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Glioblastoma neurological diffusion comparative medecinal study using finite element method (FEM) and boubaker polynomial expansion scheme (BPES)

M.Garshasbi[1], K.Boubaker[2]*

[1]School of Mathematics & Computer Sciences, Damghan University, Damghan, (IRAN)

[2]ESSTT/ 63 Rue Sidi Jabeur 5100, Mahdia, (TUNISIA)

E-mail: mmbb11112000@yahoo.fr

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ABSTRACT

In this paper, a continuum mathematical model of Glioblastoma neurological diffusion has been developed in order to identify and characterize discrete cellular mechanisms underlying altered cells motility. The mathematical model has been treated by two different methods: Finite Element Method (FEM) and Boubaker polynomial expansion scheme (BPES). The Finite Element Method has been emphasized as a platform for discretization of a basic parabolic equation using variational analyses and Fourier transform. The same parabolic model has been subjected to the Boubaker polynomial expansion scheme analyses in order to monitor the evolution of tumor from the non-vascular stage to the vascular one. Obtained results have been successfully compared to some recently proposed profiles.

KEYWORDS

Glioblastoma;
Diffusion;
Mathematical modeling;
Motility.

INTRODUCTION

Gliomas are highly diffuse brain tumors that grow by invading adjacent tissues[11,27,28]. They occur in the brain by altration of glial cells which are support cells of the central nervous system.

While glial cells can belong to several families of cells, most gliomas are made up of either oligodendrocytes or astrocytes, thus, these tumors are also frequently called Oligiodendrogliomas or Astrocytomas, respectively.

High grade (malignant) forms of these gliomas are called Glioblastoma Multioforme (GBM), Anapalastic Astrocytoma, and Anaplastic Oligodendroglioma. They are considered fast growing, rapidly invading nearby tissue (Figure 1).

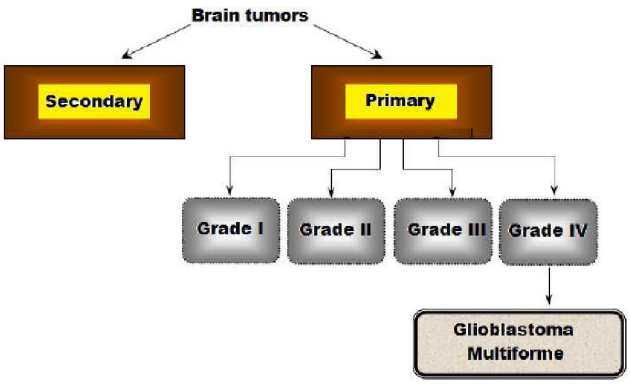

Figure 1 : Brain tumors clasification scheme

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Secondary tumors are often methastasial forms appearing consequently to cancer proliferation starting from other parts of the body, while primary tumors start in brain and remain inside it.

Glioblastoma Multioforme (GBM) is the most common malignant brain tumor in adults. It infiltrate to healthy brain tissue (mostly white matter), grow very fast by forming a necrotic core and making a parallel network of blood vessels for feeding purpose, which causes edema and brain tissue deformation.

One of the fundamental difficulties in treating gliomas is their ability to infiltrate healthy tissue beyond initial tumor boundary. Due to this particularity, radical resection of gliomas rarely succeeds. Meanwhile, considering the mathematical modeling would be necessary for comparison, observation, speculation and development of hypotheses to be tested along with references to well-established matheatical functions. These mathematical investigations, iteratively compared with experimental and clinical work, demonstrate the essential experiment-theorey interaction.

In this paper, we provide, in the context of the notes of Nieder[25] and Chicoine *et al.*[10], two resolution protocol under the same model of Glioblastoma Multioforme (GBM) diffusion.

The model presents a supply to works giving evidence to ability of a given treatment to identify and seek out, in a given region and at a given time, tumor than healthy rather cells locii.

PROBLEM FORMALIZATION

The earliest mathematical formulation of the growth of Glioblastoma Multioforme (GBM) has been was provided by Murray *et al.*[24] in the early 1990s, and confirmed later by Swanson *et al.*[33,34]. The formulated problem consisted of a conservation equation under the assumption of classical gradient-driven Fickian diffusion[33] and considering higher motility in white matter than in grey matter[32,33]. The model can be written as follows:

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

where $u(x,t)$ designates the tumor cell density at location x and time t, ρ denotes the net proliferation rate, and $D(x)$ is the diffusion coefficient ($D(x) = D_g$ in grey matter and $D(x) = D_w$ in white matter, with $D_g < 0.2\ D_w$)

Boundary conditions impose no migration of cells beyond physical boundary and initial conditions are governed by the equation:

$$u(x,t)\big|_{t=0} = u_0 \qquad (2)$$

where u_0 is the initial spatial distribution of malignant cells.

Several models and solution have been proposed in the last decades[2,3,16,17,20-23], sharing the basic form of the reaction-diffusion:

$$\begin{cases} \dfrac{\partial u}{\partial t} = \overbrace{\mathrm{div}(\vec{D}\nabla u)}^{\text{Diffusion}} + \overbrace{f(u)}^{\text{Proliferation}} - \overbrace{T(u)}^{\text{Treatment}} \\ \vec{D}\nabla u.\vec{n}_{\partial\Omega} = 0 \quad \text{(Boundary conditions)} \end{cases} \qquad (3)$$

where $\vec{D}$ is the diffusion tensor.

Despite the multitude forms allocated to the treatment term T(u) (depending on the treatment procedure: chemical, thermal, ultrasound…), the proliferation term exists under three main formulations (Linear (ρu), Logistic ($\rho u(1 - u/u_{max})$) and Gompertz ($\rho u Ln(u_{max}/u)$) laws)

SOLUTION USING FINITE ELEMENT METHOD (FEM)

In this section, we consider diffusion of tumor cells, for a representative class of one-dimensional problems. The main aim is to present the analytical and numerical solution of Eq. (1). For this purpose we first derive the analytical solution of proposed equation in one-dimensional space. The numerical procedure based on finite element method is developed.

We first write the associated mathematical time-dependent differential equation. Initial diffusion equation of tumor cells in the brain is:

$$\begin{cases} \dfrac{\partial u(x,t)}{\partial t} = D\dfrac{\partial^2 u(x,t)}{\partial x^2} + \rho u(x,t), & x \in [0,1] \\ \vec{n}.\vec{\nabla}u(x,t) = 0, & \text{on } \partial\Omega \\ u(x,t)\big|_{t=0} = u_0, & x \in [0,1] \end{cases} \qquad (4)$$

with:

$\partial\Omega$: Domain boundary (The domain is denoted Ω

$\vec{n}$: Unitary vector (normal to the domain boundary $\partial\Omega$).

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u_0 : Initial spatial concentration of malignant cells.

The solution is given by u(x,t) satisfying Eq. (4) with boundary condition imposing zero flux of cells at the brain boundaries and initial condition. The boundary condition simply requires that glioma cells are not allowed to migrate outside of the human tissue.

Assume that the tumor has grown to about 4000 cells as a local mass before it begins to diffuse. We used the growth rate $\rho \approx 0.012$/day[33,34] and diffusion coefficient D ˜ 0.0013 cm2 /day in the model as suggested for high-grade gliomas[34]. The comparison between analytical and numerical results are derived to assess numerically the accuracy and stability of the method[10,24].

Resolution protocol starts from integrating by parts the weighted integral of Eq. (4), which gives:

$$\int_{[0,1]}(u_t - \nabla(D\nabla u) - \rho u)v dx = 0 \quad (5)$$

for all weighting function v. It gives:

$$\int_{[0,1]}(u_t v + (D\nabla u)\nabla v - \rho u v)dx - \int_{\partial\Omega}(\vec{n}.(D\nabla u)v)ds = 0 \quad (6)$$

and:

$$\int_0^1(u_t v + (Du_x v_x) - \rho u v)dx - Du_x v\Big|_0^1 = 0 \quad (7)$$

Then, using the supplementary conditions Using $v(0) = 0$ and $v(1) = 0$, the remaining variational problem is to find u(x,t) which satisfies the initial data and main boundary condition, such that:

$$\int_0^1(u_t v + (Du_x v_x) - \rho u v)dx = 0 \quad (8)$$

For this purpose, let's consider Let Λ_h the finite element discretization of the domain and Ψ_j the finite element basis so that the finite element expansion has the form:

$$u_h(x,t) = \sum_{j=1}^{n} u_j(t)\Psi_j(x) \quad (9)$$

Setting c_h for c and $v_h = \Psi_j$ for v gives the semidiscrete system of ordinary differential equations of the form:

$$M\frac{d}{dt}C + KC - PC = F \quad (10)$$

Finally, this system is integrated using badcward differencing of $\dot{u}$ and Fourier transform. It gives:

$$u(x,t) = \sum_{n=1}^{\infty} Ae^{(\rho-(D+((n+\frac{1}{2})\pi)^2))t}\sin(n+\frac{1}{2})\pi x \quad (11)$$

SOLUTION USING THE BPES

The BPES[1,4-9,12-15,18,19,21,22,29,30,34,36] is applied to Eq. (4) through setting the expression:

$$u(x,t) = \frac{1}{2N_0}\sum_{k=1}^{N_0}\lambda_k \times B_{4k}(xr_k)e^{-\varpi_k t} \quad (12)$$

where B_{4k} are the 4k-order Boubaker polynomials, $x \in [0,1]$ is the normalized variable, r_k are B_{4k} minimal positive roots, N_0 is a prefixed integer, $\lambda_k|_{k=1..N_0}$ and $\varpi_k|_{k=1..N_0}$ are unknown pondering real coefficients. Consequently, it comes for Eq. (4) that:

$$\frac{-\varpi_k}{2N_0}\sum_{k=1}^{N_0}\lambda_k \times B_{4k}(xr_k)e^{-\varpi_k t} - \frac{D}{2N_0}\sum_{k=1}^{N_0}\lambda_k r_k^2\frac{d^2B_{4k}(xr_k)}{dx^2}e^{-\varpi_k t} - \frac{\rho}{2N_0}\sum_{k=1}^{N_0}\lambda_k \times B_{4k}(xr_k)e^{-\varpi_k t} = 0 \quad (13)$$

simplified to:

$$-(\varpi_k + \rho)\sum_{k=1}^{N_0}\lambda_k \times B_{4k}(xr_k) - D\sum_{k=1}^{N_0}\lambda_k r_k^2\frac{d^2B_{4k}(xr_k)}{dx^2} = 0 \quad (14)$$

The BPES protocol ensures the validity of the related boundary conditions expressed through Eq. (4), regardless main equation features. In fact, thanks to Boubaker polynomials first derivatives properties:

$$\begin{cases}\sum_{q=1}^{N} B_{4q}(x)\Big|_{x=0} = -2N \neq 0; \\ \sum_{q=1}^{N} B_{4q}(x)\Big|_{x=r_q} = 0;\end{cases} \quad (15)$$

and:

$$\begin{cases}\sum_{q=1}^{N}\frac{dB_{4q}(x)}{dx}\Big|_{x=0} = 0 \\ \sum_{q=1}^{N}\frac{dB_{4q}(x)}{dx}\Big|_{x=r_q} = \sum_{q=1}^{N} H_q \\ \text{with : } H_n = B'_{4n}(r_n) = \left(\frac{4r_n[2-r_n^2]\times\sum_{q=1}^{n}B_{4q}^2(r_n)}{B_{4(n+1)}(r_n)} + 4r_n^3\right)\end{cases} \quad (16)$$

boundary conditions are inherently verified.

The BPES solution is obtained through four steps:

- Integrating, for a given value of N_0, the whole expression given by Eq. (13) along the interval [0,1].
- Determining the set of coefficients $\tilde{\lambda}_k|_{k=1..N_0}$ and

$\tilde{\varpi}_k\big|_{k=1..N_0}$ that minimizes the absolute difference Δ_{N_0} :

$$\begin{cases} \Delta_{N_0} = \left| -(\varpi_k + \rho)\left(\frac{1}{2N_0}\sum_{k=1}^{N_0}\tilde{\lambda}_k \times \Lambda_k\right) - D\left(\frac{1}{2N_0}\sum_{k=1}^{N_0}\tilde{\lambda}_k \times \Lambda'_k\right)\right| \\ \text{with :} \\ \Lambda_k = \int_0^1 B_{4k}(xr_k)dx \\ \Lambda'_k = \int_0^1 r_k^2 \frac{d^2 B_{4k}(xr_k)}{dx^2}dx \end{cases}$$

- Incrementing N_0.
- Testing the convergence of the coefficients $\tilde{\lambda}_k\big|_{k=1..N_0}$ and $\tilde{\varpi}_k\big|_{k=1..N_0}$.

The final result is hence (for $N_0 = 29$):

$$u(x,t) = \frac{1}{2N_0}\sum_{k=1}^{N_0}\tilde{\lambda}_k \times B_{4k}(xr_k)e^{-\tilde{\varpi}_k t} \qquad (17)$$

RESULTS AND DISCUSSION

In this section to examine the ability of the proposed numerical procedures, a test case problem is investigated. TABLE 1 shows the parameters values. Figures 2 and 3 show the plots of numerical solutions.

TABLE 1 : Main parameters values

Parameter	Figure 1	Figure 2
Mesh points	20	20
D	D_w	D_g
ρ	0.0012	0.0012
N_0	29	33
c(0, t)	0	0
$c_x(1, t)$	0	0
c_0	4000	4000

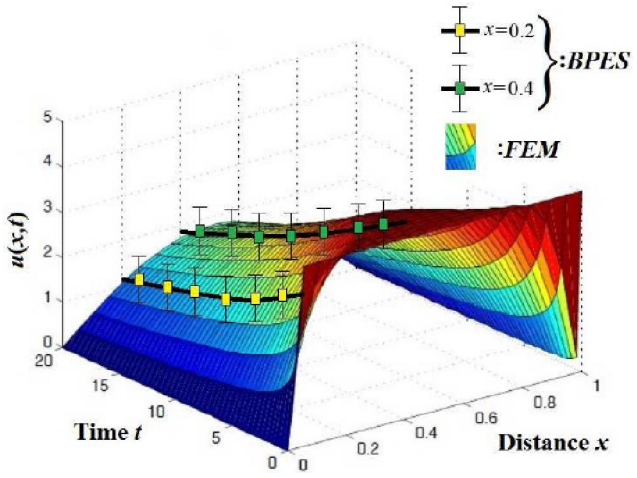

Figure 2 : Solution patterns in white matter

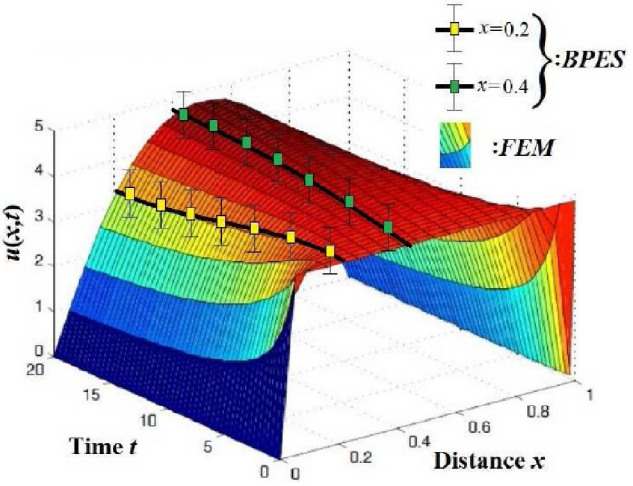

Figure 3 : Solution patterns in grey matter

Results have been obtained for parameters values gathered in TABLE 1.

First, it can be noted that the starting profile is the same for the two cases. This is conform to the adopted presumptions (same initial and boundary conditions). Time-dependent evolutions are in good agreement with the data given in §2 about higher motility in white than in grey matter, as recorded earlier by Swanson *et al.*[33,34].

In fact, it is noticed that, during the same period, the first time-dependent profile decreases down to approximately 40% at the core region, while the second is quite unaltered along the domain Ω. Inertia of grey matter in terms of cells diffusion seems to be preponderant.

Furthermore, results obtained using both methods performed a good concordance. Error analysis (Figure 4) showed a maximum relative quadratic error (mean quadratic difference between the results) of around 4.5% for the sampled data (x = 0.2 and x =0.4).

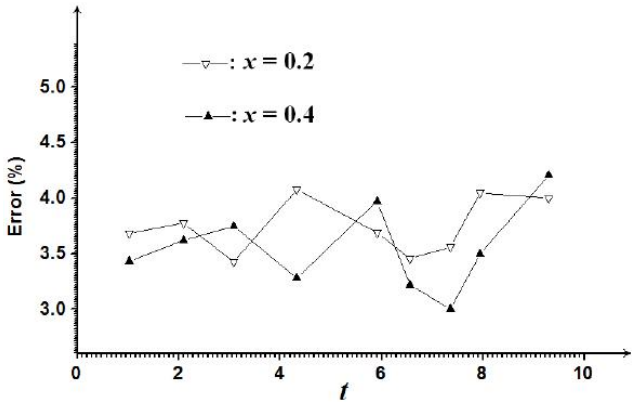

Figure 4 : Relative quadratic error

Evolution time range could also be satisfactorily compared to that recorded in the few last years by Stein *et al.*[25] in terms of brain tumors radii. Accurate

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calculation of this range could present a good supply to prediction of lifespan or tumor's response to eventual treatments.

CONCLUSION

We have presented solutions to the expansion-dispersion equation governing Glioblastoma Multiforme tumor growing. We developed a continuum model which describes invasion using three main parameters: the unbiased motility, D, the medium nature (white/grey matter) and the proliferation rate, ρ.

We focused on a mathematical model describing glioma cells intrinsic diffusion in absence of any chemotherapy or radiotherapy treatment. The finite element method *FEM* and the Boubaker polynomial expansion scheme *BPES* have s been applied to the proposed equation. Analytical investigations performed in one dimension illustrated the efficiency and convergence of the two methods and revealed some patterns of the solution behavior related to the medium.

In summary, we have shown how analytical mathematical models can be used to gain a better understanding of the parameters that effect brain tumor diffusion and prognosis improvement for patients who are diagnosed with Glioblastoma. Future studies will be directed toward the solution of two-dimensional version of the problem associated with chemotherapy and radiotherapy, namely by inserting standardized therapy-governed loss terms in the main equation.

REFERENCES

[1] M.Agida, A.S.Kumar; El Journal of Theoretical Physics, **7**, 319-326 **(2010)**.

[2] V.Amberger-Murphy; Acta Neurochirurgica, **145**, 613-614 **(2003)**.

[3] M.Aubert, M.Badoual, S.Fereol, C.Christov, B.Grammaticos; Physical Biology, **3**, 93-100 **(2006)**.

[4] P.Barry, A.Hennessy; Journal of Integer Sequences, **13**, 1-34 **(2010)**.

[5] A.Belhadj, O.Onyango, N.Rozibaeva; J.Thermophys.Heat.Transf., **23**, 639-642 **(2009)**.

[6] A.Belhadj, J.Bessrour, M.Bouhafs, L.Barrallier; J.of Thermal Analysis and Calorimetry, **97**, 911-920 **(2009)**.

[7] B.K.Ben Mahmoud; Cryogenics, **49(5)**, 217-220 **(2009)**.

[8] K.B.Ben Mahmoud, M.Amlouk; Materials Letters, **63(12)**, 991-994 **(2009)**.

[9] K.Boubaker; F.E.Journal of A Math., **31**, 299-320 **(2008)**.

[10] M.R.Chicoine, D.L.Silbergeld; J.Neurosurg., **82**, 615-622 **(1995)**.

[11] A.Corcoran, R.F.Del Maestro; Neurosurgery, **53**, 174-184 **(2003)**.

[12] M.Dada, O.B.Awojoyogbe, K.Boubaker; Current Applied Physics, **9(3)**, 622-624 **(2009)**.

[13] S.Fridjine, K.B.Ben Mahmoud, M.Amlouk, M.Bouhafs; Journal of Alloys and Compounds, **479(1-2)**, 457-461, **(2009)**.

[14] J.Ghanouchi, H.Labiadh, K.Boubaker; International Journal of Heat and Technology, **26**, 49-53 **(2008)**.

[15] T.Ghrib, K.Boubaker, M.Bouhafs; Modern Physics Letters B, **22**, 2893-2907 **(2008)**.

[16] A.Giese, R.Bjerkvig, M.E.Berens, M.Westphal; J.Clin.Oncol., **21**, 1624-1636 **(2003)**.

[17] C.Hogea, G.Biros, F.Abraham, C.Davatzikos; Physics in Medicine and Biology, **52**, 6893-6908 **(2007)**.

[18] C.Khélia, K.Boubaker, T.Ben Nasrallah, M.Amlouk, S.Belgacem; Journal of Alloys and Compounds, **477(1-2)**, 461-467 **(2009)**.

[19] A.S.Kumar; Journal of the Franklin Institute, **347**, 1755-1761 **(2010)**.

[20] S.K.Kyriacou, C.Davatzikos, S.J.Zinreich, R.N.Bryan; IEEE Transactions On Medical Imaging, **18(7)**, 580-592 **(1999)**.

[21] S.Lazzez, K.B.Ben Mahmoud, S.Abroug, F.Saadallah, M.Amlouk; Current Applied Physics, **9(5)**, 1129-1133 **(2009)**.

[22] A.Milgram; J.of Theoretical Biology, **271**, 157-158 **(2011)**.

[23] K.Miller, K.Chinzei; J.of Biomechanics, **35**, 483-490 **(2002)**.

[24] P.Murray, G.F.Carey; Finite Element Analysis of Diffusion with Reaction at a Moving Boundary, **(1984)**.

[25] C.Nieder; Int.J.of Radiation Oncology Physics, **69**, 640-641 **(2007)**.

[26] T.G.Oliver, R.J.Wechsler-Reya; Neuron., **42**, 885-888 **(2004)**.

[27] G.Panagiotakos, V.Tabar; Current Neurology and Neuroscience Reports, **7**, 215-220 **(2007)**.

[28] S.Singh, P.B.Dirks; Neurosurgery Clinics of North America, **18**, 31-38 **(2007)**.

[29] S.Slama, J.Bessrour, K.Boubaker, M.Bouhafs; Eur.Phys.J.Appl.Phys., **44**, 317-322 **(2008)**.

[30] S.Slama, M.Bouhafs, K.B.Ben Mahmoud; International Journal of Heat and Technology, **26(2)**, 141-146 **(2008)**.

[31] A.M.Stein, T.Demuth, D.Mobley, M.Berens, L.M.Sander; Biophysical Journal, **92**, 356-365 **(2007)**.

[32] K.Swanson, E.Alvord, J.D.Murray; Cell.Prolif., **33**, 317-329 **(2000)**.

[33] K.Swanson, E.Alvord, J.D.Murray; Washington, **43**, 223-237 **(2007)**.

[34] S.Tabatabaei, T.Zhao, O.Awojoyogbe, F.Moses; Int.J.Heat Mass Transfer., **45**, 1247-1255 **(2009)**.

[35] W.Weiss, K.Aldape; Nervous System Cancer Models. W.Weiss, K.Aldape, (Eds); National Cancer Institute, **(2007)**.

[36] A.Yildirim, S.T.Mohyud-Din, D.H.Zhang; Computers and Mathematics with Applications, **59**, 2473-2477 **(2010)**.