HelmholtzZentrum münchen
German Research Center for Environmental Health

Microdosimetry and nanodosimetry for internal emitters – changing the scale

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EURADOS Winter School, 02/03/2017, Karlsruhe

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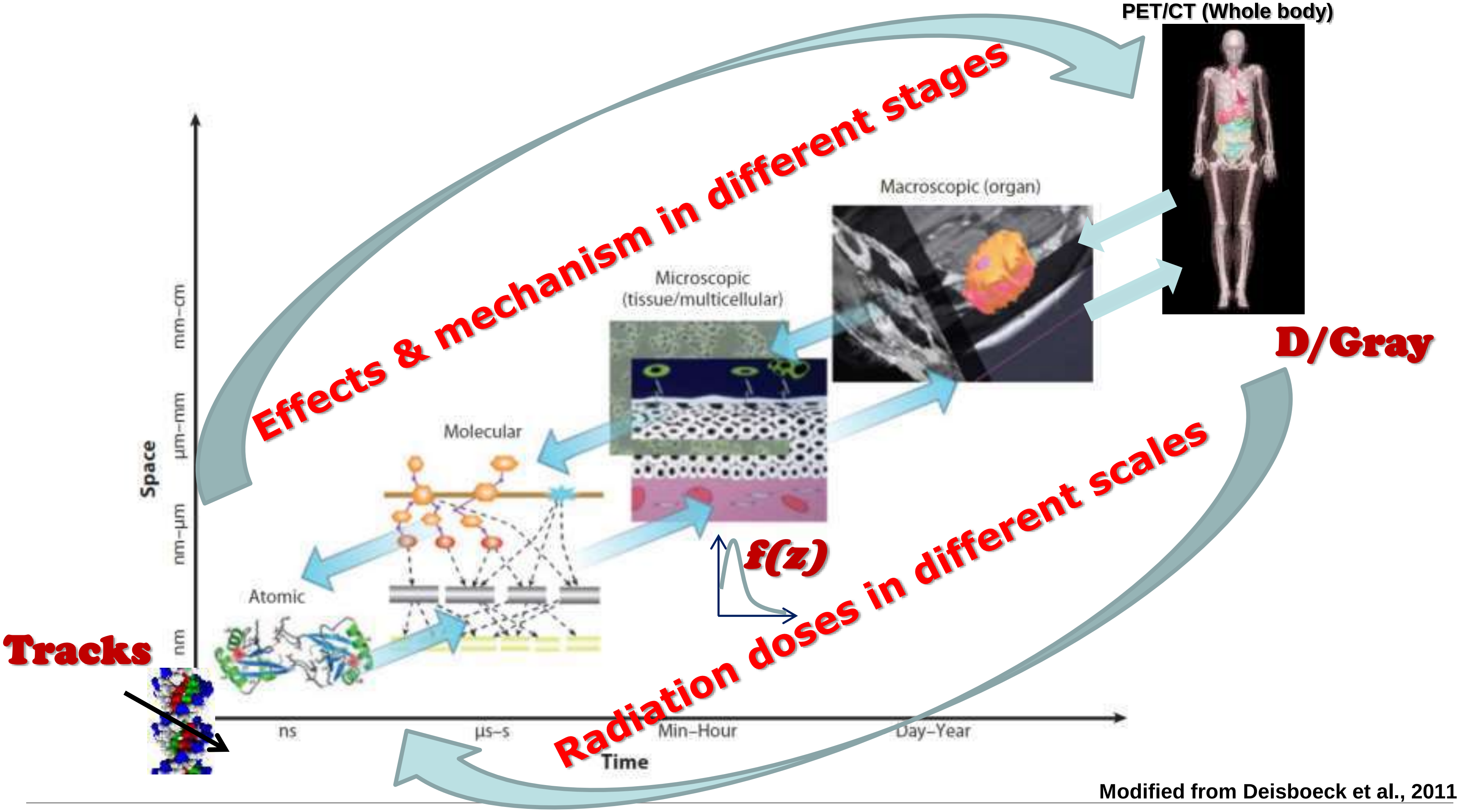
Motivation and Innovation

Multistage mechanism needs Multiscale dosimetry



Modified from Deisboeck et al., 2011

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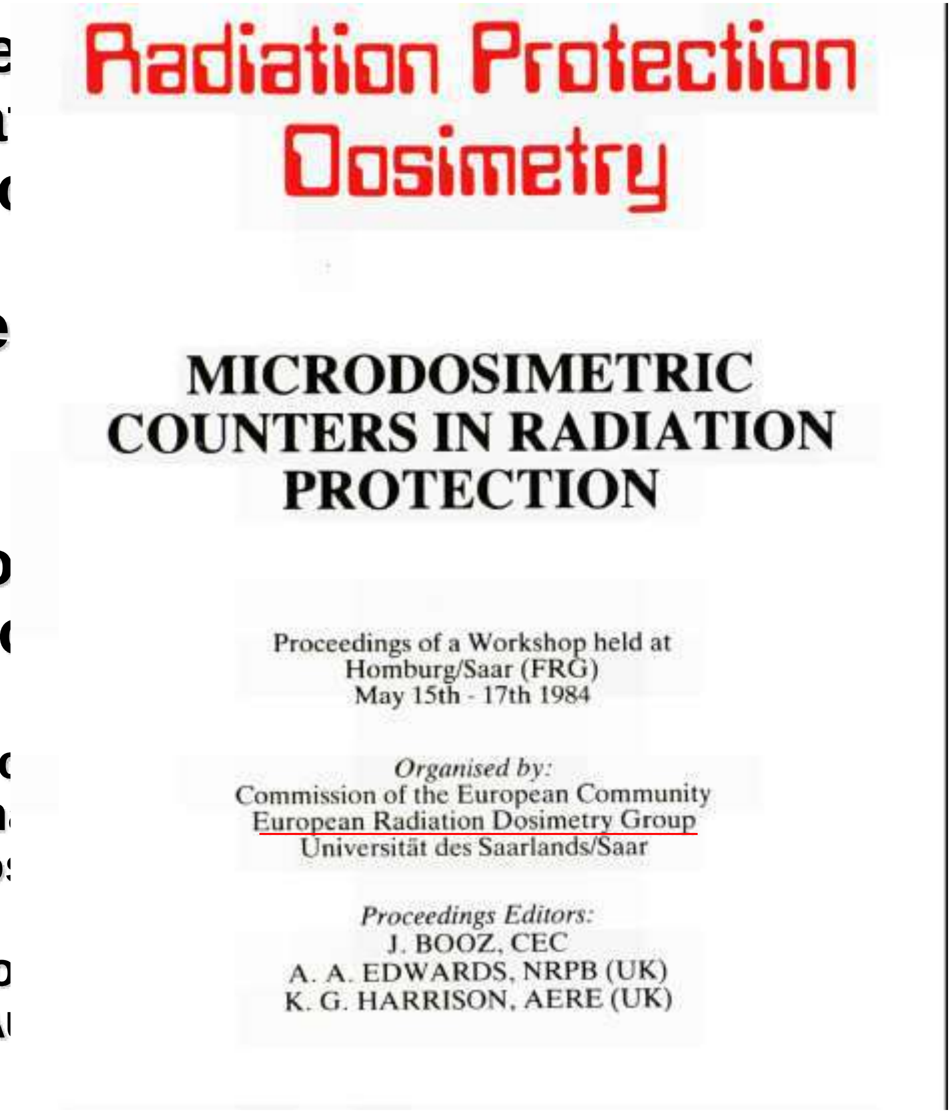
HELMHOLTZ ASSOCIATION

Microdosimetry and nanodosimetry in EURADOS

- 1982, EURADOS establishe
  Working Group 1 – Applica
  principle in radiation prote
- Workshop on Microdosime
  protection, 1984
- EURADOS 6th Winter Scho
  Perspectives of Computati
  Nanodosimetry (AM2013):
  - Davidkova - Introduction to mic
  - Grosswendt - Introduction to n
  - Villagrasa - Micro- and nanodo
    DNA Monte Carlo code
  - Hofmann - Alpha particle micro
  - Bordage - Microdosimetry of A



Radiation Protection Dosimetry

MICRODOSIMETRIC COUNTERS IN RADIATION PROTECTION

Proceedings of a Workshop held at
Homburg/Saar (FRG)
May 15th - 17th 1984

Organised by:
Commission of the European Community
European Radiation Dosimetry Group
Universität des Saarlands/Saar

Proceedings Editors:
J. BOOZ, CEC
A. A. EDWARDS, NRPB (UK)
K. G. HARRISON, AERE (UK)

Overview

- **Radiation dosimetry**
  - Roentgen, *r*
  - Absorbed dose, *D*
  - Linear energy transfer, *LET*
- **Microdosimetry for cellular biological effects**
  - Cellular effects cannot be explained by absorbed dose
  - Lineal energy and specific energy
  - Proximity function
  - Compound Poisson process
- **Nanodosimetry for molecular radiation mechanism**
  - Tracks and initial events lead to molecular damages
  - Radiation track structure theory
  - Physical tool for molecular mechanism of radiation effects
- **Internal micro- and nanodosimetry**
  - Cellular dosimetry of targeted radionuclides
  - Microdosimetry of radon progeny
  - Dose–response relationship
- **Future development**

Radiation dosimetry

- 1895 Wilhelm Röntgen discovered X-rays
- 1896 Dermetitis and damages to hands
- 1902 Skin cancer
- 1925 Measurement of X-rays by free-air chamber
- 1928 ICRU established a unit “roentgen” for that “quantity” which was measured by free-air chamber
- 1953 ICRU established “absorbed dose”
- 1956 ICRU used the unit “roentgen” for established “exposure dose” and later “exposure” (ICRU 1962), now the SI unit “C kg^{-1}”

- 1538 Paracelsus “Dosis sola facit venenum” – the dose makes the poison – Rühm, 2016 in Rösch ed. Nuclear- and Radiochemistry Vo.II

- ***Radiation Dosimetry deals with the measurement of absorbed dose / dose rate resulting from the interaction of ionizing radiation with matters***

Absorbed dose

- The *absorbed dose*, *D*, is the quotient of $d\bar{\varepsilon}$ by d*m*, where $d\bar{\varepsilon}$ is the <u>mean</u> energy imparted by ionizing radiation to matter of mass d*m*, thus

$$D = \frac{d\bar{\varepsilon}}{dm}.$$

Unit: J kg^{-1} (special name is gray: Gy)

Note: The absorbed dose, *D*, is considered a point quantity, but it should be recognized that the physical process does not allow d*m* to approach zero in the mathematical sense.

The *energy imparted*, ε, to the matter in a given volume is the sum of all energy deposits in the volume, thus

$$\varepsilon = \sum_i \varepsilon_i,$$

where the summation is performed over all energy deposits, ε_i, in that volume.

Unit: J

The *energy deposit*, ε_i, is the energy deposited in a single interaction, *i*, thus

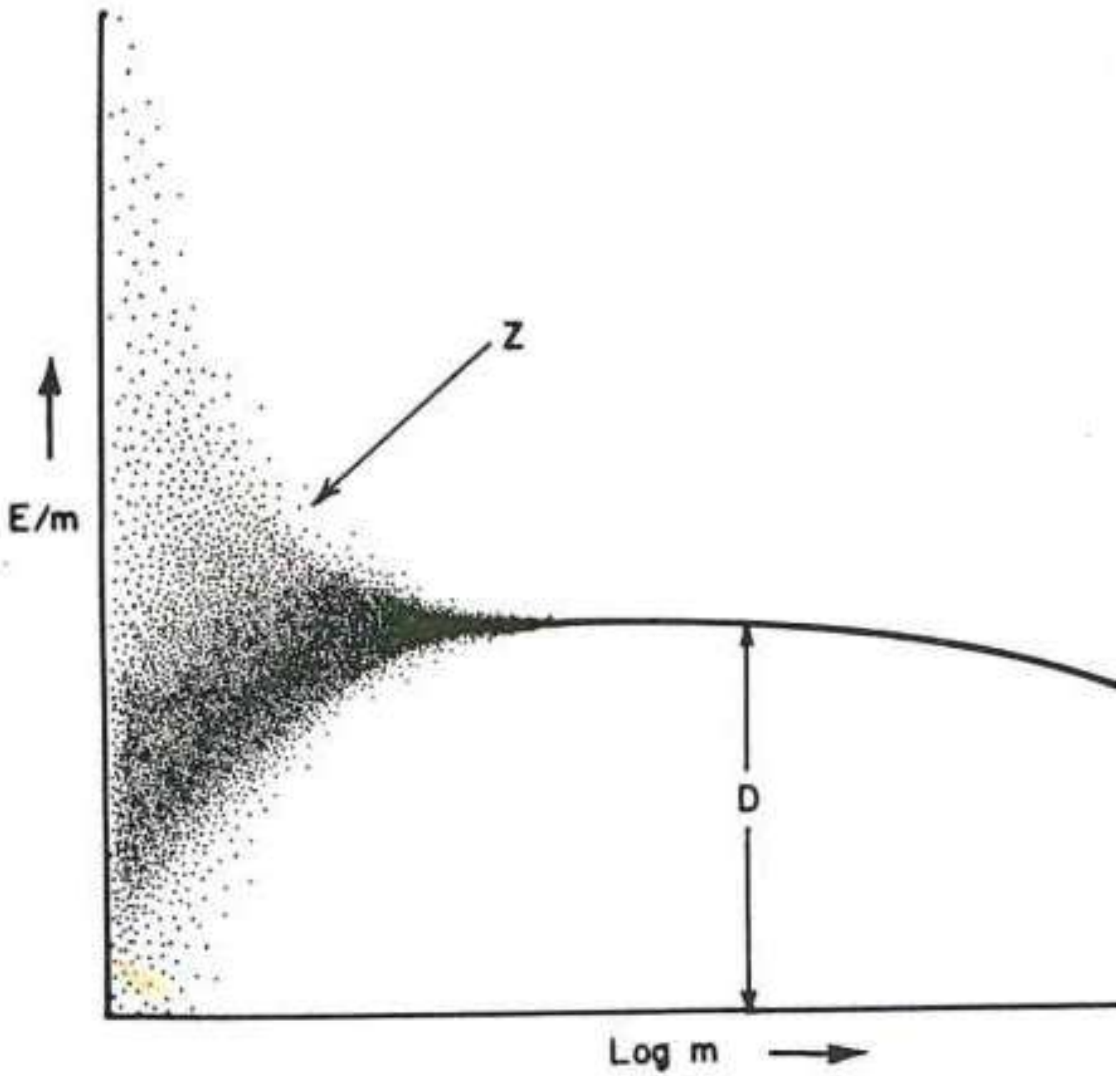
$$\varepsilon_i = \varepsilon_{in} - \varepsilon_{out} + Q,$$

where ε_{in} is the energy of the incident ionizing particle (excluding rest energy), ε_{out} is the sum of the energies of all charged and uncharged ionizing particles leaving the interaction (excluding rest energy), and Q is the change in the rest energies of the nucleus and of all elementary particles involved in the interaction ($Q > 0$: decrease of rest energy; $Q < 0$: increase of rest energy).

Unit: J

ICRU 85a, 2011

Absorbed dose and limitations



- Absorbed dose is a statistic average quantity and disregarded the random fluctuations
- However, the biological effects are related to the energy deposit and event in cellular region
- If the volume under investigation becomes smaller, the absorbed dose becomes fluctuant or random
- Absorbed dose is still used as basic quantity for other derived dosimetric quantities in radiation protection and medicine

Rossi, 1968

Microdosimetric quantities and distributions

➔ Stochastic quantities *y* and *z* for microscopic distribution of energy deposition

- The *lineal energy*, *y*, is the quotient of ε_S by $\bar{l}$, where ε_S is the energy imparted by ionizing radiation to the matter in a given volume by a single energy-deposition event, and $\bar{l}$ is the mean chard length of that volume, thus

  $$y = \frac{\varepsilon_S}{\bar{l}}.$$

  Unit: J m^{-1} (keV μm^{-1}, this makes you recall LET)

- The *specific energy* (imparted) *z*, is the quotient of ε by *m*, where ε is the energy imparted by ionizing radiation to the matter in a volume of mass *m*, thus

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

  Unit: J kg^{-1}, special name is gray (Gy)

- In practice, the probability density of *y* and *z*, i.e. *f*(*y*) and *f*(*z*) are measured and calculated
- For convex volumes, $y = \frac{\rho A}{4} z$, with *A* the surface area and ρ density

ICRU 36, 1983; Kellerer, 1985; Rossi and Zaider, 1996

Microdosimetric quantities and distributions

➔ *Proximity function* *T*(*x*) and *t*(*x*)

Integral proximity function *T*(*x*) is defined as:

$$T(x) = \lim_{n\to\infty} \frac{1}{n} \sum_{j=1}^{n} \tilde{T}_j(x)$$

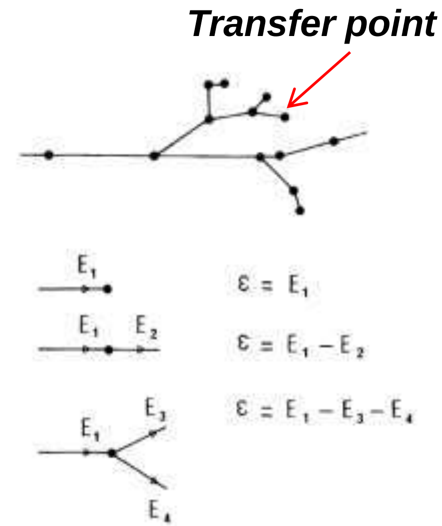
$$\tilde{T}_j(x) = \sum_i \sum_k \varepsilon_i \varepsilon_k \Big/ \sum_i \varepsilon_i$$

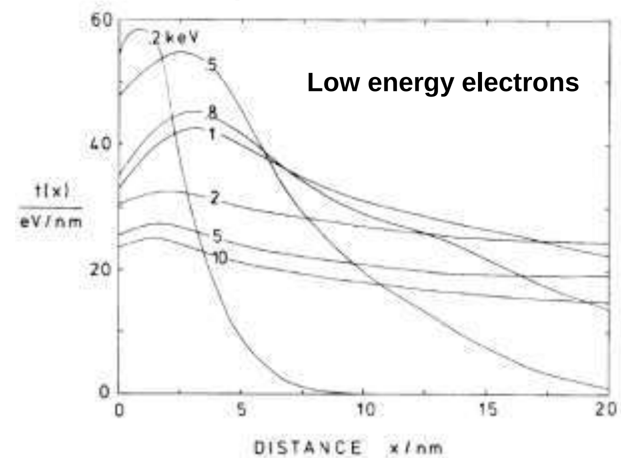
The differential proximity function *t*(*x*) is the derivative of *T*(*x*)

$$T(x) = \int_0^x t(x')\,dx'$$

- *T*(*x*) can be also named as *point-pair distance distributions*, of the geometric objects T and S

- *t*(*x*) can be understood as *distance distribution of energy transfers* multiplied by total energy of the tracks





ICRU 36, 1983; Kellerer, 1985; Chmelevsky et al. 1980

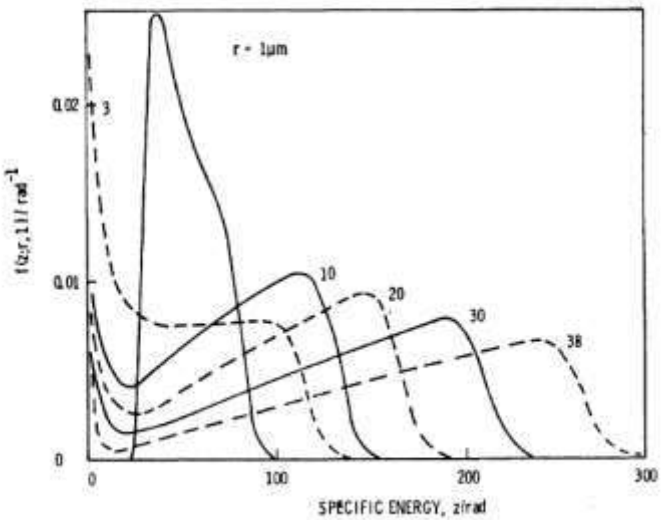
Central issues in microdosimetry

- **Compound Poisson process**

$$f(z;\, D) = \sum_{\nu=0}^{\infty} e^{-n} \frac{n^{\nu}}{\nu!} f_{\nu}(z), \qquad \text{with} \quad n = \frac{D}{\bar{z}_{\mathrm{F}}}$$

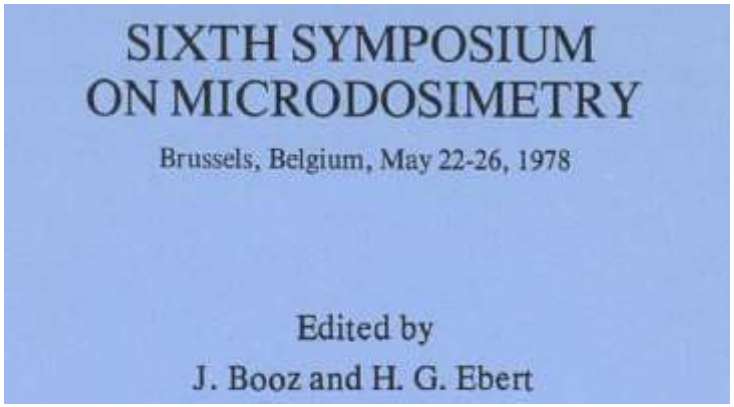
$$f_{\nu}(z) = \int_0^z f_1(x) f_{\nu-1}(z - x)\, dx \qquad (\nu = 2, 3, \ldots)$$

- **Single-event distribution calculation**
  - **Measurement**
  - **Energy-loss straggling**
  - **Monte Carlo track structure calculatio**



Microdosimetry for internal emitters

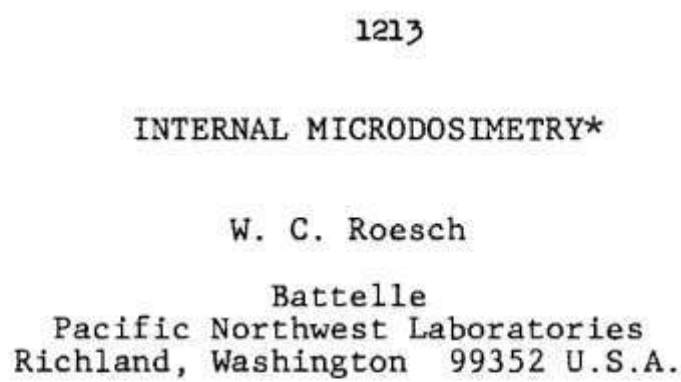
➔ **William Carl Roesch explicitly highlighted a treatise on Internal Microdosimetry**


SIXTH SYMPOSIUM ON MICRODOSIMETRY

Brussels, Belgium, May 22-26, 1978

Edited by

J. Booz and H. G. Ebert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INTERNAL MICRODOSIMETRY*

W. C. Roesch

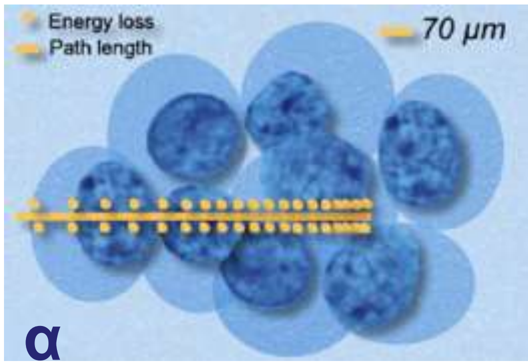
Battelle
Pacific Northwest Laboratories
Richland, Washington 99352 U.S.A.

- **Applications of microdosimetry in internal dosimetry**
  - **Inhomogeneous distributions of radionuclides in cells**
  - **Determination of $f_1(z;D)$**
  - **Calculating $f(z;D)$ through Compound Poisson process**
- **Microdosimetric biokinetic modelling**

Roesch, 1977; Roesch, 1978

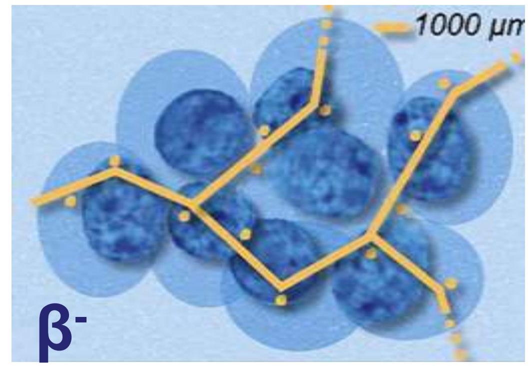
Microdosimetry of targeted radionuclides

- Advantages of α particles



α

vs



β^-

  - Short range: 50 – 80 µm
  - High LET : ~100 keV/µm vs 0,2 keV/µm for β^- particles

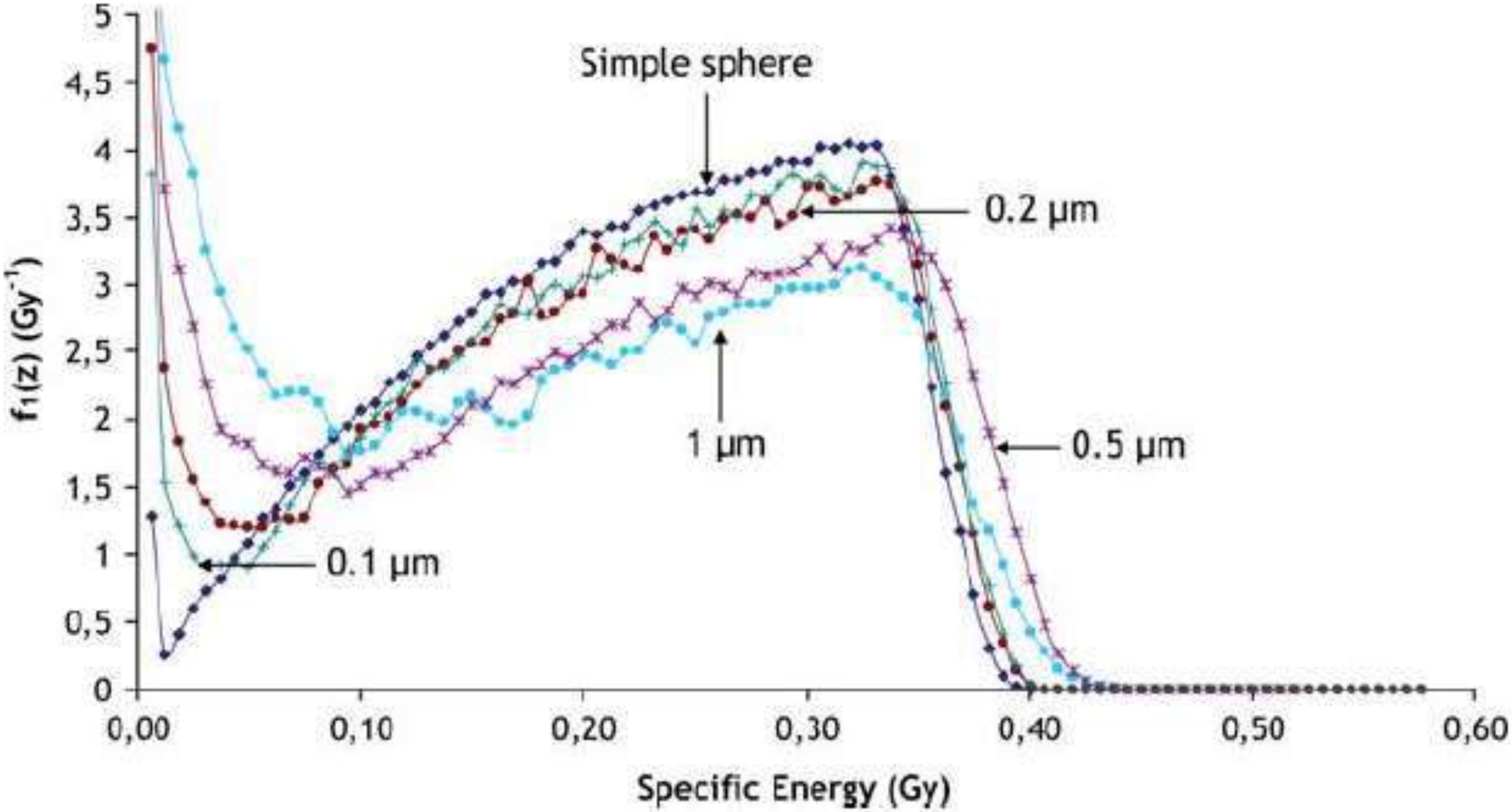
↗ High cytotoxicity for cancer cells and limited irradiation of the non-targeted healthy tissues

- Principaly used for the treatment of metastases:
  - Bone metastases after a breast cancer, a kidney cancer ...

- Emergence of alphatherapy
  - Astatine-211 (^{211}At), Bismuth-212 (^{212}Bi), Bismuth-213 (^{213}Bi), Actinium-225 (^{225}Ac), Lead-212 (^{212}Pb), Thorium-227 (^{227}Th), ...

Desbrée, et al. 2016

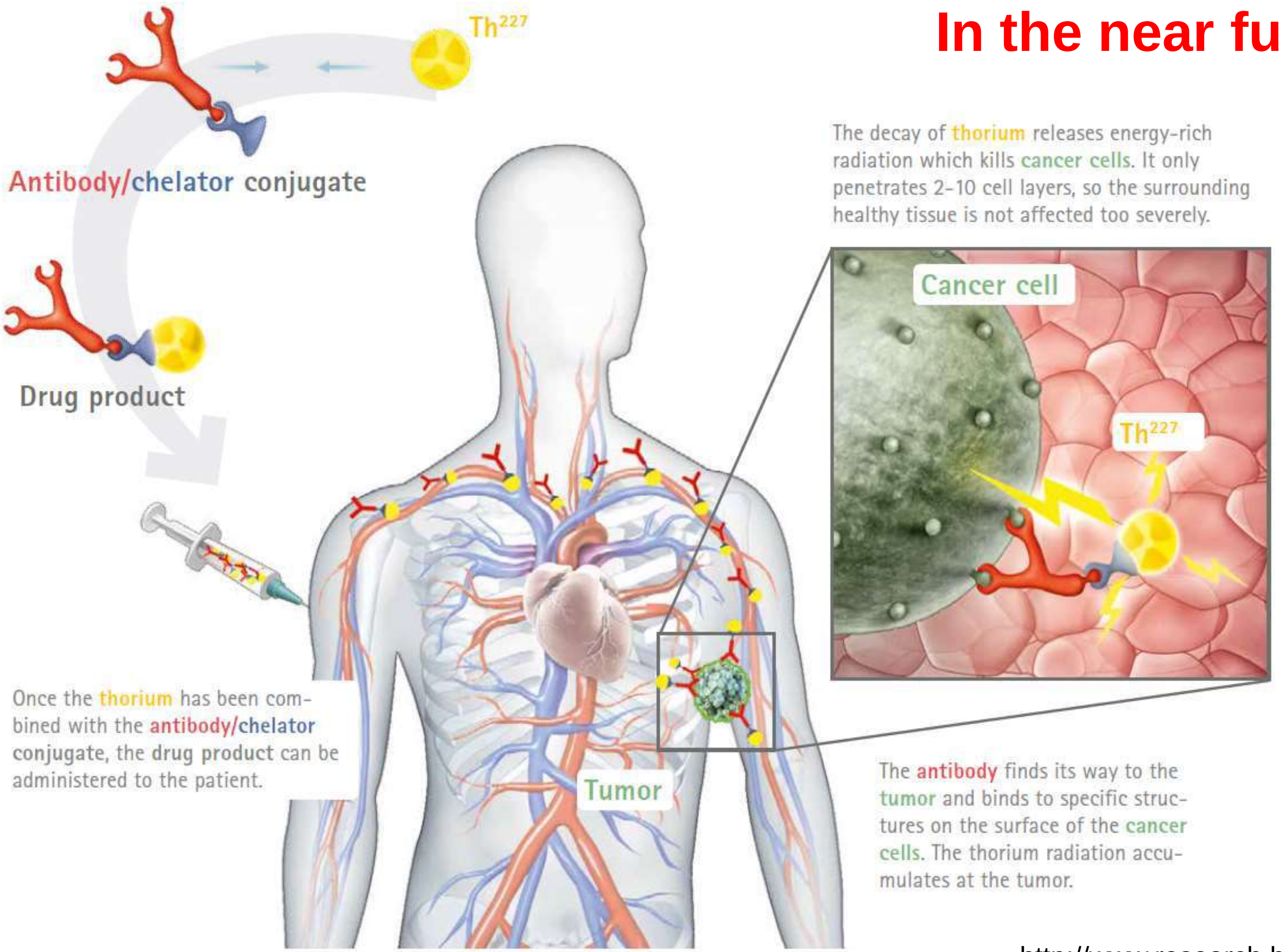
Xofigo® ($^{223}RaCl_2$)



Desbrée, et al. 2012; 2016

Microdosimetry of ^{227}Th targeted radiopharmaceutical

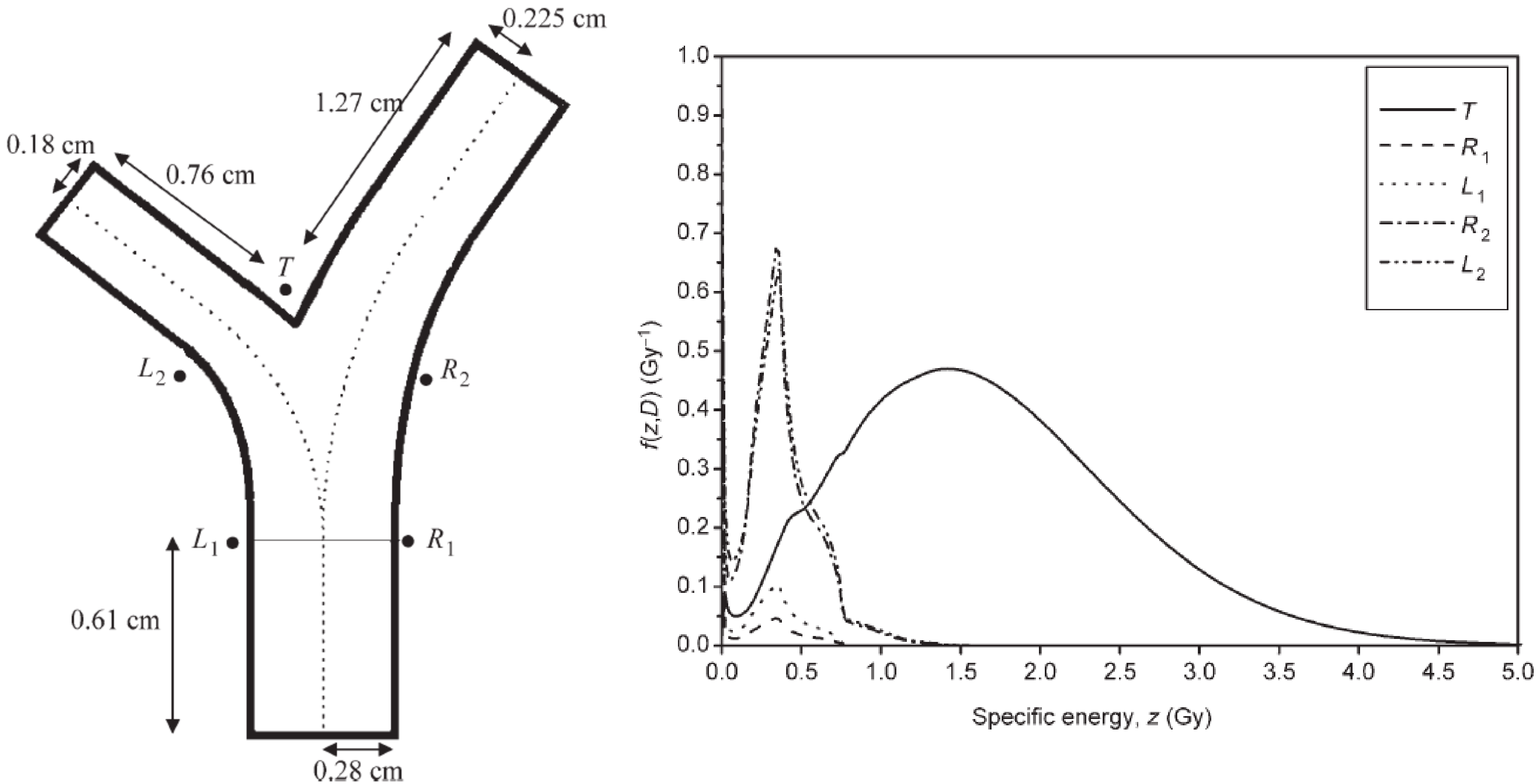
In the near future!



http://www.research.bayer.com

Microdosimetry of inhaled radon progeny

Radiation Protection Dosimetry (2007), Vol. 127, No. 1 4, pp. 40 45
Advance Access publication 6 September 2007
doi:10.1093/rpd/ncm414



Hofmann et al., 2007

Relationship - *y* and *z to LET and D*

- **LET and *y***
  - **LET is based on cut energy**
  - ***y* is based on a small volume**
  - **A cut energy is limited to a volume**

- **Absorbed dose, *D* and *z***

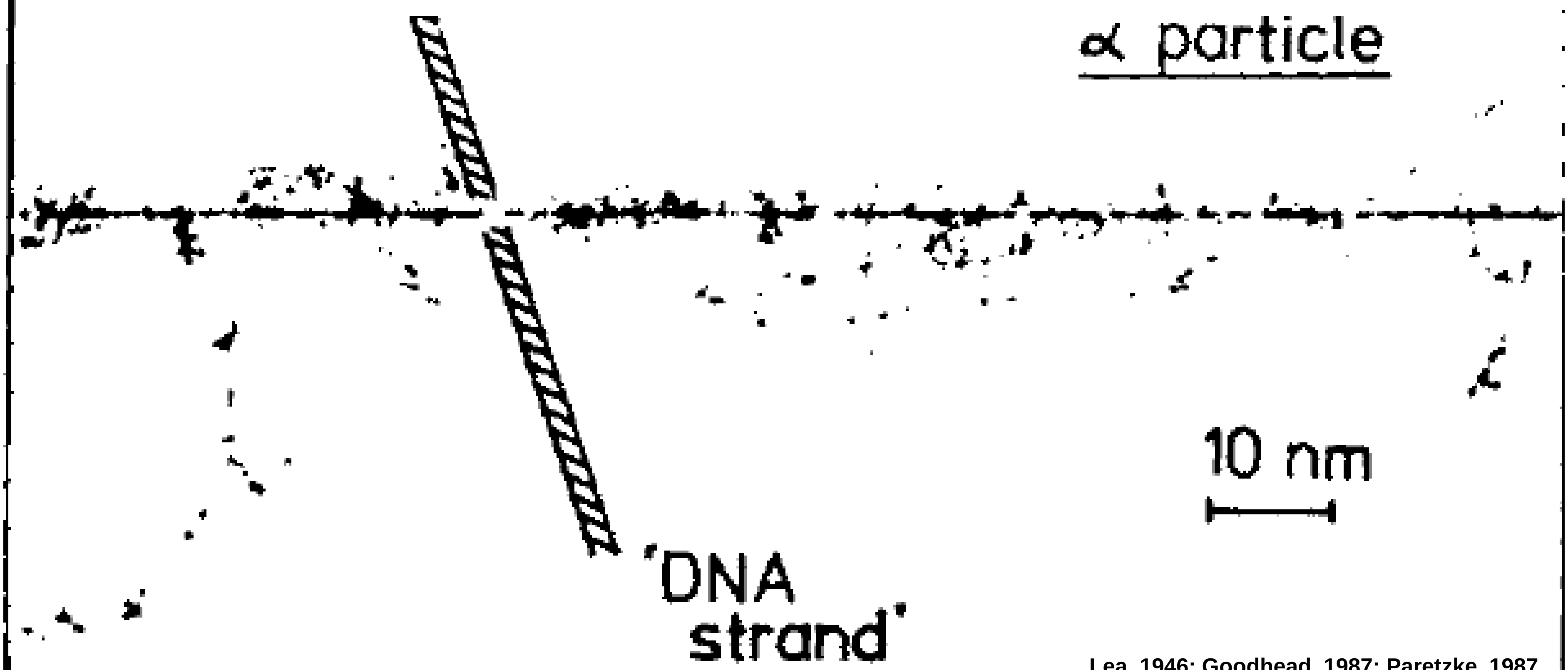
$$\bar{z} = \int_0^{\infty} z f(z; D) dz = D$$

- **Radiation quality Q based on y**

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

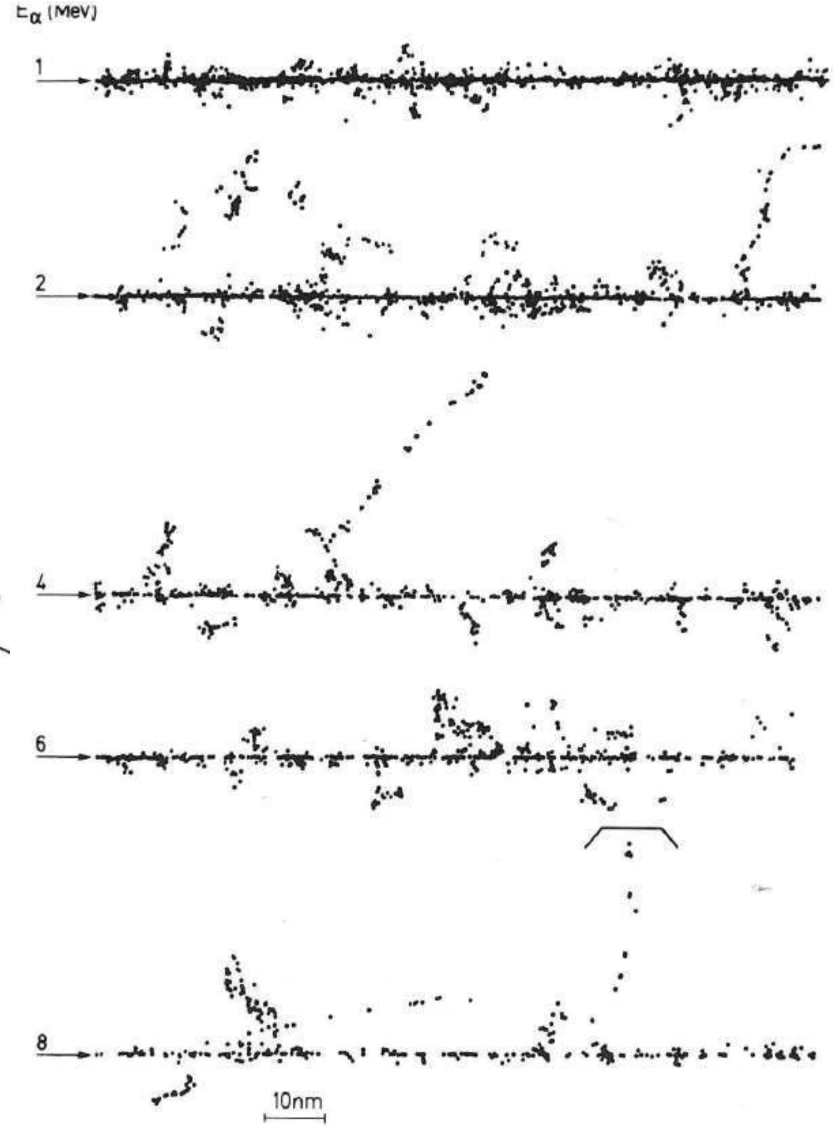
Limitations of microdosimetric quantities

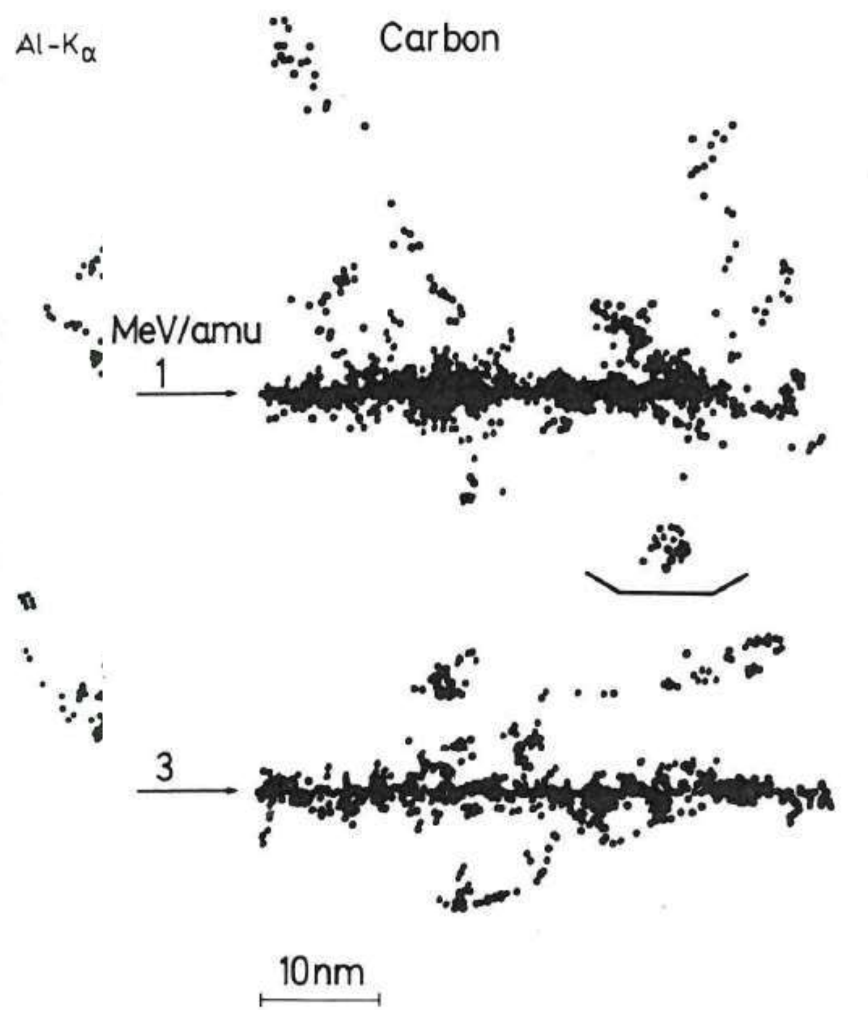
Simulation of DNA damage and chromosome aberration needs track structure and atomic structure of cell nuclei model



Lea, 1946; Goodhead, 1987; Paretzke, 1987

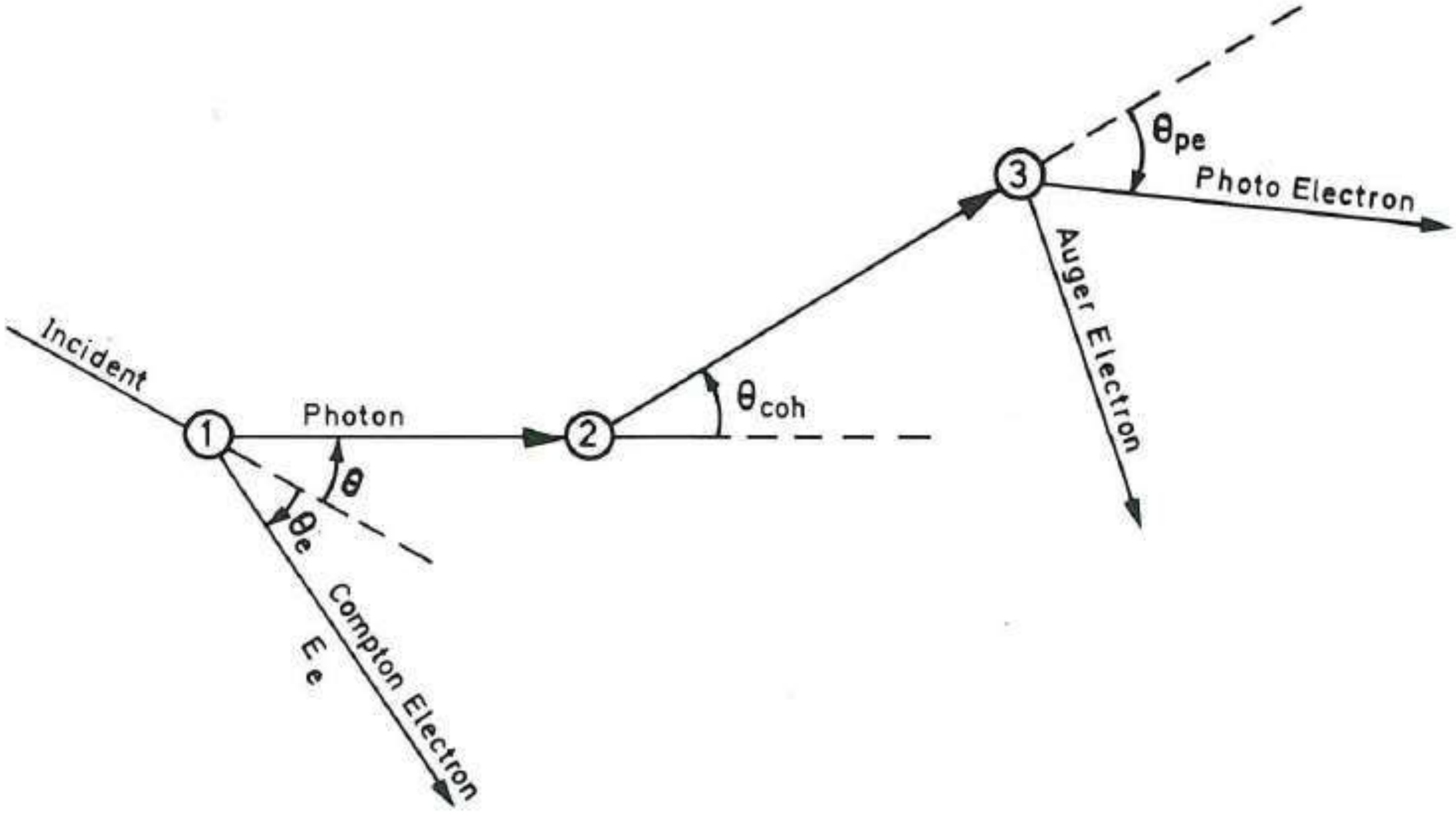
Track structure calculations -> Nanodosimetry





Paretzke, Radiation track structure theory, 1987

Interactions of radiation with matters



Bethe, 1930; Inokuti, 1971; Paretzke, 1987

Cross sections in nanodosimetry

➔ **Cross sections for track structure calculation need the full knowledge of interaction of radiation with matter, especially biological material at low energy ranges:**

- **Low-energy electrons in vapor water – Paretzke, 88'**
- **Low-energy electrons in liquid water – Dingfelder, 98'**
- **Low-energy electrons in DNA moiety – Bernhardt, 03'**
- **Alpha-particles**
- **Protons**
- **Heavy ions**

✓ **For a full discussion, refer to**
PENELOPE-2014
GEANT4 v10.3 Physics Reference Manual

Bethe, 1930; Paretzke, 1988; Dingfelder et al., 1998; Bernhardt and Paretzke, 2003
PENELOPE-2014; GEANT4 v10.3 Physics Reference Manual

Programs for track structure calculations

➔ PARTRAC
- Developed based on MOCA code series
- Especially used for low-energy electrons
- Full simulations of molecular damage to cellular effects

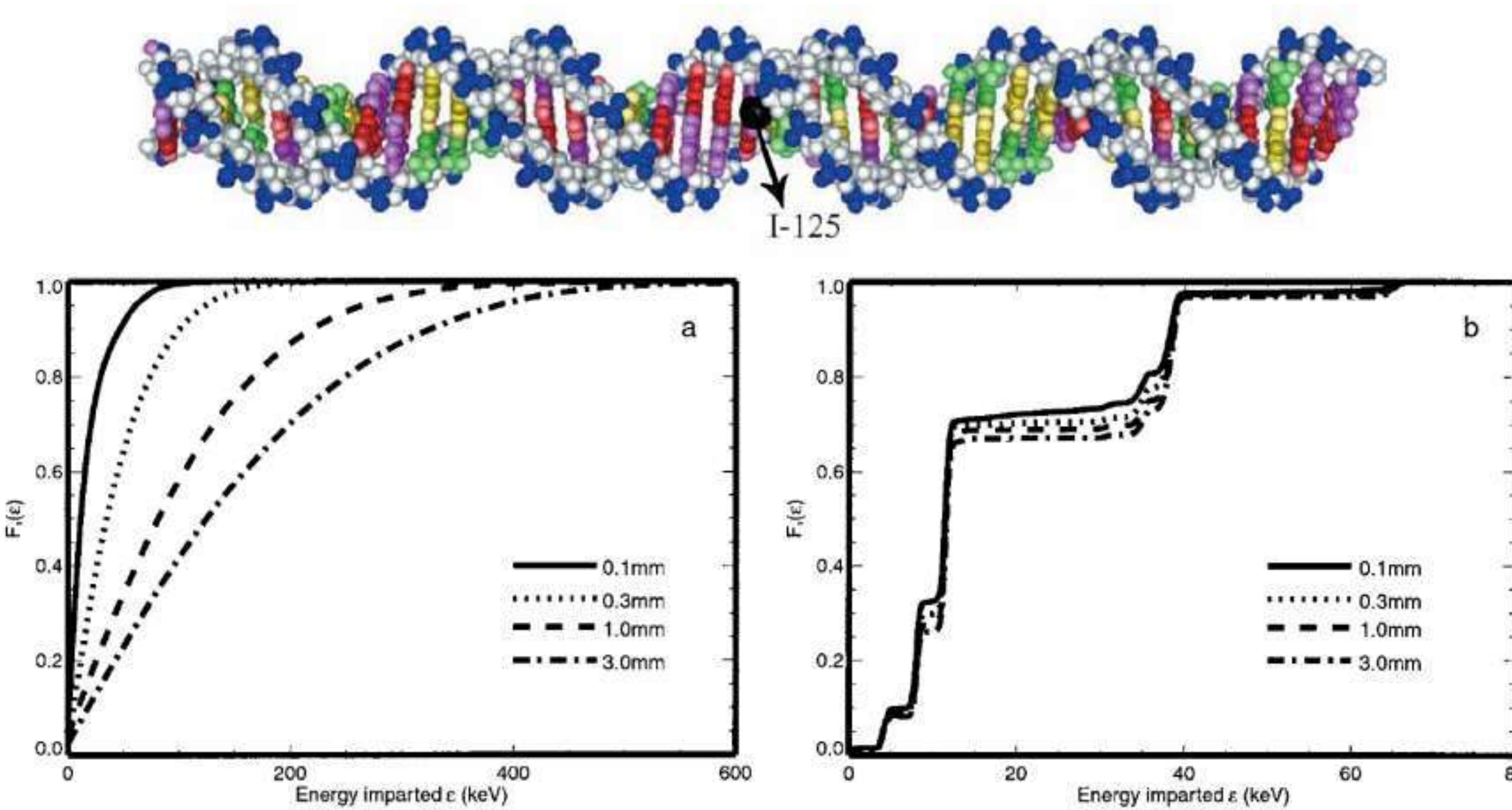
➔ PENELOPE
- Especially for low photons and electrons, 50 eV

➔ GEANT4-DNA
- Based on GEANT4
- Used for any radiation type
- Especially for very low energy of electrons
- Integrating chemical and biological modules

➔ Other codes
- MCNP6 (Los Alamos Natl. Lab.)
- NASIC (Tsinghua Uni., Beijing)

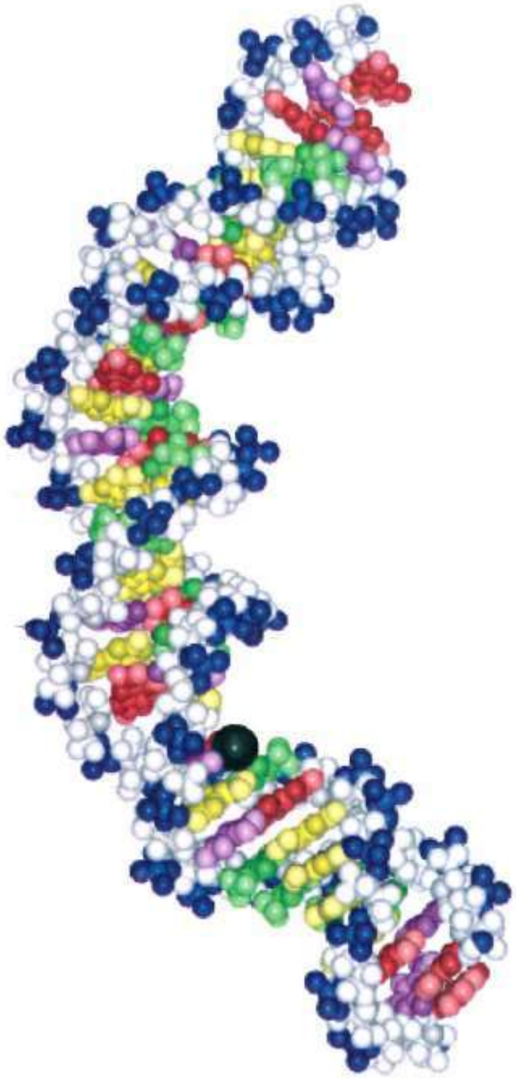
wli@helmholtz-muenchen.de

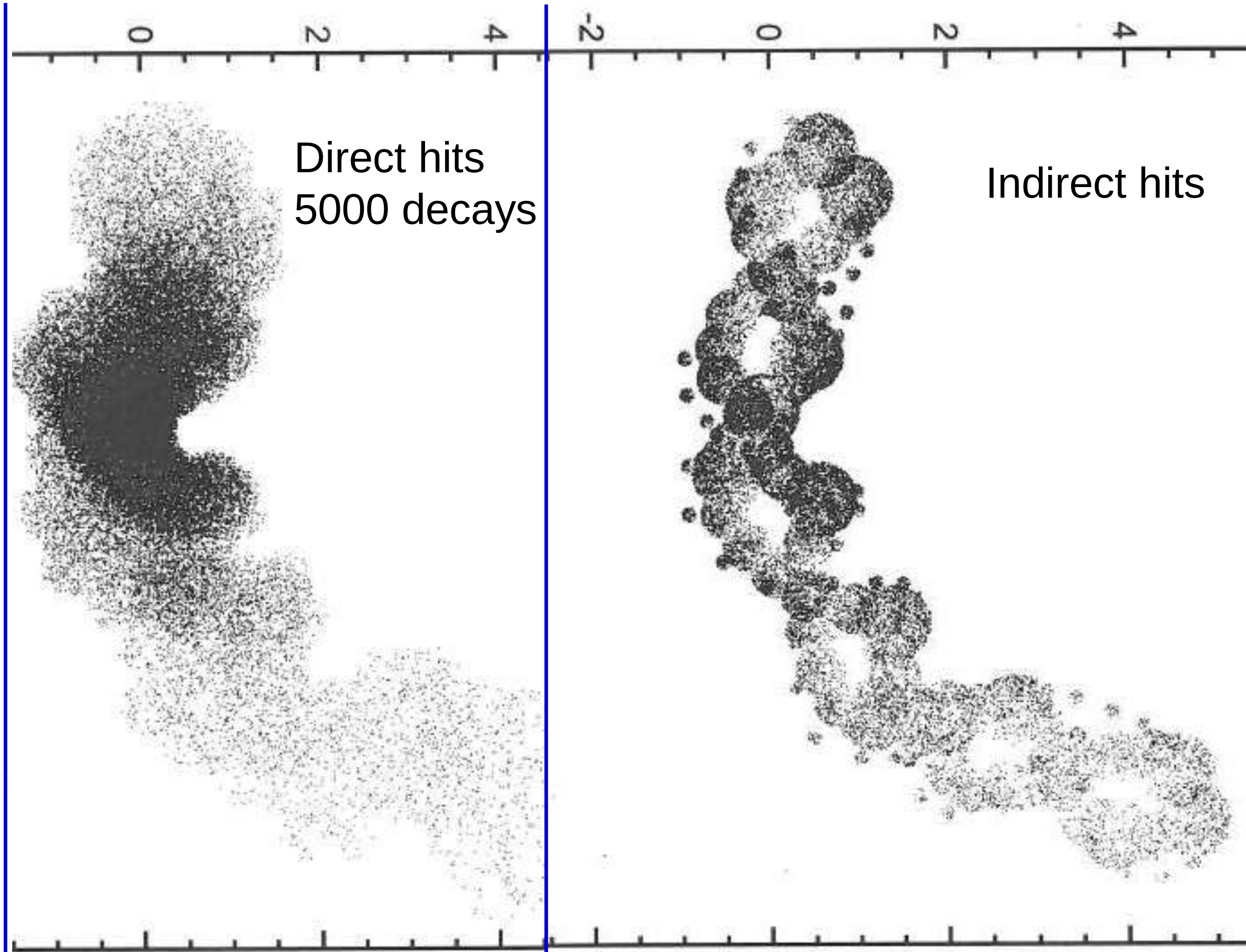
Nanodosimetry – targeted radionulcides for molecular therapy



Li et al. 2001, 2004, Friedland et al. 2001

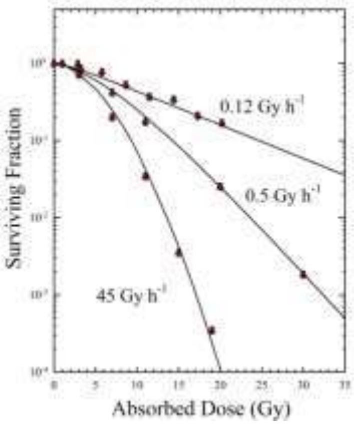
Track structures – I-125 targeted molecular therapy





Li et al. GSF-Bericht 11/00, 2000

Relationship of *D*, *f*(*z*) and tracks

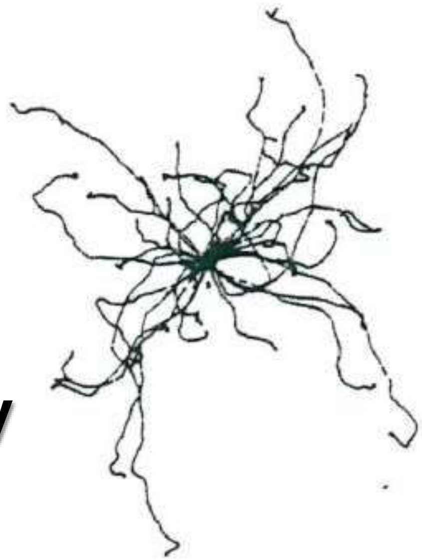


Absorbed dose

$$S(D) = \exp\{-\alpha D - \beta G D^2\} = \exp\left\{-\left(\theta\Sigma + \kappa \bar{z}_F \Sigma^2\right) D - \frac{\kappa}{2}\Sigma^2 G D^2\right\}$$

Microdosimetry

$$\bar{z}_D = \int z\, d_1(z)\, dz = \int z^2 f_1(z)\, dz / \bar{z}_F = \overline{z_F^2} / \bar{z}_F$$



Nanodosimetry

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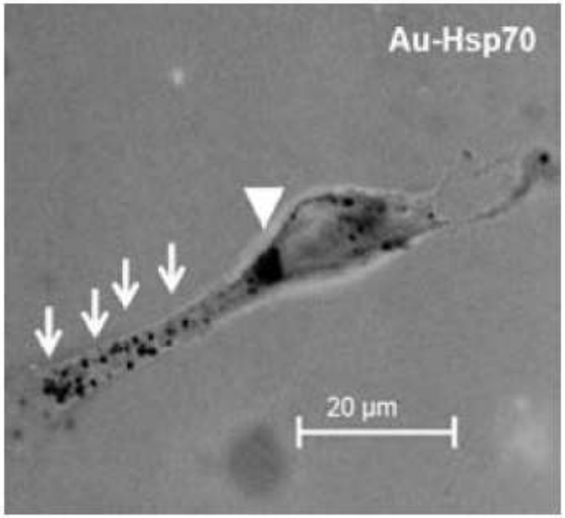
Future development

- ➔ **Validating and improving cross sections in DNA moiety and other materials for low energy radiation experimentally and theoretically**
- ➔ **Strengthen applications of internal micro- and nanodosimetry in nuclear medicine and molecular targeted radiotherapy, radiation protection as well**
- ➔ **Contributions to reveal the dose-response relationship for low and very low dose, fit to CONCERT Calls**
- ➔ **EURADOS nanodosimetry comparisons**
  - **I-125 decays – Uncertainty of cross sections**
  - **Gold nanoparticles – molecular targeted radiotherapy**

Nanodosimetry – gold nanoparticle targeted for preclinical cancer radiotherapy



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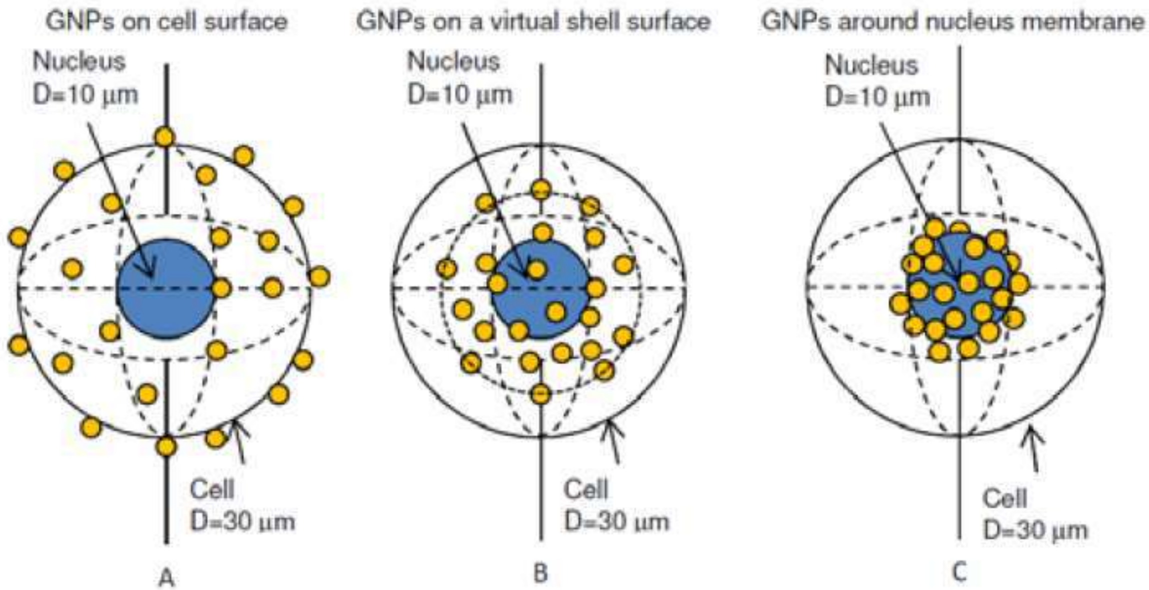
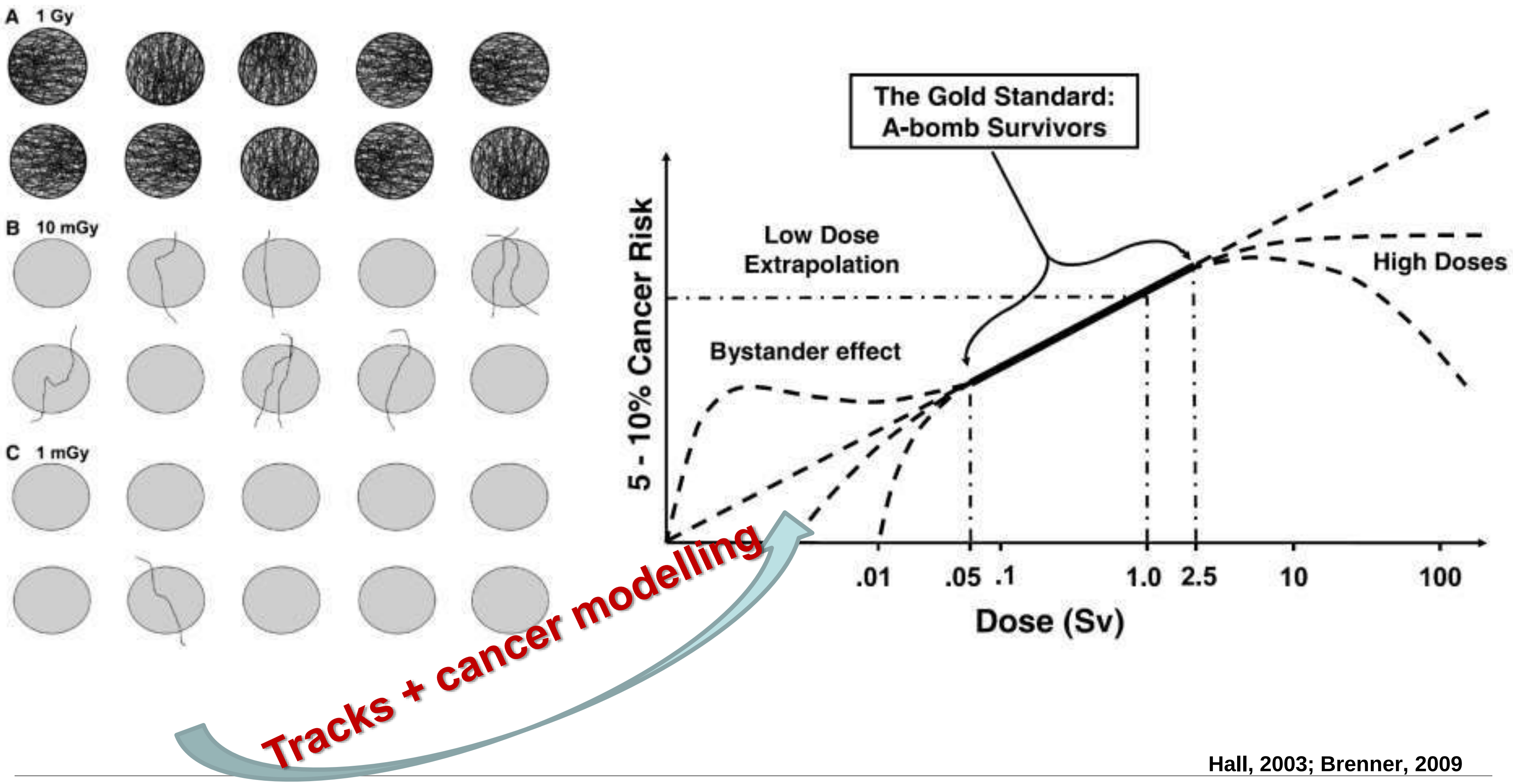


Multhoff /TUM and Li/HMGU, 2016

Nanodosimetry – A tool for interpreting the dose-response of internal emitters



Hall, 2003; Brenner, 2009

Acknowledgments

- EURADOS

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