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Radiotherapy Bed Model 2D Pareto- Multiobjective Evolutionary Optimization for Prostate Cancer Hyperfractionated Treatment

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ABSTRACT

Constrained evolutionary algorithms for BED-LQ model (Biological Effective Dose) in Prostate cancer Hyperfractionation radiotherapy TPO are optimized with Pareto-Multiobjective (PMO) methods. Genetic Algorithm (GA) software is developed based on hyperfractionation constraints with in vitro main parameters dataset. Programming method results take in handle subroutines functions and matrix-algebra method for setting constraints. Results show PMO 2D imaging charts and numerical values of PMO Prostate cancer hyperfractionated TPO parameters. Applications for prostate tumors radiotherapy and stereotactic radiosurgery treatments are briefed.

Keywords: Pareto-Multiobjective Optimization (PMO); Mathematical Methods (MM); Biological Models (BM); Radiation Therapy (RT); Initial Tumor Clonogenes Number Population (N0); Effective Tumor Population Clonogenes Number (NEffective); 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); Nonlinear Optimization, Treatment Planning Optimization (TPO); Artificial Intelligence (AI); Pareto-Multiobjective Optimization (PMO); Genetic Algorithms (GA)

Abbreviations: PMO: Pareto-Multiobjective Optimization; MM: Mathematical Methods; BM: Biological Models; RT: Radiation Therapy; LQM: Linear Quadratic Model; IE: Integral Equation; TCP: Tumor Control Probability; NTCP: Normal Tissue Complications Probability; BED: Biological Effective Model; TCCP: Tumor Control Cumulative Probability; RPD: Radiation Photon-Dose; TPO: Treatment Planning Optimization; AI: Artificial Intelligence; PMO: Pareto-Multiobjective Optimization; GA: Genetic Algorithms

Introduction

The objective of this contribution is apply Constrained Genetic Algorithms on radiotherapy BED-LQ model for prostate tumors [1-24,87-94] with an hyperfractionated schedule. BED-LQ model is considered acceptable, [1-24,40,74-79,87-94], for low dose fractions, while LQL and PTL ones are more appropriate for high doses—namely, hypofractionated treatment [94]. Prostate cancer has approximately a long average survival time of [15,20,90-94] years [87-94], compared to the rest of tumors. One of the reasons is its higher-proper T_{Pot} biological parameter (radiobiological potential doubling time), experimentally proven. Numerically, it is about 28 days *in vivo* and [2,19] *in vitro*, compared, for instance, to breast and head and neck tumors, [8.2, 12.5] and [1.8, 5.9] respectively, [87-94]. This fact implies a longer survival time with several specific caracteristics. Those are a number of different stages in Surgical, RT, Radiosurgical, Chemotherapy, Inmunotherapy, Hormonal Therapy, combinations of all of them, and treatment time related to every stage. Medical radiation oncology decisions vary case by case for each patient within a general

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protocol of the cancer center or hospital radiation oncology, medical physics, and urology team [89]. Usually, radiotherapy protocol is applied during post-surgical treatment [89]. For surgery of brain metastatic nodules, it is oncohistologically proven that around the brain metastatic border nodules, infiltrated metastatic tumoral cells could be hidden to imaging-guide radiotherapy method [89]. The 3D- 4D CT and MRI precision to determine the exact boundaries of metastatic nodules and tumor constitutes a challenge for radiosurgery optimal treatment [19-24,75,85-94].

Nonlinear GA-PMO engineering software was improved with matrix algebra constraints and designed in programs/patterns for PMO-BED models. Thorough GA hyperfractionated radiotherapy TPO findings are presented both in 2D graphics and dataset. The BED model radiobiological parameters implemented are in vitro ones from [23,24,68], (Table 1). 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. Results comprise TPO hyperfractionated RT treatment planning, graphical and numerical. 2D GA charts are presented in multifunctional format, for 100, 150, and 250 Evolutionary Optimization generations. 2D principal Pareto multiobjective graph is explained sharply. Numerical results present optimized dataset for dose fraction magnitude, number of fractions, and T_{Delay} interval. The innovation of this study, based on previous evolutionary optimization methods for breast and head and neck tumors, is its GA algorithms and computational optimization for the rather complicated RT- TPO of prostate cancer. It is focused on hyperfractionation protocols and LG-BED model, since high- dose models for BED hypofractionations are different. Original mathematical constrained algorithms and software engineering are developed to obtain graphical/numerical results. In brief, a constrained extension of previous Nonlinear Pareto-Multiobjective GA optimization was performed for radiotherapy BED models in Prostate tumors. Applications for radiotherapy hyperfractionated BED-TPO and future improvements in RT are explained in short.

Table 1: Software implemented dataset for GA programming with source references [38,43-45].

IN VITRO LQ PARAMETERS IMPLEMENTED [Chapman, Nahum, 2015]		
Asynchronous populations of human tumor cell lines [chapman, Nahum, 2015]	**α[Gy-1]**	**β[Gy-2]**
TSU	0.06	0.048
PC-3	0.24	0.068
DU-145	0.31	0.048
LnCap	0.49	0.015
INTERVAL\AVERAGE FOR SOFTWARE	[0.06, 0.049]	0.0421
LQ PARAMETERS IMPLEMENTED [From author's refs [23,24]]		
BED-PARAMETERS	**MAGNITUDE\INTERVAL**	
T_{POT}	[2.00, 19.00] (Days)	
T_k	21(Days)	
$T_{Treatment}$	[30,40] (Days)	
Number of functions	[37,45] (Fractions)	
Pareto total prostate dose objective function [89]	Pareto 1: 70Gy Pareto 2: 78Gy	

Mathematical and Computational Methods

Following previous publications for Breast, and Head-Neck cancers, the Pareto-Multiobjective Optimization foundation BEDEffective model was set in software, [1-24,40,68,74-79,87-94]. Parameters intervals are detailed in Table 1. Algorithms 1-4 set the formulas and constraints [85-88]. The radiobiological parameters alpha and beta are set as separated ones, not in quotient [alpha/beta] because of the programming patterns functionality. This low-dose LQ-BED model constitutes the fundamentals for hyperfractionated radiotherapy TPO, although there are variations among authors [20-25]. The general Pareto-Multiobjective [Algorithm 1] that was set, with Chebyshev L1 norm, [Algorithms 2-4], reads,

Minimize,

$$F(\overrightarrow{X}) = (f_1(\overrightarrow{X}), f_2(\overrightarrow{X}), ...f_N(\overrightarrow{X})),$$

Subject to,

$$K_i(\overrightarrow{X}) \geq 0, fori = 1, ...M$$

(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 ≠ M.

BED model has been adapted on the difficulty to obtain an stable and reliable T_{Pot} magnitude. PMO in Prostate, [24,88,89] tumors simplest BED model reads,

Chebyshev L_1 Optimization,

for i=1,2 minimize pareto,

$DOSE_1$ -$BED_{Effective}$| L1 With,

$$BED_{Effective} = K \times d\left[1 + \frac{d \times \beta}{\alpha}\right] - \ldots\ldots - \frac{Ln(2)}{\alpha} \times \left[\frac{T_{Treatment-}T_{Delay}}{T_{Potential}}\right];$$

(Algorithm 2)

where,

BED: The basic algorithm for Biological Effective Dose initially developed by Fowler et Al. [22-25,89- 94].

k: Optimal Number of fractions for hyperfractionated TPO. Optimization parameter [22-25,89-94].

d: Optimal Dose magnitude for every fraction. Optimization Parameter [Gy] [22-25,89-94].

α: The basic algorithm constant for Biological Effective Dose models. Radiobiological experimental parameter in vitro. [Gy^{-1}] [22-25,89-94].

β: The basic algorithm constant for Biological Effective Dose models in vitro. Radiobiological experimental parameter. [Gy^{-2}]. It is very usual to set in biological models [α / β in Gy].

$T_{Treatment}$: The overall TPO time. This parameter varies according to authors' and institutions/hospitals criteria [22-25,89-94].

T_{Delay}: The overall TPO time delay for clonogens re-activation. This parameter varies according to authors' experimental research.

$T_{Potential}$: The potential time delay for tumor cell duplication. This parameter varies according to authors' experimental-theoretical research.

DOSE: The dose magnitudes for lung cancer simulation algorithm for Biological Effective Dose [22-25,89-94]. Software patterns were calculated around intervals prostate DOSE ϵ [70,78] Gy.

Equation 1 [created for software patterns, Casesnoves, 2022, based on BED model [Fowler mainly]. - Prostate PMO algorithm [1-25,85-90] implemented in software. The intervals for optimization parameters in software are detailed. It is a constrained-subroutines Matlab® improvement from a series of previous research in radiotherapy. At programming trials it was found that precision was increased by using subroutines with algebraic constraints in principal patterns. Therefore, the constraints algebraic algorithm developed for Pareto- Multiobjective problem, [Algorithms-3-4, Casesnoves 2023] reads,

Constraints, For Pareto, Functions i=1,2, and lower- Upper limits of optimization parameters,

$$S_{Lower} \leq K_i + d_i + T_{(Treatment)i} \leq S_{Upper}$$

(Algorithm 3)

where

SLOWER: Summatory of all lower constraints for parameters [K, d, T].

SUPPER: 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 subroutines programming strategy implemented reads,

Matrix algebra subroutines For Constraints,

$$[A_1] \times \begin{pmatrix} K \\ d \\ T \end{pmatrix} \leq \begin{pmatrix} S_{K\max} \\ d_{d\max} \\ T_{T\max} \end{pmatrix},$$

$$[A_2] \times \begin{pmatrix} K \\ d \\ T \end{pmatrix} \geq \begin{pmatrix} S_{K\min} \\ d_{d\min} \\ T_{T\min} \end{pmatrix}$$

(Algorithm 4)

were,

$S_{K,d,T}$: Upper (maximum) and Lower boundaries for parameters [K, d, T], according to Algorithms 1- 2.

$A_{1,2}$: Matrices for numerical values, (Table 1).

The programming method(s) used for this study are based on previous algorithms papers [1- 20,24,68,74,88,89]. For GA-PMO modeling, Equation 1 and Algorithms 1-2 are implemented on 2D programs. However, Algorithm 2 was programmed with Algorithm 3 matrix constraints subroutines- functions. Table 1 shows Constrained GA Optimization selected parameters according to Algorithms 1-4. Table 1 presents the 2D GA-PMO simple programming method variations to

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get accurate calculations, 2D Graphical Optimization 2D imaging-processing charts, error determinations, and get precise approximations for hyperfractionated PMO-BED model.

Programming Dataset

Matlab Constrained GA optimization dataset is detailed, Table 1. Constraints matrix algebra are implemented through [Algorithms 3-4]. In Matlab and other similar systems, the constraints can be set as a matrix equation. Simulation dataset from comes from [20-25,68,74,75,80,81,85-94]. The GA simulations were done with numerical-experimental interval-data for GA implemented arrays. TPotential in prostate neck cancer for in vitro experimental data is about [2,19] days. Table 1 shows all dataset implemented with references for in vitro parameters at BED-LQ model at low doses. The reason to use in vitro dataset in this first prostate study is that currently the in vivo radiobiological differences differ in the literature.

2D Optimization Results

2D GA Graphical results are shown in (Figures 1-4). The constrained optimization results are presented sharply in 2D multifunctional charts. Constrained optimization with [Algorithms 1-4] gets better results than unconstrained one in previous publications [68,87,89-94]. However, differences are not very high in magnitude orders.

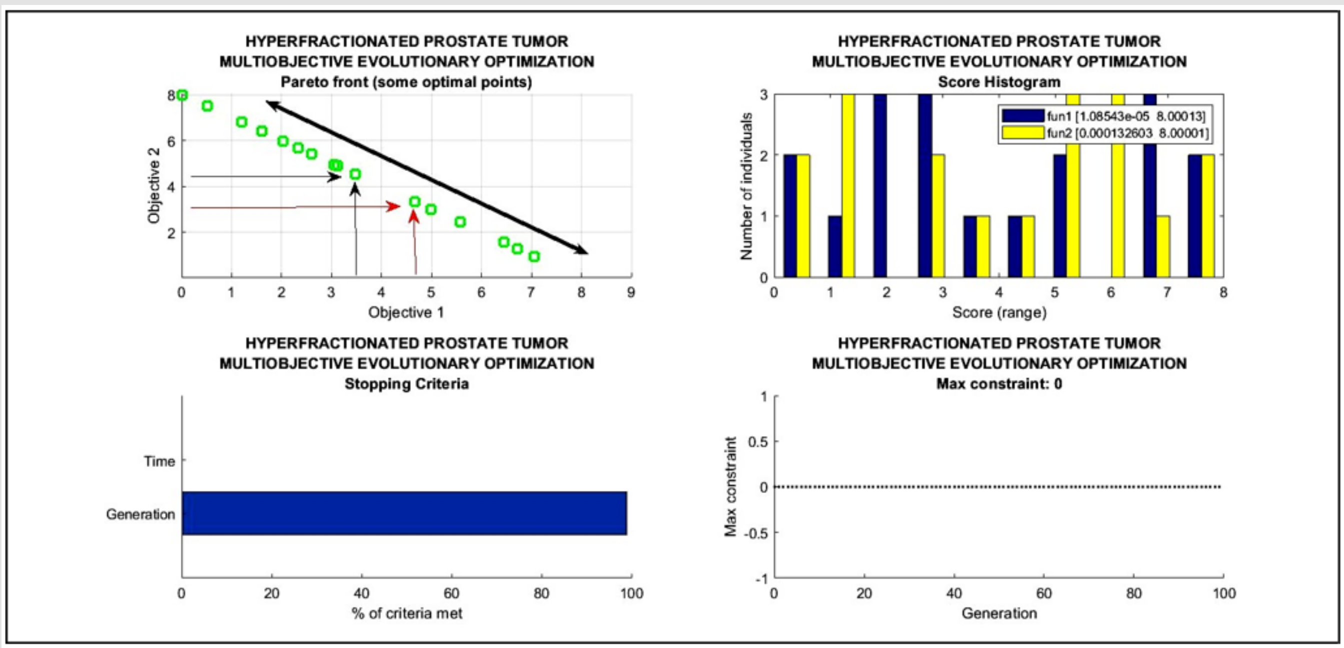

Figure 1: 100 generations constrained optimization Multifunctional GA 2D graph. The first one is the most important graph given by software when PMO is performed to validate the GA-optimization precision. Two optimal Pareto-value choices, inset, are marked, red and black arrows. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study all programmed optimizations show low residuals, therefore, results are acceptable.

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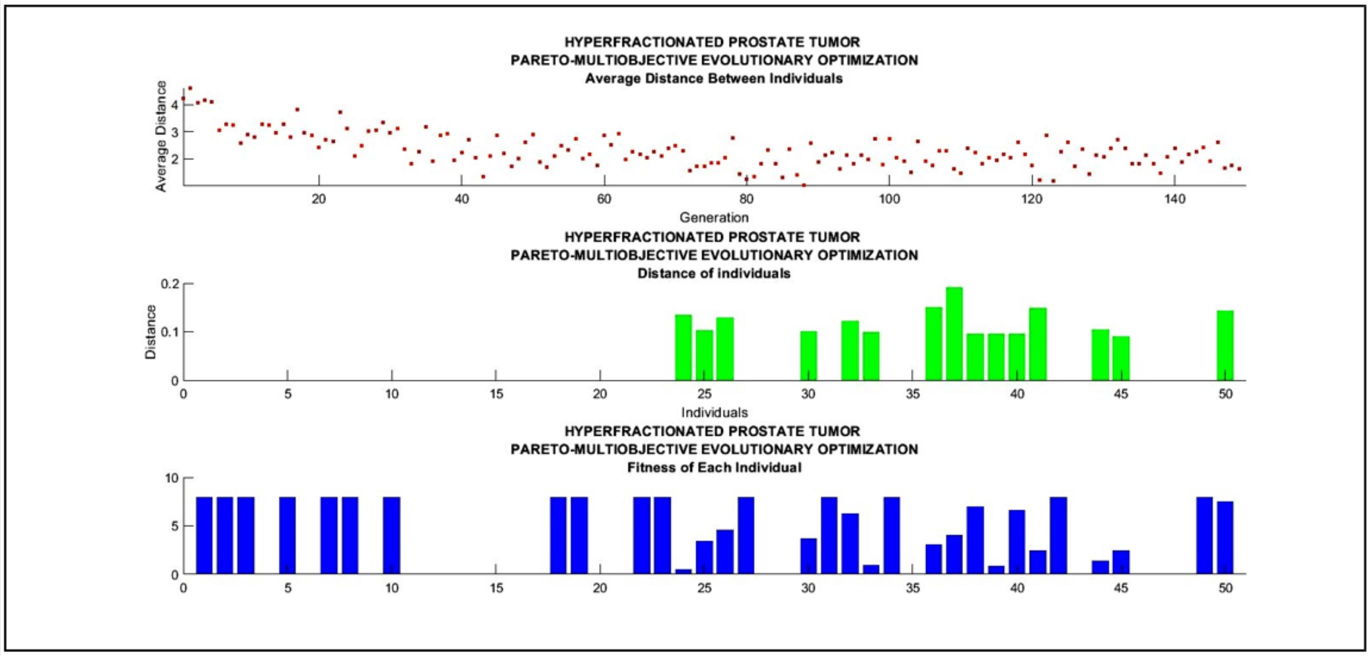

Figure 2: 150 generations constrained optimization Multifunctional GA 2D graph. The first one is the most important graph given by software when PMO is performed to validate the GA-optimization precision. Since generation number is 150, the average distance among individuals remains a bit unclear. Then, at Figure 4, with 250 generations, the precision jump is got sharply. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study all programmed optimizations show low residuals, therefore results are acceptable.

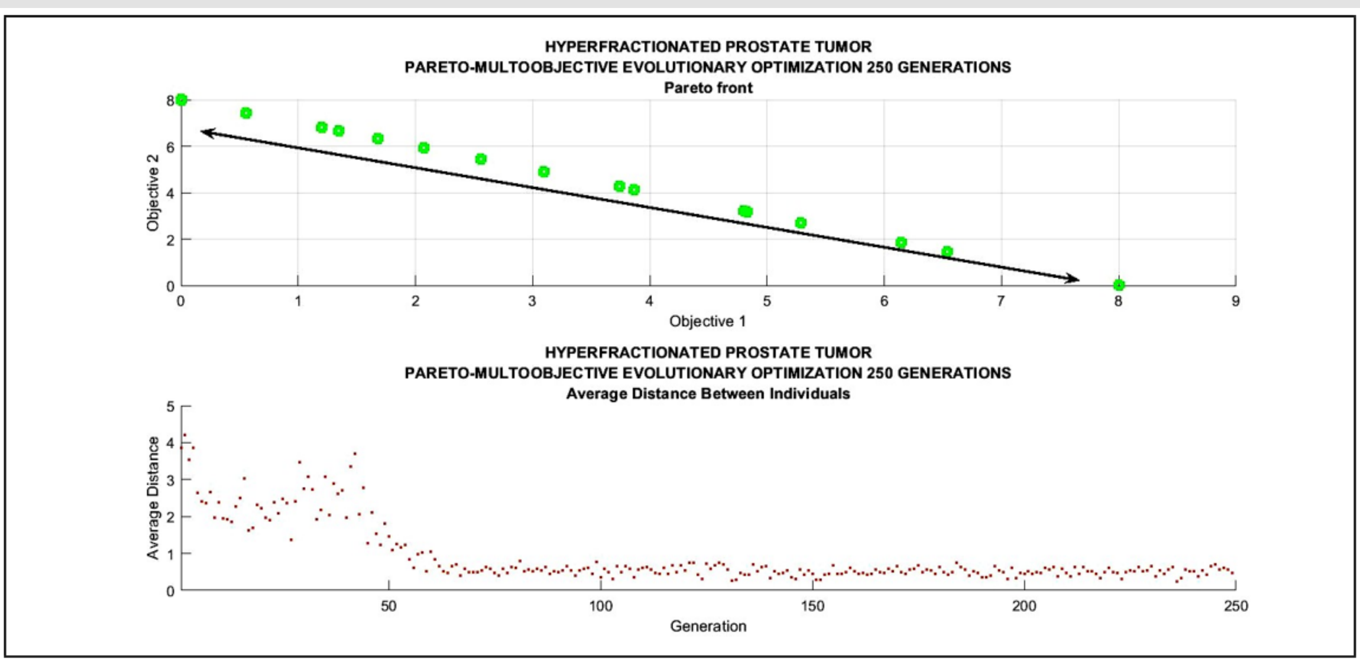

Figure 3: First 250 generations constrained optimization Multifunctional GA 2D graph. The upper image, enhanced, is the most important graph given by software when PMO is performed to validate the GA-optimization precision. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study all programmed optimizations show low residuals, therefore, results are acceptable.

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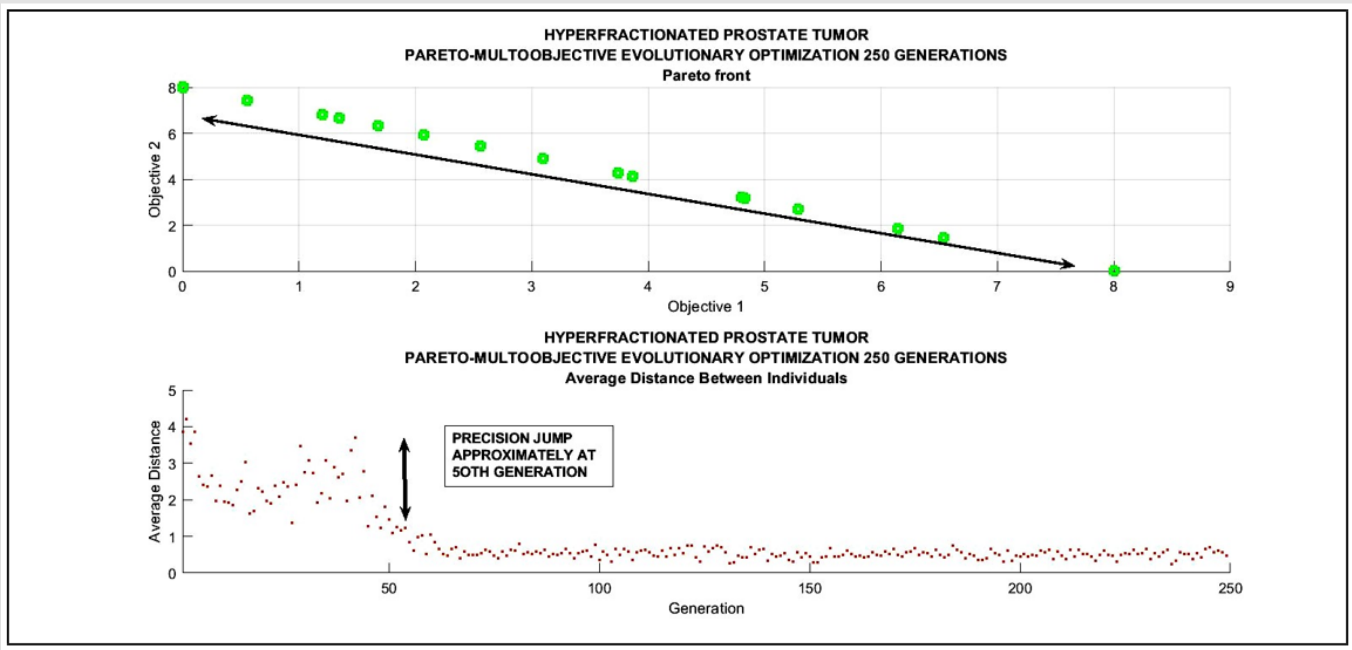

Figure 4: Second 250 generations constrained optimization Multifunctional GA 2D graph. Program and subroutines got to get precision jump clearly, approximately around 50th generation. The upper image, enhanced, is the most important graph given by software when PMO is performed to validate the GA-optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study all programmed optimizations show low residuals, therefore, results are acceptable.

Numerical Results

Constrained PMO-GA optimization numerical data is shown in (Table 2). Constrained optimization show be acceptable within numerical intervals [1-24,40,68,74-79,87-94]. Format presented as in previous publications for other types of cancer [85-94].

Table 2: Brief of constrained optimization Algorithms 1-4 numerical results. Pareto distance is about 10-2 magnitude order.

GENETIC ALGORITHM ARTIFICAL INTELLEGENCE OPTIMIZATION NUMERICAL RESULT FOR PROSTATE TUMORS HYPERFRACTIONATED RT TREATMENT [250 GENERATIONS]		
PARAMETER	MANITUDE INTERAVAL RESULT	COMMENTS
optimal dose fractions number	[38,44] integers	According to literature standards [1-21,74-86].
optimal dose fractions magnitude	[1.5655, 1.6103] Gy	within usual protocol in literature [1-21,74-86]. set with intervals according to different criteria
Optimal TTreatment	[32,34] days	within 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 circumstance, etc.
pareto Distance	[0.0177829, 0.0413472	Acceptable 10-2 magnitude order

Radiotherapy Medical Physics Applications

(Table 3) shows a resume of radiotherapy hyperfractionated treatment applications for prostate tumors. Medical Physics principal applications for radiotherapy TPO are explained briefly.

Table 3: Some radiotherapy and radioprotection for RT head and neck cancer TPO Medical Physics study applications derived from results.

BED-LQ RADIO THERAPY OPTIMIZATION APPLICTIONS FOR HYPERFRACTIONATED RT PROTOCOL		
APPLICATION	MEDICAL PHYSICS AND RADIATION ONCOLOGY FILED	ADDITIONAL
Optimal number of fractions	RT schedule	Avoid side effects
Biological Models TCP TCCP Improvements	Patient Treatment Precision	Radio protection impartments, more Quality Life and OARs Radioprotection
Post-RT treatment survival time	Decrease of TCP, and TCCP	Increase of Survival Time
Biological Models Research	improvements	improvements LINAC software, Cyberknife®, Gammaknife® and imaging guided TR Treatment
NTCP models	Possible applications also	Decrease of Side-Effects at OARs

Discussion and Conclusion

The objective of the study was to apply constrained GA Optimization for prostate cancer hyperfractionated RT treatment with BED-LQ model. For low doses, LQ model is suitable in RT treatment planning. A constrained PMO-Multiobjective method was programmed with subroutines. Mathematical Algorithms 1-4 for the objective are presented/explained. Results comprise a series of 2D GA graphical series and numerical dataset, Tables 1 & 2. Constrained Optimization with Algorithms 1-4 got to get a Pareto Distance of about 10-2 magnitude order with 250 generations. When number of generations increases from 100, the running time of the constrained programs rises to approximately 2-3 minutes. Grosso modo, a constrained RT-BED hyperfractionation model with GA was performed with Pareto- Optimization in one of the highest incidence/prevalence prostate tumors. sApplications for optimal RT planning come forward from results.

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