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New Mathematical Model for Cancer Treatment Optimization by Using Differential Equations (DEs)

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إقرار

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New Mathematical Model for Cancer Treatment Optimization by Using Differential Equations (DEs)

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ABSTRACT

Cancer tumors are very dangers diseases which killed many patients in short time. There are many types of cancer tumors such as skin tumors, brain tumor, etc. Glioblastomas are one famous form of the cancer tumors. They have been considered one of the most malignant primary brain tumors. The highly aggressive growth and invasion are known characterized features of Glioblastomas. Another danger feature of this type of cancers is the ability to kill the patient within approximately one year even after extensive surgery radiotherapy and chemotherapy [1, 2,3]. In this thesis we have studied the advantages of using mathematical models in medical application. In the first part, the well-known mathematical model by Meaney [2] for obtaining the best conditions in cancer treatments has been introduced and studied in details. The model is specified for use in case of brain tumor (Glioblastomas) and radiation treatments (one-step). So, we have extended the range of calculated values of treatment parameters up to 10 values instead of only five values. However, we applied the model on different cases that differ in the value of initial tumor cell density. We found that the model is somewhat linearly applicable for different cases. In second part, we have reported the application of a mathematical model for onestep with multiple fractions in cancer treatment optimization [2, 5]. In addition to the correction and extending for some previously calculated, we studied the important role of the initial tumor cell density on optimization results. We found similar behavior with different values but not equivalent. In the improved model we presented more physically reasonable new cases of (one-step) radiation profiles during the two-fractions, three-fractions, ..., i fractions. By examining cases and expansion on the results by using the partial dif-

ferential equation models which solved by using computational methods (MATLAB, we have obtained a great results of reducing the number of cancer cells. Then we have compared different cases of one-Step i.e. with individual multiple fractions in mathematical models of cancer treatments optimization.

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Dedication

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To my parents whose love for me knew no bounds and, who

taught me the value of hard work.

They always inspire me.

To my beloved Wife, without her endless love and encouragement I would never have

been able to complete my work

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Chapter 1

Introduction

1.1 Cancer Background

Cancer is consider a major global issue. Because it represents the second leading cause of death globally. Recently where it turned out that 7.6 million deaths worldwide were due to cancer. As reported International Agency for Research on Cancer (IARC) reported Similarly, 12.7 million new cases are estimated in the year[5]. According to a survey, 63 of cancer-related deaths were reported only from developing countries [5, 6]. This leads that developing countries are at a higher risk of cancer [6]. Cancer is a very famous and dangerous disease. It attacks the cells and destroys them. Cancer is characterized by unregulated proliferation and invasion caused by underlying genetic mutations. Cancer is usually accompanied with many diseases [2,5]. These effects call the Hallmarks of Cancer [46]. They describe the behaviors typical of cancer cells, which result in or accompany their problematic growth. The discovery was the oldest cancer by Egypt and dating back to 3000 BC. (although the word cancer was not used). This was in a copy of part of an old Egyptian book on shock surgery (called Edwin Smith Papyrus). It describes 8 tumors or breast sorts that have been removed by cauterization with a tool called the fire drill. The writing says about the disease, There is no treatment. While The origin of the word cancer returns to the Greek physician Hippocrates (460-370 BC,The term Abrota refers in Greek on the crab, most likely applied to disease because the expectations of the spread of finger is called crab

shape. Then the Greek doctor translated later into cancer (28-50 BC), the Latin word for crab. Galen (130-200 AD), another Greek physician, used the word oncos (Greek for swelling) to describe tumors. Although crab similarity is similar to the Celsus is still used to describe malicious tumors, but the term galen is now used as part of the name of the cancer scientists [9]. Cancer cells are neglecting some physiologic rules for the cell department and makes them grow in non-regular manner [8,10], cells can described in their way that grow interconnected unlike cancerous alternaria that grow independently. However, that cancerous cells do not respond to external grow factors [8,11]. Additional cells are characterized by the ability to stop in a division in case the cells are existing [8,12]. Moreover, the regular cell division is a programmer in an organized manner where it reaches a stage and dies and replaced new. This is in accordance with a limited efficiency of DNA replication [8,13].

1.2 Tumor

Tumor is a pathological disorder of cell growth, which is characterized by excessive and abnormal cell proliferation. A tumor is an abnormal mass of tissue that may be full of solid or liquid. When the growth of tumor cells is limited to the site of origin and has normal physical properties, they are considered to be benign tumors. When the cells are abnormal and their growth is not controlled, they are judged as cancer cells, that is, malignant tumors. Tumors are also called ”NEOPLASM”, judge by types of tumors, sometimes tumors are not cancerous, these are called benign tumors. They are made up of cells much like healthy tissue. This tumor stays in one area and will not spread to healthy tissues and organs. Cancer tumors are also called malignant tumors. Cancer from these tumors spreads to other parts of the body through the blood and lymphatic system. When cancer spreads, it is called metastasis. Cancer cells pass through the blood or lymphatic system from [14].

1.3 Cancer Tumors Disease

Cancer is a disease in which some of the bodys cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they should not. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Cancerous tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukemias, generally do not. Benign tumors do not spread into, or invade, nearby tissues. When removed, benign tumors usually do not grow back, whereas cancerous tumors sometimes do.

Benign tumors can sometimes be quite large, however. Some can cause serious symptoms or be life threatening, such as benign tumors in the brain. The cancers are classified in two ways, first way, classification of cancers according to type of cells and site of origin:

1. Carcinoma: the most common type of cancer, which originates from the epithelial layer of cells that form the lining of external parts of the body or the internal linings of organs within the body.

2. Sarcoma: These cancers originate in connective and supporting tissues including bones, muscles, cartilage, fats and blood vessels.

3. Leukemia: These cancers affect the bone marrow, which is the site for blood cell production.

4. Lymphoma: These cancers begin in the lymphocytes (B lymphocytes and T lymphocytes).

5. Germ cell tumors: Germ cell tumors are a type of tumor that begins in the cells that give rise to sperm or eggs.

6. Neuroendocrine tumor: Neuroendocrine tumors form from cells that release hormones into the blood in response to a signal from the nervous system.

7. Carcinoid tumor: Carcinoid tumors are a type of neuroendocrine tumor. They are slow-growing tumors that are usually found in the gastrointestinal system (most often in the rectum and small intestine).

Second way, classification of cancers according to region or organ they started, Leukemia, Brain Tumor, Spinal Tumor, Liver Cancer, Lung Cancer, Melanoma, Non-Hodgkin Lymphoma, Pancreatic, Cancer, Prostate Cancer, Thyroid Cancer, Bladder Cancer, Breast Cancer, Colon and Rectal Cancer, Endometrial Cancer and Kidney Cancer.

Brain Tumors: A brain tumor, known as an intracranial tumor, is an abnormal mass of tissue in which cells grow and multiply uncontrollably, seemingly unchecked by the mechanisms that control normal cells. More than 150 different brain tumors have been documented, but the two main groups of brain tumors are termed primary and metastatic.

Primary brain tumors include tumors that originate from the tissues of the brain or the brain's immediate surroundings. Primary tumors are categorized as glial (composed of glial cells) or non-glial (developed on or in the structures of the brain, including nerves, blood vessels and glands) and benign or malignant.

Metastatic brain tumors include tumors that arise elsewhere in the body (such as the breast or lungs) and migrate to the brain, usually through the bloodstream. Metastatic tumors are considered cancer and are malignant.

1.4 Cancer Treatment Methods

1.4.1 Surgery Therapy

Is a tool to prevent or reduce the spread of disease and remove cancer from the body. It is one of the most important traditional treatments as it assures least damage to the surrounding tissues as compared to chemotherapy and radiotherapy after anesthesia was invented in 1846, surgeons bilroth, handley and halsted led cancer operations by removing entire tumor together with lymph nodes. Later Paget a surgeon reported that cancer cells were spread from primary tumor to other places through the blood stream (metastasis). Understanding the mechanism(s) of cancer spreading became a key element in recognizing the limitations of cancer surgery. Using miniature video cameras and endoscopy, surgeons can remove colon, esophagus and bladder tumors through tubes. Recently, less invasive ways of destroying tumors without removing them are being studied including liquid nitrogen spray to freeze and kill cancer cells (cryosurgery). Lasers also can beused to cut the tumor tissue of cervix, larynx, liver, rectum, skin and other organs [15, 16].

1.4.2 Radiation Therapy

The discovery of x-rays by German Physicist Wilhelm Conrad Rontgen in 1895, also marked their clinical importance in the treatment of cancer and after 3 years later radiation was used for cancer diagnosis and in treatment. In this therapy high doses of radiation are used to treat cancer by shrinking tumors and to kill cancer cells. The adverse effect of radiation therapy is that it also hits normal cells lying in the peripheries of the main tumorous mass [8,17, 18].

1.4.3 Chemotherapy

Chemotherapy is the use chemicals to treat cancer by killing cancer cells and also by shrink tumors but have severe side effects. Because that chemotherapeutic drugs

also target normal cells, which could result in a variety of side effects depending on the dosage such as hair loss, nausea, fatigue, vomiting, etc. As a result of vigorous chemotherapy treatment, patients become immunocompetence. This can result in complicated infections and consequently death [8,19].

1.4.4 Immunotherapy and Hormone therapy

Immunotherapy is the treatment of diseases on how to address the immune system by medicine or by other treatments [**??**]. While hormone therapy is the treatment of cancer by using powers similar to hormones such as lymphoma, leukemias [8,20].

1.5 Radiation Therapy Advantage and Disadvantage

Radiation therapy : is one the medical ways which used for cancer treatment. This method is using a dose of ionizing radiation to control tumor (malignant cells) with the optimal treatment of cancer cells and non- damage the surrounding plummeting. The general use of radiation in treatment of tumors has been marked after the discovery of X-rays by German physicist Wilhelm Conrod Rontgen in 1895. The application of X-rays in diagnostic and treatments highlights their clinical importance in the treatment of cancer. Just 3 years later, the radiation has a rang wide of medical applications specially in cancer therapy. However, a therapy high doses of radiation are used to treat cancer tumors by shrinking tumors and to kill cancer cells. Sadly, the radiation method has some important side effects. During the application of radiation doses on tumor area, the radiation hits normal cells that lying in the peripheries of the main tumorous mass. The biological mechanism for radiation therapy is: radiation damaging the DNA of human cells and destroys their ability to reproduce. Both normal and cancer cells can be affected by radiation, but cancer cells have generally impaired ability to repair this damage, leading to cell death all tissues have a tolerance level, or maximum dose, beyond which irreparable damage may occur [8, 21].

1.5.1 Advantage

The main advantage point of radiation therapy is called ”Targeted accuracy” where the radiation covering the whole tumor area. This allow the radiation to direct effect with cancer cells [35, 36, 37]. This resulting in access deep places and treatment without surgery.

1.5.2 Disadvantage

We can summarized the main disadvantage points of radiation therapy as following:

1. Side effects: the first problem has been observed in radiation therapy is the side effect where the radiation not only destroyed cancer cells but also it destroyed the normal cell that received some amount of applied doses. General that normal cells are located beside/behind the cancer cells.

2. Radiation Dermatitis: this is well known as a common adverse effect of radiation therapy. The radiation dermatitis is making the treatment of different type of tumors such as breast, prostate, perineal, head and neck malignancies very complicated. It late adverse effects include pigmentation changes, telangiectasias, etc. [21, 22, 23].

3. Salivary gland inflammation, dry mouth, nausea.

4. Nausea, diarrhea, bone marrow suppression.

5. Dry mouth, difficulty swallowing, jaw stiffness, cataracts, cognitive impairment, hair loss [21, 23-26].

6. Symptoms of radiation pneumonia, including low-grade fever, congestion, dry cough, pleuritic chest pain and chest tightness [21, 24- 27].

7. Radiation esophagitis is a common, dose-limiting, early adverse reaction of thoracic tumor radiotherapy. Higher radiation dose and concurrent chemotherapy have a higher incidence [21,28-29].

8. Radiation proctitis is seen in the radiotherapy of anal cancer, rectal cancer, cervical cancer, uterine cancer, bladder cancer, testicular cancer, especially prostate cancer. Increasing radiation dose and concurrent chemotherapy are risk factors, as are the inflammatory bowel disease in patients who receive external radiation from the pelvis oral sulfasalazine (Azulfidine) can effectively prevent [21, 30].

9. Radiation cystitis Acute radiation cystitis, including more severe hemorrhagic cystitis, is a rare adverse reaction of radiation [21, 31].

10. Sexual dysfunction, including impotence, is common after radiotherapy for prostate cancer and, to a lesser extent, colorectal malignancies. Erectile dysfunction is more common in brachytherapy than external beam radiation [21, 32].

1.6 Mathematical Modeling in Cancer

1.6.1 Mathematical Models Basis

Mathematical models are a special form of mathematical equations (differential and partial equations) which is built to simulate the complex systems such as a dynamics, statistics, biological systems. It dos that by testing hypotheses and confirming experiments. However, the mathematical model is designed to analyzed, expected results and understand basics of the mechanical systems [2].

1.6.2 Application of Mathematical Models in Radiation Therapy Optimization

Mathematical modeling is a powerful tool to test hypotheses, confirm experiments, and simulate the dynamics of complex systems,mathematical models enjoyed for their presence in all biological sciences, and the dominant attribute of mathematical models is in the great impact on clinical practice, as they are widely integrated into medical imaging technologies (see [33]). The advantage of mathematical models in providing insight into disease growth, treatment response, and ultimately building the framework

for precision medicine [34]. Because the cancer is complex disease one practical way for treatment this type of cancers is the radiation therapy. This is due to the precision of radiation therapy. Its covering fully the tumor region which allow to direct effect of radiation on cancer cells [4, 35, 36]. But after the use of radiation therapy shows effects and problems leading collapse of the patients health. Due to the inaccuracy used for the appropriate dose in terms of half of the diameter, severity, oscilloscope and tumor size. It is therefore the importance of modeling in solving these problems during radiation therapy in order to determine the appropriate dose.

1.7 Objectives of the Study

1. To build a new and effective mathematical model for optimization the best conditions of cancer treatments of radiation therapy.

2. To compar our model with previous models and prove the superiority our model.

1.8 Important of Study:

Cancer tumors are very dangers diseases that killed many patients in short time. The reasons of creation of cancer tumors are many and uncontrollable mostly. The number of cancer victims are increasing annually. One of the famous therapy method that used in cancer treatments is called radiation therapy. The most advantage of this method is the accuracy in covering whole cancer cells by radiations dose. However, the radiation treatment has many disadvantage points such as side effect and non-accurate intensity value that required for the specific tumor and specific patient. The mathematical models are introducing the solutions to overcome the disadvantage points of radiation therapy. It control and produce the exact optimize values of intensity, radius and all other variables in radiation therapy.

1.9 Outline of the Thesis

This thesis is divided into five chapters. These chapters contain on three original research works on mathematical oncology published or in submission to scientific journals. In first chapter we have given background information about cancer in general. In terms of cancer definition, tumor cancer, cancer tumors desises and cancer treatment methods. We also introduced the role of radiotherapy for cancer where we showed the most important advantage of radiation therapy as well as radiotherapy disadvantages on treatment the cancer. We also reviewed the role and importance of mathematical modeling in solving problems resulting from the use of radiotherapy. Also we presented objectives of the study and important of study.

Chapter 2: In this chapter, we have introduced a literature review of some important previous studies which focused on mathematical models developments in the field of brain tumors treatments. In addition, we have presented basic equations of well known mathematical model that used in cancer tumor optimization.

Chapter 3: In this chapter we presented the well-known mathematical model [2] for obtaining the best conditions in cancer treatments. The model has been introduced and studied in details. The model is specified for use in case of brain tumor (Glioblastomas) and radiation treatments (one-step), reviewed some important mathematical models on brain tumor (Glioblastomas). modeling and cancer dynamics, and outlined some of the important methods which we employ in this thesis.

Chapter 4: We have extended the range of calculated values of treatment parameters up to 10 values instead of only five values. However, we applied the model on different cases that differ in the value of initial tumor cell density. We found that the model is somewhat linearly applicable for different cases. In second part, we have reported the application of a mathematical model for one-step with multiple fractions in cancer treatment optimization [1, 2]. In addition to the correction and extending for some previously calculated, we studied the important role of the initial tumor cell density on optimization results. We found similar behavior with different values but not equivalent. In the improved model we presented more physically reasonable new

cases of (one-step) radiation profiles during the two-fractions, three-fractions, ... , i fractions. By examining cases and expansion on the results by using the partial differential equation models which solved by using computational methods (MATLAB, we have obtained a great results of reducing the number of cancer cells. Then we have compared different cases of one-Step i.e. with individual multiple fractions in mathematical models of cancer treatments optimization.

Chapter 5: Contains a general conclusion of the findings in this thesis and suggestions for areas of further study.

Chapter 2

Basic Theory and Literature Review

2.1 Literature Review

2.1.1 Introduction

Glioblastomas are one famous form of the cancer tumors. They have been considered one of the most malignant primary brain tumors. The highly aggressive growth and invasion are known characterized features of Glioblastomas . Another danger feature of this type of cancers is the ability to kill the patient within approximately one year even after extensive surgery radiotherapy and chemotherapy [1 - 3]. One practical way for treatment this type of cancers is the radiation therapy. This is due to the precision of radiation therapy. Its covering fully the tumor region which allow to direct effect of radiation on cancer cells [35-37]. Many researchers show that, the mathematical models can be used for a precise modeling, simulation and predication of optimization results in cancer treatment using Beam Radiation Therapy (XRT). It utilizes both analytical and computational mathematical methods as well as data from MRI imaging [1, 2, 37 - 39, 46]. In addition, a mathematical model can be applied for developing an analytical method to describe the response to radiotherapy (RT). Model Ribba et al. [40] developed an ODE model of the response of low-grade glioma to different therapies with a number of undetermined parameters that can be fit to describe the individual patients response with a good qualitative agreement [41-44]. In our previous paper

we have successfully studied the capability of the mathematical model in optimization brain tumor radiation treatment (onestep) [2, 5]. We have corrected some previously calculated values and extended the range of calculations up to 10 value. In addition, we studied the dependency of results on the initial tumor cell density and found that the behavior is similar but not equivalent. Now since the current efforts focus on the using the radiation therapy treatments. Because of the precision with which it targets of the tumor region. Leading to longer survival times. In this thesis we present more physically reasonable new cases of one-step radiation profiles during the 2^{nd} fraction, 3^{rd} fraction,..., i^{th} fraction. By examining cases and expansion on the results by using the partial differential equation models which solved by using computational methods (MATLAB). Finally we have compared different cases of one-Step i.e. with individual multiple fractions in mathematical models of cancer treatments optimization.

2.1.2 Previous Study

Mathematical models play an essential role in the development of knowledge in cancer research, where we can use models to understand the behaviour of a biological phenomenons. Due to its importance in the applications the mathematical models has attracted the attention of many world class researchers. Mathematical modeling of tumours and their environment have been studied by many mathematicians. We mention, here, only those papers that are close to our interest, [47 - 55]. Fisher [37] was the first whose introduce the optimization of dose distribution in radiotherapy, and further developed by Brahme [38]. Benzekry et al [47], offered a serial of applications and experiments for several classical mathematical models for tumor growth. While a general mathematical approach to dose distribution optimization which allows tumours with different degrees of complexity was offered by Stavrev [51]. The development of mathematical models that deal with different stages of cancer growth were tendered in many review articles. For example, The mathematical model for the proliferation and infiltration of glioma was introduced by Traqui et al. [56]) when tried to describe the effects of chemotherapy on the spatio-temporal growth of the tumour. [48], have been developed different radiobiological models to describe experimental

outcomes and understand how physical parameters of irradiation impact the biological response of cells and tissues. A comprehensive historical and critical review of linear-quadratic (LQ) model was discussed [48]. A three dimensional model was offered and studied by Burgess et al. [49]. A brief summary of various approaches in modelling tumour dynamics and radiotherapy can be found in the review by Enderling et al. [50], Harpold et al [41] have presented a biomathematical proliferation-invasion model of glioma growth that predicts linear growth of the radius of the tumor and describes growth rates as velocities of radial expansion. Stavreva et al. [51] applied an extremization of TCP subject to a constraint on the mean dose. A Mathematical Approach to Optimizing the Radiation dose Distribution in Heterogeneous Tumours). Alfonso [53] examined optimization of radiation therapy incorporating normal tissue complication probability (NTCP) in addition to TCP. Also he addressed the issue of whether an optimal radiation distribution can be determined for a Planning Target Volume (PTV) to be irradiated. Hong and Zhang [54] Construct a three component tumor growth mathematical model and discuss its basic application in tumor fractional radiotherapy with computer simulation.

2.2 Basic Theory

Equation for tumor growth is found mostly in [1, 2, 37, 38, 39, 46]

$$\frac{\partial n(\vec{x},t)}{\partial t} = D_n \nabla^2 n(\vec{x},t) + \rho n(\vec{x},t)\left(1 - \frac{an(\vec{x},t)}{n_{max}}\right) \tag{2.1}$$

Here, $n(\vec{x},t)$ is the tumour cell density at position $\vec{x} = (x_1, ..., x_d)$, $\nabla^2 = \sum_{\alpha=1}^{n} \partial^2/(\partial x_\alpha^2)$ is the Laplace operator, D_n is the tumor cell diffusivity, ρ is the tumor cell proliferation rate, and d is the dimensional, so that we focused on the two dimensional i.e. $d = 2$. Exponential growth corresponds to $a = 0$. From the equation (2.1) we find that $n(x, t_0)$ is density profile, now we have to apply XRT to this tumor, we presented the function $f(\vec{x},t)$ which we call the cytotoxic profile. Hence when the action of most therapeutic interventions is to remove a fraction of existing cells, we have added a

term $-\gamma f(\vec{x},t)\ \ n(\vec{x},t)\left(1-\left(\frac{bn(\vec{x},t)}{n_{max}}\right)\right)$ to the right hand side of equation (2.1) to become:

$$\frac{\partial n(\vec{x},t)}{\partial t} = D_n\nabla^2 n(\vec{x},t) + \rho n(\vec{x},t)\left(1-\frac{an(\vec{x},t)}{n_{max}}\right) - \gamma f(\vec{x},t)n(\vec{x},t)\left(1-\frac{bn(\vec{x},t)}{n_{max}}\right). \quad (2.2)$$

Where the parameter γ is a measure of the radiation rate, and we can write as $\gamma = \alpha D(\frac{1}{day})$. Thus, during each fraction, the first two terms on the right hand side of equation (2.2) can be neglected, leading to

$$\frac{\partial n(\vec{x},t)}{\partial t} = -\gamma f(\vec{x},t)n(\vec{x},t)\left(1-\frac{bn(\vec{x},t)}{n_{max}}\right). \quad (2.3)$$

For the exponential case ($b = 0$), the equation (2.3) becomes,

$$\frac{\partial n(\vec{x},t)}{\partial t} = -\gamma f(\vec{x},t)n(\vec{x},t), \quad (2.4)$$

or

$$\frac{\partial n(\vec{x},t)}{n(\vec{x},t)} = -\gamma f(\vec{x},t)\partial t. \quad (2.5)$$

In the logistic case ($b = 1$) Equation (2.3) becomes,

$$\frac{\partial n(\vec{x},t)}{\partial t} = -\gamma f(\vec{x},t)n(\vec{x},t)\left(1-\frac{bn(\vec{x},t)}{n_{max}}\right), \quad (2.6)$$

implies to

$$\frac{\partial n(\vec{x},t)}{n(\vec{x},t)\left(1-\frac{bn(\vec{x},t)}{n_{max}}\right)} = -\gamma f(\vec{x},t)\partial t. \quad (2.7)$$

By integrating Equation (2.5) which (now ordinary) differential equation in the interval $[t_0, t_0+\Delta t]$ we get:

$$\begin{aligned} &\int_{t_0}^{t_0+\Delta t}\frac{\partial n(\vec{x},t)}{n(\vec{x},t)} = \int_{t_0}^{t_0+\Delta t} -\gamma f(\vec{x},t)\partial t \\ &\Longrightarrow [\ln|n(\vec{x},t)|]|_{t_0}^{t_0+\Delta t} = -\gamma f(\vec{x},t)(t_0+\Delta t-t_0) \\ &\Longrightarrow n(\vec{x},t_0+\Delta t) = n(\vec{x},t_0)e^{-\gamma f(\vec{x},t_0)\Delta t}. \end{aligned} \quad (2.8)$$

Now for the logistic growth, i.e. in case ($b = 1$), integrating Equation (2.6) in the interval $[t_0, t_0+\Delta t]$ we get:

$$\int_{t_0}^{t_0+\Delta t}\frac{\partial n(\vec{x},t)}{n(\vec{x},t)[1-\frac{bn(\vec{x},t)}{n_{max}}]} = \int_{t_0}^{t_0+\Delta t} -\gamma f(\vec{x},t)\partial t \quad (2.9)$$

Using partial fraction:

$$\frac{A}{n(\vec{x},t)} + \frac{B}{1-\frac{n(\vec{x},t)}{n_{max}}} = \frac{1}{n(\vec{x},t)(1-\frac{n(\vec{x},t)}{n_{max}})}$$

$$A - A\frac{n(\vec{x},t)}{n_{max}} + Bn(\vec{x},t) = 1$$

So $A = 1$ and $B = \frac{1}{n_{max}}$. Then

$$\begin{aligned} &\int_{t_0}^{t_0+\Delta t} \frac{\partial n(\vec{x},t)}{n(\vec{x},t)} + (-1)\int_{t_0}^{t_0+\Delta t}(-1)\frac{(\frac{\partial n(\vec{x},t)}{n_{max}})}{1-\frac{n(\vec{x},t)}{n_{max}}} = \int_{t_0}^{t_0+\Delta t} -\gamma f(\vec{x},t)\partial t \\ &\Rightarrow \ln n(\vec{x},t)|_{t_0}^{t_0+\Delta t} - \ln(1-\frac{n(\vec{x},t)}{n_{max}})|_{t_0}^{t_0+\Delta t} = -\gamma f(\vec{x},t)|_{t_0}^{t_0+\Delta t} \end{aligned} \tag{2.10}$$

$$\ln\frac{n(\vec{x},t_0+\Delta t)}{n(\vec{x},t_0)} - \ln\frac{(\frac{n_{max}-n(\vec{x},t_0+\Delta t)}{n_{max}})}{\frac{n_{max}-n(\vec{x},t_0)}{n_{max}}} = -\gamma f(\vec{x},t_0)\Delta t$$

$$\ln[\frac{n(\vec{x},t_0+\Delta t)}{n(\vec{x},t_0)} * \frac{n_{max}-n(\vec{x},t_0)}{(n_{max}-n(\vec{x},t_0+\Delta t)}] = -\gamma f(\vec{x},t_0)\Delta t$$

or

$$\frac{n(\vec{x},t_0+\Delta t)}{n(\vec{x},t_0)} * \frac{n_{max}-n(\vec{x},t_0)}{(n_{max}-n(\vec{x},t_0+\Delta t)} = e^{-\gamma f(\vec{x},t_0)\Delta t}$$

or equivalently,

$$\frac{n(\vec{x},t_0+\Delta t)}{n_{max}-n(\vec{x},t_0+\Delta t)} = \frac{n(\vec{x},t_0)e^{-\gamma f(\vec{x},t_0)\Delta t}}{(n_{max}-n(\vec{x},t_0)}$$

From this we get

$$\frac{n_{max}-n(\vec{x},t_0+\Delta t)}{n(\vec{x},t_0+\Delta t)} = \frac{(n_{max}-n(\vec{x},t_0)}{n(\vec{x},t_0)e^{-\gamma f(\vec{x},t_0)\Delta t}}$$

or

$$\frac{n_{max}}{n(\vec{x},t_0+\Delta t)} - 1 = \frac{(n_{max}-n(\vec{x},t_0)}{n(\vec{x},t_0)e^{-\gamma f(\vec{x},t_0)\Delta t}}$$

Therefore, the required solution is

$$n(\vec{x},t_0+\Delta t) = \frac{n_{max}}{1+\frac{n_{max}-n(\vec{x},t_0)}{n(\vec{x},t_0)}e^{\gamma f(\vec{x},t_0)\Delta t}} \tag{2.11}$$

Now from the first and second fractions of XRT, we present a simple upper bounded for $f(\vec{x},t)$ which adhere to patient safety standards, We write this constraint as

$$0 \le f(\vec{x},t) \le C \quad for \ \ some \ \ C. \tag{2.12}$$

Where C is dose limiting parameter. The final constraint on $f(\vec{x},t)$ is limits the total dose received by the patent, This constraint is mathematically represented by

$$\gamma \int d^d\vec{x}dtf(\vec{x},t) \leq F, \tag{2.13}$$

where the integral is over the inter treatment length. The goal now is to determine the function $f(\vec{x},t)$ that minimizes the total number $N(T)$, obtained by integrating the tumor cell density as

$$N(T) = \int d^d\vec{x}n(\vec{x},T). \tag{2.14}$$

where $N(T)$ is the number of cells surviving by the treatment.

2.2.1 Optimal Profile with one Fraction of Exponential Death:

In this section, we will take the case of exponential cytotoxic action. We represent the first constraint in Equation (2.12) with a Lagrange multiplier λ, which requires extremizing, [2]

$$\tilde{N} = \int d^d\vec{x}\ \ n(\vec{x},t_0)e^{-f(\vec{x},t_0)} + \lambda\left(\int d^d\vec{x}\ \ (f(\vec{x},t_0) - F\right), \tag{2.15}$$

where $\Delta t = \gamma = 1$, for convenience, solving the resulting Euler Lagrange Equation for $f(x,t)$, we find the optimal profile by differentiation (2.15) with respect to f as

$$0 = \int d^d\vec{x}\ \ n(\vec{x},t_0)e^{-f(\vec{x},t_0)}(\partial f) + \lambda\int d^d\vec{x}\ \ f(\vec{x},t_0)(\partial f),$$

$$0 = \int d^d\vec{x}\Big(n(\vec{x},t_0)e^{-f(\vec{x},t_0)}(\partial f) + \lambda(\partial f)\Big)$$

$$\implies (-n(\vec{x},t_0)e^{-f(\vec{x},t_0)} + \lambda)(\partial f) = 0$$

$$\implies n(\vec{x},t_0)e^{-f(\vec{x},t_0)} = \lambda$$

$$\implies -f(\vec{x},t_0) = \ln\left(\tfrac{\lambda}{n(\vec{x},t_0)}\right)$$

$$\implies f(\vec{x},t_0) = \ln\left(\tfrac{n(\vec{x},t_0)}{\lambda}\right),$$

$$\implies f(\vec{x}, t_0) = \ln\left(\frac{n(\vec{x}, t_0)}{\lambda}\right), \tag{2.16}$$

With λ chosen such that (2.13) is satisfied. Note that the above result is independent of parameters ρ and D_n and since the cytotoxic profile in Equation (2.16) is not guaranteed to satisfy the constraint of $0 \leq f(x,t) \leq C$. In particular, it leads to non-physical negative values when $n(\vec{x}, t) < \lambda$. For better understanding of this result, we consider the simple case of a Gaussian profile arising from radially of a single cell in exponential growth. Thus the exponential growth for time t_0 leads to the cell density profile:

$$n(r, t_0) = n_0 e^{\frac{-r^2}{2s^2}}, \tag{2.17}$$

where r is the radial distance from the initial cell (tumor center). The width of the Gaussian profile is $s = \sqrt{2D_n t_0}$ while $n_0 = \frac{e^{\rho t_0}}{(2\pi s^2)^{\frac{d}{2}}}$ is the cell density at its center. Equation (2.16) at cutting off the negative profile of the parabola leads to the semi-circular profile

$$f(\vec{x}, t_0) = f_1(r) = \ln(\frac{n_0}{\lambda}) - \frac{r^2}{2s^2} = \begin{cases} f_m(1 - \frac{r^2}{r_m^2}) & if \quad r \leq r_m \\ 0 & if \quad r \geq r_m \end{cases} \tag{2.18}$$

where $f_m = \ln \frac{n_0}{\lambda}$ and $r_m = s\sqrt{2f_m}$. The total radiation dose in this fraction is given by

$$F = \int d^d x f_1(r) = \frac{2k_d}{d(d+2)} f_m r_m^d \tag{2.19}$$

Where K_d is the d-dimensional solid angle with $K_2 = 2\pi$ and $K_3 = 4\pi$. Now since $F = (2k_d)/(d(d+2))f_m r_m^d$, using $f_m = (r_m^2)/(2s^2)$ from equation (2.19) we get

$$F = \frac{2k_d}{d(d+2)} r_m^d (\frac{r_m^2}{2s^2}) \tag{2.20}$$

Solving the last equation for r_m, we get

$$r_m = \left(\frac{d(d+2)}{k_d}\right)^{\frac{1}{d+2}} F^{\frac{1}{d+2}} s^{\frac{2}{d+2}}, \tag{2.21}$$

where r_m is optimal radius of the semicircular, while its maximal intensity can be rewritten as

$$f_m = \frac{1}{2}\left(\frac{d(d+2)}{k_d}\right)^{\frac{2}{d+2}} F^{\frac{2}{d+2}} s^{\frac{-2(d+1)}{d+2}}, \tag{2.22}$$

since $r_m^2 = \left(\frac{d(d+2)}{k_d}\right)^{\frac{2}{d+2}} F^{\frac{2}{d+2}} s^{\frac{4}{d+2}}$, and $f_m = \frac{r_m^2}{2s^2}$

Chapter 3

Models and Methodology

3.1 Review of Published Work [2]

In 2019, Meaney studied the spatial optimization for radiation therapy of brain tumours through the one-step and two-step radiation profiles as following:

3.1.1 One- Step, One-Fraction

The simplest step−function case of XRT (External-Beam Radiation Therapy) involves a uniform beam of radius r_1 and strength f_1 applied for a duration Δt at time t_0, i.e.

$$f(r,t) = \begin{cases} f_1 & , \quad 0 \le r \le r_1 \\ 0 & , \quad otherwise. \end{cases} \tag{3.1}$$

(see Figure 3.1, (a)). The goal is minimize $N(t_0 + \Delta t) = 2\pi \int rn(r, t_0 + \Delta t)dr$ subject to a constrain $F' = \frac{F}{\pi\gamma\Delta t} = r_1^2 f_1$. Approximating the partial differential equation (PDE) as an ordinary differential equations (ODE) as before, the tumor cell density distribution immediately after the fraction as

$$n(r, t_0 + \Delta t) = \begin{cases} n(r,t_0)e^{-f_1\gamma\Delta t} & 0 \le r \le r_1, \\ n(r,t_0) \quad , & r_1 < r < R. \end{cases} \tag{3.2}$$

3.1.2 Two-Step, One-Fraction

Two-step with one-fraction where f_2 give different dose to the outer region of the tumor, where the radiation function given by.

$$f(r, t_0 \le t \le t_0 + \Delta t) = \begin{cases} f_1 \quad , & 0 \le r \le r_1; \\ f_2 \quad , & r_1 < r < r_2; \\ 0 \quad , & r_2 < r < R. \end{cases} \tag{3.3}$$

Figure 3.1 (*b*), illustrates the model. The goal is minimize

$$N(t_0 + \Delta t) = 2\pi \int [rn(r, t_0 + \Delta t)]dr,$$

subject to a constrain $F' = \frac{F}{\pi\gamma\Delta t} = r_1^2 f_1$. The tumour cell density distribution immediately after the fraction is obtained as

$$n(r, t_0 + \Delta t) = \begin{cases} n(r, t_0)e^{-f_1\gamma\Delta t} \quad , & 0 \le r \le r_1; \\ n(r, t_0)e^{-f_2\gamma\Delta t} \quad , & r_1 \le r \le r_2; \\ n(r, t_0) & r_2 < r < R. \end{cases} \tag{3.4}$$

3.1.3 Two-Step, Two-Fraction

For case two-step with two separate fractions, also different dose are given for each (see Figure 3.1 (c)).

$$f(r_1, t_0^*) = \begin{cases} f_{11} \quad , \quad 0 \le r \le r_{11}, \\ f_{21} \quad , \quad r_{11} < r < r_{21}, \\ 0 \quad , \quad otherwise, \end{cases} \quad and \quad f(r, t_1^*) = \begin{cases} f_{12} \quad , \quad 0 \le r \le r_{12}, \\ f_{22} \quad , \quad r_{12} < r < r_{22}, \\ 0 \quad , \quad otherwise, \end{cases} \tag{3.5}$$

where $t_0^* \in [t_0, t_0 + \Delta t]$ and $t_1^* \in [t_0 + \Delta t + \tau, t_0 + 2\Delta t + \tau]$, and τ indicate the interval between the two fractions. we further assume that the time interval τ between the fractions is small enough to neglect spatial migrations described by the diffusion term. If so, the density profile simply grows exponentially, by a factor $e^{\rho\tau}$ without changing its spatial form, and immediately before the second fraction is given by

$$n(r, t_0 + \Delta t + \tau) = \begin{cases} n(r, t_0)e^{-f_{11}\gamma\Delta t} & 0 \le r \le r_{11} \\ n(r, t_0)e^{-f_{21}\gamma\Delta t} & r_{11} \le r \le r_{21} \\ n(r, t_0) & r_{21} < r < R \end{cases} \tag{3.6}$$

The density profile immediately after application of the second fraction is then given by:

$$n(r, t_0 + 2\Delta t + \tau) = \begin{cases} n(r, t_0 + \Delta t + \tau)e^{-f_{12}\gamma\Delta t} & 0 \le r \le r_{12} \\ n(r, t_0 + \Delta t + \tau)e^{-f_{22}\gamma\Delta t} & r_{12} \le r \le r_{22} \\ n(r, t_0 + \Delta t + \tau) & r_{22} < r < R \end{cases} \tag{3.7}$$

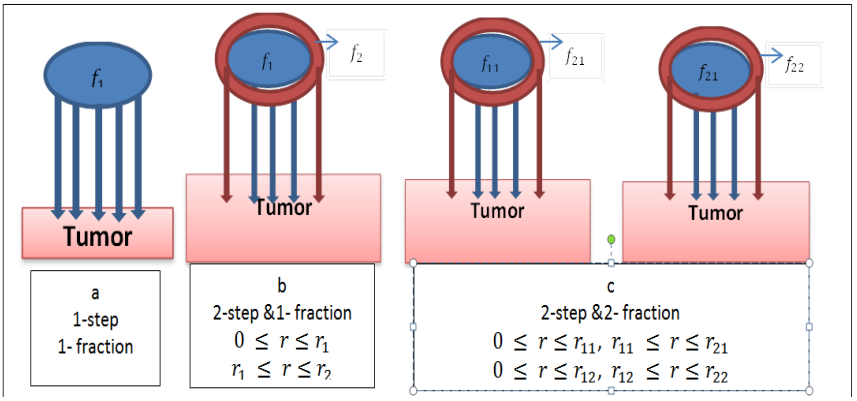

Figure 3.1: Model 1

we can observe the effect of previous model on first stage and second stage of the cancers as flowing:

1. The previous first model one-step, one-fraction expose the tumor to radiation profile which is suitable for1^{st} stage.

2. The second model two-step, one-fraction extended the area of exposed tumor with additional hole radiation profile in the outer side beyond first radiation profile limit which is suitable for 2^{nd} stage. i.e. as in the first model, the same area received same amount of radiation without any further modification.

3. In the third model the similar technique that used in second model has been repeated with different profiles only.

4. The cell density distribution mostly is not regular over surface, but it follows in somewhat the Gaussian distribution.

5. The radiation profile has also Gaussian distribution which make the first model is suitable of tumor treatment in 1^{st} stage where the maximum power in the beam center that applied on the maximum cell density which is in the tumor center. However, these advantage no more applicable in the second and third models.

6. In second model the area close to r_1 is receiving low intensity of radiation, never the less it may from a part from proliferation area.

3.2 The Improved Models

In our model we have work on the fact that, the amount of applied radiation in treatment should be used in higher intensity over the central of tumor cells more than outer tumor cells even in more distribution of radial profile. We have started with introduced the one-step, two fractions model. In this model the two radiation profile used in one step simultaneously. First fraction radial started from 0 to r_1 while second fraction started from 0 to r_2 where r_2 larger than r_1. Therefore, the second fraction is again covering first area that covered by first fraction and increased the exposer area beyond r_1. The resulting the first area 0 to r_1 which represent the central area of tumor will be under exposure to the radiation more than that of outer limit of tumor, this will reduce the tumor cells rabidly. We have extended our model to one-step with individual two fractions, 3- fractions, ... , n-fractions (see Figure 3.4). Accordingly,tumor cancers have two distingue stages

3.2.1 First Stage (Primary Tumors)

In this stage, the tumor cells are existing in specific node or small area. They did not diffuse out. The maximum cells density are in the center area of the tumor as shown in Figure (3.2), [6, 58].

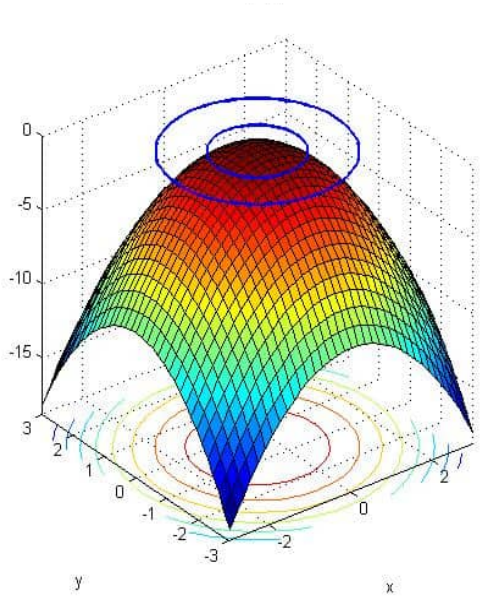

Figure 3.2: Simulation of primary tumor cells density

3.2.2 Second Stage (Metastatic Tumors)

In this stage, three main regions are dividing the whole tumor volume which called proliferative, hypoxic and necrotic zones. The adequate nutrients are available for all cells in the proliferative zone. Therefore, the maximum rate of cells growth is in proliferative zone. The nutrients and oxygen are supplying the cells growth even in the tumor center, but, due to the increment in the cells size in the center which leads to shortage the delivery of nutrients, the cells are stop growth then finally die and consisting the necrotic core as shown in Figure (3.3), [6, 58]. In other words, in second stage the most central cancer cells are death while the proliferation area is the outer ring of cancer volume. Therefor we focused in our model on the applying the radiation in more intensity on the proliferation area. However, we can not define exactly the bound limit of this area but we surly know that it is in outer ring.

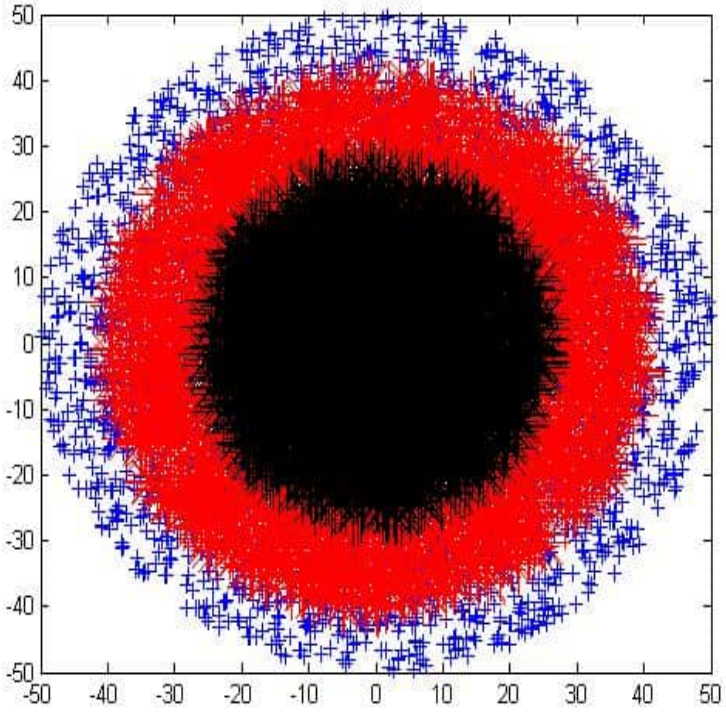

Figure 3.3: Necrotic zones(black), hypoxic(red), proliferative(blue)

In this model we have studied the application of $2, 3, ..., n-$fractions of radiation with one-step. As shown previously, to describe the one fraction we need to introduce two variables r_1, f_1, but in describing two fractions we need four variables r_1, f_1, r_2, f_2. Therefore, we can write $f(r,t)$ during separate fractions as

$$f(r,t) = \begin{cases} f_1 & , \quad 0 \le r \le r_1 \\ 0 & , \quad otherwise \end{cases} \quad and \quad f(r,t) = \begin{cases} f_2 & , \quad 0 \le r \le r_2 \\ 0 & , \quad otherwise. \end{cases} \tag{3.8}$$

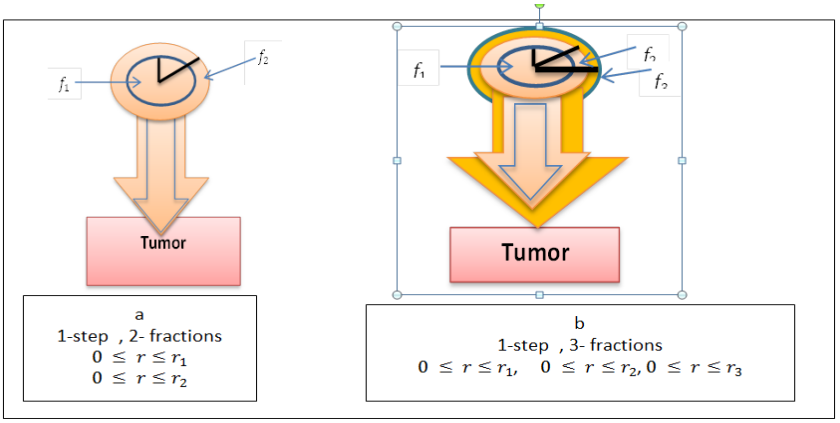

Figure 3.4: Model 2

Chapter 4

Results and Discussions

4.1 Correction and Extension to a Pre-Existing Model

In first part of this chapter, we will start by correcting some prior calculations, then extend the pre-existing model, and then look at how the initial tumor cell density affects the optimization outcomes. We have extended the range of calculated values of treatment parameters up to 10 values instead of only five values. However, we applied the model on different cases that differ in the value of initial tumor cell density. We found that the model is somewhat linearly applicable for different cases. In second part, we have build a new mathematical model in cancer treatment optimization.

4.1.1 One-Step Radial and Profile Relations:

The calculated values of final tumor cell density were calculated in all three cases of initial tumor cell density. It is presented in table 4.1. The terms ($Nt, Nt1$ and $Nt2$) are assigned to the calculated remaining final tumor cell density that count initial tumor cells density $1 \times 10^7, 5 \times 10^6$ and 2×10^7, respectively [2]. In other words, we have chosen the half and double values of Nt. Also, we have calculated the number of tumor cells at t_0 for the three cases. We assigned them as ($n_0, n_0 1$ and $n_0 2$) respectively. It's very clear that the radiation optimization values of radiation radius r_1 and profile f_1 do not depend on Nt. However, we have corrected the first two values of r_1, f_1 and n_0

published in reference [2]. In addition, we extend the calculated values of them up to ten values.

Table 4.1: Optimization values in one-step fraction

s	r_1	f_1	$n_0 * e6$	$Nt * e6$	$n_01 * e5$	$Nt1 * e6$	$n_02 * e6$	$Nt2 * e7$
1	2.14	5.45	1.5915	1.9204	7.9577	0.9602	3.1831	0.3841
2	3.02	2.72	0.3979	5.3490	1.9894	2.6745	0.7958	1.0698
3	3.707	1.81	0.1768	7.1475	0.8842	3.5737	0.3537	1.4295
4	4.281	1.36	0.0995	8.0984	0.4974	4.0492	0.1989	1.6197
5	4.786	1.091	0.0637	8.6486	0.3183	4.3243	0.1273	1.7297
6	5.24	0.909	0.0442	8.9924	0.2210	4.4962	0.0884	1.7985
7	5.66	0.779	0.0325	9.2207	0.1624	4.6104	0.0650	1.8441
8	6.054	0.68	0.0249	9.3798	0.1243	4.6899	0.0497	1.8760
9	6.422	0.606	0.0196	9.4948	0.0982	4.7474	0.0393	1.8990
10	6.7	0.545	0.0159	9.5807	0.0796	4.7903	0.0318	1.9161

The relation between tumor size (s) with radiation radius (r_1) and radiation profile (f_1) are presented in Figure 4.1.

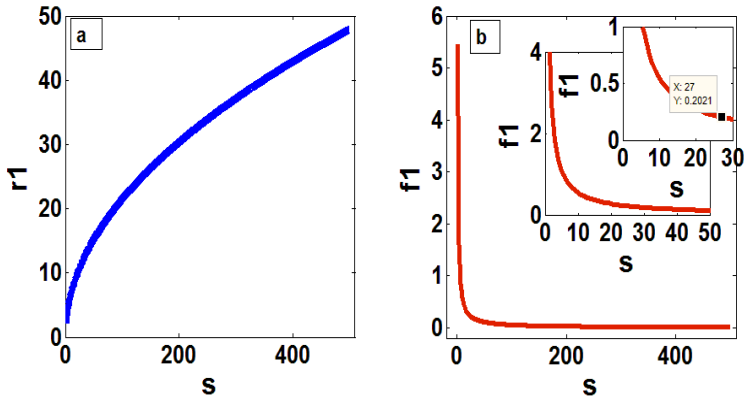

Figure 4.1: a) Relation between r_1 and s, b) Relation between f_1 and s

Figure 4.1(a) shows the exponential growth between radiation beam radius and tumor size. While the relation between f_1 and s is presented in Figure 4.1 (b). It shows

that the relation between them is inversely. It means that when the function of energy distribution of radiation beam is increasing, the tumor size will reduce and vice versa. The inside small figures show the limitation or threshold of radiation beam profile that lose its effect with the increase of tumor size. Its noted that the value of tumor size is more than 22 which breaks the threshold of radiation profile.

4.1.2 Relation between Final Tumor Cell Density with Optimal Radiation Radius and Profile:

We have studied the variation of the final three values of $Nt, Nt1$ and $Nt2$ with radiation beam radius and profile. It is presented in Figure 4.2. From Figure 4.2 (a) one can observe that the increase in relation for $Nt2$ is not equivalent to the decrease in relation for $Nt1$. However, we can state that, although the presented mathematical model shows similar behavior with half and double value of initial tumor density but not equivalent

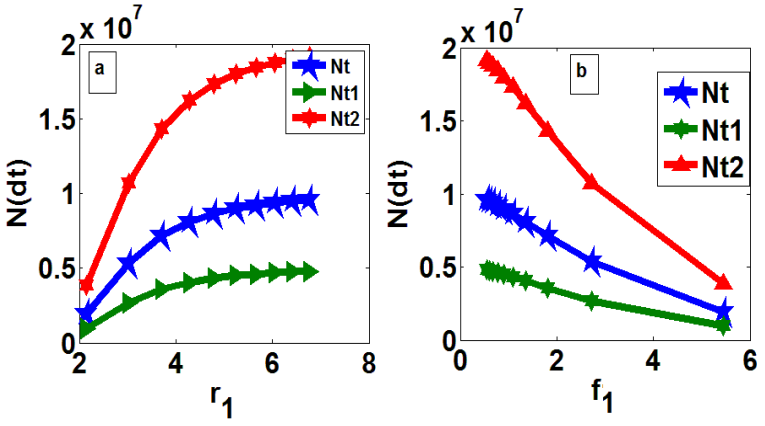

Figure 4.2: a) Relation between r_1 and $N(dt)$, b) Relation between f_1 and $N(dt)$.

4.1.3 Relation between Final Tumor Cell Density with Tumor Size and Initial Number of Tumor Cells

Figure 4.3 shows the plotted relation between tumor size and cell tumor $n_0, n_0 1$ and $n_0 2$ with $Nt, Nt1$ and $Nt2$ at t_0 The similar results observed in the previous section

is supported here. The behavior of model for $Nt, Nt1$ and $Nt2$ is similar either with tumor size s or cell tumor ($n_0, n_0 1$ and $n_0 2$) at t_0 but not equivalent.

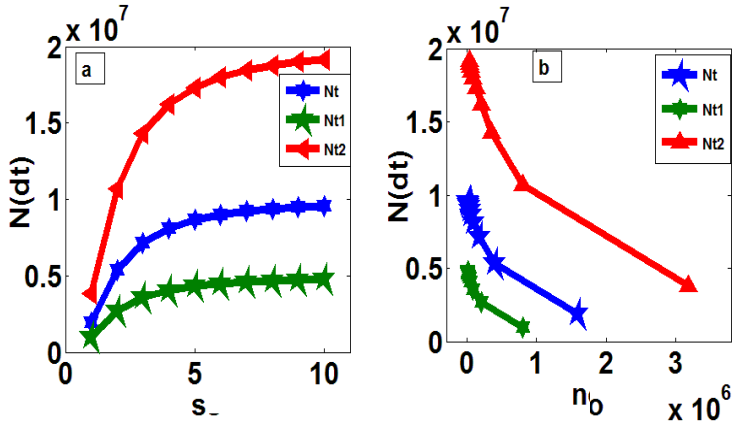

Figure 4.3: a) Relation between s and $N(dt)$ b) Relation between n_0 and $N(dt)$.

4.2 The Improved Models

We start with one-step with one- fraction that assumed by [2], the simplest step−function case of XRT in values a uniform beam of radius r_1 and strength f_1 applied for a duration Δt at time t_0, i.e.

$$f(x,t) = \begin{cases} f_1 & 0 \le r \le r_1 \\ 0 & otherwise. \end{cases} \tag{4.1}$$

The goal is to minimize $N(t_0 + \Delta t) = 2\pi \int r \ n(r, t_0 + \Delta t)dr)$, subject to a constrain $F' = \frac{F}{\pi \Delta t \gamma} = r_1^2 f_1$. Approximating the partial differential equation (PDE) as an ordinary differential (ODE) as before, the tumor cell density distribution immediately after the function is obtained as

$$n(r, t_0 + \Delta t) = \begin{cases} n(r,t_0)e^{-f_1 \gamma \Delta t} & 0 \le r \le r_1 \\ n(r,t_0) & r_1 < r < R \end{cases} \tag{4.2}$$

Integrating this result gives total number of cells as:

$$\begin{aligned} n(r, t_0 + \Delta t) &= \int\int n(r, t_0 + \Delta t)dA \\ &= 2\pi[e^{-f_1 \gamma \Delta t} n_0 \int_0^{r_1} re^{-r^2/2s^2 dr} + n_0 \int_{r_1}^{R} re^{-r^2/2s^2} dr] \\ &= 2\pi n_0 s^2 [e^{-f_1 \gamma \Delta t}(1 - e^{-r^2/2s^2}) + e^{-r^2/2s^2} - e^{-R^2/2s^2}] \end{aligned} \tag{4.3}$$

The constraint on the total beam flux can be imposed through a Lagrange multiplier λ create an augmented N,

$$N = 2\pi n_0 s^2[e^{-f_1\gamma\Delta t}(1 - e^{-r_1^2/2s^2}) + e^{-r_1^2/2s^2} - e^{-R^2/2s^2}] - \lambda(f_1 r_1^2 - F) \tag{4.4}$$

Extremizing with respect to r_1, f_1 and λ, and after eliminating f_1 and λ, we arrive at the following expression for r_1:

$$0 = (e^{\frac{F'\gamma\Delta t}{r_1^2}} + (\frac{r_1^4}{2F'\gamma\Delta t s^2} - 1)e^{\frac{-r_1^2}{2s^2} - \frac{F'\gamma\Delta t}{r_1^2}} - (\frac{r_1^4}{2F'\gamma\Delta s^2})e^{\frac{-r_1^2}{2s^2}} \tag{4.5}$$

Values of r_1 that satisfy Eq. (4.5) can be used to find a corresponding f_1, together specifying the optimal $N(r_1; f_1)$. Table 4.2 shows an overview of the parameter values utilized in computations, are the same as those utilized by [2].

Table 4.2: parameters used in the various calculations

Parameter	*Symbol*	*unit*
Initial Total Cell Number	N	10^7 , 5×10^6, 2×10^7 (cells)
Radiation effect Parameter	γ	60 (1/day)
The duration of radiation	Δt	0.007 (days)
	F'	25 (mm^2)

4.2.1 One-Step with Individual $2-$fractions

We have studied the application of two-fractions of radiation with one-step. As shown previously, to describe the one fraction we need to introduce two variables r_1, f_1, but in describing two fractions we need four variables r_1, f_1, r_2, f_2. Therefore, we can write $f(r, t)$ during separate fractions as

$$f(r, t_0^*) = \begin{cases} f_1 & , \quad 0 \le r \le r_1 \\ 0 & , \quad otherwise, \end{cases} \tag{4.6}$$

and

$$f(r, t_1^*) = \begin{cases} f_2 & , \quad 0 \le r \le r_2 \\ 0 & , \quad otherwise. \end{cases} \tag{4.7}$$

To minimize $N(t_0 + \Delta t) = 2\pi \int rn(r, t_0 + \Delta t)dr$, where the fractions constrained individually, such that $F' = F/\pi\Delta t\gamma = r_1^2 f_1$ and $F' = F/\pi\Delta t\gamma = r_2^2 f_2$. $f(r, t_0)$ is the same as one-step with one-fraction which has been studied previously [2], then the values related to $f(r, t_0)$ does not change. We consider τ the time between the fractions where the τ is small enough to neglect spatial migrations described by the diffusion term. Thus, the density profile simply grows exponentially, by a factor $e^{\rho\tau}$,

$$n_1(r, t_0 + \Delta t) = \begin{cases} n(r, t_0)e^{\rho\tau}e^{-f_1\gamma\Delta t} & , \quad 0 \le r \le r_1 \\ n(r, t_0)e^{\rho\tau} & , \quad r_1 < r < R, \end{cases} \tag{4.8}$$

where $n(r, t_0) = n_0 e^{-\frac{r^2}{2s^2}}$. Thus

$$n_1(r, t_0 + \Delta t) = \begin{cases} n_0 e^{-r^2/2s^2} e^{\rho\tau} e^{-f_1\gamma\Delta t} & , \quad 0 \le r \le r_1 \\ n_0 e^{-r^2/2s^2} e^{\rho\tau} & , \quad r_1 < r < R. \end{cases} \tag{4.9}$$

But after application of the second fraction its given by:

$$n_2(r, t_0 + 2\Delta t + \tau) = \begin{cases} n_1(r, t_0 + \Delta t)e^{-f_2\gamma\Delta t} & , \quad 0 \le r \le r_2 \\ n_1(r, t_0 + \Delta t) & , \quad r_2 < r < R \end{cases} \tag{4.10}$$

The factor of $e^{-f_1\gamma\Delta t}$ is specifying the effect of one-step with $1 - fraction$ that is before second fraction immediately. It is only have effect on the range $0 \le r \le r_1$. So during the second fraction we should multiply its effect, $e^{-f_2\gamma\Delta t}$ by the effect of first fraction as following:

$$n_2 = \begin{cases} n_1 e^{-f_2\gamma\Delta t} & , \quad 0 \le r \le r_2 \\ n_1 & , \quad r_2 < r < R, \end{cases} \tag{4.11}$$

which leads to

$$n_2 = \begin{cases} n_0 e^{-r^2/2s^2} e^{\rho\tau} e^{-\gamma[f_1+f_2]\Delta t} & , \quad 0 \le r \le r_2 \\ n_0 e^{-r^2/2s^2} e^{\rho\tau} & , \quad r_2 < r < R. \end{cases} \tag{4.12}$$

Integrating this result gives total number of cells as:

$$\begin{aligned} N(r, t_0 + \Delta t) &= \int\int e^{\rho\tau} n(r, t_0 + \Delta t)dA \\ &= 2\pi e^{\rho\tau}\left[e^{-\gamma[f_1+f_2]\Delta t} n_0 \int_0^{r_2} re^{-r^2/2s^2}dr + n_0 \int_{r_2}^{R} re^{-r^2/2s^2}dr\right] \\ &= 2\pi e^{\rho\tau} n_0 s^2 \left[e^{-\gamma[f_1+f_2]\Delta t}(1 - e^{-r_2^2/2s^2}) + e^{-r_2^2/2s^2} - e^{-R^2/2s^2}\right], \end{aligned} \tag{4.13}$$

where τ is very small, it can be neglected ($e^{\rho\tau} = 1$) then

$$N(t_0 + \Delta t) = 2\pi n_0 s^2 \left(e^{-\gamma[f_1+f_2]\Delta t}(1 - e^{-r_2^2/2s^2}) + e^{-r_2^2/2s^2} - e^{-R^2/2s^2}\right) \tag{4.14}$$

The constraint on the total beam flux can be imposed through a Lagrange multiplier λ create an augmented N,

$$\begin{aligned} N(t_0 + \Delta t) = 2\pi n_0 s^2 \left(e^{-\gamma[f_1+f_2]\Delta t}(1 - e^{-r_2^2/2s^2}) + e^{-r_2^2/2s^2} - e^{-R^2/2s^2}\right) \\ -\lambda(f_2 r_2^2 - F') \end{aligned} \tag{4.15}$$

Extremizing with respect to r_2, f_2 and λ, we get

$$\begin{aligned} 0 &= 2\pi n_0 r_2 e^{-r_2^2/2s^2}(e^{-\gamma[f_1+f_2]\Delta t} - 1) - 2\lambda f_2 r_2 \\ 0 &= 2\pi n_0 s^2 \gamma \Delta t e^{-\gamma[f_1+f_2]\Delta t}(e^{-r_2^2/2s^2} - 1) - \lambda r_2^2 \\ 0 &= f_2 r_2^2 - F' \end{aligned}$$

By eliminating f_2 and λ, from the above equations we arrive at the following expression for r_2 :

$$0 = e^{-\frac{\gamma[r_2^2 f_1 + F']\Delta t}{r_2^2}} \left[1 + \left(\frac{r_2^4}{2F'\gamma\Delta t s^2} - 1\right) e^{\frac{-r_2^2}{2s^2}}\right] - \left(\frac{r_2^4}{2F'\gamma\Delta t s^2}\right) e^{\frac{-r_2^2}{2s^2}} \tag{4.16}$$

We can easily note that at t_0 , i.e. $\Delta t = 0$, Equation 4.14 becomes

$$N = 2\pi n_0 s^2 \tag{4.17}$$

which shows the relation between initial number of tumor cells N_0 and cell density n_0 at center

4.2.2 One-Step with Individual 3-Fractions

We consider that one-step case of (XTR) with the three fractions individually consist a beam of radius r_1, r_2 and r_3 and strength are f_1, f_2 and f_3. The radiation profiles is:

$$\begin{aligned} f(r, t_0^*) &= \begin{cases} f_1 & , \quad 0 \le r \le r_1 \\ 0 & , otherwise, \end{cases} \\ f(r, t_1^*) &= \begin{cases} f_2 & , 0 \le r \le r_2 \\ 0 & , otherwise, \end{cases} \quad and \\ f(r, t_2^*) &= \begin{cases} f_3 & , \quad 0 \le r \le r_3 \\ 0 & , \quad otherwise. \end{cases} \end{aligned} \tag{4.18}$$

The goal is minimize $N(t_0 + \Delta t) = 2\int rn(r, t_0 + \Delta t)dr$, where the fractions constrained individually, such that $F' = F/\pi\Delta t\gamma = r_1^2 f_1$ and $F' = F/\pi\Delta t\gamma = r_2^2 f_2$ and $F' = F/\pi\Delta t\gamma = r_3^2 f_3$. Since $f(r, t_1)$ is the same as one-step with 2−fractions, then $f(r, t_1)$ does not change from that for one-step with 2−fractions, we consider the τ the time between the fraction where the τ is small enough to neglect spatial migrations described by the diffusion term. Where the density profile simply grows exponentially, by a factor $e^{\rho\tau}$, then second fraction of radiation is given by

$$n_2(r, t_0 + 2\Delta t + \tau) = \begin{cases} n_1(r, t_0 + \Delta t)e^{-f_2\gamma\Delta t} & 0 \le r \le r_2 \\ n_1(r, t_0 + \Delta t) & r_2 < r < R \end{cases} \tag{4.19}$$

but after application of the third fraction is given by:

$$n_3(r, t_0 + 3\Delta t + 2\tau) = \begin{cases} n_2(r, t_0 + 2\Delta t + \tau)e^{-f_3\gamma\Delta t} & 0 \le r \le r_3 \\ n_2(r, t_0 + 2\Delta t + \tau) & r_3 < r < R \end{cases} \tag{4.20}$$

The factor of $e^{-\gamma[f_1+f_2]t}$ is specifying the effect of One-step with One and two fractions that are before third fraction immediately. It is only have effect on the range $0 \le r \le r_1, r_2, r_3$, so it will be multiply in the function in this rang only.

$$n_3 = \begin{cases} n_2 e^{-f_3\gamma\Delta t} & 0 \le r \le r_3 \\ n_2 & r_3 < r < R \end{cases} \tag{4.21}$$

Which implies to

$$n_3 = \begin{cases} n_0 e^{-r^2/2s^2} e^{\rho\tau} e^{-\gamma[f_1+f_2+f_3]\Delta t} & 0 \le r \le r_3 \\ n_0 e^{-r^2/2s^2} e^{\rho\tau} & r_3 < r < R \end{cases} \tag{4.22}$$

integrating this result gives total number of cells as:

$$\begin{aligned} N(r, t_0 + \Delta t) &= \int\int e^{\rho\tau} n(r, t_0 + \Delta t)dA \\ &= 2\pi e^{\rho\tau}[e^{-\gamma[f_1+f_2+f_3]\Delta t} n_0 \int_0^{r_3} re^{-r^2/2s^2}dr + n_0 \int_{r_3}^{R} re^{-r^2/2s^2}dr] \\ &= 2\pi n_0 s^2 e^{\rho\tau}[e^{-\gamma[f_1+f_2+f_3]\Delta t}(1 - e^{-r_3^2/2s^2}) + e^{-r_3^2/2s^2} - e^{-R^2/2s^2}] \end{aligned} \tag{4.23}$$

Where τ is very small it can be neglected ($e^{\rho\tau} = 1$) then

$$N(r, t_0 + \Delta t) = 2\pi n_0 s^2[e^{-\gamma[f_1+f_2+f_3]\Delta t}(1 - e^{-r_3^2/2s^2}) + e^{-r_3^2/2s^2} - e^{-R^2/2s^2}] \tag{4.24}$$

The constraint on the total beam flux can be imposed through a Lagrange multiplier λ create an augmented N,

$$N(r, t_0 + \Delta t) = 2\pi n_0 s^2[\rho\tau e^{-\gamma[f_1+f_2+f_3]\Delta t}(1 - e^{-r_3^2/2s^2}) + e^{-r_3^2/2s^2} - e^{-R^2/2s^2}] - \lambda(f_3 r_3^2 - F') \tag{4.25}$$

Extremizing with respect to r_3, f_3 and λ, we get

$$0 = 2\pi n_0 r_3 e^{-r_3^2/2s^2}(e^{-\gamma[f_1+f_2+f3]\Delta t} - 1) - 2\lambda f_3 r_3$$
$$0 = 2\pi n_0 s^2 \gamma \Delta t e^{-\gamma[f_1+f_2+f3]\Delta t}(e^{-r_3^2/2s^2} - 1) - \lambda r_3^2$$
$$0 = f_3 r_3^2 - F'$$

By eliminating f_3 and λ, from the above equations we arrive at the following expression for r_3 :

$$0 = e^{\frac{\gamma[r_3^2[f_1+f_2]+F']\Delta t}{r_3^2}}\left((\frac{r_3^4}{2F'\gamma\Delta s^2} - 1)e^{\frac{-r_3^2}{2s^2}} + 1\right) - (\frac{r_3^4}{2F'\gamma\Delta s^2})e^{\frac{-r_3^2}{2s^2}} \tag{4.26}$$

4.2.3 One-Step with Individual i-Fractions:

In the section for applying $i-$fractions, describing $i-$fraction requires introducing i new variables to parameterize $f(r,t)$, we can write the $f(r,t)$of $i's$ separate fractions as.

$$f(r, t_0^*) = \begin{cases} f_1 & , \quad 0 \le r \le r_1 \\ 0 & , \quad otherwise, \end{cases}$$
$$f(r, t_1^*) = \begin{cases} f_2 & , \quad 0 \le r \le r_2 \\ 0 & , \quad otherwise, \end{cases} \tag{4.27}$$
$$\vdots$$
$$f(x, t_{i-1}^*) = \begin{cases} f_i & , \quad 0 \le r \le r_i \\ 0 & , \quad otherwise. \end{cases}$$

since the $i's$ fractions apply individually, we get $F' = r_i^2 f_i$. Density profile immediately after application i^{th} fraction individually is given by

$$n_i = \begin{cases} n_{i-1}e^{-f_i\gamma\Delta t} & , \quad 0 \le r \le r_i \\ n_{i-1} & , \quad r_i < r < R, \end{cases} \tag{4.28}$$

which implies to

$$n_i = \begin{cases} n_0 e^{-r^2/2s^2} e^{\rho\tau} e^{-\gamma[\sum_{k=1}^{i} f_k]\Delta t} & , \quad 0 \le r \le r_i \\ n_0 e^{-r^2/2s^2} e^{\rho\tau} & , r_i < r < R. \end{cases} \tag{4.29}$$

integrating this result gives total number of cells as:

$$\begin{aligned} N(r, t_0 + \Delta t) &= \int\int e^{\rho\tau} n_i(r, t_0 + \Delta t + (i-1)\tau) dA \\ &= 2\pi e^{\rho\tau} [e^{-\gamma[\sum_{k=1}^{i} f_k]\Delta t} n_0 \int_0^{r_i} r e^{-r^2/2s^2 dr} + n_0 \int_{r_i}^{R} r e^{-r^2/2s^2} dr] \\ &= 2\pi n_0 s^2 e^{\rho\tau} [e^{-\gamma[\sum_{k=1}^{i} f_k]\Delta t} (1 - e^{-r_i^2/2s^2}) + e^{-r_i^2/2s^2} - e^{-R^2/2s^2}] \end{aligned} \tag{4.30}$$

Where τ is very small it can be neglected ($e^{\rho\tau} = 1$) then

$$N(r, t_0 + \Delta t) = 2\pi n_0 s^2 [e^{-\gamma[\sum_{k=1}^{i} f_k]\Delta t} (1 - e^{-r_i^2/2s^2}) + e^{-r_i^2/2s^2} - e^{-R^2/2s^2}] \tag{4.31}$$

The constraint on the total beam flux can be imposed through a Lagrange multiplier λ create an augmented N,

$$N(r, t_0 + \Delta t) = 2\pi n_0 s^2 [^{\rho\tau} e^{-\gamma[\sum_{k=1}^{i} f_k]\Delta t} (1 - e^{-r_i^2/2s^2}) + e^{-r_i^2/2s^2} - e^{-R^2/2s^2}] - \lambda(f_i r_i^2 - F') \tag{4.32}$$

Extremizing with respect to r_i, f_i and λ, we get

$$\begin{aligned} 0 &= 2\pi n_0 r_i e^{-r_i^2/2s^2} (e^{-\gamma[\sum_{k=1}^{i} f_k]\Delta t} - 1) - 2\lambda f_i r_i \\ 0 &= 2\pi n_0 s^2 \gamma \Delta t e^{-\gamma[\sum_{k=1}^{i} f_k]\Delta t} (e^{-r_i^2/2s^2} - 1) - \lambda r_i^2 \\ 0 &= f_i r_i^2 - F' \end{aligned}$$

By eliminating f_i and λ, from the above equations we arrive at the following expression for r_i :

$$0 = e^{\frac{\gamma[r_i^2[f_1+f_2+\ldots+f_{i-1}]+F']\Delta t}{r_i^2}} \left((\frac{r_i^4}{2F'\gamma\Delta s^2} - 1) e^{\frac{-r_i^2}{2s^2}} + 1 \right) - (\frac{r_i^4}{2F'\gamma\Delta s^2}) e^{\frac{-r_i^2}{2s^2}}$$

4.2.4 Numerical Discussion for improved Model

4.2.4.1 Optimization the Radiation Profile for One-Step Profile with 2-Fractions

In the Table 4.3 we have calculated values of $N(t + dt)$ in two cases: 1) One-step, One-fraction (N_1); 2) One-step, two-fractions, N_2, where $N(t + dt)$ are the final tumor

cell number at the end of radiation, s is the tumor size while r_1, r_2, f_1 and f_2 are the two radiuses and strengths of the (one-step, two-fraction), respectively.

Table 4.3: Optimization values in One-step with two-fractions

s	n_0	r_1	f_1	r_2	f_2	$N_1(1.0e+006)$	$N_2(1.0e+006)$
1	1591549	2.140695	5.455447	3.113118	2.579578	1.9204	0.4182
2	397887.4	3.0274	2.727724	5.339606	0.876842	5.3490	2.4214
3	176838.8	3.707793	1.818482	7.945889	0.395963	7.1475	4.1267
4	99471.84	4.28139	1.363862	10.85839	0.212036	8.0985	5.2804
5	63661.98	4.78674	1.091089	13.96681	0.128158	8.6486	6.0735
6	44209.71	5.243611	0.909241	17.20539	0.084452	8.9924	6.6438
7	32480.6	5.663747	0.77935	20.53785	0.059269	9.2207	7.0714
8	24867.96	6.0548	0.681931	23.94278	0.04361	9.3798	7.4031
9	19648.76	6.422085	0.606161	27.40649	0.033284	9.4948	7.6676
10	15915.49	6.769472	0.545545	30.91958	0.02615	9.5806	7.8833

The listed values in Table 4.3 conform the validity and superiority of our model. The last columns that contain the total number of remaining tumor cell N_1 and N_2 show clearly the effective reducing in total number of tumor cells when second fraction applied with first fraction in the same time. Other parameters show logical sequence which comfortable with all results. For example, the model suppose that r_2 larger than r_1 which is clearly verified in columns 3 and 5. Similar logic for relation between r_1 with f_1 and r_2 with f_2 values. However, there is another interesting results about the decreasing steps of N_1 and N_2 with size of tumor (s). The table shows the very slow effect of radiation with increases of tumor size (s). In fact, this behavior is due to the constraints condition for limiting the total dose received by patient which is reported in equation (2.13)

4.2.4.2 The Comparison between the Final Tumor Cell Density in (One-Step ,with One-Fraction) and (One-Step, with two-Fractions) :

Figure 4.4 shows the plotted comparison between $N(t + dt)$ in the cases One-step with One-fraction and One-step with two-fraction. The curves has been plotted for N_1

with r_1, f_1 and s. similar plotting is done for N_2 with r_2, f_2 and s. The curves in all graphs in Figure 4.4 shown clearly the advantage for using our proposed model. The valuable rate of difference between N_1 and N_2 conforms our model in tumor treatment optimization.

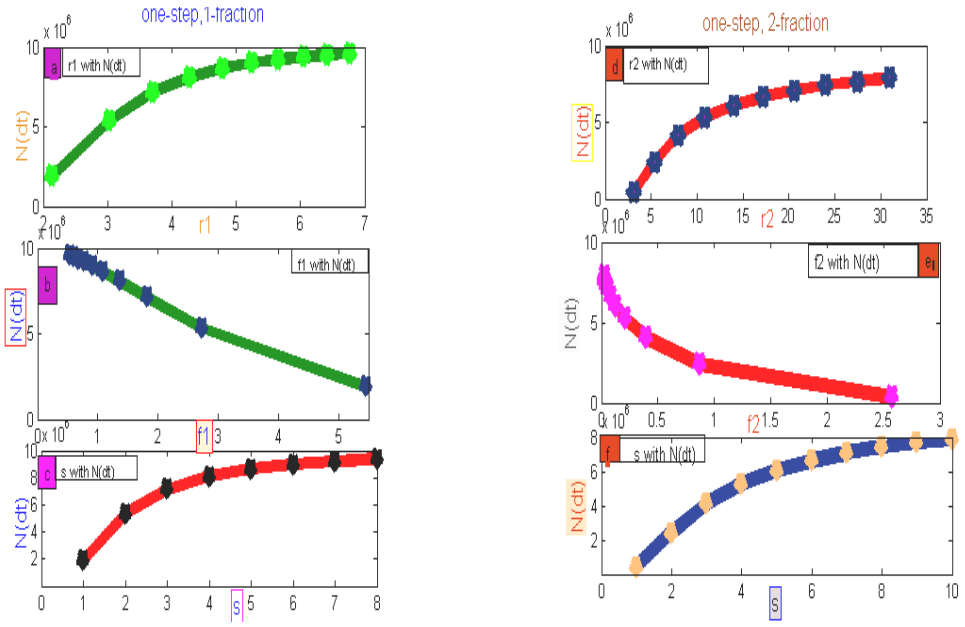

Figure 4.4: Comparison between the final tumor cell density in onestep with One-fraction and one-step with two-fraction

4.2.4.3 Optimization the Radiation Profile for One-Step Profile with 3-Fractions

In the Table 4.4 we have calculated values of $N(t + dt)$ in the case one-step with 3−fraction, where $N(t + dt)$ are the final tumor cell number at the end of radiation. And s is the tumor size. r_1, r_2, r_3, f_1, f_2 and f_3 are the two radii and strengths of the one-step 3−fraction. Also in the Table 4.4 we presented the $N(t + dt)$ in the case One-step One-fraction and one-step with One-fractions for the explain that in the case one-step with three-fractions response to radiation therapy is better than cases of (one-step,one-fraction and one-step, two-fractions).

Table 4.4: Optimization values in one-step with three-fraction

s	n_0	r_1	f_1	r_2	f_2	r_3	f_3	N_1 $1.0e+6$	N_2 $1.0e+6$	N_3 $1.0e+6$
1	1591549	2.140695	5.455447	3.113118	2.579578	3.521225	2.016288	1.9204	0.4182	0.16676
2	397887.4	3.0274	2.727724	5.339606	0.876842	5.866417	0.726431	5.3490	2.4214	1.7353
3	176838.8	3.707793	1.818482	7.945889	0.395963	8.464817	0.348903	7.1475	4.1267	3.5306
4	99471.84	4.28139	1.363862	10.85839	0.212036	11.32512	0.194919	8.0985	5.2804	4.8486
5	63661.98	4.78674	1.091089	13.96681	0.128158	14.38081	0.120885	8.6486	6.0735	5.7646
6	44209.71	5.243611	0.909241	17.20539	0.084452	17.57601	0.080928	8.9924	6.6438	6.4175
7	32480.6	5.663747	0.77935	20.53785	0.059269	20.87415	0.057375	9.2207	7.0714	6.9006
8	24867.96	6.0548	0.681931	23.94278	0.04361	24.25184	0.042506	9.3798	7.4031	7.2706
9	19648.76	6.422085	0.606161	27.40649	0.033284	27.69362	0.032597	9.4948	7.66767	7.5624
10	15915.49	6.769472	0.545545	30.91958	0.02615	31.18873	0.025701	9.5806	7.8833	7.7981

In similar logic, the listed values in Table 4.4 again conform the validity and superiority of our model. The last three columns that contain the total number of remaining tumor cell N_1, N_2 and N_3 show more clearly the effective reducing in total number of tumor cells specially after second and third fraction applied with first fraction in the same time. Also, in similar resulting to previous model. Other parameters show logical sequence that comfortable with all remaining results. For example, the model suppose that r_3 larger than r_2 which is larger than r_1, that is clearly verified in columns $3, 5$ and 7. The similar logic for relation between r_1 with f_1 and r_2 with f_2 and r_3 with f_3 values. However, the most interesting results is about the decreasing steps of N_2 and N_3 with size of tumor (s). The table shows that at high values of S, the values of N_2, almost become very close to N_3 values. This is another result controlled by the constraints condition for limiting the total dose received by patient which is reported in equation (2.13).

4.2.4.4 The Comparison between the Final Tumor Cell Density in the Cases (One-Step with one-Fraction, One-Step with two-Fractions and One-Step with tree-Fractions)

Figure 4.5 shows the plotted comparison between of $N(t + dt)$ in the cases (one-step with two-fraction, one-step with one-fraction and one-step with three-fraction) where the one-step with three-fractions is most effect of XRT.

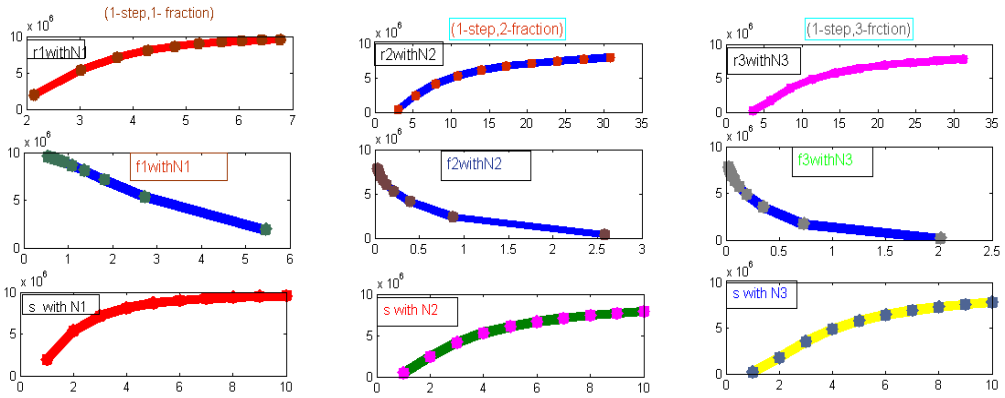

Figure 4.5: The comparison between the final tumor cell density in the cases one-step with one-fraction, one-step with two-fractions and one-step with three-fractions

Chapter 5

Conclusions and Recommendations

5.1 Conclusions

We have successfully studied the capability of the mathematical model in optimization brain tumor radiation treatment. We have corrected some previously calculated values and extended the range of calculations up to 10 values. In addition, we studied the dependency of results on the initial tumor cell density and found that the behavior is similar but not equivalent.

Improved Model: We have successively introduced a new effective mathematical model for tumor treatment optimization. The obtained results of the total number of remaining tumor cell N_1, N_2 and N_3 show more clearly the effective reducing in total number of tumor cells specially after second and third fraction applied with first.

5.2 Recommendations

1. We recommend to extend our study upto $2, 3, ..., n-$steps.
2. We recommend to apply our models in real data and real images of tumors that exposed to radiation therapy at Cancer Center in Sanaa.
3. We recommend our university to adopting such studies in its scientific projects

and supporting this field.

4. We recommend the ministry of higher education and scientific research with Cancer Fund to create specific research centers to support the researchers in field of development mathematical models for optimization factors in cancer tumor therapy.

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