# A Short Review and the Prediction of Tumor Growth based on Numerical Analysis

**Abstract**

In this study, we consider Murray's and Glioma's tumor growth models based on reaction-diffusion equation. Mathematical modeling of tumor development are involved with the associated experimental work, reasoning the final relationship between experimental and theoretical approaches and these lead a path to model the prediction of tumor growth. We predict the tumor growth model using numerical study and the observation in different zone of time. The goal of tumor growth prediction is to model the tumor growth process, which can be achieved by theoretical mathematical modeling collaboration with the model personalization from clinical assessment. After certain time period, it is proven that the mathematical model shows the tumor cell population reaching a maximum cell number that the tissue can carry.

**Keywords:** Tumors growth; reaction-diffusion; spatial heterogeneity; numerical analysis.

**AMS subject classification (2010):** 92D25, 35K57 (primary), 35K61, 37N25.

## 1 Introduction

To predict the growth, volume and development of tumors, mathematical modeling is one of the most effective and accessible approach. In this paper, we will use the model based on reaction-diffusion equation. Even though tumors growth sounds like biological issues but scientists often have asylum to mathematical modeling in order to explain and illustrate these experimental discovery. Now-a-days, scientists are becoming aware of the possibilities offered by mathematical modeling of tumor development. Important thing is that, this investigation for mathematical modeling of tumor development are involved with the associated experimental work, reasoning the final relationship between experimental

and theoretical approaches and these lead a path to model the prediction of tumor growth. It is also noted that tumor growth is the abnormal growth of tissue, which usually involves cell invasion and mass effect [1, 2].

Despite internal complexity, tumor growth kinetics follow relatively simple laws that can be expressed as mathematical models. Murray concurs, asserting that the goal is to develop models which capture the essence of various interactions allowing their outcome to be more fully understood [3, 4]. Indeed, Byrne asserts that in order to develop effective treatments, it is important to identify the mechanisms controlling cancer growth, how they interact, and how they can most easily be manipulated to eradicate (or manage) the disease [5].

In order to gain such insight, it is usually necessary to perform large numbers of time-consuming and intricate experiments but not always. Through the development and solution of mathematical models that describe different aspects of solid tumor growth, applied mathematics has the potential to prevent excessive experimentation and also to provide biologists with complementary and valuable insight into the mechanisms that may control the development of solid tumors. Differential equation models paved the way into quantitative cancer biology about two decades ago.

In the present study, we will give a description on how reaction-diffusion equation are derived and how they can be utilized to simulate prediction of tumor growth. The goal of tumor growth prediction is to accurate model the tumor growth process, which is mainly achieved by physiological modeling and model personalization from clinical measurements. If accurate prediction can be achieved from non-invasive measurements, better treatment planning and patient prioritization can be determined, allowing more efficient use of resources. For example, if tumor doubling times of pancreatic neuroendocrine tumors can be estimated, the risk of metastatic disease, operative resection, and unnecessary testing can be better managed [6].

Furthermore, if phenotype or genotype information can be revealed from the personalized growth model, outcomes of drug treatments can be improved with reduced toxicity [1]. Tumor growth modeling is particularly pertinent for tumors that are either unresectable, or that are not removed until they reach a certain size threshold [6]. Therefore, image-based tumor growth modeling has been actively researched. Image-based tumor growth personalization requires three key components:

- a tumor growth model,
- medical images, and
- a parameter estimation algorithm.

The tumor growth model accounts for the general physiological properties derived from ex vivo, in vitro experiments, or in vivo animal tests which providing a powerful tool for tumor growth prediction. On the other hand, medical images provide the in-vivo measurements of the patient, revealing the structural or functional information of the underlying

physiological status. Through computational or mathematical algorithms, the complementary information from the model and images can be combined together to provide patient-specific tumor growth prediction.

The rest of the paper is organized as follows. In Section 2, we discuss the basic mathematical model of tumor growth without diffusion and their solutions behaviour. In Section 3, we putted various reaction-diffusion model of tumors growth and their initial study. In this portion, we consider the Murray's tumor growth model as studied in this paper. In the corresponding Section 4, the solution methodology and error analysis of Murray's reaction-dispersion equation is studied. Graphical presentation and the result discussions are presented in Section 5. Finally, in Section 6, we conclude the summery and discussion of the paper.

# 2 Preliminaries of Tumor Growth Model

The number of cancer cells in a tumor is difficult to estimate due to constant changes in time. Tumor cells may proliferate, rest in a quiescent state, or die. Describing the number of tumor cells as a function of time is therefore remarkably challenging. The number of living cells only changes when cells proliferate or die:
**Difference in live cells over time= number of cells created and died over time.** Consider the time difference, $dt$, where $d$ stands for difference and $t$ for time. Let us assume the cell cycle length of an arbitrary cancer cell is 24 hours. Then, over the course of one day, the probability that the cell divides is close to 100%. For a population of unsynchronized cells with a cell cycle length of 24 hours, we can assume that all cells divide once if $dt = 24$ hrs. We therefore must introduce the time difference as well as two parameters into the above equation [7]:

$$\frac{\text{difference in number of cells}}{dt} = \alpha(\text{number of cellls}) - \beta(\text{number of cells}) \tag{2.1}$$

Where $\alpha$ and $\beta$ are respectively understood as the fraction of dividing and dying cells at each $dt$, and hence denote the per capita growth and death rates of the total cell population.

Let us introduce variable $c$ as number of cells. The difference in cell number then becomes $dc$, and the equation (2.1) can be written as:

$$\frac{dc}{dt} = \alpha c - \beta c \tag{2.2}$$

Such equation is one of the basic tumor growth model presented via ordinary differential equation.

Let us assume that at time $t = t_0 = 0$, i.e. the starting point of an experiment, we have one million cells, i.e. $c = 10^6$ and the population growth dynamics can follow one of three facts as shown in Figure 1 [7]:

1. if $\alpha = \beta$, then $\frac{dc}{dt} = 0$. In this case the number of cells in the population does not change and the population exhibits a state of tumor dormancy. It is remark that

either $\alpha = \beta = 0$, that is all cells in the population are in state of cellular dormancy or quiescence, or $\alpha = \beta > 0$ in which case cell proliferation is balanced by cell death.

2. if $\alpha > \beta$ then $\frac{dc}{dt} > 0$ and the cell population will continuously grow with greater $\alpha - \beta$ rates yielding faster growth. On the other hand, the population will monotonically decrease.

3. if $\alpha < \beta$ and thus $\frac{dc}{dt} < 0$.

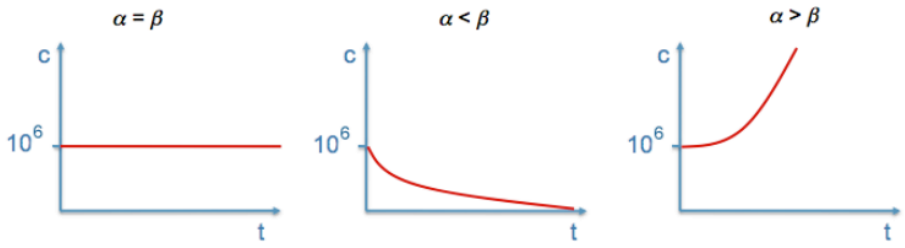


Figure 1: Growth dynamics of cell population $c$ over time $t$ for different relative rates of cell proliferation $\alpha$ and cell death $\beta$ when $c = 10^6$ at time $t = 0$ [7].

Equation (2.2) can be reduced to a one-parameter problem. The terms $\alpha c - \beta c$ can be combined by introducing the single parameter, $\lambda$, where $\lambda = \alpha - \beta$, which is called the net population growth rate. The differential equation describing cell population change over time is then

$$\frac{dc}{dt} = \lambda c. \tag{2.3}$$

As before, if $\lambda < 0$, $\lambda = 0$, or $\lambda > 0$ the population decreases, remains at constant, or increases, respectively.

The choice of a model is largely guided by the available data. In fact, observations at the microscopic scale are used to design very detailed mathematical tumour growth models [8] and those models are involving only the density of cells in the tumour:

$$\frac{du}{dt} = f(u) \tag{2.4}$$

where $u(t) > 0$ is the tumour cells density at time $t$ and $f \in C^1$ is a function describing the cells proliferation rate through general frameworks for tumour growth kinetics. Its expression is given by the generalized logistic equation:

$$f(u) = \rho u^{\alpha} \beta (1 - u^{(\frac{1}{\beta})})^{\gamma}$$

where $\alpha$ ,$\beta$, $\gamma$ are non-negative real numbers and $\beta > 0$. Standard models for the growth of brain tumours are classified according to the function $f$ and include:

$$f(u) = \begin{cases} \rho u & \alpha = 1, \beta = 1, \gamma = 0 \quad \text{Exponential} \\ \rho u(1-u) & \alpha = 1, \beta = 1, \gamma = 1 \quad \text{Logistic} \\ -\rho u \ln u & \alpha = 1, \beta \to +\infty, \gamma = 0 \quad \text{Gompertz} \end{cases} \tag{2.5}$$

where $\rho > 0$ is the proliferation rate.
The simplest growth assumes a linear relationship of the tumor cell density, resulting in exponential growth stating that cellular division obeys a cycle, with doubling time $\frac{\ln 2}{\rho}$ . This renders a biologically accurate description of tumor growth on time scales that are short in comparison to the life expectancy after the initial tumor development [9].

# 3 Description of the Model

## 3.1 Glioma Tumor Growth by Reaction-Diffusion Equation

The first attempts to model glioma tumor growth by means of a reaction-diffusion mathematical model [10] were performed by Cruywagen et al. [11], Tracqui et al. [12] and Woodward et al. [13] in order to account for the effect of therapies on glioma growth and later by Burgess et al. [14] to emphasize the importance of diffusion on glioma growth. The model is described by the following partial differential equation [10]

$$\frac{\partial c}{\partial t} = D\Delta c + S(c,t) - T(c,t),\ t > 0,\ c \in \Omega \tag{3.1}$$

where $c$ is the tumor cell concentration, $S(c,t)$ is a term that accounts for cellular proliferation and $T(c,t)$ represents the contribution of treatment and the proliferation term is set to produce an exponential growth, then equation (3.1) leads to

$$\frac{\partial c}{\partial t} = D\Delta c + \rho c \tag{3.2}$$

where $D$ is a diffusion coefficient that accounts for tumor invasiveness and $\rho$ is the tumor cell proliferation rate. The solution of equation (3.2) is restricted by the boundary condition that the flux of cells outside the brain or into the ventricles is zero

$$\vec{n} \cdot \nabla c = 0 \tag{3.3}$$

where $\vec{n}$ is a unitary vector normal to the cortical and ventricular surfaces. Experiments performed on rats demonstrated that glioma cells disperse more effectively along white matter axon tracts [15, 16, 17] than along neuronal cell bodies in gray matter, which leads to a variation of equation (3.2), proposed by Swanson et al. [18, 19, 20], which includes the spatial dependence of the diffusion coefficient $D$ such that

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(x)\nabla c) + \rho c \tag{3.4}$$

To evaluate the differences between grey and white matter motilities, Swanson et al. [18, 19, 21] used the Fisher approximation [10, 22] which stablishes that a travelling wave solution of equation (3.4) propagates with a terminal velocity given by

$$v = 2(\rho D)^{\frac{1}{2}} \tag{3.5}$$

Equation (3.5) allows for the estimation of the diffusion coefficient knowing the wave front propagation velocity and the proliferation rate, $\rho$.

## 3.2 Model with Spatial Heterogeneity

We can account for spatial heterogeneity in our model by taking the diffusion D to be a function of the spatial variable, $x$, thereby differentiating regions of grey and white matter. This gives,

$$\frac{\partial c}{\partial t} = \nabla \cdot (\mathrm{D}(x)\nabla c) + \rho c \tag{3.6}$$

We take zero flux boundary conditions on the anatomic boundaries of the brain and the ventricles. So, if $B$ is the brain domain on which the equation (4.24) is to be solved, the boundary conditions are

$$\mathbf{n} \cdot \mathrm{D}(x)\nabla c = 0 \quad \text{for } x \text{ on } \partial B \tag{3.7}$$

where $\mathbf{n}$ is the unit normal to the boundary $\partial B$ of $B$. With the geometric complexity of an anatomically accurate brain (which we shall in fact use) it is clearly a very difficult analytical problem and a nontrivial numerical problem, even in two dimensions.
We first nondimensionalise the spatially heterogeneous model, which as usual, also decreases the number of effective parameters in the system, and get some idea of the relative importance of various terms (without regard to units). To give some concept of the numbers involved there can be $10^{11}$ cancerous cells in a small tumour while the diffusion coefficient can be of the order 104 $cm^2/day$.
We consider the diffusion coefficients to be constant, but different, in each of the two tissues, the white matter and the grey matter. So, we have to solve

$$\frac{\partial c}{\partial t} = \nabla \cdot (\mathrm{D}(x)\nabla c) + \rho c \tag{3.8}$$

where

$$D(x) = \begin{cases} D_w & \text{for } x \text{ in white matter.} \\ D_g & \text{for } x \text{ in gray matter.} \end{cases} \tag{3.9}$$

and initial condition $c(x, o) = f(x)$.

## 3.3 Estimation of Survival Time

In reality, tumour cells can not be detected at very low densities. On a MRI, the profile of the tumour is defined by some nonzero level of resolution corresponding to a cellular density $c^*$ (roughly $40,000$ $cells/cm^2$) [24].
In the case of a constant growth rate $\rho$ and homogeneous diffusion $D(x) = D$,

$$\text{Survival Time} = t_{lethal} - t_{detect} = \frac{1}{\sqrt{D\rho}}(r_{lethal} - r_{detect})$$

where $r$ is the radius of the tumour. So, if the tumour is identified when it has a radius $r_{detect}$ and the tumour is fatal when it has a radius $r_{lethal}$.
This shows that $D$ and $\rho$ are both important parameters in determining survival time: increasing either $\rho$ or $D$ will decrease survival time.

# 4 Solution Methodology and Stability Analysis

We consider the numerical solution of the non-linear equations (3.6)-(3.9) considered in Sub-section 3.2 for tumour growth in a finite domain $B$ . The first step is to choose integers $n$ to define step sizes $h = \frac{b-a}{n}$. Partition the interval $[a, b]$ into $n$ equal parts of width $h$. Place a grid on the rectangle $R$ by drawing vertical and horizontal lines through the points with coordinates $(x_i)$, where $x_i = a + ih$ for each $i = 0, 1, 2.....n$ also the lines $x = x_i$ represent grid lines. We also assume $t_n = nt$ for $n = 0, 1....$ where $t$ is the time grid step size. We denote the exact and numerical solutions at the grid point $(x_m, t_n)$ by $c_n^m$ and $C_n^m$ respectively. To solve the problem, we consider the finite difference method. Let us first recall the governing equation to get it in non-dimensional form for simplicity:

$$c_t = Dc_{xx} + \rho c$$

where D is the diffusion constant, $\rho$ is the net proliferation rate in units $day - 1$ and $c(x, t)$ is considered as the density in space $x$ and at time $t$. It is also used as the logistic population growth models, chemical wave propagation models and neutron population models in nuclear reactors. The Murray's equation can be reduced to non-dimensional form with the scaling factors

$$t^1 = rt,\ x^1 = x/L,\ c^1 = c/k.$$

Then the equation becomes

$$c_t = c_{xx} + \rho c$$

To get the solution, we consider forward in time and center in space (FTCS) explicit scheme by substituting the forward difference approximation for the time derivative and the central difference approximation for the space derivative in the equation,

$$c = c_i^n,\ c_t = \frac{c_i^{n+1} - c_i^n}{p},\ c_{xx} = \frac{c_{i+1}^n - 2c_i^n + c_{i-1}^n}{h^2}$$

which leads to the following,

$$c_i^{n+1} = c_i^n(1 + \rho - 2R_1) + R_1(c_{i+1}^n + c_{i-1}^n)$$

where $R_1 = \frac{p}{h^2}$. Since the one dimensional diffusion-reaction equation is non-linear and wellposed, Lax's equivalence theorem indicates that consistency and stability of the FTCS finite difference approximation is necessary and sufficient for FD solution to converge to diffusion reaction equation . Once convergence has been proved, the solution to the given partial differential equation can be obtained to any desired degree of accuracy . Make sure the spacing $h$ for spatial and $p$ for time of the finite difference grid are made sufficiently small. The FTCS scheme is classified as explicit because the value of $c_i^{n+1}$ at the (n +1)th time level may be calculated directly from known value of $c_i^n$ at previous time levels. It is a two level method because values of $c$ at only two levels of time are involved in the

approximating finite difference equation.

**Error Analysis and Stability Test:**

To find accuracy of the FTCS scheme, we apply Taylors series on each term of the equation. Let us consider the Taylors series in the following way:

$$c_t = c_i^{n+1} - c_i^n$$

$$c_{xx} = c_{i+1}^n - 2c_i^n + c_{i-1}^n$$

Take above equation into account, and apply this scheme with Taylors series on each term, updated equation is as follows

$$\text{Eq} = (c_t - c_{xx} - c(1-c))p + \frac{1}{2}c_{tt}k^2 - R_1 c_{xx}h^2 + \frac{1}{6}c_{ttt}p^3 - \frac{1}{12}R_1 c_{xxxx} + .....$$

Now principle part of the truncation error is along with above equation. So first part of the above equation goes to zero if we consider the above equation.

$$\text{PPTE} \;\; of \;\; c = \frac{1}{2}c_{tt} - R_1 c_{xx}h^2 + \frac{1}{6}c_{ttt}k^2 - \frac{1}{12}R_1 c_{xxxx}h^4 + .....$$

Which shows that this scheme is first order accurate in time and 2nd order accurate in space, such as $O(k, h^2)$ .

We want to study under what condition the error can be magnified. Many methods can be used to study this issue. We consider only Von-Neumann stability analysis to explain this method on FTCS scheme. Consider the scheme in the following way

$$c_m^{n+1} = c_m^n + R_1 \delta_x^2 c_m^n + \rho c_m^n$$

According to Von-Neumann stability analysis, let us consider the solution as:

$$c_m^n = e^{\alpha np} e^{i\beta mh}$$

The Von-neumann stability condition is

$$|e^{\alpha p}| \leq 1$$

Note that,

$$c_m^{n+1} = e^{\alpha(n+1)p} e^{i\beta mh}, \; c_m^{n-1} = e^{\alpha(n-1)p} e^{i\beta mh}$$
$$c_{m+1}^n = e^{\alpha np} e^{i\beta(m+1)h}, \; c_{m-1}^n = e^{\alpha np} e^{i\beta(m-1)h}$$

Also

$$\delta_x^2 C_m^n = -4\sin^2(\frac{\beta h}{2}[e^{\alpha nk} e^{i\beta mh}]), \; \delta_x^2 C_m^{n+1} = -4\sin^2(\frac{\beta h}{2}[e^{\alpha(n+1)k} e^{i\beta mh}])$$

Apply above terms to the respective equation, we get the following

$$e^{\alpha k} = 1 - 4R_1 \sin^2(\frac{\beta h}{2}) + k(1 - const)$$

Since $|e^{\alpha p}| \leq 1$ which produces $-1 \leq e^{\alpha k} \leq 1$. Take left hand side of above equation along equation

$$1 - 4R_1 \sin^2(\frac{\beta h}{2}) + \rho \leq 1$$

which yields

$$R_1 \geq \frac{\rho}{4}$$

Similarly, from the right hand side of the equation, we obtain

$$R_1 \leq \frac{2+\rho}{4}$$

where $R_1 = \frac{p}{h^2}$. According to Von-Neumann stability analysis on both sides as left and right, it concludes that FTCS scheme is conditionally stable for Murray's equation.

# 5 Numerical Examples

In this Section, we recall our governing reaction-diffusion tumor growth model and introduce some constant values of $D(x)$ as considered in [25, 26].
The system is then modified to the particular partial differential equation

$$\frac{\partial c}{\partial t} = \nabla \cdot (\mathrm{D}(x)\nabla c) + \rho c$$

where,

$$D(x) = \begin{cases} D_g = 0.0013\, cm^2/day & 0 \leq x \leq 7.5 \text{ (gray region)} \\ D_w = 0.0065\, cm^2/day & 7.5 \leq x \leq 42.5 \text{ (white region)} \\ D_g = 0.0013\, cm^2/day & 42.5 \leq x \leq 50 \text{ (gray region)} \end{cases} \tag{5.1}$$

With the no-flux Neumann boundary conditions

$$c_x(0,t) = 0 \tag{5.2}$$
$$c_x(50,t) = 0 \tag{5.3}$$

and the initial condition is taken as Gaussian initial tumor profile:

$$c(0,x) = g(x) = \frac{1}{\sqrt{2\pi}\varepsilon} e^{-\frac{1}{2}(\frac{x-xo}{\varepsilon})^2} \tag{5.4}$$

where $c = c(t,x)$ denoted the tumor concentration of glioma cells at time $t$ and spatial location $x$ and $x_0 = 25cm$ (the middle of the considered interval) and $\varepsilon = 0.01$ suggested by Becker et al. [2]. Here, $\rho = 0.012$ is the net proliferation rate in units day-1 and Fickian diffusion has been used to quantify the random motility of a variety of invading cells (Cozens-Roberts et al [3]). A factor of 5, $D_w = 5D_g$, was used by Swanson et al. [21] but this may vary from patient to patient.

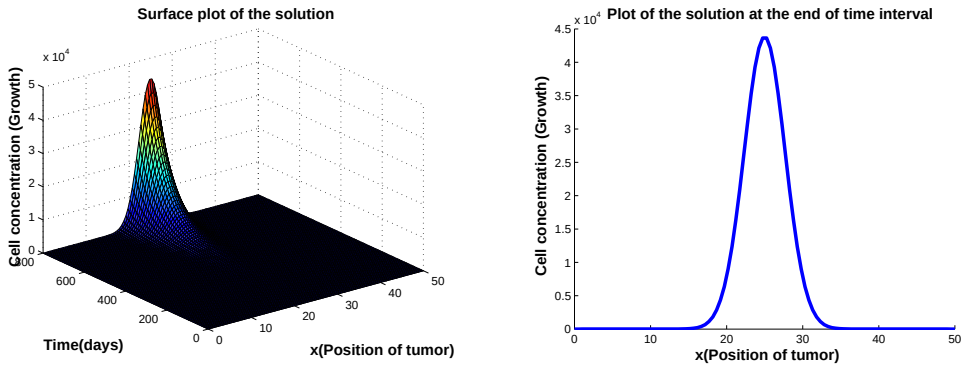


Figure 2: Comparative study at each moment (left diagram) and in the domain at time $t = T$ (right diagram).

To get the solution profiel, we introduce the programming language MATLAB. In Fig. 2, this is the growth of a tumour in 800 days with those boundary conditions and initial conditions. The mathematical model shows the tumor cell population reaching a maximum cell number that the tissue can carry. However, in reality, after this point, new mutations will continue to occur within the nuclear DNA, providing advantages in their proliferation, survival and invasion. We assume that the diffusion coefficient $D$ depends on the tissue environment, thus we consider $D$ as a function of $x$ having finite number of discontinuities and this results in the lack of smoothness in our model solution.

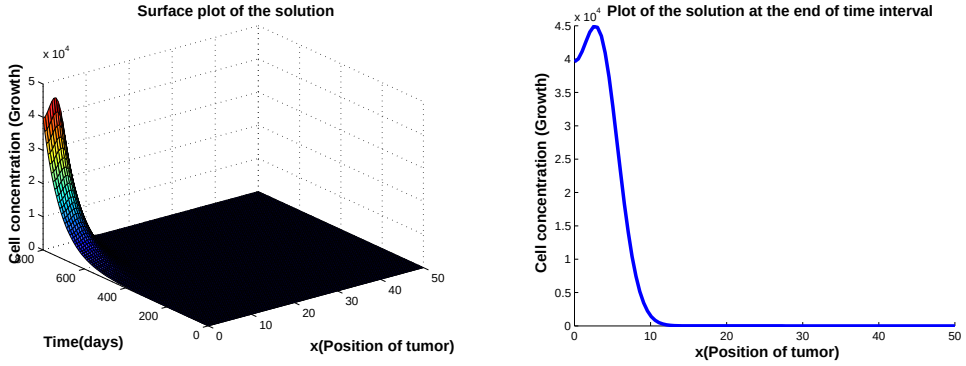


Figure 3: **(Zone 1)** $x_0 = 3$ **means** $x_0$ **in grey region and the corresponding growth result.**

Here in Fig. 2, we set $x_0 = 25$, which is the center of space for gaussian initial condition. If we vary the $x_0$ from grey region to white region, then we can see some difference.

So after these results, it is observed that initial location of a tumor is very important and plays the significant role to predict the growth.

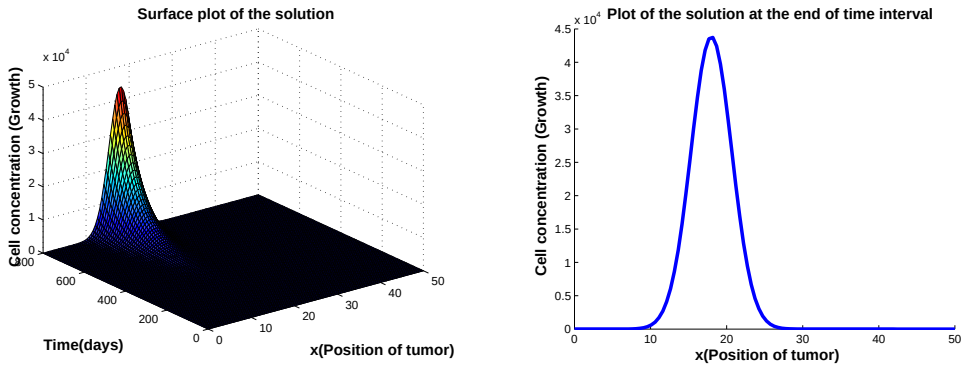


Figure 4: (**Zone 2**) $x_0 = 18$ **means** $x_0$ **in white region and the respective growth result.**

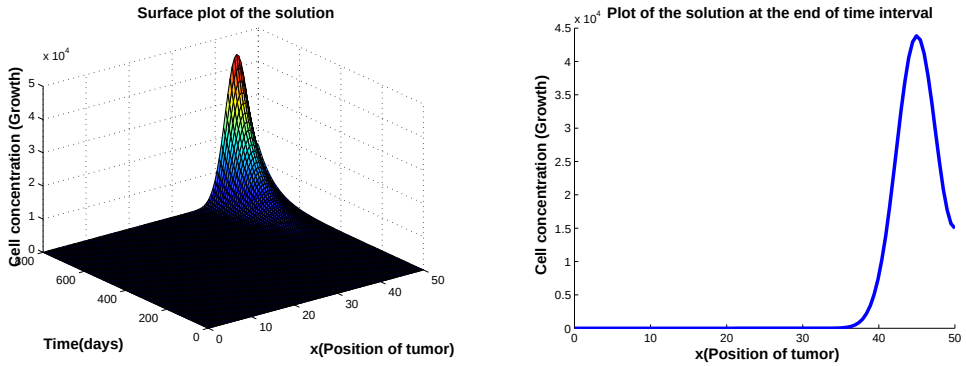


Figure 5: (**Zone 3**) $x_0 = 45$ **means** $x_0$ **in grey region and the corresponding growth result.**

# 6 Conclusion

In this paper, we study reaction-diffusion model using one dimensional equation regarding the growth of human tumors. We analysis the result numerically by Finite difference method. It is consider that the diffusion coeffitient is spatially distributed and we have also numerically studied the behavior of the evolution of tumor concentration of the Glioma in term of the speed of tumor cells for different center position values $x_0$ of Gaussian initial profile for each zone. Sequentially, we get a growth for 800 days in simulations and also get some result for different zones. It is seen that the difference for grey matter and white matter. Also, we observe that initial location of a tumour is very important to predict the growth. Without any laboratories test, we can predict about the growth of a tumour. This is the beauty of Mathematics and here is the collaborating scenario of Mathematics and Biology.

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