ACCEPTED TO BE PUBLISHED IN
JOURNAL OF APPLIED ELECTROMAGNETISM IN 2017

IN SILICO SIMULATION OF GLIOBLASTOMA GROWTH AND INVASION INTO THE HUMAN BRAIN INCLUDING AN EXPLICIT MODELLING OF THE ADIABATIC BOUNDARY CONDITION IMPOSED BY THE SKULL

Stavroula G. Giatili, and Georgios S. Stamatakos*

Institute of Communication and Computer Systems,
School of Electrical and Computer Engineering
National Technical University of Athens,
In Silico Oncology and *In Silico* Medicine Group,
9 Iroon Polytechniou, GR157 80, Zografos, Greece.
* (corresponding author) gestam@central.ntua.gr

Abstract

The diffusive and infiltrative nature of glioma brain tumours and in particular glioblastoma constitutes a major barrier to their effective treatment. The present paper focuses on the numerical handling of a pertinent Neumann boundary value problem in the three-dimensional space acting as a tri-scale reaction – diffusion model of primary glioma growth and invasion into the surrounding normal brain. A complex anatomical and geometrical domain bounded by the skull is considered. The model takes into account the highly inhomogeneous nature of human brain. The generic finite difference – time domain (FDTD) method and more specifically the Crank – Nicolson technique in conjunction with the biconjugate gradient system solver have been utilized for the numerical solution of the problem. The model has been partly validated through comparing its predictions with real values of clinically pertinent macroscopic tumour characteristics. Numerical results are presented. They illustrate the potential of the model to support the clinician in designing the optimal individualized treatment scheme and/or schedule by using the patient's personal multiscale data and by experimenting in silico (=on the computer).

1. INTRODUCTION

Malignant gliomas, in general, and astrocytomas, in particular, account for approximately 50% of primary central nervous system (CNS) tumours in adults [1]. The median survival for glioblastoma multiforme (GBM) is 10-12 months. Because of the infiltrative nature of malignant gliomas [1,2], even a gross total resection is associated with tumour recurrence. In order to partly alleviate the corresponding complex treatment problem, cancer mathematical modelling [3] of diffusive tumour

growth has been proposed and a number of models have been developed [2, 4]. The practical goal of this work, which can be viewed as a synthesis and an important extension of previous efforts [4], is to develop a "bottom-up" tri-scale diffusion-reaction based mathematical model of glioma growth and invasion that would serve as the core of the "Continuous Mathematics Based GBM Oncosimulator." [3]. For a biologically meaningful and computationally reliable diffusion-reaction based solution to the problem, consideration of the actual physical boundary of the cranium is important. An improper handling of the boundary conditions may lead to an unnatural behaviour of the simulated system and artificial loss of tumour cells. The model focuses primarily on the detailed numerical handling of the adiabatic Neumann boundary conditions imposed by the presence of the skull, considering the spatiotemporal characteristics of glioblastoma invasion.

2. THE TRI-SCALE REACTION – DIFFUSION MODEL

If Ω is the brain domain, GBM tumour growth and brain infiltration can be expressed by equation [5]:

$$\frac{\partial c(\vec{x},t)}{\partial t} = \nabla\cdot[D(\vec{x})\,\nabla c(\vec{x},t)] + \rho\, c(\vec{x},t) - G(t)c(\vec{x},t) \text{ in } \Omega \qquad (1)$$

where $\frac{\partial c(\vec{x},t)}{\partial t}$ denotes the rate of change of tumour cell concentration c at any spatial point $\vec{x}$ and time t, D denotes the diffusion coefficient and represents the active motility of tumour cells, $\rho\, c(\vec{x},t)$ expresses the net proliferation of tumour cells and $G(t)c(\vec{x},t)$ defines the loss of tumour cells due to treatment and also indirectly involves insufficient and inadequate angiogenesis.

The model takes into account the highly inhomogeneous nature of human brain. Two different approaches have been developed: the homogeneous and the inhomogeneous approach. In the inhomogenous approach, the structures of white matter, grey matter, cerebrospinal fluid (CSF) are taken into consideration and three values of the parameter D are considered: D_g, D_w and D_{CSF} if $(\vec{x})$ belongs to grey matter, white matter and CSF respectively. In the homogenous approach, where for simplification homogeneous brain tissue is considered, D has the same value all over the intracranial space.

Regarding the initial condition for the reaction–diffusion system, it is assumed that the initial spatial distribution of malignant cells is described by a known function $f(\vec{x})$. In order to complete the model formulation, appropriate boundary conditions have to

be added precluding migration beyond the skull boundary. Neumann boundary conditions, which correspond to no net flow of tumour cells out of or into the brain region across the brain-skull boundary, have been imposed.

In order to numerically apply the Neumann boundary condition, "fictitious nodes", $F_{i,j,k}$, have been used [6]. Their number is equal to the number of the adjacent nodes that belong to the cranium. An indicative case of numerically applying the boundary condition at the boundary point (x_i, y_j, z_k) in the negative z direction is the following:

$$-\left.\frac{\partial c}{\partial z}\right|_{(x_i,y_j,z_k)} = 0 \Rightarrow c_{i,j,k+1} = c_{F_{i,j,k-1}} \tag{2}$$

An indicative equation at the boundary grid point (x_i , y_j, z_k) where skull tissue is found only in the negative x and the negative y direction by applying the Crank - Nicolson scheme is (3) for the homogeneous and (4) for the inhomogeneous approach respectively.

$$[1+6\lambda-\frac{\Delta t}{2}(\rho-G)]c_{i,j,k}^{t+1}-\lambda(2c_{i+1,j,k}^{t+1}+2c_{i,j+1,k}^{t+1}+c_{i,j,k+1}^{t+1}+c_{i,j,k-1}^{t+1})=$$
$$[1-6\lambda+\frac{\Delta t}{2}(\rho-G)]c_{i,j,k}^{t}+\lambda(2c_{i+1,j,k}^{t}+2c_{i,j+1,k}^{t}+c_{i,j,k+1}^{t}+c_{i,j,k-1}^{t}) \tag{3}$$

$$\left[1+6\lambda_{i,j,k}-\frac{\Delta t}{2}(\rho-G)\right]c_{i,j,k}^{t+1}-2\lambda_{i,j,k}c_{i+1,j,k}^{t+1}-2\lambda_{i,j,k}c_{i,j+1,k}^{t+1}-\left(\lambda_{i,j,k}+\frac{\lambda_{i,j,k+1}-\lambda_{i,j,k-1}}{4}\right)c_{i,j,k+1}^{t+1}-\left(\lambda_{i,j,k}-\frac{\lambda_{i,j,k+1}-\lambda_{i,j,k-1}}{4}\right)c_{i,j,k-1}^{t+1}=$$
$$\left[1-6\lambda_{i,j,k}+\frac{\Delta t}{2}(\rho-G)\right]c_{i,j,k}^{t}+2\lambda_{i,j,k}c_{i+1,j,k}^{t}+2\lambda_{i,j,k}c_{i,j+1,k}^{t}+\left(\lambda_{i,j,k}+\frac{\lambda_{i,j,k+1}-\lambda_{i,j,k-1}}{4}\right)c_{i,j,k+1}^{t}+\left(\lambda_{i,j,k}-\frac{\lambda_{i,j,k+1}-\lambda_{i,j,k-1}}{4}\right)c_{i,j,k-1}^{t} \tag{4}$$

where $c_{i,j,k}^{t}$ is the finite difference approximation of c at the grid point $(x_i \ \ y_j, z_k)$ at time t, Δt is the time step size for the time discretization, h is the space step size at each axis of the gridding scheme for the space discretization, $\lambda = D\Delta t / [2(h)^2]$ and $\lambda_{i,j,k} = D_{i,j,k}\Delta t / [2(h)^2]$. The resulting system of equations may be written equivalently in the form $\overleftrightarrow{A}\,\vec{x} = \vec{b}$ where $\vec{x}$ denotes a vector that contains an approximation of the solution c at the mesh nodes at time t. Due to the high complexity of the biological system the Bi-Conjugate Gradient method (BiCG) has been applied [6].

3. MODEL SIMULATIONS

Three-dimensional simulations of untreated glioma growth, assuming a complex anatomical and also geometrical domain bounded by the skull, have been performed. A three dimensional image of a typical real human head has been considered. The dataset used has been acquired from 3d Slicer which is a freely available application for image analysis and automatic segmentation of brain structures from MRI data. Two different scenarios have been executed and mutually compared; the homogeneous and the inhomogeneous scenarios. In the first case homogeneous brain tissue is considered. In the second case the structures of white matter, grey matter, CSF and skull have been segmented. Following the delineation of the skull boundary, a fictitious growing virtual spherical glioblastoma tumour of radius equal to 0.7 cm has been virtually placed inside the cranial cavity. It should be noted that glioblastoma diagnosis is possible when the volume of an enhanced CT-detectable tumour has reached a size equivalent to a sphere with an average 3 cm diameter [5].

The typical values of the parameters that have been used for the production of the results have been carefully selected from pertinent literature so as to best reflect aspects of glioblastoma dynamics. The net tumour growth rate ρ, which represents the net rate of tumour growth including tumour cell proliferation, loss and death has been set equal to 0.012 d-1 [5]. For the inhomogeneous scenario the value of the space dependent diffusion coefficient $D_{i,j,k}$, has been calculated as the average value of the growing diffusion coefficient and the migrating diffusion coefficient (D_g =0.000102cm^2/d, D_w=0.00051cm^2/d and D_{CSF}=0.000001 cm^2/d) [7].

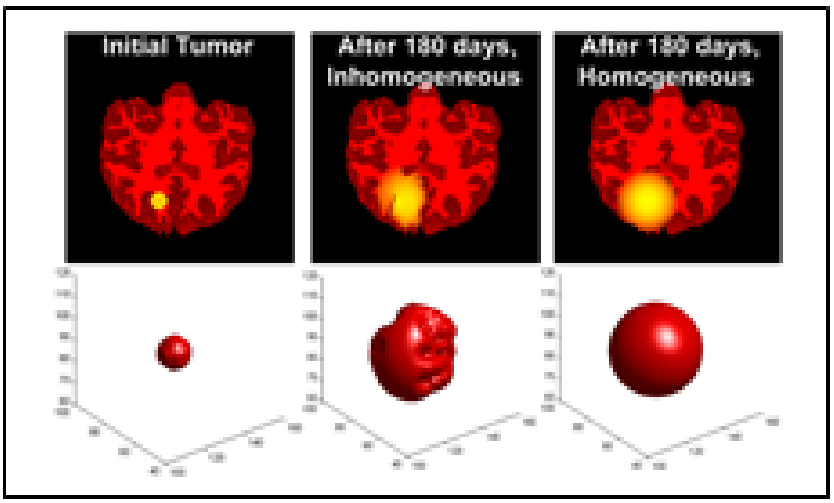

Figure 1. Coronal slice and a three dimensional snaphot of a virtual tumour for the inhomogeneous (second panel column) and homogeneous (third panel column) case after 180 simulated days. In the upper panels, the colour intensity level depends logarithmically on the tumour cell concentration.

The value of D for the homogeneous case has been estimated as the weighted average value of the diffusion coefficient for white matter, grey matter and CSF ($D=0.00038 cm^2/day$). The concentration of tumour cells within the initial tumour has been arbitrarily assumed uniform and equal to 10^6 cells/mm^3 [8]. Diffusion phenomena before the time point corresponding to the start of the simulation have been ignored. Regarding the parameters associated to the numerical methods used, the time step Δt, the space step size h and the convergence tolerance for the bi-conjugate gradient method have been chosen equal to 0.5 d, 0.1 cm and 10^{-6} respectively. The virtual tumour grows for 180 days after the initialization time point. Figure 1 shows a virtual tumor on the first and the 180th simulated day for the inhomogeneous and homogeneous scenario. Figure 2 depicts tumour cell density for the inhomogeneous case. The simulated volume appears to meet the expected clinical macroscopic behaviour of glioblastoma. Moreover, the resulting virtual tumours proved the adiabatic behaviour of the skull without artificial cell loss in the skull-brain barrier. It is noted that the threshold of tumour detection has been set equal to 8000 tumour cells/mm^3 according to [5].

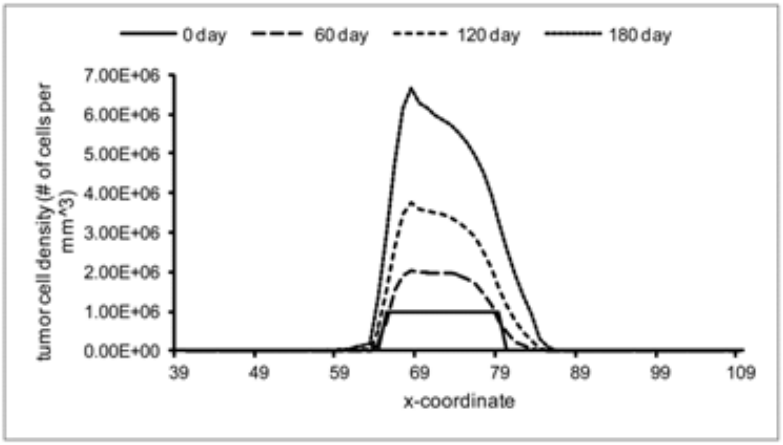

Figure 2. Tumour cell density along the x axis (the horizontal axis of the coronal plane) passing through the centre of the initial tumour for different simulated time points.

The doubling time for gliomas, which is a classical metric of glioma growth quantification, ranges from 1 week to 12 months covering the range of high to low grade gliomas [9]. Predictions of the doubling time for both cases lie within published ranges. The typical value of 2 months is observed on the 33th simulated day. Following an in silico theoretical exploration indicates that even by using a pertinent

homogeneous brain based model, a rough but nonetheless informative estimate of the expected tumour doubling time can be achieved.

4. CONCLUSION

The major highlight of the paper is an explicit and thorough tri-scale numerical handling of the Neumann boundary value problem of GBM growth and invasion into the surrounding normal brain tissue in three dimensions. The heterogeneous nature of human brain and the complexity of skull geometry have been taken into consideration. Comparison of the simulation predictions with clinical observational data has supported the reliability of the model. It has also illustrated the model's potential to be used as a basis for an individualized treatment planner through in silico experimentation by exploiting the patient's multiscale data. The presented model could serve as the main component of a continuous mathematics based GBM Oncosimulator. Moreover, the study has established a generic methodology which could be translated into other mathematically similar phenomena of physics, chemistry biology and other domains. Further model development will also include explicit tumour response to treatment and an extensive clinical adaptation and validation of the extended model.

5. ACKNOWLEDGMENTS

This work has been supported in part by the European Commission in the framework the projects "p-Medicine: Personalized Medicine (FP7-ICT-2009.5.3-270089)", "CHIC: Computational Horizons in Cancer: Computational Horizons In Cancer: Developing Meta- and Hyper-Multiscale Models and Repositories for In Silico Oncology" (FP7-ICT-2011-9-600841), MyHealthAvatar (PI: 600929) and DR THERAPAT (PI: 600852). The authors would like to thank Prof. Dr med N. Graf, Director of the Pediatric Oncology and Hematology Clinic, University Hospital of Saarland, Germany and Dimitra Dionysiou PhD, ICCS, NTUA, Greece for fruitful discussions.

REFERENCES

[1] C.A. Perez, L.W. Brady, "Principles and Practice of Radiation Oncology", Lippincott-Raven, Philadelphia, 1997.

[2] J.D. Murray, “Mathematical Biology II: Spatial Models and Biomedical Applications”, Springer-Verlag, New York, USA, 2003.

[3] G. Stamatakos, D. Dionysiou, A. Lunzer, et al. “The Technologically Integrated Oncosimulator: Combining Multiscale Cancer Modeling with Information Technology in the In Silico Oncology Context”, IEEE J. Biomed. Health Inform, 18, 2014, pp. 840-854.

[4] S. Giatili, G. Stamatakos, “A detailed numerical treatment of the boundary conditions imposed by the skull on a diffusion–reaction model of glioma tumor growth. Clinical validation aspects”, Applied Mathematics and Computation, 218, 2012, 8779-8799.

[5] K. Swanson, E. Alvord, J. Murray, “Virtual brain tumors (gliomas) enhance the reality of medical imaging and highlight inadequacies of current therapy”, Br J Cancer, 86, 2002,14 – 18.

[6] B. Bradie, “A friendly Introduction to Numerical Analysis”, Pearson International, USA, 2006.

[7] S. Eikenberry, T. Sankar, M. Preul, et al., “Virtual glioblastoma: growth, migration and treatment in a three-dimensional mathematical model”, Cell Prolif., 42, 2009, 511-528.

[8] G. Steel, “Basic Clinical Radiobiology”, Arnold, London, UK, 2002.

[9] E. Alvord, C. Shaw, “Neoplasm affecting the nervous system in the elderly”. In: Duckett S, eds. The Pathology of the Aging Human Nervous System, Lea & Febiger, Philadelphia, 1991.