Introduction to Radiobiology
Lesson 1

Master of Advanced Studies in Medical Physics
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Radiation damages all kinds of human tissues – both healthy and diseased – as well as other materials

An area of ulceration on the hand, caused by exposure to radiation therapy

Aim of radiotherapy: destroy cancer cells, limit damage to healthy tissues

The purpose of these lessons is:

1. to learn the very basics of biology

2. to gain a basic knowledge of the phenomenology of radiation damage to tissues

3. to understand the fundamentals of therapy optimization, based on the concept of maximum damage to cancer cells, minimum damage to healthy tissues

Radiation damage in materials

Radiation damage in CR-39 plastic

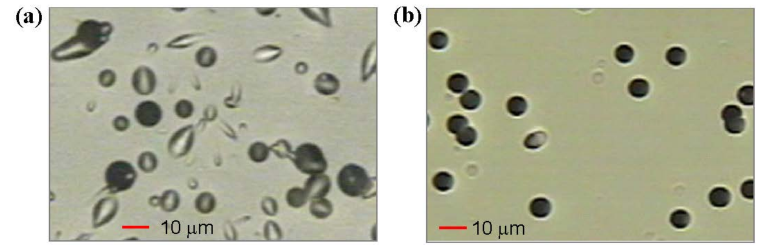
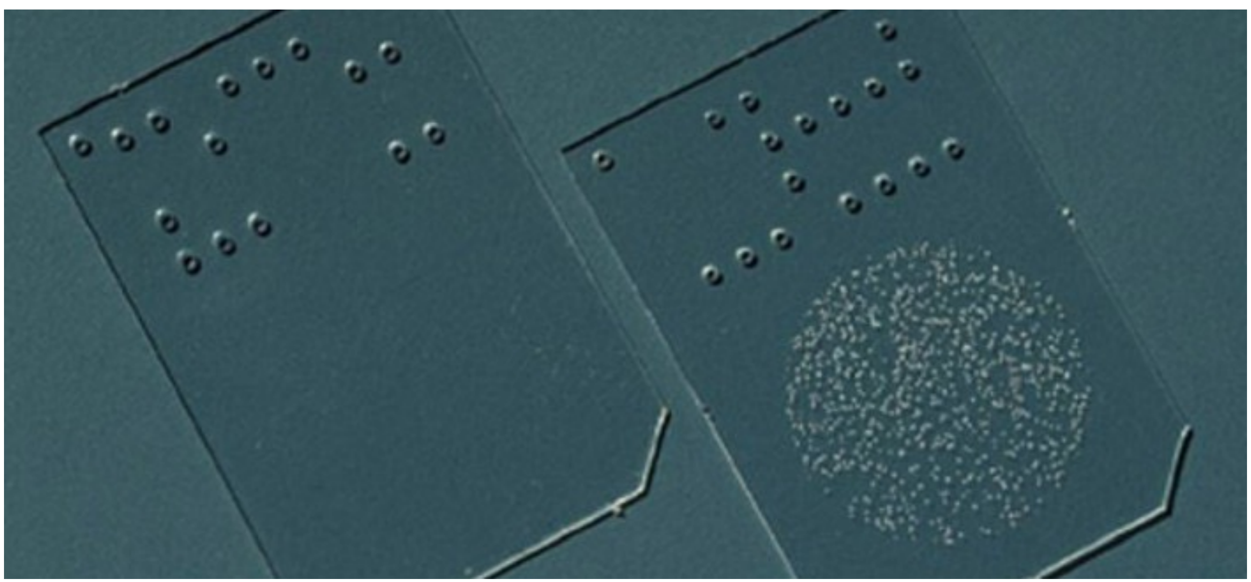


Fig. 3. Typical pictures of etched track pits caused by two different particles. (a) 5.4-MeV α particles (b) ~0.9-MeV protons.



CR-39 dosimeter

Radiation damage to plastic scintillators

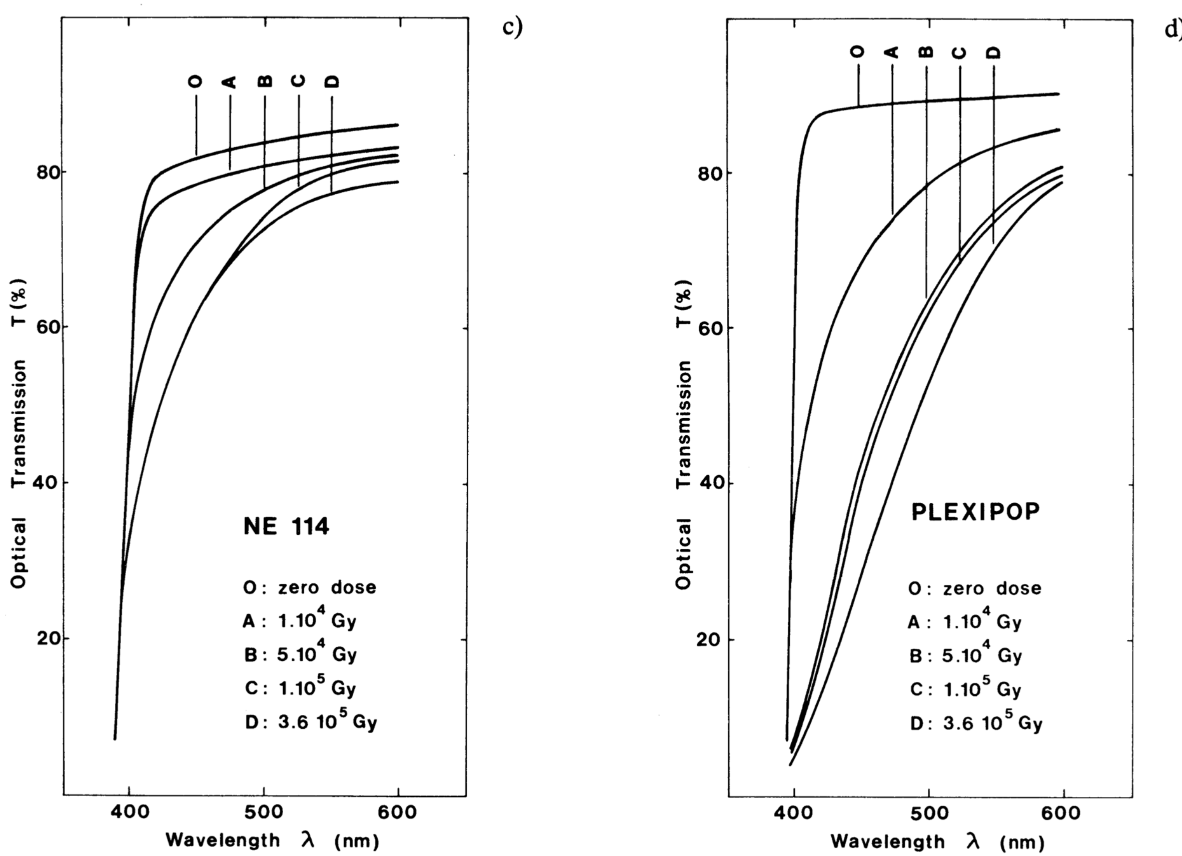


Fig. 1: Optical transmission T as a function of the wavelength through 1 cm of scintillator measured against air as the reference medium: a) NE 102A; b) NE 110; c) NE 114; d) PLEXIPOP 1922. The curves correspond to samples of different total doses as indicated in the figure.

Radiation damage to human tissues is different from damage in inert material

1. The details of damage mechanisms are different
2. Cells and tissues have (limited) self-repair capabilities

In these lessons we are going to learn about both topics

Ionizing radiation

Table I: Comparison of Ionizing Radiation

Characteristic	Radiation (E_K = 1 MeV)				
	Alpha (α)	Proton (*p*)	Beta (β) or Electron (*e*)	Photon (γ or X ray)	Neutron (*n*)
Symbol	${}^{4}_{2}\alpha$ *or* He^{2+}	${}^{1}_{1}p$ *or* H^{1+}	${}^{0}_{-1}e$ *or* β	${}^{0}_{0}\gamma$	${}^{1}_{0}n$
Charge	+2	+1	–1	neutral	neutral
Ionization	Direct	Direct	Direct	Indirect	Indirect
Mass (amu)	4.001506	1.007276	0.00054858	—	1.008665
Velocity (cm/sec)	6.944×10^{8}	1.38×10^{9}	2.82×10^{10}	$c=2.998\times10^{10}$	1.38×10^{9}
Speed of Light	2.3%	4.6%	94.1%	100%	4.6%
Range in Air	0.56 cm	1.81 cm	319 cm	82,000 cm*	39,250 cm*

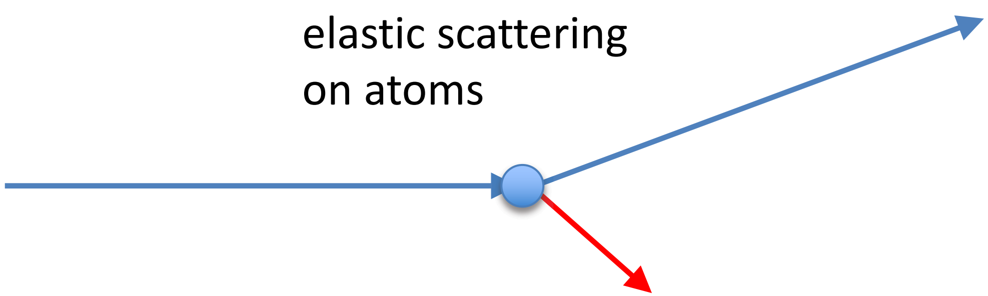
* range based on a 99.9% reduction

Charged particles can lose energy in two ways

I = ionization event
E= excitation event

electronic stopping power (= Linear Energy Transfer)

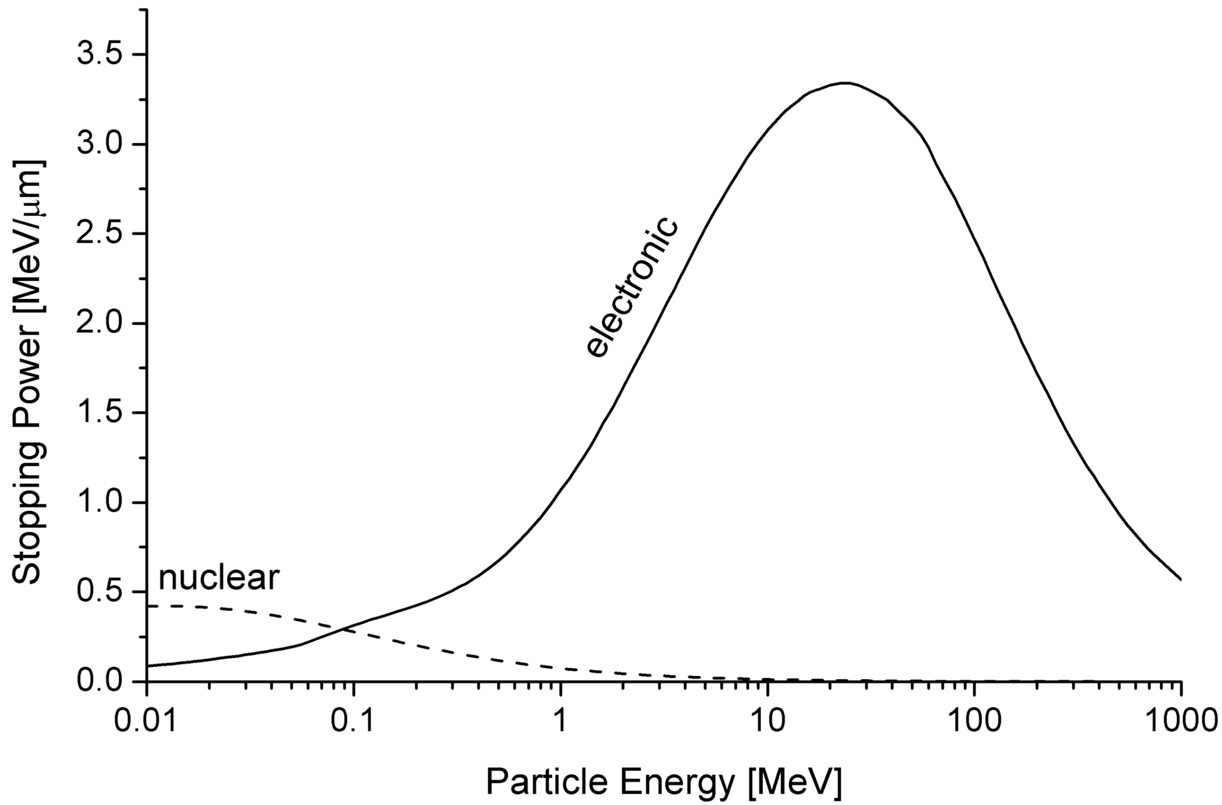
elastic scattering on atoms



atomic recoil carries energy away

nuclear stopping power (coherent atomic scattering)

Atomic stopping power is only relevant at low energy.

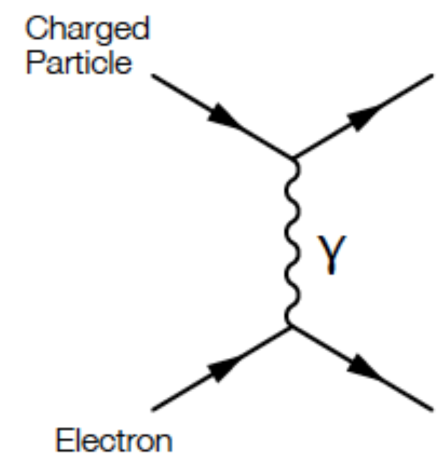


Electronic and nuclear stopping power for aluminum ions in aluminum, versus particle energy per nucleon.

Energy loss by ionization/excitation – dE/dx

For now assume: $Mc^2 \gg m_e c^2$

i.e. energy loss for heavy charged particles
[dE/dx for electrons more difficult ...]



Interaction dominated
by elastic collisions with electrons ...

Bethe-Bloch Formula

$$-\left\langle \frac{dE}{dx} \right\rangle = Kz^2 \frac{Z}{A} \frac{1}{\beta^2} \left[\frac{1}{2} \ln \frac{2m_e c^2 \beta^2 \gamma^2 T_{\max}}{I^2} - \beta^2 - \frac{\delta(\beta\gamma)}{2} \right]$$

$\propto 1/\beta^2 \cdot \ln(\text{const} \cdot \beta^2\gamma^2)$

Energy Loss of Charged Particles

Dependence on

Mass A
Charge Z
of target nucleus

Minimum ionization:

ca. 1 - 2 MeV/g cm^{-2}
[H_2: 4 MeV/g cm^{-2}]

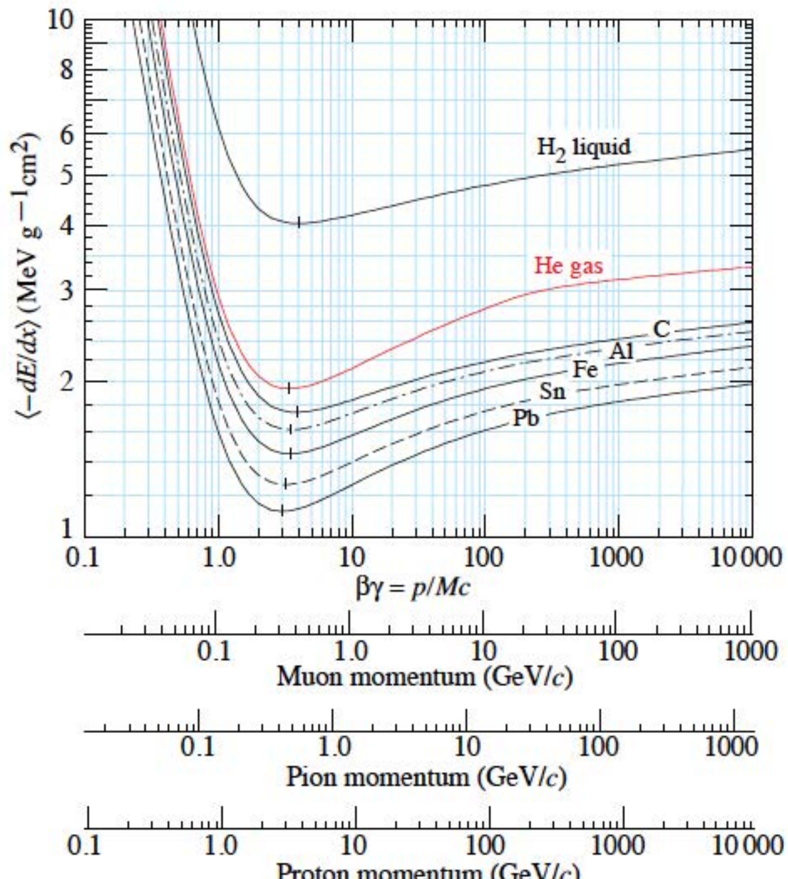
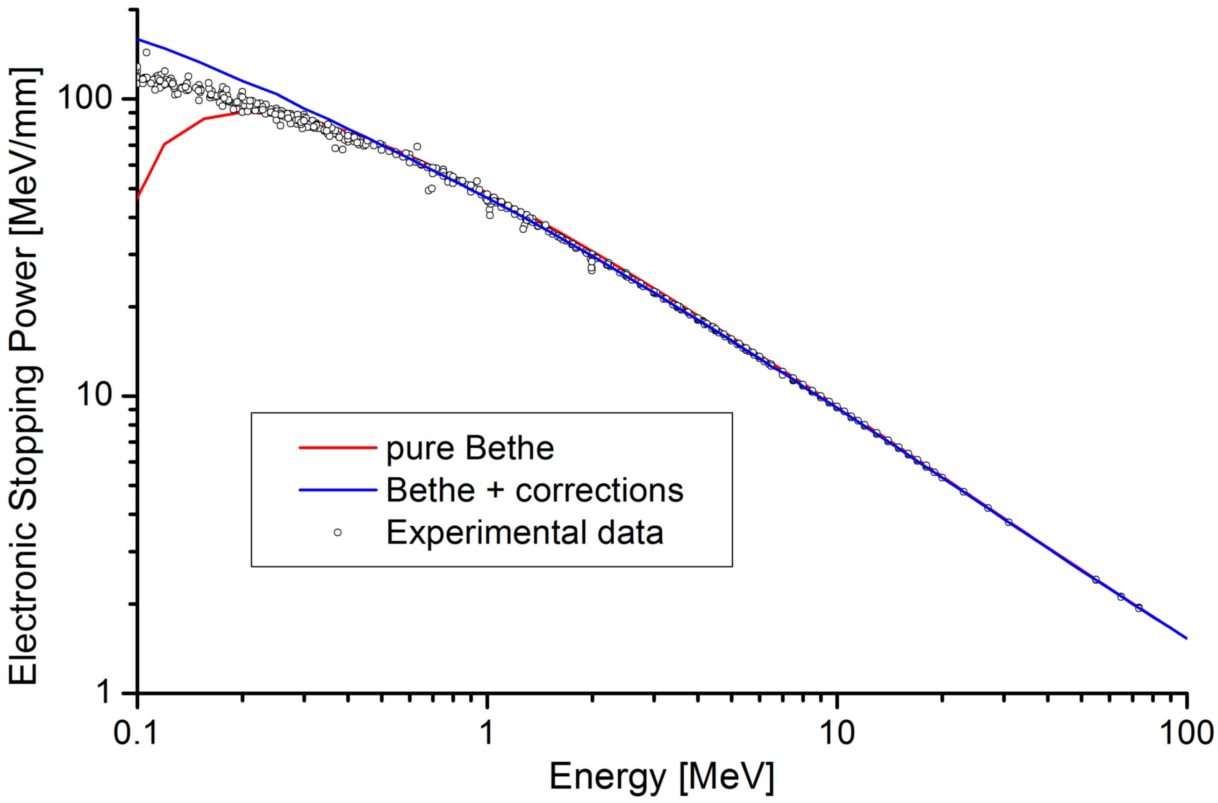


Figure 31.2: Mean energy loss rate in liquid (bubble chamber) hydrogen, gaseous helium, carbon, aluminum, iron, tin, and lead. Radiative effects, relevant for muons and pions, are not included. These become significant for muons in iron for $\beta\gamma \gtrsim 1000$, and at lower momenta for muons in higher-Z absorbers. See Fig. 31.23.

Stopping Power of Aluminum for Protons versus proton energy



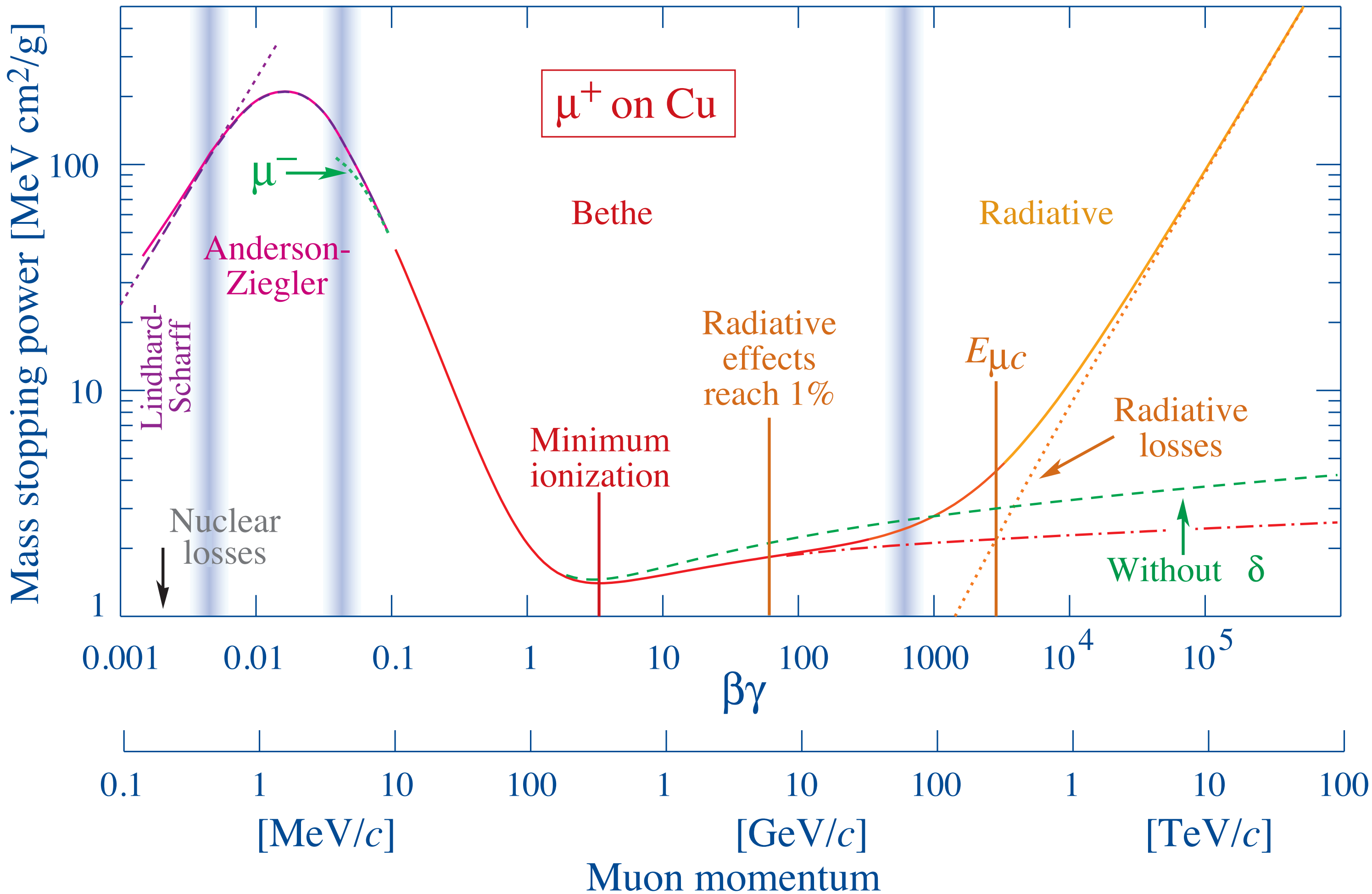


Fig. 33.1: Mass stopping power $(= \langle -dE \;\; dx \rangle)$ for positive muons in copper as a function of $\beta\gamma = p \;\; Mc$ over nine orders of magnitude in momentum (12 orders of magnitude in kinetic energy). Solid curves indicate the total stopping power. Data below the break at $\beta\gamma \approx 0\ 1$ are taken from ICRU 49 [4], and data at higher energies are from Ref. 5. Vertical bands indicate boundaries between different approximations discussed in the text. The short dotted lines labeled π^- illustrate the Barkas effect, the dependence of stopping power on projectile charge at very low energies [6]. $dE \;\; dx$ in the radiative region is not simply a function of β.

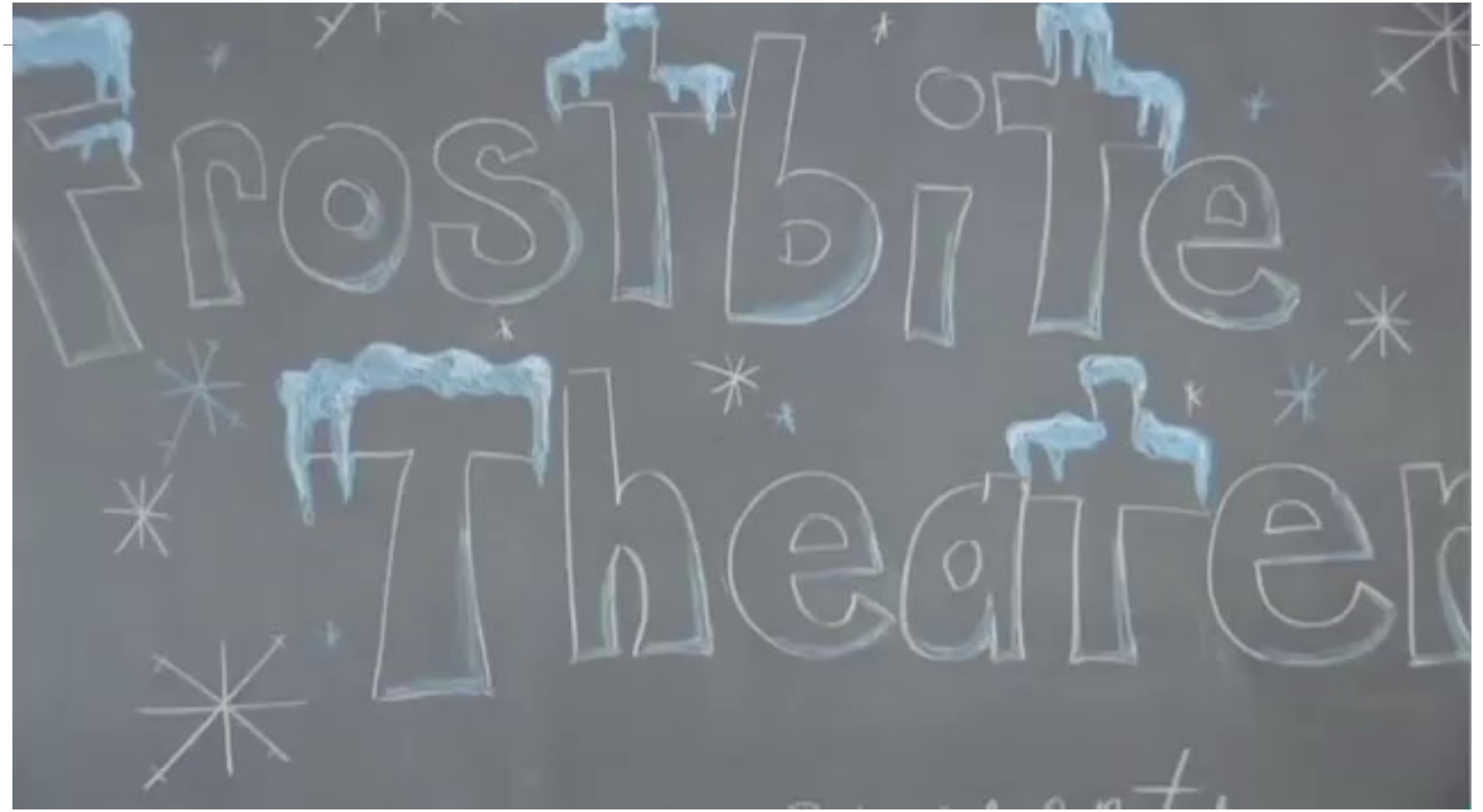
Particles heavier than electrons

$$-\left\langle \frac{dE}{dx} \right\rangle \approx \frac{4\pi}{m_e c^2} \cdot \frac{n z^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0} \right)^2 \cdot \ln\left(\frac{2 m_e c^2 \beta^2}{I \cdot (1-\beta^2)} \right)$$

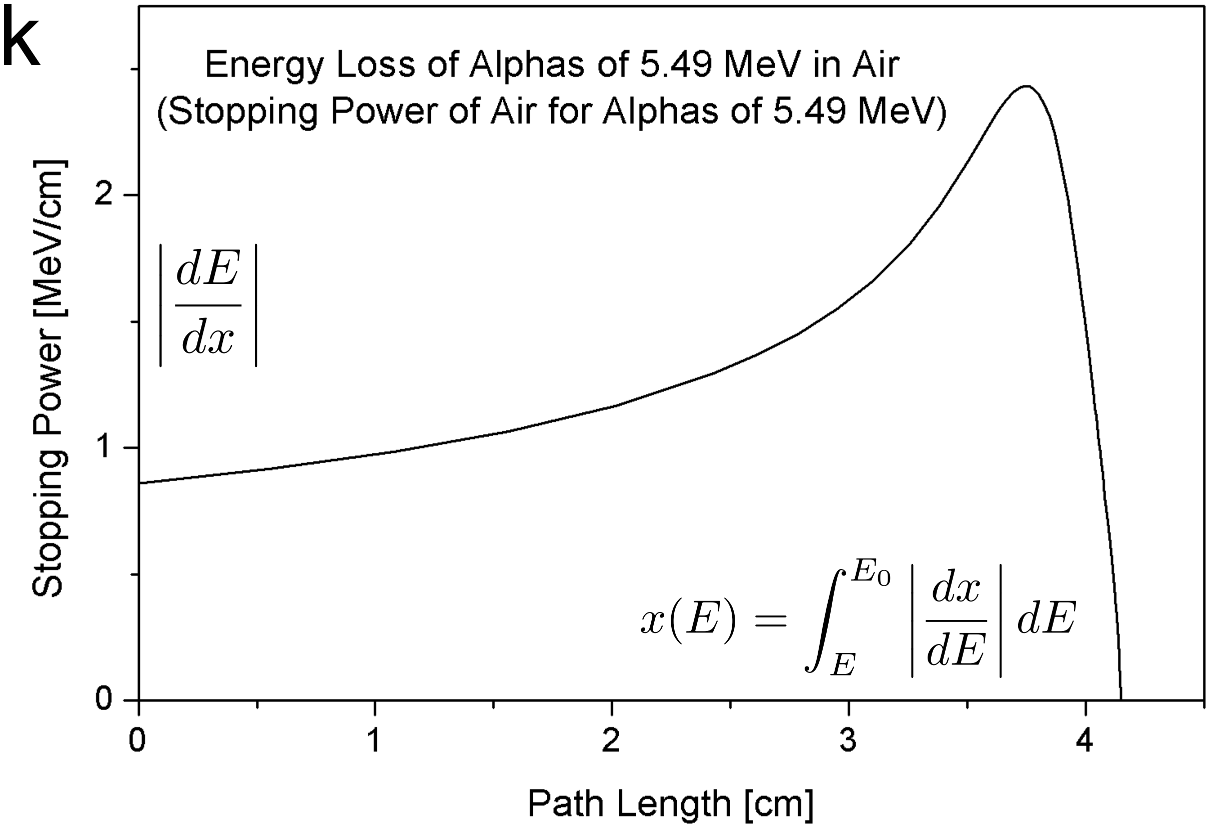
$$n = \frac{N_A \cdot Z \cdot \rho}{A}$$

$$\Rightarrow \quad -\left\langle \frac{dE}{dx} \right\rangle \sim \frac{Z z^2 \rho}{A \beta^2}$$

Particle tracks with the cloud chamber



The Bragg peak



Bragg curve of 5.49 MeV alpha particles in air. This radiation is produced from the initial decay of radon (^{222}Rn). Stopping power (which is essentially identical to LET) is plotted here versus particle range.

(Adapted from the Wikipedia article http://en.wikipedia.org/wiki/Linear_energy_transfer)

Particle Energy Deposit

βγ > 3.5:

$$\left\langle \frac{dE}{dx} \right\rangle \approx \left. \frac{dE}{dx} \right|_{\min}$$

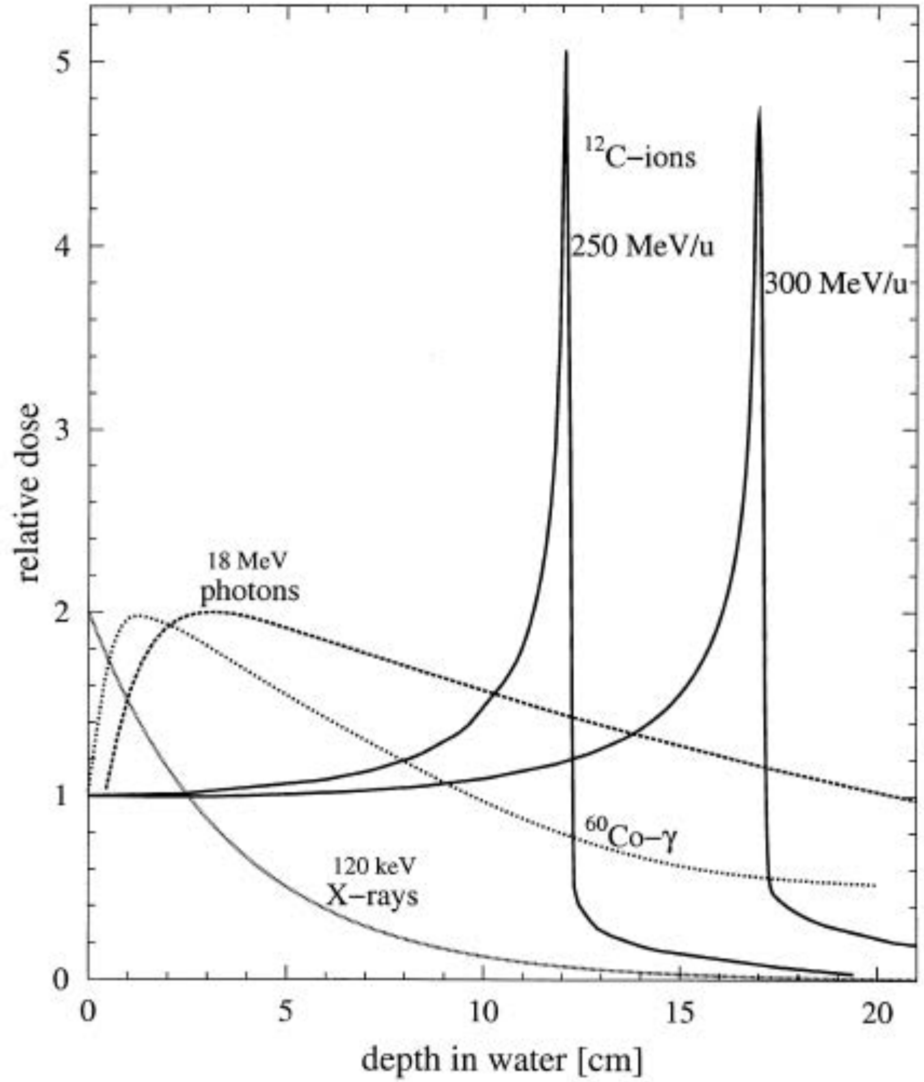
βγ < 3.5:

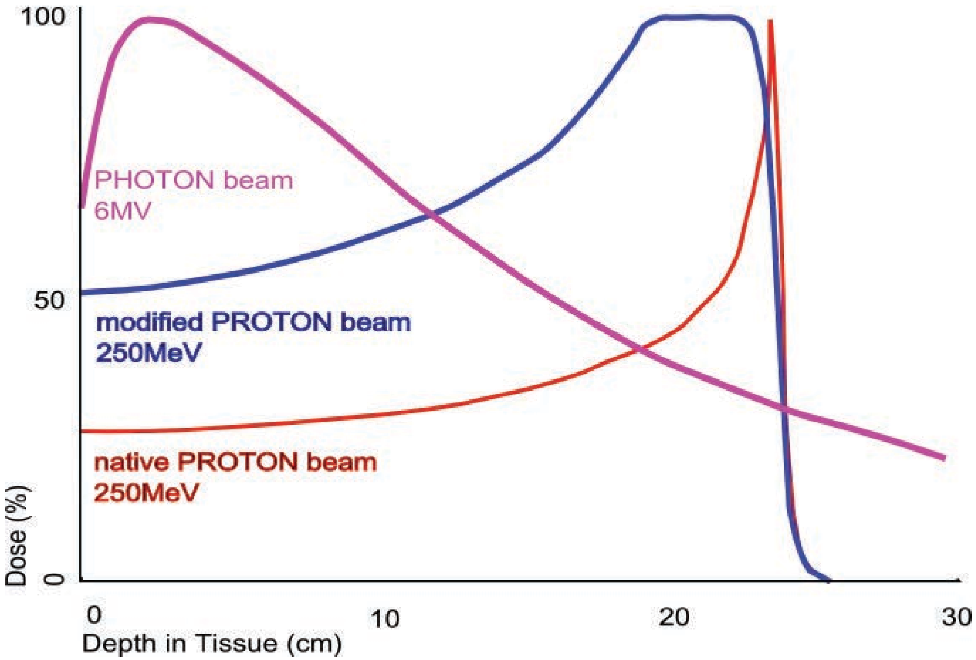
$$\left\langle \frac{dE}{dx} \right\rangle \gg \left. \frac{dE}{dx} \right|_{\min}$$

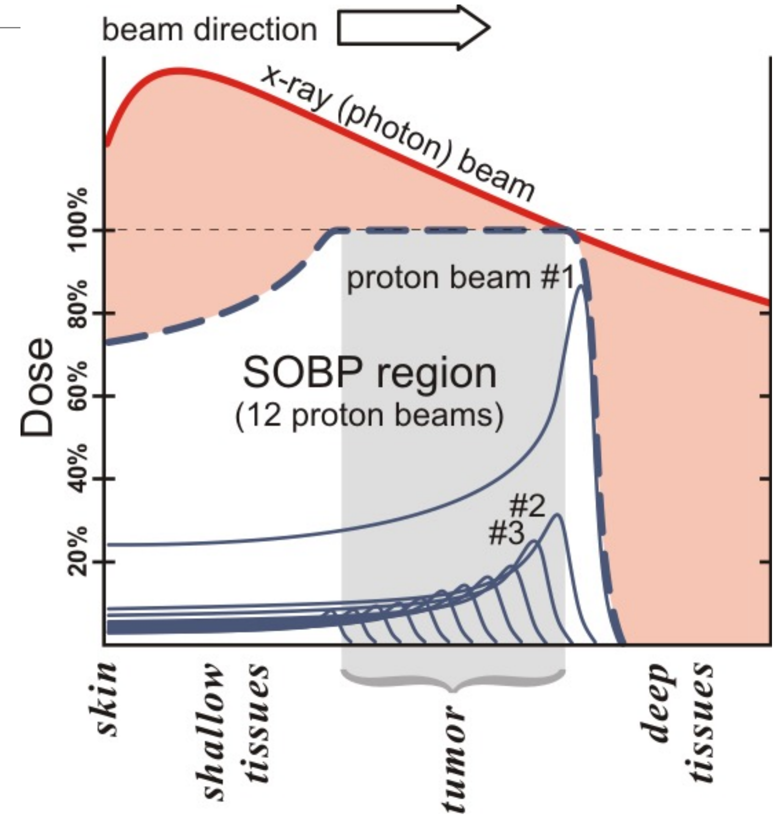
Applications:

Tumor therapy

Possibility to precisely deposit dose at well defined depth by E_{beam} variation

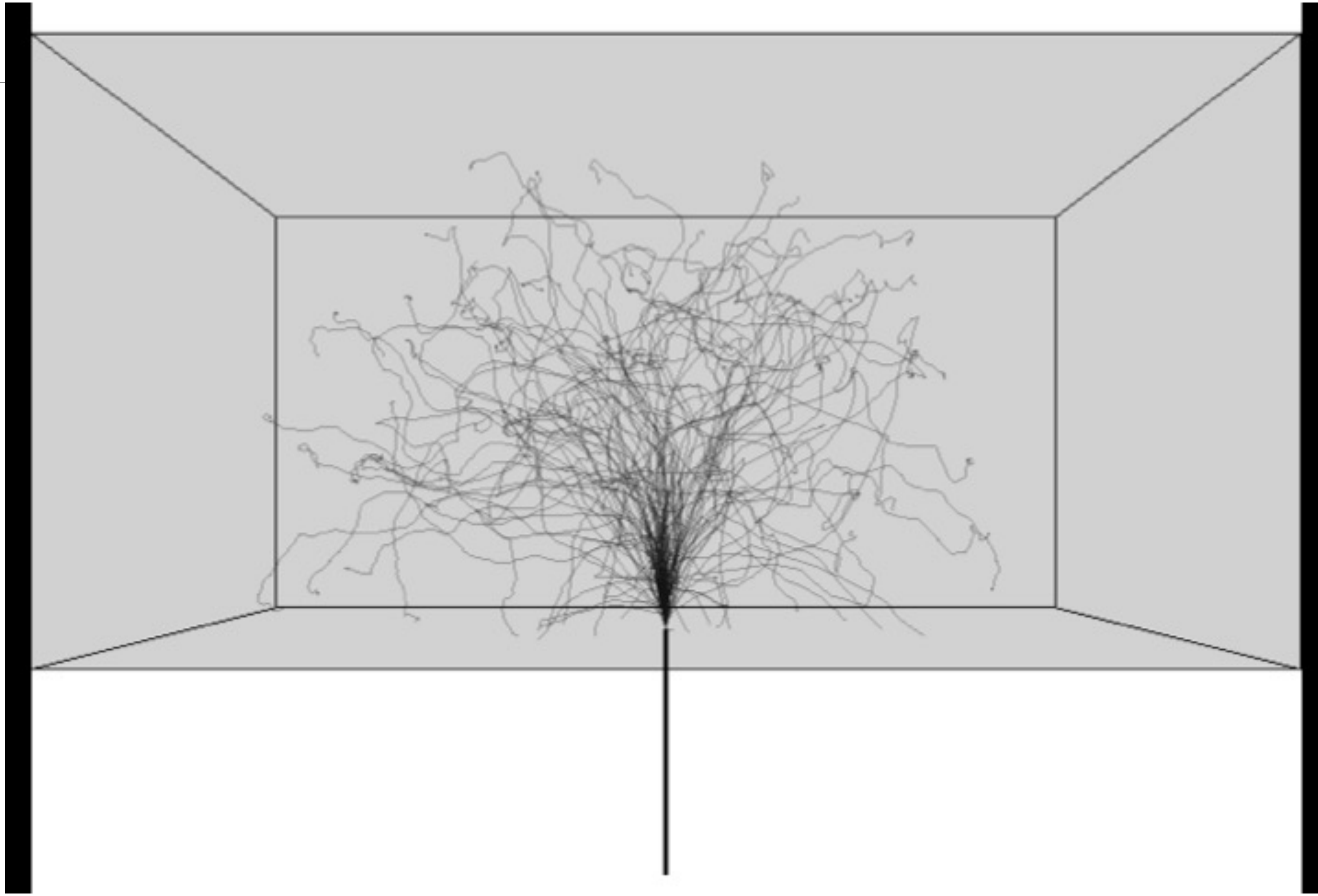


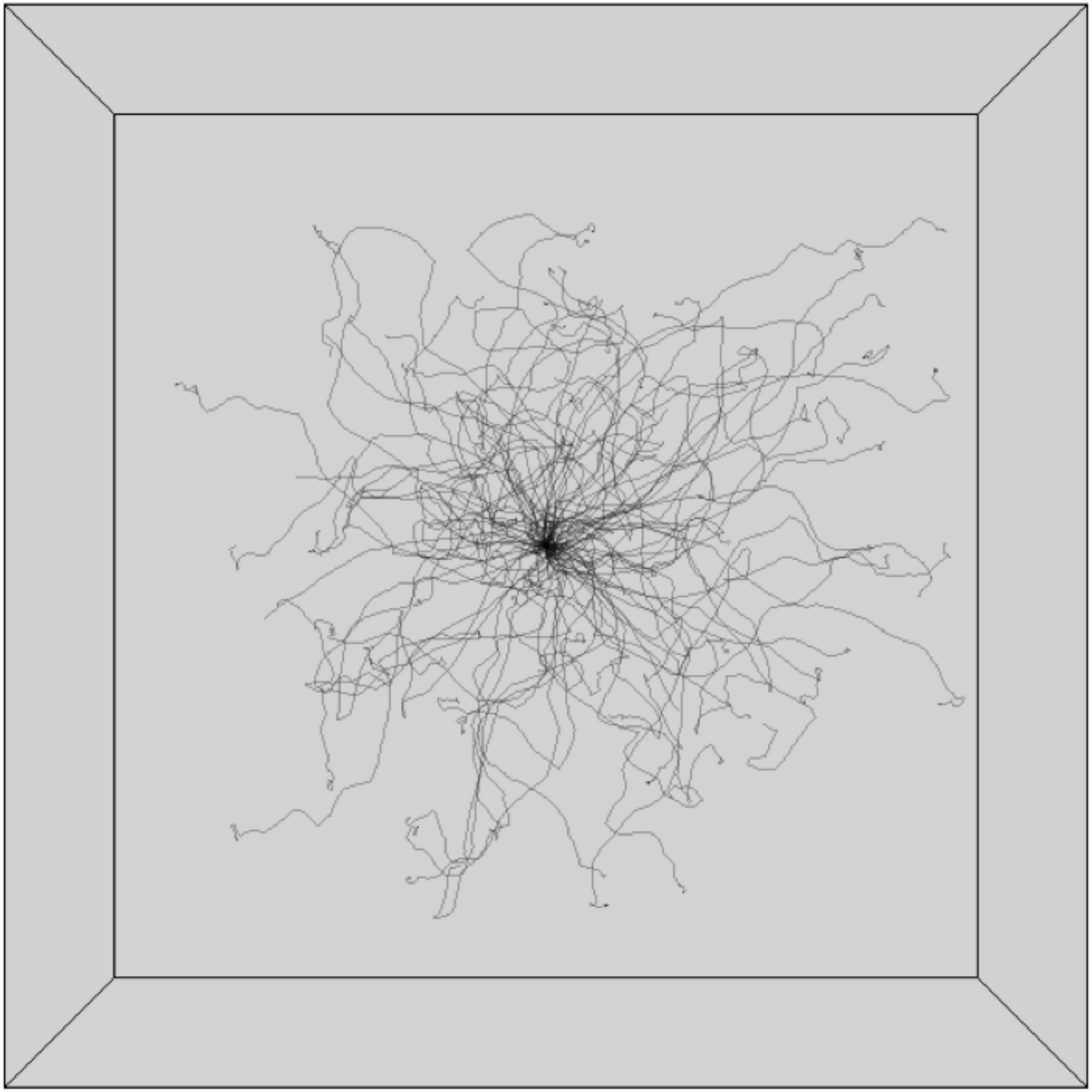




(adapted from http://en.wikipedia.org/wiki/Bragg_peak and http://en.wikipedia.org/wiki/Proton_therapy)

Track structure (example, low-energy electrons)





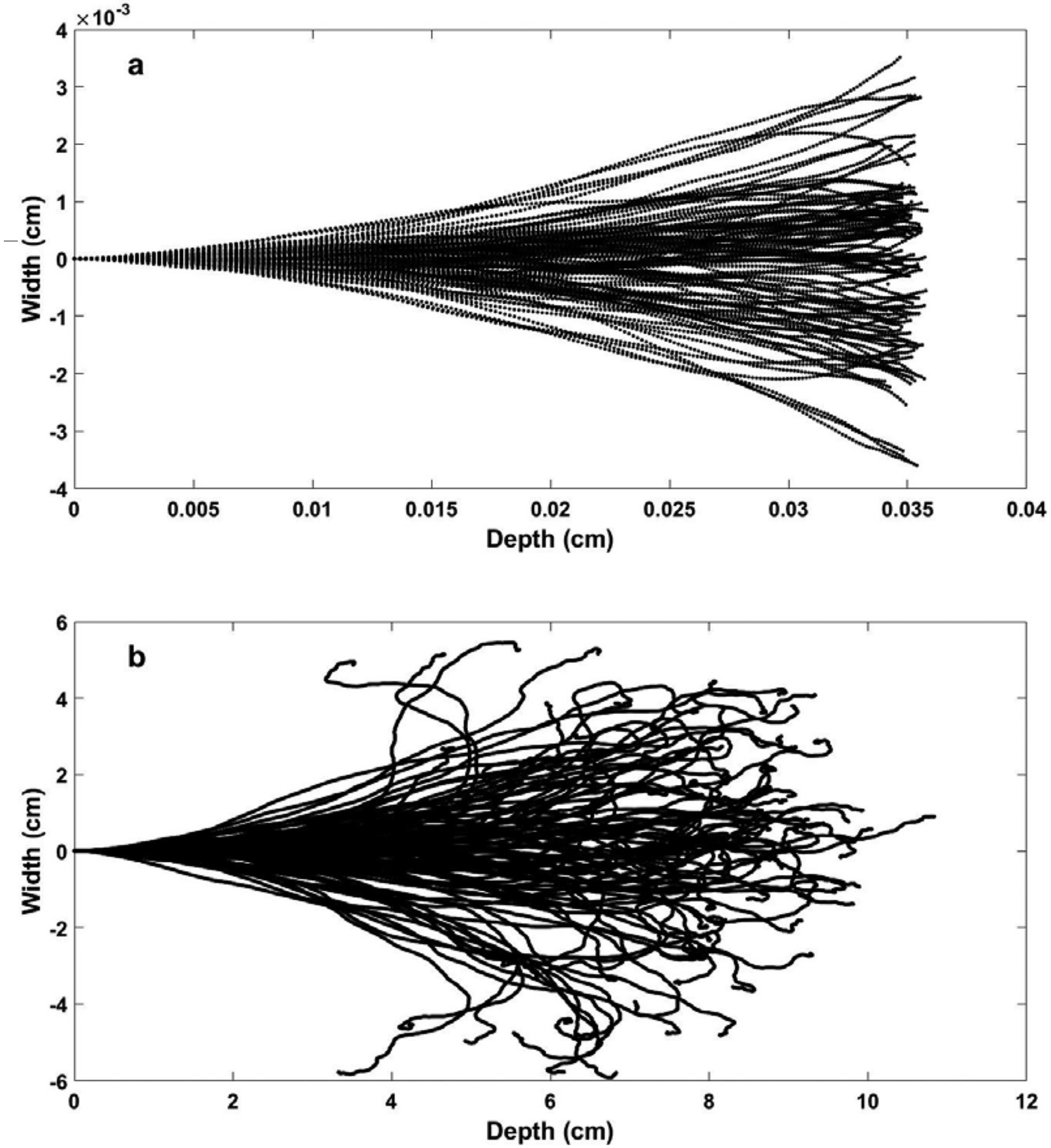
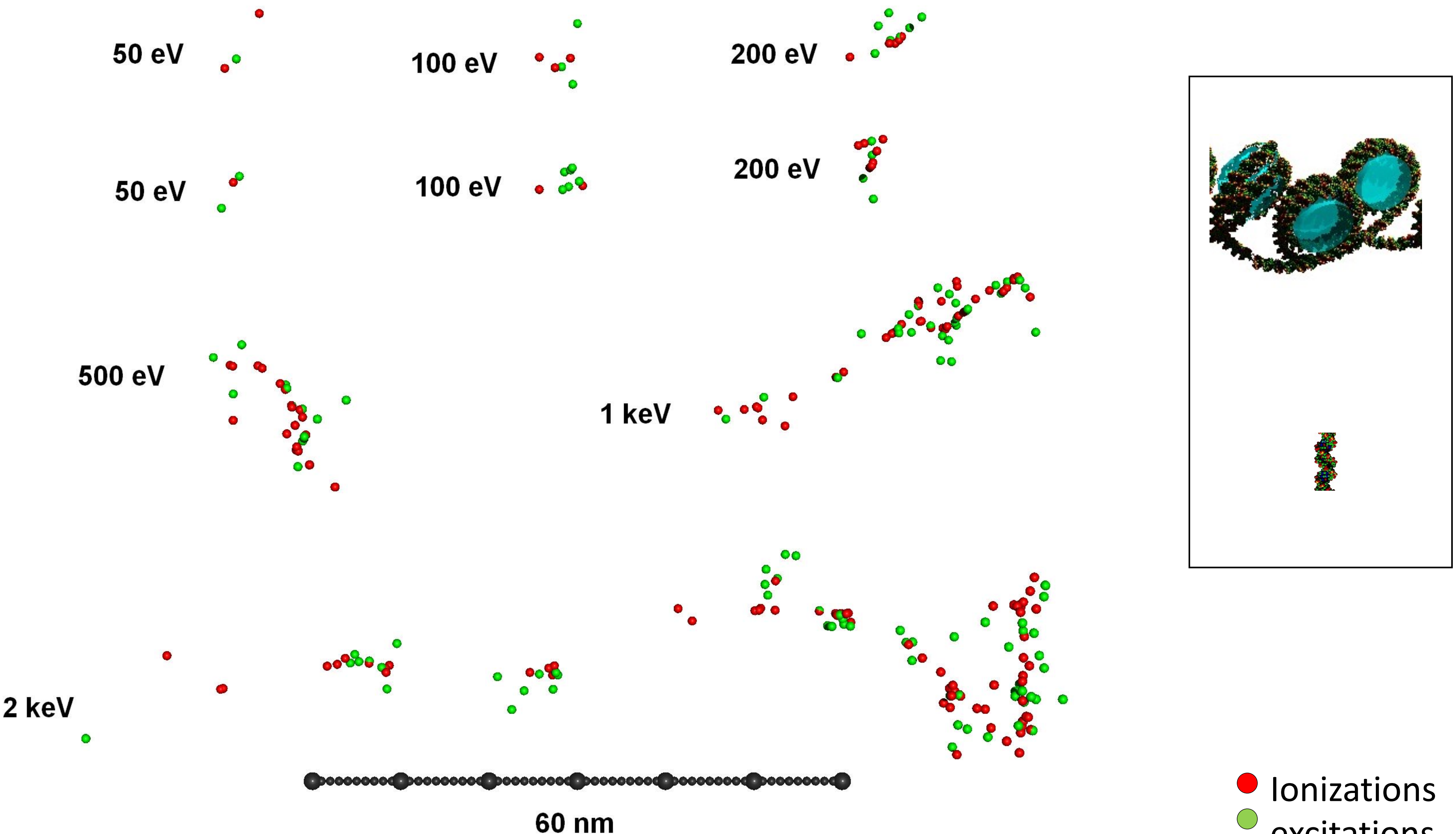


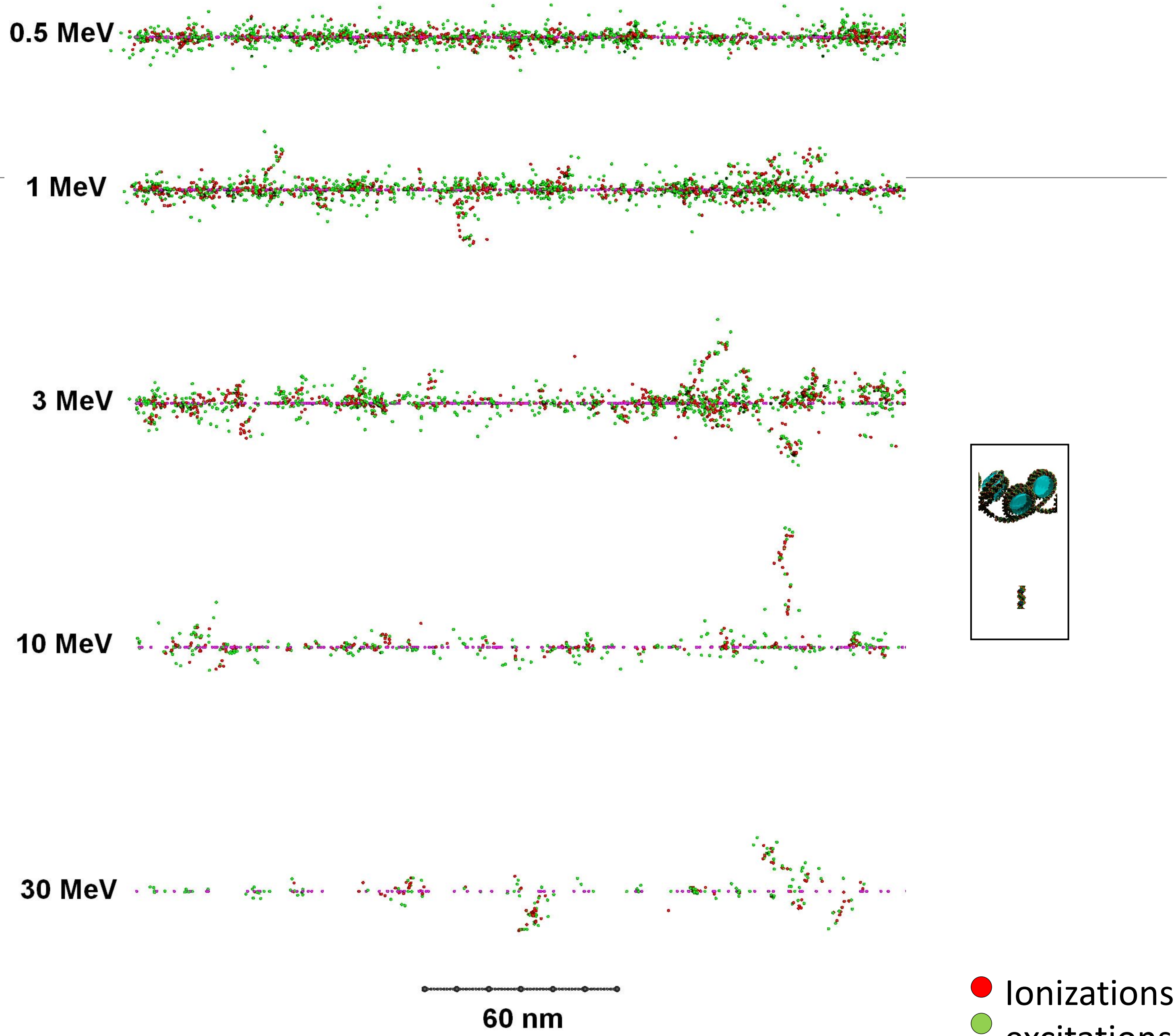
FIG. 2. Trajectories for 100 protons (a) and 100 electrons (b) with the incident energy of 5 MeV in liquid water.

from M. R. Kia , and H. Noshad, Phys. Plasmas **23**, 053120 (2016)

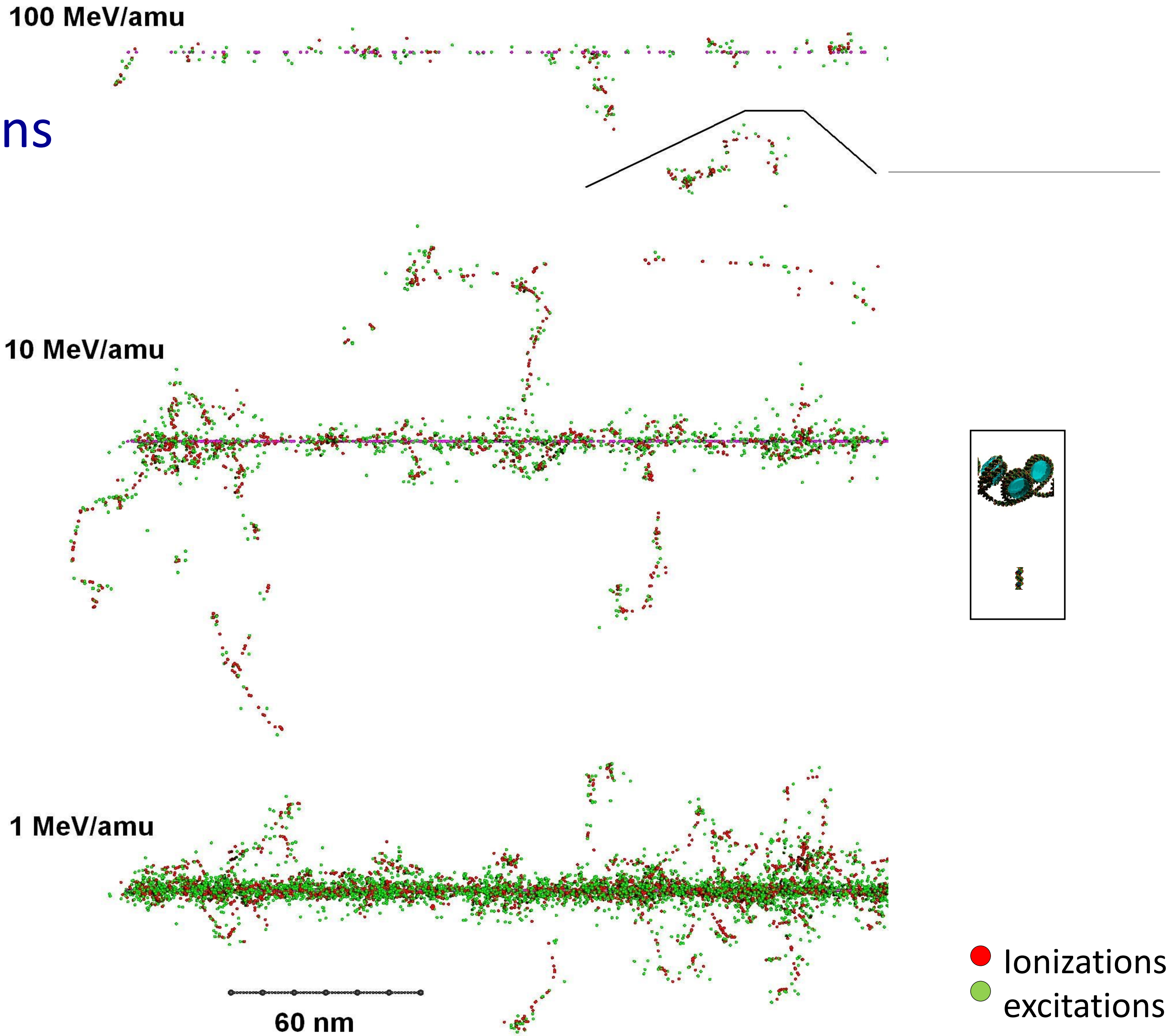
electrons in water



α particles



Carbon ions


100 MeV/amu
10 MeV/amu
1 MeV/amu
60 nm
Ionizations
excitations

Water radiolysis and production of ROS (Reactive Oxygen Species)

- Irradiated water contains many unstable and very reactive chemical species, mostly related to the very special properties of oxygen.
- Collectively, they are called Reactive Oxygen Species (ROS)

Water radiolysis and production of ROS (Reactive Oxygen Species)

For indirect action of x rays the chain of events from the absorption of the incident photon to the final biological damage is as follows:

Incident x-ray photon

Fast electron or positron

Ion radical

Free radical

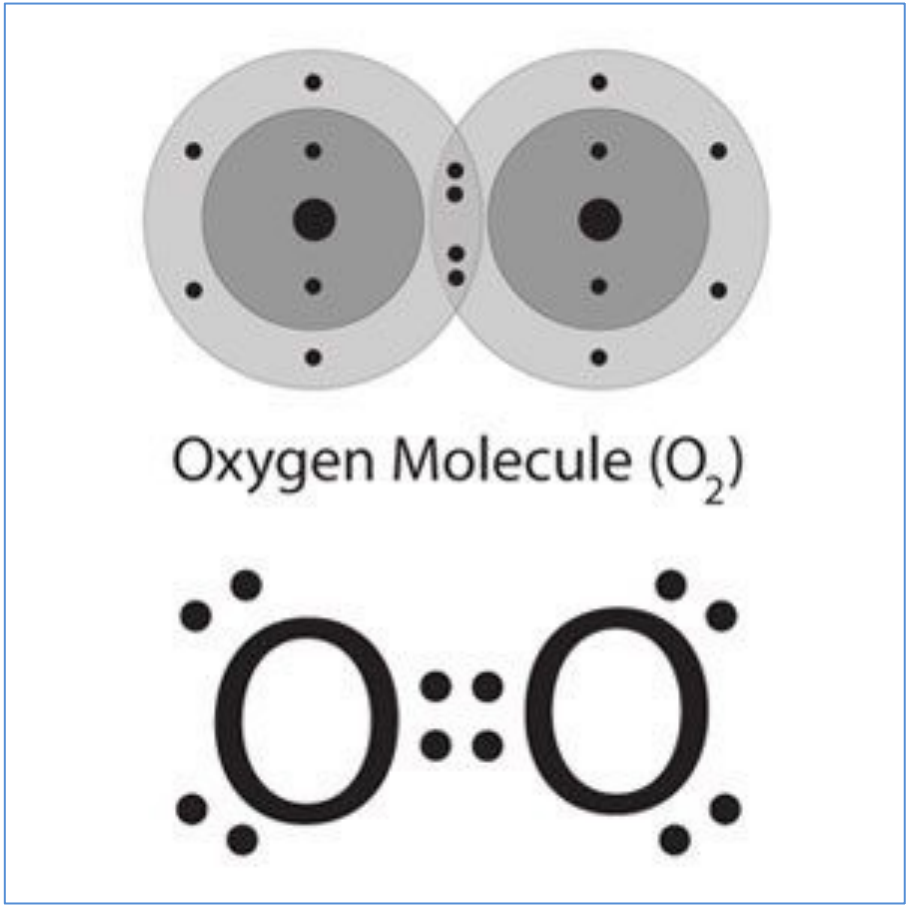
Breakage of bonds

Biological effect

Typical time scale involved in these 5 steps:

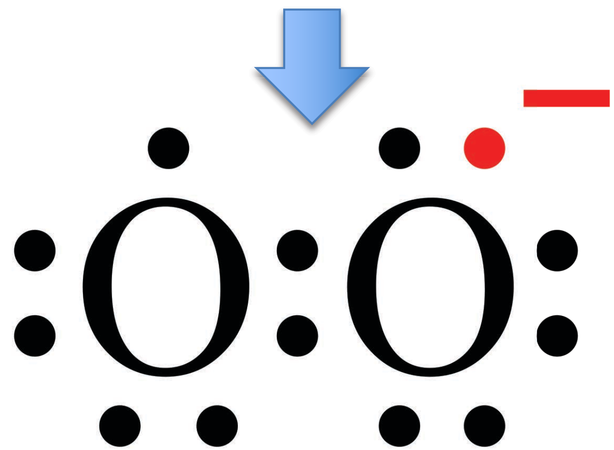
- (1) The physics of the process takes of the order of 10^{-15} s.
- (2) The ion radicals have a lifetime of the order of 10^{-10} s.
- (3) The free radicals have a lifetime of the order of 10^{-5} s.
- (4) The step between the breakage of bonds and the biological effect may take hours, days or years.

Molecular oxygen and the superoxide anion



Oxygen molecule: double bond ”hides” the electrons

Superoxide anion: added electron forces one of the atoms to “display” an unpaired electron, which makes the anion extremely reactive.



The reactivity of molecular oxygen: "triplet oxygen" and "singlet oxygen"

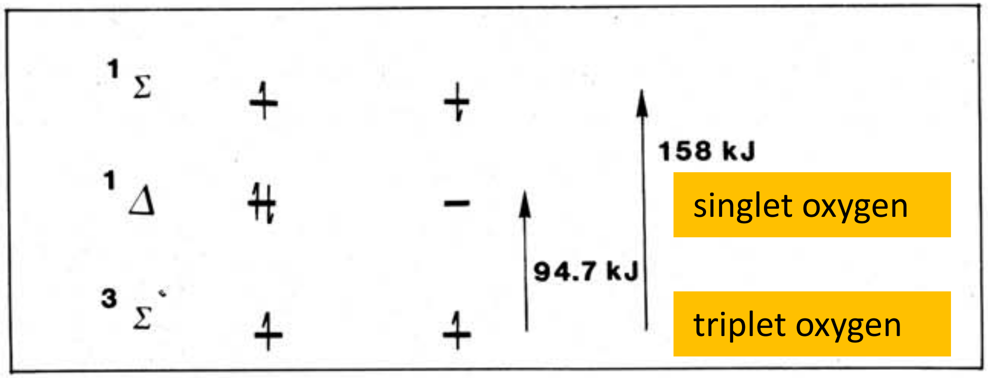
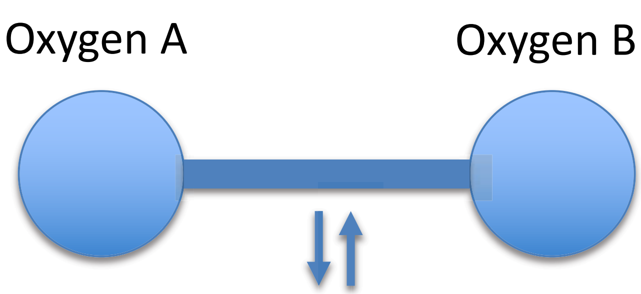


Figure 4. Schematic diagram showing the relative energies of the highest occupied orbitals of the oxygen molecules in the three states: $^3\Sigma$, $^1\Delta$, $^1\Sigma$.

Singlet oxygen is *very* reactive!!!



Bond with paired electrons: this pair can easily fit into existing molecular double bonds.

Hund's rule states that

- Every orbital in a sublevel is singly occupied before any orbital is doubly occupied.
- All of the electrons in singly occupied orbitals have the same spin (to maximize total spin).

In the case of oxygen, the triplet state fits the rule and is the ground state.

This is clearly displayed in the behavior of oxygen, which, when liquid, is paramagnetic (electrons with aligned spins)

However, three different states are actually possible, two of them with paired electrons.

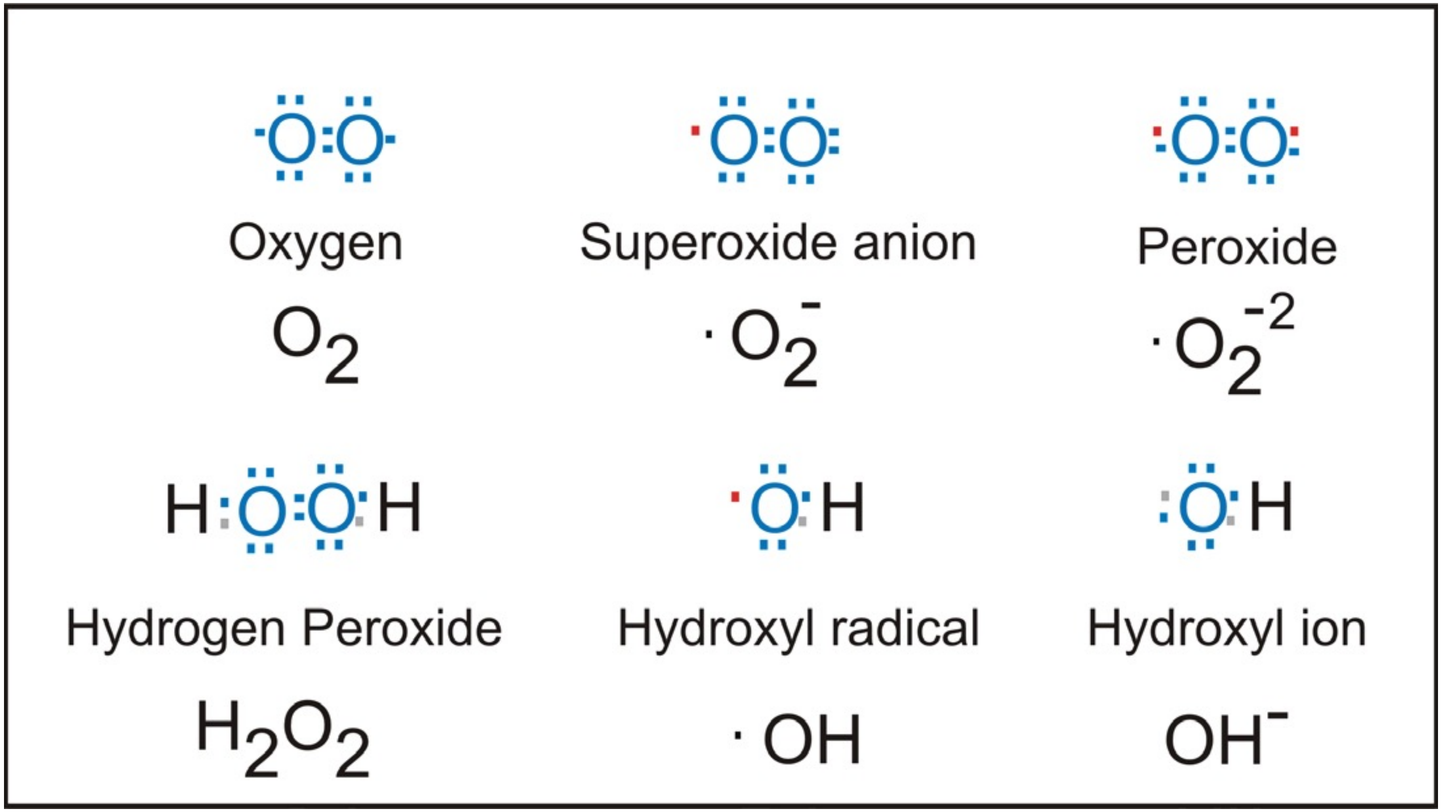
Singlet oxygen is common, an easy way to produce it is by mixing hydrogen peroxide with sodium hypochlorite. It displays only residual paramagnetism, associated with the orbital angular momentum.

The superoxide anion is highly reactive and toxic

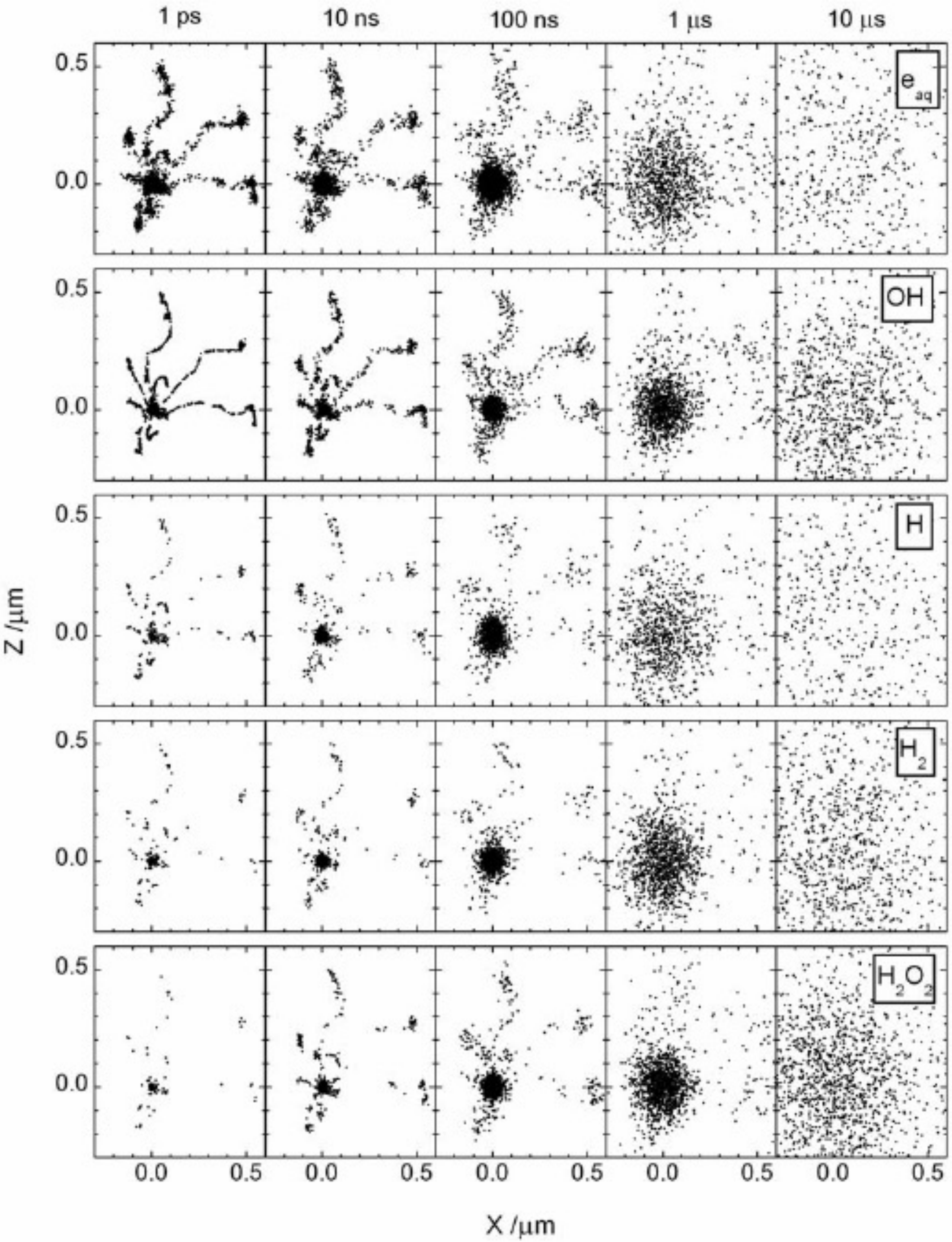
- The superoxide anion can easily convert into singlet molecular oxygen.
- Human cells use the superoxide anion to kill bacteria.
- The enzymes of the complex *NADPH oxidase* (NOX) produce superoxide.
- The absence of NADPH oxidase leads to the *chronic granulomatous diseases*.

- The superoxide anion is toxic to human cells, and this requires mechanisms to get rid of it, like the enzyme *superoxide dismutase*.

Main types of ROS (Reactive Oxygen Species)

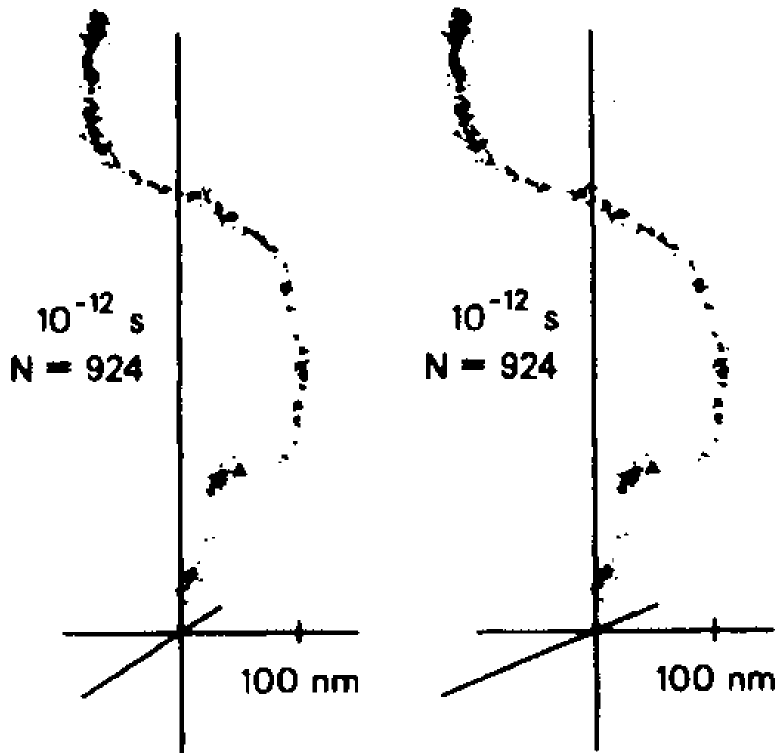


Electron structures of common reactive oxygen species. Each structure is provided with its name and chemical formula. The • designates an unpaired electron.

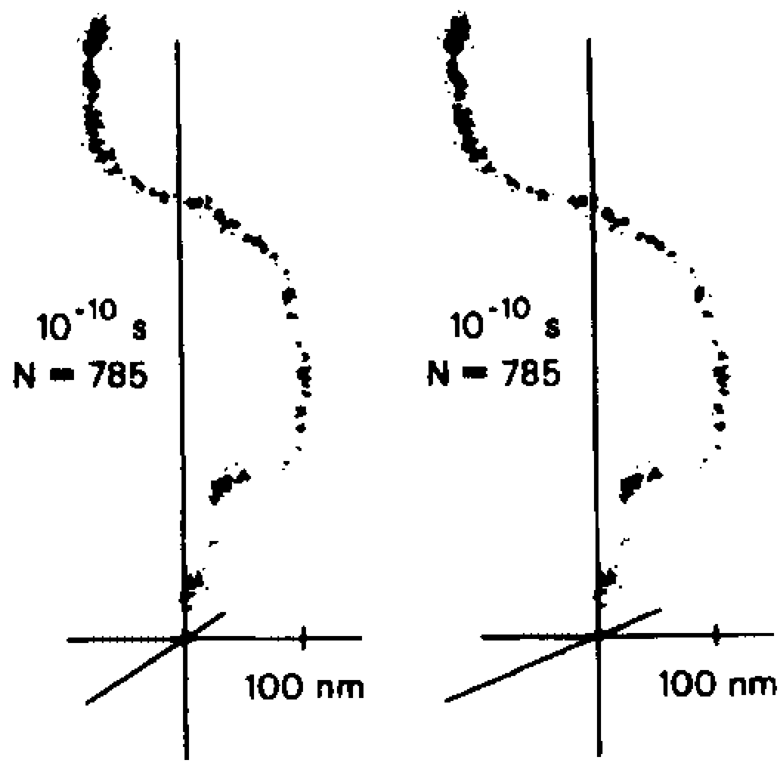


Time-dependent cross sections of the nonhomogeneous spatial distributions of the main radiolytic species (e_{aq}, .OH, H., H_2, and H_2O_2) in liquid water exposed to 24-MeV $^4He^{2+}$ ions from 1 ps to 10 µs.

Adapted from I. Plante and J.-P. Jay-Gerin: "Monte-Carlo step-by-step simulation of the early stages of liquid water radiolysis: 3D visualization of the initial radiation track structure and its subsequent chemical development", Journal of Physics: Conference Series **56** (2006) 153-155



Chemical development of a 4-keV electron track in liquid water, calculated by Monte Carlo simulation. Each dot in these stereo views gives the location of one of the active radiolytic species, OH, H_3O^+, e^{-aq}, or H, at the times shown. Note structure of track with spurs, or clusters of species, at early times. After 10^{-7} s, remaining species continue to diffuse further apart, with relatively few additional chemical reactions. (Adapted from James E. Turner*:* "Atoms, Radiation, and Radiation Protection, 3rd ed." Wiley 2007)



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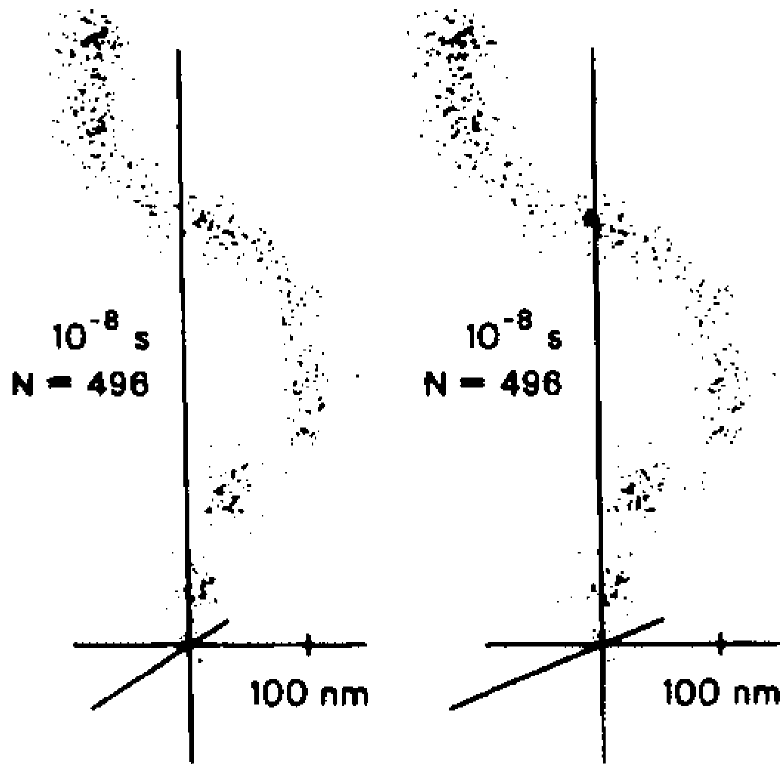

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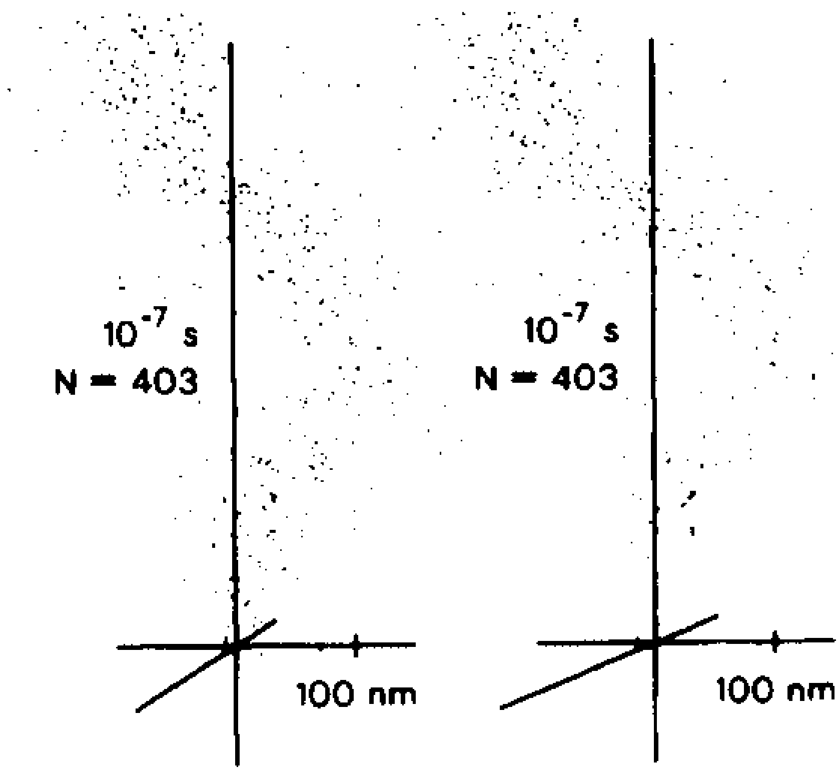


Chemical development of a 4-keV electron track in liquid water, calculated by Monte Carlo simulation. Each dot in these stereo views gives the location of one of the active radiolytic species, OH, H_3O^+, e^{-aq}, or H, at the times shown. Note structure of track with spurs, or clusters of species, at early times. After 10^{-7} s, remaining species continue to diffuse further apart, with relatively few additional chemical reactions. (Adapted from James E. Turner*:* "Atoms, Radiation, and Radiation Protection, 3rd ed." Wiley 2007)

Track of a 300 MeV $^{12}C^{6+}$ ion, from ~10^{-12} to ~10^{-6} s, front view

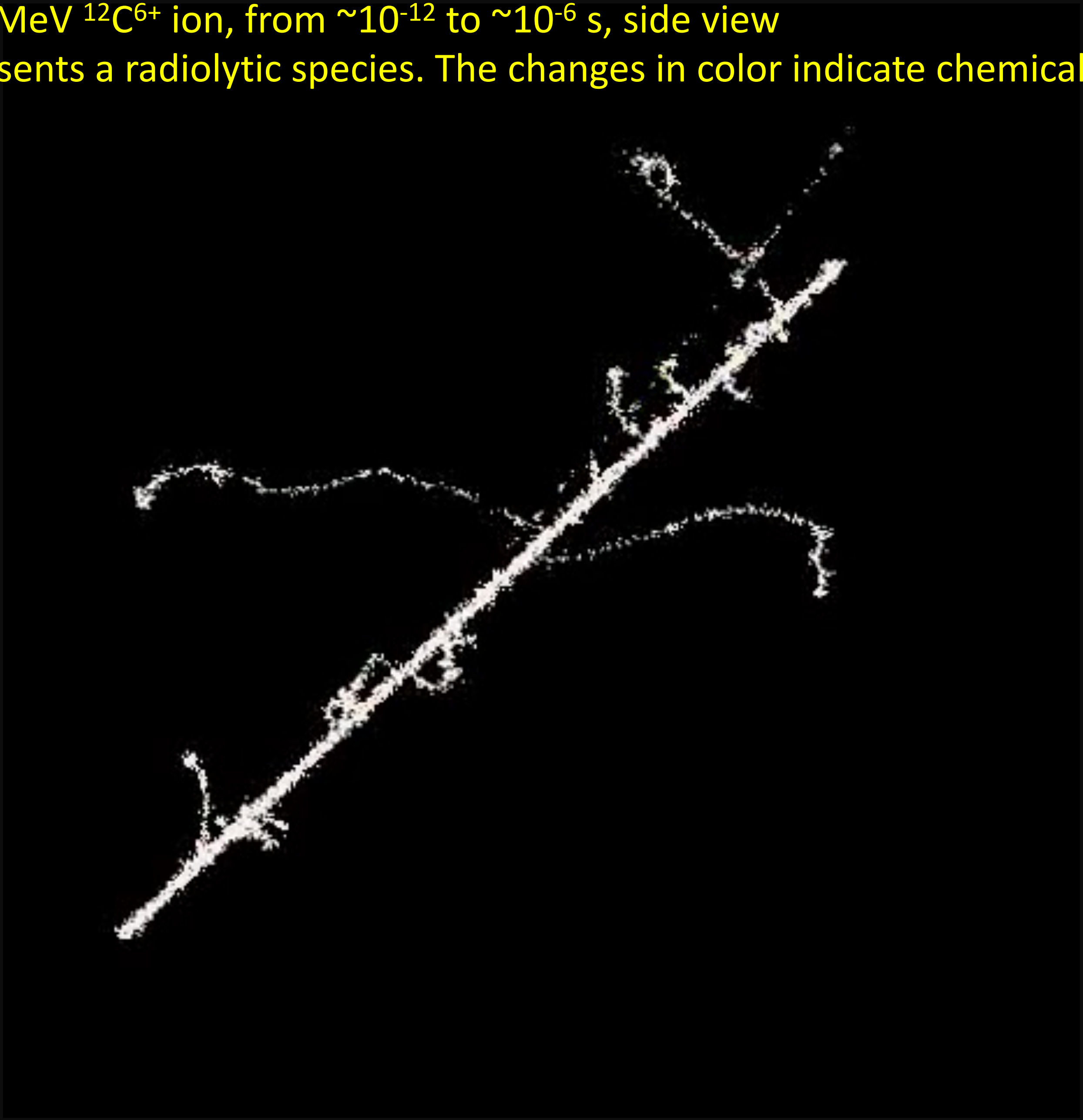
Each dot represents a radiolytic species. The changes in color indicate chemical reactions.

from https://three.jsc.nasa.gov

Track of a 300 MeV $^{12}C^{6+}$ ion, from ~10^{-12} to ~10^{-6} s, side view

Each dot represents a radiolytic species. The changes in color indicate chemical reactions.

from https://three.jsc.nasa.gov



G value: number of a given species produced per 100 eV of energy loss by the original charged particle and its secondaries, on the average, when it stops in the water.

Table 13.3 *G* Values (Number per 100 eV) for Various Species in Water at 0.28 μs for Electrons at Several Energies

	Electron Energy (eV)							
Species	**100**	**200**	**500**	**750**	**1000**	**5000**	**10,000**	**20,000**
OH	1.17	0.72	0.46	0.39	0.39	0.74	1.05	1.10
H_3O^+	4.97	5.01	4.88	4.97	4.86	5.03	5.19	5.13
e^-_{aq}	1.87	1.44	0.82	0.71	0.62	0.89	1.18	1.13
H	2.52	2.12	1.96	1.91	1.96	1.93	1.90	1.99
H_2	0.74	0.86	0.99	0.95	0.93	0.84	0.81	0.80
H_2O_2	1.84	2.04	2.04	2.00	1.97	1.86	1.81	1.80
Fe^{3+}	17.9	15.5	12.7	12.3	12.6	12.9	13.9	14.1

Table extracted from Turner: “Atoms, Radiation, and Radiation Protection”

G value: number of a given species produced per 100 eV of energy loss by the original charged particle and its secondaries, on the average, when it stops in the water.

Table 13.4 *G* Values (Number per 100 eV) for Various Species at 10^{-7} s for Protons of Several Energies and for Alpha Particles of the Same Velocities

Species	Protons (MeV)				Alpha Particles (MeV)			
Type	1	2	5	10	4	8	20	40
OH	1.05	1.44	2.00	2.49	0.35	0.66	1.15	1.54
H_3O^+	3.53	3.70	3.90	4.11	3.29	3.41	3.55	3.70
e^-_{aq}	0.19	0.40	0.83	1.19	0.02	0.08	0.25	0.46
H	1.37	1.53	1.66	1.81	0.79	1.03	1.33	1.57
H_2	1.22	1.13	1.02	0.93	1.41	1.32	1.19	1.10
H_2O_2	1.48	1.37	1.27	1.18	1.64	1.54	1.41	1.33
Fe^{3+}	8.69	9.97	12.01	13.86	6.07	7.06	8.72	10.31

Table extracted from Turner: “Atoms, Radiation, and Radiation Protection”

Exercise:

If a 20-keV electron stops in water and an average of 352 molecules of H_2O_2 are produced, what is the G value for H_2O_2 for electrons of this energy?

G value: number of a given species produced per 100 eV of energy loss by the original charged particle and its secondaries, on the average, when it stops in the water.

Exercise:

If a 20-keV electron stops in water and an average of 352 molecules of H_2O_2 are produced, what is the G value for H_2O_2 for electrons of this energy?

Answer:

20 keV/100 eV = 200 therefore G = 352/200 = 1.76

G value: number of a given species produced per 100 eV of energy loss by the original charged particle and its secondaries, on the average, when it stops in the water.

Electrons, protons, and alpha particles all produce the same species in local track regions at 10^{-15} s: H_2O^+, H_2O^*, and subexcitation electrons.

The chemical differences that result at later times are presumably due to the different spatial patterns of initial energy deposition that the particles have.

Table 13.3 *G* Values (Number per 100 eV) for Various Species in Water at 0.28 μs for Electrons at Several Energies

	Electron Energy (eV)							
Species	**100**	**200**	**500**	**750**	**1000**	**5000**	**10,000**	**20,000**
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H_3O^+	4.97	5.01	4.88	4.97	4.86	5.03	5.19	5.13
e^-_{aq}	1.87	1.44	0.82	0.71	0.62	0.89	1.18	1.13
H	2.52	2.12	1.96	1.91	1.96	1.93	1.90	1.99
H_2	0.74	0.86	0.99	0.95	0.93	0.84	0.81	0.80
H_2O_2	1.84	2.04	2.04	2.00	1.97	1.86	1.81	1.80
Fe^{3+}	17.9	15.5	12.7	12.3	12.6	12.9	13.9	14.1

Homework

A 50 cm^3 sample of water is given a dose of 50 mGy from 10-keV electrons.

If the yield of H_2O_2 is G = 1.81 per 100 eV, how many molecules of H_2O_2 are produced in the sample?

The radiolysis of water is known to damage metal pipes, but how do the radiolytic species act in cells and organisms?

- Radiobiology is a branch of science which combines basic principles of physics and biology and is concerned with the action of ionizing radiation on biological tissues and living organisms.

- Ionizing radiation acts at the molecular and cellular level, while in this Master's course we are interested in the medical issues: in this Radiobiology course we try to understand how the action of radiation at the microscopic level affects human health