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ALPHA PARTICLE MICRODOSIMETRY IN THE LUNGS: VARIABILITY OF ENERGY DEPOSITION AT THE CELLULAR LEVEL

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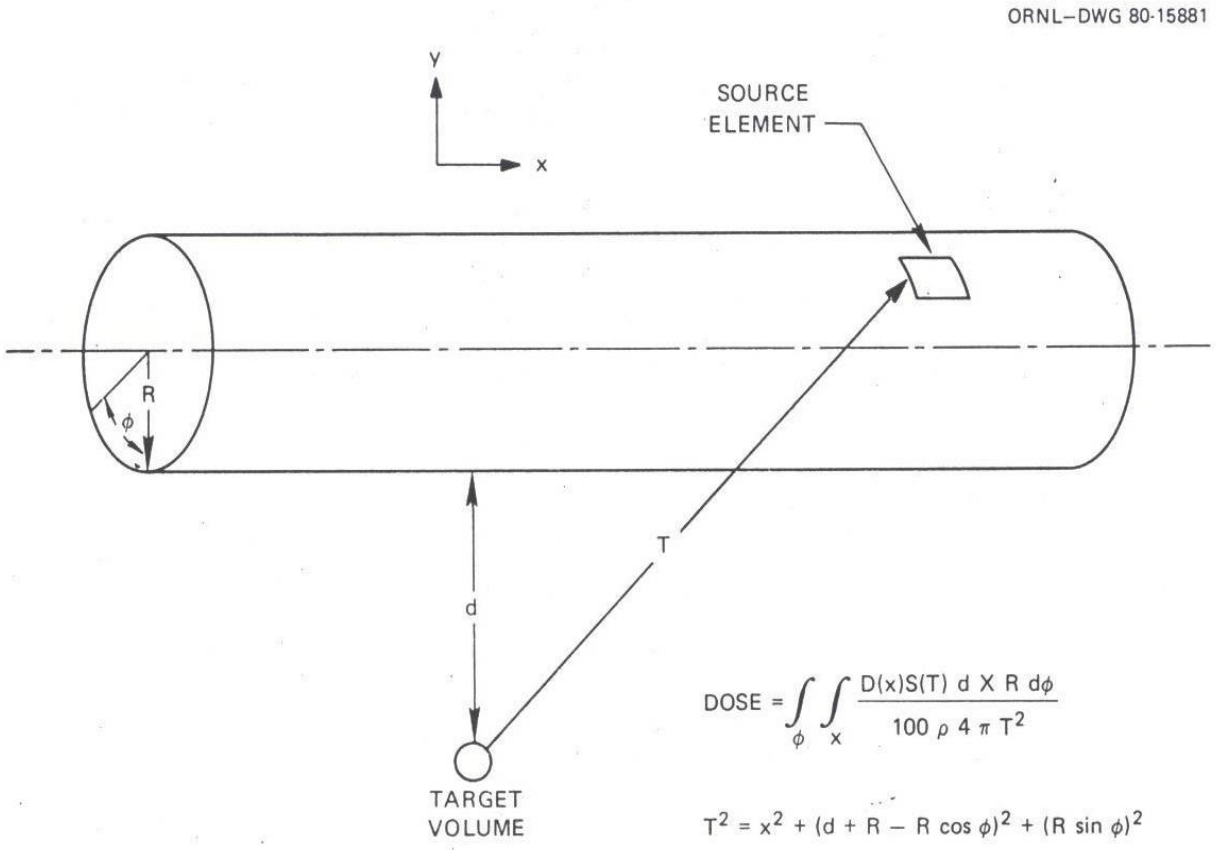
Irradiation of sensitive target cells in bronchial epithelium by radon progeny alpha particles



Source: steady-state ^{218}Po and ^{214}Po surface activities
Target: basal and secretory cell nuclei

The variability of energy deposition at the cellular level results from random variations of stochastic macroscopic factors (**source variability**) and microscopic factors (**target variability**)

Variability of energy deposition at the cellular level: macroscopic factors

Macroscopic factors, affecting the variability of radon progeny surface activities (source variability):

(i) Inter- and intrasubject variability of radon progeny deposition and clearance in an asymmetric, stochastic airway structure

(ii) Microdistribution of radon progeny surface activities on bronchial airway surfaces, e.g. accumulations at bronchial airway bifurcations

(iii) Distribution of basal and secretory cell nuclei across bronchial epithelium and diameter-related thickness of bronchial epithelium and resulting depth distribution of basal and secretory cell nuclei

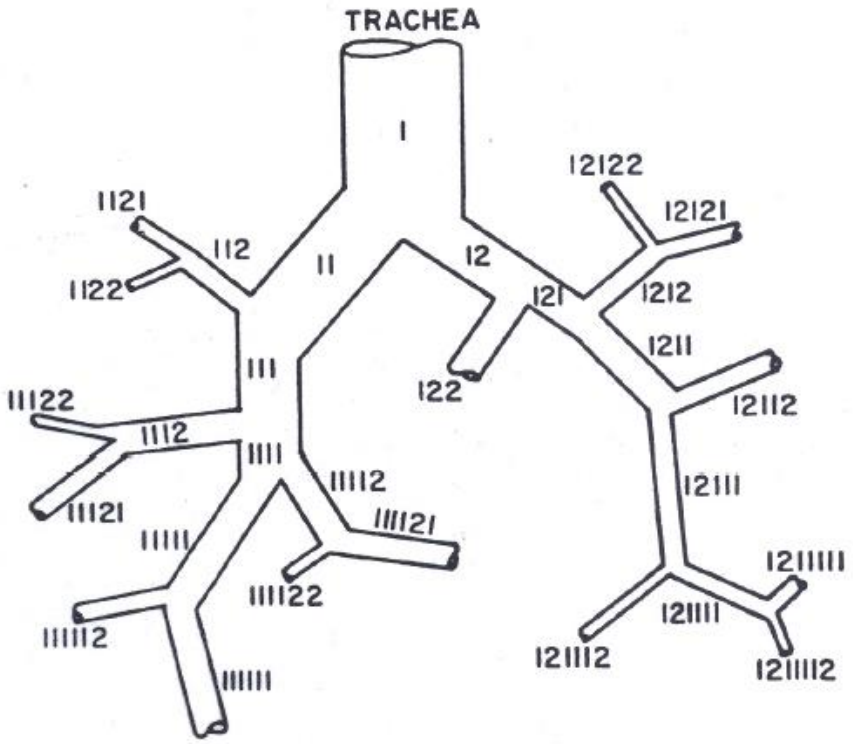
These macroscopic factors are described by parameter distributions and thus require the application of stochastic modeling techniques (Monte Carlo methods):

Stochastic macroscopic dosimetry

Macroscopic dosimetry refers to average energy deposition in a target volume (cell nucleus)

Variability of lung morphology

Koblinger and Hofmann (1985, 1990):
Asymmetric stochastic lung geometry based on morphometric measurements (Raabe et al., 1976)



Morphological variability:
Asymmetry and variability of airway diameters and lengths and their correlations
Lognormal distributions of airway diameters and lengths in a given airway generation

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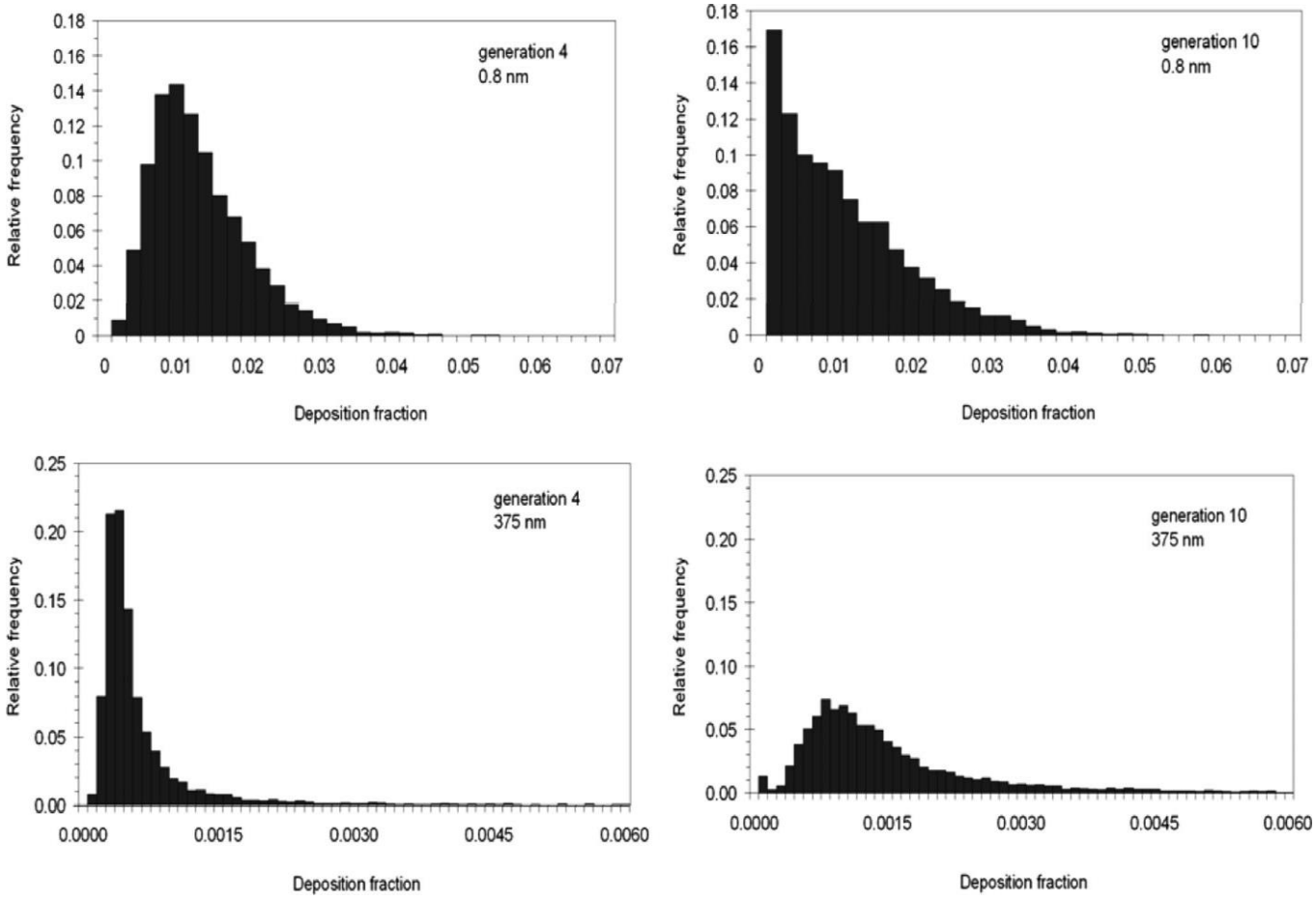
Effect of morphological variability on radon progeny deposition

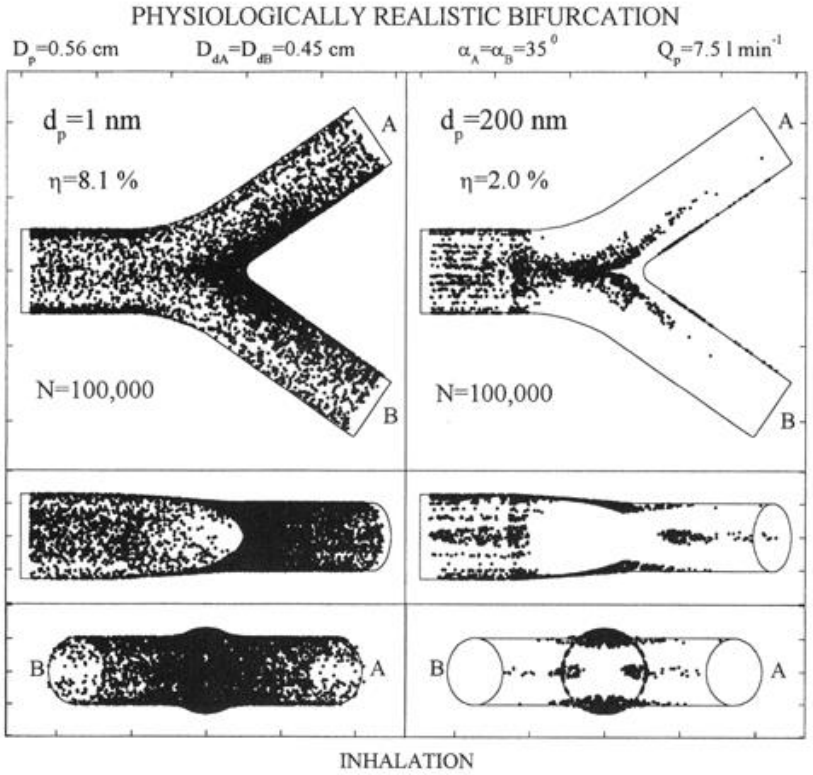
Breathing parameters: V_T = 1250 ml, f = 20 min^{-1} (light exercise)



Microdistribution of radon progeny in airway bifurcations

Balásházy and Hofmann (2000):

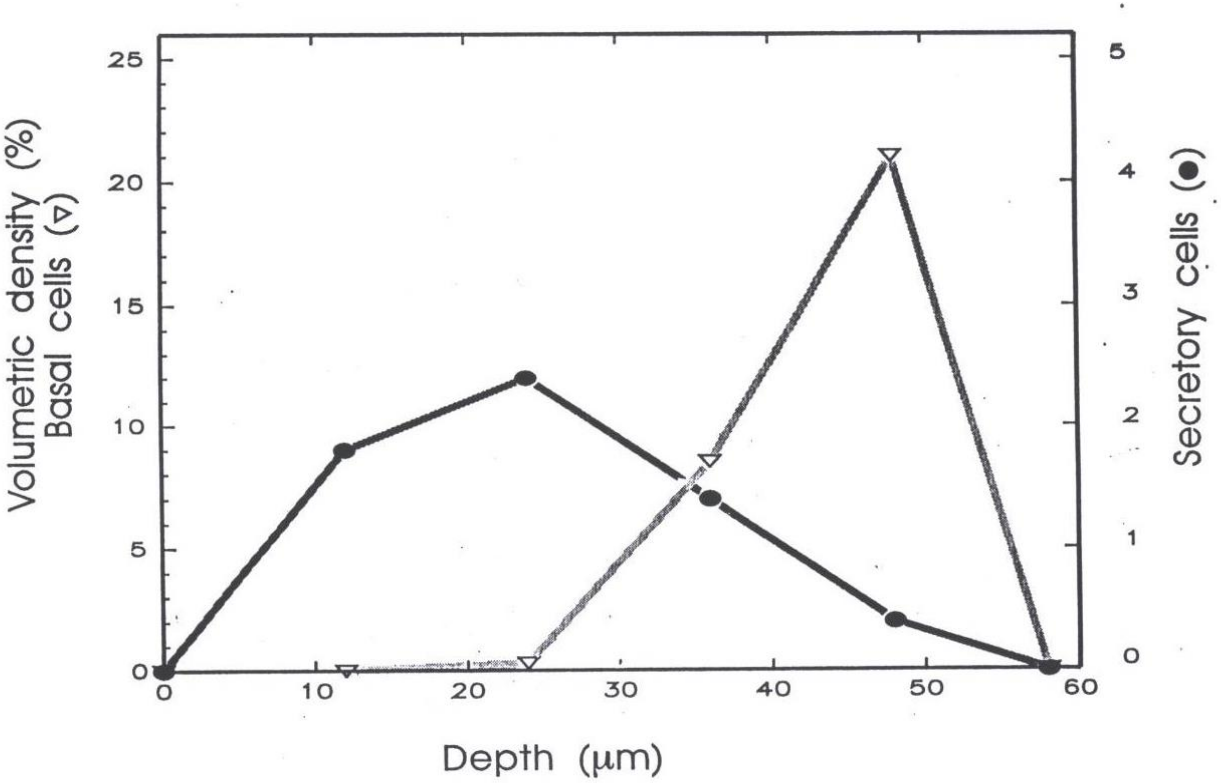
Spatial deposition patterns of unattached and attached radon progeny in human bronchial airway bifurcation 3-4 (bronchi)



Local of deposition enhancement is caused by secondary motions, which are a function of the flow rate. Thus enhanced deposition at bifurcations is effective only in large bronchial airways, moderately increasing average bronchial cellular doses relative to a uniform distribution (**BUT:** big difference in terms of microdosimetry)

Variability of basal and secretory cell depths in bronchial epithelium

Mercer et al. (1991):
Distribution of volumetric densities of basal and secretory cell nuclei in large bronchial airways (airway generations 0-4)



Effect of morphological variability on the thickness of the bronchial epithelium and hence on basal and secretory cell depths: correlation of basal and secretory cell depths with corresponding airway diameter through a polynomial function derived from morphometric data (Mercer et al., 1991)

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Effect of morphological variability on radon progeny steady-state surface activities

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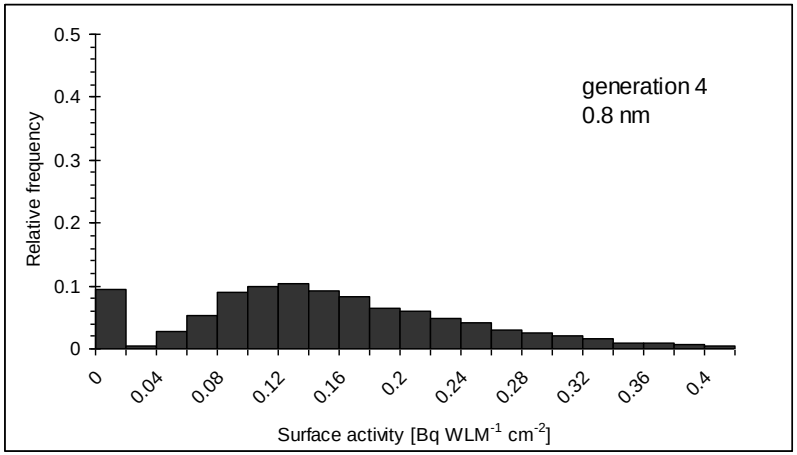
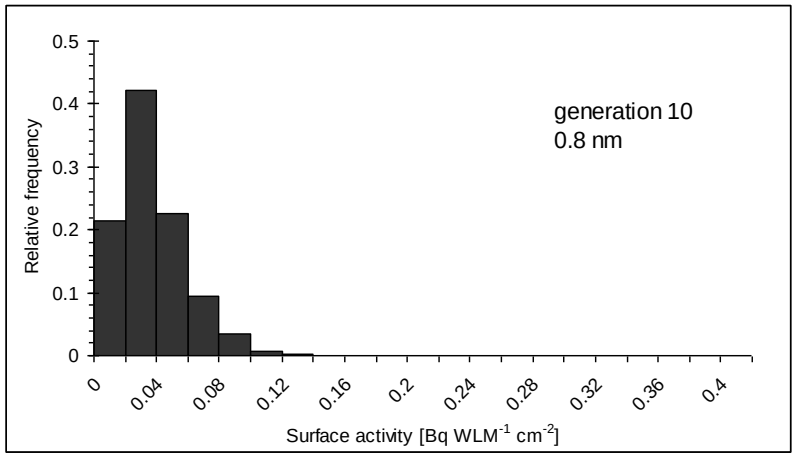
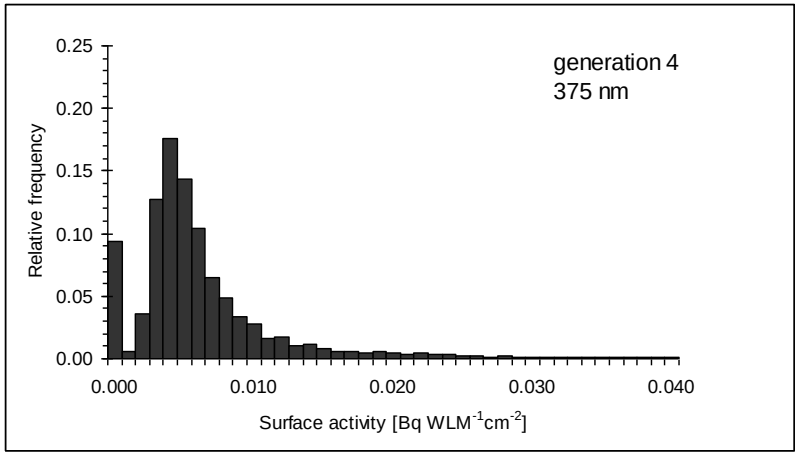
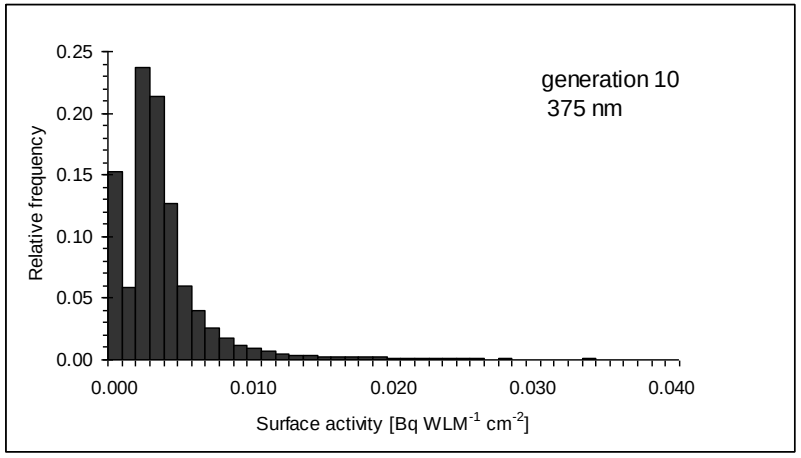
^{218}Po steady-state surface activities resulting from deposition, clearance and radioactive decay in bronchial (4) and bronchiolar (10) airway generations



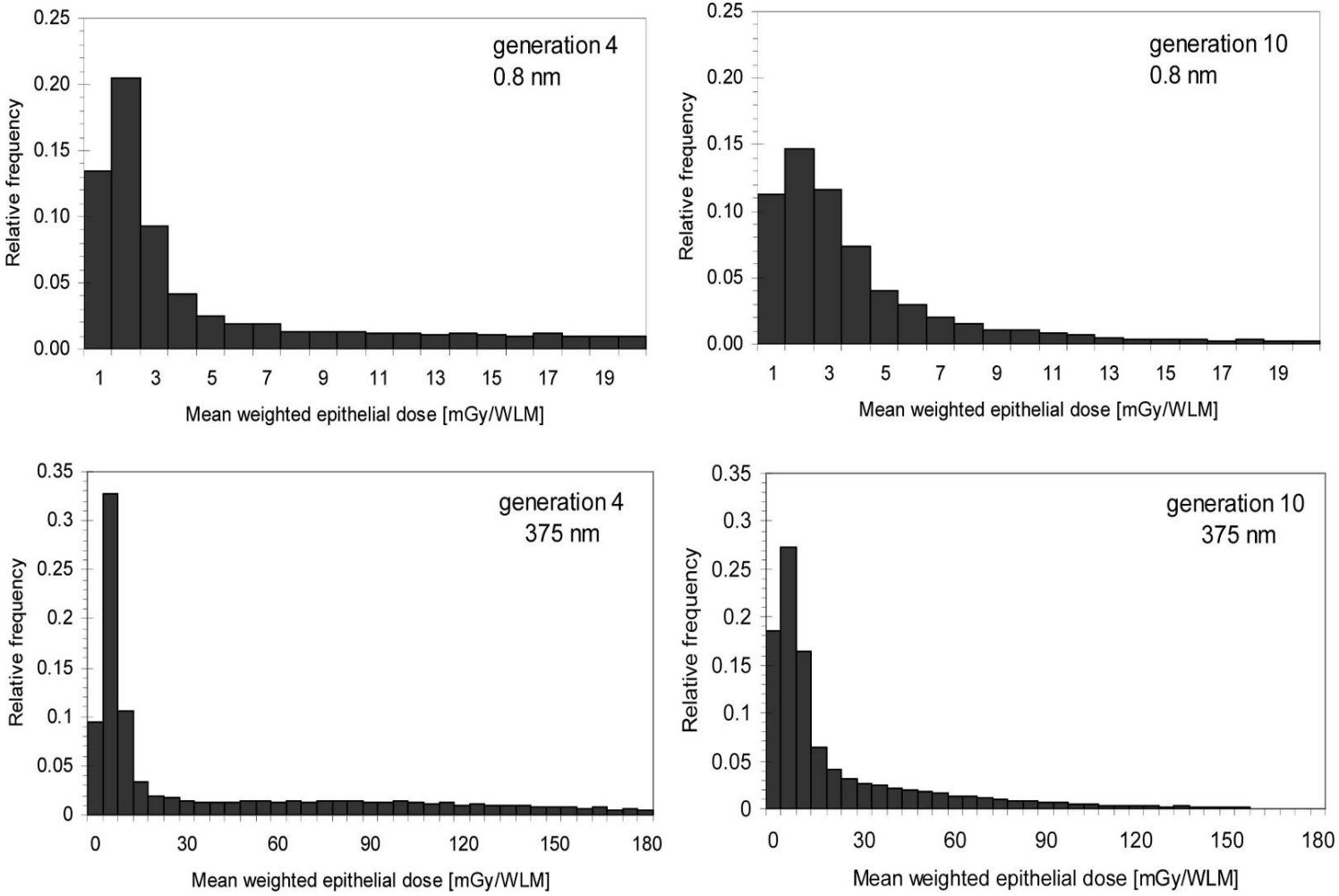






Variability of cellular doses caused by macroscopic factors

Effect of source variability, variability of depths of target cell nuclei and variability of source-target distances on average basal and secretory cell doses



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Results of the effect of macroscopic factors on cellular doses (source variability)

Macroscopic factors describe the source variability affecting the doses received by basal and secretory cell nuclei

Macroscopic factors of variability lead to significant variations of average doses in individual cell nuclei in bronchial and bronchiolar epithelium and thus this approach is sometimes referred to as “microdosimetry”

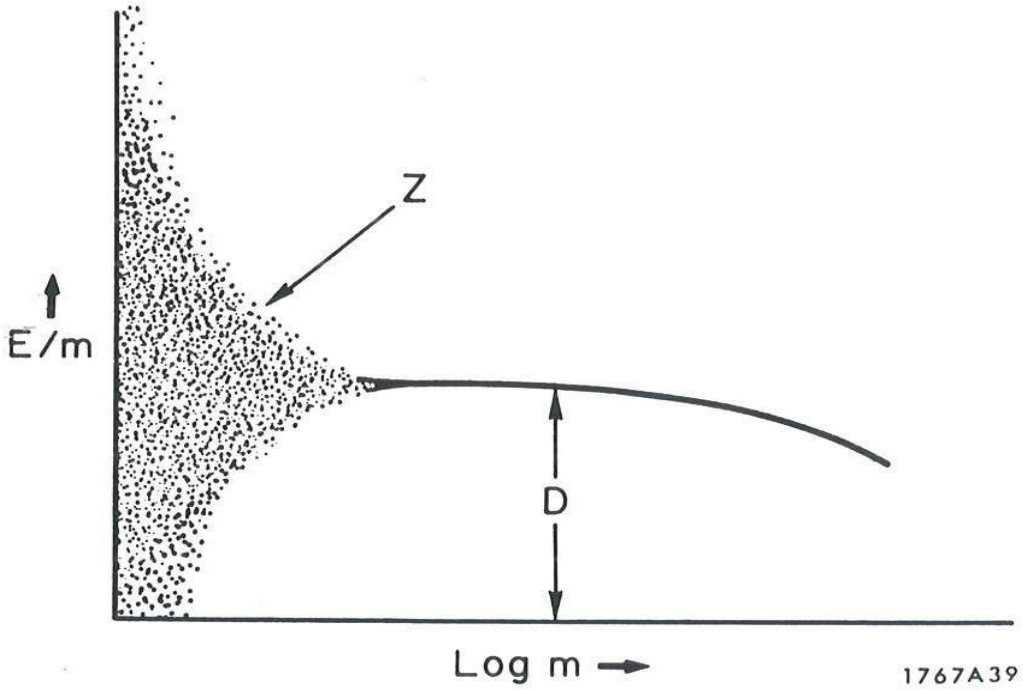
However, this approach is still based on the macroscopic dose concept as it does not consider the variability of energy deposition within cell nuclei

Since the simulation of the effect of macroscopic factors on average cellular doses in basal and secretory cell nuclei requires the application of stochastic modeling techniques (Monte Carlo methods), the most appropriate terminology is:

Stochastic macroscopic dosimetry

Variability of energy deposition in microscopic targets: microdosimetry

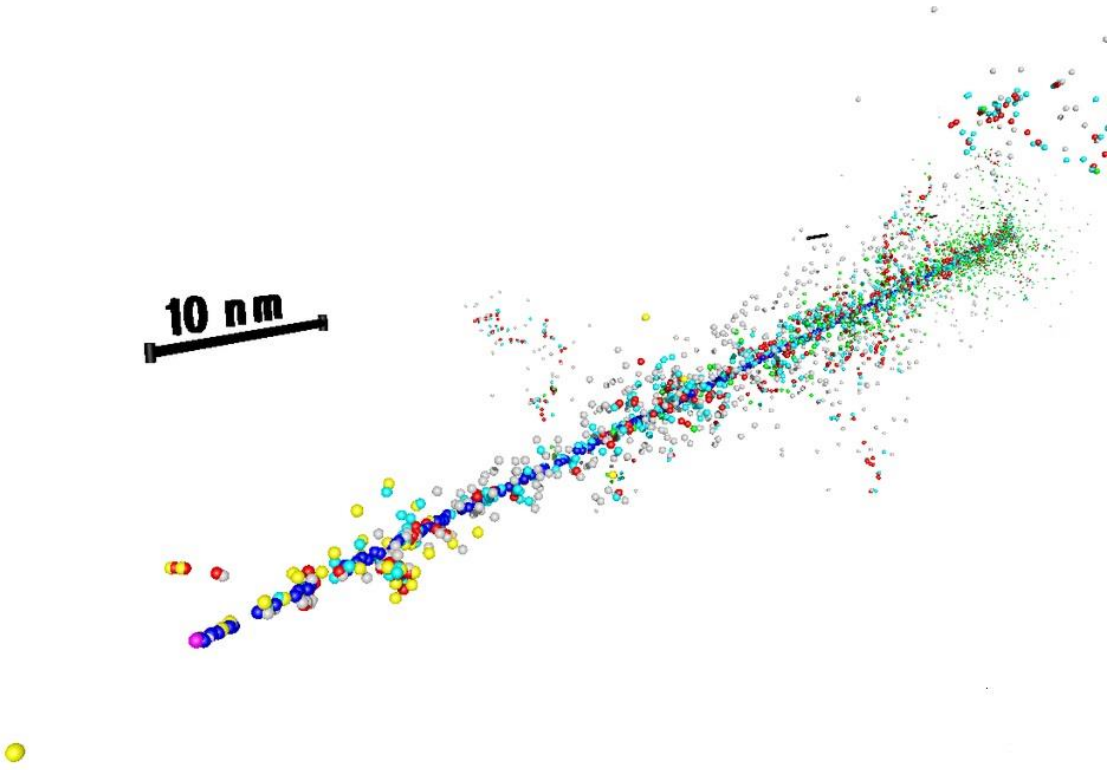
Rossi (1968):
Variation of the specific energy with mass (size) of a microscopic target



Caveat: Random fluctuations of energy deposition in microscopic targets are smaller for high LET radiations, such as alpha particles

Track structure of alpha particles

Friedland (2019):
Perspective view of an alpha particle track simulated by PARTRAC:
The primary particle has entered the scenery with 4 MeV energy at right end and moved about 0.4 µm during 30 fs towards the foreground on the left.



Variability of energy deposition at the cellular level: microscopic factors

Microscopic dosimetry (microdosimetry) refers to the distribution of energy deposition in a micrometer-sized target volume, which is typically the nucleus of a cell

Microscopic factors affecting the variability of energy deposition in cell nuclei **(target variability)**:

Hit probability:

Probability of hitting a cell nucleus due to the limited range of alpha particles and the related frequency of single and multiple hits (Poisson distribution)

Energy deposition in cell nuclei in case of a hit (specific energy f(z)):

(i) Random track lengths of traversing alpha particles in spherical cell nuclei (crossers) or incomplete traversal (stoppers)

(ii) Random energy deposition along the traversal of a nucleus as a result of the range distribution of alpha particles from source site to target site and the corresponding LET dependence of the intersecting tracks (Bragg curve)

(iii) Energy straggling (Vavilov distribution) of traversing alpha particles and contribution from grazing alpha particles ejecting electrons into the target volume

Note: Contributions of energy straggling and grazing alpha particles to energy deposition in spherlcal cell nuclei are small compared to that produced by intersecting tracks

Microdosimetric quantities

Specific energy z: stochastic equivalent of absorbed dose D

$z = \varepsilon / m$

The distribution of z can be described by the probability density f(z), which contains a δ-function at z = 0 for the probability of no energy deposition

Mean specific energy is a non-stochastic quantity conceptually equivalent to the average absorbed dose D in a micrometer-sized target volume

$f_1(z)$: specific energy distribution for a single deposition event

$f_n(z)$: specific energy distribution for exactly n single deposition events

f(z;D): specific energy distribution for single and multiple deposition events at dose D

Lineal energy y: stochastic equivalent of LET (defined only for single energy deposition events)

$Y = \varepsilon / L$ (spherical volume: $L = 4/3\ r$)

The distribution of y can be described by the probability density f(y)

The mean lineal energy is a non-stochastic quantity conceptually equivalent to LET

Approximations for alpha particles:

f(z) can be approximated by the track length distribution for a given LET

f(y) can be approximated by the LET distribution

Microdosimetry of internal alpha-emitters

Roesch (1977):

Extended the fundamental concepts of external microdosimetry to internally deposited alpha-emitting radionuclide sources

The alpha activity is represented by a distribution of point sources, where $f_1(r;z)$ is the single event density for point source as a function of distance r from the target

If the target receives exactly n single energy deposition events from several point sources, $f_n(z)$ can be calculated as the n-fold convolution of $f_1(z;r)$ using the Fourier transform technique

Since the probability of exactly n energy deposition events at dose D follows the Poisson distribution, f(z;D) is given by the compound Poisson process

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

Microdosimetric concepts

In the case of high LET radiations, such as alpha particles, two microdosimetric concepts have been proposed to describe the variability of energy deposition in microscopic targets (cell nuclei):

The **hit probability** and the frequency of cellular hits, following a Poisson distribution

and

the **specific energy distribution** f(z), expressed either by the specific energy for single hits, $f_1(z)$, or by the specific energy distribution for single and multiple hits at a given absorbed dose, f(z;D)

Hit probability concept:

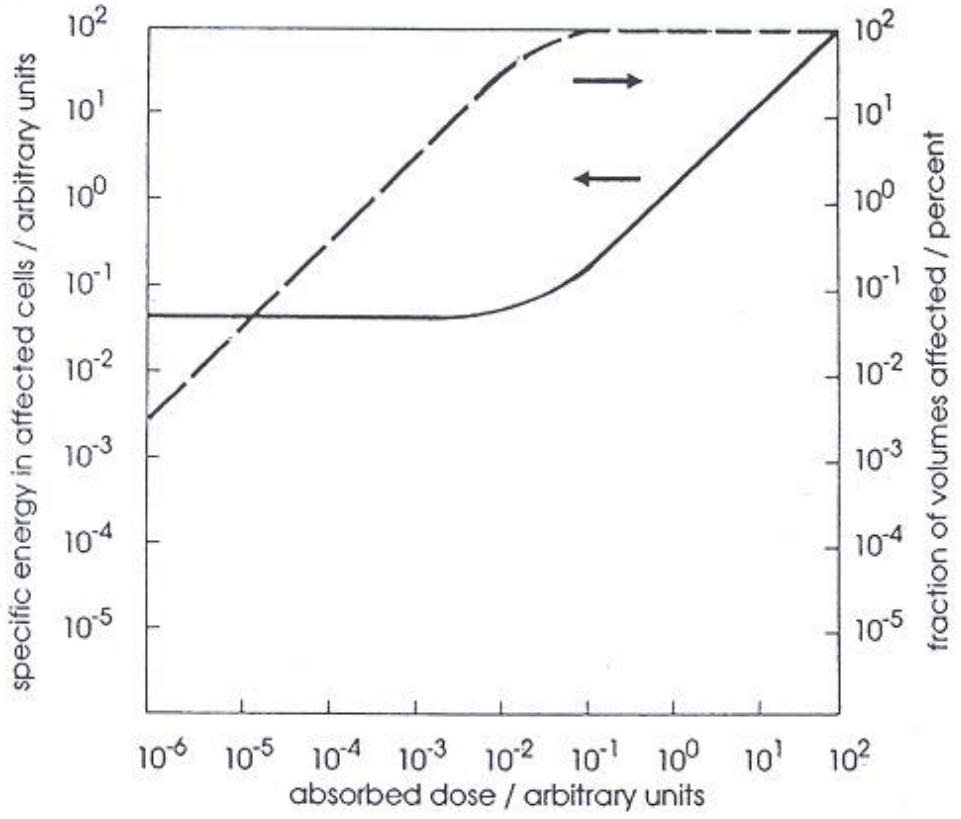
Considers the variability of cellular hits, while energy deposition in a given target is expressed by the mean specific energy, i.e. it does not consider the variability of energy deposition within cell nuclei

Specific energy distribution concept:

Includes both the variability of cellular hits and the variability of energy deposition within cell nuclei

Low dose effects of alpha particles

Hit probability (fraction of cellular hits) and average specific energy of low doses of alpha particles



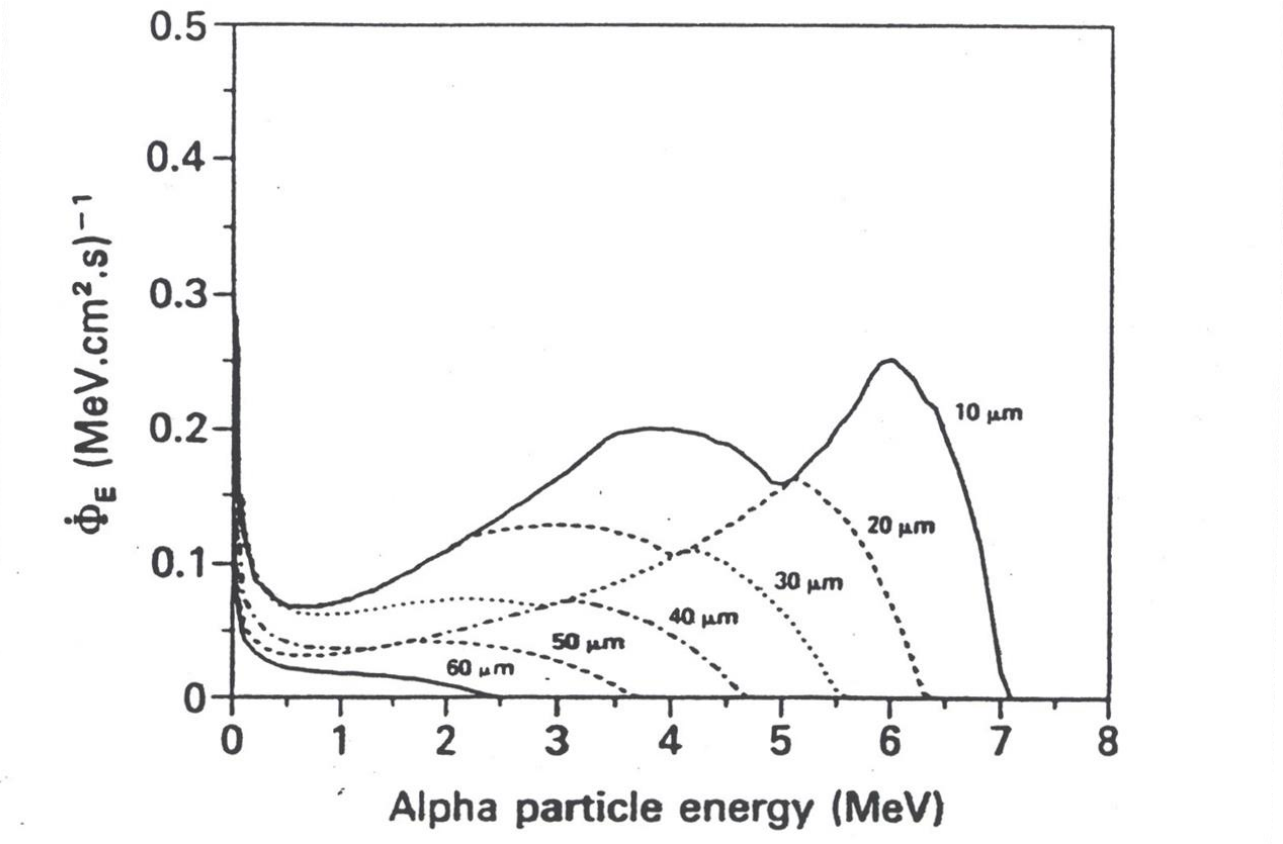
The microdosimetric approach is especially relevant for low level radon exposures, e.g. radon in homes, where low doses of alpha particles are characterized by a small number of cells affected, i.e. small hit probability, which however may receive relatively high doses, while the majority of cells are not hit at all.

Alpha particle energy spectra for different target cell depths

Caswell et al. (1994):

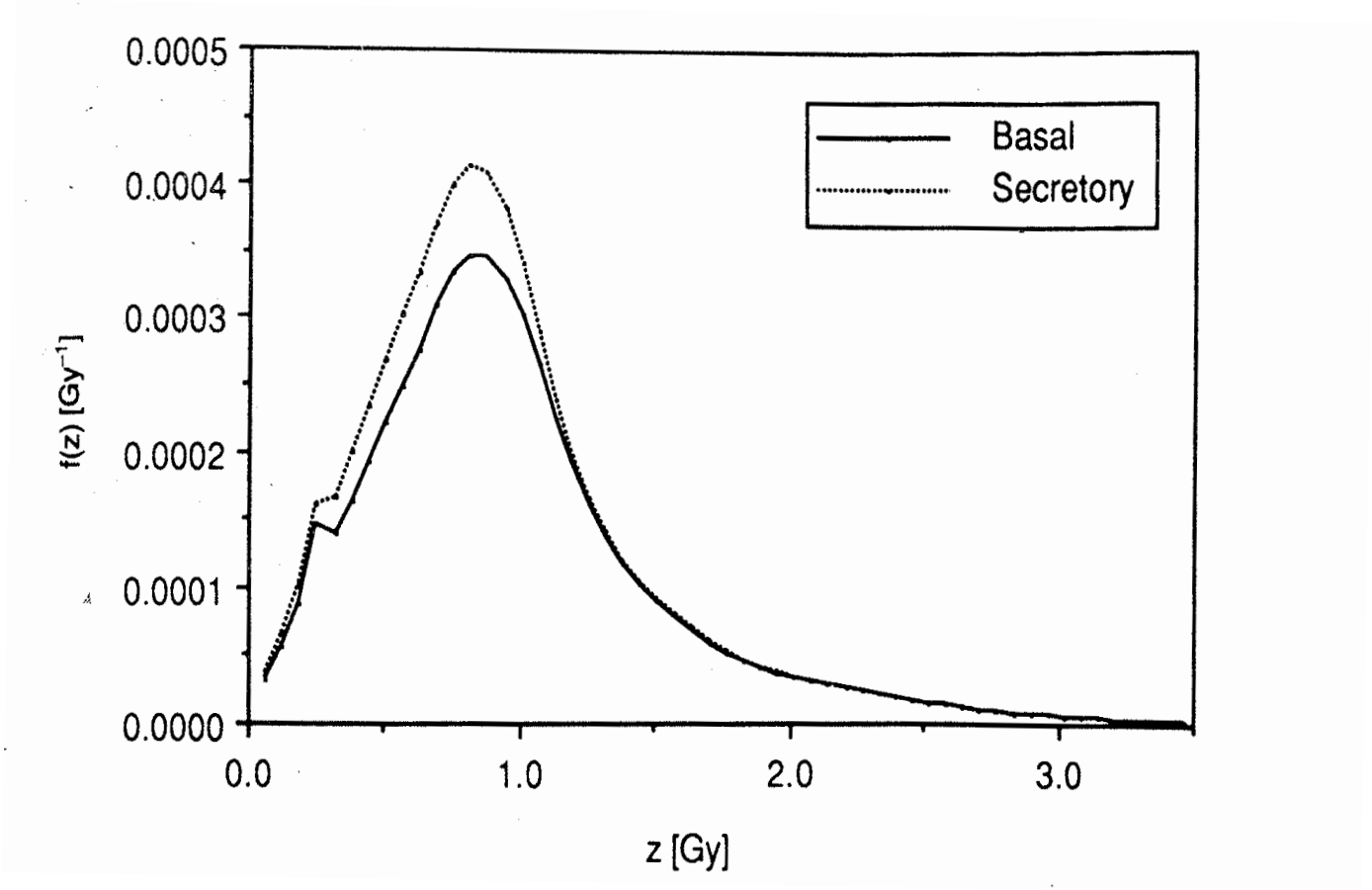
Alpha particle fluence rate spectra for ^{214}Po alpha particles in generation 2 illustrate the number of particles hitting the target at different depths and hence represent the corresponding hit probablities

Hit probabilities decrease in a roughly linear fashion with depth in bronchial epithelium



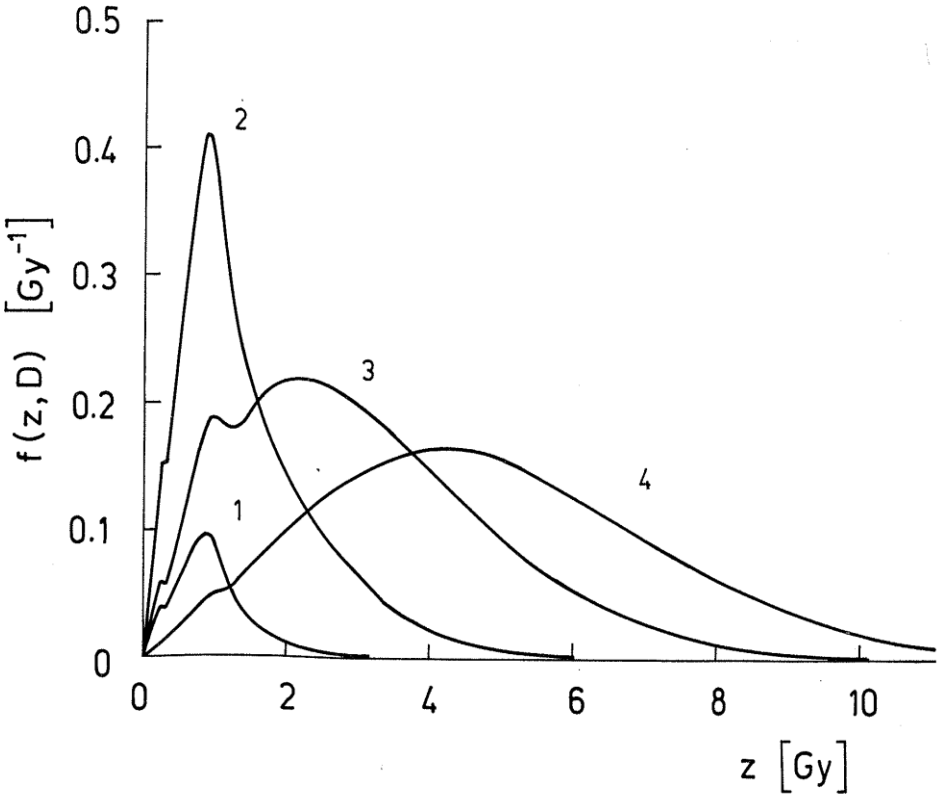
Specific energy distribution for single hits (low doses)

Hui et al. (1990):
Single-event specific energy distributions $f_1(z)$ of ^{218}Po and ^{214}Po alpha particles in basal and secretory cell nuclei for a cumlative exposure of 0.023 WLM over a period of 30 days



Specific energy distributions for single and multiple hits

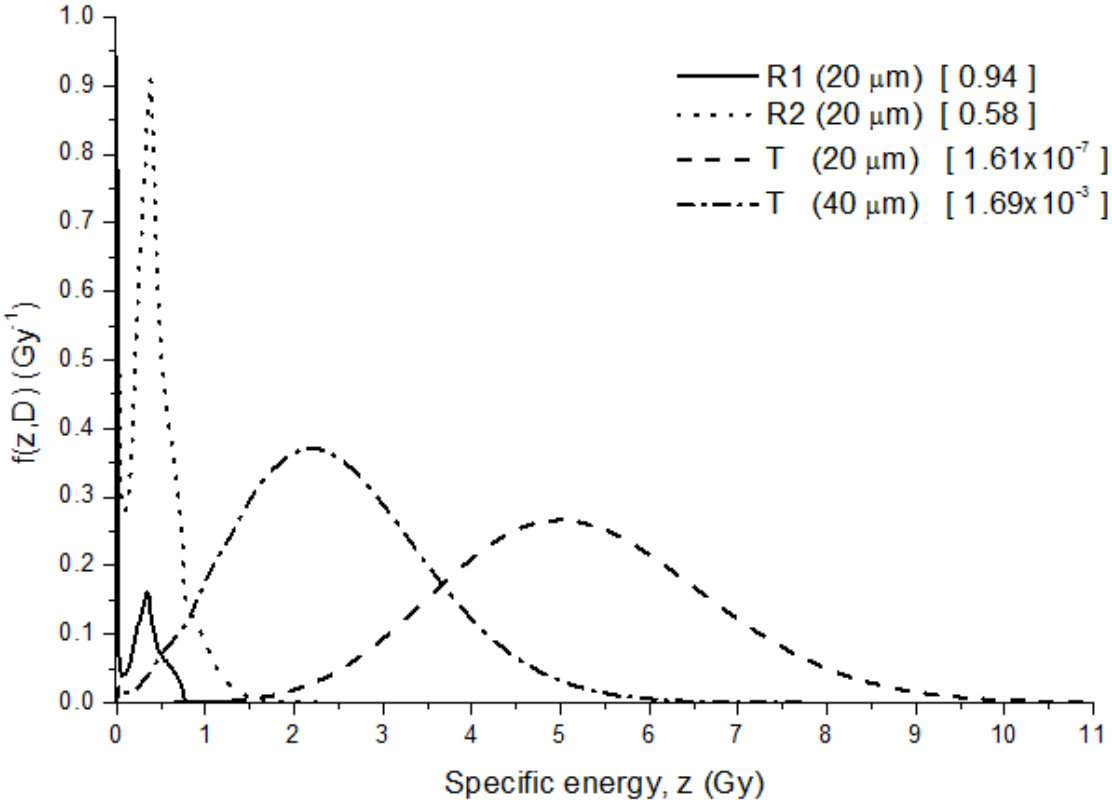
Sedlak (1996):
Specific energy distributions f(z;D) in basal cell nuclei for absorbed dose ranging from 0.1 ot 5 Gy:
Curve 1: 0.1 Gy, curve 2: 1 Gy, curve 3: 3 Gy, curve 5: 5 Gy



The corresponding fraction of cells nuclei missed by alpha particles is given by the delta function δ. Curve 1: δ = 0.90, curve 2: δ = 0.35, curve 3: δ = 0.043, curve 4: δ = 0.0053

Specific energy distributions for cells located at airway bifurcations

Fakir et al. (2005):
Three selected sites of cell nuclei: R1: cylindrical airway, R2: transition zone, T: carinal ridge



Residential radon exposures (20 WLM). **Non-uniform** surface activity distribution.

In parenthesis are the probabilities of zero events, indicating the fraction of cells not hit at all.

Microdosimetric approaches

Question: How to relate microdosimetric parameters to cellular biological effects?

Problem: no unique relationship with microdosimetric parameters

Hit-related models:

Biological effects are related to the fraction of cells hit by alpha particles, and the number of cellular alpha particle hits.

Effect-specific track length models:

The random intersection of cell nuclei and the multiplicity of cellular traversals are related to effect-specific probabilities per unit track length (PPUTL) as functions of LET. Specific energy distribution $f_1(z)$ is approximated by the track length distribution and the lineal energy distribution f(y) is approximated by the LET distribution

Effect-specific interpretation of specific energy distributions:

Direct relation between specific energy distributions and specific cellular effects

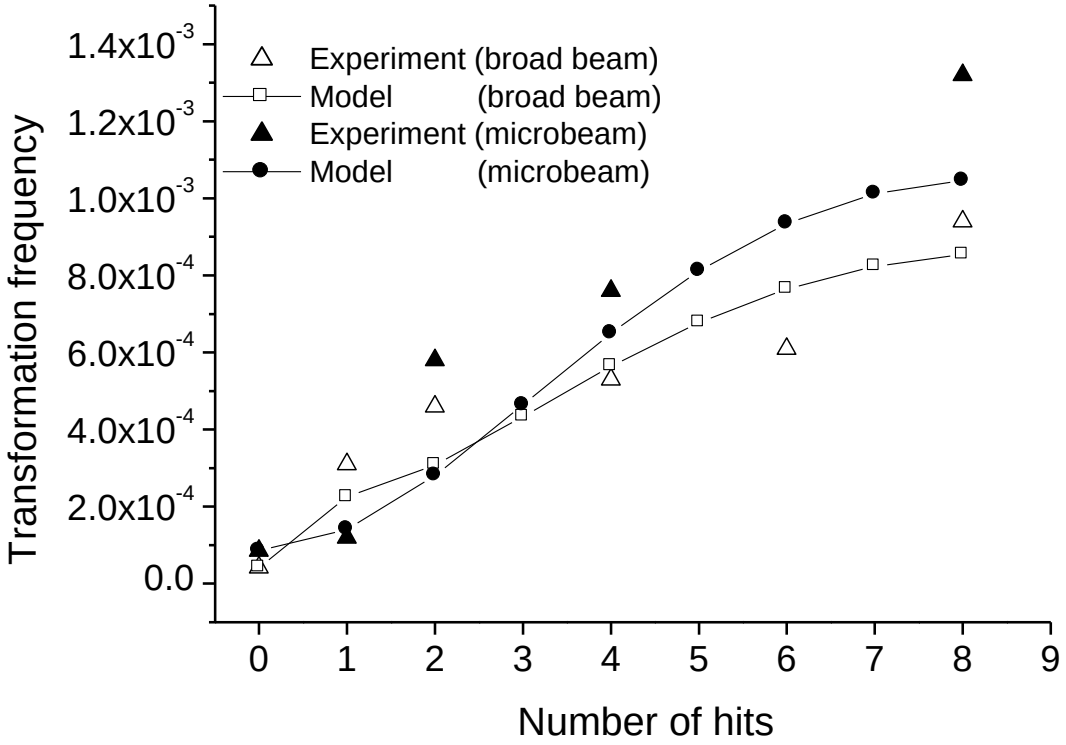
- Theory of dual radiation action (classical microdosimetry)
- Effect-specific threshold models
- Hit-size-effectiveness function

Track structure models (nanodosimetry):

Biological effects are related to the structure of charged particle tracks

Hit-related models

Fakir and Hofmann (2006)
Relationship between transformation frequency and number of alpha particle hits

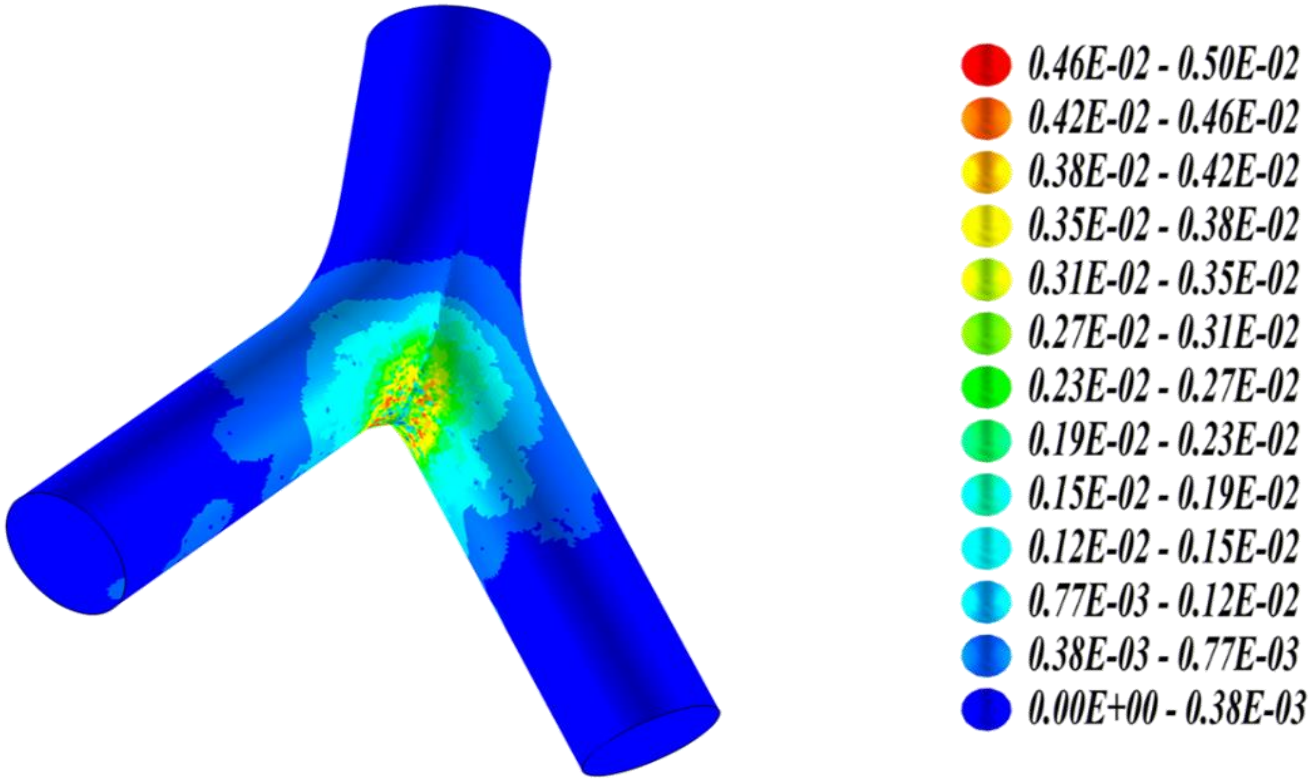


Transformation frequencies per surviving cell in a C3H 10T1/2 cell nuclei produced by 0, 1, …8 alpha particle traversals with an energy of 5.3 MeV (LET = 90 keV/µm) (Miller et al., 1995, 1999).

Effect-specific track length model

Szöke et al. (2012):

Distribution of transformed basal and secretory cells in a bronchial airway bifurcation model following exposure to radon progeny alpha particles based on direct plus indirect contributions of bystander cells

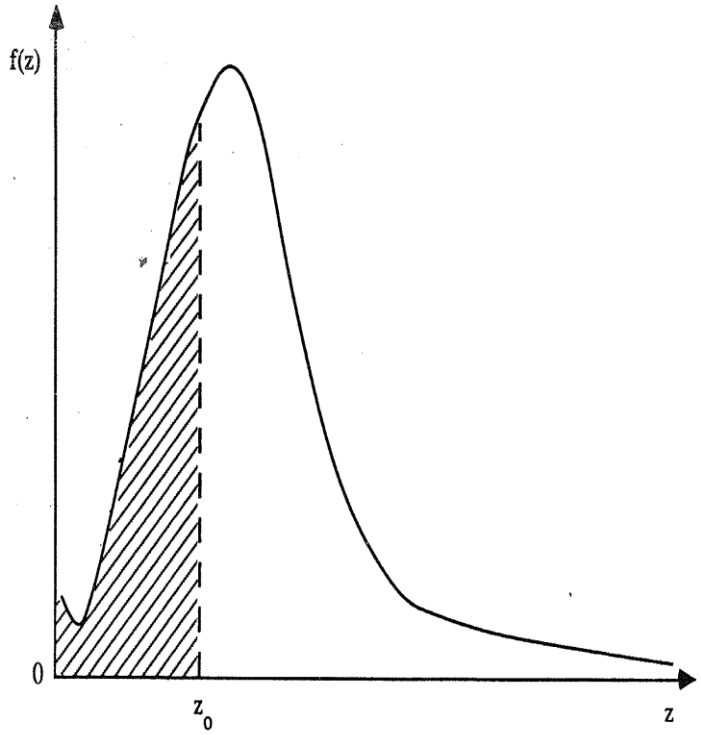


Effect-specific threshold models

The concept of effect-specific threshold is based on the assumption that specific energies below and above a defined threshold specific energy z_o can be related to specific radiobiological effects, such as cell killing (above z_o) or transformation and carcinogenesis (below z_o).

Area below z_o: probability of transformation, area above z_o: probability of cell killing

Sedlak (1996):

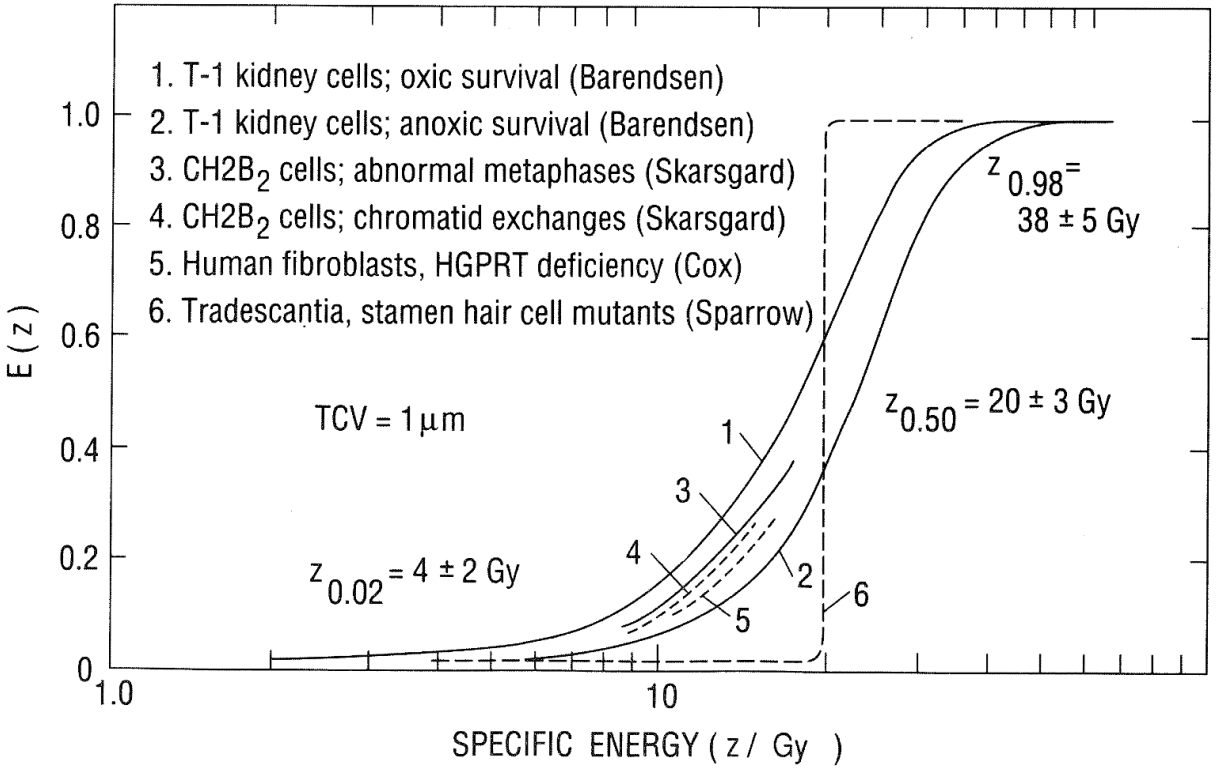


Analyses of *in vitro* experimental data with different radiations and cell lines:
Cell killing: z_o = 0.44 Gy; oncogenic transformation: z_o = 0.43 Gy

Hit-size-effectiveness function

Sondhaus et al. (1990):

Hit-size-effectiveness functions E(z) for six different biological endpoints derived from measurements with various types of radiations with LETs ranging from 1 to 350 keV μm^{-1}. Values of E(z) represent the probability of a quantal response to a hit of size z calculated for each z interval.



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Conclusions

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- The variability of energy deposition at the cellular level results from random variations of stochastic **macroscopic factors (source variability)** and **microscopic factors (target variability).** **Internal microdosimetry** comprises both source and target variability
- The **source variability** can be described by distributions of average doses (mean specific energy) in individual cell nuclei **(stochastic macroscopic dosimetry)**
- The **target variability** can be described by **hit probabilities**, which considers the variability of cellular hits but not the variability of energy deposition within cell nuclei, and **specific energy distributions**, which include both the variability of cellular hits and the variability of energy deposition within cell nuclei **(microdosimetry)**
- The microdosimetric approach is especially relevant for low level radon exposures, where **low doses of alpha particles** are characterized by a small number of cells affected, while the majority of cells in bronchial epithelium are not hit at all
- At present, **cellular radiobiological effects** cannot directly be predicted on the basis of computed specific energy distributions. However, several substitute microdosimetric approaches have been proposed to establish such a relationship, such as hit-related concepts, effect-related track length models, and effect-specific interpretation of specific energy distributions
- Since microdosimetry refers to energy deposition at a given point in time, the application of microdosimetry to predict **lung cancer risk** is limited by two factors: (i) bystander or non-targeted effects and (ii) biological modifications of the initial response after alpha particle exposure (systems biology)

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