

MRI-image based radiotherapy treatment optimization of brain tumours using stochastic approach

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Abstract

The dismal outcome of brain tumours, particularly gliomas or glioblastoma, furnishes a unique motivation for developing computational imaging and treatment planning tools that can help design the most optimal management. We present a novel scheme for simulation of radiotherapy in MRI images, by which we may visualize the changes in the tumor response. The first step is to discriminate the different type of cells present in the tumor by means of image processing techniques. The next step deals with the simulation of the actual tumour cytolysis operation. First, from an MRI image of a brain, the tumor is delineated carefully, either with the help of a medical practitioner or with the help of basic tumor detection algorithms. The three types of cells that exist within the tumor are proliferating, necrotic and hypoxic. The region-of-interest of the extracted image is now divided into 4 parts, each part signifying a different variety of cells, (3 varieties of tumor cells and the 4th due to normal brain tissue). This cell assignment is accomplished using stochastic activation technique for cellular allocation as Monte-Carlo technique. After the cellular tissual regions are delineated in the MR image, it is now ready for the simulation of the tumour cell cytolysis process. We use the well-known Linear Quadratic Equation for the cytolysis, using a requisite radiobiological dose of 2 gray/day and biological efficacy factor $\alpha/\beta = 10$. The prospects of this newer approach in image-based treatment planning and optimization are explored, particularly for gliomas and glioblastoma.

Keywords: Tumour, Radiotherapy, Apoptosis, MRI, cell cycle.

1) Introduction

Cancer [1] is known to be the second most frequent cause of death in the developed countries. Most of the cancer patients receive radiation therapy as a therapy. In order to achieve the best results with radiation therapy, an efficient planning is necessary before the actual treatment. Generally, the treatment planners ignore the effect of malignant cells and tissues and rely mainly upon the primitive biological models of tumour and normal tissue response. However, it may be proposed that with the introduction of simulations, which derive knowledge from the cell cycles as well as from the molecular properties of malignancy, the therapy-planning efficacy would be enhanced.

Researchers from different parts of the world have engaged themselves in computer simulations of radiotherapy for a long time. Duechting et al.[2] presented a 3-D simulation model of tumor growth involving cell cycle as well as the Linear Quadratic Model. This algorithm was improved by [3,4,5] to visualize both the internal and external structure of a dynamic tumour. Wasserman and Acharya [6] developed a tumour growth

model based on the mechanical properties of the tumour and the surrounding tissues. Qi et al [7] proposed a 2-D tumour growth technique taking into account the proliferation of cancer cells, the effect of cytotoxic cells, the limited supply of nutrients and the mechanical pressure inside the tumour. A 3-D model of brain tumour growth was proposed by Kansal et al. [8] by introducing an adaptive grid lattice. Smolle and Stettner[9] presented another model of tumour growth that took into account the influence of surrounding stroma and tumour cells on cell division.

The LQ model, which gives the survival fraction of the cells after being exposed to radiation, is the main framework, on which researchers are trying to incorporate other biological parameters that properly describe the situation. An important factor that plays an important role in the simulation is radiation-induced apoptosis. Apart from the normal cell death due to apoptosis and irradiation, a fraction of the cells also die of apoptosis, which is caused by radiation. This was first studied by [11] and [12]. In the past, most of the cell survival data that had been obtained lack the apoptotic data. However, a solution to incorporate apoptosis in the LQ model was formulated by [13], which gives a comprehensive view of the tumour response incorporating this vital factor.

This paper aims to simulate a model of the tumour response to radiotherapy incorporating all the possible biological factors and hence, attempts to simulate an almost exact model of the system, which will help in pre-planning of the therapy for optimizing the dose and fractionation schemes, in order to produce the best effect. It includes not only the different simulation models that were proposed by [14], but also includes several biological factors [10,13]. The constraints imparted by these factors give the proper understanding of the science behind the system. Thus, this model will help to realize an exact situation, which is an utmost need in proper therapy planning. Not only does the paper amalgamate the different factors that were expressed by various researchers, but also, it attempts to make an original contribution in the stochastic allocation of the of the various biological components in the model as well as formulate the cell-kill in a stochastic pattern.

2) Data Acquisition and Visualization

The imaging data is obtained along with the histopathologic data of the patient. A well-trained doctor delineates the tumour using a computer tool. The tumour consists of mainly three type of cells—the proliferating ones, the hypoxic or G_0 ones and the necrotic ones. All these three types are separated using the intensity values of the MRI data. Each set is given a different intensity. The normal brain cells, which are outside the tumour boundary, should also be given a separate intensity.

3) Tumour growth biology

As shown in Fig.1, the tumor cells pass through the different phases of the cell cycle. However, they may suffer deaths due to apoptosis. Due to ageing and spontaneous apoptosis, the cells residing in any phase other than necrosis dies with a probability of 1% per hour.

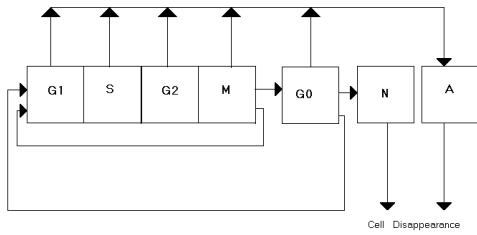


Fig.1. Cytokinetic model of tumor cell

4) Tumour Cell Response to Radiotherapy

The following assumptions are made in this context:

1) The response of each cell to the absorbed radiation dose D is given by the Linear Quadratic model. According to this model, the survival probability S of the cell is given by the following:

$$S = \exp[-(\alpha D + \beta D^2)] \dots (1)$$

where α and β are the radiosensitive parameter for the cells.

2) It has been found that of the different cell cycle phases, cells in the S phase are the most radiosensitive and those in the G_0 phase the least. Hence, three sets of values for the α and β parameters for the LQ model are assumed; one set for the proliferating cell cycle phases, except for the S phase, one set for the S phase and a third set for the G_0 phase.

3) The flowchart for the response of a single tumour cell to irradiation is shown in Fig.2.

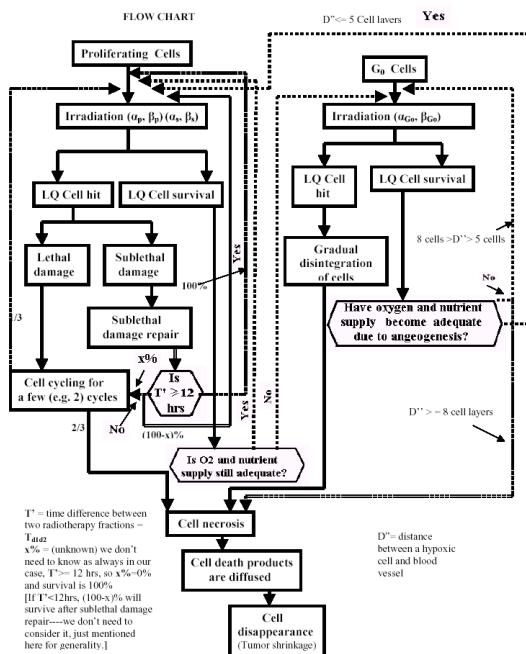


Fig.2. Flowchart for response of a single cell to irradiation

5) Assumptions on time Quantization

- 1) Time is quantized and measured in appropriate units. Here, we have assumed units of 1 hour.
- 2) Normal Gaussian distribution is assumed for the cell cycle phase durations.

6) Visualization and Cell Allotments

We have processed our system in a MATLAB software environment for 3-D visualization. Here, each pixel is assumed to be one cell. The initial classification of the cells is done by utilizing the intensity variation of the MRI image in the different regions of the tumour region. The well-oxygenated cells, different from the intensity nature, are chosen as proliferating ones. As stated by [14,15], the cell distribution is altered in the following manner. In the proliferating cell layer, 70% of the clonogenic cells are assumed to be in the cycling phase while the rest 30% are assumed to be in the G_0 phase. Other cell layers also have similar distributions. In the G_0 cell layer, 30% of the clonogenic cells are in the cycling phases and 70% in the G_0 phase. In the dead cell layer, 10% of the cells are in the cycling phase and 90% in the G_0 phase. All these cell allotments are done using the Monte-Carlo Technique, which is suitable for these types of allotments in biological models.

Care should be taken to include the time durations for the different phases as well as the cell cycle. The cell cycle duration is taken as 30 hour, the cell cycle phase durations $T_{G1}=11$ hours, $T_S= 13$ hours, $T_{G2}=4$ hours, $T_M= 2$ hours, $T_{G0}= 25$ hours and cell loss factor is taken as 0.9 [16] The cell loss factor is assumed to be the sum of cell loss factor due to necrosis (0.8) and due to apoptosis (0.1).

A standard dose (2 Gy once a day, 5 days a week, 60 Gy in total) has been simulated. The distribution of the absorbed dose in the tumour region is assumed to be uniform. The cell kill due to this radiation is formulated using the LQ model. However, the exact locations of the cells that are to be killed have been simulated using standard Monte-Carlo Techniques or Random Scanning Procedure.

7) Center of Mass Algorithm

During tumor shrinkage, the shrinkage process is generally conformal in nature [10]. This can be simulated using the 'Centre of Mass Algorithm'. In this process, the individual tumor cells are pulled towards the center of the mass of the entire tumor. The biological cause for this pull can be attributed to the force exerted by the surrounding normal cells on the tumor as the brain tries to recover its normal shape. After each iteration, a part of the boundary cells are estimated to be tending to move inwards. This follows for the entire therapy duration.

8) Radiation Induced Apoptosis.

Apoptosis, as was mentioned before is a process of random cell death. Along with the normal apoptosis that we have earlier considered, a new model of apoptosis needs to be included which is solely responsible due to radiation. It is seen that, the dose response curve for radiation-induced apoptosis [13] repeats rapidly with dose and then reaches an almost saturated value. The shape of the curve can be described by the equation

$$F_a(1-e^{-\zeta D}) \dots\dots\dots(2).$$

Where F_a is the fraction of the cells that are susceptible to radiation induced apoptosis, D is the dose and ζ is the coefficient of radiation inactivation via apoptosis. Once we have obtained equation (2), we can readily state that if we consider only cell death due to apoptosis, the fraction of the cells surviving would be

$$S = 1 - F_a(1-e^{-\zeta D}) = F_a e^{-\zeta D} + (1-F_a) \dots\dots(3)$$

To introduce cell death due to radiation induced apoptosis in the LQ model; we need to multiply the equation by the LQ equation. Thus we get,

$$S = [F_a e^{-\zeta D} + (1-F_a)] \exp [-(\alpha D + \beta D^2)] \dots\dots\dots (4)$$

This is the desired cell death equation including radiation-induced apoptosis.

9) Results

We have conducted a simulation run, to validate our scheme. The different parameters chosen are shown in Table 1. and Table 2.

<u>Parameter</u>	<u>Value with Units.</u>
Capillary Response Time T_{cap}	2-5 days
α/β Ratio	10 Gy
Cell Cycle Delay due to repair	6 hours
Probability for Postmitotic Survival	1/3rd
ζ --Coefficient of radiation inactivation via apoptosis	0.2 Gy ⁻¹
Fraction of cells subjected to radiation induced apoptosis	0.5

Table1. Parameters needed for simulation

Cell Type	Colour
Proliferating	Light Yellow
Hypoxic	Deep Yellow
Necrotic	Black
Normal Brain Cells and Tissue	Pink
Blood Capillaries	Red

Table 2. Intensity values of various types of cells used in the model.

Once we have received all the information, our next task would be to simulate the situations for treatment using standard dose.

For the simulation, the parameters chosen are $\alpha_p=0.6 \text{ Gy}^{-1}$, $\alpha_s=0.5 \text{ Gy}^{-1}$, $\alpha_{G0}= 0.4 \text{ Gy}^{-1}$. The dose used is 2 Gy per day, 5 days a week, for a period of 6 weeks. The results obtained are shown in the figures list from Fig.3. to Fig. 6. Fig.7. shows the temporal variation of the number of surviving cells during the radiotherapy procedure.



Fig.3. Day 0. Showing the beginning of radiotherapy.

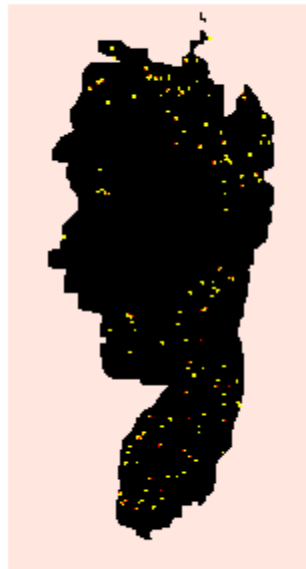


Fig.4. 5th Day of Radiotherapy.



Fig.5. 10th day of radiotherapy



Fig.6. End of radiotherapy treatment

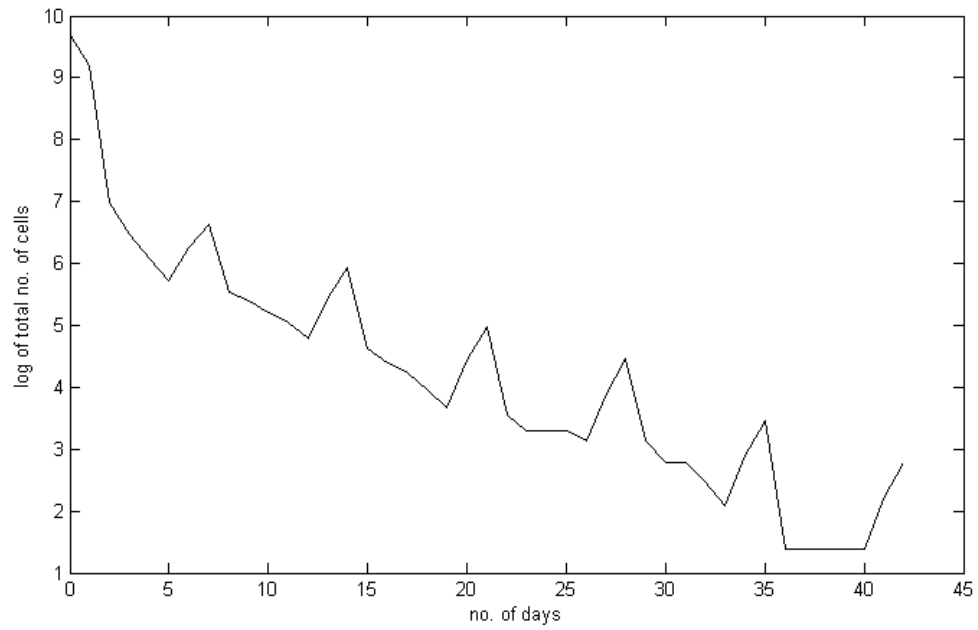


Fig.7. Logarithmic variation of number of surviving cells with number of days.

Conclusion

The paper attempts to produce an exact model of the course of radiotherapy treatment and the effect of radiation on tumour cells. The parity that these results bear with standard results mentioned in other works validate their usefulness. The objective of the paper is to provide the simulation results in order to pre-plan for a better treatment. Future works may include variation of the radiotherapy dose in order to foster the cell-kill.

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