A computational framework for the personalized clinical treatment of glioblastoma multiforme

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In this work, we develop a computational tool to predict the patient-specific evolution of a highly malignant brain tumour, the glioblastoma multiforme (GBM), and its response to therapy. A diffuse-interface mathematical model based on mixture theory is fed by clinical neuroimaging data that provide the anatomical and microstructural characteristics of the patient brain. The model is numerically solved using the finite element method, on the basis of suitable numerical techniques to deal with the resulting Cahn-Hilliard type equation with degenerate mobility and single-well potential. The results of simulations performed on the real geometry of a patient brain quantitatively show how the tumour expansion depends on the local tissue structure. We also report the results of a sensitivity analysis concerning the effects of the different therapeutic strategies employed in the clinical Stupp protocol. The simulated results are in qualitative agreement with the observed evolution of GBM during growth, recurrence and response to treatment. Taken as a proof-of-concept, these results open the way to a novel personalized approach of mathematical tools in clinical oncology.

KEYWORDS
diffuse–interface model, finite element, glioblastoma multiforme, mixture theory, personalized medicine

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1 | INTRODUCTION

Glioblastoma multiforme (GBM) is the most complex and deadliest brain malignancy. Along with the typical hallmarks of cancer (e.g. uncontrolled cellular proliferation, intense resistance to apoptosis, rampant genomic instability [33]), the GBM has a high invasive potential and peculiarly grows along white matter fibers or along vessels, following physical structures in the brain extracellular environment [40,60]. The resulting diffuse infiltration, as well as the impenetrability of the blood-brain barrier for many conventional drugs, makes the GBM particularly aggressive and difficult to be treated: even after extensive surgery and therapies, the median patient survival does not exceed 10-16 months [39,40] and the five-years survival rate is around 5% [37,56]. The currently approved treatment schedule is known as Stupp protocol [71]; it involves a surgical removal of the cancerous mass, without injuring eloquent areas and structures of the brain whenever possible, followed by radiotherapy and concurrent and adjuvant chemotherapy. Radiation therapy is used as a treatment because of its precision in targeting the tumour region and its ability to increase the patient survival time, doubling it compared to surgery alone. Since radiotherapy affects both healthy and tumorous cells, it is performed in various sessions to maximize the effect on cancerous cells and simultaneously minimize the toxicity on normal tissue [62]. In order to obtain the best outcomes with minimal additional toxicity, the Stupp protocol combines the radiation therapy with concurrent chemotherapy, followed by cycles of adjuvant chemotherapy with the cytotoxic agent temozolomide (TMZ) [59,71].
A key step in order to improve the patient survival rate is the early detection of GBM. Several techniques can be employed for the diagnosis. Nowadays, magnetic resonance imaging (MRI) is the election technique, since it is versatile, noninvasive, harmless and it can provide extraordinarily detailed images of the brain at any location and orientation with sub–millimeter resolution. Although conventional MRI easily allows to identify the functional centers of the brain and the possible location of a brain tumour, it cannot give any insight on the microscopic structure of tissues, e.g. the spatial distribution of the fiber network within the brain. An advance in this direction is given by the diffusion-weighted magnetic resonance imaging (DWI), which is a form of MR imaging used to estimate water diffusivity within the tissue, so that it indirectly provides some information at a microscopic scale.\cite{50} In some areas of the brain, mostly composed by either grey matter or cerebrospinal fluid, a single scalar diffusion coefficient is sufficient to characterize the diffusion properties, since the measured apparent diffusivity is largely independent on the orientation of the applied gradient (i.e. isotropic diffusivity). On the other hand, in areas where the white matter is dominant, the water mobility is restricted by the tightly packed multiple myelin membranes encompassing the axons, so that the apparent diffusion values strongly depend on the measurement orientation. Addressing this issue, DWI has been developed into a new technique, the diffusion tensor imaging (DTI), in which the water diffusivity within each voxel (i.e. a volumetric element) of the brain is described through a tensor. The diagonal elements of the tensor are proportional to the apparent diffusivity along the three measurement directions, whereas the off–diagonal elements are the correlation terms between molecular displacements in directions perpendicular to the measurement direction in a given time. The diffusion tensor is symmetric and positive definite, which implies that there are six unknown independent tensor components to be estimated by acquiring at least six DWIs along linearly independent, non-coplanar directions, plus a non-diffusive weighted image giving the reference signal. The DTI technique is nowadays the only non-invasive method for characterizing the micro-structural architecture of the brain bundles and for deriving the preferential direction of water diffusion and, consequently, of cell migration. Indeed it was experimentally proved that glioma cells motion is positively correlated with the white matter fiber tracts, since the tumour cells tend to migrate when attached to a rigid support.\cite{22,82} Nonetheless, we remark that DTI does not give a direct measurement of the extent of cell motion and growth along the fiber paths, which is regulated by different chemical and mechanical cues.\cite{48,67}

Mathematical models provide powerful tools to foresee GBM infiltration and progression and foster our understanding on new patient-specific therapeutic strategies. Indeed, in the past few decades, a multitude of increasingly advanced and refined mathematical studies of GBM evolution have been proposed. The models can be gathered into three main categories, depending on the observation scale at which the phenomenon is studied: discrete models\cite{17,47,53} keep track of the single cell behaviour and its interactions with other agents, updating the system status according to a specific set of biophysical rules; hybrid models\cite{20,30,31} combine a continuous deterministic model describing the collective evolution of cancer spreading with a discrete model for single cells behaviour and evolution; continuous models\cite{13,18,32,39,75,76} describe tumour evolution at the tissue macroscopic scale through continuous fields and variables, such as cell densities, volume fractions and biochemical concentrations. The latter class is the most widely used, due to the high number of cells involved in GBM growth and the necessity to describe the tumour evolution at the tissue level in order to obtain clinically meaningful results. In particular, the state-of-the-art relies on the macroscopic diffusion models of GBM growth developed by Swanson and coworkers,\cite{74} which takes into account for a reaction-diffusion equation describing GBM cells concentration. Despite its simplicity, this Proliferation-Infiltration (PI) model can account for the augmented tumour motility in white matter as compared with grey matter thanks to either a heterogeneous diffusion coefficient (i.e. a piecewise-function with two different constant values for grey and white matter),\cite{74,75} or the definition of an anisotropic and heterogeneous diffusion tensor\cite{43} directly computed from DTI images. Nevertheless, these models\cite{43,74,75} do not provide insights on the chemical and mechanical cues that drive cell motion along fibers tracks, lacking a mechanistic connection between water diffusion, brain geometry and tumour cell invasion. Some efforts in this direction have been done in \cite{27,57,73}, where an anisotropic diffusion equation\cite{57,73} or an advection-diffusion model\cite{27} for GBM invasion have been derived through the parabolic scaling limit of mesoscopic transport equations, and by defining a systematic approach for connecting DTI data to parameters in the macroscopic model, through a bimodal von Mises-Fisher distribution.\cite{57} However, all these models\cite{27,43,57,73–75} neglect the generation and accumulation of forces between the host and the malignant tissue and the mechanical interactions occurring within the tumour itself, which should be incorporated in a continuous mechanical model.

In particular, multiphase models,\cite{4} based on the theory of mixtures,\cite{11} represent a natural modelling framework for studying the GBM evolution (and, more generally, solid tumour growth) at a macroscopic scale. Indeed, they allow taking into account mechanical and biochemical interactions among multiple solid cell species and extra- or intra-cellular liquids.\cite{4,14,21,81} Multi-phase models consider the tumour as a saturated medium, comprising at least one solid phase (e.g. cells, extracellular matrix, etc) and one liquid phase (e.g. water), and incorporate mass, momentum and energy balances to describe the evolution of the system. A first attempt to study GBM evolution with a multi–phase model is found in Colombo et al.,\cite{19} where clinical neuroimaging patient-specific data have been combined with a continuous multiphase mechanical model. Specifically, the mass
and momentum balance laws of a binary mixture composed by tumour cells and healthy environment lead are coupled with a reaction-diffusion equation for the nutrients, guiding the proliferation and the motion of tumour cells.

In this work, we extend the model proposed in [19] by introducing an anisotropic description of the dissipative and conservative interactions between the phases and we provide a more accurate calculation of the tensor of preferential directions accounting for the local orientation of the fiber network. Furthermore, we account for the tumour response to the standard therapeutic treatment. The proposed mechanical model introduces nontrivial differences with respect to the state-of-the-art PI model and the standard examples found in the literature. In particular, the resulting degenerate Cahn–Hilliard type equation, describing the tumour phase dynamics, introduces some analytical and numerical difficulties, such as non-uniqueness of the solution and presence of solutions with unphysical behaviour, which must be properly addressed in order to select the physically meaningful solution and to avoid the onset of numerical instabilities. Moreover, a naive discretization of the model would lead to discrete solutions which do not fulfill the positivity property of the corresponding continuous solution. Following and extending the analysis introduced in [1], the present model is conveniently discretized in order to select the physical viable solution, and the positivity property on the discrete solution is imposed as a constraint through a variational inequality.

The paper is structured as follows. In Section 2 the mathematical model of a GBM growth is introduced. In Section 3 we describe how the numerical model and the patient-specific data have been obtained from the MRI and DTI images, kindly provided by the Istituto Neurologico Carlo Besta (Milan, Italy), and we present the discretized model and the numerical algorithm used to solve it. Finally, the numerical results are illustrated and discussed in Section 4.

## 2 | MATHEMATICAL MODEL

In this section we derive a continuum multiphase diffuse-interface model of GBM accounting both for its growth (Section 2.1) and its response to therapies, according to the standard Stupp protocol, (in order to study cancer recurrence (Section 2.2)). The biologically meaningful range of the model parameters is discussed in Section 2.3.

### 2.1 | GBM growth model

Following [14,15,19] we represent the tumour as a binary, saturated, closed mixture of incompressible constituents, which is composed by a cellular phase of proliferating tumour cells, with volume fraction $\phi_c$, and a liquid phase, with volume fraction $\phi_l$, resuming hosts cells, nutrient, water, blood and interstitial fluid. We do not distinguish between dead and viable tumour cells, the former being considered to belong to the liquid phase. We denote by $\mathbf{v}_i(x,t)$, $i = \{c, l\}$, the convective velocity of each phase; the true mass densities of each species is constant and equal to the water density $\gamma$ (since the cells are mostly composed by water), and the mass balance for each phases reads

$$\frac{\partial \phi_i}{\partial t} + \nabla \cdot (\phi_i \mathbf{v}_i) = \frac{\Gamma_i}{\gamma} + \nabla \cdot \mathbf{k}_i$$

where $i = \{c, l\}$. Here, $\Gamma_i$ represents the volumetric mass production (respectively loss) of the corresponding phase, $\mathbf{k}_i$ is the non-convective mass flux of the $i$-th phase. Being the mixture closed, $\Gamma_c = -\Gamma_l$ and $\mathbf{k}_c = -\mathbf{k}_l$ in order for the mixture to locally satisfy the conservation of mass exchanged between the phases.

The growth-loss and the mass flux are modulated by the local concentration of nutrients and possibly other chemicals (e.g. growth factors). Here, we consider oxygen as the main nutrient for tumour cells and we define $n(x,t)$ as the dimensionless concentration of the diffusing nutrient, normalised with respect to the typical physiological concentration $n_s$ of nutrient in the capillaries. For simplicity of notation, in the following, $\phi_c$ will be replaced by $\phi$. Now, we set

$$\Gamma_c = v\gamma[n - \delta]_+ \phi(1 - \phi) - v_d\gamma[\delta - n]_+ \phi - R(\phi, t) - G(\phi, t),$$

where $[\cdot]_+$ stands for the positive part of its argument, $v$ and $v_d$ are the neoplastic cells proliferation and death rates respectively and $\delta$ is a threshold value for hypoxia. According to the functional form (2), the cells proliferate as long as the nutrient concentration is above $\delta$ and the saturation state is not reached (contact inhibition); in hypoxia conditions ($n < \delta$) the rate of apoptosis prevails over the mitotic rate and $\Gamma_c$ is negative. The loss terms $R(\phi, t)$ and $G(\phi, t)$, whose form is to be detailed in Section 2.2, represent cell death due to radiotherapy and chemotherapy, respectively.

The non-convective mass flux describing the chemotactic motion of cells is proportional to the nutrient gradient

$$k_c = -k_n \phi_n T \nabla n.$$
Here, \( k_n \) is a specific chemotactic parameter and \( T \) is a positive definite symmetric tensor, called the "anisotropy tensor", defining the preferential directions of the chemotactic movement, obtained from Diffusion Tensor Imaging measurements. This term is analogous to the standard equation used to model chemotaxis\(^{21,34,41} \) to take into account the preferential motion of cells along fibers. Thereby, the term \( k_n \) is able to describe the tendency of tumour cells to direct their movements uphill the gradient of nutrients. Note that \( T \), being a positive definite symmetric tensor, does not contain a rotation component.

In order to close the equations system, we derive the constitutive laws for \( \mathbf{v}_i \), following the thermodynamically consistent approach proposed by Doi and Onuki\(^{23} \) and defining an energy formulation of viscous interactions and mechanical forces involved in cell-cell and cell-matrix (ECM) adhesion. Differently from\(^{19} \) we assume that the viscous interactions due to the relative motion between the cells and the healthy phase, which are the main source of energy dissipation in the system, have the following anisotropic distribution

\[
W = \frac{1}{2} \int_\Omega \phi(\mathbf{v}_c - \mathbf{v}_l)^T M (\mathbf{v}_c - \mathbf{v}_l) \, d\Omega,
\]

where \( M = M_0 T^{-1} \), and \( M_0 \) is a friction parameter. According to energy dissipation rate (4), the directions of higher diffusion of water molecules, captured by DTI and encoded in the largest eigenvalues of the tensor \( T \), are also the ones most easily accessed by the cells in their motion. Here \( \Omega \subset \mathbb{R}^3 \) is the fixed spatial domain occupied by the mixture at any time instant and coinciding, in our case, with the whole brain of the patient, which remains unchanged while the tumour evolves. The introduction of the tensor \( T \) to account for non-isotropic dissipative and mechanical interactions inside the mixture is an innovative aspect of this work, in order to mimic the preferential directions of motion of cells along white matter fiber tracts\(^{36,43,47} \) whose orientation can be inferred by the diffusion tensor. The Helmholtz free energy of the system takes into account both the local interaction among cells within each phase and the interaction between the two phases:

\[
F = \int_\Omega \left( \psi(\phi) + \frac{\epsilon^2}{2} |\nabla \phi|^2 \right) \, d\Omega.
\]

The first term \( \psi(\phi) \) is the free energy per unit volume due to cell-cell and cell-matrix adhesion of the two phases, whereas the second term represents the non-local intermixing and adhesion forces that generate a surface tension between the tumour and the host tissue, across a diffuse interface of thickness proportional to the value of \( \epsilon \). According to\(^{23} \) the minimization of the Rayleighian \( R = W + dF/dt \) with respect to \( \mathbf{v}_c \) and \( \mathbf{v}_l \) after the introduction of a Lagrange multiplier in order to account for the incompressibility constraint of the mixture lead to the following relation for the relative velocities of the two phases:

\[
\mathbf{v}_c - \mathbf{v}_l = - \left( \frac{1-\phi}{M_0} \right) T \nabla \left( \frac{\partial \psi}{\partial \phi} - \epsilon^2 \Delta \phi \right).
\]

In the absence of external forces and considering a high viscosity for the mixture, the center of mass of the mixture does not move\(^{15} \) so that (6) reduces to a Darcy-like law for the velocity of the cell phase:

\[
\mathbf{v}_c = -K(\phi) \nabla \Sigma.
\]

where

\[
K(\phi) := \frac{(1-\phi)^2}{M_0} T,
\]

\[
\Sigma := \frac{\partial \psi}{\partial \phi} - \epsilon^2 \Delta \phi = f(\phi) - \epsilon^2 \Delta \phi.
\]

\( K(\phi) \) is a motility tensor depending on the cells volume fraction and motion preferential directions, whereas \( \Sigma \) is the excess of pressure exerted by the cells. Cell-cell interactions are expected to be attractive at a moderate cell volume fraction and repulsive at higher densities. Hence it exists a threshold value \( \phi_c \), called state of equilibrium or undeformed state, corresponding to which no action is exerted on the neighbours, i.e. \( f(\phi_c) = 0 \). For \( \phi < \phi_c \) cells are attracted to each other and \( f(\phi) < 0 \), while for \( \phi > \phi_c \) cells experience a repulsive force and \( f(\phi) > 0 \).\(^{14} \) In order to obey to the observed physical and biological behaviours, we replace the double-well potential usually employed in phase transformations\(^{81} \) with a phenomenological form of \( f(\phi) \) (Figure 1) as in \( 4,14,15 \), i.e. a single-well Lennard-Jones type potential:
When two cells (here represented with blue and red circles) are sufficiently far from each other, they do not interact; as soon as the distance between them falls below a certain value, e.g. because of an increase in density, they are affected by the closeness and experience attractive forces (red and blue arrows) until they come in contact \( f(\phi) < 0 \); if the cell volume fraction \( \phi \) goes beyond the equilibrium value \( \phi_e \), the forces become repulsive \( f(\phi) > 0 \) and tend towards infinity as \( \phi \rightarrow 1 \), i.e. when cells fill the whole volume. Image adapted from [14]

\[
f(\phi) = E \frac{\phi^2(\phi - \phi_e)}{1 - \phi}, \quad \phi > 0,
\]

where \( E \) is the Young modulus of the cancerous phase.

Lastly, we have to predict the evolution of the nutrient concentration \( n \) inside the brain. For the sake of simplicity, we assume that the blood vasculature is homogeneous in the whole domain and angiogenesis can be neglected. Nutrients are released from the vasculature at a rate \( S_n \) as long as \( n < 1 \), while they are back absorbed by the vasculature when \( n > 1 \). The nutrients supply is also slowed down by the proliferation of the tumorous cells destroying blood vessels. Then the released oxygen diffuses into the interstitial fluid as described by the diffusion tensor \( D \) and it is eventually consumed by the neoplastic cells at a constant rate \( \delta_n \), whereas the net nutrient uptake by the host tissue is negligible since all the oxygen absorbed by the healthy cells is instantaneously replaced by the vasculature. We remark that, in principle, we should also account for the transport of nutrients inside the different constituents of the mixture describing the brain healthy and tumor tissue. However, it is possible to show that the related drift term can be neglected in most applications, since diffusion dominates convection as a transport mechanism of soluble molecules inside living tissues away from capillaries.

Therefore, a simple reaction-diffusion equation completely defines the dynamics of nutrients (see [7] for an exhaustive derivation) and the complete system representing GBM growth reads:

\[
\begin{align*}
\frac{\partial \phi}{\partial t} &= \nabla \cdot \left( \frac{\phi(1-\phi)^2}{M_0} \nabla(f(\phi) - e^2 \Delta \phi) \right) + v \phi[n - \delta]_+ (1 - \phi) - v_d \phi[\delta - \phi]_+ \\
&\quad - \nabla \cdot (k_n \phi n \nabla n) - R(\phi, t) - G(\phi, t), \\
\frac{\partial n}{\partial t} &= \nabla \cdot (D \nabla n) + S_n(1 - n)(1 - \phi) - \delta_n \phi n.
\end{align*}
\]

with proper initial and boundary conditions (see Section 4.2). We note that Equation 10a is a degenerate Cahn-Hilliard type equation with a single well potential and source terms. It is important to remark that Equation 9 describes the tumour cells as an elastic fluid with cell-matrix mechanical adhesion forces, without taking into account for the elasticity of the brain tissue. This approximation is justified by the observation that glioblastoma cells are highly infiltrating inside the surrounding gray and white matter tissues, and the high porosity of the brain parenchima makes the mechanical effects of the tissue deformation less important than diffusive and chemical effects. Notwithstanding, this model is unable to describe the effects of brain tissue deformation on the interstitial porosity and on the blood flows, which may be important for drug delivery problems (see e.g. [25]). This model also neglects the existence of a feedback between mechanical stresses and tumor growth. This effect is generally important in the description of the growth of tumor spheroids in confined geometries (see e.g. [3]).

### 2.2 | Modeling the therapy effects

In this section, we detail the modeling of the clinical therapy, consisting of surgical resection followed by external beam radiation therapy (RT) and chemotherapy (CHT), according to the standard Stupp protocol. Radiotherapy consists of fractionated focal
irradiation at a dose of 2 Gy per fraction (1 Gy = 1 J/kg) given once daily, five days per week (Monday through Friday) over a period of six weeks, for a total dose of 60 Gy. Concomitant chemotherapy consists of TMZ at a dose of 75 mg/m² irradiation at a dose of 2 Gy per fraction (1 Gy)

*FIGURE 2* The standard Stupp protocol: RT (in red) at 2 Gy/day five days per week, for six weeks; concomitant CHT (in green) with TMZ at a daily dose of 75 mg/m² from beginning until ending of RT; six cycles of adjuvant CHT at a dose of 150 mg/m² (only first cycle) and 200 mg/m² (remaining cycles). Image adapted from

The loss terms \( R(\phi, t) \) and \( G(\phi, t) \) in Equation 12 represent cell death due to radiotherapy and chemotherapy respectively and they are assumed to be proportional to the tumour cell concentration, as in [59]:

\[
R(\phi, t) = k_R(t)\phi, \quad G(\phi, t) = k_C(t)\phi. \tag{11}
\]

We assume that they have different toxicity profiles (toxicity independence); hence they can both be added to the first equation of the system (10). The functions \( k_R(t) \) and \( k_C(t) \) are the temporal profiles of the therapeutic schedules: they are zero on rest days, when no therapy is provided, while they are equal to the cell death rate due to the administration of radiation or drug on treatment days. Therefore, they are here represented by the following piecewise constant functions:

\[
k_R(t) = \begin{cases} R_{eff} & t_i \leq t \leq t_{i+1} \\ 0 & \text{otherwise} \end{cases} \quad k_C(t) = \begin{cases} k_{C1} & s_0 \leq t \leq s_1 \\ k_{C2} & s_2 \leq t \leq s_3 \\ k_{C3} & s_j \leq t \leq s_{j+1} \\ 0 & \text{otherwise} \end{cases} \tag{12}
\]

where the coefficients \( k_{C1}, k_{C2} \) and \( k_{C3} \) are estimated from clinical data and reflect the increasing drug dosage (75 mg/m², 150 mg/m² and 200 mg/m² respectively), while \( t_i \) with \( i = 0, \ldots, 10 \) are, alternately, the days at the beginning and at the end of radiotherapy administration periods and \( s_j \) with \( j = 4, \ldots, 12 \) are, alternately, the days at the beginning and at the end of chemotherapy administration cycles (\( t_0 = s_0 \)), according to the standard Stupp protocol (see Figure 2).

On the other hand, the radiotherapy death rate \( R_{eff} \) is modelled via the linear-quadratic (LQ) model, which is the best description model for the radiation induced damage in the clinically relevant low-dose region (0-3 Gy).\(^{80}\) Assuming that the irradiation duration of the single fraction per day is very short, \( R_{eff} \) remains constant throughout the entire period of the treatment and the radiotherapy death rate can be expressed by:

\[
R_{eff} = \alpha m d + \beta m d^2, \tag{13}
\]

where \( d \) [Gy] is the dose of radiation for every fraction, \( m \) is the number of fractions per day (here, \( n = 1 \) day\(^{-1} \)), \( \alpha \) [Gy\(^{-1} \)] and \( \beta \) [Gy\(^{-2} \)] are two tissue-dependent parameters, called respectively the *linear* and *quadratic* coefficients for cell kill.\(^{62,65}\) We remark that the LQ model takes into account both *lethal* lesions (i.e. when a single ionizing particle provokes a double-strand break in DNA) and *sublethal* lesions (i.e. a single-strand break in DNA that may be repaired if no further damage occurs): the linear term \( \alpha d \) in (13) is related to double-strand breaks, whereas the term \( \beta d^2 \) accounts for the misrepair of repairable damage, which gives rise to superlinear effects. The dose at which the contributions from the first and second term, i.e. the probability \( \alpha d \) of lethal damages and the probability \( \beta d^2 \) of misrepaired sublethal ionizing events, are equal is given by \( \alpha / \beta \) [Gy], generally called the *alpha-beta ratio*. This parameter is an inverse measure of a tissue’s sensitivity to fractionation, i.e. the size of dose given on each treatment, distinguishing late responding tissues, with low alpha-beta ratios (\( \alpha / \beta \approx 2 \) Gy), and early responding tissues, with high alpha-beta ratios (\( \alpha / \beta \approx 10 \) Gy).\(^{20,55}\)
## Table 1

<table>
<thead>
<tr>
<th>Parameter description</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E$ Brain Young modulus</td>
<td>694 Pa</td>
<td>[18]</td>
</tr>
<tr>
<td>$\nu$ Tumour cells proliferation rate</td>
<td>0.012 – 0.5 day$^{-1}$</td>
<td>[54,74]</td>
</tr>
<tr>
<td>$v_d$ Tumour cells death rate</td>
<td>0.06 – 0.15 day$^{-1}$</td>
<td>[35]</td>
</tr>
<tr>
<td>$M_{th}$ Healthy tissue inter-phase friction</td>
<td>1753.64 – 5032.2 (Pa day)/mm$^2$</td>
<td>[72]</td>
</tr>
<tr>
<td>$M_0$ Tumour inter-phase friction</td>
<td>1377.86 – 3991.06 (Pa day)/mm$^2$</td>
<td>[72]</td>
</tr>
<tr>
<td>$\phi_e$ Equilibrium cell volume fraction</td>
<td>0.389</td>
<td>[12]</td>
</tr>
<tr>
<td>$r$ Tumour cell radius</td>
<td>0.005 – 0.01 mm</td>
<td>[77,79]</td>
</tr>
<tr>
<td>$\chi_h$ Healthy tissue interstitial fluid pressure</td>
<td>106.66 Pa</td>
<td>[10]</td>
</tr>
<tr>
<td>$\chi$ Tumour interstitial fluid pressure</td>
<td>866.7 – 1533.3 Pa</td>
<td>[10]</td>
</tr>
<tr>
<td>$\epsilon$ Diffuse interface thickness, $2\epsilon$</td>
<td>0.29 – 0.78 Pa$^{1/2}$/mm</td>
<td></td>
</tr>
<tr>
<td>$k_n$ Chemotactic coefficient</td>
<td>1296 mm$^2$/((mM day))</td>
<td>[28]</td>
</tr>
<tr>
<td>$\delta$ Hypoxia threshold</td>
<td>0.15 – 0.5</td>
<td>[31,35]</td>
</tr>
<tr>
<td>$n_s$ Oxygen concentration in vessels</td>
<td>0.07 mM</td>
<td>[79]</td>
</tr>
<tr>
<td>$S_n$ Oxygen supply rate</td>
<td>$10^4$ day$^{-1}$</td>
<td>[15]</td>
</tr>
<tr>
<td>$D_n$ Oxygen diffusion coefficient</td>
<td>86.4 mm$^2$/day</td>
<td>[54]</td>
</tr>
<tr>
<td>$l_n$ Oxygen penetration distance</td>
<td>0.1 mm</td>
<td>[31]</td>
</tr>
<tr>
<td>$\delta_n$ Oxygen consumption rate, $D_n/l_n^2$</td>
<td>8640 day$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$m$ Radiation fractions per day</td>
<td>1 day$^{-1}$</td>
<td>[70]</td>
</tr>
<tr>
<td>$N_{days}$ Total radiotherapy treatment days</td>
<td>30 day</td>
<td>[70]</td>
</tr>
<tr>
<td>$N_d$ Total radiation doses, $NN_{days}$</td>
<td>30</td>
<td>[70]</td>
</tr>
<tr>
<td>$d$ Radiation dose</td>
<td>2 Gy</td>
<td>[70]</td>
</tr>
<tr>
<td>$\alpha$ Linear coefficient for RT induced cell kill</td>
<td>0.027 Gy$^{-1}$</td>
<td>[59,62]</td>
</tr>
<tr>
<td>$\alpha/\beta$ Alpha-beta ratio</td>
<td>10 Gy</td>
<td>[29,59,63]</td>
</tr>
<tr>
<td>$\beta$ Quadratic coefficient for RT induced cell kill, $(\alpha/\beta)^{-1}$</td>
<td>0.0027 Gy$^{-2}$</td>
<td></td>
</tr>
<tr>
<td>$R_{eff}$ Radiotherapy death rate, $\alpha d + \beta d^2$</td>
<td>0.0648 day$^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$k_{C1}$ Concomitant chemotherapy death rate</td>
<td>0.00735 day$^{-1}$</td>
<td>[59]</td>
</tr>
<tr>
<td>$k_{C2}$ First cycle of adjuvant CHT death rate</td>
<td>0.0147 day$^{-1}$</td>
<td>[59]</td>
</tr>
<tr>
<td>$k_{C3}$ Remaining cycles of adjuvant CHT death rate</td>
<td>0.0196 day$^{-1}$</td>
<td>[59]</td>
</tr>
</tbody>
</table>

### 2.3 Parameters estimation

A mathematical model is clinically useful and potentially predictive only if its parameters can be measured from independent and, possibly, patient-specific biological experiments. In principle, each parameter appearing in (10) can be estimated from either in-vitro or in-vivo biological tests. However, we were able to obtain patient-specific data directly from clinical exams only for some parameters, as detailed in the following sections. In the present work, the tensor $\mathbf{D}$ and $\mathbf{T}$ are extrapolated from patient-specific DTI images, whereas the other parameters have been derived from either in vitro or in vivo experiments found in literature. A comprehensive list of reference values for the introduced parameters and the corresponding source is reported in Table 1. In the following, we discuss the parameters whose derivation from the literature is not straightforward.

According to,[42] $M_0$ can be estimated as the inverse of the hydraulic conductivity found in [72]. The equilibrium cell volume fraction $\phi_e$ can be estimated as the complementary value of the extra–cellular space (ECS) studied in [12], which is composed of vascular and interstitial space. Moreover, $\epsilon$ can be inferred by the characteristic distance for cell–cell interaction $\epsilon/\sqrt{\chi}$, which is taken to be of the order of the cell size (with radius $r$). Here, we interpret the characteristic pressure $\chi$ as the interstitial fluid pressure (IFP):[10] it is renowned that the fluid flowing in the interstitial compartment, which is the space between blood vessels walls and cellular membranes, exerts a different pressure depending on the tissue being healthy or neoplastic; namely in cancerous tissues the IFP is much greater than in normal tissues. The reasons can be multiple: the absence of a well functioning lymphatic system in the tumour, an increased permeability of tumour vessels or the proliferation of tumour cells in a confined area.[42] Lastly, the chemotactic coefficient $k_n$ is difficult to estimate. In fact, data on the chemotactic coefficient of glioma cells in response to oxygen concentration are not reported in literature, thus we refer to the order of magnitude found in [28] for bacterial chemotaxis in response to attractants, as amino acids and sugars.
In future refinements of this work some of these parameters could be potentially measured using recent technological advances in a patient–specific manner. For example, magnetic resonance elastography (MRE)\cite{38,66} may allow to measure in vivo the brain visco-elastic properties. It is a noninvasive technique based on a phase-sensitive MR sequence, detecting the propagation of shear waves generated by an external vibrator. However, the MRE spatial resolution is intrinsically limited (since it is linked to acquisition time) and furthermore this technique is mainly limited to small strain regime.\cite{64} Ultrasound transient elastography by shear wave imaging (SWI) technique may be more suitable to detect not only the linear but also the nonlinear elastic properties of brain matter, with high enough resolution to provide detailed mapping of the brain ex vivo\cite{64} and in vivo.\cite{52} Another coefficient that can be potentially inferred by clinical measurements is $S_n$, representing the homogenized nutrient released rate from the vasculature. This might be done using Perfusion Weighted Imaging (PWI) techniques,\cite{61} providing the patient-specific data on brain perfusion and vessel location.

3 | NUMERICAL MODEL

In this section we describe the numerical scheme adopted to approximate numerically the system of partial differential Equations 10 with patient-specific data. In particular, in Subsection 3.1 we briefly describe the procedures to generate a patient-specific mesh and additional meshes containing the values of the independent components of the tensors $D$ and $T$, starting from MRI and DTI images. In Subsection 3.2 we define the finite element approximation of (10), reporting the numerical algorithm used to solve it. In the following, $[0, T]$ is the finite time interval in which we are considering the tumour evolution. The value of $T$ will be specified in Section 4 for each test case.

3.1 | Mesh creation and preprocessing

We generate patient-specific computational meshes elaborating the clinical post-contrast T1-magnetic resonance images of a patient affected by GBM; the data are kindly provided by Istituto Neurologico Carlo Besta. Starting from the greyscale MRI images, we create a computational mesh reproducing the shape of the patient's brain, conveniently refined in the area surrounding the tumour. Secondly, we generate several additional meshes carrying informations defined on each cell of the computational mesh: a labelled mesh carrying the information about the cerebral tissues position; six meshes representing the independent components of the symmetric diffusion tensor $D$, describing water diffusion as given by the DTI images; six meshes associated with each independent component of the anisotropy tensor $T$, created from the components of $D$ as explained below.

As oxygen is carried by the fluid component, the local values of tensor $D$, which describes how nutrients diffuse effectively in a specific point of the brain, can be directly derived from DTI images. On the other hand, the tensor $T$, representing the preferential movement directions of cells inside the brain, has the same eigenvectors of the tensor $D$ but it is parameterised by a tuning parameter which modulates the anisotropy of DTI, as done in [43]. Namely, given

$$D = \lambda_1 e_1 \otimes e_1 + \lambda_2 e_2 \otimes e_2 + \lambda_3 e_3 \otimes e_3,$$

where $\lambda_i$ and $e_i$ for $i = 1, 2, 3$ are the descending ordered eigenvalues and the corresponding eigenvectors of $D$, we set:

$$\hat{T} = a_1(r)\lambda_1 e_1 \otimes e_1 + a_2(r)\lambda_2 e_2 \otimes e_2 + a_3(r)\lambda_3 e_3 \otimes e_3,$$

$$T = \frac{1}{T_{aw}}\hat{T} = \frac{3}{tr(\hat{T})}\hat{T} = \frac{3}{a_1(r)\lambda_1 + a_2(r)\lambda_2 + a_3(r)\lambda_3}\hat{T},$$

where $T_{aw} = \frac{1}{3}tr(\hat{T})$ is the mean diffusivity of $\hat{T}$, characterizing the overall intensity of the diffusion process, and $a_i(r)$ for $i = 1, 2, 3$ are functions of the anisotropy controlling factor $r$ given by:

$$\begin{pmatrix} a_1(r) \\ a_2(r) \\ a_3(r) \end{pmatrix} = \begin{pmatrix} r & r & 1 \\ 1 & r & 1 \\ 1 & 1 & 1 \end{pmatrix} \begin{pmatrix} c_r \\ c_p \\ c_s \end{pmatrix}$$

(15)

In (15), $c_r$, $c_p$ and $c_s$ are respectively the linear, planar and spherical anisotropy coefficients, defined as follows:

$$c_r = \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}, \quad c_p = \frac{2(\lambda_2 - \lambda_3)}{\lambda_1 + \lambda_2 + \lambda_3}, \quad c_s = \frac{3\lambda_3}{\lambda_1 + \lambda_2 + \lambda_3}.$$  \hspace{1cm} (16)

By construction, $c_r + c_p + c_s = 1$. If $c_r \approx 1$ the diffusion is linear, along the main eigenvector $e_1$; if $c_p \approx 1$, the diffusion is planar and confined within the plane generated by $e_1$ and $e_2$; lastly, if $c_s \approx 1$, we have isotropic, spherical diffusion. As a consequence
of (14) and (15), when \( c_\nu \approx 1 \) only the eigenvalue along the main diffusion direction is multiplied by \( r \), while in the planar case \( (c_\nu \approx 1) \) only the two largest eigenvalues are modified. The tensor is not changed when the diffusion is isotropic \( (c_\nu \approx 1) \). Therefore, the introduction of the functions \( q_i(r) \) has the purpose of controlling the tensor anisotropy preserving the principal directions. Moreover, in order to respect the constraint \( tr(T) = 3 \), the tensor is multiplied by an appropriate scalar factor.

When \( r \) equals 1, i.e. when the anisotropy is not emphasized, the tensor is not changed, while \( r < 1 \) corresponds to a decrease in anisotropy and \( r > 1 \) to an increase in anisotropy. If \( r = 1 \) we have that \( \hat{T} = D \) and the tensor \( T = \frac{1}{D_{uu}} D \) is reduced to a simple re-scaling of the diffusion tensor: the existence of a relationship between \( D \) and \( T \) is supported by the fundamental hypothesis that the chemotactic movement of cells is similar to the diffusion of water measured by DTI since both of them follow the alignment of fibers. Indeed, it has been observed that glioma cells velocity on aligned fibers is five times greater than on randomly oriented fibers. \[^{[45]}\]\n
In the following simulations, we will set \( r = 3 \).

### 3.2 Finite element discretization

In this section we introduce the finite element and time discretization of the system (10).

Let \( T_h \) be a quasi-uniform conforming decomposition of \( \Omega \) into tetrahedra \( K \), and let us introduce the following finite element spaces:

\[
Q_h := \{ \chi \in C(\Omega) \setminus \chi|_K \in P^1(K) \forall K \in T_h \} \subset H^1(\Omega),
\]

\[
Q^+_h := \{ \chi \in Q_h : \chi \geq 0 \text{ in } \Omega \}
\]

where \( P^1(K) \) indicates the space of polynomials of total order one on \( K \).

Let \( J \) be the set of nodes of \( T_h \) and \( \{x_j\}_{j \in J} \) be the set of their coordinates. Moreover, let \( \{\varphi_j\}_{j \in J} \) be the Lagrangian basis functions associated with each node \( j \in J \). Denoting by \( x^h : C(\Omega) \to S^0 \) the standard Lagrangian interpolation operator we define the lumped scalar product as

\[
(\eta_1, \eta_2)^h = \int_{\Omega} x^h(\eta_1(x))\eta_2(x) \, dx \equiv \sum_{j \in J}(1, \chi_j)\eta_1(x_j)\eta_2(x_j),
\]

for all \( \eta_1, \eta_2 \in C(\Omega) \).

We set \( \Delta t = T/N \) for a \( N \in \mathbb{N} \) and \( t_n = n\Delta t, n = 0, \ldots, N \). Starting from data \( \phi_0, n_0 \in H^2(\Omega) \) and \( \phi^0_h = x^h\varphi_0, n^0_h = x^h n_0 \), with \( 0 \leq \phi^0 \leq 1 \), we consider the following fully discretized problem: for \( n = 1, \ldots, N \), given \( (\phi^{n-1}_h, n^{n-1}_h) \in Q^+_h \times Q^+_h \), find \( (\phi^n_h, n^n_h) \in Q^+_h \times Q^+_h \), such that, \( \forall (v_h, w_h, q_h) \in Q_h \times Q^+_h \times Q^+_h \),

\[
\left( \frac{\phi^n_h - \phi^{n-1}_h}{\Delta t}, v_h \right) = -\frac{1}{M_0} \left( \phi^{n-1}_h(1 - \phi^{n-1}_h)^2 T \nabla \Sigma_h, \nabla v_h \right) + \nu \left( \phi^{n-1}_h [n^n_h - \delta]_+(1 - \phi^{n-1}_h), v_h \right) + \nu_d \left( \phi^{n-1}_h [\delta - n^n_h]_+, v_h \right) + k_n n_i \left( \phi^{n-1}_h T \nabla n^n_h, \nabla v_h \right) - \left( (k_R + k_c) \phi^{n-1}_h, v_h \right),
\]

(18a)

\[
e^2 \left( \nabla \phi^n_h, \nabla (w_h - \phi^n_h) \right) + \left( \psi_1(\phi^n_h), w_h - \phi^n_h \right) \geq \left( \Sigma^n_h - \psi_2(\phi^{n-1}_h), w_h - \phi^n_h \right),
\]

(18b)

\[
\frac{n^n_h - n^{n-1}_h}{\Delta t}, q_h \right) = -\left( D \nabla n^n_h, \nabla q_h \right) + \delta_n \left( (1 - n^n_h)(1 - \phi^{n-1}_h), q_h \right) - \left( \phi^{n-1}_h n^n_h, q_h \right),
\]

(18c)

where \((\cdot, \cdot)\) denotes the standard \( L^2 \) inner product over \( \Omega \), and the following convex splitting of the potential is considered:

\[
\psi_1(\phi) = -E(1 - \phi) \ln(1 - \phi), \quad \psi_2(\phi) = -E \left[ \frac{1}{3} \phi^3 + \frac{1}{2} \phi^2 + (1 - \phi) \phi \right].
\]

(19)

In (18) Equation 10a is discretized starting from its dual mixed weak formulation, introducing the chemical potential variable \( \Sigma \), defined in (8b).

The variational inequality (18b) enforces the positivity of the discrete solution since it implies that \( \phi^n_h \) is projected onto the space with positive values \( Q^+_h \). This projection aims at recovering the analytical properties of the continuous solution. Indeed, the solution of (10a) can be shown to satisfy a positivity constraint. Entropy estimates which guarantee the positivity of the continuous solution can be obtained by formally multiplying (10a) by \( \log(\phi(x, t)) \), integrating on \( \Omega_T \) and
using Gronwall arguments. Since these estimates are not straightforwardly available at the discrete level, as \( \log(\phi_h^n) \) is not available as test function in the space \( Q_h \) in (18), we impose this property as a constraint through a variational inequality. In particular, choosing \( \omega_h \equiv 0 \) and \( \omega_h \equiv 2\phi_h^n \) in (18) yields, for all \( j \in J \), that either \( \phi_h^n(x_j) = 0 \) or \( \phi_h^n(x_j) > 0 \) and 
\[
e^{2(\nabla \phi_h^n, \nabla \phi_j)} + (\psi'_1(\phi_h^n) + \psi_2'(\phi_h^n - 1)) - \Sigma_h^\nu(\phi_j)^h = 0 \text{ (see [1] for details).}
\]
Moreover, from energy estimates it is possible to show that the logarithmic singularity of \( \psi_1 \) guarantees that \( \phi_h^n < 1 \forall n \) if \( \phi_h^0 < 1 \).

The lumping approximation of the \( L^2 \) scalar product introduced at the left hand side of (18) allows the discrete solution to track compactly supported solutions of (10) with a free boundary which moves with a finite speed of velocity, selecting the physical solutions with compact support and moving boundary from the ones with fixed support. The presence of these unphysical discrete solutions with fixed support is linked to the non-uniqueness of the solution of the degenerate Cahn-Hilliard equation, as described in [9]. Indeed, let us introduce a proper subdivision of \( J \) into a set of passive nodes \( J_0(\phi_h^{n-1}) \subset J \) such that \( (\phi_h^{n-1}, \nu_i) = 0 \) for \( j \in J_0(\phi_h^{n-1}) \) and a set of active nodes \( J_+(\phi_h^{n-1}) = J \setminus J_0(\phi_h^{n-1}) \). A passive node is thus characterized by the fact that \( \phi_h^{n-1} \equiv 0 \) on the support of the basis function associated to it. Choosing \( v_h \equiv \nu_i \), \( i \in J_0(\phi_h^{n-1}) \), in (18), and noting that the right hand side of the first Equation of 18 is equal to zero, we get that the values of \( \phi_h^n(x_j) \), for each \( i \in J_0(\phi_h^{n-1}) \), are set to zero, leaving the values on the other nodes where \( \phi_h^{n-1} = 0 \) free to take non-zero values. This introduces the property of a moving support with finite speed for the discrete solution, since the support can expand at most of a length equal to \( h_K \), the diameter of the tetrahedra to which the passive node belongs, at each time step.

In order to solve the system (18) for every time step \( n \), we generalize the iterative procedure introduced in [8] and [1] and formulate the following algorithm:

**Require:** \( \mu > 0 \) (a relaxation parameter), \( \phi_h^{n-1}, \Sigma_h^{n-1}; \)

**For** \( k \geq 0 \)

**Initialization**

\[
\phi_h^{n,0} = \phi_h^{n-1}, \Sigma_h^{n,0} = \Sigma_h^{n-1};
\]

**Step 1** Find \( z^{n,k} \in Q_h \) such that \( \forall w_h \in Q_h: \)

\[
(z^{n,k}, w_h)^h = (\phi_h^{n,k}, w_h)^h - \mu \left[ e^{2(\nabla \phi_h^{n,k}, \nabla w_h)} + (\psi'_1(\phi_h^{n,k}) - \Sigma_h^{n,k}, w_h)^h \right];
\]

**Step 2** Find \( \phi_h^{n,k+1/2} \in Q_h^+, \forall r \geq 0 \), such that:

**If** \( j \in J_0(\phi_h^{n-1}) \) **then**

\[
\phi_h^{n,k+1/2}(x_j) \leftarrow \phi_h^{n-1}(x_j)
\]

**else**

\[
\left( \phi_h^{n,k+1/2}(x_j) + \mu \psi'_1(\phi_h^{n,k+1/2})(x_j) - z^{n,k}(x_j), r - \phi_h^{n,k+1/2}(x_j) \right) \geq 0
\]

**end if**

**Step 3** Find \( (\phi_h^{n,k+1}, \Sigma_h^{n,k+1}, n_h^n) \in Q_h \times Q_h \times Q_h, \forall (v_h, w_h, q_h) \in Q_h \times Q_h \times Q_h \), such that:

\[
\begin{align*}
\frac{1}{\Delta t} (\nabla \phi_h^{n,k+1}, v_h)^h + & \frac{1}{M_0} \left( T \nabla \Sigma_h^{n,k+1} + \nabla v_h \right) - k_n n_h (\phi_h^{n-1} T \nabla n_h^w + \nabla v_h) = 0, \\
& \frac{1}{\Delta t} (\phi_h^{n,k+1}, v_h)^h + \nu (\phi_h^{n-1}[n_h - \delta]_+ (1 - \phi_h^{n-1}), v_h)^h - v_d (\phi_h^{n-1}[\delta - n_h]_+, v_h)^h + \\
& \left( \frac{1 - \phi_h^{n-1}(1 - \phi_h^{n-1})^2}{M_0} T \nabla \Sigma_h^{n,k} + \nabla v_h \right) - ((k_R + k_C) \phi_h^{n-1}, v_h)^h, \\
& (\phi_h^{n,k+1}, w_h)^h + \mu e^{2(\nabla \phi_h^{n,k+1}, \nabla w_h)} - \mu (\Sigma_h^{n,k+1}, w_h)^h = (2 \phi_h^{n,k+1/2} - z^{n,k} - \mu \psi'_2(\phi_h^{n-1}), w_h)^h, \\
& \frac{1}{\Delta t} (n_h^n, q_h)^h + (D \nabla n_h^n, \nabla q_h) + S_n (n_h^n (1 - \phi_h^{n-1}), q_h)^h + \delta_n (\phi_h^{n-1} n_h^n, q_h)^h = 0, \\
& \frac{1}{\Delta t} (n_h^{n-1}, q_h)^h + S_n (1 - \phi_h^{n-1}, q_h)^h = 0.
\end{align*}
\]
if \( \| \phi_h^{n,K+1} - \phi_h^n \|_\infty < 10^{-6} \) then
\[
\left( \phi_h^n, \Sigma_h^n, n_h^n \right) \leftarrow \left( \phi_h^{n,K+1}, \Sigma_h^{n,K+1}, n_h^n \right); \text{ break.}
\]
end if
end for

The variational inequality (20) contains the elliptic terms in the forcing term \( z^{n,k} \) only, which is a known term at the step \( k + 1/2 \), and hence can be solved as a projection problem on each active node independently. In order to solve it, we solve the following projected gradient method in the index \( l \), \( l = 0, \ldots, L \), starting from \( \phi_h^{n,k+1/2,0} = \phi_h^{n,k} \):

\[
\phi_h^{n,k+1/2,l+1}(x_j) = \max \left\{ 0, \phi_h^{n,k+1/2,l}(x_j) - \omega \phi_h^{n,k+1/2,l}(x_j) + \mu \phi'_h(\phi_h^{n,k+1/2,l}(x_j)) - z_h^{n,k} \right\},
\]

where \( \omega \) is a relaxation parameter. If \( \| \phi_h^{n,k+1/2,\Delta t+1} - \phi_h^{n,k+1/2,\Delta t} \|_\infty < 10^{-6} \), we stop the cycle and set \( \phi_h^{n,k+1/2} = \phi_h^{n,k+1/2,\Delta t+1} \).

Note that, since the operator acting on \( \phi_h^{n,k+1/2} \) in the square bracket in (21) is continuous and strictly monotone, the projection map defined in (21) has a unique fixed point.[26]

4 | RESULTS

In this section we illustrate the numerical results obtained solving the GBM growth model (10). The GBM evolution is simulated without and with therapies after surgical removal. The patient-specific mesh obtained with the method presented in Section 3 is adopted. The numerical algorithm is implemented by means of FEniCS,[2] a computing platform for partial differential equations with high-level Python and C++ interfaces.[51]

Throughout the computations we have introduced a numerical analogue of the set \( J_0(\phi_h^{n-1}) \) where \( \phi_h^{n-1} < 10^{-6} \) is meant for \( \phi_h^{0} = 0 \). Furthermore, we implement an adaptive time step in order to avoid numerical errors associated to an excessively long time interval. Since the support of the discrete solution can move at most for a length \( h_K \) locally at each time step, where \( h_K \) is the diameter of a tetrahedra \( K \) which contains a passive node, the CFL-type condition \( \Delta t < h_{min}/v_{max} \) must be guaranteed, being \( h_{min} \) the smallest edge length among the mesh cells and \( v_{max} \) the maximum on \( \Omega \) of the infinity norm of the tumour expansion velocity, calculated as the phase velocity of the tumour cells in (1). Namely, we use

\[
\Delta t = \min \left( 100 \cdot \frac{M_0}{E^2} \frac{v_{max}}{e^2}, \frac{h_{min}}{2v_{max}} \right)
\]

(22)

where \( M_0 e^2/E^2 \) is the typical time scale for the spinodal decomposition dynamics of \( \phi \).[15] The phase velocity of the tumour cells \( V \) is set to zero on the passive nodes and otherwise is calculated by considering both the chemotactic and the mechanical expansion of the tumour cells, i.e.

\[
V = k_n n_3 T \nabla n - \frac{(1 - \phi)^2}{M_0} T \nabla \Sigma .
\]

Hence,

\[
v_{max} := \max_j |V_{x_j}(x_j)| + |V_{y_j}(x_j)| + |V_{z_j}(x_j)| ,
\]

(24)

being \( V_j \) the components of the velocity vector \( V \). Thereby, the expansion of the support of the solution is not blocked by the presence of passive nodes.

Throughout the simulations reported in the next subsections, the values of the following biological and numerical parameters, established on the basis of Table 1, are kept fixed: \( E = 694 \) Pa, \( \nu = 0.08 \) 1/day, \( v_d = 0.04 \) 1/day, \( M_0 = 5000 \) (Pa day)/mm\(^2\), \( \phi_e = 0.389 \), \( e = 0.35 \) Pa/mm\(^2\), \( \delta = 0.3 \), \( n = 0.07 \) mM, \( S_n = 10^4 \) 1/day, \( D_n = 86.4 \) mm\(^2\)/day, \( \delta_n = 8640 \) 1/day, \( k_n = 2 \) mm\(^2\)/(mM day), \( \mu = 0.0046875 \) and \( \omega = 0.0646 \). The basic temporal step is \( \Delta t = 100 \cdot M_0 e^2/E^2 = 0.1225 \) day, which is approximately equivalent to 3 hours.
4.1 | Boundary and initial conditions in simulations

Since GBM has a high infiltrating nature, it does not exhibit a sharp interface at the tumour-host boundary, hence we assume that at the initial instant $t = 0$ the neoplastic volume fraction $\phi_0(\mathbf{x}) := \phi(\mathbf{x}, 0)$ follows a normal distribution in space, for suitable coefficients $a$ and $b$:

$$\phi_0(\mathbf{x}) = ae^{-\frac{1}{2b^2}(\mathbf{x} - \mathbf{x}_c)^2}.$$  \hspace{1cm} (25)

In particular we choose $a = 0.3$ and $b^2 = 20$, $b \sim \sqrt{20}$ being the (conventional) radius of the tumour. The initial datum has thus a maximum, smaller than $\phi_e$, located in the center $\mathbf{x}_c$ of the tumour (identified from the medical images) and decreases smoothly to zero (Figure 3a). The initial oxygen distribution $n_0(\mathbf{x}) := n(\mathbf{x}, 0)$ is obtained by solving the steady version of the nutrient governing equation:

$$-\nabla \cdot (\mathbf{D} \nabla n_0) = S_n(1 - n_0)(1 - \phi_0) - \delta_n \phi_0 n_0,$$  \hspace{1cm} (26)

where $\phi_0$ is the initial cancerous cells distribution. Thus the oxygen distribution reflects the profile of $\phi_0$: outside the tumour, where the tissue is healthy and $\phi_0$ close to 0, the nutrient concentration is equal to 1, whereas it decreases to its minimum while approaching to the core of the tumour (Figure 3b).

As the tumour can not grow beyond the cranial skull, we impose a homogeneous Neumann condition on the cell volume fraction and on the chemical potential, while a non homogeneous Dirichlet condition applies for the nutrient:

$$\nabla \phi \cdot \mathbf{n} = 0 \quad \forall \mathbf{x} \in \partial \Omega,$$  \hspace{1cm} (27a)

$$\nabla \Sigma \cdot \mathbf{n} = 0 \quad \forall \mathbf{x} \in \partial \Omega,$$  \hspace{1cm} (27b)

$$n = 1 \quad \forall \mathbf{x} \in \partial \Omega$$  \hspace{1cm} (27c)

where $\mathbf{n}$ is the outward boundary normal.

4.2 | Effect of anisotropy and heterogeneity on GBM growth

To study the influence of anisotropy and heterogeneity on tumour evolution, we examine three different cases:

- **isotropic homogeneous** growth: the GBM grows inside an homogeneous and isotropic environment, i.e. $\mathbf{T} = \text{diag}(1, 1, 1)$ and $\mathbf{D} = D_n \mathbf{T}$;
- **anisotropic homogeneous** growth: patient-specific anisotropic diffusion of nutrients and cell motion is considered, i.e., $\mathbf{D}$ and $\mathbf{T}$ are obtained from DTI images as explained in Section 3.1, whereas the other model parameters are assumed homogeneous inside the brain;
- **anisotropic heterogeneous** growth: using anisotropic $\mathbf{D}$ and $\mathbf{T}$ data, we choose the value of the chemotaxis parameter $k_n$ to be four times the basic value inside the white matter, where cells can easily migrate along the fibers bundles. Thus, $k_n = 8$ mm$^2$/mM day in white matter and $k_n = 2$ mm$^2$/mM day in grey matter and cerebrospinal fluid.

The results of the simulations reporting GBM growth over a period of nearly six months are compared in Figure 4. In the isotropic and homogeneous case, the tumour expands with the same velocity in all directions, preserving the initial spherical.
shape and nearly doubling its radius (Figure 4, first column). When the actual anisotropic diffusion is considered, with chemo-
tactic parameter $k_n$ homogeneous, the tumour takes a more sharp-cornered shape, especially in yz- and xz-planes, whereas in
the xy-plane the tumour section appears essentially equal to the isotropic case. The tumour size is comparable with the isotropic
homogeneous simulation, the cell volume fraction reaching almost the same maximum value $\phi_{\text{max}} = 0.68$ (Figure 4, second col-
umn). When considering an heterogeneous chemotactic coefficient $k_n$, the velocity of growth clearly increases and the tumour
is mainly located in the white matter, where the value of $k_n$ is higher. Therefore, the cell volume fraction $\phi$ expands more
rapidly its support, while its maximum increases more slowly, with respect to the previous cases. We notice also that the shape
is more notched and irregular, reflecting the same preferential directions in the yz and xz planes highlighted by the homogeneous
anisotropic case (Figure 4, third column).

In all cases, the maximum value of the expansion velocity of the tumour front follows a Gompertzian profile\cite{49} (Figure 5),
reaching values in the same order of magnitude of the maximal expansion speed reported in the literature, i.e. 0.09–0.11
mm/day.\cite{45} The maximum value of expansion velocity is calculated as $v_n := \max_x V \cdot n$, where $V$ is defined in (23) and
The shape evolution recorded during the anisotropic GBM growth is strongly affected by the underlying fiber orientation, encoded in the tensor $T$. In Figure 7 is plotted the final pattern of $\phi$ superimposed onto the plots of the diagonal components of the tensor $T$ along the $xy$, $xz$ and $yz$ planes. We observe that, in the $yz$-plane, the high value of $T_{yy}$ in the lower region of the tumour causes an elongation in the $y$ direction when the tumour is extended enough to reach this zone, whereas the high $T_{zz}$ on the right-hand side of the tumour in the $xz$-plane creates a flattened border along the $z$ direction. On the other hand, the almost isotropic expansion in the $xy$-plane reflects the moderate values of $T_{xx}$ and $T_{yy}$ in the surroundings of the tumour.
These results show how the growth of the tumour is greatly influenced by the diffusion tensor $D$ and the tensor of preferential directions $T$. The tumour location largely determines the shape generated during the evolution, as in the so-called butterfly gliomas,\textsuperscript{[24]} a particular type of GBM that extends through both the cerebral hemispheres via the corpus callosum, creating the image of a bilateral symmetric lesion resembling the wings of a butterfly. Indeed, the corpus callosum is the largest white matter structure inside the brain, located in its center, and formed by a thick bundle of aligned neural fibers connecting the two hemispheres so that they can communicate with each other. Within it, cells are forced to migrate in one specific direction, causing the tumour to spread into both the hemispheres and gets this particular shape. Even though the tumour considered in our simulations does not originate inside the corpus callosum, in accordance with medical data, from the first and second row of Figure 7 it is clear that the presence of this anatomical structure attracts the tumour infiltration (i.e., the central red zone in the $T_{xx}$ map).

### 4.3 Effect of therapies on GBM regrowth after resection

Finally, we simulate a GBM treated with surgical resection, chemotherapy and radiotherapy, according to the standard Stupp protocol explained in Section 2.2, by discretizing the system of Equations 12. We assume that the removed region coincides with the tumour visible in the magnetic resonance images. However, due to the very strong infiltrating attitude of glioblastoma, the removal of the whole cancerous mass is almost impossible, hence some neoplastic cells generally remain in the peritumoral area. After resection, the cavity is filled by fluid, forming an edema.

The incomplete removal of malignant cells is represented in the initial datum: small islands of neoplastic cells, with $\phi = 0.3$, surround the removed tumour. The computational meshes are modified accordingly to reproduce the edema inside the cavity (Figure 8). The diffusion tensor in the cavity is given by the isotropic tensor $D = d_m \text{diag}(1, 1, 1)$, being $d_m$ the medium diffusion coefficient inside the fluid; then we change the heterogeneous parameter $k_n$ accordingly and assign the parameter $S_n$ a normal
FigurE 9  Stages of anisotropic heterogeneous tumour evolution at $t = 42, 75, 103, 131, 159, 187, 215$ days with no therapy and three different therapeutic schemes: standard Stupp protocol, a ten-fold higher CHT dose and a ten-fold higher sensitivity to RT.

profile going from zero in the center of the cavity up to its former value $10^4$ 1/day in healthy tissue, in order to replicate the absence of vasculature inside the removed region.

We run four types of heterogeneous anisotropic simulations considering the following conditions:

- **no therapy**: neither chemotherapy nor radiotherapy are administered after resection;
- **standard therapy**: after resection, the remaining tumour mass is treated accordingly to the standard Stupp protocol;
- **increased CHT**: the cytotoxic effect on cancer cells of the chemotherapeutic agent is boosted, maintaining the same cycles of administration of the Stupp protocol;
- **increased RT**: the sensitivity of the brain tissue to radiotherapy is enhanced, while keeping the chemotherapy dose and cycles of administration scheduled by the Stupp protocol.

The evolution of the tumour mass, for the four considered cases, is reported in Figure 9 at $t = 42, 75, 103, 131, 159, 187$ days, which correspond to the end of every cycle of chemotherapy (when simulated).

Firstly, we observe the evolution of the islands of cancerous cells when neither chemotherapy nor radiotherapy are administered (first column of Figure 9). The islands become increasingly broader in time until blending into a whole mass, which
The curves show the values of $\phi_{\text{max}}$ at $t = 0, 5, 7, 12, 14, 19, 21, 26, 28, 33, 35, 40, 42, 70, 75, 98, 103, 126, 131, 154, 159, 182, 187, 210, 215$ days, i.e. at the beginning and at the end of each RT and CHT administration period (highlighted in the topmost part of the graphic with red and green rectangles, respectively), for the three analysed therapeutic schemes: standard therapy (STD, red dashed line), higher CHT dose (green dot-dashed line) and higher sensitivity to RT (continuous orange line).

expands following the same preferential paths of the previous anisotropic heterogeneous simulation. After 187 days, the tumour mass has almost reached the brain border. We remark that, at the center of the cancerous mass, cells remain separated, forming a hole, since there the source term for the nutrient vanishes. Moreover, although the maximum of $\phi$ constantly grows, it reaches a lower value than the corresponding anisotropic heterogeneous simulation. Let us notice that the island appearing and growing in the top-left corner of the tumour is due to a little group of neoplastic cells already present in the initial datum, which is however not visible on the mesh clipped along the $yz$-plane (cf. Figure 8a).

Afterwards, we simulate the tumour treatment according to the standard Stupp protocol, by using the model (10) and the parameters reported in Table 1. As shown in Figure 9 (second column), for the set of parameters considered, the standard Stupp protocol is ineffective in stopping the tumour evolution. Indeed, the tumour islets become broader and ultimately blend into a single one, assuming a shape analogous to the simulation in absence of treatment. However, in this case, the cancer front velocity and the maximum tumour cell volume fraction $\phi_{\text{max}}$ at each time step are lower than in the simulation without therapy.

Therefore, we present two hypothetical variations of the standard therapeutic treatment, boosting chemotherapy and radiotherapy separately: in the increased CHT case, we raise ten-fold the effect of the daily doses of chemotherapy, setting $k_{C_1} = 0.0735$ 1/day, $k_{C_2} = 0.147$ 1/day and $k_{C_3} = 0.196$ 1/day, whereas in the increased RT case we choose a ten-fold higher sensitivity of the tissue to radiotherapy, namely $\alpha = 0.27$ Gy$^{-1}$. The evolution steps are shown in the second and third columns of Figure 9, respectively. In both cases the GBM expansion is greatly reduced in comparison with the standard therapeutic schedule. Particularly, while CHT alone does not prevent tumour regrowth, the boost in sensitivity to radiotherapy leads to complete regression of the tumour: at the end of the RT treatment $\phi_{\text{max}}$ reaches a minimum value that can be approximated by zero. This result is in accordance with clinical evidences \cite{78} that have demonstrated a statistically significant survival benefit from postoperative radiotherapy compared with different chemotherapy schedules without radiation. The efficacy of chemotherapy in treating brain tumours is hampered by the presence of the blood-brain barrier, which notably reduces the dose of drug that actually reaches the tumour region, and by the non-responsiveness to chemotherapy of some types of cancer. Indeed, GBM is traditionally considered very refractory to chemotherapy and post-operative external beam radiotherapy has been the standard treatment for GBM until, in the late 1990s, the addition of TMZ to radiotherapy was proved to add some benefits to radiotherapy alone \cite{70,71,78}.

It is interesting to notice that the trend of $\phi_{\text{max}}$ during each treatment is not monotonic (cf. Figure 10). Indeed the tumour strongly regresses during the radiotherapy administration period, specifically during the 5-days cycles, assuming a nearly exponential profile. After radiotherapy, the tumour resumes to grow, experiencing decrease only during the chemotherapy administration weeks. In Figure 10 we report the values of $\phi_{\text{max}}$ for each considered therapeutic treatment, at the beginning and at the end of every RT or CHT cycle. We notice that the previously mentioned oscillatory behaviour is evident in all the simulations besides the last one, in which the tumour is essentially eradicated after the cycle of radiotherapy with concurrent chemotherapy.

### 5 | DISCUSSION AND CONCLUSION

In this work we have illustrated a continuous mechanical model and a computational tool for reproducing the personalised GBM growth and progression after resection and therapies. The diffuse-interface model consists in a degenerate Cahn-Hilliard...
equation with single-well potential for the cancer cells volume fraction, coupled with a reaction diffusion equation for the nutrient. The effects of therapies, such as chemotherapy and radiotherapy, have been incorporated in the model in order to predict the progression of the disease after the standard clinical protocol.

We have designed a novel stable numerical algorithm to discretize the system of equations, selecting the physical meaningful solution and enforcing the positivity constraint, generalizing recently developed algorithms proposed for the degenerate Cahn-Hilliard equation. The numerical code has been implemented by using the finite element method for a patient-specific 3D geometry, reconstructed from MRI clinical data, in order to simulate the spatio-temporal evolution of the cancerous mass inside the brain. Moreover, we included in the model the heterogeneity and the anisotropy of the brain fiber bundles, directly obtained from the neuroimaging DTI data on the same patient.

This approach represents an advancement with respect to the state-of-the-art GBM models. Indeed, the proposed model takes into account not only biochemical factors, such as nutrients availability and the chemotactic motion of cells, but also mechanical interactions occurring between the local micro-environment and the tumour, which play a fundamental role in cancer progression and invasion. Another point of strength of this computational model is the ability to support clinical strategies in a virtual environment using patient-specific data, mainly through the exploitation of the tensor of preferential directions $T$, which make the cells movements dependent on the brain architecture of each patient. In particular, in the case of a free growing GBM, the comparison between the fully anisotropic heterogeneous simulation and the isotropic homogeneous one suggests that the integration of DTI data in the model is of fundamental importance in order to reproduce a patient-specific tumour evolution. In addition, the expansion velocity of the tumour front has the same order of magnitude of the one reported in clinical studies.

Finally, the model can be used to reproduce both the clinically-relevant case of GBM recurrence after incomplete surgical resection, where a group of cancerous cells is left into the peritumoral area, and the effect of subsequent cycles of radiotherapy and chemotherapy treatments. In particular, resection and therapies have been simulated according to the standard Stupp protocol, which seems to have limited efficacy in preventing GBM regrowth in the numerical simulations. A sensitivity analysis of the results for a single therapeutic action has been performed. The simulations have highlighted a high sensitivity to radiotherapy, displaying a strong regression with the increase of the radiation dose.

The results presented in this work can be evaluated as a proof-of-concept, a further step towards the ambitious goal to provide a computational tool that support medical doctors in clinical practice in a patient-specific manner. Nonetheless, these results need to be quantitatively validated by comparing the predicted evolution with the real progression of the disease inside the patient brain, directly measured from neuro-imaging data. Future developments of the model will focus on the role of the stress exerted by the healthy brain on the growing GBM, e.g. by considering more complex mechanical constitutive equations of the cancer cell phase. In particular, we aim to consider the elastic deformation of the brain during tumor growth and after its surgical removal, following the numerical strategy in [16]. This refinement will allow describing the structural changes within the brain tissues and the availability of nutrients depending on the spatial distribution of the blood vessels.

The description of the heterogeneous and time-dependent vascular system and blood flow can be implemented as a new phase in the mixture, as proposed in [25]. The most appropriate kinetic and growth/death (angiogenesis/obstructions) terms should be supported by patient-specific data about brain perfusion and vessel location. They could be derived from PWI techniques, such as the Dynamic Contrast Enhancement (DCE) MRI and the Dynamic Susceptibility Contrast (DSC) MRI.

In conclusion, this work represents one more step towards the definition of a computational tool combining clinical data with a mathematical model that is able to capture both chemical and mechanical phenomena driving GBM evolution. This multidisciplinary approach has the potential to aid clinicians in the definition of therapeutic strategies in personalised oncology.

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