The Capability of Mathematical Models in Glioblastomas Cancer Treatments Optimization

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Abstract

We have studied the advantages of using mathematical models in medical application. In this paper, we have applied the well-known mathematical model [Meaney. 2019] for obtaining the best conditions in cancer treatments.

The model is Specified for use in case of brain tumor (Glioblastomas) and radiation treatments (one-step).

We have extended the range of calculated values of treatment parameters. 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. Finally, we have analyzed our *result and compared them with other's data.*

Keywords: Mathematical, Models, Cancer, Radiation, Equation

Introduction

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.

Hanahan and Weinberg, call these effects the 'Hallmarks of Cancer'. They describe the behaviors typical of cancer cells, which result in or accompany their problematic growth.

Gliomas, the most common primary brain tumor is found to arise from the supporting glial cells of the brain or their precursors.

Many reasons such as the gilomas extensive growing and invading before the patient notes any symptoms make the gliomas almost impossible to cure. [Meaney. 2019, Hanahan. 2011, Sanai. 2005, Fisher. 1969,] One method of cancer treatments is called the radiation treatment.

The cancer cells are irradiated with a homogeneous dose in external beam radiotherapy in the treatments. The first introduction of radiotherapy optimization is done by Fisher and further developed by Brahme Hanahan. 2011, Sanai. 2005, Fisher. 1969, Brahme. 1984 &1987] Brahme. 1984 &1987]

The benefits of mathematical modeling have been realized in many different fields of sciences.

Mathematical modeling has become increasingly applied by both biologists and mathematicians.

They are used to optimize the spatial application of External-Beam Radiation Therapy (XRT).

It utilizes both analytical and computational mathematical methods as well as data from MRI imaging. [Meaney. 2019, Hanahan. 2011, Sanai. 2005, Fisher. 1969, Brahme. 1984 &1987]

Many authors develop many mathematical models to describe the response to radiotherapy (RT).

Ribba et al. [Ribba. 2012] 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 patient's response with a good qualitative agreement. Swanson's reaction-diffusion model which describes the diffusion and proliferation of tumor cells in addition to the effects of precisely delivered radiation therapy [Brahme. 1984 &1987, Ribba. 2012, Harpold. 2007, Swanson. 1999, Woodward. 1996, Tracqui. 1995, Sachs,19997].

In this paper, we have used the well-known mathematical model for obtaining the best conditions in cancer treatments [Meaney. 2019]. The work is specified for use in case of brain tumor (Glioblastomas) and radiation treatments (one-step) [Meaney. 2019]. we have extended the range of calculated values of treatment parameters that in Ref [Meaney. 2019] and also corrected some wrong values

We applied the model on different cases that differ in the value of initial tumor cell density and go to higher values.

Theoretical Background

Equation for tumor growth is found mostly in Ref. [Meaney. 2019] and somewhere in Hanahan. 2011, Sanai. 2005, Fisher. 1969, Brahme. 1984 &1987]:

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

Here, $n(\vec{x},t)$ is the tumour cell density at position $\vec{x} = (x_1,\cdot\cdot\cdot,x_d)$, $\nabla^2 = \sum \frac{\partial^2}{\partial x_\alpha^2}$ 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 (1) we find that $n(x,t_0)$ is density profile, now we have to apply XRT to this tumor, we represent the function $f(x,t)$ which we call cytotoxic profile.

Hence when the action of most therapeutic interventions is to remove a fraction of existing cells, we have added a term $-\gamma f(\vec{x},t)\, n(1 - \frac{nb}{n_{max}})$ to the hand side of equation (1) to become

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

Where the parameter γ is a measure of the radiation rate, and we can write as $\gamma = \alpha\dot{D}(^1/_{day})$, Thus, during each fraction, the first two terms on the right hand side of Eq. (2) can be neglected, leading to

$$\frac{\partial n(\vec{x},t)}{\partial t} \cong -\gamma f(\vec{x},t)\, n(\vec{x},t)\left(1 - \frac{b\, n(\vec{x},t)}{n_{max}}\right) \qquad (3)$$

For the exponential case ($b = 0$), the equation (3) becomes

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

Or

$$\frac{\partial n(\vec{x},t)}{n(\vec{x},t)} \cong -\gamma f(\vec{x},t)\, \partial t \qquad (4)$$

For the logistic case ($b = 1$) then the equation (3) become

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

Or

$$\frac{\partial n(\vec{x},t)}{n(\vec{x},t)\left(1 - \frac{n(\vec{x},t)}{n_{max}}\right)} \cong -\gamma f(\vec{x},t)\, \partial t \qquad (5)$$

By integrating Eq. (4) which (now ordinary) differential equation in the interval $[t_0, t_0 + \Delta t]$ we get:

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

$$\Rightarrow \quad (\ln|n(\vec{x},t)|)\Big|_{t_0}^{t_0+\Delta t} = -\gamma f(\vec{x},t)(t_0 + \Delta t - t_0)$$

$$\Rightarrow \quad n(\vec{x},t_0 + \Delta t) = n(\vec{x},t_0)e^{-\gamma f(\vec{x},t)\Delta t} \qquad (6)$$

Now for the logistic growth, i.e. in case ($b = 1$), integrating Eq. (5) in the interval $[t_0, t_0 + \Delta t]$ we get:

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

Using partial fraction:

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

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

$$A = 1 \;\&\; B = \frac{1}{n_{max}}$$

Thus,

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

$$\ln[n(\vec{x},t)]\,\begin{matrix} t_0+\Delta t \\ t_0 \end{matrix} - \ln\left[\left(1-\frac{n(\vec{x},t)}{n_{max}}\right)\right]\begin{matrix} t_0+\Delta t \\ t_0 \end{matrix} = -\gamma f(\vec{x},t)[t]\,\begin{matrix} t_0+\Delta t \\ t_0 \end{matrix}$$

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

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

Or

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

or equivalently,

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

From this we get

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

Or

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

Therefore, the required solution is

$$n(\vec{x},t_0+\Delta t) = \frac{n_{max}}{1-\left(\frac{n(\vec{x},t_0)-n_{max}}{n(\vec{x},t_0)}\right)e^{\gamma f(\vec{x},t)\Delta t}} \qquad (7)$$

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

$$0 \le f(\vec{x},t) \le F \;\; \textbf{for some} \;\; \mathrm{C} \qquad (8)$$

Where C is Dose Limiting parameter. This is constraint on limiting the total dose received by the patent, therefore the mathematical equation is represented by

$$\gamma\int d^d\,x\,dtf(\vec{x},t) \le F \qquad (9)$$

Where the integral is over the inter treatment length. Now our goal is to determine the function $f(x,t)$ that minimizes the total number $N(T)$ obtained by integrating the tumor cell density as

$$N(T) = \int d^d\, x f(\vec{x},t) \qquad (10)$$

To contrast, Brahme and Agren [11] instead optimized the TCP, where $TCP = e^{-N(T)}$ where $N(T)$ is the number of cells surviving by the treatment. It can be clearly seen that minimizing $N(T)$ is equivalent to maximizing $e^{-N(T)}$.

Results and Discussion

This part consists of two sections and each section contains several parts. The first section is the continuous profile optimization which consists of two parts as follows:

- **Optimal profile with one fraction of exponential death:**

In this part we will take the case of exponential cytotoxic action. We represent the first constraint in equation (8) with a Lagrange multiplier λ, which requires extremizing

$$\tilde{N} = \int d^d\, x\, n(\vec{x},t) e^{-f(\vec{x},t)} + \lambda\left(\int d^d\, x\, f(\vec{x},t) - F\right) \qquad (11)$$

Where $\Delta t = \gamma = 1$ for convenience solving the resulting Euler–Lagrange equation for $f(x,t)$, we find the optimal profile by differentiation (11) with respect to f as

$$0 = n(\vec{x},t) e^{-f(\vec{x},t)}(-df) + \lambda\, df$$

$$\Rightarrow \quad \left(-n(\vec{x},t) e^{-f(\vec{x},t)} + \lambda\right) df = 0$$

$$\Rightarrow \quad n(\vec{x},t) e^{-f(\vec{x},t)} = \lambda$$

$$or \quad e^{-f(\vec{x},t)} = \frac{\lambda}{n(\vec{x},t)}$$

$$\Rightarrow \quad f(\vec{x},t) = \ln \frac{\lambda}{n(\vec{x},t)} \qquad (12)$$

With λ chosen such that (8) is satisfying. Note that the above result is independent of parameters ρ and D_n and since the cytotoxic profile in equation (12) is not guaranteed to satisfy the constraint of $0 \le f(\vec{x},t) \le F$. In particular, it leads to unphysical negative value when $n(\vec{x},t) < \lambda$. For better understanding of this result, we consider the simple case a Gaussian profile arising from radially of a single –cell in exponential growth. Thus the exponential growth for time to leads to the cell density profile:

$$n(\vec{x},t_0) = n_0 e^{-\frac{r^2}{2s^2}} \qquad (13)$$

where r is the radial distance from the initial cell (tumor center). The width of the Gaussian profiles $s = \sqrt{2D_n t_0}$ while $n_0 = e^{\rho t_0}/(2\pi s^2)^\wedge \frac{d}{2}$ the cell density at its center equation (12) at cutting off the negative profile the parabola leads to the semicircular profile

$$f(\vec{x},t) = f_1(r) = ln\frac{n_0}{\lambda} - \frac{r^2}{2s^2} = \begin{cases} f_m\left(1 - \frac{r^2}{r_m^2}\right) & if \quad r \le r_m \\ 0 & if \quad r \ge r_m \end{cases} \qquad (14)$$

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

$$F = \int d^d\, x f_1(r) = \frac{2K_d}{d(d+2)} f_m r_m^d \qquad (15)$$

Where $K_d = is\ the\ d - dimensinoal\ \ solid$ angle with $K_3 = 4\pi$ and $K_3 = 2\pi$.
Now since $= \frac{2k_d}{d(d+2)} f_m r_m^d$, using $f_m = \frac{r_m^2}{2s^2}$ from equation (14) we get

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

Solving the last equation for r, we get

$$r_m = (\frac{d(d+2)}{K_d})^{\frac{1}{d+2}} F^{\frac{1}{d+2}}\ s^{\frac{2}{d+2}}$$

Where $r_m$is optimal radius of the semi–circular, while its maximal intensity can be rewritten as

$$f_m = \frac{1}{2}(\frac{(d+2)}{K_d})^{\frac{2}{d+2}} F^{\frac{2}{d+2}} s^{\frac{d(d+1)}{d+2}} \quad (17)$$

Since $r_m^2 = [\frac{(d+2)}{(k_d)}]^{\wedge \frac{2}{d+2}} F^{\ \frac{2}{d+2}} s^{\ \frac{2}{d+2}}$ ***and*** $f_m = \frac{r_m^2}{2s^2}$ **.**

- **The second section is discrete profile optimization**

The second section consists of three parts as follows:

D1 (one- step radial profile):

Note 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.

$$f(r,t) = \begin{cases} f_1 & 0 \le r \le r_1 \\ 0 & otherwise \end{cases} \quad (18)$$

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 $F' = \frac{F}{\pi\gamma\Delta t} = r_1^2 f_1$. 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

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

Integrating this result gives total number of cells as:

$$N(t_0 + \Delta t) = \iint n(r, t_0 + \Delta t)\, dA$$

$$= 2\pi \left[e^{-f_1\gamma\Delta t} n_0 \int_0^{r_1} r\, e^{-\frac{r^2}{2s^2}} dr + n_0 \int_{r_1}^{R} r\, e^{-\frac{r^2}{2s^2}}\, dr \right]$$

$$= 2\pi n_0 s^2 \left[e^{-f_1\gamma\Delta t}(1 - e^{-\frac{r^2}{2s^2}}) + e^{-\frac{r^2}{2s^2}} - e^{-\frac{R^2}{2s^2}} \right] \quad (20)$$

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

$$\widetilde{N} = 2\pi\, n_0 s^2 \left[e^{-f_1\gamma\Delta t}(1 - e^{-\frac{r^2}{2s^2}}) + e^{-\frac{r^2}{2s^2}} - e^{-\frac{R^2}{2s^2}} \right] - \lambda(f_1 r_1^2 - F) \quad (21)$$

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:

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

We can easily note that at t_0 , i.e. $\Delta t = 0$, equation (21) becomes

$$N(t_0) = 2\pi n_0\, \sigma^2 \quad (22)$$

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

This part consists of three sections: 1) One- step radial and profile relations (extension and correction) .2) Relation between final tumor cell density with optimal radiation radius and profile 3) Relation between final tumor cell density with tumor size and initial number of tumor cells.

❖ 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-1. The terms (Nt, Nt1 and Nt2) are assigned to the calculated remaining final tumor cell density that count initial tumor cell density is 1e7 [Meaney. 2019], 5e6 and 2e7, respectively. In other words, we have chosen the half and double values of (Nt). Also, we have calculated the number of tumor cell at (t_0) for the three cases. We assigned them as (no, no1 and no2) respectively. It's very clear that the radiation optimization values of radiation radius ($r1$) and profile ($f1$) do not depend on Nt. However, we have corrected the first two values of ($r1$), ($f1$) and ($n0$) published in reference [Meaney. 2019]. In addition, we extend the calculated values of them up to ten values.

Table-1: optimization values in one-step fraction

Nt2*e7	no2*e6	Nt1*e6	no1*e5	Nt*e6	$n0$*e6	f1	r1	Ss
0.3841	3.1831	0.9602	7.9577	1.9204	1.5915	5.45	2.14	1
1.0698	0.7958	2.6745	1.9894	5.3490	0.3979	2.72	3.02	2
1.4295	0.3537	3.5737	0.8842	7.1475	0.1768	1.81	3.707	3
1.6197	0.1989	4.0492	0.4974	8.0984	0.0995	1.36	4.281	4
1.7297	0.1273	4.3243	0.3183	8.6486	0.0637	1.091	4.786	5
1.7985	0.0884	4.4962	0.2210	8.9924	0.0442	0.909	5.24	6
1.8441	0.0650	4.6104	0.1624	9.2207	0.0325	0.779	5.66	7
1.8760	0.0497	4.6899	0.1243	9.3798	0.0249	0.68	6.054	8
1.8990	0.0393	4.7474	0.0982	9.4948	0.0196	0.606	6.422	9
1.9161	0.0318	4.7903	0.0796	9.5807	0.0159	0.545	6.7	10

The relation between tumor size (ss) with radiation radius (r1) and radiation profile (f1) are presented in figure-1.

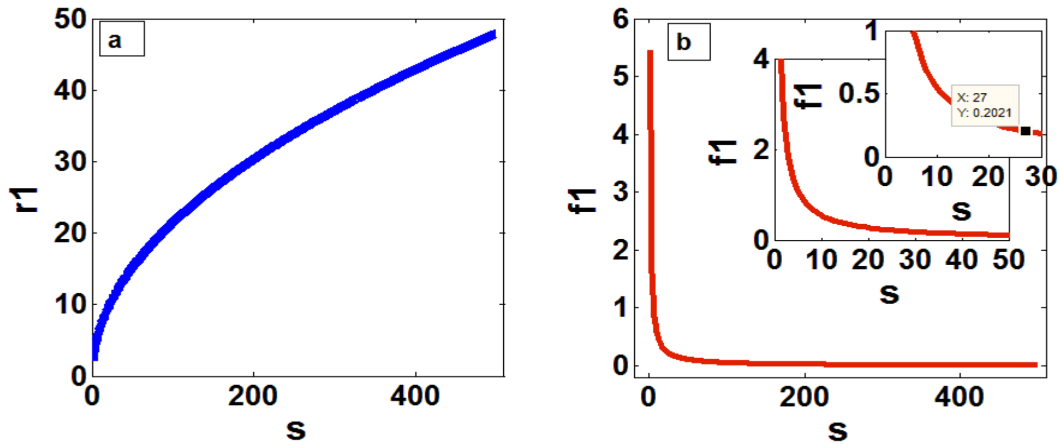

Figure-1: a) relation between r1 &s, b) relation between f1 &s

Figure-1(a) shows the exponential growth between radiation beam radius and tumor size. While the relation between f1 and s is presented in figure-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.

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❖ 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-2. From figure-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

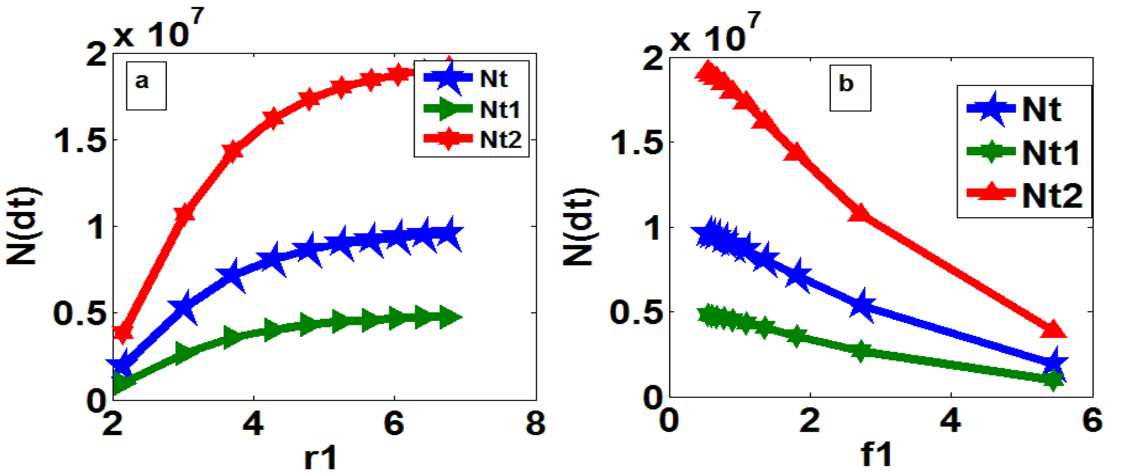

Figure-2:Relation between a) r1 &N(dt) b) f1&N(dt).

❖ Relation between final tumor cell density with tumor size and initial number of tumor cells:

Figure-3 shows the plotted relation between tumor size and cell tumor at (t_0) (no, no1 and no2) with Nt, Nt1 and Nt2.

The similar results observed in the previous section is supported here. The behavior of model for Nt, Nt1 and Nt2 is similar ether with tumor size (ss) or cell tumor at (to) (no, no1and no2) but not equivalent.

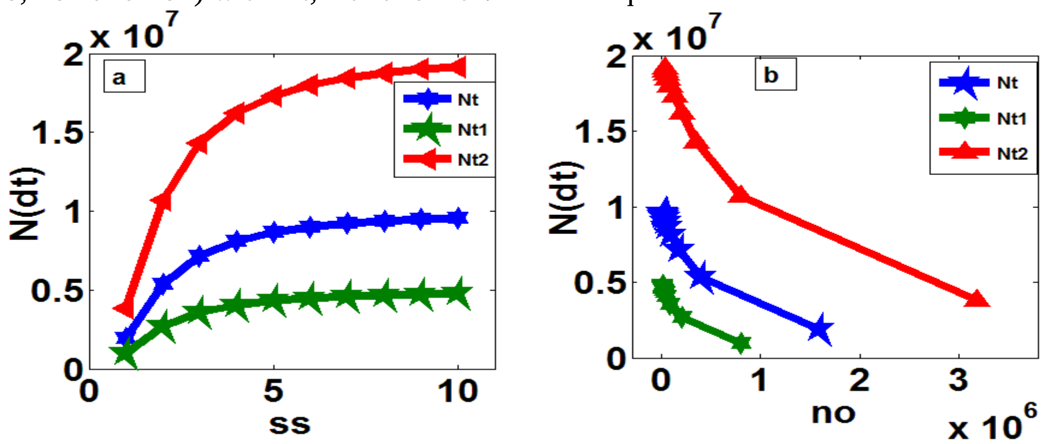

Figure-4: Relation between a) ss& N(dt) b) n0&N(dt).

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 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.

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