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Microdosimetry: Principles and applications

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ABSTRACT

Aim: to present the most important aspects of Microdosimetry, a research field in radiation biophysics.
Background: microdosimetry is the branch of radiation biophysics that systematically studies the spatial, temporal and spectral aspects of the *stochastic nature* of the energy deposition processes in microscopic structures.
Materials and Methods: we briefly review its history, the people, the formalism and the theories and devices that allowed researchers to begin to understand the true nature of radiation action on living matter.
Results and Conclusions: we outline some of its applications, especially to Boron Neutron Capture Therapy, attempting to explain the biological effectiveness of the boron thermal neutron capture reaction.

1. Background and Aim

The early target theories[1,2] attempted to describe the discrete acts of energy transfer, termed "hits" identifying them with individual ionizations or clusters of ions. The spatial correlation of these events was not considered, and target theory in this earliest form could not explain the relative biological effectiveness of different types of ionizing radiation. A far more realistic treatment emerged in the work of Lea,[3] who attempted a more detailed description of the "random" configurations of energy deposition in the tracks of charged particles. He used the term "energy dissipation" which was later called "Linear Energy Transfer" or LET, by Zirkle et al.[4]

Microdosimetry,[5–10] in its present sense, was founded entirely on an original approach introduced by Harald H. Rossi (1917–2000), when he recognized the fundamental difference between macroscopic absorbed dose and the energy deposition in microscopic structures. He realized that the important quantities that described the problem at microscopic scale were inherently "stochastic variables". He and his colleagues proceeded then to develop sophisticated techniques for measuring the random fluctuations of energy deposition, to construct a novel conceptional and mathematical framework, and to apply the new concepts and methods to radiobiology.

1.1. *Why microdosimetry?*

- Ionizing radiations interact in a discontinuous form with matter; dose and dose rate are statistical averages that disregard the inherent random fluctuations.

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- The knowledge of the macroscopic absorbed dose gives little information about the energy deposited in cellular and subcellular structures.
- Fluctuations are more substantial for smaller volumes, smaller doses and for more densely ionizing radiations.

2. Materials and methods

2.1. Formulations of microdosimetry

Two different formulations were developed,[11] depending on the need of considering a detailed description of the inchoate distribution of energy deposited by charged particles in a microscopic sensitive volume, or site:

Regional microdosimetry (or the microdosimetry of Rossi counters): This approach considers the process of energy deposition in a site of specified dimensions without regard to the microscopic distribution of energy transfers, that is, the "pattern" of ionizations produced by the charged particle trajectory. This formulation is especially important because it involves quantities that can, in principle, be measured and correlated with biological effects.

Structural microdosimetry: This more advanced alternative, by the contrary, permits a detailed description of the microscopic pattern of energy absorption, or inchoate distribution. The immediate effect of radiation is essentially determined by the intersection of this pattern and that of sensitive components in irradiated matter. It makes strong use of Integral Geometry and Geometric Probability.[12,13]

2.2. Microdosimetric quantities and distributions

In regional microdosimetry, two fundamental quantities are defined as the microscopic, stochastic analogs of dose and LET: specific energy (z) and lineal energy (y). These two quantities are random variables and can be experimentally measured under certain conditions. The *specific energy*, z (Gy), is the quotient of ε by m, where ε is the energy imparted by one or more events in a site of mass m. The *lineal energy* y (keV/μm) is defined as the energy imparted **in one event** divided by the *mean chord length* that results from the random intersection of the site by straight lines. Under an isotropic and uniform field of random straight lines, the mean chord length $\bar{l}$ of a convex body is given by the Cauchy's formula $\bar{l} = 4(V/S)$, V being its volume and S its surface area.

Usually, the energy deposited in a microscopic site spans several orders of magnitude; a large number of events in a site typically occurs in the low energy region and a few but important high LET events in the high energy region. One possibility for visualizing the distribution is to use a semi-logarithmic representation; usually the distribution is "rebinned" on a histogram with logarithmic intervals. This procedure has several advantages, other than providing a better visualization of the spectrum. The statistical representations are the *frequency* distribution and the *dose* distribution, $f(y)$ and $yf(y)$, both multiplied by y after logarithmic rebinning. In the $yf(y)$ vs. log y representation (frequency distribution), equal areas under the curve represent equal fraction of events. In the $y^2f(y)$ vs. log y representation (dose distribution), equal areas under the curve represent equal fractional doses.

The so-called "multi-event" distribution accounts for the fact that a given amount of energy can be deposited in a site by one or more concurrent events. It is therefore the composition of a homogeneous spatial compound Poisson process with intensity $n = D/Z_F$ (the mean number of events in the site) and the specific energy densities for "exactly" ν events in a site:

$$f(z, D) = \sum_{\nu=0}^{\infty} \frac{e^{-n} n^{\nu}}{\nu!} f_{\nu}(z), \tag{1}$$

The quantity Z_F is the first moment of the specific energy single-event density, the dose-mean specific energy. The density $f_{\nu}(z) = \int_0^z f_1(x) f_{\nu-1}(z-x)dx$ can be obtained from the single event density by convolution with itself, $f_{\nu}(z) = \int_0^z f_1(x) f_{\nu-1}(z-x)dx$. For completeness, $f_0(z) = \delta(z)$, the Dirac delta function at $z = 0$.

2.3. Experimental microdosimetry

Nowadays, instrumentation for microdosimetry and nanodosimetry covers a great number of devices and techniques,[11] but the classical instrument designed by Rossi and still in use today for characterizing complex radiation fields is the Tissue-Equivalent (spherical) Proportional Counter, or TEPC. It is based on a relationship that, under certain conditions, relates the energy deposited in a gas-filled, centimeter-sized cavity (g) with that actually deposited in a micrometer-sized site of living tissue (t):

$$\overline{\Delta\varepsilon} = \Delta x_g \left(\frac{S}{\rho}\right)_g \rho_g = \Delta x_t \left(\frac{S}{\rho}\right)_t \rho_t \tag{2}$$

where Δx is the distance traveled by a particle, S/ρ the mass-stopping power and ρ the density, either in the gas cavity or in the tissue microscopic site. If the detector cavity is made of "tissue equivalent" gas and walls, the mass-stopping power cancels out and a direct relationship arises that permits obtaining microdosimetric spectra representative of the actual energy deposition in a microscopic site.

2.3.1. Neutrons and photons

Neutrons and photons constitute some of the most important types of radiation, for radiotherapy and radiation protection. Elastic and inelastic scattering, nonelastic reactions, capture and spallation are possible reactions that a neutron of certain energy can produce in tissue. In a (nearly) monoenergetic beam of 14 MeV neutrons, for example, it is possible to observe several distinct regions of the measured microdosimetric spectrum indicating the contribution from protons, alpha particles and heavy recoils to the total absorbed dose, which is proportional to the area under the curve. The first important characteristic is the proton recoil peak, which ends slightly above 100 keV/μm. This cut-off, known as *proton edge*, represents the maximum energy that can be deposited by a recoil proton along a diameter of the gas cavity. Above 2.5 MeV, (n,α) reactions become important and an alpha edge is also visible at 360 keV/μm. At lineal energies greater than the alpha