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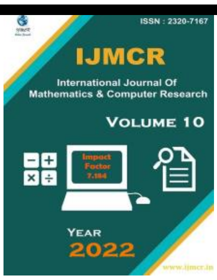

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Radiotherapy Complete Mathematical Demonstration for Biological Tumor Control Cumulative Probability Integral Equation Model with Applications

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ABSTRACT

The complete mathematical biological Integral Equation Model (IEM) for Tumor Control Cumulative Probability (TCCP) development and demonstration is explained. Results for algebraic variables change to obtain a suitable Tumor Control Probability (TCP) in convolution at IEM for getting an analytic solution is detailed step by step. Results comprise estimates with further explanations. Solutions for algebraic variable changes to make the Integral Operator analytically solved are demonstrated. Applications in Radiotherapy Treatment Planning Optimization (TPO) with biological Linear Quadratic Model based on 2D [α and β biological modelling parameters] are explained.

KEYWORDS: Mathematical Methods (MM), Biological Models (BM), Clonogenes Population Survival Rate, (SR), Integral Equation (IE), Integral Equation Model (IEM), Linear Quadratic Model (LQM), Tumor Control Probability (TCP), Tumor Control Cumulative Probability (TCCP), Normal Tissue Complication Probability (NTCP), Radiation Photon-Dose (RD), Organ at Risk (OAR), Nonlinear Optimization, Integral Approximations, Anisotropic Analytic Model (AAA), Radiotherapy Treatment Planning Optimization (TPO).

I. INTRODUCTION

In Radiation Therapy research series, [1-8, 17-24, 31, 32], a new Integral Biological Model (BM) step-forward study was developed [1] for Tumor Control Cumulative Probability (TCCP). Biological Models rationale are based on molecular biology and biochemistry/biomedical proven evidences [64-67] for tumor clonogenes growth and radiobiological interaction with radiation particles. It is very frequent to determine the BMs parameters with ***in vitro*** radiobiological experimental [64-67]. Usually, BM equations are exponentials and integral equations of first kind for Tumor Control Probability (TCP) [64-67]. TCP models are based on BMs exponentials implemented into Statistical Distributions, such as Poisson, Binomial, or Gaussian. Normal Tissue Complication Probability (NTCP) models were also developed based on BMs theory and experimental. However, NTCP models are more complex and varied compared to TCP ones. NTCP is an important radioprotection parameter in TPO with BMs, because the better optimization obtained by using BMs instead simple photon-dose delivery is subject to also optimize the minimum OARs doses. In plain language, what is got with BMs TPO patient benefit could be devalued if NTCP is high.

The objective of this research is to explain the mathematical method developed to reach the IEM [1]. To demonstrate the exactness of the IEM analytic solution obtained in [1]. The method based on algebraic variable changes is not considered the unique solution to get hold of an IEM analytical result for fast computation/simulation.
In brief, from the two new Biomodels presented and mathematically developed in [1], the sharp complete explanation to obtain IEM is presented.

II. MATHEMATICAL INTEGRAL EQUATION METHOD

The initial mathematical algorithm, [1], is the exponential Linear Quadratic Model for surviving clonogenes and the TCP basic statistical ones [64-67]. The variation of these models were introduced [1]. Instead the Poisson TCP model, an approximation with Binomial TCP distribution was proven. This study explains all the algebraic model variations that are set into the Gaussian convolution integral equation for TCP cumulative prediction step by step [Casesnoves, 2022].

The model can be modified for easier mathematical methods. As previously explained, Lea-Catcheside function-factor K [1,64,69], has to be introduced. Hypofractionated delivery, Fractional Dose Factors, d, and number of fractions n, [1,64-67,69], are omitted for simplification, and are not relevant for the mathematical method development. In the standard BM research, [1,64-67,69], the quotient [σ/β] is generally considered constant, and it is frequent to present [$(\beta)^{1/2}$] magnitude. As set in [1,69], for this research model IE, alpha and betha radiosensitive parameters are set independent to avoid excessive approximations. From [1,69], by using percentages and 1% rates, the model can set better implemented in Statistical Distributions and IE, such as,

$$\begin{aligned}
&\text{Modified Model [\% or 1\%],}\\
&N_S\,[\%] = N_0\,[100\%]\;x\;e^{-[\alpha D+\beta K\,D^2]}\;;\\
&\text{or}\\
&N_S\,[1\%] = N_0\,[1\% = 1]\;x\;e^{-[\alpha D+\beta K\,D^2]}\;;\\
&[\text{Casesnoves, 2022}]\;;
\end{aligned}\tag{1}$$

where

Ns : Initial number of tumor clonogens
No : Surviving number of tumor clonogens
α : Clonogen radiosensitivity parameter
β : Clonogen radiosensitivity parameter
D : Total radiation dose delivered
K : Lea-Catcheside function-factor K, [64]

However, this model variant, using percentages and rates of N_0 implies to make calculations constrained to parameters [α, mainly, and β] numerical changes in function of N_0 , for example [66, Table 44.2] . In other words, both parameters [α, mainly, and β] numerical values depend on N_0 .

Integral Equation Approximated-Model Operator

TCCP can be analyzed as a 2D integral operator whose compactness and boundary properties will be set in next contributions. The kernel is positive and given with a Gaussian and the complementary function is unity for I_1 , (2), and an exponential depending on binomial distribution, (2). The TCCP reads,

$$K\quad (TCCP(\overline{\alpha},\overline{\beta})) = \frac{1}{2\pi\sigma^2}\cdots \\ \cdots\int_{\beta_1}^{\beta_2} k_2\,(\beta\,,\;\overline{\beta}\,)\,f(\beta)\,d\beta\int_{\alpha_1}^{\alpha_2} k_1\,(\alpha\,,\;\overline{\alpha}\,)\,f(\alpha)\;d\alpha\,;\tag{2}$$

where,
α : Clonogen radiosensitivity integral parameter.
β : Clonogen radiosensitivity integral parameter.
K_1 : Gaussian Kernel for β .
K_2 : Gaussian Kernel for α .
f (α) , f (β) : Proper functions of Integral Operator.

The product [f (α) x f (β)] is unity for I_1 and a exponential for I_2 . Probability Function (2,3), TCP, is convoluted in the same method of [1,64,66,69] with a 2D Gaussian Kernel to obtain the final cumulative TCCP (α , β) distribution. The new technique is to use the Binomial approximation of (1,2,3) to reach an analytic determination. Therefore, see (9), in IEM, TCCP reads,

$$TCCP(\overline{\alpha},\overline{\beta}\,) = \frac{1}{2\pi\sigma^2}\cdots \\ \cdots\int_{\beta_1}^{\beta_2}\int_{\alpha_1}^{\alpha_2}[1-P(\,\alpha\,,\beta\,)]\;x\ldots \\ \ldots e^{\left[-\frac{1}{2\,\sigma^2}\left[(\alpha-\overline{\alpha})^2+(\beta-\overline{\beta})^2\,\right]\right]}\cdots \\ \ldots d\alpha\,d\beta = I_1 - I_2\quad ;\tag{3}$$

where
α : Clonogen radiosensitivity integral parameter
β : Clonogen radiosensitivity integral parameter
σ : Approximated standard deviation both for α , β parameters
I_1 : First Gaussian integral, Normal Distribution
I_2 : Second Probability Function Gaussian convolution

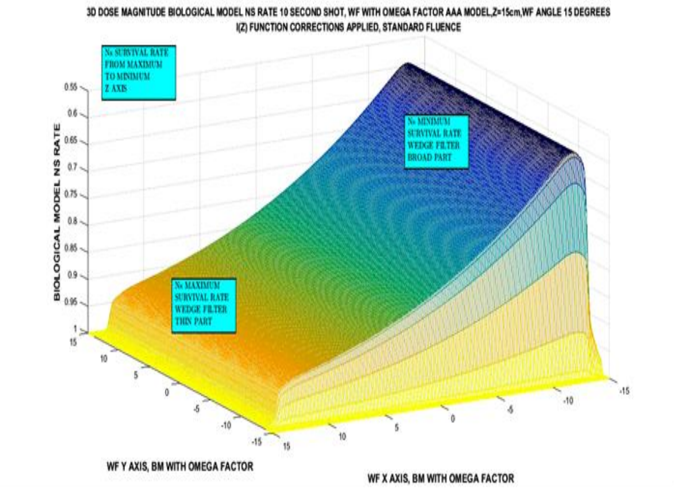

Figure 1 .- From [69], an illustrative example of Matlab N_S Rate simulation 3D image for 18 Mev photon-beam, Wedge Filter dose delivery. According to [69] dataset, 10 shots, at 5 cm depth-dose with Omega Factor and I(z) corrected. The photon-dose delivery time shot is 1 second. Matrices for Image Processing have about [350 x 350] elements. Imaging Processing Method 1. Inset, explanations for Maximum and Minimum N_S Rates . This study, [69], was specifically focused on BMs TPO for breast tumors.

Probability Function Model Variation-Approximation

The next step is to use the Binomial Probability Function for TCP, which is set as an approximation at [1,66,69] and reads,

$$
\begin{aligned}
&\text{Binomial}-\text{Approx TCP Model,}\\
&P(\alpha,\beta)=\left[1-e^{-[\alpha D+\beta K D^2]}\right]^{N_s};\\
&\text{Modified Rate}-\text{Model, } N_0=1,\\
&P(\alpha,\beta)=\left[1-e^{-[\alpha D+\beta K D^2]}\right];
\end{aligned}
\qquad (4)
$$

where

P (α , β) : Tumor Control Probability function depending on [α , β] .

Mathematical Algebraic-Variable Changes with Complete Further Implementation

Observing the formulas (1-4), it is seen that P (α , β) depends on those [α , β] integral parameters. That cause the difficulty to get a simple analytic solution. Therefore, if an algebraic variable change is introduced, the parameters [α , β] can be set exclusively at Gaussian integral convolution part. That was the method got in [1], and in this study the complete development for IEM is proven.

Thus, for getting to work out the analytic solution of I_2 , the following algebraic-variable changes, are applied exclusively at I_2 . A and B notation, are constants depending on D and K as described in (1-3). Note that this is not the unique algebraic-variable change. Algebraic-variable changes result be as follows,

$$
\begin{aligned}
&(\alpha-\overline{\alpha})\Rightarrow\left(\alpha-\left(\overline{\alpha}-\sigma^2 A\right)\right);\ (1)\\
&(\beta-\overline{\beta})\Rightarrow\left(\beta-\left(\overline{\beta}-\sigma^2 B\right)\right);\ (2)\\
&\text{with complement}\\
&+\left[\frac{\sigma^2 A^2}{2}\right]+\left[-\overline{\alpha}\,A\right];\ \text{for (1)};\\
&+\left[\frac{\sigma^2 B^2}{2}\right]+\left[-\overline{\beta}\,B\right];\ \text{for (2)};\\
&\text{where,}\\
&A=D;\\
&\text{and,}\\
&B=KD^2;
\end{aligned}
\qquad (5)
$$

where

α : Clonogen radiosensitivity integral parameter variable change

β : Clonogen radiosensitivity integral parameter variable change

σ : Approximated standard deviation both for α , β parameters

D: Total dose, either in fractionated in standard TPO protocol or in Hypofractionated RT methods.

From (5), the right side alpha part-(1) is spread out, and summed to complement part-(1) to demonstrate that the result is equal to the exponentials depending on [α , β] of the IE (2). The proof for betha parameter part-(2) is equal.

FIRST PART :

$$(\alpha-\overline{\alpha})\Rightarrow\left(\alpha-\left(\overline{\alpha}-\sigma^{2}A\right)\right);(1)$$

with complement ,

$$+\left[\frac{\sigma^{2}A^{2}}{2}\right]+\left[-\overline{\alpha}A\right];\ \text{for }(1);$$

where,

$$A=D;$$

and,

$$B=KD^{2};$$

Hence,[note at exp onential negative],

$$-\left(\alpha-\left(\overline{\alpha}-\sigma^{2}A\right)\right)^{2}=-[\ldots$$
$$\ldots\alpha^{2}+\left(\overline{\alpha}-\sigma^{2}A\right)^{2}-\ldots$$
$$\ldots2\alpha\left(\overline{\alpha}-\sigma^{2}A\right)^{2}]=\ldots$$

(6)

where all parameters and constants are described in (1-4).

Hence the development of the quadratic continues,

SECOND PART :

$$-\left(\alpha-\left(\overline{\alpha}-\sigma^{2}A\right)\right)^{2}=-[\ldots$$
$$\ldots\alpha^{2}+\left(\overline{\alpha}-\sigma^{2}A\right)^{2}-\ldots$$
$$\ldots2\alpha\left(\overline{\alpha}-\sigma^{2}A\right)^{2}]=..-.$$
$$\ldots.[\alpha^{2}+\overline{\alpha}^{2}+\sigma^{4}A^{2}-\ldots$$
$$\ldots2\,\overline{\alpha}\,\sigma^{2}A-\ldots..$$
$$\ldots.2\ \alpha\,\overline{\alpha}+\ldots.$$
$$\ldots.2\,\alpha\,\sigma^{2}A];$$

(7)

where all parameters and constants are described in (1-5).

Finally complementary parts are added to set complete equality,

THIRD PART :

$$-\left(\alpha-\left(\overline{\alpha}-\sigma^{2}A\right)\right)^{2}=-[\ldots$$
$$\ldots\alpha^{2}+\left(\overline{\alpha}-\sigma^{2}A\right)^{2}-\ldots$$
$$\ldots2\alpha\left(\overline{\alpha}-\sigma^{2}A\right)^{2}]=..-..$$
$$\ldots[\alpha^{2}+\overline{\alpha}^{2}+\sigma^{4}A^{2}-\ldots$$
$$\ldots2\,\overline{\alpha}\,\sigma^{2}A-\ldots..$$
$$\ldots.2\ \alpha\,\overline{\alpha}+\ldots.$$
$$\ldots.2\,\alpha\,\sigma^{2}A]..+..$$
$$\ldots[\sigma^{4}A^{2}-\overline{\alpha}\,2\sigma^{2}A]..=$$
$$..=[-\alpha A-..$$
$$\ldots(\alpha-\overline{\alpha})^{2}];$$

(8)

where all parameters and constants are described in (1-7).

These algebraic-variable changes obtain the same IE expression than (3) and are reverted for IE Model final result formulation at I_2 . As a result, final calculations, (4-12) will be got.

I_1 Determination

The integral I_1 is a 2D Gaussian distribution. Therefore, variable changes from (5-8) are not necessary. Erf functions usage for convolution integral equations is tabulated, and systematically determined [68]. The straightforward analytic result with Erf functions reads,

$$I_1(\overline{\alpha},\overline{\beta})=\frac{1}{4}\,x\left[\left[\mathrm{Erf}\left(\frac{\alpha_2-\overline{\alpha}}{\sqrt{2}\,\sigma}\right)\right]-\left[\mathrm{Erf}\left(\frac{\alpha_1-\overline{\alpha}}{\sqrt{2}\,\sigma}\right)\right]\right]\ldots x$$
$$\ldots x\left[\left[\mathrm{Erf}\left(\frac{\beta_2-\overline{\beta}}{\sqrt{2}\,\sigma}\right)\right]-\left[\mathrm{Erf}\left(\frac{\beta_1-\overline{\beta}}{\sqrt{2}\,\sigma}\right)\right]\right];$$

(9)

where

α_1 : Inferior 2D IE limit

α_2 : Superior 2D IE limit

β_1 : Inferior 2D IE limit

β_2 : Superior 2D IE limit

α : Clonogen radiosensitivity integral parameter

β : Clonogen radiosensitivity integral parameter

I_2 Determination

The integral I_2 is a convolution of P (α , β) with a 2D Gaussian Kernel. The integral model operator has a Gaussian kernel and Just remark that in total computation I_2 is resting for the total TCCP (2,3). Before setting the algebraic-variables changes (2-8) I_2 results as follows,

$$I_2(\bar{\alpha},\bar{\beta}) = \frac{1}{2\pi\sigma^2}\ldots$$
$$\ldots\int_{\beta_1}^{\beta_2}\int_{\alpha_1}^{\alpha_2}[e^{-[\alpha D+\beta K D^2]}]\,x\ldots$$
$$\ldots x\, e^{\left[-\frac{1}{2\sigma^2}[(\alpha-\bar{\alpha})^2+(\beta-\bar{\beta})^2]\right]}\ldots$$
$$\ldots x\, d\alpha\, d\beta\,;$$

(10)

where all parameters and constants are described in (1-8)

After applying the completely explained algebraic-variable changes (5-8), and for final solution reverting them, the I_2 result reads,

$$I_2(\bar{\alpha},\bar{\beta}) = \frac{1}{4}\,x(\exp[\frac{\sigma^2}{2}(A^2+B^2)-.$$
$$\ldots-(\bar{\alpha}A+\bar{\beta}B)].)..x\ldots$$
$$\ldots.x[[\mathrm{Erf}\left(\frac{\alpha_2+(\bar{\alpha}-\sigma^2 A)}{\sqrt{2}\,\sigma}\right)]-..$$
$$\ldots.-[\mathrm{Erf}\left(\frac{\alpha_1+(\bar{\alpha}-\sigma^2 A)}{\sqrt{2}\,\sigma}\right)]]\ldots x..$$
$$\ldots.x[[\mathrm{Erf}\left(\frac{\beta_2+(\bar{\beta}-\sigma^2 B)}{\sqrt{2}\,\sigma}\right)]-..$$
$$\ldots.-..[\ \mathrm{Erf}\left(\frac{\beta_1+(\bar{\beta}-\sigma^2 B)}{\sqrt{2}\,\sigma}\right)]]\quad;$$

(11)

where all parameters and constants are described in (1-8)

III. INTEGRAL EQUATION MODEL RESULT

According to all the IE model previous mathematical development, the IE analytical determination is set. The complete model analytic result, following (6,7,8) reads,

$$TCCP(\bar{\alpha},\bar{\beta}) = I_1(\bar{\alpha},\bar{\beta}) - I_2(\bar{\alpha},\bar{\beta})\,;$$
$$[\text{Casesnoves 2022}]\,;$$

(12)

where all parameters and constants are described in (1-8).

Therefore, the model is set in function of previous determinations/approximations (1-8). The previous contributions in the Radiotherapy Treatment Planning Optimization [1-8, 17-24, 31, 32,69], were applied/developed for the IE model elaboration. This formula sets a cumulative TCCP function P (α , β) for any parameter values (α , β) ϵ [(α_1 , β_1) , (α_2 , β_2)] .

IV. RADIOTHERAPY TREATMENT PLANNING OPTIMIZATION APPLICATIONS BRIEF

TPO applications from IEM in BMs could be multiple [69]. IEM can be set for rapid TPO simulations [69]. For radiotherapy simulations and research applications IEM could be useful [69]. LQMs improvements could be obtained for planning system with IEM starting algorithm.

V. DISCUSSION AND CONCLUSIONS

The study objective was to explain/develop all the algebraic development of IEM published in [1,69]. Therefore, the analytic solution is proven.

Results show step by step the necessary changes to obtain an exact equality that sets the integral variables exclusively at the Gaussian exponential. Applications for TPO and radiotherapy research are explained.

In summary, the IEM [1,69] was completely explained in its mathematical demonstration. IEM main application is fast computation of BMs for TPO.

VI. SCIENTIFIC ETHICS STANDARDS

IEM was developed by Dr F Casesnoves in 15th March 2022. All initial equations were developed from previous researchers contributions [64-67]. The IE initial integral formula was published in [64]. From those equations, all the mathematical development is original from the author [1]. This article has previous papers mathematical techniques, [1-9, 17-24, 31, 32], whose use was essential to make IE model analytic solution, approximations, and Probability Function. Figure 1 is a necessary example from [69]. The complete mathematical development will be carefully reviewed/checked in subsequent publications. When a citation such as ‘ [Casesnoves, year] ‘ is included, it does not mean any vanity and/or intention to brag. The reason is to set clearly, for the current scientific times, the intellectual property. This study was carried out, and their contents are done according to the European Union Technology and Science Ethics. Reference, ‘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 [60-63]. And based on ‘The European Code of Conduct for Research Integrity’. Revised Edition. ALLEA. 2017. 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. 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 [60-63].

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