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COMPUTATIONAL MODELLING OF SOLID TUMOR GROWTH

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ABSTRACT

In this article we review some of the recent developments in mathematical modeling of tumor. Despite internal complexity, tumor growth kinetics follow relatively simple laws that can be expressed as mathematical models. Parabolic partial differential equations with nonlocal boundary conditions arise in modeling of tumor invasion. The 2D diffusion equation allows us to talk about the statistical movements of randomly moving particles in two dimensions. The movement of each individual particle moving in a Brownian (diffuse) way does notfollow the diffusion equation. However, many identical particles each obeying the same boundary and initial conditions share some statistical properties dealing with their spatial and temporal evolution. In this paper, we present the implementation of positivity preserving Padé numerical schemes to the two-dimensional diffusion equation with nonlocal time dependent boundary condition. The goals were threefold: 1) to conclude a mathematical model for description of the measurement error, 2) to establish the descriptive power, using several goodness-of-fit, and 3) to measure the models' ability to estimate future tumor growth. We successfully implemented these numerical schemes and the numerical results show that these Padé approximation based numerical schemes are quite accurate and easily implemented.

Key Words: Positivity preserving Padéapproximation, Solid tumor growth, Reaction-diffusion equations

I. INTRODUCTION

Cancer is the second most fatal disease worldwide after heart disease [1]. A cancer cell evolves from normal due to genetic mutations, which abnormally alter the cell proliferation rate. In particular, glioma is a rapidly evolving type of brain cancer, well known for its aggressive and diffusive behavior [2]. This diffusive invasion has lead several research efforts to explore the tumor's progression with the aid of mathematical diffusion equations [3-5], aiming to predict its spatial and temporal evolution. The high diffusion rate of tumor cells from the core tumor into the surrounding brain tissue often leads to treatment failure and tumor recurrence, even after the surgical resection. Brain tumor vary from low- to high-grade, namely glioblastomas, which constitute the most malignant form of brain cancer, having an extremely poor prognosis.

In parallel to identification of tumor characteristics, the prediction of tumor growth and diffusion can lead to useful insight into the disease dynamics, which may improve clinical outcomes. To this respect, several mathematical and computational models have appeared in the literature, which investigate the mechanisms that govern tumor's progression and invasion, with the aim of predicting its future spatial and temporal evolution, with or without the effects of therapy [7]. The models may constitute valuable tools for assisting the clinical practice towards the optimal individualized treatment, while facilitating medical research analysis.

II. MATHEMATICAL STRUCTURE

The tumor growth has been usually modeled as a reaction diffusion process in the many literature. Jones et al. [1] have given a simple tumor model based upon this idea. A model describing the growth of the tumor in brain taking into account diffusion ormotility as well as proliferation of tumor cells has been developed in a series of papers [2, 3]. In continuation of this approach, Tracqui et al. [4] suggest a model which takes into account treatment and thus killing rate of tumor cells along with the above factors.The governing equation in this case is

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2}\right) + Mc - Nc \tag{1}$$

Where $c$is the concentration of tumor cells, $D$is the diffusion coefficient, M is the proliferation rate, and N is the killing rate.

Assuming complete radial summery, Moyo and Leach [3] have studied this model with $K(c,t) = M - N$being variable.

The resulting governing equation reduces to the simple form,

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2}\right) - Kc \tag{2}$$

The present study is based upon the fact that the diffusivity is not necessarily a constant and may depend upon the concentration of tumor cells. Moreover, the net killing rate $K$is also taken to be c-dependent. This introduces nonlinearity in the governing equation. Keeping these assumptions in mind (1) becomes,

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2}\right) - K(c)\, c, \tag{3}$$

Where D(c) is the diffusivity of the medium and K(c) is the net killing rate. One may refer to [7–10] for a good account of this method. Some recent studies in nonlinear diffusion equations using this approach can be found in [1, 6].

Modeling assumptions:

The following modeling assumptions are made (from a biological viewpoint) in order to specify the exact form of Eq.2 for each of the continuum model field variables Pertaining to the tumor cells (living and dead).

1. Living tumor cells proliferate (cellular mitosis) only if the levels of nutrient reaching them are sufficient (i.e., above a certain threshold)

2. Living tumor cells die if the levels of nutrient reaching them are too low. (i.e., below the threshold)

3. Once a number of living cells inside the tumor have died due to insufficient nutrient, the nutrient becomes sufficient for the remaining ones to survive; thus, there is a smooth transition to a necrotic region;

4. When crowded by their neighbors, the living tumor cells have the ability to migrate towards lower density areas where they have higher chances of surviving and proliferating;

5. Dead tumor cells do not move;

6. Dead tumor cells are assumed to naturally disintegrate into waste products (water).

III.DESCRIPTION OF METHOD OF SOLUTION

The two-dimensional parabolic partial differential equation with nonlocal boundary conditions arise in many important applications in sciences. In recent years, a number of numerical techniques for solving two-dimensional parabolic partial differential equations with nonlocal boundary condition have been studied.

In this paper, we consider the implementation of positivity preserving Padé schemes for two dimensional diffusion equations with nonlocal boundary conditions. $(0, 2m-1)$-Padé schemes are known as positivity-preserving Padé schemes. The name "Positivity-Preserving Padé" was given by Wade et al. [13]. The positivity-preserving Padé schemes are relatively a new research area; they have captured the interest of mathematicians and scientists. In the past few years, much attention has been devoted to the development of positivity-preserving schemes. The concept of positivity has emerged prominently because it has been found to be an important factor in controlling spurious oscillations.

The outline of this paper is as follows: In section 3.1 we will give a brief review of Padé approximants. In section 3.2 we will discuss the positivity-preserving Padé schemes. In section 4 we present numerical experiments. Concluding remarks are given in section 5.

3.1 PADE` APPROXIMANTS

Padé approximants are generalizations to power series approximations. If $P_n\ (x)$and $Qm\ (x)$ are polynomials of degree *n* and *m* respectively, then " $\frac{P_n\ (x)}{Qm\ (x)}$ is a Padé approximation of a function *f* (*x*) " means that

$$f(x) = \frac{P_n\ (x)}{Qm\ (x)} + O(x^{n+m+1})$$

As in [34], Padé proposed that one can find the closest approximation to a given series $\sum_{k=0}^{\infty} c_k x^k$by defining a rational function,

$$R_{n,m}(x) = \frac{P_n\ (x)}{Qm\ (x)}$$

Where,

$$P_n(x) = \sum_{k=0}^{\infty} c_k x^k$$

and

$$Qm\ (x) = 1 + \sum_{k=1}^{\infty} c_k x^k$$

Let $f\ (z)$ be analytic in a region of the complex plane containing the origin $z = 0$. A Padé approximation $R_{n,m}(x)$to the function $f\ (z)$ is defined by,

$$R_{n,m}(z) = \frac{P_n\ (z)}{Qm\ (z)}$$

Where $Pn\ (x)$ and $Qm\ (x)$ are polynomials in *z* of degree *n* and *m* respectively with leading coefficients unity. For eachpair of non-negative integers *n* and *m*,$Pn\ (x)$ and $Qm\ (x)$are those polynomials for which the Taylor series expansion of

$Rn,m\ (z)$about the origin agrees with the Taylor series expansion of $f\ (z)$ for as many terms as possible. Since the ratio contains essentially $(n + m + 1)$ unknown coefficients, the requirement that $Qm\ (z)f(z) - P_n(z) = O(|z|^{n+m+1})$ gives rise to $(n + m + 1)$ linear equations for these coefficients.

In the present work, we utilized (n, m) $-$Padé approximations for $f(z) = e^{-z}$following.ThePadé approximant $R_{n,m}\ (z)$ to the exponential function is defined as for $f(z) = e^{-z}$follows:

Let,

$$R_{n,m}(z) = \frac{P_n\ (z)}{Qm\ (z)}$$

where

$$P_n(z) = \sum_{j=0}^{n} \frac{(n + m - j)!\, n!}{(m + n)!\, j!\, (n - j)!} (-z)^n$$

and

$$P_n(z) = \sum_{j=0}^{m} \frac{(n + m - j)!\, m!}{(m + n)!\, j!\, (n - j)!} (z)^n$$

Satisfying

$$R_{n,m}(z) = e^{-z} + \ O(|z|^{n+m+1})$$

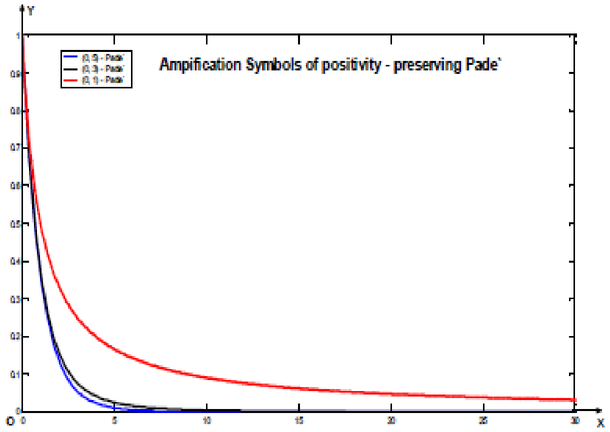
We will call $R_{n,m}\ (z)$ as (*n*,*m*)-Padé scheme of order (*n* + *m*).

3.2 POSITIVITY-PRESERVING PADE` SCHEMES

The positivity-preserving schemes are relatively a new research area; they have captured the interest of mathematicians and scientists. The notion of a positive scheme was introduced as a refinement of 0 L-stability. A positive scheme has a positive symbol on the positive real axis and is monotonically decreasing to 0. In the past few years, much more attention has been devoted to the development of positivity preserving schemes and the concept of positivity has come out prominently because it has been found to be an important factor in controlling spurious oscillations. Wade et al. [21] has discussed many application problems, taken from the literature, reflecting the importance of positivity-preserving schemes and concluded the increasing interest of researchers in the development and application of positivity-preserving related work. Wade et al. [13, 14] and Siddique [25] have used the positivity preserving Padé schemes to construct smoothing schemes for parabolic partial differential equations.

Definition 3.1: A numerical scheme is called positivity preserving if the graph of its stability function stays above x-axis and converges to zero monotonically. The (0, 2*m* -1)-Padé schemes are positivity-preserving schemes where *m* = 0,1,2,….. (0,1)-Padé, (0,3)-Padé, (0,5)-Padé, etc are all positivity-preserving Padé` schemes.

The graphs of amplification symbols of (0,1)-Padé, (0,3)-Padé, (0,5)-Padé are shown in Figure 1.



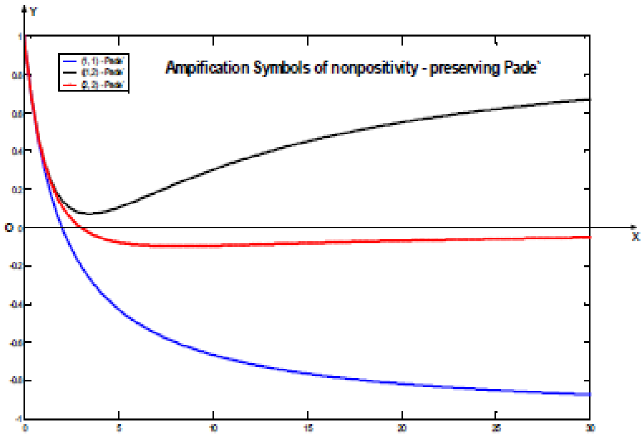


Figure 1. Positivity preserving Padé` ***Figure 2. Non-positivity preserving Padé***

(1,1)-Padé, (1,2)-Padé and (2,2)-Padé are nonpositivity-preserving Padé. The graphs of amplification symbols of (1,1)-Padé, (1,2)-Padé and (2,2)-Padé are shown in Figure 2.

The (n,m)-Padé approximation of $e^{-kA}$is approximated by

$$e^{-kA} \approx \left(Q_m(kA)\right)^{-1} P_n(-kA) \equiv R_{n,m}\,(kA)$$

where$k$is the time step.

Approximating the matrix exponential $e^{-kA}$by (0,1)-Padé, denoted by $R_{0,1}(kA)$to give

$$v_{n+1} = (I + kA)^{-1} v_n$$

which is the backward Euler's method.

(0,3)-Padé approximation to the matrix exponential e^{-kA} is given by

$$v_{n+1} = (I + kA + \frac{1}{2}k^2A^2 + \frac{1}{6}k^3A^3)^{-1}v_n$$

(0,5)-Padé approximation to the matrix exponential e^{-kA} is given by

$$v_{n+1} = (I + kA + \frac{1}{2}k^2A^2 + \frac{1}{6}k^3A^3 + \frac{1}{24}k^4A^4 + \frac{1}{120}k^5A^5)^{-1}v_n$$

The matrix *A* is a tridiagonal matrix. The number of diagonals of A increases with the powers of *A*. For example A^2 is a five diagonal matrix, A^3 is seven and A^4 is a nine diagonal matrix and so ill-conditioning of the matrix *A* comes into picture.

Definition 3.2: The condition number of a matrix *A* denoted by $cond(A)$ and is defined by

$$cond(A) = \|A\|\|A^{-1}\|$$

The condition number of a matrix measures the sensitivity of the solution of a system of linear equations to errors in the data.It gives an indication of the accuracy of the results from matrix inversion and the linear equations solutions..

3.3 PARAMETER ESTIMATION

Step 1. For $i = 1,2,3 \ldots q_1 + q_2$, solve $(kA - c_i I) = v_i = v_s$ in parallel.

Step 2. Compute

$$v_{n+1} = \sum_{i=1}^{q_1} w_i v_i + 2\sum_{i=q_1+1}^{q_1+q_2} Re(w_i v_i)$$

We have used this algorithm for the implementation of our Padé schemes. Maple is used to compute the poles and weights of Padé approximants. The poles and weights for (0, 3)-Padé are as follows:

$c_1 = 1.5960716379833,\ w_1 = 1.475686517795720,$

$c_2 = -0.7019641810083 - 1.807339494452i, \quad w_2 = -0.7378432588979 + 0.365017840801i$

For (0,3)-Padé, we have q_1=q_2=1 and the algorithmsolve

$$(kA - c_1 I)y1 = v_s \ and \ (kA - c_2 I)y2 = v_s$$

and compute

$$v_{s+1} = w_1 y_1 + 2Re(w_2 y_2)$$

IV.NUMERICAL SOLUTION AND RESULT

In this section we present the performance of positivity preserving Padé schemes by implementing these schemes to solve three problems from literature. Twizell et al. [25], Ishak [26] and many others considered these problems as test problems. We have considered both homogeneous and inhomogeneous problems. All positivity-preserving Padé schemes are implemented by using partial fraction decomposition techniques described earlier. We present graphs of the exact and numerical solution of different parameter values.

Consider the resulting governing equation reduces to the simple form that is given by,

$$\frac{\partial c}{\partial t} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2}\right) - Kc$$

in which $c = c(x, y, t)$, with Dirichlet time-dependent boundary conditions on the boundary $\partial\mathbb{S}$of the square $\mathbb{S}$defined by the lines $x = 0, y = 0, x = 1, y = 1$, given by

$$c(0, y, t) = e^{(y+2t)}, 0 \le t \le T, 0 \le y \le 1$$

$$c(1, y, t) = e^{(1+y+2t)}, 0 \le t \le T, 0 \le y \le 1$$

$$c(x, 0, t) = e^{(x+2t)}, 0 \le t \le T, 0 \le x \le 1$$

$$c(x, 1, t) = e^{(1+x+2t)}, 0 \le t \le T, 0 \le x \le 1$$

and nonlocal boundary condition

$$\int_0^1 \int_0^1 c(x, y, t)\, dx dy = (e-1)^2 e^{2t}$$

with initial conditions $c(x, y, t) = e^{x+y}$.

Theoretical solution is given by $c(x, y, t) = e^{x+y+2t}$

x	y	Numerical Solution	Exact Solution	Errors
0.0	0.0	7.38905610	7.38905610	0.0000e+000
0.1	0.1	9.04041689	9.02501350	1.7038e-003
0.2	0.2	11.06951484	11.0231763804	6.0224e-003
0.3	0.3	13.54531347	13.46373804	6.0224e-003
0.4	0.4	16.55780082	16.44464677	6.8339e-003
0.5	0.5	20.21997846	20.08553692	6.6489e-003
0.6	0.6	24.67258833	24.53253020	5.6767e-003
0.7	0.7	30.09034598	29.96410005	4.1956e-003
0.8	0.8	36.69004490	36.59823444	2.5023e-003
0.9	0.9	44.74237856	44.70118449	9.2069e-004
1.0	1.0	54.59815003	54.59815003	0.0000e+000

Table 1. Exact and Num. Sol. for (0, 1) – Padé

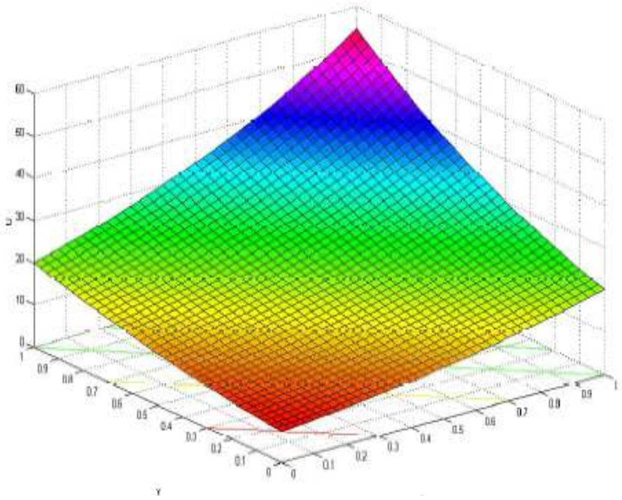


Figure 3. Graph of (0, 1) – Padé

Table:1 and Figure:3 show the numerical and exact solution for Padé (0, 1),

V.CONCLUSIONS

The need for Reaction-Diffusion equation of space and time while modeling cancer tumor with profile treatment is the major concern of this paper. To do this, we successfully implement the positivity-preserving Padé numerical schemes and implementation of these schemes on two dimensional diffusion equations with nonlocal boundary conditions on four boundaries. We also affirm that the therapy-dependent killing rate K need not be a function of time or of both position and time only but could be dependent on the concentration of the cancer cells. We considered a test problems taken from the literature. To verify the accuracy of these schemes, the absolute relative errors between the exact and numerical solutions are computed. Numerical results show that these schemes are efficient and provide very accurate results.

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