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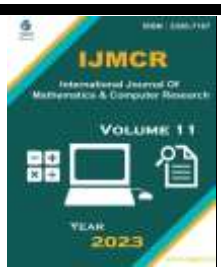

Radiotherapy Bed Model Multiobjective Pareto-Interior Dual-Optimization for Prostate Cancer Hyperfractionated Treatment Planning and Isodoselines Invention

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ABSTRACT

In a previous publication, constrained evolutionary algorithms for IN-VITRO-BED-LQ model (Linear Quadratic Biological Effective Dose Model) in prostate cancer Hyperfractionation radiotherapy TPO were optimized with Pareto-Multiobjective (PMO) methods. This study improves the research with a further comparative IN-VIVO-BED-LQ model optimization followed by a precision-refinement with Interior Optimization (IO) methods. Complex software is developed based on hyperfractionation constraints, but with in vivo main parameters dataset, and IO programming. Results with software design algorithmic method take in handle subroutines functions and matrix-algebra method for setting constraints and 3D IO surfaces. Results with 3D Interior Optimization by using the Genetic Algorithms (GA) previous numbers show get very good precision with new-invention of isodoselines sharp determination. Solutions dataset is shortly compared with previous in vitro study. Findings prove comparative PMO 2D imaging charts and numerical values of PMO prostate cancer hyperfractionated TPO parameters. Applications for prostate tumors radiotherapy planning, especially with new Surfactal-Isodoselines, brain prostate metastases 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 (N_0), Effective Tumor Population Clonogenes Number ($N_{Effective}$), Linear Quadratic Model (LQ), 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)

I. INTRODUCTION AND OBJECTIVES

From a previous publication, [98], the objective of this contribution is apply Constrained Genetic Algorithms and 3D Interior Optimization on radiotherapy BED-LQ model for prostate tumors [1-24,87-94] with in vivo dataset for an hyperfractionated schedule. The BED-LQ model [1-24,40,74-79,87-94], is useful for low dose fractions, while LQL and PTL ones are more appropriate for high dose delivery RT treatment schedules—namely, hypofractionated treatment [94]. The numerical difference between in vitro LQ parameters for prostate LQ model can be considered important [1-24,40,74-79,87-99]. It is not subject of this article any discussion about hyperfractionation versus hypofractionation dose delivery. Prostate cancer epidemiology statistics-figures are within the group of highest incidence-prevalence cancers, but lower than lung and breast tumors, [99].

Therefore, the objective of the study is to carry out a double optimization process. Firstly, 2D GA optimization with in vivo data for LQ model. Secondly, making the most of the firstly GA obtained results, to get an improved refinement by using 3D Interior Optimization methods. Numerically, TPot magnitude difference in vivo values, prostate cancer, are about 28 days in vivo and [2 , 19] in vitro ones are lower. In general also, both in vitro and in vivo TPot parameters for prostate tumors are greater than other types of cancer [20-25]. This fact implies a longer survival time with several proper caracteristics related to different treatment stages.

Namely, surgical, RT, radiosurgical, chemotherapy, inmunotherapy, hormonal therapy, combinations of all of them. Today, biomarkers are getting an important role in order to predict the survival time, optimal chemotherapy, and both characteristics at the same time [95]. Table 1 shows a biomarkers classification into P-Biomarkers (Biomarkers for Prognosis, [96]), T-Biomarkers (Biomarkers for Optimal Treatment), and H-Biomarkers (Hybrid Biomarkers Group), [Author's proposal].

BIOMARKERS GENERAL CLASSIFICATION FOR CANCER RADIOTHERAPY TREATMENT
[Author's proposal]

TYPE	APPLICATION	ADDITIONAL	EXAMPLES
P-BIOMARKER (PROGNOSIS BIOMARKER)	Prediction of approximate survival time subject to optimal treatment	Prediction for approximate survival based on specific tumor cell histology, and according to the relation histology-efficacy of drugs. Drug failure investigation utility.	Research clinical trial example, [from 96]: investigation data show that patient survival time in PD-L1–positive patients who are treated with combined anti-CTLA-4 and anti-PD-1 is not superior to nivolumab monotherapy. That implied that was necessary further research. This clinical-trial study area is difficult
T-BIOMARKER (TREATMENT BIOMARKER)	Selection of approximate optimal choice for effective chemo-inmuno drug-target treatment	Optimization of the best effective drug type for personalized tumor at every patient. Detection of optimal drug-target and pharmacokinetics. Drug failure patient-personalization investigation. Target characterization.	HSP90α is an inducible molecular chaperone that functions as a homodimer [ref 96, Chapter 2.4, Table 2.4.2]
H-BIOMARKER (HYBRID BIOMARKER)	Both prediction of survival time and optimal treatment	Those ones that can make both functions, or one of them better than the other	Nano-Biomarkers actually in investigation can modify the inmuno-cells and efficacy of drugs over cells tumor

Table 1.-General Biomarkers classification, [Author's proposal]. Nano-Biomarkers is an open research field with potential perspectives in future [96,99]. Just remark that Biomarkers are is extent, diverse and difficult as involves biochemistry, molecular biology, medicine-pharmacology, medical physiology and several other fields. Therefore this Table is simple based on Author's proposal classification. Enhanced in Appendix.

The programming design has two parts: Nonlinear GA-PMO engineering software with matrix algebra constraints, similar to the previous publication in codes/patterns for PMO-BED models. Second part is rather more difficult. That is, 3D Interior Optimization with the new useful-practical finding of isodoselines for radiotherapy planning hyperfractionated schedule. Those new Isodoselines along the Interior Optimization surface constitute a TPO advance and innovation of this contribution.

Results comprise Graphical and Numerical TPO hyperfractionated RT treatment planning. 2D GA graphics are presented in several formats, for 100, 150, and 250 generations. 3D Interior Optimization charts are illustrated with Isodoselines, optimal areas, and numerical data inset. Numerical results show first GA figures and Interior Optimization refined values. Therefore, the novelty of this article, based on the previous evolutionary optimization paper, [98],is its GA algorithms and computational optimization with in vivo parameters, 3D Interior Optimization improvements, and the practical definition of 3D Isodoselines for RT planning hyperfractionated schedule. It is objective, according to the precision of numbers obtained, that the mathematical and software developed is considered appropriate.

Grosso modo, a double constrained optimization based on previous Nonlinear Pareto-Multiobjective GA optimization was developed with the addition of 3D Interior Optimization refinement and the new-practical Isodoselines definition. Applications for radiotherapy hyperfractionated BED-TPO planning are presented. Numerical Analysis precision results is gonna be promising for improvements of the method.

II. MATHEMATICAL METHOD

Following previous studies, mainly the prostate cancer one [98], and publications for Breast, Head-Neck cancer, here the Pareto-Multiobjective Optimization Fowler-foundation $BED_{Effective}$ model was programmed, [1-24,40,68,74-79,87-94,98,99]. Alpha, Betha, and rest of parameters intervals are detailed in Table 2. Algorithms 1-5 set the 2D GA and 3D IO formulas and constraints [85-88]. Radiobiological parameters Alpha and Betha are implemented independently, not in quotient [alpha/beta] because of the programming patterns purpose. This low-dose LQ-BED model constitutes the foundations for hyperfractionated radiotherapy TPO, though there are dissimilarities among authors [20-25]. Therefore, the Pareto-Multiobjective [Algorithm 1] that was set, with Chebyshev L_1 norm, [Algorithms 2-4] is presented firstly. The IO method is explained secondly.

Evolutionary Algorithms Mathematical Method

The GA algorithms used are approximately the same than in previous prostate cancer publication, [98]. The sequence of the formulas development is as follows,

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

(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 $N \neq M$.
BED nonlinear-quadratic model has been adapted for ***in vivo*** parameter T_{Pot} magnitude. Then, PMO in Prostate, [24,88,89,98] tumors simplest BED model reads,

$$\text{Chebyshev } L_1 \text{ Optimization,}$$
$$\text{for } i = 1, 2 \ldots \text{minimize pareto,}$$
$$\left| DOSE_i - BED_{Effective} \right|_{L_1} \text{ with,}$$
$$BED_{Effective} = k \times d \times \left[1 + \frac{d \times \beta}{\alpha} \right] - \ldots$$
$$\ldots - \frac{Ln(2)}{\alpha} \times \left[\frac{T_{Treatment} - T_{Delay}}{T_{Potential}} \right];$$

(Algorithm 2)
Where,
BED : The basic algorithm for Biological Effective Dose initially developed by Fowler et Al. [22-25, 89-94,98].
k : Optimal Number of fractions for hyperfractionated TPO. Optimization parameter. [22-25,89-94,98].
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 vivo***. [Gy^{-1}]. [22-25, 89-94].
β : The basic algorithm constant for Biological Effective Dose models ***in vivo***. Radiobiological experimental parameter . [Gy^{-2}]. Note that 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, 89-94,98].
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, 89-94,98]. Software patterns were calculated around intervals prostate DOSE ϵ [70 , 78] Gy.
Algorithm 2 [Fowler mainly, modified by Casesnoves, 98].- Prostate PMO algorithm [1-25,85-90] implemented in software. Table 2 shows these intervals for optimization parameters details. Programming was developed in Matlab® system. At programming trials it was found that precision was increased related to ***in vitro*** parameters [98]. The constraints algebraic algorithm developed for Pareto-Multiobjective problem, [Algorithms-3-5, Casesnoves 2023] reads,

$$\text{Constraints,}$$
$$\text{For Pareto Functions } i = 1, 2,$$
$$\text{and lower} - \text{upper limits of}$$
$$\text{optimization parameters,}$$
$$S_{Lower} \leq K_i + d_i + T_{(Treatment)i} \leq S_{Upper} \text{ ,}$$

(Algorithm 3)
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 subroutines programming strategy, as in [98], which are 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)

where,

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

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

Sofware used for this study continues previous algorithms papers [1-20,24,68,74,88,89,98] with modifications, and addition of IO programs. For GA-PMO modeling, Equation 1 and Algorithms 1-4 are implemented on 2D programs, with application of Algorithm 5 basic model formula. Algorithm 2 was programmed with Algorithm 3 matrix constraints subroutines-functions. Table 2 shows Constrained GA Optimization ***in vivo*** parameters, different from [98], implemented in Algorithms 1-5. From Table 3 results, after IO implementation, 3D IO dataset for Table 4 is got. From all these numbers, 3D IO and 2D Genetic Algorithms Graphical Optimization imaging-processing charts, error determinations, pareto-distance, get precise approximations for hyperfractionated PMO-BED model. In general, precision obtained is more than expected, Tables 3-4.

Interior Optimization Computational Method

3D Interior and Graphical Optimization methods are used to confirm and refine the ***in vivo*** precision of the GA results from [98]. This is an advance as it was found that by using Interior Optimization the precision is increased and Isodoselines can be set for TPO. The method and software developed is a potential new application for accurate TPO.

Programming Dataset

Table 2 shows Matlab Constrained GA optimization dataset is detailed, for first optimization stage. As in [98], constraints matrix algebra are implemented through [Algorithms 3-5]. All these simulation techniques come from [20-25,68,74,75,80,81,85-94,98] . The ***in vivo*** $T_{Potential}$ in prostate cancer for setting data is $T_{Potential} \in [\ 26,30\ ]$ days. The reason to use ***in vivo*** dataset in this second prostate study is that, although currently the ***in vivo*** radiobiological differences differ in the literature, more realistic results are gonna get.

IN VIVO LQ MODEL PARAMETERS IMPLEMENTED	
LQ MODEL PARAMETERS [Chapman, Nahum, 2015, Joiner, Kogel, 2019]	
BED-PARAMETER	MAGNITUDE/INTERVAL
T_{Pot}	[26.00 , 30.00] (Days)
T_K	21 (Days)
$T_{Treatment}$	[30 , 40] (Days)
α [Gy^{-1}]	[0.09 , 0.43] [Gy^{-1}]
β [Gy^{-2}]	0.0313 [Gy^{-2}]
Number of Fractions	[37 , 45] (Fractions)
Fraction Dose	[1.00 , 2.00] (Gy)
Pareto Total Prostate Dose Objective Function [89]	Pareto 1 : 70 Gy Pareto 2 : 78 Gy

Table 2.-Software implemented dataset for GA programming with source references [38,43-45, 96,97,98].

III. 2D EVOLUTIONARY ALGORITHM RESULTS

2D GA Graphical results are shown in Figures 1-4. The constrained optimization results are presented sharply in 2D multifunctional charts. This constrained optimization with ***in vivo*** parameters, [Algorithms 1-5] gets better results than ***in vitro*** one in the previous prostate cancer study [98].

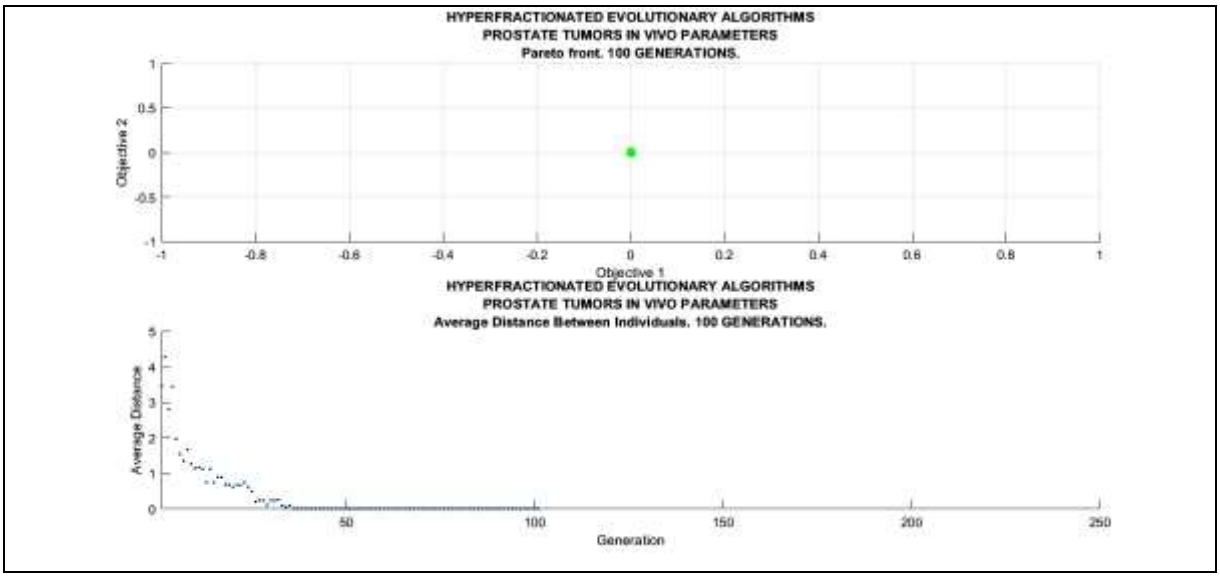

Figure 1.-High precision, almost null average distance, reached with 100 generations constrained optimization Multifunctional GA 2D graph. Note the total accomplishment of both pareto functions. The upper chart is the most important graph given by software when PMO is performed to validate the GA-optimization precision. In this study all programmed optimizations show null residuals, therefore, results are better than [98].

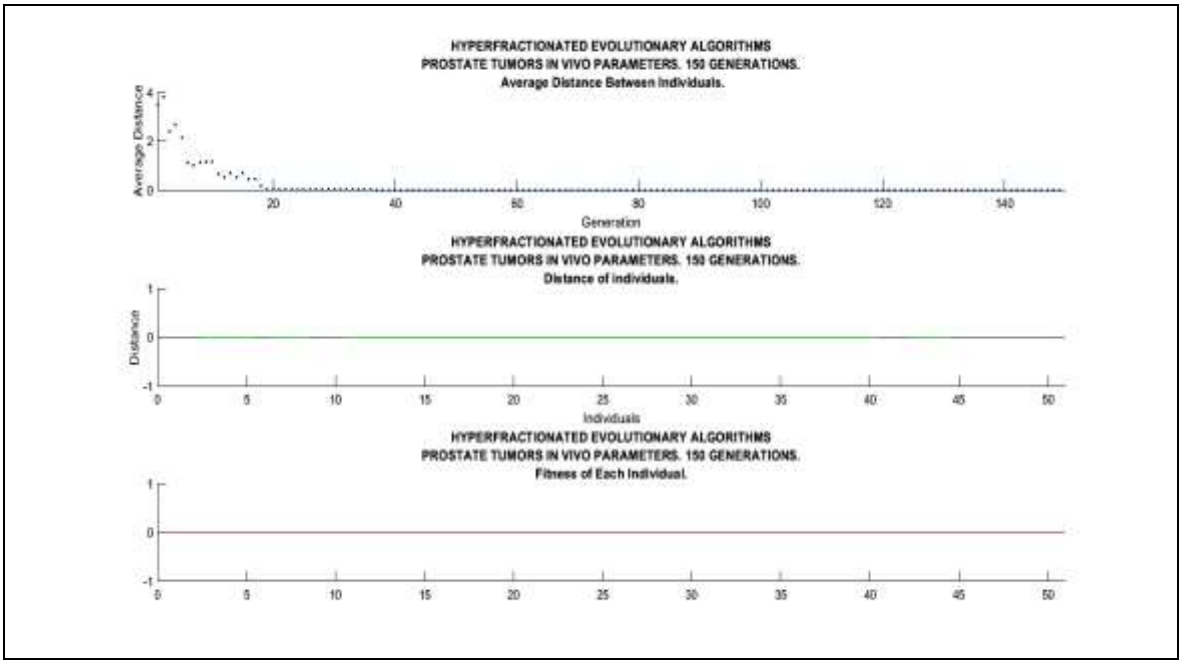

Figure 2.-Stepping up to 150 generations, image shows triple-graph for GA constrained optimization. The first one is the most important graph given by software when PMO is performed to validate the GA-optimization precision. Average distance among individuals is almost null, exact fitness. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts.

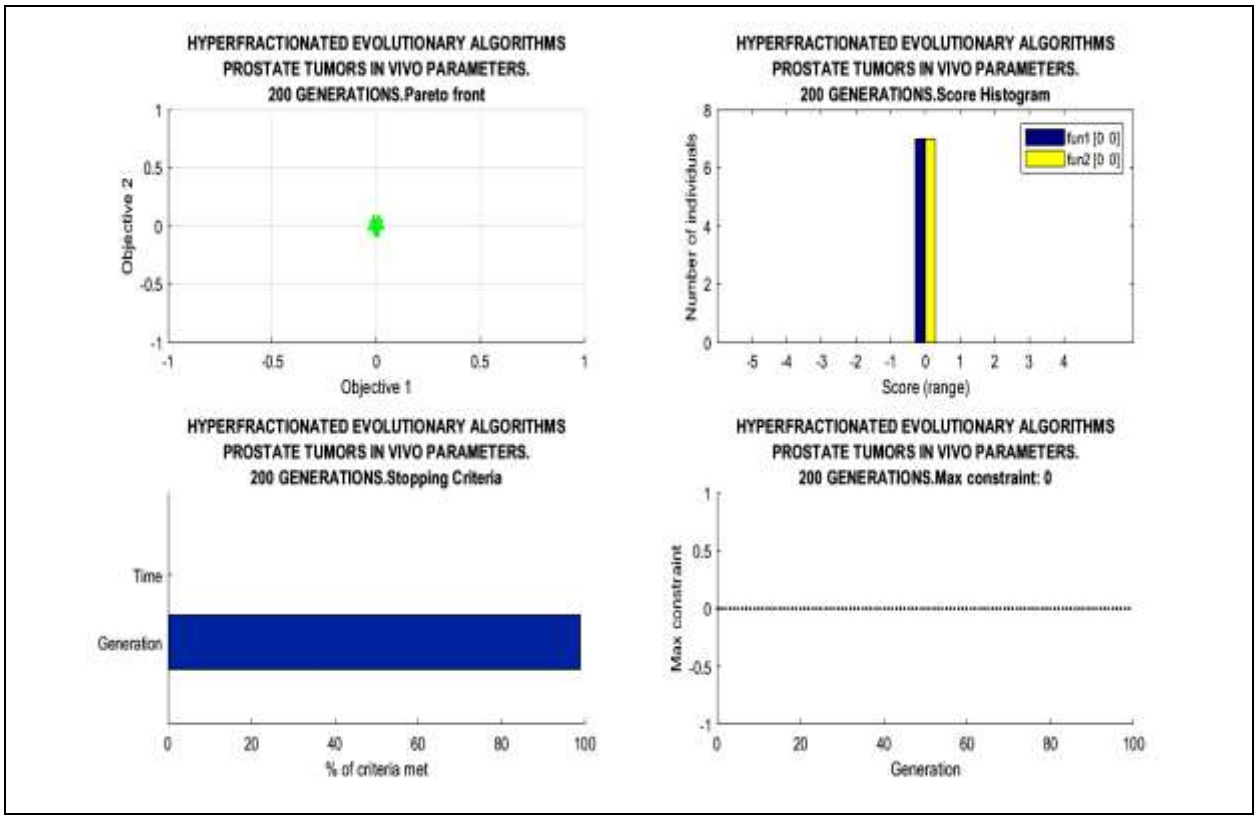

Figure 3.- 200 generations constrained optimization Multifunctional GA 2D graph. Score Histogram shows the accuracy. The upper-left image is the most important graph given by software when PMO is performed to validate the GA-optimization precision. 100% of criteria is met. Enhanced in Appendix.

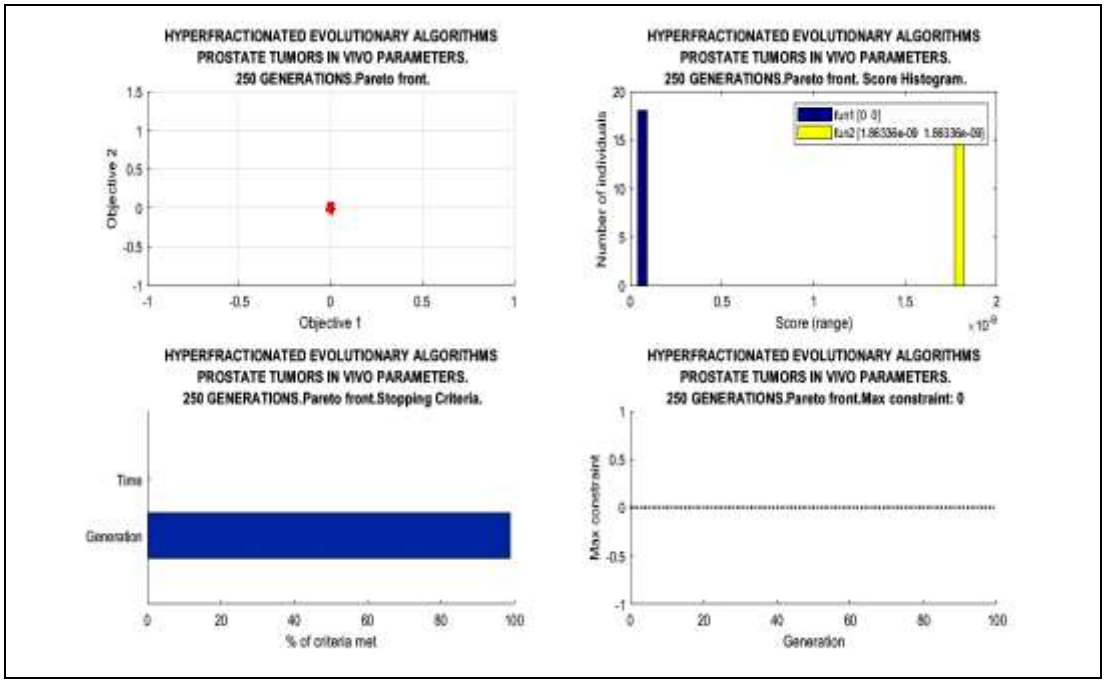

Figure 4.- 250 generations constrained optimization Multifunctional GA 2D graph. Score Histogram shows the accuracy. The upper-left image is the most important graph given by software when PMO is performed to validate the GA-optimization precision. 100% of criteria is met. Enhanced in Appendix.

IV. 3D INTERIOR OPTIMIZATION RESULTS

The imaging process software shows the results got with 3D Interior Optimization, Figs 5-7. Results are very acceptable. Isodoselines are marked inset every image. The radiotherapy planner gets multiple choices by using this 3D IO method.

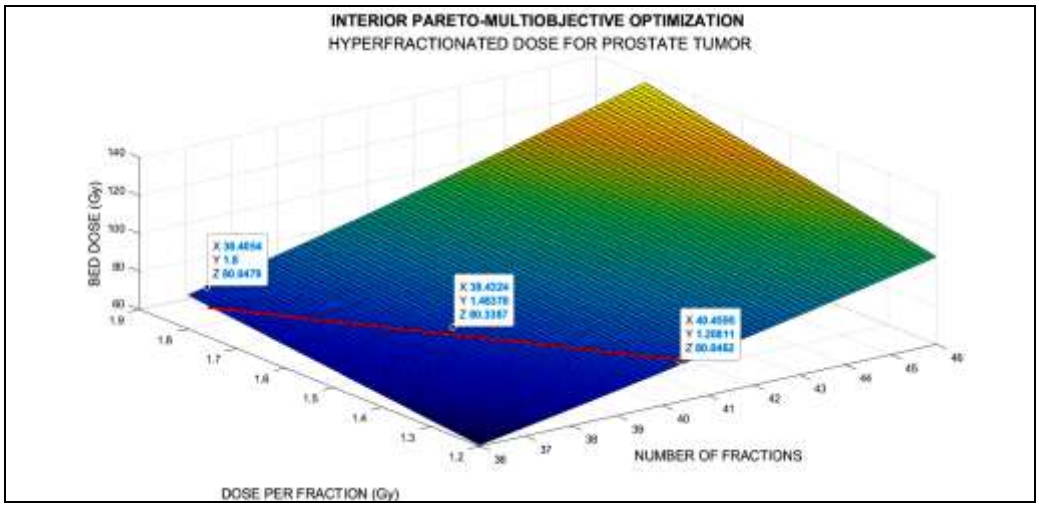

Figure 5.- The fundamentals of IO calculations are implemented into a 3D surface. Pattern intervals for plotting were taken from PMO Table 3 figures. Note that about 80 Gy BED total dose is fixed along Isodoseline, while (k) and (d) parameters vary when cursor is moved along this Isodoseline.

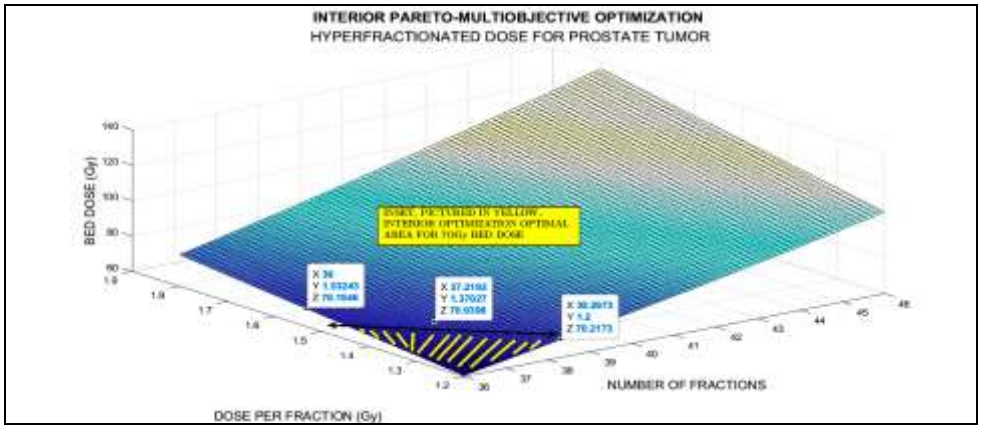

Figure 6.- Area for BED doses lower/equal than 70 Gy is marker in yellow inset. That is under the Isodoseline. Pattern intervals for plotting were taken from PMO Table 3 figures. Note that about 70 Gy BED total dose is fixed along Isodoseline, while (k) and (d) parameters vary when cursor is moved along this Isodoseline.

Invention of Interior Optimization Isodoselines

When performing the 3D Interior Optimization refinement, it was found that Isodoselines can be feasible and useful. Figure 7 can be considered a definite demonstration. It shows a number of selected Isodoselines for a number of TPO-dose magnitudes to prove the new utility found. For IO,the algorithm to be set on program patterns reads,

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

Algorithm (5)

where all the parameters description are at Algorithms 1-4.

An image processing showing the utility for PTO of this IO with several Isodoselines is presented, Fig. 7. Note that Algorithm 5 is converted when running software in a nonlinear-quadratic system of equations. As it is quadratic, the rationale of the precise results is justified.

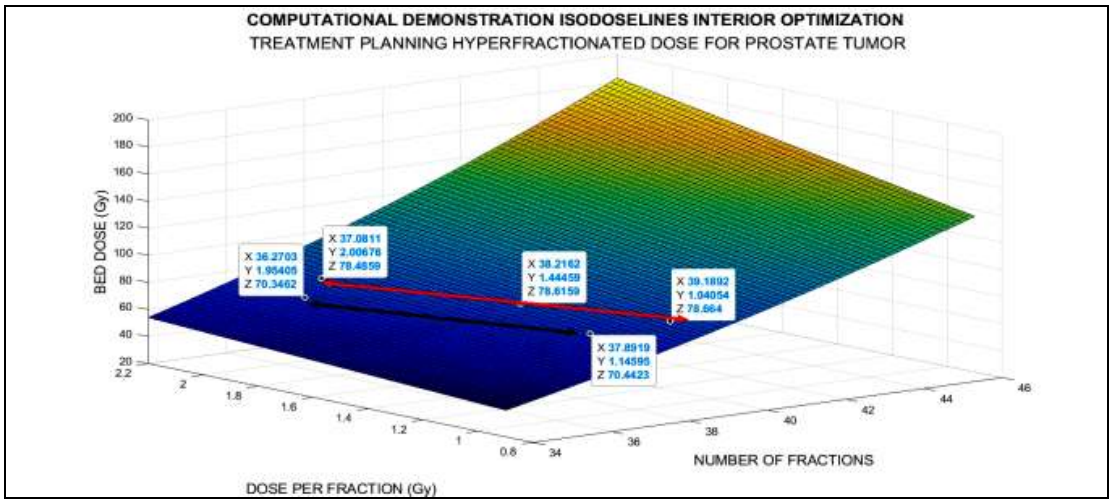

Figure 7.- The Isodoselines fundamentals for IO calculations are implemented into a 3D surface with two examples. Namely, about 70 and 78 Gy. Pattern intervals for plotting were taken from PMO Table 3 figures. Note that each BED total dose is fixed along Isodoseline, while (k) and (d) parameters vary when cursor is moved along this Isodoseline. Intermediate values are marked in-between the Isodoseline for 78 Gy. Enhanced in Appendix.

V. NUMERICAL RESULTS

Numerical results can be divided into to parts. First one is the GA numerical figures, Table 3. Secondly IO results brief based on Figure 7 mainly. In Fig. 7 Isodoselines demonstrate their efficacy for TPO choice. That is, once fixed total dose, e.g., 70 or 78 Gy, any planner can select the desired number of fractions, and the convenient figure of fraction-dose along a Isodoseline, Fig. 7 proof.

Genetic Algorithm Optimization Numerical Results

Figures for constrained PMO-GA optimization numerical data are presented shown in Table 3. As occurred in [98], constrained optimization display acceptable numbers within numerical intervals [1-24,40,68,74-79,87-94,98]

.

Table 3.- Constrained optimization Algorithms 1-4 numerical results. Pareto distance is almost exact, in contrast with previous *in vitro* research (in [98], was about 10^{-2} magnitude order).

GENETIC ALGORITHM OPTIMIZATION NUMERICAL RESULTS FOR PROSTATE TUMORS IN VIVO PARAMETERS HYPERFRACTIONATED RT TREATMENT		
PARAMETER [Optimization with [refs 25,83] and related author's radiotherapy text books] criteria]	**MAGNITUDE INTERVAL/EXACT NUMERICAL GA RESULT**	**ADDITIONAL**
Optimal Dose fraction number	[40] Fractions	Usual protocol in literature [1-21,74-86].
Optimal Dose fraction magnitude	[1.7319] Gy	Usual protocol in literature [1-21,74-86]. Set with intervals according to different criteria.
$T_{Treatment}$	[38] 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.
Dose interval in Objective Function That was set at software patterns	70 Gy for Pareto F function 1 78 Gy for Pareto F function 2	Usual protocol in literature [1-21,74-86]. Set with two total dose Pareto Functions according to different criteria.
Pareto Distance	0 Almost exact	Usual protocol in literature [1-21,74-86]. Set with two total dose Pareto Functions according to different criteria.
Average Distance	0 Almost exact	Usual protocol in literature [1-21,74-86]. Set with two total dose Pareto Functions according to different criteria.

Interior Optimization Optimization Numerical Results

Table 4 show the accurate numerical results got with IO refinement method. Example-dataset included comes from Isodoselines of Figure 7.

INTERIOR OPTIMIZATION NUMERICAL RESULTS FOR PROSTATE TUMORS IN VIVO PARAMETERS HYPERFRACTIONATED RT TREATMENT [DATASET FROM FIGURE 7]		
FRACTIONS NUMBER k [Trunkated]	FRACTION DOSE d Gy	TOTAL DOSE Gy
37	2.00	ISODOSELINE 78 Gy
38	1.44	ISODOSELINE 78 Gy
39	1.04	ISODOSELINE 78 Gy
36	1.95	ISODOSELINE 70 Gy
38	1.14	ISODOSELINE 70 Gy

Table 4.- Brief of IO constrained optimization Algorithms 1-4 numerical results, with description of two Isodoselines, Fig. 7. From Table 2, Lower Isodoseline is for 70 Gy, Upper for 78 Gy. K figures are truncated to integers.

VI. RADIOTHERAPY MEDICAL PHYSICS APPLICATIONS

Table 5 presents details and applications of both optimization techniques. Radiotherapy hyperfractionated treatment planning applications for prostate tumors are specified. Medical Physics principal applications for radiotherapy research emerge from the data.

Table 5- Details for radiotherapy and radioprotection for RT prostate cancer TPO Medical Physics study applications. Derived from these results, dual-optimization (GA+IO) can be considered acceptable.

BED-LQ RADIOTHERAPY OPTIMIZATION APPLICATIONS FOR HYPERFRACTIONATED RT PROTOCOL WITH *IN VIVO* PARAMETERS [GA + 3D INTERIOR OPTIMIZATION]		
APPLICATION	MEDICAL PHYSICS AND RADIATION ONCOLOGY FIELD	INTERIOR OPTIMIZATION AND ADDITIONAL
Optimal number of fractions	RT schedule	All variety of selection within Isodoselines/Avoid side effects [Figure 7]
Optimal fraction dose	RT schedule	All variety of selection within Isodoselines/Avoid side effects [Figure 7]
Change/chose the total dose with Isodoselines At 3D IO surface	RT schedule	All variety of selection within Isodoselines/Avoid side effects [Figure 7]
Biological Models TCP TCCP Improvements	Patient Treatment Precision	Radioprotection improvements, 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

VII. DISCUSSION AND CONCLUSIONS

The objective of the study was to apply firstly constrained 2D GA Optimization for prostate cancer hyperfractionated RT treatment with BED-LQ model and ***in vivo*** parameters. Secondly to get precise numbers by using 3D Interior Optimization methods. Constrained PMO-Multiobjective method was programmed with subroutines. A rather difficult software for 3D Interior Optimization to determine optimal surfaces and Isodoselines was designed. In general, for first stage, the previous publication algorithms were set.

First part of results comprise a group of 2D GA plots and numerical dataset. Constrained Optimization with Algorithms 1-5 got to get a Pareto Distance almost exact, null, with 250 generations. Interior Optimization application in second stages resulted in the invention of Isodoselines along the optimal surface, also with accuracy, Fig. 7. These Isodoselines give a large number of alternatives in terms of number of fractions and magnitude of fractions keeping the same total BED dose. It is considered a practical invention for RT planning with BED models. When number of generations increases from 100, the running time of the constrained programs rises to approximately 1-3 minutes. As a rule, numerical and graphical results are better than expected.

One of the reasons because of which GA-***in vivo*** parameters method gonna get such precision, is the parameter magnitude of T_{Pot} ***in vivo***. The second part of BED equation becomes lower and the model results almost be a quadratic nonlinear equation with k and d variables. As a result, the GA Optimization is simpler for computation and reaches more computational precision.

The method can be considered somehow laborious but the precision gained results are justified. Inconvenient is the increase of running time when using GA in direct proportion to the increment of generations number. The software to construct precise 3D Interior Surfaces and Isodoses has to be checked and done carefully.

Grosso modo, a prostate cancer constrained RT-BED hyperfractionation model with GA and ***in vivo*** data was performed with Pareto-Optimization and refined with 3D Interior Optimization. Isodoselines constitute a practical results for BED RT accurate planning. Applications for prostate tumors and radiation therapy in general optimal TPO emerge from all the study.

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SCIENTIFIC ETHIC STANDARDS

Formulas applied/included are from previous prostate article with in vitro data. Model is a modification from several authors, based also on [20,24,25,83,88,89] techniques. Mathematical Algorithms 1-4 formulas are modificated from previous publications [20,24,25,83,88,89]. RT applications methods for these publications were created by Dr Casesnoves in 2021-2. Methods from [20,87,88] 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 [1-21], 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 [38,43-45]. References [38,43,44,45]: '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. When a formula is presented, all parameters are detailed or referred. If any results inconsistency is found after publication, it is clarified in subsequent contributions [Note: in at least one article of theses series, it was written by mistake that radiation is previous to surger. That is a mistake, for cancer treatment, surgery, when possible, is previous to radiation]. 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, 43-45].

AUTHOR'S BIOGRAPHY

Dr Francisco Casesnoves earned the Engineering and Natural Sciences PhD by Talllinn University of Technology (started thesis in 2016, thesis Defence/PhD earned in December 2018, official graduate Diploma 2019). He works as independent research scientist in computational-engineering/physics. Dr Casesnoves earned MSc-BSc, Physics/Applied-Mathematics (Public Eastern-Finland-University, MSc Thesis in Radiotherapy Treatment Planning Optimization, which was developed after graduation in a series of Radiation Therapy Optimization-Modelling publications [2007-present]). Dr Casesnoves earned Graduate-with-MPhil, in Medicine and Surgery [1983] (Madrid University Medicine School, MPhil in Radioprotection Low Energies Dosimetry [1985]). He studied always in public-educational institutions, was football player 1972-78 (defender and midfielder) and as Physician, supports healthy life and all sports activities. Casesnoves resigned definitely to his original nationality in 2020 for ideological reasons, democratic-republican ideology, and ethical-professional reasons, and does not belong to Spain Kingdom anymore. His constant service to the International Scientific Community and Estonian technological progress (2016-present) commenced in 1985 with publications in Medical Physics, with further specialization in optimization methods in 1997 at Finland—at the moment approximately 100 recognized publications with approximately 62 DOI papers. His main branch is Computational-mathematical Nonlinear/Inverse Methods Optimization. Casesnoves best-achievements are the Numerical Reuleaux Method in dynamics and nonlinear-optimization [books 2019-2020], The series of Radiotherapy Improvements for AAA superposition-convolution model, the Graphical and Interior Optimization Methods [2016-8], the new Computational Dissection-Anatomical Method, [2020], invention of Forensic Robotics [2020-2021], and Molecular Effect Model for High

Temperature Superconductors [2020]. Dr Casesnoves scientific service since 2016 to the Free and Independent Republic of Estonia for technological development (and also at Riga technical University, Power Electrical and Electronics Department) is about 37 physics-engineering articles, two books series, and 1 industrial radiotherapy project associated to Europe Union EIT Health Program (Tartu University, 2017). Treatment planning Optimization Invention of Isodoselines was created in July 2023.

APPENDIX

BIOMARKERS GENERAL CLASSIFICATION FOR CANCER RADIOTHERAPY TREATMENT
[Author's proposal]

TYPE	APPLICATION	ADDITIONAL	EXAMPLES
P-BIOMARKER (PROGNOSIS BIOMARKER)	Prediction of approximate survival time subject to optimal treatment	Prediction for approximate survival based on specific tumor cell histology, and according to the relation histology-efficacy of drugs. Drug failure investigation utility.	Research clinical trial example, [from 96]: investigation data show that patient survival time in PD-L1–positive patients who are treated with combined anti-CTLA-4 and anti-PD-1 is not superior to nivolumab monotherapy. That implied that was necessary further research. This clinical-trial study area is difficult
T-BIOMARKER (TREATMENT BIOMARKER)	Selection of approximate optimal choice for effective chemo-inmuno drug-target treatment	Optimization of the best effective drug type for personalized tumor at every patient. Detection of optimal drug-target and pharmacokinetics. Drug failure patient-personalization investigation. Target characterization.	HSP90α is an inducible molecular chaperone that functions as a homodimer [ref 96, Chapter 2.4, Table 2.4.2]
H-BIOMARKER (HYBRID BIOMARKER)	Both prediction of survival time and optimal treatment	Those ones that can make both functions, or one of them better than the other	Nano-Biomarkers actually in investigation can modify the inmuno-cells and efficacy of drugs over cells tumor

Table 1 [Enhanced].-General Biomarkers classification, [Author's proposal]. Nano-Biomarkers is an open research field with potential perspectives in future [96,99]. Just remark that Biomarkers are is extent, diverse and difficult as involves biochemistry, molecular biology, medicine-pharmacology, medical physiology and several other fields. Therefore this Table is simple based on Author's proposal classification.

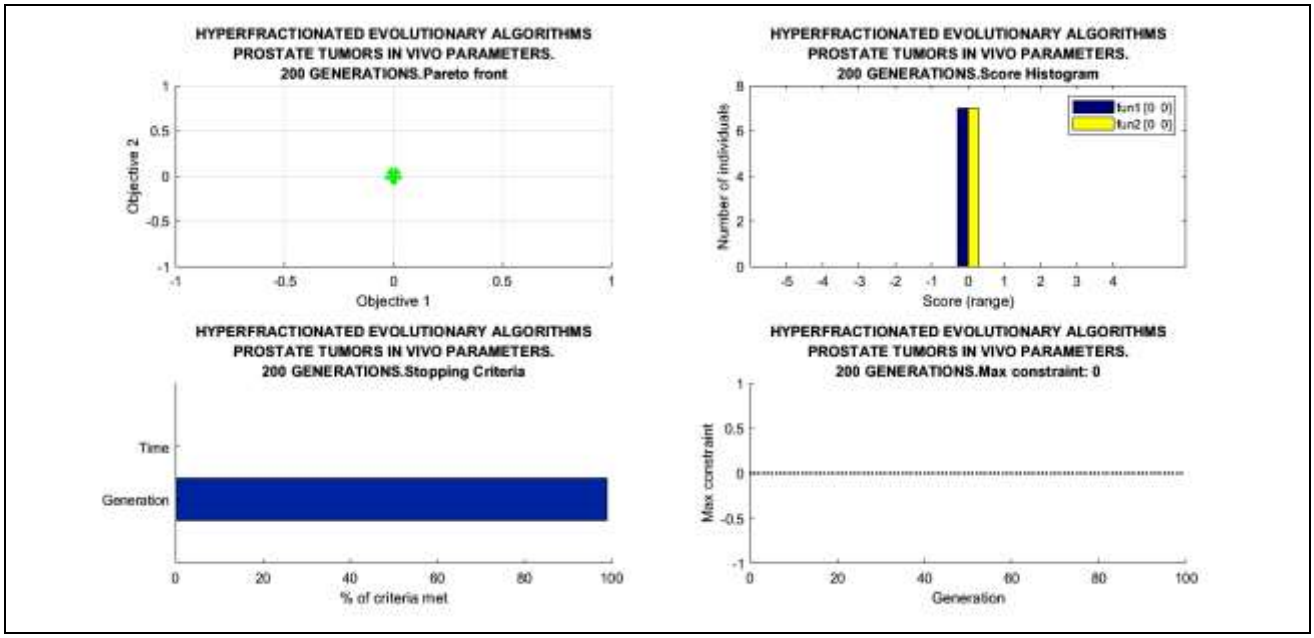

Figure 3 [Enhanced].-200 generations constrained optimization Multifunctional GA 2D graph. Score Histogram shows the accuracy. The upper-left image is the most important graph given by software when PMO is performed to validate the GA-optimization precision. 100% of criteria is met.

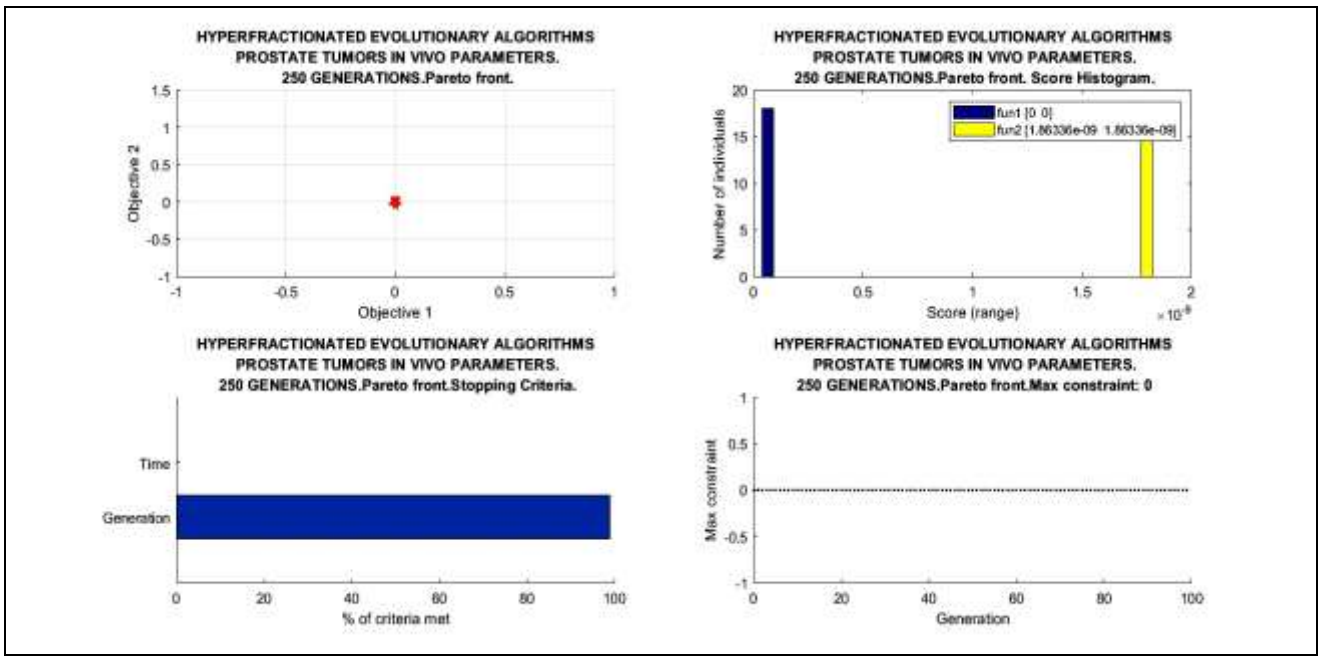

Figure 4 [Enhanced].- 250 generations constrained optimization Multifunctional GA 2D graph. Score Histogram shows the accuracy. The upper-left image is the most important graph given by software when PMO is performed to validate the GA-optimization precision. 100% of criteria is met.

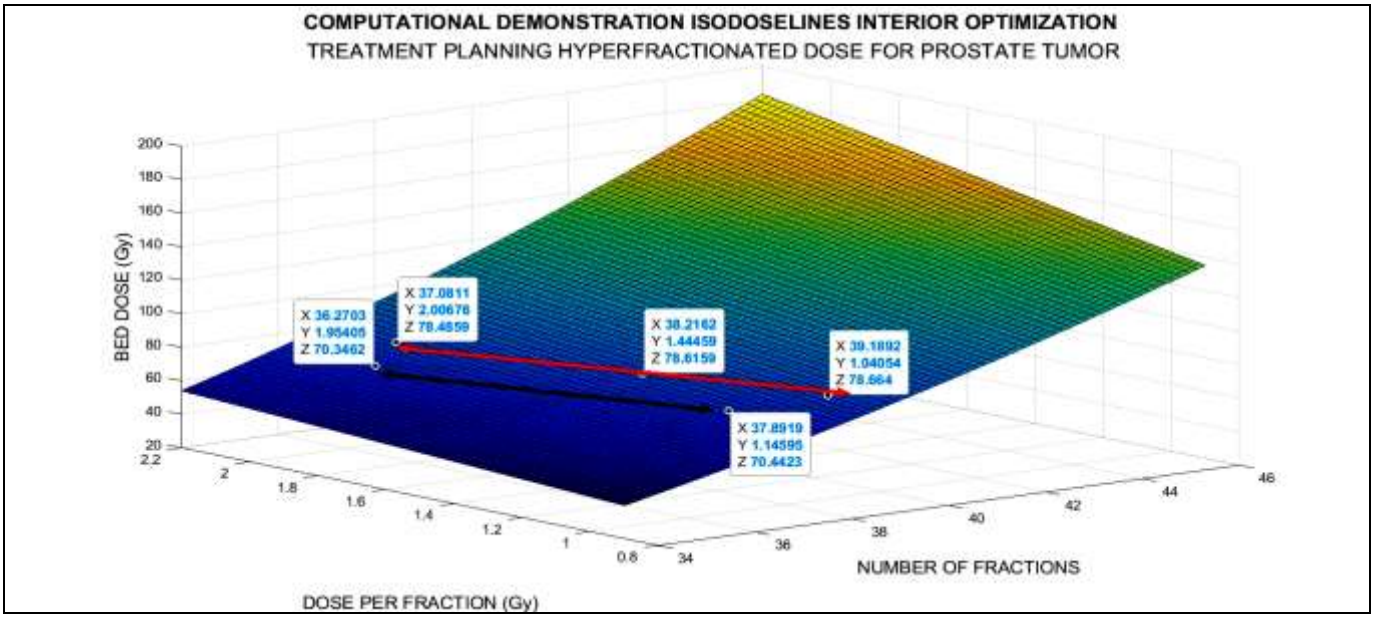

Figure 7 [Enhanced].- The Isodoselines fundamentals for IO calculations are implemented into a 3D surface with two examples. Namely, about 70 and 78 Gy. Pattern intervals for plotting were taken from PMO Table 3 figures. Note that each BED total dose is fixed along Isodoseline, while (k) and (d) parameters vary when cursor is moved along this Isodoseline. Intermediate values are marked in-between the Isodoseline for 78 Gy.