Numerical Study of Mathematical Model Related to Brain Tumor

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Abstract: Over the last few decades, there have been significant developments in clinical, theoretical and experimental approaches to understand the dynamics of tumor growth. In biological processes mathematical modelling is widely used to enhance the quantitative understanding of bio-medical phenomenon. Glioblastomas are one of the destructive primary brain tumors that are characterized by widespread infiltration into the brain and are highly resilient to treatment. The present work is the numerical study of the mathematical model related to the brain tumor using applications of the well-known differential quadrature method.

Keywords: Differential quadrature method, Gliomas, Coupled Fisher Equation, B-Spline.

I. Introduction

Mathematical modeling plays an important role in describing various phenomena that occurred in medical science, may it be the spreading of the infectious disease or the growth of abnormal cells in human body. The present work is an attempt to discuss the mathematical models that has been given by researchers to describe the condition of brain tumor along with the numerical simulation using differential quadrature method.

Tumor is like a swelling or morbid enlargement that results from an overabundance of cell growth and division. Tumor can be benign (non-cancerous) and malignant (cancerous). There are a lot of reasons for the cause of tumor mainly as inherited genetic defects, exposed to some chemicals or ionized radiation, lifestyle factors and many more[1]. When the cells in tumor are normal and will not spread to other tissues, it is defined as benign that grow slowly, but when cells are cancerous and can spread to other tissues and grow uncontrollably then it is malignant tumor. It usually grows rapidly and need aggressive treatment including surgery, radiotherapy or chemotherapy etc.

One of the conditions in which the abnormal growth of cells forms the mass of tissue within the brain is known as brain tumor. Brain tumor can be categorized into primary and secondary brain tumor. A primary brain tumor gets its origin in the brain from either the brain cells, nerve cells, glands or the membrane which surrounds the brain (i.e., meninges). Secondary brain tumors are always malignant and can spread from one body part to another thus lead to lung cancer, breast cancer, kidney cancer or skin cancer.

Gliomas is a term used for primary brain tumor that can be classified according to grade ranging from 1 to 4 [2]. Astrocytoma's (originated from abnormal astrocyte glial cells) are the least aggressive gliomas and are at the lowest grade in classification [3]. Low Grade Glioma (LGG) lies in grade 2, and patients of LGG have a survival period of greater than 5 years and are highly infiltrative, invasive and have low proliferation but Glioblastoma (GBM) patients that lie in grade 3 / 4 have less chances of survival [2], [4]. GBM is an aggressive type of primary brain tumor which derives its characteristics as invasion of normal brain tissue, cell proliferation and formation of necrotic core [5].
The treatment of brain tumor depends on the type, size, location and the stage of the tumor. The common treatment for malignant tumor is surgery. In surgery the tumor is removed as much as possible without damaging the healthy parts of the brain[6]. Sometimes the tumor is in that area which restricts to remove the entire tumor. So, partial removal of tumor is an option and is beneficial too. There are other methods like Radiation therapy and chemotherapy to cure the tumors[7] whose effectiveness has been studied with help of mathematical modeling.

Various mathematical models have been used for the study of brain tumors[8]–[12]. In most of these given models, the evolution of the tumor is anticipated to fall in the form of a nonlinear reaction–diffusion equation in which the rate of change of tumor cell density is written in terms of diffusion and growth of tumor cells. Fisher's equation (FE) is one of the differential equation that is used to model the slow growing brain tumor, whose location and size are being measured with the help of Magnetic Resonance Imaging (MRI) while the growth rate and diffusion coefficient of the cells are obtained from computerized tomography (CT) scans[6], [7]. FE helps to describe cancer cell destiny which changes over space and time where patient data is being compared with tumor growth rate[13], [14]. The general form of Fisher's equation is as follows:

$$\frac{\partial u(x,t)}{\partial t} = D\,\frac{\partial^2 u(x,t)}{\partial x^2} + \rho f\big(u(x,t)\big), \tag{1}$$

Here D represent the diffusion coefficient that shows the cell migration$[mm^2/years]$, ρ is the growth rate that governs proliferation rate$[years^{-1}]$ and $u(x,t)$ is the carrying capacity that signifies the maximum tumor cell density over space x $[mm]$ and time t $[years]$.

The present paper is focused on the application of the differential quadrature method with the trigonometric B-spline basis functions to discuss the numerical solutions of a mathematical model, a variant system of FE in coupled form that considered the impact of the tumor growth on the normal adjacent cells and discuss the rate of dead cells in response. The paper is organized in the different sections as follows: The models for the brain tumors are described in section two followed by the description of method in section three. In fourth section, the method implementation is discussed on the coupled system of equations. The numerical simulations are given with the interpretation of results with the help of figures in section five after which the remarks are given as conclusion in the last section.

II. Model for Brain Tumor

In this paper, the considered model for brain tumor is a simple description of invasion phenomenon in brain tumor dynamics with three positive relevant densities. The considered model is an extended form of FE with three coupled system of equations. The model is given as follows:

$$\frac{\partial u(x,t)}{\partial t} = \nabla.\big(D(x)\nabla u(x,t)\big) + \rho(x,t)\left(1 - \frac{u(x,t)+v(x,t)+w(x,t)}{u_*(x)}\right)u(x,t) - \alpha(x,t)u(x,t) \quad 2(a)$$

$$\frac{\partial v(x,t)}{\partial t} = -f(x,t,u(x,t),v(x,t),w(x,t)) \quad 2(b)$$

$$\frac{\partial w(x,t)}{\partial t} = f\big(x,t,u(x,t),v(x,t),w(x,t)\big) + \alpha(x,t)u(x,t) \quad 2(c)$$

Here, function $u(x,t)$ is a tumor cell density; $v(x,t)$ is a function of adjacent normal cells with negligible proliferation rate due to their differentiation state with the density of dead cells (necrotic core) denoted by function $w(x,t)$. This mathematical model is discussed by Arturo et.al[12] for the study of existence of the bright solitary waves during glioblastoma (GBM) using geometric perturbation theory.

In the above coupled system of equations, the nonnegative and continuous function $D(x)$ represent diffusion coefficient; $\rho(x,t)$ represent proliferation rate; $u_*(x,t)$ represent carrying capacity or maximum cell density that depend on space, but without loss of generality here it is taken as a constant. Tumor cell death rate is given by $\alpha(x,t)$ that depend on time and correspond to the administration of radiotherapy and/or chemotherapy. In average, the characteristic tumor cell life is $\frac{1}{\alpha}$. For tumor growth it is necessary that ρu_*must be greater than α.

On putting, $v = w = \alpha = 0$, in equation 2(a-c) results in the form of the standard Fisher-Kolmogorov equation (FKE). This is another differential equation which is framed as a result of the mathematical modeling for the study of brain tumors [15]. It is a simple nonlinear reaction-diffusion equation that helps in determining diffusion coefficients of the cells in terms of the growth rate of tumor cells along with linear velocity[7]. FKE appears in description of many phenomenon such as gene propagation, population growth-diffusion of organisms, spread of infectious disease, traveling waves, tissue engineering, thermo-nuclear reaction and many more[16], [17]. Description of brain tumor dynamics is one of the most important applications of FKE. It has been considered in two main features of tumor cells: diffusion and proliferation. FKE helps in determining diffusion coefficients of the cells in the terms of growth rate of tumor cells along with linear velocity which is given as $v = 2\sqrt{\rho D}$ where v is linear velocity, ρ and D are linear growth rate and diffusion coefficient respectively. [18].

This equation was proposed by Fisher and Kolmogorov (1937) as the natural extension of the logistic growth population with $f\big(u(x,t)\big) = \rho u(1-u)$. It is also a deterministic version of a stochastic model for the spatial spread of gene propagation and has been widely studied for travelling wave solutions. The classic simplest version of FK equation is given as:

$$\frac{\partial u(x,t)}{\partial t} = D\,\frac{\partial^2 u(x,t)}{\partial x^2} + \rho u(x,t)(1-u(x,t)) \quad (3)$$

The value of D *and* ρ can be derived from parameter estimation tumor techniques or with the help of analytic expression of parameters that is a result from an approximation of Fisher's equation and can be calculated from MR images.

III. Description of the method

One of the well-known numerical methods for solving differential equations is differential quadrature method. This method is used to approximate the spatial derivative of the function at the grid points of the domain as the weighted sum of the values at the computational domain. Consider the discretization of the spatial coordinates: $x_i, i = 0, 1, 2, \ldots, N$, using N grid points with uniform step length.

The numerical value of the first and the second derivatives at a point xi is given by the following equations:

$$u_x(x_i,t) = \sum_{j=1}^{N} v_{ij}u(x_j,t);\ i = 1-N,\ j = 1-N$$

$$u_{xx}(x_i,t) = \sum_{j=1}^{N} w_{ij}u(x_j,t);\ i = 1-N,\ j = 1-N$$

where V_{ij} and W_{ij} represents the weighting coefficients of the first and the second derivatives.

Many researchers have contributed to find these weighting coefficients by various approaches. For example Shu's approach[19], Bellman's approach [20], Quan and Chang's approach[21]. Out of these famous approaches, Shu's approach is a general one that allows the different test functions to be used as basis function. Some of the famous basis functions are Lagrange polynomial, Legendre polynomial, Spline functions[22] sine-cosine expansions and polynomial based differential quadrature method[23], [24].

3.1. Trigonometric B-Spline Differential Quadrature Method

Let $TB_i(x)$ define the trigonometric cubic B-splines with knots at the points $x_i, i = 0, 1, 2, \dots, N$ on domain $[a, b]$. The splines are arranged as a span given by $\{TB_{-1}, TB_0, TB_1, \dots, TB_{N_1}, TB_{N_1+1}\}$ over the domain. The approximate solution is given by $U(x_i, t)$ for $i = 1, 2, \dots, N$ at each node point.
The cubic trigonometric basis $TB_m(x)$, is defined as:

$$TB_m(x) = \frac{1}{w}\begin{cases} A^3(x_m), & if\ x \in [x_m, x_{m+1}) \\ B(x_m)\big(A(x_m)B(x_{m+2}) + B(x_{m+3})p(x_{m+1})\big) + B(x_{m+4})A^2(x_{m+1}), & if\ x \in [x_{m+1}, x_{m+2}) \\ B(x_{m+4})\big(A(x_{m+1})B(x_{m+3}) + B(x_{m+4})p(x_{m+2})\big) + B(x_m)B^2(x_{m+3}) & if\ x \in [x_{m+2}, x_{m+3}) \\ B^3(x_{m+4}), & if\ x \in [x_{m+3}, x_{m+4}) \\ 0, & otherwise \end{cases}$$

where $A(x_m) = \sin\left(\frac{x-x_m}{2}\right)$, $B(x_m) = \sin\left(\frac{x_m-x}{2}\right)$, $w = \sin\left(\frac{h}{2}\right)\sin(h)\sin\left(\frac{3h}{2}\right)$ and $h = \frac{b-a}{N}$ and $TB(x_m)$ is a piecewise trigonometric function having properties such as C^∞ continuity, non-negativity and partition of unity[25]. The values trigonometric functions along with their derivatives are tabulated as follows:

$$\begin{aligned} TB_m(x_{m-1}) &= a1; \quad TB_m(x_m) = a2;\ TB_m(x_{m+1}) = a1; \\ TB'_m(x_{m-1}) &= a3; \quad TB'_m(x_m) = 0;\ TB'_m(x_{m+1}) = a4; \\ TB''_m(x_{m-1}) &= a5; \quad TB''_m(x_m) = a6;\ TB''_m(x_{m+1}) = a5; \end{aligned}$$

The constants a1 to a5 can be given with $\frac{h}{2} = d, \frac{3h}{2} = e$ as follows:

$$a_1 = \frac{\sin^2(d)}{\sin(h)\sin(e)}, a_2 = \frac{2}{1+2\cos(h)}, a_3 = -\frac{3}{4\sin(e)}, a_4 = \frac{3}{4\sin(e)},$$
$$a_5 = \frac{3(1+3\cos(h))}{16\sin^2(d)(2\cos(d)+\cos(e))}, \quad and\ a_6 = -\frac{3\cos^2(d)}{\sin^2(d)(2+4\cos(h))}$$

IV. Numerical Solutions of Coupled Fisher Equation

Differential quadrature method with trigonometric B-Spline basis function[25] has been implemented successfully to discuss the numerical solution of various well-known partial differential equations such as nonlinear Schrödinger equation, hyperbolic telegraph equation, Burger's equation, Fisher's equation in 2-dim, Cable equation etc.

To apply the discussed approach, let the domain is divided into uniform partition by the grid space using the knots $x_i$such that $a = x_0 < x_1 < x_2 < \dots < x_n = b$.

The numerical values of space derivatives are calculated using the relation given by:

$$U_x = \sum_{j=1}^{N} p_{ij}u(x_j, t), \quad U_{xx} = \sum_{j=1}^{N} q_{ij}u(x_j, t), \quad i = 1, 2, \dots, N_1$$

where $p_{ij}, and\ q_{ij}$are the weighting coefficients used to approximate space derivatives with respect to x.

On substituting the value of derivative of the function u(x, t) in equation 2(a) results in the coupled system of equation as a coupled system of ordinary differential equation. This obtained system of ODEs can then be solved using any numerical approach. Here RK method is used to solve the coupled system of equations that leads to the solution at different values of time (in days) to obtain the tumor cell density $u(x, t)$, the behavior and growth of adjacent normal cells given by $v(x, t)$ and $w(x, t)$ that define the density of dead cells. To consider the dependency of the adjacent cells growth and death on the growth rate of tumor cells the function is taken as $f = \gamma u(x,t)v(x,t)$ in equation 2(b) and 2(c) where γ represents the invasion parameter.

V. Numerical Simulation

To discuss and analyze the presented mathematical model of brain tumor, the related parameters to tumor growth are generally considered from mathematical models and the references therein. For numerical simulation the values are taken as follows: diffusion coefficient D = $v^2/4\rho = 0.0013 cm^2/day^{-1}$ [26], for cell proliferation rate, $\rho = 0.012\ day^{-1}$ [27], death rate $\alpha = 0.0196\ day^{-1}$ [28] and invasion parameter $\gamma = 0.25\ day^{-1}$ [3] and maximum cell density, u_* = 1.

For numerical simulation the initial values are taken as $u(x,0) = 0.1\,\mathrm{sech}(5x)$, $v(x,0) = v_* = 0.4, w(x,0) = 0$ with all densities are measured in units of u_*.

The obtained numerical solutions for the above discussed parameters are represented in form of figures Figure 1-3 for the values of time at t=15, 30, 60, 90, 120, 150 and 180 (days). From the pattern shown by the behavior of the solution for u, v *and* w it can be concluded that the tumor cells first proliferate without any diffusion in the initial phase but later on when diffusion starts, number of cells replicates, and tumor cell density raised to 0.1 where after 30days tumor cell density hit around 0.6 as shown in Figure 1. At the initial location when time increases as 60days, it touches maximum about 0.35 then came back to 0.26 as cells could not survive longer as space saturates due to gathering of dead tissue and tumor cells. The behavior is being moved in periodic waves with the increase of time, it first proliferate and then gather at the initial location.

For adjacent normal cells, the behavior is shown by $v(x,t)$ with initial values 0.4 in Figure 2. At T=15 days, the cell density observed to be 0.4 with a minute fall in the values at x=0, whereas at T=30days it is observed that cells density reduced to 0.2. As the time progresses from 60 days, the normal cell density gets reduced to zero at the initial location with growth of tumor cells and continue depleting with time.

Similar behavior is shown by the dead cell density in Figure 3. It can be seen that with increase of time T, dead cells density increases. Initially at T=15 days, dead cells density is observed to be zero where at T =30, it raised to 0.3. For different time T = 60, it reaches around 0.7 and for T=90, it is 0.9 but with increase in the time from 120 to 180 days the dead cell density approaches 1 and shows in periodic waves pattern in space.

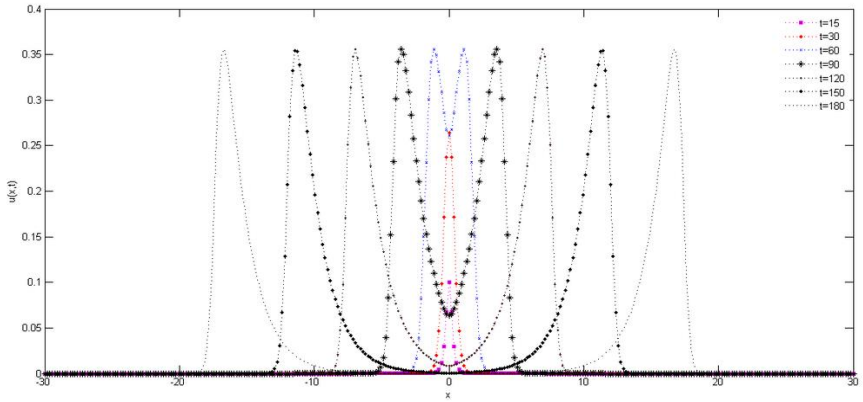

Fig. 1. Time dependent profile for tumor growth u(x,t) at different time period (days).

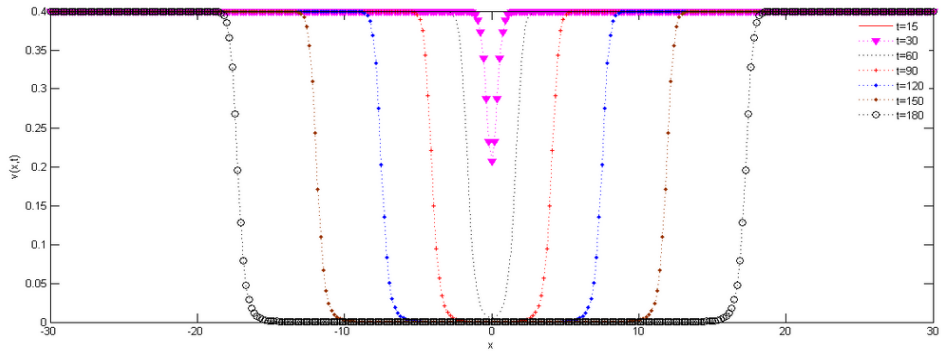

Fig.2. Time dependent profile for tumor growth v(x,t) at different time period (days).

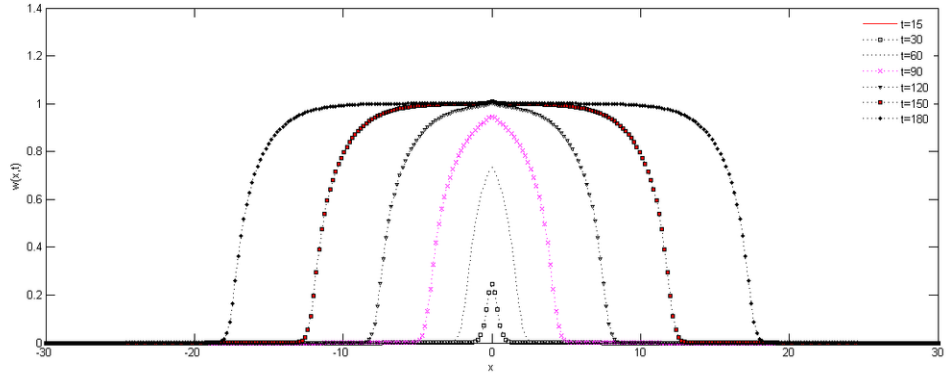

Fig. 3. Time dependent profile for tumor growth w(x,t) at different time period (days).

VI. Conclusion

Glioblastomas is one of the malicious forms of the primary brain tumors which proliferate and invade widely. From the presented mathematical model for the growth of glioma, the effect of the cell density or carrying capacity is investigated for the effect on the solution of the given coupled model of the brain tumor for various parameters. The taken parameters are the real values from the literature where the data has been collected from the patients. For the numerical simulation the well-known numerical approach of differential quadrature method is implemented with trigonometric cubic B-spline basis function. The performed numerical simulations are showing the behavior of the cell density for normal cells, the dead cells and the cells adjacent to the tumor. The present analysis is helpful to medical professionals in understanding the effects of the various factors effective in brain tumor. The present model results are similar as given by the researcher who developed this model and can be further verified in presence of available clinical studies.

VII. Acknowledgement

To be inserted

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