Original research article

Design of spread-out Bragg peaks in hadron therapy with oxygen ions

Ladan Rezaee*

Department of Physics, Shiraz Branch, Islamic Azad University, Shiraz, Iran

ABSTRACT

Aim: Design of a numerical method for creating spread-out Bragg peak (SOBP) and evaluation of the best parameter in Bortfeld Model to this aim in oxygen ion therapy.

Background: In radiotherapy, oxygen ions have more biological benefits than light beams. Oxygen ions have a higher linear energy transfer (LET) and larger relative biological effectiveness (RBE) than lighter ones.

Materials and methods: For the design of the spread-out Bragg peak (SOBP) for oxygen beam, we designed a numerical method using the Geant4 Monte Carlo simulation code, along with matrix computations.

Results: The profiles of the Bragg Peak have been calculated for each section in the target area by the Geant4 tool. Then, in order to produce SOBP smoothly, a set of weighting factors for the intensity of oxygen ion radiation in each energy was extracted through a numerically designed method. This method was tested for producing SOBP at various widths and at different depths of a phantom. Also, weighting factors of intensity for producing a flat SOBP with oxygen ions were also obtained using the Bortfeld model in order to determine the best parameters. Then, the results of the Bortfeld model were compared with the outcomes of the method that was developed in this study.

Conclusions: The results showed that while the SOBP designed by the Bortfeld model has a homogeneity of 92–97%, the SOBP designed by the numerical method in the present study is above 99%, which in some cases even closed to 100%.

1. Background

High energy ionizing radiation, through delivering dose to matter, and creating Bragg peaks in a particular area in the target, is an appropriate option for radiation therapy. The radi- ation dose in the entrance area is low, while the maximum dose in the target area is delivered. Compared to light ions, oxygen is classified as a beam with a high linear energy transfer (LET). A beam with a high LET has a larger RBE than low LET such as photons and protons.[1] In addition, the dose of the oxygen beam at the end of the Bragg peak leads to a large slope

that prevents the absorption of unwanted doses to sensitive organs.

Obviously, because of Bragg peaks thinness, a monochromatic ionizing ray is not suitable for cancer treatment. Therefore, we need to extend Bragg peak to produce a smooth dose in the tumor area, which is possible by preparing an ion beam array with appropriate energy distribution. The problem of the production of an SOBP through a weighted unit of monochromatic proton beams has been investigated by various researchers, in particular by Bortfeld and Schlegel,[2] Bortfeld,[3] Pedroni et al.,[4] Hérault et al.,[5] Hérault et al.,[6] Kooy et al.,[7] and Jette and Chen.[8] In these studies, the SOBP design was investigated in a variety of ways, such as analytical methods, Monte Carlo methods and, based on the results, were mainly compared with empirical findings. However all of these studies were performed for proton irradiation.

With the development of hadron therapy with ions other than proton therapy, it is necessary to design methods for modulating the intensity of ions such as helium, carbon, oxygen, or other ions that are involved in the Hadron therapy at the research stage. Most carbon studies, e.g. Sakama et al.[9] and Suit et al.[10] examined filters for smoothing SOBP in passive scattering proton beams method. For the pencil beam scanning method, these studies have not been actively pursued until now, and only few studies have addressed this issue until now. For example, the SOBP design for carbon monoxide irradiation in the Hadron Therapy has been studied in Kim et al.[11] But no specific study has been done on heavy ions such as oxygen.

For proton, there is a variety of algorithms for modulating the intensity of ion beams to produce a smooth SOBP in previous research. Bortfeld and Schlegel[2] reported a simple way of determining the weights of primary energies to the creation of SOBP for proton beams. Jette and Chen[8] improved the results obtained by Bortfeld by introducing corrections to this method. The smoothness of the SOBP obtained by this method (i.e. the *Bortfeld model*) is strongly dependent on the parameter *p* which refers to the power of energy in the power-low energy-range relation in Eq. (1) presented below. Since the value of this parameter, depends on the type of ion, ion energy, and also the width of the SOBP, it is difficult to guess the *p* value for designing the treatment. Hence, finding more suitable methods for producing a smooth SOBP is necessary.

2. Aim

In this study, due to the irradiation of oxygen ions, a numerical method was proposed based on Monte Carlo and Matrix Computations (that we call the MCMC method) to generate weighting factors. This method can be used for the other ions, too. In this process, we first find the profiles of the Bragg peaks at various depths of a phantom using the Monte Carlo calculations (in this study, by the Geant4 tool), then using an algorithm of matrix computation, we calculate the weights for the intensity of each monochromatic ion beam. Here, the MCMC method has been used for 5 different SOBPs with different depths and widths. In each case, the SOBP's homogeneity ratio has been calculated and compared with the results of the Bortfeld model.

3. Materials and methods

3.1. Simulation by Geant4 code

The Geant4 computing code is a package used for the Monte Carlo simulations of interacting particles with materials.[12] The system designed in the Geart4 Monte Carlo code is as shown in Fig. 1. The world is an air cube with dimensions of $2 \times 2 \times 4$ m and a cylindrical phantom with a radius of 0.5 m and a height of 1.8 m is in the world's volume so that the cylinder axis of the phantom is in the direction of the z-axis. The phantom is made from water. According to the energy of the oxygen ions, the length of the phantom was chosen in such a way that all the major ions in the phantom interior were stopped.

Due to SOBP production, the dose in each point overlaps with different depth-dose distributions that have been generated from different incident energies. So, for example, for producing an SOBP with a width of 3 cm at a depth of 3.5 to 6.5 cm in the phantom, the required ion energies will be from 140 MeV/u to 195 MeV/u for oxygen ions. This band of energy is divided into 22 sections (i.e. 23 monochromatic oxygen beams, with a difference of 2.5 MeV/u between two consecutive beams). The diameter of pencil beam is chosen 0.4 cm without divergence. The pencil beam of the oxygen ions, along with z-axis, hits the phantom and enters it.

To calculate the absorbed dose at different points of the phantom, we can use the cube scoring mesh. To evaluate the depth-dose distribution along the axial direction of the main beam, we used a cubic mesh and calculated the dose on the main axis of the incident beam at intervals of 0.1 mm.

Fig. 2 shows the distribution of the normalized dose along the z-axis for 23 different beams with the lowest energy ($E = 140$ MeV/u) that make a Bragg peak at $x = 3.5$ cm and the Bragg peak of the beam with maximum energy ($E = 195$ MeV/u) is at $x = 6.5$ cm (by this Bragg peak suite, we want to create a smooth SOBP, called SOBP1). Also, the second set of Bragg peaks, shown in Fig. 2, is from $x = 11$ cm to $x = 14$ cm (we also intend to create a flat SOBP from this set, called SOBP2).

The sum of these two sets of 23 dose profiles is also shown in Fig. 3. It is clear that these diagrams have not a desired smoothness of SOBP and it is strongly necessary to consider suitable weights for the intensity of each incident beam so that
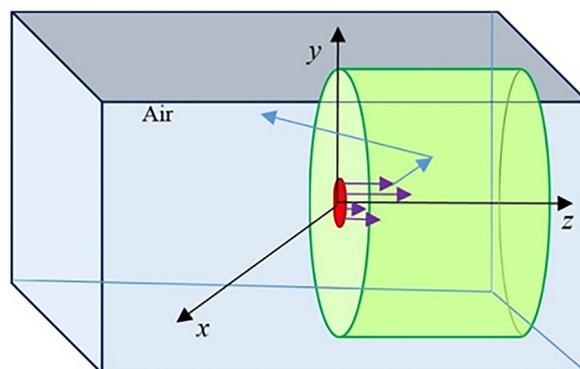

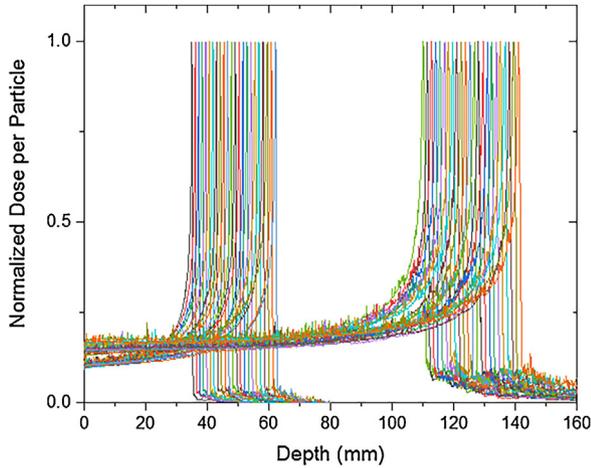**Fig. 1 – The geometry of system in the Monte Carlo simulation.**

Fig. 2 – Depth-dose profiles for two sets of 23 energy beams from oxygen ions.
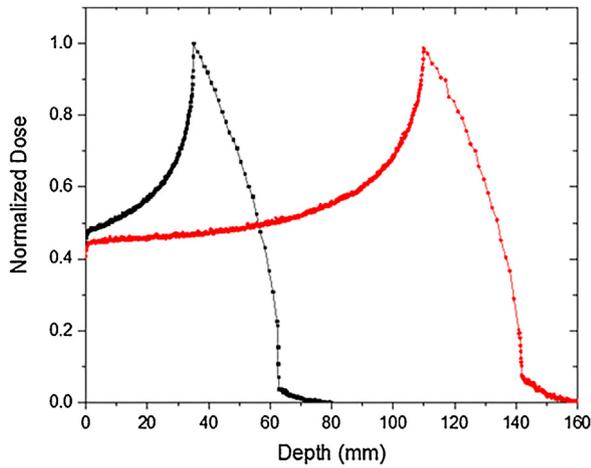

Fig. 3 – Total dose of oxygen ions without weighting factors of intensity.

the sum of the dose profiles results in a flat graph. It is evident from the figure that the intensity of the more energetic beams should be greater than those with less energy.

3.2. Using Bortfeld model to produce proper weights

In Bortfeld and Schlegel,[2] a simple method of modulating the intensity of proton beams and determining the appropriate weight for each beam has been developed for generating a smooth SOBP. Their work was based on a power law relationship between the proton range and energy:

$$R = \alpha E^p \qquad (1)$$

The parameters of this relation for proton beams, $p = 1.77$ and $\alpha = 0.022$, were obtained in their next study.[3] Jette and Chen,[8] by introducing corrections in the Bortfeld method, tried to create a SOBP with more smoothness. The computed weighting factors were as follows[8]:

$$w_k = \begin{cases} 1 - \left(1 - \frac{1}{2n}\right)^{1-1/p} & k = 0 \\ \left[1 - \frac{1}{n}\left(k - \frac{1}{2}\right)\right]^{1-1/p} - \left[1 - \frac{1}{n}\left(k + \frac{1}{2}\right)\right]^{1-1/p} & k = 1, \dots, n-1 \\ \left(\frac{1}{2n}\right)^{1-1/p} & k = n \end{cases}$$

$$(2)$$

In these relations, n is equal to the number of energy intervals (number of beams with different energies is $n+1$) and p is in the power law of Eq. (1). So, it is necessary that we know the precise value of p to produce a smooth SOBP. The problem with this is that the value of p depends on different parameters. Obviously, the exact value of p is different for each type of ions, such as protons, deuterons, carbon ions, or oxygen (this difference is due to the differences in the relation between the range and energy for each ion). On the other hand, even for any particular type of ion, calculations show that the value of p depends on several other factors. For example, in Jette and Chen,[8] which produces SOBP for proton beams, it is evident that the p-value influences the SOBP's width. Otherwise, it can be seen that (as discussed in the present paper) p-value is also affiliated to the energy of the beams required to create an SOBP with specific characteristics (here, we consider the maximum energy in the desired range). Even p-value is also sensitive to the difference of energy of two consecutive rays and it strongly affects the smoothness of the SOBP design. Therefore, it is difficult to find a p-value for the treatment planning, for any type of ion, and for designing each SOBP with desired depth and width.

In this study, using the Bortfeld model, several SOBPs with different depths and widths (5 cases) were produced. In each case, we allowed the value of p to be varied (eleven different values). Then by Eq. (2), the appropriate weights for the intensity of the beams were calculated, and the SOBP diagrams were plotted and their homogeneities were evaluated. Among the obtained graphs, the best p-value relates to the graph with the highest homogeneity.

3.3. Numerical method for calculating appropriate weights for the intensity of ion beams

The intensity of each beam in the required energy range should be adjusted so that the sum of the doses of all the beams in the all points within the interval of spatial SOBP's width is a constant value. After calculating the dose profiles by the Monte Carlo tool, we apply the following method to calculate the weight of each beam. This numerical method, that is a combination of Monte Carlo calculations and Matrix Computations, will be called a numerical MCMC method.

By Geant4 calculations, for every energy step on the phantom's axis, the numerical data of dose is available from E_{min} to E_{max} (For each particular energy, a point is known as the exact location of the Bragg peak). To determine the proper intensity weights, we only need to consider the points within the SOBP's width (M points in one dimension). Thus, we define a matrix that is represented by D in dimension $M \times M$, where the element $D_{i,j}$ represents the amount of dose in Gray delivered by

the beam with energy E_j in place x_i (normalized dose per particle). The energy and spatial steps for this matrix elements to design of SOBP1 are shown in Table 1. The places x_1 to x_M are the exact locations of the Bragg peaks that are derived from the Monte Carlo calculations, and all are within the desired SOBP range. The column with header $E_1 = E_{min}$, show the normalized dose at these points, that are related to ion beam with energy E_1. This energy is the lowest oxygen energy to produce the desired SOBP. Similarly, the elements of the next column are the normalized doses so that every element is related to a particular energy and at a Bragg peak.

Determination of the weighting factors $\{w_1, w_2, \ldots, w_M\}$ for the intensity of any given beam with a certain energy means that by multiplying each factor w_j in the column j of the matrix D, the sum of the elements of each row of this matrix is equal to a constant value d_{Max} that is the dose within the SOBP width. Since the sum of the doses in the first row of the matrix D is maximized (which we select as d_{Max}), then for the second row and etc. in the matrix D, we must have

$$\begin{cases} w_1 D_{2,1} + w_2 D_{2,2} + \ldots + w_M D_{2,M} = d_{Max} \\ \vdots \\ w_1 D_{M,1} + w_2 D_{M,2} + \ldots + w_M D_{M,M} = d_{Max} \end{cases} \quad (3)$$

By deleting the first row of the matrix D, we construct the matrix D_1, which is a matrix in dimension $(M-1) \times M$:

$$D_1 = \begin{pmatrix} D_{2,1} & \ldots & D_{2,M} \\ \vdots & \vdots & \vdots \\ D_{M,1} & \ldots & D_{M,M} \end{pmatrix} \quad (4)$$

By defining a matrix in dimensions $1 \times M$ as a weighting factor with the symbol W, we have from Eq. (3):

$$(w_1, w_2, \ldots, w_M)_{1 \times M} \begin{pmatrix} D_{2,1} & \ldots & D_{M,1} \\ \vdots & \vdots & \vdots \\ D_{2,M} & \ldots & D_{M,M} \end{pmatrix}_{M \times (M-1)}$$

$$= (d_{Max}, d_{Max}, \ldots, d_{Max})_{1 \times (M-1)} \quad (5)$$

The first side of the expression is the multiplication of the W matrix in the transpose matrix of the D_1, namely $(D_1)^T$. Therefore, by introducing a matrix d, in dimension $1 \times (M-1)$ and all its elements equal to d_{Max}, we will have a matrix equation such that the elements of the matrix W are unknown.

$$W(D_1)^T = d \quad (6)$$

Obviously, by multiplying the sides of this equation from the right in the inverse of the matrix $(D_1)^T$, the elements of the matrix W can be computed:

$$W = d((D_1)^T)^{-1} \quad (7)$$

Table 1 – Elements of dosimetry matrix to design of SOBP1. Radiation dose is expressed in terms of Gray.

	Energy (MeV/u)				
Depth in phantom (mm) (Δx is the spatial difference between two consecutive Bragg peaks which has a value about 1.1)	$E_1 = E_{min} = 140$	$E_2 = E_{min} + \Delta E = 140 + 2.5$	$E_3 = E_{min} + 2(\Delta E) = 140 + 2(2.5)$	$\ldots$	$E_M = E_{max} = 195$
$x_1 = x_{min} = 35$	$D_{1,1} = 2.82 \times 10^{-5}$	$D_{1,2} = 1.05 \times 10^{-5}$	$D_{1,3} = 8.45 \times 10^{-6}$	$\ldots$	$D_{1,M} = 2.99 \times 10^{-6}$
$x_2 = x_{min} + \Delta x = 35 + \Delta x$	$D_{2,1} = 5.02 \times 10^{-7}$	$D_{2,2} = 2.68 \times 10^{-5}$	$D_{2,3} = 1.11 \times 10^{-5}$	$\ldots$	$D_{2,M} = 2.96 \times 10^{-6}$
$x_3 = x_{min} + 2(\Delta x) = 35 + 2(\Delta x)$	$D_{3,1} = 2.80 \times 10^{-7}$	$D_{3,2} = 9.31 \times 10^{-7}$	$D_{3,3} = 2.73 \times 10^{-5}$	$\ldots$	$D_{3,M} = 3.23 \times 10^{-6}$
$\ldots$	$\ldots$	$\ldots$	$\ldots$	$\ldots$	$\ldots$
$x_M = x_{min} + (M-1)(\Delta x) = x_{max} = 65$	$D_{M,1} = 1.22 \times 10^{-7}$	$D_{M,2} = 3.41 \times 10^{-8}$	$D_{M,3} = 7.74 \times 10^{-8}$	$\ldots$	$D_{M,M} = 8.02 \times 10^{-8}$

Therefore, the value of any weighting factor is:

$$w_j = d_{Max} \sum_{i=1}^{i=M-1} (((D_1)^T)^{-1})_{i,j} \qquad (8)$$

which is equal to the product of d_{Max} and the sum of the elements of the column j of $((D_1)^T)^{-1}$ matrix. Thus, the intensity weighting factors are calculated for the M ion beams.

4. Results

To evaluate and compare the smoothness of the dose in each SOBP, we introduce the homogeneity (HOM). The dose homogeneity, defined as the ratio between the lowest and the highest calculated dose within 80% of the SOBP.

Here, in the Bortfeld model, we look at the effect of the following factors on the p-value and, therefore, on the smoothness of the dose: (a) maximum energy value, which means the location of the SOBP at the depth of the phantom, (b) SOBP width and (c) the energy difference between consecutive beams, which can be interpreted as the spatial interval between two successive peaks.

First, using the Bortfeld model, we design five SOBPs with different widths and depths by calculating the appropriate weighting factors for each SOBP, and select the best p-value for each, given the obtained HOM. After that, by using the MCMC method, and for the same five SOBP cases, we derive the weighting factors and obtain the HOM for each case. Comparing the computational results of these two methods is then done.

In order to use the Bortfeld model, determination of the best value of p, which yields the highest HOM, has no other way than the test-error method, and hence, in order to determine the most suitable weighting factors of intensity, a large volume of numerical computations for creating an SOBP desirable characteristics is necessary. In this paper, in order to determine the best p-value, we first compute the weighting factors for several values of p with intervals of 0.05, in the guessing range $p = 1.4$ to $p = 2.1$. Guessing the interval is also based on the value of p for proton beam which was performed in Bortfeld and Schlegel.[2] Then, by plotting SOBP and calculating the homogeneity in each case, we determined the probable interval of the p-value.

For example, to create an SOBP that will be called SOBP1, after examining a large number of guessed p values, the probability range for the best value of p was determined in [1.85,1.95] or to create SOBP2, was in [1.70,1.80]. Then, in the second step, we continued the calculations within the probability range found in each case and repeated the calculations for the values of p with the 0.01 steps. Finally, we computed the homogeneity for each case. This suggests that in order to create an SOBP with a satisfactory HOM, at least over one hundred series of calculations with various p values must be repeated, which is a very demanding practice. Finally, the best p-value will be the value that results in the highest HOM.

The results of Bortfeld model calculations for different values of p were plotted in Fig. 4. In this figure, to evaluate the effect of SOBP location at the best value of p, two SOBPs were designed with a width of 3 cm, centered at $x_{mid} = 5$ cm
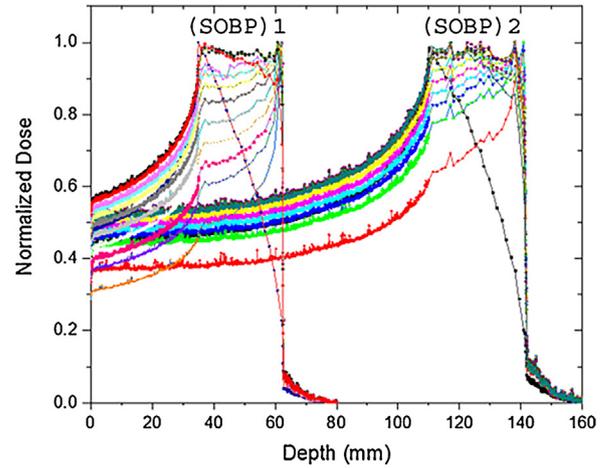

Fig. 4 – Design of two SOBPs with the same width 3 cm and at different depths of the phantom using Bortfeld model.

(SOBP1), and the other that centered at $x_{mid} = 12.5$ cm (SOBP2). The required energy of oxygen ions for SOBP1 was [140,195] Mev/u and for SOBP2 was [273,317] Mev/u. The difference between the energy of the consecutive beam, for both cases, was $\Delta E = 2.5$ MeV/u. Therefore, 23 ions beams with different energies were required.

The results of calculations (see Fig. 7 and Table 2) show that the best value of p for design SOBP1 is $p = 1.89$ (with HOM 97.5%), whereas for SOBP2, it is equal to $p = 1.74$ (with HOM 96.1%). The considerable difference between these two values of p indicates that the creation of a smooth SOBP with the same width, but with different locations at the depth of the phantom, requires two sets of weighting factors that are related to very different p-values. Even their best homogeneity is different.

To appraise the effect of various SOBP widths and depths on the best p-value, in Fig. 5, two SOBPs, one with 1 cm width, centered at $x_{mid} = 13.5$ cm (SOBP3), and the other with 1.7 cm width, centered at $x_{mid} = 4.35$ cm (SOBP4), were plotted for different p-values. The required energy range for SOBP3 is [303,317] Mev/u with the number of 8 ion beams and for
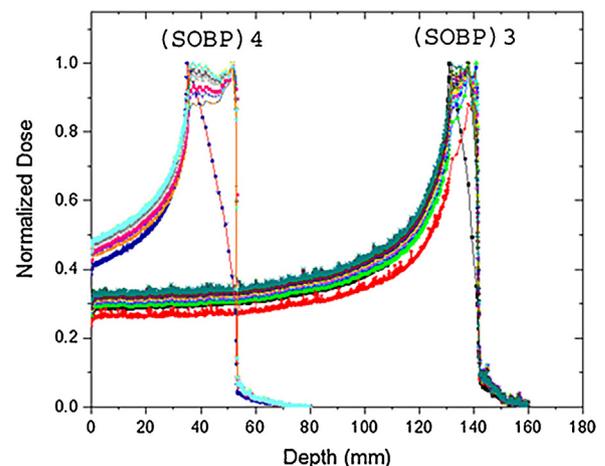

Fig. 5 – Design of two SOBPs with different widths and at different depths of the phantom using Bortfeld model.

Table 2 – The homogeneity of each SOBP for the best value of p and comparison of the results of the two models.

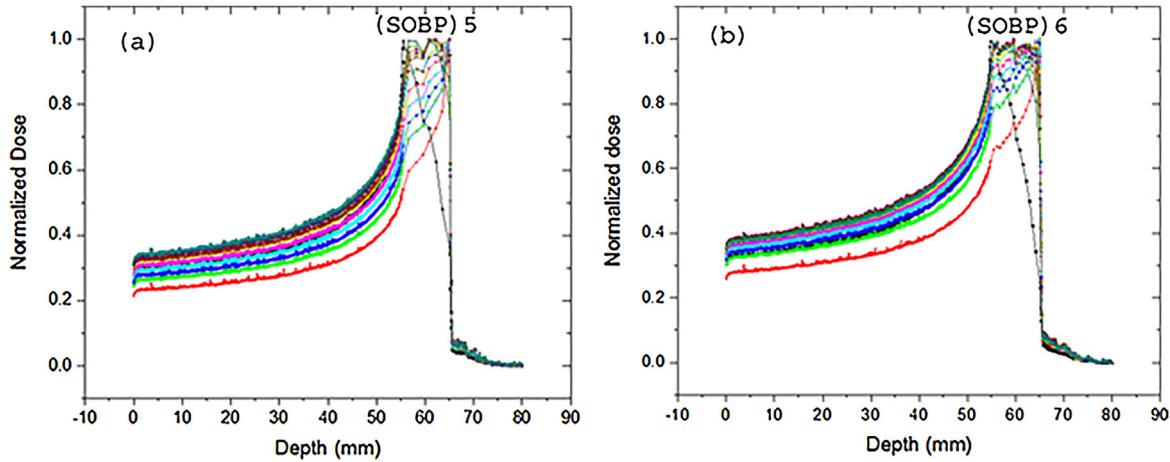|	(SOBP)1	(SOBP)2	(SOBP)3	(SOBP)4	(SOBP)5	(SOBP)6
Best value of p from Bortfeld model	1.89	1.74	1.75	1.95	2.04	1.78
HOM (from Bortfeld model)	97.5%	96.1%	92.7%	97.2%	97.8%	95.8%
HOM (from matrix calculation)	99.68%	99.99%	100%	99.99%	99.99%	99.12%

Fig. 6 – Design of two SOBPs with the same width and depth in the phantom and with the different number of energy steps using Bortfeld model.

SOBP4 is [140,177] Mev/u with 15 ions beams. The difference between the energy steps is also considered in both cases $\Delta E = 2.5$ MeV/u.

Calculations show that (see Fig. 7 and Table 2) the best value of p to design SOBP3 is equal to $p = 1.75$ (with HOM 92.7%), while for SOBP4 it is equal to $p = 1.95$ (with HOM 97.2%). The great difference between these two values of p and the difference between the best HOM in these two cases suggests that the creation of a smooth SOBP with different widths and a different location needs very different weighting factors.

To estimate the effect of the difference between the energy steps on the best p values, two SOBPs, each with 1 cm width, and both centered at $x_{mid} = 6$ cm (SOBP5 and SOBP6) were plotted in Fig. 6. The required energy range for both SOBPs was [180,200] Mev/u. But the length of the energy steps in SOBP5 was equal to $\Delta E = 2.5$ MeV/u (corresponding to $\Delta x \approx 11$ mm for two consecutive Bragg peaks) with 8 ions beams and for SOBP6 it was equal to $\Delta E = 1.25$ MeV/u (corresponding to $\Delta x \approx 7$ mm) with 15 ions beams.

The results (see Fig. 7 and Table 2) show that the best p-value to design SOBP5 was $p = 2.04$ (with HOM 97.8%), while for SOBP6, it was equal to $p = 1.78$ (with HOM 95.8%). It can be concluded that the creation of a smooth SOBP with the same location and width, but with different energy steps, requires very different weighting factors.

Homogeneity curve in terms of the p-value for each of the six SOBPs was plotted in Fig. 7. At points where each graph is peaked, the most suitable value of p is detectable for the highest HOM. In this way, it is clear that there is a significant difference in the appropriate value of p in each case.

We also used the numerical MCMC method and determined the weighting factors (weighting factors of the two models were compared in Fig. 9). SOBPs curves in Fig. 8, using the weighting factors derived from the MCMC model were plot-
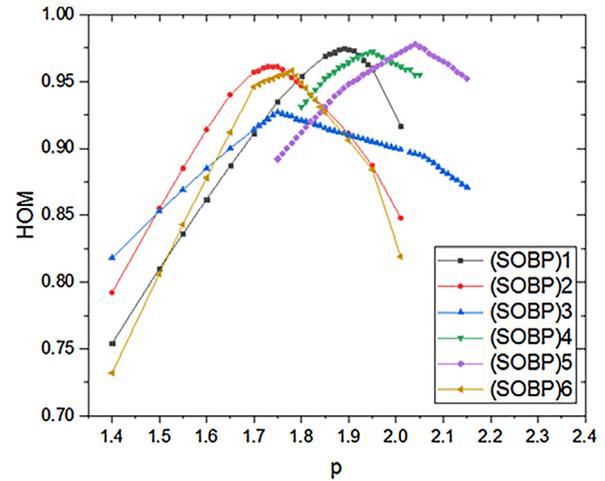

Fig. 7 – The homogeneity in terms of the p-value for six cases of SOBP.

ted which were already designed with the weighting factors derived from the Bortfeld model.

To compare the outcomes of the Bortfeld model and the MCMC computations, the results were summarized in Table 2. In this table, for each SOBP, the HOM values related to the best p-value were shown. It can be seen that despite the large calculations in the Bortfeld model, the highest HOM obtained was 97.8%, while the homogeneity derived from the MCMC method was above 99% which, in most cases, was approximately close to 100%.

In Fig. 9, the best-normalized weighting factors obtained from the Bortfeld model were compared with the weighting factors derived from the MCMC model. In this figure, the high-
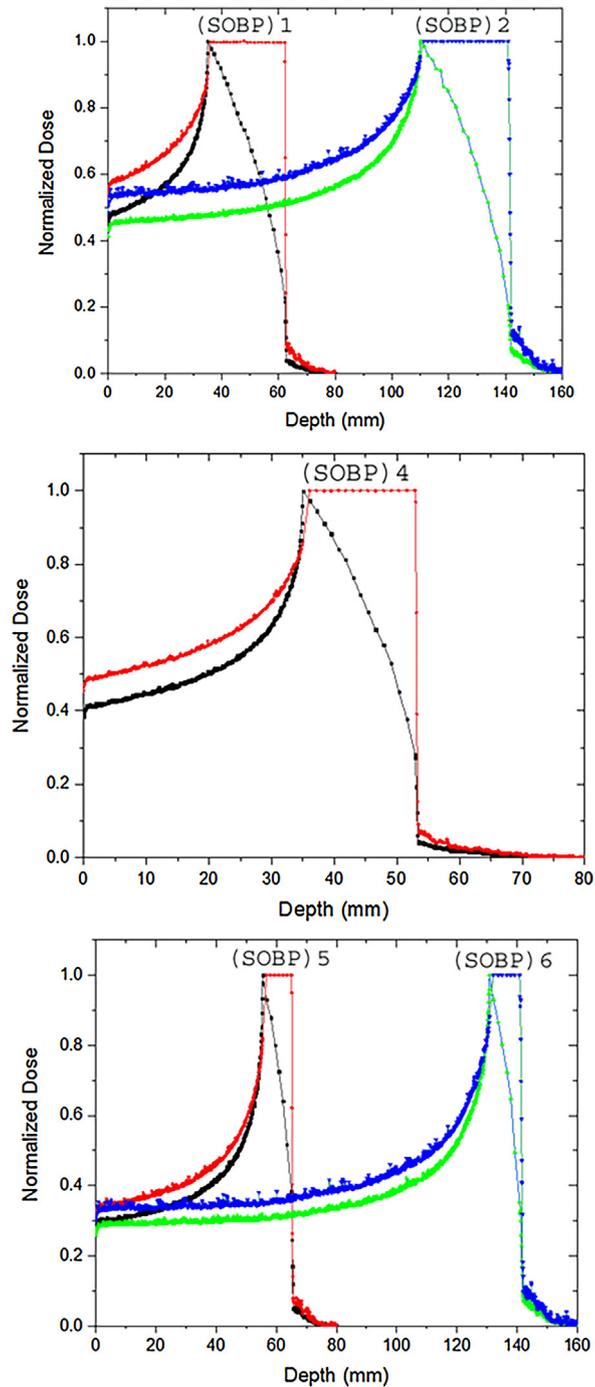
Fig. 8 – Design of the SOBPs using MCMC method.

est adaptation between them is related to SOBP1 and SOBP4, which, according to Table 2 has a homogeneity over 97% of the Bortfeld model. The difference between the weighting factors SOBP2 and SOBP6 is negligible and for SOBP5, and SOBP3, it is noteworthy that these four items have a homogeneity (95% to 96%) less than the others (over 97%). These results show that if the weighting factors obtained from the Bortfeld model are closer to the results of the MCMC method, the SOBP obtained from the Bortfeld model will be more satisfactory.

Dose fluctuations in SOBP, in the use of the Bortfeld model, and the presence of local holes, are the main disadvantages of using this model. Since the Bortfeld model is an analytical model and because the evaluation of the intensity factors in beam modulation is based on the power law between particle energy and range, the calculated values in the Bortfeld model do not provide appropriate results. Considering that a power law relationship is the simplest possible assumption by increasing the incident ion energy, more intense nonlinear effects occur. This issue causes a flaw in the above assumption, and for this reason, the results are severely mistaken. In contrast, using the Monte Carlo method and, consequently, matrix computations to determine the factors, we do not consider a
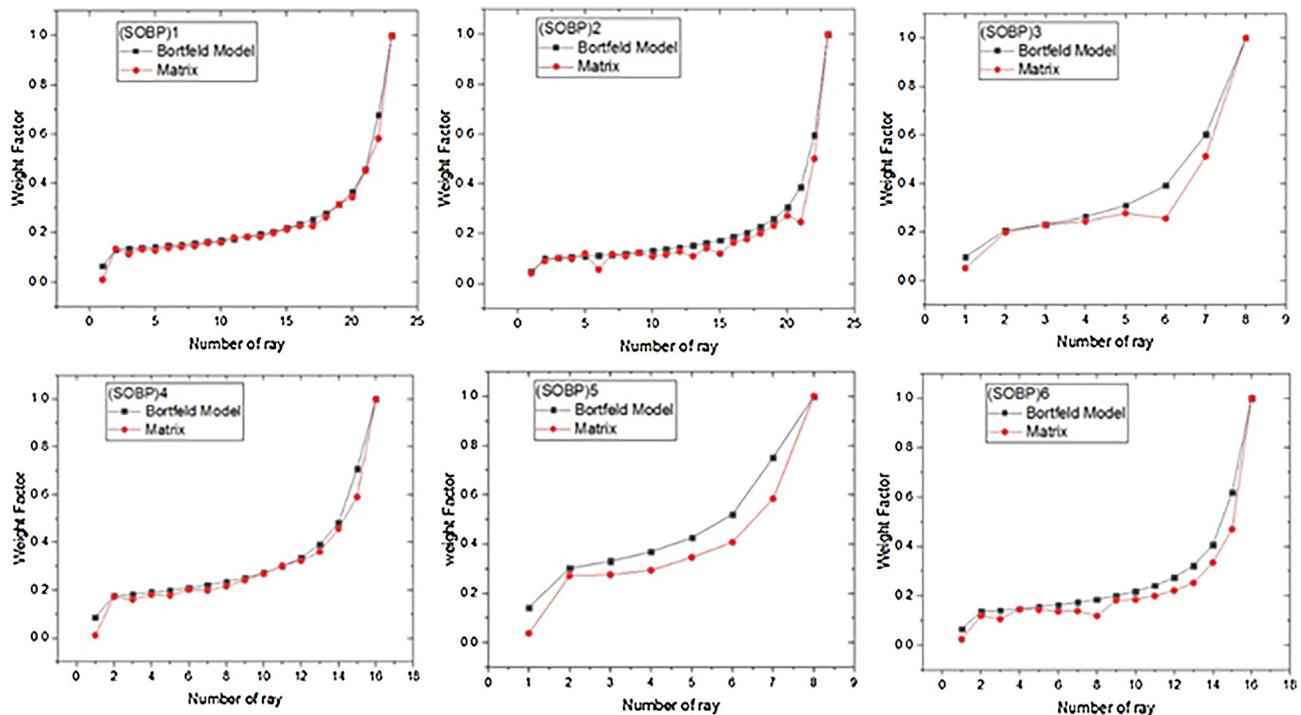
Fig. 9 – Comparison of the weighting factors of ion beam intensities in terms of the number of beams in the Bortfeld model and the MCMC method.

particular hypothesis for the relationship between energy and range. The range of each particle with a given energy is calculated at each run of the program and, thus, the above error is not generated. Thus, the results of the Monte Carlo method in assessing the intensity factors can increase the homogeneity of SOBP by one hundred percent.

5.   Conclusions

We have succeeded in designing a numerical method based on a combination of Monte Carlo calculations and matrix computations called the MCMC method, by which we calculate suitable weighting factors for the production of SOBP with a homogeneity of close to 100%. This numerical method can be used for any kind of hadron. In this study, we have calculated the appropriate weighting factors for the oxygen ion beams and compared the outcomes with the results of the Bortfeld model. The cases we examined by both models had different widths of SOBP and at different depths of the phantom. The smoothness of the SOBPs produced by the MCMC method was generally very good (with a homogeneity over 99%). The effect of three parameters for the best value of p, i.e. the SOBP width, the SOBP's location in the phantom, and the lengths of the energy steps of each ion beams, by varying p-value in the Bortfeld model was also tested. The results of the calculations showed that the best p-value was strongly influenced by all the three parameters, and so choosing p was not a simple task and required a large amount of computations. However, we obtained the best value of p for the five cases of SOBP creation, which yields the highest homogeneity. By comparing the best homogeneity obtained from the Bortfeld model and

the results of the MCMC method for studied cases, we conclude that using the MCMC method in comparison with the Bortfeld model ensures the ease, speed, and precision of the result in the design of SOBP in the radiation of ions in the hadron therapy.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Loeffler JS, Durante M. Charged particle therapy—optimization, challenges and future directions. *Nat Rev Clin Oncol* 2013;**10**:411–24.
2. Bortfeld T, Schlegel W. An analytical approximation of depth–dose distributions for therapeutic proton beams. *Phys Med Biol* 1996;**41**:1331–9.
3. Bortfeld T. An analytical approximation of the Bragg curve for therapeutic proton beams. *Med Phys* 1997;**24**:2024–33.
4. Pedroni E, Scheib S, Böhringer T, et al. Experimental characterization and physical modelling of the dose distribution of scanned proton pencil beams. *Phys Med Biol* 2005;**50**:541–61.
5. Hérault J, Iborra N, Serrano B, Chauvel P. Monte Carlo simulation of a protontherapy platform devoted to ocular melanoma. *Med Phys* 2005;**32**:910–9.

6. Hérault J, Iborra N, Serrano B, Chauvel P. Spread-out Bragg peak and monitor units calculation with the Monte Carlo Code MCNPX. *Med Phys* 2007;**34**:680–8.

7. Kooy HM, Schaefer M, Rosenthal S, Bortfeld T. Monitor unit calculations for range-modulated spread-out Bragg peak fields. *Phys Med Biol* 2003;**48**:2797–808.

8. Jette D, Chen W. Creating a spread-out Bragg peak in proton beams. *Phys Med Biol* 2011;**56**:N131–8.

9. Sakama M, Kanai T, Kase Y. Design of ridge filters for spread-out Bragg peaks with Monte Carlo simulation in carbon ion therapy. *Phys Med Biol* 2012;**57**:6615–33.

10. Suit H, DeLaney T, Goldberg S. Proton vs carbon ion beams in the definitive radiation treatment of cancer patients. *Radiother Oncol* 2010;**95**:3–22.

11. Kim CH, Lee HR, Chang S. Practical biological spread-out Bragg peak design for a carbon beam. *J Korean Phys Soc* 2015;**67**:1440–3.

12. Agostinelli S, Allison J, Amako K. Geant4—a simulation toolkit. *Nucl Instrum Methods Phys Res A* 2003;**506**: 250–303.