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Int. J. Appl. Math. Comput. Sci., 2023, Vol. 33, No. 4, 569–581
DOI: 10.34768/amcs-2023-0041

amcs

TRAVELLING WAVES FOR LOW–GRADE GLIOMA GROWTH AND RESPONSE TO A CHEMOTHERAPY MODEL

AGNIESZKA BARTŁOMIEJCZYK [a], MAREK BODNAR [b], MAGDALENA U. BOGDAŃSKA [c], MONIKA J. PIOTROWSKA [b,*]

[a]Faculty of Applied Physics and Mathematics/BioTechMed Centre
Gdańsk University of Technology
ul. Narutowicza 11/12, 80-233 Gdańsk, Poland
e-mail: agnbartl@pg.edu.pl

[b]Institute of Applied Mathematics and Mechanics
University of Warsaw
ul. Banacha 2, 02-097 Warsaw, Poland
e-mail: {monika,mbodnar}@mimuw.edu.pl

[c]IT Analytics
Equinix
pl. Europejski 1, 00-844 Warsaw, Poland
e-mail: Magdalena.Bogdanska@eu.equinix.com

Low-grade gliomas (LGGs) are primary brain tumours which evolve very slowly in time, but inevitably cause patient death. In this paper, we consider a PDE version of the previously proposed ODE model that describes the changes in the densities of functionally alive LGGs cells and cells that are irreversibly damaged by chemotherapy treatment. Besides the basic mathematical properties of the model, we study the possibility of the existence of travelling wave solutions in the framework of Fenichel's invariant manifold theory. The estimates of the minimum speeds of the travelling wave solutions are provided. The obtained analytical results are illustrated by numerical simulations.

Keywords: glioma, tumour, generalized model, treatment, partial differential equations, wave solutions, chemotherapy.

1. Introduction

Low-grade gliomas (LGGs) are brain tumours having a poor prognosis and causing premature death for almost all patients. The median survival of LGG patients is between 5 and 10 years (Keles *et al.*, 2011). The clinical course of this disease is usually very difficult to predict, thus posing challenges in its treatment (Pouratian and Schiff, 2010). Some of these tumours remain stable for years, while others undergo rapidly a malignant transformation, i.e., a transition into their more malignant counterparts known as high-grade gliomas, which induce the appearance of major neurological deficits and, eventually, death (Sakarunchai *et al.*, 2013).

Based on the previous research in this matter, we model the evolution of the LGG volume and its response to chemotherapy as a system of partial differential equations and study the resulting model analytically. Formerly (Bogdańska *et al.*, 2017), we formulated and investigated the mathematical properties of an ODE model describing the LGG growth due to proliferation and its response to the chemotherapeutic drug currently in use, that is, temozolomide (TMZ). It was shown that the model proposed fits very well longitudinal volumetric data of patients diagnosed with LGGs. The paper also suggested the relationship between the time of response to chemotherapy and patient prognosis, which has relevant clinical implications. In another work (Bogdańska *et al.*, 2017) we developed a simple model relating the onset of malignant transformation with the increased local density of tumour cells. We managed to describe a malignant

*Corresponding author

transformation in a minimal way using a model of two coupled Fisher–Kolmogorov-type equations in which the total tumour density is a driving force of the phenotypic change. We also showed that there is a chance for an improvement in the current treatment protocols.

Note that in the clinical realm, it is not viable to study multiple treatment scenarios due to ethical and practical reasons, including the typical survival times of LGGs patients. However, these obstacles are clearly not present when attempting to optimise mathematical models. We indicated that a treatment which delays the onset of a malignant transformation the most might be a more effective one. On the other hand, in the work by Bodnar *et al.* (2019), we considered a generalization of the model proposed by Bogdańska *et al.* (2017) and focused on its mathematical properties proving, *inter alia*, the global stability of the tumour-free steady state and, in some cases, justifying the existence of periodic solutions. Moreover, assuming constant in time chemotherapy effectiveness, we provided analytical estimates and calculated minimal drug doses guaranteeing tumour eradication for particular LGG patients.

The focus of this paper is on the model with continuous chemotherapy administered to tumours evolving not only due to proliferation, but also due to the diffusion process, as considered in previous works on mathematical modelling of gliomas (see, e.g., Murray, 1989; Wang *et al.*, 2009; Adenis *et al.*, 2021). Here we study thoroughly the mathematical properties of this model. In particular, we investigate the possibility of the existence of travelling waves. Travelling waves were also studied in different context (see, e.g., Gugat and Wintergerst, 2018; Kowal *et al.*, 2021).

The paper is organised as follows. In Section 2 we formulate the complete model and describe its parameters. In Section 3 we prove the basic mathematical properties of the model and recall some properties of the corresponding simplified ODE model. The analytical and numerical study of the PDE model is included in Section 4, with the main result being the demonstration of the existence of travelling wave solutions. In Section 5 we conclude and discuss the results.

2. Model presentation

In this paper, we consider a modification of the model proposed by Bogdańska *et al.* (2017). The main components of the model are the concentration of the drug in the tumour tissue ($C(t,x)$), the local density of proliferating tumour cells ($P(t,x)$), the local density of irreversibly damaged tumour cells ($D(t,x)$).

We assume that the growth of proliferating cells follows the logistic law and that these cells are subject to chemotherapy, which turns them into irreversibly damaged tumour cells. When they try to undergo mitosis, at the same rate as non-damaged cells, they eventually die due to a mitotic catastrophe (see Bogdańska *et al.*, 2017). What is new here is that we include an additional term describing the motility of tumour cells with a constant rate δ, resulting in the following reaction-diffusion system:

$$\begin{aligned}\frac{\partial \tilde{P}}{\partial \tilde{t}} &= \delta \Delta \tilde{P} + \rho \tilde{P}\left(1 - \frac{\tilde{P}+\tilde{D}}{K}\right) - \alpha C \tilde{P},\\ \frac{\partial \tilde{D}}{\partial \tilde{t}} &= \delta \Delta \tilde{D} - \frac{\rho}{k}\tilde{D}\left(1 - \frac{\tilde{P}+\tilde{D}}{K}\right) + \alpha C \tilde{P},\end{aligned} \tag{1}$$

where $(\tilde{t},\tilde{x}) \in [0,+\infty) \times \Omega$ and $\Delta = \sum_{j=1}^{n} \partial^2/\partial x_j^2$.

In general, $\Omega \subset \mathbb{R}^n$ is assumed to be an open subset with a smooth boundary. System (1) is complemented by non-negative C^2 class (on $\bar{\Omega}$) initial conditions with $\tilde{D}(0,x) = 0$ and homogeneous von Neumann boundary conditions. We also assume a constant concentration C of chemotherapy drug acting on the tumour.

The parameters of model (1) have the following interpretation: α denotes the rate of the proliferating tumour cells damage induced by chemotherapy, ρ is the net proliferation rate, k denotes the average number of mitotic cycles that damaged cells enter before dying, and K denotes carrying capacity, i.e., the maximal cellular density.

We re-scale system (1) by taking

$$P = \frac{\tilde{P}}{K}, \quad D = \frac{\tilde{D}}{K}, \quad t = \rho\tilde{t}, \quad x = \sqrt{\frac{\rho}{\delta}} \cdot \tilde{x}, \tag{2}$$

obtaining the non-dimensional system

$$\begin{aligned}\frac{\partial P}{\partial t} &= \Delta P + P(1-P-D) - \beta P,\\ \frac{\partial D}{\partial t} &= \Delta D - \frac{1}{k} D(1-P-D) + \beta P,\end{aligned} \tag{3}$$

with $\beta = \alpha C/\rho$, von Neumann boundary conditions

$$\left.\frac{\partial P}{\partial \vec{n}}\right|_{\partial\Omega} = \left.\frac{\partial D}{\partial \vec{n}}\right|_{\partial\Omega} = 0, \tag{4}$$

and initial conditions

$$P(0,x) \in [0,1], \quad D(0,x) = 0, \tag{5}$$

where $P(0,x)$ is a class C^2 function on $\bar{\Omega}$.

3. Basic mathematical properties of the model

Theorem 1. *There exists a local unique classical solution to system* (3)–(5). *Moreover, if the initial function is non-negative, solutions remain non-negative on the whole interval of existence.*

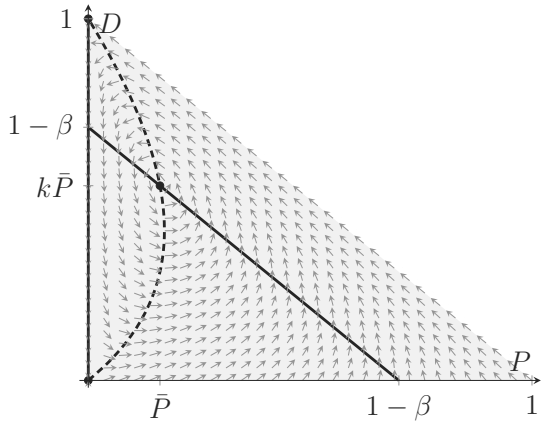


Fig. 1. Phase portrait for system (6) for $\beta < 1$. The black solid lines indicate null-clines for the variable P while the dashed line stands for a null-cline for D. The dots mark steady states.

Proof. The reaction term of system (3)–(5) and initial conditions are C^2 functions; thus, a solution to system (3)–(5) exists locally and is unique due to general properties of reaction-diffusion systems (see, e.g., Henry, 1981, Theorem 3.3.3). The non-negativity of the solutions for non-negative initial data follows from the fact that the reaction part of the right-hand side of system (3)–(5) is non-negative if $P = 0$ or $D = 0$ (see Fife, 1979, Theorem 1.4). ∎

Recall that system (3) without diffusion has the following form:

$$\begin{aligned} \frac{\mathrm{d}P}{\mathrm{d}t} &= P(1-P-D) - \beta P, \\ \frac{\mathrm{d}D}{\mathrm{d}t} &= -\frac{1}{k} D(1-P-D) + \beta P, \end{aligned} \tag{6}$$

and it was mathematically studied in detail by Bogdańska *et al.* (2017), where it was shown that it has at most three steady states:

- $A_1 = (0,0)$ which is either a stable node for $\beta > 1$ or a saddle for $\beta < 1$,
- $A_2 = (0,1)$ which is a saddle,
- $A_3 = (\bar{P}, k\bar{P})$, $\bar{P} = (1-\beta)/(1+k)$, which exists for $\beta < 1$ and is either a stable node or a stable focus.

Moreover, it is easy to see that, for $\beta < 1$, system (6) has a heteroclinic orbit connecting steady states $(0,1)$ and $(0,0)$ given by $\{P = 0\} \times [0,1]$; cf. Fig. 1.

The stability of spatially homogeneous steady states of system (3)–(5) is the same as the local stability of the steady states of the system without diffusion.

Theorem 2. *The steady state* $(0,0)$ *of system* (3)–(5) *is locally stable for* $\beta > 1$ *and unstable for* $\beta < 1$*; steady state* $(0,1)$ *is always unstable, while the positive steady state* $(\bar{P}, k\bar{P})$ *is locally stable whenever it exits.*

Proof. The stability matrix of system (3) is given by

$$J(A_i) = J_{\mathrm{ODE}}(A_i) + \begin{bmatrix} -\kappa_i^2 & 0 \\ 0 & -\kappa_i^2 \end{bmatrix},$$

where $J_{\mathrm{ODE}}(A_i)$ is a stability matrix for the ODE system (6) for the steady state A_i and κ_i are the corresponding eigenvalues of the Laplace operator. The Laplace operator with zero-flux boundary always has a zero eigenvalue; thus, diffusion cannot stabilise unstable steady states $(0,1)$ and $(0,0)$ for $\beta < 1$. On the other hand, matrix $J((0,0))$ is lower triangular (see Bogdańska *et al.*, 2017); thus, for $\beta > 1$ diffusion cannot destabilise steady state $(0,0)$.

For the positive steady state $(\bar{P}, k\bar{P})$ we have

$$J((\bar{P}, k\bar{P})) = \begin{bmatrix} -\bar{P} - \kappa^2 & -\bar{P} \\ \bar{P} + \beta & \bar{P} - \frac{\beta}{k} - \kappa^2 \end{bmatrix}.$$

It is easy to see that $\operatorname{tr} J\big((\bar{P}, k\bar{P})\big) = -\frac{\beta}{k} - 2\kappa^2 < 0$ and $\det J\big((\bar{P}, k\bar{P})\big) = \frac{\beta(1-\beta)}{k} + \kappa^2 \left(\frac{\beta}{k} + \kappa^2\right) > 0$; thus, for $\beta < 1$ steady state $(\bar{P}, k\bar{P})$ stays locally stable. ∎

4. Existence of travelling waves

Travelling wave analysis is an important aspect of the analysis of the tumour growth, since if travelling waves exist, then we may estimate the aggressiveness of tumour progression. We verify whether for system (3) with $\beta < 1$ there exist travelling waves which connect the two space homogeneous steady state solutions $(0,0)$ and $(\bar{P}, k\bar{P})$. From now on, for simplicity, we assume that $\Omega \subset R$. Specifically, by a travelling wave we mean a wave which propagates with a constant velocity ϑ without changing the shape (Murray, 1989), i.e., we look for the solutions $P(t,x),\ D(t,x)$ of system (3) corresponding to the front

$$P(t,x) = U(w), \quad D(t,x) = V(w), \quad w = x + \vartheta t,$$

and satisfying boundary conditions

$$\begin{aligned} P(t,-\infty) &= 0, & D(t,-\infty) &= 0, \\ P(t,+\infty) &= \bar{P}, & D(t,+\infty) &= k\bar{P}. \end{aligned}$$

In the following, we use the geometric singular perturbation theory (to be specific, the Fenichel invariant manifold theory (Fenichel, 1979; Jones, 1995)) to prove that such waves exist for sufficiently large speed $|\vartheta|$. First, we show the existence of an invariant manifold for the ODE system describing the desired front (Jones, 1995). Next, we study the dynamics of a new perturbed system in this invariant manifold. Finally, we employ the Fredholm alternative to prove the existence of the front in this

invariant manifold (Gourley and Bartuccelli, 2000). A similar method has been used to prove the existence of travelling wave solutions by Belmonte-Beitia (2016), Gourley and Bartuccelli (2000) or Jones (1995), to cite a few. Recall the fundamental definition and theorem of Fenichel's theory (see Jones, 1995).

4.1. Fenichel theorem. Consider the following system:

$$u' = f(u, v, \epsilon), \quad v' = \epsilon g(u, v, \epsilon), \tag{7}$$

where the functions f and g are C^∞. Letting $\epsilon \to 0$ we can rewrite (7) as

$$u' = f(u, v, 0), \quad v' = 0.$$

We assume that the critical manifold $\mathcal{M}^0$ contains the set $\{f(u, v, 0) = 0\}$.

Definition 1. We say that $\mathcal{M}^0$ is a normally hyperbolic manifold if the linearisation of system (7) at each point in $\mathcal{M}^0$ restricted to $\mathcal{M}^0$ (i.e., for $\epsilon = 0$) has exactly $\dim \mathcal{M}^0$ eigenvalues on the imaginary axis.

Theorem 3. (Fenichel first theorem (Jones, 1995)) *Let $\mathcal{M}^0$ be a normally hyperbolic manifold. For any sufficiently small $\epsilon > 0$ there exists a manifold $\mathcal{M}^\epsilon$ which is within distance ϵ of $\mathcal{M}^0$ and is diffeomorphic to $\mathcal{M}^0$. Furthermore, $\mathcal{M}^\epsilon$ is locally invariant under the flow of system* (7) *and of class C^p for any $p < +\infty$.*

4.2. Normally hyperbolic manifold. For $P(t, x) = U(w)$, and $D(t, x) = V(w)$ with $w = x + \vartheta t$ we obtain an ODE system describing the dynamics of $U(w)$ and $V(w)$:

$$\begin{aligned} U'' - \vartheta U' + U(1 - U - V - \beta) = 0, \\ V'' - \vartheta V' - \frac{1}{k} V(1 - U - V) + \beta U = 0, \end{aligned} \tag{8}$$

subject to boundary conditions

$$\begin{aligned} U(-\infty) = 0, \qquad V(-\infty) = 0, \\ U(+\infty) = \bar{P}, \qquad V(+\infty) = k\bar{P}. \end{aligned} \tag{9}$$

Note that partial differential equations in x and t in system (3) become ODEs (8) in w. We consider a small perturbation, that is, we assume that $\vartheta^2 \gg 1$, and write $\epsilon := 1/\vartheta^2 \ll 1$, $\xi = w/\vartheta = w\sqrt{\epsilon}$. Then system (8) for $U(\xi)$ and $V(\xi)$ is

$$\begin{aligned} \epsilon U_{\xi\xi} - U_\xi + U(1 - U - V - \beta) = 0, \\ \epsilon V_{\xi\xi} - V_\xi - \frac{1}{k} V(1 - U - V) + \beta U = 0, \end{aligned} \tag{10}$$

with conditions (9), where U_ξ and V_ξ denote the derivatives of U and V with respect to variable ξ. Defining $M = U_\xi$, $N = V_\xi$, we recast system (10) into the so-called "slow system":

$$U_\xi = M, \tag{11a}$$
$$\epsilon M_\xi = M - U(1 - U - V - \beta), \tag{11b}$$
$$V_\xi = N, \tag{11c}$$
$$\epsilon N_\xi = N + \frac{1}{k} V(1 - U - V) - \beta U. \tag{11d}$$

Let $\zeta = \xi/\epsilon = \vartheta w$. Then $U_\zeta = \epsilon U_\xi$, $M_\zeta = \epsilon M_\xi$ and

$$\begin{aligned} U_\zeta &= \epsilon M, \\ M_\zeta &= M - U(1 - U - V - \beta), \\ V_\zeta &= \epsilon N, \\ N_\zeta &= N + \frac{1}{k} V(1 - U - V) - \beta U, \end{aligned} \tag{12}$$

which is called the "dual fast system" associated with the slow system (11) (cf. Gourley and Bartuccelli, 2000).

For $\epsilon = 0$ from Eqs. (11b) and (11d) we have

$$M = U(1 - U - V - \beta), \quad N = -\frac{1}{k} V(1 - U - V) + \beta U.$$

Thus, the evolution of U and V is described by a system of two ODEs

$$\begin{aligned} U_\xi &= U(1 - U - V - \beta), \\ V_\xi &= -\frac{1}{k} V(1 - U - V) + \beta U, \end{aligned}$$

which has the same dynamic as system (6).

For $\epsilon = 0$ we define the set

$$\mathcal{M}^0 = \Big\{(U, M, V, N) \colon\ M = U(1 - U - V - \beta), \\ N = -\frac{1}{k} V(1 - U - V) + \beta U \Big\}, \tag{13}$$

which is a two-dimensional submanifold on $\mathbb{R}^4$.

Lemma 1. *The set $\mathcal{M}^0$ given by* (13) *is a normally hyperbolic manifold.*

Proof. The Jacobi matrix of the linearisation of system (12) for $\epsilon = 0$ has the following form:

$$J(U, V) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 2U + V + \beta - 1 & 1 & U & 0 \\ 0 & 0 & 0 & 0 \\ -\frac{V}{k} - \beta & 0 & \frac{1}{k}(1 - U - 2V) & 1 \end{bmatrix}. \tag{14}$$

Matrix (14) has two double eigenvalues: $\lambda_1 = 0$ and $\lambda_2 = 1$. As a consequence, $\mathcal{M}^0$ is normally hyperbolic. ∎

Subsequently, we study a perturbation $\mathcal{M}^\epsilon$ of manifold $\mathcal{M}^0$, which is invariant for the flow of system (12). Its existence for sufficiently small $\epsilon > 0$ is guaranteed by the Fenichel first theorem (Jones, 1995).

4.3. Main result. Let us formulate the main outcome of our paper.

Theorem 4. *If $\beta < 1$, there exists a sufficiently large $\vartheta_0 > 0$ such that for every $\vartheta > \vartheta_0$, system* (3) *admits a travelling wave solution $P(t,x) = U(x+\vartheta t)$, $D(t,x) = V(x+\vartheta t)$ satisfying boundary conditions* (9)*.*

Proof. Let us recall that $\epsilon = 1/\vartheta^2$, thus we show that a travelling wave exists for a sufficiently small ϵ. In Lemma 1 we showed that the set $\mathcal{M}^0$ is a normally hyperbolic manifold and, as a consequence of Theorem 3, there the manifold $\mathcal{M}^\epsilon$ exists. Thus, it is enough to investigate the dynamics of $\mathcal{M}^\epsilon$.

Because U, V are slow variables and M, N are fast ones, the manifold $\mathcal{M}^\epsilon$ is given by

$$\begin{aligned}\mathcal{M}^\epsilon = \{\,&(U,M,V,N)\in\mathbb{R}^4:\\ &M = U(1-U-V-\beta)+g^\epsilon(U,V),\\ &N = -\frac{1}{k}V(1-U-V)+\beta U+h^\epsilon(U,V)\,\},\end{aligned} \tag{15}$$

for some functions $g^\epsilon(U,V)$, $h^\epsilon(U,V) \in C^p, p < +\infty$ such that

$$g^0(U,V) = h^0(U,V) = 0, \tag{16}$$

and the equations describing evolution of U and V in $\mathcal{M}^\epsilon$ are

$$\begin{aligned}U_\xi =& U(1-U-V-\beta)+g^\epsilon(U,V),\\ V_\xi =& -\frac{1}{k}V(1-U-V)+\beta U+h^\epsilon(U,V).\end{aligned} \tag{17}$$

We differentiate the equations in (15) describing M and N,

$$\begin{aligned}M_\xi &= (1-U-V-\beta)\cdot U_\xi - U\,(U_\xi+V_\xi)\\ &\quad+\frac{\partial g^\epsilon(U,V)}{\partial U}U_\xi+\frac{\partial g^\epsilon(U,V)}{\partial V}V_\xi\\ &= U_\xi(1-2U-V-\beta)-UV_\xi\\ &\quad+\frac{\partial g^\epsilon(U,V)}{\partial U}U_\xi+\frac{\partial g^\epsilon(U,V)}{\partial V}V_\xi,\\ N_\xi &= -\frac{1}{k}V_\xi(1-U-V)+\frac{1}{k}V(U_\xi+V_\xi)+\beta U_\xi\\ &\quad+\frac{\partial h^\epsilon(U,V)}{\partial U}U_\xi+\frac{\partial h^\epsilon(U,V)}{\partial V}V_\xi.\end{aligned}$$

Now, taking into account Eqns. (17) and the fact that $U_\xi = M$, $V_\xi = N$ (see Eqns. (11a) and (11c)), we have

$$\begin{aligned}M_\xi &= (U(1-U-V-\beta)+g^\epsilon(U,V))\\ &\quad\times(1-2U-V-\beta)\\ &\quad+U\left(\frac{1}{k}V(1-U-V)-\beta U-h^\epsilon(U,V)\right)\\ &\quad+\frac{\partial g^\epsilon(U,V)}{\partial U}M+\frac{\partial g^\epsilon(U,V)}{\partial V}N\\ &= (1-U-V-\beta)\,((1-2U-V-\beta)U\\ &\quad+g^\epsilon(U,V))+U\Big(\frac{1}{k}V(1-U-V)\\ &\quad-\beta U-g^\epsilon(U,V)-h^\epsilon(U,V)\Big)\\ &\quad+\frac{\partial g^\epsilon(U,V)}{\partial U}M+\frac{\partial g^\epsilon(U,V)}{\partial V}N,\\ N_\xi &= -\frac{1}{k}(1-U-V)\Big(-\frac{1}{k}V(1-U-V)\\ &\quad+\beta U+h^\epsilon(U,V)\Big)\\ &\quad+\frac{1}{k}V\Big(U(1-U-V-\beta)+g^\epsilon(U,V)\\ &\quad-\frac{1}{k}V(1-U-V)+\beta U+h^\epsilon(U,V)\Big)\\ &\quad+\beta\,(U(1-U-V-\beta)+g^\epsilon(U,V))\\ &\quad+\frac{\partial h^\epsilon(U,V)}{\partial U}U_\xi+\frac{\partial h^\epsilon(U,V)}{\partial V}V_\xi\\ &= \frac{1}{k}(1-U-V)\Big(\frac{1}{k}(1-U-2V)+U(V-\beta)\\ &\quad-h^\epsilon(U,V)\Big)+\beta\,(U(1-U-V-\beta)+g^\epsilon(U,V))\\ &\quad+\frac{1}{k}V(g^\epsilon(U,V)+h^\epsilon(U,V))\\ &\quad+\frac{\partial h^\epsilon(U,V)}{\partial U}M+\frac{\partial h^\epsilon(U,V)}{\partial V}N.\end{aligned}$$

We substitute the obtained equations for M_ξ and N_ξ into Eqns. (11b) and (11d) and deduce that g^ϵ and h^ϵ satisfy the following partial differential equations:

$$\begin{aligned}&g^\epsilon(U,V)\\ &=\epsilon\Big[(1-U-V-\beta)\Big((1-2U-V-\beta)U\\ &\quad+g^\epsilon(U,V)\Big)+U\Big(\frac{1}{k}V(1-U-V)\\ &\quad-\beta U-g^\epsilon(U,V)-h^\epsilon(U,V)\Big)\\ &\quad+\frac{\partial g^\epsilon(U,V)}{\partial U}M+\frac{\partial g^\epsilon(U,V)}{\partial V}N\Big],\\ &h^\epsilon(U,V)\\ &=\epsilon\Big[\frac{1}{k}(1-U-V)\Big(\frac{1}{k}(1-U-2V)+U(V-\beta)\\ &\quad-h^\epsilon(U,V)\Big)+\beta\,(U(1-U-V-\beta)+g^\epsilon(U,V))\end{aligned}$$

$$+\frac{1}{k}V\Big(g^\epsilon(U,V)+h^\epsilon(U,V)\Big) + \frac{\partial h^\epsilon(U,V)}{\partial U}M+\frac{\partial h^\epsilon(U,V)}{\partial V}N\Big]. \tag{18}$$

Next, we expand h^ϵ and g^ϵ in the Taylor series around $\epsilon=0$, obtaining

$$g^\epsilon(U,V)=g^0(U,V)+\epsilon\frac{\partial g^0(U,V)}{\partial\epsilon}+\ldots + \frac{\epsilon^{n-1}}{(n-1)!}\frac{\partial^{n-1}g^0(U,V)}{\partial\epsilon^{n-1}}+\epsilon^n R_n^g(\epsilon),$$

$$h^\epsilon(U,V)=h^0(U,V)+\epsilon\frac{\partial h^0(U,V)}{\partial\epsilon}+\ldots + \frac{\epsilon^{n-1}}{(n-1)!}\frac{\partial^{n-1}h^0(U,V)}{\partial\epsilon^{n-1}}+\epsilon^n R_n^h(\epsilon),$$

where R_n^g, R_n^h are such that $\lim_{\epsilon\to0}R_n^g(\epsilon)=0$ and $\lim_{\epsilon\to0}R_n^h(\epsilon)=0$. Clearly, due to (16), we have $g^0(U,V)=h^0(U,V)=0$. Using Eqns. (18), we calculate the partial derivatives of g^ϵ and h^ϵ with respect to ϵ, arriving at

$$\frac{\partial g^0(U,V)}{\partial\epsilon}=U\Big[(1-U-V)\times\Big(1-2U-\frac{k-1}{k}V-2\beta\Big)+\beta^2\Big],$$

$$\frac{\partial h^0(U,V)}{\partial\epsilon}=\frac{1}{k}(1-U-V)\Big(\frac{1}{k}(1-U-2V)+U(V-\beta)\Big)+\beta U(1-U-V-\beta).$$

Hence, the Taylor series of g^ϵ and h^ϵ have the following forms:

$$g^\epsilon(U,V)=U\Big[(1-U-V)\Big(1-2U-\frac{k-1}{k}V-2\beta\Big)+\beta^2\Big]\epsilon+O\left(\epsilon^2\right),$$

$$h^\epsilon(U,V)=\Big[\frac{1}{k}(1-U-V)\Big(\frac{1}{k}(1-U-2V)+U(V-\beta)\Big)+\beta U(1-U-V-\beta)\Big]\epsilon+O\left(\epsilon^2\right).$$

Substituting the Taylor series, and omitting terms of the order of ϵ^2, into system (17) we obtain

$$U_\xi=U(1-U-V-\beta)+U\Big[(1-U-V)\Big(1-2U-\frac{k-1}{k}V-2\beta\Big)+\beta^2\Big]\epsilon, \tag{19}$$

$$V_\xi=-\frac{1}{k}V(1-U-V)+\beta U+\Big[\frac{1}{k}(1-U-V)\Big(\frac{1}{k}(1-U-2V)+U(V-\beta)\Big)+\beta U(1-U-V-\beta)\Big]\epsilon, \tag{20}$$

which approximate the dynamics on the manifold $\mathcal{M}^\epsilon$ for a sufficiently small ϵ.

Now, let us denote by (U_0,V_0) the solution of system (19)–(20) for $\epsilon=0$, that is,

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}\xi}U_0&=U_0(1-U_0-V_0-\beta),\\ \frac{\mathrm{d}}{\mathrm{d}\xi}V_0&=-\frac{1}{k}V_0(1-U_0-V_0)+\beta U_0,\end{aligned} \tag{21}$$

which is equivalent to system (6). Hence, a heteroclinic orbit connecting the steady states $(0,0)$ and $(\bar P,k\bar P)$ exists. For $\epsilon>0$ system (19)–(20) has two steady states

$$P_2=\Big(0,\frac{\epsilon}{k+2\epsilon}\Big)$$
$$P_3=\left(\bar P+\epsilon\bar u,k\bar P+\epsilon\bar v\right).$$

Note that $\epsilon/(k+2\epsilon)\to0$ as $\epsilon\to0$. Thus, it is enough to show that for a sufficiently small $\epsilon>0$ there exists a heteroclinic orbit connecting, the steady states P_2 and P_3 of system (19)–(20). This orbit corresponds to a travelling wave solution of system (3). To find such a connection, we write

$$U=U_0+\epsilon U_1,\quad V=V_0+\epsilon V_1. \tag{22}$$

In what follows, we determine the dynamics of U_1 and V_1. Substituting new variables (22) into system (19)–(20), we get

$$\begin{aligned}U_\xi&=U_0(1-U_0-V_0-\beta)+\epsilon U_1(1-2U_0-V_0-\beta)\\&\quad+\epsilon U_0\Big[(1-U_0-V_0)\Big(1-2U_0-\frac{k-1}{k}V_0-2\beta\Big)\\&\quad-\epsilon U_0V_1+\beta^2\Big]+O(\epsilon^2),\\ V_\xi&=-\frac{1}{k}V_0(1-U_0-V_0)+\beta U_0\\&\quad-\epsilon\frac{1}{k}\left(V_1(1-U_0-2V_0)-U_1V_0\right)+\epsilon\beta U_1\\&\quad+\epsilon\Big[\frac{1}{k}(1-U_0-V_0)\Big(\frac{1}{k}(1-U_0-2V_0)\\&\quad+U_0(V_0-\beta)\Big)+\beta U_0(1-U_0-V_0-\beta)\Big]\\&\quad+O(\epsilon^2).\end{aligned}$$

Clearly, $U_\xi=\frac{\mathrm{d}}{\mathrm{d}\xi}U_0+\epsilon\frac{\mathrm{d}}{\mathrm{d}\xi}U_1$ and $V_\xi=\frac{\mathrm{d}}{\mathrm{d}\xi}V_0+\epsilon\frac{\mathrm{d}}{\mathrm{d}\xi}V_1$. Moreover, as (U_0,V_0) satisfy system (21), omitting terms

of the order of ϵ^2, we have

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}\xi}U_1 &= U_1(1-2U_0-V_0-\beta)-V_1U_0\\ &\quad+U_0\Big[(1-U_0-V_0)\\ &\quad\times\Big(1-2U_0-\frac{k-1}{k}V_0-2\beta\Big)+\beta^2\Big],\\ \frac{\mathrm{d}}{\mathrm{d}\xi}V_1 &= U_1\Big(\frac{1}{k}V_0+\beta\Big)\\ &\quad-\frac{1}{k}V_1(1-U_0-2V_0)\\ &\quad+\beta U_0(1-U_0-V_0-\beta)+\frac{1}{k}(1-U_0-V_0)\\ &\quad\times\Big(\frac{1}{k}(1-U_0-2V_0)+U_0(V_0-\beta)\Big).\end{aligned}$$

We rewrite the system of equations governing U_1 and V_1 in the following way:

$$\frac{\mathrm{d}}{\mathrm{d}\xi}\begin{bmatrix}U_1\\V_1\end{bmatrix}-\begin{bmatrix}1-2U_0-V_0-\beta & -U_0\\ \frac{1}{k}V_0+\beta & -\frac{1}{k}(1-U_0-2V_0)\end{bmatrix}\times\begin{bmatrix}U_1\\V_1\end{bmatrix}=\begin{bmatrix}f_1(U_0,V_0)\\f_2(U_0,V_0)\end{bmatrix},\quad(23)$$

where

$$\begin{aligned}f_1(U_0,V_0) &= U_0\Big[(1-U_0-V_0)\\ &\quad\times\Big(1-2U_0-\frac{k-1}{k}V_0-2\beta\Big)+\beta^2\Big],\\ f_2(U_0,V_0) &= \beta U_0(1-U_0-V_0-\beta)\\ &\quad+\frac{1}{k}(1-U_0-V_0)\Big(\frac{1}{k}(1-U_0-2V_0)\\ &\quad+U_0(V_0-\beta)\Big).\end{aligned}$$

Using (22), we transform steady states P_2 and P_3 obtaining

$$\begin{aligned}P_2 &= (0,0)+\epsilon\cdot\Big(0,\frac{1}{k+2\epsilon}\Big),\\ P_3 &= (\bar P,k\bar P)+\epsilon\cdot(\bar u,\bar v).\end{aligned}$$

Our aim is to prove that system (23) has a solution satisfying the conditions

$$\begin{aligned}&\lim_{\xi\to-\infty}U_1(\xi)=0, && \lim_{\xi\to-\infty}V_1(\xi)=\frac{1}{k+2\epsilon},\\ &\lim_{\xi\to+\infty}U_1(\xi)=\bar u, && \lim_{\xi\to+\infty}V_1(\xi)=\bar v.\end{aligned}$$

Note that the functions

$$\begin{aligned}F(\xi) &= \bar u\cdot\frac{1}{1+\mathrm{e}^{-\xi}},\\ G(\xi) &= \frac{1}{k+2\epsilon}+\Big(\bar v-\frac{1}{k+2\epsilon}\Big)\cdot\frac{1}{1+\mathrm{e}^{-\xi}}\end{aligned}$$

satisfy $\lim_{\xi\to-\infty}F(\xi)=0$, $\lim_{\xi\to+\infty}F(\xi)=\bar u$ and $\lim_{\xi\to-\infty}G(\xi)=\frac{1}{k+2\epsilon}$, $\lim_{\xi\to+\infty}G(\xi)=\bar v$. Thus, we make the change of variables $U_1=W_U+F$, $V_1=W_V+G$, and now (23) reads

$$\frac{\mathrm{d}}{\mathrm{d}\xi}\begin{bmatrix}W_U\\W_V\end{bmatrix}-\begin{bmatrix}1-2U_0-V_0-\beta & -U_0\\ \frac{1}{k}V_0+\beta & -\frac{1}{k}(1-U_0-2V_0)\end{bmatrix}\times\begin{bmatrix}W_U\\W_V\end{bmatrix}=\begin{bmatrix}h_1(U_0,V_0,\xi)\\h_2(U_0,V_0,\xi)\end{bmatrix},\quad(24)$$

where

$$\begin{aligned}h_1(U_0,V_0,\xi) &= f_1(U_0,V_0)+F(\xi)(1-2U_0-V_0-\beta)\\ &\quad-U_0G(\xi)-\bar u\frac{\mathrm{e}^{-\xi}}{(1+\mathrm{e}^{-\xi})^2},\\ h_2(U_0,V_0,\xi) &= f_2(U_0,V_0)+F(\xi)\Big(\frac{1}{k}V_0+\beta\Big)\\ &\quad-\frac{1}{k}(1-U_0-2V_0)G(\xi)+\frac{1}{k+2\epsilon}\\ &\quad+\Big(\bar v-\frac{1}{k+2\epsilon}\Big)\frac{\mathrm{e}^{-\xi}}{(1+\mathrm{e}^{-\xi})^2}.\end{aligned}$$

As a consequence, we verify the existence of the solution of system (24) with homogeneous boundary conditions $\lim_{\xi\to\pm\infty}W_U(\xi)=\lim_{\xi\to\pm\infty}W_V(\xi)=0$. To this end, we use the Fredholm alternative as formulated by Bressloff (2013). Suppose that $\mathbb{L}$ is a linear differential operator acting on a subspace of $L^2(\mathbb{R}^2)$ of square-integrable functions. Given the standard inner product $\langle\cdot,\cdot\rangle$ on $L^2(\mathbb{R}^2)$:

$$\langle f,g\rangle=\int_{-\infty}^{+\infty}(f(\xi),g(\xi))\,\mathrm{d}\xi,$$

where $(\cdot,\cdot)$ is the Euclidean inner product on $\mathbb{R}^2$, the adjoint linear operator $\mathbb{L}^*$ is defined as $\langle f,\mathbb{L}g\rangle=\langle\mathbb{L}^*f,g\rangle$. The Fredholm alternative theorem states that the inhomogeneous equation $\mathbb{L}f=h$ has a solution if and only if the condition $\langle\nu,h\rangle=0$ is fulfilled for all ν satisfying the homogeneous equation $\mathbb{L}^*\nu=0$.

In our case, the linear operator $\mathbb{L}$ is defined by the left-hand side of system (24). We claim that system (24) has a solution if and only if

$$\int_{-\infty}^{+\infty}\Big(s_1(\xi)h_1(U_0,V_0,\xi)+s_2(\xi)h_2(U_0,V_0,\xi)\Big)\,\mathrm{d}\xi=0\quad(25)$$

holds for all solutions (s_1,s_2) of the adjoint problem

$$\frac{\mathrm{d}}{\mathrm{d}\xi}\begin{bmatrix}s_1\\s_2\end{bmatrix}=\begin{bmatrix}-1+2U_0+V_0+\beta & -\frac{1}{k}V_0-\beta\\ U_0 & \frac{1}{k}(1-U_0-2V_0)\end{bmatrix}\begin{bmatrix}s_1\\s_2\end{bmatrix}\quad(26)$$

subject to boundary conditions $\lim_{\xi\to\pm\infty} s_i(\xi) = 0$ for $i \in \{1,2\}$. Recall that (U_0, V_0) corresponds to the heteroclinic solution of system (21). Letting $\xi \to -\infty$, we have that $(U_0, V_0) \to (0,0)$; then the matrix in system (26) is a constant one with eigenvalues $\lambda_1 = \beta - 1$, $\lambda_2 = \frac{1}{k}$. The eigenvalue λ_1 is negative due to our assumption that $\beta < 1$, while λ_2 is positive. Thus, as $\xi \to -\infty$, any solution of system (26), different from the zero solution, is a sum of two exponentially increasing and decreasing functions. Therefore, the only solution of the adjoint problem (26) in space $L^2(\mathbb{R}^2)$ is $(s_1, s_2) \equiv (0,0)$. Thus, condition (25) holds. ■

4.4. Existence of the trivial travelling wave. The analytical results confirm the existence of the travelling wave solutions. However, they do not exclude the possibility that the wave is trivial, meaning that only one variable changes. In order to verify this, we set $P = 0$ obtaining

$$\frac{\partial D}{\partial t} = \Delta D - \frac{1}{k} D(1-D).$$

Recall $w = x + \vartheta t$, $D(t,x) = V(w)$. Thus, we arrive at

$$V'' = \vartheta V + \frac{1}{k} V(1-V), \tag{27}$$

which is equivalent to the system

$$V' = U, \quad U' = \vartheta U + \frac{1}{k} V(1-V).$$

After the change of the variables $z = 1 - V$ and $s = -t$, we get

$$z' = U, \quad U' = -\vartheta U - \frac{1}{k} z(1-z). \tag{28}$$

Clearly, (28) is the same system as the one obtained for the classic Fisher–Kolmogorov indicating that for $\vartheta^2 \geq 4/k$ system (3) has a trivial travelling wave solution such that $\lim_{s\to-\infty} z(s) = 1$, $\lim_{s\to+\infty} z(s) = 0$, thus $\lim_{t\to-\infty} z(t) = 0$ and $\lim_{t\to+\infty} z(t) = 1$. This indicates that

$$\lim_{t\to-\infty} V(t) = 1, \quad \lim_{t\to+\infty} V(t) = 0.$$

Hence, the travelling wave has the velocity opposite to that for the Fisher–Kolmogorov equation, as we considered $x + \vartheta t$. Thus, the wave travels from 0 to 1 (i.e., the steady state 0 is filling the space), while for the Fisher–Kolmogorov equation, it travels from 1 to 0 (i.e., the steady state 1 is filling the space).

4.5. Estimation of the speed of the travelling wave. In Section 4.3 we proved the existence of a travelling wave solution between steady states $(0,0)$ and $(\bar{P}, k\bar{P})$, while in Section 4.4 we showed the existence of the trivial travelling wave connecting steady states $(0,1)$ and $(0,0)$ (i.e., for which $P \equiv 0$) and we calculated its minimal speed. Now we provide an estimate of the speed of any travelling wave solution (if such a solution exists) for the re-scaled model (3).

Theorem 5. *If the travelling wave solution of Eqn.* (3) *connects any steady state with*

(i) the steady state $(0,0)$ *and the first coefficient of the travelling wave is not identically equal to 0, then the velocity* ϑ *of this wave must fulfil* $|\vartheta| > 2\sqrt{1-\beta}$,

(ii) the steady state $(0,1)$ *and the second coefficient of the travelling wave is not identically equal to 1, then velocity* ϑ *of this wave must fulfil* $|\vartheta| > 2/\sqrt{k}$.

Proof. Recall that the substitutions $P(x,t) = U(x+\vartheta t)$ and $D(x,t) = V(x+\vartheta t)$ in (3) lead to (8) yielding

$$\begin{aligned} U' &= M, \\ M' &= \vartheta M - U(1-U-V) + \beta U, \\ V' &= N, \\ N' &= \vartheta N + \frac{1}{k} V(1-U-V) - \beta U. \end{aligned} \tag{29}$$

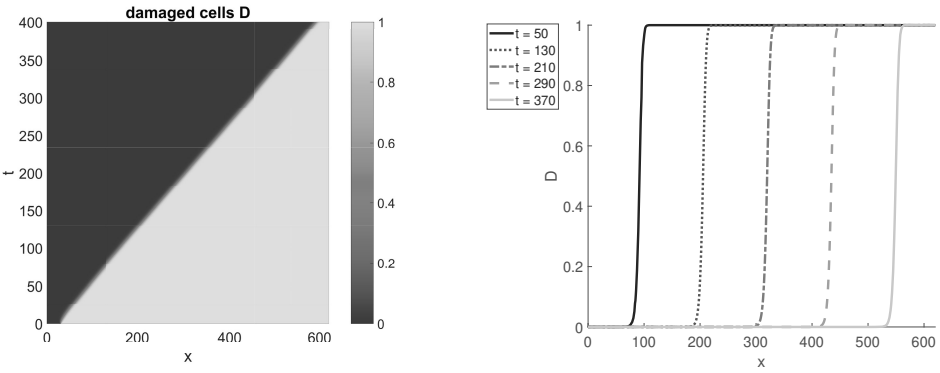
System (29) has at most three steady states $(\bar{U}, \bar{M}, \bar{V}, \bar{N})$: $(0,0,0,0)$, $(0,0,1,0)$ and, additionally, $(\hat{U}, 0, k\hat{U}, 0)$, where $\hat{U} = (1-\beta)/(k+1)$ provided $\beta < 1$. The Jacobian matrix of (29) evaluated at steady state $(\bar{U}, \bar{M}, \bar{V}, \bar{N})$ has the following form:

$$\begin{bmatrix} -\lambda & 1 & & \\ -(1-2\bar{U}-\bar{V})+\beta & \vartheta-\lambda & & \\ 0 & 0 & & \\ -\beta - \frac{1}{k}\bar{V} & 0 & & \\ & & 0 & 0 \\ & & \bar{U} & 0 \\ & & -\lambda & 1 \\ & & \frac{1}{k}(1-\bar{U}-2\bar{V}) & \vartheta-\lambda \end{bmatrix}.$$

Case (i) Consider the travelling wave solution from or to $(0,0,0,0)$. The characteristic polynomial for this steady state is

$$W(\lambda) = \left(\lambda(\lambda-\vartheta) + 1 - \beta\right)\left(\lambda(\lambda-\vartheta) - \frac{1}{k}\right). \tag{30}$$

Thus, the trivial steady state is always unstable. Additionally, whenever $\vartheta^2 < 4(1-\beta)$, polynomial (30) has complex eigenvalues connected with subsystem U. Thus, the travelling wave can exist as long as $|\vartheta| \geq 2\sqrt{1-\beta}$ or $U = 0$, with the latter condition indicating the existence of the trivial travelling wave. Therefore, the minimum wave speed is $|\vartheta_{\min}| = 2\sqrt{1-\beta}$.



(a) (b)

Fig. 2. Solutions of system (3) with the initial condition $P(0,x) = 0$ for all x, $D(0,x) = 1$ for $x > 30$, and $D(0,x) = 0$ for all $x \leq 30$, $x \in [0, 620]$, $t \in [0, 400]$. Parameters: $\beta = 0.05$, $k = 2$. Panel (a): propagation of variable D in (x,t) space, panel (b): selected profiles for variable D. The wave moves right with a numerically calculated speed 1.43. An analytical estimate of the minimum speed is $|\vartheta| \geq 2/\sqrt{k} \approx 1.41$.

Case(ii) Consider the travelling wave solution from or to $(0,0,1,0)$. For the steady state $(0,0,1,0)$ we get

$$W(\lambda) = \Big(\lambda(\lambda - \vartheta) - \beta\Big)\Big(\lambda(\lambda - \vartheta) + \frac{1}{k}\Big),$$

implying that the considered steady state is always unstable. Moreover, for $|\vartheta| < 2/\sqrt{k}$ the characteristic equation has complex eigenvalues connected with subsystem V. Thus, whenever the travelling wave for V is not equal to 1, then its speed has to be greater than $2/\sqrt{k}$. ■

4.6. Numerical simulations. In this section, we numerically illustrate, with the use of the Matlab software, the existence of travelling wave solutions of system (3). First, we present the trivial travelling wave between $(0,0)$ and $(0,1)$. Second, we show results of simulations that indicate the existence of the travelling wave solution between $(0,0)$ and a positive steady state. Finally, our simulations suggest that there is only a trivial travelling wave between $(0,0)$ and $(0,1)$. In the work of Joiner and van der Kogel (2019) parameter k was estimated to be between 1 and 3; hence we choose $k = 2$ for all simulations, while the value of β varies.

Clearly, the travelling wave is a solution defined on the whole real line, which cannot be, of course, simulated. We perform our simulations for $t \in [0, 400]$ and $x \in [0, x_{\max}]$. We impose that for $t = 0$ the initial function is equal to the value of one of the steady states (say A_i) for $x \in [0, 30)$ and it is equal to the value of another steady state (say A_j, $j \neq i$) for $x \geq 30$. We choose $x_{\max}$ in such a manner that the value of the solution is close to the value of A_j steady state for $t = 400$ and x near to $x_{\max}$.

In Fig. 2 we present numerical solutions of system (3) with the initial condition $P(0,x) = 0$ for all $x \in [0, 620]$, $D(0,x) = 0$ for $x \in [0, 30]$, and $D(0,x) = 1$ for all $x \in (30, 620]$. We chose $\beta = 0.05$. We see a propagating wave front for the variable D, while the variable P is equal to zero. We see that $D = 0$ fills the space. Moreover, for the chosen set of parameters, a numerically calculated speed of the travelling wave equals 1.43 which is close to the analytical estimate $2/\sqrt{k} \approx 1.41$.

In Fig. 3 we present solutions of system (3) with the initial condition $P(0,x) = \bar{P}$ and $D(0,x) = k\bar{P}$ for all $x \leq 30$ (i.e., the solution is equal to a spatially homogeneous positive steady state for $x \leq 30$), while $P(0,x) = D(0,x) = 0$ for $x \in (30, 700]$. This time we choose $\beta = 0.3$. In Fig. 3 we see that now it is the positive steady state that fills the space. The numerically calculated speed of the travelling wave is equal to 1.68 which is close to the analytically estimated minimal speed $2\sqrt{1-\beta} \approx 1.67$. Note that oscillations arise around the positive steady state. If we run the simulation for the initial condition $P(0,x) = 0.05$ for $x \leq 30$ and $P(0,x) = 0$ for $x \in (30, 800]$, and $D(0,x) = 0$ for all $x \in [0, 800]$ and for $\beta = 0.05$, we observe that the solution of the equation on the left-hand side border (that is close to $x = 0$) converges to the positive steady state, while the solution on the right-hand border (i.e. for x close to $x_{\max} = 800$) remains close to the zero steady state, see Fig. 4. Hence, the space is homogeneously filled with the value of the solution at the positive steady state. In addition, for smaller β oscillations' dumping is slower (cf. Figs. 3 and 4), and therefore, the profile of the wave seems to be changing when we simulate the solution on the finite interval.

We note a strikingly similar solutions' behaviour if the initial condition on the left-hand side border is close, but not equal, to $(0,1)$; these results are not presented due to their similarity to the ones in Fig. 4. These simulations

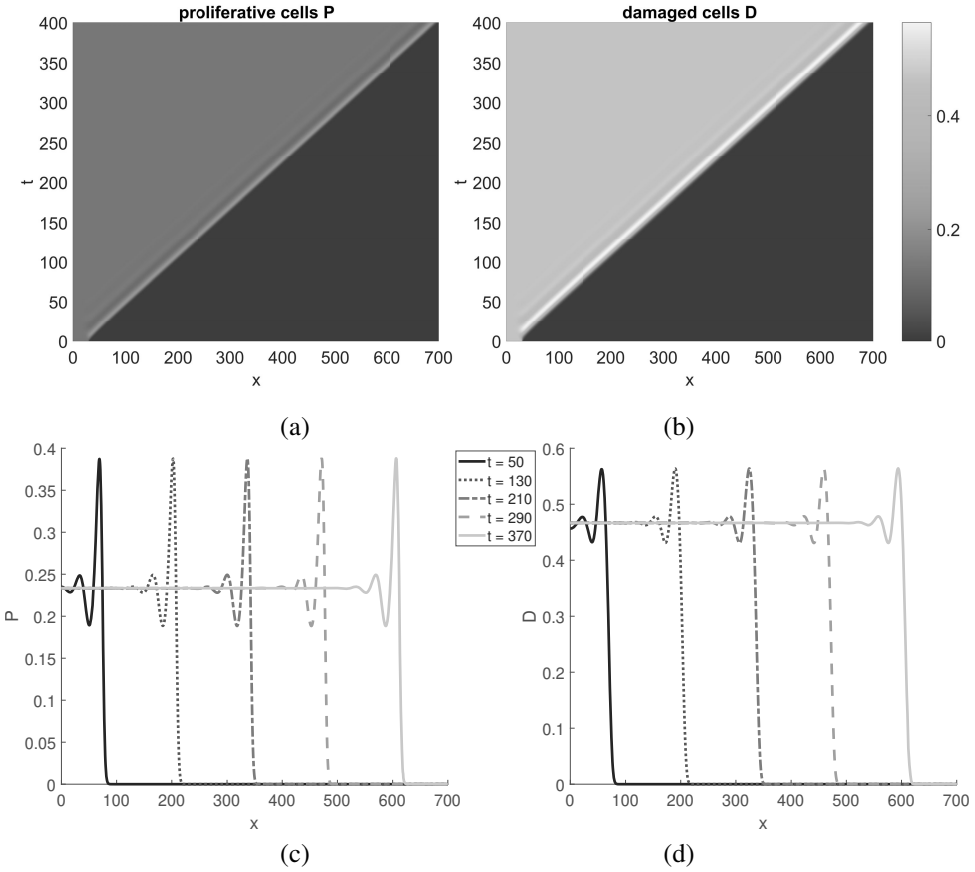


Fig. 3. Solutions of system (3) with the initial condition $P(0,x) = \bar{P}$ and $D(0,x) = k\bar{P}$ for all $x \leq 30$, while $P(0,x) = D(0,x) = 0$ for $x > 30$, $x \in [0, 700]$, $t \in [0, 400]$. Parameters: $\beta = 0.3$, $k = 2$. Panel (a): propagation of variable P in (x,t) space, panel (b): propagation of variable D in (x,t) space, panel (c): selected profiles for variable P, panel (d): selected profiles for variable D (selected times as in panel (c)). The wave moves right with a numerically calculated speed 1.68. An analytical estimate for of the minimum speed is $|\vartheta| \geq 2\sqrt{1-\beta} \approx 1.67$.

suggest that a non-trivial travelling wave between $(0,0)$ and $(0,1)$ does not exist, at least for k between 1 and 3 and $\beta \in (0,1)$ for which we run the simulations.

5. Conclusions

In this paper, we focus on proving the mathematical properties of the mathematical model (1) that could reflect some aspects of brain tumour growth and response to chemotherapy. What is different here from our previous works on modelling chemotherapy in LGGs (Bogdańska *et al.*, 2017; Bodnar *et al.*, 2019) is that, first, we include diffusion of tumour cells, and second, we allow for constant chemotherapy. We demonstrate basic mathematical properties of system (1) such as the local existence of the solutions, and their non-negativity for the non-negative initial data. We also studied the stability of spatially homogeneous steady states.

Based on the Fenichel invariant manifold theory we show that the tumour spreads like a travelling wave, meaning that the solutions of the corresponding mathematical model move at a constant speed without changing their shape.

We also calculate analytically the minimum speed of the travelling wave which is very close to the numerically calculated speed. This would definitely help us to estimate the model parameters, as the speed of the tumour progression can be estimated directly from the experimental data, although it is not an easy task. The travelling wave connecting $(0,0)$ with a positive steady state exists for $\beta < 1$, which means that the treatment is insufficient to eradicate the tumour completely. In order to estimate the lower bound for the tumour expansion speed, we assume $\beta = 0$ and thus the minimal speed would be $2\sqrt{\rho\delta}$, which is the same as the one obtained by Swanson *et al.* (2008). For the parameters used by Pérez-García *et al.* (2014), the minimal speed of the travelling wave is approximately 4.35 mm per year indicating a tumour diameter growth of 8.7 mm per year. This agrees with the speed of LGGs' progression reported by Pallud *et al.*

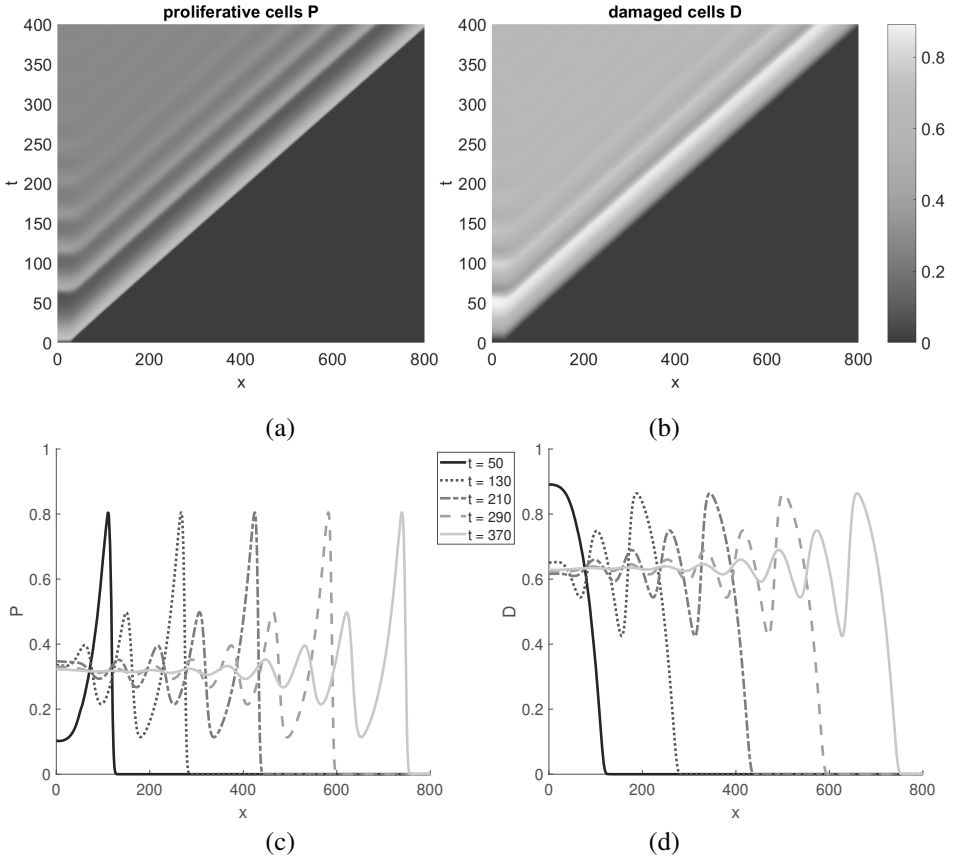


Fig. 4. Solutions of system (3) with the initial condition $P(0,x) = 0.05$ for $x \leq 30$ and 0 otherwise, while $D(0,x) = 0$ for all x, $x \in [0, 800]$, $t \in [0, 400]$. Parameters: $\beta = 0.05$, $k = 2$. Panel (a): propagation of variable P in (x,t) space, panel (b): propagation of variable D in (x,t) space, panel (c): selected profiles for variable P, panel (d): selected profiles for variable D (selected times as in panel (c)). The wave moves right with a numerically calculated speed 1.97.

(2013; 2012) and Adenis *et al.* (2021). In real life, the travelling wave connecting $(0,1)$ with $(0,0)$ can happen only within a limited part of the tumour, where almost all tumour cells are damaged (by the treatment). However, derived results suggest that the speed of the tumour's diameter decrease during chemotherapy should be similar to the speed of tumour progression, which also happens in the case of LGG (cf. Bogdańska *et al.*, 2017).

Clearly, a lower bound to the speed of this travelling wave could help us to estimate model parameters in a tumour regression phase and predict a relapse time drawing us closer to the ultimate goal of a large portion of mathematical oncology research which is to forecast tumour growth individually for each patient. The relevance of estimating the speed of tumour growth has been also raised in other studies, including the one attempting to estimate the length of the silent phase of LGGs growth (see Pallud *et al.*, 2013).

Furthermore, we believe that this paper brings inspiration for future research works in the area of mathematical analysis. One particular example might be to verify how other types of diffusion (e.g., porous medium or fractional diffusion) fit to the description of tumour growth. This would be challenging not only from the applicational but also from the analytical point of view. Note also, that in the presented study, following Pérez-García *et al.* (2014), the same diffusion rates of damaged and non-damaged cells are considered. That comes from the assumption that a chemotherapy-induced damage is manifested only during mitosis. This might be a slight oversimplification and the different diffusion rates for the two cell populations might be considered in the future. In the work of Bodnar and Vela Pérez (2019) a modification of the model studied here, without diffusion but with an explicit death term, was considered. Verifying how such a modification affects the existence and the speed of the travelling wave might become yet another potential direction of future works.

Acknowledgment

The part of the work by M.U. Bogdańska presented in Sections 2, 3 and 4.1–4.3 was supported by the

National Science Centre (Poland) under the grant 2015/17/N/ST1/02564. The part of the work by A. Bartłomiejczyk, M. Bodnar and M.J. Piotrowska conveyed in Sections 2, 3 and 4.1–4.3 was supported by the National Science Centre (Poland) under the grant 2015/19/B/ST1/01163. Further results, demonstrated in Sections 4.3–4.6, were supported by the programme *Excellence Initiative—Research University*, University of Warsaw, New Ideas in Priority Research Area III: Mathematical modelling of brain tumours growth dynamics.

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Agnieszka Bartłomiejczyk holds a PhD from the Faculty of Mathematics and Computer Science of Nicolaus Copernicus University in Toruń. She is an associate professor at the Faculty of Applied Physics and Mathematics of the Gdańsk University of Technology. She works on the development of mathematical methods useful for applications. She is interested in mathematical modelling in biology and chemistry, including the investigation of gene expression and structured populations.

Marek Bodnar works as an associate professor in the Institute of Applied Mathematics and Mechanics, Faculty of Mathematics, Informatics and Mechanics, University of Warsaw. He is interested in application of dynamical systems (mainly delay and differential equations, but also partial differential equations) in the modelling of biological and medical phenomena, in particular, tumour growth, tumour-immune system interactions as well as anticancer therapies.

Magdalena U. Bogdańska holds a MSc in mathematics (data analysis in business and logistics) and a PhD in mathematics from the University of Warsaw and Universidad de Castilla–La Mancha, with the focus on mathematical models of brain tumours and their treatment. Since 2018 she has been working in the field of data science and AI, currently as a senior data scientist at Equinix, the world's top digital infrastructure company.

Monika J. Piotrowska is an associate professor at the Institute of Applied Mathematics and Mechanics, University of Warsaw. In 2016 she obtained a habilitation in mathematics. She is interested in the mathematical and computational modelling of various natural phenomena, including tumour growth, angiogenesis, tumour-immune system interactions, transmissions of pathogens within hospitals, investigation of anticancer therapies and infection control strategies.

Received: 11 November 2022
Revised: 6 June 2023
Accepted: 30 June 2023