January 1990

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Published in *Appl. Radial. Isot.* 41:6 (1990), pp. 563-567; formerly *Int. J. Radiat. Appl. Instrum. Part A*

Submitted August 21, 1989; revised October 12, 1989.

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Abstract: In radiobiology the term cross section is used in ways that depart from its original physical meaning. Some of these conceptual extensions represent significant distortions of the original concept. These distortions lead to the misinterpretation of experimental findings.

1. Introduction

Experiments in physics in which beams of particles are directed at targets have as their goal the determination of the interaction cross section for the particular process of interest. All cases involve single interactions between projectile and target. One assumes that a single projectile is launched down a channel 1 cm^2 in area toward a target located somewhere within the channel. Neither the trajectory of the projectile nor the position of the target is specified. One tallies the fraction of successes in a large number of identical trials, the probability of success. This probability (an average quantity) is then reported as though it represents a target area, in units of cm^2. The cross section is not an area but rather is a probability. Its numerical value may be smaller or larger than the geometric area of the target by orders of magnitude. It is only equal to the cross sectional area of the target if the probability of achieving the measured end point is 1 when the projectile passes through the target and is 0 otherwise. The cross section never represents a phenomenon in which more than one incident particle is required to interact with the target to achieve the observed end point. Though the end point is unique, the interactions that lead to that end point may not be unique. The cross section is an anhistoric concept. That is, each trial of the experiment is independent of the number of prior trials. As in the case of radioactive decay this results in exponential response. In the language of the cumulative Poisson distribution these are one-or-more hit interactions.

In many experiments, typically when particle beams are directed at condensed matter, the measured effects arise from secondary particle production. The irradiated material is both the source of secondary particles and the location of the aggregate of targets with which the primary and secondary particles interact.

It is useful to examine a nest of cylindrical shells of unit length whose axis is the ion's path. Each shell makes a contribution to the total interaction probability equal to the fraction of affected targets within that shell. The sum of these contributions, the radial integral of the probability, is the cross section. Thus

$$\sigma = 2\pi \int_0^\infty \mathrm{P}(t)\, t\, \mathrm{d}t \qquad (1)$$

where P(t) is the probability of affecting a target at radial distance t from the path of the primary particle.

One may also think of the cross section as the number of interactions per unit path length, as

$$\mathrm{d}n/\mathrm{d}x = \sigma N \qquad (2)$$

where dn/dx is the number of affected targets per unit path length, and N is the number of targets per unit volume.

In some cases, as in the study of particle tracks in nuclear emulsion, the probability of affecting a target in a cylindrical shell is directly measurable by use of a microdensitometer that measures the opacity caused by developed grains as a function of the distance from the ion's path. The number of targets affected per unit path length may also be directly measurable by counting the number of developed grains per unit path length. When one counts the number of developed grains per unit path length it is not required that these affected targets are intersected by the passing ion. They may have been activated by δ rays at some distance from the ion's path. One may imagine that there are slices of the medium normal to the path and count the average number of affected targets per slice of unit thickness.

In heavy ion radiolysis, in scintillation counters, in the inactivation of dry enzymes and viruses, it is only the total number of activated targets which is accessible to measurement. Sometimes these are

from single ions, and sometimes from a beam containing many ions.

In a scintillation counter or a thermoluminescent dosimeter the light per unit path length is proportional to dn/dx, and is therefore proportional to σ. The number of affected targets per unit energy, called the G value in heavy ion radiolysis, and proportional to the scintillation efficiency in scintillation counters, or to the thermoluminescent efficiency in TLD's, is then given by

$$G = \sigma N/L \tag{3}$$

where L is the stopping power or the linear energy transfer (LET) (Katz and Huang, 1989).

2. Theoretical Evaluation of the Cross Section

To evaluate the cross section theoretically one must have a means of evaluating $P(t)$, the radial distribution of the activation probability about the path of the projectile (equation (1)). When heavy ions are incident upon a target and the effect is primarily due to δ rays, the average effect from many ions is calculable from the average energy deposition in shells. One may then use as the basis of the calculation the response of the detector to equal doses of x or γ rays in bulk matter, where the response is also due primarily to secondary electrons. Sometimes this information is available from experiment. More frequently, however, one must approximate this response as having the shape of a multi-hit or a multi-target function. The characteristic dose of x-rays at which there is an average of one hit per target is taken to be an adjustable parameter, E_0. A second parameter is the radius of the sensitive target, a_0. A third is the quantity C, the "hittedness," or m, the "target number," required for activation. If it is true that no single electron can activate a target, whatever its energy, the hittedness for x or γ irradiation must exceed 1, and the survival curve for such an irradiation must display an initial shoulder. Thus while the track of a heavy ion in electron sensitive (1-hit) emulsion always exhibits a brush of δ rays, the tracks of single δ rays are not visible about the tracks of heavy ions in insensitive, many hit, emulsions. Here several electrons must pass through a grain to create a latent image.

In radiobiology it has been proposed that the RBE for sister chromatid exchanges is infinite (Aghamohammadi *et al.*, 1988), suggesting that different electrons must pass through each of the sister chromatids. For thermoluminescent dosimeters a "track interaction model" has been proposed to explain "supralinearity" in the response of LiF to high doses of γ rays (Attix, 1974), implying that supralinearity is caused by pairs of electron tracks, and is thus a 2-hit process.

3. Abuse of the Concept of "Cross Section"

When either a single electron or a single heavy ion serves to inactivate a target the response to fluence, F, is exponential, and

$$N/N_0 = \exp(-\sigma F). \tag{4}$$

Since the dose D is the product of fluence F by the stopping power L

$$N/N_0 = \exp(-D/D_0) = \exp(-D/\lambda) \tag{5}$$

and the radiosensitivity (for that irradiation) is

$$\lambda = 1/D_0) \tag{6}$$

and

$$\sigma = \lambda L. \tag{7}$$

When equation (7) is applied to a survival curve resulting from neutron or γ ray irradiation, and L is replaced by the average stopping power of all the secondary particles, the equation results in nonsense. Nevertheless we frequently find the results of such a calculation in the radiobiological literature (Goodhead, 1984) to yield an "action cross section" for photons or neutrons.

It has become commonplace in radiobiology to derive an experimental "cross section" from the final slope of shouldered survival curves, when this region can be fitted by a straight line on a typical semi-logarithmic plot of the surviving fraction vs dose. The radiosensitivity is calculated as if this line passed through the "origin," at $N/N_0 = 1$ at zero dose. But the cross section obtained from the final slope of a survival curve has a totally different implication when the survival curve is shouldered than when it is exponential. At most one may infer an "extrapolated cross section" in this case. For shouldered survival curves, the numerical value of the extrapolated cross section cannot be interpreted as giving the effect of a single particle on the target. The final slope of the curve results from the interaction of the δ rays from several ions upon the target. In the language of track theory there are contributions both from "γ-kill" most important at low LET and from "ion kill" which dominates at high LET.

The slope of a curve of the extrapolated cross section vs LET is nearly 1 at low LET, and the RBE at low LET is nearly 1 because of the underlying physical resemblance of the distribution of secondary electron energies from γ rays and from energetic protons or a particles at low LET.

As long as cell killing is in the "grain count regime," there is always a mixed contribution, principally from γ kill at low LET and principally from ion kill at high LET. Since the γ kill contribution has slope 1 and the ion kill contribution has slope m, these plots of extrapolated cross section vs LET undergo a change in slope on their way to plateau. Here also plots of RBE vs LET pass through a max-

imum at $P = 0.5$, where about half the intersected cells are inactivated. These quantities are described by our equations (Katz *et al.,* 1971),

$$\sigma_{(ext)} = \sigma_0 P + (1 - P)L/E_0 \quad (8)$$

and

$$\mathrm{RBE}_{(ext)} = (\sigma_0 E_0/L)P + (1 - P) \quad (9)$$

where P is the probability that a cell will be inactivated by an ion passing through it, as given by

$$P = [1 - \exp(-z^{*2}/\kappa\beta^2)]m \quad (10)$$

where z* is the "effective charge" of the ion and σ_0, E_0, κ, and m are the radiosensitivity parameters appropriate to the cell line and end point which are measured by fitting theoretical to experimental dose-response curves at several different LET values.

4. Interpretation of the Cross Section

One hit detectors are those with exponential response to γ rays. A single electron passing through a target may activate it. Such detectors cannot be described by a linear-quadratic model. It is difficult to understand how any detector can be described by a linear quadratic model unless one supposes that there are both 1 -hit and 2-hit targets which lead to the same end point. Thus far, while the linear quadratic equation form is commonly used in radiobiology because it provides a convenient fit to experimental data, no one has identified the separate 1-hit and 2-hit targets implied by the formula. An alternate supposition is that "track and effects" in single electron tracks are equivalent to high LET radiations, and can therefore result in "ion-kill" thus yielding an initial linear slope for survival curves. This assumption is in conflict with recent experimental work on the RBE of carbon K x-rays on thin cells, where it is shown that the RBE of these ultrasoft x-rays is 1, even where one has a superabundance of electron track ends in proportion to the number of energetic electrons (Cornforth *et al.,* 1989).

For 1-hit detectors the cross section for heavy ion bombardment gives no hint of target size. Frequently one may calculate that cross section by using the point distribution of radial dose. This we call the point target approximation. When all targets close to the ion's path are activated, mistakes made in neglecting target size are obscured, for the target size is only significant in the grain count regime.

Models that assume the ion track to be needle-like and the target to be large lead to incorrect conclusions. This is the basic error in the associated volume model of Lea (1946). In Lea's model the inactivation cross section of a virus molecule is taken to be the physical cross sectional area, modified by a small δ ray correction. Experience has shown that this construct can be wrong by orders of magnitude, for it neglects the dominant importance of δ rays in the track of a 1-hit detector (Butts and Katz, 1967).

For many-target detectors the true (ion kill) cross section increases with LET raised to the mth power in the grain count regime (Katz and Sharma, 1973), (though this is hidden by the greater effect of γ kill at low LET in plots of the extrapolated cross section vs LET). At the end of the grain count regime a plateau is reached at a cross section approximating the cross sectional area of the target. With further increase in LET, the cross section then increases linearly (because the radial dose distribution varies inversely with the square of the radial distance from the ion's path, and varies quadratically with z^*/β) until thindown. Then there is a decline in cross section with an increase in LET, seen as "hooks" on a plot of σ vs LET. Exactly where the hooks occur depends on the detector parameters, but they are always associated with the kinematic limit on δ ray energy.

Though the true explanation of the hooks is relatively simple, and applies globally to all detectors, one finds a variety of rather imaginative mechanistic explanations of this phenomenon in the literature. For scintillation counters we read of "ionization quenching" and "a second order annihilation process" (Salamon and Ahlen, 1981). For biological cells we read of recombination in the "track core" (Kraft, 1987), and of a "deep sieve" effect (Almasi *et al.,* 1985) such that at low speeds the "track core" is sufficiently small to pass through the space between cellular targets in the nucleus without affecting them.

5. Interpretation of Measured Cross Sections for Biological Cells

Biological cells pose a particular problem, for the targets we presume to exist within the cell may have a relatively specific focus, as for mutation, or a rather general focus, as for cell killing, where the targets seem to be well distributed through the cell and the end point may be achieved through a wide variety of initial interactions. Here an appropriately heavy ion passing through the cell may inactivate it by intersecting an appropriate number of subtargets within the nucleus. But we do not know the size, radiosensitivity, number of targets which must be activated, their location, nor whether they are all the same in these properties. These points must be borne in mind when measured cross sections are interpreted.

Rather than using dose as the parameter through which to attempt to systematize an understanding of cell killing, one should focus attention on fluence, on the number of particles which must interact with the nucleus of a cell in order to generate the observed end point. Conceptually, dose is typically a misleading parameter on which to

base an interpretation. As an example, if the radiosensitivity of a mammalian cell is compared to that of a virus on the basis of the dose, one would conclude that the cell is orders of magnitude more radiosensitive. Yet a single electron through a virus molecule will inactivate it, but hundreds of electrons must pass through the nucleus of a cell to do so. On the basis of fluence the virus is more radiosensitive. The virus is simply much smaller so that it takes a high dose for electron tracks to intersect a significant number of virus molecules.

In track theory a "bean bag" model is used for biological cells, with the bag being the nuclear membrane, and the beans being the otherwise unidentified sensitive targets. Some number, m, of the beans must be activated for cell killing. The model is purely parametric and phenomenological rather than mechanistic. Nevertheless it is consistent with the observation that flattened cells require the transit of a greater number of a particles for killing them than round cells (Lloyd *et al.,* 1979). It is consistent with the notion that we must consider that there is a probability for cellular inactivation per unit path length of a heavy ion in its passage through the cell. Goodhead (1984) points out that, for slow a particles that are most effective per unit dose (100-200 keV/μm), there is an average of 1 lethal lesion per 0.03-0.06/μm of integrated track length through nuclear material, for a variety of cells. The bean bag model is also consistent with calculations explaining the "hooks" observed at Darmstadt in plots of cross section vs LET (Katz *et al.,* 1985). The track width regime and the subsequent thindown is generated by the interaction between beans and δ rays rather than between the entire nucleus and δ rays. When the cross section for bean inactivation exceeds its plateau value, so also will the cross section for cellular inactivation. Our prediction of these hooks may well be the only prediction in real time that any physical model has made in radiobiology, for the hooks were predicted some 15 years before they were observed. Though the present model is quantitative, it is parametric and phenomenological. We would prefer a quantitative mechanistic model. Unfortunately there is presently no quantitative mechanistic model describing the several end points relevant to the response of biological cells to irradiation.

The reason the measured cross section approximates the geometric cross section of the nucleus for cell killing is that there is a sufficient number of intersectable beans along many chords through the nucleus. But we do not require that there be a sufficiency of beans even to the outermost fringe of the nucleus. It should not therefore be surprising that the inactivation cross section is somewhat smaller than the cross sectional area of the cell nucleus, for cell killing, even into the track width regime.

This model disagrees with a current view that the shoulders of survival curves after γ irradiation are always due to repair processes. Our model also disagrees with some strongly held views about the sizes of relevant targets and the energy deposition required for their inactivation (Goodhead, 1989). There is also a conflict between the use of a multi-target model for γ ray inactivation and the frequently observed initial slope of these survival curves. Yet this model is the only one presently available which has explained and even predicted the Darmstadt hooks, or the variation of RBE and OER with LET. One must separate the cases of agreement from those of disagreement, as a spur to further insights.

Where the targets are more specific than for cell killing, as for mutations, one may expect that these targets are not so generously distributed through the nucleus. The bean bag is then smaller, and correspondingly so is the measured cross section. If the targets are quite specific, and are indeed very small we return to the situation earlier observed with dry enzymes and viruses, or with nuclear emulsions, namely that the inactivation cross section of these targets may be many times larger than the targets themselves because of the importance of the δ ray brush (Waligorski *et al.,* 1987). Such large cross sections do not necessarily arise from damage outside the immediate area of the target (Upton, 1988).

6. Cross Sections vs Microdosimetry

The principal goal of a physical experiment with beams of particles is the determination of an interaction cross section. This tells us the probability that the end point has been achieved by the passage of a single particle. It represents the maximum amount of information that can be achieved from such experiments. The cross section can only be determined from track segment irradiations.

Experiments using a spread Bragg peak are of no use to this end, nor are experiments performed with neutrons, whatever their practical importance. Irradiations with beams of electrons or photons cannot yield a cross section if interaction with a single electron or photon cannot yield the end point of interest. Though extensive microdosimetric and radiobiological measurements have been made with these irradiations, they cannot result in the determination of cross sections.

By its very nature microdosimetry is unable to yield a cross section. When the radiation field produced by a homogeneous beam of particles is decomposed to individual energy depositions and their fluctuation, knowledge of track structure is completely lost. But it is only through knowledge of track structure that a cross section can be calculated. Even when the radial distribution of event sizes is measured microdosimetrically, a cross section cannot be obtained unless one converts these

measurements to the average radial dose, after the fashion of track theory. This is because there is no experimental basis for calibrating the effect of energy depositions, for making a translation from energy depositions in small volumes to the probability of creating a biological effect in these volumes. Many claims have been made of the essential and fundamental character of energy deposition in volumes of size appropriate to DNA molecules. Yet neither prediction nor correlation with experimental radiobiology has been made. Nor can it be made without calibration. Often one hears of energy deposition thresholds in radiation effects. But radiation effects are statistical in character and have no energy deposition thresholds.

Experience has shown that not a single cross section has been calculated from microdosimetric information, from knowledge of the energy deposition in small volumes, whether determined by proportional counters or from Monte Carlo calculations, whether from γ rays or neutrons or heavy ion beams. This in spite of the fact that such studies have been undertaken for more than 30 years, worldwide. Where the goal of radiobiological modeling is the calculations of action cross sections, microdosimetry has been impotent and will continue to be so for inherent and fundamental reasons.

Acknowledgments

This work is supported by the U.S. Department of Energy.

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