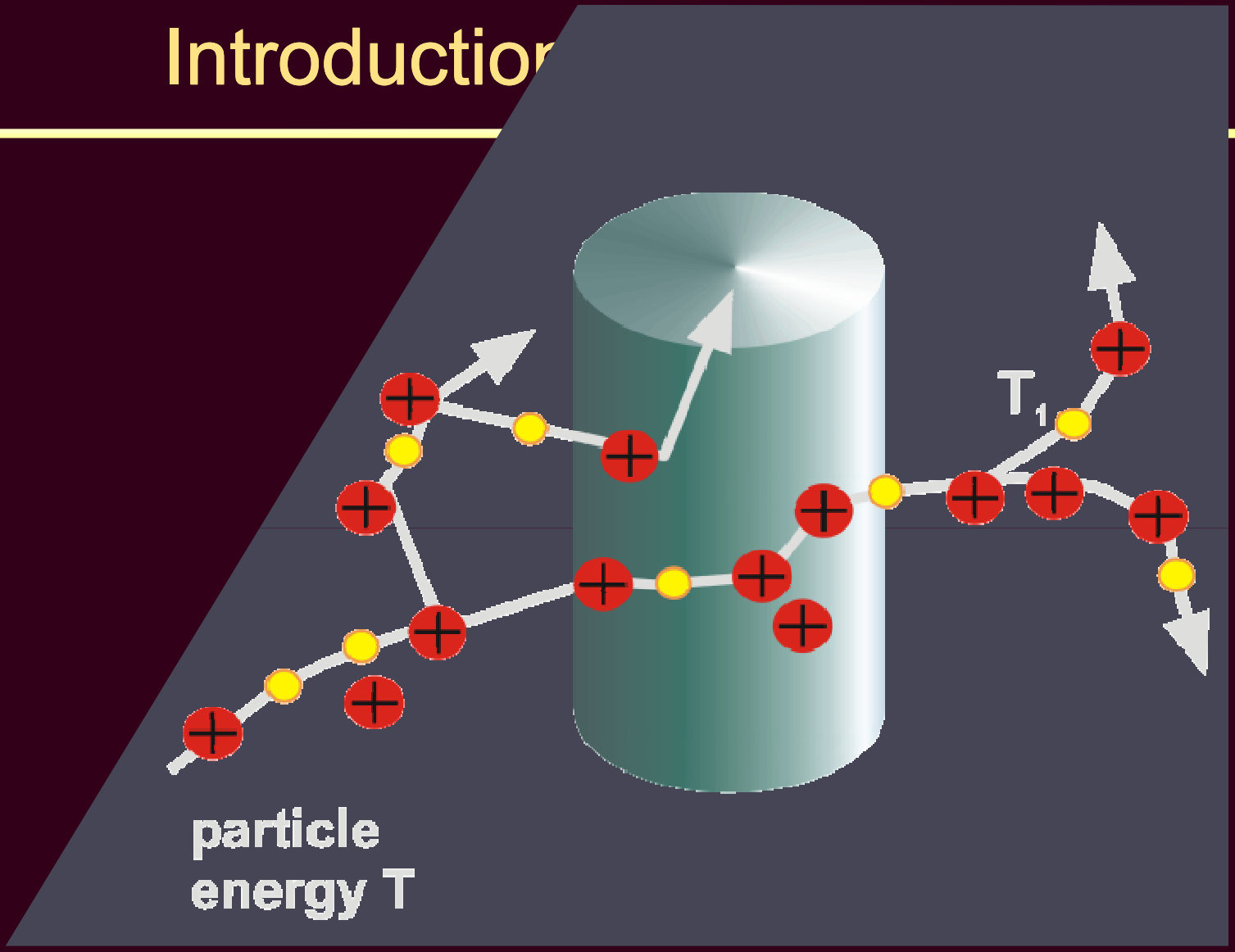
Introductio

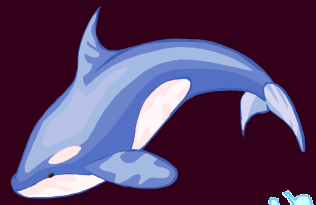


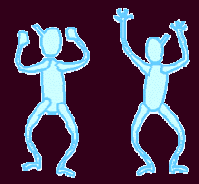
Bernd Grosswendt (retired), Physikalisch-Technische Bundesanstalt, Braunschweig, Germany

Radiation Damage: The Characteristic Target Sizes in Life Science

Typical Sizes of 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

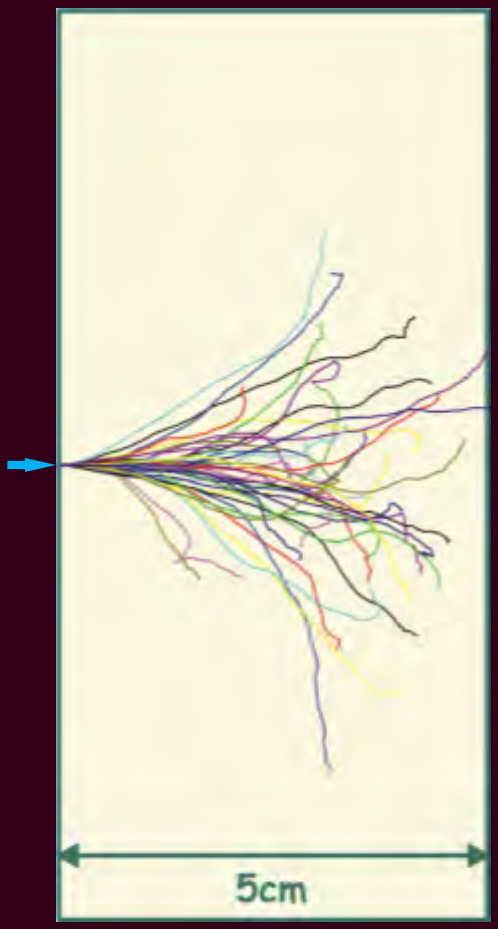
Chromosome fibre

DNA molecule

H_2 molecule

Radiation protection

Treatment planning in radiation therapy



The absorbed-dose concept

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

The 'Golden Rule' of Conventional Applied Radiation Physics

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

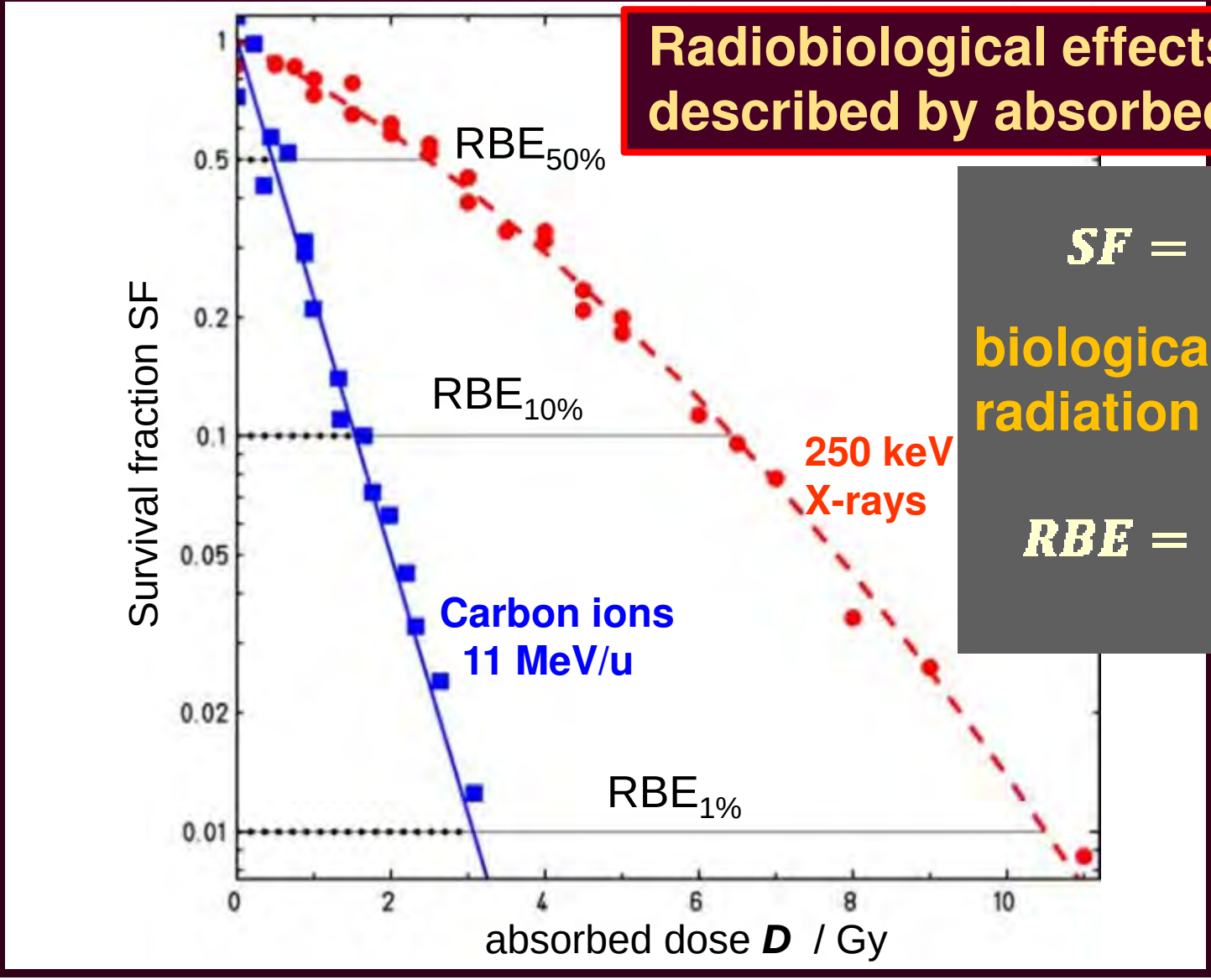
- *Radiation Biology*
- *Radiation Therapy*
- *Radiation Protection*

The necessary conditions:

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

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

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



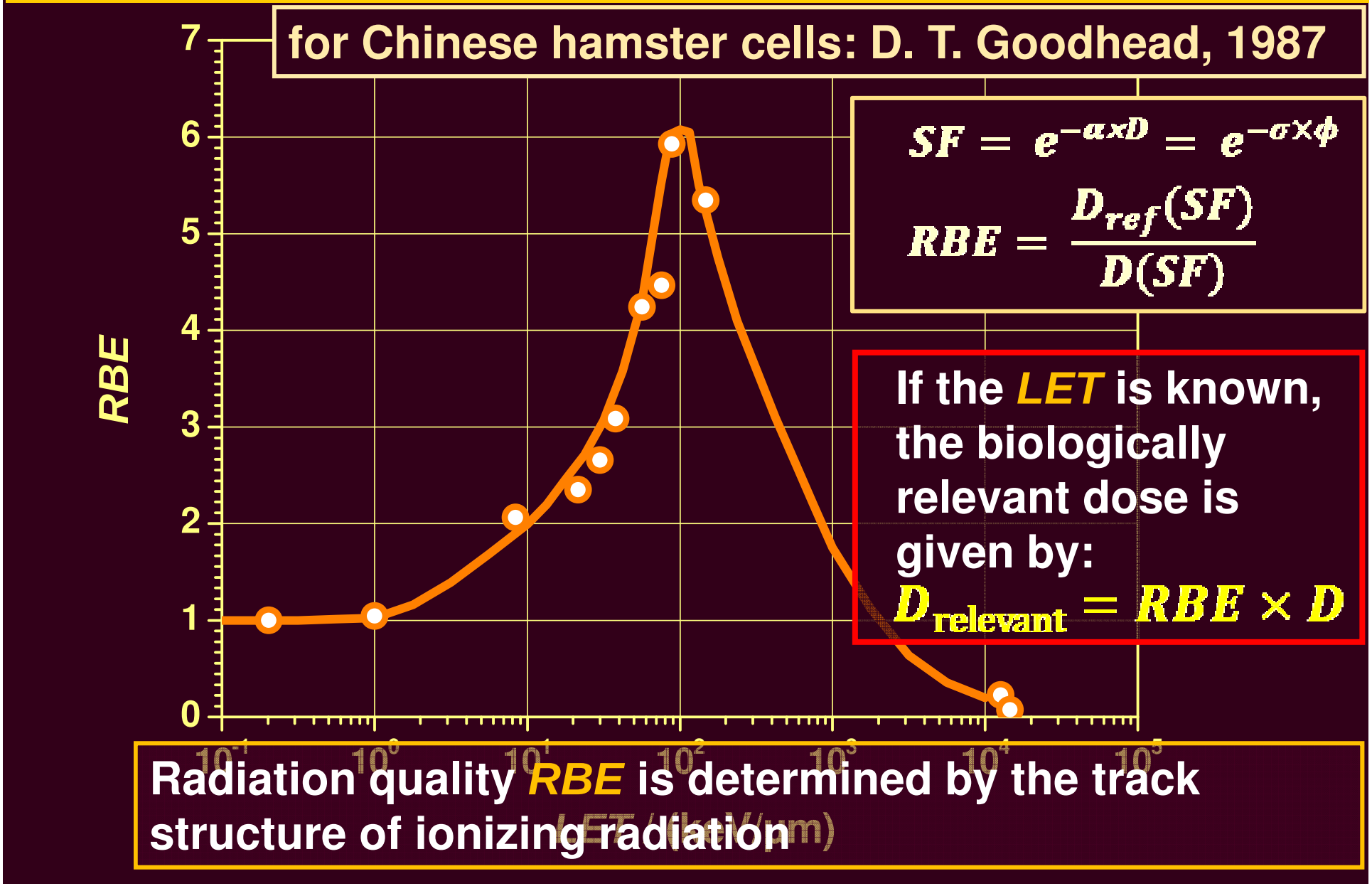
Radiobiological effects cannot be described by absorbed dose

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

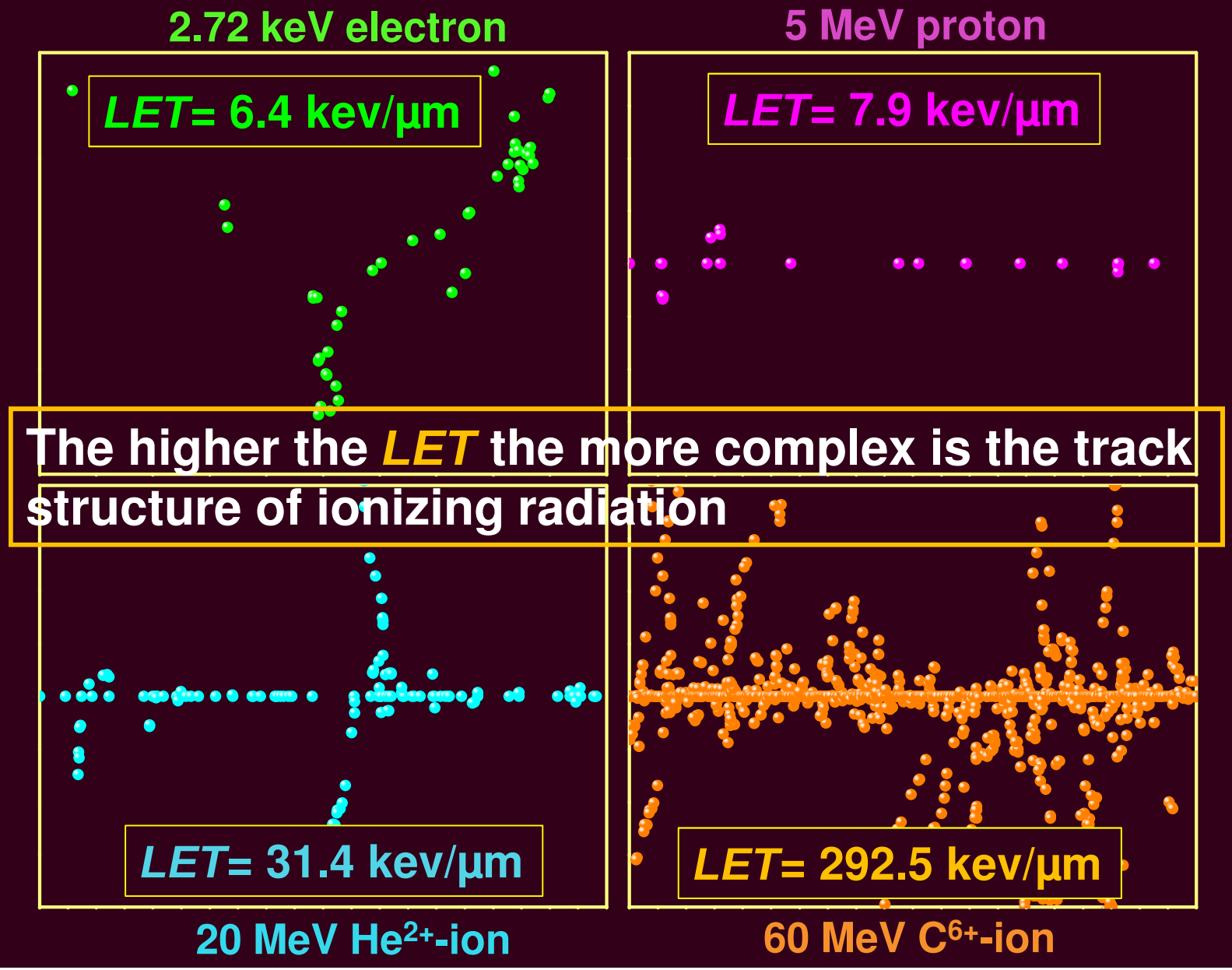
biologically defined radiation quality

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

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

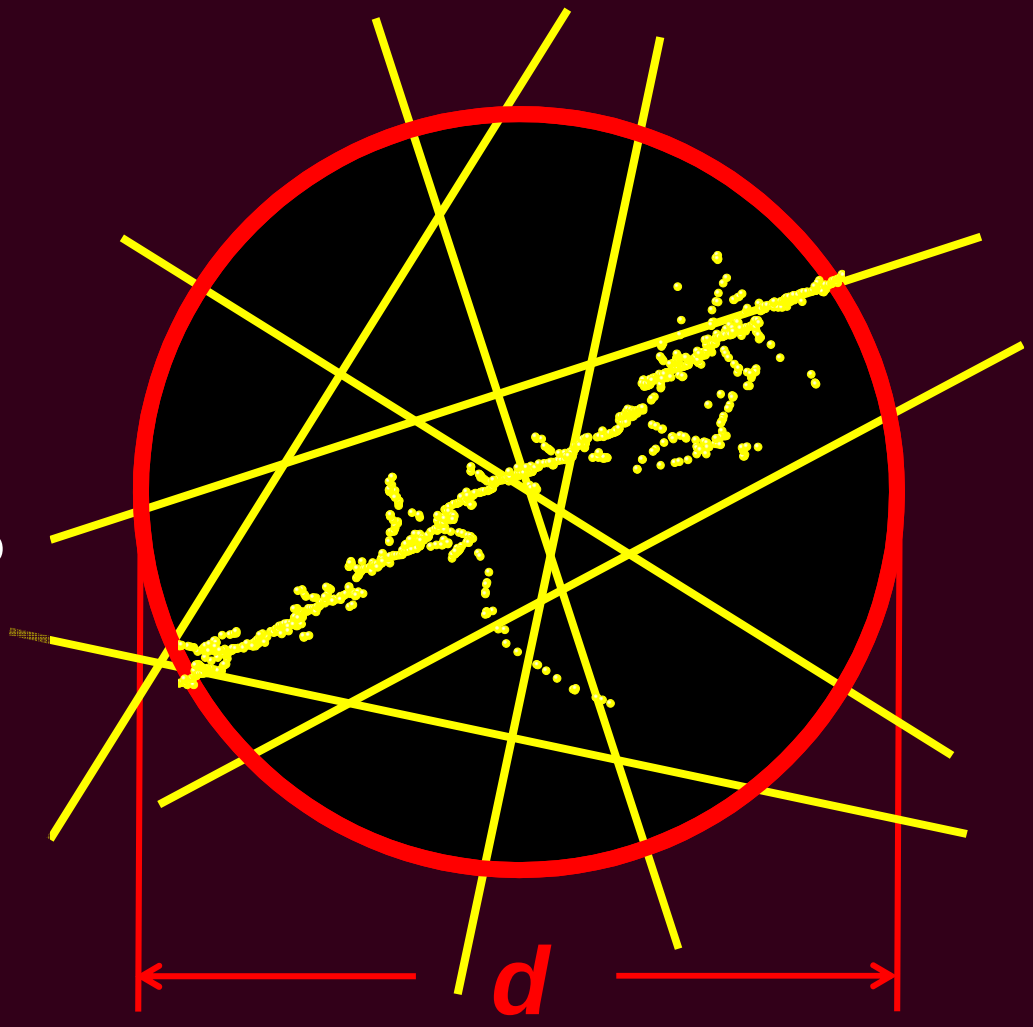


Particle Track Structures: Track Segments in Water, 100 nm in Length



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

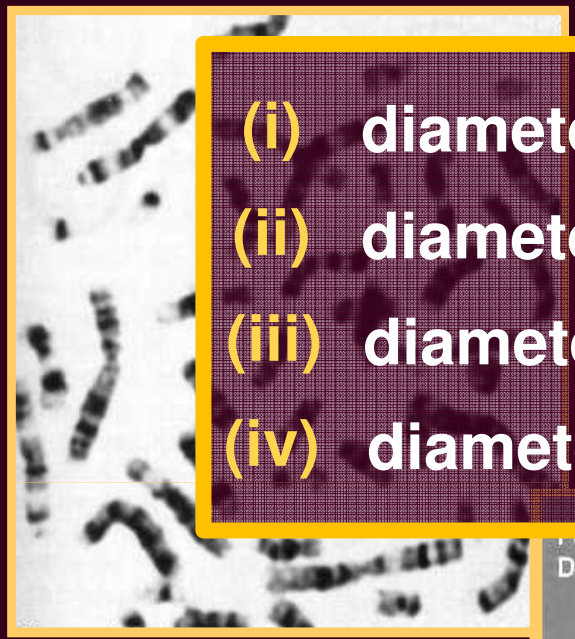
The measurements are made in gaseous volumes the typical size of which corresponds to that of liquid water spheres, 1 µm in diameter

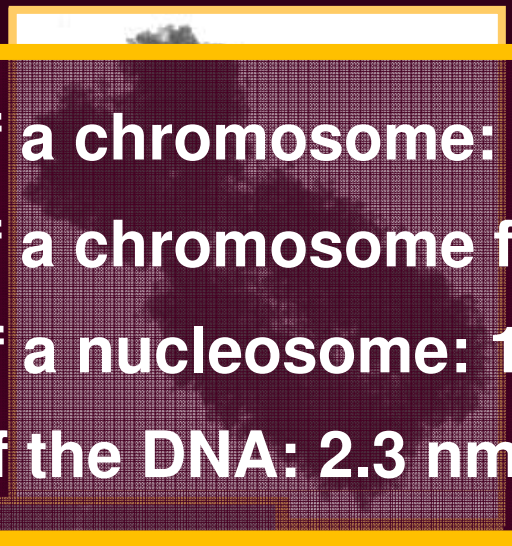


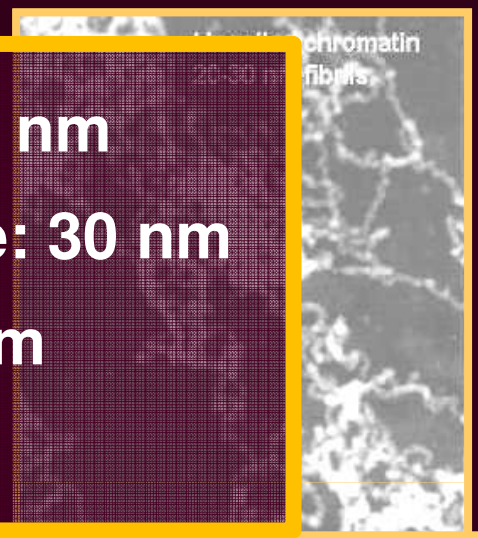
The disadvantage of this procedure is the averaging over comparably large track lengths: hence, a detailed information on track structure is lost

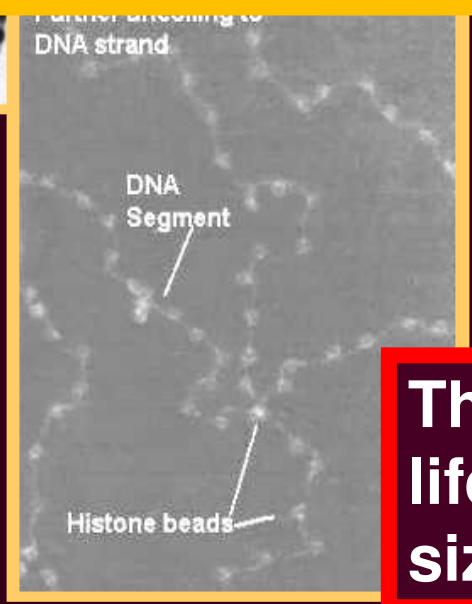
The "True" Target Volumes of Life Science

(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





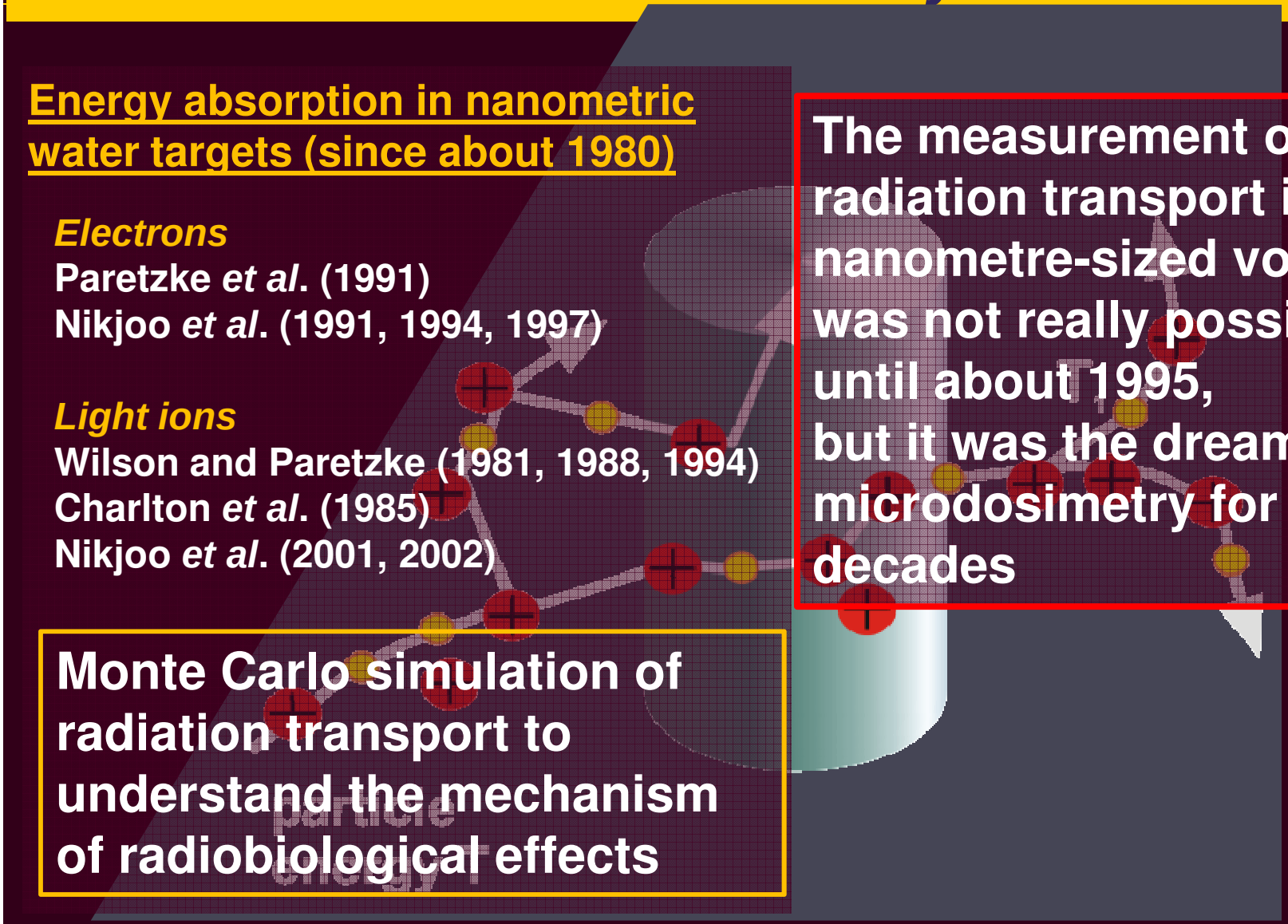




The real target volumes of radio-biology and also of radiation physics are those of the substructures of cell nuclei

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

Radiation Physics in Nanometre-sized Volumes, a Short History



Energy absorption in nanometric water targets (since about 1980)

Electrons

Paretzke *et al*. (1991)
Nikjoo *et al*. (1991, 1994, 1997)

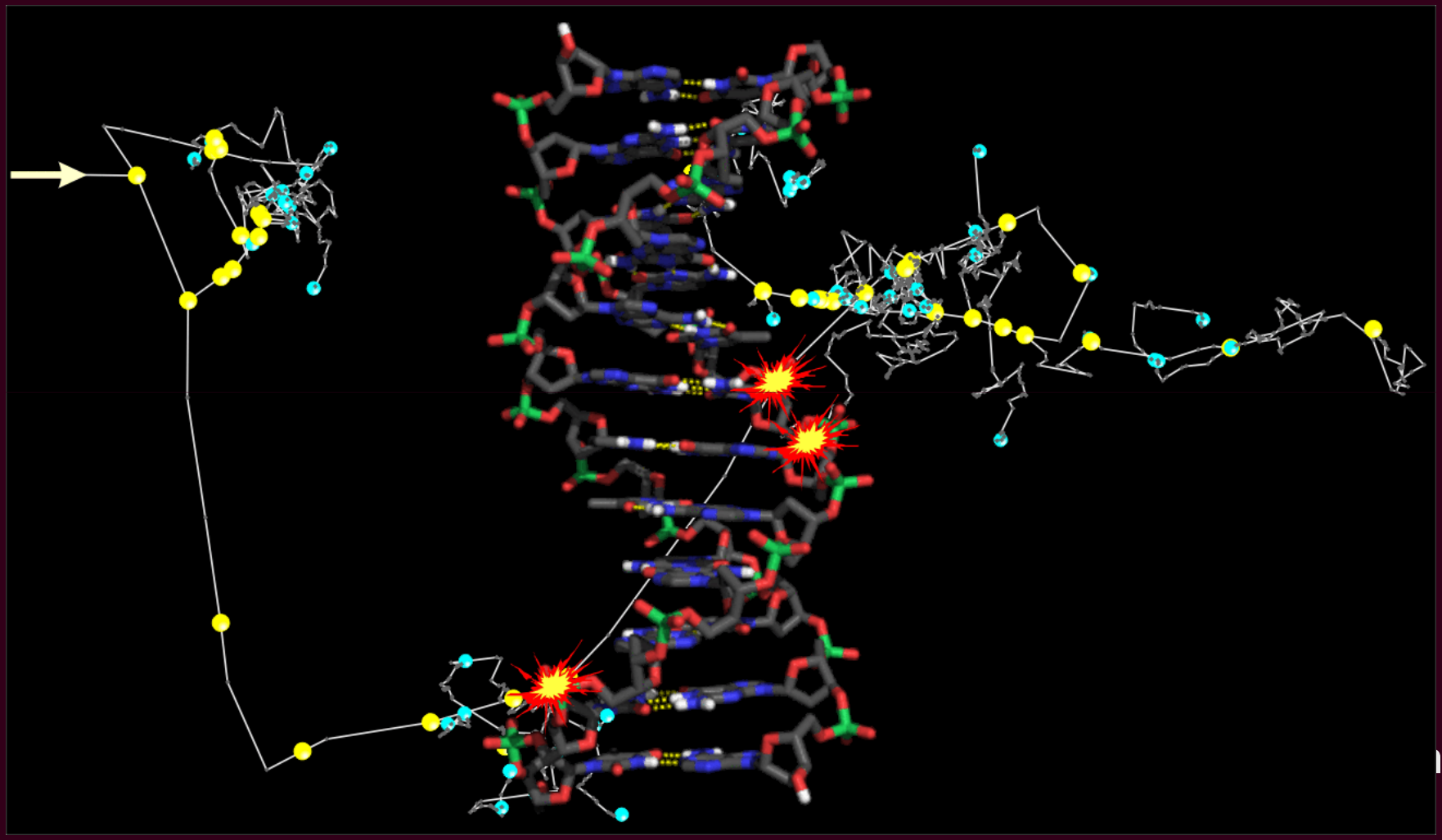
Light ions

Wilson and Paretzke (1981, 1988, 1994)
Charlton *et al*. (1985)
Nikjoo *et al*. (2001, 2002)

Monte Carlo simulation of radiation transport to understand the mechanism of radiobiological effects

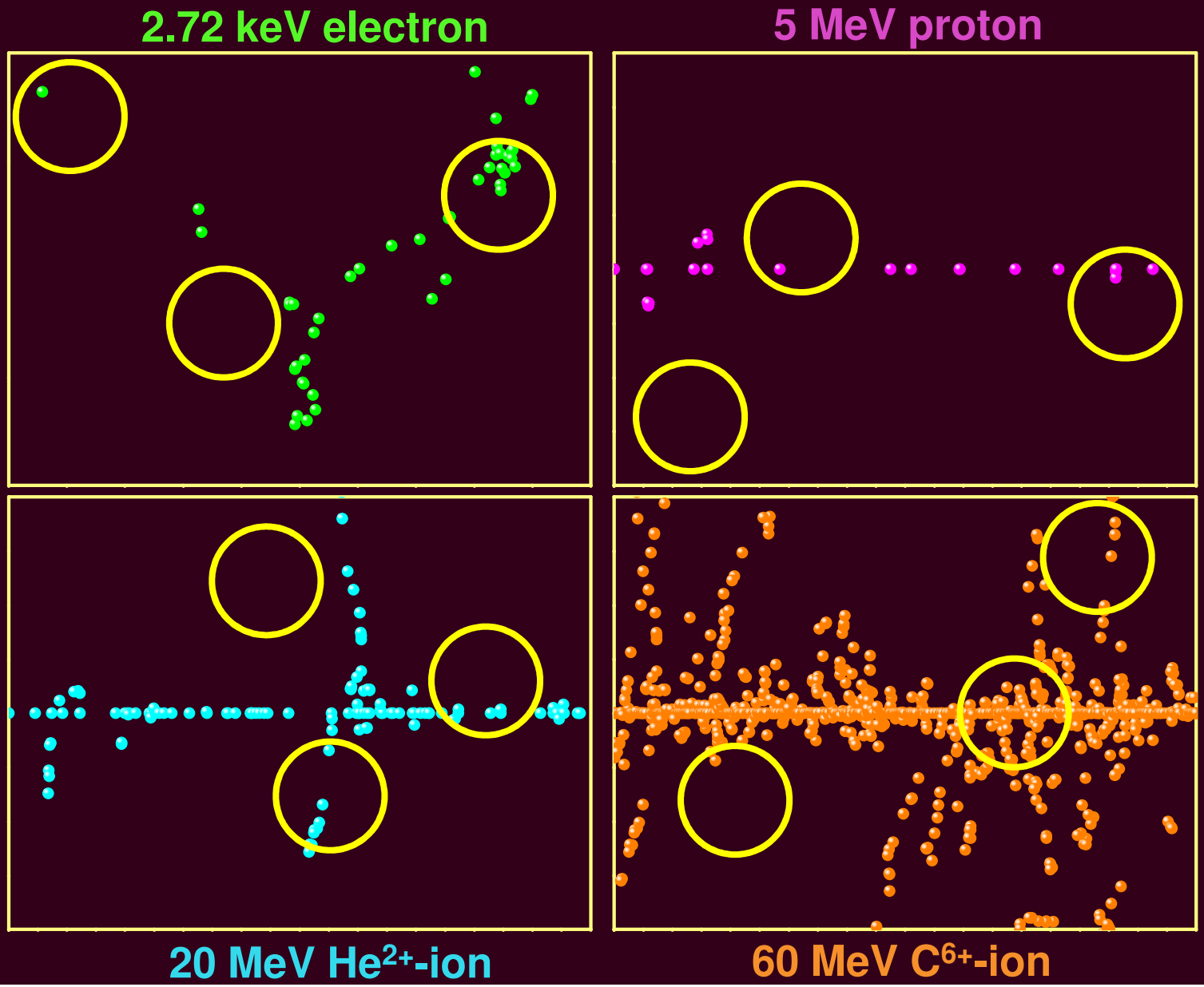
The measurement of radiation transport in nanometre-sized volumes was not really possible until about 1995, but it was the dream of microdosimetry for several decades

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



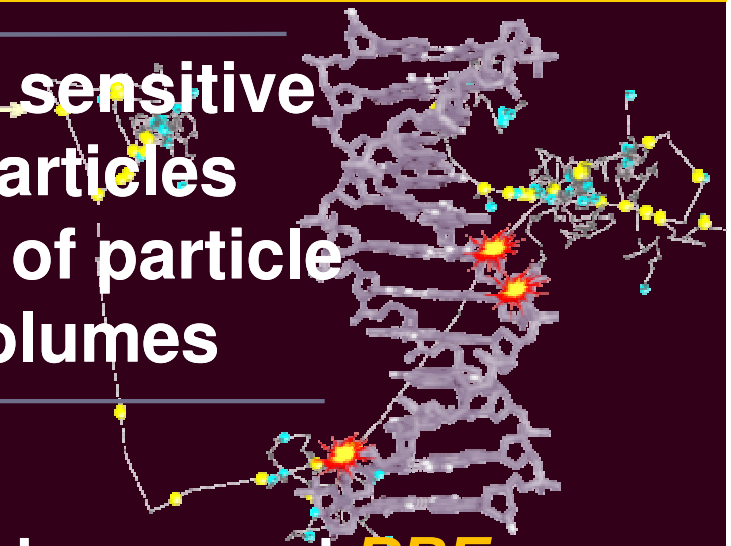
Radiation damage strongly depends on the number of relevant particle interactions, and, in consequence, on particle track structure

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



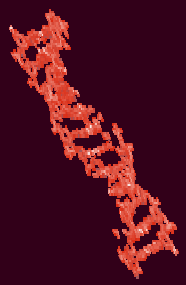
The Characterization of Particle Track Structure by Measurement: a Challenge to the Metrology of Ionizing Radiation

The measuring quantities must be sensitive to the track structure of ionizing particles and able to reflect the stochastics of particle interactions in nanometre-sized volumes

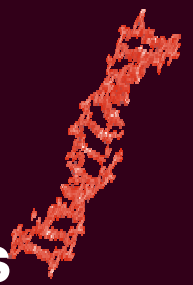


The needs for metrology:

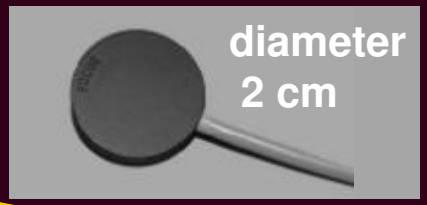
- ❖ measuring quantities which take into account ***RBE***
- ❖ an appropriate measuring procedure
- ❖ validation of the procedure

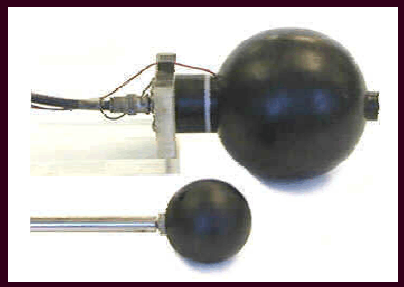


The hypothesis: **The damage to segments of the DNA behaves, as a function of radiation quality (track structure), similarly to the number of particle interactions in nanometre-sized volumes**

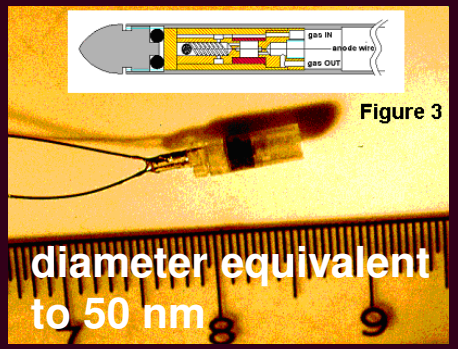


To Take into Account Particle Track Structure in Metrology Requires a Drastic Reduction of the Target Volume





diameter
equivalent to 1 µm



3 cm
typical tumor diameter

100 µm
typical cell diameter

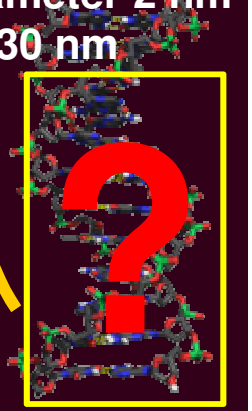
5 µm
cell nucleus

human cell

cell nucleus

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: The damage to segments of the DNA is initiated to a great part by ionization processes

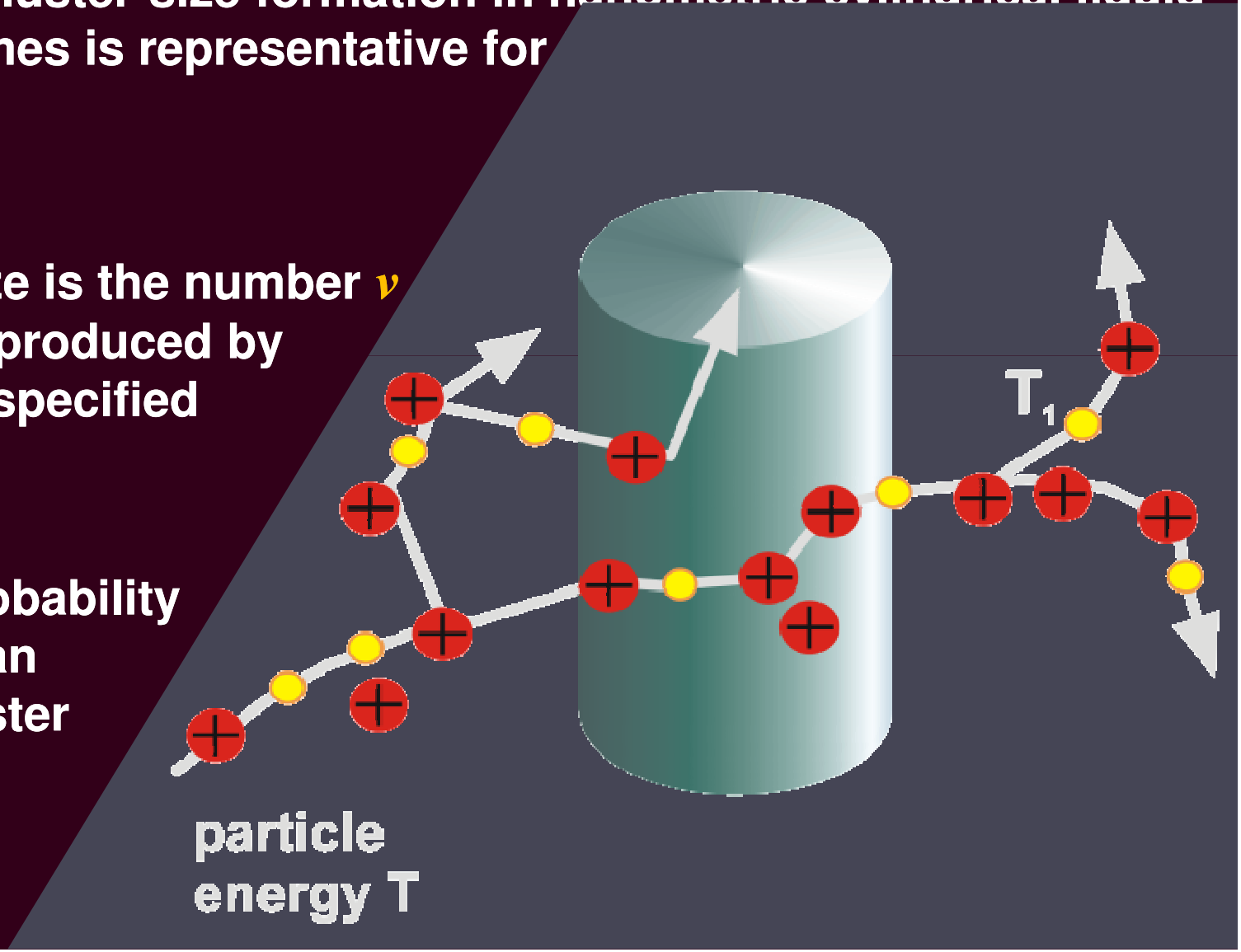
The Idea of Experimental Nanodosimetry

- Ionization cluster-size formation in nanometric cylindrical liquid water volumes is representative for

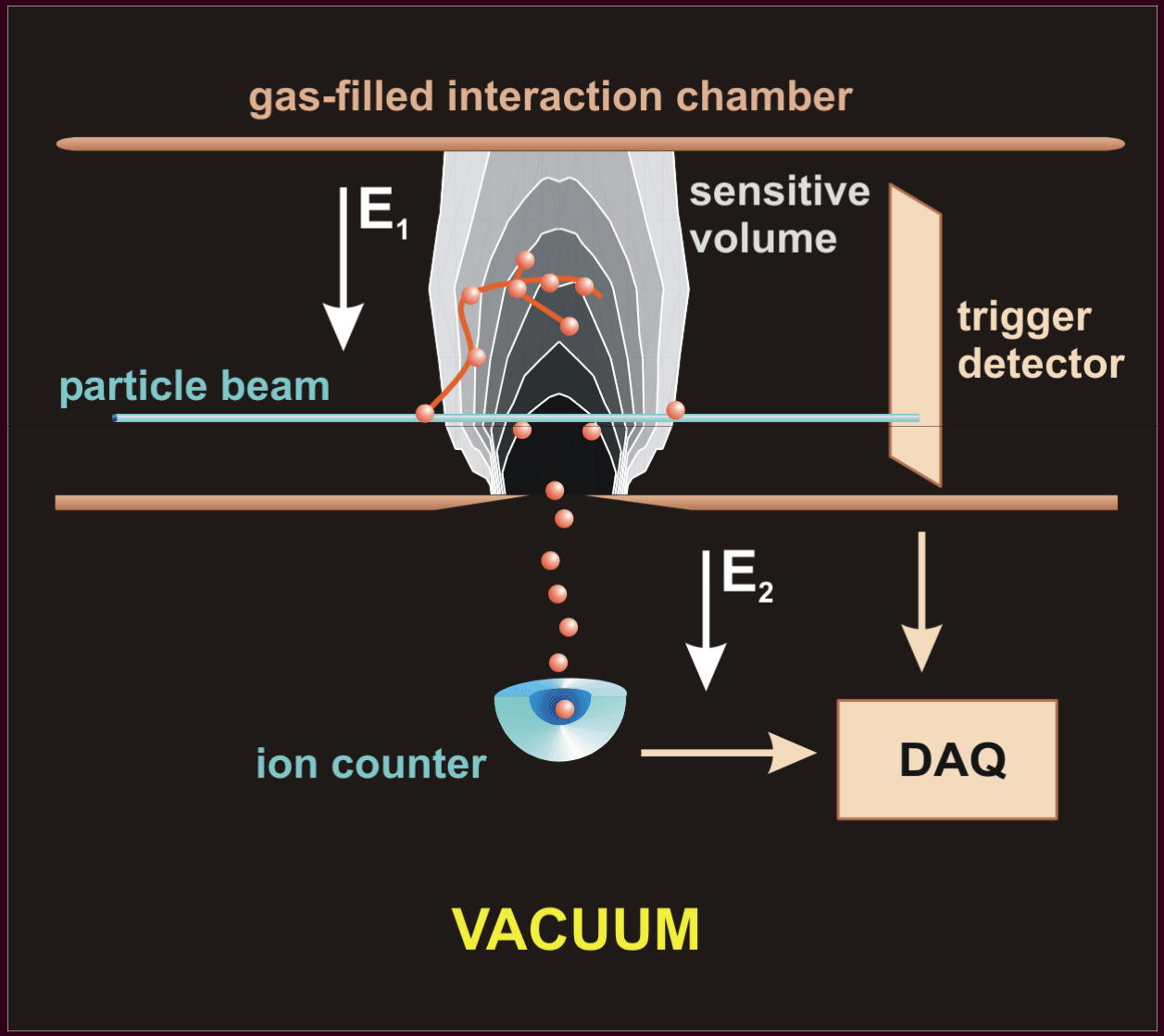
Definitions:

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

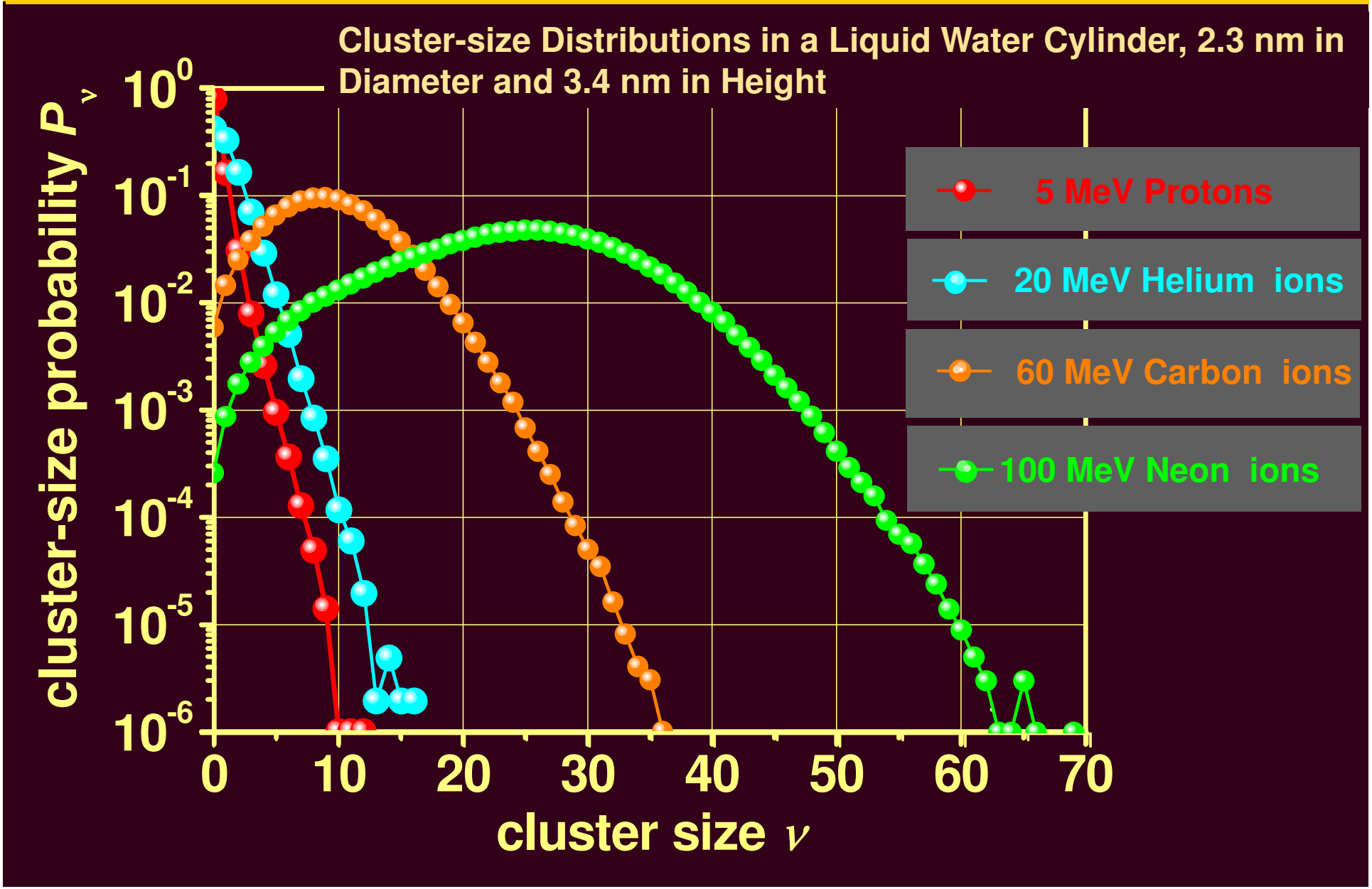
$P_\nu(T)$ is the probability of producing an ionization cluster of size ν



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

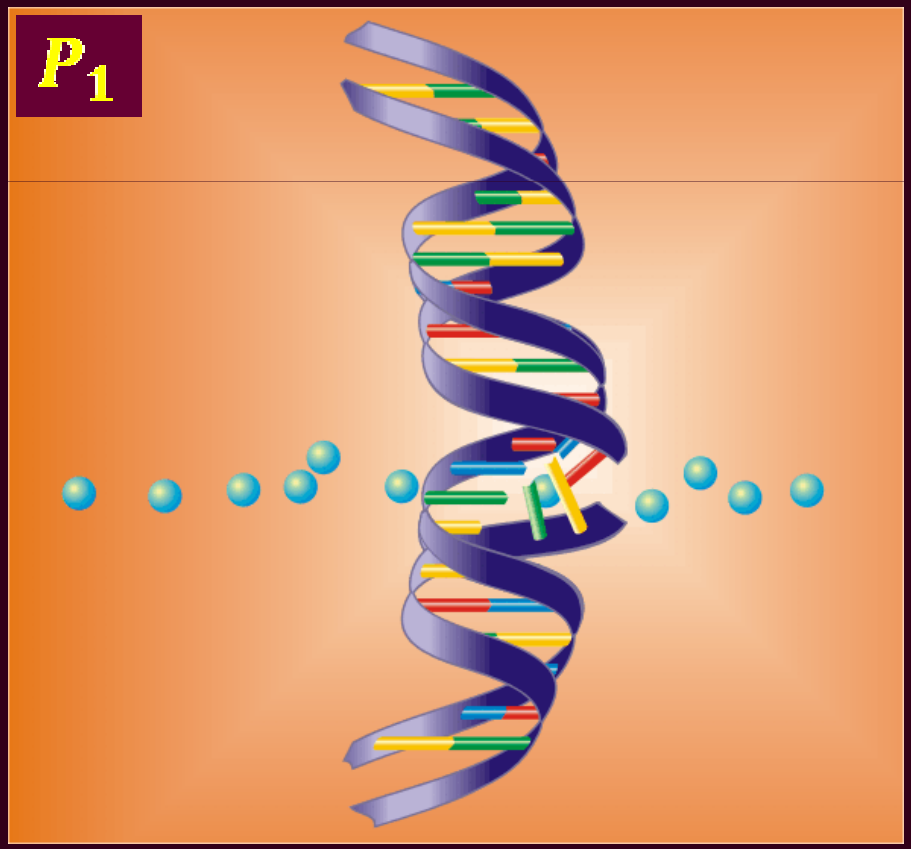


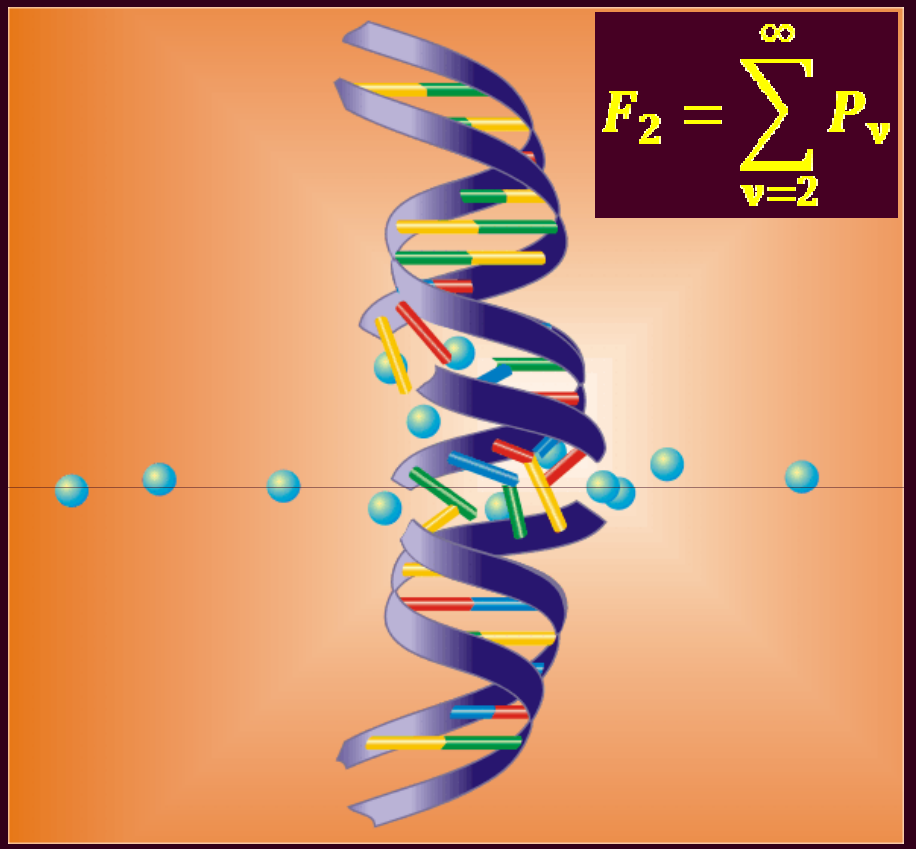
The Particle Track Structure Is Reflected by Cluster-size Probabilities in Nanometre-sized Volumes



The Relation Between Ionization Cluster-size Formation and Life Science

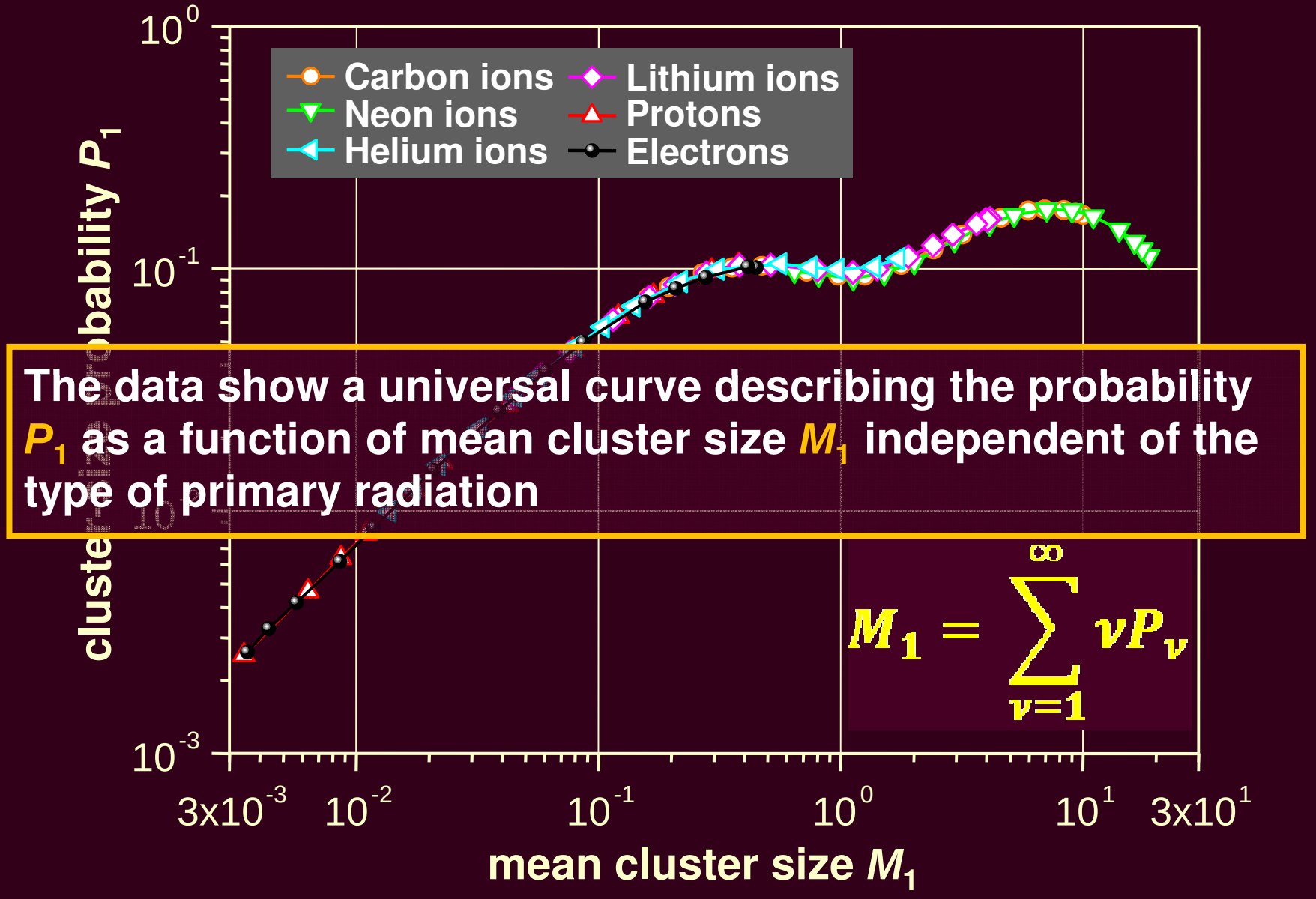
The probability P_1 to create a cluster size $\nu = 1$ should be proportional to the probability of SSB formation in the DNA





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

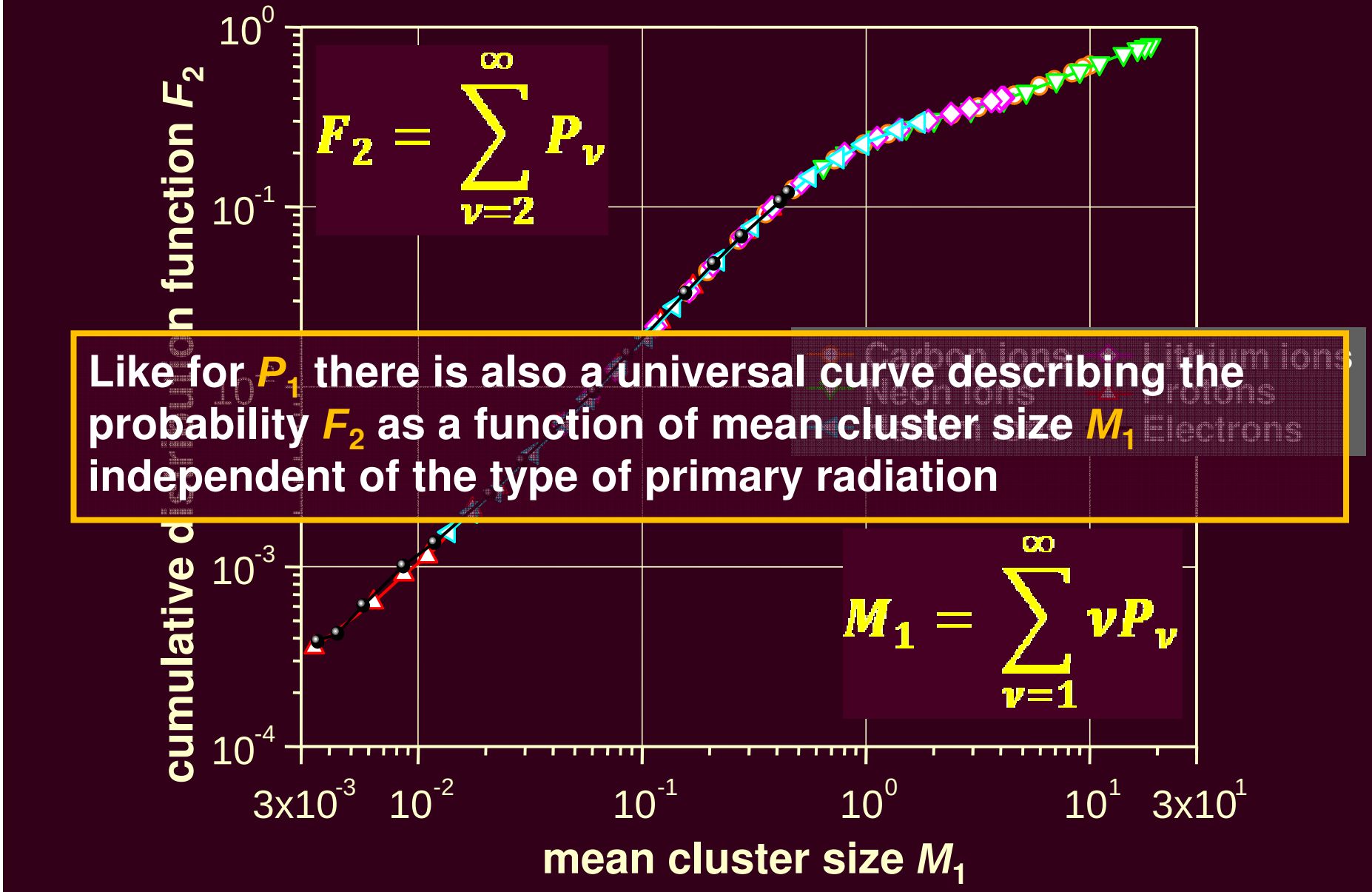
Cluster-size Probability P_1 in a Liquid Water Cylinder, 2.3 nm in Diameter and 3.4 nm in Height



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

$$M_1 = \sum_{\nu=1}^{\infty} \nu P_\nu$$

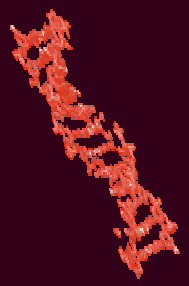
Cluster-size Probability F_2 in a Liquid Water Cylinder, 2.3 nm in Diameter and 3.4 nm in Height



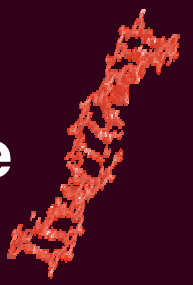
Nanodosimetry, the Missing Link Between Radiation Metrology and Life Science

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

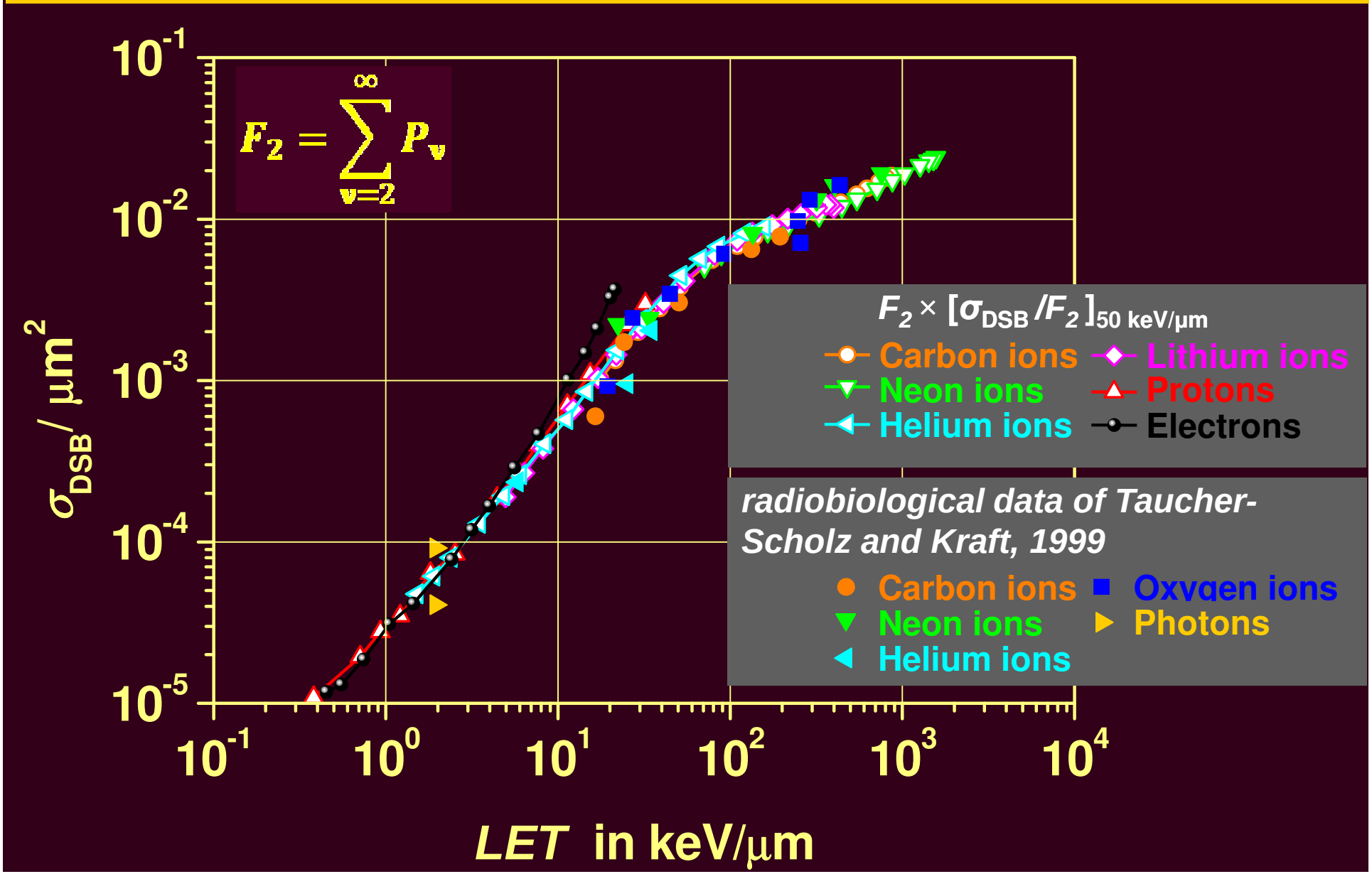
Radiation quality: **The probabilities P_1 and F_2 are the natural nanodosimetric parameters to describe the radiation quality of ionizing particles**



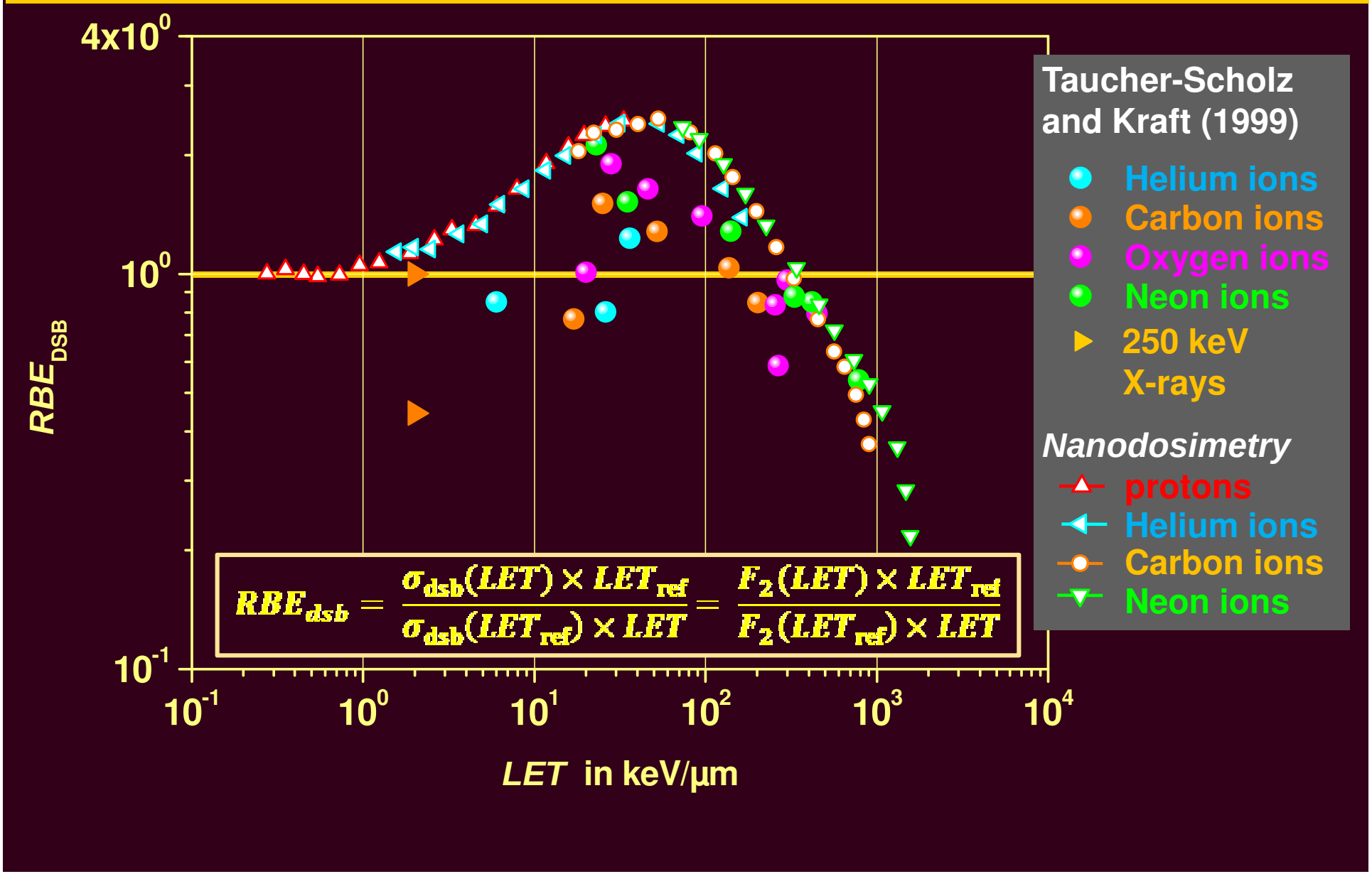
The hypothesis: **The cluster-size probabilities P_1 and F_2 are directly correlated with the damage to the DNA**



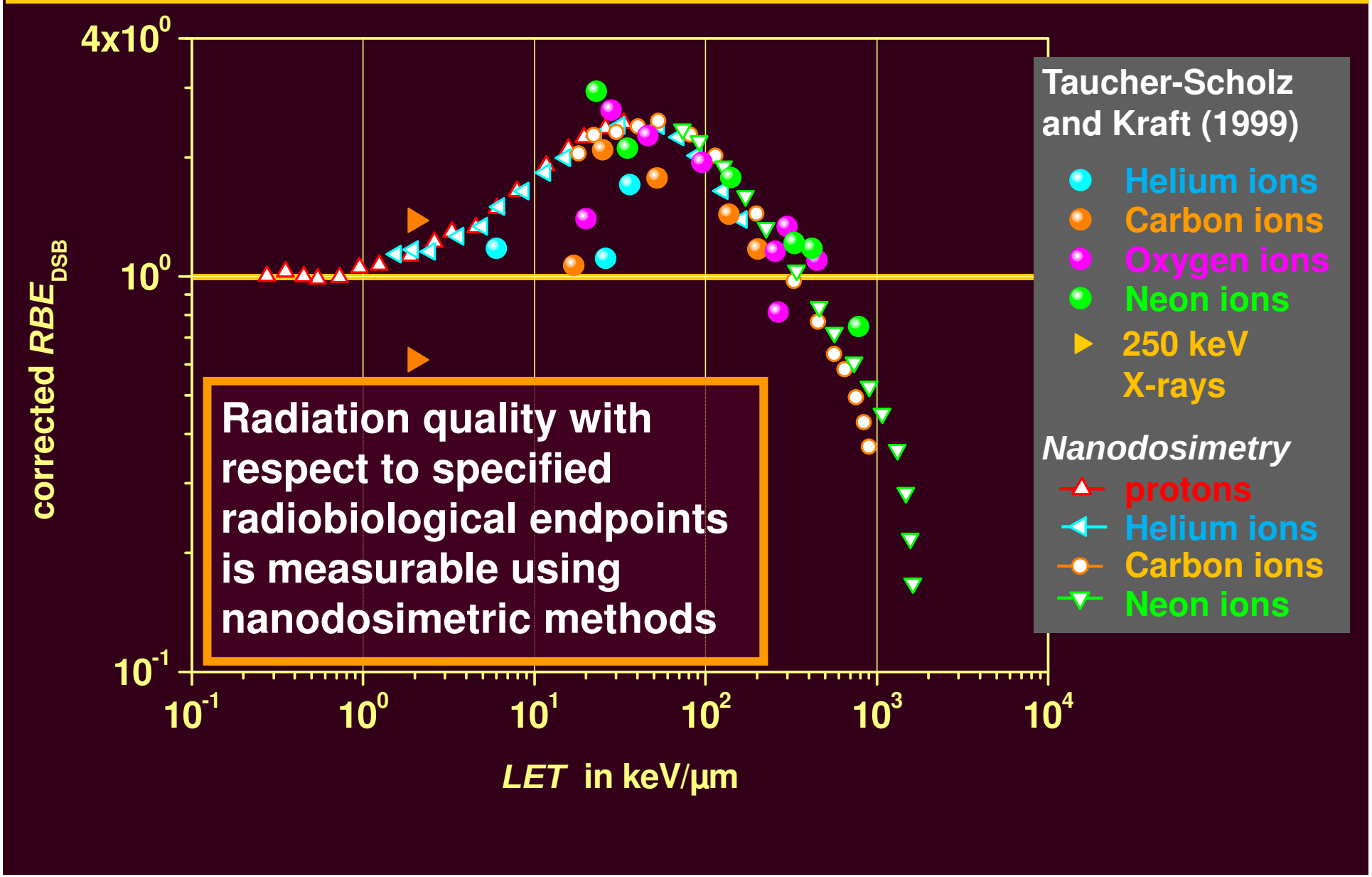
Cross Section of SV40 Viral DNA for Double-strand-break Formation, as a Function of LET



Relative Biological Effectiveness of Light Ions for Double-strand Breaks in SV40 Viral DNA



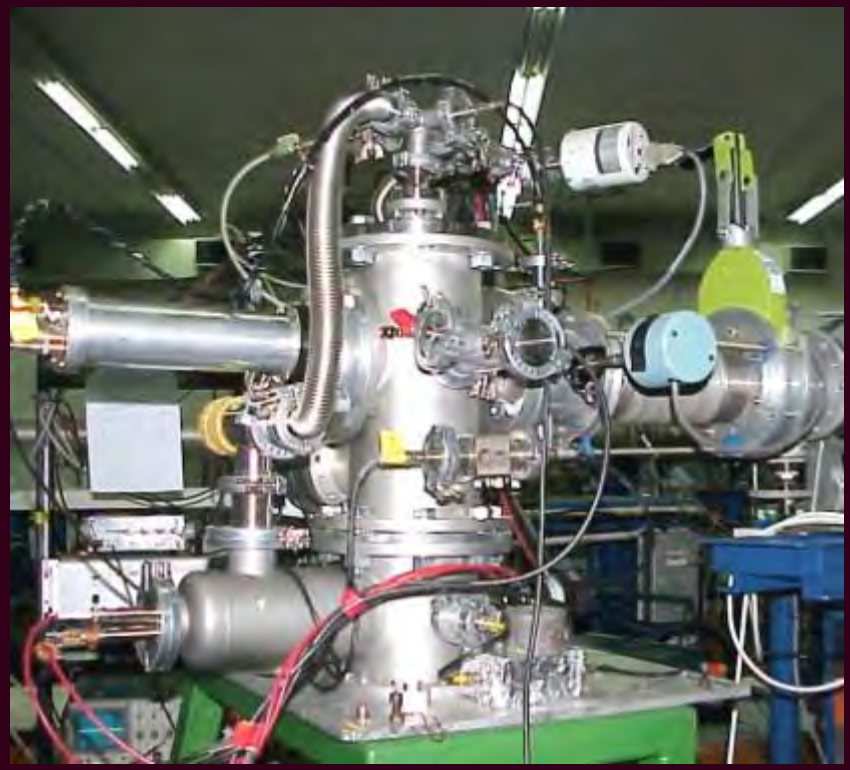
Renormalized RBE of Light Ions for Double-strand Breaks in SV40 Viral DNA



Size and Shape of Existing Nanodosimeters

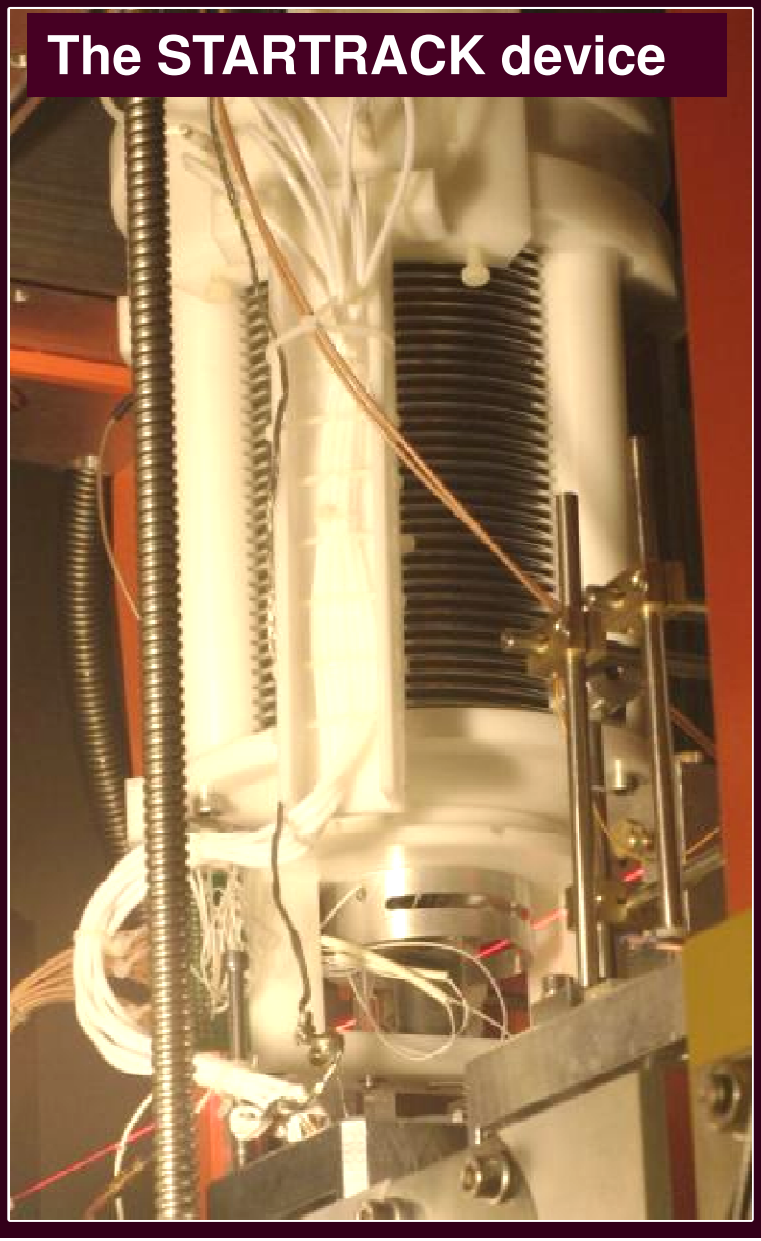
The STARTRACK device at INFN-Legnaro Laboratories

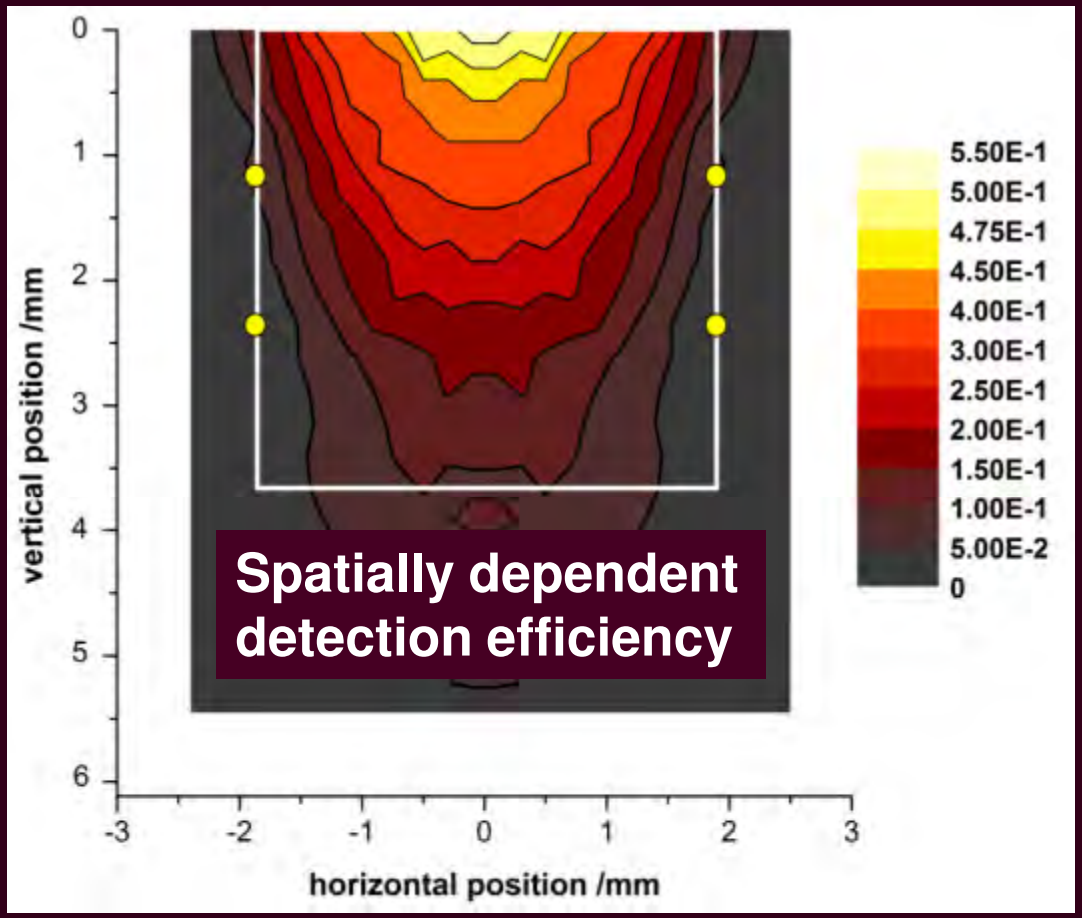
Nanodosimeter at PTB developed at Weizmann-Institute, Israel



For practical applications these nanodosimeters are (i) too large, and have (ii) a rather long dead-time, and (iii) a restricted intrinsic detection efficiency

But these Nanodosimeters Are Able to Reflect Main Characteristics of Particle Track Structure

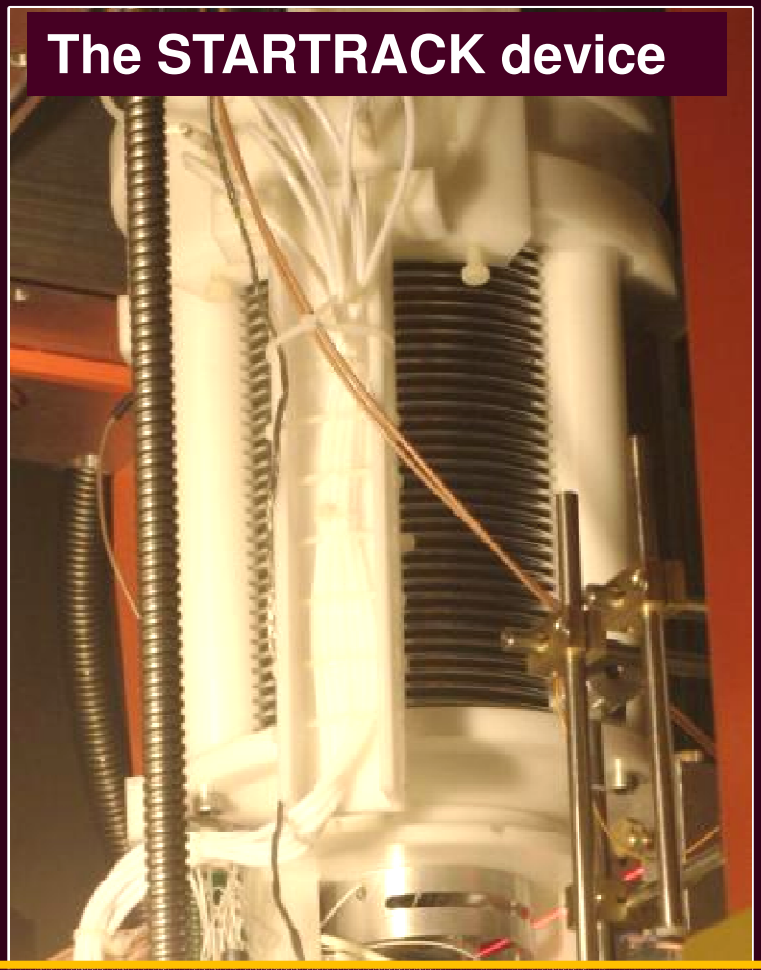


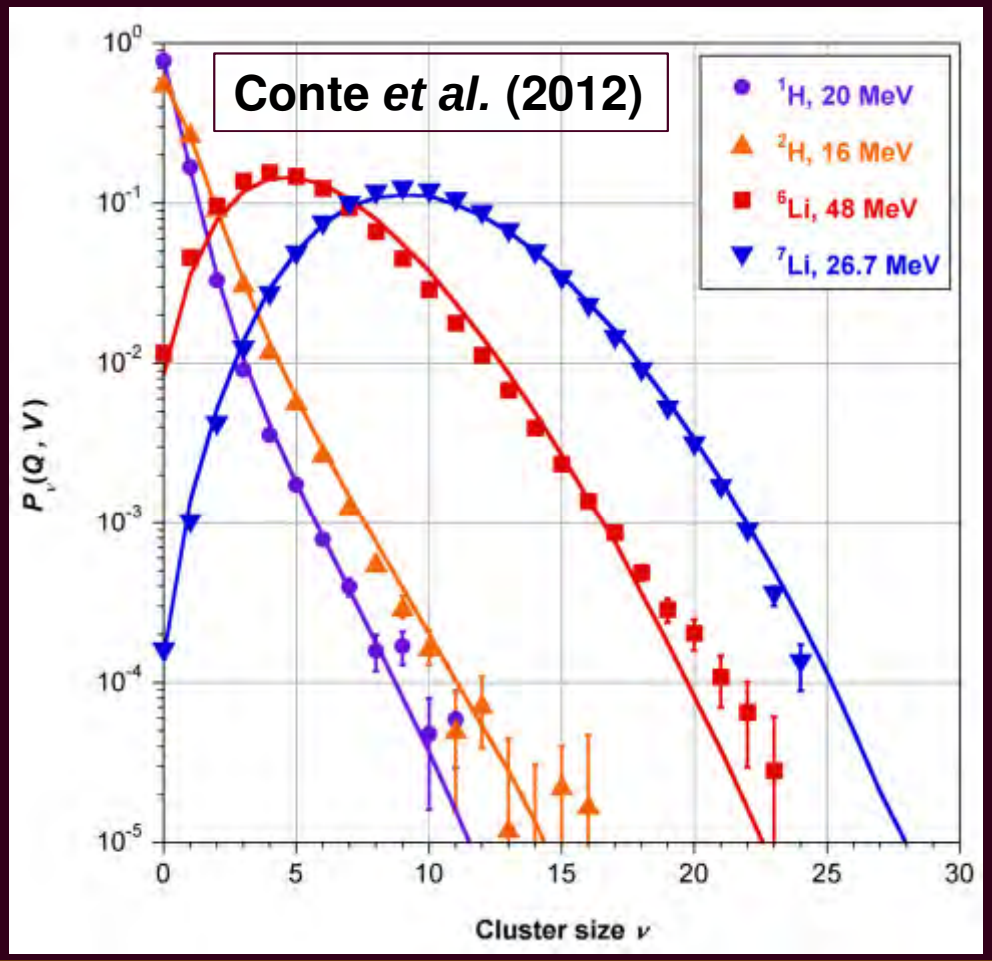


The STARTRACK device is based on single-electron counting
Filling gas: Propane at 3 mbar

But these Nanodosimeters Are Able to Reflect Main Characteristics of Particle Track Structure

The STARTRACK device

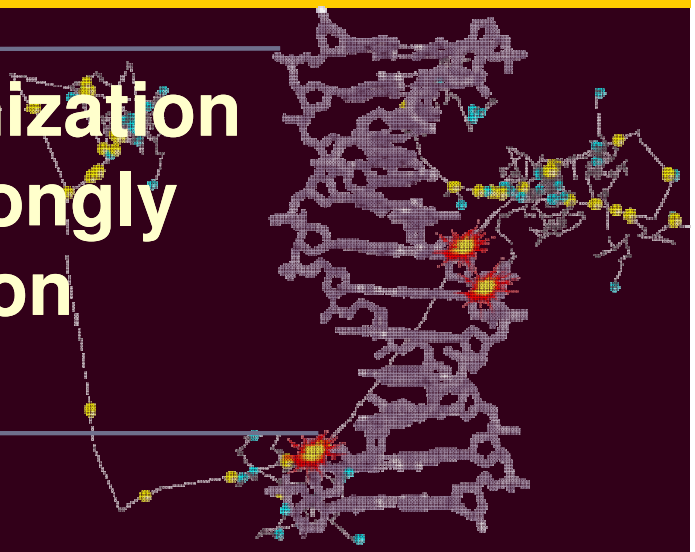




Validation by Monte Carlo track-structure simulations taking into account the main properties of the experimental devices like filling gas and detection efficiency

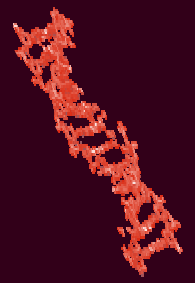
Cluster-size Probabilities in Nanometre-sized Volumes are Descriptors of Particle Track Structure

The probabilities P_1 and F_2 of ionization cluster-size distributions 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 measure radiation quality



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

Introduction to Nanodosimetry - a Summary

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
- can be validated by track-structure Monte Carlo simulations