Target Effects vs. Non-Target Effects in Estimating the Carcinogenic risk due to Galactic Cosmic Rays in Exploratory Space Missions

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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 and sun-generated radiation.
Galactic Cosmic Rays (GCR) 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 a significant concern for human exploratory space missions.
In this talk, the tumour prevalence is used to investigate the effects of Non-Target Effects (NTE) in predictions of chronic GCR exposure risk. The NTE model led to a predicted risk 2-fold higher compared to a targeted effects model. Therefore, it is nowadays accepted that the detrimental effects of ionizing radiation are not restricted only in the irradiated cells but also to non-irradiated bystanders or even distant cells manifesting various biological effects.
In this talk, an extensive study will be presented about the risk increase due to the Non-Target Effects that the GCRs radiation will imply when added to the Target one.
Status of the art results will be summarized, recent observations and theoretical framework presented, and some new hints derived from the data collected from the AMS02 detector.
Finally, the possible future development will be highlighted about the possibility of an accurate estimate of the tumour prevalence function for different exposure exploratory space mission scenarios.

Key words: Space Radiation, Space Radiobiology, Target Effects, Non-target Effects, Tumour Prevalence, Galactic Cosmic Ray

Outline

- AMS INFN Roma Sapienza Research Group
- Space Radiation Environment
- Target Effects vs Non Target Effects

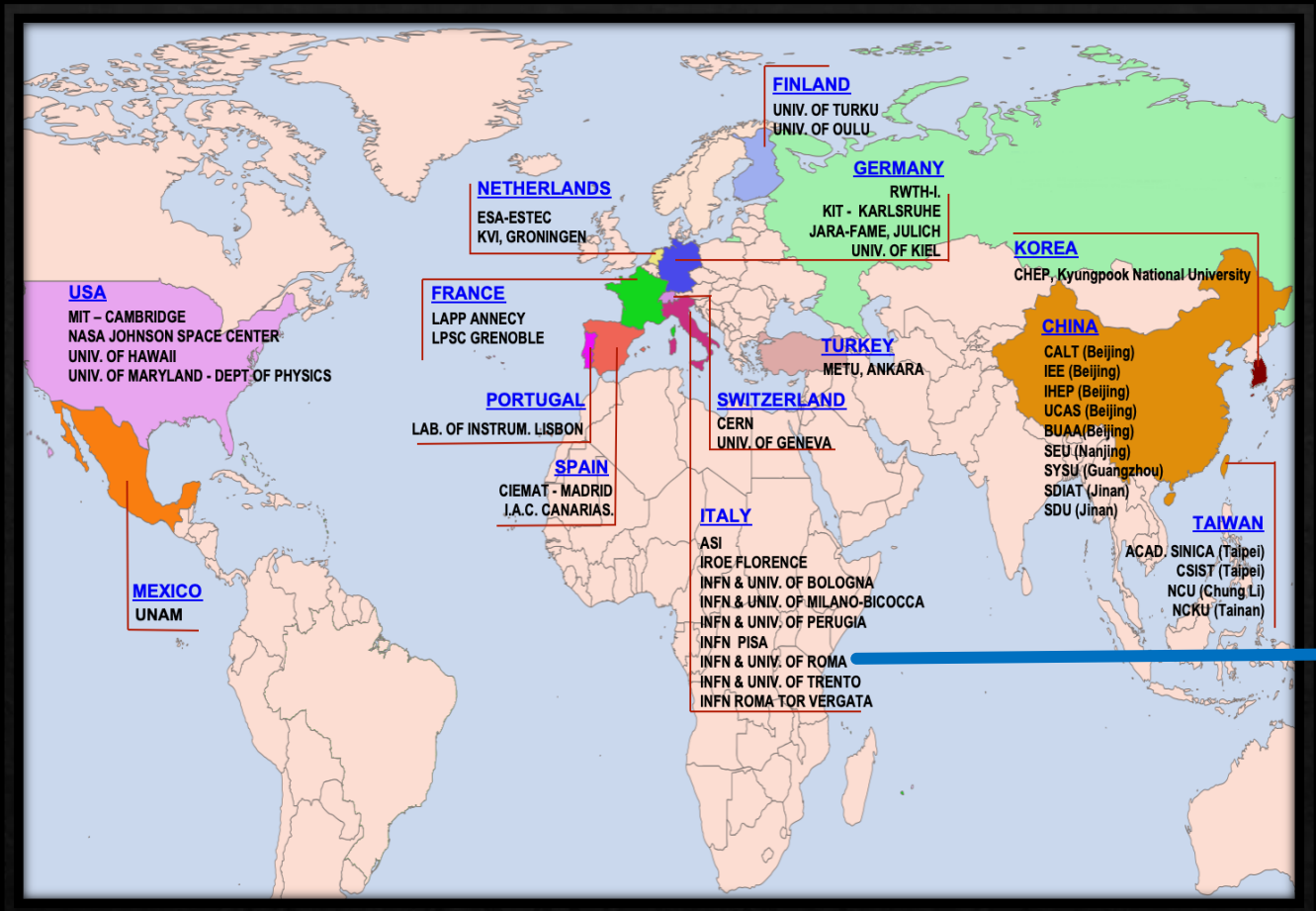
INTRODUCTION

Alpha Magnetic Spectrometer (AMS)

INFN ROMA SAPIENZA RESEARCH GROUP

Alpha Magnetic Spectrometer AMS02

AMS is a particle detector measuring Galactic Cosmic Ray fluxes.
It was installed on the International Space Station (ISS) on May 19, 2011



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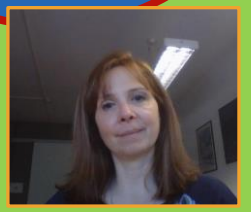

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The AMS collaboration

(http://ams02.space)

An international collaboration made of 44 Institutes from America, Asia and Europe

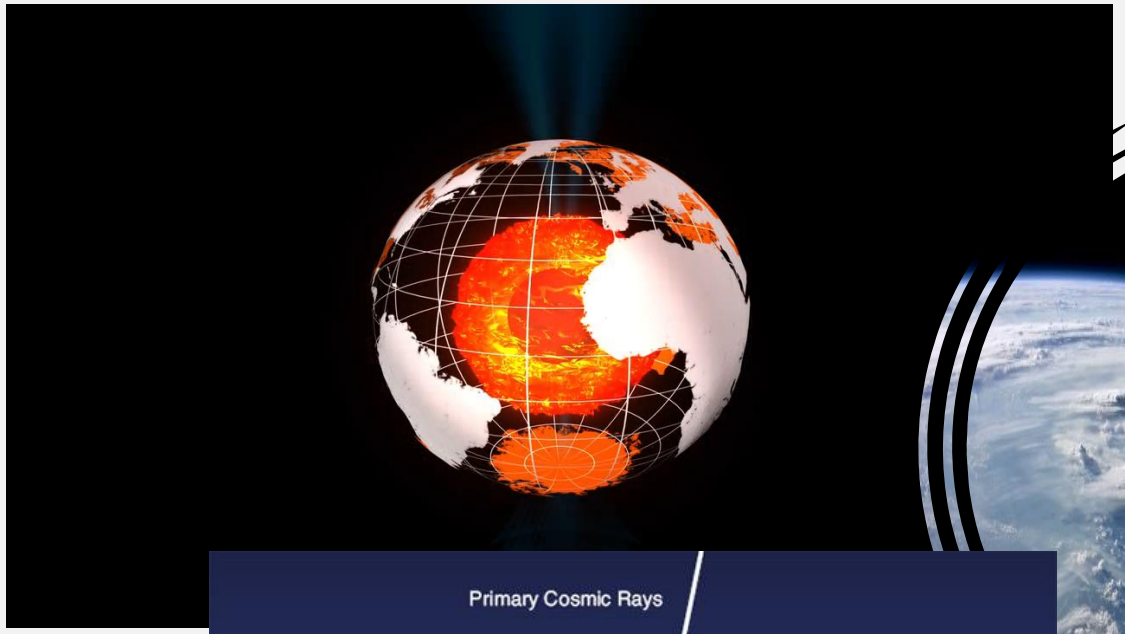
The AMS02 detector has collected so far more than **200 billion** Cosmic Rays events.

More Info in the AMS-02 webpage:

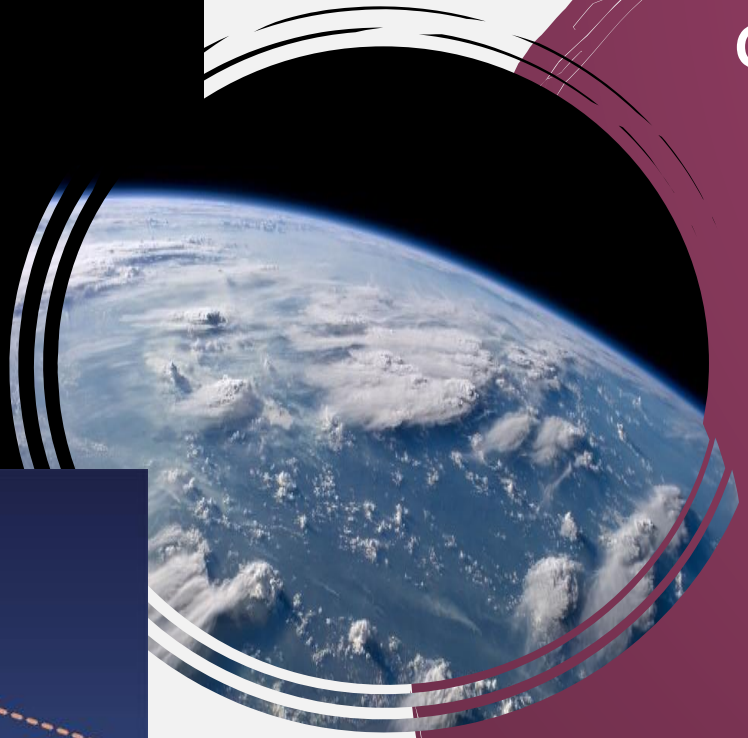
https://ams02.space

SPACE RADIATION & ASTRONAUT SAFETY

«To fully understand the relationship between ionizing radiation and biology, and to solve problems in this field, researchers incorporate fundamentals of **biology, physics, astrophysics, planetary science, and engineering**» *(credit : NASA)*



(credit : ESA)

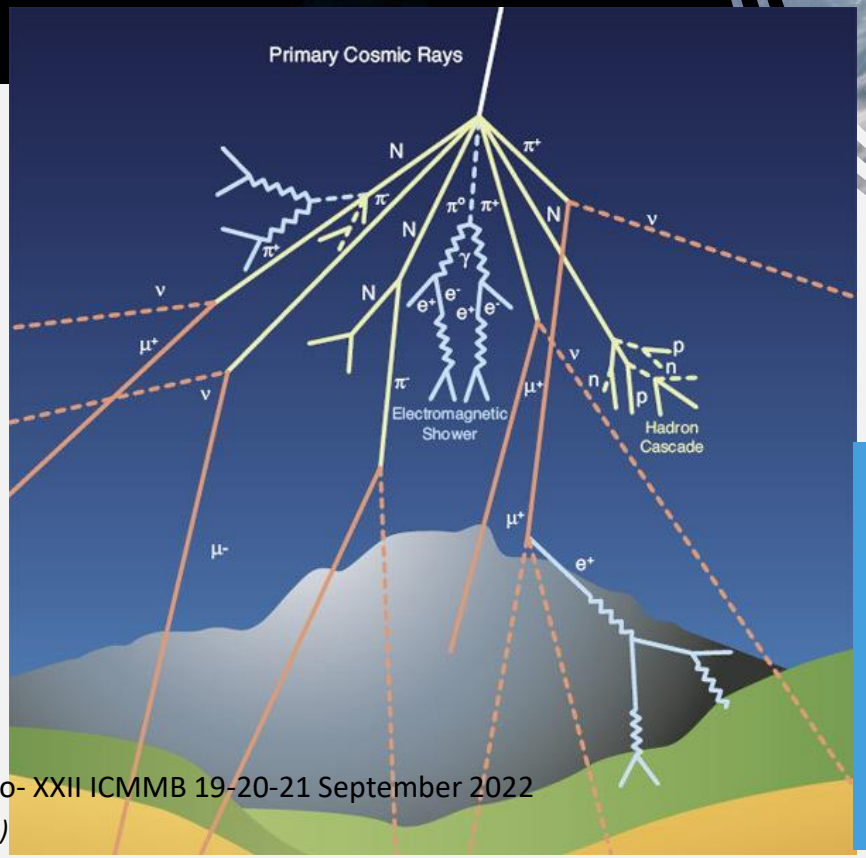


Cosmic Rays Interactions with the geo-magnetosphere

Earth is a safe place!!!

Magnetosphere stops/deflects 99.9% of charged particles

the Earth Atmosphere is equivalent to a metal shielding 1 meter thick



(credit : CERN)

The annual cosmic ray "dose" at sea level is around **0.27 mSv**

<10% of "background radiation"
(Radon, Soils, Foods, Medical,..)

Origin of Space Radiation and Consequent Risk

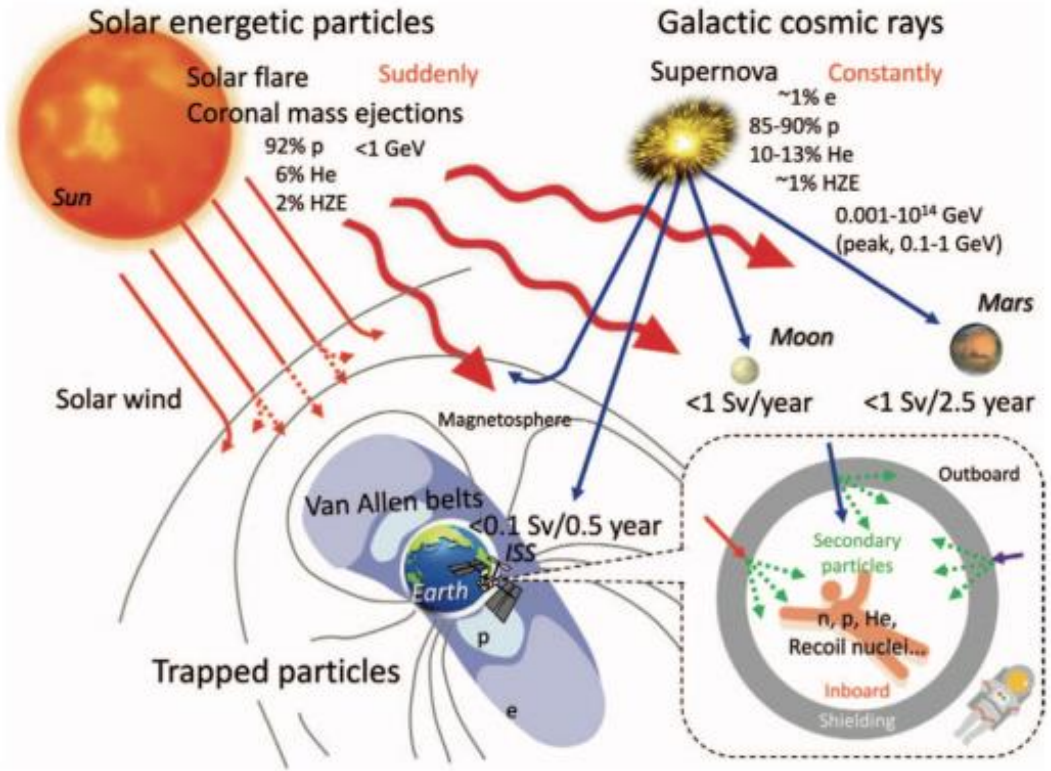
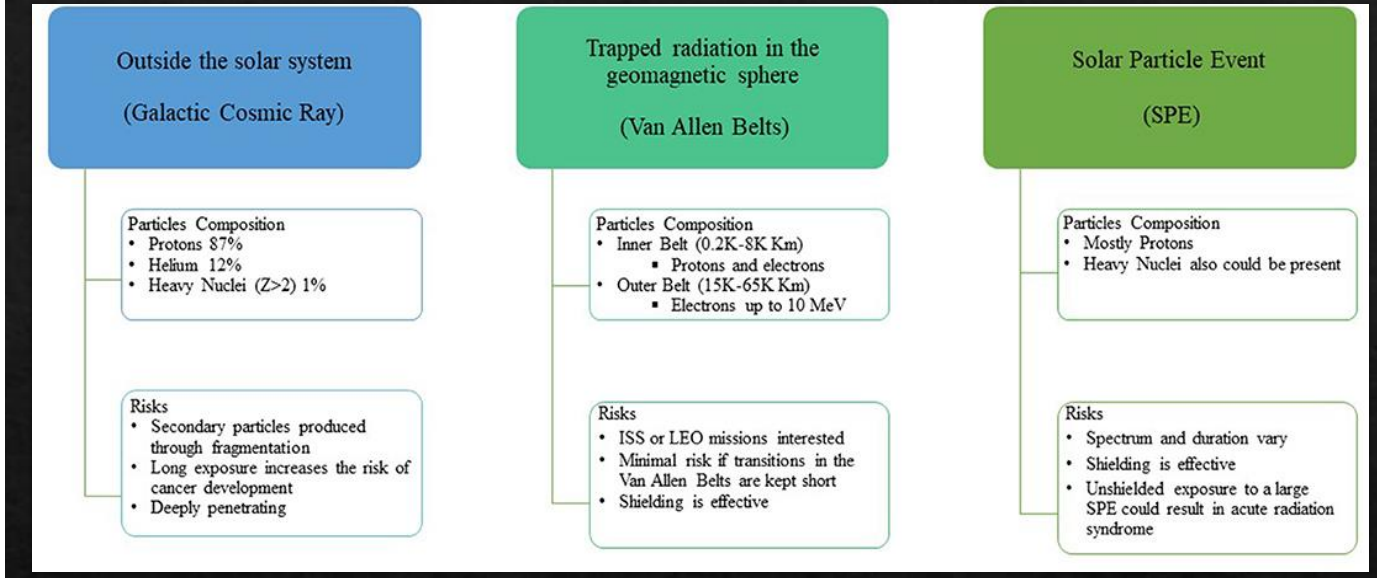


Image courtesy of European Space Agency (ESA)



From Strigari et Al Front. Public Health, 08 November 2021 | https://doi.org/10.3389/fpubh.2021.733337

Space Radiation composition

- Galactic Cosmic Rays (**GCR**)
- Particle emitted by the Sun (**SEP**) during isolated events
- Particle trapped in Earth's magnetic field (**Radiation Belt**)

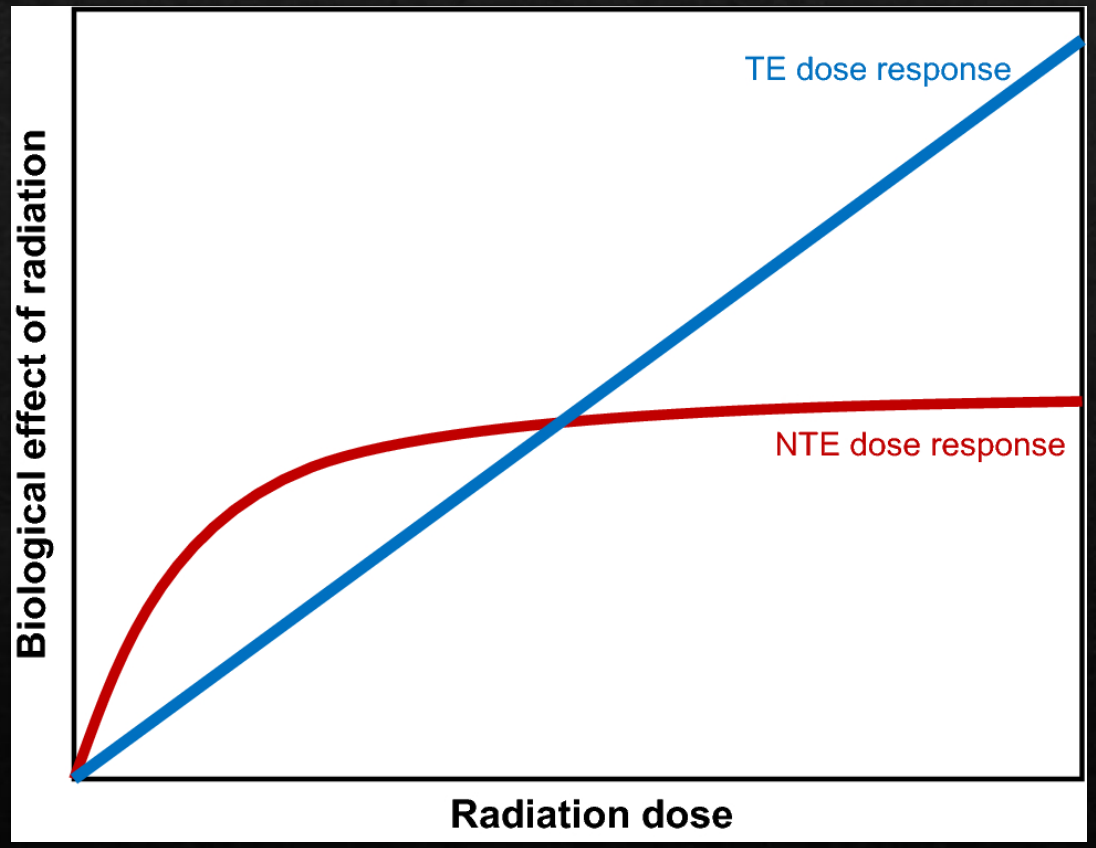
None of the 3 components is constant in time, mainly due to the solar activity

Human Space activities must cope with the high radiation environment of outer space.

Dose-Effect Relationship

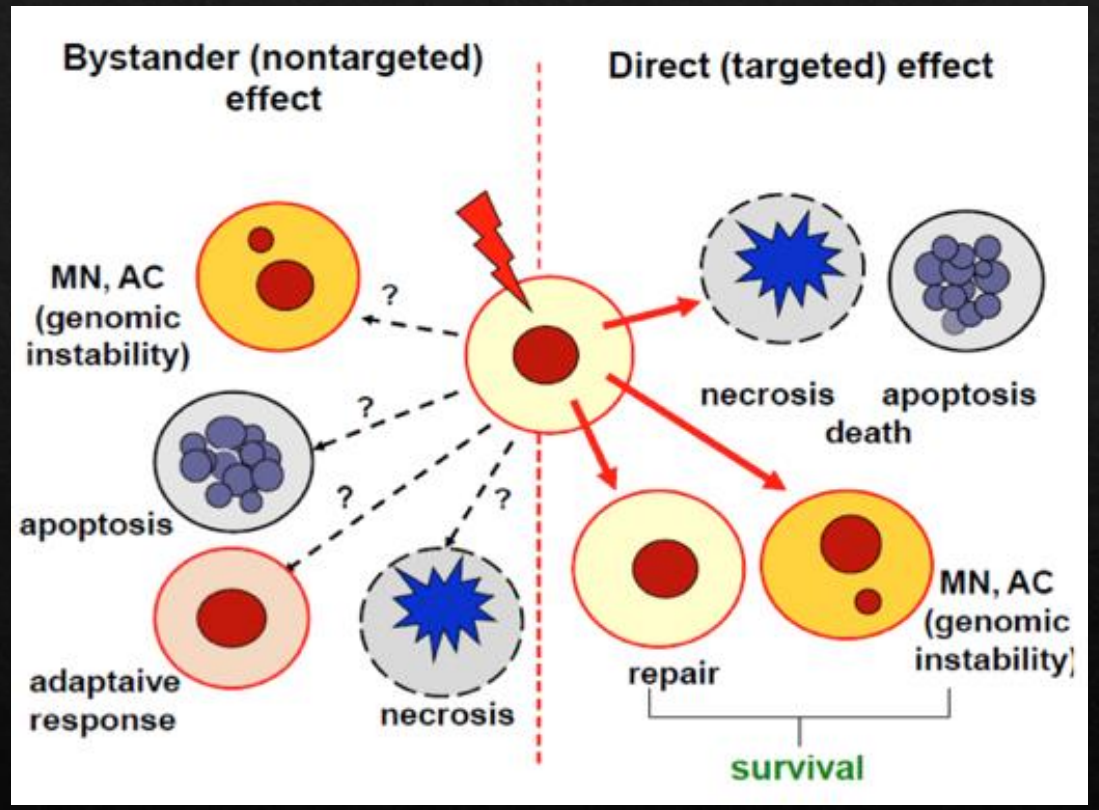
Crucial point is to predict the toxicity of the space radiation expected for the astronauts/space workers and the creation of reliable ***mathematical models*** that describe the correlation between the exposition to IR and the possible damages to the organs at risk

Aim: to implement a platform including the more reliable dose-effect models for space radiation, we developed an ad hoc software in R-script language



Materials & Methods: Target Effects vs Non Target Effects

- Non-targeted effects (NTEs) include bystander effects where cells traversed by heavy ions transmit oncogenic signals to nearby cells, and genomic instability in the cell's progeny.
- Studies on the Harderian gland, chromosomal aberrations at low dose and many mechanistic studies support the NTE model, with evidence of a supra-linear effect at low doses of NTE compared to a linear effects for TE .
- This NTE are expected also at the dose-rates that occur in space.



Non-Targeted Effects Models Predict Significantly Higher Mars Mission Cancer Risk than Targeted Effects Models

F. Cucinotta, Eliedonna E. Cacao • Published 12 May 2017 • Biology, Physics • Scientific Reports

Work in progress at Roma AMS group

Materials & Methods: Hazard Function for Tumor Prevalence (TP)

Prevalence is the number of people/cell with a specific disease or condition in a given population at a specific time. This measure includes both newly diagnosed and pre-existing cases of the disease.

Tumor prevalence (TP) is described by a Hazard function, H, which is dependent on radiation type for γ-rays while for charged particles is dependent on the charge number (Z), kinetic energy (E) and fluence (F).

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

$$H_\gamma = H_0 + \left[\alpha_\gamma D + \beta_\gamma D^2\right] * S(D)$$

$$H_{CP}(Z,E,F) = H_0 + \left[\Sigma F + \beta D^2\right] * S(D)$$

Where:

- H_0 represents the background prevalence
- α_γ and β_γ are the linear and quadratic coefficient with dose Induction terms
- Σ is pseudo-biological action cross section taking in account the particle track structure models
- ***S(D)*** is the ***Cell Survival Probability.***

Results: R-script Library includes the most used Cells Survival Probability models

To be used in the calculation of hazard functions of Tumor Prevalence.

1. Theory n-target N-hit model (nTNH)
   Two special case of nTNH including:
   - Theory single Target single hit model (sTSH)
   - Theory single Target N-hit model (sTNH)
2. Theory Linear Quadratic Model (LQ)
3. Linear Quadratic Model modified by hyper-radiosensitivity(HRS) effect.
4. Theory Linear Quadratic Cubic Model (LQC) for high dose.
5. Sublesion Theory Repair – misRepair Model (S-RMR)
6. Sublesion Theory Lethal – potentially lethal Model (S-LPL)
7. Sublesion Theory Saturable Repair Model (S-SR)

1. $S(D) = 1 - (1 - B)^n,\ B = e^{\frac{-D}{D_0}}[1 + \sum_2^N \frac{\left({}^{D}/_{D_0}\right)^{N-1}}{(N-1)!}]$

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

3. $S(D) = exp\{-\alpha\left(1 + \left(\frac{\alpha_s}{\alpha} - 1\right)e^{\frac{-D}{D_0}}\right)D - \beta D^2\}$

4. $S(D) = e^{-\alpha D - \beta D^2 - \gamma D^3}$

5. $S(D) = e^{-aD}[1 + (\frac{aD(1-e^{(-\lambda T)})}{\varepsilon})]^{\varepsilon\phi}$

6. $S(D) = e^{-(n_L - n_{PL})D}[1 + \frac{n_{PL}D}{\epsilon}\ (1 - e^{-\epsilon_{PL}t_r})]^{\epsilon}$

7. $S(D) = e^{-\frac{n_0 - C_0}{1 - \frac{C_0}{n_0}e^{kT(C_0 - n_0)}}}$

Materials and Methods: Experimental Data Set (Alpen et. al. 1993)

Prevalence of Harderian Gland Tumors

- Gammas 55.5TBq Co60
- Hydrogen with energy 250A, LET 0.4 KeV/μm
- Exposition time in between 60 sec. to 120 sec.
- Irradiation field is 3 x 5 cm^2.
- Background Prevalence is $H_0 = 0.026$

Table II

Prevalence of Harderian Gland Tumors

After 60Co Gamma Irradiation

	Mice			
Dose (Gy)	Number	At risk	With tumors	Prevalence[a] (%)
0	198	155	4	2.6 ± 2.5
0.4	292	229	11	4.8 ± 2.7
0.8	278	161	15	9.3 ± 4.5
1.6	244	117	16	13.7 ± 6.2
3.2	181	115	37	32.2 ± 8.5
7.0	90	52	24	46.2 ± 13.6

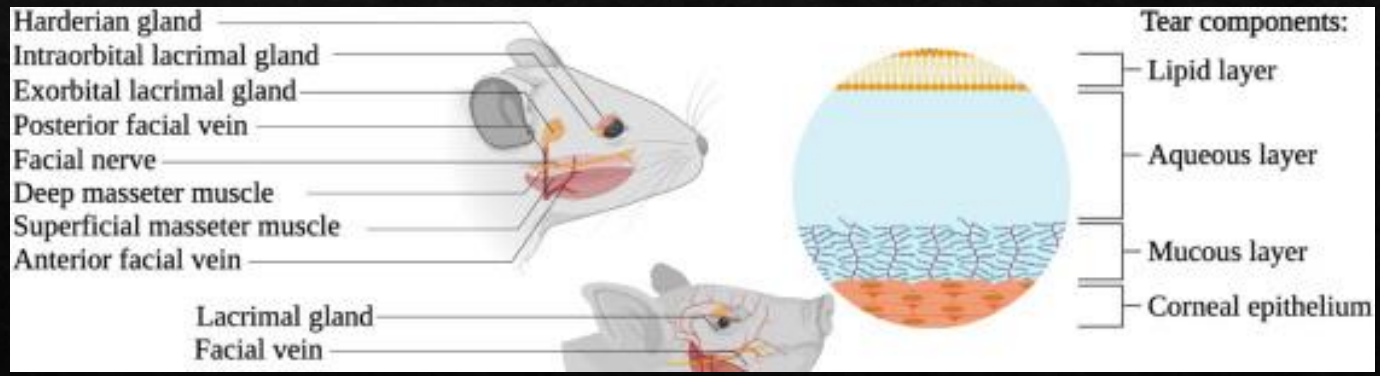
[a] ±95% CI

Table III

Prevalence of Harderian Gland Tumors after Irradiation with Proton ions

	Mice			
Dose (Gy)	Number	At risk	With tumors	Prevalence[a]
0	198	155	4	2.6 ± 2.5
0.4	47	44	43	9.3 ± 6.1
0.8	42	41	8	19.5 ± 12.1
1.6	48	43	13	30.2 ± 13.7
3.2	28	24	7	29.2 ± 18.2

[a] ±95% CI



Hazard Function
Targe Effect (TE) vs Non-Target Effects (NTE)

The NTE model assumes a non-linear type response in addition to the linear dose term at low doses.

The η function represents the NTE contribution, which is parameterized as a function of the particle Linear Energy Transfer (L).

We tuned the radiobiological parameters to reproduce available experimental data

$$H_{TE}(Z,E,F) = H_0 + \left[\Sigma F + \beta D^2\right] * S$$

$$H_{NTE}(Z,E,F) = \left[H_0 + \Sigma F + \beta D^2 + \eta\right] * S$$

$$\eta = \eta_0 L e^{-\eta_1 L}\left[1 - e^{-N_{Bys}}\right]$$

Where:

- L is the Linear Energy Transfer of the particle
- N_{Bys} is the number of bystander
- $N_{Bys} = Fluence * A_{Bys}$
- A_{Bys} is an area corresponding to the number of bystander cells surrounding a cell traversed directly from a HZE particle that receive an oncogenic signal.

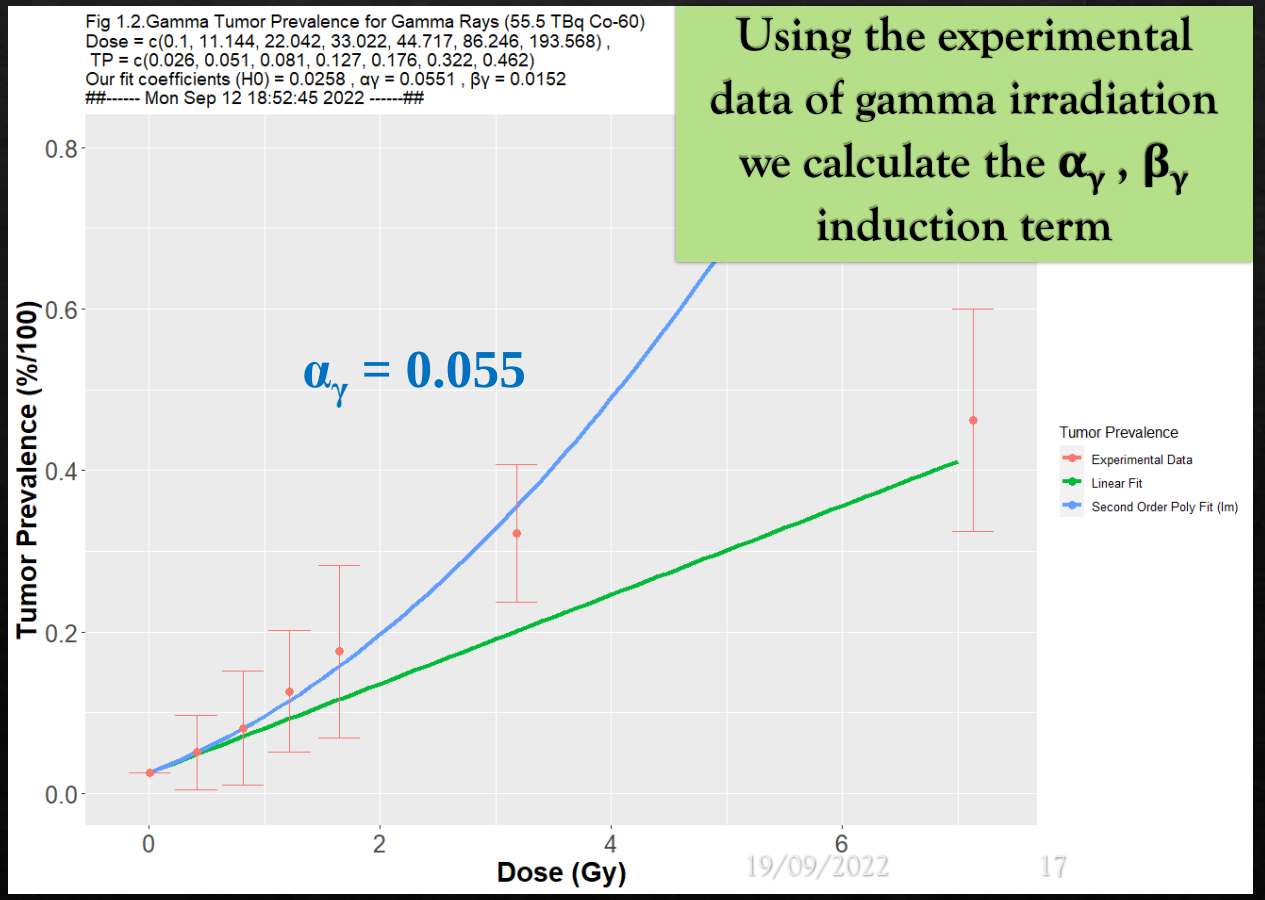
Results: Effective Pseudo-Biological Action Cross Section

$$\Sigma(Z,E) = \Sigma_0 P(Z,E) + \frac{\alpha_\gamma L}{6.24}[1 - P(Z,E)],\ P(Z,E) = [1 - e^{\left(-\frac{Z^{*2}}{kv_c^2}\right)}]^m$$

$$\Sigma(1,250) = \Sigma_0 P(Z,E) + \frac{0.55*0.4}{6.24}[1 - P(1,250)]\,,\ P(1,250) = [1 - e^{\left(-\frac{Z^{*2}}{kv_c^2}\right)}]^3$$

Where:

* Σ_0 and k are parameters of his cellular track structure model
* α_γ is the linear regression coefficient for acute doses of γ-rays for the same endpoint
* Z^* is the effective charge number of the particle,
* *Vc* is the particle velocity relative to the velocity of light
* *m* is the number of target in a single cell



Results: α_H and β_H Calculation

$$TP_H = 1 - e^{-H_H(1,250,F)}$$

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

$$H_{NTE}(1,250,F) = 0.026 + [\Sigma(1,250) * F + 0.1092 * D^2 + \eta_H] * S$$

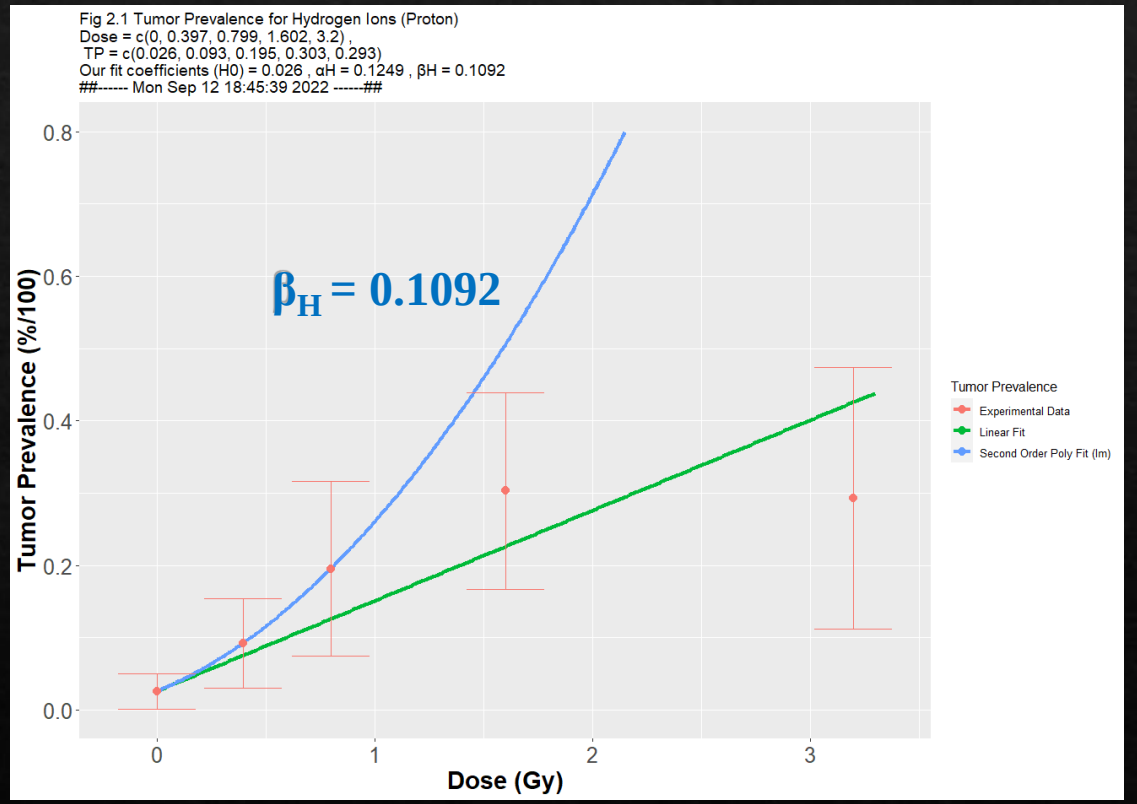
$$\eta_H = 0.00048 * 0.4e^{-0.00281*0.4}\,[1 - e^{-216*F}]$$

Where:

* β_H is the quadratic coefficient with dose Induction terms, irradiation for hydrogen

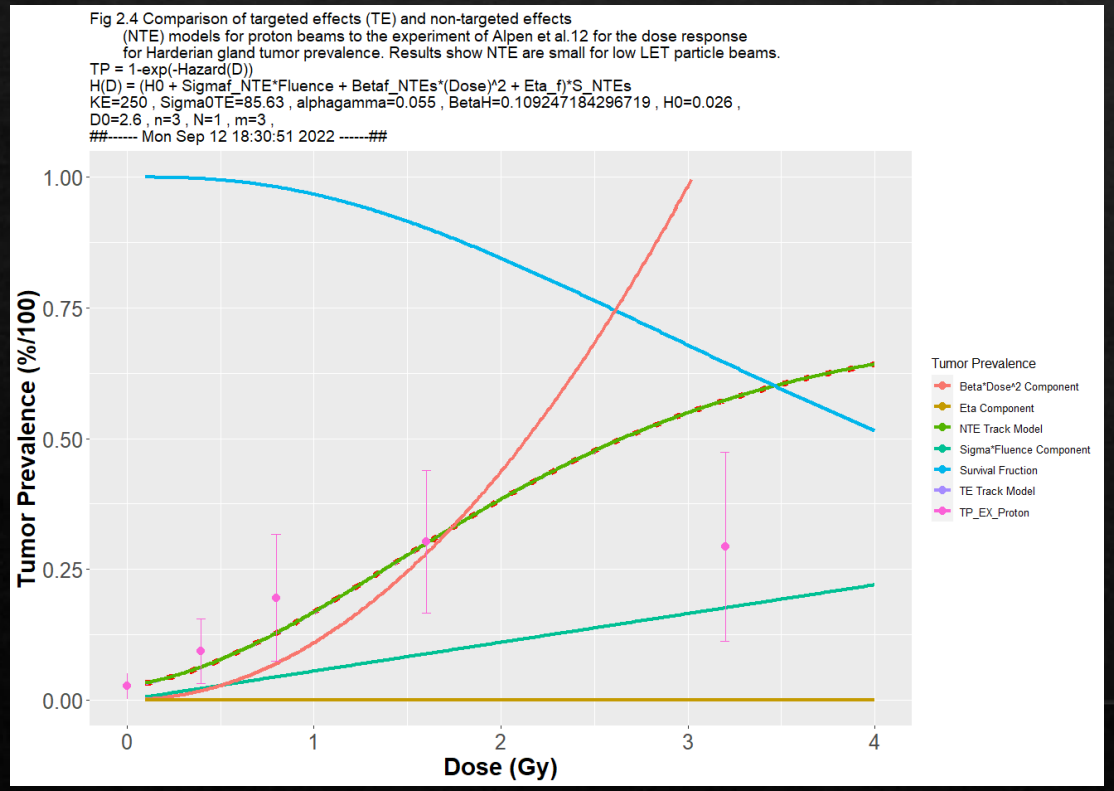
For the cell survival probability is used the target theory n-target N-hit model (nTNH) with n =3 , N = 1

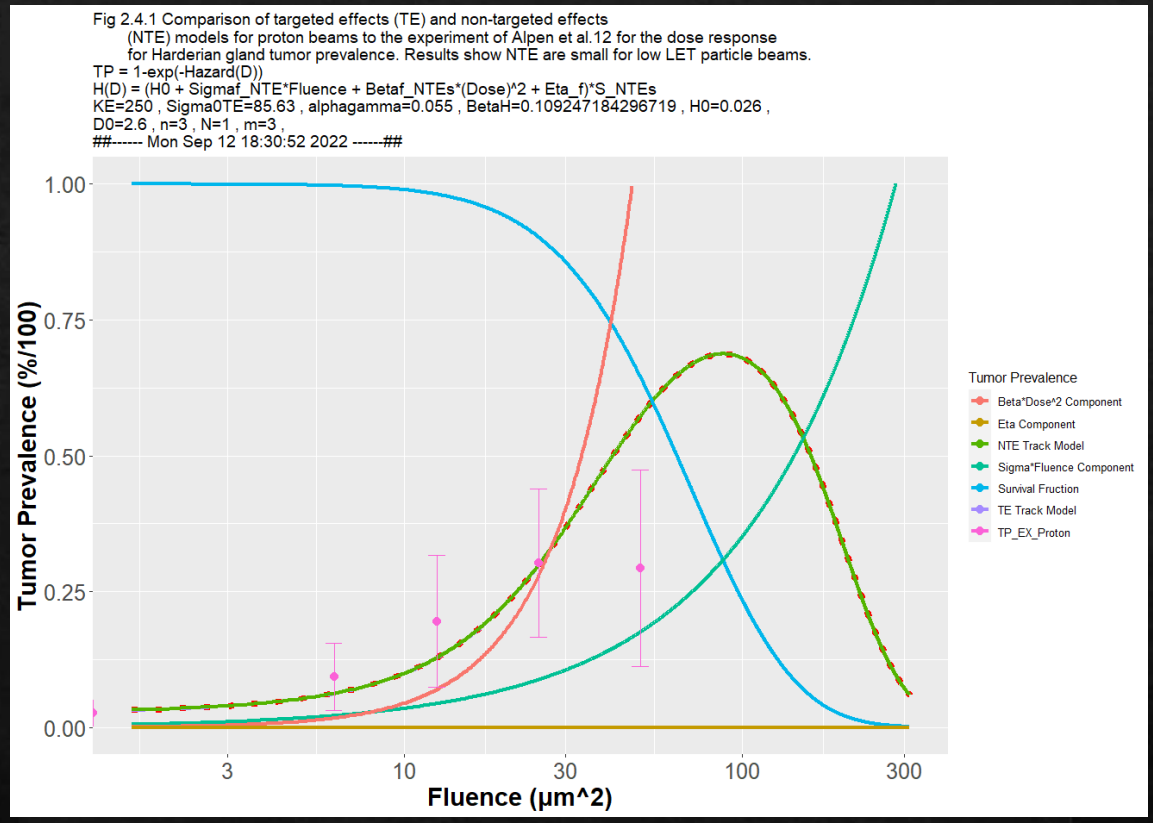
Using the experimental data of 250A MeV Hydrogen irradiation we calculate the α_H , β_H induction term



Results: TE vs NTE for Proton

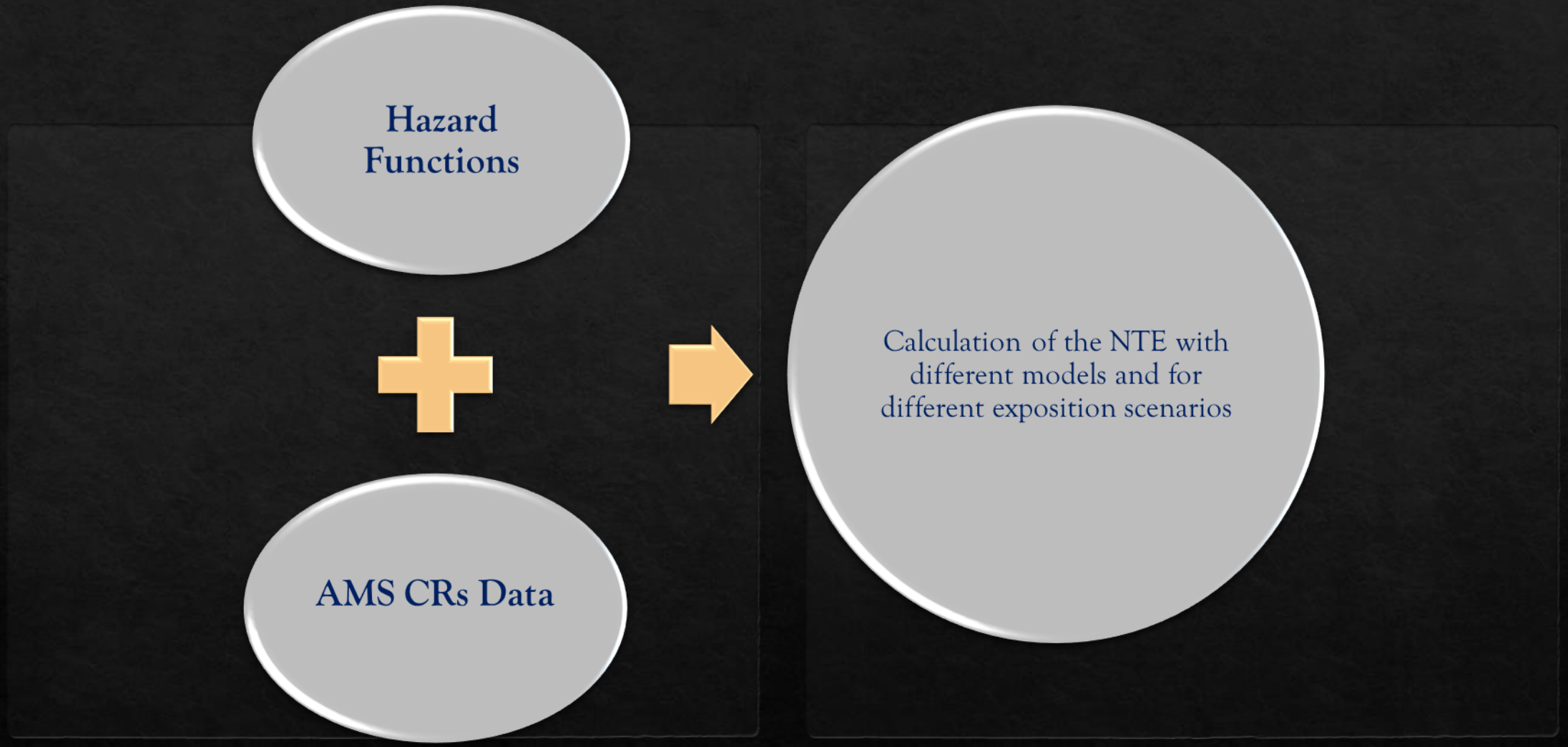
Calculation of the TE and NTE TP models showing for Proton 250A MeV there is no relevant differences in the tumor Prevalence versus dose as expected (NTE models predict same tumor prevalence at low doses compared to the TE model).





The shape of the tumor response curve found in the NTE model is shallow non-linear dose responses curve. It has important implications for space travel because would alter how mission design factors such as duration and radiation shielding are analyzed for radiation protection purposes.

Results: Tool for NTE components evaluation



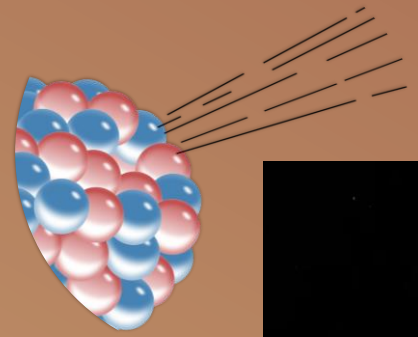
Summary

We developed an ad hoc software in R-script language for Tumor Prevalence risk calculation including the more reliable dose-effect models for space radiation

An r-script library with different Cell Survival Probability models was developed to be used in the calculation of hazard functions of Tumor Prevalence.

Using the software and the experimental data set of Harderian Gland Tumor we tune all the parameter for the Tumor Prevalence Model for protons and we show that there are no substantial differences between the Target and Non-Target Effect as expected.

In the future, we extend the analysis to heavy ions, and we will use the data collected from the AMS02 detector to increase the modelling accuracy and risk prediction.



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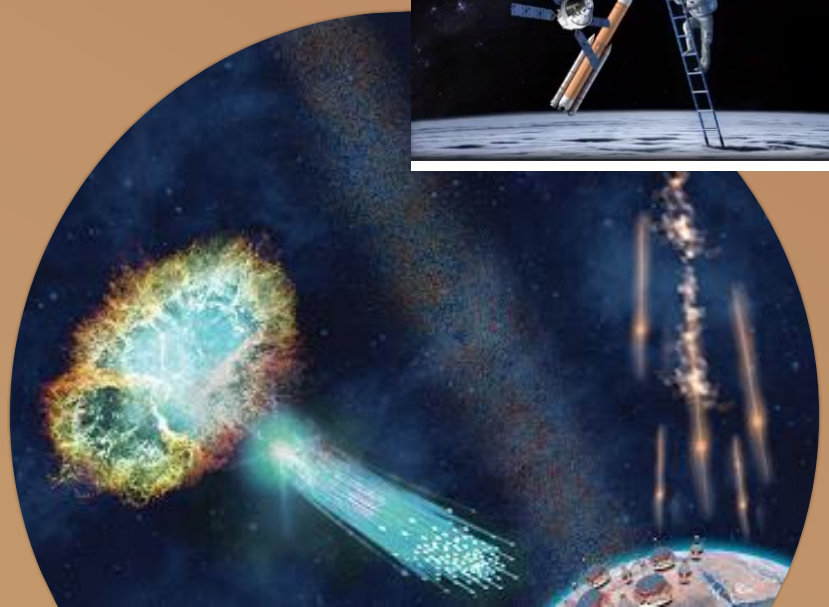

THANKS FOR THE ATTENTION !

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AMS02 INFN ROMA and Sapienza University Web Site

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