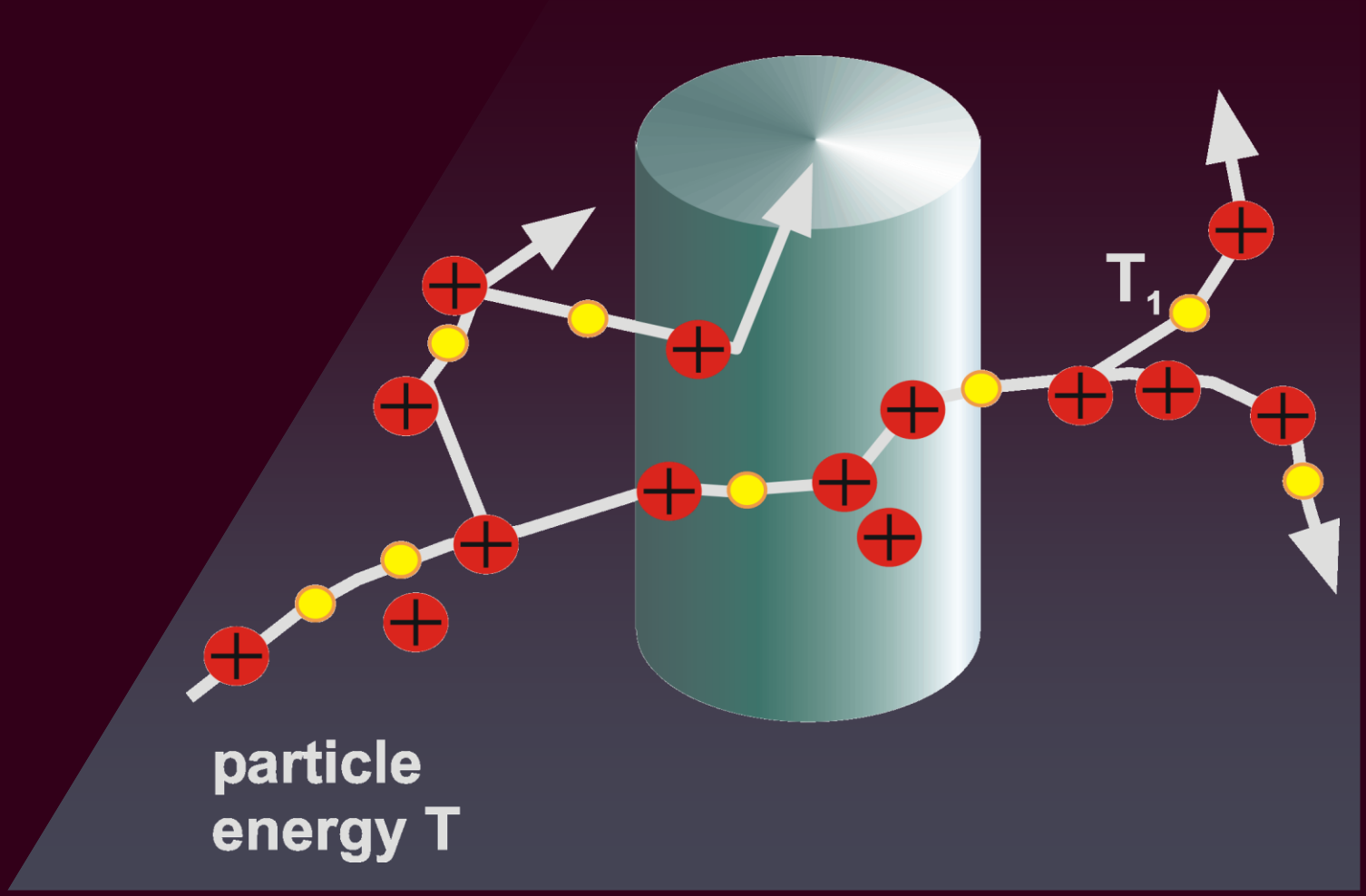
From Microdosimetry to Nanodosimetry

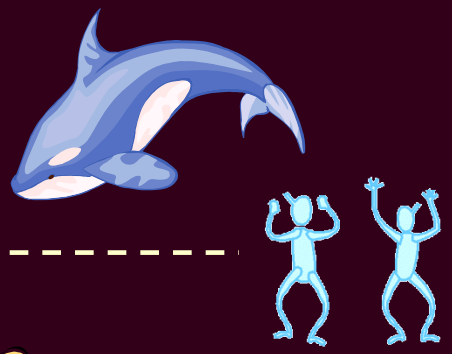


Bernd Grosswendt (retired), Physikalisch-Technische Bundesanstalt, Braunschweig, Germany; guest at LNL-INFN, Legnaro, Italy

Radiation Damage: The Characteristic Target Sizes in Life Science

Typical Biological Systems/µm

10^{8}
10^{7}
10^{6}
10^{5}
10^{4}
10^{3}
10^{2}
10^{1}
1
10^{-1}
10^{-2}
10^{-3}
10^{-4}



Hen's egg

Living cells

Cell nucleus

Chromosome fibre

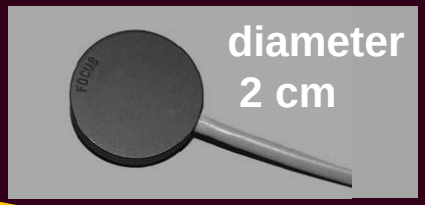
DNA molecule

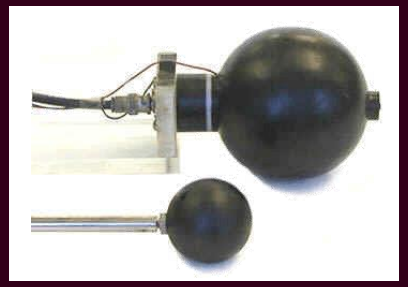
H_2 molecule

Radiation protection

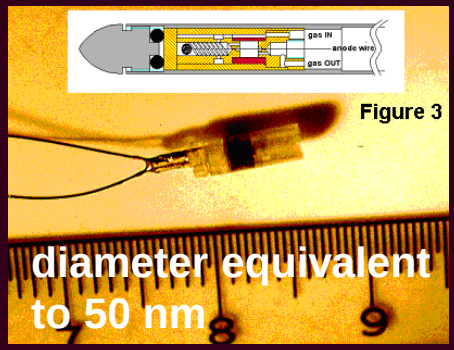
Treatment planning in radiation therapy

The Transition from Radiation Dosimetry to Radiobiology Is Characterized by a Dramatic Reduction of the Target Volume





diameter
equivalent to 1 μm

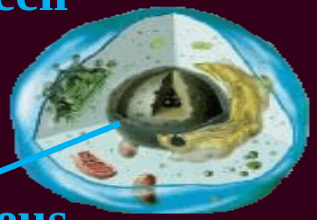


3 cm
typical tumor diameter

100 μm
typical cell diameter

5 μm
cell nucleus

human cell



25 nm
chromosome fibre

diameter 2 nm
to 30 nm

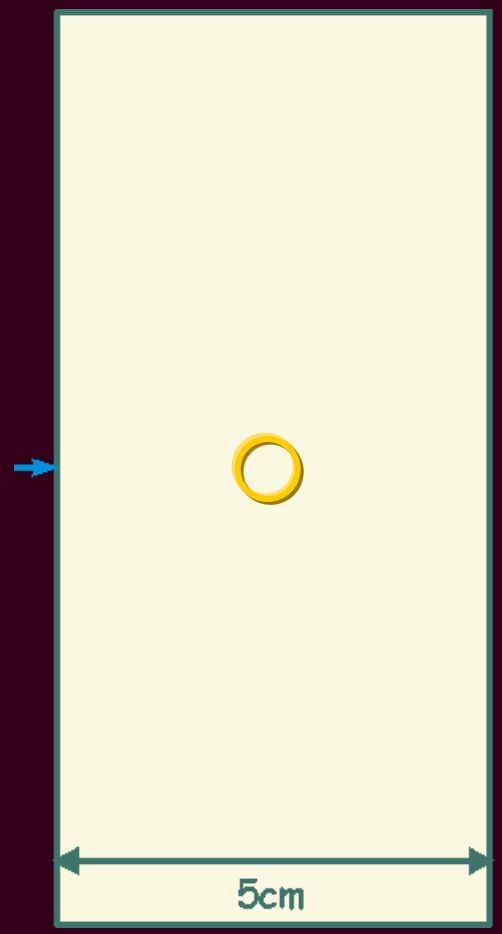
2,3 nm
DNA molecule

Traditional dosimetry — 1900

Micro-dosimetry — 1960

Nano-dosimetry — 2000

The hypothesis: Traditionally it is assumed that radiation damage is related to the energy absorbed in a target volume



$$D = \frac{\Delta E}{\Delta m}$$

The 'Golden Rule' of Conventional Applied Radiation Physics

Radiation effects in matter are related to the amount of energy deposited within a target

- ***Radiation Biology***
- ***Radiation Therapy***
- ***Radiation Protection***

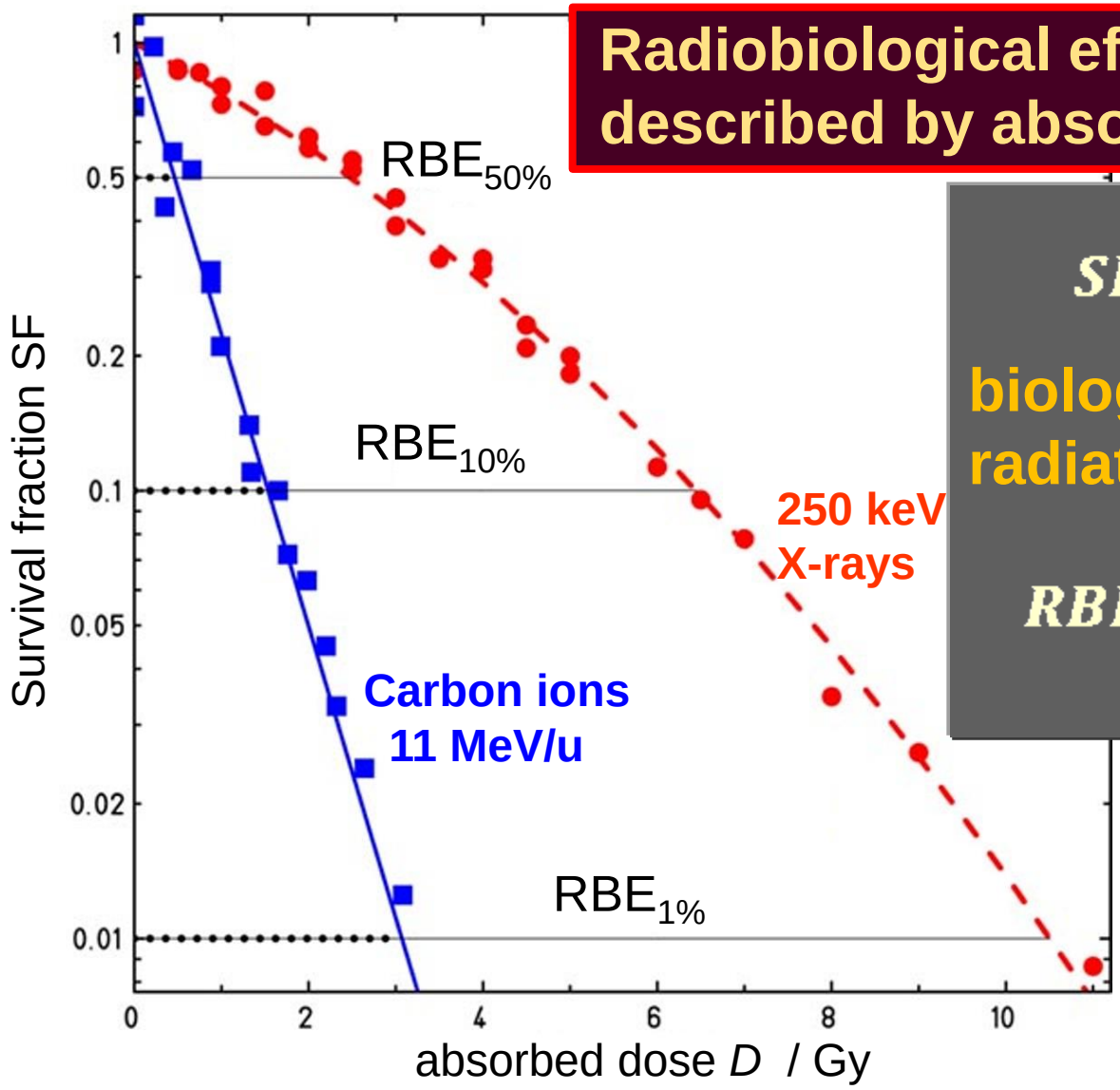
The absorbed dose concept

- **A homogeneous distribution of energy depositions**
- **A secondary particle equilibrium**
- **The initiation of radiation effects is really proportional to absorbed dose**

$$D = \frac{\Delta E}{\Delta m}$$

The Failure of Absorbed Dose: Definition of the Relative Biological Effectiveness (RBE)

Survival of CHO-K1 Chinese Hamster Cells (Weyrather *et al.*, 1999)



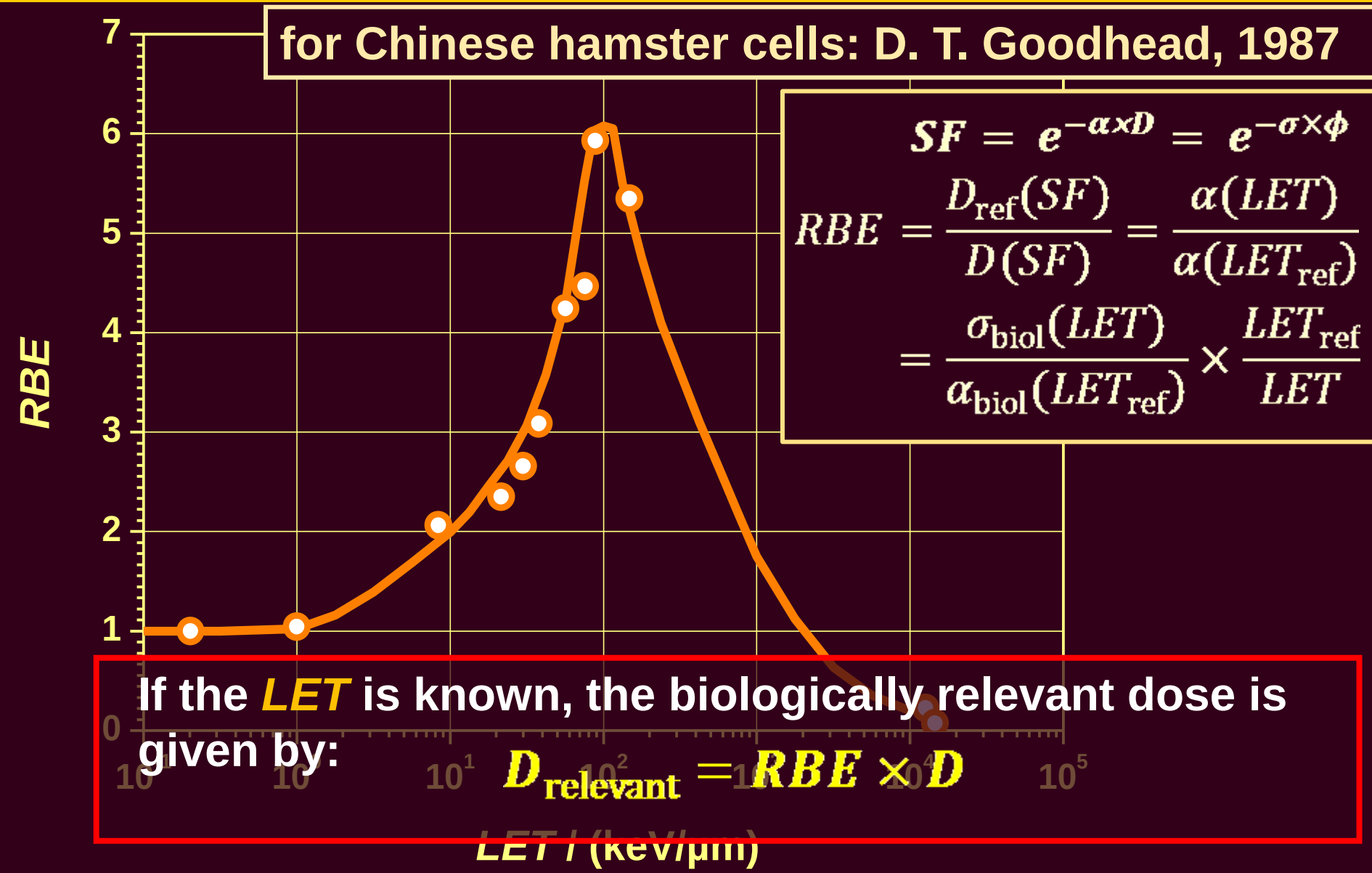
Radiobiological effects cannot be described by absorbed dose

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

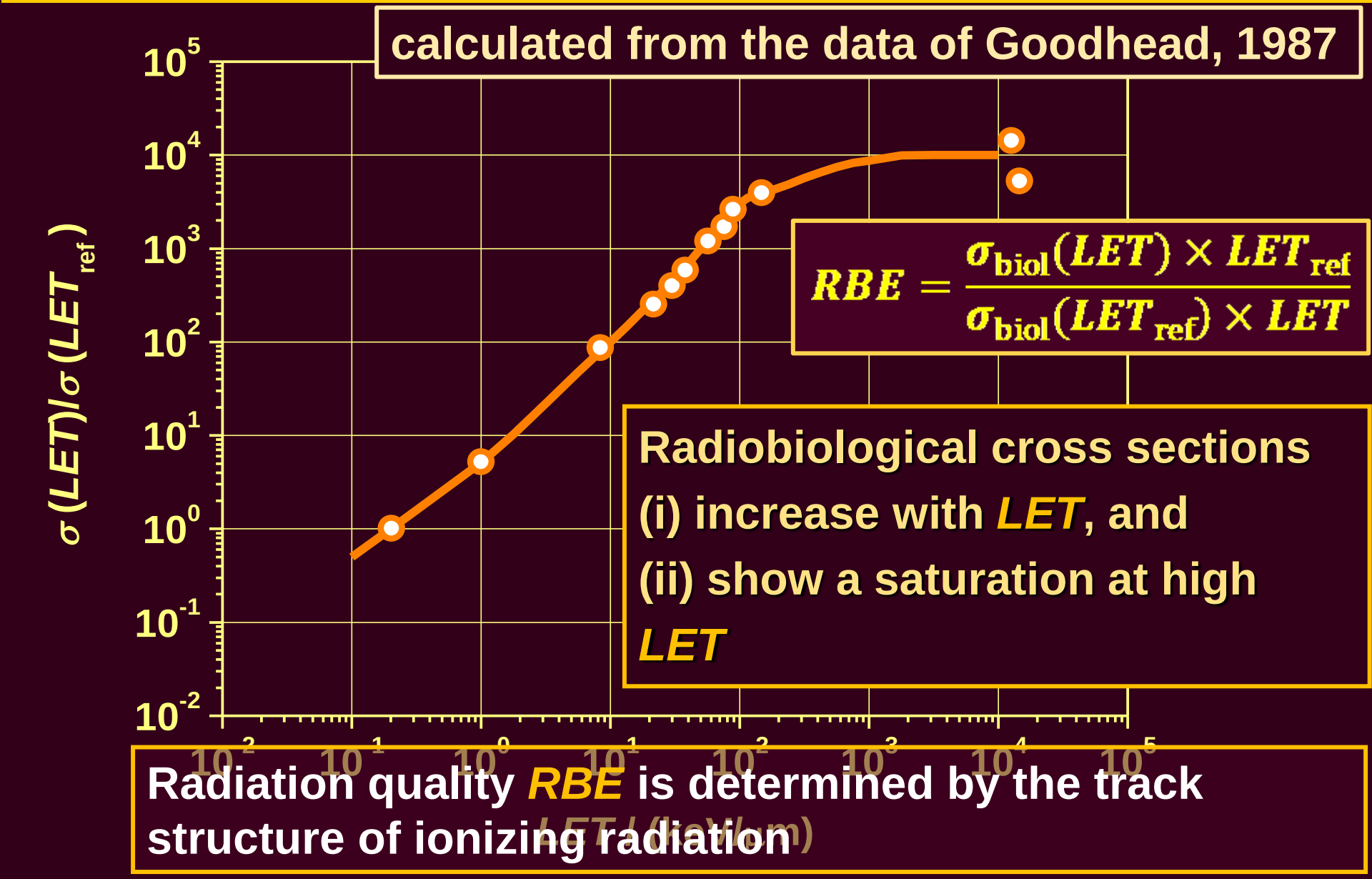
biologically defined radiation quality

$$RBE = \frac{D_{ref}(SF)}{D(SF)}$$

Relative Biological Effectiveness (RBE) of Ionizing Radiation as a Function of Linear Energy Transfer (LET)

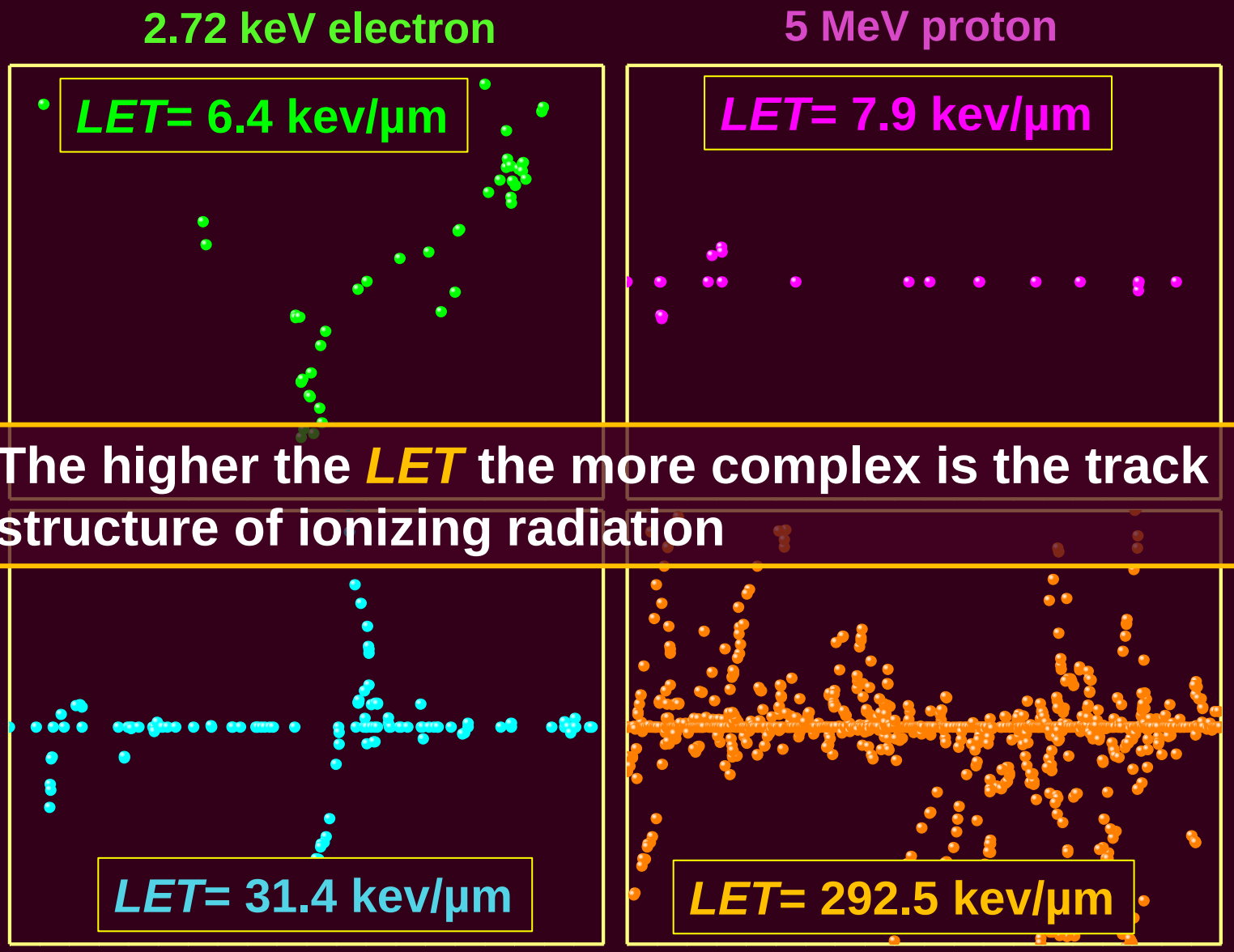


Radiobiological Cross Section for Ionizing Radiation as a Function of Linear Energy Transfer (LET)



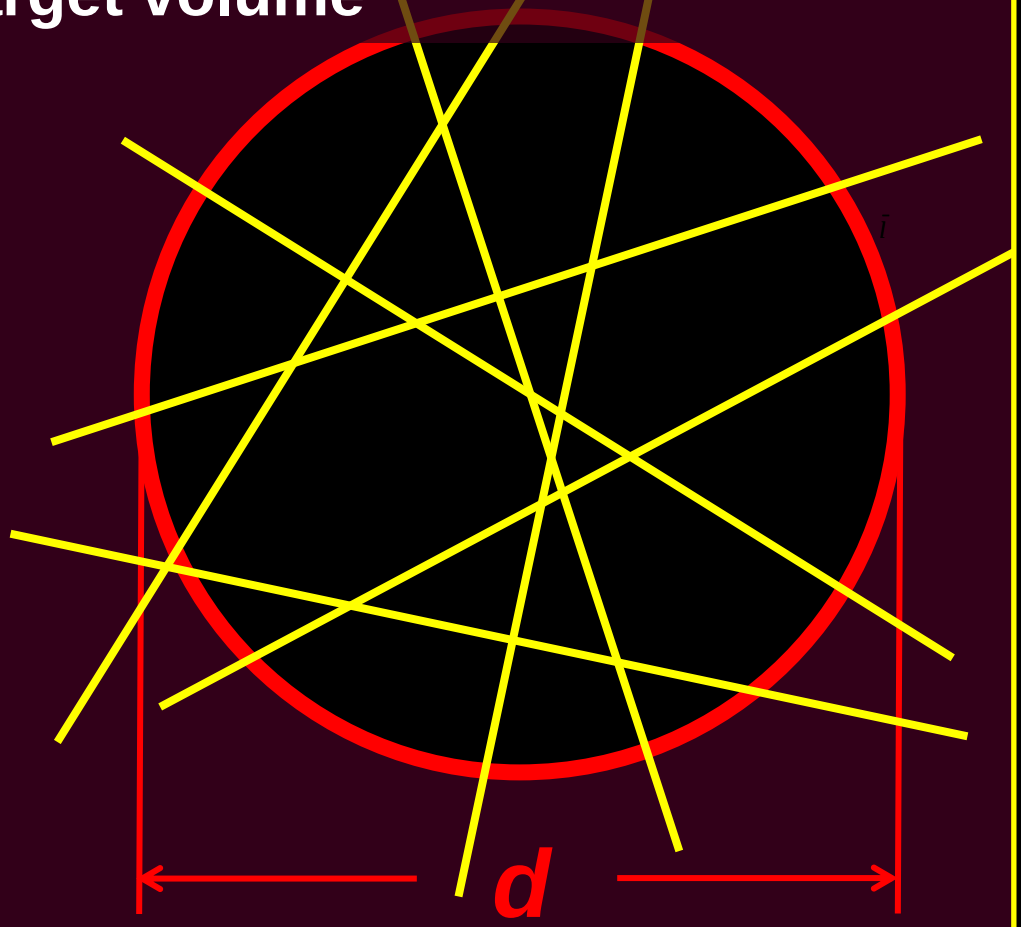
Radiation quality *RBE* is determined by the track structure of ionizing radiation

The Track Structure of Ionizing Radiation: Track Segments in Water, 100 nm in Length



The Idea of Microdosimetry: to Measure the Lineal Energy as a Substitute of LET

LET **is related to the energy loss of an ionizing particle and lineal energy to the energy deposit in a target volume**



lineal energy: $y = \frac{\varepsilon}{\bar{l}}$

relative frequency of y:

$f(y)\mathrm{d}y$ with

$$\int_0^\infty f(y)\mathrm{d}y = 1$$

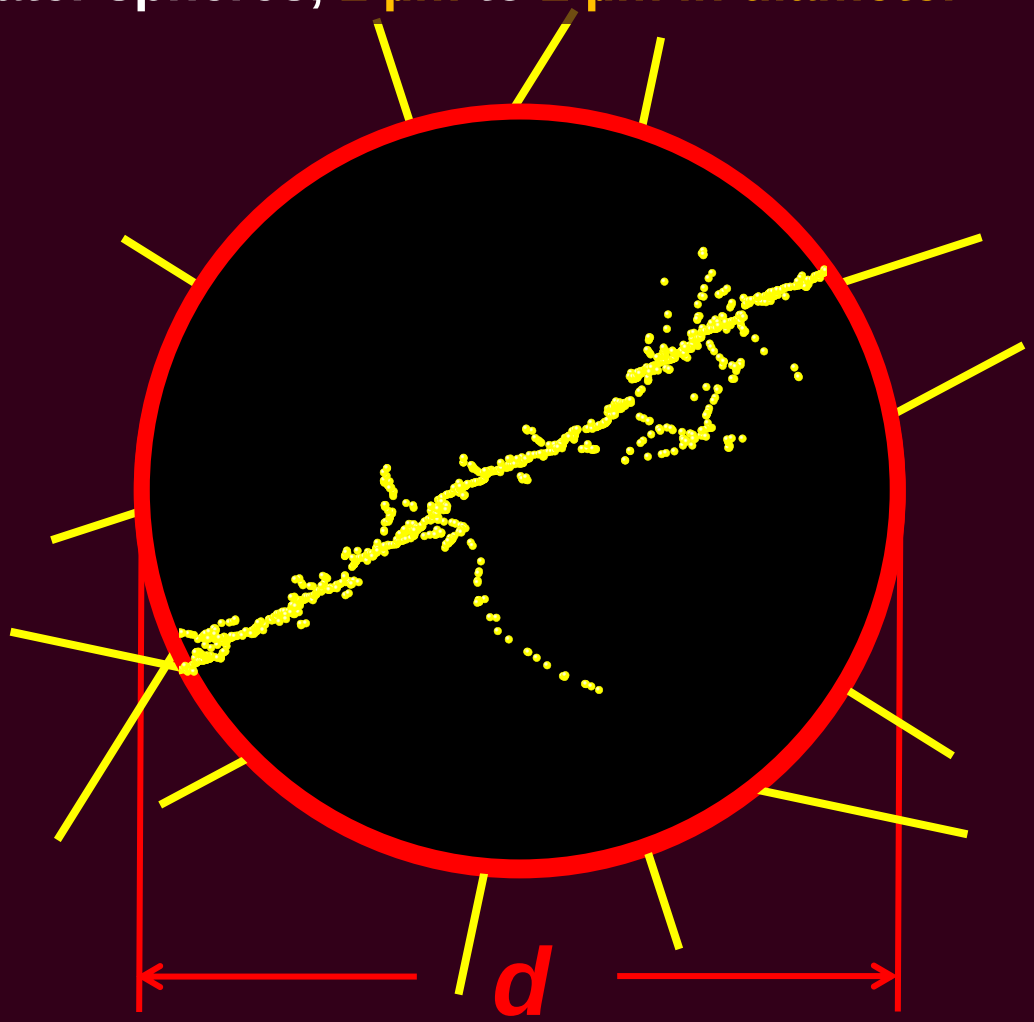
and the mean values:

$$y_F = \int_0^\infty y\, f(y)\, \mathrm{d}y$$

$$y_D = \frac{1}{y_F}\int_0^\infty y^2 \times f(y)\, \mathrm{d}y$$

The Idea of Microdosimetry: the Sensitive Volumes Are the Nuclei of Living Cells (a Few µm *in Diameter)*

The measurements are made in gaseous volumes corresponding in size to liquid water spheres, 1 µm to 2 µm in diameter



lineal energy: $y = \frac{\varepsilon}{\bar{l}}$

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$f(y)\mathrm{d}y$ **with**

$$\int_0^\infty f(y)\mathrm{d}y = 1$$

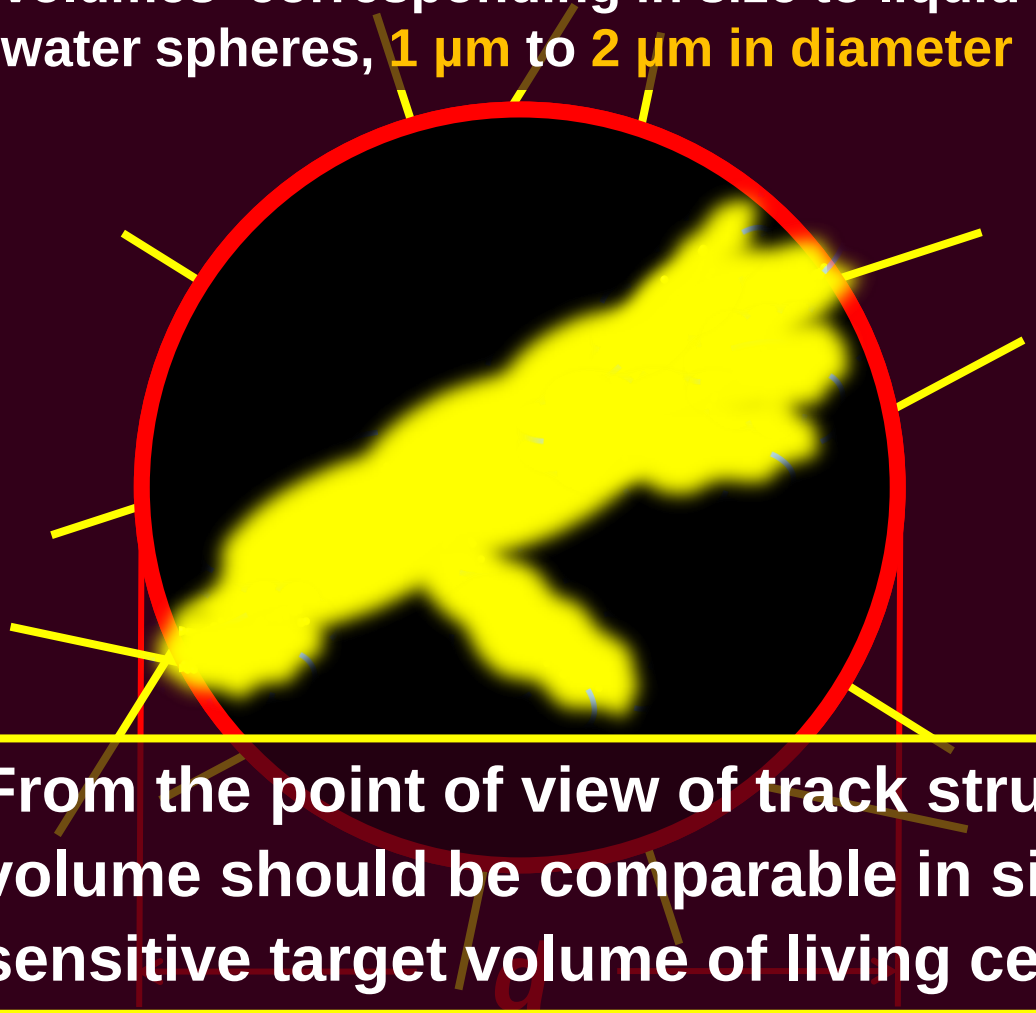
and the mean values:

$$y_F = \int_0^\infty y\, f(y)\, \mathrm{d}y$$

$$y_D = \frac{1}{y_F}\int_0^\infty y^2 \times f(y)\, \mathrm{d}y$$

The Idea of Microdosimetry: the Lineal Energy is Determined by Measuring the Amount of Ionization per Energy-deposition Event

The measurements are made in gaseous volumes corresponding in size to liquid water spheres, 1 µm to 2 µm in diameter



The consequence of this procedure is the averaging over comparably large track lengths:

Hence, a detailed information on track structure is lost.

From the point of view of track structure, the measuring volume should be comparable in size to that of the most sensitive target volume of living cells

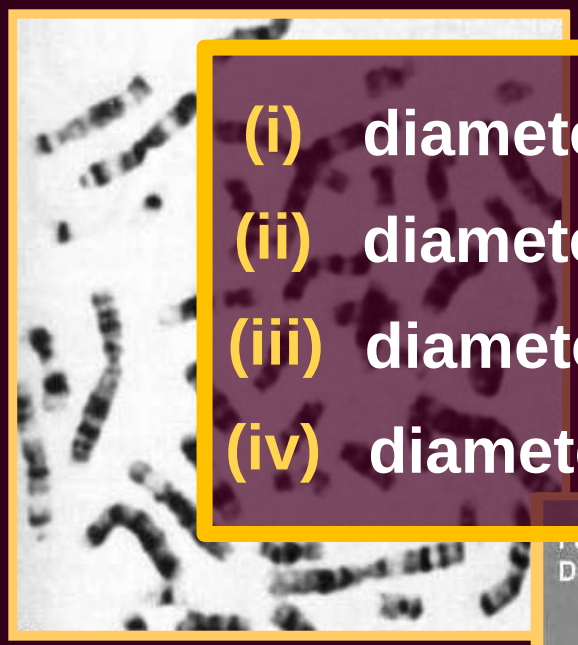
The "True" Target Volumes of Life Science

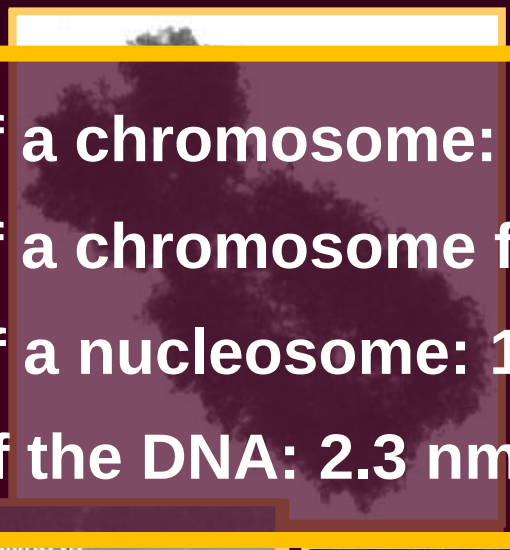
(i) diameter of a chromosome: 300 nm

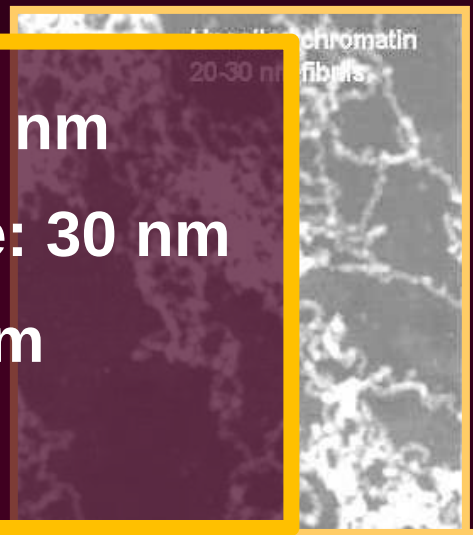
(ii) diameter of a chromosome fibre: 30 nm

(iii) diameter of a nucleosome: 11 nm

(iv) diameter of the DNA: 2.3 nm



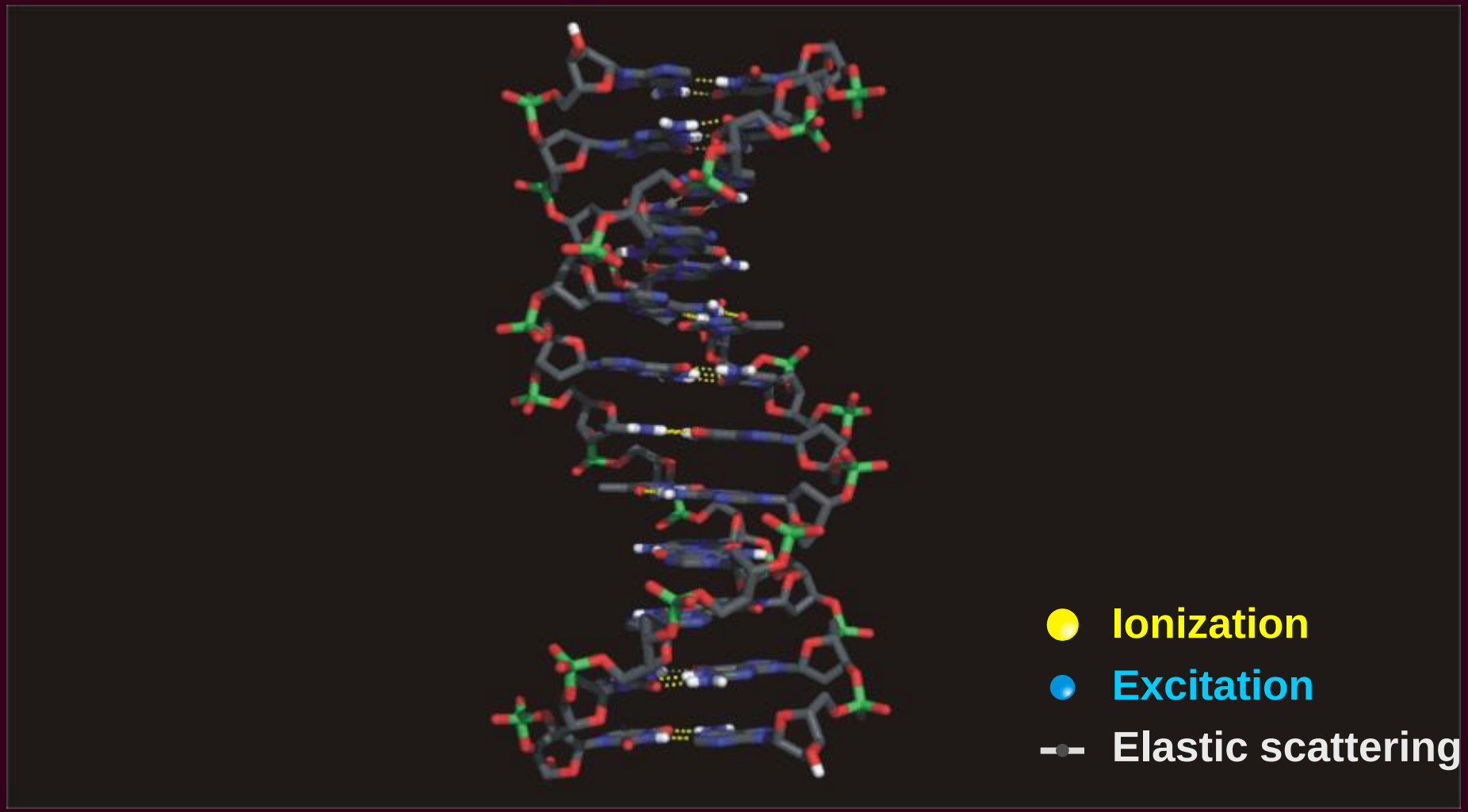




The real target volumes of radio-biology and also of radiation physics are those of the substructures of cell nuclei

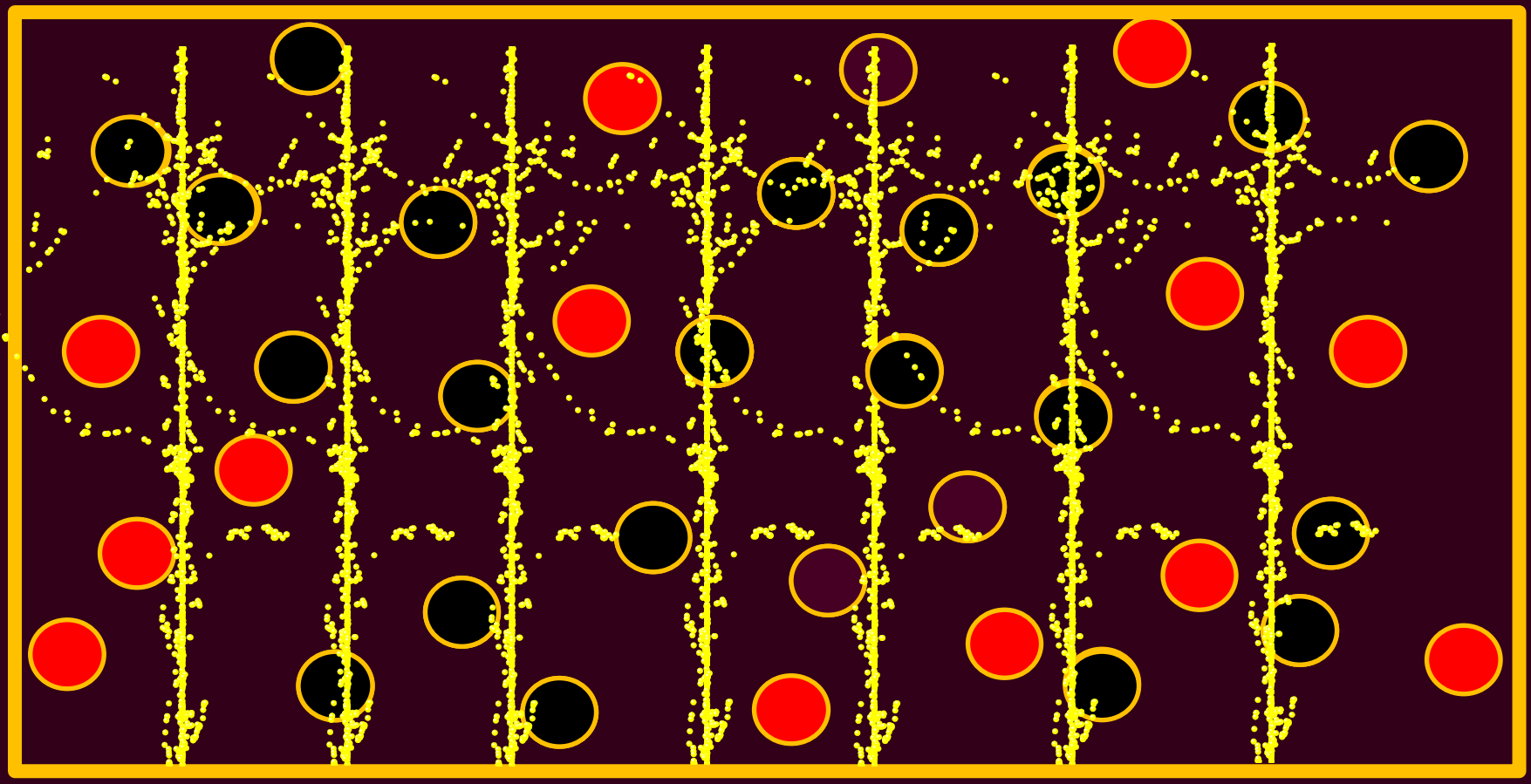
The "true" target volumes of life science are of nanometre size

Radiation Damage to Genes or Cells Starts with the Initial Damage to Segments of the DNA



Radiation damage strongly depends on the number of relevant particle interactions within then DNA, and, hence, on particle track structure

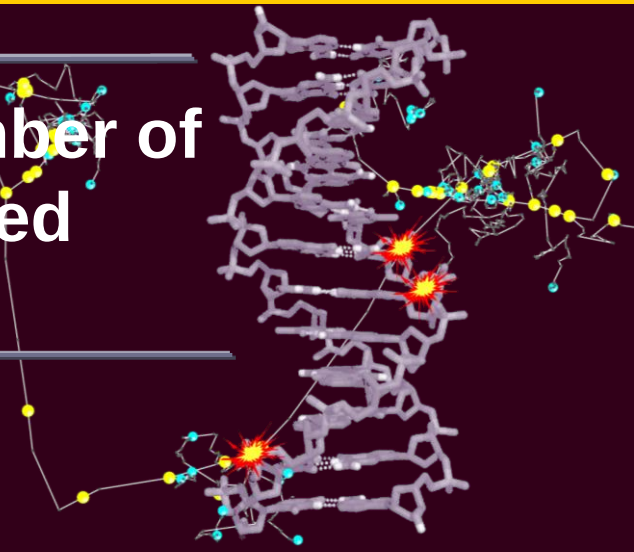
The Number of Particle Interactions in Nanometric Volumes gives a Picture of Particle Track Structure



The track structure of ionizing particles is expressed by the frequency distribution of the number of particle interactions in nanometre-sized volumes

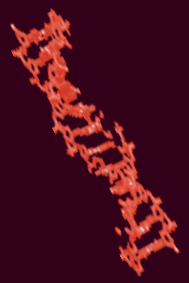
The Characterization of Particle Track Structure by Measurement

The frequency distribution of the number of particle interactions in nanometre-sized target volumes must be measured



<u>The needs for metrology:</u>

- **an appropriate measuring procedure**
- **measuring quantities which take into account *RBE*: they must show, for instance, a saturation effect as a function of *LET* like radiobiological cross sections**



<u>The hypothesis:</u> The damage to segments of the DNA is initiated to a great part by ionizing processes

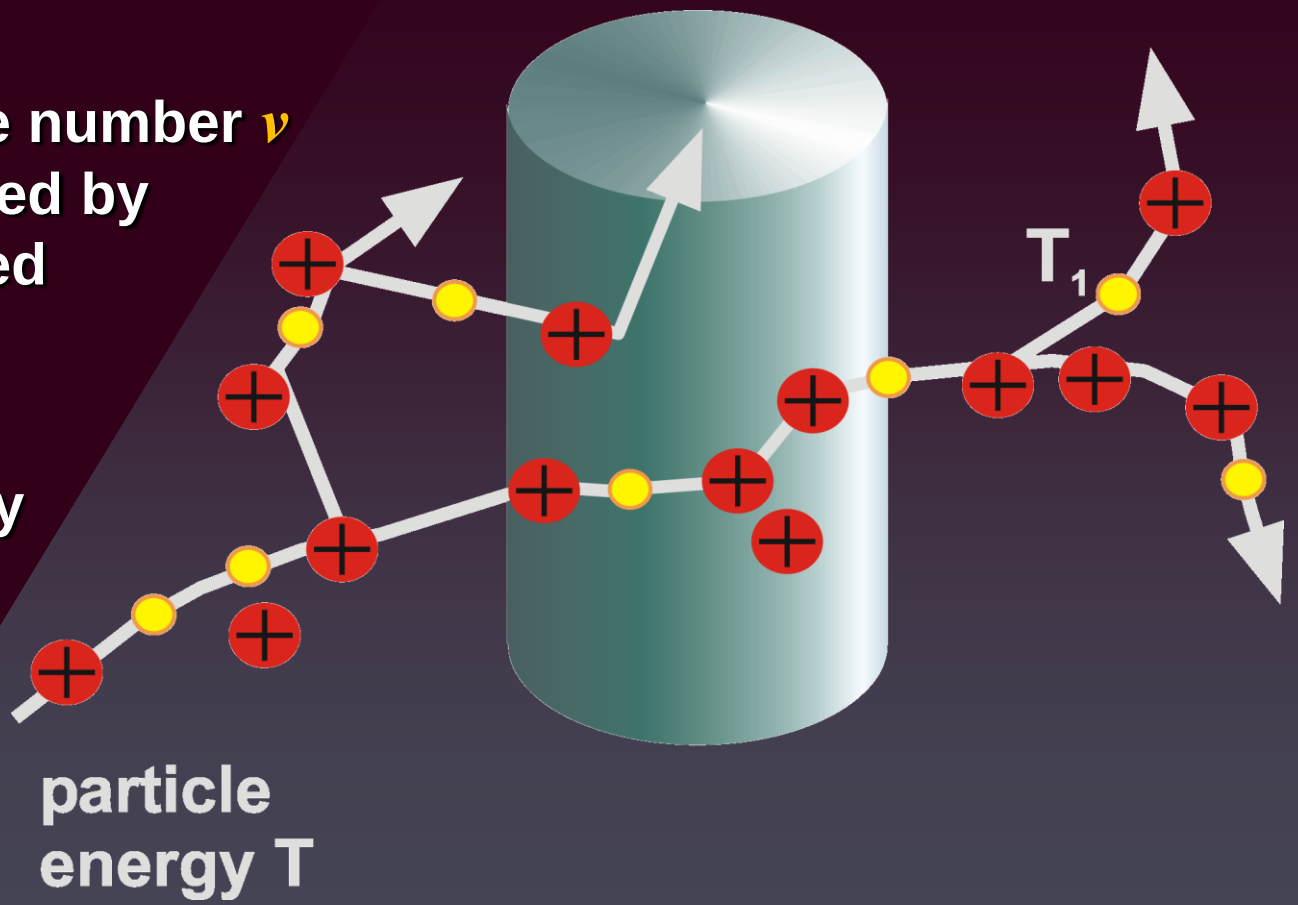
The Idea of Experimental Nanodosimetry

- Ionization cluster-size formation in nanometric cylindrical liquid water volumes is representative for the damage to the DNA

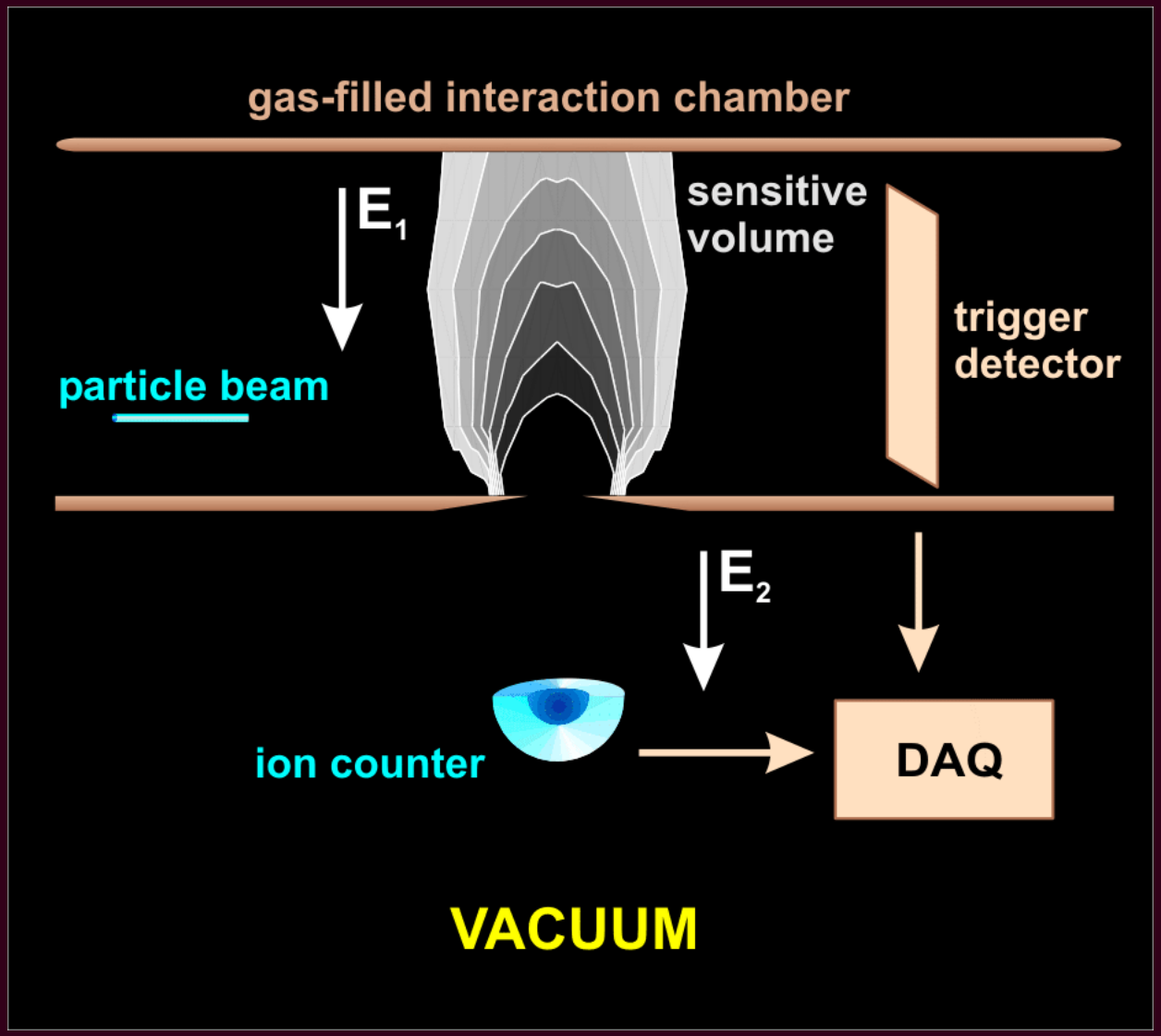
Definitions:

The cluster size is the number ν of ionizations produced by a particle in a specified target volume

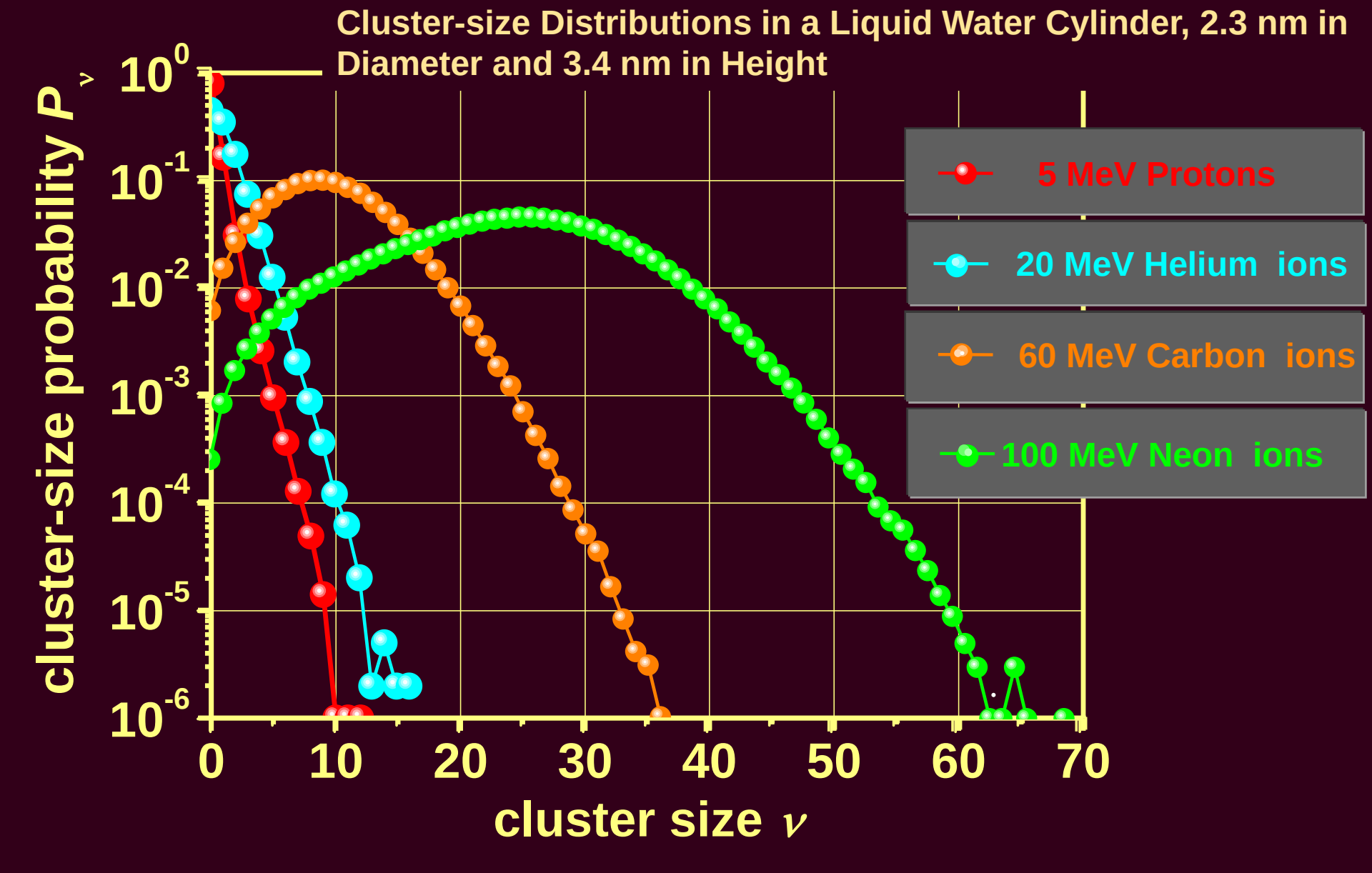
$P_\nu(T)$ is the probability of producing an ionization cluster of size ν



Principle of a Nanodosimetric Measuring Device Based on Single-ion Counting

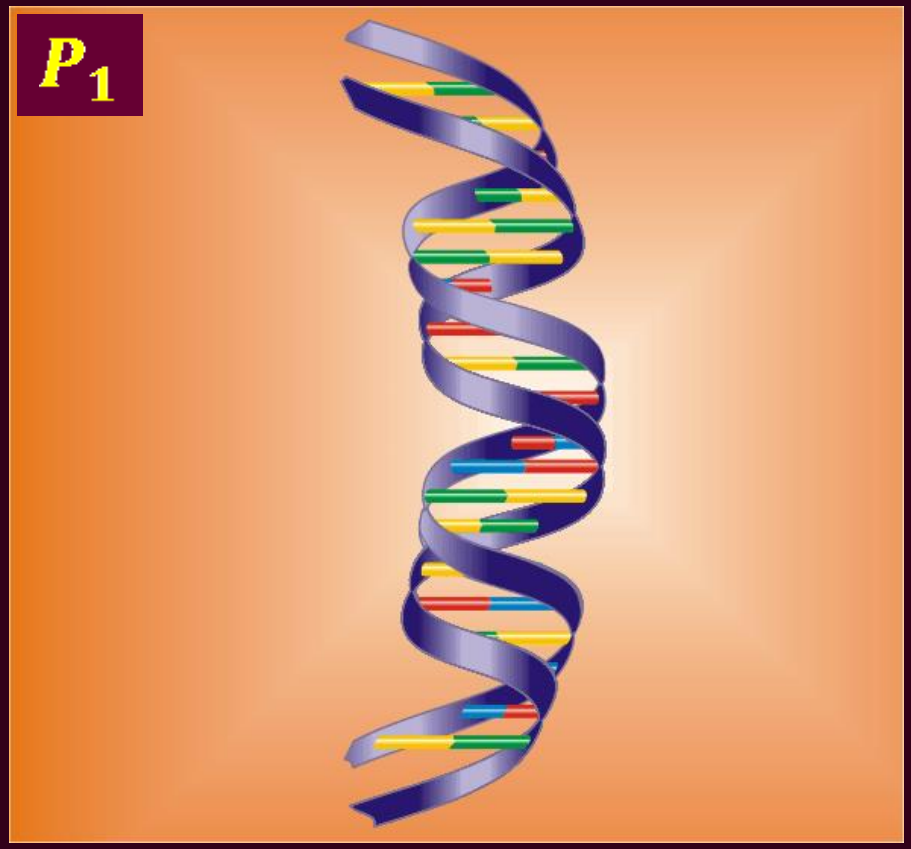


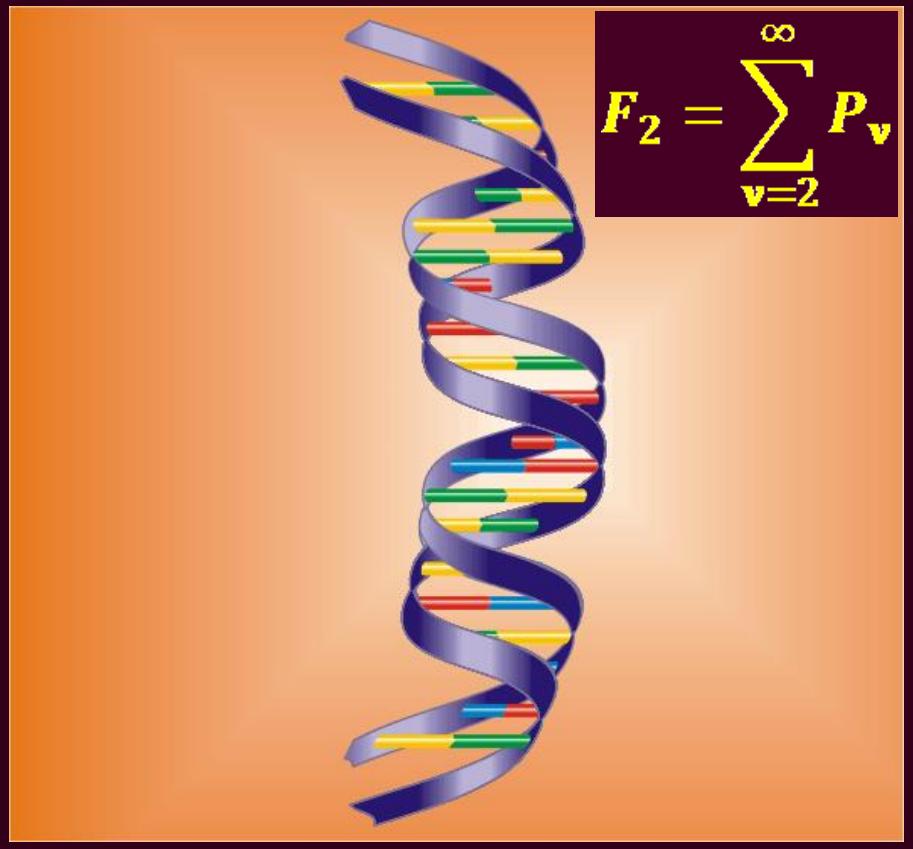
The Particle Track Structure Is Reflected by Cluster-size Probabilities in Nanometre-sized Volumes



The Relation Between Ionization Cluster-size Formation and Life Science

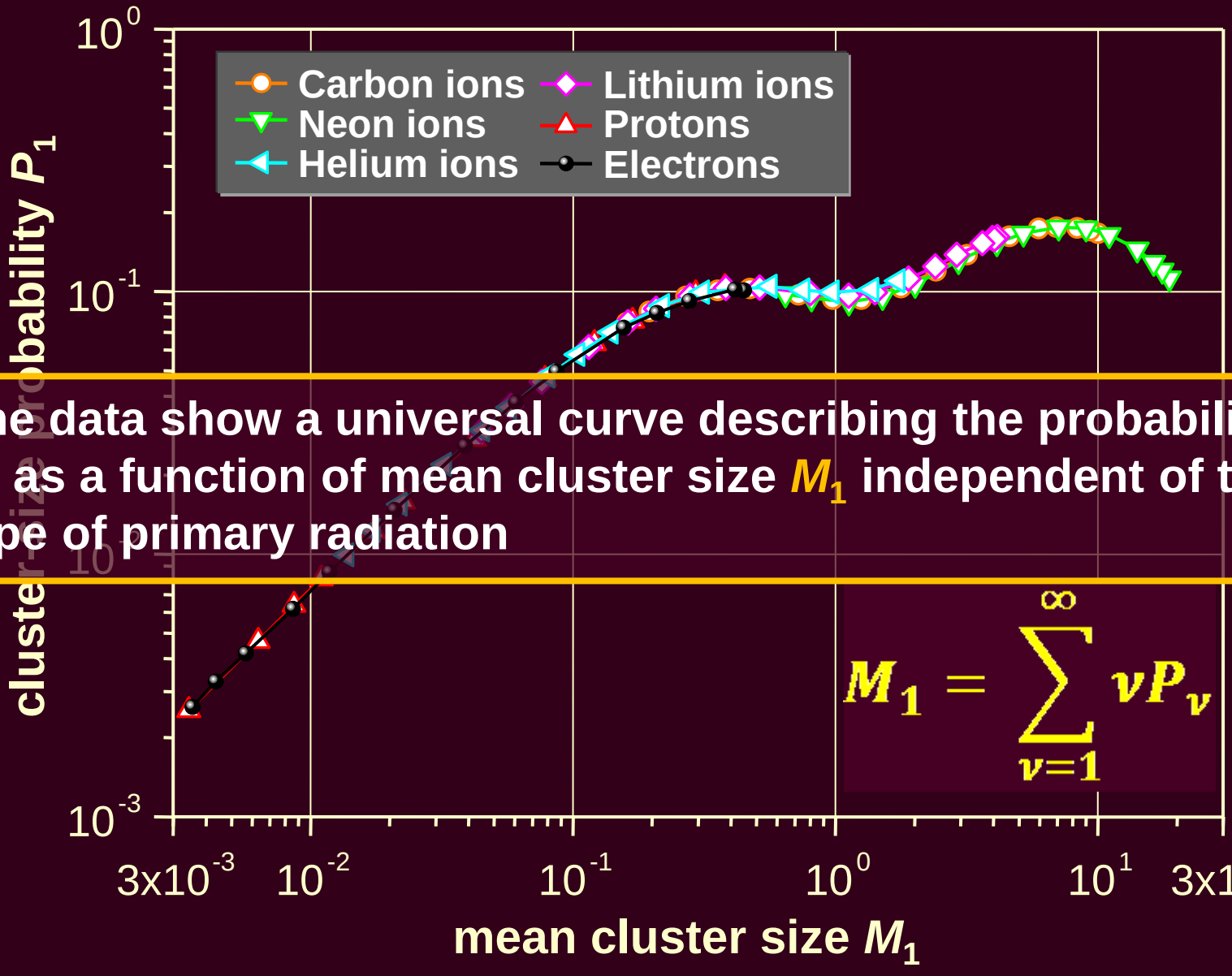
The probability P_1 to create a cluster size $\nu = 1$ should be proportional to the probability of SSB formation in the DNA





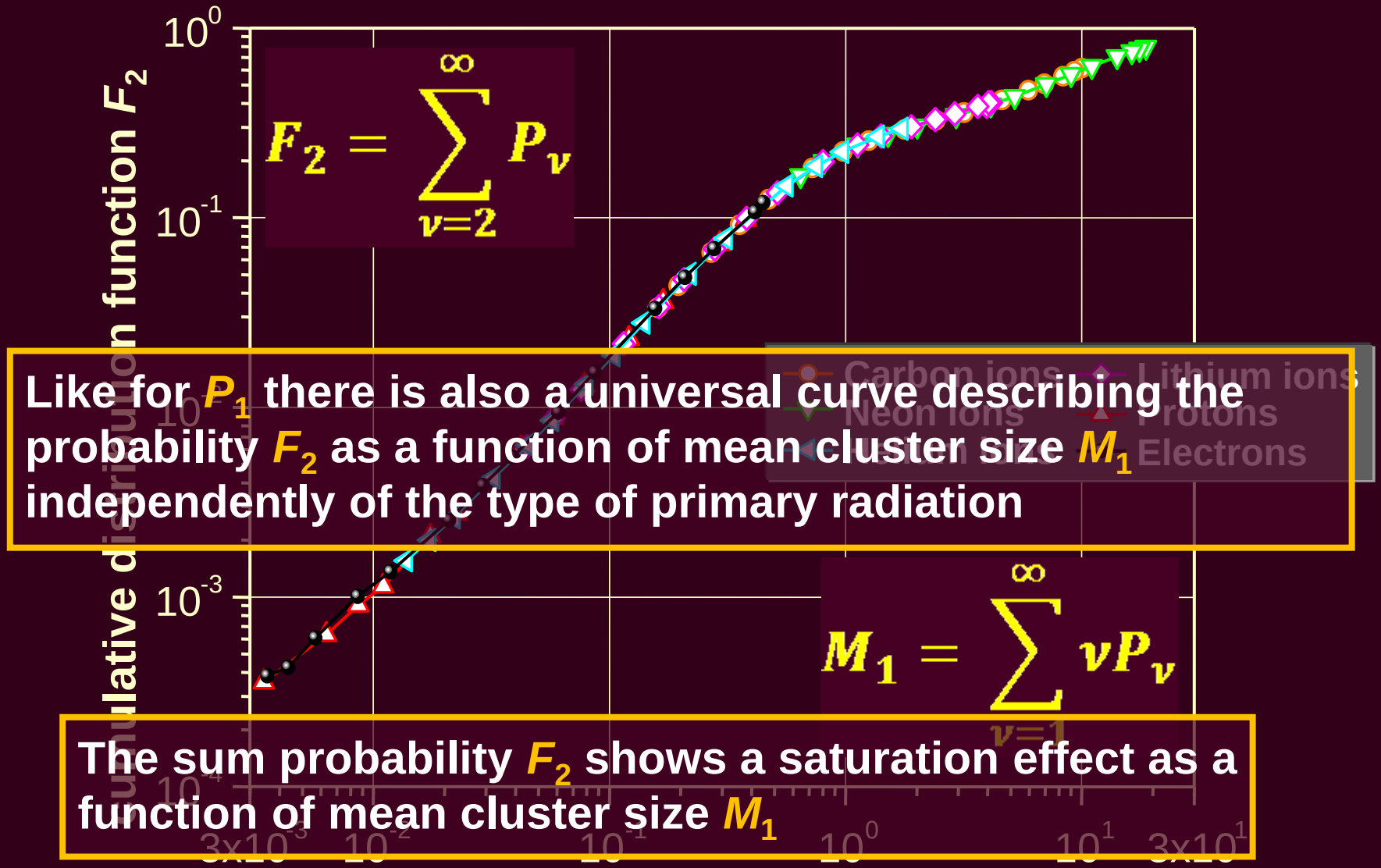
The probability F_2 to create a cluster size $\nu \geq 2$ should be proportional to the probability of DSB formation in the DNA

Cluster-size Probability P_1 in a Liquid Water Cylinder, 2.3 nm in Diameter and 3.4 nm in Height



The data show a universal curve describing the probability P_1 as a function of mean cluster size M_1 independent of the type of primary radiation

Cluster-size Probability F_2 in a Liquid Water Cylinder, 2.3 nm in Diameter and 3.4 nm in Height

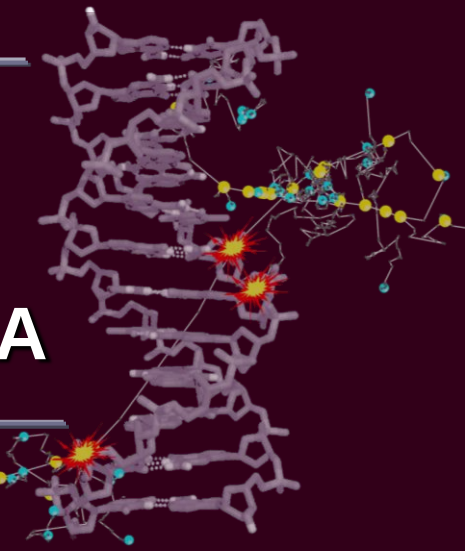


Like for P_1 there is also a universal curve describing the probability F_2 as a function of mean cluster size M_1 independently of the type of primary radiation

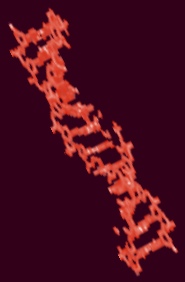
The sum probability F_2 shows a saturation effect as a function of mean cluster size M_1

Nanodosimetry, the Missing Link Between Radiation Metrology and Life Science

The greater part of radiation damage to genes or cells starts with the initial damage to segments of the DNA

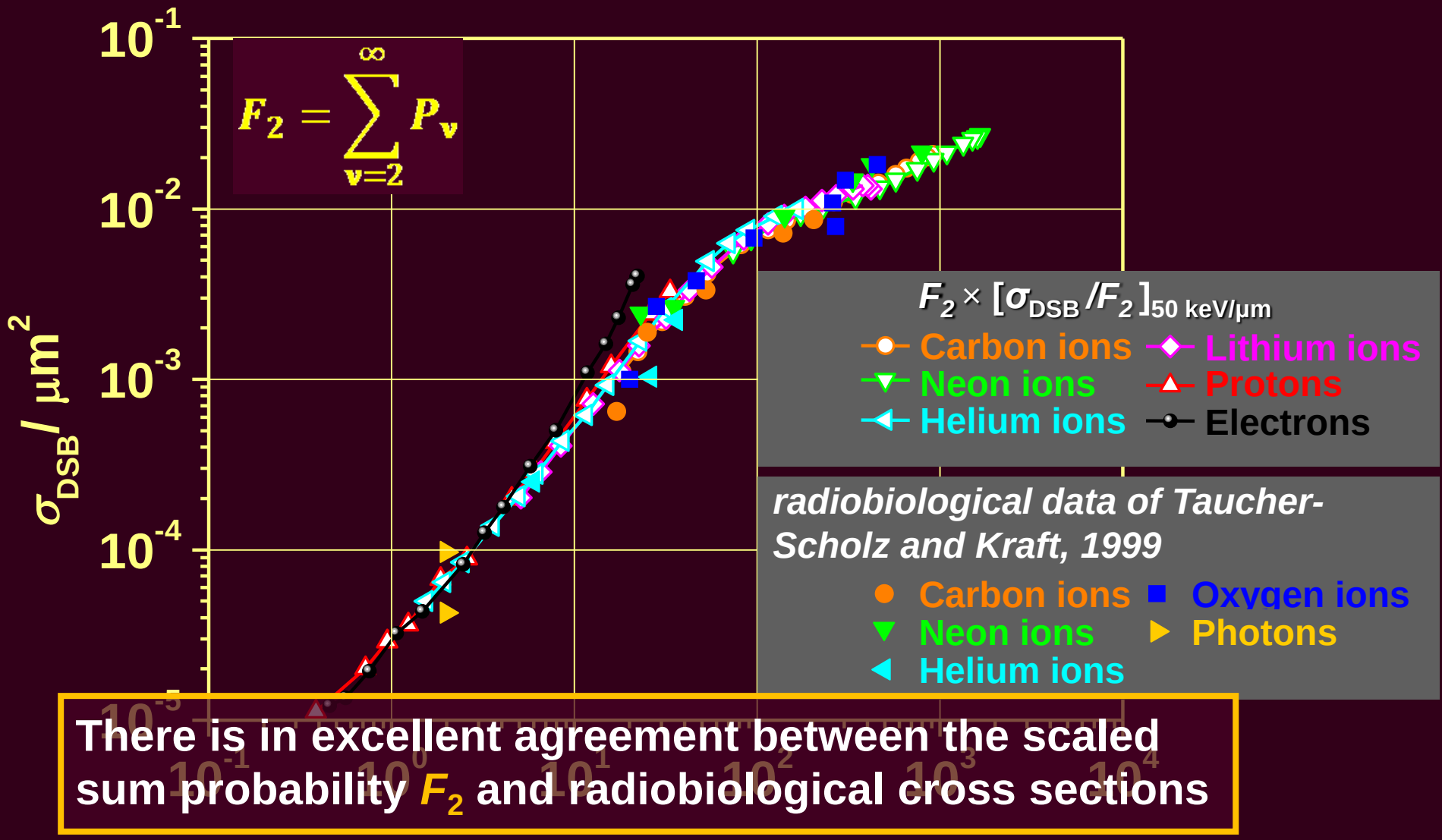


Radiation quality: **The cluster-size probability F_2 shows a saturation effect like radiobiological cross sections. Hence, F_2 is a natural parameter to describe radiation quality**



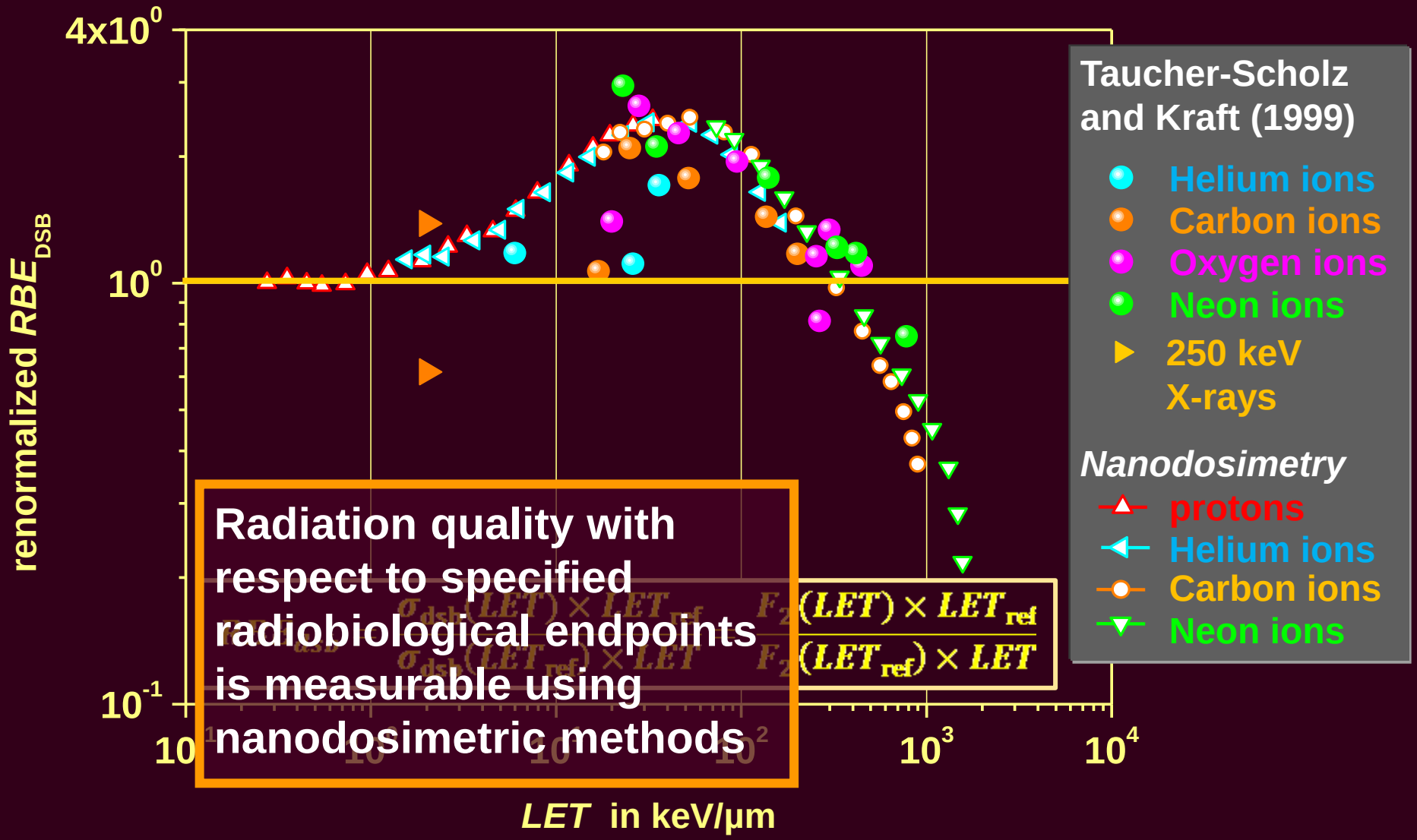
The hypothesis: **The cluster-size probabilities P_1 and F_2 are directly correlated with the damage to the DNA**

Cross Section of SV40 Viral DNA for Double-strand-break Formation, as a Function of LET

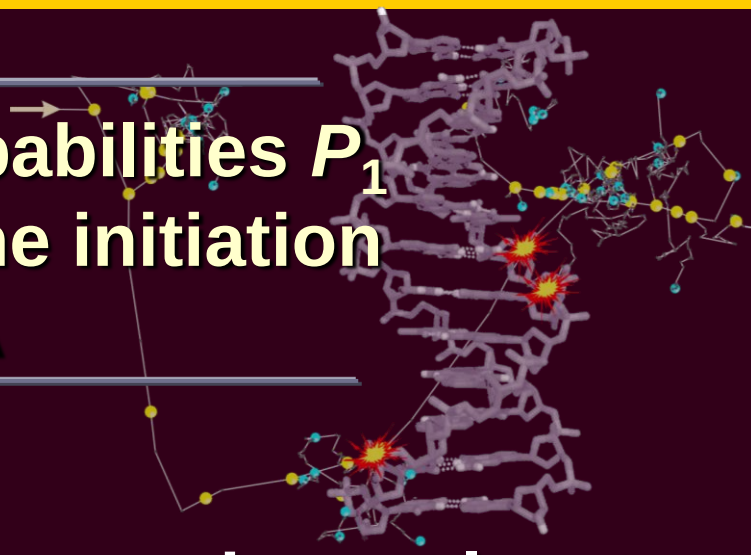


There is in excellent agreement between the scaled sum probability F_2 and radiobiological cross sections

Renormalized RBE of Light Ions for Double-strand Breaks in SV40 Viral DNA



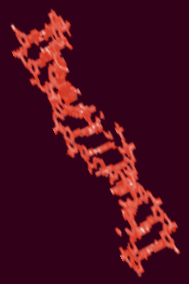
Cluster-size Probabilities in Nanometre-sized Volumes are Descriptors of Particle Track Structure



The ionization-cluster-size probabilities P_1 and F_2 are strongly related to the initiation of radiation damage to the DNA

Vision of the future:

Absorbed dose will be exchanged or, at least, supplemented by nanodosimetric quantities to characterize radiation quality in unknown radiation fields



The precondition: **Practical instruments are available which can be used in unknown radiation fields**

From Microdosimetry to Nanodosimetry, a Summary

Microdosimetry

- Practical instruments are available but should be extended to nanometric sizes

Nanodosimetric quantities

- reflect the track structure of ionizing radiation
- behave, as a function of radiation quality, similarly to radiation-induced damages to the DNA
- are measurable using single-ion or single-electron counting techniques but practical instruments are not yet available