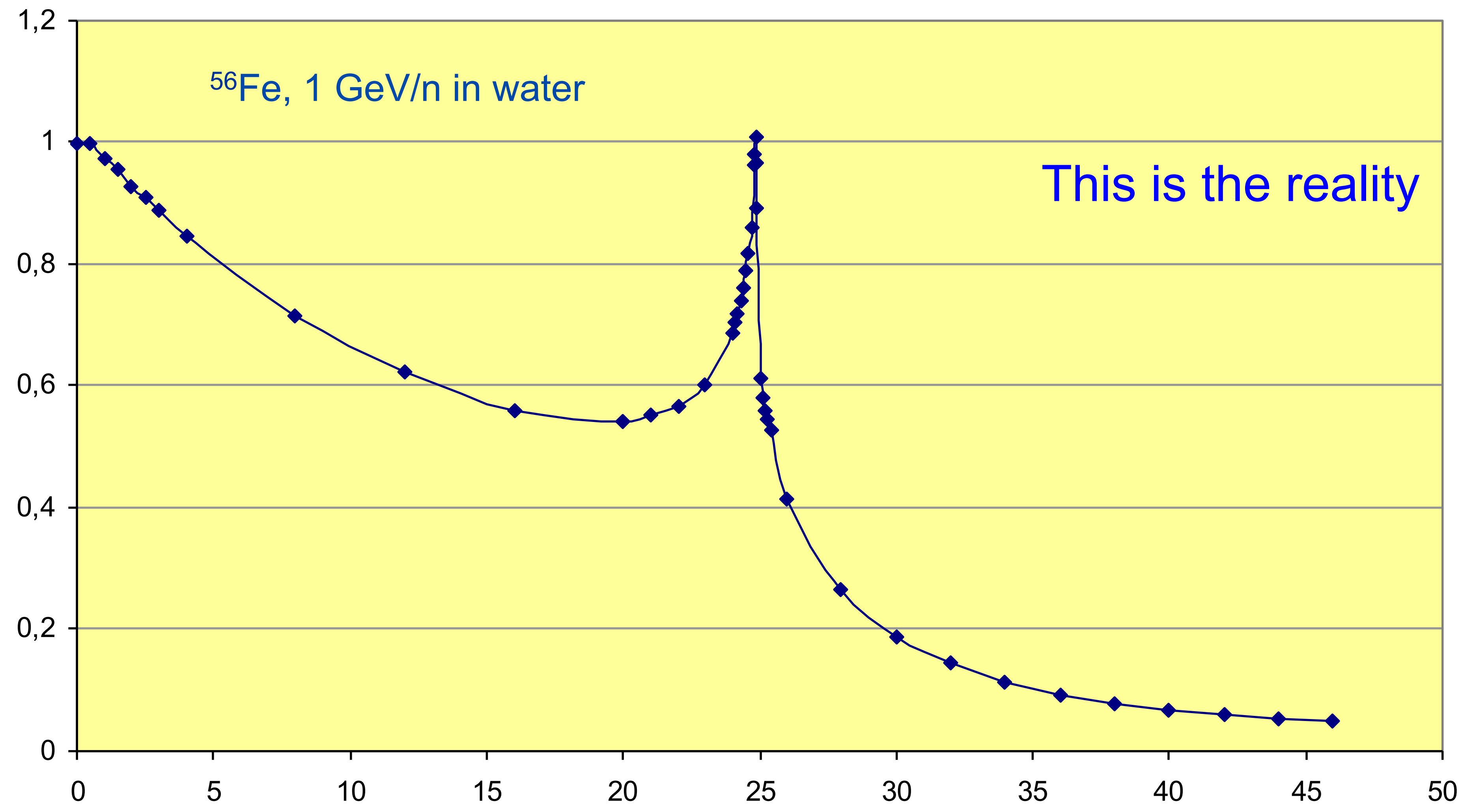
Cancer	Heart	CNS	Work Related Accidents	Other Accidents	Other causes
11	4	1	18	5	5

Ionization energy loss (Bethe-Bloch formula)

$$-\frac{dE}{\rho dx} = k\frac{Z}{A}\cdot\frac{z^{*2}}{\beta^2}\left(\log\frac{2\gamma^2\beta^2 m_e c^2}{I} - \eta\right)$$



Bragg curve + fragmentation



Computing dose in Spacecraft

Quality factors → **MC code**

Yields of "Complex Lesions" → **MC code**

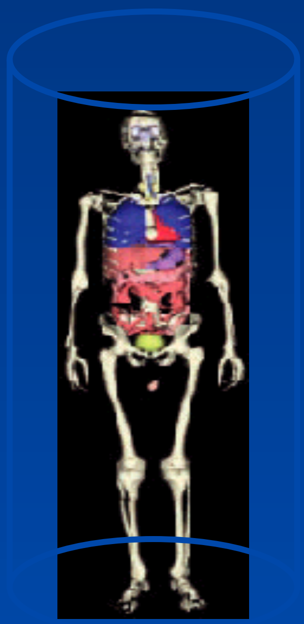
GCR and SPE spectra → **MC code**

Spacecraft material and geometry → **MC code**

MC code ⇒
- **Dose**
- **Dose Equivalent**
- **"Biological Dose"**

Mostly used MC code:
FLUKA
GEANT4

Watch out!!!! Fragmentation cross section are badly needed also for GCR fragmentation on shielding materials: by the way, same of that one needed by PT but higher energy!!



"voxel" phantom

(Zankl et al.)

"Best" shielding materials

- Liquid H_2
- Liquid CH_4
- Polyethylene (CH_2)
- H_2O
- Al—Inadequate shielding
- Pb

Best

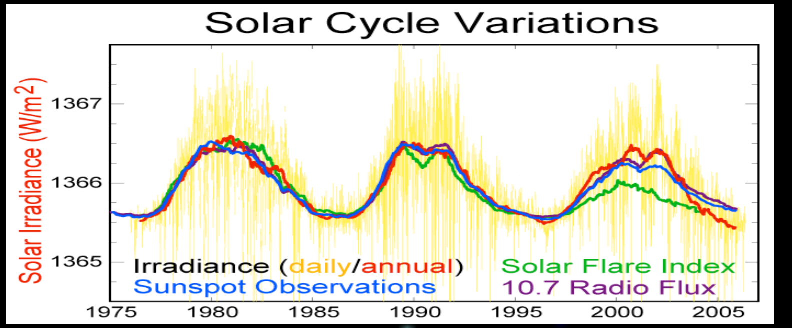
Potential range for new and multi-functional shielding materials: CH_4 adsorption on carbon forms; polymer composites; hydrides and hydride/carbon or hydride/polymer composites

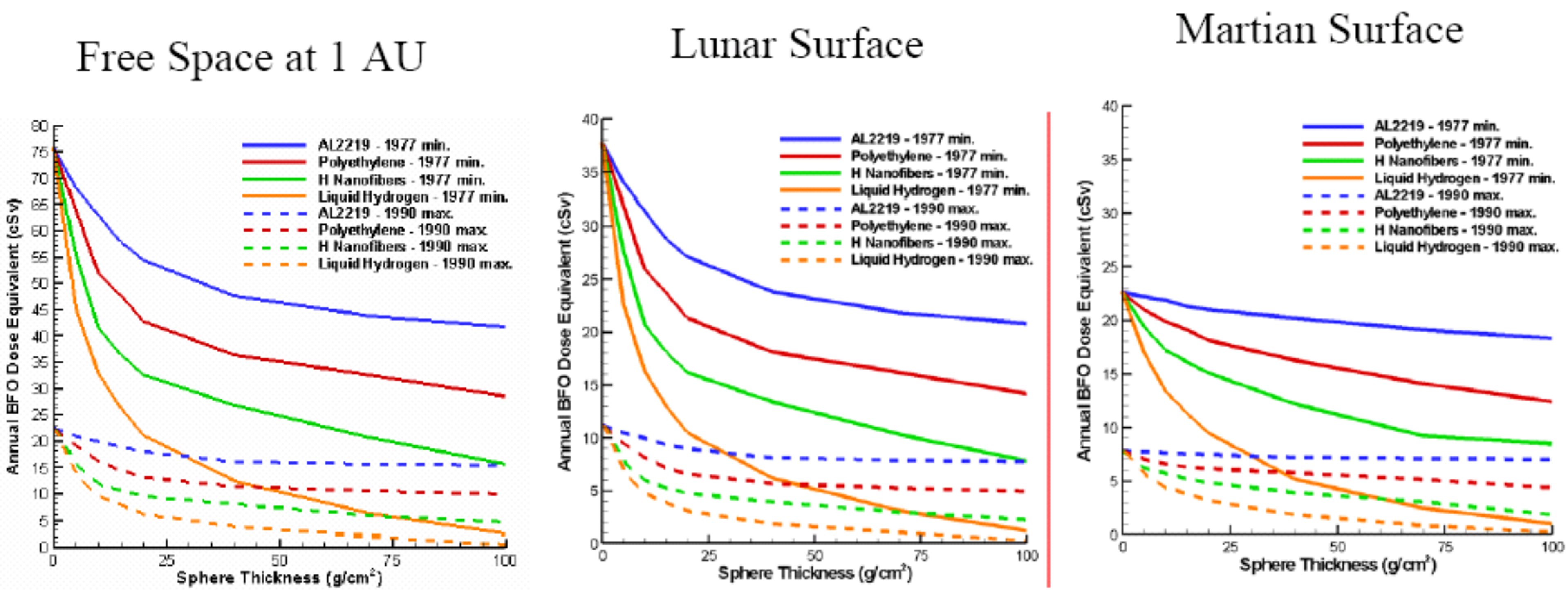
Trial and error approach based on measurements: no reliable data

Worst

Projectile interactions per unit target mass:
Ionization ~ Z/A (Bethe-Bloch formula)
Fragmentation ~ $A^{-1/3}$ (Bradt-Peters formula)

Is shielding a solution?





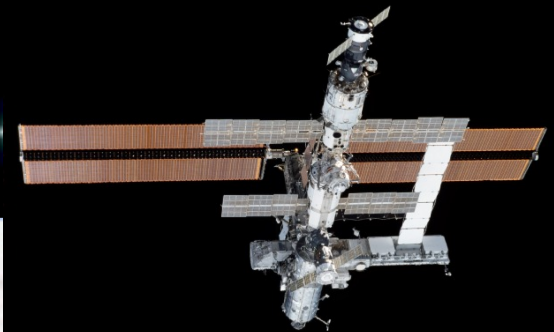
Max GCR dose reduction →

Aluminum ~ 30%

Polyethylene ~ 50%

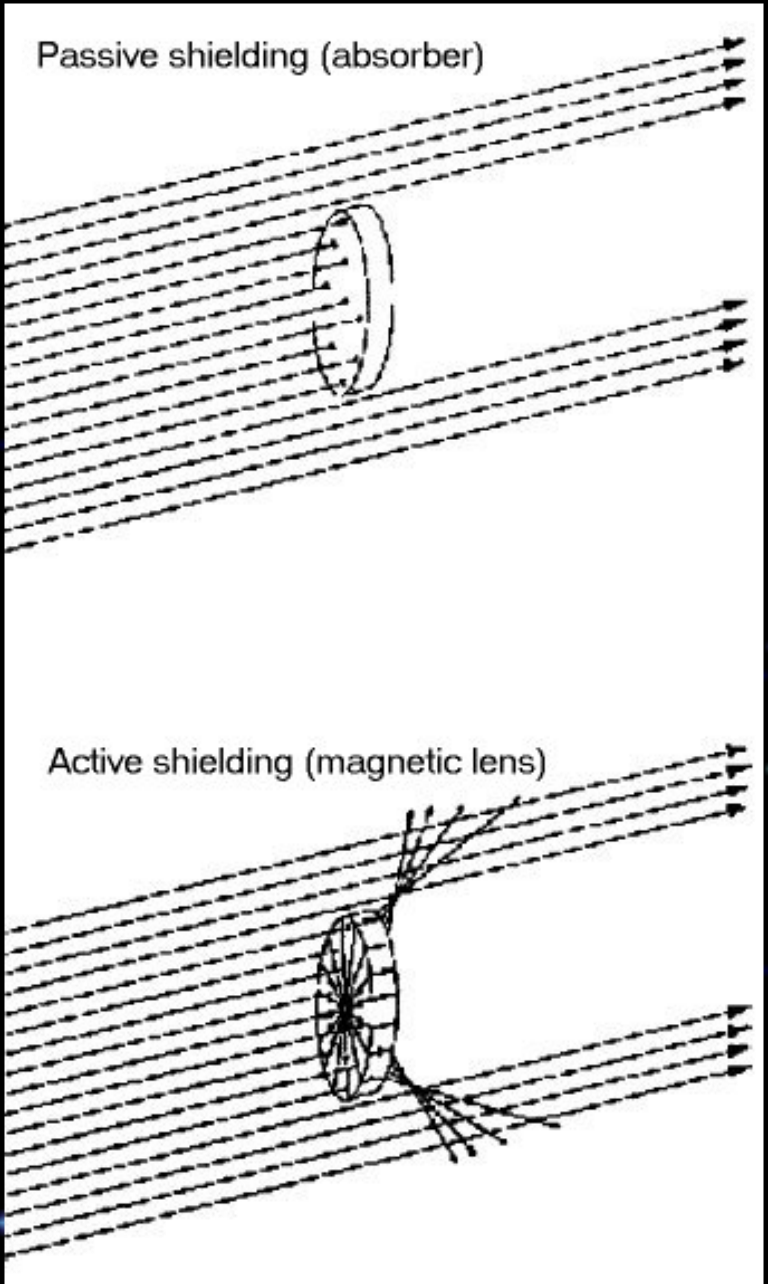
Liquid hydrogen ~ 90%

Shielding on ISS



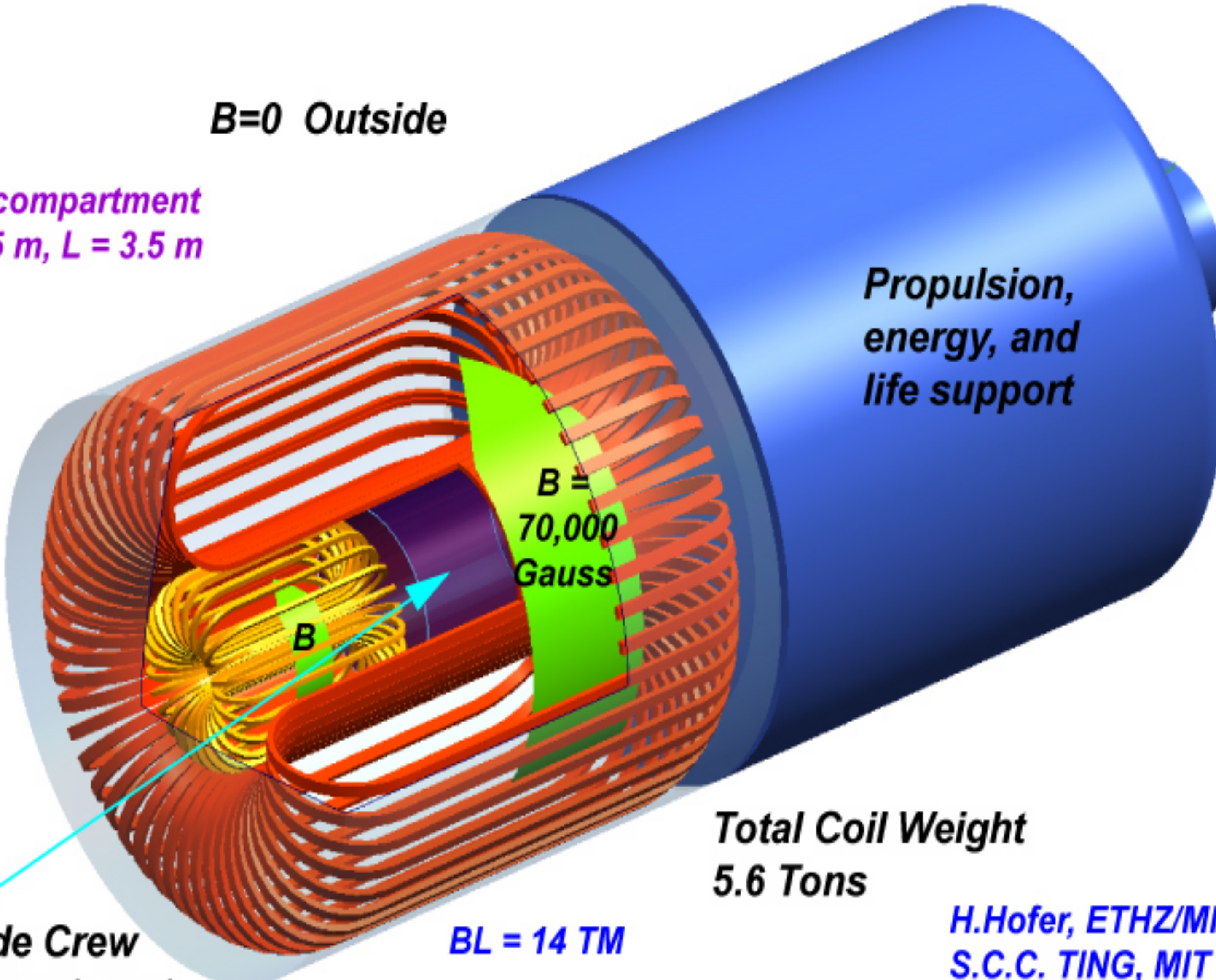
- Sleep station outfitted with PE and water
- Thin, flat panels are PE shields
- Stowage water packaging above the sleep station

Active shielding



- Earth’s magnetic field is effective in shielding SPE and GCR
- Unconfined magnetic fields represent an attractive possibility for space radiation shielding
- SPE are highly directional: superconducting magnetic lenses
- Toroidal or solenoidal?
- Effective for GCR?
- High-temperature superconductors may provide a large impact in this field

"Magnetic Faraday Cage" for Manned Flight to Mars



H.Hofer, ETHZ/MIT
S.C.C. TING, MIT

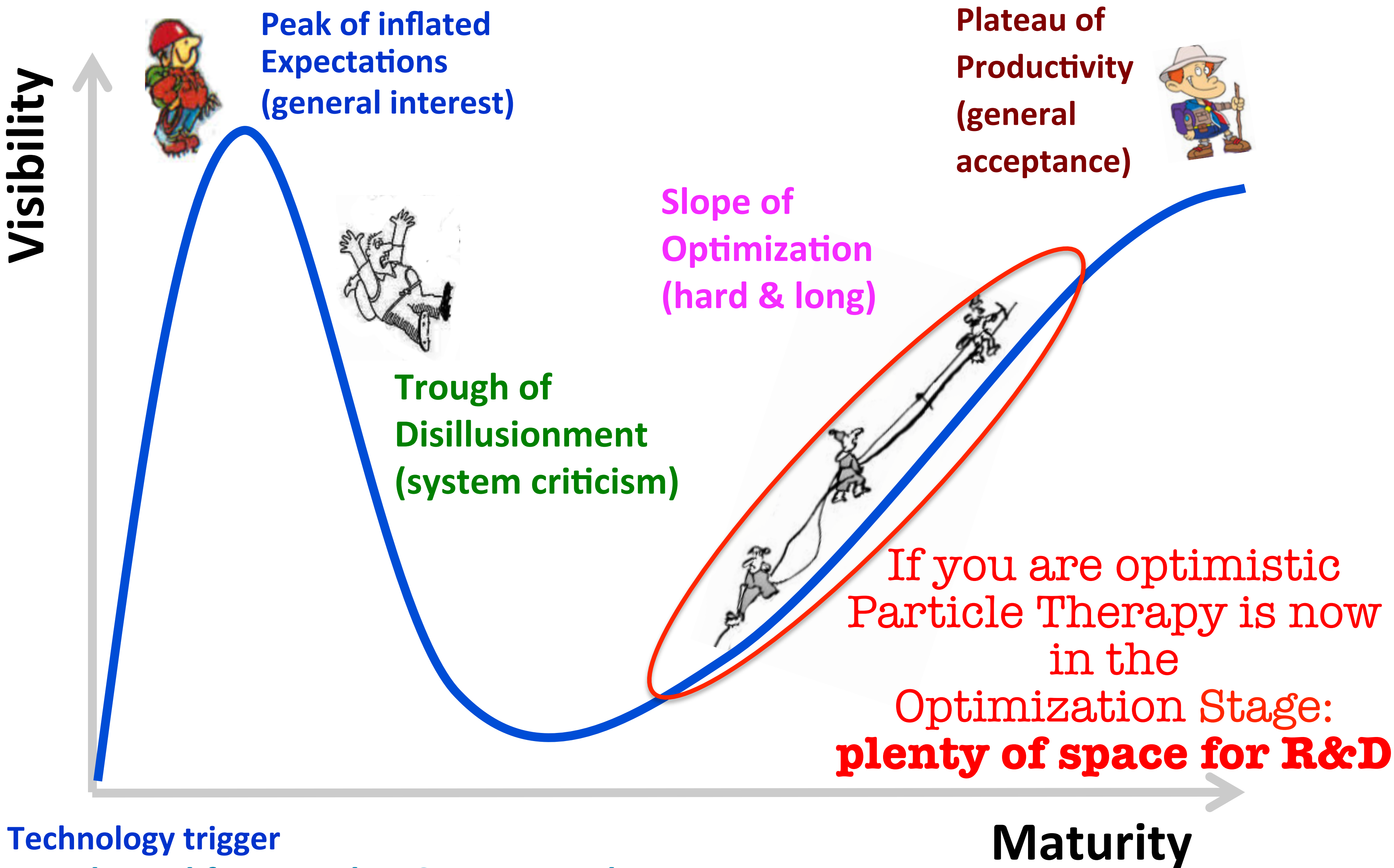
Summary & conclusions

- Particle therapy is becoming a new tool to help oncologist in the multi-approach war to cancer.
- The higly conformal dose release (all hadron) and the high biological efficency in killing tumor (light ions) gives new treatment possibilities for radio-resistant tumor or seated near organ at risk
- Nuclear fragmentation of the beam prevents the use of ions heavier then Oxygen and must be taken into account in the Treatment Planning System: the nuclear measurements go directly in the clinical practice

Summary & conclusions II

- Nuclear fragmentation of target can have an impact on the proton therapy: new measurement/experiment ongoing
- The nuclear interactions of the beam provide also a method to monitor the released dose, back-tracking the produced secondaries : γ from β^+ emitters, prompt photons from nuclear excitation and light charged fragments
- The radio protection in space (a show-stopper for human exploration of solar system) needs the same knowledge on fragmentation of light ion at intermediate energy of PT
- INFN is very active in the field: the building of a multimodal beam monitor device and of a new detector for the measurement of the cross section of interest have been both funded

Typical Hype Cycle for Innovation Technology



adapted from Becker & Townsend

Thanks….

CREDITS

I am in debt for a lot of slides, plots, comments, discussions and with many collegues…

M.Durante, G.Battistoni, K.Parodi, S.Rossi, A. Ferrari, U.Amaldi, F.Tommasino & many others…

Vincenzo Patera

Universita’ di Roma “La Sapienza” & INFN

Pisa 28 July 2017

Outline

Neutron production in PT and long term effect of the dose induced by neutrons on patient has been a long standing "hot" item in the querelle RT vs PT

(Short) Introduction to particle therapy

Proton beam & target fragmentation

Dose Release

Nuclear Interactions (fragmentation, excitation..)

Range Monitoring

Neutron production

Summary & conclusions

Radiotherapy and secondary cancers

Cancer survivors represent about 3.5% of US population

Second primary malignancies in this high-risk group accounts for about 16% of all cancers

Three possible causes:

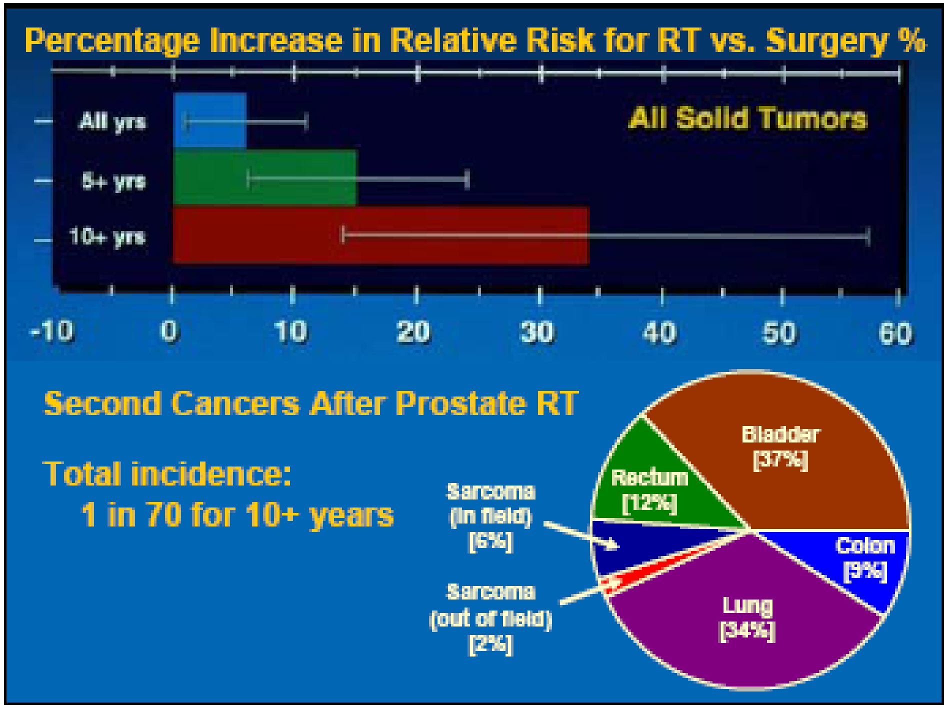
- Continuing lifestyle
- Genetic predisposition
- Treatment of the primary cancer

Assessment is difficult because of lack of controls

Prostate and cervix cancer: surgery is an alternative

Hodgkin's lymphoma: risk of breast cancer very high

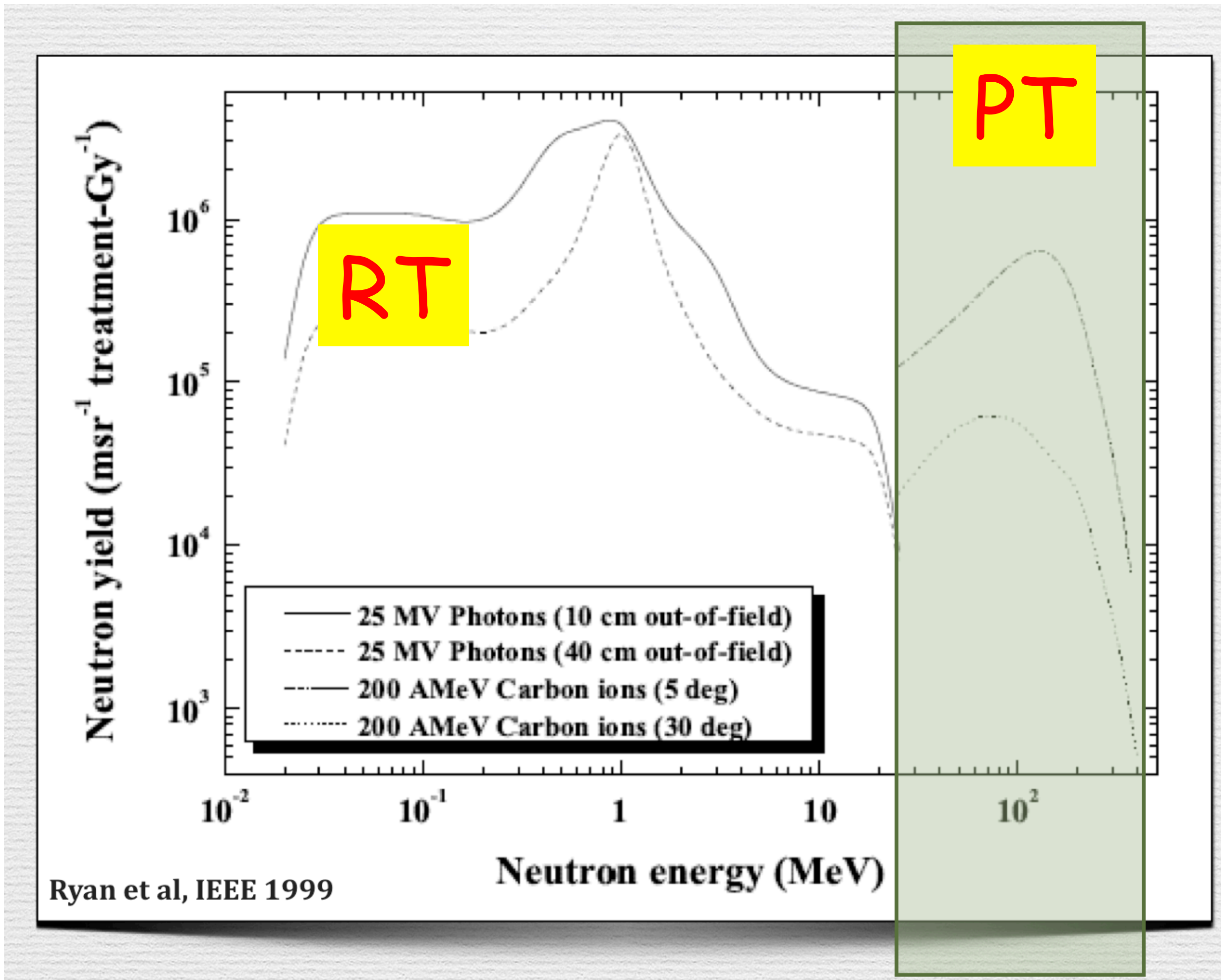
Radiation-induced secondary cancers are mostly carcinomas, but a sarcomas in heavily irradiated sites are also observed



Brenner *et al.*, *Cancer* (2000)

Courtesy M.Durante

Neutrons & Radio/Proton/Carbon therapy



The expected neutron flux dominates, by orders of magnitude, the total secondary flux nearly at all energies.

Neutrons produced by the beam in PT treatments are mainly fast neutrons [20-200 MeV]

Degradation by scattering with patient/materials produces large flux of slow neutrons.

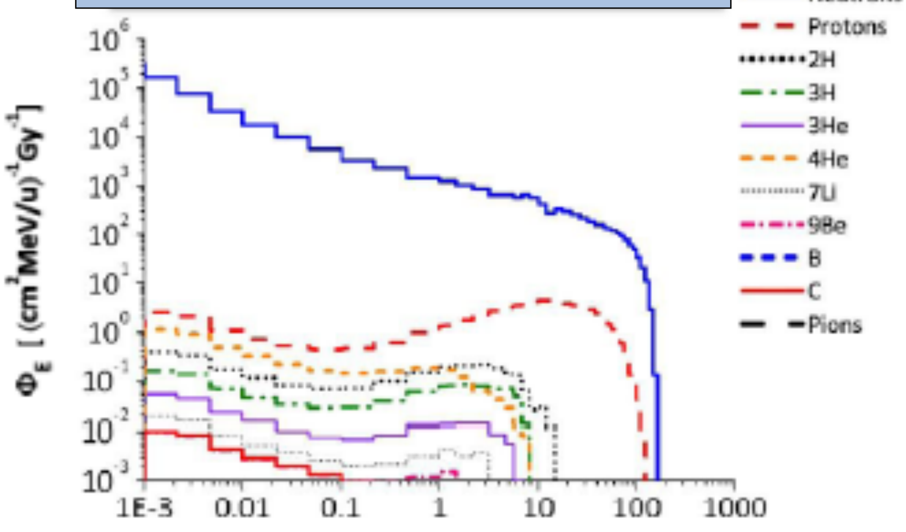
Neutron quest… old saga!

- ✓ Accurate measures of n production X-section by p,^{12}C beam on needed materials (O,C), with angle and energy distribution, is still missing.
- ✓ Due to their intrinsic detection efficiency, neutron on line monitoring during PT is particularly difficult, (no directionality, scattering from environment, probabilistic releas of energy, PID?, etc..)

172 MeV Proton beam

Hultqvist and Gudowska, PMB 55,2010

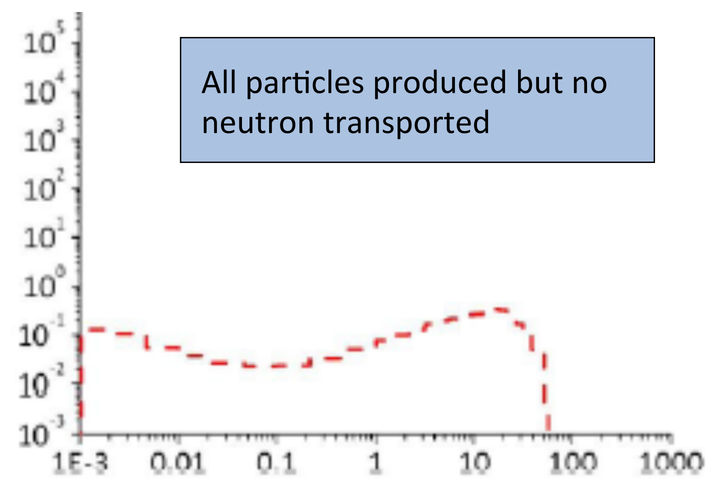
All particles produced and transported



Energy (MeV/u)

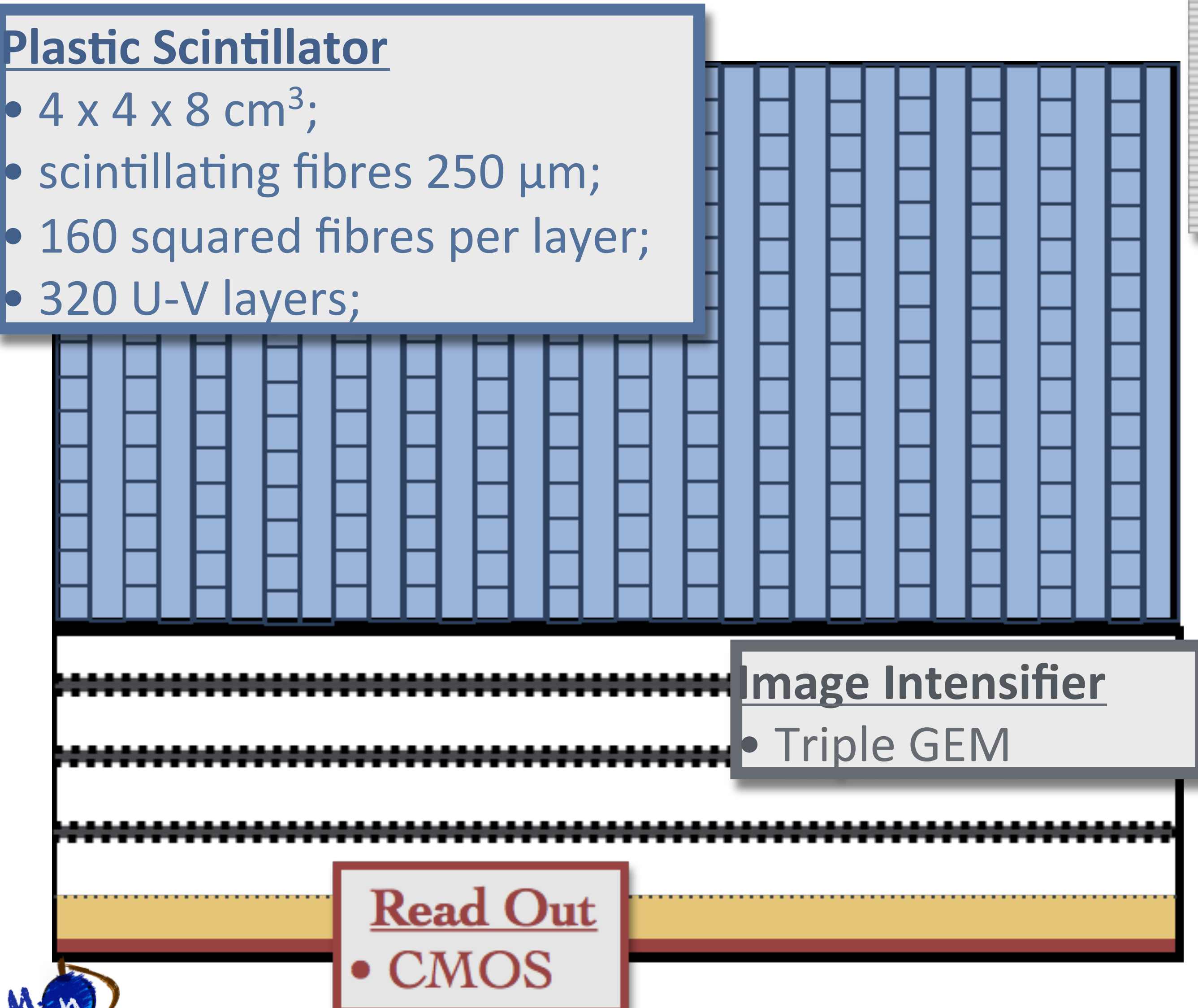
Gonads ~12 cm from target
Particles flux

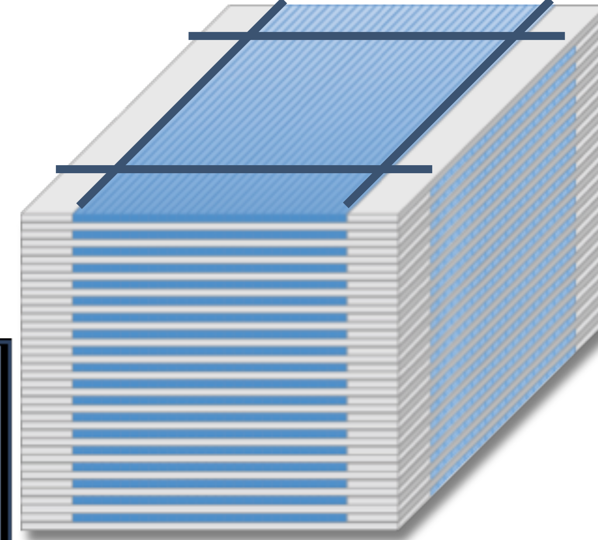
All particles produced but no neutron transported



Energy (MeV/u)

MOnitor for Neutron Dose in hadrOntherapy



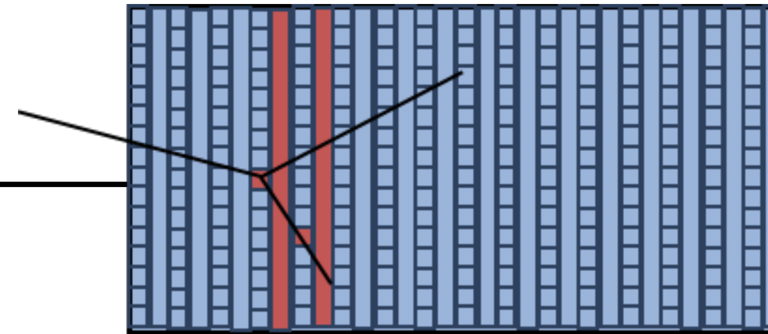


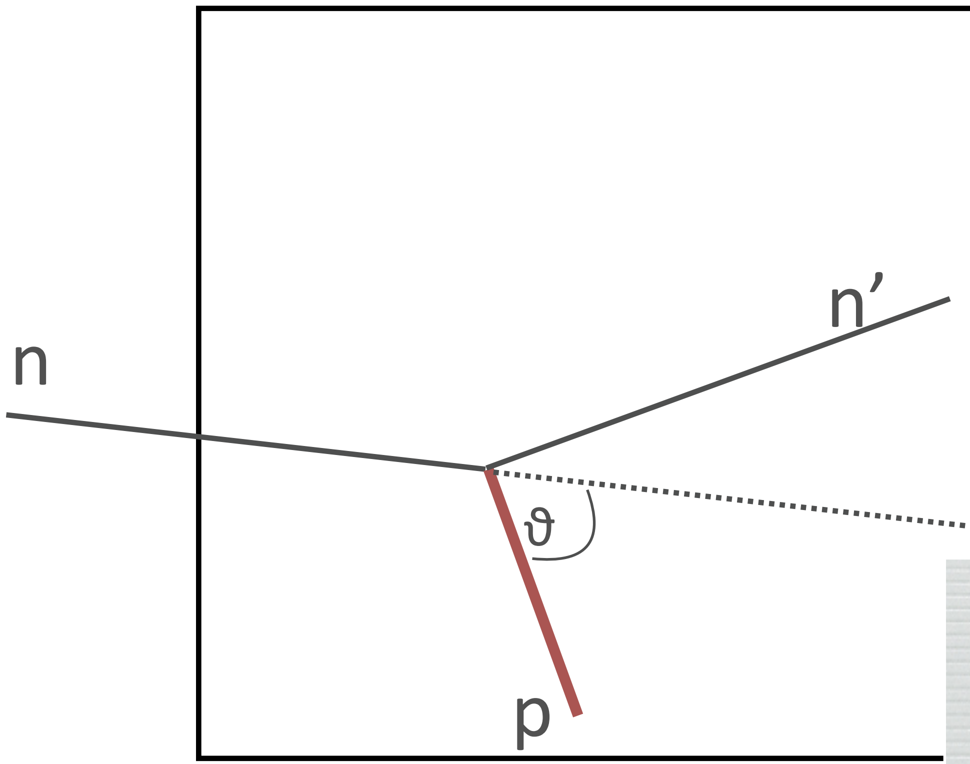
TRACKING the neutron !!

- Tracking device for 20:300 MeV neutrons
- Efficiency in 10^{-2} – 10^{-3} range
- Funded by MIUR (PRIN) +INFN Young Grant (2016-2018)

MONDO

Impinging neutron kinematic from double n-p elastic scattering on fiber



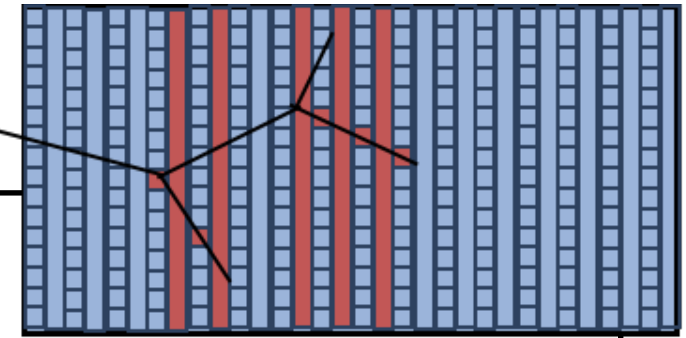


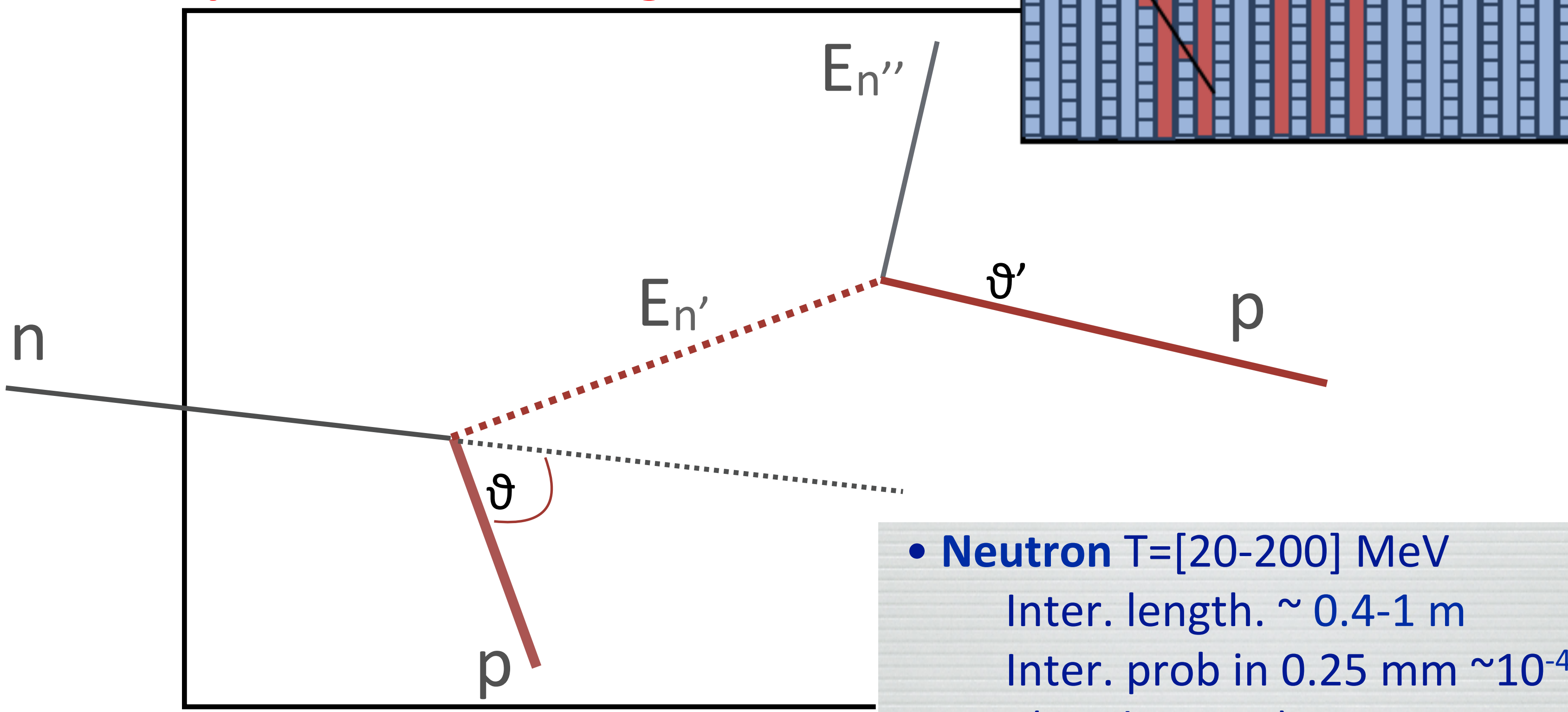
- **Neutron** T=[20-200] MeV
  - Inter. length. ~ 0.4-1 m
  - Inter. prob in 0.25 mm ~10^{-4}
  - P(single scatt.) ~ 7%
- **Proton range**
  - T = 100 MeV=> 8 cm
  - T = 50 MeV=> 2 cm
  - T = 30 MeV=> 1 cm
  - T = 10 MeV=> 0.1 cm

Single hit resolution:
E_{kin} = 10 -100 MeV => 7-20 %
40 hit/cm sampling
Read out by SPAD (digital SiPM)

MONDO

Impinging neutron kinematic from double n-p elastic scattering on fiber





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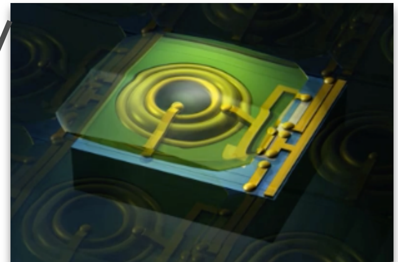
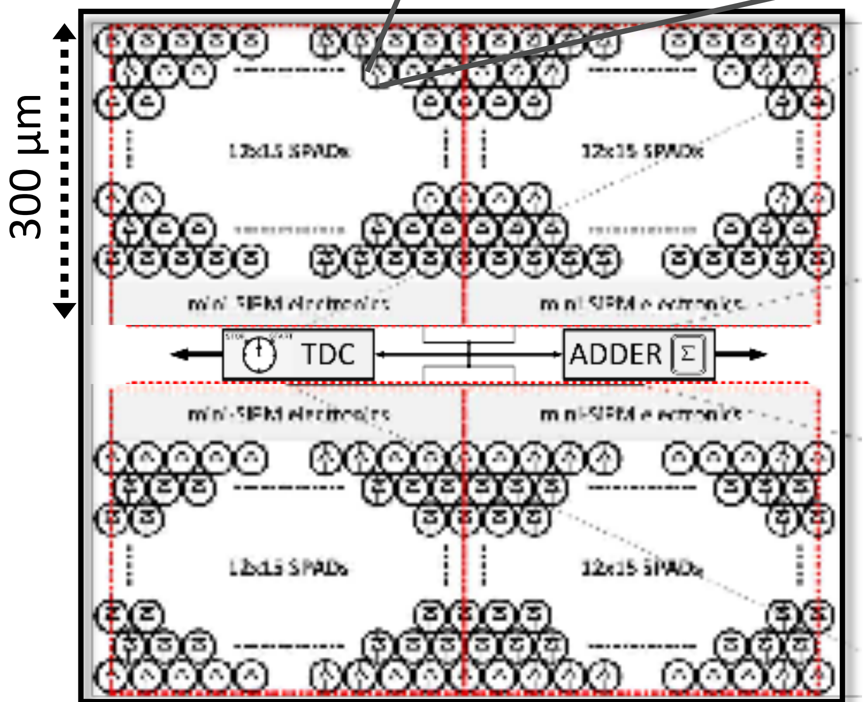
Read out by SPAD (digital SiPM)

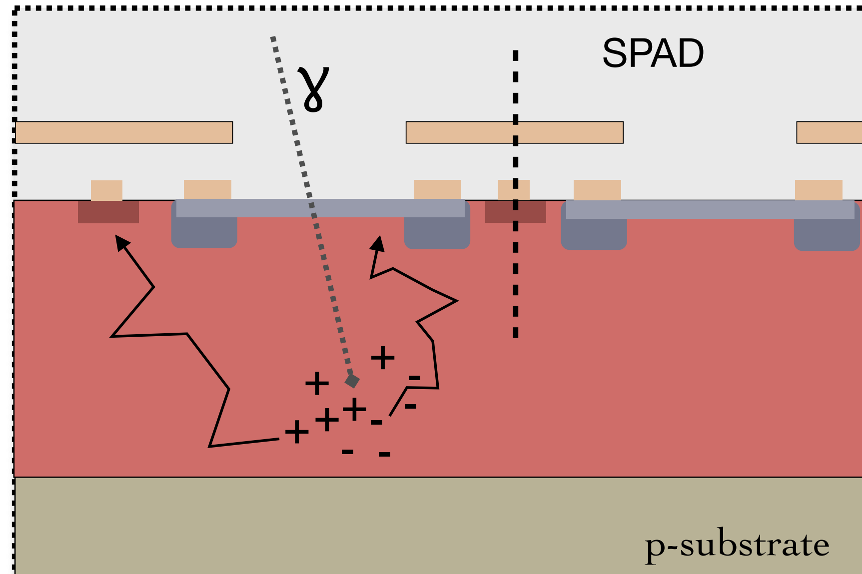
MOnitor for Neutron Dose for hadrOntherapy

SPAD Matrix prototype: digital output of the # of SiPM fired in 10 ns





Photon ReadOut



- integrated TDC (resolution ~65 ps)
- self triggered sensor
- pixel 600 μm (-> 300 μm)

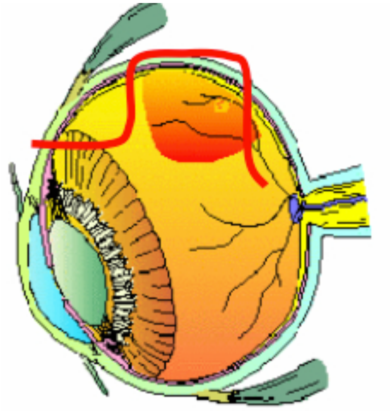
Development of the sensor in collaboration with FBK (Trento)

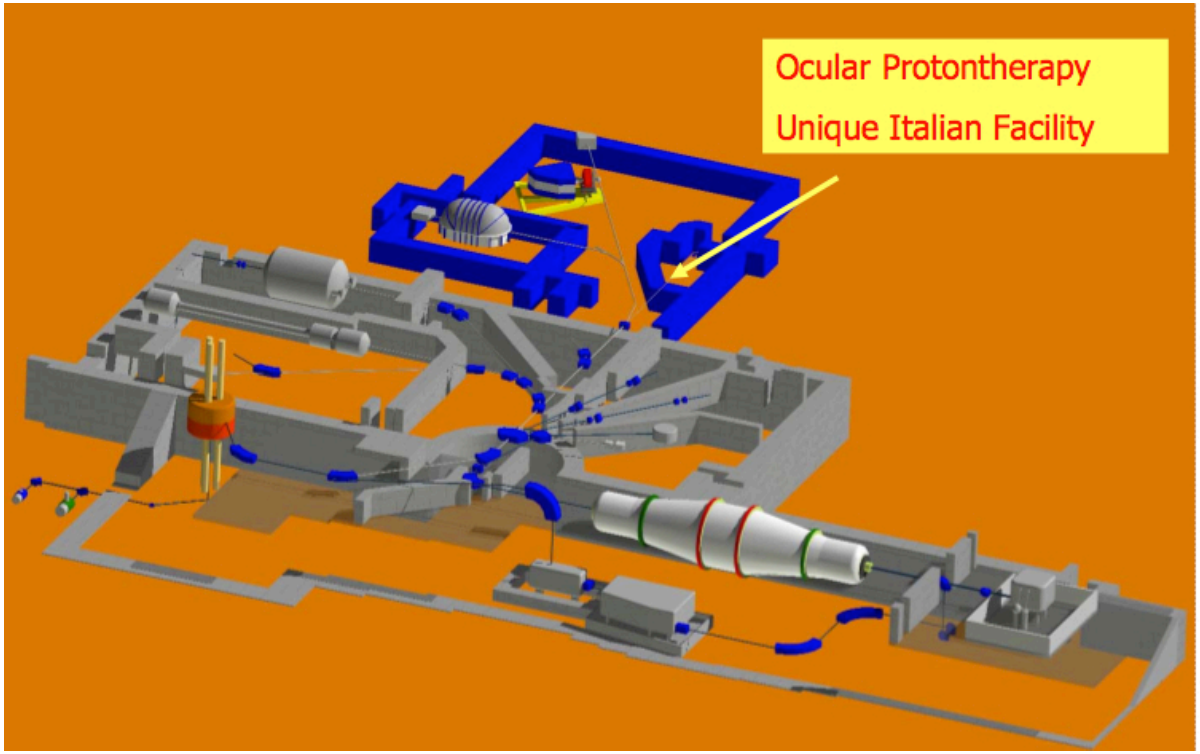
INFN & hadrontherapy
CATANA @LNS

Proton 80MeV beam

Treatment of the choroidal and iris Melanoma.

In Italy about300 new cases/year

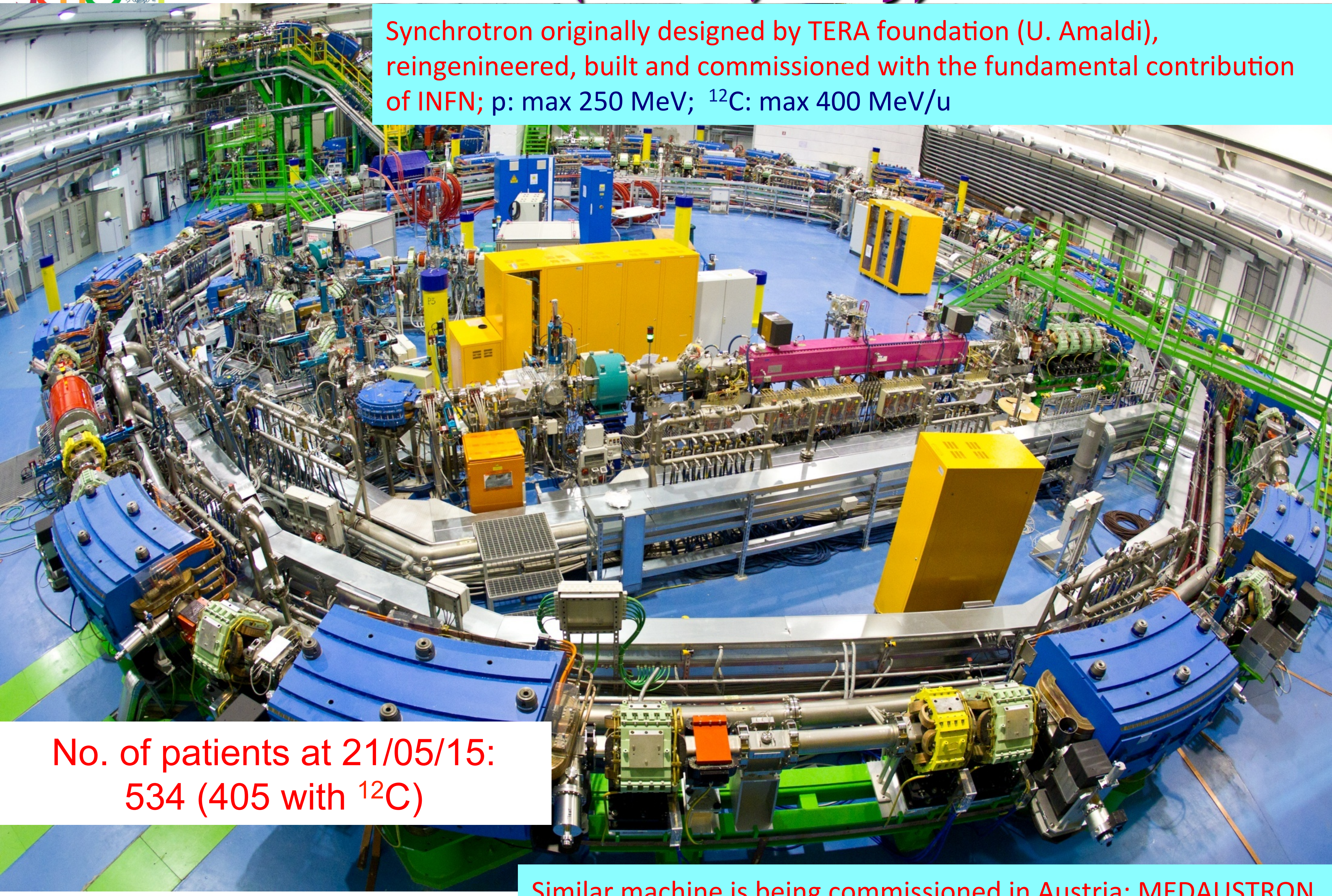




Centro di AdroTerapia ed Applicazioni Nucleari Avanzate

CNAO (Pavia, Italy)

Synchrotron originally designed by TERA foundation (U. Amaldi), reingenineered, built and commissioned with the fundamental contribution of INFN; p: max 250 MeV; ^{12}C: max 400 MeV/u

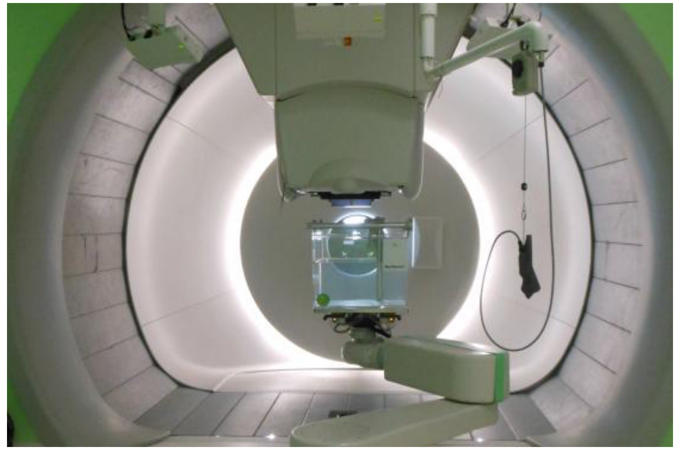


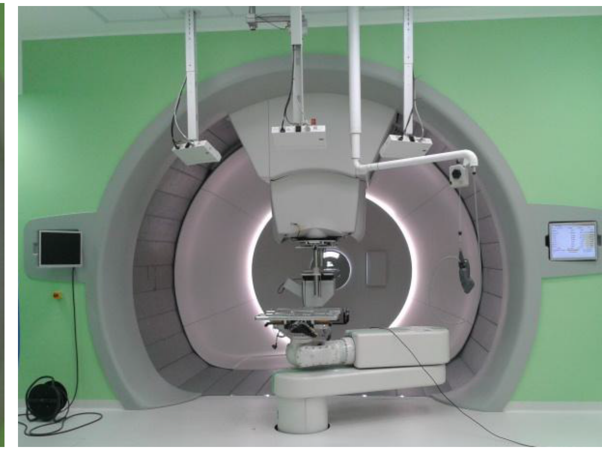
No. of patients at 21/05/15:
534 (405 with ^{12}C)

Similar machine is being commissioned in Austria: MEDAUSTRON

New Proton Therapy in Trento (Italy)

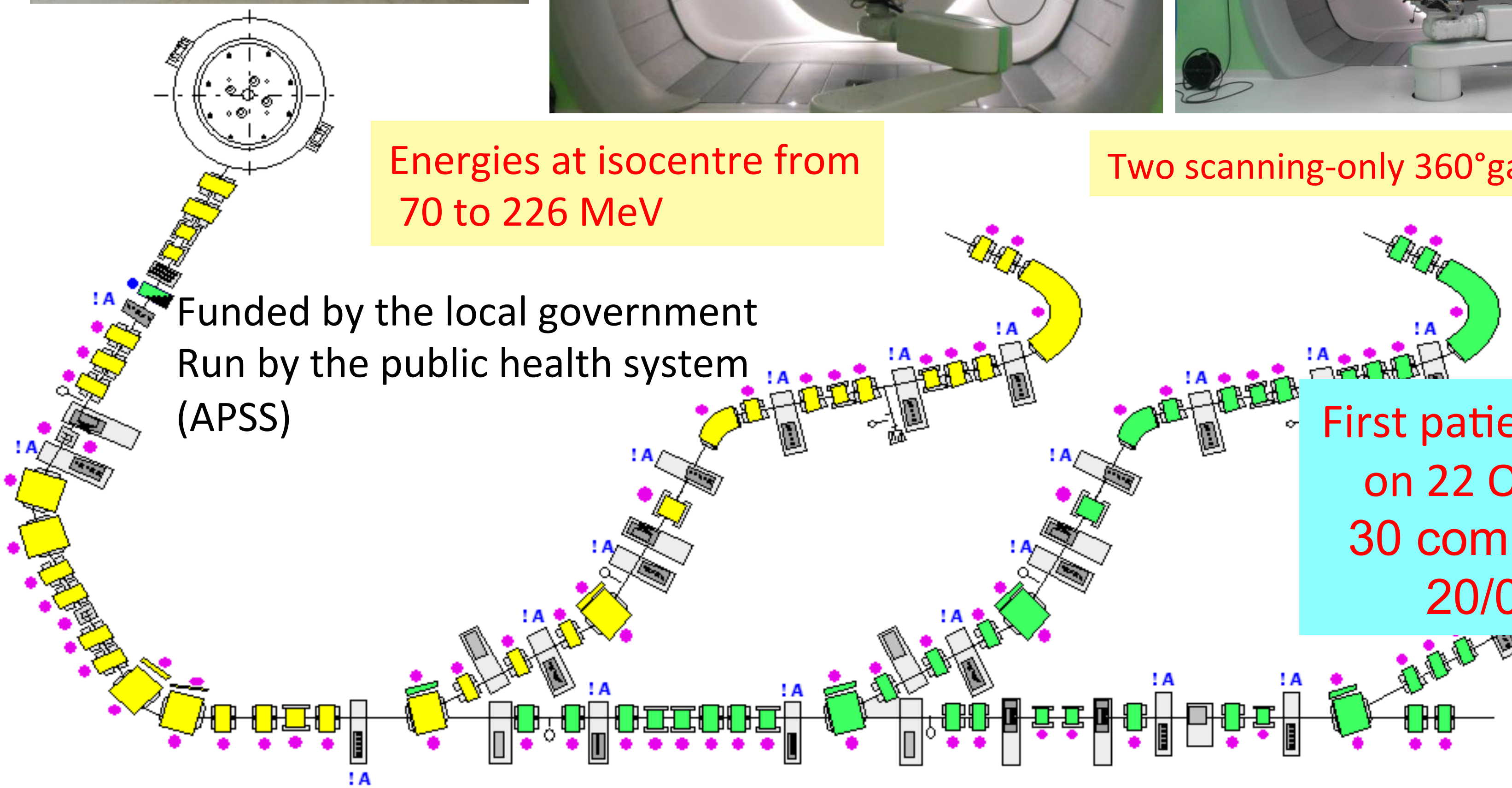
2D imaging in one gantry room Ct on rail being installed in the second gantry room





Energies at isocentre from 70 to 226 MeV

Two scanning-only 360°gantries

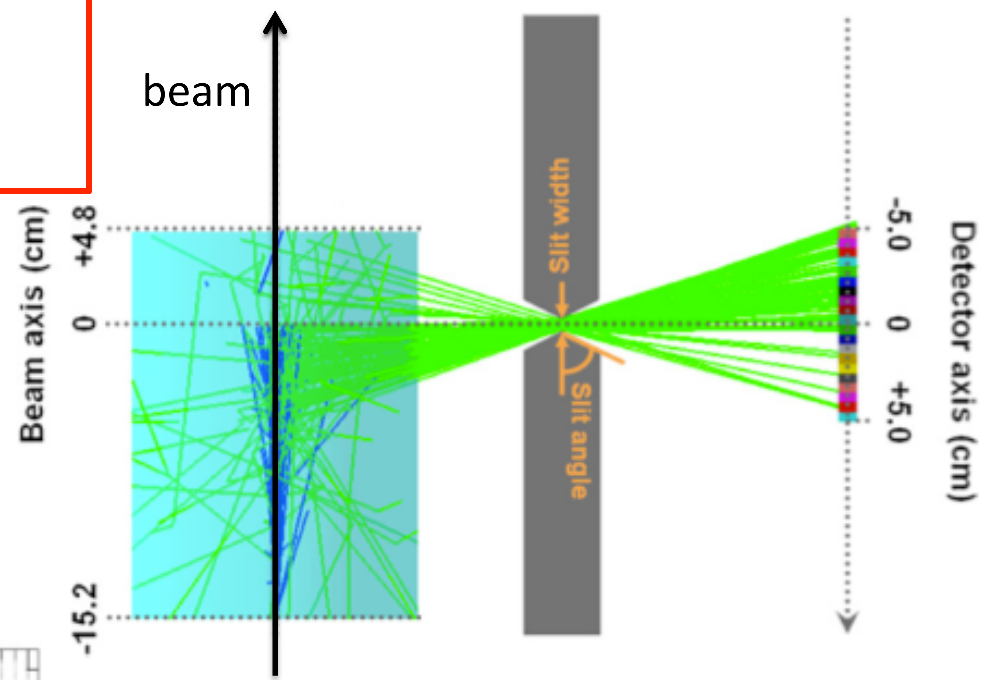


Funded by the local government
Run by the public health system (APSS)

First patient treated on 22 Oct. 2014
30 completed at 20/05/15

spares

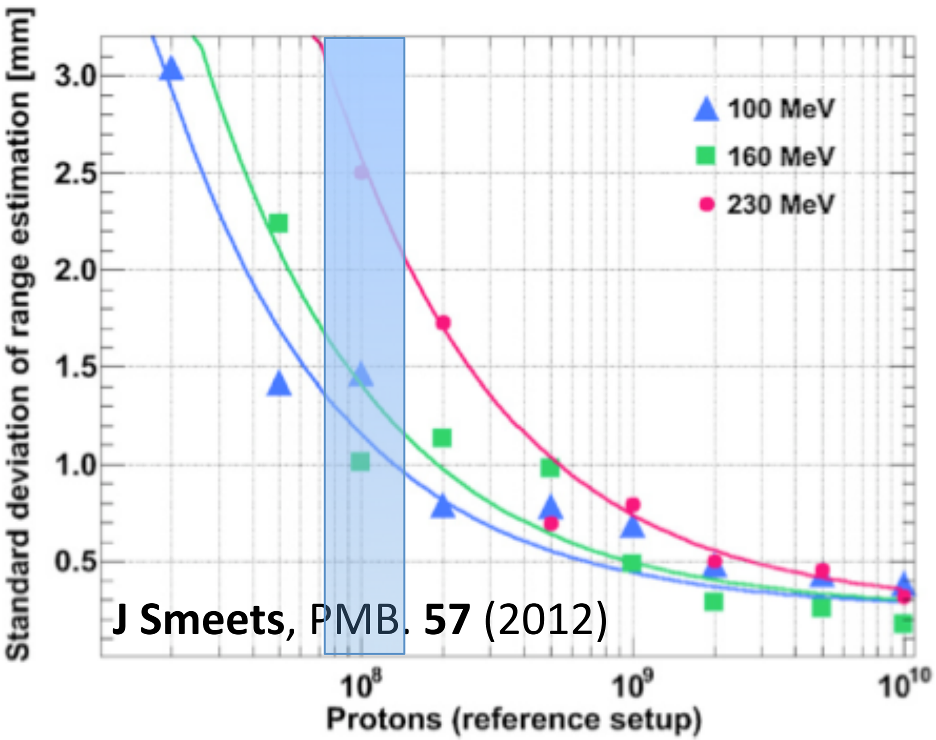
Range monitor for proton beam: the slit camera



Optimized on proton beam

Several groups working also on:

- electronic collimated (Compton) camera
- Multi-slit collimated camera



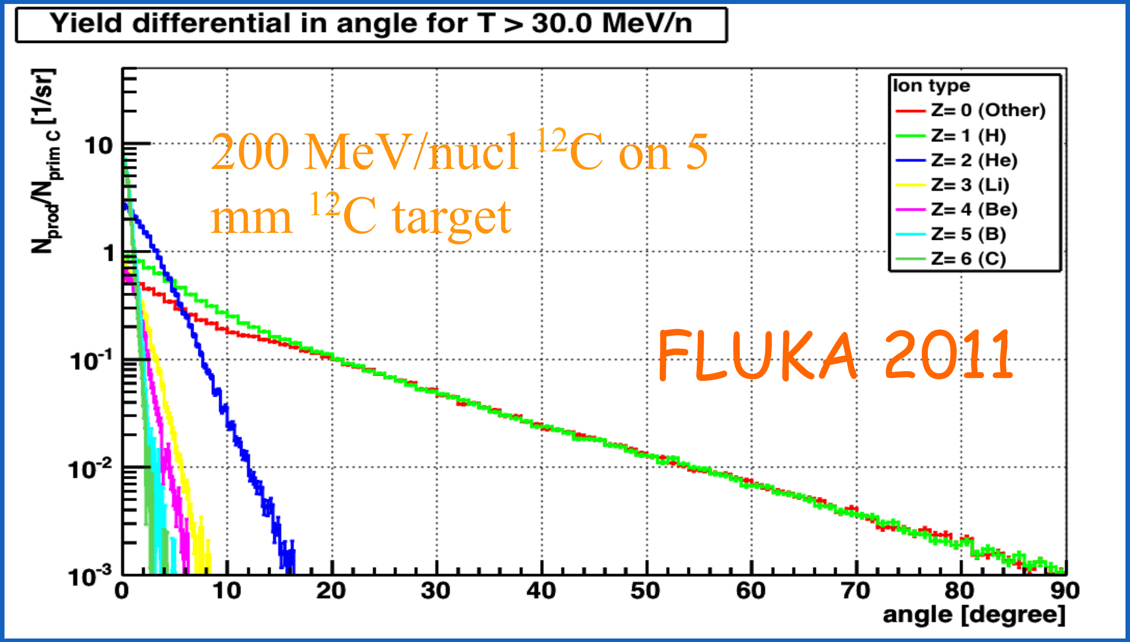
J Smeets, PMB. **57** (2012)

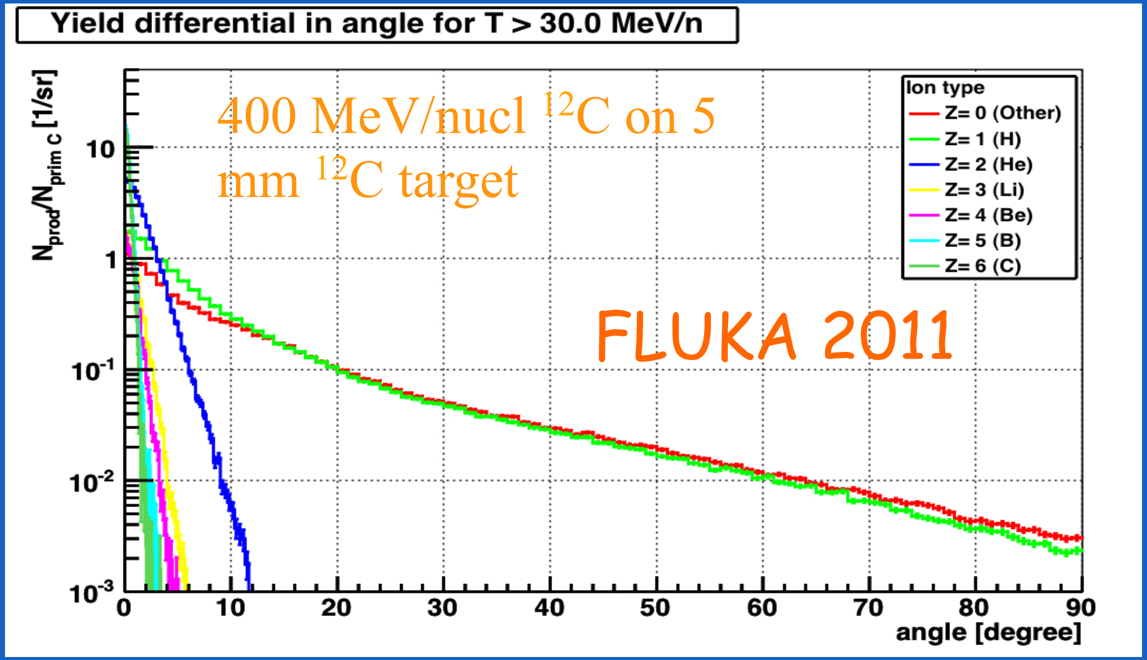
Possible clinical solution envisaged for proton beam, but what about heavier beam (^{12}C) ? LET grows as Z^2 and the nuclear interaction increase with A. Thus, for the given dose, ^{12}C gives:

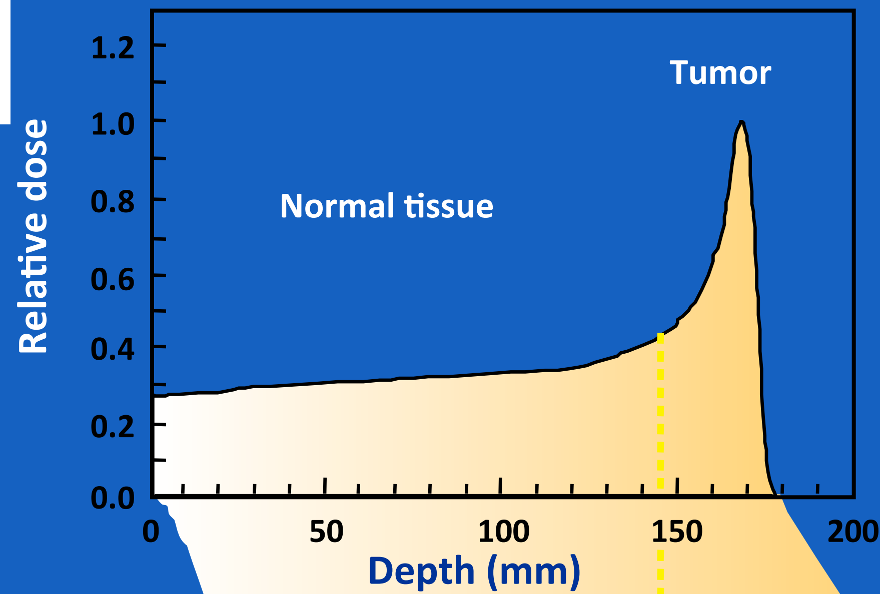
- less prompt γ than proton
- more background than proton

What MC tell us about fragments: ^{12}C before the BP

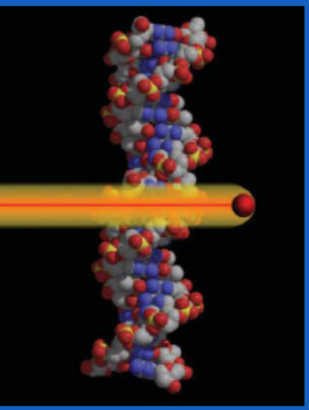
- The Z>2 fragment are well collimated in the forward direction
- The protons are emitted also at large angle
- The protons could be a possible candidate for beam imaging… if they can escape the patient!! (E_{kin} >100 MeV)







Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low
Angiogenesis	Increased	Decreased
Cell migration	Increased	Decreased



Durante & Loeffler,

Nature Rev Clin Oncol 2010

Potential advantages

- High tumor dose, normal tissue sparing
- Effective for radioresistant tumors
- Effective against hypoxic tumor cells
- Increased lethality in the target because cells in radioresistant (S) phase are sensitized
- Fractionation spares normal tissue more than tumor
- Reduced angiogenesis and metastatization

Courtesy M.Durante

Frag meas: thick target

A lot of integral measurements measurements are already around..

Projectile	Energy[MeV/N]	Target	
^{4}He	100, 180	C, Al, Cu, Pb	
^{12}C	100, 180,400	C, Al, Cu, Pb	
^{20}Ne	100, 180,400	C, Al, Cu, Pb	
^{28}Si	800	C, Al, Cu, Pb	HIMAC by Kurosawa et al.
^{40}Ar	400	C, Al, Cu, Pb	
^{56}Fe	400	C, Al, Cu, Pb	
^{126}Xe	400	C, Al, Cu, Pb	
^{20}Ne	337	C, A, Cu and U	BEVALAC by Schimmerling et al.
^{93}Nb	272	Al, Nb	BEVALAC by Heilbronn et al.
^{93}Nb	435	Nb	
^{4}He	155	Al	NSRL by Heilbronn et al.
^{12}C	155	Nb	
^{4}He	160	Pb	SREL by Cecil
^{4}He	180	C, H_2O, steel, Pb	
^{12}C	200	H_2O	GSI by Günzert-Marx et al.
^{12}C	400	H_2O	GSI by Haettner et al.

Tentative & incomplete list

Courtesy of M. Durante

Frag meas: thin target

A lot of measurements on thin target are already around.. but not wrt angle and energy

Projectile	Energy[MeV/N]	Target	
^{4}He	135	C, Poly, Al, Cu, Pb	
^{12}C	135	C, Poly, Al, Cu, Pb	RIKEN by Sato et al.
^{20}Ne	135	C, Poly, Al, Cu, Pb	
^{40}Ar	95	C, Poly, Al, Cu, Pb	
^{12}C	290, 400	C, Cu, Pb	
^{20}Ne	400, 600	C, Cu, Pb	HIMAC Iwata et al.
^{40}Ar	400, 560	C, Cu, Pb	
^{4}He	230	Li, C, CH_2, Al, Cu, Pb	
^{14}N	400	Li, C, CH_2, Al, Cu, Pb	
^{28}Si	600	Li, C, CH_2, Al, Cu, Pb	HIMAC Heilbronn et al.
^{56}Fe	500	Li, C, CH_2, Al, Cu, Pb	
^{86}Kr	400	Li, C, CH_2, Al, Cu, Pb	
^{126}Xe	400	Li, C, CH_2, Al, Cu, Pb	

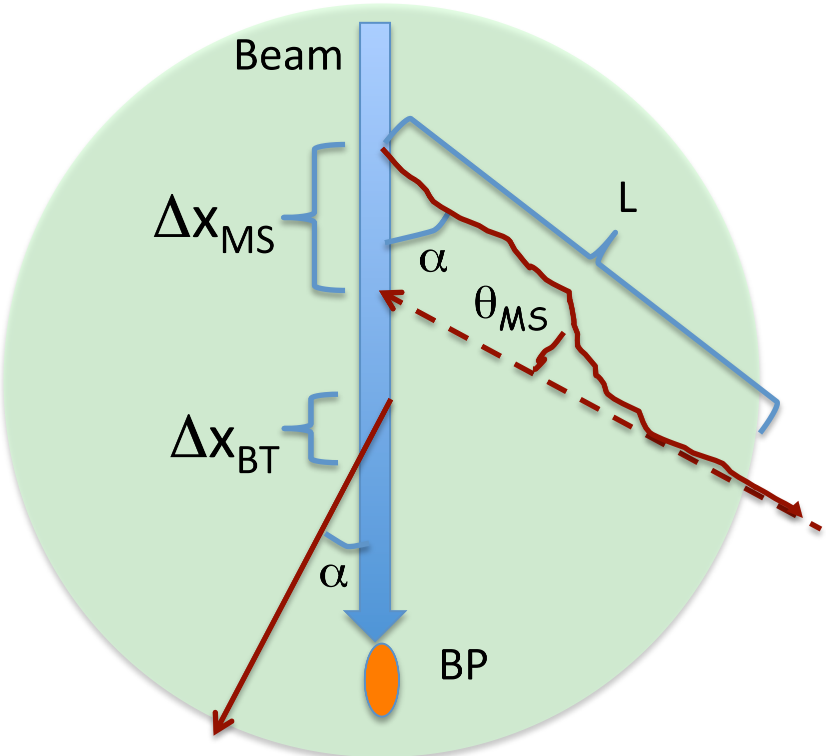
Tentative & incomplete list

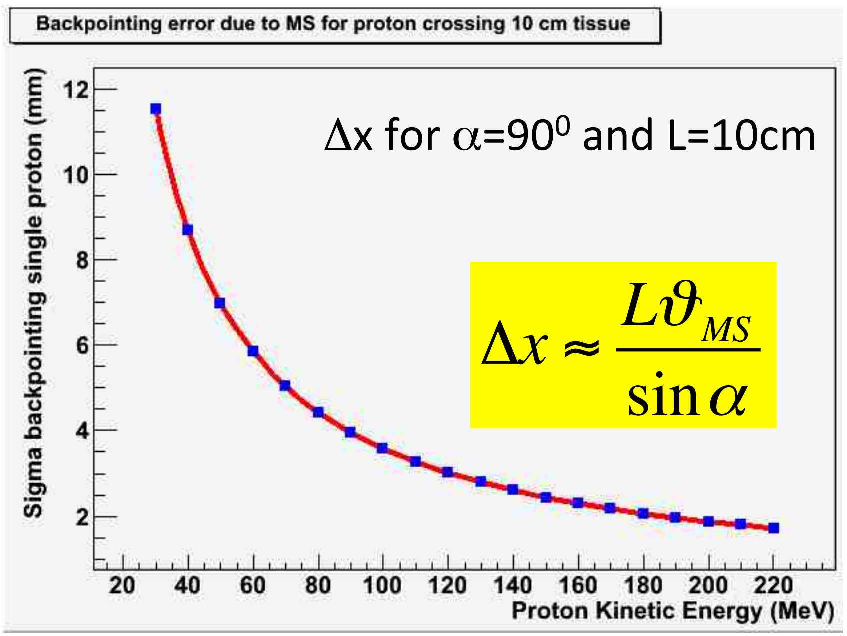
Courtesy of M. Durante

only with detectors at 0°!

detector: which & where?

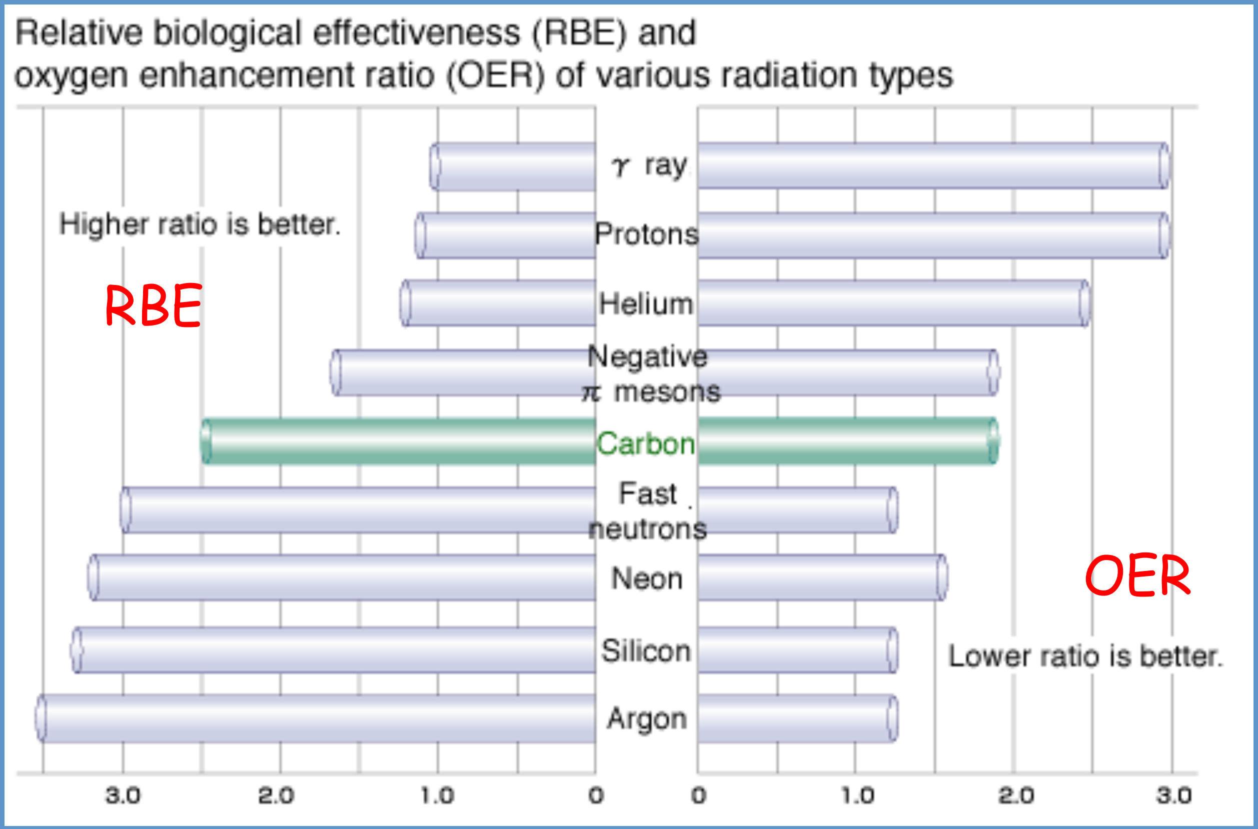
Any large area tracking detector!! The resolution of the back-tracking is limited by the multiple scattering in the patient, not by the detector resolution..

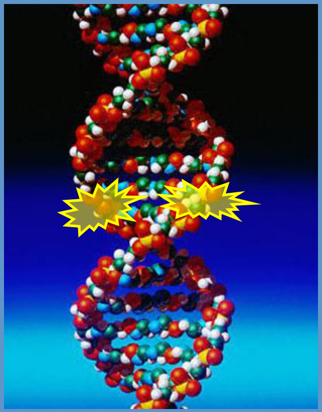




Small angle	Large angle
• higher momentum -> less MS • Higher statistic • Back-tracking is much worse	• Optimal back-tracking • lower momentum -> more MS • Less statistics

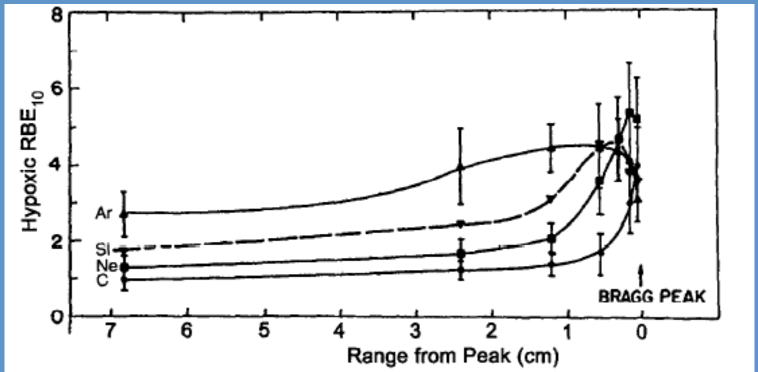
Radiations vs Biological effects





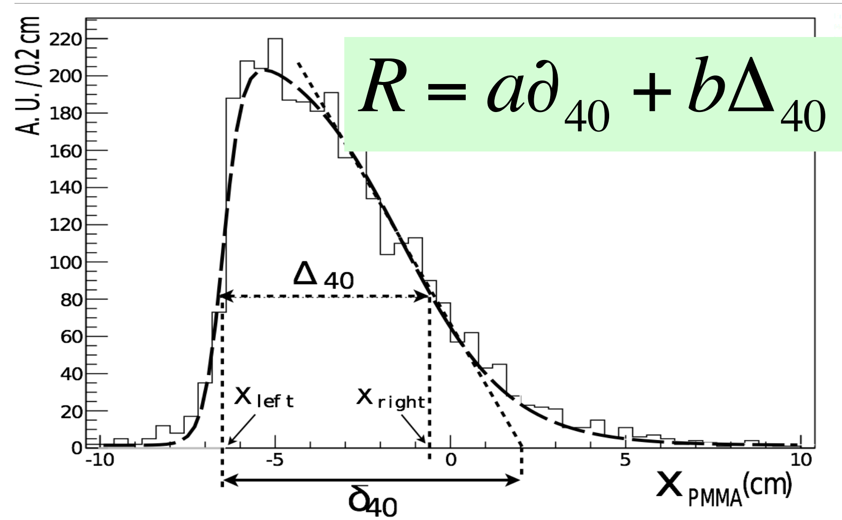
^{12}C -> good compromise between RBE and OER.

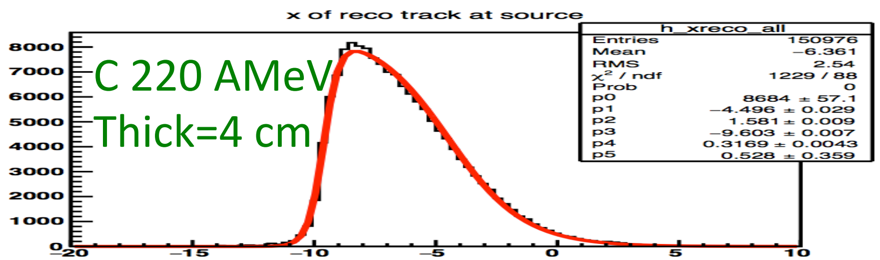
Optimal RBE profile vs penetration depth position.

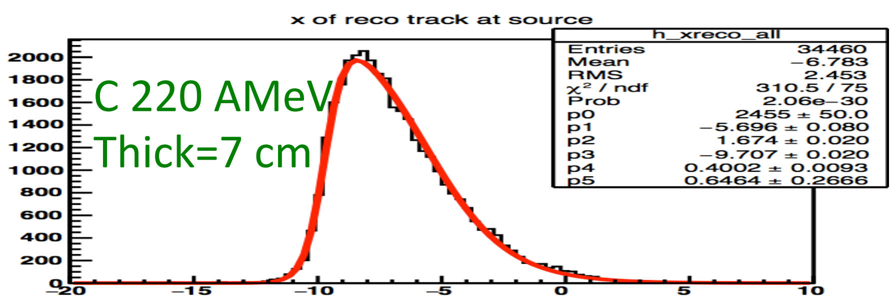


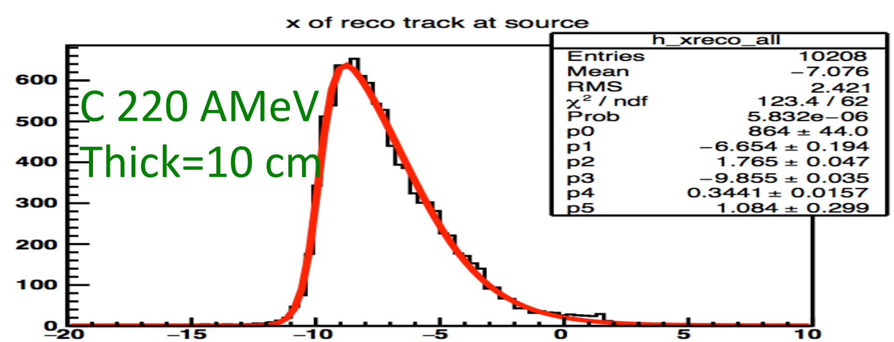
BP vs thickness

The reconstructed emission shape can be calibrated to retrieve a BP estimate (almost) insensible to the thickness

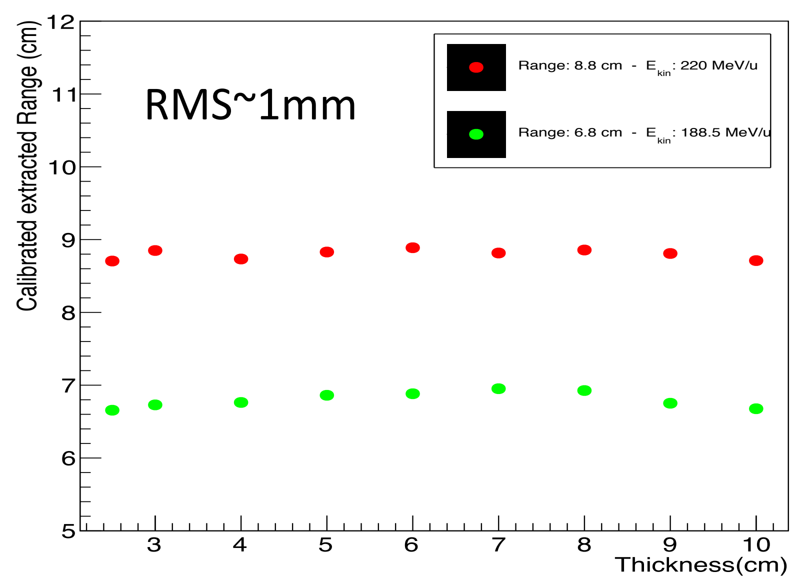








A linear combination of the emission shape parameters ("calibrated range") is constant wrt the "patient "thickness crossed:



Fragments Charge ID techniques

Standard techniques exploit the de/dx measurement (ΔE), calorimetric E measurement, Time of Flight (β) measurement, magnetic momentum (p) measurement

All this measurement are closely related with the particle identification (PID)

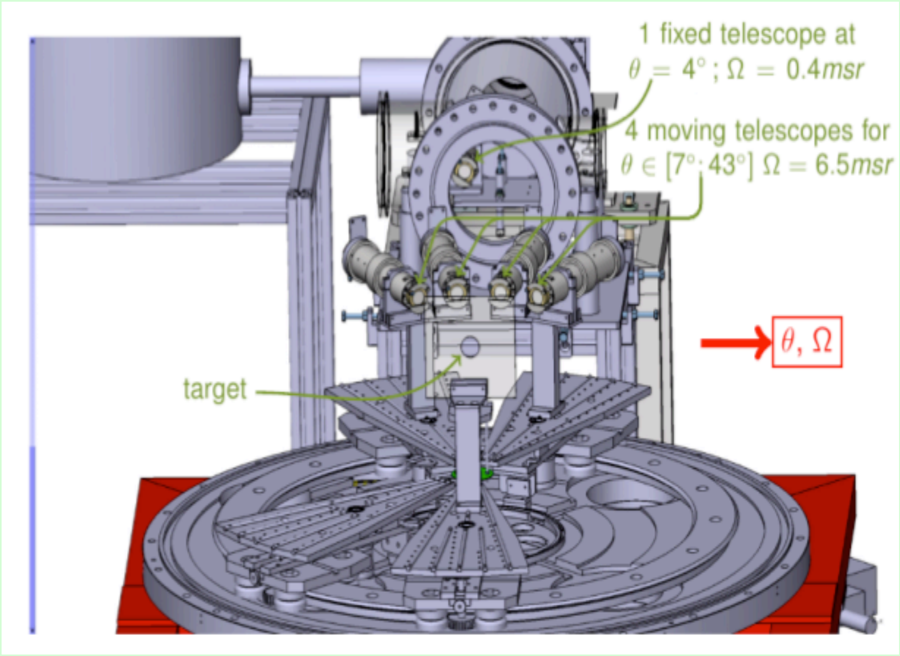
- ΔE vs E -> PID
- ΔE measurement provided PID -> E
- ToF (β) measurement provided PID -> E
- Very different De/Dx !! Need for large dynamic range detectors

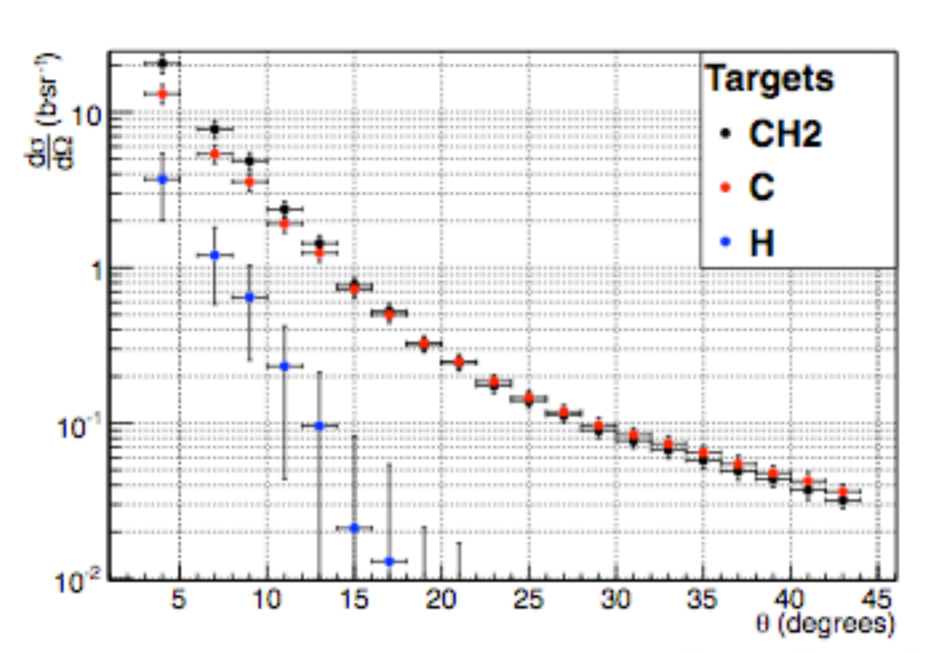
particle	Ekin/nucl (MeV)	De/dx (MeV/cm)	Range (cm)
proton	200	4.6	25.9
proton	100	7.4	7.6
He	200	18	25.6
He	100	29	7.6
Be	200	70	13.5
Be	100	114	4.4
Carbon	200	155	9.4
Carbon	100	259	2.5

C-H X-section extraction: ^{12}C beam on C,CH_2 target @ 95AMeV

GANIL experiment of C-C fragmentation. Obtained results for Single and Double Diff. X Section.

- interesting conclusion: X-sections for composite targets can be deduced from the cross sections of elemental targets (-> organic tissues)
- Systematics???

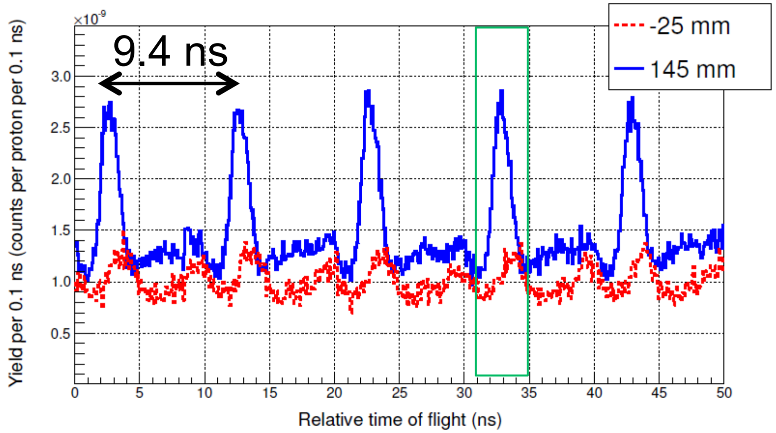


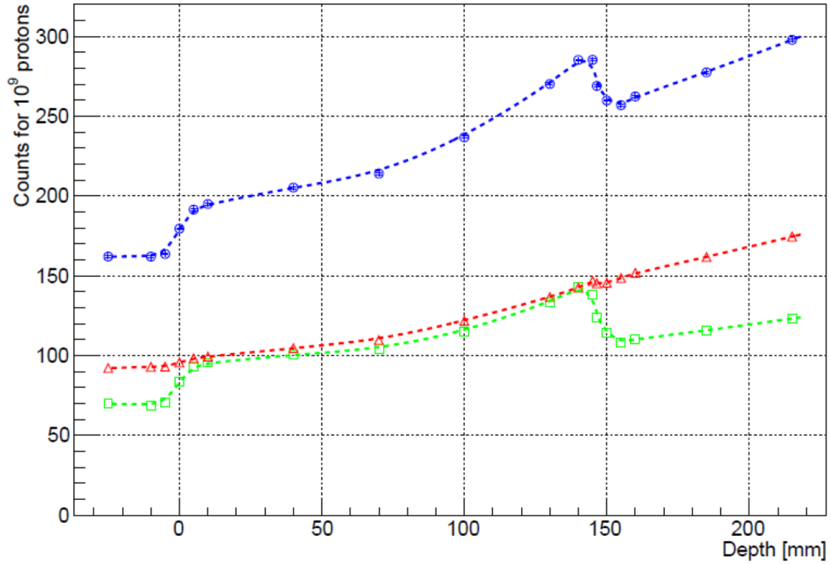


Courtesy of M. Labalme

Influence of TOF on PG profiles (collimated cameras)

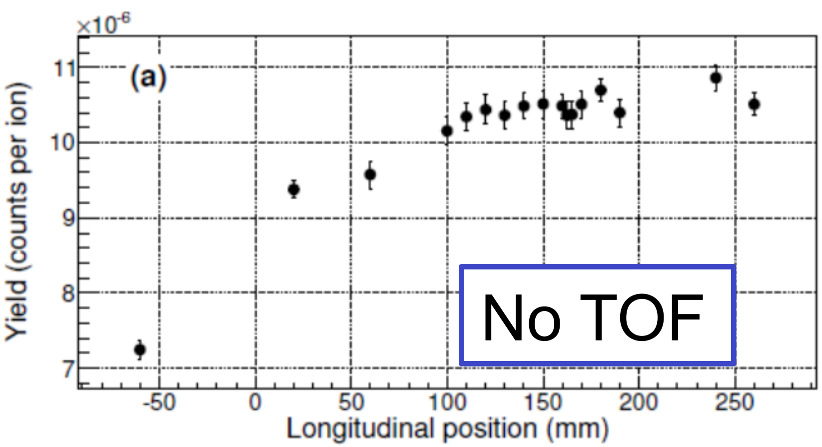
160 MeV protons in PMMA
IBA C230 cyclotron

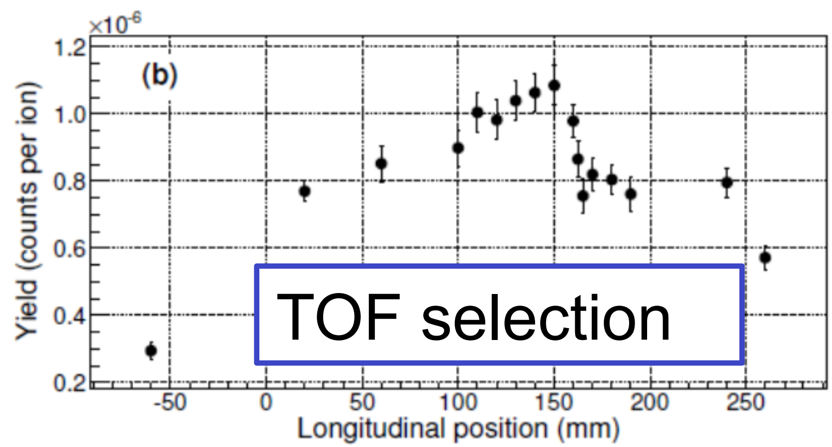




Roellinghoff PMB 2014

310 *A*MeV carbon ions in PMMA





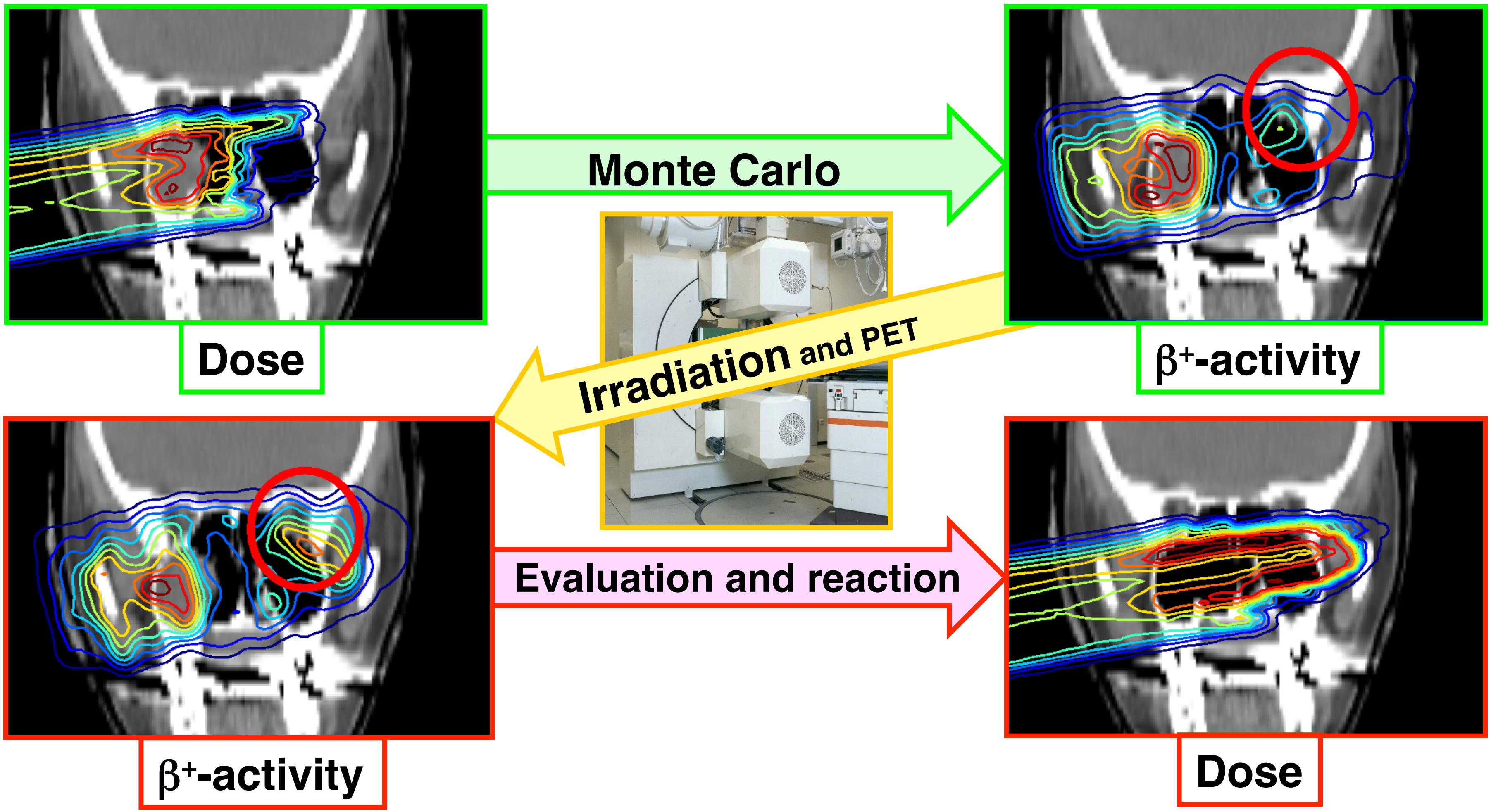
TOF : mandatory for carbon ions

M. Pinto, submitted New J Phys

Courtesy of D. Dauvergne

In-Vivo range with PET workflow

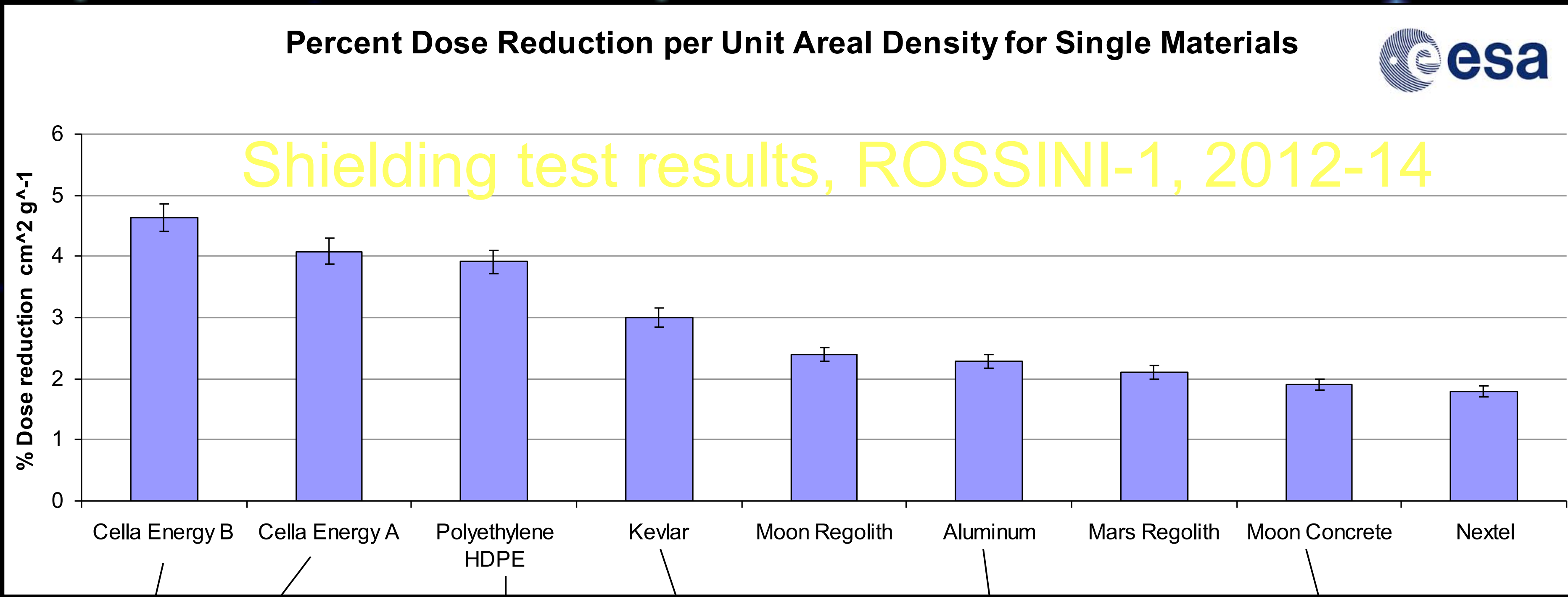
Enghardt et al.: Radiother. Oncol. 73 (2004) S96



Problem to solve: Metabolic Washout! In-beam measurement is really necessary, but difficult. Trade-off: in-room or off-room measurement after irradiation

Guide lines for the detector

- Main focus on fragment yields & emission energy. Precise angle measurement are also needed to apply correct inverse boost transformation for inverse kinematic method.
- The fragment charge ID is the basis of the measurement.
- The fragment mass ID is a challenge and can be performed after a Z ID. An eventual wrong A assignment has an effect on the range evaluation-> less severe at high A
- Highly reliable PID achieved using E_{kin}, momentum and TOF measurement of fragment
- The fragmentation contribution of the detector material MUST be kept as low as possible and eventually subtracted
- Detector portability to different beams is an absolute need: size of the detector should be in the 2 meters range



cella energy