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TITLE THE SOFT-X-RAY EXPERIMENT REVISITED: A THEORETICAL ANALYSIS

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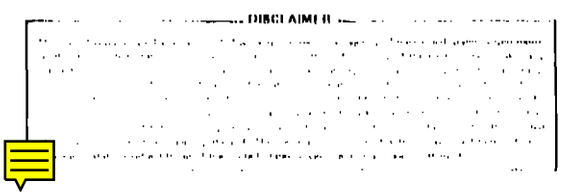

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THE SOFT X-RAY EXPERIMENT REVISITED - A THEORETICAL ANALYSIS

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Abstract

The generalized formulation of the theory of Dual Radiation Action (TDRA) deals quantitatively with the process of sublesion-lesion production in sensitive sites irradiated with *uniform* fields of ionizing radiation. In this paper modifications of this formalism necessary to treat the case of *attenuated* fields of radiations are described. As an application recent survival data obtained with soft x-ray experiments are analyzed. It is shown that a) given a linear-quadratic dose-effect relation with constant β (the coefficient of D^2 in this relation), b) the function $\gamma(x)$ (i.e., probability for two energy transfers separated by x to produce a lesion) can be obtained with the aid of Monte-Carlo generated proximity functions, and c) this $\gamma(x)$ may be successfully utilized to account for survival results obtained, with the same cell line, using α particles.

A. Introduction

It is currently accepted that the initial spatial distribution of primary radiation products in irradiated biological material is fundamental to the observed effect. Recently, experimental and theoretical evidence have indicated that physical quantities averaged over cellular (i.e., micrometer) dimensions may not be sufficient, and finer details of the energy deposition processes may be required. In this respect, some data which have the potential to yield useful information are the results (1,2) of cell survival and chromosome aberration measurements after irradiation by soft x-rays whose secondary electrons have ranges significantly smaller than cell dimensions.

The generalized formulation of the Theory of Dual Radiation Action (TDRA) (3) treats the formation of lesions in sensitive sites exposed to uniform fields of radiation. Because of the strong attenuation suffered by very soft x-rays in traversing a cell a modification of the original treatment is necessary. The basic theory and its modifications for attenuated fields are first

described. The cell survival results of the soft and hard x-ray experiments (1) are then analyzed in terms of this modified formalism which is then used to account for the effects of high-LET α-particles measured in the same series of experiments (4).

B. Theoretical treatment

The TDRA (3) assumes that:

a) ionizing radiation produces units of elementary injury, termed sublesions, in the sensitive part of the cell at a rate proportional to the energy transferred (deposited) locally, and

b) sublesions interact pairwise in a distance-related manner with probability g(x) to produce lesions, i.e., injury directly responsible for the observed end-point.

Thus the average number of lesions in a volume, V, of uniform sensitivity for producing sublesions is:

$$\bar{\epsilon} = \int_0^\infty g(x)\,\tau(x)\,dx \qquad (1)$$

where $\tau(x)\,dx$ is the average number of pairs of sublesions per cell whose distance apart is between x and x + dx. $\tau(x)$ is comparatively simple to evaluate and for a given dose, D and density ρ is given by (3)

$$\tau(x)\,dx = \tfrac{1}{2} c^2 \rho V D\,[t(x) + 4\pi x^2 \rho D]dx, \qquad (2)$$

where c is a constant relating the energy deposited locally to the number of sublesions produced (see "assumption a", above) and t(x)dx, termed the *proximity function* of energy transfers, is the expected energy in a spherical shell of radius x and thickness dx centered at a randomly selected energy transfer point (here the random selection of transfer points is weighted by the energy deposited at these points). The two terms in Eq(2) correspond to the interaction of ($c\rho VD$) sublesions produced throughout the sensitive volume with other sublesions coming from the same track (intratrack lesions first term) or from different, uncorrelated tracks (intertrack lesions second term).

It is also necessary to account for the fact that, on average, only a

fraction (≤ 1) of the spherical shell considered above will contribute to sublesion formation, i.e., to consider the random geometric overlap between the track and the matrix. For a uniform field, this fraction is denoted $s(x)/4\pi x^2$ yielding a final expression for $\bar{\varepsilon}$ of the familiar linear-quadratic type:

$$\bar{\varepsilon} = \tfrac{1}{2} c^2 \rho V D \left[\int_0^\infty g(x) \frac{s(x)}{4\pi x^2} t(x)dx + \rho D \int_0^\infty g(x)s(x)dx \right] \quad (3)$$

The situation for an attenuated radiation field is rather more complex. Consider a sensitive matrix of arbitrary shape exposed to an exponentially attenuated x-ray field in the z direction (Fig. 1). The expected number of sublesions in a slice of area A(z) and width dz centered at z is

$$c\rho A(z)dz\ D_0 \exp(-\mu z) \quad (4)$$

where D_0 is the dose at $z = 0$ and μ is the relevant absorption coefficient for the radiation.

The number of intra-track sublesions in a spherical shell of radius x centered in the slice is

$$c\ t(x)\ dx\ \ s(x|z)/4\pi x^2 \quad (5)$$

where $s(x|z)/4\pi x^2$ is the expected fraction of the volume of the spherical shell overlapping the sensitive matrix at a given z.

The average number of intra-track lesions per cell is then given by:

$$\bar{\varepsilon}_1 = \tfrac{1}{2} c^2 \rho D_0 \int_0^\infty dx\ t(x)\ g(x) \int dz \frac{s(x|z)}{4\pi x^2} A(z)e^{-\mu z} \quad (6)$$

For a spherical sensitive matrix $s(x|z)$ and $\bar{\varepsilon}_1$ can be evaluated in closed form (5). Practically, those x-rays which suffer significant attenuation across the cell also have secondary electrons whose ranges are considerably smaller than a reasonable estimate of the size of the sensitive matrix. Thus for values of x within the range of the proximity functions $s(x|z)/4\pi x^2$ 1

and Eq(6) yields

$$\bar{\epsilon}_1 = c^2 \rho V \bar{D} \int_0^\infty t(x)\, g(x)\, dx \qquad (7)$$

where $\bar{D}$ is the average dose over the sensitive matrix. $s(x|z)$ was calculated using Monte-Carlo techniques, utilizing the fact (3) that this function is proportional to the distribution of distances between random points in the sensitive matrix. For all the geometries considered the approximation used in obtaining Eq(7) was found to be justified.†

To examine inter-track lesions consider again Fig. 1. The number of sublesions in a small volume dv at the center of the shell is

$$c\rho D_0 \exp(-\mu z)\, dv \qquad (8)$$

and the number of sublesions in a small volume dv_1 in the shell is

$$c\rho D_0 \exp(-\mu z_1)\, dv_1 \qquad (9)$$

Multiplying expressions (8) and (9) together with $g(x)$ and integrating over all the allowed values of x, z and z_1, the expected yield of inter-track lesions per cell is obtained. An analytical calculation of this quantity for a spherical sensitive matrix can be found in Ref. 5.

The final expression, however, can be obtained using the following observations. Consider a matrix with a *uniform* distribution of sensitive sites irradiated with an *attenuated* radiation field. With respect to any sublesion, all the sublesions produced by independent events (i.e., those sublesions responsible for inter-track lesions) are distributed in an attenuated fashion across the matrix. Formally, this is equivalent to the situation where a matrix with an *attenuated* distribution of sensitive sites is exposed to a *uniform* field of radiation. The result, Eq(3), for the yield of inter-track lesions can therefore be directly applied:

†For hard x rays this approximation is not correct. However in this case Eq(3), can be applied with no modification.

$$\bar{\varepsilon}_2 = \tfrac{1}{2} c^2 \bar{V}(\mu) \rho^2 D_o^2 \int_0^\infty g(x)\, s(x;\mu)\, dx \qquad (10)$$

where

$$\bar{V}(\mu) = \int A(z)dz\, e^{-\mu z}$$

and $s(x;\mu)$ is the function corresponding to $s(x)$ of Eq(3), for the case of an attenuated matrix [$s(x;0) \equiv s(x)$]. The notation in Eq(10) shows explicitly the μ dependence, where applicable. $s(x;\mu)$ may be calculated, using Monte Carlo techniques, for any geometric configuration describable on a computer. Thus an exponentially decreasing sample of points is generated in the volume and then the distribution of distances between all points in the sample is calculated. Fig. 2 shows calculated values of $s(x;\mu)$ for two geometries and different values of μ.

From Eqs(7) and (10) the average yield of lesions may be expressed in the form

$$\bar{\varepsilon}(\bar{D}) = \alpha\bar{D} + \beta \cdot \kappa(\mu)\, \bar{D}^2 \qquad (11)$$

where

$$\alpha = \tfrac{1}{2} c^2 \rho V \int t(x) \frac{s(x;0)}{4\pi x^2} g(x)\, dx, \qquad (12)$$

$$\beta = \tfrac{1}{2} c^2 \rho^2 V \int g(x)\, s(x;0)\, dx \qquad (13)$$

$$\kappa(\mu) = \frac{V}{\bar{V}} \int \gamma(x) \frac{s(x;\mu)}{s(x;0)} 4\pi x^2 \rho\, dx, \qquad (14)$$

$$\gamma(x) = \frac{s(x;0)\, g(x)}{4\pi x^2 \rho \int s(x;0)\, g(x)\, dx} \qquad (15)$$

Also, from Eqs(12-15):

$$\kappa(0) = 1 \qquad (16)$$

and

$$\xi = \alpha/\beta = \int t(x)\,\gamma(x)dx \qquad (17)$$

For short-ranged particles the approximation $s(x;0)/4\pi x^2 \approx 1$ was used in Eq(12).

For a given cell line, β in Eq(11) is a constant independent of the radiation quality. However the coefficient of $\bar{D}^2$ does depend on μ.

C. Application to experimental results

The analysis of the V79 cell survival data (1) after irradiation with soft and hard x-rays was performed under the assumption (6) that each increment in the number of lesions eliminates a proportionate fraction of cells able to form colonies, i.e.

$$S(\bar{D}) = \exp[-\varepsilon(\bar{D})] \qquad (18)$$

The immediate object of the analysis is to evaluate the function $\gamma(x)$ of Eq(14). In principle, using Eqs(18) and (11) the data may be fitted to obtain the parameters α and β. Then using the values of ξ corresponding to different radiations and known proximity functions, Eq(17) may be unfolded to yield $\gamma(x)$. Here, however, $\kappa(\mu)$ itself depends on the unknown $\gamma(x)$. An iterative procedure was thus followed. In the first step, in Eq(15) $s(x;\mu)/s(x;0)$ was replaced by $\delta_0 = s(0;\mu)/s(0;0)$. Then $\kappa(\mu)$ becomes:

$$\kappa_0(\mu) = \frac{V}{\bar{V}}\,\delta_0$$

Using this value the experimental data were fitted, using a maximum likelihood criterion, to yield an initial estimate of α and β. An estimate of $\gamma(x)$ was then obtained yielding [Eq(14)] an improved value of $\kappa(\mu)$. The procedure was repeated until convergence was obtained, which in the present case occured after one iteration.

The proximity functions, $t(x)$ were calculated using a detailed Monte Carlo electron transport code (7) in which the energies and positions of all non-elastic events were recorded and analyzed according to the definition of $t(x)$ given above. The results are shown in Fig. 3 for the three soft x-rays (carbon, electron energy 270 eV; aluminum 955 and 516 eV; titanium, 4026 and 516 eV) and for 250 kVp x-rays. $\gamma(x)$ was then obtained by solving, using

numerical methods (8), the following set of linear algebraic equations and inequalities:

$$\xi_i = \sum_j t_i(x_j)\,\gamma(x_j)\,\Delta x_j \qquad i = 1,2,3,4 \tag{19}$$

$$\sum_j x_j^2\,\gamma(x_j)\,\Delta x_j = (4\pi\rho)^{-1} \tag{20}$$

$$\gamma(x_j) \geq 0 \tag{21}$$

Eq(20) follows directly from Eq(15). The result is shown in Fig. 4.

Fitted survival curves calculated with Eqs(11), (14) and (18) are shown in Fig. 5 (solid lines). A fit was also carried out allowing β to change between radiation (Fig. 5, broken lines). Using the standard F test it was not possible to reject the hypothesis of a constant β at a 95% level of confidence. It is interesting to note, however, that when the attenuation factor, $\kappa(\mu)$, was removed from Eq(11) the hypothesis of a constant β *could* be rejected indicating the importance of treating attenuation adequately.

The calculated function $\gamma(x)$ shown in Fig. 4 can be used predictively. This was done for the survival data following irradiation with 28 keV/μm α-particles, obtained in the same series of experiments (4). Again, the proximity function was calculated using a proton Monte Carlo transport code (7). The value of ξ [Eq(17)] and β thus obtained yield the theoretical survival curve shown in Fig. 6. The agreement with the data is gratifying.

Acknowledgements

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Figure Captions

Fig. 1 Schematic representation of the irradiation geometry discussed in the text.

Fig. 2 Results of Monte-Carlo calculations of the function $s(x;\mu)$ for a 3.5 μm-radius spherical site and a 7 μm-radius hemispherical site. The dotted, dashed and full curves, respectively, were calculated using the attenuation coefficients of titanium, aluminum and carbon x rays. In subsequent caculations the hemispheriodal geometry was used as being the most realistic.

Fig. 3 Calculated proximity functions of energy transfer for carbon, aluminum, titanium and 250 kVp x rays, and for 28 keV/μm α particles.

Fig. 4 Calculated gamma function for V79-4 Chinese hamster cells.

Fig. 5 Linear-quadratic fits to experimental data for V79 cell survival after irradiation by carbon, aluminum, titanium and 250 kVp x rays. The full curves are the results of global fits using a constant β (see text); the dashed curves are the results of individual fits in which β was allowed to vary.

Fig. 6 Calculated survival curve for 28 keV/μm α particles using the proximity function of Fig. 4. The experimental survival data are from Ref. 4.

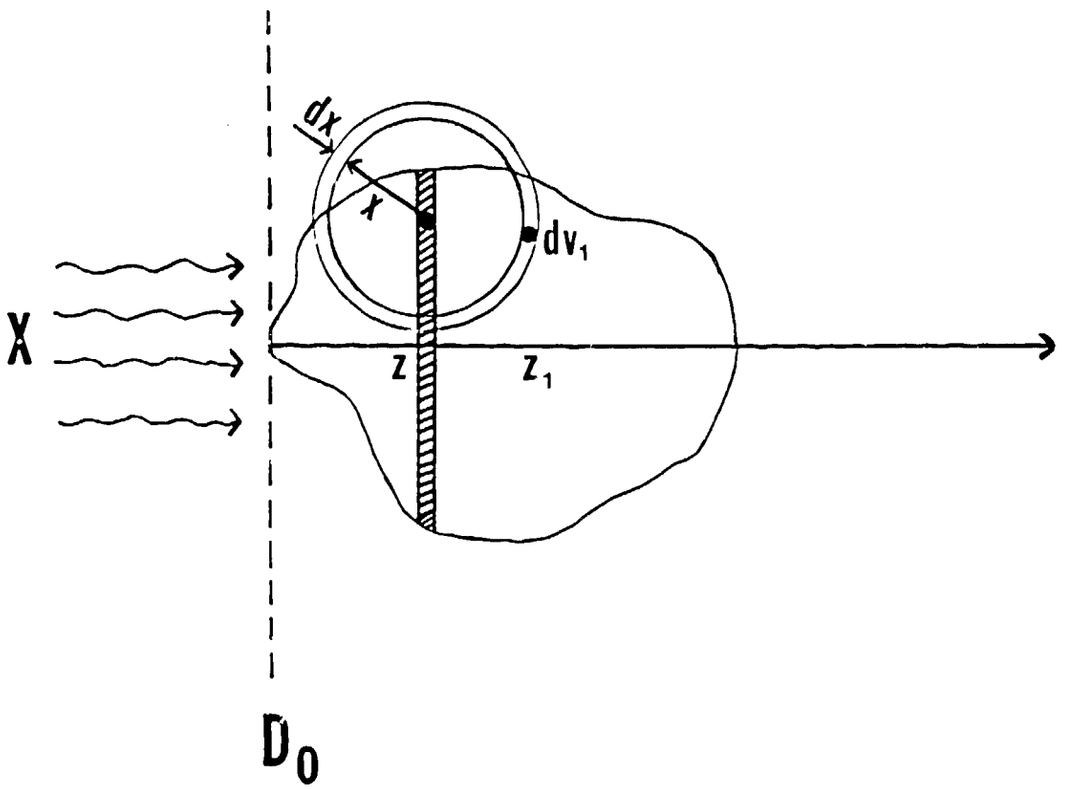

Fig.1

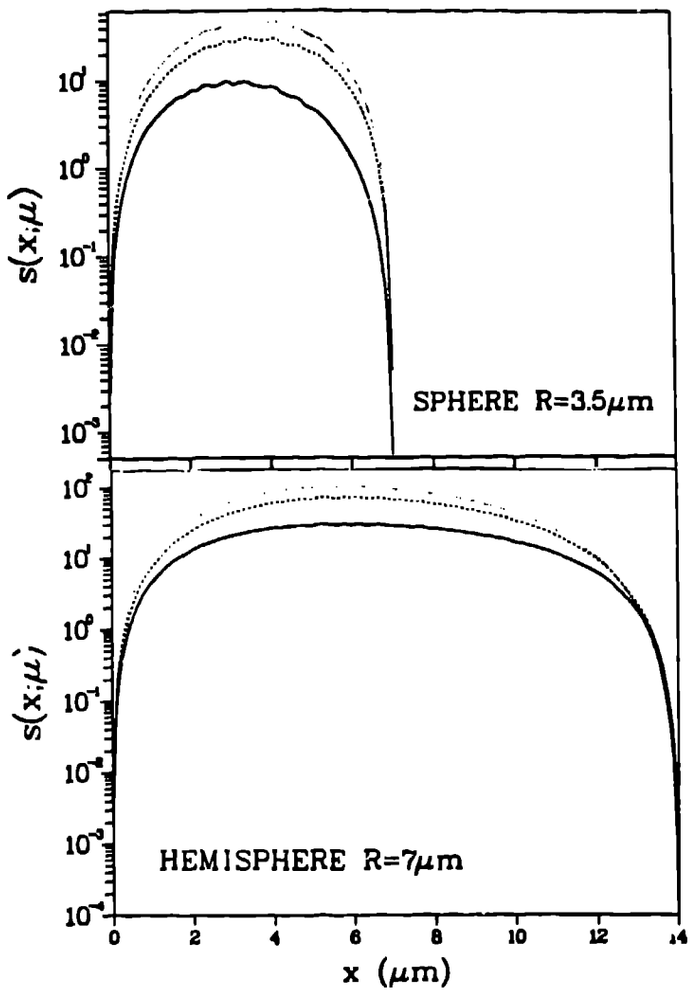

Fig. 2

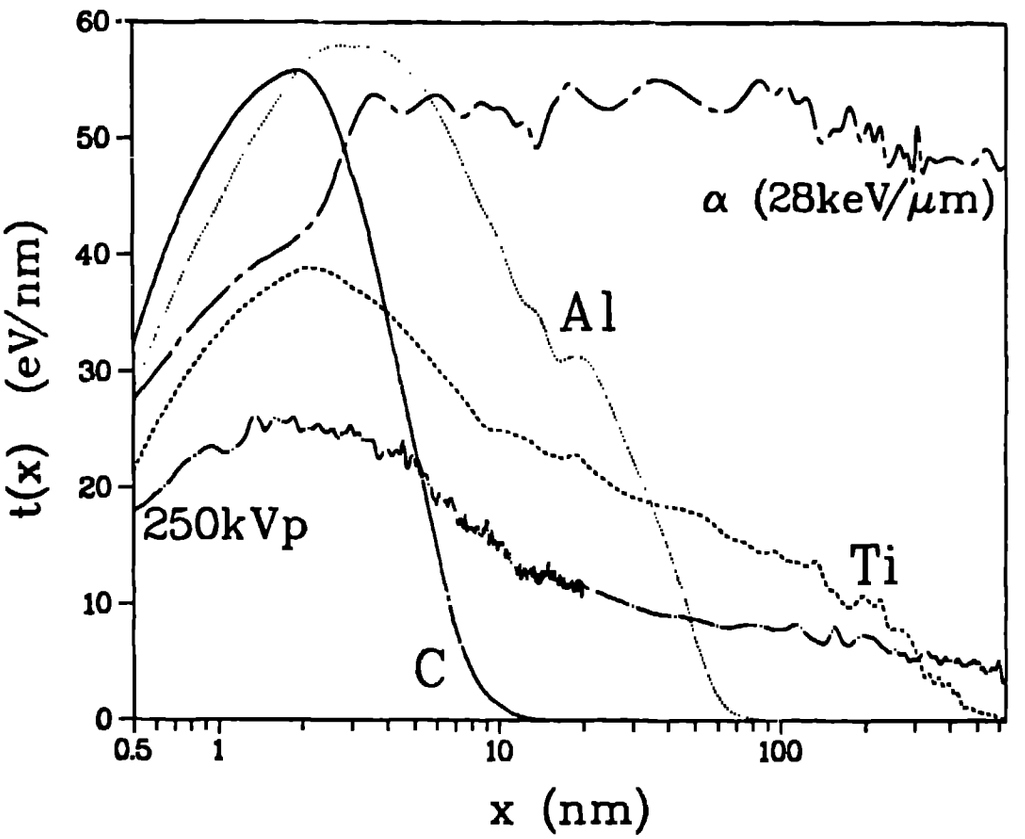

Fig. 3

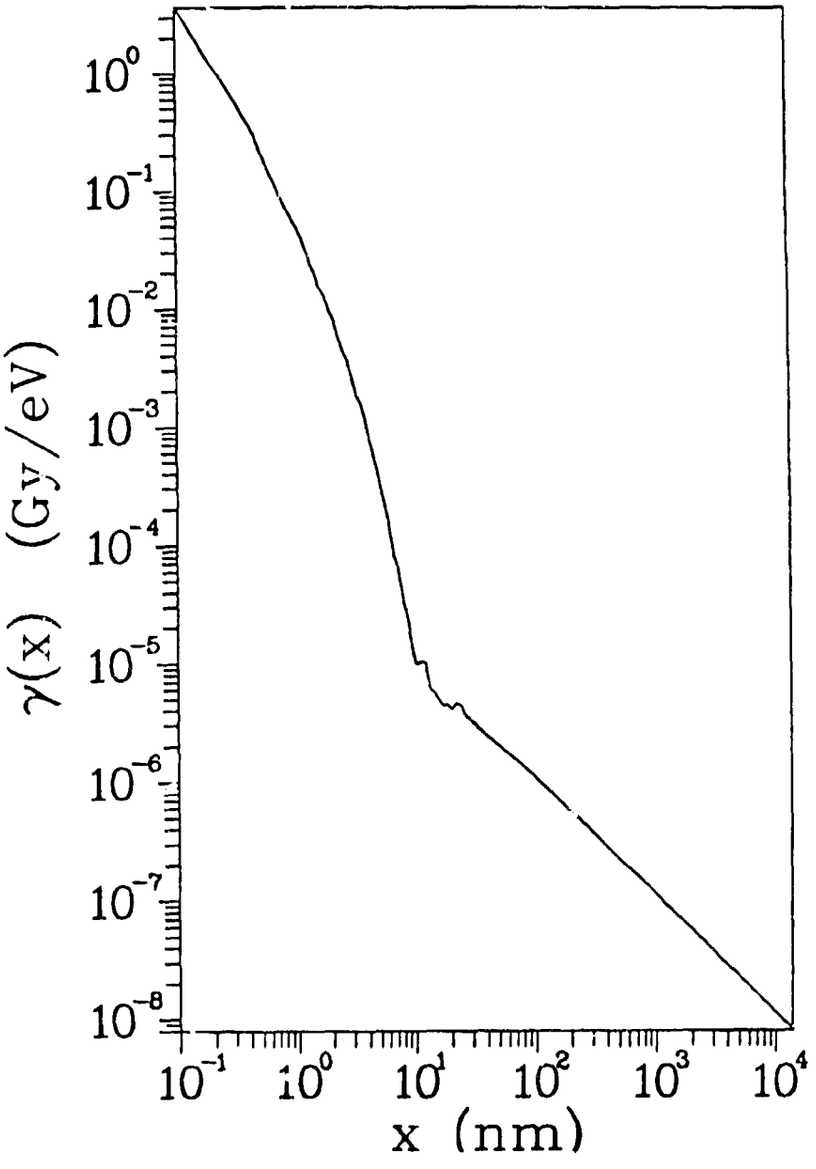
$\gamma(x)$ (Gy/eV)
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
10^{-7}
10^{-8}
10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4}
x (nm)

Fig.4

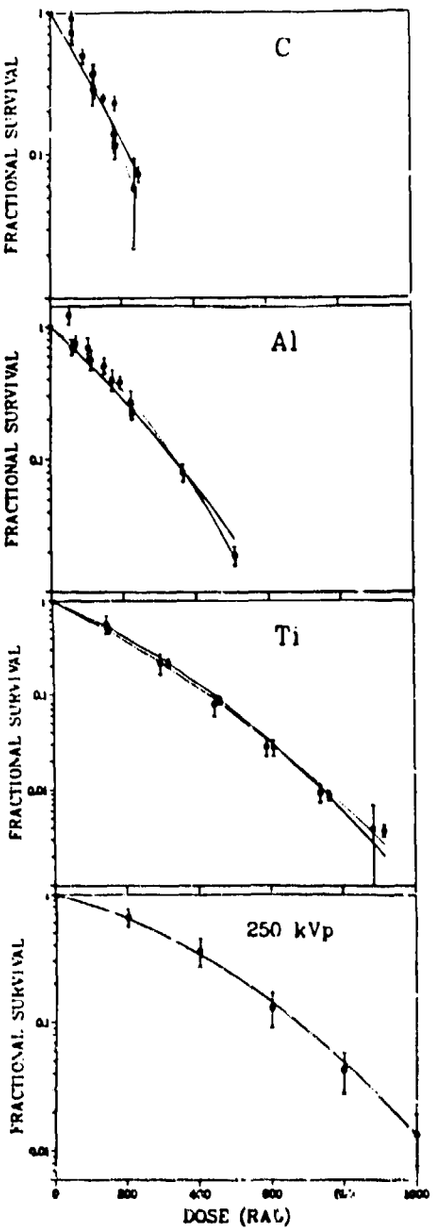

Fig.5

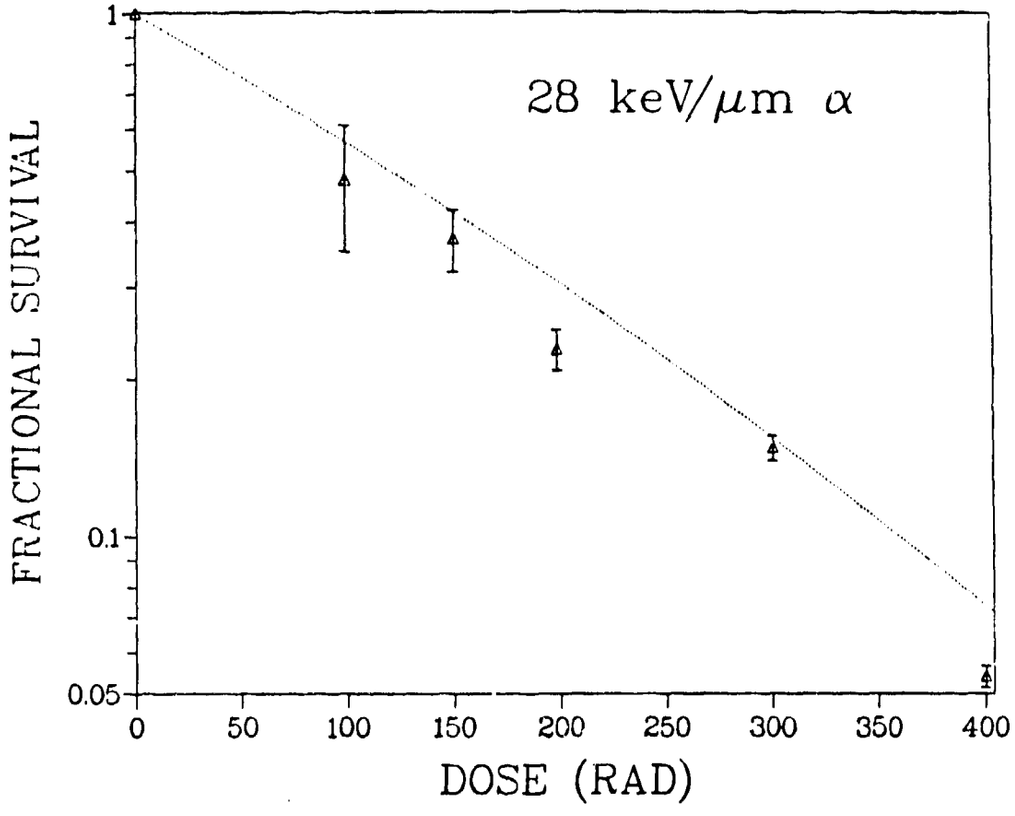
28 keV/μm α
FRACTIONAL SURVIVAL
1
0.1
0.05
0
50
100
150
200
250
300
350
400
DOSE (RAD)

Fig.6