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An interface between the FLUKA transport code and the BIANCA biophysical model to predict the biological effectiveness of hadrontherapy beams

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Summary. — In the context of cell death induced by ionizing radiation, the BIANCA biophysical model was used to produce tables of biological effectiveness, in terms of α and β parameters typical of the linear quadratic model for cell survival curves; the tables were produced for irradiation by protons, helium ions and carbon ions over a wide energy range and for two cell lines of different radiosensitivity. By using these values, the predictions of BIANCA were compared with experimental data of RBE, and good agreement was found. After this validation step, the FLUKA radiation transport code, which can produce physical dose profiles for typical hadrontherapy beams, could read the α and β tables; thanks to such an interface between FLUKA and BIANCA, probabilities of cell death were predicted along depth-dose profiles. An example of a carbon spread out Bragg peak is shown, highlighting the differences in the biological response of different cell lines and the possible importance of using more than one cell line in the context of treatment plan optimization.

1. – Introduction

Hadrontherapy is a tumor therapy that is rapidly spreading worldwide, and which makes use of charged particle beams in order to maximize the damage in the tumor, while sparing the healthy tissues around it. It is thus important to evaluate the biological effects on tissues, starting from the physical absorbed dose, usually by means of the Relative Biological Effectiveness (RBE, defined as the ratio between a photon dose and the ion dose necessary to induce the same effect). It is well known that RBE depends on many factors, like particle type and energy, dose level, tissue type and considered endpoint, and

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it is thus fundamental to use a tool (*e.g.*, a biophysical model) that is able to quantify the RBE, in principle in each position and for each physical and biological configuration.

In clinics, only two biophysical models are currently adopted for carbon ions and coupled with Treatment Planning Systems (TPS): the Local Effect Model (LEM), which is adopted in European hadrontherapy centres, and the Microdosimetric-Kinetic Model (MKM), used in Japan [1-3]. These models are also coupled with radiation transport codes, like FLUKA [4,5], in order to provide a benchmark to support and validate clinical activities. FLUKA is commonly used in this context for treatment plan verification and re-calculation.

Following the same philosophy, an interface between FLUKA and the BIANCA (BIophysical ANalysis of Cell death and chromosome Aberrations) biophysical model [6-8] is presented. The procedure consists of producing tables of biological effectiveness (in terms of cell death and chromosome aberrations) with the BIANCA code, which can be read and interpreted by FLUKA, in order to provide a biological output along hadrontherapy dose profiles. The method for the production of Spread Out Bragg Peaks (SOBPs) by FLUKA is also illustrated in the present work. After testing the agreement between the BIANCA predictions and experimental data, in terms of RBE, the BIANCA/FLUKA interface was also applied to the case study of a C-ion irradiation.

2. – Materials and methods

2˙1. *The BIANCA model.* – The BIANCA model, which is implemented as a Monte Carlo code, is based on the following mechanistic assumptions: i) ionizing radiation can induce DNA "Cluster Lesions" (CLs), each one producing two independent chromosome fragments; ii) distance-dependent fragment mis-rejoining or un-rejoining give rise to chromosome aberrations; iii) certain aberrations (dicentrics, rings and large deletions) lead to cell death. These assumptions are discussed in detail in other works, *e.g.*, [9].

Although a previous study [10] suggested that a CL may consist of a cluster of double-strand breaks at the kilobase-pair scale, CLs are not defined *a priori*, and their yield is the first adjustable parameter of the model. Its value mainly depends on radiation quality (*i.e.*, particle type and energy), but it is also modulated by the target cell features.

Concerning the distance dependence of chromosome fragment end-joining, while in some works focused on chromosome aberrations it has been modelled by a Gaussian or an exponential function [11,12] in the present work it is assumed to have the shape of a step function, with threshold distance d equal to the average distance between two adjacent chromosome territories, as described in [9]. A fragment un-rejoining probability, f, is also adopted: each chromosome fragment has a probability f to remain un-rejoined even if there are possible partners within the distance d. The value of f is the second, and last, adjustable parameter of the model: it is assumed to be cell line dependent but independent of radiation quality.

In order to simulate experiments of radiation-induced chromosome aberrations and cell death, BIANCA starts from the Linear Energy Transfer (LET), the absorbed dose and the mean number of CLs distributed along each ion track traversing the cell nucleus, as described in [13]. An actual number of CLs for each track is extracted from a Poisson distribution, and the lesions are distributed within the nucleus, according to the procedure presented in [10]. The identification of hit chromosomes and chromosome-arms, the simulation of the chromosome fragment rejoining process and the scoring of the different aberration types are then performed.

2˙2. *SOBP production with FLUKA.* – The versatility of the approach presented in this work mainly relies on the SOBP production procedure, which allows to easily simulate, by FLUKA, physical dose profiles by protons, He and C ions, at any depth of interest and with arbitrary longitudinal and lateral extension. The procedure, consisting of the calculation of the initial energies and weights of the different monoenergetic Bragg peaks that are summed up to shape the SOBP, is described in detail in [13].

Briefly, by knowing the desired extension of the SOBP plateau, which is determined by the position and dimensions of the tumour, the ranges of n monoenergetic Bragg peaks can be easily calculated. The initial energies of these peaks can be deduced, assuming that the energy-range relationship of ions in a material like water can be of the form

$$R = \alpha E^{p_0}, \tag{1}$$

where α and p_0 are free parameters. This relationship was actually verified in [13] for protons, helium and carbon ions independently, and the corresponding parameters were derived. The experimental data used as a reference were taken from [14].

At this stage, the weights for the different pristine Bragg peaks are computed in order to produce a flat SOBP, as illustrated in [15]. Finally, a routine was implemented in the FLUKA code, in order to automatically sum up the different Bragg peaks, with the proper energies and weights. Physical dose 3D profiles can thus be easily produced, and in each voxel of the FLUKA geometry the information about the particle types, their energy and the corresponding absorbed dose are thus available: these represent the starting physical information for the BIANCA model, which will be able to provide a biological output, according to a procedure described in the next sections.

3. – Results and discussion

3˙1. *Alpha/beta tables.* – In [3] a systematic comparison between BIANCA simulations and proton, helium and carbon ion data over a wide energy range was performed for two cell lines of different radiosensitivity (V79 cells, which are rather radioresistant and are widely used to characterize hadrontherapy beams, and AG01522 cells, which can be considered as representative of normal cells). The mean number of CLs/μm used to obtain the best agreement with the experimental data was fitted by a linear-quadratic function of the form $Y(L) = a \cdot L + b \cdot L^2$, where Y is the CL yield expressed in CL/μm, L is the LET in keV/μm, and a and b are fitting parameters. This relationship was found to hold independently for the three considered ion types (although with different numerical values of a and b) till the overkilling region, *i.e.*, around 150 keV/μm for carbon ions. In order to describe the trend over the whole LET range, a function of the form $Y(L) = c \cdot \mathrm{arctg}(a \cdot L + b \cdot L^2)$ was found to work better.

In the present work, focusing on the case of carbon ions, the one-to-one relationship established between CLs and LET was used to simulate many cell survival curves at several LET values, using the CL values provided by the fits as input parameters for BIANCA. For V79 cells, 15 curves were simulated from 10 to 150 keV/μm, with LET steps of 10 keV/μm each, and 14 curves from 175 to 500 keV/μm, with LET steps of 25 keV/μm each. For AG01522 cells, 15 curves were simulated between 10 and 150 keV/μm, with LET steps of 10 keV/μm each.

For each curve, the BIANCA simulations of the cell surviving fraction were performed at doses of 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 Gy. Each simulated dose-response curve thus

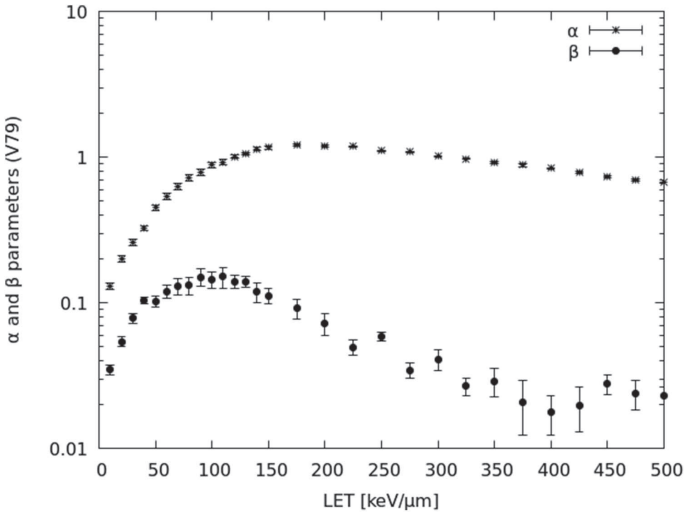

Fig. 1. – Values of α and β parameters calculated by the BIANCA model, as a function of LET. These values refer to V79 cells irradiated by carbon ions.

consisted of 6 points, each one with its statistical uncertainty; each set was then fitted by a function of the form

$$S(D) = e^{-(\alpha D + \beta D^2)}, \tag{2}$$

where S is the surviving fraction, D is the dose, and α and β are two fitting parameters. Tables of α and β parameters as a function of LET for the two cell lines independently were derived. The values of α and β for carbon ions are graphically reported in figs. 1 and 2, both for V79 and for AG01522 cells.

In the context of hadrontherapy, in each voxel of a three-dimensional SOBP, produced as described in sect. **2**˙2, FLUKA can read the tables produced by BIANCA and associate an α and β couple to each particle, which has a well-defined LET, traversing the voxel itself; the routine performing this procedure was written by Alfredo Ferrari and Andrea Mairani. Since in general a number N of particles traverses each voxel, the approach to mixed fields already presented in [16] was adopted: dose-averaged α and β parameters are calculated as

$$\bar{\alpha} = \frac{\sum_{i=1}^{N} \alpha_i D_i}{D}; \quad \bar{\beta} = \left(\frac{\sum_{i=1}^{N} \sqrt{\beta}_i D_i}{D} \right)^2, \tag{3}$$

where D_i is the dose deposited by the i-th particle, a_i and b_i are its associated parameters, and D is the total dose deposited in the considered voxel. It is thus possible to associate a cell survival level to each voxel and to calculate quantities like cell death probability and RBE along the whole dose profile of arbitrary SOBPs.

3˙2. *RBE calculations by BIANCA.* – Before moving to the calculation of biological effectiveness along hadrontherapy beams, it is important to verify the agreement between the predictions of the BIANCA model and experimental results taken from the literature.

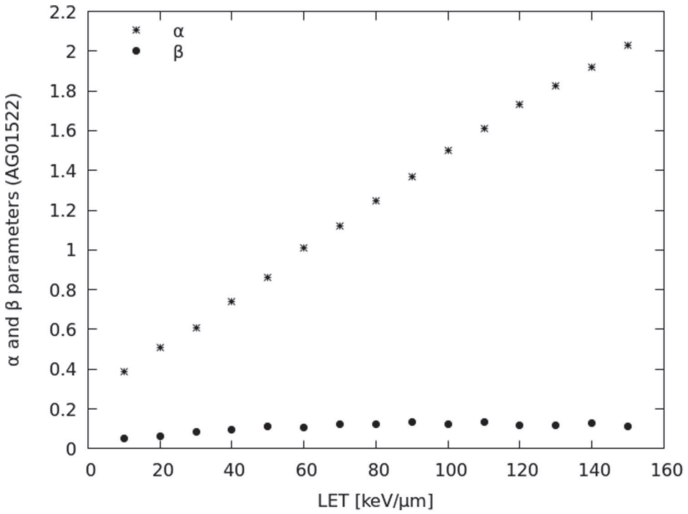

Fig. 2. – Values of α and β parameters calculated by the BIANCA model, as a function of LET. These values refer to AG01522 cells irradiated by carbon ions.

To this aim, the RBE data reported in [17] were considered for comparison in the case of V79 cells: we focused in this case on RBE_{10}, since these cells may be considered as representative of the behavior of the tumor, for which low survival levels are of primary importance. For AG01522 cells, on the other hand, we focused on RBE_{50}, since these cells show a behavior similar to that of normal tissues, for which higher survival levels are more interesting: the experimental data taken for comparison are those reported in [18, 19].

The RBE predictions by the BIANCA model are computed for many LET values according to the following expression:

$$RBE = \frac{D_X}{D_I} = \frac{\beta_I}{\beta_X} \cdot \frac{-\alpha_X + \sqrt{\alpha_X^2 - 4\beta_X lnS}}{-\alpha_I + \sqrt{\alpha_I^2 - 4\beta_I lnS}}, \tag{4}$$

obtained by eq. (2) and by the definition of RBE, where the indices X and I refer to photons and ions, respectively, α and β are those reported in figs. 1 and 2, and S is equal to 0.1 in the case of RBE_{10} or 0.5 in the case of RBE_{50}. In figs. 3 and 4 the data on RBE_{10} for V79 and RBE_{50} for AG01522 are shown, respectively; again, we considered the case of carbon ions. The points represent the experimental RBE data taken from the literature, whereas the lines are the results of BIANCA predictions. The good agreement supports the use of the FLUKA/BIANCA interface to evaluate the biological effectiveness levels along hadrontherapy dose profiles.

3˙3. *Biological effectiveness along a SOBP.* – By applying the approach described in sect. **3**˙1 it is now possible to simulate arbitrary depth-dose profiles and to make predictions of biological effectiveness by the BIANCA/FLUKA tool. This method is versatile, since it allows to simulate SOBPs at different depths and with different extensions, for irradiations by protons, helium ions or carbon ions; moreover, it allows to make predictions, in terms of cell death and chromosome aberrations, for two cell lines of different

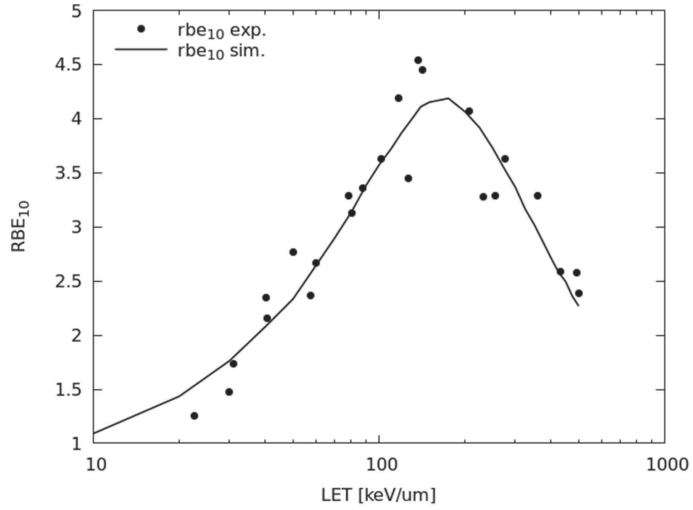

Fig. 3. – Comparison between experimental data (points) and BIANCA predictions (line) for RBE_{10}, as a function of LET. These values refer to V79 cells exposed to carbon ions. The experimental data are taken from [17].

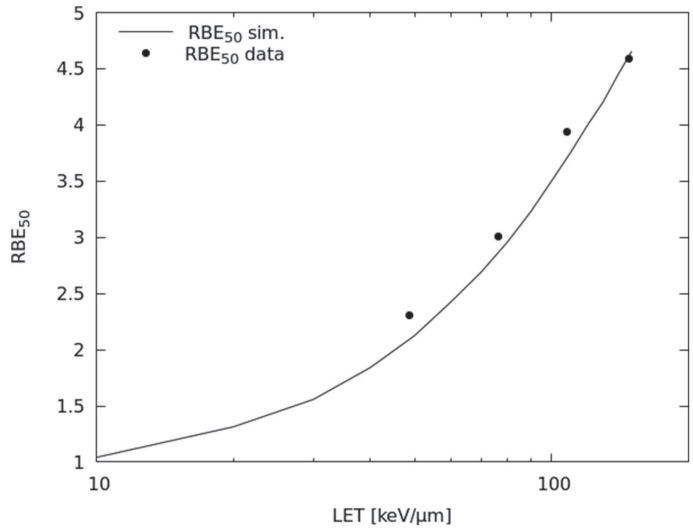

Fig. 4. – Comparison between experimental data (points) and BIANCA predictions (line) for RBE_{50}, as a function of LET. These values refer to AG01522 cells exposed to carbon ions. The experimental data are taken from [18, 19].

radiosensitivity.

As an example, in fig. 5 a carbon SOBP calculated by FLUKA is presented; the extension of the SOBP is of 5 cm and its maximum depth is placed at 15 cm. The physical dose in water is shown, along with the fraction of inactivated cells (cell death) for both V79 and AG01522 cells. The three quantities are normalized with respect to the proximal point of the SOBP, since it is interesting to show the variations of the biological quantities with depth and the differences in the responses of the two cell lines, under the

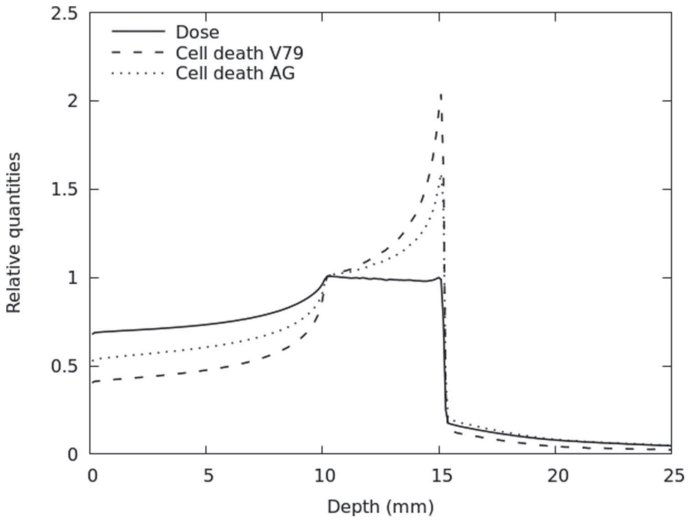

Fig. 5. – Carbon SOBP at a depth of 10–15 cm: physical dose (calculated by FLUKA) and fraction of inactivated cells (calculated by BIANCA) for both V79 and AG01522 cells.

same physical conditions. The longitudinal profiles shown in fig. 5 are the result of a radial integration of the quantities obtained in all the voxels that have the same depth (or z coordinate).

It is well known that the biological effectiveness of heavy ions tends to increase along the SOBP plateau, even along a flat physical dose profile; for this reason, in clinical practice, a decreasing physical dose is usually adopted. Nevertheless, it is interesting to observe that the trend is different for the two considered cell lines: the increase in cell death is in particular much sharper for V79 cells, reaching at the distal position *a value* twice as great as the value at the proximal position. Moreover, it is fundamental to focus also on the normal tissues surrounding the tumour region, where the more radiosensitive cell line (AG01522 in this case) shows a higher level of cell death. Therefore, considering only one cell line (typically V79) for the dose profile optimization might lead to an underestimation of the damage to healthy tissues; taking into account at least two cell lines of different radiosensitivity may lead to an improvement in treatment planning.

4. – Conclusions

An interface between the FLUKA radiation transport code and the BIANCA biophysical model was presented. The production of tables of cell survival levels, in terms of α and β parameters, was illustrated for two cell lines of different radiosensitivity, V79 and AG01522, for the specific case of carbon ions. After a validation step, showing the good agreement between BIANCA predictions and experimental data, in terms of RBE, the produced tables were read by FLUKA, allowing to predict cell death along depth-dose profiles typical of hadrontherapy treatments. As an example, a carbon SOBP was produced, and levels of cell death for both the considered cell lines were calculated along it by the FLUKA/BIANCA tool. In the future we will move towards more realistic situations, like a typical two-port carbon irradiation.

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