"Survival": a simulation toolkit introducing a modular approach for radiobiological evaluations in ion beam therapy

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Abstract.
One major rationale for the application of heavy ion beams in tumour therapy is their increased relative biological effectiveness (RBE). The complex dependencies of the RBE on dose, biological endpoint, position in the field *etc.* require the use of biophysical models in treatment planning and clinical analysis. This study aims at introducing a new software, named "Survival", to facilitate the radiobiological computations needed in ion therapy. The simulation toolkit was written in C++ and it was developed with a modular architecture in order to easily incorporate different radiobiological models. The following models were successfully implemented: the local effect model (LEM, version I, II and III) and variants of the microdosimetric-kinetic model (MKM). Different numerical evaluation approaches were also implemented: Monte Carlo (MC) numerical methods and a set of faster analytical approximations. Among the possible possible applications, the toolkit was used to reproduce the RBE versus LET for different ions (proton, He, C, O, Ne) and different cell lines (CHO, HSG). Intercomparison between different models (LEM and MKM) and computational approaches (MC and fast approximations) were performed. The developed software could represent an important tool for the evaluation of the biological effectiveness of charged particles in ion beam therapy, in particular when coupled with treatment simulations. Its modular architecture facilitates benchmarking and inter-comparison between different models and evaluation approaches. The code is *open source* (GPL2 license) and available at https://github.com/batuff/Survival.

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1. INTRODUCTION

Nowadays, hadrontherapy has reached an unprecedented precision in the delivery of the prescribed dose to the target volume thanks to the clinical experience gained over years of treatments and to the huge efforts made by the particle therapy community in the development of innovative technologies and increasingly sophisticated treatment planning systems (TPS) (Krämer & Scholz 2000, Krämer et al. 2000, Böhlen et al. 2013, Krämer et al. 2014, Russo et al. 2016). Nevertheless, the overall precision also requires a deep understanding of the radiobiological aspects which determine the effectiveness of a particle therapy treatment. In particular, ion beam radiotherapy is known to be more effective in cell killing if compared to conventional radiation therapy due to the higher linear energy transfer (LET), which results in more clustered DNA damages far more difficult to be repaired by the cell (Joiner & Van der Kogel 2009). This leads to a higher relative biological effectiveness (RBE) with respect to the photon irradiation, which depends on many different factors and which behaviour is very complex to model.

At present, a number of radiobiological models have been developed and it is possible to roughly divide them in two categories: some models, like that of Friedland *et al.* (Friedland et al. 2006), try to reproduce in great detail the chain of physical, molecular and biological events which lead to cell inactivation; other models are limited to a more phenomenological description of the problem based on macroscopic experimental observations. Despite the promising results obtained following the first approach, the second is so far the most sustainable for treatment planning applications since it provides simpler models which can be easily tuned to reproduce experimental evidences by adjusting few phenomenological parameters. Among these latter, the most acknowledged models are the local effect model (LEM) (Scholz & Kraft 1996, Scholz et al. 1997, Elsässer & Scholz 2006, Elsässer & Scholz 2007, Elsässer et al. 2008) and the microdosimetric-kinetic model (MKM) (Hawkins 1994, Hawkins 1996, Hawkins 1998, Hawkins 2003).

The aim of this paper is to present a new software, developed by the Istituto Nazionale di Fisica Nucleare (INFN) in collaboration with the University of Torino (UniTO), which provides different implementations of some radiobiological models, namely LEM I (Scholz & Kraft 1996, Scholz et al. 1997), LEM II (Elsässer & Scholz 2006, Elsässer & Scholz 2007), LEM III (Elsässer et al. 2008), MKM (Hawkins 1994, Hawkins 1996, Hawkins 1998, Hawkins 2003) and MCt-MKM (Manganaro et al. 2017). The code is written in C++ and it is *open source* for the benefit of the scientific community (published under the GNU general public licence (GPL), version 2); it is available at `https://github.com/batuff/Survival`. In the following sections, the present paper provides a brief description of the included models and the way they are implemented, showing some usage examples and possible applications. More detailed description of each model can be found on their reference papers respectively, while a

complete description of the code is available in the user's manual¶.

2. MATERIALS AND METHODS

Different versions and implementations of the LEM and the MKM are integrated in the software. The two models have many similarities both in the structure and in the computational methods, as already shown for example by Kase *et al.* (Kase et al. 2008). In the following, particular importance is given to the parallelism between them, since the code has been designed exploiting this parallelism in such a way to have a common structure, as general as possible, which can be suited to host all the different implementations.

2.1. The Local Effect Model

The LEM was conceived in the 90's by Gerard Kraft and Michael Scholz at the GSI Biophysical division (Scholz & Kraft 1996). It has been incorporated in the clinical TPS of the GSI carbon ion therapy project (Krämer & Scholz 2000), and it is currently used in many facilities such as the Heidelberg Ion-Beam Therapy Center (HIT, Heidelberg, Germany), the Centro Nazionale di Adroterapia Oncologica (CNAO, Pavia, Italy) or MedAustron (Vienna, Austria). This makes the LEM one of the most employed models to date in hadrontherapy. To overcome some discrepancies with experimental evidences, several improvements have been proposed, which led to the so-called LEM II (Elsässer & Scholz 2006, Elsässer & Scholz 2007) and III (Elsässer et al. 2008). On 2010, a new version of the LEM has been introduced, named LEM IV (Elsässer et al. 2010), which presents notable differences from the previous versions, but it has not been implemented in the presented software yet, hence here omitted.

In its full implementation, the LEM is a Monte Carlo (MC) algorithm based on repeated simulations of the irradiation process of a cell nucleus. Repeating the simulation of the irradiation process for different track deposition on the nucleus for a set of imposed macroscopic doses and averaging the outcome for each dose level, the LQ α and β parameters for ion irradiation are finally extrapolated via the fit of the resulting survival curve $S(D)$ (see figure 1).

2.1.1. LEM approximate implementations Performing numerical evaluations following the LEM original MC implementation is not straightforward nor fast because of the accurate sampling of the local dose distribution required by the model. For this reason, approximate fast approaches to the LEM calculations have been implemented in the software, besides the MC implementation. One of this approaches was proposed by the GSI (Krämer & Scholz 2006). In the present implementation, a novel improved approximated approach to increase the accuracy of the GSI approach has been also

¶ `https://github.com/batuff/Survival/blob/master/Documentation/Survival_USERS_MANUAL.pdf`

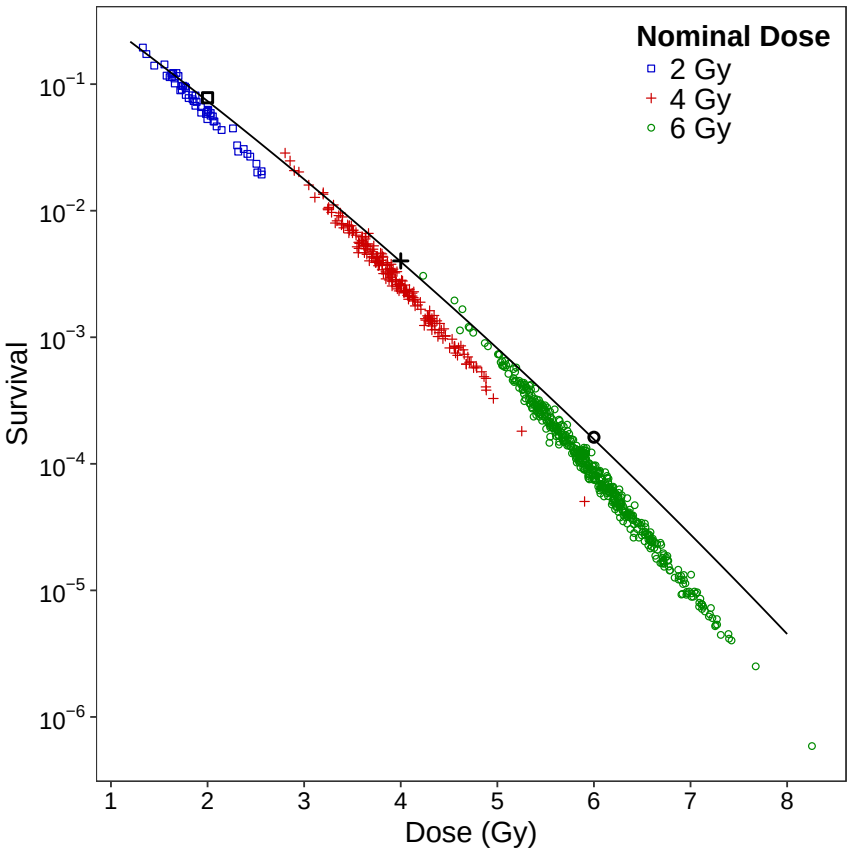

Figure 1. A simulated survival curve obtained for mono-energetic (43.5 MeV/u) carbon ion irradiation with imposed doses of 2, 4, and 6 Gy respectively. The dots represent the values of cell survival (a dot for each cell) obtained through the MC simulation. The solid line represents the LQ fit of the mean survival for each level of imposed dose from which the LQ parameters are obtained. The model parameters used are: $R_N = 5\,\mu m$, $\alpha_X = 0.313\,\mathrm{Gy}^{-1}$, $\beta_X = 0.0615\,\mathrm{Gy}^{-2}$ and $D_t = 30\,\mathrm{Gy}$

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included in the software and benchmarked. Details of the novel algorithm are given in the user's manual.

2.2. The Microdosimetric Kinetic Model

The MKM was formulated in 1994 by Roland B. Hawkins as an elaboration of the theory of dual radiation action (TDRA) (Kellerer & Rossi 1978, Zaider & Rossi 1980), the repair-misrepair (Tobias 1985) and the lethal-potentially lethal (LPL) models (Curtis 1986) and then modified over subsequent years. Similarly to the LEM, the MKM considers the cell nucleus as the sensitive target of the irradiation. It also assumes that, for what concerns the determination of the lethal events caused by ionizing radiation, the cell nucleus can be virtually divided into subnuclear structures called *domains*, similar to the *sites* defined in the TDRA. Contrarily to the LEM, the MKM tries to describe

the temporal evolution of the DNA damages caused by the radiation in the cell nucleus by means of kinetic equations.

In a more recent formulation of the MKM, in analogy with the LEM, Kase and colleagues (Kase et al. 2008) introduced the adoption of an amorphous track structure, obtained by the combination of the Kiefer model for the penumbra region (Kiefer & Straaten 1986) and the Chatterjee model for the core radius (Chatterjee & Schaefer 1976), to describe the local dose deposition pattern of the ions traversal, in order to evaluate the specific energy deposited by each ion.

2.2.1. MKM Monte Carlo implementation A rigorous method to implement the MKM is a MC algorithm, as recently shown by Manganaro *et al.* (Manganaro et al. 2017) in their last formulation of the model named MCt-MKM (Monte Carlo temporal microdosimetric kinetic model). The MC approach takes into account the stochastic nature of the irradiation process, highlighting the spatial and temporal correlations between different interactions. Moreover, it gives the possibility to implement the exact solution of the kinetic equations at the domain level, quantifying the temporal effect of the irradiation, intended as the increase in the cell survival observed for non-instantaneous time structures.

It is worth to remark that the MC approach strengthen the analogy between the LEM and the MKM previously highlighted by Kase *et al.* (Kase et al. 2008). In particular, from the mechanistic point of view, in both the formulations it is possible to identify the same main constituents, namely an amorphous track structure and the hypothesis of the cell nucleus as sensitive target of the irradiation. Moreover, even though the used photon dose response curves are different between the two models, as the LEM considers a LQ-linear relation while the MKM assumes a pure LQ parametrization. The overall effect, in fact, is obtained considering the microscopical effect in a subnuclear region, represented by the domain in the case of the MKM and by an infinitesimal pixel in the case of the LEM. Through the MC approach, the analogy is extended also to the computational method and the prediction on the behaviour of the LQ parameters becomes qualitatively similar between the two models (see figures 5 and 6).

2.2.2. MKM approximate implementation Since the MC approach is a slow method to simulate the irradiation process, an approximate faster implementation was introduced by Hawkins and gradually refined.

On 2003, Hawkins introduced a correction to the MKM (Hawkins 2003), adopted also by Kase *et al.* (Kase et al. 2008), to account for the non-Poissonian distribution of the lethal events in the nucleus. Both MC and non-Poissonian approximate correction approaches are implemented in the code.

2.3. Code structure

The code was conceived in order to exploit the similarities in the general structure between the LEM and the MKM, which have been illustrated in the previous sections. These were, the nucleus structure, the amorphous track structure, the parametrization of the X-ray dose response curve, the MC approach and different approximated implementations and the ion beam used. This led to the idea of exploiting the features of an object-oriented programming language and designing the code in order to build a common general structure, which could support the implementation of different models. A multi-thread system based on the open multi-processing (OpenMP) libraries[+] was designed to perform the MC simulations, which are the most expensive in terms of needed time and computing power. Appendix A contains a brief description of the developed classes, while the unified modeling language (UML) diagram representing the class hierarchy is shown in figure 2.

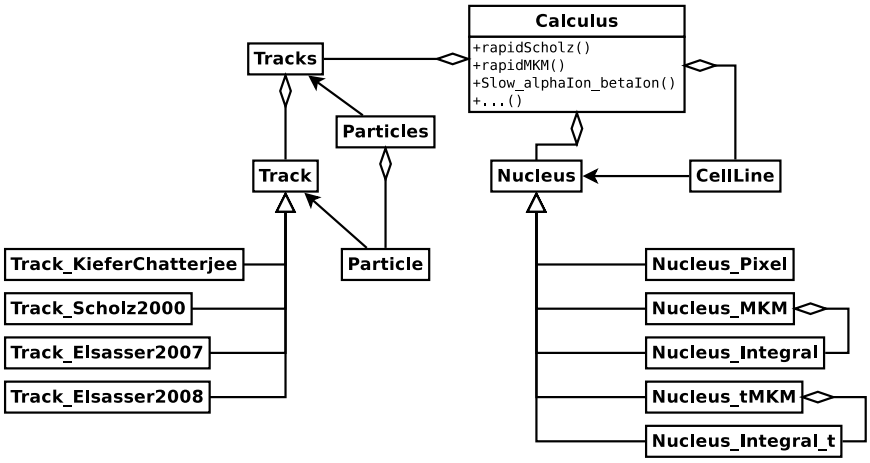

Figure 2. UML diagram representing the relationship between the main classes of the "Survival" code. For the *Calculus* class, some of the main methods are listed, corresponding to the computational methods described in sections 2.1 and 2.2. In particular the *rapidScholz()* and *rapidMKM()* methods refer to the GSI and MKM approximate implementations respectively (sections 2.1.1 and 2.2.2) while the *slow_alphaIon_betaIon()* indicates the MC approach for both the LEM and the MKM models.

2.4. Inputs and Outputs

The software needs as input a number of parameters, some of them are specific of the chosen model, some are specific of the irradiation conditions and some others specify the output desired.

The model-specific parameters in the case of the LEM are the nucleus radius R_N, the LQ α_X and β_X parameters corresponding to the X-ray irradiation and the threshold

[+] http://www.openmp.org

dose D_t beyond which the behaviour of the survival curve is assumed to become linear (see section 2.1). The first three parameters are also needed in the case of the MKM, while the last one is substituted by the domain radius R_D and the X-ray parametrization is assumed to be LQ (see section 2.2). The user should keep in mind that one of the main issues in using a radiobiological model is the definition of the model parameters, which are characteristics of the cell line and determine the behaviour of the model itself. These should be defined through the fit of the experimental data, depending on the endpoint: from the clinical point of view the best choice would be fitting the RBE as a function of the particle energy but, depending on the final goal of the study, one could be more interested in fitting directly the LQ parameters or other quantities such as the D_{10}. To help the user in getting the best performances from the software, table 1 summarize the LEM and MKM main parametrizations used in the literature (Scholz & Kraft 1996, Scholz et al. 1997, Elsässer & Scholz 2006, Elsässer & Scholz 2007, Elsässer et al. 2008, Kase et al. 2008) for some of the most common cell lines.

Table 1. LEM and MKM model parameters published for different cell lines. α_X and β_X represent the LQ X-ray parametrization and R_N and R_D the nucleus and domain radius respectively. D_t^I, D_t^{II} and D_t^{III} represent the threshold doses in the case of LEM I, II and III respectively.

Cell line	Model	α_X	β_X	R_N	R_D	D_t^I	D_t^{II}	D_t^{III}
HSG	MKM	0.313	0.0615	4.1	0.34			
HSG	LEM	0.313	0.0615	5		30	6	19
CHO	MKM	0.228	0.02	4.1	0.2			
CHO	LEM	0.228	0.02	4.7		40	9.5	55
T1	MKM	0.0305	0.0585	3.5	0.35			
V79	MKM	0.184	0.02	4.1	0.26			
V79	LEM	0.184	0.02	4		60	5.5	60
V79	LEM	0.093	0.026	3.8		30	7.5	30

The radiation-specific parameters, in the case of mono-energetic irradiations, are the imposed doses, the ion species and its kinetic energy or LET expressed in MeV or in keV/μm respectively. The energy-LET conversion is internally managed by means of look-up tables generated through the *Stopping and Range of Ions in Matter* (SRIM) software. Alternatively, it is possible to manage a complex spectrum of particles, built through the definition of more than one particle type, each one associated with a weight representing its relative abundance in the beam. Then, the MC implementation of each model naturally manages the spectrum in analogy with the mono-energetic case, while the approximate implementations make use of the mixed field approximation (Zaider & Rossi 1980).

The software can provide two or three kind of outputs, depending on the specific computational approach. In particular, the main output is a file listing the value of the LQ α and β parameters for the specified model and irradiation conditions. A second output, if requested, is another file listing the value of expected survival corresponding

to each level of imposed dose. Finally, only limited to the MC computational method, it is possible to get the values of dose and survival for each of the cell irradiated in the simulation (see for example figure 1).

3. RESULTS

In the following, some exemplary figures are shown to highlight the potential of the software and the kind of information which is possible to derive from it.

Figures 3 and 4 show the comparison between different models in the prediction of the RBE_{10} as a function of the particle LET for the chinese hamster ovary (CHO) and human salivary gland (HSG) cell line respectively. The experimental data are taken from the particle irradiation data ensemble (PIDE) (Friedrich et al. 2013), while the model parameters used in the computation are the ones published in the reference paper of each model respectively, summarized in table 1.

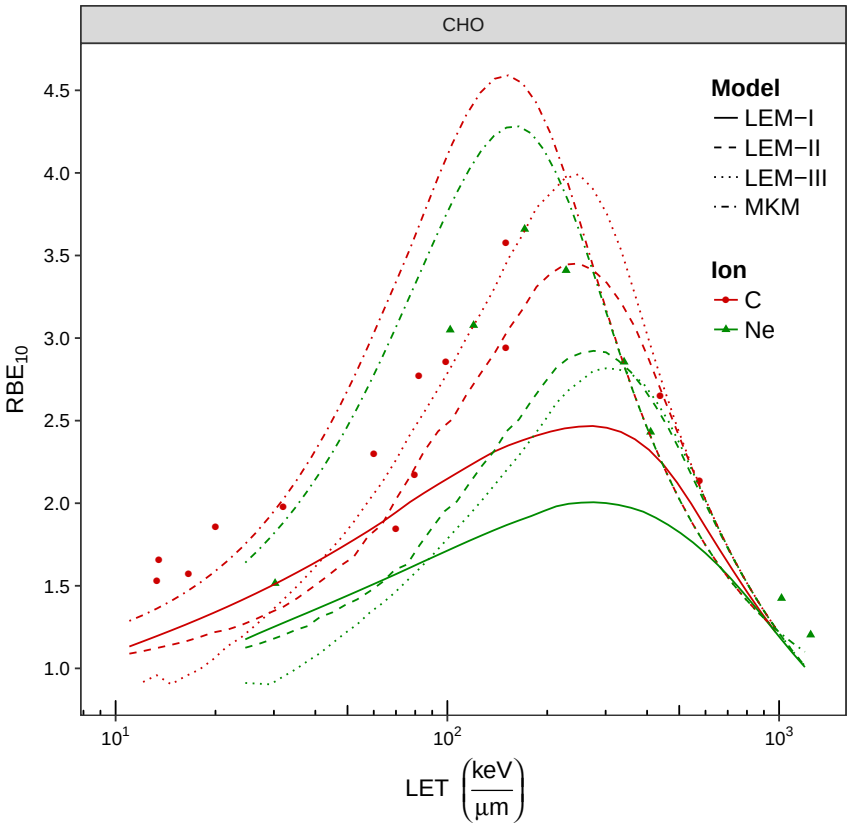

Figure 3. RBE_{10} as a function of LET for the irradiation of CHO cells with different ions. Points represent experimental data taken from PIDE (Friedrich et al. 2013), different colors/gray levels and shapes refer to C and Ne ions respectively. Line types represent the prediction of different models, namely LEM I, LEM II, LEM III and MKM, evaluated with the GSI (LEM) and MKM approximated methods respectively (see sectios 2.1.1 and 2.2.2), using the parameters reported in table 1.

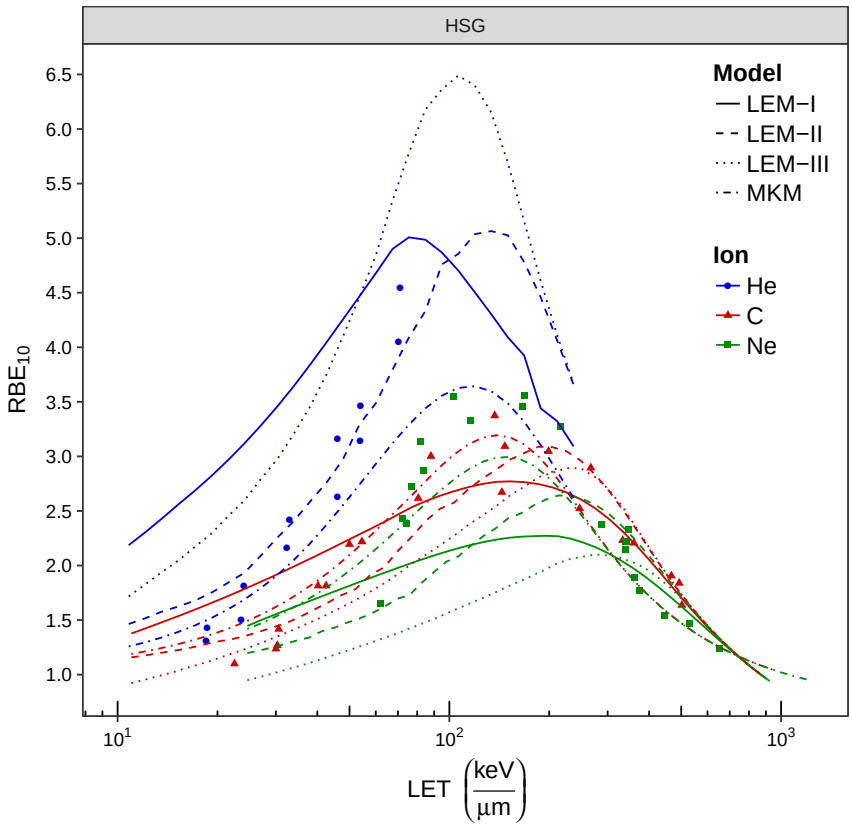

Figure 4. RBE_{10} as a function of LET for the irradiation of HSG cells with different ions. Points represent experimental data taken from PIDE (Friedrich et al. 2013), different colors/gray levels and shapes refer to He, C and Ne ions respectively. Line types represent the prediction of different models, namely LEM I, LEM II, LEM III and MKM, evaluated with the GSI (LEM) and MKM approximated methods respectively (see sections 2.1.1 and 2.2.2), using the parameters reported in table 1.

Figures 5 and 6 show comparisons between the different computational approaches of the LEM and MKM models respectively, presenting the LQ α and β parameters as a function of the particle LET. The model parameters are the same of figure 4 and are summarized in table 1.

4. DISCUSSION

As exemplified in figure 3 and 4, the present software represents a valuable tool, which allows the user to evaluate the outcomes of different radiobiological models. Moreover, it provides an easy way to make comparisons between them, and between different computational approaches (see for example figures 5 and 6). This is extremely important in a context where the biological response represents one of the main sources of uncertainty, and consequently one of the main drawbacks, in particle therapy, especially when dealing with heavy ions like carbon. The computation examples provided (figures

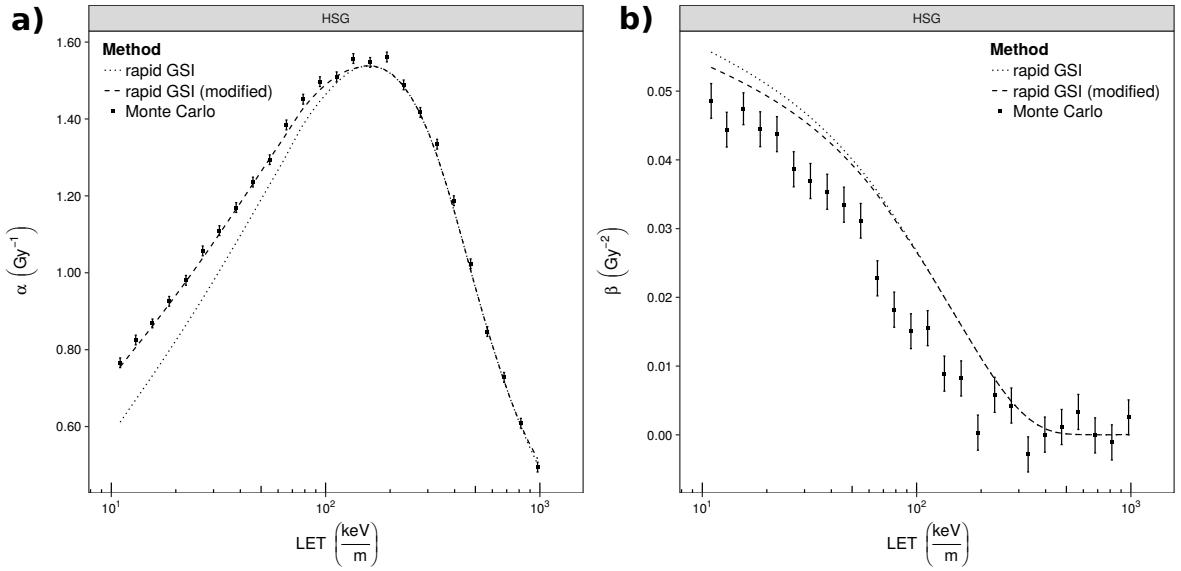

Figure 5. LQ α (panel a) and β (panel b) parameters as a function of LET for the irradiation of HSG cells with carbon ions, comparing the output of different LEM I computational methods. Points with error bars represent the parameters obtained with the full MC implementation (section 2.1) with their associated uncertainties, while dotted and dashed lines represent the output corresponding to the GSI and INFN (GSI-modified) approximated implementations respectively (see section 2.1.1).

3 and 4) also highlight the variability in the outcomes between the different models. This variability is identically transferred to the clinics when optimizing the treatment plan relying on a particular model or parametrization. Coupled with a TPS, the present software provide the possibility to concurrently optimize the treatment considering different radiobiological responses, leading to more robust treatment plans.

One of the key aspects of the tool is the flexibility which comes from its modular architecture. This gives the chance to incorporate different models under a common framework, which allows to switch from one to the other or even build new models by mixing their features such as nuclear architecture and track structure. This framework can be extended to host some of the models which are not implemented yet, such as the other versions of the MKM (see e.g. Inaniwa *et al.* 2010 (Inaniwa et al. 2010)) or the last version of the LEM, namely the LEM IV (Elsässer et al. 2010), or even completely different models such as the repair-misrepair fixation (RMF) model by Carlson *et al.* (Carlson et al. 2008), the repairable-conditionally-repairable (RCR) model by Brahme (Brahme 2011) or the NanOx model (Cunha et al. 2017). Moreover, it would also be interesting to include models which, instead of the RBE, aims at evaluating other factors that can modify the biological dose, such as the oxygen enhancement ratio (OER). In this regard, this tool would be open to easily host OER models such as that of Antonovic *et al.* (Antonovic et al. 2013), Stewart *et al.* (Stewart et al. 2011), Bopp *et al.* (Bopp et al. 2016) or Scifoni *et al.* (Scifoni et al. 2013).

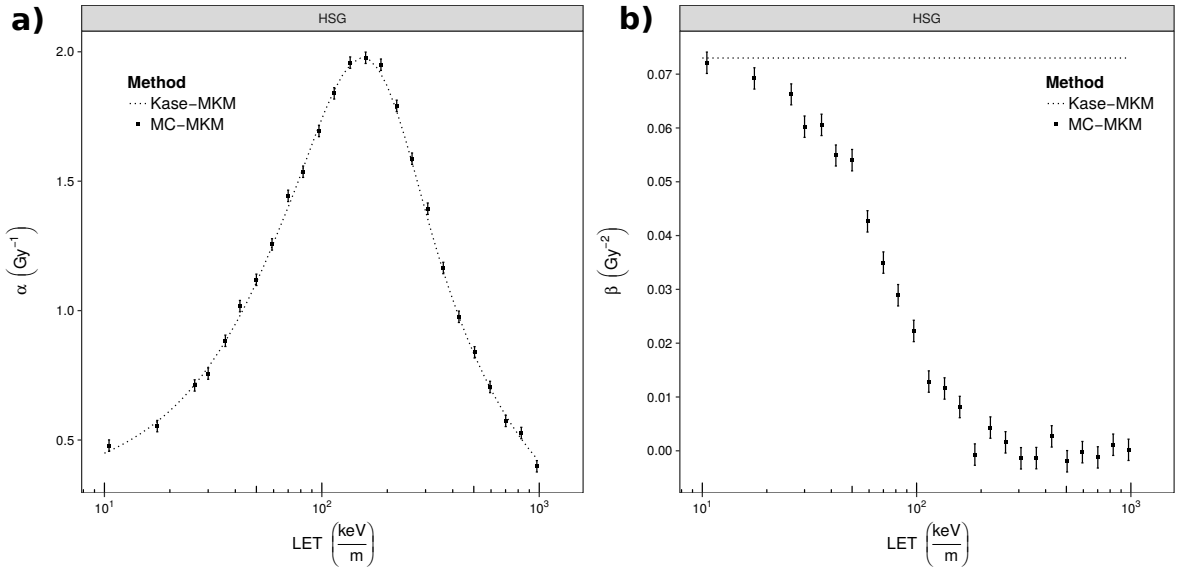

Figure 6. LQ α (panel a) and β (panel b) parameters as a function of LET for the irradiation of HSG cells with carbon ions, comparing the output of different MKM computational methods. Points with error bars represent the parameters obtained with the MC implementation (section 2.2.1) with their associated uncertainties, while dotted lines represent the output corresponding to the Kase approximated implementation (see section 2.2.2).

It is finally valuable to remark that the user has full access to the source code, so that he would be able to modify it or implement new models and possibly to interact with the authors in order to update it. This will hopefully lead to a significant improvement through the interaction with the scientific community.

5. CONCLUSIONS

A new software, providing different implementations of the LEM and MKM models, has been introduced. It has been conceived as a modular and flexible tool which can be extended to host many of the existing radiobiological models and it is *open source* for the benefit of the scientific community. The authors believe that it could represent a valuable tool for the evaluation of the biological effectiveness of the charged particles in ion beam therapy, especially if coupled with treatment planning simulations.

Disclosure of conflict of interest

The authors declare that they do not have any conflict of interest.

Appendix A. "Survival" classes

Here follows a brief description of the C++ classes; more details can be found in the user's manual.

Particle It is used as a C struct to contain, for a certain particle in a given position in space, recorded characteristics such as type, charge, mass number, kinetic energy, LET in water and position.

Particles It is a container class used to group together *Particle* objects. It provides functionalities to select particles belonging to a specific region of space or corresponding to a certain category.

Track Constructed on the base of an ion *Particle* object, it represent the local dose distribution around that ion. It is a pure virtual class defined by the inherited *Track_Scholz2000*, *Track_Elsasser2007*, *Track_Elsasser2008* and *Track_KieferChatterjee*, which implement the track structures of LEM I, LEM II, LEM III, MKM and MCt-MKM respectively.

Track_Scholz2000 Inherited from the *Track* class, it implements the LEM I track structure as defined in the paper of Scholz *et al.* (Scholz & Kraft 1996) with an update from (Elsässer & Scholz 2006).

Track_Elsasser2007 Inherited from the *Track* class, it implements the LEM II track structure as defined in the papers of Elsässer *et al.* (Elsässer & Scholz 2006, Elsässer & Scholz 2007). With respect to the LEM I formulation, the track model is extended to explicitly include the effect of radical diffusion: the ionization pattern is now convoluted with a Gaussian kernel which models the spreading of the induced radical species.

Track_Elsasser2008 Inherited from the *Track* class, it implements the LEM III track structure, as defined in the paper of Elsässer *et al.* (Elsässer et al. 2008).

Track_KieferChatterjee Inherited from the *Track* class, it implements the MKM track structure as defined in the paper of Kase *et al.* (Kase et al. 2008). The average local dose deposition pattern is considered constant in the core of the track and decreasing with the distance squared in the lateral penumbra. Both the core and penumbra radii are dependent on the energy of the incident ion.

Tracks It is a container class for *Track* objects. It can be created directly from a *Particles* object, specifying a unique track type, or it can be leaded with single *Track* objects, making use of polymorphism.

Nucleus Linked to a specific *CellLine* object, it represent the sensitive target of the irradiation. It has several functions, namely to superimpose tracks in order to compute the composite local dose distribution, to transform local doses in local number of lethal events by queries to the *CellLine* object, to integrate the local dose and the local number of lethal events and to evaluate the mean dose and the mean survival estimations. Since these tasks can be in principle accomplished in several

ways, depending also on the selected model, this class has been declared `abstract`. The present derived implementation are the *Nucleus_Pixel*, *Nucleus_MonteCarlo*, *Nucleus_MKM/_tMKM* and *Nucleus_Integral/_Integral_t*.

Nucleus_Pixel Inherited from the *Nucleus* class, it performs the integration on several grids of pixels of varying resolution. Those grids sample with higher spatial frequency only the regions where the gradient of the local dose is high (Russo 2007, Russo 2011).

Nucleus_MonteCarlo Inherited from the *Nucleus_Pixel* class, it performs the integration via the Monte Carlo *importance sampling* method.

Nucleus_MKM Inherited from the *Nucleus* class, it implements the cell nucleus as defined in the MKM model and it provides methods to integrate the dose and the lethal events observed in the domains in which it is divided.

Nucleus_tMKM Inherited from the *Nucleus* class, it has the same structure of the *Nucleus_MKM* class but extended to consider the temporal effect of the irradiation.

Nucleus_Integral Inherited from the *Nucleus* class, it implements a nucleus as a 2D circular object, which represents the cross section shown by the cell to the particle. It is used to define the domains constituting the MKM nucleus.

Nucleus_Integral_t As in the case of the *Nucleus_tMKM*, it has the same structure of the *Nucleus_Integral* class but extended to consider the temporal dimension.

CellLine This class hosts the radiobiological characteristics of a given cell line, such as its conventional name, the nucleus dimension or the parametrization of the survival curve. Furthermore, it computes the local number of lethal events corresponding to a local dose deposition.

Calculus It manages the simulation of the irradiation process, both with Monte Carlo or analytic approaches depending on the model chosen and its implementation.

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