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Variance-based sensitivity analysis of biological uncertainties in carbon ion therapy

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ABSTRACT

Purpose: Biological models to estimate the relative biological effectiveness (RBE) or the equivalent dose in 2 Gy fractions (EQD2) are needed for treatment planning and plan evaluation in carbon ion therapy. We present a model-independent, Monte Carlo based sensitivity analysis (SA) approach to quantify the impact of different uncertainties on the biological models.

Methods and materials: The Monte Carlo based SA is used for the evaluation of variations in biological parameters. The key property of this SA is the high number of simulation runs, each with randomized input parameters, allowing for a statistical variance-based ranking of the input variations. The potential of this SA is shown in a simplified one-dimensional treatment plan optimization. Physical properties of carbon ion beams (e.g. fragmentation) are simulated using the Monte Carlo code FLUKA. To estimate biological effects of ion beams compared to X-rays, we use the Local Effect Model (LEM) in the framework of the linear-quadratic (LQ) model. Currently, only uncertainties in the output of the biological models are taken into account.

Results/conclusions: The presented SA is suitable for evaluation of the impact of variations in biological parameters. Major advantages are the possibility to access and display the sensitivity of the evaluated quantity on several parameter variations at the same time. Main challenges for later use in three-dimensional treatment plan evaluation are computational time and memory usage. The presented SA can be performed with any analytical or numerical function and hence be applied to any biological model used in carbon ion therapy.

Introduction

In ion beam therapy, biological models to estimate the relative biological effectiveness (RBE) or the equivalent dose in 2 Gy fractions (EQD2) are frequently used in treatment planning and plan evaluation. This is especially important if new techniques like particle radiosurgery are investigated. In the context of the linear-quadratic model [1] these quantities depend on biological parameters (α and β) for ions as well as for the reference radiation (X-rays) and the dose per fraction as well as the number of fractions. Typically the needed biological parameters for in vivo situations cannot be determined directly in experiments, and they are subject to large (relative) uncertainties of up to 20–40% or even more. Therefore it is necessary to estimate the resulting uncertainties in e.g. RBE or EQD2 caused by the uncertainties of the relevant input parameters.

Sensitivity analysis approaches have already been used successfully in ion beam therapy, especially to address the biological effects of carbon ion beams (e.g. Refs. [2–4]). The authors of these papers reported significant variations due to systematic change in one or two parameters at a time.

We present here a Monte Carlo based SA approach, allowing the change of all relevant input parameters at once. The quantification by a variance-based algorithm enables ranking of the parameters as well as a clear visualization of the result's sensitivity on different input parameter variations.

Methods and materials

In the following section we first describe the SA used here. In a second step we outline how the fragmentation spectra for carbon

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ions were obtained and how the biological models are implemented in treatment plan optimization.

Variance-based sensitivity approach

The used SA is an adapted implementation of the Factor Priorization approach described by Saltelli et al. [5], which aims to rank input factors according to their influence on the result. In this context, the influences of different input uncertainties can be examined by variance-based SA method. In this Monte Carlo approach a function is evaluated $n = 10^3$ to 10^6 times, depending on the number of input parameters. For each of those runs all parameters are changed simultaneously, using random numbers according to their associated uncertainties. Variance-based statistic formalisms then rank the input parameter/uncertainty pairs according to their impact on the result of the function. This sensitivity S (first order sensitivity index) on the i-th input parameter X_i is defined as:

$$S_i = \frac{\mathrm{var}(\mathrm{mean}(Y|X_i = \mathrm{const}))}{\mathrm{var}(Y)} \quad (1)$$

with Y being a result vector of n function evaluations. The numerator is calculated following [5] by first sorting the $(X_i;Y)$ pairs by increasing X_i. The sorted pairs are divided into n_{par} equally sized partitions containing n/n_{par} entries with increasing X_i. The mean value is taken over these partitions, the variance then from the n_{par} mean values. In the scope of this work, n_{par} was set to 200. Calculated in this way, the sensitivity ranges from $S = 0$ (no influence) to $S = 1$ (only influential part).

Figure 1 shows an example SA where RBE is assumed to be only a function of the biological parameters (α_{P}, β_{P}) for particles/ions and the dose per fraction (d_{P}), while the biological parameters of the reference radiation (α_{X}, β_{X}) are kept constant. Hence the iso-effective RBE can be calculated within the LQ model using the relation

$$\mathrm{RBE}(\alpha_{\mathrm{P}}, \beta_{\mathrm{P}}, d_{\mathrm{P}}) = \frac{-\alpha_{\mathrm{X}} + \sqrt{\alpha_{\mathrm{X}}^2 + 4\beta_{\mathrm{X}}\left(\alpha_{\mathrm{P}} d_{\mathrm{P}} + \beta_{\mathrm{P}} d_{\mathrm{P}}^2\right)}}{2\beta_{\mathrm{X}} d_{\mathrm{P}}}. \quad (2)$$

In general, the distribution of the input variables can be chosen to best represent the (assumed) variation, e.g. normal, constant or any other distribution. In this work, as a first estimate, normal distributions described by a mean value and a standard deviation are used. The uncertainties can easily be described with another distribution by simple changes in the random generator properties.

Sensitivity values are calculated using Eq. (1), ranking the input variations according to their influence on the variation of the result. The major advantage of this SA method is that the function is not just evaluated at a single, fixed input parameter set, but over the whole range of all input parameter uncertainties. The quantification (Eq. (1)) allows to display and to compare several input uncertainties at once. The SA described here is not bound to analytical functions but can be performed with arbitrary numerical functions.

Fragmentation of the carbon ion beam

The Monte Carlo code FLUKA [6,7] is used as described by Parodi et al. [8] but for a generic beamline to generate the fragmentation spectra of incident carbon ions, which are needed for biological modeling. In total 32 carbon ion beams with energies ranging from 90 to 400 MeV/u in 10 MeV/u steps are simulated. This energy range covers treatment depths up to 27 cm in water with a mean distance of 0.8 cm between the single Bragg peaks. Necessary spots in between are implemented by a simplified range shifter, shifting the next Bragg peak with higher energy to the desired depth. In the simulations for this work the fully ionized elements H, He, Li, Be, B and C are scored. The resulting fragmentation spectra are described as particle fluence $\phi(z, Z, E)$ which in general depends on the depth z, the atomic number Z of the ion and its energy E.

Implementation of fragmentation and biological model into treatment plan optimization

In order to demonstrate the possibilities of the presented SA, we implemented it in a simple one-dimensional treatment plan optimization routine. Carbon ion treatment plan optimization has to take, additionally to the fragmentation of the carbon ion beam, the dependencies of α and β on the ion type and energy into account.

Following Zaider and Rossi [9] we can calculate the depth dependent dose averaged LQ parameters for a pristine Bragg peak by

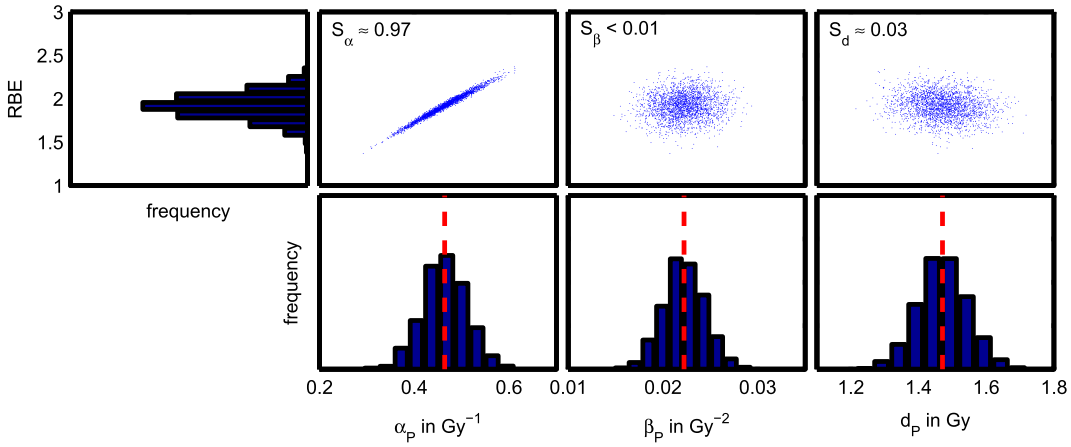

Figure 1. Example sensitivity analysis of RBE as a function of α_{P}, β_{P} and d_{P}. Their uncertainty is simulated using a normal distribution with a standard deviation of 10% (for α_{P} and β_{P}) and 5% (for d_{P}) relative to the mean value marked with a dashed line in the histograms. The mean values indicated here are the unchanged results of the biological modeling (α_{P} and β_{P}) and effect optimization (d_{P}) in a depth of 10 cm in water in the treatment geometry as described in Fig. 2. A subset of 2500 runs is displayed in the scatter plots. The sensitivity S of RBE on the three input parameter is marked in the respective scatter plot. The reference parameters $\alpha_{\mathrm{X}} = 0.18\ \mathrm{Gy}^{-1}$ and $\beta_{\mathrm{X}} = 0.028\ \mathrm{Gy}^{-2}$ are kept constant.