2nd ANNUAL ARDENT WORKSHOP

Introductory Lecture on Microdosimetry

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We are well equipped with plots and tables to calculate the effects due to the exposition to known radiation fields.

HOWEVER

What doing when the radiation field is unknown? Or when we have not previous empirical data concerning the effects of that peculiar field?

IS IT POSSIBLE

to perform some kind of measurement, the data of which can be used to assess the biological damage of that radiation field?

MICRODOSIMETRY TRIES

to reply to this old question both with a full theoretical body, which *differently describe* the radiation interaction and with the matter, and with special detectors that able to measure new physical quantities.

The energy paradigm

Assumption: the effects are proportional to the absorbed energy

Macroscopic world.
It works.

M E S O S C O P I C W O R L D

Microscopic world.
It das not works.

Initial radiation effects occur in the mesoscopic world: 1 nm – 1 µm

The mesoscopic world is highly structured

Ionisation events occur stochastically around a carbon-ion track

The DNA wire and nucleosomes

The absorbed- energy density (absorbed dose) loses its original meaning in the mesoscopic world, since neither the radiation and the target can be described with continuous functions.

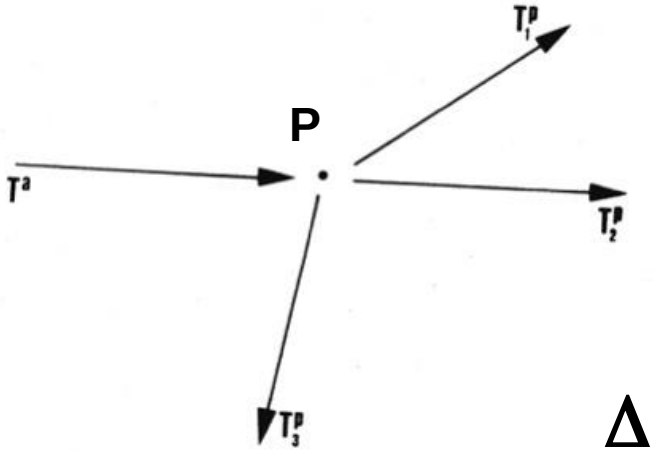
MICRODOSIMETRY

Microdosimetry is the theoretical and experimental investigation of imparted-energy *probability distributions* in a *"macroscopic"* volume of matter that is crossed by a *single ionizing particle*.

Dosimetry is the theoretical and experimental investigation of the *mean* imparted-energy in a "point" of the irradiated volume.

Microdosimetry is not a "small" dosimetry or a "microscopic" dosimetry

Ionizing particles transfer energy to the target through collisions with atoms and nuclei



Example of collision in the point P with 3 emerging particles

$$\Delta\varepsilon = T^a - \sum_i T_i^p + Q$$

Q ᵕ expended energy in the (possible) nuclear reaction

T^a ᵕ primary particle kinetic energy

T^p ᵕ secondary particle kinetic energy

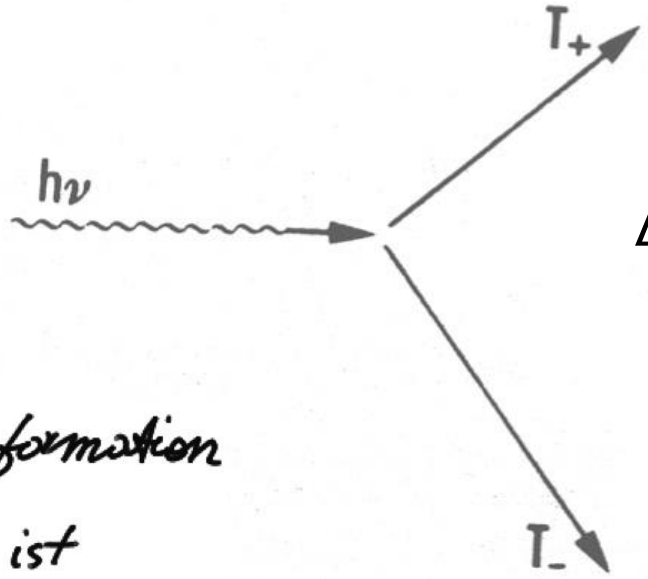
The energy transfer modalities are three

Interactions with Q-value < 0

Interactions with Q-value = 0

Interactions with Q-value > 0

Q < 0



$$\Delta\varepsilon = T^a - \sum_i T_i^p - |Q|$$

Example of pair formation

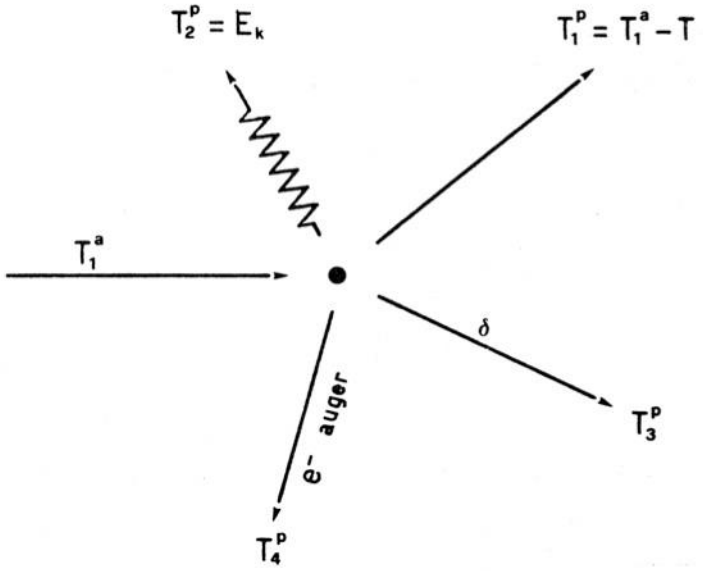
The photon energy ist converted in kinetic energy and mass of e^- and e^+

$$\Delta\varepsilon = Tr \approx 0$$

T_r ᵕ the small residual energy of the recoil, if it exists

Q = 0

Charged particle interacts with atomic electrons



$$\Delta\varepsilon = T^a - \sum_i T_i^p$$

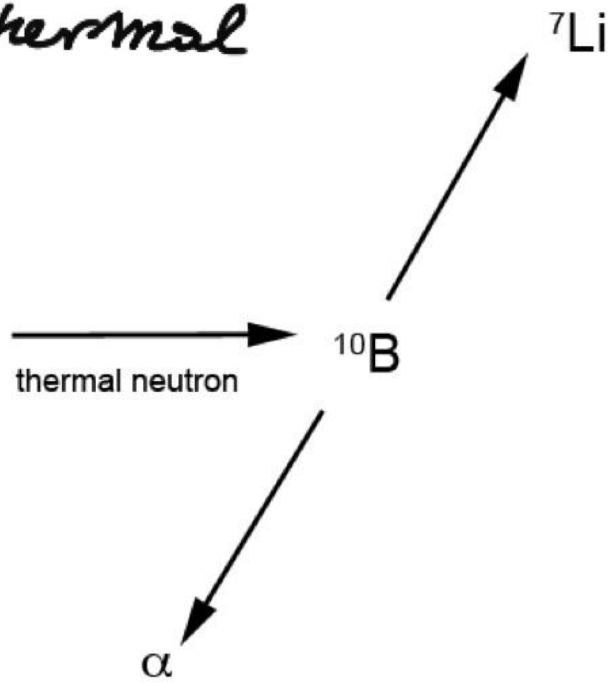
$\Delta\varepsilon > 0$

$\Delta\varepsilon =$ energy expended for exitations, variation in binding energy, heat, non-ionizing recoils, etc…

All the interactions of interest for microdosimetry belong to this category

Q > 0

The boron nucleus captures a thermal neutron.



$$\Delta\varepsilon = T^{a} - \sum_{i} T_{i}^{p} + |Q|$$

$$\Delta\varepsilon = Tr \approx 0$$

$T_a = 0$

T_r is the residual energy of all non ionizing particles

The transferred-energy time duration

The particle velocity ***v*** is:

$$v^2 = \left[1 - \frac{M^2}{(T+M)^2}\right] \cdot \beta^2$$

M ≡ particle mass
T ≡ particle kinetic energy
β ≡ particle / light velocity

Nucleus radius :

$$R = R_0 \times A^{1/3}$$

A ≡ particle mass number
$R_0 \simeq 10^{-15}$ m

Atoms radius R_{atom} depends on ***Z***, temperature, chemical bond and molecular bond

$R_{HYDROGEN} \simeq 2.5 \cdot 10^{-11}$ m

$R_{FERMIO} \simeq 2.9 \cdot 10^{-10}$ m

The interaction time of a minimum ionising energy (10 eV) particle

Interaction with the nucleus: ***~10^{-21} s*** for an electron ***~10^{-19} s*** for proton

Interaction with a hydrogen atom: ***~10^{-16} s*** for an electron ***~10^{-15} s*** for proton

Interaction with a fermio atom: ***~10^{-15} s*** for an electron ***~10^{-14} s*** for proton

The energy-degradation time duration

The physical-chemical stage: 10^{-11} – 10^{-12} s

The absorbed energy gives rise to primary chemical species, which are highly unstable. At the end, only few free radicals survive

The chemical stage: 10^{-8} s

To the end, free radicals like ***OH***, ***H*** and e_{aq} slow down, diffuse and reacts with the medium molecules. At the end of this stage there is the chemical equilibrium.

The biological-physiological stage

At the end of the chemical stage, the biological system reacts to the primary damages produced directly by the ionizing particle or indirectly by the free radicals. This stage can last a long time.

Thick targets: the spatial inchoate distribution

The energy transferred $\Delta\varepsilon$ in the point *P* does not depend on the time neither on the target volume

When the target is thick, the ionising particle interacts in different points P_j

The spatial distributions of P_j is called *inchoate distribution*

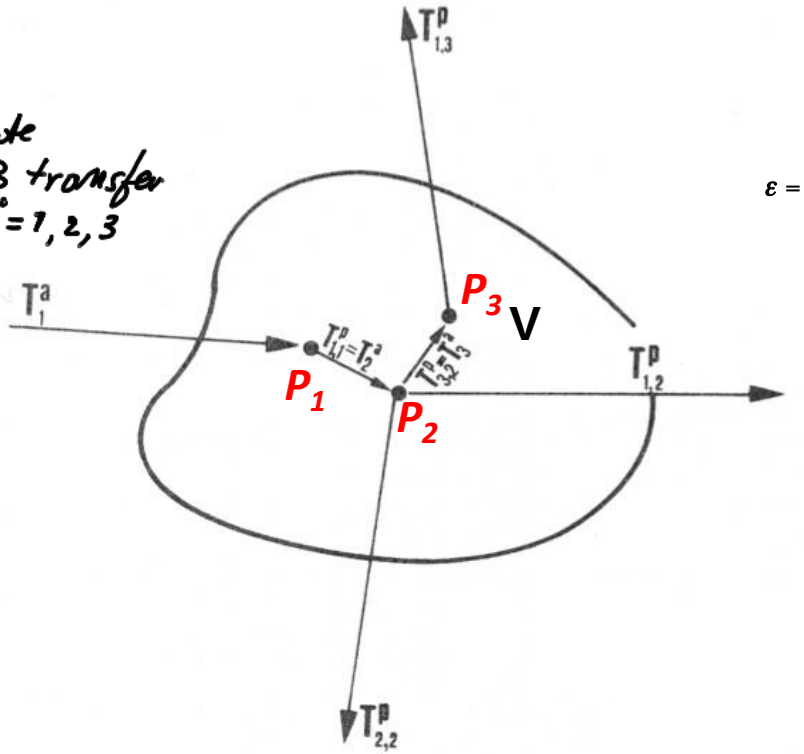
Are all the $\Delta\varepsilon_j$ contemporary?

A slow (10 eV) oxigen nucleus passes through 1 μm target in **about 10^{-10} s**

It is a good approximation to assume that all the P_j transfer points are contemporary

The imparted energy ε *in a volume V*

Example of inchoate distribution with 3 transfer points P_j with $j = 1, 2, 3$



$$\varepsilon = \sum_1^3 \Delta\varepsilon_j = \sum_j T^a_j - \sum_j \sum_i T^p_{ij} + \sum_j Q_j$$

$j \equiv$ transfer point

$i \equiv$ emerging particle at the transfer point j

Since the particle $j+1$ arriving at P_{j+1} is one of the particles leaving P_j:

$$\varepsilon = T^a_1 - \sum_{ij} T^p_{ij} + \sum_j Q_j$$

where T^p_{ji} is the kinetic energy of all the particles leaving the volume V

The event

"*An event is the imparted energy to the volume **V** by an ionizing particle entering into the volume **V** or by a radioactive decay inside it.*"

The ***event size*** is the energy-imparted **value** ε

The event size is 0 when

$$T_1^a = \sum_{ij} T_{ij}^p - \sum_j Q_j$$

The event site and its size

"The volume ***V*** is the event ***site***"

"The site mean chord $\bar{d}$ is the site ***size***"

If ***V*** is a convex body, $\bar{d} = 4V / A$

where A is the volume surface

For a sphere $\bar{d} = 2/3 \times D$

where D is the sphere diameter

For a cylinder of diameter ***D*** and height ***D***

$$\bar{d} = 2/3 \times D$$

N.B. The expression "site size" is also used to point out the "equivalent value" of ***D***. See later on.

The mean imparted energy

The mean imparted energy $\bar{\varepsilon}$ is a deterministic quantity, while ε is a stochastic quantity

$$\bar{\varepsilon} = \frac{\sum_{0}^{N} \varepsilon_j \cdot n_j}{\sum_{0}^{N} n_j}$$

N number of single events in V

ε_j energy imparted to V by the jth event

Since the main contribution to the imparted energy is due to reactions with $Q = 0$, $\bar{\varepsilon}$ can be approximated with the energy released by a charged particle in continuous slowing down approximation (CSDA).

$$\varepsilon = T_1^a - \sum_{ij} T_{ij}^p$$

$$\bar{\varepsilon} = \left(S/\rho\right)_V \cdot \rho_V \cdot \bar{d}_V$$

mass stopping power in the volume V

density of the volume V

size of volume V

The site equivalence

"Two different sites are said to be equivalent when the ***mean imparted energies*** to the sites are equal"

The equivalence of a human tissue site and a gas site is of great interest for experimental microdosimetry

$$\bar{\varepsilon}_T = \bar{\varepsilon}_G$$

Substituting:

$$\left(S/\rho\right)_T \cdot \rho_T \cdot \bar{d}_T = \left(S/\rho\right)_G \cdot \rho_G \cdot \bar{d}_G$$

If the gas has the same atomic composition of the tissue, then $(S/\rho)_T = (S/\rho)_G$, then

$$\rho_T \cdot \bar{d}_T = \rho_G \cdot \bar{d}_G$$

this equation is used in experimental microdosimetry to properly fill the TEPC with a tissue-equivalent gas mixture

Two equivalent sites have different mass

The mass of a site of density ρ and mean chord $\bar{d}$ is:

$$M = f \cdot \rho \cdot \bar{d}^3$$

where f is volume-shape-depending constant

Therefore, if the site shapes are equal:

$$M_G = M_T \left(\frac{\bar{d}_G}{\bar{d}_T} \right)^2 \cdot \frac{(S/\rho)_T}{(S/\rho)_G}$$

The masses of two equivalent sites of the same shape scale with the square of the mean chord ratio

Limitations of the equivalence definition

It does not takes into account the matter phase

It does not takes into account the particle track size. When the lateral extension of the primary track is larger than the site mean chord, we enter in the "nanometric domain".

The maximum δ-ray energy

$$T_{el}^{max} = 4 \times \frac{m_{el}}{m_p} \times T_{spec}$$

electron mass

ion energy per unit of mass

proton mass

number of electrons of kinetic energy T emerging from the ion track

$$N_{el}(T) \gg 1/T^2$$

However

Therefore 99% of δ-rays have **T < 1 keV**

When the site equivalent size is < 100 nm we enter into the nanometric domain

The nanometric domain

The nanometric world is weird

$$\bar{\varepsilon} \neq \left(S/\rho\right)_V \cdot \rho_V \cdot \bar{d}_V$$

Since CSDA is no more a good approximation

number of ionisations in the volume V

mean energy to create an ion pair at the energy T

$$\nu \cdot w^a(T) \neq \varepsilon$$

Since $w^a(T)$ becomes a stochastic quantity

$$f(\nu) \neq f(\varepsilon)$$

Since ν fluctuates differently than ε

N.B. $w^a(T) = \P(W^a(T))/\P T$

The lineal energy, *y and the quality concept*

It is the quotient of the energy imparted to the volume, by a single particle or radioactive decay inside it, and the volume mean chord

$$y = \frac{\varepsilon}{\bar{d}}$$

The physical dimension is ***J/m*** but, similarly to LET, ***y*** is used to be expressed in ***keV/µm,*** where the linear dimension is that one of the tissue-equivalent site size.

Differently than ***LET***, ***y*** is a stochastic variable, the value of which fluctuates. For a given site size and radiation field, there is only some probability ***F(y)*** that the lineal energy is equal or less than ***y***. The probability density function of ***y*** is: ***f(y)=∂F(y)/∂y***

We can define ***D(y)*** as the fraction of dose delivered by an event equal or less than ***y***. The dose probability density, called also weighted distribution, is: ***d(y)=∂D(y)/∂y***

The ***y*** mean-values define the ***"quality"*** of the radiation field for a given site size.

The y mean-values

first moment of f(y)

The frequency-mean lineal energy

$$\bar{y}_F = \int y \times f(y) \times dy$$

The dose-mean lineal energy

$$\bar{y}_D = \int y \times d(y) \times dy$$

The dose probability density can be calculated, if ***f(y)*** is known

$$d(y) = \frac{y}{\bar{y}_F} f(y)$$

The dose-mean lineal energy is then

$$\bar{y}_D = \frac{1}{\bar{y}_F} \int y^2 \times f(y) \times dy$$

second moment of f(y)

The specific energy, *z*

Differently than y, z may be due to 1 or more events

Z distributions due to 1 energy deposition event only

It is the quotient of the energy imparted to the volume, by one particle or a radioactive decay inside it, and the volume mass

$$z = \frac{\varepsilon}{m}$$

The physical dimension is ***J/Kg*** but, similarly to absorbed dose, ***z*** is used to be expressed in ***Gray,*** where the mass ***m*** is that one of the site.

Differently than ***absorbed dose***, ***z*** is a stochastic variable, the value of which fluctuates. For a given site size and radiation field, there is only some probability $F_1(z)$ that the specific energy, due to only 1 event, is equal or less than ***z***. The associated probability density function of is:

$$f_1(z)=\partial F_1(z)/\partial z$$

We define $D_1(z)$ as the fraction of dose delivered by an event equal or less than ***z***. The associated probability density, is:

$$d_1(z)=\partial D_1(z)/\partial z$$

The *z mean values for 1 single event*

The frequency-mean specific energy per event

$$\bar{z}_{1F} = \int z \times f_1(z) \times dz$$

The dose-mean specific energy per event

$$\bar{z}_{1D} = \int z \times d_1(z) \times dz$$

The dose- and frequency- probability densities are each other depending

$$d_1(z) = \frac{z}{\bar{z}_{1F}} f_1(z)$$

Therefore, the dose-mean specific energy per event

$$\bar{z}_{1D} = \frac{1}{\bar{z}_{1F}} \int z^2 \times f_1(z) \times dz$$

Relationship between y and z

for single event distributions only

$$y = \frac{\varepsilon}{\bar{d}} \qquad z = \frac{\varepsilon}{m}$$

Therefore

$$y = \frac{m}{\bar{d}} \cdot z = \frac{\rho \cdot V}{\bar{d}} \cdot z = \frac{\rho \cdot V}{4\frac{V}{A}} \cdot z = \frac{\rho \cdot A}{4} \cdot z$$

$y = 4.902 \cdot Z \cdot D^2$ $\qquad$ $z = 0.204 \cdot y / D^2$

$y = 7.365 \cdot z \cdot D^2$ $\qquad$ $z = 0.136 \cdot y / D^2$

where

Equivalent-site diameter ***D [µm]***
Lineal energy ***y [keV/µm]***
Specific energy ***z [Gray]***

The multi-event specific energy ➡ the microdosimetry-dosimetry bridge

z distribution due to 0 energy-deposition events is the Dirac δ function

$$f_0(z) = \delta(z)$$

z distribution due to 2 energy-deposition events is the convolution of 2 single-event distributions

$$f_2(z) = \int f_1(z') \times f_1(z - z') \times dz'$$

z distribution due to 3 energy-deposition events is the convolution of 3 single-event distributions

$$f_3(z) = \int f_1(z') \times f_2(z - z') \times dz'$$

.....

z distribution due to n energy-deposition events is the convolution of n single-event distributions

$$f_n(z) = \int f_1(z') \times f_{n-1}(z - z') \times dz'$$

N.B. 1) Differently than single-event distributions, multi-event distribution includes the 0 events. 2) $d_n(z)$ is not defined

The absorbed dose is the microdosimetric-distribution mean value

The mean value of the multi-event specific energy distribution ***f(z)*** is:

$$\bar{z} = \int z \times f(z) \times dz$$

By definition the absorbed dose ***D*** is:

$$D = \lim_{m \to 0} \bar{z}$$

For microscopic volumes and a large number of events, we can assume that the specific energy is almost uniformly distributed in the site. Therefore, we can write :

$$D \approx \bar{z}$$

The mean event number for a given absorbed dose ***D*** is:

$$\bar{n} = \frac{\bar{z}}{\bar{z}_{1F}}$$

total dose

single-event dose

The Compound Poisson Process

The multi-event imparted-energy ε is the summation of n independent single-event contributions ε_i, which are Poisson distributed. Also ε_i is the summation of independent $\Delta\varepsilon_i$ energy-transfer points, which are in turn Poisson distributed. The absorbed dose D is therefore the result of a ***Compound Poisson Process*** (convolution of different populations of objects, all of them Poisson distributed).

Let $P(n;\bar{n})$ the probability to get in the site exactly n single events, where $\bar{n}$ is the mean event number at the dose D, then:

$$P(n;\bar{n}) = \frac{\bar{n}^n}{n!} \times e^{-\bar{n}}$$

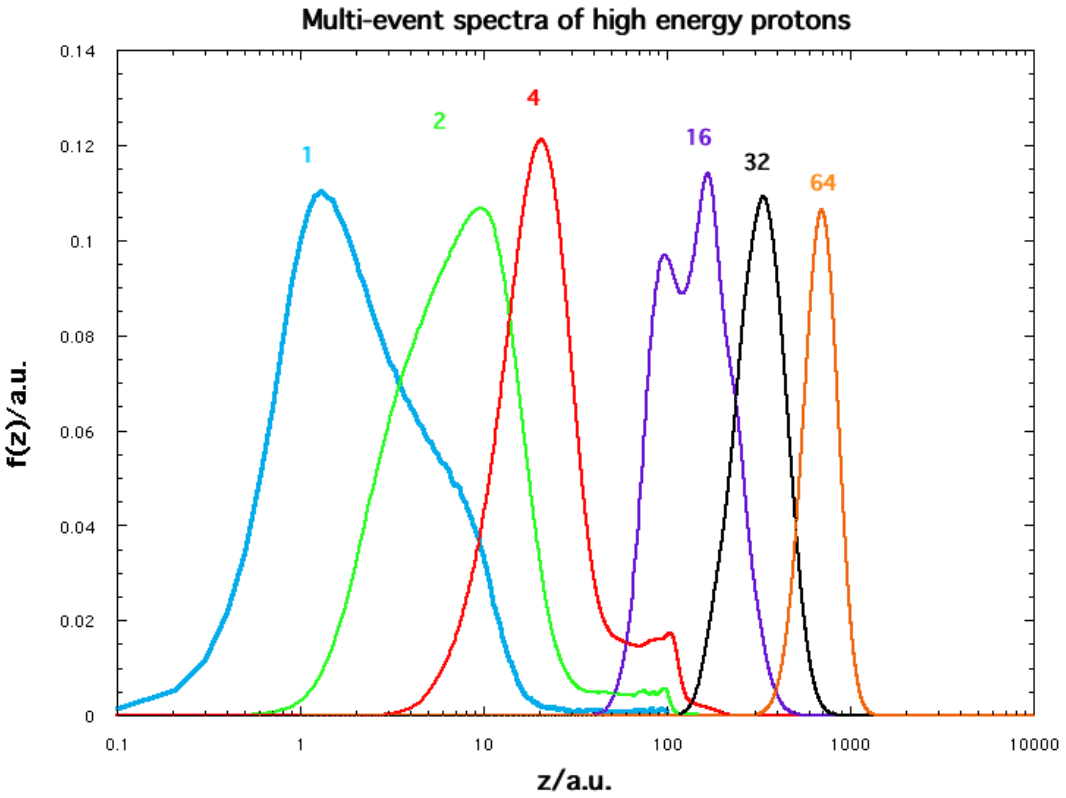
That is:

$$P(n) = \frac{\left(\frac{D}{\bar{z}_{1F}}\right)^n}{n!} \times e^{-\frac{D}{\bar{z}_{1F}}}$$

The specific energy distribution at the dose *D*

It is the probability to get in the site just ***n*** events by the ***n***-event ***z***-distribution:

$$f(z;D)=\sum_{0}^{n}\frac{\left(\frac{D}{\bar{z}_{1F}}\right)^{n}}{n!}\times e^{-\frac{D}{\bar{z}_{1F}}}\times f_n(z)$$



Critical sites

They are the sites that have experienced at least 1 event ≠ 0

In order to calculate the mean specific energy $\bar{z}^*$ in critical sites, it is necessary to remove the 0-event contribution from $\bar{z}$

$$\bar{z}^* = \frac{\int z \times f(z;D) \times dz}{1 - P(0)}$$ ← the macroscopic dose

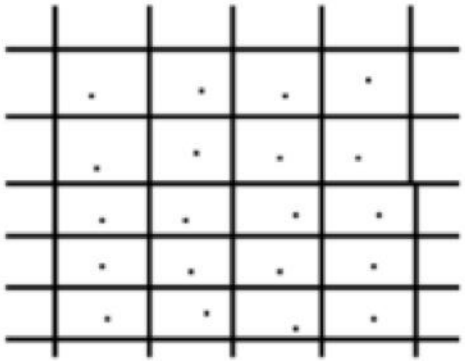
$$\bar{z}^* = \frac{D}{1 - e^{-D/\bar{z}_{1F}}}$$ ← the microscopic dose

The mean event number in critical sites at a given D absorbed dose is:

$$\bar{n}(D) = \frac{D}{\bar{z}^*}$$

Critical sites

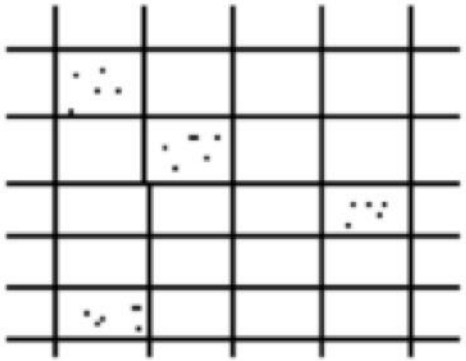
Low LET



$\bar{n}(D) = 20$

$\bar{z}^* = 1$

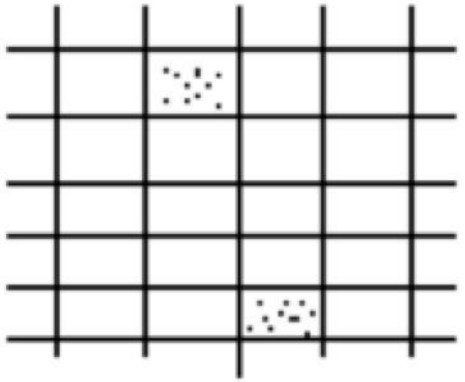
Medium LET



$\bar{n}(D) = 4$

$\bar{z}^* = 5$

High LET



$\bar{n}(D) = 2$

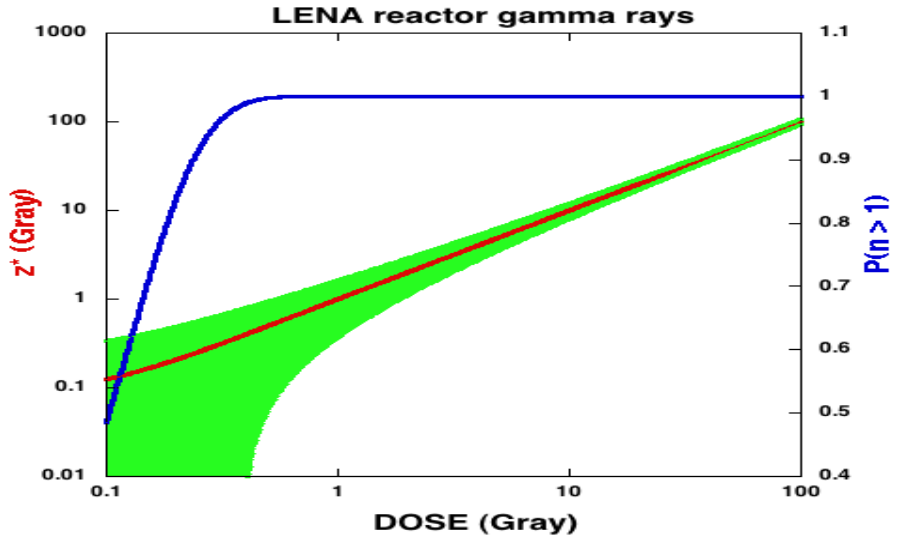
$\bar{z}^* = 10$

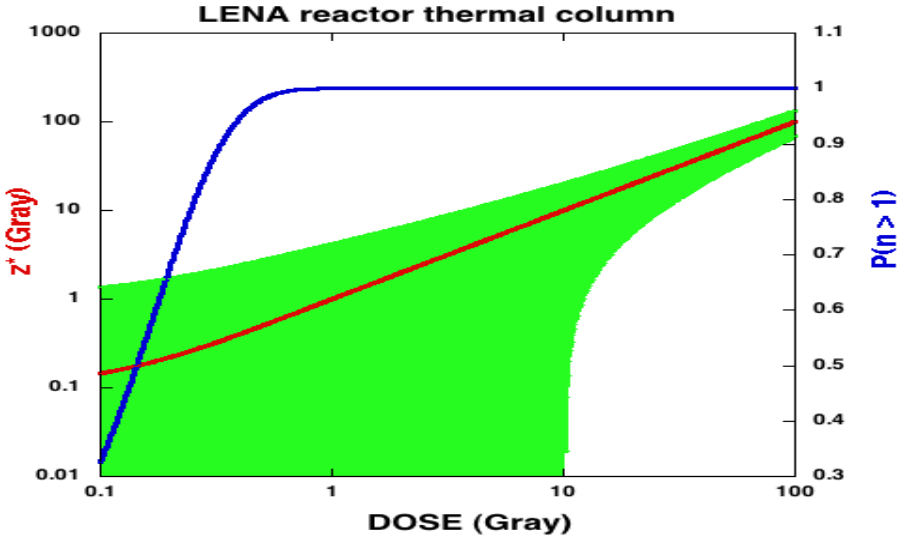
The mean event number in critical sites at a given ***D*** absorbed dose is:

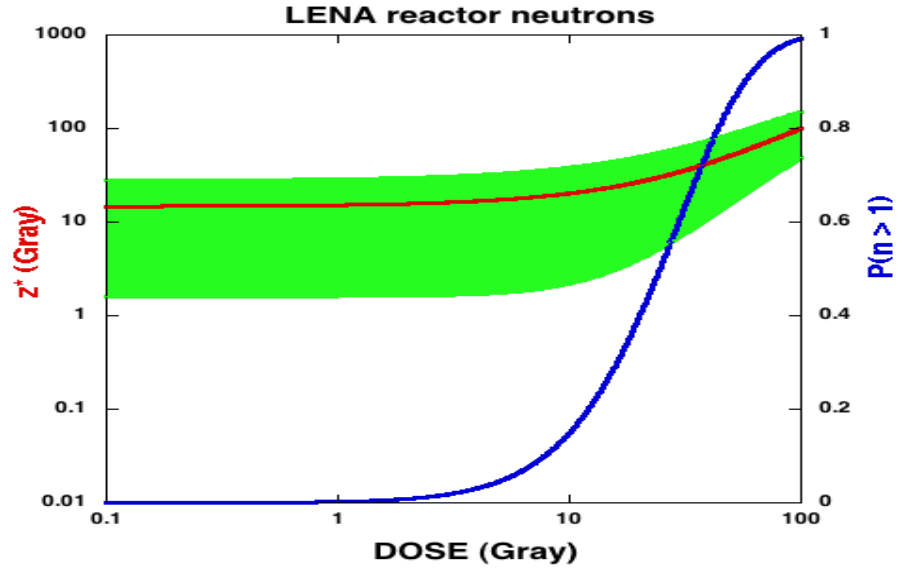
$$\bar{n}(D) = \frac{D}{\bar{z}^*}$$

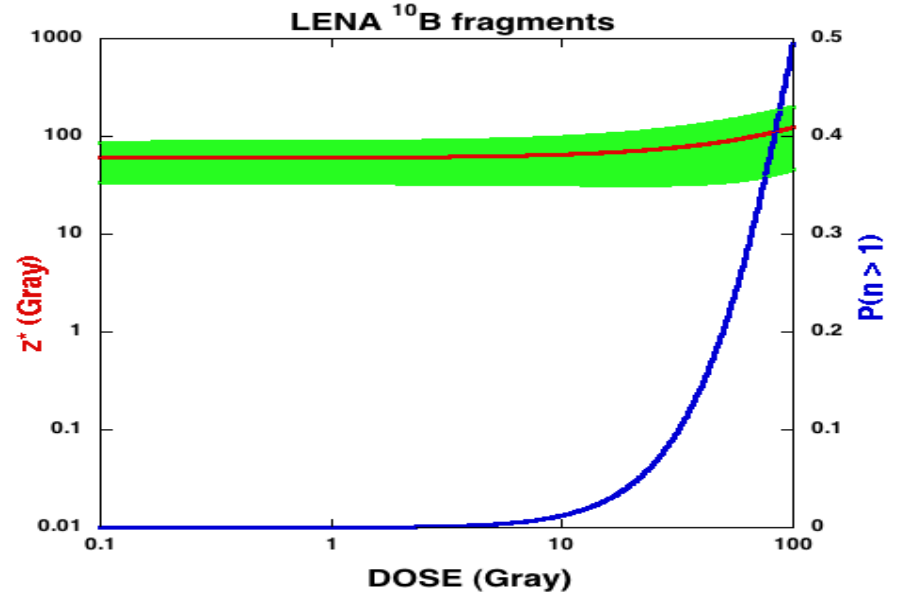
When microscopic and macroscopic dose are equal?

For a given radiation field and site size, it depends on ***the absorbed dose***

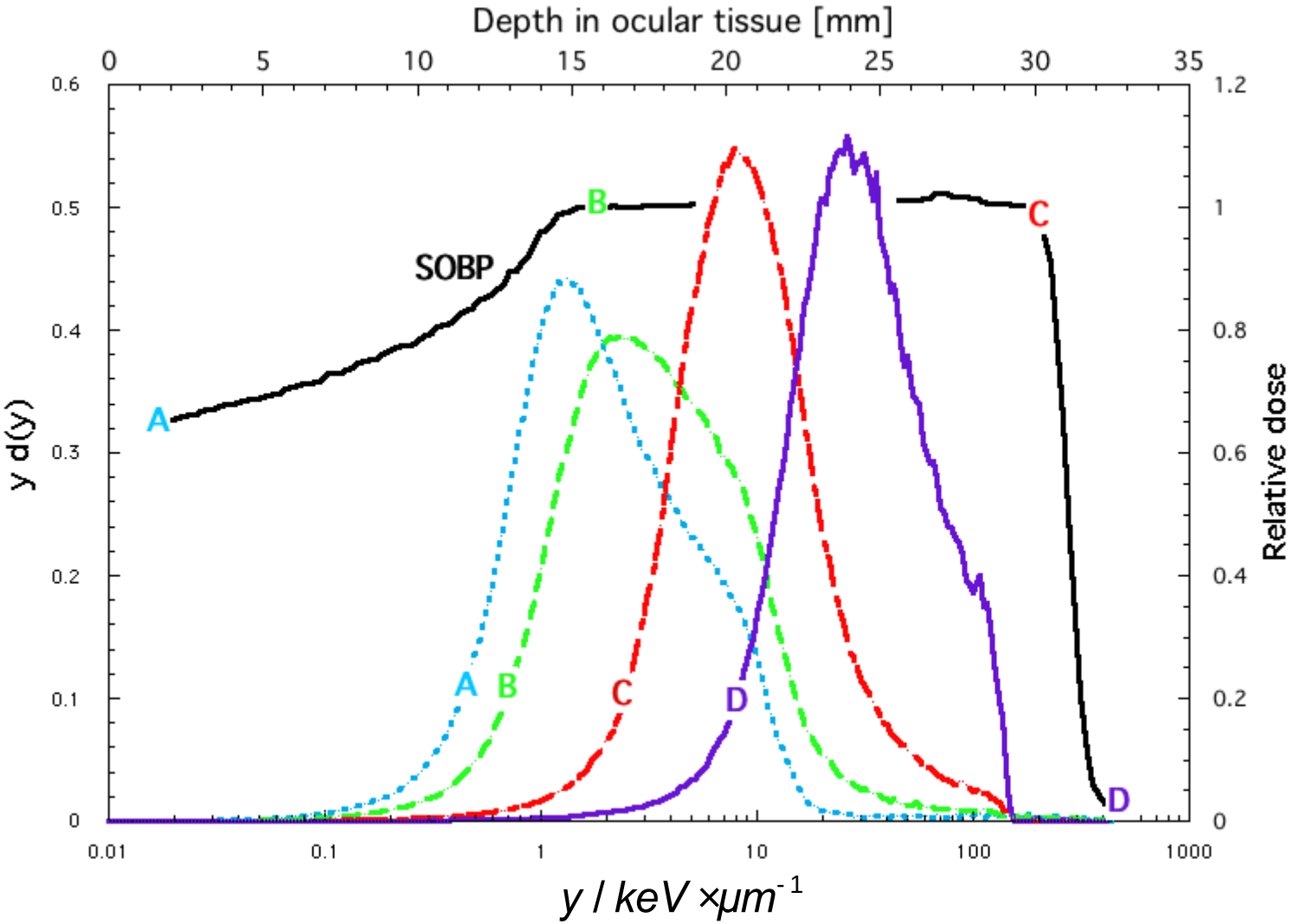




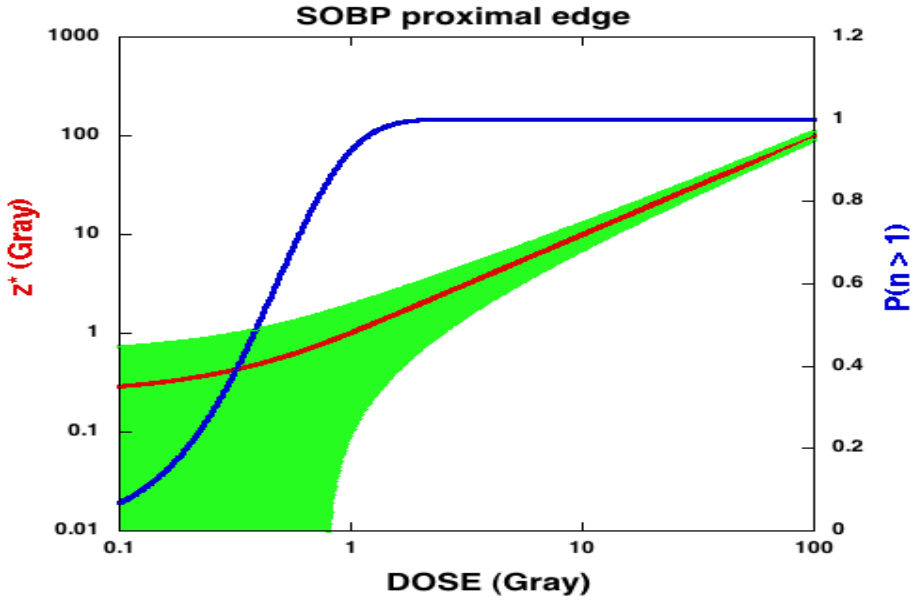


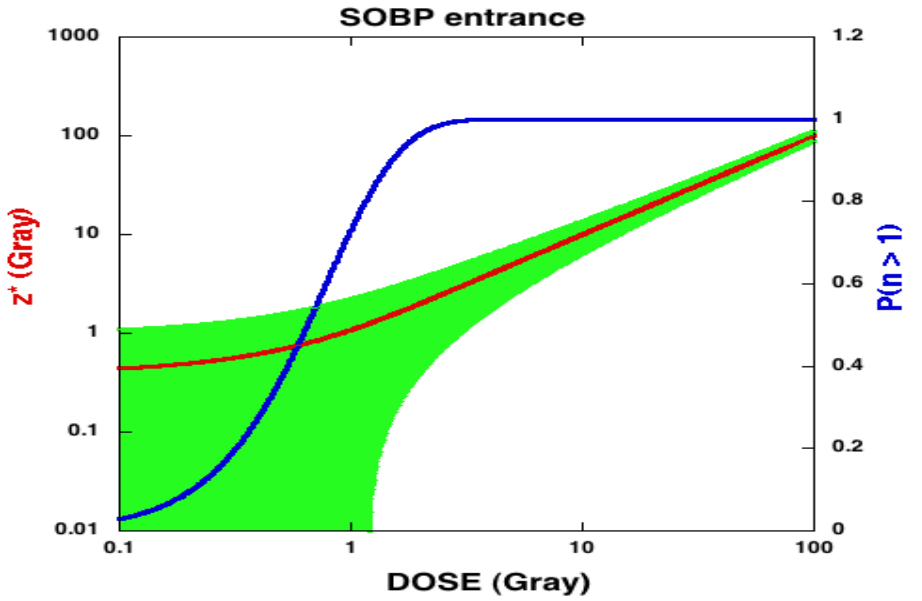


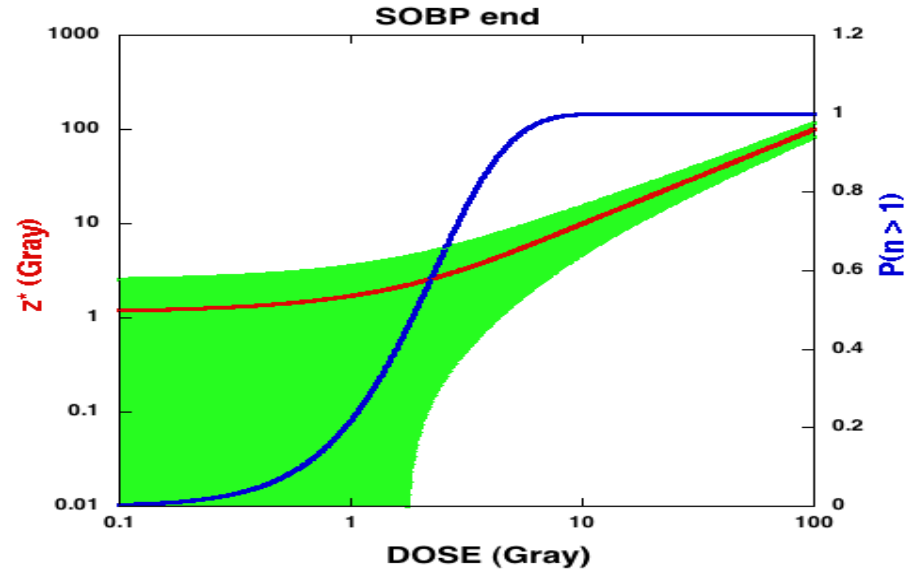
The therapeutic 62 MeV-proton beam of Lacassagne (Nice) medical centre

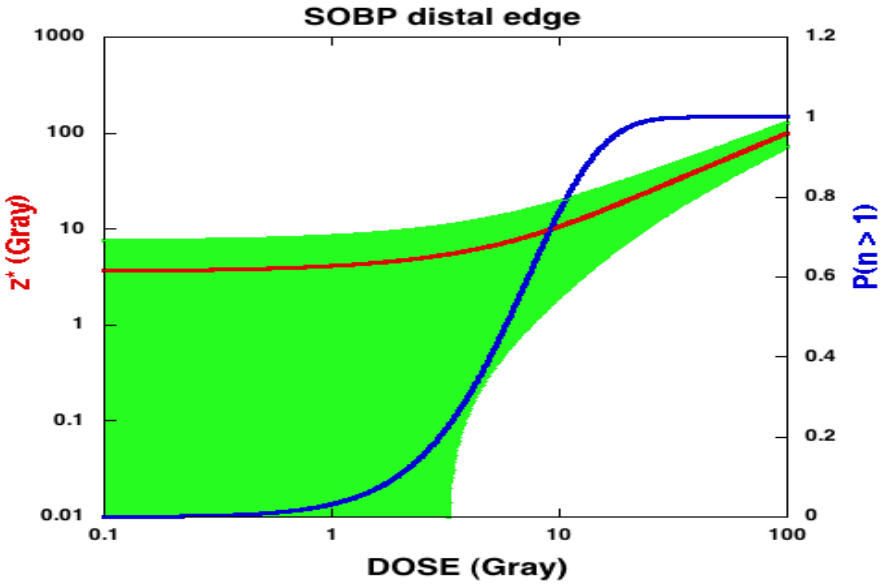


Microscopic and macroscopic dose in therapeutic 62 MeV-proton beam









Suggested lectures

- H.H. Rossi, M. Zaider. *Microdosimetry and Its Applications*. Springer-Verlag Berlin Heidelberg 1996

- Albrecht M. Kellerer. *Fundamental of Microdosimetry*. IN The Dosimetry of Ionizing Radiation. Eds. K.R.Kase, B.E.Bjärngard, F.H.Attix. Academic Press,Inc. 1985, 77-162

- ICRU Report 36. *Microdosimetry*. 1983