

A GENERALISED FORMULATION OF MICRODOSIMETRIC QUANTITIES

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INVITED PAPER

Abstract — The microdosimetric quantities energy imparted, lineal energy, and specific energy are defined with reference to certain volumes but are quantified in terms of frequency distributions of possible values without regard to spatial interrelations. Computer simulations of the patterns of energy deposits seem, therefore, only loosely related to the microdosimetric distributions. In a more general formulation one treats the specific energy and the related microdosimetric quantities as point functions; one deals then with the spatial distribution of their random values and not merely with the frequency of different values. A further extension of the formalism admits reference regions of vanishing size; the inchoate distribution of energy deposits is then the limit case of specific energy. The definitions are related to Matheron's concept of the regularisation of a spatial variable; this is a convolution process that permits a flexible mathematical treatment. One resulting possibility is the definition of specific energy with reference not to the conventional geometry of a sphere or a cylinder but to a disperse region of support. This extension provides distributions of specific energy that are relevant to diffusion or transport processes and it can help to free biophysical models from a one-sided fixation on the concept of geometric targets. The formalism is applied also to the definition of the proximity functions and the related spatial autocorrelation functions.

INTRODUCTION

Microdosimetry has been conceived primarily as a tool to elucidate basic mechanisms of radiation action^(1,2). But, in contrast to earlier expectations, it has now found its most extensive application in measurements for the specification of radiation fields in therapy and in radiation protection.

Concepts of microdosimetry are, of course, essential in any analysis of the action of ionising radiation on the cell. Their employment has led to important insights but not, as yet, to a quantitative treatment of the primary cellular changes. In part this may be a reflection of the still limited scope of mechanistic studies in radiation biology. The advances of molecular biology are bound to change the situation, and in radiation chemistry microdosimetric data are already applied in quantitative analyses (see e.g. Klots *et al.*⁽³⁾). But even allowing for a gradual development, one can not fail to note the continued reappearance of models that remain unrelated to actual molecular or cytogenetic processes. Such models, although they contain elements of microdosimetry, tend to be mere variations of target theory. They indicate an unreflected use of microdosimetric concepts that may have become sufficiently indurate to require a critical reassessment.

SPECIFIC ENERGY AND INCHOATE DISTRIBUTION

The major root of microdosimetry are measure-

ments, with spherical or cylindrical proportional counters, of energy imparted, specific energy, or lineal energy. These quantities measure energy concentrations in certain assumed critical regions in the cell. They are described by probability distributions that involve — apart from the choice of a reference region — no geometric notions. The more recent aspects of microdosimetry, the simulation of charged particle tracks and the analysis of the resulting spatial patterns of energy, are more closely related to geometric problems, as they arise also in stereology, image analysis, and stochastic geometry (see e.g. References 4-6).

The separation of the different aspects is not complete, since simulations are often used to compute conventional distributions of specific energy in assumed spherical or cylindrical targets. But this linkage remains tenuous and unsupported by theory; the disregard for mathematical considerations is, for example, exhibited when extensive computations of energy imparted to microscopic regions are still performed without weighted sampling^(7,8). The divergence of approaches results from the failure to recognise and use mathematical interrelations. But this failure, in turn, may result from a certain narrowness of the definition of basic quantities and concepts. It will be seen that even slight modifications of the definitions can close the seeming gap between the different branches of microdosimetry.

Current definitions

The various microdosimetric quantities^(9,10) can all be defined in terms of the *energy deposits* that occur in single interactions.

Definition

The *energy deposit*, ϵ , is the energy deposited in a single interaction:

$$\epsilon = T_{in} - T_{out} + Q$$

T_{in} = the energy of the incident ionising particle (exclusive of rest mass energy)

T_{out} = the sum of energies of all ionising particles emerging from the interaction (exclusive of rest mass energies)

Q = the changes of rest mass energy of the atom and all particles involved in the interaction ($Q > 0$: decrease of rest mass; $Q < 0$: increase of rest mass).

It is usually permissible to disregard quantum mechanical uncertainties of location and to postulate that a collision takes place at a point; this point is termed the *transfer point*.

The random configuration of transfer points, x_i , and the associated energy deposits, ϵ_i , in a receptor is termed the *inchoate distribution* of energy. One may refer to the inchoate distribution produced by the multiplicity of particles at a specified dose, or to the inchoate distribution of a single *particle track*, which is the configuration of energy deposits produced by an ionising particle and its secondaries.

It will be sufficient for the subsequent considerations to refer to the specific energy, z . Other basic quantities, such as energy imparted, ϵ , or lineal energy, y , are closely related to z . The present definition of specific energy will be considered first, and modifications will then be introduced that permit a more general formulation of microdosimetry.

Definition

The *specific energy*, z , to a volume, S with mass m is:

$$z = \frac{1}{m} \sum_i \epsilon_i$$

where the summation is performed over all energy deposits, ϵ_i , that are contained in S .

The spatial aspect of specific energy

Energy imparted, specific energy, or lineal energy are related to a reference site, S , and they are quantified in terms of probability distributions that determine the relative frequencies of different

values in a series of repeated exposures to a specified dose or in a succession of *energy deposition events*^(9,10).

The notion of repeated observations at the same location corresponds to measurements where a fixed detector registers a series of values. A different but largely equivalent principle corresponds to simulation studies; the distribution of random values is then obtained by spatial sampling, i.e. sampling at different locations, of the same inchoate distribution.

'Spatial' sampling is — under evident conditions of stationarity — equivalent to 'temporal' sampling. But it has implications that will be apparent from a slightly reformulated definition of specific energy.

Definition

The *specific energy*, $z_S(x)$, at a point x is:

$$z_S(x) = \frac{1}{m} \sum_{y \in S(x)} \epsilon_i \quad (m = \text{mass of } S)$$

where the summation is performed over all energy deposits, ϵ_i , at transfer points, x_i , that are contained in the reference region, S , if it is centred at x .

The meaning of the term 'centred' is clear for a symmetrical S ; in the more general case one can specify any reference point of S as centre. Frequently one postulates a spherical S , in other cases a fixed directional orientation of S needs to be assumed. Simplified notations, such as $z(x)$ or z , may be utilised where the reference to the support, S , or the location, x , is clear. When one refers to a spherical S , one may also use its radius, r , in the notation $z_r(x)$.

The formulation of specific energy as *point function* may seem an undesirable complication, but it is essential in biophysical applications where spatial integrals over functions of $z(x)$ need to be considered, whenever one deals with the interaction of radiation products or lesions that are dependent on local energy concentrations.

Figure 1 is a schematic representation of the spatial distributions of specific energy that result with an assumed inchoate distribution (left top panel) for spherical reference regions of different size. The diagrams make two essential points. The first point is, that distributions of specific energy need not be understood merely as probability distributions that represent repeated measurements at one location. They can equally be seen as spatial random distributions. The connection to Lea's concept of *associate volume*⁽¹¹⁾ is evident, but there is also a range of further implications.

The second important point is that the inchoate

distribution is merely the limit of the spatial distribution of specific energy as the reference region is reduced to a point. The limit of a sphere of radius zero leads, of course, to infinite values of the specific energy, but in the sense of the distribution theory which uses Dirac delta functions this is admissible. Accordingly one can identify the inchoate distribution with the specific energy relative to a vanishing reference region and one can represent it as a sum of Dirac delta functions:

$$z_0(\mathbf{x}) = \frac{1}{\rho} \sum_i \varepsilon_i \delta(\mathbf{x}-\mathbf{x}_i) \quad (\rho = \text{density of the medium}) \quad (1)$$

This establishes a conceptual link between the patterns of energy deposition and the familiar microdosimetric quantities. It permits, furthermore, convenient formulations of a variety of relations that are essential in microdosimetry.

AN EXTENDED INTERPRETATION OF SPECIFIC ENERGY

These explanatory remarks can not deal with the formal instruments of stochastic geometry⁽⁴⁾, but they can make them more accessible for use in microdosimetry. For further guidance one can refer to a treatment that has found applications in a variety of fields, although it has originated from a specific technical area, the geostatistical problems of the spatial distribution of minerals. Matheron's imaginative and influential work^(12,13) contains a multiplicity of results that could, by analogy, be applied to microdosimetry. Brief reference will, therefore, be made in the following to some of the formalism and the terminology employed by Matheron.

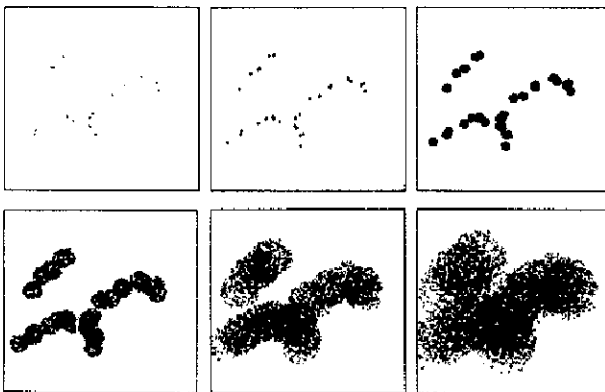


Figure 1. Schematic 2-dimensional diagrams of an inchoate distribution (left top corner), and the distributions of specific energy, $z_r(\mathbf{x})$, for a spherical support of increasing radius, r . The value of the specific energy at a point is represented by the scatter density.

The generalised definition

Assume that the region S is centred at $\mathbf{x}=0$. Its indicator function is then:

$$j(\mathbf{x}) = \begin{cases} 1 & \text{if } \mathbf{x} \in S \\ 0 & \text{if } \mathbf{x} \notin S \end{cases}$$

The use of the indicator function permits a convenient formulation of $z_S(\mathbf{x})$:

$$\begin{aligned} z_S(\mathbf{x}) &= \frac{1}{V} \int z_0(\mathbf{s}) j(\mathbf{s}-\mathbf{x}) \, ds \\ &= \frac{1}{V} z_0 \check{j} \quad (V = \text{volume of } S) \end{aligned} \quad (2)$$

where $\check{j}(\mathbf{x}) = j(-\mathbf{x})$ is the reflection of $j(\mathbf{x})$, while the star is the conventional symbol for a convolution.

To simplify notation one can use the scaled function $h(\mathbf{x}) = j(\mathbf{x})/V$, and one has then the equation:

$$z_S(\mathbf{x}) = z_0 \check{h} \quad (V = \text{volume of } S) \quad (3)$$

The relation shows that the specific energy is a moving average over the inchoate distribution z_0 . Matheron terms this average the regularisation of $z_0(\mathbf{x})$ over the support S .

The concept is valuable because it is readily generalised. Instead of a 'solid' reference region one can consider a 'disperse' support, i.e. one can use a distance dependent rather than a constant weight function in the definition of specific energy. This is most readily explained by an example. For a spherical support of radius r one has:

$$h(\mathbf{x}) = \begin{cases} k & \text{for } x = |\mathbf{x}| \leq r \\ 0 & \text{otherwise} \end{cases} \quad (4)$$

The normalisation factor is $k=1/V = 3/4\pi r^3$. Because of the isotropy of S one can write the weight function with scalar argument $x=|\mathbf{x}|$.

A 'solid' reference region corresponds to the assumption of a target that reacts to total energy imparted, regardless of its location within the target. This is an evident abstraction, and usually it is more plausible that radiation products interact with probabilities that are controlled by diffusion and are, therefore, distance dependent. One can then use the weight function:

$$h(\mathbf{x}) = k \exp(-x^2/a^2) \quad (5)$$

The normalisation factor is:

$$k = 1/\int 4\pi x^2 \exp(-x^2/a^2) dx = \pi^{-3/2} \cdot a^{-3}$$

Figure 2 represents the weight functions for the two simple examples. The schematic diagrams of Figure 3 compare the resulting patterns of specific energy. Even these simplified diagrams suggest that the patterns are essentially similar. It is, therefore, a mere convenience, adopted for extraneous reasons, that microdosimetric data are usually employed to derive 'site' sizes or 'target' diameters; the results can equally — and usually with better justification — be interpreted as effective diffusion or migration distances that govern interaction processes in cellular radiation action.

These observations pose the obvious question for the equivalent values of the site radius, r , and the diffusion distance, a . The question will be answered in a later subsection in terms of the LET concept, and it will necessitate future microdosimetric computations, e.g. of the distribution functions of z

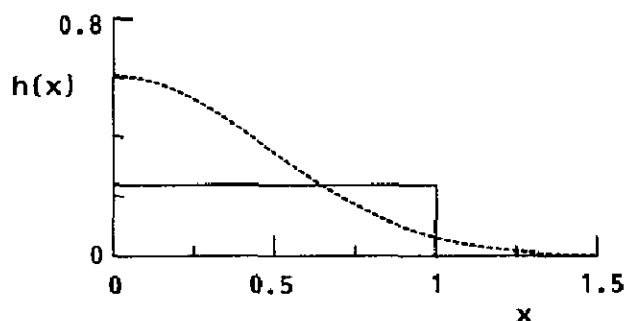


Figure 2. The weight functions, $h(x)$, for a spherical support of radius 1 and a disperse support (according to Equation 5) with $a=2/3$.

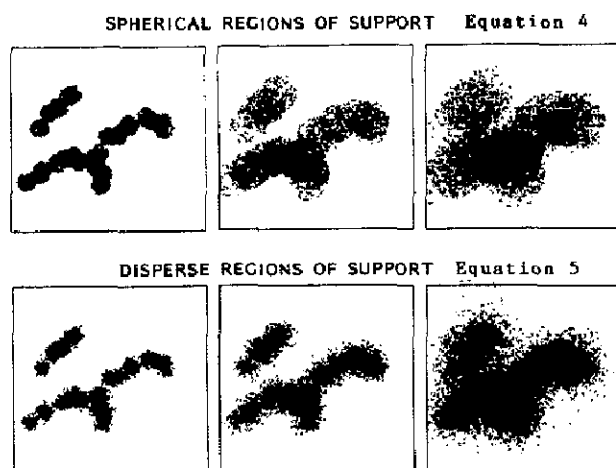


Figure 3. Schematic 2-dimensional diagrams of specific energy for spherical supports with increasing radius (top panels), and for disperse supports (according to Equation 5) with increasing diffusion parameter (bottom panels).

or y that result from the altered function of support. Before dealing with some of these matters one may, however, note a few direct implications of the generalised definition of microdosimetric quantities.

Some implications

The generalised definition of specific energy has certain consequences that are apparent even without a detailed examination and that will be briefly indicated.

Relaxation of response requirements for proportional counters

There is no *a priori* reason to postulate a constant function of support, and there is, accordingly, no need to require uniform sensitivity for a proportional counter. It is, instead, sufficient to assess the weight function, $h(x)$, or its directional average, $\bar{h}(x)$, that corresponds to the sensitivity distribution in the counter. One can then examine in terms of computations, how the changed support function influences the resulting distributions of z or y . These considerations are of especial interest with regard to recent developments that may permit measurements on the nanometre scale⁽¹⁴⁾.

Need for a modified definition of y

A 'disperse' function of support as in Equation 5, reaches out to infinity, and any parameter that corresponds to a (frequency) average mean chord length, \bar{l} , must therefore be zero. A cut-off in x , introduced in $h(x)$ to avoid this difficulty, would not remove the fact that the parameter is ill defined or meaningless. The conventional definition of lineal energy as energy imparted divided by \bar{l} is, therefore, inapplicable. One can, however, utilise a weighted mean chord length in the definition of y , and this would be a more meaningful choice even with reference to a sphere or another solid reference volume.

Assume that S is centred at the origin. A generalised 'chord length', l , for the specified 'impact parameter' c can then be defined as integral over $h(x)/k$ along a straight line with distance c from the origin. Assuming proper frequencies for all impact parameters from 0 to ∞ one finds then, for the example of Equation 5, a frequency distribution of l that is proportional to l^{-1} and that can not be normalised, since it extends from $l=0$ to the maximum value $4a/3$. This implies, of course, that the mean chord length is zero. The weighted distribution of chord length, however, is constant between $l=0$ and $4a/3$, and the weighted mean chord length is, accordingly, $2a/3$. This value compares to the weighted mean chord length $3r/2$ for a spherical

region of radius r .

The applicability of the weighted mean chord length suggests its utilisation, instead of the frequency average, in the definition of lineal energy y . This modification would decrease the values of y for a spherical reference volume by the factor $8/9$ and it would simplify the current LET approximation $\bar{y}_D = 9/8 \bar{L}_D$ to $\bar{y}_D = \bar{L}_D$.

Inapplicability of frequency averages

The frequency average of the chord length distribution vanishes, as stated, for the disperse support function. This is only one aspect of the more principal difficulty that all frequency averages of event sizes y , z , or ϵ vanish in the case of an unbounded support, and that they would remain poorly defined or meaningless, even if some cut-off were applied to x . The difficulty is a necessary consequence of the assumption that the support has no defined boundaries, and that radiation products or radiation induced lesions have no defined maximum interaction distance but exhibit, instead, gradual dependences.

Frequency averages of event sizes and their reciprocals, the mean event frequencies, can have heuristic value. In biophysical applications and in the parameterisation of microdosimetric spectra they can, however, be gravely misleading. Their restricted applicability must, therefore, be noted.

SPATIAL CORRELATION

The essential point in the more general formulation of microdosimetry is the explicit consideration of the spatial distribution of specific energy. In the conventional treatment one disregards this aspect, utilising only the probability distribution of the relative frequency of different values of specific energy. This restricted point of view may have been the reason that comparatively little use is being made of the fundamental relation that links the dose averages of y or z to the proximity functions which are basic measures of spatial correlation.

A formalism that accounts explicitly for the spatial aspect will lead more naturally to the use of basic tools, such as the correlation functions. The present discussion can, therefore, be helpful even without a detailed consideration of these functions. Brief explanatory sections will, nevertheless, be added to indicate essentials.

The role of the distance distribution

A cellular radiation effect may require an elementary lesion in each of two mass elements separated by distance x . If a lesion is produced in

one element, there will be a probability for a lesion due to the same particle in the adjacent element that is proportional to L in the LET approximation and inversely proportional to the square of x . This probability determines the ratio, α/β , of coefficients in the linear quadratic dose dependence.

In actuality one will deal with complex targets that exhibit a distribution of distances between their mass elements, and α/β will then be proportional to the mean of x^{-2} .

The distance distribution, $p(x)$, and the mean value \bar{x}^{-2} can be computed readily for the sphere of radius r :

$$p(x) = \frac{3x^2}{r^3} \left(1 - \frac{3x}{4r} + \frac{x^3}{16r^3}\right) \quad 0 < x < 2r$$

$$\bar{x}^{-2} = 9/4r^2$$
(6)

$$\alpha/\beta = L_D/2\pi\rho \bar{x}^{-2} = 0.0574 \bar{L}_D/r^2$$

(Gy. μm^3 .keV $^{-1}$)

For a disperse region, as described by Equation 5, one has:

$$p(x) = \frac{1}{a^3\sqrt{\pi/2}} x^2 \exp(-x^2/2a^2)$$

$$\bar{x}^{-2} = 1/a^2$$
(7)

$$\alpha/\beta = 0.0255 \bar{L}_D/a^2 \quad (\text{Gy} \cdot \mu\text{m}^3 \cdot \text{keV}^{-1})$$

One obtains, therefore, equality of the values α/β for $a=2r/3$. This answers the question posed previously. If, for example, one infers in a microdosimetric study spherical targets of 30 nm diameter, one can equally — and usually with more justification — speak of a diffusion process with characteristic distance 10 nm. The observations will not permit us to discriminate between the two interpretations or an in-between situation; the assumption of energy migration or diffusion processes will usually be more meaningful than the postulate of distinct target regions.

The argument is here given in terms of the LET approximation and in terms of an assumed distribution of target structures, but the mathematical relations will remain largely unchanged, even for different conditions that may involve complex particle tracks and diffusion or migration processes. The resulting formulae (see e.g. References 15 and 16) contain integrals over the distance distribution of the reference region, the distance dependent interaction probability, and the distance distribution of the radiation, the so-called proximity function.

The essential point in the present context is the similarity of the distance distribution for the spherical and the disperse reference region (see Figure 4), which indicates that the two conditions are substantially equivalent.

Definition of the proximity function and its relation to the autocorrelation function

This concluding section deals first with the definition of the proximity functions and it then uses analogies to the definition of specific energy to indicate in general terms the flexibility and some of the potential of the mathematical formalism.

Current definitions

The proximity function of a radiation can be defined in analogy to a formulation in ICRU 36⁽¹⁰⁾ which was restricted to ionising particles of specified energy:

Definition

The *integral proximity function*, $T_p(x)$, of a particle track in a material is:

$$T_p(x) = \sum_i (\epsilon_i \sum_{\substack{k \\ (x_{ik} \leq x)}} \epsilon_k) / \sum_i \epsilon_i$$

where i runs over all energy deposits of the track,

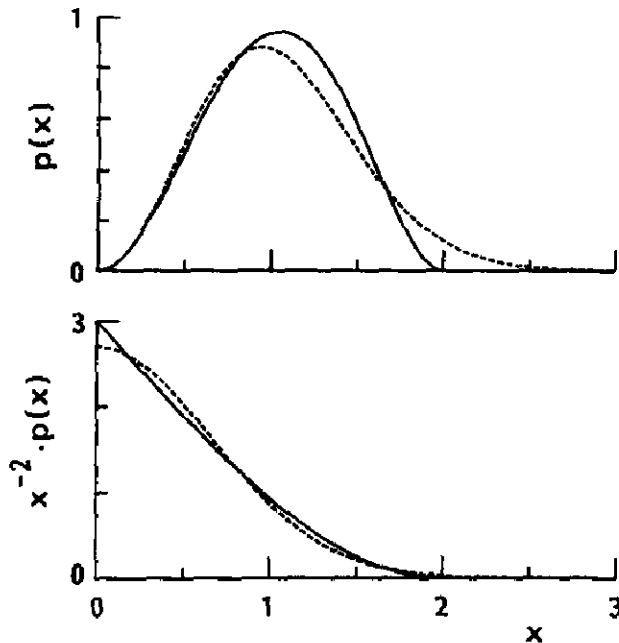


Figure 4. The point-pair distance distributions, $p(x)$, for a sphere with radius $r=1$ (solid line) and for a disperse region, according to Equation 5, with $a=2/3$ (broken line). The lower panel represents the contribution, $x^{-2} \cdot p(x)$, of the different distances to the 'intra-track effect' in the LET approximation.

and k runs over all energy deposits in the track with distance x_{ik} between the transfer points up to x .

Definition

The *integral proximity function*, $T(x)$, of a radiation in a material is the weighted average of $T_p(x)$ over all particle tracks:

$$T(x) = \overline{E_p T_p(x)} / \overline{E_p}$$

$E_p = \sum_i \epsilon_i$ is the total energy imparted by a particle track. The bars indicate expectation values, i.e. the average over all tracks.

$T_p(x)$ is a stochastic function that assumes different forms, even for a particle of specified energy and type in a specified material. $T(x)$, on the other hand, depends only on the radiation and the material. It is a continuous function except for the discontinuity at $x=0$ which equals the weighted average of the energy deposits:

$$T(0) = \overline{\epsilon_i^2} / \overline{\epsilon_i}$$

Sacrificing rigour, one can say that $T(x)$ is the expected energy imparted by the same particle track to a sphere of radius x centred at a 'typical' energy deposit.

The derivative of $T(x)$ is the differential proximity function, $t(x)$, which is also a continuous function except for the singularity at $x=0$. The function $t(x)$ is, apart from its normalisation, equal to the probability distribution of distances between energy deposits in the particle tracks.

The definitions are here given for the (energy) proximity function, $t(x)$, of a radiation, but analogous definitions apply to the (geometric) proximity function, $s(x)$, which is, again apart from the normalisation, equal to the point-pair distance distribution of the reference region, S . The functions appear in the fundamental relation for the weighted mean event size of energy imparted:

$$\overline{\epsilon_D} = \int_0^\infty \frac{t(x) s(x)}{4\pi x^2} dx$$

which has been used in microdosimetry⁽⁸⁾ and has in analogous form applications also in other areas^(17,18).

Modified formulation in terms of specific energy

A modified formulation can use the notation z_x for the specific energy in a sphere of radius x . The formulation is given without derivation, to serve merely as an illustration for the applicability of the notation.

GENERALISED FORMULATION OF MICRODOSIMETRY

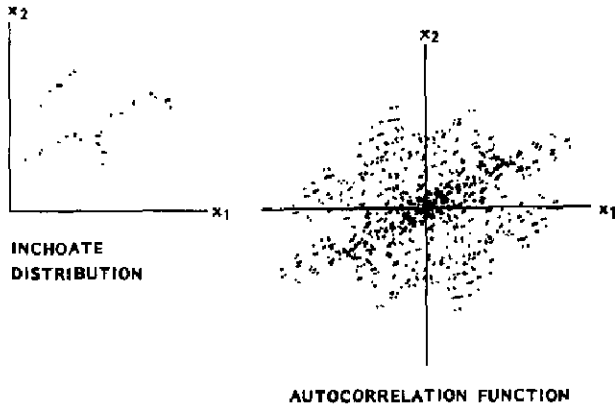


Figure 5. Schematic 2-dimensional diagram of an inchoate distribution, $z_0(\mathbf{x})$, and the corresponding directional proximity function or autocorrelation function, $t(\mathbf{x})$. The dots in the diagrams represent Dirac functions.

Definition

The integral proximity function, $T(\mathbf{x})$, of a radiation in a material is:

$$T(\mathbf{x}) = m_x (\overline{z_0 \cdot z_x} / D - D)$$

$\overline{z_0 \cdot z_x}$ is the expectation value of $z_0 \cdot z_x$, while D is the absorbed dose, and m_x is the mass of a spherical region of radius x .

Relation to the autocorrelation function

A brief concluding discussion will deal with the autocorrelation function — or covariogramme in the terminology of Matheron — of a spatial variable. The variable $z_0(\mathbf{x})$ for a single particle track, will be taken as example, but it can stand for any spatial variable.

The autocorrelation function is:

$$t(\mathbf{x}) = c \int z_0(\mathbf{s}) z_0(\mathbf{s} - \mathbf{x}) d\mathbf{s} \tag{10}$$

$$= c z_0 \check{z}_0$$

The scaling factor, c , need not to be considered here. The notation $t(\mathbf{x})$ has been chosen in analogy to $t_p(\mathbf{x})$ since $t(\mathbf{x})$ can be seen as a directional

proximity function. To simplify notation the index p is from here on omitted. Figure 5 exemplifies the directional proximity function that corresponds to the simple 2-dimensional pattern that has been used in earlier diagrams.

The conventional proximity function with scalar argument, x , results from $t(\mathbf{x})$ by integration over all directions. In Matheron's terminology this can be called directional grading:

$$t(x) = \int_{|\mathbf{x}|=x} t(\mathbf{x}) d\mathbf{x} \text{ and } T(x) = \int_{|\mathbf{x}|\leq x} t(\mathbf{x}) d\mathbf{x} \tag{11}$$

Equation 10 is notable because it implies that $t(\mathbf{x})$ is the autoregularisation of $z_0(\mathbf{x})$. In analogy one can term the directional distance distribution or autocorrelation function, $s(\mathbf{x})$, the autoregularisation of $h(\mathbf{x})$:

$$s(\mathbf{x}) = c h \check{h}$$

The commutative and transitive properties of the convolution and the convenient use of the Fourier transform provide a variety of notable results. Using the indices S and a to refer to a reference site S and to the diffusion parameter a one has, for example:

$$z_a \check{h}_s = z_0 \check{h}_a \check{h}_s = z_0 \check{h}_s \check{h}_a = z_s \check{h}_a$$

This means that one obtains the same distributions of specific energy, regardless whether the inchoate distribution or the 'target structure' is subjected to a diffusion process. As a further example one may consider the proximity function of a 'blurred' inchoate distribution:

$$t_a(\mathbf{x}) = c z_a \check{z}_a = c z_0 \check{h}_a \check{z}_0 \check{h}_a = c z_0 \check{z}_0 \check{h}_a \check{h}_a = c t s$$

The proximity function can thus be computed from the original proximity function without the need to go back to the inchoate distribution. In the familiar case of isotropy there is no directional dependence, and the conclusion applies, therefore, equally to the conventional function, $t(x)$. Analogous relations hold for the functions, $s(x)$, that quantify target structure and diffusion or migration processes.

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