In Silico Oncology: a Novel and Explicit Numerical Treatment of the Neumann Boundary Conditions Imposed by the Skull on a Multiscale Diffusion-Reaction Model of Glioblastoma Growth. Clinical Validation Aspects.

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Abstract- Modelling of the diffusive-invasive behaviour of glioma tumour growth is an active field of Virtual Physiological Human (VPH) research with considerable therapeutic implications. A crucial component of the corresponding computational problem is the numerical handling of the adiabatic Neumann boundary conditions imposed by the skull on the diffusive growth of gliomas and in particular glioblastoma multiforme (GBM). In order to become clinically acceptable such a numerical handling should ensure that no potentially life-threatening glioma cells disappear artificially due to oversimplifying assumptions applied to the simulated region boundaries. However, to the best of the authors' knowledge no explicit numerical treatment of the 3D boundary conditions under consideration has appeared in the literature. Therefore, this paper aims at providing an outline of a novel, explicit and thorough numerical solution to this problem. Additionally, a brief exposition of the numerical solution process for a homogeneous approximation of glioma diffusion-invasion using the Crank – Nicolson technique in conjunction with the Conjugate Gradient system solver is outlined. The entire mathematical and numerical treatment is also in principle applicable to mathematically similar physical, chemical and biological phenomena. A comparison of the numerical solution for the special case of pure diffusion in the absence of boundary conditions with its analytical counterpart has been made. *In silico* experimentation with various adiabatic boundary geometries and non zero net tumour growth rate support the validity of the corresponding mathematical treatment. Through numerical experimentation on a set of real brain imaging data, a simulated tumour has shown to satisfy the expected macroscopic behaviour of glioblastoma multiforme including the adiabatic behaviour of the skull. The expected GBM macroscopic behaviour has been based on concrete published clinical imaging data. The paper concludes with a number of remarks pertaining to the potential and the limitations of the diffusion-reaction approach to modelling multiscale malignant tumour dynamics.

I. INTRODUCTION

Glioblastoma multiforme (GBM) is a very aggressive glioma and a classical example of a highly invasive and diffusive tumour. GBM cell diffusion in the brain is a reasonable first approximation of the migration of glioma cells along structures such as the basement membranes of blood vessels or the glial limitans externa that contain extracellular matrix (ECM) proteins. Frequentlty, invasive glioma cells are also found to migrate along myelinated fiber tracts of white matter. Due to its markedly diffusive character, a significant component of the tumour cannot be delineated based on standard tomographic imaging techniques such as CT, MRI and PET. This constitutes an important limitation to the optimal design of both surgical excision and therapeutic irradiation of the tumour. In order to partly alleviate the problem, mathematical modelling of diffusive tumour growth has been proposed. To this end a number of diffusion-reaction based models dealing primarily with the morphology of tumour growth have been developed [1 – 3].

According to the diffusion-reaction based approach, the tumour is considered a spatiotemporal distribution of continuous cell density which follows the general diffusion-reaction law. The macroscopic formulation of diffusion, leads to a partial parabolic differential equation. A single tumour cell may constitute the initial tumour within a three-dimensional medium. Tumour growth can be expressed by the following statement [1,2]:

Rate of change of tumour cell population= diffusion (motility) of tumour cells + net proliferation of tumour cells - loss of tumour cells due to treatment

In the case of glioma, the simulated region of interest may include part of the skull. The latter acts as an adiabatic boundary for the diffusion of the brain tumour, precluding migration beyond it. As a result, the mathematical treatment of the biophysical processes taking place in the vicinity of anatomic boundaries must satisfy specific constraints. Zero flux boundary conditions have to be applied on the anatomic boundaries of the skull surface. Thus if Ω is the brain domain on which the diffusion equation is to be solved the previous statement can be symbolically formulated through the following differential equation [1]:

$$\begin{cases} \frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \rho c - G(t)c \quad in\ \Omega \\ c(\vec{x}, 0) = f(\vec{x}), \qquad initial\ condition \\ \hat{n} \cdot D \nabla c(\vec{x}, t) = 0 \ \ on\ \ \partial\Omega, \ \ Neumann\ boundary\ condition \end{cases} \tag{1}$$

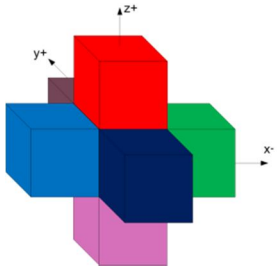
The variable c denotes the cell concentration at any spatial point defined by the position vector $\vec{x}$ and time t. The parameter D denotes the diffusion coefficient and represents the active motility of tumour cells. The term ρ represents the net rate of tumour growth including proliferation, loss and death, $\hat{n}$ is the unit vector normal to the boundary $\partial\Omega$ of the domain Ω and $f(\vec{x})$ is a known function that defines the initial spatial distribution of malignant cells. The term $G(t)$ accounts for the temporal profile of treatment and as a first facilitating approximation $G(t) = k$ may be assumed constant. The latter may crudely model a continuous administration of radiation e.g. through special radioisotope based

implants. A more realistic assumption is to assign $G(t)$ different values for different time intervals reflecting various chemotherapeutic and/or radiotherapeutic schedules. The simulation domain R of which Ω is a subdomain is defined as:

$$R = \{(x, y, z) | a < x < b, s < y < d, e < z < f\} \quad (2)$$

II. EXPLICIT NUMERICAL FORMULATION OF THE BOUNDARY CONDITIONS

The diffusion component of the problem is numerically solved using the Crank Nicolson numerical method in conjunction with the conjugate gradient method. The glioma invasion problem involves an irregularly shaped domain. Therefore, a biologically meaningful solution has to allow for the investigation of a wide range of elementary local domain geometries. Several specific cases have been examined in order to address the geometry of the irregularly shaped skull boundary. For each boundary mesh node (lying at the center of the multi-grey level structure of Fig.1 (and therefore not visible) all its 6 adjacent nodes (lying towards all the $x+, x-, y+, y-, z+, z-$ directions) are considered in order to numerically apply the boundary condition on it i.e. on (x_i, y_j, z_k) [4]



Fi.1 A boundary mesh node with its 6 adjacent nodes. For each boundary mesh node (lying at the center of the multi-coloured structure and therefore not visible) all its 6 adjacent nodes (lying towards the $x+, x-, y+, y-, z+, z-$ directions) are considered in order to numerically apply the boundary conditions on the node under consideration.

The boundary condition according to Eq.1 is:

$$\hat{n} \cdot D\nabla c = 0 \quad on \quad \partial\Omega \quad (2)$$

In order to evaluate the boundary condition for each grid point (x_i, y_j, z_k) and maintain the block tridiagonal structure of the coefficient matrix $\vec{A}$ of the resulting linear system of algebraic equations $\vec{A}\,\vec{x} = \vec{b}$ and the second-order accuracy of the approximation we introduce a "fictitious node" into the computational grid. The "fictitious node" produces an extra row of unknowns in the computational grid. Evaluating the boundary condition at each boundary grid point (x_i, y_j, z_k) yields six equations mathematically similar (but not identical) to the equation corresponding to the following case:

At the boundary grid point (x_i, y_j, z_k) in the negative x direction $x-$:

$$-\left.\frac{\partial c}{\partial x}\right|_{(x_i, y_j, z_k)} = 0 \Rightarrow c_{i+1,j,k} = c_{F_{i-1,j,k}} \quad (3)$$

where $F_{i,j,k}$ denotes a fictitious node.

The total number of the different cases of nodes having boundary node(s) as their neighbour(s) that have been considered is 26. This has led to the formulation of 26 algebraic equations mathematically similar (but not identical) to Eq. (4). An appropriate equation out of the set of these 26 equations is used for any index triplet (i, j, k) belonging to the boundary. By fixing indices i, j, k to specific values, the 26 equations can produce all elementary boundary arrangements encountered in the case of an arbitrarily shaped boundary. An indicative case and equation is the following:

At the boundary grid point (x_i, y_j, z_k) where the skull lies only in the positive x direction:

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

where $\lambda = D\Delta t \,/\, [2(h)^2]$, $h = \Delta x = \Delta y = \Delta z$, $t_n = n\,\Delta t$, for $n = 0,1,2\ldots.$ (5)

III. NUMERICAL EXPERIMENTS

In order to test the numerical schemes implemented for solving Eq. (1) and support the correctness of the overall mathematical treatment presented, a number of pertinent computational scenarios have been executed. They have included inter alia: numerical checks regarding convergence and stability of the algorithm and the code, checks regarding mass conservation and linearity for the theoretical case of pure diffusion, comparison of the model with the analytical solution to the special case of an initial Gaussian cell concentration profile, spatial symmetry studies for simple symmetric geometries and numerical validation of the adiabatic behaviour of the boundary implementation.

IV CLINICAL VALIDATION ASPECTS

Several snapshots of a growing virtual glioblastoma tumour corresponding to various time points are depicted in Fig. 2. It is noted that although the internal anatomy of brain is visible in the panels of this figure, homogeneous diffusion of tumour cells has been assumed within the skull cavity as a first approximation. The concentration of tumour cells within the initial simulated tumour has been arbitrarily assumed uniform and equal to 10^6 cells/ mm^3. The following parameter values have been used: diffusion coefficient $D = 0.0065$ cm^2/d, [1], $h = 0.2$ cm, $\Delta t = 0.5$ d , and net tumour growth rate $\rho = 0.012$ d^{-1}. [1] It should be noted that the gross spatial pattern of glioblastoma growth, especially in the vicinity of the skull boundary, is in very good agreement with actual published clinical observations [5-6]. The diameter of a sphere with volume equal to a glioblastoma tumour of fatal imageable dimensions is about 6 cm. [1] The latter corresponds to a volume V_{fatal} of 113.04 cm^3. In order for the tumour to increase in imageable volume from $V_{fatal}/2$ to V_{fatal}, 26 days are needed according to the simulations. This approximation to doubling time is in good agreement with the clinically reported glioblastoma doubling time in [7]. It is noted that in order to avoid a somewhat artificial diffusion behaviour during the first simulated days which would be dictated by the deliberately assumed abrupt boundaries of the initial tumour, the first 14 simulated days have not been taken into account in the

theoretical estimation of doubling time. A typical execution instance of the code for 6 simulated months, $\Delta t = 0.5d$ and for descritized mesh 130x130x130, on a 32-bit Windows Vista Platform, 4 GB RAM and processor Intel® Core™2 Duo CPU P8600 @ 2.4GHz, takes 214 sec. Further acceleration of the code execution could be achieved by using high performance computing resources.

V. CONCLUSIONS

A novel explicit numerical treatment of the boundary conditions to be used in conjunction with a homogeneous diffusion - reaction based glioma growth model has been presented.

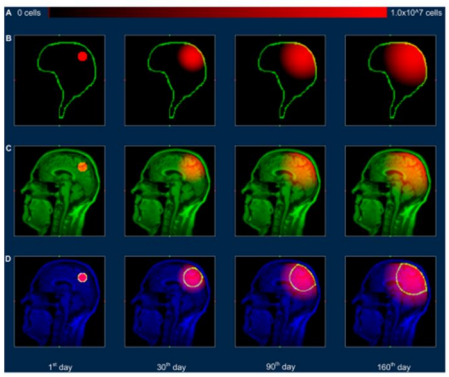


Fig.2 Schematic representation of the growth of a virtual glioblastoma tumour *in vivo* in sagittal planes at various time points (panel columns from left to right correspond to days 1, 30, 90 and 160 respectively). (A) The red colour intensity level I depends on cell concentration according to the function $I = k \log_{10} c$, where c denotes tumour cell concentration, the constant $k = 255/\log_{10} c_{max}$, c_{max} is the maximum value of tumour cell concentration *over the entire space and time range* considered during all simulations that have been included in this figure. Maximum and zero cell concentration corresponds to RGB(255,0,0) and RGB(0,0,0) respectively. The numerical values appearing on the intensity scale of panel A are per 8 mm^3. It is noted that the voxel in the present simulation had dimensions 2mm x 2mm x 2mm (B), (C) As time increases, the tumour diffuses theoretically over the interior space of the skull cavity of the human head. (D) The yellow/bright contour defines the boundary of the tumour component in 2D that is tomographically detectable and has a cell density higher than the assumed threshold of 8000 cells/mm^3.

Systematic checking of the corresponding computer code based on numerical simulations for various adiabatic boundary geometries, zero and non zero net tumour growth rate and zero and non zero loss rate due to treatment have supported the validity of the corresponding mathematical treatment. Numerical experimentation on a set of real brain imaging data has demonstrated that a simulated glioblastoma tumour can satisfy the expected macroscopic behaviour of its real counterpart, including the adiabatic behaviour of the skull. The detailed treatment of the boundary conditions presented could considerably contribute to the accuracy of the solution to the diffusion-reaction equation in particular for glioblastoma tumours having their main bulk close to the skull. The composite model proposed appears to have the potential to correctly predict clinically meaningful and measurable quantities of critical importance related to the course of the disease, such as the imaging based doubling time. Obviously a strict clinical adaptation and validation procedure is a *sine qua non* requirement before clinical translation is envisaged. Additionally, translation or extension of the analysis presented to mathematically similar physical systems is a possibility. Extension to both inhomogeneous and anisotropic glioma diffusion is pretty straightforward. It should be noted, however, that although the continuous - finitized approach partly delineated in this paper appears to be a good choice for pure tumour growth-invasion-diffusion modelling, it seems not to be ideal for the integration of the massive multiscale biological complexity that is necessary in order to study in depth tumour response to treatment. Discrete entity – discrete event based approaches [8-11] on the contrary have demonstrated considerable integrative potential in the context of cancer response o treatment due to the discrete character of many biological entities and features involved in this domain (e.g. discrete cell categories based on their mitotic potential such as stem cells, progenitor cells, differentiated cells; discrete cell cycle phases generally characterized by differing treatment sensitivities; discrete character of cell state transitions etc.). Nevertheless, both continuous/finitized and discrete approaches are important for the development [10] and the clinical translation [12] of the emerging oncosimulators [10].

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