August 1985

Thindown in Radiobiology

Robert Katz
University of Nebraska-Lincoln, rkatz2@unl.edu

D. E. Dunn
University of Nebraska-Lincoln

G. L. Sinclair
University of Nebraska-Lincoln

Published in *Radiation Protection Dosimetry* **13**:1–4 (1985), pp. 281–284.

Thindown in Radiobiology

R. Katz, D. E. Dunn, and G. L. Sinclair
University of Nebraska–Lincoln, Lincoln, NE 68588-0111, USA

Abstract: A new expression for the radial dose distribution, tested against available data, and yielding good agreement with enzyme and virus cross sections, is used to calculate cellular inactivation cross sections from track theory models and parameters. We use a cellular model and radiosensitivity parameters, fitted to HILAC data 15 years ago, to represent mammalian cells irradiated at the UNILAC. The observed branching with Z and the decline in cellular action cross sections with an increase in ion LET are attributed to thindown; that is, to the limits imposed by the maximum radial penetration of delta rays. Target size and structure (hence the model) also play a role. Similar effects are observed with nuclear emulsions, scintillation counters, and thermoluminescent crystals at ion speeds approaching the Bragg peak, where, in the track width regime, the cross sections depend more on the ion speed than on LET.

Introduction

Track theory [1] connects the response of a detector of gamma rays to action cross sections through the radial distribution of dose. For this model the central contribution of atomic physics is the radial distribution of dose, at all distances from the ion's path, for all detector media, and for ions of all energies. The information available from experiment or from *a priori* calculation is very limited. At this time any attempt to explain experimental action cross sections from track theory depends on the development of an extrapolative dose formula which is verified to the extent possible by comparison with existing data.

Such a dose formula has been developed using a power law expression for the electron range, an assumption of normal ejection, the Rutherford formula for delta ray production from a medium having an ionisation potential I (=10 eV), a power law electron range-energy relation (using constants measured for aluminum), and the Barkas formula for effective charge. While these procedures are somewhat arbitrary we must keep in mind that we do not seek a rigorous *ab initio* development but rather a formula which agrees with both measurement [2–5] and and calculation [6] of the dose distribution. With this formula our calculations for the inactivation of dry enzymes and viruses are now within about 15% of the experimental data, much improved from our earlier work.[7] We discuss these results in greater detail elsewhere in the present symposium (see Zhang *et al,* pp. 215-218).

Thindown arises from the variation of the maximum radial penetration of delta rays with ion speed. The dose at these distances must result in inactivation of a large fraction of the sensitive targets near the region of greatest delta ray penetration. Our assumption of normal ejection is expected to overestimate this distance and thus to yield an overestimate of the cross sections at thindown. Here we have no guidance from experiment to test our formula. We have adjusted this distance to give the best agreement between our calculations and the measurements for mammalian cells in the thindown region.

Our thesis, that the branching with Z of plots of the cross section for cells as a function of LET is a function of the kinematic constraint on the delta ray distribution rather than of biology, is well supported by similar studies of the response of TLD crystals [8,9] and inorganic scintillators,[10] as well as observations with nuclear emulsions. In the track width regime, as the ion slows down toward the Bragg peak and the dose near maximal delta ray penetration suffices to activate a large fraction of sensitive targets in the region, the cross section reflects the radial penetration of the electrons much more than the energy loss of the ion. It reflects the ion's speed rather than the LET. Target size and structure also play a role, important in the radiobiology of mammalian cells where the sub-nuclear target structure is both complex and relatively unknown.

The biological findings we seek to explain are the action cross sections for the inactivation of spores,[11] yeast, [12] and mammalian cells [13] by very heavy ions, measured at the UNILAC. These data are not wholly consistent with the demands of track theory. We expect, but do not always find, that survival curves are exponential for bombardments with ions heavier than neon, at energies less than 10 MeV.amu^{-1}. We interpret this disagreement as an experimental problem, but are uncertain as to whether it arises from physics (as from non-uniform

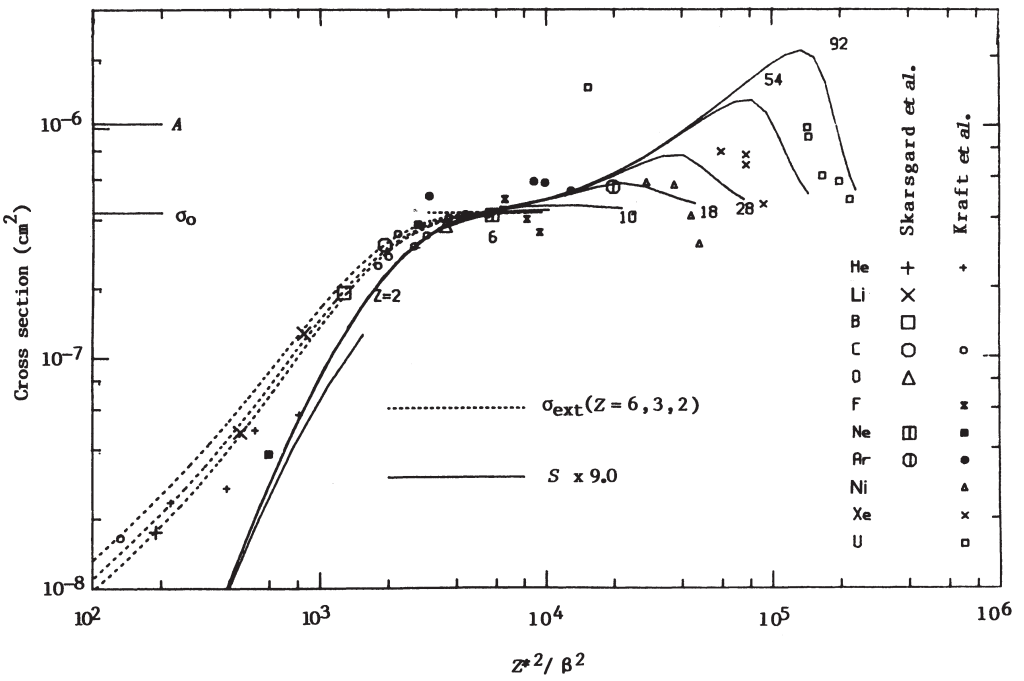

Figure 1. From cellular radiosensitivity parameters fitted to the survival data for Chinese hamster cells in 1971, inactivation cross sections have been calculated for the hypothetical sub-nuclear target appropriate to these cells for a series of energetic heavy ions. These are multiplied by an appropriate proportionality factor to bring them into agreement with the ion-kill cross sections for the cells in the grain count regime. The new calculations then extend the earlier results into the track width regime. Data of Skarsgaard *et al.* (see Reference 1) from which the parameters were extracted, and the more recent data of Kraft ***et al.***[13] are superimposed on the curves, plotted as the extrapolated cross sections relative to z^{*2}/β^2. Note that the "hooks" in the calculated curves, at the right, do not lie on the experimental data.

$a_0 = 1.23 \times 10^{-4}$ cm^2 $\quad E_0 = 1.82 \times 10^{-3}$ J.cm^3
$\sigma_0 = 4.28 \times 10^{-7}$ cm^2 $\quad m = 3$
k = 1100

beams) or biology. The available survival data for both spores and yeast cells suffer this difficulty somewhat more than those reported for mammalian cells. In consequence we focus our attention on the mammalian cell data.

Details of the Model; Results

The model we have used for mammalian cells makes use of a hypothetical sub-nuclear target of radius a_0, whose response to gamma rays has the functional form of the multitarget statistical model. It thus has additional parameters m and E_0. We take it that there are internal targets in the nucleus, rather like beans in a bean bag, whose number, radiosensitivity, and position are unknown, but that perhaps m of these must be inactivated for cellular inactivation. The collective effect of these is represented by our single sub-nuclear target. We calculate the action cross section for this target, and propose that it is proportional to the action cross section for the irradiated cell. Thus, if empirically we can determine the numerical values of these three parameters for a cell and the proportionality constant relating the target cross section to the cellular action cross section, we can calculate the ion kill cross section for all particle beams. This is to be compared with the experimental cross section at high LET, in the track width regime.

Almost 15 years ago parameters of this model were fitted to survival data for hamster cells. We thus have cellular radiosensitivity parameters E_0, κ, σ_0, and m. From κ and E_0 we have extracted the value of a_0 appropriate to these cells. We have then calculated the action cross sections for this sub-nuclear target for a series of bombardments with energetic heavy ions. We apply a proportionality factor determined from the ratio of the "plateau" values of the experimental and calculated cross sections

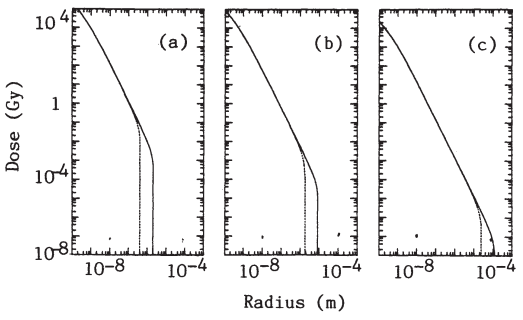

Figure 2. To repair the disagreement between calculation and observation we have constrained the maximum radial penetration of delta rays, T, as calculated from the assumption that delta rays are normally ejected to T/5. The effect of this constraint on the radial distribution of dose, for protons. is calculated from our formula for three ion speeds, $\beta = 0.10$, 0.15, 0.30, as shown.There is little change in the distribution except in the outermost decade. In each part of the figure: $\alpha = 1.667$ and $T \rightarrow T/5$.

(a) E = 4.7 MeV.amu^{-1}, $\beta = 0.10$
(b) E = 10.6 MeV.amu^{-1}, $\beta = 0.15$
(c) E = 44.9 MeV.amu^{-1}, $\beta = 0.30$

to extend the cross sections fitted to the earlier data into the track width regime to be expected from the newer bombardments at GSI.

We show in Figure 1 the curves which result after calculation. We plot the extrapolated cross section against z^{*2}/β^2. The value of all calculated cross sections, S, for the hypothetical target have been multiplied by 9.0, so that the newly calculated cross sections for neon and lighter particles coincide with the plot of ion kill cross sections determined from the original parameter fits. In Figure 1 the solid lines are ion kill cross sections while the dashed lines represent extrapolated cross sections, including the effect of gamma kill. Note that at highest LET the locations of the calculated "hooks" do not correspond to the experimental findings. We attribute this failure of the model to our anticipated over-estimate of the maximal radial delta ray penetration.

A better result is obtained if the maximal radial penetration T is reduced by factor 5 in our expression for the radial dose distribution. Except in the outermost decade the dose distribution is but little altered by this change, as shown in Figure 2 calculated for protons at three different speeds, $\beta = 0.10$, 0.15, and 0.30. Since the

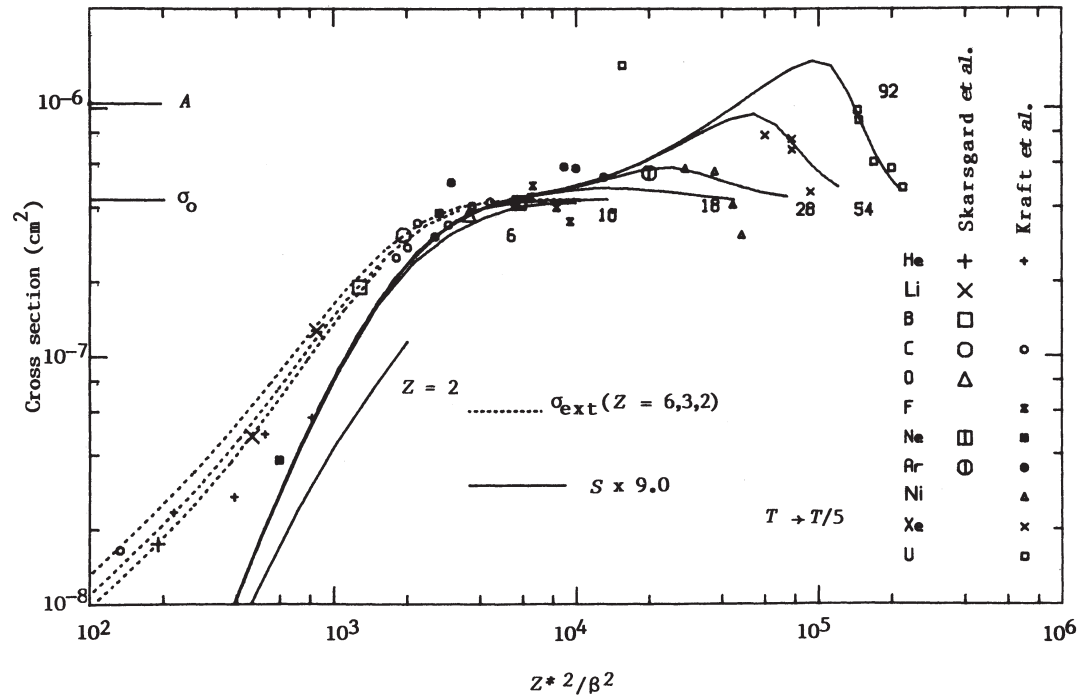

Figure 3. Using the dose distribution based on maximal radial penetration of delta rays of T/5, we have recalculated the ion-kill cross sections. The agreement with data is substantially improved over that of Figure 1. Symbols etc. as for Figure 1.

dose varies roughly as r^{-2}, nearly equal energy is deposited in each radial decade. The fractional energy suppressed in our calculation by this reduction in T is something less than the reciprocal of the number of decades from 10^{-10} *m* to T.

In Figure 3 we show the recalculated cross sections. For heavier ions one notes a small alteration, of the order of 10%**,** in the value of the calculated cross sections except at the location of the "hooks" where the change is substantial. The calculated cross sections in this region have now been brought into agreement with experimental data.

There remain some discrepancies which require further examination. Particularly the measured cross section for fast uranium ions, determined at Berkeley, seems inconsistent with our calculations. It is possible that this inconsistency is due to our very poor knowledge of the radial dose distribution from fast uranium ions. A second problem arises from the relatively large difference between the physically measured cross sectional area of the cell nucleus and the plateau value of the inactivation cross section. For this we have no explanation, but observe that the physical size of sensitive volumes and the plateau value of the inactivation cross section are much closer for spores and yeast cells. We see this as a biological problem rather than a physical one. Our model does not speculate about the relative sizes of these quantities, other than to note their approximate equality.

Our results further emphasise the importance of accurate knowledge of the average radial dose distribution over the entire range of radial distances in which energy is deposited. It is not enough to calculate or to measure out to distances where, say, 90% of the total energy is included. We need measurements of the dose distributions. We need as source functions the singly (or preferably the doubly) differential cross sections for delta ray production for input into Monte Carlo calculations. We need measured cross sections for enzymes and viruses (along with gamma ray D_{37} doses) with which to test these dose distributions. Such information is prerequisite to a quantitative understanding of heavy ion radiobiology.

Acknowledgments

This work was supported by the US Department of Energy.

References

1. Katz, R., Sharma, S. C., and Homayoonfar, M. The Structure of Particle Tracks. In: *Topics in Radiation Dosimetry, Suppl. 1,* ed. F. H. Attix (New York: Academic Press) pp. 317-383 (1972).
2. Varma, M. N., Baum, J. W., and Kuehner, A. V. Energy Deposition in a Tissue Equivalent Gas. *Radiat. Res.* **62**, l-11 (1975).
3. Varma, M. N., Baum, J. W., and Keuhner, A. V. Stopping Power and Radial Dose Distribution for 42 MeV Bromine Ions. *Radiat. Res.* **81**, 355-363 (1980).
4. Varma, M. N., and Baum, J. W. Energy Deposition in Nanometer Regions by 377 MeV/Nucleon ^{20}Ne Ions. *Radiat. Res.* **81**, 355-363 (1980).
5. Varma, M. N., Paretzke, H. G., Baum, J. W., Lyman, J. T., and Howard, J. Dose as a Function of Radial Distance from a 930 MeV ^{4}He Ion Beam. In: *5th Symp. on Microdosimetry,* eds. J. Booz, H. G. Ebert, and B. G. R. Smith (Luxembourg: Commission of the European Communities) pp. 75-95 (1976).
6. Fain, J., Monnin, M., and Montret, M. Energy Density Deposited by a Heavy Ion Around its Path. In: *4th Symp. on Microdosimetry,* eds. J. Booz, H. G. Ebert, R. Eickel, and A. Waker (Luxembourg: Commission of the European Communities) pp. 169-186 (1974).
7. Butts, J. J., and Katz, R. Theory of RBE for Heavy Ion Bombardment of Dry Enzymes and Viruses. *Radiat. Res.* **30**, 855-871 (1967).
8. Montret-Brugerolle, M. Distribution Spatial de l'Energie Deposée par des Ions Energetiques dans les Milieux Condenses. Etude par Thermoluminescence. Thesis Université de Clermont Ferrand II. (1980).
9. Kalef-Ezra, J., and Horowitz, Y. S. Heavy Charged Particle Thermoluminescence Dosimetry: Track Structure Theory and Experiments. *Int. J. Appl. Radiat. Isot.* **33**,1085-1100 (1982).
10. Newman, E., and Steigert, F. E. Response of NaI(Tl) to Energetic Heavy Ions. *Phys. Rev.* **118**, 1575-1578 (1960).
11. Facius, R., Bucker, H., Reitz, G., and Schafer, M. Contribution of Ion-Kill and δ Electrons to Inactivation Cross Sections of Bacillus Subtilus Irradiated with Very Heavy Ions. In: *Proc. 7th Symp. on Microdosimetry,* eds. J. Booz, H. G. Ebert, and H. D. Hartfiel, (London: Harwood Academic) pp. 1331-1340 (1981).
12. Schopfer, F., Schneider, E., Rase, S., Kiefer, J., and Kraft, G. Heavy Ion Effects on Yeast: Survival and Recovery in Vegetative Cells of Different Sensitivity. *Radiat. Res.* **92**, 30-46 (1982). Also H. Liesem, personal communication.
13. Kraft, G., Kraft-Weyrather, W., Meister, H., Miltenburger, H. G., Roots, R., and Wulf, H. The Influence of Radiation Quality in the Biological Effectiveness of Heavy Charged Particles. In: *Proc. 8th Symp. on Microdosimetry,* eds. J. Booz and H. G. Ebert (Luxembourg: Commission of the European Communities), pp. 743-753 (1983).