THE THIRD BIENNIAL AFRICAN SCHOOL OF FUNDAMENTAL PHYSICS AND ITS APPLICATIONS

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Radionuclide production and radiation therapy

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- A brief recall on particle accelerators (for medical uses)

- Radionuclide production

- Radiation therapy

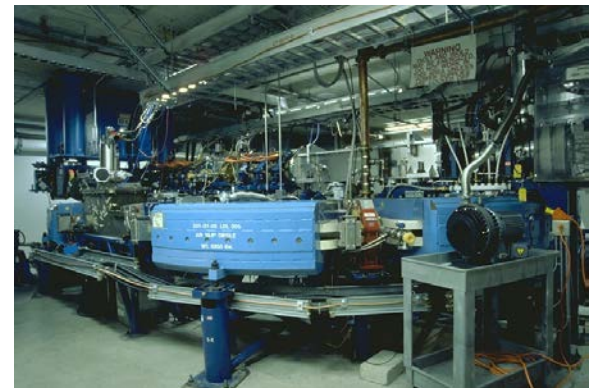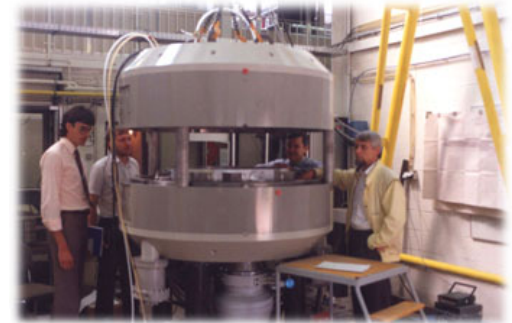# *Particle accelerators operational in the world*

Three main applications:

1) **Scientific research**
2) **Medical applications**
3) **Industrial uses**

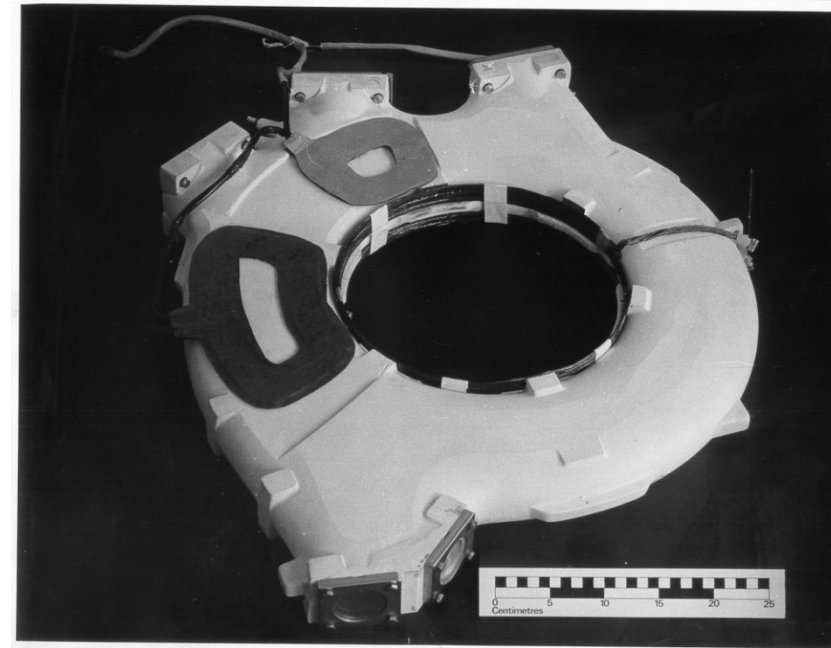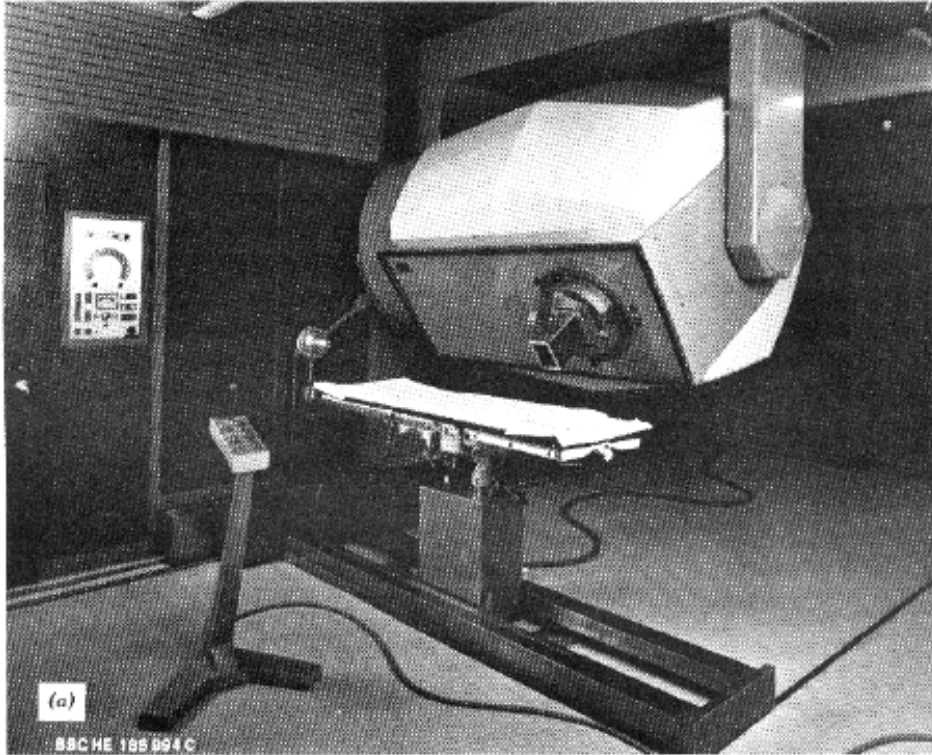| CATEGORY OF ACCELERATORS	NUMBER IN USE (*)	
High-energy accelerators (E >1 GeV)	~ 120	
Synchrotron radiation sources	> 100	
Medical radioisotope production	~ 1,000	
Accelerators for radiation therapy	> 7,500	10,000
Research accelerators including biomedical research	~ 1,000	
Industrial processing and research	~ 1,500	
Ion implanters, surface modification	> 7,000	
TOTAL	> 18,000	

Adapted from "Maciszewski, W. and Scharf, W., *Particle accelerators for radiotherapy, Present status and future*, Physica Medica XX, 137-145 (2004)"

- Production of radionuclides with (low-energy) cyclotrons
    o Imaging (PET and SPECT)
    o Therapy

- Electron linacs for conventional radiation therapy, including advanced modalities

- Medium-energy cyclotrons and synchrotrons for hadron therapy with protons (250 MeV) or light ion beams (400 MeV/u ^{12}C-ions)
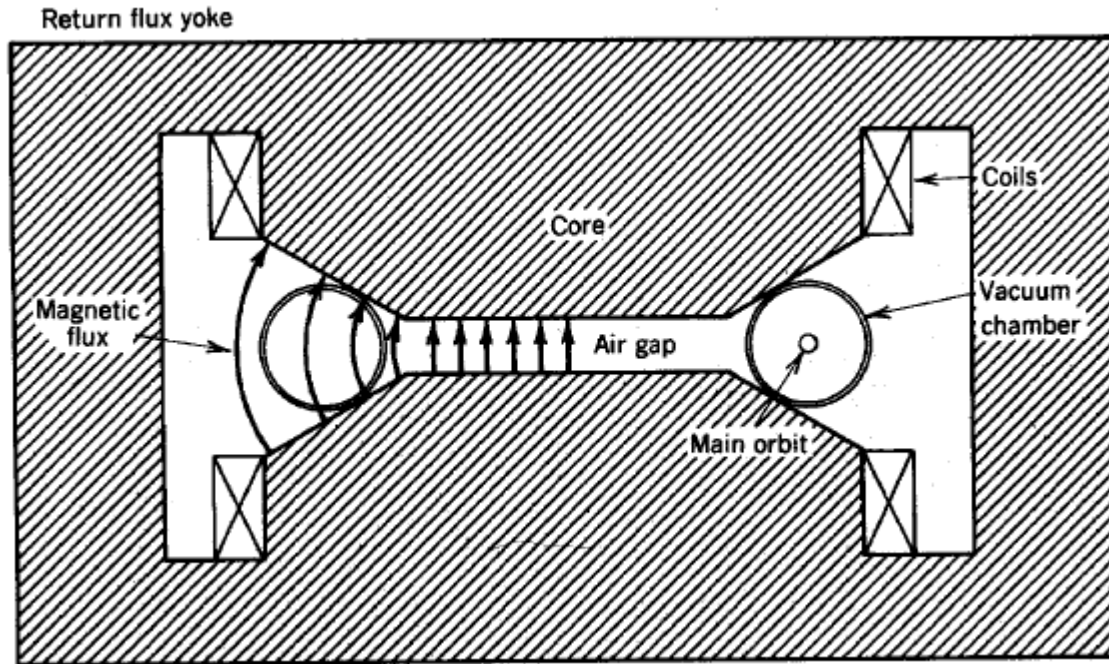   o Accelerators and beam delivery
    o New concepts

CERN accelerators

velocity

CPS

c

Medical cyclotrons
and synchrotrons

SPS / LHC

Einstein:
energy increases
not velocity

$\left.\begin{array}{c} \\ \\ \\ \end{array}\right\} E = mc^2$

energy

Newton: $E = \dfrac{1}{2}mv^2$

PSB
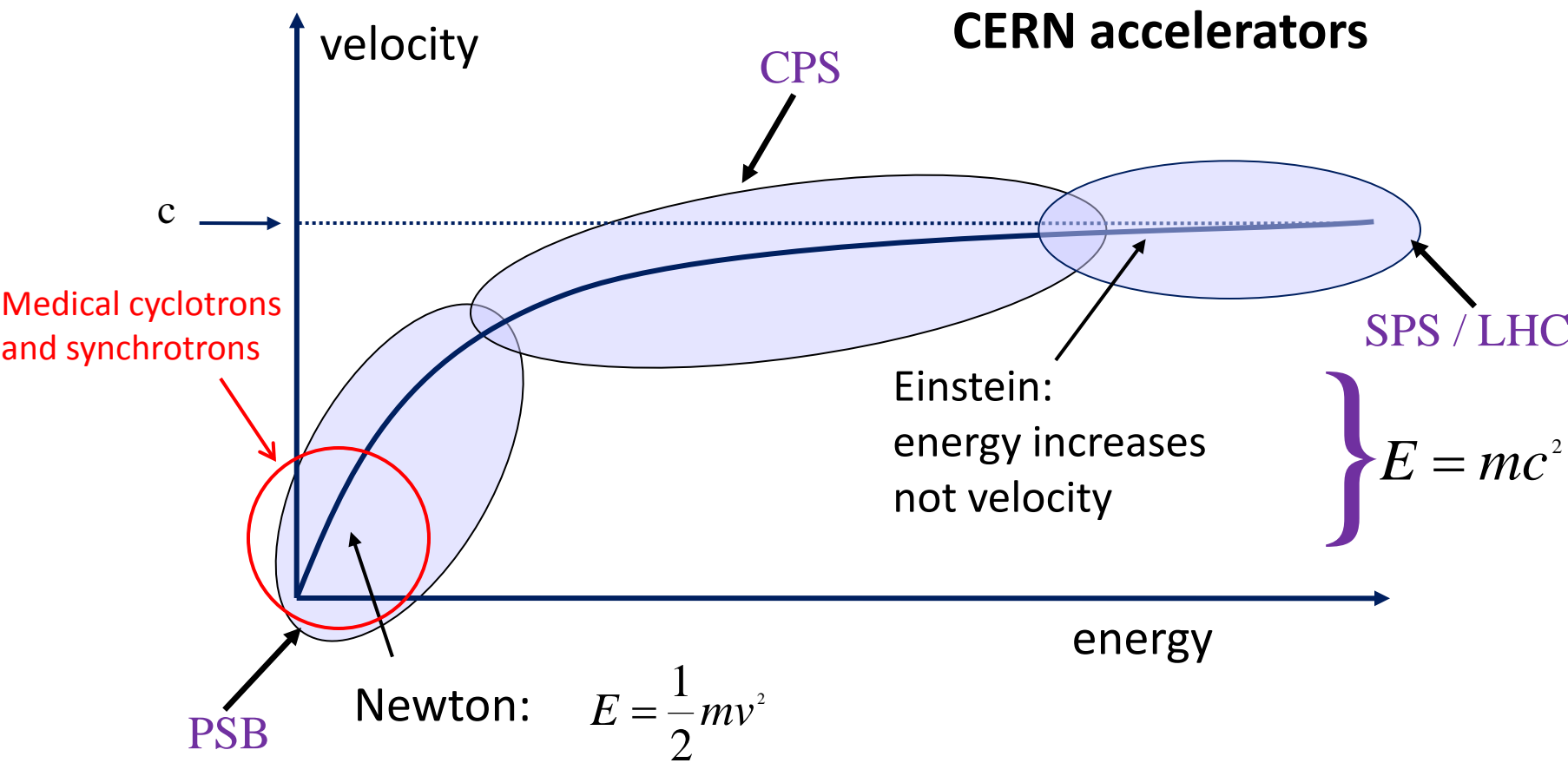
The betatron

Schematic diagram of betatron with air gap

$$B(R) = \frac{1}{2}\overline{B}(R)$$

$B(R)$ = field at the orbit

$\overline{B}(R)$ = average flux density through the orbit

- Magnetic field produced by pulsed coils
- The magnetic flux inside the radius of the vacuum chamber changes with time
- Increasing flux generates an azimuthal electric field which accelerates electrons in the chamber

Radionuclide production

The use of radionuclides in the physical and biological sciences can be broken down into three general categories:

- Radiotracers
- Imaging (95% of medical uses)
  SPECT (^{99m}Tc, ^{201}Tl, ^{123}I)
  PET (^{11}C, ^{13}N, ^{15}O, ^{18}F)
- Therapy (5% of medical uses)
  Brachytherapy (^{103}Pd)
  Targeted therapy (^{211}At, ^{213}Bi)

Relevant physical parameters (function of the application)

- Type of emission (α, β^+, β^-, γ)
- Energy of emission
- Half-life
- Radiation dose (essentially determined by the parameters above)

All radionuclides commonly administered to patients in nuclear medicine are artificially produced

Three production routes:

- (n,γ) reactions (**nuclear reactor**): the resulting nuclide has the same chemical properties as those of the target nuclide
- Fission (**nuclear reactor**) followed by separation
- Charged particle induced reaction (**cyclotron**): the resulting nucleus is usually that of a different element
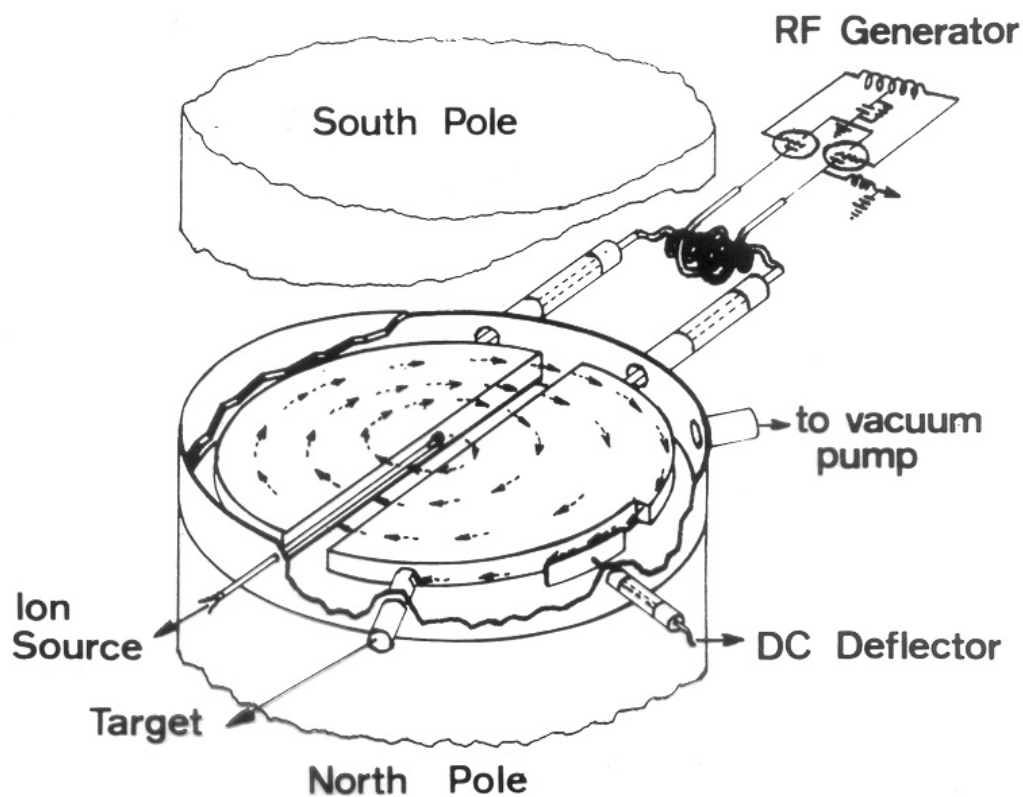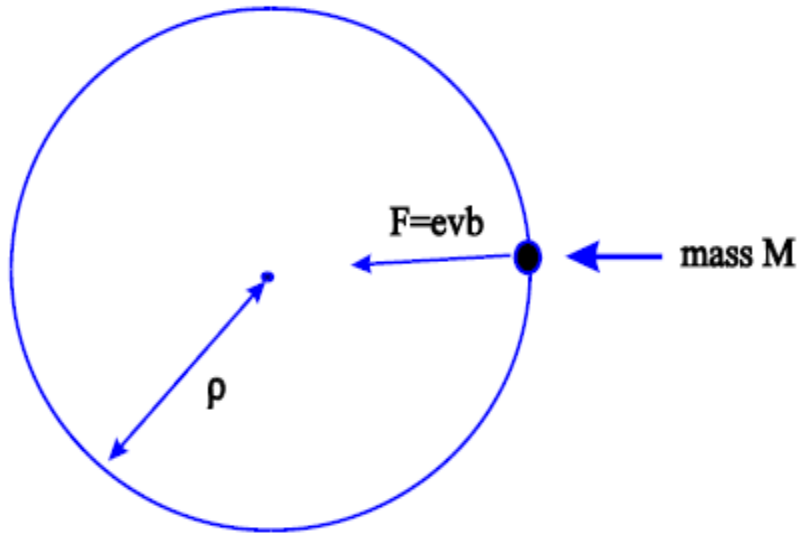
Scanditronix MC40

Motion of a particle in a dipole magnetic field

(the field is in/out of the plane of this slide)

F=evb

mass M

$$F = \frac{mv^2}{\rho}, \quad \text{where } \rho = \text{radius of curvature of the path}$$

$$F = evB = \frac{mv^2}{\rho}$$

(p = momentum = mv)

$$B\rho = \frac{mv}{e} = \frac{p}{e}$$

Bρ = 33.356·p [kG·m] = 3.3356·p [T·m] (if p is in GeV/c)

Bρ is called "magnetic rigidity" of the particle and is an index of how difficult is to bend the motion of a charged particle by a magnetic field

$F = q(\mathbf{E} + \mathbf{v} \times \mathbf{B})$

$mv^2 / \rho = qvB \qquad \omega = 2\pi f = v / \rho$

Rev. frequency $f = qB/2\pi m$

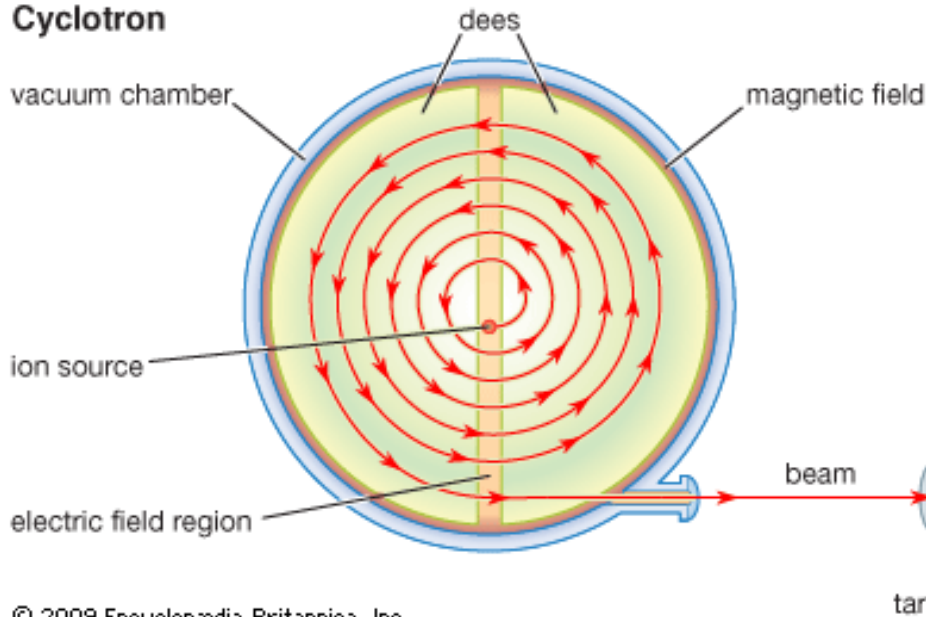Rev. period $\tau = 1/f$ is independent of v

Resonant acceleration with $f_{RF} = h \cdot f$

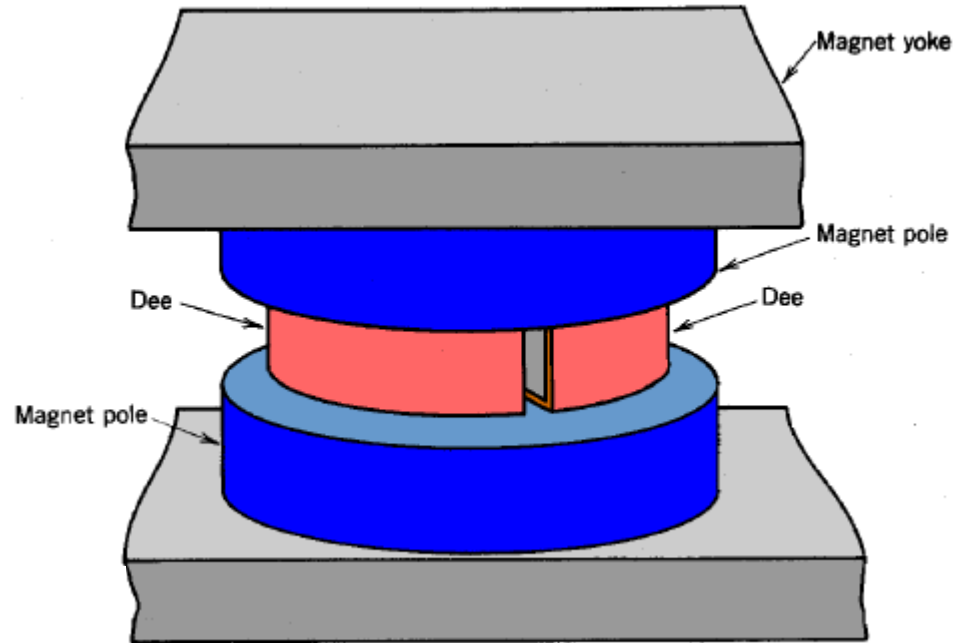⟹ Isochronism

Maximum energy/nucleon:

$T/A = k \, (B\rho)^2 \, (Z/A)^2$
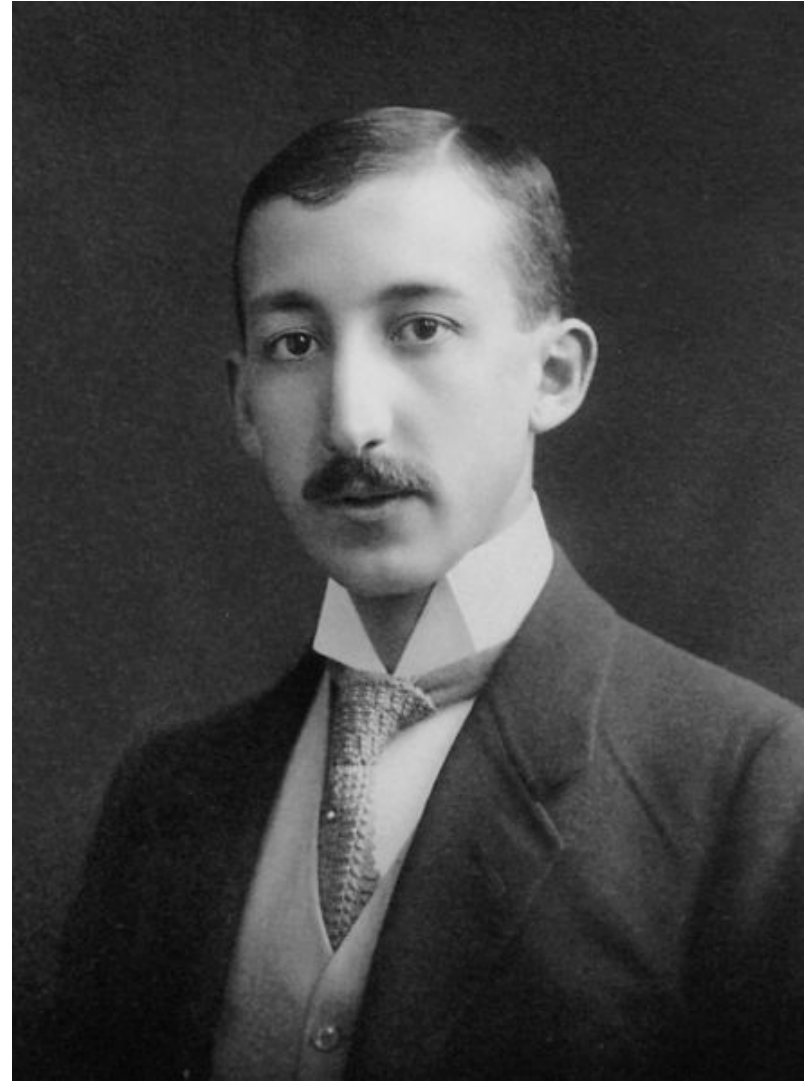
with $k = e^2 / 2m_p$

$K = k \, (B\rho)^2$ is called "bending limit"
$K = 48 \, (B\rho)^2 \quad$ (MeV)
if B is in teslas and m in metres

- 1911: **first practical application of a radioisotope** (as *radiotracer*) by G. de Hevesy, a young Hungarian student working with naturally radioactive materials in Manchester

- 1924: de Hevesy, who had become a physician, used radioactive isotopes of lead as tracers in bone studies

- 1932: the invention of the cyclotron by E. Lawrence makes it possible to produce radioactive isotopes of a number of biologically important elements

- 1941: **first medical cyclotron** installed at Washington University, St. Louis, for the production of radioactive isotopes of phosphorus, iron, arsenic and sulphur

- After WWII: following the development of the fission process, most radioisotopes of medical interest begin to be produced in nuclear reactors

- 1951: Cassen et al. develop the concept of the rectilinear scanner

- 1957: the ^{99}Mo/^{99m}Tc generator system is developed by the Brookhaven National Laboratory

- 1958: production of the first gamma camera by Anger, later modified to what is now known as the Anger scintillation camera, still in use today

External versus internal radiation sources
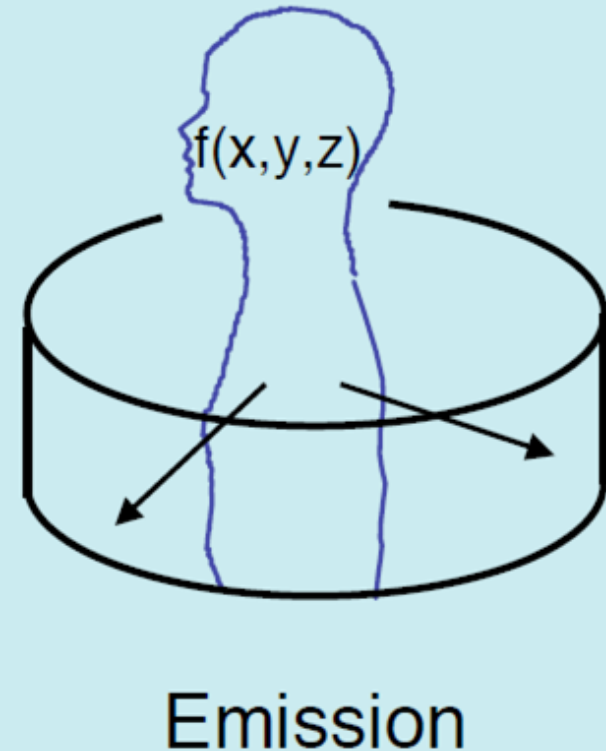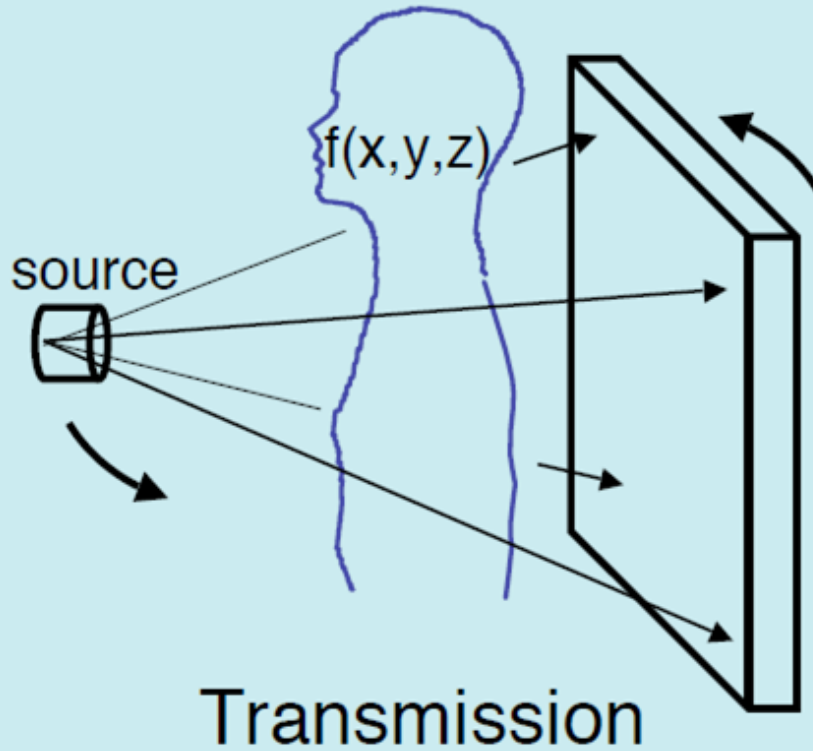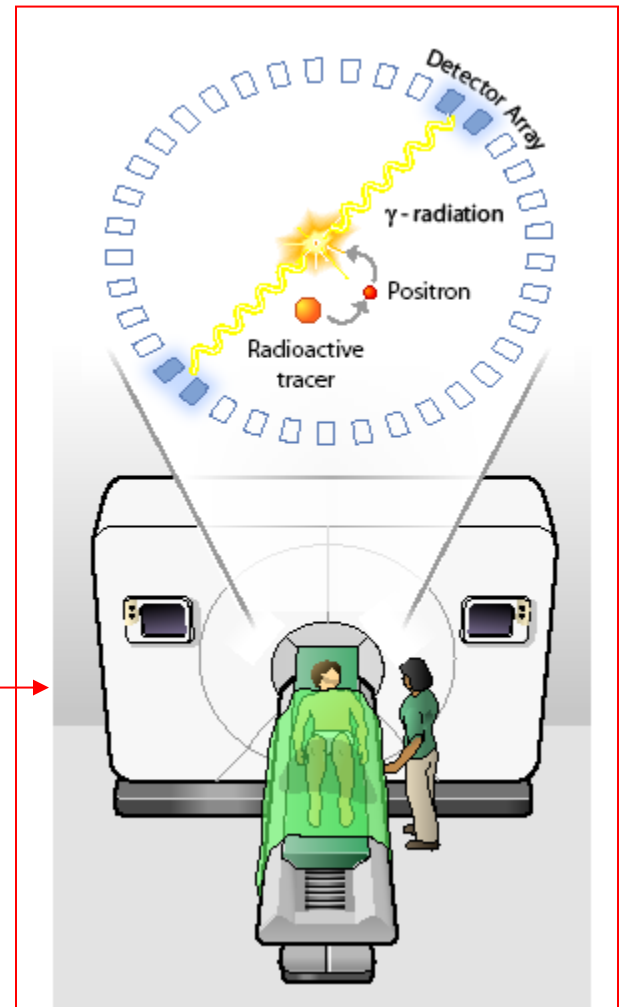

Transmission

Emission

Courtesy P. Kinahan
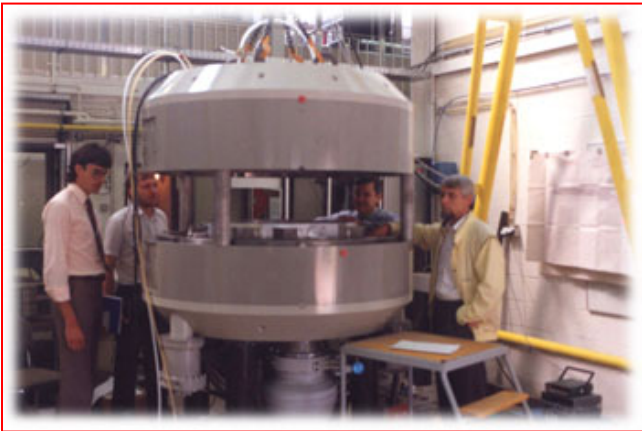
Cyclotron

PET camera

Radiochemistry

J. Long, "The Science Creative Quarterly",scq.ubc.ca

$$N(t) = N_0 e^{-\lambda t} \text{ or } A(t) = A(0)e^{-\lambda t}$$

where:

$N(t)$ = number of radioactive atoms at time t

N_0 = initial number of radioactive atoms at $t = 0$

$A(t)$ = activity at time t

$A(0)$ = initial activity at $t = 0$

e = base of natural logarithm = 2.71828...

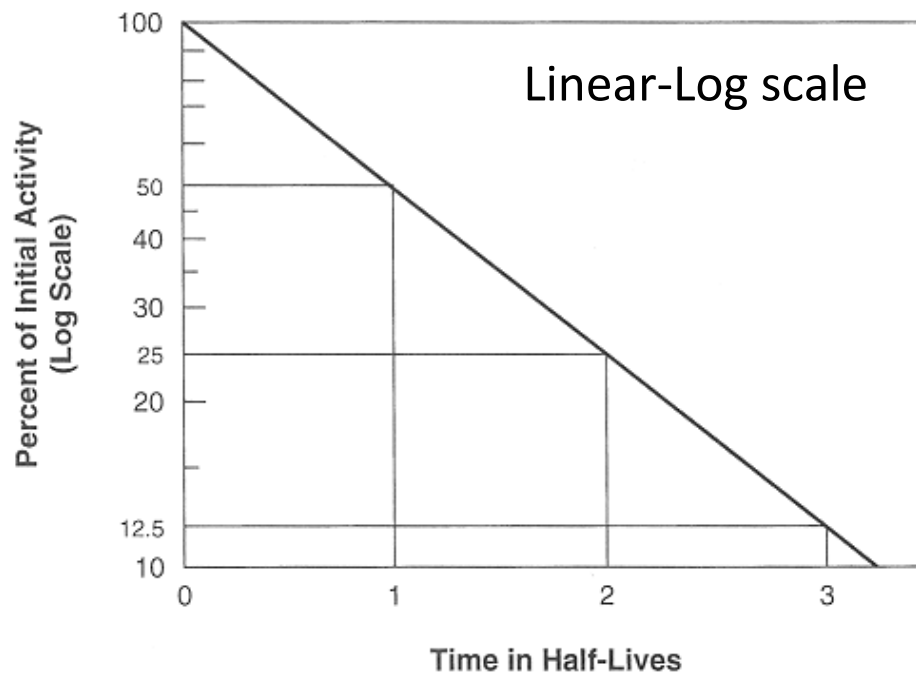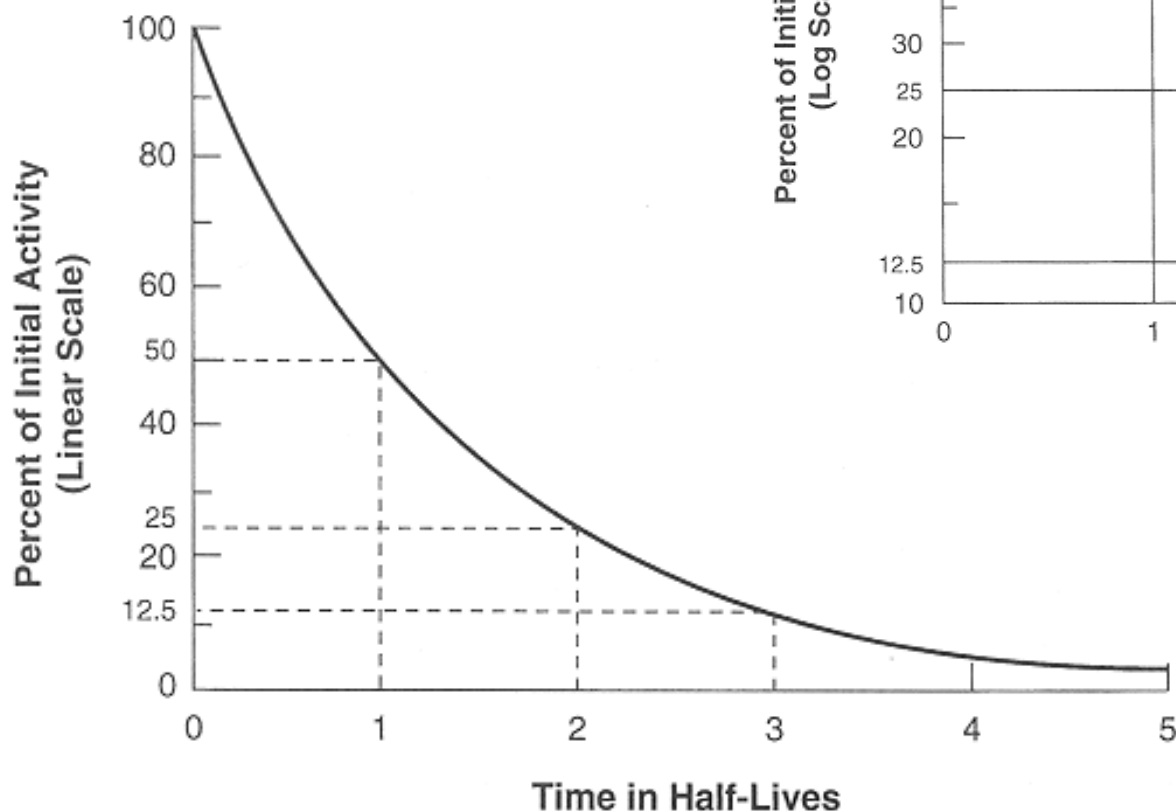λ = decay constant = $1/\tau$ = $\ln 2/T_{1/2}$ = $0.693/T_{1/2}$

t = time
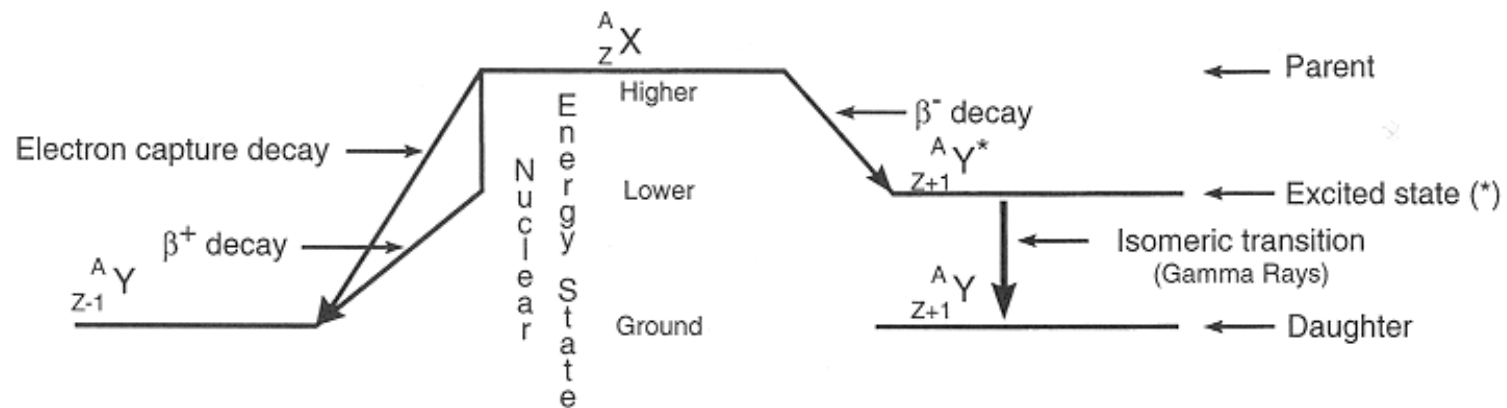
and remembering that:

$-dN/dt = \lambda N$

$A = \lambda N$

Linear-Linear scale

Linear-Log scale

The "ideal" diagnostics radiopharmaceutical

a) Be readily available at a low cost
b) Be a pure gamma emitter, i.e. have no particle emission such as alphas and betas (these particles contribute radiation dose to the patient while not providing any diagnostic information)
c) Have a short effective biological half-life (so that it is eliminated from the body as quickly as possible)
d) Have a high target to non-target ratio so that the resulting image has a high contrast (the object has much more activity than the background)
e) Follow or be trapped by the metabolic process of interest
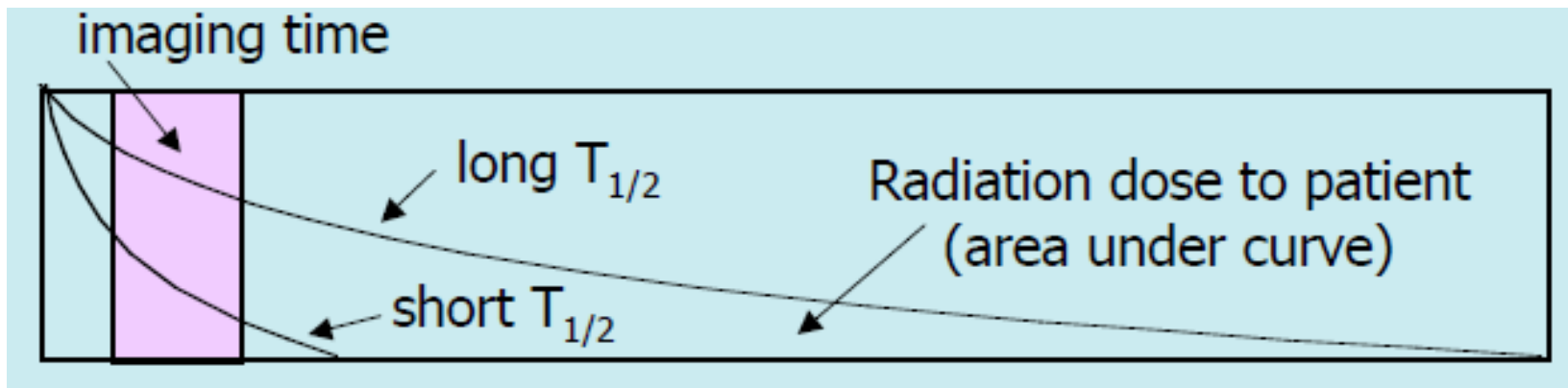
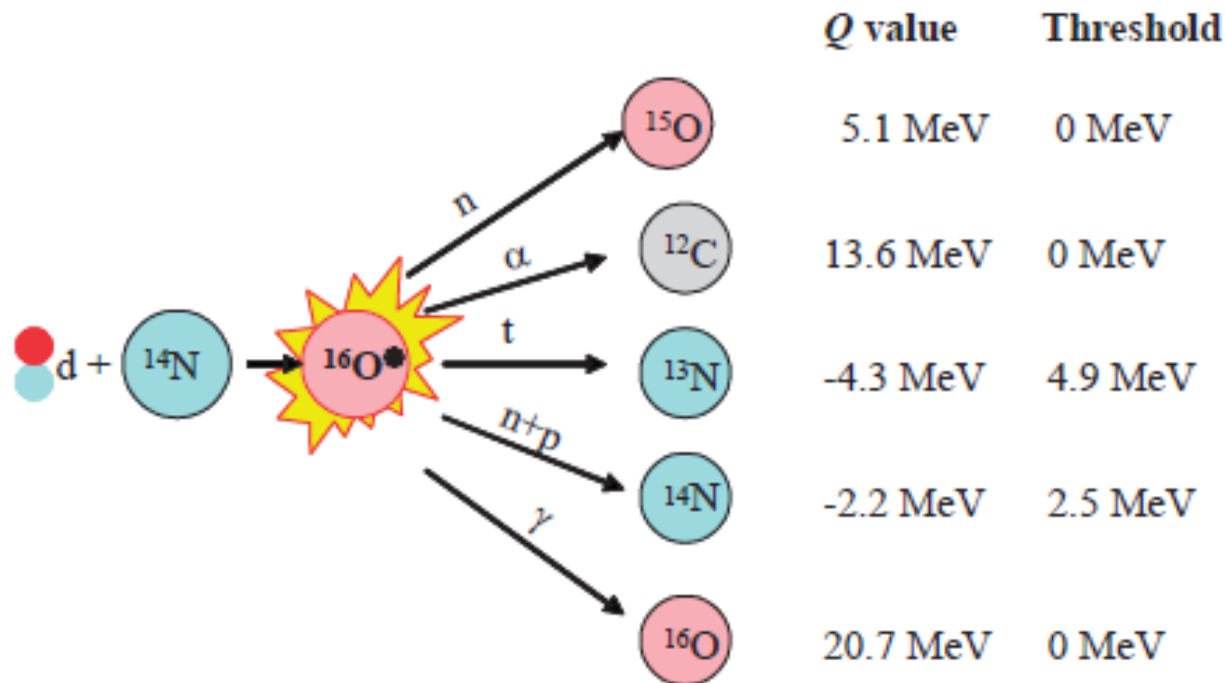$$A(t) = A(0)e^{-t(\ln(2)/T_{1/2})}$$

1. Acceleration of charged particles in a cyclotron
2. Beam transport (*or not*) to the irradiation station via a transfer line
3. Irradiation of target (solid, liquid, gas) – *internal or external*
4. Nuclear reaction occurring in the target (e.g. $^{A}X_{Z}(p,n)^{A}y_{Z+1}$)
5. Target processing and material recovering
6. Labeling of radiopharmaceuticals and quality control
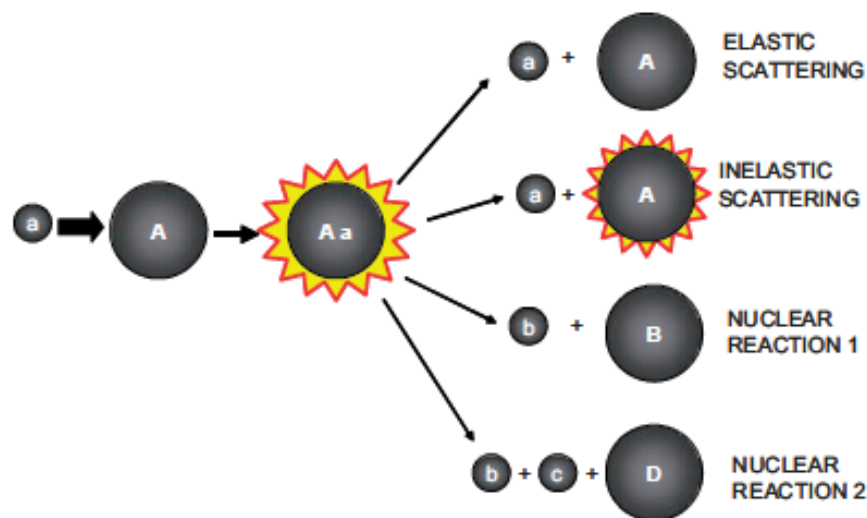
a = bombarding particle
b, c = emitted particles
A, B, D = nuclei
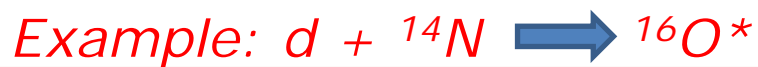
Q values and thresholds of nuclear decomposition for the reaction of a deuteron with a ^{14}N nucleus after forming the compound nucleus ^{16}O

	Q value	Threshold
^{15}O	5.1 MeV	0 MeV
^{12}C	13.6 MeV	0 MeV
^{13}N	-4.3 MeV	4.9 MeV
^{14}N	-2.2 MeV	2.5 MeV
^{16}O	20.7 MeV	0 MeV

$$\frac{dn}{dt} = R = nI(1 - e^{-\lambda t}) \int\limits_{Eth}^{E0} \frac{\sigma(E)}{dE / dx} dE$$

R = the number of nuclei formed per second

n = the target thickness in nuclei per cm^2

I = incident particle flux per second (related to the beam current)

λ = decay constant = (ln 2)/$T_{1/2}$

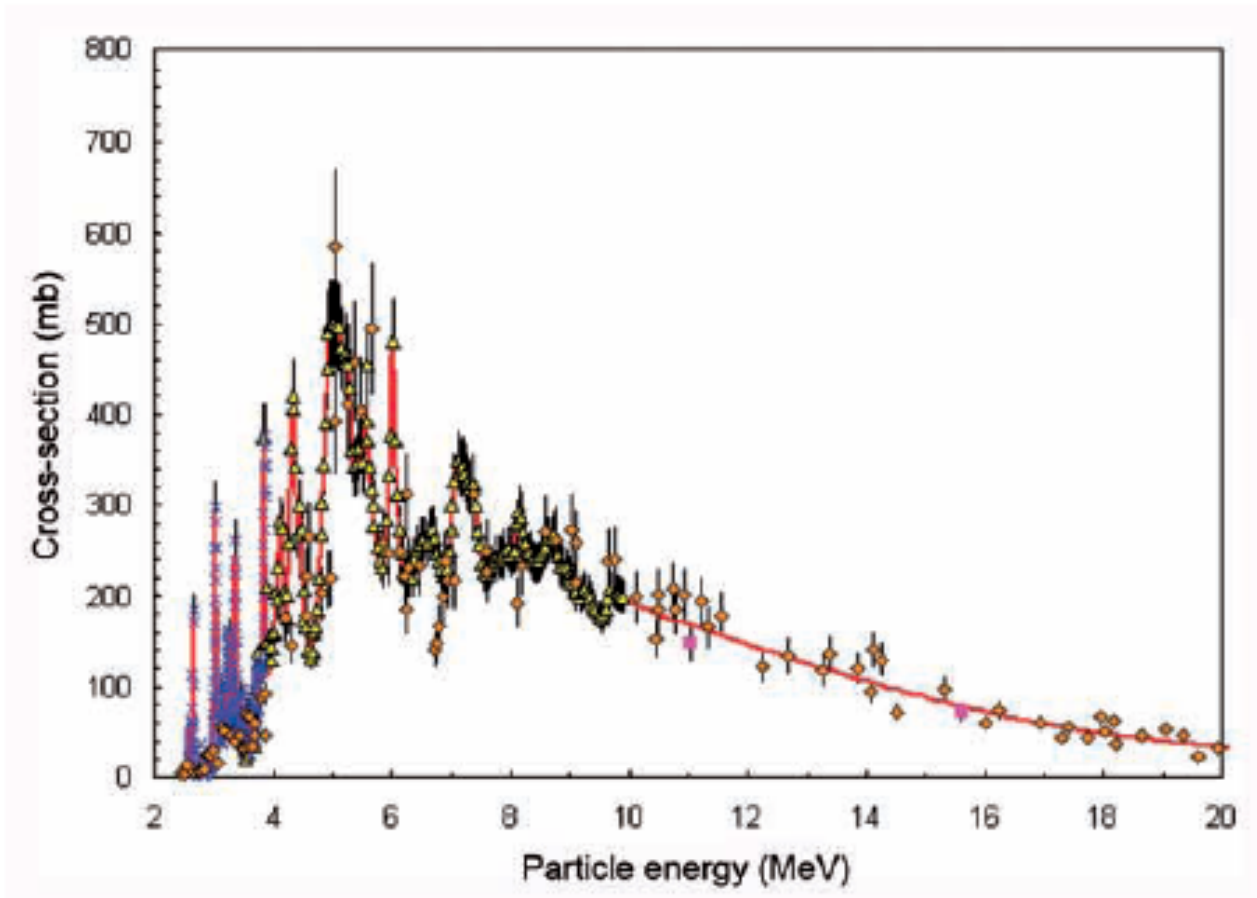**t** = irradiation time in seconds

σ = reaction cross-section, or probability of interaction (cm^2), function of E

E = energy of the incident particles

x = distance travelled by the particle

and the integral is from the initial energy (threshold of reaction) to the final energy of the incident particle along its path

Excitation function of the $^{18}O(p,n)^{18}F$ reaction

$$R_i = I n x \sigma_i$$

where

R_i = number of processes of type i in the target per unit time
I = number of incident particles per unit time
n = number of target nuclei per cm^3 of target = $\rho N_A / A$
σ_i = cross-section for the specified process in cm^2
x = the target thickness in cm

and assuming that

1. The beam current is constant over the course of the irradiation
2. The target nuclei are uniformly distributed in the target material
3. The cross-section is independent of energy over the energy range used

Saturation factor, $SF = 1 - e^{-\lambda t}$

T_{irr} = 1 half-life results in an activity of 50% of the saturation (max) activity

2 half-lives → 75%

3 half-lives → 90%

The practical production limits of a given radionuclide are determined by the half-life of the isotope, e.g.

^{15}O, $T_{1/2}$ = 2 minutes
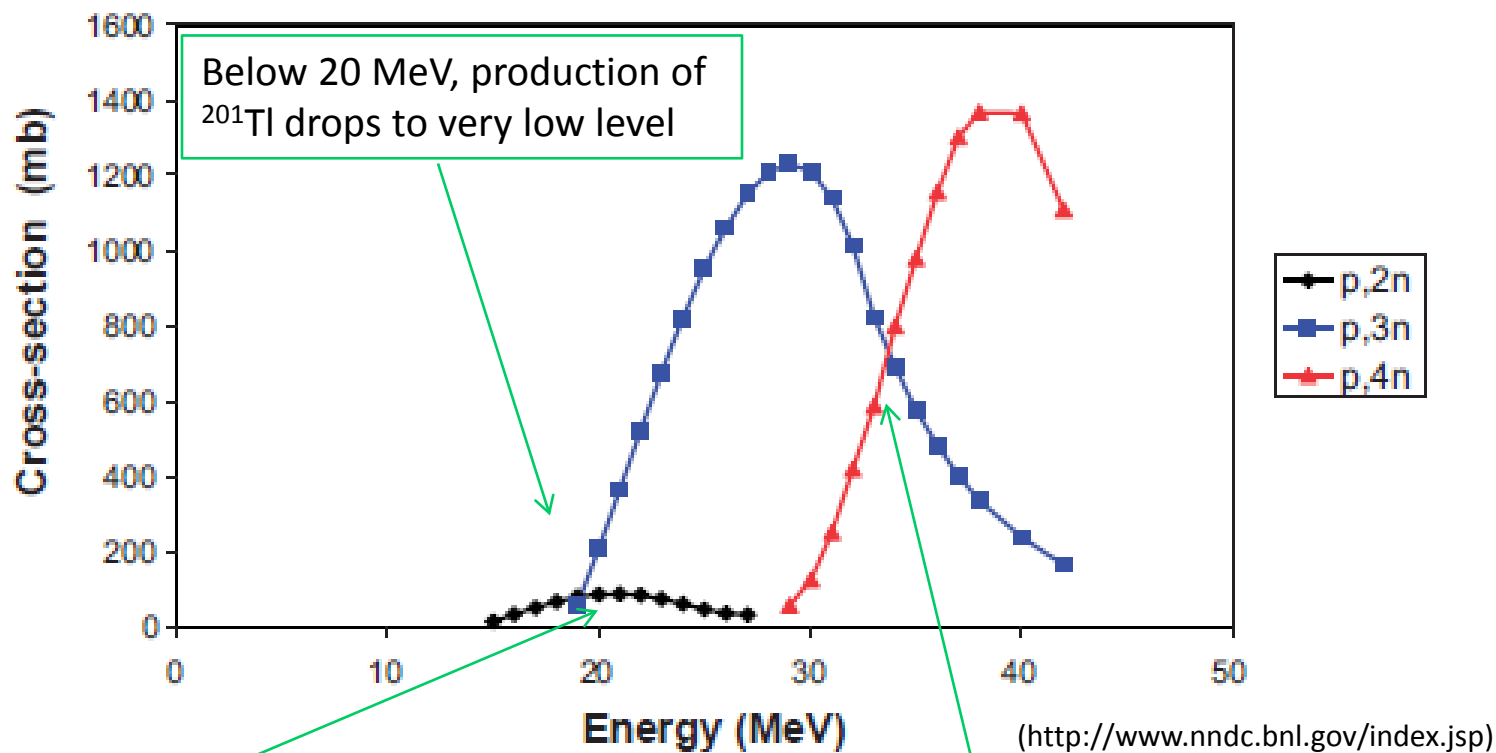^{18}F, $T_{1/2}$ = almost 2 hours

$1 - e^{-\lambda t}$
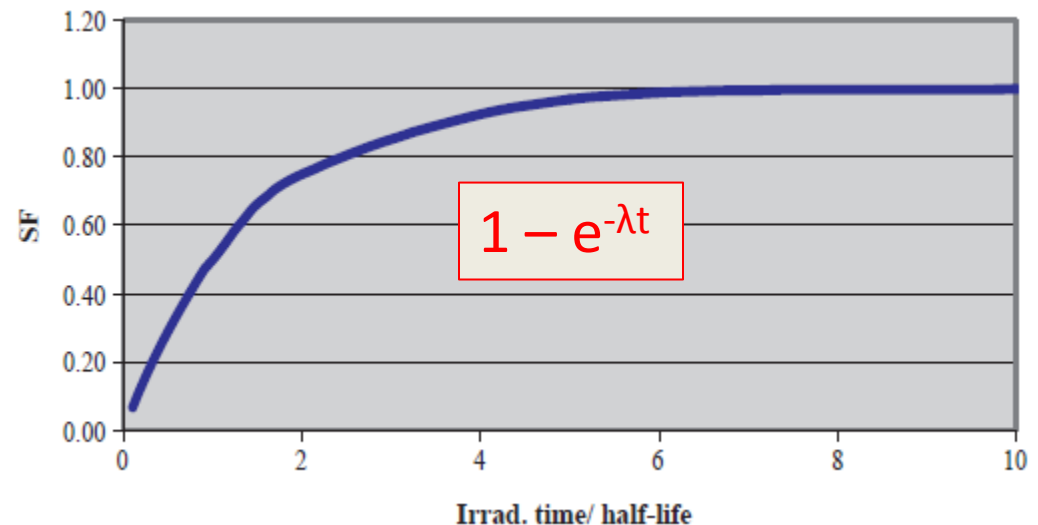
For *long lived species*, the production rates are usually expressed in terms of integrated dose or total beam flux ($\mu A \cdot h$)

The nuclear reaction used for the production of ^{201}Tl is the $^{203}Tl(p,3n)^{201}Pb$
^{201}Pb ($T_{1/2}$ = 9.33 h) $\longrightarrow$ ^{201}Tl ($T_{1/2}$ = 76.03 h)

Cross-section versus energy plot for the $^{203}Tl(p,2n)^{202}Pb$, $^{203}Tl(p,3n)^{201}Pb$ and $^{203}Tl(p,4n)^{200}Pb$ reactions

Below 20 MeV, production of ^{201}Tl drops to very low level

(http://www.nndc.bnl.gov/index.jsp)

Around threshold, production of ^{201}Tl is comparable to that of ^{202}Pb

Above 30 MeV, production of ^{200}Pb becomes significant

Internal (beam is not extracted from the cyclotron)
External (extracted beam + beam transport to target)

Simultaneous irradiation of more than one target (H⁻ cyclotrons)

The target can be
- **Solid**
- **Liquid**
- **Gaseous**

^{18}O water target

Principal constraints on gas targets
- removal of heat from the gas (gases are not very good heat conductors)
- the targets must be quite large in comparison with solid or liquid targets in order to hold the necessary amount of material.

Radionuclide	Use	Half-life	Reaction	Energy (MeV)
^{99m}Tc	SPECT imaging	6 h	^{100}Mo(p,2n)	30
^{123}I	SPECT imaging	13.1 h	^{124}Xe(p,n)^{123}Cs ^{124}Xe(p,pn)^{123}Xe ^{124}Xe(p,2pn)^{123}I ^{123}Te(p,n)^{123}I ^{124}Te(p,2n)^{123}I	27 15 25
^{201}Tl	SPECT imaging	73.1 h	^{203}Tl(p,3n)^{201}Pb $\rightarrow$ ^{201}Tl	29
^{11}C	PET imaging	20.3 min	^{14}N(p,α) ^{11}B(p,n)	11–19 10
^{13}N	PET imaging	9.97 min	^{16}O(p,α) ^{13}C(p,n)	19 11

Production reactions (2)

Radionuclide	Use	Half-life	Reaction	Energy (MeV)
^{15}O	PET imaging	2.03 min	^{15}N(p,n) ^{14}N(d,2n) ^{16}O(p,pn)	11 6 > 26
^{18}F	PET imaging	110 min	^{18}O(p,n) ^{20}Ne(d,α) ^{nat}Ne(p,X)	11-17 8-14 40
^{64}Cu	PET imaging and radiotherapy	12.7 h	^{64}Ni(p,n) ^{68}Zn(p,αn) ^{nat}Zn(d,αxn) ^{nat}Zn(d,2pxn)	15 30 19 19
^{124}I	PET imaging and radiotherapy	4.14 d	^{124}Te(p,n) ^{125}Te(p,2n)	13 25

- High LET decay products (Auger electrons, β-particles or α-particles)
- Radionuclide linked to a biologically active molecule that can be directed to a tumour site
- Beta emitting radionuclides are neutron rich ⟶ they are in general produced in reactors
- Some of the radionuclides that have been proposed as possible radiotoxic tracers are:

Sc-47	Cu-64	Cu-67	Br-77	Y-90
Rh-105	Pd-103	Ag-111	I-124	Pr-142
Pm-149	Sm-153	Gd-159	Ho-166	Lu-177
Re-186/188	Ir-194	Pt-199	At-211	Bi-213

- Technetium-99m (^{99m}Tc) has been the most important radionuclide used in nuclear medicine
- Short half-life (6 hours) makes it impractical to store even a weekly supply
- Supply problem overcome by obtaining parent ^{99}Mo, which has a longer half-life (67 hours) and continually produces ^{99m}Tc
- A system for holding the parent in such a way that the daughter can be easily separated for clinical use is called a *radionuclide generator*

Cross Section of a Generator

Detail of Column

- Between elutions, the daughter (^{99m}Tc) builds up as the parent (^{99}Mo) continues to decay

- After approximately 23 hours the ^{99m}Tc activity reaches a maximum, at which time the production rate and the decay rate are equal and the parent and daughter are said to be in *transient equilibrium*

- Once transient equilibrium has been reached, the daughter activity decreases, with an apparent half-life equal to the half-life of the parent

- Transient equilibrium occurs when the half-life of the parent is greater than that of the daughter by a factor of about 10

Parent	Decay mode Half-life	Daughter	Time of maximal ingrowth (equilibrium)	Decay mode Half-life	Decay product
Germanium 69 (^{69}Ge)	EC $\longrightarrow$ 271 days	Gallium 68 (^{68}Ga)	~6.5 hr (S)	β^+, EC $\longrightarrow$ 68 min	Zinc 68 (^{68}Zn), stable
Rubidium 81 (^{81}Rb)	β^+, EC $\longrightarrow$ 4.5 hr	Krypton 81m (^{81m}Kr)	~80 sec (S)	IT $\longrightarrow$ 13.5 sec	Krypton 81 ^{81}Kr[a]
Strontium 82 (^{82}St)	EC $\longrightarrow$ 25.5 days	Rubidium 82 (^{82}Rb)	~7.5 min (S)	β^+ $\longrightarrow$ 75 sec	Krypton 82 (^{82}Kr), stable
Molybdenum 99 (^{99}Mo)	β^- $\longrightarrow$ 67 hr	Technetium 99m (^{99m}Tc)	~24 hr (T)	IT $\longrightarrow$ 6 hr	Technetium 99 (^{99}Tc)[a]

Radiation therapy

Radiotherapy Machines Per Million People

- no machines
- less than 1
- between 1 and 3
- between 3 and 5
- 5 or more

Source: DIRAC/IAEA
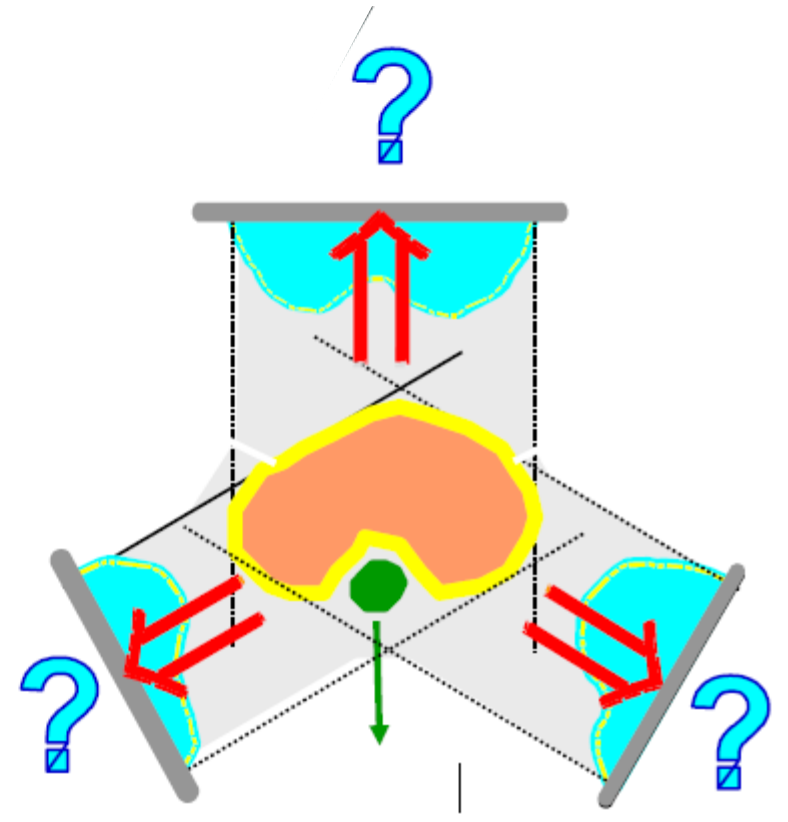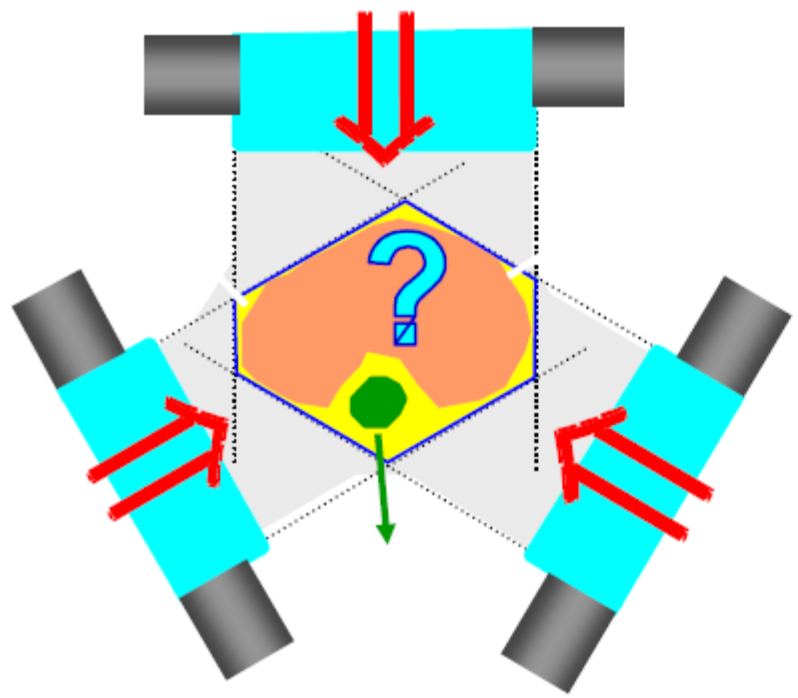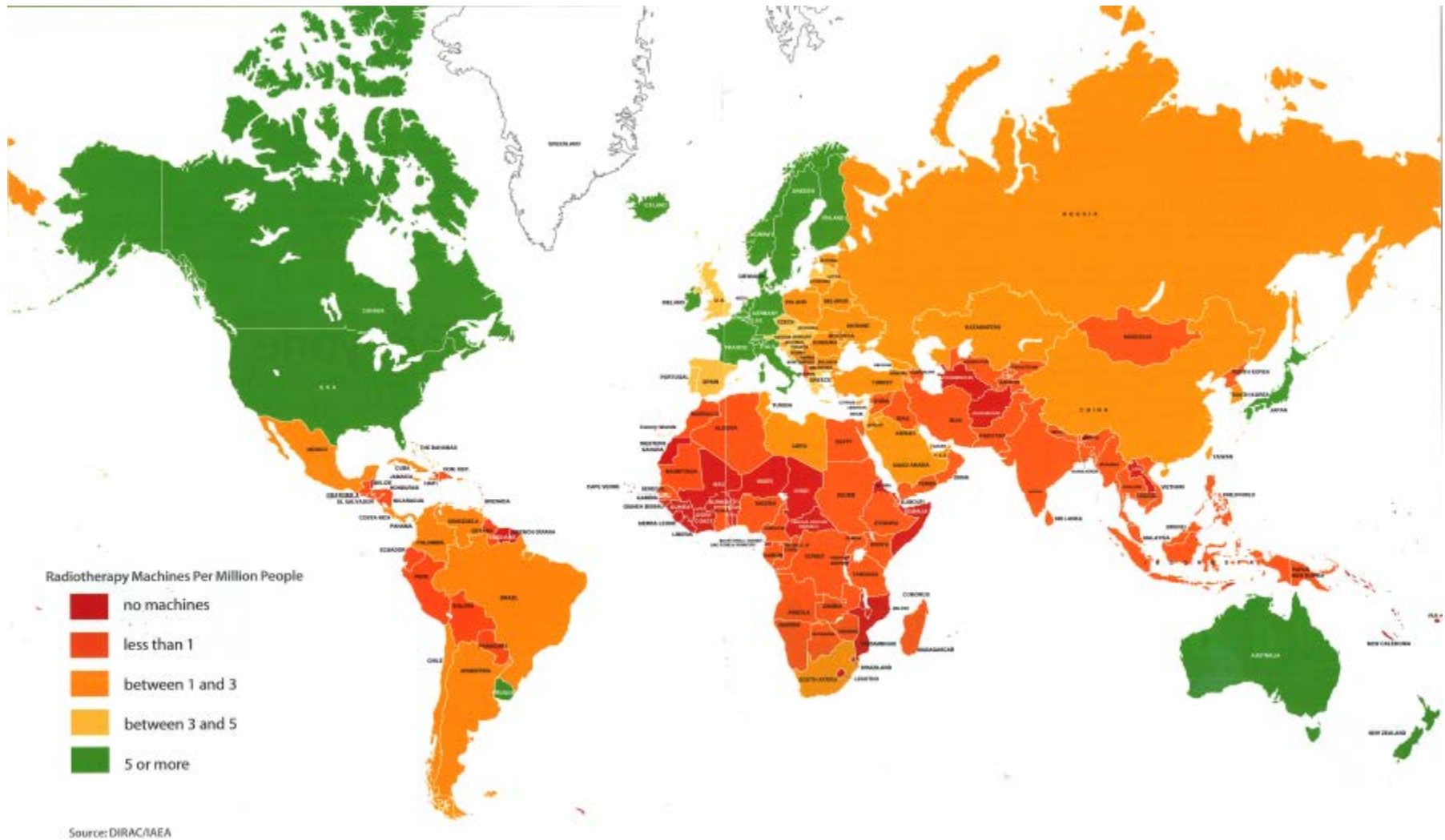
Operation of Linear Accelerators
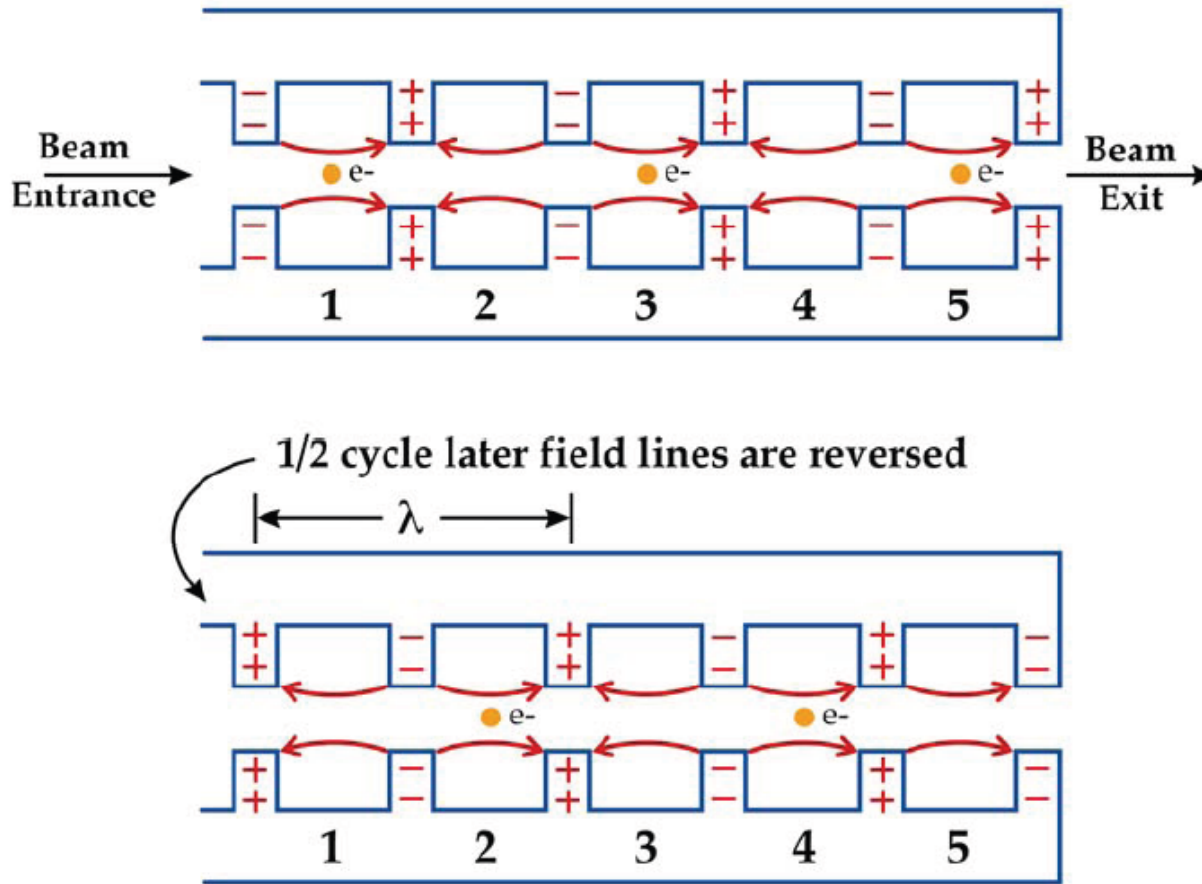
Particles initially in cell 1 arrive in cell 2 to get further accelerating kick. Frequency must match particles velocity and cell periodicity = ½ λ:
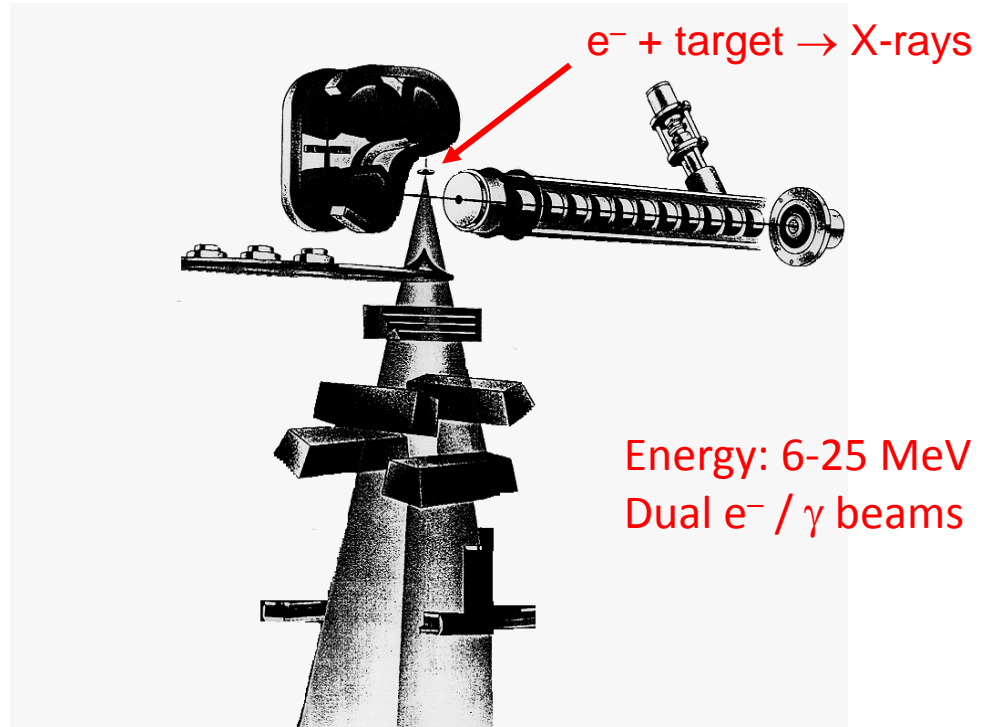
$$f = \frac{v}{\lambda}$$

Medical electron linacs

Varian Clinac 1800

e^- + target $\rightarrow$ X-rays

Energy: 6-25 MeV
Dual e^- / γ beams

target

Multi-leaf collimator
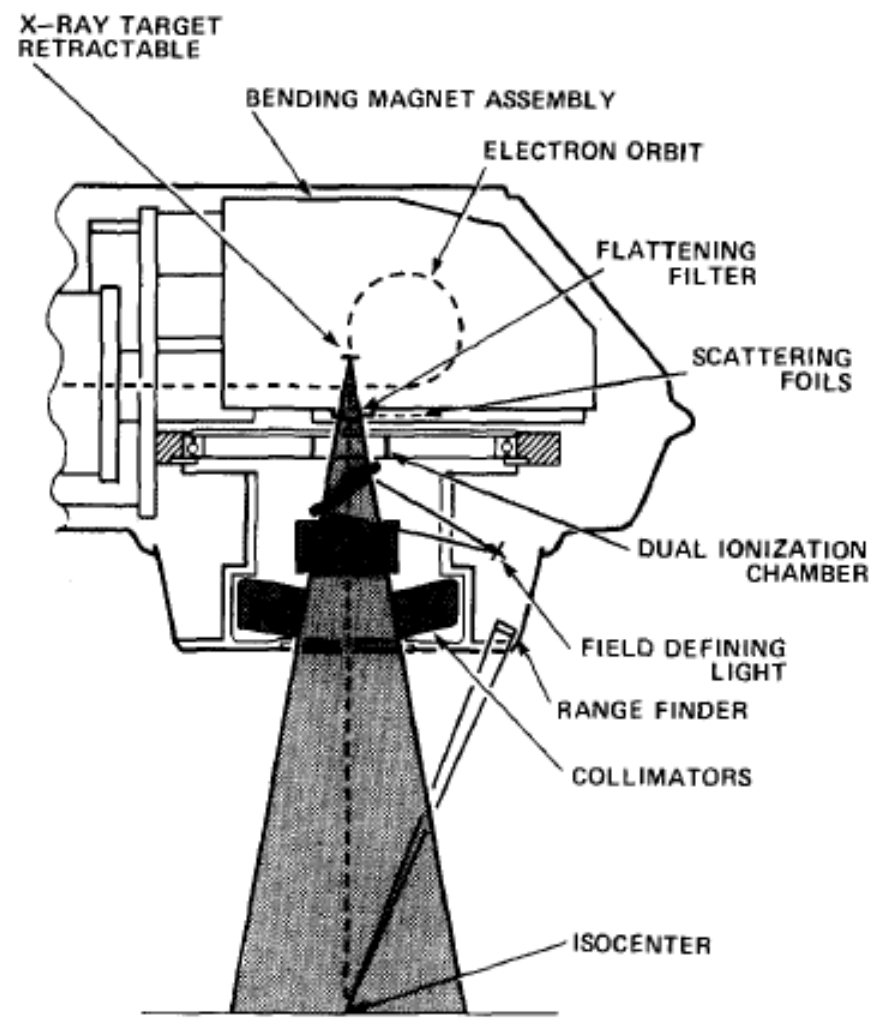
Intra-operative radiation therapy (IORT)
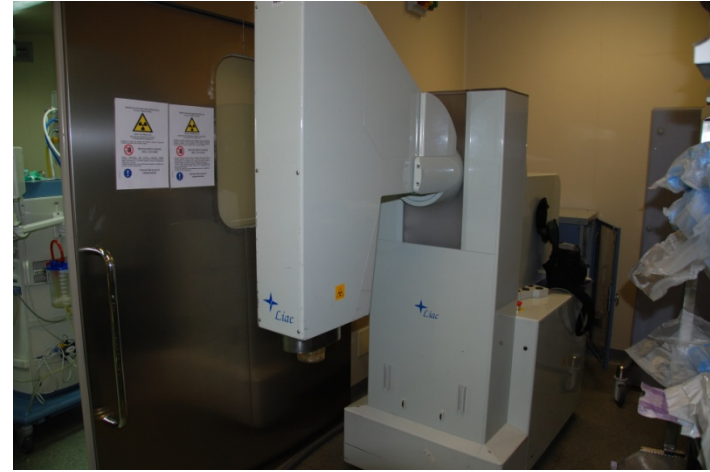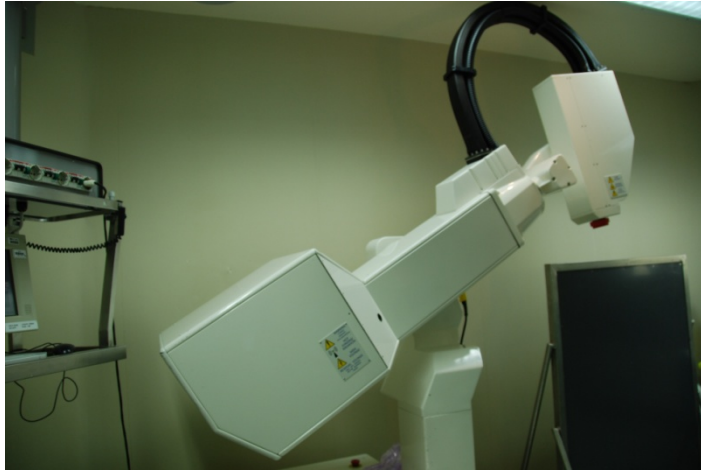
- Small electron linac
- Energy 6 – 12 MeV
- Treatment with electrons only
- Single irradiation
- Three models of linac produced by three manufacturers

Cyber-knife robotic surgery system

6 MV Linac mounted on a robotic arm
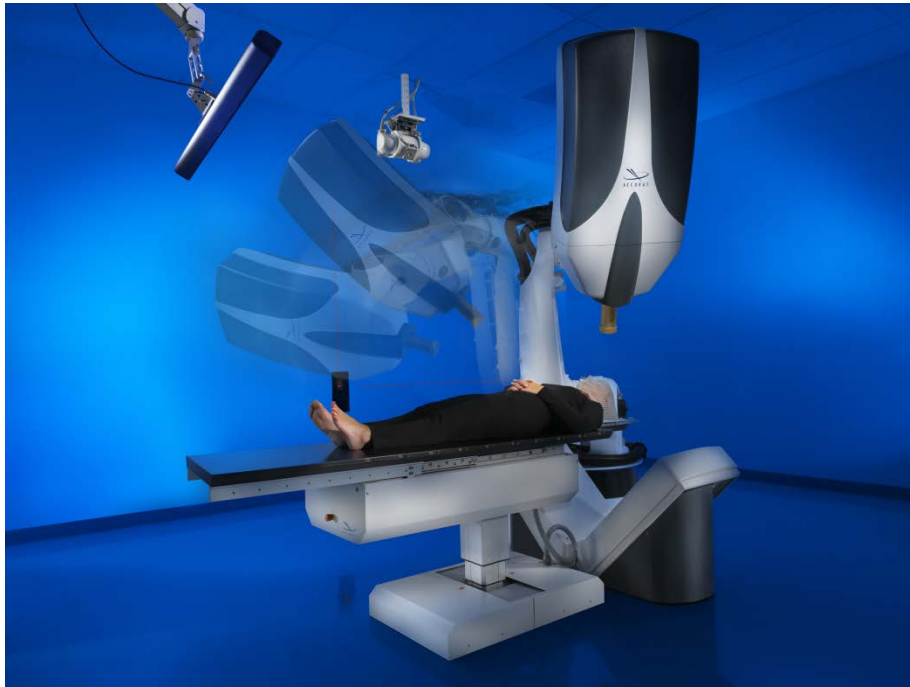
- No flattening filter
- Uses circular cones of diameter 0.5 to 6 cm
- Non-Isocentric
- Average dose delivered per session is 12.5 Gy
- Dose rate @ 80 cm = 400 cGy/min

http://www.accuray.com/Products/Cyberknife/index.aspx
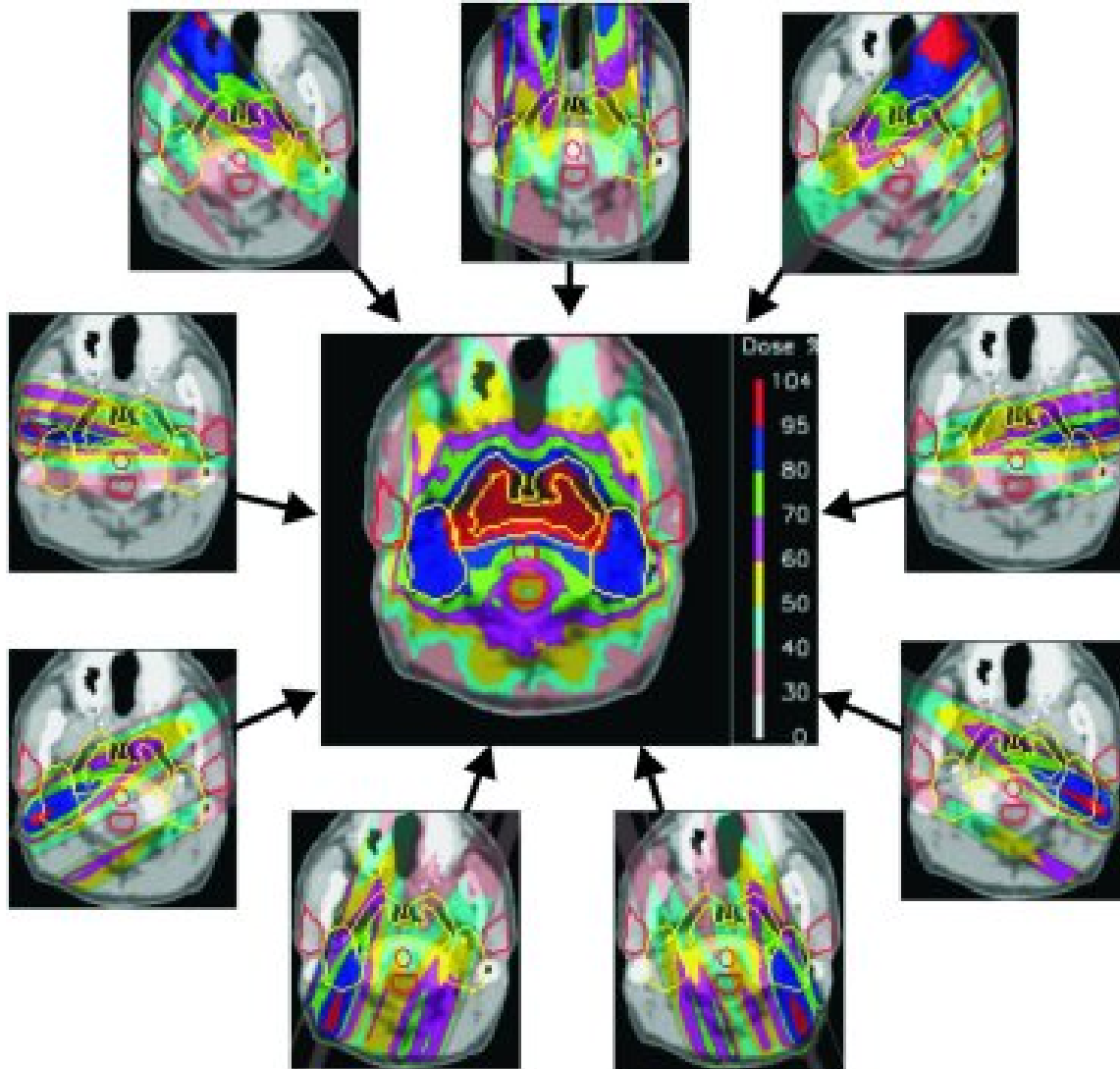
An example of intensity modulated treatment planning with photons. Through the addition of 9 fields it is possible to construct a highly conformal dose distribution with good dose sparing in the region of the brain stem (courtesy of T. Lomax, PSI).

E. Pedroni, Europhysics News (2000) Vol. 31 No. 6

Helical tomotherapy
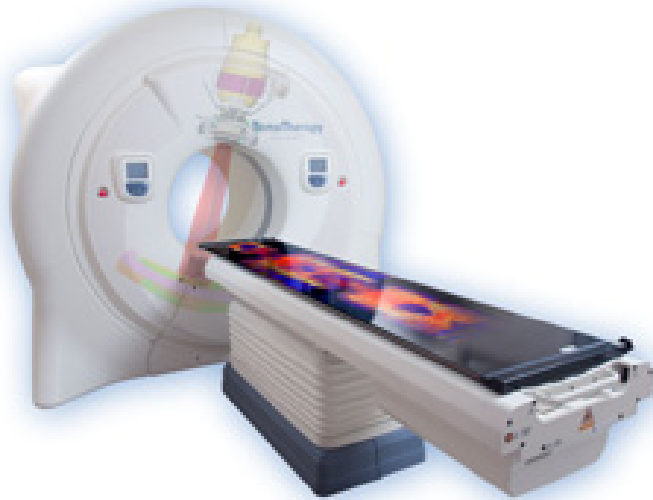
www.tomotherapy.com
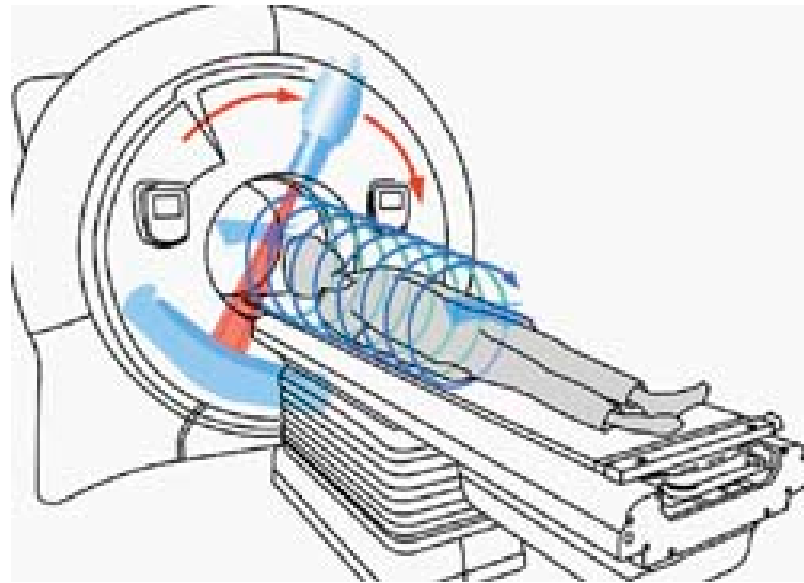
- Integrated CT guidance
  - Integrated CT scanner allowing efficient 3D CT imaging for ensuring the accuracy of treatment
- A binary multi-leaf collimator (MLC) for beam shaping and modulation
- A ring gantry design enabling TomoHelical delivery
  - As the ring gantry rotates in simultaneous motion to the couch, **helical fan-beam IMRT** is continuously delivered from all angles around the patient
  - Very large volumes can be treated in a single set-up
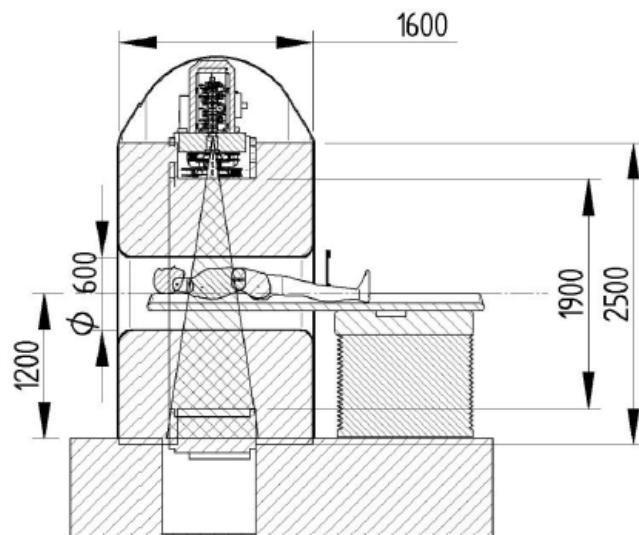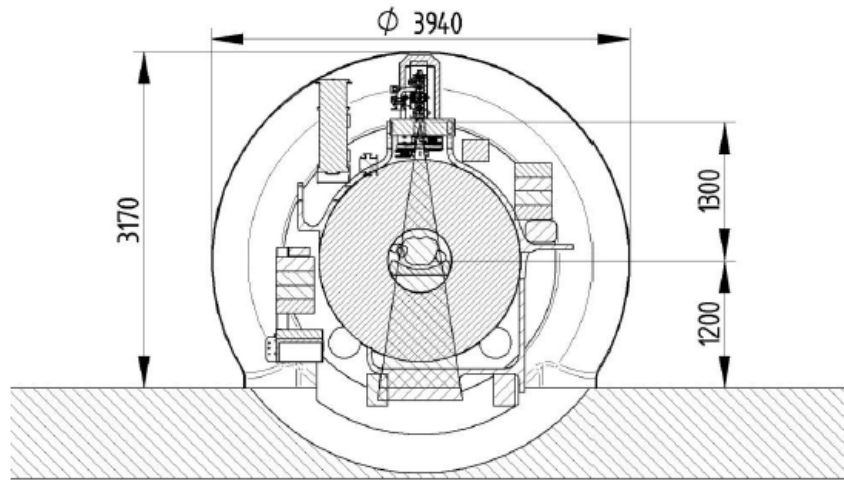
- Closed bore high field MRI

- Gantry ring based 6 MV accelerator with MLC

  → accelerator and MRI system have to operate simultaneously and independently

Courtesy J. Lagendijk
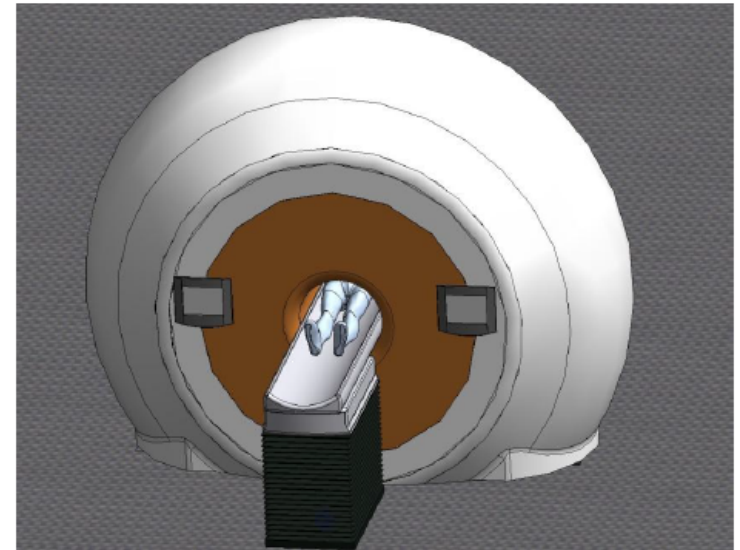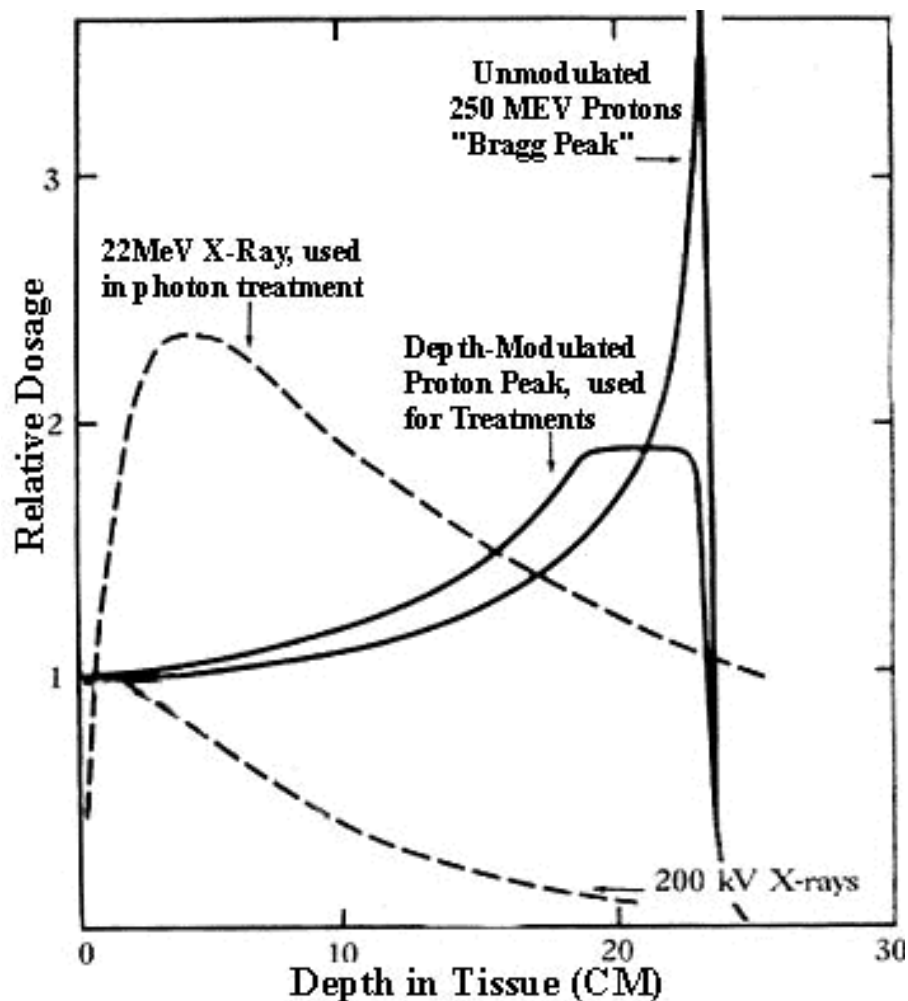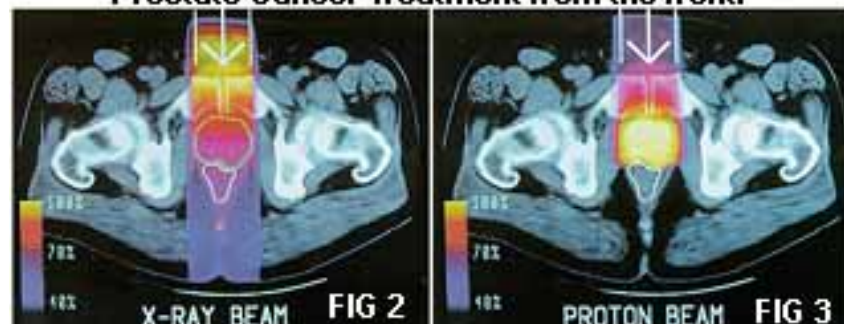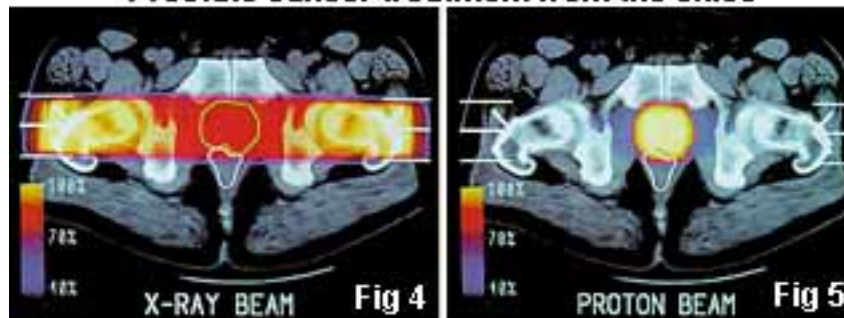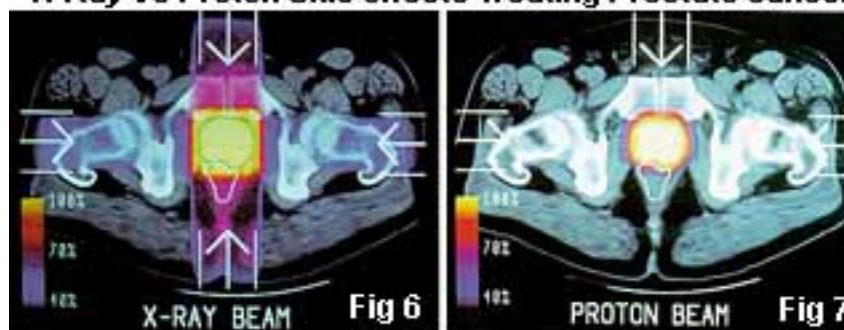
Particle therapy (hadron therapy)

200 MeV
protons

4800 MeV
carbon ions

27 cm

tumour

target

charged hadron beam
that loses energy in matter
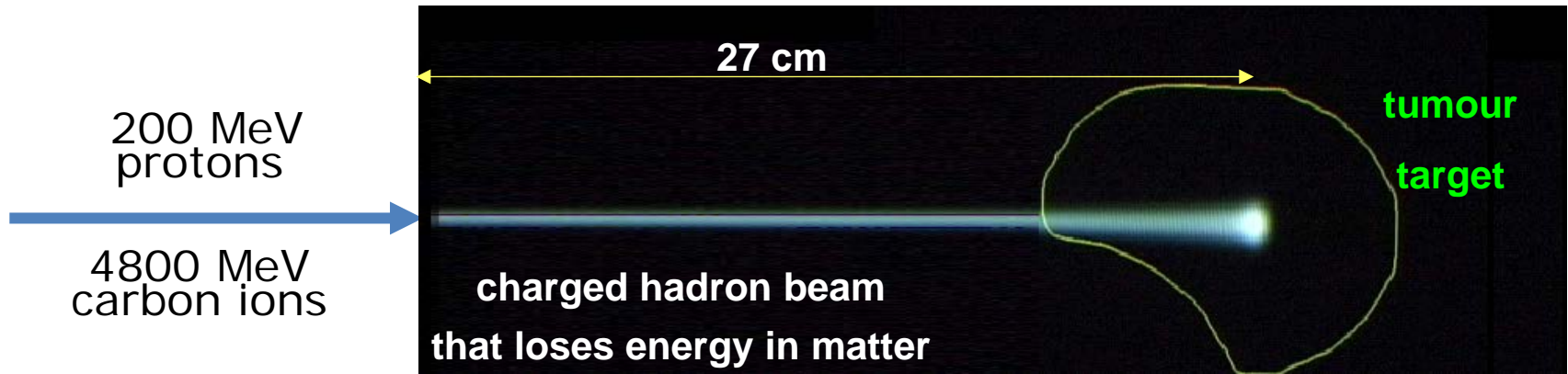
47 particle therapy facilities operation worldwide (mostly protons)

Number of patient treated until end of 2013

2054	He ions
1100	pions
13119	Carbon ions
433	other ions
105743	protons
122449	**Grand Total**

Accel-Varian
(superconducting)

IBA

Hitachi

Loma Linda (built by FNAL)
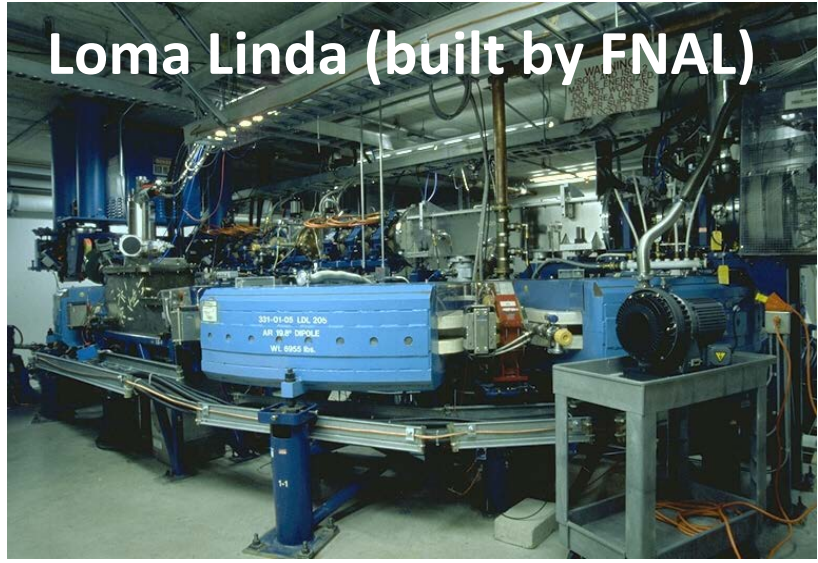
Loma Linda University Medical Center
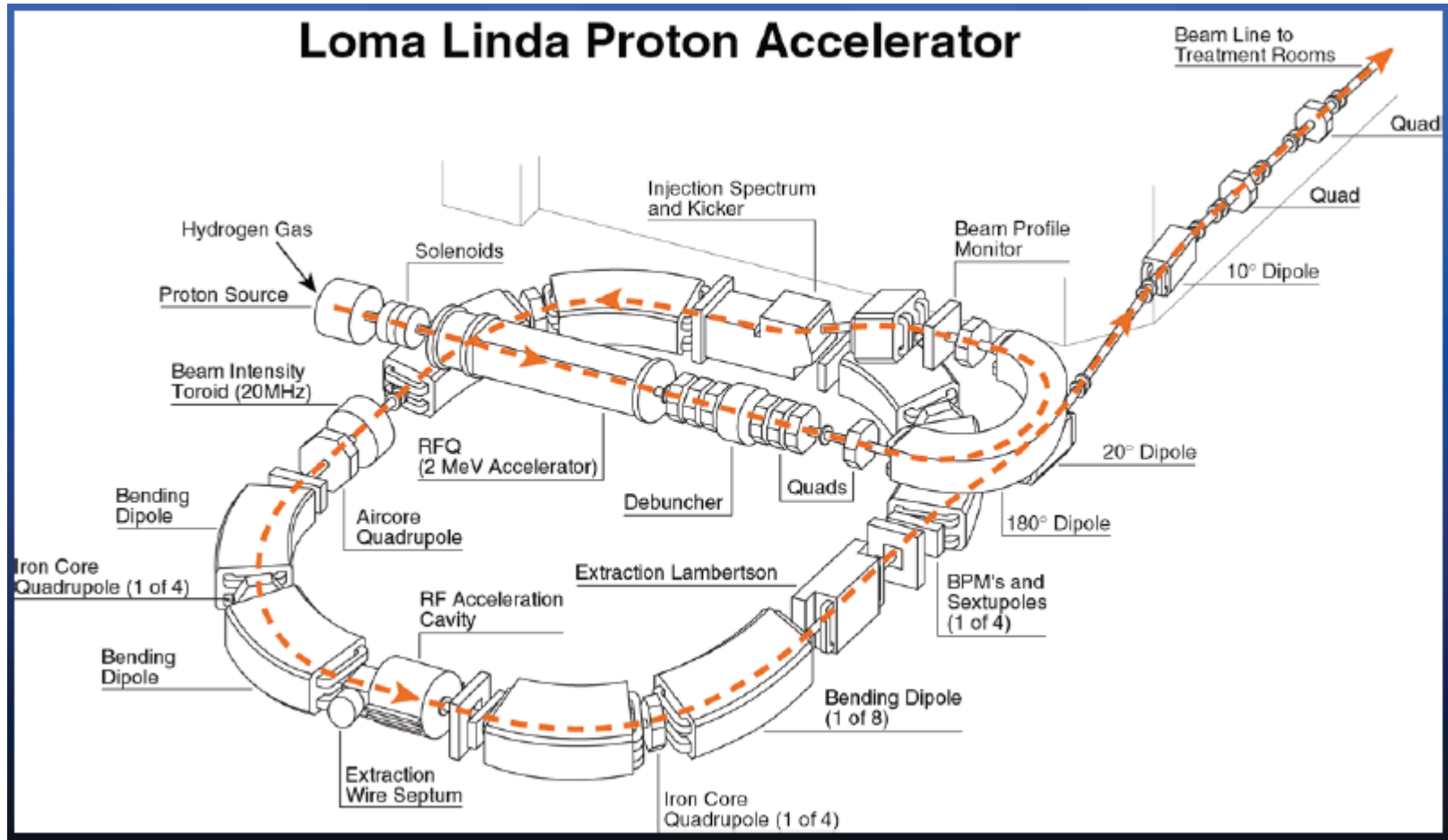
(the field is in/out of the plane of this slide)

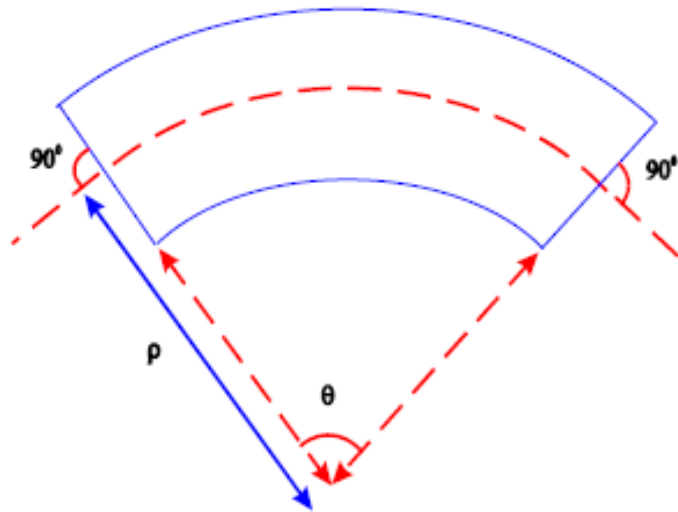F=evb — mass M
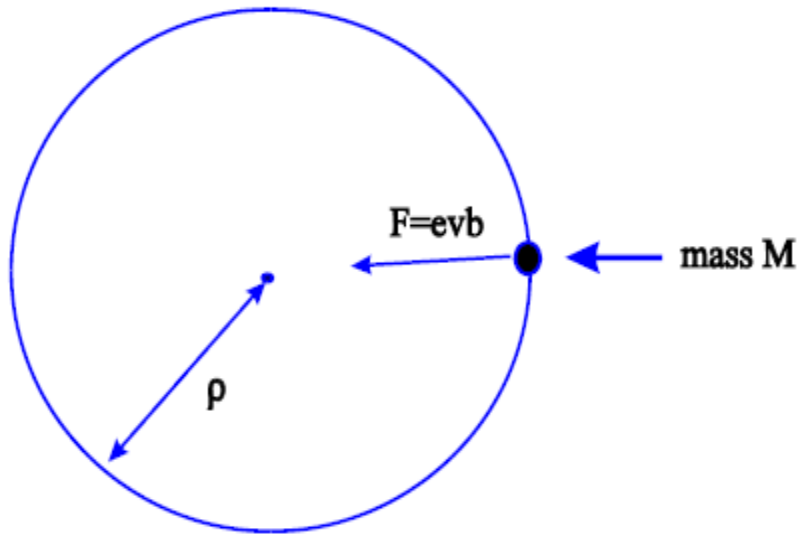
$$F = \frac{mv^2}{\rho},$$ where ρ = radius of curvature of the path

$$F = evB = \frac{mv^2}{\rho}$$

(p = momentum = mv)

$$B\rho = \frac{mv}{e} = \frac{p}{e}$$

Bρ = 33.356·p [kG·m] = 3.3356·p [T·m] (if p is in GeV/c)

Bρ is called "magnetic rigidity" of the particle and is an index of how difficult is to bend the motion of a charged particle by a magnetic field
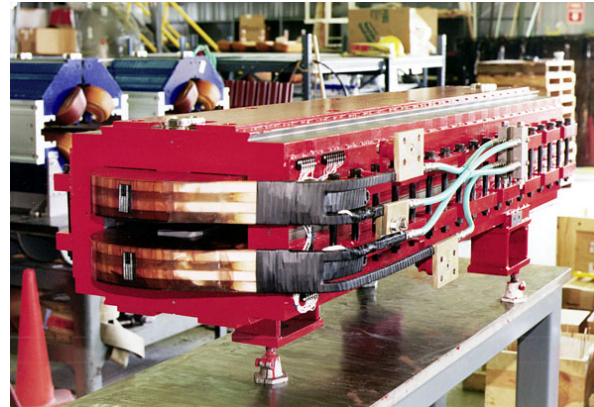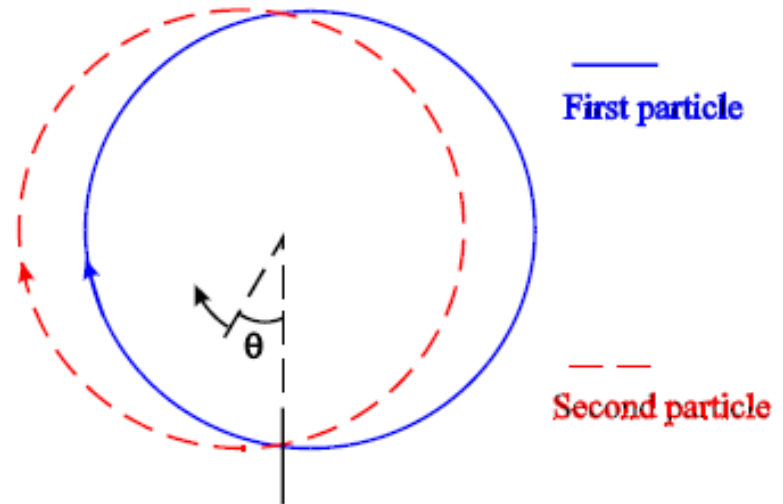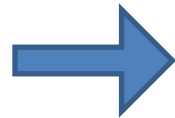
Trajectory of a particle in a bending magnet

Photo: courtesy ANL

Unfortunately an accelerator contains more than one particle!

Number of circulating particles in a synchrotron is typically in the order of 10^{10} - 10^{12} or more

First particle

Second particle

Two particles in a dipole field, with same momentum but different initial angles

Light rays passing through a series of focusing and defocusing lenses

The lenses, which are concave in one plane, are convex in the other
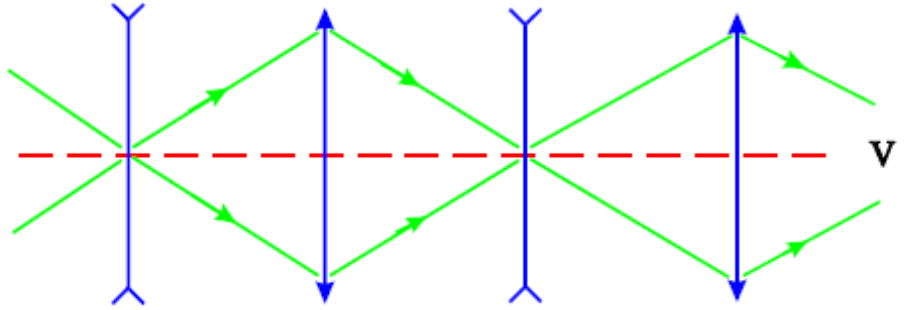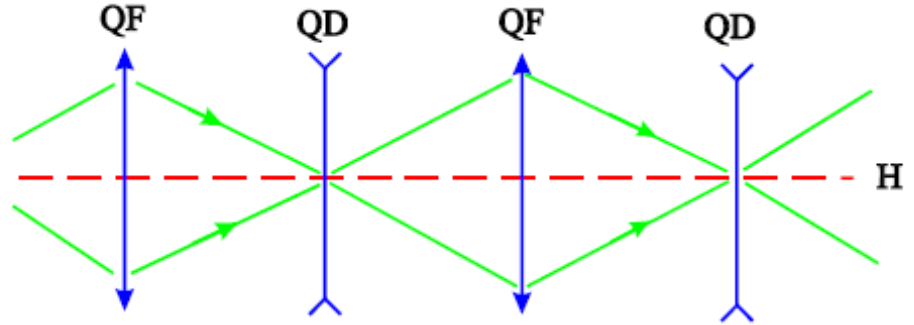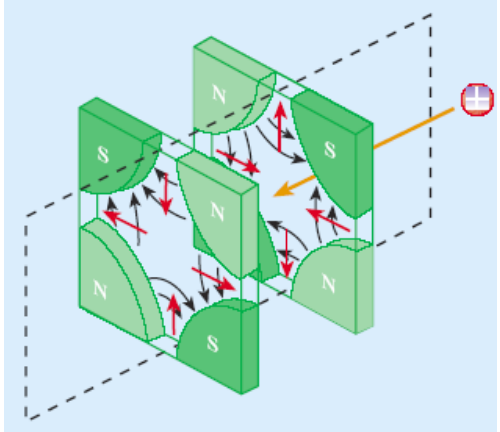
In both cases the concave lenses will have little effect as the light passes very close to their centre, and the net result is that the light rays are focused in both planes

✓ **The gutter below illustrates how the particles in a synchrotron behave due to the quadrupole fields.**
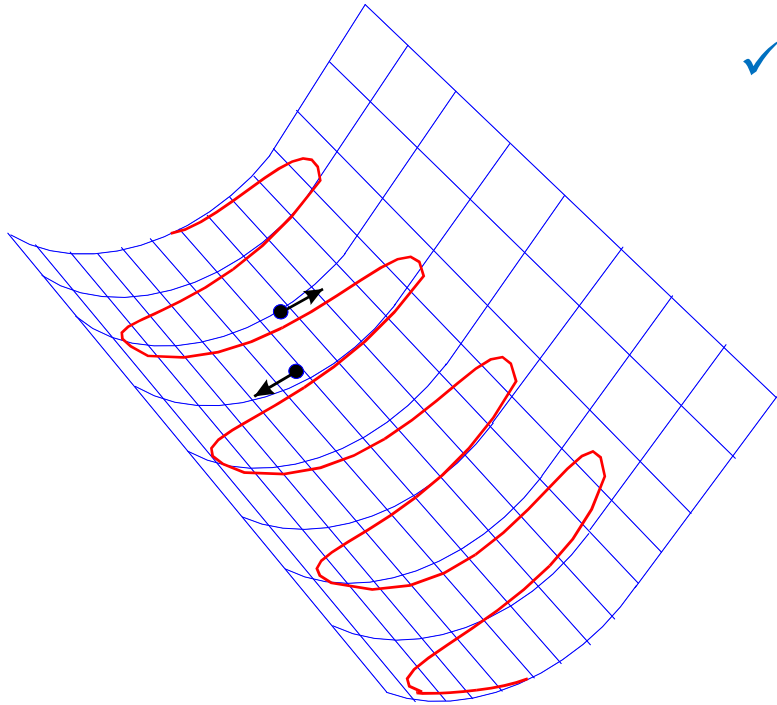
✓ **Whenever a particle beam diverges too far away from the central orbit the quadrupoles focus them back towards the central orbit.**

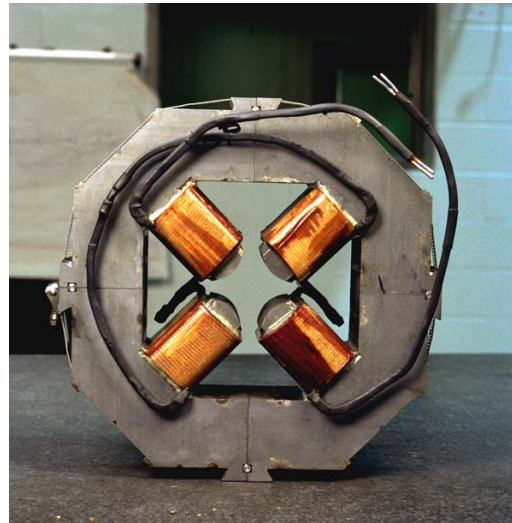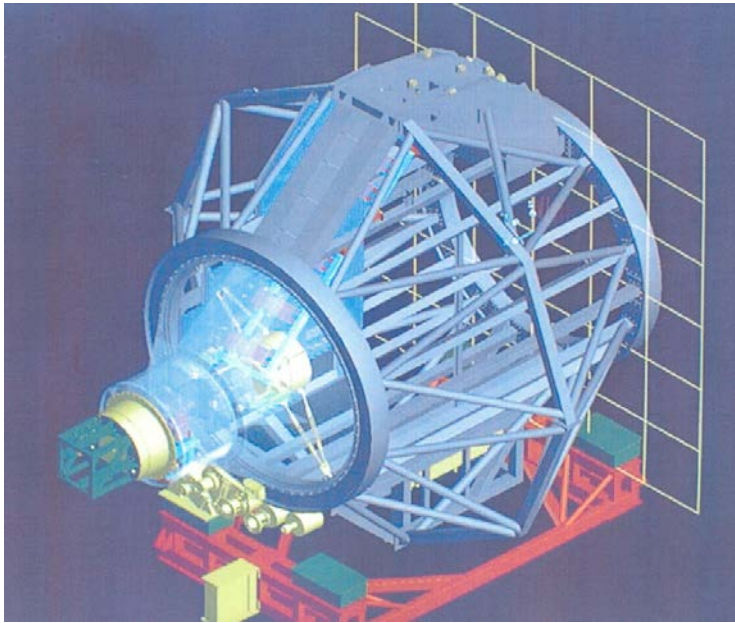**Beam "envelope" defined by the β function**

Photo courtesy Fermilab Visual Media Services

The IBA proton gantry

A gantry is a massive structure that allows directing the beam to the tumour from any direction. It carries
- **the final section of the beam line**
- **the beam spreading 'nozzle'**
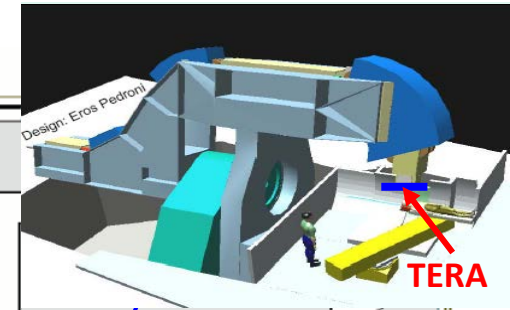- **the proton 'snout' which carries the aperture and range compensator**
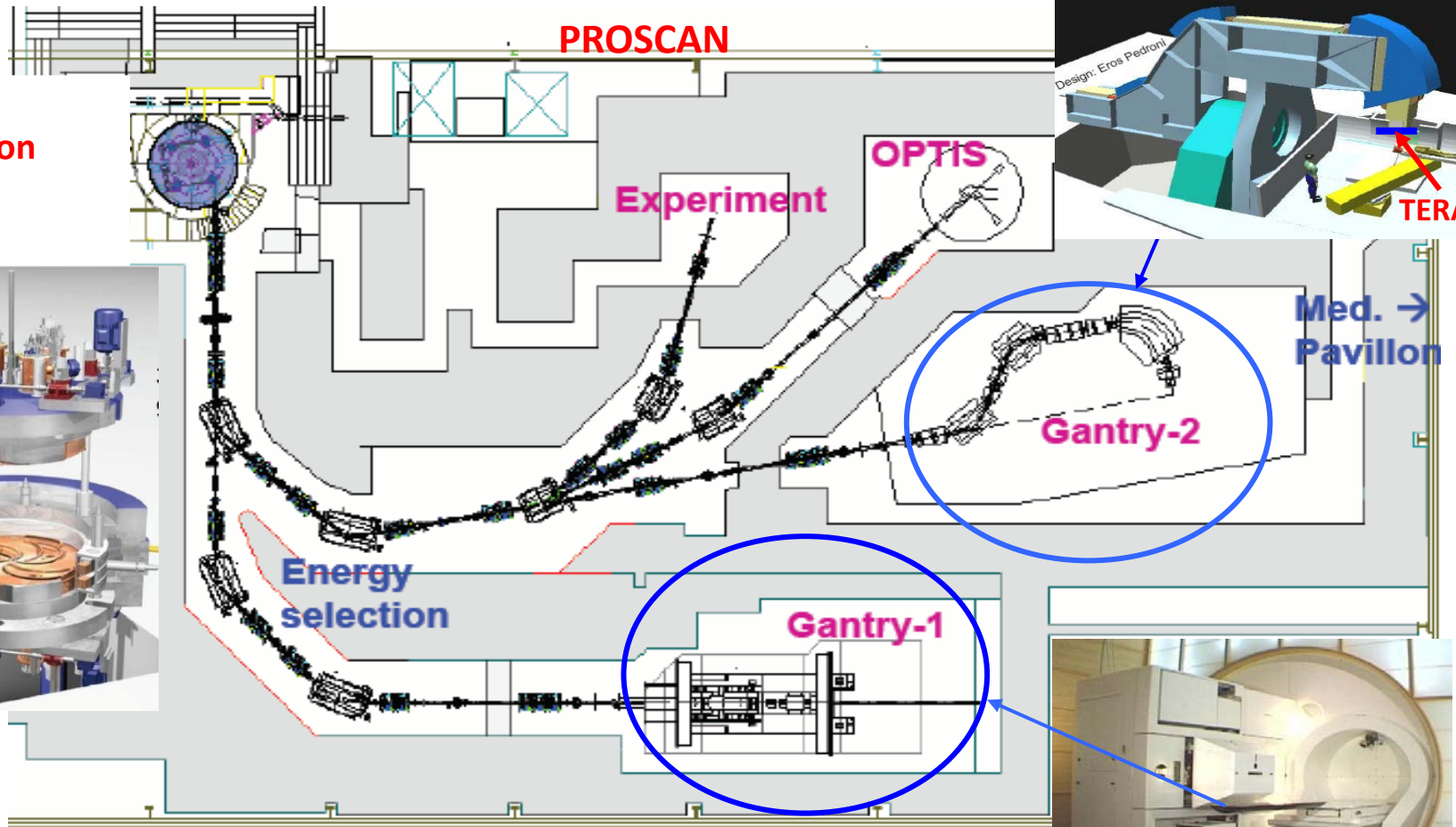

What it looks like to the patient: gantry room at the Midwest Proton Radiotherapy Institute (MPRI) (modified IBA gantry)

Adapted from B. Gottschalk

PROSCAN

ACCEL
SC cyclotron
250 MeV protons

Design: Eros Pedroni

TERA

OPTIS

Experiment

Med. →
Pavillon

Gantry-2

Energy selection

Gantry-1

Courtesy PSI and U. Amaldi , *TERA*

J.M. Schippers et al., NIM BB 261 (2007) 773–776

$$RBE = \frac{D_{x\text{-}ray}}{D_{particle}}$$
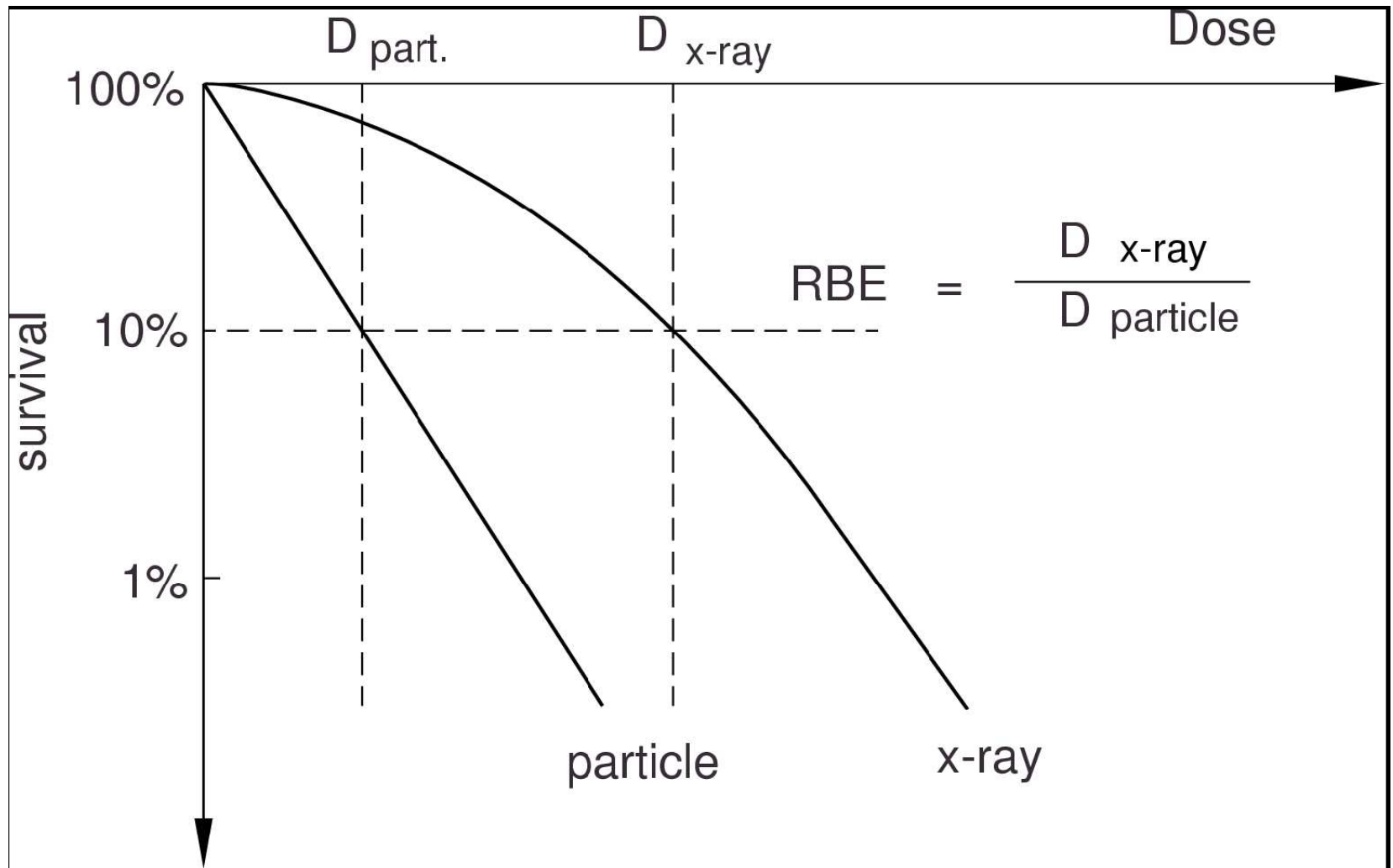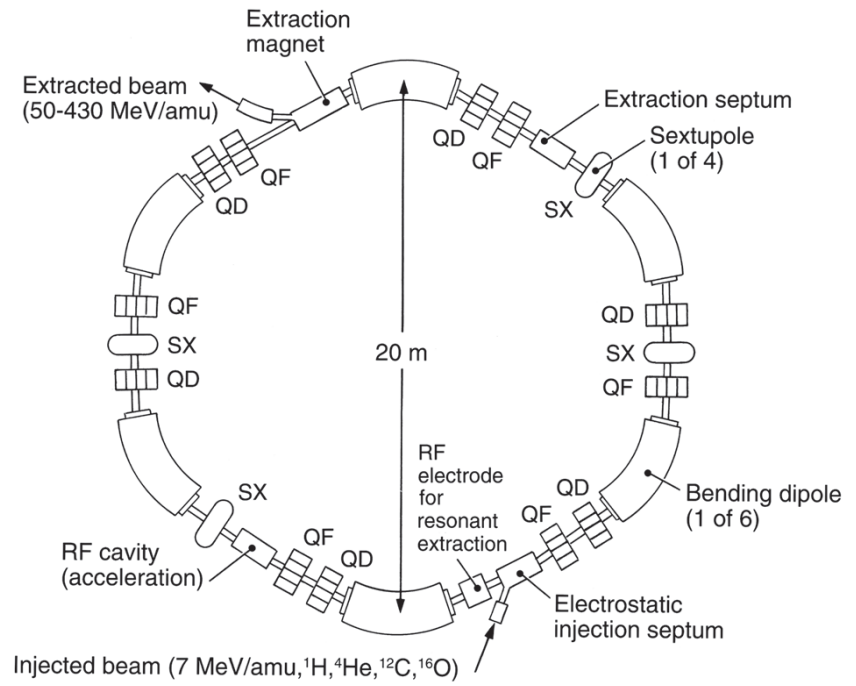
- Ion beam therapy is more conformal than photon beam RT

- Sharper dose fall off

- Range of ions much more influenced by tissue heterogeneitie: than photon beams with direct impact on TCP and NTCP

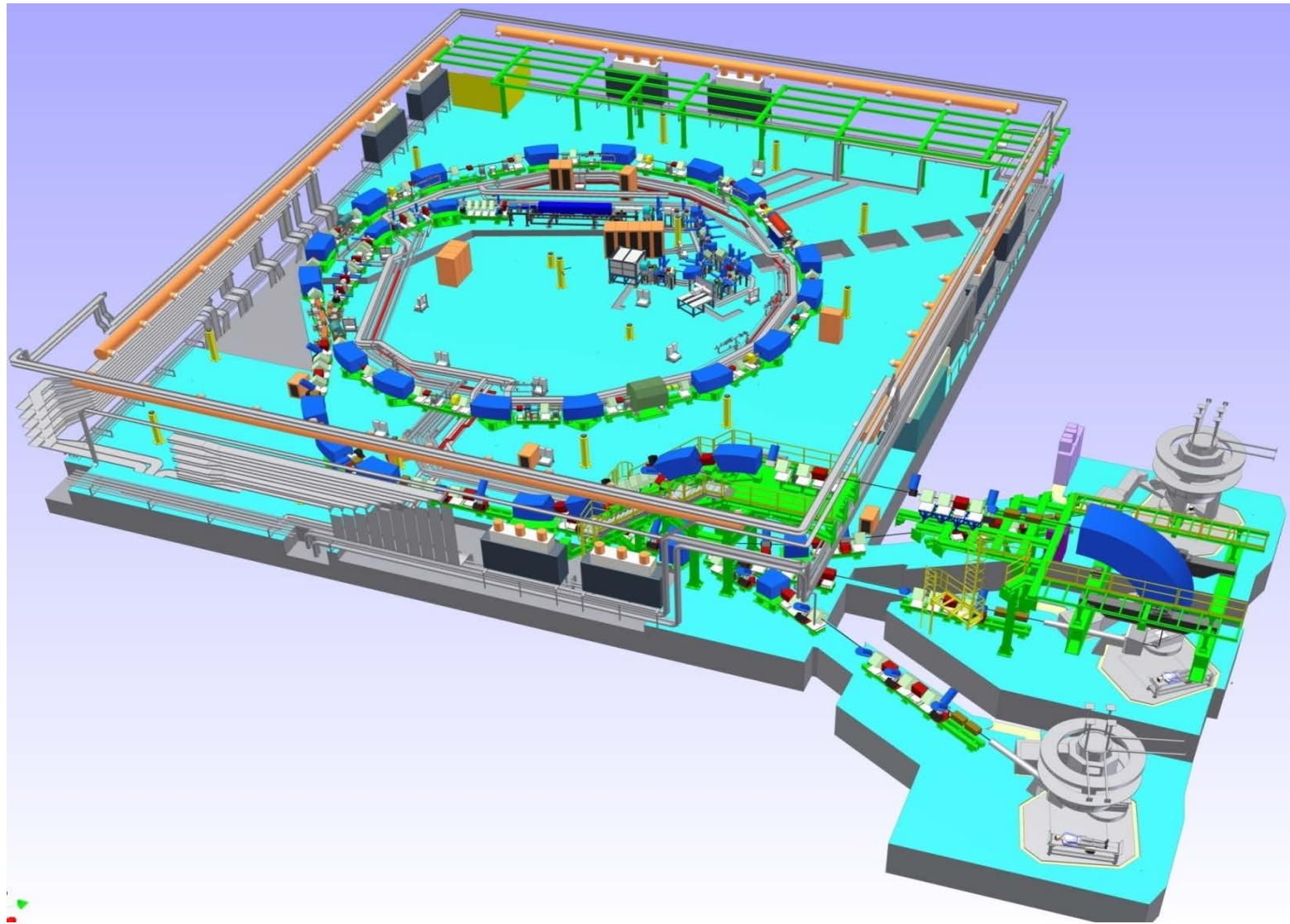- Image guidance is necessary for ion beam therapy
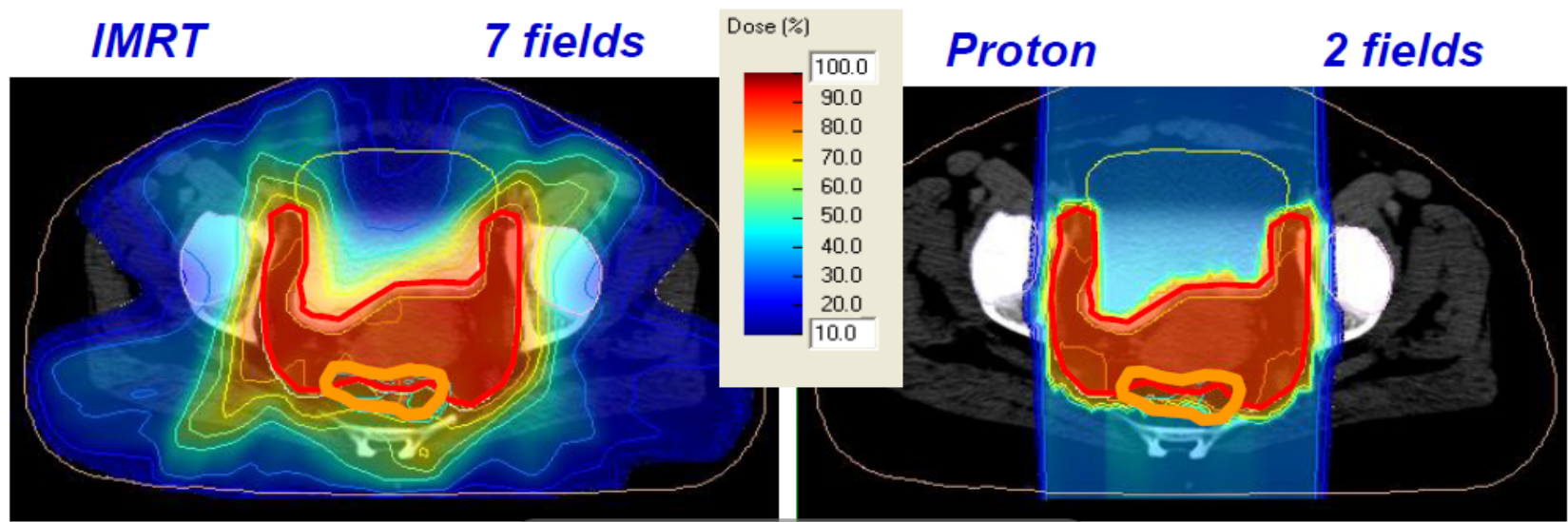
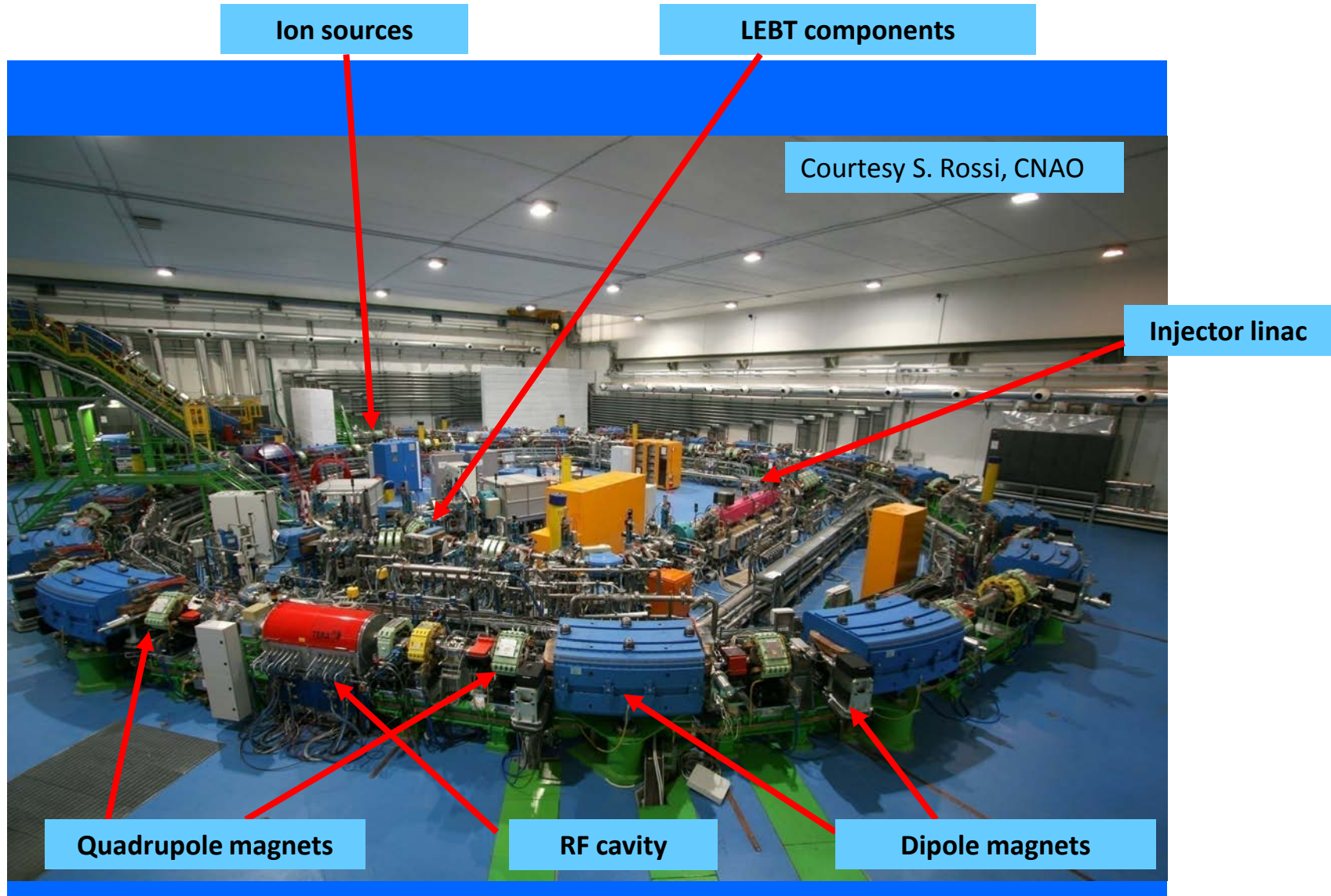## Hitachi proton synchrotron
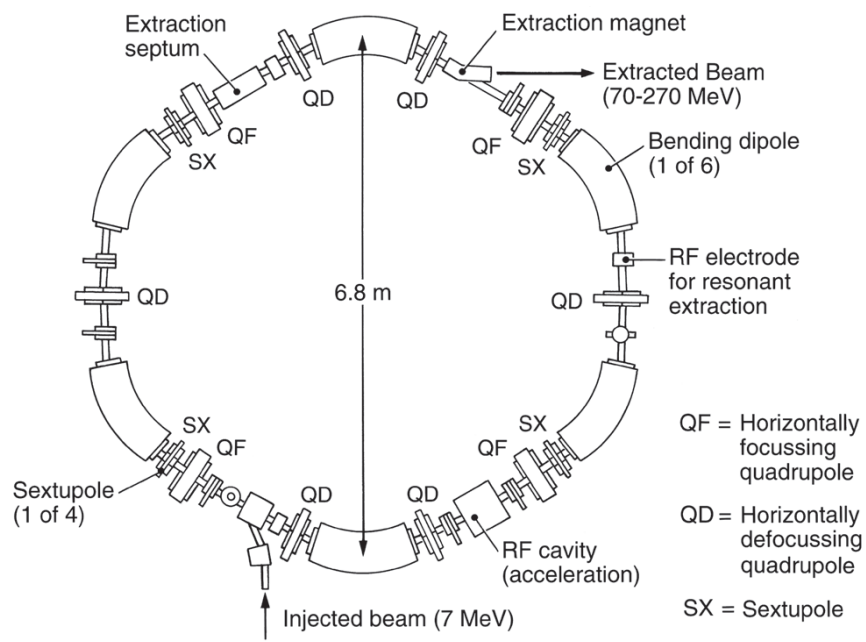
Siemens ion synchrotron

G. Coutrakon, Accelerators for Heavy-charged-particle Radiation Therapy,
Technology in Cancer Research & Treatment, Volume 6, Number 4 Supplement, August 2007

Courtesy S. Rossi, CNAO

Ion sources

LEBT components

Injector linac

Quadrupole magnets

RF cavity

Dipole magnets

Results for carbon ion therapy (G. Kraft, 2007)

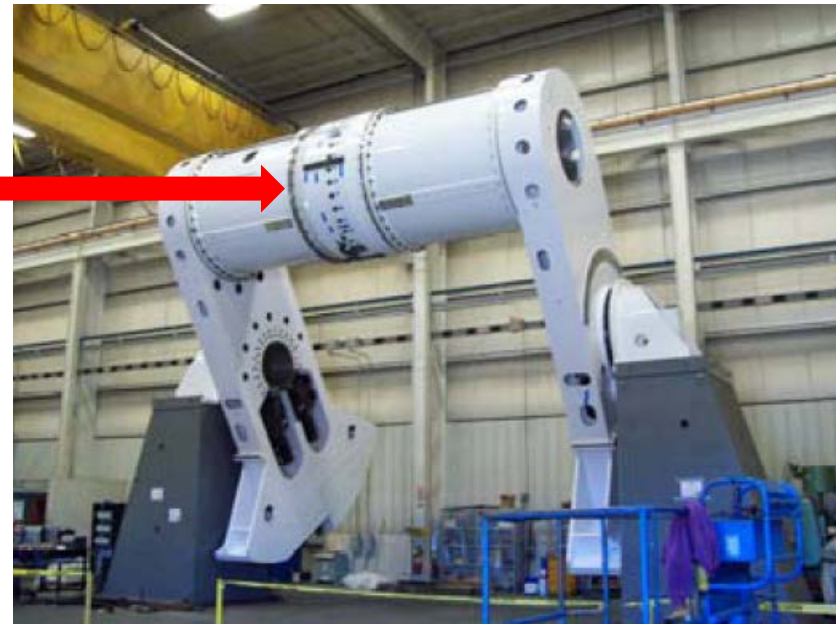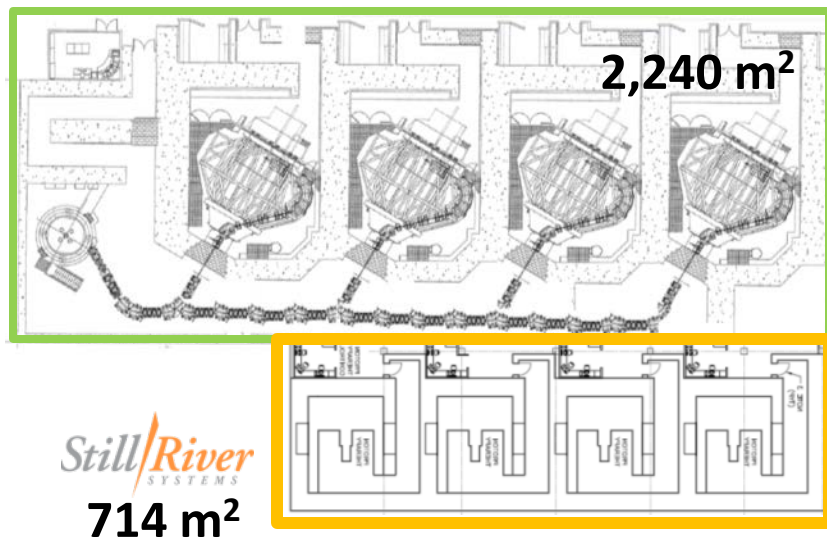| Indication	End point	Results photons	Results carbon HIMAC-NIRS	Results carbon GSI
Chordoma	local control rate	30 – 50 %	65 %	70 %
Chondrosarcoma	local control rate	33 %	88 %	89 %
Nasopharynx carcinoma	5 year survival	40 -50 %	63 %	
Glioblastoma	av. survival time	12 months	16 months	
Choroid melanoma	local control rate	95 %	96 % (*)	
Paranasal sinuses tumours	local control rate	21 %	63 %	
Pancreatic carcinoma	av. survival time	6.5 months	7.8 months	
Liver tumours	5 year survival	23 %	100 %	
Salivary gland tumours	local control rate	24-28 %	61 %	77 %
Soft-tissue carcinoma	5 year survival	31 – 75 %	52 -83 %	

Synchrocyclotron
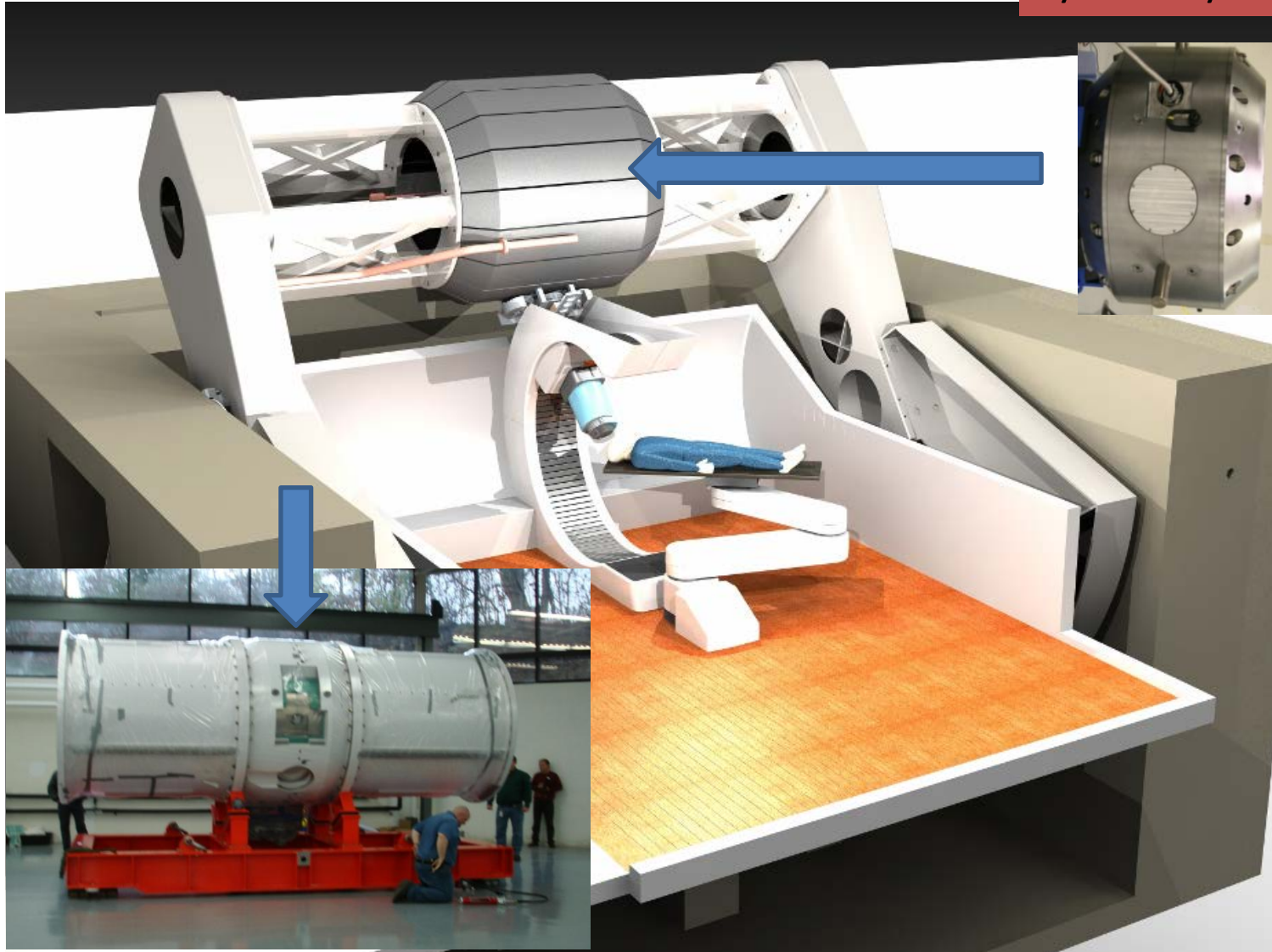
Synchrocyclotron operating with 10 Tesla magnetic field
Proton energy: 250 MeV
Cooling is through cryo-compressors (NO liquid Helium)
Low maintenance requirements – quarterly only

Weight ≈ 20 tons

2,240 m²

714 m²

29 m (87ft)

Other Proton Systems

812 m²

28 m (84 ft)

13 m (39 ft)

182 m²

14 m (41 ft)

Advantages of single-room facility:
- ✓ **Modularity**
- ✓ **Reliability / back-up**
- ✓ **PT treatment available at more hospitals**
- ✓ **(Hopefully) cost**
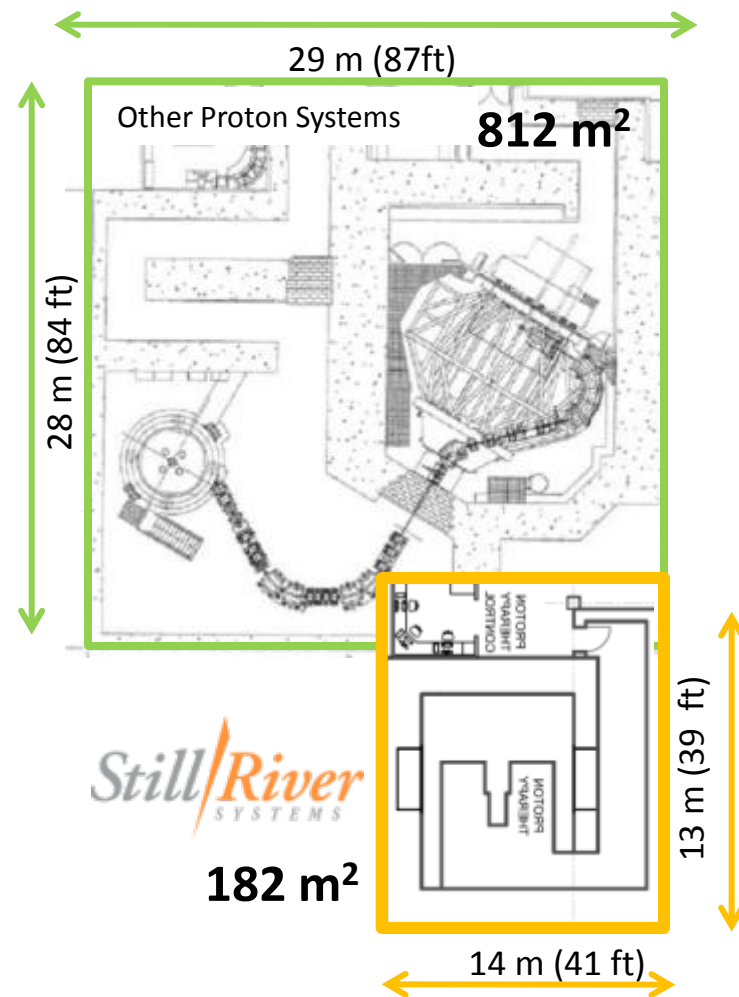
Courtesy L. Bouchet, *Still River Systems*

On accelerators & radiation therapy:

- C.K. Karzmark, Advances in linear accelerator design for radiotherapy, Medical Physics 11, 105- 128 (1984)
- S. Humphries, Principles of charged particle acceleration, John Wiley and Sons
- H. Wiedemann, Particle accelerator physics, Springer- Werlag
- S. Baird, Accelerators for pedestrians, CERN AB-note-2007-014
- PTCOG: Particle Therapy Co-Operative Group (http://ptcog.web.psi.ch/)

On radionuclide production:

- Cyclotron Produced Radionuclides: Principles and Practice, IAEA Technical Reports Series No. 465 (2008)
  (Downloadable from IAEA web site)
- Targetry and Target Chemistry, Proceedings Publications, TRIUMF, Vancouver
  (http://trshare.triumf.ca/~buckley/wttc/proceedings.html)
- CLARK, J.C., BUCKINGHAM, P.D., Short-Lived Radioactive Gases for Clinical Use, Butterworths, London (1975