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Hit-Size Effectiveness Theory Applied to High Doses of Low LET Radiation for Pink Mutations in Tradescantia

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Hit-Size Effectiveness Theory Applied to High Doses of Low LET Radiation for Pink Mutations in *Tradescantia**

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Abstract

A hit-size effectiveness function which represents the probability of inducing a pink mutation in *Tradescantia* as a function of lineal energy density has been obtained (1) using observed pink mutation data for seven different radiation qualities and their respective single event microdosimetric spectra. In obtaining this function only the linear portions of dose-response curves were used. A significant improvement of the concepts embodied in the proposed hit-size effectiveness theory would be the demonstration of its applicability at high doses (where multiple hits are produced) and high dose rates (at which no significant biological repair takes place). In this article details are given on preliminary calculations of the pink mutation frequency in *Tradescantia* at 1, 5, 10, 20, and 60 rads for 250 kVp x rays, using the multi-hit spectra and the hit-size effectiveness function obtained on the basis of single hit microdosimetric spectra as outlined in (1). A comparison of the calculated and observed pink mutation frequencies indicate excellent agreement and suggests the possibility of obtaining the hit-size effectiveness function from high dose biological-effect data obtained using low-LET radiations.

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Introduction

A hit-size effectiveness theory has been proposed and developed by Bond and Varma (2) to predict pink mutations in Tradescantia at low doses and dose rates. If the applicability of this concept can be shown over a wide range of biological end points and systems, then this theory can provide reliable risk estimates at low doses for radiation protection purposes. A hit-size effectiveness function was obtained from single event microdosimetric spectra and the observed pink mutation frequency for seven different radiation qualities at low dose, where the condition that number of cells hit or dosed was much less than those exposed, was satisfied. Applicability and predictive power of this theory has been tested for the production of pink mutations in Tradescantia exposed in a mixed radiation field (gamma and neutron) produced by a californium source (3). A significant improvement on this theory would be the demonstration that the hit-size effectiveness function can be obtained from a single dose-response curve for low LET radiation. As a first step towards testing the feasibility of obtaining a hit-size effectiveness function from a single dose-response curve, we have made preliminary calculations of multi-hit spectra at four selected high doses and used this spectra and the hit-size effectiveness function previously obtained to calculate the pink mutation frequency for 250 kVp x rays.

Approach

A measured single event microdosimetric spectrum for 215 kVp x rays (4) was used to calculate the multi-hit spectra at doses of 1, 5, 10, 20, and 60 rads. Knowing the mean frequency F of events per rad for a given simulated

site diameter, mean number of events m produced by an absorbed dose D was calculated using the following expression:

$$m = F \cdot D \tag{1}$$

This mean frequency of events or hits was calculated at doses of 1, 5, 10, 20, and 60 rads. Multi-hit spectra at these doses were calculated using standard procedures already published by Kellerer et al. (5). Since details are provided in reference (5) only a brief description of the procedure is provided. The probability P(n) for the occurrence of n events is given by the Poisson distribution as

$$P(n) = \frac{e^{-m} m^n}{n!} \tag{2}$$

where m is the number of events at a given absorbed dose D. Let $f_n(y)$ represent the probability that in n events a total lineal energy density of y is produced then $f_n(y)$ is given by:

$$f_n(y) = \int_0^\infty f_1(y') f_{n-1}(y-y') dy' \tag{3}$$

where $f_1(y')$ is the probability that a linear energy density y' is produced in a single event, this probability is measured using a proportional counter. $f_D(y)$ is defined as the probability that a lineal energy density y will be deposited due to a mean number of events m produced by an associated absorbed dose D.

$$f_D(y) = \sum_{n=0}^{\infty} P(n) f_{n(y)} \tag{4}$$

From the above it is clear that $f_1(y)$ is independent of dose whereas $f_D(y)$ is not.

These multi-hit spectra calculations were made using the Central Computing Facility of the Brookhaven National Laboratory.

The hit-size effectiveness function obtained by using the single event microdosimetric spectra and published in reference (1) had the following form:

$$E(y) = 0 \qquad y \leq 0.4$$

$$E(y) = 1 \qquad y \geq 76.0 \qquad (5)$$

$$E(y) = 1.5 \times 10^{-4}\, y + 1.9 \times 10^{-5}\, y^2, \qquad 4 < y < 76 \text{ keV}$$

where y is the lineal energy density($\varepsilon / \bar{\ell}$) in keV/μm, and ε is energy deposited in keV in a simulated site diameter d, and $\bar{\ell}$ = 2/3 d in microns. E(y) is the probability of inducing pink mutation as a function of y. This function is plotted in Figure 1.

Predicted pink mutation frequency M for 215 kVp x rays at doses of 1, 5, 10, 20, and 60 rad was obtained by integrating the product of multi-hit spectra and the effectiveness function E(y), over all possible values of y. Thus,

$$M = \int_0^\infty E(y)\, f_D(y)\, dy \qquad (6)$$

Results and Discussions

Figure 2 shows previously measured (6) variation of pink mutation frequency per hair as a function of absorbed dose for 250 kVp x rays. Also, shown are the presently calculated values at doses of 1, 5, 10, 20, and 60 rads. Table 1 lists the calculated pink mutation frequencies per hair at 1, 5, 10, 20, and 60 rads for simulated site diameters of 2, 3, and 4 microns. Table 2 lists the observed and predicted pink mutation frequencies at different doses for a site diameter of 3.0 microns, also listed are 100 x the (predicted-observed)/predicted. Table 3 lists the microdosimetric quantities

y_F, y_D, and mean number of events m for various doses and simulated site sizes. Figure 3 shows a typical plot of $y^2f(y)$ vs y for multi-hit and single hit spectra at a dose of 20 rads.

From Table 2 it can be seen that agreement between the observed and calculated values is within $\pm$ 15%, this is excellent since the uncertainty associated with observed values is about $\pm$ 15%. It should be emphasized that none of the parameters in the hit-size effectiveness function developed in reference (1) were adjusted for these calculations. A simulated site diameter of 3 micron was obtained. Maximum dose chosen for these calculations was 60 rads to avoid complications that arise in interpretation of observed dose response curves for pink mutations in Tradescantia at higher doses due to cell killing and other modifying factors. A site diameter of 5.3 microns was obtained in the analysis using single hit spectra. This site diameter depends on the number of cells per hair. The number of cells per hair was estimated at 2.5, since, this number is an estimate the difference obtained for the single hit and multi-hit analysis is not considered significant.

From these preliminary studies it is clear that the hit-size weighting theory can be used to predict reasonably well the pink mutation frequency for Tradescantia at low as well as high doses for low-LET radiation. The possibility of obtaining a hit-size effectiveness function from a single low-LET dose response curve is being explored. Although the hit-size effectiveness function has been developed for autonomous single cell systems, data now becoming available for animal tumor systems for several radiation qualities may permit evaluation of a hit-size effectiveness function for various animal cancer types. If the applicability of this approach is shown to be valid over

a wide range of biological end points and systems, then this approach would obviate the need for determination of future "absorbed dose-response," functions over a wide range of LETs. This approach would also simplify concepts of quality factor and "standard radiation," Relative Biological Effectiveness (RBE), Q (quality factor), which are currently used in radiation protection.

Table 1

Predicted Pink Mutations Per Hair at Doses of 1, 5, 10, 20, and 60 rads for Simulated Site Diameters of 2.0, 3.0, and 4.0 Microns

Dose	Pink Mutation/Hair x 10^{-3}		
(rads)	2.0 micron	3.0 micron	4.0 micron
1	.55	.57	.61
5	3.1	3.7	4.3
10	7.1	9.1	12.0
20	18.0	25.0	33.0
60	85.0	144.0	269.0

Table 2

Observed and Predicted Pink Mutations Per Hair At Various Doses for a Simulated Site Diameter of 3.0 Microns

Dose (rads)	Pink Mutation/hair x 10^{-3}		$\frac{\text{(Predicted-Observed)}}{\text{Predicted}} \times 100$
	Observed	Predicted	
1	0.59	0.57	- 3.5
5	3.5	3.7	+ 5.0
10	9.0	9.1	+ 1.0
20	25.0	24.6	- 2.0
60	125.0	144.0	+13.0

Table 3

$\bar{y}_F$, $\bar{y}_D$, and Mean Number of Hits for Various Doses and Simulated Site Sizes

Dose (rads)	$\bar{y}_F$ keV/μm			$\bar{y}_D$ keV/μm			m		
	2.0 μ	3.0 μ	4.0 μ	2.0 μ	3.0 μ	4.0 μ	2.0 μ	3.0 μ	4.0 μ
1	1.4	1.6	1.8	3.2	3.4	3.8	0.15	0.33	0.59
5	1.9	2.7	4.1	4.0	5.2	6.9	0.7	1.7	3.0
10	2.5	4.6	7.9	4.9	7.4	11.0	1.5	3.3	5.9
20	4.1	8.8	16.0	6.9	12.0	19.0	3.0	6.6	12.0
60	12.0	27.0	47.0	15.0	29.0	50.0	8.9	20.0	35.0

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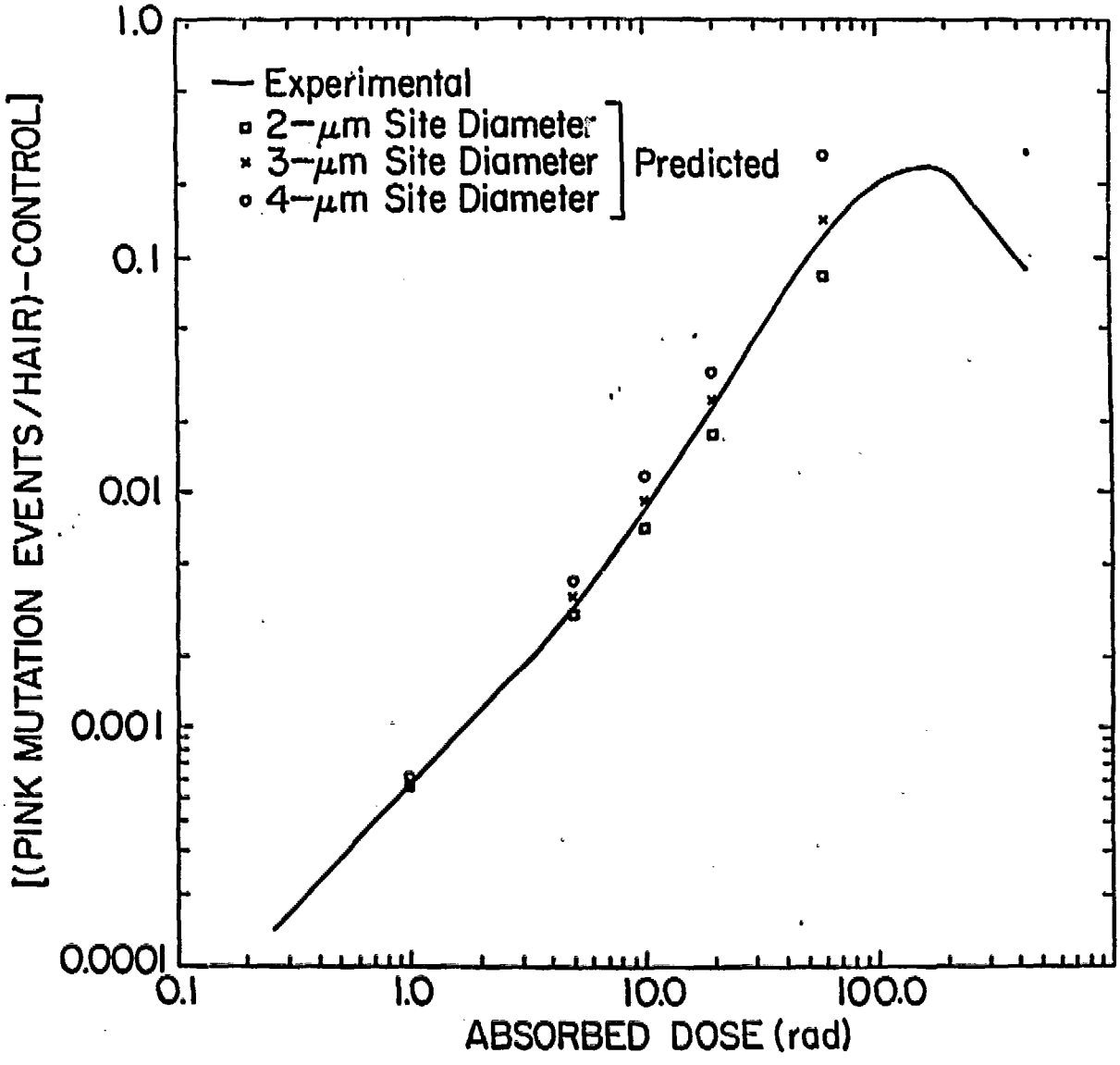
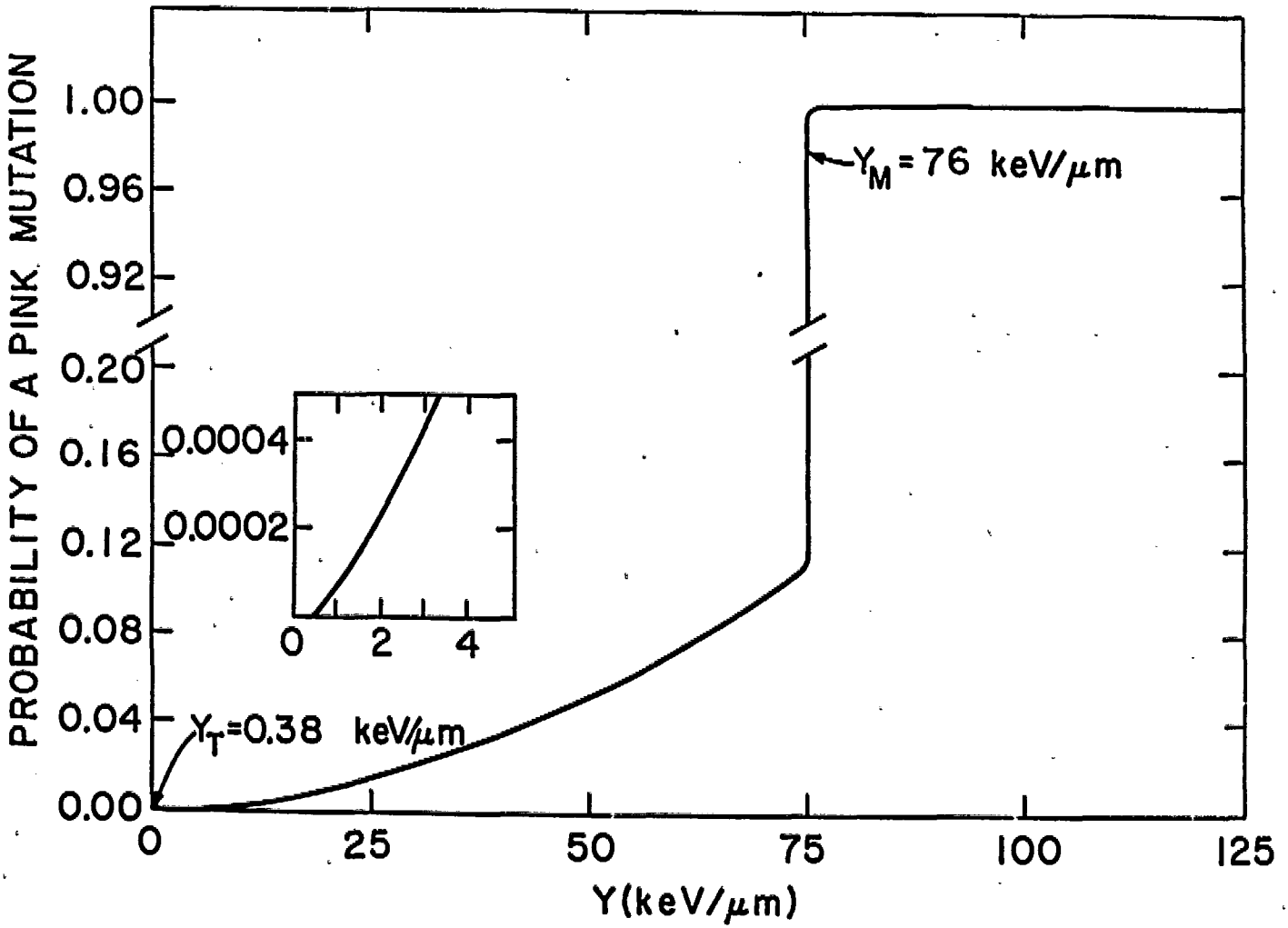
Figure Captions

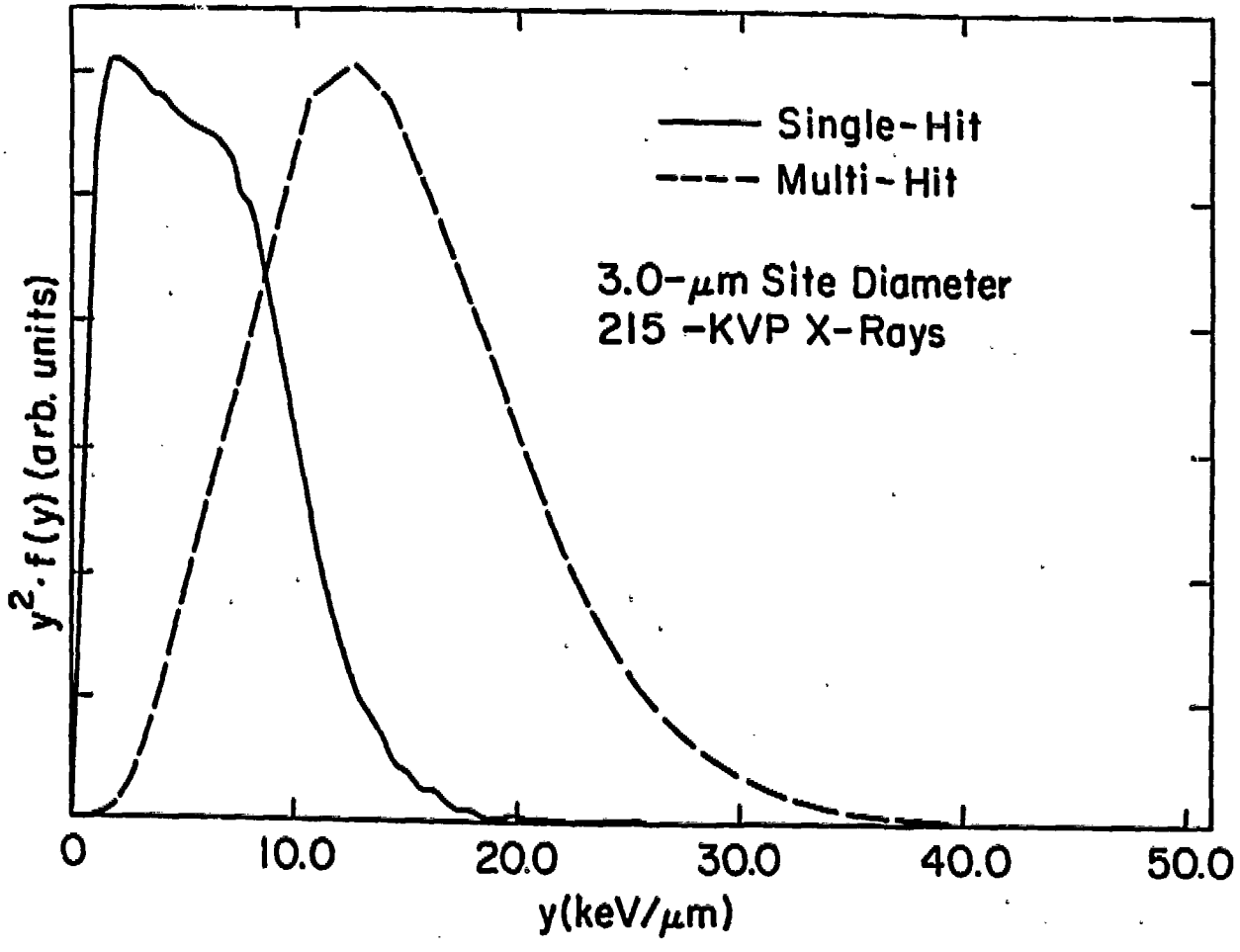
Figure 1 - A plot of (pink mutation events/hair) - control as a function of absorbed dose for 250 kVp x rays. Also shown are predicted values of pink mutations/hair obtained using multi-hit spectra and the hit-size effectiveness theory.

Figure 2 - A plot of the probability of a pink mutation as a function of lineal energy y, obtained using the single-hit microdosimetric spectra and hit-size effectiveness theory.

Figure 3 - A plot of $y^2f(y)$ as a function of y for 215 kVp x rays, both single-hit (-) and multi-hit (---) distributions are plotted. These plots are at a dose of 20 rad in a 3 micron site diameter.


1.0
0.1
0.01
0.001
0.0001
[(PINK MUTATION EVENTS/HAIR)-CONTROL]
Experimental
2-μm Site Diameter
3-μm Site Diameter
4-μm Site Diameter
Predicted
0.1
1.0
10.0
100.0
ABSORBED DOSE (rad)


PROBABILITY OF A PINK MUTATION
1.00
0.96
0.92
0.20
0.16
0.12
0.08
0.04
0.00
0.0004
0.0002
0
2
4
Y_M = 76 keV/μm
Y_T=0.38 keV/μm
0
25
50
75
100
125
Y(keV/μm)


Single-Hit
Multi-Hit
3.0-μm Site Diameter
215 -KVP X-Rays
$y^2 \cdot f(y)$ (arb. units)
0
10.0
20.0
30.0
40.0
50.0
y(keV/μm)