Introduction to microdosimetry

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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 an 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
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”
In that example (A Malaroda):

Spatial heterogeneity of absorbed dose distribution,
But what is calculated is a mean absorbed dose...
... this is a macrodosimetric approach!
We’ll see, through an example, what microdosimetry can provide:

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!

(As mentioned in Goodhead in *Dosimetry of ionizing radiations*, Kaze, Bjarngard and Attix ed., Orlando 1987)

Other (classical) example:

1 cGy gamma photons
50 ± 7 electron tracks/cell (on average)
1 cGy alpha
Dose spectrum, from 0 to 30 cGy
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(As mentioned in Goodhead in *Dosimetry of ionizing radiations*, Kaze, Bjarngard and Attix ed., Orlando 1987)
Rationale for alpha-radioimmunotherapy
Biologic effect of $^{213}$Bi and $^{131}$I labelled BB4 MoAB on Multiple Myeloma cell lines
Key features of $\alpha$ emitters proposed for MRT

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>4 to 8 MeV</td>
</tr>
<tr>
<td>Range</td>
<td>40 to 80 $\mu$m</td>
</tr>
<tr>
<td>High LET</td>
<td></td>
</tr>
<tr>
<td>Straight particle track (canon ball)</td>
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</table>

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

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

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
$^{213}\text{Bi}$

Generator ($^{225}\text{Ac}$)

$E_\alpha \approx 8.5$ 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

\[
\text{dE/dx} \quad \text{keV/µm}
\]

\[ ^{211}\text{At} \]

Range (water): µm
Simplified dosimetric approach


$R_C = 10 \mu m$

$R_N = 5 \mu m$

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

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

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

If $D_0 = 70$ cGy,
4.3 hits for 37% cell inactivation
4.3 x 15 $\approx$ 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 $\Psi$

$$\phi_{(\text{Nucleus} \leftarrow \text{Cell Surface})} = \int_{0}^{\infty} \psi(x)_{(\text{Nucleus} \leftarrow \text{Cell Surface})} \frac{1}{E} \frac{dE}{dX} \bigg|_{x(E)-x} \, dx$$

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

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

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

(To compare with: $^{131}I$: $6.5 \times 10^{-3} \text{ cGy/(Bq.s)}$ or $^{90}Y$: $2.8 \times 10^{-3} \text{ cGy/(Bq.s)}$)
Analytic microdosimetric approach:
(Stinchcomb and Roeske, Med. Phys. 19 1385-1393, 1992)

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

$R_C = 10 \, \mu m$
$R_N = 5 \, \mu m$
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:

\[
\langle z \rangle = 0.305 \text{ Gy}, \quad \langle n \rangle = 1.67 \quad (\text{Solid angle 0.067}),
\]

\[
[P(z) = 0] = 0.178 \quad (17.8 \% \text{ non irradiated nuclei...})
\]

And \( S = 1.22 \text{ cGy} / (\text{Bq.s}) \) (0.305/25 sources)
Application to $\alpha$ 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 ($^{213}\text{Bi}$):
- $E_\alpha = 8.376$ 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)

\( \langle f_1(z) \rangle = 3.22 \text{ cGy} \)

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

\( \langle f(z) \rangle = 102.30 \text{ cGy} \)

\( \langle f_1(z) \rangle = 5.35 \text{ cGy} \)

\( \langle f(z) \rangle = 13.31 \text{ cGy} \)
Still mean doses (cGy)...

<table>
<thead>
<tr>
<th>Ab</th>
<th>IgG BB4</th>
<th>Fab’2</th>
<th>IgG 134</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>1.4</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>17.6</td>
<td>35.6</td>
<td>1.5</td>
</tr>
<tr>
<td>1</td>
<td>115.6</td>
<td>249.9</td>
<td>14.3</td>
</tr>
<tr>
<td>10</td>
<td>325.8</td>
<td></td>
<td>137.7</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td>269.5</td>
</tr>
</tbody>
</table>
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%.

Relative s.d. vs. Dose
$R_N = 10 \, \mu m$
Homogeneous $^{212}$Bi solution

Graph showing relative standard deviation versus dose.
And for $\beta$ emitting radionuclides?

The situation is somehow simpler...

$\beta$ 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: $^{193\text{m}}\text{Pt}$ emission spectrum (Howell et al. 86)
Example: microdosimetry of Auger electrons

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:
ICRU 36 (1983)
Bardiès and Pihet *Cur Pharm Design* 6 1469-1502 2000

/ Alpha dosimetry:

/ Auger dosimetry: AAPM task group