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

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COMMENTARY

The Parameter-Free Track Structure Model of Scholz and Kraft for Heavy-Ion Cross Sections

Robert Katz[1]

University of Nebraska, Lincoln, Nebraska 68588-0111

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The "parameter-free", "local effects" theory of Scholz and Kraft is an extension to mammalian cells of the theory of RBE for dry enzymes and viruses of Butts and Katz. Its claim for parameter freedom has been challenged elsewhere. Here we examine its conceptual base and find errors in its use of the physical concept of cross section and its neglect of the radiobiological relationship between target size and radiosensitivity in evaluating the radiation damage to "point targets".

INTRODUCTION

Motivated by a desire to correct aspects of the Katz theory of RBE (*1–3*) that they find unacceptable (average dose, ion kill and gamma kill), Scholz and Kraft (*4–7*) have constructed a ''local effects'' model. An amorphous, cylindrical cell nucleus, 50 μm^2 in area and 5 μm thick, is dissected into a bundle of rods of 1-nm^2 cross-sectional area and 5 μm long (referred to as ''point targets''). These rods are damaged individually by δ rays from a beam of heavy ions moving parallel to the axis of the cylinder. The local dose at these sites is the collective dose from appropriately spaced ions, found by use of a simplified radial dose track structure model, which follows extensive theoretical and experimental studies (*8*). The damage to individual rods is based on an approximation to the dose–effect relationship found for mammalian cells after irradiation with γ rays. The average damage to the nucleus is obtained from Monte Carlo calculations. The initial slope of the collective dose–effect relationship, found to be exponential in form, is used as the basis for a ''differential cross-section'' called ''the initial slope cross section''. Differential cross sections are physically undefined. True cross sections in radiobiology (*9*) demand completely exponential survival curves. Cross sections reflect the interaction of single projectiles (including their secondary electrons) with biological targets. In the ''local effects model'' the damage to a ''point target'' in a cell nucleus is the result of the cumulative damage from intersecting δ rays from many independent projectiles, as shown in Fig. 4 of ref. (*7*).

A second problem with this calculation is the use of a cell survival curve as the dose–effect relationship for ''point targets''. In target theory, the D_{37} dose for one-hit detectors, whose dose–effect relationship is exponential, is inversely proportional to target volume (*10, 11*). Here the volume of the cell nucleus is 5×10^7 times greater than the ''point target''.

Following is a brief development of this relationship.

Specific volume, in cm^3/g, is the reciprocal of the density, ρ. In 1 g of matter, there are $1/\rho v$ targets of volume v. Consider that the deposit of energy w, in eV, constitutes a ''hit'' that is able to inactivate a target. An average energy deposition of w per target leaves 37% of the targets unaffected, according to the Poisson distribution. Then the D_{37} dose of a one-hit detector irradiated by γ rays is $w/\rho v$, in eV/g. This treatment parallels the calculation of target molecular weight for enzymes (*10*), and it is validated by its success. Reference (*10*) also presents clear presentation of the theory of Butts and Katz.

In the Scholz-Kraft model, the initial slope is found to be exponential, as for one-hit detectors. Thus the radiosensitivity of a ''point target'' is vastly different from that of a mammalian cell. The dose that ''kills'' a mammalian cell can be expected to leave a point target essentially unaffected. In this model, the inferred damage to ''point targets'' is the basis for all subsequent conclusions. The model stands or falls on its validity.

Some of these dimensions are inferred from the language of their paper, where the meaning is vague and the dimensions are not stated.

On parameters. A careful and comprehensive study of the calculations employed in the Scholz-Kraft model has been made by Paganetti and Goitein (*12*). They have con-

[1] Address for correspondence: 5850 Sunrise Road, Lincoln, NE 68510-4049; e-mail: rkatz@unlserve.unl.edu.

cluded that the ''parameter-free'' claim is questionable. Specifically, the form of the cell survival curve invented by Scholz and Kraft is a combination of the customary α-β model for low doses attached to an exponential relationship at high doses. These are joined at a dose, D_t, which must be adjusted, because the outcome of the model depends strongly on its choice. Besides the parameter D_t, a second parameter, the radial cut-off parameter r_{min}, which restrains high local-dose effectiveness (in their inverse-square simplified model of the radial dose distribution), is necessary because there is no dose averaging over subtargets. Again, the outcome of the model depends strongly on the choice of this parameter. This parameter is subject to the requirement that the integral of the radial dose must agree with the LET of the projectile, but this is not a unique constraint. A third parameter is the specified cross-sectional area of the nucleus. These geometrical sizes are dependent on the cell, cell cycle, and cell age, and they have been stated by others to lie in the range of 50 to several hundred μm^2. Additionally, mammalian cells exhibit values for the characteristic dose, D_0, a parameter of the Katz theory (*13*), from 0.5 to 4.6 Gy. The choice of this parameter influences damage to the ''point targets''. And since the probability of damage to the ''nucleus'' is found as the ratio of the damaged surface area to the area of the entire nucleus, the area of the ''nucleus'' also plays a significant role in these calculations. Since the resulting calculations are used in tumor therapy (*7*), it may be consequential to find the range of results attributable to the range of all parameter values.

The paper of Paganetti and Goitein (*12*) also contains a section critical of the Katz theory.

On cross section. A paper by the present author entitled ''Cross Section'' (*9*) clarifies the meaning of cross section, with special reference to radiobiology, through a thought experiment. We imagine that a projectile is directed down a channel 1 cm^2 in cross-sectional area toward a target at the end of that channel. Neither the trajectory of the projectile nor the location of the target is known. The success or failure of the interaction in achieving a specified end point is recorded. The experiment is repeated many times, and the fraction of successes is tallied. That fraction is imagined to be the area in cm^2 of a ''bull's eye'' target placed at the end of the channel, so that the probability, or fraction, of the interactions is the ratio of the area of the bull's eye (the cross section) to that of the channel. Note that each interaction is independent of all previous trials. The cross section is anhistoric. The units in which cross section is expressed arise from its description as probability per unit fluence (nominally one particle per cm^2). Cross sections can range in size from decades lower than to decades higher than the geometric cross-sectional area of the target, as is well illustrated by microphotographs of particle tracks in electron-sensitive nuclear emulsion (*14*). There we can see the size of a developed grain, somewhat larger than an undeveloped grain, the dotted tracks where the cross section is smaller than the grain size, and the opaque tracks whose cross-sectional area approximates the interaction cross section of the projectile with emulsion grains.

SOME ADDITIONAL REFERENCES TO KATZ THEORY

To assist the reader who is unfamiliar with Katz theory, reference is made to both supportive and critical material.

Reference (*1*) is an extended review of work on the Katz theory up to 1972. Reference (*2*) describes later work, to 1993, much of it in collaboration with Cucinotta and other NASA personnel, beginning after my retirement in 1979. Reference (*3*) presents a critical evaluation of that theory. Following are a number of additional references to assist the reader in evaluating the work in relation to the theory of Scholz and Kraft. Critical remarks by Goodhead in 1991 may be found as ref. (*15*). Reference (*16*) is an intermediate review article written by Katz in 1978. Figure 15 of that paper is a photograph of the stopping end of heavy-ion tracks in emulsion which makes it clear that the greatest damage is not done at the Bragg peak. LET is not necessarily a good indicator of radiation damage. Additional papers on particle tracks in nuclear emulsion are found in refs. (*17*) and (*18*). Reference (*19*) treats beams of particles and the effect of mixed radiation fields. Reference (*20*) relates experiment and theory for cellular inactivation by a mixed field of neutrons and γ rays. Its results demonstrate the validity of separating the action of heavy ions into two modes, ion kill and γ kill, where the dose from supplementary exposure to γ rays is simply added to the γ-kill dose. Reference (*21*) describes cellular radiosensitivity parameters achieved by least-squares computer fits. In Table 3 of that paper, the parameters achieved from the entire set of data and from a reduced number of data points, restricted to the second or third decade of surviving fractions, are shown. These are in remarkable agreement. This demonstrates the strength of the constraint of data for high-LET radiation on the radiosensitivity parameters of Katz theory. Note that these include the multitarget survival model for γ rays, an item of contention by those favoring the LQ model. Reference (*23*) displays the relationship between experimental and calculated RBE values for 10, 100 and 1000 MeV protons, displaying the influence of fragmentation. In all cases the calculated surviving fraction of Chinese hamster cells is represented by a survival curve with a shoulder. Reference (*24*) describes the relationship between the model of Butts and Katz and measured cross sections for both single- and double-strand breaks of SV-40 virus in EO buffer after heavy-ion irradiation, leading to the conclusion that both sets of data may be ascribed to one-hit detectors. Reference (*25*) describes similar fits for *E. coli* mutants. Reference (*26*) shows the increase in these ion-kill probability with atomic number in the spread Bragg peak of the bombarding ions. This result is consistent with the findings of Castro that the benefits of fractionation decrease with an increase in the atomic number of the bombarding ion. This leads to the suggestion that problems with fractionation

may be encountered with carbon-ion and neutron therapy. Indeed, in both cases, it has been expeditious to reduce the number of fractions with no clinically observed loss of effectiveness. The ability to reduce the number of fractions seems to imply that some of the benefits of fractionation are lost in these modalities. One is also led to wonder whether the neglect of ion kill in treatment planning has contributed to the failure of neutron therapy in some installations. Reference (*27*) takes a different turn. It examines the meaning of dose at low fluence and notes that there is an implicit radiobiological approximation that both dose and biological matter are amorphous, like butter, an approximation that is reasonable at high fluence but surely questionable at low fluence. Radiation is particulate, due to a ''rain'' of charged particles. When only a few particles ''rain'' on 100 μm^2 of tissue, the effect cannot be imagined as a uniform distribution. This suggests that the extrapolation of experimental findings to a fluence below one particle per square micrometer in tissue violates a proposed low-fluence threshold and may be invalid. A redefinition of dose to include a low-fluence proviso is suggested. Reference (*28*) describes the Katz theory's prediction of microbeam experiments with protons and α particles.

Katz theory, with reference to the model of Scholz and Kraft. Some of the points illuminated in Katz theory should be self evident once they are identified. To name a few: (1) The effects of high-LET radiation have their biological origin in the response to γ rays. That response is transferred to *identical* targets exposed to heavy ions by the physics of track structure, for in both cases secondary electrons are the basis of damage. Note in particular that the target for γ rays must be identical in all respects to the target for δ rays. In the Scholz-Kraft model, the targets for γ rays are living cells in culture, while δ rays see ''point targets'' in an amorphous approximation to a cell nucleus. (2) In Katz theory, at low fluence, all effects are due to single heavy-ion transits, computed from fluence and cross section, and the effect is thus exponential in form and is labeled ion kill; its probability arises from the value of z^{*2}/β^2 of the projectile, where z^* is the effective charge and β is the projectile speed relative to the speed of light, a parameter named κ which combines size and radiosensitivity, and a target parameter, m, the ''hittedness'' or the ''target number'' in the dose–effect relationship for γ radiation. (3) At high fluence there is an additional contribution from collaborating δ rays from neighboring ions called γ kill, which is best described by the dose–effect relationship for γ rays. (4) The probability for ion kill is used as an approximation to the portion of the dose assigned to ion kill. (5) Note that Katz theory uses two modes of radiation action. This makes it possible to explain the difference between the effects of low- and high-LET radiations. All effects of low-LET radiations are attributed to γ kill, and all effects of high-LET radiations are attributed to ion kill. (6) Cross section is the probability per unit fluence. In Katz theory, it is calculated as the radial integral of the probability of achieving the observed end point. This is calculated from the dose–effect relationship observed with γ rays, coupled to the radial distribution of dose about an ion's path, to yield the radial distribution of the probability for inactivating a target exposed to δ rays. A further approximation made is that the average dose a relatively small target experiences is adequate for the intended purpose. (7) Note also that the Katz theory is predictive, even when its calculated results follow the publication of specific radiobiological experiments, because all its calculations are based on published equations and published cell parameters (*13*) that have been fitted previously to sets of survival curves arising from an array of bombardments with high-LET particles. Its calculations may be repeated by anyone proficient in computer code. What is required in addition is knowledge of the particle-energy spectrum of all projectiles in the radiation field, including any γ-ray admixture. (8) Its predictions include the prediction of inactivation cross sections for dry enzymes and viruses, the results of microbeam experiments with single α particles and single protons, survival curves for neutrons even when admixed with γ rays, and dose–effect relationships for varied distances along the path of an ion beam and of a range-modulated beam. Neither a microdosimetric distribution, a distribution in LET, nor Monte Carlo calculations suffice. (9) Microbeam experiments with counted numbers of protons incident on V79-379A cell nuclei (*29*) have displayed a response with a shoulder after exposure to 5, 15, 30 and 60 3 MeV protons, while no inactivated cells have been observed for single proton transits through nuclei. (10) Note that the decrease in inactivation cross section with an increase in the LET of the bombarding ion was predicted by Katz a generation before it was observed experimentally (*1*) and was identified as ''thin-down'' from its relationship to the appearance of heavy-ion tracks in nuclear emulsion as the ion approached the end of its range (*30*). These results and more have been achieved with what is now called the amorphous track model to emphasize the detail in Monte Carlo calculations. (11) Katz theory makes use of a multitarget expression to describe the survival of cells after γ irradiation. This is essential to the model, since otherwise it is not possible to achieve a single four-parameter fit (with the same four parameters) for all members of a family of survival curves for high-LET radiations. (12) The linear-quadratic formula makes no predictions and is not falsifiable. Further, its extrapolation to low dose is questionable, by experiment (*31*), and because it neglects the low-fluence limit for the concept of dose. Dose is customarily approximated as amorphous, like butter, an approximation valid at high fluence but questionable at low fluence. For cells and tissue, the low-fluence limit where the amorphous approximation at low dose fails is one particle per square micrometer, where 37% of the 1-μm^2 pixels covering the irradiated area are not traversed by a bombarding particle. It is surely absurd at a fluence of one particle per 100 μm^2. Yet this low-fluence limit for the validity of the extrapolation to low dose is ignored in most treatments, for

both low- and high-LET radiations, largely as a result of their focus on dose, without regard to the implied fluence.

On equality with Katz theory. Let us suppose that Scholz and Kraft reject the above criticisms as invalid and seek to demonstrate that their model is at least equal to Katz theory. They might seek to emulate selections from the preceding list of its accomplishments.

On superiority to Katz theory. There are tasks that the Katz theory has not been able to perform. Thus it has not been able to create a predictive model of repair or of cellular response to variable dose rates with either γ rays or heavy ions. It is not yet able to predict the production of micronuclei in microbeam experiments with protons or α particles. Nor is it able to predict the probability of cell killing with somewhat more than one proton or α-particle transit through a single nucleus. Nor has it been able to create a predictive model of cancer production. These accomplishments would yield a clear indication of superiority.

CONCLUSIONS

The local effects model of Scholz and Kraft is not parameter-free, as claimed. Additionally, it suffers from defects in both physics and radiobiology. Its claim to be superior to, more refined than, and more sophisticated than the Katz theory is without foundation. Yet one should not neglect its merit for the instruction of students in radiobiology and radiation oncology, so that they may resolve for themselves the questions at issue here.

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REFERENCES

1. R. Katz, S. C. Sharma and M. Homayoonfar, The structure of particle tracks. In *Topics in Radiation Dosimetry* (F. H. Attix, Ed.), pp. 317–383. Academic Press, New York, 1972.
2. R. Katz, F. A. Cucinotta, J. W. Wilson, J. L. Shinn and D. M. Ngo, A model of cell damage in space flight. In *Biological Effects and Physics of Solar and Galactic Cosmic Radiation, Part A* (C. E. Swenberg, G. Horneck and E. G. Stassinopoulos, Eds.), pp. 235–268. Plenum Press, New York, 1993.
3. F. A. Cucinotta, H. Nikjoo and D. Goodhead, Applications of amorphous track models in radiation biology. *Radiat. Environ. Biophys.* **38**, 81–92 (1999).
4. M. Scholz and G. Kraft, A parameter free track structure model for heavy ion action cross sections. In *Biophysical Modelling of Radiation Effects* (K. H. Chadwick, G. Moschini and M. N. Varma, Eds.), pp. 185–192. Adam Hilger, New York, 1992.
5. M. Scholz and G. Kraft, Calculation of heavy ion inactivation probabilities based on track structure, X-ray sensitivity and target size. *Radiat. Prot. Dosim.* **52**, 29–33 (1994).
6. M. Scholz, W. Kraft-Weyrather and G. Kraft, Calculation of mammalian cell survival in complex charged particle fields. In *Scientific Report 1994* (U. Grundinger, Ed.), p. 222. GSI 94-1, Gesellschaft fur Schwerionenforschung, Darmstadt, 1995.
7. G. Kraft, M. Scholz and U. Bechthold, Tumor therapy and track structure. *Radiat. Environ. Biophys.* **38**, 229–237 (1999).
8. R. Katz and M. N. Varma, Radial Distribution of Dose. In *Physical and Chemical Mechanisms in Molecular Radiation Biology* (W. A. Glass and M. N. Varma, Eds.), pp. 163–180. Plenum Press, New York, 1991.
9. R. Katz, Cross section. *Appl. Radiat. Isot.* **41**, 563–567 (1990).
10. H. Dertinger and H. Jung, *Molecular Radiation Biology*. Springer-Verlag, New York, 1970.
11. F. Hutchinson and E. Pollard, Target theory and radiation effects in biological molecules. In *Mechanisms in Radiobiology*, Vol. 1 (M. Errera and A. Forssberg, Eds.), pp. 71–92. Academic Press, New York, 1961.
12. H. Paganetti and M. Goitein, Biophysical modelling of proton radiation effects based on amorphous track models. *Int. J. Radiat. Biol.* **77**, 911–928 (2001).
13. R. Katz, R. Zachariah, C. X. Zhang and F. A. Cucinotta, A survey of cellular radiosensitivity parameters. *Radiat. Res.* **137**, 356–365 (1994).
14. C. F. Powell, P. H. Fowler and D. H. Perkins, *The Study of Elementary Particles by the Photographic Method*. Pergamon Press, New York, 1959.
15. D. T. Goodhead, Biophysical modelling in radiation protection. In *Biophysical Modelling of Radiation Effects* (K. H. Chadwick, G. Moschini and M. N. Varma, Eds.), pp. 113–124. Adam Hilger, Bristol 1992.
16. R. Katz, Track structure theory in radiobiology and in radiation detection. In *Solid State Nuclear Track Detectors*, Vol. 1 (F. Granzer, H. Paretzke and E. Schopper, Eds.), pp. 1–28. Pergamon Press, New York, 1978.
17. R. Katz and E. J. Kobetich, Particle tracks in emulsion. *Phys. Rev.* **186**, 344–351 (1969).
18. R. Katz, A. S-F. Li, Y-L. Chang, R. L. Rosman and E. V. Benton, Tracks of argon ions in Ilford K-series nuclear emulsions. In *Solid State Nuclear Track Detectors* (H. Francois, N. Kurtz, J. P. Massue, M. Monnin, R. Schmitt and. A. Durrani, Eds.), pp. 101–109. Pergamon Press, New York, 1980.
19. R. Katz and S. C. Sharma, Response of cells to fast neutrons, stopped pions, and heavy ion beams. *Nucl. Instrum. Meas.* **111**, 93–116 (1973).
20. R. Katz and S. C. Sharma, Cellular survival in a mixed radiation environment. *Int. J. Radiat. Biol.* **26**, 143–146 (1974).
21. R. A. Roth, S. C. Sharma and R. Katz, Systematic evaluation of cellular radiosensitivity parameters. *Phys. Med. Biol.* **21**, 491–503 (1976).
22. R. A. Roth and R. Katz, Heavy ion beam model for radiobiology. *Radiat. Res.* **83**, 499–501 (1980).
23. F. A. Cucinotta, R. Katz, J. W. Wilson, L. W. Townsend, J. Shinn and F. Hajnal, Biological effectiveness of high-energy protons: Target fragmentation. *Radiat. Res.* **127**, 130–137 (1991).
24. R. Katz and S. Wesely, Cross sections for single and double strand breaks in SV-40 virus in EO buffer after heavy ion irradiation: experiment and theory. *Radiat. Environ. Biophys.* **30**, 81–85 (1991).
25. R. Katz and R. Zachariah, Experimental and theoretical cross sections for *Escherichia coli* mutants, B, B/r and B_{S-1} after heavy ion irradiation. *Radiat. Res.* **134**, 261–264 (1993).
26. R. Katz and F. A. Cucinotta, Tracks to therapy. *Radiat. Meas.* **31**, 379–388 (1999).
27. R. Katz and F. A. Cucinotta, Low fluence. *Adv. Space Res.* **31**, 1553–1555 (2003).
28. R. Katz and F. A. Cucinotta, Track theory predictions for single-hit cell survival. *Radiat. Res.* **153**, 225–226 (2000).
29. M. Folkard, K. M. Prise, B. Vojnovic, A. G. Bowey, G. Schettino

and B. D. Michael, Targeting cells individually using a charged-particle microbeam: The biological effects of single or multiple traversals of protons and $^{3}He^{2+}$ Ions. In *Microdosimetry, An Interdisciplinary Approach* (D. T. Goodhead, P. O'Neill and H. G. Menzel, Eds.), pp. 323–326. The Royal Society of Chemistry, London, 1997.

30. R. Katz, D. E. Dunn and G. L. Sinclair, Thindown in radiobiology. *Radiat. Prot. Dosim.* **13**, 281–284 (1985).

31. L. D. Skarsgard, A. A. Hill and D. K. Acheson, Evidence for two forms of substructure in the cell survival curve. *Acta Oncol.* **38**, 895–902 (1999).