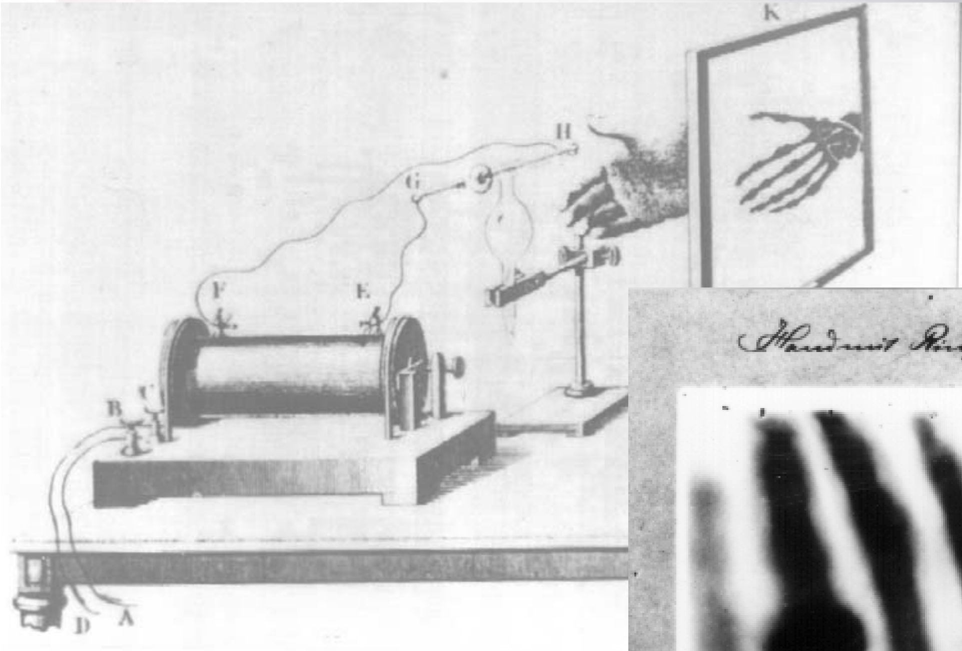
Hadrons for cancer therapy at CNAO

Marco Pullia

CNAO Foundation

Tumours and radiotherapy

Physics and medicine together since long: diagnosis and therapy



1895

X ray discovery

Wilhelm Conrad Röntgen

(1845 – 1923)

(courtesy of U. Amaldi)

Tumours

- Errors in cell DNA and no apoptosis
- They grow in an uncontrolled way
- They infiltrate the surrounding tissues and can originate metastasis (malignant)
- When metastatic, only chemotherapy is possible
- If localised, surgery or **radiotherapy**

Energy and Efficacy

Administered dose

1 Gy = 1 J / 1Kg

(typical dose in radiotherapy 35 X 2 Gy)

How many cells do I kill?

Potential energy (1 m fall = 10 Gy)

Heat (fever 38° = 4185 Gy)

Ionizing radiation (little energy, many damages)

Radiation damage

- Ionization breaks chemical bonds
- Free radicals creation (mainly hydroxyl radical, OH^-, and superoxide, O_2^- . Poison for the cell!)
- The target is DNA, ionization distribution is relevant

Cancer therapy

100 % of cancer patients

Cured
45 %

Not cured
55 %

Local treatments
(surgery, radiotherapy)
40 %

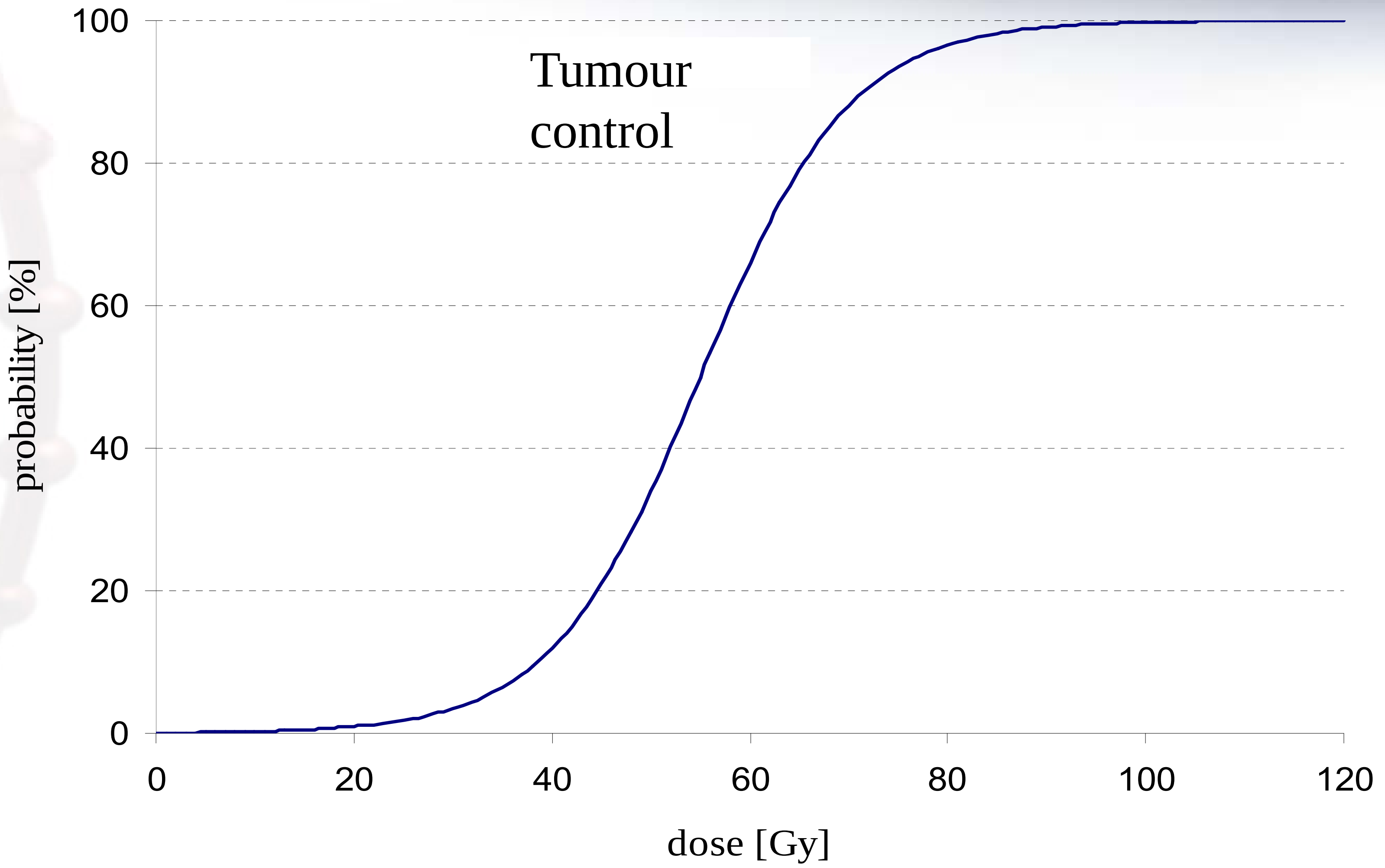
Other treatments
(chemotherapy, etc)
5 %

Surgery
alone
22 %

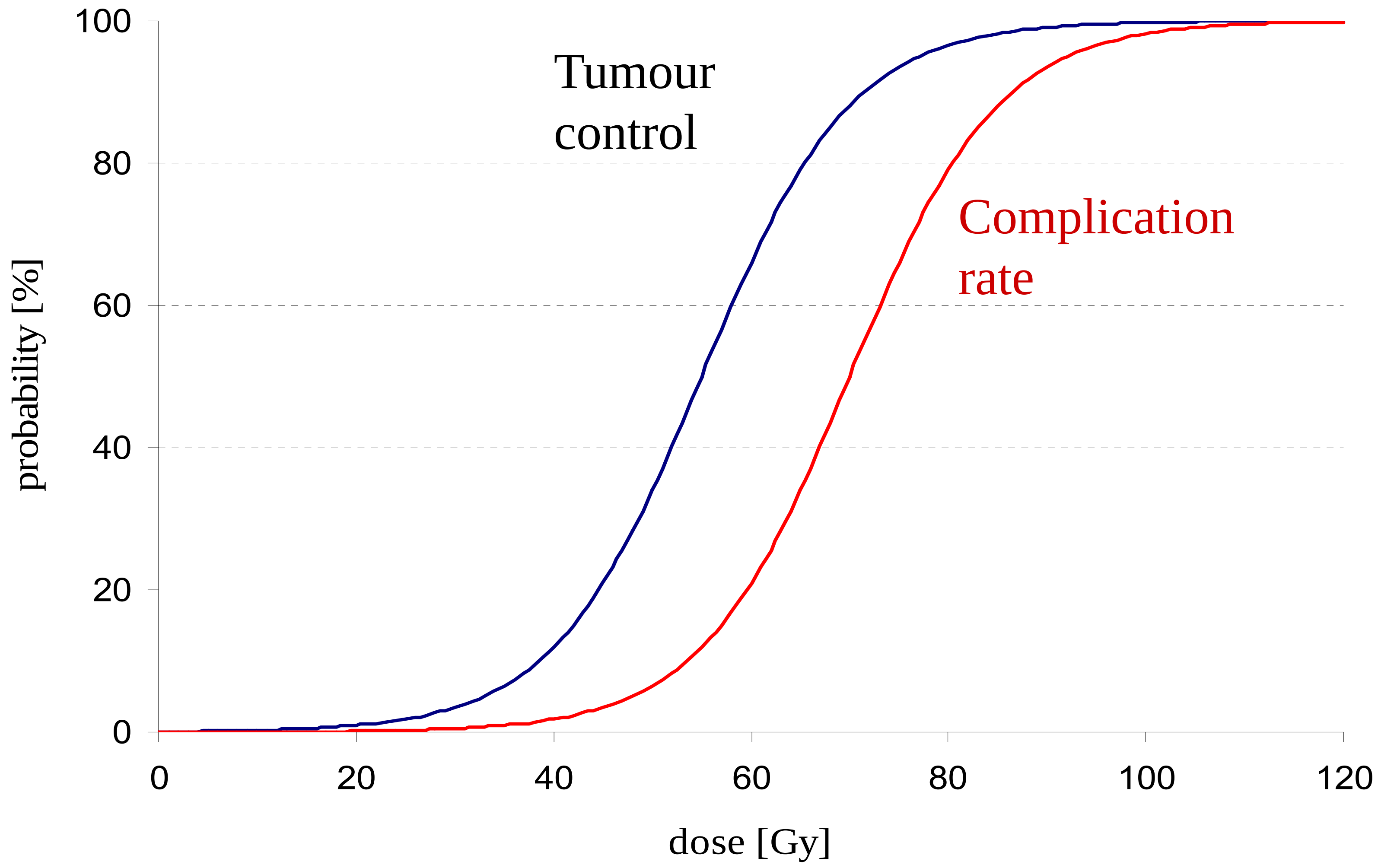
By
radiotherapy
18 %

RT in 40%
OF CURED
PATIENTS

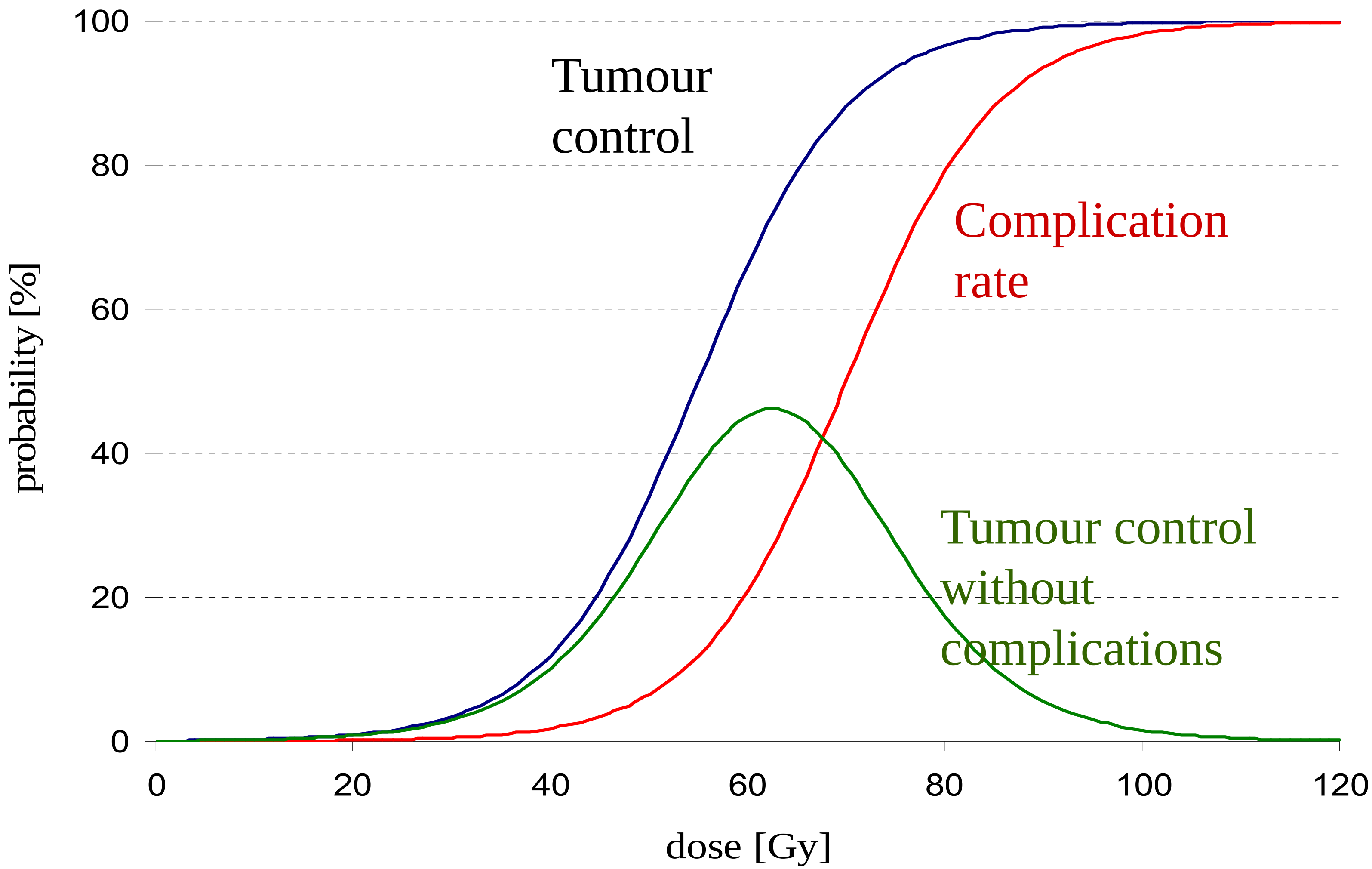
General principle of radiation therapy



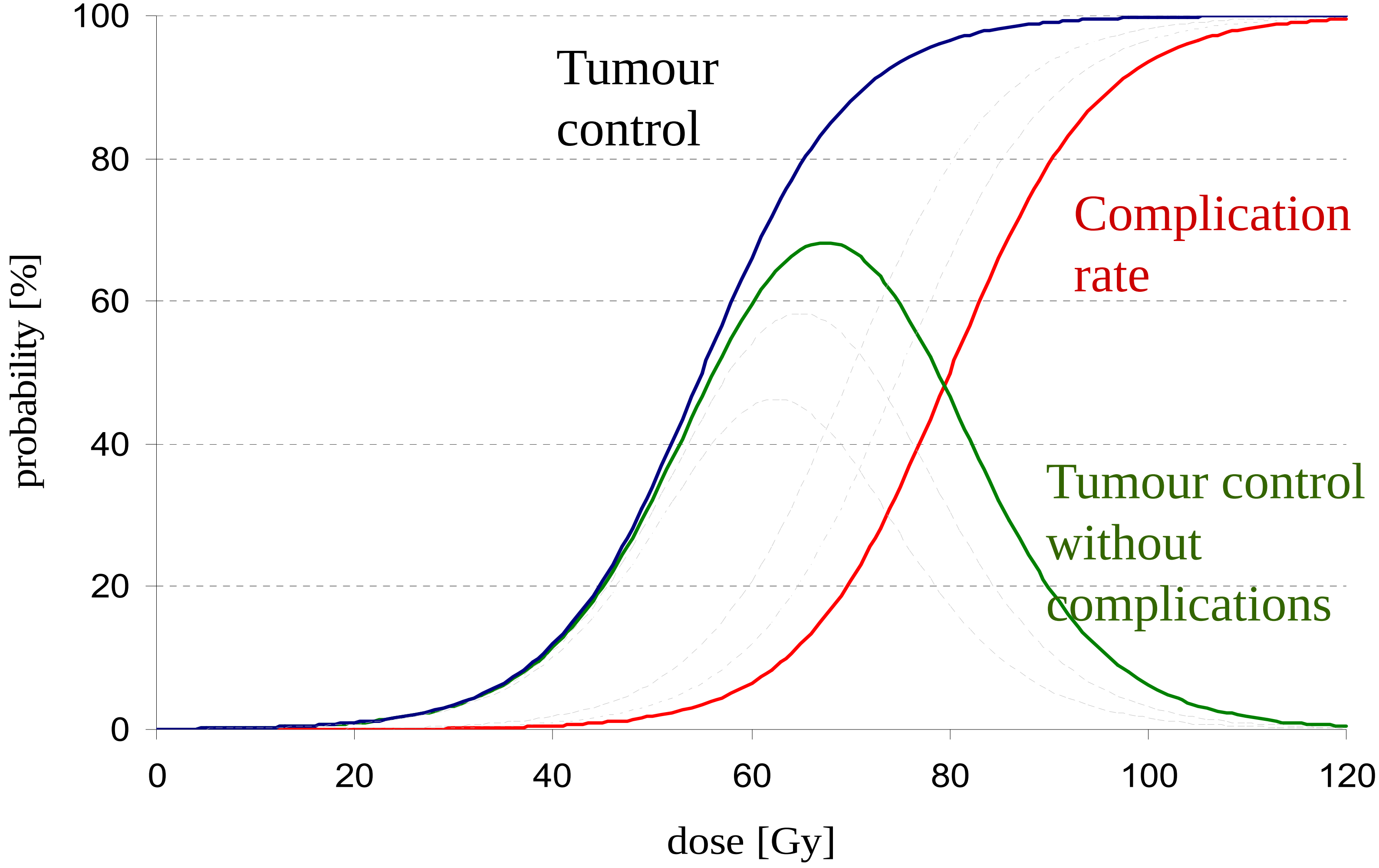
General principle of radiation therapy



General principle of radiation therapy



General principle of radiation therapy



Hadron RT proposed by Wilson in 1946

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

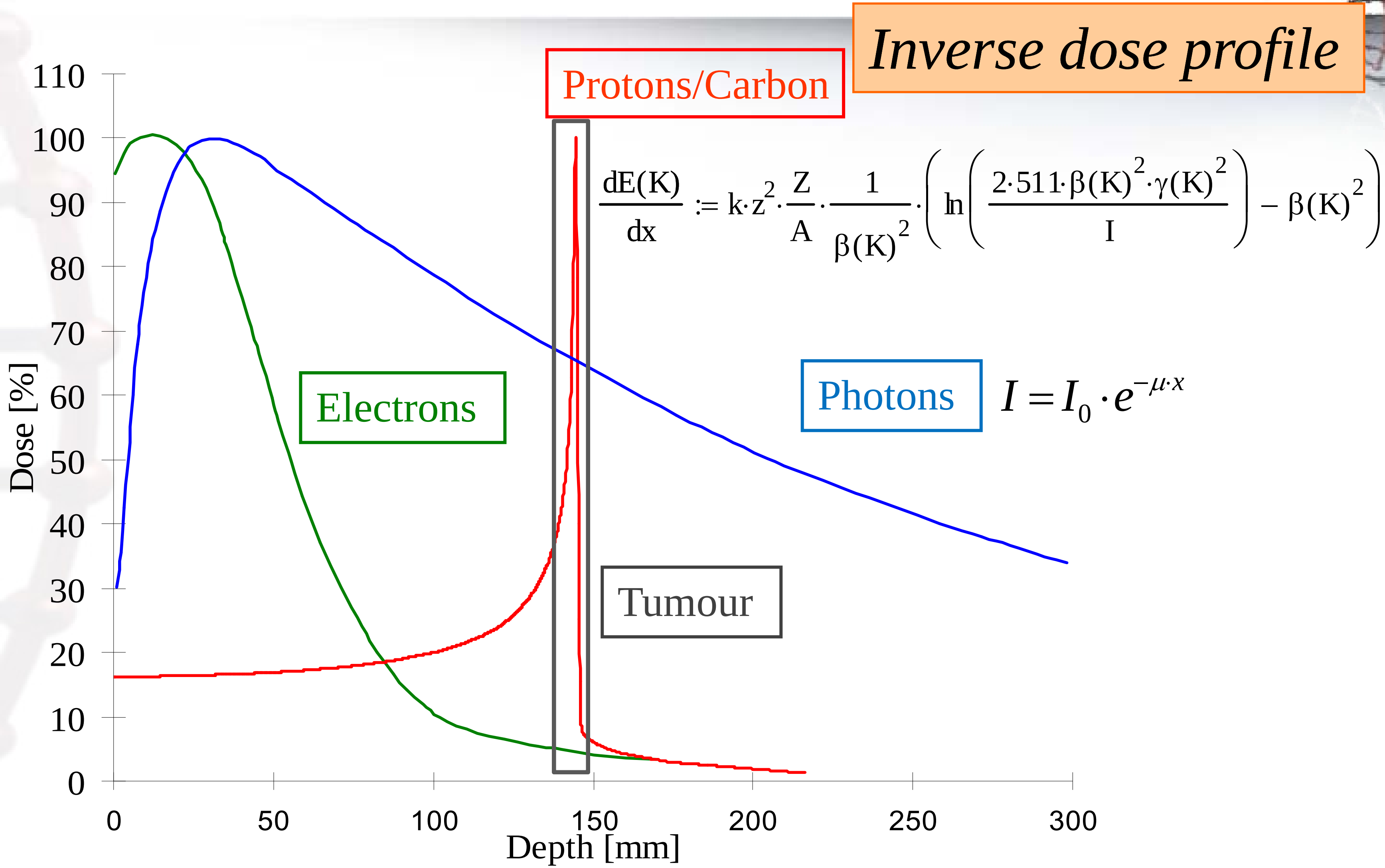
EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles 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.

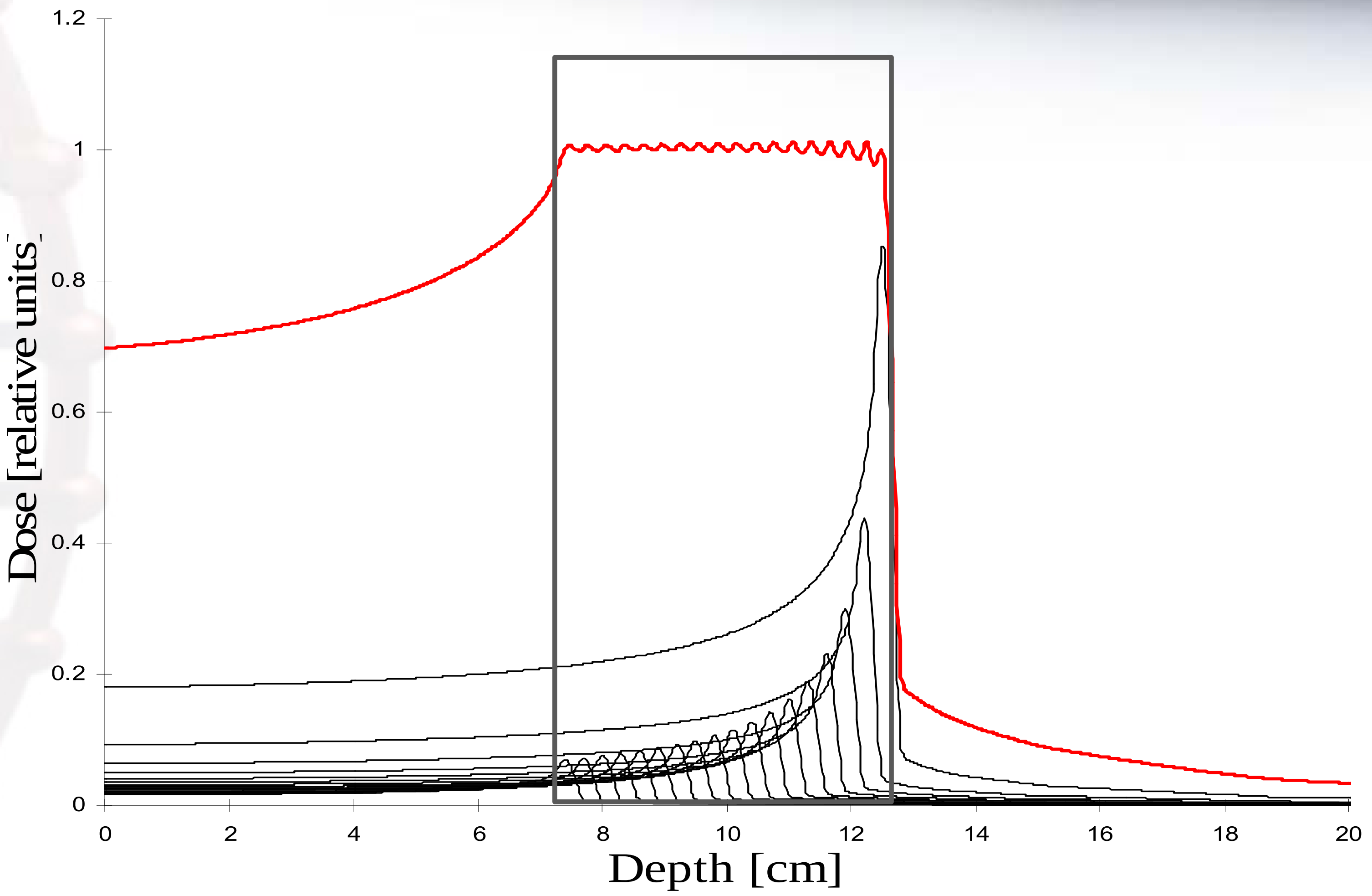
These properties make it possible to irradiate inter ly a strictly localized region

Radiology 47: 487-491, 1946

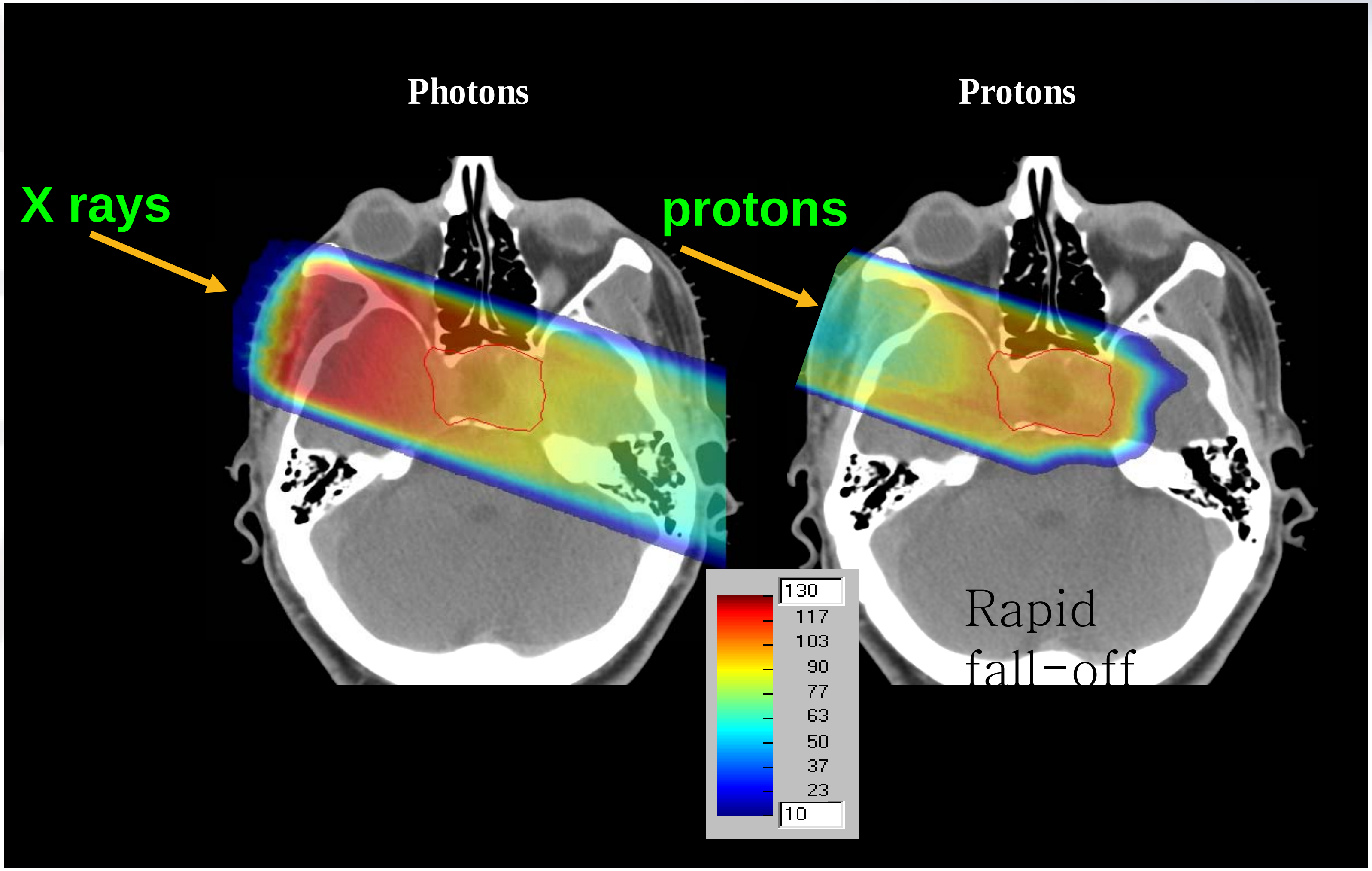
Comparison of the depth dose profiles



Longitudinal - Spread Out Bragg Peak

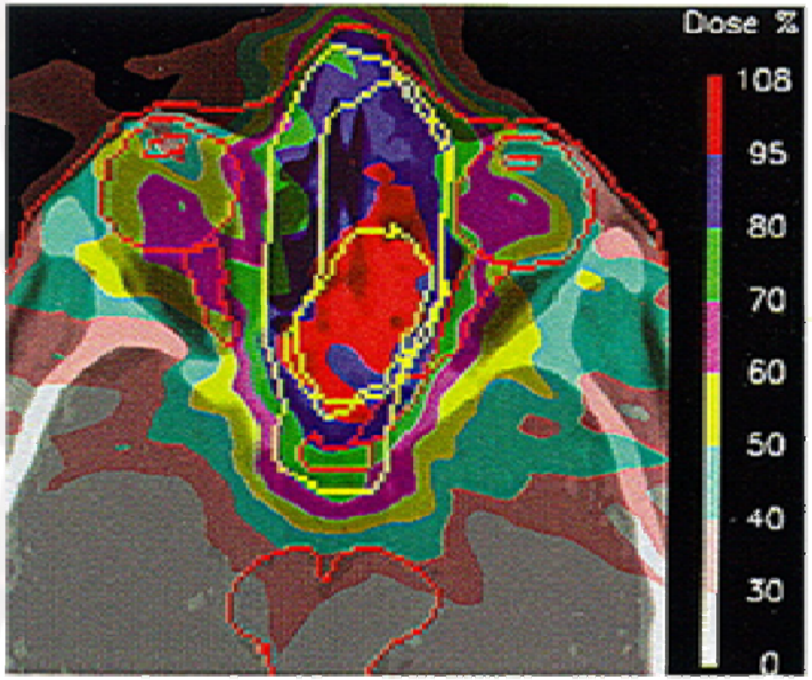


Macroscopic advantage of hadrons

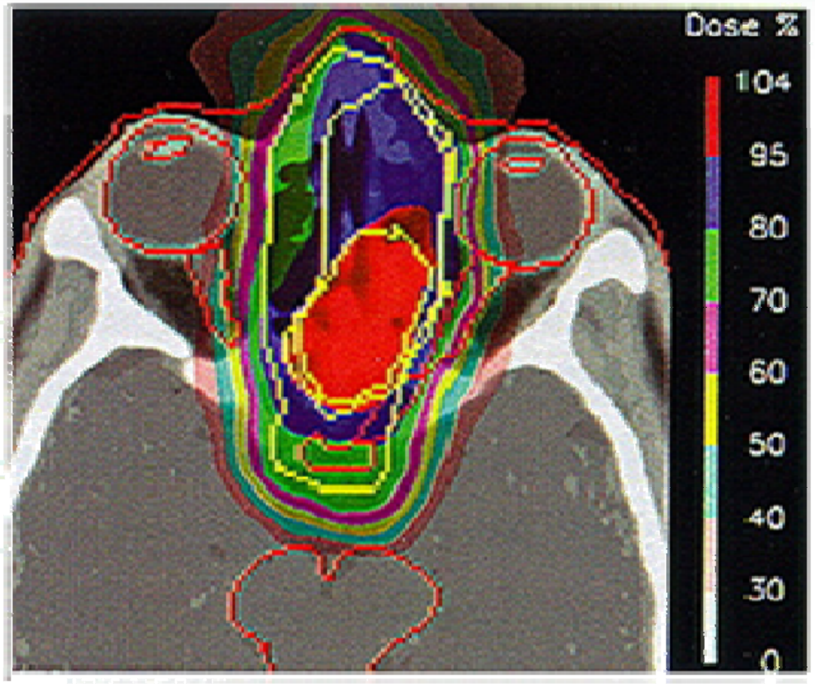


Better dose distribution

9 X beams



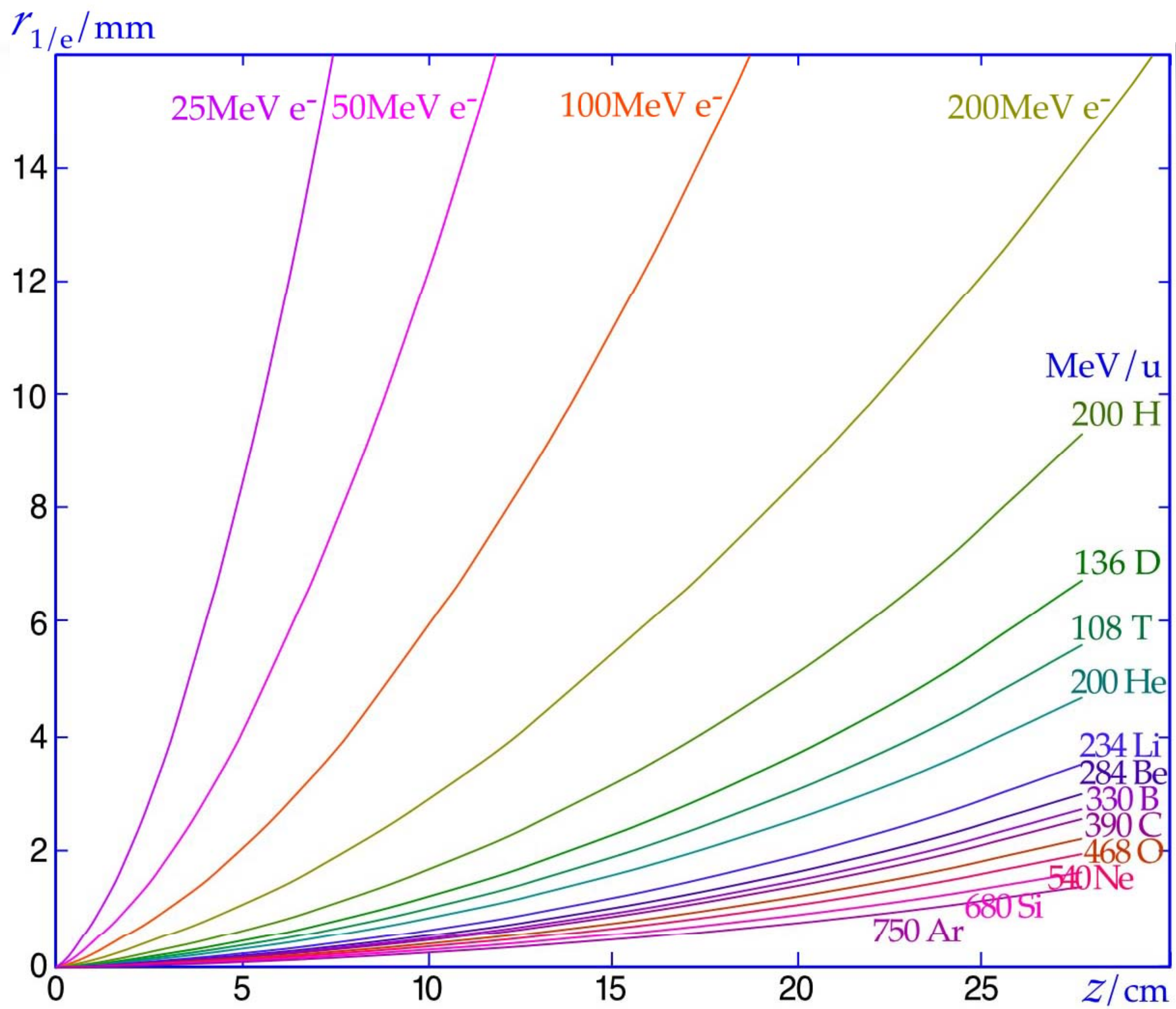
1 proton beam



tumor between eyes

Lateral radii of elementary beams of electrons and light ions (range of 26 cm) as a function of depth in water

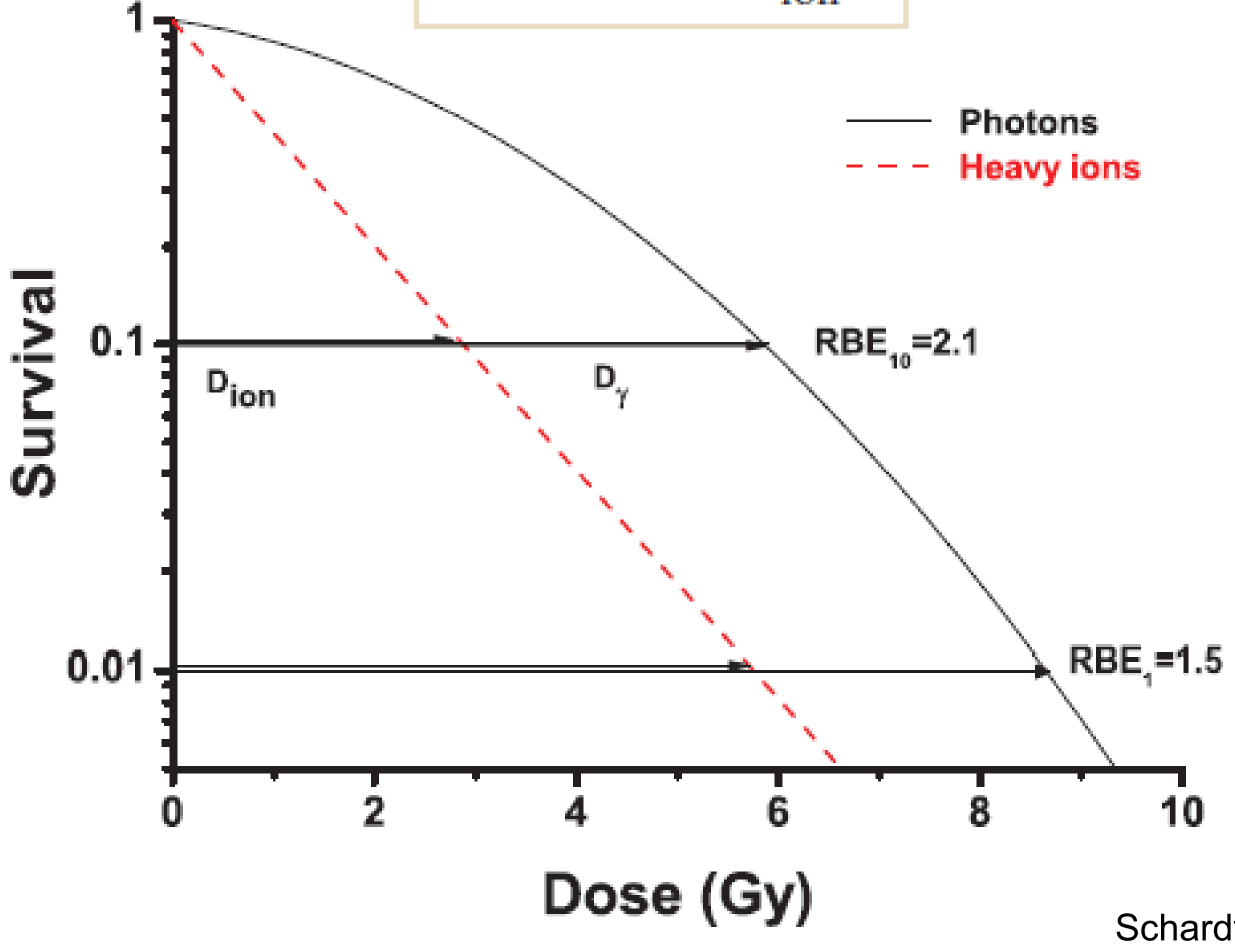
Carbon scatters
Less than protons



(A. Brahme, S.Rossi et al., NIM B 184 (2001) 569-588)

Radiobiological advantage of C

$$\mathrm{RBE}_{\mathrm{iso}} = \frac{D_{\mathrm{ref}}}{D_{\mathrm{ion}}}.$$



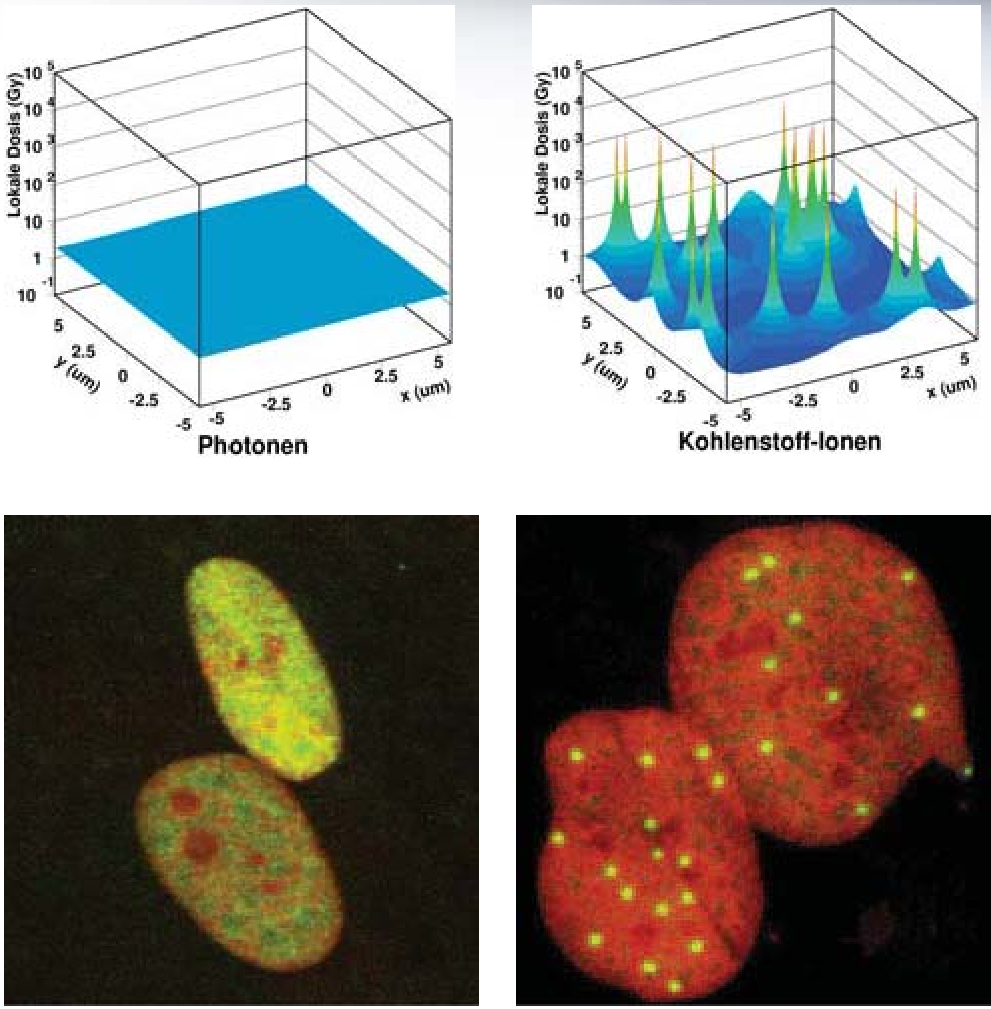
Schardt & Elsasser, 2010

Warning: RBE depends on

- Biological endpoint
- LET
- Particle type
- Cell/tissue
- Dose rate
- Fractionation
- etc…

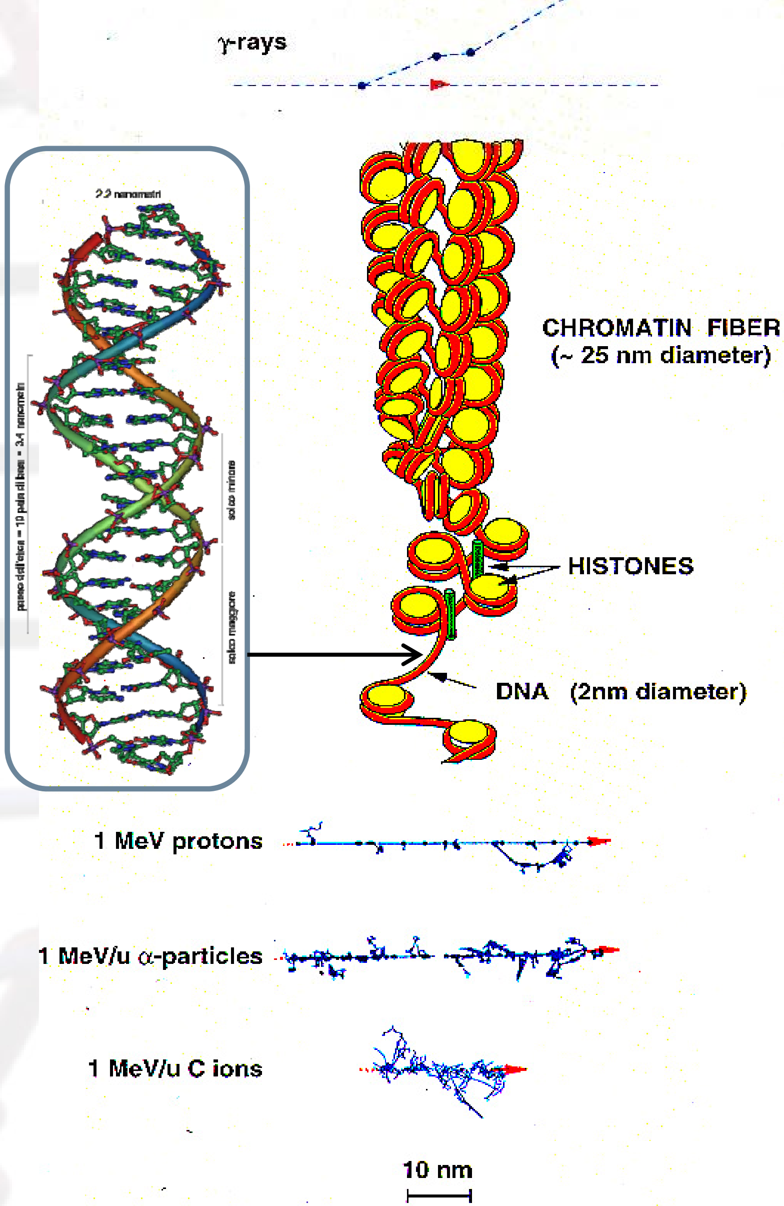
Different types of radiations

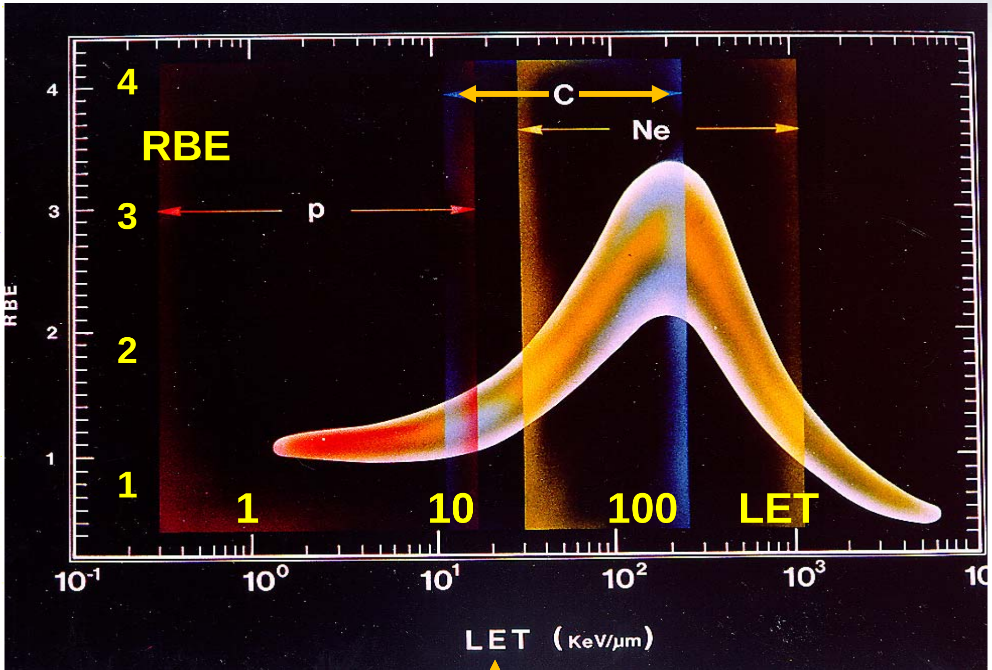
Distribution of dose and of damage (yellow) on the cell nucleus scale (microns) for photons and carbon ions



(from G. Kraft, Tumor therapy with heavy ions)

Microscopic advantage of C ions





10 – 20 keV/μm =

100 – 200 MeV/cm =

20 – 40 eV/(2 nm)

The optimal LET

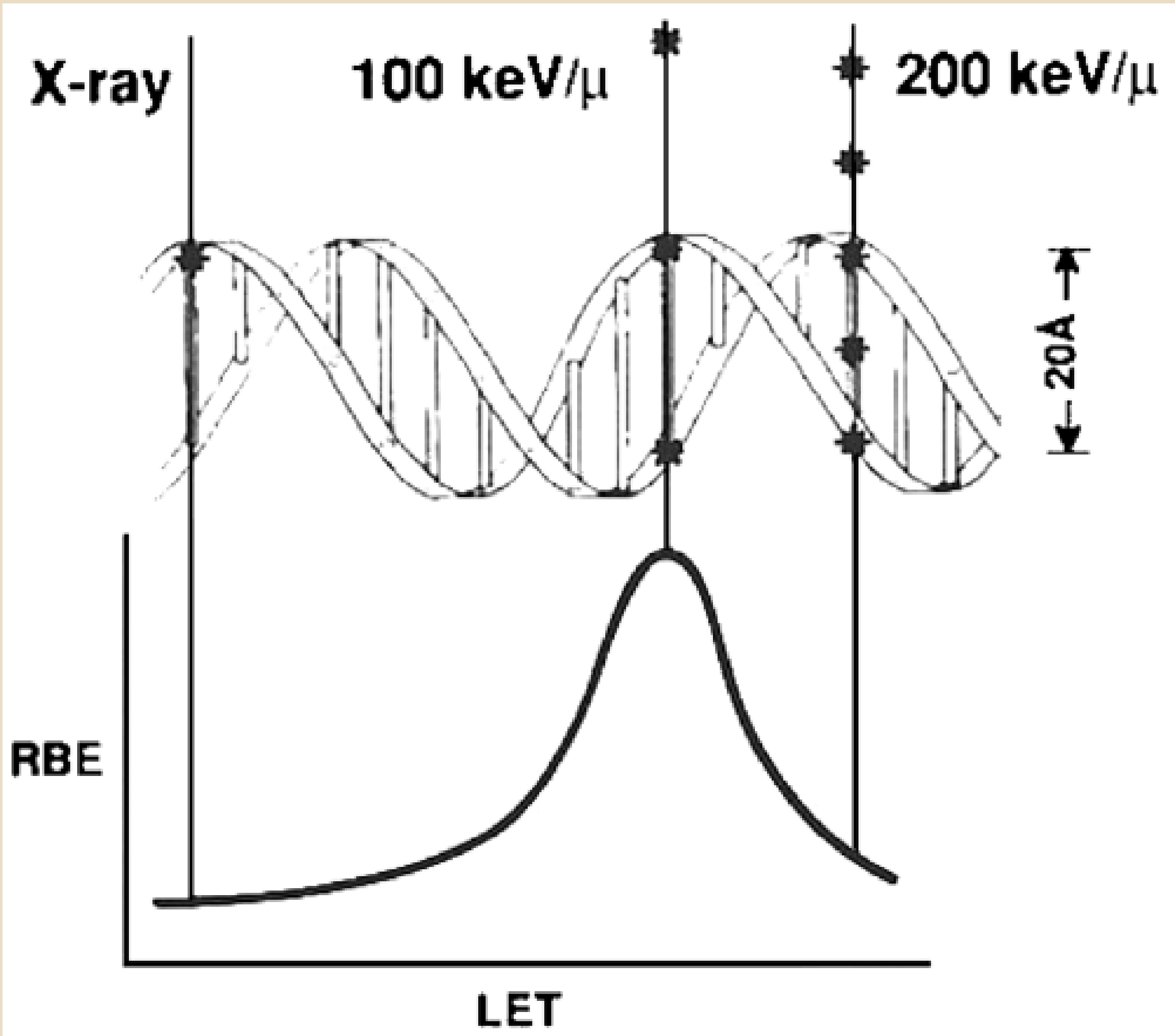


Diagram illustrating why radiation with a LET of 100 keV/µm has the greatest RBE for cell killing, mutagenesis, or oncogenic trasformation.

Fot this LET, the average separation between ionizing events coincides with the diameter of the DNA double helix (i.e. about 2 nm).

Radiation of this quality is most likely to produce a double strand break from one track for a given absorbed dose.

Radiobiology for the radiologist, 7th edition

3 different cases

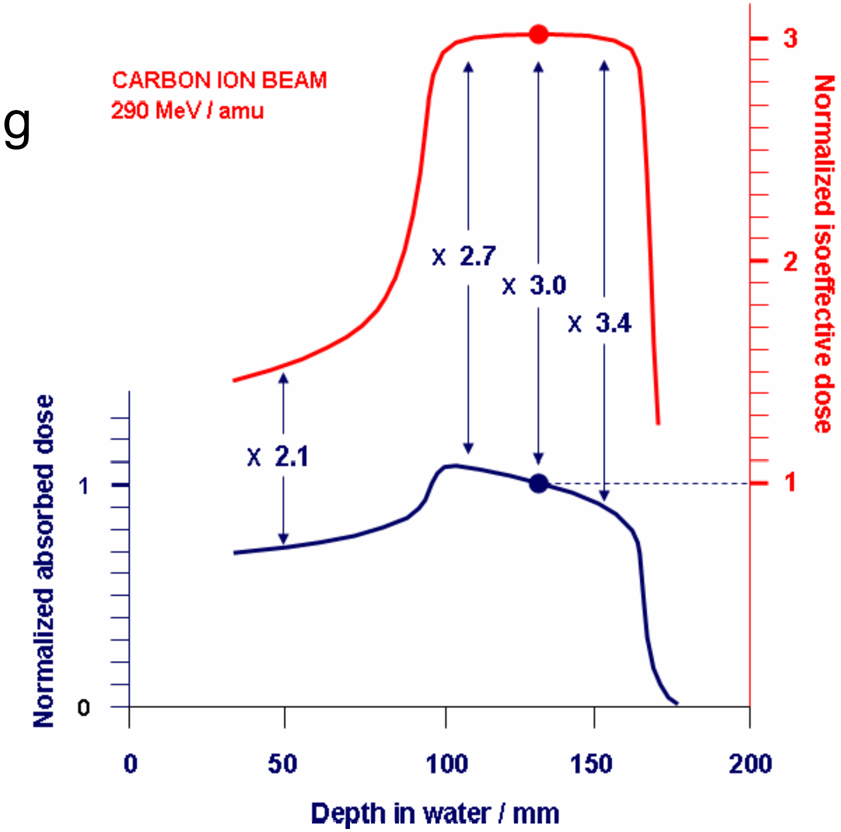
-1 Low LET(<20 keV/micron)
Distance between ionizations larger than DNA diameter. Classical radiotherapy; Fractionation very important.

-2 High LET(50 – 200 keV/micron)
Distance between ionizations comparable with DNA diameter. C-ion therapy; Fractionation less important.

-3 Very high LET(> 1000 keV/micron)
Distance between ionizations smaller than DNA diameter; energy in excess in ionizations (overkill).

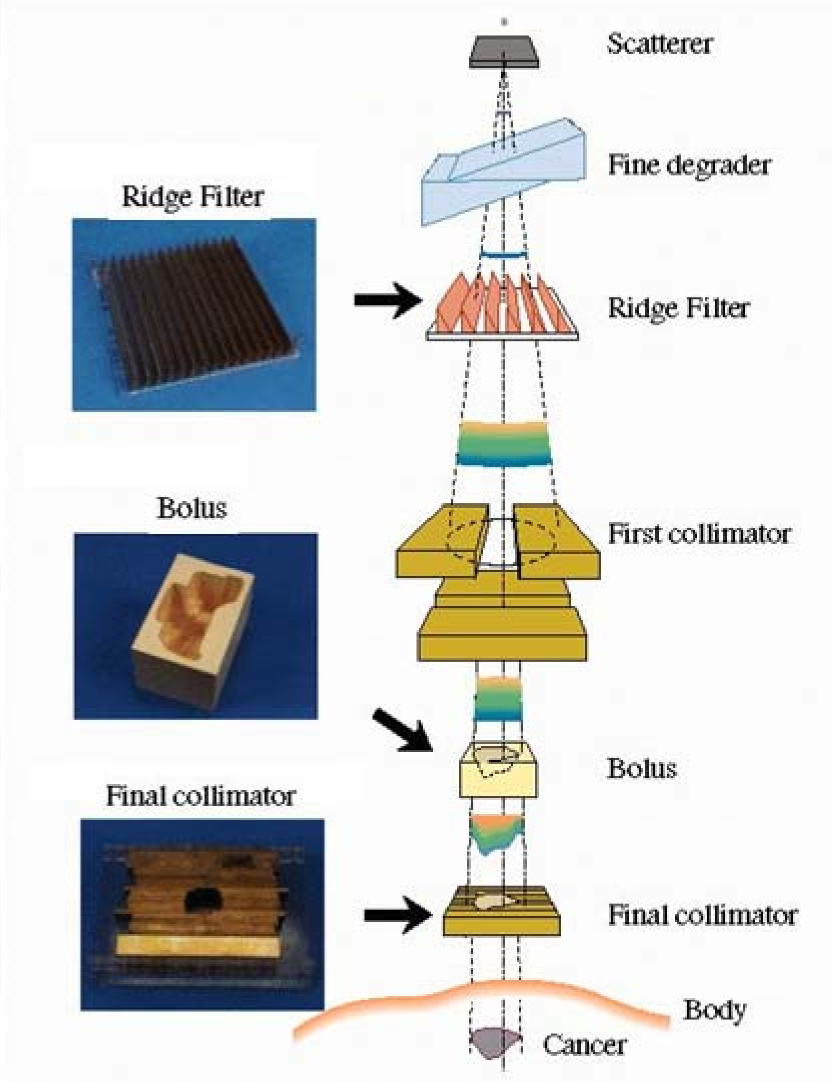
Physical and biological dose

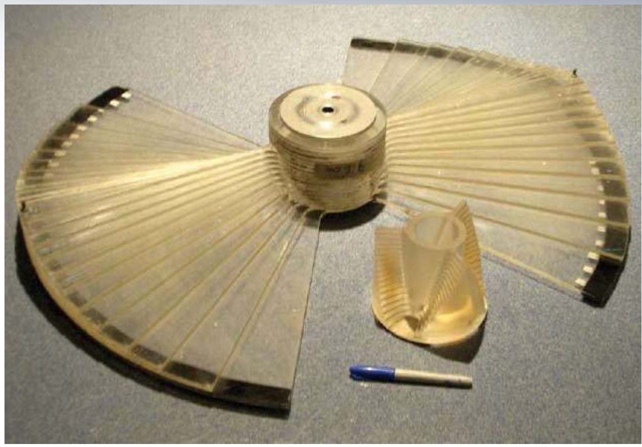
Complicated treatment planning

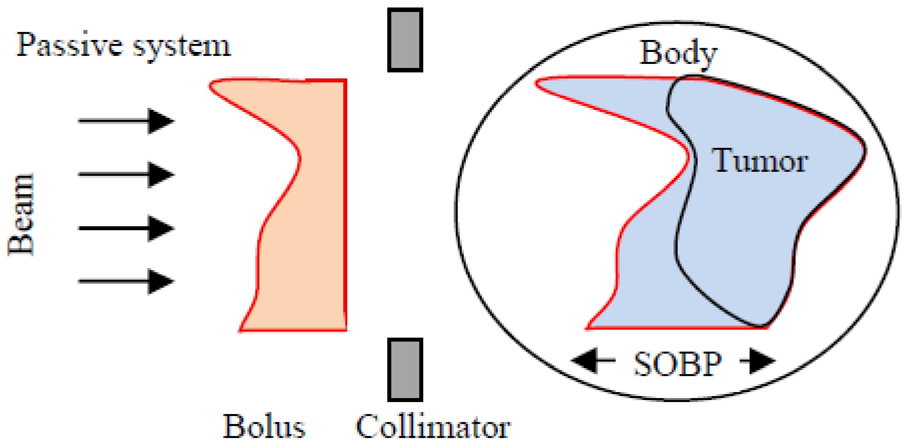


Beam Delivery

Beam delivery: passive systems







Passive systems for Carbon

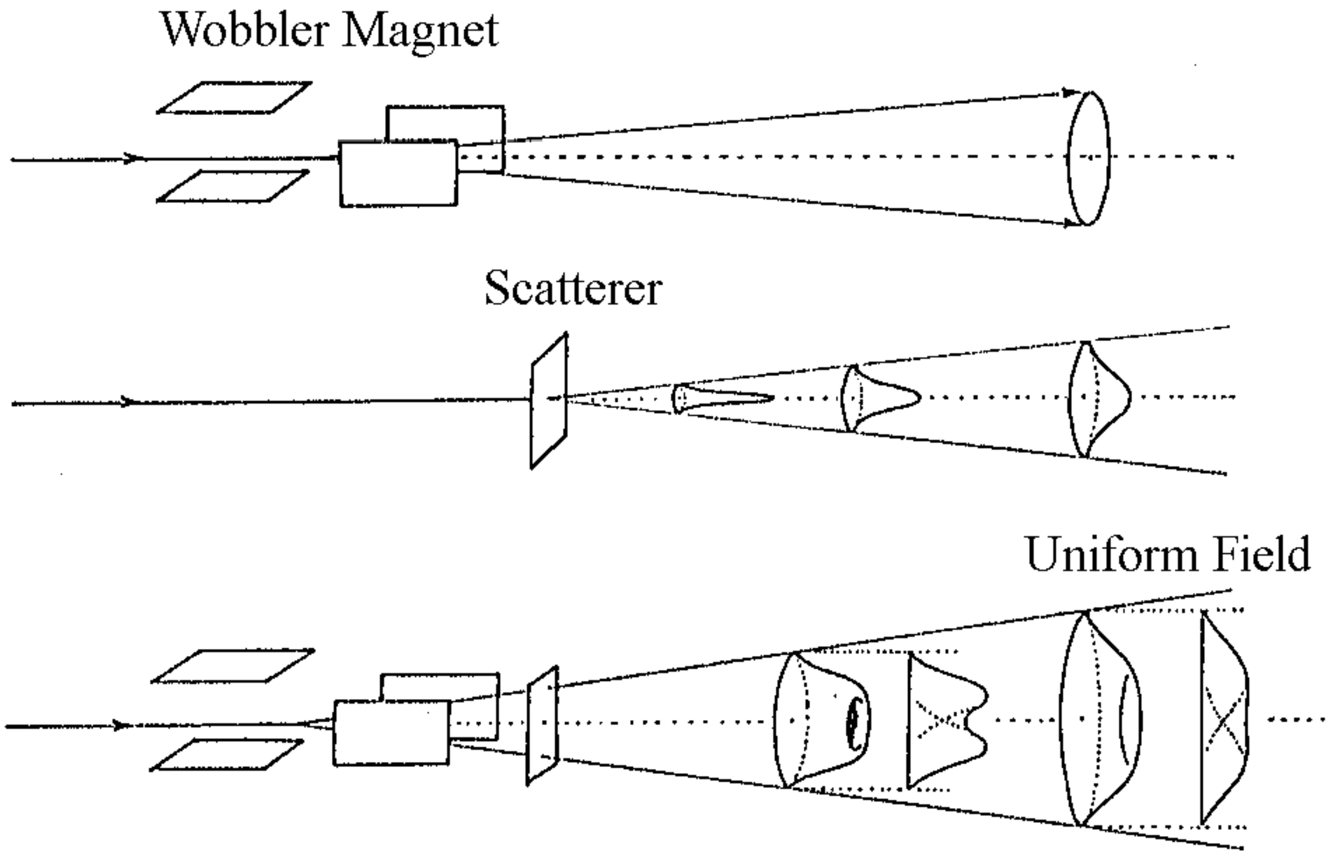
Completely passive system not advisable:

-Smaller scattering implies larger thicknesses and distances and thus larger energy loss and beam loss which implies larger energy and current from the accelerator

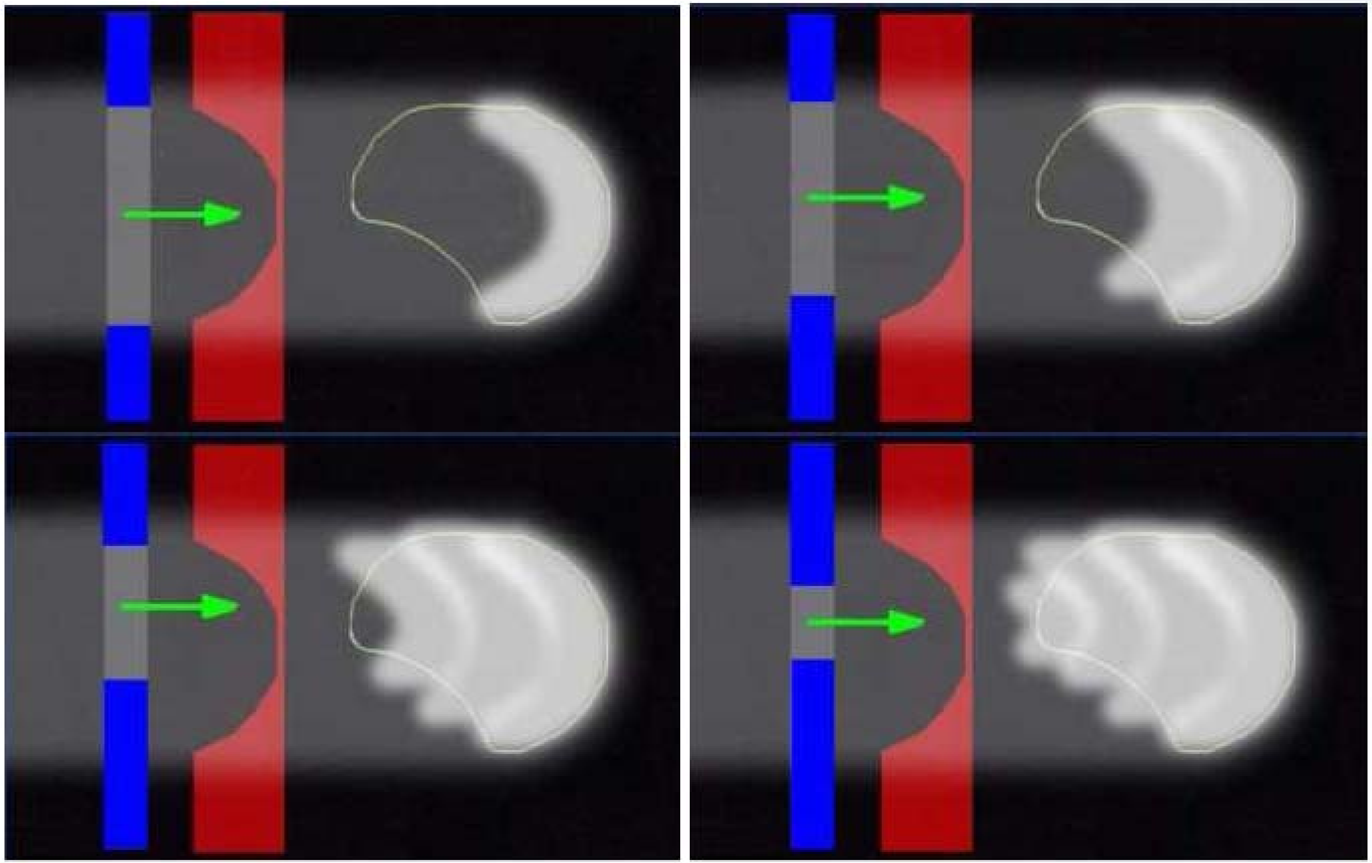
-Fragmentation of impinging ions which causes more dose delivered after the tumor and larger production of neutrons.

-The amount of material in the beam line is considerable, leading to an increase in nuclear fragments produced by nuclear interactions with the material of the beam modifiers. These nuclear fragments have lower energies and lead to a higher LET and thus an increased biological effective dose of the beam already in the entrance region.

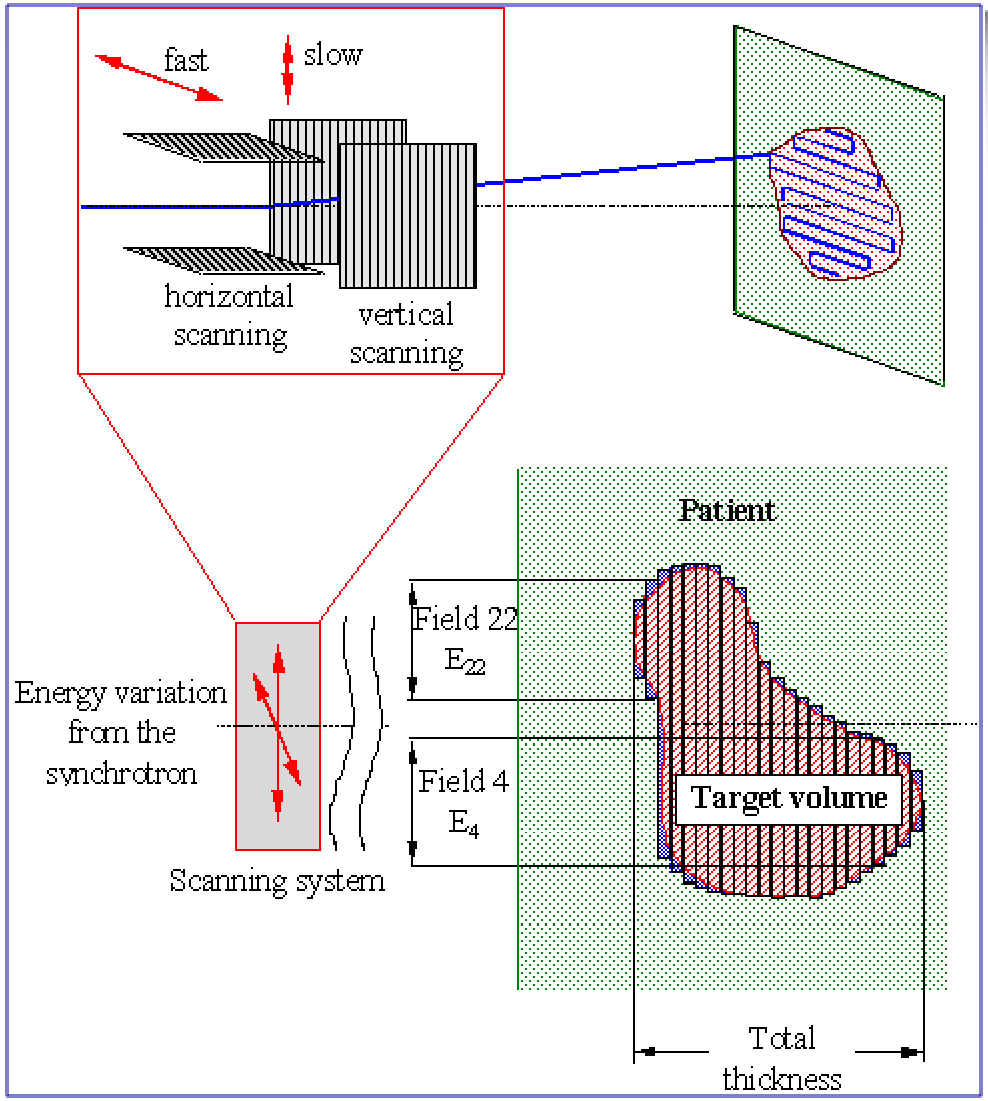
Wobbling



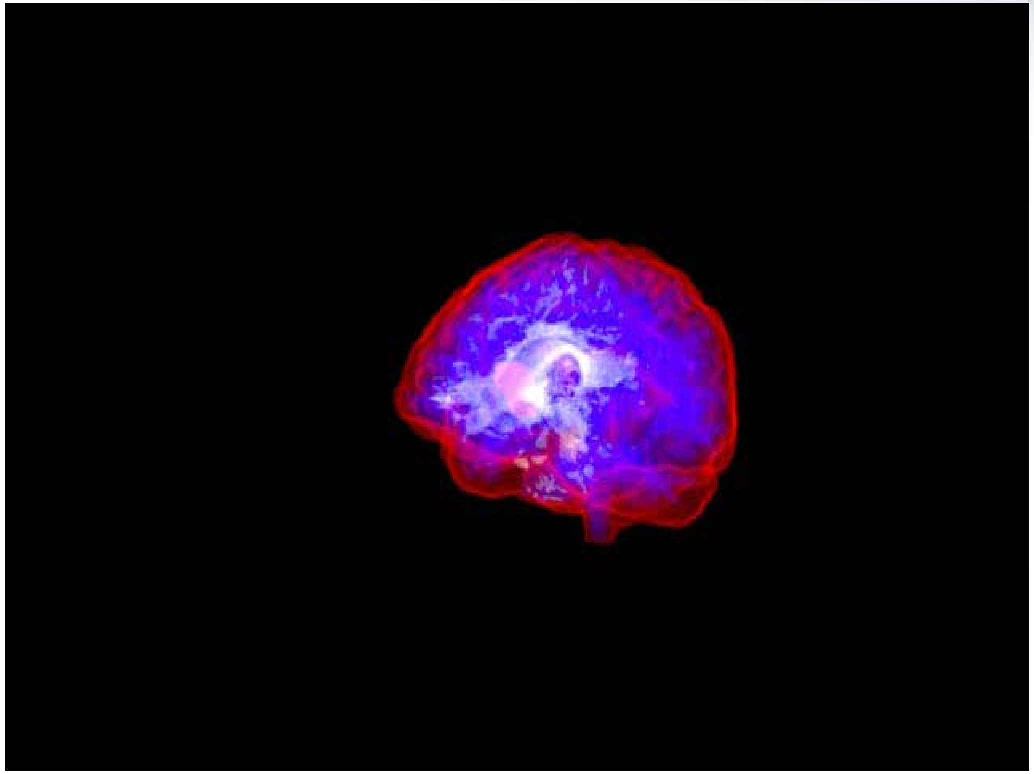
Layer stacking



Active systems

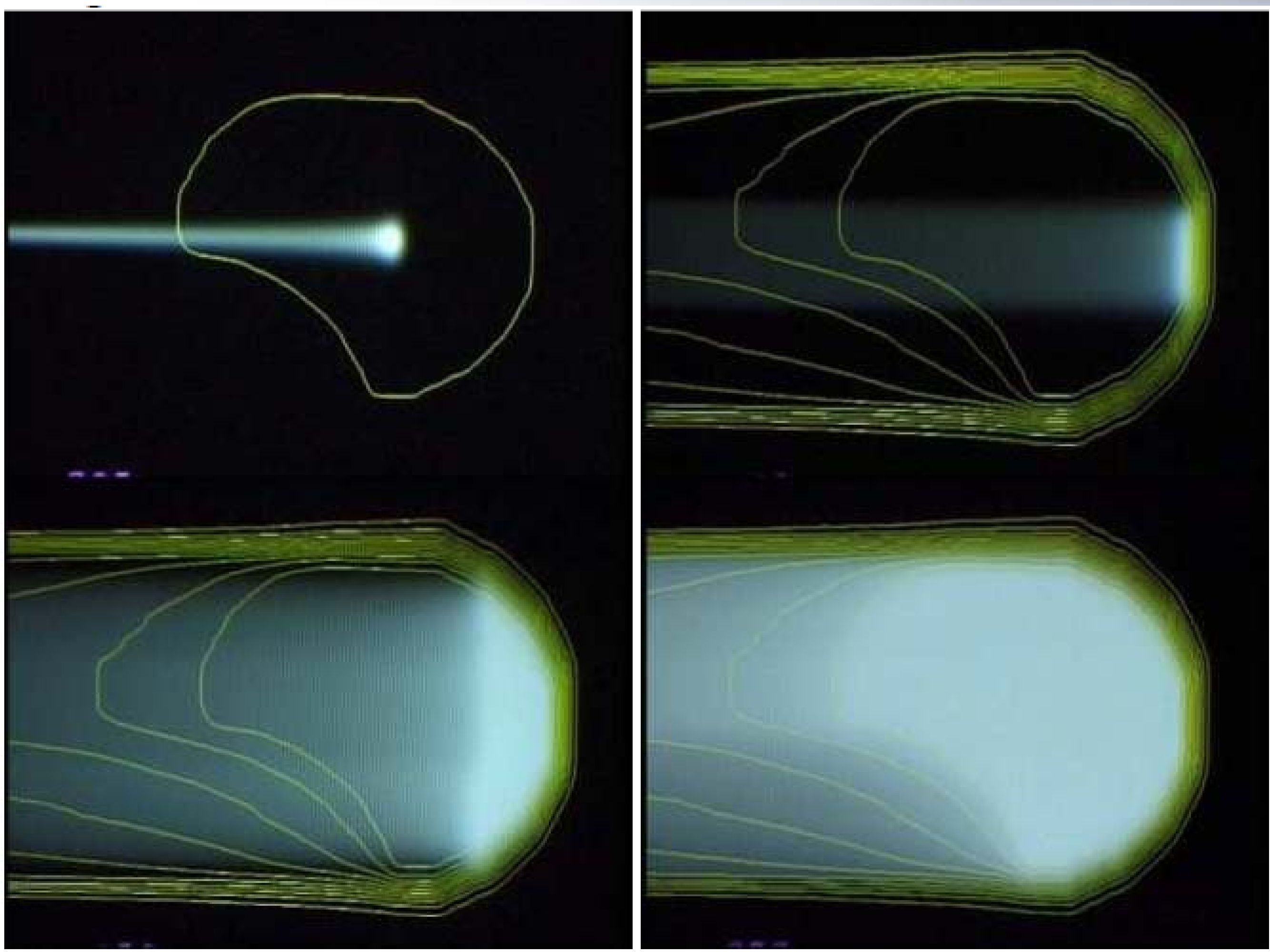


Scanning Beam



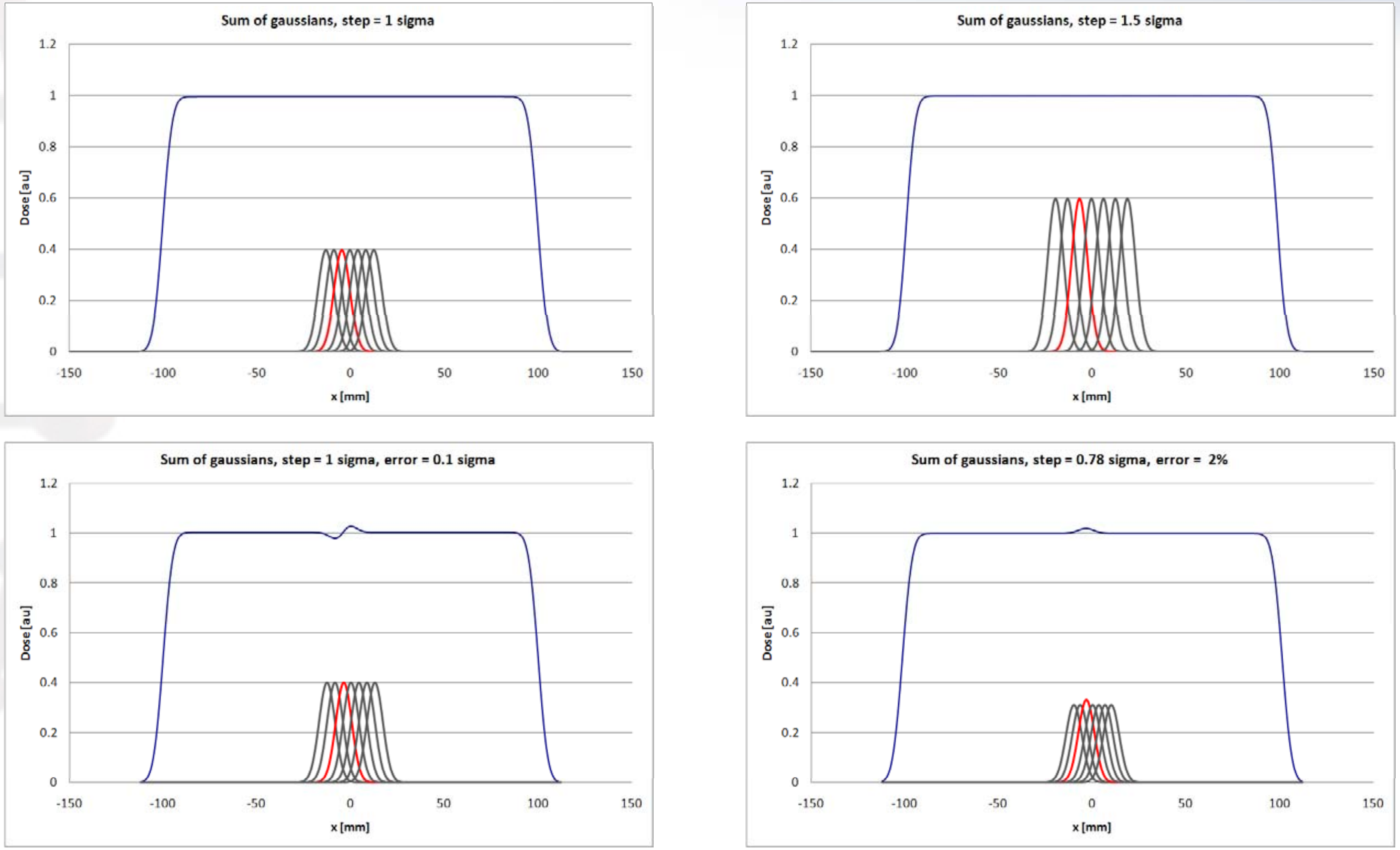
(Found on the web, forgot where... presumably Siemens or HIT)

Active systems

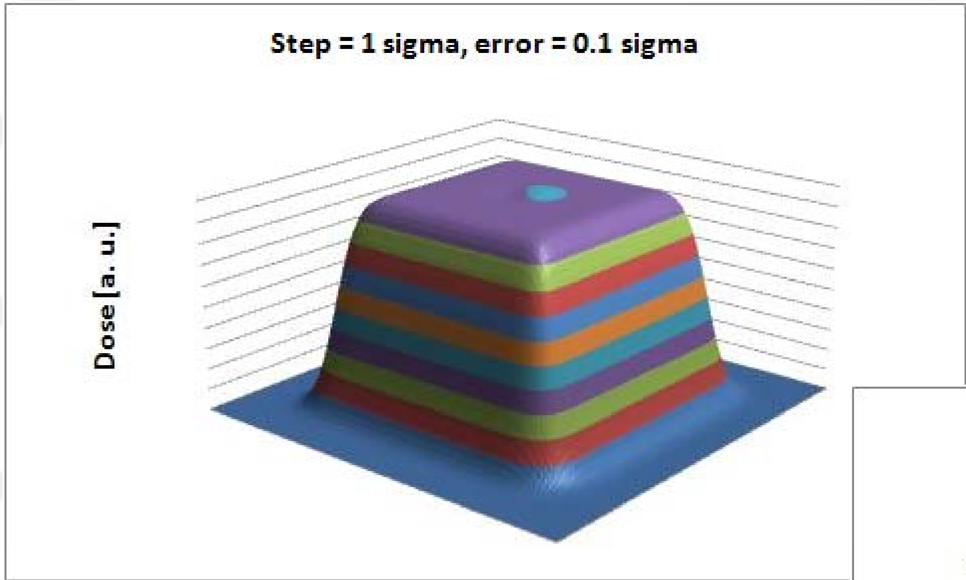


(Courtesy of E. Pedroni)

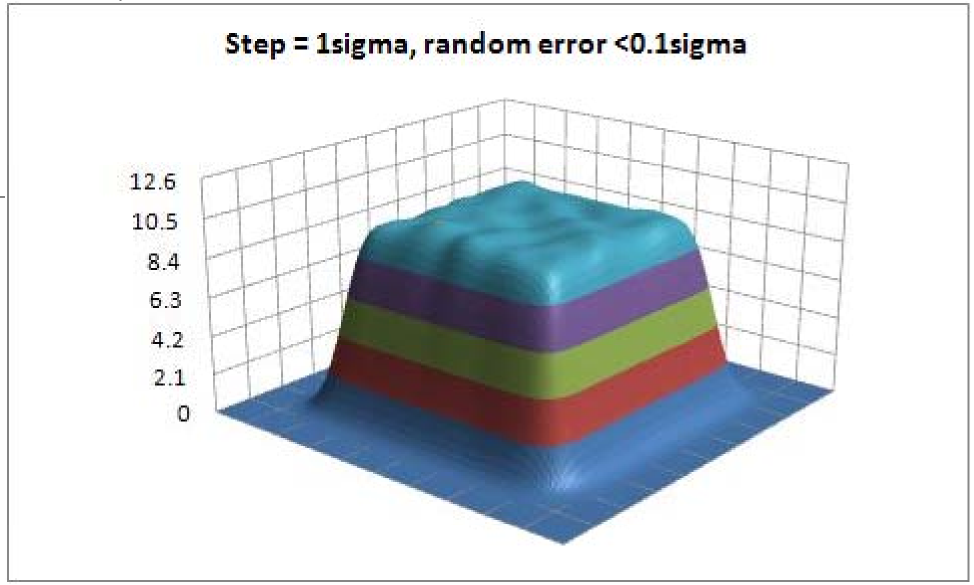
Beam position precision



2D



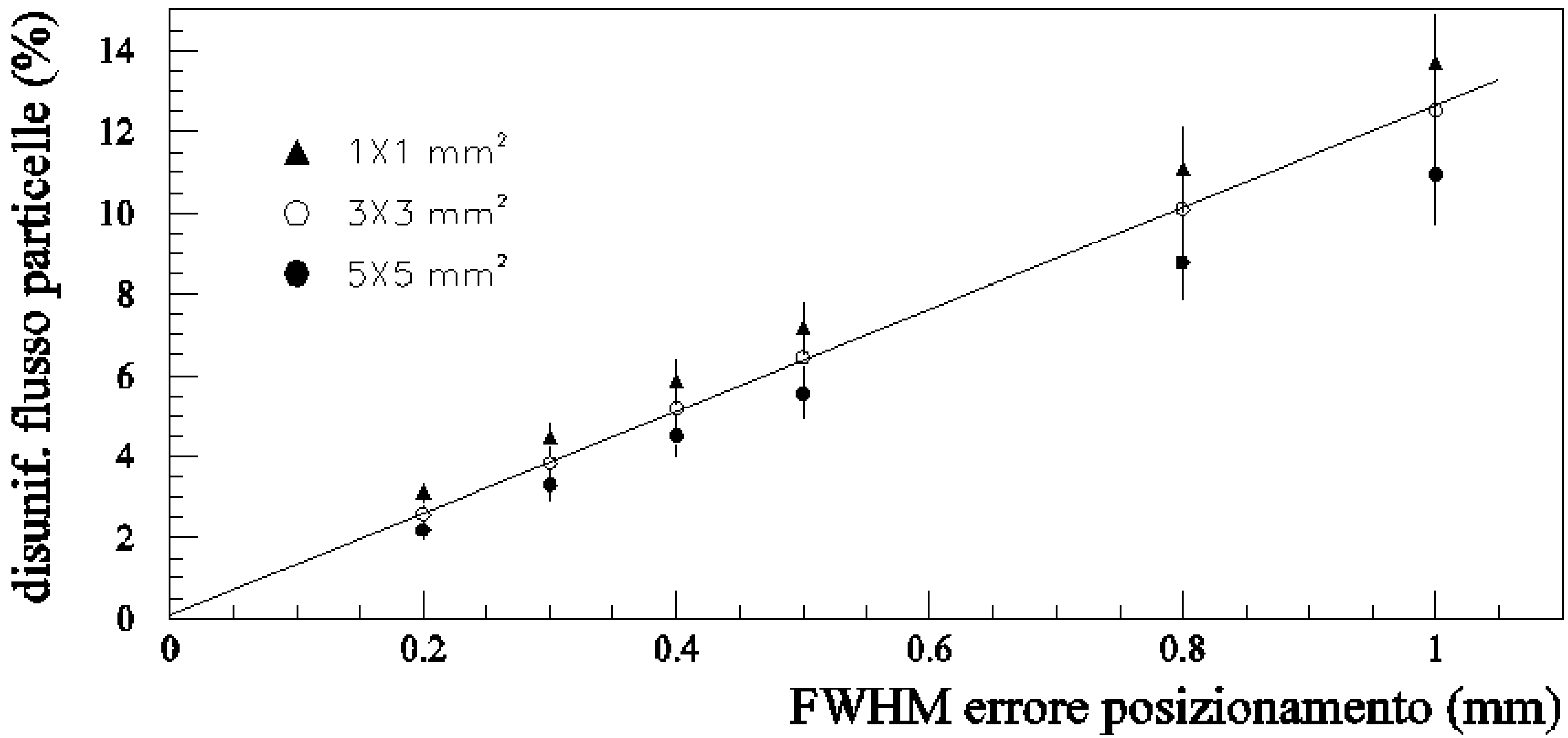
Step = 1 sigma, error = 0.1 sigma
Dose [a. u.]



Step = 1sigma, random error <0.1sigma
12.6
10.5
8.4
6.3
4.2
2.1
0

Beam position requirement

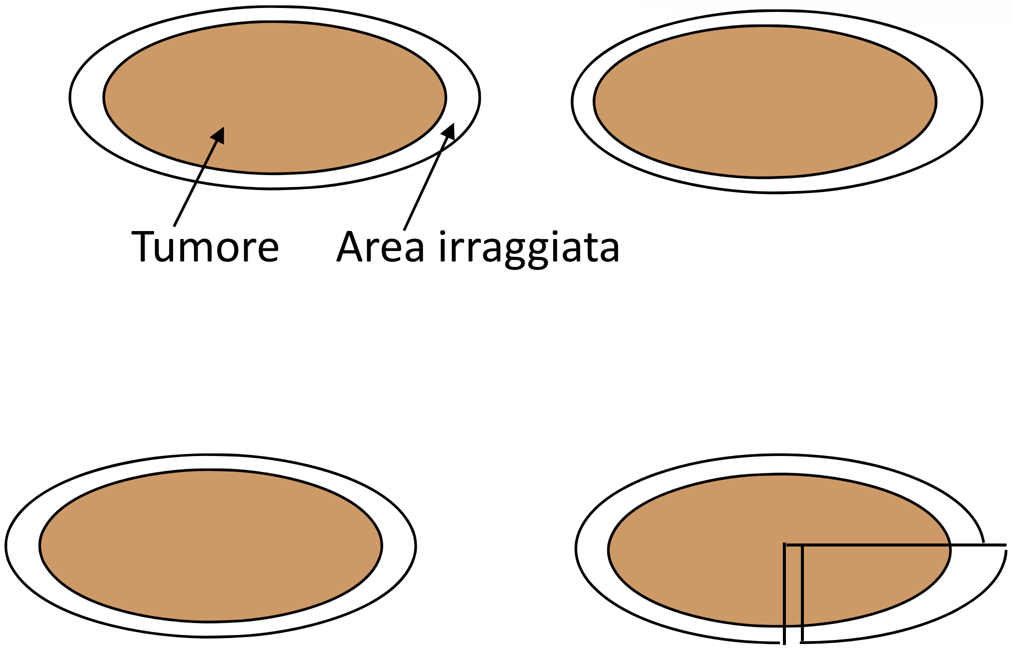
Gaussian beam, FWHM = 10 mm



Beam position error ~ 0.1 mm

(M. Donetti)

Beam position errors



Long and medium term stability
(large slices, breath synchronization)

The CNAO Foundation

No profit organisation (Foundation) created with the financial law 2001 to build the National Center for Hadrontherapy designed by TERA Foundation

Founders:

Fondazione Policlinico Ospedale Maggiore- Milano
Fondazione Istituto Neurologico C. Besta - Milano
Fondazione Istituto Nazionale dei Tumori - Milano
Istituto Europeo di Oncologia - Milano
Fondazione Policlinico San Matteo - Pavia
Fondazione TERA - Novara

Institutional Participants:

Istituto Nazionale di Fisica Nucleare
Università di Milano
Politecnico di Milano
Università di Pavia
Comune di Pavia

Participants:

Fondazione Cariplo

National collaborations

TERA Foundation: final design and high tech specifications

INFN: co-direction HT, technical issues, radiobiology, research, formation

University of Milan: medical coordination and formation

University of Pavia: technical issues, radiobiology, formation

University of Catania: medical physics

University of Florence: medical physics

University of Turin: interface beam-patient, TPS

Polytechnic of Milan: patient positioning, radioprotection, authorisations

European Institute of Oncology: medical activities, authorisations

San Matteo Foundation: medical activities, logistics

Town of Pavia: land and authorisations

Province of Pavia: logistics and authorisation

International collaborations

CERN (Geneva): technical issues, PIMMS heritage

GSI (Darmstadt): linac and special components

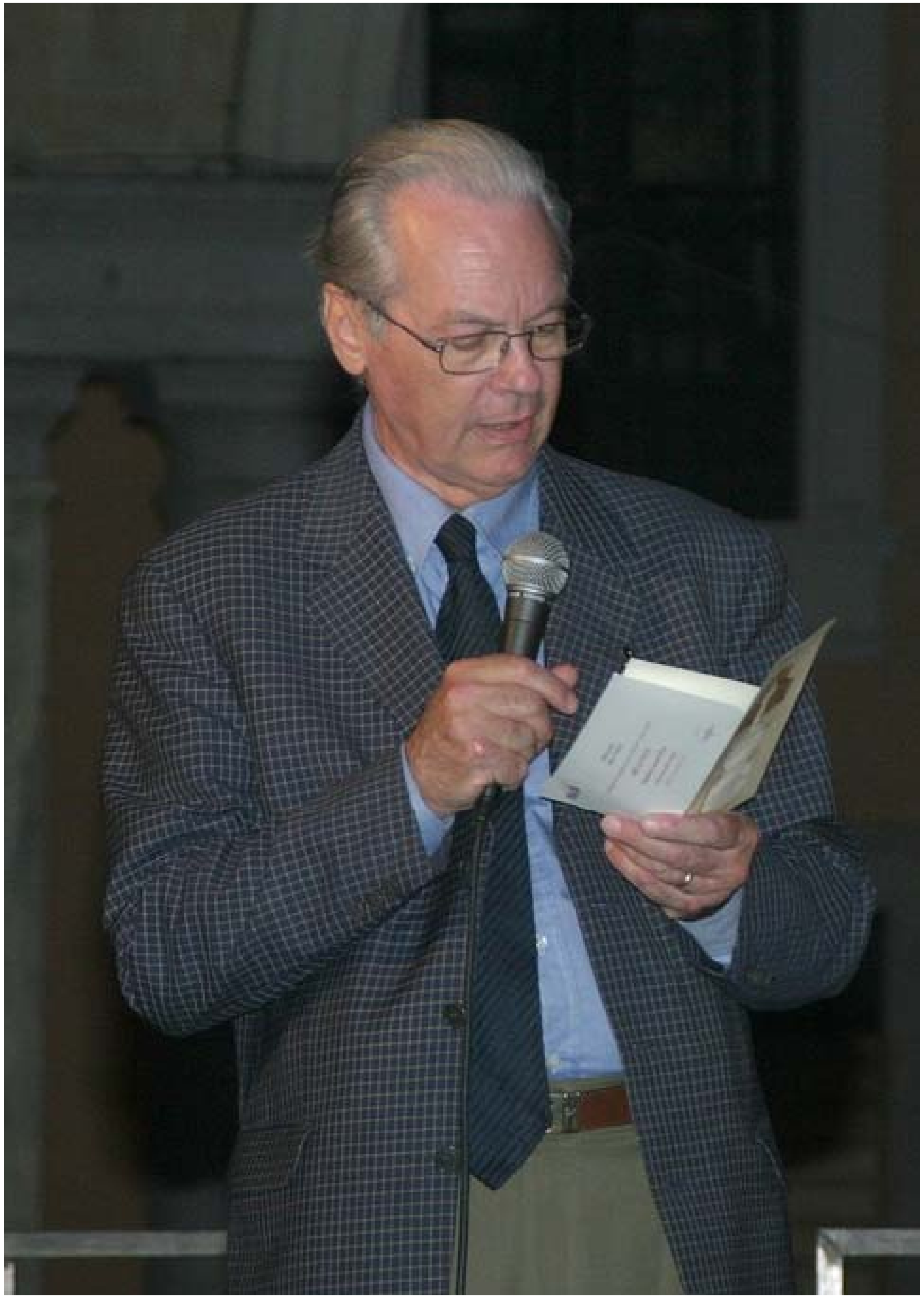
LPSC (Grenoble): optics, betatron, low-level RF, control system

Med-Austron (Vienna): technical collaboration for MA centre

Roffo Institute (Buenos Aires): medical and research activities

NIRS (Chiba): medical activities, radiobiology, formation

HIT (Heidelberg): research activities



CERN/PPE/UA/eo

25 Maggio 1991

Per un Centro di Teleterapia con Adroni

Ugo Amaldi

CERN e Università di Milano

Giampiero Tosi

Ospedale di Niguarda, Servizio di Fisica Sanitaria,
e Università di Milano

Origins - History

1990 – U. Amaldi and G. Tosi have the idea of promoting hadrontherapy in Italy

1991 – U. Amaldi and G. Tosi, “Per un centro di teleterapia con adroni”

1991 – ATER experiment at INFN

1992 – **TERA** Foundation is founded

1996 – PIMMS starts (TERA+CERN+MedAustron+Onkologie2000+GSI)

2000 – 2001 the **CNAO** foundation is created within the Financial Law

2003 – CNAO gets the project and hires the design group

The CNAO Phases

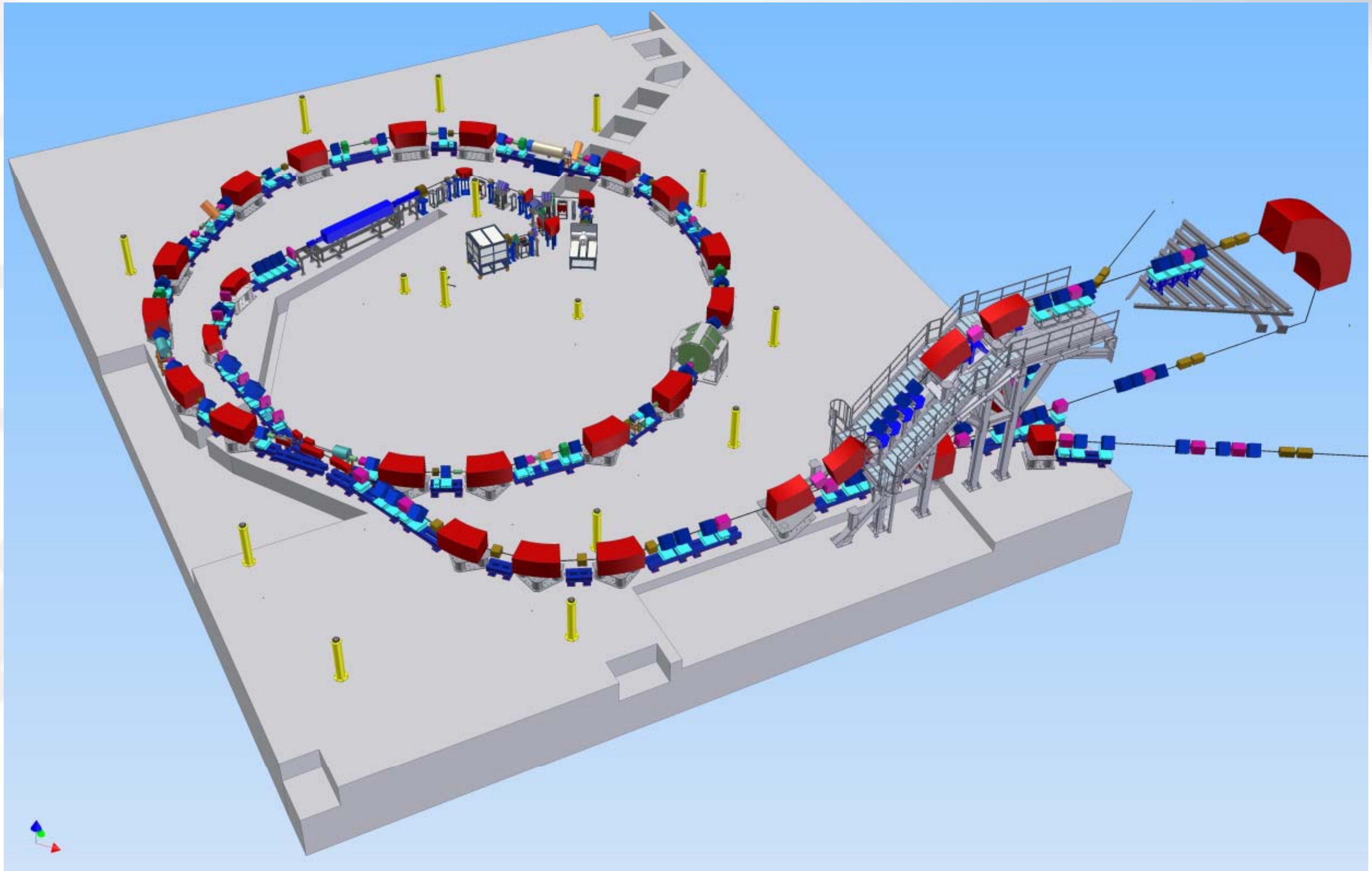
Phase 0: organisation → Years: 2002 - 2004

Phase 1: construction → Years: 2005 - 2009

Phase 2: experimentation → Years: 2010 - 2013

Phase 3: running → Years : 2014 …

The CNAO accelerator and lines



Aim of the center

AIM OF THE PROJECT

To treat deep tumours :

•With ion beams in the range $1 \leq Z \leq 6$

•With active scanning

•In approximately 3 min/field

•Dose uniformity ±2.5%

Synchrotron with slow extraction!

Everything safe, proven and/or redundant

Design Parameters I

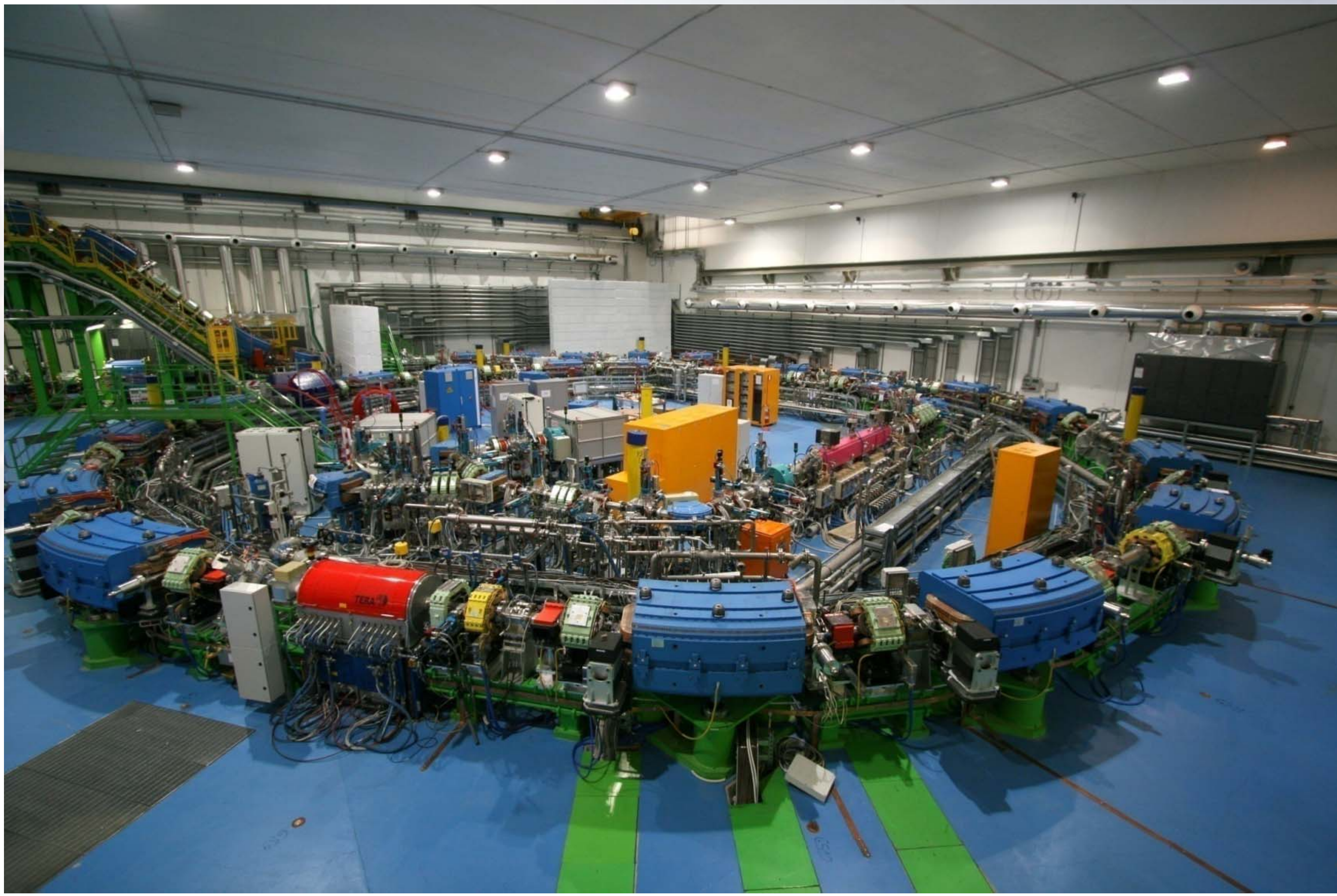
Protons (10^{10}/spill)				
	LEBT (*)	MEBT	SYNC	HEBT
Energy [MeV/u]	0.008	7	7-250	**60-250**
Imax [A]	1.3×10^{-3} (0.65, 0.45)	0.7×10^{-3}	5×10^{-3}	**7×10^{-9}**
Imin [A]	1.3×10^{-3} (0.65, 0.45)	70×10^{-6}	0.12×10^{-3}	17×10^{-12}
$\varepsilon_{rms,geo}$ [π mm mrad]	45	1.9	0.67-4.2	0.67-1.43(V)
$\varepsilon_{90,geo}$ [π mm mrad]	180	9.4	3.34-21.2	3.34-7.14 (V) 5.0 (H)
Magnetic rigidity [T m]	0.013 (0.026)	0.38	0.38-2.43	0.38-2.43
$(\Delta p/p)_{tot}$	±1.0‰	±(1.2-2.2)‰	±(1.2-3.4)‰	±(0.4-0.6)‰

* (H_2^+, H_3^+)

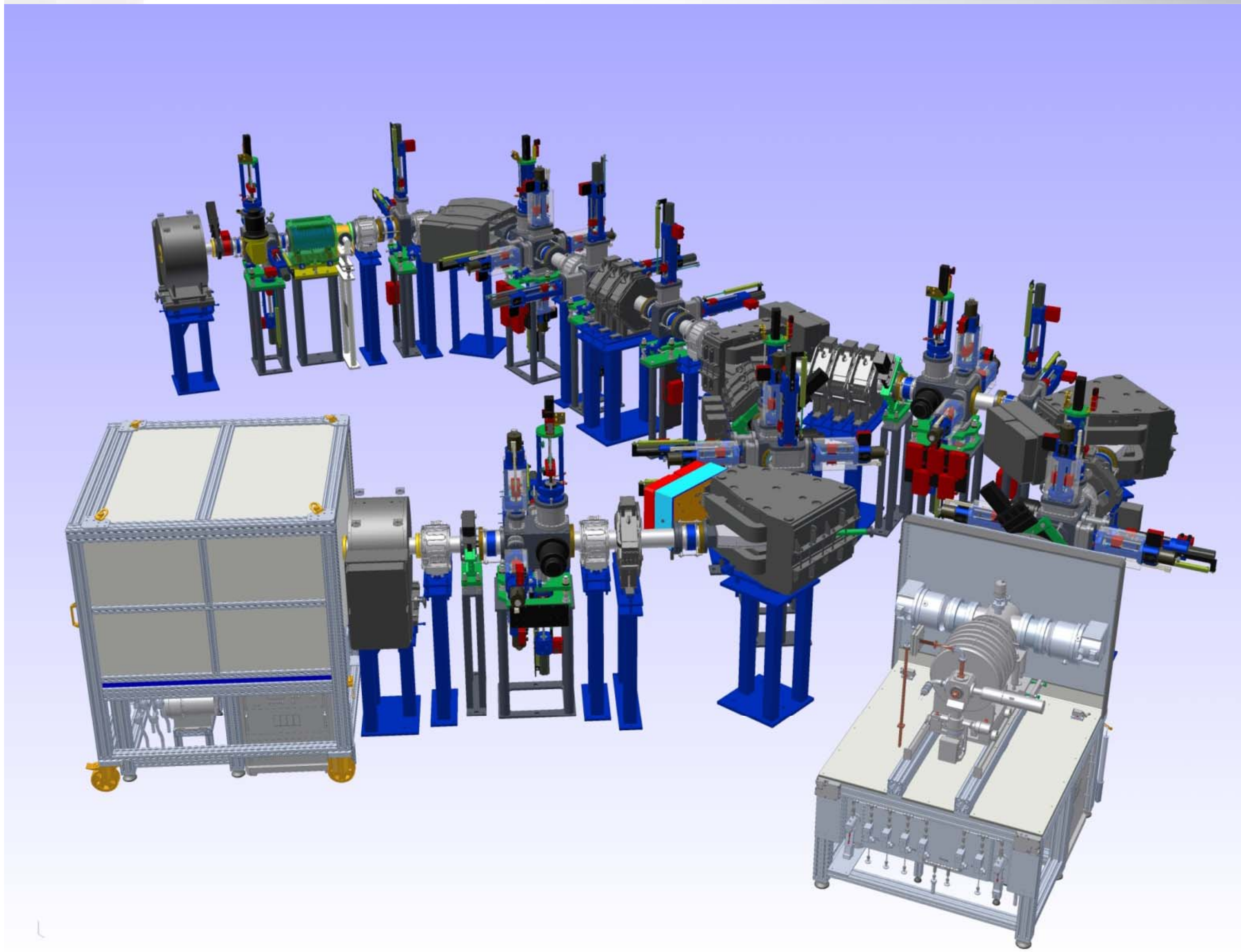
Design Parameters II

Carbon ($4\cdot10^8$ C/spill)				
	LEBT (C^{4+})	MEBT	SYNC	HEBT
Energy [MeV/u]	0.008	7	7-400	**120-400**
Imax [A]	0.15×10^{-3}	0.15×10^{-3}	1.5×10^{-3}	$\mathbf{2\times10^{-9}}$
Imin [A]	0.15×10^{-3}	15×10^{-6}	28×10^{-6}	4×10^{-12}
$\varepsilon_{rms,geo}$ [π mm mrad]	45	1.9	0.73-6.1	0.73-1.43(V)
$\varepsilon_{90,geo}$ [π mm mrad]	180	9.4	3.66-30.4	3.66-7.14 (V) 5.0 (H)
Magnetic rigidity [T m]	0.039	0.76	0.76-6.34	3.25-6.34
$(\Delta p/p)_{tot}$	±1.0‰	±(1.2-2.0)‰	±(1.2-2.9)‰	±(0.4-0.6)‰

Facciamo un giro della facility



Sources and LEBT



0.008 MeV/u H_3^+
0.008 MeV/u C^{4+}

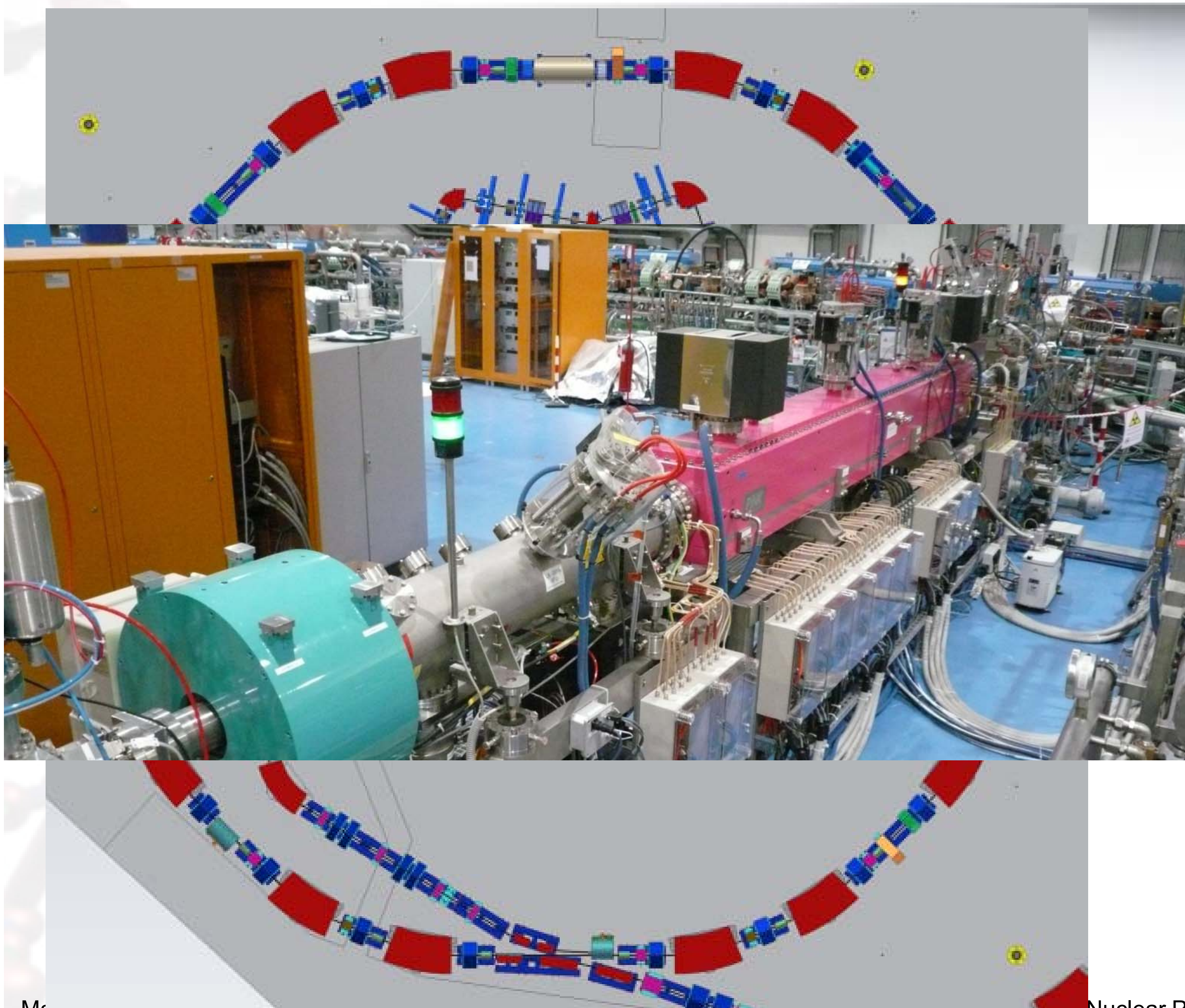
I ~ 0.5 mA (H_3^+)
I ~ 0.2 mA (C^{4+})

Two ECR sources

Continuous beam

LEBT Chopper

LINAC system

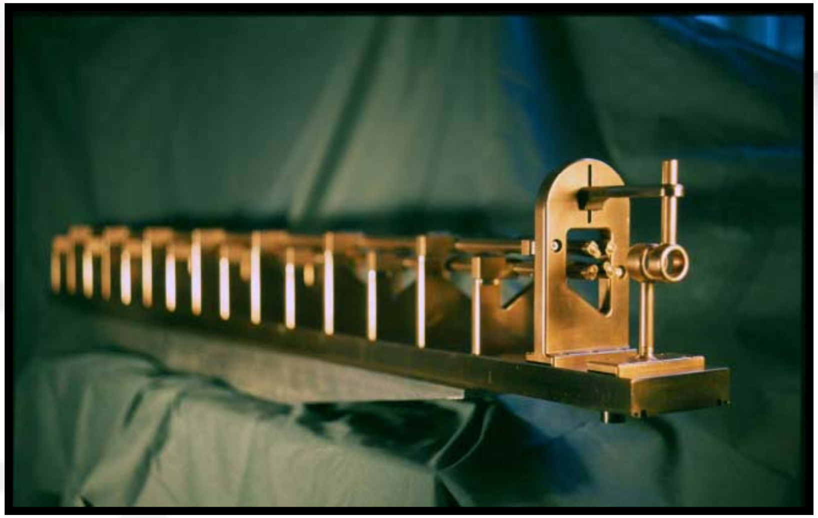


217 MHz

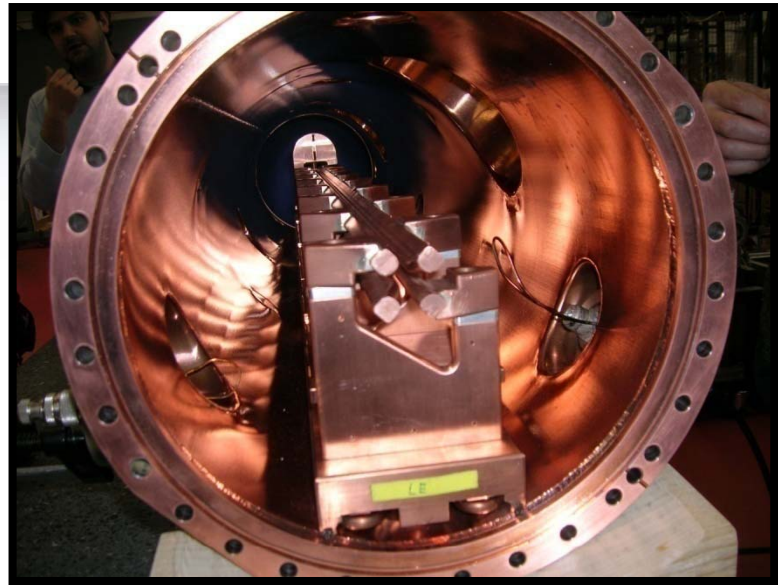
RFQ
0.008-0.4 MeV/u H_3^+
0.008-0.4 MeV/u C^{4+}

IH
0.4-7 MeV/u H_3^+
0.4-7 MeV/u C^{4+}

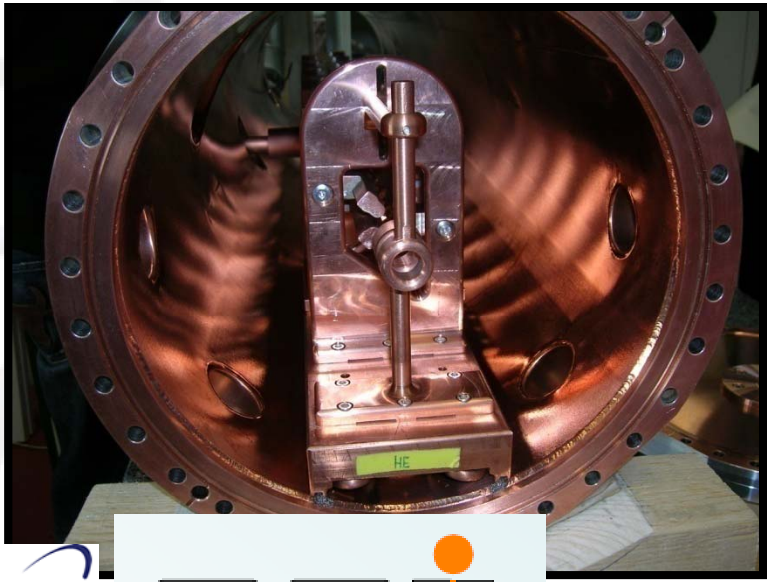
CNAO RFQ



Struttura interna



Ingresso ioni



Uscita ioni

217 MHz

Four-rod like type

Energy range = 8 – 400 keV/u

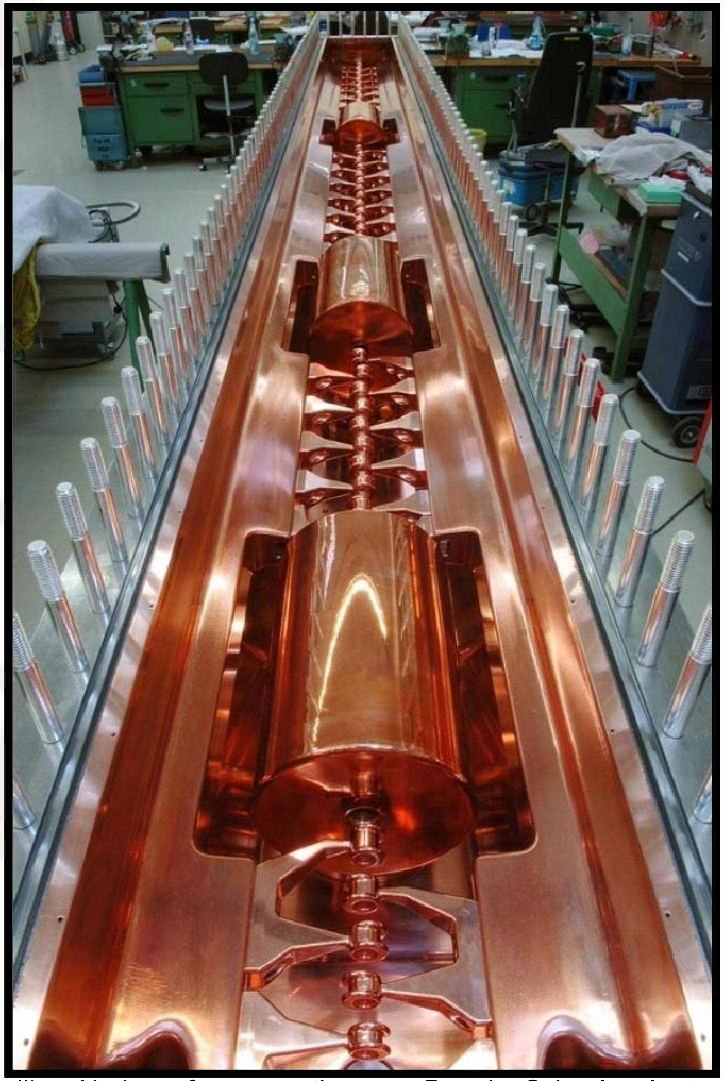
Electrode length = 1.35 m,

Electrode voltage = 70 kV

RF power loss (pulse): about 100 kW

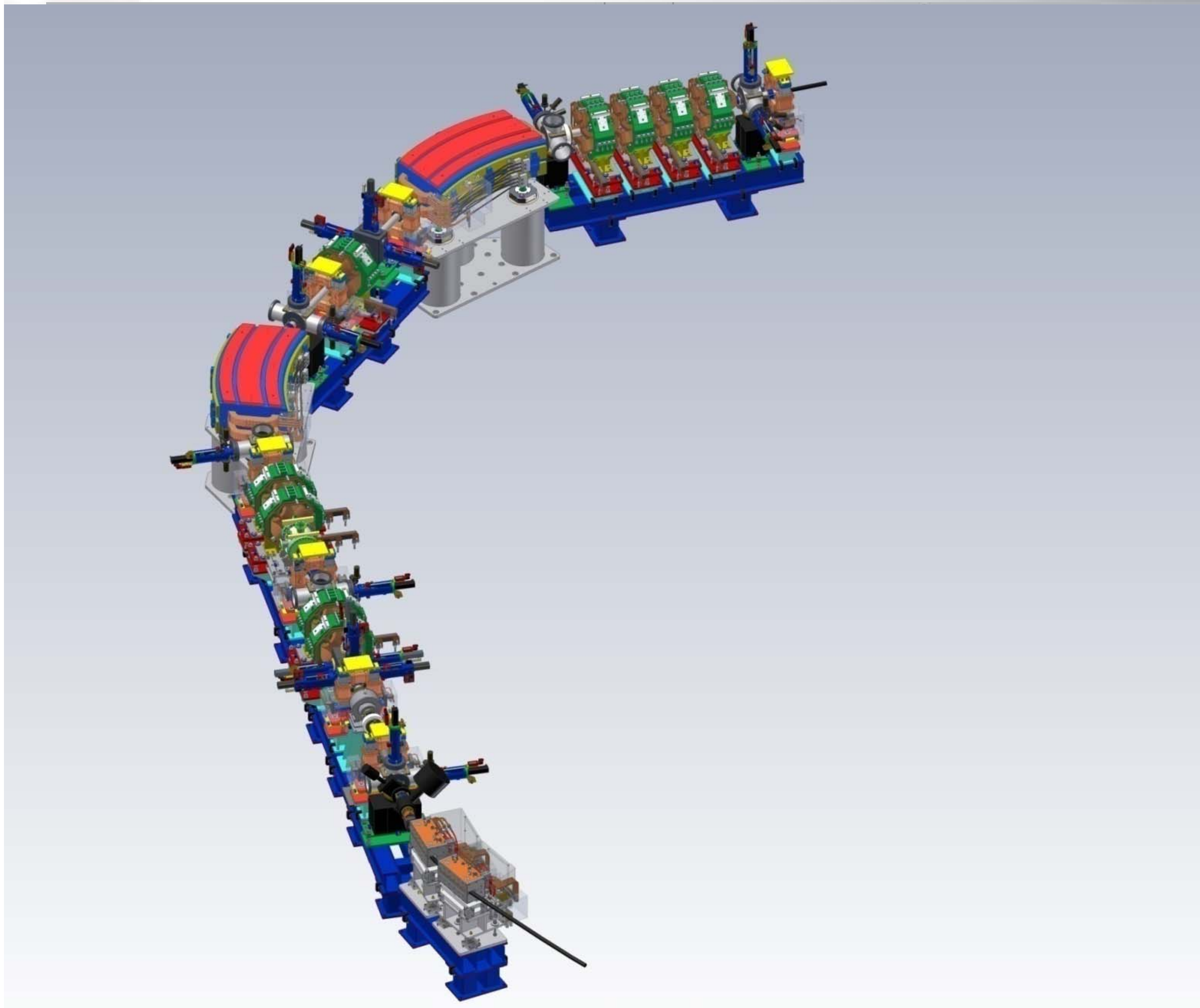
Low duty cycle: around 0.1%

LINAC



3	Integrated magnetic triplet lenses	
56	Accelerating gaps	
Energy range		0.4 – 7 MeV/u
Tank length		3.77 m
Inner tank height		0.34 m
Inner tank width		0.26 m
Drift tube aperture diam.		12 – 16 mm
RF power loss (pulse)		≈ 1 MW
Averaged eff. volt. gain		5.3 MV/m

MEBT Layout



7 MeV p
7 MeV/u C^{6+}

I ~ 0.75 mA (p)
I ~ 0.12 mA (C^{6+})

Stripping foil

Current selection

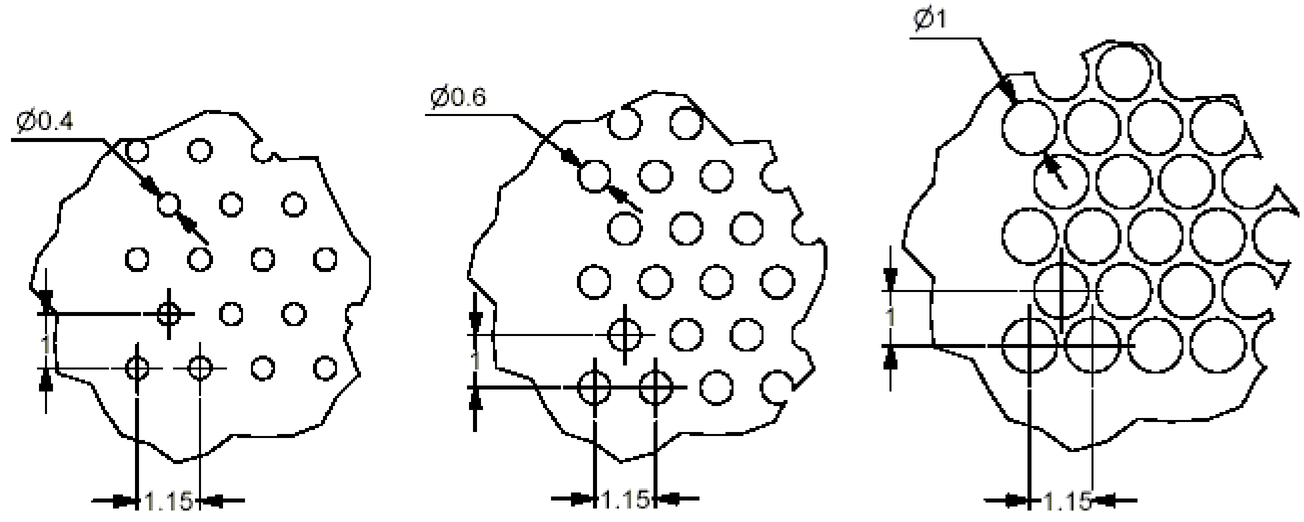
Debuncher

Emittance dilution

Match betas

$(x,x')_{Inj}$

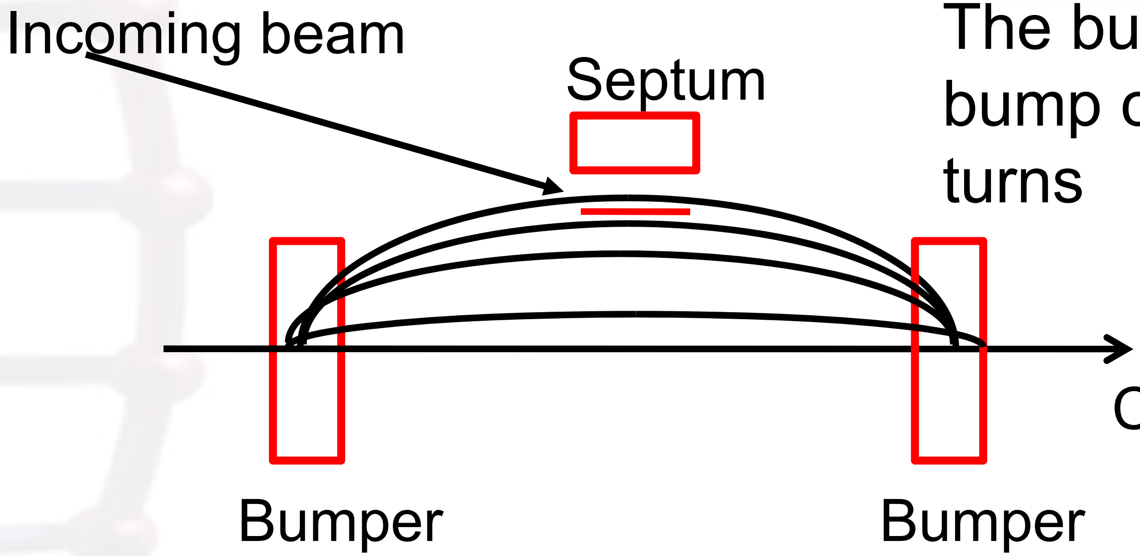
Intensity degrader



F10 Filter   F20 Filter   F50 Filter

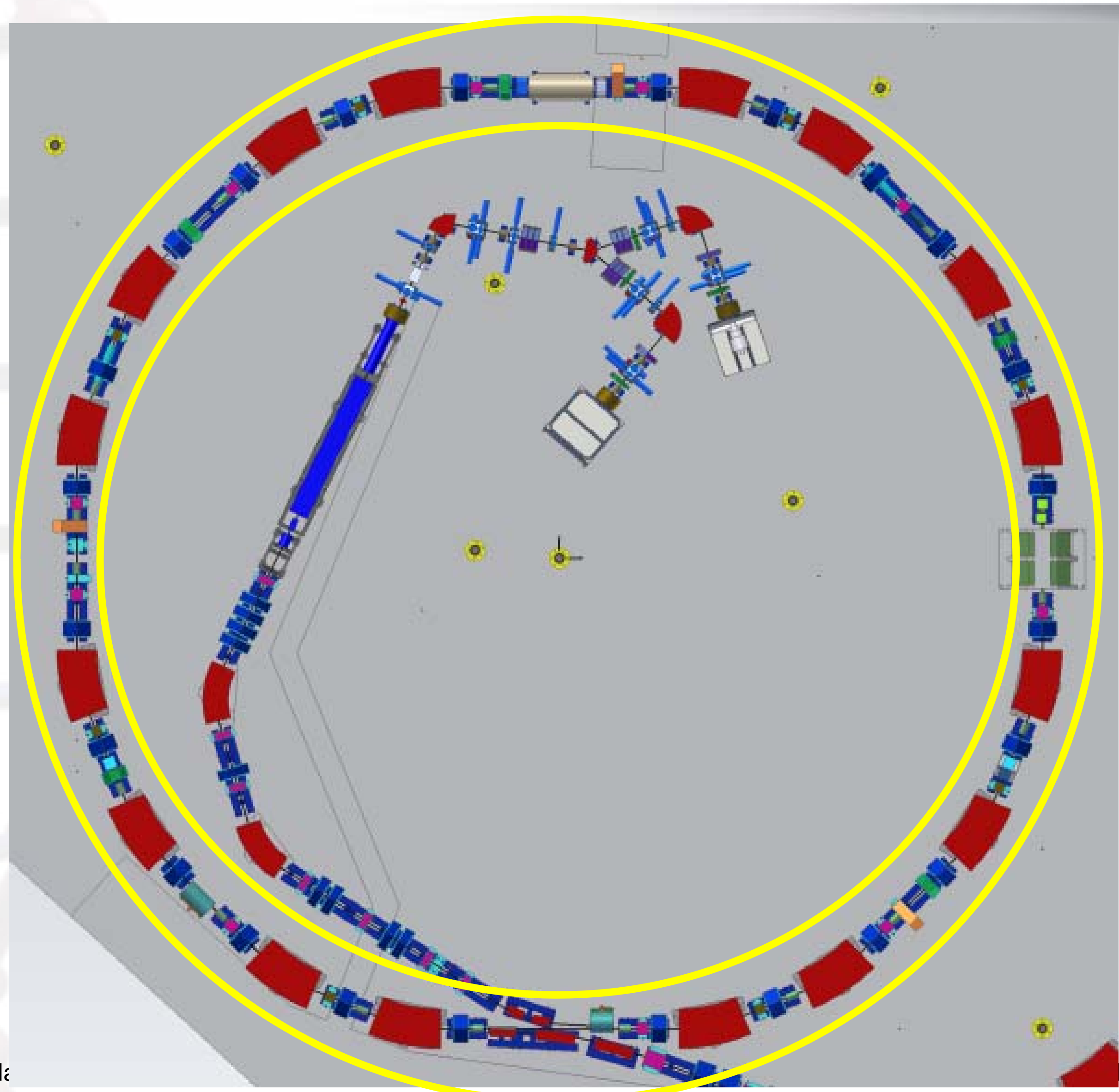
4 transmission levels: 100%, 50%, 20%, 10%
Keep overall emittance unchanged

Multiturn injection



The bump
bump coll
turns

Synchrotron

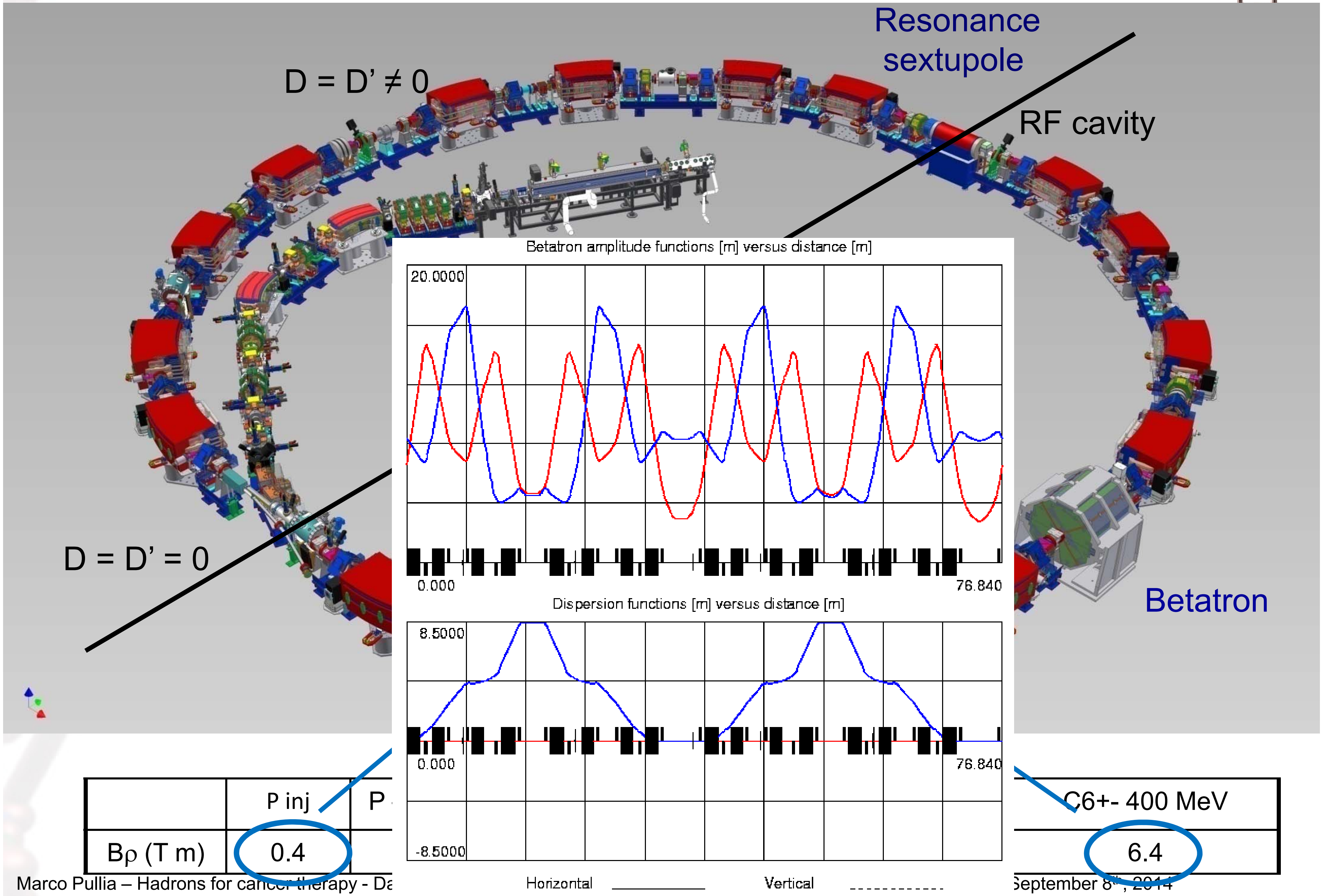


7-250 MeV p
7-400 MeV/u C

I ~ 0.1-5 mA (p)
I ~ 0.03-1.5 mA (C)

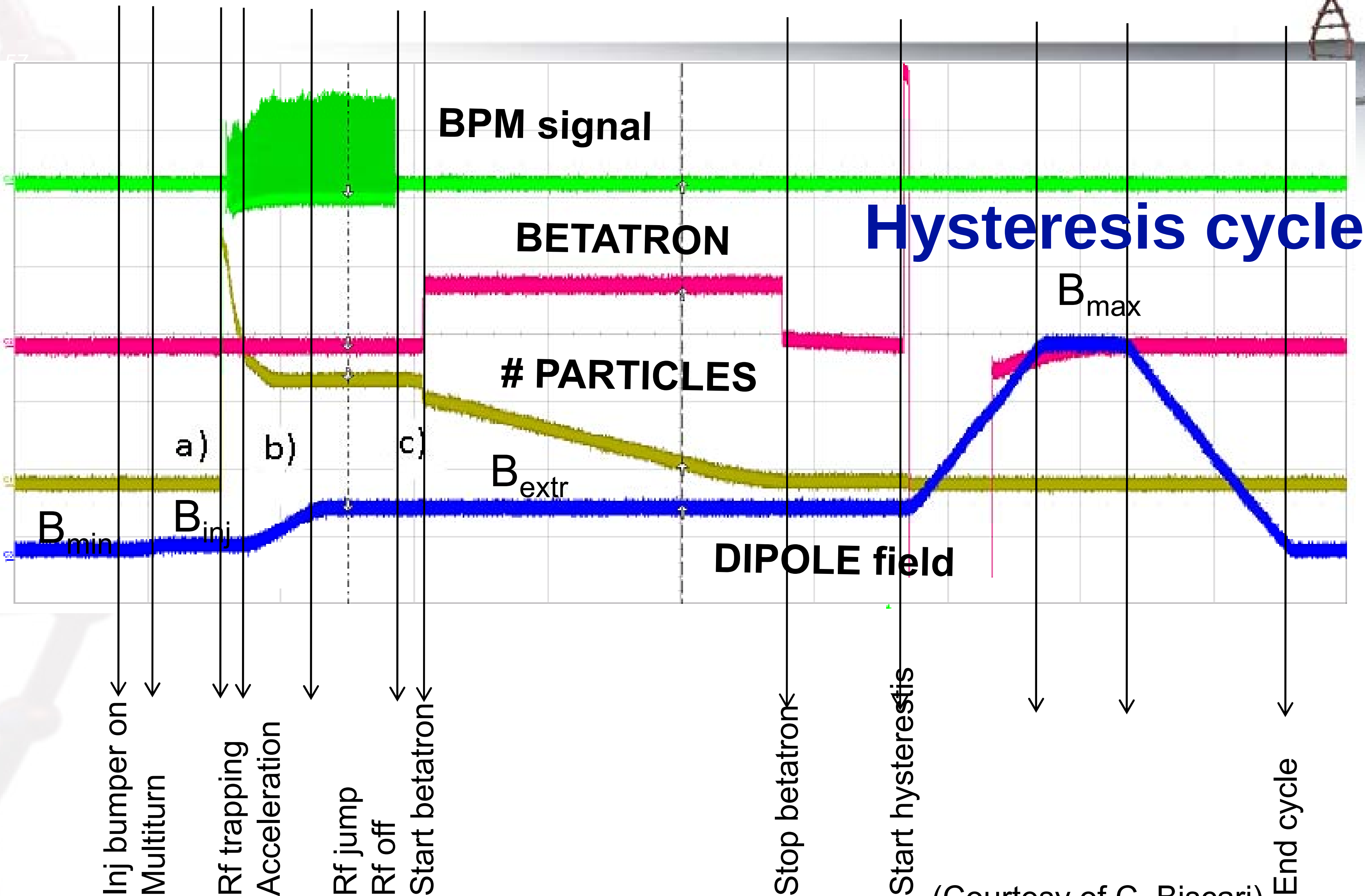
Slow extraction

Betatron core



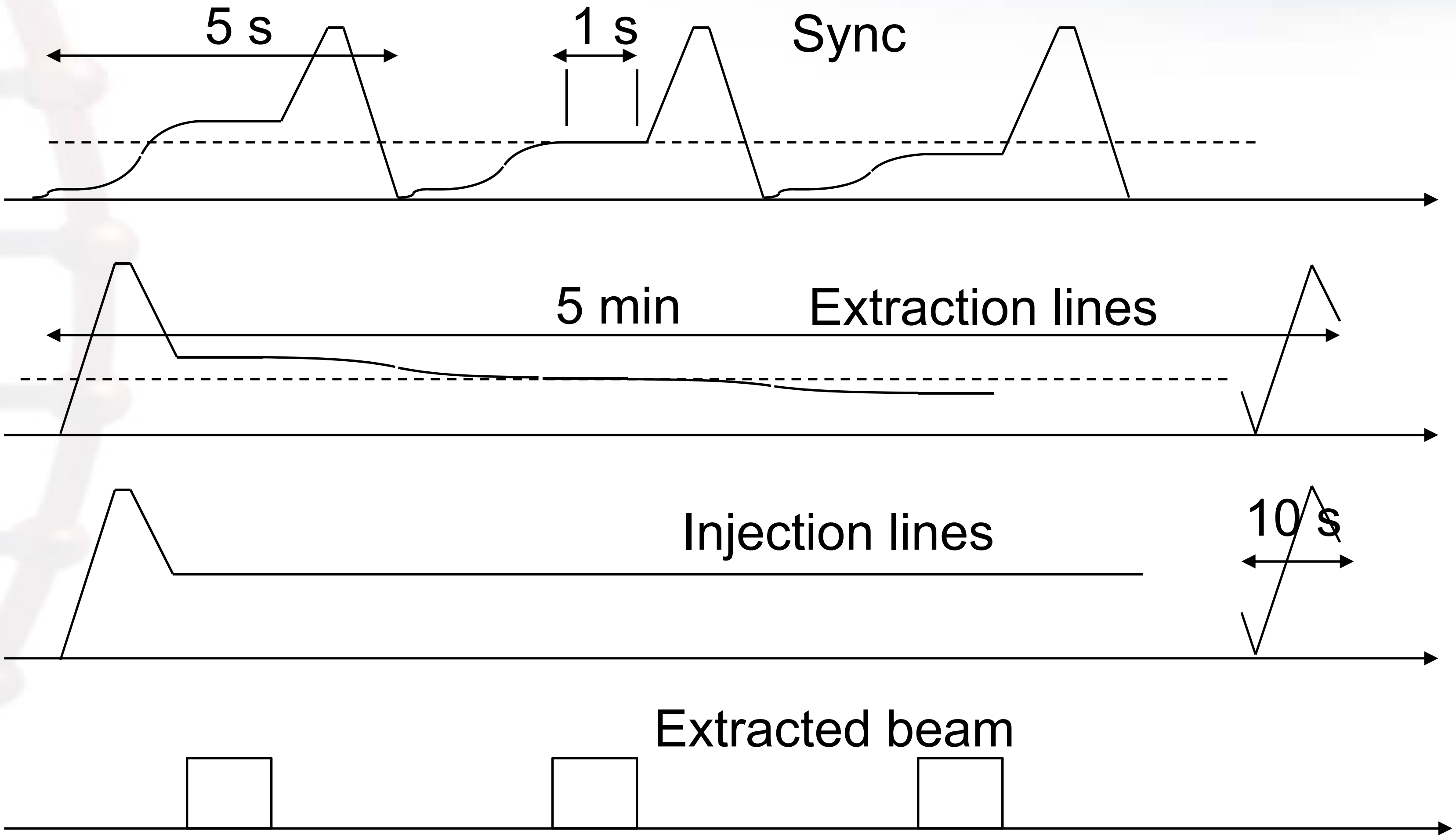
	P inj	P	C6+- 400 MeV
Bρ (T m)	0.4		6.4

Machine Cycle



(Courtesy of C. Biscari)

Treatment execution



Extraction possibilities at CNAO

Betatron core

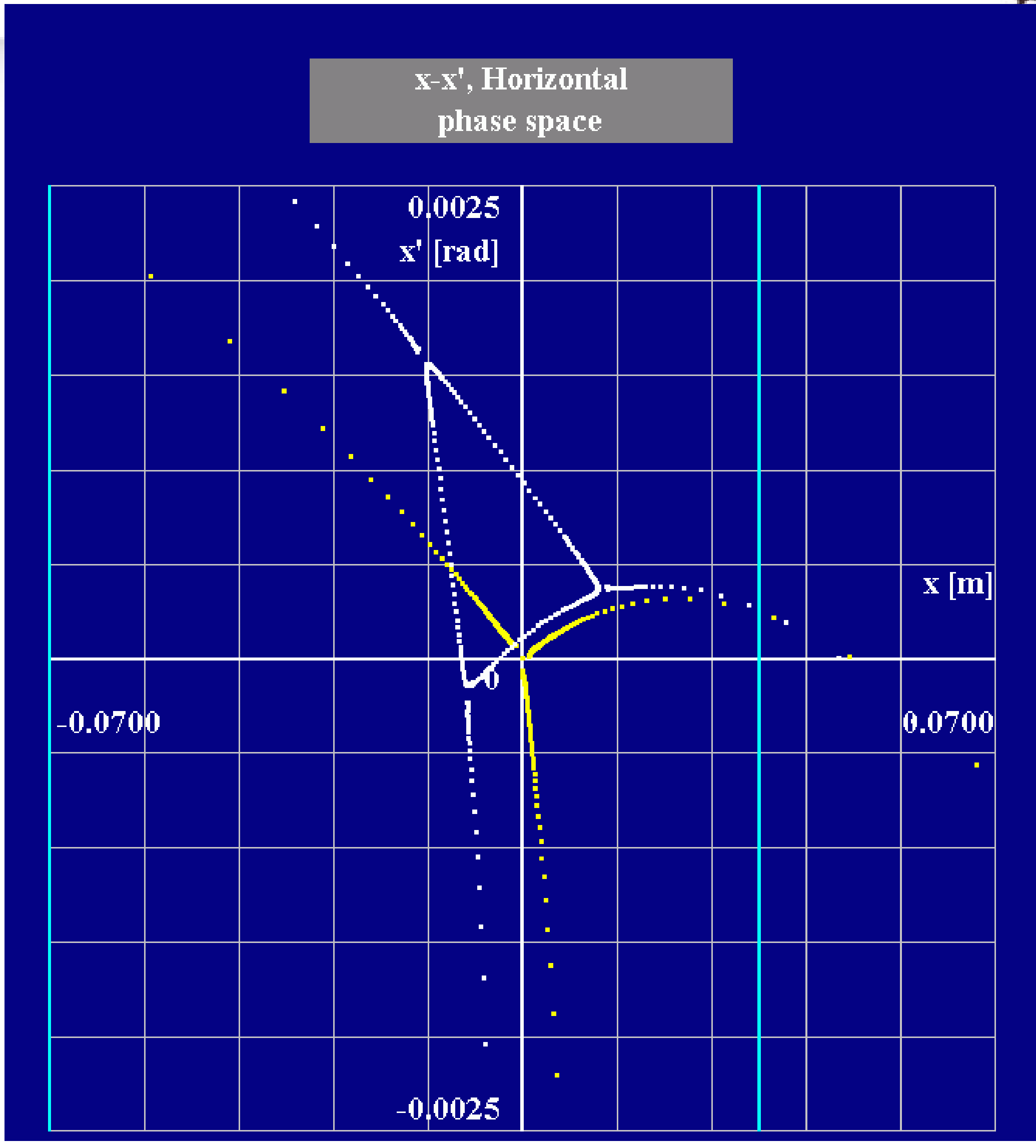
Empty bucket

Air core quadrupole

RF-KO with Schottky Pick-up

Beam shaping with Schottky PU

Additional quad winding

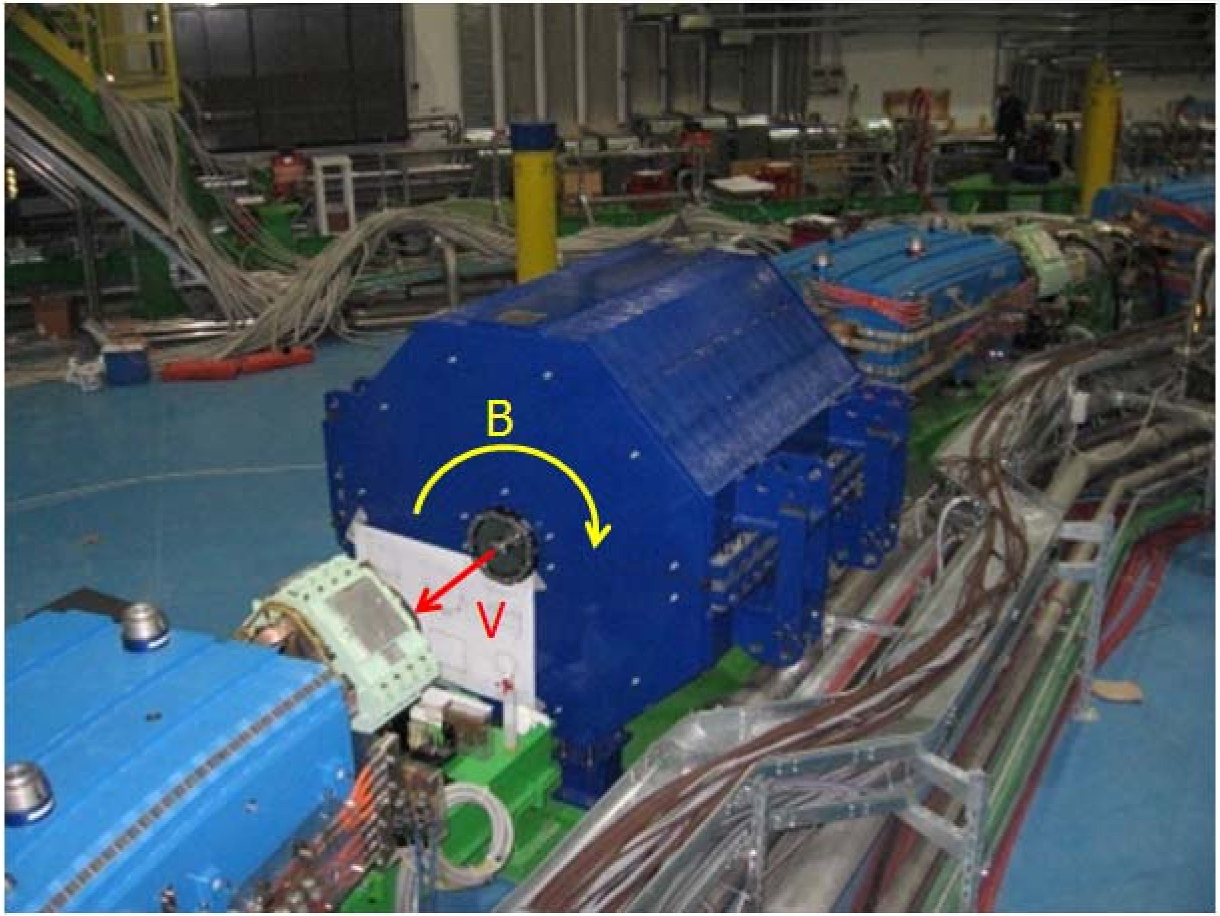


Betatron core

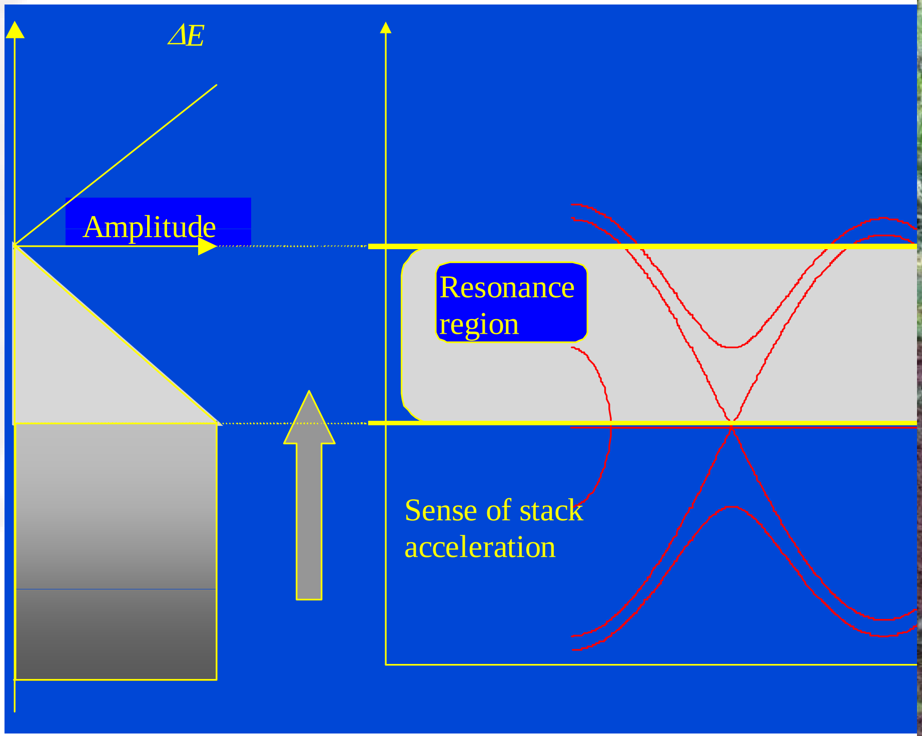
Pushes the beam against the resonance

$\Delta\Phi$ = 2.46 Wb

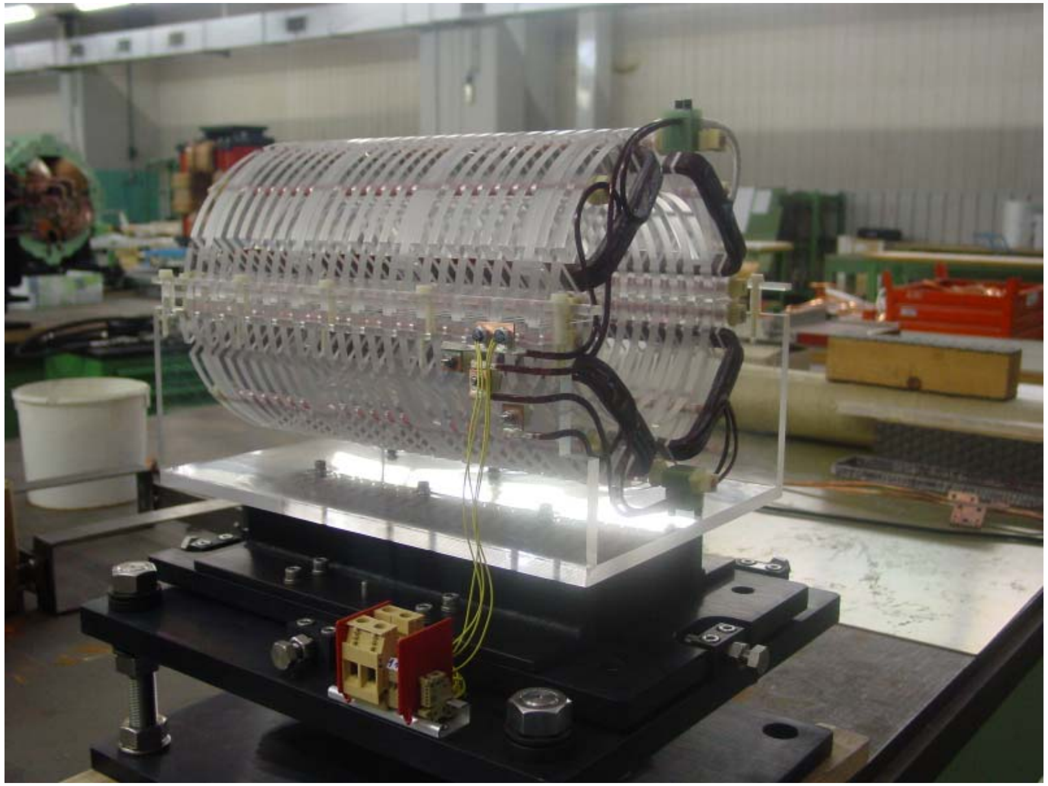
Magnetic screen needed



Empty bucket

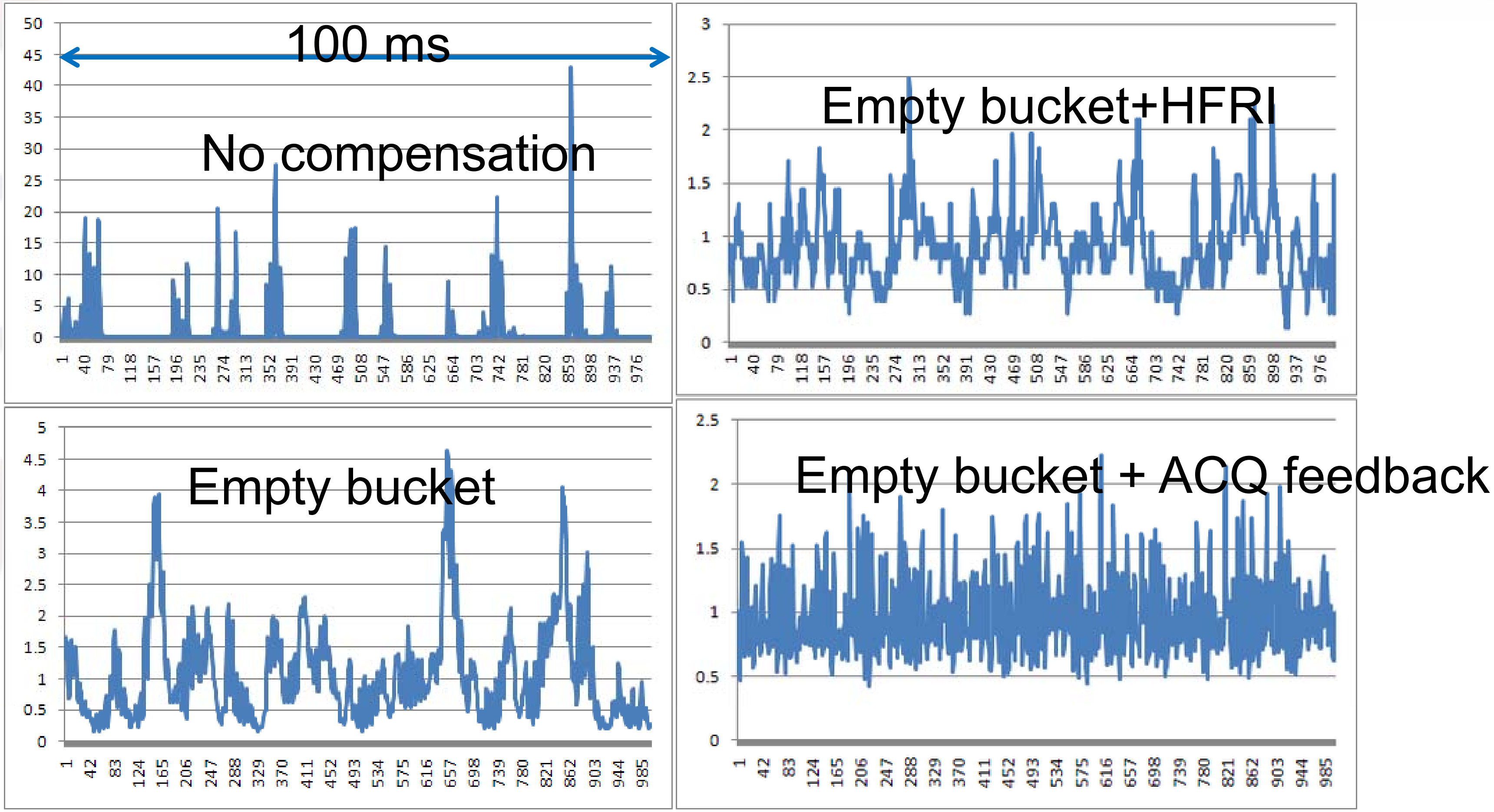


Air core quadrupole

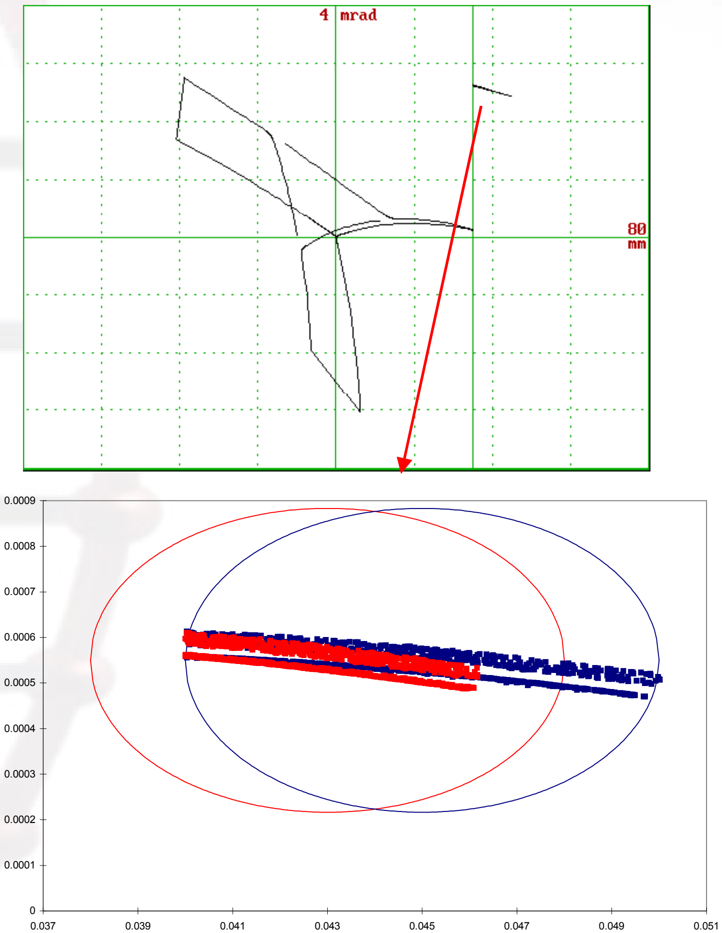


Ripple compensation

Integration time 100 us (10 kHz data)



Extracted beam

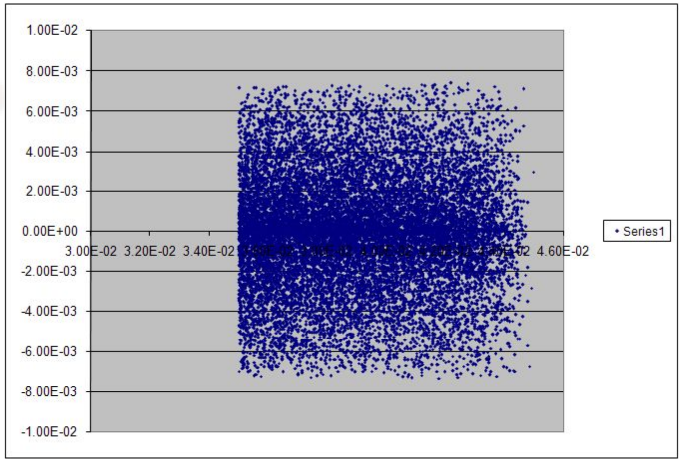


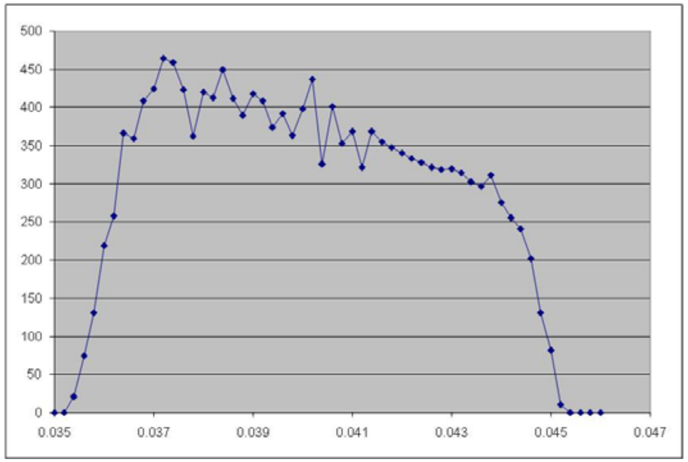
Twiss functions at entry (ES in ring)		
$\beta_x = 5$ m	$\alpha_x = 0$	'Free' parameter.
Ex = 5π mm mrad		'Unfilled' ellipse - 'free'.
$\beta_z = 7.16$ m	$\alpha_z = -0.18$	Values from ring.
$E_{z,RMS} = 0.7324$ to $1.4286\ \pi$ mm mrad $E_{z,RMS} = 0.6679$ to $1.4286\ \pi$ mm mrad		Carbon range from ring. Proton range from ring.
$D_x = 2.095$ m	$D'_x = -0.0393$	Determined by extraction.
$D_z = 0$	$D'_z = 0$	
Twiss functions at exit (all beam exits)		
$\beta_x = 7.2$ m	$\alpha_x = 0$	According to medical specifications and earlier choice of 'free' parameters.
$\beta_z = 2$ to 27 m	$\alpha_z = 0$	
$D_x = 0$	$D'_x = 0$	
$D_z = 0$	$D'_z = 0$	

Beam shape

Vertical distribution: bell shape/gaussian like

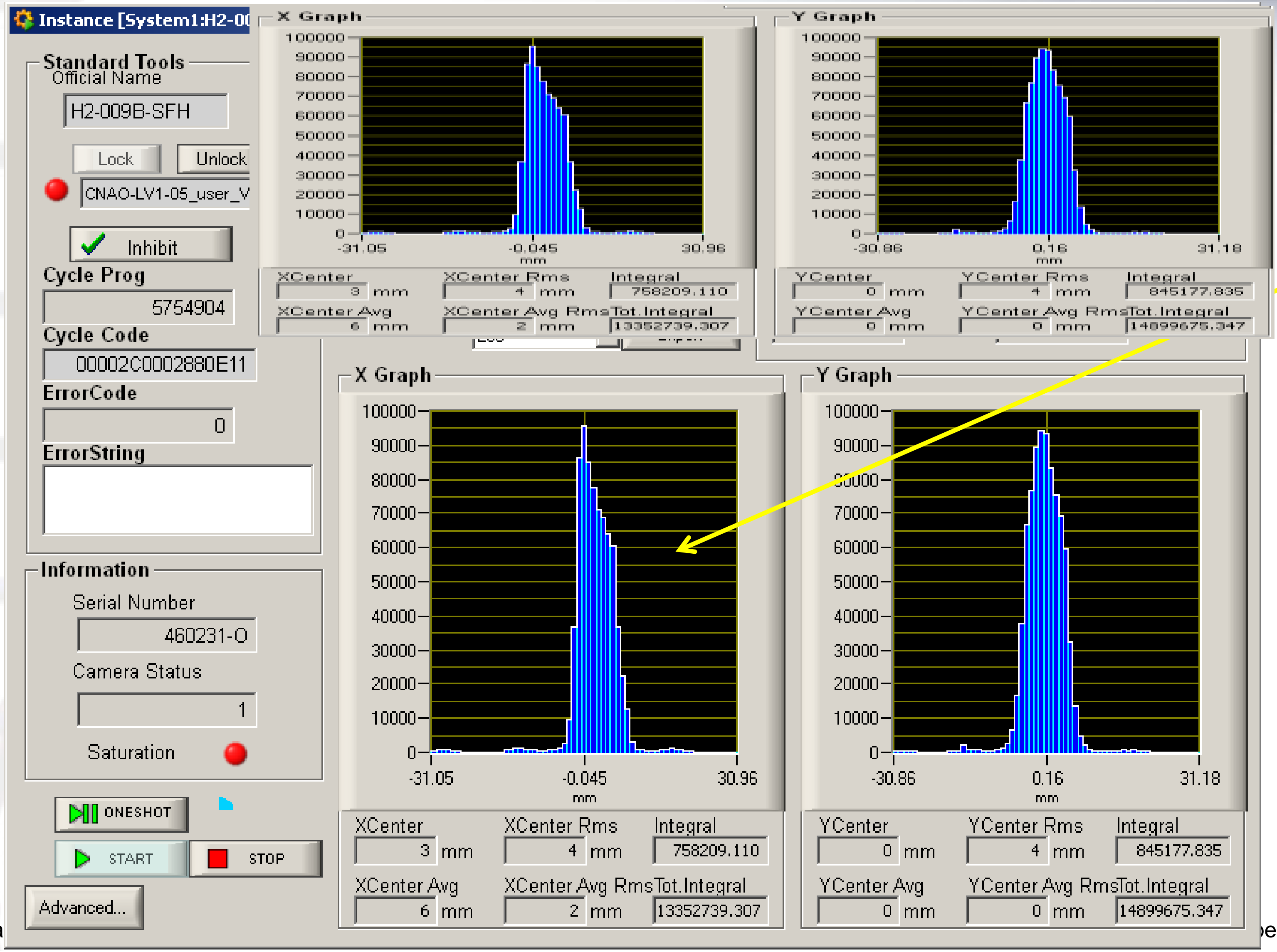
Horizontal distribution: bar of charge





At extraction septum (x y) In the line

Beam at HEBT entrance



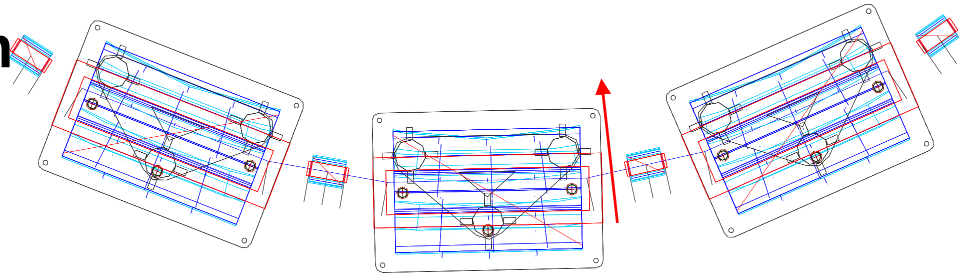
ar of charg

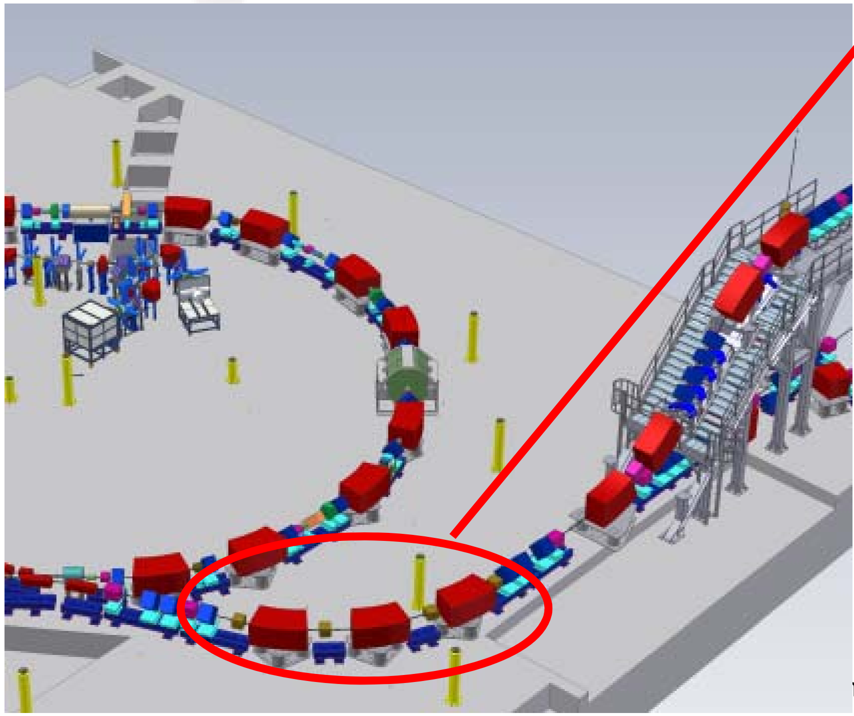
Chopper

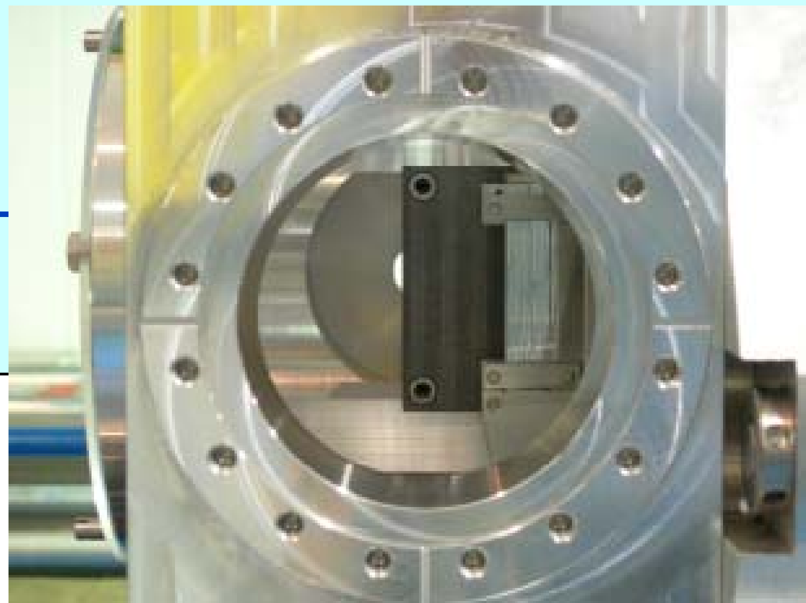
Fast turn on/off for the beam

Intrinsically safe

Allows beam qualification

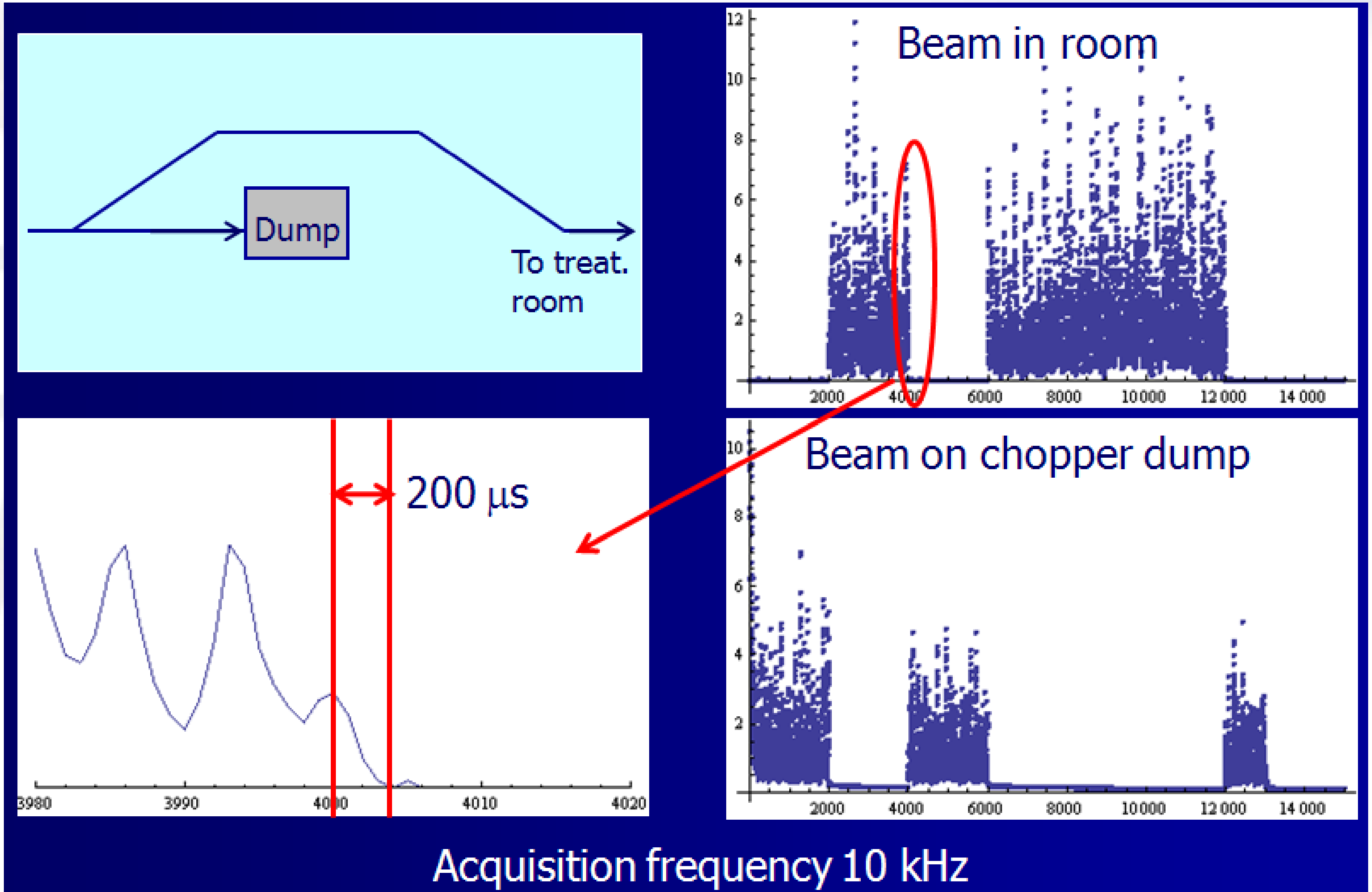






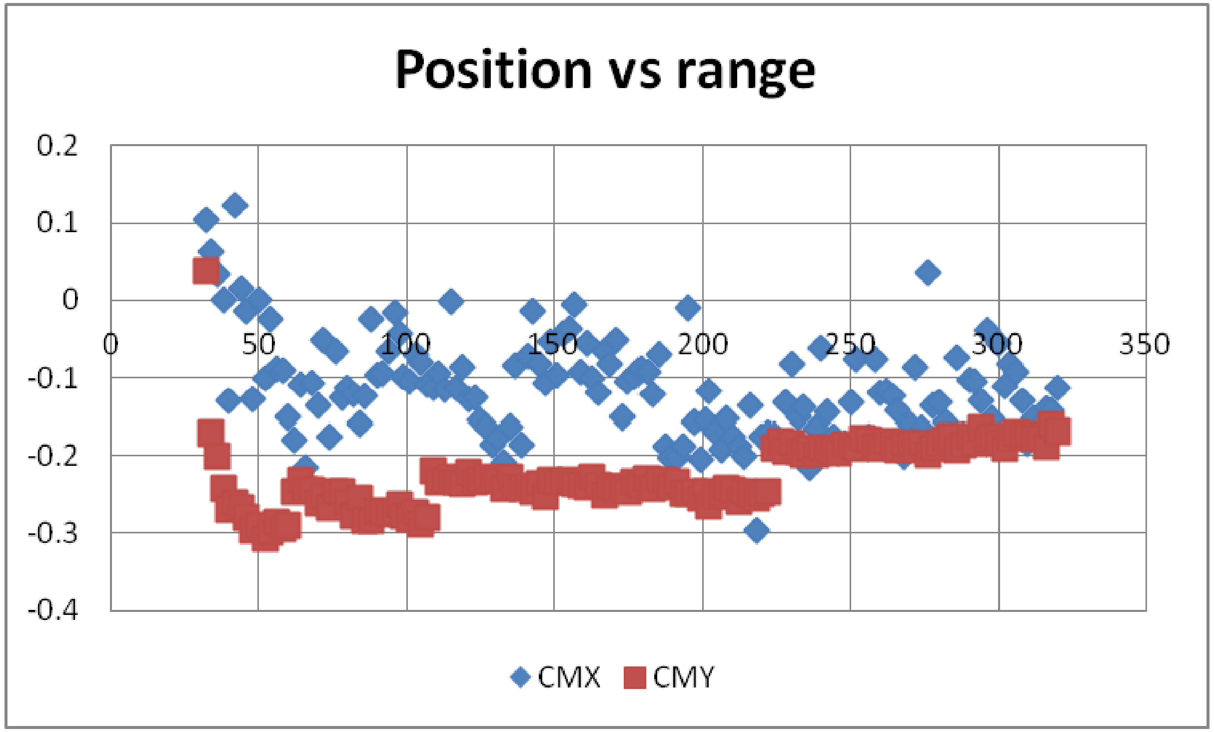
parts
with
breathing

Chopped beam

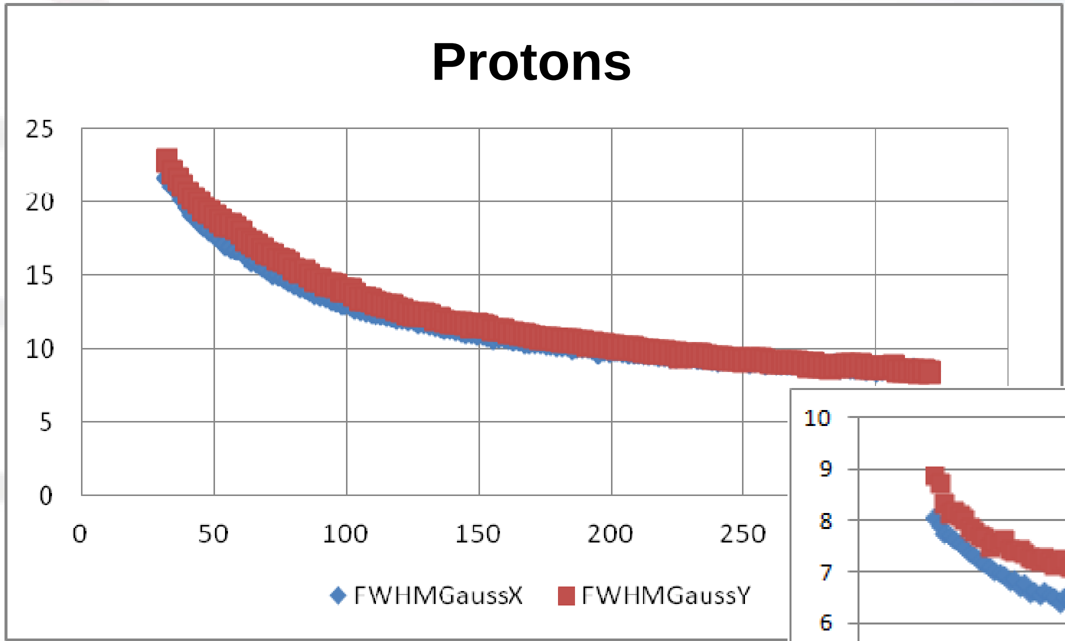


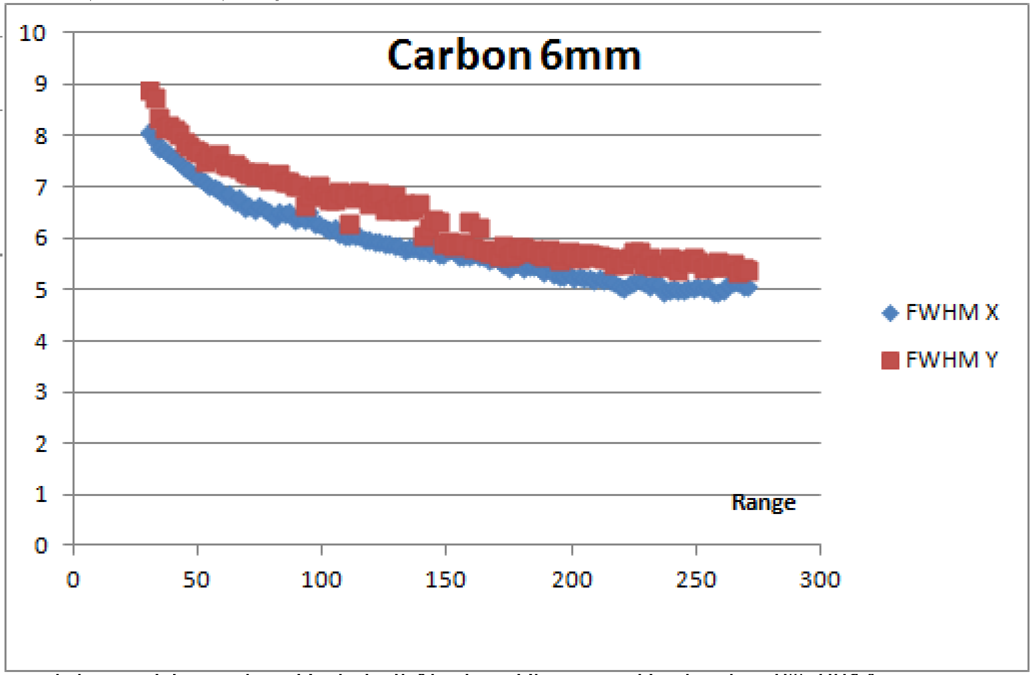
Beam position at HEBT end

Beam position repeatability (at the same energy): 0.2 mm
Beam position precision (at different energies): 0.3 mm

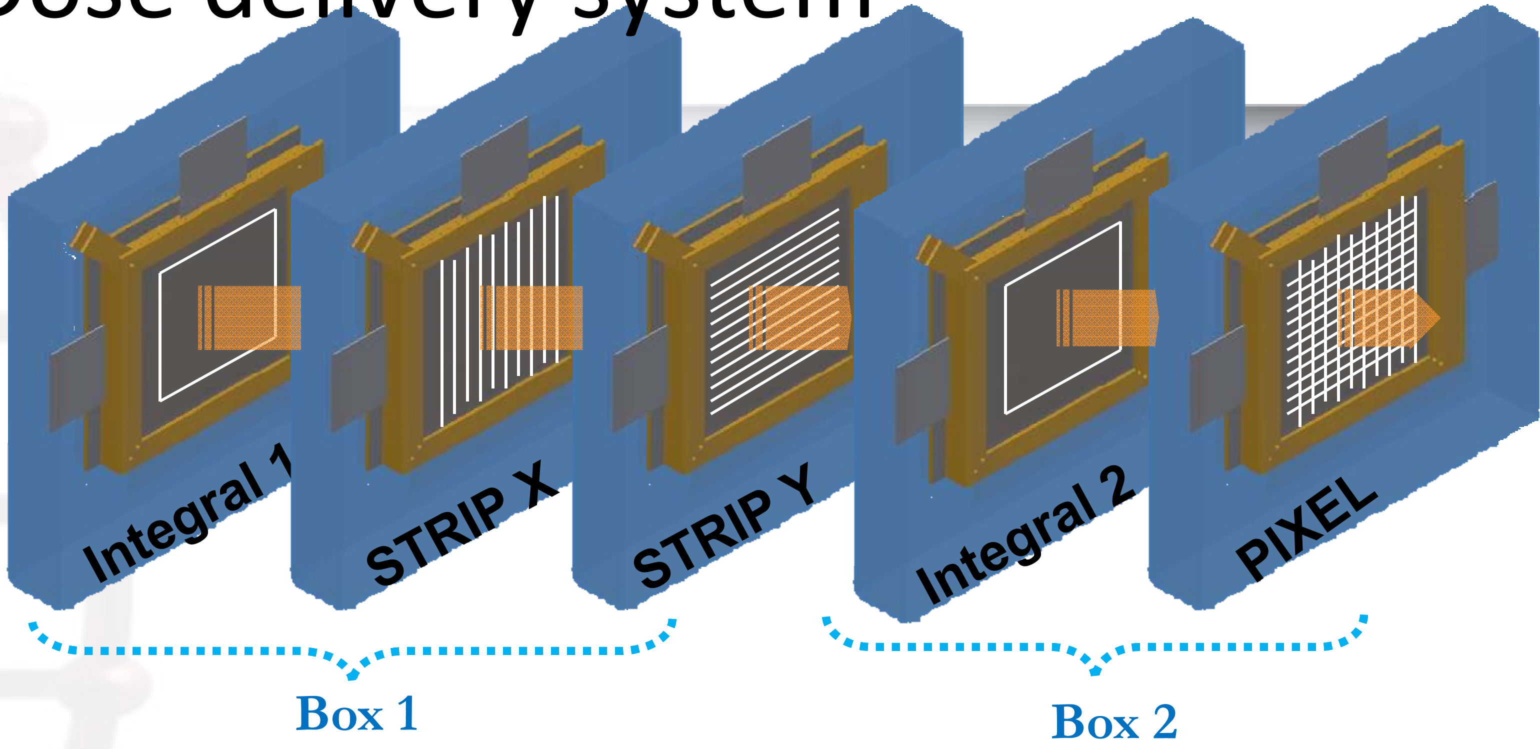


Beam size at isocenter





Dose delivery system



1 Integral chamber:

- Beam Intensity measure every 1 μs

2 Strip chambers (X and Y):

- Beam position measure every 100 μs, with 100 μm of precision

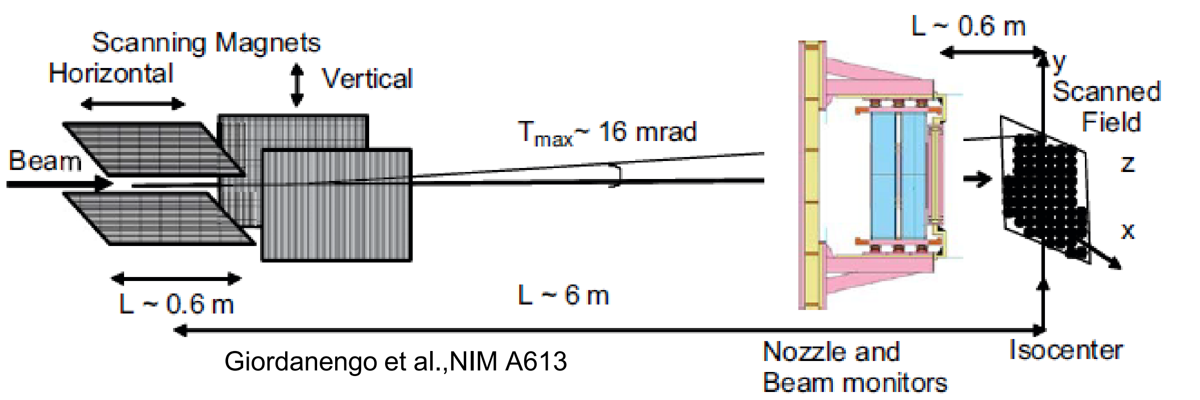
1 Integral chamber:

- Beam Intensity measure every 1 μs

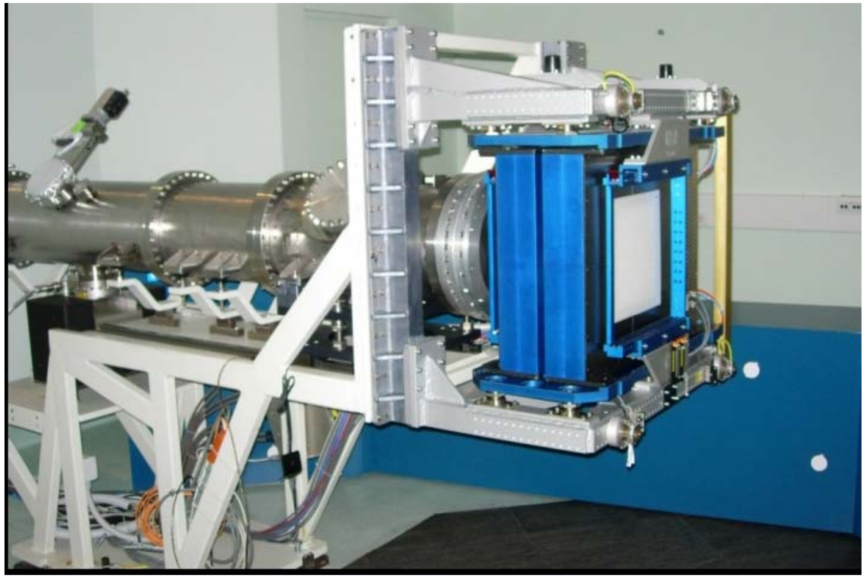
1 Pixel chamber:

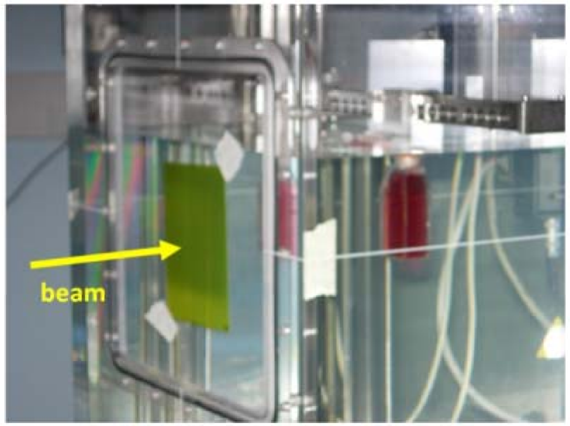
- Beam position and dimension measure every 100 μs/1 ms, with 200 μm of precision

Dose delivery

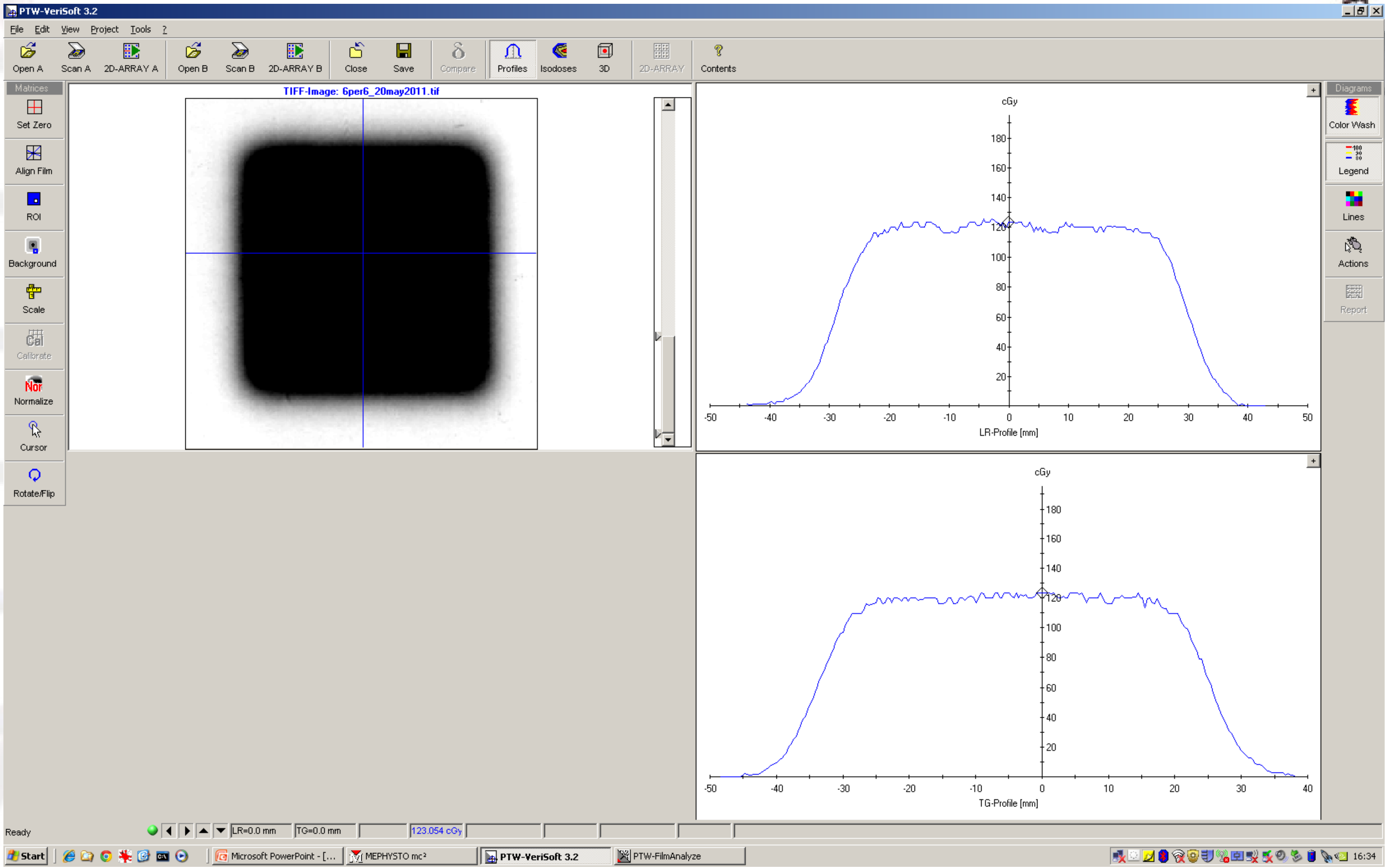


Giordanengo et al.,NIM A613



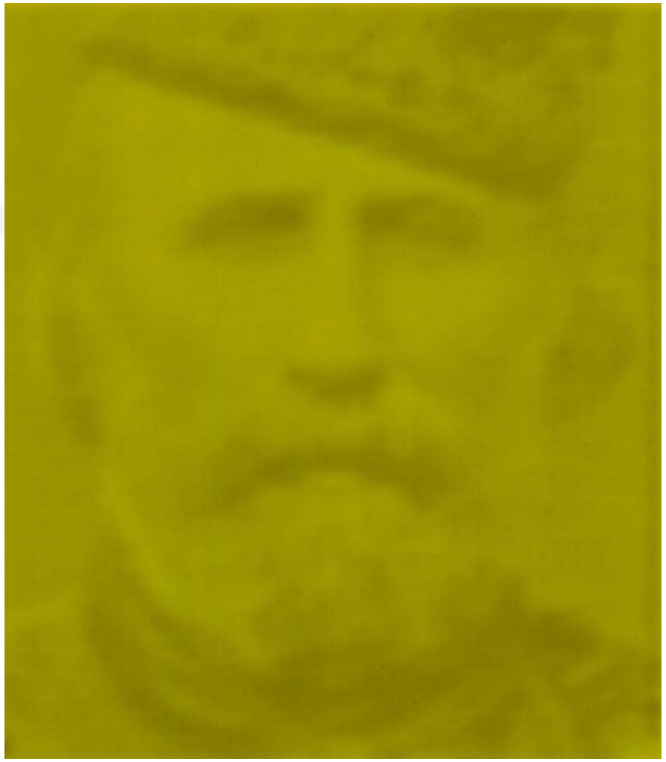


First scannings

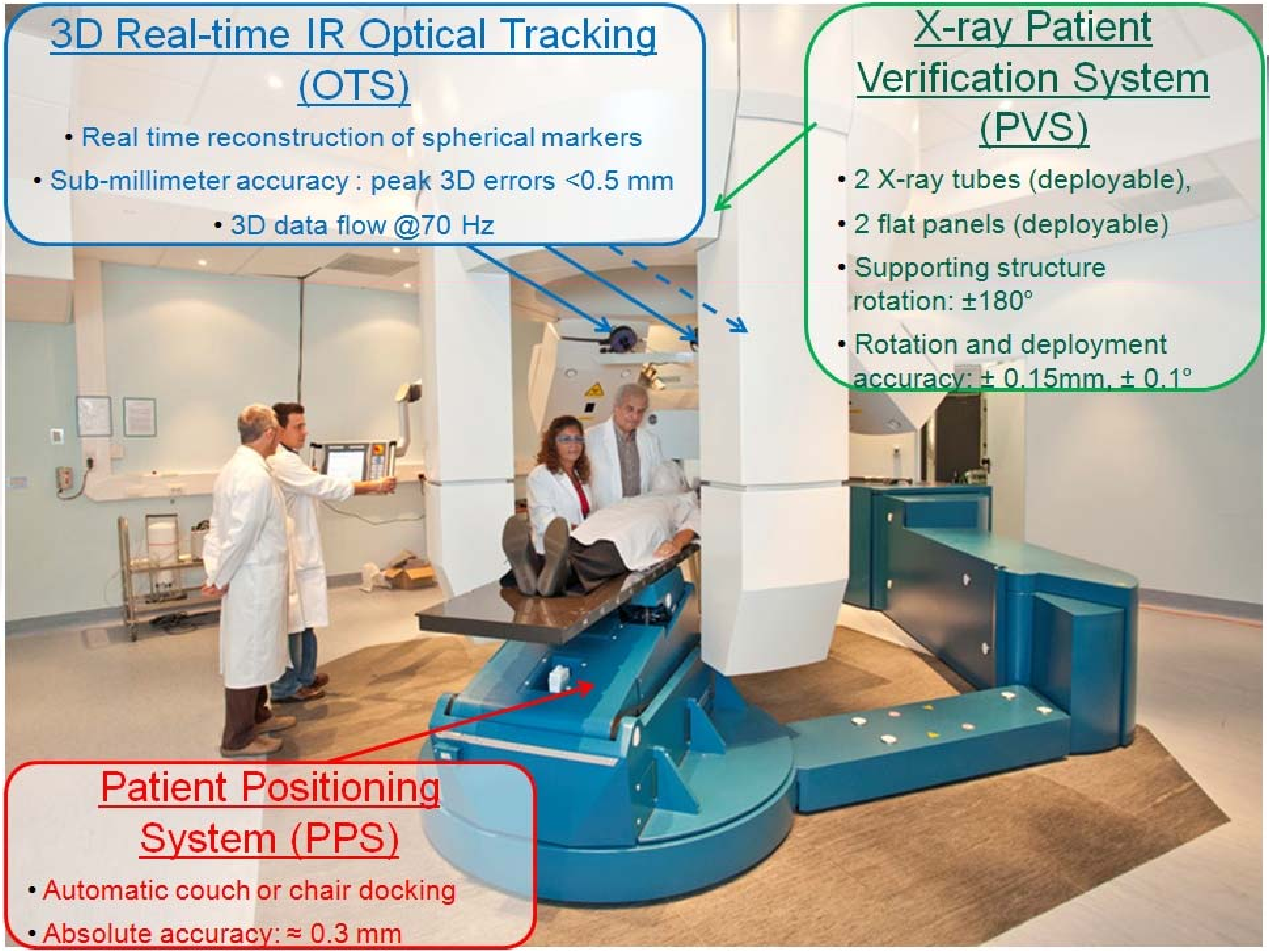


Artistic use of the beam

Radiochromic film



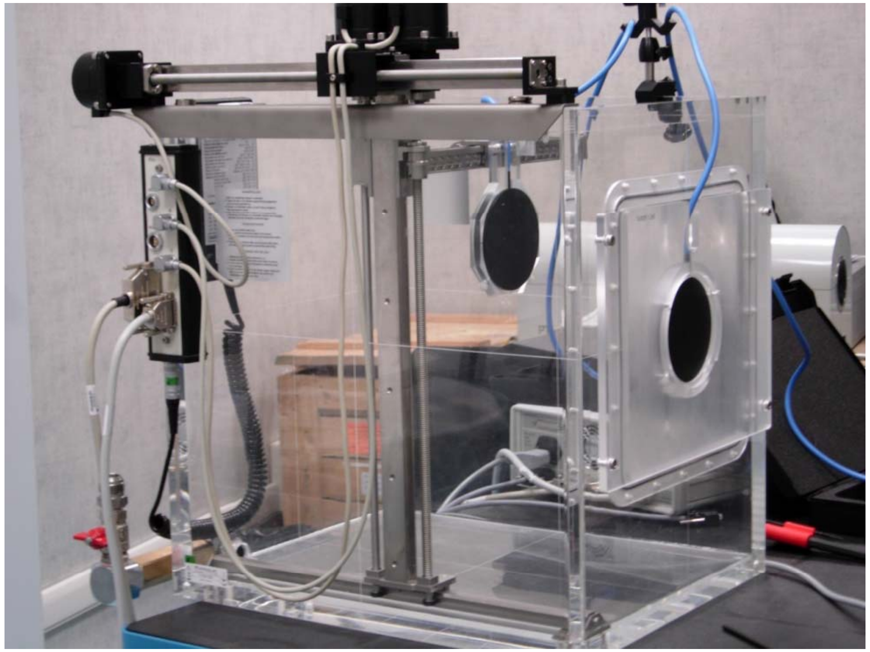
Patient Positioning and Verification strategy at CNAO
Integrated robotic, X-ray and IR localization system



Beam measurements

Depth Dose Distributions (mono-en. pencil beams)

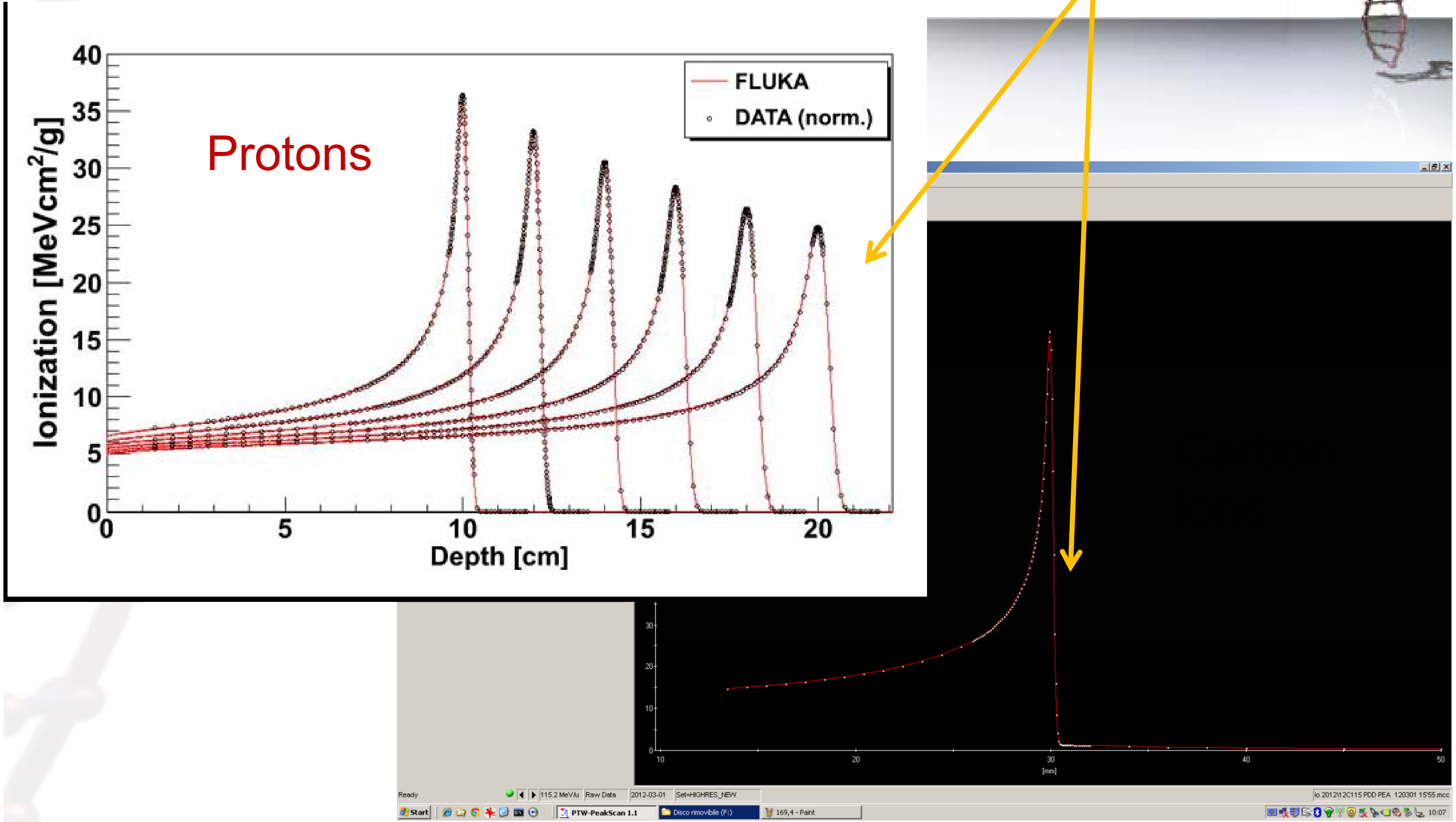
Peakfinder water column



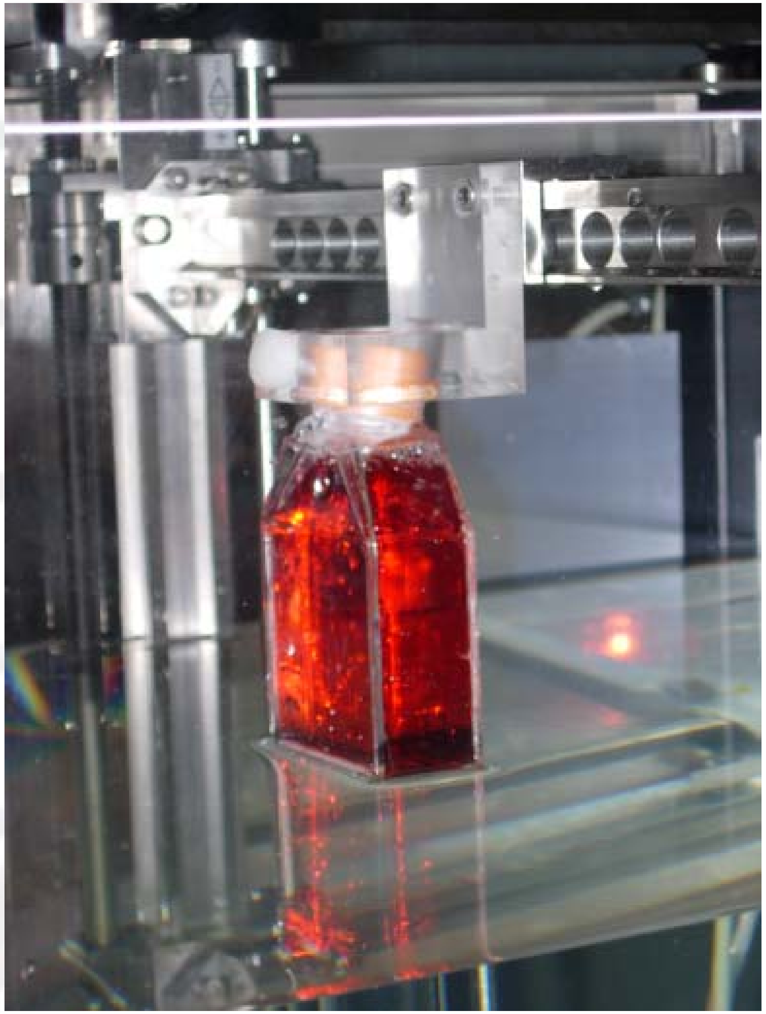
3-D motorized water ph.

Measured Bragg Peaks

Different fall-off

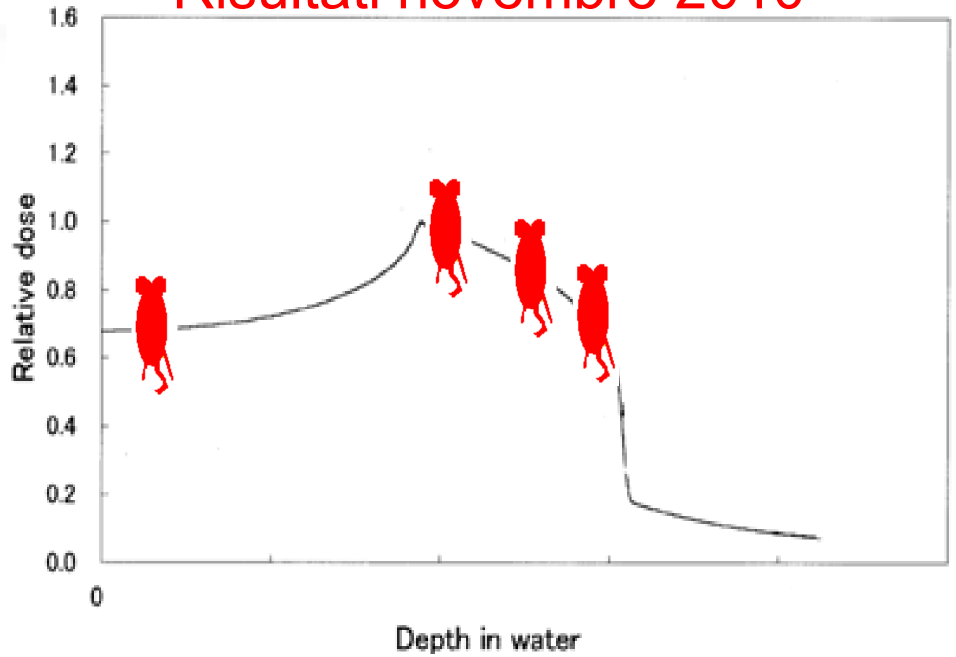


In vitro measurements



Mice crypt survival assay

Risultati novembre 2010



- 2 beam time sessions
- 3 points in the SOBP
- 6 dose levels, 4 mice per position

(Courtesy of B. Vischioni)

Start of medical activities

First patient with Proton beam (September 2011)

First patient with Carbon beam (November 2012)

Patients treated

28 open protocols

Mainly tumors in the head and neck or sacral region

Recently added: prostate, liver and pancreas

344 (246C + 98p) patients treated + 28 under treatment

CE Label

Mod. 2200 - ISS

ISTITUTO SUPERIORE DI SANITÀ

Istituto Superiore di Sanità

Organismo Notificato N° 0373

Sez. presso il Dipartimento di Tecnologie e Salute

Notified Body N° 0373 – Unit relating to Department Technology and Health

Roma, 13 DIC 2013

VIALE REGINA ELENA, 299
00161 ROMA
TELEGRAMMI: ISTISAN ROMA
TELEFONO: 06 49901
TELEFAX: 06 49387118
http: //www.iss.it

CERTIFICAZIONE CE

Secondo l'allegato III della Direttiva Europea 93/42/CEE e successive modifiche
Attuata con DLgs. 37 del 25.01.2010

EC CERTIFICATION

According to Annex III of Directive 93/42/EEC and subsequent modifications
Transposed by DLgs. 37 of 25.01.2010

Certificato n° 20131213 036 3303 CT
Certificate n°

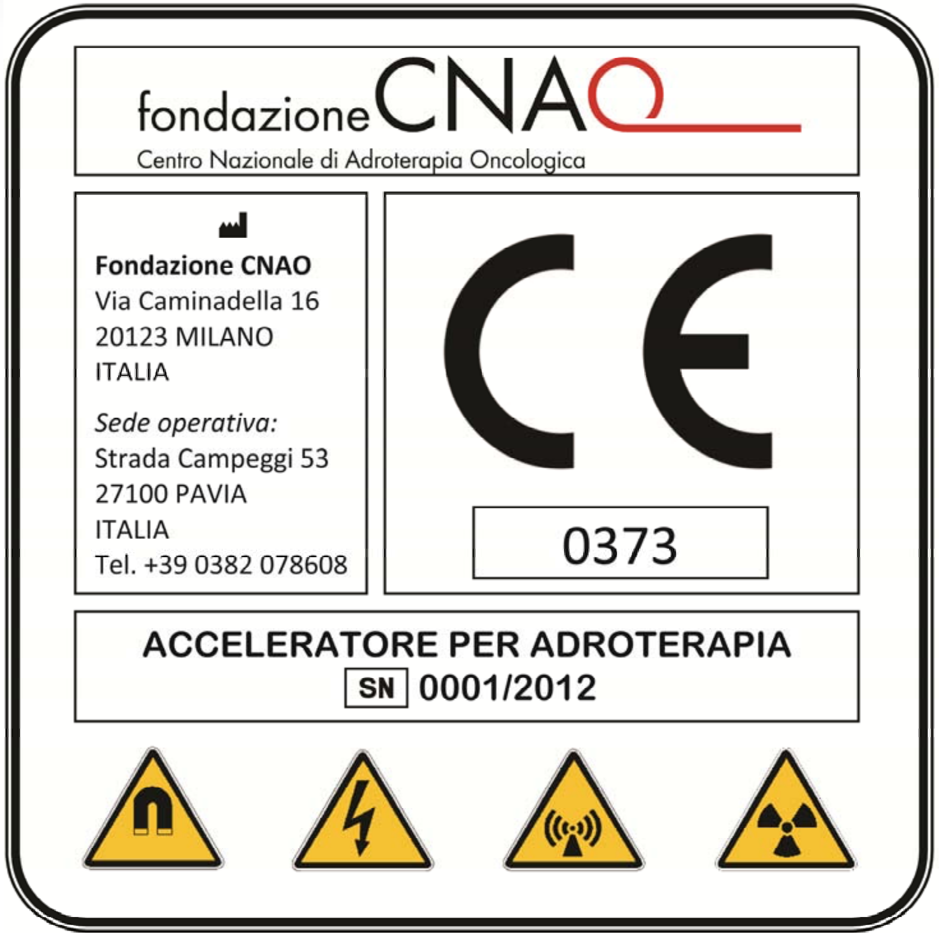
L'Istituto Superiore di Sanità, Organismo Notificato n° 0373, certifica che il prodotto sotto menzionato soddisfa i requisiti essenziali di cui all'allegato I della Direttiva 93/42/CEE e successive modifiche verificati in accordo all'allegato III della stessa Direttiva.

The Italian National Institute of Health, as Notified Body n° 0373, certifies that the product hereinbelow described satisfies the essential requirements set out in Annex I and verified in compliance with Annex III of Directive 93/42/EEC and subsequent modifications.

Tipo e modello: Type and model:	Acceleratore per adroterapia / Accelerator for hadrontherapy
Descrizione: Description:	[34469] ACCELERATORE DI PARTICELLE, RADIOTERAPIA / [34469] PARTICLE ACCELERATOR, RADIOTHERAPY
Destinazione d'uso: Intended use:	Vedi allegato di 3 pagine / See annex of 3 pages
Numero di serie: Serial number:	**0001/2012**
Fabbricante: Manufacturer:	**Fondazione CNAO (Centro Nazionale Adroterapia Oncologica)** **Sede Legale:** Via Caminadella,16 – 20133 Milano **Sede Operativa:** Strada Campeggi, 53 – 27100 Pavia

Rapporto di conformità n° Conformity report n°	2013 003 33 003	**del** of	13/12/2013 dd/mm/yyyy
Il presente certificato è valido dal This certificate is valid from	13/12/2013 dd/mm/yyyy	**al** until	08/07/2018 dd/mm/yyyy

Il Direttore del Dipartimento Tecnologie e Salute F.F.
The Acting Director of Department Technology and Health
(Ing. Pietro Bartolini)



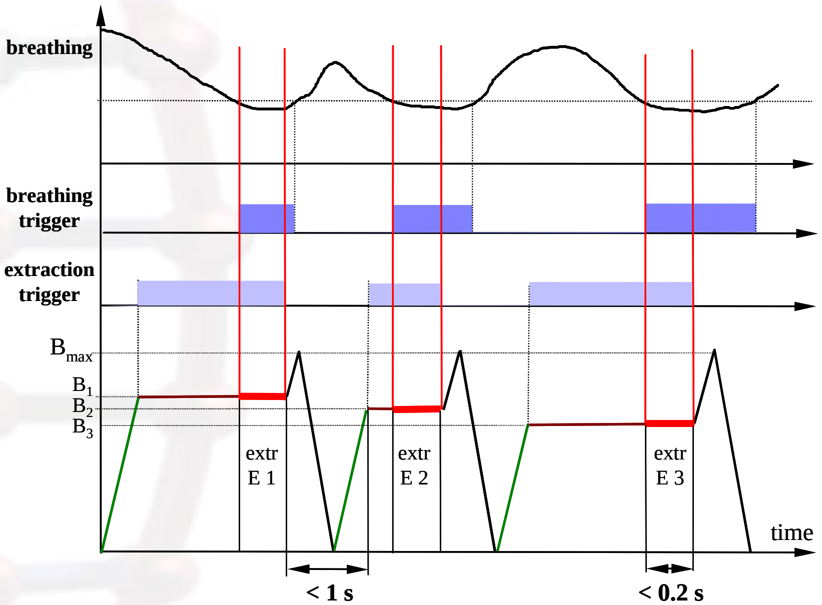
Future and R&D

Future developments

- Coping with tumor motion

On-line imaging

"Minimal" choice: breathing synchronisation (already applied in Chiba, HIT and CNAO)



Interesting also for IMRT: lots of efforts and devices

External surrogates with correlation models

X-rays

Ultrasound, MRI

Particle radiography

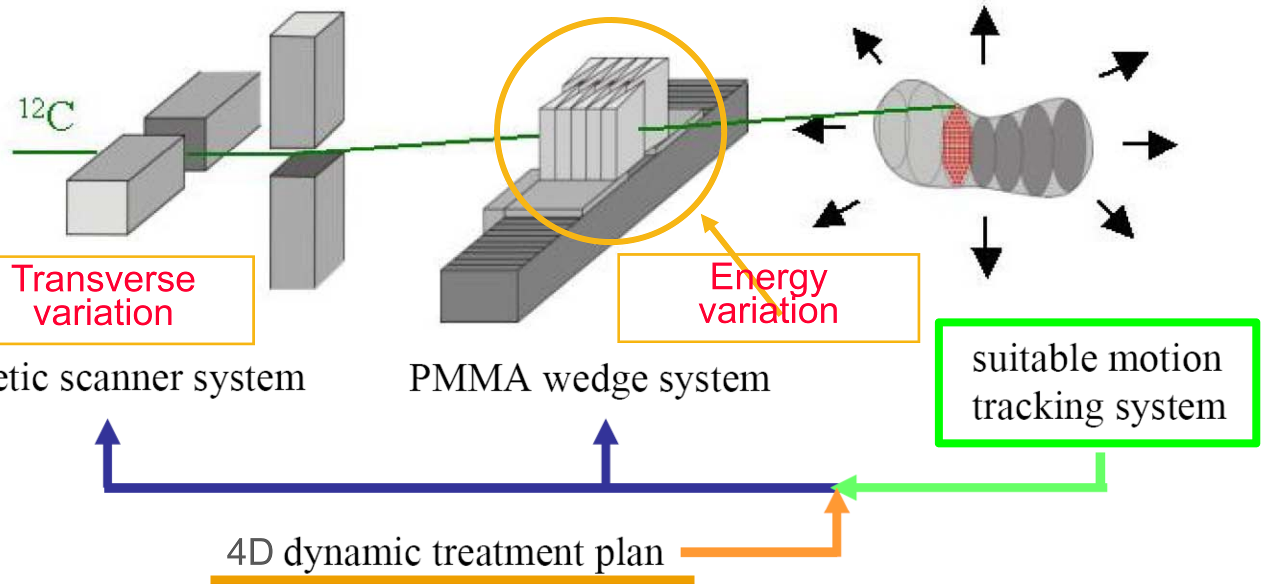
(Courtesy of Medical Intelligence)

(Review in Riboldi et al, Lancet Oncology 2012)

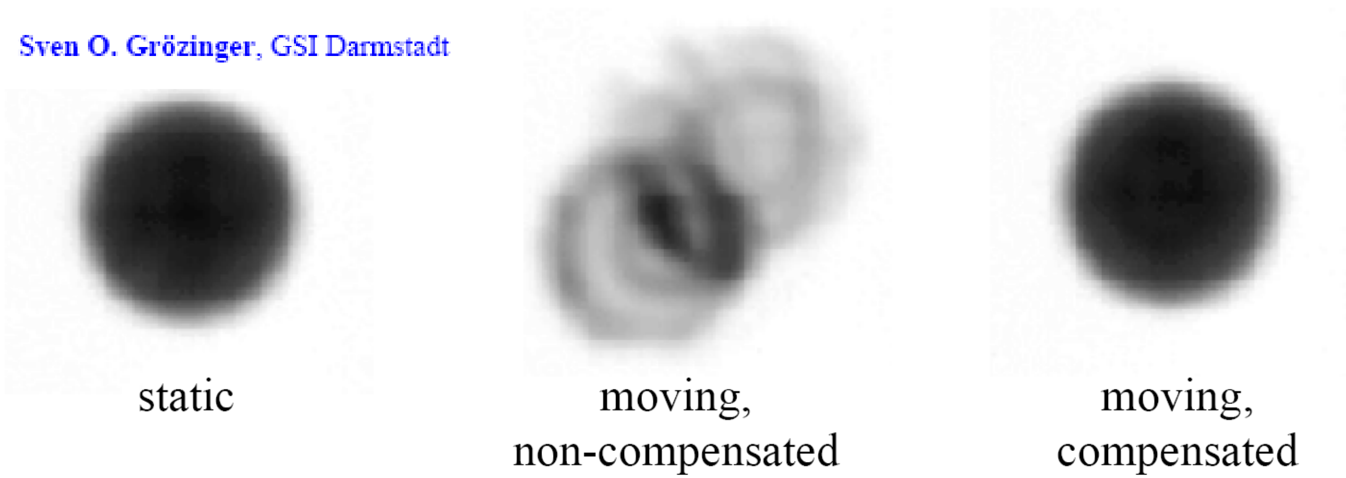
Tumour tracking

GSI approach

p^{+1} or C^{+6}



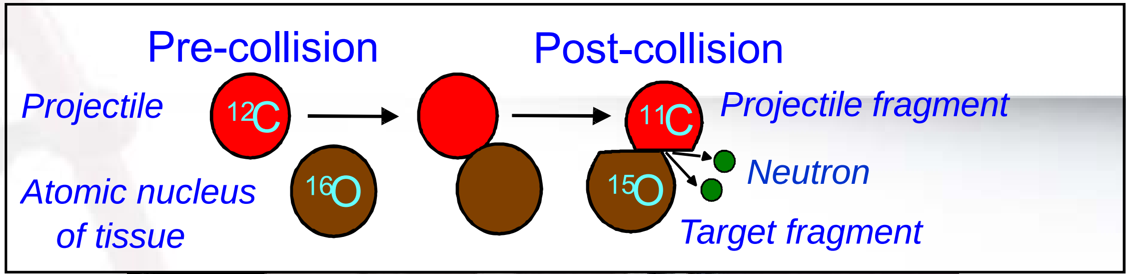
Sven O. Grözinger, GSI Darmstadt

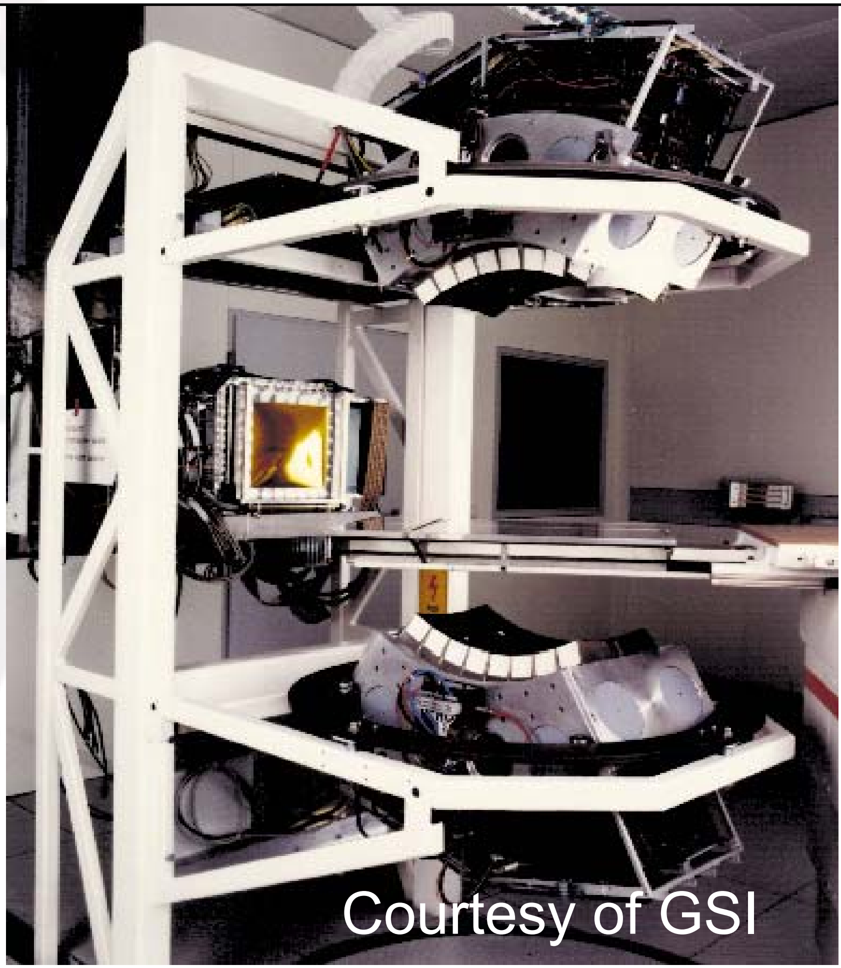


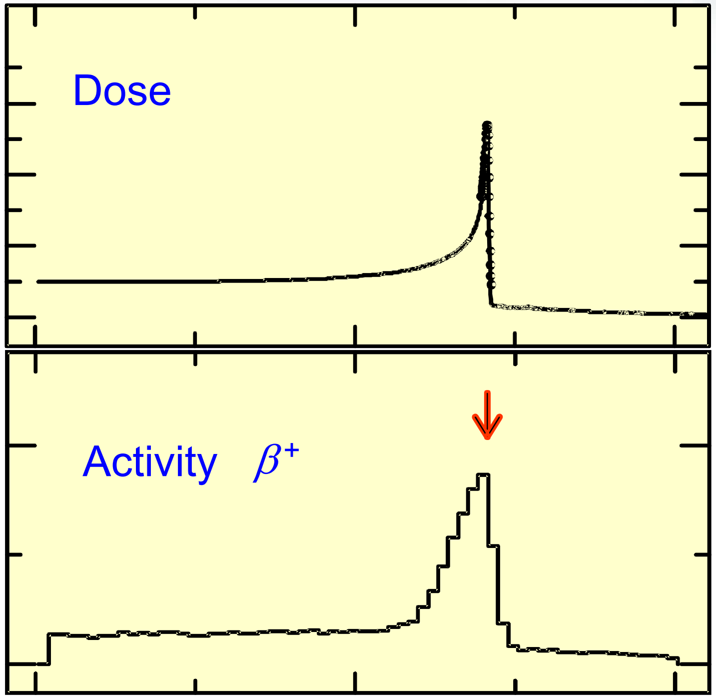
Future developments

- Real time dose visualization

Dose visualisation: “in beam PET”





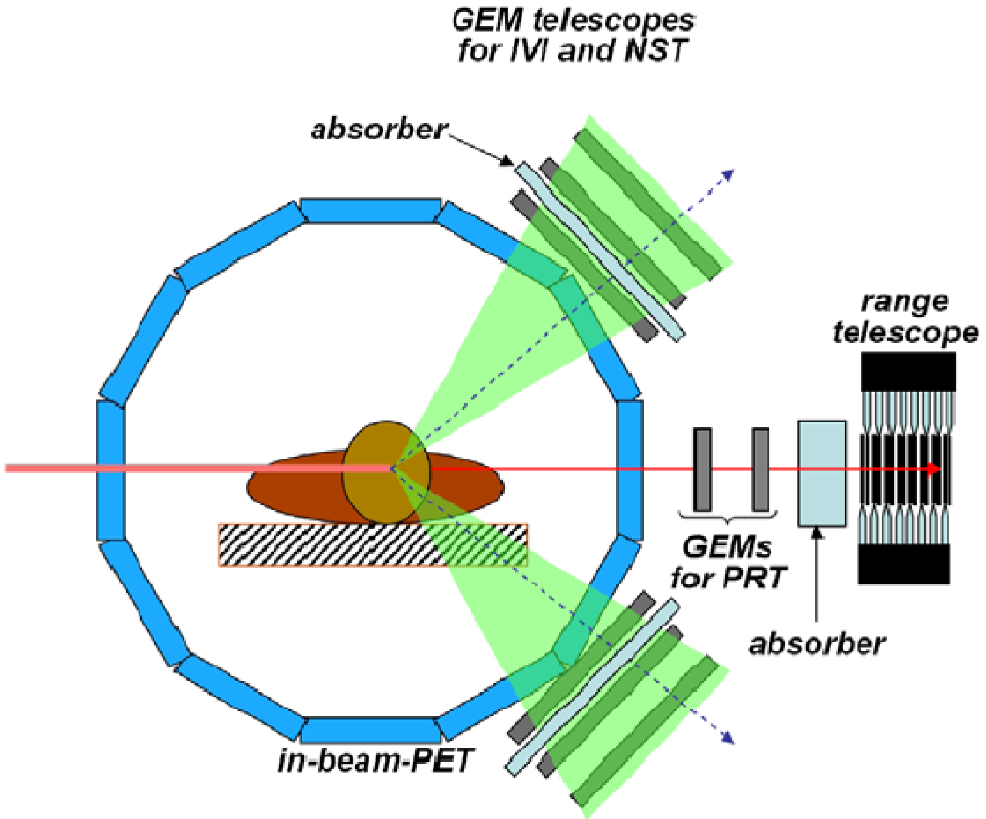


ISSUES: low statistics;
blood flow dilution;
off-line PET → logistics

Secondaries emission and reconstruction

Proton Range Radiography (PRR)

Electronic telescope for the measure of position and residual range of protons; it gives the density map of the traversed volumes; it permits to check in real time the treatment planning assumptions on position and dimensions of the traversed tissues and organs.



Nuclear Scattering Tomography (NST)

Three-dimensional map of the tissues densities obtained by vertex reconstruction of high energy protons interactions (> 600 MeV).

Interaction Vertex Imaging (IVI)

Density of interaction vertex reconstruction gives information on the Bragg peak position.

(U. Amaldi et al.)

PROMPT radiation (Gamma) - Enlight

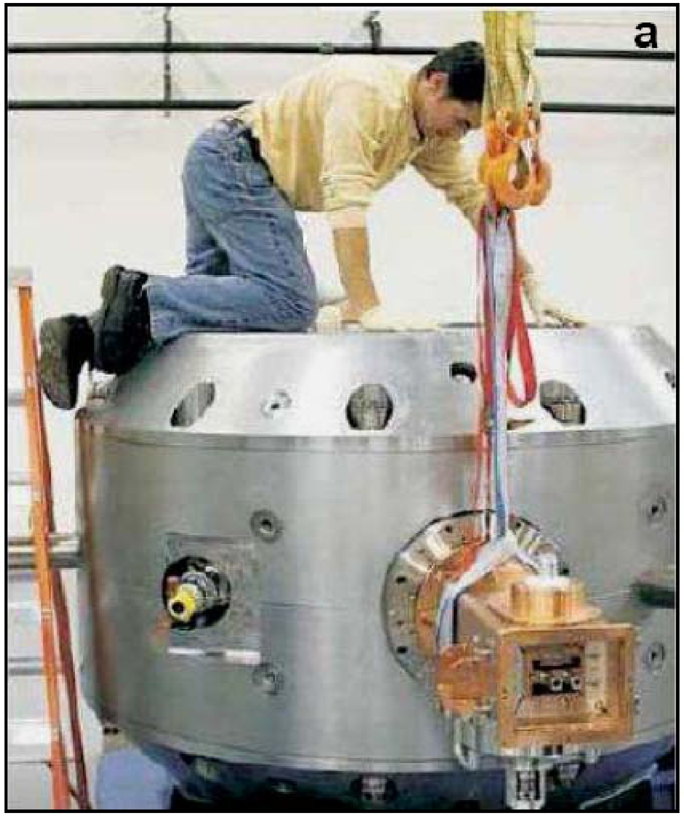
Future developments

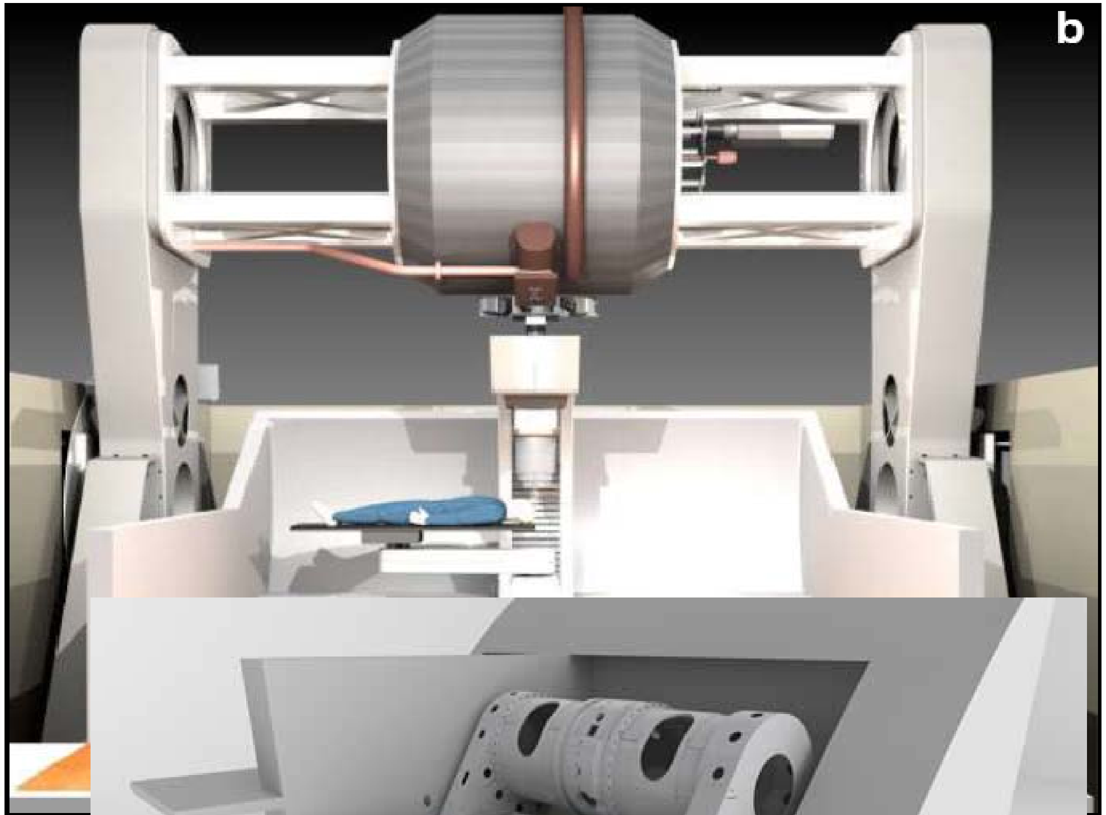
- Treatment Planning System (TPS) improvement
  - Radiobiology measurement and models
  - Speed up calculation (adaptive treatment)
  - Self contouring
  - Real time imaging and calculation
- Improve density measurement in imaging
- Biomarkers

Future developments

- Proton centers are already commercial products (tens worldwide); Carbon ion centers not yet really (only 7 worldwide).
- Cost reduction for treatment diffusion

- Single room facilities
- Next generation of accelerators
- Carbon Ion Gantries



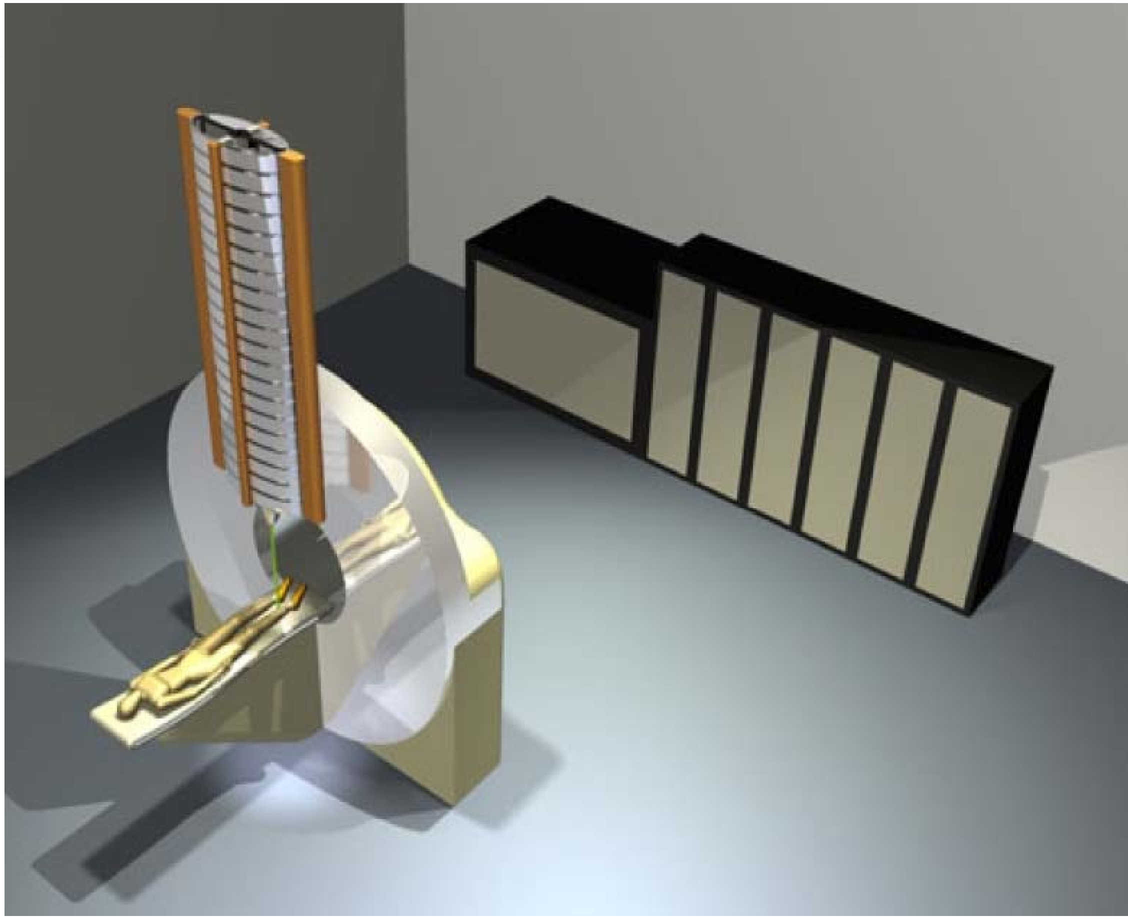


MEVION S250

Superconducting SC
Diameter 1.8 m

December 19th, 2013-First treatment at S. Lee Kling Center for Proton Therapy at the Siteman Cancer

Dielectric Wall Accelerator (DWA)

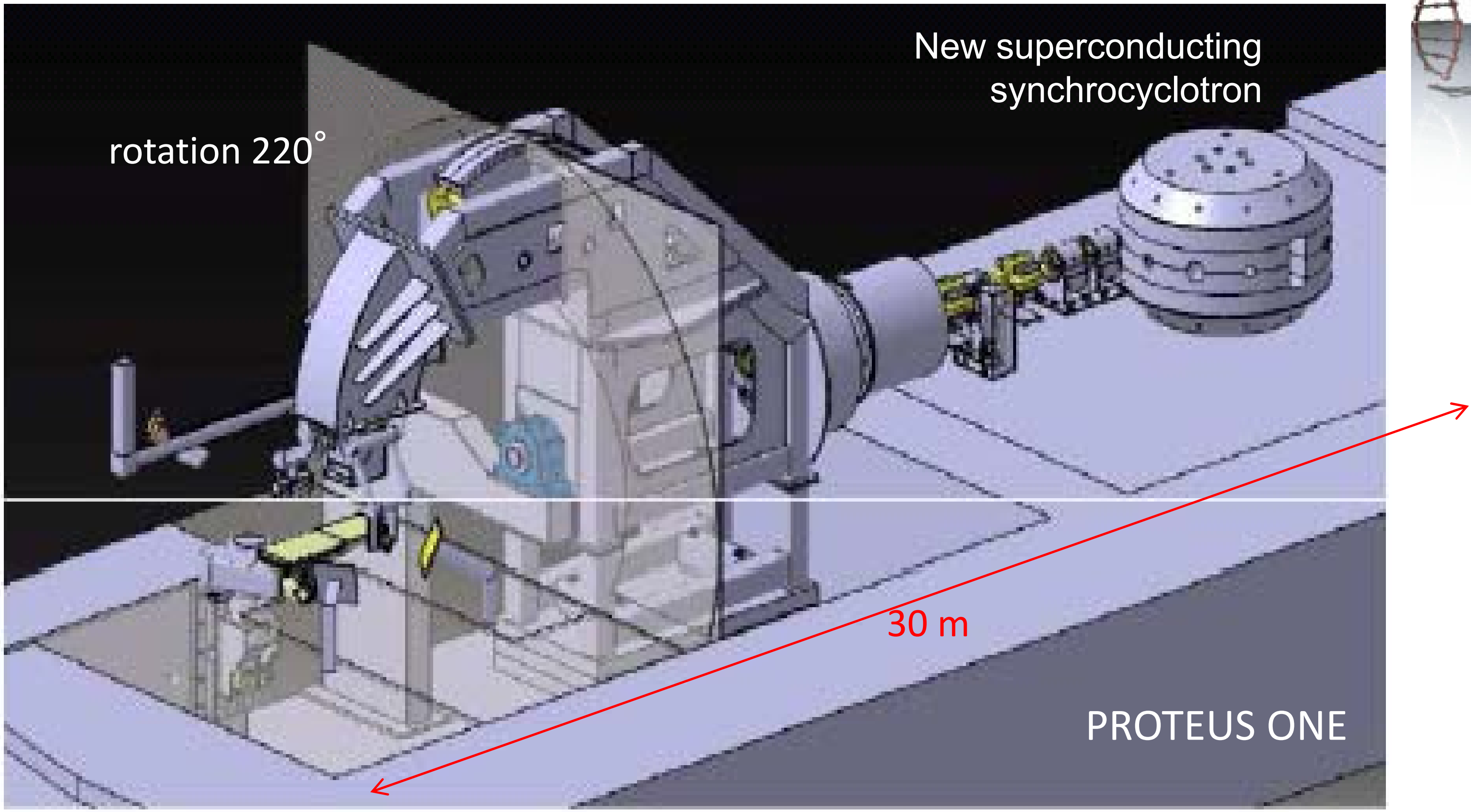


Pulsed High-Voltage accelerators (G. Caporaso et al)

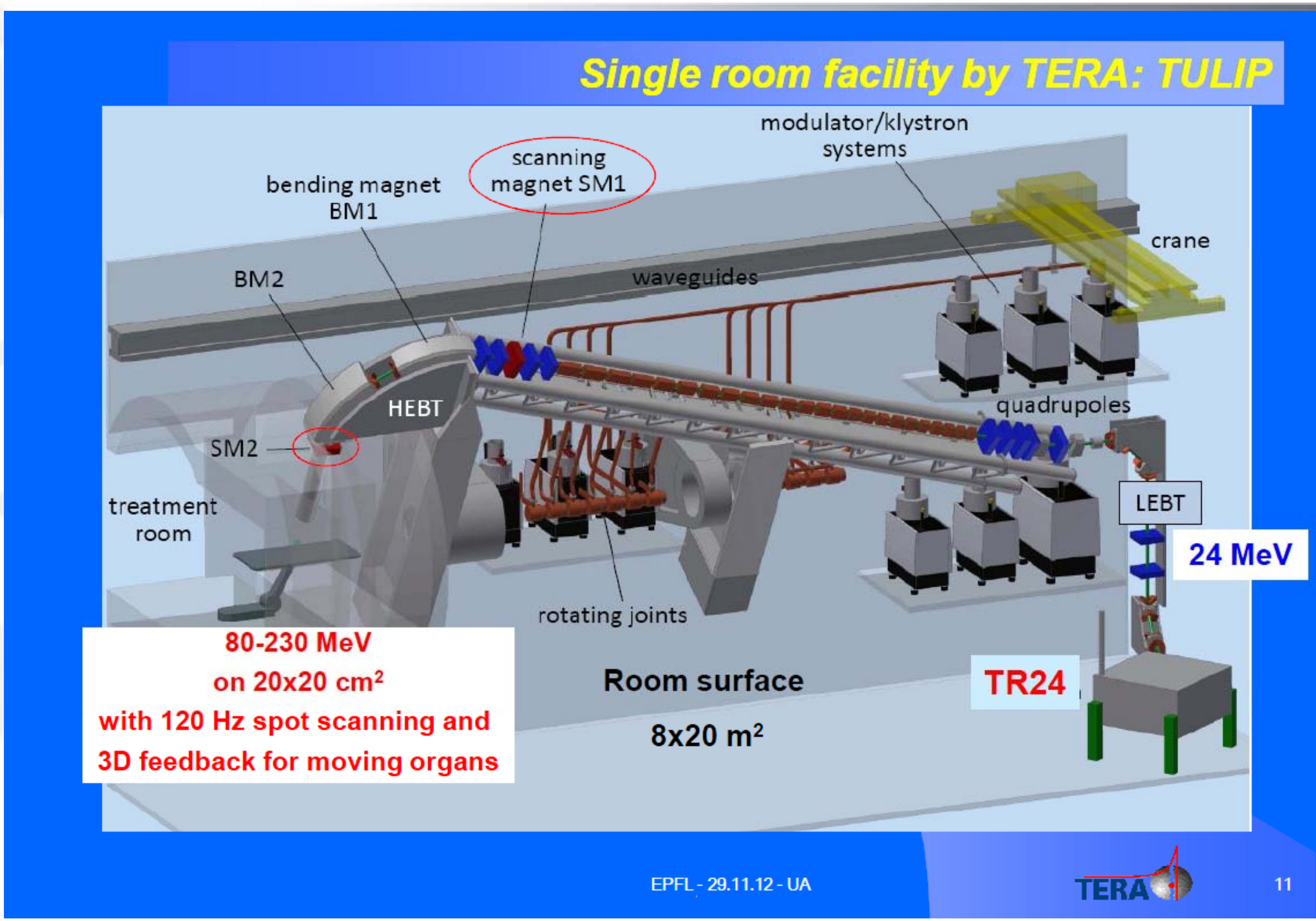
built in collaboration with Tomotherapy – Madison (T. Mackie)

Far into the future

Single room facility by IBA



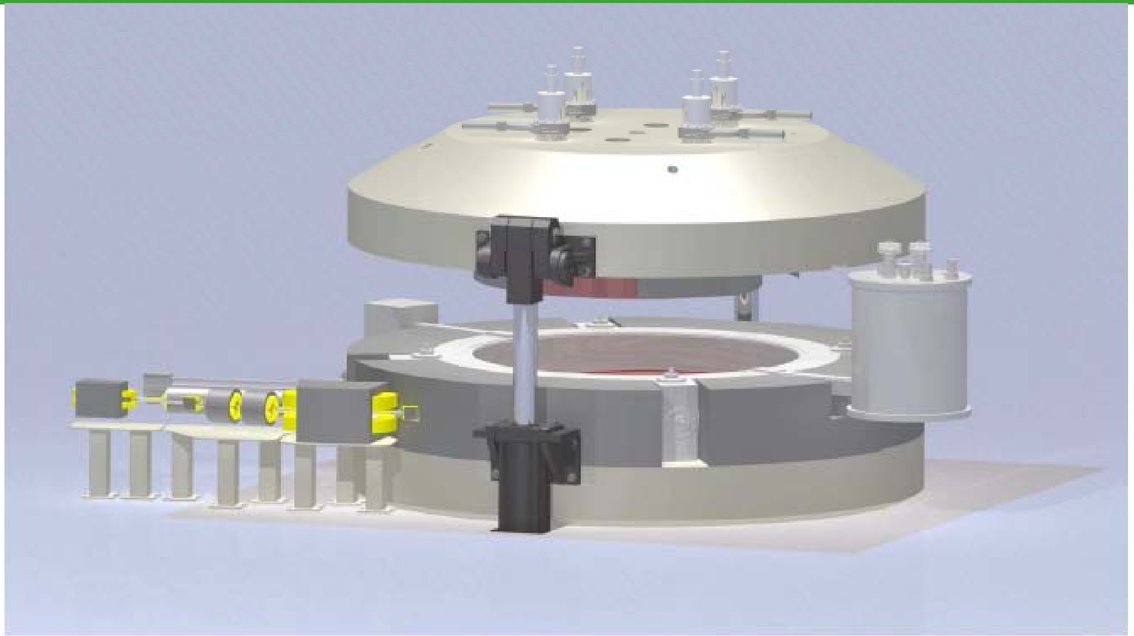
TULIP



(Courtesy of U. Amaldi)

The only ion therapy cyclotron

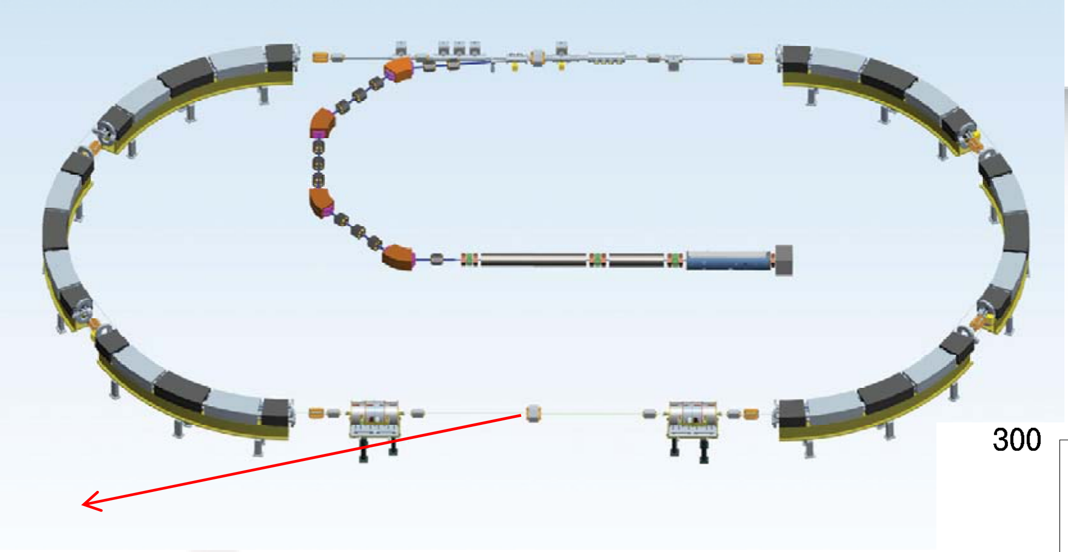
The IBA C400 cyclotron



- Superconducting isochronous cyclotron, accelerating Q/M = 1/2 ions up to 400 MeV/u (H2 + up to 250 MeV/u, Alphas, Li6 3+, B10 5+, C12 6+, N14 7+, 016 8+, Ne20 10+)

- **Design very similar to IBA PT cyclotron**, but with higher magnetic field thanks to superconducting coils, and increased diameter (6.3 m vs. 4.7 m)

Rapid cycling synchrotron (first publication 1999's, S. Peggs et al.)



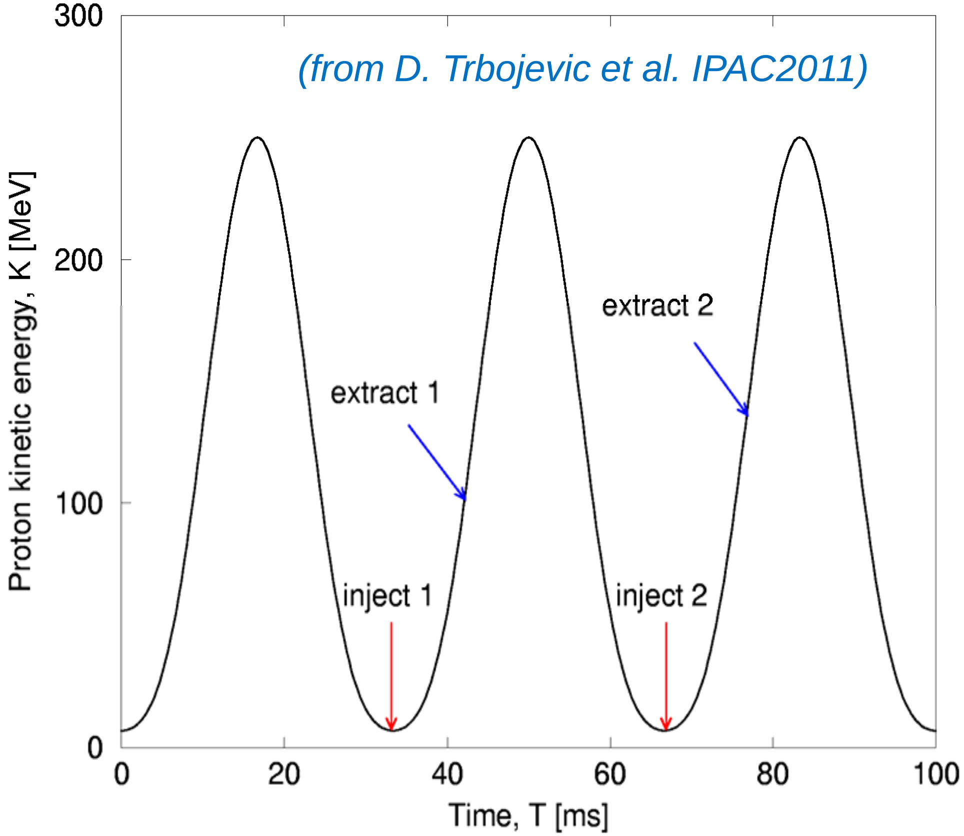
Injection linac at 8 MeV/u

Racetrack, FODO in the arcs, D=0 ss

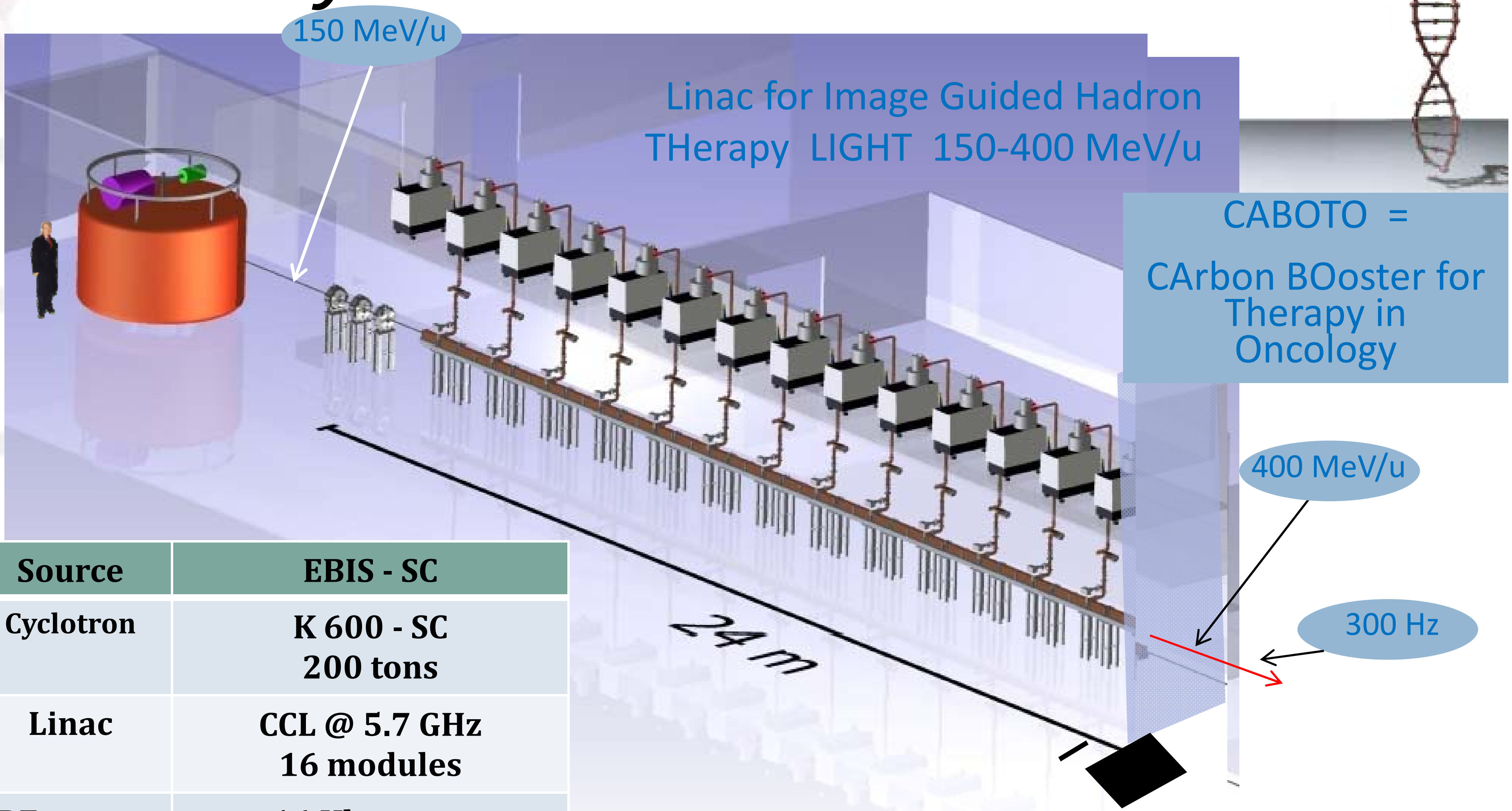
Fast inj+extr, C = 60 m

30 Hz repetition rate (repainting?)

Fast energy change



TERA cyclinac for C-ions

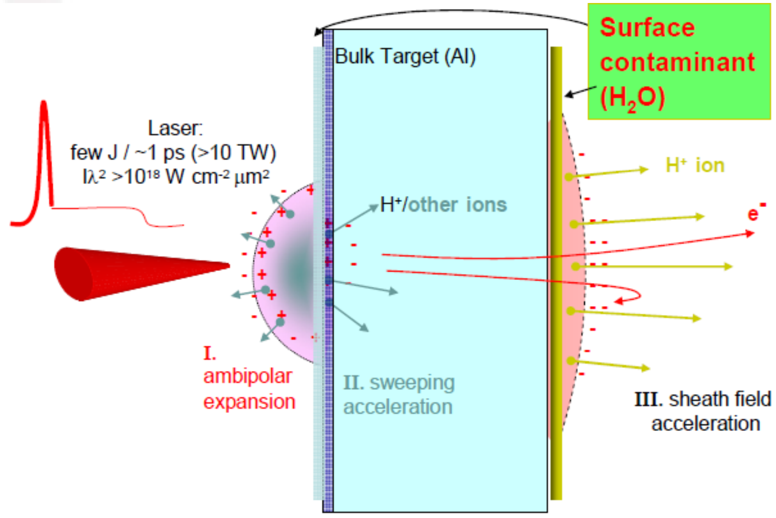


Source	EBIS - SC
Cyclotron	K 600 - SC 200 tons
Linac	CCL @ 5.7 GHz 16 modules
RF power system	16 Klystrons (P_{peak} = 12 MW)

Energy is adjusted in 2 ms in the full range by changing the power pulses sent to the accelerating modules

Charge in the spot is adjusted every 2 ms with the computer controlled source

Laser + linac



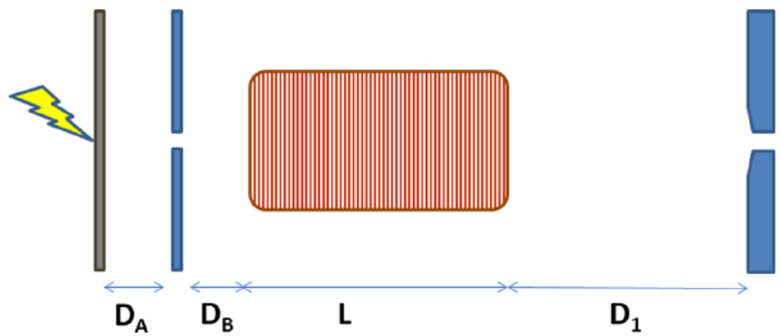


FIG. 4. Schematic drawing of the transport line: $D_A = D_B = 10$ mm, $D_1 = 510$ mm, $L = 300$ mm, first iris radius = 0.5 mm, second iris radius = 0.5 mm, second iris minimum thickness = 5 mm.

5 10^6 p at 60 MeV @ 10 Hz

Fuchs, Antici et Al, Proc HB2006 Review of proton beams 2006

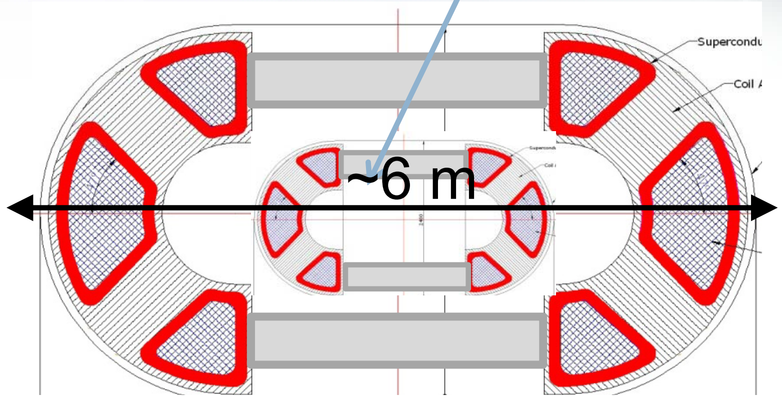
Rossi F., Londrillo P., Sinigardi S., Turchetti G., Giove D., De Martinis C.; questa conferenza et PRSTAB 16, 031301 (2013)

Dual-stage ion FFAG proton FFAG with pCT

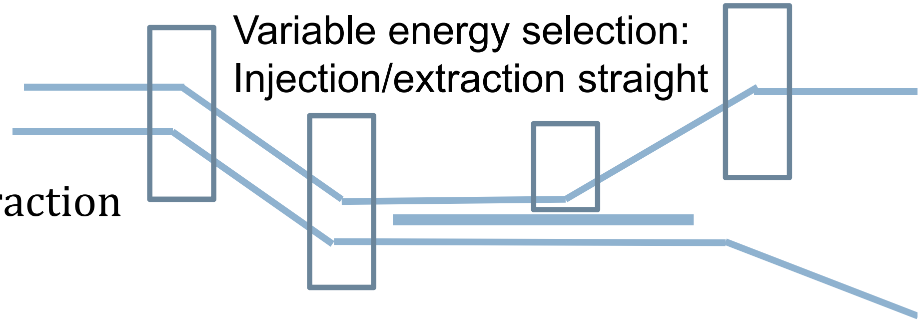
- 1^{st} stage
  - 18 – ~250-330 MeV H^-
    - Fixed or swept-frequency RF, DC beam
    - Low intensity for pCT
    - Stripping controls extraction energy and intensity in addition to source modulation

    OR
  - 9-~70-90 MeV charge to mass ratio of ½
    - Fixed-frequency RF, DC beam for all ions
    - Variable energy extraction
    - Upstream injector for high-energy ring
- 2^{nd} stage (~4 m x 5-6 m long)
  - 70/90 MeV – 430 MeV/nucleon
  - Variable energy extraction
  - Adjustable, fast orbit bump magnets/extraction septum in long straight
    - DC extracted beam
    - Variable energy on scale of tens of microseconds
    - Investigating extracted energy range

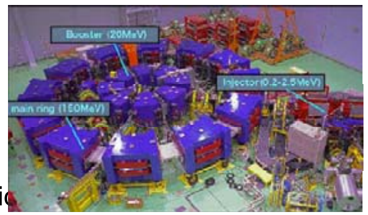
1^{st} stage: Cyclotron or FFAG



2^{nd} stage: 70/90 – 430 MeV/nucleon ions

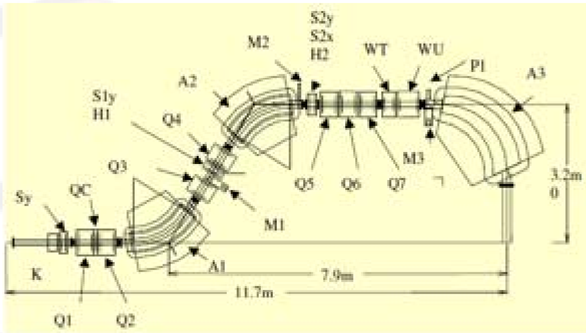


(Courtesy of C. Johnstone)



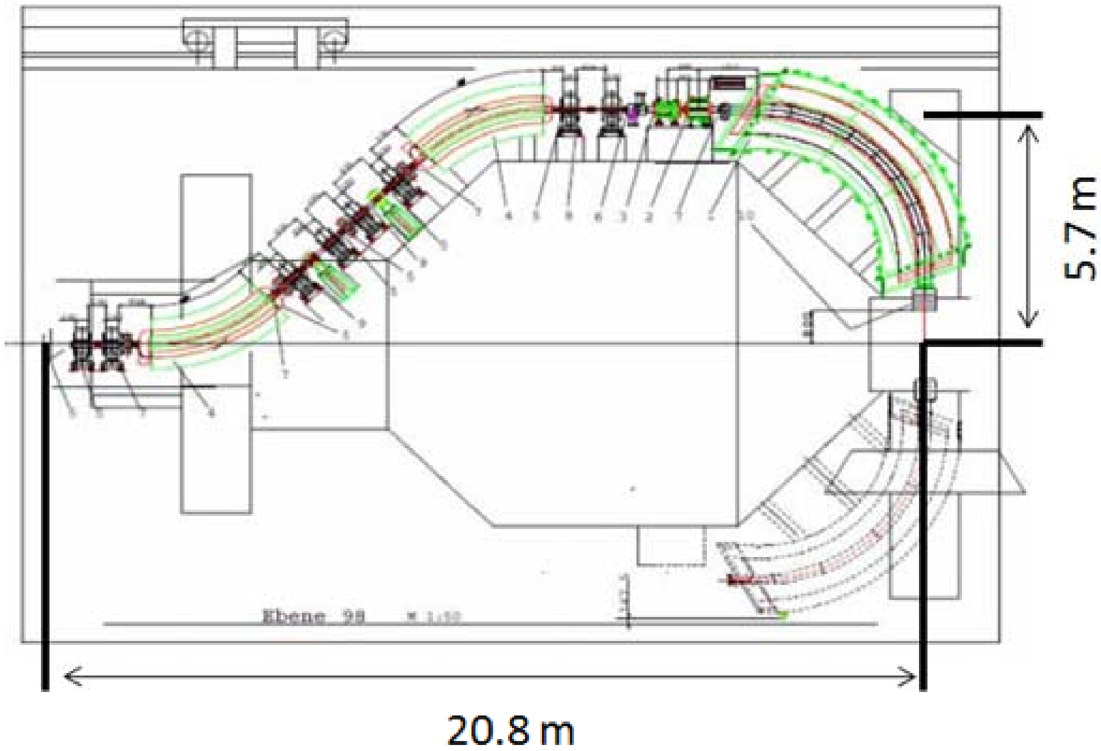
Gantries

Conventional RT



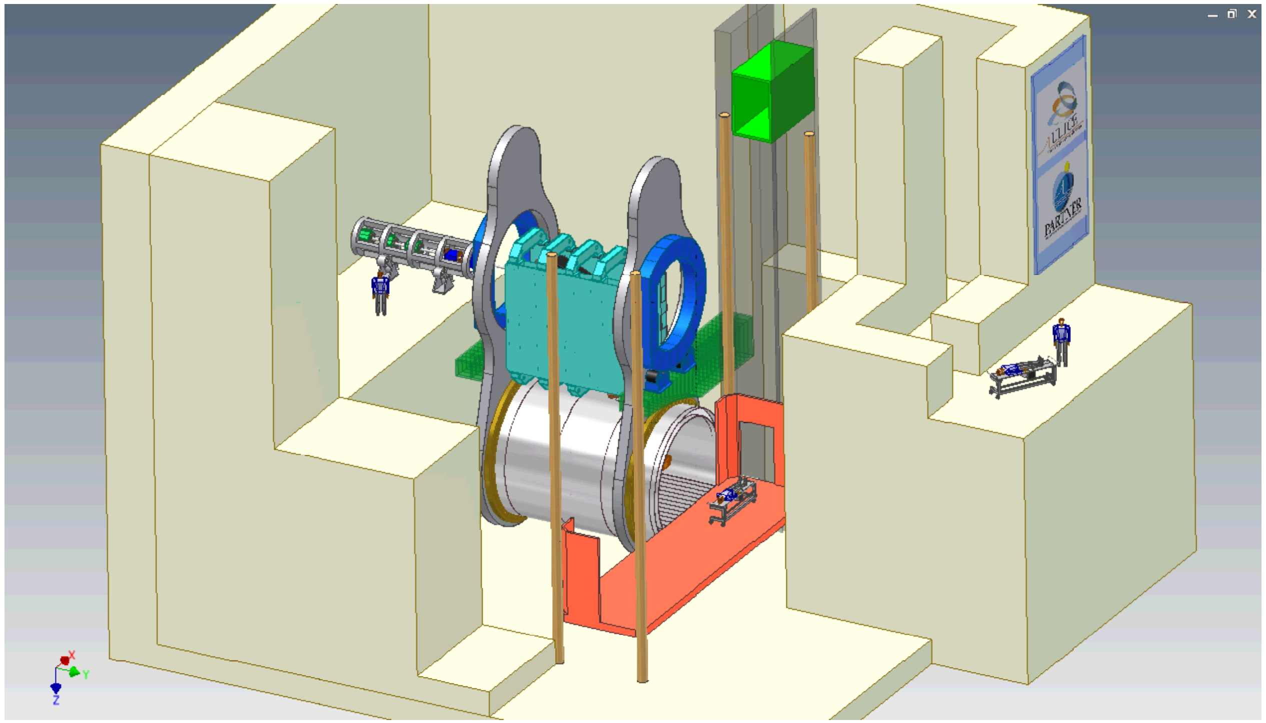
Proton Gantry
Bρ < 2.4 Tm

Carbon Ion Gantry
Bρ < 6.4 Tm



Future gantries

- Superconducting magnets
- FFAG
- Mobile isocenter



NCI-DOE Ion Therapy workshop, Jan 2013

- Further R&D and requirements for future machines

Requirements: next-generation ion therapy*

- ***Multi-ion capability***
  - ✓ *Recommended : p, He, Li, B, C, O, Ne*
  - ✓ *Essential : p, He, Li, B, C*
  - ✓ 1 - 30 cm for treatment
    - ✓ 60 MeV/nucleon – 430 MeV/nucleon (for carbon)
- **Treatment Options -**
  - Vary single treatment parameter (e.g., low vs high LET) in clinical trials
  - Multi-ion treatment option including within a single fraction
    - Better conformal dose with high dose to hypoxic GTV
    - Avoid dose to normal tissue from fragmentation tail
  - Hypofractionation with higher RBE ions
- **Imaging:**
  - Automatically integrated (20 - 60 cm available for imaging†)
  - Full scope of imaging technologies existing in photon facilities

(Courtesy of C. Johnstone)

*from final report of the joint NCI-DOE Ion Therapy workshop, Jan, 2013

†imaging with carbon will be limited to 20 -30 cm

Requirements: next-generation ion therapy*

❑ *Treatment Monitoring and Adaptation*

❖ Targeting and Image Guidance

- With imaging, all motion management capabilities available in photon facilities including gated beam delivery
- Pre- and intra-treatment verification with particle beam CT and radiography
  - ✓ Pre-treatment 3D target position and range verification
  - ✓ Simultaneous "real-time" radiographic target position and integrated range verification during treatment
- Post-treatment verification of delivered dose with particle beam CT (patient position) and with PET (dose confirmation)

❖ Adaptive Therapy

- Low-dose particle-beam CT allows unlimited scans
  - ✓ Plan modification using pre-treatment particle-beam CT
  - ✓ Plan modification using post-treatment CT or PET imaging

(Courtesy of C. Johnstone)

*from final report of the joint NCI-DOE Ion Therapy workshop, Jan, 2013

Requirements: next-generation ion therapy*

- ***Dose Delivery Rate for Treatment***
  - **20 Gy/min/liter has been defined as the minimum "standard" for the ion accelerator***
    - ✓ Two fields (represent different technical specifications for beam):
      - ✓ 30 cm x 30 cm (single layer field)
      - ✓ 10 x 10 x 10 cm^3
        - ✓ Requires ~40 energy steps to evenly cover in depth; (assumes 0.25 cm /layer, ~ 2 MeV energy step)
  - **1 Gy/sec/liter**
    - ✓ Based on DNA repair time for single strand break

- ***Hypofractionation***
  - **1 Gy/sec/liter**
    - ➢ For 20 Gy Total Dose
    - ➢ 4 fractions, 5 Gy/fraction
      - ✓ 1 to 5-8 sec, or breath-hold delivery (1 sec challenging for beam monitoring)

- ***Radiobiology***
  - **5 Gy/sec/liter**
    - ✓ Single Fraction, 20 Gy/fraction
      - ✓ 4-8 sec delivery (corresponding timescale if possible)

(Courtesy of C. Johnstone)

* from final report of the joint NCI-DOE Ion Therapy workshop, Jan, 2013

Requirements: next-generation ion therapy*

❑ *Additional Accelerator and Beam Delivery Parameters*

- **Beam Properties:**
  - ✓ Selectable spot size: 3, 5, and 10 mm (FWHM)
  - ✓ Profile characterized and stable (transverse, energy, preferably Gaussian)
- **Energy /Range Modulation:**
  - ✓ 2 MeV steps for protons (~0.25 cm step in range)
  - ✓ 2 MeV/nucleon steps for carbon (~0.1 cm step in range)
    - ✓ 100 millisec step rate
- **Field Size:**
  - ✓ Maximum - 40 x 40 cm^2, minimum - 20 x 20 cm^2
- **Lateral targeting accuracy @Bragg peak**
  - ✓ Protons: ±0.5 mm
  - ✓ Carbon: ±0.2 mm (needs to be studied)
- **Dose accuracy/fraction**
  - ✓ 2.5% monitored at ≥40 kHz during dose deposition
- **Real-time Beam monitoring**
  - ✓ Fast nondestructive monitoring and feedback
  - ✓ Analysis of patient-induced secondaries during treatment

(Courtesy of C. Johnstone)

* from final report of the joint NCI-DOE Ion Therapy workshop, Jan, 2013

Next-generation ion therapy accelerators*

❑ *Dose Delivery for Treatment*

- ❖ **20 Gy/min/liter has been defined as the minimum "standard" for the ion accelerator***
  - ✓ Two fields (represent different technical specifications for beam):
    - ✓ 30 cm x 30 cm (single layer field)
    - ✓ 10 x 10 x 10 cm^3
      - ✓ Requires ~40 energy steps to evenly cover in depth; (assumes 0.25 cm /layer, ~ 2 MeV energy step)
  - ✓ Scanning Rate: 5 cm/msec (10 cm/msec is current state of the art)
  - ✓ Energy modulation, ≤100 msec/energy step
  - ✓ ~10^9 p/Gy/cm^2 (for carbon divide by ratio of RBEs, ~3).

- ❖ **For 20 Gy Total Dose**
  - ➢ <u>Normal Fraction:</u>
    - ✓ 20 treatments, 1 Gy/fraction, 1 sec delivery
      - ✓ 10^{12}p/sec for 30 cm x 30 cm (single layer field)
      - ✓ 4x10^{12} p/sec for and 10 x 10 x 10 cm^3 fied (40 layers)
  - ➢ <u>Hypofractionation</u>:
    - ✓ 4 fractions, 5 -8 Gy/fraction
      - ✓ 1 sec delivery increases intensity by dose factor
        - ✓ up to 2-3 x 10^{13} p/sec
      - ✓ 5-8 sec delivery
        - ✓ Same intensities as normal fraction and 1 sec delivery
  - ➢ <u>Radiobiology</u>:
    - ✓ Single Fraction, 20 Gy/fraction, 5-8 sec delivery (if possible)
      - ✓ 2-4x10^{12}p/sec for 30 cm x 30 cm (single layer field)
      - ✓ 1-1.6-4x10^{13} p/sec for and 10 x 10 x 10 cm^3 fied (40 layers)

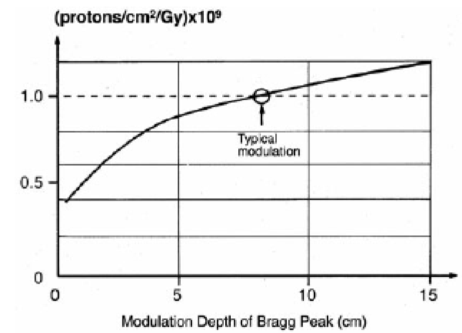


Fig. 4b: Proton fluence/Gray versus width of SOBP for 155 MeV maximum energy[4]. The proton fluence per Gray for 250 MeV maximum energy is about 30% higher than this curve and about 30% less for SOBPs with 100 MeV maximum energy.

G. Coutrakon, et. al., Proceedings 1999 PAC

(Courtesy of C. Johnstone)

Conclusions

Protontherapy centres are commercial systems (and single room solutions are coming up). This is not true for carbon facilities yet (space and need for firms involvement).

CNAO is now treating patients with both protons and carbon, but improvements and R&D are always ongoing.

Improvements of technology in hadrontherapy are not limited to accelerators, but invest a wide spectrum of systems: some more urgent than others.

Collaborations, intercomparisons, networking are key issues for the success of hadrontherapy and are needed to establish Evidence Based Medicine (patient throughput is an issue) .


That's all Folks!