These notes were written by Matteo Fonsetti a student who followed this course in 2022. I personally thank him for the great work he has done and I am sure that these will be of great help to all the students who will come.

Thanks again Matteo

roberto spighi

Physics applied to Medicine

1. Introduction

2. Interaction of radiation with matter

3. Interaction of charged particles with matter
3.1. Electromagnetic interactions
3.2. Nuclear interactions

4. The Spread-Out Bragg's Peak

5. Radiobiology

6. Machines to accelerate electrons to produce gamma beams
6.1 Teletherapy
6.2 Medical Linear Accelerator

7. Machines to accelerate charged particles
7.1 Cyclotron
7.2 Synchrotron

8. Boron-neutron's Capture Therapy

9. Diagnostic

10. New Frontiers + a quick refresher

Color legend

bold blue → new chapter
bold green → new sub-chapter
bold black → new paragraph
___ → end of the lesson

1. Introduction

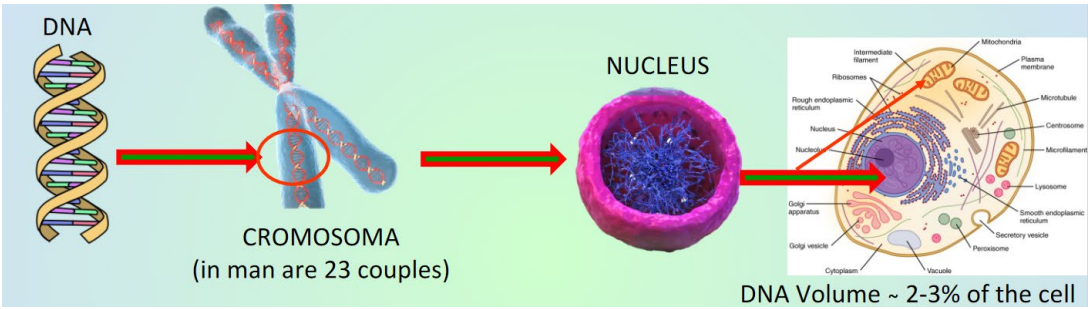
We currently have two possible ways of defeating a cancer:

- destroy the cancerous cells;
- **prevent their proliferation**…

… these can be achieved by using chemotherapy or radiotherapy, the latter external (beams) or internal (brachytherapy, systemic therapy) in the form of conventional radiotherapy (photons and electrons) or particle radiotherapy (neutrons, protons and light ions (Z < 18)).

But how can we prevent a cancerous cell from reproducing itself?

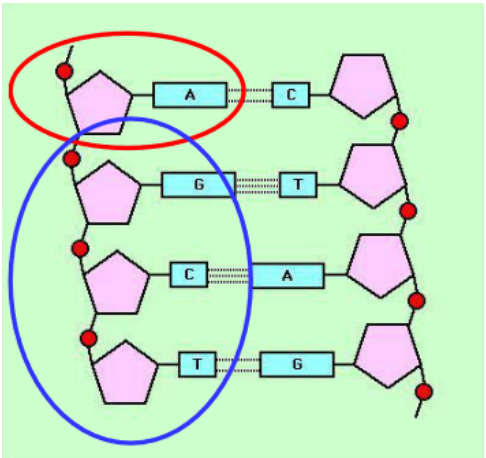
The key factor resides in the DNA, stored inside the chromosomes into the nucleus, which represents just a very small volume (2-3%) of the cell



DNA is composed by:

- sugar (deoxyribose), the skeleton;
- phosphate, links sugar in chains;
- nitrogen bases (adenine, cytosine, thymine, guanine)

each combo sugar+phosphate+nitrogen base forms a nucleotide and 3 of them form an amino acid

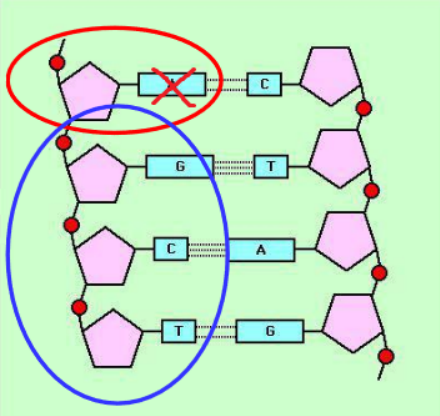


Main DNA goals are:

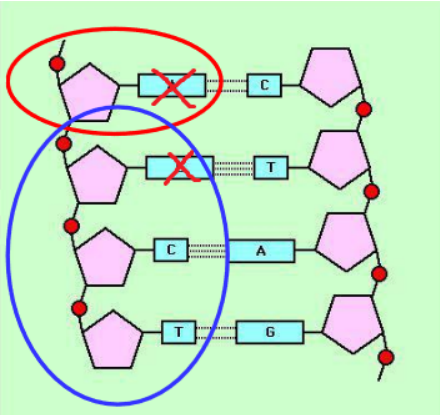
- producing proteins necessary to build cells, tissues and organisms;
- make the biochemical reactions necessary for the organism operations;
- **manage the duplication process**…

… the latter is what we are interested in…

Let’s consider the structure seen above and assume the hypothesis that we have been able to damage one adenine (**single strand break**)

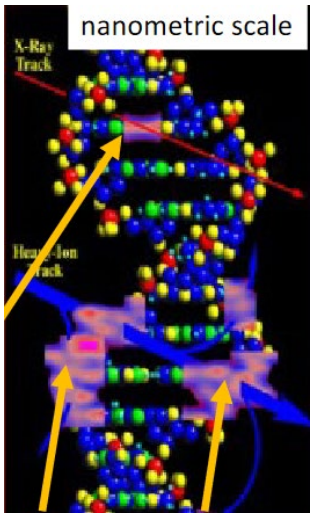


… the DNA is very clever and if the components around are still intact it can understand that an adenine is needed, hence it creates an adenine and replaces the damaged one with the new one ⇒ order to disable the DNA we must create **multiple damage in a limited portion of the chain**, for example damaging adenine and guanine (**double strand break**)



in this case, the DNA is no more able to understand how to repair itself, its reproduction functionality is compromised and the cell, unable to reproduce itself, eventually dies: this is the **direct way** to produce damage

repairable damage →

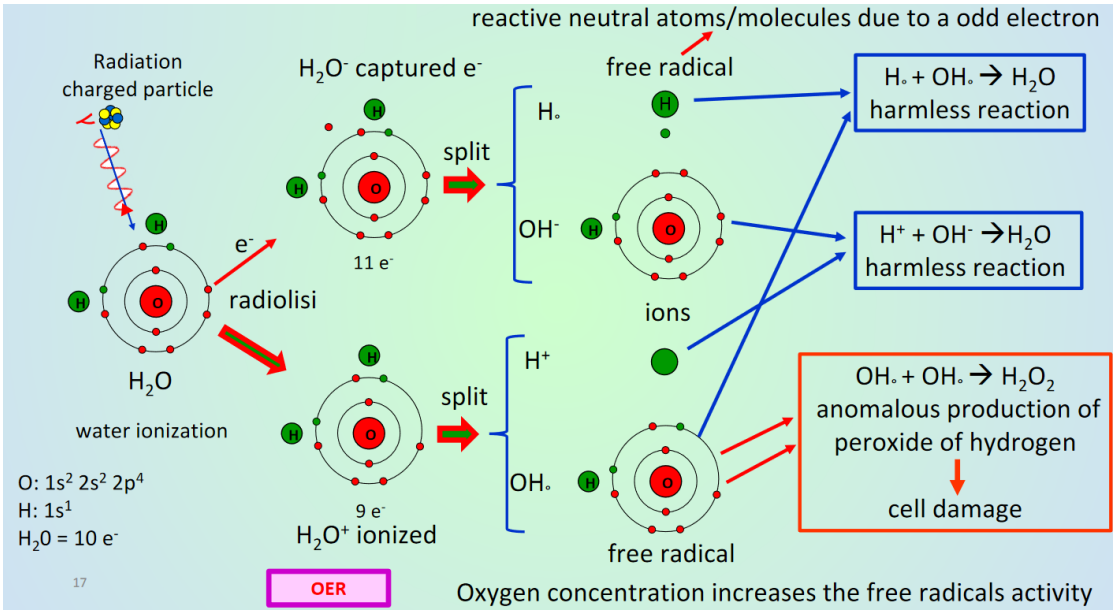


← irreparable damage

irreparable damage →

It is also possible to use an **indirect way** based on the ionization of water inside the cell.

Let's consider a H_2O molecule and an incoming gamma photon (5-10 MeV), the photon extracts one electron leading to two outputs: a H_2O^+ molecule and a H_2O^- molecule



… the H_2O^- molecule splits into a free radical H∘ and an OH^- molecule:

- the free radical H∘ links to an OH∘ giving a water molecule;
- the OH^- links to a H^+ giving again a water molecule…

… the H_2O^+ molecule splits into a H^+ ion and a free radical OH∘:

- the H^+ ion links with the OH^- giving a water molecule;
- the free radical OH∘ can link to a free radical H∘ giving again a water molecule but also to another OH∘ giving peroxide of hydrogen, H_2O_2…

… the first four reactions are harmless, the last one may cause cell damage…

… hence, via the reaction OH∘+ OH∘→ H_2O_2 it is possible to trigger an anomalous production of peroxide of hydrogen which may cause cell damage.

Giving some numbers:

regarding time:

- ~ 10^{-15} s → excitation and ionization;
- ~ 10^{-12} s → dissociation and production of water radicals;
- ~ 10^{-6} s → damage to DNA and other molecules;
- minutes → DNA breaks/chromosomal aberrations;
- hours → damage at cell level;
- years → possible cancer outbreak.

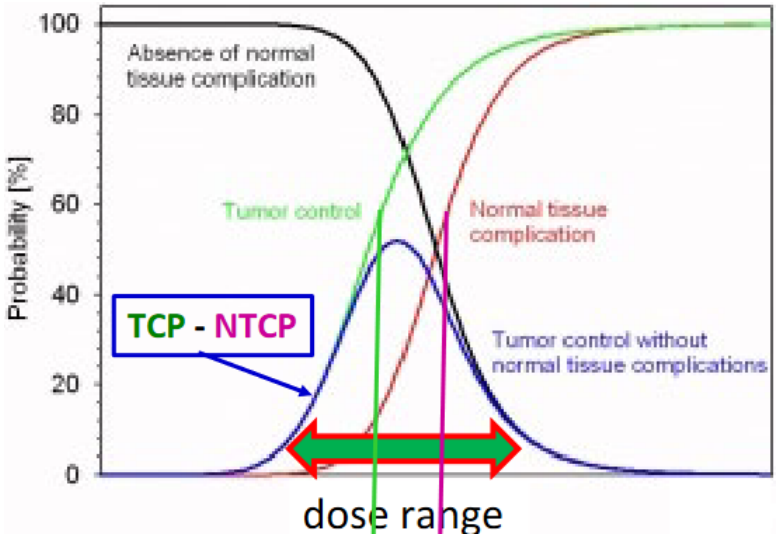
Regarding the effects: 1 Gy of dose produces on average ~ 100000 ionizations of which ~ 2000-3000 in the DNA corresponding to ~ 40 double strand break events, corresponding to ~ 0.5-1 chromosome's aberration, corresponding to ~ 0.5-1 lethal lesion, which corresponds to a probability of ~ 10^{-5} of developing a new cancer…

… this is a problem, by performing the treatment we can create a new cancer, hence the key question is: **when can a patient be treated?**

In order to give an answer, we must consider two different parameters:

- **TCP** (Tumor Control Probability) → probability to control (kill) the cancer;
- **NTCP** (Normal Tissue Complication Probability) → probability to have complications (create a new cancer) in the healthy tissue…

… obviously, **we want to maximize TCP and minimize NTCP**…
… as we can see below, both TCP and NTCP increase with the dose given, but TCP increases sooner than NTCP, hence we can identify an optimal region for treatment



… the delay happens because *__healthy cells better repair damages than mutated ones__, this is what makes it possible to cure cancer with radiotherapy and hadrontherapy.

The quantity of dose needed depends on many factors such as the type of cancer, its stage and the patient's conditions: typically a dose of 20-80 Gy with a tolerance of ~ 5-7% ~ 3 mm around the cancer is given, in ~ 30-35 treatments of ~1-2 Gy each from Monday to Friday.

Multiple treatments are mandatory for multiple reasons:

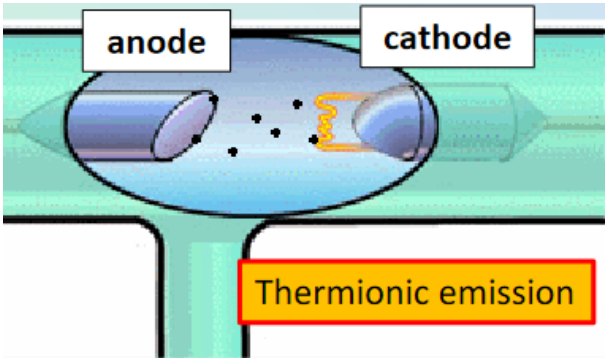
1) for * ;
2) to take care of the fact that during a treatment's session the cancerous cells could be in a phase of treatment resistivity;
3) to enhance treatment's effectiveness by eventually enriching the region with O;
4) because 20-80 Gy is a very high dose which is lethal if given all in one shot also if in a very localized region (just to make a comparison, Hiroshima-Nagasaki bomb emitted ~ 6 Gy of radiation) ___

2. Interaction of radiation with matter

To understand radiotherapy, we must consider the interaction between radiation and matter.

How to create X rays

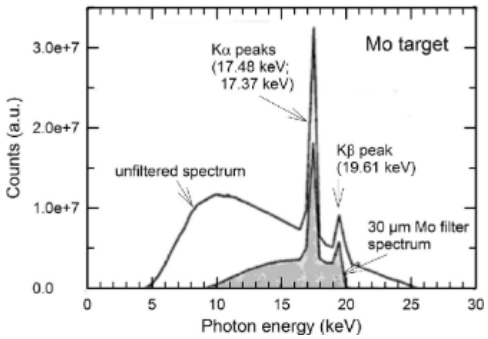
In order to create X rays we use the so called "**thermionic emission**"



… once heated, the cathode emits electrons in all directions, and by inserting a heavy material anode (such as tungsten or molybdenum) a ddp hence a flux is created → typical ddp applied is **50-150 kV** corresponding to **50-150 keV**.

Electrons hit the anode and produce X rays via:

- **bremsstrahlung** (continuous emission)
- **emission from shell K** ("spike emission")



… the energy of the created photons has a peak typically at around 1/3 the energy of the electrons, and it can ofc reach as maximum value the maximum value of the electrons.

Some numbers:

- diagnostic X rays → 35-500 keV;
- radiotherapy → 60-150 keV (very superficial cancer), 1-15 MeV (standard-deep).

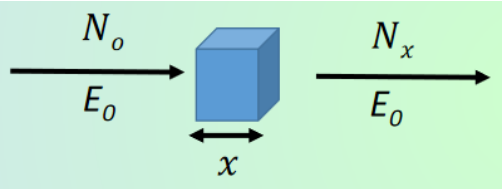
Besides the energy reached, another important specific of the machine is the **tube current**, that is the flux (number of electrons traveling the electrode) in mA, where 1 mA ~ 10^{15} e^-/s… → typical tube current is ~ **50-300 mA**.

How does radiation interact with matter?
Depending on the energy, radiation interacts with matter via 5 main processes:

- **Rayleigh and Thomson** → elastic scattering with free electron;
- **Photoelectric effect** → photon with bound electron;
- **Compton scattering** → photon with free electron;
- **Pair production** → photon with nucleus;
- **Photonuclear reaction** → photon with nucleus;

Rayleigh-Thomson scattering and photonuclear reaction are outside the energy range of radiotherapy, the first because it happens at too low energies, the latter because it requires energies far above the MeV.

An important thing to point out is the destiny of the photon in the three processes we study: both in photoelectric effect and pair production the photon disappears, while in Compton scattering the photon survives but is scattered hence changes direction with respect to its initial one…



… this means that considering an incoming flux of N_0 photons having E_0 energy passing through a material of thickness x, some of them will disappear due to pair production and photoelectric effect, some will be scattered at some angle due to Compton interaction and some will not interact with the material hence, after the passage inside the material, a weaker flux $N_x < N_0$ of same energy E_0, corresponding to the gammas which have not interacted at all will be measured..

The decrement of photons along the x axis is proportional to the incident number of photons

$$* \; -\frac{dN}{dx} = \mu N_0$$

… through a parameter $\boldsymbol{\mu}$ called **attenuation (absorption) coefficient** which represents the attenuation probability per unit length and depends on both the number of scattering centers per unit volume of the material and the total cross section

$$\mu = n\sigma_{tot} = \frac{N_A\,\rho}{M_{mol}}\,\sigma_{tot}$$

… by doing some simple calculation on * we get

$$\frac{dN}{N_0} = -\mu dx =$$

$$= \int_{N\prime=N(0)}^{N\prime=N(x)} \frac{dN\prime}{N_0\prime} = -\mu \int_{x\prime=x_i}^{x\prime=x_f} dx' \;\Rightarrow\; ln\left(\frac{N(x)}{N(0)}\right) = -\mu x \Rightarrow N(x) = N(0)e^{-\mu x}$$

… hence the decrement is exponential…

Observe that since the exponential must be adimensional, μ must be $[L^{-1}]$.

By considering the mean free path $\lambda = \frac{1}{\mu}$ the result becomes $N(x) = N(0)e^{-\frac{x}{\lambda}}$.

What is the value of μ?
In literature it is more convenient to refer to the **mass attenuation coefficient** $\boldsymbol{\frac{\mu}{\rho}}$ instead of μ, in order to remove the dependence from the density of the material.
Considering $\frac{\mu}{\rho}$, typical values vary from 0.02 to 0.05 cm^2/gr.

Achtung!
As seen, photons interact with matter in many ways, so μ is additive

$$\mu_{tot} = \mu_{phot} + \mu_{compt} + \mu_{pair}$$

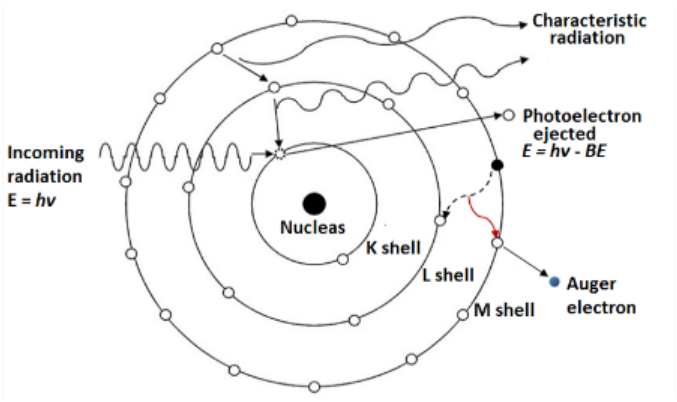
hence in the case of composed materials (ρ different) $\frac{\mu}{\rho}$ is additive

$$\frac{\mu}{\rho} = \sum_0^i p_i \left(\frac{\mu}{\rho}\right)_i$$

with p_i mass fraction of i-th element.
This is because the cross section itself is an additive quantity, hence if the cross section is additive then also both the attenuation coefficient and the mass attenuation coefficient (which as we have seen contain the cross section) are additive.

Now we will see for each different interaction how the effect is on the attenuation coefficient and on the cross section.

Photoelectric effect
Interaction between an incoming photon and an electron of the inner shell



… the incoming photon disappears and the electron gains a kinetic energy

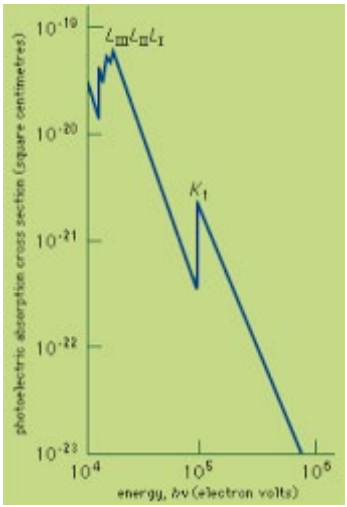
$$E_k = h\nu - E_{bound}$$

… since part of the photon's energy is used to free the electron, we have that

$$E_k \neq E_{ph}$$

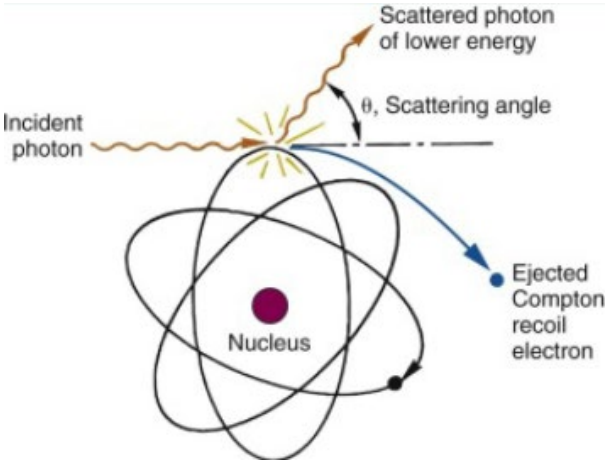
hence the interaction is inelastic.

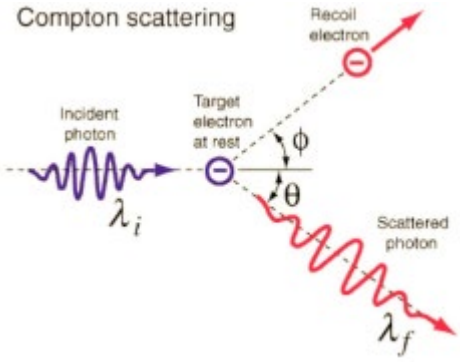
The electron is ejected from the atom and a gap forms, an outer shell's electron fills the gap emitting a photon in the X ray band; sometimes it can happen that such photon is absorbed by another electron in an outer shell which gets ejected as an Auger electron (Auger effect).



Compton scattering

Interaction between an incoming photon and an electron of the outer shell

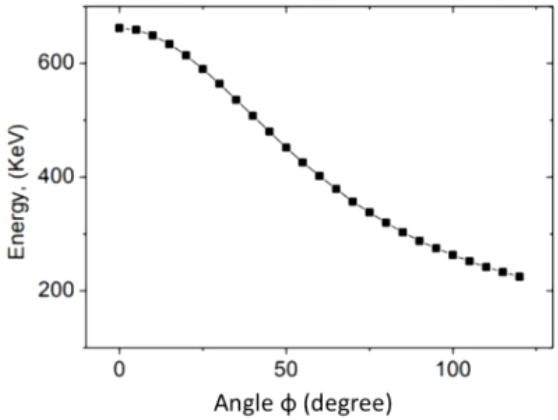




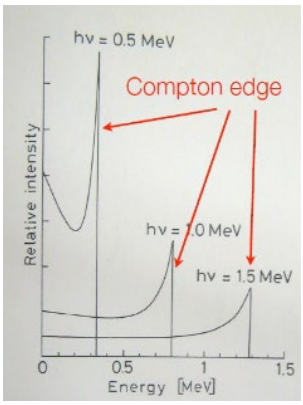
… in principle, both photoelectric effect and Compton scattering are inelastic interactions, but since the energy needed here to extract the electron is negligible with respect to the energy of the photon, the electron can be considered "free" and the interaction elastic.

The photon survives and its energy after the interaction depends on the scattering angle θ

$$E_f \; \alpha \; \theta^{-1}$$



the greater the angle, the lower the energy, the higher the energy transferred to the electron; the maximum energy is transferred to the e^- when the γ is backscattered.



… so, you can select a gamma with a particular energy just by selecting a particular angle.

Pair production

Interaction between photon and nucleus: the photon disappears and an e^--e^+ pair is created. In order to create a pair e^--e^+ an energy at least two times the mass of the electron is needed, hence this process is not possible for energies below 1 MeV, so here there is an energy threshold

$$E_{threshold} = 2m_{e^-} = 2 \cdot 511\ keV = 1.022\ MeV$$

The presence of the nucleus is required because of the square of quadrimomentum conservation: the square quadrimomentum of gamma is zero, while the one of the pair e^--e^+ is not zero, so you need something that gives the energy needed: the nucleus of the atom.

The absorption energy coefficient

It is crucial to take care not only of the mass attenuation coefficient, but also of the energy deposited by the electrons with respect to the initial energy carried by the photon; this is parameterized by the absorption energy coefficient

$$\left(\frac{\mu}{\rho}\right)_{en} \equiv \left(\frac{\mu}{\rho}\right)\frac{E_{e^-}}{E_\gamma}$$

For the three processes considered the absorption energy coefficient is:

- Photoelectric → $\left(\frac{\mu}{\rho}\right)_{en,ph} = \left(\frac{\mu}{\rho}\right)_{ph}\frac{E_{e^-}}{E_\gamma} = \left(\frac{\mu}{\rho}\right)_{ph}\frac{E_\gamma - E_b}{E_\gamma} \sim \left(\frac{\mu}{\rho}\right)_{ph}$;
- Compton → $\left(\frac{\mu}{\rho}\right)_{en,C} = \left(\frac{\mu}{\rho}\right)_{C}\frac{E_{e^-}}{E_\gamma} = \left(\frac{\mu}{\rho}\right)_{C}\frac{E_\gamma - E'_\gamma}{E_\gamma} < \left(\frac{\mu}{\rho}\right)_{C}$;
- Pair production → $\left(\frac{\mu}{\rho}\right)_{en,pp} = \left(\frac{\mu}{\rho}\right)_{pp}\frac{E_{e^-}}{E_\gamma} = \left(\frac{\mu}{\rho}\right)_{pp}\frac{E_\gamma - 2m_{e^-}}{E_\gamma} \sim \left(\frac{\mu}{\rho}\right)_{pp}$.

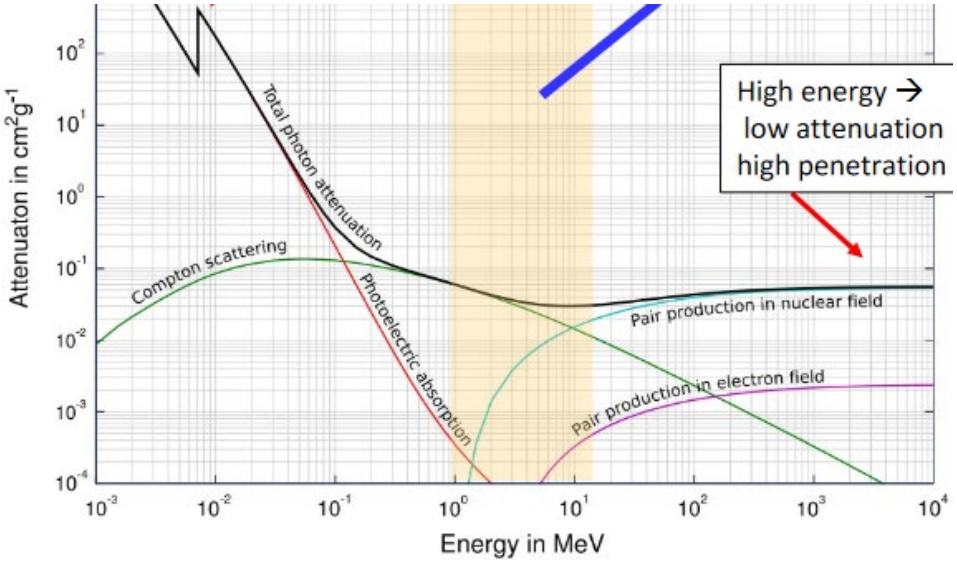
Cross section in the three interactions

With respect to E of γ and Z of the target:

- Photoelectric → $\sigma\ \alpha\ Z^4/E^{3.5}$ → important in heavy materials and at low energies;
- Compton → $\sigma\ \alpha\ Z/E$ → ~ linear attenuation with respect to energy;
- Pair production → $\sigma\ \alpha\ Z^2/ln(E)$ → strongly depends on Z, ~ constant at high E.

With respect to Z and A of the target:

- Photoelectric → $\sigma\ \alpha\ Z^5/A$;
- Compton → $\sigma\ \alpha\ Z/A$;
- Pair production → $\sigma\ \alpha\ Z^2/A$



… this means that depending on the energy and on the material the attenuation changes with the interaction considered, from a regime at low energies in which photoelectric attenuation is dominant to a high energy one in which pair production is.
The total cross section is given by the integration of the three contributes: it's relatively very high at low energies decreasing and becoming approx constant at high energies, this means that high energy photons interact less with matter wrt low energy ones, crossing larger portions of materials and requiring higher doses to gain the same treatment's effectiveness.
In water, similar to the human body, for an energy of 1 MeV the attenuation is 0.75 barns which is very little, so the penetration is high; high penetration means high dosage needed because the radiation rarely interacts with the atoms, hence few electrons are produced, hence little energy is deposited ___

Resume
If a photon crosses a material at our energies, for example water, it can undergo three types of interactions: photoelectric effect, Compton scattering and pair production; in photoelectric effect and pair production the photon disappears, in Compton scattering it is scattered in a different direction than the initial one.
So, if we evaluate the gamma outside the material in the same direction of the previous one, we find only the gammas that weren't absorbed by the material, so these gammas have exactly the same energy as the input.
This is described by the **absorption law**, an exponential function which tells us that the number of gammas that cross a material of length x is equal to the initial gamma number cross an exponential which depends both on the length of the material and on the attenuation coefficient, the latter given by a characteristic of the material (n) and the total cross section → total means that if the gamma interacts with photoelectric, Compton and pair production the final cross section is given by the sum of the cross sections of the single interactions.
At very low energy the most important interaction is the photoelectric one, while at the energy typically used in radiotherapy (1-10 MeV) photoelectric effect is negligible and the dominant ones are Compton scattering (99% around 1 MeV, 50% around 10 MeV) and pair production (50% around 10 MeV) → after pair production an electron is produced, this electron can ionize other atoms and having lower energy than the initial incoming photon can trigger photoelectric interactions.

3. Interaction of charged particles with matter

Charged particles can interact with matter in two ways:

(i) **Electromagnetic interactions**, because both the beam and the human body are electrically charged, these are:

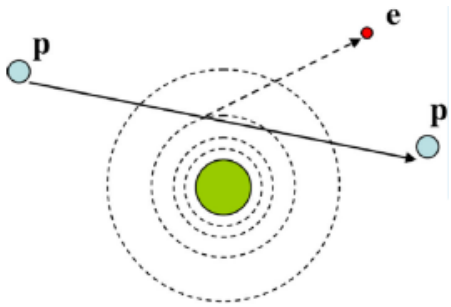
- **Bethe-Bloch Interaction** ;
- **Rutherford (Multiple Coulomb Scattering)** ;
- **Bremsstrahlung** ;
- **Cherenkov Effect** ;

(ii) **Nuclear interactions**.

3.1 Electromagnetic interactions

Bethe-Bloch Interaction

Interaction between a charged particle and an electron in the electronic cloud of the atom.



This is an inelastic collision because part of the initial energy of the proton is spent to excite or ionize the electron.

Due to the fact that the mean cross section is huge (*~10^6 barns!) the interaction happens for sure (hundreds of interactions!) hence it makes no sense to speak about “cross section” but it is more convenient to consider the energy lost in the material during the passage.

We can have two scenarios:

- **Soft collision** → atom excitation → during de-excitation one photon is emitted;
- **Hard collision** → atom ionization → one low energy electron (δ ray) and one photon are emitted.

In both cases, being the proton’s mass much higher than of the electron (1 GeV vs 0.5 MeV), the proton undergoes a negligible deviation hence proceeds ~ in the same direction.

* implies that Bethe-Bloch interaction is by far the dominant process, in fact the cross section can be visualized as the overlapping area between target and projectile, hence having R_1 projectile radius and R_2 target radius we have that

$$\sigma \sim \pi(R_1 + R_2)^2$$

… R_1 is negligible with respect to R_2 hence

$$\sigma \sim \pi {R_2}^2$$

… and by putting inside the equation some realistic values for the atom and the nucleus we get

$$\sigma_{atom} \sim \pi(10^{-8})^2 \sim 10^{-16}\, cm^2 \sim 100\, Mbarn$$
$$\sigma_{nucleus} \sim \pi(10^{-12})^2 \sim 10^{-24}\, cm^2 \sim 1\, barn$$

… a difference of $\sim 10^8 - 10^{10}$ which justifies why the Bethe-Bloch interaction is dominant with respect to the Rutherford scattering.

So we focus on the energy loss, the so-called “Stopping Power”.
The stopping power is described by the **Bethe-Bloch formula**:

$$-\frac{dE}{dx} = \frac{\rho Z}{A}\,\frac{4\pi N_A m_e c^2}{M_U}\left(\frac{e^2}{4\pi\epsilon_0 m_e c^2}\right)^2\,\frac{z^2}{\beta^2}\left[\ln\left(\frac{2m_e c^2\beta^2}{I(1-\beta^2)}\right) - \beta^2 - \frac{\delta}{2} - \frac{C}{Z}\right]$$

Medium properties

- ρ material density
- Z: atomic number
- A: mass number
- I: ionization potential

General constants

- N_A Avogadro number
- m_e: electron mass
- M_U: molar mass 1/12 C mass
- ϵ_0: empty dielectric constant
- e2: electric charge

Beam characteristics (z, β)

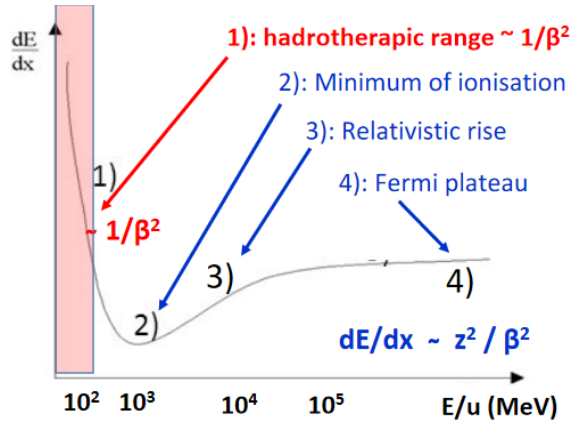
- z (lower case): beam atomic number
- β: beam velocity
- δ: density correction , important at high energy
- C: shell correction, important for low energy

This formula can be divided in four different parts:

- a part describing the properties of the medium crossed by the projectile;
- a part composed by physical constants;
- a part describing the beam characteristics → this is the most important one, in particular the term z^2/β^2;
- a part including corrections: a density correction important at high energies which is negligible in our case, and a shell correction, important at low energies which we must consider.

The Bethe-Bloch formula describes a **stochastic process**, hence the stopping power above is an average; in other words, being this a statistical process, we can have n projectiles of the same type and energies with different stopping powers, hence there’s a fluctuation described by a **Landau distribution**.

By plotting the stopping power as a function of the projectile’s kinetic energy per nucleon we have essentially four regimes:

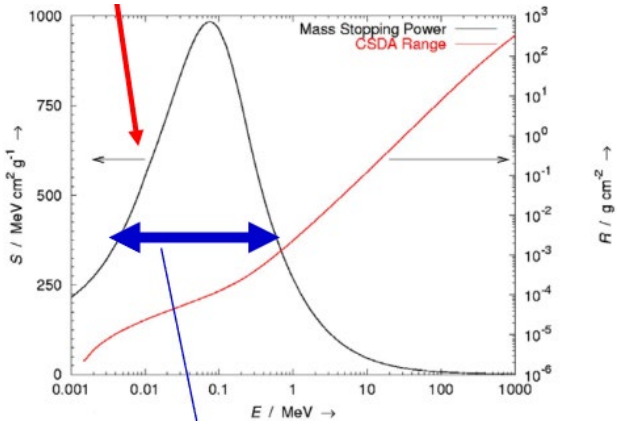


- a Fermi plateau at very high energies;
- a relativistic rise;
- a minimum of ionization;
- and a slope which scales as β^{-2} in the typical hadrotherapic range within 100 MeV…

hence, when a charged particle enters the body it first deposits little energy, then once its kinetic energy dropped enough it deposits most of the energy, that scales as β^{-2}.

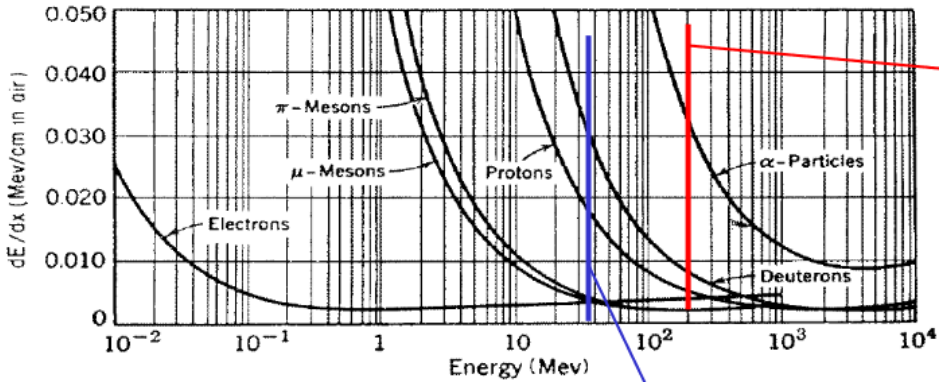
Achtung!
"per nucleon" means that if for example a proton has 100 MeV of energy a Carbon, having 12 protons, has $100 * 12 = 1200\ MeV$ and, on the other hand, if a Carbon has 100 MeV each nucleon has 100/12 $100/12 \sim 8.3$ MeV; a proton of 100 MeV and a Carbon of 100 MeV/n they have the same β.

Note that in the plot of the previous slide if $E \to 0$, $-dE/dx \to \infty$, that is a non-physical solution which arises because the Bethe-Bloch model is built around the condition that the electron's velocity is negligible with respect to the projectile's one: at low energies such approximation fails and a corrective effect must be taken into account, the **shell correction**, and by including it we get the more accurate plot below



where the right side is the one of the first plot and the left side is given by the shell correction which drops the mass stopping power at zero; hence if a charged particle interacts with the human body, it releases low energy, then most of the energy, then again low energy until 0.

This is the same plot for different particles



- if we fix β (red line), for a given E we have that *$-\frac{dE_\alpha}{dx} > -\frac{dE_{deut}}{dx}$, this because in the Bethe-Bloch equation $-\frac{dE}{dx}\ \alpha\ Z^2$ and being $Z_\alpha > Z_{deut}$ we have *;
- if we fix Z (blue line), for a given E we have that *$-\frac{dE_{deut}}{dx} > -\frac{dE_p}{dx}$, this because in the Bethe-Bloch equation $-\frac{dE}{dx}\ \alpha\ \beta^{-2}$ and being $M_{deut} > M_p$ we have that $\beta_{deut} < \beta_p$ hence *... the dependence from β is also into the logarithm inside the parentheses, but its contribution is negligible with respect to the β^{-2} term outside.

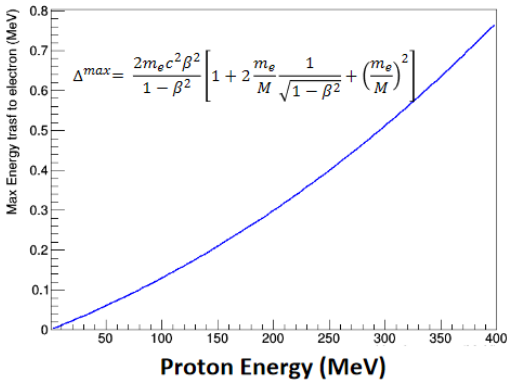
Regarding the part of the Bethe-Bloch equation talking about the material, while Z/A may range from 0.42 to 0.5 (for the human body it is about 0.5, so approximately constant) and I may vary between 19 eV for H and 820 eV for Pb (and it's inside a logarithm), ρ may vary by many orders of magnitude hence gives by far the dominant contribution.

In general we have that:

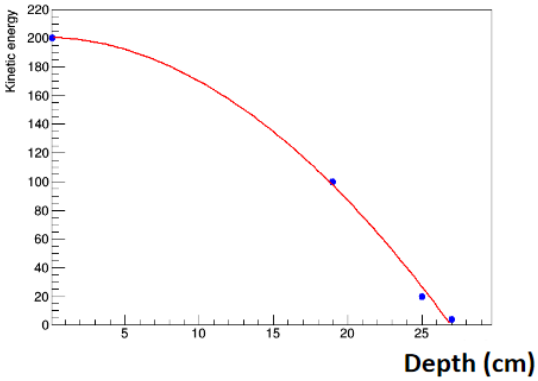
- **in low density materials** there are few collisions, some with high energy transfer, hence there are high fluctuations describable with a **Landau distribution**;
- **in high density materials** there are a lot of collisions, hence the stopping power shows small fluctuations describable with a **Gaussian distribution**.

In cases where prosthesis are present, this could represent a serious problem, because many prosthesis are made in tungsten which is a very heavy material which can give rise to many complications in terms of nuclear interactions; extensive studies have brought plastic prosthesis, made of carbon, hydrogen, silicon and so on, such prosthesis are less problematic but are not always viable.
In general, when a prosthesis is present you try to avoid it unless you can't do otherwise.

This is the maximum energy released to an electron by a proton during an interaction



… as we can see, just a small fraction of the kinetic energy of the proton is transferred to the electron, hence in order to stop the proton hundreds of interactions are needed.
As an example, the typical energy transferred to an electron is around 500 eV, hence, to stop a 200 MeV proton around 400 collisions are needed…
… this translates into a range of material crossed



…we can see that after about 20 cm the proton has lost half of its energy, and in just 6-7 more cm it releases all the energy left: this is very important because it means that **we can decide where to stop the beam**…

… how? thanks to the strict **relation between range and energy**

$$R = \int_0^R dx = \int_0^{E_0} \frac{dE}{\frac{dE}{dx}} = {E_0}^{1.75} \sim {E_0}^2$$

considering that in the integral enters $\frac{dE}{dx}$, which we know contains the dependence on the material and on the beam (Bethe-Bloch equation), we have that in general

$$\boldsymbol{R(E) = \alpha E^p}$$

with

- α depending on the material;
- p depending on the beam.

Hence, **the range of charged particles depends on their kinetic energy**, this is very useful in hadrontherapy because it allows us to go more or less deep in the human body by changing the beam's energy and/or the projectile's type; considering for example Carbon instead of protons, Z increases, hence dE/dx increases, hence R decreases, and to reach the same range as protons the energy of the beam must be increased.

Giving some values:

- proton → 200 MeV, 25.8 cm;
- Carbon → 200 MeV/n, 8.75 cm… to reach the range above requires 390 MeV/n.

With hadrontherapy it is possible to reach up to about 26 cm depth inside the human body.

A few important points:

(i) This is a great advantage hadrontherapy offers compared to conventional radiotherapy: in the latter the photon either interacts or not interacts with the material, hence a gamma beam crosses all the body irradiating also the tissues behind the treatment's region;

(ii) The values given above must be considered as average values.
As we said, Bethe-Bloch is a stochastic interaction, hence there are fluctuations which must be taken into account: for a 200 MeV proton the fluctuation, called **longitudinal straggling**, is about 2.5 mm, around 1%, hence a more correct estimate is given by

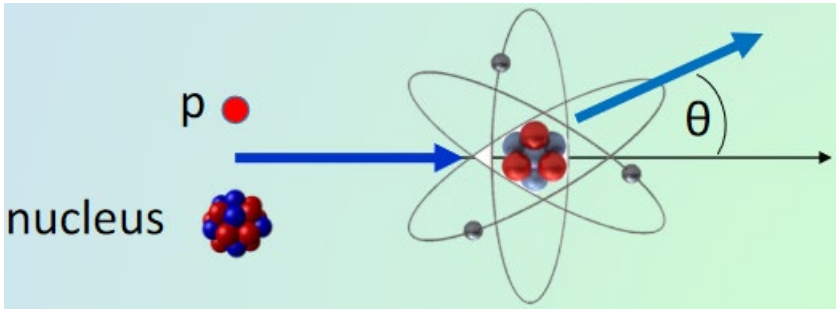
$$25.8 \pm 0.25 \text{ cm}$$

… this is important because in the case an organ at risk is present behind the cancer zone ("at risk" means "required to live") the problem whether or not irradiate till the end arises;

(iii) When energy is transferred to an electron ionization can occur and δ particles may be created, such particles may represent an adding source of excitation/ionization and must be considered; fortunately, δ particles' mean range is around 2 mm, hence they do not travel too far from the zone interested by the beam.

Rutherford (Multiple Coulomb Scattering)

Here we have the electromagnetic interaction between a charged particle and the nucleus



the first important difference between Rutherford and Bethe-Bloch is that here the particle feels a very strong magnetic field and is deflected of a theta angle.

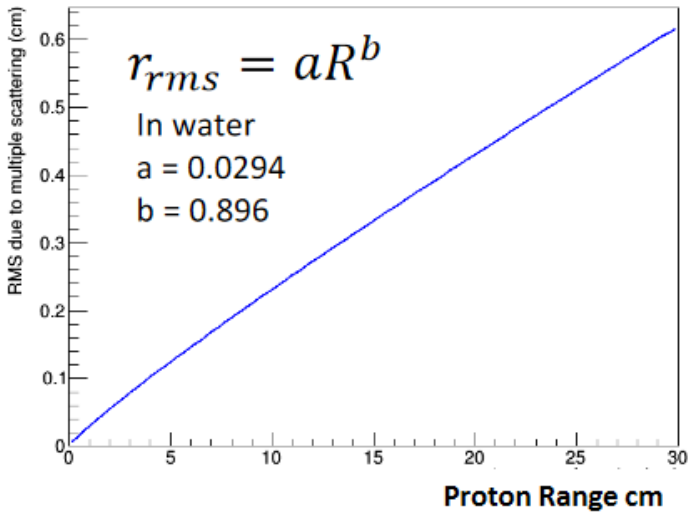
The equation describing this is the **Rutherford formula**

$$\frac{d\sigma}{d\Omega} = \left(\frac{1}{4\pi\varepsilon_0}\frac{Z_1 Z_2 e^2}{4E_0}\right)^2 \frac{1}{sin^4\left(\frac{\theta}{2}\right)}$$

which tells us that the differential cross section varies proportionally with the atomic number of the projectile (Z_1) and of the target (Z_2) square and with the initial beam energy (E_0) to the minus two and the angle of deflection to the minus four, so essentially

$$\sigma = f(Z_1, Z_2, E_0, \theta)$$

Due to the fact that there is a deviation, a **lateral displacement** is introduced



… the displacement can vary between 0 and 6 mm depending on the range crossed by the projectile: for a 200 MeV proton this is about 5 mm, 0.5 cm, 2% of the range so a factor 2 higher than the longitudinal straggling due to Bethe-Bloch.

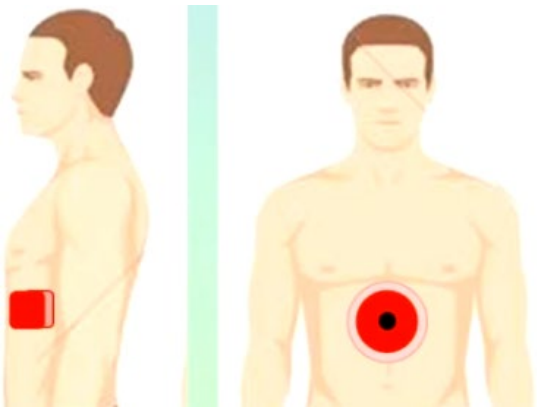
Likewise in Bethe-Bloch, also Rutherford's lateral displacement must be taken into account.

Hence, given a 200 MeV proton beam entering the human body, it covers a range of

$$25.8 \pm {}^{*}0.25 \pm {}^{*}0.5 \text{ cm}$$

with

- * longitudinal straggling due to Bethe-Bloch interaction;
- * lateral displacement due to Rutherford scattering.



Both the displacements should not be seen as something negative because we are talking about "millimeters" on an overall extension both for the beam and the treatment region of "centimeters", hence the uncertainty is very small and the beam delivery is very precise.

In case the cancerous region is far from an organ at risk, the displacements may be used to treat a halo around the high density cancerous zone, including also the zones where the density of cancerous cells are lower, increasing the therapy's effectiveness.

Rutherford scattering can be elastic or inelastic, depending if the nucleus is excited or not during the interaction: in the second case also a photon is emitted.

The more the energy increases the more the electromagnetic interactions disappear and the nuclear interactions appear; however, also at the energies used in hadrontherapy a small contribution given by nuclear interactions is present and must be taken into account.

What is the cross section expected for a p-p Rutherford scattering? and for a p-nucleus one?
In order to answer we take the Rutherford formula and integrate it over the solid angle

$$\sigma = \int \frac{d\sigma}{d\Omega} d\Omega =$$

$$= 2\pi \int_0^{\pi} \frac{d\sigma(\vartheta)}{d\Omega} dcos(\vartheta) =$$

$$= 2\pi \int_0^{\pi} \frac{d\sigma(\vartheta)}{d\Omega} sin(\vartheta) d\vartheta =$$

$$= 2\pi \left(\frac{1}{4\pi\varepsilon_0} \frac{Z_1 Z_2 e^2}{4E_0}\right)^2 \int_0^{\pi} \frac{sin(\vartheta) d\vartheta}{sin^4(\vartheta/2)} =$$

(... after some calculation we get…)

$$= 4\pi \left(\frac{1}{4\pi\varepsilon_0} \frac{Z_1 Z_2 e^2}{4E_0}\right)^2 \left[\frac{1}{tg^2(0)} - \frac{1}{tg^2(\pi/2)}\right] =$$

($tg^2(\pi/2)$ gives ∞ hence $\frac{1}{tg^2(0)}$ is 0, so we get)

$$= 4\pi \left(\frac{1}{4\pi\varepsilon_0} \frac{Z_1 Z_2 e^2}{4E_0}\right)^2 \frac{1}{tg^2(0)} =$$

… now $tg^2(0)$ gives 0 hence $\frac{1}{tg^2(0)}$ diverges hence it's a non physical solution, this was evident also in the Rutherford formula

$$\frac{d\sigma}{d\Omega} = \left(\frac{1}{4\pi\varepsilon_0} \frac{Z_1 Z_2 e^2}{4E_0}\right)^2 \frac{1}{sin^4\left(\frac{\theta}{2}\right)}$$

in which by putting $\vartheta = 0$ we get the divergence.

The problem can be solved by considering all the solutions except the non-physical one, hence by considering a ϑ_{min} angle instead of $\vartheta = 0$

$$= 4\pi \left(\frac{1}{4\pi\varepsilon_0} \frac{Z_1 Z_2 e^2}{4E_0}\right)^2 \frac{1}{tg^2(\vartheta_{min})}$$

… and by assuming realistic values we get ~ 20-30 mb for p-p and ~10x more for p-nucleus.

Bremsstrahlung and Cherenkov contributions

When a charged particle interacts with a nucleus also bremsstrahlung and Cherenkov interactions take place; considering hadrontherapy, however, **both are negligible**.

Why?

Regarding bremsstrahlung, the stopping power can be written as

$$-\frac{dE}{dx} \sim \frac{Z^2}{m^2}$$

with Z and m atomic number of the target and mass of the beam's particle respectively. It appears clear why the bremsstrahlung contribution is crucial considering a beam composed by electrons but negligible considering one composed by protons or Carbon: electrons have low m hence high energy loss, while protons and ions have a much higher m hence a negligible energy loss.

Regarding Cherenkov, the speed of light in a medium can be calculated with the formula

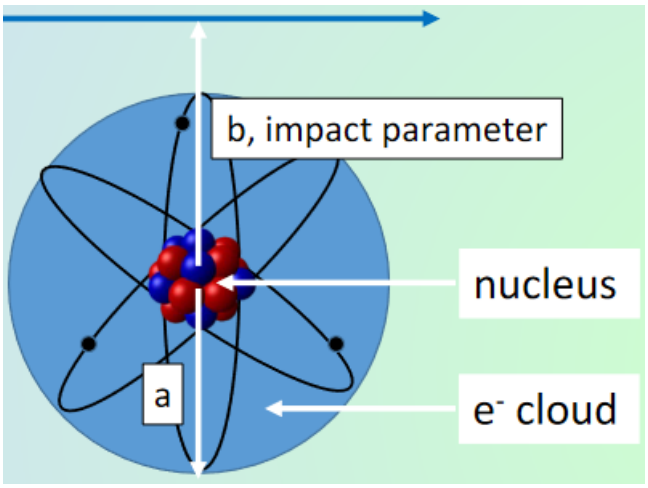
$$\beta = \frac{1}{n}$$

with n refractive index of the medium.

Considering the human body (water at 37 °C) n is ~1.33 hence light travels at ~0.75c. This means that in order to have Cherenkov effect β_{proton} should be higher than 0.75c, while its actual value is ~0.57c (considering a 200 MeV proton), hence in the range of hadrontherapy Cherenkov effect does not trigger in the human body and can be neglected

Interactions of electrons with matter

Electrons can interact with matter via three main processes



- soft collision $\rightarrow b \gg a$, low energy transferred from the e^- to the orbital ones;
- hard collision $\rightarrow b \sim a$, appreciable fraction of energy transferred from // // //;
- bremsstrahlung $\rightarrow b \ll a$, the energy of the γ emitted increases as b decreases…

… hence the total energy loss is given by

$$\left(\frac{dE}{dx}\right)_{tot} = \left(\frac{dE}{dx}\right)_{coll} + \left(\frac{dE}{dx}\right)_{rad}$$

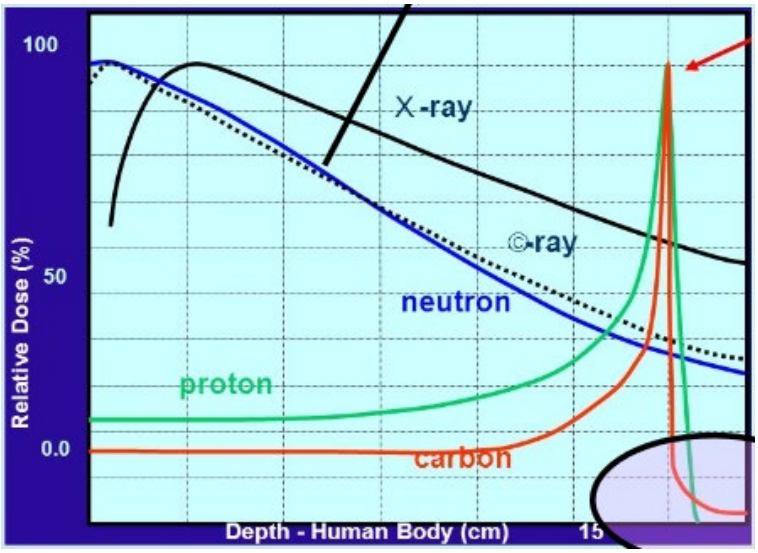
- $\left(\frac{dE}{dx}\right)_{coll} \alpha\, Zln(E_0)^3$ emitted continuously along the path, is given by the Bethe-Bloch equation but with two important differences: both the particles here are (1) small and (2) identical $\rightarrow$ the z^2/β^2 term in the equation becomes equal to $1/\beta^2$ because for electrons $z = 1$ and inside the parentheses the electrons' kinetic energy expressed in units of $m_e c^2$ appears;
- $\left(\frac{dE}{dx}\right)_{rad} \alpha\, E_0 Z^2 ln(E_0)$ emitted in few (1, 2) photons… the bremsstrahlung's cross section for electrons is higher of a factor 10^6 than the one for protons ($\sigma \sim m^{-2}$).

So, to summarize, which is the main difference between radiotherapy and hadrontherapy?

Radiotherapy is based on high energy (1-15 MeV) photons, hadrontherapy on charged particles, now protons and carbons, but also helium and oxygen are in study. Hadrontherapy is in general much more efficient than radiotherapy because it allows both to irradiate the cancerous zone in a more precise way (Bragg's peak) and to reduce the irradiation of healthy zones, in particular of the organs at risk located behind the zone to treat, while radiotherapy does not allow us to reach such accuracy because photon beams deposit the energy across the whole body hence also healthy zones and organs at risk are irradiated.

However, the majority of cancer treatments are based on radiotherapy, why?
This is because hadrontherapy is much more expensive than radiotherapy: while a small cyclotron costs around 2-3 million euros, a synchrotron costs around 25-30 million euros (CNAO one costs around 250-300 million euros) → there are hundreds of centers for radiotherapy and only 6 in the world for hadrontherapy.

The heaviest ion used for hadrontherapy is Oxygen, why?
Because of nuclear interactions: increasing Z brings an increasing of nuclear interactions, which represent a problem for hadrontherapy because they imply as side effect the fact that a portion of energy is deposited beyond the cancer volume



as we can see, photons deposit their energy across all the body, especially at the beginning (hence in the superficial region), while hadrons deposit a few energy at high energies then they lose energy and at low energy, almost at zero, hence at the end of their range, deposit the majority of the dose (Bragg's peak)… we can also note that as z increases the Bragg's peak becomes less wider, hence the accuracy increases… but let's focus at the end of the Bragg's peak: while proton's dose goes to zero after the peak, Carbon's one does not go to zero, there is a non-zero dose beyond the peak, this is the effect of nuclear interactions, and such effect increases with the increasing of z → hence, higher z means higher accuracy but also higher side effect due to nuclear interactions, such effect becomes so marked for z higher than 18 to render elements heavier than Oxygen not viable for hadrontherapy.

3.2 Nuclear interactions

Nuclear force is a short-range interaction (~1 Fermi, the scale of a nucleon) which takes place when charged projectile travels close to the nucleus.
The fact that the interaction is a short range one is connected to the short range property of the strong force, opposite to the electromagnetic one which is virtually infinite.

In general, in a nuclear reaction we have

$$a + X \rightarrow Y + b$$

with

- a projectile;
- X target, usually at rest;
- Y and b reaction products, usually heavy and light respectively…

… a more compact notation is the following

$$X(a, b)Y$$

… so for example:

- $(\alpha. n) \rightarrow$ hit any target with an α particle to produce neutrons;
- $(n, \gamma) \rightarrow$ hit any target with neutrons to produce gammas.

Nuclear interactions are independent on charge but dependent on spin, and must conserve energy, p, angular momentum, parity and isospin; at our energies, also the total number of protons and neutrons must be conserved (at higher energies - GeV range - where you have the degree of freedoms of quarks, the conservation of p and n are no more needed).

The condition needed for a nuclear reaction to take place is quantified by the Q value defined as

$$E_a + E_X = E_Y + E_b =$$
$$= m_a c^2 + T_a + m_X c^2 + T_X = m_Y c^2 + T_Y + m_b c^2 + T_b =$$
$$(\dots\ c = 1 \dots)$$
$$= m_a + T_a + m_X + T_X = m_Y + T_Y + m_b + T_b =$$
$$= m_a + m_X - m_Y - m_b = T_Y + T_b - T_a - T_X = T_{final} - T_{initial} = Q,$$

hence

$$-\Delta m = \Delta T = Q$$

where

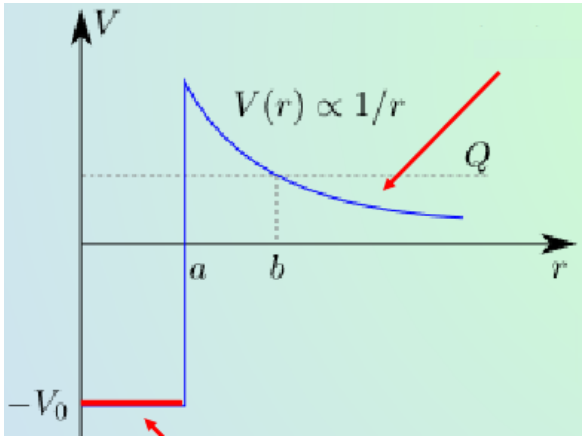
$$Q \equiv T_{final} - T_{initial}$$

… every change in kinetic energy is balanced by a change in mass…

- $Q > 0 \rightarrow$ exothermic reaction $\rightarrow$ gives kinetic energy $\rightarrow$ always possible;
- $Q < 0 \rightarrow$ endothermic reaction $\rightarrow$ absorbs kinetic energy $\rightarrow$ possible if $T_a > threshold$;

Of course, in order for the reaction to take place the nuclear barrier must be overcome.

We know that the nuclear potential is given by two contributions:



- the electromagnetic Coulomb potential, which scales as r^{-1};
- and a negative nuclear potential, essential to make bound states…

The Coulombian barrier is given by

$$E_B = \frac{1}{4\pi\varepsilon_0}\frac{Z_1 Z_2 e^2}{R_1+R_2}$$

… the nuclear radius is $\sim r_0 {A_N}^{1/3}$, hence we get

$$E_B = \frac{1}{4\pi\varepsilon_0}\frac{Z_1 Z_2 e^2}{r_0\left({A_1}^{1/3}+{A_2}^{1/3}\right)}$$

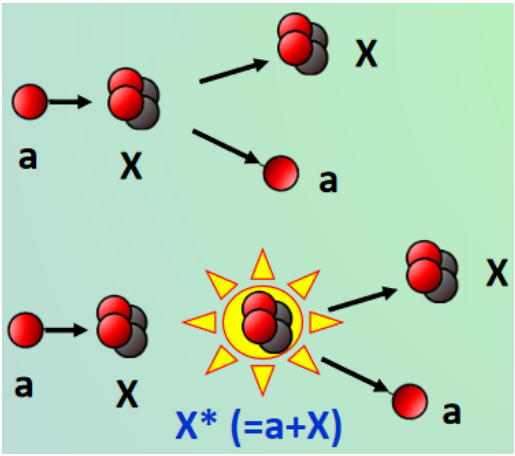
… which gives:

- $E_{p\text{-}p}$ ~0.9 MeV;
- $E_{p\text{-}12C}$ ~2.1 MeV;
- $E_{12C\text{-}12C}$ ~8.9 MeV;

… all below the energies reached in hadrontherapy, hence nuclear interactions do take place.

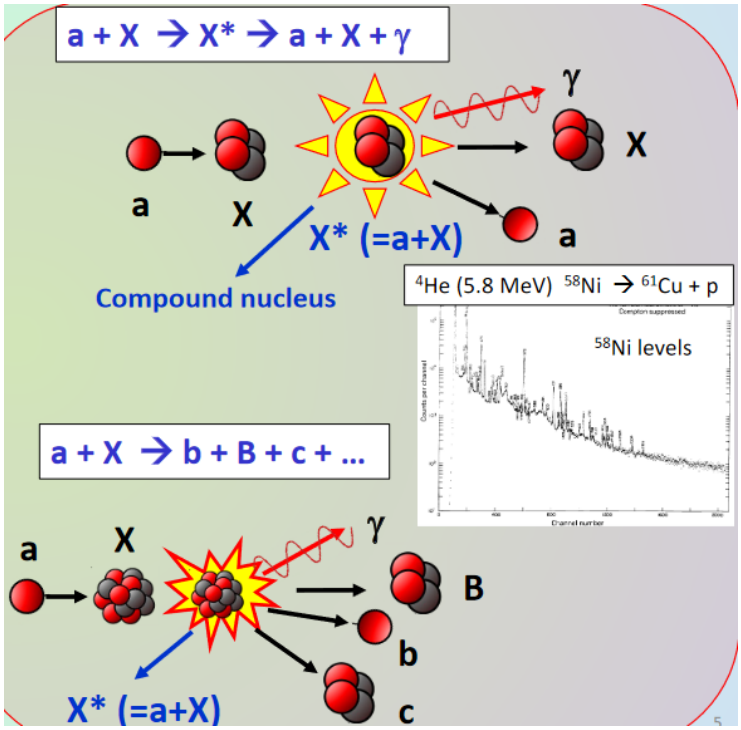
We have **two types of nuclear interactions**:

(i) **elastic** → kinetic energy is conserved, final state equal to initial state



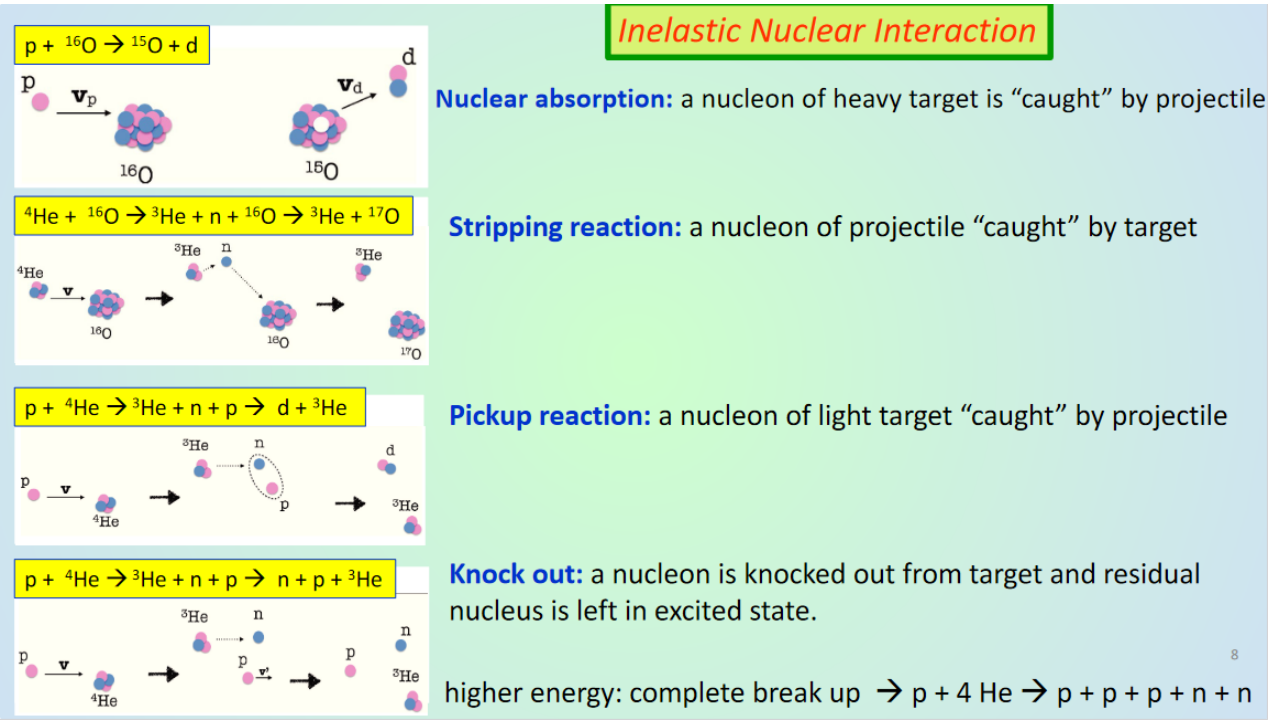
… in case of nuclear excitation, during the relative de-excitation kinetic energy is distributed between the final products in order to be equal, in total, as the initial one.
Elastic interactions do not require a threshold and play an important role at low energies until few hundreds of MeV;

(ii) **inelastic** → kinetic energy is not conserved, final state not equal to initial state



… here you can have a final state similar to the initial one, but with the production of a photon, or a final state completely different to the initial one: in both cases, the total kinetic energy in the final state is not the same as the one in the initial one.
Inelastic interactions do require a threshold and are responsible for the side effects.

Inelastic nuclear interactions



While for heavy targets:
Spallation → interaction between proton and very heavy nucleus (iron, lead…) → production of one heavy fragment + many light fragments (n, p…) → typically used to produce a neutron beam (not frequent in our body);

Induced fission → neutron-heavy nucleus → output: 2 heavy fragments + some little products (not frequent in our body);

Fragmentation → proton-heavy nucleus → this is the reaction we have in hadrontherapy → **peripheral interaction** (projectile and target overlap not completely but in the peripheral region), peripheral because both projectile and target are positive charges so if the projectile is not exactly on the same line of the nucleus then once close the e.m. force deviates it outwards → the higher the energy, the higher the probability to have central fragmentation → the output is a heavy target, a bit lighter than the initial one + light fragments (p, d, n…);

Multi-fragmentation → the same as fragmentation but at higher energy → the collision is more central and more light fragments are produced;

Vaporization → the same as multi-fragmentation but at higher energy → the collision takes place to the center and both target and projectile are completely vaporized into light nuclei.

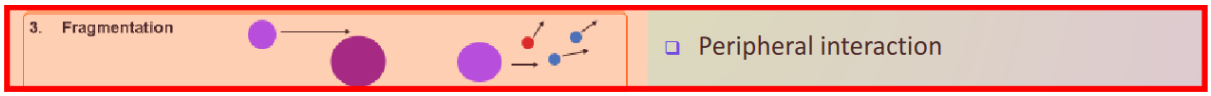
At this energy, fragmentation is the most frequent nuclear reaction.

Fragmentation can be seen as a two-steps process:

(i) **Abrasion** → superimposition of projectile and target during which the overlapping part (fireball) is extracted from the twos and all the threes reach a very excited state.
The timescale of abrasion is of the order of 10^{-22}-10^{-23} s, the time of the nuclear force;

(ii) **Ablation** → thermalization and de-excitation phase, all the three parts (projectile, target and fireball) de-excitate producing the fragments and photons of the final state.
The timescale of ablation is of the order of 10^{-16}-10^{-18} s

So the most important interaction we have at the energies of hadrontherapy is fragmentation, in particular peripheral fragmentation, so the interaction is between a projectile and a target just partially overlapped → the output are 1-2 fragments similar to the projectile or to the target and many little fragments



… this can be described by Monte Carlo models.

In particular, depending on the nature of projectile and target we can have four different scenarios of fragmentation:

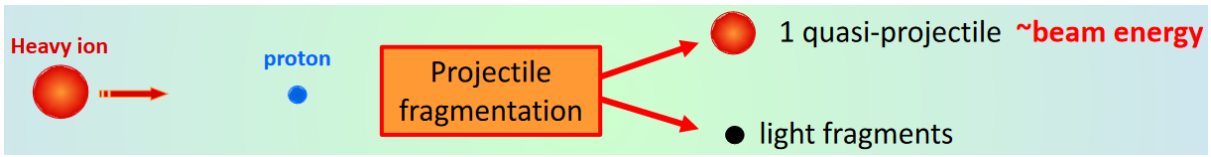
- proton - proton → at our energies no fragmentation at all;
- **proton - heavy ion → target fragmentation;**
- **heavy ion - proton → projectile fragmentation;**
- heavy ion - heavy ion → both projectile and target fragmentation

… we focus on target and projectile fragmentation:

- **target fragmentation**

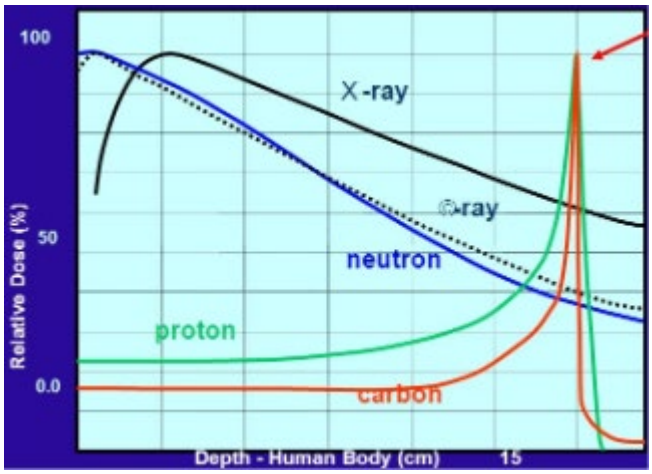
Fragment	E (MeV)	LET (keV/μm)	Range (μm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

- **projectile fragmentation**



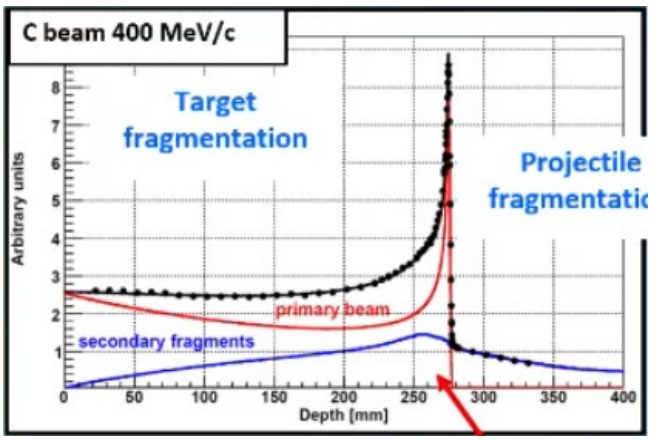
… undergoing fragmentation, projectile's Z decreases and according to the Bethe-Bloch equation the fragments' range increases hence their remaining energy is deposited beyond Bragg's peak…

… hence we have two totally different situations which lead to the same problem: in both cases we have a release of energy in a position we don't want this to happen.
This underlines the importance of nuclear fragmentations' studies in hadrontherapy



… it is certainly true that heavier ions - for example Carbon - grant a narrower Bragg's peak hence a higher precision than lighter ones - for example protons - , as well as a lower loss of energy before the peak, but heavier ions also release part of the energy beyond the BP…

… in particular, for heavy proj.+target both the effects given by the two fragmentations seen above trigger: a decreasing of the primary beam's contribution in conjunction with an increasing of the secondary fragments' one due to target's fragmentation before the Bragg's peak, and a release of energy beyond it due to projectile's fragmentation…

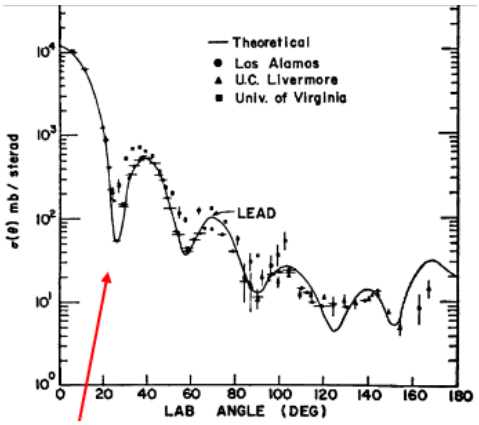


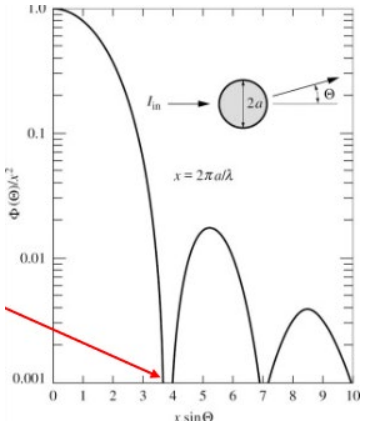
… and if beyond the target there's an organ at risk this is a critical problem.

The cross section

Considering a 200 MeV proton beam crossing human body about 20% of the beam is lost before the Bragg's Peak due to nuclear interactions: 20% is a lot, because in order to treat a patient which has cancer high precision is required, so to be very precise it is mandatory to properly study the nuclear cross section.

The first studies regarding nuclear cross section, which took place around one century ago, showed a significant similarity between nuclear elastic scattering at low energies and the diffraction of light from a circular sphere

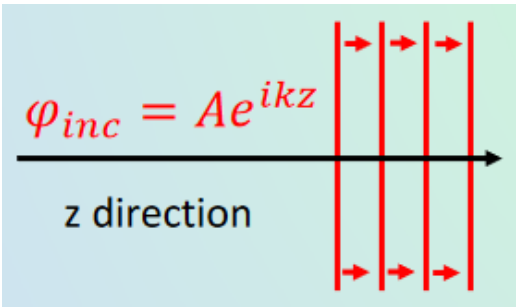




… in the nuclear elastic scattering case the cross section with respect to the angle is always different from zero, while in the diffraction of light there are angles with zero emission, but the behavior is in general very similar: this suggested to the scientists of that time to describe the **nuclear force as an opaque disk**.

To study the cross section we will use the **center of mass system** instead of the lab one, because in the latter the energies are in general different from one lab to the other.

According to quantum mechanics, the incident particle can be described as a plane wave

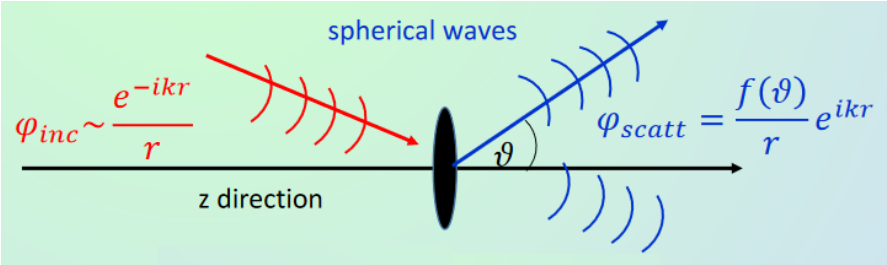


… hence as a quantity described by a constant (A) containing the information regarding the amplitude and by an exponential containing the information regarding the momentum (k) and the direction (z)

$$\varphi = Ae^{ikz}$$

to have a plane wave the projectile must undergo zero interactions (vacuum) because the structure of the wave must remain the same during time…

… by moving from the lab system to the CM we no more have a plane wave projectile colliding vs a target at rest, but one incident spherical wave moving towards a central potential and one outgoing spherical wave leaving it



… mathematically, the spherical wave has the form of the plane wave divided by r.

More in detail, a plane wave can be described as

$$* \quad \varphi = Ae^{ikz} = A\sum_{l=0}^{\infty} i^l (2l+1) J_l(kr) P_l(cos(\theta))$$

where the summation takes into account the sum of the all possible angular momentums l, the spherical Bessel functions $J_l(kr)$ associated at each angular momentum l and the Legendre polynomials $P_l(cos(\theta))$ associated at different θ emissions.
Increasing the angular momentum l, the energy of the incoming particle increases, hence at low energies (<20 MeV) an angular momentum $l = 0$ can be considered, and by substituting in * we get

$$\varphi = Ae^{ikz} = Ai^0 (2 \cdot 0 + 1) J_0(kr) P_0(cos(\theta)) = AJ_0(kr) P_0(cos(\theta))$$

… the Bessel spherical function and Legendre polynomial associated to $l = 0$ are

$$J_0(kr) = \frac{sin\left(kr - \frac{1}{2}l\pi\right)}{kr} = \frac{sin(kr)}{kr} \qquad P_0(cos(\theta)) = 1$$

hence

$$\varphi = \frac{Asin(kr)}{kr} = \frac{A}{2ik}\left(\frac{e^{ikr}}{r} - \frac{e^{-ikr}}{r}\right)$$

… an outgoing and an incoming spherical wave; we note that the dependence on the angle theta has disappeared, hence at low energies the cross section has an isotropic behavior.

If the incident wave and the outgoing wave are very distant one to each other, the Bessel spherical function includes an exponential term which takes care of that

$$J_0(kr) = \frac{sin\left(kr - \frac{1}{2}l\pi\right)}{kr} = i\frac{e^{-i(kr - l\pi/2)} - e^{i(kr - l\pi/2)}}{2kr}$$

hence * becomes

$$\varphi = \frac{A}{2kr}\sum_{l=0}^{\infty} i^{l+1}(2l+1)\left(e^{-i(kr - l\pi/2)} - e^{i(kr - l\pi/2)}\right) P_l(cos(\theta))$$

so the total cross section is given by a part, $e^{-i(kr - l\pi/2)}$, representing the incoming wave and a part, $e^{i(kr - l\pi/2)}$, representing the outgoing wave.

What happens if we have an interaction?

It happens that the outgoing wave will be modified; we can have:

- a change in amplitude, which can be parameterized by a coefficient $\eta \leq 1$
- or a change in phase (so in the distribution of the cross section), this means that eta is not a real number but a complex number, so it is composed by a real part times a phase

$$\eta = |\eta| e^{i\delta}$$

… hence the total wave can be parameterized as

$$\varphi = \frac{A}{2kr} \sum_{l=0}^{\infty} i^{l+1}(2l+1)\left(e^{-i(kr-l\pi/2)} - \eta_l e^{i(kr-l\pi/2)}\right)P_l\left(cos(\theta)\right)$$

… where the part related to the scattering - hence to the outgoing particle - can be obtained just by subtracting the incoming part to the total one

$$\varphi_{scat} = \varphi_{tot} - \varphi_{inc} =$$

$$= \frac{A}{2kr} \sum_{l=0}^{\infty} i^{l+1}(2l+1)\left(e^{-i(*)} - \eta_l e^{i(*)}\right)P_l\left(cos(\theta)\right) - \sum_{l=0}^{\infty} i^{l}(2l+1)e^{-i(*)}P_l\left(cos(\theta)\right) =$$

$$= \frac{A}{2kr} \sum_{l=0}^{\infty} i(2l+1)\left(1 - \eta_l e^{i(kr-l\pi/2)}\right)P_l\left(cos(\theta)\right) =$$

$$= \frac{A}{2k}\frac{e^{ikr}}{r} \sum_{l=0}^{\infty} i(2l+1)(1-\eta_l)P_l\left(cos(\theta)\right)$$

… in order now to move from a wave function to a cross section we first evaluate the current density J from the scattered wave function and then apply the formula

$$d\sigma = \frac{J_{scat} r^2 d\Omega}{J_{inc}}$$

… so the cross section is given by the current density of the scattered function divided by the current density of the incident function multiplied by the phase space, that is the volume considered, and by doing the calculation we obtain

$$\sigma_{sc} = \pi \lambda\!\!\!^{-2} \sum_{l=0}^{\infty} (2l+1)\,|1-\eta_l|^2 = \frac{\pi}{k^2} \sum_{l=0}^{\infty} (2l+1)|1-\eta_l|^2$$

… let's analyze this expression:

we have pi multiplied by the *De Broglie wavelength square, multiplied by the sum of the different angular momentums of the incident particle, where the part describing the interaction is $|1-\eta_l|^2$, hence the cross section is not a constant.

In the case of **elastic interaction**, the outgoing particle is the same as the incident one, hence $|\eta| = 1$ and only the phase δ may change, hence the cross section becomes

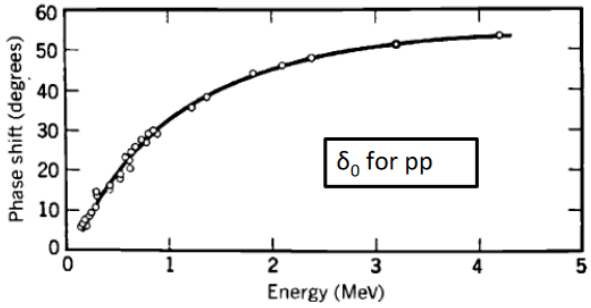
$$\sigma_{el} = 4\pi \lambda\!\!\!^{-2} \sum_{l=0}^{\infty} (2l+1) sin^2\delta_l = \frac{4\pi}{k^2} \sum_{l=0}^{\infty} (2l+1) sin^2\delta_l$$

… if the elastic scattering is at low energy then $l = 0$ and the cross section becomes

$$\sigma_{el,low} = 4\pi \lambda\!\!\!^{-2} sin^2\delta_0 = 4\pi \frac{1}{k^2} sin^2\delta_0$$

… so the elastic cross section depends on the energy: the higher the energy (hence p, hence k) the lower the cross section…

… if $l = 0$ (low energies) then $\delta_0 \to 0$



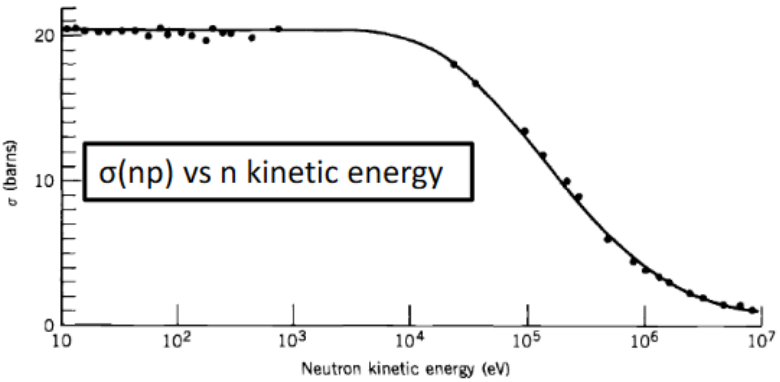
hence $sin^2(\delta_0) \sim {\delta_0}^2$ → and the equation can be simplified as

$$\sigma_{el,low} = 4\pi\lambda\bar{}^2 {\delta_0}^2 = 4\pi \frac{1}{k^2} {\delta_0}^2$$

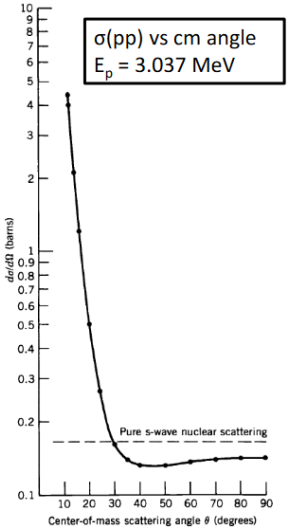
… and by defining the scattering length as $a = \lambda^- \delta_0 = \frac{\delta_0}{k}$ we finally get

$$\sigma_{el,low} = 4\pi a^2$$

… with a not a constant because it depends both on the energy and on the angle:



It decreases if the energy increases beyond a certain value…



… and is very high at very small angles - hence more or less in the same direction - becoming ~constant at high angles, again beyond a certain value.

Which are the values of η and δ?
It depends: their values are derived by the cross section, hence by physical measurements; inside η and δ there is the information regarding the nuclear potential between the incident beam and the target.

And regarding the **inelastic cross section**?

"Inelastic" means that the final state is different with respect to the initial state, we have new particles, hence $|\eta_l| < 1$… how much lesser than 1? it depends from the nuclear cross section (it is measured), hence the inelastic (reaction) cross section has the form

$$\sigma_r = \pi\lambda\!\!\!^{-2} \sum_{l=0}^{\infty} (2l+1)(1-|\eta_l|^2) = \frac{\pi}{k^2} \sum_{l=0}^{\infty} (2l+1)(1-|\eta_l|^2)$$

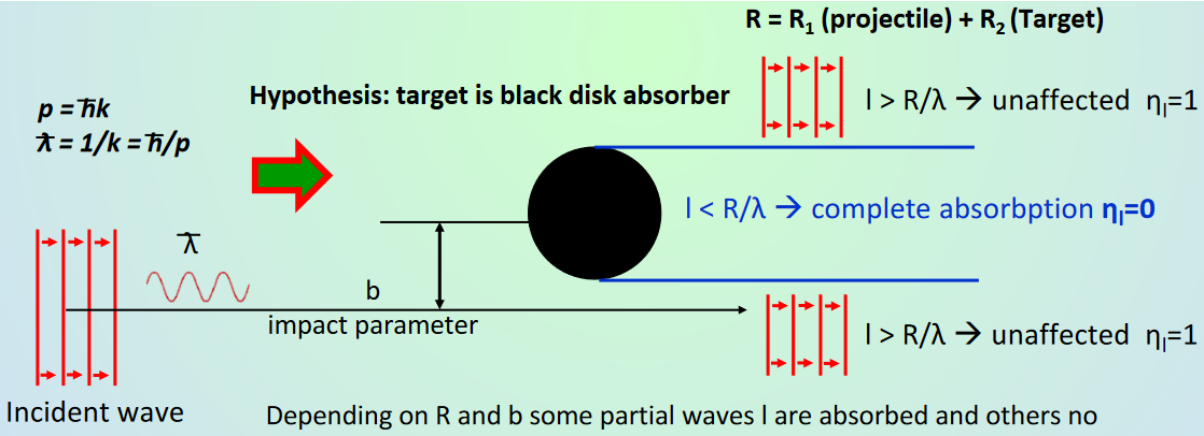
… hence the **total cross section** is the sum of elastic cross section and inelastic one

$$\sigma_{tot} = \sigma_{sc} + \sigma_r = \pi\lambda\!\!\!^{-2} \sum_{l=0}^{\infty} (2l+1)\big(1-Re(\eta_l)\big) = \frac{\pi}{k^2} \sum_{l=0}^{\infty} (2l+1)\big(1-Re(\eta_l)\big)$$

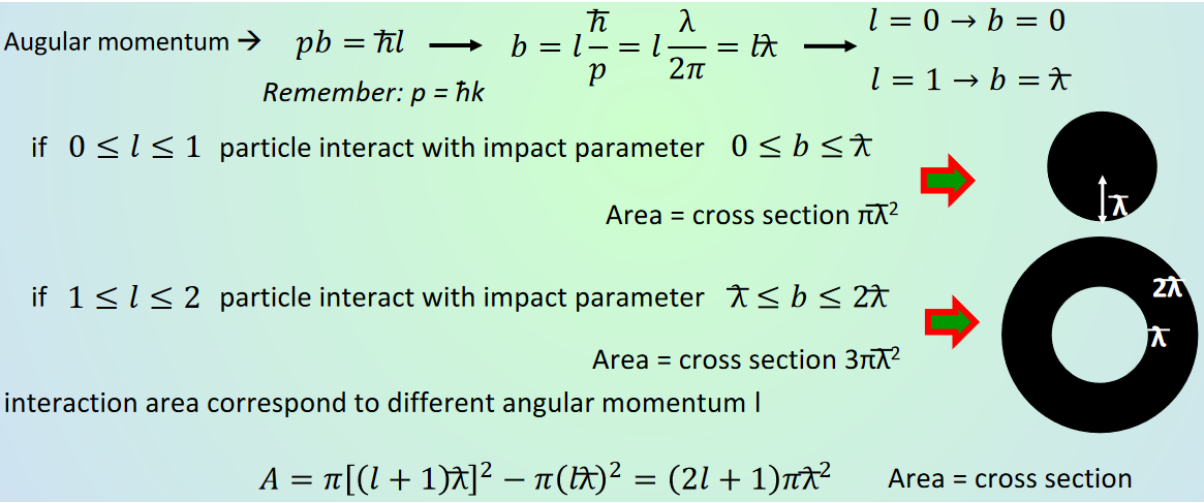
* The De Broglie wavelength is defined as the inverse of the *momentum and represents the dimension of the incident particle having momentum p; such dimension depends on the energy: the higher the energy the lower the De Broglie wavelength, this is the reason why if we want to obtain very little dimensions we need accelerators with very high energies.

* In quantum mechanics the momentum can be written as $p = h^{-}k$, with $h^{-} = \frac{h}{2\pi}$.

We can also consider a **semi-classical approximation**.
Let's consider an incident wave described by a wave function given by the superimposition of different angular momentum waves



… varying the angular momentum l means varying the impact parameter b with which particles interact



it is often sufficient to consider the effect of the nuclear potential on the lowest partial waves..

… the total radius of interaction is given by the radius of the projectile particle (λ bar) plus the radius of the target (the impact parameter)

$$R = R_1 + R_2 = \lambda_{bar} + b$$

hence the corresponding cross section

$$\sigma = \sum_{l=0}^{R_2/\lambda} (2l+1)\pi {\lambda_{bar}}^2 = \pi(R_2 + \lambda_{bar})^2$$

depends by both the projectile and target radii (we can note that this is in fact an area (πr^2)).

So if $l < R/\lambda$ we have complete absorption, while if $l > R/\lambda$ there is no absorption, and this gives us the formula (valid in case the assumed potential is central)

$$\sigma_{tot} = \sigma_{elastic} + \sigma_{reaction} = \pi(R_2 + \lambda_{bar})^2 + \pi(R_2 + \lambda_{bar})^2 = 2\pi(R_2 + \lambda_{bar})^2$$

… so we have learnt that the interaction cross section can be written as πr^2, but what about the **reaction cross section of a nucleus composed of many nucleons**?

In this case, the interaction cross section is given by the **Bradt-Peters law**

$$* \quad \sigma_r = \pi {r_0}^2 c_1 \left({A_p}^{1/3} + {A_t}^{1/3} - b_0 \right)^2$$

where

- $r_0 = 1.25\ fm$;
- A_p, A_t mass numbers of projectile and target respectively;
- b_0, c_1 tabulated corrections…

… for high energy protons, the interaction cross section can be written as

$$* \quad \sigma_r \approx 53 \cdot {A_t}^{2/3}\ mb$$

… both from * and * we can see that the heavier the target the higher the cross section.

Another model useful to describe the reaction cross-section is based on the number of nucleons of both the projectile and the target and their total cross section

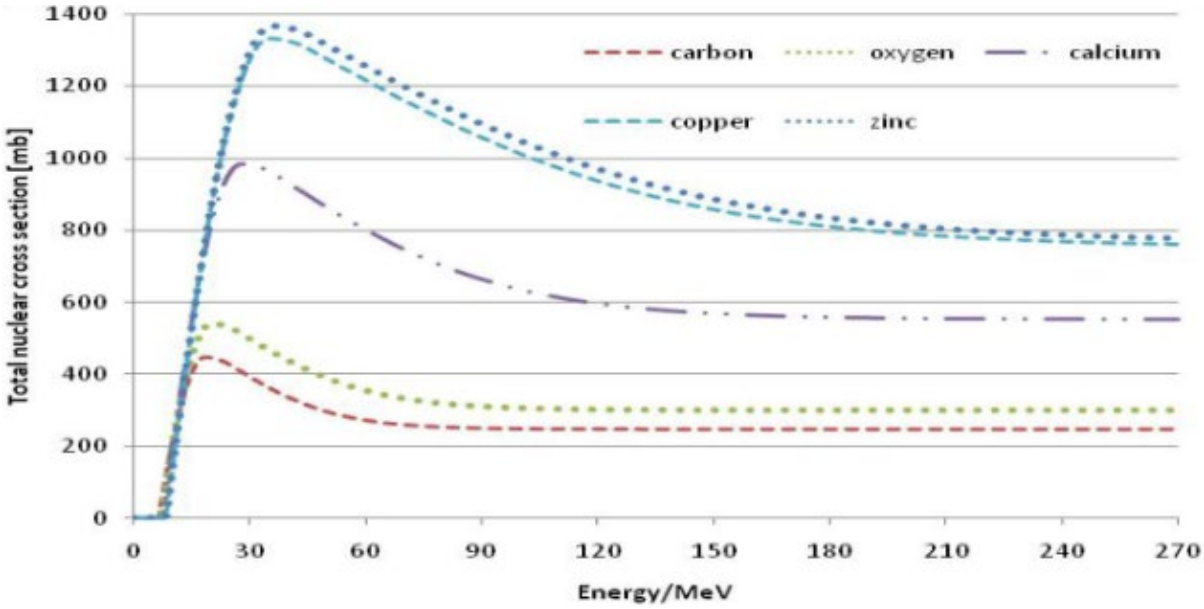
$$\sigma_r(Z_1, N_1, Z_2, N_2, E) = \pi C(E) \left(\sqrt{{Z_1}^{2/3} \sigma_{tot,pp}(E) + {N_1}^{2/3} \sigma_{tot,pn}(E)} + \sqrt{{Z_2}^{2/3} \sigma_{tot,pp}(E) + {N_2}^{2/3} \sigma_{tot,pn}(E)} \right)^2$$

the model is valid in a range from ~30 MeV to ~400 GeV and from 8 to 100 regarding A with an accuracy of ~10% ⇒ both the Bradt-Peters semi-empirical law and this model are approximations, useful to have an estimate of the reaction cross section but not enough for hadrontherapy; in particular the reaction cross section obtained with these two models is the total one, i.e. the one associated to any of the possible outputs an interaction can produce, but for hadrontherapy we want the cross section of each singular channel, not just the sum of all of them ___

So, in general we have these two facts:

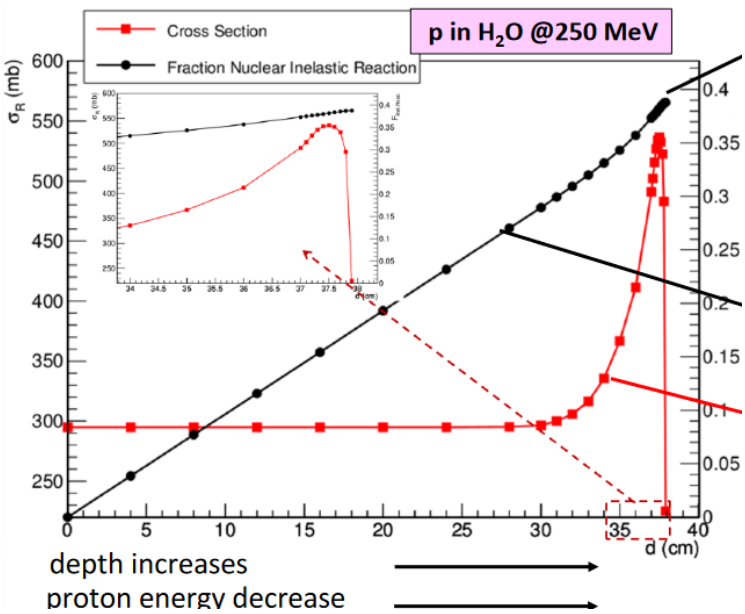
1. fragmentation depends both on the projectile's energy/type and on the target type;
2. cross section depends on the particle type and on range.

Here we can see the behavior of nuclear cross section for different particles



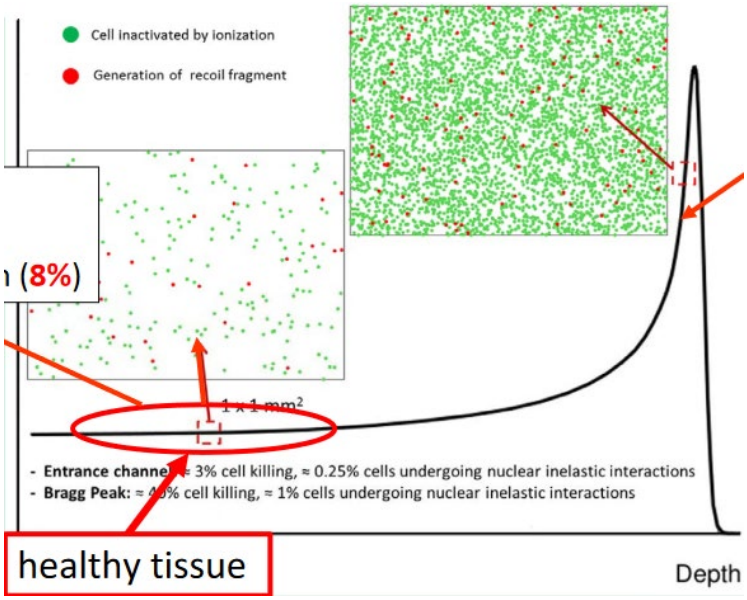
at high energies the cross section is ~ constant with a peak at low energies typical for each specific particle, in accordance with the cross section's equation we presented in which the term speaking about the energy is at the denominator; both the average and the cumulative cross section increase with the dimension of the particle, as well as the peak's value.

Here we have the cross section for protons at 250 MeV in water



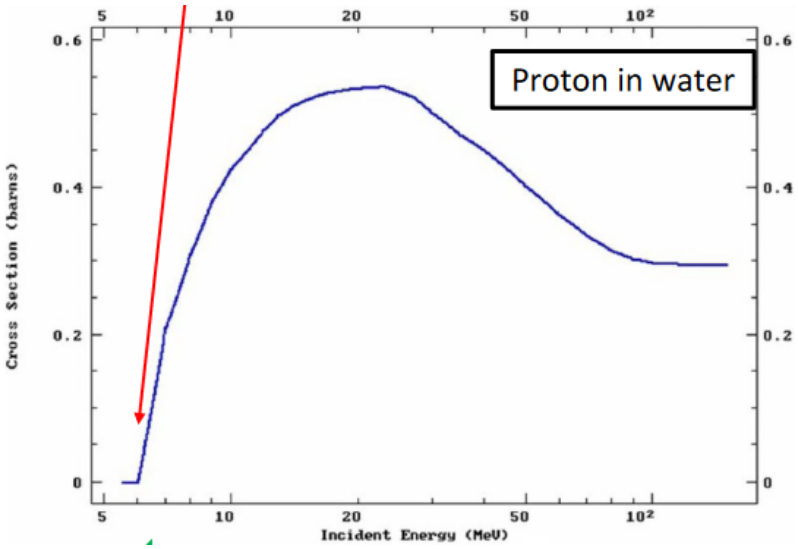
as expected, the proton's cross section is lower than the ones of the nuclei above, both in the constant range and on the peak… for a proton's flux of such energy, ~40% of the beam undergoes nuclear interaction before reaching the target, ~1% for every cm of path…

… here we can see the effect on the cells, in particular the fraction of cells killed by nuclear interactions with respect to the ones killed via electromagnetic ones



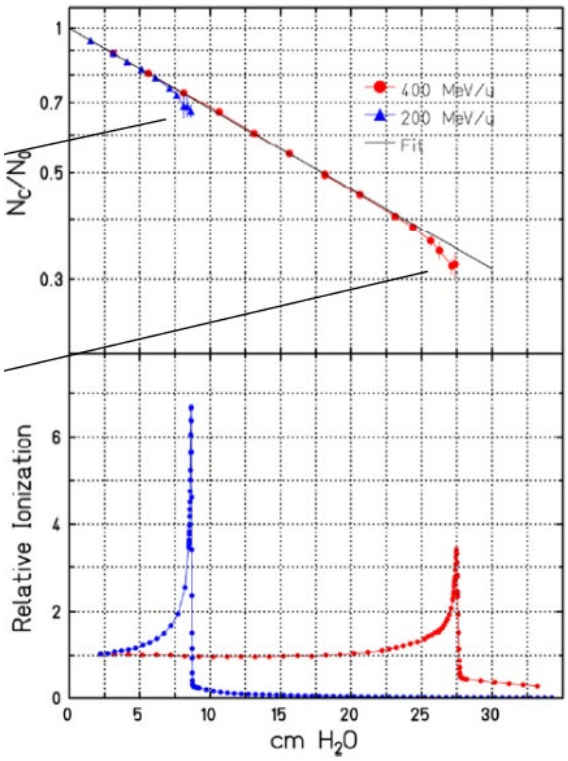
… in the constant range ~3% of the total cells are killed of which ~0.25% due to the energy released by nuclear interactions, while in proximity of the Bragg's peak the amount becomes ~40% and ~2% respectively; in other words, ~8% of the cells killed at higher energies are due to nuclear interactions, while at lower energies the amount becomes ~2%, this because we know that the Bragg's peak flags the maximum release of energy due to electromagnetic interactions hence they become more frequent with respect to the nuclear ones; however, we are speaking about percentage points of energy released by nuclear interactions, a not negligible contribution which must be taken into account.

With respect to the energy, the total nuclear cross section for a proton in water shows



- a 6 MeV threshold in order to win the Coulomb potential;
- a rise with a peak at ~20 MeV, not far from the end of its path (for the 250 MeV case seen in the slide before it was around 35 cm);
- an asymptotic decrease to about half to the max from about 100 MeV…

… and this is the number of Carbons absorbed by water for 200 and 400 MeV/u



… as we can see, a 200 MeV/u Carbon beam reaches the Bragg's Peak having undergone about 30% nuclear reactions, while a 400 MeV/u reaches the peak with about 70% of its component gone via nuclear interactions…

… we recall that for a proton of 250 MeV the amount was about 40%...

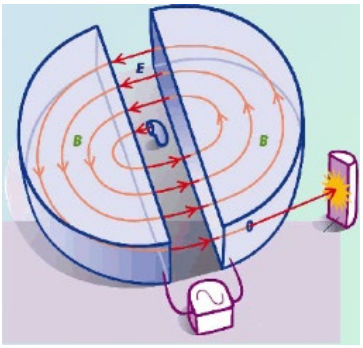
… morale: heavy nuclei are more likely to have nuclear reactions (having higher cross section) than lighter ones, hence inelastic collisions are more frequent…

4. The Spread-Out Bragg's Peak

We have seen that the Bragg's Peak depends on the mass and on the charge of the particle and represents the main feature which allows hadrontherapy to reach a much higher accuracy than conventional radiotherapy, but there is a problem: the peak extends on a mm scale, while cancers typically extend for cm.
In other words, the Bragg's Peak is too precise to be used as it is in hadrontherapy treatments; how can we solve this?

To use the Bragg's Peak in hadrontherapy we must enlarge it from the initial scale to the scale affected by the cancer in order to cover the cancer region both in energy (z) and position (x,y), obtaining the so-called Spread Out Bragg's Peak (SOBP).

We can do this by creating a beam at the maximum energy required by the treatment and gradually lowering it by using both a cyclotron or a synchrotron



… a cyclotron is a machine which produces a monochromatic proton beam (most recent cyclotrons allow the user to select among 2-3 energy values, but traditionally only one is available)...

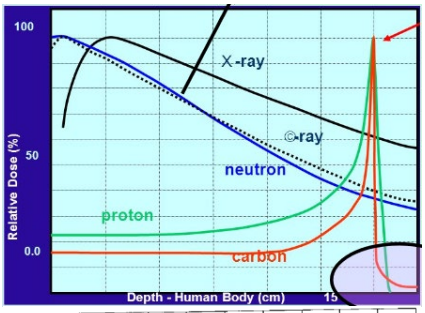
… a synchrotron is a larger machine which can produce many beam types (p, C, He, O…) of many energies…

… while with synchrotrons the SOBP production is quite automatic (you just have to produce n beams of n contiguous energies setting the energy values), with cyclotrons the process is more complex because the energy available is just one → hence what is typically done is choose the maximum energy available (for example 200 MeV), use a **degrader** to reduce the beam's energy and later a **ridge filter** to create the SOBP itself.

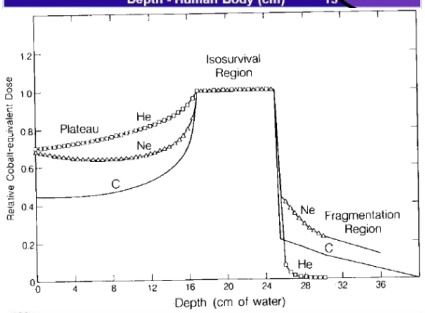
The degrader is essentially a material interposed on the beam's trajectory: during the crossing the beam loses energy; warning: during the passage a certain amount of neutrons is created hence a proper screening is required.

The ridge filter is a filter composed by many cones separated by a distance d: across d the beam does not interact with the material hence does not lose energy, while in the interaction with the cones the amount of energy lost is proportional (considering statistical uncertainties always present) to the section of cone crossed

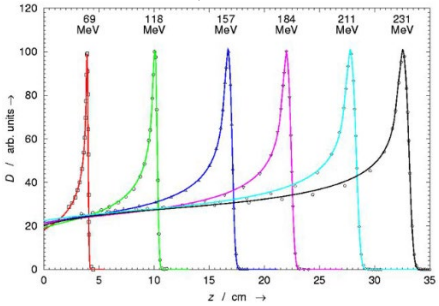
So the idea is to transform this



… into this



… doing this



Some observations:

(i) During the process, the amount of dose given by the constant region (hence released before the cancer) increases because the contributions are summed, hence it is preferable to treat from different directions in order to dilute the total dose on a much larger area;

(ii) Which is better between radiotherapy and hadrontherapy?
In general, hadrontherapy represents a better choice than radiotherapy because it allows to treat the cancer in a more accurate way limiting the amount of dose released in the healthy regions and allowing to give to the patient a higher dose;

(iii) … and which is better between protons and ions?
It depends from the specific case: while ions release a lower dose before the Bragg's Peak and sharpens the peak itself, they are affected by the nuclear interactions given by the projectile fragmentations, absent in the case of protons

5. Radiobiology

Effects of radiotherapy and hadrontherapy on the human body.

Some useful definitions:

- Fluence

$$\phi \equiv \frac{dN}{dA} \quad [\text{particles/cm}^2]$$

with
  - N number of particles;
  - A infinitesimal area normal to the beam;

- Fluence rate

$$\dot{\phi} \equiv \frac{d\phi}{dt} \quad [\text{particles/cm}^2\text{s}]$$

- Dose → absorbed energy (given by radiation) per unit mass

$$D \equiv \frac{dE}{dm} = \frac{(dE/dx) \times \Delta x \times N}{\rho \times \Delta x \times A} = \phi \frac{(dE/dx)}{\rho}$$

hence it depends on the number of particles, on their type (different dE/dx) and on the density of the target.
The unit of measure is the Gray ≡ 1 J/kg (SI), or the rad ≡ 100 erg/g = 10^{-2} Gy (cgs)

… in our context, instead of J it's more convenient to use MeV and instead of the number of particles the gigaprotons (Gp), hence the unit of measure for the dose can also be written as [Gp MeV cm^2 gr^{-1}];

- Stopping power → dE/dx, energy released per unit distance focusing on the particle;
- Linear energy transfer (L.E.T.) → // focusing on the material surrounding the particle;

The distinction between stopping power and linear energy transfer makes sense in the cases in which there is the production of fragments, for example high energy electrons, which can travel and release their energy far from the initial region, in such cases the corresponding amount is not counted, hence

$$L.E.T. \equiv dE/dx - K_{E>\Delta}$$

with K kinetic energy of the electrons having energies higher than a proper threshold Δ.

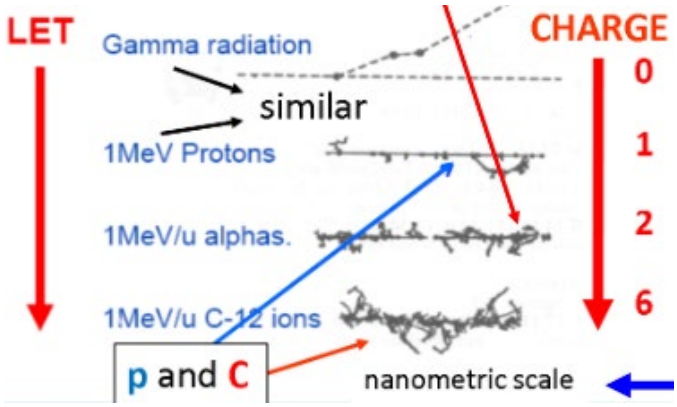
If

$$\Delta \to \infty, L.E.T. = dE/dx$$

… this is what we assume in our scenario.

- Mass Stopping Power → often it is more useful to normalize the stopping power to the density, in order to remove the dependence of the latter → $dE/dx\rho$.

Our aim is to maximize the energy deposited in a small volume of the cell, in order to create double strand breaks, hence the **density of energy** deposited is crucial



LET increases with the particle's charge, hence heavy ions do more damage (more DSBs) than light particles: C does a lot of damage in just 1 micrometer, so very locally because the dimension of the strand is around 2 micrometers, so in this terms C is better than protons which are better than gammas, but also nuclear interactions must be taken into account.
All these depends also on the energy because, according to Bethe-Bloch, the higher is the energy the higher is β the lower is dE/dx.

How much is the typical dose given in radio/hadron therapy?
It depends on many factors, such as the cancer type, its stage, the age of the patient and so on, but in general the dose is around 1-2 Gy for each fraction with a total of 30-35 fractions. This is a lot of radiation, but it's feasible because the dose is focused on a little volume of the body, hence the damage is localized and most of the healthy body cells are preserved.

The choice of giving the dose not one shot but splitted in 30-35 fractions of 1-2 Gy each derives also from this important evidence

… once damaged, healthy cells recover better than cancerous ones (and this is the very reason we can do radio/hadron therapy), but only below a threshold of dose, after that the trend inverts and healthy cells ability to repair themselves drops dramatically.

Hence, the best choice is to maximize the density of energy deposited, splitting the total dose in many fractions in order to exploit the better ability of healthy cells to recover from damage with respect to the cancerous ones.

Equivalent dose and effective dose

The dose is an absolute parameter, in the sense that it does not take into account the effects a certain radiation produces on the human body; such effects may vary depending on the type of radiation used, the dose delivered and the target tissue.

Considering the type of radiation used we define the equivalent dose

$$D_{eq} \equiv \sum_R w_R D$$

where $\boldsymbol{w_R}$ is the **quality factor**, defined as the ratio of the biological damage produced by the absorption of 1 Gy of that particle to the biological damage produced by 1 Gy of gamma for all the R particles involved

$$w_R \equiv \frac{Damage\ (p)}{Damage\ (\gamma)}$$

… w_R is equal to 1 for gamma and electrons, 2 for protons and up to 20 for heavy ions.

The unity of measure is the Sievert (Sv) → 1 Sv is the effect of 1 Gy of gamma radiation, hence 1 Sv produces the same damage independently of the radiation considered.

If we include also the type of target tissues considered we define the effective dose

$$D_{eff} \equiv \sum_T w_T D_{eq} = \sum_T w_T \sum_R w_R D$$

where $\boldsymbol{w_T}$ is the **tissue weight**.

Depending on w_T values we have

- **Sensitive tissues**, for which radiation destroys the cancer more easily. These are typically tissues with high cell reproduction;
- **Resistive tissues**, typically tissues with low cell reproduction.

Cell survival

Damage produced by radiation is estimated by the capacity of the cells involved to survive, the so-called "**cell survival**".

Ionizations produced by the radiation are distributed randomly following Poisson statistics.

A dose which reduces the cell survival to 50%, if repeated reduces survival at 25%, then 12.5% and so on, hence on a logarithmic scale we expect a linear curve, hence an **exponential behavior** of the form

$$S = e^{-\alpha D} = e^{-D/D_0}, \quad \text{with } D_0 = \alpha^{-1}.$$

If $D_0 = D \rightarrow S = e^{-1}$ hence we have the dose required to have cell survival of $*e^{-1} \sim 37\%$.
Two useful quantities are

- $D_{50} = 0.69 D_0 \rightarrow$ dose needed to have cell survival of 50%;
- $D_{10} = 2.3 D_0 \rightarrow$ dose needed to have cell survival of 10%.

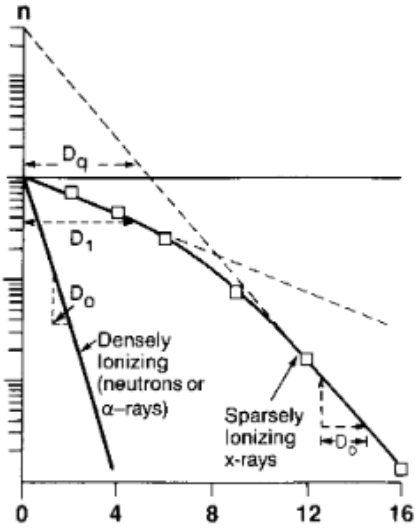
From * follows that $D_{37} = D_0$.

But is the exponential behavior what we observe?
Not really: the exponential behavior works for bacteria which cells are less developed and do not recover, regarding human body we have a more complex behavior, in particular:

- S associated to **high densely ionizing particles** can be well described with a **single exponential law**, very similar to the one valid for bacteria…;
- … while S associated with **low densely ionizing particles** needs **at least two exponential laws** to be properly described…

… but we do not want two different equations → the overall situation is at now best described by the **Linear Quadratic Model**, a model characterized by an initial slope D_0, a shoulder and a final slope D_1

high L.E.T. →



← low L.E.T.

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

where α, β depend on a variety of factors (type of radiation, tissue, status of the cell…).

Hence cell survival depends on two components, one proportional to the dose and one proportional to the square of the dose: the first includes the non-repairing damage, the second includes the repairing one…

… more on α, β parameters:

α, β both depend on L.E.T.:

- $\alpha \sim$ linearly;
- $\beta \sim$ constant…

… and their dimensions are Gy^{-1} and Gy^{-2} respectively.

The ratio α/β is the dose at which the linear and the quadratic part of the Linear Quadratic Model give the same contribution, and is very useful to characterize tissues:

- **late responders** ($0.5 < \alpha/\beta < 6$ Gy) → tissues with low reproduction activity, more resistant to radiation, ex: spinal cord, lung, kidney, bone, cartilage…;
- **early responders** ($7 < \alpha/\beta < 20$ Gy) → tissues with high reproduction activity, less resistant to radiation, ex: most tumors, mucosa, skin…

… in general, for healthy tissues $\alpha/\beta \sim 2$ while for cancerous ones $\alpha/\beta \sim$10-20.

Given the Linear Quadratic Model's formula, if α/β is low (low L.E.T.) the dominant part is the parabolic one, while if α/β is high (high L.E.T.) the dominant part is the linear one.

Relative Biological Effectiveness (R.B.E.)

R.B.E → parameter that compares different types of radiation, it is given by the ratio of two doses: dose delivered by X ray / dose delivered of the particle to study in order to have the same effect (a particular % of cells' survival)

$$R.B.E. \equiv \left(\frac{D_{X-ray}}{D_H}\right)_{same\ effect}$$

… if R.B.E. > 1 the particle releases more energy per interaction wrt the photon hence a lower dose to have the same effect is needed.

In general, for hadrons R.B.E. > 1, in particular *:

- R.B.E. gamma = 1;
- R.B.E. protons = 1.1;
- R.B.E. Carbon = 3-4;
- R.B.E. Neon = 3-4.

Achtung! R.B.E. for protons is just 10% greater than the one of gamma, but attention, this is a huge difference because for gammas the effect is sparse in the body while for protons it is localized in the cancerous region, preserving the grand part of the healthy cells.

R.B.E.'s value is not easy to evaluate because it depends on many factors such as the type of radiation and its energy (*), the L.E.T. (it increases with energy till a saturation located in the middle of the Neon range), the type of cell involved (healthy cells have a survivability higher than cancerous ones, hence RBE is higher in the first wrt to the latter → typically the RBE is evaluated in the middle of the cancerous region, hence in the middle of the SOBP, where in any case a big variation is still present - 1.8 - 2.5 -) and the definition of survival (that is, the % of survival we choose to adopt to calculate the R.B.E.).
In addition, RBE is different between experiments in vivo and in vitro, probably because of target-projectile fragmentation, which can increase proton RBE → necessary to measure the differential cross sections of all fragments produced wrt energy and direction.

Oxygen Enhancement Ratio (O.E.R.)

Biological effect of radiation depends on the oxygen concentration.

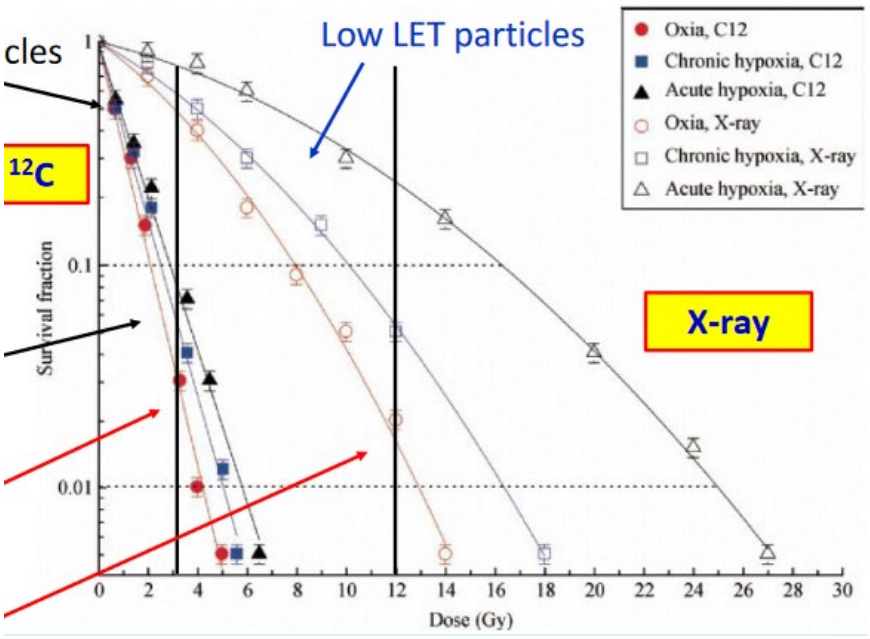
We distinguish among:

- Anoxia → absence of oxygen;
- Normal;
- Hyperoxia → abnormal presence of oxygen…

… to quantify this we use the O.E.R

$$O.E.R. \equiv \left(\frac{D_{anoxia}}{D_{normal}}\right)_{same\ effect}$$

… **adding Oxygen in the cancer voxel the treatment's effects increase**

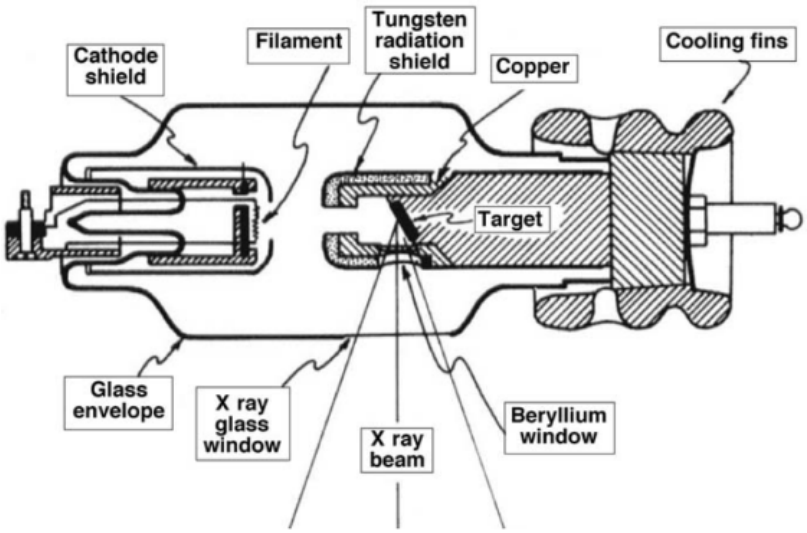


… this is because the presence of O_2 amplifies the action of free radicals hence the production of peroxide of hydrogen which produces cell damage.

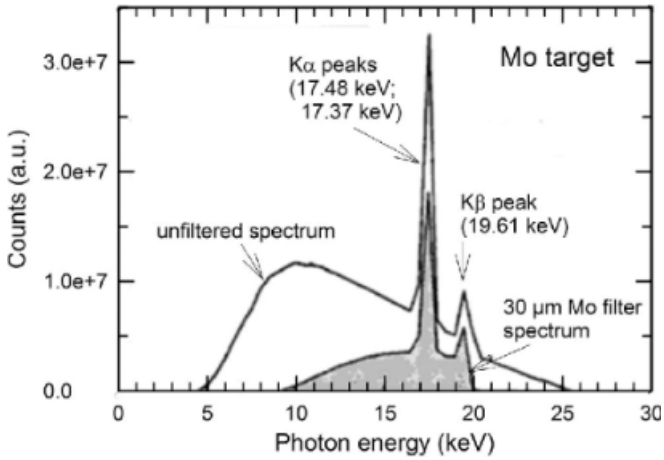
In particular, this is true in case of low L.E.T., where O.E.R. can reach up to 3 (hence 3x treatment effectiveness); in the case of high L.E.T. the quantity of H_2O_2 produced by the radiation is already very high so the presence of Oxygen does not significantly increase its production (saturation effect, O.E.R. around 1): this is why the pre-therapy assumption of Oxygen is sometimes done in radiotherapy but only rarely in hadrontherapy ___

6. Machines to accelerate electrons to produce gamma beams

X ray gammas are produced by thermionic effect heating a cathode with a hot filament



… the photons are emitted by the hot filament in all the directions, hence just a small portion of them reach the target (the cathode) → from the heated cathode an electron flux forms and such flux is attracted by the anode: also in this case the electrons are emitted in all the directions so just the ones in the right orientation to pass through a specific door reach the anode → here they give rise at two interactions: bremsstrahlung and inner shell's excitation and de-excitation, producing X rays photons which exhibit a spectrum composed by a continuous emission given by the bremsstrahlung (~80%) and some peaks given by the energetic difference between the inner shell and the shell of the electron that, during de-excitation, fills the gap created by the excitation (~20%)



… the typical energies involved in this process are in the range 1-100 keV, hence these machines are used for diagnostic purposes, not for treatment.

The efficiency of the process, that is the portion of gammas created by the incoming electrons, is very low, about 1%: this means that given 100 electrons just 1 gamma is produced (this is quite intuitive because most of the electrons don't pass through the door) while 99% of the contribution goes into heating, hence a proper cooling system is needed.

6.1 Teletherapy

Type of therapy used in the 50-60's based on an external beam produced by a machine containing an artificial radioactive source, the most used were Co-60 and Cs-137.

Co-60 decays in Ni-60 producing an electron, an antineutrino and two gammas

$$^{60}_{27}Co \rightarrow {}^{60}_{28}Ni + e^- + \bar{\nu}_e + \gamma + \gamma$$

with a half life of around 5 years and an activity of 44 *PBq per kilo…

… while Cs-137 decays in Ba-137 producing an electron, an antineutrino and one gamma

$$^{137}_{55}Cs \rightarrow {}^{137}_{56}Ba^* \rightarrow {}^{137}_{56}Ba + e^- + \bar{\nu}_e + \gamma$$

with a half life of around 30 years and an activity of around 3 TBq per kilo.

* Bq = Becquerel → unit of measure of radionuclide activity in the S.I.
It is defined as one decay/second, hence 1 kg of Co-60 has about $44*10^{15}$ decays every second; typically, the amount of radionuclide used in teletherapy is not of the order of "kilos" but of "grams", hence a division by 10^3 is done.
Another used unit of measure is the Ci, which stands for "Curie", which is defined as the activity of 1 gr of Ra-226: 1 Ci = 37 GBq.

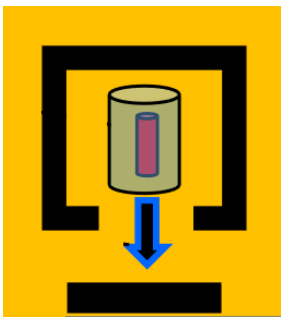
Which characteristics a good radioactive source must have to be used for teletherapy?
In order to be useful for teletherapy, the radioactive source must have high activity (high number of disexcitations per second), high long life (in order to be used for a long time) and the electron produced must be a low energy one in order to be easily absorbed by a filter and not by the patient (the treatment is done using the produced photons).

Both Co-60 and Cs-137 fulfill these requirements and both are artificial elements: this is another advantage because they can be synthesized quite easily.

Which are the most important parameters for teletherapy?

Dose ($D = \frac{dE_{kin}}{dm} = \frac{dE_{kin}}{\rho dV}$), specific activity → $a = \frac{\Lambda}{m} = \frac{N_A\, ln(2)}{t_{1/2}A}$ and distance.

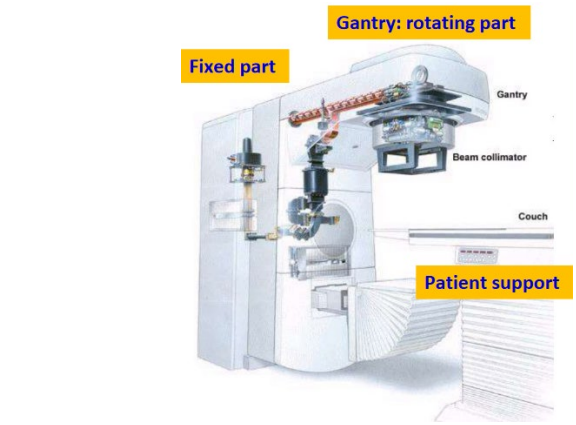
Structure of the head of a teletherapy machine

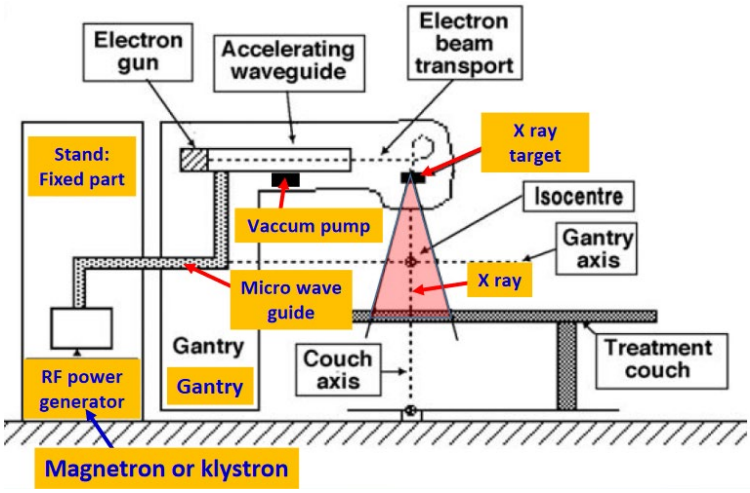


… the source is confined into a steel capsule, and both are stored inside the housing → when the machine operates the source moves out from the housing delivering the dose through a collimator which can be adjusted according to the region to cover; the head is about 80 cm far from the patient, and the typical dose delivered is about 0.1-0.2 Gy per minute; the source is typically replaced after half-life.

6.2 Medical Linear Accelerator

This machine has been developed from the mid 50's until today and is composed by a fixed part and a rotating part, the "gantry", which can rotate by 180° around the patient in order to deliver the treatment from many directions; the system of reference for the treatment is the isocenter, the intersection between the gantry's rotational axis and the direction of the beam





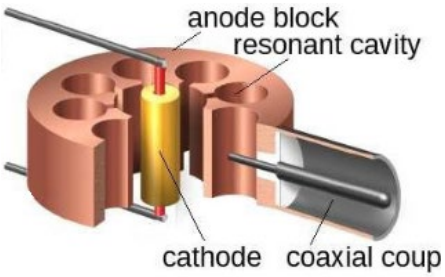
The fixed part contains a structure (magnetron or klystron) which produces a radiofrequency. Through a microwave guide, the radiofrequency is transmitted to the accelerating waveguide, here a very hot filament produces electrons (electron gun) which are accelerated into the AW within which vacuum is realized using a vacuum pump: the longer is the AW, the higher is the acceleration, the higher is the energy of the electron beam reachable; typical lengths are about 1.5 meters (Achtung! We are talking about electron's beams, can a photon beam be accelerated? No! because photons have no charge!).

The horizontal accelerated beam now needs to be bent in order to reach the patient; this can be done by deviating it of an angle of 90, 112.5 or 270 degrees.

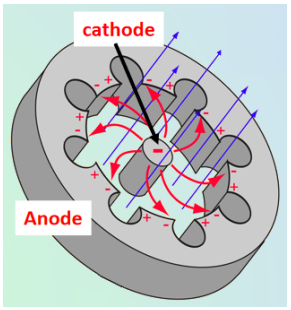
After the bending, the electron beam must be converted into a photon beam: this is done using a target which produces the required photons via bremsstrahlung; after the bremsstrahlung both photons and electrons are present, hence in order to have a beam composed only by photons the electrons must be stopped → this is done by using another material which absorbs the electrons letting pass only photons → the photons are emitted in all the directions hence a collimator is present; in all this, a proper cooling system is required.

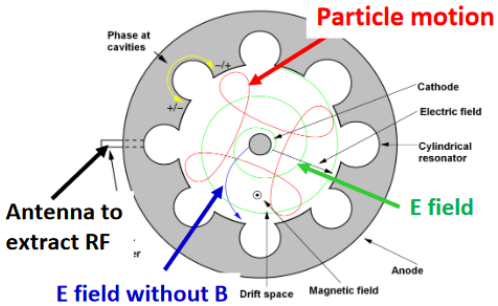
The radio frequency generator
The most used radiofrequency generators are magnetron or klystron.

The **magnetron** is composed by a very complicated structure which in the middle has a cathode that once heated emits thermionic electrons



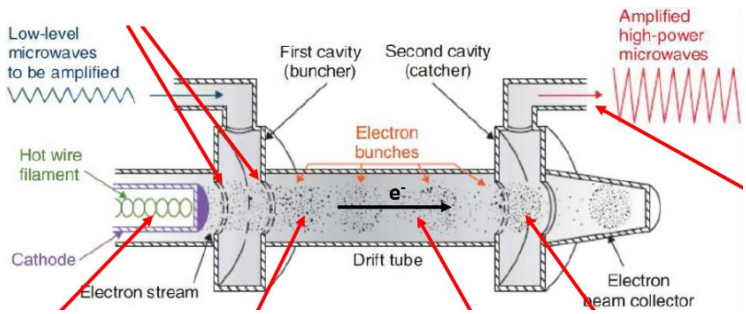
… inside the structure a stable magnetic field perpendicular to the electric one is present: electrons feel Lorentz force and move to the anode traveling very complex spirals





… along these spirals, the electrons emit microwave gammas (our radiofrequency), which is collected by an antenna and transferred to the microwave guide, which transports the signal as it is from the magnetron to the linear accelerator.

The **klystron** is a little more complicated than magnetron but is based on the same concept



… electrons produced by a hot cathode reach a first cavity (buncher) where they start being accelerated, then they reach a drift tube where an electric field creates some bumps and, after that, a second cavity (catcher) where another electric field keeps on the acceleration. At the end, the accelerated electrons reach a third cavity where a collimator is present.

Which are the main differences between magnetron and klystron?
Magnetrons are smaller than klystrons, hence are typically used for low energy accelerations; being smaller and less complicated, they are also less expensive but also of shorter duration and less reliable. Klystrons are more stable and can reach higher energies than magnetrons, but are larger, more expensive and complex.
Overall, the most used of the twos is the klystron.

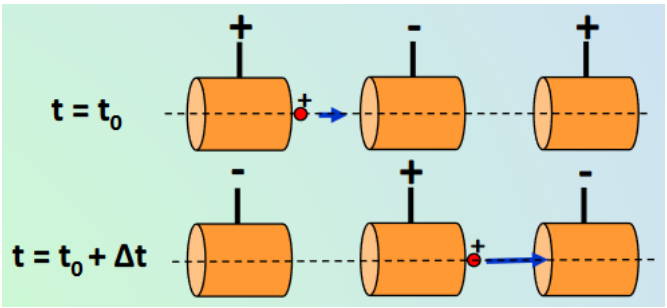
The electron gun
The radiofrequency has been produced and transported to the accelerating waveguide.

Electrons are produced by a hot filament and enter in the accelerating waveguide with a very low energy, typically from 50 to 70 keV, the energy we saw before in the X-ray production. We need to accelerate this beam, and the acceleration is gained through the radiofrequency.

Before entering the AW, the beam passes through a grid which performs two functions:

- modulation of the flux, by varying the opening;
- stopping of the beam in case of any problem.

The accelerating waveguide
The AW is composed by many tubes, each of them connected to the radiofrequency



… when the electron arrives, the first station is set at a positive potential: seeing in front of it a positive charge structure, the electron is accelerated.
The tubes are built using a conductor material, hence while the electron is inside it feels an electric field equals to zero → during this time, the polarity is changed in order to set the next tube from its previous negative potential to the positive one → the electron exits the first tube and sees again a positive charge structure in front of it remaining accelerated → during the cross of the electron in the second tube the polarity is again changed and so on, keeping the acceleration going: **so the radiofrequency is a potential built in a way that the electron sees always a positive potential in front of it**, hence the radiofrequency must be made in a way that each maximum corresponds to the time the electron needs to cross the stations; this is why the dimension of the stations increase going on, because the energy of the electron increases so the crossing time decreases, and to have the same modulation the size of the stations must be increased.
The more stages we have, the more the energy can be increased, the more the acceleration gain is, the longer is the machine.

There are two main types of accelerating waveguides:

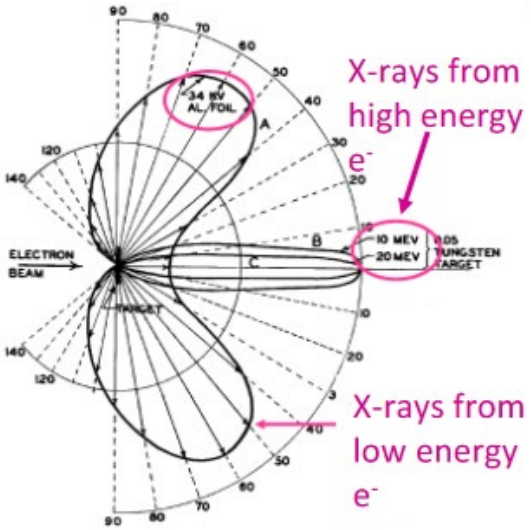
- **traveling waveguide system** → the maximum follows the electron in its travel through the many stations;
- **standing waveguide system** → there's an alternation between positive and negative.

In all of these, a magnetic field is required in order to keep the beam collimated, because being the beam composed of particles of the same charge it would spread due to electromagnetic forces.

How much energy can we reach with a radiotherapy machine?
It depends on the machine used.
Typically, there are two types of machines: Low Energy Machines, which have a vertical gantry (hence a shorter one) and High Energy Machines, which have a horizontal gantry. Low Energy Machines can produce electrons up to 6 MeV, while High Energy Machines can reach energies of about 18-20 MeV.

Achtung!
These are the energies of the electrons! by producing photons through bremsstrahlung effect their energy is peaked at about 1/3 the maximum energy of the electron.

An important point is that the high energy gamma part tends to be emitted along the original electrons' direction, while the low energy part tends to be emitted at a direction of around 90°



hence the gammas used for treatment (100% bremsstrahlung) tend to be emitted along the electrons' direction while the gammas used for diagnostic (80% bremsstrahlung, 20% from K-shells' peaks) tend to be emitted along the 90° direction.

Today, practically all the machines are of the High Energy type because with them you can produce both high and low energy beams, while in the case of Low Energy machines you can only have low energies.

The treatment head

All the steps explained until now are common to any particle accelerator: the main difference between a researching machine and a treatment machine resides in the treatment head; inside the treatment head the electron beam is modified into a photon beam with the characteristics needed to perform the treatment.

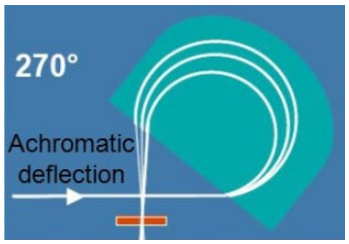
The treatment head is composed by a dipole+quadrupole to bend and collimate the beam, *by a target to create the gamma ray, by collimators which allow only the particles on a particular direction, by a second set of mechanized collimators which allow to adjust the beam of the form that we want depending on the cancer and by an ionization chamber which allows to monitor in real-time the intensity and the shape of the beam in order to check the beam's status; all the structure must be properly screened using heavy materials.

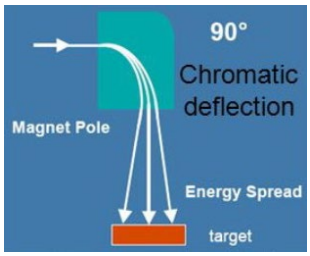
* In the case a treatment using electrons instead of photons is preferred (for example for a surface cancer), the material used to convert the electron beam into a gamma beam is retracted and the original beam is used in pairs with a scattering foil or a magnet.

Now we will look more in detail at all these parts.

The magnet

Depending on the solution chosen, many types of magnets can be used.
The most used solutions involve a 270° bent (Siemens/Varian), a simple 90° bent or a more complicated slalom of 112.5° bent (Elekta)





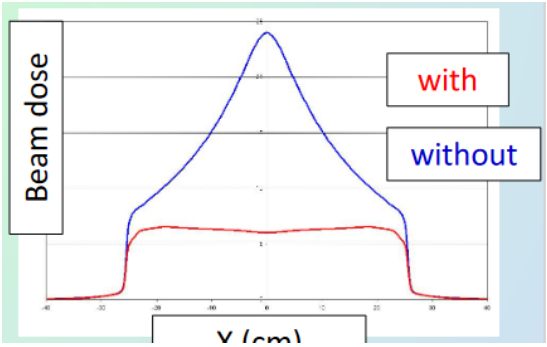
… inside the magnet undergo some monochromatic corrections in order to have a more monochromatic beam.
In the 90° bending case the outcoming beam is a little more spread than in the others; typically, **the outcoming beam's transverse dimension is around 1 mm**.

The target to create the gamma beam
Here we want to transform the electron beam into a gamma beam.

The target to use (hence the material of which it is composed of) depends on the energy we want to achieve for the gamma beam: for gamma energies above 15 MeV it is better to use low Z targets in order to avoid neutron production, while for energies below 15 MeV it is better to use high Z targets because bremsstrahlung is proportional to Z^3 hence the heavier the target the more photons are produced and we are under the neutrons' production threshold so the problem of neutrons creation which arises at higher energies is not present.

After the bremsstrahlung interaction the production of gamma is more or less in the same direction of the incoming electron but with a little spread in the transverse direction, hence the beam is more intense in the central region and less intense in the outer one:
we don't want this situation, the beam must have the same intensity on a large area, so proper **flattening filters** are used

… such filters are cone-shaped in order to absorb more radiation in the inner region and less in the outer one, hence after this operation a ~ uniform beam on a large area is achieved

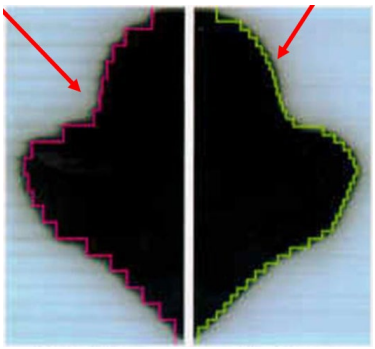


In the case we want to use the original electron beam, the target is removed and at its place is located a scattering foil (or some, depending on the enlargement we want to obtain) in order to enlarge the beam: as we know, when an electron crosses a material it is deflected by the other electrons composing the material itself, hence considering a beam the final result is the enlargement of the area covered (**pencil beam scattering**): this is necessary because, as seen, the outcoming beam after the magnetic bending has a typical transverse dimension of 1 mm, while cancers have dimensions of centimeters.
An alternative to pencil beam scattering is represented by **pencil beam scanning**, the use of a magnet to control the beam and make it scan the area needed.

The targets to modify/correct the beam
We have a uniform flat beam, now we need to modify it in order to follow the cancer's shape. The old technology consisted of using targets of various materials and forms put by hand according to the specific requests of the treatment.

The multileaf collimator
This is the new technology used to give the beam the exact conformation of the cancer. After passing through a first collimator which selects only the radiation in the perpendicular direction the beam reaches a system of n diaphragms ("leaves") each independently moved by a computer controlled motor, reproducing the required shape with high accuracy.

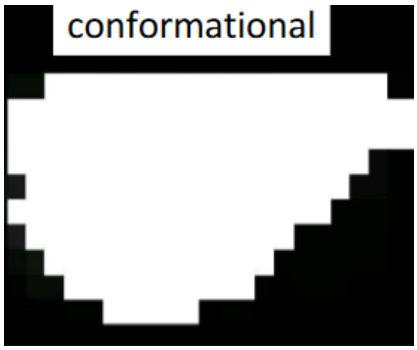
The higher is the number of the leaves (hence the smaller are their dimensions), the higher is the accuracy achieved in reproducing the treatment's shape

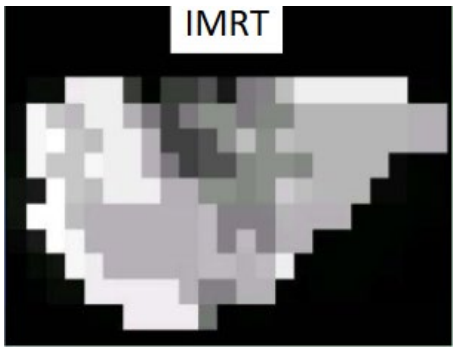


… depending on whether the multileaf system can move or not during the treatment we distinguish between:

- **IMRT** (Intensity Modulated Radiotherapy Technique) → can move, producing a modulated irradiation;
- **Conformational Technique** → cannot move, producing a flat irradiation.

… of course, IMRT is a more advanced technique than the Conformational one.

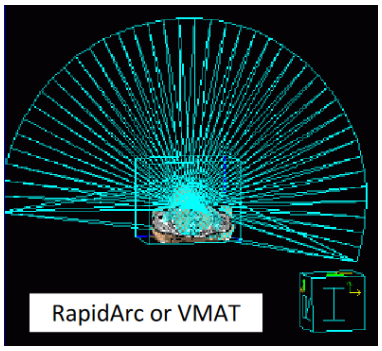




Before reaching the multileaf collimator, the beam must be monitored in terms of stability, intensity and constance of the intensity: for this purpose we use the **ionization chamber**, a chamber containing a gas in which the beam travels; the reason we use ionization chamber instead of scintillators is because during the passage into the first the number of ionizations is very low so we can check the conformity of the beam without modifying it.

In all this, a proper treatment's planning is required in the form of evaluating the patient's position (by immobilizing it and using a laser beam to verify his position and a light beam to check the trajectory of the treatment's beam), checking the machine's performance and delineating both the **Clinical Target Volume (CTV)**, that is the cancer volume, and the **Planning Target Volume (PTV)**, that is the zone to be effectively irradiated given by the CTV + a surplus region which takes care of the patient's movements; in case an organ at risk is not present in the vicinity of the cancer, the PTV can be enlarged for conservative reasons.

The actual most advanced technique available is represented by the **Rapid Arc**, or **VMAT** which stands for Volumetric Modulated Arc Therapy.



… the VMAT allows to choose at every point the velocity of the machine, the quantity of beam to be delivered and the shape of the multileaf collimator.

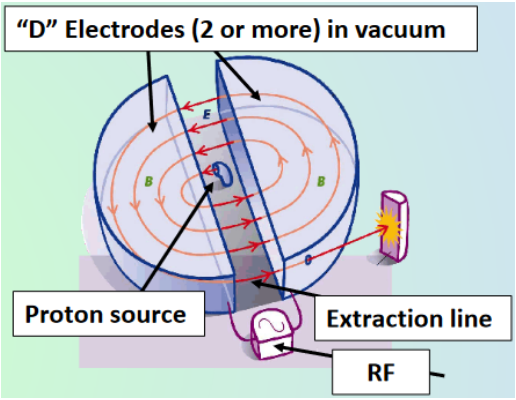
Hence, even if hadrontherapy represents a better solution with respect to conventional radiotherapy, also with the latter it is today possible to achieve outstanding results in terms of treatment's accuracy, allowing to preserve the greater part of the healthy tissues ___

7. Machines to accelerate charged particles

Charged particles can be accelerated using cyclotrons (only for protons) and synchrotrons.

7.1 Cyclotron

The basic structure of a **cyclotron** is given by two or more D shaped electrodes ("Dees"), a protons' source and a radio frequency generator



The protons' source is located at the center of the cyclotron and is composed of a H_2 gas confined into a chimney; a hot filament heats the cathode making it to produce thermal electrons which are then attracted by an anode: during their travel the electrons cross the gas ionizing it hence producing protons → a fraction of these protons will pass through a little hole and leave the chimney feeling the electric field generated by the nearest Dee.

The Dees are metal magnets of different shapes and dimensions, hence Faraday chambers, so the proton crossing them feels a zero electric field but a non zero magnetic field: the overall effect is a deflection of the particle into a curve trajectory thanks to Lorentz force

$$\frac{mv^2}{r} = Bqv \rightarrow \frac{mv}{r} = Bq \rightarrow \frac{v}{r} = \frac{Bq}{m}$$

$$\left(\dots \frac{v}{r} = \omega = 2\pi\nu = \frac{2\pi}{T}\dots\right)$$

$$\frac{2\pi}{T} = \frac{Bq}{m}$$

… the period (and the frequency) does not depend on radius hence the beam and the RF are apparently isochronous… this is not true because here relativistic effects are not negligible hence mass changes according to special relativity as

$$m = \gamma m_0$$

with $\gamma = \frac{1}{\sqrt{1-\beta^2}}$ and m_0 mass at rest.

So, the beam and the RF are not in phase: if the energy of the beam increases γ increases, m increases hence T increases ⇒ relativistic corrections must be considered.

Current cyclotrons are able to produce beams only at one fixed energy which is given by

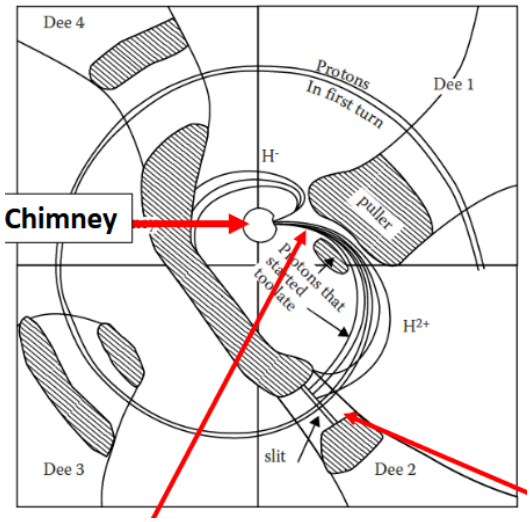
$$v = \frac{Bqr}{m},\ E = \frac{1}{2}mv^2 \Rightarrow E = \frac{1}{2}\frac{B^2q^2r^2}{m} \Rightarrow E\ \alpha\ B^2r^2$$

so in order to have higher energies we need a stronger magnetic field or a greater radius.

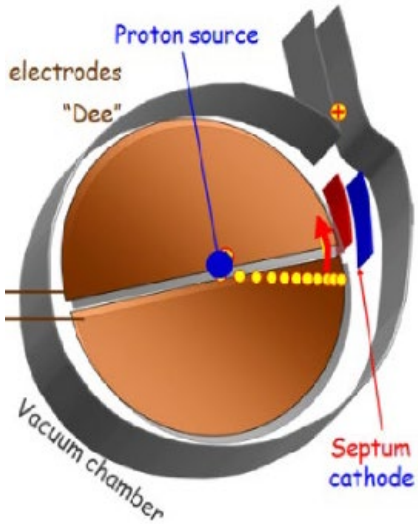
Outside Dees, in the space between them, a radio frequency generator is installed with the aim to provide a proper sinusoid signal in order to accelerate the crossing particles.
As we have just seen, the beam and the RF are not in phase do to relativistic effects hence the required synchronization can be obtained using two possible solutions:

- changing the RF maintaining B constant generating a pulsed beam of typically 1 KHz → we have a synchrocyclotron, not very used;
- increasing B maintaining the RF constant → in this case we have a continuous beam and a "pure" cyclotron, this is the most used solution.

Only particles with the energy needed keep travel and reach the final stage of the cyclotron: this is done by using proper collimators which select the correct trajectories (energies); all the remaining particles are absorbed by the machine



The final stage consists in the so called "protons' extraction": once the beam is ready a little more energy is given and the beam enters the exit lane composed by a thin vertical blade, called "septum", parallel to the beam, a cathode parallel to the latter but at a higher radius to better deflect the beam and other magnets to correct defocusing effects



… the extraction efficiency must be at least 60-70%; if lower, beam losses increase, decreasing the treatment's efficiency → cyclotron may also activate: hazard for personnel!

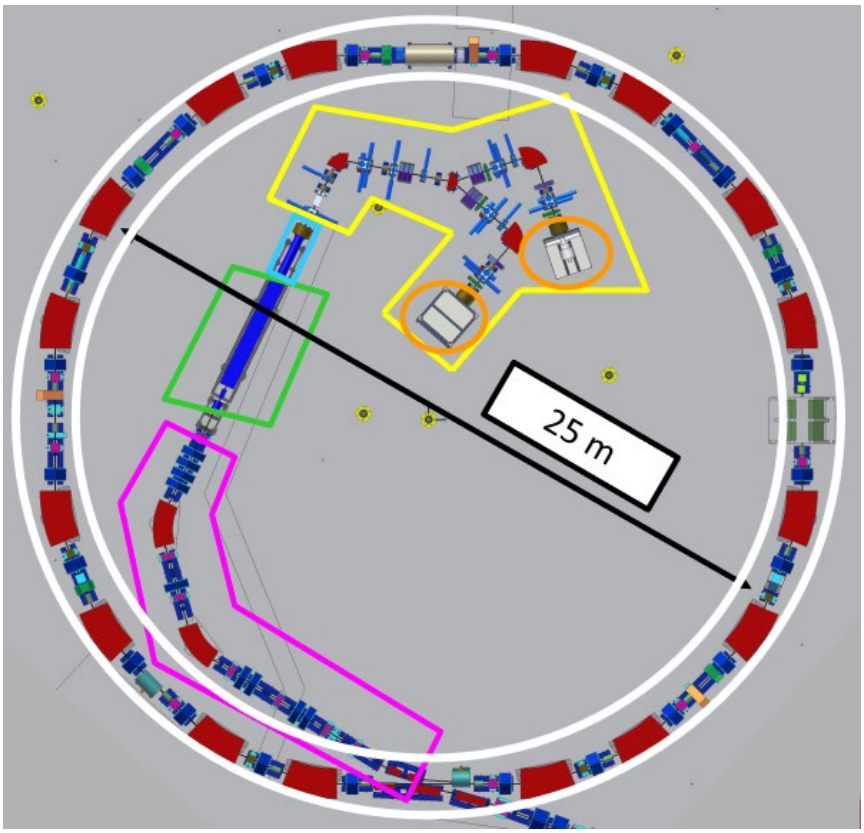
7.2 Synchrotron

This is a much complex, expensive and greater machine than a cyclotron, which can create beams spacing from protons to Carbon, Oxygen and Neon in a wide range of energies.

The latter grants also that these machines produce much less radiation than cyclotrons, because while for cyclotrons energies are fixed hence proper targets are needed to decrease the beams' energy (the best choice to choose a cyclotron for treatments is to choose the one at highest energies, but if for a particular treatment a lower energy is needed the initial beam must be forced to cross through a material → this drops down the energy but also produces particles, in particular neutrons, which can exit the cyclotron activating the room) in the case of synchrotrons the required energy can directly be selected.

Hence to summarize synchrotrons are much more powerful, flexible and "safe" machines than cyclotrons, but also much more expensive, complex and larger to install.

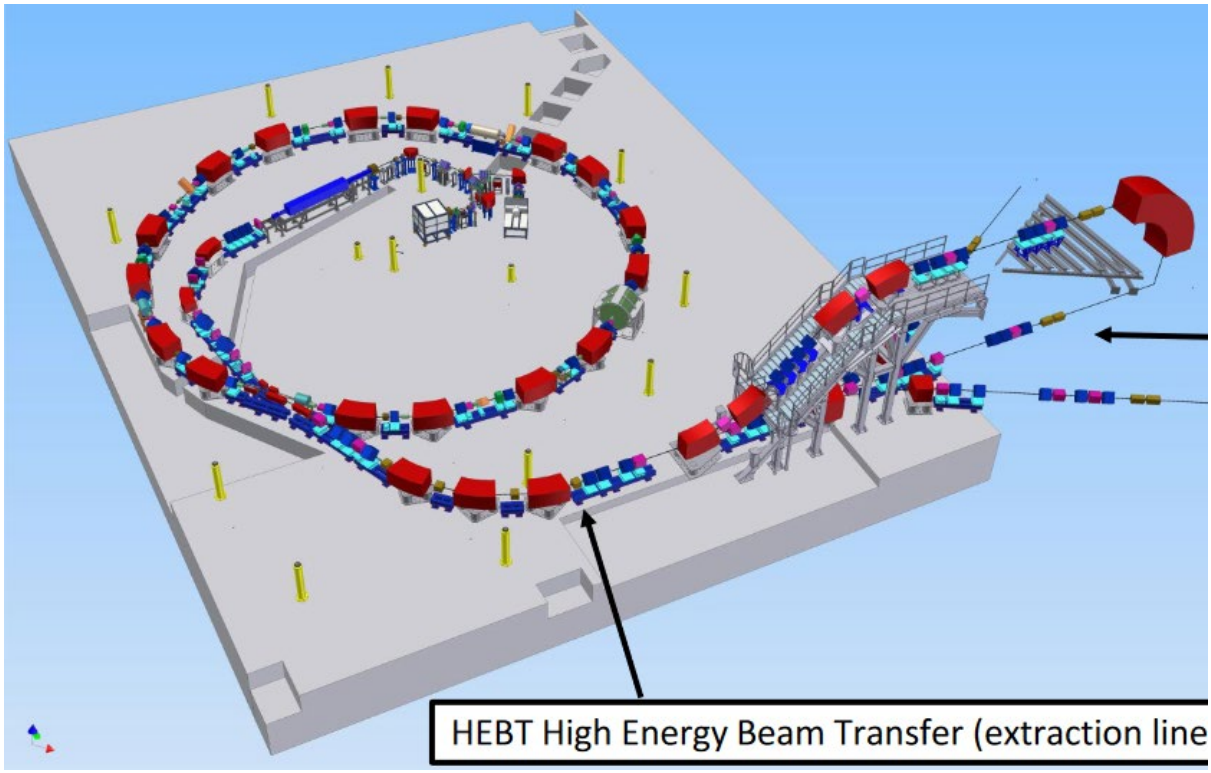
This is the synchrotron installed at CNAO, in Pavia



it is composed by:

- two sources, one for protons and one for Carbon-12 (orange);
- the LEBT (Low Energy Beam Transport) (yellow);
- the RFQ (azure);
- the LINAC (green);
- the MEBT (Medium Energy Beam Transport) (magenta);
- the synchrotron itself (white)...

… at the end are located three treatment rooms, one of which also has a vertical beam



… and from 2022 also one experimental room used by researchers to test new potential applications such as the promising Helium and Oxygen treatments.

(Why are He and O so promising for hadrontherapy? Because being magic numbers they are more stable hence less susceptible to projectile fragmentation).

The sources are based on the same principles seen for cyclotrons: a thermionic reaction produces electrons that ionize a gas, H_2 or CO_2.
In the case of CO_2 also Oxygen is produced, hence the resulting proto-flux passes through a mass spectrometer which selects the particles via a two-step process: in the first step particles cross a condenser with also a magnetic field normal to the electric one, in the second step the selected particles are deflected via Lorentz force, selected and injected into the LEBT.

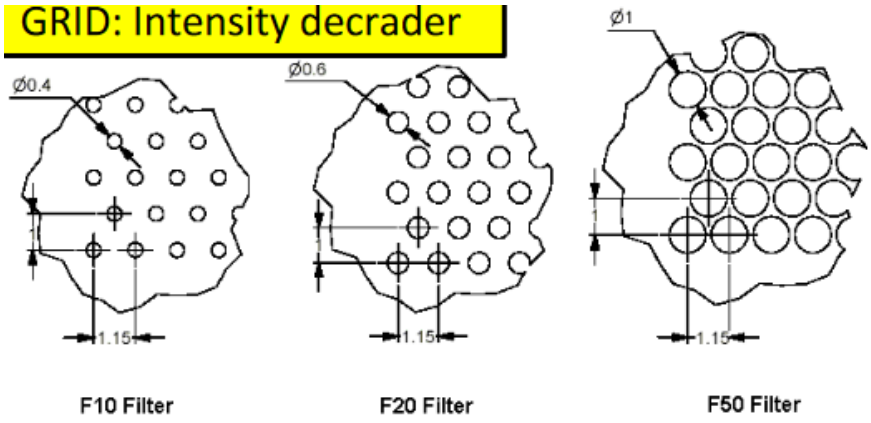
Typical energies inside the **LEBT** are around 8 keV/n with currents of fractions of mA, around 0.7 for protons and 0.2 for Carbons that at this stage are not completely ionized yet. At the end of the LEBT a first chopper is located.

The beam then enters the **RFQ**, which gives the first boost before the LINAC, setting the energy at 400 keV/n.

Into the **LINAC** (which is 3.77 meters long) the beam is further accelerated at 7 MeV/n passing through 56 accelerating gaps, and focalized by 3 quadrupoles.
Beyond the LINAC, a series of carbon foils perform the final ionizations stripping the last electrons from $3H^+$ and C: we have protons and C^{6+}.

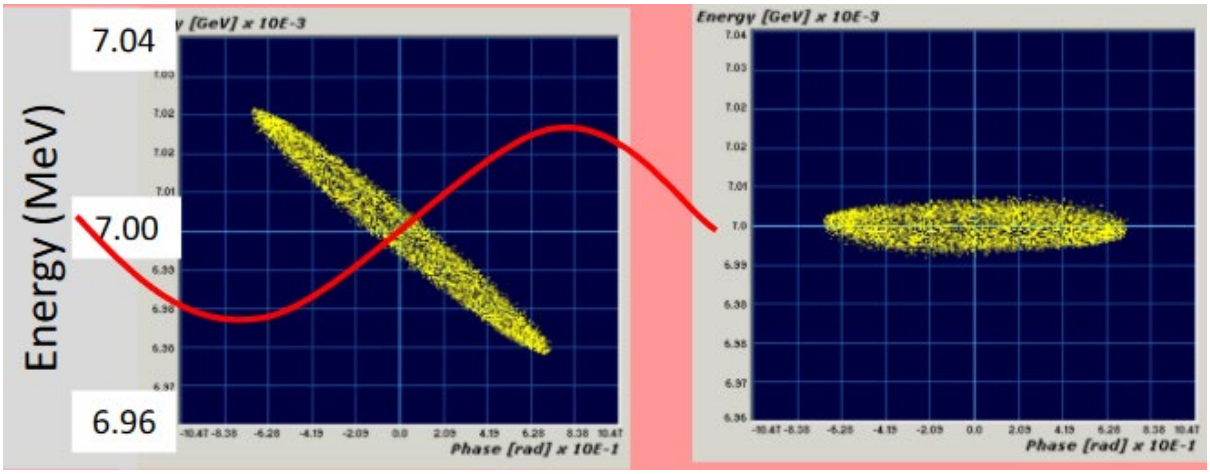
We are in the **MEBT**: here the beam is no more accelerated but undergoes a series of adjustments for the final injection in the synchrotron, the most importants are:

- the **eventual variation of the beam's intensity**, through proper transmission filters



  available in three types: F10, F20 and F50, meaning 10%, 20% and 50% intensity transmitted respectively;

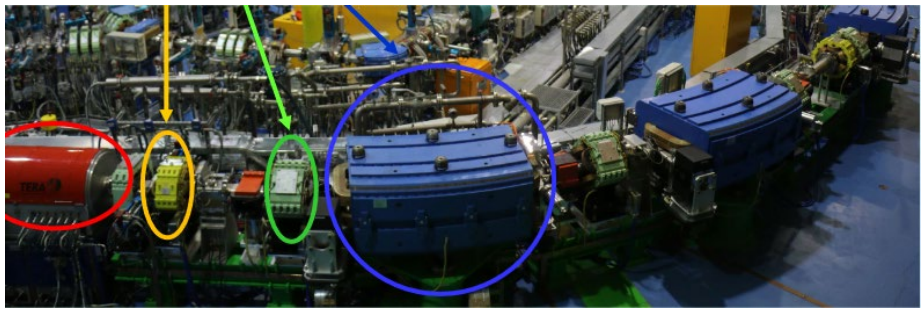
- the **change of the injected beam's momentum (energy) (debunching)**, this is crucial because it lets to reduce the momentum spread of the beam



  very important because we want the beam injected into the synchrotron to be the most homogeneous possible → **7 MeV/n**.

The beam is then injected into the synchrotron with a multi-turn procedure using magnets, typically the procedure requires around 15 turns corresponding to about 30 microseconds…

Now we are into the **synchrotron**, the outer ring in which the beam undergoes the final acceleration before reaching the experimental/treatment rooms.
The ring is built with four main pieces coloured in a proper way depending on their nature

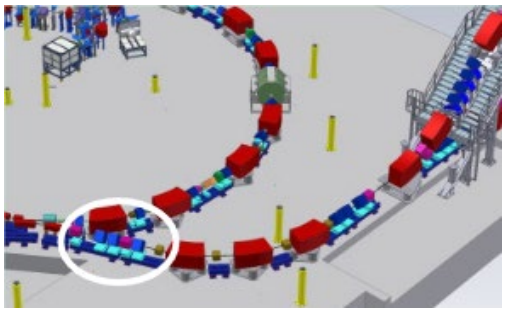


… they are:

- RFQ → red, it accelerates the beam;
- dipoles → blue, they curve the trajectory of the beam;
- quadrupoles → green, they focus the trajectory of the beam;
- sextupoles → yellow, they focus the energy of the beam.

Synchrotron repeats cycles with different energies (depending on the treatment) typically performing one cycle every 5 seconds; after each cycle the unused beam is removed and all the magnets are resetted in order to take care of hysteresis.

The beam is extracted from the synchrotron by producing a small perturbation which injects it in the **HEBT** and using a varying B which creates an electric field that boosts the beam a little bit in order to facilitate its extraction.
In the HEBT a chopper composed by 4 magnets is present; the chopper works as a check station: if we want to use the beam the beam proceeds to the scanning control, otherwise it is redirected to a dump (usually a large water reservoir or a thick material) where it stops.



… before the dump a beam monitor to check the beam's status is present.

The final check is performed by the **scanning control**, the brain of the treatment, in charge of controlling the beam's energy, position and other important parameters.
The entire process is managed by a complex code which must coordinate all the machines.

The SOBP can be created by

- scanning system → change the beam's energy (more precise but slow);
- scattering system → using ridge filters (less precise but faster)...

… the latter can be used when the cancer is not in a critical zone and when there are difficulties holding the patient in position, but usually the first one is preferred ___

8. Boron Neutron Capture Therapy (BNCT)

This is an alternative technique, still in development, to be used to treat cancer.

BNCT is based on two facts:

- the cross section between low energy neutrons and Boron-10 is very high;
- cancerous cells absorb a higher fraction of Boron-10 than healthy ones do…

… so a vector, typically an aminoacid molecule, in which one component is substituted with Boron-10 to enrich the cancer region with a lot of Boron (about 10^9 Boron/cell) is used in order to irradiate it with low energy (~0.025 eV, $\sim 10^{-8}$ MeV) neutrons:

$$* \; n + {}^{10}B \rightarrow {}^{11}B * \rightarrow \alpha + {}^{7}Li + \gamma \quad (94\%)$$
$$* \; n + {}^{10}B \rightarrow {}^{11}B * \rightarrow\rightarrow \alpha + {}^{7}Li \quad (6\%)$$

* the energies of α and Li-7 are around 1.5 and 1 MeV, hence we have two low energy fragments with charge 2 and 3 respectively, so better than protons (which have Z=1) and little worse than Carbon (which has Z=6), so these can give rise to high ionization in a very small range (mms); the gamma's energy is around 0.5 MeV, this represents a problem because the photon's range could be also infinite, so it could traverse all the body…

* only the two fragments are produced, with energies around 2 and 1 MeV respectively…

⇒ thanks to the fact that cancerous cells absorb more Boron than the healthy ones, it is possible to treat cancer using low energy neutrons.

Why do cancerous cells absorb more Boron than the healthy ones?
Because they want to grow, so they absorb proteins and amino acids, hence the use of amino acids molecules to deliver markers/enrichers to cancerous cells is commonly used.

Why Boron?
For three main reasons:

1. Boron-10 is a non radioactive isotope easily available;
2. Neutron capture's cross section in Boron-10 is almost 4×10^3 barns; as an example, the cross section between neutron and Hydrogen and between neutron and Nitrogen are around 0.3 and 1.75 barns respectively;
3. The fragments produced, α and Li-7, are strongly ionizing particles in a limited range, around 10 micrometers so inside the cell's dimension.

The difficulties are the following:

1. It is hard to inject Boron-10 only in the cancer volume;
2. It is hard to control the neutrons' beam because magnets can not be used (only collimators) and neutrons can also travel for long distances (cm, m), a situation completely different with respect to charged particles which having Z≠0 makes them stop when crossing a material thanks to the electromagnetic interactions.

In all this a very well structured screening system (meters for each beam) is mandatory.

9. Diagnostic

Depending on the particles emitted during the treatment it is possible to perform the following types of diagnostic:

- * Scintigraphy;
- * SPECT (Single Photon Emission Computed Tomography);
- * PET (Positron Emission Tomography);
- * CT (Computed Tomography);
- * NMR (Nuclear Magnetic Resonance).

* are based on γ emitters radionuclides (Tc-99, Tl-201, I-123)

* is based on β^+ emitters radionuclides (C-11, N-13, O-15, F-18)

* is an algorithm to obtain a 3D image from many 2D slices

* does not use radionuclides

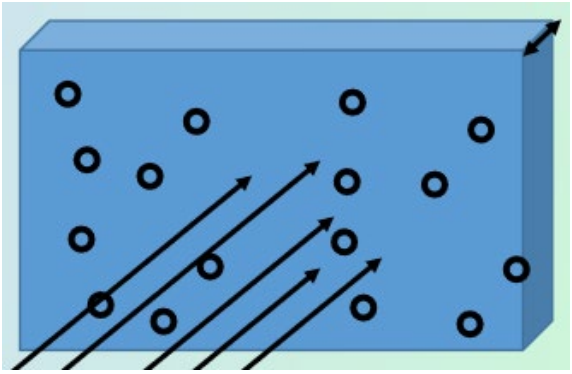
Radionuclides can be produced via nuclear reactors or particle accelerators (mainly cyclotrons) and must satisfy the following requirements:

1. be readily available at low cost;
2. be pure γ or β emitters;
3. * have a short effective biological $T_{1/2}$, in order to be fastly eliminated by the body;
4. be trapped by the metabolic process of interest.

* is quite a delicate requirement because decreasing $T_{1/2}$ means that the patient's body eliminates the radionuclide faster but also that the treatment must be performed right after the radionuclide's production → just as an example, Oxygen-15 has an half time of two minutes, hence the patient must be treated within this time.

The production of radionuclides

Radionuclides are produced using a flux of particles (typically protons) against a target



… the number of particles produced is proportional to the flux of the beam, to the number of scattering centers per unit volume and to the cross section beam-target

$$\left(\frac{dN}{dt}\right)_a = \varphi \cdot n \cdot \sigma$$

and is called Production (or Activation) Frequency, which is the number of radionuclides produced for unit time.

The number of scattering centers, n, is a known number depending on the target used.

During production, radionuclides decay following their decay constant λ proportionally to the number of particle N produced according to the decaying law

$$\left(\frac{dN}{dt}\right)_d = -\lambda \cdot N$$

… hence the number of particles that we have at a time t after decay is given by

$$N = N_0 e^{-\lambda t}$$

… or using the half time

$$\frac{N_0}{2} = N_0 e^{-\lambda t_{1/2}}$$

… from which we can extract the relation between λ and $t_{1/2}$

$$= \frac{1}{2} = e^{-\lambda t_{1/2}} =$$

$$= ln\left(\frac{1}{2}\right) = -\lambda t_{1/2} =$$

$$\Rightarrow \lambda = \frac{ln(2)}{t_{1/2}} \sim 0.693\ {t_{1/2}}^{-1}$$

…

… hence the number of radionuclides that we have at a time t is given by the number of radionuclides activated minus the number of radionuclides decayed

$$\left(\frac{dN}{dt}\right) = \left(\frac{dN}{dt}\right)_a + \left(\frac{dN}{dt}\right)_d = n \cdot \sigma \cdot \varphi - \lambda \cdot N =$$

(... separate the variables…)

$$= \frac{dN}{n\sigma\varphi - \lambda N} = dt =$$

(... change the integration variable multiplying by $-\lambda$…)

$$= \frac{d\lambda N}{\lambda N - n\sigma\varphi} = -\lambda dt =$$

(... integrate…)

$$= \int_0^N \frac{d\lambda N}{\lambda N - n\sigma\varphi} = -\int_0^t \lambda dt =$$

(... make the substitution $y = \lambda N - n\sigma\varphi \Rightarrow dy = d\lambda N$…)

$$= \int_0^N \frac{dy}{y} = -\int_0^t \lambda dt =$$

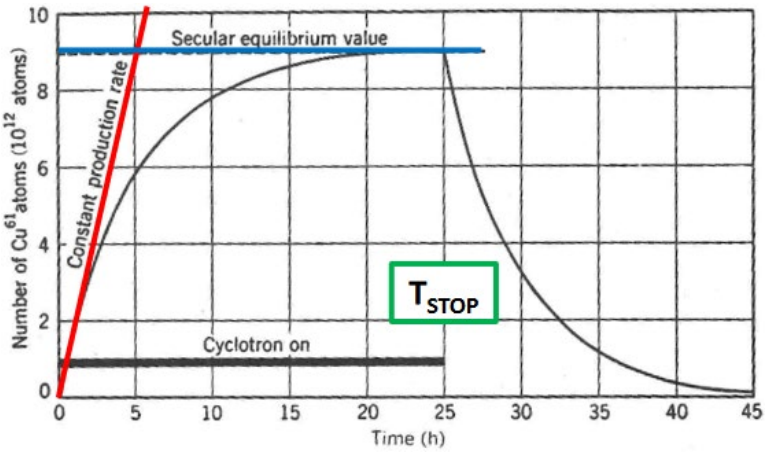
$$= ln\left(\frac{\lambda N - n\sigma\varphi}{-n\sigma\varphi}\right) = -\lambda t =$$

$$\Rightarrow N(t) = \frac{n\sigma\varphi}{\lambda}\left(1 - e^{-\lambda t}\right) = \frac{n\sigma\varphi}{\lambda}\left(1 - e^{-0.693t/t_{1/2}}\right)$$

… so this means that:

- if $t \ll t_{1/2}$ we can Taylor expand → $N(t) \sim \frac{n\sigma\varphi}{\lambda}\left(1 - 1 + \frac{0.693t}{t_{1/2}}\right) \sim \frac{n\sigma\varphi 0.693}{\lambda t_{1/2}} t$;
- if $t \gg t_{1/2}$ the parenthesis gives ~1 ⇒ $N(t) \sim \frac{n\sigma\varphi}{\lambda} =$ const…

⇒ ~ linear production at the beginning followed by a plateau and an exponential decay



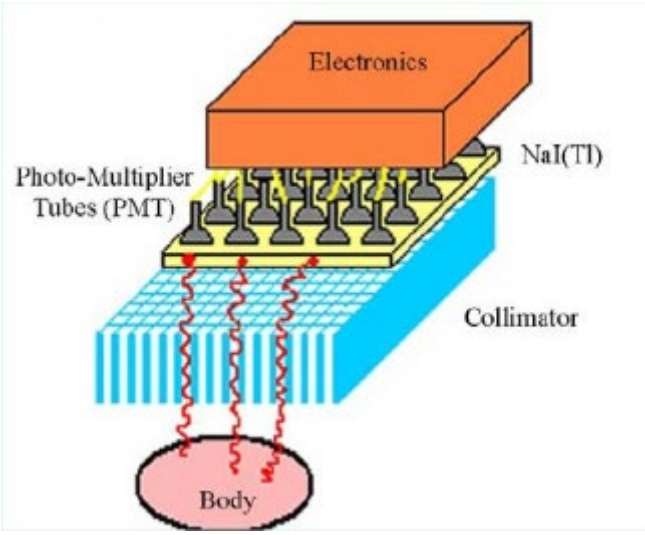
… switching on a cyclotron costs money ⇒ the aim is to produce the highest nuclides' number with the lowest cost → typically the production stops at ~90% saturation (~ $3t_{1/2}$).

The targets used to produce radionuclides can be solid, liquid or gaseous and they can be inserted internally to the cyclotron or be external; in the first case the main difficulty is represented by the fact that inside the cyclotron there is vacuum, hence after the installation of the target vacuum must be reproduced, while in the second case this problem does not sussist and the beam must be transported outside the machine; in both cases a proper cooling system is required in order to prevent the target's liquefaction.

Once the radionuclides are produced we can use them for diagnostic in different ways:

Scintigraphy (gamma camera)
Uses radionuclides γ emitters and is essentially composed by three main parts:

- a **collimator**, which selects only the photons perpendicular to the holes;
- a **scintillating crystal** which converts high energy gammas into low energy ones;
- **photomultipliers**, which through a system of dynodes convert photons into electrons: the gamma enters the photomultiplier and colliding with a thin metallic foil extracts an electron via photoelectric effect that is accelerated passing through a system of dynodes → the output is an electric signal.



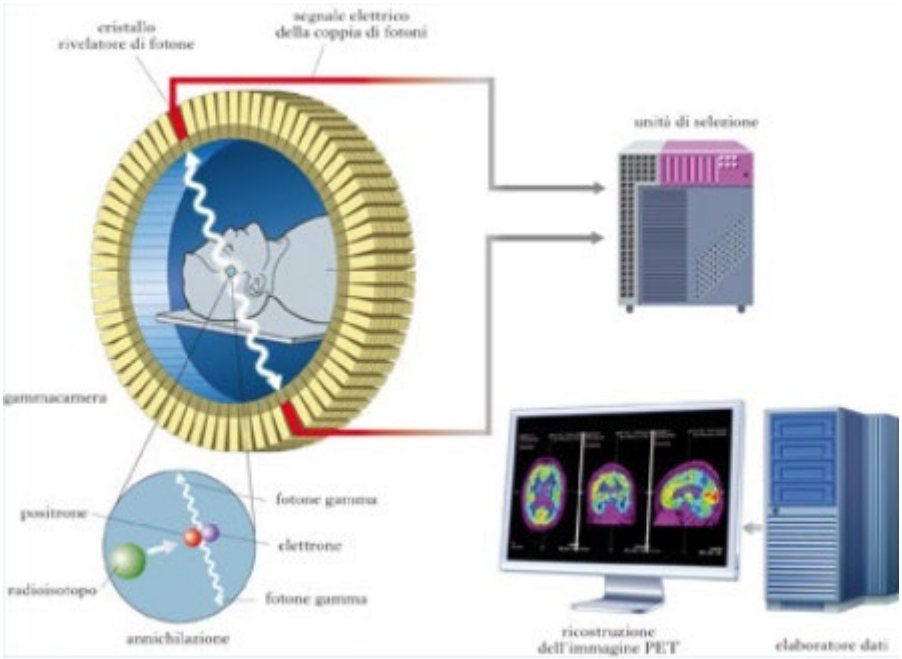
… traditional photomultipliers need very high tension (1000-2000 Volts), and if you are inside the magnet this deflects the electrons reducing the photomultipliers' global efficiency.
This is the reason why today's silicon photomultipliers are preferred to traditional ones: in this new type of photomultiplier a signal is produced every time the electron hits the silicon pixel, with a required alimentation of just 5-10 volts and with the additional advantage that also if a magnet is present the efficiency of the photomultiplier is not affected.

SPECT (Single Photon Emission Computed Tomography)
The evolution of scintigraphy: instead of having just 1 image you can rotate the gamma camera in order to collect n 2D images and obtain a 3D image.
This technology combines the gamma camera technique with the one of computed tomography.

PET (Positron Emission Tomography)

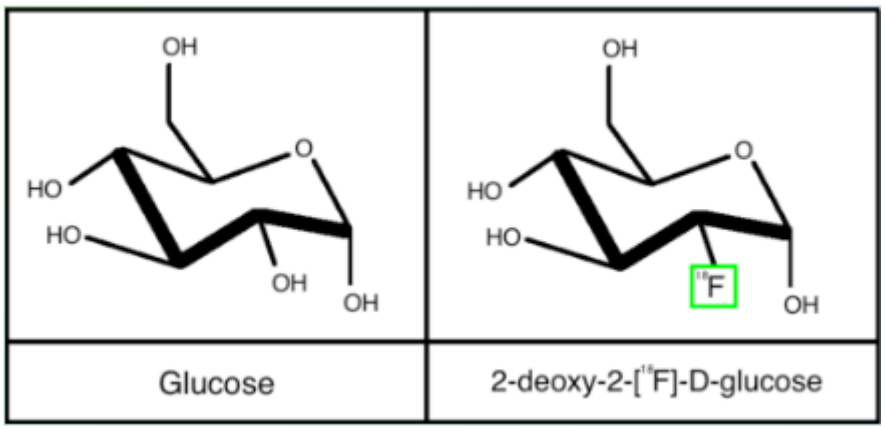
It uses β^+ emitters, hence radionuclides which emit positrons.

Positrons are anti-matter hence they annihilate with atomic electrons producing 2 gammas emitted in opposite directions (the γ are two due to the conservation of the initial momentum)



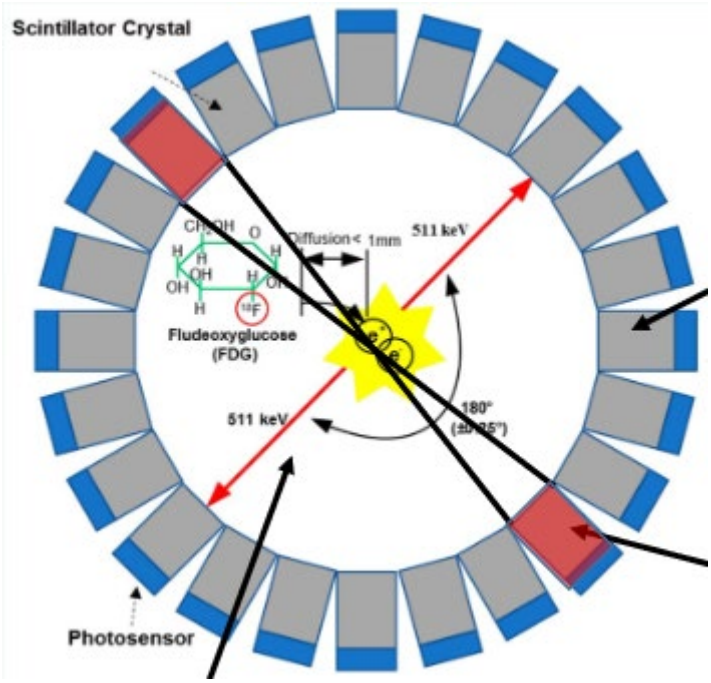
We remind that “annihilation” means total conversion of the initial mass in energy, hence photons: in an annihilation process all the initial mass is converted into energy.

The source of positrons is typically represented by F-18, injected in the patient’s body using glucose as a vector molecule: as we said, cancerous cells want to grow hence the big part of the injected glucose is absorbed by them; in particular, the injection is done substituting one of the OH groups in glucose with F



… the emitted photons are registered by a system of detectors all around the patient; in new generation PETs also the evaluation of the receiving time is available.

The detectors are ring shaped crystals composed by many scintillator crystals



in the inner part of each scintillator is located a photo sensor which detects the incoming γ.

The spatial resolution obtained in PET depends on many factors, the most importants are:

- **crystal dimension** → the higher the dimension of the crystal the lower the resolution, in order to have the best resolution we must use smaller (hence more) crystals.
  In general, the FWHM dependent on the dimension of the crystals is calculable as

$$FWHM_D = \frac{w_D}{2}$$

  where w_D is the crystal's dimension, typically between 4 and 8 mm, hence the related uncertainty is about 2-4 mm;

- * **not collinearity of the emitted photons** → if the interaction is not at rest the photons may be emitted in different directions and the corresponding uncertainty is around 1.5-2 mm;

- **positron range in matter before interacting**→ $FWHM_P = 0.1 - 0.5$ mm;

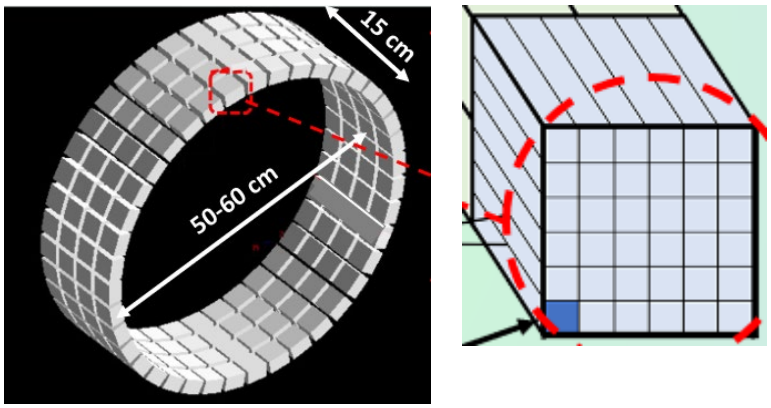
… plus other effects, such as the crystal's efficiency (maximum at the center, it degrades outwards), the uncertainties related to the reconstruction program used in * and the scintillating block's performance…

… all these contributions are taken into account to define the total FWHM

$$FWHM_{TOT} = \sqrt{FWHM_D{}^2 + FWHM_N{}^2 + FWHM_P{}^2 + FWHM_B{}^2}$$

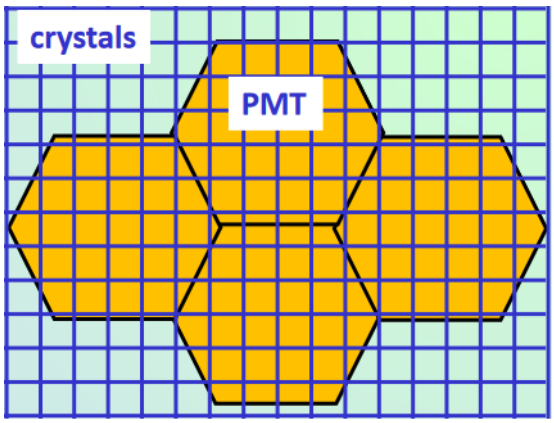
… the typical total spatial resolution for a PET process may vary between 2.5 to 4.5 mm.

In a little more detail, each ring is subdivided into modules, and each module is subdivided into crystals representing the single detector element



… each ring is formed by ~40 blocks of 6x6 or 8x8 crystals, for a total of ~300 blocks and ~15000 crystals per machine.

Theoretically, each crystal would require a photomultiplier: too expensive.
An alternative solution consists of using just a limited number of photomultipliers covering more crystals and perform a weighted mean on the counts in order to reconstruct the position of the detected photon



… this cheaper alternative allows to achieve the resolution needed.

An important requirement these crystals must satisfy is to produce a lot of light per particle in order to have more precise measurements (because fluctuations' statistics is lower); for this, some specific materials are used to build scintillators, the most used of which are NaI(Tl), BGO and LSO.
Regarding BGO, the luminosity intensity produced is very low compared to the one of the other twos, 15 instead of 100 (NaI(Tl)) and 50-75 (LSO).
So why is it still used?
Because new PETs take not only the position of the gamma, but also its time of arrival, so a crystal which reacts very fast to the gamma arrival is required: BGO is a very fast detector which allows to do this type of measurements, while NaI(Tl) is not so fast, so we need a compromise between the intensity of light produced and the reaction speed.

10. New frontiers

Theranostic → therapy and diagnostic at the same time.

Let's consider Carbon: as we know, C-12 makes nuclear interactions and produces charged particles and positrons; in particular, C-10 and C-11 are beta plus emitters, hence by coupling a PET it is possible to track the exact position of the beam during the treatment, this is very important because it would allow to adjust the beam in accordance to variables such as the patient's movements and breath, and also to evaluate if the calculations done to design the treatment are correct and in case are not to modify them.
Also, a dose profiler can be used, in order to detect also the other fragments produced.
The experiment INSIDE has proven this way is possible, hence theranostic may represent the evolution of treatment in the next future ___

Which is the maximum energy used for protons and Carbon in hadrontherapy?
max E p → 250 MeV
max E C → 440 MeV.

… why for C the energy is greater?
Because C has higher Z hence -dE/dx is higher hence to reach the same range a higher E is required.

What is the cross section?
The cross section is the interaction's probability between the incoming particle and the scattering centers → it can be viewed as the superimposed area between the particle and the scattering center: the larger the overlapped area the higher the cross section → its dimension is an area, hence its unit of measure is the barn, 1 barn = 10^{-24} cm^2.

… how much is the typical value of gamma's cross section in the human body?
Human body means water, the typical value of cross section for gammas in water are around 1 barn, which drops to fractions of 1 barn for energies of 5-10 MeV typical for treatments → this means that if a deep cancer's treatment is needed, a higher energy gamma beam is required but the cross section is lower, hence a higher dose is needed; on the other side, if a treatment more on the surface is needed, low energies are required hence low doses can be used because the cross section is higher.
In general, we are talking about fractions of barn, which is quite a low value: this means that gammas are able to travel a lot of distance without interacting, crossing all the human body.