AMS 4 SPACE RADIOBIOLOGY

1. Description and context of the project

The Alpha Magnetic Spectrometer (AMS-02) is a particle physics experiment that is mounted on the International Space Station (ISS) and is also a recognized CERN experiment. AMS-02 is a cosmic rays (CRs) detector able to measure all the charged components of the CRs. AMS-02 is the result of nearly two decades of effort of an international collaboration to design and build a state-of-the-art detector capable of performing high-precision CRs measurement. The AMS-02 will use the unique environment of space to advance knowledge of the Universe and lead to the understanding of its origin by searching for primordial antimatter, dark matter and measuring with great accuracy the CRs. So far, more than 218 billion CR events have been collected.

The INFN Roma and the Sapienza University AMS research group [1] joined the international AMS collaboration in 2001. Part of the AMS-02 experiment was built in Rome by the group, that has taken part in the construction of the Transition Radiation Detector (TRD), having as its main task the responsibility to develop the slow control electronics of the GAS System of the TRD (UG-Crate). The UG-Crate was part of a safety-critical system, and the group took care of all the phases of the development (design–test-integrate-fly) following the NASA requirements. Current group members are:

> Alessandro Bartoloni (INFN Roma)
> Francesca Bisello (IRCCS AOUBo)
> Bruno Borgia (INFN Roma & Sapienza University)
> Aboma N. Guracho (INFN Roma)
> Giulia Paolani (IRCCS AOUBo)
> Sara Parsaei (Shahid Bahonar University of Kerman)
> Mustafa M. Rafiei (Shahid Bahonar University of Kerman)
> Miriam Santoro (IRCCS AOUBo)
> Lorenzo Spagnoli (IRCCS AOUBo)
> Lidia Strigari (IRCCS AOUBo)
> Silvia Strolin (IRCCS AOUBo)
> Klarisa Elena Szilagyi (IRCCS AOUBo)
> Faith Tng (Space Generation Advisory Council)
> Vincenzo Valente (GARR & INFN Roma)

After the installation of the AMS-02 on the International Space Station (ISS) in May 2011, the AMS Roma-Sapienza group is participating in the data-taking operations at CERN and the data analysis. In 2017 the group started to investigate some new potential use of the AMS-02 data for variable scientific research in space life sciences, space radiobiology (SPRB), and dosimetry. The AMS SPRB collaboration was created in 2017 by the synergy of the AMS INFN Roma Sapienza group headed by Alessandro Bartoloni with the medical physics research group headed by Lidia Strigari, currently at

IRCCS Azienda Ospedaliero-Universitaria di Bologna (AOUBo) [2]. This collaboration was created to foster the synergy of the two research groups' complementary competencies, knowledge and skills. The expertise of INFN in the space radiation environment, CRs data analysis and AMS-02 detector were complemented with the ones in radiobiology, dosimetry and dose-effect models of AOUBo. In July 2017, this collaboration was announced to the INFN Roma Division Council and to the INFN National Scientific Committee 2 (CSN2) referees [3,4].

SPRB is an interdisciplinary science that examines the biological effects of ionizing radiation (IR) on humans involved in aerospace missions. Living things in the solar system are continuously exposed to Galactic Cosmic Ray (GCR) particles and rarely to more energetic particles emitted by the Sun named Solar Energetic Particles (SEP). The knowledge of the risk assessment of the health hazard related to human space exploration is crucial to reducing damages induced to astronauts from GCRs and SEP. GCRs have been identified as one of the primary sources of radiation exposure in space. Therefore, health risks associated with IR exposure play an essential role in space missions whose safety depends on detailed characterization of the space radiation environment. Table 1 evidences it by comparing the expected ionization doses for different expectation scenarios in space to what happens on the earth's surface and in the clinical application exposition [5].

Exposure Scenario	Ratio[#]	Daily Absorbed Dose (mGy)	Daily Equivalent Dose (mSv)	Daily Effective Dose (mSv)
Earth surface[#]	1.00	2.92	0.01	0.01
Earth surface (Cosmic radiation only)	0.13	0.37	0.00	0.00
Mars surface (Solar maximum)	37.50	0.12	0.30	0.28
Mars surface (Solar minimum)	76.25	0.25	0.61	0.54
Lunar surface (Solar maximum)	72.50	0.10	0.58	0.38
Lunar surface (Solar minimum)	195.00	0.27	1.56	0.84
Clinical Examples (diagnosis)	Ratio[#]	Absorbed Dose (mGy)	Equivalent Dose (mSv)	Effective Dose (mSv)
Whole Body CT (per exam.)	482.00			4.82
PET/CT (per exam.)	1840.00			18.4
Cardiac SPECT/CT (per exam.)	1270.00			12.7
Clinical Examples (treatment)	Ratio[#]	Absorbed Dose (mGy)	Equivalent Dose (mSv)	Effective Dose (mSv)
Proton therapy dose/fraction (typical)	220000.00		2200	

The ratio is calculated using the equivalent doses except for the CT, PET/CT and SPECT/CT cases in which the effective doses are used.

Table 1. Daily absorbed Dose, equivalent Dose, and effective Dose of ionization radiation in different exposure scenarios. Also, some IR doses typical of clinical use are reported.

The scope of this research is using the information of charged particle measurement of AMS to develop a new model on the ionization radiation damage on living things in the space regions that humans will explore in the following decades (LEO, Moon and Mars exploration). The research will produce new models of the expected damage of ionization radiation exposure in space using the AMS data to characterize the inputs to the model (spectra, fluences and doses) and the data presented in the existing relevant literature. The produced models will be helpful for the radiation health risk assessment for humans in space missions and design R&D activities for new dosimetry instrumentation for space.

Since 2018, after the approval of the research activities from INFN Scientific Committees, the group has collaborated with researchers and scientists to investigate the topic. The following paragraph will briefly describe the activities done up to the present.

2. Description of the previous years' project activities.

2018 - 2020

The first result of the research was a study of the capabilities and possibilities for using Cosmic Ray Detector (CRD) data to improve knowledge in the space radiobiology field, especially regarding the AMS-02. In particular, we elaborated a GCR sensitivity analysis showing that the AMS-02 detection capability includes all the elementary particles and nuclei of interest for the space radiobiology investigations and also covers the more significant part of the space radiation energy range of interest (>70%) [6].

Also, we were focused on creating synergies within different scientific communities (radiobiology, medical physics, radiotherapy, and nuclear medicine) and institutions playing a crucial role in human space exploration (Universities, Research and National Space Agencies). To reach this purpose, in 2019, we organized at INFN Roma Sapienza a thematic workshop named "Space Radiobiology and Precision Galactic Cosmic Ray Measurements", on how the AMS-02 experiment on the International Space Station can help the radiation health hazard assessment in exploratory space missions. We invited people from the European Space Agency (ESA), Thales Alenia Space (TAS) and the AMS collaboration [7]. During the workshop addressed three main aspects starting with a detailed description of the AMS-02 experiment, followed by a discussion on the current and future research activities done by ESA for the radiation health hazard assessment in exploratory space missions and concluded with an overview of the problems related to space IR in design and build space infrastructures, with particular attention to shielding solutions for human-crewed lunar/mars missions. In the following days, a fruitful discussion led to the writing of a proposal for creating an ESA topical team on the subject forecast for the following years.

The second step was to deeply analyze how and where the CRD data can be used for the improvement of the risk assessment process for human health during space exploration in the near (LEO) and deep space (BLEO). The results of these studies were presented at different conferences and papers [8-10].

During this period, part of the activities was funded through an agreement between the Italian Space Agency (ASI) and the INFN (n. 2013-002-R.0). In October 2018, using the funding deriving from such agreement, two half-year contracts were activated for the study of possible applications of the data collected by AMS in the field of research activity in radiobiology of space and in particular of protons. The fellowships were attributed to Dr E. Solfaroli Camillocci and Dr E. Loi.

The research status and activities done in this period were presented to the ASI-INFN agreement review committee [11,12], INFN Roma council [13-15], INFN CNS2 referees [16-17], the INFN CNS2 council [19,20] and the international AMS collaboration in a general meeting at CERN [21].

2021 - 2022

During this period, the research focused on the dose-effect relationship (DER) and model (DEM) due to exposure to space radiation in exploratory space missions. Such mathematical models describe the correlation between the exposition to IR and the possible damage to the organs at risk. They are crucial to predicting the space radiation toxicity expected for astronauts/space workers. In particular, in 2021,

we completed and published an extensive review of the existing literature we started in the previous years [22]. DERs describe the observed damages to normal tissues or cancer induction during and after space flights. They are developed for the various dose ranges and radiation qualities characterizing the actual and forecast space missions. In this paper, based on a PubMed search including 53 articles reporting the collected dose-effect relationships after space missions or in-ground simulations, we identified seven significant DERs (e.g., eye flashes, cataracts, central nervous systems, cardiovascular disease, cancer, chromosomal aberrations, and biomarkers). The absorbed dose thresholds and the uncertainties/limitations of the developed relationships are summarized and discussed for each considered effect. The manuscript had a remarkable impact on the scientific community having about 4k views from all over the world and gained after 14 months from the publication a position in the 93rd percentile for download rank and 81st percentile for view rank of the papers published on the Frontiers editor journals [23]. Also, it was included in a collection published in 2022 [24]. After the publication, we presented this work at different conferences and continued to improve it [25-29].

Among the many ways that we identified in the paper to improve the DERs knowledge (e.g., computer simulation of interactions of IR with biological matter, synergy with the clinical field, quantitative meta-analysis, radioprotectors effects, individual radio-susceptibility, DEM integration platform, synergy with astroparticle experiments) we decided to focus our research activities on the development of a platform for the production of reliable DEM that will allow us to predict the possible risk due to radiation during space exploration including also all the information coming from cosmic ray detectors [30-33]. We also promoted a research topic initiative supported by the Frontiers Media SA publisher [34]. The research topic initiative was launched in November 2021 and supported by an interdisciplinary and international editorial team. This initiative was presented at different international conferences [35-38] and in a workshop organized by the United Nations [39].

Following this analysis, we started the development of an ad hoc software tool (NTE-DEM) to investigate one of the promising and not yet understood effects of ionization radiation, usually referred to as the non-targeted effect (NTE) of great relevance for space radiation. NTEs include bystander effects where cells traversed by heavy ions transmit oncogenic signals to nearby cells and genomic instability in the cell's progeny. The NTE-DEM aims to combine the existing experimental data (clinical, pre-clinical and in vitro), the cosmic ray fluences, as measured by the AMS detector and the cell survival probability function existing in the literature to produce reliable DEMs. We use the R-Studio integrated development environment to code it. The first NTE-DEM release (Fig. 1) comprises a main program and several libraries for>10K lines of code.
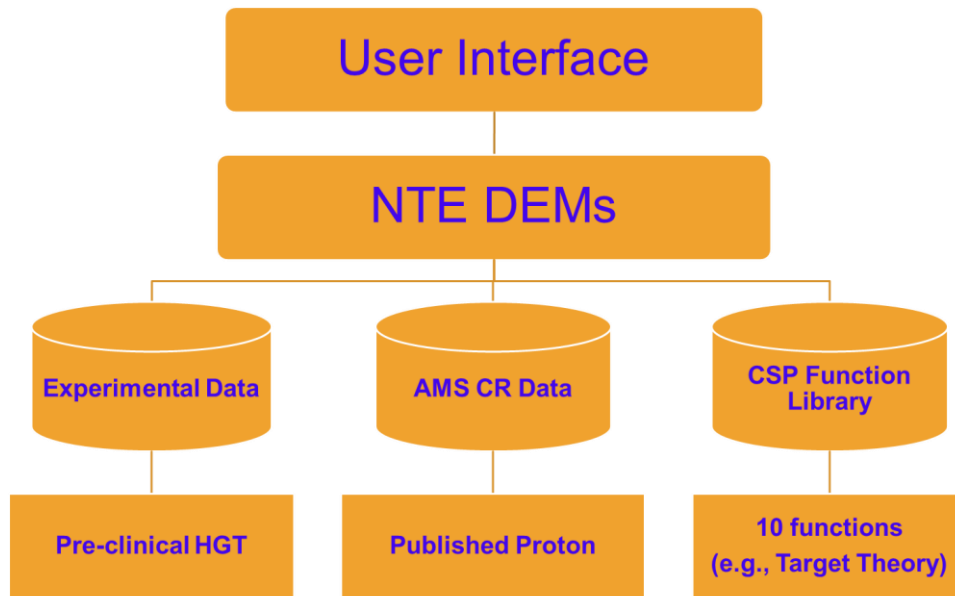
Fig.1 The NTE-DEM v1.0 architecture.

We use it to tune the DEM for the calculation of Tumor Prevalence (TP) in the NTE case induced by space radiation protons. We check the consistency of the results with a reliable dataset of pre-clinical in vivo experimental data related to the Harderian gland tumour (HGT) induced by radiation in rats [40-42]. Also, we check the model consistency by applying it to protons using the published data from the AMS collaboration of the fluxes of the GCRs protons components as an example (i.e., TP was calculated in terms of protons flux and exposition time for different bin energy ranges from 492.4 ± 7 MeV to 1.46 ± 0.335 TeV).

The software also used a software library of cell survival probability (CSP) functions in which we included all the models relevant to this kind of investigation.

We reported such results in an article [43] and presented them at an international meeting [44] and the international conference [45]. Both presentations aroused the interest of representatives of the scientific community of space sciences present in the audience (ASI, ESA and NASA).

For the Roma Sapienza division, this research project is also present in the DOE-INFN Summer Students Exchange Program 2023 Edition [46].

During this period, part of the activities was funded through an agreement between the ASI and the INFN (n. 2019-19-HH.0). In October 2021, using the funding deriving from such agreement, a year contract (art.22 Dlgs 240/2010) was activated for production and analysis of particle fluxes with the AMS-02 experiment to support studies in space radiobiology and dosimetry. The research grant was attributed to Dr A.N. Guracho. In November 2022, the grant was extended for a second year using INFN Roma Sapienza funds.

The activities done in this period were presented to the ASI-INFN agreement review committee [47], INFN Roma council [48,49], INFN CNS2 referees [50,51], to the INFN CNS2 council [52] and at the AMS-Italy Collaboration meeting [53].

3. Project future activities

In the future, we will extend our investigations and studies and the NTE-DEM software in three different main directions, that will regards (see Fig.2):

- The experimental data includes the other diseases expected from space radiation exposure.
- The AMS-02 detector measures the CRs components (electrons, heavy nuclei).
- The Radiobiology Mathematical models' library addresses specific NTE biologic mechanisms and AI-based data analysis technique.
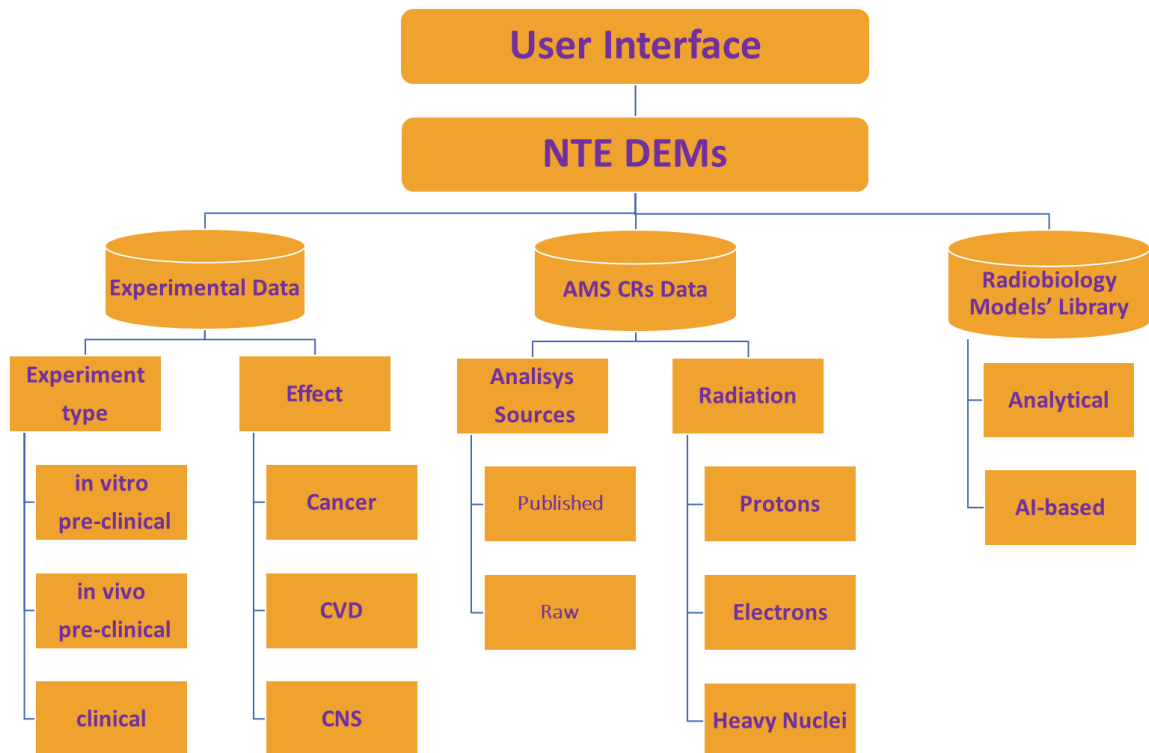

Fig.2 The NTE-DEM software architecture

Experimental data

We will also extend our tools to generate NTE DEMs for other possible effects. As identified in [26], three are the effects resulting crucial for space exploration from the point of view of the risk to human health and, at the same time, requires substantial improvements in the DEMs to forecast in a precise way the impact of radiation exposure.

- radiation-induced cancer
- radiation-induced effects on the central nervous system (CNS)
- radiation-induced cardiovascular disease (CVD)

Further, not only for cancer, there is a clear understanding of the importance of NTEs, but also of CVD and CNS [54-57]. The extension will include the experimental data available in the literature from

different existing stages of studies (i.e. pre-clinical in vitro, pre-clinical in vivo and clinical) referred to these effects starting from the ones we previously identified in the scientific literature [58-92].

A database will be generated and updated.

A database will be generated and updated to enable the training, test and validation of proposed Artificial Intelligence-based models.

AMS data analysis

We will extend our studies of NTEs, including the effects due to electrons and nuclei (Z>=2). In table 2 are represented the actual published AMS data, which are and will be part of the NTE-DEM tool, with also reported some information and characteristics about the published data analysis (particle type, rigidity ranges, time period, …).

Particle	Rigidity Range (GV)	Measurement Type	Time Period	Number of Events
Electron (e$^+$ + e$^-$)	0.5 – 350	Absolute Flux	2011/2012	Over 6.8×10^6
Electron (e$^+$, e$^-$)	0.5 - 1000	Absolute Flux	2011/2013	10.1×10^6
Electron (e$^+$ + e$^-$)	0.5 – 1400	Absolute Flux	2011/2017	28.1×10^6
Electron (e$^+$ + e$^-$)	1 – 50	Time Variation (79)	2011/2017	23.5×10^6
Proton (p$^+$ + p$^-$)	1 - 1800	Absolute Flux	2011/2013	
Proton (p$^+$ + p$^-$)	1 - 450	Absolute Flux	2011/2015	2.8×10^9
Proton (p$^+$ + p$^-$)	1 - 100	Time Variation (114)	2011/2019	5.5×10^9
Helium (He)	1.9 - 60	Time Variation (79)	2011/2017	112×10^6
Helium (He)	1.9 - 3000	Absolute Flux	2011/2013	50×10^6
Helium (He)	1.9 - 3000	Absolute Flux	2011/2016	90×10^6
Helium (He)	1.71 - 100	Time Variation (2824d)	2011/2019	7.6×10^8
Lithium (Li)	1.9 - 3300	Absolute Flux	2011/2016	1.9×10^6
Beryllium (Be)	1.9 - 3300	Absolute Flux	2011/2016	1.9×10^6
Boron (B)	1.9 - 3300	Absolute Flux	2011/2016	2.6×10^6
Carbon (C)	1.9 - 3000	Absolute Flux	2011/2016	8.4×10^6
Oxygen(O)	1.9 - 3000	Absolute Flux	2011/2016	7×10^6
Nitrogen (N)	2.15 - 3300	Absolute Flux	2011/2016	2.2×10^6
Neon (Ne)	2.15 - 3000	Absolute Flux	2011/2018	1.8×10^6
Sodium (Na)	2.15 - 3000	Absolute Flux	2011/2019	0.46×10^6
Magnesium (Mg)	2.15 - 3000	Absolute Flux	2011/2018	2.2×10^6
Silicon (Si)	2.15 - 3000	Absolute Flux	2011/2018	1.6×10^6
Florine (F)	2.15 - 2900	Absolute Flux	2011/2019	0.29×10^6
Iron (Fe)	2.65 - 3000	Absolute Flux	2011/2019	0.62×10^6

Table 2. The AMS published data of particles flux with energy range in different time periods.

Further, we will extract information from the AMS raw data by ad hoc data analysis that will allow improving our understanding of radiobiology aspects related to:

- isotopes not included in the published one,
- period still needs to be published,
- specific space weather event (SEP, CME, …),
- monoenergetic fluences (narrow statistical bin ranges).

We will use it for the risk assessment of NTE induced by IR in different exposure scenarios for the risk assessment of the health hazard related to human space exploration to reduce the damages caused to astronauts from GCRs and sun-generated radiation in a more precise way.

Radiobiology mathematical models' library

In the first version of the tool was developed a software library including all the relevant cell survival probability (CSP) models both for the gamma-ray and charged particles relevant for radiobiology and in particular for space radiation; we coded 10 different mathematical models [99] to be used for the dose-effects relationships description and development:

- Target Theory - n-Targets N-Hits Model - nTNH
- Cellular Track Structure Theory (TST) for charged particles.
- Linear Quadratic Model- LQ
- Linear Quadratic Hyper-RadioSensitivity Model - LQ-HRS
- Linear Quadratic Cubic Model - LQC
- Sublesions Theory Linear Eurepair- Quadratic Misrepair (phi = 1) Model - LE-QM
- Sublesions Theory Linear Eurepair-Linear & Quadratic Misrepair (phi =1) Model- LE
- Sublesions Theory Lethal-Potentially Lethal Model - LPL
- Sublesions Theory Saturable Repair Model- SR-D
- Sublesions Theory Saturable Repair Model- SR-RT

In the future, we will extend such part to include radiobiological mathematical models deeply describing the phenomenology of the NTE biological behaviours (e.g. gap junction intercellular communications) [100]. In addition, artificial intelligence-based models will be developed using the database as mentioned above necessary for their training, testing and validation [101-104].

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