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Nonlinear waves in a simple model of high-grade glioma

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Abstract

We present an analysis of a mathematical model describing the key features of the most frequent and aggressive type of primary brain tumor: glioblastoma. The model captures the salient physiopathological characteristics of this type of tumor: invasion of the normal brain tissue, cell proliferation and the formation of a necrotic core. Our study, based on phase space analysis, geometric perturbation theory, exact solutions and numerical simulations, proves the existence of bright solitary waves in the tumor coupled with kink and anti-kink fronts for the normal tissue and the necrotic core. Finally, we study the linear stability of the solutions to calculate the time of tumor recurrence.

Keywords: Solitary waves; bright solitons; dark solitons, mathematical oncology.
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1 Introduction

The application of tools from nonlinear dynamical systems to describe in a quantitative manner the underlying mechanisms encountered in a number of biologically- and/or medically-oriented scenarios has attracted an increasing interest in recent years [2, 11–13, 19, 32, 44, 45, 56]. As multidisciplinary collaboration between mathematical modelers with experimental biologists and/or clinicians is becoming a more common practice, it is possible to tackle complex problems and develop new armamentaria that could potentially display a great impact in public health, with cancer being a quite prominent example [38].

Here, we analyze in detail a mathematical model that was proposed in [39] to describe the salient physiopathological hallmarks of a very aggressive type of primary brain tumor: glioblastoma (GBM), the most

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frequent high-grade glioma in adults. At present, GBM carries a dismal prognosis; the median overall survival from diagnosis is 14.6 months with the current standard therapy [46], which includes neurosurgery followed by radiotherapy in combination with the alkylating agent temozolomide, and various salvage therapies (e.g., antiangiogenic) once tumor progression recurs [51]. Large-scale research endeavors are ongoing to provide a comprehensive understanding of all the genetic and epigenetic alterations that underlie GBM [48]. Despite all of these efforts, GBM remains incurable (the five-year overall survival rate is less than 10%), although it should be mentioned that, albeit still very small, a slow but steadily increase in the number of long-term surviving patients (more than five years) has been reported [47].

Various mathematical models have been proposed to describe specific aspects of GBM in vivo [3–7, 18, 23, 28, 40, 49, 50, 54]. Most of these models assume that the tumor evolves according to a simple reaction-diffusion equation (or a combination of): the Fisher-Kolmogorov (FK) equation [33], which epitomizes the simplest form of a nonlinear reaction-diffusion process

$$\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u) + \rho \left(1 - \frac{u}{u_*} \right) u, \quad (1)$$

where D , ρ and u_* are positive parameters accounting, in the case of GBM, for the diffusion constant (cell migration), the proliferation rate and the maximum cell density (carrying capacity). This equation was first proposed by Fisher [17] in a completely different scenario; as a deterministic version of a stochastic model for the spatial spread of a favoured gene in a population. It is also the natural extension of the logistic growth population model when the population disperses via linear diffusion [10, 34]. The same equation appears in flame propagation [55], neurophysiology [53], and Brownian motion processes [8] among other situations. This equation and its variants have attracted the attention of many mathematicians, which have calculated different exact solutions under various conditions (see for instance [41, 42] and references therein).

In one-dimensional scenarios the FK equation has solitary wave solutions of kink-type [1, 29], which account for the progression of the tumor front edge. In dimensions higher than one, the FK equation does not display any kind of travelling wave solution [9], thus its analysis must resort to numerical methods. However, some essential features of brain tumor lesions in their transit to high-grade gliomas (i.e. from low-grade astrocytoma to GBM) are neglected by the FK model, such as the formation of a necrotic core responsible for the increase of the interstitial pressure and the subsequent intracranial deformation that may result in patient death. Furthermore, they do not incorporate the interaction of the tumor with the adjacent normal tissue (brain parenchyma).

Consequently, in order to understand glioma progression from low to high grade and thinking of connections with clinical practice there is a need for: (i) models accounting for the key features of the tumor microenvironment dynamics without involving too many details on any of the intervening specific processes, and (ii) models that are simple enough to allow for some quantitative understanding, e.g. using the tools of nonlinear dynamical systems and/or nonlinear waves well developed in other scenarios [45].

In this paper we present in detail one of those models allowing both for a description of features seen in real GBM and for a theoretical analysis. Interestingly, this model leads to the existence of multicomponent solitary waves encompassing bright solitary waves in the glioma compartment coupled with kink and antikink waves for the normal tissue and necrotic core respectively. We will study the model's phenomenology using a combination of numerical simulation methods, dynamical systems theory and qualitative analysis. In the course of the study we wish to bring out a number of distinguishing features with respect to the FK model that are also relevant when comparing their predictions of how GBMs evolve.

Our plan is as follows, first in Sec. 2 we present the model in detail. Next in Sec. 3 we analyze the existence of traveling wave solutions of the system of equations using qualitative analysis and geometric perturbation theory. Then in Sec. 4 we calculate bright soliton solutions and determine numerically the minimum speed of these solitary waves solutions. The linear stability analysis of small initial data is discussed in Sec. 5 together with its application to the computation of the relapse time after surgery. Finally Sec. 6 summarizes our conclusions.

2 A simple extension of the Fisher equations

The model to be discussed in detail in this paper for describing the progression of GBM was proposed in [39]. To account for the spatial structure occupied by the malignant glioma cells and their environment, let Ω be a domain of \mathbb{R}^n , for $n = 1, 2, 3$, which is open, bounded, connected and measurable with a given size (length, area or volume) $\mu(\Omega)$. The model incorporates three relevant real functions u , v and w , defined on the closure of $\Omega \times \mathbb{R}^+$, which are nonnegative, twice differentiable in the interior of their domain and satisfy the initial-value problem

$$\frac{\partial u}{\partial t}(x, t) = \nabla \cdot (D(x)\nabla u(x, t)) + \rho(x, t) \left(1 - \frac{u(x, t) + v(x, t) + w(x, t)}{u_*(x)} \right) u(x, t) - \alpha(x, t)u(x, t), \quad (2a)$$

$$\frac{\partial v}{\partial t}(x, t) = -\mathcal{F}(x, t, u(x, t), v(x, t), w(x, t)), \quad (2b)$$

$$\frac{\partial w}{\partial t}(x, t) = \mathcal{F}(x, t, u(x, t), v(x, t), w(x, t)) + \alpha(x, t)u(x, t), \quad (2c)$$

$\forall x \in \Omega$ and $\forall t \in \mathbb{R}^+$

$$u(x, 0) = u_0(x), \quad \forall x \in \overline{\Omega}, \quad (3a)$$

$$v(x, 0) = v_0(x), \quad \forall x \in \overline{\Omega}, \quad (3b)$$

$$w(x, 0) = w_0(x), \quad \forall x \in \overline{\Omega}, \quad (3c)$$

for some nonnegative continuous functions $u_0, v_0, w_0 : \overline{\Omega} \rightarrow \mathbb{R}$, together with the homogeneous Neumann boundary conditions

$$\frac{\partial u}{\partial \mathbf{n}}(x, t) = 0, \quad \forall x \in \partial\Omega, \forall t \in \mathbb{R}^+ \cup \{0\}, \quad (4a)$$

$$\frac{\partial v}{\partial \mathbf{n}}(x, t) = 0, \quad \forall x \in \partial\Omega, \forall t \in \mathbb{R}^+ \cup \{0\}, \quad (4b)$$

$$\frac{\partial w}{\partial \mathbf{n}}(x, t) = 0, \quad \forall x \in \partial\Omega, \forall t \in \mathbb{R}^+ \cup \{0\}. \quad (4c)$$

The biological meaning of all the above quantities is the following: u denotes the tumor cell density, v the adjacent normal cell density (brain parenchyma) and w the density of dead cells (necrotic core). The nonnegative and continuous functions $D(x)$, $\rho(x, t)$, $u_*(x)$ and $\alpha(x, t)$ represent the diffusion coefficient (or more generally, a tensor), the proliferation rate, the carrying capacity (or maximum cell density) and the tumor cell death rate, respectively.

Eqs. (2) add a number of quantities with respect to the Fisher-Kolmogorov Eq. (1). The standard FK equation is recovered by setting $\alpha = v = w = 0$. However, in order to properly account for the observed physiopathology, we include both the population of the normal tissue and the developing necrotic core, the last one being a distinctive clinical feature of GBM observable in magnetic resonance images as well as in histopathological examination of the tumor samples from patients.

In Eqs. (2), tumor cell spreading is taken into consideration by using a standard Fickian diffusion term in (2a). This is the simplest transport mechanism and the one employed in most of the continuous mathematical models on cell motility. More realistic and complicated diffusion terms in gliomas should probably be governed by fractional (anomalous) diffusion [14, 16, 35] or other more elaborate approaches [15, 27, 52] to account for the high infiltration observed in this type of tumors [21, 36] and the fact that cells do not behave like purely random walkers and may actually remain immobile for a significant amount of time before compelled to migrate to a more favorable place in terms of resources. Other possibilities are to build in (at least) two cell phenotypes observed in malignant gliomas [26, 43]: one of invasive type migrating through the brain parenchyma and the

other, more proliferative, dependent on angiogenesis and migrating due to the effect caused by the destruction of the anomalous tumor vasculature. A number of mathematical models have been proposed to incorporate such a tumor heterogeneity [24,30,31], however, here we will maintain a single tumor cell phenotype that encompasses many of the features observed in GBM progression.

The nonlinear term in (2a) corresponds to proliferation and is mediated by a competition for space that is occupied by the two cell types and the necrotic core, which comprises apoptotic cells and cell debris. There is a *maximum* cell density u_* that may depend on space without loss of generality but, here, we will assume u_* to be a constant. We also explicitly add a tumor cell death term to include the fact that tumor cells, although generally lacking the apoptotic (programmed cell death) mechanisms [22], may succumb by means of a number of mechanisms that include the interaction with the immune system (e.g. microglia) in the normal tissue, hypoxia and acidosis generated by the anomalous metabolism of the glioma cells in the high density tumor areas, and deficiency of nutrients and physical support in the necrotic core. This tumor cell death term assumes that, on average, the characteristic tumor cell life time is $1/\alpha$. The fact that α may depend on time would correspond to the administration of radiotherapy and/or chemotherapy.

As to the normal cell dynamics, via Eq. (2b), due to their differentiation state, the proliferation of normal brain tissue is almost negligible within the characteristic time scales of GBM progression, thus we will assume that the normal tissue will not be able to regenerate. This is why in Eq. (2b) we have represented the cell loss due to the interaction with the tumor by means of an arbitrary form $\mathcal{F}(x, t, u, v, w)$ depending on all the densities and/or space and/or time. The details of the interaction may be very complicated and remain unclear. Finally, the space occupied by the necrotic core is the same space occupied by the original cells and grows at the expense of the other two compartments, as described by Eq. (2c). More elaborate models could include a reduction coefficient to account for the shrinkage of the cells and/or the destruction of their cytoplasm and the release of the cellular content to the necrotic area. Notice that the imposed boundary conditions (4) reflect the fact that, in GBM, the tumor cells are confined within the brain during progression since metastasis from the brain to other ectopic organs and tissues is a very rare event.

To simplify the analysis and to focus on the main dynamical features, we will restrict ourselves to a one spatial dimension and assume that $D(x)$, $\rho(x, t)$, $u_*(x)$ and $\alpha(x, t)$ are constants (do not depend on space and/or time), although we emphasize that, on a qualitative basis, many of the phenomena persist in higher dimensions.

It is convenient to introduce the new functions

$$\begin{aligned} U(x, t) &= u(x, t)/u_*, \\ V(x, t) &= (v(x, t) + w(x, t))/u_*, \end{aligned}$$

and the rescaled variables

$$\begin{aligned} s &= x\sqrt{\rho/D}, \\ \tau &= \rho t. \end{aligned}$$

Notice that V represents the normal cell and the necrotic tissue compartments altogether (henceforth referred to as the normal-necrotic compartment); it accounts for the effect of the peritumoral environment [39]. Then, Eqs. (2) in one dimension can be cast in the form

$$\frac{\partial U}{\partial \tau} = \frac{\partial^2 U}{\partial s^2} + U(1 - \beta - U - V), \quad (5a)$$

$$\frac{\partial V}{\partial \tau} = \beta U, \quad (5b)$$

with $0 \leq \beta = \alpha/\rho < 1$.

3 Analysis of travelling waves

Travelling waves with constant speed are solutions of Eq. (5) depending on $z = s - c\tau$ ($' = d/dz$)

$$U'' + cU' + U(1 - \beta - U - V) = 0, \tag{6a}$$

$$cV' + \beta U = 0. \tag{6b}$$

Using Eq. (6b) to get U and substituting into Eq. (6a), we obtain a third order nonlinear differential equation

$$V''' + cV'' + (1 - \beta)V' + \frac{c}{\beta} (V')^2 - VV' = 0. \tag{7}$$

3.1 Fast solitons

Let us first consider the case $c \gg 1$. To do so we define the new variable $\xi = z/c = \varepsilon z$, and the new function $\mathcal{V}(\xi) = V(z)$. Then, Eq. (7) becomes

$$\varepsilon^2 \mathcal{V}_{\xi\xi\xi} + \mathcal{V}_{\xi\xi} + (1 - \beta)\mathcal{V}_{\xi} + \frac{(\mathcal{V}_{\xi})^2}{\beta} - \mathcal{V}\mathcal{V}_{\xi} = 0. \tag{8}$$

In the limit $c \gg 1$, $\varepsilon \ll 1$ and Eq. (8) is equivalent to

$$\mathcal{V}_{\xi\xi} + (1 - \beta)\mathcal{V}_{\xi} + \frac{(\mathcal{V}_{\xi})^2}{\beta} - \mathcal{V}\mathcal{V}_{\xi} = 0. \tag{9}$$

Defining $\mathcal{V}_{\xi} = \mathcal{W}$, Eq. (9) can be written as the autonomous system

$$\mathcal{V}_{\xi} = \mathcal{W}, \tag{10a}$$

$$\mathcal{W}_{\xi} = -(1 - \beta)\mathcal{W} - \frac{1}{\beta}\mathcal{W}^2 + \mathcal{W}\mathcal{V}. \tag{10b}$$

The equilibria of Eqs. (10) are of the form $(\mathcal{V}, \mathcal{W}) = (\mathcal{V}_*, 0)$, with \mathcal{V}_* being an arbitrary real number. We are interested in values of $\mathcal{V}_* \geq 0$. Thus, linearizing Eq. (10) around $(\mathcal{V}_*, 0)$, we obtain that the eigenvalues of the Jacobian matrix are given by

$$\lambda_1 = 0, \quad \lambda_2 = \mathcal{V}_* - (1 - \beta), \tag{11}$$

and its corresponding eigenvectors are $(1, 0)$ and $(1, \mathcal{V}_* + \beta - 1)$, respectively (we are assuming that $\lambda_2 \neq 0$). These points are nonhyperbolic points. If $\mathcal{V}_* > 1 - \beta$, then, the fixed point $(\mathcal{V}_*, 0)$ possesses a local unstable manifold and a local center manifold. Otherwise, $(\mathcal{V}_*, 0)$ has a local stable manifold and a local center manifold. Thus, to get a heteroclinic orbit joining two points, say $(\mathcal{V}_-, 0)$ and $(\mathcal{V}_+, 0)$, with $\mathcal{V}_- > \mathcal{V}_+$, it is a necessary condition that $\mathcal{V}_+ < 1 - \beta$ and $\mathcal{V}_- > 1 - \beta$ (we are further interested in $\mathcal{V}_- < 1$). These two conditions can be summarized in the physical constraint imposing that the normal-necrotic compartment density is always strictly larger than the normal compartment density; the difference originating in the fraction of tumor cell loss.

Bright solitons, when existing, correspond to positive $U(z)$ solutions, thus to negative $\mathcal{W} \sim V'$ heteroclinic orbits connecting two positive equilibria for \mathcal{V} . The equation of the orbits can be obtained from Eqs. (10) and reads as

$$\frac{d\mathcal{W}}{d\mathcal{V}} = \mathcal{V} - \mathcal{W}/\beta - (1 - \beta). \tag{12}$$

Its solution is

$$\mathcal{W}(\mathcal{V}) = Ce^{-\mathcal{V}/\beta} + \beta(\mathcal{V} - 1), \tag{13}$$

for any arbitrary C . Our solutions, when existing, must satisfy $\mathcal{V}(\pm\infty) = \mathcal{V}_{\pm}$ with $\mathcal{V}_* = \mathcal{V}_- > \mathcal{V}_+$ (cf. Eq. (6b)) and $\mathcal{W}(\pm\infty) = 0$, thus C must be chosen to allow for the equation

$$Ce^{-\mathcal{V}/\beta} + \beta(\mathcal{V} - 1) = 0, \tag{14}$$

to have two positive roots $\mathcal{V}_- > \mathcal{V}_+ > 0$. Thus, for the initial condition $\mathcal{W}(\mathcal{V}_+) = 0$, Eq. (13) becomes

$$\mathcal{W}(\mathcal{V}) = \beta(\mathcal{V} - 1) + \beta(1 - \mathcal{V}_+)e^{(\mathcal{V}_+ - \mathcal{V})/\beta}. \tag{15}$$

It is straightforward to prove that, given the initial condition $\mathcal{W}(\mathcal{V}_+) = 0$, with $0 < \mathcal{V}_+ < 1 - \beta$, there exists a value, say \mathcal{V}_- , with $\mathcal{V}_+ < 1 - \beta < \mathcal{V}_- < 1$, such that there exists a heteroclinic orbit joining both values, \mathcal{V}_- and \mathcal{V}_+ ; the function $\mathcal{W}(\mathcal{V})$ has a single minimum at

$$\mathcal{V}_m = \mathcal{V}_+ - \beta \log \left(\frac{\beta}{1 - \mathcal{V}_+} \right), \tag{16}$$

which is larger than \mathcal{V}_+ for $\mathcal{V}_+ < 1 - \beta$. As $\mathcal{W}(\mathcal{V}_+) = 0$ and the function $\mathcal{W}(\mathcal{V})$ is decreasing in the interval $(\mathcal{V}_+, \mathcal{V}_m)$, it is clear that

$$\mathcal{W}(\mathcal{V}_m) < 0. \tag{17}$$

Therefore, as $\mathcal{W}(1) > 0$, the existence of a value \mathcal{V}_- in the interval $(\mathcal{V}_m, 1)$, such that $\mathcal{W}(\mathcal{V}_-) = 0$, follows from a direct application of Bolzano’s Intermediate Value Theorem.

Moreover, it is straightforward to verify that no orbits can cross the triangle T , given by

$$0 \leq \mathcal{V} \leq 1, \quad \beta(\mathcal{V} - 1) \leq \mathcal{W} \leq 0, \tag{18}$$

from the outside. Therefore, T is a negative invariant region. Thus, all orbits inside T must emanate from equilibrium points \mathcal{V}_- such that $1 - \beta < \mathcal{V}_- < 1$, since these points have an unstable manifold inside T . However, the points \mathcal{V}_+ , which satisfy $\mathcal{V}_+ < 1 - \beta$, have a stable manifold inside T . Now, let a point $\mathcal{V}_+ \in T$ such that $0 \leq \mathcal{V}_+ < 1 - \beta$. As this point has a stable manifold and belongs to T , its orbit is in T . Thus, \mathcal{V}_+ is a ω -limit point. Hence, there must exist a point $\mathcal{V}_- \in T$, with $1 - \beta < \mathcal{V}_- < 1$, such that there is always an orbit connecting \mathcal{V}_- to \mathcal{V}_+ inside T .

Thus, we have shown the following result: there exists a heteroclinic orbit that connects \mathcal{V}_- and \mathcal{V}_+ and, therefore, $\mathcal{V} > 0$, (i.e. to remain entirely in the fourth quadrant).

In general, these fast moving solitons are small ones as Fig. 1(c) shows. Let us notice that

$$\mathcal{V}_\xi = \beta(\mathcal{V} - 1) + \beta(1 - \mathcal{V}_+)e^{(\mathcal{V}_+ - \mathcal{V})/\beta}, \tag{19}$$

that allows for a solution for \mathcal{V} in the form of quadratures, once initial data is specified,

$$\xi - \xi_0 = \frac{1}{\beta} \int_{\mathcal{V}_+}^{\mathcal{V}} \frac{ds}{(1 - \mathcal{V}_+)e^{-(s - \mathcal{V}_+)/\beta} + s - 1}. \tag{20}$$

Finally, in the limit $\xi \rightarrow +\infty$, the asymptotic behavior of \mathcal{V} is $\mathcal{V} \sim \mathcal{V}_+ + e^{-(1 - \beta - \mathcal{V}_* - \mathcal{V}_+)(\xi - \xi_0)}$. In a similar way, for $\xi \rightarrow -\infty$, $\mathcal{V} \sim \mathcal{V}_- + e^{-(1 - \beta - \mathcal{V}_* - \mathcal{V}_-)(\xi - \xi_0)}$.

3.2 Finite speed solutions

Our previous analysis proves the existence of the heteroclinic orbit in the limit $c \gg 1$, when $\varepsilon \rightarrow 0$. If $\varepsilon \ll 1$ (but not zero), we can recast Eq. (8) as a system

$$\mathcal{V}_\xi = \mathcal{W}, \tag{21a}$$

$$\mathcal{W}_\xi = \mathcal{U}, \tag{21b}$$

$$\varepsilon^2 \mathcal{U}_\xi = \mathcal{V} \mathcal{W} - \frac{\mathcal{W}^2}{\beta} - (1 - \beta) \mathcal{W} - \mathcal{U}, \tag{21c}$$

which has the critical points $(\mathcal{V}_*, 0, 0)$, for $\mathcal{V}_* \in \mathbb{R}$.

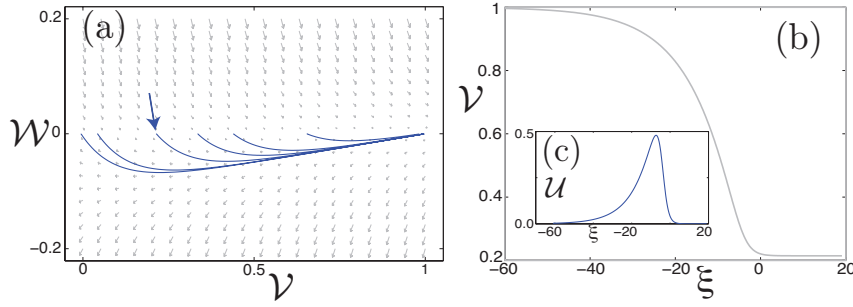


Fig. 1 (a) Heteroclinic orbits of Eq. (10) for $\beta = 0.1$. (b) Kink solution for $\beta = 0.1$ corresponding to the marked heteroclinic orbit in (a). (c) The bright soliton solution \mathcal{U} corresponds to the kink obtained in (b)

On the other hand, writing $\zeta = \xi/\varepsilon^2$, system (21) becomes

$$\mathcal{V}_\zeta = \varepsilon^2 \mathcal{W}, \quad (22a)$$

$$\mathcal{W}_\zeta = \varepsilon^2 \mathcal{U}, \quad (22b)$$

$$\mathcal{U}_\zeta = \mathcal{V}\mathcal{W} - \frac{\mathcal{W}^2}{\beta} - (1-\beta)\mathcal{W} - \mathcal{U}, \quad (22c)$$

which is the dual fast system associated to (21) (see, for instance, [20]). For $\varepsilon \neq 0$, systems (21) and (22) are equivalent.

If in the system (21) ε is set to zero, then \mathcal{V} and \mathcal{W} are governed by Eqs. (10), while \mathcal{U} lies on the set

$$\{(\mathcal{V}, \mathcal{W}, \mathcal{U}) \in \mathbb{R}^3 : \mathcal{V}\mathcal{W} - \frac{\mathcal{W}^2}{\beta} - (1-\beta)\mathcal{W} - \mathcal{U} = 0\}, \quad (23)$$

which is a two-dimensional submanifold of \mathbb{R}^3 . We choose any compact subset of such manifold and designate this compact subset as M_0 . Geometric perturbation theory uses both the above systems: (22) provides us with an invariant manifold M_ε close to M_0 and we study the flow of (21) restricted to this manifold.

Let us introduce the following definition, which is useful for our purposes:

Definition 1. The manifold M_0 is said to be normally hyperbolic if the linearisation of (22) at each point in M_0 , restricted to M_0 , has exactly $\dim M_0$ eigenvalues on the imaginary axis.

Now, we use the Fenichel's invariant manifold theory [20, 25] to prove that for ε sufficiently small, there exists a two-dimensional submanifold M_ε of \mathbb{R}^3 which is within distance ε of M_0 and which is invariant for the flow (22):

Theorem 1. If $\varepsilon > 0$, but sufficiently small, there exists a manifold M_ε that lies within $\mathcal{O}(\varepsilon)$ of M_0 and is diffeomorphic to M_0 . Moreover, it is locally invariant under the flow of (22), and C^r for any $r < +\infty$.

Thus, from the previous definition, such a perturbed invariant manifold M_ε will exist if M_0 is normally hyperbolic.

The linearisation of the fast system (22), restricted to M_0 has the matrix

$$J = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ \mathcal{W} & \mathcal{V} - 2\frac{\mathcal{W}}{\beta} - (1-\beta) & -1 \end{pmatrix}, \quad (24)$$

and the eigenvalues of this are $\lambda = 0$ (double) and $\lambda = -1$ (simple). Thus, M_0 is normally hyperbolic and, by Fenichel's theory, for sufficiently small ε , there exists a perturbed manifold M_ε with the properties listed above.

We would like to determine the dynamics on M_ε . Since $(\mathcal{V}, \mathcal{W})$ are the slow variables and \mathcal{U} is the fast variable, the manifold M_ε is given by

$$M_\varepsilon = \{(\mathcal{V}, \mathcal{W}, \mathcal{U}) \in \mathbb{R}^3 : \mathcal{U} = \mathcal{V}\mathcal{W} - \frac{\mathcal{W}^2}{\beta} - (1 - \beta)\mathcal{W} + h^\varepsilon(\mathcal{V}, \mathcal{W})\}, \tag{25}$$

where $h^\varepsilon(\mathcal{V}, \mathcal{W}) \in C^r$ for any $r < +\infty$ satisfying $h^0(\mathcal{V}, \mathcal{W}) = 0$, and the equations on M_ε are

$$\mathcal{V}_\xi = \mathcal{W}, \tag{26a}$$

$$\mathcal{W}_\xi = \mathcal{V}\mathcal{W} - \frac{\mathcal{W}^2}{\beta} - (1 - \beta)\mathcal{W} + h^\varepsilon(\mathcal{V}, \mathcal{W}), \tag{26b}$$

Now, substituting (25) into (21) yields that $h^\varepsilon(\mathcal{V}, \mathcal{W})$ satisfies the partial differential equation

$$\begin{aligned} \varepsilon^2 \left[\frac{\mathcal{W}^2}{\beta} + \mathcal{V}\mathcal{W} - 3\frac{\mathcal{W}^2}{\beta}\mathcal{V} - 2(1 - \beta)\mathcal{W}\mathcal{V} + \mathcal{V}h^\varepsilon + 2\frac{\mathcal{W}^3}{\beta^2} + 2\frac{1 - \beta}{\beta}\mathcal{W}^2 - \frac{2}{\beta}\mathcal{W}h^\varepsilon \right. \\ \left. + (1 - \beta)^2\mathcal{W} - (1 - \beta)h + \mathcal{W}\frac{\partial h^\varepsilon}{\partial \mathcal{V}} + \left(\mathcal{V}\mathcal{W} - \frac{\mathcal{W}^2}{\beta} - (1 - \beta)\mathcal{W} + h^\varepsilon \right) \frac{\partial h^\varepsilon}{\partial \mathcal{W}} \right] \\ = -h^\varepsilon. \end{aligned} \tag{27}$$

We Taylor expand h^ε in the variable ε around $\varepsilon = 0$,

$$h^\varepsilon(\mathcal{V}, \mathcal{W}) = h^0(\mathcal{V}, \mathcal{W}) + \frac{\partial h^0(\mathcal{V}, \mathcal{W})}{\partial \varepsilon} \varepsilon + \frac{1}{2} \frac{\partial^2 h^0(\mathcal{V}, \mathcal{W})}{\partial \varepsilon^2} \varepsilon^2 + \dots, \tag{28}$$

where $\frac{\partial h^0(\mathcal{V}, \mathcal{W})}{\partial \varepsilon} = \frac{\partial h^\varepsilon(\mathcal{V}, \mathcal{W})}{\partial \varepsilon} \Big|_{\varepsilon=0}$ and $\frac{\partial^2 h^0(\mathcal{V}, \mathcal{W})}{\partial \varepsilon^2} = \frac{\partial^2 h^\varepsilon(\mathcal{V}, \mathcal{W})}{\partial \varepsilon^2} \Big|_{\varepsilon=0}$.

Equating powers of ε , we get the following hierarchy of equations for $\varepsilon^i, i = 0, 1, 2, \dots$

$$\mathcal{O}(\varepsilon^0) : h^0(\mathcal{V}, \mathcal{W}) = 0, \tag{29}$$

$$\mathcal{O}(\varepsilon^1) : \frac{\partial h^0(\mathcal{V}, \mathcal{W})}{\partial \varepsilon} = 0, \tag{30}$$

$$\begin{aligned} \mathcal{O}(\varepsilon^2) : -\frac{1}{2} \frac{\partial^2 h^0(\mathcal{V}, \mathcal{W})}{\partial \varepsilon^2} = (1 - \beta)^2\mathcal{W} + \left[\frac{3(1 - \beta)}{\beta} - 2\frac{\mathcal{V}}{\beta} + 1 \right] \mathcal{W}^2, \\ - 2(1 - \beta)\mathcal{V}\mathcal{W} + \mathcal{V}^2\mathcal{W} - \frac{\mathcal{V}\mathcal{W}^2}{\beta} + \frac{2}{\beta^2}\mathcal{W}^3. \end{aligned} \tag{31}$$

Thus

$$\begin{aligned} h^\varepsilon(\mathcal{V}, \mathcal{W}) = \left[-(1 - \beta)^2\mathcal{W} - \left[\frac{3(1 - \beta)}{\beta} - 2\frac{\mathcal{V}}{\beta} + 1 \right] \mathcal{W}^2 + 2(1 - \beta)\mathcal{V}\mathcal{W} \right. \\ \left. - \mathcal{V}^2\mathcal{W} + \frac{\mathcal{V}\mathcal{W}^2}{\beta} - \frac{2}{\beta^2}\mathcal{W}^3 \right] \varepsilon^2 + \dots, \end{aligned} \tag{32}$$

and the equations on M_ε become

$$\mathcal{V}_\xi = \mathcal{W}, \tag{33a}$$

$$\begin{aligned} \mathcal{W}_\xi = \mathcal{V}\mathcal{W} - \frac{\mathcal{W}^2}{\beta} - (1 - \beta)\mathcal{W} + \varepsilon^2 \left[-(1 - \beta)^2\mathcal{W} - \left[\frac{3(1 - \beta)}{\beta} - 2\frac{\mathcal{V}}{\beta} + 1 \right] \mathcal{W}^2 \right. \\ \left. + 2(1 - \beta)\mathcal{V}\mathcal{W} - \mathcal{V}^2\mathcal{W} + \frac{\mathcal{V}\mathcal{W}^2}{\beta} - \frac{2}{\beta^2}\mathcal{W}^3 \right]. \end{aligned} \tag{33b}$$

These equations determine the dynamics on the manifold M_ε .

When $\varepsilon = 0$, (33) reduces to system (10). Existence of a heteroclinic orbit joining the points $(\mathcal{V}_-, 0)$ and $(\mathcal{V}_+, 0)$, $\mathcal{V}_- > \mathcal{V}_+ \geq 0$, of (10) was proved in the previous subsection. Note that when $\varepsilon > 0$, the system (33) still has the same critical points as system (10). Let $(\mathcal{V}_0, \mathcal{W}_0)$ be the solution of (33) for $\varepsilon = 0$, we are going to use the Fredholm alternative to show that when $\varepsilon > 0$ is sufficiently small a heteroclinic connection exists between the critical points $(\mathcal{V}_-, 0)$ and $(\mathcal{V}_+, 0)$.

To prove the existence of such a connection, we write

$$\mathcal{V} = \mathcal{V}_0 + \varepsilon^2 \mathcal{V}_1, \tag{34a}$$

$$\mathcal{W} = \mathcal{W}_0 + \varepsilon^2 \mathcal{W}_1. \tag{34b}$$

where $\mathcal{V}_1, \mathcal{W}_1 \in C^\infty(\mathbb{R})$. We assert that (34) is a heteroclinic connection of system (33). To see it, we substitute (34) in (33). To order ε^2 the coupled system of differential equations governing \mathcal{V}_1 and \mathcal{W}_1 is

$$\frac{d\mathcal{V}_1}{d\xi} = \mathcal{W}_1, \tag{35a}$$

$$\frac{d\mathcal{W}_1}{d\xi} = \mathcal{W}_0 \mathcal{V}_1 + \left[\mathcal{V}_0 - 2 \frac{\mathcal{W}_0}{\beta} - (1 - \beta) \right] \mathcal{W}_1 + \frac{1}{2} \frac{\partial^2 h^0(\mathcal{V}, \mathcal{W})}{\partial^2 \varepsilon}, \tag{35b}$$

and we wish to prove that this system has a solution satisfying

$$\lim_{\xi \rightarrow \pm\infty} \mathcal{V}_1 = 0, \quad \lim_{\xi \rightarrow \pm\infty} \mathcal{W}_1 = 0. \tag{36}$$

In matrix notation, we can write Eqs. (35) as

$$\frac{d}{d\xi} \begin{pmatrix} \mathcal{V}_1 \\ \mathcal{W}_1 \end{pmatrix} - \begin{pmatrix} 0 & 1 \\ \mathcal{W}_0 \mathcal{V}_0 - 2 \frac{\mathcal{W}_0}{\beta} - (1 - \beta) & \end{pmatrix} \begin{pmatrix} \mathcal{V}_1 \\ \mathcal{W}_1 \end{pmatrix} = \begin{pmatrix} 0 \\ \frac{\partial^2 h^0(\mathcal{V}_0, \mathcal{W}_0)}{2\partial \varepsilon^2} \end{pmatrix}. \tag{37}$$

Let us denote

$$g(\mathcal{V}_0, \mathcal{W}_0) = \begin{pmatrix} 0 \\ \frac{\partial^2 h^0(\mathcal{V}_0, \mathcal{W}_0)}{2\partial \varepsilon^2} \end{pmatrix}. \tag{38}$$

By using the Fredholm alternative, we state that problem (37) has a solution if, and only if,

$$\int_{-\infty}^{\infty} \left\langle s(\xi), g(\mathcal{V}_0(\xi), \mathcal{W}_0(\xi)) \right\rangle d\xi = 0, \tag{39}$$

where $\langle \cdot, \cdot \rangle$ is the Euclidean inner product on \mathbb{R}^2 and for all solutions $s = (s_1, s_2)$ of the adjoint problem

$$\frac{d}{d\xi} \begin{pmatrix} s_1 \\ s_2 \end{pmatrix} = \begin{pmatrix} 0 & -\mathcal{W}_0(\xi) \\ -1 & 2 \frac{\mathcal{W}_0(\xi)}{\beta} + (1 - \beta) - \mathcal{V}_0(\xi) \end{pmatrix} \begin{pmatrix} s_1 \\ s_2 \end{pmatrix}, \tag{40}$$

with boundary conditions $\lim_{\xi \rightarrow \pm\infty} s = 0$. Note that we are working in the space $L^2(\mathbb{R})$. Now, our goal is to know the number of solutions of the adjoint problem. Although the matrix in (40) is non-constant, $(\mathcal{V}_0, \mathcal{W}_0)$ is the front of (10) about which we know a great deal. Letting $\xi \rightarrow \infty$ we have $\mathcal{V}_0 \rightarrow \mathcal{V}_+$ and $\mathcal{W}_0 \rightarrow 0$ and the matrix is then a constant matrix with eigenvalues λ satisfying

$$\lambda(1 - \beta - \mathcal{V}_+ - \lambda) = 0 \Rightarrow \begin{cases} \lambda_1 = 0, \\ \lambda_2 = 1 - \beta - \mathcal{V}_+ > 0. \end{cases}$$

Thus, as $\xi \rightarrow \infty$, any solution of (40) is a sum of constant and exponential functions. Thus, the only solution in L^2 for the adjoint problem is therefore the zero solution $s(\xi) = 0$ and consequently the Fredholm orthogonality conditionally holds. We have proved the existence of the searched connection in the manifold M_ε . Thus, we have the following theorem

Theorem 2. *There exists $\delta > 0$ sufficiently small such that, for every $\varepsilon \in (0, \delta]$, Eq. (8) admits a travelling front solution $\mathcal{V}(\xi)$ satisfying $\mathcal{V}(-\infty) = \mathcal{V}_-$ and $\mathcal{V}(\infty) = \mathcal{V}_+$.*

Since the relationship between $\mathcal{V}(\xi)$ and $\mathcal{U}(\xi)$ is given by (6b), we have the following corollary about the existence of bright solitons

Corollary 3. *Let a travelling wave front solution $\mathcal{V}(\xi)$ of Eq. (8) whose existence is given by Theorem 2. Then $\mathcal{U}(\xi)$ is a homoclinic solution or bright soliton solution of the system (6), with $\xi = \varepsilon z$ and $z = s - c\tau$.*

4 Bright solitons

Instead of considering kink solutions, via Eq. (7), we can work in the variable U that represents a localized unimodal function of tumor cell density (corresponding to homoclinic paths in the phase plane).

From Eqs. (5) and defining $S = V - 1 + \beta$ we have

$$\frac{\partial U}{\partial \tau} = \frac{\partial^2 U}{\partial s^2} - (U + S)U, \tag{41a}$$

$$\frac{\partial S}{\partial \tau} = \beta U. \tag{41b}$$

Combining Eqs. (41) into a single (and more general) equation for the tumor density we get

$$\left[\frac{1}{U} (U_\tau - U_{ss} + U^2) \right]_\tau = -\beta U, \tag{42}$$

where subscripts denote partial differentiation. Notice that Eq. (42) admits (trivial) exact solutions of the form

$$U(s, \tau) = U_0(s)e^{-\beta\tau}, \tag{43}$$

where $U_0(s)$ is a sufficiently regular arbitrary function of the spatial coordinate. Also, if $\beta = 0$, (42) possesses the following exact solution in terms of the rational function

$$U(s, \tau) = \frac{6C_1^2 + 12(2 + \sqrt{6})C_2 + 120(12 + 5\sqrt{6})\tau + 12(4 + \sqrt{6})C_1s + 12(4 + \sqrt{6})s^2}{(C_2 + 10(3 + \sqrt{6})\tau + C_1s + s^2)^2}, \tag{44}$$

where C_1 and C_2 are arbitrary constants. (44) remains localized if $4C_2 + 40(3 + \sqrt{6})\tau > C_1^2, \forall \tau \geq 0$. However, just as is occurs with (43), it decays to zero for $\tau \rightarrow \infty$. We will be interested in searching for solutions which remain finite (but nonzero) for arbitrary large times.

4.1 Solitary wave solutions

We will look for bright solitary solutions of Eq. (42) in the form $U(s - c\tau) = \phi(\eta)$, where c is their velocity (positive or negative for right- or left-moving fronts, respectively). These solutions will be required to satisfy $\phi < 1 - \beta$, together with $\phi \rightarrow 0$ and $\phi_\eta \rightarrow 0$ as $|\eta| \rightarrow \infty$. Upon substitution in Eq. (42) and defining $\xi = \eta/c$, we arrive at a third order nonlinear autonomous differential equation

$$\beta\phi^3 - \phi_\xi^2 - \phi^2\phi_\xi + \phi\phi_{\xi\xi} - \frac{1}{c^2}(\phi_\xi\phi_{\xi\xi} - \phi\phi_{\xi\xi\xi}) = 0. \tag{45}$$

Just as we did with the kink-type solutions of Eq. (7) representing the normal-necrotic compartment, within the fast limit $c \gg 1$ and assuming $\phi < 1 - \beta$, it can be shown [39] that Eq. (45) admits the approximate explicit form

$$\phi(\xi) = \phi_0 \operatorname{sech}^2 \left[\sqrt{\frac{\phi_0 \beta}{2}} (\xi - \xi_0) \right], \tag{46}$$

with constants ϕ_0 and ξ_0 , representing the amplitude and a shift, respectively, which, without loss of generality, can be set $\xi_0 = 0$. Figure 2 compares the exact numerical profile from Eq. (45) to the explicit form Eq. (46) and their corresponding homoclinic orbits.

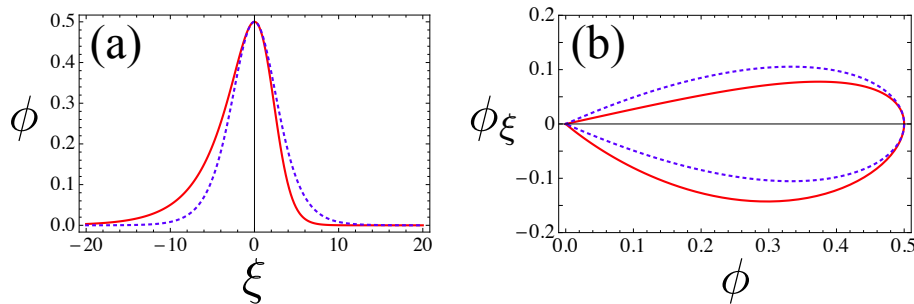


Fig. 2 Bright solitary waves for $\beta = 0.3$, $\phi_0 = 0.5$ and $c = 2.5$. (a) Profiles from Eq. (45) (solid curve) and the explicit solution given by Eq. (46) (dashed curve). (b) Homoclinic orbits from Eq. (45) (solid curve) and Eq. (46) (dashed curve).

4.2 Minimum speed of positive solutions

We now wish to determine the minimum speed c_0 above which the solutions of Eq. (45) are positive for all ξ , since biologically feasible solutions for the tumor density must be positive for all ξ . Let $\chi = \phi_\xi / \phi$, then Eq. (45) becomes

$$\beta - \chi + \left(1 + \frac{3\chi}{c^2} \right) \chi \chi_\phi + \frac{\phi \chi}{c^2} (\chi_\phi^2 + \chi \chi_{\phi\phi}) = 0. \tag{47}$$

By probing the parameter space for $0 < \phi < 1 - \beta$ we have verified numerically that the following approximation $3\chi^2 \chi_\phi + \phi \chi (\chi_\phi^2 + \chi \chi_{\phi\phi}) \simeq 2\chi^2 \chi_\phi$ holds. Hence, Eq. (47) reduces to

$$\beta - \chi + \left(1 + \frac{2\chi}{c^2} \right) \chi \chi_\phi = 0. \tag{48}$$

This autonomous differential equation possesses an exact explicit quadrature. Assuming that $\chi < \beta$, together with the conditions $\phi = \phi_0$ and $\chi = 0$ at $\xi = 0$, we obtain

$$\left(1 + \frac{2\beta}{c^2} \right) \left(\chi + \beta \log \left| 1 - \frac{\chi}{\beta} \right| \right) + \frac{\chi^2}{c^2} = \phi - \phi_0. \tag{49}$$

Positive solutions of Eq. (45) require that χ remains finite for all ξ (if $c < c_0$, χ exhibits discontinuities and ϕ becomes negative in nonzero measure sets for $\xi > 0$). As $\xi \rightarrow \infty$ ($\xi \rightarrow -\infty$), $\chi \rightarrow \chi_+ < 0$ ($\chi \rightarrow \chi_- > 0$). These asymptotic values can be found from Eq. (49) by means of the ancillary function

$$G = \chi - \beta + \beta \exp \left[-\frac{1}{\beta} \left(\chi + \frac{c^2 \phi_0 + \chi^2}{c^2 + 2\beta} \right) \right]. \tag{50}$$

The nonlinear equation $G(\chi, c, \beta, \phi_0) = 0$ has two real roots $\chi_+ < 0$ and $\chi_- > 0$ if $c \geq c_0$, whereas for $0 < c < c_0$ the only root of G is $\chi_- > 0$. At $c = c_0$, χ_+ satisfies

$$G(\chi = \chi_+, c = c_0) = 0, \quad \left. \frac{\partial G}{\partial \chi} \right|_{\chi=\chi_+, c=c_0} = 0, \quad \left. \frac{\partial^2 G}{\partial \chi^2} \right|_{\chi=\chi_+, c=c_0} < 0, \tag{51}$$

that is, χ_+ becomes a double root of G .

By imposing the first two conditions of Eq. (51) to Eq. (50) we arrive at the two simultaneous transcendental equations

$$\chi_+ - \beta + \beta \exp \left[-\frac{1}{\beta} \left(\chi_+ + \frac{c_0^2 \phi_0 + \chi_+^2}{c_0^2 + 2\beta} \right) \right] = 0, \tag{52a}$$

$$1 - \left(1 + \frac{2\chi_+}{c^2 + 2\beta} \right) \exp \left[-\frac{1}{\beta} \left(\chi_+ + \frac{c_0^2 \phi_0 + \chi_+^2}{c_0^2 + 2\beta} \right) \right] = 0. \tag{52b}$$

Eqs. (52) give rise to two solutions for χ_+ , $\chi_+ = 0$ and $\chi_+ = -\frac{c_0^2}{2}$, the second one being the only biologically meaningful one ($\chi_+ = 0$ leads to $c_0 = 0$). Upon substitution of $\chi_+ = -\frac{c_0^2}{2}$ into Eq. (50), we derive an implicit expression for the speed c_0 in terms of β and ϕ_0

$$1 + \frac{c_0^2}{2\beta} - \exp \left[\frac{(c_0^2 + 4\beta - 4\phi_0)c_0^2}{4(c_0^2 + 2\beta)\beta} \right] = 0. \tag{53}$$

The dependence of c_0 on β and ϕ_0 is depicted in Fig. 3.

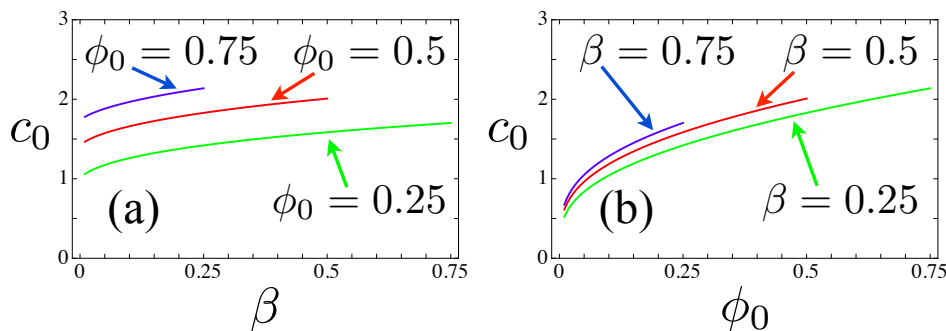


Fig. 3 Characteristic curves of the minimum speed c_0 for positive bright solitary solutions, in terms of (a) β and (b) ϕ_0 , calculated from Eq. (53).

It is worth comparing the values of the minimum velocity that arise in the present model with those of the FK equation. It is well known [33] that the only solution of the FK equation evolving from positive compactly supported initial data that remains bounded and propagates as an antikink solitary wave is the one with the constant minimal speed $c_{\min}^{(FK)} = 2\sqrt{D\rho}$. In view of the profiles displayed in Fig. 3, we observe that the minimal speed $c_{\min} = c_0\sqrt{D(\rho - \alpha)}$, where $c_0 > 0$, can actually be lower than the limit set by the FK equation. The consequence of this is that for the same values of D and ρ , the predicted velocities of tumor expansion by the FK equation are generally larger than the ones resulting from the present model.

5 Linear Stability

In this section we explore the possibility of calculating the time of tumor recurrence after the macroscopic tumor volume (detectable in MRI) has been surgically removed. To study this scenario from a mathematical

point of view we examine the linear stability of the solutions

$$U(s) = 0, \quad V(s) = V_*, \tag{54}$$

for the system (5), where V_* is a positive constant. In fact, we are interested in the stability of the tumoral density U . Since the brain is bounded, we can consider a characteristic length of the brain, $2L$ say, for our problem.

Now consider a small perturbation on (U, V) of the form

$$U_p(s, \tau) = U(s) + \varepsilon u(s, \tau), \tag{55a}$$

$$V_p(s, \tau) = V(s) + \varepsilon v(s, \tau), \tag{55b}$$

with $0 < \varepsilon \ll 1$. The solution U is stable to perturbations $u(s, \tau)$ if

$$\lim_{\tau \rightarrow \infty} u(s, \tau) = 0 \quad \text{or} \quad \lim_{\tau \rightarrow \infty} \frac{dU(s)}{d\tau} = 0. \tag{56}$$

Otherwise, U is unstable. In a similar way, V is stable to perturbations $v(s, \tau)$ if an analogous relation as (56) for $v(s, \tau)$ is satisfied. Otherwise, V is unstable.

The fact that $U(s)$ is stable if the second of these holds is because $u(s, \tau)$ then represents a small translation of the wave along the s -axis since

$$U(s + \delta s) \approx U(s) + \delta s \frac{dU}{ds}. \tag{57}$$

Substituting Eqs. (55a) into Eq. (5) and keeping only the first-order terms in ε we get the equations governing $(u(s, \tau), v(s, \tau))$ as

$$u_\tau = u_{ss} + (1 - \beta - V_*)u, \tag{58a}$$

$$v_\tau = \beta u. \tag{58b}$$

We now look for solutions to the linear Eqs. (58a) by setting

$$u(s, \tau) = g_1(s)e^{-\lambda_1\tau}, \quad v(s, \tau) = g_2(s)e^{-\lambda_2\tau}, \tag{59}$$

which, upon substituting into (58a) and (58b), gives

$$g_1'' + (\lambda_1 - \{\beta + V_* - 1\})g_1 = 0, \tag{60a}$$

$$\lambda_2 g_2 e^{-\lambda_2\tau} + \beta g_1 e^{-\lambda_1\tau} = 0. \tag{60b}$$

From Eq. (60b) we obtain that

$$\lambda_1 = \lambda_2 = \lambda, \quad \lambda g_2(s) + \beta g_1(s) = 0. \tag{61}$$

Therefore, one has the following condition for the instability of the solution $U = 0$

$$\lambda < 0. \tag{62}$$

Thus, if $\lambda < 0$, from (59), both $u(s, \tau)$ and $v(s, \tau)$ tend to ∞ as $\tau \rightarrow \infty$. Now we use the fact that $u(s, \tau)$ and $v(s, \tau)$ are nonzero only in a finite domain which, from (59), means that the boundary conditions

$$g_1(\pm L_s) = 0, \quad g_2(\pm L_s) = 0, \tag{63}$$

with L_s being a dimensionless characteristic length, $L_s = L\sqrt{\rho/D}$ and where g_1 and g_2 are the respective solutions to Eqs. (60a) and (60b). Notice that Eq. (60a), together with boundary conditions (63), is a regular Sturm-Liouville problem and has two infinite families of solutions for

$$\lambda < \beta + V_* - 1, \tag{64}$$

and for

$$\beta + V_* - 1 < \lambda. \quad (65)$$

For the first case, the only solution of Eq. (60a) satisfying the boundary conditions (63) is the trivial solution. Thus, we focus on the second case: $\beta + V_* - 1 < \lambda < 0$. For this case, the eigenvalues of the Sturm-Liouville problem (60a), (63) are given by

$$\lambda_n = (\beta + V_* - 1) + \left(\frac{(2n-1)\pi}{2L_s} \right)^2, \quad n = 1, 2, 3, \dots \quad (66)$$

Hence, the most unstable eigenvalue is achieved for $n = 1$, i.e., for the lowest frequency. From (66), it is straightforward to prove that there exists a value for n , say n_1 , such that $\lambda_{n_1+1} > 0$ and $\lambda_{n_1} < 0$. For this value of n_1 , L_s must verify

$$|L_s| > \frac{(2n_1 - 1)\pi}{2\sqrt{(1 - \beta - V_*)}}. \quad (67)$$

Therefore, the eigenfunctions are given by

$$g_1(s) = \cos\left(\frac{(2n-1)\pi s}{2L_s}\right), \quad n = 1, 2, 3, \dots \quad (68)$$

and, from (61), we obtain the function g_2

$$g_2(s) = -\frac{\lambda_n}{\beta} \sin\left(\frac{(2n-1)\pi s}{2L_s}\right), \quad n = 1, 2, 3, \dots \quad (69)$$

Equivalently, another way to get the same result is by the following way: If we multiplying both sides of Eq. (58a) by $\exp(-(1 - \beta - V_*)\tau)$ and rearranging the terms, we have

$$\frac{\partial (ue^{-(1-\beta-V_*)\tau})}{\partial \tau} = \frac{\partial^2 (ue^{-(1-\beta-V_*)\tau})}{\partial s^2}. \quad (70)$$

This equation has the same form as the heat equation. The boundary conditions for such equation are

$$u(\pm L_s, \tau) = 0, \quad u(s, 0) = f(s), \quad (71)$$

where

$$f(s) = \begin{cases} be^{a(s+s_0)}, & s < -s_0, \\ 0, & s \in [-s_0, s_0], \\ be^{-a(s-s_0)}, & s > s_0, \end{cases} \quad (72)$$

is the profile of the initial condition, where $a, b, s_0 > 0$.

The solution of Eq. (70) is given by

$$u(s, \tau) = \sum_{n=1}^{\infty} B_n \cos\left(\frac{(2n-1)\pi s}{2L_s}\right) e^{-\lambda_n \tau}, \quad (73)$$

where λ_n is provided by (66) and B_n is

$$B_n = \frac{2b}{L_s \left(a^2 + \left[\frac{2n-1}{2} \frac{\pi}{L_s} \right]^2 \right)} \left[\frac{(2n-1)\pi}{2L_s} \left((-1)^{n-1} e^{-a(L_s-s_0)} - \sin\left(\frac{(2n-1)\pi s_0}{2L_s}\right) \right) + a \cos\left(\frac{(2n-1)\pi s_0}{2L_s}\right) \right]. \quad (74)$$

Now, we wish to calculate the time of tumor recurrence. We assume that the amplitude of the perturbation is appreciable for a value M , for $s = s_0$. It is clear that the most unstable modes occur when $\lambda_n < 0$. Thus, from Eq. (66), it is straightforward to find the first value of n for which $\lambda_n > 0$, namely

$$n = \left\lfloor \frac{1}{2} + \frac{L_S}{\pi} \sqrt{(1 - \beta - V_*)} \right\rfloor, \tag{75}$$

where the symbol $\lfloor \cdot \rfloor$ denotes the integer part of a number. In the biological literature, there is a vast range of values for the diffusion and proliferation coefficients. To carry out the estimations, we resort to the following value for the proliferation $\rho = 0.2 \text{ day}^{-1}$, which is in the range $[0.01 - 0.5] \text{ day}^{-1}$, taken from [28, 54] and $D = 0.05 \text{ mm}^2/\text{day}$ (which is in the range $[0.0004 - 0.1] \text{ mm}^2/\text{day}$) [39].

Finally, we take $\alpha = 1/10 \text{ day}^{-1}$, $L = 85 \text{ mm}$, $x_0 = 10 \text{ mm}$, $c = c_{\min} = 2\sqrt{(1 - \beta)}$, $M = 0.3$, $b = 0.005$, $a = \left(c - \sqrt{c^2 - 4(1 - \beta - V_*)} \right) / 2$, and $V_* = 0.3$ in units of u_* . Therefore, the recurrence time is $t \cong 6$ months, which is in the range clinically observed for GBM. In Figs. 4 (a) and (b), the relationship between the depth of resection b in the surgery and the recurrence time t is depicted for different values of ρ .

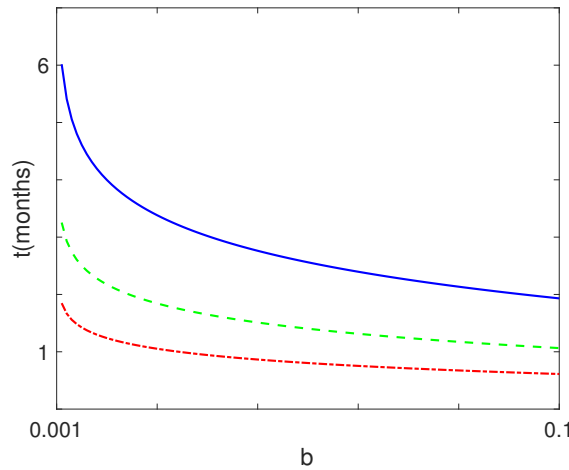


Fig. 4 Plot of the depth of resection b versus the recurrence time t for different values of the proliferation rate: $\rho = 1/5$ (blue solid line), $\rho = 1/4$ (green dashed line) and $\rho = 1/3$ (red dotted-dashed line).

6 Conclusions

In this paper we have analyzed a simple model of glioma progression incorporating the normal tissue, tumor cells and the necrotic core. In comparison with the Fisher-Kolmogorov equation, widely used to model GBM, the model studied here only adds a single extra effective parameter accounting for the finite tumor cell lifetime in the tumor microenvironment due to the effect of vascular degeneration, competition for space and resources, hypoxia, acidosis and interaction with the immune system. Remarkably, with only this simple addition the model displays many of the signatures of GBM embodied as bright solitary wave solutions behaving as attractors of the dynamics of the tumor rim. We have studied the formation and propagation speed of this tumor front, we have proven numerically (and analytically in certain limits) that it takes the form of a solitary wave, indeed a vector soliton composed of a bright soliton in the malignant cell population coupled to a kink in the normal cell population and an antikink in a necrotic core compartment. We have also computed what is the relapse time of the tumor after surgical extirpation of the tumor even when it is possible to achieve total resection of the visible part of the tumor. It is worth mentioning that the outcomes of this model, such as the relation between the width

of the bright solitons with the biological constants (diffusion, proliferation and death reate constants), have been used to predict novel imaging biomarkers for GBM patients [37]. In particular, the average size of the tumor rim, as observed in contrast enhanced T1-weighted magnetic resonance images, is a statistically significant metric for predicting the overall survival of GBM patients.

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