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Radiotherapy Hyperfractionated 3D Isodosezones Planning Optimization Method for Lung Tumors with BED Pareto-Multiobjective Model

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ABSTRACT

3D Isodoselines and Isodosezones were presented in previous publication. Isodosezones were put out and applied on prostate tumors. In this further improvement, 3D Isodosezones are got with programming innovation with new software-engineering programming for lung cancer. BED model for radiotherapy hypofractionated treatment planning optimization is used. Interior Optimization (IO) for lung tumor BED model hyperfractionated Treatment Planning Optimization (TPO) application is further demonstrated. The implemented data was got with additional-dual constrained evolutionary algorithm for BED-LQ model (Biological Effective Dose) in this cancer type. Results for TPO with 3D IO-Graphical Optimization show a number of surfactal IO 3D Isodoselines/zones with proven accuracy-feasibility of the novelty of the technique. Programming software for surfactal-isodoselines/zones methods solutions show a series of 3D IO graphs for TPO. Applications for lung 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 (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

3D Isodosezones (Casesnoves imaging-software and optimization invention, 2022) are developed from a previous 3D Isodoselines and 3D Isodosezones, published definition-invention [101], for prostate treatment planning optimization (TPO), a primary group of demonstrating graphs were shown. This study deals with an extension/improvement of 3D Graphical-Interior Optimization obtained with perfected software. Isodoselines and Isodosezones are proven be practical and complementary useful in TPO.

Advantages and inconvenients of BED model as a several variables function to be optimized are explained. A series of imaging processing 3D charts are presented for Isodosezones in lung cancer BED model for TPO. The BED parameters used are based on ***in vivo*** tumor radiobiological parameters (α , β), Treatment-Time variable, $T_{K\ (delay)}$, and $T_{Potential}$ ones, Table 1, [98]. The research presented is based/intended on 3D charts to prove TPO usage, rather than a numerical series results. Original Fowler model has got an extensive number of variations and types along the literature. This study is grounded on a number of previous research in biological models optimization contributions, and contains innovations of software developed in other science areas [1-21, 28, 86,88,89,99,101] .

The radiotherapy TPO applications outcome for this Isodosezones involves optimization of main parameter magnitudes, namely, number of fractions, total dose, treatment total time, and others for BED model.

Results comprise illustrative examples for BED model TPO refined with 3D Isodosezones series for several magnitudes of total doses. Numerical values are detailed.

In brief, a number of 3D imaging processing graphics for lung tumors TPO by using BED model are proven and explained. Confirmation of findings of [101] is got. Applications for lung tumor radiotherapy TPO are briefed.

II. MATHEMATICAL AND PROGRAMMING METHOD

This section comprises the dataset that was used for programming improvements from [100]. The mathematical algorithms and software methods are also developed from [86,88,89,99,101]. The basic dataset reminder of ***in vivo*** is included in Table 1 from [98].

Definition 1.- In RT-3D Treatment Planning, a 3D Isodoseline is demarcated by a line whose dose-distribution parameters can vary for optimal planner choice while keeping constant the total dose delivery magnitude [Casesnoves, 2022] .

Definition 2.- In RT-3D Treatment Planning, a 3D Isodosezone is demarcated by a polygon whose dose-distribution parameters can vary for optimal planner choice while keeping constant the total dose delivery magnitude [Casesnoves, 2022] .

As in constrained GA optimization previous dataset was detailed, [86, 88, 89, 99, 101], Table 1. Constraints matrix algebra are implemented through [Algorithms 1-5 from 86, 88, 89, 99, 101]. In Matlab and other similar systems, the constraints can be set as a matrix equation. Main simulation dataset comes from [20-25,68,74,75,80,81,85-94,99,101] . The GA simulations results that were done [98,99,101] with numerical-experimental interval-data for GA implemented arrays were used for imaging process. $T_{Potential}$ in lung for ***in vivo*** experimental data is about [26 , 30] days. That Table 1 shows all dataset implemented with references for ***in vivo*** parameters at BED-LQ model at hyperfractionated low dose fractions [numerical experimental data from refs in 86, 88, 89, 99, 101].

Brief Review of Algorithms

The GA algorithms used are approximately the same than in previous prostate cancer publication, [98,101, Casesnoves, 2022]. The sequence of the formulas development, with few numerical variations, is as follows,

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

(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 nonlinear-quadratic model has been adapted for ***in vivo*** parameter T_{Pot} magnitude. Then, PMO in lung, [24,88,89,98, 101] 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 DOSE ϵ [70 , 80] Gy.

Algorithm 2 [Fowler mainly, modified by Casesnoves, 98].- Prostate PMO algorithm [1-25,85-90, 99, 101] implemented in software. Table 1 shows these intervals for optimization parameters details. Programming was developed in Matlab system. The constraints algebraic algorithm developed for Pareto-Multiobjective problem, [Algorithms-3-5, Casesnoves 2023] reads,

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

(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 [99,101], which are implemented reads,

$$\begin{aligned}&\text{Matrix Algebra Subroutines}\\&\text{For Constraints,}\\&[A_1] \times \begin{pmatrix} K \\ d \\ T \end{pmatrix} \le \begin{pmatrix} S_{K\,max} \\ d_{d\,max} \\ T_{T\,max} \end{pmatrix},\\&[A_2] \times \begin{pmatrix} K \\ d \\ T \end{pmatrix} \ge \begin{pmatrix} S_{K\,min} \\ d_{d\,min} \\ T_{T\,min} \end{pmatrix},\end{aligned}$$

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 1.

Software used for this study continues previous algorithms papers and literature data [1-20,24,68,74,88,89,98,99, 101] with modifications, and addition of IO programs. For GA-PMO modeling, Equation 1 and Algorithms 1-4 are implemented on 3D programs, with application of Algorithm 5 basic model formula. Algorithm 2 was programmed with Algorithm 3 matrix constraints subroutines-functions. Table 1 shows Constrained GA Optimization ***in vivo*** parameters, in Algorithms 1-5. 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.

The algorithm function mathematical analysis for 3D IO charts and numerical optimization

The algorithm function constitutes a several variables one, [101]. This implies that the 3D IO can be made selecting 3 of them for the IO graph, to chose the most convenient TPO data, Figures 1-3.

The optimization for BED model, in order to obtain 3D graphs for Isodosezones, should get 3 variables. However, in the BED model the parameters number could be higher. These mathematical options imply that graphical optimization process could be set in a number of graphs, where everyone holds any convenient 3 variables combination. In terms of software, the task is more complicated for constraints and precision. Figures 1-3, show these different options.

Computational Implemented Dataset

In Table 1, software implemented dataset for GA programming with source references [38,43-45,98,100].

Table 1.- Software implemented dataset for GA programming with source references [38,43-45,98].

***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}]	[0.2556 , 0.4009] [Gy^{-1}]
β [Gy^{-2}]	0.0581 [Gy^{-2}]
Number of Fractions	[30 , 45] (Fractions)
Fraction Dose	[1.00 , 2.00] (Gy)
Pareto Total Lung Dose Objective Function [89]	Pareto 1 : 70 Gy Pareto 2 : 80 Gy

III. 3D ISODOSEZONES- RESULTS

In this extended study, 3D Interior and Graphical Optimization methods are used in parallel-refinement to confirm results from [98,101], with the ***in vivo*** dataset from

[23,24,97,98,101] . The 3D imaging process, Figures 1-3, programming demonstrate the results got with 3D IO in [101]. 3D Isodosezones are cursor-marked inset within every 3D graph. The radiotherapy planner obtains the desired combination of fractions (**k**), and fraction dose (**d**), for a fixed total BED dose delivery. That is considered a consistent, easy, fast, and simple advance in modern TPO and RT research.

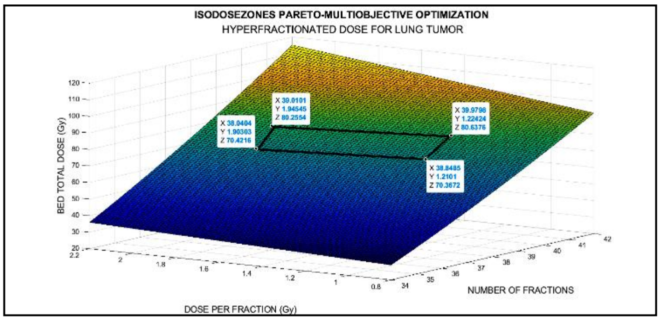

Figure 1.- 3D Isodosezone for two variables, at XY plane, number of fractions and dose per fraction, the choice. Namely, Number of fractions and dose per fraction in lung TPO. series of BED doses. Namely, marked inset, [70,80] Gy. The Isodosezone fundamentals for IO calculations are implemented into a 3D surface with two examples. Pattern intervals for plotting were taken from PMO but with ***in vivo*** lung tumor parameters. Each BED total dose is fixed along 3D Isodozone, while (**k**) and (**d**) parameters vary when cursor is moved over this Isodosezone. This software numerical method was also developed in F # and Fortran. Enhanced in Appendix.

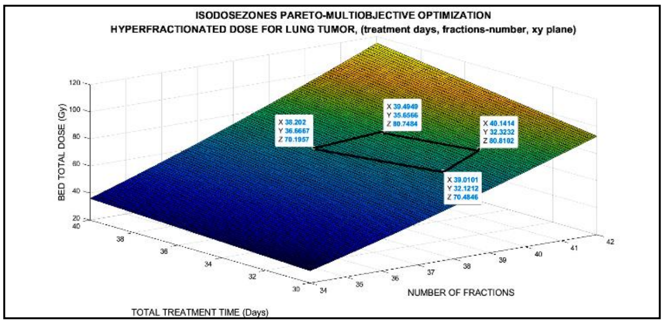

Figure 2.- 3D Isodosezone for two variables. Namely, the choice is number of fractions and total treatment time in lung TPO. series of BED doses. Namely, marked inset, [70,80] Gy. The 3D Isodosezone fundamentals for IO calculations is implemented into a 3D surface with two examples. Pattern intervals for plotting were taken from PMO but with ***in vivo*** lung tumor parameters. Each BED total dose is fixed along 3D Isodozone, while (**k**) and (**d**) parameters vary when cursor is moved over this Isodosezone.

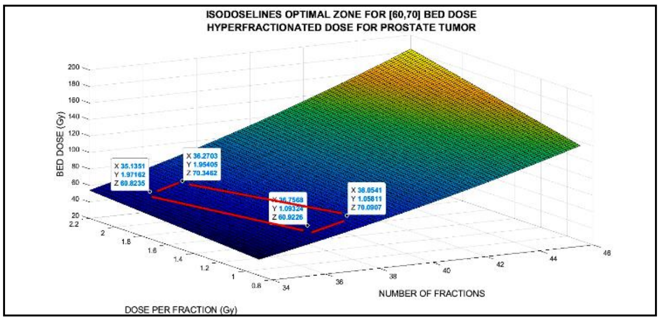

Figure 3.- Prostate tumor review of previous publication, [101]. Parameters selection at XY is number of fractions and dose per fraction. 3D Isodosezone fundamentals for IO calculations within interval of total BED prostate dose [60,70] Gy. In this area the planner can select any convenient choice for the patient treatment.

IV. RADIOTHERAPY MEDICAL PHYSICS APPLICATIONS

Table 2, modified/improved from [101], shows radiotherapy applications for RT treatment based on biological models, and specifically also for this study. Medical physics principal applications for radiotherapy TPO are explained briefly.

Table 2.- From previous publications, [23,24,97,98,101], brief of radiotherapy and radioprotection applications derived from imaging results.

3D ISODOSELINES RADIOTHERAPY TREATMENT PLANNING OPTIMIZATION APPLICATIONS BRIEF		
APPLICATION	**MEDICAL PHYSICS FIELD**	**ISODOSELINES FOR TPO**
Optimal Dose Fractions Magnitude	Patient Treatment Precision	Increase TCP, TCCP, and possible decrease of NTCP
Optimal Dose Fractions	Patient Treatment Precision	Increase TCP, TCCP, and possible decrease of NTCP
Planner Selection of Optimal Dose and number of Fractions	Patient Treatment Schedule Precision	Increase TCP, TCCP, and possible decrease of NTCP
Post-RT Treatment Survival time	Optimization Time Schedule	Better life-quality for patient. Increase of Survival Time
Biological Models Research	Improvements in research and applications	Improvements LINAC Software And Imaging guided RT Treatment. Improvements in Gamma-Knife, and Cyber-Knife
NTCP Models	Possible applications also	Decrease of Side-Effects at OARs

V. DISCUSSION AND CONCLUSIONS

The objective of the study was to get a series of 3D Isodosezones charts to evidence and verify the results from [98,101] in prostate cancer, but for lung tumors hyperfractionated RT treatment with BED-LQ model and ***in vivo*** parameters dataset. An improved and rather difficult software for 3D Interior Optimization to determine optimal surfaces and Isodosezones was designed. All imaging processing results confirm the previous studies [98,101].

The programming method has the inconvenient that the 3D surfaces are specific for each and every model and cancer type. However, to change formulas and/or parameters in software is not complicated. Running time for 3D surfactal Isodoselines is acceptable.

The research presented is based/intended on 3D imaging-processing to prove TPO usage, rather than a numerical series results. Therefore, results can be considered acceptable at present.

The radiotherapy TPO applications outcome for this Isodosezones involves optimization of main parameter magnitudes, namely, number of fractions, total dose, treatment total time, and others for BED model. The mathematical analysis for the model variables was justified.

Succintly, an extensive lung cancer constrained RT-BED hyperfractionation model with 3D imaging processing and ***in vivo*** data was performed with 3D Isodosezones software engineering work. 3D Isodosezones constitute a practical result for BED RT accurate planning. Applications for hyperfractionated dose delivery in lung tumors and radiation therapy optimal TPO in general arise from all the study.

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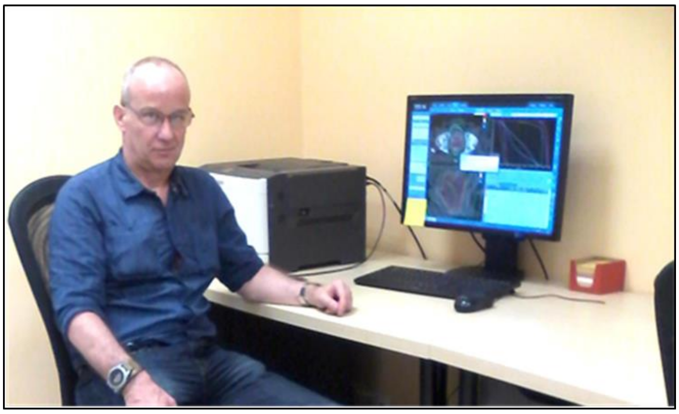
SCIENTIFIC ETHIC STANDARDS

Formulas applied/included are from previous prostate article with in vitro data. Model is a modification from several authors, based also on [20,24,25,83,86,88,89,99,101] 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 [39,44-46]. References [39,44-46]: '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 tumor-surgery. 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, any 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 [39, 44-46]. Number of references is large to provide literature in open access for public health care institutions.

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]). Casesnoves resigned definitely to his original nationality in 2020 for ideological reasons, anti-monarchy-corruption, democratic-republican ideology, and ethical-professional reasons, and does not belong to Spain Kingdom anymore. His constant service to the International Scientific Community and Estonia Republic technological progress involves about 80 articles, more than 100 total publications, and about 3 books. Recent advances published are in Superconductors Mathematical Modelling and Radiotherapy Brain Neurobiological Models, 3D-AI Isodosezones and Isodoselines. Among Dr Casesnoves inventions and scientific creations are:

Numerical Reuleaux Method

Radiotherapy Omega Factor correction for AAA model wedge filters dose delivery

Integral-Differential materials erosion model

Graphical Optimization

Interior Optimization

Superconductors Molecular Effect Model

Superconductors Multifunctional Transmission Line

BED radiotherapy model GA optimization

RT Isodoselines and Isodosezones

APPENDIX

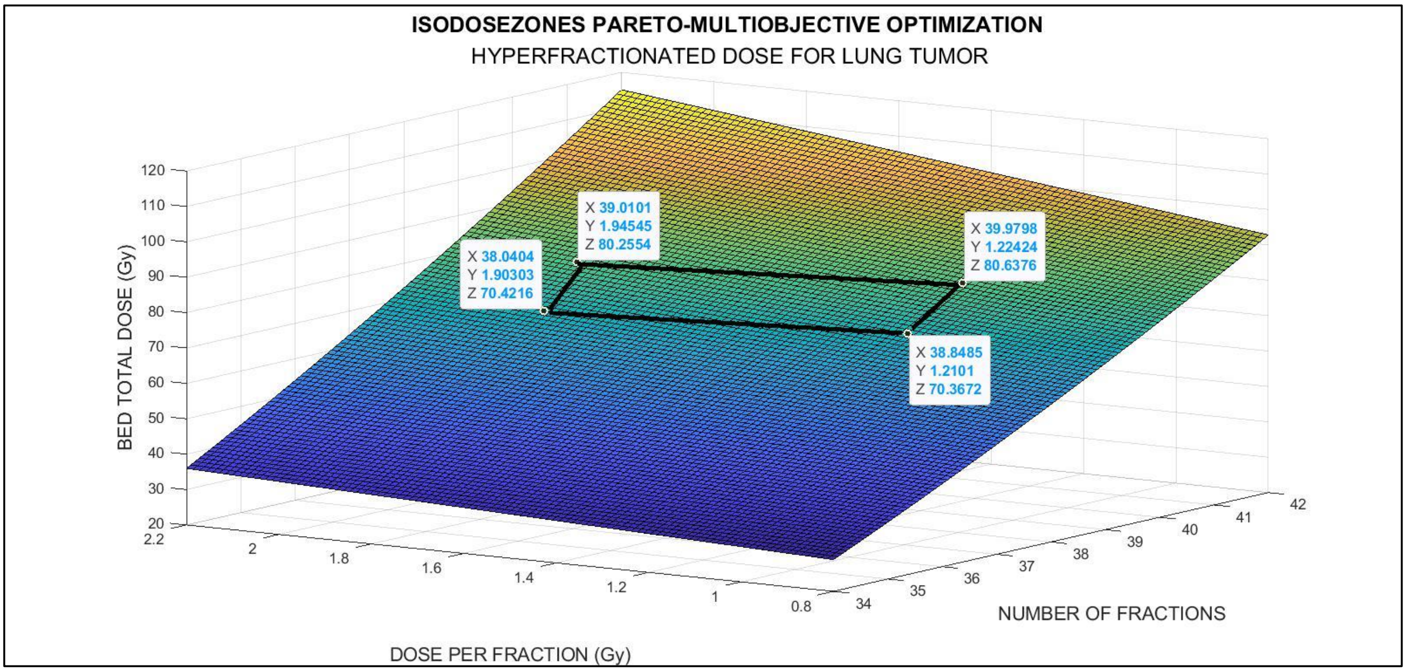


Figure 1. enhanced.- 3D Isodosezone for two variables, at XY plane, number of fractions and dose per fraction, the choice. Namely, Number of fractions and dose per fraction in lung TPO. series of BED doses. Namely, marked inset, [70,80] Gy. The Isodosezone fundamentals for IO calculations are implemented into a 3D surface with two examples. Pattern intervals for plotting were taken from PMO but with ***in vivo*** lung tumor parameters. Each BED total dose is fixed along 3D Isodozone, while (**k**) and (**d**) parameters vary when cursor is moved over this Isodosezone. This software numerical method was also developed in F # and Fortran.