A Novel Optimization Method for the Latest Model of GBM Tumor in Order to Decrease the Total Amount of Dose Delivery

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ABSTRACT
In this article a brief story of mathematical model for one of the most lethal tumor, GBM, is considered, and it tries to reduce the amount of dose delivery to the patient by using genetic algorithm (GA). Since this tumor kills many of its patients, lots of efforts have been done in the previous decades in order to cure this cancer or at least increase its patients' lifetime. Most of previous models have not been associated with a treatment term but in this investigation the latest model of the tumor which contains the input term of radiotherapy has been utilized. This paper shows a new optimization solution on the latest model of GBM and reduces the total dose received by the patient while he or she has the same lifetime.

Keywords
Radiotherapy, GBM tumor, GA, state space model, optimization

1. INTRODUCTION
Glios-cells are the main components of human brain that can cause cancer when the brain loses its control over their reproduction. A high-grade type of this cancer is called GBM (Glioblastoma Multiform) which mostly ends in death. Despite deep advances in surgery, radiotherapy and other schemes of treatment during the past decades, no crucial treatment for this type of tumor has been proposed and it takes the patients' lives in an approximate period of 6 months. That is related to the reason that this tumor has high rate of reproduction and doubling. In other words, the doubling time for that is very low and each 24 days, the number of cancerous cells are doubled. Mathematical modeling is a method of solving for most clinical problems while it uses different types of optimization methods for the best solution for the problems.

Radiotherapy is one of the main clinical ways of curing cancers and the most advantageous type of treatment after surgery. Radiotherapy affects the both the normal and cancerous cells, therefore damaging the cancerous cells as much as possible and the least effect on the normal cells are the main target of radiotherapy. In order to track the status of normal and cancerous cells, and predicting the future amount of cells a mathematical model is the most reliable method.

This investigation shows that using radiotherapy as an input term in the GBM tumor model can lead to precise estimation of normal and cancerous cell after different schemes of radiotherapy and also by applying intelligent algorithm one can reduce the amount of total dose delivered to the patient, while he or she can live the same period of time

2. METHODOLOGY
2.1 Previous Models Review
Now let's take a tour to the depth of the previous models to see the advantageous and disadvantageous of their work. Year 2009[1] a precise hybrid model was proposed by Tanaka and his colleagues which shows the increase of cancerous cells which radius of the tumor was the main input.

The model is as follows:

$$C(r)=C_0-\left(\frac{s}{6D}\right)\left(R^2-r^2\right)K_1\left(\frac{1}{r}-\frac{1}{R_T}\right) \quad (1)$$

It is easily seen in this model that it is not dependent to the time variable but it precisely shows the radius of the tumors. It also lacks control over the treatment of the tumors and it needs an input parameter which relates the treating condition.

In 2007 [2] a model with radiotherapy input was introduced by Harpold, Swanson and other teammate and improved the same year.

Their final outcome are as follows:[2]

$$\frac{\partial c}{\partial t}=\nabla.\left(D\nabla c\right)+\rho c-G\left(t\right)c \quad (2)$$

Swanson et al. [2] continued the model development and their new model has slight difference with the above formula:

$$\frac{\partial c}{\partial t}=\left(D\nabla^2 c\right)+\rho c\left(1-\frac{c}{k}\right) \quad (3)$$

In the above model the rate of gliomas cells concentration and its variance is $\frac{\partial c}{\partial t}$, while the net invasion of gliomas and the

net proliferation of that are $(D\nabla^2 c)$ and $\rho c(1-\frac{c}{k})$ respectively.

The above formula has a good sort of information about the cancer cells rate but still it has no details of normal cells and its experimental nature reduces its mathematics face. Death is another parameter that is important for the patient and is not considered here.

That year [3] Andrew M. Stein et al. developed a continuum mathematical model for the invasive cell treatment in this way:

$$\chi^2(D, v_i, s, g) = \frac{1}{N-n-1}\left[\sum_t\left(\frac{R_i(t)-\bar{R}_i(t)}{\sigma_R}\right)^2 + \sum_r\left(\frac{u_i(r,t_3)-\bar{u}_i(r,t_3)}{\sigma_u}\right)^2\right] \quad (4)$$

This is one of the most precise models with too many parameters that runs statistically, but still lacks normal cells and the input of treatment.

Rockne in 2008 [4] by using the model of Swanson proposed a new model consisting the radiobiological effect but in a fuzzy method. In the model, this issue is not precisely defined. Here is the model:

$$\frac{\partial c}{\partial t} = \nabla.\left(D(x)\nabla c\right) + \rho c - R(x,t)c \quad (5)$$

In this model $\frac{\partial c}{\partial t}$ is the variation of cancerous cells, $\nabla.(D(x)\nabla c)$ is the net dispersal of gliomas cells and ρc the net growth of gliomas cells. $R(x,t)$ is the decrease of living cells (either normal or cancerous) due to radiation which follows the LQ model as follows:

$$E = \alpha.Dose + \beta.Dose^2$$
$$S = e^{-E} \quad (5')$$

Where S is the survival fraction of cells facing the therapeutic rays and α and β are the radiobiological parameters which varies in each person's body.

Scientists show that in a 9 patient study [5] who were under radiotherapy treatment a new model of cancer cell growth is reachable containing the radiotherapy input. This was the first time that a model of GBM is summed with an input term. The model is:

$$\frac{\partial c}{\partial t} = \nabla.\left(D(x)\nabla c\right) + \rho c\left(1-\frac{c}{k}\right) - R(x,t,Dose)c\left(1-\frac{c}{k}\right) \quad (6)$$

In the above model, R is defined as:

$$\mathbf{R(x,t,Dose(x,t))} \equiv \begin{cases} \mathbf{0} & \mathbf{for} \quad \mathbf{t \notin therapy} \\ \left(\mathbf{1 - S(\alpha,\beta,Dose(x,t))}\right) & \mathbf{for} \quad \mathbf{t \in therapy} \end{cases}$$

(7)

S is also the survival rate according to the LQ model.

All of the above models and other similar works are from great investigations and are used in many ways, but still some weaknesses are seen in them. Some of them have lots of parameters which are not fully utilized. They mostly lacks information about the normal cells itself and the effect of treatment is not fully defined.

Later in 2010 in a study with 9 patients [5] which their illness had been diagnosed soon enough and being engaged under radiotherapy treatment, they improve their model on the basis of radiobiology of each patient for the increase of GBM cells. This model contains the LQ model of radiology in a more effective manner. This model response to the treatment and for the first time the GBM model is combined with dose delivery input, which make the further investigation on the type of treatment schemes possible.

Here are the deficiencies of the above models:

1- All has no idea about the normal cells
2- Some have very complicated parameters that may not effective in practice.
3- A state space model is missing in all models
4- Most models contains many statistics that have no computation over it.
5- Experimental data here is not precisely defined.

2.2 Latest Best Models

The best work in the writers' aspect (since it fulfills the above deficiencies) are the models as follows:

The first model is a sophisticated model [6], which contains both normal and cancer cell growth in a simple nonlinear model. Kirkby and his colleagues presented that in 2007 and 2009 [7]. The proposed models have similar states but the 2009 model has an input of radiotherapy. Here is the model [7]:

$$\frac{dN}{dt} = -k_n.N.C$$
$$\frac{dC}{dt} = k_c.C \quad (8)$$

As it is clear this model has no input term is associated to the model, so controlling over the cancerous cells will be difficult. Below is the table of parameters that are used in this model,

In the first step the above equation must be digitized and converted to a discrete form like this:

$$N_i = -\Delta t\left(k_n * N * C\right) + N_{i-1}$$
$$C_i = \Delta t\left(k_c * C\right) + C_{i-1} \quad (9)$$

In [12] the model is connected to the input term of radiotherapy using the GEP algorithm which made possible calculations of normal and cancerous cell while time propagates. Below is the discrete form of model: [12]

$$N_{i+1} = -k_n.N_i.C_i.dr - (1-doseEff).kk\,2.dt\left(1-\exp\left(-\alpha d-\beta d^2\right)\right)N_i + N_i$$
$$C_{i+1} = 1 + dt.k_c - tt.kk\,2.dt.doseEff.\left(1-\exp\left(-\alpha d-\beta d^2\right)\right)C_i \quad (10)$$

If the above model is converted to a differential equation form the below model is achieved:

$$\frac{dN}{dt} = -k_n .N .C - (1 - doseEff).kk2.\left(1 - e^{-\alpha.d - \beta d^2}\right)N$$

$$\frac{dC}{dt} = k_c .C - tt.(doseEff).kk2.\left(1 - e^{-\alpha.d - \beta d^2}\right)C \quad (11)$$

The formula parameters are as follows:[12]

d	dose delivery amount
α and β	radiobiological ratios β=α/9
K_N , K_C	the parameters of (8)-normal and cancer ratio
kk2	Proportional coefficient made by GEP
tt	1 day in normal dose delivery and 1.15 for twice a day
N and C	the effectiveness percent of dose delivery to N and N, C: normal and cancer cells

2.3 GA Implementing

Our world with its all variety of species and creatures is the product of a three billion years experiment, which is called "evolution". Genetic algorithm is a one of the evolutional intelligent algorithms that searches through its patterns and finds the optimal answers. [9,10]

Since this model is the latest model that contains the status of both normal and cancerous cells with or without therapy, in this paper the optimization of this model is investigated. The main goal here is to decrease the amount of dose delivery to the patient while he or she lives the same period. Changing the amount of dose delivery in the input term makes a series of values that generates better treatment condition of a patient with GBM tumor.[8,9]

20 patients in a 6-week or 30 days of treatment are participated. Since the sequence of dose delivery is constant (72 gray which is 2.4 gray each session of treatment (2.4*30)) the patients' lifetime average is 520 days while the average number for the patients with no cure was 435 days. An increase about 19 percent exists here ($\frac{520}{435}$x100=19.54%). After this, a simple intelligent algorithm in the form of genetic algorithm is applied, that allows the varying amount of dose instead of constant rates. In this case, a 60.5 gray of radiation dose is needed, while the previous test 72 gray is applied for the patients. Therefore a decrease about 19 percent is created in this case($\frac{72}{60.5}$x100=19.008%). It is easily seen that using variating amount of dose to the patients can lead to a better statistical results. [10, 11, 12]

3. RESULTS AND FIGURES

Here is the experimental and computational curves simultaneously, both for normal and cancerous cells after the therapy [12]. As it is easily seen, the number of cancer cells are decreasing in the beginning of the therapy but due to the high rate growth of this tumor, the number of the cancer cells increases.

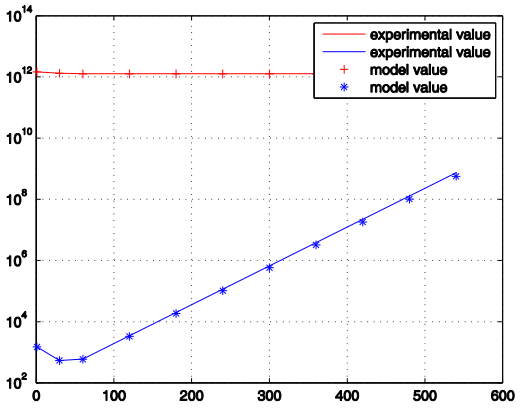

Fig1: The growth of cancer cells in comparison with decay of normal brain cells.

The below figure shows the GA performance while it goes through its final iterations. As it is clear on the figure the last iteration shows that instead of 72 man can apply 60.5 Gy in order to have the same lifetime results [12].

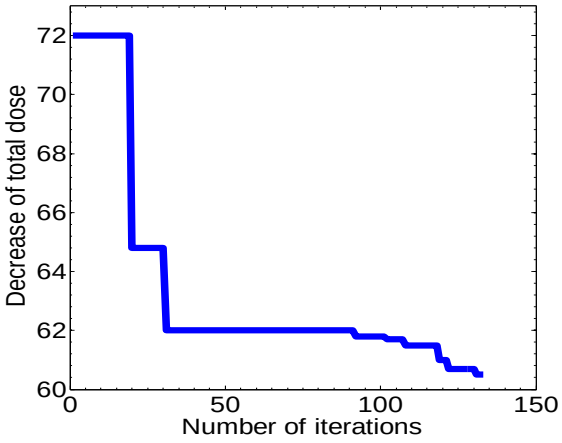

Fig 2: the dosage of radiation as an output of GA. The decrease of dose for 520 days of life

4. CONCLUSION

The results show that using radiotherapy for a patient with GBM tumor prolongs his lifetime from 435 to 520. Besides using intelligent algorithms specially GA in this paper decreases the amount of total dose delivery from 72 gray to 60.5 for patients with nearly the same conditions (like age, sex, number of initial cancerous cells and etc.). This investigation shows that if an alternation amount of dose is applied to a patient instead of constant ratios, it can cause better results. Here exists a very important question that is there a way to prolong the patients' life if the treatment plans designed with varying amount of dose delivery. Further studies can be done on this subject.[11]

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