Modeling the Action of Protons and Heavier Ions in Biological Targets: Nuclear Interactions in Hadrontherapy and Space Radiation Protection

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Abstract. Tumor treatment with protons and Carbon ions can allow for a better optimization of Tumor Control Probability and Normal Tissue Complication Probability, especially for radio-resistant tumors. Exposure to protons and heavier ions is also of concern for manned space missions such as future travels to the Moon and Mars. Nuclear reactions with the human body constituents, the beam line components (for hadrontherapy), and the spacecraft walls and shielding (for space radiation protection) can significantly modify the characteristics of the primary radiation field and thus the dose distributions in the various target tissues. In this context the FLUKA Monte Carlo transport code, integrated with radiobiological data and coupled with anthropomorphic phantoms, was applied to the characterization of therapeutic proton beams and the calculation of space radiation organ doses, with focus on the role of nuclear interactions. Besides absorbed and equivalent doses, distributions of "biological" dose (modeled as the average number of DNA clustered lesions per cell induced in a given organ or tissue) were calculated as well. Concerning space radiation protection, exposure to Galactic Cosmic Rays (GCR) and Solar Particle Events (SPE) under different shielding conditions was simulated. Both for hadrontherapy and for space radiation exposure, nuclear reaction products were found to play a more important role for the equivalent and "biological" dose than for the absorbed dose. Furthermore, while for SPEs the doses (both absorbed and equivalent/"biological") decreased dramatically by increasing the shield thickness, the GCR doses showed a slight shielding dependence. Overall, these examples of application of FLUKA to radiotherapy and radiation protection problems emphasized the need of further models and data, typically double-differential cross sections for nucleus-nucleus interactions at energies below a few hundred MeV/n.

INTRODUCTION

Human beings can be exposed to ionizing radiation from different sources such as the Earth natural background, medical diagnostics or treatment, and occupational exposure. In most cases, low-LET (Linear Energy Transfer) radiation types, typically x rays, are involved. However, an increasing number of radiotherapy facilities are now making use of protons or heavier ions, typically Carbon [1]. The latter are currently used at HIMAC in Japan (more than 700 patients treated up to now) and GSI in Germany (more than 150 patients). New Carbon facilities are under construction in Pavia, Italy, and Heidelberg, Germany. Both protons and heavier ions are characterized by a localization of energy deposition in the so-called "Bragg peak" region, which can allow for an improved optimization of Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). While heavy ions such as Argon have shown unacceptable complications to normal tissues, Carbon beams are particularly suitable because their Relative Biological Effectiveness is sufficiently low (approximately 1, as for protons) in the plateau before the Bragg peak, whereas it is higher (up to 3-4 and even more, to be compared with the typical 1.1 value of proton beams) in the region of the peak. These features are relevant,

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especially for the treatment of hypoxic tumors, which are more radio-resistant due to ionization clusters induced by low-energy highly charged ions. Human exposure to high-LET radiation also occurs in manned space missions, where astronauts continuously receive doses from Galactic Cosmic Rays. The GCR spectrum consists of about 87% protons, 12% He ions, and 1% heavier ions in fluence. Although the dose rate is relatively low (1 mSv/day on the average), radiation can represent a serious risk for the crewmembers of long-term missions. This is especially true for missions in deep space outside the Geomagnetic field, which is the case for lunar missions and possible travels to Mars. The exposure scenario in space is further complicated by "Solar Particle Events" (SPEs), which are occasional but almost unpredictable injections of high fluxes (up to more than 10^{10} particles·cm^{-2} within some hours, to be compared with 4 particles·cm^{-2}·s^{-1} for GCR) of charged particles coming from the Sun, mainly protons with energies below a few hundred MeV.

A detailed knowledge of the action mechanisms of ions is of utmost importance both for hadrontherapy treatment planning and for performing reliable space radiation risk estimates. Nuclear interactions occurring in the human body, the beam line components (for hadrontherapy), and the spacecraft walls and shielding (for radiation protection in space) represent a key issue, since they can significantly modify the primary radiation field and thus its effects on biological targets. In this regard, the FLUKA code used in this work (see below) was recently applied to the characterization of 1-GeV/n Fe ion beams, which are frequently used in radiobiological experiments aimed at evaluating the effects of the heavy-ion component of space radiation. More specifically, the following quantities were simulated under different shielding conditions: primary-ion "survival," fragment spectra, absorbed dose, track-average LET, and dose-average LET, also taking into account specific features of the experimental set up at the NASA Space Radiation Laboratory (NSRL) in Brookhaven, NY [2]. The present paper reports on applications of FLUKA to the characterization of therapeutic hadron beams and the calculation of organ doses from GCR and SPE in deep space, with focus on the role of nuclear interactions. FLUKA is a multi-purpose Monte Carlo code able to deal with transport and interaction of electromagnetic and hadronic particles over a wide energy range in any material [3,4]. To the aims of this work, it is worth reporting that nucleus-nucleus interactions below 5 GeV/n down to 100 MeV/n, which are of concern for space research as well as for hadrontherapy, have recently been implemented thanks to the coupling with a modified version of the Relativistic Quantum Molecular Dynamics code RQMD-2.4 [5]. To allow dose calculation in the various organs of the human body, FLUKA was coupled with two anthropomorphic phantoms. Besides absorbed doses, distributions of equivalent dose were calculated as well. At GSI, the development of treatment plans that take into account the specific Relative Biological Effectiveness (RBE) of the various beam components was faced by calculating separately the RBE for each target voxel on the basis of the Local Effect Model. According to this model, the biological response is the convolution of the x-ray lethal damage probability with the different values of the radial dose distribution integrated over the cell nucleus [1]. The approach adopted in this work is based on the calculation of a quantity that we call "biological dose," defined as the average number of "Complex Lesions" (CLs) per cell in a given organ or tissue. CLs are clustered lesions of the DNA double helix and are of particular interest since they represent a critical step in the processes leading to cell death and cell conversion to malignancy.

METHODS

Integration of Data into "Condensed-History" Codes

As mentioned in the Introduction, neither the dose nor the equivalent dose are sufficient to fully characterize the radiation effects in biological targets, especially if one takes into account that the DNA linear dimensions are of the order of the nm [6]. Such effects can be well described by the so-called "event-by-event" track structure codes, which simulate each single energy deposition (essentially atomic/molecular ionizations and excitations) at the nm level. Event-by-event codes can be successfully applied up to the cellular level, i.e., at the μm scale. Examples of applications of such codes to the simulation of DNA damage, cell death, and chromosome aberrations can be found in [7-10]. However, the "event-by-event" approach cannot be applied to the case of tissues and organs since it would require unacceptable computing time.

A possible solution consists of integrating data (either from event-by-event simulations or from radiobiology experiments) into condensed-history codes such as FLUKA. To this aim, each energy deposition calculated by FLUKA for a given radiation type and energy was associated to the corresponding yield of induced "Complex Lesions" (CLs) per cell.

CLs are clustered DNA lesions that can be taken as a reference parameter to evaluate "biological" doses, since they have been shown to play a key role in the induction of both cell death [8], important for radiotherapy, and chromosome aberrations [9-10], important for radiation protection. The yields of these lesions have been calculated in a previous work based on an event-by-event code [7]. For light ions, the average number of $CL \cdot Gy^{-1} \cdot cell^{-1}$ was found to increase with the radiation LET up to a maximum in correspondence of about 100 keV/μm. Furthermore, protons showed a higher effectiveness with respect to alpha particles of the same LET, reflecting the track structure features of these particles.

Coupling of FLUKA with Anthropomorphic Phantoms

In view of applications to radiotherapy and radiation protection, FLUKA was coupled with two anthropomorphic phantoms, i.e., a mathematical model based on combinatorial geometry and a "voxel" model constructed starting from whole-body CT data. The mathematical model is a hermaphrodite phantom derived from "ADAM," a male model originally developed at the GSF Institute in Munich, Germany, and subsequently translated in terms of FLUKA geometry after addition of the female organs and separation between red bone marrow and bone surface [11]. This phantom (height 180 cm, mass 70.65 kg) consists of 68 FLUKA regions, each of them representing an organ/tissue or a part of it. The second phantom is a voxel model called GOLEM, also developed at GSF [12]. GOLEM derives from a whole-body CT examination of a leukemia patient who was a 38-year-old male, 176 cm in height and 68.9 kg in weight. The segmentation process (220 slices, each consisting of 256x256 pixels) resulted in a particularly realistic model of an adult male person described by more than 2.2×10^6 voxels, each voxel being a cuboid element of $2 \times 2 \times 8$ mm^3. Coupling of GOLEM with FLUKA and further separation of bone marrow regions according to the proportion of red and yellow marrow resulted into 287 different FLUKA regions. Recently, the coupling with voxel geometries was extended to directly import into FLUKA raw CT-scan outputs on the basis of automated algorithms that assign material compositions to CT scans; work is in progress on the implementation of *variable* density FLUKA materials to simulate transport through micro-porous media like trabecular bone and lung tissues [13].

Both phantoms can be inserted into a shielding structure of variable shape and dimensions, thickness and material. As in previous studies [14,15], an Al cylindrical shell was used in the work presented herein. The values considered for the shell thickness were 1 and 2 $g \cdot cm^{-2}$ (nominal spacesuit and lightly shielded spacecraft), 5 $g \cdot cm^{-2}$ (nominal spacecraft), and 10 $g \cdot cm^{-2}$ (storm shelter to be used in case of SPE). In some simulations a 0.3 $g \cdot cm^{-2}$ thickness (light spacesuit) was considered as well. The space between the shielding box and the phantom was filled with air, and the phantom was irradiated isotropically. As suggested in other works [16], the integral proton fluence data of the August 1972 Solar Particle Event were represented by an exponential function of the form $\Phi = 6.6 \times 10^8 \exp[-(E-100)/30]$, where Φ is the number of $protons \cdot cm^{-2}$ with energy > E, and E is expressed in MeV. The GCR spectra were taken from the model of Badhwar and O'Neill [17], with solar modulation parameters φ=465 MV for solar minimum and φ=1440 MV for solar maximum. All ions with atomic number in the range 1-28 were considered. The equivalent dose was calculated according to ICRP 60 [18].

RESULTS

Applications to Hadrontherapy

The integration method described above was applied to the characterization of the 72-MeV proton beam used for the treatment of ocular tumors at the Paul Sherrer Institute (PSI) in Switzerland [19]. The geometry of the apparatus, purposely set up to obtain a fully Spread-Out Bragg Peak (SOBP) in a perspex phantom, was faithfully reproduced in the simulations. Particular attention was devoted to the various beam-line constituents, where nuclear interactions can take place. The beam modulation, which is obtained at PSI by means of Al profiles of variable thickness mounted on a rotating wheel, was dynamically simulated by random mapping of a single profile along the beam axis. Importantly, the beam Relative Biological Effectiveness (RBE) was found to be 1.2 along most of the SOBP (except for an increase in the distal part), consistent with the constant value of 1.1 adopted in therapeutic practice with protons. A constant RBE can be explained by the "balance" between proton slowing down and the progressive decrease in the contribution of nuclear reaction products.

In order to quantify the role of nuclear interactions, the contributions from the various radiation field components were calculated separately. Secondary hadrons (including ions) produced by nuclear interaction accounted for less than 4% of the total absorbed dose in most of the SOBP, and disappeared in its distal part. In contrast with the absorbed dose, which was roughly constant with depth throughout the entire SOBP, the calculated profile of "biological" dose (i.e., average number of CL/cell) showed a sharp increase at the distal part of the SOBP due to the presence of protons with low energy and thus high LET and biological effectiveness. The relative contribution of nuclear reaction products to the biological dose was larger with respect to the absorbed dose, reaching values of about 12% in the proximal part of the SOBP. The method described above was then extended to the characterization of a "virtual" 160-MeV proton beam, modulated to obtain a typical SOBP suitable for the treatment of deep solid tumors [20]. Qualitatively similar results (absorbed dose constant in the SOBP, sharp increase of the biological dose at the distal part of the peak, constant RBE of ≈1.2, and larger role of nuclear interactions for the biological dose than for the absorbed dose) were obtained.

Applications to Space Radiation Protection

The August 1972 Solar Particle Event

Table 1 shows skin doses (absorbed, equivalent, and "biological") calculated by simulating exposure to the August 1972 SPE proton spectrum. The results were obtained by irradiating the mathematical phantom inserted into a cylindrical Al shell, and the calculations were repeated for values of the shell thickness in the range 1-10 $g \cdot cm^{-2}$. For each thickness, the dose due to the products of nuclear reactions of primary protons with the shield and the human body is reported in parenthesis (e.g., *0.15* in parenthesis next to 8.2 in the first row means that, over a total dose of 8.2 Gy, 0.15 Gy were delivered by nuclear reaction products). As expected, all dose types decrease dramatically by increasing the shielding. The ratio between equivalent and absorbed dose provides an effective quality factor of about 1.5, which is higher than the value of 1 usually associated with protons. This mainly reflects the presence of slowing down protons with low energy and thus high LET and quality factor. Although the role of nuclear reaction products is not negligible (especially for the equivalent and biological dose with respect to the absorbed dose, and for heavy shielding with respect to light shielding), a major role is played by primary protons. With respect to skin, larger relative contributions of nuclear reaction products were found for internal organs (e.g., 14% and 30% to the liver equivalent dose behind 1 and 10 $g \cdot cm^{-2}$, respectively). The relative contribution of nuclear reaction products increases with increasing the shield thickness (e.g., from 1.8% to 5% for the absorbed dose, from 6.9% to 20% for the equivalent dose, from 8.7% to 22% for the "biological" dose). This can be explained by the fact that since the primary particles are protons, nuclear interactions mainly consist of target fragmentation. Furthermore, the role of nuclear interactions was found to be more important for the equivalent and "biological" doses than for the absorbed dose. Again this is due to the fact that most of the nuclear interaction products are slow particles with high LET and thus high quality factors.

The results obtained in terms of "biological dose" (average number of CLs per cell) can be interpreted on the basis of our model of chromosome aberration induction, e.g., [9,10], which is based on the hypothesis that two CLs in the same cell can give rise to a chromosome aberration if they are induced sufficiently close. According to this model, a yield of 4.8 CL/cell (that is what we found for skin behind 1 g/cm^2 Al) implies that each exposed cell has about a 0.3 probability to be affected by a translocation, which is an important aberration type because it is correlated with cell conversion to malignancy. However, this consideration has to be taken with caution because the present version of our model is specific for acute irradiation, whereas the typical duration of a SPE is of the order of hours or days. Concerning eye lenses and Blood Forming Organs (BFO), which together with skin are the reference organs for radiation protection against deterministic effects, the equivalent doses calculated in this work (mathematical phantom) were 6.89 Sv (eye) and 1.8 Sv (BFO) behind 1 g/cm^2 Al and 0.56 Sv (eye) and 0.25 Sv (BFO) for 10 g/cm^2 Al. Slightly different values (lower for skin and eye, higher for BFO) were found with the voxel phantom, mainly due to differences in the organ description (e.g., skin thickness and bone marrow distribution). According to these calculations, an Al storm shelter of 10 g/cm^2 Al would be sufficient to respect the NCRP limits for 30-day missions in Low Earth Orbit [21] in case of a solar event similar to the August 1972 SPE. However, comparisons with these limits have to be taken with caution because they refer to Low Earth Orbit within the Geomagnetic field. These numbers have to be taken as mere guidelines, while waiting for the introduction of new reference values specific for deep space.

TABLE 1. Skin doses from the August 1972 SPE with different Al shielding. The numbers in parenthesis represent the contributions due to nuclear reaction products

Al shield [g/cm^2]	Absorbed Dose [Gy]	Equivalent Dose [Sv]	"Biological" Dose [CL/cell]
1	8.2 *(0.15)*	13.3 *(0.92)*	4.83 *(0.42)*
2	4.7 *(0.11)*	7.2 *(0.62)*	2.68 *(0.28)*
5	1.5 *(0.05)*	2.2 *(0.27)*	0.84 *(0.12)*
10	0.4 *(0.02)*	0.6 *(0.12)*	0.23 *(0.05)*

Galactic Cosmic Rays

Figure 1 shows the skin dose (in mGy/day) and equivalent dose (in mSv/day) calculated with the mathematical phantom in case of exposure to a GCR solar minimum spectrum (modulation parameter φ=465 MV). As like as for the August 1972 SPE, for each Al thickness value the contributions from primary ions and nuclear interaction products ("secondary hadrons" in the figures), as well as from the electromagnetic component, were calculated separately.

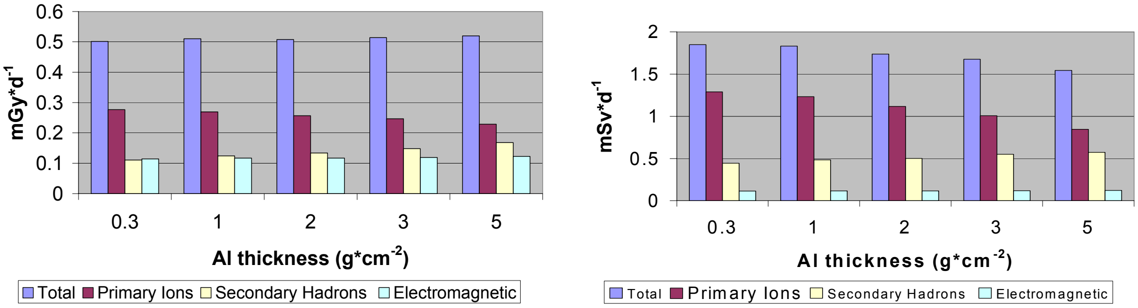

FIGURE 1. Skin dose (left) and equivalent dose (right) from GCR at solar minimum for different values of Al shield thickness.

In contrast with SPE results, the GCR absorbed dose does not decrease by increasing the Al shielding due to the high energies of primary ions and to the decrease in the primary-ion contribution, which is balanced by an increase in the contribution of secondary hadrons and electromagnetic particles. The equivalent dose, as well as the biological dose, shows a (slight) decrease starting from 2 g/cm^2 Al. This can be explained by taking into account that projectile fragmentation can give rise to charged particles with roughly the same velocity as the incident ion but lower charge, and thus lower LET and quality factor. Similarly to what obtained for SPEs, both for the absorbed dose and for the equivalent dose the relative contribution of nuclear reaction products was found to increase with the Al shield thickness. However, the role played by nuclear interactions for the equivalent dose was not substantially different with respect to the absorbed dose. Internal organs showed similar doses but smaller equivalent doses with respect to skin, although the differences were not so dramatic as those found for SPEs. Similarly to what obtained for SPEs, for internal organs the relative contribution from nuclear reaction products was larger than for skin due to nuclear interactions occurring in the human body.

Annual effective doses for GCR exposure at solar minimum were calculated as well. According to these results, a hypothetical 2-year mission in deep space (typical duration of a possible mission to Mars) under solar minimum conditions would allow respect of the NCRP career limits [21] for males who are at least 35 years old (limit: ≥ 1 Sv) and females of at least 45 (limit: ≥ 0.9 Sv). Again, comparisons with these limits have to be considered with caution due to the differences between the radiation environment in deep space and that within the Geomagnetic field. Indeed in case of deep space missions, the LEO limits have to be considered as mere guidelines while waiting for recommendations relative to missions in deep space, which will be available only when our knowledge of the action of heavy ions is improved.

CONCLUSIONS

Examples of applications of the FLUKA code to hadrontherapy and space radiation protection problems were provided, focusing on the role of nuclear interactions. The results presented herein allowed us to quantify the contribution of nuclear reaction products, which were found to play a key role in the case of exposure to heavy ions. This is the case of tumor treatment with Carbon and exposure to Galactic Cosmic Rays. Furthermore, these studies emphasized the need of further data on the action of heavy ions, not only in terms of biological effects but also in terms of interactions with matter. In particular there is a strong need of data (typically double-differential cross sections) on nuclear interactions of heavy ions with fundamental constituents of the human body such as Carbon and Oxygen. In this respect the authors of the present paper are involved in a collaboration with Italian experimental groups, directed at the measurement of nuclear cross sections that can be of interest for radiotherapy and space research [22]. In parallel, efforts are devoted to the implementation in FLUKA of nucleus-nucleus interactions for incident energies below 5 GeV/n [23,24]. While in the range 0.1-5 GeV/n the problem was faced by means of Quantum Molecular Dynamics approaches; a possible solution for lower energies may be based on the Boltzmann Master Equation (BME) theory [25].

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