# Introduction to microdosimetry

Manuel Bardiès, INSERM UMR 892, Nantes, France
manuel.bardies@inserm.fr

# Introduction to microdosimetry

In general, NM dosimetry: macrodosimetry, but:
macrodosimetry ≠ macroscopic scale dosimetry
& microdosimetry ≠ microscopic scale dosimetry!

Macrodosimetry: mean parameters (mean absorbed doses)
However, energy deposition is a stochastic phenomenon
It has a inherent fluctuation (statistical)
If particle flux - and deposited energy - are large enough:
The mean dose is a relevant parameter (std deviation is small)

Microdosimetry: study of the whole energy deposition process.
Results are expressed as energy deposition events probabilities

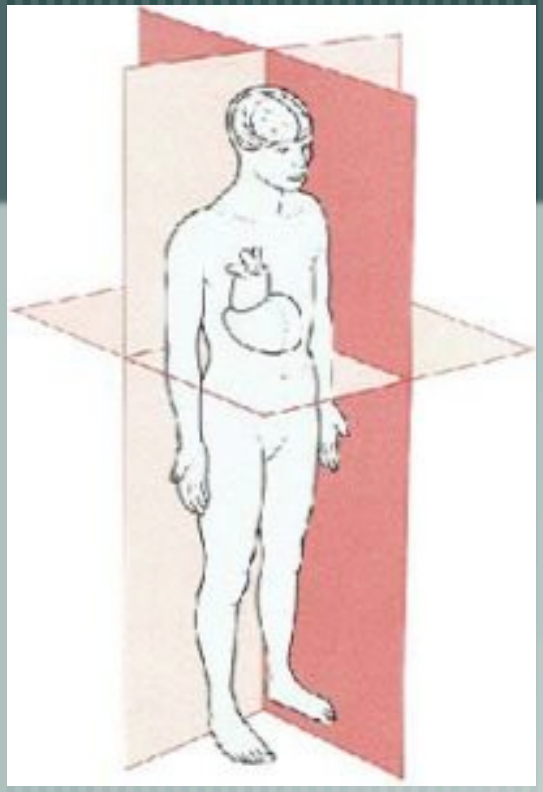
# Link between microdosimetry and geometry:

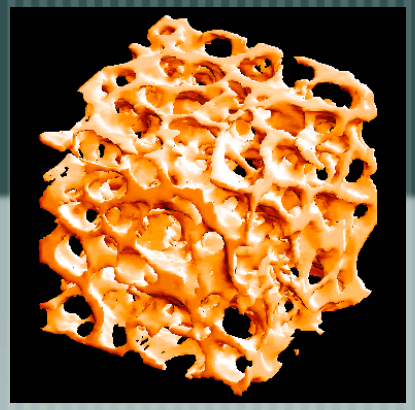
When the problem is treated at a smaller and smaller scale,
a microdosimetric description becomes necessary:

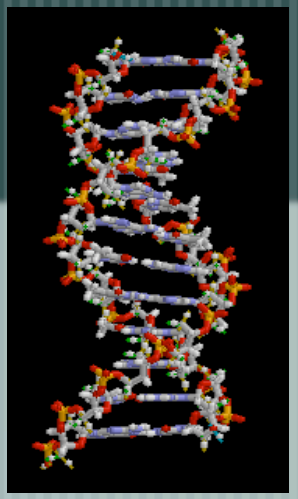
| | |
|---|---|
| Patient: | 1-2 m |
| Organ: | 1-10 cm |
| Tissue fragment: | mm |
| Cell: | ~20 μm |
| DNA: | 2 nm |

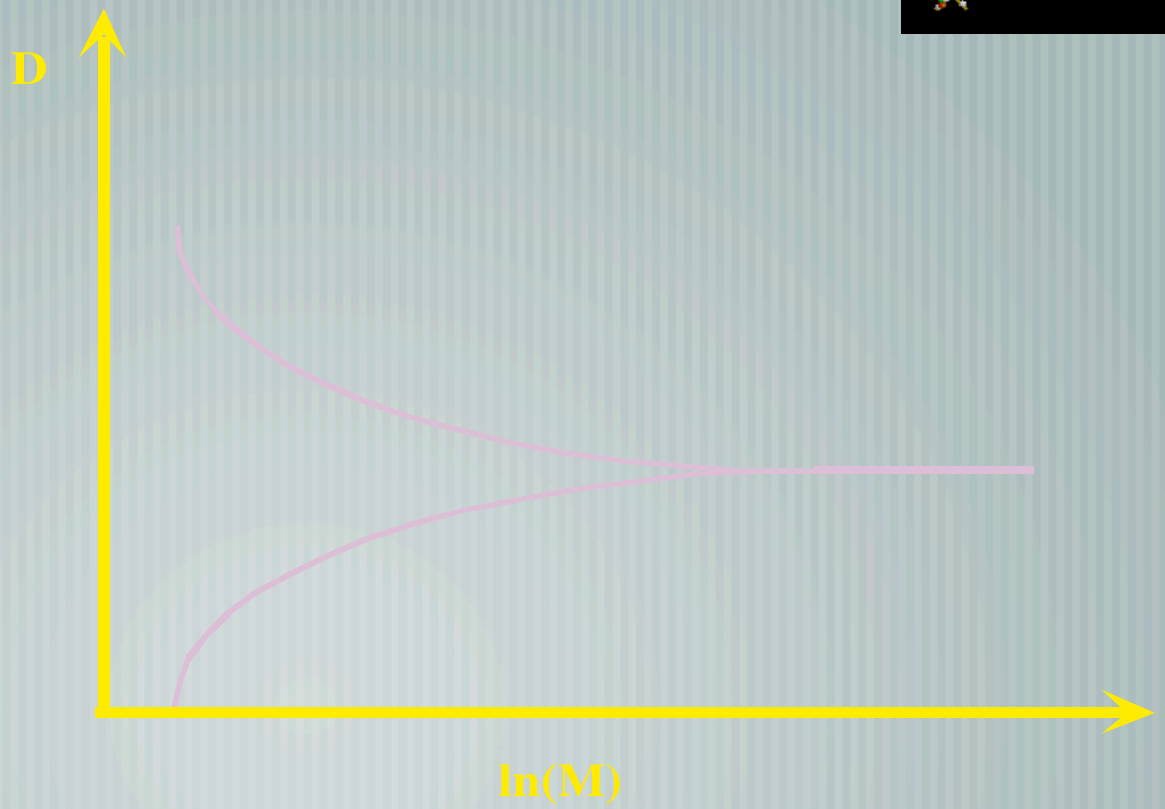
Concept of deposited energy/unit mass still valid,
But the diminishing size of the target:

stochastic events more "apparent"

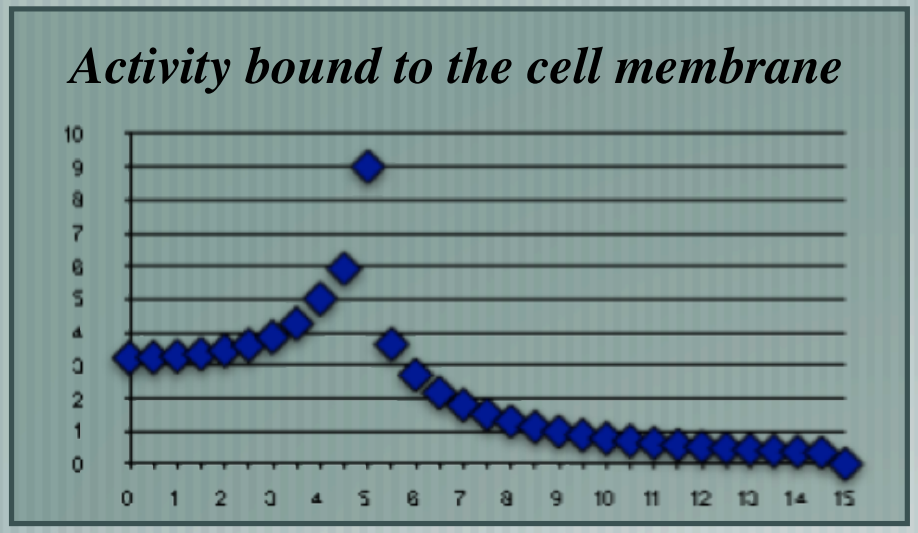


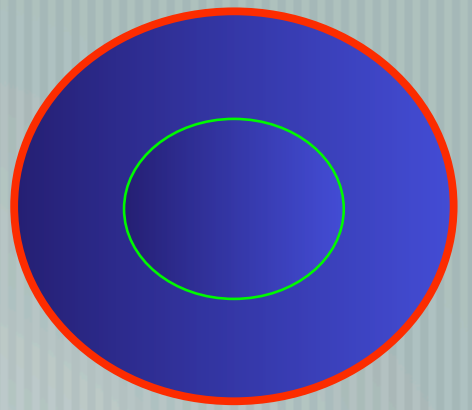





D
ln(M)

# In that example (A Malaroda):



Rc = 5 μm
Rn = 2.5 μm

Spatial heterogeneity of absorbed dose distribution,
But what is calculated is a mean absorbed dose...
... this is a macrodosimetric approach!

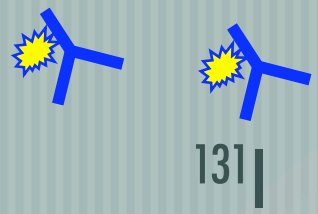
# Other (classical) example:

1 cGy gamma photons
50 ± 7 electron tracks/cell (on average)
1 cGy alpha
Dose spectrum, from 0 to 30 cGy
Mean number of hits: 0.1
90% of cells are spared!

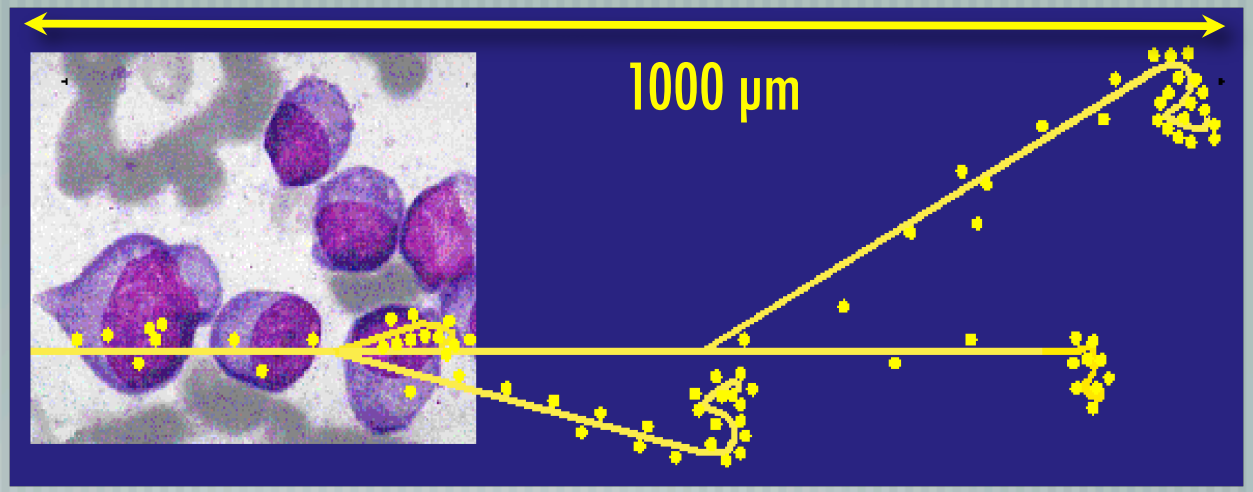
(Goodhead in *Dosimetry of ionizing radiations*, Kaze, Bjarngard and Attix ed., Orlando1987)

We'll see, through an example,what microdosimetry can provide:
Single cell labelled by alpha particles

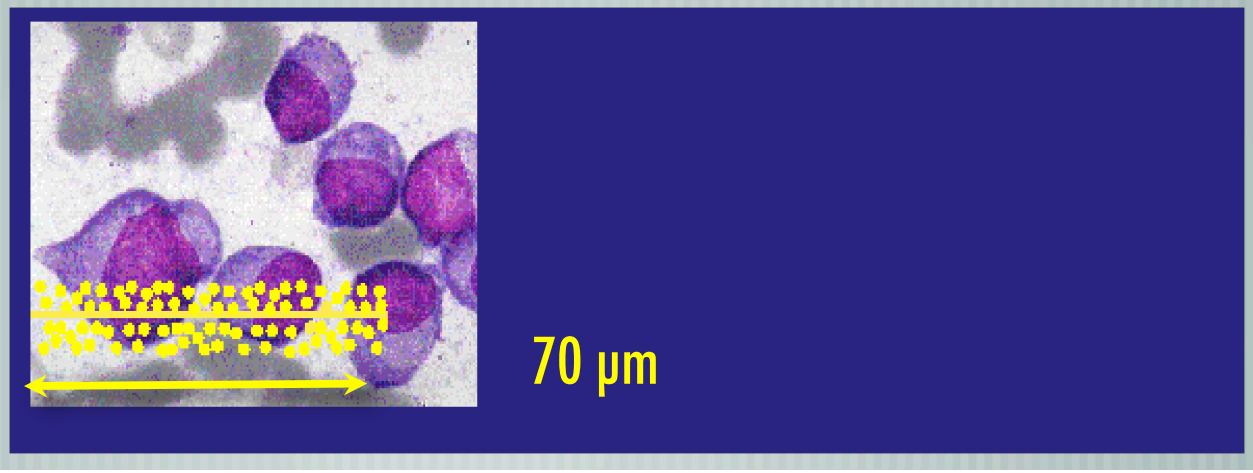
# Rationale for alpha-radioimmunotherapy



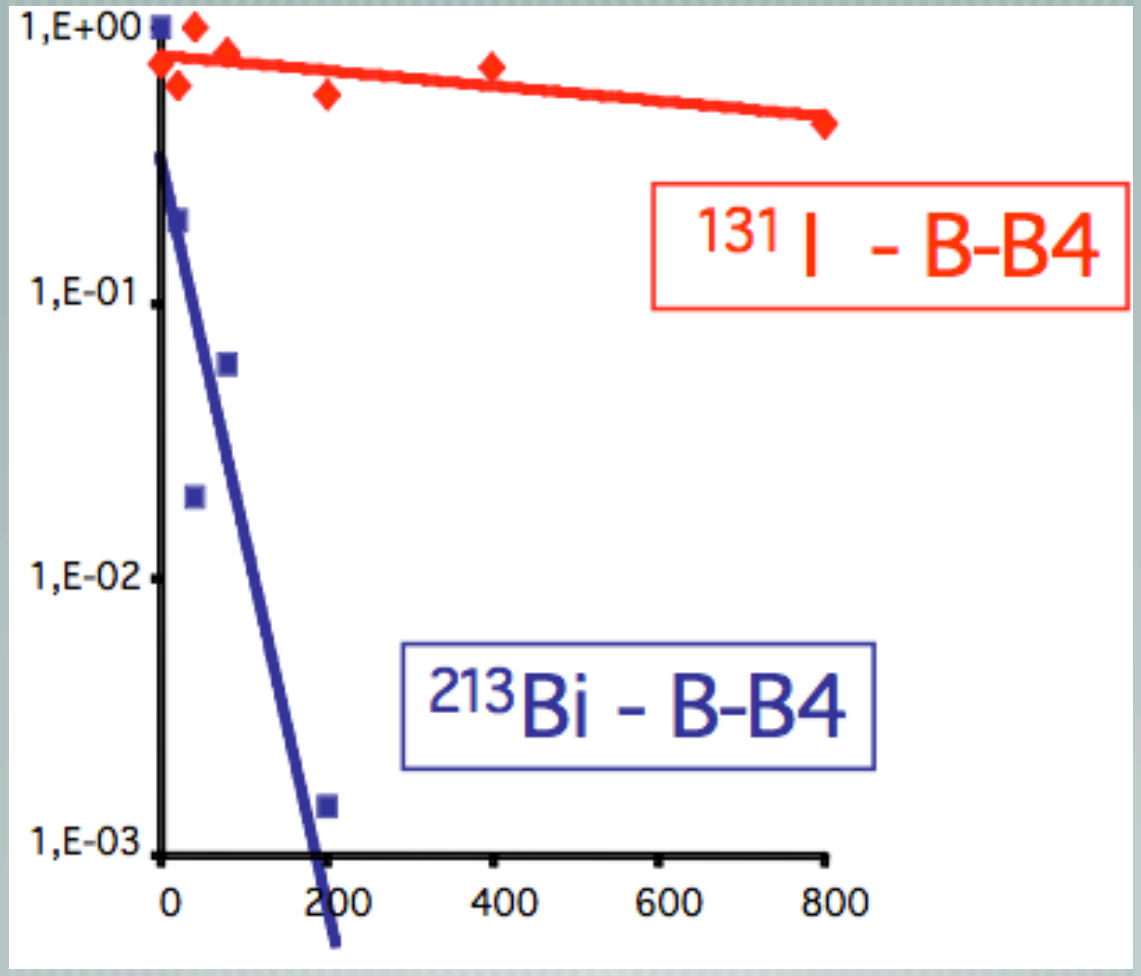
$^{131}I$



$^{213}Bi$



# Biologic effect of $^{213}Bi$ and $^{131}I$ labelled BB4 MoAB on Multiple Myeloma cell lines



# Key features of α emitters proposed for MRT

- Energy: 4 to 8 MeV
- Range : 40 to 80 µm
- High LET
- Straight particle track (canon ball)

Physical half-life?
Stable decay product?
Production and availability?

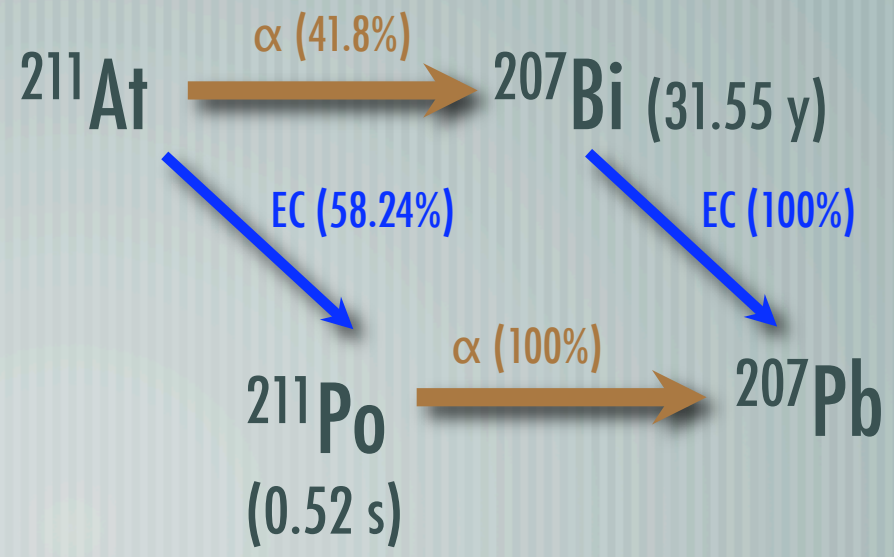
There are only a few alpha emitters proposed in the literature!

## $^{212}Bi$

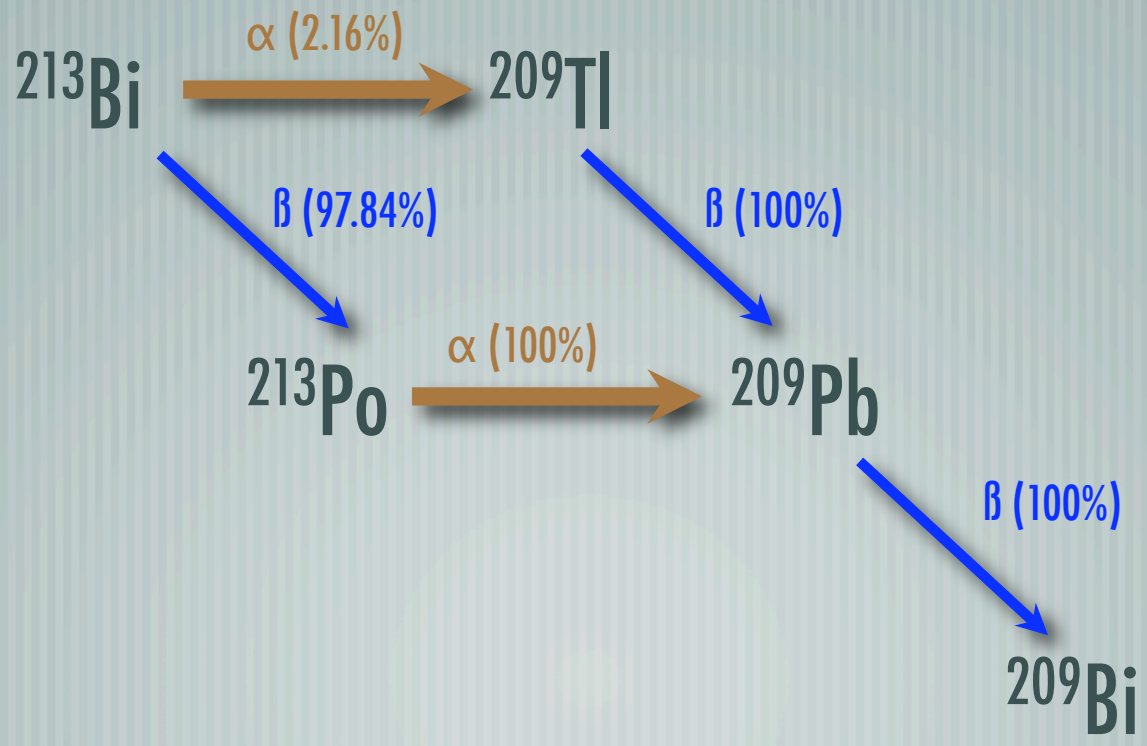
- Generator ($^{224}Ra$) but high energy gamma emission!
- $E\alpha \approx 6.2$ and 8.95 MeV
- $T_{1/2} = 60.6$ mn (but parent $^{212}Pb$ : $T_{1/2} = 10.6$ h)
- price...

## $^{211}At$

- Produced by cyclotron
- $E\alpha \approx 5.9$ MeV/$^{211}At$
- $E\alpha \approx 7.6$ MeV/$^{211}Po$
- $T_{1/2} = 7.2$ h



- $^{213}Bi$
  - Generator ($^{225}Ac$)
  - $E\alpha \approx 8.5$ MeV
  - $T_{1/2} = 46$ mn!

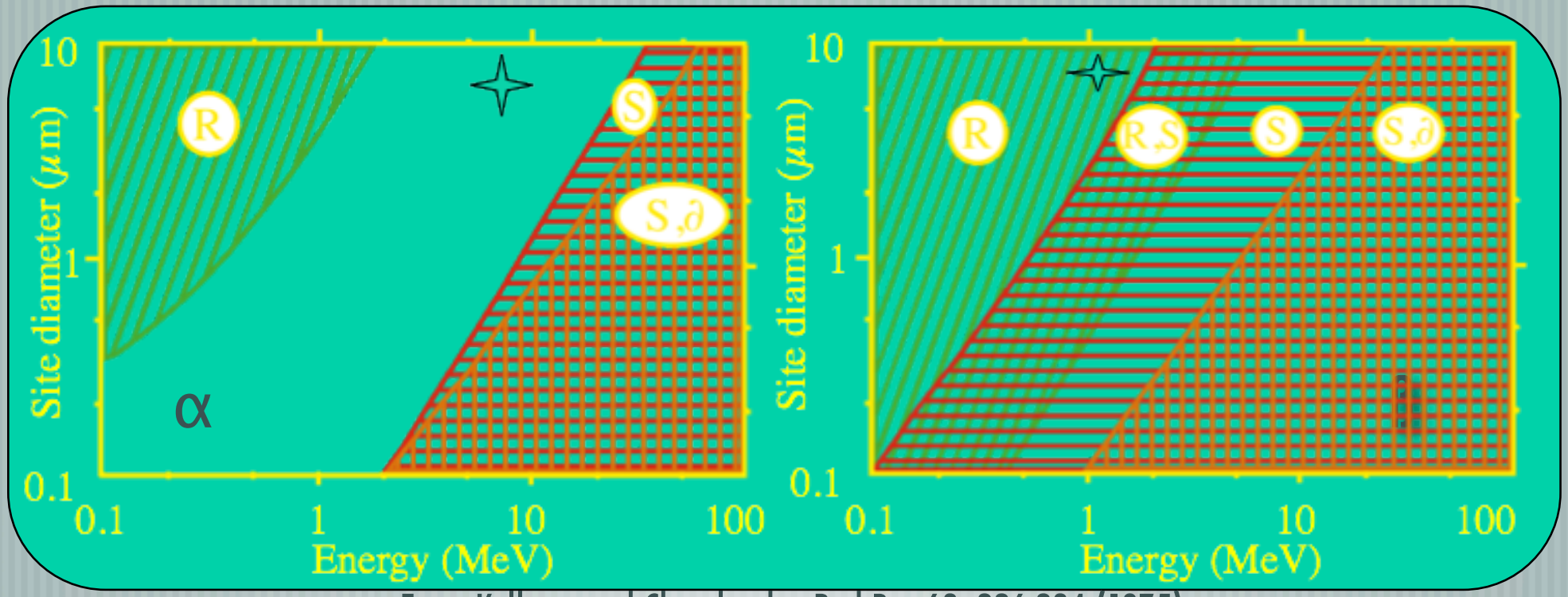


# Alpha particles dosimetry:

Monoenergetic emissions (4 to 9 MeV), small range (< 100 µm)

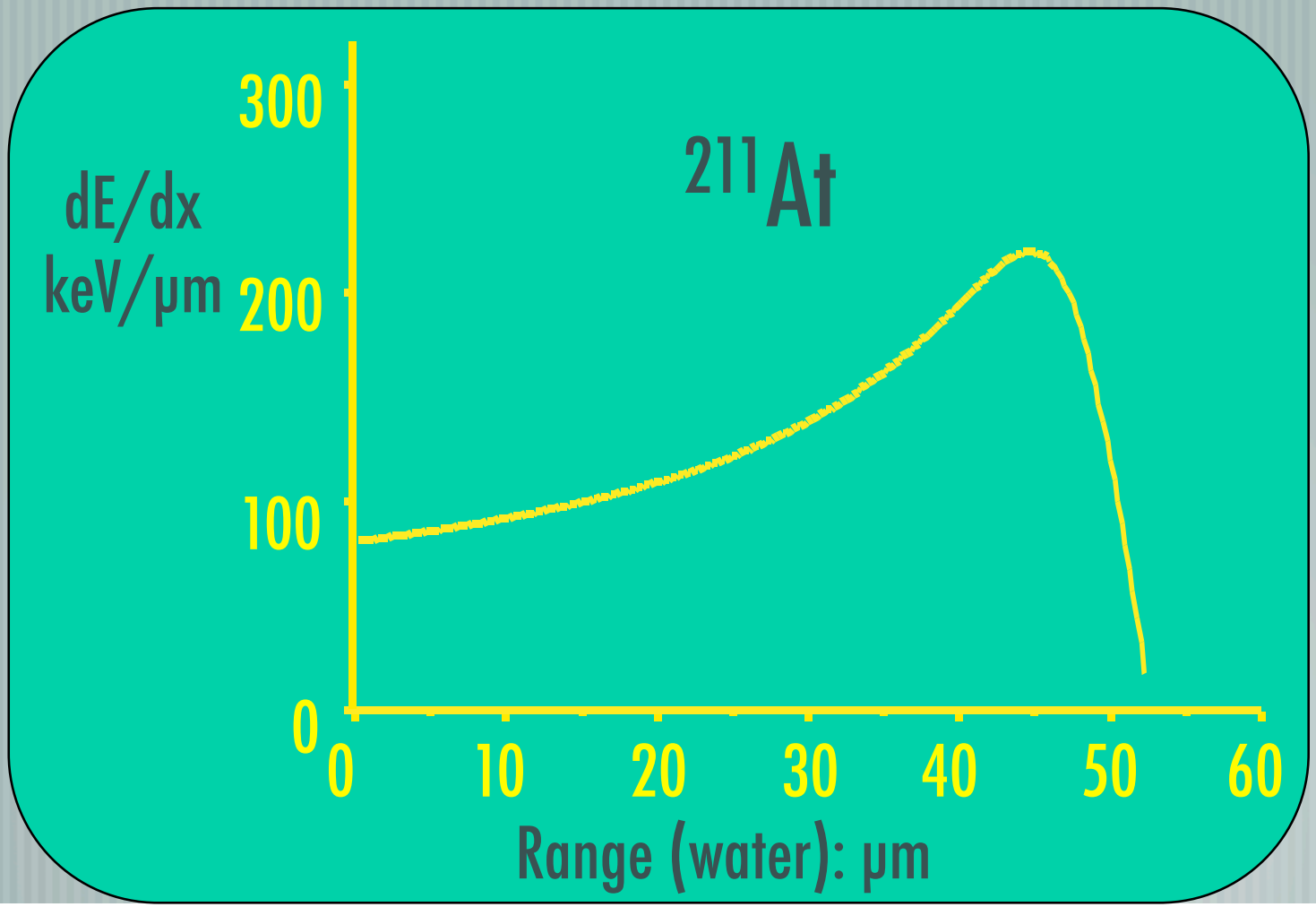
LET is the relevant parameter at the cell level

LET determination => Energy deposition in the target

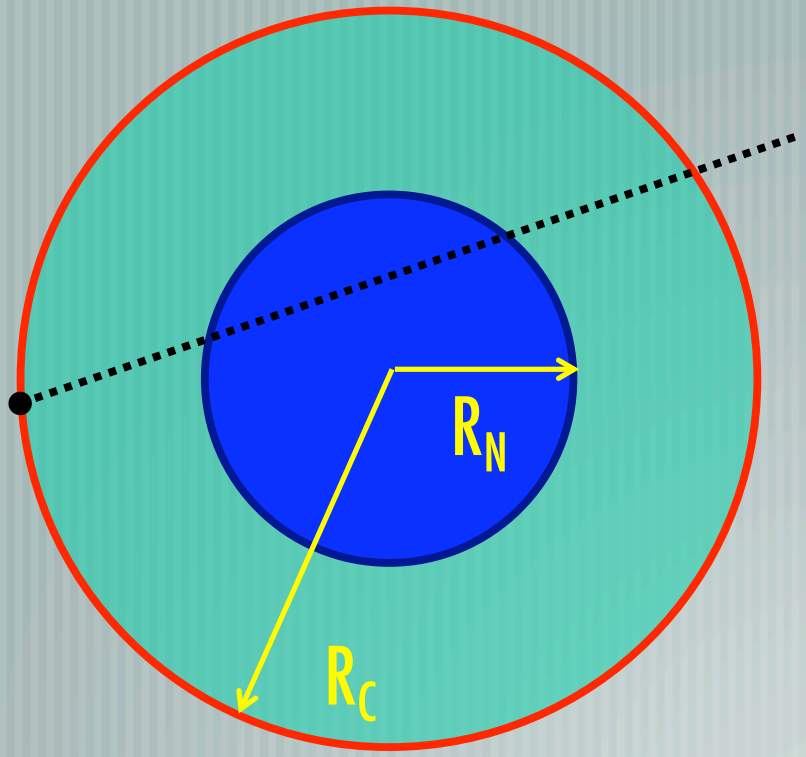



From Kellerer and Chmelevsky, Rad Res 63, 226-234 (1975)

# In general: LET determination is sufficient



# Simplified dosimetric approach
## (J Humm *Int. J. Radiat. Oncol. Biol. Phys.* **16** 1767-1776, 1987)




$R_C$ = 10 µm
$R_N$ = 5 µm

LET ≈ 80 keV/µm ($^{211}$At)
Mean chord length= 6.63 µm

Energy imparted to the nucleus:
530 keV per particle hit (16.3 cGy)

Ω : 1 particle / 15 hits the nucleus
Mean dose per disintegration:
$S_{(\text{nucleus} \leftarrow \text{cell surface})}$ = 1.1 cGy/Bq.s

If $D_0$ = 70 cGy,
4.3 hits for 37% cell inactivation
4.3 x 15 ≈ 65 emitted alpha particles (Bq.s)

# Standard dosimetric approach

## (Goddu *et al. J. Nucl. Med.* **35**: 303-316 and 521-530, 1994) + MIRD cellular S values

Integration of LET variation along the track

Introduction of a geometric factor $\Psi$

$$\phi_{(Nucleus \leftarrow Cell\ Surface)} = \int_0^{\infty} \psi(x)_{(Nucleus \leftarrow Cell\ Surface)} \frac{1}{E} \frac{dE}{dX}\bigg|_{X(E)-x} dx$$

$$\frac{dE}{dX} = 260 X^{-\frac{1}{3}}$$

$$\psi(x)_{(Nucleus \leftarrow Cell\ Surface)} = \begin{cases} 0 & 0 \le x \le R_C - R_N \\ \dfrac{2xR_C - R_C^2 - x^2 + R_N^2}{4xR_C} & R_C - R_N \le x \le R_C + R_N \\ 0 & x \ge R_C + R_N \end{cases}$$

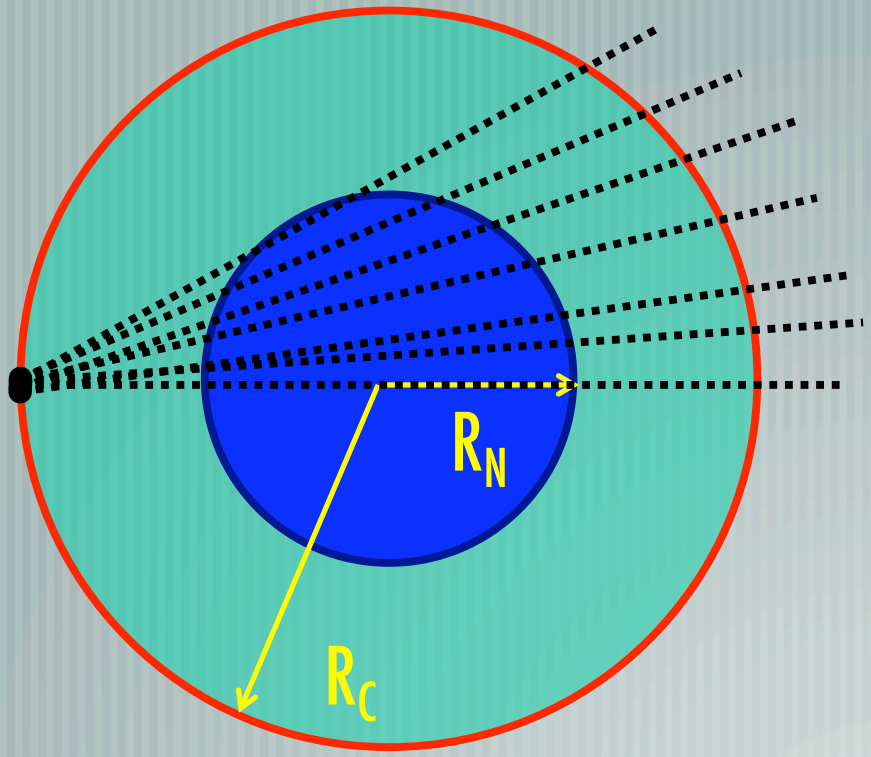
Mean dose dose /emitted alpha particle: $S_{(Nucleus <- Cell\ Surface)}$ = 1.2 cGy/Bq.s

(To compare with: $^{131}I$: 6.5 $10^{-3}$ cGy /(Bq.s) or $^{90}Y$: 2.8 $10^{-3}$ cGy /(Bq.s)

# Analytic microdosimetric approach:

(Stinchcomb and Roeske, Med. Phys. 19 1385-1393, 1992)

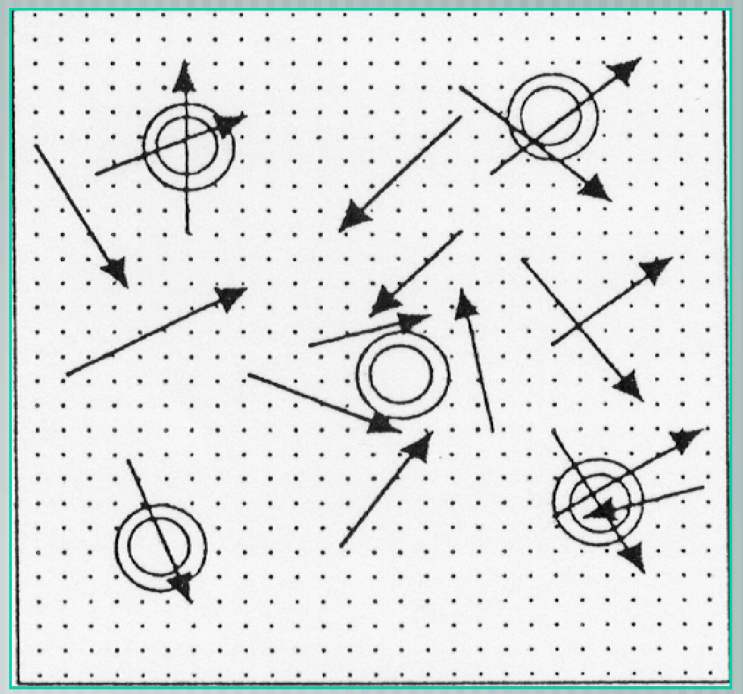
(Roeske J. Nucl. Med. 38 1923-1929, 1997)



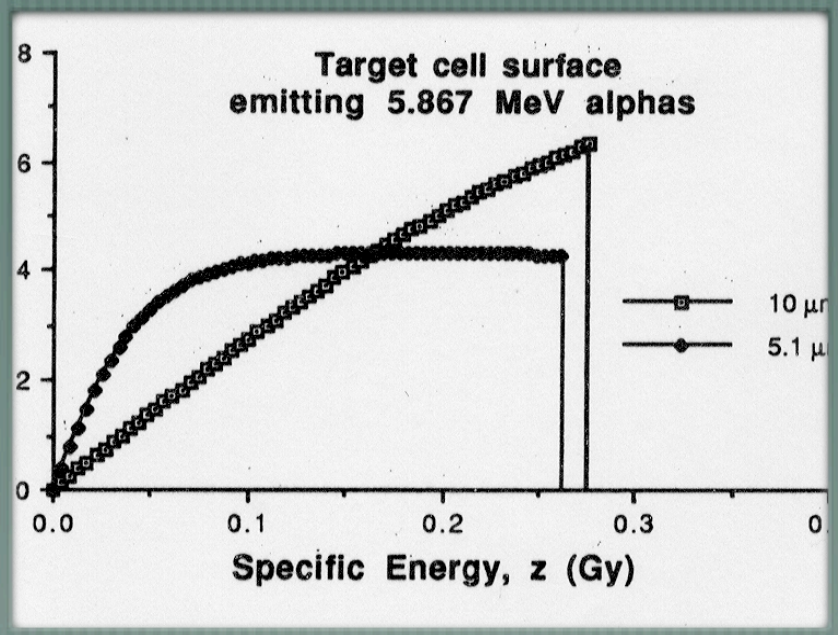

$R_C$ = 10 μm

$R_N$ = 5 μm

## Specific energy (z) distribution $f_1(z)$ (single events)



Specific energy spectrum, from 0 to 27.8 cGy




Mean specific energy: 18.3 cGy per hit

No 0 Gy probability for single events specific energy,
(The particle always hits the nucleus...)

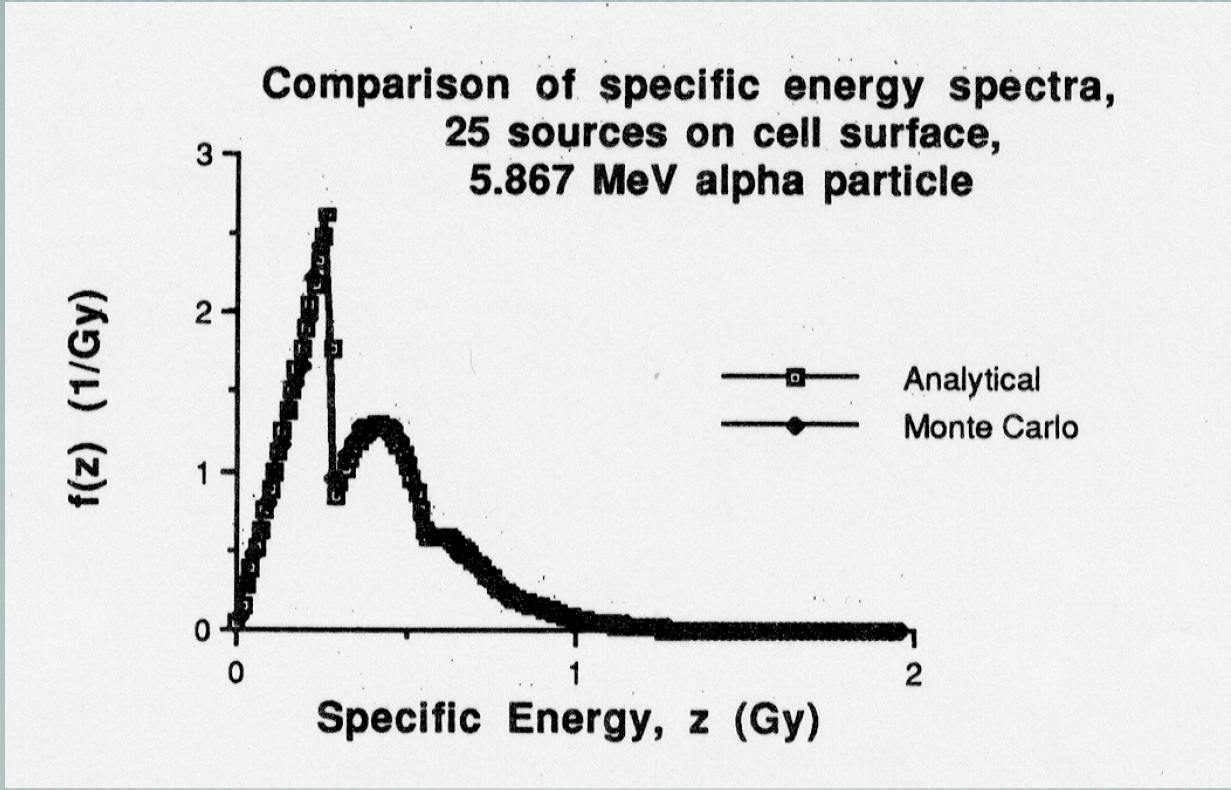
# Convolution of single event energy deposition spectra

According to geometry, activity,...
There will be multiple energy deposition events

$$f_n(z) = \left[ f_1(z) \right]^{*n}$$

$$f(z;D) = \sum_{0}^{\infty} \left[ f_1(z) \right]^{*n} \times \frac{e^{-M}}{n!} M^n$$

# Results:

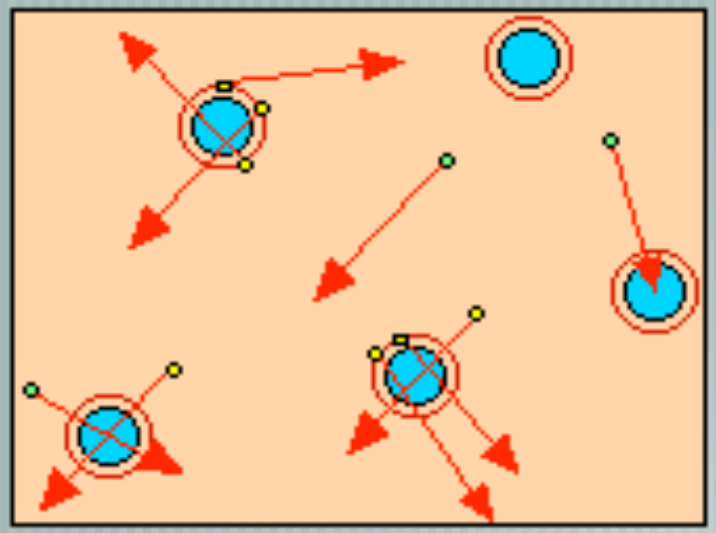



<z> = 0.305 Gy, <n> = 1.67 (Solid angle 0.067),

[P(z) = 0] = 0.178 (17.8 % non irradiated nuclei...)

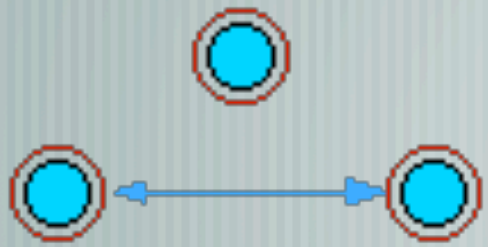
And S = 1.22 cGy / (Bq.s) (0.305/25 sources)

# Application to α RIT:



- Specific monoclonal antibody BB4:
  IgG: 0.01 to 10 nM (As=8.57 mCi/mg)
  $F(ab')_2$ fragments: 0.01 to 1 nM (As=14.7 mCi/mg)
- Non-specific antibody:
  IgG 134: 0.1 to 20 nM (As=5.57 mCi/mg)

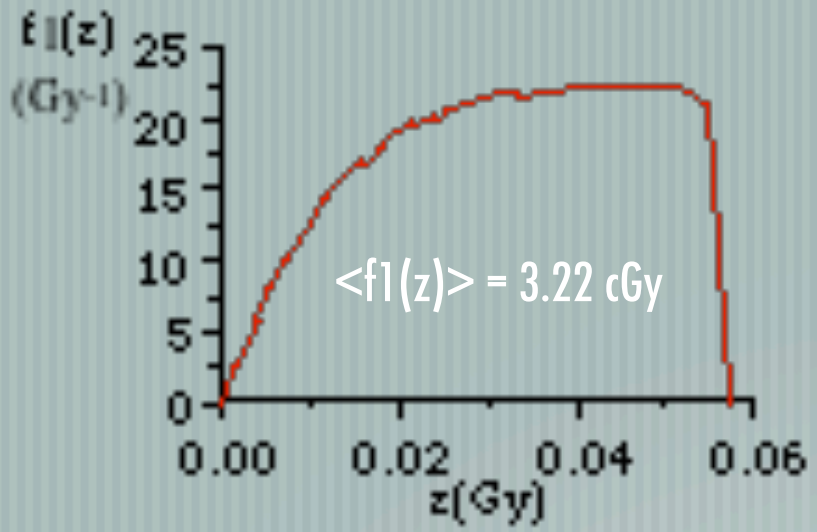
Alpha particle tracks ($^{213}Bi$):
$E_\alpha$ = 8.376 MeV, range : $R_\alpha = R(E_\alpha) \approx 85$ µm

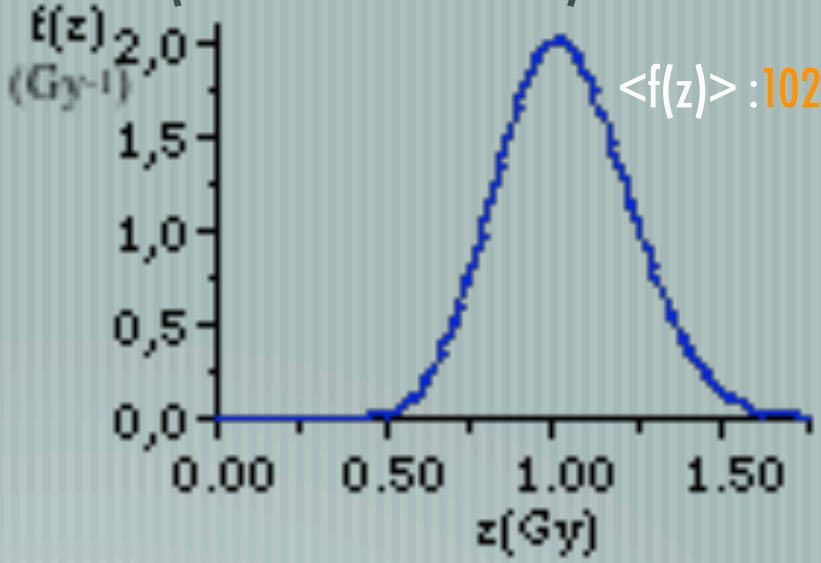


MM Human cell line : RPMI 8226 $R_c$=10 µm, $R_n$=9.5 µm

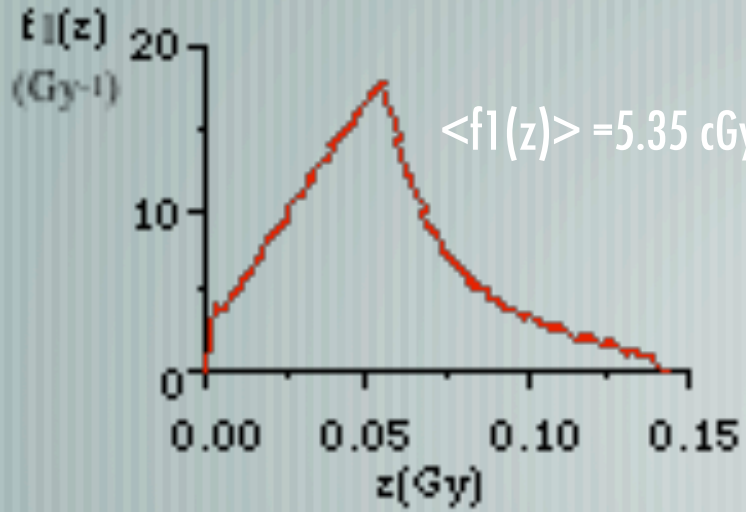
Mean intercellular distance > $R_\alpha$

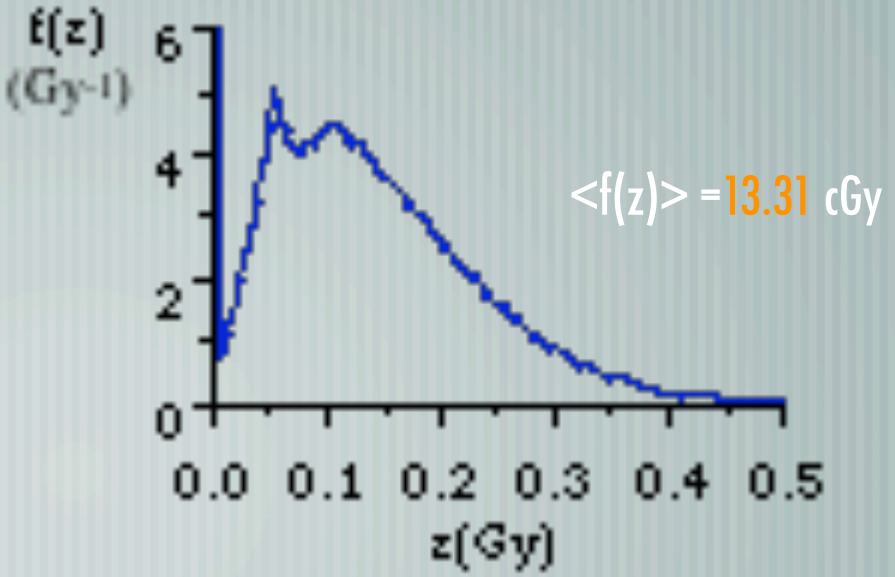
## IgG BB4, 1.0 nM, Specific dose (surface distribution)



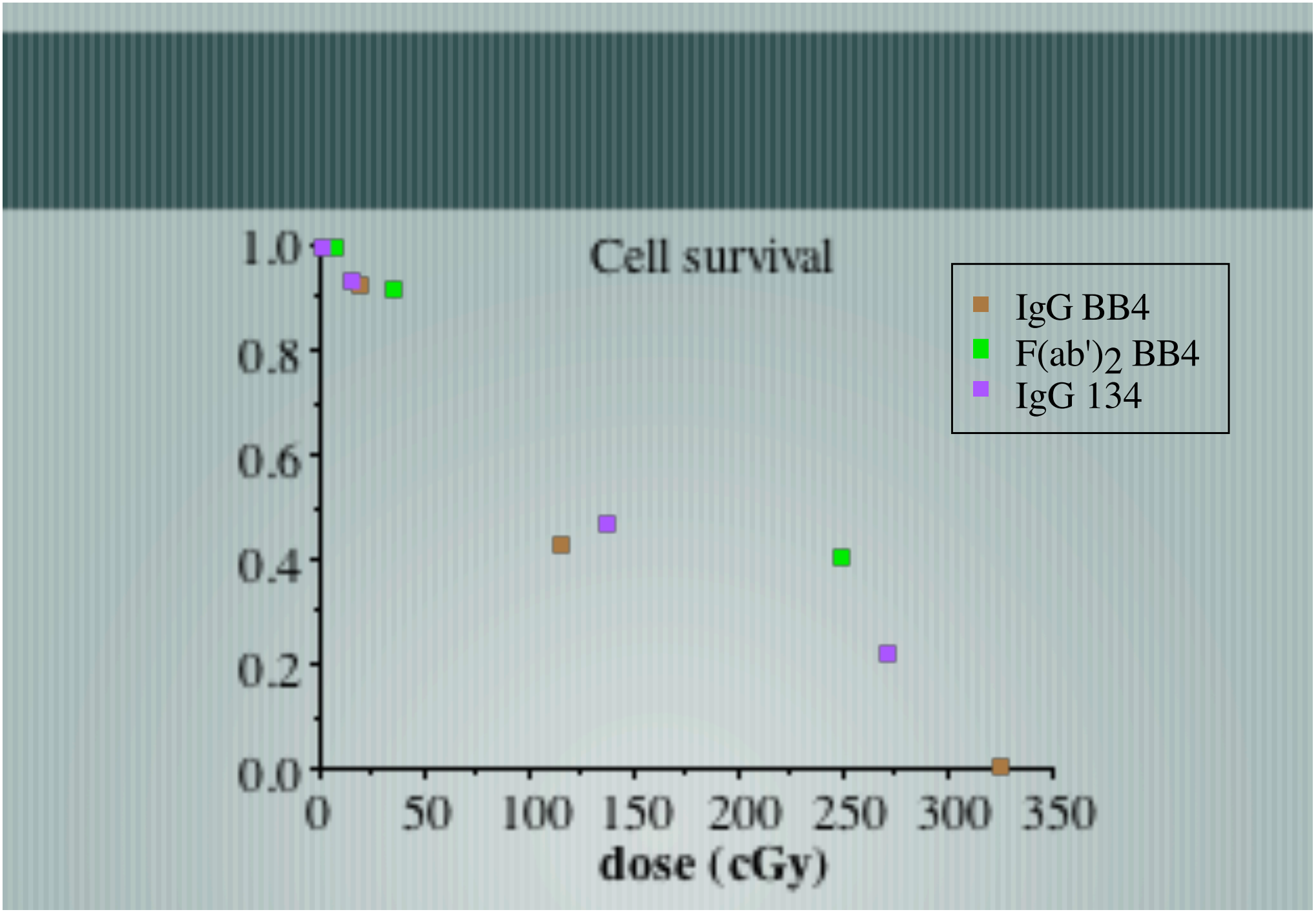

## IgG BB4, 1.0 nM, Non-specific dose (volume distribution)



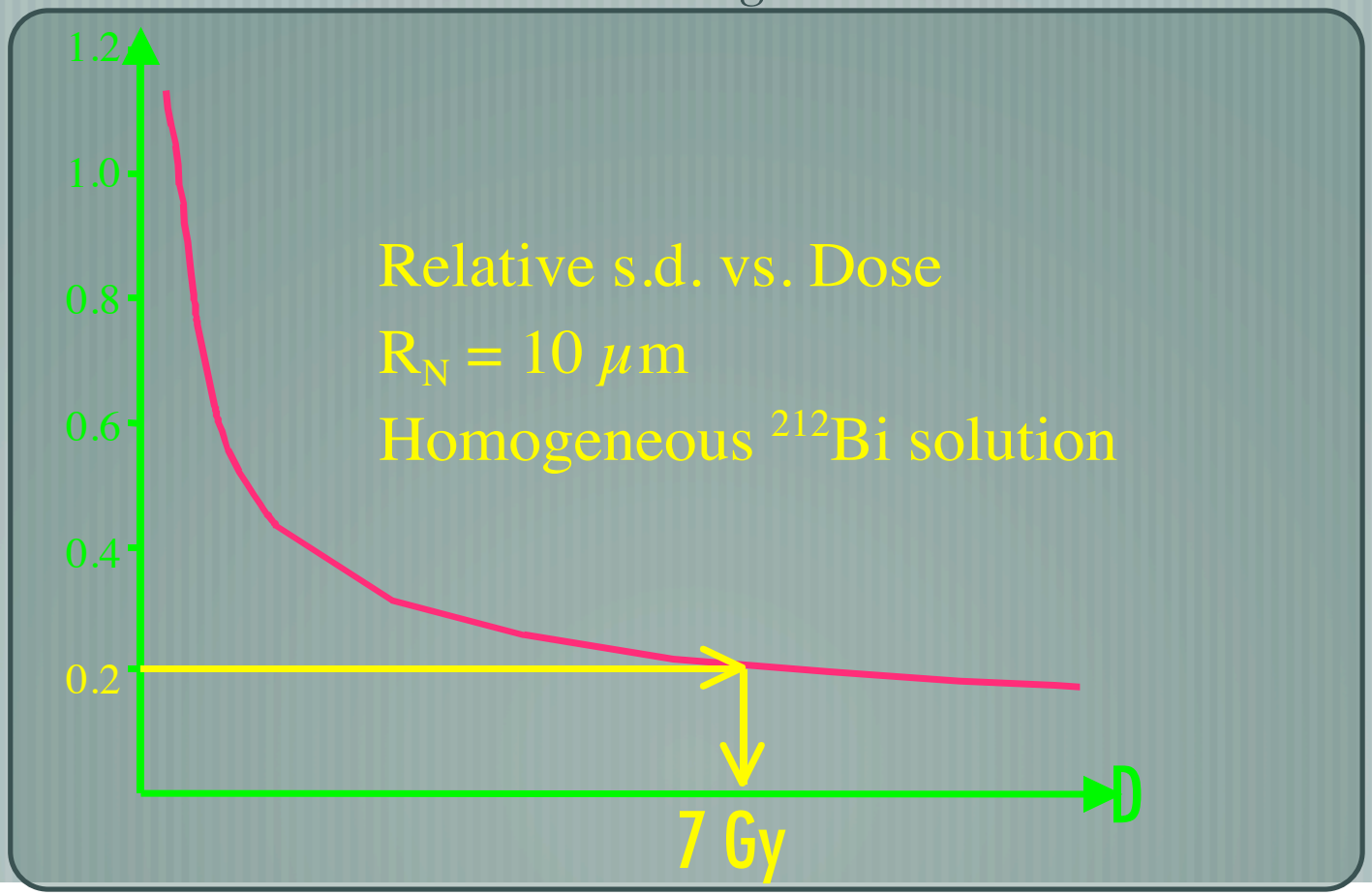
# Still mean doses (cGy)…

| Ab | IgG BB4 | Fab'2 | IgG 134 |
|---|---|---|---|
| 0,01 | 1.4 | 5.9 | |
| 0,1 | 17.6 | 35.6 | 1.5 |
| 1 | 115.6 | 249.9 | 14.3 |
| 10 | 325.8 | | 137.7 |
| 20 | | | 269.5 |


Cell survival
IgG BB4
F(ab')2 BB4
IgG 134
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
200
250
300
350
dose (cGy)

# When should we use a microdosimetric approach?

ICRU 36: When statistical fluctuation in energy deposition is high,
When the relative std dev *in a given volume* is ≥ 20%



# And for ß emitting radionuclides?

The situation is somehow simpler...

ß emitters LET << $\alpha$ emitters LET

Much more particle are needed in order to observe deterministic effects ...

In general, macrodosimetry is considered as relevant, even at the cell scale

But who knows...

# And for Auger emitting radionuclides?

Situation both easier and more complex...
Auger: monoenergetic electrons

Very low energy (down to some eV)
range is *very* small in biologic media (some nm)

Therefore: If energy > some keV

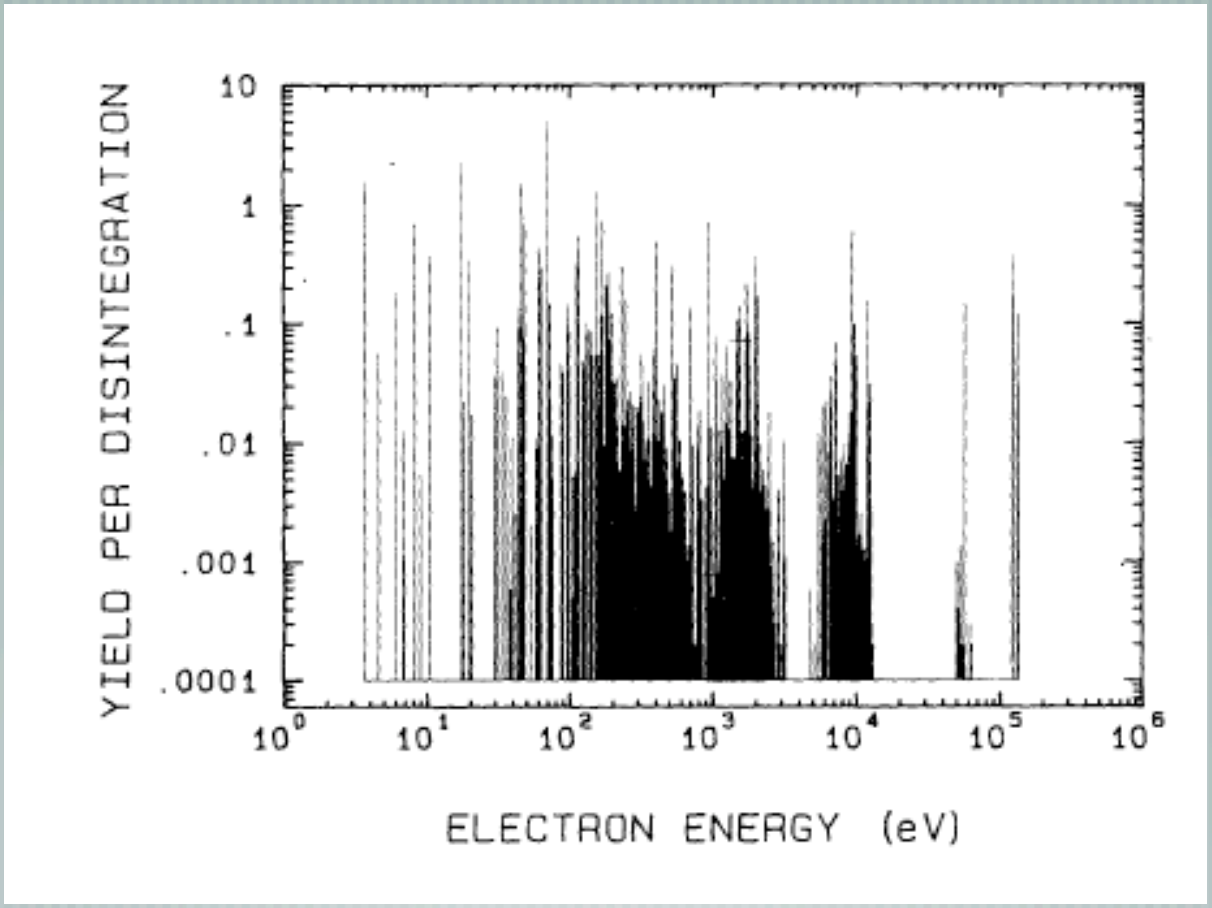
Auger dosimetry is 'conventional' electron dosimetry

Very low energy electrons

- Emitted in cell cytoplasm, membrane: 'normal' electrons? ( this is discussed...)
- Emitted near DNA: Auger ~ high LET particles

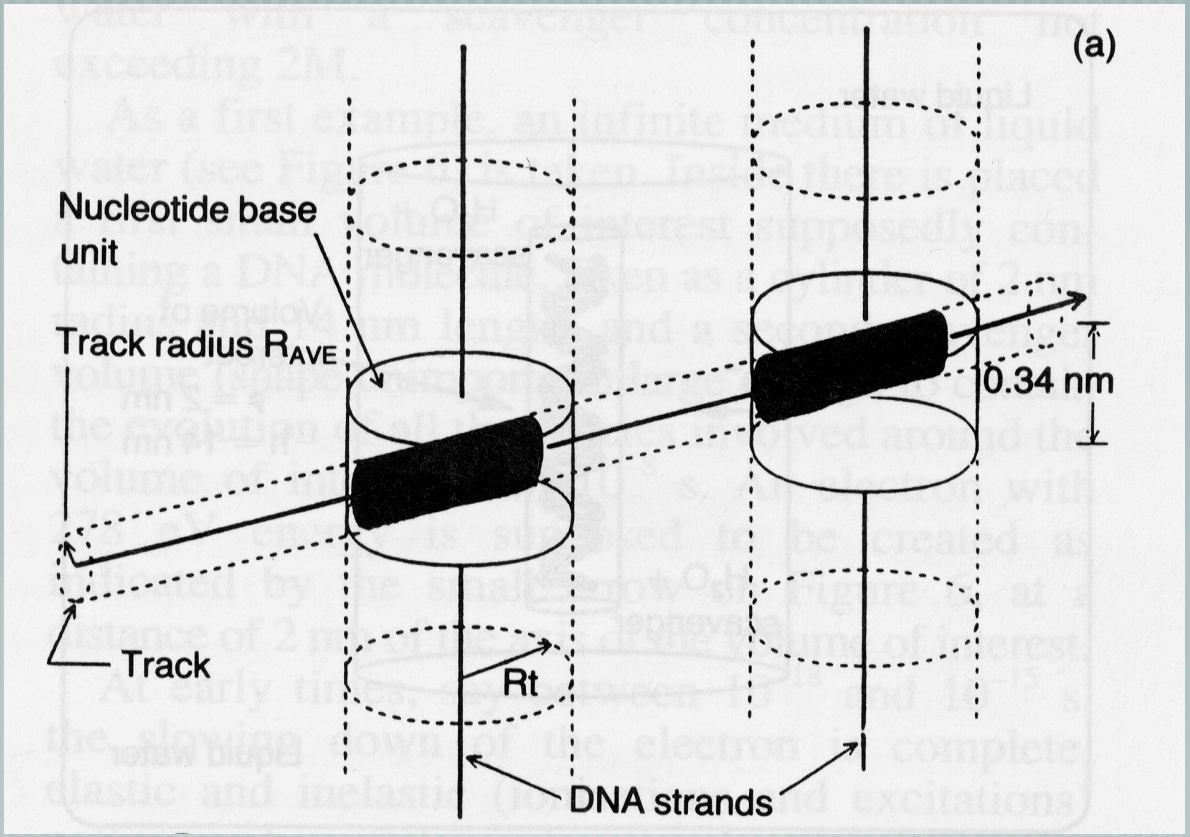
Microdosimetric studies are usually required...

# Auger emitters: complex emission spectra

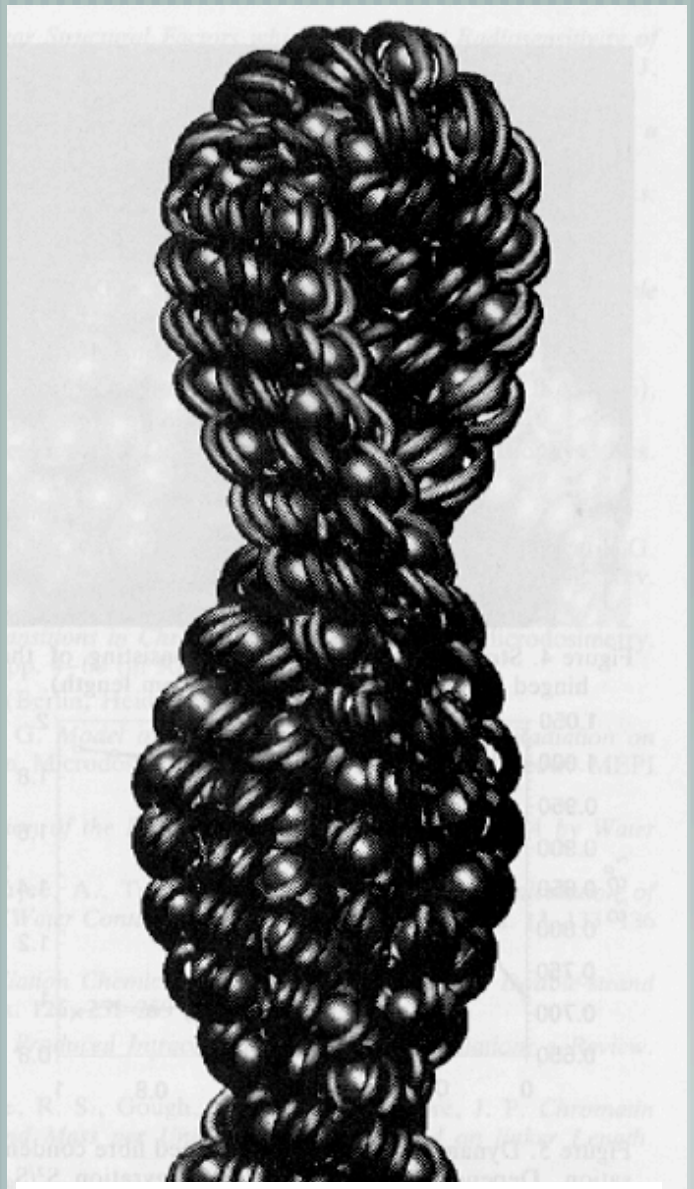



Example: $^{193m}$Pt emission spectrum (Howell *et al*. 86)

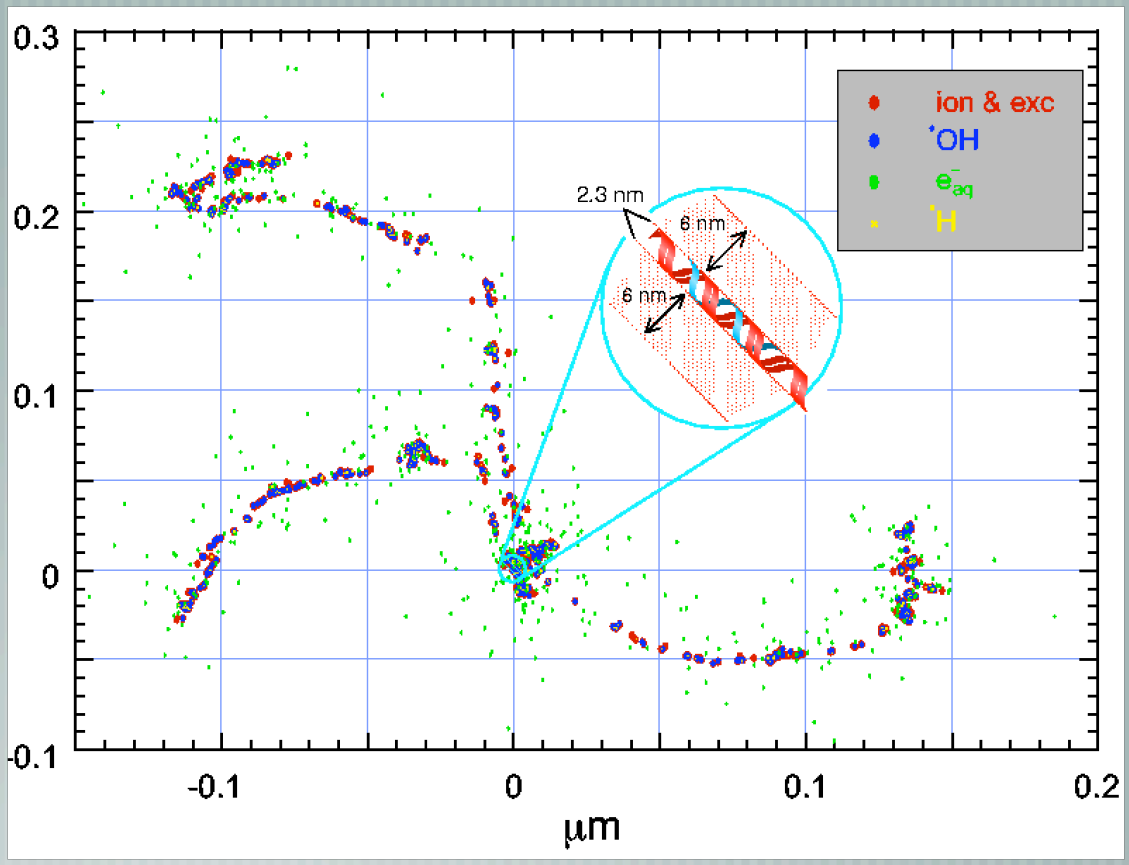
# Example: microdosimetry of Auger electrons



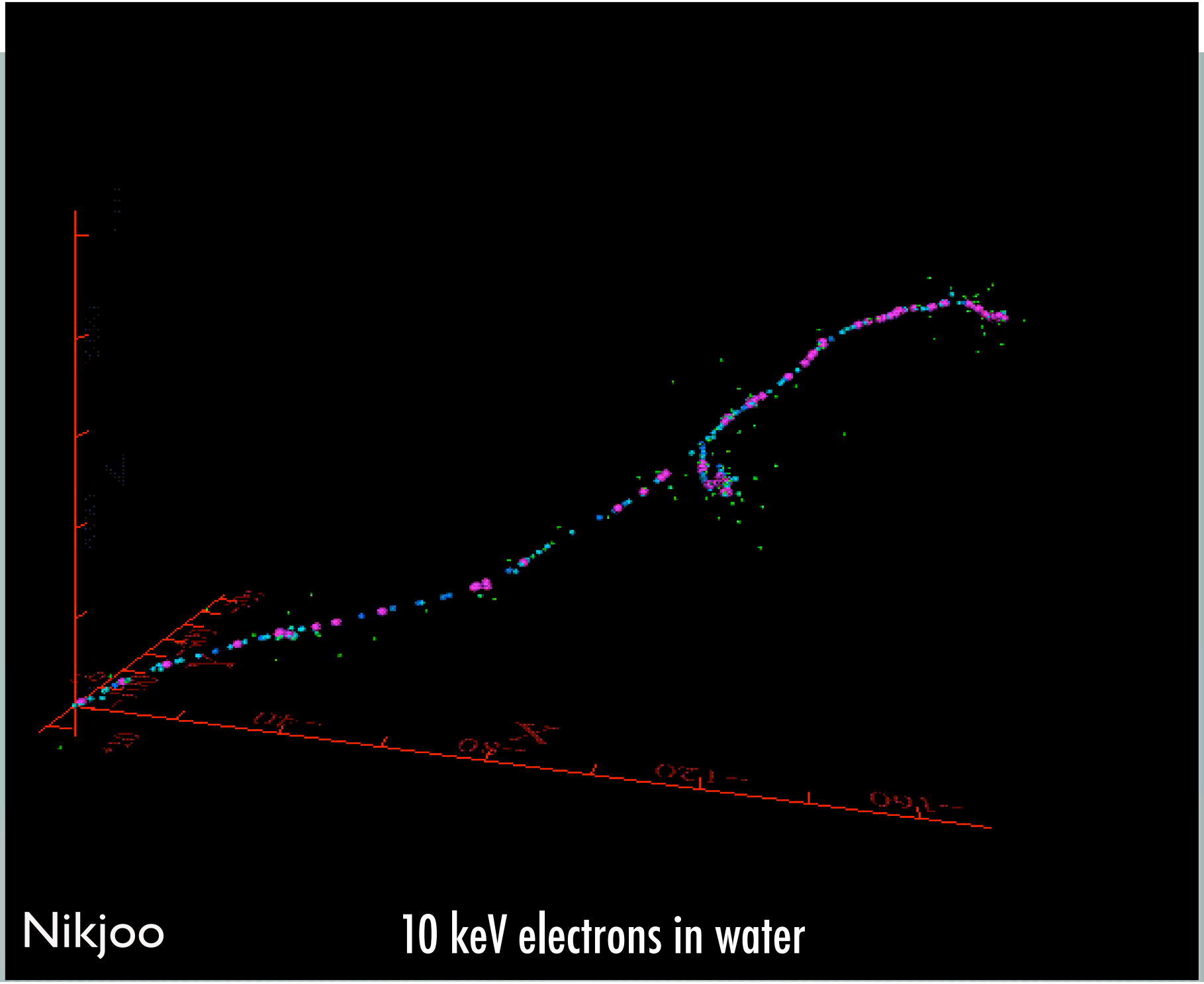

Goodhead *et al*. Rad. Prot. Dos. 52 : 217-223, 1994



Chepel *et al.*
Rad. Prot. Dos. 52 : 259-263, 1994




Nikjoo et al. 2001



Nikjoo

10 keV electrons in water

# Conclusions

No *conceptual* difference between micro and macrodosimetry

Microdosimetric models are available (sometimes...)
Microdosimetry can provide a lot of relevant information (too much?)

For TRT, i.e. for high particle flux,
Microdosimetry may not be necessary...
(if statistical fluctuations around the mean deposited energy are small)

Survival curves with mean absorbed doses ...
Is it necessary to refine the dosimetric approach?
The answer comes from the biologist...

# References


/ microdosimetry:

Roesch, *Rad. Res.* **70** 494-510, 1977

ICRU 36 (1983)

Bardiès and Pihet *Cur Pharm Design* **6** 1469-1502 2000

/ Alpha dosimetry:

Stinchcomb and Roeske, *Med. Phys.* **19** 1385-1393, 1992

Roeske *J. Nucl. Med.* **38** 1923-1929, 1997

/ Auger dosimetry: AAPM task group

Sastry, *Med. Phys.* **19** 1361-70 1992

Howell, *Med. Phys.* **19** 1371-83 1992

Humm, *Med. Phys.* **21** 1901-15 1994