# A phenotype-structured reaction-diffusion model of avascular glioma growth

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#### Abstract

We consider a phenotype-structured reaction-diffusion model of avascular glioma growth. The model describes the interaction dynamics between tumour cells and oxygen, and takes into account anisotropic cell movement and oxygen diffusion related to structural anisotropy of the brain's extracellular environment. In this model, phenotypic heterogeneity of tumour cells is captured by a continuous phenotype-structuring variable, the value of which evolves due to phenotypic changes. We first analyse a one-dimensional version of the model and formally show, through a Hopf-Cole transformation, that it admits, in appropriate asymptotic regimes, phenotypically heterogeneous travelling wave solutions, wherein the locally prevailing cell phenotype varies across the wave due to the presence of oxygen gradients. This provides a mathematical formalisation for the emergence of intratumour phenotypic heterogeneity driven by differences in oxygen availability across the tumour. We then report on the results of both 1D simulations, which corroborate the results of formal asymptotic analyses, and 2D simulations, which also demonstrate the impact of anisotropy in cell movement and oxygen diffusion on tumour growth and on the phenotypic composition of the tumour edge. These results are complemented with additional results of 3D simulations, which are carried out on the geometry of the brain by using a hybrid finite difference-finite element method and integrating patient-specific magnetic resonance imaging data with diffusion tensor imaging data.

**Keywords:** Reaction-diffusion models of glioma growth, Phenotype-structured partial differential equations, Anisotropic diffusion, Phenotypically heterogeneous travelling waves, Hybrid finite difference-finite element methods

# 1 Introduction

Reaction-diffusion (RD) models of glioma growth play a prominent role in the mathematical modelling of the progression and response to therapy of brain tumours [3, 28, 51, 77, 82]. Following the pioneering studies [90, 91, 92, 93, 94, 98, 102], models of this type of increasing levels of biological realism and mathematical sophistication have been developed over the years [41, 50, 57, 58, 59, 60, 78, 81, 83, 89, 95].

Stripped to an essential form, RD models of glioma growth comprise a RD equation for the density of tumour cells, wherein the reaction term takes into account cell proliferation and death, while an anisotropic diffusion term models cell movement through anisotropic fibres in the brain. This equation can then be coupled with additional RD equations for the dynamics of other biotic and abiotic components of the tumour micro-environment.

The majority of the existing RD models of glioma growth rely on the assumption that cells in the tumour share the same phenotypic characteristics, which do not evolve in time. As such, these models implicitly ignore the fact that gliomas, like tumours with other cells of origin, exhibit significant phenotypic heterogeneity, which results from dynamic adaptations driven by selective pressures exerted by different components of the tumour micro-environment [29, 37, 45, 65, 74, 87].

In particular, similarly to other types of a vascular tumours, central to phenotype heterogeneity in a vascular gliomas are differences in micro-environment between the hypoxic tumour core, where oxygen levels

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are significantly depleted due to consumption and limited diffusion of oxygen, and the well-oxygenated tumour edge, where oxygen is supplied through diffusion from surrounding tissues [2, 16, 40, 56, 75]. The former is predominantly populated by slow-proliferating cells displaying a primarily glycolytic phenotype, which enables them to thrive in hypoxic conditions. The latter mainly comprises cells which instead display a more oxidative phenotype, exhibiting lower levels of resistance to hypoxia and faster proliferation rates.

A possible way of incorporating intratumour phenotype heterogeneity, rooted in spatial variability in oxygen distribution, into models of tumour dynamics consists in introducing a continuous structuring variable which represents the cell phenotype [68, 79]. This variable provides a simple aggregate representation of the energy metabolism of tumour cells and its value can be related, for instance, to the cell level of expression of hypoxia-inducible factors (e.g. HIF-1) [42, 62, 84]. Such a modelling approach, previously employed, for instance, in [17, 18, 19, 21, 22, 30, 31, 70, 71, 99], makes it possible to simultaneously describe the spatial and evolutionary dynamics of tumour cells and their adaptation to spatially heterogeneous oxygen levels.

In this paper, we consider a phenotype-structured RD model of avascular glioma growth. The model describes the interaction dynamics between tumour cells and oxygen, and takes into account anisotropic cell movement and oxygen diffusion related to structural anisotropy of the brain's extracellular environment. In this model, phenotypic heterogeneity of tumour cells is captured by a continuous phenotype-structuring variable, the value of which evolves due to phenotypic changes. The model is then formulated as a non-local RD equation for the local phenotype density of tumour cells coupled with a RD equation for the local oxygen concentration. Based on the observation that glucose levels in biological tissues are usually high enough not to represent a limiting factor for the proliferation of cells [38, 39, 47], for the sake of simplicity, the dynamics of the glucose concentration are not incorporated in the model, as previously done, for instance, in [6, 99].

We first analyse a one-dimensional version of the model and formally show, through a Hopf-Cole transformation, that it admits, in appropriate asymptotic regimes, phenotypically heterogeneous travelling wave solutions, wherein the locally prevailing cell phenotype varies across the wave due to the presence of oxygen gradients. We then report on the results of both 1D simulations, which corroborate the results of formal asymptotic analyses, and 2D simulations, which also demonstrate the impact of anisotropy in cell movement and oxygen diffusion on tumour growth and on the phenotypic composition of the tumour edge. These results are complemented with additional results of 3D simulations, which are carried out on the geometry of the brain by integrating patient-specific magnetic resonance imaging data with diffusion tensor imaging data.

The RD system considered here can be regarded as a generalisation of the one presented in [99], wherein additional effects of anisotropy in cell movement and oxygen diffusion related to non-uniform alignment of the fibres composing the brain's extracellular environment are incorporated. From the analytical point of view, a key novelty of the present work is that, in contrast to [99], where the long-time behaviour of the solutions to the model equations was studied, here phenotypically heterogeneous travelling wave solutions are investigated. From the numerical point of view, while in [99] numerical simulations were carried out, through an explicit finite difference method, for the model posed on a square spatial domain, here the model is solved numerically by using a hybrid finite difference-finite element method and employing a semi-implicit time discretisation, which makes it possible to carry out numerical simulations of the model posed on a wide range of spatial domains and incorporating anisotropic diffusion.

Th rest of the paper is organised as follows. In Section 2, we describe the mathematical model. In Section 3, through formal asymptotic analyses, we study phenotype-structured travelling wave solutions. In Section 4, we present the main results of numerical simulations. In Section 5, we conclude with a summary of key findings and a discussion of future directions.

# 2 Mathematical model

The dynamics of the density of tumour cells with phenotype  $y \in [0,1]$  (i.e. the local phenotype density),  $n(t, \boldsymbol{x}, y)$ , and the oxygen concentration,  $S(t, \boldsymbol{x})$ , at position  $\boldsymbol{x} \in \Omega$  and time  $t \in [0, \infty)$  are governed by

the following RD system

$$\begin{cases}
\partial_{t} n - \operatorname{div}\left(\mathbf{D}_{n}(\boldsymbol{x}) \nabla n\right) = R(y, \rho, S) n + \beta \partial_{yy}^{2} n, & y \in (0, 1), \\
\rho(t, \boldsymbol{x}) := \int_{0}^{1} n(t, \boldsymbol{x}, y) \, \mathrm{d}y, & \boldsymbol{x} \in \Omega, \\
\partial_{t} S - \operatorname{div}\left(\mathbf{D}_{S}(\boldsymbol{x}) \nabla S\right) = -\nu S \int_{0}^{1} r(y) n(t, \boldsymbol{x}, y) \, \mathrm{d}y,
\end{cases}$$
(1)

where  $\rho$  is the cell density. Here the spatial domain  $\Omega \subset \mathbb{R}^d$ , with  $d \geq 1$ , is a bounded and connected set with boundary  $\partial\Omega$ . The variable y represents the cell metabolic phenotype. Specifically, building on the modelling approach adopted in [6, 99], we assume cells with phenotype y=0 to have a fully oxidative metabolism and produce energy via aerobic respiration only, while cells with phenotype y=1 express a fully glycolytic metabolism and produce energy through anaerobic glycolysis only. Moreover, cells with phenotypes  $y \in (0,1)$  produce energy via aerobic respiration and anaerobic glycolysis, and smaller values of y correlate with a more oxidative and less glycolytic metabolism.

# 2.1 Summary of the terms in the non-local RD equation (1) for n

The second term on the left-hand side of the non-local RD equation (1) for n models anisotropic random movement of cells, which is (for simplicity) described as a diffusion process with diffusivity modelled by the symmetric positive-definite tensor  $\mathbf{D}_n(\boldsymbol{x})$ , the form of which depends on the alignment of the extracellular fibres. Moreover, the second term on the right-hand side takes into account spontaneous, heritable phenotypic changes across tumour cells [55]. These are modelled through a linear diffusion term with coefficient  $\beta \in \mathbb{R}^+$ , which represents the rate of phenotypic changes [20, 68]. Finally, the first term on the right-hand side is a non-local reaction term that takes into account proliferation and death of tumour cells. In more detail, the function  $R(y, \rho, S)$  is the net proliferation rate (i.e. the difference between the rate of proliferation and the rate of death) of cells with phenotype y at time t, under the local environmental conditions at position  $\boldsymbol{x}$ , which are determined by the cell density,  $\rho(t, \boldsymbol{x})$ , and the oxygen concentration,  $S(t, \boldsymbol{x})$ . This function, which can be regarded as the fitness landscape of the tumour [20, 68], is defined as

$$R(y,\rho,S) := \alpha \left( r(y) \frac{S}{S_0} + f(y) - \frac{\rho}{\rho_0} \right). \tag{2}$$

In the definition (2), the parameter  $S_0 \in \mathbb{R}^+$  is linked to the tissue oxygen concentration in physiological conditions (i.e. when there are no tumour cells), the parameter  $\rho_0 \in \mathbb{R}^+$  is linked to the local carrying capacity of the tumour, and  $\alpha \in \mathbb{R}^+$  is a scaling parameter that provides a measure of the intensity of phenotypic selection acting on tumour cells (i.e. larger values of  $\alpha$  correlate with stronger phenotypic selection). The last term in the definition (2) incorporates the effect of density-dependent inhibition of growth (i.e. the cessation of growth at sufficiently high cell density) [64], while the first term and the second term take into account cell proliferation fuelled by aerobic respiration and anaerobic glycolysis, respectively. The functions r(y) and f(y) are smooth and bounded real functions that satisfy the following assumptions:

$$r(0) = \gamma, \quad r(1) = 0, \quad \frac{\mathrm{d}r}{\mathrm{d}y} < 0 \text{ on } (0,1), \quad \gamma \in \mathbb{R}^+,$$
 (3)

and

$$f(0) = 0$$
,  $f(1) = \zeta$ ,  $\frac{\mathrm{d}f}{\mathrm{d}y} > 0$  on  $(0,1)$ ,  $\zeta \in \mathbb{R}^+$ . (4)

Where possible, we retain general functional forms for r(y) and f(y). However, where needed, building upon the definitions employed in [6, 99], we consider the functions

$$r(y) := \gamma (1 - y^2), \quad f(y) := \zeta [1 - (1 - y)^2],$$
 (5)

which clearly satisfy the general assumptions (3) and (4). Furthermore, in the following we will assume that  $\zeta < \gamma$ . This assumption, together with (3) and (4), ensures that the maximum of r(y),  $\gamma$ , attained

at y = 0, is greater than the maximum of f(y),  $\zeta$ , attained at y = 1, which is consistent with biological evidence indicating the presence of a fitness cost associated with a less efficient glycolytic metabolism [11]. Similarly to [6], the ratio  $\gamma/\zeta$  can be regarded as a measure of the fitness cost of glycolytic metabolism.

# 2.2 Summary of the terms in the RD equation (1) for S

The second term on the left-hand side of the RD equation (1) for S corresponds to anisotropic diffusion of the oxygen molecules, with diffusivity modelled by the symmetric positive-definite tensor  $\mathbf{D}_S(\mathbf{x})$ . The term on the right-hand side models oxygen consumption by cells whose proliferation is fuelled by aerobic respiration, and the parameter  $\nu \in \mathbb{R}^+$  is a conversion factor linking cell proliferation to oxygen consumption. The form of this term relies on the assumption that faster cell proliferation fuelled by aerobic respiration may conceivably demand greater consumption of oxygen (i.e. cells with phenotypes represented by smaller values of the structuring variable y consume more oxygen) [6, 99].

# 2.3 RD system for the nondimensionalised local phenotype density and oxygen concentration

To nondimensionalise the dependent variables in the RD system (1) complemented with the definition (2), we divide the equation for n by  $\rho_0$  (i.e. the parameter linked to the local carrying capacity of the tumour) and the equation for S by  $S_0$  (i.e. the parameter linked to the tissue oxygen concentration in physiological conditions). In so doing, introducing the notation

$$\hat{n} = \frac{n}{\rho_0}, \quad \hat{\rho} = \frac{\rho}{\rho_0}, \quad \hat{S} = \frac{S}{S_0}, \quad \hat{\nu} = \rho_0 \nu,$$
 (6)

we obtain the following system

$$\begin{cases}
\partial_{t}\hat{n} - \operatorname{div}\left(\mathbf{D}_{n}(\boldsymbol{x}) \nabla \hat{n}\right) = \alpha \left(r(y)\hat{S} + f(y) - \hat{\rho}\right) \hat{n} + \beta \partial_{yy}^{2} \hat{n}, & y \in (0, 1), \\
\hat{\rho}(t, \boldsymbol{x}) := \int_{0}^{1} \hat{n}(t, \boldsymbol{x}, y) \, \mathrm{d}y, & \boldsymbol{x} \in \Omega, \\
\partial_{t}\hat{S} - \operatorname{div}\left(\mathbf{D}_{S}(\boldsymbol{x}) \nabla \hat{S}\right) = -\hat{\nu}\hat{S} \int_{0}^{1} r(y) \, \hat{n}(t, \boldsymbol{x}, y) \, \mathrm{d}y,
\end{cases}$$
(7)

subject to initial data such that

$$\hat{n}(0, \boldsymbol{x}, y) = \hat{n}^{0}(\boldsymbol{x}, y) \quad \hat{n}^{0} \ge 0 \quad \text{on} \quad \overline{\Omega} \times [0, 1], \quad 0 \le \int_{0}^{1} \hat{n}^{0}(\cdot, y) \, \mathrm{d}y \le 1 \quad \text{on} \quad \overline{\Omega}$$
 (8)

and

$$\hat{S}(0, \boldsymbol{x}) = \hat{S}^0(\boldsymbol{x}), \quad 0 \le \hat{S}^0 \le 1 \quad \text{on} \quad \overline{\Omega}.$$
 (9)

We complement the non-local RD equation (7) for  $\hat{n}$  with zero-flux boundary conditions on  $\partial\Omega$  and at the endpoints of the phenotype domain, i.e. we impose the following homogeneous Neumann boundary conditions

$$\nabla \hat{n} \cdot \boldsymbol{u} = 0 \quad \text{on} \quad \partial \Omega \tag{10}$$

and

$$\partial_y \hat{n}\big|_{y=0} = 0, \quad \partial_y \hat{n}\big|_{y=1} = 0,$$
 (11)

where u is the unit normal to  $\partial\Omega$  that points outwards from  $\Omega$ . On the other hand, we complement the RD equation (7) for  $\hat{S}$  with the following Dirichlet boundary conditions

$$\hat{S} = 1 \text{ on } \partial\Omega,$$
 (12)

which implicitly rely on the assumption that, being the boundary of the spatial domain sufficiently far from the tumour, the oxygen concentration along it remains equal to the tissue oxygen concentration in physiological conditions.

# 3 Main analytical results

In this section, we formally show that, in appropriate asymptotic regimes, the RD system (7) admits phenotype-structured travelling front solutions, wherein the locally prevailing cell phenotype varies across the front as a result of variability in the oxygen concentration.

# 3.1 Travelling wave problem

First, for compactness of notation, we drop the carets in the system (7). Then, to strip down the problem to its essence and facilitate analysis of the model, we restrict our attention to a one-dimensional spatial domain, thereby setting  $\mathbf{x} \equiv x \in \mathbb{R}$ , and assume  $\mathbf{D}_n(x) \equiv D_n \in \mathbb{R}^+$  and  $\mathbf{D}_S(x) \equiv D_S \in \mathbb{R}^+$ . Next, to investigate the dynamics of the system for large t, we introduce a small parameter  $\varepsilon \in \mathbb{R}^+$  and employ the time scaling  $t \to t/\varepsilon$ . Finally, we consider a scenario where oxygen diffusion and consumption occur on a slower time scale compared to cell proliferation and death, and cell movement and phenotypic changes occur on a slower time scale compared to oxygen diffusion and consumption. We thus employ the following parameter scaling:

$$D_S := \varepsilon$$
,  $\nu := \varepsilon$ ,  $D_n := \varepsilon^2$ ,  $\beta := \varepsilon^2$ .

In this framework, the local phenotype density,  $n_{\varepsilon}(t, x, y) \equiv n(\frac{t}{\varepsilon}, x, y)$ , and the oxygen concentration,  $S_{\varepsilon}(t, x) \equiv S(\frac{t}{\varepsilon}, x)$ , satisfy the following rescaled RD system:

$$\begin{cases}
\varepsilon \,\partial_t n_{\varepsilon} - \varepsilon^2 \,\partial_{xx}^2 n_{\varepsilon} = \alpha \left( r(y) \, S_{\varepsilon} + f(y) - \rho_{\varepsilon} \right) n_{\varepsilon} + \varepsilon^2 \partial_{yy}^2 n_{\varepsilon} \,, & y \in (0, 1) \\
\rho_{\varepsilon}(t, x) := \int_0^1 n_{\varepsilon}(t, x, y) \, \mathrm{d}y \,, & x \in \mathbb{R}. \\
\partial_t S_{\varepsilon} - \partial_{xx}^2 S_{\varepsilon} = -S_{\varepsilon} \int_0^1 r(y) \, n_{\varepsilon}(t, x, y) \, \mathrm{d}y \,,
\end{cases}$$
(13)

We seek travelling wave solutions of the system (13) with the  $n_{\varepsilon}$ -component that exhibits phenotype structuring, that is, solutions of the following form

$$n_{\varepsilon}(t, x, y) \equiv n_{\varepsilon}(z, y), \quad S_{\varepsilon}(t, x) \equiv S_{\varepsilon}(z), \quad z = x - ct, \quad c \in \mathbb{R}^+,$$

where c is the wave speed. Substituting this ansatz into the system (13) and rearranging terms we obtain the following system:

$$\begin{cases}
-\varepsilon^{2} \partial_{zz}^{2} n_{\varepsilon} - \varepsilon c \partial_{z} n_{\varepsilon} = \alpha \left( r(y) S_{\varepsilon} + f(y) - \rho_{\varepsilon} \right) n_{\varepsilon} + \varepsilon^{2} \partial_{yy}^{2} n_{\varepsilon}, & y \in (0, 1) \\
\rho_{\varepsilon}(z) := \int_{0}^{1} n_{\varepsilon}(z, y) \, \mathrm{d}y, & x \in \mathbb{R}. \\
S_{\varepsilon}'' + c S_{\varepsilon}' = S_{\varepsilon} \int_{0}^{1} r(y) n_{\varepsilon}(z, y) \, \mathrm{d}y,
\end{cases}$$
(14)

We consider travelling fronts corresponding to an invading tumour whereby: the hypoxic tumour core (i.e. where the rescaled oxygen concentration attains the minimum value 0, and we thus expect the mean phenotype of tumour cells to be y=1) is located at  $z=-\infty$ ; the region ahead of the tumour (i.e. where the rescaled oxygen concentration attains the maximum value 1 and there are no tumour cells) is located at  $z=\infty$ . Hence, we seek solutions of the system (14) that meet the following conditions

$$S_{\varepsilon}(-\infty) = 0, \quad S_{\varepsilon}(\infty) = 1$$
 (15)

and

$$\rho_{\varepsilon}(-\infty) > 0, \quad \int_{0}^{1} y \, \frac{n_{\varepsilon}(-\infty, y)}{\rho_{\varepsilon}(-\infty)} \, \mathrm{d}y = 1, \quad \rho_{\varepsilon}(\infty) = 0.$$
(16)

# 3.2 Formal asymptotic analysis

Building on previous studies of phenotypic structuring across travelling waves, see the recent review [68] and references therein, we make the Hopf-Cole transformation [10, 27, 33]

$$n_{\varepsilon}(z,y) = e^{\frac{u_{\varepsilon}(z,y)}{\varepsilon}}. (17)$$

Moreover, we denote by  $\rho(z)$ , u(z,y), and S(z) the leading-order terms of the asymptotic expansions for  $\rho_{\varepsilon}(z)$ ,  $u_{\varepsilon}(z,y)$ , and  $S_{\varepsilon}(z)$  as  $\varepsilon \to 0$ .

#### 3.2.1 Concentration phenomena along travelling waves

Considering  $z \in \mathbb{R}$  such that  $\rho(z) > 0$ , i.e.  $z \in \text{Supp}(\rho)$ , substituting the ansatz (17) into the equation (14) for  $n_{\varepsilon}$  and letting  $\varepsilon \to 0$  we formally obtain the following Hamilton-Jacobi equation for u(z, y):

$$-c \partial_z u - (\partial_z u)^2 = \alpha \Big( r(y)S + f(y) - \rho(z) \Big) + (\partial_y u)^2 , \quad (z, y) \in \operatorname{Supp}(\rho) \times (0, 1) . \tag{18}$$

Moreover, when  $\rho_{\varepsilon}(z) < \infty$  for all  $\varepsilon > 0$ , if  $u_{\varepsilon}(z,y)$  is a strictly concave function of y and u(z,y) is also a strictly concave function of y, with a unique non-degenerate maximum point at  $\bar{y}(z)$ , then letting  $\varepsilon \to 0$  in (17) formally gives the following constraint

$$u(z, \bar{y}(z)) = \max_{y \in [0,1]} u(z, y) = 0, \quad z \in \text{Supp}(\rho),$$
 (19)

which implies that

$$\partial_u u(z, \bar{y}(z)) = 0, \quad \partial_z u(z, \bar{y}(z)) = 0, \quad z \in \text{Supp}(\rho),$$
 (20)

and

$$n_{\varepsilon}(z,y) \xrightarrow{\varepsilon \to 0} \rho(z) \, \delta_{\bar{y}(z)}(y)$$
 weakly in measures, (21)

where  $\delta_{\bar{y}(z)}(y)$  is the Dirac delta centred at  $y = \bar{y}(z)$ . The result (21) indicates that concentration phenomena emerge for  $\varepsilon \to 0$ , i.e.  $n_{\varepsilon}(z,y)$  becomes concentrated as a weighted Dirac mass along the y-dimension. The concentration point  $y = \bar{y}(z)$  (i.e. the centre of the Dirac mass) can thus be biologically interpreted as the phenotype that is expressed by tumour cells at position z along the front (i.e. the locally prevailing cell phenotype), and the weight  $\rho(z)$  is the cell density at position z along the front.

#### **3.2.2** Expression of $\rho(z)$ and differential equations for S(z) and $\bar{y}(z)$

Evaluating (18) at  $\bar{y}(z)$  and using (19) and (20), we find the following expression of  $\rho$ :

$$\rho(z) = r(\bar{y}(z)) S(z) + f(\bar{y}(z)), \quad z \in \text{Supp}(\rho).$$
(22)

Moreover, letting  $\varepsilon \to 0$  in the differential equation (14) for  $S_{\varepsilon}(z)$  and using (21), we formally obtain the following differential equation for S:

$$S''(z) + c S'(z) = S(z) r(\bar{y}(z)) \rho(z), \quad z \in \mathbb{R}.$$
 (23)

Furthermore, differentiating (18) with respect to y yields

$$-c\,\partial_{zy}^2 u - 2\,\partial_z u\,\partial_{zy}^2 u = \alpha\left(\frac{\mathrm{d} r(y)}{\mathrm{d} y}S + \frac{\mathrm{d} f(y)}{\mathrm{d} y}\right) + 2\,\partial_y u\,\partial_{yy}^2 u\,, \quad \ (z,y) \in \mathrm{Supp}(\rho) \times (0,1)\,.$$

Evaluating the above equation at  $\bar{y}(z)$  and using conditions (20) we obtain

$$-\partial_{zy}^{2}u(z,\bar{y}(z)) = \frac{\alpha}{c} \left( \frac{\mathrm{d}r}{\mathrm{d}y}(\bar{y}(z))S(z) + \frac{\mathrm{d}f}{\mathrm{d}y}(\bar{y}(z)) \right), \quad z \in \mathrm{Supp}(\rho).$$
 (24)

Then, differentiating the first condition of (20) with respect to z, and using the fact that  $\partial_{yy}^2 u(z, \bar{y}(z)) < 0$ , since  $\bar{y}(z)$  is the unique non-degenerate maximum point of u(z, y), formally gives

$$\partial_{zy}^{2}u(z,\bar{y}(z)) + \partial_{yy}^{2}u(z,\bar{y}(z))\,\bar{y}'(z) = 0 \implies \bar{y}'(z) = \frac{-\partial_{zy}^{2}u(z,\bar{y}(z))}{\partial_{yy}^{2}u(z,\bar{y}(z))}, \quad z \in \operatorname{Supp}(\rho)\,.$$

Finally, substituting the expression (24) of  $-\partial_{zy}^2 u(z, \bar{y}(z))$  into the above equation leads to the following differential equation for  $\bar{y}$ :

$$\bar{y}'(z) = \frac{\alpha}{c \,\partial_{yy}^2 u(z, \bar{y}(z))} \left( \frac{\mathrm{d}r}{\mathrm{d}y} (\bar{y}(z)) S(z) + \frac{\mathrm{d}f}{\mathrm{d}y} (\bar{y}(z)) \right) \,, \quad z \in \mathrm{Supp}(\rho) \,. \tag{25}$$

## 3.2.3 Boundary and complementary conditions

Letting  $\varepsilon \to 0$ :

(i) from the conditions (15) we formally obtain the following boundary conditions for the differential equation (23)

$$S(-\infty) = 0, \quad S(\infty) = 1; \tag{26}$$

(ii) from the second condition in (16), using (21), we formally obtain the following boundary condition for the differential equation (25)

$$\bar{y}(-\infty) = 1, \tag{27}$$

and this, along with the expression (22) of  $\rho(z)$  and the first condition in (26), formally gives

$$\rho(-\infty) = f(1) = \zeta > 0,$$

which ensures that the first condition in (16) is met in the asymptotic regime  $\varepsilon \to 0$ ;

(iii) finally, from the last condition in (16), we formally obtain the following complementary condition

$$\rho(\infty) = 0. (28)$$

#### 3.2.4 Monotonicity of S and formula for the wave speed

For  $c \in \mathbb{R}^+$  fixed, in light of the nonnegativity of r(y) and  $\rho(z)$ , the maximum principle ensures that the solution to the differential equation (23) subject to the boundary conditions (26) satisfies the following properties:

$$0 < S(z) < 1$$
 and  $S'(z) > 0$  for all  $z \in \mathbb{R}$  (29)

and

$$S'(-\infty) = 0 \quad \text{and} \quad S'(\infty) = 0. \tag{30}$$

Moreover, integrating the differential equation (23) over  $\mathbb{R}$ , imposing the boundary conditions (26), and using (30) as well as the expression (22) of  $\rho(z)$ , we find the following formula for the wave speed:

$$c = \int_{\mathbb{R}} S(z) r(\bar{y}(z)) \rho(z) dz = \int_{\text{Supp}(\rho)} S(z) r(\bar{y}(z)) \left[ r(\bar{y}(z)) S(z) + f(\bar{y}(z)) \right] dz.$$
 (31)

## 3.2.5 Shape of phenotype-structured travelling fronts

Under definitions (5), the function r(y) S + f(y) can be rewritten as

$$r(y) S + f(y) = a(S) - b(S) (y - h(S))^{2}$$
 (32)

with

$$h(S) := \frac{\zeta}{\zeta + \gamma S}, \quad a(S) := \gamma S + \zeta h(S), \quad b(S) := \zeta + \gamma S.$$

$$(33)$$

Substituting (32) into (22) and (25) yields, respectively,

$$\rho(z) = a(S(z)) - b(S(z)) \left(\bar{y}(z) - h(S(z))\right)^2, \quad z \in \text{Supp}(\rho)$$
(34)

and

$$\bar{y}'(z) = -\alpha \frac{2b(S(z))}{c \,\partial_{yy}^2 u(z, \bar{y}(z))} \left( \bar{y}(z) - h(S(z)) \right), \quad z \in \operatorname{Supp}(\rho).$$
 (35)

Letting  $\alpha \to \infty$  in the differential equation (35), which corresponds to considering the asymptotic regime of strong phenotypic selection, and recalling the expression (33) of h(S) formally gives

$$\bar{y}(z) = h(S(z)) = \frac{\zeta}{\zeta + \gamma S(z)}, \quad z \in \text{Supp}(\rho).$$
 (36)

In turn, substituting (36) into (34), and recalling the expression (33) of a(S), we find

$$\rho(z) = a(S(z)) = \gamma S(z) + \frac{\zeta^2}{\zeta + \gamma S(z)}, \quad z \in \text{Supp}(\rho).$$
 (37)

Under the boundary conditions (26) and (27), the properties (29) and (30) of S(z) along with the expression (36) of  $\bar{y}(z)$  and the expression (37) of  $\rho(z)$ , as well as the fact that  $0 < \zeta < 1$ , allow us to conclude that

$$\bar{y}'(z) < 0 \text{ and } \rho'(z) > 0 \text{ for all } z \in \mathbb{R}$$
 (38)

and

$$\rho(z) \to \gamma + \frac{\zeta^2}{\zeta + \gamma}, \quad \bar{y}(z) \to \frac{\zeta}{\zeta + \gamma}, \quad \text{as } z \to \infty^-.$$
(39)

Therefore, for the complementary condition (28) to hold,  $\rho(z)$  has to jump to 0 at  $z=\infty$ .

In summary, the analytical results formally obtained in this section, which are confirmed by the results of numerical simulations presented in Figure 1, as discussed in detail in Section 4.2, indicate that: the oxygen concentration increases monotonically along the front, going from S=0 to S=1 (cf. (26) and (29)). The locally prevailing cell phenotype decreases monotonically along the front, connecting  $\bar{y}=1$  to  $\bar{y}=\frac{\zeta}{\zeta+\gamma}<1/2$  (cf. (36), (38), and (39), and recall that we work under the assumption  $\gamma>\zeta$ ). On the other hand, the cell density increases monotonically along the front, departing from  $\rho = \zeta$  and approaching  $\rho = \gamma + \frac{\zeta^2}{\zeta + \gamma} > \zeta$  (cf. (37), (38) and (39), and recall again that  $\gamma > \zeta$ ). Hence, taken together, these results formalise the idea that differences in oxygenation across the tumour create distinct micro-environments, whereby the oxygenated edge and the hypoxic core of the tumour exhibit distinct phenotype compositions, with fast-proliferating cells with a more oxidative metabolism being located around the edge of the tumour, while the regions in the proximity of the core are predominantly composed of slow-proliferating cells with a primarily glycolytic metabolism. This promotes the emergence of intratumour phenotypic heterogeneity. Note also that the value of the locally prevailing cell phenotype,  $\bar{y}$ , at the edge of the front, that is,  $\frac{\zeta}{\zeta + \gamma}$ , approaches 0 as the ratio  $\gamma/\zeta$  increases. This, along with the monotonicity of  $\bar{y}$  and the fact that at the back of the wave  $\bar{y} = 1$ , indicates that the spectrum of values spanned by  $\bar{y}$  widens in the presence of larger values of  $\gamma/\zeta$ . Since, as mentioned earlier, the ratio  $\gamma/\zeta$  provides a measure of the fitness cost of glycolytic metabolism, these theoretical results indicate that higher fitness costs of glycolytic metabolism correlate with higher levels of intratumour phenotypic heterogeneity.

# 4 Main numerical results

In this section, we present the main results of numerical simulations. In Section 4.1, the scheme employed to solve numerically the initial-boundary value problem for the RD system of the model is described. In Section 4.2, we compare the numerical solutions of the rescaled one-dimensional model (13) with the results of the formal asymptotic analyses carried out in Section 3. In Sections 4.3 and 4.4 we present numerical solutions of the RD system (7) posed, respectively, on a square spatial domain and on the 3D-geometry of the brain.

# 4.1 Numerical scheme

We present the numerical scheme employed for the RD system (7). This scheme is based on a hybrid finite difference-finite element method and relies on a time-splitting approach, which makes it possible to solve separately the conservative and non-conservative parts of the model equations. One can similarly derive the finite difference scheme used to solve the rescaled one-dimensional model (13).

# 4.1.1 Time-splitting approach underlying the scheme

Adopting a time-splitting approach, we decompose the RD equation (7) for  $\hat{S}$  into the diffusion equation

$$\partial_t \hat{S} - \operatorname{div}\left(\mathbf{D}_S(\boldsymbol{x})\,\nabla\hat{S}\right) = 0\,,\quad \boldsymbol{x} \in \Omega\,,$$
 (40)

subject to the boundary conditions (12), and the reaction equation

$$\partial_t \hat{S} = -\hat{\nu} \, \hat{S} \int_0^1 r(y) \, \hat{n}(t, \boldsymbol{x}, y) \, \mathrm{d}y \,, \quad \boldsymbol{x} \in \overline{\Omega} \,. \tag{41}$$

These equations are sequentially solved at each time step.

Similarly, for the non-local RD equation (7) for  $\hat{n}$ , at each time step we solve sequentially the diffusion equation

$$\partial_t \hat{n} - \operatorname{div}\left(\mathbf{D}_n(\mathbf{x}) \nabla \hat{n}\right) = 0, \quad (\mathbf{x}, y) \in \Omega \times [0, 1],$$
 (42)

subject to the boundary conditions (10), then the diffusion equation

$$\partial_t \hat{n} = \beta \, \partial_{nn}^2 \hat{n} \,, \quad (\boldsymbol{x}, y) \in \overline{\Omega} \times (0, 1) \,,$$
 (43)

subject to the boundary conditions (11), and lastly the non-local reaction equation

$$\begin{cases}
\partial_t \hat{n} = \alpha \left( r(y) \hat{S} + f(y) - \hat{\rho} \right) \hat{n}, & (\boldsymbol{x}, y) \in \overline{\Omega} \times [0, 1], \\
\hat{\rho}(t, \boldsymbol{x}) := \int_0^1 \hat{n}(t, \boldsymbol{x}, y) \, \mathrm{d}y.
\end{cases} \tag{44}$$

In particular, since we will be employing a semi-implicit time discretisation to ensure a balance between numerical stability and computational efficiency, instead of solving directly the above non-local reaction equation, we make the change of variables  $\hat{u} = \ln(\hat{n})$ , as similarly done in [69], to obtain the following equation

$$\begin{cases}
\partial_t \hat{u} = \alpha \left( r(y) \hat{S} + f(y) - \hat{\rho} \right), & (\boldsymbol{x}, y) \in \overline{\Omega} \times [0, 1], \\
\hat{\rho}(t, \boldsymbol{x}) := \int_0^1 e^{\hat{u}(t, \boldsymbol{x}, y)} \, \mathrm{d}y,
\end{cases} \tag{45}$$

which is easier to be numerically solved implicitly.

#### 4.1.2 Summary of the scheme

We consider a uniform discretisation of the phenotype domain [0,1] of step  $\Delta y := 1/N_y$ , with  $N_y \in \mathbb{N}$ , whereby  $y_j = j \Delta y$  for  $j = 0, \ldots, N_y$ . Similarly, we consider a uniform discretisation of the time domain  $[0, t_f]$  of step  $\Delta t := t_f/N_t$ , with  $t_f \in \mathbb{R}^+$  and  $N_t \in \mathbb{N}$ , whereby  $t_k = k \Delta t$  for  $k = 0, \ldots, N_t$ . On the other hand, we employ a finite-element discretisation for the spatial domain  $\Omega$  by considering the following finite element spaces

$$V_h := \{ f \in C^0(\overline{\Omega}) : f|_T \in P_1(T) \ \forall T \in \mathcal{T}_h \} \subset H^1(\Omega) ,$$
$$V_h^0 := \{ f \in V_h : f \equiv 0 \text{ on } \partial\Omega \} \subset H_0^1(\Omega) ,$$
$$V_h^1 := \{ f \in V_h : f \equiv 1 \text{ on } \partial\Omega \} ,$$

where  $\mathcal{T}_h$  is a partition of  $\Omega$  into tetrahedral elements and  $P_1(T)$  is the space of polynomials of order 1 on the tetrahedral element T. Here, the numerical approximations of  $\hat{S}(t_k, \boldsymbol{x}) \in V_h^1$ ,  $\hat{n}(t_k, \boldsymbol{x}, y_j) \in V_h$ , and  $\hat{u}(t_k, \boldsymbol{x}, y_j) \in V_h$  are denoted by  $S^k$ ,  $n_j^k$ , and  $u_j^k$ , respectively, and the standard  $L^2$ -inner product over  $\Omega$  is denoted by  $<\cdot,\cdot>$ .

First we solve the diffusion equation (40) subject to the boundary conditions (12) through the following finite element scheme

$$\left\langle \frac{S^* - S^k}{\Delta t}, v_h \right\rangle = -\left\langle \mathbf{D}_S(\mathbf{x}) \, \nabla S^*, \nabla v_h \right\rangle \,, \quad \forall v_h \in V_h^0 \tag{46}$$

to obtain  $S^*$ , and subsequently we compute  $S^{k+1}$  by solving the reaction equation (41) through the following finite difference scheme

$$\frac{S^{k+1} - S^*}{\Delta t} = -\hat{\nu} \ S^{k+1} \ \sum_{j=1}^{N_y} \frac{r_{j-1} n_{j-1}^k + r_j n_j^k}{2} \ \Delta y \,, \tag{47}$$

where  $r_j = r(y_j)$ .

Next we solve the diffusion equation (42) subject to the boundary conditions (10) through the following finite element scheme

$$\left\langle \frac{n_j^* - n_j^k}{\Delta t}, v_h \right\rangle = -\left\langle \mathbf{D}_n(\boldsymbol{x}) \, \nabla n_j^*, \nabla v_h \right\rangle, \quad \forall v_h \in V_h, \quad j = 0, \dots, N_y$$
(48)

to obtain  $n_i^*$ .

Then, looping over all the elements of  $\mathcal{T}_h$ , we solve the diffusion equation (43) subject to the boundary conditions (11) through the following finite difference scheme

$$\begin{cases}
\frac{n_j^{**} - n_j^{*}}{\Delta t} = \beta \frac{n_{j+1}^{**} + n_{j-1}^{**} - 2n_j^{**}}{(\Delta y)^2}, & j = 0, \dots, N_y \\
n_{-1}^{**} = n_1^{**} \\
n_{N_y+1}^{**} = n_{N_y-1}^{**}
\end{cases}$$
(49)

to obtain  $n_j^{**}$ , where the ghost points j = -1 and  $j = N_y + 1$  have been introduced to gain second-order numerical accuracy.

Finally, we compute  $n^{k+1} = e^{u^{k+1}}$  by solving the reaction equation (45) through the following finite difference scheme

$$\frac{u_j^{k+1} - u_j^{**}}{\Delta t} = \alpha \left( r_j S^{k+1} + f_j - \rho^{k+1} \right), \quad j = 0, \dots, N_y.$$
 (50)

In (50),  $r_j = r(y_j)$ ,  $f_j = f(y_j)$ ,  $u_j^{**} = \ln(n_j^{**})$ , and  $\rho^{k+1}$  is obtained by solving, through a root-finding algorithm, the following transcendental equation

$$\rho^{k+1} = \Delta y e^{\left(-\alpha \Delta t \rho^{k+1}\right)} \sum_{j=1}^{N_y} \frac{m_{j-1}^{k+1} + m_j^{k+1}}{2} \quad \text{with} \quad m_j^{k+1} = n_j^{**} e^{\left[\alpha \Delta t \left(r_j S^{k+1} + f_j\right)\right]}.$$

The above transcendental equation is derived, with a little algebra, by first approximating the integral in the definition (44) of  $\hat{\rho}$  with the corresponding Riemann sum and then using (50) along with the fact that  $u_i^k = \ln(n_i^k)$ .

## 4.2 Simulations of the rescaled one-dimensional model (13)

#### 4.2.1 Set-up of simulations

We solve numerically the initial-value problem defined by the rescaled RD system (13), with  $x \in [0, L]$  and  $L = 3 \times 10^4$ , subject to the boundary conditions (10)-(12) and the following initial data

$$n_{\varepsilon}(0, x, y) = \frac{e^{-\frac{(y-0.5)^2}{\varepsilon}}}{\int_0^1 e^{-\frac{(y-0.5)^2}{\varepsilon}} dy} e^{-x^2}, \quad S_{\varepsilon}(0, x) = 1 - \int_0^1 n_{\varepsilon}(0, x, y) dy = 1 - \rho_{\varepsilon}(0, x).$$
 (51)

All simulations of the rescaled RD system (13) are performed considering dimensionless space and time variables, and using the definitions (5) of the model functions, with  $\gamma=1$  and  $\zeta=0.1$ . Finally, since the formal asymptotic results of Section 3 are obtained by letting first  $\varepsilon\to 0$  and then  $\alpha\to\infty$ , we choose  $\varepsilon=10^{-4}$  and  $\alpha=20$ . Note that the excellent quantitative agreement between the analytical results presented in Section 3 and the numerical results presented in this section (cf. Figure 1) indicates that these values of  $\varepsilon$  and  $\alpha$  can be regarded, respectively, as suitably small and suitably large for the employed model set-up.

# 4.2.2 Main results

The right panels of Figure 1 display the plots of the normalised local phenotype density,  $n_{\varepsilon}(t, x, y)/\rho_{\varepsilon}(t, x)$ , at two successive time instants, i.e. t = 400 (top panel) and t = 600 (bottom panel). These plots indicate that, for all  $x \in \text{Supp}(\rho_{\varepsilon})$ , the normalised local phenotype density is concentrated as a sharp Gaussian

Par.	Biological meaning	Value	Units	Ref.
$\rho_0$	Local carrying capacity of the tumour	$3.183 \times 10^{3}$	$cells/mm^2$	[48]
$S_0$	Tissue oxygen conc. in physiological conditions	$6.3996 \times 10^{-9}$	$g/mm^2$	[61, 99]
$\hat{\nu}$	Conversion factor linked to oxygen consumption	9.95	-	[70, 99]
$  \gamma  $	Maximum prolif. rate via aerobic respiration	0.864	$day^{-1}$	[46, 70]
ζ	Maximum prolif. rate via anaerobic glycolysis	0.0864	$day^{-1}$	[46, 70]
$\beta$	Rate of phenotypic changes	$8.64 \times 10^{-8}$	$day^{-1}$	[31, 99]
$D_n$	Diffusion coefficient of glioma cells	0.13	$\rm mm^2/day$	[90]
$D_S$	Diffusion coefficient of oxygen	86.4	$\mathrm{mm}^2/\mathrm{day}$	[52, 99]

Table 1: List of the values of the model parameters employed for the numerical simulations in Sections 4.3 and 4.4.

with maximum at a point,  $\bar{y}_{\varepsilon}(t,x)$ , which can be regarded as the locally prevailing cell phenotype – i.e.  $n_{\varepsilon}(t,x,y)/\rho_{\varepsilon}(t,x) \approx \delta_{\bar{y}_{\varepsilon}(t,x)}(y)$  for all  $x \in \operatorname{Supp}(\rho_{\varepsilon}(t,\cdot))$ .

As shown by the plots in the left panels of Figure 1, the locally prevailing cell phenotype,  $\bar{y}_{\varepsilon}(t,x)$ , the cell density,  $\rho_{\varepsilon}(t,x)$ , and the oxygen concentration,  $S_{\varepsilon}(t,x)$ , behave like monotonic travelling fronts. In particular, on  $\operatorname{Supp}(\rho_{\varepsilon})$ , the numerical values of  $\bar{y}_{\varepsilon}$  and  $\rho_{\varepsilon}$  coincide with the predicted analytical values obtained by inserting the numerical values of  $S_{\varepsilon}$  into the formulas given by (36) and (37), respectively. Consistently with the results of the formal asymptotic analyses presented in Section 3, the value of  $S_{\varepsilon}$  grows monotonically from 0, attained at the rear of the front, to 1, attained at the edge of the front. Furthermore,  $\rho_{\varepsilon}$  jumps to zero at the edge of the front.

The inset of the left-bottom panel of Figure 1 displays the plots of  $x_{1\varepsilon}(t)$ ,  $x_{2\varepsilon}(t)$ , and  $x_{3\varepsilon}(t)$  such that  $\rho_{\varepsilon}(t, x_{1\varepsilon}(t)) = 0.3$ ,  $\rho_{\varepsilon}(t, x_{2\varepsilon}(t)) = 0.5$ , and  $\rho_{\varepsilon}(t, x_{3\varepsilon}(t)) = 0.7$ . These plots show that  $x_{1\varepsilon}(t)$ ,  $x_{2\varepsilon}(t)$ , and  $x_{3\varepsilon}(t)$  are straight lines of slope  $\approx 40$ , which supports the idea that  $\rho_{\varepsilon}$  behaves like a travelling front of speed  $\approx 40$ . Such a value of the speed is coherent with the predicted analytical value obtained by approximating the integral in (31) with the corresponding Riemann sum and then substituting the definitions (5) of the functions r(y) and f(y) along with the numerical values of  $\bar{y}_{\varepsilon}(t,x)$  and  $S_{\varepsilon}(t,x)$  into the resulting formula.

#### 4.3 Simulations of the model (7) posed on a square spatial domain

## 4.3.1 Set-up of simulations

We pose the RD system (7) on the square spatial domain  $[-L, L] \times [-L, L]$  with L = 75 mm. We complement the system (7) with the boundary conditions (10)-(12) and the following initial data

$$\hat{n}(0, \boldsymbol{x}, y) = \frac{e^{-\frac{(y-0.2)^2}{0.1}}}{\int_0^1 e^{-\frac{(y-0.2)^2}{0.1}} dy} e^{-|\boldsymbol{x}|^2}, \quad \hat{S}(0, \boldsymbol{x}) = 1 - \int_0^1 \hat{n}(0, \boldsymbol{x}, y) dy = 1 - \hat{\rho}(0, \boldsymbol{x}).$$
(52)

Moreover, we choose  $\alpha = 1$  and use the definitions (5) of the model functions along with

$$\mathbf{D}_n(\mathbf{x}) := D_n \mathbf{D}(\mathbf{x}) \text{ and } \mathbf{D}_S(\mathbf{x}) := D_S \mathbf{D}(\mathbf{x}),$$
 (53)

with  $\mathbf{D}(x) := \operatorname{diag}(D_1, D_2)$ . Specifically, to investigate the impact of anisotropy in cell movement and oxygen diffusion on the dynamics of tumour cells, we set  $D_1 = 1.6$  and  $D_2 = 0.4$ . The values of the other model parameters are those listed in Table 1, which are chosen to be consistent with the existing literature. We note that, taken together, these parameter values correspond to a fast-growing and highly aggressive tumour, a choice we make to facilitate early emergence of observable effects of phenotypic evolution dynamics, in order to reduce the computational time of simulations. However, we remark that the phenotype-structured RD system (7) constitutes a flexible modelling framework that can also accommodate parameter values for slow-growing and less aggressive tumours.

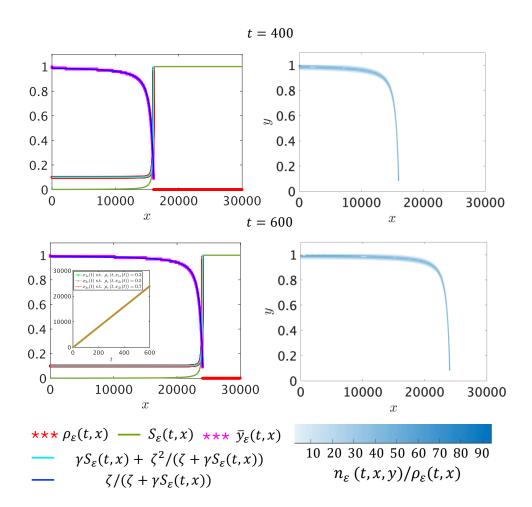


Figure 1: Simulations of the rescaled one-dimensional model (13). Left panels. Plots of  $\rho_{\varepsilon}(t,x)$  (red),  $S_{\varepsilon}(t,x)$  (green), and  $\bar{y}_{\varepsilon}(t,x)$  (magenta), with  $\bar{y}_{\varepsilon}(t,x)$  being the maximum point of  $n_{\varepsilon}(t,x,y)/\rho_{\varepsilon}(t,x)$  at  $x \in \text{Supp}(\rho_{\varepsilon}(t,\cdot))$ , for t=400 (top panel) and t=600 (bottom panel). The blue line and the cyan line highlight, respectively, the predicted analytical values of  $\bar{y}_{\varepsilon}$  and  $\rho_{\varepsilon}$ , which are obtained by inserting the numerical values of  $S_{\varepsilon}$  into the formulas given by (36) and (37). The inset of the bottom panel displays the plots of  $x_{1\varepsilon}(t)$  (green),  $x_{2\varepsilon}(t)$  (grey), and  $x_{3\varepsilon}(t)$  (red) such that  $\rho_{\varepsilon}(t,x_{1\varepsilon}(t))=0.3$ ,  $\rho_{\varepsilon}(t,x_{2\varepsilon}(t))=0.5$ , and  $\rho_{\varepsilon}(t,x_{3\varepsilon}(t))=0.7$ . Right panels. Plots of  $n_{\varepsilon}(t,x,y)/\rho_{\varepsilon}(t,x)$  at t=400 (top panel) and t=600 (bottom panel), with the corresponding colour scale displayed below the bottom panel. The set-up of simulations is summarised in Section 4.2.1.

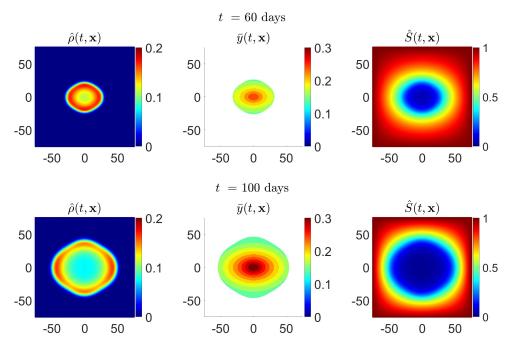


Figure 2: Simulations of the model (7) posed on a square spatial domain. Plots of  $\hat{\rho}(t, \boldsymbol{x})$  (left),  $\bar{y}(t, \boldsymbol{x})$  defined via (54) (centre), and  $\hat{S}(t, \boldsymbol{x})$  (right), at time t = 60 days (top panels) and t = 100 days (bottom panels).

#### 4.3.2 Main results

The dynamics of numerical solutions are summarised by the plots in Figure 2, which display the rescaled cell density,  $\hat{\rho}(t, \boldsymbol{x})$ , the locally prevailing cell phenotype,  $\bar{y}(t, \boldsymbol{x})$ , that is,

$$\hat{n}(t, \boldsymbol{x}, \bar{y}(t, \boldsymbol{x})) = \max_{y \in [0, 1]} \hat{n}(t, \boldsymbol{x}, y) , \qquad (54)$$

and the rescaled oxygen concentration,  $\hat{S}(t, x)$ , at the times t = 60 days and t = 100 days.

Consistently with what observed in the results of simulations of the one-dimensional model (13) displayed in Figure 1, the plots in Figure 2 show that the rescaled oxygen concentration exhibits monotonic behaviour, being approximately 0 at the centre of the tumour, where a hypoxic core is formed, and being 1 in regions that have not yet been invaded by tumour cells. Accordingly, the locally prevailing cell phenotype decreases monotonically moving from the core to the edge of the tumour, indicating that the hypoxic core is occupied by cells with a less oxidative metabolism (i.e. cells with phenotypes corresponding to larger values of y), which rely less on aerobic respiration to produce the energy required for cell division, and thus proliferate more slowly, while the more oxygenated regions towards the tumour edge are occupied by cells with a more oxidative metabolism (i.e. cells with phenotypes corresponding to smaller values of y), which rely more on aerobic respiration for producing the energy to fuel cell division, and thus proliferate more quickly. As a result of this, the rescaled cell density is also monotone, being minimal in the hypoxic core and maximal at the tumour edge.

In addition, the results in Figure 2 demonstrate the impact of anisotropy in cell movement and oxygen diffusion on tumour growth and on the phenotypic composition of the tumour edge. Specifically, these results indicate that, compared to the other directions, along the anisotropy preferential direction both tumour growth (i.e. the expansion of the support of  $\hat{\rho}$ ) and oxygen consumption (i.e. the decay of  $\hat{S}$ ) are faster, and the tumour edge comprises cells with a less oxidative metabolism (i.e. the values attained by  $\bar{y}$  in the proximity of the outer boundary of the tumour are larger in the anisotropy preferential direction than in the other directions).

# 4.4 Simulations of the model (7) posed on the 3D-geometry of the brain

#### 4.4.1 Set-up of simulations

We pose the RD system (7) on the 3D-geometry of the brain. The corresponding computational mesh was constructed by using Magnetic Resonance Imaging (MRI) data from a single patient, which had been acquired during routine clinical practice at the Istituto Neurologico Carlo Besta in Milan, Italy. Moreover, we define the diffusion tensors  $\mathbf{D}_n(x)$  and  $\mathbf{D}_S(x)$  via (53), where the tensor  $\mathbf{D}(x)$  is reconstructed from Diffusion Tensor Imaging (DTI) data<sup>1</sup> [7, 12] and represents the spatially varying diffusion directions. Specifically, the components derived from medical images are normalised by the mean diffusivity, so that the resulting tensor encodes only the principal diffusion directions, excluding the contribution of the mean water diffusivity.

To construct the computational mesh, we first segmented the MRI grey-scale images in order to partition them into segments and then labelled each pixel to reconstruct the brain boundary. This process was carried out by using the software package Slicer3D [1]. After segmentation, we generated the computational mesh by means of Tetgen [96], a tool for generating tetrahedral meshes of any 3D polyhedral domain.

To construct the tensor  $\mathbf{D}(x)$ , the DTI images corresponding to the six independent components of the diffusion tensor were aligned with the MRI images through FSL (FMRIB Software Library) [63], and the values of the six components of the tensor  $\mathbf{D}(x)$  were then defined throughout the computational mesh by means of custom scripts implemented in the VMTK software library [97].

Simulations are carried out by complementing the system (7) with the boundary conditions (10)-(12) and the initial data (52). Moreover, we choose  $\alpha = 1$  and use the definitions (5) of the model functions, and we set the values of the model parameters as in Table 1.

#### 4.4.2 Main results

The dynamics of numerical solutions are summarised by the plots in Figure 3, which display the rescaled cell density,  $\hat{\rho}(t, \boldsymbol{x})$ , the locally prevailing cell phenotype,  $\bar{y}(t, \boldsymbol{x})$ , which is defined via (54), and the rescaled oxygen concentration,  $\hat{S}(t, \boldsymbol{x})$ , at the times  $t \in \{5, 15, 25, 35\}$  days.

These plots support the idea that the conclusions we have drawn based on the outputs of the model (7) posed on a square spatial domain remain intact when posing the model on the 3D-geometry of the brain (compare the plots in Figures 2 and 3). Namely, as we move from the centre to the edge of the tumour, both the rescaled cell density and the rescaled oxygen concentration increase, while the locally prevailing cell phenotype decreases. Moreover, as the simulation time progresses, we observe the formation of a less densely populated and hypoxic tumour core, where cells exhibit a less oxidative metabolism, and a more densely populated and well oxygenated tumour edge, where cells express a more oxidative metabolism. Finally, tumour growth and oxygen consumption are faster along the preferential directions of the diffusion tensor  $\mathbf{D}(x)$  and, in these directions of faster tumour expansion, the tumour edge is characterised by a more pronounced cell accumulation and a larger presence of cells with a less oxidative metabolism, compared to the other directions.

As mentioned earlier in the paper (cf. Section 4.3.1), the employed parameter values listed in Table 1 correspond to a fast-growing and highly aggressive tumour. To verify this, we use the results of numerical simulations displayed in Figure 3 to compute tumour growth metrics commonly employed in the clinical literature, so as to facilitate comparison with clinical references. In summary, we estimate a volume doubling time (VDT) of approximately 5.94 days, indicating that the tumour is growing substantially fast – for comparison, on the basis of average data from clinical studies, Stensjøen et al. [86] reported a median VDT of 29.8 days, while Ellingson et al. [26] found a median VDT of 21.1 days. The specific growth rate (SGR), or percentage increase per unit time, defined as (ln 2)/VDT, is 11.66% per day, which is higher compared to typical values reported in [26, 86], and the average radial expansion velocity (VRE) is approximately 0.62 mm/day, which, as expected, exceeds average values reported in previous theoretical [9] and clinical [86, 100] studies on brain tumour growth. It is also worth noting that Figure 3 shows that the cell density remains relatively low throughout the tumour, indicating a diffusely distributed

<sup>&</sup>lt;sup>1</sup>By capturing the anisotropic diffusion of water molecules, DTI enables the identification and visualisation of white matter tract orientations and the preferential directions of cell migration. This information is essential for modelling processes such as tumour infiltration in brain tissues. DTI provides a symmetric, positive-definite tensor that characterises water diffusivity within each voxel.

pattern of invasion. This suggests that the simulated tumour grows predominantly by spreading its cells outwards over a broader area, rather than by increasing the concentration of cells in its immediate vicinity through rapid cell division. This behaviour is characteristic of highly invasive tumour types, in which cell dispersal dominates over local cell proliferation.

# 5 Conclusions and research perspectives

The results of formal asymptotic analyses and numerical simulations presented in this work recapitulate the findings of previous experimental [15, 34, 49, 88, 101] and theoretical [36, 38, 80] studies on key features of avascular tumour growth, including the formation of a hypoxic core that comprises cells with a less oxidative metabolism, which exhibit greater ability to survive at low oxygen levels, and the appearance at the tumour's edge, where cells have access to oxygen, of a proliferative rim consisting of cells with a more oxidative metabolism. This offers a theoretical basis for experimental observations suggesting that the edge and the core of avascular tumours function as distinct ecological niches [14, 53, 65, 103], and aligns with the idea that spatial gradients of abiotic factors, such as oxygen, across the tumour play a pivotal role in the emergence of intratumour phenotypic heterogeneity [2].

Furthermore, the obtained results of 2D and 3D numerical simulations indicate that, along the preferential directions of cell movement and oxygen diffusion, there is faster tumour expansion and oxygen consumption, and a larger fraction of cells with less oxidative metabolism is localised at the tumour edge. These findings support the idea that structural anisotropy of the extracellular environment can impact both on tumour growth and on phenotypic selection occurring at the invasive tumour front [32, 73, 76, 85]. It would be of interest to complement these numerical results with analytical results shedding light on the impact of anisotropic diffusion on the properties of the locally prevailing cell phenotype at the leading edge of phenotypically heterogeneous travelling waves. In this respect, while the Hopf-Cole transformation used here might still prove useful, we envisage substantial changes in the formal asymptotic methods underlying our study of phenotype-structured travelling waves to be required to tackle such an intricate problem. On a related note, in the vein of [35, 66, 67, 69], it would be interesting to further generalise the model presented here by making the diffusion tensor in the equation for the local phenotype density dependant on the phenotype-structuring variable, and then extend the analytical and numerical results presented here by examining how trade-offs between cell proliferation and migration related to the "goor-grow" hypothesis, which posits a dichotomy between proliferation and migration and was conceived following observations of glioma cell behaviour [43, 44], may shape the phenotypic structuring of invading waves in the presence of anisotropic diffusion.

Our approach could also extend to other types of tumours growing in different anisotropic environments and to integrate additional patient specific imaging data, such as those acquired by means of Magnetic Resonance Spectroscopy (MRS) – an advanced MRI technique that provides information on the concentrations of water-soluble metabolites, thus enabling detection of tumour-specific mutations and assessment of intratumoural heterogeneity. MRS is frequently employed to study metabolic alterations within tumours, as it offers valuable insight into tumour grade and aggressiveness. Integrating imaging data of this type into the model could significantly improve the precision and predictive capabilities of our approach, opening an avenue to investigate in silico how structural anisotropy of the extracellular environment may shape the growth and phenotypic composition of solid tumours.

Building upon the modelling approach presented here, another avenue for future research would be to explore ways of incorporating a continuous phenotype structure in mechanical models of glioma growth based on either linearly elastic [13, 23, 54] or nonlinearly elastic [4, 5, 8, 9, 24, 25, 72] constitutive equations, which would make it possible to take into account intratumour phenotypic heterogeneity when investigating the impact of brain deformations induced by tumour expansion in disease progression and patient prognosis.

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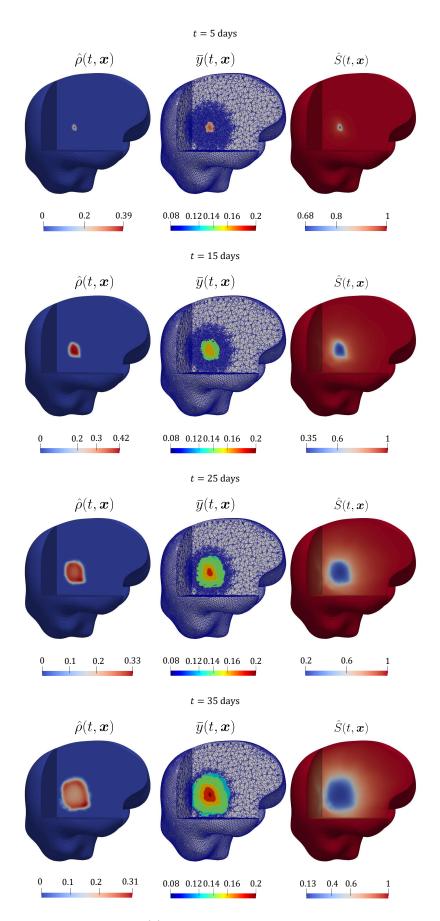


Figure 3: Simulations of the model (7) posed on the 3D-geometry of the brain. Plots of  $\hat{\rho}(t, \boldsymbol{x})$  (left),  $\bar{y}(t, \boldsymbol{x})$  defined via (54) (centre), and  $\hat{S}(t, \boldsymbol{x})$ 1 (right), at time t = 5 days (first row), t = 15 days (second row), t = 25 days (third row), and t = 35 days (fourth row).

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