L’adroterapia e la ricerca in fisica medica a LNS

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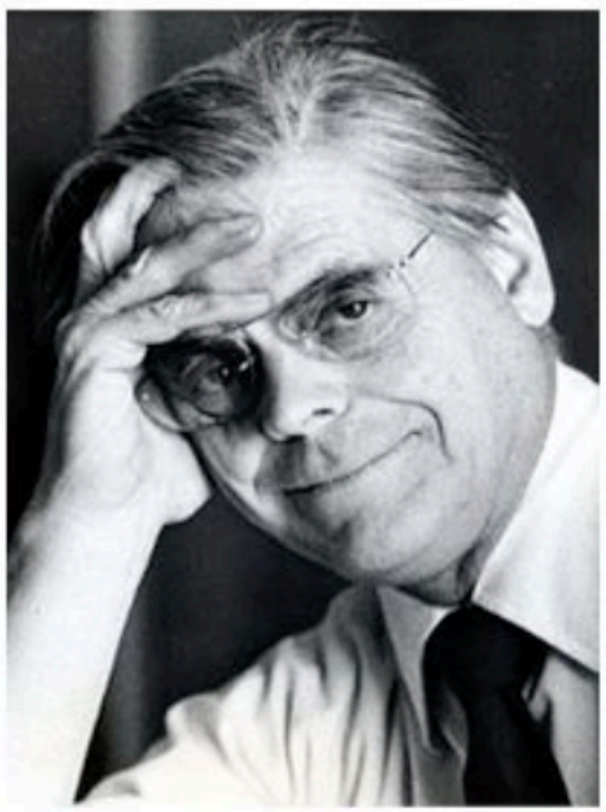
Istituto Nazionale di Fisica Nucleare

Indice

Un pò di storia

1946: R. Wilson propone per la prima volta l'utilizzo di fasci di protoni e ioni per applicazioni terapeutiche



Robert Rathbun Wilson

R. Wilson, Radiologial use of fast protons, Radiology 47, 487-491, 1946

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 large part, been due to the very short

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 intensely a strictly localized region within the body, with but little

1954: Presso il Lawrence Berkeley Laboratory viene trattato il primo paziente

Un pò di storia

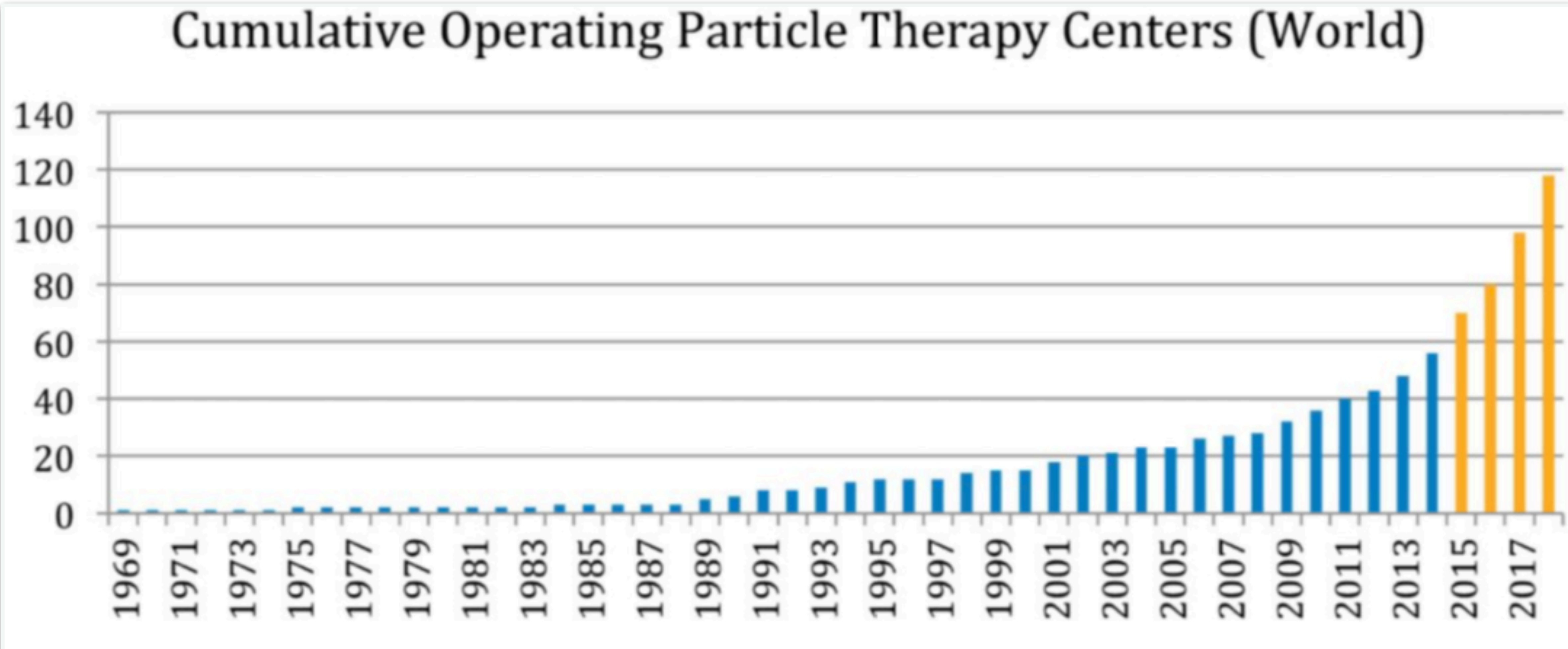
I primi centri di adroterapia nascono nei grandi laboratori di fisica nucleare e particellare

- 1957: Uppsala (Sweden);
- 1961: Massachusetts General Hospital and Harvard Cyclotron Laboratory (USA);
- 1967: Dubna (Russia);
- 1979: Chiba (Japan);
- 1985: Villigen (Switzerland).

1990: **the first hospital-based proton therapy facility at *Loma Linda University Medical Center* (LLUMC).**

LLUMC (California, USA)

I centri di adroterapia nel mondo



Particle Therapy
Co-Operative Group
(PTCOG)

Due aspetti importanti

- **La fisica:** i meccanismi di rilascio energetico nei tessuti
- **La biologia:** il danneggiamento cellulare

Interazione radiazione-materia: Beth-Block

Il trasferimento di energia ai tessuti si basa essenzialmente su:

✱ Interazioni di tipo Coulombiano (Stopping)

i protoni interagiscono con gli elettroni appartenenti alle shell più esterne degli atomi che compongono i tessuti
→ fenomeni di eccitazione e ionizzazione degli atomi
→ i protoni rallentano → viene persa circa l'80%-90% dell'energia

- loss per interaction small -> **continuously slow down**
- secondary electrons have range < 1mm -> **dose absorbed locally**

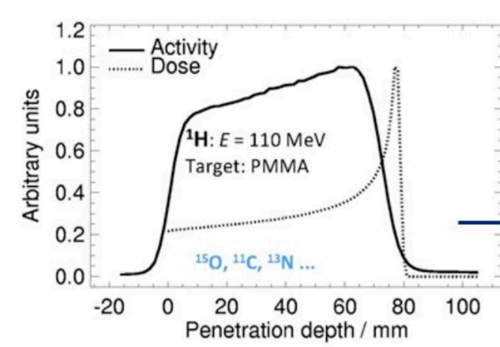
Energy loss is given by **Bethe-Bloch equation**:

$$-\left\langle \frac{dE}{dx} \right\rangle = K z^2 \frac{Z}{A} \frac{1}{\beta^2} \left[\frac{1}{2} \ln \frac{2 m_e c^2 \beta^2 \gamma^2 T_{\max}}{I^2} - \beta^2 - \frac{\delta(\beta\gamma)}{2} \right]$$

✱ Reazioni Nucleari

interazioni non elastiche con i nuclei che compongono i tessuti (viene persa circa il 5-20% dell'energia) → vengono prodotte particelle secondarie

- protons, α ,recoils nuclei, γ-rays (nuclei excitation), **neutrons -> radiation safety**
- **radioactive isotopes (tissue activation)**, es. ^{15}O, ^{11}C, ^{13}N **(β^+-emitters)** -> from isotopes activity 3D **dose verification** with PET/CT



K. Parodi et al., IEEE MIC CR, 2002

→ **Proton beam @ 110 MeV**

Interazione radiazione-materia: Beth-Block

[see e.g. PDG 2010]

$$-\left\langle \frac{dE}{dx} \right\rangle = Kz^2 \frac{Z}{A} \frac{1}{\beta^2} \left[\frac{1}{2} \ln \frac{2m_e c^2 \beta^2 \gamma^2 T_{\max}}{I^2} - \beta^2 - \frac{\delta(\beta\gamma)}{2} \right] [\cdot \rho]$$

density

$K = 4\pi N_A r_e^2 m_e c^2 = 0.307$ MeV g^{-1} cm^2

$T_{max} = 2m_e c^2 \beta^2 \gamma^2 / (1 + 2\gamma m_e/M + (m_e/M)^2)$

[Max. energy transfer in single collision]

z : Charge of incident particle
M : Mass of incident particle

Z : Charge number of medium
A : Atomic mass of medium

I : Mean excitation energy of medium
δ : Density correction [transv. extension of electric field]

$N_A = 6.022 \cdot 10^{23}$
[Avogardo's number]

$r_e = e^2/4\pi\varepsilon_0 m_e c^2 = 2.8$ fm
[Classical electron radius]

$m_e = 511$ keV
[Electron mass]

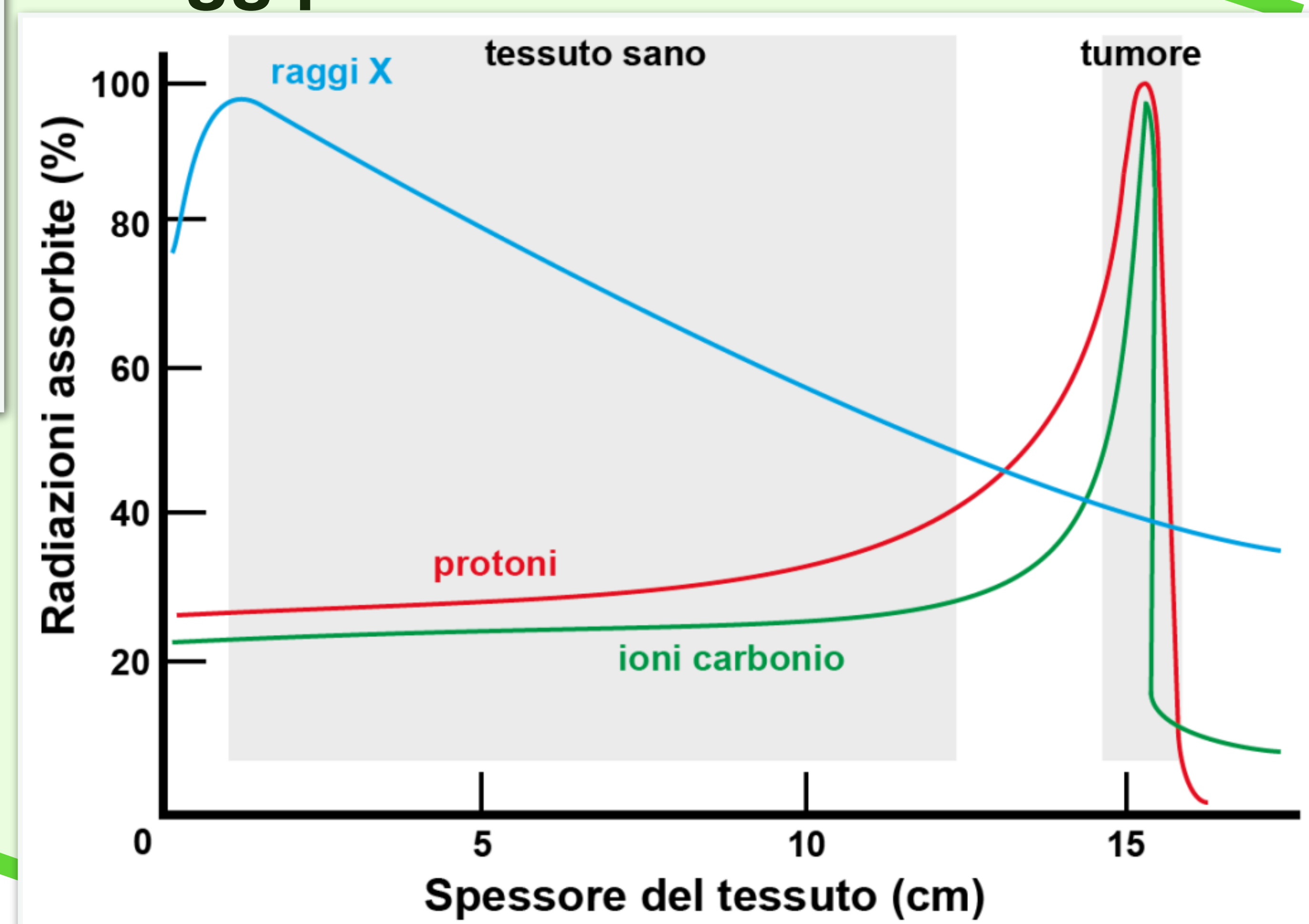
$\beta = v/c$
[Velocity]

$\gamma = (1-\beta^2)^{-2}$
[Lorentz factor]

Validity:
$.05 < \beta\gamma < 500$
$M > m_\mu$

Beth-Block Formula

Bragg peak



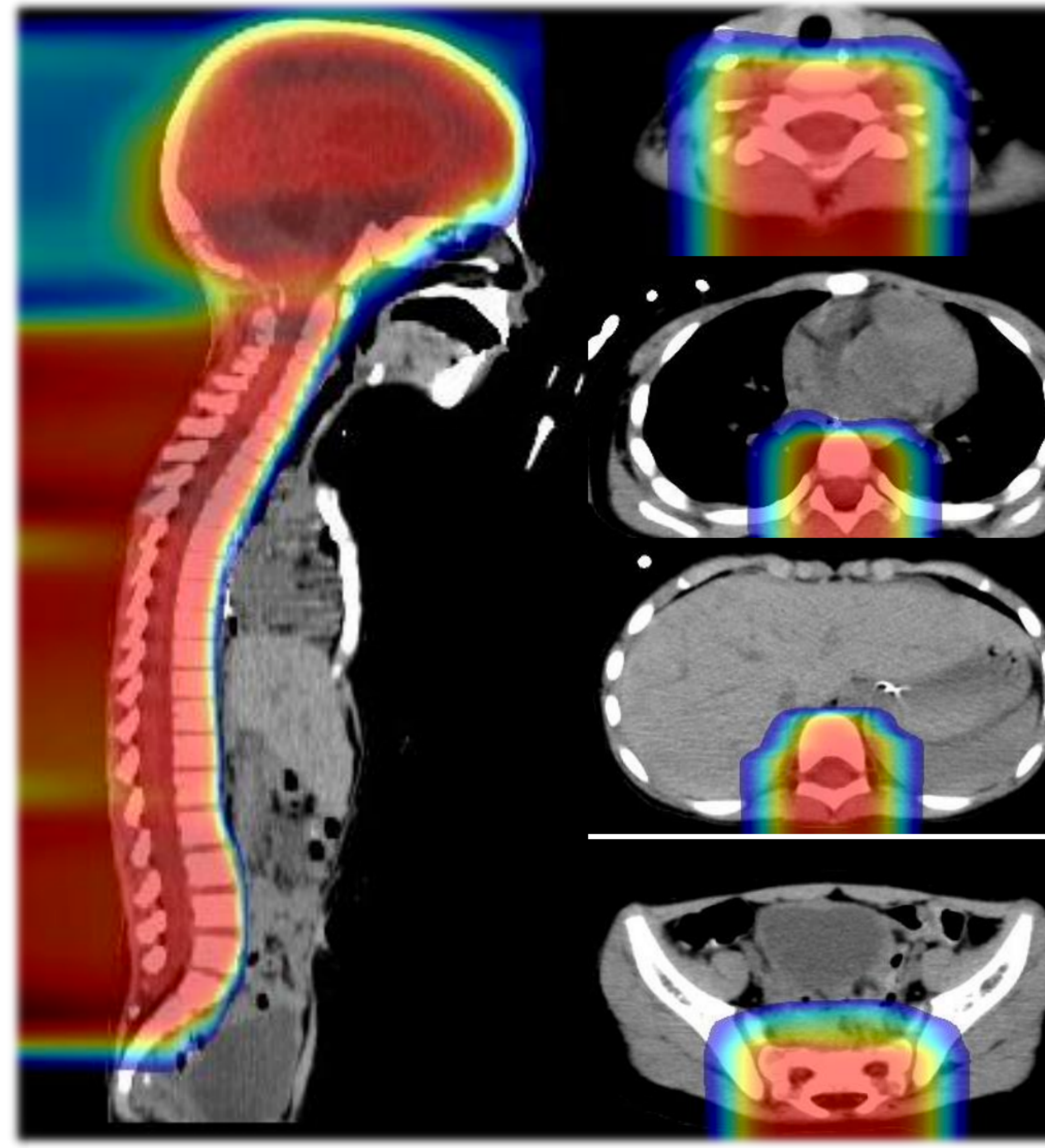
Una quantità importante: la dose

$$\boxed{D = \frac{dE}{dm} \quad [Gy = J/Kg]}$$

$$\boxed{D_W(Gy) = \frac{1}{A}(S(E))_W \frac{Q}{e} 1.602 \cdot 10^{-10}}$$

Radioterapia convenzionale Vs Protonterapia

x-Ray therapy



Protontherapy

Mirabell RA et al.
Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumor,
Int. Jour. Rad. Onc. Phys. 2002, 54 (3) 824

Radioterapia convenzionale Vs Protonterapia

Vantaggi *fisici*:

- Range finito ed elevata densità di ionizzazione
- Basse dosi integrali

Vantaggi clinici:

- Trattamento di tumori in profondità posti in prossimità di organi a rischio
- Bassa probabilità di avere effetti collaterali
- Trattamento di elezione per i tumori pediatrici

Pediatric Medulloblastoma: The yearly risk of getting a secondary tumor was estimated to be 8 times greater with X-rays than with proton therapy [2]

Tumor Site	Proton Therapy	X-rays/IMRT
Stomach and esophagus	0%	11%
Colon	0%	7%
Breast	0%	0%
Lung	1%	7%
Thyroid	0%	6%
Bone and connective tissue	1%	2%
Leukemia	3%	5%
All Secondary Cancers	**5%**	**43%**

This chart compares the rates of secondary tumors for a pediatric patient treated for medulloblastoma.

Data shown are from a study that compared treatment plans.

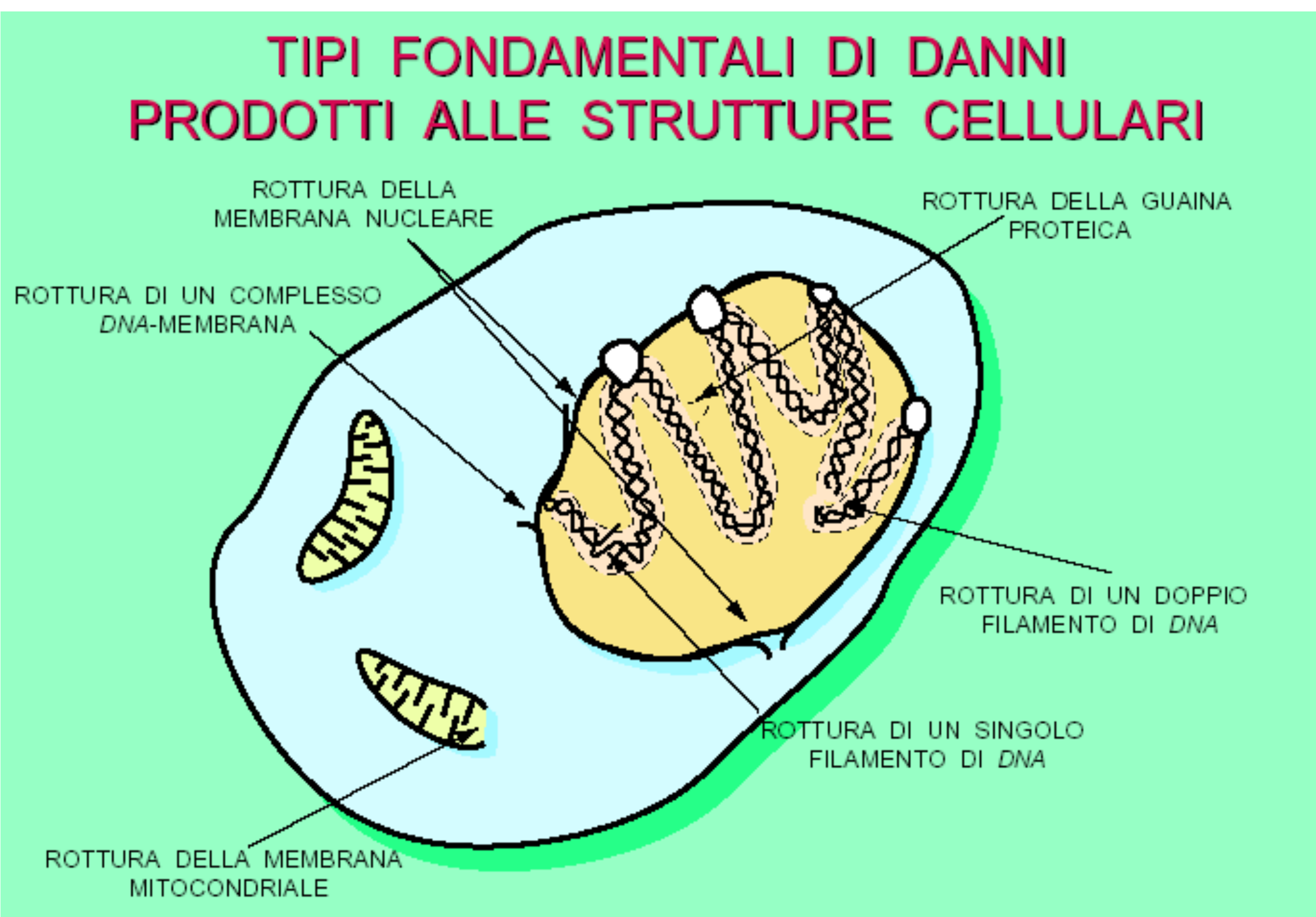
IMRT= intensity modulated radiation therapy (a type of X-ray therapy)

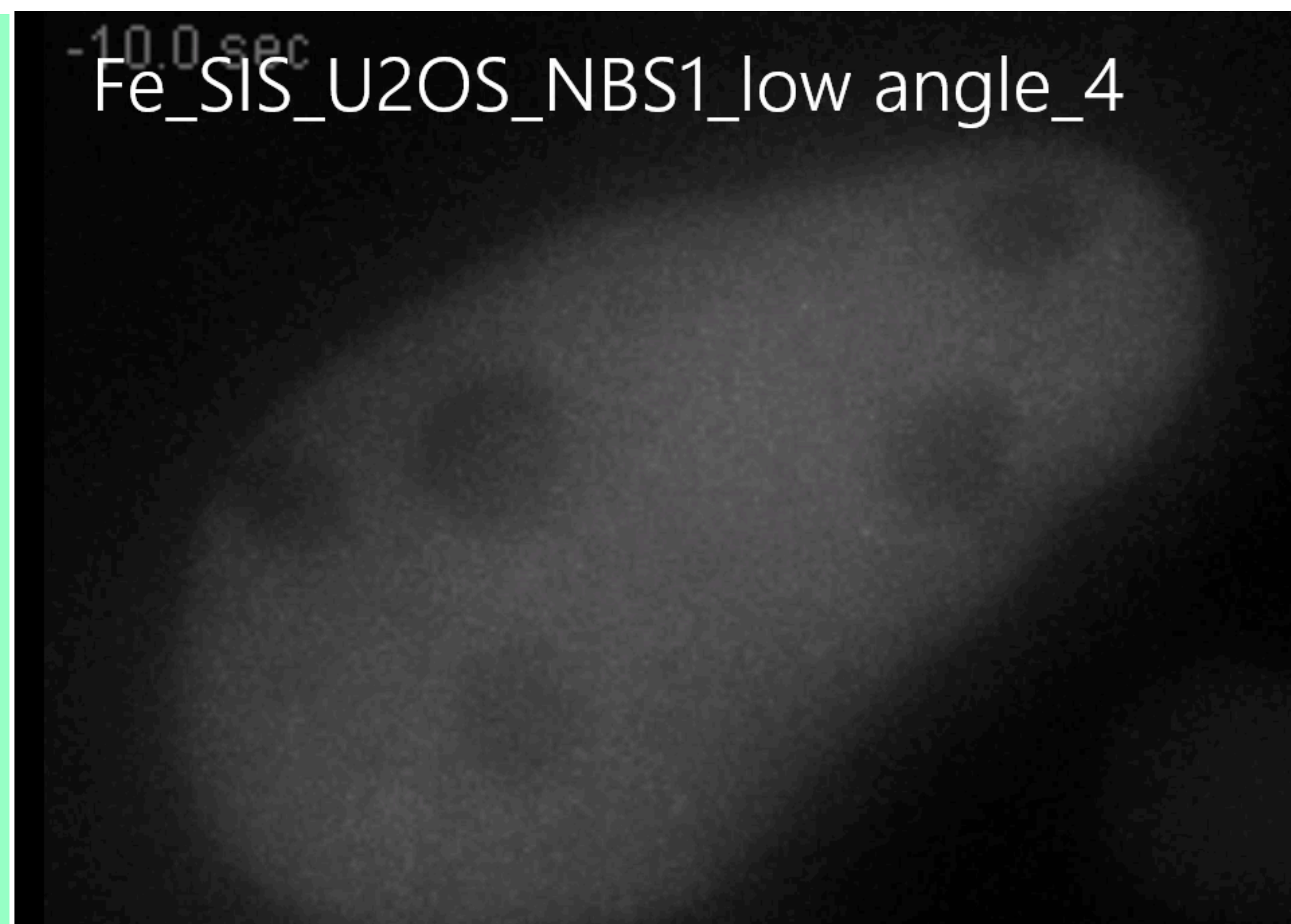
L’effetto biologico

Le radiazioni ionizzanti possono danneggiare le cellule causandone talvolta la morte.

Esistono due tipi di danni:

- Stocastici (basse dosi/basso LET)
- Deterministici (alte dosi/alto LET)

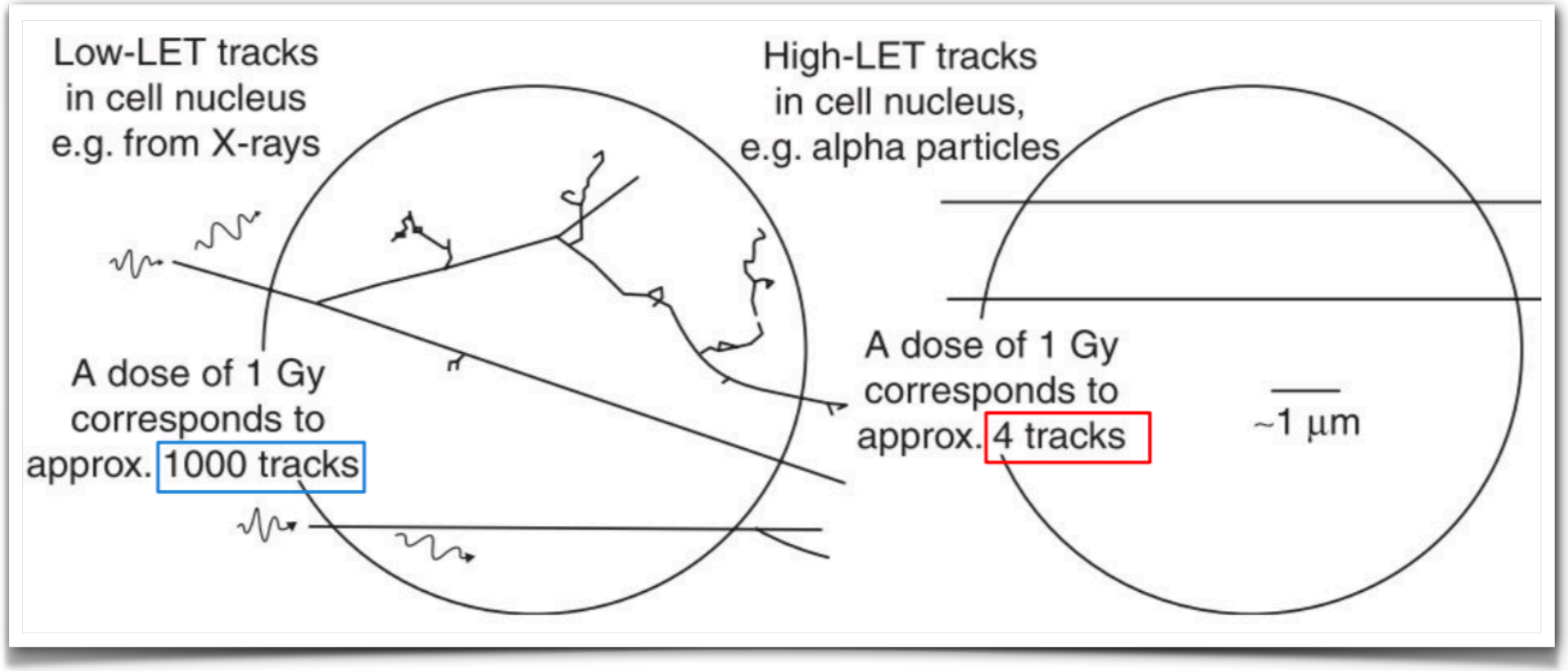


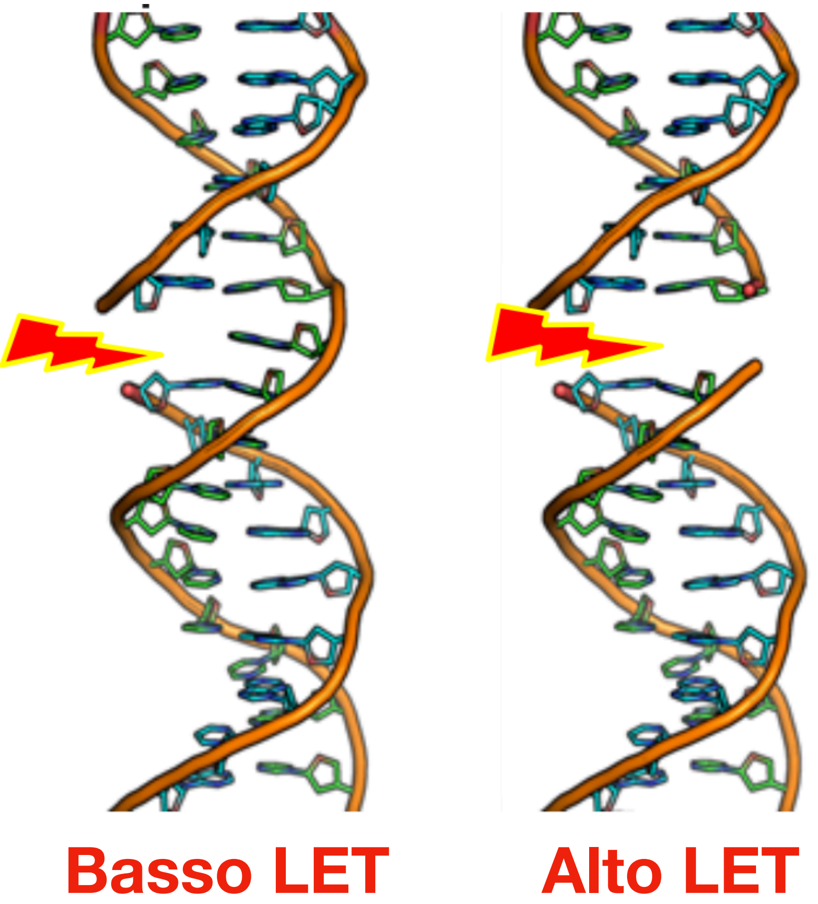


Il rilascio locale di energia

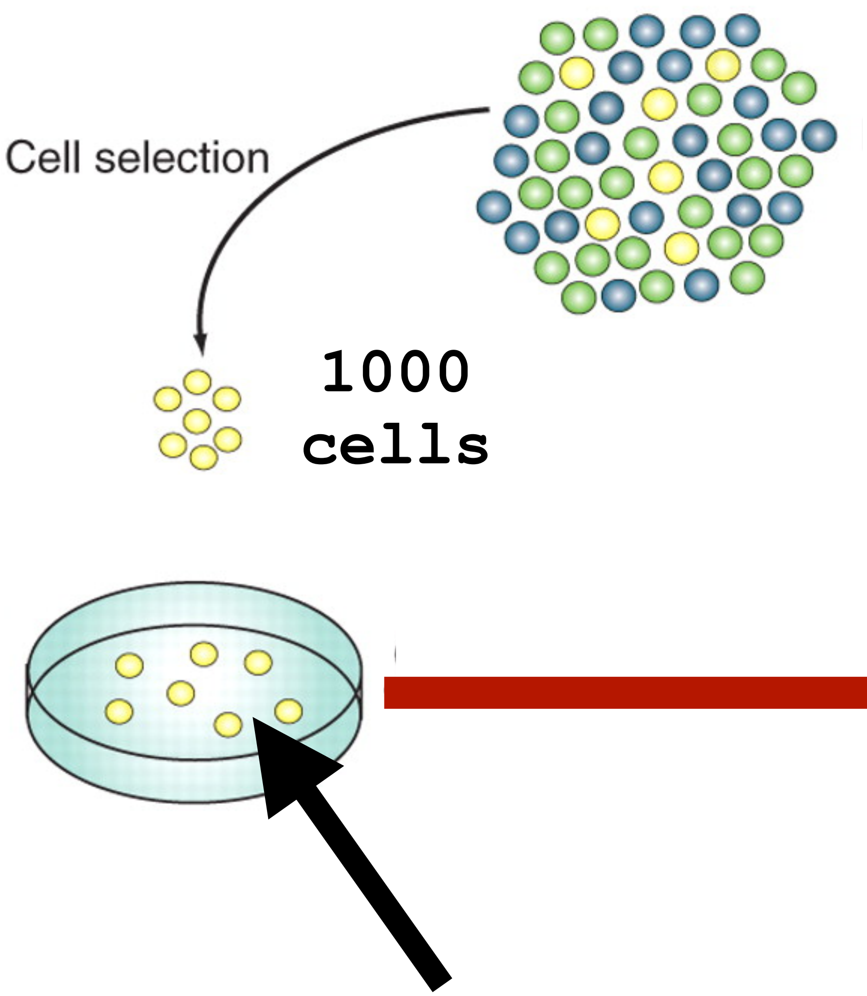
Linear Energy Transfer (LET)

$$LET = \frac{dE}{dl} \quad [\text{keV}/\mu\text{m}]$$





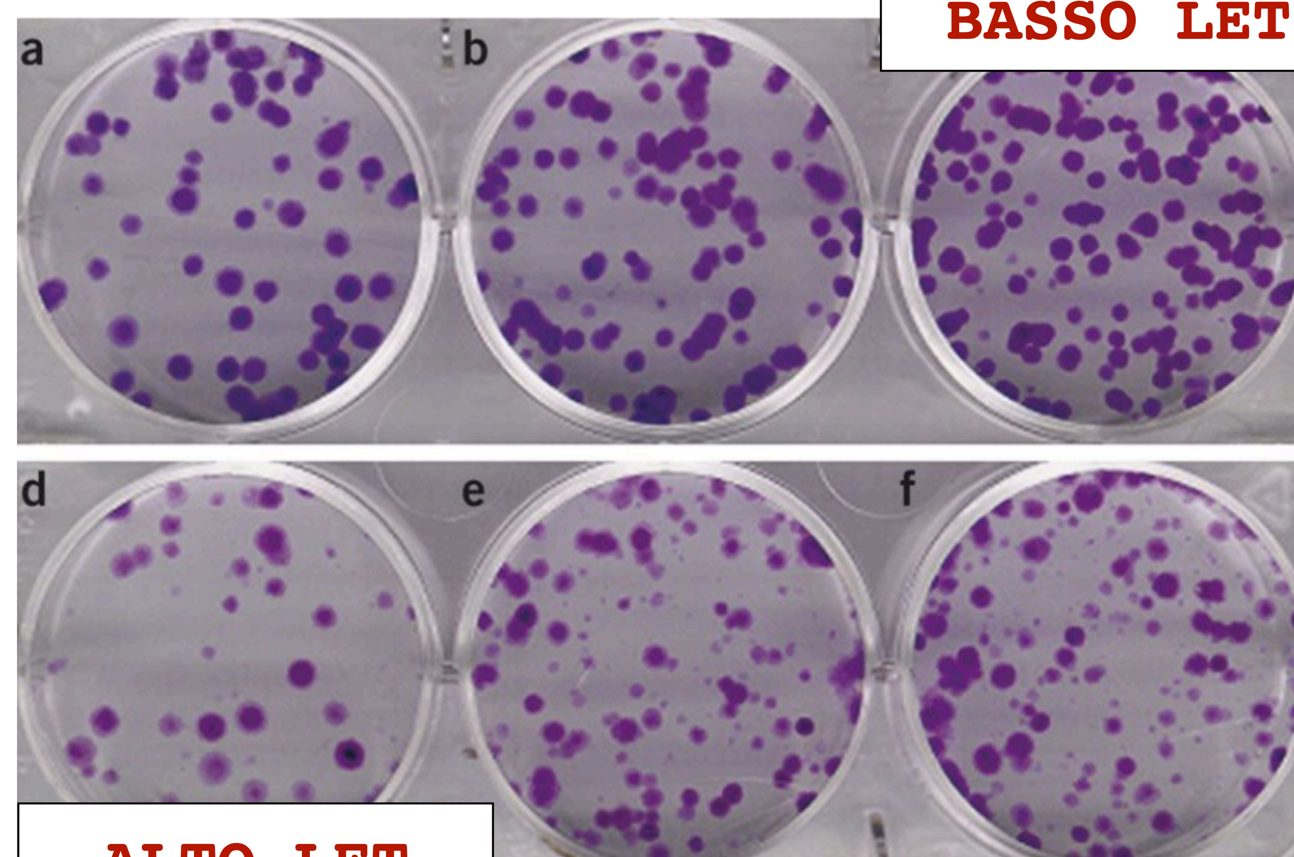
Il danneggiamento cellulare



1000 cells

Ionizing radiations

BASSO LET



ALTO LET

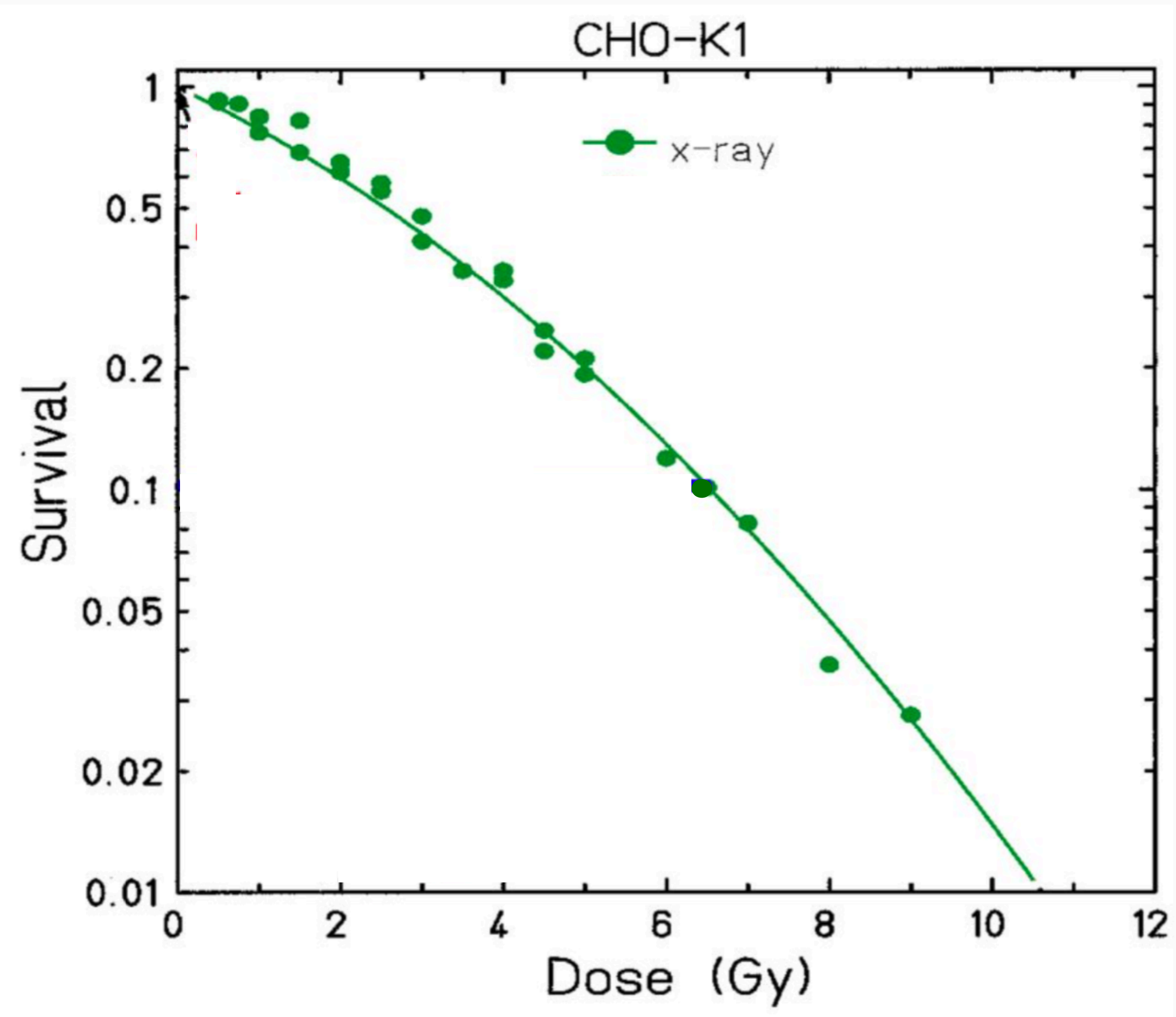
Il modello lineare quadratico

$$S = e^{(-\alpha \cdot D - \beta \cdot D^2)}$$

Survival Fraction

Parametro Lineare

Parametro Quadratico



L'RBE per quantificare il danno

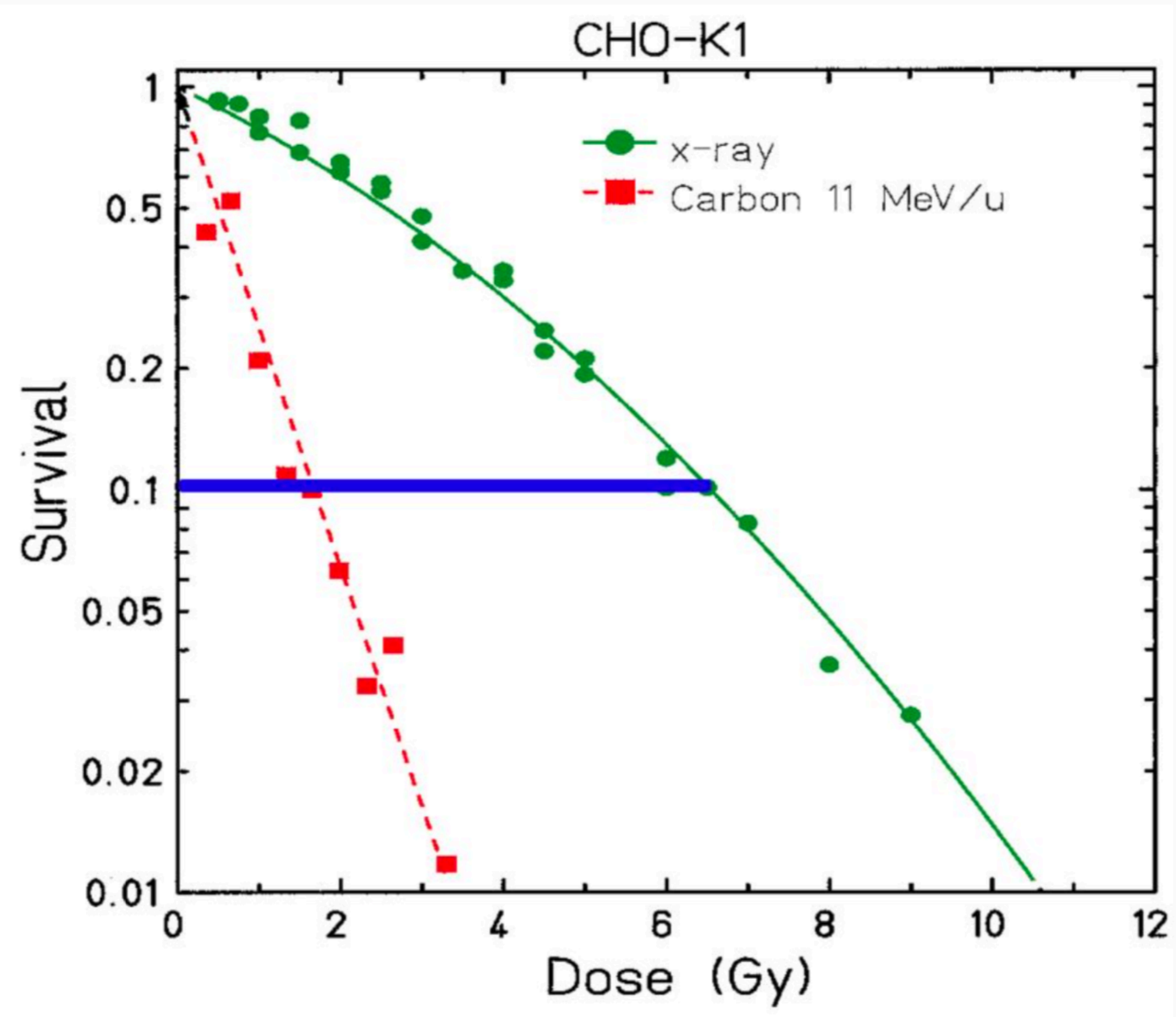
Relative Biological Effectiveness

$$RBE_n = \frac{D_X}{D_{Ion}}\bigg|_{S_X=S_{Ion}=n}$$

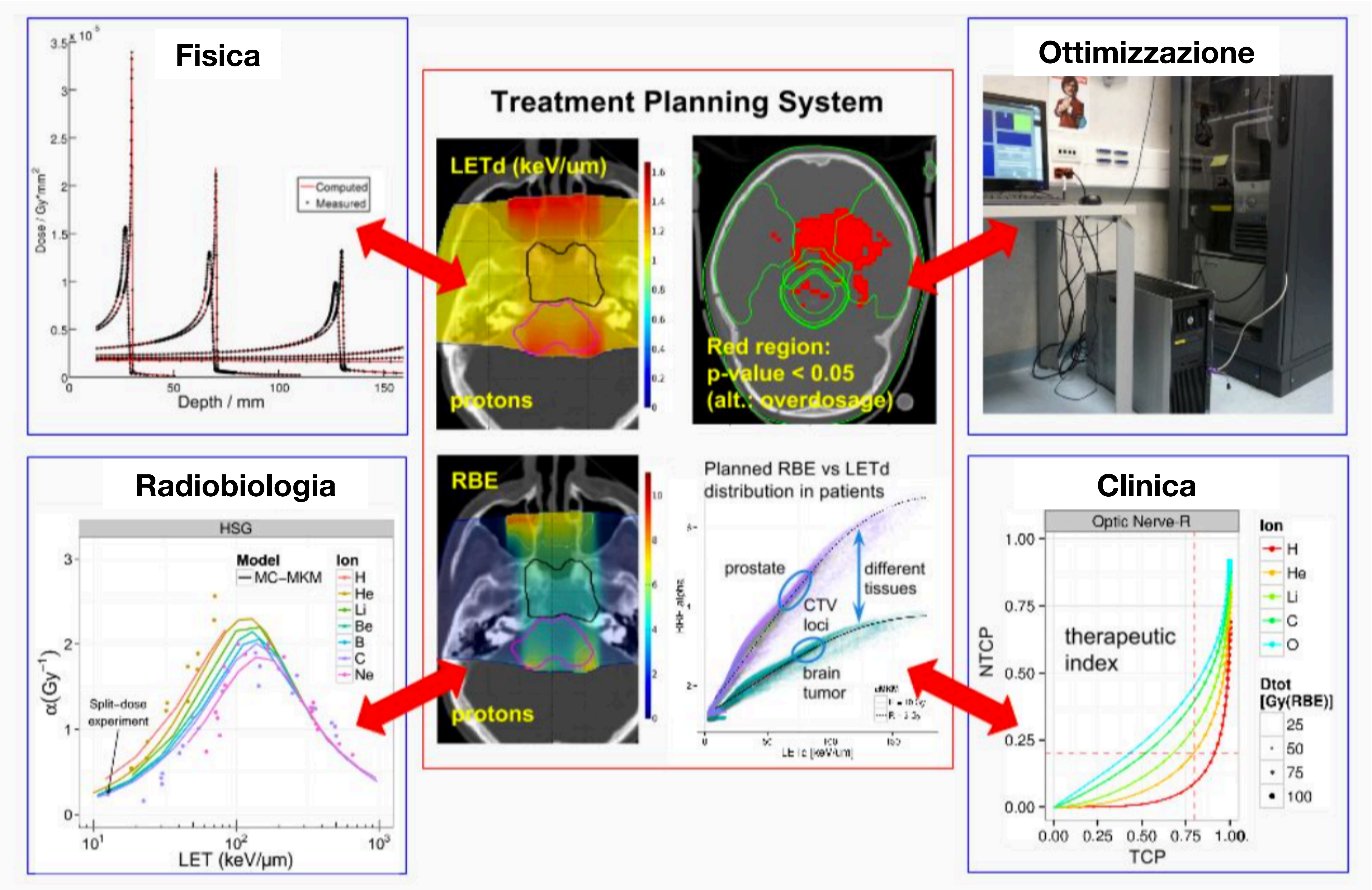
RBE-Weighted Dose (RWD):
RWD = D x RBE

Protons:
RBE $\sim$ 1.1

Carbon Ions:
RBE $>$ 1

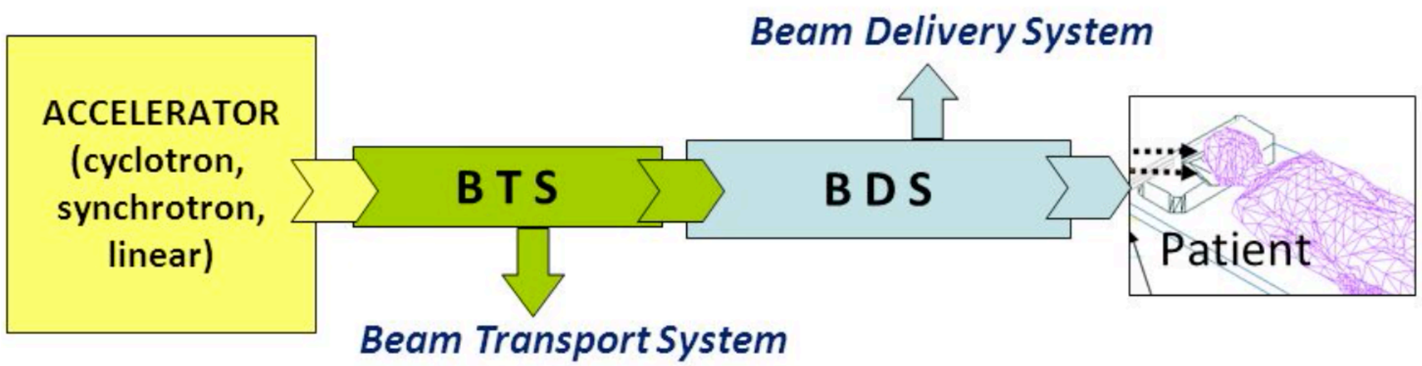


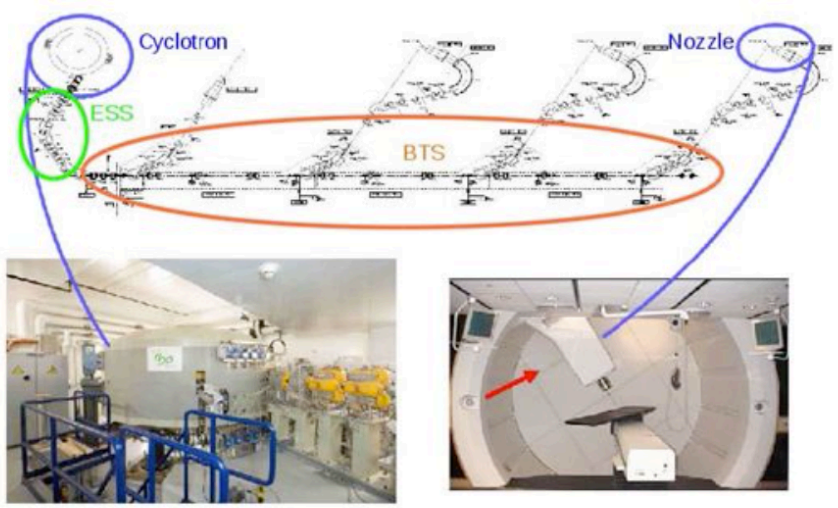
I piani di trattamento



G Petringa, PhD - giada.petringa@lns.infn.it

La parti pricipali di una facility di adroterapia



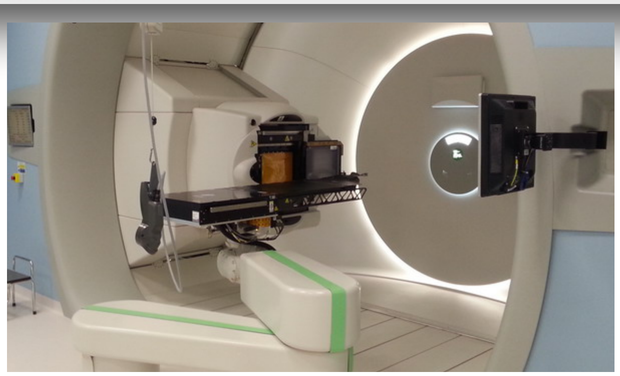


Hadron therapy facility scheme – IBA (Belgium)

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica per il trattamento dei tumori

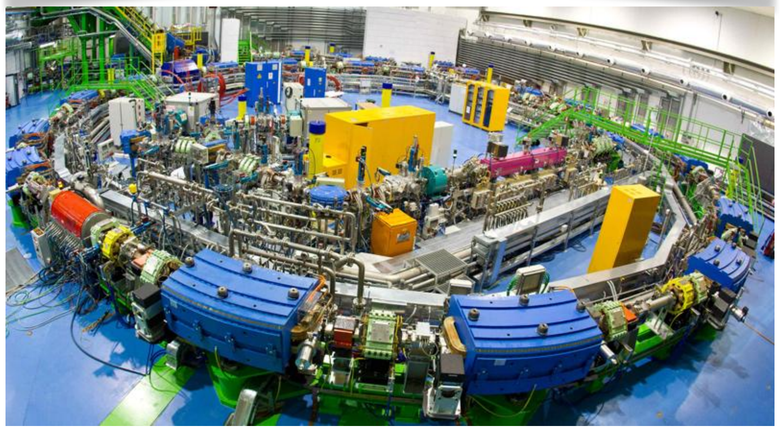
L'adroterapia in italia

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento



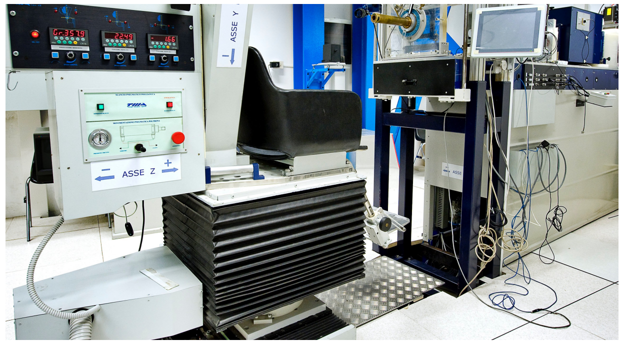
Ciclotrone
protoni fino a 250 AMeV
Pazienti Trattati:600

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica per il trattamento dei tumori



Sincrotrone
protoni e 12C fino a 250 AMeV
Pazienti Trattati:
12C 1044
p 565

CATANA
INFN LNS
Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali del Sud

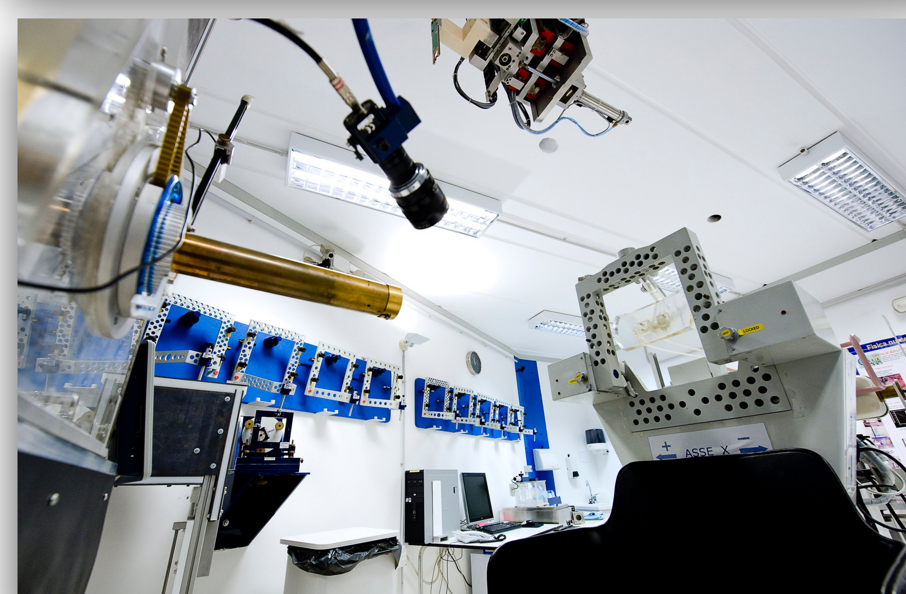


Ciclotrone
protoni di 62 MeV
Pazienti trattati:500

Il trattamento del melanoma oculare a LNS

CATANA

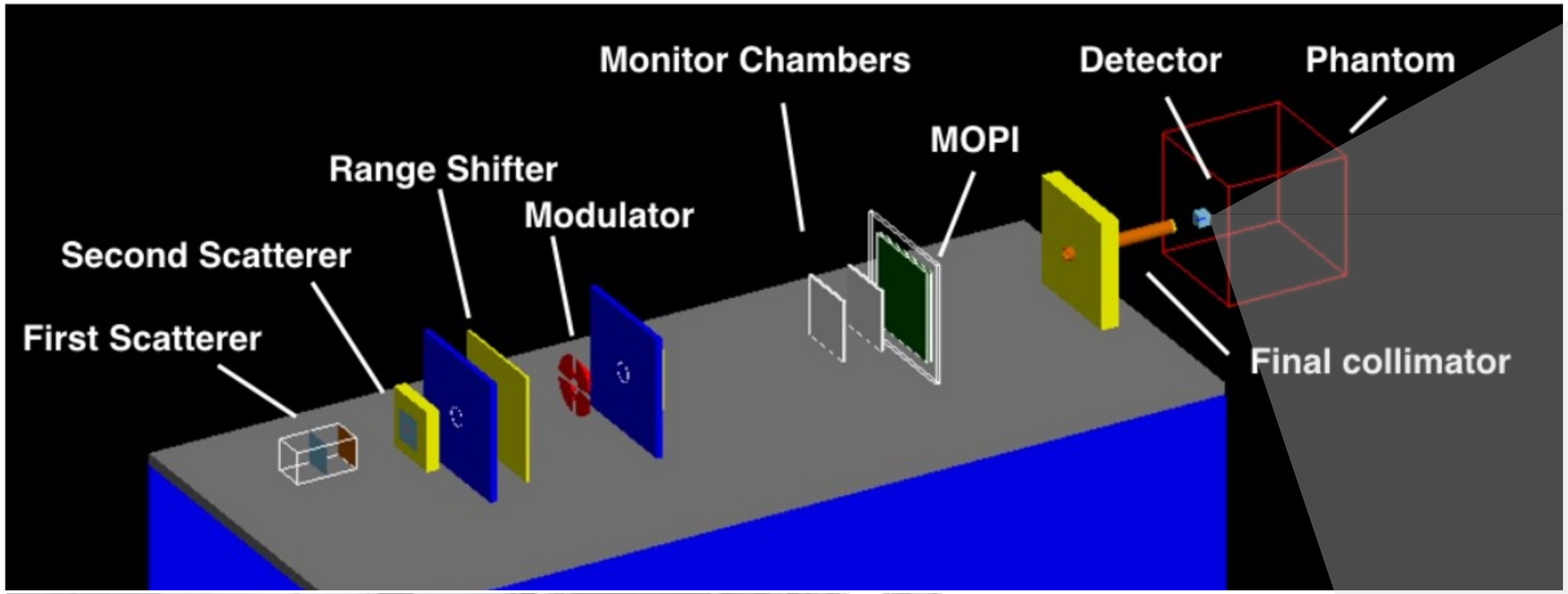
Cuttone et al. EPJ **126** (2011)

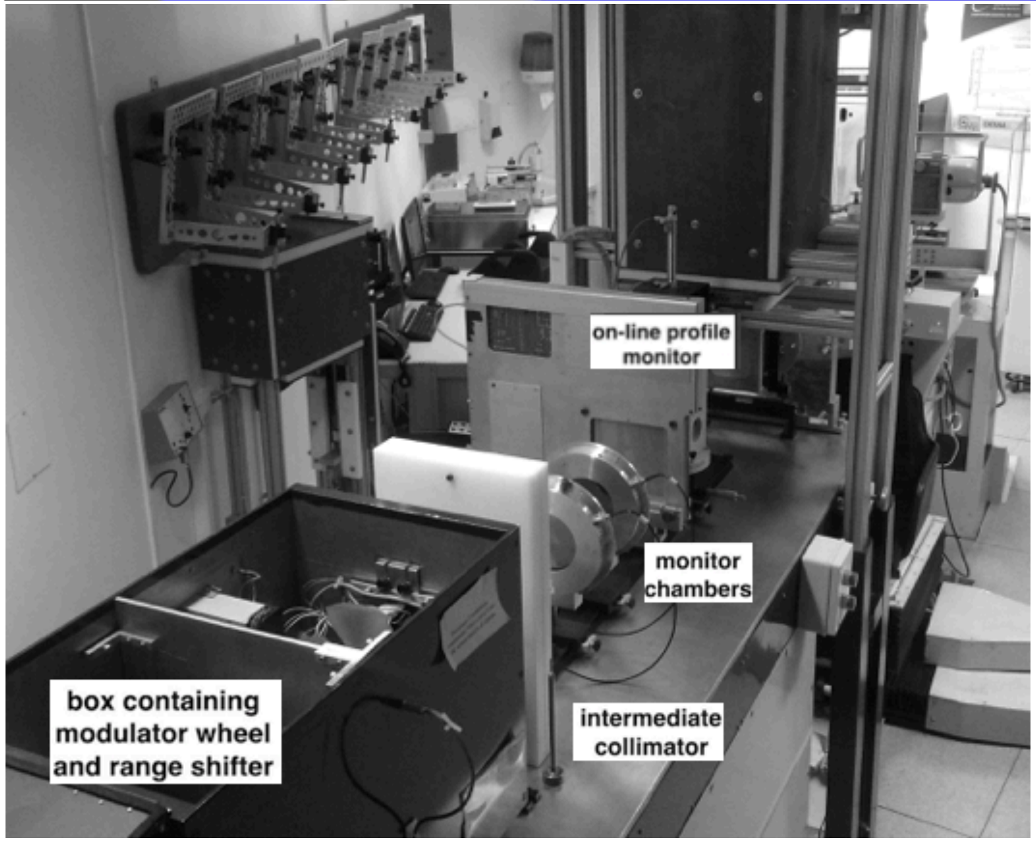


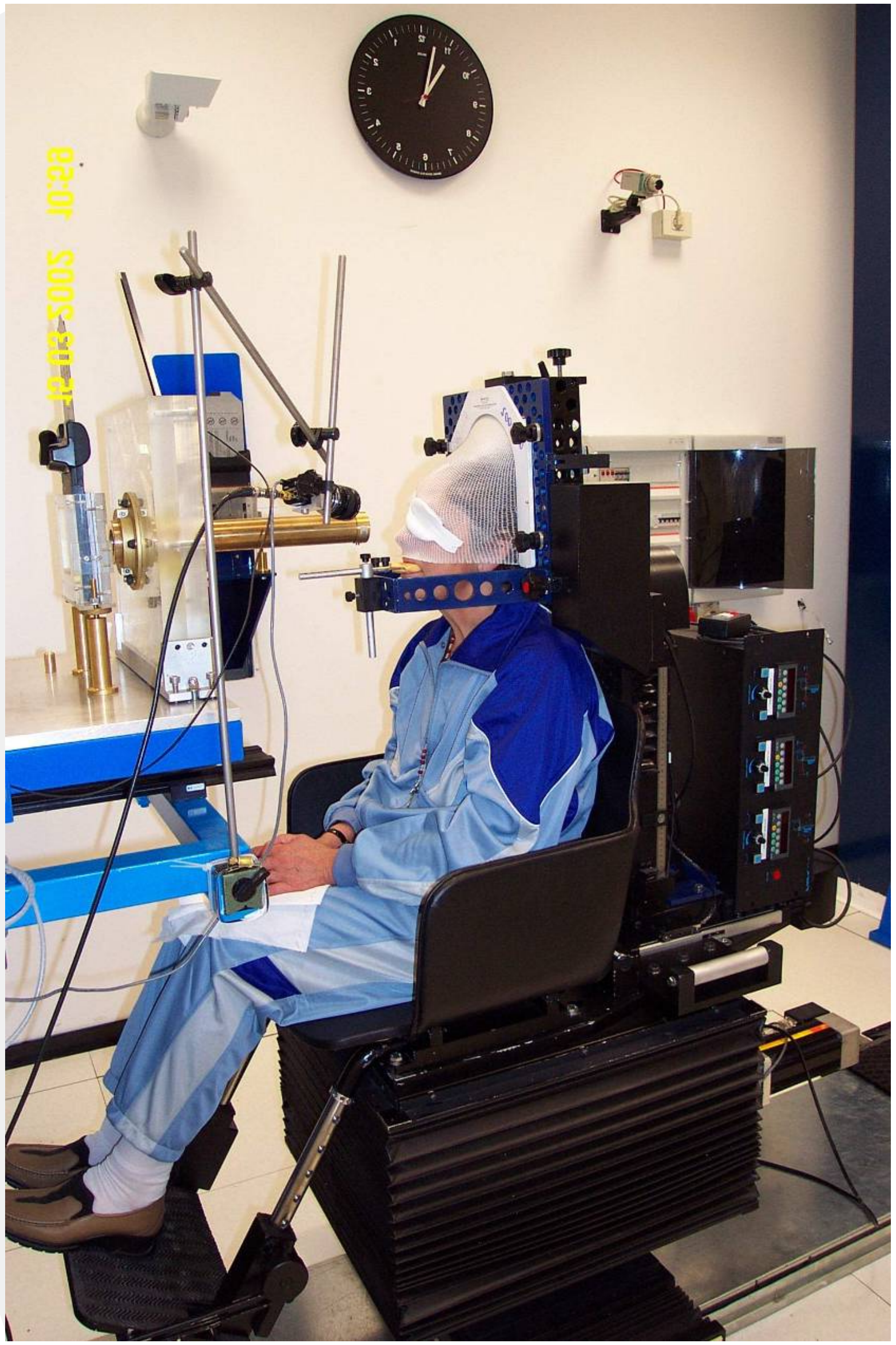
CATANA
Centro di AdroTerapia ed Applicazioni Nucleari Avanzate

- Primo centro di protonterapia in Italia
- Marzo 2002: primo paziente trattato
- 500 pazienti trattati
- Linea passiva di protonterapia
- 62 MeV di energia

CATANA







Dose:15 CGE per fraction

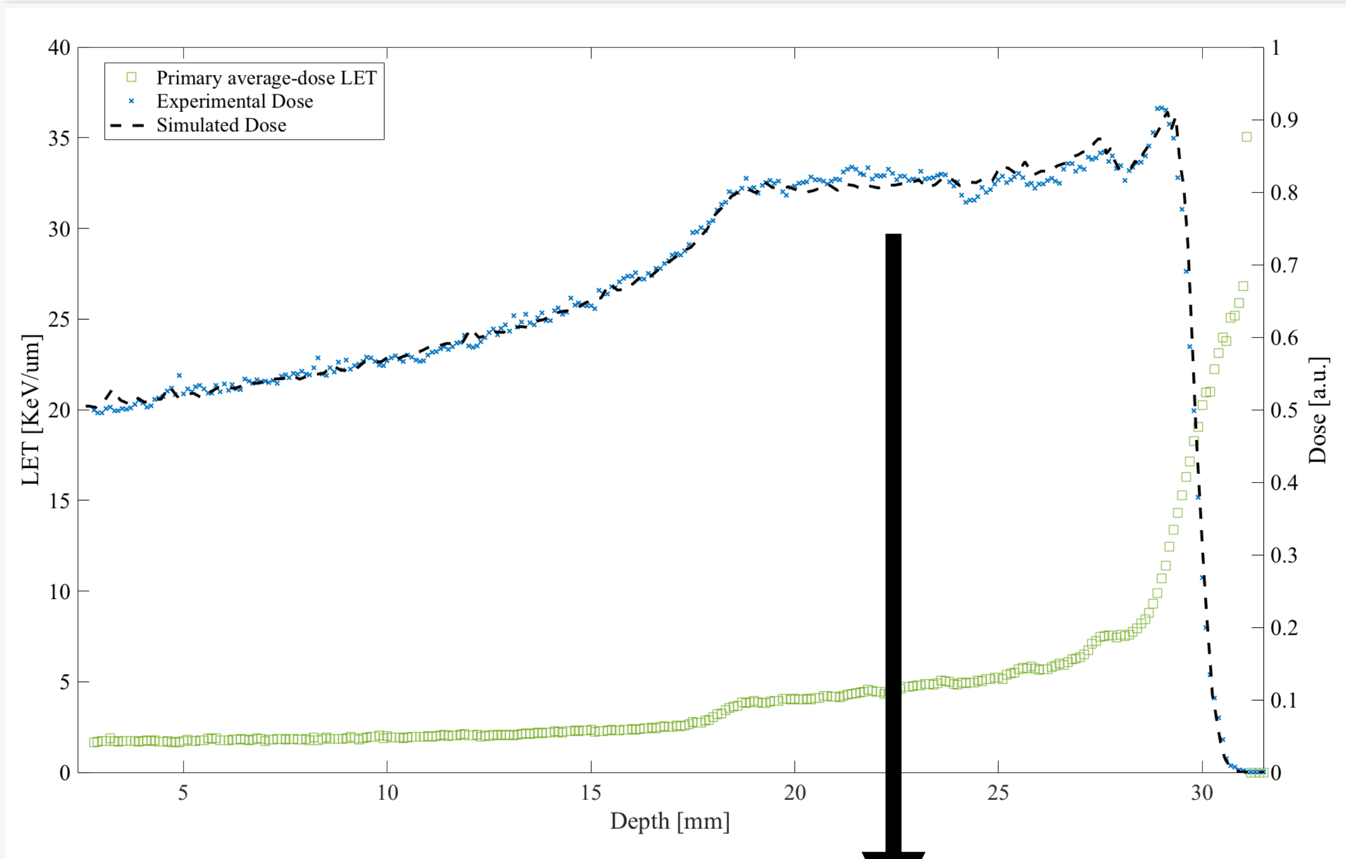
Treatment time: 40-50 sec

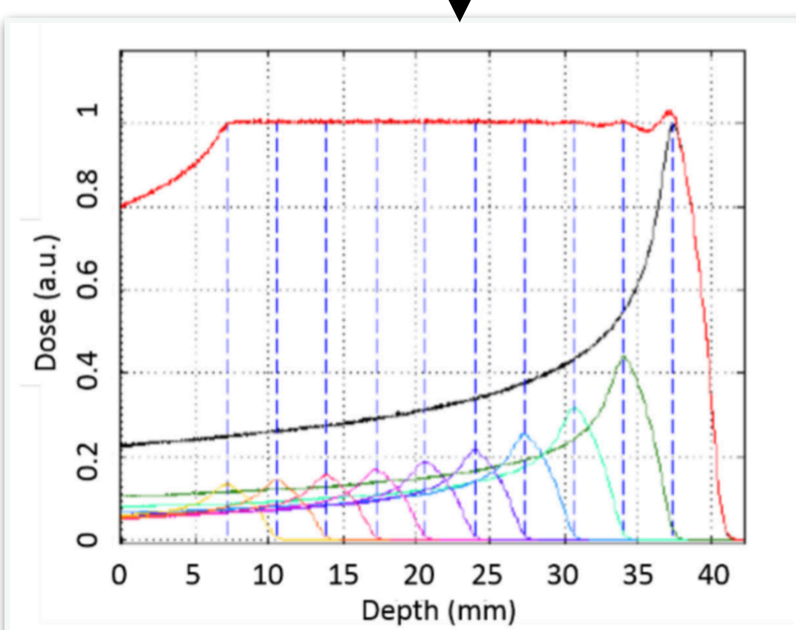
Total dose: 60 CGE

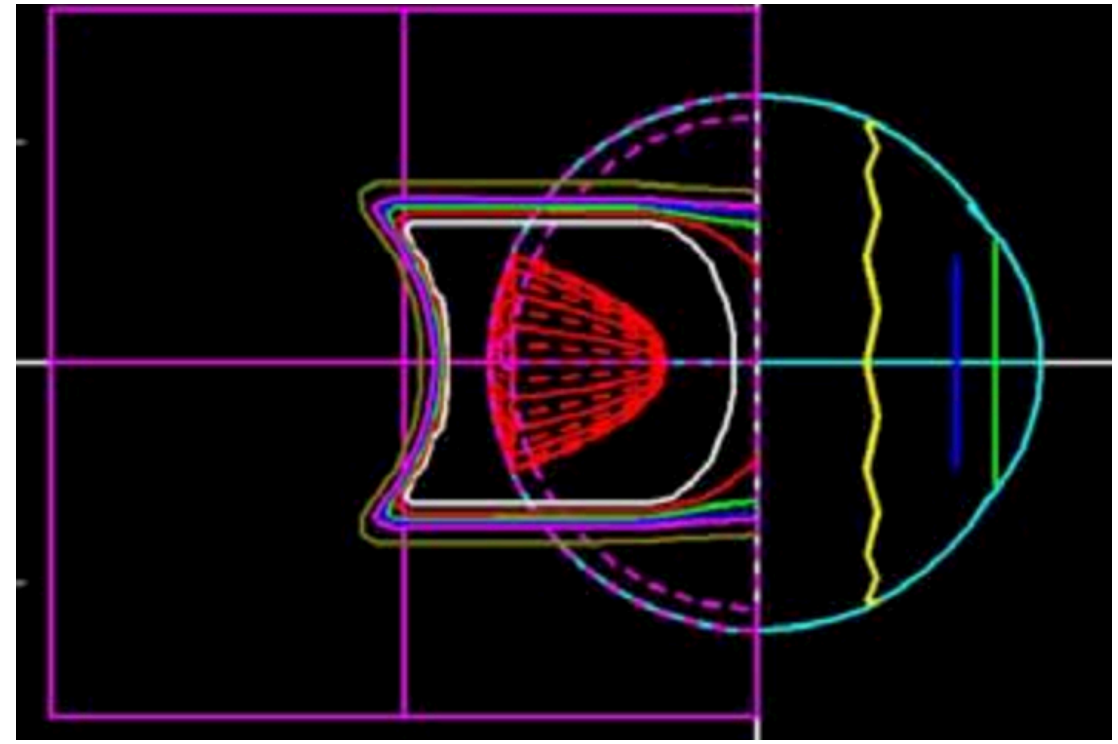
Fractions:4

Ottimizzazione del trattamento

Depth-dose distribution







Dead patients	4	
	Metastatis	3
	Other	1
Eye retention rate	92,68 %	
TOTAL SURVIVAL	95 %	
LOCAL CONTROL	97 %	

La ricerca in fisica medica (facciamo qualche esempio)

- Algoritmi per prevedere il danno biologico e la distribuzione di dose in profondità

- Sviluppo di rivelatori per controllare il rilascio di dose

- Tecniche per aumetare l’efficacia biologica dei protoni

- Sviluppo di rivelatori per misurare il LET

Modellizzare il “danno”

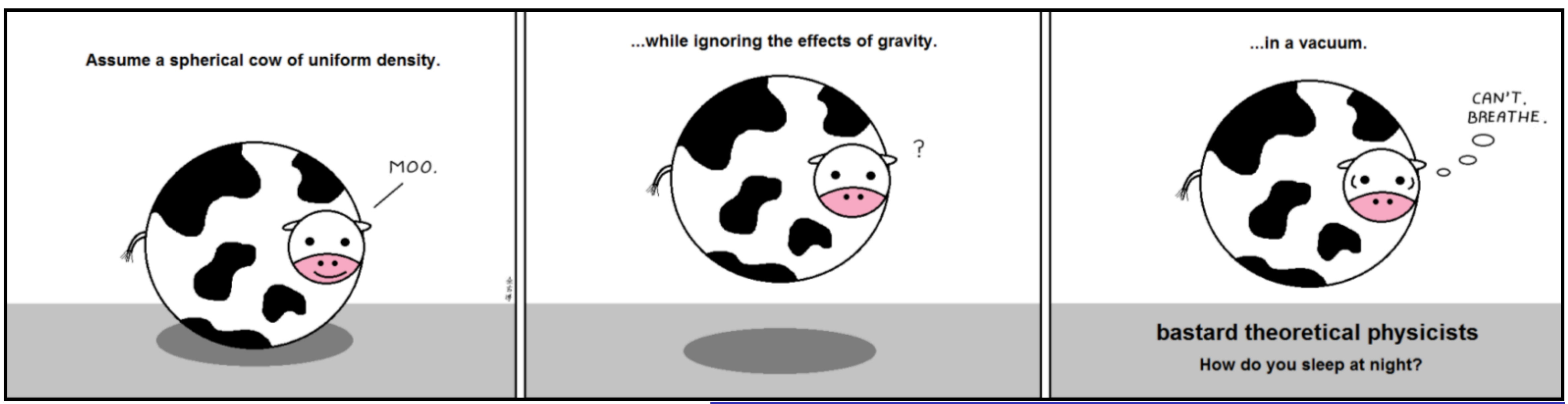
Parametri Fisici

- Dose
- Energia
- LET
- Tipo di Particella

Biological Parameters

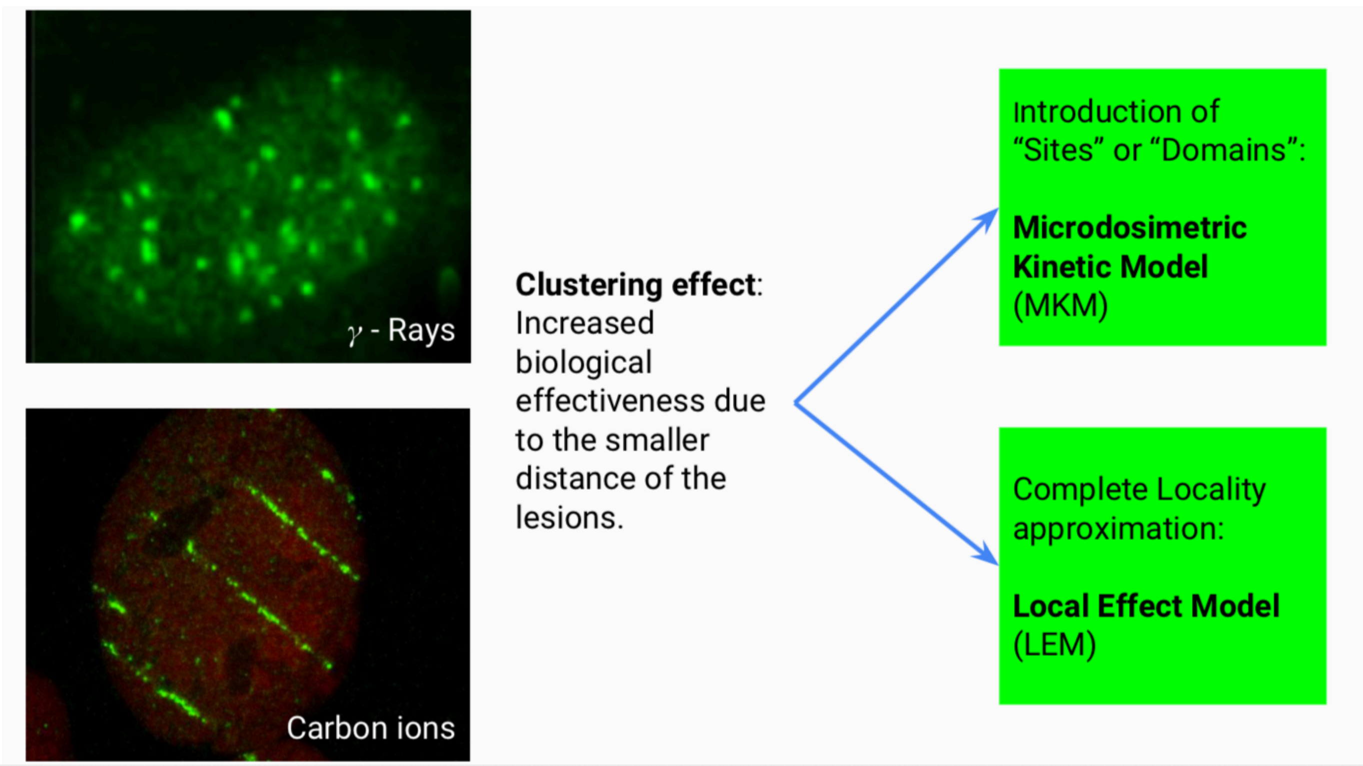
- Tipologia di Tessuto
- Ossigenazione
- Capacità di Riparo
- Endpoint Biologico

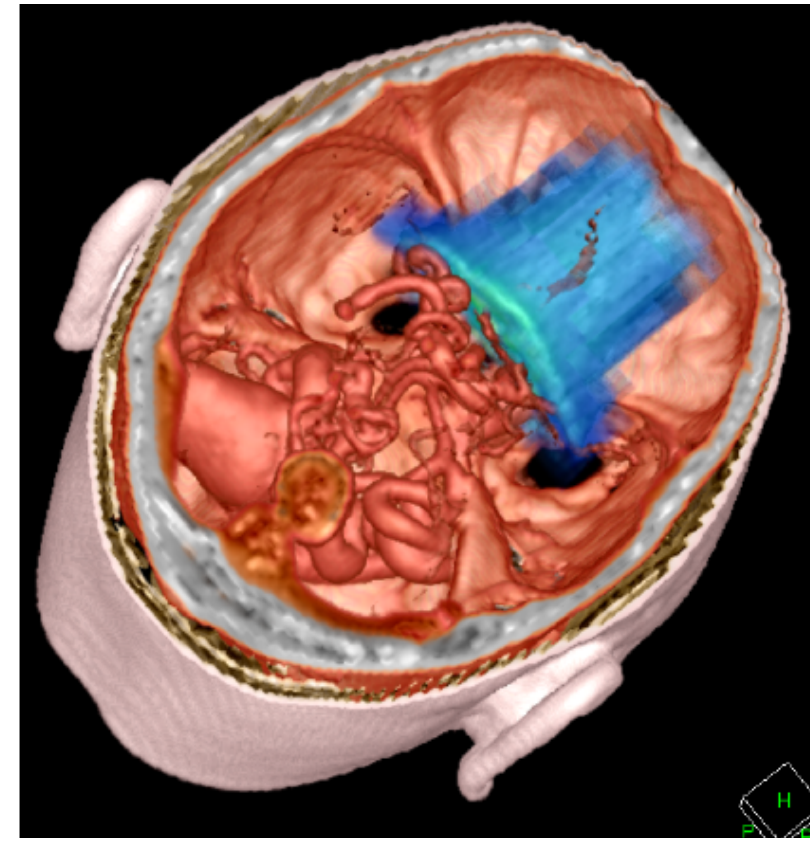
- “Linear” models (protons)
- Local Effect Model (**LEM**)
- Microdosimetric Kinetic Model (**MKM**)
- Repair-Misrepair-Fixation (**RMF**) Model

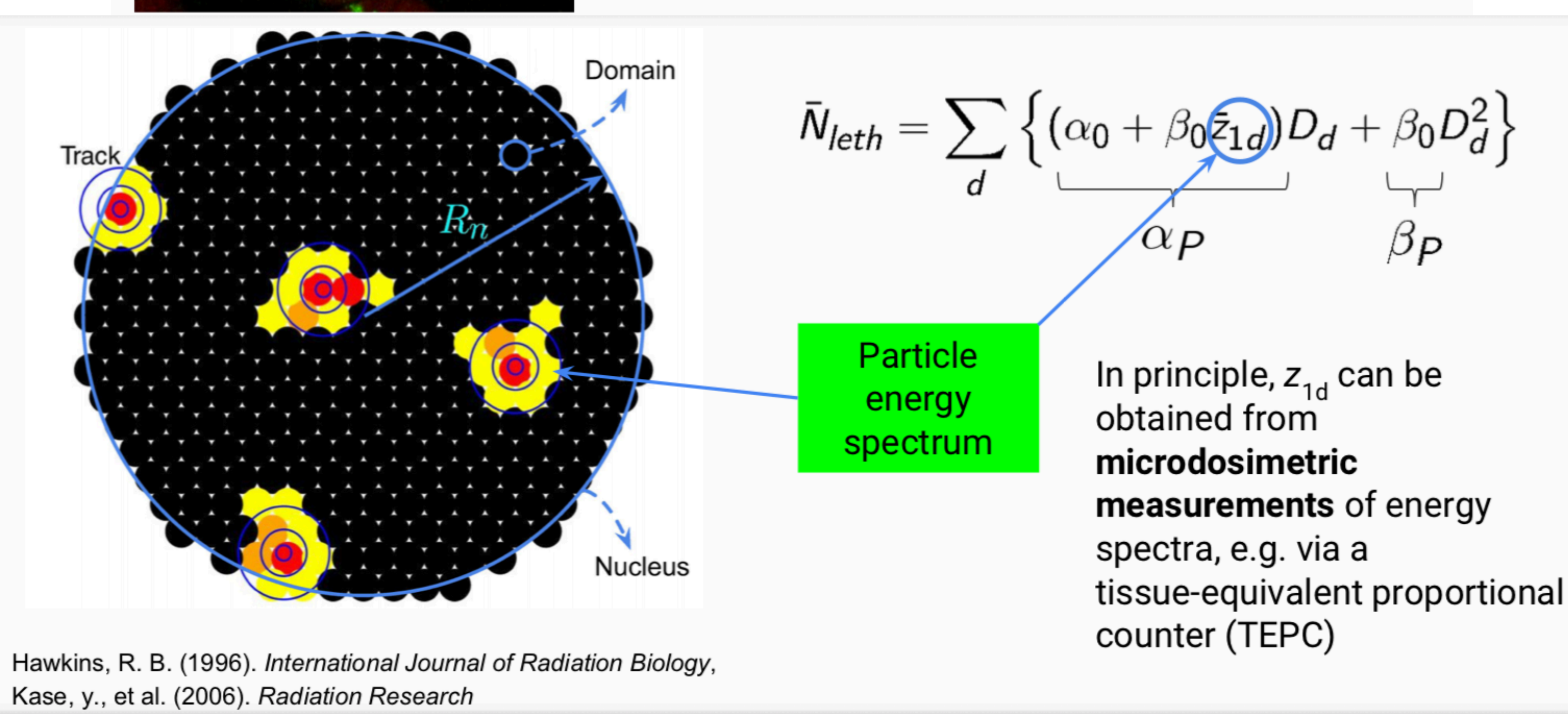


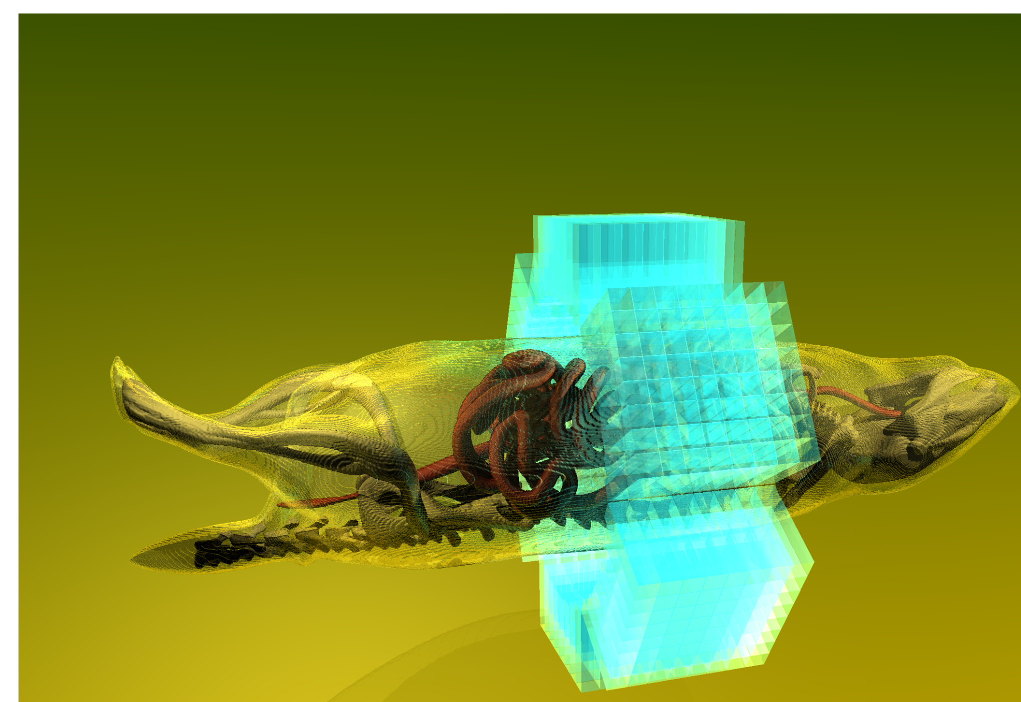
Modelling Biological Systems as a physists

I modelli radiobiologici & il Monte Carlo









- Algoritmi per prevedere il danno biologico e la distribuzione di dose in profondità
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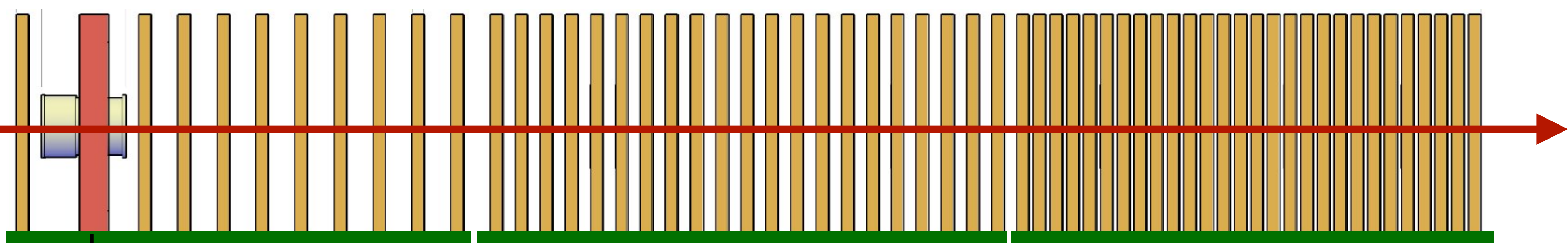
Misurare il picco di Bragg

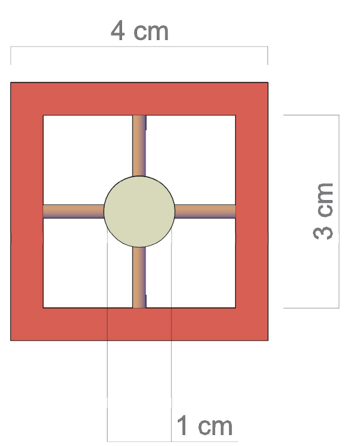
60 Silicon Carbide in stack configuration

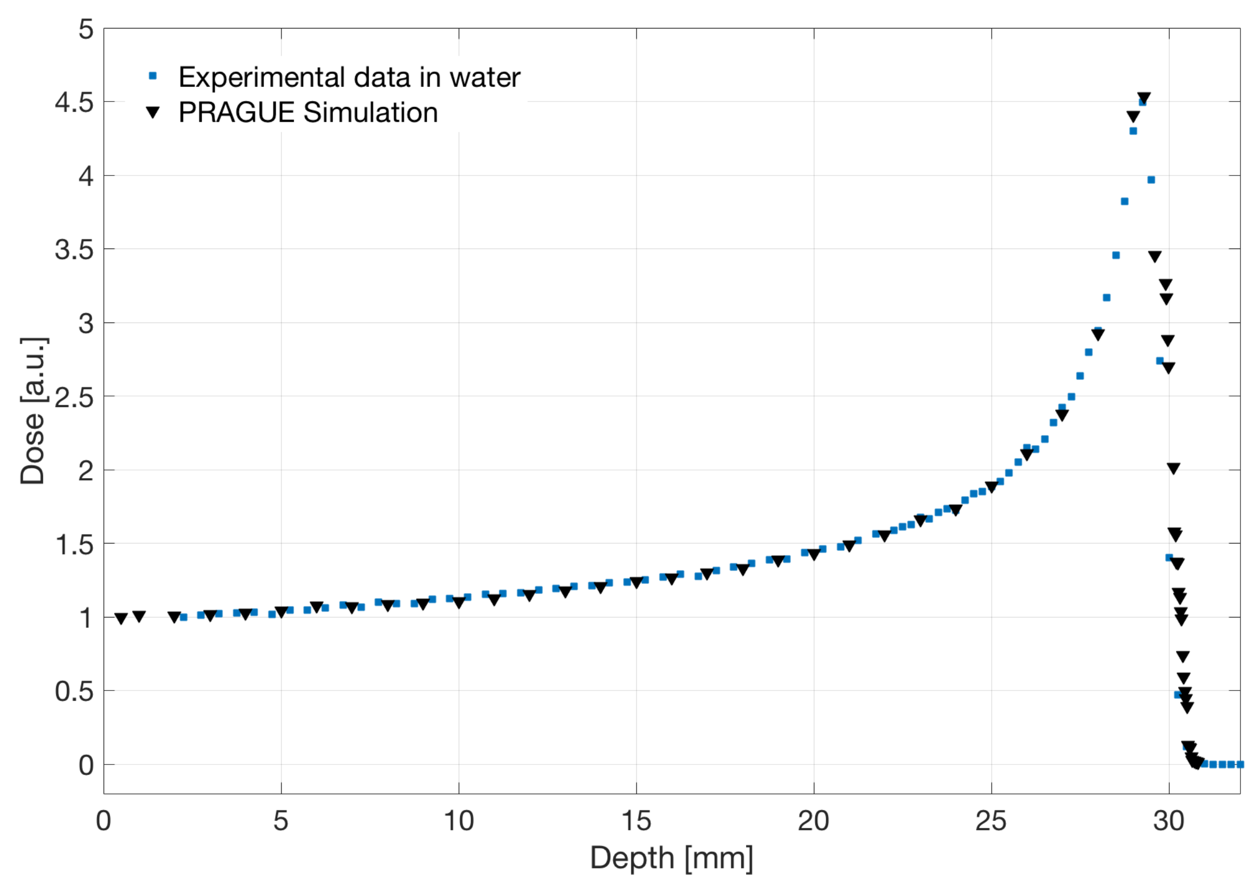
Incident proton



30 up to 150 MeV

Holder for Biological Sample





PRAGUE

Proton RAnGe measure Using silicon carbidE

- Algoritmi per prevedere il danno biologico e la distribuzione di dose in profondità
- Sviluppo di rivelatori per controllare il rilascio di dose
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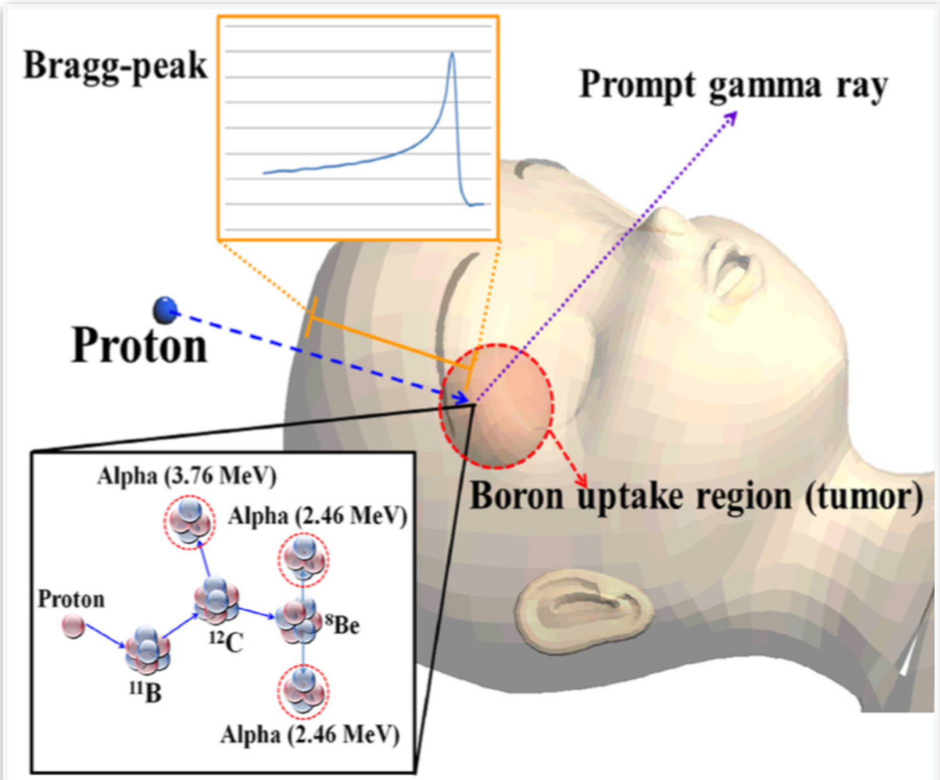
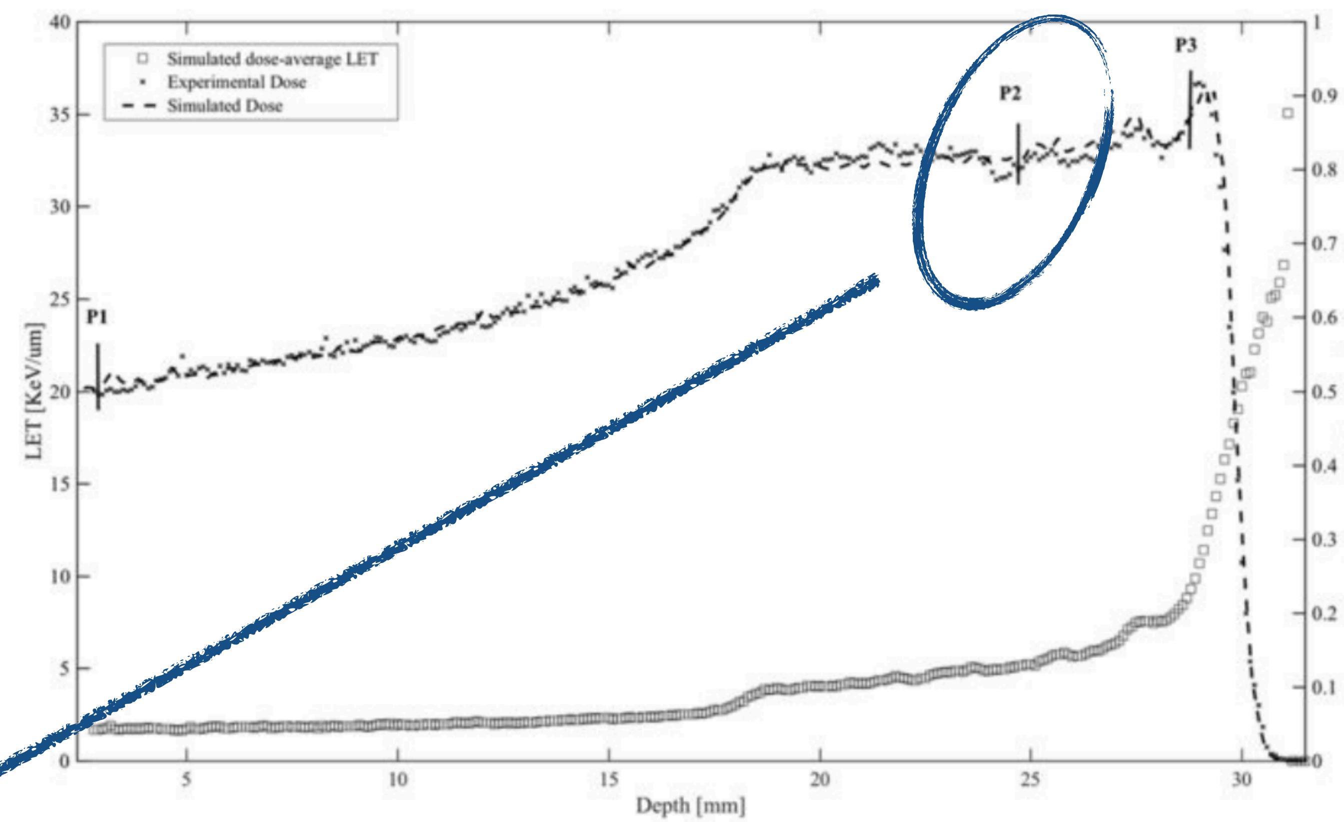
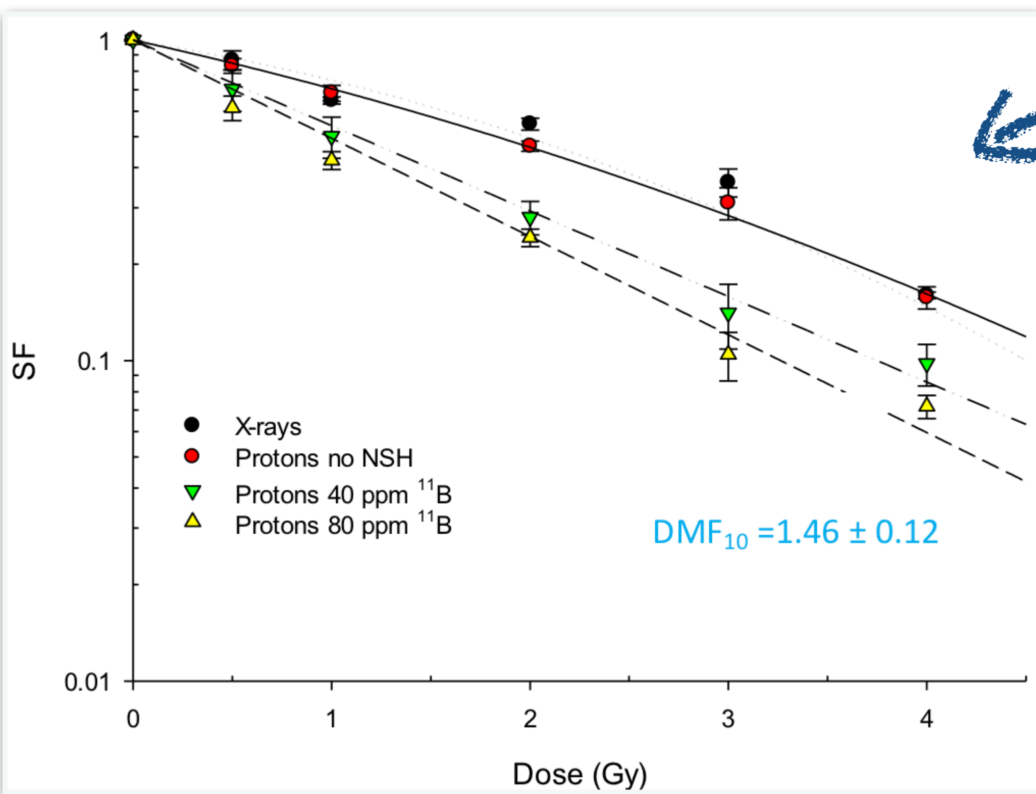
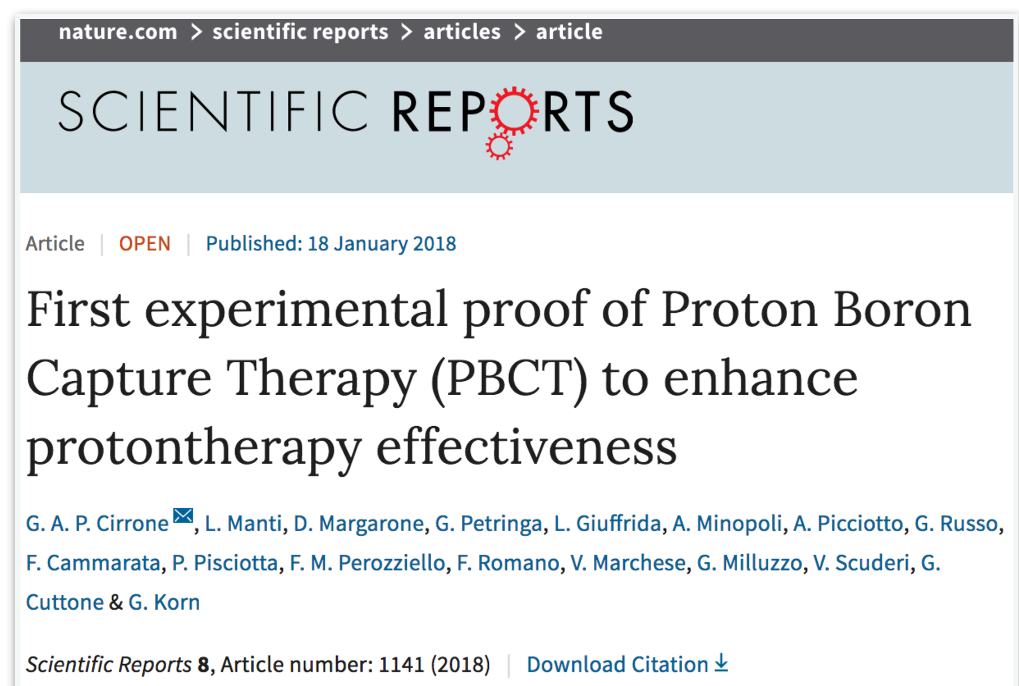
Proton Boron Capture Therapy





Irradiation @MID-SOBP

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SCIENTIFIC REPORTS

Article | OPEN | Published: 18 January 2018

First experimental proof of Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness

G. A. P. Cirrone, L. Manti, D. Margarone, G. Petringa, L. Giuffrida, A. Minopoli, A. Picciotto, G. Russo, F. Cammarata, P. Pisciotta, F. M. Perozziello, F. Romano, V. Marchese, G. Milluzzo, V. Scuderi, G. Cuttone & G. Korn

Scientific Reports **8**, Article number: 1141 (2018) | Download Citation

- Algoritmi per prevedere il danno biologico e la distribuzione di dose in profondità
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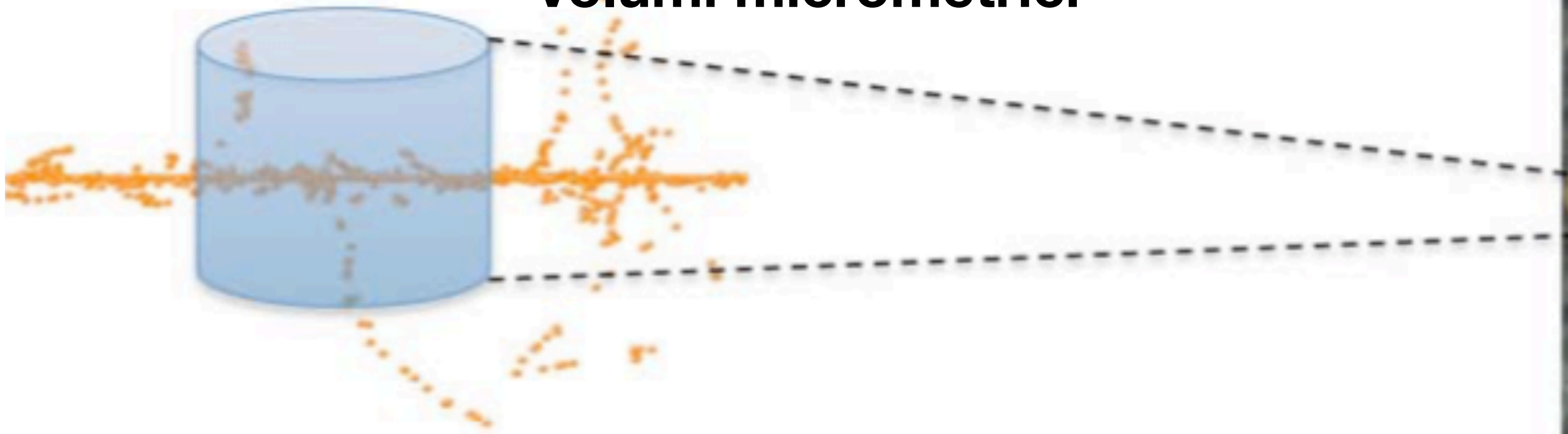
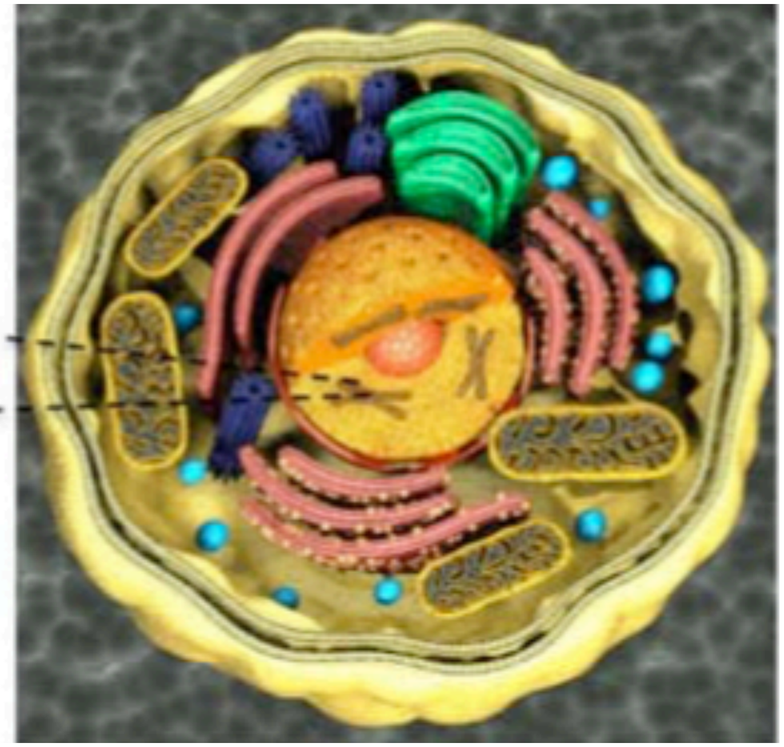
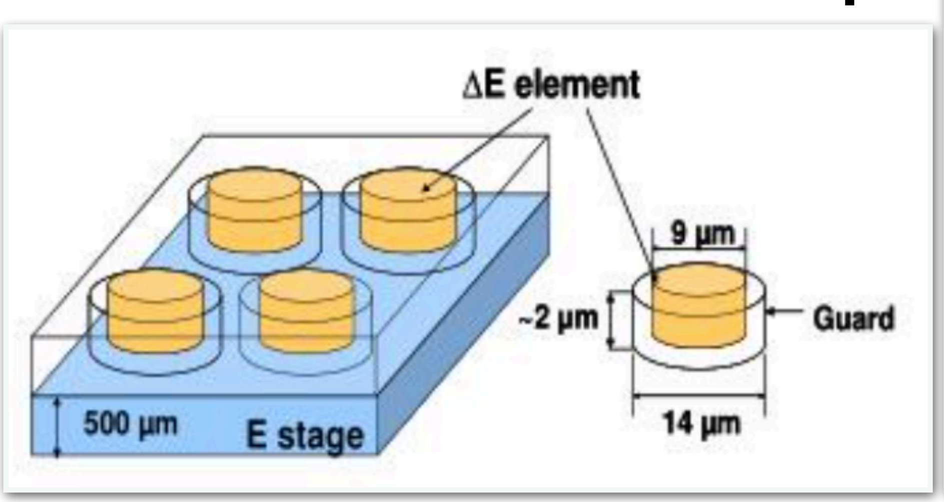
La misura del LET

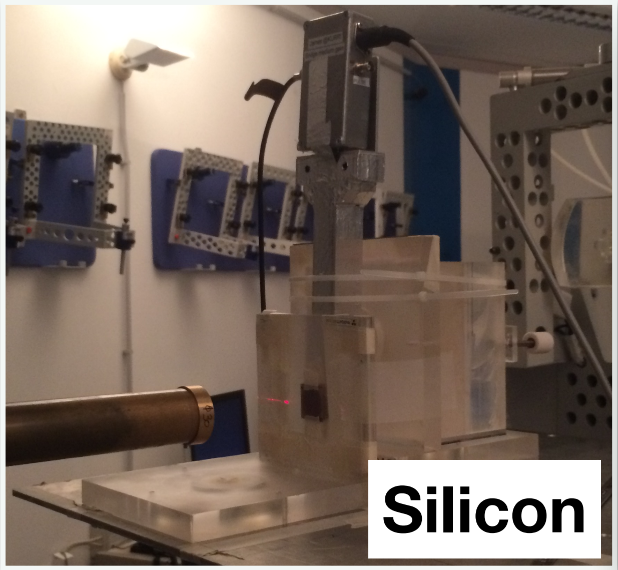
distribuzione energetica viene misurata su volumi micrometrici

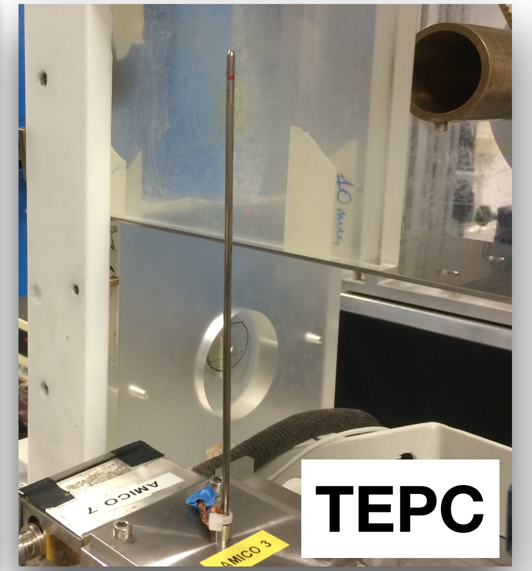


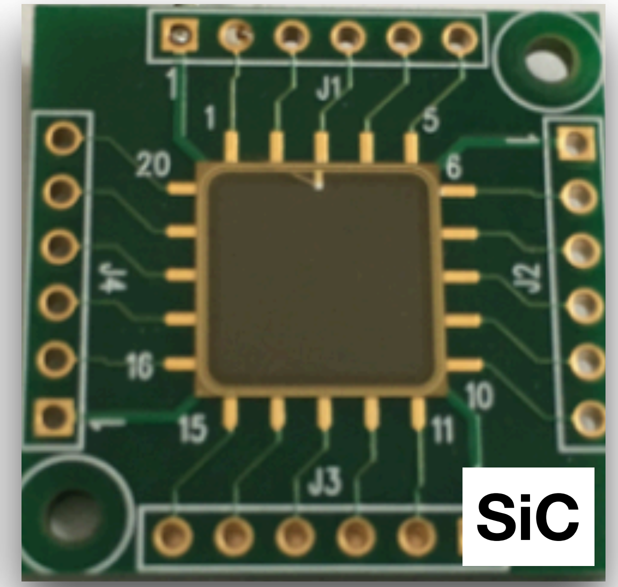


Si-Telescope



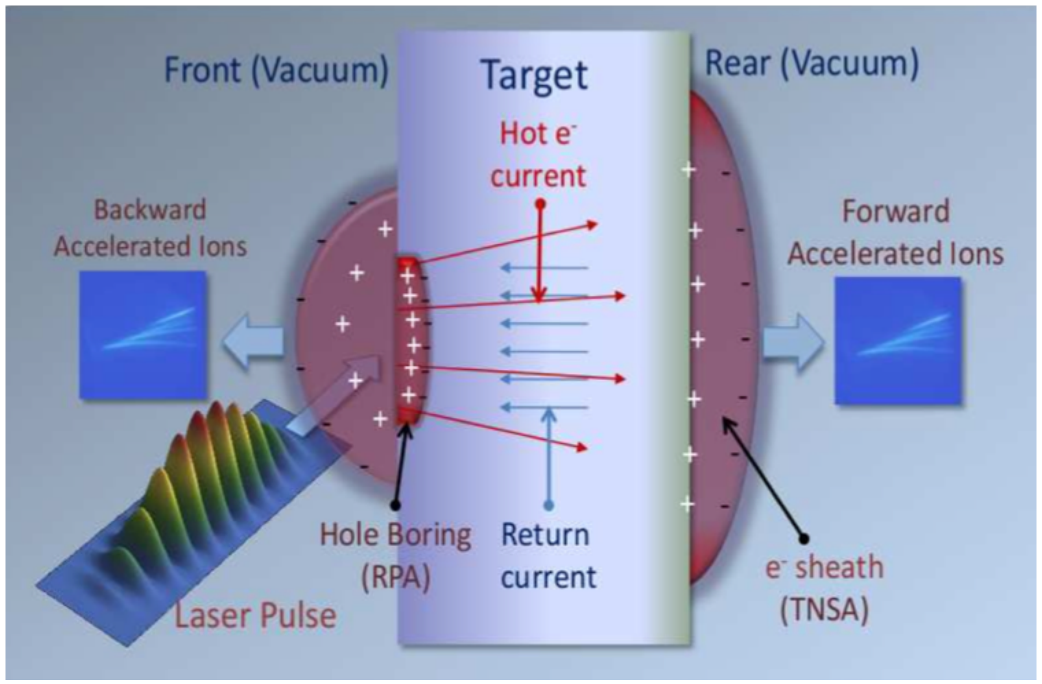


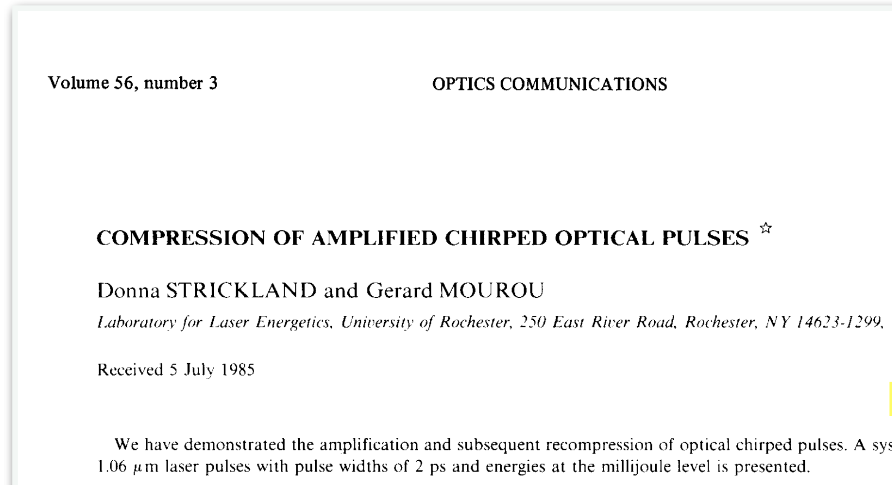




I protoni accelerati da laser: il futuro dell'adroterapia?

Le particelle accelerate con i laser




Volume 56, number 3 OPTICS COMMUNICATIONS

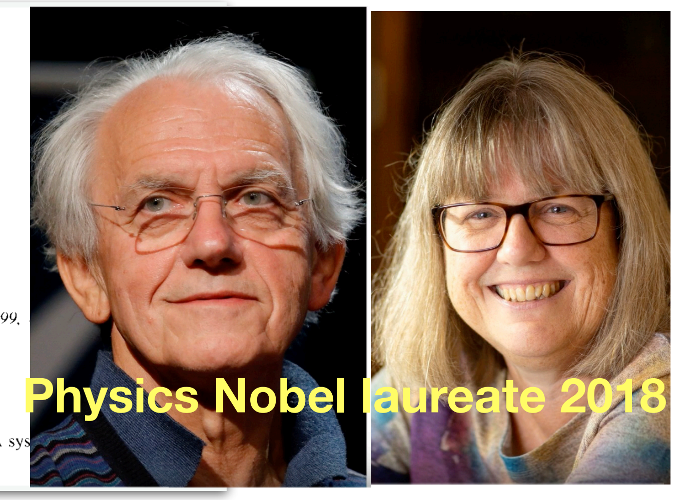
COMPRESSION OF AMPLIFIED CHIRPED OPTICAL PULSES ☆

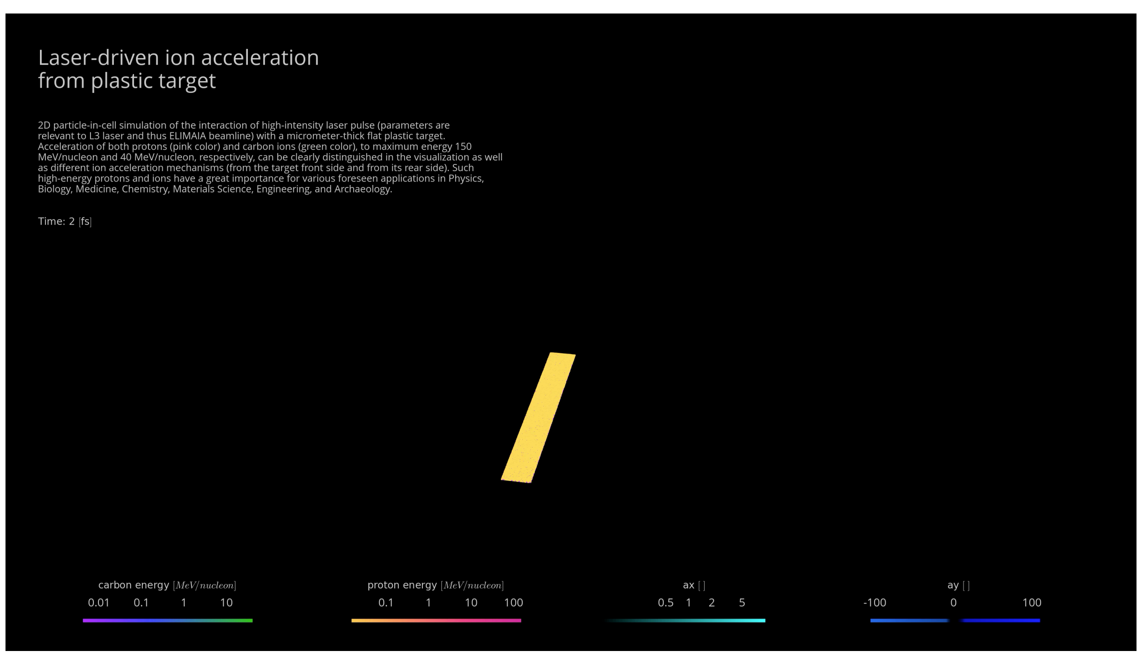
Donna STRICKLAND and Gerard MOUROU

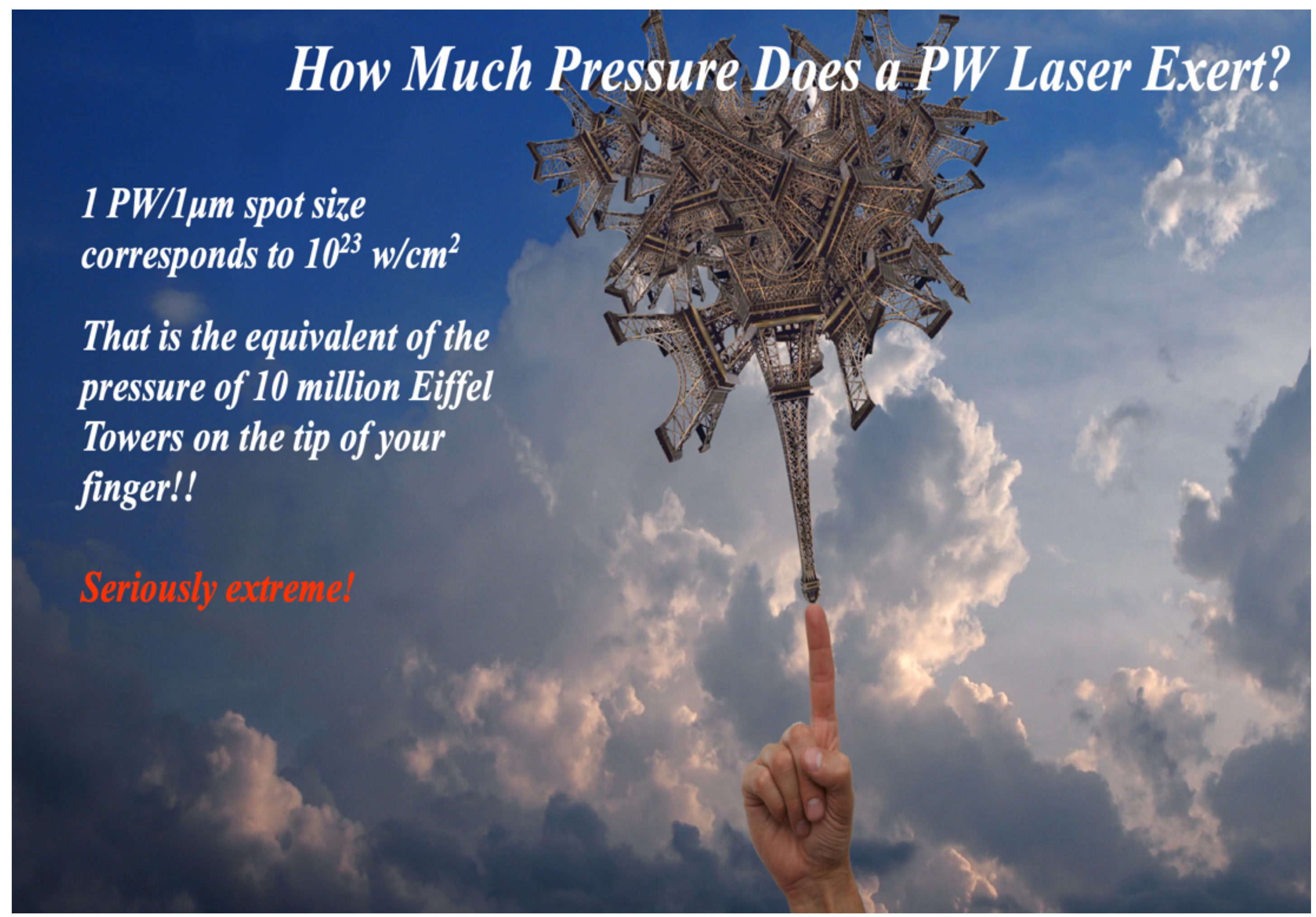
Laboratory for Laser Energetics, University of Rochester, 250 East River Road, Rochester, NY 14623-1299,

Received 5 July 1985

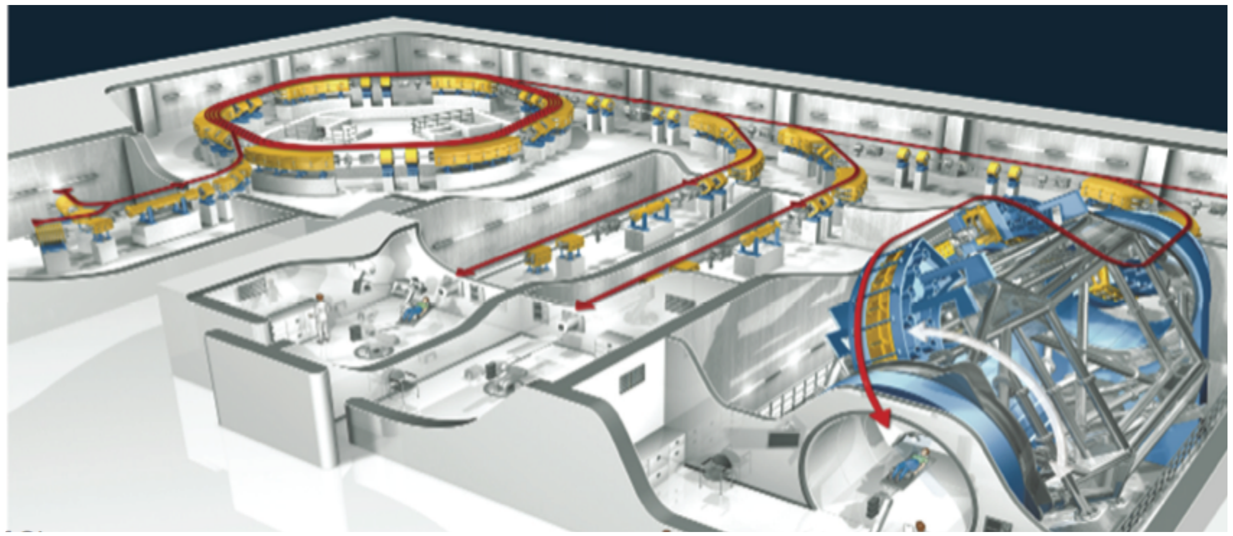
We have demonstrated the amplification and subsequent recompression of optical chirped pulses. A sys
1.06 μm laser pulses with pulse widths of 2 ps and energies at the millijoule level is presented.





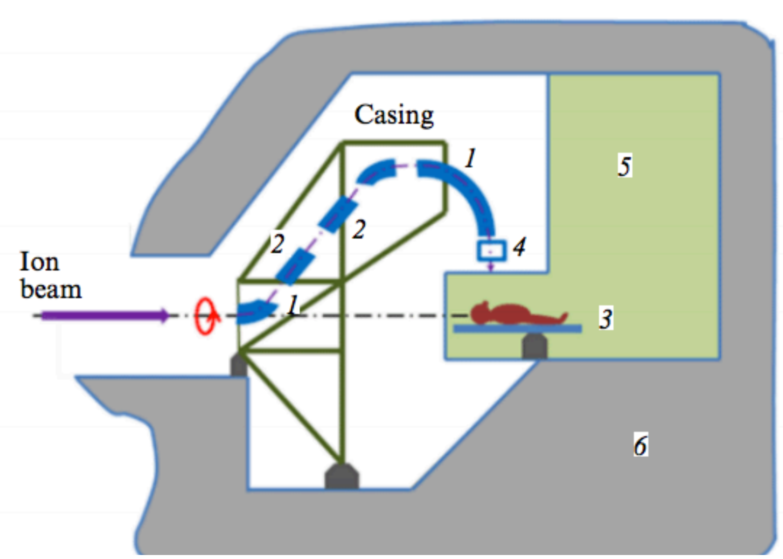


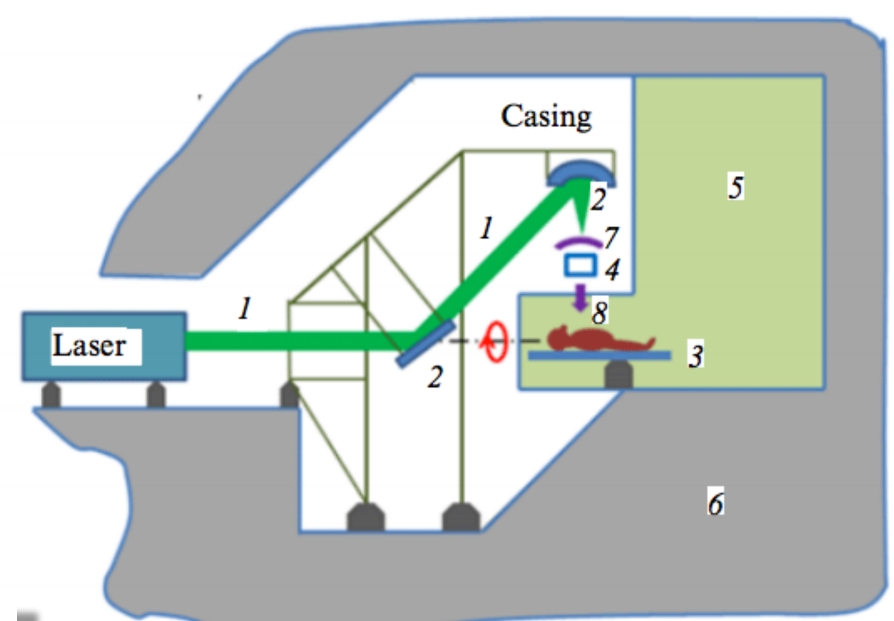
I laser-driven per applicazioni mediche?



- Grandi macchine acceleratrici
- Sistemi sofisticati per il trasporto del fascio(gantry)
- Costi elevati
- Numero limitato di centri

"If 200 MeV proton accelerators would be as cheap and small as the 10 MeV electron linacs used in conventional radiotherapy, at least 90% of the patients would be treated with proton beams"
U. Amaldi et al., NIM A 2010.

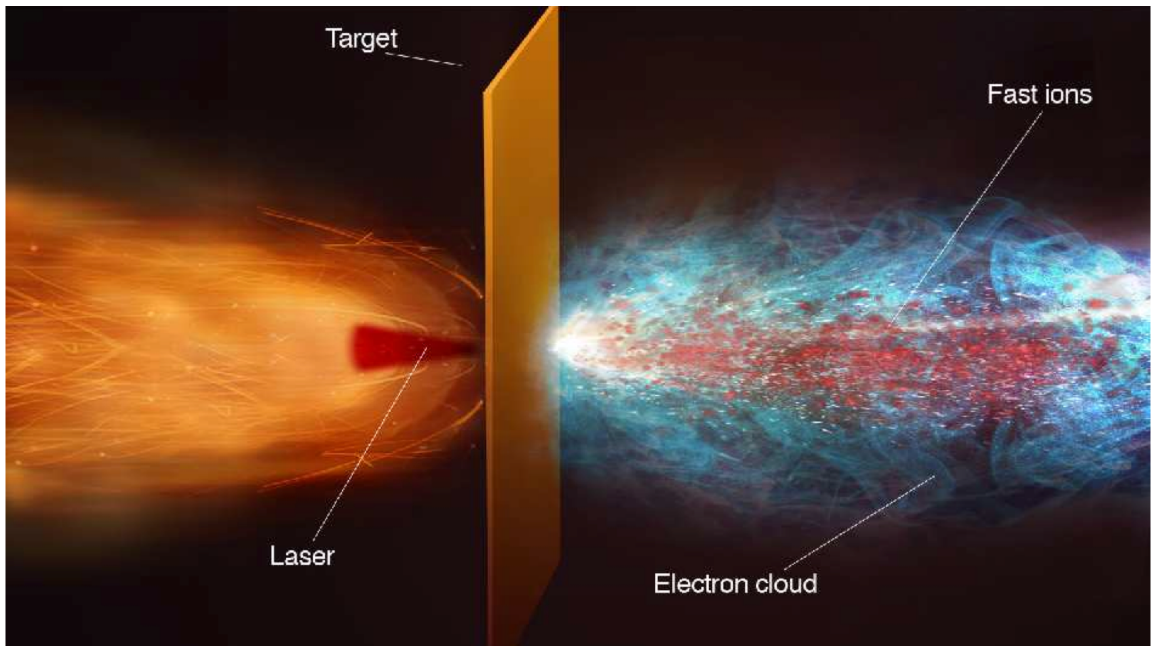




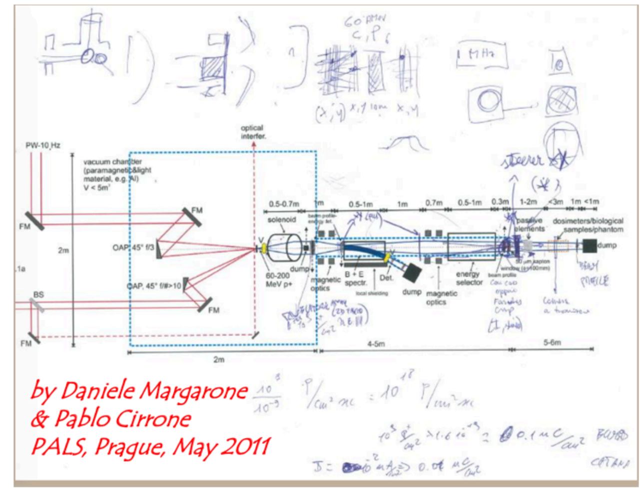
Multi-source machine to deliver different kinds of beams according to the specific requirements: γ, e-, p, n, ions.

Il progetto ELIMED

una nuova sorgente …



2011



2012


Fyzikální ústav
Akademie věd ČR, v. v. i.

Memorandum of Understanding for a scie
collaboration towards medical applicatio

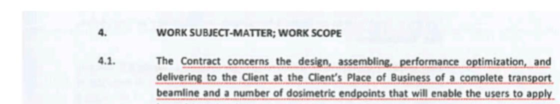
Between the

Eli-Beamlines, Institute of Physics of AS CR, public r
Prague, Czech Republic

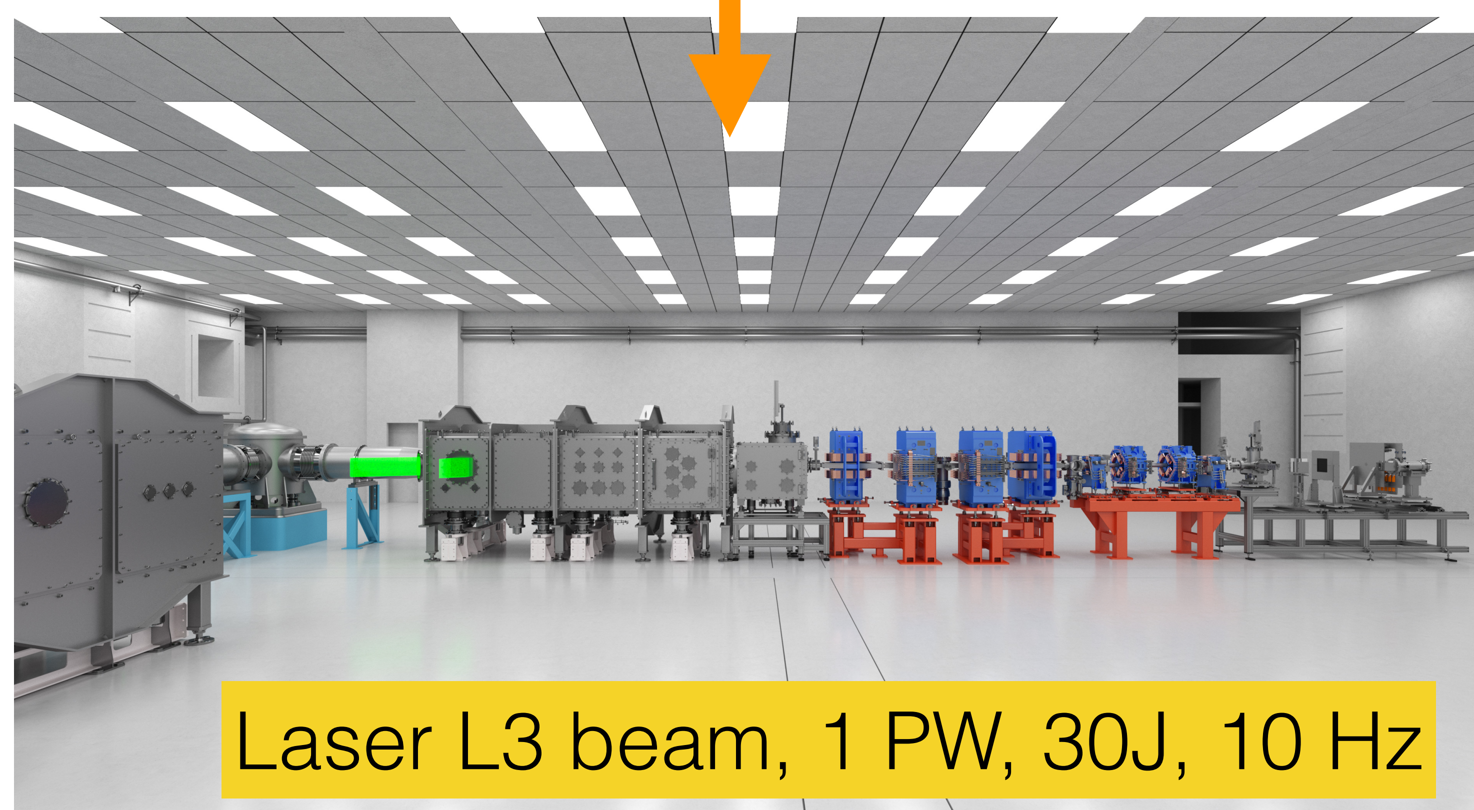
And

Laboratori Nazionali del Sud (LNS), of INFN, public research institution,
Catania, Italy

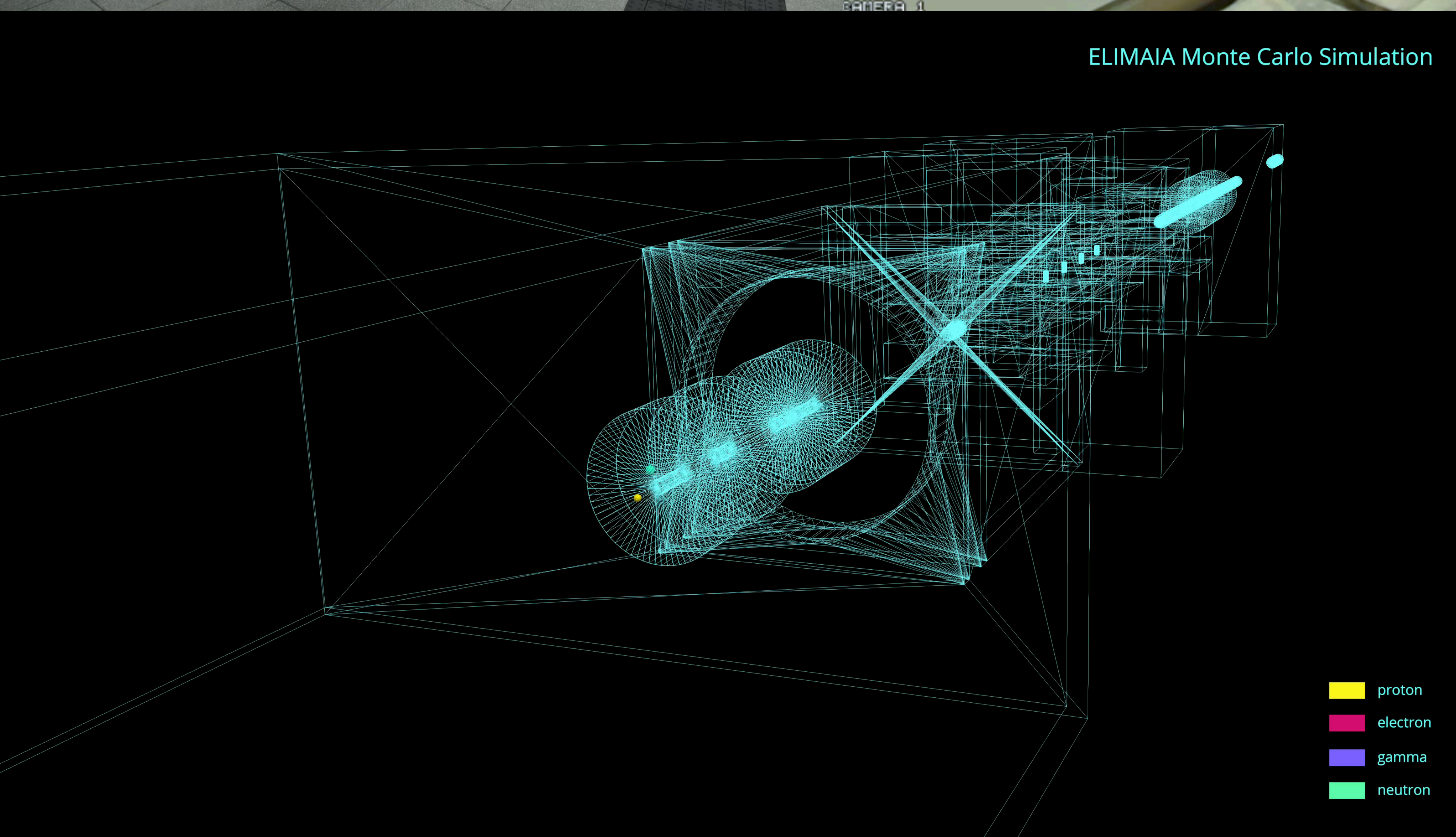
2014


4. WORK SUBJECT-MATTER; WORK SCOPE

4.1. The Contract concerns the design, assembling, performance optimization, and delivering to the Client at the Client's Place of Business of a complete transport beamline and a number of dosimetric endpoints that will enable the users to apply

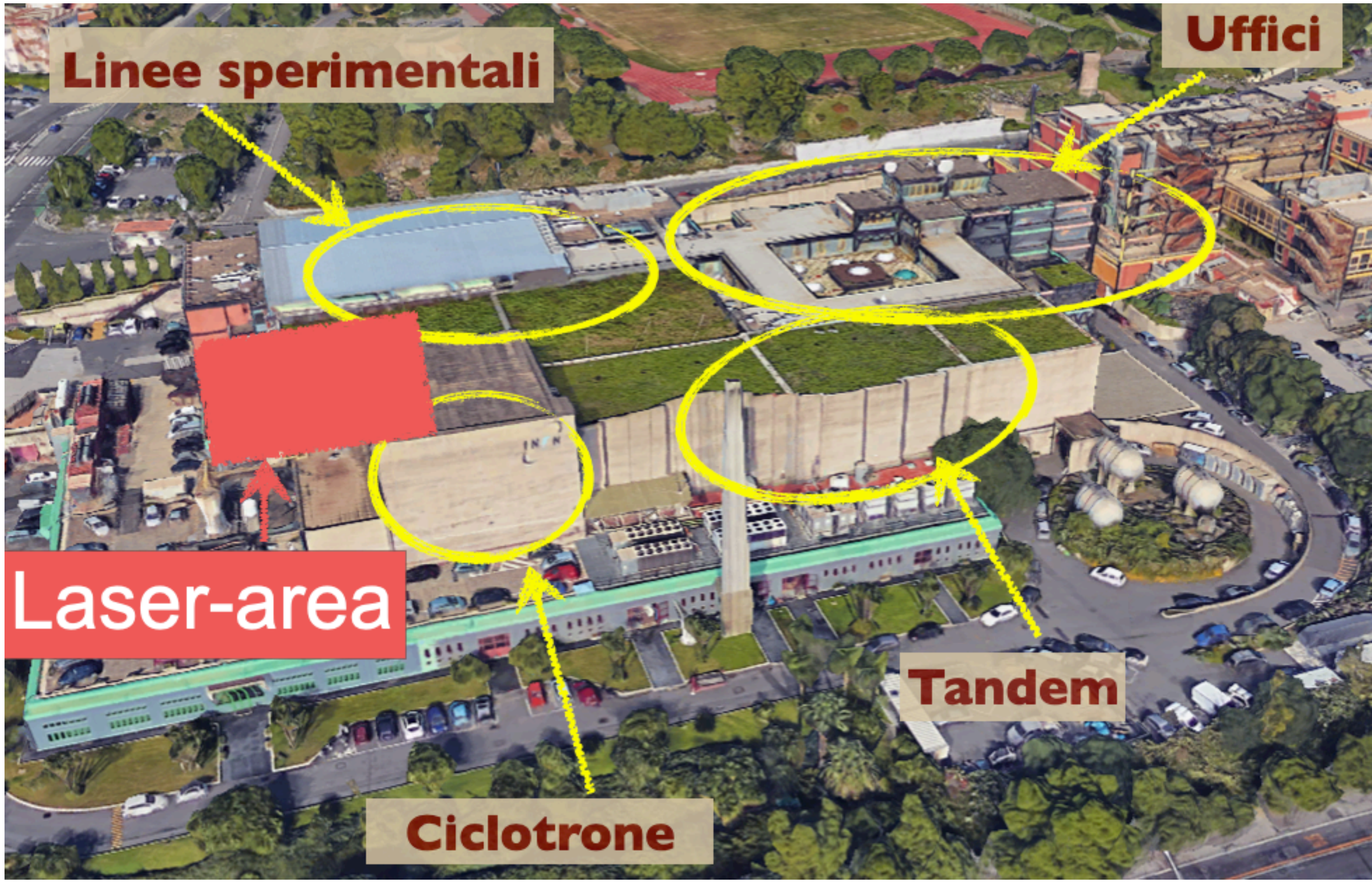


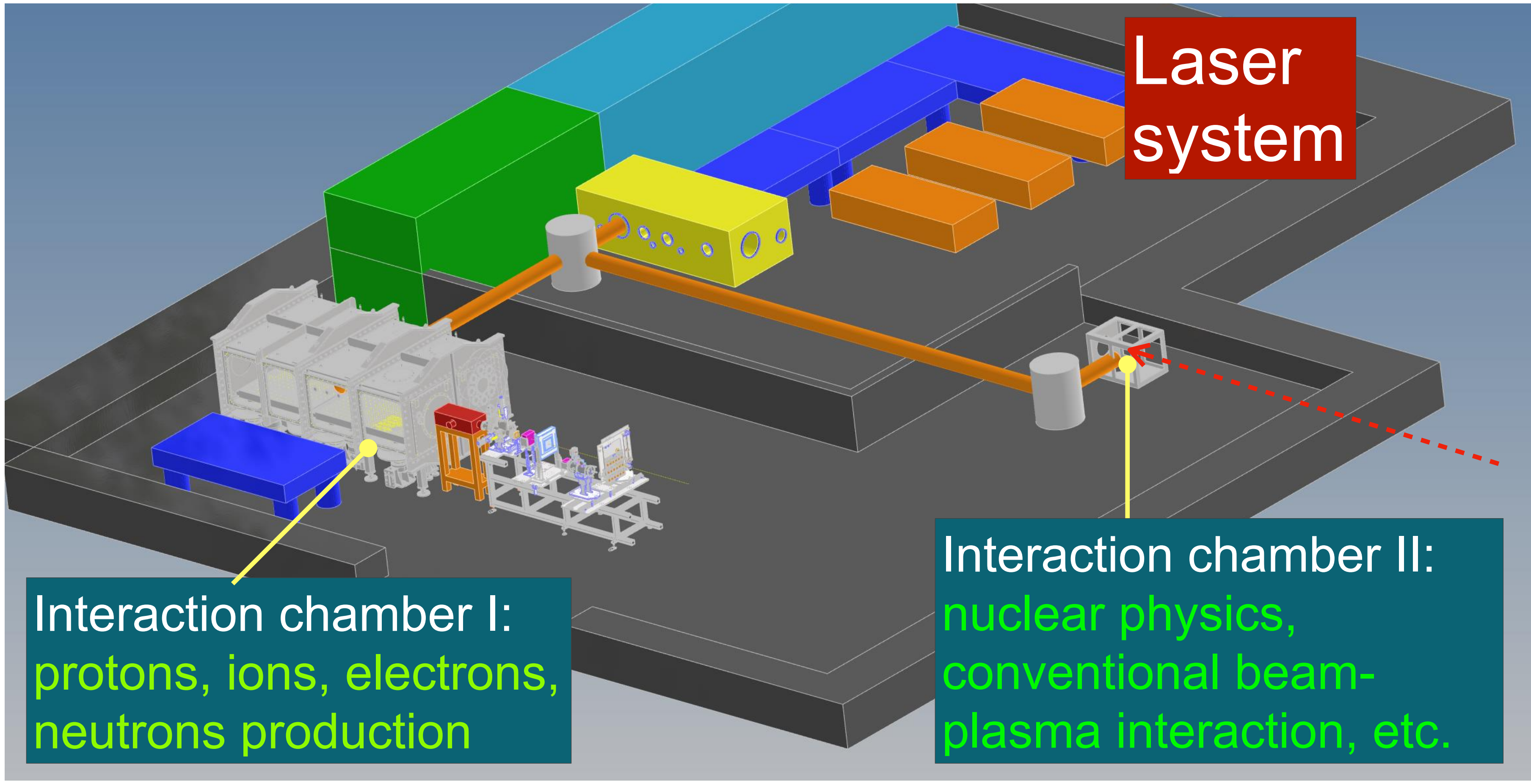
ELI-Beamlines, Prague (CZ)



eli beamlines

INFN - Laser indUCEd radiation production





per
concludere…

Fisica Applicata

- Sviluppiamo rivelatori
- Studiamo algoritmi per stimare il danno biologico
- Simuliamo l'effetto delle radiazioni
- Studiamo tecniche per incrementare l'efficienza dei trattamenti
- Studiamo nuove tecniche per accelerare le particelle
- Collaboriamo con le aziende
- Lavoriamo in un team che non comprende soltanto "fisici"

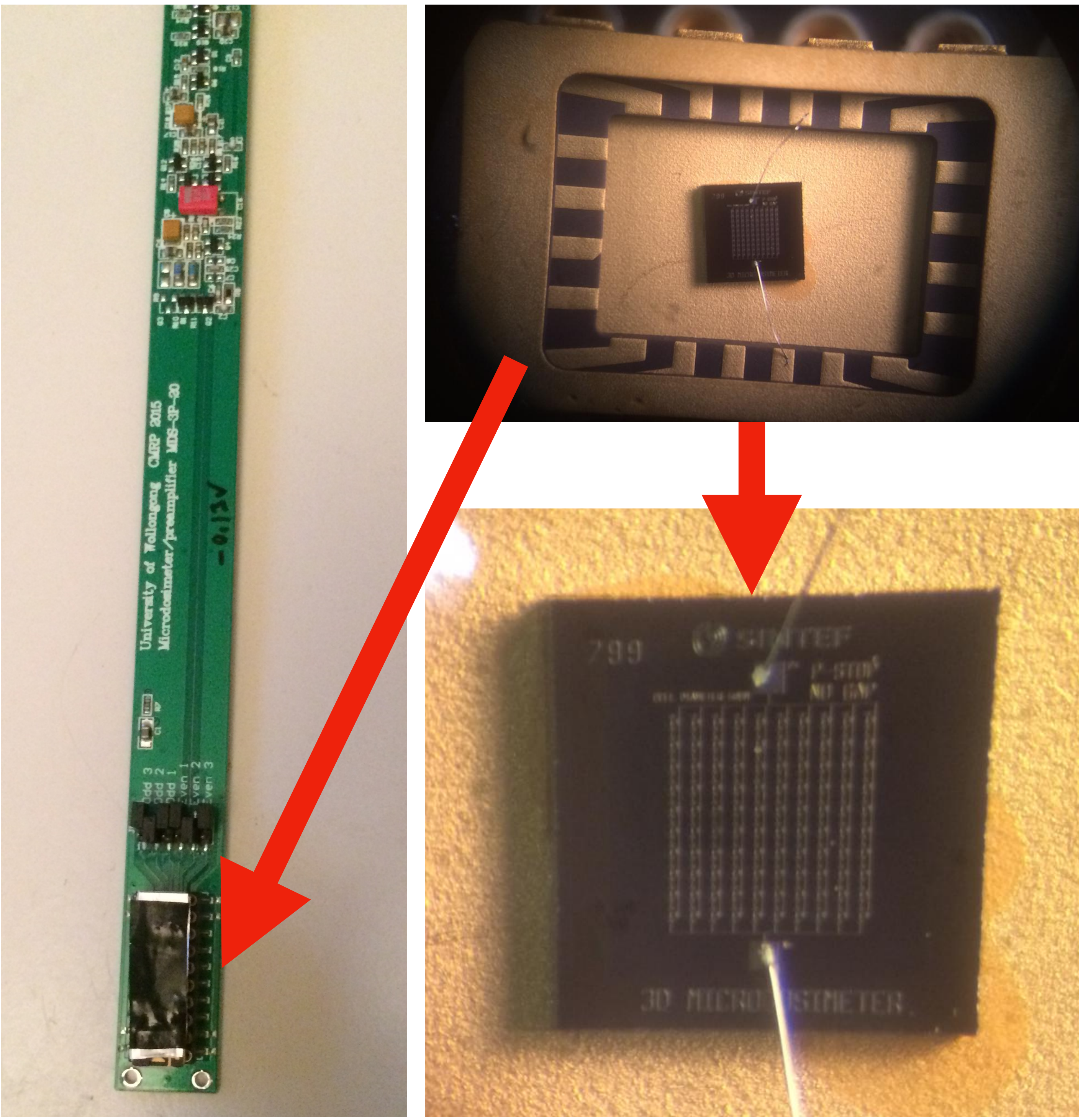
Fisici
Tecnici (meccanici ed elettronici)
Biologi
Ingegneri

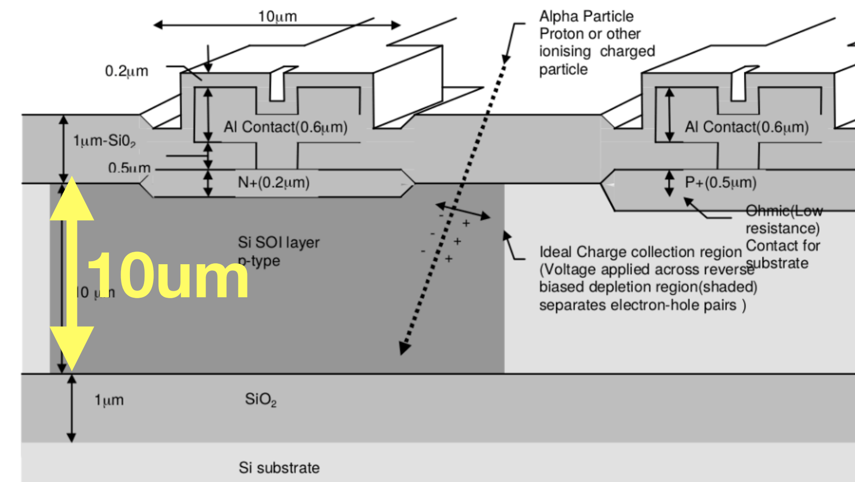
Le attività che faremo insieme nei prossimi giorni

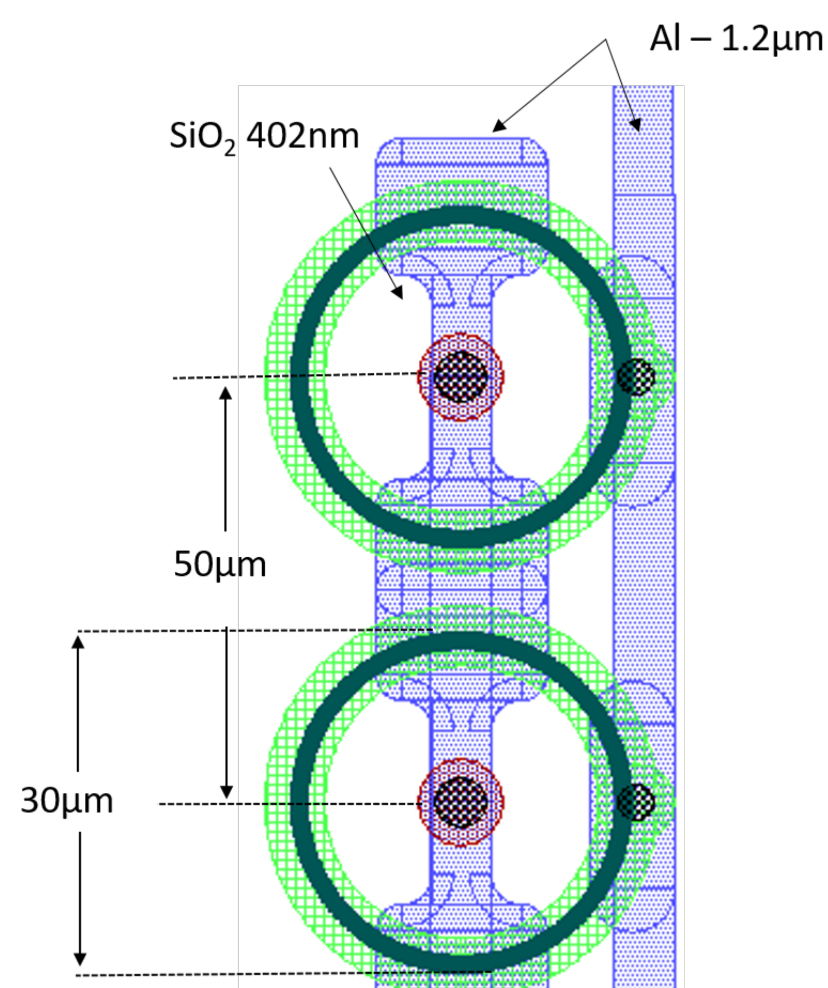
Le attività che faremo

- ❑ **Visita della sala CATANA**
- ❑ **Misura del LET con una sorgente di particelle alpha**
- ❑ **Lettura di un rivelatore a traccia di tipo CR39**
- ❑ **Lettura di un rivelatore passivo di tipo RCF**

La misura del LET



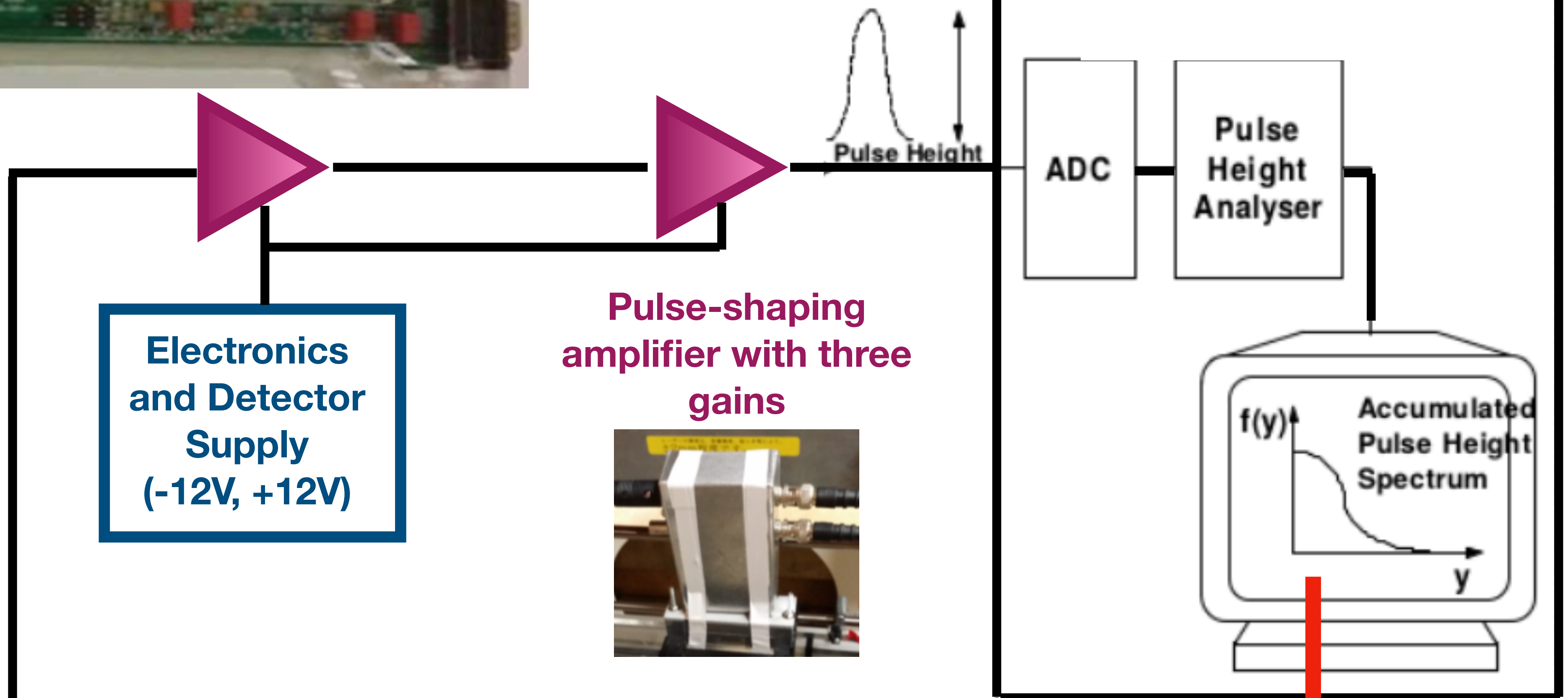


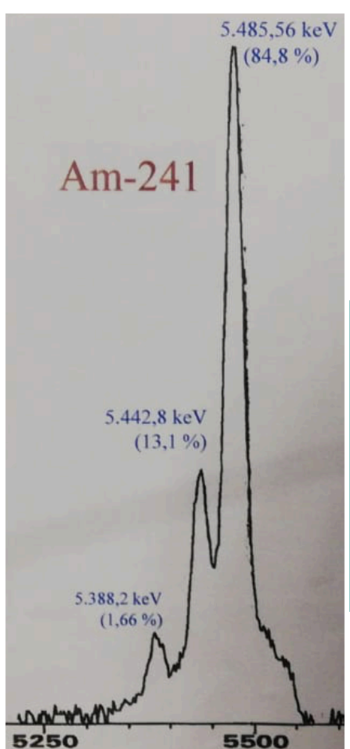


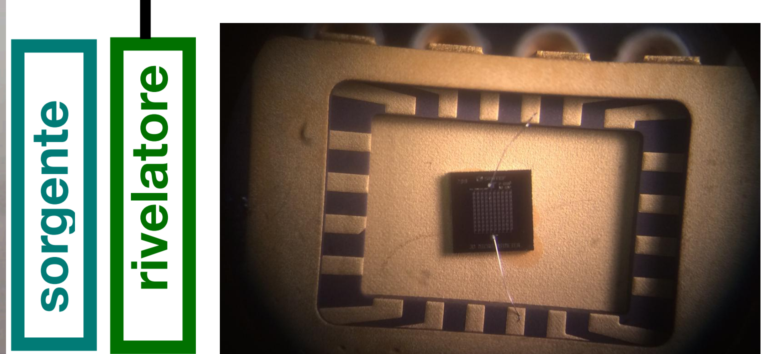
G Petringa, PhD - giada.petringa@lns.infn.it

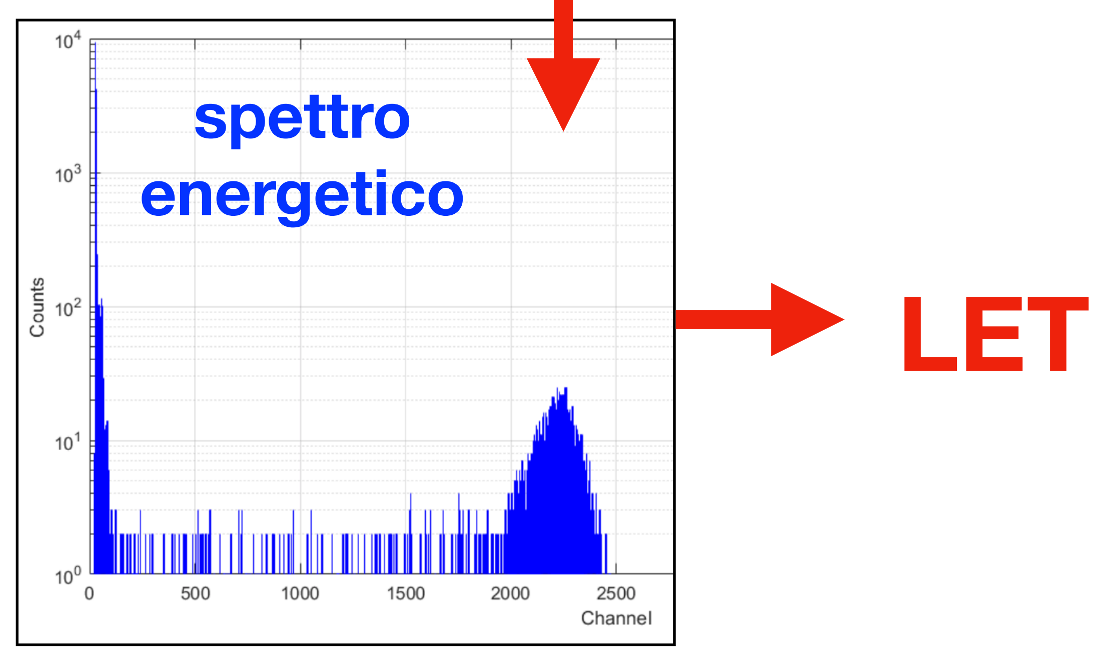
La misura del LET

Low noise front-end electronics
(Preamplifier integrated circuit)



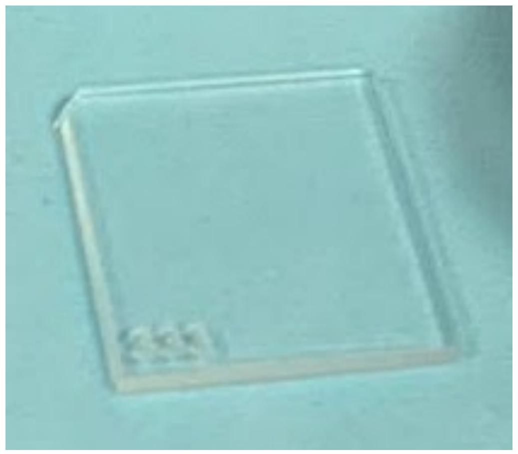


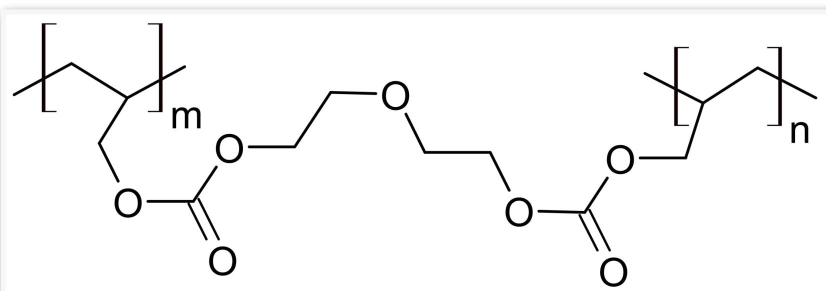




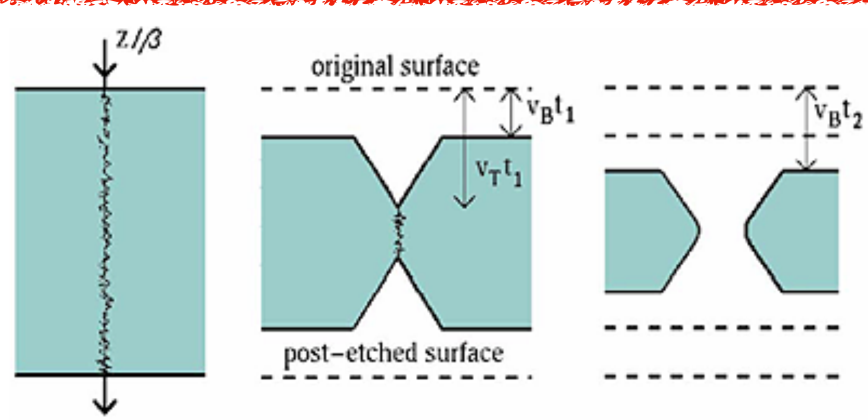
Lettura di un rivelatore di tipo CR39

CR39

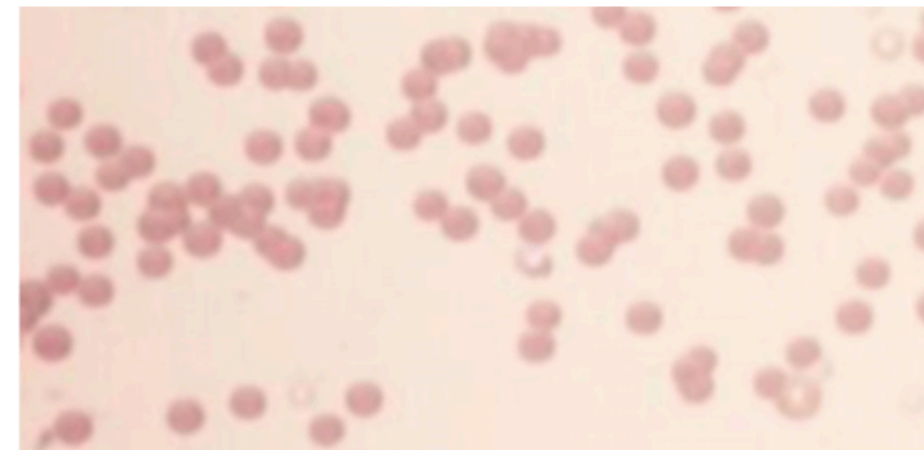


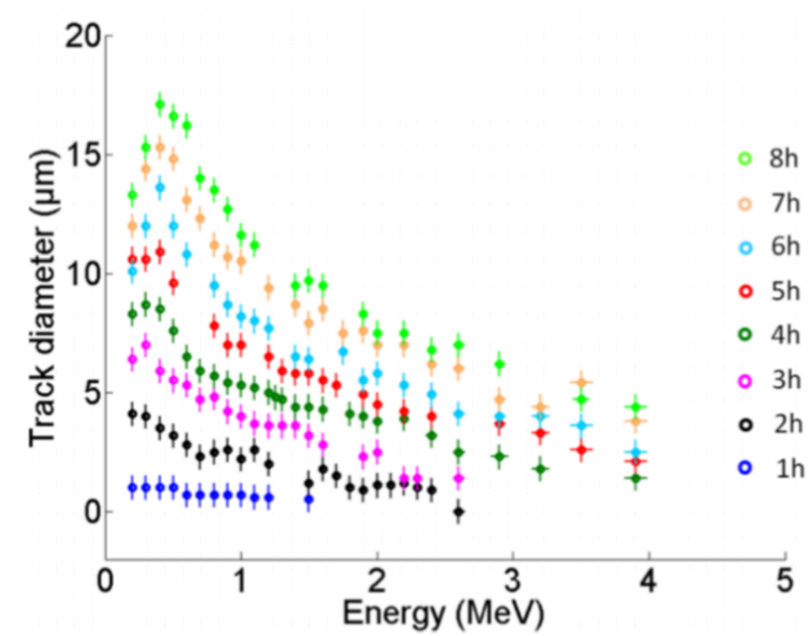


Etching NaOH 70°



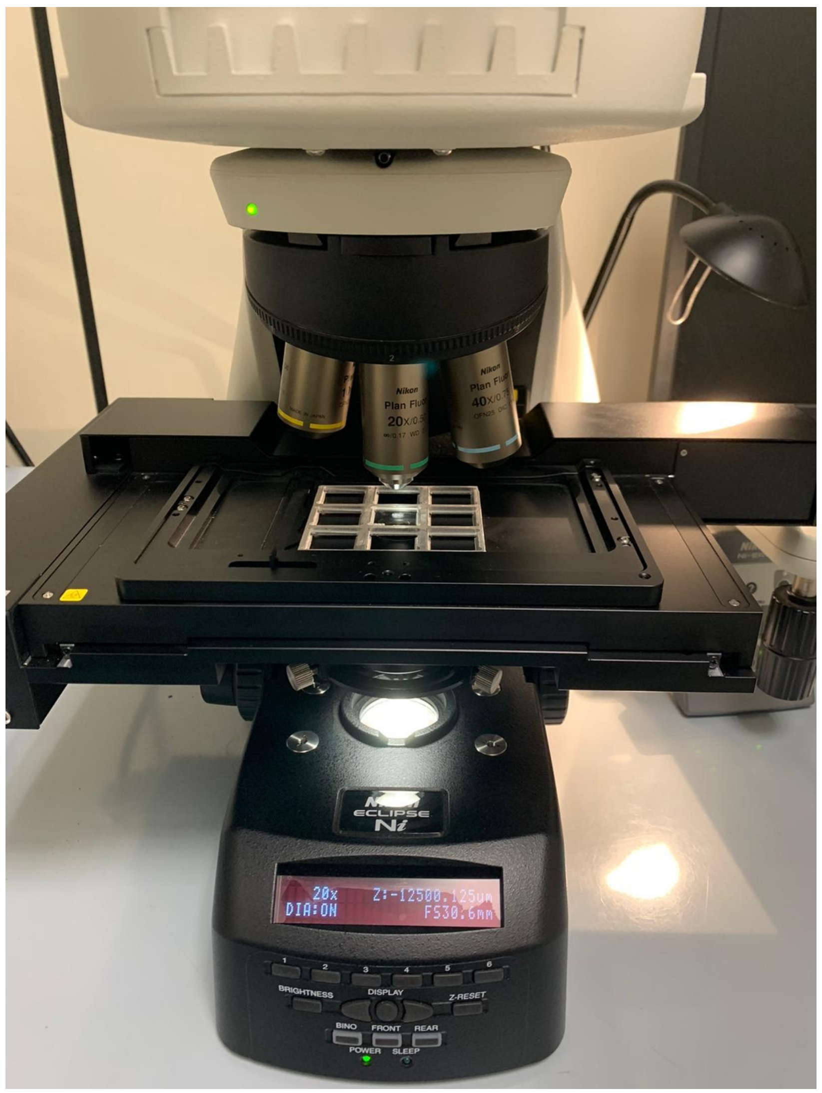
Dimensione tracce Vs Energia



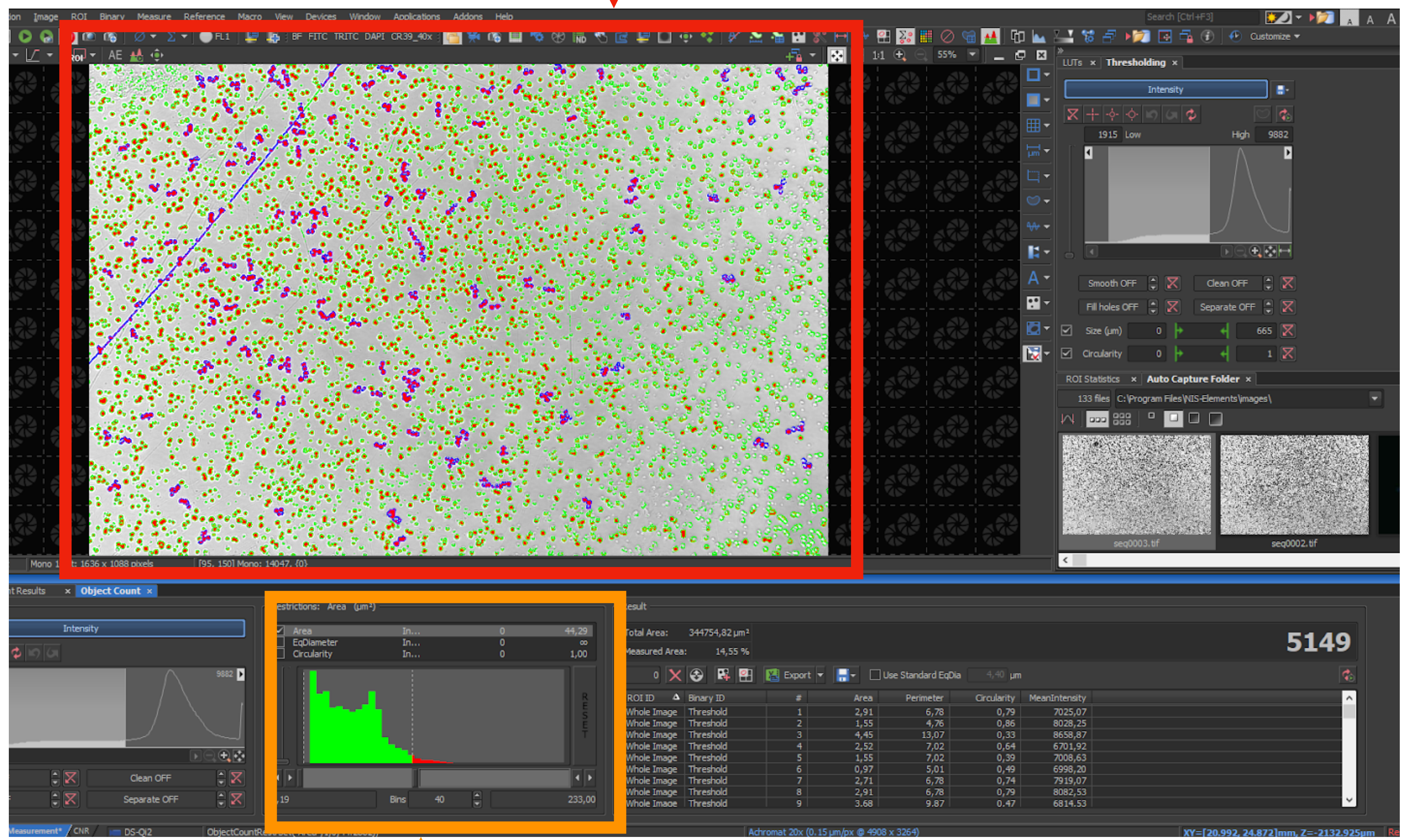


G Petringa, PhD - giada.petringa@lns.infn.it

Lettura di un rivelatore di tipo CR39

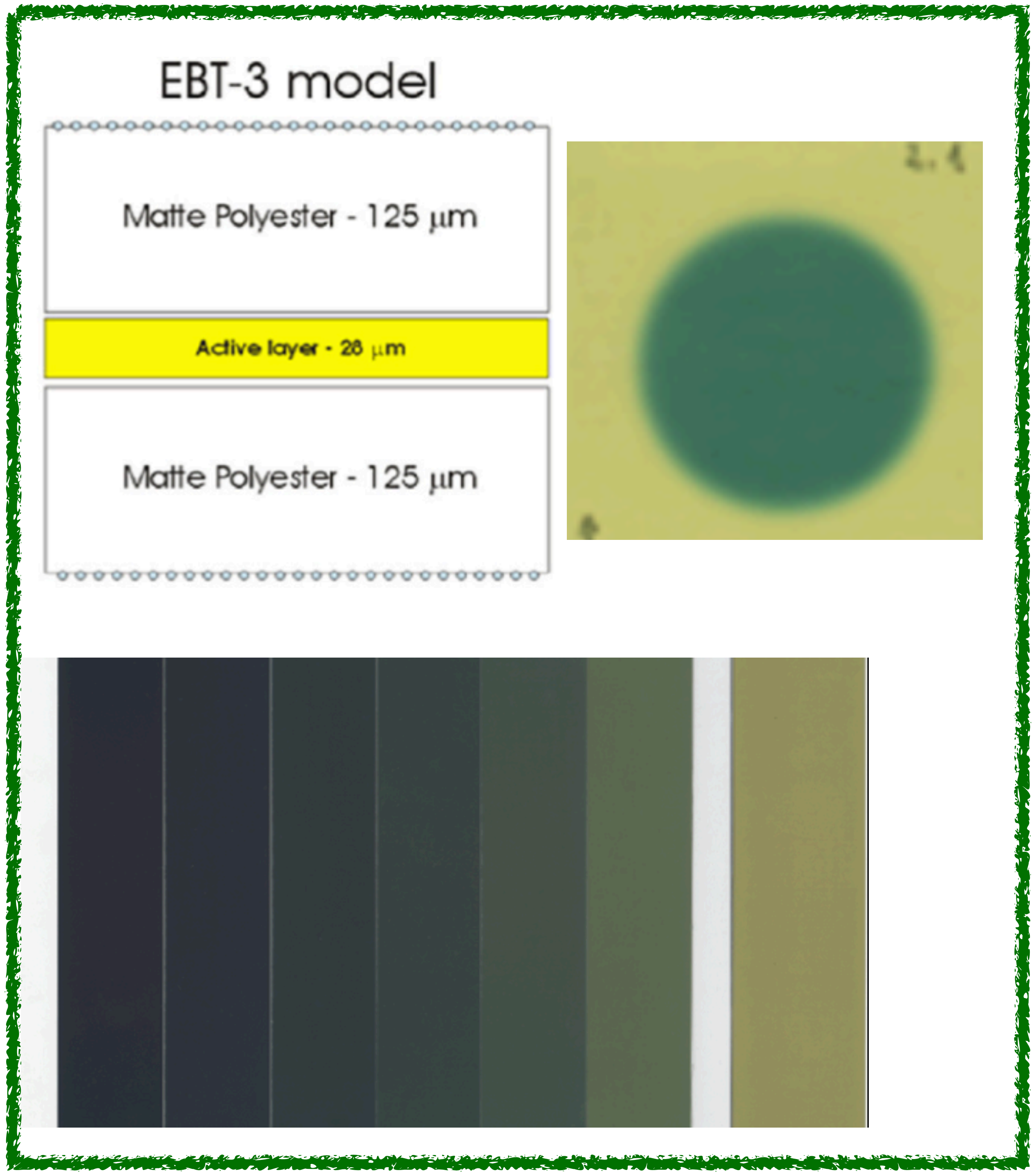


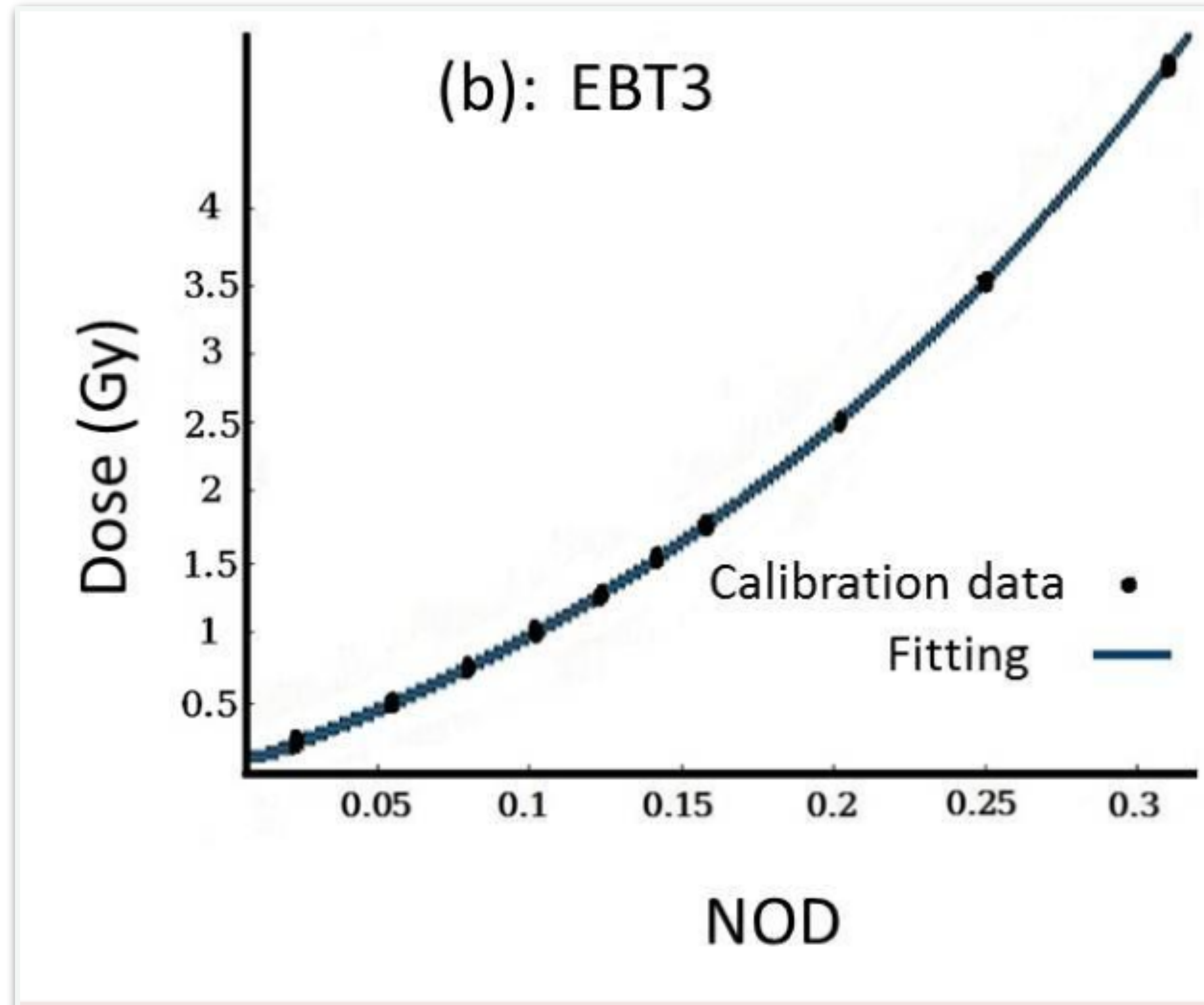
selezioniamo le tracce che ci interessano



distribuzione delle tracce

Lettura di un rivelatore di tipo RCF





$$OD = log_{10}T = log_{10}\frac{I_0}{I}$$

$$\downarrow$$

Dose [Gy]

Grazie per l’attenzione