# RADIOTHERAPY CANCER TREATMENT MODEL WITH FRACTIONAL DERIVATIVE COUPLED WITH LINEAR-QUADRATIC MODEL

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## DEDICATION

This thesis is dedicated to my father, who taught me that the best kind of knowledge to have is that which is learned for its own sake. It is also dedicated to my mother, who taught me that even the largest task can be accomplished if it is done one step at a time.

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## ABSTRACT

A mathematical model that simulates a radiotherapy cancer treatment process is presented in this thesis. The model takes two important radiobiological factors into consideration, which are repair and repopulation of cells. The model is used to simulate the fractionated radiotherapy treatment processes of six patients. The results give the population changes in the cells and the final volumes occupied by the normal and cancer cells. The model is formulated by integrating the Caputo fractional derivative with the previous cancer treatment model. Thereafter, the linear quadratic with the repopulation model is coupled into the model to account for the cells' population decay due to radiation. The treatment processes are then simulated in MATLAB with numerical variables, numerical parameters, and radiation parameters. The numerical parameters which include the proliferation coefficients of cells, competition coefficients of cells, and the perturbation constant of the normal cells are obtained from a previous research. The radiation parameters are obtained from another previous research that reported clinical data of six patients treated with radiotherapy. From the reported clinical data, the patients had tumor volumes of $24.1cm^3$, $17.4cm^3$, $28.4cm^3$, $18.8cm^3$, $30.6cm^3$, and $12.6cm^3$ and were treated with fractionated doses of 2.0 Gy for the first two patients and 1.8 Gy for the other four. Next, the integrity of the formulated model is established with the proof of the existence of unique solutions, the stability analysis, the sensitivity analysis, the bifurcation analysis, and the comparative analysis. Also, 96 radiation protocols are simulated by using the biologically effective dose formula. All these protocols are then used to obtain regression equations connecting the value of the Caputo fractional derivative with the fractionated radiation dose, and these regression equations are used to simulate various radiotherapy treatments in four different categories. The final tumor volumes, from the results of the simulations, are $3.58cm^3$, $8.61cm^3$, $5.68cm^3$, $4.36cm^3$, $5.75cm^3$, and $6.12cm^3$. Meanwhile the volumes occupied by the normal cells are $23.87cm^3$, $17.29cm^3$, $28.17cm^3$, $18.68cm^3$, $30.33cm^3$, and $12.55cm^3$. The stability analysis shows that the model is asymptotically and exponentially stable. Also, the solutions of the simulations are unique and stable even there are changes in initial values. The sensitivity analysis shows that the most sensitive controllable model factor is the value of the Caputo fractional derivative and this model factor has bifurcation values. Furthermore, the comparative analysis shows that the fractional derivative model encompasses the memory effect of the radiotherapy process. The predicted simulated final tumor volumes obtained with the regression equations are then compared with the corresponding reported clinical final tumor volumes. The results of these comparisons show that the predictions have minimal errors, hence they are acceptable. Finally, optimal and complete treatment solutions are simulated and predicted.

# ABSTRAK

Model matematik yang mensimulasikan proses rawatan barah radioterapi dipersembahkan dalam tesis ini. Model ini mengambil kira dua faktor radiobiologi yang penting, iaitu pembaikan dan populasi semula sel. Model ini digunakan untuk mensimulasikan proses rawatan radioterapi berbahagi terhadap enam pesakit. Hasilnya memberikan perubahan populasi dalam sel dan isipadu akhir yang terisi oleh sel normal dan sel barah. Model ini dirumuskan dengan mengintegrasikan pecahan terbitan Caputo dengan model rawatan barah terdahulu. Setelah itu, kuadratik linear dengan model populasi semula digandingkan menjadi model untuk menjelaskan kerosakan populasi sel akibat radiasi. Proses rawatan kemudiannya disimulasikan dalam MATLAB dengan pembolehubah berangka, parameter berangka, dan parameter radiasi. Parameter berangka yang merangkumi pekali pemproliferatan sel, pekali persaingan sel, dan pemalar usikan sel normal diperoleh dari kajian terdahulu. Parameter radiasi diperoleh dari penyelidikan terdahulu yang melaporkan data klinikal enam pesakit yang dirawat dengan radioterapi. Dari data klinikal yang dilaporkan, pesakit mempunyai isipadu tumor $24.1cm^3$, $17.4cm^3$, $28.4cm^3$, $18.8cm^3$, $30.6cm^3$, dan $12.6cm^3$ dengan dos berbahagi 2.0 Gy untuk dua pesakit pertama dan 1.8 Gy untuk empat pesakit yang lain. Selepas itu, integriti model yang dirumuskan diperkuatkan lagi dengan pembuktian kewujudan penyelesaian unik, analisis kestabilan, analisis kepekaan, analisis bifurkasi, dan analisis perbandingan. Juga, 96 protokol radiasi disimulasikan dengan menggunakan formula dos berkesan secara biologi. Semua protokol ini kemudiannya digunakan untuk mendapatkan persamaan regresi yang menghubungkan nilai terbitan pecahan Caputo dengan dos radiasi berbahagi, dan persamaan regresi ini digunakan untuk mensimulasikan pelbagai rawatan radioterapi dalam empat kategori yang berbeza. Isipadu tumor akhir, hasil dari simulasi adalah $3.58cm^3$, $8.61cm^3$, $5.68cm^3$, $4.36cm^3$, $5.75cm^3$, dan $6.12cm^3$. Sementara itu, isipadu yang terisi oleh sel normal adalah $23.87cm^3$, $17.29cm^3$, $28.17cm^3$, $18.68cm^3$, $30.33cm^3$, dan $12.55cm^3$. Analisis kestabilan menunjukkan bahawa model tersebut stabil secara asimptot dan eksponen. Juga, penyelesaian dari simulasi adalah unik dan stabil walaupun ada perubahan dalam nilai awal. Analisis kepekaan menunjukkan bahawa faktor model terkawal yang paling sensitif adalah nilai terbitan pecahan Caputo dan faktor model ini mempunyai nilai bifurkasi. Selanjutnya, analisis perbandingan menunjukkan bahawa model pecahan terbitan merangkumi kesan ingatan terhadap proses radioterapi. Isipadu tumor akhir simulasi yang diramalkan yang diperoleh dengan persamaan regresi kemudiannya dibandingkan dengan isipadu tumor akhir klinikal yang dilaporkan. Hasil perbandingan ini menunjukkan bahawa ramalan tersebut mempunyai ralat minimum, oleh itu ramalan tersebut boleh diterima. Akhirnya, penyelesaian rawatan yang optimum dan lengkap disimulasikan dan diramalkan.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| ODE | - | Ordinary Differential Equation |
| FDE | - | Fractional Differential Equation |
| DNA | - | Deoxyribonucleic Acid |
| LQ | - | Linear-Quadratic |
| FO | - | Fractional Order |
| LTI | - | Linear Time-Invariant system |
| Gy | - | Gray |
| DSB | - | Double-Stranded Breaks |

## LIST OF SYMBOLS

| | | |
|---|---|---|
| $\mu$ | - | Fractional order |
| $p_1$ | - | Population of the normal cells |
| $p_2$ | - | Population of the cancer cells |
| $\alpha_1$ | - | Proliferation coefficient of the normal cells |
| $\alpha_2$ | - | Proliferation coefficient of the cancer cells |
| $K_1$ | - | Carrying capacity of the normal cells |
| $K_2$ | - | Carrying capacity of the cancer cells |
| $\beta_1$ | - | Competition coefficient of the normal cells |
| $\beta_2$ | - | Competition coefficient of the cancer cells |
| $D(t)$ | - | Strategy of radiation |
| $\varepsilon$ | - | Perturbation constant |
| ${}_0^C D_T^\mu$ | - | Caputo fractional derivative |
| $\chi(p_i,t)$ | - | Cells' population decay and cancer cells' repopulation due to radiation |

## LIST OF APPENDICES

# CHAPTER 1

# INTRODUCTION

## 1.1 Problem Background

Cancer, as a result of its high mortality rate, is an acknowledged global disease that has attracted contributions from researchers in different disciplines. Unfortunately, despite these contributions, the disease still has a high mortality rate especially amongst women and the elderly, and in North America, it is ranked as the second major cause of death after heart disease (Belostotski and Freedman, 2005). In a country like Malaysia, ovarian cancer is a major cause of death among women (Lokman et al., 2017). It was reported that lung, bowel, prostate, and female breast cancer are the most common worldwide, and about 100,000 new cases of cancer were detected in Malaysia between the period of 2007-2012 (Firdaus et al., 2018). Also, the risk of dying from the disease increases with age and most patients are above 55 years. Furthermore, the probability of developing cancer in a human lifetime is 1 in 2 for males while it is 1 in 3 for females (Nawrocki and Zubik-Kowal, 2015). Hence, cancer treatment research is not only significant, but it is also very necessary.

The success of treating cancer depends solely on understanding the cellular characteristics of the disease. The sustainability of any living organism depends on the cellular interactions of millions of cells. But when a biological disruption causes a collapse in these cellular interactions, there is an uncontrolled proliferation of cells thus triggering the onset of cancer. These cancerous cells can later invade the neighboring tissues, thereby forming a tumor. If the tumor is left untreated via medical intervention, it will lead to the death of the patient (Nawrocki and Zubik-Kowal, 2015). However, in handling these cancer cases, the cancer treatment procedure is either aimed at being a curative or a palliative measure. Nonetheless, irrespective of the treatment's aim, every cancer patient is always optimistic about being completely cured. The medical practitioner, on the other hand, is not only interested in the

treatment but is also interested in the outcomes and effects of such treatments on the patient. As a result, it is important to have a foreknowledge of the outcomes of different cancer treatment procedures. The clinical procedures for treating or managing cancer are mainly surgery, immunotherapy, radiotherapy, hyperthermia, and chemotherapy. At times, one or more of these procedures can be combined for a patient. In this thesis, the focus is on radiotherapy cancer treatment. Radiotherapy is the most cost-effective treatment procedure because the rapidly proliferating cancer cells are destroyed with doses of irradiation. Besides, radiotherapy accounts for only about five percent of the total cost of treatment and it can also be used for curative or palliative purposes (Barnett et al., 2009). Moreover, an important factor considered when administering cancer treatment is the cost that might be prohibitive for a low or an average-income earner, therefore radiotherapy is a viable option.

However, for a successful radiotherapy treatment process, it is imperative to monitor the progress of treatment by knowing the effects of radiation on both the tumor and the patient. Furthermore, a foreknowledge of treatment outcomes for different radiation protocols will assist the medical team to choose an optimal radiation schedule. Most times the choice of a radiotherapy plan is based on clinical records as well as the amount of experience and expertise of the medical practitioner. But apart from clinical records, mainly based on the results of clinical trials and the use of animal models, it is also possible to know the outcome of a radiation schedule or predict an approximate result of a radiation protocol with the use of mathematical models. Generally, a mathematical model represents a real-life process and from this model, the process can be analyzed and future outcomes can be predicted.

The administration of radiotherapy involves a lot of calculations and planning in order not to harm the patient. The main aim of radiotherapy is to eliminate the cancerous cells without harming the normal cells. The rapidly proliferating cancer cells are targeted and destroyed by doses of radiation, thereby reducing the active population of the cancer cells. Cancer treatment can be interpreted mathematically as the reduction of cancer cells and the treatment is completed when the active population becomes zero. Unfortunately, when radiation is administered, the untargeted slowly proliferating normal cells are also affected. Although this effect is to a lesser degree,

it also damages the normal cells and reduces their population. The elimination of cancerous cells is of benefit to the patient while the destruction of normal cells can be detrimental to the patient (Emami, 2013). As a result, it can be proposed that the extent of normal cells' damage suffered by a patient is proportional to the population of the destroyed normal cells. Therefore, the status of treatment is directly linked to the populations of the normal and cancer cells. A successful treatment signifies a zero population of the cancer cells while an unchanged population of normal cells can mean no normal cells' damage. Most treatments are partially successful and normal cells' damage does occur, this implies that the populations of both normal and cancer cells are both reduced. Therefore, to properly administer radiotherapy and manage normal cells' damage, the population dynamics of the normal and cancer cells during radiotherapy must be known. To achieve this objective, the use of mathematical models is of immense importance.

There have been many proposed mathematical models aimed at describing the radiotherapy cancer treatment process. Some of these models approached the cancer treatment process from the molecular or cellular point of view, whereas, some other models used the macroscopic continuous fluid dynamics approach by treating the tumor as a system or body that grows uniformly (Laubenbacher et al., 2009). This thesis focuses on the latter type of models. The most prominent of these latter types of models is the cancer treatment model proposed by Belostotski and Freedman (2005). The proposed cancer treatment model was based on the Lotka-Volterra competitive model and it represented the treatment process by assuming that the cancer region was made up of two competing species. The two competing species are cancer cells and normal cells. The proliferation of the cells was represented with proliferating coefficients and this proliferation followed a logistic equation pattern with a carrying capacity bounding the populations of the cells. Although cancer and normal cells proliferate, the proliferation of the cancer cells is uncontrollable and is much more aggressive resulting in the formation of a tumor (Nawrocki and Zubik-Kowal, 2015). Also, since cancer and the normal cells are in continuous competition for resources, the cells' populations will decrease due to this competition, and the authors represented this feature with competition coefficients. Since radiotherapy is aimed at treating cancer, then the administration of radiation is aimed at greatly reducing the population

of cancer cells. The cancer cells' population decay due to radiation was represented by a harvesting control mechanism in the model.

However, the bottleneck of the model proposed by Belostotski and Freedman (2005) was the assumption that only the targeted rapidly proliferating cancer cells were affected by the radiation doses while the slowly proliferating normal cells were spared. This assumption goes against clinical evidence because radiation also affects untargeted normal cells (Rashid et al., 2018). Therefore, the cancer treatment model was improved by Freedman and Belostotski (2009) with the inclusion of a perturbation constant to account for the normal cells' population decay due to radiation doses. This improved cancer treatment model was later analyzed numerically by Liu and Yang (2014). Liu and Yang (2014) further explored the modified model and presented a periodic cancer treatment model. For the periodic model, conditions for the coexistence of the normal and cancer cells were established. But the analysis was not done with clinical data, giving room for more work.

To make the mathematical models more clinically relevant, Nawrocki and Zubik-Kowal (2015) developed a model that described the proliferation and spread of tumors from a primary region to a secondary region. This model only considered the proliferation and metastasis of the cancer cells under radiotherapy. The normal cells were not considered. The model consists of a proliferation constant for population increase, a dispersion model for the spread of cancer cells, and the linear-quadratic (LQ) model for the populations of cancer cells destroyed by radiation. The model was corroborated with clinical data. Despite the contribution of these mathematical models, a more accurate model can still be obtained. This cancer treatment model, like the previous ones, was based on the ordinary differential equation.

Improvements to the current cancer treatment are still in progress with the introduction of fractional derivatives into the cancer treatment model. Recently, Dokuyucu et al. (2018) integrated the Caputo-Fabrizio fractional derivative into the cancer treatment model. The structure of the new model was similar to that introduced by Belostotski and Freedman (2005). However, the major difference was the replacement of the ordinary derivative with the Caputo-Fabrizio fractional derivative.

The authors used the fixed-point theorem to show the conditions for the existence and uniqueness of solutions for the fractional cancer treatment model. Similarly, Awadalla et al. (2019) integrated the Hadamard fractional derivative into the cancer treatment model. The authors also showed the conditions for the existence and uniqueness of solutions for their model. The integration of fractional derivatives into the cancer treatment model included the memory feature, which is part of all biological processes (Ahmed et al., 2012). The physical explanation of the memory feature is given in Section 4.4.5. Although the integration of fractional derivatives improved the cancer treatment model, the establishment of unique solutions is a mathematical exercise that might not be meaningful to a typical medical practitioner. This is because a typical medical practitioner is mainly interested in treating the cancer patient and not in the formulation and analysis of the mathematical model. Furthermore, the unique solution of the cancer treatment model is a mathematical analysis that proves that by simulating a cancer treatment with the model, only one reliable solution will be obtained and this solution will be the final cells' populations from which the final tumor volumes can be obtained. Therefore, it is necessary to give the cancer treatment model clinical relevance.

## 1.2 Problem Statement

As a result of the necessity discussed above, it is imperative to use the fractional cancer treatment model to simulate the treatment processes of cancer patients treated with radiotherapy. Also, to make the model more relevant, these simulations should be done with real clinical data whose results should give the final populations of the tumors and normal cells' volume. The previous mathematical model formulated by Belostotski and Freedman (2005) was used in analyzing the radiotherapy treatment process. From this model, the only information that had been obtained is the existence and uniqueness of solutions of the models (Dokuyucu et al., 2018; Awadalla et al., 2019). This information might be elegant to mathematicians, but it is incomprehensible and irrelevant to medical practitioners because they are more concerned about the clinical treatment than the analysis of the model.

In this thesis, an improved cancer treatment model that simulates the processes involved during radiation treatment is presented. These processes include the proliferation of the cells, the decline in populations of cells due to competition, the decline in populations due to radiation doses, and the repopulation of the cancer cells after the "kick-off" time. Although Dokuyucu et al. (2018) and Awadalla et al. (2019) justified the use of the fractional cancer treatment model with the establishment of unique solutions, there are still important questions left unanswered and these questions need clarification. As such, there are still research gaps to be filled.

## 1.3 Research Questions

At present, the formulated cancer treatment model by Belostotski and Freedman (2005) has not been used to simulate cancer treatments of cancer patients. The model has also not been used to predict the results of different radiotherapy treatments. This is because some research questions still need to be answered to make the cancer treatment model more clinically relevant. These research questions are addressed in this study and they include, can the radiotherapy cancer treatment model be improved to simulate clinical radiotherapy cancer treatments? Will these simulations consider the repair and repopulation of the cancer cells? Will this improved model be well-posed? How can the cancer treatment model be used to predict results for different radiation protocols such as with different doses, with a different number of fractions, and when the number of fractions is reduced to avoid repopulation of cancer cells? Can the radiotherapy cancer treatment be optimized, and which radiation protocol produces optimal treatment, or which radiation protocols will produce complete treatment? Will the ordinary derivative model and fractional derivate model give the same solution? Is there any advantage in using an ordinary or fractional derivative? Does the fractional derivative model have a bifurcation value? These questions which constitute the research gaps in cancer treatment research are addressed in this thesis. By addressing these research questions, the cancer treatments can be simulated and analyzed. The results of various radiotherapy protocols can also be predicted, and optimal radiation protocols can be selected.

## 1.4 Research Objectives

This research aims to formulate an improved fractional cancer treatment model that will be corroborated with previously published clinical data of six uterine cervical cancer patients treated with radiotherapy. After the formulation, the model will be mathematically analyzed to simulate radiotherapy cancer treatment processes and predict approximate treatment outcomes of different radiotherapy protocols. Therefore, the objectives of this research are presented below

(a) To develop an improved fractional radiotherapy cancer treatment model and corroborate the formulated model with published clinical data. Thereafter, to establish the existence and uniqueness of solutions for the formulated model.

(b) To assess dynamically, the stability, the bifurcation, and the sensitivity analysis on the formulated model.

(c) To simulate six cancer treatment processes with the formulated model and mathematically analyze the treatment process as well as the normal cells' damage. Then, to obtain a regression equation that uses the value of the radiation dose to calculate an appropriate fractional-order for the Caputo fractional derivative.

(d) To implement a comparative analysis between the fractional derivative cancer treatment model and the ordinary derivative cancer treatment model.

(e) To simulate different radiotherapy protocols and predict their approximate treatment outcomes. Hence, obtaining simulated optimal solutions from the different radiotherapy protocols.

## 1.5 Significance of the Study

This research is important in furthering the effort of finding a solution to cancer treatment because by formulating a mathematical model that simulates a treatment process, the results of different radiotherapy protocols can be simulated. The

simulation of the treatment process will enable the status of the treatment to be analyzed. The predicted outcome of a radiotherapy protocol will assist in selecting an optimal protocol. Ideally, the success of radiotherapy depends largely on the knowledge of populations of the cells. The elimination of cancer cells is the primary objective of treatment. The previous cancer treatment model of Belostotski and Freedman (2005) had not been successful in predicting the populations of the eliminated cancer cells and the damaged normal cells. Without this information, the progress of cancer treatment cannot be analyzed because the population of eliminated cancer cells will signify cancer treatment while the population of eliminated normal cells will signify normal cells' damage. However, with the use of the proposed improved cancer treatment model, cancer treatments can be simulated with values of radiation dosage rates and their corresponding effects on cells' populations can be simulated.

The use of the mathematical model for predicting the outcome of physical processes is always challenged by the unavailability of real data to corroborate the model. The pioneers of the cancer treatment models were only able to establish the uniqueness of solutions for the model (Dokuyucu et al., 2018; Belostotski and Freedman, 2005; Freedman and Belostotski, 2009; Awadalla et al., 2019). Also, numerical analysts could only use empirical values in analyzing cancer treatment with the model (Liu and Yang, 2014). Therefore, the previous cancer treatment models have remained more descriptive of the process rather than being predictive. The improved model, that will be formulated in this research, is expected to be analytic and predictive. Therefore, published clinical data of treated cancer patients are used in the improved model to execute simulations. The use of clinical data is aimed at enhancing the predictiveness of the improved model. Such predictions will assist in selecting good treatment schedules. Finally, the use of a predictive mathematical model is more economical and more ethical than the use of animal models because animal models involve the use of animals like rats, mice, and rabbits (Laird, 1964) for studying radiation effects.

## 1.6 Scope of the Study

This research is limited to cancer treatment with radiotherapy. The formulated model only considered the repair and repopulation of the cancer cells. The redistribution and reoxygenation of cancer cells are not included in the model because these two processes are still being researched and numerical values representing these processes have not been proposed. Also, only a local tumor is considered and the spread of cancer cells to a secondary region of the body (metastasis) is not considered. The numerical values for the model factors are obtained from previous literature while the clinical data are obtained from published clinical data. Although the radiotherapy process is dependent on time, this dependence on time is neglected for the model factors and the radiation parameters. This is because the values for the model factors presented by Belostotski and Freedman (2005) and the radiation parameters presented by Belfatto et al. (2016) were constants and not functions of time. The analysis of the cancer treatment and the normal cells' damage effects are done from the mathematical point of view. Lastly, the initial population of cancer cells is obtained from the tumor volumes while the normal cells' initial population is assumed to be equal to the initial population of cancer cells. This assumption is made because values for the initial population of normal cells are not available.

## 1.7 Methodology

This research is carried out by first formulating the improved cancer treatment model. In formulating the radiotherapy model, there are two things to be considered. The first thing is to define the model variables which are the independent and dependent variables. In the case of radiotherapy, the dependent variables are the populations of the normal and cancer cells while the independent variable is the time of the process which in this case is the treatment time. Since the model's dependent variables are two, then the improved model will have two differential equations. The second thing is to define the model parameters which will represent the radiotherapy process that affects the populations of the normal and cancer cells. In any population, the population increases and decreases and is always bounded by a carrying capacity

beyond which the population ceases to increase. In the radiotherapy model, the proliferation of the cells follows a logistic pattern, and the Lotka-Volterra model with a carrying capacity is used to represent the process.

The second process involved in radiotherapy is the decrease in the populations of the cells. The decrease in populations takes place in two categories. The first category is the decrease in population due to competition of cancer and normal cells (Belostotski and Freedman, 2005). In every population, where the entities are competing for resources, then the populations will be reduced. The model parameter used to represent this process is the competition coefficient. The second category is the decrease in population due to radiation. During radiation, the cancer cells are targeted, and the normal cells are supposed to be unaffected. However, the effects of radiation are also felt by the normal cells (Rashid et al., 2018). This effect is to a lesser degree and the perturbation constant is the model parameter used to represent this process. The change in the population of cells is represented with the Caputo fractional derivative to include the memory effect of the radiotherapy process in the model (Ahmed et al., 2012; Balcı et al., 2019). Thus, the improved model is formulated with the radiotherapy cancer treatment process illustrated below

Change in the population of normal cells = (increase in population bounded by carrying capacity) – (decrease in population due to competition) – (perturbation constant) (decrease in population due to radiotherapy)

Change in the population of cancer cells = (increase in population bounded by carrying capacity) – (decrease in population due to competition) – (decrease in population due to radiotherapy)

After formulating the model, the metric space analysis is used to show the uniqueness of the solutions of the model. Thereafter, the model is used to simulate cancer treatments of six patients treated with radiotherapy in MATLAB. The cancer treatments are then analyzed mathematically as follows

Cancer treatment = Population of eliminated cancer cells
Normal cells' damage = Population of eliminated normal cells
Percentage cancer treatment = Percentage of eliminated cancer cells
Percentage normal cells' damage = Percentage of eliminated normal cells

The sensitivities of the model factors are then investigated with the variance-based approach sensitivity analysis (Saltelli et al., 2008). The variance-based approach is a global sensitivity analysis in which all the model factors are investigated simultaneously to find the most sensitive model factor and this factor is then be investigated for bifurcation. The sensitivity and bifurcation analyses are done in MATLAB. The cancer treatments are then simulated in MATLAB with both fractional derivative model and ordinary derivative model to investigate the comparative advantage of the fractional derivative radiotherapy cancer treatment model. The biologically effective dose (BED) is then used to simulate 96 different radiation protocols and from these protocols, a regression equation is formulated for obtaining an approximate fractional-order for the Caputo fractional derivative in the model.

The last part of the research involves the use of the improved fractional derivative cancer treatment model to simulate different radiotherapy protocols in MATLAB. This is done by using the BED to obtain six regression equations for the six patients. These regression equations are used to obtain the approximate fractional orders for the Caputo fractional derivatives in the simulations. The simulations are done in four categories. These four categories of simulations include varying the doses of the patients from 1.0 Gy to 6.0 Gy, varying the doses of the patients from 1.0 Gy to 6.0 Gy but without repopulation of the cancer cells, varying the number of fractions from 25 to 35 fractions, and the use of a single regression equation for simulating the six patients' cancer treatments. From these four categories of simulations, the optimal solutions and the complete cancer treatment solutions are obtained for the six patients.

## 1.8 Thesis Organization

This thesis is arranged into six chapters. Firstly, Chapter 2 is the Literature Review where the previous contributions are presented. The review is divided into three parts, the first part reviewed tumor growth models from 1932-2020, the second part reviewed radiotherapy models from 1990-2020, and the third part reviewed fractional derivative cancer treatment models from 2014-2020. This review shows that the tumor growth models represent the problem (cancer evolution), the radiotherapy models represent the solution (cancer treatment), and the fractional derivative cancer treatment models represent the method (fractional derivative).

Chapter 3 is the Mathematical Formulation where the model is formulated, and the model parameters are presented. Thereafter, the existence and uniqueness of solutions of the model are established, and the cancer treatments are simulated. Also, the stability analysis of the model is shown. Furthermore, Chapter 4 is the Mathematical Analysis where the cancer treatments are simulated, and the sensitivity analysis of the model factors is shown. Also, the bifurcation analysis and the comparative analysis between the fractional derivative and the ordinary derivative model are shown.

Chapter 5 is the Numerical Simulation where the regression equation for obtaining the fractional-order of the Caputo fractional derivative from radiation doses is formulated. Thereafter, the model is used to simulate different radiotherapy protocols and optimal solutions for each simulation are identified. Finally, Chapter 6 is the Conclusion and Recommendations where the future direction and recommendations for the fractional derivative cancer treatment model are presented.

# REFERENCES


Adam J and Maggelakis S. (1990) Diffusion regulated growth characteristics of a spherical prevascular carcinoma. *Bulletin of mathematical biology* 52: 549-582.

Adam JA. (1986) A simplified mathematical model of tumor growth. *Mathematical Biosciences* 81: 229-244.

Adam JA. (1987a) A mathematical model of tumor growth. II. Effects of geometry and spatial nonuniformity on stability. *Mathematical Biosciences* 86: 183-211.

Adam JA. (1987b) A mathematical model of tumor growth. III. Comparison with experiment. *Mathematical Biosciences* 86: 213-227.

Adam JA and Maggelakis S. (1989) Mathematical models of tumor growth. IV. Effects of a necrotic core. *Mathematical Biosciences* 97: 121-136.

Ahmed E, Hashish A and Rihan F. (2012) On fractional order cancer model. *Journal of Fractional Calculus and Applied Analysis* 3: 1-6.

Akman Yıldız T, Arshad S and Baleanu D. (2018) Optimal chemotherapy and immunotherapy schedules for a cancer-obesity model with Caputo time fractional derivative. *Mathematical Methods in the Applied Sciences* 41: 9390-9407.

American Cancer Society medical and editorial content team (2019). Getting external beam radiation therapy. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/radiation/external-beam-radiation-therapy.html#written_by. Accessed February 6, 2020.

Araujo RP and McElwain DS. (2004) A history of the study of solid tumour growth: the contribution of mathematical modelling. *Bulletin of mathematical biology* 66: 1039-1091.

Asjad MI. (2019) Fractional mechanism with power law (singular) and exponential (non-singular) kernels and its applications in bio heat transfer model. *International Journal of Heat and Technology* 37: 846-852.

Atangana A and Baleanu D. (2016) New fractional derivatives with nonlocal and non-singular kernel: theory and application to heat transfer model. *arXiv preprint arXiv:1602.03408*.

Atangana A and Secer A. (2013) A note on fractional order derivatives and table of fractional derivatives of some special functions. *Abstract and applied analysis*. Hindawi.

Awadalla M, Yameni Y and Abuassba K. (2019) A new Fractional Model for the Cancer Treatment by Radiotherapy Using the Hadamard Fractional Derivative. *Online Math.* 1: 14-18.

Balcı E, Öztürk İ and Kartal S. (2019) Dynamical behaviour of fractional order tumor model with Caputo and conformable fractional derivative. *Chaos, Solitons & Fractals* 123: 43-51.

Baleanu D, Jajarmi A, Sajjadi S, et al. (2019) A new fractional model and optimal control of a tumor-immune surveillance with non-singular derivative operator. *Chaos: An Interdisciplinary Journal of Nonlinear Science* 29: 083127.

Barnett GC, West CM, Dunning AM, et al. (2009) Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. *Nature Reviews Cancer* 9: 134.

Belfatto A, Riboldi M, Ciardo D, et al. (2016) Kinetic Models for Predicting Cervical Cancer Response to Radiation Therapy on Individual Basis Using Tumor Regression Measured In Vivo With Volumetric Imaging. *Technology in Cancer Research & Treatment* 15: 146-158.

Belostotski G and Freedman H. (2005) A control theory model for cancer treatment by radiotherapy. *Int. J. Pure Appl. Math* 25: 447-480.

Benzekry S, Lamont C, Beheshti A, et al. (2014) Classical mathematical models for description and prediction of experimental tumor growth. *PLoS computational biology* 10: e1003800.

Bertuzzi A, Bruni C, Papa F, et al. (2013) Optimal solution for a cancer radiotherapy problem. *Journal of mathematical biology* 66: 311-349.

Bhaumik K and Jain V. (1987) Mathematical models for optimizing tumour radiotherapy. I: A simple two compartment cell-kinetic model for the unperturbed growth of transplantable tumours. *Journal of Biosciences* 12: 153-164.

Borisut P, Khammahawong K and Kumam P. (2018) Fixed Point Theory Approach to Existence of Solutions with Differential Equations. *Differential Equations: Theory and Current Research*: 1.

Breward CJ, Byrne HM and Lewis CE. (2003) A multiphase model describing vascular tumour growth. *Bulletin of mathematical biology* 65: 609-640.

Bryne HM. (2003) Modelling Avascular Tumour Growth. In: Preziosi L (ed) *Cancer Modelling and Simulation.* Cancer Modelling and Simulation ed. UK: Chapman & Hall/CRC.

Byrne H. (1997) The effect of time delays on the dynamics of avascular tumor growth. *Mathematical Biosciences* 144: 83-117.

Byrne H and Chaplain MAJ. (1995) Growth of nonnecrotic tumors in the presence and absence of inhibitors. *Mathematical Biosciences* 130: 151-182.

Byrne H and Gourley S. (1997) The role of growth factors in avascular tumour growth. *Mathematical and Computer Modelling* 26: 35-55.

Byrne HM and Chaplain MA. (1996) Modelling the role of cell-cell adhesion in the growth and development of carcinomas. *Mathematical and Computer Modelling* 24: 1-17.

Caputo M and Fabrizio M. (2015) A new definition of fractional derivative without singular kernel. *Progr. Fract. Differ. Appl* 1: 1-13.

Casares-Magaz O, Van der Heide UA, Rørvik J, et al. (2016) A tumour control probability model for radiotherapy of prostate cancer using magnetic resonance imaging-based apparent diffusion coefficient maps. *Radiotherapy and Oncology* 119: 111-116.

Castorina P, Deisboeck T, Gabriele P, et al. (2007) Growth laws in cancer: implications for radiotherapy. *Radiation research* 168: 349-356.

Çelik C and Duman M. (2012) Crank–Nicolson method for the fractional diffusion equation with the Riesz fractional derivative. *Journal of computational physics* 231: 1743-1750.

Chaplain M. (1996) Avascular growth, angiogenesis and vascular growth in solid tumours: The mathematical modelling of the stages of tumour development. *Mathematical and Computer Modelling* 23: 47-87.

Chen C, Byrne H and King J. (2001) The influence of growth-induced stress from the surrounding medium on the development of multicell spheroids. *Journal of mathematical biology* 43: 191-220.

Chvetsov AV, Dong L, Palta JR, et al. (2009) Tumor-volume simulation during radiotherapy for head-and-neck cancer using a four-level cell population model. *International Journal of Radiation Oncology* Biology* Physics* 75: 595-602.

Csercsik D, Sápi J and Kovács L. (2017) A bicompartmental dynamic tumor growth model. *IFAC-PapersOnLine* 50: 12216-12221.

Dadras S, Dadras S, Malek H, et al. (2017) A note on the lyapunov stability of fractional-order nonlinear systems. *International Design Engineering Technical Conferences and Computers and Information in Engineering Conference*. American Society of Mechanical Engineers, V009T007A033.

Dalir M and Bashour M. (2010) Applications of fractional calculus. *Applied Mathematical Sciences* 4: 1021-1032.

Damor R, Kumar S and Shukla A. (2014) Numerical simulation of fractional bioheat equation in hyperthermia treatment. *Journal of Mechanics in Medicine and Biology* 14: 1450018.

De Angelis E and Preziosi L. (2000) Advection-diffusion models for solid tumour evolution in vivo and related free boundary problem. *Mathematical Models and Methods in Applied Sciences* 10: 379-407.

Dean JA, Wong KH, Welsh LC, et al. (2016) Normal tissue complication probability (NTCP) modelling using spatial dose metrics and machine learning methods for severe acute oral mucositis resulting from head and neck radiotherapy. *Radiotherapy and Oncology* 120: 21-27.

Dehghan M and Mohammadi V. (2017) Comparison between two meshless methods based on collocation technique for the numerical solution of four-species tumor growth model. *Commun Nonlinear Sci Numer Simulat* 44: 204–219.

Diethelm K. (2003) Efficient solution of multi-term fractional differential equations using P (EC) m E methods. *Computing* 71: 305-319.

Diethelm K, Ford NJ and Freed AD. (2004) Detailed error analysis for a fractional Adams method. *Numerical algorithms* 36: 31-52.

Diethelm K and Freed AD. (1998) The FracPECE subroutine for the numerical solution of differential equations of fractional order. *Forschung und wissenschaftliches Rechnen* 1999: 57-71.

Dokuyucu MA, Celik E, Bulut H, et al. (2018) Cancer treatment model with the Caputo-Fabrizio fractional derivative. *The European Physical Journal Plus* 133: 92.

Du M, Wang Z and Hu H. (2013) Measuring memory with the order of fractional derivative. *Scientific reports* 3: 1-3.

Ebenbeck M and Garcke H. (2019) Analysis of a Cahn–Hilliard–Brinkman model for tumour growth with chemotaxis. *Journal of Differential Equations* 266: 5998-6036.

Emami B. (2013) Tolerance of normal tissue to therapeutic radiation. *Reports of radiotherapy and Oncology* 1.

Erdélyi A and Kober H. (1940) Some remarks on Hankel transforms. *The Quarterly Journal of Mathematics*: 212-221.

Firdaus A, Khalid J and Yong YK. (2018) Malaysian Tualang Honey and Its Potential Anti-Cancer Properties: A Review. *Sains Malaysiana* 47: 2705-2711.

Folkman J and Hochberg M. (1973) Self-regulation of growth in three dimensions. *The Journal of experimental medicine* 138: 745-753.

Fowler JF. (2006) Development of radiobiology for oncology—a personal view. *Physics in Medicine & Biology* 51: R263.

Fowler JF, Harari PM, Leborgne F, et al. (2003) Acute radiation reactions in oral and pharyngeal mucosa: tolerable levels in altered fractionation schedules. *Radiotherapy and Oncology* 69: 161-168.

Freedman H and Belostotski G. (2009) Perturbed models for cancer treatment by radiotherapy. *Differential Equations and Dynamical Systems* 17: 115-133.

Freyer J, Tustanoff E, Franko A, et al. (1984) In situ oxygen consumption rates of cells in V-79 multicellular spheroids during growth. *Journal of cellular physiology* 118: 53-61.

Friedman A and Reitich F. (1999) Analysis of a mathematical model for the growth of tumors. *Journal of mathematical biology* 38: 262-284.

Garrappa R. (2010) On linear stability of predictor–corrector algorithms for fractional differential equations. *International Journal of Computer Mathematics* 87: 2281-2290.

Gerdes J, Lelle R, Pickartz H, et al. (1986) Growth fractions in breast cancers determined in situ with monoclonal antibody Ki-67. *Journal of clinical pathology* 39: 977-980.

Gerlee P. (2013) The model muddle: in search of tumor growth laws. *Cancer research* 73: 2407-2411.

González SJ and Carando DG. (2008) A general tumour control probability model for non-uniform dose distributions. *Mathematical medicine and biology: a journal of the IMA* 25: 171-184.

Guiot C, Degiorgis PG, Delsanto PP, et al. (2003) Does tumor growth follow a "universal law"? *Journal of theoretical biology* 225: 147-151.

Hadamard J. (1892) *Essai sur l'étude des fonctions, données par leur développement de Taylor*: Gauthier-Villars.

Hairer E, Lubich C and Schlichte M. (1985) Fast numerical solution of nonlinear Volterra convolution equations. *SIAM journal on scientific and statistical computing* 6: 532-541.

Hawkins-Daarud A, van der Zee KG and Tinsley Oden J. (2012) Numerical simulation of a thermodynamically consistent four-species tumor growth model. *International journal for numerical methods in biomedical engineering* 28: 3-24.

Helmlinger G, Netti PA, Lichtenbeld HC, et al. (1997) Solid stress inhibits the growth of multicellular tumor spheroids. *Nature biotechnology* 15: 778-783.

Hobbs RF and Sgouros G. (2009) Calculation of the biological effective dose for piecewise defined dose-rate fits. *Medical physics* 36: 904-907.

Huang Z, Mayr NA, Yuh WT, et al. (2010) Predicting outcomes in cervical cancer: a kinetic model of tumor regression during radiation therapy. *Cancer research* 70: 463-470.

Jalalimanesh A, Haghighi HS, Ahmadi A, et al. (2017) Simulation-based optimization of radiotherapy: Agent-based modeling and reinforcement learning. *Mathematics and Computers in Simulation* 133: 235-248.

Jones A, Byrne H, Gibson J, et al. (2000) A mathematical model of the stress induced during avascular tumour growth. *Journal of mathematical biology* 40: 473-499.

Jones B. (1999) Mathematical models of tumour and normal tissue response. *Acta oncologica* 38: 883-893.

Jones GS. (1964) Fundamental inequalities for discrete and discontinuous functional equations. *Journal of the Society for Industrial and Applied Mathematics* 12: 43-57.

Jumarie G. (2006) Modified Riemann-Liouville derivative and fractional Taylor series of nondifferentiable functions further results. *Computers & Mathematics with Applications* 51: 1367-1376.

K. Sachs PH and DJ Brenner R. (1997) Review the link between low-LET dose-response relations and the underlying kinetics of damage production/repair/misrepair. *International journal of radiation biology* 72: 351-374.

Katugampola UN. (2014a) A new approach to generalized fractional derivatives. *Bull. Math. Anal. Appl* 6: 1-15.

Katugampola UN. (2014b) A new fractional derivative with classical properties. *arXiv preprint arXiv:1410.6535*.

Khalil HK and Grizzle JW. (2002) *Nonlinear systems*: Prentice hall Upper Saddle River, NJ.

Khalil R, Al Horani M, Yousef A, et al. (2014) A new definition of fractional derivative. *Journal of Computational and Applied Mathematics* 264: 65-70.

Kilbas AA, Srivastava HM and Trujillo JJ. (2006) *Theory and applications of fractional differential equations*: elsevier.

Kumar D and Rai K. (2017) Numerical simulation of time fractional dual-phase-lag model of heat transfer within skin tissue during thermal therapy. *Journal of Thermal Biology* 67: 49-58.

Laird AK. (1964) Dynamics of tumour growth. *British journal of cancer* 18: 490.

Laubenbacher R, Hower V, Jarrah A, et al. (2009) A systems biology view of cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* 1796: 129-139.

Lee SP, Leu MY, Smathers JB, et al. (1995) Biologically effective dose distribution based on the linear quadratic model and its clinical relevance. *International Journal of Radiation Oncology* Biology* Physics* 33: 375-389.

Levine H and Sleeman B. (2003) Modelling Tumour-Induced Angiogenesis. Cancer Modelling and Simulation ed. UK: Chapman & Hall/CRC.

Li Q-W, Qiu B, Wang B, et al. (2019) Comparison of hyper-and hypofractionated radiation schemes with IMRT technique in small cell lung cancer: Clinical outcomes and the introduction of extended LQ and TCP models. *Radiotherapy and Oncology* 136: 98-105.

Li R and Hu B. (2019) A parabolic–hyperbolic system modeling the growth of a tumor. *Journal of Differential Equations* 267: 693-741.

Liotta LA, Saidel GM and Kleinerman J. (1977) Diffusion model of tumor vascularization and growth. *Bulletin of mathematical biology* 39: 117-128.

Liu Z and Yang C. (2016) A mathematical model of cancer treatment by radiotherapy followed by chemotherapy. *Mathematics and Computers in Simulation* 124: 1-15.

Liu Z, Zhong S, Yin C, et al. (2011) Permanence, extinction and periodic solutions in a mathematical model of cell populations affected by periodic radiation. *Applied mathematics letters* 24: 1745-1750.

Liu ZJ and Yang CX. (2014) A Mathematical Model of Cancer Treatment by Radiotherapy. *Comput Math Methods Med*: 12.

Lokman N, Hamid SAA and Bachok Na. (2017) Survival Study and Prognostic Factors of Ovarian Cancer Registered in a Teaching Hospital in Malaysia. *Sains Malaysiana* 46: 559-565.

Losada J and Nieto JJ. (2015) Properties of a new fractional derivative without singular kernel. *Progr. Fract. Dıffer. Appl* 1: 87-92.

Macías-Díaz JE and Gallegos A. (2018) A structure-preserving computational method in the simulation of the dynamics of cancer growth with radiotherapy. *Journal of Mathematical Chemistry* 56: 1985-2000.

Maggelakis S and Adam J. (1990) Mathematical model of prevascular growth of a spherical carcinoma. *Mathematical and Computer Modelling* 13: 23-38.

Mahasa KJ, Ouifki R, Eladdadi A, et al. (2016) Mathematical model of tumor–immune surveillance. *Journal of theoretical biology* 404: 312-330.

Marcu LG and Marcu D. (2019) The role of hypofractionated radiotherapy in the management of head and neck cancer–a modelling approach. *Journal of theoretical biology* 482: 109998.

Mayneord WV. (1932) On a law of growth of Jensen's rat sarcoma. *The American Journal of Cancer* 16: 841-846.

McElwain D and Pettet G. (1993) Cell migration in multicell spheroids: swimming against the tide. *Bulletin of mathematical biology* 55: 655-674.

McElwain D and Ponzo P. (1977) A model for the growth of a solid tumor with non-uniform oxygen consumption. *Mathematical Biosciences* 35: 267-279.

Michel T, Fehrenbach J, Lobjois V, et al. (2018) Mathematical modeling of the proliferation gradient in multicellular tumor spheroids. *Journal of theoretical biology* 458: 133-147.

Mínguez P, Gustafsson J, Flux G, et al. (2016) Biologically effective dose in fractionated molecular radiotherapy—application to treatment of neuroblastoma with 131I-mIBG. *Physics in Medicine & Biology* 61: 2532.

Mohammadi V and Dehghan M. (2019) Simulation of the phase field Cahn–Hilliard and tumor growth models via a numerical scheme: element-free Galerkin method. *Computer Methods in Applied Mechanics and Engineering* 345: 919-950.

Morales-Delgado VF, Gómez-Aguilar JF, Saad K, et al. (2019) Application of the Caputo-Fabrizio and Atangana-Baleanu fractional derivatives to mathematical model of cancer chemotherapy effect. *Mathematical Methods in the Applied Sciences* 42: 1167-1193.

Moore EJ, Sirisubtawee S and Koonprasert S. (2019) A Caputo–Fabrizio fractional differential equation model for HIV/AIDS with treatment compartment. *Advances in Difference Equations* 2019: 1-20.

Murphy H, Jaafari H and Dobrovolny HM. (2016) Differences in predictions of ODE models of tumor growth: a cautionary example. *BMC Cancer* 16: 1-10.

Nawrocki S and Zubik-Kowal B. (2015) Clinical study and numerical simulation of brain cancer dynamics under radiotherapy. *Communications in Nonlinear Science and Numerical Simulation* 22: 564-573.

Niemierko A. (1997) Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Medical physics* 24: 103-110.

O'Rourke S, McAneney H and Hillen T. (2009) Linear quadratic and tumour control probability modelling in external beam radiotherapy. *Journal of mathematical biology* 58: 799.

Orme M and Chaplain M. (1996) A mathematical model of vascular tumour growth and invasion. *Mathematical and Computer Modelling* 23: 43-60.

Ortigueira MD and Machado JT. (2015) What is a fractional derivative? *Journal of computational Physics* 293: 4-13.

Osler TJ. (1970) Leibniz rule for fractional derivatives generalized and an application to infinite series. *SIAM Journal on Applied Mathematics* 18: 658-674.

Please C, Pettet G and McElwain D. (1998) A new approach to modelling the formation of necrotic regions in tumours. *Applied mathematics letters* 11: 89-94.

Podlubny I. (1998) *Fractional differential equations: an introduction to fractional derivatives, fractional differential equations, to methods of their solution and some of their applications*: Elsevier.

Rashid H, Siam FM, Maan N, et al. (2018) Parameter Estimation for a Model of Ionizing Radiation Effects on Targeted Cells using Genetic Algorithm and Pattern Search Method. *Matematika* 34: 1-13.

Ribba B, Colin T and Schnell S. (2006) A multiscale mathematical model of cancer, and its use in analyzing irradiation therapies. *Theoretical Biology and Medical Modelling* 3: 7.

Ross B. (1975) A brief history and exposition of the fundamental theory of fractional calculus. *Fractional calculus and its applications*. Springer, 1-36.

Sadi MV and Barrack ER. (1991) Determination of growth fraction in advanced prostate cancer by Ki-67 immunostaining and its relationship to the time to tumor progression after hormonal therapy. *Cancer* 67: 3065-3071.

Saltelli A, Ratto M, Andres T, et al. (2008) *Global sensitivity analysis: the primer*: John Wiley & Sons.

Sarapata EA and de Pillis L. (2014) A comparison and catalog of intrinsic tumor growth models. *Bulletin of mathematical biology* 76: 2010-2024.

Scott JG, Berglund A, Schell MJ, et al. (2017) A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *The Lancet Oncology* 18: 202-211.

Sham E and Durand RE. (1998) Cell kinetics and repopulation mechanisms during multifraction irradiation of spheroids. *Radiotherapy and oncology* 46: 201-207.

Shen H and Wei X. (2019) A qualitative analysis of a free boundary problem modeling tumor growth with angiogenesis. *Nonlinear Analysis: Real World Applications* 47: 106-126.

Sherratt JA and Chaplain MA. (2001) A new mathematical model for avascular tumour growth. *Journal of mathematical biology* 43: 291-312.

Siam FM, Grinfeld M, Bahar A, et al. (2018) A mechanistic model of high dose irradiation damage. *Mathematics and Computers in Simulation* 151: 156-168.

Sontag W. (1987) A cell survival model with saturable repair after irradiation. *Radiation and environmental biophysics* 26: 63-79.

Sousa JVdC and de Oliveira EC. (2018) On the ψ-Hilfer fractional derivative. *Communications in Nonlinear Science and Numerical Simulation* 60: 72-91.

Stewart RD. (2001) Two-lesion kinetic model of double-strand break rejoining and cell killing. *Radiation research* 156: 365-378.

Sun W, Caraballo T, Han X, et al. (2020) A free boundary tumor model with time dependent nutritional supply. *Nonlinear Analysis: Real World Applications* 53: 103063.

Sutherland WA. (2009) *Introduction to metric and topological spaces*: Oxford University Press.

Sweilam N and AL-Mekhlafi S. (2018) Optimal control for a nonlinear mathematical model of tumor under immune suppression: A numerical approach. *Optimal Control Applications and Methods* 39: 1581-1596.

Wang P and Feng Y. (2013) A mathematical model of tumor volume changes during radiotherapy. *The Scientific World Journal* 2013.

Ward J and King J. (1999) Mathematical modelling of avascular-tumour growth II: modelling growth saturation. *Mathematical Medicine and Biology: A Journal of the IMA* 16: 171-211.

Ward JP and King J. (1997) Mathematical modelling of avascular-tumour growth. *Mathematical Medicine and Biology: A Journal of the IMA* 14: 39-69.

Watanabe Y, Dahlman EL, Leder KZ, et al. (2016) A mathematical model of tumor growth and its response to single irradiation. *Theoretical Biology and Medical Modelling* 13: 6.

Wheeler N. (1997) Construction and physical application of the fractional calculus. *Reeds College Physics Seminar.*

Wu J. (2017) Analysis of a mathematical model for tumor growth with Gibbs–Thomson relation. *Journal of Mathematical Analysis and Applications* 450: 532–543.

Xu J, Vilanova G and Gomez H. (2016) A mathematical model coupling tumor growth and angiogenesis. *PloS one* 11.

Xu J, Vilanova G and Gomez H. (2020) Phase-field model of vascular tumor growth: Three-dimensional geometry of the vascular network and integration with imaging data. *Computer Methods in Applied Mechanics and Engineering* 359: 112648.

Yang TC-H, Craise LM, Mei M-T, et al. (1985) Neoplastic cell transformation by heavy charged particles. *Radiation research* 104: S177-S187.

Yıldız TA, Arshad S and Baleanu D. (2018) New observations on optimal cancer treatments for a fractional tumor growth model with and without singular kernel. *Chaos, Solitons & Fractals* 117: 226-239.

Zaider M, Zelefsky MJ, Hanin LG, et al. (2001) A survival model for fractionated radiotherapy with an application to prostate cancer. *Physics in Medicine & Biology* 46: 2745.

Zhang Y, He Y and Chen H. (2019) Boundary element method for a free third boundary problem modeling tumor growth with spectral accuracy. *Journal of Computational and Applied Mathematics* 345: 434-451.

Zhao XE and Hu B. (2020) The impact of time delay in a tumor model. *Nonlinear Analysis: Real World Applications* 51: 103015.

## LIST OF PUBLICATIONS

Farayola, M. F., Shafie, S., Siam, F. M., and Khan, I. (2020) Mathematical modeling of radiotherapy cancer treatment using Caputo fractional derivative. *Computer Methods and Programs in Biomedicine* 188: 105306.

Farayola, M. F., Shafie, S., Siam, F. M., and Khan, I. (2020) Numerical simulation of normal and cancer cells' populations with fractional derivative under radiotherapy. *Computer Methods and Programs in Biomedicine* 187: 105202.

Farayola MF, Shafie S and Siam FM. (2019) Population dynamics of normal and cancer cells under radiotherapy. *Science Proceedings Series* 1: 51-54.

Farayola MF, Shafie S and Mohd Siam F. (2020) Stability analysis of radiotherapy cancer treatment model with fractional derivative. *Sains Malaysiana* 49 (11): 2833-2846.

Farayola, M., Shafie, S., Mohd Siam, F., Rozi, M., and Ajadi, S. (2020) Mathematical modeling of cancer treatments with fractional derivatives: An Overview. *Malaysian Journal of Fundamental and Applied Sciences* In Review.

Farayola, M., Shafie, S., Mohd Siam, F., Rozi, M., and Ajadi, S. (2020) Numerical simulation and optimization of radiotherapy cancer treatments using the Caputo fractional derivative *Malaysian Journal of Mathematical Sciences* Accepted Manuscript.

Farayola M, Shafie S and Mohd Siam F. (2020) Mathematical modeling and simulation of radiotherapy cancer treatment with fractional differential equations. *Fluid Mechanics and its Application.* Universiti Teknologi Malaysia. Submitted Manuscript (Edited book)