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RBEOER: A FORTRAN Program for the Computation of RBEs, OERs, Survival Ratios, and the Effects of Fractionation Using the Theory of Dual Radiation Action

M. Zaider
J. F. Dicello

los alamos
scientific laboratory
of the University of California
LOS ALAMOS, NEW MEXICO 87545

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RBEOER: A FORTRAN PROGRAM FOR THE COMPUTATION OF RBEs, OERs, SURVIVAL RATIOS, AND THE EFFECTS OF FRACTIONATION USING THE THEORY OF DUAL RADIATION ACTION

by

M. Zaider and J. F. Dicello

ABSTRACT

The computer code RBEOER calculates RBEs, OERs and survival curves as a function of the dose delivered to a biological system and the temporal distribution of the dose (fractionation). The method of calculation is based on the theory of dual radiation action. The basic formalism and the input parameters are described. A sample output is presented.

I. INTRODUCTION

This report describes the computer program RBEOER, which calculates relative biological effectiveness (RBE) and oxygen enhancement ratios (OER) as a function of the dose delivered to a biological system while taking into account the effects of the temporal distribution of the dose (fractionation). Survival curves, under both aerobic and anoxic conditions are calculated also. The program is based on the theory of dual radiation action as developed by Kellerer and Rossi.[1] The main input to the program consists of microdosimetric spectra characterizing the distributions of the energy deposited by the radiation. Other parameters, related to the type of particle utilized in irradiations, the size of the sensitive site in the biological system, and the temporal conditions of the irradiations are read in as input data. In its most complete form, the calculation describes an experimental situation in which the dose is delivered at a specified dose rate, in a number of fractions separated by a constant time interval, with recovery, repair, saturation, and oxygen effects specifically included. Less complex experiments (e.g., single dose, no recovery, etc.) can be described also.

The RBEOER program was written for the needs of the research work at the biomedical channel at LAMPF. In its present form, this code runs on a PDP-11/45 computer under the RSX-11 6.2D version. A plotting package[2] for the Tektronix 4010 terminal is used for graphic displays. With minimal changes, this program could be run on any medium-size memory computer.

II. CALCULATIONAL METHOD

A. Basic Formalism

This section briefly describes the theoretical concepts utilized in the RBEOER code. A more complete and detailed description of these concepts can be found in the original paper by Kellerer and Rossi.[1]

The basic assumption in the theory of dual radiation action is that the yield of elementary biological lesions, $\varepsilon(z)$, is a quadratic function of the specific energy, z:

$$\varepsilon(z) = kz^2 , \qquad (1)$$

where z is the local energy concentration per unit mass within microscopic regions (sites). It should be noted that Eq.(1) is also a working definition of a biological lesion; i.e., any process satisfying Eq.(1) can be described by this theory. Let $f(z;D)dz$ be the probability that, for a given absorbed dose D, the specific energy z has a value between z and z + dz. Then, the yield of elementary lesions corresponding to an absorbed dose D can be calculated:

$$\varepsilon(D) = \int_0^\infty \varepsilon(z) f(z;D)dz = k \int_0^\infty z^2 f(z;D)dz = k\, \overline{z^2}(D). \qquad (2)$$

As shown in Ref. 1,

$$\overline{z^2}\,(D) = z_{1D}\, D + D^2, \qquad (3)$$

where

$$z_{1D} = \int_0^\infty z^2 f_1(z)dz \Big/ \int_0^\infty z f_1(z)dz. \qquad (4)$$

Here $f_1(z)$ is the probability distribution of z for single-event depositions (called single-event spectrum). $f_1(z)$ can be calculated from a measured microdosimetric spectrum. From (2), (3), and (4), it follows that:

$$\varepsilon(D) = k(z_{1D}D + D^2). \qquad (5)$$

Equation (5) is the basic description of the relationship between delivered dose and biological effect in the theory of dual radiation action. One can see that for doses much smaller than z_{1D}, the dose-effect dependence is practically linear, while for doses much larger than z_{1D} we have a quadratic dependence of the biological effect on dose. This can explain, for instance, the known quadratic and linear dose-effect relations for x rays and neutrons, respectively (z_{1D} for 14-MeV neutrons is about 50 times higher than for x rays) in the range of low doses.

On a practical side, one has to determine $f_1(z)$ through a microdosimetric measurement and then calculate z_{1D}. z_{1D} is a function of the simulated site diameter d. Correspondingly, the biological interpretation of the results is, therefore, dependent on the site size chosen.

If a linear term is present in Eq. (1)

$$\varepsilon(z) = k(\lambda_o z + z^2), \tag{6}$$

one can show that the new dose-response relation becomes

$$\varepsilon(D) = k[(z_{1D} + \lambda_o)\, D + D^2]. \tag{7}$$

Let D and D_x be the doses delivered utilizing heavy particles and x rays, respectively, in order to obtain the same effect

$$\varepsilon(D) = \varepsilon(D_x). \tag{8}$$

One can calculate the RBE

$$RBE = \frac{D_x}{D}\ , \tag{9}$$

or

$$RBE = \frac{2k/k_x(\lambda_o + z_{1D} + D)}{\lambda_{ox} + z_{1Dx} + \sqrt{(\lambda_{ox} + z_{1Dx})^2 + 4[(\lambda_o + z_{1D})D + D^2]k/k_x}}\ , \tag{10}$$

with obvious notations for the heavy particles and the x rays. There are four quantities: k/k_x, λ_{ox}, λ_o, and the site diameter d (through z_{1D}, z_{1Dx}) that must be specified from microdosimetry or biology. For a spherical site of diameter d, the specific mean energy $\bar{z}_1$ is related to the mean lineal energy y_D by:

$$\bar{z}_{1D}(\text{rad}) = 20.4 \frac{\bar{y}_D(\text{keV}/\mu\text{m})}{d^2(\mu\text{m}^2)} . \quad (11)$$

The lineal energy is defined as the energy deposited in a site divided by the mean pathlength through the site. Throughout the rest of the report y and z will be used interchangeably. One should keep in mind that in most of the cases, microdosimetric spectra are expressed in terms of y, while the expression (11) can be used to convert from one quantity to another. Also, we shall restrict ourselves to the simplified case for which $\lambda_o = \lambda_{ox} = 0$.

D. Saturation Effect

It has been observed experimentally[3,4] that the RBE decreases for particles having a mean lineal energy of more than about 125 keV/μm. This "saturation effect" has been interpreted as an overkill effect resulting from a waste of energy deposited in the biological sites. In order to take into account this effect in the present model, Eq.(1) is changed to

$$\varepsilon(z) = kz_o^2[1 - e^{-(z/z_o)^2}]. \quad (12)$$

z_o is a parameter characterizing the specific energy at which saturation effects become important. For $z << z_o$ we regain the original relation (1). One has now:

$$\varepsilon(D) = kz_o^2 \int_0^\infty [1 - e^{-(z/z_o)^2}] f(z;D)dz. \quad (13)$$

This expression is not a simple function of D. One can make, however, the following remark: the saturation effect is expected to be important for particles characterized by a high z_{1D}. For these particles, the dose-effect relation (5) will be dominated by the linear term for doses not exceeding z_{1D}. It is therefore reasonable to account for the saturation effect by writing:

$$\varepsilon(D) = k(z_{1D}^* D + D^2) \quad (14)$$

with

$$z_{1D}^* = z_o^2 \int_0^\infty [1 - e^{-(z/z_o)^2}] f_1(z)dz \Big/ \int_0^\infty zf_1(z)dz . \quad (15)$$

C. The Oxygen Effect

In order to account for the oxygen effect, the assumption is made that under anoxic conditions the relation (1) becomes

$$\varepsilon_A(z) = k\rho(z)\, z^2 , \tag{16}$$

or, considering the saturation effect:

$$\varepsilon_A(z) = kz_o^2[1 - e^{-(\rho\, z/z_o)^2}] \tag{17}$$

and

$$\varepsilon_A(D) = kz_o^2 \int_0^\infty [1 - e^{-(\rho\, z/z_o)^2}]\, f(z;D)dz , \tag{18}$$

where $\rho(z)$ is determined from experimental data. Figure 1 shows the results of such an analysis obtained from data presented in Refs. 1, 3, and 4. One can see that for lineal energies up to about 10 keV/μm, ρ is constant and equal to 0.62. For lineal energies above 170 keV/μm, ρ is equal to 1 (no oxygen effect). One can use arguments similar to those utilized in obtaining the relations (14) and (15) for the saturation effect and write:

$$\varepsilon_A(D_A) = k[z_A^* D_A + \rho^2(o) D_A^2] , \tag{19}$$

with the subscript A denoting the anoxic case, and

$$z_A^* = z_o^2 \int_0^\infty [1 - e^{-(\rho\, z/z_o)^2}]\, f_1(z)dz \Big/ \int_0^\infty zf_1(z)dz .$$

The oxygen enhancement ratio (OER) is defined:

$$\mathrm{OER} = \frac{D_A}{D} \tag{20}$$

for

$$\varepsilon(D) = \varepsilon_A(D_A). \tag{21}$$

$$\mathrm{OER} = \frac{2(z^*_{1D} + D)}{z^*_{1DA} + \sqrt{{z^*_{1DA}}^2 + 4\rho^2(o)D(z^*_{1D} + D)}} \quad . \tag{22}$$

D. Dose-Rate Effects and Fractionation

The relation (5) is interpreted in the theory of dual radiation action[1] as representing contributions from intratrack interactions (the linear term) and intertrack interactions (the quadratic term). Under this interpretation, the linear term is independent of dose-rate effects, while the quadratic term should decrease with increasing exposure time. This decrease is formally represented by a coefficient q defined as:

$$q = \int_0^\infty \tau(t)\ h(t)dt, \tag{23}$$

where $\tau(t)$ is the recovery function. For the present, it has been assumed that

$$\tau(t) = e^{-t/t_o} . \tag{24}$$

$h(t)$ is the distribution of time intervals t between dose increments. $h(t)$ can be expressed as:

$$h(t) = \frac{2}{D^2} \int_0^\infty I(s)\ I(s + t)ds , \tag{25}$$

where $I(s)$ is the dose rate as a function of time. It can be shown (see the Appendix) that if the dose is delivered in n equal fractions of c min each, and which are separated by the time b min, then:

$$q = \frac{2}{n^2c^2} \left\{ nt_oc + nt_o^2(1 - \frac{1}{x}) + t_o^2(x + \frac{1}{x} - 2)[\frac{n}{1-s} - \frac{s(1-s^n)}{(1-s)^2}] \right\} , \tag{26}$$

$$\text{with} \quad x = e^{-c/t_o} \qquad s = e^{-b/t_o} . \tag{27}$$

In the special case of a single fraction dose (n = 1) one obtains:

$$q = \frac{2t_o^2}{c^2} [\frac{c}{t_o} + e^{-c/t_o} - 1]. \tag{28}$$

The dose-effect relation becomes

$$\varepsilon(D) = k[z^*_{1D} D + qD^2] . \tag{29}$$

New expressions for RBE and OER, which include the dose-rate effects, could now be easily calculated, and will be presented in the next section.

E. Summary

In this section the relations presented before, which include effects from saturation, oxygen, dose rate, and fractionation, are summarized. These expressions are utilized in the RBEOER computer code:

$$RBE = 2\frac{k}{k_x}\frac{q}{q_x}\frac{\frac{z^*_{1D}}{q} + D}{\frac{z^*_{1Dx}}{q_x} + \left[\left(\frac{z^*_{1Dx}}{q_x}\right)^2 + 4\frac{k}{k_x}\frac{q}{q_x} D \left(\frac{z^*_{1D}}{q} + D\right)\right]^{\frac{1}{2}}} \tag{30}$$

$$OER = \frac{2\left(\frac{z^*_{1D}}{q} + D\right)}{\frac{z^*_{1DA}}{q} + \left[\left(\frac{z^*_{1DA}}{q}\right)^2 + 4\rho^2(o)D\left(\frac{z^*_{1D}}{q} + D\right)\right]^{\frac{1}{2}}} \tag{31}$$

$$z_{1D} = 20.4\,\frac{y_D}{d^2} \tag{32}$$

$$z^*_{1D} = z_o^2 \int_0^\infty [1 - e^{-(z/z_o)^2}]\, f_1(z)dz \Big/ \int_0^\infty z f_1(z)dz \tag{33}$$

$$z^*_{1DA} = z_o^2 \int_0^\infty [1 - e^{-(\rho(z)z/z_o)^2}]\, f_1(z)dz \Big/ \int_0^\infty z f_1(z)dz \tag{34}$$

$$q = \frac{2}{n^2c^2}\left\{nt_oc + nt_o^2\left(1-\frac{1}{x}\right) + t_o^2\left(x + \frac{1}{x} - 2\right)\left|\frac{n}{1-s} - \frac{s(1-s^n)}{(1-s)^2}\right|\right\} \tag{35}$$

where: $x = e^{-c/t_o}$ $\qquad$ $s = e^{-b/t_o}$ (36)

z = specific energy (rad)
y = lineal energy (keV/μm)
d = site diameter (μm)

z_o = saturation-effect constant (rad)
$\rho(z)$ = oxygen-effect parameter
n = number of fractions
t_o = recovery-effect constant (min)
c = time/fraction (min)
b = time between fractions (min)
$f_1(z)$ = distribution of single-event energy depositions

Survival curves are calculated from

$$S/S_o = e^{-k(z^*_{1D} D + qD^2)} . \tag{37}$$

III. THE CODE RBEOER

A. Input

The program RBEOER is written in FORTRAN IV. In its present form, the program reads the input through any PDP computer terminal. Although most of the question-answer type of input is self-explanatory, a description of some of the input parameters follows.

As mentioned in the Introduction, the main input of the RBEOER code consists of microdosimetric spectra. These spectra, for the heavy particles and x rays, should exist on the system disc as data files NAMEIN.DAT, where NAMEIN can be any 6-character name. Among the many ways a microdosimetric spectrum can be represented, we have chosen the $Y^2f(Y)$ vs Y representation, where Y is the event size in keV/μm. The event size is defined as the energy deposited in a site divided by the site diameter. A data file consists of 50 numbers $Y^2f(Y)$ (in format 5F10.2) corresponding to event sizes Y equally spaced on a logarithmic scale. The Y values are calculated in the program from

$$Y(i) = 10^{(0.1 \times i - 2.1)}, \qquad I = 1,2,3,\ldots,50 . \tag{38}$$

For other representations of the microdosimetric distributions, straightforward changes could be made in the program.

The next two input data consist of y_o [as defined in Eqs.(11)and(12)] and the average pathlength in the detector. For a spherical counter, for instance, the average pathlength is 2/3 of the detector diameter.

There is no prediction given in the present model for the value of the proportionally constant k between $\varepsilon(z)$ and z^2 [see Eq.(1)]. k may be empirically deduced from a measured survival curve, if a fit of the type

$$S/S_o = e^{-(\alpha D + \beta D^2)} \tag{39}$$

is made. As recognized by Kellerer and Rossi[1] k represents a problematic parameter, as the values of predicted RBEs depend directly on the ratio k/k_x. Only a direct comparison with experimental data could show whether, and under what conditions, unique values for k and k_x could fit a complete set of results consistently.

The program can be run with or without recovery effects. In the first case, the dose rate (rad/min), number of fractions, the time between fractions (h) and the recovery constant t_o [see Eq. (24)] for both the heavy particle and x rays are read in.

The plotting of the survival curves and RBE as a function of dose is performed using subroutines from a Tektronix 4010 graphical package.[2] Should any other type of terminal be used, the plotting routines should be turned off. This is done in the program by a YES/NO input parameter corresponding to the last question.

A sample of the input procedure is shown in Fig. 2.

B. Output

RBE, OER, and survival ratios are calculated for doses ranging from 10 to 10 000 rads in 16 steps. Survival curves for the heavy particles and x rays (aerobic and anoxic) are plotted as $\log_{10}(10^5 S/S_o)$ vs dose. RBE is plotted as a function of dose on a logarithmic scale. In order to obtain the next plot one has to hit a "carriage return."

Figures 3-8 show a sample output corresponding to microdosimetric spectra for pions (Fig. 9) and x rays[6] (Fig. 10).

A detailed analysis with the present code of the available experimental data (biology and physics) obtained for pion fields at the biomedical channel at LAMPF is in progress and will be reported elsewhere.

IV. COMMENTS

The present treatment of recovery and fractionation effects is simplified. A more realistic model should include such factors as changes in the cell radiosensitivity throughout the fractionation scheme, repopulation of surviving cells, tumor regrowth, etc. A comparison between the model in its present form and biological data will reveal the extent to which these additional factors must be incorporated.

ACKNOWLEDGMENTS

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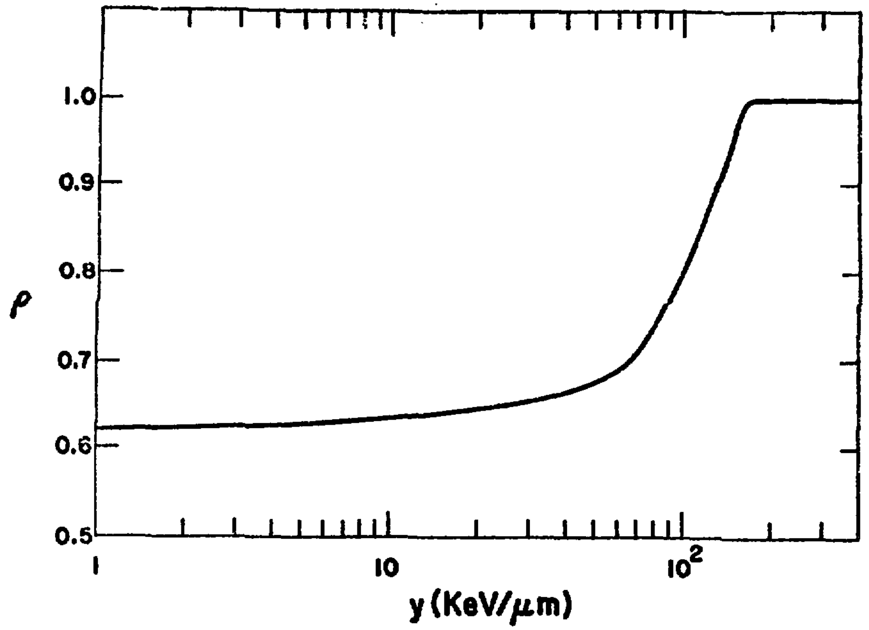

Figure 1
The dependence of the factor ρ on the lineal energy y. The data are obtained from Refs. 1, 3, and 4.

```
MCR>RUN RBEOER
IF YOU WANT OUTPUT ON TI TYPE 5, ON LP TYPE 6:  6
TYPE IN DATA FILE NAME FOR PARTICLE (6 CHAR.):  BFOA12
TYPE IN DATA FILE NAME FOR X-RAYS (6 CHAR.):  XRAY12
ALL THE INPUT FORMATS ARE F10.5
Y ZERO FOR THE SATURATION EFFECT (KEV/MICR)=125.
DETECTOR DIAMETER (MICR.)=1.0
K FOR HEAVY PARTICLE=    0.0000021
K FOR X-RAYS=    0.0000021
ANY RECOVERY EFFECTS ? YES OR NO :  Y
FIRST,THE HEAVY PARTICLE
DOSE RATE (RAD/MIN) =  5.
T ZERO FOR RECOVERY (MIN) =  300.
HOW MANY FRACTIONS ?  10.
TIME BETWEEN FRACTIONS (HOURS)  24.
NOW,FOR X-RAYS
DOSE RATE (RAD/MIN) =  5.
T ZERO FOR RECOVERY (MIN) =  300.
HOW MANY FRACTIONS ?  10.
TIME BETWEEN FRACTIONS (HOURS)  24.
        **WARNING !!**
IF YOU DON T USE A 4010 TERMINAL,
THE ANSWER TO THE NEXT QUESTION
IS NO
DO YOU WANT PLOTS ?  N
```

Figure 2
An example of an input procedure for the code RBEOER.

```
DATA FILE FOR HEAVY PARTICLE:  BROA12
DATA FILE FOR X-RAYS:  >RAYS1
  YZERO=  125.0  KEV/MICRON
  DIAMETER=   1.30  MICRONS

 HEAVY PARTICLE

   YF         YD          YSTAR     YSTAR ANOXIC
   0.79       13.86       14.09      7.54

 DOSE RATE (RAD/MIN)       T ZERO        K        FRACTIONS   TIME BETWEEN FRACTIONS
   5.00                   300.00     0.21E-05      10.              24.0 HOURS

 X-RAYS

   YF         YD          YSTAR     YSTAR ANOXIC
   1.76       3.81        5.70       2.20

 DOSE RATE (RAD/MIN)       T ZERO        K        FRACTIONS   TIME BETWEEN FRACTIONS
   5.00                   300.00     0.21E-05      10.              24.0 HOURS
```

DOSE(RAD)	RBE	OER	OERX	Q(T)	Q(T)X	S/S0 HP	S/S0 ANOXIC	S/S0 X	S/S0 XANOXIC
10.	2.40	1.87	2.54	0.10	0.10	0.10E+01	0.10E+01	0.10E+01	0.10E+01
20.	2.34	1.86	2.49	0.10	0.10	0.99E+00	0.10E+01	0.10E+01	0.10E+01
30.	2.28	1.86	2.45	0.10	0.10	0.99E+00	0.99E+00	0.10E+01	0.10E+01
50.	2.19	1.85	2.37	0.10	0.10	0.98E+00	0.99E+00	0.99E+00	0.10E+01
100.	2.02	1.84	2.24	0.10	0.10	0.96E+00	0.98E+00	0.98E+00	0.99E+00
200.	1.81	1.81	2.09	0.10	0.10	0.92E+00	0.96E+00	0.96E+00	0.98E+00
300.	1.68	1.79	1.99	0.10	0.10	0.88E+00	0.94E+00	0.94E+00	0.96E+00
400.	1. 9	1.78	1.93	0.10	0.10	0.84E+00	0.91E+00	0.91E+00	0.95E+00
500.	1.52	1.76	1.89	0.10	0.10	0.79E+00	0.88E+00	0.88E+00	0.92E+00
1000.	1.34	1.72	1.78	0.10	0.10	0.57E+00	0.75E+00	0.74E+00	0.77E+00
2000.	1.26	1.68	1.71	0.10	0.10	0.21E+00	0.50E+00	0.37E+00	0.40E+00
3000.	1.15	1.66	1.68	0.10	0.10	0.57E-01	0.22E+00	0.11E+00	0.14E+00
4000.	1.12	1.65	1.67	0.09	0.09	0.10E-01	0.14E+00	0.25E-01	0.35E-01
5000.	1.10	1.65	1.66	0.09	0.09	0.14E-02	0.61E-01	0.40E-02	0.63E-02
8000.	1.07	1.64	1.64	0.09	0.09	0.50E-06	0.26E-02	0.31E-05	0.62E-05
10000.	1.06	1.63	1.64	0.08	0.08	0.22E-09	0.19E-03	0.63E-08	0.17E-07

Figure 3
A sample output listing for the code RBEOER.

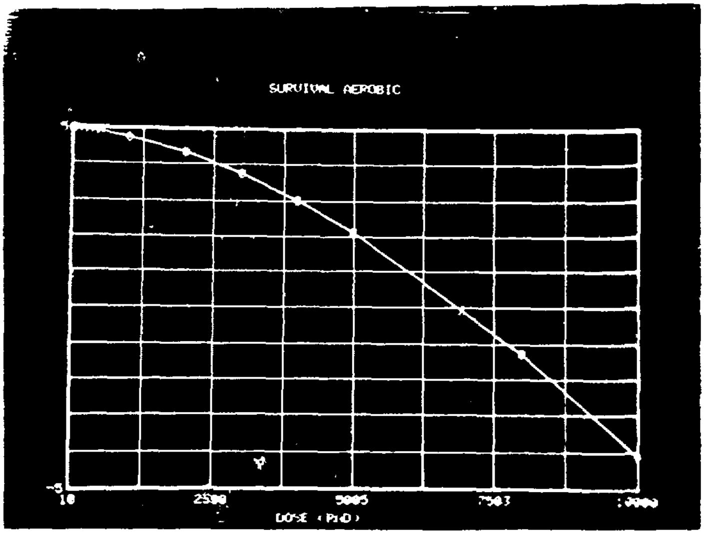

Figure 4
Calculated aerobic cell-survival curve for negative pions.

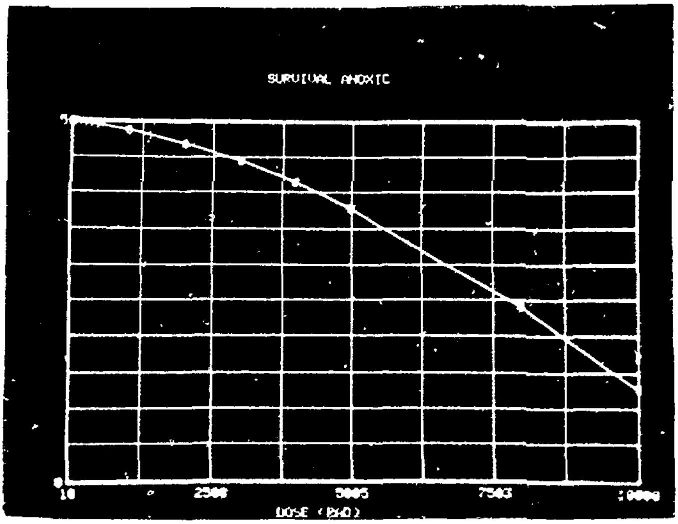

Figure 5
Calculated anoxic cell survival curve for negative pions.

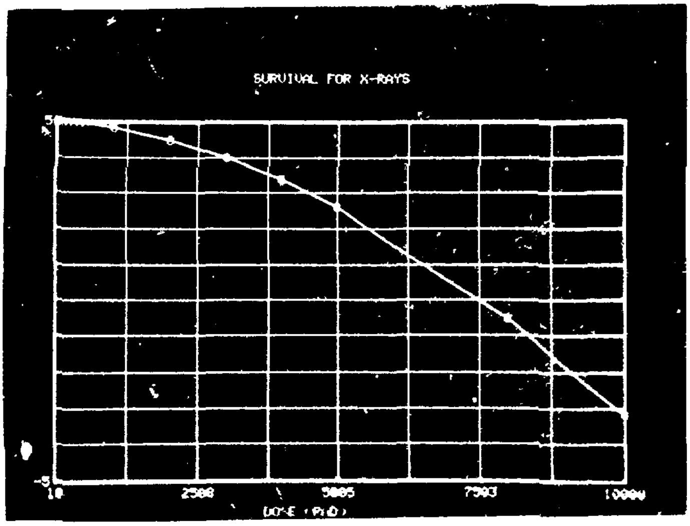

Figure 6
Calculated aerobic cell survival curve for x rays.

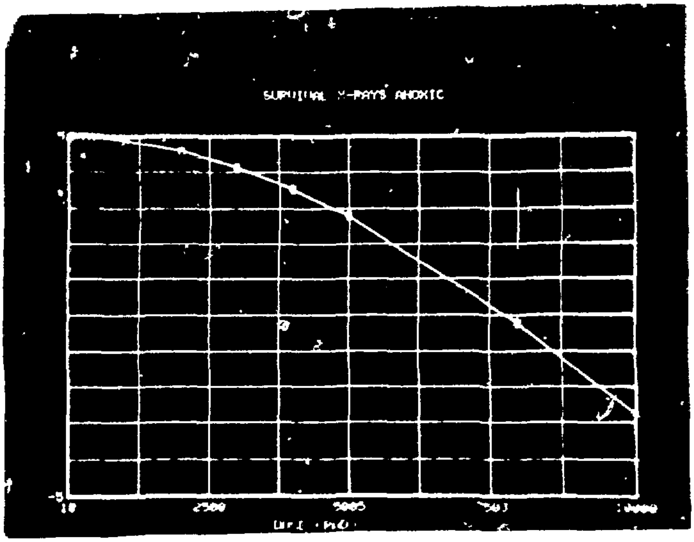

Figure 7
Calculated anoxic cell survival curve for x rays.

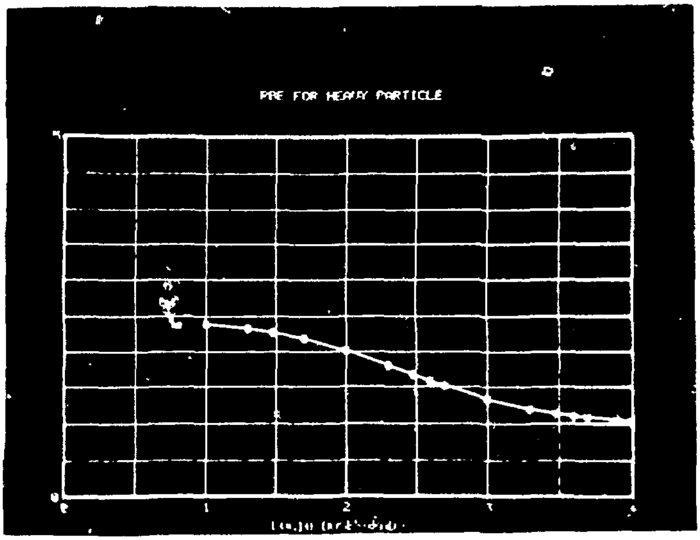

Figure 8
Calculated RBE as a function of the dose delivered for negative pions.

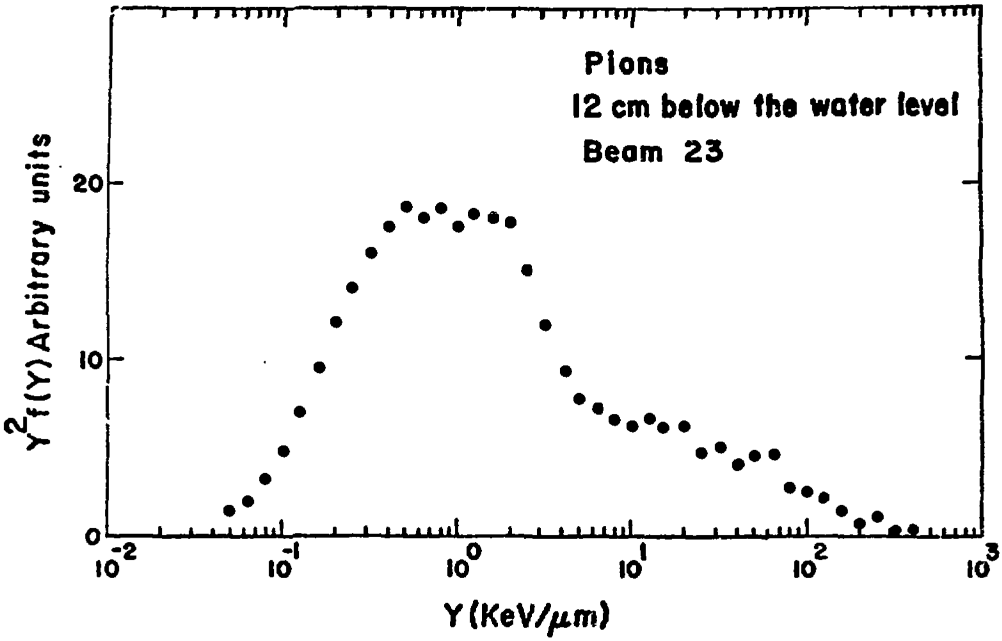

Figure 9
Microdosimetric distribution for negative pions (Ref. 5) The abscissa represents the event size Y and the ordinate is the product of Y and the dose distribution Yf(Y), where f(Y) is the frequency distribution in Y.

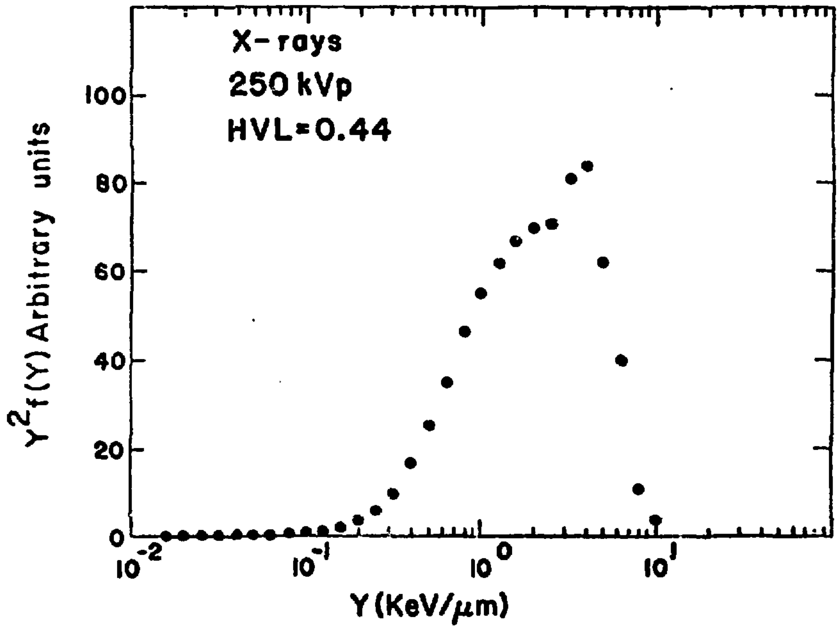

Figure 10
Microdosimetric distribution for x rays (Ref. 6). The same representation as in Figure 9 was used.

APPENDIX

In this Appendix, we calculate explicitly the factor q defined in Sec. II, Eq. (23). Suppose the dose is delivered in n equal fractions, separated by the time b. The dose rate a is constant and each fraction is delivered over a time c. This situation is represented in Fig. A-1.

Analytically, this dose-rate distribution can be represented by

$$f(x) = a \sum_{m=1}^{n} \Pi\left(\frac{x - mb}{c}\right) , \tag{A1}$$

where $\Pi(x)$ is defined

$$\Pi(x) = \begin{cases} 1 & |x| < \frac{1}{2} \\ 0 & |x| > \frac{1}{2} \end{cases} \tag{A2}$$

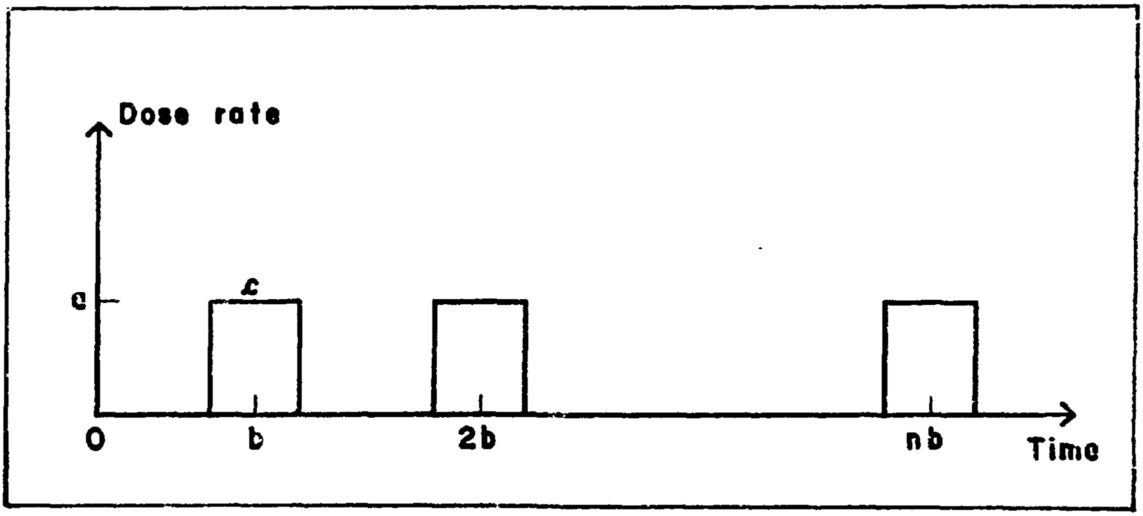

Figure A-1
Schematic representation of the temporal distribution of the dose rate used in the calculation of the Appendix.

The distribution of time intervals x between dose increments can be calculated from

$$I(x) = \int_{-\infty}^{+\infty} f(u)\ f(u + x)du. \tag{A3}$$

This expression can be evaluated using the convolution theorem for Fourier transforms.[7] If we define the Fourier transform F(s) of a function f(x) as

$$F(s) = \int_{-\infty}^{+\infty} f(x)e^{-2\pi ixs}\ dx, \tag{A4}$$

it can be easily seen that the Fourier transform of a function $a\Pi(\frac{x-mb}{c})$ is given by

$$F(s) = ac\ e^{-2\pi imbs}\ \text{sinc}\ (cs), \tag{A5}$$

where

$$\text{sinc}\ (s) = \frac{\sin\ (\pi s)}{\pi s}\ . \tag{A6}$$

Using the convolution theorem,[7] we have

$$I(x) = \int_{-\infty}^{+\infty} F(s)\ F(-s)\ e^{2\pi isx}\ ds \tag{A7}$$

$$= (ac)^2 \int_{-\infty}^{+\infty} \text{sinc}^2(cs)e^{2\pi ixs}\ (\sum_{m=1}^{n} e^{-2\pi imbs})(\sum_{j=1}^{n} e^{2\pi ijbs})\ ds.$$

Further,

$$(\sum_{m=1}^{n} e^{-2\pi imbs})(\sum_{j=1}^{n} e^{2\pi ijbs}) = n + \sum_{m=1}^{n-1} 2(n-m)\cos(2\pi smb), \tag{A8}$$

And, replacing (A8) in (A7):

$$I(x) = (ac)^2 n \int_{-\infty}^{+\infty} \mathrm{sinc}^2(cs)\cos(2\pi xs)\,ds \qquad \text{(A9)}$$

$$+ 2(ac)^2 \sum_{m=1}^{n-1} (n-m) \int_{-\infty}^{+\infty} \mathrm{sinc}^2(cs)\cos(2\pi xs)\cos(2\pi smb).$$

After a few simple trigonometric transformations, the expression (A9) can be written:

$$I(x) = \frac{n}{2}\left(\frac{a}{\pi}\right)^2 \left[\int_{-\infty}^{+\infty} \frac{\sin(\pi cs)\sin(\pi c + 2\pi x)s}{s^2}\,ds \right.$$

$$\left. + \int_{-\infty}^{+\infty} \frac{\sin(\pi cs)\sin(\pi c - 2\pi x)s}{s^2}\,ds \right]$$

$$+ \left(\frac{a}{\pi}\right)^2 \sum_{m=1}^{n-1} (n-m) \left[\int_{-\infty}^{+\infty} \frac{\sin\pi(c+2x)s \cdot \sin\pi(c+2mb)s}{s^2} \right.$$

$$- \int_{-\infty}^{+\infty} \frac{\sin\pi(c+2x)s \cdot \sin\pi(2mb-c)s}{s^2}\,ds$$

$$+ \int_{-\infty}^{+\infty} \frac{\sin\pi(c-2x)s \cdot \sin\pi(c+2mb)s}{s^2}\,ds$$

$$\left. - \int_{-\infty}^{+\infty} \frac{\sin\pi(c-2x)s \cdot \sin\pi(2mb-c)}{s^2}\,ds \right]. \qquad \text{(A10)}$$

The integrals in (A10) can be solved using the result:

$$\int_{0}^{+\infty} \frac{\sin ax \, \sin bx}{x^2} = \frac{\pi a}{2} \qquad (a \le b)\,. \qquad \text{(A11)}$$

If we consider only positive time intervals, the result is

$$I(x) = \begin{cases} 2a^2 n[c-x] & x\epsilon[0,c] \\ 2a^2(n-m)[-(mb-c)+x] & x\epsilon[mb-c,\ mb] \\ 2a^2(n-m)[+(mb+c)-x] & x\epsilon[mb,\ mb+c] \\ 0 & \text{elsewhere} \end{cases} \qquad m = 1,2,\dots,n-1 \tag{A12}$$

In order to normalize I(x), we calculate:

$$\int_0^\infty I(x)dx = (acn)^2 , \tag{A13}$$

which represents the square of the total dose delivered. Now, we can calculate the factor q:

$$q = \frac{1}{(acn)^2} \int_0^\infty I(x)\tau(x)\ dx \quad , \tag{14}$$

with

$$\tau(x) = e^{-x/x_o} \tag{A15}$$

being the function describing the recovery process.

One obtains

$$q = \frac{2}{(nc)^2}\left\{ nx_oc + nx_o^2(1-\frac{1}{z}) + x_o^2(z+\frac{1}{z}-2)[\frac{n}{1-y} - \frac{y(1-y^n)}{(1-y)^2}]\right\} , \tag{A16}$$

with

$$z = e^{-c/x_o} \quad , \qquad y = e^{-b/x_o} . \tag{A17}$$

For the case of one single fraction (n = 1),

$$q = \frac{2x_o^2}{c}[\frac{c}{x_o} + e^{-c/x_o} - 1] , \tag{A18}$$

which is identical with the expression obtained in Ref. 1 [Eq.(5.35)]. As a further check, one can show that for a system with no recovery [$\tau(x) = 1$] one obtains

$$\lim_{x_0 \to \infty} q = 1 \quad , \tag{A19}$$

as expected.

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