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Radiotherapy Genetic Algorithm Pareto-Multiobjective Optimization of Biological Effective Dose and Clonogens Models for Breast Tumor Improved Treatment

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ABSTRACT

BED model (Biological Effective Dose) for Hyperfractionation TPO was optimized with Pareto-Multiobjective Genetic Algorithms (GA) software. Secondly, the $N_{Effective}$ (Effective Tumor Population Clonogens Number) model optimization for breast cancer clonogens parameters determination in TPO (Treatment Planning Optimization) is carried out with 3D Graphical and Interior Optimization methods. BED model (Biological Effective Dose) for Hyperfractionation TPO was optimized with Pareto-Multiobjective GA software. Results comprise imaging process series and numerical values of $N_{Effective}$ model for breast cancer parameters. Additional results demonstrate Pareto-Multiobjective GA BED model both with Pareto-Optimal Front graphics, charts and numerical dose fractionation datasets. For all these findings, supplementary new recent applications with 3D Isodoses TPO with AAA (Anisotropic Analytic Algorithm) model wedge filters dose delivery is shown. Modern RT treatment breast cancer, and tumors in general for Fractionation-dose protocols are explained.

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_{Eff}), Linear Quadratic Model (LQM), Integral Equation (IE), Tumor Control Probability (TCP), 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) .

I. INTRODUCTION

The objective of this research is to apply Evolutionary Algorithms Pareto-Multiobjective Optimization on two radiotherapy BMs. Additionally, computational software to present new 3D Isodoses graphs with WF dose delivery in AAA model is shown.

Evolutionary Algorithms constitute a fundamental base for Artificial Intelligence fundamentals in radiotherapy TPO. BMs provide with better experimentally-based accuracy for RT optimal treatment, in order to avoid excess of radiation on OARs and get the best NTCP [1-21,74-85]. Evolutionary Algorithms are similar, but different than Monte Carlo stochastic methods.

For these purposes Nonlinear GA engineering software was designed in a number of programs. The 3D Graphical optimization programs and imaging processing techniques constitute an improvement from previous contributions [75,85].

The innovation of this article is to present and prove the GA utility to obtain optimal results for two BMs. First one, BED model for breast cancer RT treatment. Its Hyperfractionation doses, treatment time with delays tolerance intervals, and optimal number of fractions were determined. The second model [75,85], corresponds to $N_{Effective}$ (Effective Tumor Population Clonogens Number) model, [Fowler, J, 1989-2010,83] . It is a review and innovation from [20,21,75,85].

3D Graphical Optimization for $N_{Effective}$ rate with a range of N_0 clonogens magnitude was shown in improved results from [20,21,75,85].

GA findings are presented both in 2D graphics and dataset. Numerical results and applications to improve breast tumor RT treatment are detailed in Tables 2-3. Additionally, new 3D Isodose graphics for TPO with AAA model in WF beam-modification delivery, at isocenter depths [z = 5,15 cm], is proven and graphically detailed.

Succintly, Nonlinear Pareto-Multiobjective GA optimization was performed for BED and $N_{Effective}$ models in breast cancer TPO. Further, 3D Graphical Optimization and 3D Isodoses are shown and demonstrated.

II. MATHEMATICAL METHODS AND SOFTWARE

Two models have been optimized. The first one, Equation 1, is the most innovative, based on artificial intelligence basics of Evolutionary Algorithms. $BED_{Effective}$ model implemented is the primary one, because refinements/variations were presented in literature later on [24].

The second model constitutes an improvement for [20,75,85] publications. Its software and imaging processing perspectives were enriched, Eq. 2.

Formulation for Pareto-Multiobjective GA BED Model

Designed for Pareto-Multiobjective Optimization, the basic $BED_{Effective}$ model was implemented, [24]. This BED model constitutes the fundamentals for fractionate radiotherapy. Therefore, the following algorithm was set [Sketch 1],

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

(1)

where

$BED_{Effective}$: Number of tumor clonogens in function of RT treatment protocol time [Gy].
k: Number of fractions, PMO parameter [50 , 60]. From [24,25,26].
d: PMO parameter of fraction dose [0.9 , 1.7] [Gy] from [24,26].
T : PMO Total RT Treatment time course, [42-56, days]. From [24-26].
T_{Delay} : PMO number of delay days after standard RT treatment time [days]. PMO interval [21, standard].
$T_{Potential}$: Potential Tumor Doubling Clonogens time, [days, standard breast cancer 14 days].
α : PMO Clonogen radiosensitivity parameter, [0.36-0.25 , 0.36+0.25] from [24].
β : Clonogen radiosensitivity parameter [0.0581] from [24].

Sketch 1.- PMO algorithm [Casesnoves, 2021-2022] implemented in software, Figures 1-4. The intervals for optimization parameters in software are detailed.

Formulation for $N_{Effcetive}$ Clonogens Model

For determination of $N_{Effective}$ Clonogens population number, [75,85], a standard model was selected for [Fowler, J, 1989-2010]. The experimental parameters for breast cancer RT treatment TPO protocol are shown in Table 1, based on [20-25,75,85]. This mathematical model for Effective Number of Clonogens population during RT treatment time, [Fowler, J, 1989- 2010,83], whose equation was detailed from [23,24] reads,

$$N_{Effective} = N_0 \times 2^{\left[\frac{(T-T_{Del})}{T_{Pot}}\right]};$$

(2)

where

$N_{Effective}$: Number of tumor clonogens in function of RT treatment protocol time.
N_0 : Initial Clonogens Number at starting RT time.
T : Total RT Treatment time.
T_{Delay} : Number of delay days after standard RT treatment time.
$T_{Potential}$: Potential Tumor Doubling Clonogens time.

$N_{Effective}$ parameter is important for TPO with BMs. The implementation of this parameter into BMs provides with accuracy in TCP, BED, and NTCP essential determinations for TPO. Biomodels equations depending on N_0 and $N_{Effective}$ are not very complicated, and based usually on exponential functions, statistical distributions [Binomial or Poisson] usually, and two radiosensitivity key parameters. Namely, [α and β biological modelling parameters], whose magnitudes intervals can be determined by ***in vitro*** or ***in vivo*** experimental. An Integral Equation Model (IEM) for TCCP, based on new Linear Quadratic Model and Statistical Binomial Distribution approximation was published in recent contributions [20,75,85]. The simplest Linear Quadratic model modified equation was published [75,85].

Dataset and approximations for breast cancer implemented into Eq.2 model is shown in Table 1, [20-25,75,85] .

Table 1.- The simultions were done with approximate numerical-experimental data from several authors. $T_{Potential}$ in breast cancer is taken 14 days. However, that figure is an approximation based on radiobiological experimental. Simulation dataset from [19,21-25,74,75,80,81,85] .

BREAST TUMORS CLONOGEN REPOPULATION DURING TREATMENT RT TIME MODEL DATASET FOR SIMULATIONS		
PARAMETER	**COMPUTATION INTERVAL**	**REFERENCES AND DETAILS**
Breast Tumor N_0 magnitude	[10^3 , 10^{10}] clonogens	This interval was selected from [Mayles, W, et al., 2022]
T Standard RT Time	Fixed 21 days	This interval was selected from [Mayles, W, et al., 2022] , However it varies according to authors, depending on Conventional, Hiper or Hypo Fraccionated RT treatment time
T_{Delay}	[22 , 40] days	It was supposed weekends or hospital break days and unpredictable delays
Breast Tumor $T_{Potential}$	14 days	Approximate breast cancer in vivo data selected from [Haydaroglu A, Ozyigit G, 2013].

III. RESULTS

Figures 1-4 show PMO results. Table 2 details numerical PMO results. The most important to check the validity of results is Figure 1 that shows Pareto Front of the objective function of Equation 1. Average distance among generations is presented in Figure 2. Number of generations selected was 300-800. Score histograms, Figure 3, prove the validity of the software and PMO done.

Results for Pareto-Multiobjective GA BED Model

Imaging processing PMO results are presented in imaging processed chart commented, Figures 1-4. Brief of Numerical Results from software are included in Table 2.

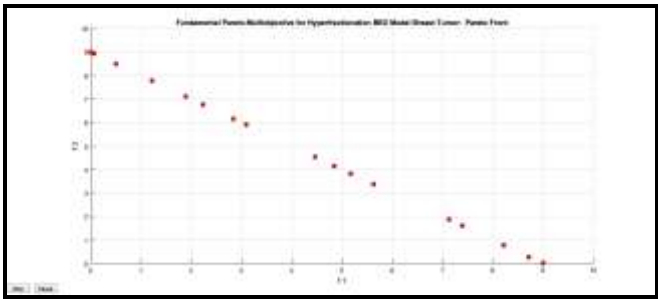

Figure 1.-This is the most important graph given by Matlab when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f_1 and f_2 show low residuals. Therefore, results are acceptable.

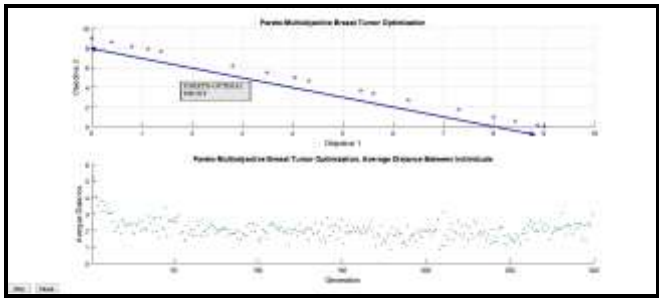

Figure 2.- This is the lined-marked inset graph showing the Pareto Front. The lower chart details the average distance among generations. Since the number of functions calculated is quite high, the points that show the distance vary significantly for 800 generations. The fundamentals of PMO calculations are usually based on 2D PMO functions charts. In this study both Objective f_1 and f_2 that show low residuals.

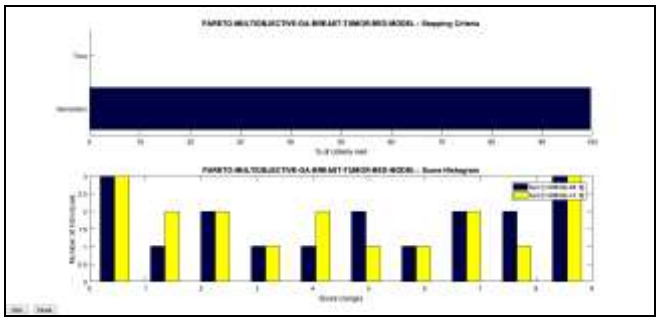

Figure 3.-Complementary 2D graphs showing that 100% criteria is met and number of individuals paired-histograms. Objective f_1 and f_2 are differentiated by blue and yellow colors.

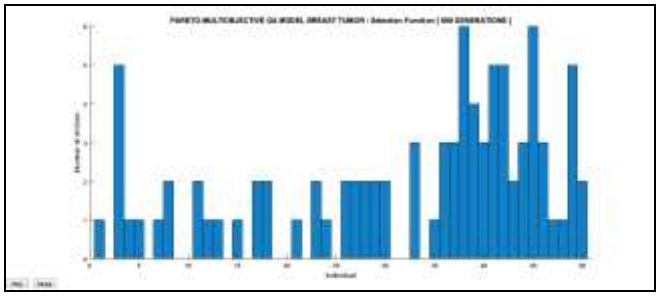

Figure 4.- Complementary 2D graphs details showing number of children in function of individuals.

Results and Review for $N_{Effcetive}$ Clonogens Model

This section shows a review of $N_{Effective}$ model of Eq. (2). Figures 5-7 show 3D results od Eq, 2 for $N_{Effective}$ magnitude determination [Z axis] in function of N_0 and RT breast cancer parameters from [20,75,85]. Namely, treatment extension time for unexpected delays or weekends gaps, $T_{potential}$, N_0 standards, and total RT time-schedule. Figures,

6-7 are set with logarithmic scales. The gaps in RT treatment schedule could very because the weekends, holidays, patient secondary effects, psychological difficulties, hospital technical equipment/facilities, etc.

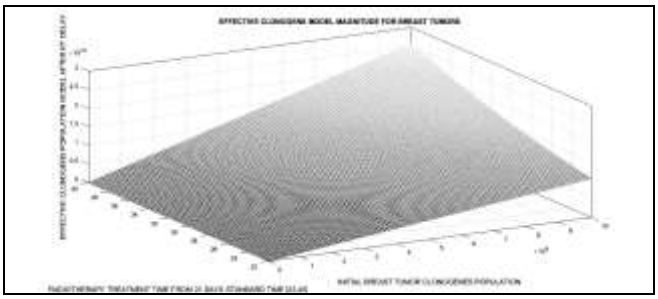

Figure 5.- Matlab $N_{Effective}$ Rate simulation 3D image for breast tumors. Analytic geometry for large clonogens magnitude trend is smooth exponential or parabolic. Image was set without any logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. Matrices for Image Processing have about [200-250 x 200-250] elements.

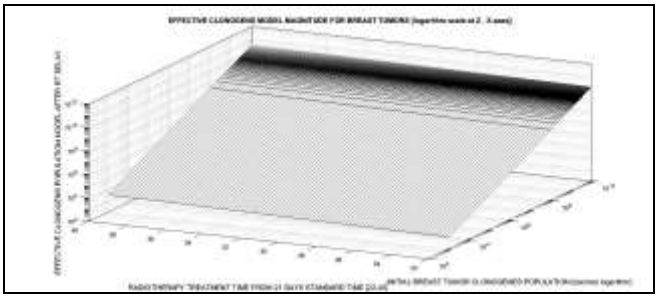

Figure 6.- Matlab $N_{Effective}$ Rate simulation 3D image for breast tumors. At Z and X axes, logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. Matrices for Image Processing have about [200-250 x 200-250] elements.

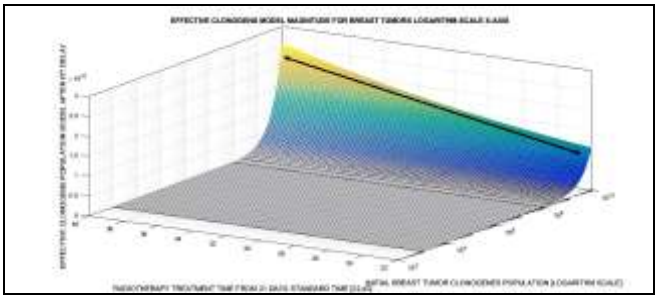

Figure 7.- Matlab $N_{Effective}$ Rate simulation 3D image for breast tumors. Analytic geometry is shown with arrow at high magnitude clonogens. At X axis, logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. The peak is better seen with this double logarithmic scale. Matrices for Image Processing have about [200-250 x 200-250] elements. At figure, inset, axes interval modifications explained.

Brief of Numerical Results

Numerical results resume is detailed in Table 2. Chebyshev norms were set for [60 , 70] Gy interval. Dose fraction magnitude should be less than 2 Gy approximately. Numerical Results for $N_{Effective}$ model are developed and reviewed from the innovation from [20,21,75,85].

Table 2.-Brief of PMO optimization numerical results.

NUMERICAL RESULTS FOR BED MODEL BREAST TUMORS RADIOTHERAPY PARETO-MULTIOBJECTIVE OPTIMIZATION [f_1 is optimized for 60 Gy, f_2 for 70 Gy]				
OPTIMAL FRACTIONS NUMBER	**OPTIMAL FRACTION DOSE**	**OPTIMAL DAYS AFTER POTENTIAL TIME**		
[53 , 56]	**[1.0572 ,1.1215] Gy**	**[24 ,29]**		
NUMERICAL RESULTS FOR $N_{Effective}$ MODEL BREAST TUMORS RADIOTHERAPY OPTIMIZATION				
Minimum [N_0] Minimum [T_{Delay}]	**Maximum [N_0] Minimum [T_{Delay}]**	**Minimum [$N_{Effective}$] Minimum [T_{Delay}]**	**Maximum [N_0] Maximum [T_{Delay}]**	**Maximum [$N_{Effective}$] Maximum [T_{Delay}]**
1.01×10^2 1.18 days	**1.00×10^{10} 1.18 days**	**1.06×10^{10} 1.18 days**	**1.00×10^{10} 19 days**	**2.562×10^{10} 19 days**

IV. 3D ISODOSES APPLICATIONS

Primary demonstration of new 3D Isodoses Treatment Planning System, [Casesnoves invention, 2022], were explained and published previously [85]. There are three 3D Isodoses types. Namely, Type 1 [Vertical 3D Isodoses, Figure 8], Type 2 [Horizontal 3D Isodoses, Figure 9], and Type 3 [Combination of Vertical and Horizontal 3D Isodoses, according to requirements of the planning systems, an dthe geometry of the tumor for imaging guided RT] in contrast to classical 2D Isodoses. 3D Isodoses radiotherapy simulations software was presented through a 3D graphics series engineering software [85]. Figures 8-9 show improved 3D Isodoses image processing for 18 Mev with [z= 5,15 cm] AAA model dose-deposition isocenter depths [1-20,83-85]. These depths are convenient for TPO in mammary glands size ranges, from small glands to bigger ones.

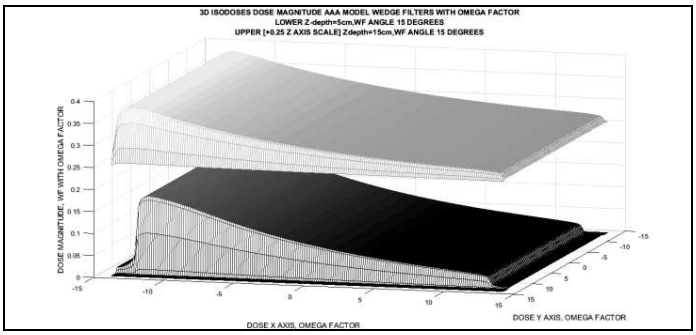

Figure 8.- [Grayscale imaging processing software] . For future implementation of BMs, a new 3D isodoses perspective in imaging-software developed from [85]. It is a Type I lateral-oblique imaging perspective of 3D Isodoses for z=5 cm [first], and z=15 cm [upper, scaled +0.25]. It is clear the height dose difference related to depth absorbed dose deposition. This Type I lateral imaging perspective of 3D Isodoses for z=15 cm [upper, scaled +0.25], and z=5 cm [lower] demonstrate the utility and innovation, [84], for TPO modern systems [Casesnoves, 2022]. It is sharp the dose difference magnitudes that can be get related to depth absorbed dose deposition. Dosimetry calculations,TPO, and photon-dose approximations can be carried out with these 3D Isodoses charts.

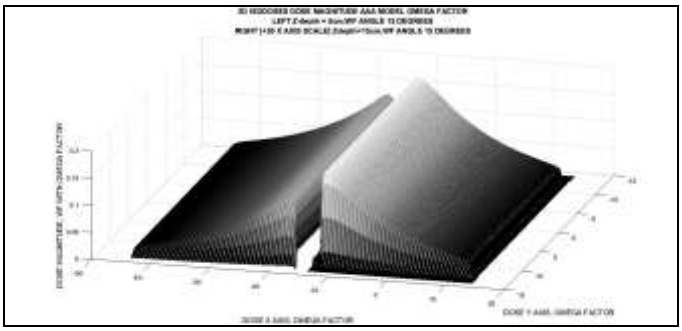

Figure 9.- [Grayscale imaging processing software] .For future implementation of BMs, a new 3D isodoses perspective in imaging-software developed from [85]. It is a Type II lateral imaging perspective of 3D Isodoses for z=5 cm [left], and z=15 cm [right, scaled +30]. It is clear the height dose difference related to depth absorbed dose deposition.

V. RADIOTHERAPY MEDICAL PHYSICS APPLICATIONS

Table 3 shows main applications for TPO in breast tumors derived from the study. The most important utility is the efficacious precision of time, dose and fractions RT treatment.

Table 3.- Radiotherapy medical physics basic applications to improve the quality of RT breast tumors treatment.

APPLICATIONS OF BIOLOGICAL BED MODELS RADIOTHERAPY FOR BREAST TUMOR BRIEF	
RT METHOD	**EFFECT**
BED and N_{Eff} Implementation in Survival Fraction Models	Dose Delivery Precision because it minimizes Clonogenes growth during radiotherapy Treatment Time, Maximum Effect/Maximum Tumor Control Probability [TCP]
BED and N_{Eff} Implementation in Survival Fraction Models for exact calculation of NTCP instead N_0 . Then, Radioprotection is more efficacious.	Radioprotection OARs Dose Precision because it sets exact Clonogenes growth during radiotherapy Treatment Time, Maximum Effect/Maximum Normal Tissue Complications Probability [NTCP]
BED Optimization of Biological Models	Dose Delivery Precision, minimum dose/ maximum effect
Previous Photon-dose Optimization	Dose Delivery Precision to be implemented in BM, minimum dose/ maximum effect
Normal Tissue Complications Probability Models [NTCP]	Dose-Volume-Histogram Dose Delivery Precision to be implemented in BED models, minimum dose at OARs
FOR PATIENT DIRECT EFFECTS	
RT BED METHOD	**EFFECT**
OARs at risk Radioprotection	Avoid Damage at any FSUs [Organ Funcional Subunits]
Radiation Therapy Secondary Effects	Hyperfractionations decreases Radiation Undesirable Symptoms
Patient Life Quality	Not only Physical benefit but also Psychological for Patient
Aesthetic Effect	Psychological Plus for Patient in Post-Treatment Life

VI. DISCUSSION AND CONCLUSIONS

The objective of the study was to optimize BED model for Hyperfractionation TPO with Artificial Intelligence Pareto-Multiobjective Genetic Algorithms (GA) new software. The second optimization-modelling purpose was the $N_{Effective}$ algorithms(s) optimization for breast cancer clonogens parameters determination with 3D Graphical and Interior Optimization methods. Complementary, new recent applications with 3D Isodoses TPO with AAA (Anisotropic

Analytic Algorithm) model wedge filters dose delivery were improved/developed.

Results comprise acceptable Pareto-Multiobjective Genetic Algorithms (GA) 2D imaging charts and numerical dataset for breast cancer Hyperfractionation protocol, Table 2. 3D Isodose graphics for TPO with AAA model in WF beam-modification delivery, at isocenter depths [z = 5, 15 cm], were shown and graphically demonstrated.

Advantages of Artificial Intelligence GA method are the acceptable optimal results, both in 2D Pareto-Front with low residuals and numerical data. Inconvenients of GA method is the rather longer running time compared, for example, to Inverse Least Squares method [1-21]. This difficulty becomes evident from 250-300 generations figures are implemented into the programming design [from 2.5 minutes on]. The running time for the $N_{Effective}$ algorithms(s) 3D optimization charts and 3D Isodoses vary at [1 , 4] minutes interval depending on the imaging processing tiles number and selected Matlab subroutine.

Grosso modo, Pareto-Multiobjective GA optimization was performed for BED and $N_{Effective}$ models in breast cancer TPO. 3D Graphical Optimization and 3D Isodoses are proven and displayed.

VII. SCIENTIFIC ETHICS STANDARDS

GA Artificial intelligence software was developed originally by Dr Casesnoves on September2022. All initial modelling equations were developed from previous researchers contributions [22-25]. The N_S initial formulation and integral Tumor Control Cumulative Probability, (TCCP), were published in [22-25]. From those equations, all the mathematical development implementation is original from the author [1-21,75]. This article has previous papers mathematical techniques, [1-21, 75], whose use was essential to make model numerical solutions and approximations. Equation 2 and $N_{Effective}$ model are developed and reviewed from [20,21,75,85], essential for study understanding. Some information of [20,2175,85] was presented for results clarification. The number of Dr Casesnoves publications at references is intended also for reader's learning. This study was carried out, and their contents are done according to the European Union Technology and Science Ethics and International Scientific Ethics norms [38,43-45]. This research was completely done by the author, the calculations, images, mathematical propositions and statements, reference citations, and text is original from the author. When a mathematical statement, 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'] appears, there is not vanity or intention to brag. The article is exclusively scientific, without any commercial, institutional, academic, religious, religious-similar, non-scientific theories, personal opinions, friends and/or relatives favours, 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].

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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). Dr Casesnoves is European Union and Internationally qualified as Doctor in Engineering to supervise PhD Theses, Master Theses, and Bachelor Theses in science and engineering. 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, ethical-professional reasons, anti-state monarchy corruption positions, 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 65 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], invention of 3D Isodoses in radiotherapy TPO, and Molecular Effect Model for High Temperature Superconductors [2020]. Dr Casesnoves PhD thesis is an Estonian scientific service to European Social Fund and several EU Research Projects. 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 40 physics-engineering articles, two books series, and 1 industrial radiotherapy project associated to Europe Union EIT Health Program (Tartu University, 2017).

APPENDIX

This Appendix shows the most important Figures to demonstrate the results sharply.

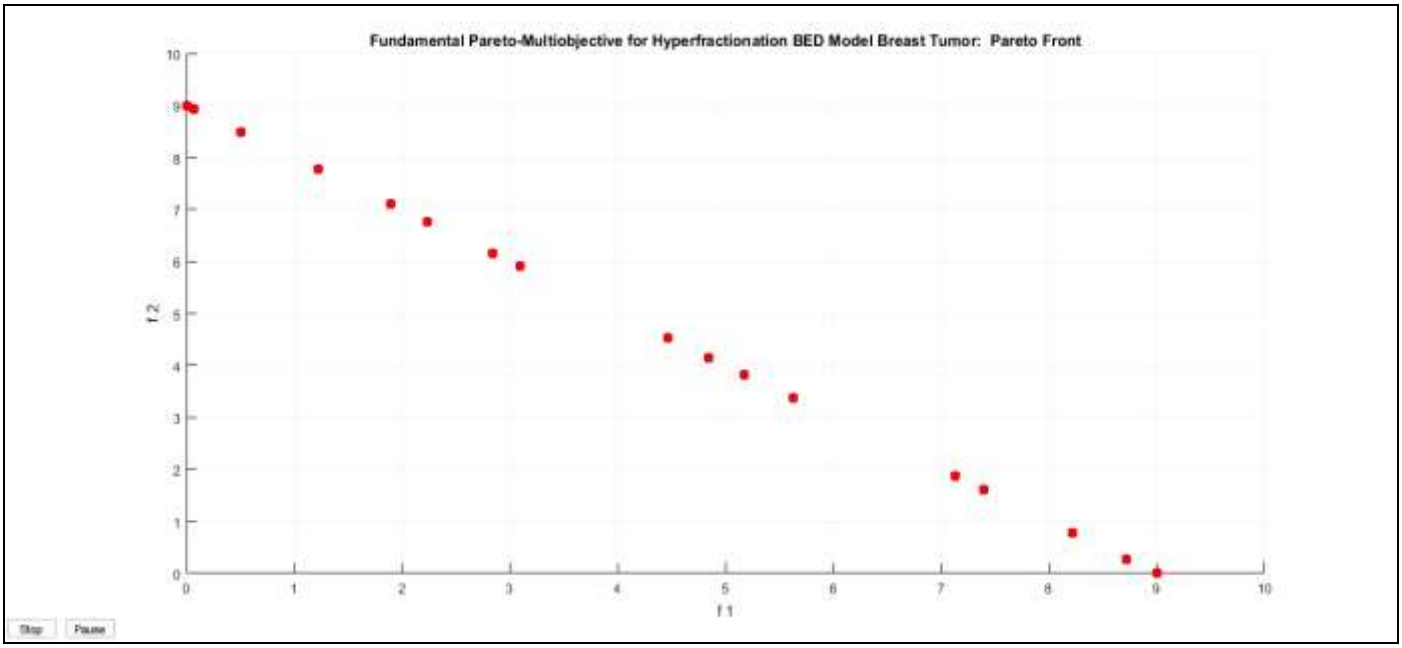

Figure 1 [enhanced].-This is the most important graph given by Matlab when PMO is performed to check the optimization accuracy. The fundamentals of Nonlinear PMO calculations are usually based on 2D PMO functions charts. In this study both f_1 and f_2 show low residuals. Therefore, results are acceptable.

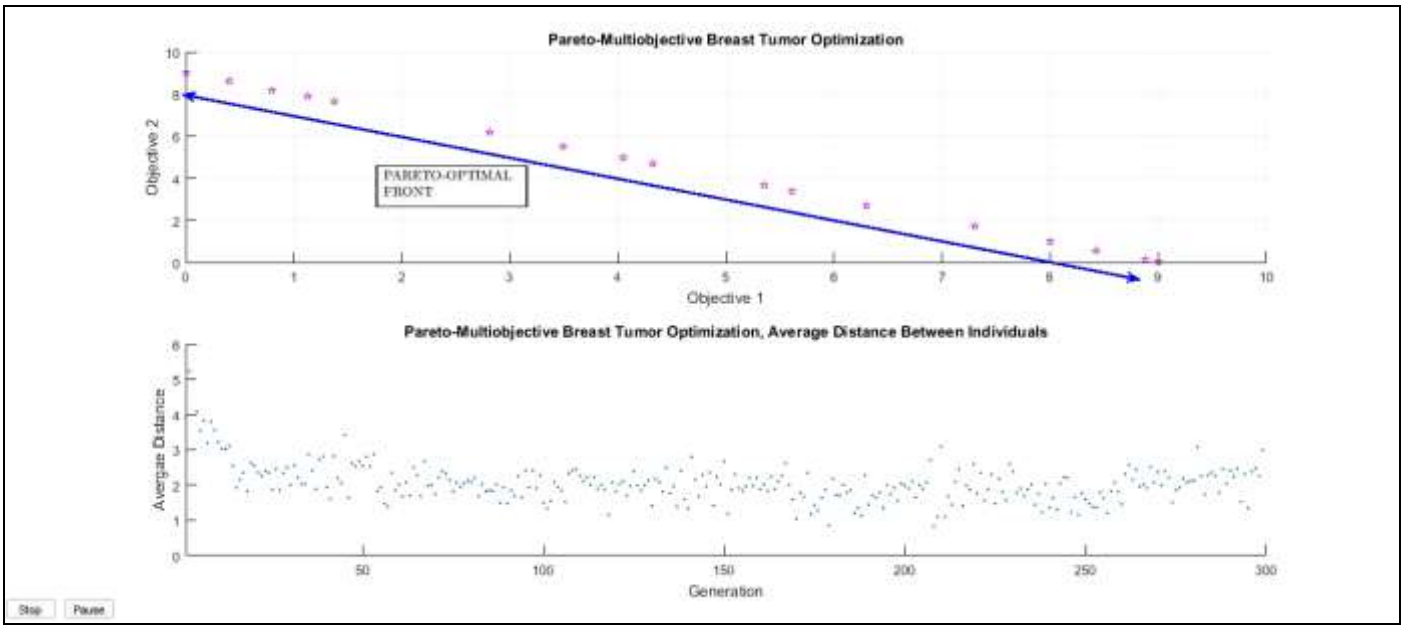

Figure 2 [enhanced].- This is the lined-marked inset graph showing the Pareto Front. The lower chart details the average distance among generations. Since the number of functions calculated is quite high, the points that show the distance vary significantly for 800 generations. The fundamentals of PMO calculations are usually based on 2D PMO functions charts. In this study both Objective f_1 and f_2 that show low residuals. Enhanced in Appendix.

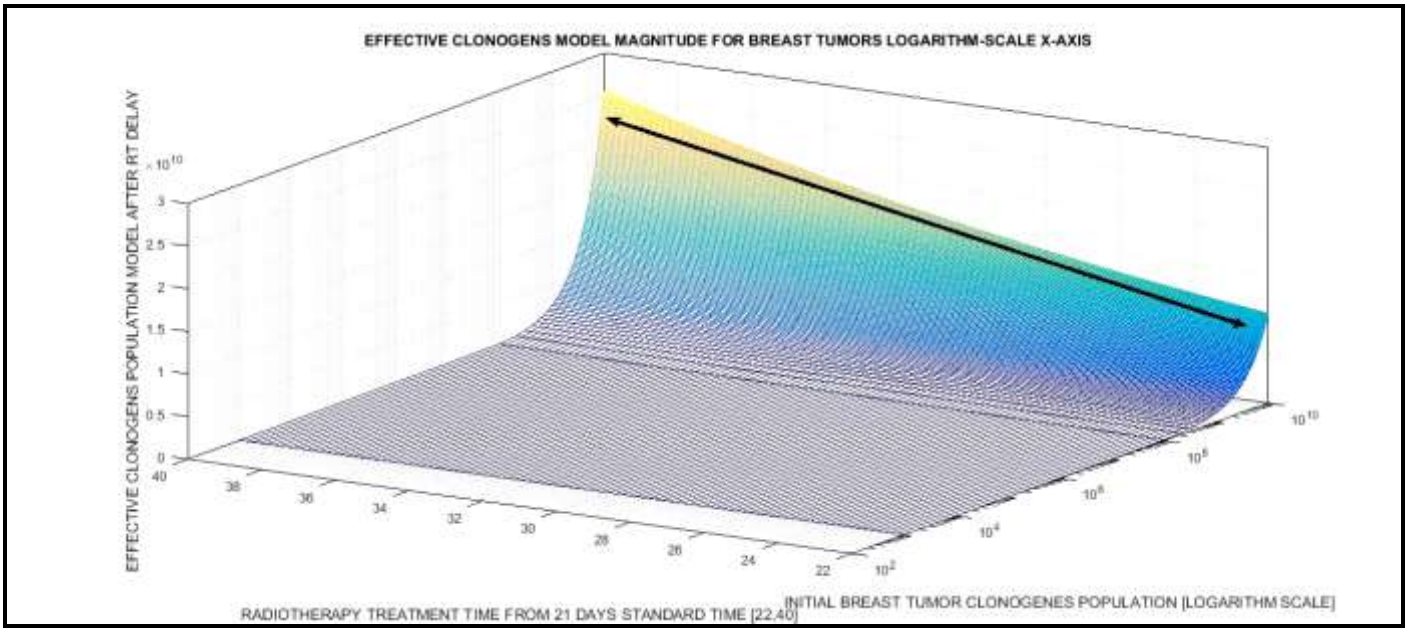

Figure 7 [enhanced].- Matlab $N_{Effective}$ Rate simulation 3D image for breast tumors. Analytic geometry is shown with arrow at high magnitude clonogens. At X axis, logarithmic scale. It is sharply seen that $N_{Effective}$ magnitude grows according to RT treatment delay time. The peak is better seen with this double logarithmic scale. Matrices for Image Processing have about [200-250 x 200-250] elements. At figure, inset, axes interval modifications explained. Enhanced in Appendix.

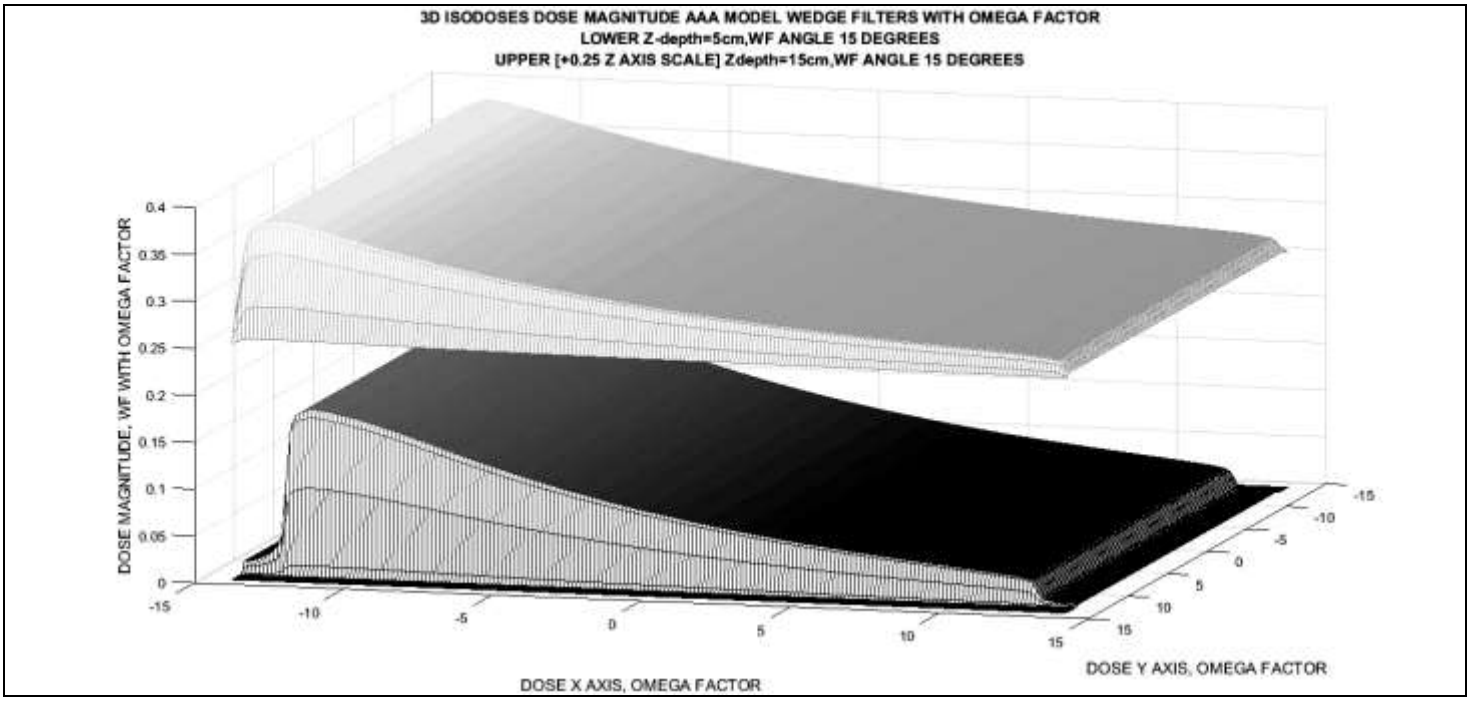

Figure 8 [enhanced].- [Grayscale imaging processing software] . For future implementation of BMs, a new 3D isodoses perspective in imaging-software developed from [85]. It is a Type I lateral-oblique imaging perspective of 3D Isodoses for z=5 cm [first], and z=15 cm [upper, scaled +0.25]. It is clear the height dose difference related to depth absorbed dose deposition. This Type I lateral imaging perspective of 3D Isodoses for z=15 cm [upper, scaled +0.25], and z=5 cm [lower] demonstrate the utility and innovation, [84], for TPO modern systems [Casesnoves, 2022]. It is sharp the dose difference magnitudes that can be get related to depth absorbed dose deposition. Dosimetry calculations,TPO, and photon-dose approximations can be carried out with these 3D Isodoses charts. Enhanced in Appendix.