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An Algorithm for Determining the Proximity Distribution from Dose-Averaged Lineal Energies[1,2]

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An algorithm is proposed for determining the proximity distribution of energy transfers from measured dose-averaged lineal energies. The applicability of the algorithm is illustrated with a calculation for a ^{60}Co beam based on a set of experimental y_D values. Practical methods for using the proposed algorithm are discussed.

INTRODUCTION

Recent developments in theoretical microdosimetry require the use of proximity functions (*1*). These functions refer to two different aspects of the process of cellular lesion induction by ionizing radiation: the geometrical distribution of sensitive loci in the cell [denoted $s(x)$] and the pattern of elementary energy transfers [$t(x)$].

The function $s(x)$ characterizes the irradiated structure; it is therefore independent of the radiation field and will not be considered here. $t(x)dx$ is the expected sum of energy transfers contained in a shell of radius x and thickness dx centered at an energy transfer point randomly selected in the irradiated medium. In this definition, it is assumed that the random selection of transfer points is made at a rate proportional to the energy transferred at that particular point.

The biophysical significance of the proximity distribution, $t(x)$, is apparent in the context of the generalized formulation of the dual radiation action theory (*1*), where it is related to the yield of lesions per cell from intratrack interactions. Further details may be found in Ref. (*1*). In particular, Kellerer and Chmelevsky (*2*) have established a direct mathematical relation between $t(x)$ and the microdosimetric quantity y_D, i.e., the dose-average of the lineal energy. For a spherical

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cavity of diameter Δ, this relation is

$$y_D(\Delta) = \frac{3}{2\Delta}\int_0^{\Delta}\left[1 - \frac{3x}{2\Delta} + \frac{x^3}{2\Delta^3}\right]t(x)dx. \tag{1}$$

To date no experimental methods are available for directly measuring $t(x)$. However, a number of calculations of $t(x)$ have been performed using Monte Carlo techniques [for example, Refs. (*3–6*)]; presently their accuracy is limited by the scarcity of reliable cross-sectional data for the primary interaction processes as simulated in the computer codes. Furthermore, Monte Carlo calculations are frequently hindered by the rather large amounts of computer storage space and running times necessary to attain a reasonable degree of statistical accuracy. It is therefore desirable to establish a more direct method for obtaining $t(x)$ from experimentally available quantities. Such a method is suggested by Eq. (1).

In the present paper, an algorithm is proposed for the unfolding of $t(x)$ from Eq. (1). The development of this algorithm was stimulated by recent measurements of y_D for photon fields over a wide range of simulated site diameters using the so-called variance technique (*7, 8*). A calculation, based on these measurements, of the proximity function for ^{60}Co is presented, together with practical methods for the application of the algorithm. The applicability of these methods is further illustrated with a set of y_D values derived from a calculated proximity function.

THE ALGORITHM FOR CALCULATING $t(x)$

Let us assume that the function $y_D(\Delta)$ is known for any value of Δ, i.e., the diameter of the spherical site. The solution of Eq. (1) can be obtained using Mellin transforms (*9*); consider Eq. (1) rewritten in the form

$$e_D(\Delta) = \int_0^{\infty} u\left(\frac{x}{\Delta}\right) t(x)dx, \tag{2}$$

where

$$u\left(\frac{x}{\Delta}\right) = 1 - \frac{3x}{2\Delta} + \frac{x^3}{2\Delta^3}, \qquad x \leqslant \Delta,$$

$$= 0, \qquad x > \Delta, \tag{3}$$

and the dose-averaged lineal energy, y_D, has been replaced for convenience by the dose-averaged energy, e_D:

$$e_D = \frac{2\Delta}{3} y_D\,. \tag{4}$$

Let $E(\sigma)$, $U(\sigma)$, and $T(\sigma)$ be the Mellin transforms of $e_D(\Delta)$, $u(x/\Delta)$, and $t(x)$, respectively. For instance, by definition, the Mellin transform of $t(x)$ is

$$T(\sigma) = \int_0^{\infty} x^{\sigma-1}t(x)dx \tag{5}$$

and the inverse transform is

$$t(x) = \frac{1}{2\pi i}\int_{C-i\infty}^{C+i\infty} x^{-\sigma}T(\sigma)d\sigma, \tag{6}$$

where C is a positive real number, sufficiently large to avoid poles in the integration kernel (9). Then, from Eq. (2),

$$E(\sigma) = \int_0^\infty \Delta^{\sigma-1} d\Delta \int_0^\infty u\left(\frac{x}{\Delta}\right) t(x) dx, \tag{7}$$

$$E(\sigma) = \int_0^\infty x^\sigma t(x) dx \int_0^\infty y^{-\sigma-1} u(y) dy, \tag{8}$$

where $y = x/\Delta$. From Eq. (8), using Eq. (5),

$$E(\sigma) = T(\sigma + 1)U(-\sigma), \tag{9}$$

and thus

$$T(\sigma) = E(\sigma - 1)/U(-\sigma + 1). \tag{10}$$

This result indicates that, given the transforms $E(\sigma)$ and $U(\sigma)$, one may calculate $T(\sigma)$ and the corresponding function $t(x)$. $U(-\sigma + 1)$ may be readily calculated using Eq. (3), and Eq. (10) becomes

$$T(\sigma) = \tfrac{1}{3}(1 - \sigma)(2 - \sigma)(4 - \sigma)E(\sigma - 1). \tag{11}$$

Thus, using Eq. (6),

$$t(x) = \frac{1}{6\pi i} \int_{C-i\infty}^{C+i\infty} x^{-\sigma}(1 - \sigma)(2 - \sigma)(4 - \sigma)E(\sigma - 1) d\sigma. \tag{12}$$

This solution of Eq. (1) can be simplified by using two theorems of the Mellin transform (*9*): Let $F(\sigma)$ be the Mellin transform of $f(x)$. Then:

Theorem 1: $F(\sigma + n)$ is the transform of $x^n f(x)$,

Theorem 2: $(-1)^n \sigma^n F(\sigma)$ is the transform of $\left(x \dfrac{d}{dx}\right)^n f(x)$,

where n is a constant integer. Using Theorem 1 with $n = 1$, one obtains, from Eq. (12),

$$\begin{aligned} xt(x) &= -\frac{1}{6\pi i} \int_{C-i\infty}^{C+i\infty} x^{-\sigma} \sigma(\sigma - 1)(\sigma - 3)E(\sigma) d\sigma \\ &= -\frac{1}{6\pi i} \int_{C-i\infty}^{C+i\infty} x^{-\sigma}(\sigma^3 - 4\sigma^2 + 3\sigma)E(\sigma) d\sigma. \end{aligned} \tag{13}$$

Using Theorem 2, this expression becomes

$$xt(x) = \frac{1}{3}\left[\left(x \frac{d}{dx}\right)^3 + 4\left(x \frac{d}{dx}\right)^2 + 3\left(x \frac{d}{dx}\right)\right] e_D(x) \tag{14}$$

or

$$t(x) = \frac{1}{3}\left[x^2 \frac{d^3}{dx^3} + 7x \frac{d^2}{dx^2} + 8 \frac{d}{dx}\right] e_D(x). \tag{15}$$

A trivial transformation, using Eq. (4), yields a similar expression relating $t(x)$ to $y_D(x)$.

The technique for deriving $t(x)$ from a set of discrete y_D values therefore involves

ascertaining the first, second, and third derivatives of y_D at all diameters between the minimum value at which y_D is known and R, the maximum range of the particle under consideration [for values $x \geq R$ the proximity function $t(x)$ is identically zero, by definition, and no calculation is necessary[3]]. Some applications of the proposed algorithm, Eq. (15), are discussed in the next section.

PROXIMITY FUNCTION FOR ^{60}Co γ RAYS

Bengtsson and Lindborg (*7*) have reported a set of experimental values of y_D for a ^{60}Co beam as a function of the site diameter. These results cover a wide range of diameters (11 nm to 22 μm) and were obtained using the variance technique. It is important to remark, however, that the detection system was sensitive to ionization processes only, and this limitation will be carried over in the associated proximity function.[4]

The calculation of $t(x)$ with Eq. (15) requires that the experimental data $e_D(x)$ be fitted by some technique yielding continuous first, second, and third derivatives. Perhaps the simplest approach is to find a simple continuous function that gives a good fit to the data in the "minimum χ-square" sense. Such a function has been reported by Forsberg *et al.* (*8*) for their ^{60}Co data,

$$y_D(x) = 2.01x^{-0.4}, \tag{16}$$

where y_D and x are, respectively, in keV/μm and μm. From Eqs. (4), (15), and (16), the proximity function can be easily calculated,

$$t(x) = \tfrac{2}{9}\,\alpha(\beta + 1)(\beta + 2)(\beta + 4)x^{\beta},$$

where, in this case, $\alpha = 2.01$ and $\beta = -0.04$ [see Eq. (16)]. The results, together with the y_D data, are shown in Fig. 1. An error band for the proximity function corresponding to one standard deviation is also shown.[5]

[3] For site diameters $x > R$ the analytical form of $y_D(x)$ is well defined and is given by

$$y_D(x) = A/x - B/x^2 + C/x^4,$$

where the constants A, B, and C are defined in terms of the zero, first, and third moments of $t(x)$, respectively:

$$A = 1.5 \int_0^\infty t(x)dx = 1.5\,E,$$

$$B = 2.5 \int_0^\infty xt(x)dx,$$

$$C = 0.75 \int_0^\infty x^3 t(x)dx.$$

Here E is the energy of the primary particle. A fit to $y_D(x)$ data for large diameters (compared to R) may therefore provide useful information concerning the moments of $t(x)$.

[4] The significance of this effect has been discussed in Ref. (*6*).

[5] If $y_D(x) = y_D(x,\alpha,\beta)$, where α and β are parameters as in Eq. (16), then from Eq. (15) one obtains $t(x) = t(x,\alpha,\beta)$. The variance of $t(x)$ can be calculated to first order using

$$\sigma_t^2 = \left(\frac{\partial t}{\partial \alpha}\right)^2 \sigma_\alpha^2 + \left(\frac{\partial t}{\partial \beta}\right)^2 \sigma_\beta^2 + 2\,\frac{\partial t}{\partial \alpha}\,\frac{\partial t}{\partial \beta}\,\sigma_{\alpha\beta},$$

where σ_α^2 and σ_β^2 are the variances of α and β and $\sigma_{\alpha\beta}$ their covariance, as obtained from the fitting procedure for evaluating α and β.

As with any functional fit to experimental data a certain bias is introduced depending on the particular analytical expression chosen. The effect of such a bias on the calculated proximity function is difficult to estimate since the choice of any particular form [such as that of Eq. (16)] is rather arbitrary. It was felt, therefore, that a more general fitting procedure should be applied such that, with only minimal constraints, a least-biased, smooth analytical representation of the data is obtained. Such a procedure, based on B-spline "minimum χ-square" fitting, was selected in order to reanalyze the same ^{60}Co data.

A short description of the theory involved in fitting data in the least-squares sense using B-splines is given in the Appendix. Further details may be found in Ref. (*10*). The basic idea in a spline calculation is to fit the data with piecewise polynomial curves (i.e., splines) defined, apart from normalization constants, by a set of breakpoints or knots. The normalization constants are calculated such that the spline functions provide a best fit to the data in the "minimum χ-square" sense. For the present application, splines of fourth degree (or more) are necessary since continuity up to the third derivative at the knots is required [see Eq. (15)].

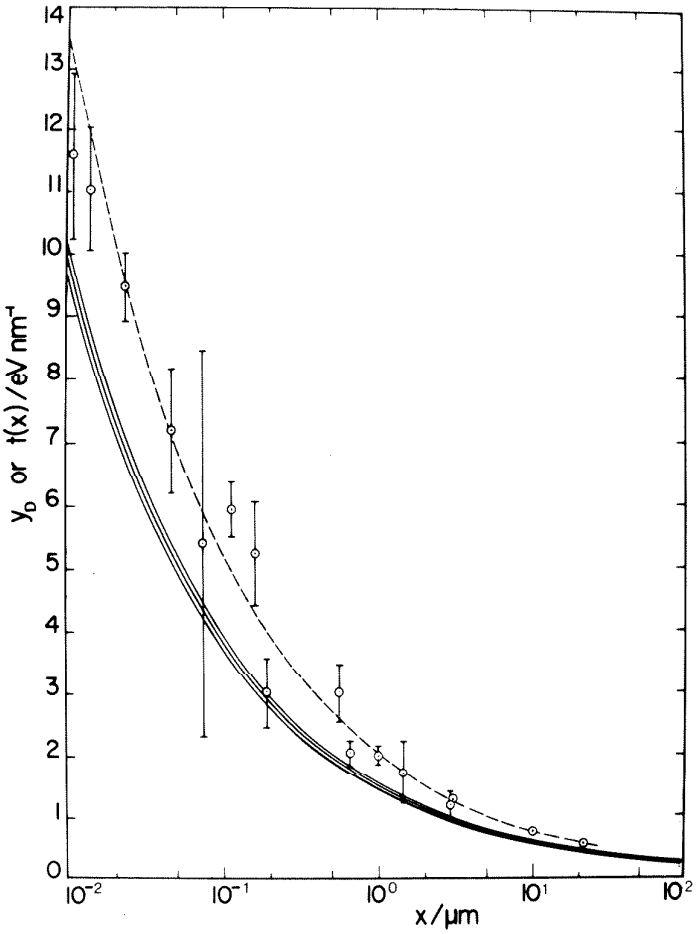

FIG. 1. Circles: Experimental values of y_D for ^{60}Co redrawn from Ref. (*7*). Broken curve: Analytic fit to y_D data using Eq. (*16*). Full curves: Proximity function calculated using the analytic fit to $y_D(x)$, with error bands corresponding to one standard deviation (see text). All distances in the figure correspond to unit density material.

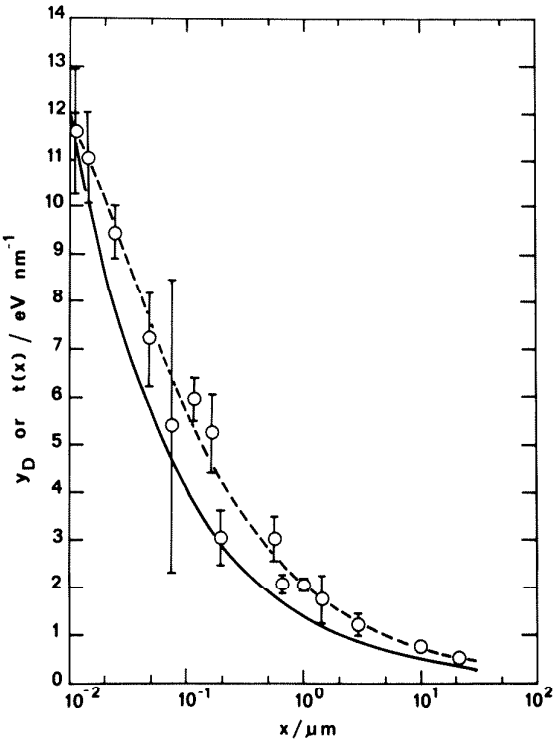

FIG. 2. Circles: Experimental values of y_D for ^{60}Co redrawn from Ref. (*7*). Broken curve: Quartic B-spline fit to y_D for ^{60}Co. Full curve: Proximity function calculated using the B-spline fit to $y_D(x)$. All distances in the figure correspond to unit density material.

We have used the computer code "FC" (*11*) from the SLATEC mathematical library (*12*) to fit discrete data in a "minimum χ-square" sense using B-splines as basis functions.[6] An important feature of this code is that it allows the user to impose equality and inequality constraints on the spline functions and their derivatives; the shape of the required curve may thus be specified.

The B-spline subroutine was used to obtain a smooth fit to the experimental data for y_D. The fit was obtained using a full logarithmic representation (i.e., ln y_D vs ln Δ) with the following constraints: (a) nonpositive derivative at the last knot, and (b) nonnegative second derivative for all the knots. The B-spline fit is shown in Fig. 2. Also shown is the proximity function calculated with Eq. (15).

In order to further test this algorithm, a proximity distribution and y_D values were calculated from 100 Monte Carlo-simulated tracks of 1.0-keV electrons in water vapor. Simulated "experimental" y_D values were generated by displacing randomly the calculated y_D values with standard deviation of 5%. Using these "experimental" data (10 points from 10 nm to 70 nm) the B-spline procedure described before was repeated. The results are shown in Fig. 3. From the good agreement between the calculated and unfolded proximity functions, it is apparent that the procedure proposed is reliable if a sufficient number of y_D values of reasonable accuracy are provided.[5]

[6] B-Splines are a special representation of spline polynomials, easier to use in computer codes. (See Appendix.)

CONCLUSIONS

An algorithm was demonstrated which allows the computation of the proximity function when the variation of y_D with site size is known. As pointed out above, with present experimental techniques for measuring y_D only a proximity function of ionizations can be obtained; the significance of this limitation remains to be investigated.

For highly stabilized photon beams, such as those used by Bengtsson and Lindborg (*7*) and Forsberg *et al.* (*8*), the acquisition of data on the variation of y_D with diameter down to nanometer diameters is now an established procedure. However, for particle beams such as neutrons, pions, and heavy ions similar techniques have not yet been established. In the authors' opinion, however, such techniques are feasible and should be developed. The advantages of such a system would lie not only in the possibility of doing basic investigations with the resultant proximity functions, but also in the ability to make fast determinations of y_D, a good indicator of gross radiation quality.

APPENDIX: MINIMUM χ-SQUARE CURVE FITTING WITH B-SPLINES

Consider a set of data points (x_i, y_i), $i = 1, \ldots, n$. The problem is to find a function (in this case a family of functions) $f(x)$ defined for all x such that

$$f(x_i) \simeq y_i, \qquad i = 1, 2, \ldots, n. \tag{17}$$

If the "minimum χ-square" principle is adopted then the function $f(x)$ should be such that the weighted sum of squares

$$r = \sum_{i=1}^{n} w_i[f(x_i) - y_i]^2 \tag{18}$$

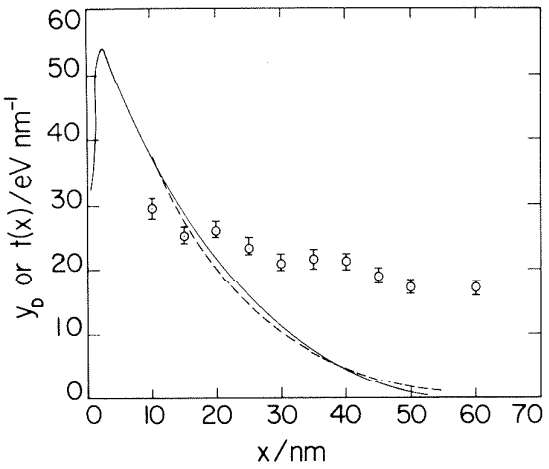

FIG. 3. Circles: Values of y_D, for 1-keV electrons in water, calculated using a Monte Carlo transport code. In order to simulate experimental data, the points were randomly displaced with standard deviation 5%. Full curve: Proximity function calculated directly from Monte Carlo energy deposition data. Broken curve: Proximity function calculated from the simulated y_D values, using the proposed algorithm. All distances in the figure correspond to unit density material.

is minimized. In Eq. (18) w_i are the weights of the observations y_i; when their standard deviations, σ_i, are known, then

$$w_i = 1/\sigma_i^2 . \tag{19}$$

In many cases the functional form of $f(x)$ is known and the problem then reduces to finding values for the parameters of the functional form that minimize Eq. (18). If no such information is available, the next best procedure is to fit the data with piecewise polynomial curves (a single, high-degree polynomial is usually not satisfactory because the solution will oscillate widely between the data points). To define this approach more precisely, consider an interval $[a,b]$ that contains the data points $\{x_i\}$ and let $\{z_i\}$, $i = 1, \ldots, n$, be an ordered set of points in $[a,b]$. The points $\{z_i\}$ are called knots. On each interval $[z_1, z_2] \cdots [z_{n-1}, z_n]$, the function $f(x)$ is a polynomial of degree k (a different polynomial for each interval). In general, a spline of degree k (or order $k + 1$) is defined as a piecewise polynomial of degree k with $k - 1$ continuous derivatives. A special subset of the spline functions that are especially amenable to computation are B-splines that have only $k_1 \leqslant k - 1$ continuous derivatives at the knots. A natural requirement for splines is continuity for $f(x)$ and for the first and second derivatives of $f(x)$ at each knot (i.e., slopes and curvatures are continuous at the knots). Clearly cubic splines are the lowest order that satisfy these requirements; it is clear, however, from Eq. (15), that for our application quartic polynomials are required to ensure continuity of the third derivative.

The basic approach in a B-spline representative is to express the spline in the form of a set of polynomials $B_i(x)$,

$$f(x) = \sum A_i B_i(x), \tag{20}$$

such that $B_i(x)$ is zero over as many intervals as possible. It can be shown (*10*) that for a spline of degree k, $B_i(x)$ can be made nonzero over a minimum of $(k + 1)$ successive intervals (for quartic splines, five intervals). Then, apart from a normalization constant, $B_i(x)$ may be written[7]

$$\begin{aligned} B_i(x) &= 0, && x \leq z_{i-k+1}, \\ &= \sum_{j=i-k}^{i}, && C_{(j-i+k+1)}(x - z_j)^k H(x - z_j) z_{i-k+1} < x < z_{i+1}, \\ &= 0, && x \geq z_{i+1}, \end{aligned} \tag{21}$$

where $H(x)$ is the Heaviside function

$$\begin{aligned} H(x) &= 1, && x \geq 0, \\ &= 0, && x < 0. \end{aligned} \tag{22}$$

For quartic splines, four of the five "C" coefficients in Eq. (21) can be evaluated using the continuity of B_i and its derivatives at the knot z_{i+1}. The general "minimum χ-square" fitting problem reduces then to determining the parameters A_i in Eq. (20).

[7] Since each polynomial B_i is defined over five intervals, it is necessary to add four additional knots at each end of the interval $[a,b]$.

The actual selection of knots in the interval $[a,b]$ is somewhat arbitrary since to date no established procedure is available. For simple curve-fitting purposes the result is frequently insensitive to the actual number or position of the knots. The situation is different, however, when the final result involves higher-order derivatives of the spline fit, as in the proposed algorithm. The B-spline calculations in the present paper were performed using the following two guidelines: (a) the number of knots was much smaller than the number of data points (a natural requirement for a minimum χ-square approach), and (b) the position of the knots was selected to obtain the minimum weighted sum of squares, r, in Eq. (18).

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REFERENCES

1. A. M. KELLERER and H. H. ROSSI, A generalized formulation of dual radiation action. *Radiat. Res.* **75,** 471–488 (1978).
2. A. M. KELLERER and D. CHMELEVSKY, Concepts of microdosimetry. III. Mean values of the microdosimetric distributions. *Radiat. Environ. Biophys.* **12,** 321–335 (1975).
3. D. CHMELEVSKY, A. M. KELLERER, M. TERRISSOL, and J. P. PATAU, Proximity functions for electrons up to 10 keV. *Radiat. Res.* **84,** 219–238 (1980).
4. H. G. PARETZKE and F. SCHINDEL, Classification of charged particle track structures by means of cluster distribution. In *Seventh Symposium on Microdosimetry, Oxford, England* (J. Booz, H. G. Ebert, and H. D. Hartfiel, Eds.), pp. 387–398. Commission of the European Communities, Harwood, London, 1981.
5. R. N. HAMM, J. E. TURNER, H. A. WRIGHT, and R. H. RITCHIE, Calculated distance distributions of energy transfer events in irradiated liquid water. In *Seventh Symposium on Microdosimetry, Oxford, England* (J. Booz, H. G. Ebert, and H. D. Hartfiel, Eds.), pp. 717–726. Commission of the European Communities, Harwood, London, 1981.
6. D. J. BRENNER, Calculation of ionization distributions in a tissue-equivalent cloud chamber gas mixture. *Radiat. Res.* **89,** 194–202 (1982).
7. L. G. BENGTSSON and L. LINDBORG, Comparison of pulse height analysis and variance measurement for the determination of dose mean specific energy. In *Fourth Symposium on Microdosimetry, Verbania-Pallanza, Italy* (J. Booz, H. G. Ebert, R. Eickel, and A. Waker, Eds.), pp. 823–841. Commission of the European Communities, Luxembourg, 1974. [EUR 5122 d-e-f]
8. B. FORSBERG, M. JENSEN, L. LINDBORG, and G. SAMUELSON, Determinations of the dose mean of specific energy for conventional x rays by variance measurements. In *Sixth Symposium on Microdosimetry, Brussels, Belgium* (J. Booz and H. G. Ebert, Eds.), pp. 261–271. Commission of the European Communities, Harwood, London, 1978. [EUR 6064 d-e-f]
9. H. BATEMAN, *Tables of Integral Transforms, Vol. I* (A. Erdélyi, Ed.). McGraw-Hill, New York, 1954.
10. C. DE BOOR, *A Practical Guide to Splines.* Springer-Verlag, Berlin/New York, 1978.
11. R. J. HANSON, *Constrained Least Squares Curve Fitting to Discrete Data Using B-Splines—A Users Guide.* Report SAND 78-1291, Sandia Laboratories, 1979.
12. B. L. BUZBEE, The SLATEC common mathematical library. In *Sources and Development of Mathematical Software* (W. Cowell, Ed.). Prentice-Hall, in press.