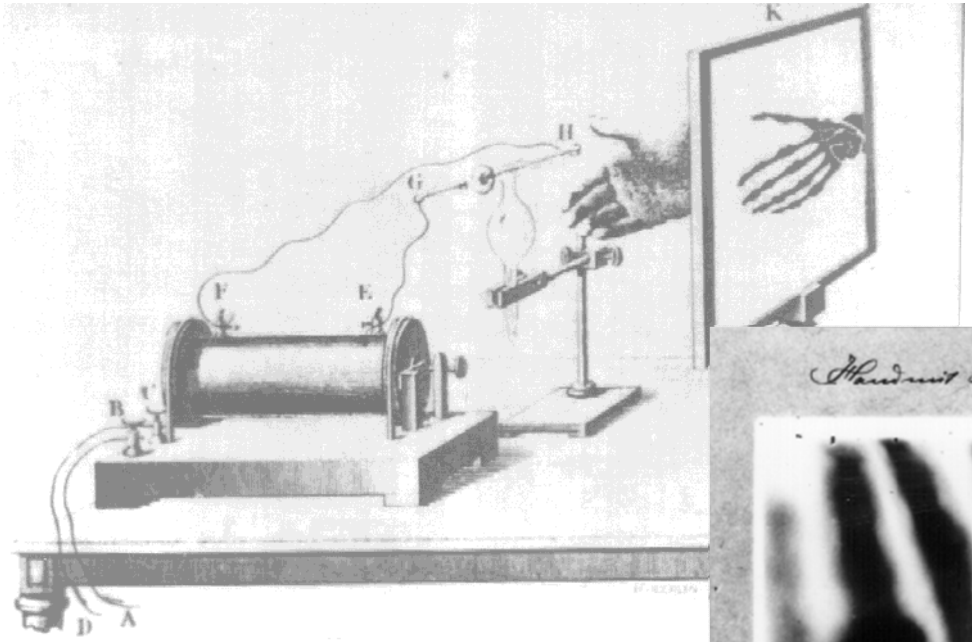
At the forefront of radiotherapy

M. Pullia

OMA School, June 6th, 2017

fondazione CNAO
Centro Nazionale di Adroterapia Oncologica

Physics and medicine together since long: diagnosis and therapy



1895

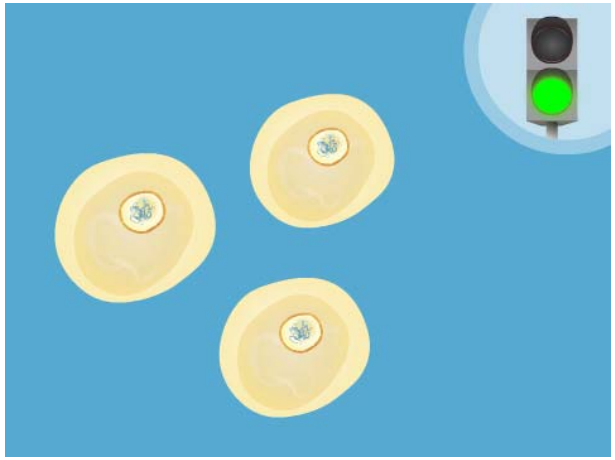
X ray discovery

(courtesy of U. Amaldi)

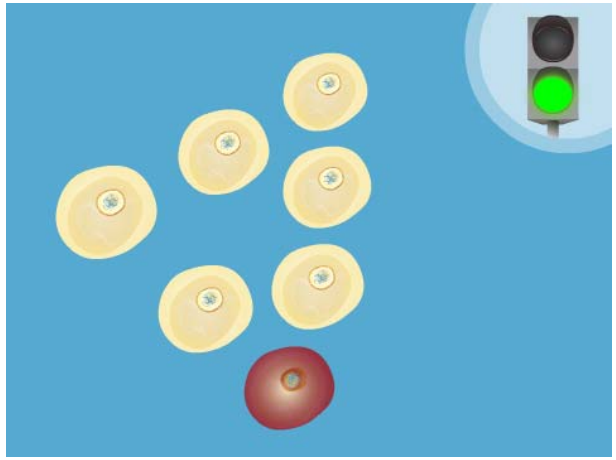
Wilhelm Conrad Röntgen

(1845 – 1923)

Cells multiply



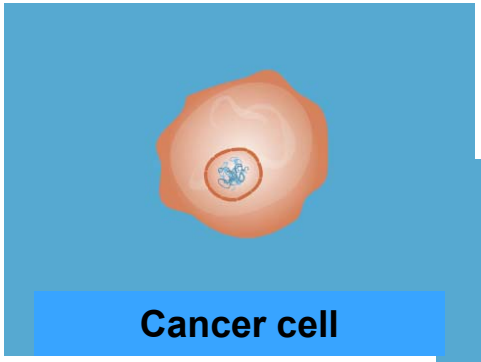
Normally cells multiply only when they are told so



If there is a mutation (DNA error)…

…the cell is told to suicide (apoptosis)

Tumour



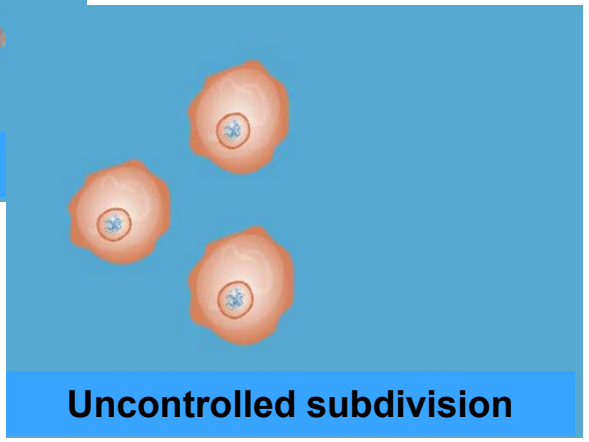
Cancer cell

Something (else) goes wrong and the mutant cell refuses to die …

No response to control signals

No apoptosis

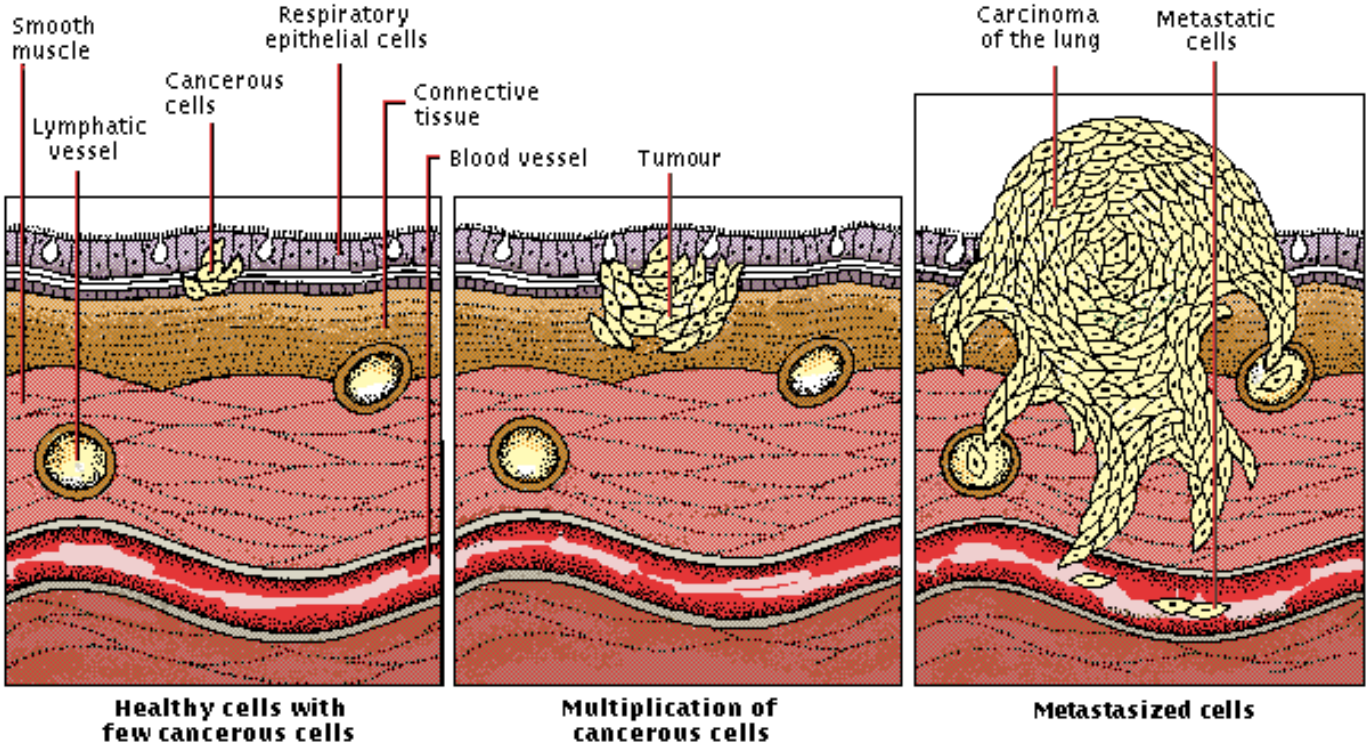
TUMOUR!



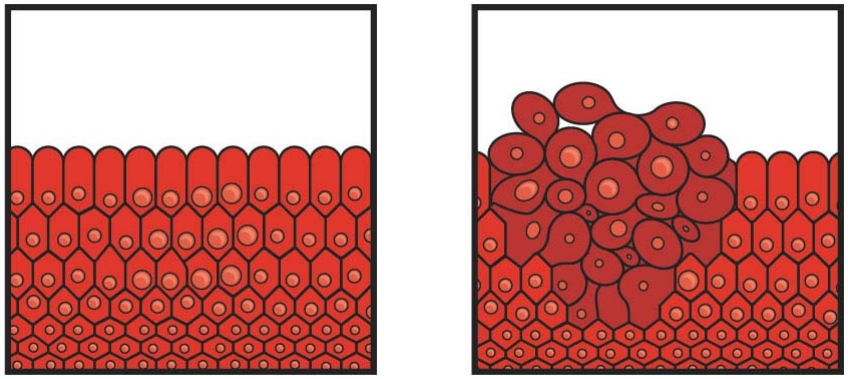
Uncontrolled subdivision

… and begins to multiply in an uncontrolled way

Tumour



(Courtesy of http://www.macmillan.org.uk)



Normal cells

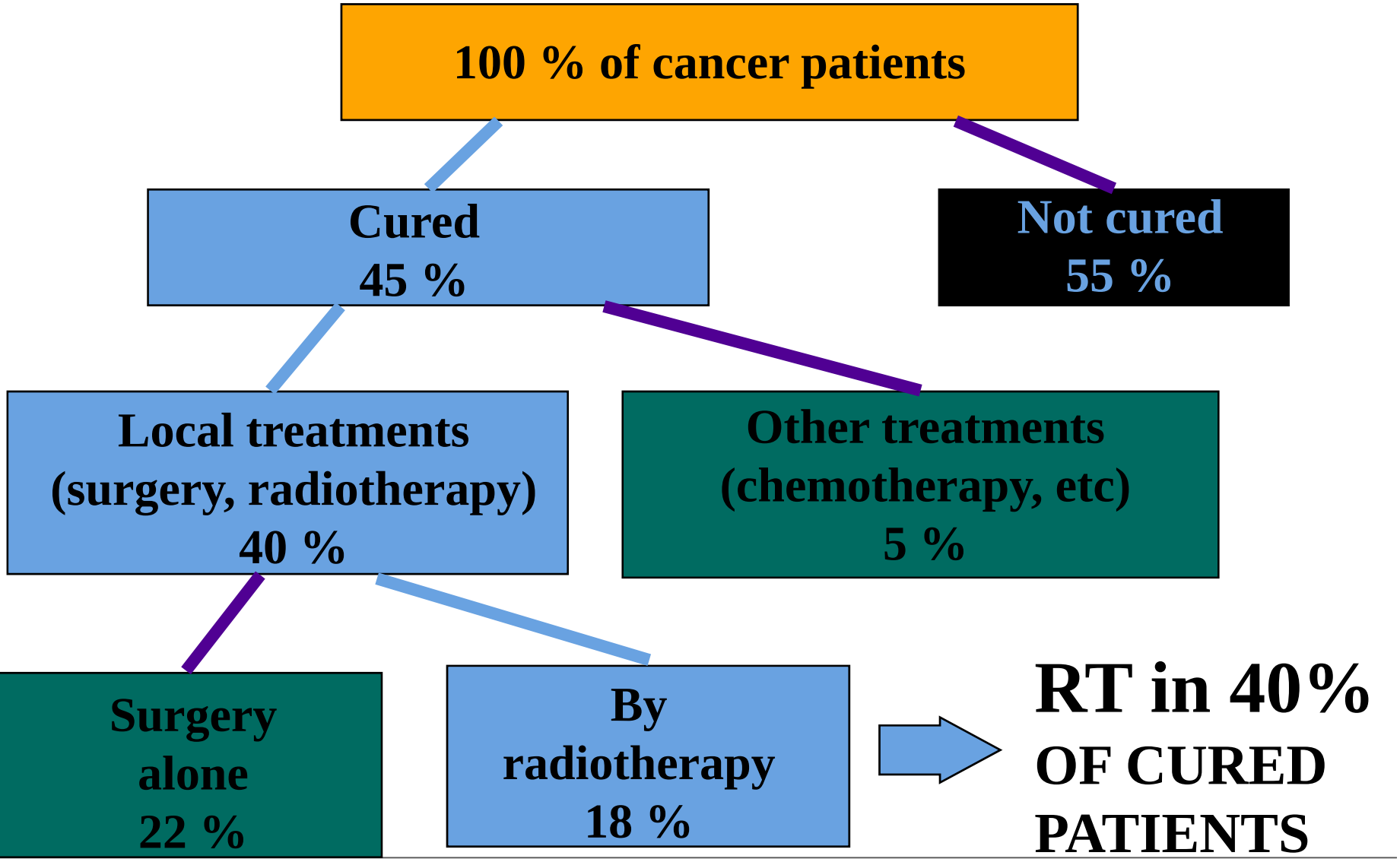
Cells forming a tumour

Cancer cells grow uncontrolled, infiltrate the surrounding tissues and can originate metastasis (malignant)

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

Cancer therapy



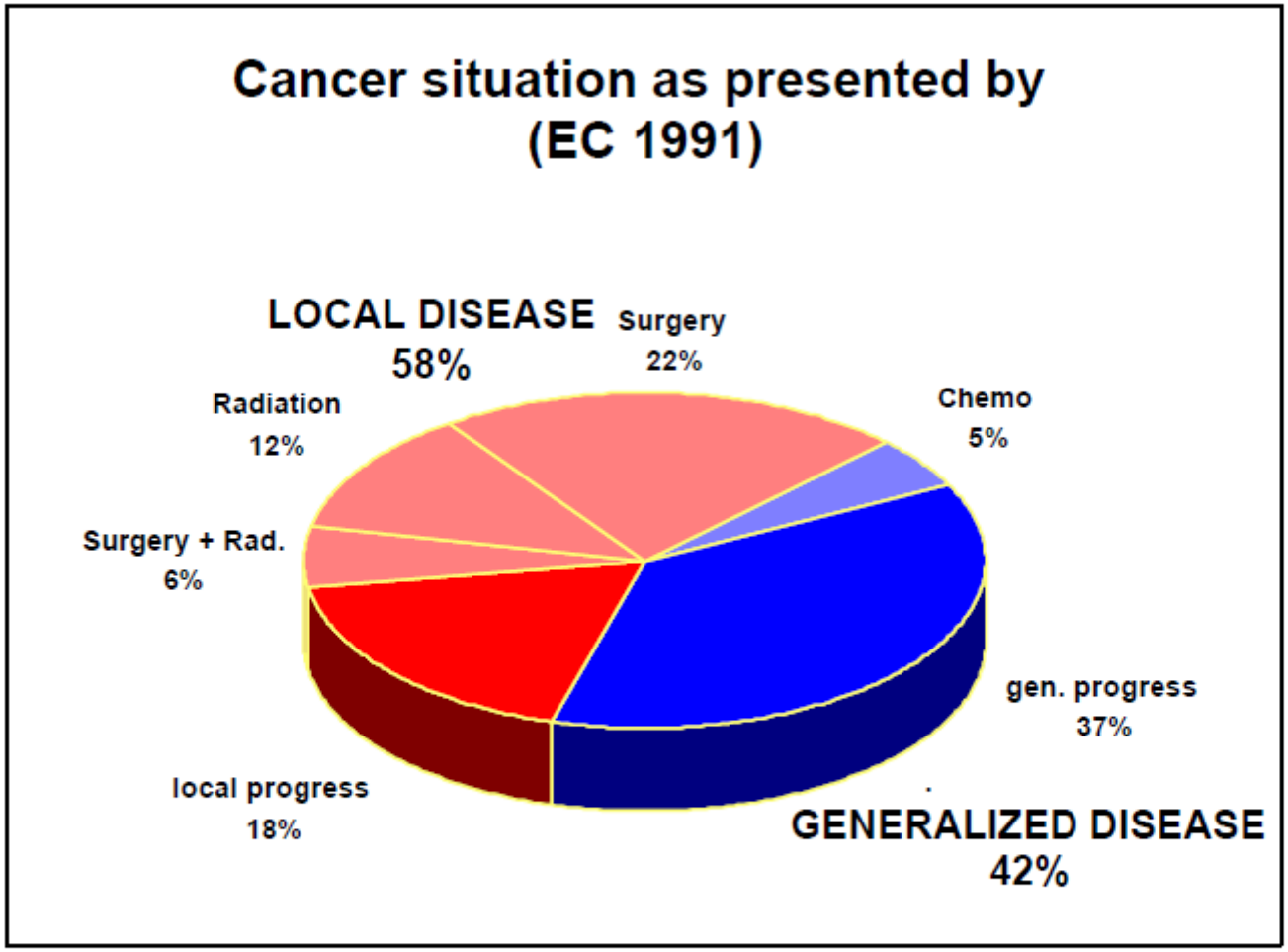
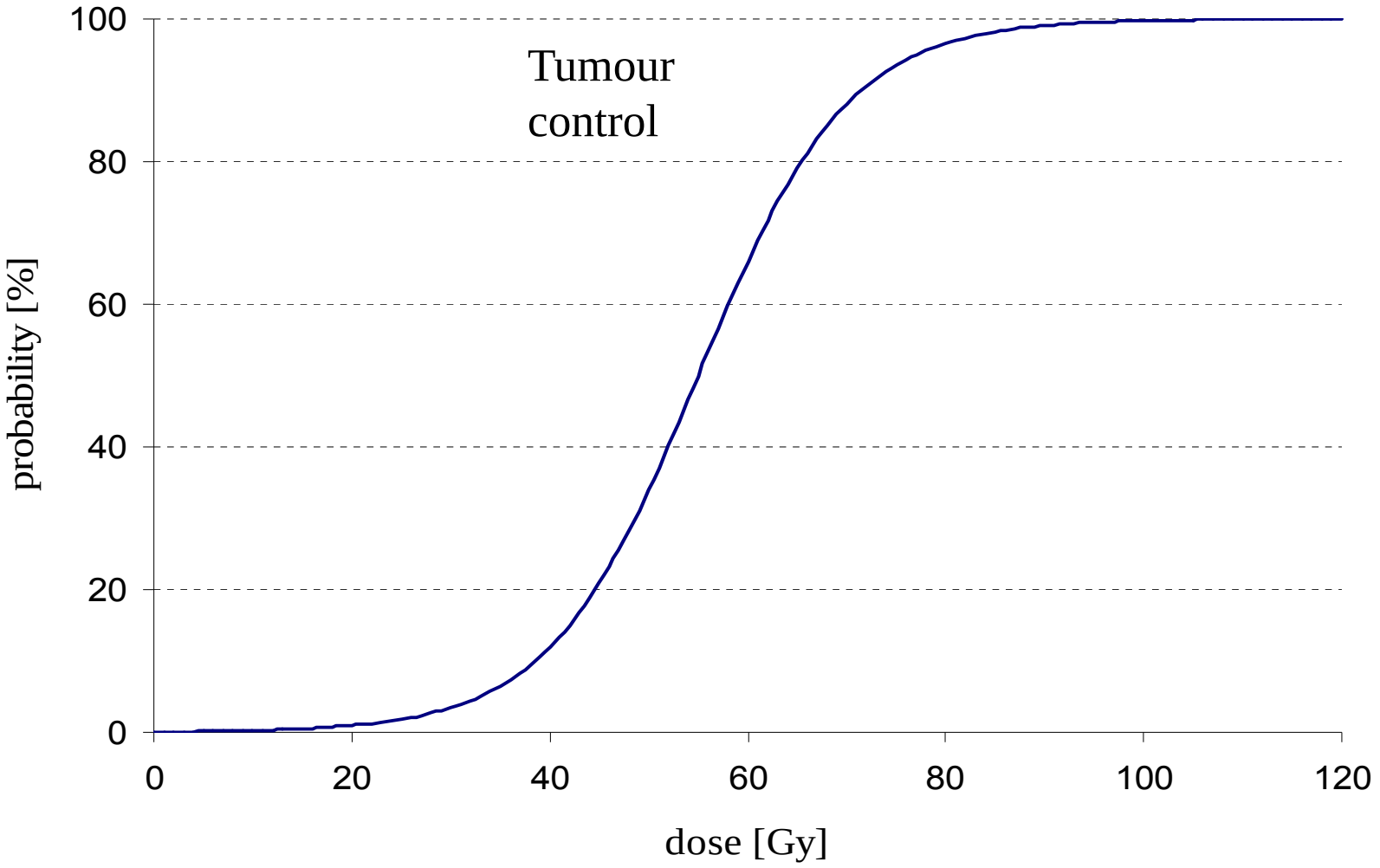


Figure 1: Distribution of the more than one million new cancer patients in Europe: Local disease (red fraction) are patients with only one well-defined tumor in the beginning. Generalized i.e. more than on tumor are given in blue. Nearly 50 % of the patients yielded a 5 year tumor free survival by the different treatment modalities but 18 % of patients with local deseases in the beginning cannot be curied. These are the candidates for particle therapy.

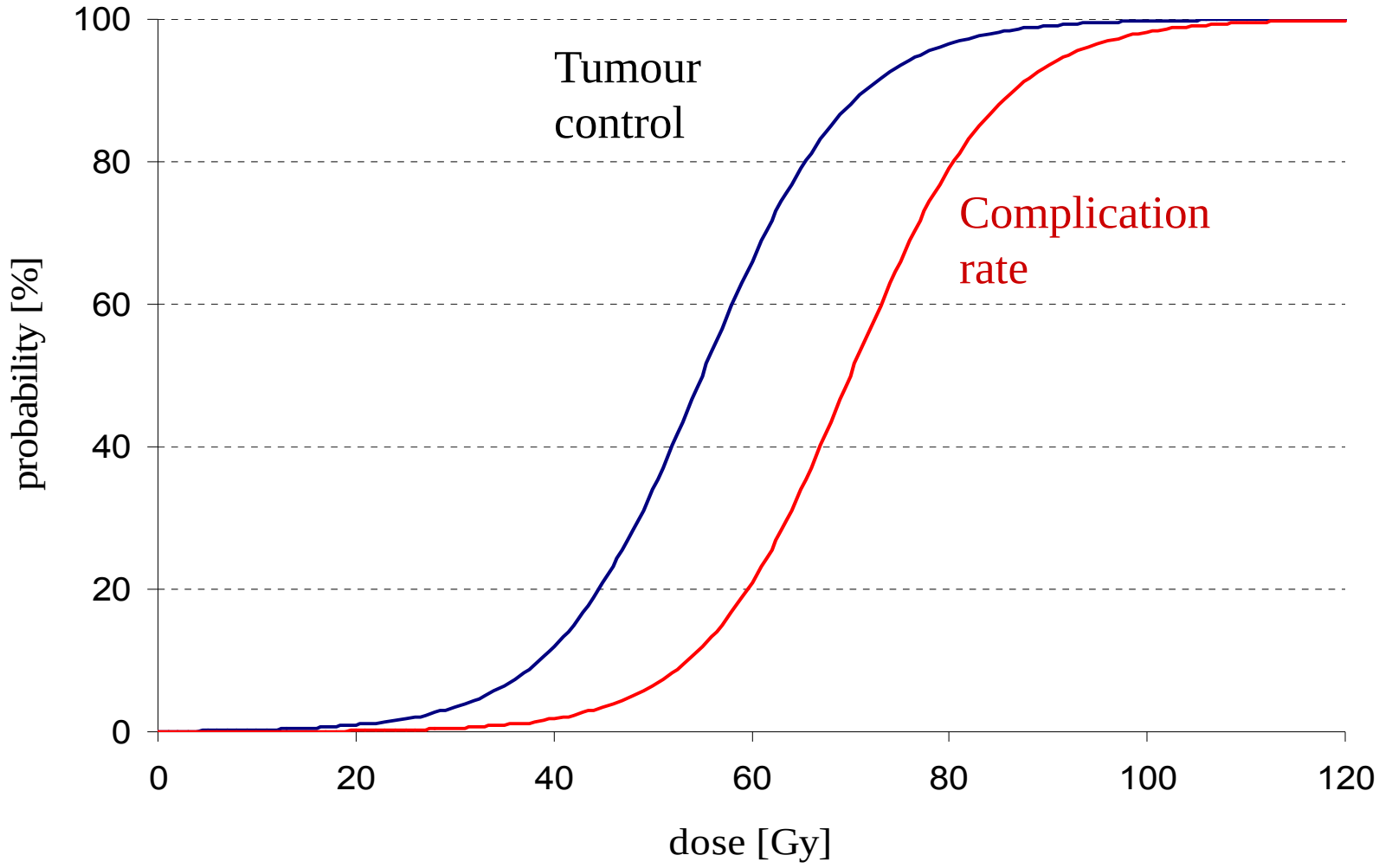
Radiation damage

- 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

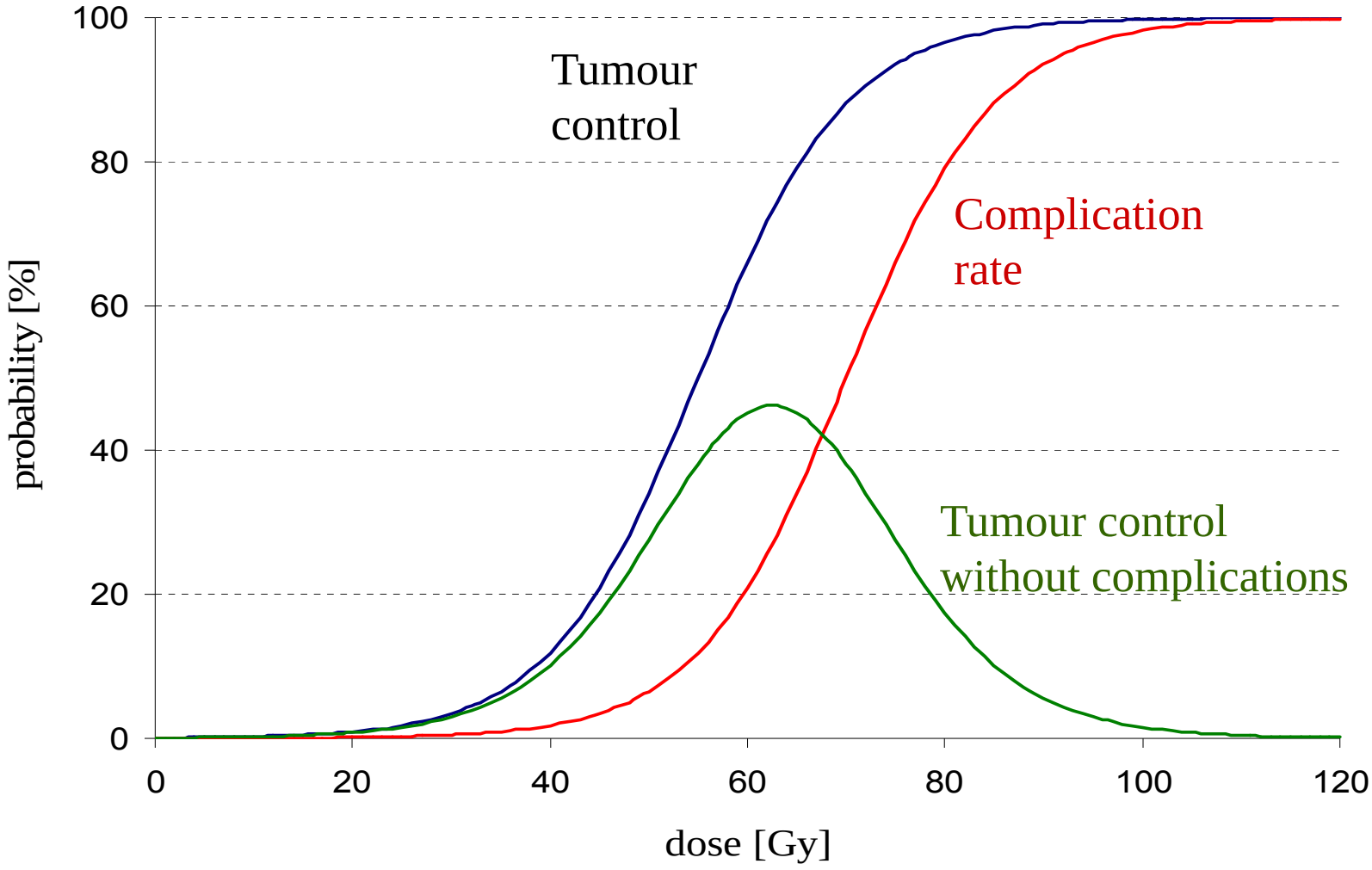
General principle of radiation therapy



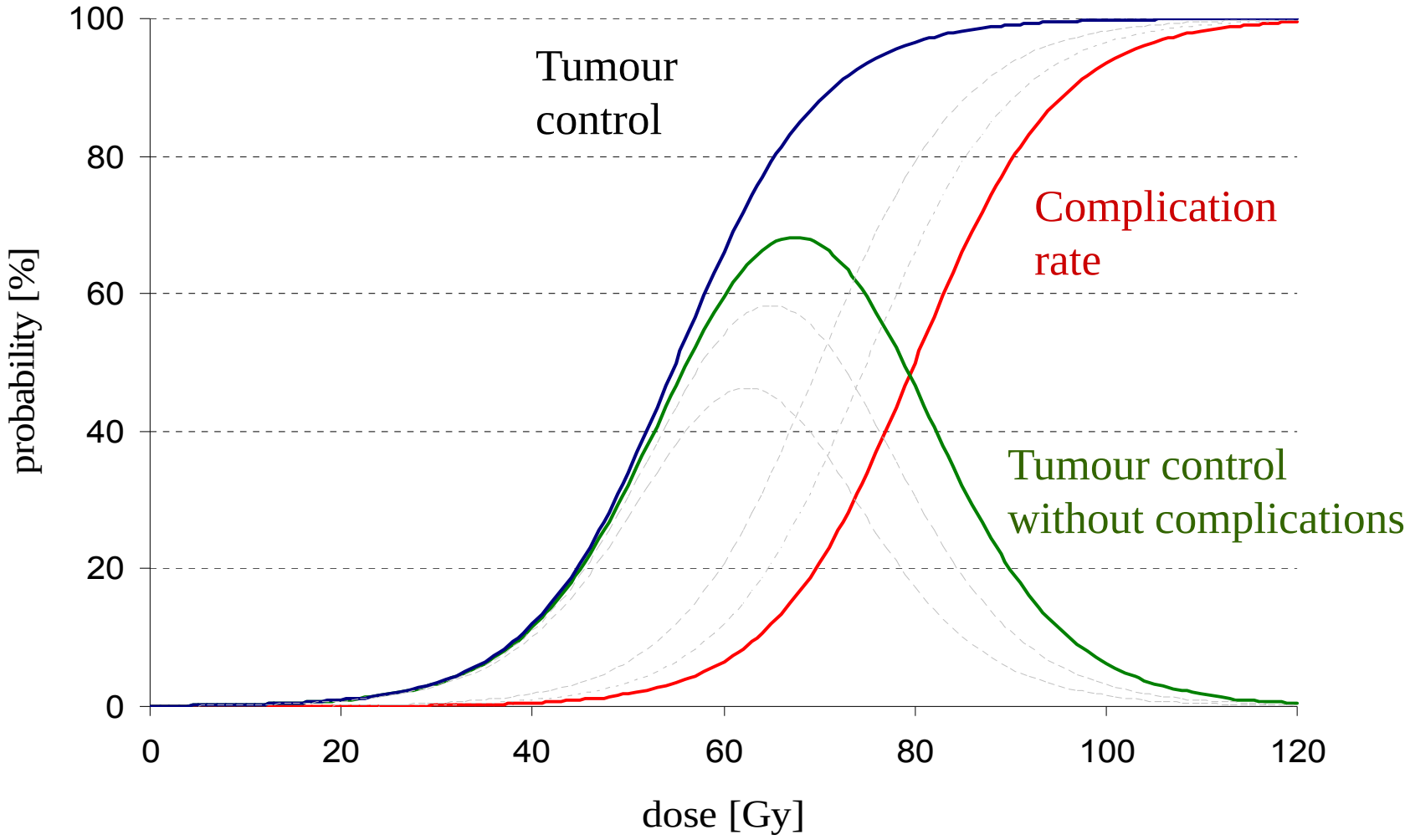
General principle of radiation therapy



General principle of radiation therapy



General principle of radiation therapy



Macroscopic (geometric) advantage of hadrons

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

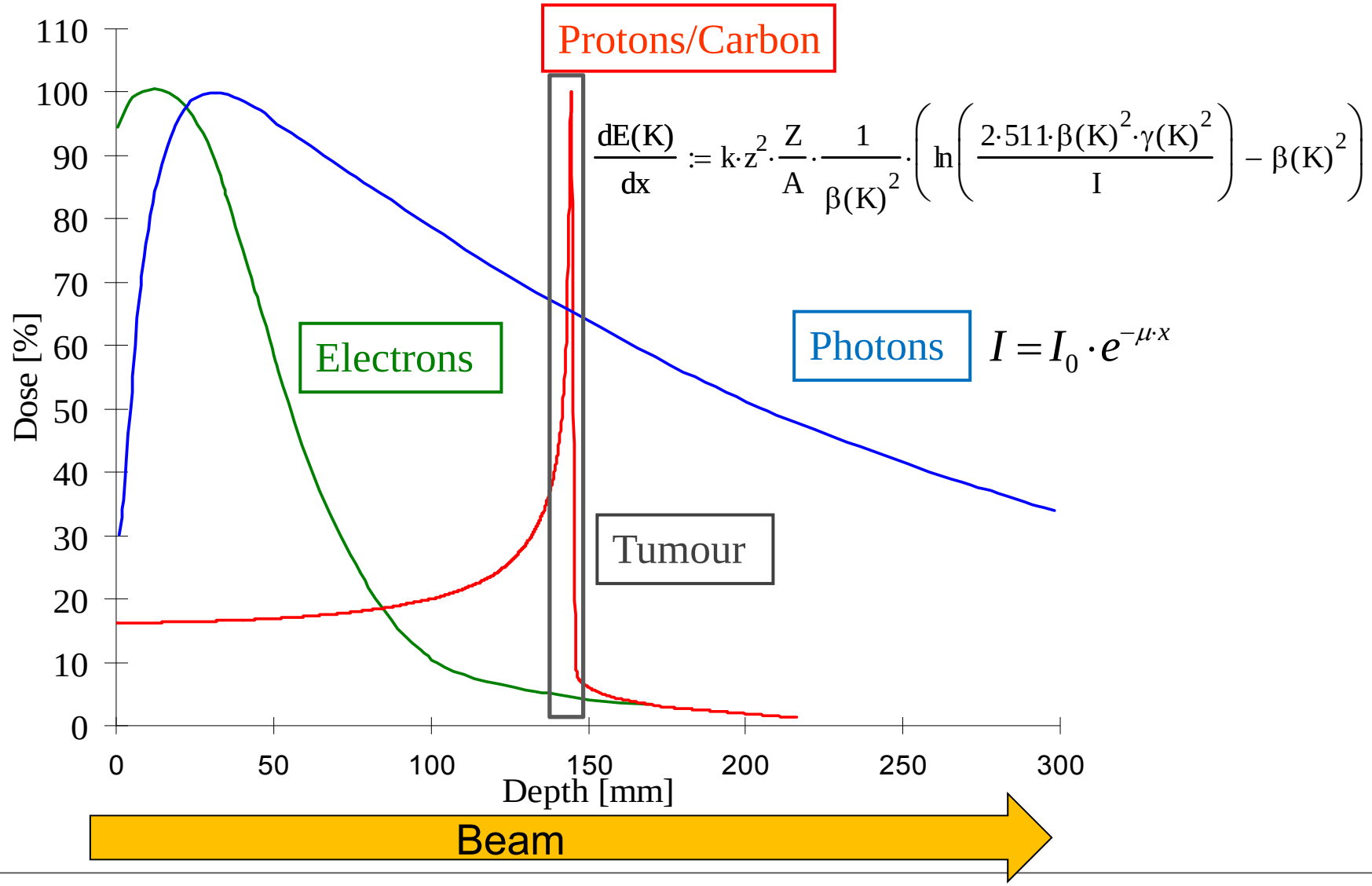
EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly, used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles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

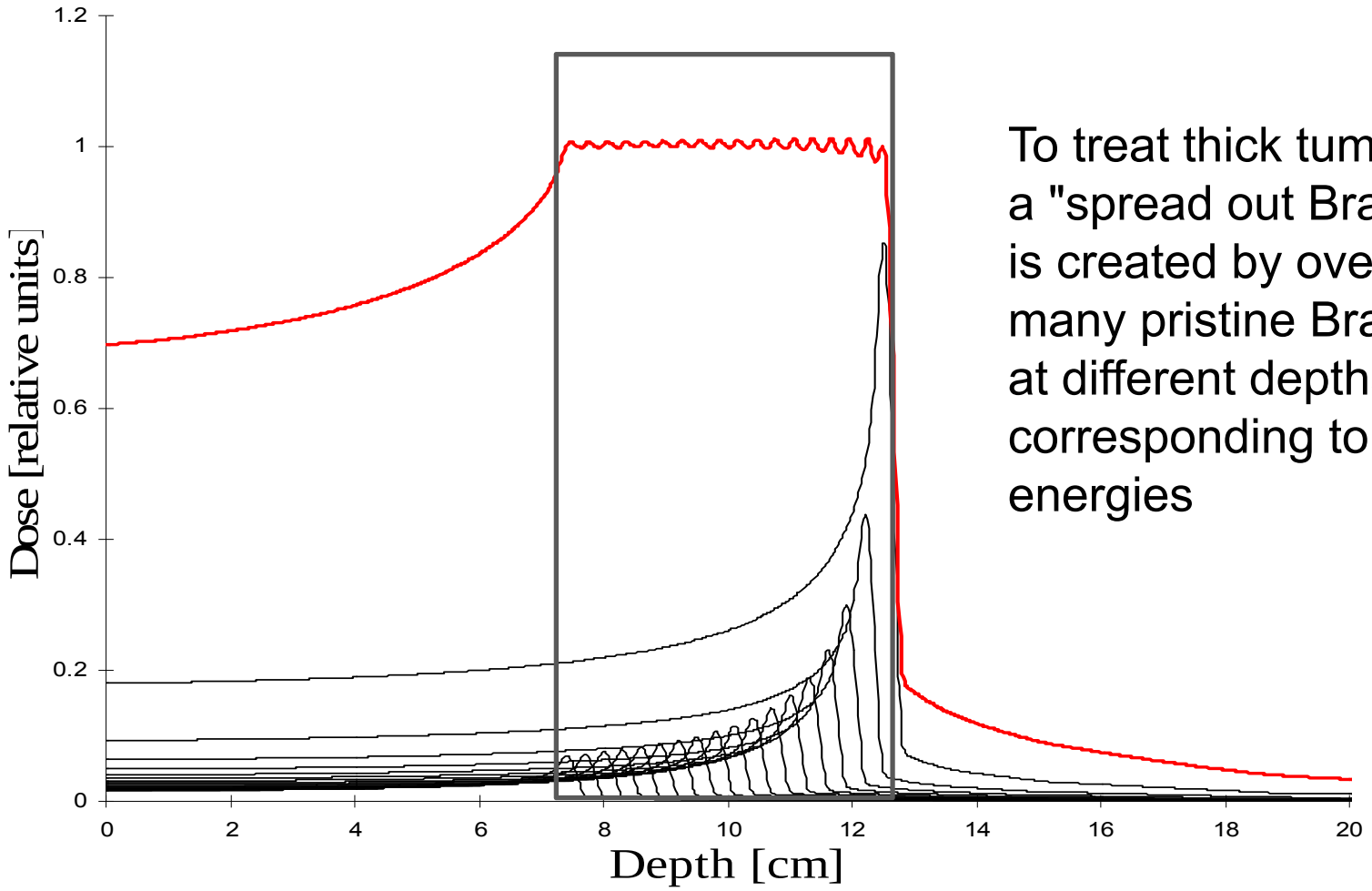
These properties make it possible to irradiate intern...ly a strictly localized region ...

Radiology 47: 487-491, 1946

Comparison of the depth dose profiles

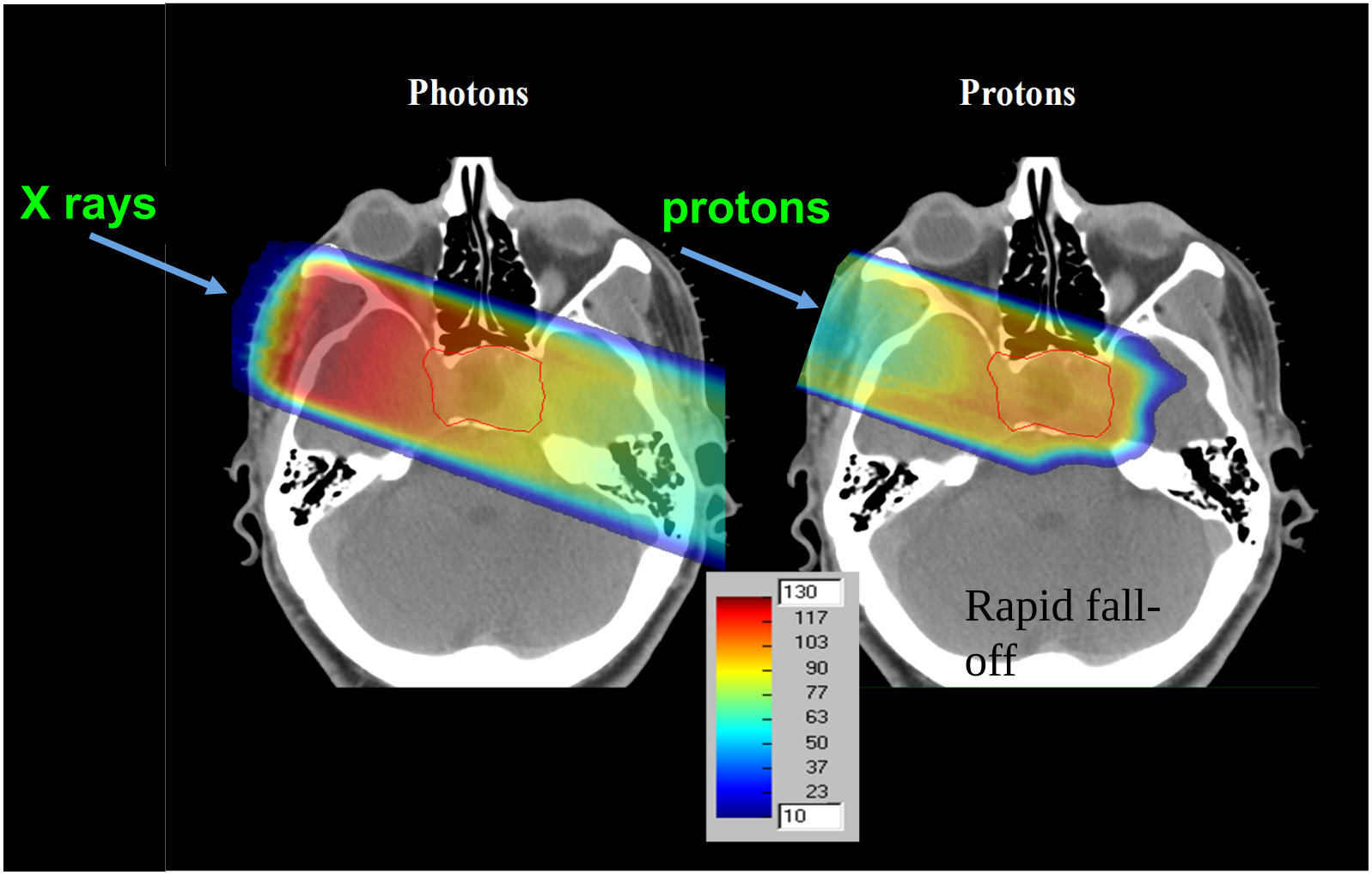


Tumour thickness - Spread Out Bragg Peak



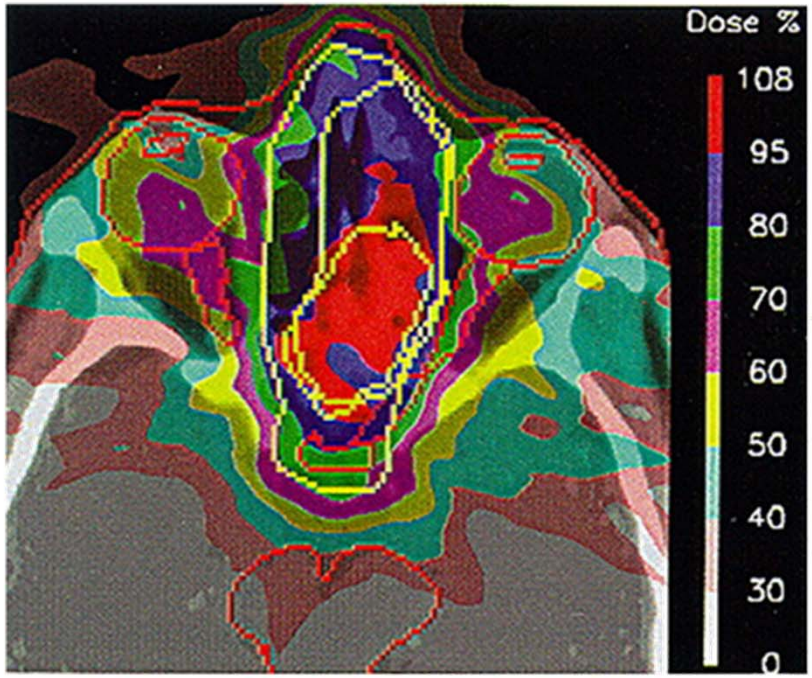
To treat thick tumours a "spread out Bragg peak" is created by overlapping many pristine Bragg peak at different depths, corresponding to different energies

Macroscopic advantage of hadrons

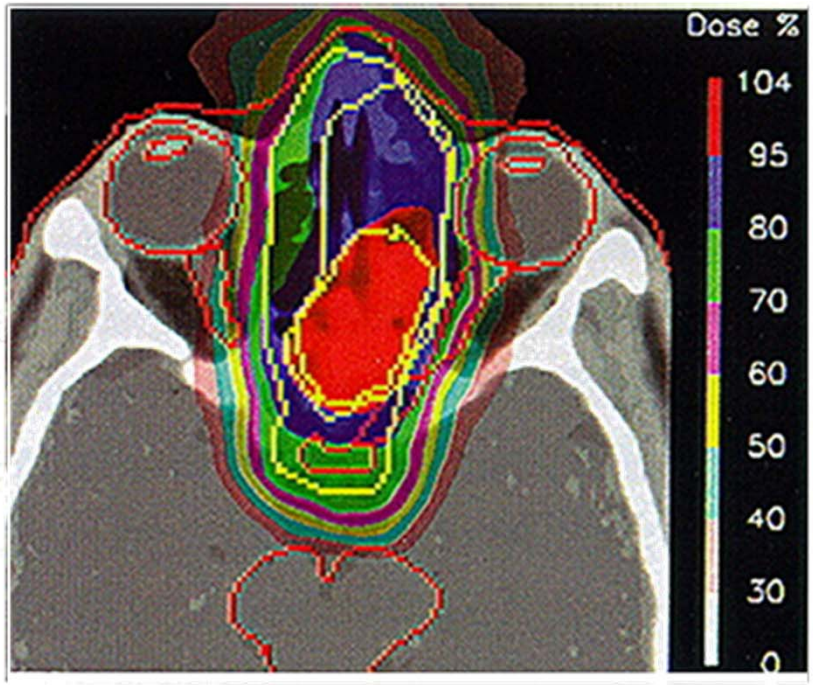


Better dose distribution

9 X beams



1 proton beam



tumor between eyes

Difference at microscopic level

Radiation damage (repeat)

- 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

If cells are irradiated with x-rays, many breaks of a single strand occur. In intact DNA however single strand breaks are of little biological consequence because they are repaired readily using the opposite strand as template.

If the repair is incorrect (misrepair), it may result in a mutation.

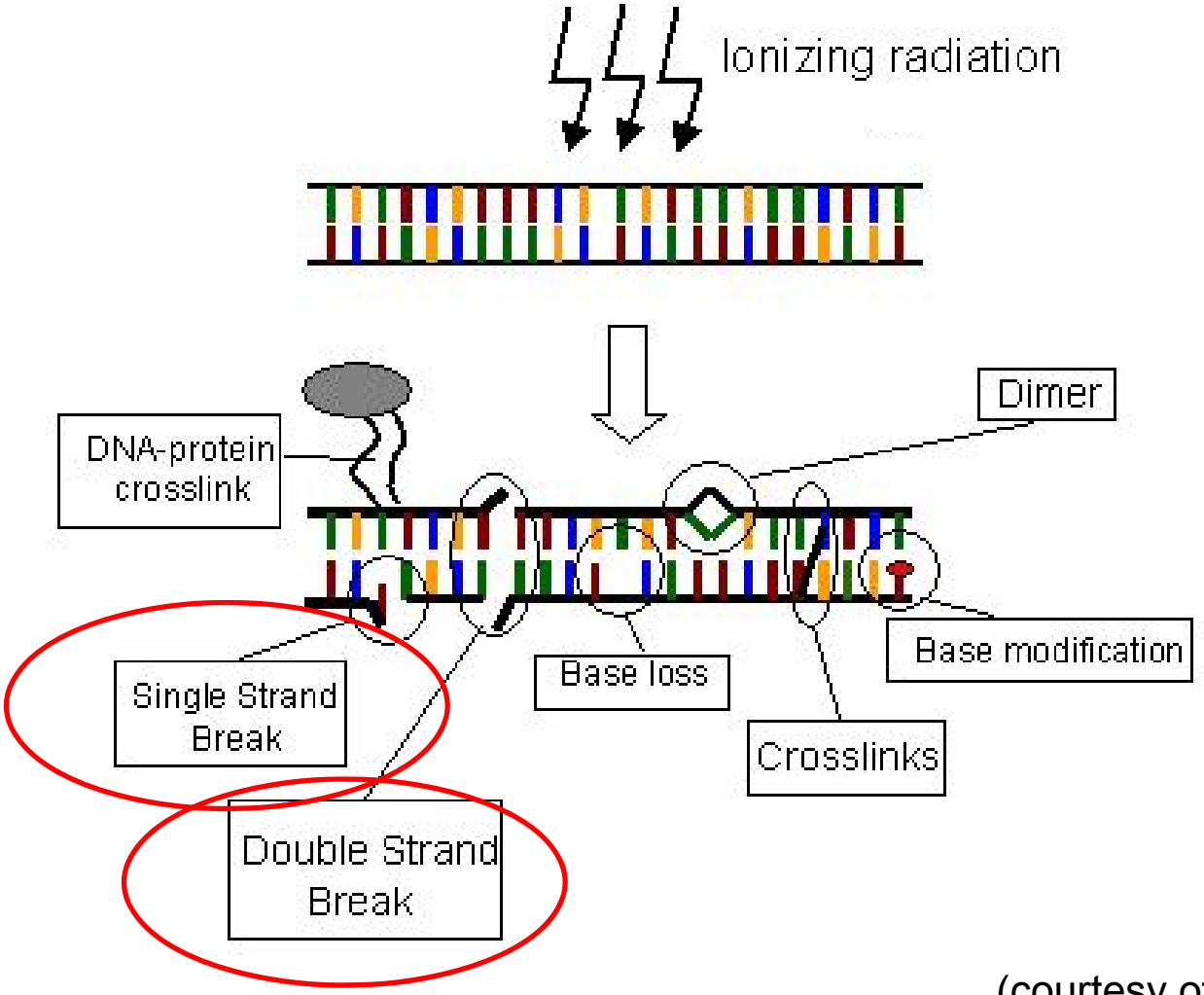
If both strands of the DNA are broken, and the breaks are well separated, repair again occurs readily because the two breaks are handled separately.

By contrast, if the breaks in the two strands are opposite one another, or separated by only a few base pairs, this may lead to a double strand break (DSB).

A DSB is believed to be the most important lesion produced in chromosomes by radiation.

(courtesy of A Facoetti)

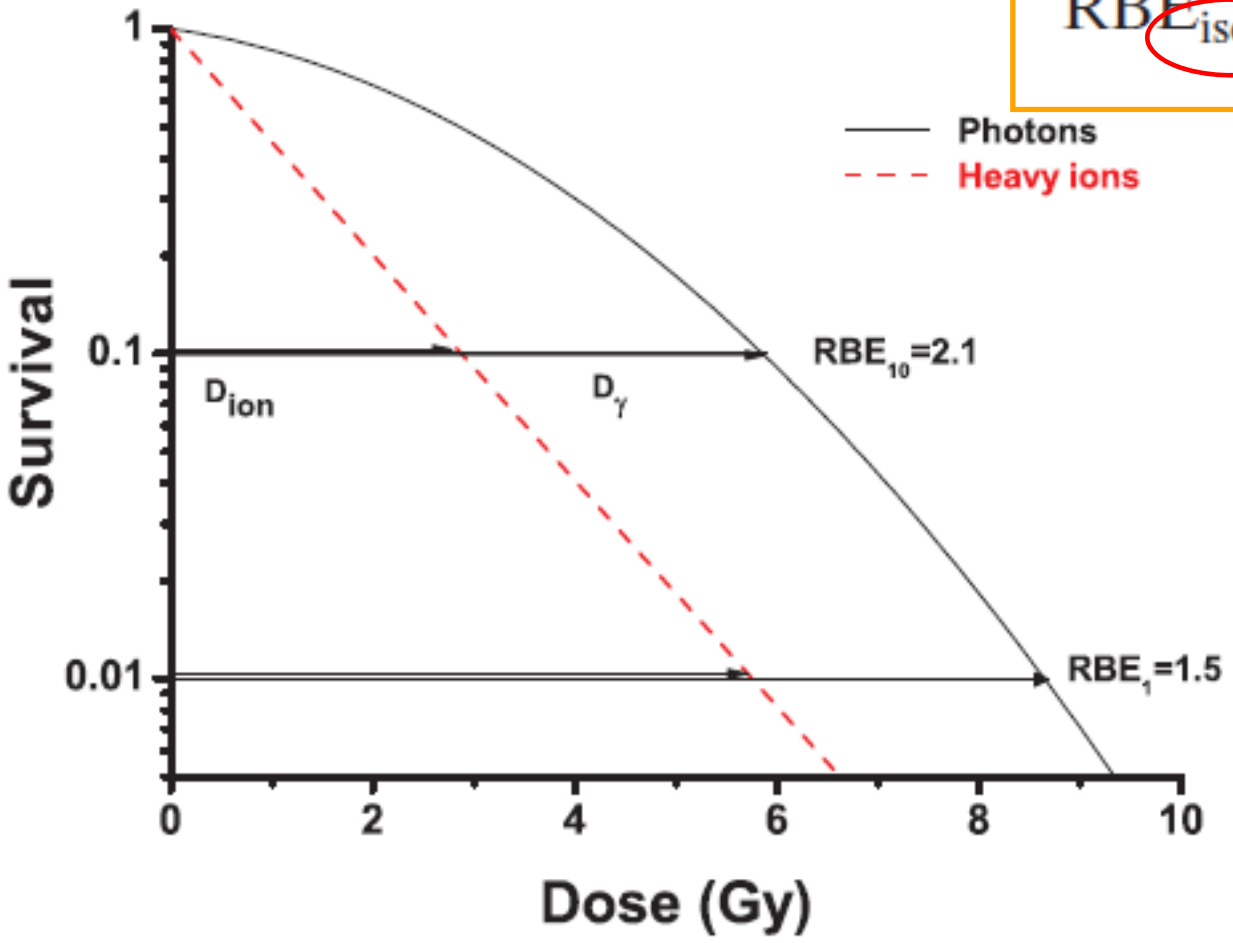
DNA damages



(courtesy of A Facoetti)

Comparing different radiations

$$RBE_{iso} = \frac{D_{ref}}{D_{ion}}.$$



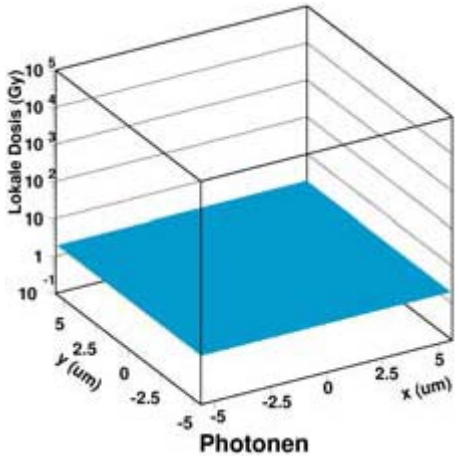
Schardt & Elsasser, 2010

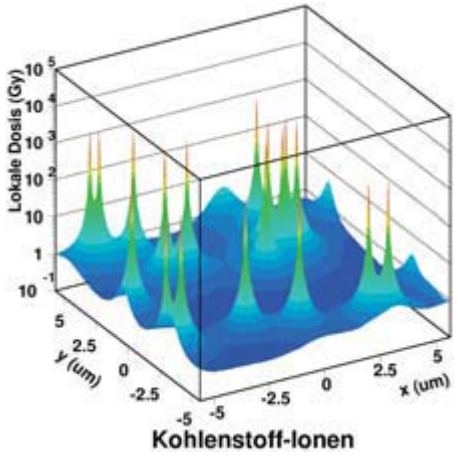
Warning: RBE depends on many parameters

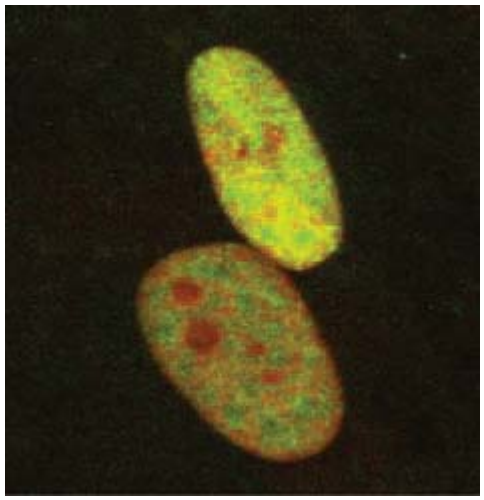
- Biological endpoint
- LET
- Particle type
- Cell/tissue
- Dose rate
- Fractionation
- etc…

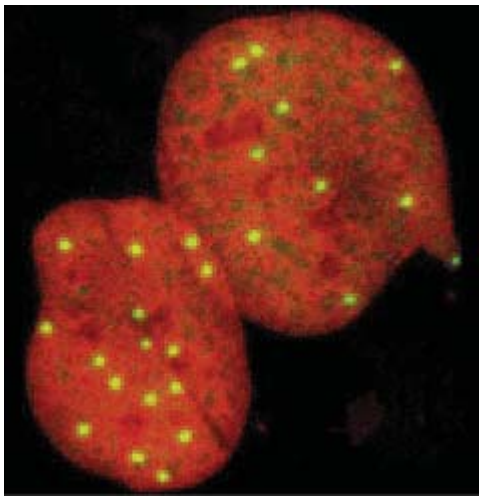
Different types of radiations

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



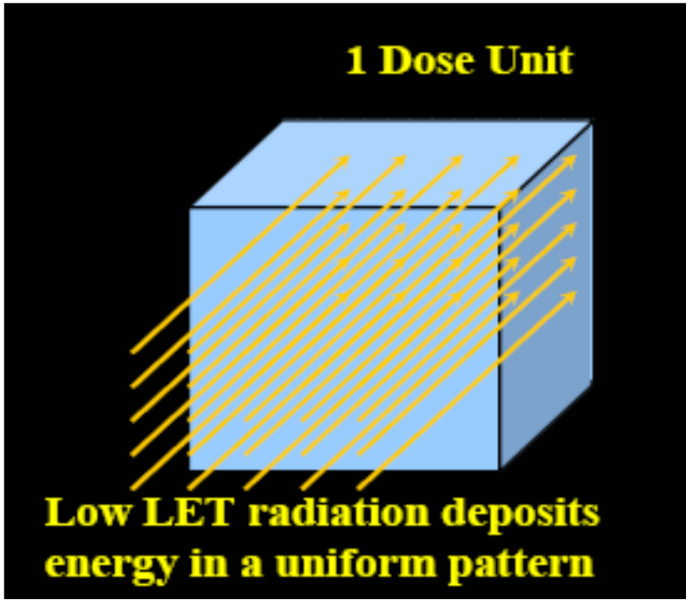




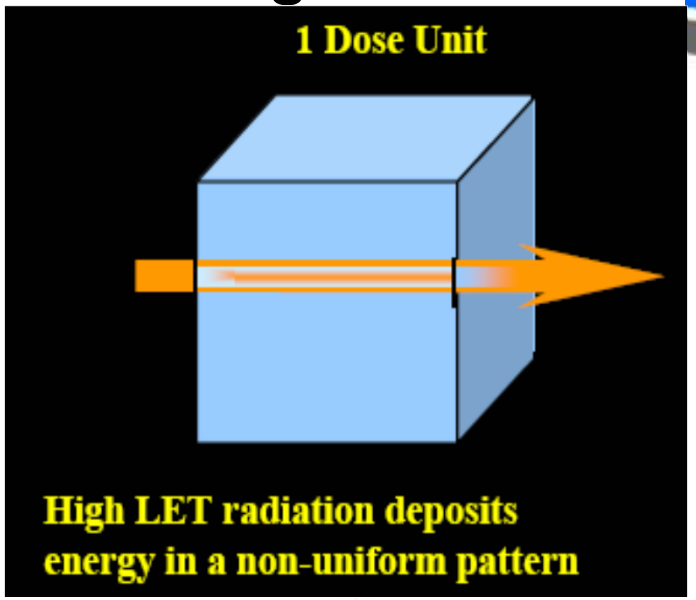


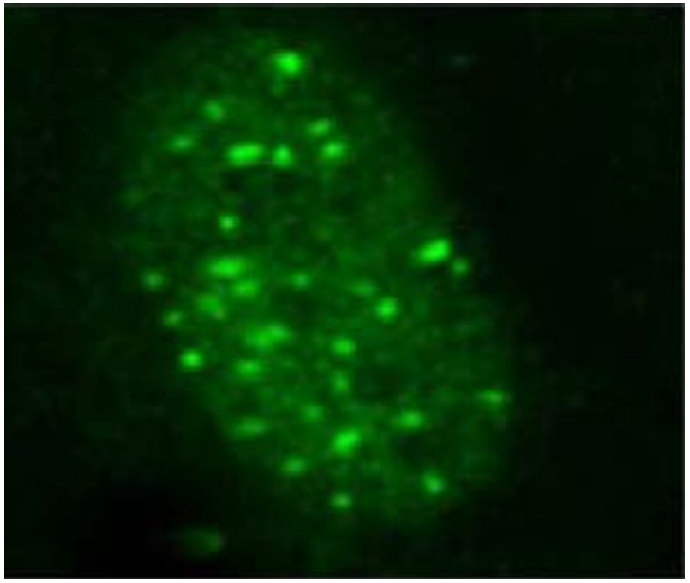
(from G. Kraft, Tumor therapy with heavy ions)

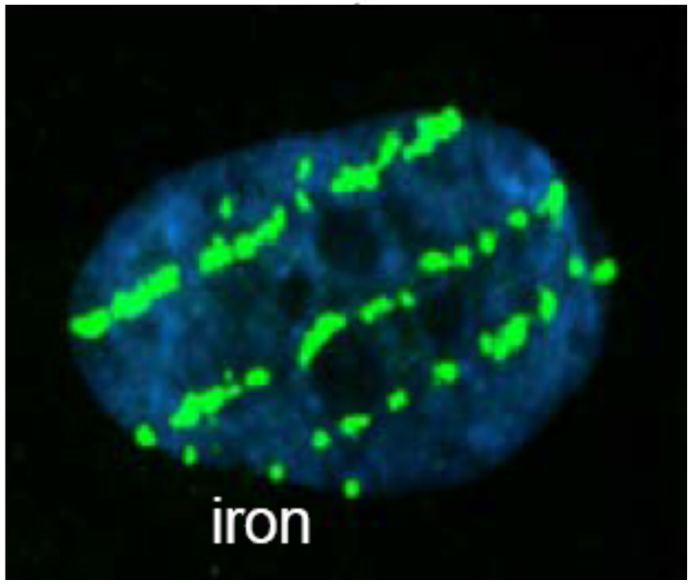
Low LET



High LET







Formation of fluorescent g-H2AX clusters in irradiated human fibroblasts at 10 min postirradiation with 2 Gy of gamma rays or 0.5 Gy of 176 keV/mm iron ions

Adapted from: IAEA R&D, 2007; Cucinotta and Durante, 2006

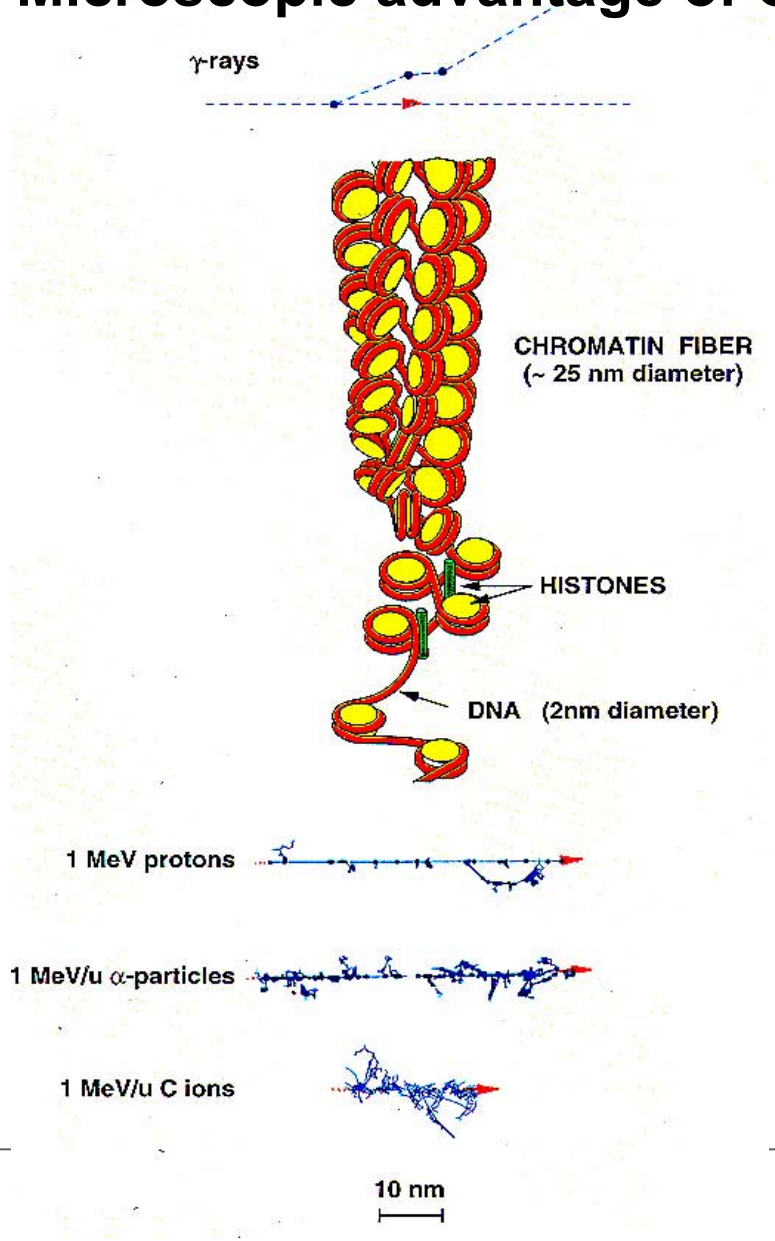
3 different cases

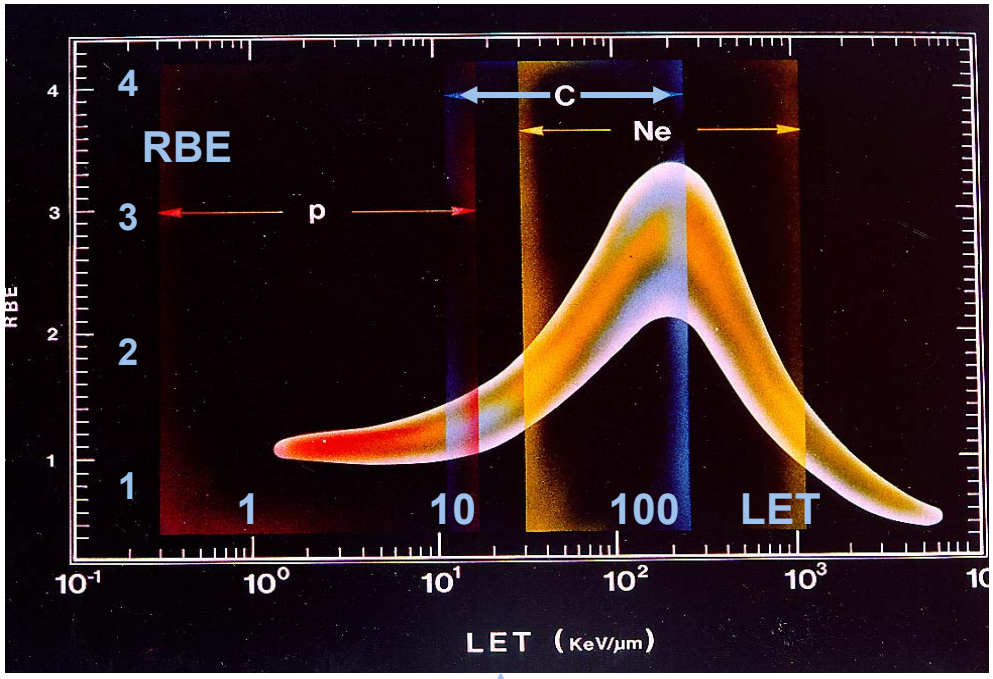
-1 Low LET(<20 keV/micron)
Distance between ionizations larger than DNA diameter.
Classical radiotherapy; Fractionation very important.

-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).

Microscopic advantage of Carbon ions

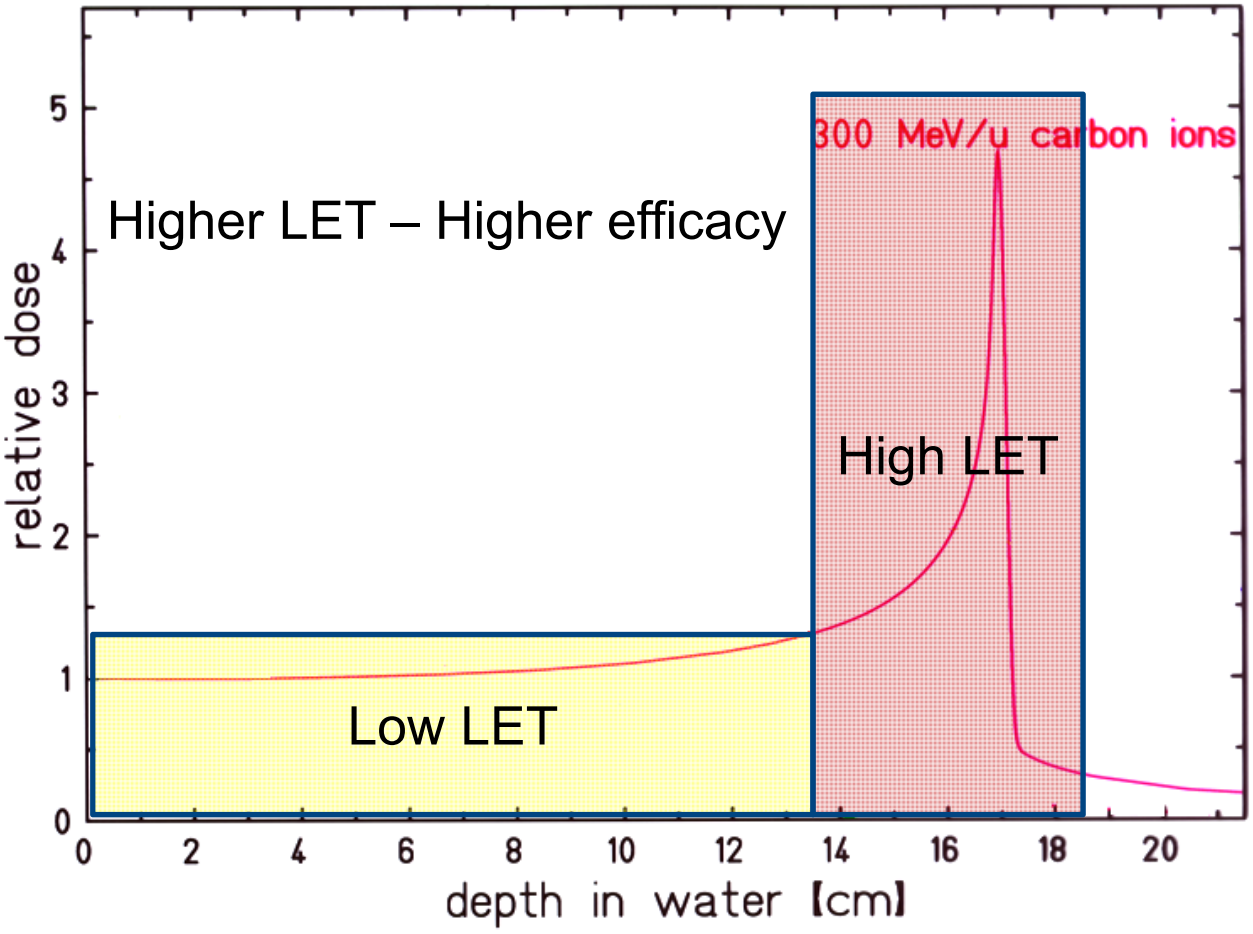




10 – 20 keV/mm = 100 – 200 MeV/cm =

20 – 40 eV/(2 nm)

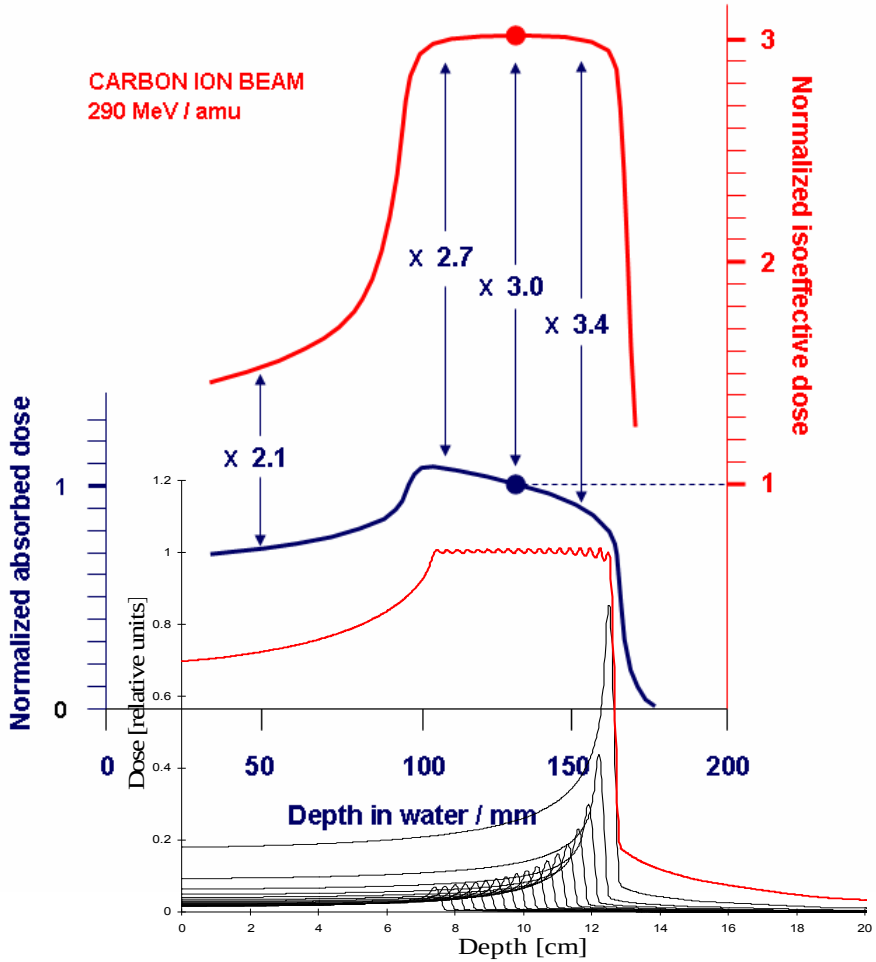
Carbon ions: high LET where needed



Physical and biological dose

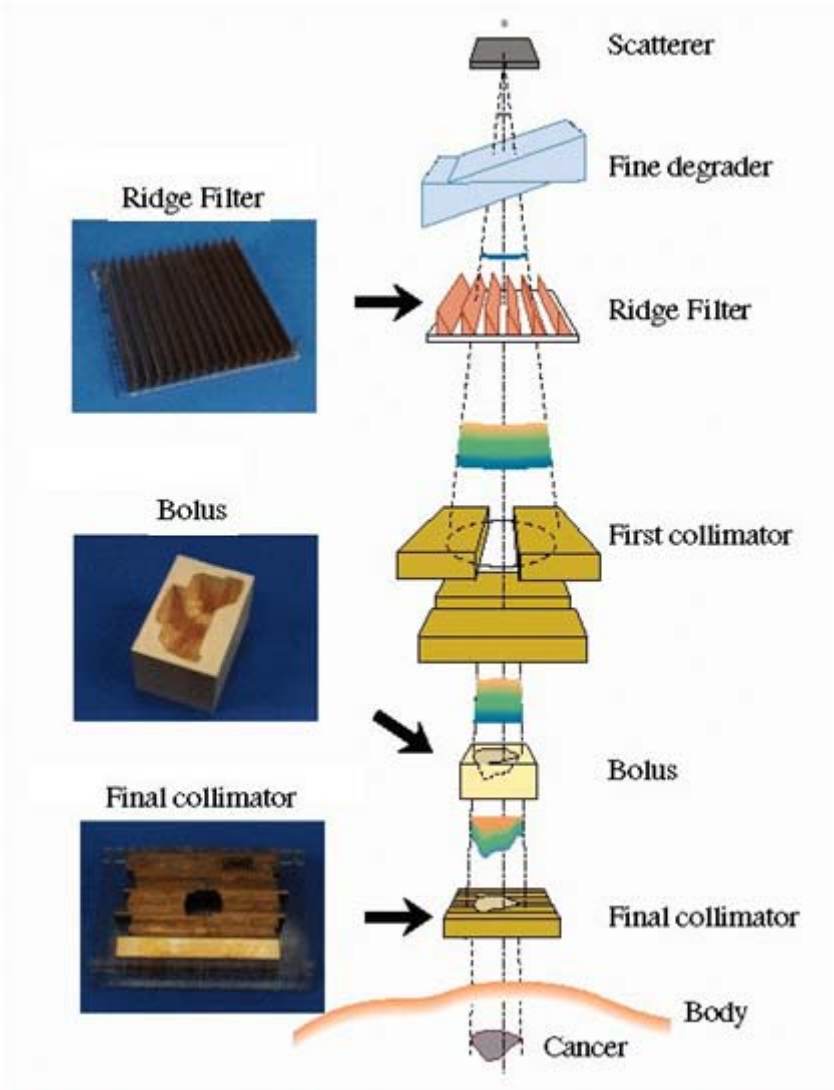
Complicated treatment planning (even worse when beam delivery is taken into account)

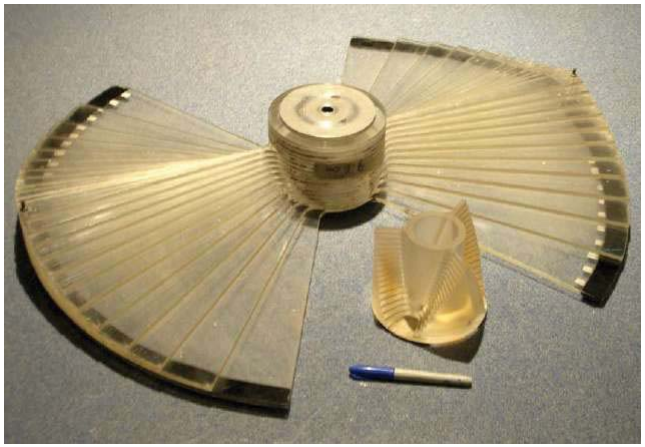
Different sharing of High and Low LET doses along the SOBP

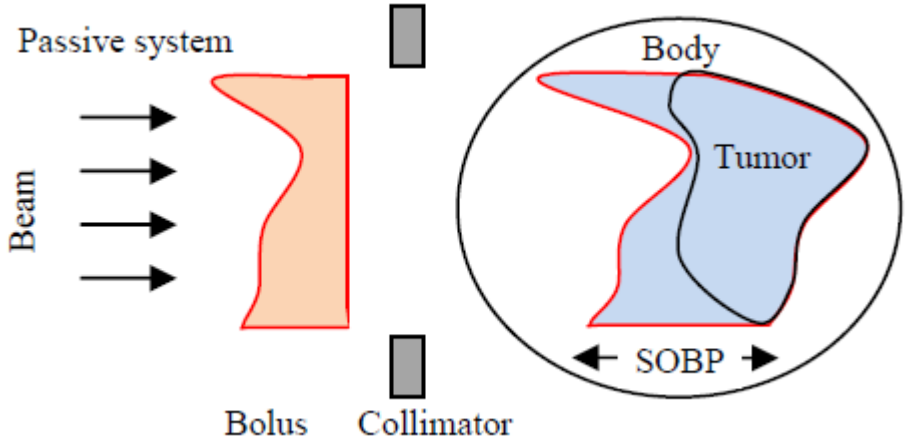


Beam delivery – dose distribution

Beam delivery: passive systems







Passive systems for Carbon

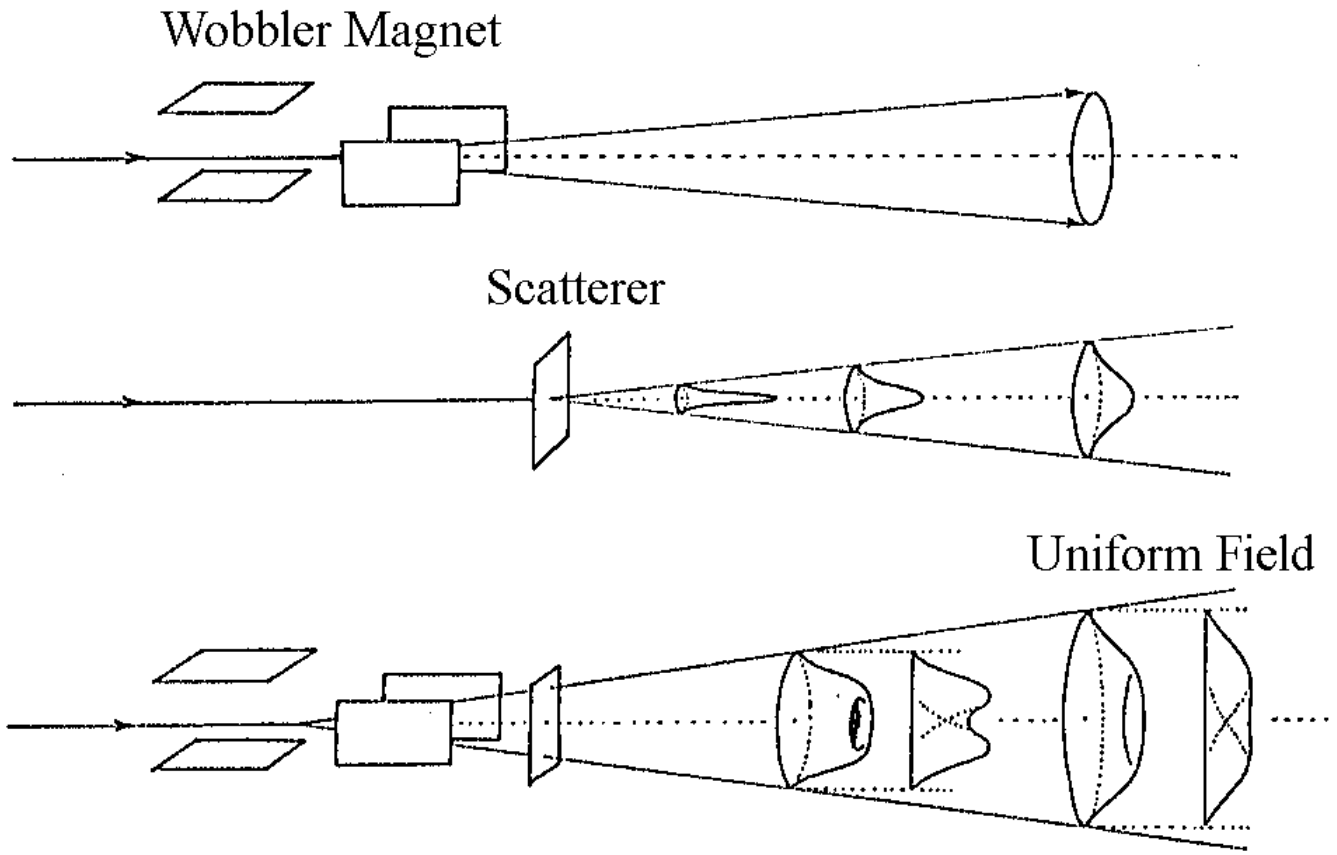
Completely passive system not advisable:

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

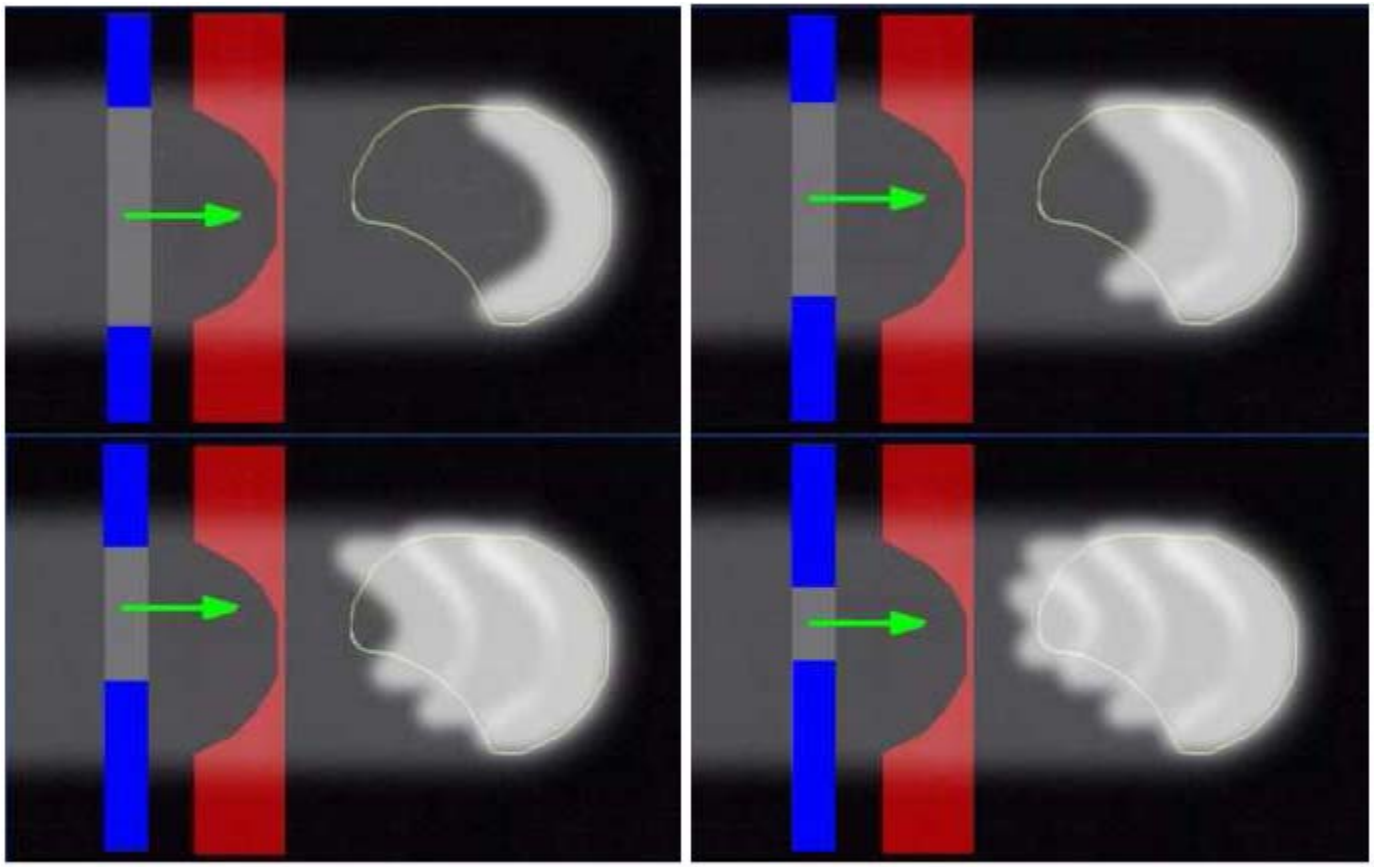
-Fragmentation of impinging ions causes a higher dose delivered after the tumor and larger production of neutrons.

-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.

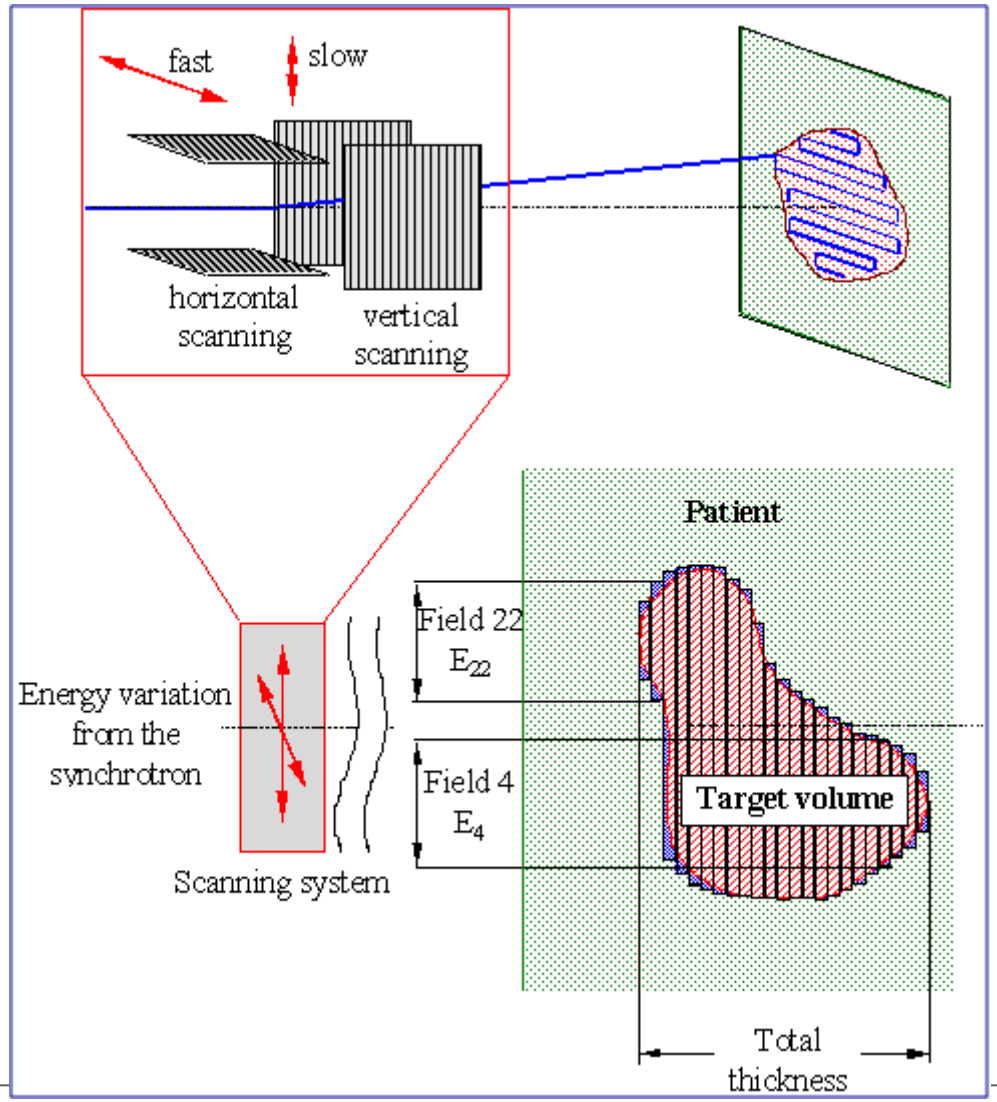
Wobbling



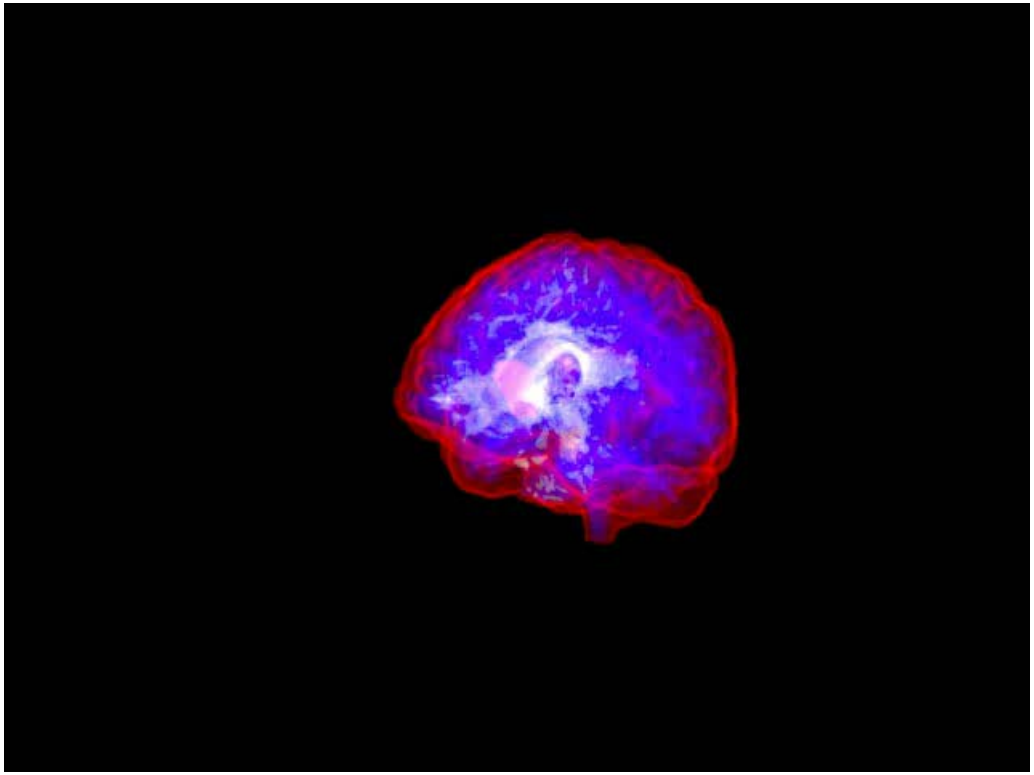
Layer stacking



Active systems

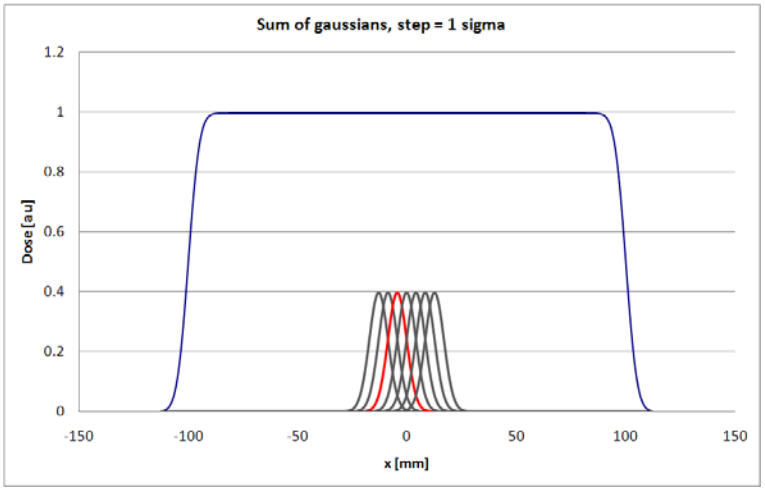


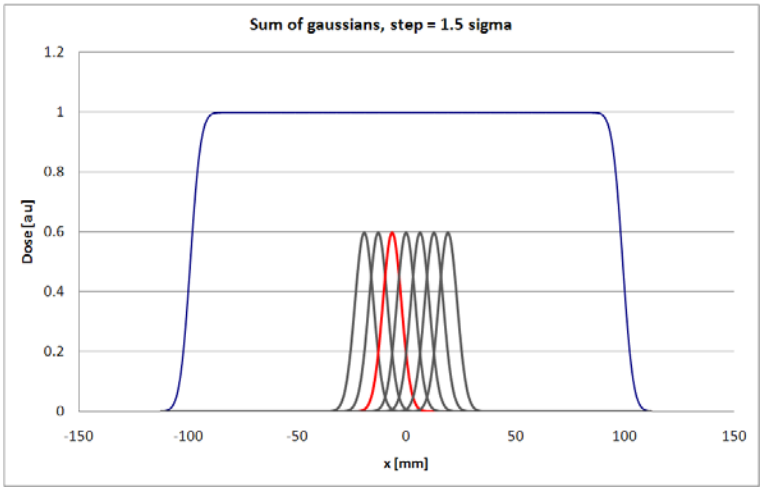
Scanning Beam

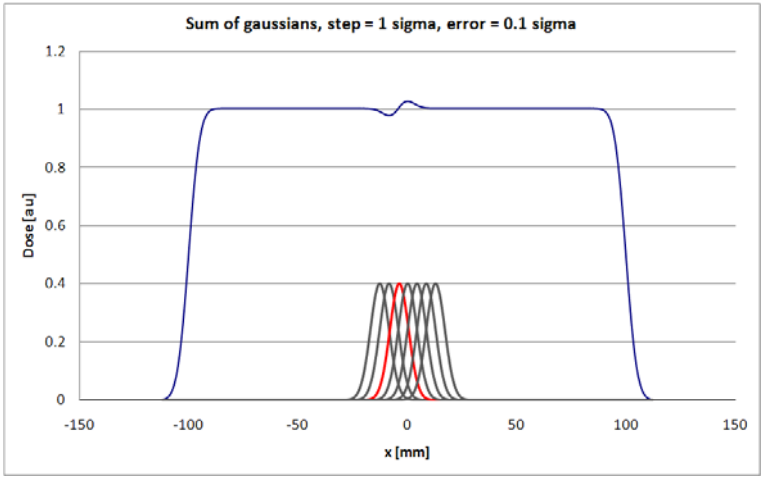


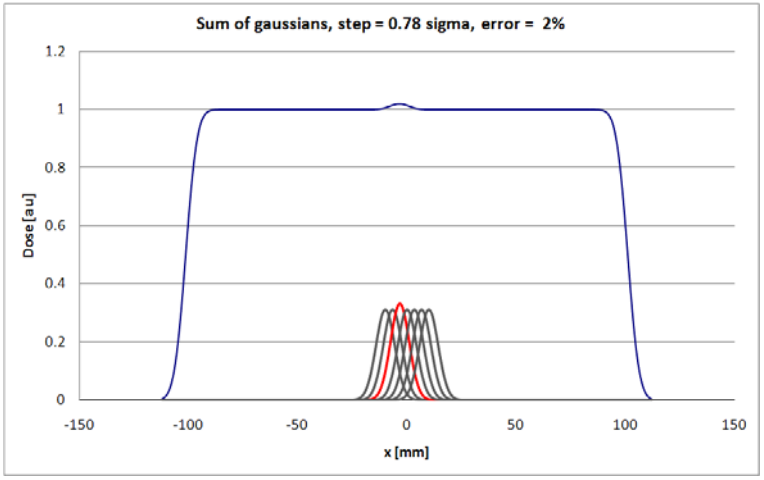
(Courtesy of A. Attili)

Beam position precision

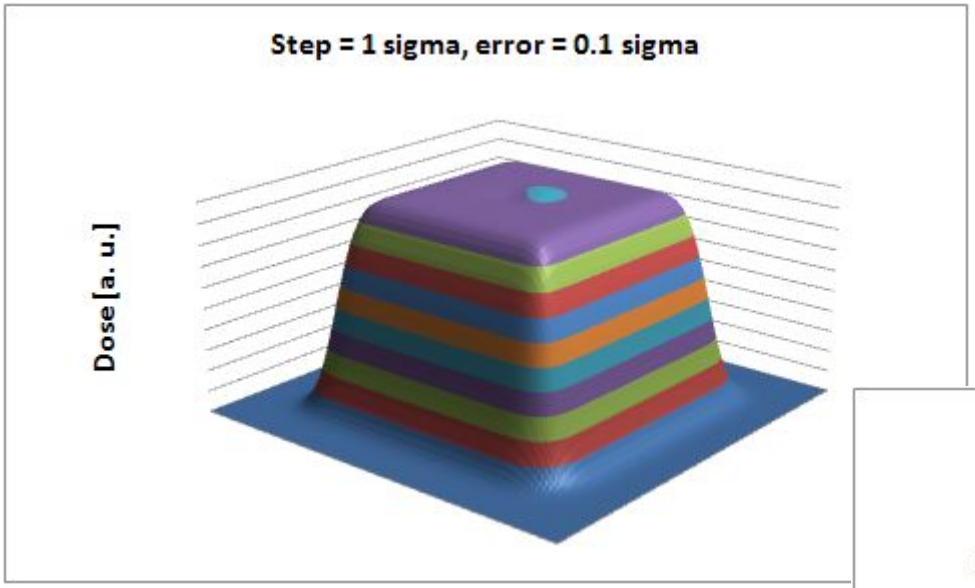


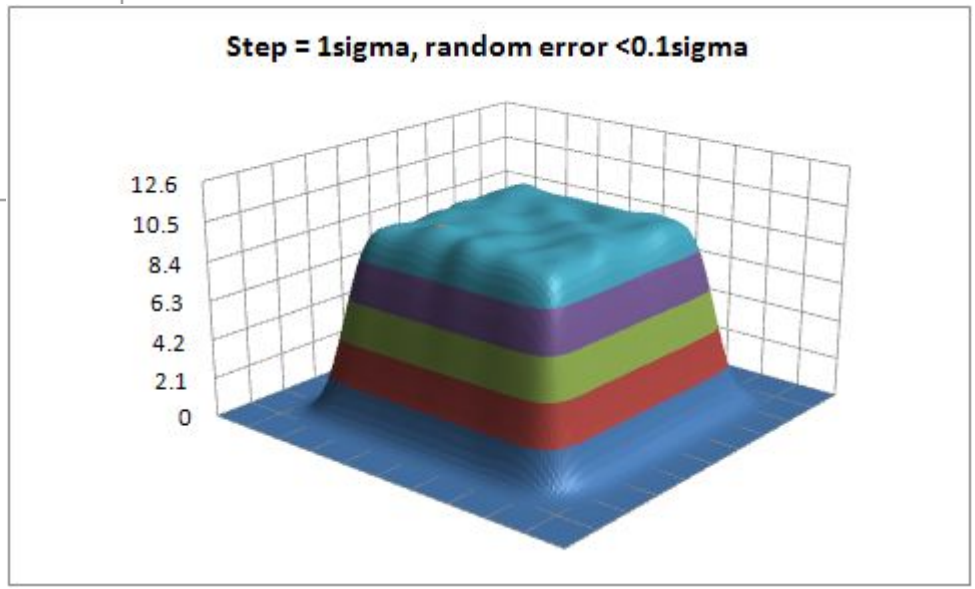






2D


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 production - accelerators

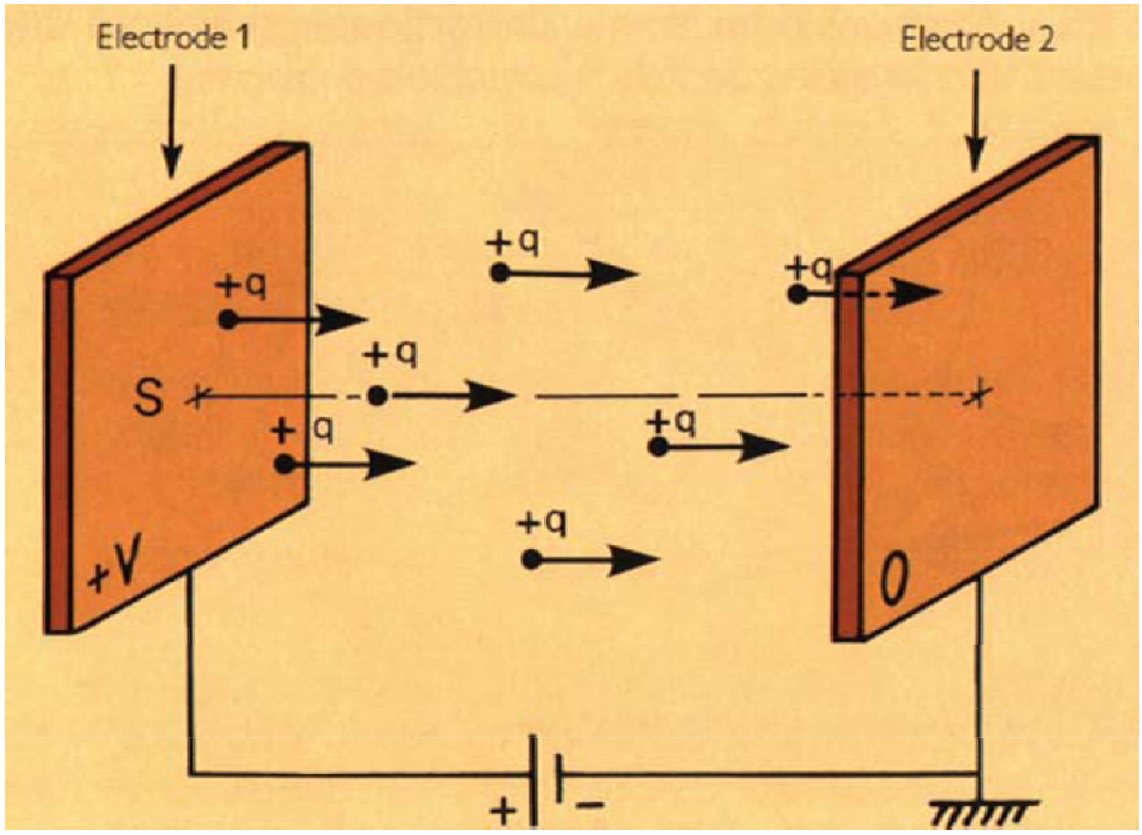
Electrostatic accelerators

Energy gained

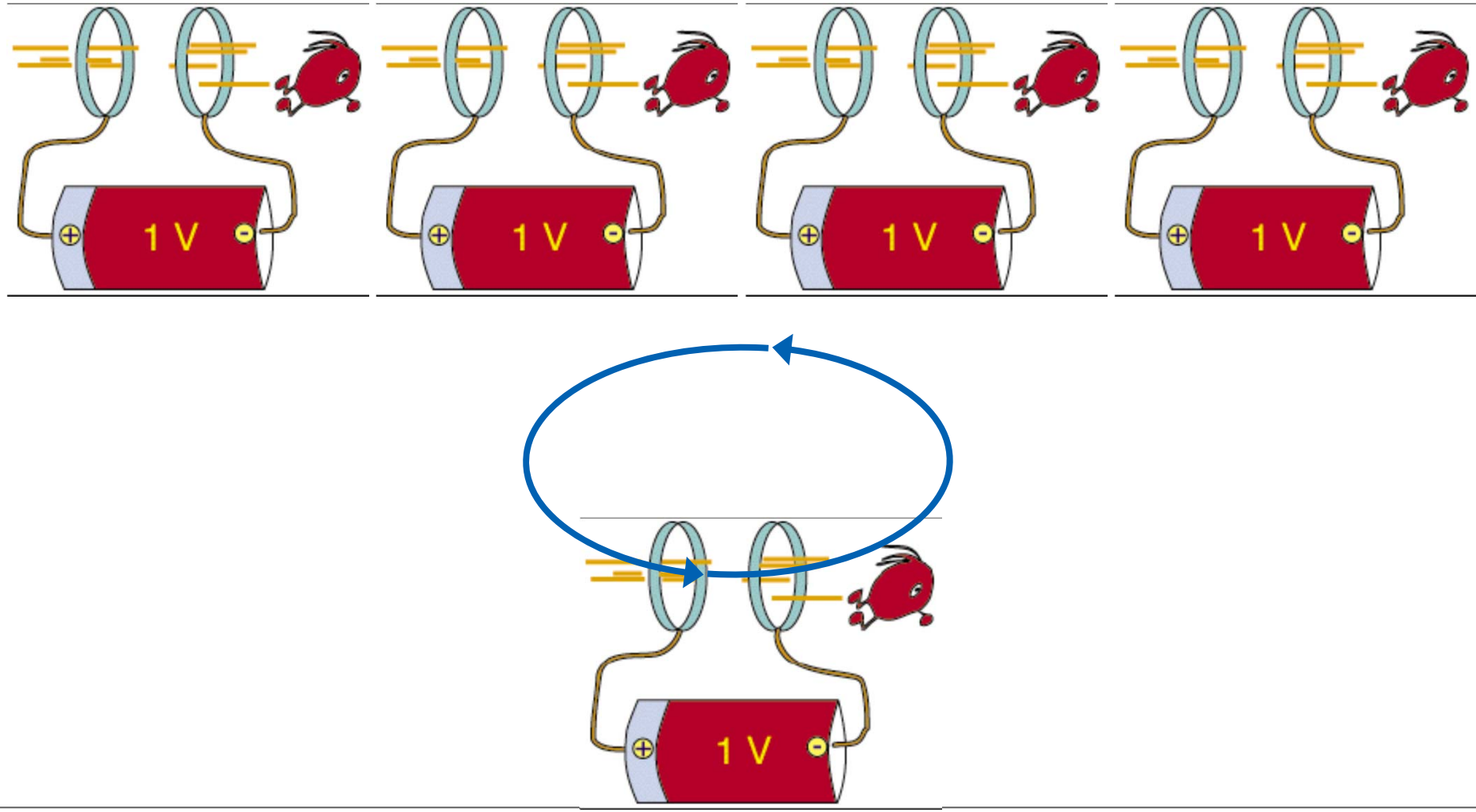
$K = q\,V$

Measured in

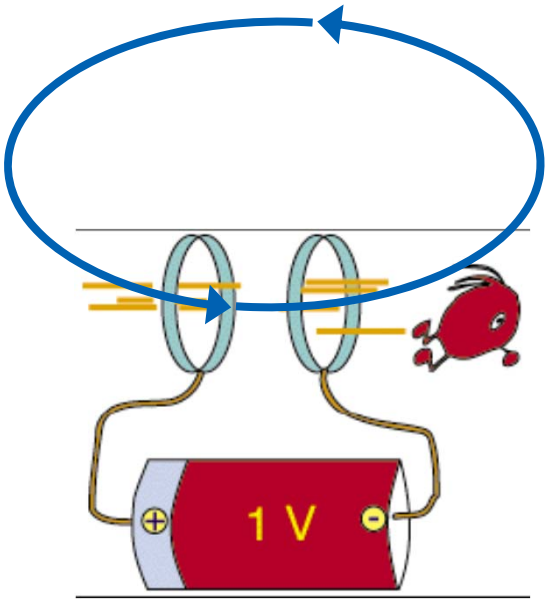
eV

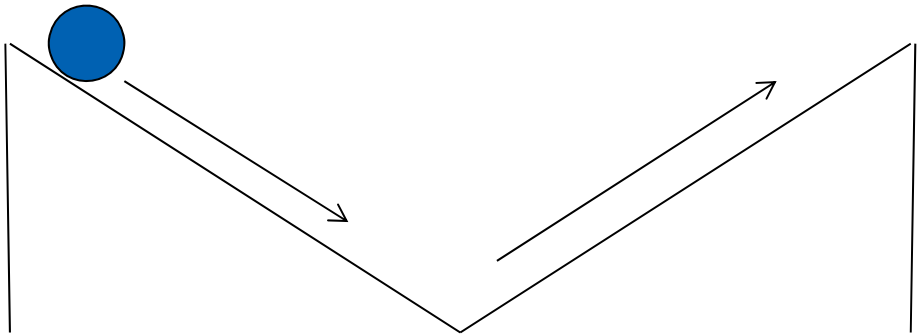


LINACs vs Circular machines



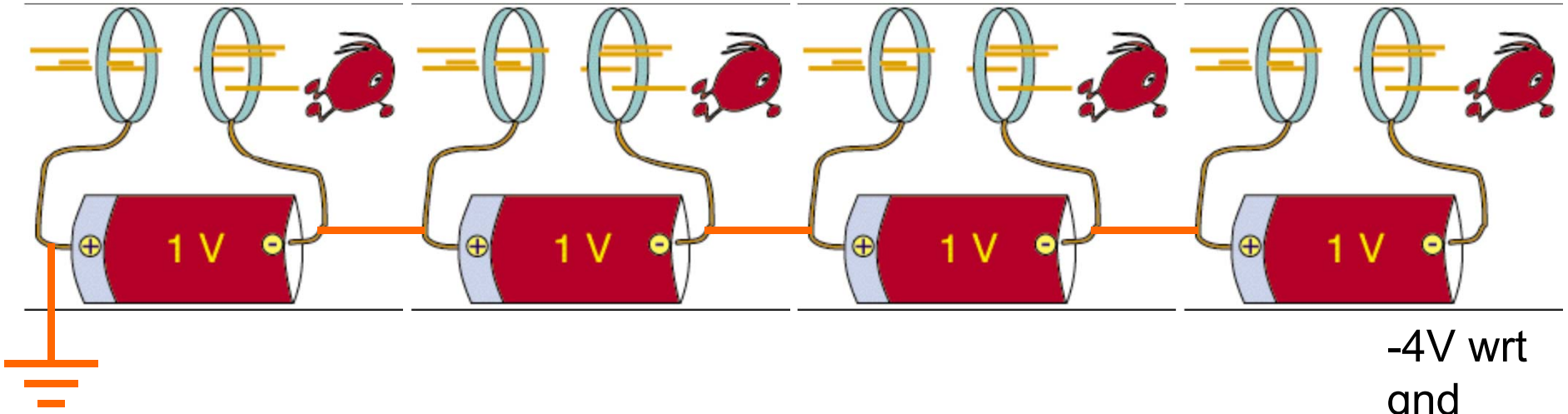
Circular accelerators



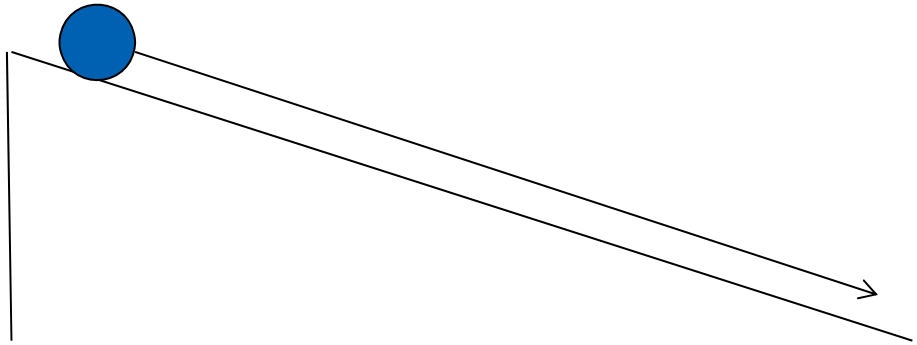


The electrostatic field is conservative, thus a circular electrostatic accelerator DOES NOT WORK

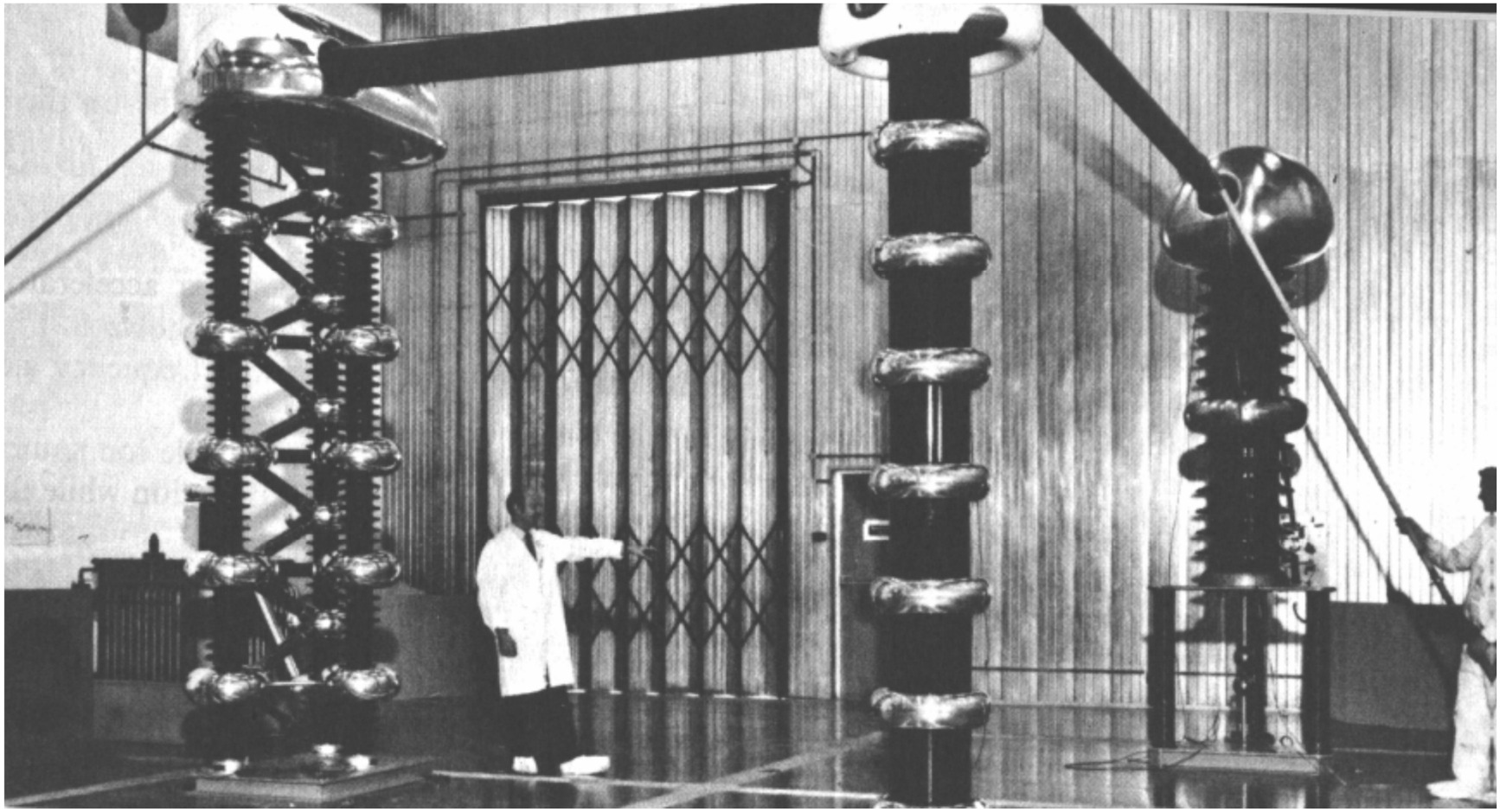
Electrostatic accelerators



Maximum electrostatic field ~ 10 MV/m

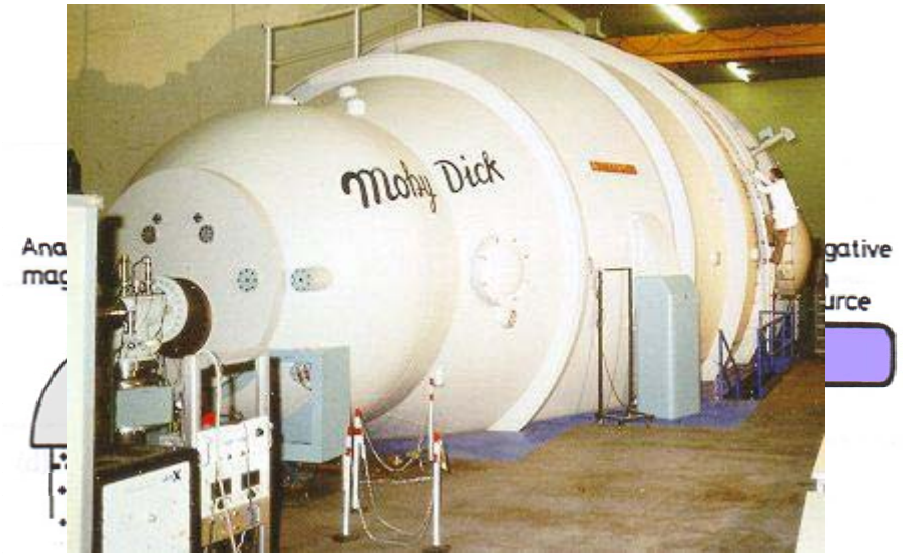


Electrostatic accelerators



70 MeV Cockcroft-Walton generator supplying the ion source which injected protons into NIMROD, the 7 GeV synchrotron at Rutherford laboratory.

Il Tandem



INFN-LNL

Use the accelerating voltage twice.

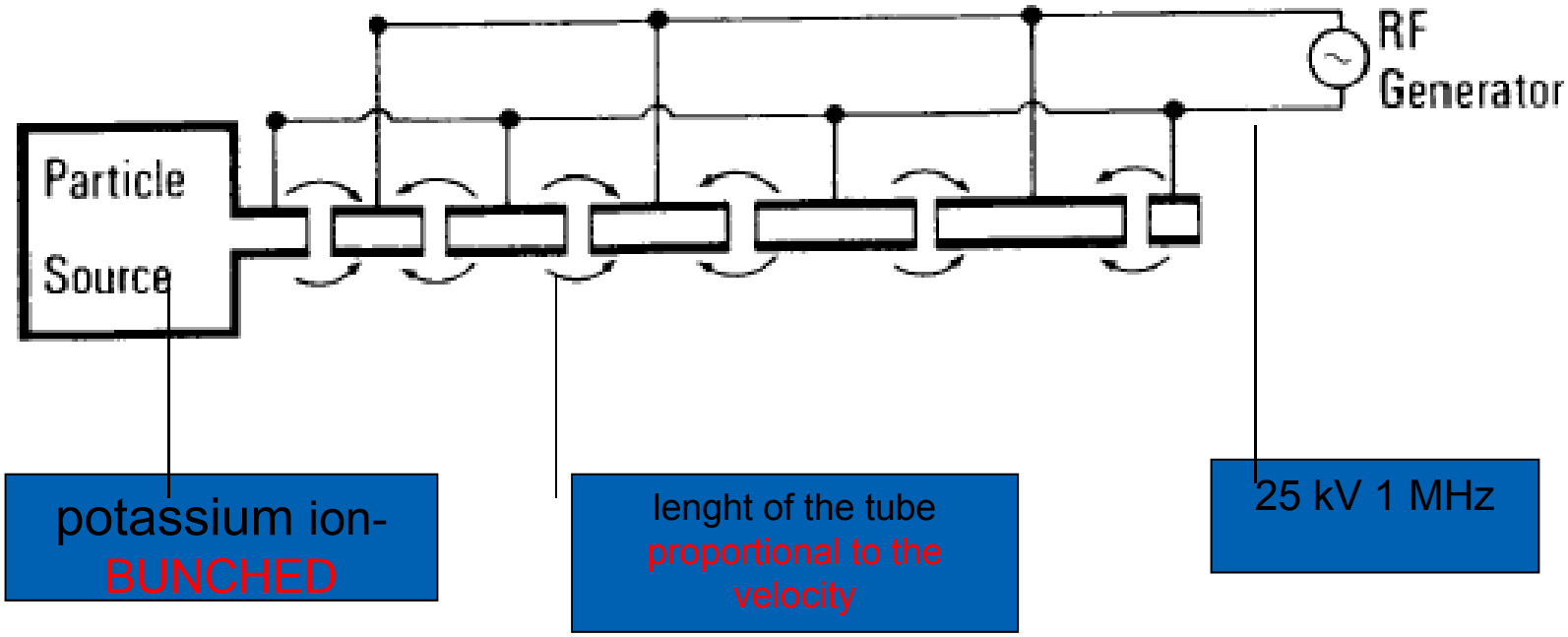
First an extra electron is attached to the neutral atoms to create negative ions.
The negative ion beam is injected at ground potential into the Tandem and accelerated up to the high-voltage terminal where it passes through a thin foil which strips at least two electrons from each negative ion converting them to positive ions. They are then accelerated a second time back to earth potential.

The right idea

- **1924 Ising proposes time-varying fields across drift tubes. This is a 'true' accelerator that can achieve energies above that given by the highest voltage in the system.**

- **1928 Wideröe demonstrates Ising's principle with a 1 MHz, 25 kV oscillator to make 50 keV potassium ions; the first linac.**

Wideroe linac



- **the energy gained by the beam (50 keV) is twice the applied voltage (25 keV at 1 MHz)**

(courtesy of A Lombardi)

from Wideroe to Alvarez linac

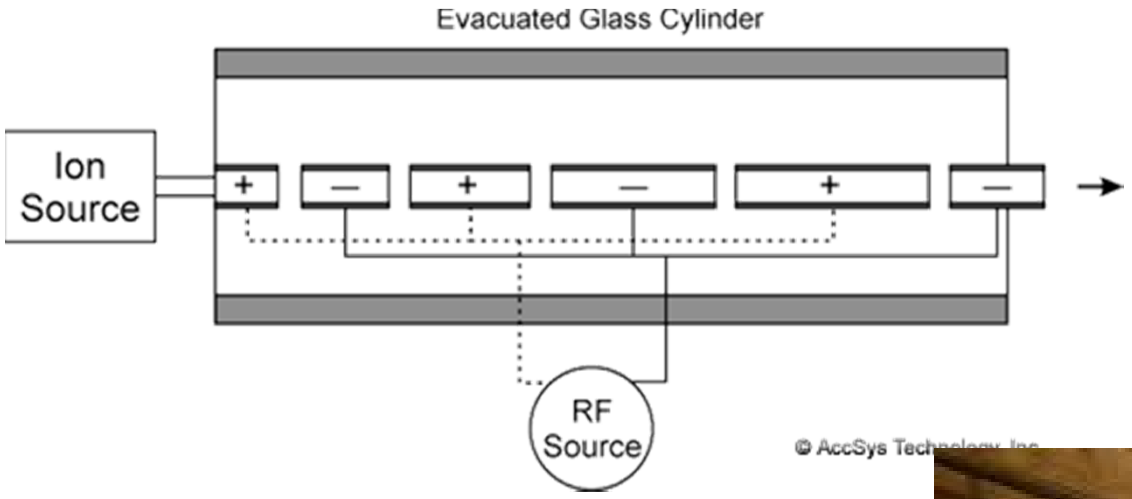
- to proceed to higher energies it was necessary to increase by order of magnitude the frequency and to enclose the drift tubes in a cavity (resonator)

- this concept was proposed and realized by Luis Alvarez at University of California in 1955 : A 200 MHz 12 m long Drift Tube Linac accelerated protons from 4 to 32 MeV.

- the realization of the first linac was made possible by the availability of high-frequency power generators developed for radar application during World War II

(courtesy of A Lombardi)

From Wideroe to Alvarez

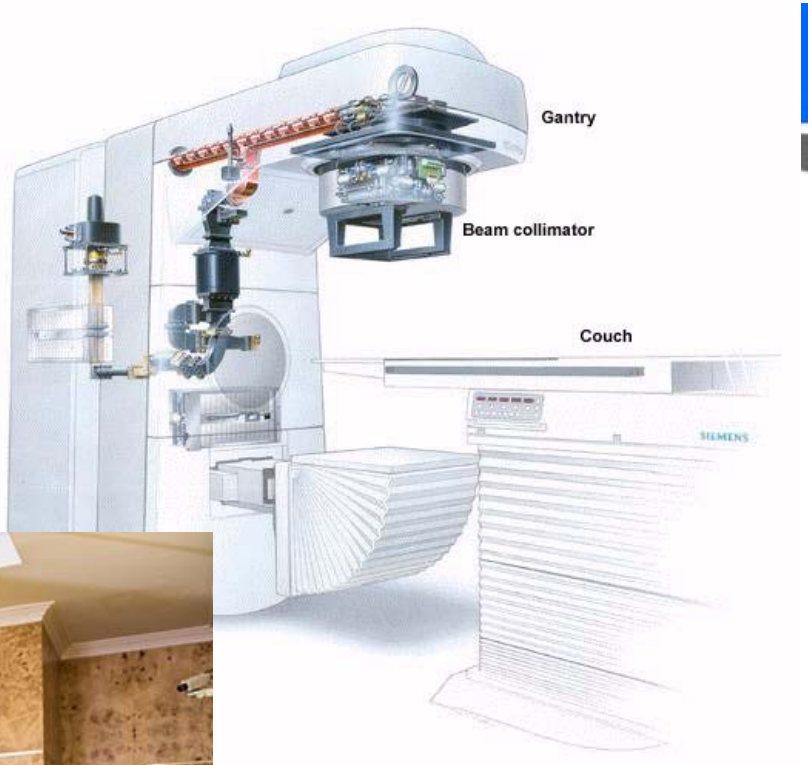


© AccSys Technology, Inc.

(courtesy of A Lombardi)

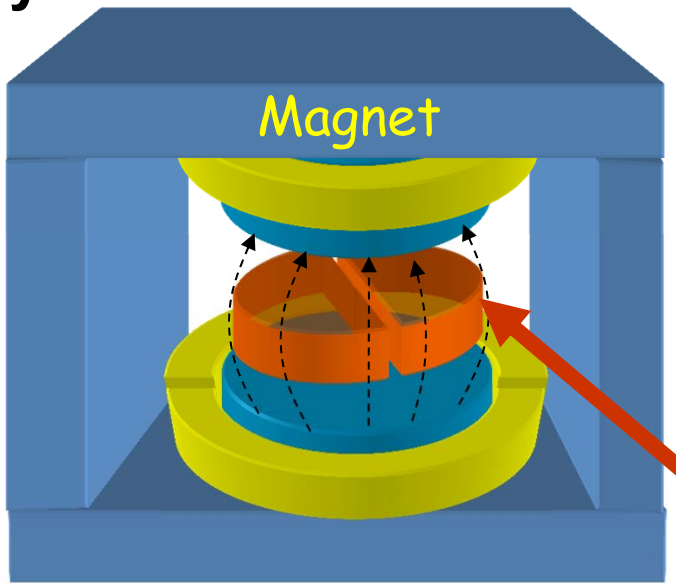
Radiotherapy linac

3 GHz RF frequency



collimator

Cyclotron



Ernest Lawrence
(1901-1958)

RF-Electrodes: 2 "Dees"

Ion source

Extractor:
-HV

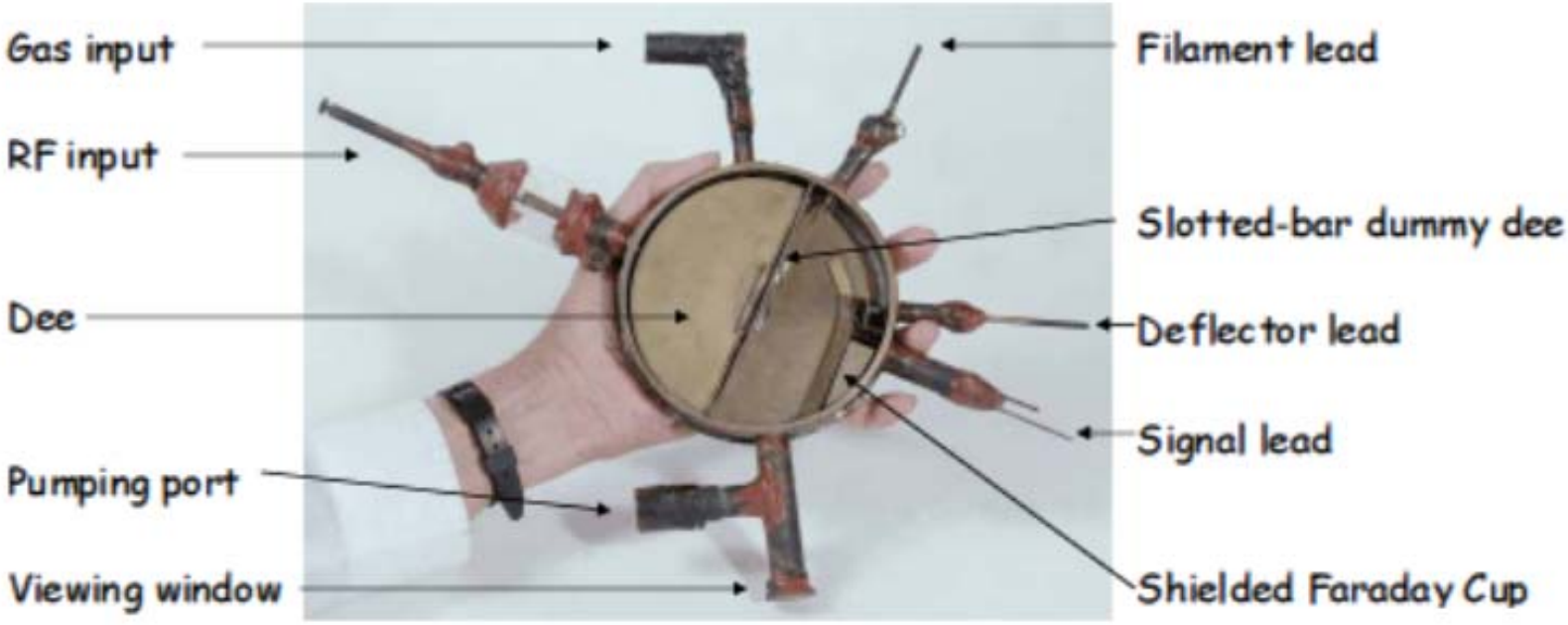
V_{dee} ~

oscillating high voltage
on "Dee" electrode

At each electrode border:

Energy gain $\Delta E = V_{dee}$

FIRST CYCLOTRON MODELS – Fall 1930

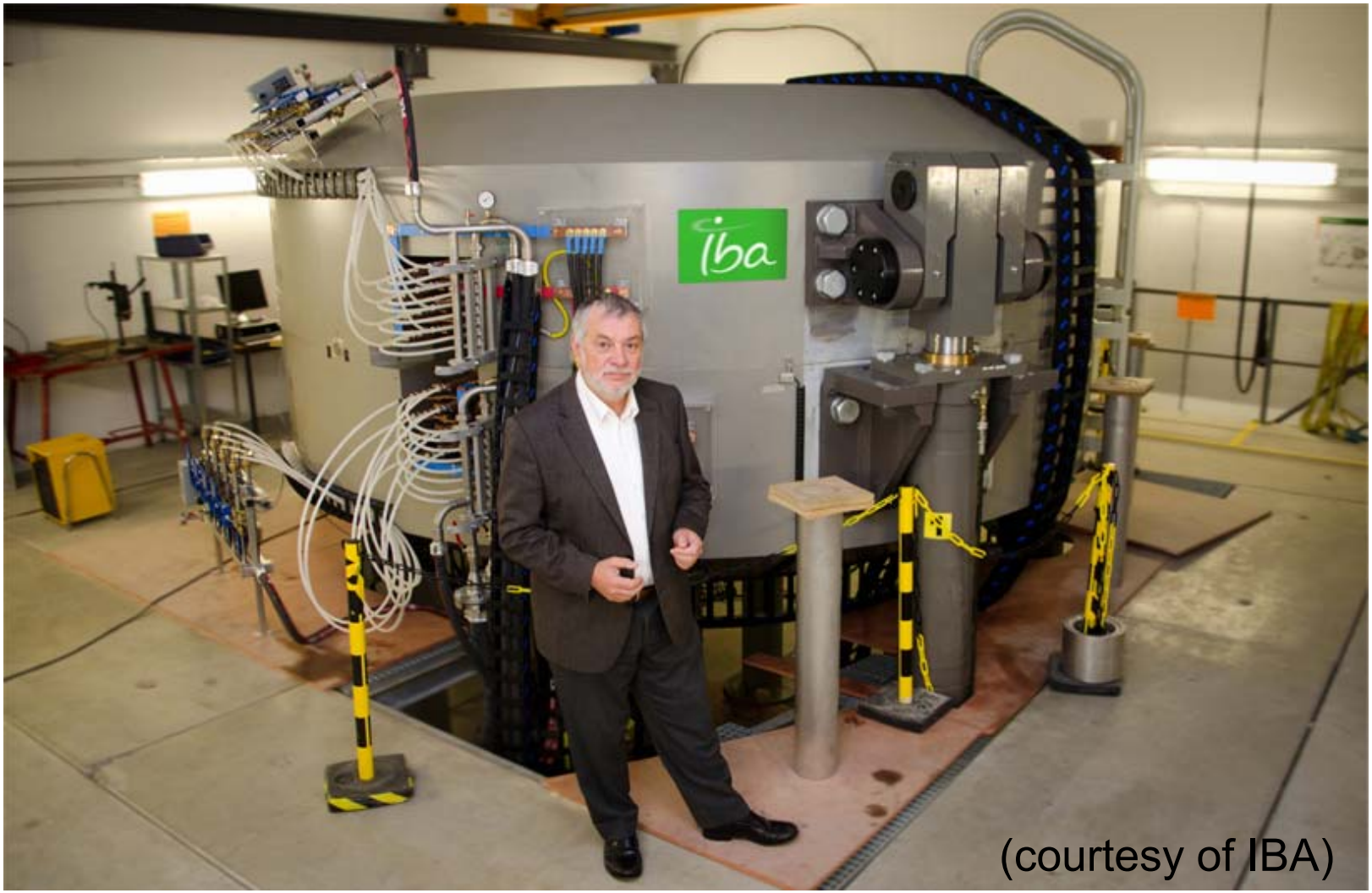


A new student, Stanley Livingston, then took over, building a "4-inch" version in brass. Clear evidence of magnetic field resonance was found in November, and in January 1931 they measured 80-keV protons.

Ions were produced from the residual gas by a heated filament at the centre. Note the liberally applied red sealing wax for vacuum tightness - and Glenn Seaborg's left hand.

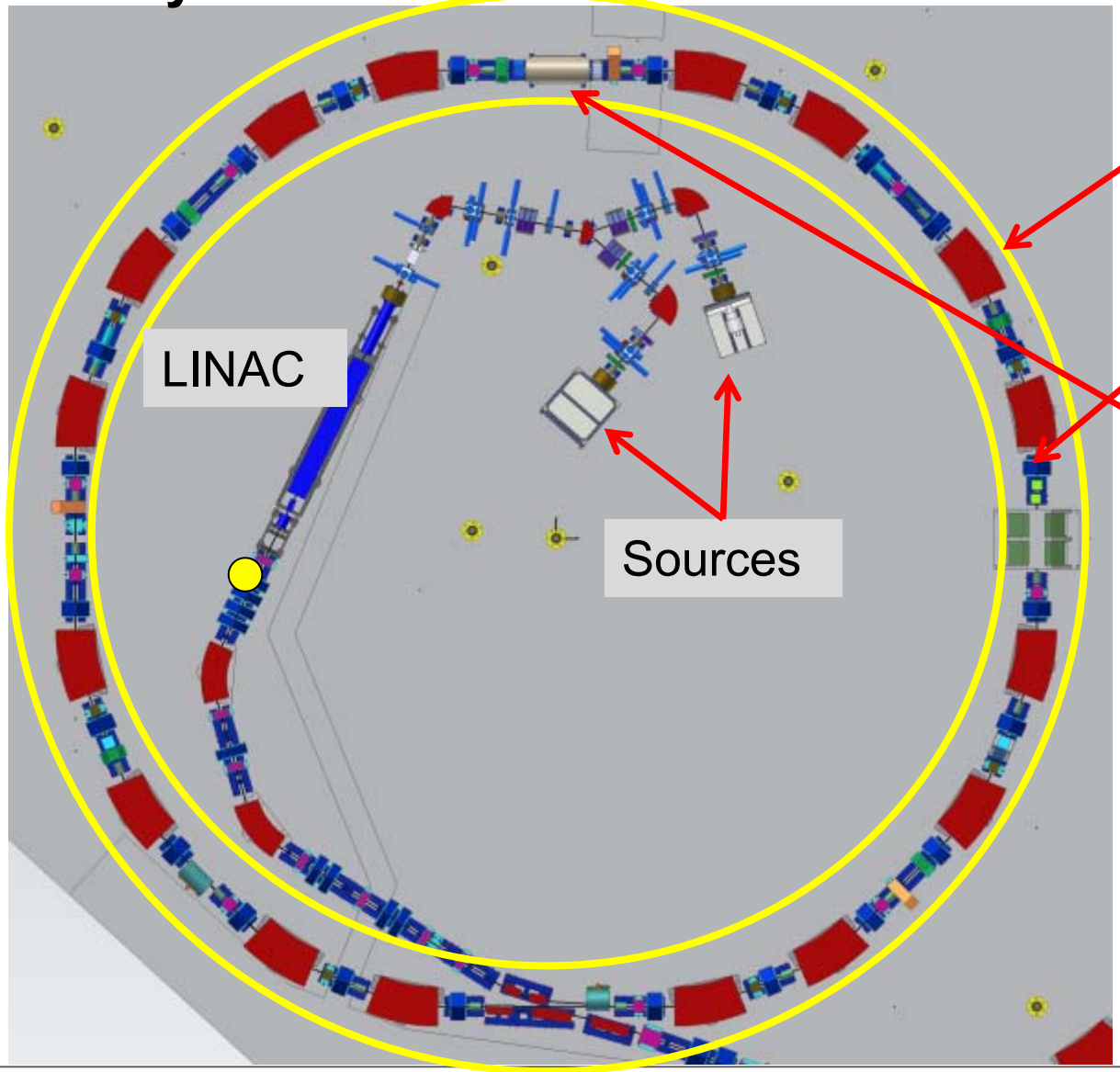
(courtesy of G. Calabretta)

Proton therapy cyclotron



(courtesy of IBA)

The Synchrotron



Dipoles (bending)

Quadrupoles (focussing, 100 000 km!)

Vacuum

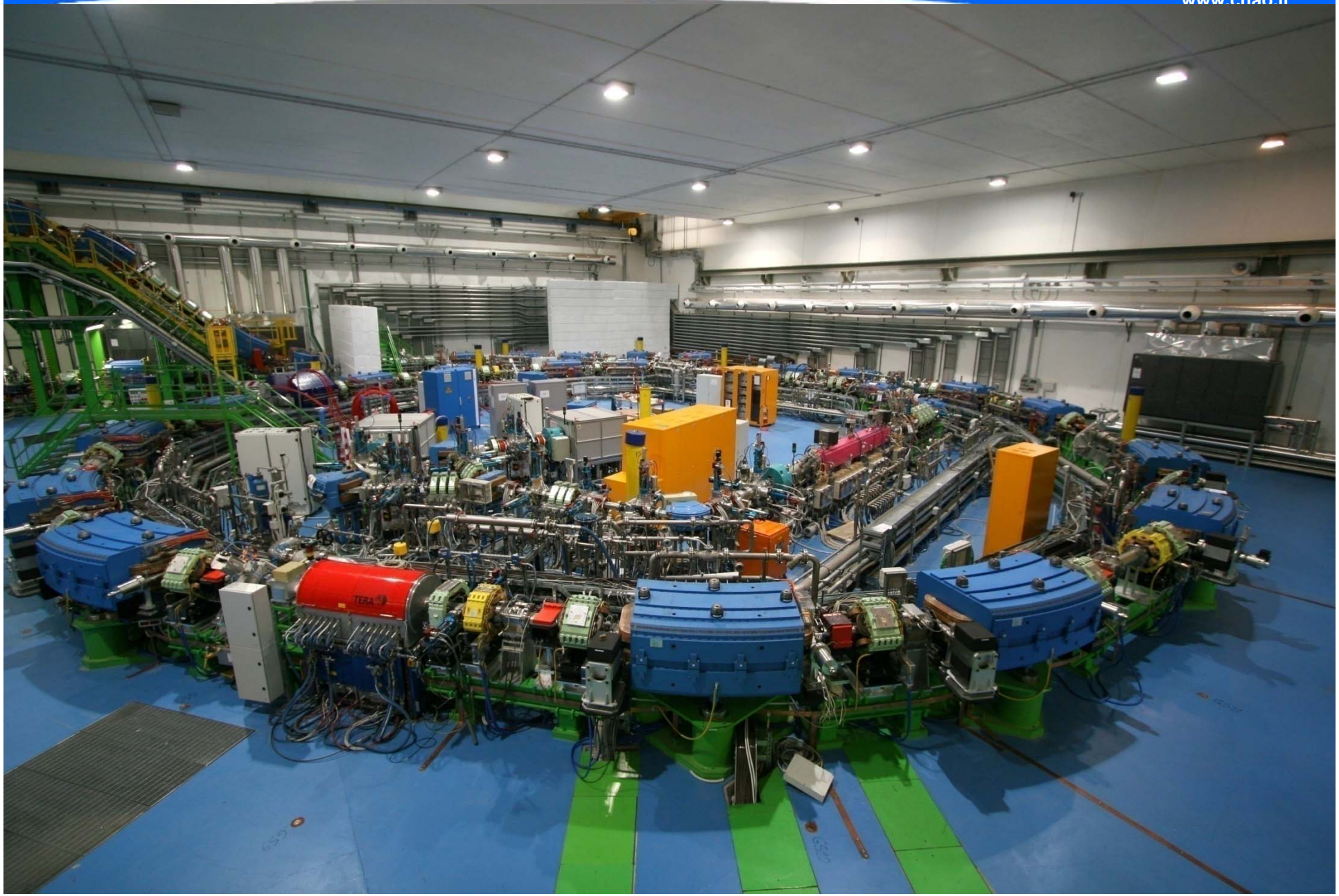
RF Cavity (acceleration)

R fixed

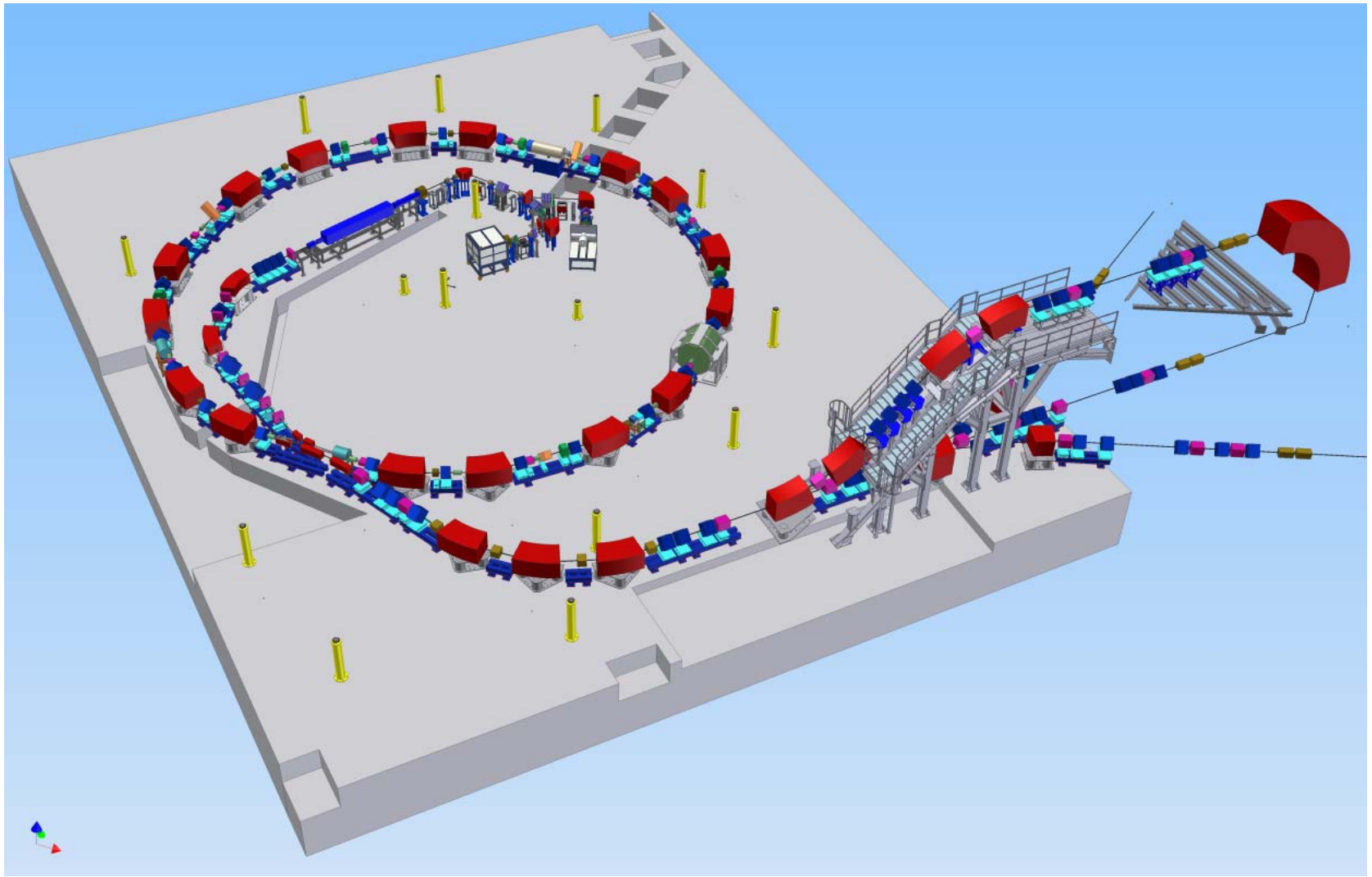
E increases

F increases

B increases

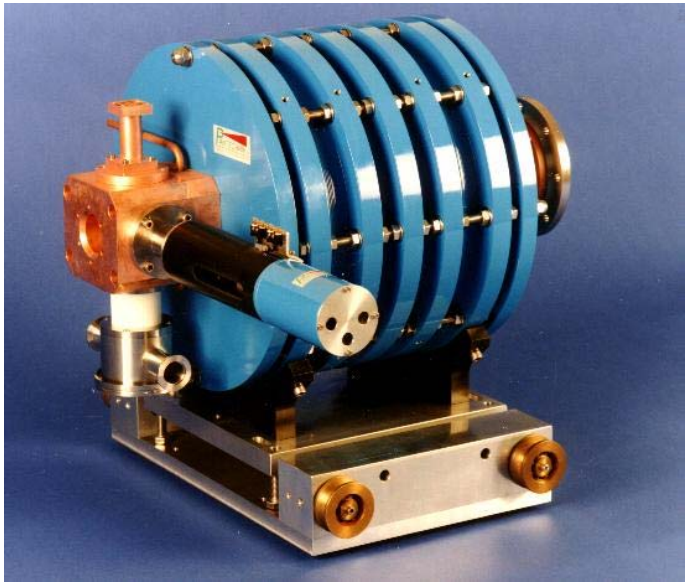

TERA

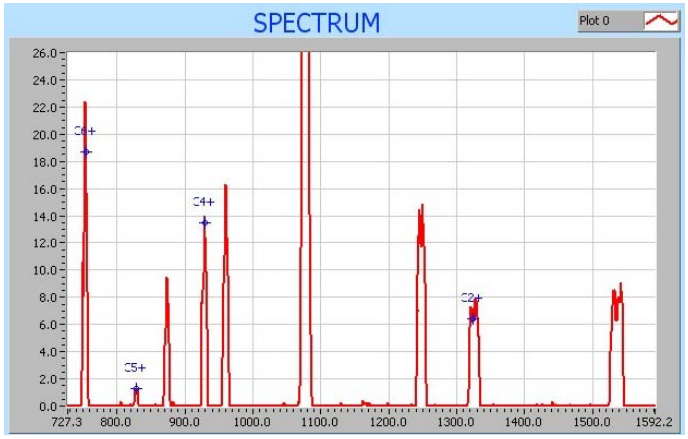
Virtual visit to the CNAO accelerator system

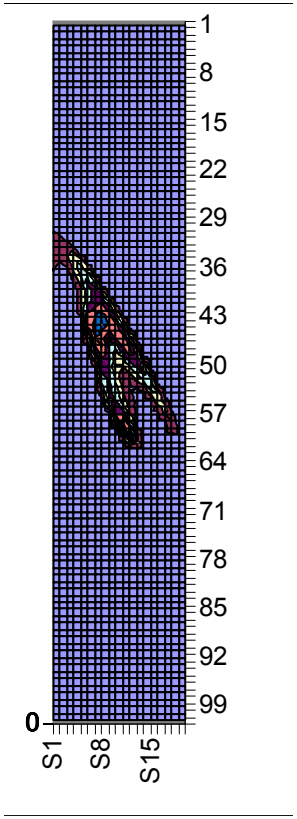


Sources

ECR, always on

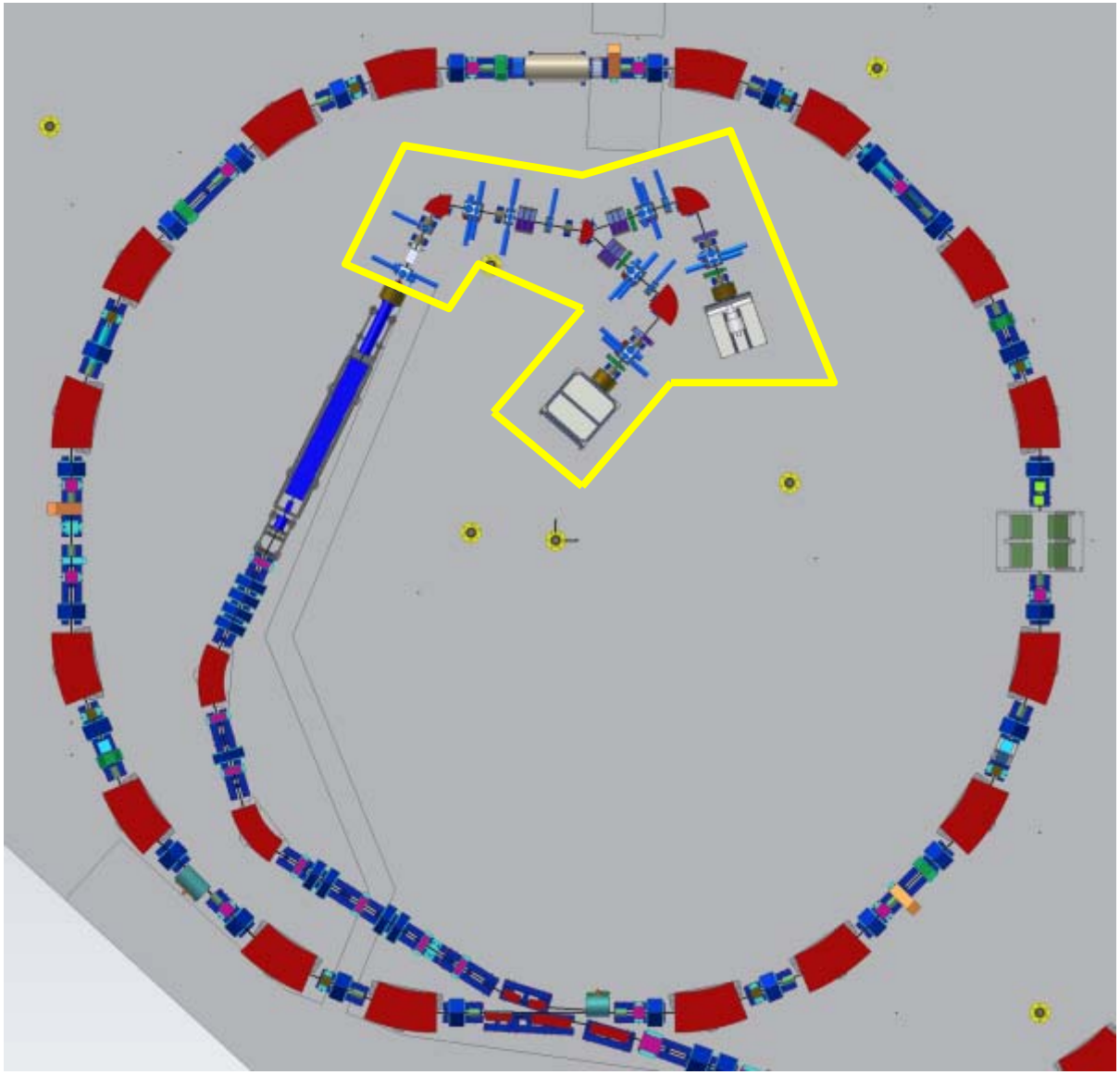






I_{tot} = 250 μA

$I_{180\pi}$ = 85% I_{tot}



LEBT

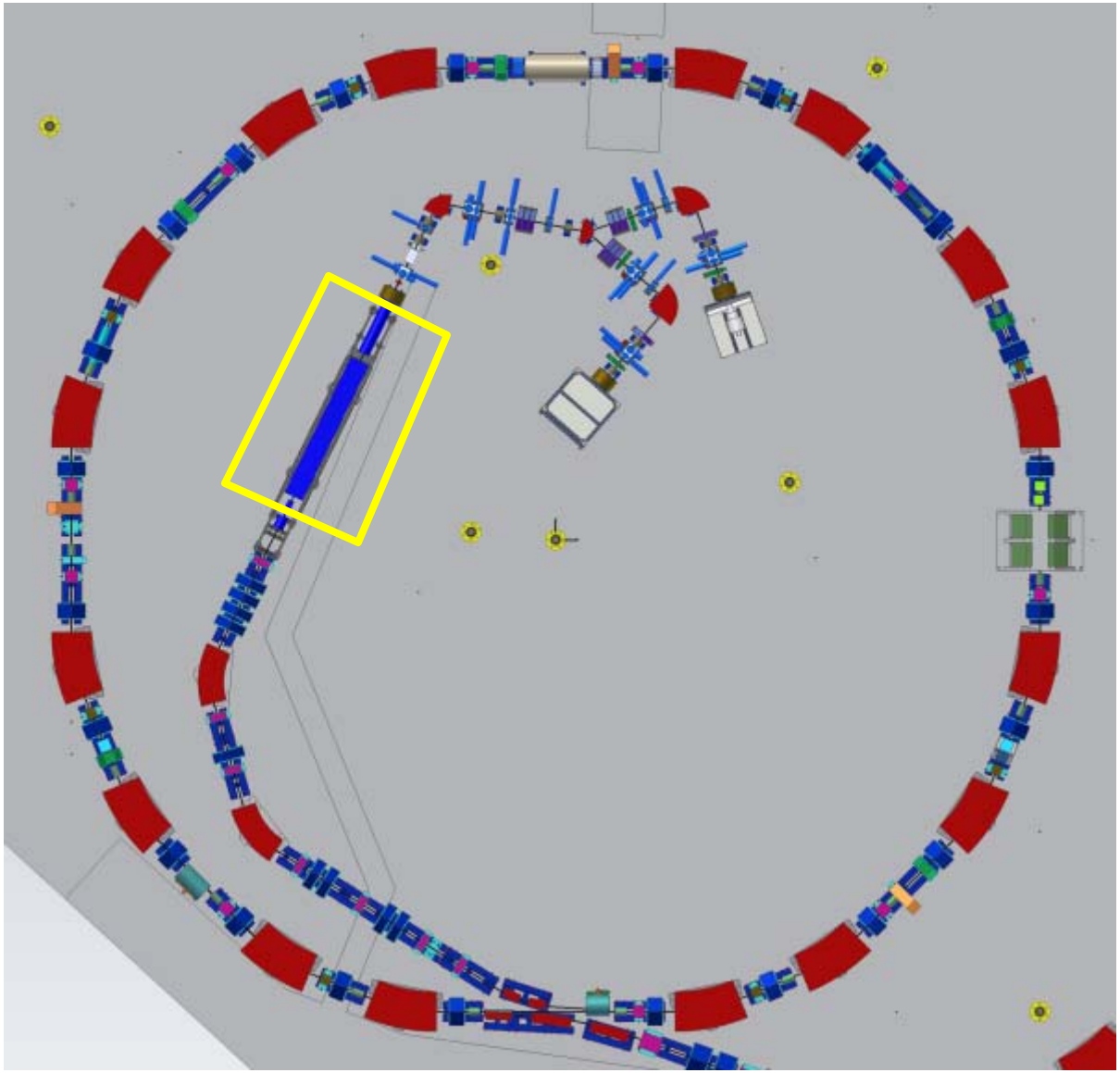
0.008 MeV/u H_3^+
0.008 MeV/u C^{4+}

I ~ 0.7 mA (H_3^+)
I ~ 0.2 mA (C^{4+})

Two sources

Continuous beam

LEBT Chopper



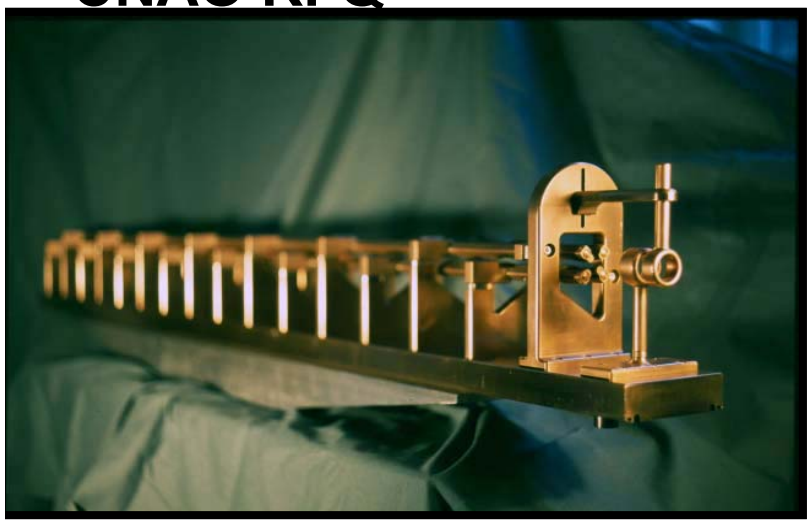
RFQ-LINAC

217 MHz

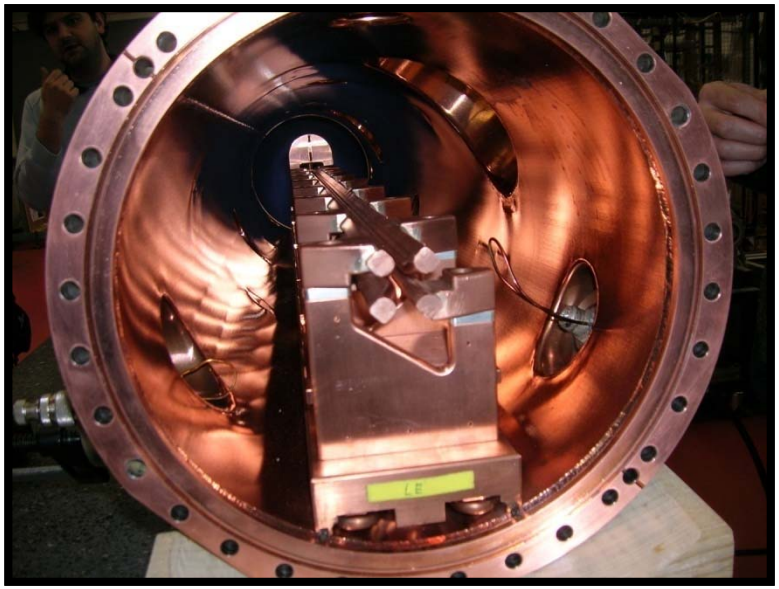
RFQ
0.008-0.4 MeV/u H_3^+
0.008-0.4 MeV/u C^{4+}

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

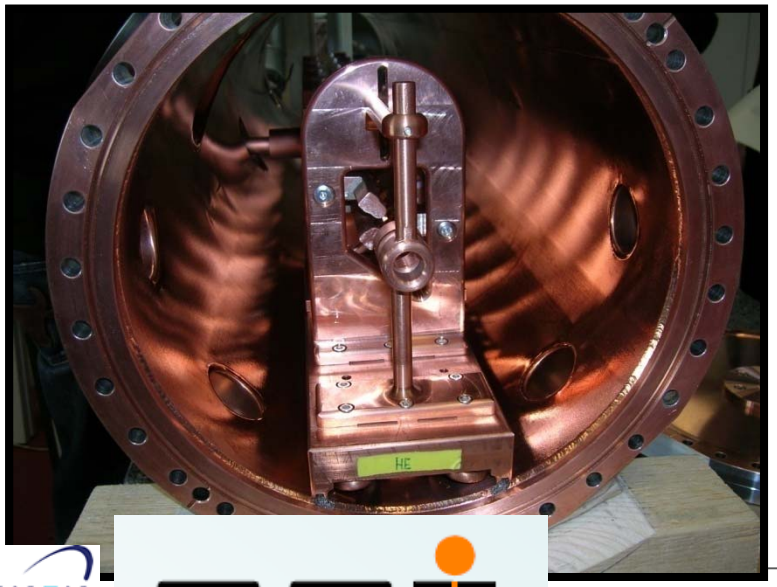
CNAO RFQ



RFQ internal structure



Ion input



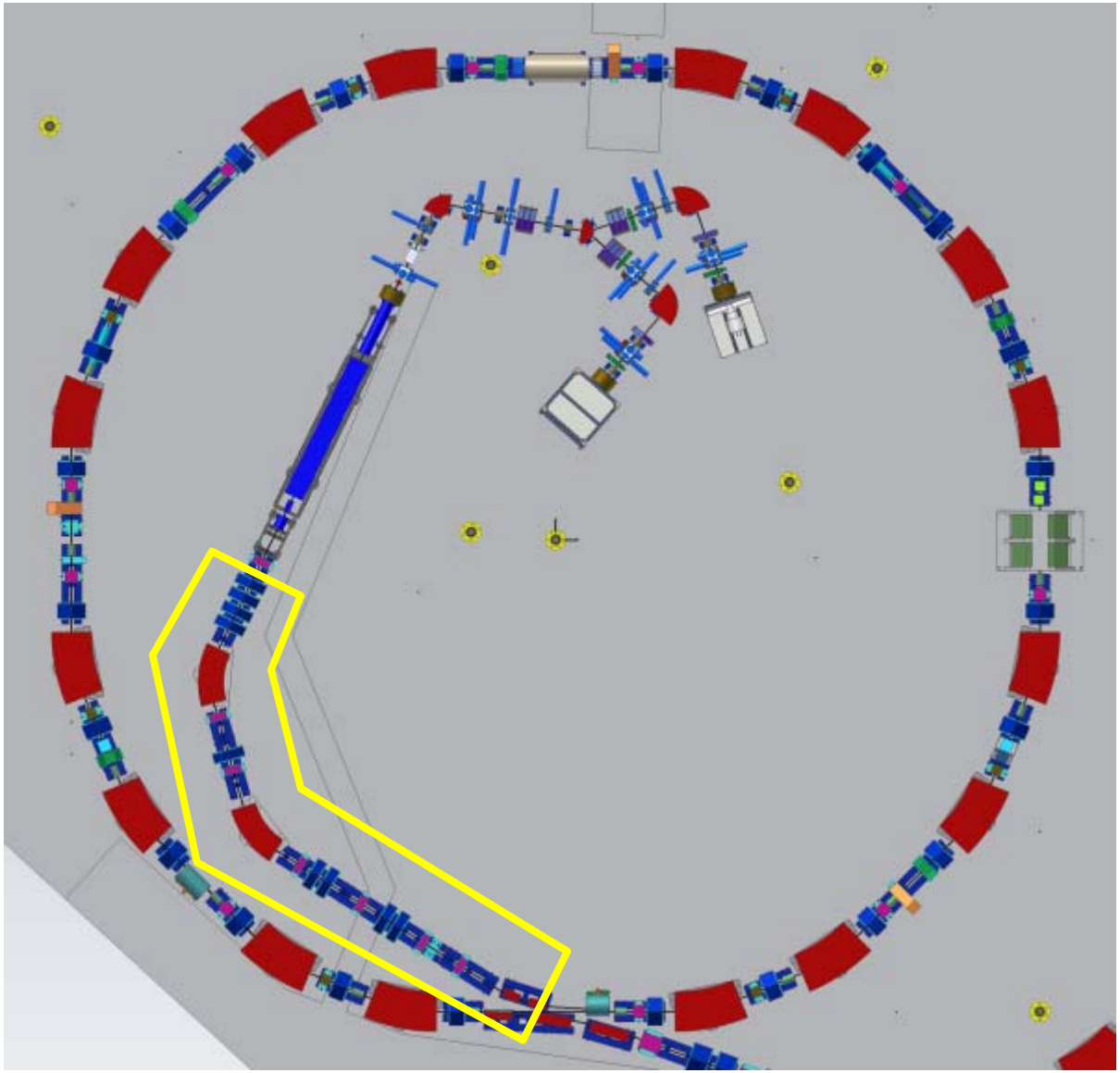
Ion exit

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



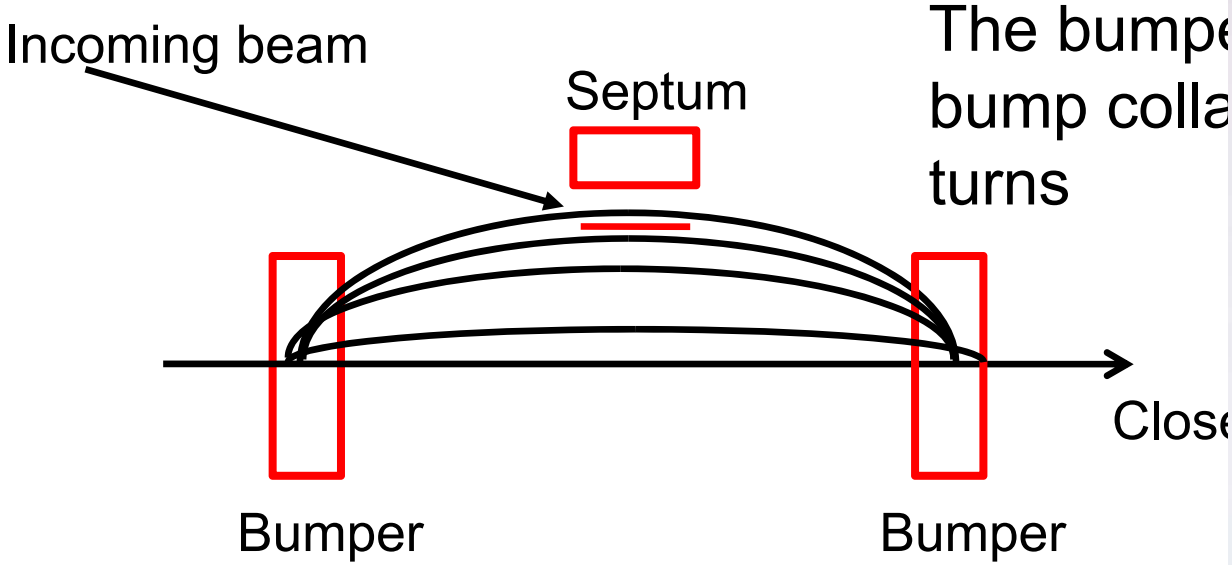
MEBT

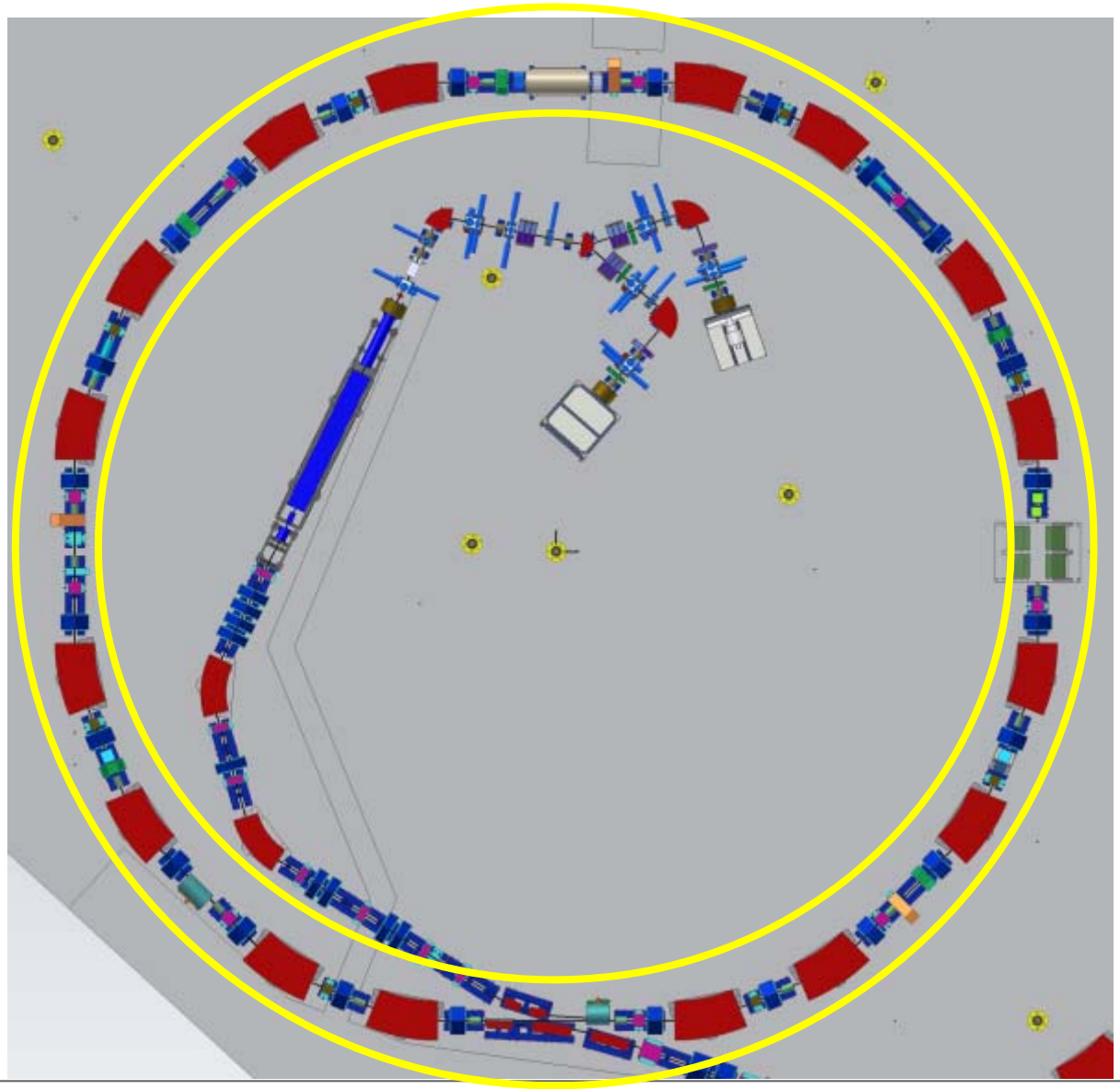
7 MeV p
7 MeV/u C^{6+}

I ~ 0.7 mA (p)
I ~ 0.15 mA (C^{6+})

Stripping foil

Multiturn injection





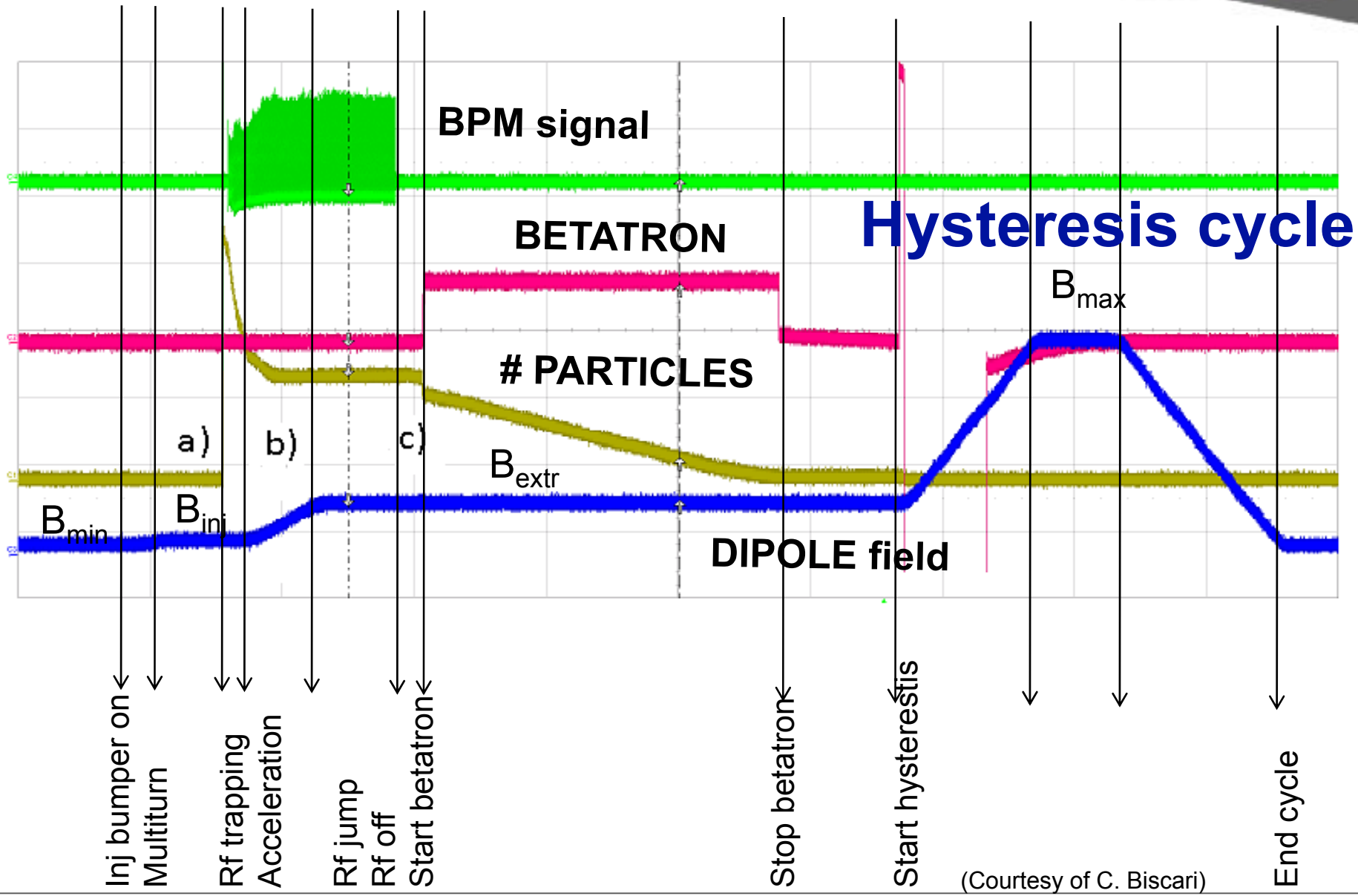
Synchrotron

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

I ~ 0.1-6 mA (p)
I ~ 0.03-1.5 mA (C)

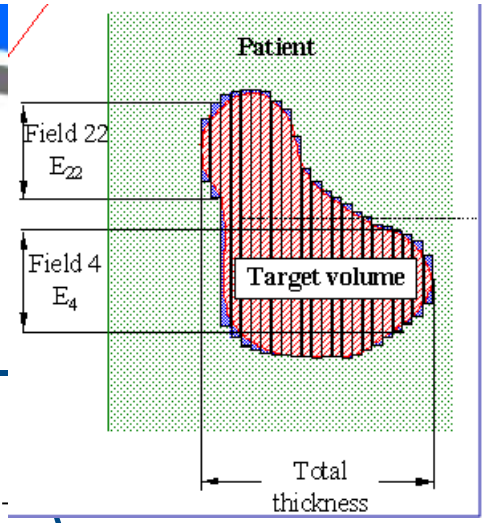
Slow extraction

Machine Cycle



(Courtesy of C. Biscari)

Treatment execution



Synchrotron magnets

1 s

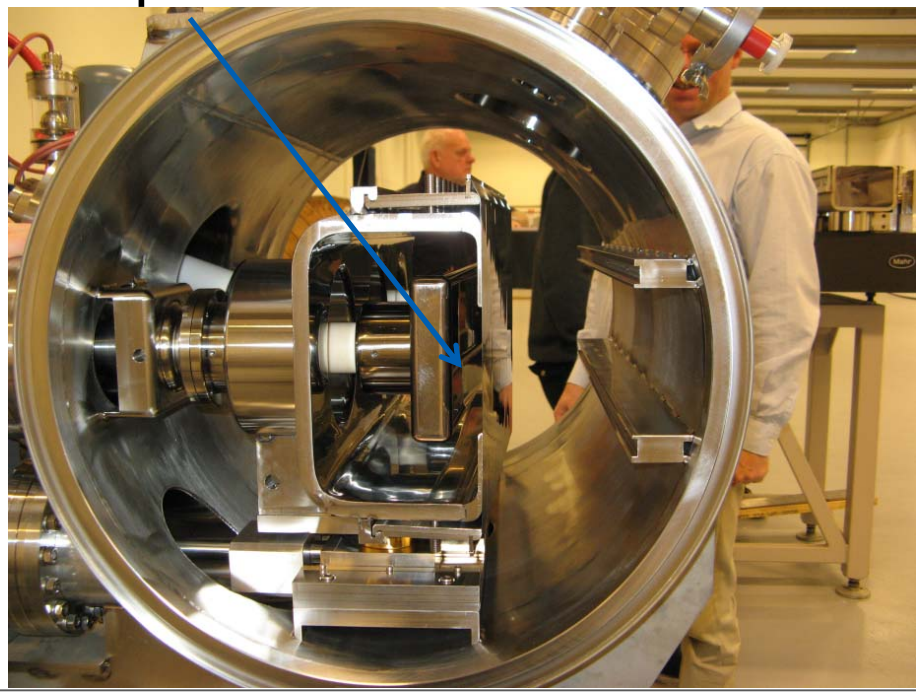
Extraction magnets

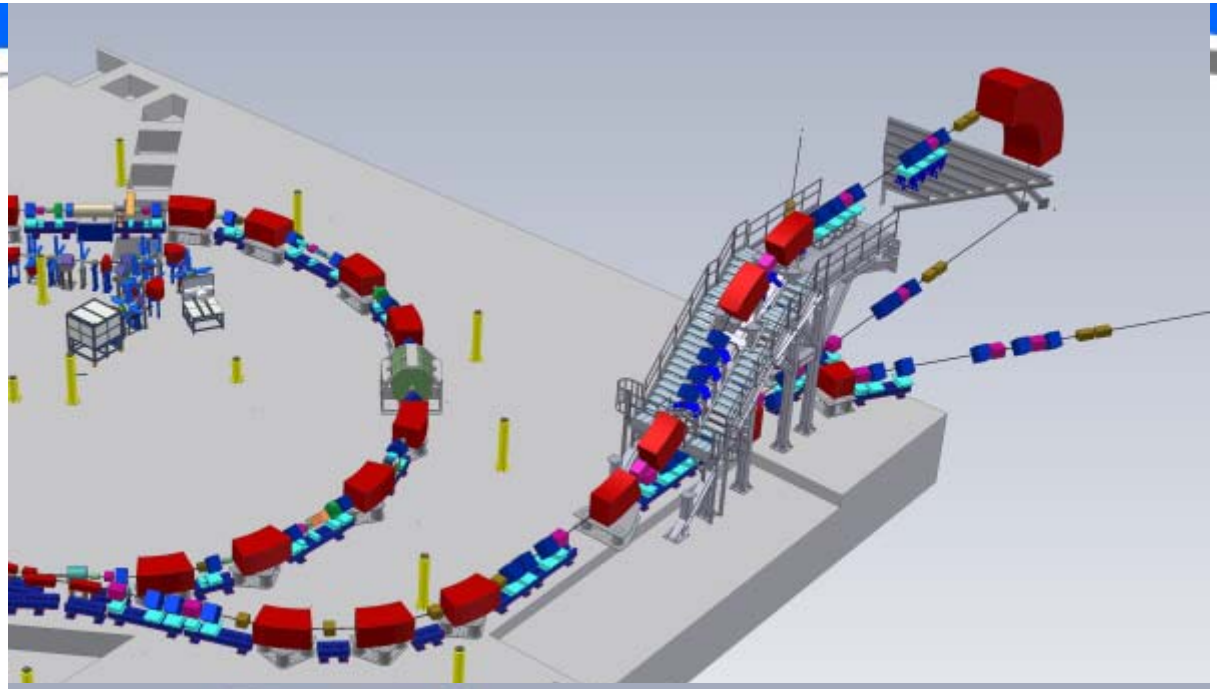
Injection magnets

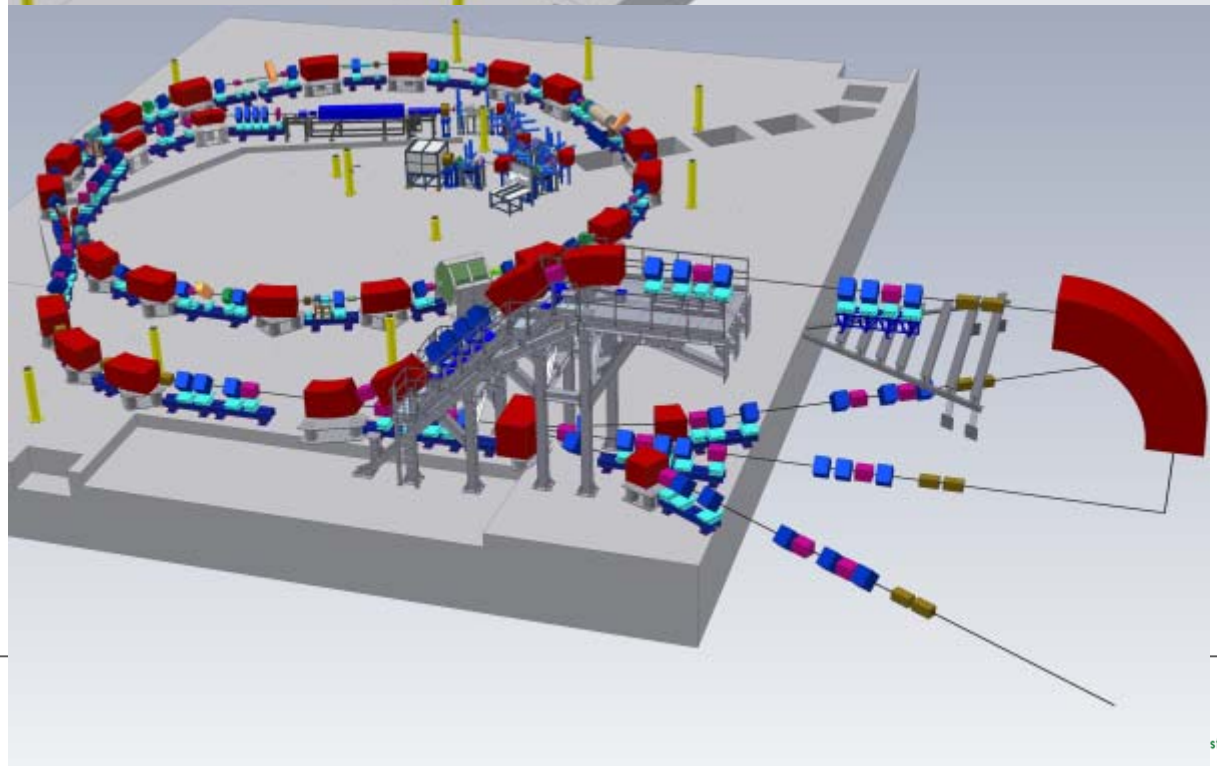
Extracted beam

Slow extraction

- Extract beam over millions turns. "Peel the beam".







HEBT

60-250 MeV p
120-400 MeV/u C

10^{10} p/spill (~2nA)
4 10^{8} C/spill (~0.4nA)

different settings for

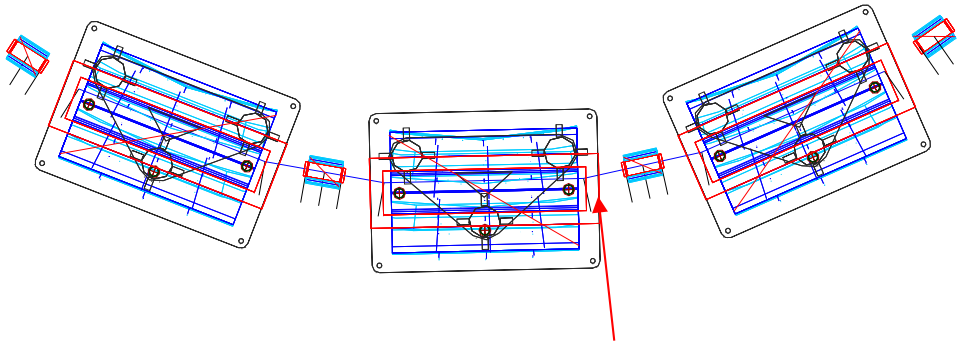
- **Treatment Line**
- **Horizontal beam size**
- **Vertical beam size**
- **Extraction energy**

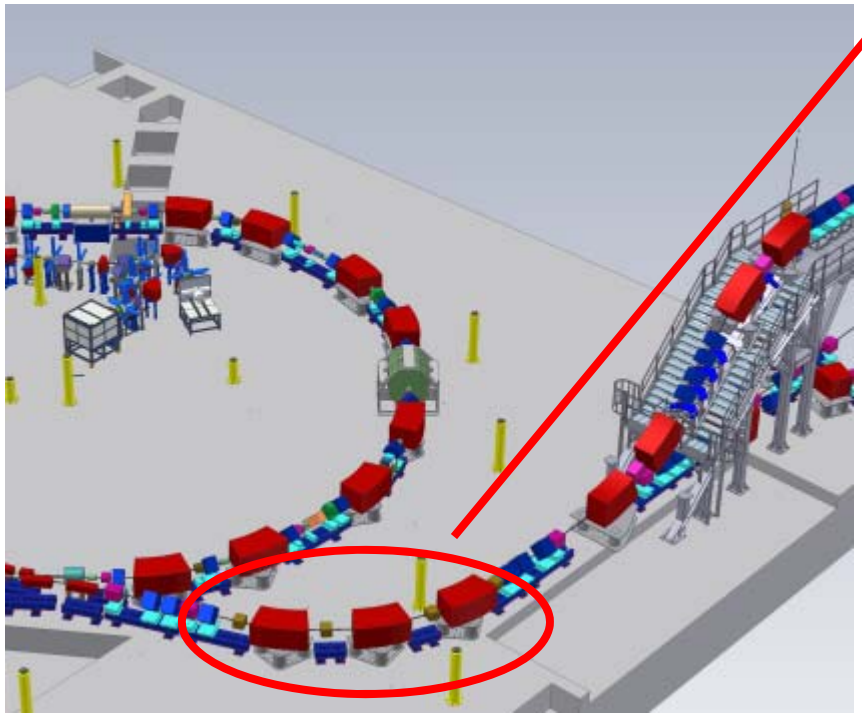
Chopper

Fast turn on/off for the beam

Intrinsically safe

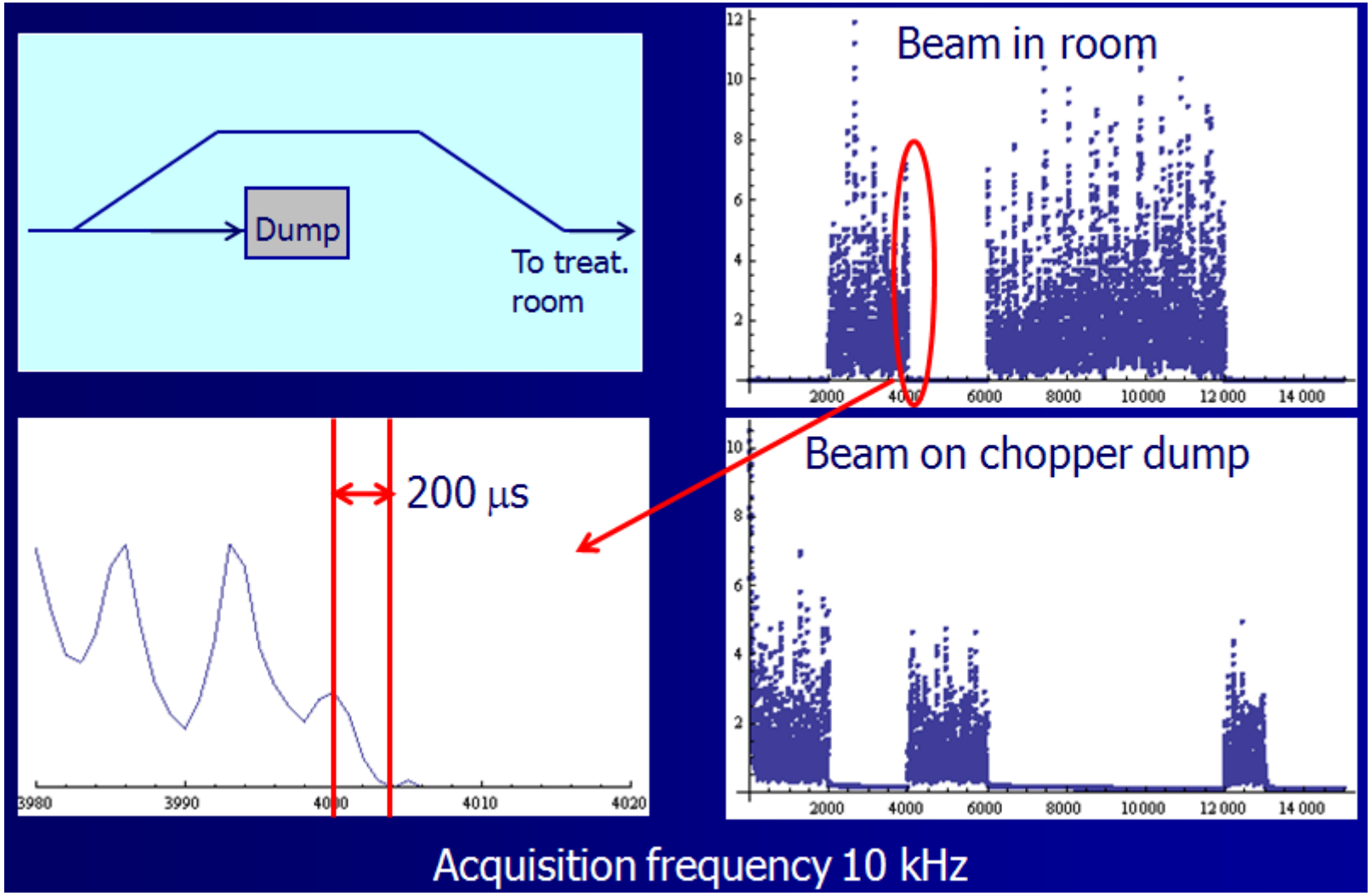
Allows beam qualification





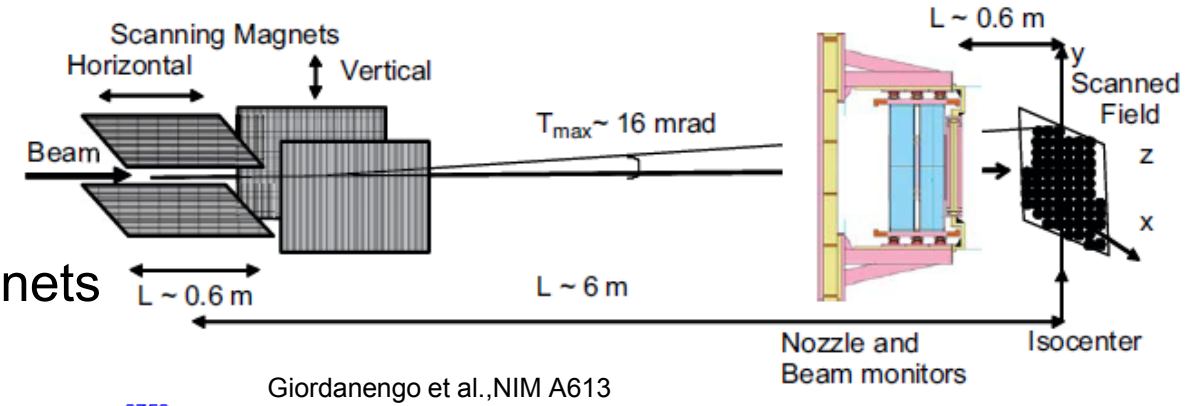
parts
with
breathing.

Chopped beam

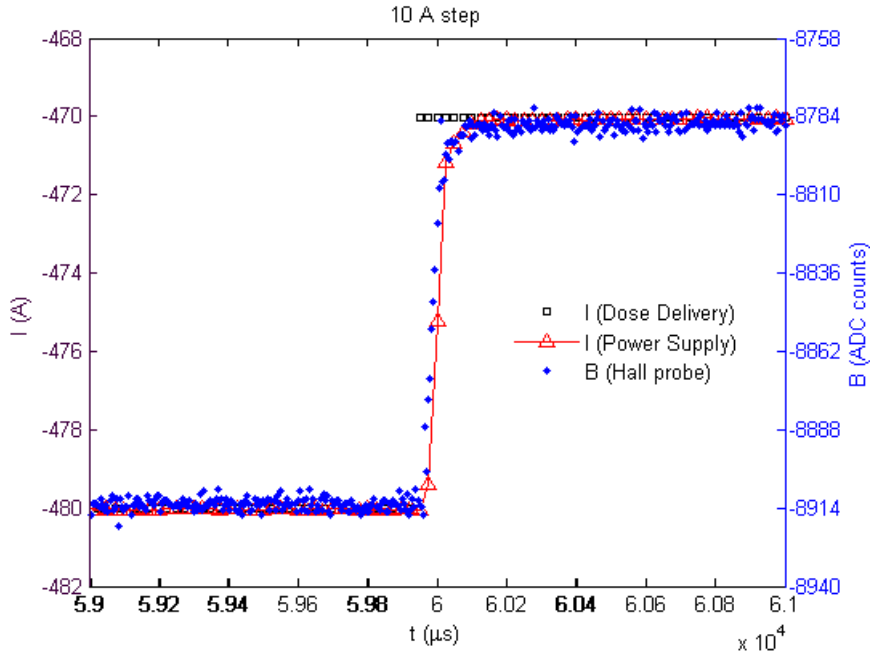


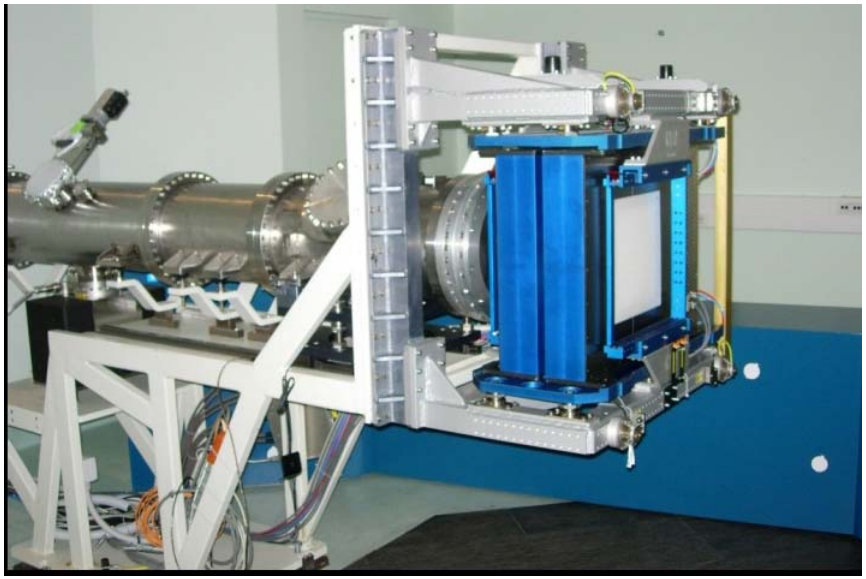
Dose delivery

- Dose driven
- Real time measurement
- Feedback on scanning magnets



Giordanengo et al.,NIM A613



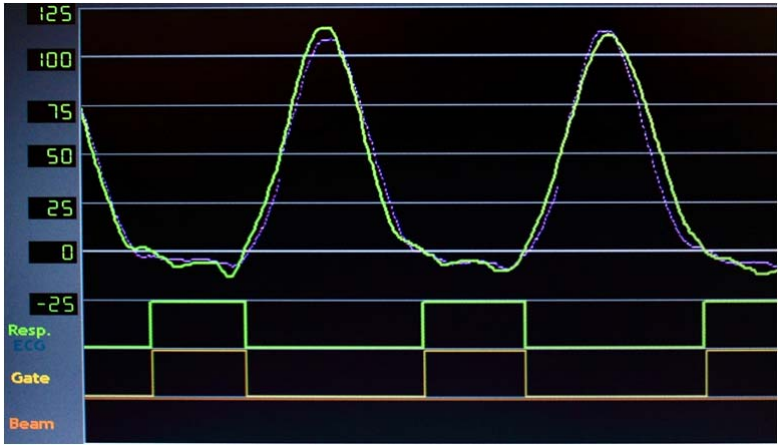


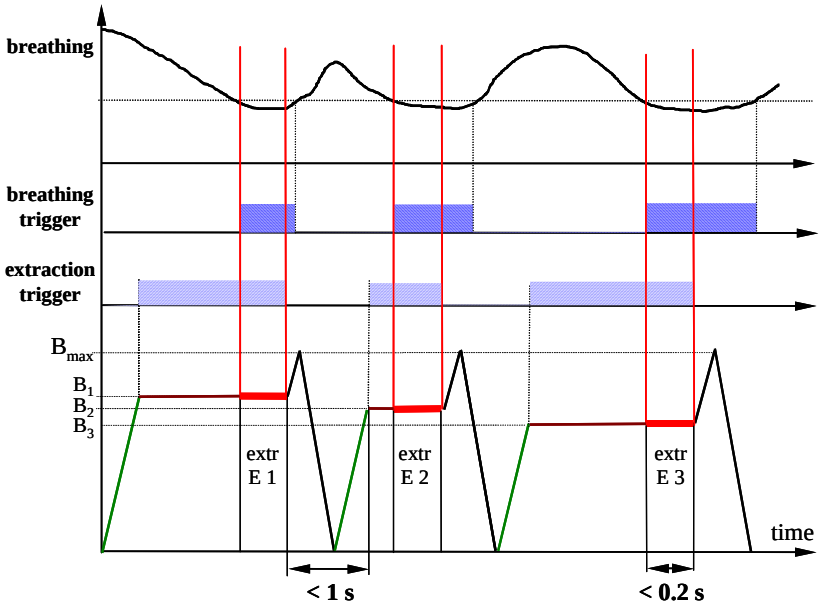
< Δt > = 35.1 ± 3.5 μs between 20% to 80%

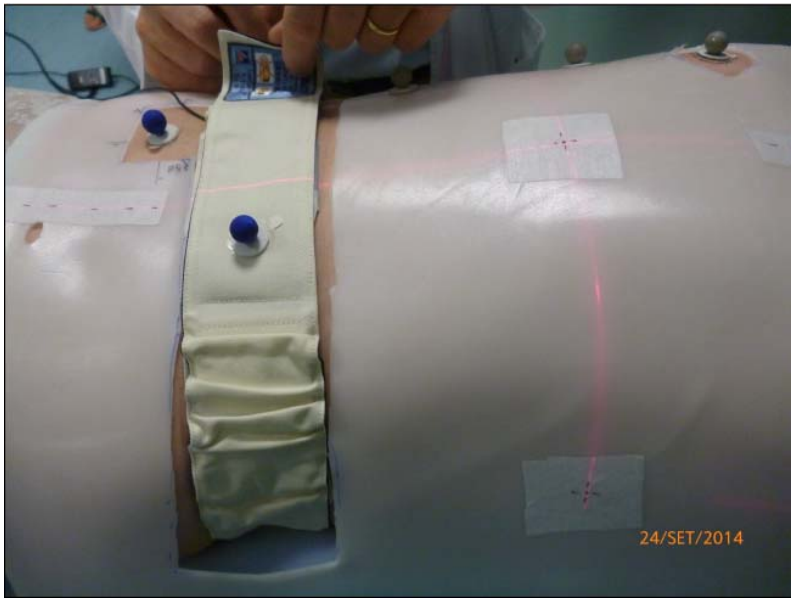
ΔI /Δt ~ 170 kA/s or ~ 85 T/sec

Gating + rescanning

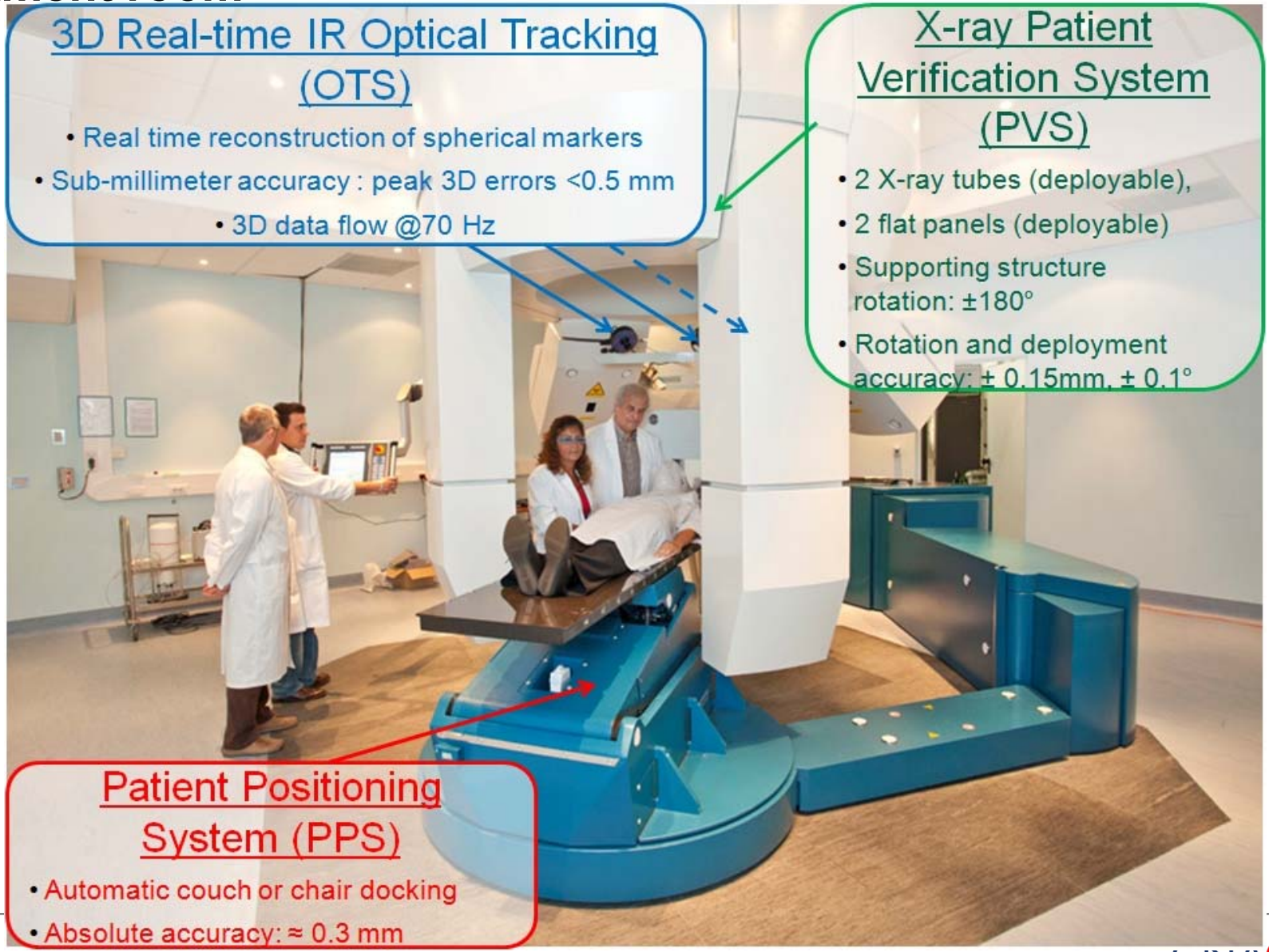
When a tumor cannot be immobilized it is treated only when it is in the "right position". Rescanning is applied to reduce the interplay effect.





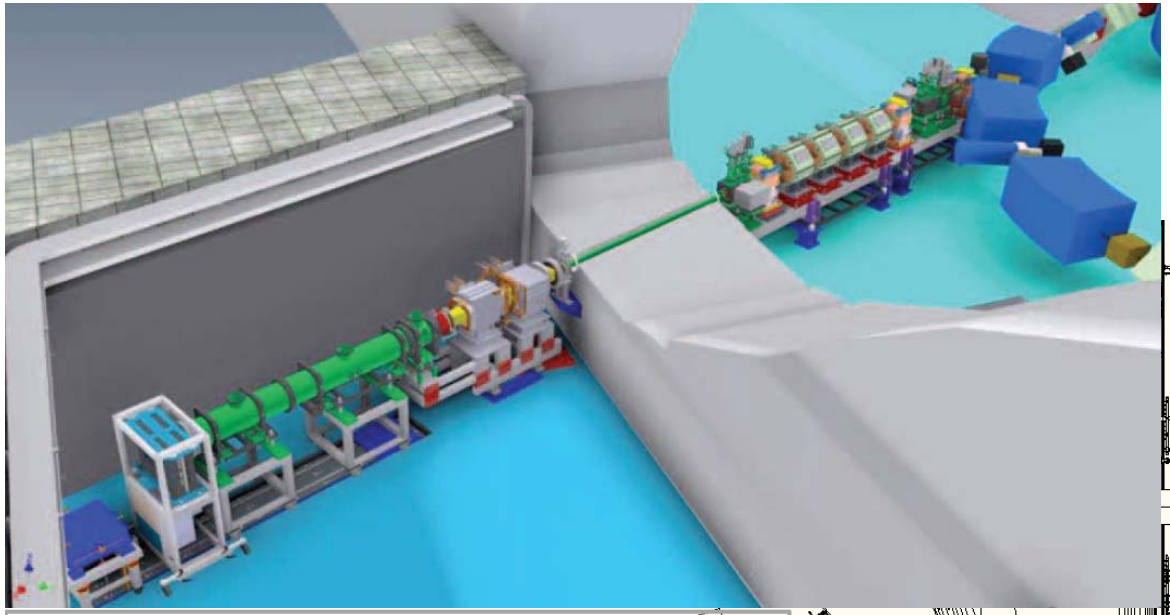


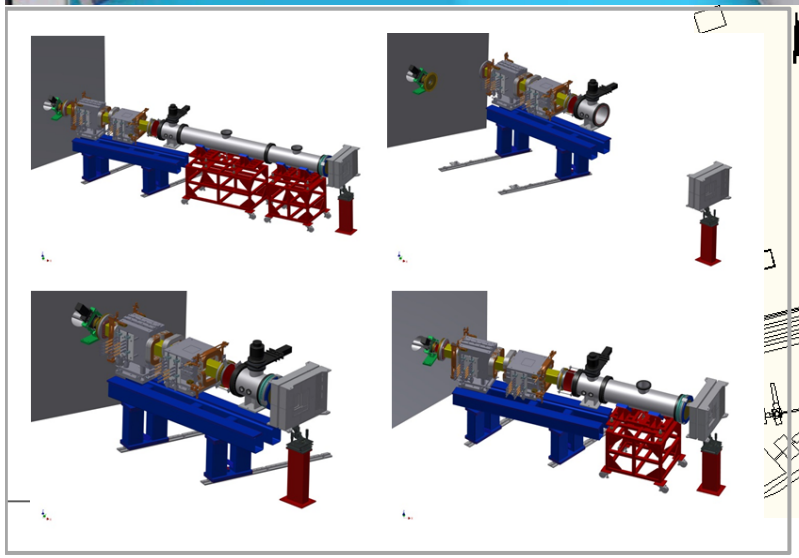
Treatment room

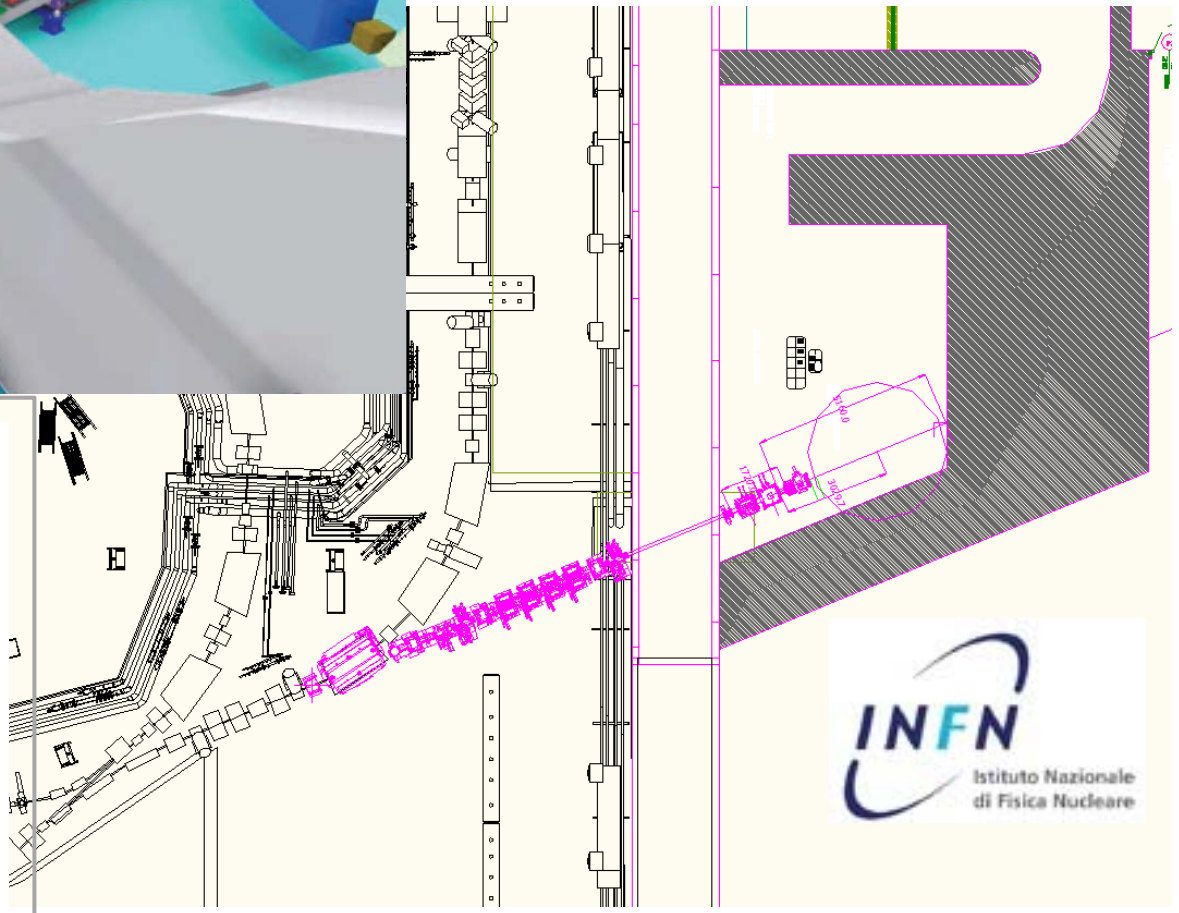


Future and R&D

Experimental room





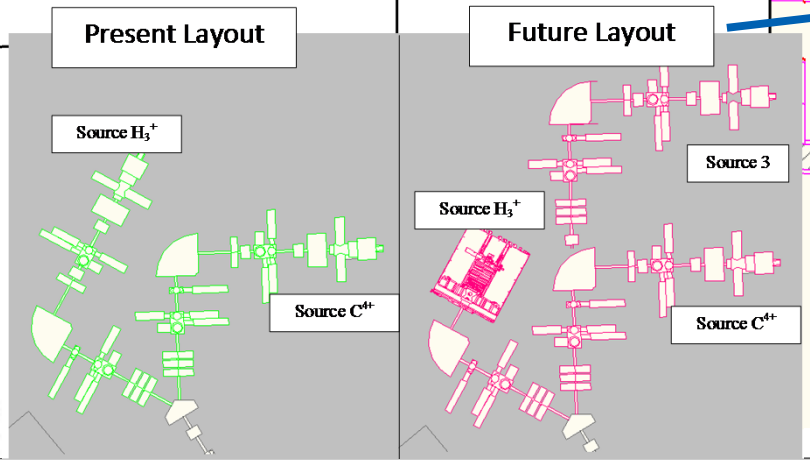


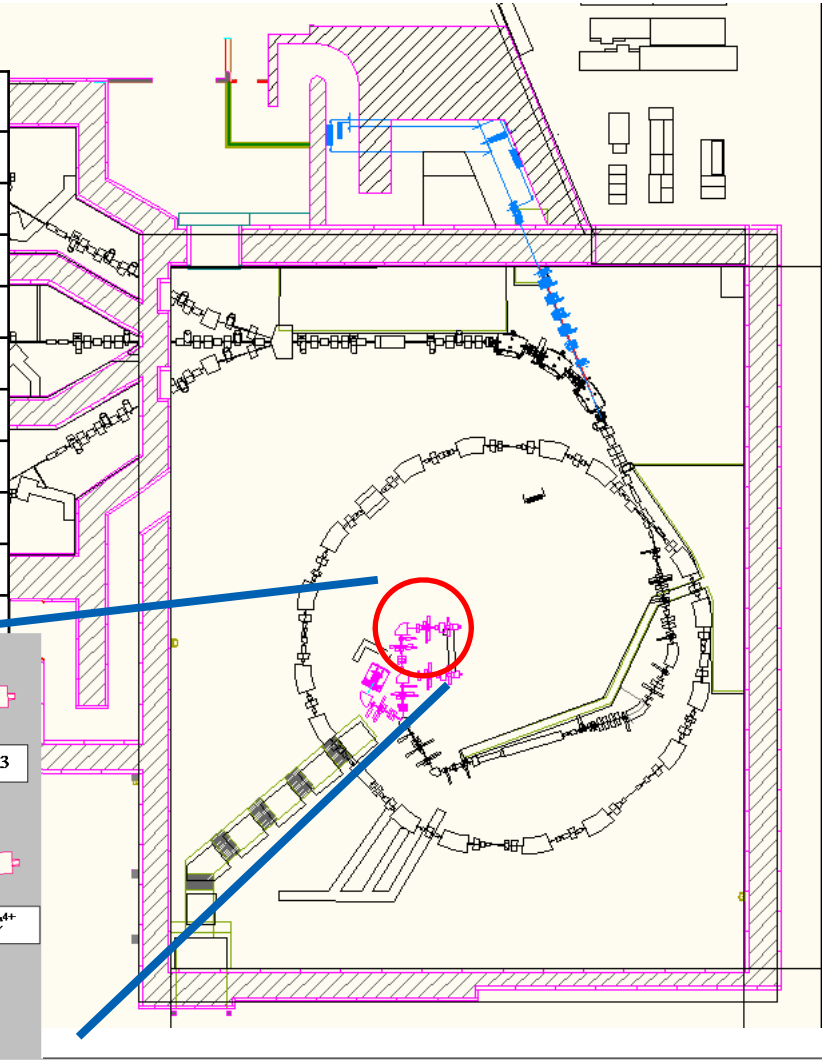
Experimental room – phase 2 – 3rd source

Additional ion species

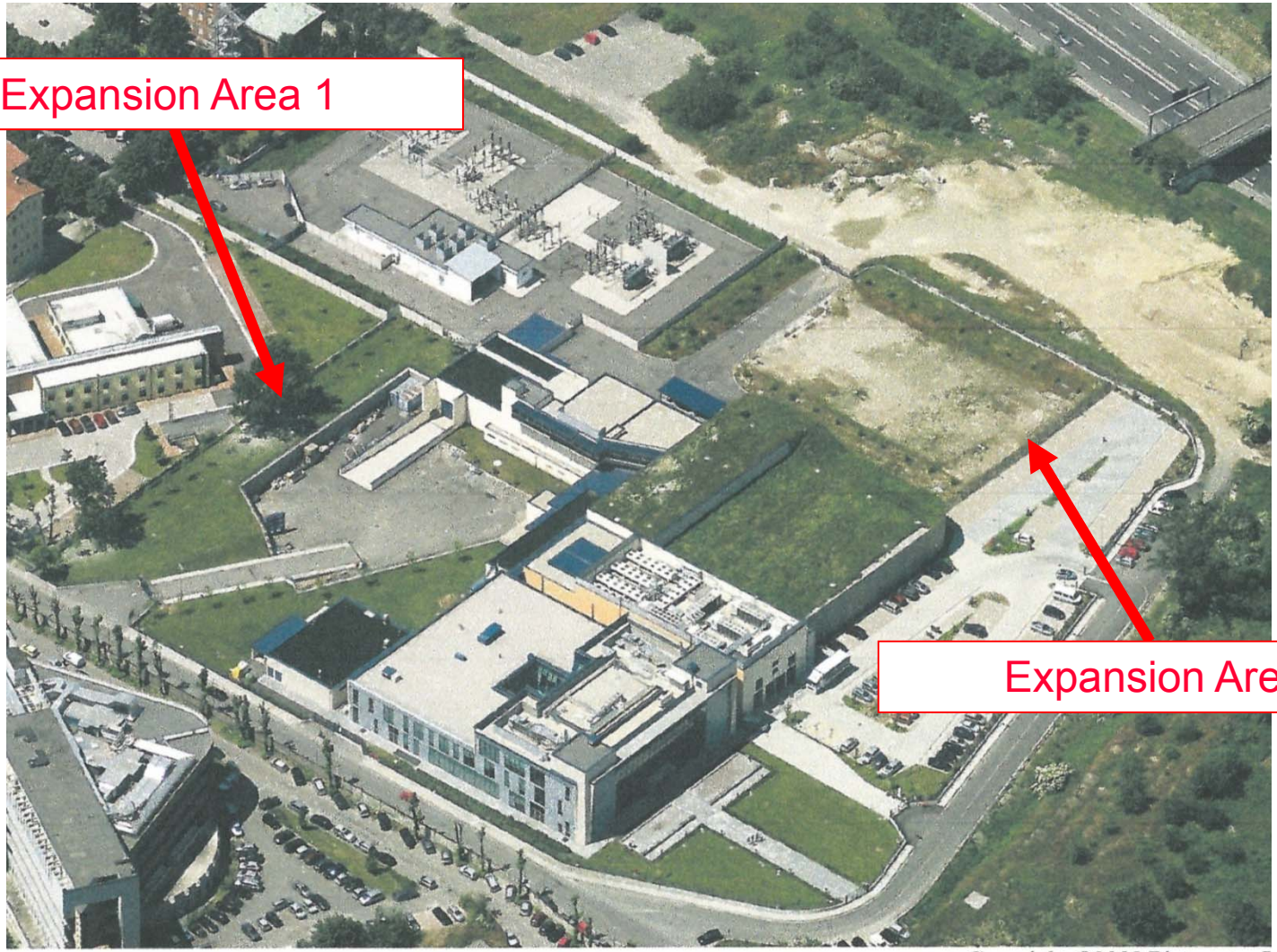
Higher performances source

Ion	SUPERNANOGAN (14.5 GHz)	AISHa (18 GHz + TFH)
	[μA]	[μA]
H^+	2000	4000
H^{2+}	1200	2000
H^{3+}	800	1000
$^3He^+$ - $^4He^+$	800	2000
$^{12}C^{4+}$	200	800
$^6Li^{2+}$	//	600
$^{18}O^{6+}$	250	1000
$^{16}O^{6+}$	400	1200
$^{21}Ne^{7+}$ - $^{20}Ne^{7+}$		



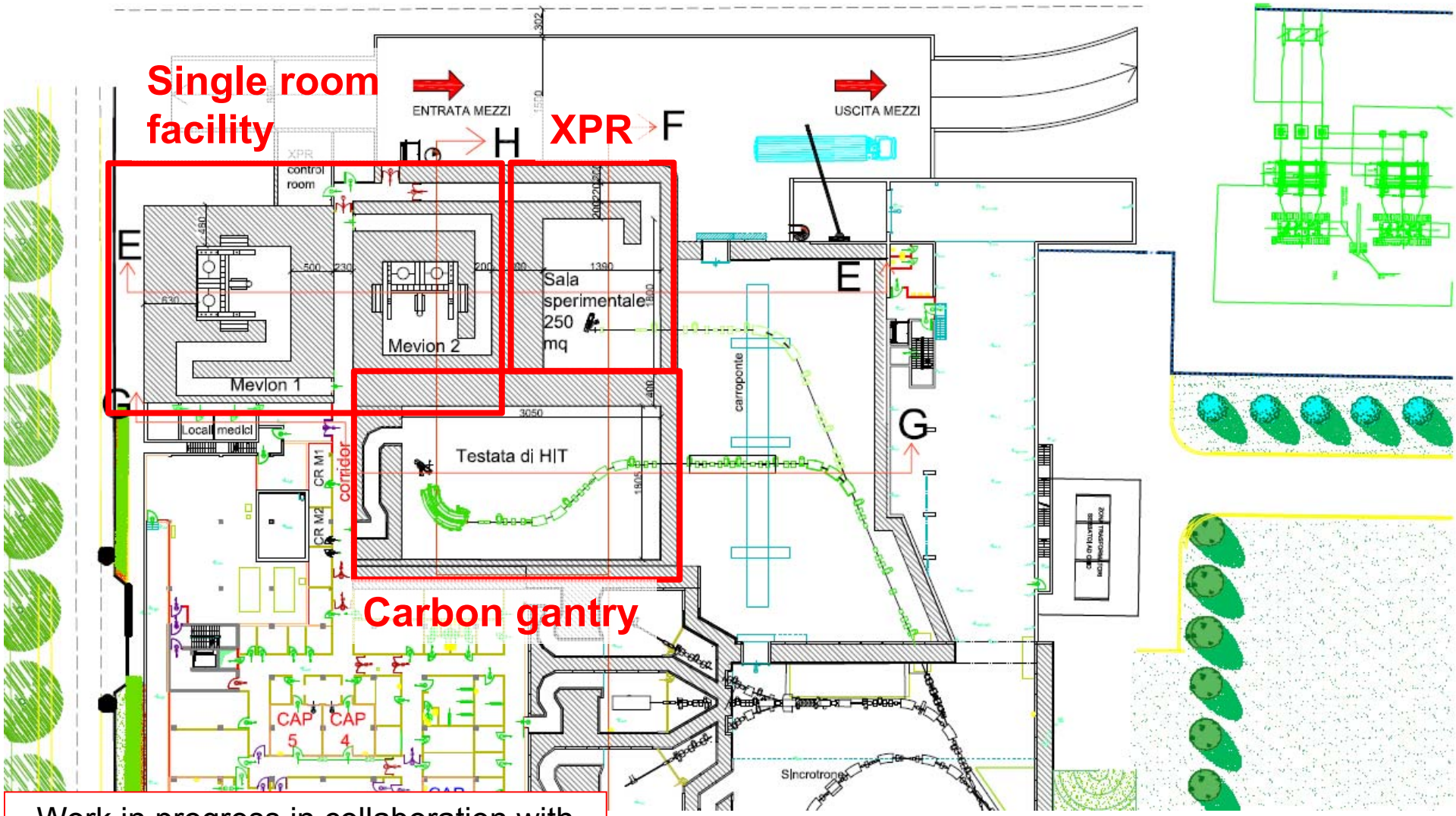


View of the site



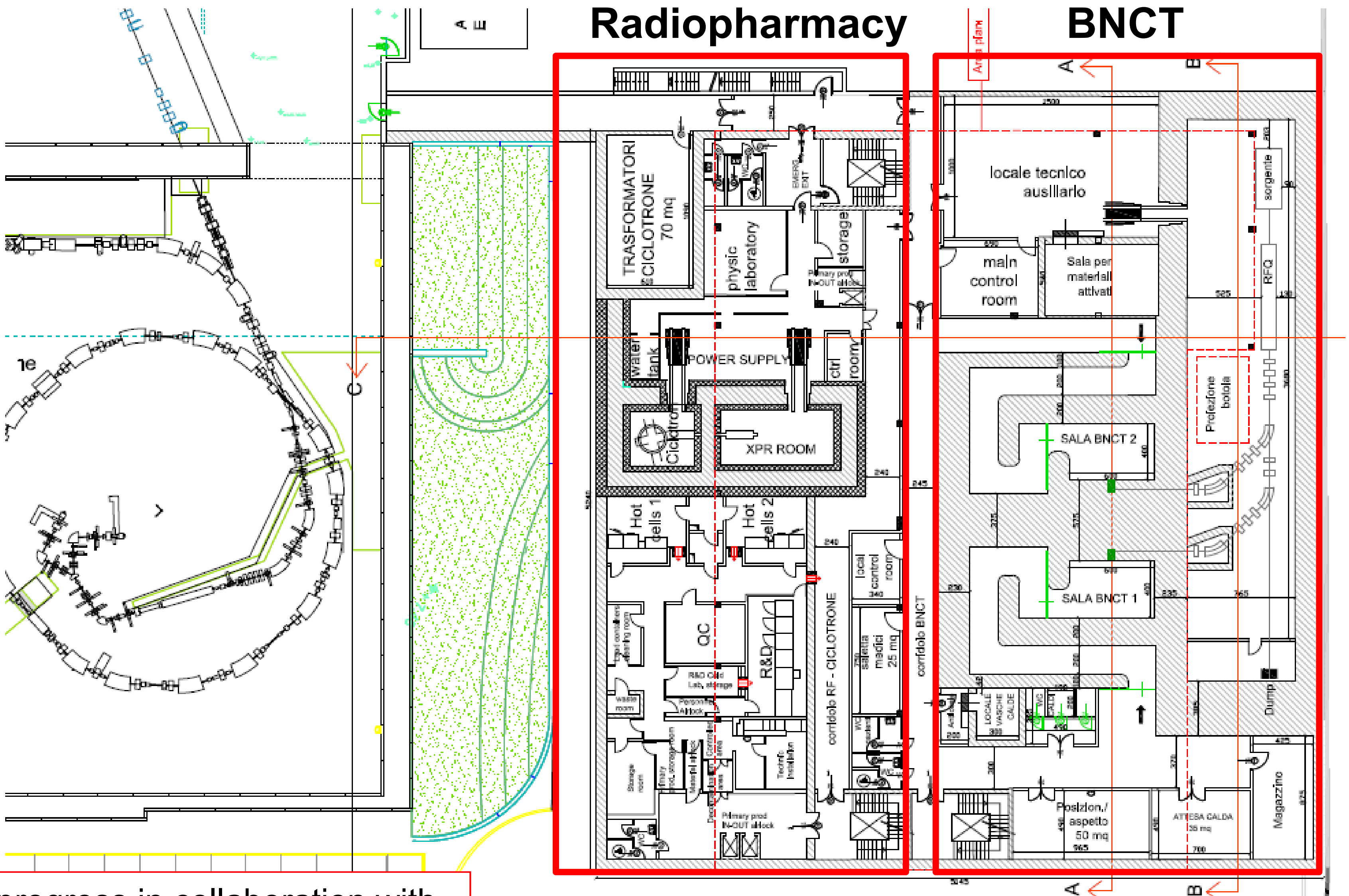
Deep wall to allow digging in the courtyard

Expansion Area 1



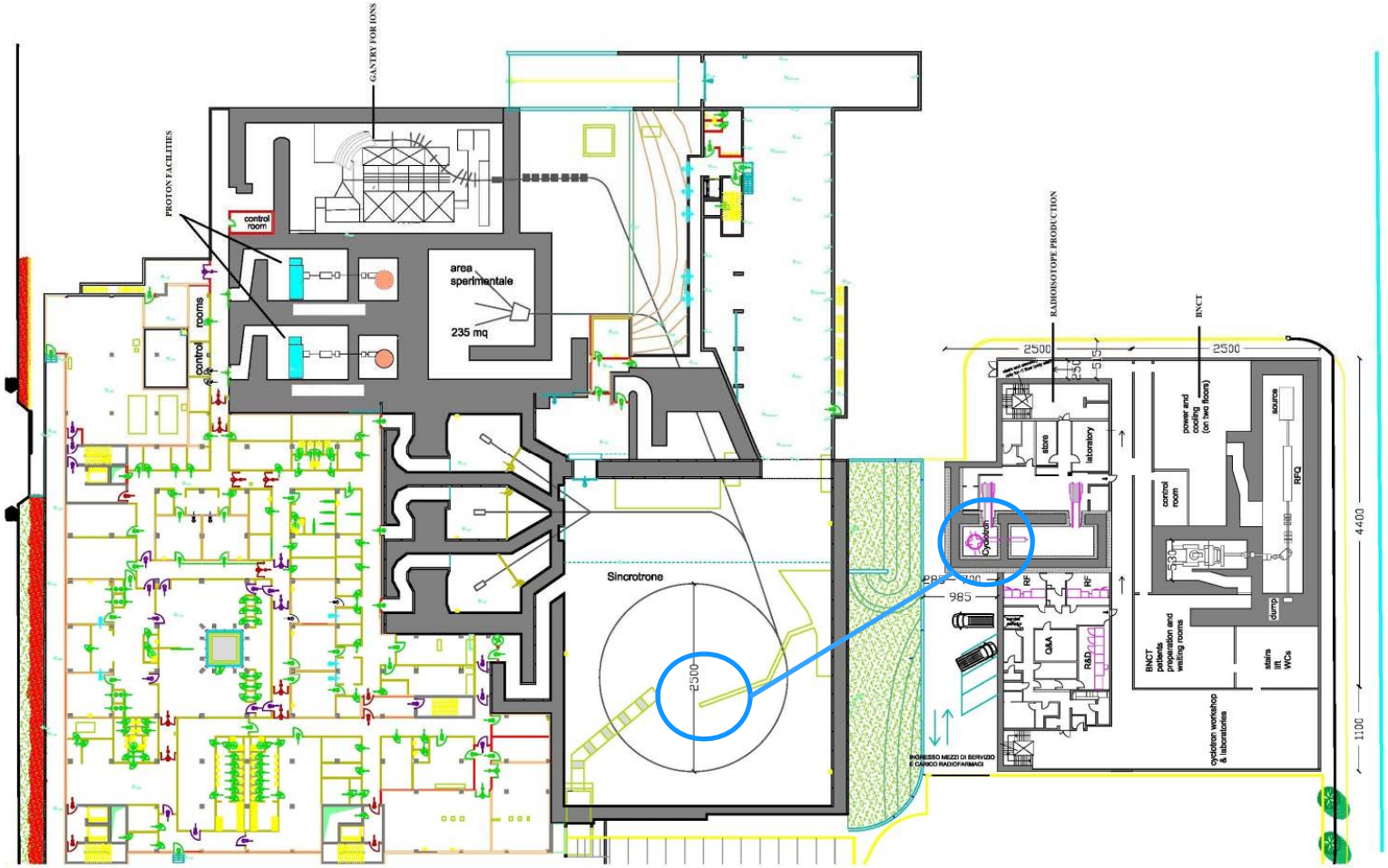
Work in progress in collaboration with TERA Foundation

Expansion Area 2



Work in progress in collaboration with TERA Foundation

C11 for improved online imaging

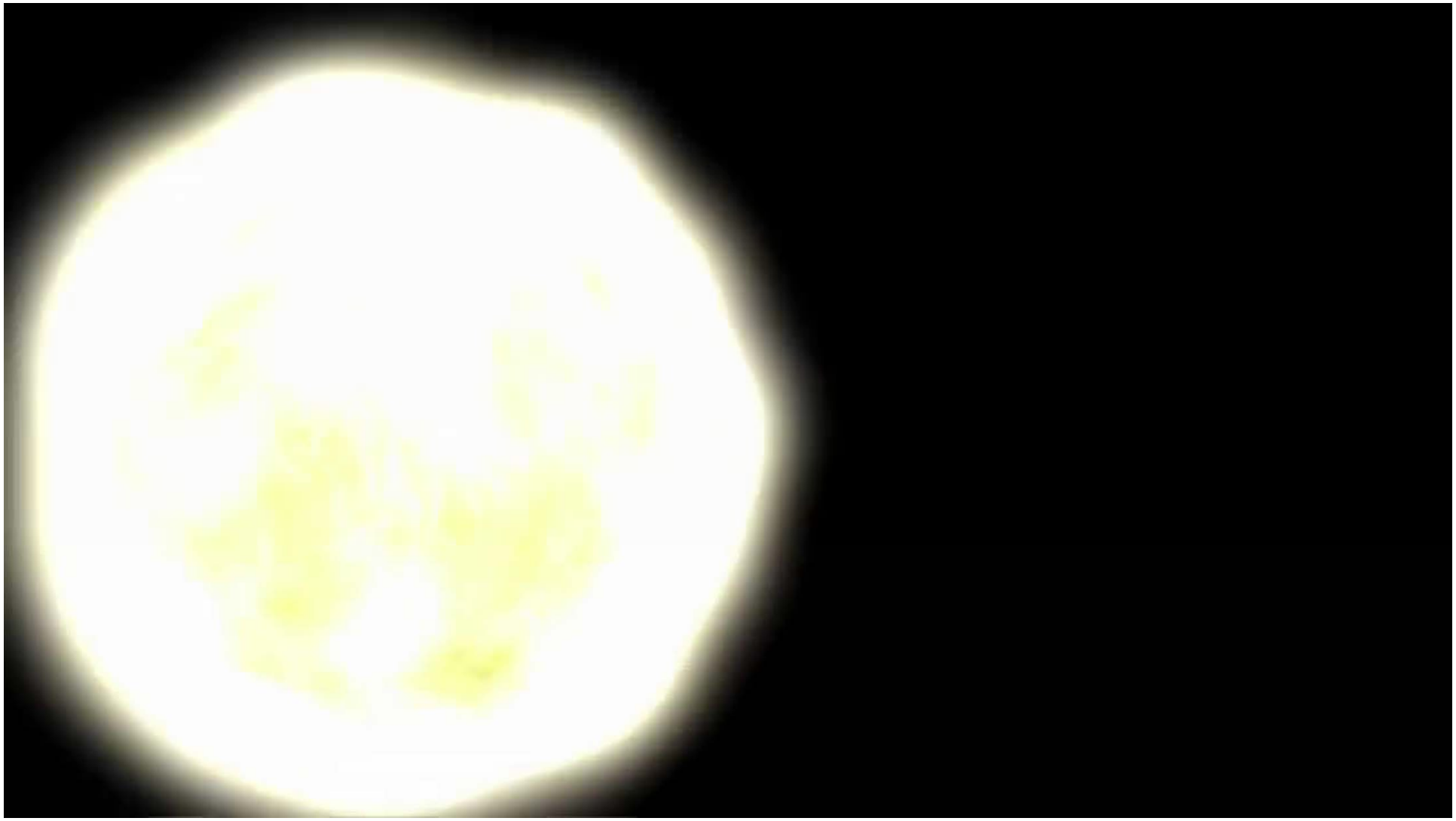


Work in progress in collaboration with TERA Foundation

Research is a must to keep CNAO up-to-date to stay always at the cutting edge

The Centre technology needs to evolve and adapt according to the research outcome: it is not a static "black box" producing beam, it is an evolving entity

And now some music



- Stolen from Alpinekat “Rare Isotope Rap”
- https://www.youtube.com/watch?v=677ZmPEFIXE

Thank you for your attention

“Physics is like sex: sure, it may give some practical results, but that's not why we do it. ”

R. Feynmann

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