A detailed numerical treatment of the boundary conditions imposed by the skull on a diffusion–reaction model of glioma tumor growth. Clinical validation aspects

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ABSTRACT

The study of the diffusive behavior of glioma tumor growth is an active field of biomedical research with considerable therapeutic implications. An important aspect of the corresponding computational problem is the mathematical handling of boundary conditions. This paper aims at providing an explicit and thorough numerical formulation of the adiabatic Neumann boundary conditions imposed by the skull on the diffusive growth of gliomas and in particular on glioblastoma multiforme (GBM). Additionally, a detailed exposition of the numerical solution process for a homogeneous approximation of glioma invasion using the Crank–Nicolson technique in conjunction with the Conjugate Gradient system solver is provided. 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 or equivalently in the presence of adiabatic boundaries placed in infinity with its analytical counterpart is presented. Numerical simulations for various adiabatic boundary geometries and non zero net tumor growth rate support the validity of the corresponding mathematical treatment. Through numerical experimentation on a set of real brain imaging data, a simulated tumor has shown to satisfy the expected macroscopic behavior of glioblastoma multiforme including the adiabatic behavior of the skull. The paper concludes with a number of remarks pertaining to both the biological problem addressed and the more generic diffusion–reaction context.

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1. Introduction

The generic diffusion–reaction equation is applicable to a wide spectrum of physical, chemical and biomedical phenomena. In the context of cancer biology and oncology, diffusion has been regarded as one of the fundamental phenomena governing tumor invasion into neighboring normal tissues. Glioblastoma multiforme (GBM), a highly aggressive brain tumor, is a classical example of a highly invasive tumor. 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. Frequently, 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 tumor cannot be delineated based on standard tomographic imaging techniques (CT, MRI, PET etc). This constitutes an important limitation...
to the optimal design of both surgical excision and therapeutic irradiation of the tumor. In order to partly alleviate the problem, mathematical modeling of diffusive tumor growth has been proposed. To this end a number of diffusion based models dealing primarily with the morphology of tumor growth have been developed [1-15].

An early study proposing a reaction–diffusion framework for the modeling of tumor growth in patients with glioma has been published by Cruywagen et al. [16] and Woodward et al. [17]. The effect of treatment has been included as a negative reaction term. Tumor cell invasion has been assumed isotropic, following homogeneous diffusion that is characterized by a global scalar diffusion coefficient. The prototypical modeling study of Burgess et al. [18] stipulates that glioma growth results from an interplay between cell diffusion and cell proliferation. The authors have introduced a simple model for glioma growth based on cell proliferation, cell loss, cell death and cell diffusion starting with an initial tumor lump. Their assumptions are spherical symmetry, homogeneous diffusion and exponential growth. It is noted that in order to facilitate focusing on the cell diffusion phenomena several models assume, either explicitly or implicitly, a mean angiogenesis potential characterizing the entire brain. Inadequate angiogenesis and poorly functioning neovascularization are taken into account indirectly through the consideration of a tumor cell loss rate which along with the tumor cell division rate produce the net tumor growth rate.

A number of publications deal with the macroscopic mechanical deformations of the brain imposed by various agents such as neurosurgery or the macroscopic volume effect of brain tumors [19]. Although such approaches usually ignore tumor cell diffusion within the brain, they may be combined with diffusion based modeling techniques dealing with glioma invasion in order to provide a more comprehensive quantitative perception of the related composite phenomena. It should be noted, however, that a tumor growth modeling approach based exclusively on the continuous and/or finitized form of the diffusion–reaction equation has a limited potential to efficiently address the complexities of the treatment response phenomena in the multiscale context. The latter include inter alia the existence and dynamics of different proliferation potential cell categories (stem cells, limited mitotic potential cells, differentiated cells), different cell cycle phases (G1, S, G2, M), differing radiosensitivities and chemosensitivities, different times spent within each cell-cycle phase etc. Particularly efficient methods to mathematically describe and simulate tumor response to treatment have been based on the consideration of discrete entities and discrete events [20-24]. Therefore, in the future a more comprehensive model addressing both glioma invasion and response to complex treatment modalities could emerge by combining the continuous with the discrete mathematics approach mentioned so far.

For a biologically meaningful and computationally reliable diffusion based solution to the problem of diffusive clinical tumor growth and in particular glioma progression, a careful boundary condition handling is a sine qua non prerequisite. However, to the best of the authors’ knowledge no explicit treatment of the numerical application of boundary conditions in this context has appeared in the literature as yet. The latter is also in contrast with the importance of a careful handling of the boundary conditions between bone and soft issue which has been demonstrated in a number of cases in the neurosurgery setting. Therefore, the aim of this paper is to outline a detailed numerical handling of the boundary conditions imposed by the presence of the skull in the case of gliomas and in particular of glioblastoma multiforme.

According to the diffusion–reaction based approach the tumor is considered a spatiotemporal distribution of continuous cell density which follows the general diffusion–reaction law [25]. The macroscopic formulation of diffusion, leads to a partial parabolic differential equation. A single tumor cell may constitute the initial tumor within a three-dimensional medium. Tumor growth can be expressed by the following statement [26,27]:

\[
\frac{\partial c}{\partial t} = D \nabla ^2 c + \rho c - G(t)c + \text{loss of tumor cells due to treatment}.
\]

Rate of change of tumor cell population = diffusion(motility) of tumor cells + net proliferation of tumor cells

\[
- \text{loss of tumor cells due to treatment}.
\]

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 tumor, 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 \( \Omega \) 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]:

\[
\begin{aligned}
\left\{ & \frac{\partial c(x,t)}{\partial t} = \nabla \cdot (D \nabla c(x,t)) + \rho c(x,t) - G(t) c(x,t) \quad \text{in } \Omega \\
& c(x,0) = f(x) \quad \text{initial condition} \\
& n \cdot D \nabla c(x,t) = 0 \quad \text{on } \partial \Omega \quad \text{boundary condition} \right.
\end{aligned}
\]

(1)

The variable \( c \) denotes the cell concentration at any spatial point defined by the position vector \( x \) and time \( t \). The parameter \( D \) denotes the diffusion coefficient and represents the active motility of tumor cells. The term \( \rho \) represents the net rate of tumor growth including proliferation, loss and death, \( n \) is the unit vector normal to the boundary \( \partial \Omega \) of the domain \( \Omega \) and \( f(x) \) 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 \( \Omega \) of which \( \Omega \) is a subdomain is defined as:
\[ R = \{(x, y, z) | a < x < b, s < y < d, e < z < f \}. \]

Little progress has been made towards developing analytical solutions to the three dimensional diffusion equation with constant diffusion coefficient \( D \) when initial and boundary conditions are complex [28]. Therefore, the study of the diffusion equation from both the analytical and even more from the numerical standpoint is still an active field of research. The objective is to approximate the exact solution to the boundary value problem at a discrete set of spatial points and convert the continuous partial differential equation into a system of discrete algebraic equations.

2. Gridding scheme

The initial steps of the numerical simulation of a diffusion–reaction process include the selection of a suitable and efficient gridding scheme in order to finitize (discretize) the partial differential equation and the introduction of a grid (computational mesh) to be applied on the simulation domain containing the anatomic region of interest. A Cartesian coordinate system and a cubic grid have been adopted and implemented in this paper (Fig. 1). The latter has become the standard (default) choice in most fields of science when it comes to the utilization of the finite difference technique. It has also been proved the simplest and most straightforward approach adopted by several brain invasion tumor modelers up to the present [2,16]. However, it should be noted that other lattices have been sporadically reported in literature too. Nevertheless, due to the complex geometry of the boundaries of the skull cavity, resorting to any coordinate system other than the Cartesian one and to any grid other than the cubic one does not seem to be an obvious optimal choice. A combination of a Cartesian coordinate system with a cubic mesh apparently provides the simplest geometrical substrate for the formulation and application of the finite difference equations. Adoption of a different gridding scheme might result to a much more complex numerical formulation of the overarching equation and boundary conditions and therefore it has been avoided in this paper. The derivatives of the variable \( c \) in Eq. (1) need to be approximated at each computational node.

By inference, with the number of subintervals in each coordinate direction already selected, the computational grid consists of those points \((x_i, y_j, z_k)\), where

\[ x_i = a + ih, \]
\[ y_j = s + jh, \]
\[ z_k = e + kh \]

for \( i = 0, 1, 2, \ldots, N, j = 0, 1, 2, \ldots, M, k = 0, 1, 2, \ldots, L \).

The discretization is completed by the division of the time axis into uniform steps of length \( \Delta t \) and \( t_n = n\Delta t \), for \( n = 0, 1, 2, \ldots \) and so on (\( n \) is a time step counter). The step size is based on the behavior of the solution and is determined through an
attempt to obtain a solution with the minimum number of steps. Values for the approximate solution will be obtained at these discrete time levels. At each node of the discretizing mesh a value of cell density is assigned. Time is initialized and the continuous diffusion–reaction equation is formulated, discretized and applied on the mesh nodes.

3. The differential-algebraic equation solver

Having defined the computational grid, finite-difference methods are applied. Many different numerical approaches, for solving multidimensional parabolic initial-boundary value problems have been proposed. Three indicative groups of methods that are widely adopted are the following:

i. The explicit method: it uses a forward difference at time $t_n$ and is conditionally stable.

ii. The implicit method: it uses a backward difference at time $t_{n+1}$.

iii. The Crank–Nicolson method: it uses the central difference at time $t_{n+1/2}$.

The evaluation of numerical methods for initial value problems focuses on the discretization error and on the important properties of consistency, convergence and stability. The Crank–Nicolson method is considered the method of choice for many diffusion problems. It is the most accurate scheme for small time steps, in contrast with the explicit method which is the easiest one to implement but the least accurate and the most unstable. The implicit scheme works best for large time steps. The Crank–Nicolson method is second-order accurate in both time and space and unconditionally stable. It is recalled that an algorithm is called numerically stable if an error, whatever its cause, does not grow to be much larger during the calculation.

It is noted, however, that for large values of $D \Delta t/\Delta x^2$ and sharp initial transient conditions, the numerical solution based on Crank–Nicolson method may show oscillations related to the initial conditions. The oscillations may persist over a large number of steps. Several methods for damping the oscillations have been investigated [29].

The three dimensional problem described by Eq. (1) can be written equivalently as follows

$$\begin{align*}
\frac{\partial c}{\partial t} + \frac{\partial c_{i,j,k} + c_{i,j,k}}{\Delta t} &= 0 \\
\frac{\partial c}{\partial x} &= -\frac{\partial c_{i,j,k} + c_{i,j,k}}{\Delta x} \\
\frac{\partial c}{\partial y} &= -\frac{\partial c_{i,j,k} + c_{i,j,k}}{\Delta y} \\
\frac{\partial c}{\partial z} &= -\frac{\partial c_{i,j,k} + c_{i,j,k}}{\Delta z}
\end{align*}$$

Replacing all spatial derivatives with the average of their values at the $t$ and $t+1$ time levels and then substituting centered-difference forms for all derivatives, we obtain the Crank–Nicolson scheme:

$$\begin{align*}
\frac{c_{i+1,j,k} - c_{i,j,k}}{\Delta t} &= \rho \frac{c_{i+1,j,k} - 2c_{i,j,k} + c_{i-1,j,k}}{\Delta x^2} \quad \text{Eq. (8)} \\
\frac{c_{i,j+1,k} - c_{i,j,k}}{\Delta y} &= -\rho \frac{c_{i,j+1,k} - 2c_{i,j,k} + c_{i,j-1,k}}{\Delta y^2} \quad \text{Eq. (9)} \\
\frac{c_{i,j,k+1} - c_{i,j,k}}{\Delta z} &= -\rho \frac{c_{i,j,k+1} - 2c_{i,j,k} + c_{i,j,k-1}}{\Delta z^2} \quad \text{Eq. (10)}
\end{align*}$$

where $c_{i,j,k}$ is the finite difference approximation of $c$ at the grid point $(x_i,y_j,z_k)$ at time $t$. So, the following formula has been used for the solution:

$$\begin{align*}
\frac{c_{i,j,k} - c_{i,j,k}}{\Delta t} &= \frac{1}{2} \left( \frac{c_{i+1,j,k} - 2c_{i,j,k} + c_{i-1,j,k}}{\Delta x^2} \right) + \frac{1}{2} \left( \frac{c_{i,j+1,k} - 2c_{i,j,k} + c_{i,j-1,k}}{\Delta y^2} \right) + \frac{1}{2} \left( \frac{c_{i,j,k+1} - 2c_{i,j,k} + c_{i,j,k-1}}{\Delta z^2} \right) \\
\frac{c_{i,j,k} - c_{i,j,k}}{\Delta t} &= \frac{1}{2} \left( \frac{c_{i+1,j,k} - 2c_{i,j,k} + c_{i-1,j,k}}{\Delta x^2} \right) + \frac{1}{2} \left( \frac{c_{i,j+1,k} - 2c_{i,j,k} + c_{i,j-1,k}}{\Delta y^2} \right) + \frac{1}{2} \left( \frac{c_{i,j,k+1} - 2c_{i,j,k} + c_{i,j,k-1}}{\Delta z^2} \right) \quad \text{Eq. (11)}
\end{align*}$$

In the case that $\rho, G$ are time independent and $\Delta x = \Delta y = \Delta z = h$, it holds:

$$\begin{align*}
1 + 6 \Delta t (\rho - G) c_{i,j,k} &= \frac{1}{2} \left( c_{i+1,j,k} + c_{i,j,k} + c_{i,j,k+1} + c_{i,j,k} + c_{i,j,k+1} \right) \\
1 - 6 \Delta t (\rho - G) c_{i,j,k} &= \frac{1}{2} \left( c_{i+1,j,k} + c_{i,j,k} + c_{i,j,k+1} + c_{i,j,k} + c_{i,j,k+1} \right)
\end{align*}$$

$$\begin{align*}
1 + 6 \Delta t (\rho - G) c_{i,j,k} &= \left( c_{i+1,j,k} + c_{i,j,k} + c_{i,j,k+1} + c_{i,j,k+1} \right) \\
1 - 6 \Delta t (\rho - G) c_{i,j,k} &= \left( c_{i+1,j,k} + c_{i,j,k} + c_{i,j,k+1} + c_{i,j,k+1} \right)
\end{align*}$$

(14)
where
\[ \lambda = D \Delta t / [2(h)^2]. \] (15)

### 4. Implementation of the iterative system solver adopted

The resulting system of Eq. (1) may be written equivalently in the form
\[ \tilde{A} \tilde{x} = \tilde{b}, \] (16)

where \( \tilde{x} \) denotes a vector that contains an approximation of the solution \( c \) at the mesh nodes at time \( t = t_n \).

To find the structure of the coefficient matrix \( \tilde{A} \), a common numbering scheme has been used namely the lexicographic ordering. The number written next to the location of each unknown is the lexicographic number associated with the unknown (Fig. 2). Supposing \( m \) denotes the number of nodes in the computational mesh, the matrix \( \tilde{A} \in \mathbb{R}^{m \times m} \) is a sparse, symmetric matrix and \( \tilde{x} \in \mathbb{R}^m \) denotes a vector that contains an approximation of the solution \( c \) at the mesh nodes at time \( t = t_n \).

There are major ways of solving linear systems of equations: direct methods such as the Lower–Upper (LU) decomposition and Cholesky and iterative methods that are more efficient. In contrast to direct methods, iterative methods are not expected to terminate in a number of steps. Starting from an initial guess, iterative methods form successive approximations that converge to the exact solution only in the limit. A convergence criterion is specified in order to decide when a sufficiently accurate solution has been found. Additionally, with an iterative technique, there is no need to store the coefficient matrix. The only thing that must be known is the structure of the equations. In addition to that, an iterative solution requires fewer total operations. Due to the nature of the three dimensional problem, direct solution methods are not suitable for their prohibitive CPU and memory expenses.

The algorithm selected for the solution of this large sparse system (Eq. (16)) is the non-stationary iterative Conjugate Gradient method (CG) which generates a sequence of approximations that converges rapidly to the desired solution and is widely used for the solution of linear sparse systems. The stationary iterative methods like Jacobi (simultaneous relaxation), Gauss–Seidel (successive relaxation), SOR (successive overrelaxation) are not used due to their slow convergence which takes place after many iterations. Non-stationary iterative methods can basically be described by an iterative scheme which assumes that the next iteration point corresponds to the sum of the value of the initial point plus the correction terms of all iterations. The correctors are vectors, which means that they have both magnitude and direction.

### 5. Explicit formulation of the boundary conditions

For a numerical simulation a region of interest within which the actual simulation is to take place is defined. This region usually possesses a boundary separating it from the surrounding environment. Numerical simulations should address the
physical processes taking place around the boundaries too. In most cases the boundary conditions are very important for the outcome of the simulation. Different boundary conditions may lead to different simulation results. Improper sets of boundary conditions may introduce non physical influences on the simulated system, while a proper set of boundary conditions can avoid that.

In a spatiotemporal model of tumor growth, any anatomic boundaries of the space where tumor can grow must be taken into account. In order to complete the model formulation for clinical glioblastoma growth boundary conditions have to be added precluding migration beyond the skull boundary. The simulation of tumor growth and invasion can be viewed as a boundary value problem strongly dependent on the values assigned on the physical boundary of the definition domain. Thus the first step to be taken is to select the appropriate type of boundary conditions.

There are three types of boundary conditions commonly encountered in the solution of diffusion and in general in the solution of partial differential equations (PDEs) [30,31]:

i. Dirichlet boundary condition: The value of the unknown function \( c \) (solution of the PDE) on some domain \( \Omega \) is specified on a boundary surface of \( \Omega \).

\[
c(x, y, z) = f(x, y, z) \quad \forall (x, y, z) \in \partial \Omega.
\]

where \( f \) is a known given function defined on the boundary \( \partial \Omega \).

ii. Neumann boundary conditions: The normal derivative of the unknown function \( c \) (solution of the PDE) is specified over a boundary \( \partial \Omega \) (that is, the derivative of the solution normal to \( \partial \Omega \)).

\[
\frac{\partial c}{\partial n}(x, y, z) = \hat{n} \cdot \nabla c = f(x, y, z) \quad \forall (x, y, z) \in \partial \Omega.
\]

iii. Robin boundary conditions (or mixed boundary conditions).

\[
a(x, y, z)c(x, y, z) + \beta(x, y, z)\hat{n} \cdot \nabla c(x, y, z) = f(x, y, z) \quad \forall (x, y, z) \in \partial \Omega.
\]

In the case of a diffusive glioma lying within the brain an eventual adoption of Dirichlet boundary conditions would lead to predefined values of tumor cell concentration on the brain–skull boundary. In the simplest case of pure diffusion, the latter could only be achieved through the emergence of (artifact) tumor cell sources and/or sinks that would keep the boundary cell concentration values constant. Obviously such an approach would be unacceptable.

On the other hand an eventual adoption of Neumann boundary conditions would impose a predefined normal derivative of the tumor cell concentration on the brain–skull boundary. In the special case that \( \frac{\partial c}{\partial n} = 0 \), where \( c \) is the tumor cell concentration, adiabatic boundary conditions are implied. These are called homogeneous Neumann boundary conditions. The latter physically correspond to no net flow of tumor cells out of or into the brain region across the brain–skull boundary. In that case the diffusion region is insulated. Therefore, Neumann boundary conditions are the most appropriate for the problem addressed.

The mathematical problem was initially defined for a cubic domain. Since, however, the real glioma problem involves an irregularly shaped domain, a biologically meaningful solution had to allow for the investigation of a wide range of 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-colored structure of Fig. 3 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 \((x_i, y_j, z_k)\).

The boundary condition according to Eq. (1) is:

\[
\hat{n} \cdot D\nabla c = 0 \quad \text{on} \quad \partial \Omega.
\]

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 \( A \) and the second-order accuracy of the approximation we introduce a “fictitious node” to 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 the following.

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

\[
\frac{\partial c}{\partial x}\bigg|_{(x_i, y_j, z_k)} = 0 \Rightarrow c_{i-1,j,k} = c_{i+1,j,k}.
\]

At the boundary grid point \((x_i, y_j, z_k)\) in the positive \( x \) direction \( x^+ \):

\[
\frac{\partial c}{\partial x}\bigg|_{(x_i, y_j, z_k)} = 0 \Rightarrow c_{i+1,j,k} = c_{i-1,j,k}.
\]

At the boundary grid point \((x_i, y_j, z_k)\) in the negative \( y \) direction \( y^- \):
is 26. This has led to the formulation of 26 algebraic equations (denoted by Eqs. (27)–(52)). An appropriate equation out of the set of Eqs. (27)–(52) is used for any index triplet (i, j, k).

At the boundary grid point (xi, yj, zk) in the positive y direction y+:

\[ \frac{\partial c}{\partial y_{(x_i,y_j,z_k)}} = 0 \Rightarrow c_{i,j+1,k} = c_{i,j-1,k}. \] (23)

At the boundary grid point (xi, yj, zk) in the negative z direction z−:

\[ \frac{\partial c}{\partial z_{(x_i,y_j,z_k)}} = 0 \Rightarrow c_{i,j,k+1} = c_{i,j,k-1}. \] (24)

At the boundary grid point (xi, yj, zk) in the positive z direction z+:

\[ \frac{\partial c}{\partial z_{(x_i,y_j,z_k)}} = 0 \Rightarrow c_{i,j,k-1} = c_{i,j,k+1}. \] (25)

where \( F_{ijk} \) denotes a fictitious node.

The total number of the different cases of nodes having boundary node(s) as their neighbor(s) that have been considered is 26. This has led to the formulation of 26 algebraic equations (denoted by Eqs. (27)–(52)). An appropriate equation out of the set of Eqs. (27)–(52) is used for any index triplet (i, j, k) belonging to the boundary. By fixing indices i, j, k to specific values, Eqs. (27)–(52) can produce all elementary boundary arrangements encountered in the case of an arbitrarily shaped boundary. The 26 different cases are the following:

At the boundary grid point (xi, yj, zk) where the skull lies only in the positive x direction:

\[
1 + 6\lambda - \frac{\Delta t}{2}(\rho - G) \left[ c^{i+1}_{i,j,k} - \lambda \left( 2c^{i+1}_{i+1,j,k} + c^{i+1}_{i,j,k+1} + c^{i+1}_{i,j,k-1} + c^{i+1}_{i,j,k-1} \right) \right] = 1 - 6\lambda + \frac{\Delta t}{2}(\rho - G) \left[ c^{i-1}_{i,j,k} + \lambda \left( 2c^{i-1}_{i,j,k-1} + c^{i-1}_{i,j,k+1} + c^{i-1}_{i,j,k+1} + c^{i-1}_{i,j,k-1} \right) \right].
\] (27)

At the boundary grid point (xi, yj, zk) where the skull lies only in the negative x direction:

\[
1 + 6\lambda - \frac{\Delta t}{2}(\rho - G) \left[ c^{i+1}_{i,j,k} - \lambda \left( 2c^{i+1}_{i+1,j,k} + c^{i+1}_{i,j,k+1} + c^{i+1}_{i,j,k-1} + c^{i+1}_{i,j,k-1} \right) \right] = 1 - 6\lambda + \frac{\Delta t}{2}(\rho - G) \left[ c^{i-1}_{i,j,k} + \lambda \left( 2c^{i-1}_{i,j,k-1} + c^{i-1}_{i,j,k+1} + c^{i-1}_{i,j,k+1} + c^{i-1}_{i,j,k-1} \right) \right].
\] (28)

At the boundary grid point (xi, yj, zk) where the skull lies only in the positive y direction:
\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i+1}_{i,j;k} - \lambda \left( c^{i+1}_{i+1,j,k} + c^{i+1}_{i-1,j,k} + 2c^{i+1}_{i,j-1,k} + c^{i+1}_{i,j,k+1} + c^{i+1}_{i,j,k-1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( c^{i}_{i+1,j,k} + c^{i}_{i-1,j,k} + 2c^{i}_{i,j-1,k} + c^{i}_{i,j,k+1} + c^{i}_{i,j,k-1} \right). \tag{29}
\]

At the boundary grid point \((x_i, y_j, z_k)\) where the skull lies only in the negative \(y\) direction:

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( c^{i+1}_{i,j+1,k} + c^{i+1}_{i,j-1,k} + 2c^{i+1}_{i,j-1,k} + c^{i+1}_{i,j,k+1} + c^{i+1}_{i,j,k-1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( c^{i}_{i,j+1,k} + c^{i}_{i,j-1,k} + 2c^{i}_{i,j-1,k} + c^{i}_{i,j,k+1} + c^{i}_{i,j,k-1} \right). \tag{30}
\]

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

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( c^{i+1}_{i,j+1,k} + c^{i+1}_{i,j-1,k} + 2c^{i+1}_{i,j-1,k} + c^{i+1}_{i,j,k+1} + c^{i+1}_{i,j,k-1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( c^{i}_{i,j+1,k} + c^{i}_{i,j-1,k} + 2c^{i}_{i,j-1,k} + c^{i}_{i,j,k+1} + c^{i}_{i,j,k-1} \right). \tag{31}
\]

At the boundary grid point \((x_i, y_j, z_k)\) where the skull lies only in the negative \(z\) direction:

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( c^{i+1}_{i,j+1,k} + c^{i+1}_{i,j-1,k} + 2c^{i+1}_{i,j-1,k} + c^{i+1}_{i,j,k+1} + c^{i+1}_{i,j,k-1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( c^{i}_{i,j+1,k} + c^{i}_{i,j-1,k} + 2c^{i}_{i,j-1,k} + c^{i}_{i,j,k+1} + c^{i}_{i,j,k-1} \right). \tag{32}
\]

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

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( 2c^{i+1}_{i+1,j,k} + c^{i+1}_{i-1,j,k} + 2c^{i+1}_{i,j-1,k} + c^{i+1}_{i,j,k+1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( 2c^{i}_{i+1,j,k} + c^{i}_{i-1,j,k} + 2c^{i}_{i,j-1,k} + 2c^{i}_{i,j,k-1} \right). \tag{33}
\]

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

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( 2c^{i+1}_{i+1,j,k} + c^{i+1}_{i-1,j,k} + 2c^{i+1}_{i,j-1,k} + c^{i+1}_{i,j,k+1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( 2c^{i}_{i+1,j,k} + c^{i}_{i-1,j,k} + 2c^{i}_{i,j-1,k} + 2c^{i}_{i,j,k-1} \right). \tag{34}
\]

At the boundary grid point \((x_i, y_j, z_k)\) where the skull lies only in the positive \(y\) direction and the positive \(z\) direction:

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( c^{i+1}_{i+1,j,k} + c^{i+1}_{i-1,j,k} + 2c^{i+1}_{i,j-1,k} + 2c^{i+1}_{i,j,k+1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( c^{i}_{i+1,j,k} + c^{i}_{i-1,j,k} + 2c^{i}_{i,j-1,k} + 2c^{i}_{i,j,k+1} \right). \tag{35}
\]

At the boundary grid point \((x_i, y_j, z_k)\) where the skull lies only in the negative \(y\) direction and the positive \(z\) direction:

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( c^{i+1}_{i+1,j,k} + c^{i+1}_{i-1,j,k} + 2c^{i+1}_{i,j-1,k} + 2c^{i+1}_{i,j,k+1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( c^{i}_{i+1,j,k} + c^{i}_{i-1,j,k} + 2c^{i}_{i,j-1,k} + 2c^{i}_{i,j,k+1} \right). \tag{36}
\]

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

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( 2c^{i+1}_{i+1,j,k} + c^{i+1}_{i-1,j,k} + 2c^{i+1}_{i,j-1,k} + 2c^{i+1}_{i,j,k+1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( 2c^{i}_{i+1,j,k} + c^{i}_{i-1,j,k} + 2c^{i}_{i,j-1,k} + 2c^{i}_{i,j,k+1} \right). \tag{37}
\]

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

\[
\left[ 1 + 6 \lambda - \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} - \lambda \left( 2c^{i+1}_{i+1,j,k} + c^{i+1}_{i-1,j,k} + 2c^{i+1}_{i,j-1,k} + 2c^{i+1}_{i,j,k+1} \right)
\]

\[
= \left[ 1 - 6 \lambda + \frac{\Delta t}{2} (\rho - G) \right] c^{i}_{i,j;k} + \lambda \left( 2c^{i}_{i+1,j,k} + c^{i}_{i-1,j,k} + 2c^{i}_{i,j-1,k} + 2c^{i}_{i,j,k+1} \right). \tag{38}
\]
At the boundary grid point \((x_i, y_j, z_k)\) where the skull lies only in the negative \(z\) direction and the positive \(y\) direction:

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

(39)

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

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

(40)

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

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

(41)

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

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

(42)

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

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

(43)

At the boundary grid point \((x_i, y_j, z_k)\) where the skull lies only in the negative \(y\) direction and the negative \(x\) direction:

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

(44)

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

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

(45)

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

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

(46)

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

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

(47)
At the boundary grid point \((x_i,y_j,z_k)\) where the skull lies only in the negative \(x\) direction, the negative \(y\) direction and the negative \(z\) direction:

\[
\left[1 + 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l+1} - \lambda \left(2c_{i-1,j,k}^{l+1} + 2c_{i+1,j,k}^{l+1} + 2c_{i,j-1,k}^{l+1} + 2c_{i,j+1,k}^{l+1}\right) = \left[1 - 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l} + \lambda \left(2c_{i-1,j,k}^{l} + 2c_{i+1,j,k}^{l} + 2c_{i,j-1,k}^{l} + 2c_{i,j+1,k}^{l}\right). \quad (48)
\]

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

\[
\left[1 + 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l+1} - \lambda \left(2c_{i-1,j,k}^{l+1} + 2c_{i+1,j,k}^{l+1} + 2c_{i,j-1,k}^{l+1} + 2c_{i,j+1,k}^{l+1}\right) = \left[1 - 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l} + \lambda \left(2c_{i-1,j,k}^{l} + 2c_{i+1,j,k}^{l} + 2c_{i,j-1,k}^{l} + 2c_{i,j+1,k}^{l}\right). \quad (49)
\]

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

\[
\left[1 + 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l+1} - \lambda \left(2c_{i-1,j,k}^{l+1} + 2c_{i+1,j,k}^{l+1} + 2c_{i,j-1,k}^{l+1} + 2c_{i,j+1,k}^{l+1}\right) = \left[1 - 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l} + \lambda \left(2c_{i-1,j,k}^{l} + 2c_{i+1,j,k}^{l} + 2c_{i,j-1,k}^{l} + 2c_{i,j+1,k}^{l}\right). \quad (50)
\]

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

\[
\left[1 + 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l+1} - \lambda \left(2c_{i-1,j,k}^{l+1} + 2c_{i+1,j,k}^{l+1} + 2c_{i,j-1,k}^{l+1} + 2c_{i,j+1,k}^{l+1}\right) = \left[1 - 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l} + \lambda \left(2c_{i-1,j,k}^{l} + 2c_{i+1,j,k}^{l} + 2c_{i,j-1,k}^{l} + 2c_{i,j+1,k}^{l}\right). \quad (51)
\]

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

\[
\left[1 + 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l+1} - \lambda \left(2c_{i-1,j,k}^{l+1} + 2c_{i+1,j,k}^{l+1} + 2c_{i,j-1,k}^{l+1} + 2c_{i,j+1,k}^{l+1}\right) = \left[1 - 6\lambda \frac{\Delta t}{2} (\rho - G)\right] c_{i,j,k}^{l} + \lambda \left(2c_{i-1,j,k}^{l} + 2c_{i+1,j,k}^{l} + 2c_{i,j-1,k}^{l} + 2c_{i,j+1,k}^{l}\right). \quad (52)
\]

### 6. 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. Initially, in order to provide quantitative checks exclusively of the linear component of the analysis presented in the most controllable way, pure diffusion has been considered in a number of numerical experiments performed. A special simplified problem for which an analytic solution is available [32] has been addressed in order to validate parts of the code and study the effects of several numerical factors on the simulation outcome.

In a cubic domain \(R = \Omega\), with boundaries at \(\partial R = \partial \Omega\) the following initial condition is assumed

\[
c(x, y, z, 0) = \exp \left(- \frac{(x-x_0)^2}{2\sigma_0^2} - \frac{(y-y_0)^2}{2\sigma_0^2} - \frac{(z-z_0)^2}{2\sigma_0^2}\right), \quad (x, y, z) \in \Omega. \quad (53)
\]

where \(\sigma_0\) is the initial standard deviation of the Gaussian hump. The net growth rate and the loss rate due to treatment are equal to zero. For an infinite domain, the analytical solution for pure diffusion [33] can be expressed as

\[
c(x, y, z, t) = \frac{\sigma_0^2}{\sigma^2} \exp \left(- \frac{(x-x_0)^2}{2\sigma^2} - \frac{(y-y_0)^2}{2\sigma^2} - \frac{(z-z_0)^2}{2\sigma^2}\right). \quad (54)
\]

\[
\sigma^2 = \sigma_0^2 + 2Dt. \quad (55)
\]

For \(\sigma_0 = 3h\) and \(t = n\Delta t\), where \(h\) is the nodal spacing, \(\Delta t\) is the time step, \(n\) is a time step counter, \(\bar{x} = (x, y, z)\) are the spatial coordinates of the node, \((x_0, y_0, z_0)\) is the center of the cube, \(D\) is the diffusion coefficient, \(c(\bar{x}, t)\) is the concentration at time and spatial point \(\bar{x}\) and \(\lambda = D\Delta t/(2h^2)\). The domain is taken sufficiently large such that the application of the boundary conditions does not significantly affect the computations in the region of interest.

At the end of each simulation aiming at validating the numerical treatment by exploiting the analytical solution, the relative percentage error \(e\) is calculated. The latter is calculated by comparing the predicted values generated by the model with the ones obtained by the analytical solution. The relative percentage error is defined as

\[
e = \left|\frac{c - c_{\text{approx}}}{c}\right| \times 100\%, \quad (56)
\]

where \(c\) is the concentration calculated using the analytical solution and \(c_{\text{approx}}\) is the numerically calculated concentration.
6.1. Convergence and stability

In this section the pure diffusion aspects of the analysis presented are addressed. Checks of the non-linear behavior of tumor cell proliferation are provided in Section 6.6. In order to study the convergence and stability characteristics of the Crank–Nicolson scheme that has been employed for the numerical solution of the partial diffusion–reaction differential equation, the spatiotemporal cell density distribution has been calculated for different values of the elementary time interval $\Delta t$ and the elementary spatial (length) interval $h$ for the initial value problem described in the previous part of Section 6. A numerical verification of the second order accuracy of the scheme in both time and space has been achieved. The diffusion coefficient $D$ has been assumed equal to 0.0065 cm$^2$/d (d denotes the time unit day here). This is an estimated value of $D$ in corpus callosum being the largest white matter structure in brain. The particular value expresses the advancing speed of the tumor margin across it [1]. It should be kept in mind that gliomas are expected to emerge within the white matter and therefore a large percentage of the spatial region with the highest concentration of tumor cells is expected to involve white matter. Since homogeneous diffusion has been assumed in this paper, for the needs of simulations presented the value of $D$ has been assumed to hold true for the entire interior of the cranial cavity. The latter obviously constitutes a first gross approximation. Fig. 4 summarizes the relative percentage error in the approximate solution at $t = 200$ d for different values of $h$. For all calculations a time step of $\Delta t = 0.1$ d has been used. Fig. 5 presents the error of the approximate solution at $t = 200$ d for different values of $\Delta t$, with $h$ fixed at 0.1 cm.

It is noted that the mean relative percentage error for the case of $h = 0.75$ cm approximately reaches the value 9% after 200 simulated days. This is pretty reasonable since the spatial discretization of the domain that includes the tumor is too sparse. The discretization of 0.1 cm is used in most of the simulations performed in the rest of the paper. The latter leads to an error of about 0.15% after 200 simulated days for typical model parameter values for the case of glioblastoma. According to Fig. 5, a temporal discretization with a temporal unit equal to 1 d would be acceptable since it leads to an error of less than 1% after 200 simulated days. In order to further improve accuracy a temporal discretization of $\Delta t = 0.5$ d is used in the rest of the paper.

6.2. Pure diffusion: mass conservation and linearity checks

Mass or matter conservation within a closed system is a fundamental law of classical physics. Based on this principle the mass of substances contained within a closed system, i.e. a completely isolated system, will remain constant over time no matter what processes are acting inside the system. In the following hypothetical problem where pure glioma cell diffusion takes place within an isolated domain in which tumor cells can neither be born nor die, mass conservation must hold true. It is stressed that this biologically unrealistic scenario has been considered exclusively for the sake of partial mathematical validation of the analysis presented. The total (non dimensional) tumor mass in this hypothetical problem is represented by the sum of tumor cells, assuming that each tumor cell possesses the same elementary cell mass. Mass conservation has been verified by the numerical experimentation described below.

An initial hypothetical spherical tumor of radius equal to 2 mm has been assumed. The computational domain has been taken sufficiently large such that the application of boundary conditions would not significantly affect the computations in the region of interest. The initial cell concentration is assumed $10^6$ cells/mm$^3$ inside the sphere and 0 cells/mm$^3$ outside the sphere. The value of the $10^6$ cells/mm$^3$ is a plausible estimate for at least an avascular glioma tumorlet of volume equal to 1 mm$^3$ according to literature [34]. Net tumor growth rate and loss rate due to treatment are considered zero. Homogeneous Neumann boundary conditions (no tumor cell flux through the boundary) have been applied on the boundaries of the domain.

Code executions have shown that the total number of tumor cells inside the mesh remains practically stable with only slight deviations due to the accumulation of minimal numerical errors for a considerable time interval. According to

---

**Fig. 4.** Relative percentage error for different values of $h$. For all calculations a constant/fixed time step of $\Delta t = 0.1$ d has been used and the approximate solution has been obtained at $t = 200$ d (see text for details).
Fig. 6 for the above mentioned parameter values this is larger than 700 d. The latter is pretty reasonable since the initial total number of cells have been placed in a region very small in comparison with the dimensions of the discretization mesh.

The relative percentage error of the total number of tumor cells with regard to the initial number of tumor cells is depicted in Fig. 7. The error shown in Fig. 7 is mainly due to the replacement of the continuous expressions of the derivatives with their numerical (algebraic) counterpart. It is noted that after 700 simulated days the percentage relative error is kept less than 5%.

For the extreme case of pure diffusion (no sources, no sinks) described above, it has been verified that if the initial cell concentration is doubled at all points of the discretization mesh i.e.

\[ c_2(x_i, y_j, z_k, 0) = 2c_1(x_i, y_j, z_k, 0), \]  

the cell concentration at any given spatiotemporal point \((x_i, y_j, z_k, t)\) is doubled in relation to its value corresponding to the reference initial cell concentration. Therefore, the new tumor cell concentration value at point \((x_i, y_j, z_k, t)\) is:

\[ c_2(x_i, y_j, z_k, t) = 2c_1(x_i, y_j, z_k, t). \]  

The ratio \(c_2(x_i, y_j, z_k, t)/c_1(x_i, y_j, z_k, t)\) is depicted in Fig. 8. It is clear that the ratio \(c_2(x_i, y_j, z_k, t)/c_1(x_i, y_j, z_k, t)\) is equal to the ratio \(c_2(x_i, y_j, z_k, 0)/c_1(x_i, y_j, z_k, 0)\). This is a validation of the purely diffusive linear component of the simulation code.

6.3. Comparison with the analytical solution for a special case

In order to study the accuracy of the diffusive component of the numerical algorithm, a comparison between the numerical and the analytical solution to the initial value problem described in the first part of Section 6 has been performed. The following parameter values have been considered: \(\Delta t = 0.5\) d, \(h = 0.1\) cm, \(D = 0.0065\) cm\(^2\)/d \((\lambda = 0.1625)\), zero net tumor growth rate and zero tumor loss rate due to treatment. The results are shown in Fig. 9. It is obvious that numerical results are in excellent agreement with the analytical solution. The mean percentage error at \(t = 25\) d, \(t = 50\) d and \(t = 100\) d is depicted in Fig. 10. As simulated time increases a damping of numerical oscillations is observed leading to the minimization of the total error.

Fig. 6. Total number of cells for an exclusively mathematically relevant scenario of pure homogeneous diffusion of glioma cells within an isolated domain. A sphere of radius equal to 2 mm has been considered. The initial cell concentration inside the sphere is supposed to be \(10^6\) cells/mm\(^3\) and 0 cells/mm\(^3\) elsewhere. The net tumor growth rate and loss rate due to treatment are considered zero. On the boundaries of the mesh homogeneous Neumann conditions (no tumor cell flux through the boundary) have been applied.
6.4. Symmetry studies

Pure tumor cell diffusion is assumed here too. The following parameter and gridding values have been used: an initial hypothetical spherical tumor of radius = 2 cm centrally positioned inside a cubic mesh of 9 cm × 9 cm × 9 cm with adiabatic boundaries, zero net tumor growth rate and zero loss rate due to treatment, cell concentration within the initial spherical tumor equal to \(10^6 \text{ cells/mm}^3\) diffusion coefficient \(D = 0.0065 \text{ cm}^2/\text{d}\). The cell concentration \(c\) at symmetric nodes has been calculated for \(h = 0.1 \text{ cm}\) and \(\Delta t = 0.5 \text{ d}\) at different simulated times. Code executions show that the shape of the tumor remains conformal to its initial geometrical form. The corresponding numerical predictions of the tumor cell concentration obtained after 100 and 200 simulated days assuming that \((x_0, y_0, z_0)\) lies at the center of the gridding cube, are (Fig. 11):

\[
\begin{align*}
    c(x_0 + 0.5, y_0 + 0.5, z_0 + 0.5, 0) &= c(x_0 - 0.5, y_0 - 0.5, z_0 - 0.5, 0) = 10^6 \text{ cells/mm}^3, \\
    c(x_0 + 0.5, y_0 + 0.5, z_0 + 0.5, 100) &= c(x_0 - 0.5, y_0 - 0.5, z_0 - 0.5, 100) = 535.358 \text{ cells/mm}^3, \\
    c(x_0 + 0.5, y_0 + 0.5, z_0 + 0.5, 200) &= c(x_0 - 0.5, y_0 - 0.5, z_0 - 0.5, 200) = 293.789 \text{ cells/mm}^3.
\end{align*}
\]

It is noted that the spatial coordinate values are in cm, whereas the temporal coordinate values are in d. Additionally, although biological cells are discrete entities, fractional values of the number of cells are accepted only as intermediate results of the mathematical treatment in order to minimize errors induced by numerical methods.

In conclusion, symmetry is conserved for the case of a symmetrical initial geometry of the purely diffusive system under consideration. Thus, for example, the symmetric points below have the same cell concentration at any time point.

\[
\begin{align*}
    c(x_0 + \xi, y_0 + \xi, z_0 + \xi, t) &= c(x_0 - \xi, y_0 - \xi, z_0 - \xi, t), \\
    c(x_0 + \xi, y_0 + \xi, z_0 + \xi, 2t) &= c(x_0 - \xi, y_0 - \xi, z_0 - \xi, 2t).
\end{align*}
\]

This observation provides further support to the correctness of the diffusive component of the simulation code.

---

**Fig. 7.** Plot of the relative percentage error of the total number of tumor cells with regard to their initial number. Pure diffusion is considered for validation purposes only. The error is mainly due to the replacement of the continuous expressions of the derivatives with their numerical (algebraic) counterpart. It is noted that after 700 simulated days the percentage relative error is kept less than 5%.

**Fig. 8.** Linearity check over a central axis of the discretization mesh. For the extreme hypothetical case of pure diffusion (no sources, no sinks), it is verified that if the initial cell concentration is doubled at all points of the discretization mesh, the cell concentration at any given spatiotemporal point \((x_i, y_i, z_i, t)\) is doubled in relation to its value corresponding to the reference initial cell concentration.
6.5. Numerical validation of the adiabatic behavior of the boundary implementation

Several pertinent boundary geometry scenarios have been addressed. In order to check the correctness of the boundary treatment component of the simulation code the following two criteria have been adopted:

i. prohibition of tumor cell transfer through the skull;
ii. conservation of the total number of tumor cells within the skull cavity in the special fictitious (and exclusively mathematically relevant) case of pure diffusion with neither cell generation nor cell death. Obviously, in the biologically relevant scenarios addressed where tumor cell proliferation and loss are present this criterion is irrelevant.

Fig. 9. Comparison between the numerical and the analytical solution for pure diffusion. The results have been obtained for points lying at the central axis of the mesh at $t = 25 \text{ d}$, $t = 50 \text{ d}$ and $t = 100 \text{ d}$. The following parameter values have been considered: $\Delta t = 0.5 \text{ d}$, $h = 0.1 \text{ cm}$, $D = 0.0065 \text{ cm}^2/\text{d}$, zero net tumor growth rate and zero tumor loss rate due to treatment. The concentration $c$ is in cells/mm$^3$ although concentration values in this figure do not necessarily correspond to biologically meaningful situations. They just correspond to a published particular general diffusion problem which is exploited for the mathematical checking of the code. It is obvious that numerical results are in excellent agreement with the analytical solution. Solid lines correspond to the analytical solutions whereas dots correspond to numerical solutions.

Fig. 10. The mean percentage error at $t = 25 \text{ d}$, $t = 50 \text{ d}$ and $t = 100 \text{ d}$. The following parameter values have been considered: $\Delta t = 0.5 \text{ d}$, $h = 0.1 \text{ cm}$, $D = 0.0065 \text{ cm}^2/\text{d}$, zero net tumor growth rate and zero tumor loss rate due to treatment. As simulated time increases damping of numerical oscillations is observed leading to the minimization of the total error.

Fig. 11. Cell concentration $c$ at symmetric nodes for an initial hypothetical spherical tumor of radius $2 \text{ cm}$ centrally positioned inside a cubic mesh of $9 \text{ cm} \times 9 \text{ cm} \times 9 \text{ cm}$. $c$ has been calculated for a diffusion coefficient $D = 0.0065 \text{ cm}^2/\text{d}$, cell concentration within the initial spherical tumor equal to $10^6 \text{ cells/mm}^3$, $h = 0.1 \text{ cm}$ and $\Delta t = 0.5 \text{ d}$ at different simulated times. Pure diffusion is considered. The corresponding numerical predictions of the tumor cell concentration obtained after 100 and 200 simulated days at the point $(x_0 + 0.5, y_0 + 0.5, z_0 + 0.5)$ and at its symmetric point $(x_0 - 0.5, y_0 - 0.5, z_0 - 0.5)$ assuming that $(x_0, y_0, z_0)$ lies at the center of the gridding cube are equal. All spatial values are in cm.
In order to check the validity of the macroscopic diffusive behavior of the mathematical treatment presented along with its boundary condition component various forms of a fictitious growing and diffusive entity starting with well defined initial cubic boundaries have been assumed.

Fig. 12, represents a two-dimensional slice of a fictitious growing and diffusive entity with the dynamic characteristics of glioblastoma with net growth rate equal to $\rho = 0.012 \text{ d}^{-1}$ [26] and loss rate due to treatment equal to $G = 0.0013 \text{ d}^{-1}$. Grey level intensity depends on cell concentration. Several snapshots of the simulation corresponding to various time points are depicted. As time increases the entity image is gradually becoming blurred due to diffusion as expected.

A three dimensional visualization of the simulation results for an arbitrary boundary geometry is shown in Fig. 13. An initial virtual spherical tumor is supposed to lie inside the boundary cavity. As time increases, the tumor grows and diffuses over the entire mesh. However, it does not migrate beyond the boundary. Thus criterion i is satisfied. Visualization details are provided in Fig. 14.

Fig. 15 demonstrate the adiabatic behavior of a perfect cubic boundary (different from the one considered in Figs. 13 and 14). The tumor located inside clearly shows a diffusive behavior. It is also noted that the final shape of the tumor is practically conformal to its initial counterpart for the first 150 simulated days.

For the case of pure diffusion described in the first part of Section 6 assuming adiabatic boundary conditions the concentration on the central axis of the mesh has been sampled at different time points (Fig. 16). As time increases all the nodes included within the domain tend to have the same cell concentration. Therefore, a state of equilibrium is approached as expected.

6.6. Towards a clinical validation of the model: initial steps

This section contains the initial steps of an envisaged systematic clinical validation of the composite model. A typical real human head has been considered (Fig. 17). The three dimensional image depicted in panel A of Fig. 17 has been constructed using a freely available T1 weighted MRI head dataset (J. Orchard, http://www.cs.uwaterloo.ca/~jorchard/mri/). To this end the Imagej software [35] has been utilized and the image has been exported in tif format. A slight size adaptation without loss of the original information has been performed by the authors for the needs of the numerical experiments described below.

The image characteristics are shown in Table 1. The embedded head atlas consists of 129 slices. In order to clinically check the tumor growth model presented, a segmentation of the internal surface of the skull cavity within which lies the brain is mandatory. This step has been implemented manually on the previously mentioned 3D MRI image using the Jasc Paint Shop Pro software [36]. In order to identify the boundaries of the region of interest the anatomical data and annotations provided in [37, pp35-104] have been used. Additionally the Mango software [38] has been used in order to obtain the virtual cuts of the head appearing in Fig. 17(B). Following the delineation of the skull/brain cavity boundary, a fictitious growing virtual spherical glioblastoma tumor of radius equal to 1.4 cm was virtually placed inside the cavity (Fig. 17(B)). The size of this virtual tumor is essentially consistent with the extensively made assumption that glioblastoma diagnosis is possible after the latter has reached a tomographically imageable size equivalent to a sphere with an average diameter of 3 cm [39].

For the sake of simplicity during the in silico model validation process the concentration of tumor cells within the initial tumor has been arbitrarily assumed uniform and equal to $10^6$ cells/mm$^3$. Diffusion phenomena have been ignored before the time point corresponding to the start of the simulation. In other words, non diffusive compact tumor growth has been assumed before the start of the simulation (but not later). The following parameter values have been used: diffusion coefficient $D = 0.0065 \text{ cm}^2/\text{d}$, $h = 0.2 \text{ cm}$ and $\Delta r = 0.5 \text{ d}$, net tumor growth rate $\rho = 0.012 \text{ d}^{-1}$. It is recalled that the net tumor growth rate $\rho$ includes proliferation, loss and death of tumor cells.

The virtual tumor grows for 200 days after the initialization time point corresponding to Fig. 17. As time increases, the tumor diffuses over the free space of the entire gridding mesh. However, it does not migrate beyond the boundary as expected due to boundary conditions. The change of the total number of tumor cells inside the mesh is depicted in Fig. 18.

![Fig. 12. Snapshots of a fictitious growing and diffusive entity with the dynamic characteristics of glioblastoma corresponding to various time points (far left hand side 1st panel: first simulated day (1 d), 2nd panel: 600 d, 3rd panel: 1000 d, 4th panel: 2000 d). The hypothetical entity starts with well defined initial cubic boundaries. A cubic mesh of $95 \text{ cm} \times 95 \text{ cm} \times 95 \text{ cm}$ has been used. The following parameter values have been considered: diffusion coefficient $D = 0.0065 \text{ cm}^2/\text{d}$, cell concentration within the initial entity equal to $10^6 \text{ cells/mm}^3$, $h = 1 \text{ cm}$ and $\Delta r = 1 \text{ d}$, net growth rate $\rho = 0.012 \text{ d}^{-1}$ and loss rate due to treatment (arbitrary value) $G = 0.0013 \text{ d}^{-1}$. Grey level intensity depends on cell concentration. As time increases the image of the entity is gradually becoming blurred due to diffusion as expected. It is noted that in this figure, the maximum and the minimum value of cell concentration over each panel has been assigned the value of pure white color (grey scale level = 255) and black color (grey scale level = 0), respectively.](http://www.cs.uwaterloo.ca/~jorchard/mri/)
The first reported work on an exponentially growing population was performed by Reverend T.R. Malthus in 1798. The exponential growth is the simplest proliferation law. It describes the population density $P(t)$ at any time $t$ as a function of the initial population density $P(0)$ and the constant growth rate $k$, which in the tumor growth context addressed depends on the intrinsic net tumor growth rate (aggressiveness of the tumor)

$$P(t) = P(0)e^{kt}.$$  

Fig. 13. An arbitrary boundary geometry. An initial virtual spherical tumor is supposed to lie inside the boundary cavity.

Fig. 14. An initial virtual spherical tumor of radius = 2 cm is supposed to lie inside the boundary cavity of Fig. 13. Panels from left to right correspond to days 1, 150, 299, 450, 899. For visualization purposes, for each time point considered, a concentration cutoff value has been assumed so that concentration values lower than the cutoff value are represented by white color. As time increases, the tumor diffuses over the free space of the entire mesh. However, it does not migrate beyond the boundary. A cubic mesh of $8 \, \text{cm} \times 8 \, \text{cm} \times 8 \, \text{cm}$ has been used. The following parameter values have been used: diffusion coefficient $D = 0.0065 \, \text{cm}^2/\text{d}$, cell concentration within the initial tumor equal to $10^6 \, \text{cells/mm}^3$, $h = 0.1 \, \text{cm}$ and $\Delta t = 1 \, \text{d}$, net tumor growth rate $\mu = 0.012 \, \text{d}^{-1}$ and loss rate due to treatment (arbitrary value) $G = 0.0013 \, \text{d}^{-1}$.

Fig. 15. Snapshots of a fictitious growing virtual spherical tumor of radius = 2 cm placed in a perfectly cubically bounded domain. Grey levels are proportional to cell concentration. In this figure, the maximum and the minimum value of tumor cell concentration over each panel is assigned the value of pure white (grey scale level = 255) and black (grey scale level = 0) respectively. A cubic mesh of $8 \, \text{cm} \times 8 \, \text{cm} \times 8 \, \text{cm}$ has been used. The following parameter values have been utilized: diffusion coefficient $D = 0.0065 \, \text{cm}^2/\text{d}$, cell concentration within the initial tumor equal to $10^6 \, \text{cells/mm}^3$, $h = 0.1 \, \text{cm}$ and $\Delta t = 1 \, \text{d}$, net tumor growth rate $\mu = 0.012 \, \text{d}^{-1}$ and loss rate due to treatment (arbitrary value) $G = 0.0013 \, \text{d}^{-1}$.

The first reported work on an exponentially growing population was performed by Reverend T.R. Malthus in 1798. The exponential growth is the simplest proliferation law. It describes the population density $P(t)$ at any time $t$ as a function of the initial population density $P(0)$ and the constant growth rate $k$, which in the tumor growth context addressed depends on the intrinsic net tumor growth rate (aggressiveness of the tumor)
In our case $P(t)$ corresponds to the total number of tumor cells within the skull cavity. Fig. 19 depicts the relative percentage error of the total number of tumor cells calculated by comparing the predicted values generated by the model with the ones obtained by the application of the exponential growth (Eq. (64)). The increase in the error observed in the case of an “arbitrarily” shaped real human head as a function of time has been expected since a complex boundary is generally a source of numerical errors. A straightforward way to decrease the error is the exploitation of higher computational power so that a denser discretization mesh can be applied.

![Fig. 16](image1.png)

**Fig. 16.** Concentration on the central axis of the mesh has been sampled at different time points (50 d, 150 d, 250 d and 700 d). The results have been obtained for pure diffusion (zero net tumor growth rate and zero loss rate due to treatment) and the diffusion coefficient $D$ has been set to 0.0065 cm$^2$/d. The concentration $c$ is in cells/mm$^3$ although concentration values in this figure do not necessarily correspond to biologically meaningful situations. They just correspond to a published particular diffusion problem which is exploited for the mathematical checking of the code. As time increases all the nodes included within the domain tend to achieve the same cell concentration.

![Fig. 17](image2.png)

**Fig. 17.** (A) A three dimensional rendering of a set of T1 weighted MRI slices of a real human head. (B) An initial fictitious virtual spherical glioblastoma tumor of radius equal to 1.4 cm (denoted by white color) lying inside the skull cavity. (C) Reconstruction of the brain cavity of the skull following segmentation of each MRI slice. Further details are available in the text.

In our case $P(t)$ corresponds to the total number of tumor cells within the skull cavity. Fig. 19 depicts the relative percentage error of the total number of tumor cells calculated by comparing the predicted values generated by the model with the ones obtained by the application of the exponential growth (Eq. (64)). The increase in the error observed in the case of an “arbitrarily” shaped real human head as a function of time has been expected since a complex boundary is generally a source of numerical errors. A straightforward way to decrease the error is the exploitation of higher computational power so that a denser discretization mesh can be applied.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the three dimensional head dataset.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
</tr>
<tr>
<td>Width (mm)</td>
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</tr>
<tr>
<td>Height (mm)</td>
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<tr>
<td>Depth (mm)</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Bits per pixel (unsigned)</td>
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</tr>
</tbody>
</table>
Several snapshots of the fictitious growing virtual glioblastoma tumor corresponding to various time points are depicted in Fig. 20. It is noted that although the internal anatomy of brain is visible in the panels of this figure, homogeneous diffusion of tumor cells has been assumed within the skull cavity. Despite the fact that CT and MRI are two medical imaging techniques with high accuracy, there is a threshold of detection below which glioma cells are not detectable. Previous reports [18] have estimated the enhanced CT-delineated tumor boundary to correspond to a tumor cell concentration of about 8000 cells/mm³. Therefore, as a first gross approximation the T1 gadolinium enhanced MRI delineated tumor boundary for the needs of the theoretical exploration presented in this paper is assumed to also correspond to a tumor cell concentration of 8000 cells/mm³.

It should be noted that the gross spatial pattern of glioblastoma growth, especially in the vicinity of the skull boundary, is in good agreement with actual clinical observations [40,41]. The diameter of a sphere with volume equal to a glioblastoma tumor of fatal imageable dimensions is usually about 6 cm [39]. The latter corresponds to a volume $V_{\text{fatal}}$ of 113.04 cm³. In order for the tumor to increase in imageable volume from $V_{\text{fatal}}/2$ to $V_{\text{fatal}}$. 26 days are needed according to the simulations. This approximation to doubling time $V_D$ is in good agreement with the clinically reported glioblastoma doubling time in [42]. It is noted that in order to avoid a somewhat artificial diffusion behavior during the first simulated days which would be dictated by the deliberately assumed abrupt boundaries of the initial tumor, 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, $\Delta t = 0.5$ d and for discretized mesh $130 \times 130 \times 130$, on a 32-bit Windows Vista Platform, 4 GB RAM and processor Intel® Core™2 Duo CPU P8600 @ 2.4 GHz, takes 214 s. Further acceleration of the code execution could be achieved by using high performance computers.

7. Discussion

Two major cancer modeling schools of thought may be identified. The predominantly continuous entity based formulation school having the diffusion–reaction equation at its core (in practice in a finitized form) and the discrete entity–discrete event formulation school dealing with purely discrete notions such as proliferative potential cell categories, cell cycle phases, cycling or non cycling cell states etc. Both intuition and research experience suggest that none of the formulations can perform equally efficiently when dealing with (a) markedly diffusive tumor growth and (b) tumor response to treatment. The continuous entity based formulation seems to be better positioned in answering questions of the type “what is the real spatial extent and the actual concentration profile of a glioblastoma tumor within the brain (including both imageable and non imageable components)?” On the other hand the discrete entity – discrete event formulation seems to be better positioned in answering questions of the type “what will spatiotemporally be the biological constitution of a tomographically, histopathologically and molecularly characterized tumor following administration of a chemotherapeutic cycle of a given drug?”. Therefore, care should be taken in formulating the questions to be addressed by mathematical and computer modeling before proceeding to the selection of the modeling approach. Obviously hybridization of major approaches is an option, especially when composite and wide scope biological and/or clinical problems are addressed. Since the subject of the present article is glioblastoma tumor growth morphology, a diffusion based continuous and subsequently finitized approach has been dealt with, focusing on the numerical handling of the boundary conditions imposed by the skull.

A detailed exposition of the mathematical treatment concerning the finitized diffusion equation with sources and sinks in conjunction with the corresponding Neumann boundary conditions has been presented. The algorithms and codes have been partly tested using an analytical solution to a simplified version of the problem. The intuitional, mathematical and logical validation of the numerical treatment presented as well as the corresponding computer codes support the validity of the latter. Pure diffusion has been considered in a number of numerical experiments performed in order to provide quantitative checks of the linear component of the analysis in the most controllable way. Qualitative and semi-quantitative checks based
Fig. 19. Plot of the relative percentage error of the total number of tumor cells for the initial tumor of Fig. 17. The error has been calculated by comparing the predicted values generated by the model with the ones obtained by application of the exponential growth law. The parameter values are available in Section 6.6.

Fig. 20. Schematic representation of the growth of a virtual glioblastoma tumor 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 color intensity level \( I \) depends on cell concentration according to the function \( I = k \log_{10} c \), where \( c \) denotes tumor cell concentration, the constant \( k = 255/\log_{10} c_{\text{max}} \) is the maximum value of tumor cell concentration over the entire space and time range considered during all simulations that have been included in this figure. It is noted that in order to ensure compatibility with the definition of \( \log_{10} \), it is assumed that if \( c < (1/8) \text{ cell/mm}^3 \) then \( I = 0 \). 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 has dimensions 2 mm \( \times \) 2 mm \( \times \) 2 mm. (B), (C) As time increases, the tumor diffuses theoretically over the interior space of the skull cavity of the human head. (D) The yellow/bright contour defines the boundary of the tumor component in 2D that is tomographically detectable and has a cell density higher than the assumed threshold of 8000 cells/mm\(^3\). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
on numerical simulations for various adiabatic boundary geometries and non zero net tumor growth rate as well as non zero loss rate due to treatment have supported the validity of the corresponding mathematical treatment. Through in silico experimentation on a set of real brain imaging data, a simulated tumor has shown to satisfy the clinically expected macroscopic behavior of glioblastoma multiforme including the adiabatic behavior of the skull.

It is worth citing that since the core biological problem addressed by the present paper is glioma cell diffusion within the brain, in vitro experimental studies might be only of limited relevance. Therefore, in vivo studies should be considered as the mainstream opportunity sources for real world validation. In this context, Section 6.6 has dealt with real brain data and has successfully attempted a comparison of the simulated GBM doubling time with a clinically reported value. Obviously, this observation cannot be considered as a statistically substantiated proof of the clinical validity of the model. It does however provide a preliminary indication of the correctness of the major aspects of the analysis presented as well as a way to proceed to a strict clinical validation of the model. Therefore, it appears that the composite model proposed has the potential – following a strict clinical adaptation and validation procedure – to predict clinically meaningful and measurable quantities of critical importance related to the course of the disease.

Possible extensions of the mathematical treatment presented might include tissue inhomogeneities and anisotropy combined with the boundary conditions numerical treatment module. Furthermore, the effect of treatment (e.g. chemotherapy, combined therapies) could be readily studied in a gross preliminary way in silico by assigning appropriate values to the term $G(t)$ in Eq. (1). The above mentioned extensions will be the subjects of future papers. Furthermore, translation or extension of the treatment presented to other mathematically similar natural phenomena (e.g. diffusion of chemicals in chemical engineering problems) could be reasonable scenarios.

8. Conclusions

An explicit numerical treatment of the boundary conditions to be used in conjunction with a homogeneous diffusion–reaction based glioma growth model has been presented. Systematic checking of the corresponding computer code based on numerical simulations for various adiabatic boundary geometries, zero and non zero net tumor 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 tumor can satisfy the expected macroscopic behavior of its real counterpart, including the adiabatic behavior 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 tumors 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.

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