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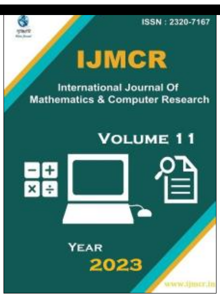

Radiotherapy Tumor Control Cumulative Probability 3d Integral Equation with Tcp Improved Model

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ABSTRACT

A triple-variable Integral Equation for Tumor Control Cumulative Probability (TCCP) is developed with the addition of the important radiotherapy Treatment-Time parameter. Based on a previous double TCCP Integral Equation depending on Biological Model parameters (α , β), the $N_{Effective}$ model is implemented in Tumor Control Probability (TCP) equation. Results comprise a TCCP Integral Equation model with three essential parameters for Radiation Therapy precise determination of TCCP. Solution shows the method to obtain a 3D Integral Equation of first kind. Results applications could involve better optimization for TCCP in radiotherapy biological models. Radiotherapy Treatment Planning Optimization (TPO) and Radioprotection consequences 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 ($N_{Effective}$), Linear Quadratic Model (LQM), Integral Equation (IE), Tumor Control Probability (TCP), Normal Tissue Complications Probability (NTCP), Biological Effective model (BED), Tumor Control Cumulative Probability (TCCP), Radiation Photon-Dose (RPD), Nonlinear Optimization, Radiotherapy Treatment Planning Optimization (TPO), Software Engineering Methods, Radiation Photon-Dose.

I. INTRODUCTION

Previously, [20,89], the TCCP Integral Equation was developed and determined with analytical result based on Erf functions. The model set for that double integral, [20,89], based on standard Biological Model parameters (α , β), is improved with the implementation of a variant of the $N_{Effective}$ model with Treatment-Time variable [90] . That is, a developed modification from [90], based on [20,24,25,83,88,89].

Therefore, the innovation of this study is the Integral TCCP Equation set on with essential TCP Biological Models parameters. In other words, TCCP depending on tumor radiobiological parameters (α , β), Treatment-Time variable, $T_{K\ (delay)}$, and $T_{Potential}$ ones. In routinary RT treatment schedule, the usual approximate 30 days for hyperfractionation dose-delivery varies due to unexpected delays, such as weekends, patient circumstances, side effects of radiation etc. In Hyperfractionated RT treatment schedule times could also adjust for several circumstances. Therefore, the practical utility of this 3D Integral Equation TCCP model is to optimize RT treatment for the interval of $T_{Treatment}$ time. TPO with biological models could get improvements from the calculations presented.

Consequently, [20,89,90], a more explicit integral equation to improve the radiotherapy treatment dose delivery schedule towards increased patient survival expectation is got. In short, a 3D TCCP Integral Equation model is set for upcoming analytic/numerical determination for improvements in Biomodels RT treatment. Applications for radiotherapy TPO RT are explained in brief.

II. MATHEMATICAL METHOD

The initial probability mathematical algorithm, [20,24,25,83,88,89], to be set in the model is the exponential Linear Quadratic Model for $N_{Effective}$ clonogenes and the TCP basic statistical ones [22-26,82,83]. Instead, the

Poisson TCP model, an approximation with Binomial TCP distribution was proven in [20,89]. In this section, cumulative probability mathematical concepts are also detailed in brief.

This study explains further 3D algebraic model variations that are set into the 3D Gaussian convolution integral equation for TCCP cumulative prediction. $N_{Effective}$ clonogenes model reads,

$$N_{EFFECTIVE} = N_0 \times 2^{\left[\frac{t-T_K}{T_P}\right]} ;$$

(1)

Where,

$N_{Effective}$: Effective N_0 surviving number of tumor clonogens.

N_0 : Surviving number of tumor clonogens .

t: Total radiation treatment parameter.

T_K: time after the start of the first fraction when clonogen proliferation starts parameter (in other publications T_{Delay}).

T_P: Average cell doubling time parameter.

From model [90, Equation (2), Chapter 12] and corroboration with other authors, on [20,24,25,83,88,89], it is guessed the following variant [Casesnoves, 2022],

$$\begin{aligned}&\text{With Binomial approximation}\\&\text{such as } N_0 \cong 1,\\&P\,(\alpha,\beta,t) = (1 - \ldots\\&\ldots\, e^{\left[-(\alpha\, D + \beta\, K\, D^2\ ) + A\right]}\ );\end{aligned}$$

(2)

where

P: TCP binomial approximation.

Ns: Initial number of tumor clonogens .

No: Surviving number of tumor clonogens .

t : Total RT treatment time, (1).

α : Clonogen radiosensitivity parameter

β : Clonogen radiosensitivity parameter

D : Total radiation dose delivered (could be hyperfractionated)

K : Lea-Catcheside function-factor K, [64]

Before implementing within integral equation, it is defined Factor A as follows,

$$\begin{aligned}&\text{The A factor,}\\&A = \text{Log}(2) \times \left(\frac{t - T_K}{T_P}\right)\\&\text{such as with binomial}\\&\text{approximation, } N_0 \cong 1,\\&P\,(\alpha,\beta,t) = (1 - \ldots\\&\ldots\, e^{\left[-(\alpha\, D + \beta\, K\, D^2\ ) + A\right]}\ );\end{aligned}$$

(3)

where

t: Total radiation treatment parameter.

T_K: time after the start of the first fraction when clonogen proliferation starts parameter.

T_P: Average cell doubling time parameter.

The integral-algebraic method can be done to get an integral equation of first kind that could be resolved analytically or numerically [89]. The results may constitute an improvement for BED models in general, TCP, TCCP, and NTCP.

The mathematical concept of cumulative probability integral convolution

The cumulative probability is an statistical mathematical concept that involves two convoluted probability functions. Namely, an statistical distribution, frequently a Gaussian, and the given specific probability function subject to the particular problem. The convolution has two kinds of parameters, the probability function itself ones, and the statistical distribution with all types of parameters, those that belong to the probability function and the ones that will give the explicit variables of the integral equation solution. Then, solutions got to get going towards an analytic and/or numerical result.

At the integrand, therefore, there is an intersection of probabilities. That is, the probability of the problem function with the probability of the Gaussian distribution. Because of the integral bounds, that intersection is performed for all the selected integral intervals. In plain language, any integral is a summatory in **R** or **C** spaces. This probability functions intersection within the integral give the cumulative total probability of the problem as follows,

$$\boxed{\begin{aligned}&\text{Cumulative Probability Integral Equation}\ldots =\\&\ldots = \int \text{Prob(specific)}\ \ \cap\ \ \text{Prob(Gaussian)}\ldots\\&\ldots\int \text{Total Prob(specific function subject to}\ldots\\&\ldots\text{Gaussian distribution)} = \ldots\\&\ldots. = \text{Total Prob explicit function}\ldots\\&\ldots\text{with its proper parameters;}\end{aligned}}$$

(Algorithm 1)

III. 3D INTEGRAL EQUATION DEVELOPMENT RESULTS

TCCP can be calculated with a 3D standard Gaussian convolution [20,89]. Algebraic changes can be set as in [20,89] . Therefore, the integral equation for TCCP results,

$$\begin{aligned}
&\text{Binomial Approx,}\\
&\text{such as } N_0 \cong 1,\\
&P(\alpha,\beta,t) = (1 - \ldots\\
&\ldots\, e^{\left[-(\alpha D + \beta K D^2) + A\right]});\\
&TCCP(\bar{\alpha},\bar{\beta},\bar{t}) = \int_{t_1}^{t_2}\int_{\beta_1}^{\beta_2}\int_{\alpha_1}^{\alpha_2}\ldots\frac{1}{2\pi\sigma^2}\ldots\\
&\ldots[1 - P(\alpha,\beta,t)] \times \ldots\\
&\ldots \times e^{\left[\frac{-1}{2\sigma^2}\left[(t-\bar{t})^2 + (\beta-\bar{\beta})^2 + (\alpha-\bar{\alpha})^2\right]\right]}\ldots\\
&\ldots\ldots\, d\alpha\, d\beta\, dt \quad ;\\
&\text{with,}\\
&\sigma = \sqrt{\sigma_\alpha^2 + \sigma_\beta^2 + \sigma_t^2} \quad ;
\end{aligned}$$

(4, Enhanced in Appendix)

where

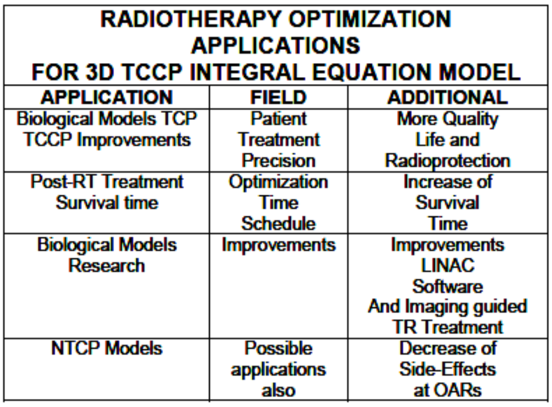
N_0 : Surviving number of tumor clonogens .
t : Total radiation treatment parameter.
α : Clonogen radiosensitivity parameter.
β : Clonogen radiosensitivity parameter.
D : Total radiation dose delivered.
K : Lea-Catcheside function-factor K, [64].
A : Factor for $T_{Treatment}$ from (2). Adimensional.
σ_α : Standard Deviation for α .
σ_β : Standard Deviation for β .
σ_t : Standard Deviation for $T_{Treatment}$.
σ : Overall normalized Standard Deviation.

This integral equation [Casesnoves, 2023], based on a variation from authors in [90, Equation (2), Chapter 12], can be determined analytically with similar algebraic method than [89] .

IV. RADIOTHERAPY PHYSICS APPLICATIONS

Table 1 developed/modified from previous publications, shows a resume of radiotherapy 3D Integral Equation applications for RT treatment based on biological models. Medical physics principal applications for radiotherapy TPO are explained briefly.

Table 1.- Brief of radiotherapy and radioprotection applications derived for Equations 1-4..



RADIOTHERAPY OPTIMIZATION APPLICATIONS FOR 3D TCCP INTEGRAL EQUATION MODEL		
APPLICATION	**FIELD**	**ADDITIONAL**
Biological Models TCP TCCP Improvements	Patient Treatment Precision	More Quality Life and Radioprotection
Post-RT Treatment Survival time	Optimization Time Schedule	Increase of Survival Time
Biological Models Research	Improvements	Improvements LINAC Software And Imaging guided TR Treatment
NTCP Models	Possible applications also	Decrease of Side-Effects at OARs

V. DISCUSSION AND CONCLUSIONS

The objective of the study was to extend the previous TCCP 2D Integral Equation to a 3D further one with the implementation of $N_{Effective}$ model parameters. The resulting three-variables integral equation of first kind was set with a Gaussian convolution to determine the statistical cumulative probability as in [20,89].

The formula developments, Equations 1-4, are also based on a binomial approximation for TCP probability function of the improved model. Algorithm, therefore, is set for next determination as was done in [89]. Mathematical probability concepts for cumulative convoluted probability are explained, Section II. An inconvenient of the equation is the increased number of variables from [89], two, to three ones. Advantages could be more precision and adaptation for a better biological model optimization.

Grosso modo, an advanced formulation for TCCP integral equation was set for further calculations in TPO. Applications for optimal RT planning and increased patient survival time and radioprotection emerge form results.

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VI. SCIENTIFIC ETHIC STANDARDS

Model is a modification from [90] authors, based also on [20,24,25,83,88,89] techniques. RT applications methods for these publications were created by Dr Casesnoves in 2021-2. Methods from [20,89] 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. 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].

VII. 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 75 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 2019-2023], 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 50 physics-engineering articles, three books series, and 1 industrial radiotherapy project associated to Europe Union EIT Health Program (Tartu University, 2017). Recently, a new book in Interior Optimization Mathematical Methods with Electronics Applications was published (2023).

APPENDIX

Binomial Approx,

such as $N_0 \simeq 1$,

$$P\,(\alpha,\beta,t) = \left(1 - e^{\left[-\left(\alpha D + \beta K D^2\right) + A\right]}\right);$$

$$TCCP\,(\bar{\alpha},\bar{\beta},\bar{t}) = \int_{t_1}^{t_2}\int_{\beta_1}^{\beta_2}\int_{\alpha_1}^{\alpha_2} \frac{1}{2\pi\sigma^2} \times \left[1 - P\,(\alpha,\beta,t)\right] \times \ldots$$

$$\ldots \times e^{\left[\frac{-1}{2\sigma^2}\left[(t-\bar{t})^2 + (\beta-\bar{\beta})^2 + (\alpha-\bar{\alpha})^2\right]\right]}\, d\alpha\, d\beta\, dt \quad ;$$

with,

$$\sigma = \sqrt{\sigma_\alpha^2 + \sigma_\beta^2 + \sigma_t^2} \quad ;$$

INTEGRAL EQUATION MODEL (4) ENHANCED
[Casesnoves, 2023]