Extension of the BIANCA biophysical model up to Fe-ions and applications for space radiation research

Ricardo Ramos[1*], *Alessia* Embriaco[1,2], *Mario* Carante[1,3], *Alfredo* Ferrari[4,5], *Paola* Sala[6], *Valerio* Vercesi[1] *and Francesca* Ballarini[1,3]

[1]INFN (Italian National Institute for Nuclear Physics), Sezione di Pavia, via Bassi 6, I-27100 Pavia, Italy

[2]ENEA, Istituto Nazionale di Metrologia delle Radiazioni Ionizzanti, Roma Italy

[3]University of Pavia, Physics Department, via Bassi 6, I-27100 Pavia, Italy

[4]University Hospital Heidelberg, Germany

[5]Gangneung-Wonju National University, Gangneung, Korea

[6]INFN (Italian National Institute for Nuclear Physics), Sezione di Milano, via Celoria 16, I-20133, Milano, Italy

Abstract. BIANCA (BIophysical ANalysis of Cell death and chromosome Aberrations) is a biophysical model, implemented as a Monte Carlo code, which simulates the induction of chromosome aberrations and cell death by different monochromatic ion beams (i.e., different ion types and energy values), as well as photons. In previous works, the model predictions for cell survival and lymphocyte dicentrics along therapeutic-like ion beams have been successfully benchmarked against experimental data. With the aim of evaluating the biological damage induced by Galactic Cosmic Rays (GCR), in this study BIANCA was extended up to Fe-ions. A radiobiological database describing human skin fibroblast cell survival and lymphocyte dicentrics as a function of ion type ($1 \leq Z \leq 26$) and energy, as well as dose, was constructed. Afterwards, interfacing BIANCA with the FLUKA Monte Carlo transport code, a feasibility study was performed to calculate the Relative Biological Effectiveness (RBE) of Galactic Cosmic Rays, both for dicentrics and for cell survival; the results were discussed with respect to available space radiation protection limits. Following this work, BIANCA can now provide RBE predictions of cell killing, which can be related to deterministic effects, and lymphocyte dicentrics, more related to stochastic effects, for space radiation exposure.

*Corresponding author: ricardo.ramos@pv.infn.it

1 Introduction

Recently, space research has gained a renewed interest, also due to the fact that NASA is planning to go back to the Moon with a human mission and that the Moon might represent an intermediate step towards Mars. Human space missions are subject to many risks, including those due to space radiation exposure [1]. Galactic Cosmic Rays (GCR), which consist of about 87% protons, 12% He ions and 1% heavier ions in fluence delivered at a relatively low dose-rate (about 1 mSv/day in free space), can represent a serious hazard for the crewmembers of long-term missions, especially outside the Geomagnetic field. In particular, heavy ions like Fe are known to be very effective at inducing DNA damage [e.g. 2], which in turn may lead to higher level damage involving chromosomes, cells and tissues/organs [e.g. 3-5]. The exposure scenario is further complicated by the so-called "Solar Particle Events" (SPEs), which are occasional injections of high fluxes (up to more than 10^{10} particles cm^{-2} in few hours) of charged particles coming from the Sun, mainly protons with energy lower than a few hundred MeV.

Many works are available in the literature on the calculation of astronauts' doses [e.g. 6]. In the past, the FLUKA Monte Carlo transport code [7-10] has been coupled with simulated anthropomorphic phantoms inserted into an aluminium shell of variable thickness; according to those calculations [10], the GCR effective dose during a 2-years mission in deep space (typical duration of a Mars mission) at solar minimum would be about 1 Sv. Furthermore, in case of a SPE similar to the August 1972 one, a 10 g/cm^2 Al storm shelter would allow to respect the equivalent dose limits for skin, eye and blood forming organs reported in the NCRP report n. 132 for 30-days missions in Low Earth Orbit [11]. Most experimental data on space radiation biological damage come from experiments performed at facilities like that available in Brookhaven, where cells and small animals can be irradiated by different heavy ion beams up to Fe. Information on the effects of space radiation on humans also comes from the observation of chromosome aberrations in peripheral blood lymphocytes (PBL) taken from astronauts' blood samples [e.g. 6,12,13]. In these measurements, pre-flight calibration curves obtained by *in vitro* gamma-ray irradiation are used to convert the post-flight aberration yields into equivalent doses. In general, such biodosimetry estimates lie within the range expected from physical dosimetry. In this work the BIANCA (BIophysical ANalysis of Cell death and chromosome Aberrations) biophysical model, which simulates the induction of chromosome aberrations and cell death by photons and different (monochromatic) ion beams, was extended up to Fe ions, also considering that a new source capable of accelerating Fe ions will be available soon at CNAO (Pavia, Italy), in the framework of the INSpIRIT project. Following interface to FLUKA, this allowed predicting RBE values (both for cell death and for chromosome aberrations) following GCR exposure, thus providing the bases for future calculations on space radiation health risk.

2 Materials and Methods

BIANCA is a biophysical model, implemented as a Monte Carlo code, which simulates the induction of cell death and chromosome aberrations by different monochromatic ion beams, as well as photons. Although detailed descriptions of the model can be found in previous works [e.g. 14-17], it is worth mentioning that BIANCA is based on the following main assumptions: i) ionizing radiation can induce DNA "Critical Lesions" (CLs), where a CL is defined as a lesion that interrupts the chromatin fibre producing two (main) independent fragments; ii) distance-dependent incorrect rejoining of such fragments, or fragment un-rejoining, produces chromosomal aberrations; iii) certain aberration types (dicentrics, rings

and large deletions, where "large" means visible when chromatin is condensed) lead to cell death. The CL yield and the fragment un-rejoining fraction (f) are the only two adjustable parameters. In previous works [15,18,19], an approach has been developed to predict cell survival following ion irradiation of an arbitrary cell line for which the photon dose-response is known, starting from a reference cell line; V79 cells have been chosen as a reference.

In the present work, based on the parameter values derived for V79 cells and the formalism described in [15], survival curves for human skin fibroblasts (HSF) exposed to different monoenergetic ion beams (protons, He-ions, C-ions, Ne-ions and Fe-ions) were predicted. These cells were chosen because they represent the radiation response of the skin, which is one of the organs that have to be considered for radiation protection. Briefly, to simulate HSF survival after irradiation with a given ion type of given energy (and thus LET), we derived the values of the two model parameters (CL and f) by rescaling the parameters previously used to reproduce the survival of V79 cells, which have been chosen as a reference; further details can be found in [15]. Afterwards, each of the (simulated) HSF survival curves was fit by the well-known linear-quadratic equation:

$$S(D) = \exp(-\alpha D - \beta D^2) \qquad (1)$$

where S(D) is the fraction of surviving cells after receiving an absorbed dose D, and α and β are fitting coefficients. These coefficients were then stored in a table constituting a radiobiological database that allows predicting HSF cell survival as a function of ion type and energy.

Concerning chromosome aberrations, we developed an analogous database that allows simulating dicentric dose-response curves in human lymphocytes. Specifically, the CL parameter has been adjusted to reproduce experimental dose-responses taken from the literature for photons and for different monochromatic ion beams (protons, He-ions, C-ions, N-ions, O-ions, Ne-ions and Fe-ions); afterwards, the LET-dependence of the CL yield has been fit for each ion type, thus allowing us to predict dose-response curves for, in principle, any LET value. Finally, each of these (simulated) curves has been fit by the following linear-quadratic function, which is considered as a good description for dicentric induction unless the dose is too high (about 10 Gy for photons, a few Gy for high-LET radiation):

$$Y(D) = \alpha D + \beta D^2 \qquad (2)$$

In eq. (2), Y(D) is the mean number of dicentrics per cell after an absorbed dose D, and α and β are fitting coefficients. Such coefficients, together with those describing the photon dose-response, have been stored in a table that describes lymphocyte dicentric dose-response for different monochromatic ion beams, as well as photons.

Finally, the radiobiological database for lymphocyte dicentrics and that for HSF cell survival were read by FLUKA, exploiting a pre-existing interface between BIANCA and FLUKA. Specifically, whenever according to FLUKA a certain amount of energy (and thus a certain dose, D_i) was deposited in a target voxel by a given particle type of given energy, FLUKA read from the tables the corresponding linear and quadratic coefficients (α_i and β_i), and used them to calculate the average coefficients (α and β) describing the fraction of surviving cells or the yield of dicentrics by the mixed field in that voxel:

$$\alpha = \frac{\sum_{i=1}^{n} \alpha_i D_i}{\sum_{i=1}^{n} D_i} \quad (3)$$

$$\sqrt{\beta} = \frac{\sum_{i=1}^{n} \sqrt{\beta_i} D_i}{\sum_{i=1}^{n} D_i} \quad (4)$$

Afterwards, the RBE in each voxel was calculated as D_X/D, where D is the total absorbed dose in the voxel and D_X for cell survival and for dicentric induction was calculated as follows, respectively:

$$D_X = \frac{\left[-\alpha_X + \sqrt{\alpha_X^2 + 4\beta_X \ln S}\right]}{2\beta_X} \quad (5)$$

$$D_X = \frac{\left[-\alpha_X + \sqrt{\alpha_X^2 + 4\beta_X Y}\right]}{2\beta_X} \quad (6)$$

More details can be found in [18-21]. This allowed performing a feasibility study to calculate the Relative Biological Effectiveness (RBE) of Galactic Cosmic Rays (GCR), both for dicentric induction and for cell survival.

3 Results and discussion

In order to obtain the α and β coefficients for HSF cell survival, we simulated 14 survival curves for proton beams (with LET in the range 2.5-35 keV/µm), 20 curves for He-ion beams (LET range: 5-200 keV/µm), 30 curves for C-ion beams (LET range: 10-500 keV/µm), 25 curves for Ne-ion beams (LET range: 20-500 keV/µm), and 26 curves for Fe-ion beams (LET range: 75-900 keV/µm). Fig.1 shows the α and β values obtained for HSF cell survival as a function of LET for protons, He-ions, C-ions, Ne-ions and Fe-ions. As expected, unless for very high LET values where the so-called overkilling dominates, the values of α increase with LET up to 100-200 keV/µm for all considered ions. Furthermore, lighter ions tend to show higher α values with respect to heavier ions having the same LET; this reflects the fact that lighter ions, having lower energy, produce lower-energy secondary electrons and thus are characterized by a denser track structure, which induces DNA damages that are more clustered and thus more difficult to be repaired by the cell. The interpretation of the behaviour of the β coefficient is less straightforward: while the very low values found at high LET confirm that at high LET the survival curve is basically linear, the increase shown by some ion types at lower LET values is more difficult to explain; however, it is worth mentioning that this increase is much less pronounced than the increase shown by coefficient α.

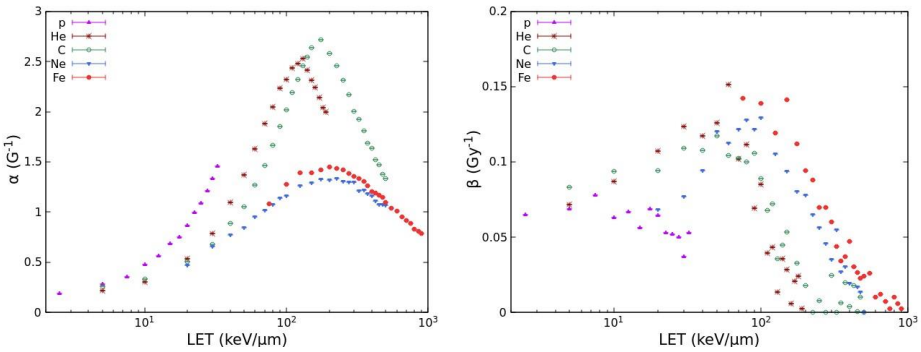

Fig. 1. Values of the coefficients α (left panel) and β (right panel) describing HSF cell survival as a function of LET for the different ion beams considered in this work.

Concerning the induction of dicentric chromosomes in human lymphocytes, we simulated 14 curves for protons (LET range: 2.5-35 keV/μm), 12 curves for He-ions (LET range: 5-110 keV/μm), and 16 curves for heavy ions between carbon and iron (LET range: 5-150 keV/μm). Fig.2 shows the values of the α and β coefficients obtained by fitting each of these curve with eq. (2). Importantly, while the β coefficients for dicentrics are in the same order than those for cell survival, the dicentric α coefficients are much smaller than those for cell survival. This implies that dicentrics have a lower α/β ratio, which is consistent with the higher degree of curvature shown by lymphocyte dicentric dose-responses with respect to survival curves.

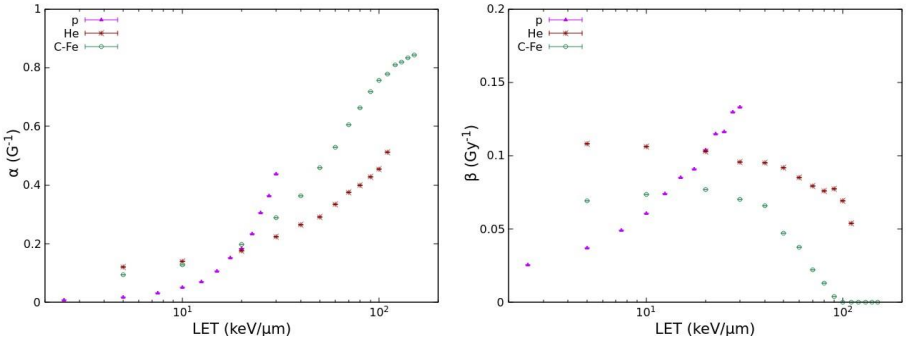

Fig. 2. Values of the coefficients α (left panel) and β (right panel) for lymphocyte dicentrics as a function of LET for the different ion beams considered in this work.

As an exercise in the framework of biological damage evaluation following space missions, the absorbed dose in a spherical water phantom (radius: 15 cm) included in a spherical, isotropic source (radius: 32 cm) was calculated by the FLUKA code. For these simulations, the GCR spectrum at solar minimum conditions embedded in FLUKA was considered. The RBE for lymphocyte dicentrics and that for cell death were calculated by reading the two radiobiological databases described in the Methods. The spherical phantom was irradiated by a total absorbed dose of 0.5 Gy, which is in the order of the dose that should be received by an astronaut during a Mars mission [e.g. 22]. Table 1 shows the RBE values and the RBE-weighted doses calculated for lymphocyte dicentrics (columns 2 and 3) and for HSF cell death (columns 4 and 5).

Table 1. RBE values and RBE-weighted doses for lymphocyte dicentrics (RBE_{dic} and $Dose*RBE_{dic}$) and for HSF cell death (RBE_{surv} and $Dose*RBE_{surv}$) induced by GCR at solar minimum for a total absorbed dose of 0.5 Gy.

	RBE_{dic}	$Dose*RBE_{dic}$ ($Gy*RBE_{dic}$)	RBE_{surv}	$Dose*RBE_{surv}$ ($Gy*RBE_{surv}$)
GCR	2.10	1.05	1.90	0.95

This exercise showed that, at least for the considered dose, the RBE for lymphocyte dicentrics tends to be higher than that for skin fibroblast cell death. This may be explained by considering that the photon dose-response for lymphocyte dicentrics is characterized by a much lower α/β ratio with respect to (fibroblast) cell survival curves, thus implying that the response for lymphocyte dicentrics has a more pronounced curvature that leads to a higher RBE at low and intermediate doses. Based on this interpretation, the difference between the RBE for dicentrics and that for cell death should increase by decreasing the dose.

A comparison with the astronauts' 10-year career limits for stochastic effects recommended by NCRP [11], which are age- and sex-dependent, shows that the calculated RBE-weighted dose for dicentrics (1.05 GyRBE) is higher than the limit for 35-years-old male astronauts (which is 1.0) and that for 45-years-old female astronauts (which is 0.9). Concerning the limits for deterministic effects, the RBE-weighted dose for skin fibroblast cell survival found in this work (0.95 GyRBE) is even lower than the 30-day-mission limit recommended by NCRP for skin, which is 1.5 GyEq. On the contrary the value found for lymphocyte dicentrics is higher than the limits for blood forming organs, which are 0.25 GyEq for a 30-days mission and 0.5 GyEq for a 1-year mission. Of course these comparisons have to be taken with caution for several reasons, including the following: 1) the limits for stochastic effects are effective doses expressed in Sv, whereas the numbers calculated in this work are RBE-weighted doses expressed in GyRBE; 2) the phantom used in this work was a water sphere, whereas in the future we plan to repeat these calculations for an anthropomorphic phantom; 3) this work did not consider any shielding, which will be included in future studies and is expected to lead to decreased doses; 4) since lymphocyte chromosome aberrations are better correlated with cancer incidence [e.g. 23,24], a comparison of the results found in this work for lymphocyte dicentrics with the blood forming organ (BFO) limits for deterministic effects is not straightforward.

4 Conclusions

The BIANCA biophysical model was extended to heavy ions up to Fe, in view of studies on space radiation effects. Specifically, two radiobiological databases were constructed for these ions: the first one allows predicting cell death for human skin fibroblasts, whereas the second one describes lymphocyte dicentrics, which are considered as indicators of stochastic damage including cancer. As a pilot study, BIANCA was interfaced with the FLUKA code and RBE values (both for lymphocyte dicentrics and for HSF cell death) were calculated for a water sphere irradiated by a GCR spectrum; the results were compared with astronauts' dose limits recommended by NCRP. This work thus allowed developing a tool that, when interfaced to a radiation transport code capable of handling the various space radiation components, can provide RBE predictions of cell death and lymphocyte dicentrics not only for ion therapy, but also for space radiation exposure. As a

future development, we plan to include the effects of shielding and, possibly, to adopt a more realistic anthropomorphic phantom.

This work was supported by INFN (project MC-INFN/FLUKA), the University and Research Ministry ("MIUR Dipartimenti di Eccellenza 2018-2022 project F11I18000680001"), and the INSpIRIT project by Regione Lombardia, ID 1161908, co-funded on resources POR FESR 2014-2020-Asse 1.

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