Small scale dosimetry: Beta emitters (ß-)

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

Introduction

- In ‘conventional’ Nuclear Medicine:
- Biological target:
- Organ or tissue
- i.e. macroscopic scale
- For diagnostic procedures:
- Gamma emitters (nuclear imaging),
- Spatial resolution: ~ cm
- Activity won’t be determined with a better resolution...

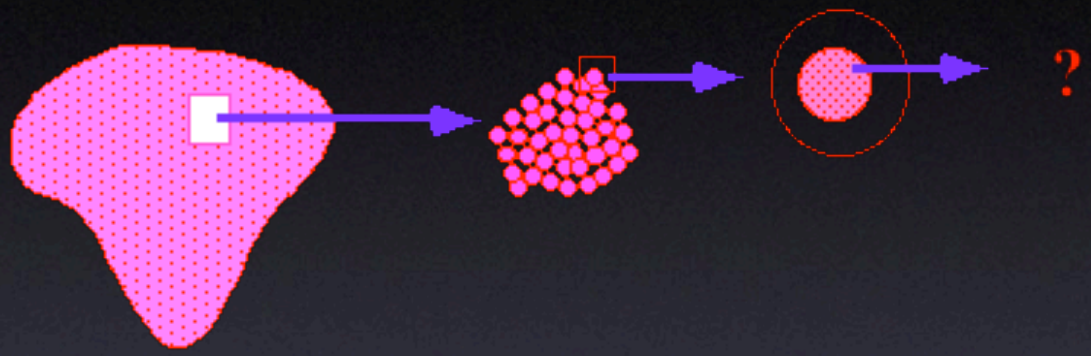
Particle range in biologic material?

Electron range in soft tissue: 0.1 mm to 1 cm
Alpha range in soft tissue: 40 to 100 µm

Beta (alpha) emitters are relevant for Molecular radiotherapy

Using a vector *specificity* to achieve *selective* irradiation

- In therapy, what are the relevant event?
- What is the right scale?

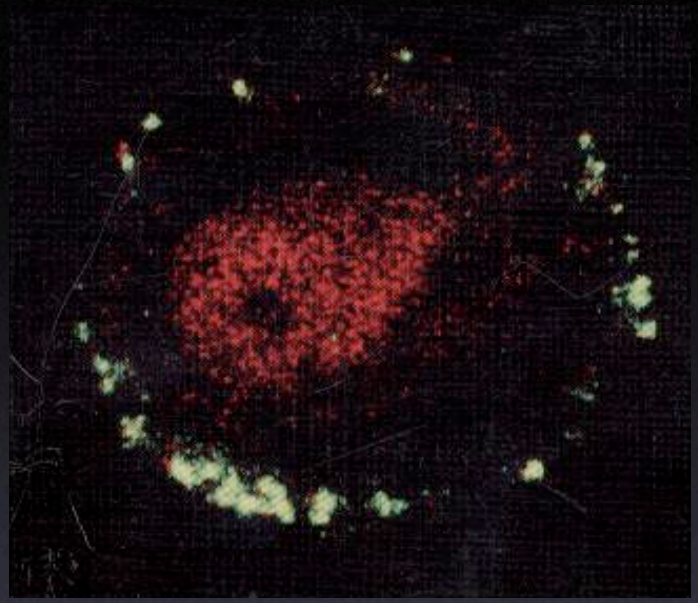


There is always a link between target size and radiation range:

Organ, tissue, cell, sub-cellular…

Gamma, beta, alpha, Auger, ...

Why at the microscopic scale?



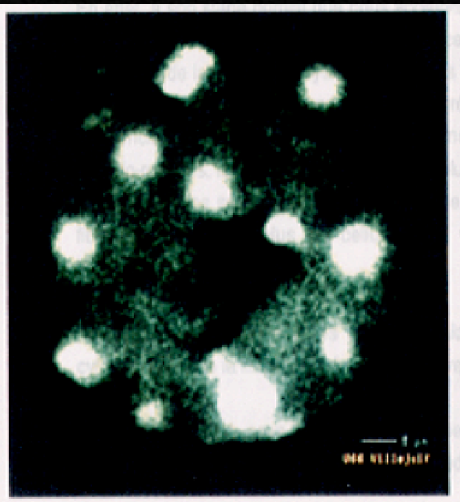


Figure II.5 - Image ionique d'une coupe de tissu surrénalien (60 µm). Distribution du phosphore 31.

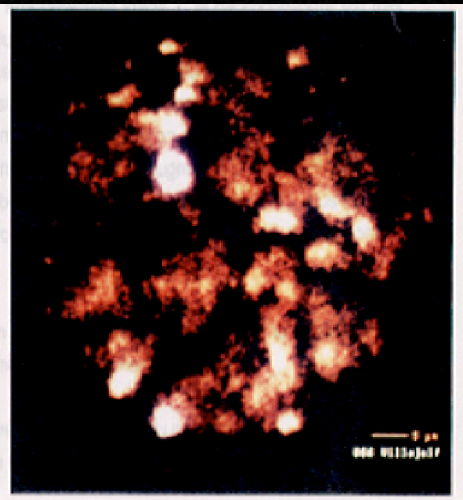
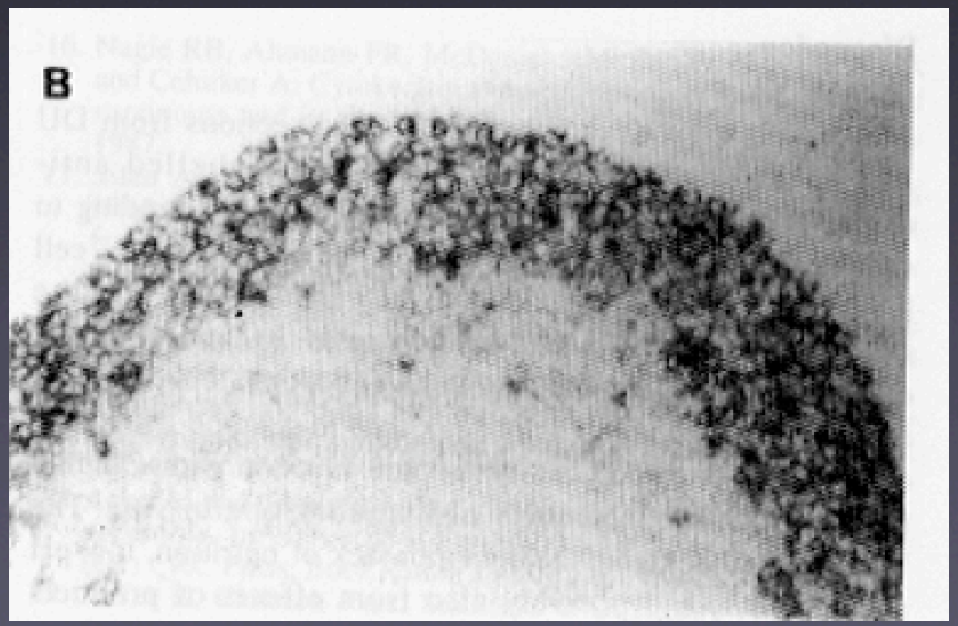


Figure II.6 - Image ionique d'une coupe de tissu surrénalien (60 µm). Distribution de l'iode 127.



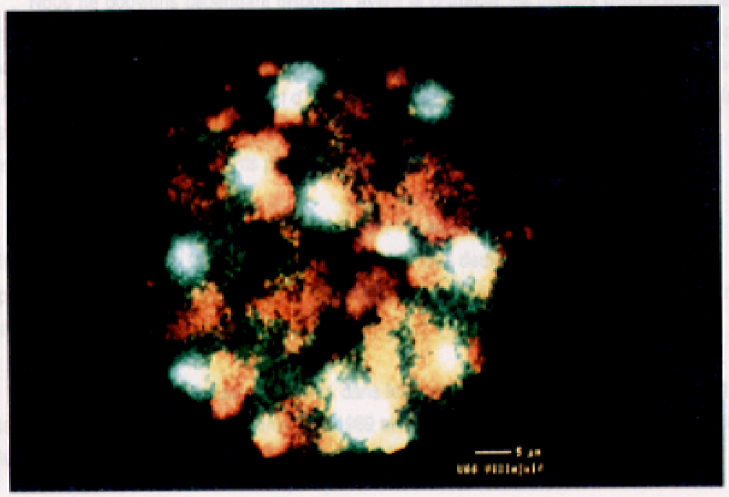
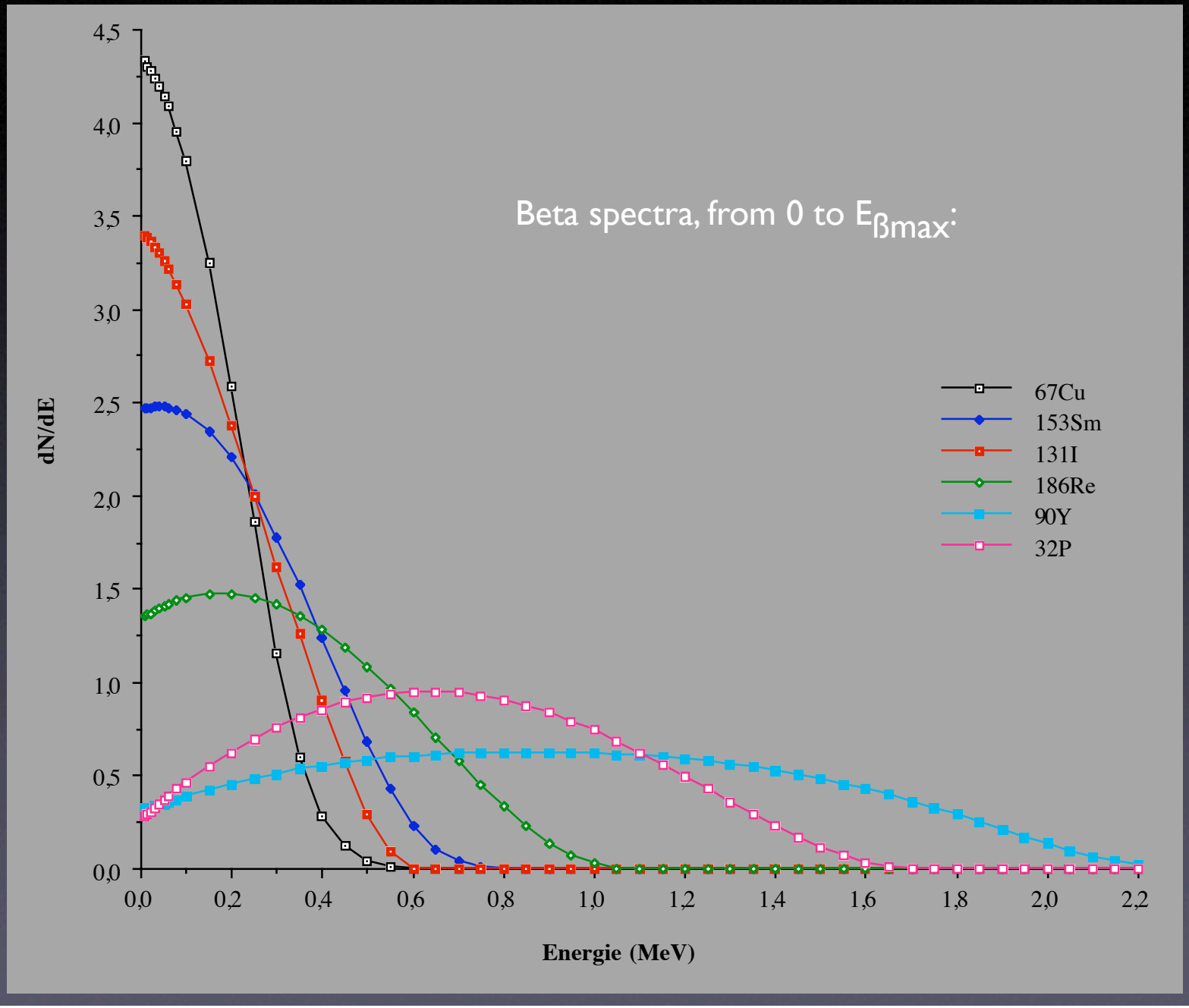


Figure II.7 - Superposition (jaune) de l'image de la distribution du phosphore 31 (vert) et de l'image de la distribution de l'iode 127 de la mIBG (rouge).

Cell/tissue dosimetry

- More in a context of preclinical studies
  - Absorbed dose -> biological effect
- Transpose modelling to the clinics?
- To understand what's observed in patients:
- What happens at the microscopic scale (in vitro) allows to understand what happens at the macroscopic scale (in vivo)

Dosimetric properties of ß- emitters



Isotope	Eßmoy (keV)	Emono (keV)	T1/2 (jours)
^{47}Sc	162.1	0.35	3.35
^{67}Cu	141.4	12.6	2.58
^{77}As	226.1	0.3	1.62
^{90}Y	948.8	0.3	2.67
^{105}Rh	151.8	1.3	1.47
^{109}Pd	360.6	75.8	0.56
^{111}Ag	349.9	0.7	7.45
^{121}Sn	114.4	-	1.13
^{131}I	181.5	10.6	8.02
^{142}Pr	819.4	-	0.80
^{149}Pm	358.3	-	2.21
^{153}Sm	226.3	42.7	1.95
^{159}Gd	305.8	4.3	0.77
^{166}Ho	672.7	28.0	1.20
^{177}Lu	132.9	13.8	6.71
^{186}Re	326.1	15.1	3.78
^{188}Re	777.0	15.1	0.71
^{194}Ir	808.1	-	0.80
^{199}Au	86.5	55.8	3.14

^{153}Sm

type	Eßmoy (keV)	Eßmax (keV	Emission (%)
ß	13.600 ± 1.1	53.200 ± 4	3.0 E-5 ± 2 E^{-5}
ß	14.500 ± 1.1	56.620 ± 4	7.7 E-4 ± 6 E^{-5}
ß	25.700 ± 1.1	98.410 ± 4	1.8 E-3 ± 2 E^{-4}
ß	29.000 ± 1.1	110.410 ± 4	0.023 ± 0.002
ß	30.500 ± 1.1	115.960 ± 4	5.7 E-3 ± 1 E^{-4}
ß	32.400 ± 1.2	122.840 ± 4	0.025 ± 0.002
ß	35.900 ± 1.2	135.180 ± 4	0.010 ± 0.000
ß	42.700 ± 1.2	159.330 ± 4	9.0 E-4 ± 1 E^{-4}
ß	48.900 ± 1.2	180.510 ± 4	0.069 ± 0.004
ß	49.400 ± 1.2	182.380 ± 4	0.066 ± 0.007
ß	**203.0 ± 1.5**	**644.149 ± 4**	**34.7 ± 1.6**
ß	210.800 ± 1.5	665.378 ± 4	0.050 ± 0.0
ß	**228.8 ± 1.5**	**713.821 ± 4**	**43.0 ± 3.0**
ß	230.900 ± 1.5	719.570 ± 4	0.610 ± 0.050
ß	**267.9 ± 1.6**	**817.000 ± 4**	**20.9 ± 1.7**

type	Energie (keV)	Emission (%)
e^-	4.690 ± 0.0	53.928 ± 4.096
e^-	**21.151 ± 0.000**	**23.52 ± 1.120**
e^-	**33.700 ± 0.0**	**4.508 ± 1.078**
e^-	34.851 ± 0.000	0.498 ± 0.071
e^-	40.961 ± 0.000	0.369 ± 0.043
e^-	48.911 ± 0.000	0.190 ± 0.005
e^-	**54.661 ± 0.000**	**40.752 ± 0.864**
e^-	**61.618 ± 0.000**	**3.832 ± 0.183**
e^-	67.870 ± 0.001	0.835 ± 0.040
e^-	69.310 ± 0.001	0.278 ± 0.013
e^-	75.318 ± 0.000	0.235 ± 0.034
e^-	**95.128 ± 0.000**	**6.169 ± 0.131**
e^-	**101.380 ± 0.001**	**1.783 ± 0.038**

Beta dosimetry: need to take all emissions into account...

"Optimal" beta emitter?

- Radionuclide choice based on:
- Dosimetric properties:
  - Energy
  - Half-life
  - ß/γ ratio (^{131}I !!!)
- Chemical properties:
  - production
  - labelling chemistry, radiopharmacy
- Availability
- Price!

Wessels and Rogus, Med. Phys. 11, 638-645, 1984

ß emitters dosimetry

In most MIRD pamphlets
β are non-penetrating particles:

$$\phi_i(k \leftarrow h) = 0 \; if \; k \neq h$$

$$\phi_i(k \leftarrow h) = 1 \; if \; k = h$$

If emitted energy is known, dose is easily calculated:

Ex: ^{131}I emits 3.04 x 10^{-14} (Gy.kg)/(Bq.s) - i.e. J/(Bq.s)

At the microscopic scale, this is no longer true!
But the MIRD scheme still applies.

It is (just!) necessary to calculate absorbed fractions at the microscopic scale...

See MIRD pamphlet 7 (Berger 1971)

Dosimetric problem:

Source:
volume
shape
density
activity

"Energy transfer function"
type of particle
energy
medium density

Target:
volume
shape
density

Sextuple integral of the 'energy transfer function'...

Analytic vs. numeric approaches:

If the energy transfer function is known (simple)
If the geometry can be simplified (spheres…)
Analytic modelling of the problem

Otherwise:
Pure *numeric* approach
Monte-Carlo simulation

Physicists love *simplifying hypothesis*:
Homogeneous medium
Symetries (spherical if possible)
Same source and target
...

Dosimetric approaches for ß emitters

- Data:
  - Interaction cross sections
  - Dose Point Kernels
  - TEL based relationships
- Geometry description:
  - analytic
  - digital (voxel)
- Calculation frame:
  - Analytic (integration, convolution)
  - Numeric (Monte-Carlo)

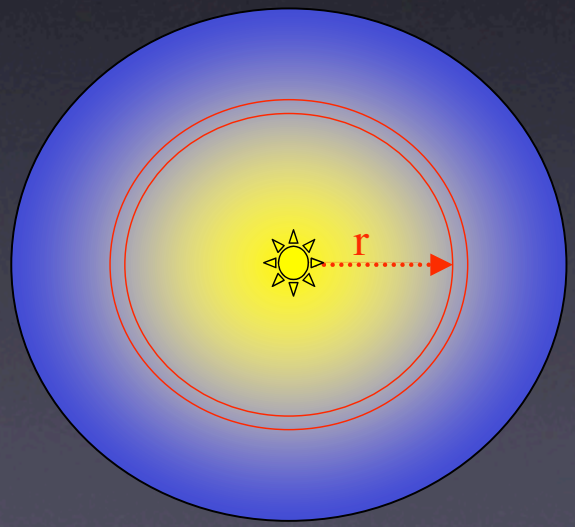
Interaction cross sections

- The basis…
- Basic data for Monte-Carlo simulations
- Available for ≠ particles, energies, media, ...
- They all result from experiments (measures/ calculations):
- Various sources
- Various hypotheses
- Various validity domains
- Various results...

Dose point kernels (DPK)

Monoenergetic dose point kernel:
Absorbed fraction of the energy
delivered at a distance
from a point source
of monoenergetic electrons

$$F\left(\frac{r}{r_0}, E_0\right) = 4\pi \cdot \rho \cdot r^2 \cdot r_0 \cdot \Phi\left(r, E_0\right)$$



In theory :

$$4\pi \cdot \rho \int_0^{\infty} r^2 \cdot \Phi\left(r, E_0\right) \cdot dr = 1$$

Obtained from:

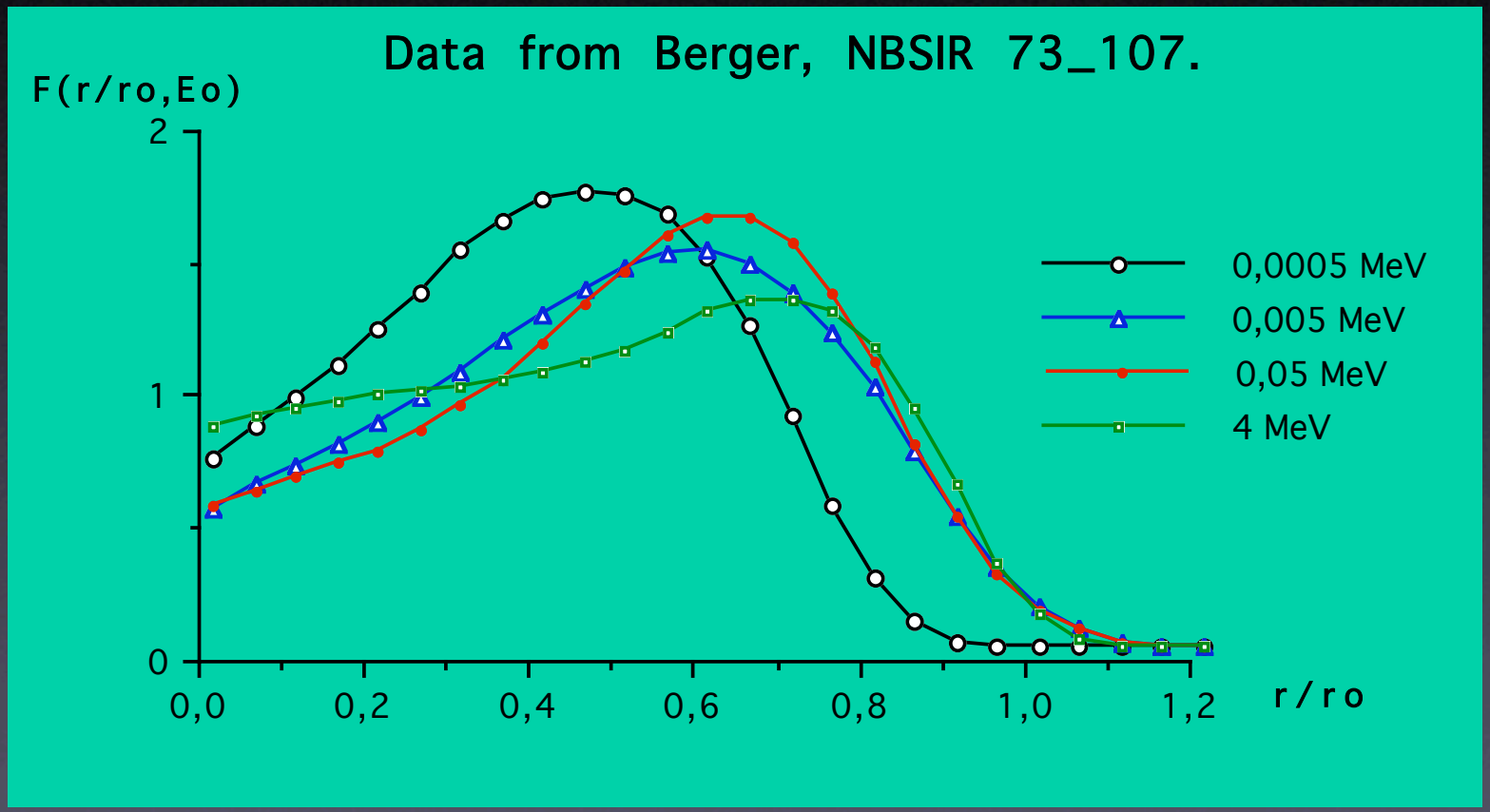
Measurements (Cross)

Calculations (Berger)

For example Prestwich J Nucl Med 30: 1036-1046, 1989

Dose point kernels (DPK)

Monoenergetic dose point kernels: Fraction of the energy delivered at a distance from a point source of monoenergetic electrons



Scaled point kernel: $F(r/r_0,E_0)$: comparison at ≠ energy

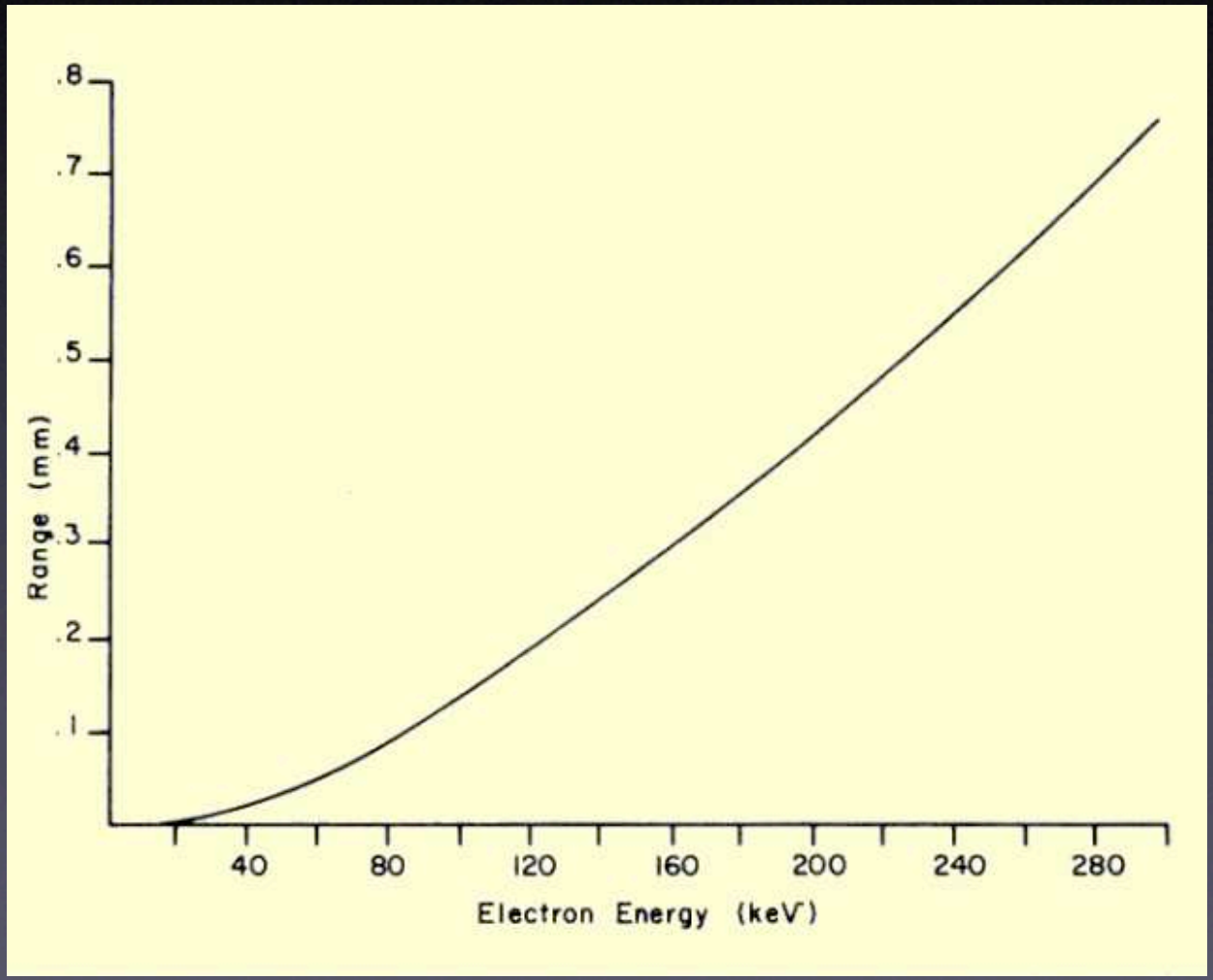
Energy	r_0	x_{90}
500 eV	22.72 nm	15.10 nm
10 keV	2.482 μm	2.04 μm
20 keV	8.374 μm	6.91 μm
100 keV	0.1401 mm	0.1131 mm
500 keV	1.735 mm	1.388 mm

From Berger, NBSIR 73-107

Dose point kernels:

- Used as input data for a more complex geometry: (superposition principle)
- Input data for "radionuclide dose point kernels"
- Always in homogeneous medium!
- Valid for energies > 10 keV(?)

Energy-range relationship: Cole
(Rad. Res. 38, 7-33, 1969)



Energy-range relationship: Cole
(Rad. Res. 38, 7-33, 1969)

Starting point: There is a link between energy (E) and electron range (X) in a given medium.
An empirical fit gives E=f(X)
It is then possible to obtain dE/dX = f(X)

$$E = 5.9(X + 0.007)^{0.565} + 0.00413\,X^{1.33} - 0.367$$

$$\frac{dE}{dX} = 3.333(X + 0.007)^{-0.435} + 0.0055\,X^{0.33}$$

E in keV, X in µm, valid from 10 eV to 50 MeV!
For monoenergetic electrons only
(e.g. when DPKs are no longer valid...)

Geometry modelling

How can a given geometry be described?

Analytically:
A spherical cell labelled on the surface,
Cell cluster targeted with antibodies,
Internalising vector (A=f(r))

Discrete:
Autoradiography, phosphor imager, etc…
Ex: Tumour fragments slices,
Random targeting (simulated),

This will condition the calculation frame...

Calculation frame:

Analytic (at least analytic description):

Integration

Geometry is defined via equations
Homogeneous medium
The energy transfer function is known (DPK, Cole)

Convolution

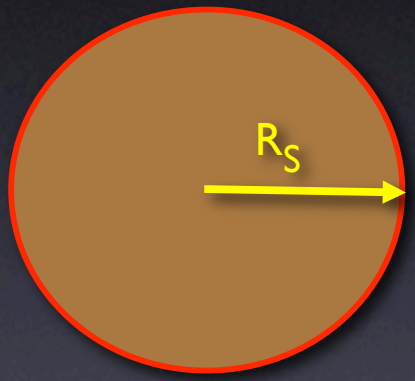
Geometry is defined via equations or sampled
Homogeneous medium
The energy transfer function is known (DPK, Cole)

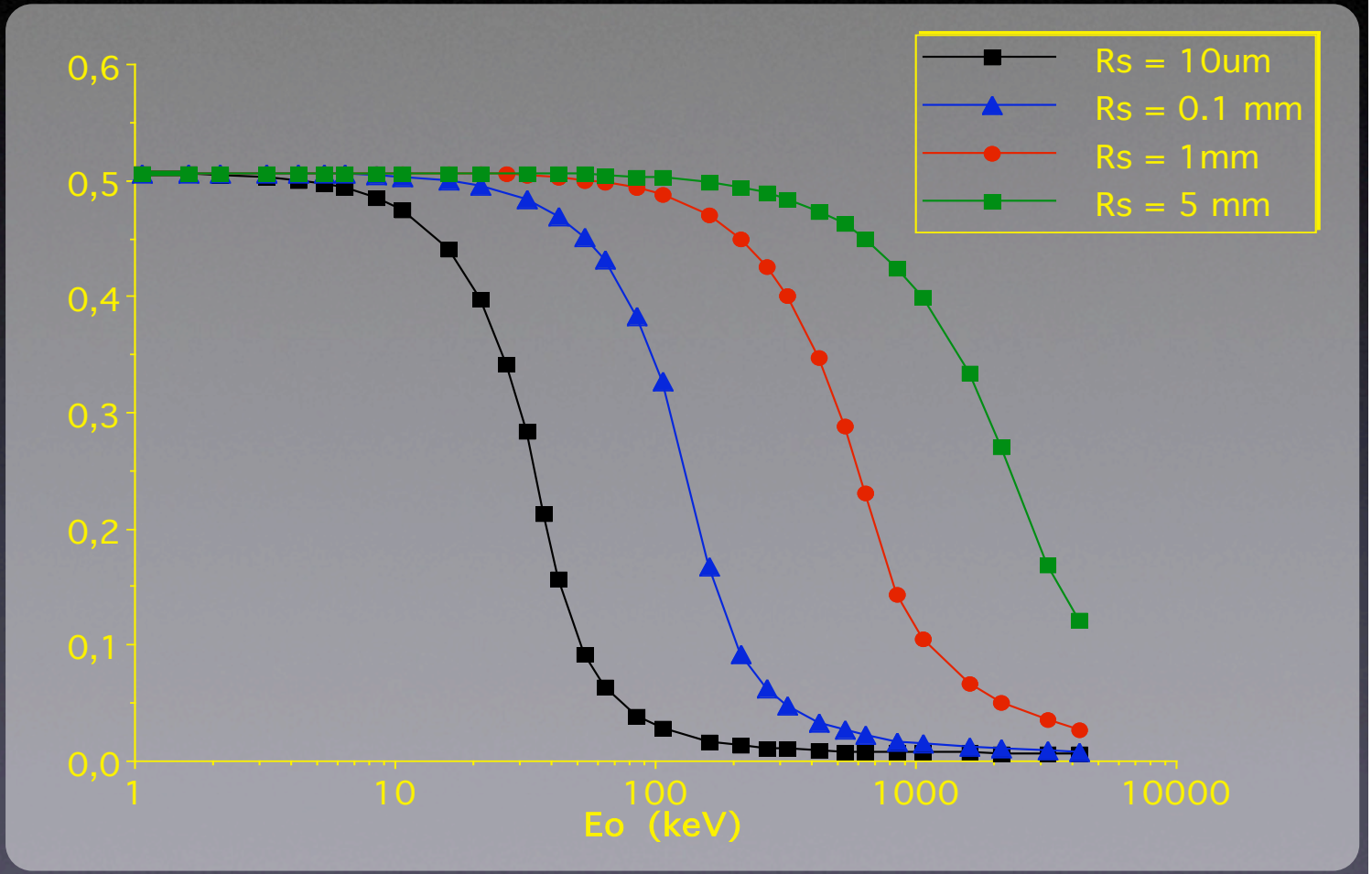
Numeric

Monte Carlo Simulation (EGS4, MCNP, others…)
On principle can solve any kind of problem
In practice, used for heterogeneous media and complex geometries

Example: Absorbed fraction calculation

Sphere labelled on the surface:

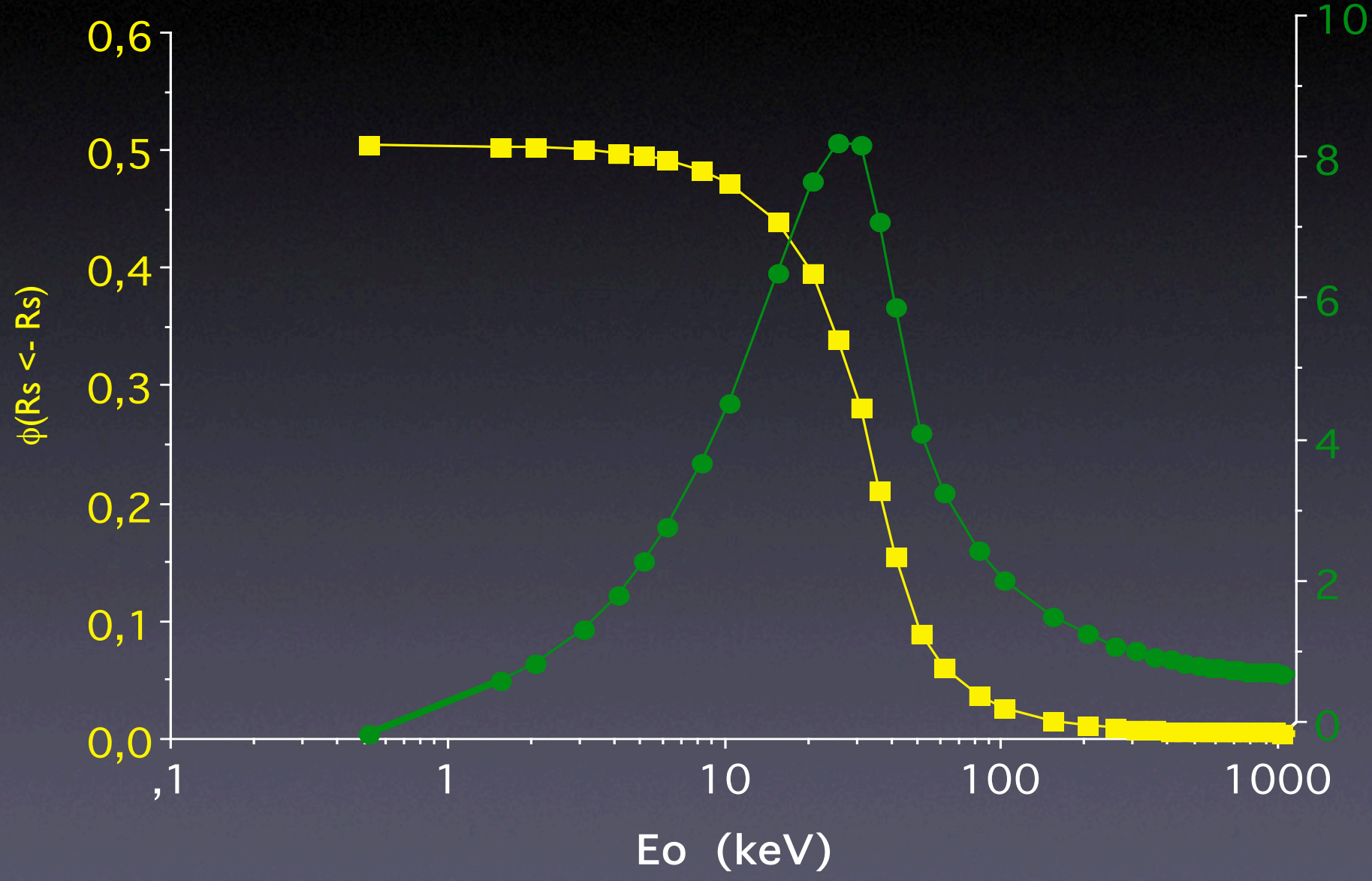




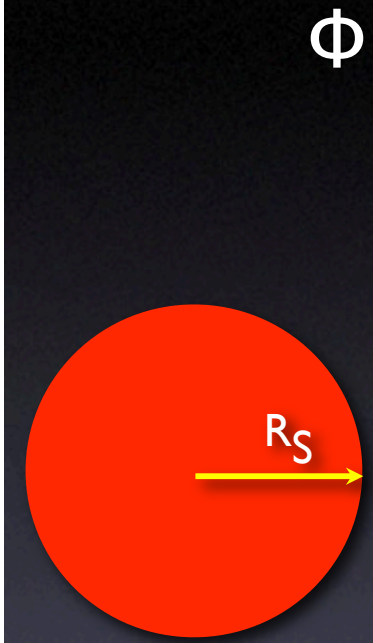
r_0 : csda range

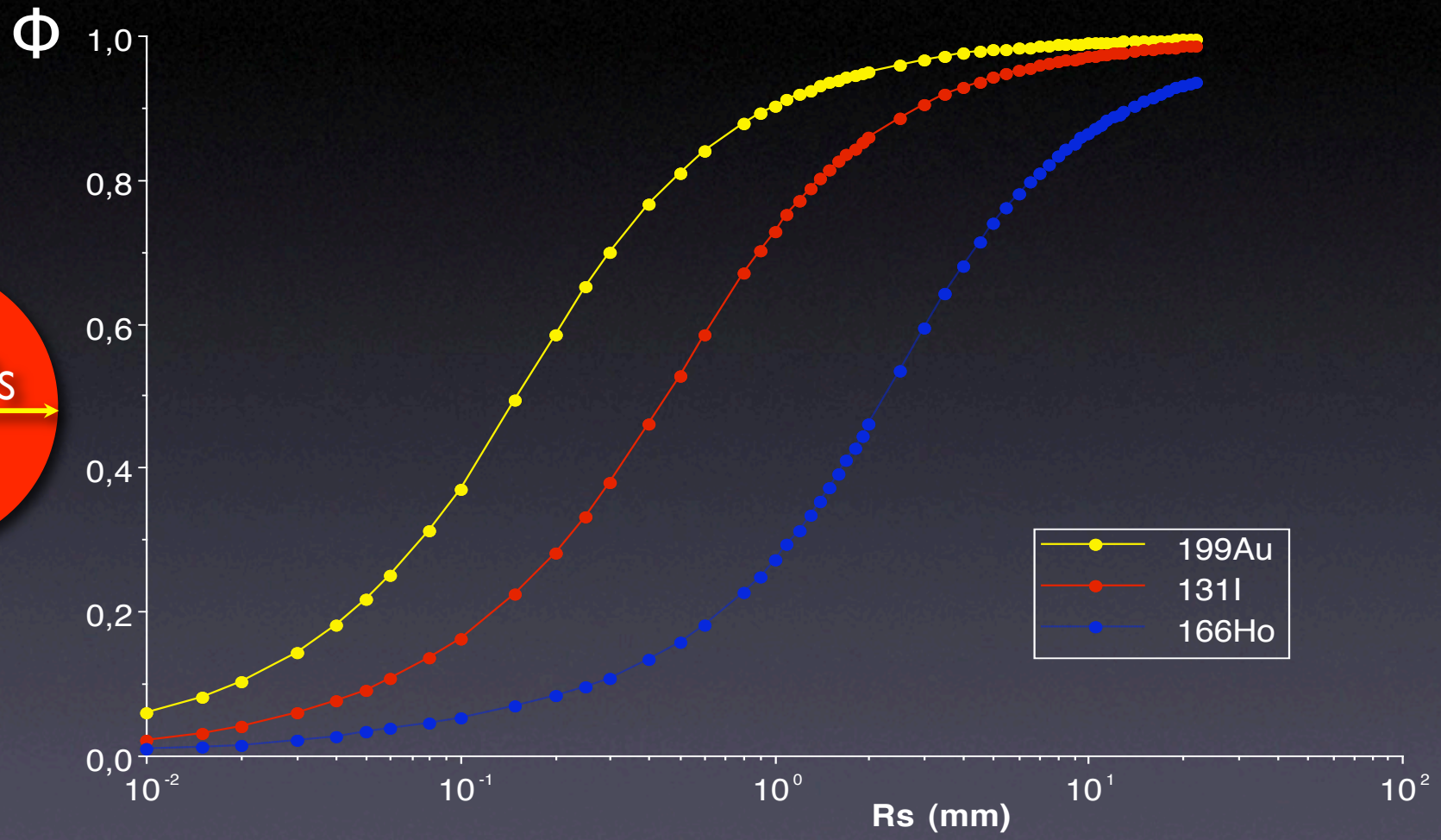
$$\phi(R_S \leftarrow R_S) = \frac{1}{2r_0}\int_0^{\infty}\left(1-\frac{x}{2R_S}\right)\times F\left(\frac{x}{r_0},E_0\right)\times dx$$

Energy absorbed:
Rs = 10 μm



Absorbed fraction for homogeneously labelled spheres (volume targeting) :





$$\phi(R_S \leftarrow R_S) = \frac{1}{r_0}\int_0^{2R_S}\left[1 - 1.5\frac{x}{2R_S} + 0.5\left(\frac{x}{2R_S}\right)^3\right]\cdot F(\frac{x}{r_0}, E_0)\cdot dx$$

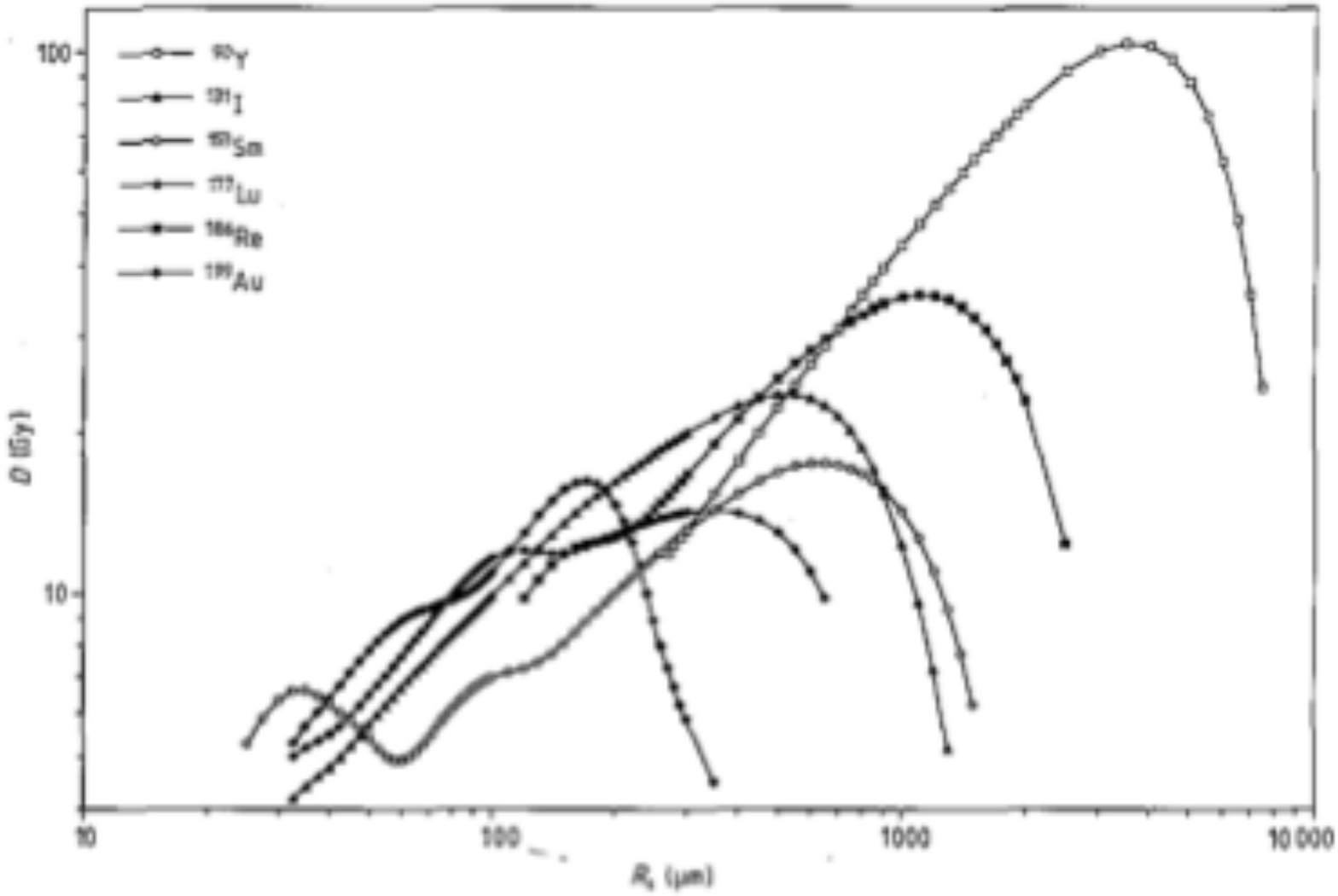
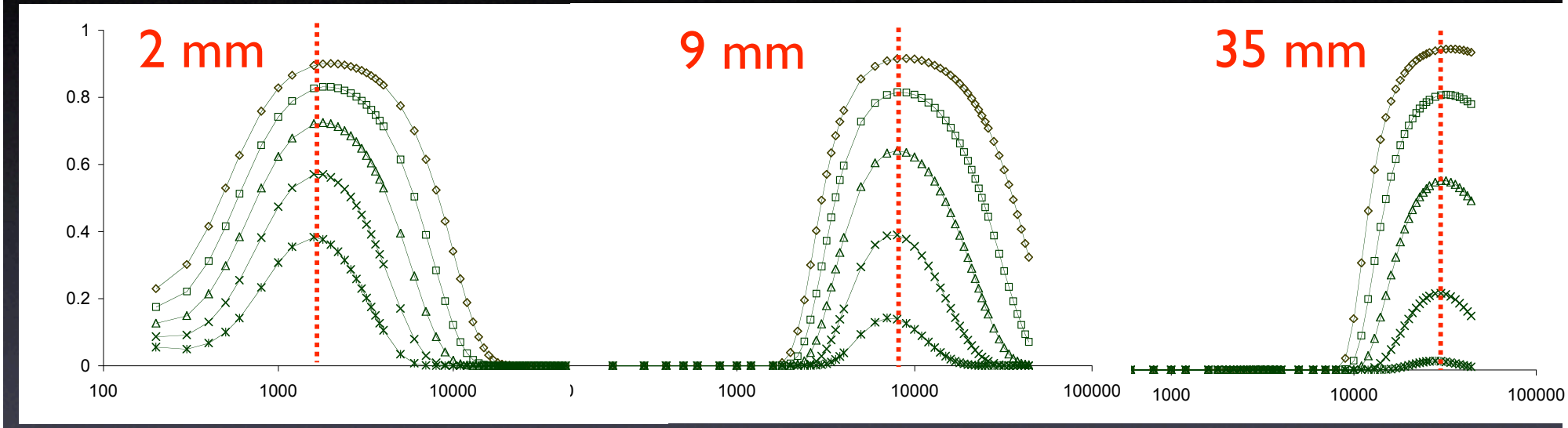


Figure 10. Mean dose (D, Gy) in the centre of a sphere labelled on its surface versus sphere radius (R_S) for six beta-emitting radionuclides. These results were obtained for a %ID g^{-1} of 0.75, a biologic half-life of 2 d and an injected activity of 3.7 GBq (100 mCi).

M Bardiès and JF Chatal, PMB 39; 961-981, 1994

Target size / particle range relationship



^{177}Lu ^{186}Re ^{90}Y

Cure probability (Pc)
as a function of the tumour diameter (µm)

JA O'Donoghue et al. J Nucl Med 1995 36: 1902-1909

MIRD cell S-factors

(Goddu et al. The SNM, NY, 1997)

For ≠ cell radii (3 to 10 µm)
For ≠ nucleus radii (2 à 9 µm)

Electrons from 1 keV to 3 MeV
Alpha particles from 3 to 10 MeV
Several (200!) radionuclides (α and ß)

Cole energy/range relationship for electrons

ICRU data for alpha

Impressive database

MIRD cell S-factors

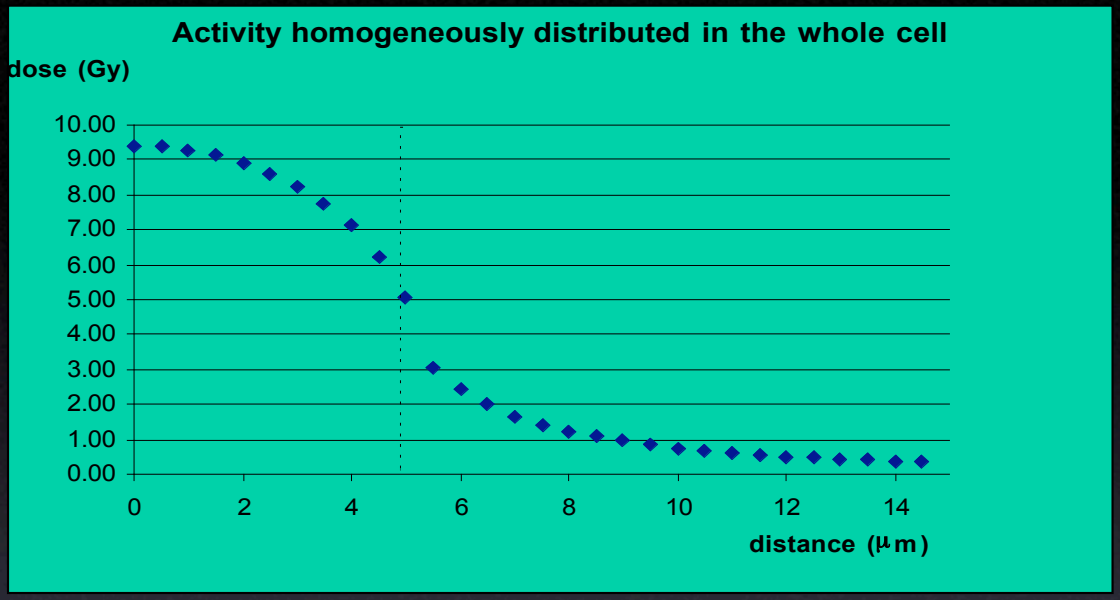
(Goddu et al. The SNM, NY, 1997)

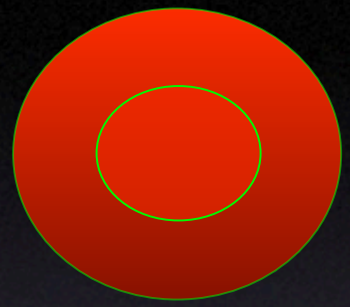
Sources: Cell, Cytoplasm, Nucleus, Cell surface

Target: Cell, Nucleus, Cytoplasm

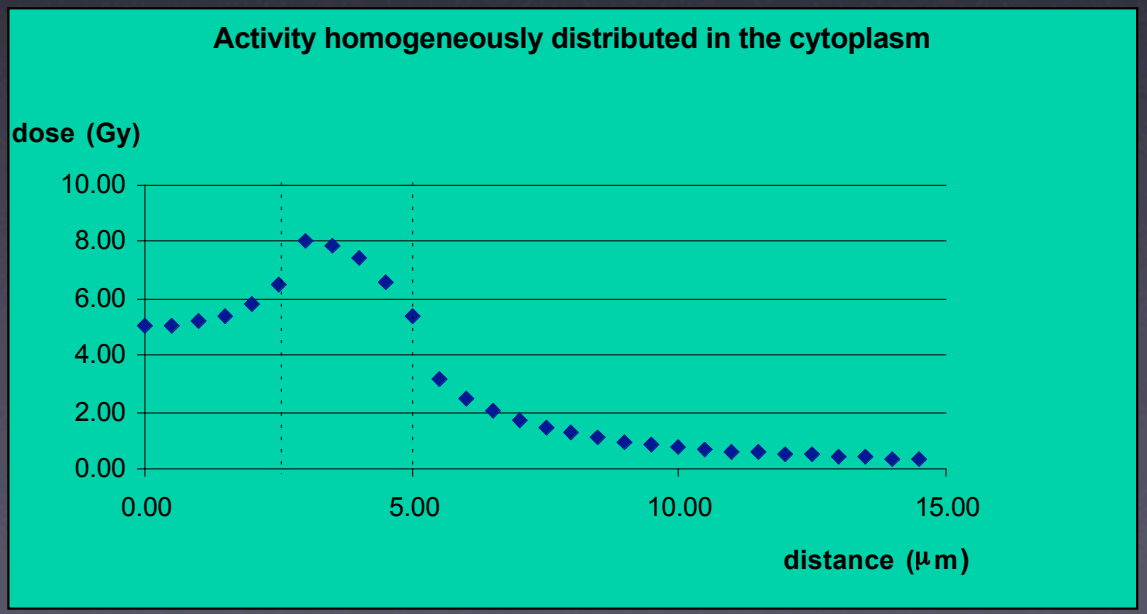
S factors: Mean values for a given volume!

Volume distribution:

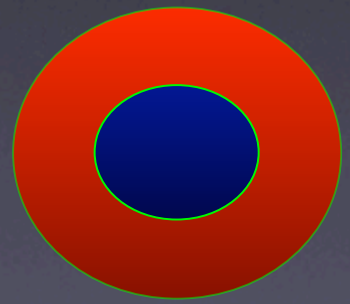




Cytoplasmic distribution:

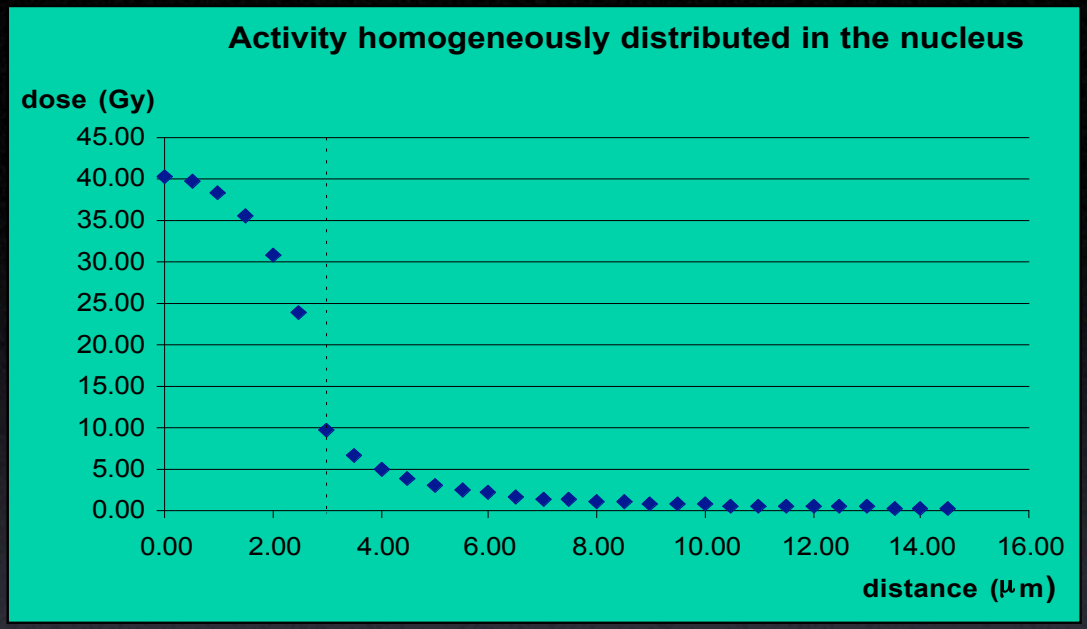


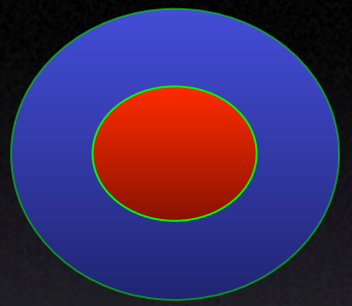
Rc = 5 µm
Rn = 2.5 µm
Membrane thickness = 0.5 µm



Thanks to A. Malaroda, RMH

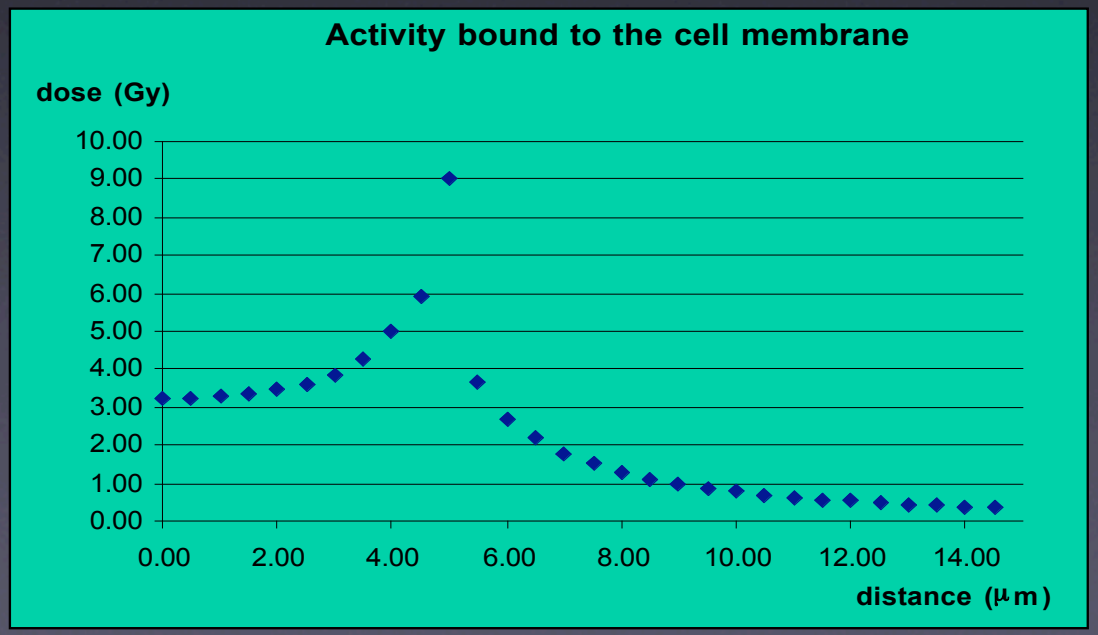
Nucleus distribution:

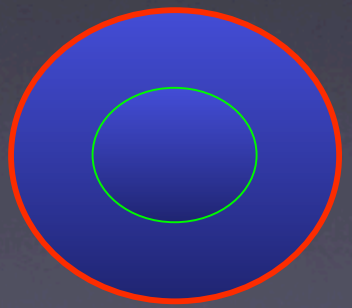




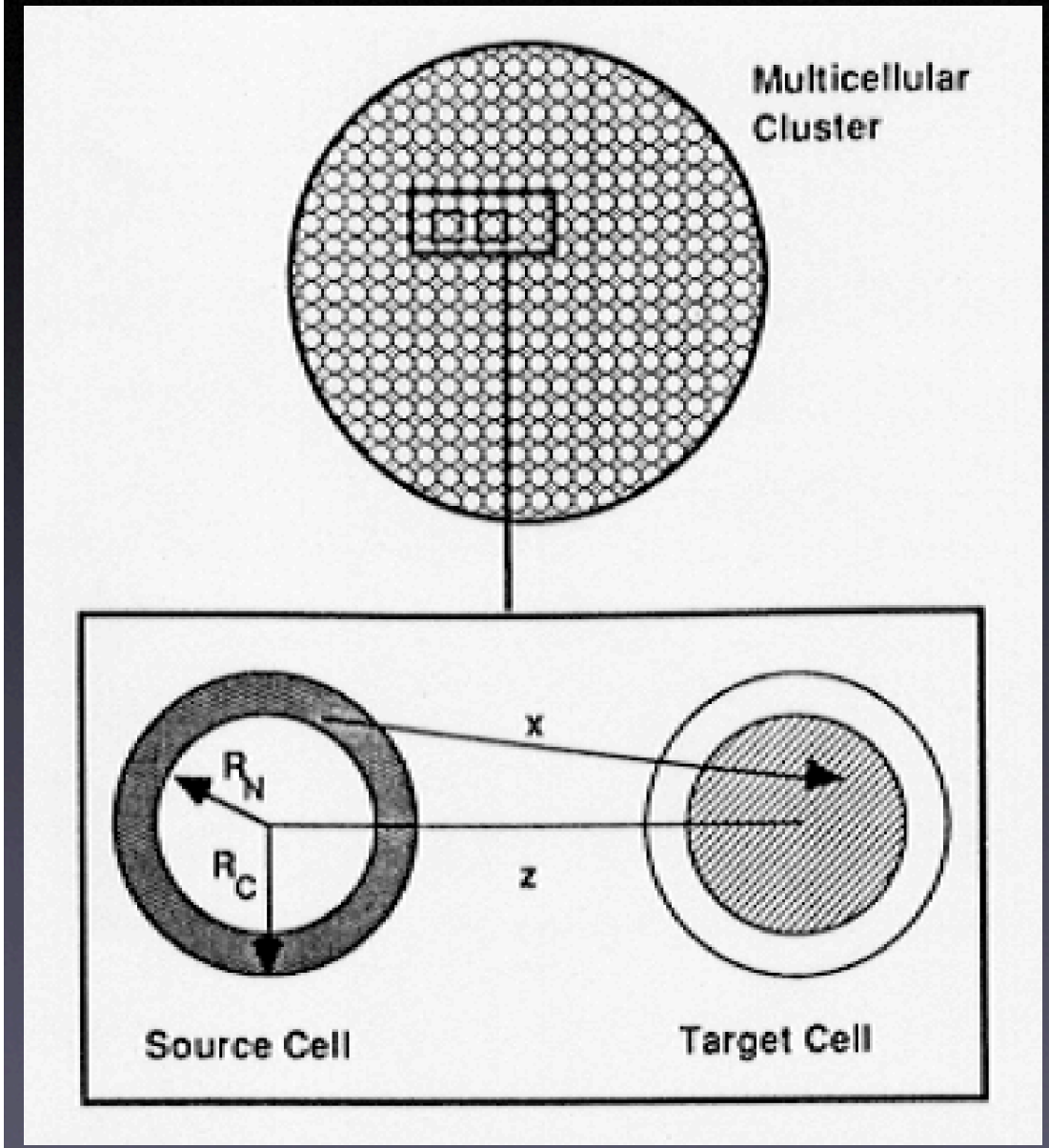
Rc = 5 µm
Rn = 2.5 µm
Membrane thickness = 0.5 µm

Surface distribution





Other example (analytic) :



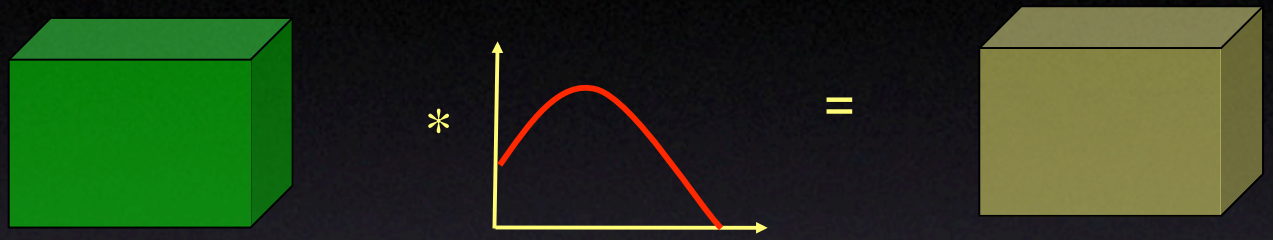
Monoenergetic electrons
(Cole data)
+
ß spectrum integration

→ Absorbed Fractions

→ S Factors

Goddu (J. Nucl. Med. 35 303-316 1994)
Goddu (J. Nucl. Med. 35 521-530 1994)

Convolution:



Activity (3D) Dose Point Kernel Dose (3D)

Calculation time optimised by the use of FFT or FHT
Home made calculations...

Simplification (MIRD Pamphlet No. 17)
Voxels S-factors
Limits
Homogeneous medium (water, soft tissue)

3D convolution of dose point kernels:

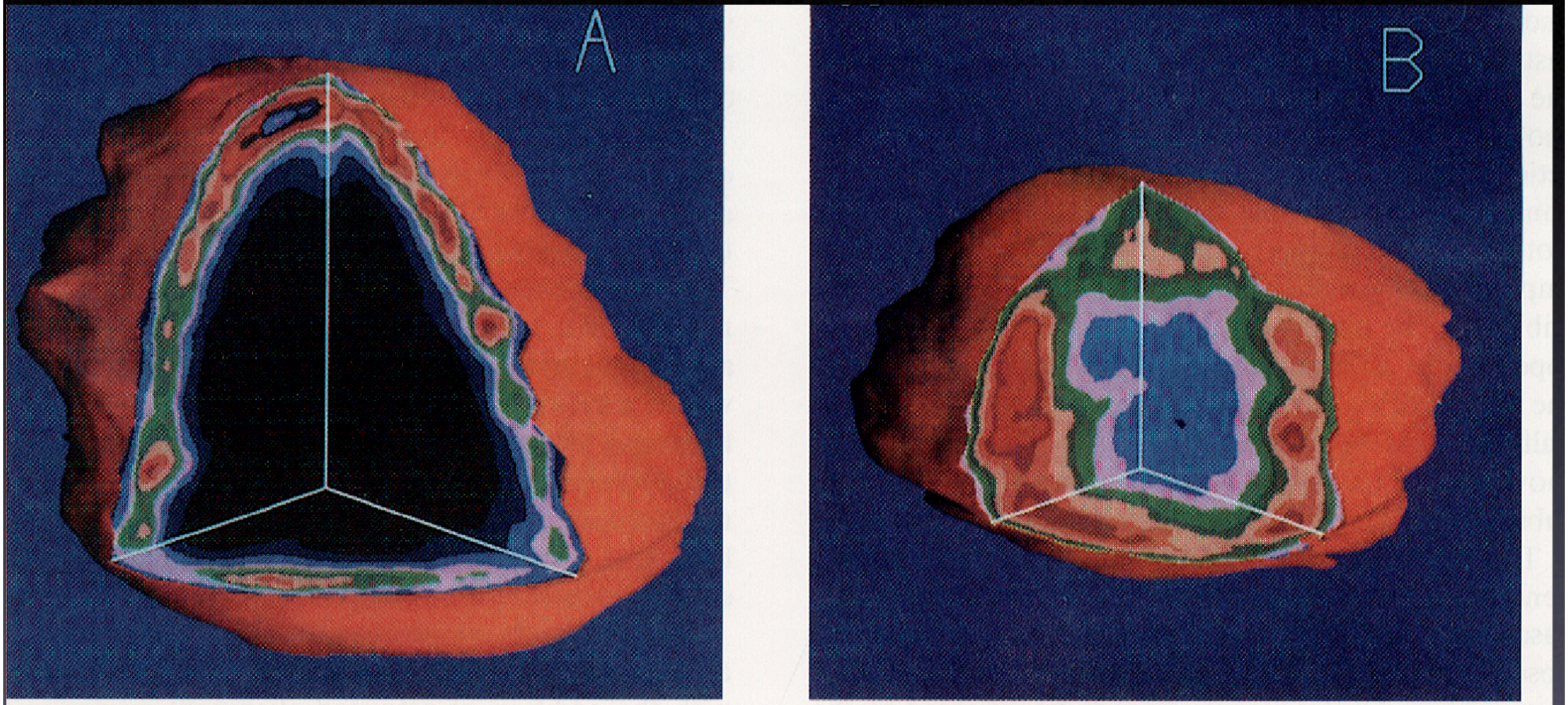
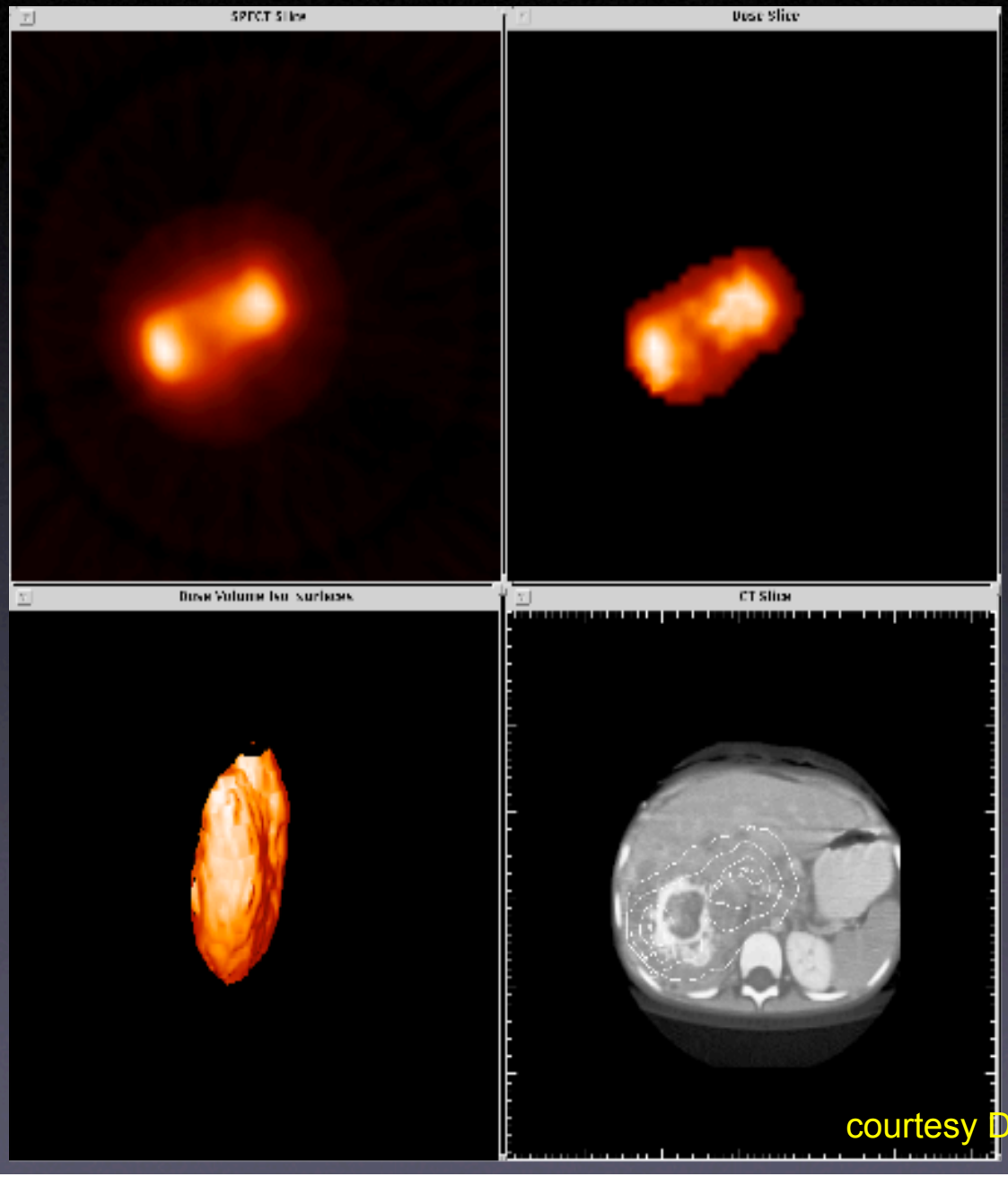


Fig. 6. Three-dimensional LS174T tumor dose distributions. (a) 1 day postinjection and (b) 4 days postinjection of 300 μCi ^{131}I-labeled 17-1A MoAb. The color scale is black, dark blue, light blue, pink, green, blue-green, light peach, dark peach, violet, and red in equal ascending dose-rate intervals of 1 cGy/hr.

Roberson et al. 1993

Clinical example

^{131}I SPECT



Dose

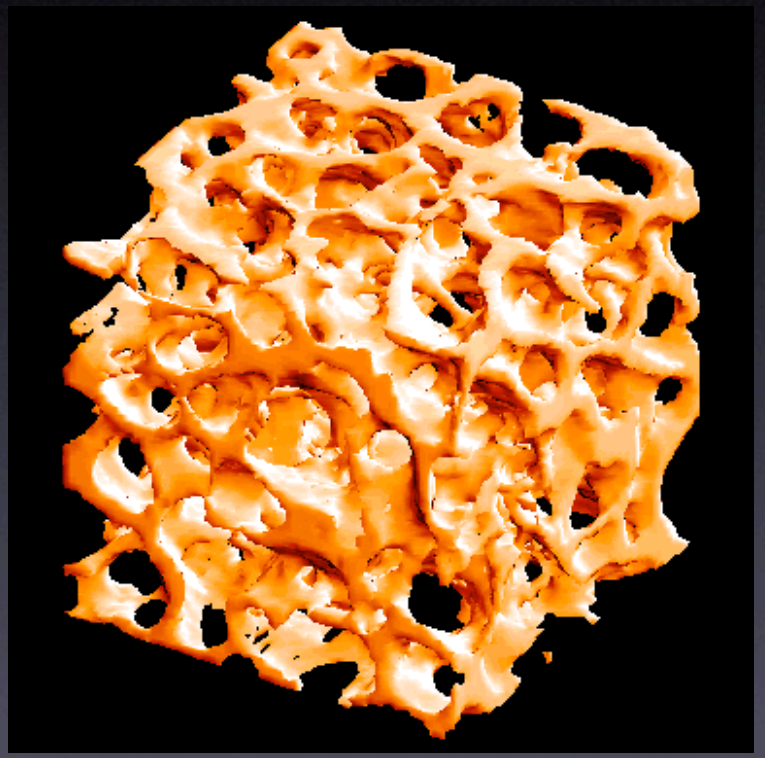
3D rendering

Isodoses

courtesy Dr G Flux, RMH, UK

Full Monte-Carlo modelling: Bone marrow dosimetry

Eckerman and Stabin,
Health Phys. 78, 199-214, 2000
7 bone types
15 osseous regions
240 radionuclides
Dose volume histograms



Bouchet et al.
J. Nucl. Med. 41, 189-212, 2000
Cortical and spongious bone (ICRP70)
22 sites on adult
10 radionuclides
3D Transport (EGS4)

Summary

- Detailed beta dosimetry is *necessary* at the tissue/cell scale.
- Several approaches
- ≠ *levels of accuracy - likeliness…*
- Abundant literature!
- Several radionuclides have been considered
- Several dosimetric approaches
- *A lot has been done in the domain…*
- But: Biologic parameters are hard to get (always)…
- However: Small scale dosimetry is relevant
- to assess targeted radiotherapy *biological efficacy*.

References

"MIRD Pamphlet No. 7:
Distribution of absorbed doses around point sources of electrons and beta particles in water and other media"
Berger MJ. J Nucl Med 12 5-23, 1971

"Beta dose point kernels for radionuclides of potential use in radioimmunotherapy"
Prestwich WV Nunes J, et al. J Nucl Med 30 1036-1046, 1989

"MIRD cellular S Values"
Goddu SM, Howell RW, Bouchet LG, Bolch WE & Rao DV
Society of Nuclear Medicine, 1997

"Small-Scale dosimetry : Challenges and future directions"
Roeske JC, et al. Semin Nucl Med 38 : 367-383, 2008

One last thing

- I'm trying to give up smoking
- Don't feed me cigarettes even if I cry
- Be nice to me, I could explode any time :-)