Received: April 24, 2022; **Accepted:** February 19, 2023.
DOI. 10.30473/coam.2023.63739.1200
Summer-Autumn (2023) Vol. 8, No. 2, (33-47)
Research Article

Open Access

Control and Optimization in Applied Mathematics - COAM

Dose Optimization in a Fuzzy Model of High-Dose Rate Brachytherapy Problem

Mohammad Mohammadi Najafabadi*, Habibeh Nazif, Fahimeh Soltanian

Department of Mathematics, Payame Noor University (PNU), P.O. Box. 19395-3697, Tehran, Iran.

Correspondence:
Mohammad Mohammadi Najafabadi
E-mail:
mm.najafabadi@pnu.ac.ir

How to Cite
Mohammadi Najafabadi, M., Nazif, H., Soltanian, F. (2023). "Dose optimization in a fuzzy model of high-dose rate brachytherapy problem", Control and Optimization in Applied Mathematics, 8(2): 33-47.

Abstract. This paper is motivated by high dose rate brachytherapy treatment planning problems which involve the specification of the movement schedule of a radiation source so that the target volumes are adequately covered with sufficient doses and organs at risk are not radiated beyond the clinical acceptance threshold. It utilizes four powerful multi-objective evolutionary algorithms (MOEA), which create a set of equally-weighted Pareto optimal solutions instead of only one and produce better results compared to other optimization methods. These algorithms include non-dominated sorting genetic algorithms, Pareto envelope-based selection algorithm, non-dominated ranking genetic algorithm, and strength Pareto evolutionary algorithm. The results indicate that the last algorithm uses the dependency between decision variables to solve them efficiently and is the best type of MOEA both in terms of convergence criteria and solution diversity maintenance for the brachytherapy problems.

Keywords. Multi-objective optimization, Fuzzy logic, Evolutionary algorithms, Brachytherapy.

MSC. 68w50.

1 Introduction

Prostate cancer has been the most common cancer and the second leading cause of cancer death in men. Researchers using all different fields of knowledge and technology, not just medicine have tried to gradually increase their knowledge so that they can find more effective treatments. Cancer treatment management can include surgery, chemotherapy, or radiation therapy. Radiation therapy can be done in two ways, Teletherapy and Brachytherapy [3].

Although Teletherapy delivers external radiation by passing rays through the patient's body, brachytherapy involves the use of radiation sources to treat cancer by irradiating cancerous tissue from inside the patient's body and has the advantage of high-dose-rate sources consumption to reduce treatment sessions [7]. Because brachytherapy radiation is performed near the target volumes [8], the distribution of radiation doses should simultaneously be changed to adapt to the target volume and protect the surrounding healthy organs from the risk of radiation. In this paper, dose optimization in high dose rate brachytherapy has been studied for prostate cancer. However, it can also be used for other types such as low dose rate in which the radiation source has a lower power. Brachytherapy treatment planning is a naturally multi-objective problem with several conflicting criteria for dose-by-volume indices (DV). However, most optimization methods in the real world for brachytherapy treat the problem in a single-objective way and do not straight optimize the DV indices used in the clinic to evaluate the treatment plan. We discuss that the problem of brachytherapy treatment planning with the main DV criteria should be managed in a multi-objective way so that treatment plans are as consistent as possible with the clinical protocol and treatment planners can examine the possible trade-offs between DV.

This study was to develop a new fuzzy approach to the problem of high dose rate brachytherapy and also to optimize the dose distribution based on dosimetry criteria. The use of fuzzy logic itself has increased the accuracy of the mathematical model of the problem. It also developed an integer programming model with fuzzy constraints and programmed a bi-objective fuzzy optimization model to calculate the dose in high dose brachytherapy. It made the method more precise and included parameters such as the patient's physical ability and age and the doctor's preferences in the problem, which by itself increased the accuracy of the method for each patient. It would result in the improvement of the final consequence and more accuracy of the executive program of the brachytherapy method.

Various optimization methods could be used to obtain the optimal dose for brachytherapy. The most important and widely used one was the use of evolutionary algorithms [5, 16]. The evolutionary algorithms approach is an optimization method that is modeled based on the natural evolutionary process and its use in dose optimization in brachytherapy had better results than other optimization methods. Therefore, these algorithms that have much simpler and more understandable structures have been widely used for brachytherapy [14]. Previous research by Vander Laarse, R., & Bosman, P. A. [19] and Luong et al. [12] had shown that if the problem of brachytherapy was modeled for two goals, it would have better results. Nicolae et al. [17] showed that if the multi-objective evolutionary algorithm were used to optimize the dose rate for the brachytherapy model with high dose rate, it would have clinically acceptable results. However, the researchers have used different objectives to model the brachytherapy problem. For example, Beaulieu et al. [2] have developed an optimization program to minimize two goals. The first goal was to optimize the dose rate and another goal was to minimize areas where more than ten percent of the prescribed dose of radiation was irradiated.

Previous research by Vander Laarse, R., & Bosman, P. A. [19] and Luong et al. [12] had shown that if the problem of brachytherapy was modeled for two goals, it would have better results. Nicolae et al. [17] showed that if the multi-objective evolutionary algorithm trials were used to optimize the dose for this model, it would have clinically acceptable results. However, the researchers have used different purposes to model the brachytherapy problem. For example, Beaulieu et al. [2] have developed an optimization program to minimize two goals. The first goal was to optimize the dose and another goal was to minimize areas where more than ten percent of the prescribed dose of radiation was irradiated.

This paper used four multi-objective evolutionary algorithms based on the multi-objective model of the problem, compared the results of these four algorithms, and proposed the best one for this model. The results of this study can lead to the presentation and design of a precise plan for prostate cancer treatment using the brachytherapy method with a fuzzy model. In this paper, fuzzy logic has been used to design a fuzzy model for brachytherapy, which has more acceptable results from the clinical point of view compared to research by Kallis et al. [9] and also Luong et al. [10].

2 Theoretical Foundations of the Research

High dose rate brachytherapy is a modality of radiation therapy used for cancer treatment, in which the radiation source is placed within the body. The treatment goal is to give a high enough dose to the tumor while sparing nearby healthy tissue and organs (organs at risk). The most common criteria for evaluating dose distributions are dosimetry indices. For the tumor, such an index is the portion of the volume that receives at least a specified dose level (e.g. the prescription dose), while for organs at risk, it is instead the portion of the volume that receives at most a specified dose level. A treatment plan has been considered clinically acceptable as long as it adhered to the protocol used to demonstrate the lowest effective dose to healthy organs. It should be borne in mind, however, that a design that did not comply with this protocol could still be clinically acceptable [4]. The acceptable degree of deviation practically depended on many factors, including whether better designs were possible or not. A clinical protocol for brachytherapy treatment often included dose-by-volume indices (DV) of which the related criteria were defined as follows [3, 14].

A) V_d^o criterion specifies the magnitude of the accumulated volume of an organ o that receives the minimum level of radiation dose d (proportional to the target dose of the design).

B) D_v^o criterion which indicates how high the dose level of the radiation with the maximum accumulated volume v of an organ o should be.

Table 1: Dosimetry criteria for high dose rate brachytherapy treatment program (adopted from Bouter et al., [3])

Vesicles	Urethra	Rectum	Bladder	Prostate
$V_{80}> 95\%$	$D_{0.1cc}<110\%$	$D_{1cc}<78\%$	$D_{1cc}<86\%$	$V_{100}>95\%$
		$D_{2cc}<74\%$	$D_{2cc}<74\%$	$V_{150}<50\%$
				$V_{200}<20\%$

To prevent necrosis (tissue death) in the prostate due to overexposure, we assumed $V_{200}^{\text{prostate}}<20\%$ to indicate that the cumulative volume of the prostate covered with at least 200% of the dose should be less than 20% of the prostate. To prevent the excessive radiation of the rectum, we assumed $D_{1cc}^{\text{rectum}}<78\%$ to indicate that maximally one $cm^3$of rectum volume should be radiated less than 78% dose. The key part of the evaluation of the treatment plan included the calculation of DV index values and their comparison with the evaluation criteria in Table 1. The dose rate was calculated based on the TG-43 protocol that involved power and form of radiation source used for treatment, space among dose calculation points, and the situations of dwell positions [3]. Dosimetry indices and their acceptable range constituted the dosimetry criteria based on the TG-43 protocol (see Table 1 in [3]).

3 Implementation Details

This study focuses only on HDR brachytherapy because it is the most popular modality. This treatment is used either as a promotion treatment after an external beam radiation therapy series or as monotherapy. This paper used the data of 14 patients aged 50 to 74 years with a mean age of 62 years for the treatment of prostate cancer through brachytherapy from the Academic Medical Center, AMC Amsterdam, Netherlands (hospital involved in this study) [10, 14]. These data were provided to us to run different algorithms. It should be noted that these 14 patients did not undergo any previous treatment (chemotherapy, radiation therapy, etc.). These patients were selected in such a way that their prostate volume ranged from 23-103 cm^3. To compare brachytherapy treatment programs with high doses, we calculated Ir 192 irradiation dose rate with 13 (Gy) radiation dose based on standard protocol TG-43.

Initially, Computed Tomography scans or Magnetic Resonance Imaging was taken off the patient's pelvis and entered into the treatment planning software for use in treatment planning sessions. Then, the planners and specialists of brachytherapy (radiation oncologists, radiotherapists, and clinicians) specified the input catheters, target volumes, and organs at risk based on the medical images. Next, the exact size and location of the target volumes, 14-20 catheters, were entered the patient's body and reached the target volumes. Each of these catheters contained several dwell positions, usually 2.5 mm. When the radiation source was passing through the catheters, it could be activated at any of the dwell positions, remained for a certain period of time (Dwell time), performed radiation, and continued to the next active dwell position [10]. The more it remained there, the more the surrounding tissues were radiated. The next stage was the extraction of data and their use as input data for optimization. After designing and approving an acceptable treatment plan, catheters were inserted into the patient's body and connected to an Afterloader that controlled the movement of the radiation source. The radiation source passed through the catheters in such a way that it stopped at each dwell position for a predetermined period of time. Finally, after the treatment program was run, the radiation source was returned to Afterloader, and catheters were separated [5, 17].

4 Mathematical Model of the fuzzy Multi-Objective Optimization Problem

In this section, a new model with two contrasting objective functions has been developed for planning high dose rate brachytherapy. First of all, we need some definitions:

Definition 1. Multi-objective optimization (also known as multi-objective programming, vector optimization, multi-criteria optimization, multi-attribute optimization, or Pareto optimization) is an area of multiple criteria decision-making that is concerned with mathematical optimization problems involving more than one objective function to be optimized simultaneously.

Definition 2. Pareto efficiency or Pareto optimality is a situation where no action or allocation is available that makes one individual better off without making another worse off.

Definition 3. The Pareto front (also called Pareto frontier or Pareto set) is the set of all Pareto-efficient situations.

In multi-objective optimization, there does not typically exist a feasible solution that minimizes all objective functions simultaneously. Therefore, attention is paid to Pareto optimal solutions; that is, solutions that cannot be improved in any of the objectives without degrading at least one of the other objectives. In mathematical terms, a solution $x_1 \in X$ dominates the solution $x_2 \in X$, if for all i, $f_i(x_1) \leq f_i(x_2)$ and there exist at least one i in which $f_i(x_1) < f_i(x_2)$.

A solution $x^* \in X$ is called Pareto optimal if there does not exist another solution that dominates it.

Descriptions of infrastructures, parameters, and variables in this model were presented in Table 2 [20].

Considering the characteristics of the brachytherapy problem, we devised two fuzzy goals. The first goal was to maximize target coverage where O specified target volume in the following fuzzy inequation.

$$f_o(t_j) = \sum_{j=1}^{N_T} D_{oij} t_j \tilde{>} R_o + \delta, \quad \forall\, i \in G_o. \tag{1}$$

The second one was to reduce the radiation of organs at risk. It entered the problem like the following fuzzy inequality where S specified the organs at risk.

$$f_s(t_j) = \sum_{j=1}^{N_T} D_{sij} t_j \tilde{<} M_s - \varepsilon, \qquad \forall\, s, i \in G_s. \tag{2}$$

In both of the above constraints, t_j was the dwell time upon which the optimization should be done,

$$0 \leq t_j \leq 3600 \text{ second}, \qquad \forall j. \tag{3}$$

Therefore, the above inequalities should be converted from fuzzy to non-fuzzy by using the corresponding membership function and modeled mathematically. The membership function of inequality (1) was defined as follows.

$$\mu_o(t_j) = \begin{cases} 1, & f_o(t_j) \geq R_o + \delta, \\ \frac{f_o(t_j) - R_o}{\delta}, & R_o \leq f_o(t_j) \leq R_o + \delta, \\ 0, & f_o(t_j) \leq R_o. \end{cases} \tag{4}$$

Table 2: Parameters description of the high-dose-rate brachytherapy treatment plan

Phrase	Description
S	Set of limbs ($s \in S$, s is one of the Organs at Risk)
I	Set of dose-points i is an index of every dose-points ($i \in I$)
J	Set of dwell positions j is an index of every dwell position ($j \in J$)
G_s	Set of dose values in the S organ
P_{si}	Three-dimensional coordinates of the dose-point in G_s
N_s	Number of dose-points in G_s
T_j	Three-dimensional coordinates of position J (3D coordinates of dwell position points on catheters)
N_T	Number of dwell positions for the patient
D_{sij}	Transfer dose rate from T_j to P_{si}
D_{si}	Dose rate in P_{si}
R_s	Value of the tolerance threshold for G_s
M_s	Maximum dose for G_s
X_{si}	Indicator variable for P_{si}
V_S	Dosimetric index for G_s
L_s	Low limit for V_S
U_s	High limit for V_S

And the membership function of in equation (2) was defined as follows.

$$\mu_s(t_j) = \begin{cases} 1, & f_s(t_j) \leq M_s - \varepsilon, \\ 1 - \frac{f_s(t_j) - (M_s - \varepsilon)}{\varepsilon}, & M_s - \varepsilon \leq f_s(t_j) \leq M_s, \\ 0, & f_s(t_j) \geq M_s. \end{cases} \tag{5}$$

As it is evident, such a formulation still did not resolve the entire clinical protocol of the 9 DV indices in Table 1 [11, 12]. Furthermore, the findings of the above study did not allow planners to easily examine Pareto fronts and interpret non-dominant solutions [11, 19]. Therefore, the DV indices in the clinical protocol were divided into two groups as follows to address these shortcomings.

1. Target coverage: $V_{100}^{\text{prostate}}$, V_{80}^{vesicles},
2. Survival of organs at risk: $V_{200}^{\text{prostate}}$, $V_{150}^{\text{prostate}}$, D_{1cc}^{rectum}, D_{2cc}^{rectum}, D_{1cc}^{bladder}, D_{2cc}^{bladder}, $D_{0.1cc}^{\text{urethra}}$.

Here, a new formulation was proposed that directly used DV indices in the clinical protocol and FMCI[1] were calculated to maximize the target coverage group for the t treatment plan as follows.

$$\text{FMCI}(t) = \sum_{j=1}^{N_T} (D_{oij} t_j) - \delta \times \mu_o(t_j) - R_o. \tag{6}$$

One of the problem's objectives was to maximize the FMCI value. Based on the threshold of DV indices in the target coverage group, this value should be positive. Positive values indicated that both

clinical protocol requirements $V_{100}^{\text{prostate}}>95$ and $V_{80}^{\text{vesicles}}>95$ were achieved. Negative values indicated that at least one of the target volumes received a lower dose.

When it was aimed to less damage at-risk organs, the FMSI[2] value was calculated as follows for the t treatment plan.

$$\text{FMSI}\,(t) = \mu_s\,(t_j) \times \varepsilon + f_s\,(t_j) - M_s. \tag{7}$$

Another objective was to reduce the amount of FMSI. Negative values indicated that all D_v^o indices have not exceeded their threshold and all the needs of the D_v^o index in Table 1 has been met. Positive values indicated that at least one index has exceeded its threshold.

The high dose rate brachytherapy problem model is designed as follows:

$$\begin{aligned} \text{Max} \quad & \text{FMCI}\,(t) = \textstyle\sum_{j=1}^{N_T} (D_{oij} t_j) - \delta \times \mu_o\,(t_j) - R_o, \\ \text{Min} \quad & \text{FMSI}\,(t) = \textstyle\sum_{j=1}^{N_T} D_{sij} t_j + \mu_s\,(t_j) \times \varepsilon - M_s, \end{aligned}$$

such that

Vesicles	Urethra	Rectum	Bladder	Prostate
$V_{80}> 95\%$	$D_{0.1cc}<110\%$	$D_{1cc}<78\%$	$D_{1cc}<86\%$	$V_{100}>95\%$
		$D_{2cc}<74\%$	$D_{2cc}<74\%$	$V_{150}<50\%$
				$V_{200}<20\%$

Any treatment plan could be evaluated with these two conflicting goals (FMSI and FMCI). Doctors can change two parameters (δ, ε) in the brachytherapy model according to the physical ability and strength of the patient. They may consider them equal to zero. A treatment plan met all the criteria of Table 1 clinical protocol if FMSI≤ 0 and FMCI$\geq$ □0. All DV indices were considered separately without the need to use a complex model having 9 separate objectives. In addition, the formulation of the problem was similar to the practical planning process because planners generally tried to adjust the treatment plan iteratively, so they first improved the DV index, which was the most limiting problem [18]. Consequently, multi-objective evolutionary algorithms have been used to optimize this bi-objective model of the brachytherapy problem.

5 Multi-Objective Evolutionary Algorithms (MOEA)

Multi-objective optimization methods are looking for optimizing conflicting goals or goals that were in some way in competition with each other and provided a set of optimal solutions instead of just one. The set of optimal solutions, also called Pareto-optimal, included solutions that considered all the goals with no superiority over each other. However, better results had been obtained from these algorithms for multi-objective problems compared to other methods [7, 12, 16].

Different types of multi-objective evolutionary algorithms had been used to optimize the brachytherapy planning problem [12, 19, 20]. In this paper, the four robust algorithms, applied and of which the results were compared, including Non-Dominant Sorting Genetic Algorithm II (NSGA-II), Non-Dominant Ranking Genetic Algorithm (NRGA), and Strength Pareto Evolutionary Algorithm II (SPEA-II) and

Pareto Envelope Based Selection Algorithm II (PESA-II). The operators we used in four evolutionary algorithms include the roulette wheel selection operator, the uniform recombination operator, and the real value mutation operator. In this research population size was 300, and the mutation rate was 0.003.

5.1 Evolutionary Algorithm: The NSGA-II

NSGA-II has been one of the most popular multi-objective optimization algorithms with three special features: a non-dominant fast sorting approach, a fast crowding distance estimation method, and a simple crowding comparison operator. This algorithm has often been used for comparative purposes at the time of new multi-objective algorithms introduction. The choice of a solution in NSGA-II was based on its non-dominant rank and the amount of crowding distance. The next generation population was selected from a set of parent and children solutions based on their fitness values so that solutions with better non-dominant ranking and less crowded distance were considered [6, 14]. In NSGA-II, first, individuals are selected from primary front. When this choice was made, there will be a situation where a front needs to be broken because not all individuals are allowed to survive. On this front, solutions are selected based on crowding distance.

5.2 Evolutionary algorithm: The PESA-II

PESA-II used an internal and external population archive simultaneously similar to most evolutionary algorithms. In the internal archive, the solutions obtained from the recombination and mutation operators were stored and the non-dominated solutions of each generation were kept in the external archive [19]. In this algorithm, a network segmentation of the target space had been used to create diversity. The number of solutions in a polyhedral space was defined as the density of that space. Although most methods of evolutionary algorithms like PESA performed the evolution process individually-based, it was performed region-based in PESA-II. That is, a polyhedral space was initially selected, then a member was randomly chosen from this polyhedral space to apply genetic operators. More crowded polyhedral spaces had a smaller share than less crowded polyhedral. Pareto Envelope-based Selection Algorithm II (PESA-II) is a multi-objective evolutionary optimization algorithm, which uses the mechanism of a genetic algorithm together with selection based on the Pareto envelope. The PESA-II uses an external archive to keep the approximate Pareto solutions.

5.3 Evolutionary algorithm: The NRGA

In this paper, the NRGA algorithm was developed, and an external population (EP) was presented to store all the non-dominated solutions and create diversity in the population. All found non-dominated solutions were stored in EP and updated at the end of each generation compared to the current population of non-dominated solutions. Excessively non-dominated solutions were removed from EP to prevent interference. A solution was considered extra when the intervals of all its variables were present in the

intervals of the variables of another solution. In addition, the size of EP was not limited to obtaining a greater number of Pareto front solutions. It helped the method convergence to be controlled better. NRGA is a new multi-objective genetic algorithm to find feasible Pareto front solutions. NRGA is similar to NSGA-II with the difference that in the selection operation the roulette wheel strategy. In NRGA, a fitness value representing rank is assigned to each individual in the population.

5.4 Evolutionary algorithm: The SPEA-II

The SPEA and the SPEA-II algorithms were efficient algorithms that utilized an external archive to store the non-dominated solutions obtained during the algorithm search. The SPEA algorithm had shortcomings in calculating fitness values â, and also, did not include a secondary criterion for comparing non-dominated solutions. Therefore, [15] a secondary version of this algorithm that eliminated the previous weaknesses. This algorithm used two internal and external population archives. The external archive was empty at the beginning. After evaluating the target functions of the internal population, all non-dominated solutions of the current population of the internal archive were transferred to the external archive was transferred to the next population in the next iteration. In each iteration, if the number of members of the external archive was less than the size predetermined for the algorithm, the non-dominated solutions of the internal archive of that iteration and the external archive of the previous iteration would be applied to complete the rest of the population. SPEA-II is a multi-objective optimization algorithm, which has few parameters, fast converging speed, good strength, and orderly distributed solution sets.

6 Results

This paper investigates the problem of high-dose brachytherapy and uses four multi-objective evolutionary algorithms, i.e., NSGA-II, PESA -II, SPEA-II, and NRGA. We are going to evaluate their performance and then, select the best one according to data obtained from 14 patients with prostate cancer with a mean age of 62. These patients were selected to have a wide range of prostate volumes between 23-103 cm^3.

Target volumes in the treatment of prostate cancer were prostate and (part of) seminal vesicles. Organs at risk organs included the bladder, rectum, and urethra. While it was taken into account that the number of catheters depended on the size and exact location of the target volumes, 14-20 were entered the patient's body to reach the target volumes. After catheters implantation, a pelvic scan (CT) was taken from each patient. The specification of coordinates of each point within the target volume was made possible by uploading those images to the treatment design software. It helped us to apply the coordinates in evolutionary algorithms. The larger the set of D dose calculation points was, the greater the accuracy of the DV index was. In this paper, set D was considered to be equivalent to 2000 points (i.e. 400 points per target volume), which made the computational accuracy better than the previous works in the literature. Each of the four algorithms (NSGA-II, NRGA), SPEA-II, and PESA-II) were run independently. Since the formulation of the model designed in this paper for the problem of high-

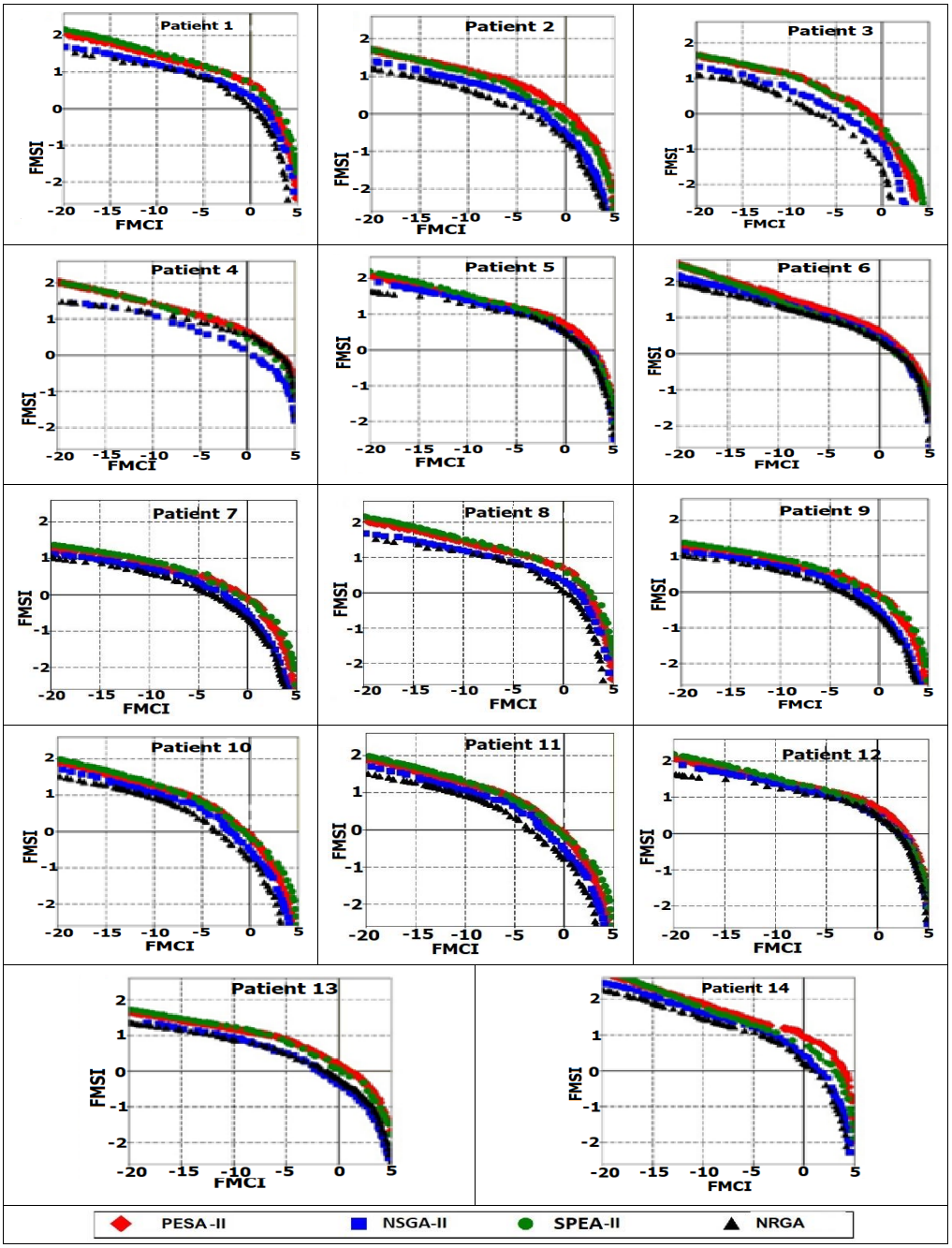

Figure 1: Comparison of four algorithms and informed decision-making based on the Pareto fronts. The FMCI and the FMSI mean Fuzzy Model Coverage Index and Fuzzy Model Survival Index respectively.

dose-rate brachytherapy had two purposes, Pareto fronts could be easily drawn, treatment planners could easily put different opinions together, and look at how one goal should be used to improve another goal. A conscious decision-making strategy was the main goal of the Pareto Front and was shaped by the

Table 3: The amount of target coverage in the duration of radiation, which is calculated by four different algorithms

PESA-II	NSGA-II	NRGA	SPEA-II	Patient ID
0.960089 (800 second)	0.958945 (857 second)	0.950003 (953 second)	0.945372 (816 second)	1
0.9600133 (897 second)	0.959127 (995 second)	0.9624 (1301 second)	0.950007 (1023 second)	2
0.969002 (925 second)	0.9412 (986 second)	0.9571 (944 second)	0.950288 (1441 second)	3
0.96 (907 second)	0.960108 (928 second)	0.960108 (1098 second)	0.953215 (1287 second)	4
0.960000 (1100 second)	0.950000 (2400 second)	0.948017 (2400 second)	0.940056 (1302 second)	5
0.960256 (1753 second)	0.959000 (2160 second)	0.949879 (2100 second)	0.956900 (1900 second)	6
0.960002 (1296 second)	0.946321 (1393 second)	0.94 (1493 second)	0.955814 (1445 second)	7
0.959000 (993 second)	0.95 (1400 second)	0.95 (1403 second)	0.947947 (1214 second)	8
0.955743 (972 second)	0.95 (1065 second)	0.95 (1283 second)	0.95 (1411 second)	9
0.950537 (923 second)	0.950006 (1090 second)	0.950320 (968 second)	0.949980 (1297 second)	10
0.95090 (1109 second)	0.95 (1324 second)	0.948250 (1400 second)	0.950187 (1348 second)	11
0.954823 (1200 second)	0.952718 (1352 second)	0.952718 (1200 second)	0.953984 (1228 second)	12
0.96 (1152 second)	0.952548 (1272 *second*)	0.952548 (1272 second)	0.95 (1493 second)	13
0.952548 (986 second)	0.950108 (1100 second)	0.950108 (1085 second)	0.949015 (1287 second)	14

solutions to the problem.

Figure 1 shows the Pareto fronts, which were the result of 20 independent runs of each MOEA. As the results show, the PESA-II obtains Pareto fronts from higher-quality treatment programs faster than both the NSGA-II and the NRGA. Table 4 confirms that the PESA-II was more compatible than other algorithms. In all cases, it was seen that the PESA-II shows more concentrated non-dominant solutions than the other MOEAs.

Table 3 showed the amount of target coverage during the irradiation period and the duration of irradiation in seconds in parentheses, calculated by four different algorithms NSGA-II, NRGA, SPEA-II, and PESA-II. It indicated that the amount of target coverage should include the desired coverage of more than 95% of the tumor volume. Therefore, according to the obtained results, the PESA-II algorithm had coverage of more than 95% for all 14 patients studied. In the column related to the NSGA-II algorithm, only two patients with numbers 3 and 7 had coverage below 95%, and in the column related to the NRGA algorithm, four patients with numbers 5, 6, 7, and 11 had coverage below 95%. In the column related to the SPEA-II algorithm, five patients from 14 had coverage below 95%. The highest coverage was for

patient number 3. It was obtained by the PESA-II algorithm and equated to 0.969002 in the duration of radiation in 925 seconds.

The standard deviation (SD) of the solutions obtained from 20 independent runs of different NSGA-II, NRGA, SPEA-II, and PESA-II algorithms are given in Table 4. It indicates that SDs obtained from the PESA-II are lower than those of the other MOEAs. Therefore, this algorithm's solutions are closer to the desired level and statistically significant (see Table 3).

Table 4: Standard deviation obtained from 20 times execution of four different algorithms

Patient ID	NSGA-II	NRGA	SPEA-II	PESA-II
1	0.001196	0.004102	0.001750	0.000971*
2	0.000929	0.002564	0.001024	0.000993*
3	0.001601	0.003331	0.000812	0.000451*
4	0.000889	0.007444	0.001528	0.000522*
5	0.000829	0.001978	0.001737	0.000687*
6	0.002493	0.005193	0.001157	0.000857*
7	0.000933	0.005809	0.000711	0.000629*
8	0.001054	0.012791	0.000955	0.000840*
9	0.000829	0.001978	0.000737	0.000987*
10	0.000933	0.005809	0.000711	0.000629*
11	0.002696	0.005102	0.001755	0.000789*
12	0.000949	0.002575	0.001046	0.000988*
13	0.001626	0.003331	0.000812	0.000672*
14	0.000889	0.007444	0.001528	0.000822*

Based on the results obtained, the PESA-II algorithm achieved the coverage of more than 95% for all 14 patients studied. This demonstrates that the PESA-II evolutionary algorithm had the best results and performance compared to other multi-objective evolutionary algorithms. These findings reveal that PESA-II is a promising multi-objective evolutionary algorithm for real-world applications, particularly for problems such as high-dose brachytherapy treatment planning.

7 Discussion and Conclusion

Brachytherapy treatment planning presents a naturally multi-objective problem with several conflicting criteria for DV indices. However, most optimization methods in the real world treat the problem in a single-objective way and do not optimize the DV indices used in the clinic to evaluate the treatment plan. In this paper, we argue that the problem of brachytherapy treatment planning with the main DV criteria should be managed in a true multi-objective way, allowing treatment plans to be as consistent as possible with the clinical protocol, and for treatment planners to examine the possible trade-offs between DV. We

have used fuzzy logic to design a fuzzy model for brachytherapy, which results in better solutions from a clinical point of view compared to previous research. In both studies, the amount of target coverage was close to 95% and for none of the patients, the amount of target coverage was more than 95%. In our research, the PESA-II algorithm achieved coverage of more than 95% for all 14 patients studied. We developed a model of brachytherapy for each patient, using two parameters (δ, ε) in the brachytherapy model, which doctors can adjust according to the physical ability and strength of the patient, leading to better solutions from a clinical point of view for each patient. The results demonstrate that the PESA-II algorithm outperforms other algorithms, including NSGA-II, NRGA, and SPEA-II, in obtaining higher quality brachytherapy treatment plans with much higher compatibility and less runtime. The PESA-II evolutionary algorithm is a promising multi-objective evolutionary algorithm for real-world applications, especially for problems such as high dose brachytherapy treatment planning, which is an area that requires further research and broader programs.

Declarations

Availability of supporting data

All data generated or analyzed during this study are included in this published paper.

Funding

This study received no funds, grants, or other financial support.

Competing interests

The authors declare no competing interests that are relevant to the content of this paper.

Authors' contributions

The main manuscript text is collectively written by all authors.

References

[1] Azizi, S., Soleimani, R., Ahmadi, M., Malekan, A., Abualigah, L., Dashtiahangar, F. (2022). "Performance enhancement of an uncertain nonlinear medical robot with the optimal nonlinear robust controller", Computers in Biology and Medicine, 146, 105567.

[2] Beaulieu, L., Al-Hallaq, H., Rosen, B.S., Carlson, D.J. (2022). "Multi-criteria optimization in Brachytherapy", International Journal of Radiation Oncology, Biology, Physics, 114(2), 177-180.

[3] Bouter, A., Alderliesten, T., Witteveen, C., Bosman, P.A. (2017). "Exploiting linkage information in real-valued optimization with the real-valued gene-pool optimal mixing evolutionary algorithm", Proceedings of the Genetic and Evolutionary Computation Conference, 705-712.

[4] Bouter, A., Luong, N. H., Witteveen, C., Alderliesten, T., Bosman, P.A. (2017). "The multi-objective real-valued gene-pool optimal mixing evolutionary algorithm", Proceedings of the Genetic and Evolutionary Computation Conference, 537-544.

[5] De Boeck, L., Belien, J., Egyed, W. (2014). "Dose optimization in high-dose-rate brachytherapy: A literature review of quantitative models from 1990 to 2010", Operations Research for Health Care, 3(2), 80-90.

[6] Deb, K., Pratap, A., Agarwal, S., Meyarivan, T.A.M.T. (2002). "A fast and elitist multi objective genetic algorithm: NSGA-II", IEEE Transactions on Evolutionary Computation, 6(2), 182-19.

[7] Dickhoff, L.R., Kerkhof, E.M., Deuzeman, H.H., Creutzberg, C.L., Alderliesten, T., Bosman, P.A. (2022). "Adaptive objective configuration in bi-objective evolutionary optimization for cervical cancer Brachytherapy treatment planning", arXiv preprint arXiv: 2203.08851.

[8] Dinkla, A.M., van der Laarse, R., Kaljouw, E., Pieters, B.R., Koedooder, K., van Wieringen, N., Bel, A. (2015). "A comparison of inverse optimization algorithms for HDR/PDR prostate brachytherapy treatment planning", Brachytherapy, 14(2), 279-288.

[9] Kallis, K., Mayadev, J., Covele, B., Brown, D., Scanderbeg, D., Simon A., Meyers S.M. (2021). "Evaluation of dose differences between intracavitary applicators for cervical brachytherapy using knowledge-based models", Brachytherapy, 20(6), 1323-1333.

[10] Luong, N.H., Alderliesten, T., Bel, A., Niatsetski, Y., Bosman, P.A. (2018). "Application and benchmarking of multi-objective evolutionary algorithms on high-dose-rate brachytherapy planning for prostate cancer treatment", Swarm and Evolutionary Computation, 40, 37-52.

[11] Luong, N.H., Alderliesten, T., Pieters, B.R., Bel, A., Niatsetski, Y., Bosman P.A. (2019). "Fast and insightful bi-objective optimization for prostate cancer treatment planning with high-dose-rate brachytherapy", Applied Soft Computing, 84, 105681.

[12] Luong, N.H., Bouter, A., Van Der Meer, M.C., Niatsetski, Y., Witteveen, C., Bel, A., Bosman, P.A. (2017). "Efficient, effective, and insightful tackling of the high-dose-rate brachytherapy treatment planning problem for prostate cancer using evolutionary multi-objective optimization algorithms", Proceedings of the Genetic and Evolutionary Computation Conference Companion, 1372-1379.

[13] Maree, S.C., Bosman, P.A.N., van Wieringen, N., Niatsetski, Y., Pieters, B.R., Bel, A., Alderliesten, T. (2020). "Automatic bi-objective parameter tuning for inverse planning of high-dose-rate prostate brachytherapy", Physics in Medicine & Biology, 65(7), 075009.

[14] Maree, S.C., Luong, N.H., Kooreman, E.S., van Wieringen, N., Bel, A., Hinnen, K.A., Alderliesten, T. (2019). "Evaluation of bi-objective treatment planning for high-dose-rate prostate brachytherapy-A retrospective observer study", Brachytherapy, 18(3), 396-403.

[15] Mohammadi, M., Nazif, H., Soltanian, F. (2022). "Optimization of the fuzzy model of high dose brachytherapy problem for the treatment of prostate cancer using evolutionary algorithms", Razi Journal of Medical Science, 12(28), 7043-2228.

[16] Mountris, K.A., Visvikis, D., Bert, J. (2019). "DVH-based inverse planning using Monte Carlo dosimetry for LDR prostate brachytherapy", International Journal of Radiation Oncology* Biology* Physics, 103(2), 503-510.

[17] Nicolae, A., Morton, G., Chung, H., Loblaw, A., Jain, S., Mitchell, D., Ravi, A. (2017). "Evaluation of a machine-learning algorithm for treatment planning in prostate low-dose-rate brachytherapy", International Journal of Radiation Oncology Biology Physics, 97(4), 822-829.

[18] Pu, G., Jiang, S., Yang, Z., Hu, Y., Liu, Z. (2022). "Deep reinforcement learning for treatment planning in high-dose-rate cervical brachytherapy", Physica Medica, 94, 1-7.

[19] Vander Laarse, R., Bosman, P.A. (2017). "Dose optimization", Emerging Technologies in Brachytherapy, 79-98.

[20] Vander Meer, M.C., Pieters, B.R., Niatsetski, Y., Alderliesten, T., Bel, A., Bosman, P.A. (2018). "Better and faster catheter position optimization in HDR brachytherapy for prostate cancer using multi-objective real-valued GOMEA", Proceedings of the Genetic and Evolutionary Computation Conference, 1387-1394.