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Supplementary File for:
SPACE RADIATION INDUCED BYSTANDER EFFECT IN ESTIMATING THE CARCINOGENIC RISK DUE TO GALACTIC COSMIC RAYS

Appendix A. HGT-CPS Library for Cells Survival Probability models to use in IR exposure Risks Assessment in Space

Using the R-Studio IDE, we developed an R-script library including all the relevant Cell Survival Probability (CSP) models both for the gamma-ray and CP relevant for space radiation and, to be used in the calculation of TP.

Cell survival curve describe the relationship between radiation dose and the proportion of cells which survive. It is quantified by the clonogenic tests that consist in determining the number of colonies resulting from a known number of irradiated cells. Several mathematical models were proposed to describe the survival curves, notably from the work done by Marie Curie at the beginning of the last century[3].

In the following CSP models the variable D refers to the Absorbed Dose.
The implemented CSP models in the library are:

(i) Target Theory n-target N-hit model (nTNH): cell survival probability
In this model, each target is destroyed after receiving N hits, and the cell is dead when all the targets in a cell are destroyed.

$$S(D) = 1 - (1 - B)^n \, , B = e^{\frac{-D}{D_0}} [1 + \sum_{2}^{N} \frac{(\frac{-D}{D_0})^{N-1}}{(N-1)!}] \, . \tag{A.1}$$

where:

D_0 is the mean lethal dose for which the mean number of lethal events per cell is equal to 1. At a dose D_0, the fraction of cell survival is equal to 1/e or 37% (for Theory single Target single hit model (sTSH)).
n is the number of identical targets in the cell that are susceptible to be damage from the IR
N is the number hit necessary to destroy a single target

Two special cases of nTNH including:

(a) Theory single Target single hit model (sTSH)
(b) Theory single Target N-hit model (sTNH)

(ii) Cellular Track Structure Theory (TST) for CP, again based on the multi-Target-Single Hit model.

TST, introduced by Katz in 1968, applies the concept of action cross section as the probability of targets in the radiation detector being activated to elicit the observed endpoint (e.g., cell).

The model takes in account that for ions the damage is produced by two different sources. The ion itself and the delta radiation production when the CP go through biological tissues or cells. That is it assumes the probability of effect (cell survival, S) to be the product of the Ion-kill and Gamma-kill probabilities (Π_i and Π_γ, respectively) [1,2].

The Gamma-kill probability is calculated by:

$$\Pi_\gamma = [1 - (1 - e^{\frac{-D}{D_0}})^{m_s}]\,. \tag{A.2}$$

The Ion-kill probability is given by:

$$\Pi_i = e^{-(\Sigma_0 P_s(Z,E)F)}\,. \tag{A.3}$$

$$where;\;\; P_s(Z_{CP}, E_{CP}) = [1 - e^{\frac{-Z^{*2}}{k\beta_c^2}}]^{m_s} \tag{A.4}$$

where:
Multi-target detectors, such as cells, are represented in TST by the following four parameter;

m_s is the Number of Target per Cell,
D_0 is the Radiosensitivity,
Σ_0 is the Cross Section Saturation Value
k is the Detector Saturation Index

while:

Z_{CP} is the charge number of the particle
E_{CP} is the kinetic energy of the particle
Z^* is the effective charge number of the particle
β_c is the particle velocity relative to the velocity of light,

Considering the track structure model equations (A.2) and (A.3), we introduced the CSP model for CP as:

$$S(D) = \Pi_\gamma * \Pi_i = [1 - (1 - e^{\frac{-D}{D_0}})^{m_s}] e^{-(\Sigma_0 P_s(Z_{CP}, E_{CP}) * \frac{(D*6.24)}{LET_{CP}})} . \quad (A.5)$$

where:

LET_{CP} is the Linear Energy Transfer of CP

(iii) Theory Linear Quadratic Model (LQ)

In 1972, Kellerer and Rossi introduced the linear-quadratic(LQ) model in which a lethal event is supposed to be caused by one hit due to one particle track (the linear component αD) or to the accumulated damage due to two particle tracks (the quadratic component βD^2).

$$S(D) = e^{-\alpha D - \beta D^2} . \quad (A.6)$$

where α and β are the linear and quadratic coefficients with dose induction terms.

(iv) Linear Quadratic Model modified by Hyper-Radiosensitivity (HRS) effect.

The LQ model is a monotonically function of dose; it cannot be used to describe the low-dose phenomena of HRS/Increased Radio-Resistance(IRR). In order to account for such phenomena, a modification of the LQ model was developed, called the Induced Repair (IR) model, given by:

$$S(D) = e^{[-\alpha(1+(\frac{\alpha_s}{\alpha}-1)e^{\frac{-D}{D_c}})D - \beta D^2]} . \quad (A.7)$$

where:

D_c is the dose at which the transition from HRS to IRR occurs,
$\alpha_s > \alpha$ is the initial slope of the surviving fraction curve at D = 0 Gy and represents the increased radio-sensitivity at low doses.

(v) Linear Quadratic Cubic Model (LQC)

This model was introduced to better describes the IR effects at the high doses usually used in the radiotherapy treatment. LQC was introduced by C.A. Tobias in 1985. By adding another cubic term to the polynomial function of the LQ model.

$$S(D) = e^{-\alpha D - \beta D^2 + \gamma D^3} . \quad (A.8)$$

where:

αD is the linear component
βD^2 is the quadratic component
γ are the cubic coefficients with dose induction terms.

(vi) Sublesion Theory Repair misRepair Model (S-RMR)

Proposed by Tobias in 1985, the repairmisrepair (RMR) model describes the evolution of the function, U(t), that reflects the mean number of lesions before any repair activation. The yield of the initially induced lesions, U_0, was considered proportional to the dose D:

$$U_0(D) = \delta D\,. \tag{A.9}$$

Where:

δ is the proportionality constant of the radiation quality

By considering that the linear repair is not a perfect process, that the repair time is limited in time, the survival equation becomes:

$$S_\phi(D) = e^{-U_0(D)}[1 + \frac{U_0(D)(1 - e^{-\lambda t_r})}{\epsilon}]^{\epsilon\phi}\,. \tag{A.10}$$

Where:

t_r is the repair time after irradiation,
λ is the rate constant for linear repair processes,
ϵ is the ratio of λ and K,
ϕ is the probability that self-repair steps are perfect eurepairs (or good repair)

(vii) Sub-lesion Theory Lethal potentially lethal Model (S-LPL)

Curtis developed in 1986 the Lethal-Potentially Lethal(LPL) model that takes the repair process into account. He proposed a classification of the radio-induced lesions:

- lesions that are unrepairable and are therefore *lethal*
- *potentially lethal lesions* for which the repair process is activated

The survival equation that allows to predict the survival ratio is:

$$S(D) = e^{-N_{tot}(D)}[1 + \frac{(N_{PL}(D))}{\epsilon(1 - e^{-\epsilon_{PL} t_\tau})}]^{\epsilon}\,. \tag{A.11}$$

where:

T is the irradiation time,
tr is the available repair time after irradiation,
$N_{tot}(D)$ is the number of total lesions (sum of lethal lesions and potentially lethal lesions) at the end of the exposure time T,
$N_{PL}(D)$ is number of potentially lethal lesions at the end of the exposure time T
ϵ_{PL} the constant per unit of time repair rate,
ϵ_{2PL} the constant per unit of time rate of interaction between two potentially lethal lesions
ϵ is the ratio between ϵ_{PL} and ϵ_{2PL}

(viii) Sublesion Theory Saturable Repair Model (S-SR)

In 1985, Goodhead proposed model, the Saturable Repair Model that was based on the hypothesis that the efficiency of the repair system decreases with the dose, and that this decrease is caused by the saturation of the repair kinetics[3].

Using this hypothesis, the survival equation becomes:

$$S(D) = e^{-\frac{n_0(D)-C_0}{1-\frac{C_0}{n_0(D)}kt_r(C_0-n_0(D))}}. \tag{A.12}$$

where:

t_r is the time available for repair after irradiation,
$n_0(D)$ is the initial number of lesion due to dose D,
C_0 is the initial number of available repair molecules or enzymes,
k is a proportionality coefficient,

Appendix B. Proton LET vs Kinetic Energy fit function

To calculate the Proton LET for the different energies present in the AMS Data set we used a function (equation B.1) that we created using published data. The data were fitted using polynomial best fit and we use the linear interpolation between the data gaps.

Proton LET data we used to generate the fit function to calculate the proton LET values at different energies were taken by the following papers: was taken from Perris et al [4] for energy range 0.01 MeV to 10 MeV and from Borak, [5] for the energy range from 50 to 200 MeV. Figure 10 represents the Proton LET vs Kinetic Energy fit function and the published data sets we used.

The implemented LET proton function in terms of kinetic energy (LETP(KE)):

$$LETP(ke) = \begin{cases} 93804(ke)^3 - 33604(ke)^2 + 3276(ke) + 31.99 & (0.01 \leq ke < 0.1) \\ -234.86(ke) + 143.04 & (0.1 \leq ke \leq 0.3) \\ 29.521(ke)^{-0.797} & (0.3 < ke) \end{cases} \tag{B.1}$$

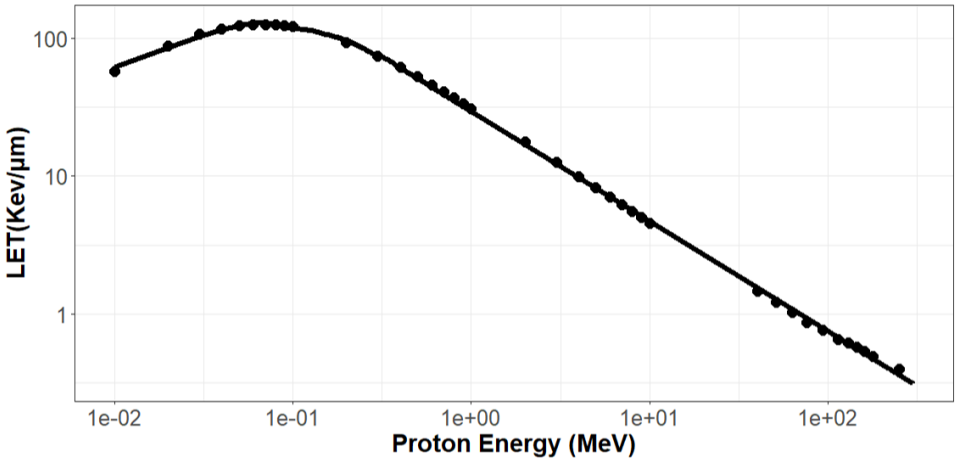

Fig. 1. Proton LET vs Kinetic Energy function plot (5 KeV to 10 GeV)

Appendix C. Parameter Values used in the Hazard functions

In the table below some of the constant parameters used in the calculations for Hazard functions.

Table 1. Parameter Values used in the H functions

Parameter	Particle's Name	TE	TE+NTE
Σ_0	TST Cross Section Saturation value	22.65±20.38	16.44±52.62
D_0	TST RadioSensitivity	2.6	2.6
k	TST Detector saturation Index	9831.25	9831.25
m_s	TST Number of Target per Cell	3	3
α_γ	Gamma Linear Induction Term Coeff.	0.55	0.55
Z^*	Particle Effective Charge	1.00	1.00
β_c	Particle velocity relative to speedlight	0.6136084	0.6136084
η_0	NTE linear proportional coeff.	-	0.00048±0.00033
η_1	NTE exponential proportional coeff.	-	0.00281±0.00320

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References

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