A model for acid-mediated tumour growth with nonlinear acid production term☆

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Abstract

This article considers a mathematical model for tumour growth based on an acid-mediated hypothesis, i.e. the assumption that tumour progression is facilitated by acidification of the region around the tumour-host interface. The resulting destruction of the normal tissue environment promotes tumour growth. We will derive and analyse a reaction-diffusion model for tumour progression that includes different aspects of pathological and healthy cell metabolism to check tumour growth. Our results can provide insights into the governing dynamics of invasive processes that may suggest possible intervention strategies, leading to the design of new and better experiments or treatments.

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1. Introduction

Mathematical modelling of tumour growth has steadily increased in popularity in recent years with a range of growth mechanisms being considered through the application of various modelling techniques. Due to the invasive nature of tumour growth one such modelling technique that has been utilised is that of *travelling waves* (TWs). The theory of TWs was introduced in seminal papers by Fisher (1937) and Kolmogorov, Petrovsky and Piskunov (1937). Models that have TW solutions are popular in the analysis of invasion, and more specifically in the field of modelling tumour invasion; some examples can be found in Ambrosi and Mollica (2003); Anderson et al. (2000); Bellomo et al. (2008); Chaplain and Anderson (2003); Gatenby (1995); Marchant et al. (1999, 2001); McGillen et al. (2013); Perumpanani et al. (1996).

In the simplest case a TW is a scalar function of the form $u(x,t) = U(x - \theta t)$ where x is the spatial variable, t is the time variable and θ is the wave speed. The solution is called a travelling wave as it has a fixed profile that moves in a fixed direction with time. The function U is often required to satisfy boundary conditions at $\pm\infty$ and these conditions will determine the wave type. Should those boundary conditions be different, the solution is called a *front*. If the boundary conditions are the same, the solution is then called a *pulse*. We note that fronts and pulses are not the only types of TWs. Depending on the nature of the problem and the spatial dimensions considered we can also consider *target*, *spiral* and *scroll* waves (Keener, 1986; Winfree, 1980).

This work will engage the use of front- and pulse-type TWs in the context of tumour invasion. The latter phenomenon is a characteristic feature of tumoural processes which largely accounts for the threat they represent to patients. In Chaplain and Anderson (2003) it is explained that primary tumour growth is initially a result of division of cells. However, once a critical size is reached, tumours require a further mechanism to enable growth within the surrounding tissue. One such mechanism is the production of angiogenic substances to encourage the growth of blood vessels towards the tumour so that the tumour can obtain a richer source of nutrients than that obtained through diffusion alone.

Gatenby and Gawlinski (1996, 2003) proposed a model in which tumour cells, due to their anaerobic, glycolytic metabolism, produce an excess of H^+ ions. This causes local acidification and subsequent destruction of the normal tissue, which enables the invasion of neoplastic tissue. The situation considered in Gatenby and Gawlinski (1996, 2003) corresponds to a one-dimensional setting and was later extended to consider higher-dimensional geometries, as well as the occurrence of necrotic cores (Smallbone et al., 2005), glucose dynamics (Bianchini and Fasano, 2009) and tumour cell death due to the acidic environment (McGillen et al., 2013). A key feature of their model is that for certain parameters an *interstitial gap* is observed, i.e. a region practically depleted of cells located right ahead of the invading tumour front. This phenomenon has been observed experimentally and was also discussed in Gatenby and Gawlinski (1996). The model's solution for the concentration of excess H^+ ions presents as a front (Fasano et al., 2009; Gatenby and Gawlinski, 1996), which suggests that the concentration of acid will be highest inside the tumour, with an almost homogeneous concentration, rather than at the tumour-host interface. Tumours tend to present with very heterogeneous acid profiles (Helmlinger et al., 1997; Lardner, 2001) and there is experimental observations of higher acid concentration near the region of the interstitial gap (Dellian et al., 1996; Helmlinger et al., 1997; Martin and Jain, 1994). A cause for this pH gradient could be a large region of necrosis (Gatenby and Gawlinski, 1996). This localised acid concentration phenomenon has also been predicted mathematically in Smallbone et al. (2008). Therefore we propose to model the acid concentration as a pulse. In this way it will then be possible for the highest concentration of H^+ ions to be observed at or close to the tumour-host interface. Should we observe an interstitial gap in which the concentration of H^+ ions is greatest in or near this region, we would have a solution in line with experimental results and thus confirm the validity of this as an alternative model to that of Gatenby and Gawlinski for acid-mediated tumour invasion.

Let us describe our model in detail. Let $\mathbf{y}$ and s denote position (in cm) and time (in sec), respectively. Let $N_1(\mathbf{y}, t)$ be the cell density of normal tissue (in $\mathrm{cells\,cm^{-3}}$), $N_2(\mathbf{y}, t)$ the cell density of neoplastic tissue (in $\mathrm{cells\,cm^{-3}}$) and $L(\mathbf{y}, t)$ be the concentration of excess H^+ ions (in M). We present the following hypotheses to govern our model:

(i) The normal and neoplastic tissues obey logistic growth dynamics with respective static growth rates r_1 and r_2 (in $\mathrm{sec^{-1}}$) and carrying capacities K_1 and K_2 (in $\mathrm{cells\,cm^{-3}}$).

(ii) We consider a population competition relationship between the normal and neoplastic tissues, and denote the respective competition (dimensionless) parameters by a_1 and a_2.

(iii) The healthy tissue interacts with the excess H^+ ions, leading to a death rate proportional to the concentration of H^+ ions. We denote the constant of proportionality by d_1 (in $\mathrm{M^{-1}\,sec^{-1}}$).

(iv) The normal and neoplastic cells undergo cell diffusion and are assumed to have a diffusion coefficient proportional to the other respective cell density, i.e. the diffusion coefficients for the normal tissue and neoplastic tissue are $D_1(N_2)$ and $D_2(N_1)$, respectively.

(v) The excess H^+ ions diffuse chemically with constant diffusion coefficient D_3 (in $\mathrm{cm}^2\,\mathrm{sec}^{-1}$) and are produced at a rate r_3 (in $\mathrm{M\,cm^3\,cells^{-1}\,sec^{-1}}$) proportional to the neoplastic cell density until the latter reaches a threshold, after which the production rate decreases as the neoplastic tissue attains its carrying capacity. Moreover, an uptake term, with constant of proportionality d_3 (in sec^{-1}), is included to take account of mechanisms for increasing extracellular pH.

The above hypotheses lead to the following system of partial differential equations:

$$\frac{\partial N_1}{\partial s} = \nabla \cdot [D_1(N_2)\nabla N_1] + r_1 N_1 \left(1 - \frac{N_1}{K_1} - a_1 \frac{N_2}{K_2}\right) - d_1 L N_1, \tag{1.1}$$

$$\frac{\partial N_2}{\partial s} = \nabla \cdot [D_2(N_1)\nabla N_2] + r_2 N_2 \left(1 - \frac{N_2}{K_2} - a_2 \frac{N_1}{K_1}\right), \tag{1.2}$$

$$\frac{\partial L}{\partial s} = D_3 \nabla^2 L + r_3 N_2 \left(1 - \frac{N_2}{K_2}\right) - d_3 L. \tag{1.3}$$

As in Gatenby and Gawlinski (1996) we will let the diffusion coefficients D_1 and D_2 be given by

$$D_1(N_2) = 0, \qquad D_2(N_1) = D\left(1 - \frac{N_1}{K_1}\right) \tag{1.4}$$

where D (in $\mathrm{cm}^2\,\mathrm{sec}^{-1}$) is constant. We will also make the assumption that the competition coefficient $a_2 = 0$ as we wish to consider a system in which a tumour is invading. Hence it is reasonable to assume that the death of tumour cells due to interaction with normal tissue will be negligible, provided the tumour is not less efficient at consuming available nutrients than the nearby normal tissue as a consequence of acid resistance. Note that Gatenby and Gawlinski (1996) assumed that both $a_1 = 0$ and $a_2 = 0$. A recent article by McGillen et al. (2013) considered a generalisation of the Gatenby and Gawlinski model with non-zero competition parameters and a destruction term for the tumour by the presence of acid. Gatenby and Gawlinksi also assumed that the excess H^+ ions are produced at a rate proportional to the neoplastic cell density throughout, i.e. in (1.3) they had the term $r_3 N_2$ instead of the logistic-type term $r_3 N_2(1 - N_2/K_2)$. This represents a notable difference in our approach to that used in the models considered by Gatenby and Gawlinski (1996) and McGillen et al. (2013). For simplicity we will consider the system given by (1.1)–(1.3) only in one spatial dimension, i.e. $\mathbf{y} = y \in \mathbb{R}$.

Making the substitutions

$$u = \frac{N_1}{K_1}, \quad v = \frac{N_2}{K_2}, \quad w = \frac{d_1}{a_1 r_1} L, \quad t = r_1 s, \quad x = y\sqrt{\frac{r_1}{D_3}}$$

and letting

$$a = a_1, \quad b = \frac{r_2}{r_1}, \quad c = \frac{d_1 r_3 K_2}{r_1^2 a_1}, \quad d = \frac{D}{D_3}, \quad r = \frac{a_1 d_3 r_1}{d_1 r_3 K_2},$$

we obtain the non-dimensionalised form of (1.1)–(1.3) given by

$$u_t = u(1-u) - au(v+w), \tag{1.5}$$
$$v_t = d[(1-u)v_x]_x + bv(1-v), \tag{1.6}$$
$$w_t = w_{xx} + c[v(1-v) - rw]. \tag{1.7}$$

In the quantitative discussions presented in Gatenby and Gawlinski (1996), d was assumed to be a small parameter, i.e.

$$0 < d \ll 1, \tag{1.8}$$

an assumption which is to be retained throughout this paper. The motivation for (1.8) comes from the fact that d is shown to be of the form $d = D/D_3$ where D and D_3 are the respective static diffusion coefficients of the neoplastic tissue and H^+ ions. It is therefore natural to assume that D_3 is much larger than D. The parameter a in (1.5) measures the destructive influence of neoplastic tissue and the H^+ ions on the healthy tissue, and therefore its value can be taken as an indicator of tumour aggressivity. Note that unlike the system examined by Gatenby and Gawlinski (1996), invasion is still possible if the acid concentration is sent to zero due to population competition. This is possible provided the tumour cell density is non-zero everywhere or if the normal cell density is below its respective carrying capacity due to the nonlinear diffusion term in (1.5). Whilst invasion is possible through competition alone, we wish to focus on the implications of acid-mediation on the system due to the increased ability to invade as a result of removal of the afore mentioned restrictions and effective increase in tumour aggressivity. The parameter b measures the growth rate of neoplastic tissue relative to the growth rate of the normal tissue. Hence, having $b > 1$ implies tumour cells reproduce faster than normal cells and $b < 1$ implies the converse. The parameter c can be thought of as a production rate of H^+ ions, with a large value for c representing a high production of acid. Lastly, the parameter r can be thought of as representing the strength of the uptake mechanisms for increasing extracellular pH relative to the production rate of the H^+ ions. The uptake of acid is mainly through the vasculature, so r changes primarily as a result of the density and proximity of blood vessels in and around the tumour and normal tissue.

The above set of equations is a reaction-diffusion system, and it should be noted that this type of system typically has TW solutions connecting some of their steady states. This is especially true here since we are considering invasive processes. With a slight abuse of notation, let

$$(u, v, w)(x, t) = (u, v, w)(z)$$

where $z = x - \theta t$ is a real number and θ is the wave speed. Substituting into (1.5)–(1.7) we obtain

$$0 = \theta u' + u(1 - u) - au(v + w), \tag{1.9}$$

$$0 = d[(1 - u)v'' - u'v'] + \theta v' + bv(1 - v), \tag{1.10}$$

$$0 = w'' + \theta w' + c[v(1 - v) - rw]. \tag{1.11}$$

Here, $(\,)'$ represents differentiation with respect to z. Since we are modelling invasion we note that $\theta > 0$ and we are solving (1.9)–(1.11) with respect to the boundary conditions (BCs)

$$(u, v, w)(-\infty) = (0, 1, 0),\ (u, v, w)(\infty) = (1, 0, 0) \tag{1.12a}$$

when $a \geq 1$, and

$$(u, v, w)(-\infty) = (1 - a, 1, 0),\ (u, v, w)(\infty) = (1, 0, 0) \tag{1.12b}$$

when $0 < a < 1$. These BCs are obtained by observing that $(1, 0, 0)$, $(0, 1, 0)$ and $(1 - a, 1, 0)$ (when $0 < a < 1$) are the relevant steady states of the associated first-order system.

This paper is organised as follows. In Section 2 we consider fast TWs and derive leading-order asymptotic formulas for these waves and analyse their stability. In Section 3 we look at slow TWs and derive asymptotic formulas for these waves. We also estimate the width of the interstitial gap. Section 4 shows the results of numerical simulations where we compare the solution of the reaction-diffusion system with our asymptotical formulas. Finally, we give some brief concluding remarks in Section 5. To keep the flow of our main arguments here, the proofs of several results needed in Sections 2 and 3 are postponed to Appendix A and Appendix B at the end of the article.

2. Fast travelling waves

2.1. Leading-order approximations

We consider the case of the fast TW solution, i.e. $\theta = O(1)$ as $d \to 0^+$. Define

$$(u_0, v_0, w_0)(z) = (u, v, w)(z; 0). \tag{2.1}$$

Letting $d \to 0^+$ in (1.9)–(1.11) yields the system of equations

$$0 = \theta u_0' + u_0(1 - u_0) - a u_0(v_0 + w_0), \tag{2.2}$$
$$0 = \theta v_0' + b v_0(1 - v_0), \tag{2.3}$$
$$0 = w_0'' + \theta w_0' + c[v_0(1 - v_0) - r w_0],$$

with boundary conditions given by (1.12). We see that (2.3) is a Bernoulli equation and can be solved explicitly to give

$$v_0(z) = \frac{1}{2}\left(1 - \tanh\frac{bz}{2\theta}\right). \tag{2.4}$$

Note that the boundary conditions $v_0(-\infty) = 1$ and $v_0(\infty) = 0$ are satisfied. To fix the phase of the TW, we assume that $v_0(0) = 1/2$ without loss of generality. For later use we observe that

$$v_0(z)[1 - v_0(z)] = \frac{1}{4}\mathrm{sech}^2\frac{bz}{2\theta}. \tag{2.5}$$

Invoking Lemma 5 in Appendix A, and recalling (2.5), we have

$$w_0(z) = \frac{1}{4}\frac{c}{\eta_1 - \eta_2}\left[\int_z^\infty \mathrm{e}^{\eta_1(z-s)}\mathrm{sech}^2\frac{bs}{2\theta}\,\mathrm{d}s + \int_{-\infty}^z \mathrm{e}^{\eta_2(z-s)}\mathrm{sech}^2\frac{bs}{2\theta}\,\mathrm{d}s\right] \tag{2.6a}$$

where

$$\eta_1 = \frac{-\theta + \sqrt{\theta^2 + 4cr}}{2}, \quad \eta_2 = \frac{-\theta - \sqrt{\theta^2 + 4cr}}{2}. \tag{2.6b}$$

We also obtain from Lemma 7 in Appendix A that

$$u_0(z) = \frac{\theta\Phi_0(z)}{\int_z^\infty \Phi_0(s)\,\mathrm{d}s}, \quad \Phi_0(z) = \mathrm{e}^{-\int_0^z [1 - a v_0(s) - a w_0(s)]/\theta\,\mathrm{d}s}. \tag{2.7}$$

Therefore we have the following result:

Proposition 1. *Suppose that $\theta = O(1)$ as $d \to 0^+$. Then, to leading order, we have*

$$u(z;d) \simeq \frac{\theta \Phi_0(z)}{\int_z^\infty \Phi_0(s)\,\mathrm{d}s},$$

$$v(z;d) \simeq \frac{1}{2}\left(1 - \tanh \frac{bz}{2\theta}\right)$$

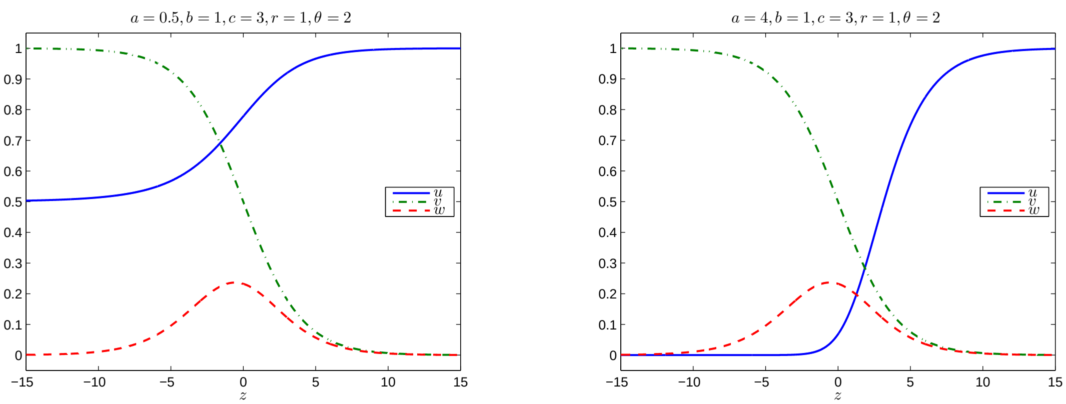
and

$$w(z;d) \simeq \frac{1}{4}\frac{c}{\eta_1 - \eta_2}\left[\int_z^\infty e^{\eta_1(z-s)}\mathrm{sech}^2\frac{bs}{2\theta}\,\mathrm{d}s + \int_{-\infty}^z e^{\eta_2(z-s)}\mathrm{sech}^2\frac{bs}{2\theta}\,\mathrm{d}s\right]$$

where

$$\Phi_0(z) = e^{-\int_0^z [1 - av_0(s) - aw_0(s)]/\theta\,\mathrm{d}s}.$$

Note that we have a regular perturbation problem since the solution of the reduced system satisfies all of the boundary conditions (Bender and Orszag, 1999). Plots of the fast TW solutions for particular parameter values are displayed in Figures 1a and 1b. Note the pulse-like nature of the acid variable.



(a) $(a, b, c, r, \theta) = (0.5, 1, 3, 1, 2)$

(b) $(a, b, c, r, \theta) = (4, 1, 3, 1, 2)$

Figure 1: Fast TW solutions given by (2.4)–(2.7): (a) A solution with BCs given by (1.12b). (b) A solution with BCs given by (1.12a)

2.2. Stability

We now show that the solution (2.4), (2.6) and (2.7) is linearly stable. Let

$$(u, v, w)(x, t; d) = (\tilde{u}, \tilde{v}, \tilde{w})(z, \tau; d)$$

where $z = x - \theta t$, $\tau = t$ and $\theta > 0$ is a fixed wave speed. Noting that

$$\frac{\partial}{\partial t} = \frac{\partial}{\partial z}\frac{\partial z}{\partial t} + \frac{\partial}{\partial \tau}\frac{\partial \tau}{\partial t} = -\theta\frac{\partial}{\partial z} + \frac{\partial}{\partial \tau}, \quad \frac{\partial}{\partial x} = \frac{\partial}{\partial z}\frac{\partial z}{\partial x} = \frac{\partial}{\partial z}$$

and substituting this into (1.5)–(1.7), we obtain

$$\tilde{u}_\tau = \theta\tilde{u} + \tilde{u}(1 - \tilde{u}) - a\tilde{u}(\tilde{v} + \tilde{w}), \tag{2.8}$$
$$\tilde{v}_\tau = d[(1 - \tilde{u})\tilde{v}_z]_z + \theta\tilde{v}_z + b\tilde{v}(1 - \tilde{v}), \tag{2.9}$$
$$\tilde{w}_\tau = \tilde{w}_{zz} + \theta\tilde{w}_z + c[\tilde{v}(1 - \tilde{v}) - r\tilde{w}]. \tag{2.10}$$

We look for a solution of (2.8)–(2.10) of the form

$$\tilde{u} = u(z; d) + \varepsilon e^{-\lambda\tau}\phi_1(z) + \dots, \tag{2.11}$$
$$\tilde{v} = v(z; d) + \varepsilon e^{-\lambda\tau}\phi_2(z) + \dots, \tag{2.12}$$
$$\tilde{w} = w(z; d) + \varepsilon e^{-\lambda\tau}\phi_3(z) + \dots. \tag{2.13}$$

Here, $0 < \varepsilon \ll 1$ and (u, v, w) is the TW solution with fixed speed θ for (1.9)–(1.12). Substituting (2.11)–(2.13) into (2.8)–(2.10) and gathering up the $O(1)$ terms we obtain the system given by (1.9)–(1.11), and thus (u, v, w) satisfies this automatically. Collecting the $O(\varepsilon)$ terms gives the system

$$\theta\phi_1' + [1 + \lambda - 2u - a(v + w)]\phi_1 = au(\phi_2 + \phi_3), \tag{2.14}$$
$$\theta\phi_2' + [b(1 - 2v) + \lambda]\phi_2 = -d[(1 - u)\phi_2' - v'\phi_1]', \tag{2.15}$$
$$\phi_3'' + \theta\phi_3' - (rc - \lambda)\phi_3 = -c(1 - 2v)\phi_2. \tag{2.16}$$

We assume for the boundary conditions

$$\phi_i(\pm\infty) = 0 \quad \text{for } i = 1, 2, 3.$$

If we can find a nontrivial solution (ϕ_1, ϕ_2, ϕ_3) for some $\lambda > 0$, then the fast TW solution will be stable as the small perturbation will decay to zero.

Assume that $\lambda = O(1)$ as $d \to 0^+$ and define

$$(\phi_{1,0}, \phi_{2,0}, \phi_{3,0})(z) = (\phi_1, \phi_2, \phi_3)(z; 0).$$

Setting $d = 0$ in (2.14)–(2.16) gives

$$\theta\phi_{1,0}' + [1 + \lambda - 2u_0 - a(v_0 + w_0)]\phi_{1,0} = au_0(\phi_{2,0} + \phi_{3,0}), \tag{2.17}$$

$$\theta\phi_{2,0}' + [b(1 - 2v_0) + \lambda]\phi_{2,0} = 0, \tag{2.18}$$

$$\phi_{3,0}'' + \theta\phi_{3,0}' - (rc - \lambda)\phi_{3,0} = -c(1 - 2v_0)\phi_{2,0}. \tag{2.19}$$

Before continuing, it is easy to see that

$$\int_0^z [1 - 2v_0(s)]\,\mathrm{d}s = \int_0^z \tanh\frac{bs}{2\theta}\,\mathrm{d}s = \frac{2\theta}{b}\ln\cosh\frac{bz}{2\theta}.$$

As (2.18) is a first-order separable equation we can solve it explicitly to give

$$\phi_{2,0}(z) = C\mathrm{e}^{-\lambda z/\theta}\mathrm{sech}^2\frac{bz}{2\theta} = \frac{C}{[\mathrm{e}^{(\lambda+b)z/(2\theta)} + \mathrm{e}^{(\lambda-b)z/(2\theta)}]^2}$$

where C is an arbitrary constant. If $0 < \lambda < b$, then we have $\phi_{2,0}(\pm\infty) = 0$. So for any $C \neq 0$ this represents a nontrivial solution for $\phi_{2,0}(z)$.

We can now solve (2.19) by noting that it is in the form of (A.1) in Lemma 5 in Appendix A where $\beta = rc - \lambda$ and $f(s) = -c[1 - 2v_0(s)]\phi_{2,0}(s)$. We can see that $f(\pm\infty) = 0$. Thus if we set $0 < \lambda < rc$, then $I_1(\pm\infty) = I_2(\pm\infty) = 0$ and $\phi_{3,0}(\pm\infty) = 0$ where

$$\phi_{3,0}(z) = \frac{c}{\rho_1 - \rho_2}\left\{\int_z^\infty \mathrm{e}^{\rho_1(z-s)}[1 - 2v_0(s)]\phi_{2,0}(s)\,\mathrm{d}s \right.$$
$$\left. + \int_{-\infty}^z \mathrm{e}^{\rho_2(z-s)}[1 - 2v_0(s)]\phi_{2,0}(s)\,\mathrm{d}s\right\}$$

and

$$\rho_1 = \frac{-\theta + \sqrt{\theta^2 + 4(rc - \lambda)}}{2}, \quad \rho_2 = \frac{-\theta - \sqrt{\theta^2 + 4(rc - \lambda)}}{2}.$$

We now consider (2.17) and note that it is a first-order linear ODE with solution given by

$$\phi_{1,0}(z) = -\frac{a}{\theta}\frac{\int_z^\infty u_0(s)[\phi_{2,0}(s) + \phi_{3,0}(s)]\Phi(s)\,\mathrm{d}s}{\Phi(z)} \tag{2.20}$$

where

$$\Phi(z) = \mathrm{e}^{-\int_0^z [2u_0(s) + av_0(s) + aw_0(s) - 1 - \lambda]/\theta\,\mathrm{d}s}.$$

We now find the positive values for λ that allow (2.20) to be consistent with the BCs. Applying Lemma 6 in Appendix A with

$$g(s) = \frac{1}{\theta}[2u_0(s) + av_0(s) + aw_0(s) - 1 - \lambda]$$

we have $g(\infty) = (1-\lambda)/\theta$. If we set $0 < \lambda < 1$, then $g(\infty) > 0$ and $\Phi(\infty) = 0$; hence we need to apply L'Hôpital's Rule to obtain the value for $\phi_{1,0}(\infty)$:

$$\lim_{z\to\infty} \phi_{1,0}(z) = \frac{a}{\theta} \lim_{z\to\infty} \frac{u_0(z)[\phi_{2,0}(z) + \phi_{3,0}(z)]\Phi(z)}{-g(z)\Phi(z)} = 0.$$

To find $\phi_{1,0}(-\infty)$ we need to consider cases. When $a > 1$ we have $g(-\infty) = (a - 1 - \lambda)/\theta$. Hence if $0 < \lambda < a-1$, then we have $g(-\infty) > 0$ and $\Phi(-\infty) = \infty$. If $0 < a < 1$, then $g(-\infty) = (1-a-\lambda)/\theta$. Therefore if $0 < \lambda < 1-a$, then we have $g(-\infty) > 0$ and $\Phi(-\infty) = \infty$. Hence for $a > 0$ and $a \neq 1$ we have conditions on $\lambda > 0$ such that $\Phi(-\infty) = \infty$. If $\int_{-\infty}^{\infty} u_0(s)[\phi_{2,0}(s) + \phi_{3,0}(s)]\Phi(s)\,\mathrm{d}s$ is finite, then $\phi(\pm\infty) = 0$; otherwise if it is infinite, then we apply L'Hôpital's Rule to obtain

$$\lim_{z\to-\infty} \phi_{1,0}(z) = \frac{a}{\theta} \lim_{z\to-\infty} \frac{u_0(z)[\phi_{2,0}(z) + \phi_{3,0}(z)]\Phi(z)}{-g(z)\Phi(z)} = 0.$$

Thus, if $0 < a < 1$ and $0 < \lambda < \min\{b, rc, 1-a\}$ or if $a > 1$ and $0 < \lambda < \min\{b, rc, a-1\}$, then $(\phi_{1,0}, \phi_{2,0}, \phi_{3,0})(\pm\infty) = 0$ as required. This implies that the fast TW solution is stable. Note that we can not make any conclusions about the stability of the fast TW solution when $a = 1$ as the above argument breaks down.

2.3. Statement of results for fast waves

The result of this section can be summarised as follows:

If the speed $\theta = O(1)$ as $d \to 0^+$, then we obtain the following leading-order asymptotic approximations for $(u, v, w)(z)$:

$$u(z; d) \simeq \frac{\theta\Phi_0(z)}{\int_z^\infty \Phi_0(s)\,\mathrm{d}s},$$

$$v(z; d) \simeq \frac{1}{2}\left(1 - \tanh\frac{bz}{2\theta}\right)$$

and

$$w(z; d) \simeq \frac{1}{4}\frac{c}{\eta_1 - \eta_2}\left[\int_z^\infty \mathrm{e}^{\eta_1(z-s)}\mathrm{sech}^2\frac{bs}{2\theta}\,\mathrm{d}s + \int_{-\infty}^z \mathrm{e}^{\eta_2(z-s)}\mathrm{sech}^2\frac{bs}{2\theta}\,\mathrm{d}s\right]$$

where

$$\eta_1 = \frac{-\theta + \sqrt{\theta^2 + 4cr}}{2}, \quad \eta_2 = \frac{-\theta - \sqrt{\theta^2 + 4cr}}{2}$$

and

$$\Phi_0(z) = \mathrm{e}^{-\int_0^z [1 - av_0(s) - aw_0(s)]/\theta\,\mathrm{d}s}.$$

A linear stability analysis showed that these solutions are linearly stable for $a \neq 1$, with no conclusion able to be made about the stability in the case $a = 1$.

3. Slow travelling waves

In this section we consider slow TW. By this we mean that their wave speed is such that:

$$\theta = \theta_0 d^{\alpha} \qquad (\theta_0, \alpha > 0) \tag{3.1}$$

where $\theta_0 = O(1)$ as $d \to 0^+$. We remark that if no other parameter assumptions are made our first-order asymptotic solution for w becomes trivial, i.e $w \simeq 0$. In order to obtain a significant matched asymptotic solution, we require the assumption that c is large. This assumption corresponds physically to a high rate of acid production which would suggest a very high dependence on the process of glycolysis for energy production. The validity of this assumption is also confirmed when finding numerical solutions to (1.5)–(1.7) as in order to obtain a solution for w that is not "small", a value of c must be used that is sufficiently large (e.g. see Figures 4c and 4d). Our assumption can also be seen to be plausible by using estimated parameter values (as stated in Fasano et al. (2009)) for the dimensional parameters that constitute c to show that it is typically large. Hence we let

$$c = c_0 d^{-\gamma} \qquad (c_0, \gamma > 0) \tag{3.2}$$

where $c_0 = O(1)$ as $d \to 0^+$. As in Fasano et al. (2009), our analysis will utilise matched asymptotic expansions such as those found in Bender and Orszag (1999).

Substituting (3.1) and (3.2) in (1.9)–(1.11) we obtain the system of equations

$$0 = \theta_0 d^{\alpha} u' + u(1-u) - au(v+w), \tag{3.3}$$
$$0 = d[(1-u)v'' - u'v'] + \theta_0 d^{\alpha} v' + bv(1-v), \tag{3.4}$$
$$0 = d^{\gamma} w'' + \theta_0 d^{\alpha+\gamma} w' + c_0[v(1-v) - rw], \tag{3.5}$$

with the BCs given by (1.12). Introducing the stretched inner variable $\xi = z/d^{\alpha}$ into (3.3)–(3.5), and letting

$$(u, v, w)(z; d) = (U, V, W)(\xi; d),$$

we have the equivalent system

$$0 = \theta_0 \dot{U} + U(1-U) - aU(V+W), \tag{3.6}$$
$$0 = d^{1-2\alpha}[(1-U)\ddot{V} - \dot{U}\dot{V}] + \theta_0 \dot{V} + bV(1-V), \tag{3.7}$$
$$0 = d^{\gamma-2\alpha} \ddot{W} + \theta_0 d^{\gamma} \dot{W} + c_0[V(1-V) - rW]. \tag{3.8}$$

Here, $(\dot{\ })$ denotes differentiation with respect to ξ.

The outer and inner solutions are defined by

$$(u_{\text{out}}, v_{\text{out}}, w_{\text{out}})(z) = (u, v, w)(z; 0)$$

and

$$(U_{\text{in}}, V_{\text{in}}, W_{\text{in}})(\xi) = (U, V, W)(\xi; 0),$$

respectively. We require that the outer and inner solutions satisfy the matching conditions

$$(U_{\text{in}}, V_{\text{in}}, W_{\text{in}})(\pm\infty) = (u_{\text{out}}, v_{\text{out}}, w_{\text{out}})(0\pm).$$

3.1. Outer solutions

The outer solution v_{out} is found by taking $d \to 0^+$ in (3.4) and hence is governed by the algebraic equation

$$bv_{\text{out}}\,(1 - v_{\text{out}}) = 0$$

where $v_{\text{out}}(-\infty) = 1$ and $v_{\text{out}}(\infty) = 0$. We can see that a function that satisfies these conditions is

$$v_{\text{out}}(z) = \begin{cases} 1 & \text{if } z < 0, \\ 0 & \text{if } z > 0. \end{cases} \tag{3.9}$$

Note that the discontinuity at $z = 0$ is not an issue as this is the outer solution only and we will find an inner solution valid for a small region about the point $z = 0$.

We find the governing equation for the outer solution w_{out} by taking $d \to 0^+$ in (3.5) to give us the algebraic equation

$$c_0[v_{\text{out}}(1 - v_{\text{out}}) - rw_{\text{out}}] = 0$$

subject to $w_{\text{out}}(-\infty) = 0$ and $w_{\text{out}}(\infty) = 0$. Using (3.9) gives

$$w_{\text{out}}(z) = 0 \quad (z \neq 0). \tag{3.10}$$

Finally, consider (3.3) and take $d \to 0^+$ to obtain

$$u_{\text{out}}(1 - u_{\text{out}}) - au_{\text{out}}(v_{\text{out}} + w_{\text{out}}) = 0 \tag{3.11}$$

where $u_{\text{out}}(-\infty) = 1 - a$ and $u_{\text{out}}(\infty) = 1$ for $0 < a < 1$, while $u_{\text{out}}(-\infty) = 0$ and $u_{\text{out}}(\infty) = 1$ for $a \geq 1$. Using (3.9) and (3.10), we solve (3.11) and obtain for $0 < a < 1$ that

$$u_{\text{out}}(z) = \begin{cases} 1 - a & \text{if } z < 0, \\ 1 & \text{if } z > 0, \end{cases} \tag{3.12a}$$

while for $a \geq 1$ we have

$$u_{\text{out}}(z) = \begin{cases} 0 & \text{if } z < 0, \\ 1 & \text{if } z > 0. \end{cases} \tag{3.12b}$$

3.2. Inner solutions

We proceed to the inner solutions by letting $d \to 0^+$ in (3.6)–(3.8). Now, if $\alpha > 1/2$ in (3.7) we have

$$(1 - U_{\text{in}})\ddot{V}_{\text{in}} - \dot{U}_{\text{in}}\dot{V}_{\text{in}} = 0,$$

which cannot satisfy the corresponding boundary conditions. Furthermore, if $\alpha = 1/2$ in (3.7) and take $d \to 0^+$ we obtain an equation for V_{in} given by

$$(1 - U_{\text{in}})\,\ddot{V}_{\text{in}} - \dot{U}_{\text{in}}\dot{V}_{\text{in}} + \theta_0\dot{V}_{\text{in}} + bV_{\text{in}}\,(1 - V_{\text{in}}) = 0.$$

However, due to the fact that this equation is part of a coupled system of equations that cannot be solved easily, the asymptotic analysis cannot be completed for this case. Note also that if $\gamma < 2\alpha$ and we take $d \to 0^+$ in (3.8) we have $\ddot{W}_{\text{in}} = 0$ and only the trivial solution can satisfy the boundary conditions. With these restrictions in mind we will therefore assume from this point onwards that

$$0 < \alpha < 1/2, \quad \gamma \geq 2\alpha. \tag{3.13}$$

Taking $d \to 0^+$ in (3.7) yields an equation equivalent to (2.3); hence the inner solution for the neoplastic tissue is given by

$$V_{\text{in}}(\xi) = \frac{1}{2}\left(1 - \tanh\frac{b\xi}{2\theta_0}\right). \tag{3.14}$$

It is clear that V_{in} satisfies

$$V_{\text{in}}(-\infty) = 1 = v_{\text{out}}(0-), \quad V_{\text{in}}(\infty) = 0 = v_{\text{out}}(0+).$$

For the H^+ ion concentration we need to consider two cases: $\gamma > 2\alpha$ and $\gamma = 2\alpha$.

Suppose first that $\gamma > 2\alpha$ and take $d \to 0^+$ in (3.8). Then the governing equation for W_{in} is

$$c_0[rW_{\text{in}} - V_{\text{in}}\,(1 - V_{\text{in}})] = 0.$$

Solving this algebraic equation gives

$$W_{\text{in}}(\xi) = \frac{1}{r}V_{\text{in}}(\xi)\,[1 - V_{\text{in}}(\xi)]\,, \tag{3.15}$$

which simplifies to

$$W_{\text{in}}(\xi) = \frac{1}{4r}\text{sech}^2\frac{b\xi}{2\theta_0} \tag{3.16}$$

from (3.14) and (2.5).

In the case $\gamma = 2\alpha$, when we take $d \to 0^+$, (3.8) becomes

$$\ddot{W}_{\text{in}} + c_0[V_{\text{in}}(1 - V_{\text{in}}) - rW_{\text{in}}] = 0,$$

which can be rewritten as

$$\ddot{W}_{\text{in}} - rc_0 W_{\text{in}} = -c_0 V_{\text{in}}(1 - V_{\text{in}}) = -\frac{c_0}{4}\text{sech}^2\frac{b\xi}{2\theta_0} \tag{3.17}$$

using (2.5). We solve this equation subject to

$$W_{\text{in}}(-\infty) = w_{\text{out}}(0-) = 0, \quad W_{\text{in}}(\infty) = w_{\text{out}}(0+) = 0.$$

Applying Lemma 5 in Appendix A to (3.17) yields

$$W_{\text{in}}(\xi) = \frac{1}{8}\sqrt{\frac{c_0}{r}}\left[\int_{\xi}^{\infty} \mathrm{e}^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s + \int_{-\infty}^{\xi} \mathrm{e}^{-\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s\right]. \tag{3.18}$$

Lastly, we find the inner solution for the normal tissue. We consider (3.6) and take $d \to 0^+$ to obtain

$$\theta_0\dot{U}_{\text{in}} + U_{\text{in}}(1 - U_{\text{in}}) - aU_{\text{in}}(V_{\text{in}} + W_{\text{in}}) = 0 \tag{3.19}$$

where

$$U_{\text{in}}(-\infty) = u_{\text{out}}(0-), \quad U_{\text{in}}(\infty) = u_{\text{out}}(0+).$$

Then using (3.12a) ((3.12b), respectively) for $0 < a < 1$ ($a \geq 1$, respectively) we obtain limits for U_{in} at $\pm\infty$ such that the governing equation for U_{in} is in the same form as (2.2). Therefore a similar application of Lemma 7 gives

$$U_{\text{in}}(\xi) = \frac{\theta_0\Phi(\xi)}{\int_{\xi}^{\infty}\Phi(s)\,\mathrm{d}s} \tag{3.20}$$

where

$$\Phi(z) = \mathrm{e}^{-\int_0^z [1 - aV_{\text{in}}(s) - aW_{\text{in}}(s)]/\theta_0\,\mathrm{d}s}.$$

3.3. *Uniform approximations*

Given that we have obtained our outer and inner solutions, we can look for uniform approximations for u, v and w. This is the result of the following proposition:

Proposition 2. *Suppose that*

$$\theta = \theta_0 d^{\alpha}, \quad c = c_0 d^{-\gamma}$$

where $\theta_0, c_0 = O(1)$ *as* $d \to 0^+$ *and*

$$0 < \alpha < 1/2, \quad \gamma \geq 2\alpha.$$

Define

$$\phi(z; d) = \frac{1}{\theta_0} \int_0^z \left[aV_{\text{in}} \left(\frac{s}{d^{\alpha}} \right) + aW_{\text{in}} \left(\frac{s}{d^{\alpha}} \right) - 1 \right] \mathrm{d}s. \tag{3.21}$$

Then uniform approximations for u, v *and* w *are respectively given by*

$$v(z; d) \simeq \frac{1}{2} \left(1 - \tanh \frac{bz}{2\theta_0 d^{\alpha}} \right), \tag{3.22}$$

$$u(z; d) \simeq \frac{\theta_0 d^{\alpha} e^{\phi(z;d)/d^{\alpha}}}{\int_z^{\infty} e^{\phi(s;d)/d^{\alpha}} \, \mathrm{d}s} \tag{3.23}$$

and

$$w(z; d) \simeq \begin{cases} \dfrac{1}{4r} \operatorname{sech}^2 \dfrac{bz}{2\theta_0 d^{\alpha}} & \text{if } \gamma > 2\alpha, \\ \dfrac{1}{8} \sqrt{\dfrac{c_0}{r}} \left[\displaystyle\int_{z/d^{\alpha}}^{\infty} e^{\sqrt{rc_0}(z/d^{\alpha} - s)} \operatorname{sech}^2 \dfrac{bs}{2\theta_0} \, \mathrm{d}s \right. & \\ \qquad \left. + \displaystyle\int_{-\infty}^{z/d^{\alpha}} e^{-\sqrt{rc_0}(z/d^{\alpha} - s)} \operatorname{sech}^2 \dfrac{bs}{2\theta_0} \, \mathrm{d}s \right] & \text{if } \gamma = 2\alpha. \end{cases} \tag{3.24}$$

Proof. Uniform approximations for u, v and w are obtained by adding the corresponding outer and inner solutions and then subtracting the common values in the overlap region. For the neoplastic tissue we have

$$v_c = \begin{cases} V_{\text{in}}(-\infty) = v_{\text{out}}(0-) = 1 & \text{if } z < 0, \\ V_{\text{in}}(\infty) = v_{\text{out}}(0+) = 0 & \text{if } z > 0, \end{cases}$$

while for the H^+ ion concentration it is

$$w_c = \begin{cases} W_{\text{in}}(-\infty) = w_{\text{out}}(0-) = 0 & \text{if } z < 0, \\ W_{\text{in}}(\infty) = w_{\text{out}}(0+) = 0 & \text{if } z > 0. \end{cases}$$

For the normal tissue the common value when $0 < a < 1$ is

$$u_c = \begin{cases} U_{\rm in}(-\infty) = u_{\rm out}(0-) = 1 - a & \text{if } z < 0, \\ U_{\rm in}(\infty) = u_{\rm out}(0+) = 1 & \text{if } z > 0, \end{cases}$$

while for $a \geq 1$ it is

$$u_c = \begin{cases} U_{\rm in}(-\infty) = u_{\rm out}(0-) = 0 & \text{if } z < 0, \\ U_{\rm in}(\infty) = u_{\rm out}(0+) = 1 & \text{if } z > 0. \end{cases}$$

Therefore a uniform approximation for the neoplastic tissue is given by

$$v(z;d) \simeq v_{\rm out}(z) + V_{\rm in}\left(\frac{z}{d^\alpha}\right) - v_c = \frac{1}{2}\left(1 - \tanh\frac{bz}{2\theta_0 d^\alpha}\right).$$

A uniform approximation for the H^+ ion concentration when $\gamma > 2\alpha$ is

$$w(z;d) \simeq w_{\rm out}(z) + W_{\rm in}\left(\frac{z}{d^\alpha}\right) - w_c = \frac{1}{4r}\mathrm{sech}^2\frac{bz}{2\theta_0 d^\alpha},$$

while for $\gamma = 2\alpha$ it is

$$\begin{aligned} w(z;d) &\simeq w_{\rm out}(z) + W_{\rm in}\left(\frac{z}{d^\alpha}\right) - w_c \\ &= \frac{1}{8}\sqrt{\frac{c_0}{r}}\left[\int_{z/d^\alpha}^{\infty} \mathrm{e}^{\sqrt{rc_0}(z/d^\alpha - s)}\mathrm{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s + \int_{-\infty}^{z/d^\alpha} \mathrm{e}^{-\sqrt{rc_0}(z/d^\alpha - s)}\mathrm{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s\right]. \end{aligned}$$

For the normal tissue a uniform approximation is given by

$$u(z;d) \simeq u_{\rm out}(z) + U_{\rm in}\left(\frac{z}{d^\alpha}\right) - u_c = \frac{\theta_0 \Phi(z/d^\alpha)}{\int_{z/d^\alpha}^{\infty}\Phi(s)\,\mathrm{d}s}$$

where

$$\Phi(z) = \mathrm{e}^{-\int_0^z [1 - aV_{\rm in}(s) - aW_{\rm in}(s)]/\theta_0\,\mathrm{d}s}.$$

By an appropriate substitution for s we obtain

$$\int_{z/d^\alpha}^{\infty}\Phi(s)\,\mathrm{d}s = \frac{1}{d^\alpha}\int_z^\infty \Phi\left(\frac{s}{d^\alpha}\right)\,\mathrm{d}s.$$

Similarly, if we define

$$\phi(z;d) = \frac{1}{\theta_0}\int_0^z \left[aV_{\rm in}\left(\frac{s}{d^\alpha}\right) + aW_{\rm in}\left(\frac{s}{d^\alpha}\right) - 1\right]\,\mathrm{d}s,$$

then

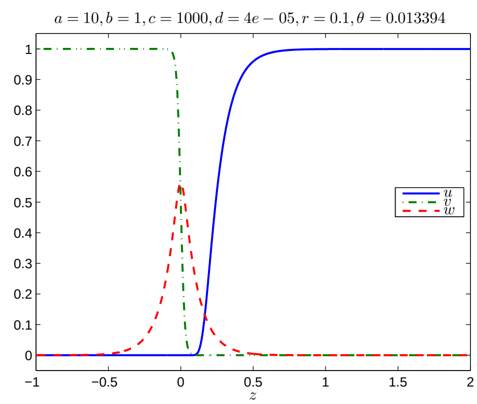
$$\Phi\left(\frac{z}{d^\alpha}\right) = \mathrm{e}^{\phi(z;d)/d^\alpha}.$$

Hence

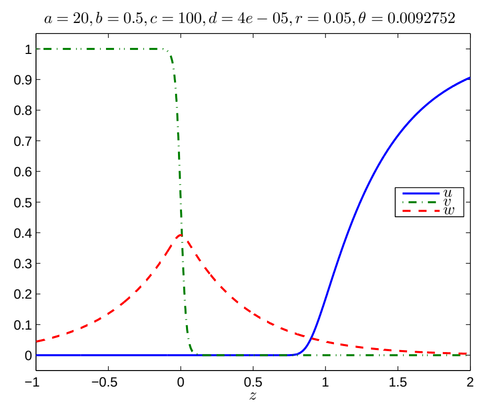
$$u(z;d) \simeq \frac{\theta_0 d^\alpha \mathrm{e}^{\phi(z;d)/d^\alpha}}{\int_z^\infty \mathrm{e}^{\phi(s;d)/d^\alpha}\,\mathrm{d}s}.$$

□

Plots of the slow TW solutions for particular parameter values are displayed in Figures 2a and 2b.



(a) $(a, b, c, d, r, \theta) = (10, 1, 1000, 4 \times 10^{-5}, 0.1, 0.0134)$



(b) $(a, b, c, d, r, \theta) = (20, 0.5, 100, 4 \times 10^{-5}, 0.05, 0.0093)$

Figure 2: Asymptotic approximations given by (3.21)–(3.24) in the case $\gamma = 2\alpha$

3.4. An estimate for the interstitial gap

Here we wish to estimate the width of the interstitial gap. To do so we need to approximate the following generalised Laplace integral appearing in the uniform approximation for u:

$$\int_z^\infty \mathrm{e}^{\phi(s;d)/d^\alpha}\,\mathrm{d}s \tag{3.25}$$

where ϕ is given by (3.21). The next lemma provides information about the behaviour of W_{in} that will be utilised for the approximation of the generalised Laplace integral.

Lemma 3. *Define*

$$W_{\text{in}}(\xi) = \begin{cases} \dfrac{1}{4r}\text{sech}^2\dfrac{b\xi}{2\theta_0} & \text{if } \gamma > 2\alpha, \\ \dfrac{1}{8}\sqrt{\dfrac{c_0}{r}}\left[\displaystyle\int_\xi^\infty e^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\dfrac{bs}{2\theta_0}\,\mathrm{d}s \right. & \\ \qquad\left. + \displaystyle\int_{-\infty}^\xi e^{-\sqrt{rc_0}(\xi-s)}\text{sech}^2\dfrac{bs}{2\theta_0}\,\mathrm{d}s\right] & \text{if } \gamma = 2\alpha. \end{cases} \tag{3.26}$$

Then $\dot{W}_{\text{in}}(\xi) > 0$ *for* $\xi < 0$ *and* $\dot{W}_{\text{in}}(\xi) < 0$ *for* $\xi > 0$*. Thus* W_{in} *has a unique global maximum at* $\xi = 0$*.*

Proof. The case when $\gamma > 2\alpha$ is trivial. Suppose that $\gamma = 2\alpha$. Since (3.26) is an even function, it has a turning point at $\xi = 0$ (i.e. $\dot{W}_{\text{in}}(0) = 0$). We see that

$$\dot{W}_{\text{in}}(\xi) = \frac{c_0}{8}\left[\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s - \int_{-\infty}^\xi \mathrm{e}^{-\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s\right]. \tag{3.27}$$

We can view (3.26) and (3.27) as a linear system with the improper integrals as the unknowns. Solving this system gives

$$\dot{W}_{\text{in}}(\xi) = -\sqrt{rc_0}W_{\text{in}}(\xi) + \frac{c_0}{4}\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s,$$

To proceed further, we shall use Lemma 8 in Appendix A. If we let

$$F(\xi, W) = -\sqrt{rc_0}W + \frac{c_0}{4}\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s$$

with $J = [0, \infty)$, then

$$D_1F(\xi, W) = \frac{c_0}{4}\left[-\text{sech}^2\frac{b\xi}{2\theta_0} + \sqrt{rc_0}\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s\right].$$

For $0 \le \xi < s$, sech^2 is strictly decreasing; hence

$$\begin{aligned}\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s &< \int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi-s)}\text{sech}^2\frac{b\xi}{2\theta_0}\,\mathrm{d}s \\ &= \frac{1}{\sqrt{rc_0}}\text{sech}^2\frac{b\xi}{2\theta_0}.\end{aligned}$$

This shows that $D_1F(\xi, W) < 0$ for all $(\xi, W) \in J \times \mathbb{R}$. From Lemma 8 (with $\xi_0 = \xi^* = 0$) we deduce that $\dot{W}_{\text{in}}(\xi) < 0$ for all $\xi > 0$.

On the other hand, since $W_{\text{in}}(\xi)$ is even, we therefore know that $\dot{W}_{\text{in}}(\xi)$ is odd. As $\dot{W}_{\text{in}}(\xi) < 0$ for $\xi > 0$, the fact that $\dot{W}_{\text{in}}(\xi)$ is odd implies $\dot{W}_{\text{in}}(\xi) > 0$ for $\xi < 0$. □

We now show that for certain values of a, the function ϕ defined in (3.21) achieves a unique maximum.

Lemma 4. *Let ϕ be defined by (3.21). If $a \geq 2$, then there exists a unique maximum of ϕ attained at a value $z_+ > 0$. Here, z_+ is the unique positive solution of*

$$aV_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + aW_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) - 1 = 0. \tag{3.28}$$

Proof. Suppose that $a \geq 2$. First we claim that $\phi'(z; d) > 0$ for $z \leq 0$. Consider

$$\theta_0\phi'(z; d) = aV_{\text{in}}\left(\frac{z}{d^\alpha}\right) + aW_{\text{in}}\left(\frac{z}{d^\alpha}\right) - 1 > aV_{\text{in}}\left(\frac{z}{d^\alpha}\right) - 1$$

as $W_{\text{in}}(\xi) > 0$ for all $\xi \in \mathbb{R}$. Note that $\dot{V}_{\text{in}}(\xi) < 0$ for all $\xi \in \mathbb{R}$, therefore for $z \leq 0$

$$V_{\text{in}}\left(\frac{z}{d^\alpha}\right) \geq V_{\text{in}}(0) = \frac{1}{2}.$$

Hence

$$\theta_0\phi'(z; d) > \frac{a}{2} - 1 \geq 0,$$

proving that $\phi'(z; d) > 0$ for $z \leq 0$.

Next we claim that ϕ has a unique turning point at some $z_+ > 0$. Define

$$G(z) = aV_{\text{in}}\left(\frac{z}{d^\alpha}\right) + aW_{\text{in}}\left(\frac{z}{d^\alpha}\right) - 1 \quad (z \geq 0).$$

We see that

$$G(0) = \frac{a}{2} + aW_{\text{in}}(0) - 1 > 0$$

and

$$G(\infty) = \lim_{z\to\infty} G(z) = -1.$$

Therefore there exists $M > 0$ such that $|G(z) + 1| < 1/2$ for all $z \geq M$, i.e.

$$-\frac{3}{2} < G(z) < -\frac{1}{2} \quad (z \geq M).$$

Hence $G(M) < -1/2 < 0$ and $G(0) > 0$. By Bolzano's Theorem there exists a value $z_+ \in (0, M)$ such that

$$G(z_+) = aV_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + aW_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) - 1 = 0$$

(i.e. $\phi'(z_+;d) = G(z_+)/\theta_0 = 0$). To prove that this point is unique we consider

$$G'(z) = \frac{a}{d^\alpha}\left[\dot{V}_{\text{in}}\left(\frac{z}{d^\alpha}\right) + \dot{W}_{\text{in}}\left(\frac{z}{d^\alpha}\right)\right].$$

We note that $\dot{V}_{\text{in}}(z/d^\alpha) < 0$ and $\dot{W}_{\text{in}}(z/d^\alpha) < 0$ for $z > 0$ by Lemma 3. Hence $G'(z) < 0$ for all $z > 0$, i.e. $G(z)$ is strictly decreasing for all $z > 0$. Therefore there can exist only one zero of the function G on $(0, \infty)$, and this occurs at $z = z_+$. Note that this implies that $G(z) > 0$ for all $0 \le z < z_+$ and $G(z) < 0$ for all $z > z_+$ (i.e. $\phi'(z;d) = G(z)/\theta_0 > 0$ for all $0 \le z < z_+$ and $\phi'(z;d) = G(z)/\theta_0 < 0$ for all $z > z_+$).

Finally, we claim that ϕ has a unique maximum at z_+. We showed that $\phi'(z;d) > 0$ for $z \le 0$ and $\phi'(z;d) > 0$ for all $0 \le z < z_+$, thus $\phi'(z;d) > 0$ for all $z < z_+$. Also, we showed that $\phi'(z_+) < 0$ for all $z > z_+$. Therefore $\phi(z;d)$ has a unique global maximum at $z = z_+$. □

We can apply Lemma 9 in Appendix A to approximate (3.25) for $a \ge 2$. Note that (3.21) implies

$$|\phi(z;d)| \le \frac{a + aW_{\text{in}}(0) + 1}{\theta_0}|z|$$

for all z. Thus ϕ remains bounded as $d \to 0^+$.

We first consider (3.25) for $z > z_+$. For $z_+ < z \le s < \infty$ (i.e. $s > z_+$) we have by Lemma 4 that $\phi'(s;d) < 0$ for all $z \le s < \infty$. Hence by Lemma 9 (i) we have for (3.25) that

$$\int_z^\infty \mathrm{e}^{\phi(s;d)/d^\alpha}\,\mathrm{d}s \simeq -\frac{d^\alpha \mathrm{e}^{\phi(z;d)/d^\alpha}}{\phi'(z;d)}.$$

Therefore (3.23) gives

$$\begin{aligned} u(z;d) \simeq &-\theta_0\phi'(z;d) \\ &= 1 - aV_{\text{in}}\left(\frac{z}{d^\alpha}\right) - aW_{\text{in}}\left(\frac{z}{d^\alpha}\right) \end{aligned} \tag{3.29}$$

for $z > z_+$.

Now we consider (3.25) for $z < z_+$. We note from Lemma 4 that ϕ has a unique maximum at z_+ where $z < z_+ < \infty$. Hence from Lemma 9 (iii) we obtain

$$\int_z^\infty \mathrm{e}^{\phi(s;d)/d^\alpha}\,\mathrm{d}s \simeq \frac{\sqrt{2\pi}\,d^{\alpha/2}\mathrm{e}^{\phi(z_+;d)/d^\alpha}}{\sqrt{-\phi''(z_+;d)}}.$$

Therefore (3.23) gives

$$u(z;d) \simeq \frac{\theta_0}{\sqrt{2\pi}} d^{\alpha/2} \sqrt{-\phi''(z_+;d)} \mathrm{e}^{[\phi(z;d)-\phi(z_+;d)]/d^\alpha} \tag{3.30}$$

for $z < z_+$. Then combining (3.29) and (3.30) we have

$$u(z;d) \simeq \begin{cases} 1 - aV_{\text{in}}\left(\dfrac{z}{d^\alpha}\right) - aW_{\text{in}}\left(\dfrac{z}{d^\alpha}\right) & \text{if } z > z_+, \\ \dfrac{\theta_0}{\sqrt{2\pi}} d^{\alpha/2} \sqrt{-\phi''(z_+;d)} \mathrm{e}^{[\phi(z;d)-\phi(z_+;d)]/d^\alpha} & \text{if } z < z_+. \end{cases} \tag{3.31}$$

We claim that the interstitial gap is approximately given by $(0, z_+)$. Mathematically, we characterise this gap as a region where $u(z;d)+v(z;d) \ll 1$ for all $z \in (0, z_+)$ and d small. Fix $z \in (0, z_+)$. Then from (3.22) we see that

$$\lim_{d\to 0^+} v(z;d) = 0.$$

Since $0 < z < z_+$, and ϕ is bounded as $d \to 0^+$ and strictly increasing on $(0, z_+)$, it follows that $\phi(z;d) < \phi(z_+;d)$ and so

$$\lim_{d\to 0^+} \mathrm{e}^{[\phi(z;d)-\phi(z_+;d)]/d^\alpha} = 0.$$

Consider

$$\phi''(z_+;d) = \frac{a}{\theta_0 d^\alpha}\left[\dot{V}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + \dot{W}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right)\right].$$

Then

$$d^{\alpha/2}\sqrt{-\phi''(z_+;d)} = \sqrt{\frac{a}{\theta_0}}\sqrt{-\dot{V}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) - \dot{W}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right)}.$$

We have

$$\left|\dot{V}_{\text{in}}(\xi)\right| = \left|-\frac{b}{4\theta_0}\operatorname{sech}^2\frac{b\xi}{2\theta_0}\right| \le \frac{b}{4\theta_0},$$

so that $\dot{V}_{\text{in}}(z_+/d^\alpha)$ remains bounded as $d \to 0^+$. When $\gamma > 2\alpha$

$$|\dot{W}_{\text{in}}(\xi)| = \left|-\frac{b}{4r\theta_0}\operatorname{sech}^2\frac{b\xi}{2\theta_0}\tanh\frac{b\xi}{2\theta_0}\right| \le \frac{b}{4r\theta_0},$$

while for $\gamma = 2\alpha$ we have

$$
\begin{aligned}
|\dot{W}_{\text{in}}(\xi)| &= \left| \frac{c_0}{8} \left[\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi - s)} \operatorname{sech}^2 \frac{bs}{2\theta_0} \, \mathrm{d}s \right.\right. \\
&\qquad \left.\left. - \int_{-\infty}^\xi \mathrm{e}^{-\sqrt{rc_0}(\xi - s)} \operatorname{sech}^2 \frac{bs}{2\theta_0} \, \mathrm{d}s \right] \right| \\
&\leq \frac{c_0}{8} \left[\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi - s)} \, \mathrm{d}s + \int_{-\infty}^\xi \mathrm{e}^{-\sqrt{rc_0}(\xi - s)} \, \mathrm{d}s \right] \\
&= \frac{1}{4} \sqrt{\frac{c_0}{r}}.
\end{aligned}
$$

In either case $\dot{W}_{\text{in}}(z_+/d^\alpha)$ remains bounded as $d \to 0^+$. Hence we deduce from (3.30) that

$$
\lim_{d \to 0^+} u(z; d) = 0,
$$

thus proving the claim that the interstitial gap can be approximated by $(0, z_+)$ with width z_+.

When $\gamma > 2\alpha$, we can actually find z_+ explicitly. Indeed, using (3.14) and (3.16) in (3.28), we obtain

$$
\tanh^2 \frac{bz_+}{2\theta_0 d^\alpha} + 2r \tanh \frac{bz_+}{2\theta_0 d^\alpha} + 4r \left(\frac{1}{a} - \frac{1}{2} \right) - 1 = 0.
$$

This is a quadratic equation in tanh and whose roots are

$$
\tanh \frac{bz_+}{2\theta_0 d^\alpha} = -r \pm \sqrt{r^2 - 2r(2-a)/a + 1}.
$$

Note that the discriminant is always positive since $a \geq 2$. Taking the positive root since $z_+ > 0$ gives

$$
z_+ = \frac{2\theta_0 d^\alpha}{b} \tanh^{-1} \left(-r + \sqrt{r^2 - 2r(2-a)/a + 1} \right).
$$

Differentiating with respect to the parameters yields

$$
\frac{\partial z_+}{\partial a} > 0, \quad \frac{\partial z_+}{\partial b} < 0, \quad \frac{\partial z_+}{\partial d} > 0, \quad \frac{\partial z_+}{\partial r} < 0
$$

for $a \geq 2$. When $\gamma = 2\alpha$, it is not possible to solve for z_+ explicitly but differentiating (3.28) implicitly with respect to the parameters a, b, d and r gives the same relations as for $\gamma > 2\alpha$ (see Appendix B for details).

3.5. Statement of results for slow waves

The results of this section can therefore be summarised as follows:

If we assume that $\theta = \theta_0 d^\alpha$ and $c = c_0 d^{-\gamma}$ where $\theta_0, c_0 = O(1)$ as $d \to 0^+$ and

$$0 < \alpha < 1/2, \quad \gamma \geq 2\alpha,$$

then we obtain the following uniform approximations for $(u, v, w)(z)$:

$$v(z; d) \simeq \frac{1}{2}\left(1 - \tanh \frac{bz}{2\theta_0 d^\alpha}\right),$$

$$u(z; d) \simeq \frac{\theta_0 d^\alpha \mathrm{e}^{\phi(z;d)/d^\alpha}}{\int_z^\infty \mathrm{e}^{\phi(s;d)/d^\alpha}\, \mathrm{d}s},$$

and

$$w(z; d) \simeq \begin{cases} \dfrac{1}{4r}\mathrm{sech}^2 \dfrac{bz}{2\theta_0 d^\alpha} & \text{if } \gamma > 2\alpha, \\ \dfrac{1}{8}\sqrt{\dfrac{c_0}{r}}\left[\displaystyle\int_{z/d^\alpha}^\infty \mathrm{e}^{\sqrt{rc_0}(z/d^\alpha - s)}\mathrm{sech}^2 \frac{bs}{2\theta_0}\,\mathrm{d}s \right. & \\ \qquad \left. + \displaystyle\int_{-\infty}^{z/d^\alpha} \mathrm{e}^{-\sqrt{rc_0}(z/d^\alpha - s)}\mathrm{sech}^2 \frac{bs}{2\theta_0}\,\mathrm{d}s\right] & \text{if } \gamma = 2\alpha. \end{cases}$$

Here,

$$\phi(z; d) = \frac{1}{\theta_0}\int_0^z \left[aV_{\text{in}}\left(\frac{s}{d^\alpha}\right) + aW_{\text{in}}\left(\frac{s}{d^\alpha}\right) - 1\right] \mathrm{d}s,$$

$$V_{\text{in}}(\xi) = \frac{1}{2}\left(1 - \tanh \frac{b\xi}{2\theta_0}\right)$$

and

$$W_{\text{in}}(\xi) = \begin{cases} \dfrac{1}{4r}\mathrm{sech}^2 \dfrac{b\xi}{2\theta_0} & \text{if } \gamma > 2\alpha, \\ \dfrac{1}{8}\sqrt{\dfrac{c_0}{r}}\left[\displaystyle\int_{\xi}^\infty \mathrm{e}^{\sqrt{rc_0}(\xi - s)}\mathrm{sech}^2 \frac{bs}{2\theta_0}\,\mathrm{d}s \right. & \\ \qquad \left. + \displaystyle\int_{-\infty}^{\xi} \mathrm{e}^{-\sqrt{rc_0}(\xi - s)}\mathrm{sech}^2 \frac{bs}{2\theta_0}\,\mathrm{d}s\right] & \text{if } \gamma = 2\alpha. \end{cases}$$

If $a \geq 2$ then we obtain an estimate for the size of the interstitial gap, $z_+ > 0$, given by the solution to the following implicit equation

$$aV_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + aW_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) - 1 = 0.$$

In the case $\gamma > 2\alpha$ we obtain the explicit formula

$$z_+ = \frac{2\theta_0 d^\alpha}{b} \tanh^{-1}\left(-r + \sqrt{r^2 - 2r(2-a)/a + 1}\right).$$

Differentiating z_+ with respect to the parameters yields

$$\frac{\partial z_+}{\partial a} > 0, \quad \frac{\partial z_+}{\partial b} < 0, \quad \frac{\partial z_+}{\partial d} > 0, \quad \frac{\partial z_+}{\partial r} < 0.$$

4. Numerical results

We performed a numerical simulation of our model to obtain an idea of important variables and terms affecting the development of the model and also to confirm the validity of the asymptotic approximations. We solved the system of partial differential equations (1.5)–(1.7) over a large time period by applying a forward finite-difference scheme. Due to boundary conditions at infinity we made the assumption that for values of x at a large enough distance from where the cell densities and acid concentration perform a rapid change, our solution will remain approximately constant for a very large period of time. Without loss of generality we make this rapid change occur initially about $x = 0$. Hence, under this assumption the gradients of u, v and w will be zero, and as such we applied a homogeneous Neumann boundary condition at large values $x = -L_1$ and $x = L_2$ where $L_1, L_2 \gg 1$. The initial conditions are given by piecewise linear functions as shown in Figure 3. The initial conditions show that the tumour population is at carrying capacity and then decreases to zero within the domain, where the normal tissue is initially present at a low density in the tumour region and then increases to carrying capacity in the tumour vacant region. The acid concentration is initially zero. Due to the nature of the initial conditions and that a travelling wave solution forms in the numerical simulations it is apparent that the system is not sensitive to initial conditions. Examples of the solutions obtained for different parameter values can be seen in Figures 4a–4e. Note that for each of these figures there is a given speed. This speed was not used in the calculation of these solutions, rather the speed has been obtained via a parameter estimation technique that determines a value for θ by matching the data obtained from solving the system of partial differential equations (1.5)–(1.7) at the final timestep to the ordinary differential equation (1.9). The technique used is an integration-based estimation technique outlined in Holder and Rodrigo (2013) (see Appendix C for further details). As a result we were able to plot the asymptotic approximations, given by Figures 2a and 2b respectively, for the parameter values used to obtain the numerical solutions displayed in Figures 4a and 4b respectively.

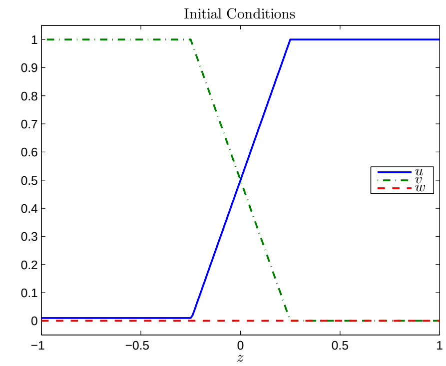
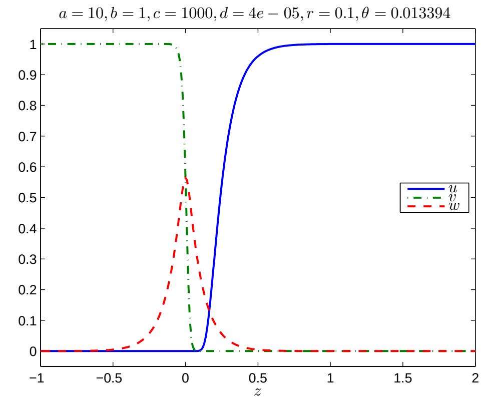
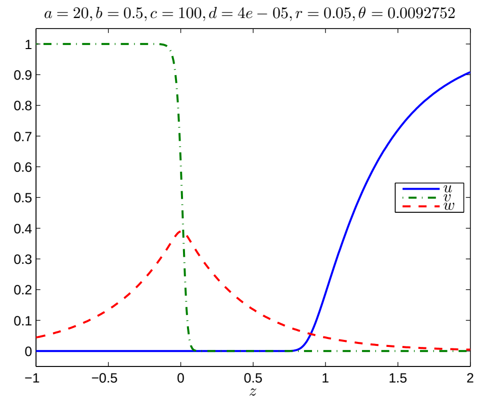


Figure 3: Initial conditions for numerical simulations

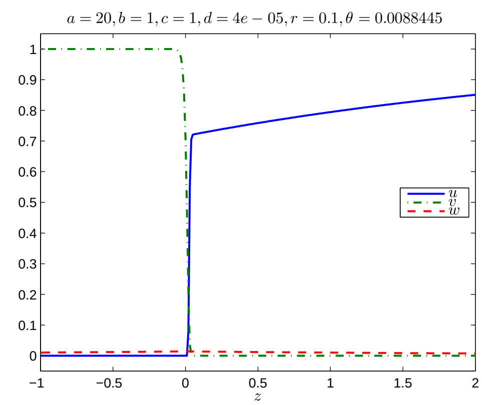
We observe from Figures 4c, and 4d that for small values of c we attain solutions of the H^+ ions that represent low concentrations at any point thus giving justification to the assumption made in the analysis of the slow TWs that c must be large. In Figure 4b we have an example of an interstitial gap predicted by the numerical modelling for certain parameter values. The analytical analysis of our estimate for the gap, in Section 3, suggests that along with the parameter assumptions $d \ll 1$ and $c \gg 1$ that if a is sufficiently large (i.e. $a \geq 2$) and b and r are sufficiently small then the numerical solutions should display an interstitial gap. We also compare Figures 2a and 2b to Figures 4a and 4b, respectively, and note that the asymptotic approximations produced in the case $\gamma = 2\alpha$ are in excellent agreement with the numerically obtained solutions. We note that in the case $\gamma > 2\alpha$ the asymptotic solutions produced did not provide a good fit to the numerical solutions for the parameter values considered. This would suggest that the values for c used in the numerical simulations were not sufficiently large so that this would provide a good approximation. However, when larger values of c were used, the numerical simulations were unstable due to the use of an explicit scheme. While an implicit scheme may be able to prevent this instability, this would not be straightforward to implement since we are considering a system of PDEs with a nonlinear diffusion term. As such, we intend to explore the issue of efficient numerical approximations elsewhere.



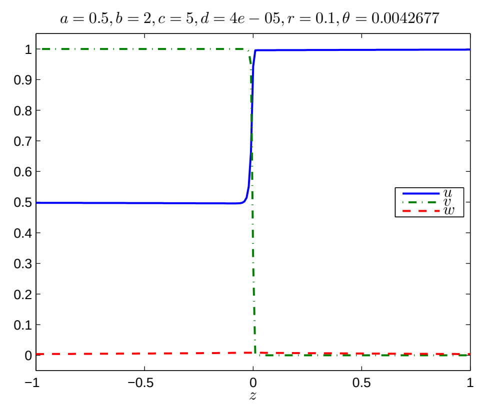
(a) $(a, b, c, d, r, \theta) = (10, 1, 1000, 4 \times 10^{-5}, 0.1, 0.0134)$



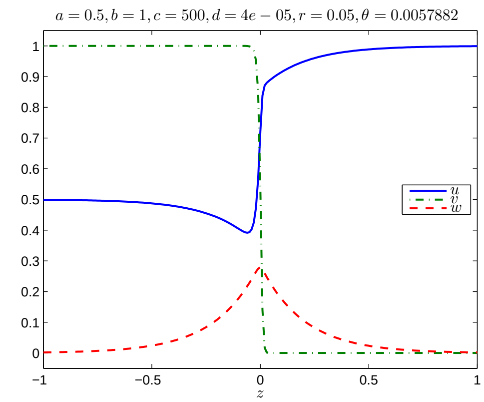
(b) $(a, b, c, d, r, \theta) = (20, 0.5, 100, 4 \times 10^{-5}, 0.05, 0.0093)$



(c) $(a, b, c, d, r, \theta) = (20, 1, 1, 4 \times 10^{-5}, 0.1, 0.0088)$



(d) $(a, b, c, d, r, \theta) = (0.5, 2, 5, 4 \times 10^{-5}, 0.1, 0.0043)$



(e) $(a, b, c, d, r, \theta) = (0.5, 1, 500, 4 \times 10^{-5}, 0.05, 0.0058)$

Figure 4: Numerical approximations of (1.5)–(1.7): In (c) and (d) a low value of c is used resulting in low levels of acid being produced and then diffusing over a wide region of the domain. As a result of this low acid concentration normal cell destruction is primarily due to competition in the region of the tumour-host interface, resulting in a steep profile change in the normal cell population when the tumour cell population undergoes a steep change. In (c) a large value of a is used and as a result of the low acid concentration over a wide region normal cell destruction decreases at a gradual rate in the tumour vacant region.

5. Conclusions

In this article we proposed a reaction-diffusion model for the process of acid-mediated tumour growth that is an altered version of the model originally proposed by Gatenby and Gawlinski (1996). While the models appear similar, their dynamics and solutions are significantly different. The model proposed by Gatenby and Gawlinski (1996) postulates that an excess of H^+ ions is produced by the tumour cells due to their anaerobic, glycolytic metabolism. The excess of H^+ ions is concentrated at the neoplastic-normal tissue interface. This creates a region of lowered pH ahead of the advancing tumour. Moreover, for certain parameter values, healthy tissue could be destroyed prior to the arrival of malignant cells. This would result in the formation of an interstitial gap, where the concentrations of neoplastic and normal tissue are close to zero. The most noticeable difference between the proposed model and that of Gatenby and Gawlinski's is that concentration of H^+ ions is in the form of a pulse and not a front. This difference is due to the hypothesis that the production of H^+ ions is considered to be proportional to the tumour cell density until the latter reaches a threshold, after which the production rate decreases as the tumour cell density reaches its saturation level. This creates a localised region of acid production and concentration. As a consequence of this hypothesis we find that a high production rate of H^+ ions is required, which would indicate a high dependence on glycolysis. This currently is only a hypothesis, but due to the positive results from our asymptotic solutions and numerical analysis, this suggests it warrants mathematical and experimental investigation. Our conducted analysis was unable to determine the dependence of the wave speed on the system parameters. Hence an analytical exploration of the effect of the system parameters on the speed would enlighten us further to the effects of the localised acid production hypothesis and allow us to better compare our model with Gatenby and Gawlinski's original model (Gatenby and Gawlinski, 1996) and that proposed by McGillen et al. (2013). This analysis of the speed and the factors that cause it to change would provide predictions that potentially could be tested experimentally assuming the relevant predictions and factors affecting them are able to be observed and quantified. We note that our investigation puts a greater importance on population competition than that proposed in Gatenby and Gawlinski (1996) and we find that our hypothesis requires competition whereas Gatenby and Gawlinski's does not. In comparison to the model proposed by McGillen et al. (2013) in which the model permits conditions on the system such that the tumour population does not invade but is cleared from the system, our model only considers invasion as in Gatenby and Gawlinski (1996).

We undertook an analytical and preliminary numerical analysis of the proposed model (1.1)–(1.3). We showed that this model is compatible with various types of fast and slow TW solutions. The biological significance of the fast TW solutions is unclear and would seem to represent a purely mathematical feature. We note the slow solution is dependent on two introduced parameters α and γ, such that the uniform approximation is obtained for $0 < \alpha < 1/2$ and $\gamma \geq 2\alpha$. This restriction on the parameters has been visualised in Figure 5 in which we can see the shaded region represents the area for which we found asymptotic solutions in the α–γ plane. The white region in the positive cone represents a region in which our analysis did not give a uniform solution.

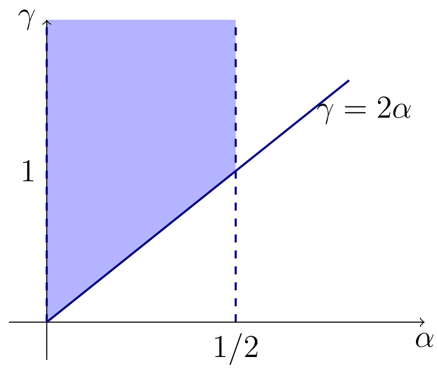


Figure 5: Shaded area represents region of uniform solutions for the slow TWs in the α–γ plane

We also characterised conditions under which an interstitial gap, a region almost devoid of neoplastic and normal cells, exists and have given an implicit formula for calculating an approximation of the gap width. This formula can be made explicit when $\gamma > 2\alpha$. Our results point to the existence of a gap when $a \geq 2$ with the estimate for its width being the value z_+ given by solving (3.28). This condition is consistent with the prediction made by Gatenby and Gawlinski (1996) and Fasano et al. (2009) that an interstitial gap can only be achieved by a sufficiently aggressive tumour. We further found that this estimate for the gap would increase with respect to the parameters a and d and decreases with respect to the parameters b and r. Specifically, the prediction that the gap increases with respect a implies that the greater the destructive influence of the tumour, the greater the size of interstitial gap as is predicted in Fasano et al. (2009). The increase in z_+ with respect to d suggests that as the cell motility decreases, so too does the size of the interstitial gap. The prediction that the gap decreases with respect to b suggests that if the production of tumour cells is faster than the normal cells, then the interstitial gap should be decreased and if the tumour cell production rate decreases or the normal cell production rate increases the converse would be true. We see that z_+ decreasing with respect to r predicts that if the uptake of acid increases then the size of the interstitial gap should decrease and if the uptake decreases the converse would be true. This analysis suggests that an examination, either mathematically or experimentally, of the distribution and density of blood vessels in the tumour region and the resulting effect that these have on acid-mediated growth would be valuable. This would represent a challenging exercise due to other system dynamics that would change as a result of changed blood vessel distribution such as nutrient dynamics. This model predicts an influence on the interstitial gap from a greater number of the parameters within this model than of that described in Fasano et al. (2009). This insight into the behaviour of the gap is valuable in developing potential treatment strategies to treat acid-mediated tumour growth. We also remark that due to the pulse-like nature of the acid profile we have that the concentration of H^+ ions is primarily located in the region of the interstitial gap. This model prediction is in line with what has been observed experimentally (Dellian et al., 1996; Helmlinger et al., 1997; Martin and Jain, 1994).

The linear stability of the fast TWs was shown to hold when $a \neq 1$ for all strictly positive parameter values. A mathematical analysis of the linear stability of the slow TWs is more involved due to the use of matched asymptotic solutions in order to obtain our approximations. However from numerical simulations conducted we would expect these solutions to be linearly stable. We note also the excellent fit of these asymptotic solutions obtained in the case $\gamma = 2\alpha$ to the data obtained from solving the system (1.5)–(1.7) numerically. The case where $\gamma = 2\alpha$ implies that the acid production is small enough in relation to the speed of the wave that acid diffusion is still an important factor in the system's dynamics. The case in which $\gamma > 2\alpha$ suggests that acid diffusion becomes less significant and hence is not a factor in determining the leading order approximation.

The model herein presented is a first attempt at considering nonlinear acid-production mechanisms. A possible extension could be carried out within the framework proposed in McGillen et al. (2013), with the inclusion of strong competition between normal and neoplastic tissue, as well as potential negative acid effect on tumour progression. We also note that the model we have proposed has the potential to be extended to include further growth promoting and inhibiting mechanisms such as haptotaxis and an immunotherapeutic response. This analysis could illuminate how to improve or develop treatment strategies for acid-mediated tumour growth. It could also guide future experimental analyses and research into the mechanisms behind acid-mediated tumour growth. An analysis in higher dimensional geometries remains to be conducted as well as a rigorous proof of existence. However, both the asymptotic and numerical analysis conducted in this article suggests the existence of a stable and unique class of solutions.

Appendix A. Auxillary results

Lemma 5. *Consider the equation*

$$W'' + \theta W' - \beta W = f(z) \tag{A.1}$$

where $\theta \geq 0$, $\beta > 0$ *and* f *is a bounded piecewise continuous function. Let*

$$W(z) = \frac{1}{\eta_2 - \eta_1}\left[I_1(z) + I_2(z)\right] \tag{A.2}$$

where

$$\eta_1 = \frac{-\theta + \sqrt{\theta^2 + 4\beta}}{2} > 0, \quad \eta_2 = \frac{-\theta - \sqrt{\theta^2 + 4\beta}}{2} < 0 \tag{A.3}$$

and

$$I_1(z) = \int_z^{\infty} e^{\eta_1(z-s)} f(s)\,\mathrm{d}s, \quad I_2(z) = \int_{-\infty}^{z} e^{\eta_2(z-s)} f(s)\,\mathrm{d}s. \tag{A.4}$$

Then (A.2)–(A.4) *solves* (A.1)*. Moreover, should* f *possess bounded limits at infinity, i.e. if* $f(\pm\infty) = \lim_{z\to\pm\infty} f(z)$ *both exist, then*

$$\begin{aligned}
I_1(\infty) &= \frac{f(\infty)}{\eta_1},\\
I_1(-\infty) &= \begin{cases} 0 & \text{if } \int_{-\infty}^{\infty} e^{-\eta_1 s} f(s)\,\mathrm{d}s \text{ is finite,}\\ \frac{f(-\infty)}{\eta_1} & \text{if } \int_{-\infty}^{\infty} e^{-\eta_1 s} f(s)\,\mathrm{d}s \text{ is infinite,}\end{cases}\\
I_2(\infty) &= \begin{cases} 0 & \text{if } \int_{-\infty}^{\infty} e^{-\eta_2 s} f(s)\,\mathrm{d}s \text{ is finite,}\\ -\frac{f(\infty)}{\eta_2} & \text{if } \int_{-\infty}^{\infty} e^{-\eta_2 s} f(s)\,\mathrm{d}s \text{ is infinite,}\end{cases}\\
I_2(-\infty) &= -\frac{f(-\infty)}{\eta_2}.
\end{aligned}$$

Proof. See Fasano et al. (2009) for a proof. □

Lemma 6. *For a continuous function* g *with bounded limits at infinity, let*

$$\Phi(z) = e^{-\int_0^z g(s)\,\mathrm{d}s}.$$

Then the following statements hold:

(i) *If* $g(\infty) > 0$*, then* $\Phi(\infty) = 0$*;*

(ii) *If* $g(\infty) < 0$*, then* $\Phi(\infty) = \infty$*;*

(iii) *If* $g(-\infty) > 0$*, then* $\Phi(-\infty) = \infty$*;*

(iv) *If* $g(-\infty) < 0$, *then* $\Phi(-\infty) = 0$.

Proof. See Fasano et al. (2009) for a proof. □

Lemma 7. *Let* $(u, v, w) = (u, v, w)(z; d)$ *denote a solution to* (1.9)–(1.12)*, if any. Then the problem* (1.9)–(1.12) *is equivalent to the following:*

$$0 = d[(1-u)v'' - u'v'] + \theta v' + bv(1-v),\ \ v(-\infty; d) = 1,\ \ v(\infty; d) = 0 \tag{A.5}$$

where

$$u(z; d) = \frac{\theta \Phi(z; d)}{\int_z^\infty \Phi(s; d)\, \mathrm{d}s},\ \ \Phi(z; d) = e^{-\int_0^z [1 - av(s;d) - aw(s;d)]/\theta\, \mathrm{d}s}, \tag{A.6}$$

$$\begin{aligned} w(z; d) = \frac{c}{\eta_1 - \eta_2} \Bigg\{ \int_z^\infty & e^{\eta_1 (z-s)} v(s; d)[1 - v(s; d)]\, \mathrm{d}s \\ & + \int_{-\infty}^z e^{\eta_2 (z-s)} v(s; d)[1 - v(s; d)]\, \mathrm{d}s \Bigg\} \end{aligned} \tag{A.7a}$$

and

$$\eta_1 = \frac{-\theta + \sqrt{\theta^2 + 4cr}}{2} > 0,\ \ \eta_2 = \frac{-\theta - \sqrt{\theta^2 + 4cr}}{2} < 0. \tag{A.7b}$$

Proof. Equation (A.5) is the same as (1.10) with corresponding boundary conditions for v. We can apply Lemma 5 to (1.11) where $\beta = cr$ and $f(s) = -cv(s; d)[1 - v(s; d)]$ to obtain (A.7). Since $f(\pm\infty) = -cv(\pm\infty; d)[1 - v(\pm\infty; d)] = 0$ we see that $I_1(\pm\infty) = I_2(\pm\infty) = 0$ from Lemma 5. Therefore $w(\pm\infty; d) = 0$ and the corresponding BCs in (1.12) hold. Equation (1.9) is a Bernoulli-type equation and can be solved explicitly to formally give (A.6).

Let

$$g(s) = \frac{1 - av(s; d) - aw(s; d)}{\theta}.$$

Then $g(\infty) = 1/\theta$ and therefore $\Phi(\infty; d) = 0$ by Lemma 6. Using L'Hôpital's Rule in (A.6) verifies that $u(\infty; d) = 1$. Similarly, $g(-\infty) = (1 - a)/\theta$.

When $a > 1$ we have $g(-\infty) < 0$; hence $\Phi(-\infty; d) = 0$ by Lemma 6. Since $0 < \int_{-\infty}^\infty \Phi(s; d)\, \mathrm{d}s \le \infty$ we infer from (A.6) that $u(-\infty; d) = 0$. In the case $0 < a < 1$ we have $g(-\infty) > 0$, and so $\Phi(-\infty; d) = \infty$. Applying L'Hôpital's Rule to (A.6) gives $u(-\infty; d) = 1 - a$. When $a = 1$ we note that $g(-\infty) = 0$, so that $0 < \Phi(-\infty; d) \le \infty$ and as a result $\int_{-\infty}^\infty \Phi(s; d)\, \mathrm{d}s = \infty$. So if $\Phi(-\infty; d)$ is finite, then it follows that $u(-\infty; d) = 0$. However if $\Phi(-\infty; d)$ is infinite, then L'Hôpital's Rule in (A.6) again gives $u(\infty; d) = 0$. □

Lemma 8. *Let $J = [z_0, \infty)$ and assume that w solves an equation of the form*

$$w'(z) = F(z, w(z)) \tag{A.8}$$

where $F \in C^1(J \times w(J))$. Suppose that

$$D_1F(z,p) < 0$$

for all $(z,p) \in J \times w(J)$.

(i) *If $w'(z^*) = 0$ for some $z^* \in J$, then $w'(z) > 0$ for all $z \in [z_0, z^*)$ and $w'(z) < 0$ for all $z \in (z^*, \infty)$;*

(ii) *If $w'(z_0) < 0$, then $w'(z) < 0$ for all $z > z_0$.*

Proof. We see that

$$w''(z) = D_1F(z, w(z)) + D_2F(z, w(z))w'(z).$$

Therefore at any point $z \in J$ where $w'(z) = 0$ we have

$$w''(z) = D_1F(z, w(z)) < 0, \tag{A.9}$$

i.e. w would have a local maximum at z. Now suppose that $w'(z^*) = 0$ for some $z^* \in J$. It then follows that w has a local maximum at z^*.

(i) Suppose that there exists $z_1 \in (z^*, \infty)$ such that $w'(z_1) \geq 0$. If $w'(z_1) = 0$, then w will also have a local maximum at z_1. Since there are two local maxima at z^* and z_1 there must exist a local minimum at some $z_2 \in (z^*, z_1)$. This implies that $w'(z_2) = 0$, which would mean that w will have a local maximum at z_2, a contradiction. On the other hand, suppose that $w'(z_1) > 0$. Since w has a local maximum at z^* we can find $\delta_1 > 0$ small enough (e.g. $\delta_1 < z_1 - z^*$) such that $w'(z) < 0$ for all $z \in (z^*, z^* + \delta_1)$. In particular, $w'(z^* + \delta_1/2) < 0$. Over the interval $[z^* + \delta_1/2, z_1]$ we therefore have $w'(z^* + \delta_1/2)w'(z_1) < 0$. By Bolzano's Theorem there exists $z_3 \in (z^* + \delta_1/2, z_1)$ such that $w'(z_3) = 0$. But this brings us back to case above when $w'(z_1) = 0$. Therefore $w'(z) < 0$ for all $z \in (z^*, \infty)$. An almost identical argument can be given to show that $w'(z) > 0$ for all $z \in [z_0, z^*)$.

(ii) Suppose that there exists $z_4 \in (z_0, \infty)$ such that $w'(z_4) \geq 0$. If $w'(z_4) = 0$, then w has a local maximum at z_4. Then there exists $\delta_2 > 0$ small enough (e.g. $\delta_2 < z_4 - z_0$) such that $w'(z) > 0$ for all $z \in (z_4 - \delta_2, z_4)$. In particular, $w'(z_4 - \delta_2/2) > 0$. Hence, over the interval $[z_0, z_4 - \delta_2/2]$, we have $w'(z_0)w'(z_4 - \delta_2/2) < 0$. By Bolzano's Theorem there exists $z_5 \in (z_0, z_4 - \delta_2/2)$ such that $w'(z_5) = 0$. This implies that w

has a local maximum at z_5; hence $w'(z_5) = 0$. Since we have two local maxima at z_4 and z_5, there must exist a local minimum of w at some $z_6 \in (z_4, z_5)$. Necessarily it follows that $w'(z_6) = 0$. But we saw that this implies that w has a local maximum at z_6, a contradiction. On the other hand, if $w'(z_4) > 0$, then $w'(z_0)w'(z_4) < 0$ and Bolzano's Theorem again implies that there exists $z_7 \in (z_0, z_4)$ such that $w'(z_7) = 0$. But this brings us back to case above when $w'(z_4) = 0$. Therefore, if $w'(z_0) < 0$, then $w'(z) < 0$ for all $z > z_0$. □

Lemma 9. *Let $\phi(\cdot; d)$ be a continuous function, $-\infty \leq s_L < s_R \leq \infty$ and $\alpha > 0$. Consider the integral*

$$I(d) = \int_{s_L}^{s_R} e^{\phi(s;d)/d^\alpha} \, \mathrm{d}s$$

as $d \to 0^+$. If $\phi(\cdot; d)$ is bounded as $d \to 0^+$, then the following statements hold:

(i) *If $\phi'(s; d) < 0$ for $s_L \leq s < s_R$, then*

$$I(d) \simeq -\frac{d^\alpha \, e^{\phi(s_L;d)/d^\alpha}}{\phi'(s_L; d)};$$

(ii) *If $\phi'(s; d) > 0$ for $s_L < s \leq s_R$, then*

$$I(d) \simeq \frac{d^\alpha \, e^{\phi(s_R;d)/d^\alpha}}{\phi'(s_R; d)};$$

(iii) *Suppose that ϕ has a unique maximum at some $s_L < s^* < s_R$. Then*

$$I(d) \simeq \frac{\sqrt{2\pi} d^{\alpha/2} \, e^{\phi(s^*;d)/d^\alpha}}{\sqrt{-\phi''(s^*; d)}}.$$

Proof. We use Laplace's method to approximate integrals containing a large parameter (Bender and Orszag, 1999, pp. 266–267). Note that a small adjustment of the proof provided in Bender and Orszag (1999) needs to be made due to the dependence of ϕ on d. □

Appendix B. Properties of interstitial gap estimate

We wish to show that for z_+ obtained from solving (3.28) in the case $\gamma = 2\alpha$, we have that differentiating with respect to the parameters yields

$$\frac{\partial z_+}{\partial a} > 0, \quad \frac{\partial z_+}{\partial b} < 0, \quad \frac{\partial z_+}{\partial d} > 0, \quad \frac{\partial z_+}{\partial r} < 0$$

for $a \geq 2$.

Suppose that $a \geq 2$, then from Lemma 4 we know that $z_+ > 0$. We determine the derivatives of z_+ with respect to the parameters by differentiating (3.28) implicitly. We first consider the derivative with respect to a, noting that $V_{\text{in}}(\xi)$ and $W_{\text{in}}(\xi)$ do not depend on a: Differentiating (3.28) with respect to a gives,

$$V_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + V_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + \frac{a}{d^\alpha}\frac{\partial z_+}{\partial a}\left[\dot{V}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + \dot{W}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right)\right] = 0.$$

Rearranging this gives

$$\frac{\partial z_+}{\partial a} = -\frac{d^\alpha}{a}\frac{V_{\text{in}}\left(z_+/d^\alpha\right) + V_{\text{in}}\left(z_+/d^\alpha\right)}{\dot{V}_{\text{in}}\left(z_+/d^\alpha\right) + \dot{W}_{\text{in}}\left(z_+/d^\alpha\right)}.$$

We know that $V_{\text{in}}(\xi), W_{\text{in}}(\xi) > 0$ and $\dot{V}_{\text{in}}(\xi), \dot{W}_{\text{in}}(\xi) < 0$ for all $\xi > 0$ and that $z_+ > 0$, therefore we can conclude

$$\frac{\partial z_+}{\partial a} > 0$$

for $a \geq 2$.

We consider the derivative of z_+ with respect to b, noting that $V_{\text{in}}(\xi)$ and $W_{\text{in}}(\xi)$ depend on b: Differentiating (3.28) with respect to b gives,

$$a\frac{\partial}{\partial b}\left(V_{\text{in}} + W_{\text{in}}\right)\Big|_{z_+/d^\alpha} + \frac{a}{d^\alpha}\frac{\partial z_+}{\partial b}\left[\dot{V}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right) + \dot{W}_{\text{in}}\left(\frac{z_+}{d^\alpha}\right)\right] = 0.$$

Rearranging this gives

$$\frac{\partial z_+}{\partial b} = -d^\alpha\frac{\frac{\partial}{\partial b}\left(V_{\text{in}} + W_{\text{in}}\right)\Big|_{z_+/d^\alpha}}{\dot{V}_{\text{in}}(z_+/d^\alpha) + \dot{W}_{\text{in}}(z_+/d^\alpha)}.$$

We see that

$$\frac{\partial V_{\text{in}}}{\partial b} = -\frac{\xi}{2\theta_0}\operatorname{sech}^2\frac{b\xi}{2\theta_0}$$

which is less than zero for all $\xi > 0$. We also have

$$\frac{\partial W_{\text{in}}}{\partial b} = -\frac{1}{8\theta_0}\sqrt{\frac{c_0}{r}}\left[\int_\xi^\infty e^{\sqrt{rc_0}(\xi-s)}s\tanh\frac{bs}{2\theta_0}\operatorname{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s + \int_{-\infty}^\xi e^{-\sqrt{rc_0}(\xi-s)}s\tanh\frac{bs}{2\theta_0}\operatorname{sech}^2\frac{bs}{2\theta_0}\,\mathrm{d}s\right].$$

We note that

$$s \tanh \frac{bs}{2\theta_0} \mathrm{sech}^2 \frac{bs}{2\theta_0},$$

is a positive even function and this implies

$$\frac{\partial W_{\mathrm{in}}}{\partial b} > 0 \quad \forall \xi \in \mathbb{R}.$$

Since $z_+ > 0$, we conclude for $a \geq 2$ that

$$\frac{\partial z_+}{\partial b} < 0.$$

We consider the derivative of z_+ with respect to d, noting that $V_{\mathrm{in}}(\xi)$ and $W_{\mathrm{in}}(\xi)$ do not depend on d: Differentiating (3.28) with respect to d gives,

$$a \left[\frac{1}{d^\alpha} \frac{\partial z_+}{\partial d} - \frac{\alpha z_+}{d^{1+\alpha}} \right] \left[\dot{V}_{\mathrm{in}} \left(\frac{z_+}{d^\alpha} \right) + \dot{W}_{\mathrm{in}} \left(\frac{z_+}{d^\alpha} \right) \right] = 0.$$

Since $\dot{V}_{\mathrm{in}}(\xi), \dot{W}_{\mathrm{in}}(\xi) < 0$ for $\xi > 0$ and $z_+ > 0$ we have that

$$\frac{\partial z_+}{\partial d} = \frac{\alpha}{d} z_+,$$

and hence for $a \geq 2$

$$\frac{\partial z_+}{\partial d} > 0.$$

We consider the derivative of z_+ with respect to r, noting that $V_{\mathrm{in}}(\xi)$ does not depend on r where as $W_{\mathrm{in}}(\xi)$ does: Differentiating (3.28) with respect to r gives,

$$a \left. \frac{\partial W_{\mathrm{in}}}{\partial r} \right|_{z^+/d^\alpha} + \frac{a}{d^\alpha} \frac{\partial z_+}{\partial r} \left[\dot{V}_{\mathrm{in}} \left(\frac{z_+}{d^\alpha} \right) + \dot{W}_{\mathrm{in}} \left(\frac{z_+}{d^\alpha} \right) \right] = 0.$$

Rearranging this gives

$$\frac{\partial z_+}{\partial r} = -d^\alpha \frac{\left. \frac{\partial W_{\mathrm{in}}}{\partial r} \right|_{z^+/d^\alpha}}{\dot{V}_{\mathrm{in}}(z_+/d^\alpha) + \dot{W}_{\mathrm{in}}(z_+/d^\alpha)}.$$

We see that

$$\begin{aligned} \frac{\partial W_{\mathrm{in}}}{\partial r} = & - \frac{1}{16r} \sqrt{\frac{c_0}{r}} \left[\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi - s)} \mathrm{sech}^2 \frac{bs}{2\theta_0} \, \mathrm{d}s + \int_{-\infty}^\xi \mathrm{e}^{-\sqrt{rc_0}(\xi - s)} \mathrm{sech}^2 \frac{bs}{2\theta_0} \, \mathrm{d}s \right] \\ & - \frac{1}{16} \frac{c_0}{r} \left[\int_\xi^\infty \mathrm{e}^{\sqrt{rc_0}(\xi - s)} (s - \xi) \mathrm{sech}^2 \frac{bs}{2\theta_0} \, \mathrm{d}s \right. \\ & \left. + \int_{-\infty}^\xi \mathrm{e}^{-\sqrt{rc_0}(\xi - s)} (\xi - s) \mathrm{sech}^2 \frac{bs}{2\theta_0} \, \mathrm{d}s \right]. \end{aligned}$$

Since for all $\xi \in \mathbb{R}$, we have $(s - \xi) > 0$ for $s > \xi$ and $(\xi - s) > 0$ for $s < \xi$, we then have

$$\left.\frac{\partial W_{\text{in}}}{\partial r}\right|_{z_+/d^\alpha} < 0,$$

for all $\xi \in \mathbb{R}$ and hence we conclude for $a \geq 2$ that

$$\frac{\partial z_+}{\partial r} < 0.$$

Appendix C. Speed Estimation

We outline the details of the parameter estimation technique used to estimate the speed of the travelling waves from the numerically generate solutions in Section 4. Following the procedure outlined in Holder and Rodrigo (2013) we consider equation (1.9) to obtain our estimate for θ. We assume that $(u, v, w)(z)$ are observed over some interval $I \subset \mathbb{R}$ and we consider a weight function $\phi : I \to \mathbb{R}$ where ϕ and ϕ' exist and are integrable. We note that (1.9) was chosen since it is first order and hence makes the application of this method slightly simpler (If we were to choose (1.10) or (1.11) to estimate θ we would require estimates for the relevant derivatives of u, v, w at the endpoints of the interval or alternatively in the case of (1.11) we would require ϕ be zero at the endpoints of the interval I). Multiply (1.9) by the weight function $\phi(z)$ and integrate over the interval I using integration by parts to obtain

$$\left[\phi(z)u(z)|_I - \int_I \phi'(z)u(z)\,\mathrm{d}z\right]\theta + \int_I \phi(z)u(z)[1 - u(z) - av(z) - aw(z)]\,\mathrm{d}z = 0. \tag{C.1}$$

Since we are estimating just one parameter we choose $\phi(z) = 1$ for simplicity. Therefore, rearranging (C.1), we obtain

$$\theta = -\frac{\int_I u(z)(1 - u(z) - av(z) - aw(z))\,\mathrm{d}z}{u(z)|_I}. \tag{C.2}$$

If we have observed data for u, v, w on some interval I, then we can then estimate the value for θ by evaluating the integrals contained in (C.2) numerically. Since our solutions for (1.5)–(1.7) are TWs, the profile of the solutions are therefore time invariant. Hence we can use the values obtained from solving this system numerically (after a sufficiently large time) as our observed values for u, v, w and the domain of our numerical solution as our interval I.

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