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SPACE RADIATION INDUCED BYSTANDER EFFECT IN ESTIMATING THE CARCINOGENIC RISK DUE TO GALACTIC COSMIC RAYS

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Space radiobiology is an interdisciplinary science that examines the biological effects of ionizing radiation on humans involved in aerospace missions. The knowledge of the risk assessment of the health hazard related to human space exploration is crucial to reducing damages induced to astronauts from Galactic Cosmic Rays (GCRs) and sun-generated radiation. GCRs have been identified as one of the primary sources of radiation exposure in space.

In this context, an accurate characterization of the possible risk of carcinogenesis induced by exposure to GCRs particles is mandatory for safe human space exploration, and one of the most crucial open problems is the contribution to carcinogenesis due to the effects on the cells directly and not directly irradiated, indicated as Target Effects (TEs) and Non-Target Effects (NTEs), respectively. It is accepted that the detrimental effects of ionizing radiation are not restricted only to the irradiated cells but also to non-irradiated distant cells manifesting various biological effects. Tumour Prevalence (TP) is often used to investigate the effects of NTEs in predictions of chronic GCR exposure risk.

This paper reports the status of the research on this topic at the INFN Roma Sapienza Alpha Magnetic Spectrometer (AMS) research group, where is in progress an extensive study about the risk evaluation of the NTEs that the GCRs radiation will imply when added to the TE. A theoretical framework is presented for TP-induced NTEs modeling, ready to be used with the data collected from the AMS02 detector.

Finally, a possible example of the use of the tool is shown for an accurate estimate of the tumor prevalence function of the exposure period for different typical space protons energies.

Keywords: Human Space exploration, Space Radiation, Space Radiobiology, Radiation Dose-Effects Model, Cancer Risk, Radiation Bystander Effects, Astroparticle Experiments.

1. Introduction

1.1. *Space Radiation induced health risk*

The health risks from GCRs exposure to astronauts include Cancer, Central Nervous System and Cardio Vascular diseases, Cataracts, and Acute Radiation Syndromes[1−8] Cancer and Cataracts are the main concern for space missions in Low Earth Orbit (LEO), while for long-term space missions Beyond LEO (BLEO), outside the protection of the Earth's magnetic field, cancer risks are predicted to exceed acceptable risk levels, and non-cancer risks are of concern for the higher doses at the organs. Annual organ absorbed doses and dose-equivalent values due to GCR vary over the solar cycle between 0.1 and 0.2 Gy/y and 0.3 and 0.6 Sv/yr, respectively, for average spacecraft shielding thicknesses[9−11]. Protons dominate absorbed doses, while heavy ions, low-energy protons, helium particles, and neutrons make essential contributions to equivalent-dose values because of their significant quality factors. The high energies of GCRs limit practical shielding from providing significant attenuation.

The exploration of Mars will require missions of 900 days or longer, with more than one year in deep space where exposures to the GCRs are unavoidable, and doses only modestly decreased by radiation shielding. Similar exposition is expected

for long-term permanence on the Moon's surface that will be the main exploration activities planned by all the national space agencies for this and the next decade (e.g., Artemis Moon Exploration Program[12]).

1.2. *Carcinogenic Risk*

Extensive studies of the life-shortening and carcinogenic effects of high-Linear Energy Transfer (LET) radiation have been reported. A few examples of these are the carcinogenic potential of neutrons in pre-clinical studies[13−14], also review by Sinclair[15] and early papers on a high-Z, high-LET charged particle(CP) from different laboratories[16−17].

There are several uncertainties in estimating space radiation cancer risks, including radiation quality, dose-rate effects, the transfer of epidemiology data between populations, and statistical and bias errors in epidemiology data.

Of these uncertainties, estimating radiation quality effects due to the lack of human data for the heavy ions and other high LET radiations in space is the largest[18]. Both quantitative and qualitative differences between high and low LET radiation cancer risks are possible, where a possible motivation resides in the inappropriate use of Relative Biological Effectiveness (RBE) factors as a basis for risk estimates.

Energy deposition by particles in biomolecules, cells, and tissues depends on several physical aspects of particle tracks, including a core of very high energy deposition events near the particle's path and a so-called penumbra of energetic electrons denoted as delta rays liberated in ionization by primary particles and electrons, which may extend for 100's of microns from the particle's path.

Other considerations are the varying ranges or cells number traversed in the tissue from particles of similar LETs but different charge numbers or kinetic energy and the effects of the projectile and target fragmentation caused by nuclear interactions.

Both theoretical analysis and experimental studies suggest that RBE depends on particle energy and charge number, not LET alone, due to the above-noted physical characteristics.

Experimental studies of tumor induction in mice and surrogate cancer risk endpoints in cell culture models are used to estimate radiation quality factors and their uncertainties. Of these studies, the tumor induction with heavy ions, HGT in female B6CF1 mice has been the only study that has used a sufficient number of particle types (e.g., H, He, Ne, Si, Fe, ...) and different irradiation doses (from <0.2 to >5 Gy) to make a detailed study of radiation quality effects[19−21]. For these characteristics, we choose the pre-clinical dataset reported in the latter references as part of the work material described in this article.

1.3. *Bystander Effects and Space Radiation*

Non-Targeted Effects (NTEs) include BEs where cells traversed by heavy ions transmit oncogenic signals to nearby cells, and genomic instability in the progeny of

irradiated cells. Analysis of the Harderian gland studies, [22−25] and experiments for chromosomal aberrations at low dose[26,27] suggests a model based on NTE is favoured over a Targeted Effects (TE) model, where the later assumes a linear dose response model consistent with DNA damage and mis-repair assumptions, while the former suggests a supra-linear dose response occurs which increases the risk at low doses compared to the TE model. The NTE model is supported by many mechanistic studies using micro-beams to direct radiation to target cells, medium transfer from irradiated to unirradiated cells, and inhibitors of reactive oxygen species, gap junctions and signalling pathways. The totality of these studies provides important evidence for NTEs, which should be prioritized in light of the scarcity of both human epidemiology and animal carcinogenesis studies for high LET radiation at the low doses and dose-rates that occur in space.

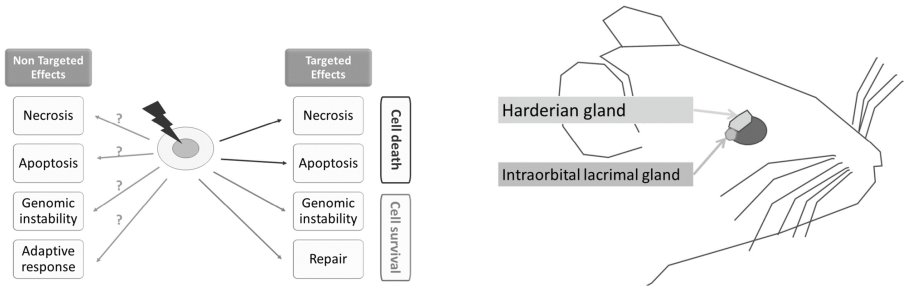
Figure 1a illustrates the cellular effects caused by the direct exposure of cells to ionization radiation, and the BEs resulting from the operation of particle signals secreted by irradiated cells. BEs in neighbour cells of cells directly hit by radiation tracks and genomic instability in the progeny of irradiated cells, challenge traditional radiation protection paradigms on Earth. It is thus of interest to understand how NTE could impact our understanding of cancer risks from GCRs, which are comprised of high-energy protons and heavy ions.

Thus it is crucial to comprehend and estimates the bystander effects(BE) and how they could impact our understanding of cancer risks from GCRs, including this kind of CP[28−31].

1.4. *Dose-Effect Relationship and Dose-Effect Model*

The Dose-Effect Relationship (DER) describes the correlation between the exposition to Ionizing Radiation(IR) and the possible damage to the organs at risk (OARs) including the carcinogenesis.

DEMs are one of the relevant topics of space radiobiology and usually consider



(a) Bystander (b) Anatomy of the Mouse

Fig. 1: a) The IR Bystander (Non-Targeted) Effect and Direct (Targeted) Effect and b) anatomy of the mouse showing Harderian Gland Tumors.

the toxicity and cell survival probability after IR exposition as output. Their knowledge is crucial for optimizing radioprotection strategies (e.g., spaceship and lunar space station-shielding and lunar/Mars village design), the risk assessment of the health hazard related to human space exploration, and reducing damages induced to astronauts from galactic cosmic radiation. Therefore, our research aims to describe the observed damages to normal tissues or cancer induction during and after space flights and to develop DEMs for different radiation qualities and dose ranges, characterizing the actual and the planned space missions[8].

This paper describes the study, design and development of a tool for DEMs production with an emphasis on analyzing the NTEs due to space radiation, including the use of the data collected by the astroparticle experiments operating in space[33−35], for which we developed ad hoc software in R-script language.

2. Material and methods

Pre-clinical studies of tumor induction in mice and surrogate cancer risk endpoints in cell culture models are used to estimate radiation quality factors and their uncertainties.

Of these studies, the Harderian Gland Tumor(HGT) induction with heavy ions in female B6CF1 mice has been one of the few using an extensive type of charged particle(CP) (e.g., H, He, Ne, Si, Fe, ...) and different irradiation doses (<0.2 to >5 Gy) for each, to make a detailed study of radiation quality effects. This study calculated DEMs for γ-ray and CPs (high-energy proton ions and heavy ions) where the output is the Tumour Prevalence (TP). Prevalence was defined as the number of mice developing HGT after irradiation with a specific CP and a measured absorbed dose. This measure includes newly diagnosed and pre-existing disease cases from previous irradiation at low doses. In experimental observation used, the HGT prevalence was expressed as the number of animals with tumor(s) divided by the total number of animals in the experimental group. In these publications, although there is two HG per mouse, one near each eye, however, the number of animals with HG tumors was used as the numerator for the prevalence calculation. More detail can be find in the related articles [19−24].

Starting from this dataset, we developed DEMs of the TP function of the CPs characteristics and, in particular, of the charge number (Z), kinetic energy (E), and fluence (F) as described by Cucinotta and Cacao in[31].

The DEMs mathematical function core is a Hazard function, H, which considers the probability of the event and the possible associated damage. The H function depends on radiation type for γ-rays, while for charged particles on Z, E, and F.

$$TP = 1 - e^{(-H(Z,E,F))} \tag{1}$$

In the remainder of this paragraph, we discuss (2.1) the expression of the H functions

to characterize TP from Gamma-Ray sources irradiation and for CPs irradiation. In the latter case, we introduce a track structure model consistent with either TE or NTE assumptions to extrapolate the results to make predictions for low-dose and dose-rate GCR exposures. Then (2.2), we provide more details about the experimental observations used to tune the radiobiological parameters used in the H functions.

2.1. *The Hazard Functions*

2.1.1. *Gamma Rays Case*

For γ-rays we used the following form for the Hazard function:

$$H_\gamma = H_0 + [\alpha_\gamma D + \beta_\gamma D^2]S(D) \tag{2}$$

where H_0 represents the background TP (i.e., the TP values corresponding to D=0), α_γ and β_γ are the linear and quadratic with dose induction terms.

S(D) is the cell survival probability, and we use the *multiple-Target-single-Hit model*[32] that correctly fits with the ex-vivo analysis that Dimajo et al.[24] of the dose-response for cell survival in the HG after χray irradiation using male CBA/Cne mice.

For the S(D) model parameters, we used an earlier estimate reported in[19] that found 3 for the target number(m_s) and 2.6 *Gray* for the radio-sensitivity(D_0).

2.1.2. *Charged Particles : TE Case*

For charged particles we used the following form (3) for the TE case:

$$H_{TE}(Z, E, F) = H_0 + [\Sigma F + \beta_{CP} D^2]S(Z, E, F)\,. \tag{3}$$

in which we assumed a track structure model that extrapolates to low doses (or low fluence) to the functional form Σ used in the NASA cancer risk assessment model[1,28] (4), which is consistent with a TE model that assumed a linear dose-response at low doses.

Following the parametric track structure model described in prior reports [1,20] we write an effective pseudo-biological action cross-section for TE per particle as:

$$\Sigma(Z, E) = \Sigma_0 P(Z, E) + \frac{\alpha_\gamma L}{6.24}[1 - P(Z, E)]\,. \tag{4}$$

where

$$P(Z, E) = [1 - e^{\frac{-Z^{*2}}{k\beta_c^2}}]^m\,, and\ \ k = \frac{D_0 * (a_0^2)}{(2 * 10^{-15})} \tag{5}$$

where Z* is the effective charge number of the particle, $a_0 = 2.75 * 10^{-6}$m is the radius of the Aptelial nucleus responsible for HG tumor and β_c is the particle velocity relative to the velocity of light.
The constant α_γ is the linear regression coefficient for acute doses of γ-rays for the same endpoint.

For the quadratic term coefficient β, we considered a best fit of the experimental observations related to CP irradiation named in the following β_{CP} (e.g., for protons β_H)

S(Z,E,F) is the cell survival probability, and we use the *Cellular Track Structure Model*[32] that correctly fits with the ex-vivo analysis that Dimajo et al.[24] of the dose-response for cell survival in the HG after protons irradiation using male CBA/Cne mice.

2.1.3. *Charged Particles : TE+NTE Case*

For the TE+NTE case we used the following form (6) :

$$H_{NTE}(Z,E,F) = H_0 + [\Sigma F + \beta_{CP} D^2 + \eta] S(Z,E,F)\,. \tag{6}$$

In this case in addition to the TE case we assumed a non-linear type of response to the linear dose term at low doses represented by the η component, which is parameterized as a function of the particle LET in the following form (7).

$$\eta = \eta_0 L e^{-\eta_1 L}[1 - e^{-N_{Bys}}]\,; \quad N_{Bys} = F * A_{Bys}. \tag{7}$$

where, L is the LET of the particle, N_{Bys} is the product of the Fluence and the area of the bystander cells surrounding a cell traversed directly from the CP that receive an oncogenic signal in the "bystander" area A_{Bys}

2.2. *Experimental Data Set*

In this study, the experimental observations data set was taken from Alpen et. al.[19], where the experimental test system of the study was on the development of neoplasia in the HGT of the mouse using different isotopes beams at different energies and a 55.5 TBq ^{60}Co γ-ray source was used as the low-LET reference radiation. Irradiation time was generally 5 to 10 min.

2.3. α_γ, β_γ *Calculation from* γ*-Ray Experimental Observations*

Using the experimental observation data of gamma source irradiation, we calculate the α_γ used in equation (4) to calculate the Effective Pseudo-Biological Action Cross

Section, and the β_γ induction term. The second-order polynomial was fitted to the data for ^{60}Co 55.5 TBq γ irradiation (Table II).

Table 1: Prevalence of Harderian Gland Tumours of Mice after a) ^{60}Co 55.5 TBq γ-ray and b) protons irradiation

Dose(Gy)	Prevalence %
0.0037	2.6 ± 0
0.4107	5.10 ± 4.60
0.8124	8.06 ± 7.06
1.2171	12.66± 7.55
1.6482	17.60 ± 10.65
3.1789	32.24 ± 8.49
7.1347	46.22 ± 13.72

[a]95%CI

(a) Gamma

Dose(Gy)	Prevalence %
0	2.6 ± 2.5
0.4	9.3 ± 6.1
0.8	19.5 ± 12.1
1.6	30.2 ± 13.7
3.2	29.2 ± 18.6

[a]95%CI

(b) protons

The higher doses, which show a significant saturation effect, are omitted from the regression analysis.

The fitting regression function for the range of doses analysed is shown in figure 2a where the dash line indicates the second-order polynomial fitted curve to the ^{60}Co 55.5 TBq γ-ray data points taken from Alpen et. al.,[19] and the dot line is the linear fit to the same data points. The fit suggests that the second-order polynomial model is a good description of the relationship between dose and TP($R^2 = 0.99$).

3. Theory and calculation

3.1. *Effective Pseudo-Biological Action Cross Section calculation for TE and NTE*

In this section the Effective Pseudo-Biological Action Cross Section or $\Sigma(1, 250)$ were calculated for protons of 250A MeV and 0.4 KeV/μm of LET both for TE and NTE, we use equation (4) and (5) where parameters values was chosen according to the table defined in[32].

$$\Sigma_{TE}(1, 250) = 22.65 + \frac{0.55 * 0.4}{6.24}[1 - [1 - e^{\frac{-1^2}{9831.25*(0.61)^2}}]^3]\,. \tag{8}$$

$$\Sigma_{NTE}(1, 250) = 16.44 + \frac{0.55 * 0.4}{6.24}[1 - [1 - e^{\frac{-1^2}{9831.25*(0.61)^2}}]^3]\,. \tag{9}$$

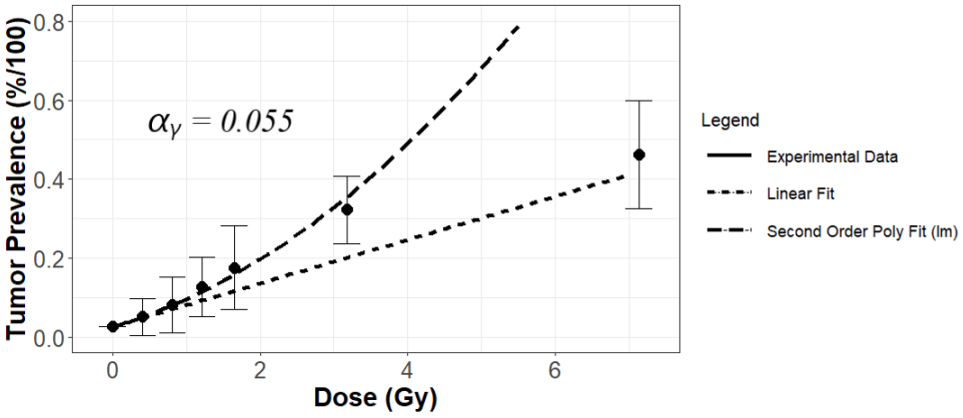
3.2. *Linear and Quadratic Coefficients (α_H, β_H) Calculation*

Using the experimental data of 250A MeV protons irradiation we calculate the α_H, β_H induction term coefficients.

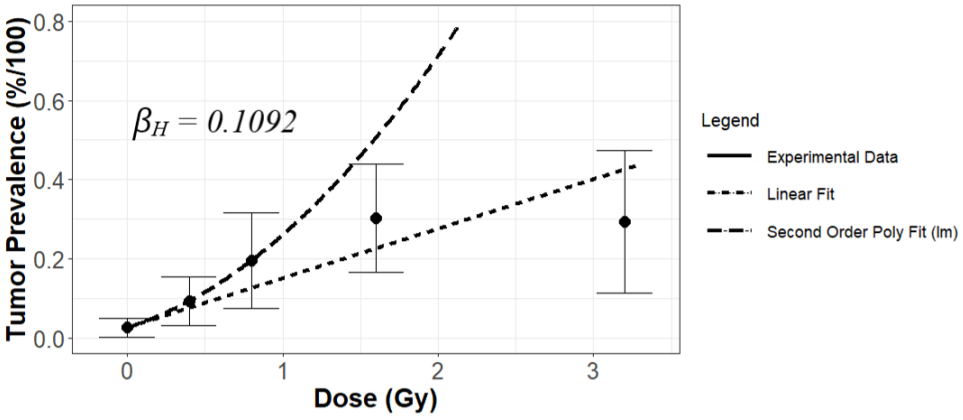
The quadratic regression coefficient (β_H) is used in equations (3) and (6) in the calculation of hazard functions of TE and TE+NTE.
In figure 2b, the dot curve indicates the second-order polynomial fitted curve to the first three protons data points taken from Alpen et. al.[19], and the dash line is the linear fit to the same data points.

3.3. *Cell Survival Probability calculation for TE and TE+NTE*

Cell Survival Probability for protons as function of the fluence(F) is calculated using equation (A.5)[32] with E=250 MeV, and LET=0.4 KeV/μm :



(a) ^{60}Co 55.5 TBq γ-ray



(b) protons

Fig. 2: Tumour Prevalence vs Dose for a) ^{60}Co 55.5 TBq γ-ray and b) protons irradiation. The points are experimental data points of ^{60}Co 55.5 TBq γ-ray taken from table 2 above, the error bars is the maximum and minimum deviation of the prevalence of the data point, the dash curve is the second order polynomial fit to the first three data points, and the dot line is the linear fit and to the data points.

$$S_{TE}(1,250,F) = [1-(1-e^{\frac{-(F*0.4)/6.24}{2.6}})^3]e^{-(22.65*[1-e^{\frac{-1^2}{9831.25*(0.61)^2}}]*F)}\,. \quad (10)$$

$$S_{NTE}(1,250,F) = [1-(1-e^{\frac{-(F*0.4)/6.24}{2.6}})^3]e^{-(16.44*[1-e^{\frac{-1^2}{9831.25*(0.61)^2}}]*F)}\,. \quad (11)$$

3.4. *H function calculation for TE and TE+NTE*

H functions for protons were calculated for TE and TE+NTE cases using equation (3) and (6) respectively, with β_{CP} equal to the quadratic induction term coefficient as calculated in section 3.2 (β_H) , and η_0 and η_1 coefficients as reported in table 3

$$H_{TE}(1,250,F) = 0.026 + [\Sigma F(1,250) + 0.1092 * D^2]S_{TE}(1,250,F)\,. \quad (12)$$

$$H_{NTE}(1,250,F) = 0.026 + [\Sigma F(1,250) + 0.1092 * D^2 + \eta]S_{NTE}(1,250,F)\,. \quad (13)$$

$$\eta = 0.00048 * 0.4e^{-0.00281*0.4}[1-e^{-216*F}]\,. \quad (14)$$

4. Results: TE vs TE+NTE Models for protons

Finally, using equation (12) and (13) in equation (1) we calculated and compare the TP function for two cases as function of Dose (Fig.5) and of Fluence (Fig.6).

$$TP_{TE} = 1 - e^{(-H_{TE}(1,250,F))} \quad (15)$$

$$TP_{NTE} = 1 - e^{(-H_{NTE}(1,250,F))} \quad (16)$$

The calculation show that there are no relevant differences in the Tumour Prevalence versus dose as expected.

In figure 3 all the components of the H functions are shown separately for the TE (3.a) and TE+NTE models respectively.

4.1. *An Example: AMS-02 protons*

In this paragraph, we show a possible example of the use of the tool using the published data from the AMS collaboration of the fluxes of the GCRs protons components[36].

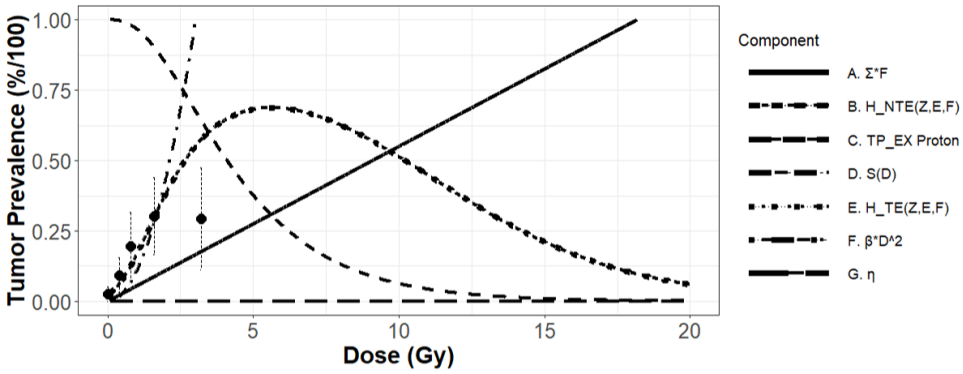
Tumor Prevalence in terms of protons flux and exposition time has been calculated using H functions derived by (3) and (6) and considering that the AMS data of protons GCRs are organised in "bins" (a kinetic energy interval) and for each "bins" a corresponding flux is measured. The bin-energy is the analogue of the protons beam energy and the corresponding flux of the beam intensity:

Tumor Prevalence as function of exposition time induced by a protons flux of a single energy bin (492.4±7 MeV) measured from AMS02 detectors is shown in figure 4.a.

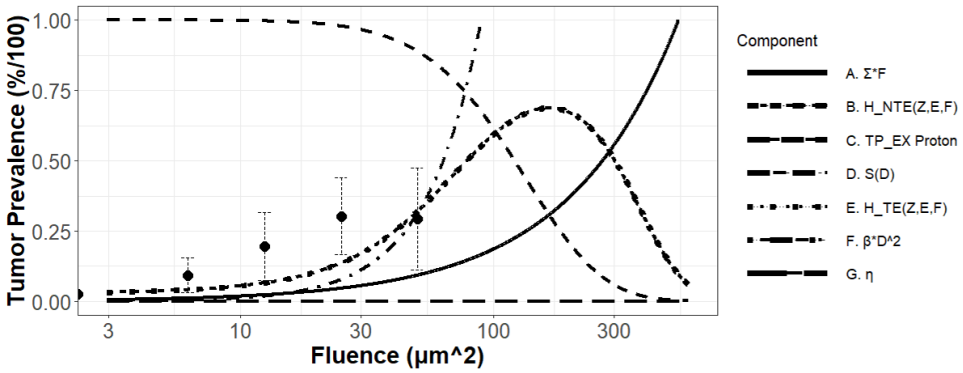
The corresponding bin energy average (492.4 MeV) proton LET is 0.24 KeV/μm[32].

Figure 4.b is the Tumor Prevalence vs exposition time plot for protons for data taken from AMS-02 for different bin energy ranges from 492.4±7 MeV to 1.46±0.335 TeV (from 0.24 KeV/μm^2 to 0.04 KeV/μm^2 LET values).

It shows that the high-energy protons, low LET, require longer exposition time with respect to the low-energy protons to induce equivalent TP values.

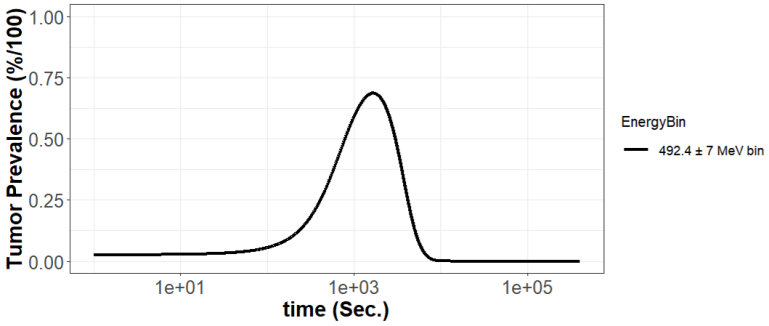


(a) Tumour Prevalence vs Dose

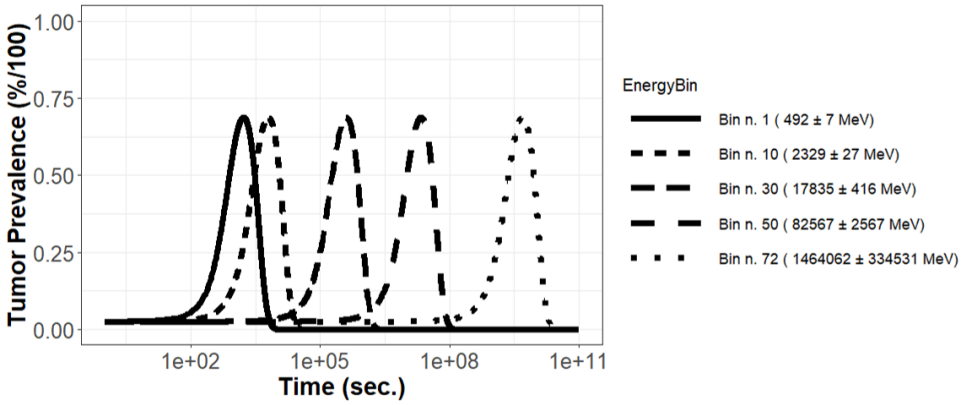


(b) Tumour Prevalence vs Fluence

Fig. 3: a) Tumour Prevalence vs Dose and b) Tumour Prevalence vs Fluence TE and NTE model for protons irradiation. The points are experimental data points of protons taken from Alpen .et .al [19], and the error bars indicate the maximum and minimum deviation of the data point. The small dash curve is the CSP model, the dash-dot curve is the βD^2 component, the solid curve is the ΣF component, and the large dash line is the η component of the hazard function. The overlapped dash and dot curves indicate the TE and NTE track models respectively.



(a) Single Energy



(b) Different Energy Range

Fig. 4: Tumor Prevalence vs exposition time for GCR protons: using a) single energy bin (492.4±7 MeV) and b) different energy bins (492.4±7 MeV to 1.46±0.335 TeV)[32].

5. Discussion and Conclusion

In this study we have developed reliable DERs for the calculation of TP of high energetic protons and heavy ions in terms both for the TE and TE+NTE cases.

We developed for this an ad hoc software tool in R-script language including also most of the CSP reported in the literature. Using the tool and the experimental data set of HGT we tuned all the parameters for the TP model for the protons case (p@250 MeV) and we showed that there are no substantial differences between the TE and NTE as expected. Also, we apply the model for protons using the cosmic ray protons component as measured and published by the AMS detector as an example.

The software comprises a main program and several libraries for a total of >10K lines of code.

Actually DERs are available not only for protons but for many different CPs Ions such as: 228A MeV Helium ($_2He^4$), 670A MeV Neon ($_{10}Ne^{20}$), 260A MeV Silicon ($_{14}Si^{28}$), 1000A MeV Titanium ($_{22}Ti^{48}$), 540A MeV, 600A MeV and 350A

MeV Iron ($_{26}Fe^{56}$), 600A MeV Niobium ($_{43}Nb^{93}$), 593A MeV Lantanio ($_{57}La^{139}$)

In the future, we extend the analysis to other heavy ions, and we will continue to expand such tool so that in the future, it will be possible to use it for the risk assessment of TE and NTE in different exposure scenarios including the data taken from AMS and other Astroparticle experiments[37−40].

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