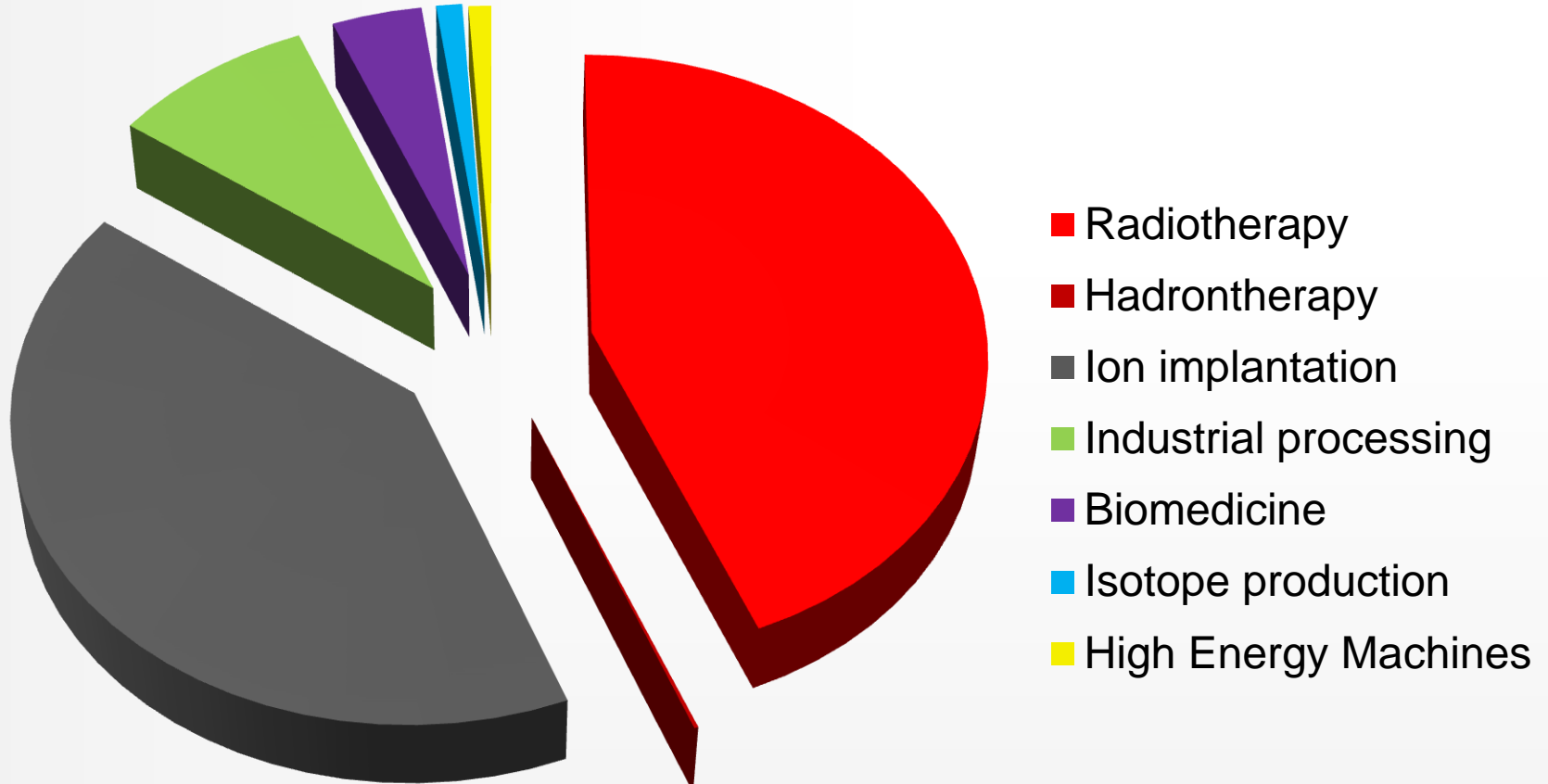


# Medical applications

Caterina Biscari

Alba-CELLS

# ~30000 accelerators in the world



# Isotope production

- Isotope production for medical diagnoses purposes - First isotopes produced by Lawrence in his cyclotron in 1934
- Since then both nuclear reactors and accelerators produce isotopes for an ever increasing demand
- Accelerators are used to bombard production targets with beams of charged nuclei impinging on targets to produce a wide range range of isotopes

The range of particle energies and intensities vary between facilities -- 10 - 100 MeV for commercial cyclotrons dedicated for isotope production, with higher energies available at some research accelerators

See for example:

[http://www.isotopes.gov/outreach/reports/Medical\\_Isotope\\_Production\\_Use.pdf](http://www.isotopes.gov/outreach/reports/Medical_Isotope_Production_Use.pdf)

Zn59 183 ms $\beta^+ 2.5, 3.1$ $\gamma 491.4, 814.2$ $\gamma 126, 208, 182$ E 9.05	Zn60 2.40 m $\beta^+ 2.5, 3.1$ $\gamma 670, 61$ E 4.16	Zn61 1.485 m $\beta^+ 4.4$ $\gamma 474.9, 1860.3$ E 5.84	Zn62 9.22 h $\beta^+ 66$ $\gamma 508.7, 40.8$ $\gamma 384.4, 357.6$ E 1.03	Zn63 38.5 m $\beta^+ 2.32$ $\gamma 589, 7, 952.1$ E 3.367	Zn64 48.6 $\beta^+ 70, 1.3$ E 3.367	Zn65 243.9 d $\beta^+ 119.5$ $\gamma 279$ E 3.367	Zn66 27.9 $\beta^+ 9, 1.9$ $\gamma 1079, 10, 104, 23$ $\gamma 438, 6$ E 3.367	Zn67 4.1 $\beta^+ 7, 29$ $\gamma 1079, 10, 104, 23$ $\gamma 438, 6$ E 3.367	Zn68 16.8 $\beta^+ 1079, 10, 104, 23$ $\gamma 438, 6$ E 3.367	Zn69 56 m $\beta^+ 438, 6$ $\gamma 574, 1$ E 3.367
Cu58 3.21 s $\beta^+ 7.44$ $\gamma 454.5, 1448.3$ E 5.509	Cu59 1.36 m $\beta^+ 2.6$ $\gamma 1201.5, 876.0$ E 4.800	Cu60 23.7 m $\beta^+ 3.00$ $\gamma 1332.5, 1791.5$ $\gamma 826.3$ E 6.127	Cu61 3.35 h $\beta^+ 1.21$ $\gamma 263.0, 656.0$ E 2.237	Cu62 9.74 m $\beta^+ 2.90$ $\gamma 1173.0, 875.7$ E 3.948	Cu63 69.17 $\beta^+ 4.5, 5.0$ $\gamma 1242.8$ $\gamma 3, 352$ E 3.948	Cu64 12.701 h $\beta^+ 5.78$ $\gamma 1242.8$ $\gamma 3, 352$ E 3.948	Cu65 30.83 $\beta^+ 2.17, 2.2$ E 3.948	Cu66 5.10 m $\beta^+ 2.63$ $\gamma 1039.3$ $\gamma 194.6, 903.3$ E 3.948	Cu67 2.580 d $\beta^+ 36, 46, 28$ $\gamma 111, 6$ $\gamma 627, 526, 6$ $\gamma 1077.3$ $\gamma 17, 12$ $\gamma 187.3$ $\gamma 156, 951$ E 3.948	Cu68 3.79 m 31 s $\beta^+ 3.5$ $\gamma 627, 526, 6$ $\gamma 1077.3$ $\gamma 17, 12$ $\gamma 187.3$ $\gamma 156, 951$ E 3.948
Ni57 35.6 h $\beta^+ 12.7, 8$ E 3.269	Ni58 68.06 $\beta^+ 4.8, 2.2$ $\gamma 76, 1363$ $\gamma 14, 20$ $\gamma 19, 2.3$ E 3.269	Ni59 7.564 s $\beta^+ 76, 1363$ $\gamma 14, 20$ $\gamma 19, 2.3$ E 3.269	Ni60 25.22 $\beta^+ 2.8, 1.5$ E 3.269	Ni61 1.14 $\beta^+ 2.5, 1.4$ $\gamma 145, 5.6$ E 3.269	Ni62 3.63 $\beta^+ 145, 5.6$ E 3.269	Ni63 105.5 $\beta^+ 2.96$ $\gamma 3, 34$ E 3.269	Ni64 0.93 $\beta^+ 1.6, 1.2$ E 3.269	Ni65 2.517 h $\beta^+ 148, 11, 119, 5$ $\gamma 23, 31$ E 3.269	Ni66 34.5 h $\beta^+ 3.8$ $\gamma 1837, 1115, 622$ E 3.269	Ni67 21 s $\beta^+ 1837, 1115, 622$ E 3.269
Co56 77.3 d $\beta^+ 1.88$ $\gamma 848.8, 1258.3$ E 4.586	Co57 271.8 d $\beta^+ 1.22, 1.36, 5$ $\gamma 144$ E 4.586	Co58 9.1 h $\beta^+ 1.88$ $\gamma 848.8, 1258.3$ E 4.586	Co59 100 $\beta^+ 1.01, 4.36, 0.94$ $\gamma 1025, 1025$ E 4.586	Co60 10.47 m $\beta^+ 1.04, 4.36$ $\gamma 1025, 1025$ E 4.586	Co61 1.650 h $\beta^+ 1.02$ $\gamma 874$ E 4.586	Co62 13.9 m $\beta^+ 2.8$ $\gamma 1126, 2.8$ $\gamma 1173.6$ E 4.586	Co63 27.5 s $\beta^+ 3.6$ $\gamma 87.2$ E 4.586	Co64 0.30 s $\beta^+ 3.6$ $\gamma 1366.8, 921.1$ E 4.586	Co65 1.17 s $\beta^+ 3.1$ E 4.586	Co66 -0.23 s $\beta^- 7.0$ E 4.586
Fe55 2.73 s $\beta^+ 1.3$ $\gamma 6, 9$ E 4.586	Fe56 91.75 $\beta^+ 2.6, 1.4$ $\gamma 58, 1048, 1$ E 4.586	Fe57 2.12 $\beta^+ 2.6, 1.4$ $\gamma 58, 1048, 1$ E 4.586	Fe58 0.28 $\beta^+ 2.3, 1.2$ E 4.586	Fe59 44.51 d $\beta^+ 468, 374$ $\gamma 1099.2, 1291.6$ $\gamma 4, 13$ E 4.586	Fe60 1.568 h $\beta^+ 147$ $\gamma 50, 70, 6$ E 4.586	Fe61 6.0 m $\beta^+ 2.8, 2.6$ $\gamma 1205, 1, 1027.5$ $\gamma 297.8$ E 4.586	Fe62 1.568 s $\beta^+ 2.5$ $\gamma 508.1$ E 4.586	Fe63 6 s $\beta^+ 3.6$ $\gamma 994.6, 1427.2$ E 4.586	Fe64 2.0 s $\beta^+ 3.1$ E 4.586	Fe65 0.4 s $\beta^-$ E 4.586
Mn54 312.1 d $\beta^+ 1.54, 3$ $\gamma 1434, 1$ E 1.377	Mn55 100 $\beta^+ 13.5, 14.0$ E 3.064	Mn56 2.578 h $\beta^+ 2.84, 1.04$ $\gamma 846.8, 1810.8$ $\gamma 213, 1$ E 3.064	Mn57 1.45 m $\beta^+ 2.55$ $\gamma 122, 1, 14, 4$ $\gamma 66, 2$ E 2.991	Mn58 30.4 m $\beta^+ 8.1$ $\gamma 1447$ $\gamma 810, 8$ $\gamma 1225, 1$ $\gamma 439, 2$ E 6.25	Mn59 6.5 s $\beta^+ 4.4, 4.7$ $\gamma 726, 1, 472.6$ $\gamma 1225, 1$ $\gamma 439, 2$ E 6.25	Mn60 1.77 s $\beta^+ 5.7$ $\gamma 824$ $\gamma 1272$ E 6.25	Mn61 90 s $\beta^+ 5.7$ $\gamma 824$ $\gamma 1272$ E 6.25	Mn62 0.9 s $\beta^+ 8.77, 94.7, 1299$ $\gamma 1815$ E 6.25	Mn63 $\beta^-$ E 6.25	Mn64 $\beta^-$ E 6.25
Cr53 9.50 $\beta^+ 18, 9$ $\gamma 31, 40, 63$ E 1.377	Cr54 2.36 $\beta^+ 36, 2$ E 3.064	Cr55 3.497 m $\beta^+ 2.40$ $\gamma 1528, 1, 6$ E 3.064	Cr56 5.9 m $\beta^+ 1.5$ $\gamma 83, 0, 26, 6$ E 1.92	Cr57 21 s $\beta^+ 93, 4, 650$ $\gamma 1752, 1535$ E 6.25	Cr58 7.0 s $\beta^+ 683, 125$ E 6.25	Cr59 1.0 s $\beta^+ 1230$ E 6.25	Cr60 0.6 s $\beta^+$ E 6.25	Cr61 $\beta^-$ E 6.25	Cr62 $\beta^-$ E 6.25	Cr63 $\beta^-$ E 6.25
V52 3.76 m $\beta^+ 2.47$ $\gamma 1434, 1$ E 3.876	V53 1.61 m $\beta^+ 2.6$ $\gamma 1008, 2$ E 3.426	V54 49.9 s $\beta^+ 3.0$ $\gamma 854.8, 998.8$ $\gamma 229, 2$ E 7.04	V55 6.5 s $\beta^+ 5.4$ $\gamma 517, 1, 630, 6$ E 6.0	V56 $\beta^-$ E 6.0	V57 $\beta^-$ E 6.0	V58 $\beta^-$ E 6.0	V59 $\beta^-$ E 6.0	V60 $\beta^-$ E 6.0	V61 $\beta^-$ E 6.0	

# Cancer therapy: X-rays

- 1937: first X-rays irradiation from van de Graaff electrostatic machine
- 1956 : first patient treated with radiotherapy at Stanford – eye tumor
- Since then 40 millions patients have been treated
- Today 50% of cancer patients are X-ray treated (70% in industrialised countries), either alone or in combination with other techniques.
- Electron Linacs (4 – 22 MeV) produce e- to be shot on a metallic target and produce X-rays

Courtesy of Department of Radiation Oncology



The first patient to receive radiation therapy from the medical linear accelerator at Stanford was a 2-year-old boy.

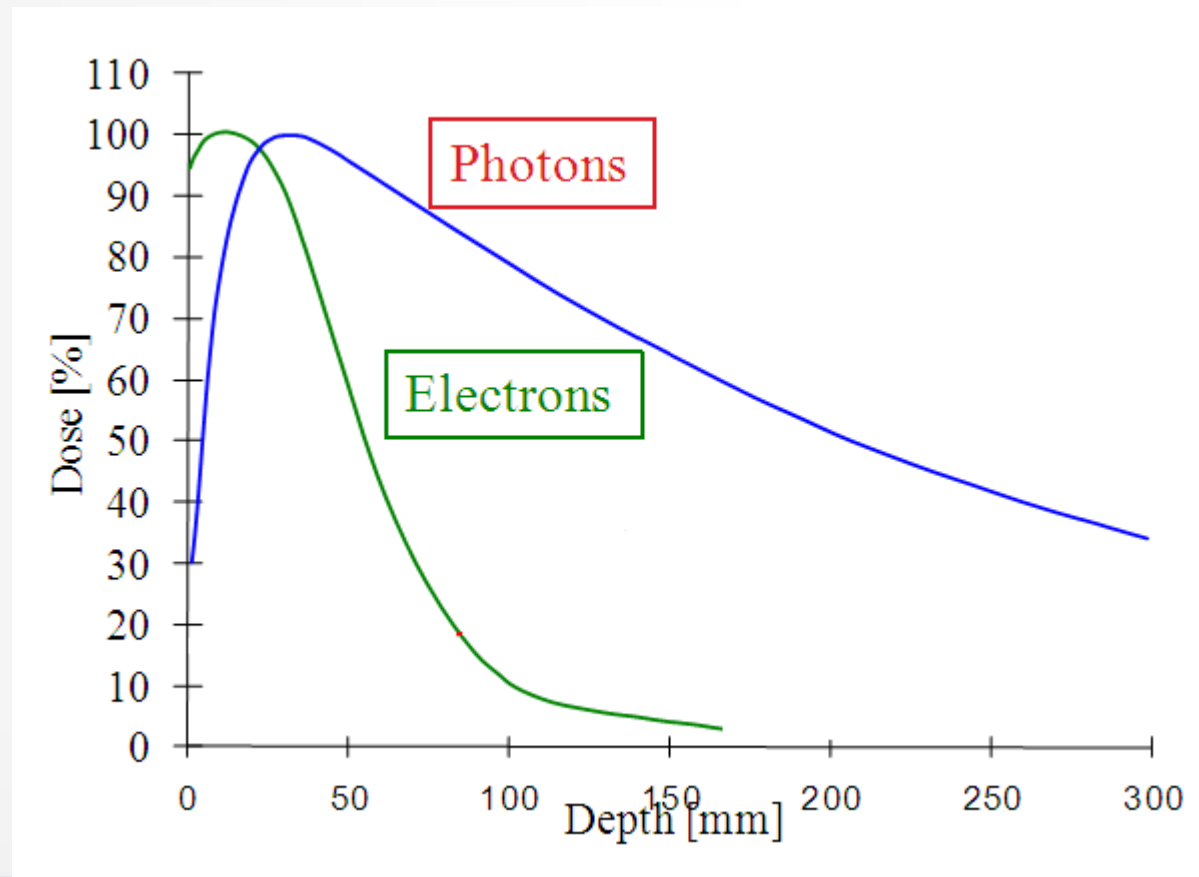


Commercially produced

- Thousands of compact and fully reliable Linacs are daily treating patients
- Control of radiation dose and radiation fields decrease collateral effects
- IMRT = intensity modulated radiation therapy

# Radiotherapy

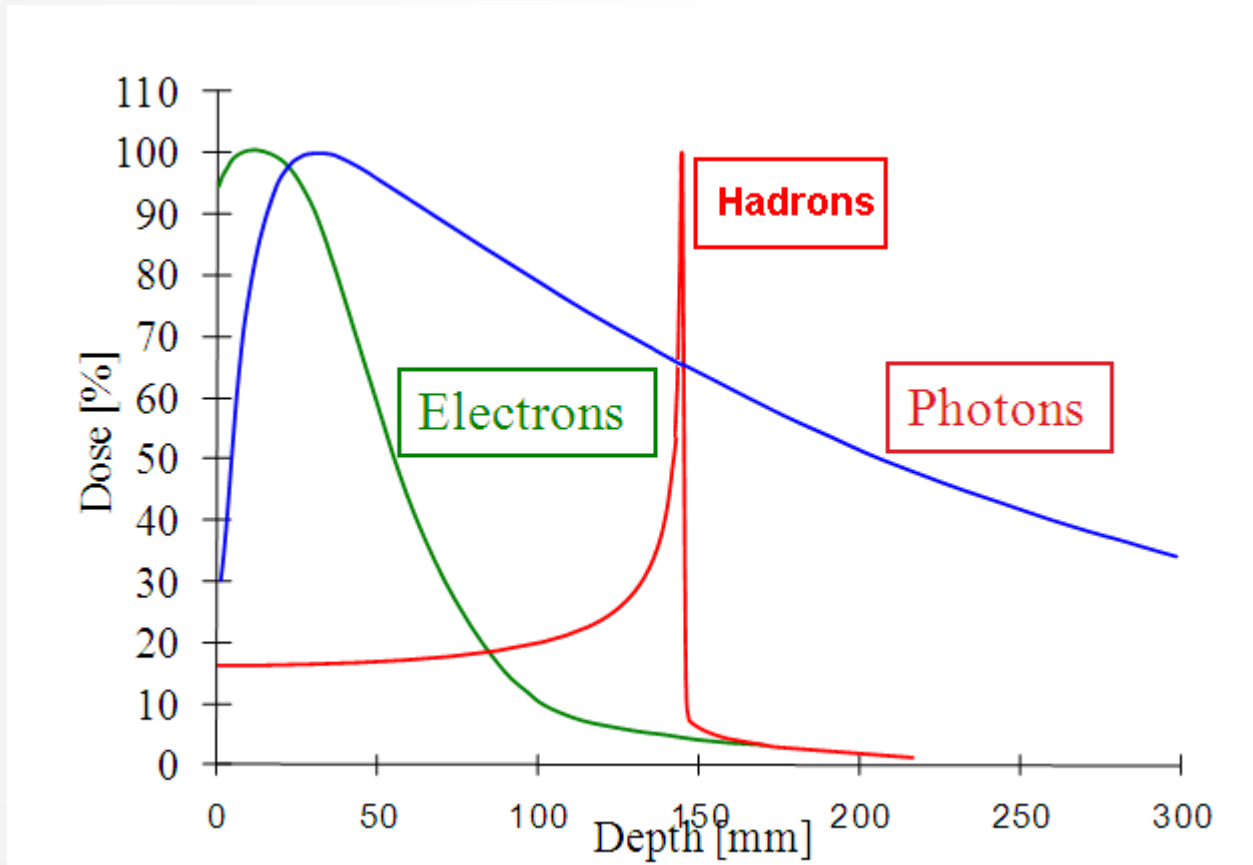
Radiotherapy uses electrons and photons to kill cancer cells damaging the DNA. These particles lose energy at beam entrance and then exponentially. The depth-dose deposition characteristics cause damage also to healthy tissues. Computer-aided treatment plans (IMRT) allow to reduce this counterpart.



# Radiotherapy and hadrontherapy

Hadrontherapy uses hadrons (protons and ions)

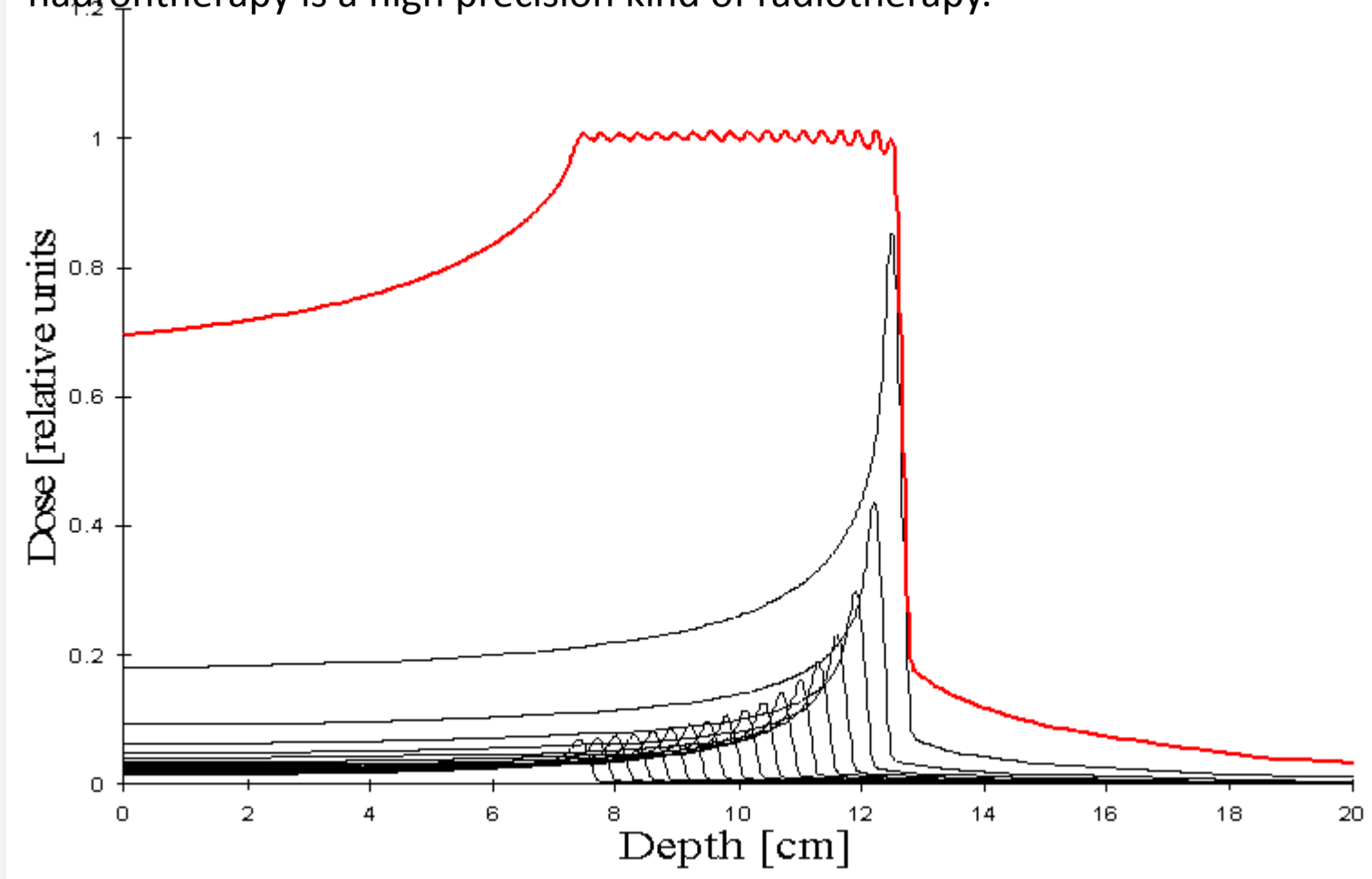
Particles at high energy deposit relatively little energy as they enter an absorbing material but tend to deposit extremely large amounts of energy in a very narrow peak, the Bragg peak, as they reach the end of their range: Very localized depth-dose deposition



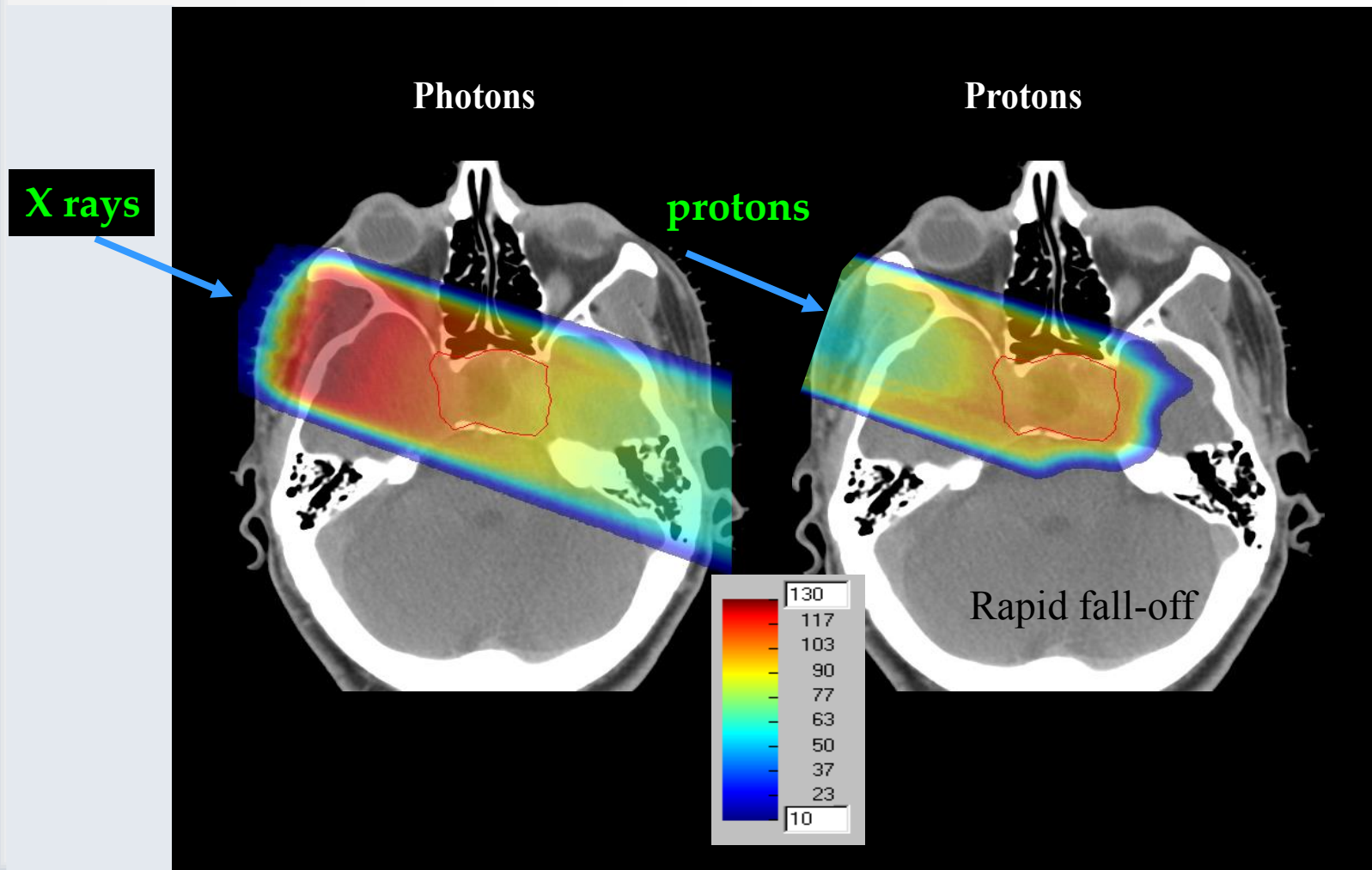
The depth and magnitude of the Bragg peak is determined by the mass and charge, as well as the particle initial energy

# Hadrontherapy: Spread Out Bragg Peak

It is possible to localize longitudinally the irradiation only on the tumor target: hadrontherapy is a high precision kind of radiotherapy.



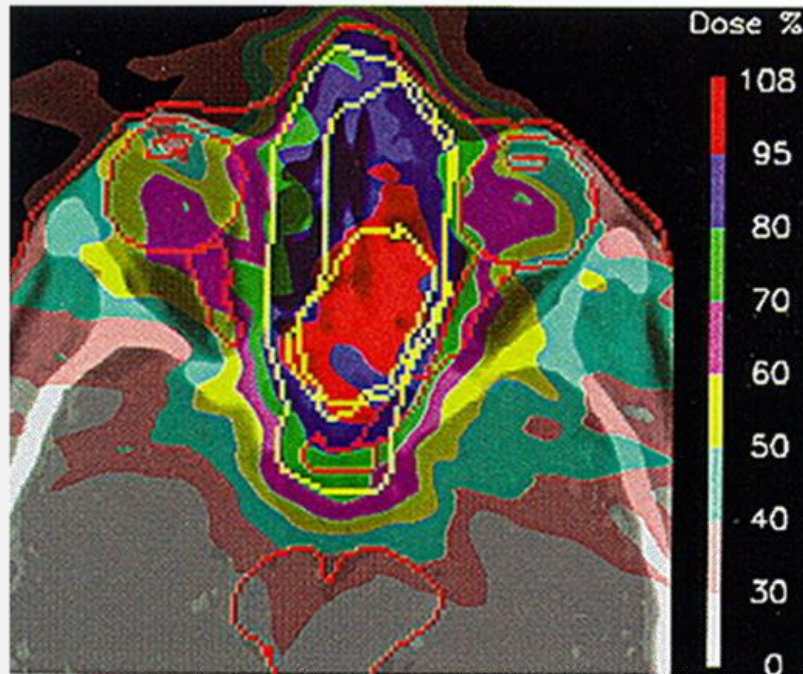
# Macroscopic advantage of hadrons



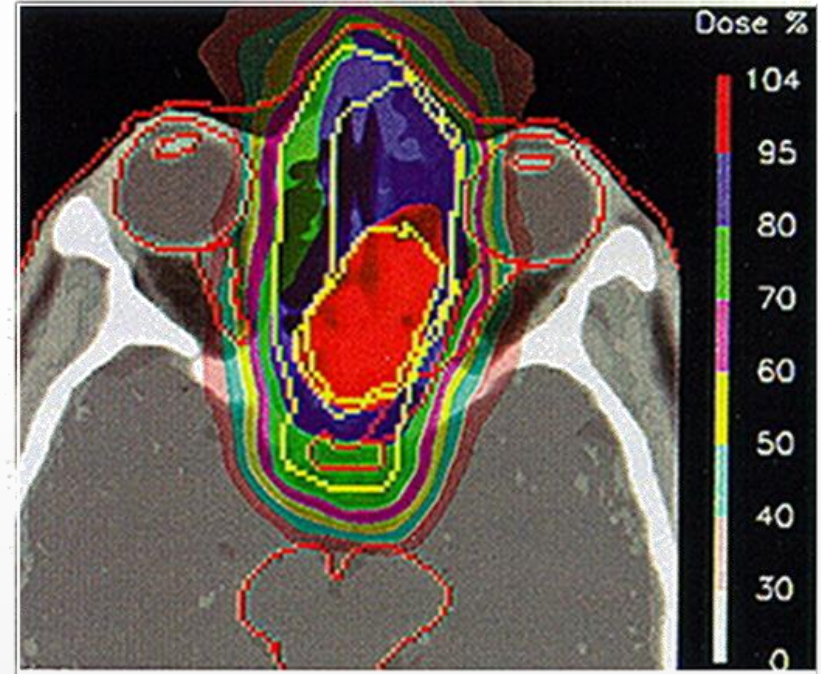


# Better dose distribution

9 X beams



1 proton beam



tumor between eyes

# Cell survival

$$SF = \exp[-(\alpha D + \beta D^2)]$$

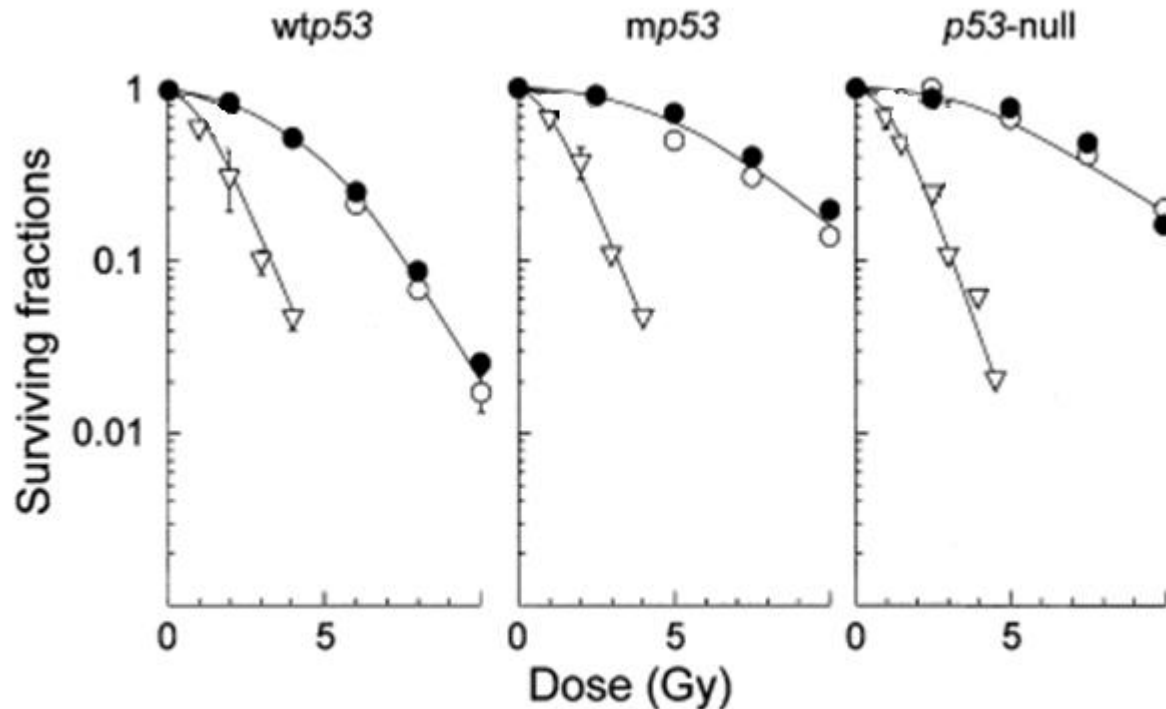
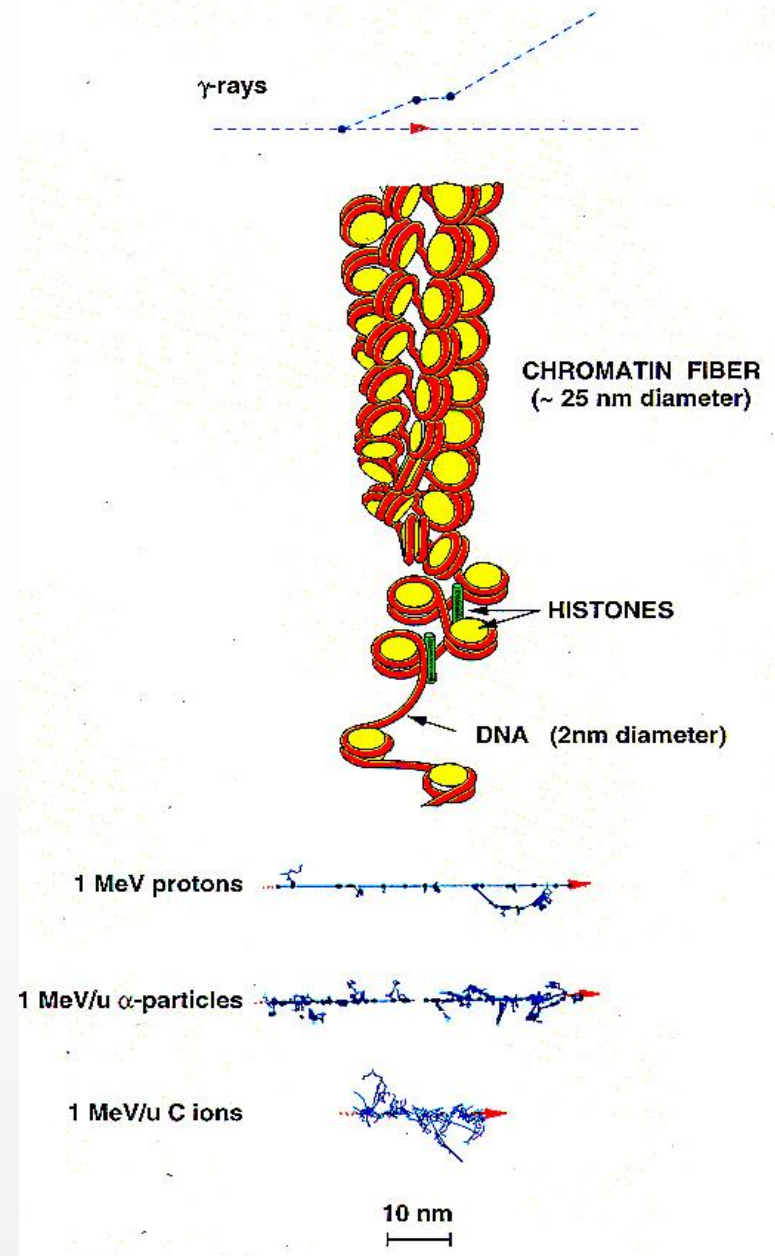


Fig. 2. Survival curves of cells exposed to X-rays (○ and ●) and 100 KeV/μm (▽) carbon beams.

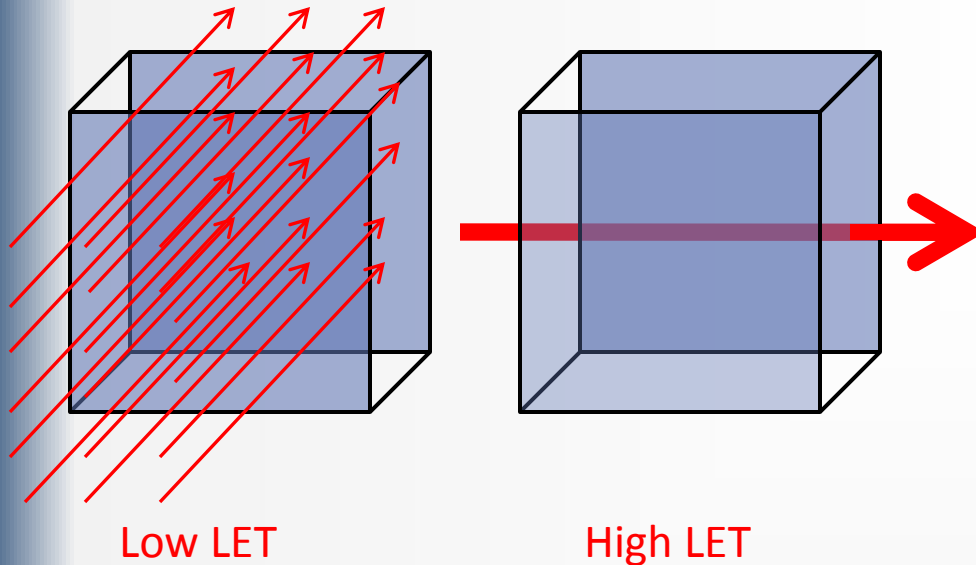
- Ionization breaks chemical bonds
- Free radicals creation (mainly hydroxyl radical,  $\text{OH}^-$ , and superoxide,  $\text{O}_2^-$ . Poison for the cell!)
- The target is DNA, ionization distribution is relevant



# LET Linear Energy Transfer

Hadrontherapy biological basis

Carbon ions have higher LET than protons

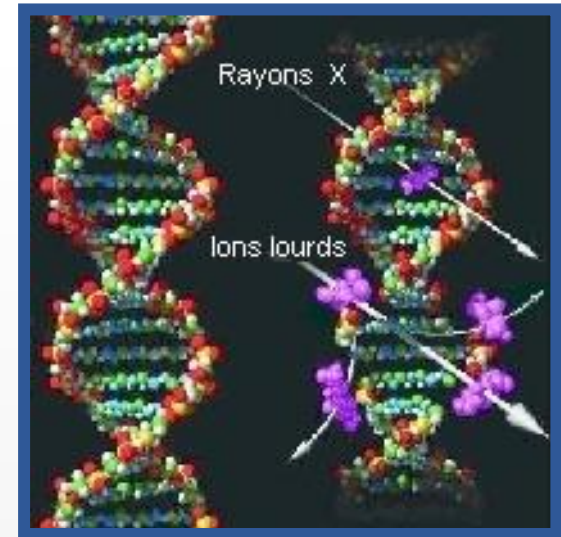
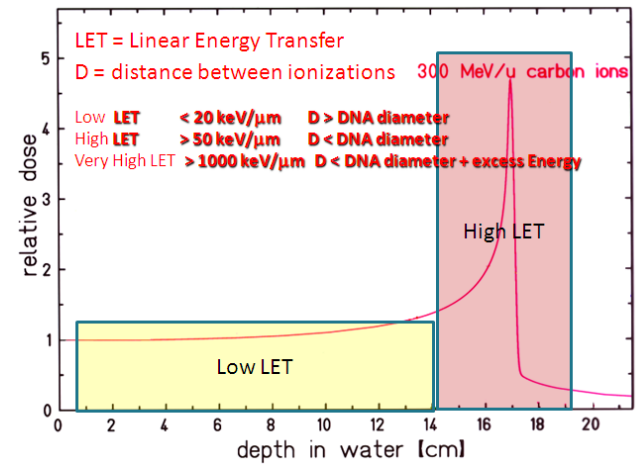


Low LET

High LET

D = distance between ionizations

- Low LET < 20 keV/mm D > DNA diameter
- High LET > 50 keV/mm D < DNA diameter
- Very High LET > 1000 keV/mm D < DNA diameter + excess Energy



Energy deposition in matter

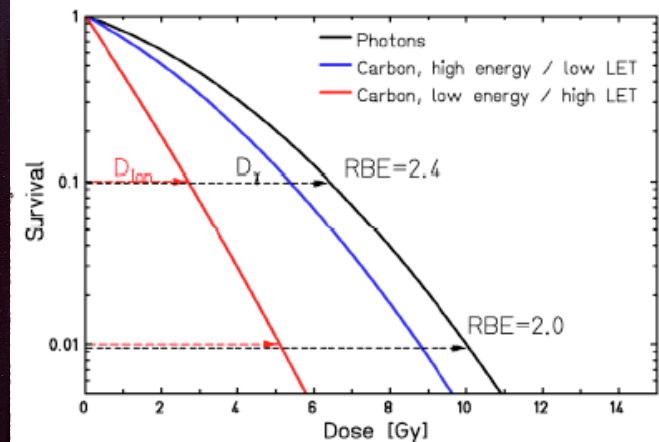
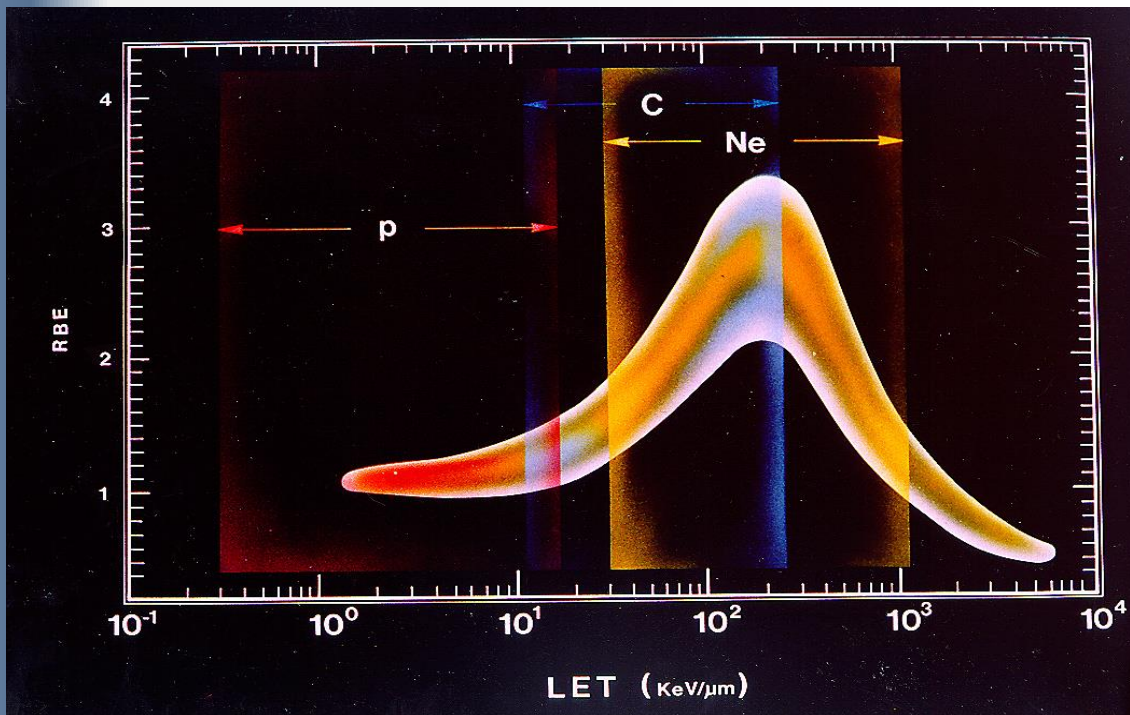


# RBE : *relative biological effectiveness*

Qualitatively the energy deposited by carbon ions is more efficient, in terms of cell destruction, than the energy deposited by protons.

The higher efficiency in killing cells is expressed by the *RBE*, which is the ratio between the photon and the ion doses which are necessary for producing the same biological effect.

Carbon RBE > 3 in the Bragg peak region  
>= 1 in the entry channel.



The survival curve for the target cells for late injury is "curvier" than that for acute effects

**RBE varies with particle type and energy, dose, dose per fraction, degree of oxygenation, cell or tissue type, biological end point, etc**

### Protons

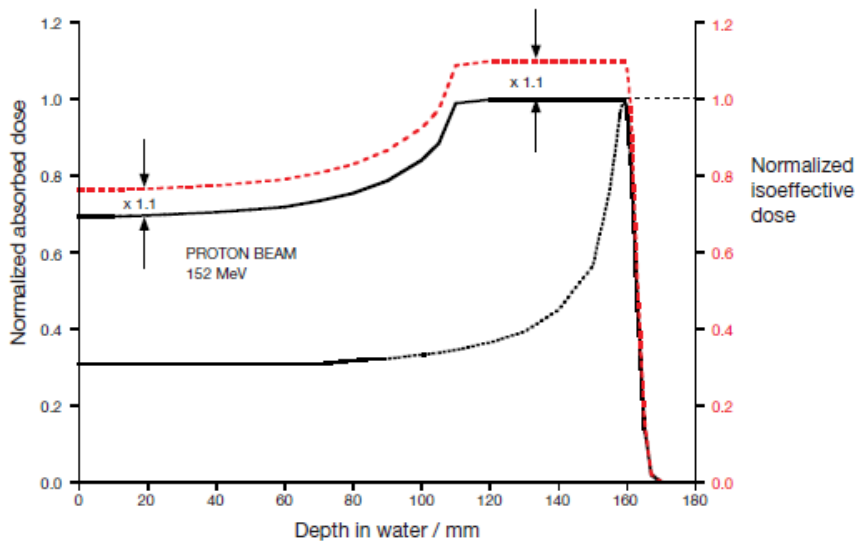


FIG. 1.1. Variation in depth of the absorbed dose of a monoenergetic (dotted line) and a spread out clinical (solid line) proton beam of 152 MeV and the corresponding weighted dose for radiation quality (RQ) (red dotted line, right ordinate). The RQ weighted dose (or RBE weighted dose) is obtained assuming a weighting factor  $W_{RQ} = 1.1$  at all depths, protons being delivered with the same fractionation conditions as photons (courtesy P. Andreo).

### Carbon Ions

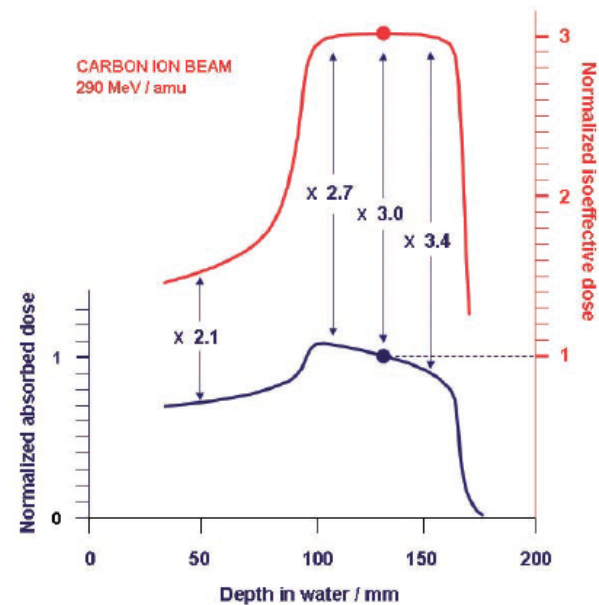


FIG. 1.2. Comparison of the absorbed dose and isoeffective dose variations with depth in a carbon ion beam. Carbon ion irradiation of a PTV located between 100 and 160 mm in depth using a 290 MeV/amu beam. The presentation is similar to Fig. 1.1. However, the RBE of a carbon beam significantly increases with depth. Therefore, in order to obtain a uniform 'isoeffective dose' (plateau) across the SOBP, the absorbed dose needs to be adapted (modulated) and decrease with depth. The weighting factors used to derive the isoeffective dose at different depths are indicated in the figure [1.12] (for more details, see Annex IV).

# Accelerator design criteria

The kind of the accelerator depends mainly on:

- The species to be accelerated

particle	Penetration range	Energy range	Brho range
Proton	30-300 mm	60-250 MeV/u	1.16-2.31 Tm
Carbon	30-300 mm	120-400 MeV/u	3.18-6.34 Tm

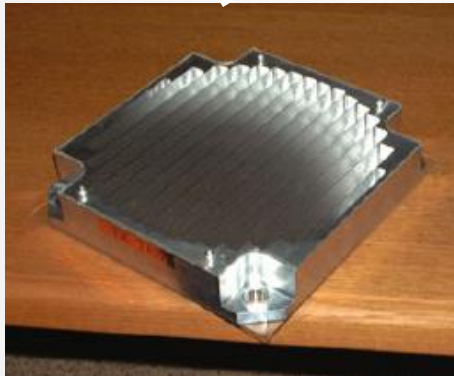
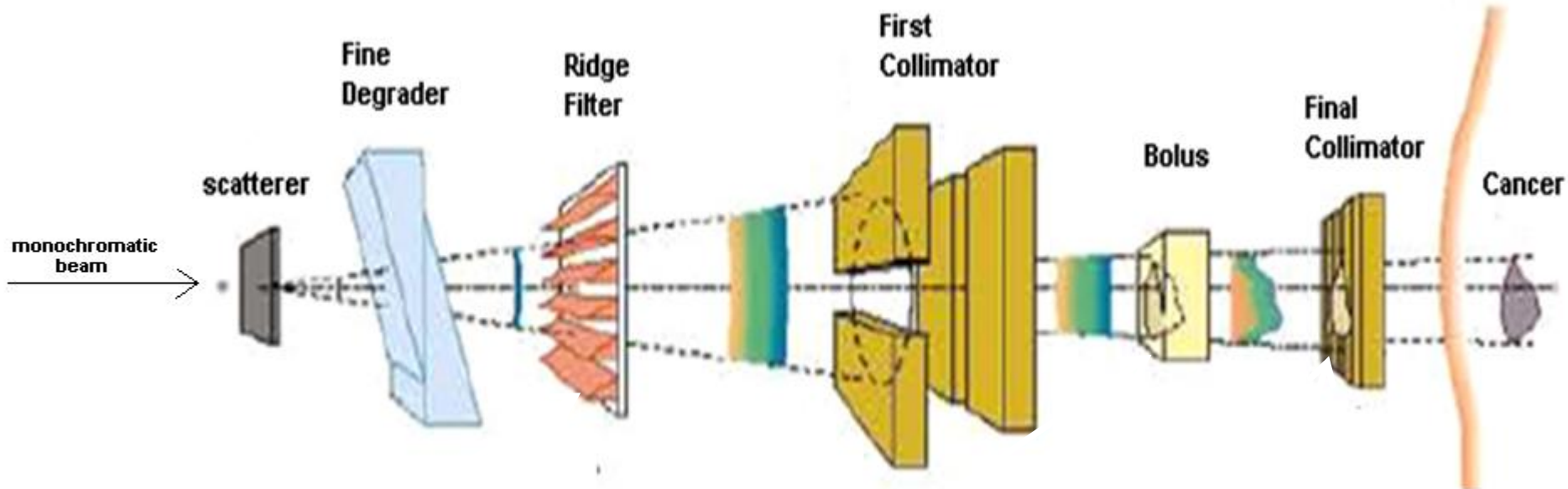
- The radiation shaping and delivery method

Passive Scanning

Active Scanning

# Passive Scanning

Passive scanning is based on putting several absorbers before the patient to change longitudinal and transverse characteristics



Ridge filter



Bolus



Multi-leaf final collimator

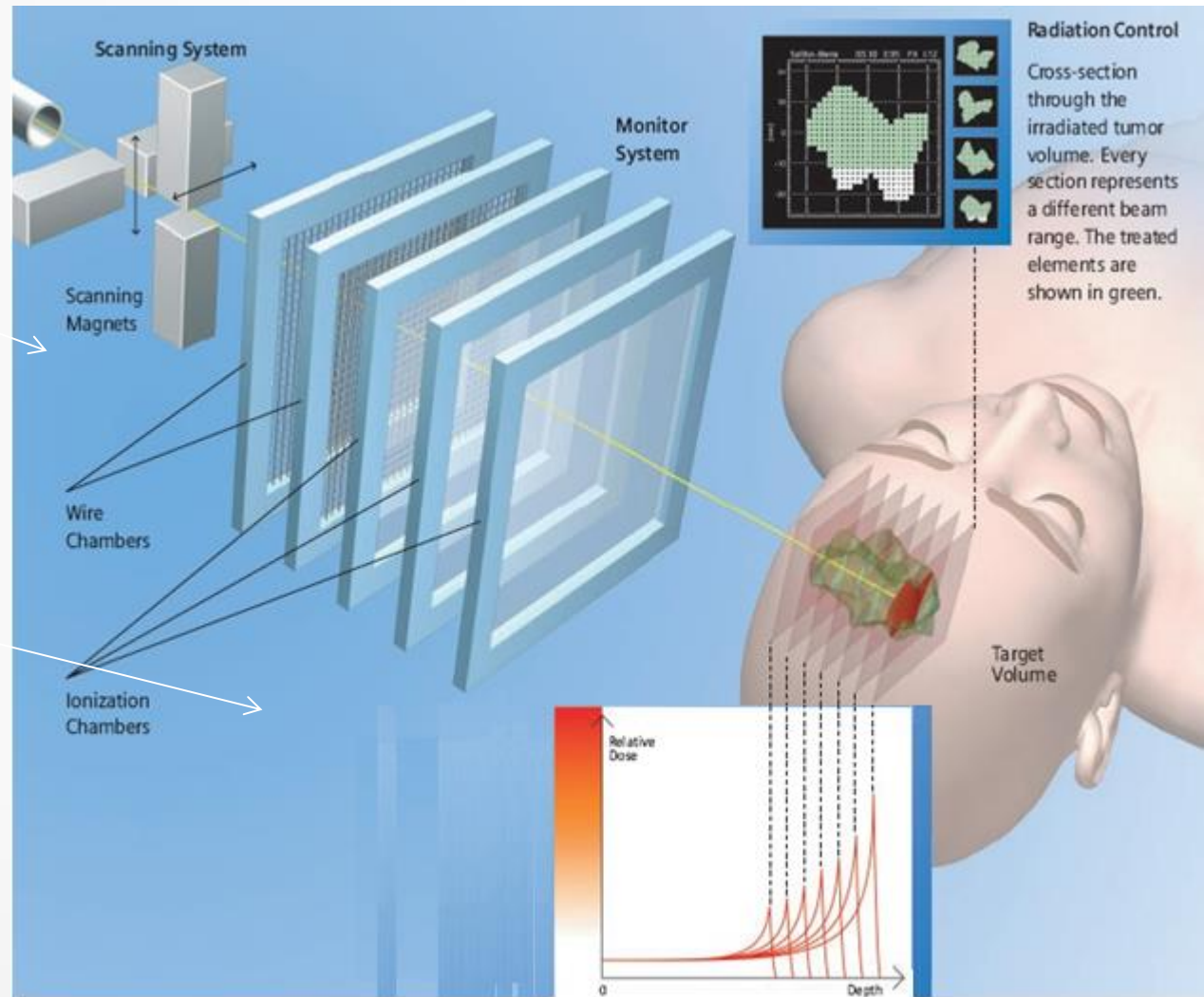


# Active Scanning

Fast magnets paint the tumour transversally  
Each voxel is irradiated during  $\sim 5$  msec

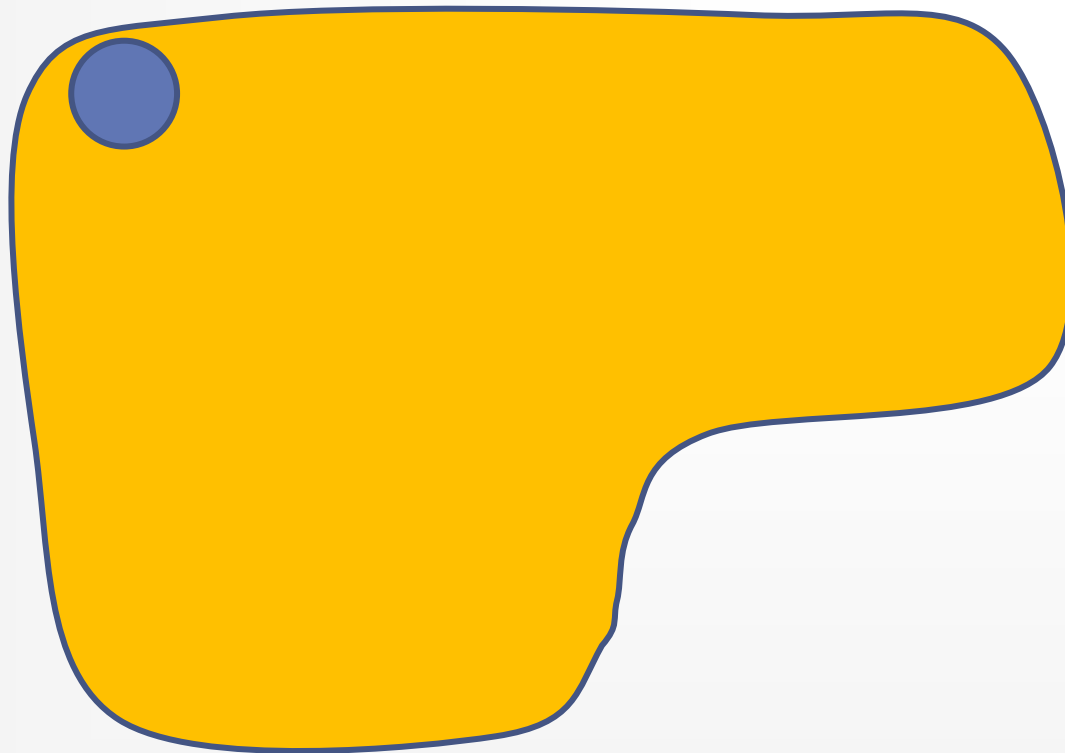
A nozzle system controls the delivered dose

Several Bragg peaks from the accelerator paint the tumour longitudinally



First use in Japan (1980) and then regularly used at GSI, PSI, HIT, CNAO

# Scanning beam



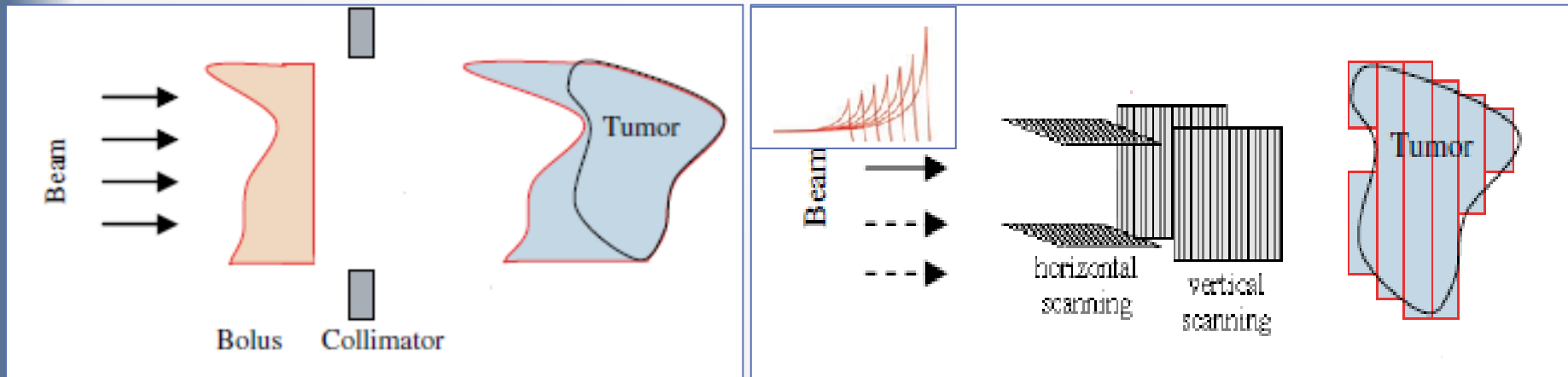
# Active vs Passive

Passive system needs patient-specific hardware: Bolus, Multileaf collimator

There are errors on dose irradiation:

- Bolus conforms the most distal surface
- Absorbers  $\longrightarrow$  Nuclear Fragmentation  $\longrightarrow$  Tailing of Bragg Peak
- Heavy ions need thicker absorbers  $\longrightarrow$  greater energy and currents from the accelerator.

Active system needs a more challenging control of beam characterizations and of the scanning magnets but **allows a more precise dose irradiation of the tumor target**

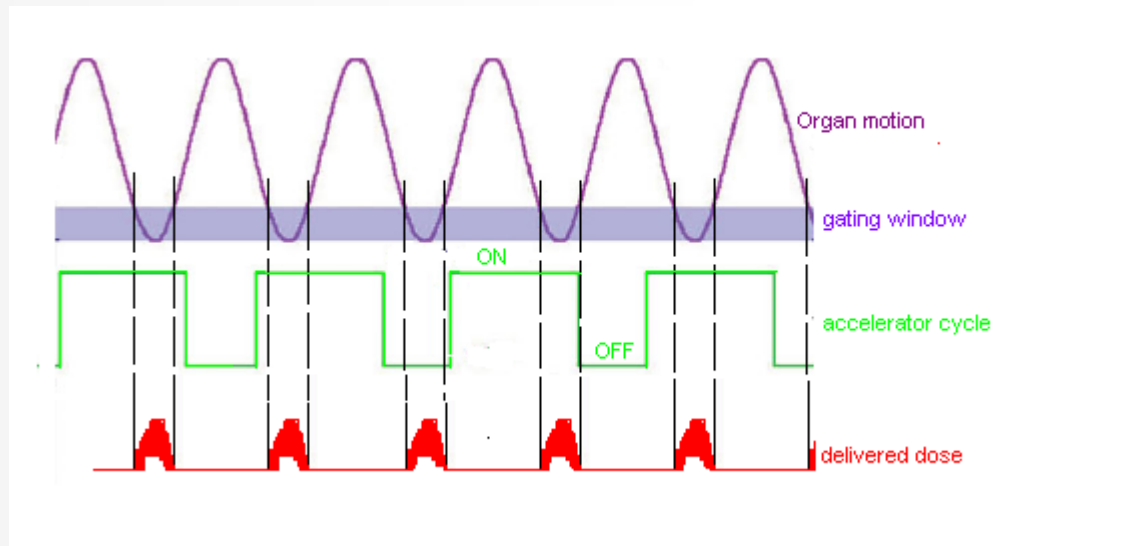


# Moving organs

Active system is critical in the case of moving organs. R&D is in progress worldwide about several techniques: Gating, repainting, beam tracking

Repainting consists in underdosing the tumour and increasing the treatment sessions

Gating consists in irradiating only at a specific position of the organ



Beam Tracking is an adjustment in real-time of treatment plan considering the 4D organ motion signal.

# Types of accelerators

Three accelerators can provide clinical beam: LINAC, Cyclotrons, Synchrotrons.  
The energy and the species of hadrontherapy make LINAC up to now not very practical and feasible



Nowadays Hadrontherapy centers are Cyclotrons and Synchrotrons

Cyclotrons	Synchrotrons
Compact (4 m diameter)	More complicated
cheaper	More expensive
DC beam	Pulsed beam
High current (hundreds nA)	Lower currents (tens nA)

**BUT...**

# Types of accelerators

**...BUT**

Cyclotrons are easy for protons; only one **CHALLENGING PROPOSAL** exists for carbon  
Cyclotron compactness is partially offset by the place required by the medical structure  
Passive scanning is needed with cyclotrons because the energy from accelerator is fixed

**while**

Synchrotrons can accelerate protons and carbons.

A synchrotron designed for 300mm C6+ can accelerate  $1 \leq Z \leq 6$  and O up to 19 cm.

Synchrotron can perform active scanning.



Nowadays the best technological layout for a hadrontherapy center is a  
**Carbon Synchrotron equipped with active scanning.**

A carbon synchrotron facility is made up of:

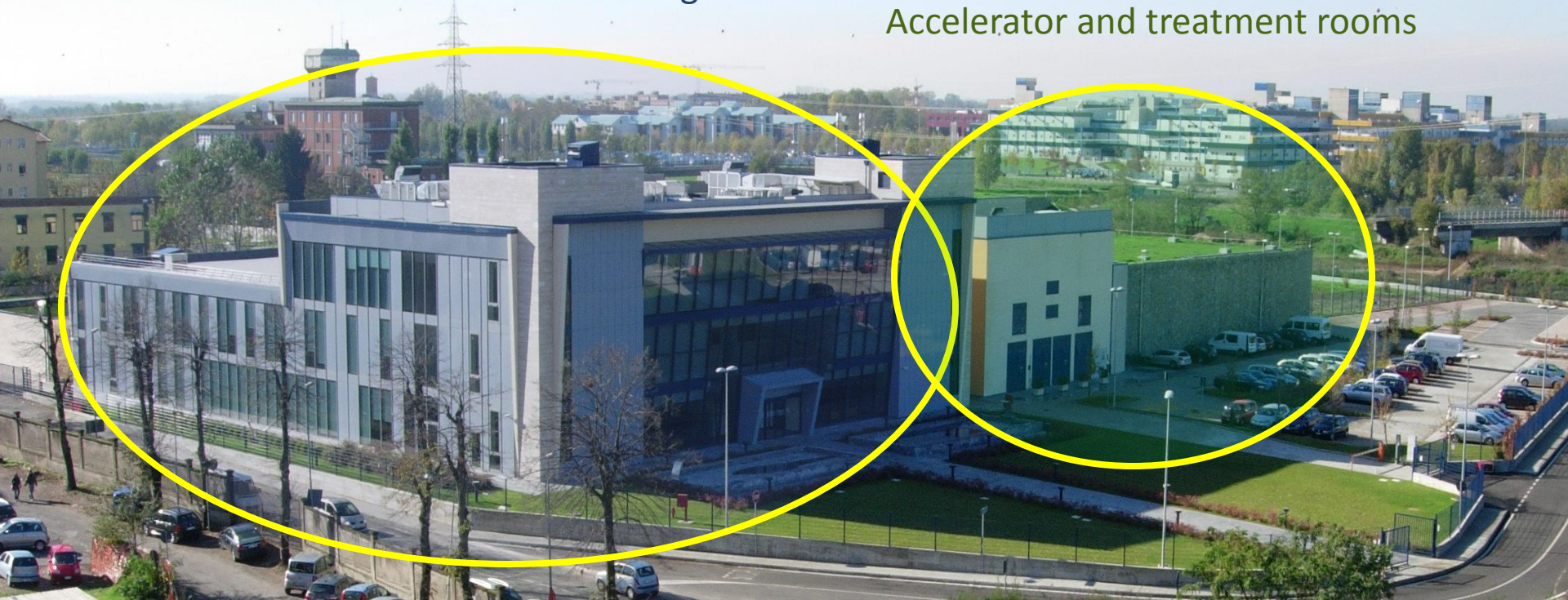
1. A low energy injector
2. A ring
3. The extraction lines



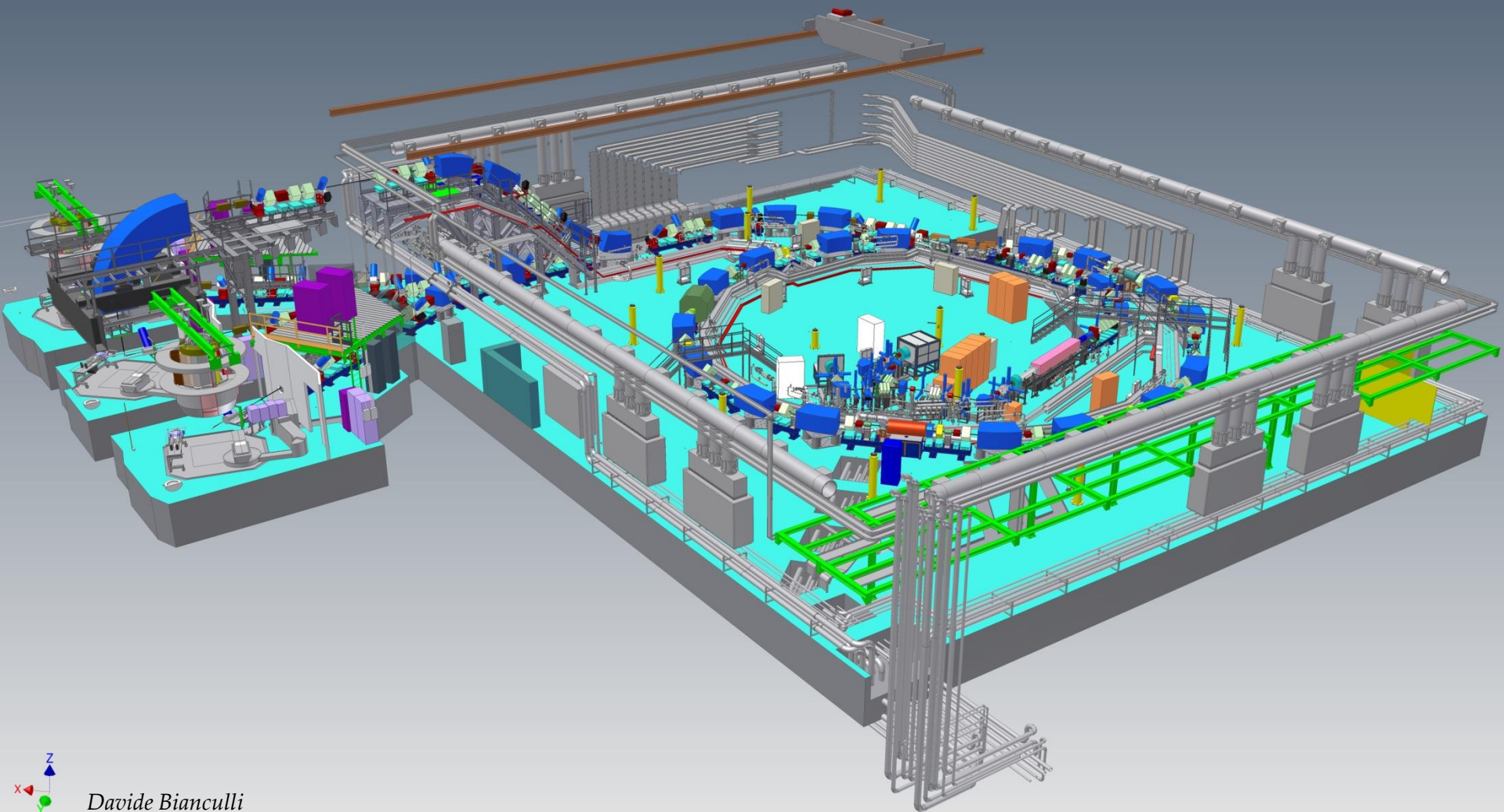
# CNAO, Pavia

Medical and Administrative buildings

Accelerator and treatment rooms



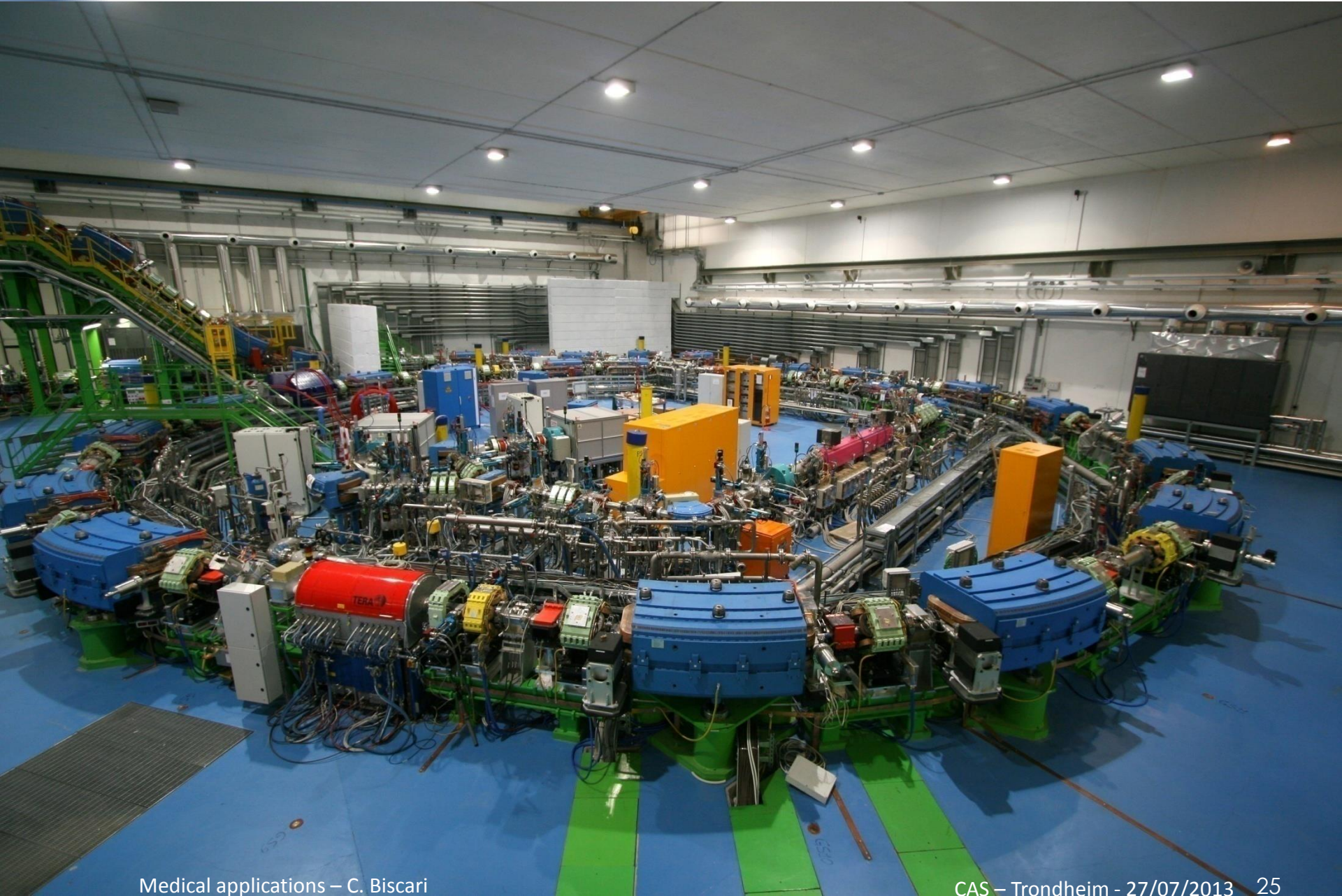
# CNAO - Accelerator and Treatment Rooms



*Daide Bianculli*

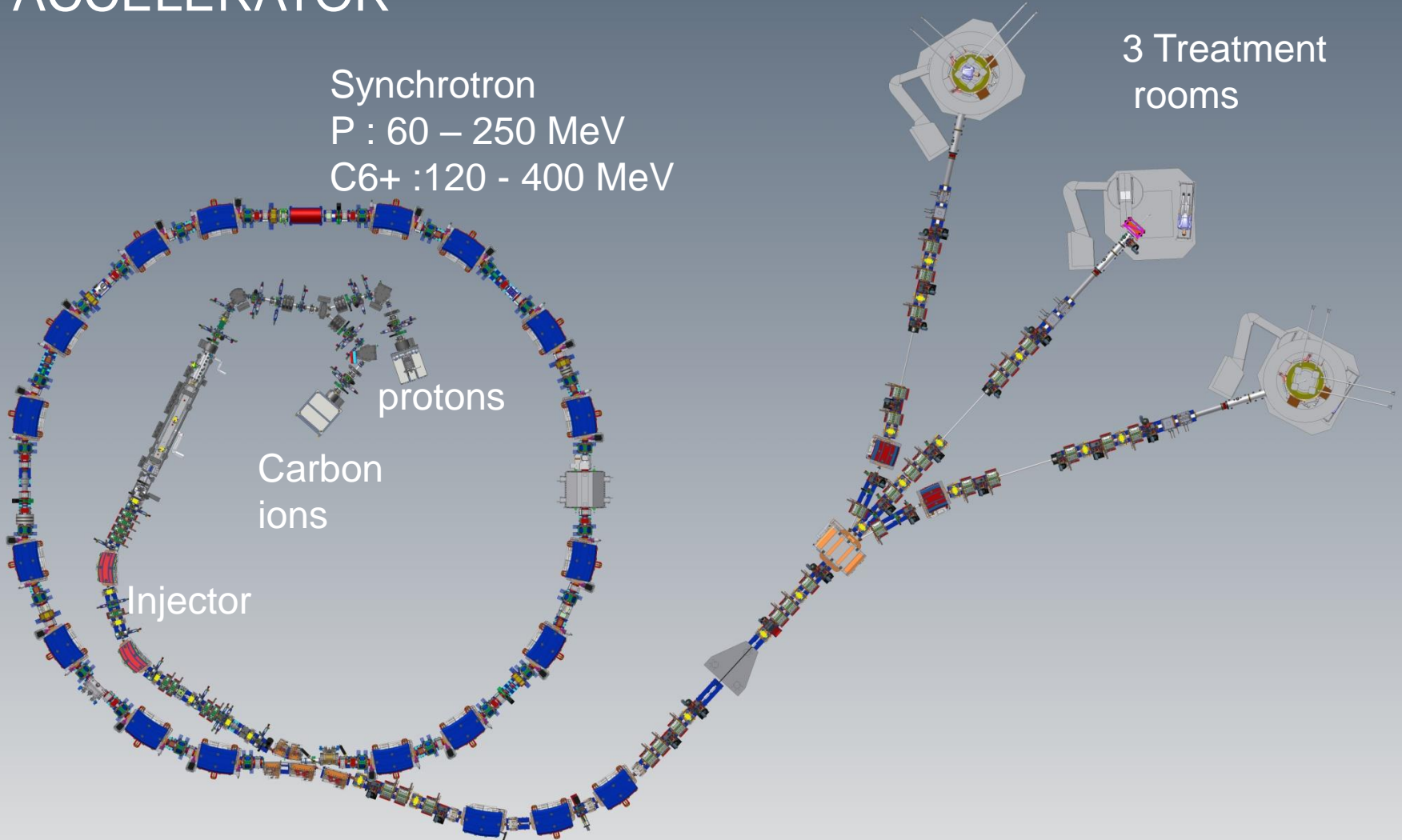


# Synchrotron hall



# ACCELERATOR

Synchrotron  
P : 60 – 250 MeV  
C6+ : 120 - 400 MeV



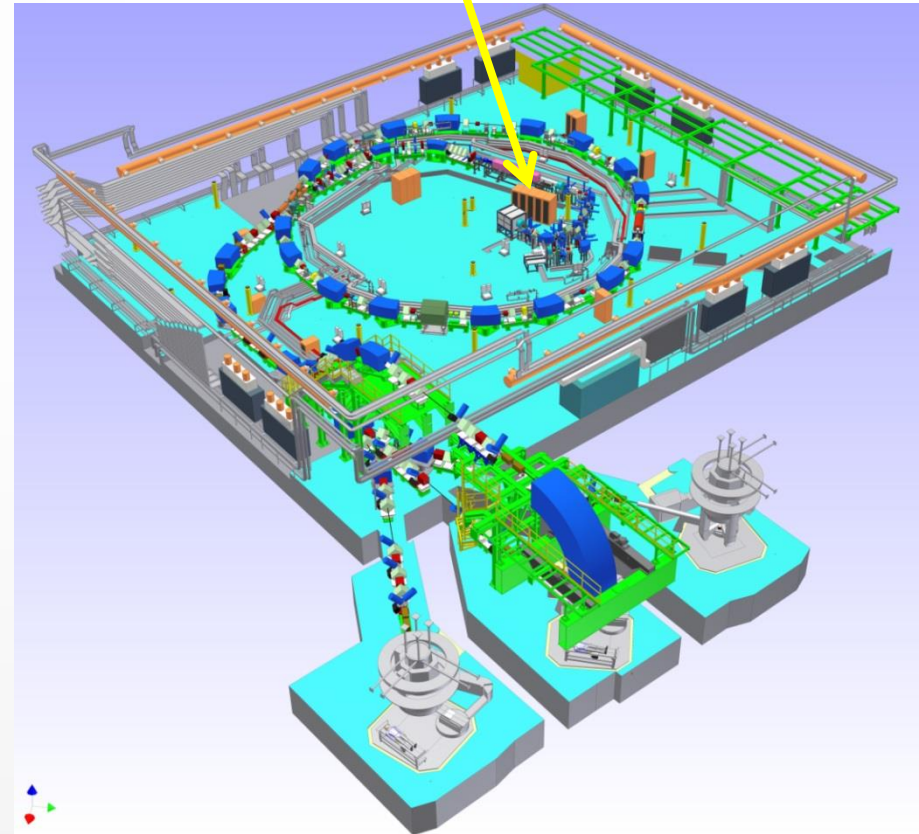


# Synchrotron facility layout: Injector

The injector is placed outside the ring for easier maintenance or inside to save space

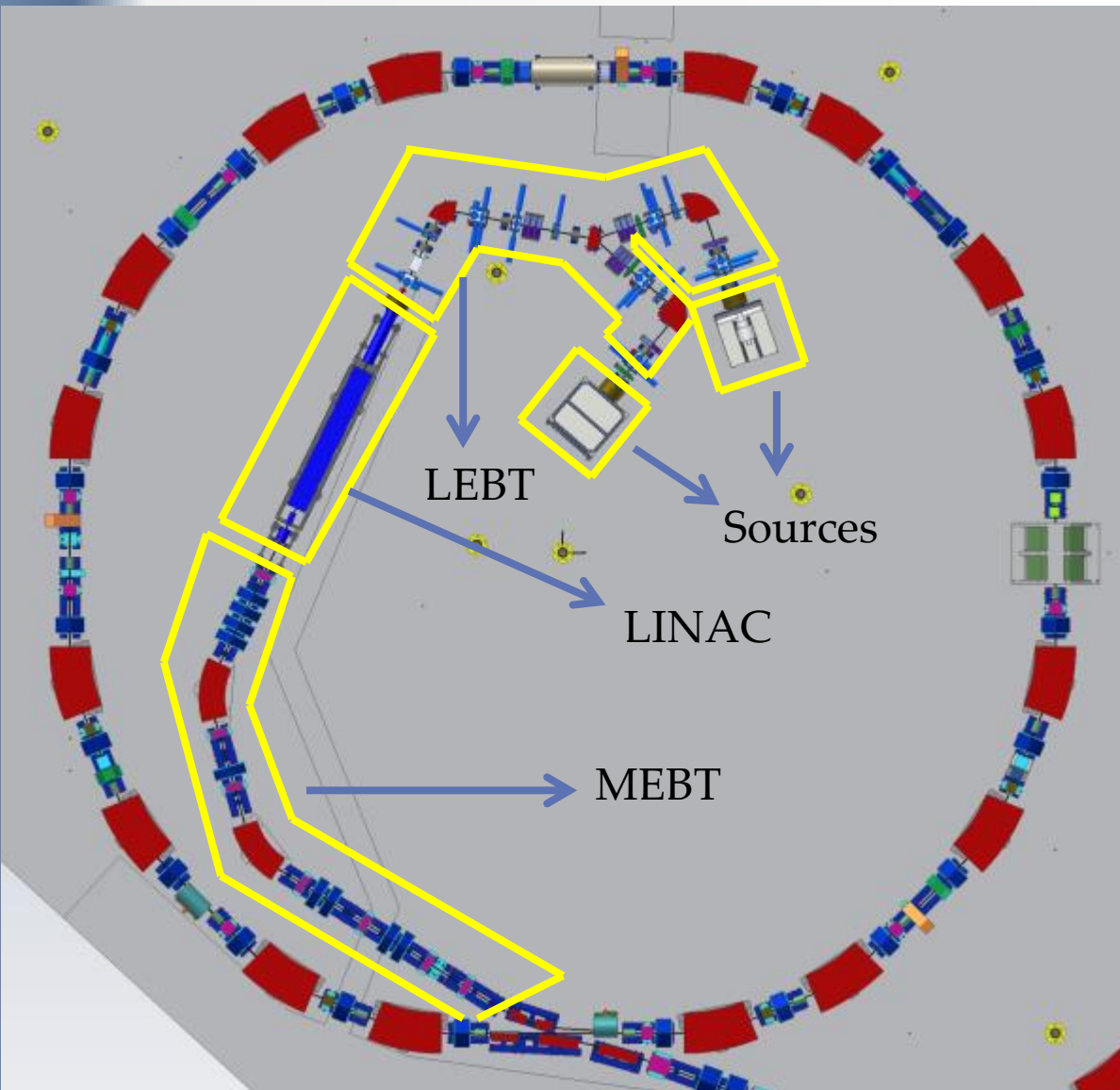


HIT (Heidelberg, Germany)



CNAO (Pavia, Italy)

# Synchrotron facility layout: Injector

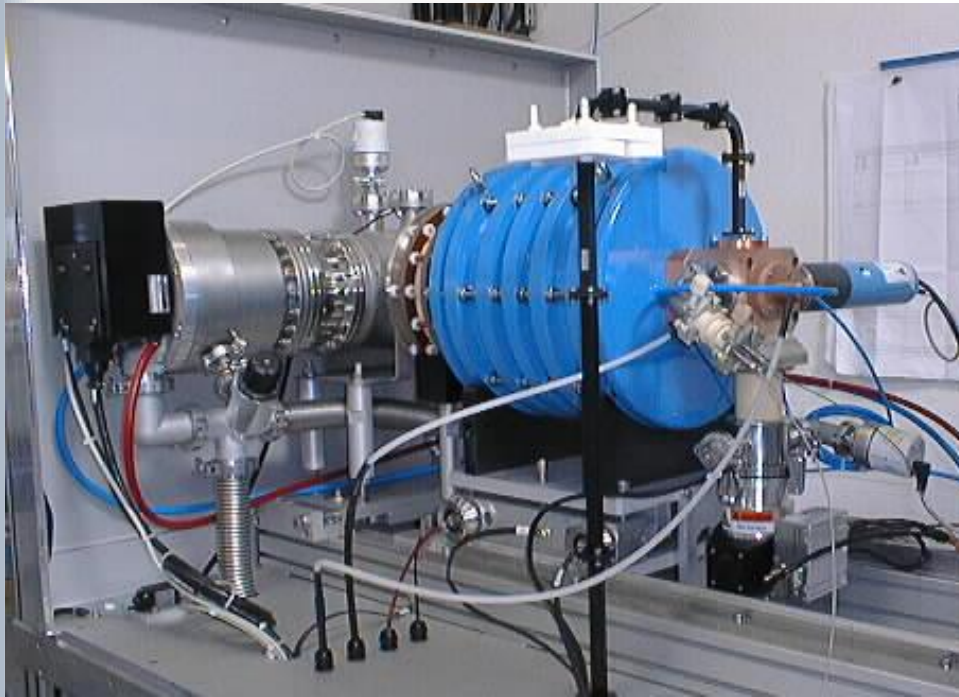


An injector is made up of:

1. Two or three sources
2. A LEBT (Low Energy Beam Transfer line)
3. A low energy Linac
4. A MEBT (Medium Energy Beam Transfer line)

# ION SOURCE

The type of ions sources are PIG, EBIS but, above all, ECR (Electron Cyclotron Resonance) Ion Sources  
At CNAO 2 ECRs: Both can deliver H<sup>3+</sup>, C<sup>4+</sup> and other species



- Double wall, water cooled plasma chamber, 7 mm diameter aperture for beam extraction.
- **Permanent magnets** system providing the axial and radial confinement (axial field from 0.4 to 1.2 T, radial field 1.1 T)
- Copper made “magic cube” for microwave injection system = waveguide to coaxial converter with a tuner to minimize the reflected power.
- RF window for the junction between the magic cube at high vacuum and the waveguide at atmospheric pressure.
- A gas injection system.
- A DC bias system to add electrons to the plasma and decrease the plasma potential.
- An RF generator of about **400 W** at 14.5 GHz (the effective power used in operation is below 300W).
- **Flexible frequency variable travelling wave tubes amplifiers (TWTA)** .

Built by Pantecknic on INFN-LNS Design

Gas are ionized by RF power at electron cyclotron resonance frequency (10-18 GHz)

The magnetic trap for the electrons is obtained with a solenoid and an exapolar magnet



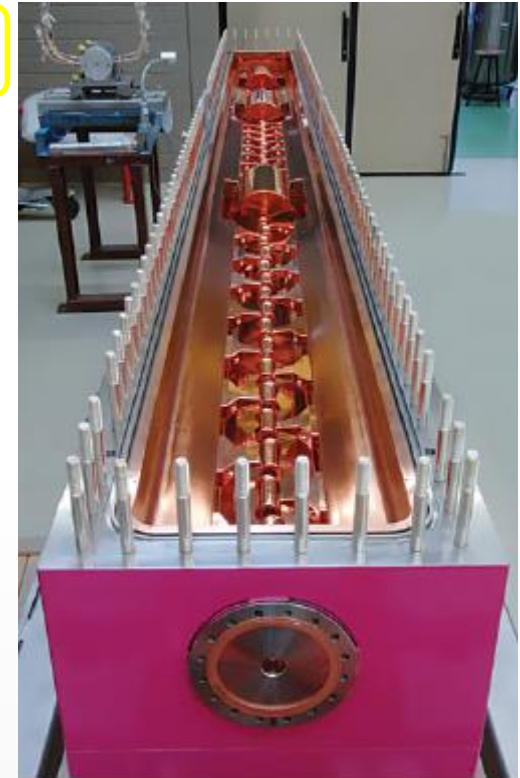
# Linac

RFQ+IH



RFQ

IH



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%

Medical applications – C. Biscari

RFQ

0.008-0.4 MeV/u H<sup>3+</sup>

0.008-0.4 MeV/u C<sup>4+</sup>

IH

0.4-7 MeV/u H<sup>3+</sup>

0.4-7 MeV/u C<sup>4+</sup>

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

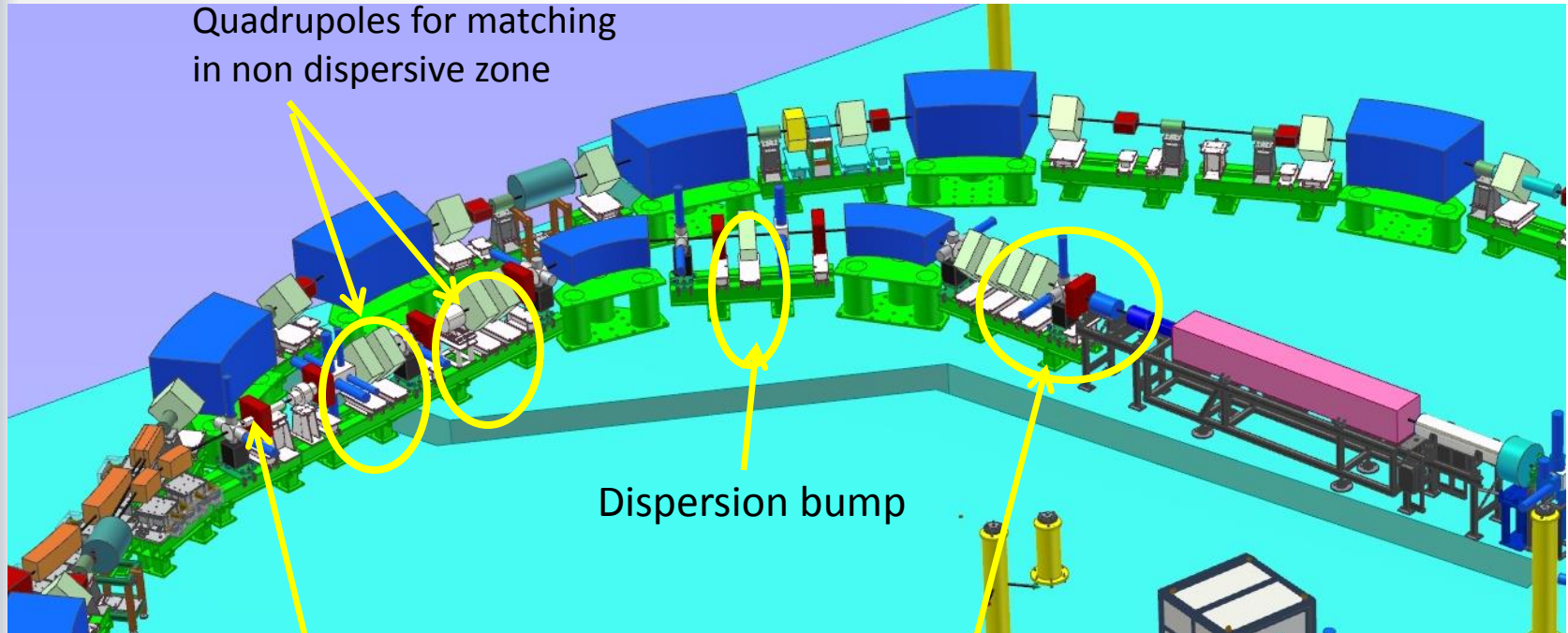
Inner tank width 0.26 m

Drift tube aperture diam. 12 – 16 mm

RF power loss (pulse) ≈ 1 MW

Averaged eff. volt. gain 5.3 MV/m

# MEBT



Quadrupoles for matching  
in non dispersive zone

Dispersion bump

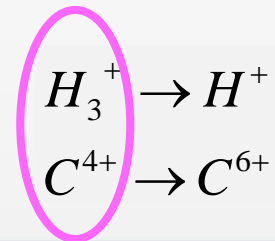
Debuncher to minimize the  
injected beam momentum  
spread

Stripping foil

Beams for  
treatments

Positions:	10
Foil material:	Carbon
Foil thickness:	100-200 $\mu\text{g}/\text{cm}^2$
Foil diameter:	15 mm
Beam diameter:	5 mm
Position accuracy:	$\pm 0,5$ mm

Same  $B\rho$



# Ring: Slow Extraction

Dose homogeneity :  $\pm 2.5\%$   a single turn extraction ( $<1 \mu\text{sec}$ ) not possible



Unstable but controlled beam betatron oscillations: the motion amplitude grows until an electrostatic septum allows the extraction of the particle.



Extraction mechanism strongly influences the ring design  
Optical layout must guarantee a machine tune near to an unstable value during the extraction.

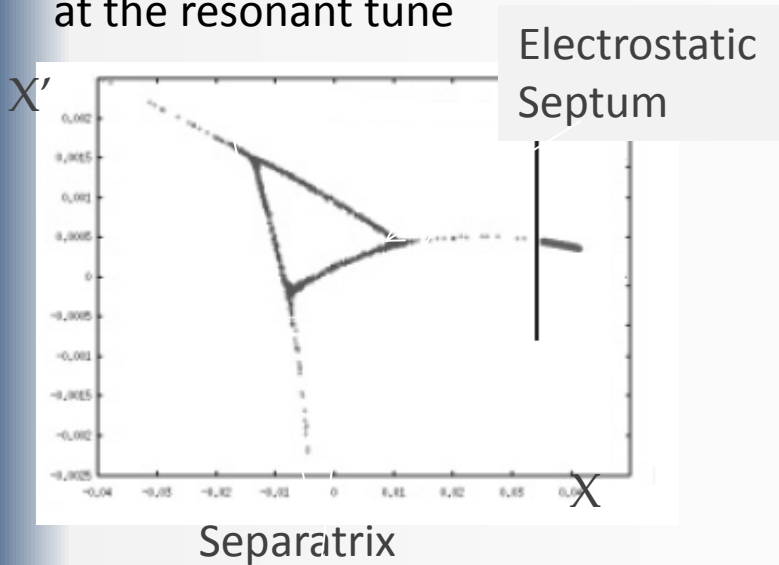
The part of the beam with the resonance tune is extracted.  
In the present facilities the unstable tune is chosen  $N/3$ . A sextupolar field feeds the resonance:

**THIRD ORDER RESONANCE SLOW EXTRACTION MECHANISM**

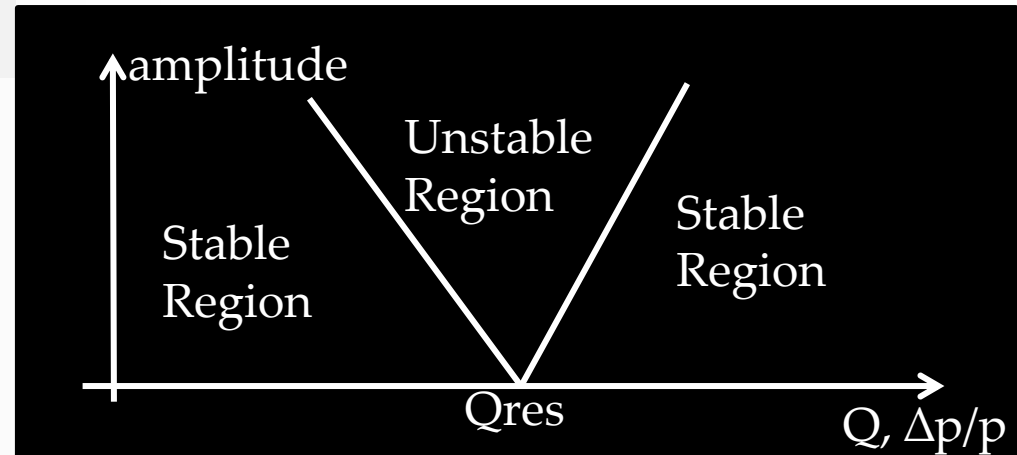


# Ring: Slow Extraction

Horizontal Phase Space  
at the resonant tune



Steinbach diagram



Beam can be driven to the resonance condition by three methods:

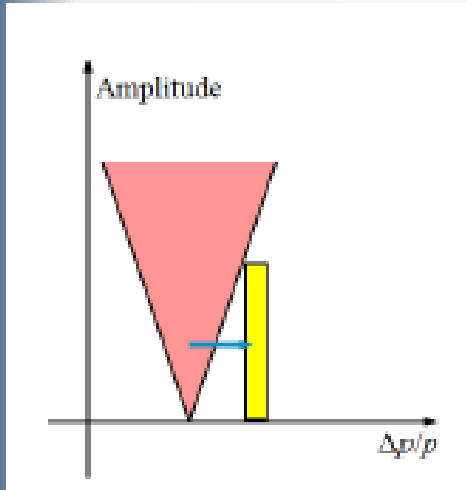
amplitude  
selection

amplitude-momentum  
selection

RFKO  
RF Knock-out

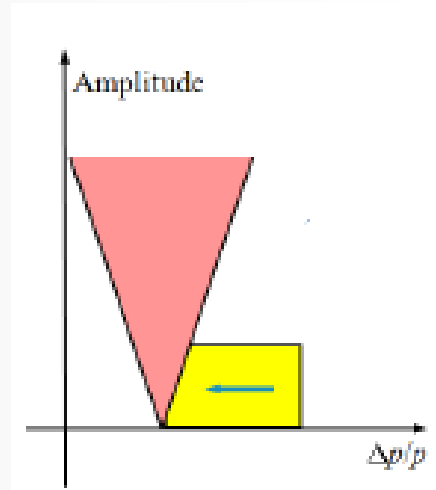
# Ring: Slow Extraction

amplitude selection



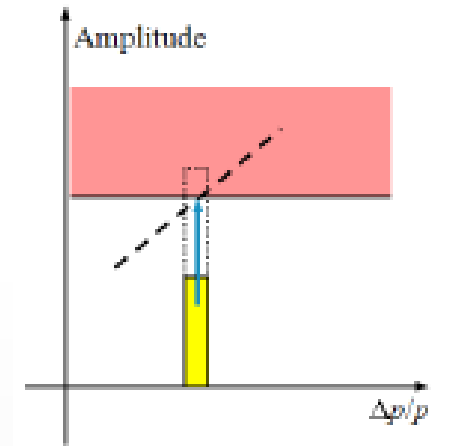
- Not constant optics
- Narrow  $\Delta p/p$
- Not constant position, size, energy of extracted beam
- No more used

amplitude-momentum selection



- Constant optics
- Large beam  $\Delta p/p$
- Constant position, size, energy of extracted beam
- Use of a betatron core

RFKO



- Constant optics
- Constant position, size, energy of extracted beam
- Use of a transverse RF exciter

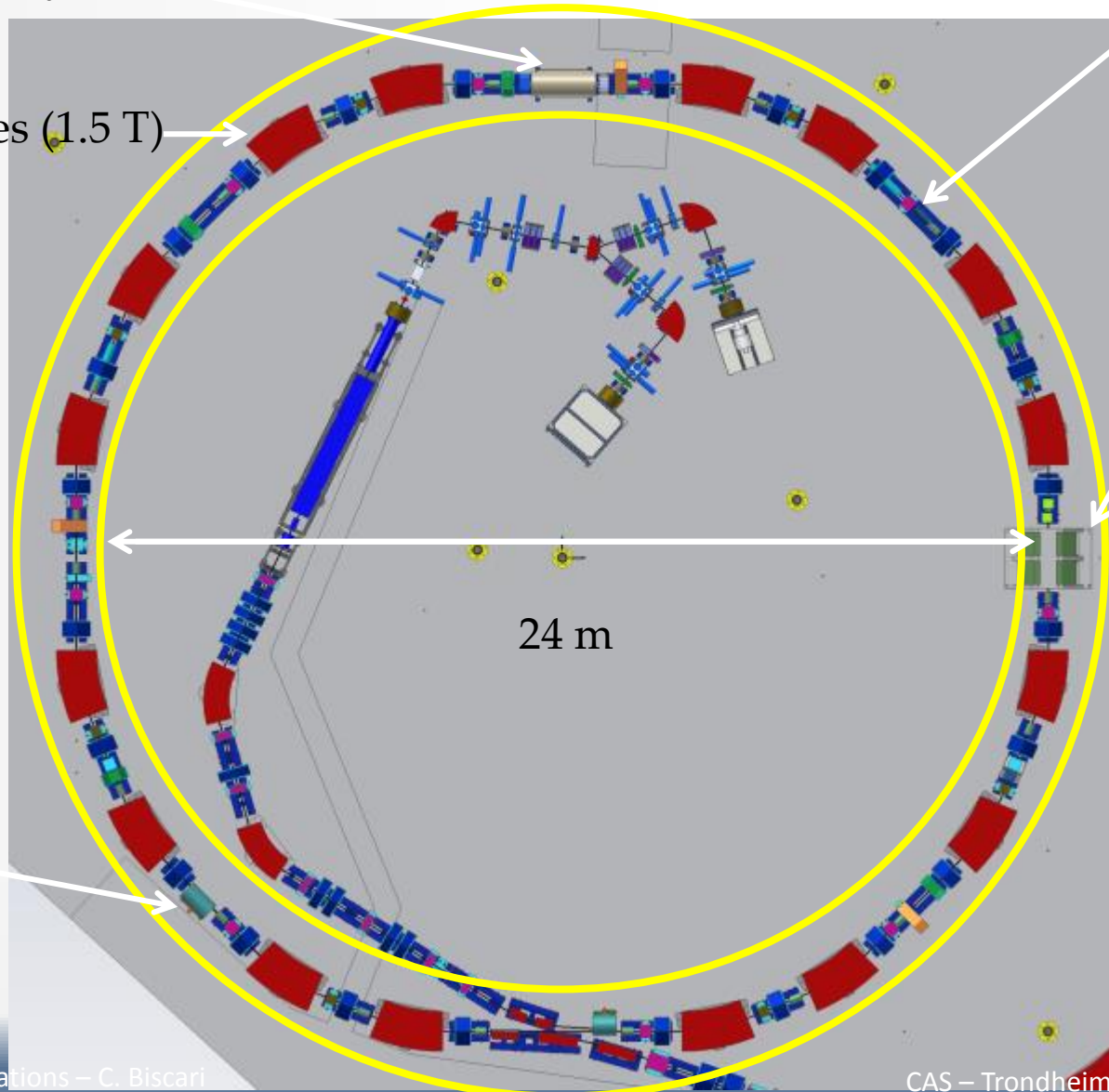
# Synchrotron facility layout: Ring

Broadband RF cavity

Air core quadrupole

16 resistive dipoles (1.5 T)

Betatron Core



Electrostatic Septum

24 m

# Ring : RF cavity

Acceleration is performed with a single RF cavity at harmonic 1 or 2 based on the principle of ferrite-loaded cavities and with tetrode or solid state technology for the amplifier. Nowadays ferrite often is replaced by amorphous alloy to reduce cavity length

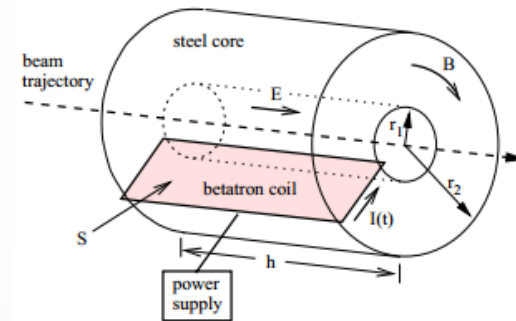
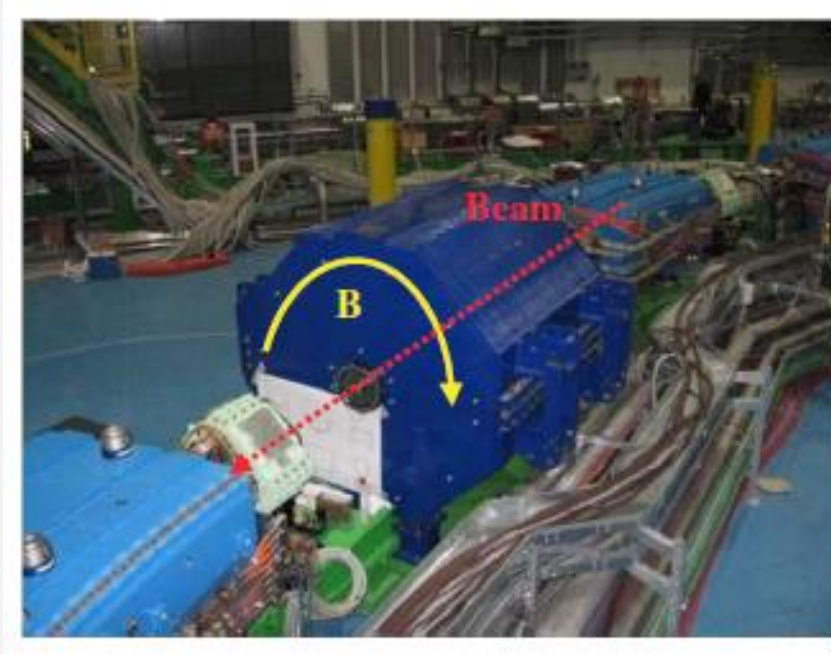


Vitrovac amorphous alloy Fe-Co

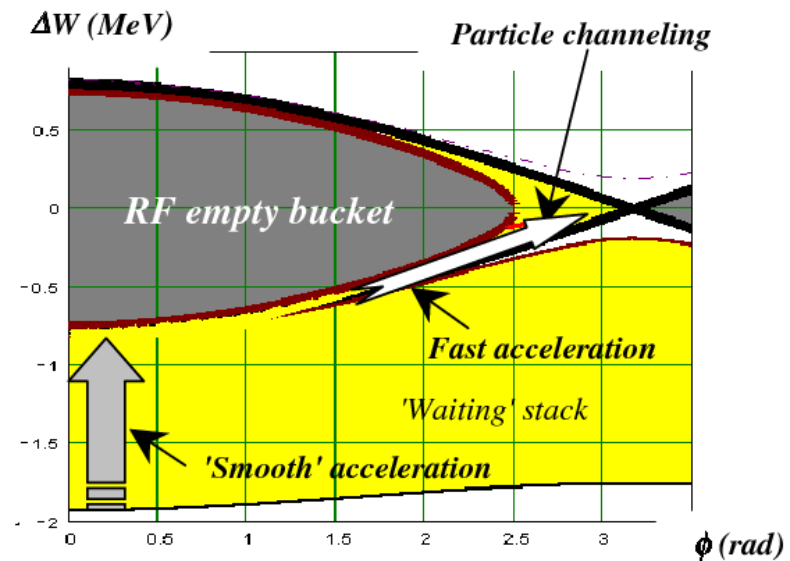
<b>Frequency Range</b>	<b>0.4 MHz-3 MHz</b>
Voltage Range	50 V-10000 V
Vitrovac current	0-10 A
Cavity length	1.3 m
Q	1-5
Rshunt	900-500 ohm

# Ring: Betatron Core

High inductance device: the only active element during extraction. All the other elements, and thus also the lattice functions, are kept static, the RF voltage is switched off. Therefore, the energy of the extracted beam is kept constant, no RF structure can appear in the spill and sources of ripples are minimised.



To reduce ripple spill RF cavity is used with the technique of empty bucket channelling





# Extraction lines

The beam quality at all the energies (stable position, possibility to have round beams with more dimensions, RT control of the dose) constraints on magnetic lattices, power supplies, magnets, control system, Nozzle.

Irradiation from different directions is mandatory. It can be realized:

1. Displacing the patient
2. Several lines in the same room
3. Gantry

Nowadays gantries for protons are present in most facilities.

A gantry for carbon is more challenging!

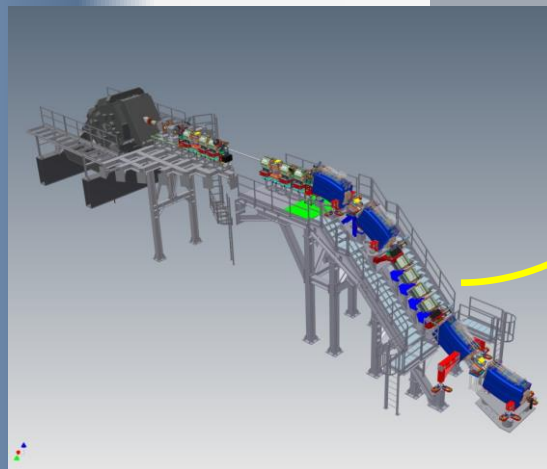
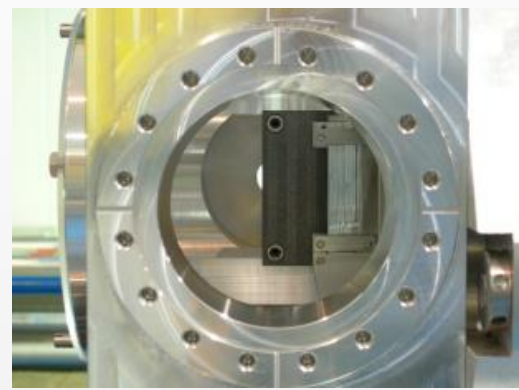
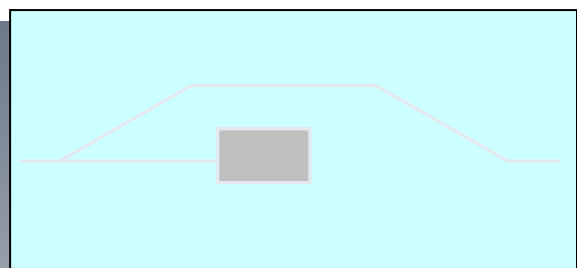
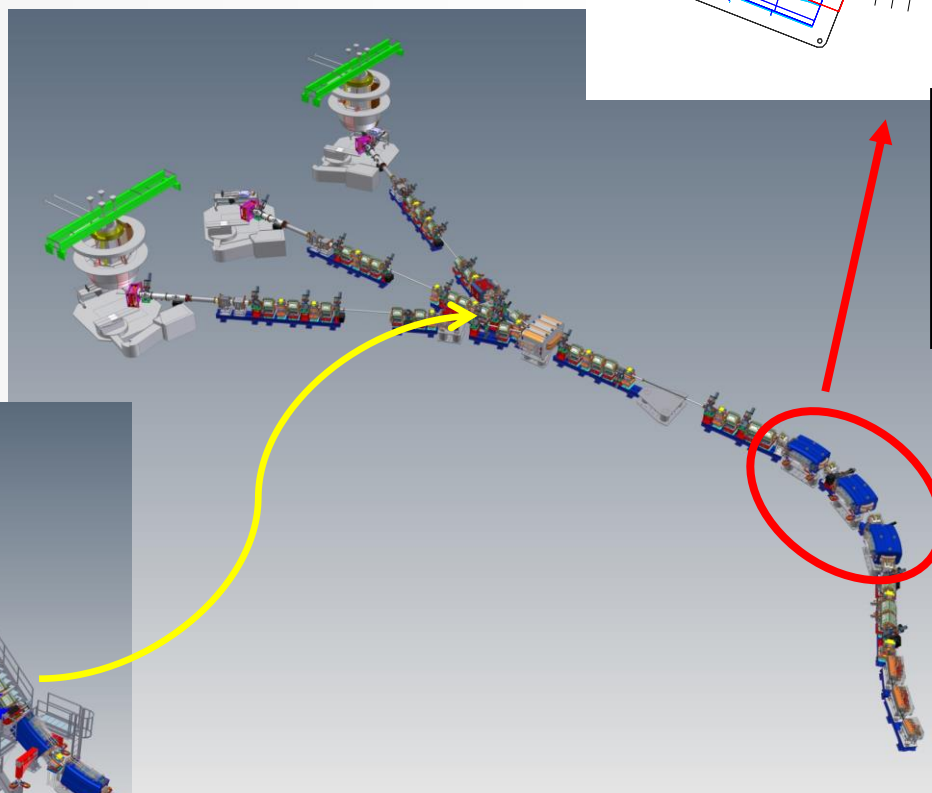
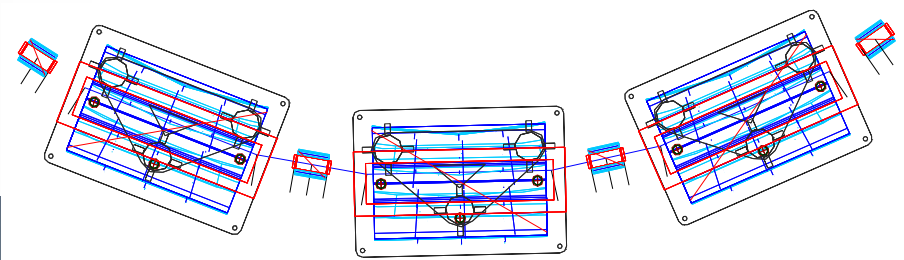
To date only HIT is equipped with a carbon ions gantry  
(600 tons at 13 m against the standard 100 tons at 10 m)



First heavy ions gantry at Heidelberg

# CNAO Extraction lines

CNAO lines: 3 treatment rooms: 2 with horizontal line and 1 with horizontal and vertical one. The beginning of the line has 4 fast magnets (100 microsec) to dump the beam for patient security.



# Orders of magnitude

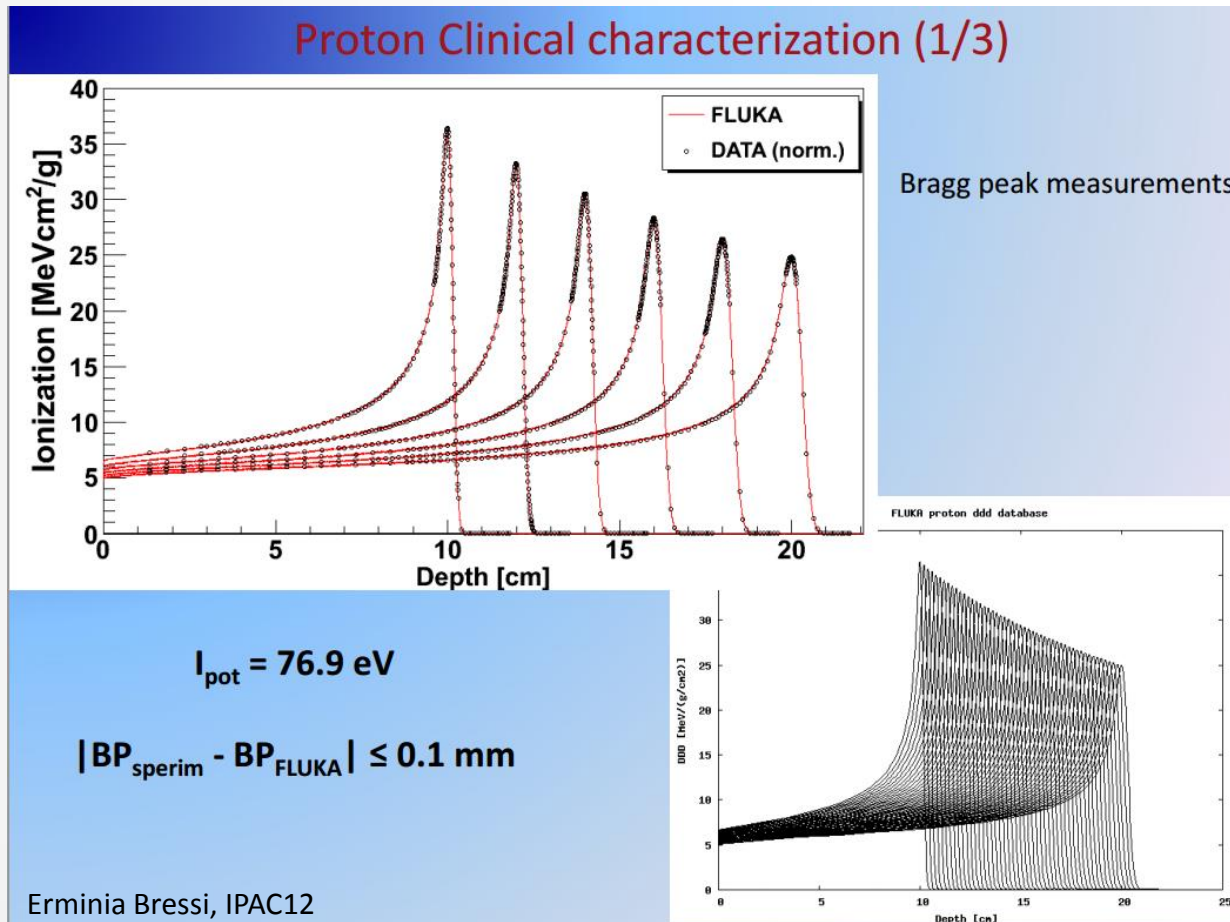
**Dose uniformity required:  $\pm 2.5\%$**

<b>Treatment session duration:</b>	<b>30 min</b>
<b>Irradiation duration:</b>	<b>3 min</b>
<b>Slice thickness:</b>	<b>2 – 4 mm</b>
<b>Spot size:</b>	<b>4 - 10 mm</b>
<b>Position precision:</b>	<b>0.1 mm</b>
<b>Energy precision:</b>	<b><math>10^{-4}</math></b>
<b>Spot duration:</b>	<b>5 - 10 ms</b>
<b>Beam current:</b>	<b>0.1 - 1 nA</b>
<b>Measurement time:</b>	<b>&lt; 100 ms</b>



# Energy precision: $10^{-4}$

Energy measured with Bragg peak on water, feedback on position at BPM in high dispersion region – Precision much better than accelerator based measurements



# CNAO Design Parameters I

Protons ( $10^{10}/\text{spill}$ )				
	LEBT (*)	MEBT	SYNC	HEBT
Energy [MeV/u]	0.008	7	<b>7-250</b>	<b>60-250</b>
$I_{\text{max}}$ [A]	$1.3 \times 10^{-3}$	$0.7 \times 10^{-3}$	$5 \times 10^{-3}$	$7 \times 10^{-9}$
$I_{\text{min}}$ [A]	$1.3 \times 10^{-3}$	$70 \times 10^{-6}$	$0.12 \times 10^{-3}$	$17 \times 10^{-12}$
$\epsilon_{\text{rms,geo}}$ [ $\pi$ mm mrad]	45	1.9	0.67-4.2	0.67-1.43(V)
$\epsilon_{90,\text{geo}}$ [ $\pi$ 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
$(\Delta p/p)_{\text{tot}}$	$\pm 1.0\%$	$\pm(1.2-2.2)\%$	$\pm(1.2-3.4)\%$	$\pm(0.4-0.6)\%$

\*( $\text{H}_2^+$ ,  $\text{H}_3^+$ )

# CNAO Design Parameters II

<b>Carbon (<math>4 \cdot 10^8</math> C/spill)</b>				
	LEBT (C <sup>4+</sup> )	MEBT	SYNC	HEBT
Energy [MeV/u]	0.008	7	7-400	<b>120-400</b>
I <sub>max</sub> [A]	$0.15 \times 10^{-3}$	$0.15 \times 10^{-3}$	$1.5 \times 10^{-3}$	$2 \times 10^{-9}$
I <sub>min</sub> [A]	$0.15 \times 10^{-3}$	$15 \times 10^{-6}$	$28 \times 10^{-6}$	$4 \times 10^{-12}$
$\epsilon_{\text{rms,geo}}$ [ $\pi$ mm mrad]	45	1.9	0.73-6.1	0.73-1.43(V)
$\epsilon_{90,\text{geo}}$ [ $\pi$ 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
$(\Delta p/p)_{\text{tot}}$	$\pm 1.0\%$	$\pm(1.2-2.0)\%$	$\pm(1.2-2.9)\%$	$\pm(0.4-0.6)\%$

# High precision devices for patient positioning

The reference fractionation scheme consists of fractions of 2 Gy/d, five times per week, specified in the planning target volume (PTV).





## 3D Real-time IR Optical Tracking (OTS)

- Real time reconstruction of spherical markers and surfaces
- Sub-millimeter accuracy : peak 3D errors  $<0.5$  mm
  - 3D data flow @70 Hz

## X-ray Patient Verification System (PVS)

- 2 X-ray tubes (deployable) ,  
2 flat panels (deployable)
- Supporting structure rotation:  $\pm 180^\circ$
- Rotation and deployment accuracy:  $\pm 0.15$ mm,  $\pm 0.1^\circ$

## Patient Positioning System (PPS)

- Automatic couch or chair docking
- Absolute accuracy:  $\approx 0.3$  mm



Markers, low density fixation materials



# CNAO medical activity

1<sup>st</sup> patient protons: September 2011

1<sup>st</sup> patient Carbon Ions: September 2012

Three treatment rooms operational

62 Patients treated with protons

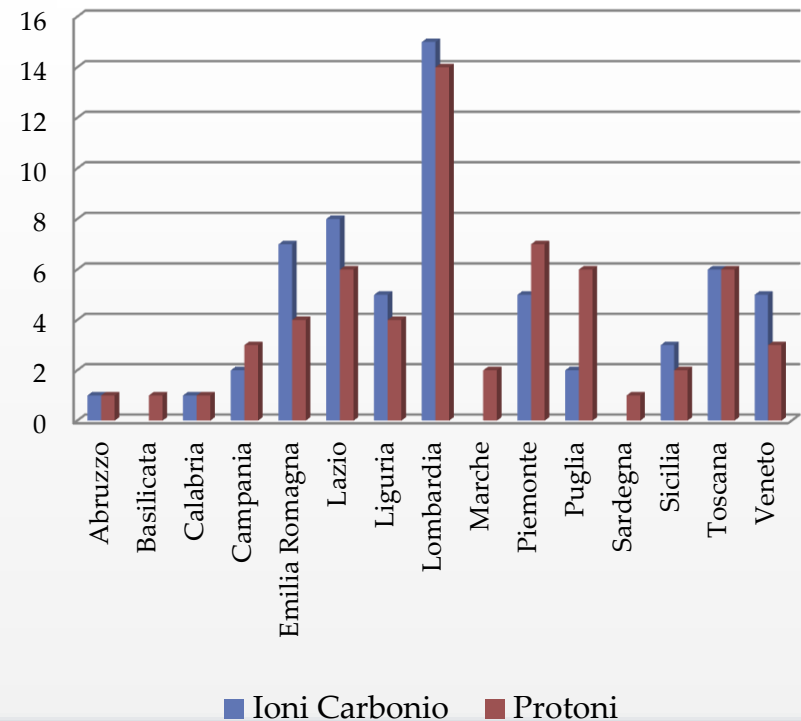
62 treated with Carbon ions

Cranium chordome and chondrosarcoma  
Sacral chordome and chondrosarcoma  
Intracranial meningioma  
Salivary glands carcinoma  
Trunk sarcoma  
Prostate carcinoma  
Aero-digestive mucosae melanoma

**Distribuzione geografica dei pazienti del CNAO**

22 Settembre 2011 – 26 Luglio 2013

Totale 124 pazienti



# Hadrontherapy first proposed by R. 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

**E**XCEPT 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 part, been due to the very short penetration in tissue of protons, deuterons, or alpha particles from present-day high-energy machines. However, the range of a proton in tissue is about 10 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 internally a strictly localized region of tissue.

Radiology 47: 487-491, 1946

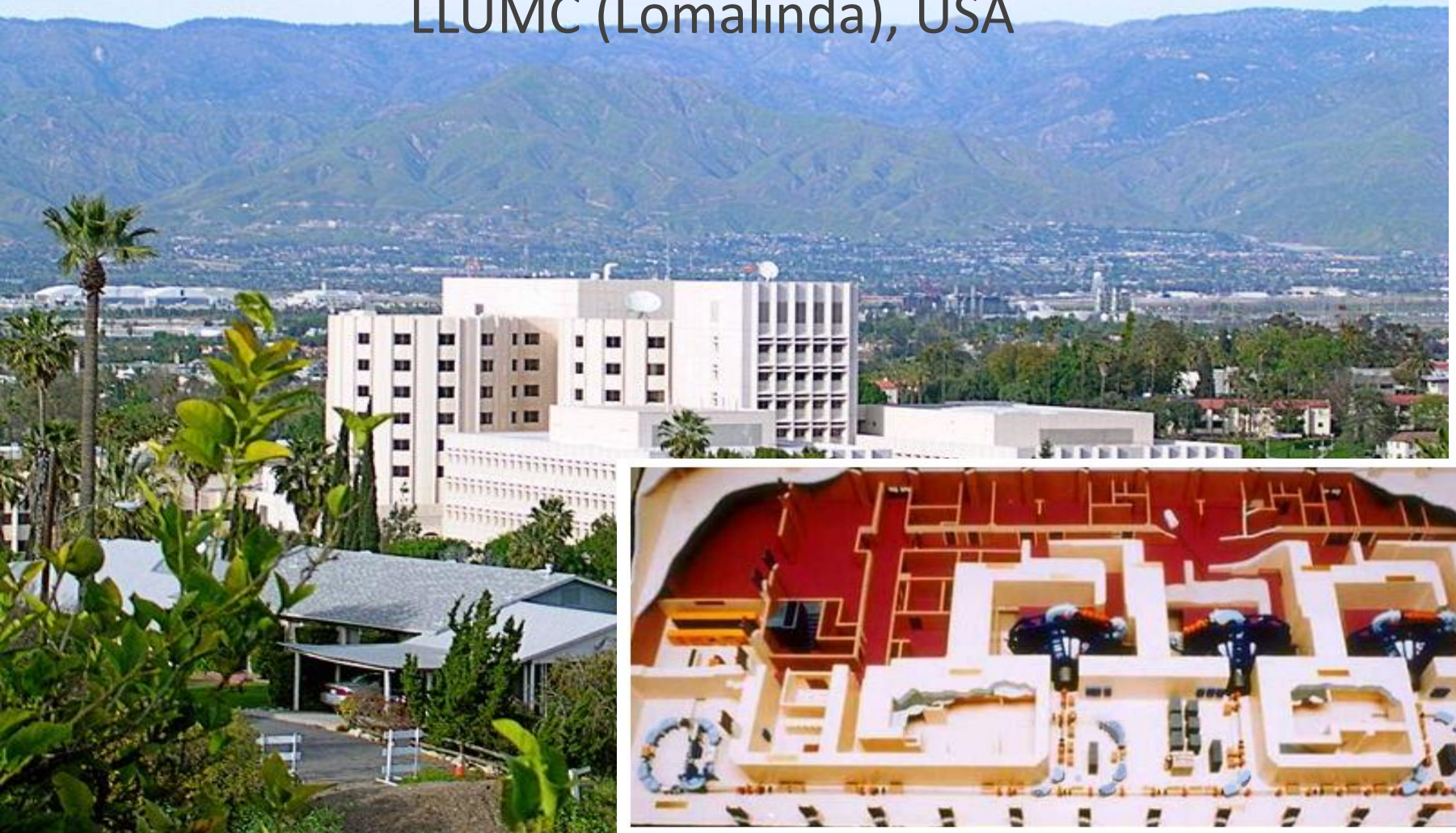
In 1954: 30 patients treated with protons at LBL (Lawrence Berkeley Laboratory)

In the next years other treatments in other research centers were performed

(Uppsala, Harvard, Dubna, St.Petersburg, Moscow, PSI, Chiba, Tsukuba)

In 1990 the first dedicated hospital facility has started treatments at Loma Linda (LLUMC)

# First dedicated hospital center for proton therapy: LLUMC (Lomalinda), USA

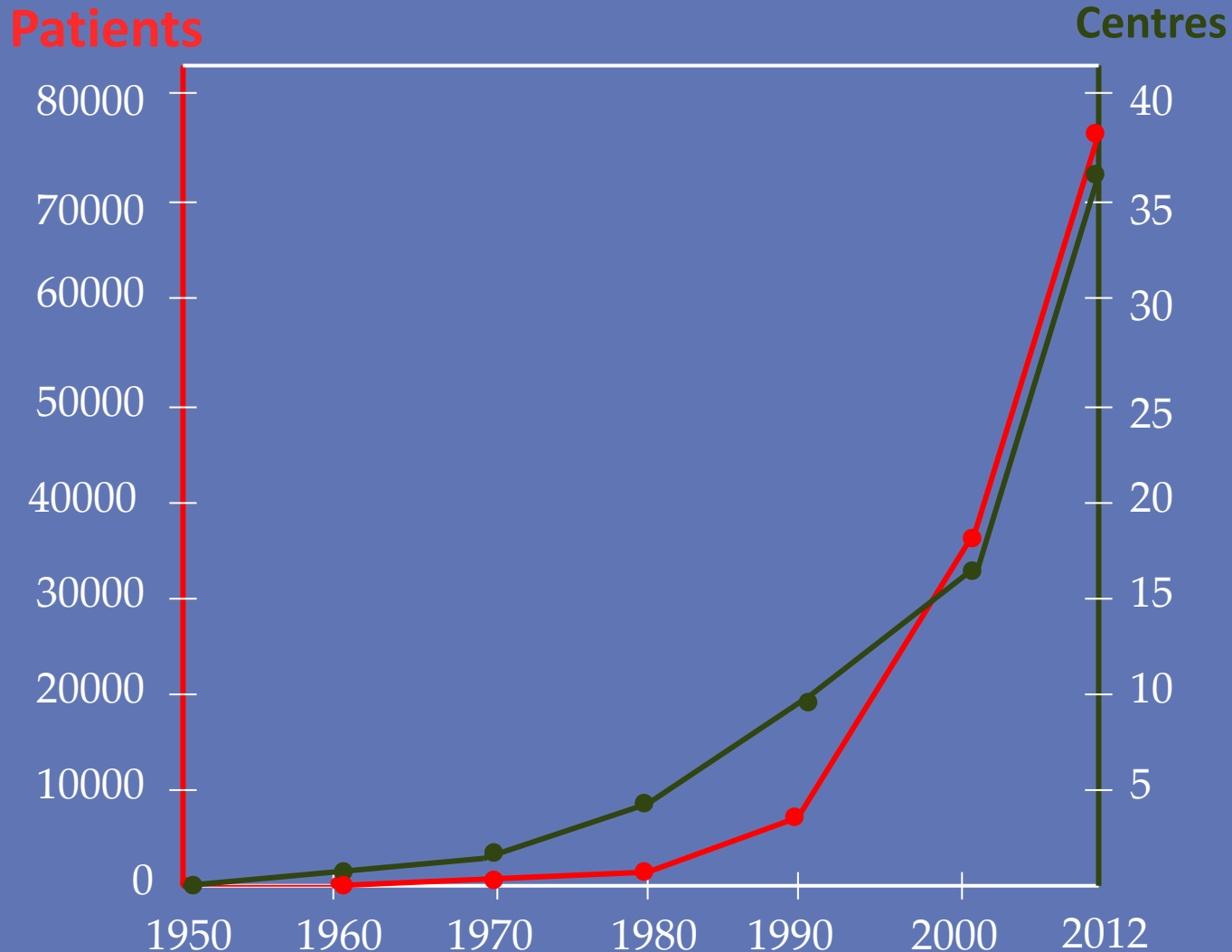


Proton synchrotron (70-250 MeV) equipped with a fixed beam room with two beam lines, three rotating gantries and a research room with three beam lines.  
To date over 15000 patients have been treated.



# Hadrontherapy history: Rapid Growth

## doubled in last decade



# Hadrontherapy in the world

TRIUMF(Vancouver),Canada

Uppsala , Sweden  
Clatterbridge, England  
Nice , France  
Orsay, France  
HZB(Berlin), Germany  
RPTC(Munich),Germany  
HIT(Heidelberg),Germany  
PSI(Villigen),Switzerland  
IFJ-PAN, Poland  
LNS(Catania), Italy  
CNAO (Pavia), Italy

ITEP(Moscow), Russia  
St. Petersburg, Russia  
Dubna, Russia  
WPTC(Zibo),China  
IMP(Langzhou), China  
NCC, South Korea

UCSF(California), USA  
LLUMC(Lomalinda),USA  
IUHealthPTC,(Bloomington),USA  
NPTC(Boston),USA  
MDACC(Houston),USA  
UFPTI(Jacksonville),USA  
Upenn(Philadelfia),USA  
CDH(Warrenville),USA  
HUPTI(Hampton),USA  
Procure PTC(New Jersey),USA  
Procure PTC(Oklahoma),USA

NCC (Kashiwa), Japan  
PMRC (Tsukuba), Japan  
WERC (Shizuoka), Japan  
PATRO (Hyogo),Japan  
HIMAC (Chiba),Japan  
GHMC (Gunma),Japan  
STPTC(Koriyama),Japan  
Medipolis Medical Research  
Institute (Ibusuki), Japan

iThemba LABS, South Africa

~ 80000 patients (8000 with Carbon ions)



# Hadrontherapy in the world: Cyclotrons

TRIUMF(Vancouver),Canada

Uppsala , Sweden  
Clatterbridge, England  
Nice , France  
Orsay, France  
HZB(Berlin), Germany  
RPTC(Munich),Germany  
PSI(Villigen),Switzerland  
IFJ-PAN, Poland  
LNS(Catania), Italy

Dubna, Russia  
WPTC(Zibo),China  
NCC, South Korea

NCC (Kashiwa), Japan

iThemba LABS, South Africa

UCSF(California), USA  
IUHealthPTC,(Bloomington),USA  
NPTC(Boston),USA  
UFPTI(Jacksonville),USA  
Upenn(Philadelfia),USA  
CDH(Warrenville),USA  
HUPTI(Hampton),USA  
Procure PTC(New Jersey),USA  
Procure PTC(Oklahoma),USA

24 cyclotron facilities



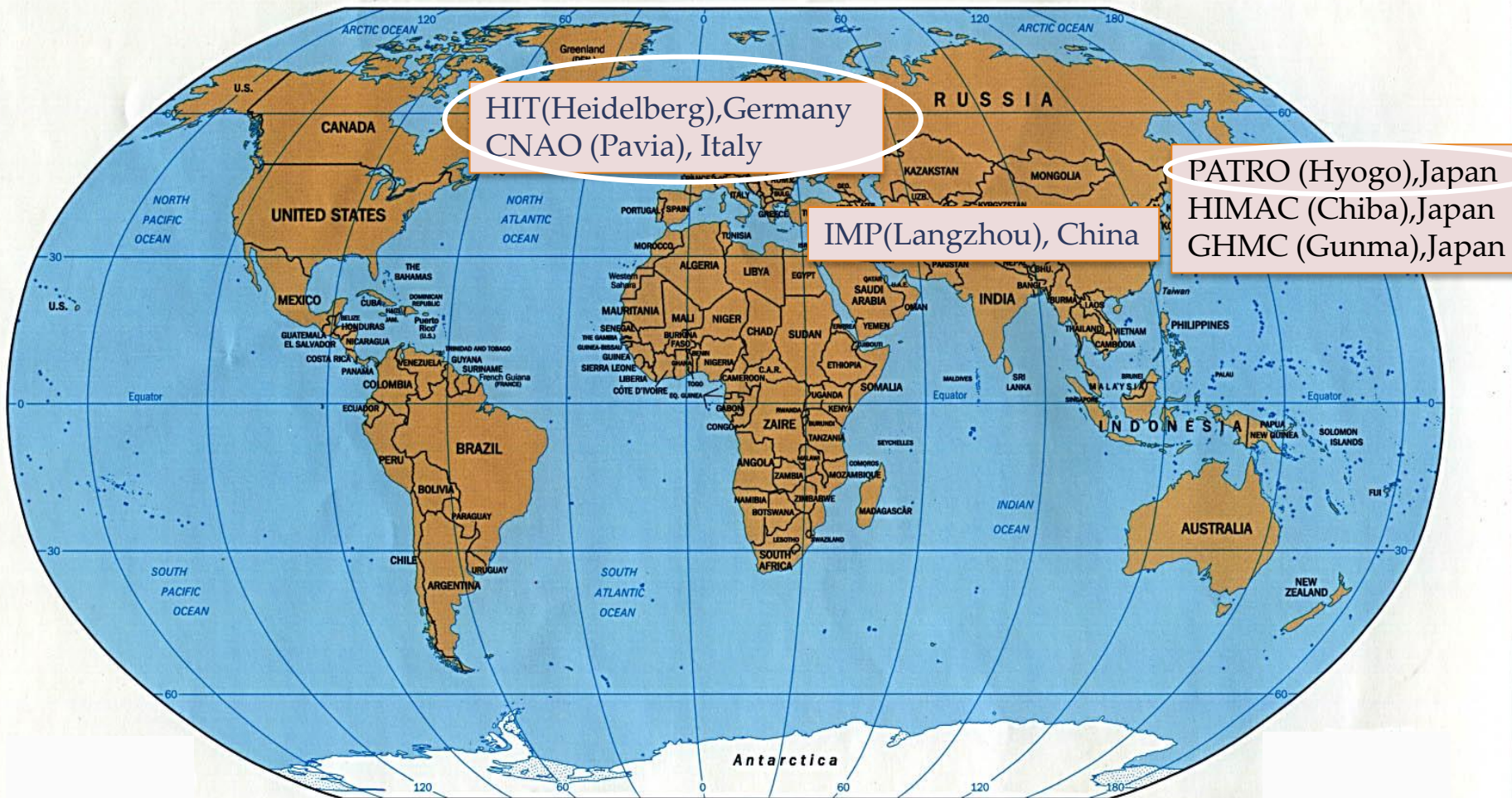
# Hadrontherapy in the world: Synchrotrons



14 synchrotron facilities



# Hadrontherapy in the world: Carbon Synchrotrons

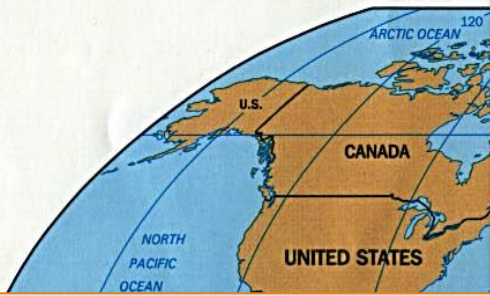


6 carbon synchrotron facilities:

only HIT, CNAO and PATRO produce both clinical protons and carbon ions



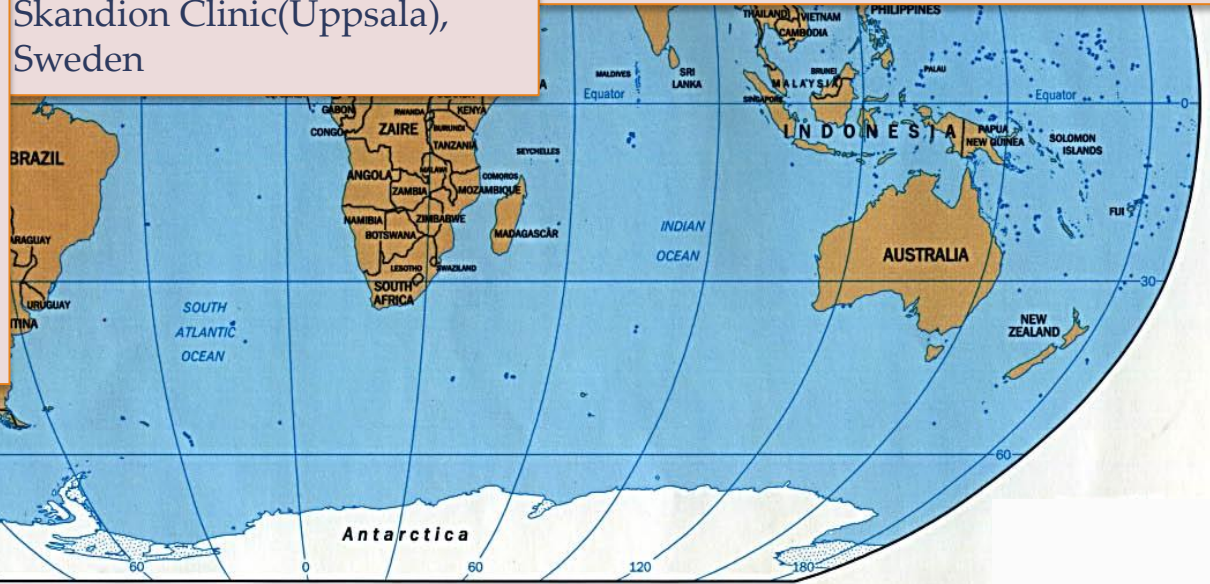
# Hadrontherapy in the world: New facilities (under construction or ready to start)



PSI(Villigen),Switzerland  
 PTC(Prague), Czech.Rep.  
 MedAustron  
 (Wiener Neustadt),Austria  
 ATREP(Trento),Italy  
 WPE(Essen),Germany  
 CMHPTC(Ruzomberok),  
 Slovak Rep.  
 CCSR(Bratislava),Slovak Rep.  
 Skandion Clinic(Uppsala),  
 Sweden

FudanUniversity(Shanghai), China  
 HITFil(Lanzhou),China  
 Chang Gung Memorial Hospital(Taipei),  
 Taiwan  
 PMHPTC(Protvino),Russia  
 SJFH(Beijing), China  
 Samsung Proton Center(Seoul), South  
 Korea

MCLarenPTC(Michigan),USA  
 Northern Illinois PT Res.Institute,  
 Chicago, USA  
 Barnes Jewish (St. Louis), USA  
 Scripps Proton Therapy Center(San  
 Diego),USA  
 SCCA Proton Therapy,(Seattle)USA



USA, Europe, Asia: 12 proton cyclotrons; 2 proton-carbon synchrotrons;  
 2 proton synchrotrons; 1 carbon synchrotron; 1 proton synchro-cyclotron

# Hadrontherapy business

The idea of hadrontherapy facilities has passed from the research field to the business field with several commercial firms:

IBA, Hitachi, Mitsubishi, Sumitomo, Varian, Still River, Optivus, Siemens

... Hadron therapy is the epitome of a multidisciplinary and transnational venture: its full development requires the competences of physicists, physicians, radiobiologists, engineers and IT experts, as well as collaboration between research and industrial partners.

The translational aspects are extremely relevant because the communities involved are traditionally separate and they have to learn to speak the same "language". Ions that are considered "light" by physicists, such as carbon, are "heavy" for radiobiologists – and this is just one of many examples (from Cern Courier, Nov 23, 2011)

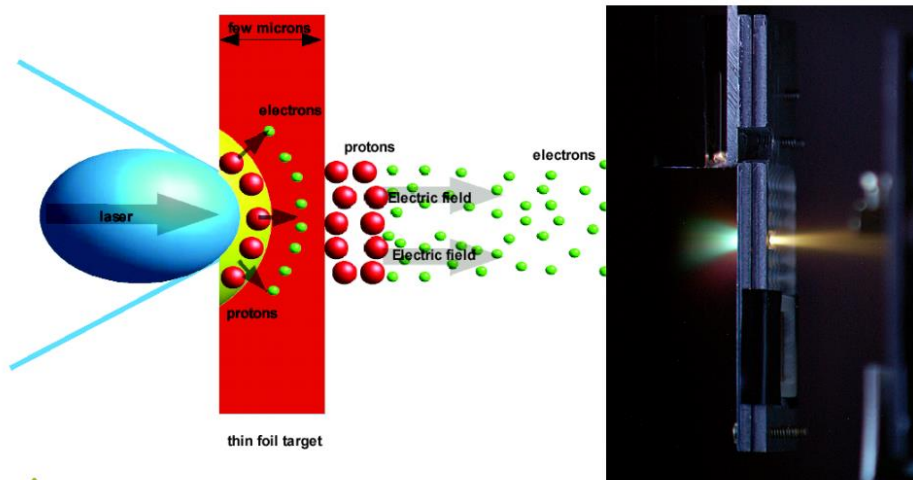


# Hadrontherapy future

Worldwide R&D for more compact and/or advanced accelerators:

- FFAG: Fixed Field alternating Gradient: in the middle between a cyclotron and a synchrotron. DC beam with fast energy change! The radius change slightly because B changes with the radius. A fast energy change could be a good solution in treating moving organs

## Protons acceleration with lasers : Static electric fields



<http://loa.ensta.fr/>

EUCARD, first annual meeting, RAL, UK, April 13-16 (2010)

UMR 7639



- LIBO: Linac Booster Linac @ 3 GHz, 27MV/m for protons from 30 MeV to 250 MeV exploiting the standard 30 MeV cyclotrons for radioisotopes as injector.
- Laser Plasma acceleration: heavy ions acceleration by high power lasers
- DWA: dielectric wall induction linac: new dielectrics 100 MV/m (instead of 10) 250 MeV proton linac 3 m long

# Acknowledgements

- To all CNAO Team, with whom I shared three years of work during the commissioning of the facility, to Marco Pullia and Erminia Bressi, for all the information and fruitful discussions, and specially to Luciano Falbo, from whom I have borrowed most of the slides (talk at HIAT2012, Chicago, <http://www.phy.anl.gov/hiat12/Proceedings/papers/proceed.pdf>, p. 156)