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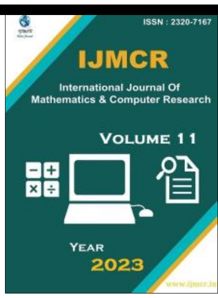

Radiotherapy Evolutionary Algorithm Further 2d Pareto-Multi Objective Optimization with Biological Effective Model for Head-Neck Cancer Hyperfractionated Treatment

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ABSTRACT

Constrained algorithms for BED model (Biological Effective Dose) in Head and Neck tumors Hyperfractionated TPO optimized with Pareto-Multiobjective (PMO) Genetic Algorithms (GA) software are obtained. The mathematical method for constrained GA is applied for a number of series of Pareto Functions. Results demonstrate PMO-AI imaging process sequences and extensive numerical values of PMO Head and Neck cancer parameters. Comparison and review with simple constrained GA Optimization is presented. Improved RT Head and Neck cancer TPO, and tumors in general for Fractional-dose photon dose delivery are explained in brief.

KEYWORDS: Pareto-Multiobjective Optimization (PMO), Mathematical Methods (MM), Biological Models (BM), Radiation Therapy (RT), Initial Tumor Clonogenes Number Population (N_0), Effective Tumor Population Clonogenes Number ($N_{Effective}$), Linear Quadratic Model (LQM), Integral Equation (IE), Tumor Control Probability (TCP), Normal Tissue Complications Probability (NTCP), Biological Effective model (BED), Tumor Control Cumulative Probability (TCCP), Radiation Photon-Dose (RPD), Nonlinear Optimization, Radiotherapy Treatment Planning Optimization (TPO), Source-Surface Distance (SSD), Software Engineering Methods, Radiation Photon-Dose, Attenuation Exponential Factor (AEF), Nonlinear Optimization, Radiotherapy Wedge Filter (WF), Anisotropic Analytic Model (AAA), Fluence Factor (FF), Omega Factor (OF), Treatment Planning Optimization (TPO), Breast Tumor (BT), Artificial Intelligence (AI), Pareto-Multiobjective Optimization (PMO), Genetic Algorithms (GA) .

I. INTRODUCTION

The objective of the contribution is apply Artificial Intelligence with Constrained Genetic Algorithms on radiotherapy BED model for Head and Neck tumors [87,88].

Nonlinear GA-PMO engineering software was improved with matrix algebra constraints and designed in programs/patterns for PMO-BED models. A review of previous research with additional numerical results for two types of selected simple-constrained BED model parameters is supplemented. Thorough GA hyperfractionated radiotherapy TPO findings are presented both in 2D graphics and dataset. The matrix-algebra constraints and the extensive comparison among several parameters selection constitutes the innovation of the study. At 2D graphics, Pareto Optimal choice is sharply indicated.

In brief, a constrained extension of previous Nonlinear Pareto-Multiobjective GA optimization was performed for radiotherapy BED models in Head and Neck tumors [87,88]. Applications for radiotherapy TPO and future improvements in RT are explained in short.

II. MATHEMATICAL AND COMPUTATIONAL METHODS

The Pareto-Multiobjective Optimization foundation $BED_{Effective}$ model was set in software, [24,88]. Parameters intervals are detailed in Tables 1-3. Algorithms 1-2 and Equation 1 set the formulas and constraints [85-88]. Two different PMO optimization programming series are presented with different parameter intervals magnitudes, Tables 1-3. This BED model constitutes the fundamentals for fractionate radiotherapy, although there are variations among authors [20-25]. Formulation is based on previous studies computational software [1-21,85-88]. The algorithm that was set, with Chebyshev L_1 norm, [Algorithm 1], reads,

The general 2D Pareto-Multiobjective problem, [Algorithm-1] with unequality constraints, either linear or nonlinear, reads,

$$\begin{aligned}&\text{Minimize,}\\&F(\vec{x})=\left(f_1(\vec{x}),f_2(\vec{x}),\ldots.f_N(\vec{x})\right),\\&\text{subject to,}\\&K_i(\vec{x})\geq 0\text{ , for } i=1,\ldots..M\end{aligned}$$

(Algorithm 1)

where

$F(x)$: Main function to be optimized.

$f_i(x)$: Every function of same variables (x).

$K_i(x)$: Constraints functions such as in general $N \neq M$.

BED model has been adapted on the difficulty to obtain an stable and reliable T_{Pot} magnitude. PMO in Head and Neck, [24,88] tumors simplest BED model reads,

$$\begin{aligned}&\text{Chebyshev } L_1 \text{ Optimization for,}\\&BED_{Effective}=k\,d\left[1+\frac{d\times\beta}{\alpha}\right]-\ldots\\&\ldots-\frac{Ln(2)}{\alpha}\left[\frac{T_{Treatment}-T_{Delay}}{T_{Potential}}\right];\end{aligned}$$

(1)

where

k : Dose fraction number for hyperfractionated RT protocol. [20-25] .
Software pattern set [35 , 45] Fractions.
d : Dose fraction for hyperfractionated RT protocol. [20-25] .
Software pattern set [1 , 2.2] Gy.
α : Clonogen Head and Neck tumor radiosensitivity parameter [0.19 , 0.61]. [20-25] .
β : Clonogen Head and Neck tumor radiosensitivity parameter [0.0581] . [20-25] .
$T_{Treatment}$: Total time for radiation dose delivered. Software pattern set [22 , 55] days. [20-25] .
T_{Delay} : Total standard repopulation delays for RT. Software set [21] days. [20-25] .
$T_{Potential}$: Total standard Head and Neck cancer potential repopulation factor.
Software pattern set [3.5 , 4.5] days. [20-25] .

Equation 1 [developed for software patterns, Casesnoves, 2022, based on classical author’ BED model, mainly Fowler] .-Head and Neck PMO algorithm [1-21,85-88] implemented in software. The intervals for optimization parameters in software are detailed. It is an improvement from a series of previous research in radiotherapy.

During programming trials it was found that precision was increased by using algebraic constraints in main patterns. Therefore, the constraints algebraic algorithm developed for Pareto-Multiobjective problem, [Algorithm-2, Casesnoves 2023] reads,

$$\begin{aligned}&\text{Constra int s,}\\&\text{For Pareto Functions}\quad i=1,2,\\&\text{and lower}-\text{upper lim its of}\\&\text{optimizati on parameters,}\\&S_{Lower}\leq K_i+d_i+T_{(Treatment)i}\leq S_{Upper}\ ,\end{aligned}$$

(Algorithm 2)

where

S_{LOWER} : Summatory of all lower constraints for parameters [K, d, T].

S_{UPPER} : Summatory of all upper constraints for parameters [K, d, T].

K_i : Dose fraction number parameter for [i = 1, 2] .

d_i : Dose fraction magnitude parameter for [i = 1, 2] .

$T_{TREATMENT}$: Treatment time magnitude parameter for [i = 1, 2] .

The programming method(s) applied for this research are based on previous papers [1-20,24,74,88]. For GA-PMO modeling, Equation 1 and Algorithms 1-2 are implemented on 2D programs. However, Algorithm 2 was programmed with constraints functions. Table 1 shows Constrained GA Optimization selected parameters according to Algorithm 2. Tables 2-3 show the 2D GA-PMO simple programming method variations to obtain acceptable better calculations, and 2D Graphical Optimization processing images, error determinations, and get good approximations for the PMO-BED model. For simple simulations, the difference between the first and second simulations is given by Dose Fraction and Dose Interval parameters, Tables 2-3.

CONSTRAINED GENETIC ALGORITHM OPTIMIZATION PARAMETER INTERVAL FOR HEAD AND NECK TUMOR ALGORITHM 2 [References at Tables 2-3]	
Parameter	**Magnitude Interval**
Constraints Interval Algorithm 2	[77.0 , -56.0] [Note that there are two linear inequality constraints in matrix]
Dose Fraction Number	[25 , 35]
Dose Fraction Magnitude	[1 , 2] Gy
$T_{Treatment}$	[30 , 40] Days
T_{Delay}	21 Days
$T_{Potential}$	[3.5 , 4.5]
α [Gy^{-1}] β [Gy^{-2}] Parameters	[0.19 , 0.61] Gy^{-1} [0.0581] Gy^{-2} fixed
Dose Interval in Objective Function	45 Gy for Pareto F 1 function 55 Gy for Pareto F 2 function

Table 1.-Matlab Constrained GA optimization dataset. Note the values of Matlab constraints matrix in Algorithm 2. In Matlab and other similar systems, the constraints can be set as a matrix equation. As in Tables 2-3, the simulations were done with approximate numerical-experimental data from several authors. $T_{Potential}$ in Head and Neck cancer is about 4 days as average. Simulation dataset from [20-25,74,75,80,81,85-88] .

GENETIC ALGORITHM ARTIFICIAL INTELLIGENCE OPTIMIZATION PARAMETER INTERVAL FOR HEAD AND NECK TUMORS FIRST GA OPTIMIZATION		
PARAMETER	**MAGNITUDE INTERVAL**	**ADDITIONAL**
Dose fraction number	[32, 40]	Usual protocol in literature [1-21,74-86].
Dose fraction magnitude	[1.2,1.5] Gy	Usual protocol in literature [1-21,74-86]. Set with intervals according to different criteria.
$T_{Treatment}$ (total)	[22,52] Days	Usual protocol in literature [1-21,74-86]. Set with intervals according to different criteria. The RT treatment varies according to weekends breaks, secondary effects, patient circumstances, etc.
T_{Delay}	[20,30] Days	Usual protocol in literature [1-21,74-86]. Set with intervals according to different criteria.
$T_{Potential}$ α [Gy^{1}] , β [Gy^{2}] radiobiological parameters	[3.5, 4.5] Days [calculated from head and neck cancer experimental α = 0.40 ±0.21 Gy^{-1} , β= 0.0581 Gy^{-2}]	Usual protocol in literature [1-21,74-86]. Set with intervals according to different criteria.
Dose interval in Objective Function	47 Gy for Pareto F 1 function 55 Gy for Pareto F 2 function	Usual protocol in literature [1-21,74-86]. Set with two total dose Pareto Functions according to different criteria.

Table 2.-First GA optimization dataset. The simulations were done with approximate numerical-experimental data from several authors. $T_{Potential}$ in head and neck cancer is about 4 days as average. Simulation dataset from [20-25,74,75,80,81,85-88] .

GENETIC ALGORITHM ARTIFICIAL INTELLIGENCE OPTIMIZATION PARAMETER INTERVAL FOR HEAD AND NECK TUMORS SECOND GA OPTIMIZATION		
PARAMETER	**MAGNITUDE INTERVAL**	**ADDITIONAL**
Dose fraction number	[35, 50]	Usual protocol in literature [1-21,74-88].
Dose fraction magnitude	[1.2 , 2.0] Gy	Usual protocol in literature [1-21,74-88]. Set with intervals according to different criteria.
$T_{Treatment}$ (total)	[22,52] Days	Usual protocol in literature [1-21,74-88]. Set with intervals according to different criteria. The RT treatment varies according to weekends breaks, secondary effects, patient circumstances, etc.
T_{Delay}	[20,30] Days	Usual protocol in literature [1-21,74-88]. Set with intervals according to different criteria.
$T_{Potential}$ α [Gy^{1}] , β [Gy^{2}] radiobiological parameters	[3.5, 4.5] Days [calculated from head and neck cancer experimental α = 0.40 ±0.21 Gy^{-1} , β= 0.0581 Gy^{-2}]	Usual protocol in literature [1-21,74-88]. Set with intervals according to different criteria.
Dose interval in Objective Function	35 Gy for Pareto F 1 function 50 Gy for Pareto F 2 function	Usual protocol in literature [1-21,74-88]. Set with two total dose Pareto Functions according to different criteria.

Table 3.-The second simulations were done with approximate numerical-experimental data from several authors. $T_{Potential}$ is taken [3.5, 4.5] days.

III. OPTIMIZATION GRAPHICAL RESULTS

2D Graphical results for first constrained optimization are shown in Figures 1-2. The simple constrained optimization results are presented in Figures 3-7. In general, constrained optimization with algorithm 2 shows be better than simple constrained one. However, differences are not very high.

Algebraic constrained Model Results

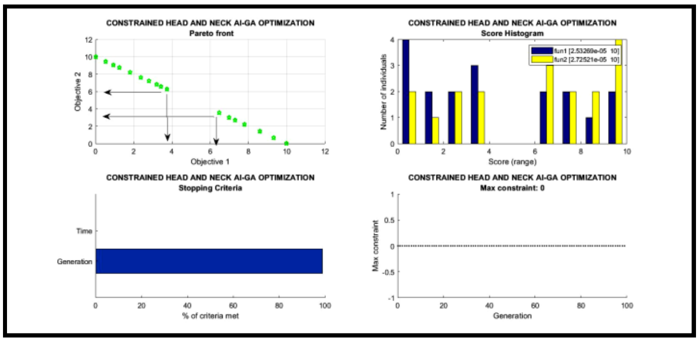

Figure 1.-Constrained optimization Multifunctional GA 2D graph (100 generations). This is the most important graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f 1 and f 2 show low residuals. Therefore, results are acceptable in first optimization for function 1 and function 2 . Enhanced in Appendix.

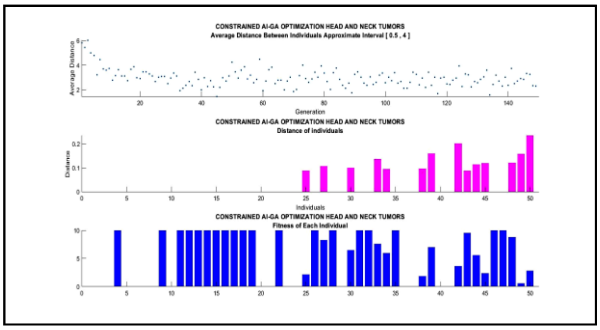

Figure 2.-Constrained optimization Multifunctional GA 2D graph (100 generations). This is the most important graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f 1 and f 2 show low residuals.

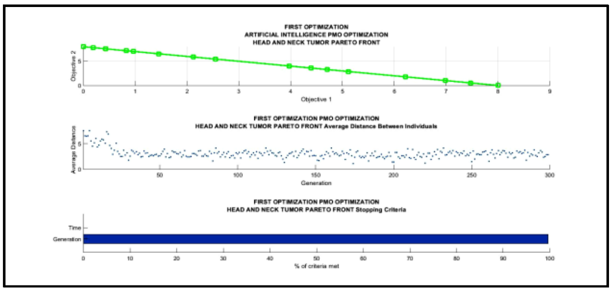

Figure 3.-First optimization Multifunctional GA 2D graph. This is the most important graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f 1 and f 2 show low residuals. Therefore, results are acceptable in first optimization for function 1 and function 2 . The number of points on the Pareto front was: 18. The number of generations was : 300.

Review Simple Constrained 2D Simulations Model Results

Figures 3-7 show PMO results. Tables 4-6 present details of both numerical PMO optimization results. Table 4 shows the constrained optimization results (100 generations, optimal fraction dose (d ϵ [1.6 , 1.7] Gy). The most important to validate the results are those ones that show the Pareto Front. Average distance among generation individuals, stopping criteria, are also important. The other details are complementary and shown in additional 2D charts for first and second PMO optimization. For simple constrained optimization maximum number of generations selected was 300-800. Score histograms also prove the validity of the software and PMO done. Running time for both processes is about 2-4 minutes. Numerical results, Tables 5-6, resume for PMO in simple constrained optimization BED model. For this simple constrained optimization dose fraction magnitude should be less than 2 Gy approximately [19-21,75,85-88].

Review PMO-GA 2D Imaging Processing First Simple Constrained Optimization Results

First optimization results are shown in Figures 3-4, Table 5. Pareto function 2 results are more accurate than Pareto function 1. Every chart of Artificial Intelligence GA is detailed with further explanations.

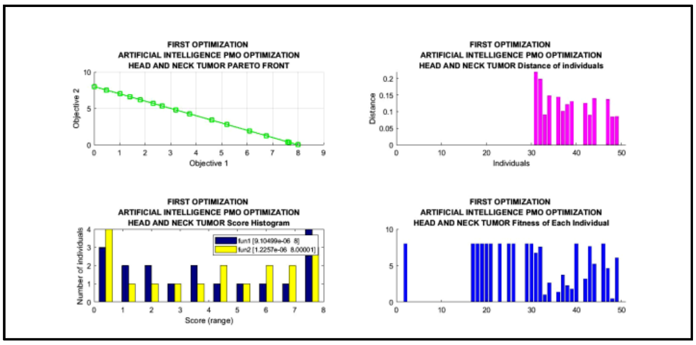

Figure 4.-First optimization Multifunctional GA 2D graph. This is the complementary multifunctional graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f 1 and f 2 show low residuals. Therefore, results are acceptable in first optimization for function 1 and function 2 The number of points on the Pareto front was: 18. The number of generations was : 300.

Review PMO-GA 2D Imaging Processing Second Simple Constrained Optimization Results

Second optimization results are shown in Figures 5-7, Table 6. Pareto function 2 results be more accurate than pareto function 1. Every chart of Artificial Intelligence GA is detailed with further explanations.

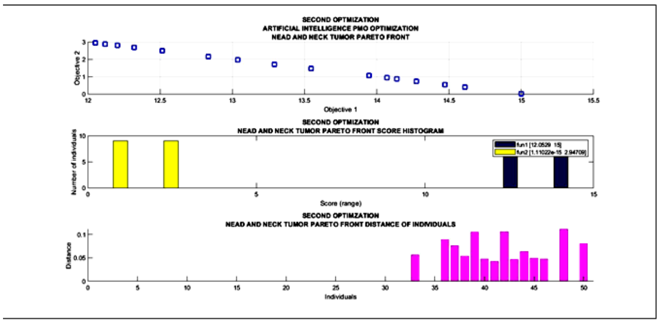

Figure 5.-Second simulation. Multifunctional GA 2D graph. This is the most important graph given by software when PMO is performed to check the optimization accuracy.

The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f 1 and f 2 show low residuals. Therefore, results are acceptable. The number of points on the Pareto front was: 18. The number of generations was : 300.

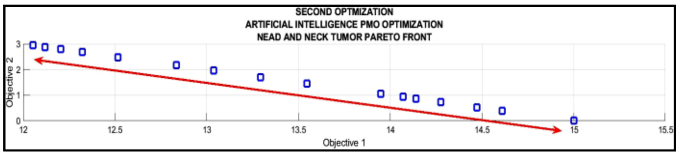

Figure 6.-This is the most important graph given by software when PMO is performed to check the optimization accuracy.

The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f1 and f2 show low residuals. Objective 2 is more accomplished. Therefore, results are acceptable. The number of points on the Pareto front was: 18. The number of generations was : 300. Enhanced in Appendix.

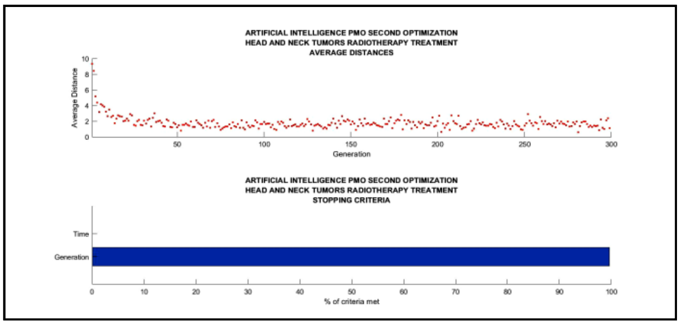

Figure 7.-This is important complementary graph given by software when PMO is performed to check the optimization accuracy.

Average Distances is an significant parameter. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f 1 and f 2 show low average distances, less than 2. Therefore, results are acceptable. The number of points on the Pareto front was: 18. The number of generations was : 300.

IV. NUMERICAL RESULTS

Constrained optimization numerical data is shown in Table 4. Large numbers for simple constrained optimization are shown in Tables 5-6.

Numerical Results Constrained Optimization

Constrained optimization show be acceptable within numerical intervals, Table 4.

Table 4. Constrained Optimization Algorithm 2 numerical results.

HEAD AND NECK HYPOFRACTIONATED NUMERICAL RESULTS FOR CONSTRAINED OPTIMIZATION FOR ALGORITHM 2		
Parameter/Settings	**Magnitude Interval**	**Additional**
Generations	150	Not too big figure
Pareto-Distance	≈ 10^{-2}	Acceptable precision
K	≈ [27 , 34]	Within literature data
d	≈ [1.6 , 1.7]	Within literature data
$T_{Treatment}$	≈ [30 , 35]	Within literature data

Numerical Results Simple Constrained Optimization Review

PMO-GA Numerical Results

Examples of Numerical results resume for PMO in BED model are detailed in Tables 5-6. Chebyshev norms were set for [55 , 65] Gy interval. Dose fraction magnitude should be less than 2 Gy approximately. Numerical Results for model are developed and reviewed from the innovation from [20,21,75,85-88].

Table 5.-First simulation. Brief of PMO Artificial Intelligence with GA optimization numerical results in Head and Neck tumors for advanced TPO.

BRIEF OF NUMERICAL FIRST PMO OPTIMIZATION RESULTS HEAD AND NECK BIOLOGICAL EFFECTIVE RADIOTHERAPY TREATMENT

Generation	Func-count	Pareto distance	Pareto spread
271	13550	0.0664648	0.233149
272	13600	0.0295673	0.123498
273	13650	0.0244215	0.0989167
274	13700	0.0424819	0.177761
275	13750	0.0179927	0.0802337
276	13800	0.0373533	0.158533
277	13850	0.0215619	0.091576
278	13900	0.0371236	0.135267
279	13950	0.0353069	0.133862
280	14000	0.0329375	0.114606
281	14050	0.0302815	0.112513
282	14100	0.0200634	0.081698
283	14150	0.0452573	0.183996
284	14200	0.0239752	0.100783
285	14250	0.023378	0.10136
286	14300	0.0466089	0.176541
287	14350	0.0571169	0.210486
288	14400	0.0350603	0.132537
289	14450	0.0168583	0.0738853
290	14500	0.0364302	0.14719
291	14550	0.0343554	0.148173
292	14600	0.0265149	0.108386
293	14650	0.0445348	0.173242
294	14700	0.018079	0.0786436
295	14750	0.0281023	0.117192
296	14800	0.0319461	0.122923
297	14850	0.0266535	0.10269
298	14900	0.0190131	0.0802516
299	14950	0.0195492	0.0867326
300	15000	0.0391879	0.150761

Optimization terminated: maximum number of generations exceeded.

population =

32.6551	1.2549	25.4416
36.3169	1.3119	26.5489
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
32.6551	1.2549	25.4416
36.3169	1.3119	26.5489
36.3169	1.3119	26.5489
36.3169	1.3119	26.5489
36.3169	1.3119	26.5489
36.3169	1.3119	26.5508
32.6551	1.2549	25.4416
36.3169	1.3119	26.5489
32.6551	1.2549	25.4416
33.4949	1.3032	25.5279
36.3169	1.3043	26.5530
34.7218	1.3080	25.5166
32.6551	1.2549	25.4416
36.3169	1.3119	26.5489
34.9485	1.2867	25.4865
32.6925	1.2656	25.4444
35.6515	1.2953	25.8327
32.6551	1.2549	25.4337

Table 6.-Second simple constrained simulation. Brief of PMO Artificial Intelligence with GA optimization numerical results in Head and Neck tumors for advanced TPO. These numerical results are an example, the dataset got is much bigger.

BRIEF OF NUMERICAL SECOND PMO OPTIMIZATION RESULTS HEAD AND NECK BIOLOGICAL EFFECTIVE RADIOTHERAPY TREATMENT

Generation	Func-count	Pareto distance	Pareto spread
271	13550	0.0264619	0.183624
272	13600	0.017658	0.128402
273	13650	0.0227234	0.15417
274	13700	0.0124722	0.0958928
275	13750	0.0215654	0.159534
276	13800	0.0153963	0.116006
277	13850	0.0294572	0.213636
278	13900	0.0318413	0.189485
279	13950	0.0176281	0.133355
280	14000	0.0214485	0.155889
281	14050	0.0307415	0.186141
282	14100	0.0176285	0.124615
283	14150	0.0357828	0.243373
284	14200	0.0144201	0.115587
285	14250	0.0150138	0.108402
286	14300	0.0203258	0.147338
287	14350	0.0224556	0.162609
288	14400	0.016788	0.116911
289	14450	0.00963603	0.0784907
290	14500	0.0108432	0.0803516
289	14450	0.00963603	0.0784907
290	14500	0.0108432	0.0803516
291	14550	0.0287958	0.205909
292	14600	0.0315205	0.205436
293	14650	0.0216337	0.147394
294	14700	0.0288101	0.209371
295	14750	0.0191258	0.12803
296	14800	0.010983	0.0858918
297	14850	0.0216991	0.136979
298	14900	0.0151757	0.0946424
299	14950	0.0256791	0.163865
300	15000	0.015325	0.106296

Optimization terminated: maximum number of generations exceeded.
The number of points on the Pareto front was: 18
The number of generations was : 300

population =

35.0000	1.2000	22.0000
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
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35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.2046	1.2294	23.3154
35.1347	1.2028	22.0698
35.3080	1.2236	23.1548
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.2739	1.2458	23.6035
35.2248	1.2465	23.0652
35.0000	1.2000	22.0000
35.1337	1.2028	22.0704
35.2062	1.2187	22.4697
35.3452	1.2473	23.6728
35.3432	1.2398	23.1952
35.3452	1.2473	23.6728
35.3452	1.2473	23.6728
35.0513	1.2010	22.1323
35.1628	1.2314	22.0871
35.2275	1.2412	22.5324
35.3112	1.2309	22.9631
35.2991	1.2168	23.0616
35.2047	1.2051	22.4210

V. RADIOTHERAPY PHYSICS APPLICATIONS

Table 7 shows a resume of radiotherapy applications in head and neck tumors. Medical physics principal applications for radiotherapy TPO are explained briefly.

Table 7 .- Some radiotherapy and radioprotection for RT head and neck cancer TPO Medical Physics study applications derived from results.

MODEL RESULTS APPLICATIONS FOR RADIOPROTECTION IN HEAD AND NECK TUMOR RT

TYPE	CLINICAL	RESEARCH	MIXED	COMMENTS
BM Treatment planning optimization	TPO precise for head and neck tumors with BMs	TPO Modelling BMs developments according to $N_{Effective}$	Clinical improvements with BMs after research according to $N_{Effective}$	Inverse planning system set up on BMs according to $N_{Effective}$
LINAC OPTIMIZATION	Optimization of photon-dose for BMs	LINACs BMs Usage for IMRT, IMPT according to $N_{Effective}$	Exploration of new possibilities for $N_{Effective}$ models	Manufacturing adaptation of LINACs fro BMs according to $N_{Effective}$
Theoretical improvements for new models	Dosimetry improvements in accuracy according to radiobiology experimental $N_{Effective}$	From tumor survival clinical statistics advances in BMs according to $N_{Effective}$	According to $N_{Effective}$ new BMs research sources, both theory and clinical experimental trials	BMs got experimental evidences to be set on TPO according to $N_{Effective}$

VI. DISCUSSION AND CONCLUSIONS

The objective of the study was to apply further constrained GA Optimization for Head and Neck Hyperfractionated RT treatment with BED model. Secondly to compare/review to simple constrained results [87,88].

Results comprise a series of 2D GA graphical series and numerical dataset, Tables 4-6. Constrained Optimization with Algorithm 2 shows a Pareto Distance of about 10^{-2} magnitude order. When number of generations increases from 150, the running time of the constrained programs rises to approximately 4-6 minutes.

Software and programming was based on previous contributions [87,88]. The Matlab function handle have to be carefully programmed to get acceptable results. In plain language, handle functions got to get built with same precision than the classical FORTRAN subroutines.

In summary, a constrained RT-BED Hyperfractionated model with GA was performed and compared to simple constrained Pareto-Optimization. Applications for optimal RT planning emerge form results.

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VII. SCIENTIFIC ETHIC STANDARDS

GA-AI RT applications methods fro these publications were created by Dr Casesnoves in 2022. 2D/3D Graphical Optimization Methods were created by Dr Francisco Casesnoves in 3rd November 2016, and Interior Optimization Methods in 2019. BED model setting in Algorithms and programming were developed by Dr Casesnoves from previously published BED models. This article has previous papers information, from [1-10], whose inclusion is essential to make the contribution understandable. This study was carried out, and their contents are done according to the International Scientific Community and European Union Technology and Science Ethics [38-41]. References [38,43,44]: 'European Textbook on Ethics in Research'. European Commission, Directorate-General for Research. Unit L3. Governance and Ethics. European Research Area. Science and Society. EUR 24452 EN. And based on 'The European Code of Conduct for Research Integrity'. Revised Edition. ALLEA. 2017. This research was completely done by the author, the computational-software, calculations, images, mathematical propositions and statements, reference citations, and text is original for the author. When a mathematical statement, algorithm, proposition or theorem is presented, demonstration is always included. If any results inconsistency is found after publication, it is clarified in subsequent contributions. When a citation such as [Casesnoves, 'year'] is set, it is exclusively to clarify intellectual property at current times, without intention to brag. The article is exclusively scientific, without any commercial, institutional, academic, religious, religious-similar, non-scientific theories, personal opinions, political ideas, or economical influences. When anything is taken from a source, it is adequately recognized. Ideas and some text expressions/sentences from previous publications were emphasized due to a clarification aim [38, 43-44].

APPENDIX

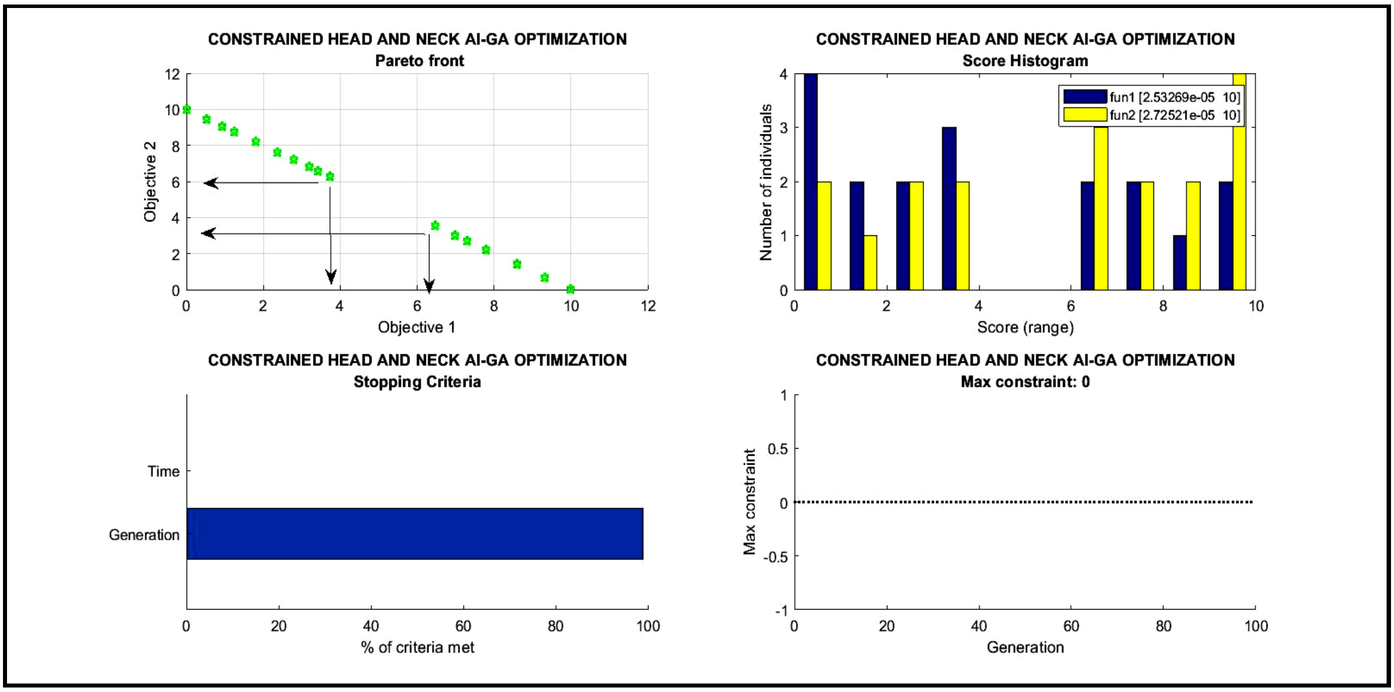

Figure 1. (Enhanced) .-Constrained optimization Multifunctional GA 2D graph (100 generations). This is the most important graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f 1 and f 2 show low residuals. Therefore, results are acceptable in first optimization for function 1 and function 2.

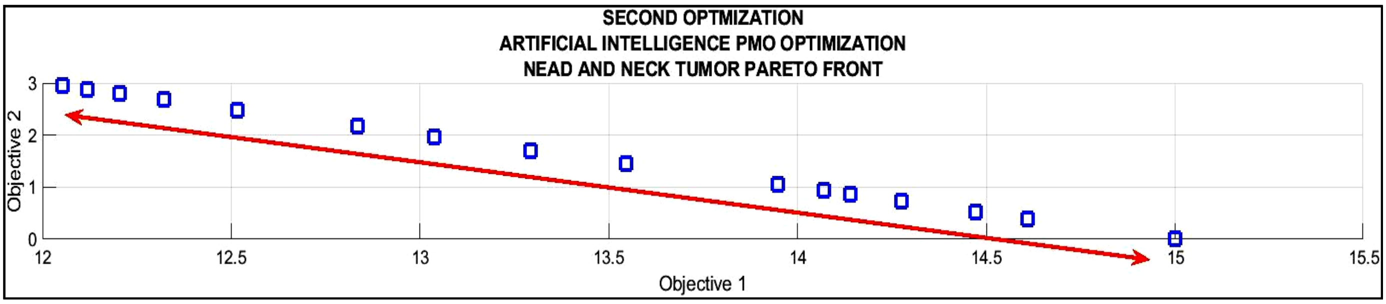

Figure 6. (Enhanced).-This is the most important graph given by software when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f1 and f2 show low residuals. Objective 2 is more accomplished. Therefore, results are acceptable. The number of points on the Pareto front was: 18. The number of generations was : 300.