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# Monte Carlo simulation of the relative biological effectiveness and DNA damage from a 400 MeV/u carbon ion beam in water

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## HIGHLIGHTS

- GATE/Geant4 + MCDS used for $^{12}$C radiotherapy modelling.
- Energy spectra of $^{12}$C and its fragments at various depths in water.
- DSB yield distributions from $^{12}$C and its fragments.
- RBE distributions from $^{12}$C and its fragments.
- DNA damage distributions from $^{12}$C and its fragments.

## ARTICLE INFO

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## ABSTRACT

A 400 MeV/u carbon ion beam incident on a water phantom was simulated with GATE/Geant4 to calculate the energy spectra of $^{12}$C and its fragments at various depths. Based on the energy spectra, the DNA double strand break (DSB) yields from $^{12}$C and its fragments were calculated with Monte Carlo Damage Simulation (MCDS) code. The relative biological effectiveness (RBE) distributions for $^{12}$C and its fragments were calculated from the DSB yields. The DNA damages from each type of the particles and their contribution to the total DNA damages at various depths were calculated from the DSB yields and dose distributions. These characteristics of $^{12}$C and its fragments are important for understanding the corresponding RBEs and the DNA damages. The purpose of this work was to obtain the RBEs and the DNA damage distributions of carbon ions and their fragments in beams used in radiotherapy by means of simulating the macroscopic phantom and microscopic cells. The simulation method can be easily extended by changing some parameters.

## 1. Introduction

The heavy-ion therapy has attracted greater attention in many countries due to its proven advantages over the conventional photon radiotherapy. An important advantage of the heavy-ion radiotherapy is a particular dose distribution with its maximum (so-called Bragg peak) near the end of the ion track. Thus, absorption of a certain dose by the target volume (tumor) is combined with reduced doses to surrounding tissues and organs. Moreover, the relative biological effectiveness (RBE) and the DNA damage yield of a carbon-ion beam are considerably higher than those of a photon beam. Monte Carlo simulations play an important role in guiding the carbon-ion radiotherapy planning because they can provide accurate RBE values and DNA damage distributions (Spezi and Lewis, 2008; Yamamoto et al., 2007). As water is considered equivalent to the body soft tissue, it is appropriate to use it as the target material.

Several Monte Carlo simulation tools are available to generate ion tracks using a simulated phantom model for macroscopic studies of dosimetry and the energy spectrum, e. g., PHITS (Niita et al., 2006), SHIELD-HIT (Hultqvist et al., 2012), FLUKA (Sommerer et al., 2006) and Geant4 (Agostinelli et al., 2003; Zahra et al., 2010; Böhlen et al., 2010; Pshenichnov et al., 2006, 2008; Napoli et al., 2014). Other Monte Carlo simulation tools can estimate the sub-cellular damages in a simulated cell for the microscopic studies of the double-strain break (DSB) yields, e. g., PARTRAC (Friedland et al., 2011), KURBUC (Nikjoo et al., 1998), Geant4-DNA (Incerti et al., 2010; Pater et al., 2016) and MCDS (Semenenko and Stewart, 2004, 2006; Stewart et al., 2015). Some researchers used these macroscopic and microscopic tools in their studies. For example, Francis et al. (2014) used Geant4 and Geant4-DNA to simulate nanometric effects of the carbon ion

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fragmentation. Pan et al. (2014) and Huang et al. (2015) used FLUKA and MCDS to calculate the RBE values of the proton and carbon ion beams.

The GATE (Santin et al., 2003; Sarrut et al., 2014; Jan et al., 2011; Thiam et al., 2008; Grevillot et al., 2011, 2012, 2010; Kurosu et al., 2014) and Geant4 codes have a great potential in the radiation therapy and dosimetry applications. Ou et al. (2016, 2017) used GATE/Geant4 to calculate distributions of doses from a beam of carbon ions and their fragments in a water phantom. In the present work, we used GATE/Geant4 and MCDS together to calculate the RBE and DNA damage caused by a beam of carbon ions and their fragments in water. First, GATE and Geant4 were used to simulate the energy spectra and dose distributions from $^{12}$C and its fragments in a water phantom. Second, MCDS was used to calculate the DSB yields of various particles at various depths. Then, the RBE values and DNA damages of various particles were calculated from their DSB yields and dose distributions.

## 2. Simulation scheme

### 2.1. Simulation tools

Geant4 and GATE were chosen as simulation tools. Geant4 (Agostinelli et al., 2003) is a Monte Carlo tool to simulate transport of particles through materials. It can be used in the high-energy physics, accelerator physics and nuclear physics, as well as in the space science and medical physics (Zahra et al., 2010; Böhlen et al., 2010; Pshenichnov et al., 2006, 2008; Napoli et al., 2014). GATE (Santin et al., 2003; Sarrut et al., 2014; Jan et al., 2011; Thiam et al., 2008; Grevillot et al., 2011, 2012), open-source software, is a toolbox based on Geant4. It is used primarily for numerical simulations in radiotherapy and medical imaging. Some articles have described applications of GATE in radiation therapy (Kurosu et al., 2014; Grevillot et al., 2010; Ou et al., 2016, 2017). In our work, a 400-MeV/u carbon-ion beam incident on a water phantom was simulated to calculate energy spectra and dose distributions of $^{12}$C and its fragments (Ou et al., 2016, 2017). The authors used GATE 7.2 and Geant4.10.2.

MCDS was chosen as another simulation tool in this work. MCDS (Semenenko and Stewart, 2004, 2006; Stewart et al., 2015, 2011) simulates induction and clustering of DNA lesions in normoxic ($O_2$ concentration ≥ 8%) and anoxic (0% $O_2$) cells uniformly irradiated with various ions. An attractive feature of MCDS is that only four adjustable parameters need to be identified to simulate a DNA damage. MCDS parameters are estimated from track structure simulations (Nikjoo et al., 1998; Semenenko and Stewart, 2004, 2006), which account for the direct and indirect (free radical-mediated) mechanisms of the DNA damage. Three out of the four MCDS parameters are the same for all types of radiation and are set to fixed values. The fourth parameter depends on type and kinetic energy of the particles. The MCDS code is fast because it captures the major trends of the DSB yields predicted by other detailed track structure simulations. DSB yields were simulated in MCDS for the various degrees of the cluster complexity, i. e., DSB0 (simple DSB), DSB+ (DSB with additional break(s) on a strand within 10 base pairs) and DSB++ (more than one DSB within 10 base pairs) (Huang et al., 2015; Watanabe et al., 2015) in the order of increasing complexity. The total DSB yield is the sum of all the sub-category DSB yields, i. e.,

$$Y_{DSB,i} = Y_{DSB0,i} + Y_{DSB+,i} + Y_{DSB++,i}. \quad (1)$$

Previous studies of the RBE values (Semenenko and Stewart, 2004, 2006; Stewart et al., 2015, 2011) provided evidence that MCDS could accurately predict the DSB yields for various ions. Moreover, $RBE_{DSB}$ (RBE for the DSB induction) increased with decreasing oxygen concentration (Stewart et al., 2011). In our work, MCDS was used to simulate the DSB yields from $^{12}$C and its fragments at various depths in a water phantom. The RBE values of the beam of carbon ions and their fragments were calculated on the basis of the DSB yields and doses. The latest MCDS version (3.10A) was used.

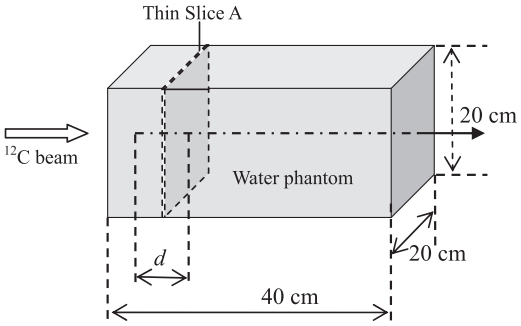


**Fig. 1.** Schematic diagram of the $^{12}$C beam incident on the water phantom.

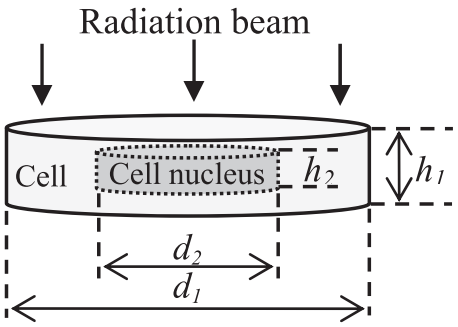


**Fig. 2.** Schematic diagram of a radiation beam incident on the cell phantom.

### 2.2. Model settings

Fig. 1 shows the first, macroscopic model built with GATE/Geant4. A beam of carbon ions is incident perpendicularly to the left facet of the cuboid water phantom at its center. The dimensions of the phantom, 20 × 20 × 40 cm$^3$ and its material parameter were set to G4_WATER. The settings of the $^{12}$C beam are consistent with the source parameters of an experiment by Haettner (Haettner et al., 2013). The $^{12}$C beam was considered as monoenergic (400 MeV/u) having a Gaussian distribution with $\delta_x = \delta_y = 2.12$ mm (the full width at half maximum, FWHM, was equivalent to 5 mm), and the angle scattering parameter was $\delta_{ang} = 1$ mrad. The number of carbon ions in this simulation was 100,000.

The detector is represented by Thin Slice A in Fig. 1 (200 × 200 × 0.02 mm$^3$) parallel to the entrance and exit facets; its material parameter was also set to G4_WATER. Thin Slice A was used to glean the energy spectrum information of $^{12}$C and its fragments. As Fig. 1 shows, the distance between the center of Thin Slice A and the incident point was set to $d$.

The second, microscopic model built with MCDS is shown in Fig. 2. Radiation beam was incident on a cylindrical cell phantom. The diameter of the cell $d_1$ was 10.00 μm, while its thickness $h_1$ was 1.667 μm. The diameter of cell nucleus $d_2$ was 5.00 μm, its thickness $h_2$ was 0.833 μm. The concentration of oxygen in the cell was set to 100%. The DNA content of the cell was 1 Gbp. (If the DNA content of the cell is set to 6 Gbp, the genomic DNA length of the human diploid cells, the DSB yield and DNA damage should be multiplied by a factor of 6.). The number of cells in the MCDS simulation was 10,000.

### 2.3. Calculation methods

Firstly, GATE/Geant4 calculates the energy spectra of $^{12}$C and its fragments at the various depths in the water phantom. The result of this part is presented in Section 3.1. In this work, the term “carbon ion beam” is used for the mixed field of all particles, including primary, secondary and tertiary ones. So, $^{12}$C includes the primary $^{12}$C, secondary $^{12}$C and tertiary $^{12}$C; Other Particle A (fragment) includes