IN 61

51145

P-11

**NASA
Technical
Paper
3124**

November 1991

Cellular
Repair/Misrepair
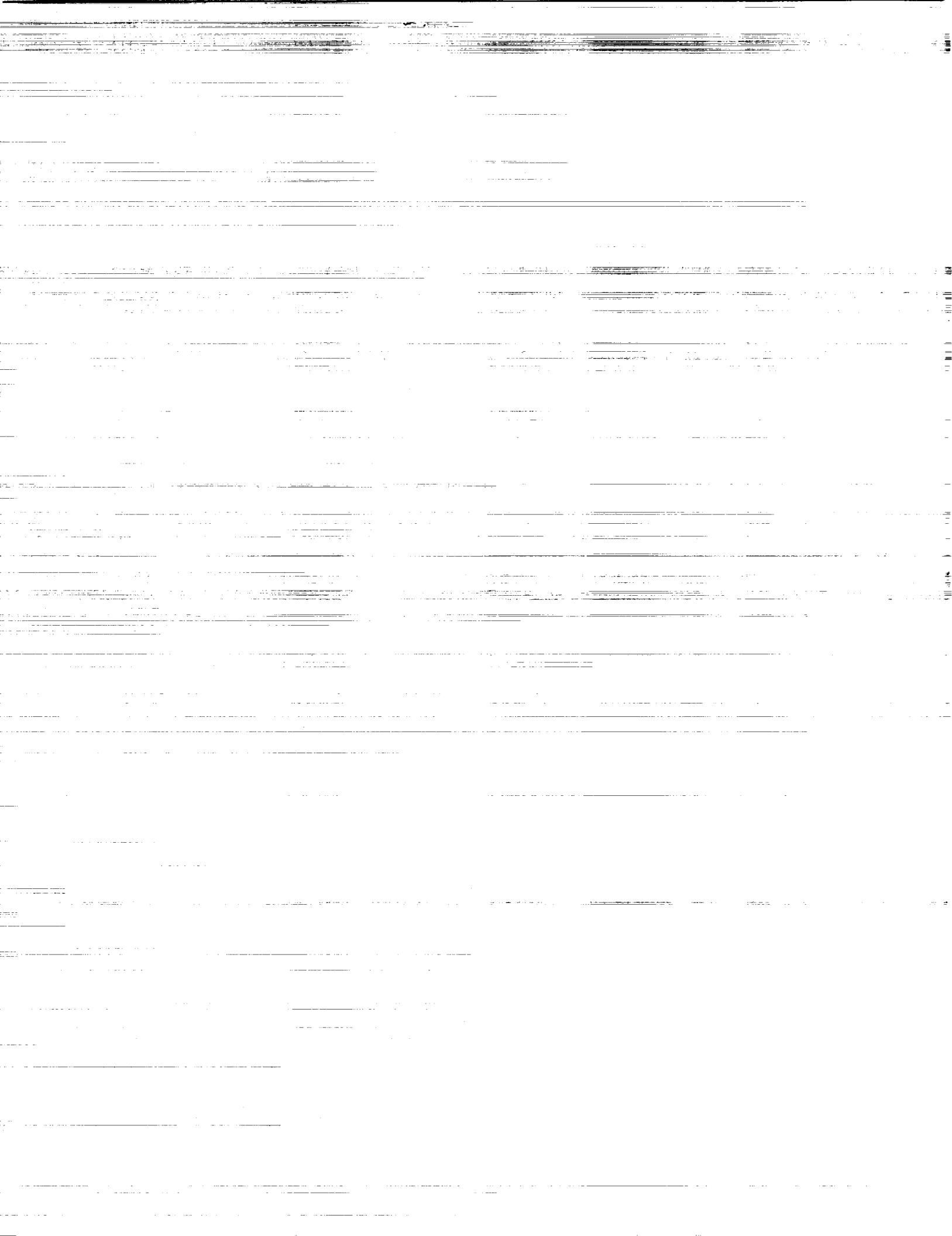Track Model

John W. Wilson and
Francis A. Cucinotta

NASA

Cellular Repair/Misrepair Track Model

John W. Wilson and
Francis A. Cucinotta
Langley Research Center
Hampton, Virginia

Summary

A repair/misrepair cell kinetics model is super-imposed onto the track structure model of Katz to provide for a repair mechanism. The model is tested on the repair-dependent data of Yang et al. and provides an adequate description of that data. The misrepair rate determines the maximum relative biological effectiveness (RBE), but similar results could arise from indirect X-ray lethality not included in the present model.

Introduction

It was Schaefer's original suggestion that track structure would be an important parameter in controlling biochemical reactions in cell response to ionizing radiation (ref. 1). Further insight was gained through Katz's introduction of a geometric view to sensitive biological sites (ref. 2), resulting in a phenomenological model that has been successful in interpreting and extrapolating cell response data for high-energy heavy ion (HZE) particles (ref. 3). The main criticism of the Katz model has been the lack of a clear mechanism for repair processes (ref. 4). We propose herein a step toward a simple repair model in which kinetic coefficients are related to the Katz parameters.

Repair/Misrepair Track Model

We consider a three-level system which contains single- and double-level ionizing radiation transitions and a repair/misrepair process for single-level cells. The appropriate equations are given as

$$\dot{n}_0 = -kn_0 + \alpha_r n_1 \tag{1}$$

$$\dot{n}_1 = k_s n_0 - k_s n_1 - \alpha n_1 \tag{2}$$

$$\dot{n}_2 = k_D n_0 + k_s n_1 + \alpha_m n_1 \tag{3}$$

where n_i is the number of cells in level i, α is the total repair/misrepair rate coefficient, α_r is the repair rate coefficient, α_m is the misrepair rate coefficient, k_s is the single-step radiation transition coefficient, k_D is the double-step radiation transition coefficient, and $k = k_s + k_D$. The uppermost level is assumed not to repair and that misrepair appears as a transition to the upper level independent of the radiation source (that is, an inherent biochemical rate). If we consider very high exposure over a limited time period, then repair processes may be neglected and the solutions to equations (1) to (3) are approximately

$$n_0(t_r) = n_0(0)e^{-kt_r} \tag{4}$$

$$n_1(t_r) \approx n_0(0)k_s t_r e^{-kt_r} \tag{5}$$

$$n_2(t_r) = n_0(0)\frac{k_D}{k}\left(1 - e^{-kt_r}\right)$$
$$+ n_0\frac{k_s^2}{k^2}\left[1 - (1 + kt_r)e^{-kt_r}\right] \tag{6}$$

where $n_i(t_r)$ is the i-level population after exposure period t_r and $n_0(0)$ is the initial population. The symbol represents reaction rates related to radiation-induced lesions within the nucleus (presumably chromosomes) and the rates are assumed proportional to particle flux (primary ions or secondary charged products). The lesions are chemically active species neutralized by enzyme activity at rate constants α_i. After the exposure, the repair processes proceed at rates dependent on the experimental protocol (ref. 5). The repair proceeds as

$$\dot{n}_0 = \alpha_r n_1 \tag{7}$$

$$\dot{n}_1 = -\alpha n_1 \tag{8}$$

$$\dot{n}_2 = \alpha_m n_1 \tag{9}$$

The solutions are found, assuming a constant rate of repair throughout the repair period, as

$$n_0(t) = n_0(t_r) + \frac{\alpha_r}{\alpha}n_1(t_r)(1 - e^{-\alpha t}) \tag{10}$$

$$n_1(t) = n_1(t_r)e^{-\alpha t} \tag{11}$$

$$n_2(t) = n_2(t_r) + \frac{\alpha_m}{\alpha}n_1(t_r)(1 - e^{-\alpha t}) \tag{12}$$

So, the final state of the system is given in terms of repair/misrepair ratios as

$$n_0(\infty) = n_0(0)\left(e^{-kt_r} + \frac{\alpha_r}{\alpha}k_s t_r e^{-kt_r}\right) \tag{13}$$

$$n_2(\infty) = n_0(0) - n_0(\infty) \tag{14}$$

In the limit of low exposure we find

$$\frac{n_0(\infty)}{n_0} \approx 1 - kt_r\left(1 - \frac{\alpha_r}{\alpha}\frac{k_s}{k}\right) - \frac{1}{2}\left(2\frac{\alpha_r}{\alpha}\frac{k_s}{k} - 1\right)k^2 t_r^2 \tag{15}$$

which displays typical two-target response in the limit as $\frac{\alpha_r}{\alpha} \rightarrow 1$ and $k_D \rightarrow 0$. We now seek an understanding of the kinetic coefficients in terms of the Katz model.

Katz Model

The cellular track model of Katz has been described extensively (refs. 2 and 3). The track model attributes biological damage from energetic ions to the secondary electrons (delta rays) produced along

the ion path. Cell inactivation is separated into a so-called grain-count regime, where inactivation occurs randomly along the path of the particle, and into the so-called track-width regime, where many inactivations occur and are said to be distributed like a "hairy rope." Four cellular parameters describe the response of the cells, two of which (m, the number of targets per cell, and D_0, the characteristic X-ray dose) are extracted from the response of the cellular system to X and γ irradiation. The other two (σ_0, interpreted as the cross-sectional area of the cell nucleus within which the inactivation sites are located, and κ, a measurement of the size of the inactivation site) are found principally from survival measurements after track-segment irradiations with energetic, charged particles. The transition from the grain-count regime to the track-width regime takes place at $Z^{*2}/\kappa\beta^2 \approx 4$, where Z^* is the effective charge number and β is the velocity. At lower values, we are in the grain-count regime and at higher values the track-width regime.

To accommodate for the capacity of cells to accumulate sublethal damage, two modes of inactivation are identified: "ion kill" (corresponding to intratrack effects) and "gamma kill" (corresponding to inter-track effects). When the passage of a single ion damages cells, the ion-kill mode occurs. In the grain-count regime, the fraction of cells damaged in the ion-kill mode is taken as $P = \sigma/\sigma_0$, where σ is the single-particle inactivation cross section and P is the probability of damage in the ion-kill mode. The track model assumes that a fraction of the ion dose $(1 - P)$ acts cumulatively with that from other particles to inactivate cells in the gamma-kill mode. The surviving fraction of a cellular population $n_0(0)$, whose response parameters are m, D_0, and κ after irradiation by a fluence of particles F, is written

$$\frac{n_0(\infty)}{n_0(0)} = \pi_i \times \pi_\gamma \qquad (16)$$

where

$$\pi_i = e^{-\sigma F} \qquad (17)$$

is the ion-kill survival probability and

$$\pi_\gamma = 1 - \left(1 - e^{-D_\gamma/D_0}\right)^m \qquad (18)$$

is the gamma-kill survival probability. The gamma-kill dose fraction is

$$D_\gamma = (1 - P)D \qquad (19)$$

where D is the absorbed dose. The single-particle inactivation cross section σ is taken in the grain-

count regime as

$$\sigma = \sigma_0 \left(1 - e^{-Z^{*2}/\kappa\beta^2}\right)^m \qquad (20)$$

where the effective charge number is given by

$$Z^* = Z\left(1 - e^{-125\beta/Z^{2/3}}\right) \qquad (21)$$

where Z is the charge number of the projectile. In the track-width regime, $P = 1$, we take $\pi_\gamma = 1$.

The relative biological effectiveness (RBE) at a specific survival level for an ion exposure D_i is given by

$$\text{RBE} = D_X/D_i \qquad (22)$$

where

$$D_X = -D_0 \ln\left\{1 - \left[1 - \frac{n_0(\infty)}{n_0(0)}\right]^{1/m}\right\} \qquad (23)$$

is the X-ray dose at which this level is obtained. Equations (16) through (23) represent the cellular track model for monoenergetic particles. We must now consider the relationship of the kinetic model to the Katz model.

For HZE particles $k_D \gg k_s \approx 0$ in accordance to Katz for the track-width region and

$$\frac{n_0(\infty)}{n_0(0)} \approx e^{-k_D t_r} \equiv e^{-\sigma F} \qquad (24)$$

Similarly, for the complete repair limit, we find

$$k_s t_r \approx \sqrt{2}\frac{D_\gamma}{D_0} \qquad (25)$$

so that equations (24) and (25) embody the track structure of a Katz model with two targets. We may now rewrite equation (13) in terms of the Katz parameters as

$$\frac{n_0(\infty)}{n_0(0)} = e^{-\sigma F - \sqrt{2}D_\gamma/D_0}$$

$$+ \frac{\alpha_r}{\alpha}\frac{\sqrt{2}D_\gamma}{D_0}e^{-\sigma F - \sqrt{2}D_\gamma/D_0} \qquad (26)$$

where σF and D_γ have their usual functional form according to Katz and the parameter $\frac{\alpha_r}{\alpha}$ describes repair/misrepair.

In the usual application of the Katz formalism, the parameter D_0 has represented the degree of repair (ref. 3). For example, in the delayed plating experiments of Yang et al. (ref. 5), D_0 was found to

be much larger than for Yang's experiments with immediate plating. (The term plating refers to the process of separating the cells after exposure and placing them into nutrient media to stimulate growth.) If we assume that repair is maximized $\left(\frac{\alpha_r}{\alpha} \approx 1\right)$ in the delayed plating experiments (refs. 6 and 7), then the higher value of D_0 is appropriate for the current two-level model, while a smaller value of $\frac{\alpha_r}{\alpha}$ is assumed for the immediate plated experiments.

Effects of RBE

We now discuss the effects of repair on the RBE in the context of the current track model. An ion of sufficient charge contributes to the σF term only while γ-rays contribute only through the D_γ/D_0 multitarget term (that is, $\sigma \neq 0$ for γ-rays implies indirect processes not presently accounted for in the Katz model). The ion linear response is

$$\frac{n_0(\infty)}{n_0(0)} = 1 - \frac{\sigma D_i}{L} - \frac{\alpha_m}{\alpha}\left(1 - \frac{\sigma}{\sigma_0}\right)\frac{\sqrt{2}D_i}{D_0} \quad (27)$$

where L is the linear energy transfer (LET). The γ-ray response is

$$\frac{n_0(\infty)}{n_0(0)} = e^{-\sqrt{2}D_\gamma/D_0} + \frac{\alpha_r}{\alpha}\frac{\sqrt{2}D_\gamma}{D_0}e^{-\sqrt{2}D_\gamma/D_0} \quad (28)$$

At low exposure, an effective γ-ray exposure can be found as

$$\frac{D_\gamma}{D_0} \approx \left[\frac{\alpha}{2(\alpha_r - \alpha_m)}\right]\left\{\left[2\frac{\alpha_m^2}{\alpha^2} + 4\left(\frac{\alpha_r}{\alpha} - \frac{\alpha_m}{\alpha}\right)\frac{\sigma}{L}D_i\right]^{1/2}\right.$$
$$\left. - \sqrt{2}\frac{\alpha_m}{\alpha}\right\} \quad (29)$$

Comparing linear terms, we find

$$\text{RBE} \approx \frac{D_0}{\sqrt{2}}\frac{\alpha}{\alpha_m}\frac{\sigma}{L} + 1 - \frac{\sigma}{\sigma_0} \quad (30)$$

which is unbound for small misrepair rates ($\alpha_m \to 0$) as is typical for the Katz multitarget model (ref. 8). In the limit of complete repair, a minimum of two γ-ray tracks is needed for a nonzero response, and we find an RBE close to the Katz model where

$$\text{RBE} \approx D_0\left(\frac{\sigma}{LD_i}\right)^{1/2} \quad (31)$$

as found by Cucinotta (ref. 8). In the present model, the linear response at low dose is related to misrepair

but may be indistinguishable from possible indirect contributions.

Three-Target Repair/Misrepair Systems

The above can be extended to an approximate three-target system as

$$\frac{n_0(\infty)}{n_0(0)} \approx \left(1 + \frac{\alpha_r}{\alpha}6^{1/3}\frac{D_\gamma}{D_0} + \frac{\alpha_r'}{\alpha'}\frac{6^{2/3}}{2}\frac{D_\gamma^2}{D_0^2}\right)$$
$$\times e^{-\sigma F - 6^{1/3}D_\gamma/D_0} \quad (32)$$

where D_γ, D_0, and σF are related to the usual Katz model for $m = 3$ and $\frac{\alpha_r}{\alpha}$, $\frac{\alpha_r'}{\alpha'}$ are the repair ratios for the once-hit and twice-hit cells. Presumably, $\frac{\alpha_r}{\alpha} \geq \frac{\alpha_r'}{\alpha'}$. We take

$$\frac{\alpha_r'}{\alpha'} = \left(\frac{\alpha_r}{\alpha}\right)^p \quad (33)$$

in the present analysis and expect p to be 2 or greater. In the limit of vanishing dose,

$$\text{RBE} \approx \frac{D_0}{6^{2/3}}\frac{\alpha}{\alpha_m}\frac{\sigma}{L} + 1 - \frac{\sigma}{\sigma_0} \quad (34)$$

similar to the two-target system discussed above. In the limit of complete repair, the RBE variation is closely related to the Katz model result of

$$\text{RBE} \approx D_0\left(\frac{\sigma}{L}\right)^{1/3}\frac{1}{D_i^{2/3}} \quad (35)$$

as noted elsewhere by Cucinotta et al. (ref. 8).

Application to Cell Survival

The experiment of Yang et al. (ref. 5) has utilized contact-stabilized mouse cells C3H10T½ in the G_1 phase. In one set of experiments, the cells remained in the G_1 phase for 24 hours before separation and introduction into a nutrient medium to stimulate growth (delayed plating). A second series of cells was immediately plated, causing them to enter the synthesis cycle (S phase) soon after exposure: This greatly alters the cell kinetics. It is well known (ref. 7) that the G_1 phase is efficient in cell repair, while the S phase is mistake prone (ref. 6). We assume the G_1 phase repair ratio $\frac{\alpha_r}{\alpha}$ is near maximum, while later phase cells have a significant rate of misrepair (especially S phase for some mouse cells). Furthermore, the survival of the mouse cell is shown by Katz to be a three-target system, and even higher rates of misrepair are expected from the doubly injured cell ($p > 2$).

3

The Katz parameters (see table I) for the delayed experiments (ref. 2) are used directly to estimate σF, D_0, D_γ with assumed $\frac{\alpha_r}{\alpha} = 1$ and provide a good fit, as expected, to the data of Yang et al. Good agreement is found for the immediately plated cells by taking $p = 6$ and $\frac{\alpha_r}{\alpha} = 0.7$. The results are shown in figure 1. The figure is arranged in the order of increasing linear energy transfer (LET), and the sigmoid behavior associated with multitarget phenomena is apparent for the lighter ions. The sigmoid behavior disappears at higher LET, and the repair processes become less effective as the ion-kill mechanism of Katz dominates.

Table I. Katz Parameters Used in the Present Track Structure Repair/Misrepair Model

	σ_0, cm^2	κ	m	D_0, Gy
C3H10T½	5×10^{-7}	750	3	2.8
Tradescantia	3.5×10^{-7}	1000	2	1.2

The radiation response of tradescantia to cell death is shown in figure 2 for the Katz parameters in table I (ref. 9) as an example of a two-target system. The effects of enhancing misrepair are shown in the figure for three different ions. The repair levels are taken for $\frac{\alpha_r}{\alpha} = 1$, 0.75, and 0.5. The effects of misrepair seem even more important for this two-target system.

Concluding Remarks

The primary hope engendered by the present study is the possibility of relating laboratory exposures at high dose rates to the continuous low exposure levels in space. The present work needs extension to cell transformation and may then provide a base for understanding cancer induction in living tissue systems.

NASA Langley Research Center
Hampton, VA 23665-5225
October 7, 1991

References

1. Schaefer, Hermann J.: Exposure Hazards From Cosmic Radiation Beyond the Stratosphere and in Free Space. *J. Aviation Med.*, vol. 23, no. 4, Aug. 1952, pp. 334-344.

2. Katz, R.; Ackerson B.; Homayoonfar, M.; and Sharma, S. C.: Inactivation of Cells by Heavy Ion Bombardment. *Radiation Res.*, vol. 47, 1971, pp. 402-425.

3. Waligorski, M. P. R.; Sinclair, G. L.; and Katz, R.: Radiosensitivity Parameters for Neoplastic Transformations in C3H10T1/2 Cells. *Radiation Res.*, vol. 111, 1987, pp. 424-437.

4. Curtis, Stanley B.: Lethal and Potentially Lethal Lesions Induced by Radiation—A Unified Repair Model. *Radiat. Res.*, vol. 106, 1986, pp. 252-270.

5. Yang, Tracy Chui-Hsu; Craise, Laurie M.; Mei, Man-Tong; and Tobias, Cornelius A.: Neoplastic Cell Transformation by High-Let Radiation: Molecular Mechanisms. *Adv. Space Res.*, vol. 9, no. 10, 1989, pp. (10)131-(10)140.

6. Radman, M.; Dohet, C.; Bourguignon, M. F.; Doubleday, O. P.; and Lecomte, P.: High Fidelity Devices in the Reproduction of DNA. *Chromosome Damage and Repair*, Erling Seeberg and Kjell Kleppe, eds., Plenum Press, c.1981, pp. 431-445.

7. Sinclair, Warren K.: Cyclic X-Ray Responses in Mammalian Cells in Vitro. *Radiat. Res.*, vol. 33, no. 3, Mar. 1968, pp. 620-643.

8. Cucinotta, Francis A.; Katz, Robert; Wilson, John W.; Townsend, Lawrence W.; Nealy, John E.; and Shinn, Judy L.: *Cellular Track Model of Biological Damage to Mammalian Cell Cultures From Galactic Cosmic Rays.* NASA TP-3055, 1991.

9. Katz, Robert: *Physical and Biological Data Used in Track Theory.* University of Kansas paper presented at the DOE/CEC Workshop on Critical Evaluation of Radiobiological Data for Use in Biophysical Modeling (Oak Ridge, Tennessee), June 22-25, 1988.
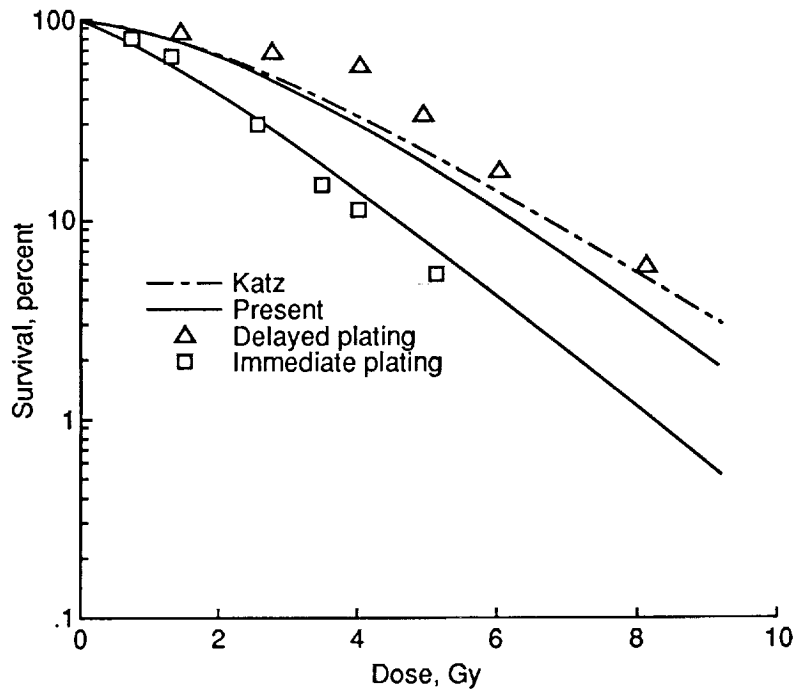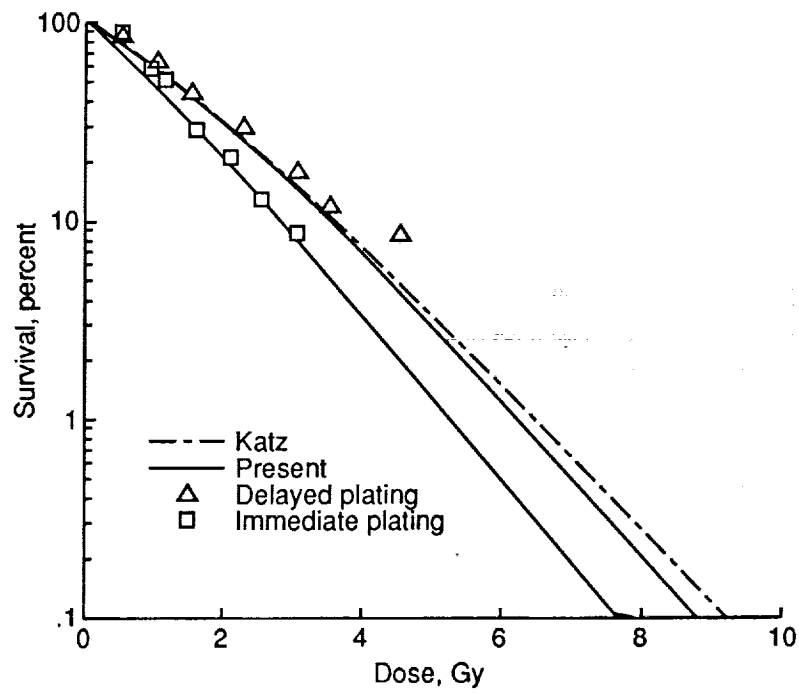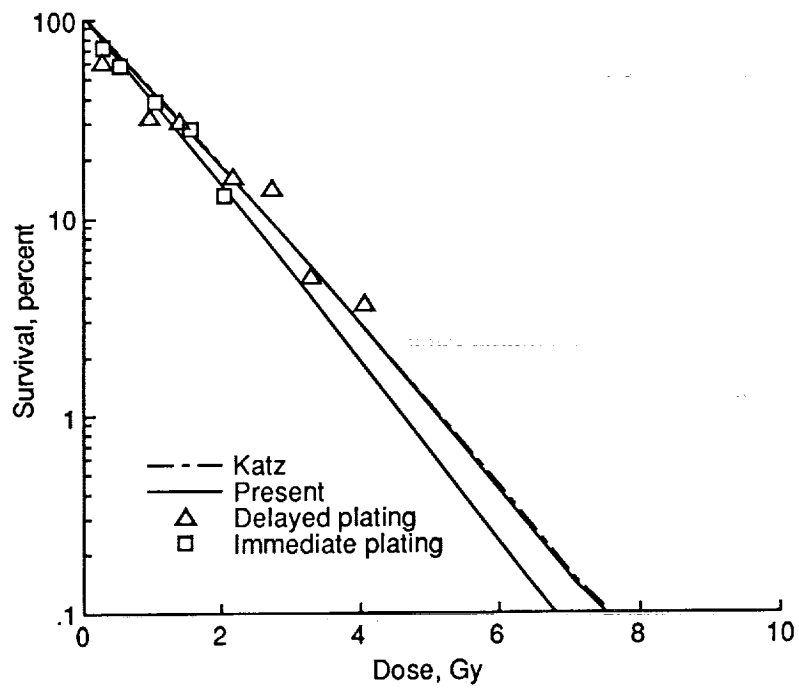
(a) ^{20}Ne, 425 MeV/amu, 32 keV/μm.
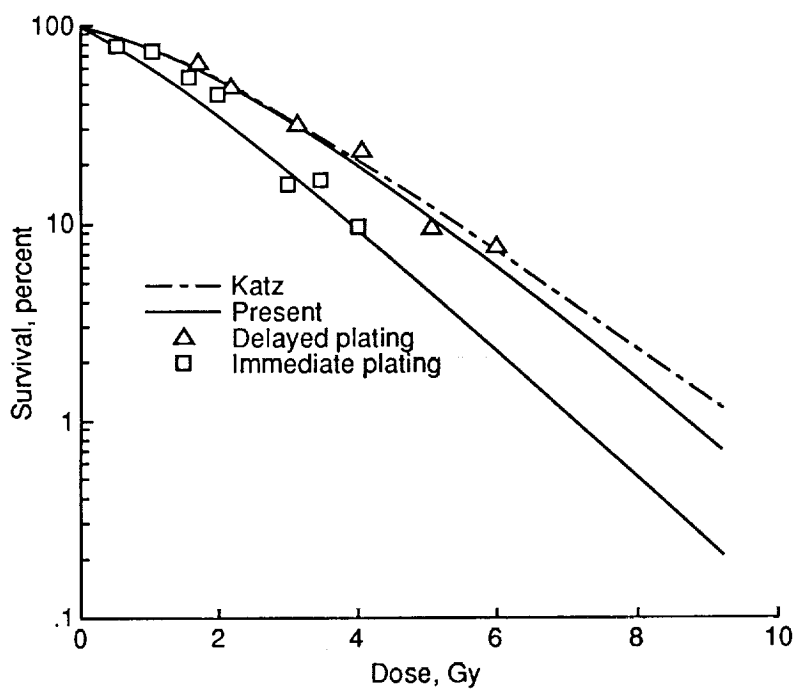
(b) ^{28}Si, 670 MeV/amu, 50 keV/μm.

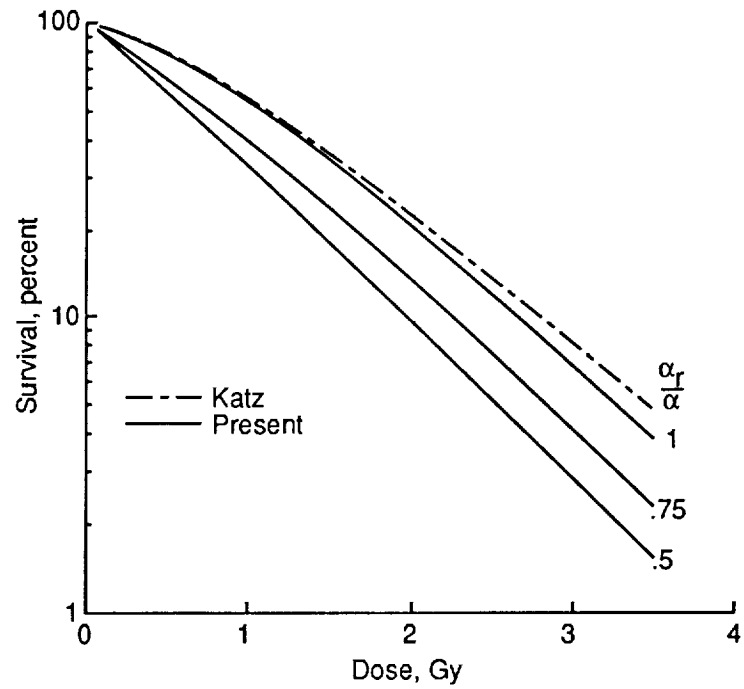Figure 1. Cell survival of C3H10T½ for delayed plating and immediate plating.
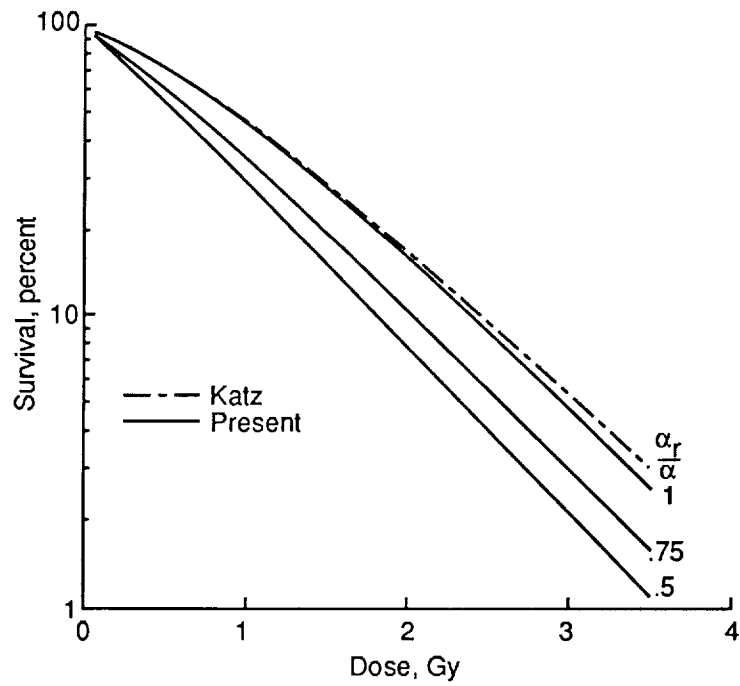
(c) ^{28}Si, 320 MeV/amu, 82 keV/μm.

(d) ^{56}Fe, 600 MeV/amu, 190 keV/μm.
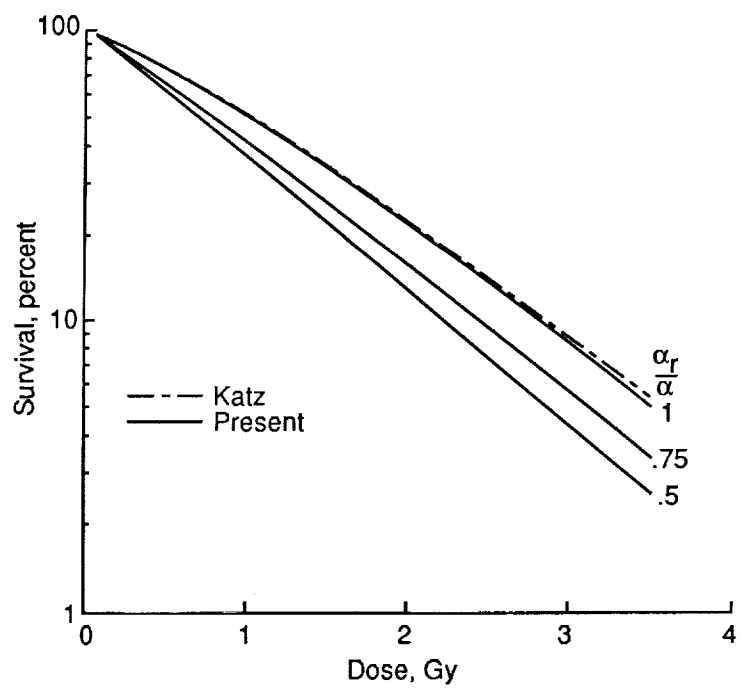
Figure 1. Concluded.

(a) ^{20}Ne, 425 MeV/amu, 32 keV/μm.

(b) ^{28}Si, 320 MeV/amu, 82 keV/μm.

Figure 2. Cell survival as a function of dose for various misrepair levels according to the present model and the original Katz model.

(c) ^{56}Fe, 600 MeV/amu, 190 keV/μm.

Figure 2. Concluded.

REPORT DOCUMENTATION PAGE

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY(Leave blank)	2. REPORT DATE November 1991	3. REPORT TYPE AND DATES COVERED Technical Paper	
4. TITLE AND SUBTITLE Cellular Repair/Misrepair Track Model			**5. FUNDING NUMBERS** WU 199-04-16-11
6. AUTHOR(S) John W. Wilson and Francis A. Cucinotta			
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) NASA Langley Research Center Hampton, VA 23665-5225			**8. PERFORMING ORGANIZATION REPORT NUMBER** L-16949
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) National Aeronautics and Space Administration Washington, DC 20546-0001			**10. SPONSORING/MONITORING AGENCY REPORT NUMBER** NASA TP-3124

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT Unclassified–Unlimited Subject Category 52	12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

A repair/misrepair cell kinetics model is superimposed onto the track structure model of Katz to provide for a repair mechanism. The model is tested on the repair-dependent data of Yang et al. and provides an adequate description of those data. Some mechanistic ambiguities are discussed.

14. SUBJECT TERMS Radiation injury; Repair model; Track structure		15. NUMBER OF PAGES 9
		16. PRICE CODE A02

17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

NSN 7540-01-280-5500

PAGE _____ INTENTIONALLY BLANK