

Slow and fast invasion waves in a model of acid-mediated tumour growth

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Abstract

This work is concerned with a reaction-diffusion system that has been proposed as a model to describe acid-mediated cancer invasion. More precisely, we consider the properties of travelling waves that can be supported by such a system, and show that a rich variety of wave propagation dynamics, both fast and slow, is compatible with the model. In particular, asymptotic formulae for admissible wave profiles and bounds on their wave speeds are provided.

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1 Introduction

In recent years quantitative models of tumour growth have attracted considerable attention [1]–[4], [6]–[8], [12], [23]. Amongst the various modelling tools that have been employed, the use of travelling waves (TWs) plays a prominent role. Indeed, ever since their introduction in the seminal papers by Fisher [9] and Kolmogorov, Petrovsky, and Piskunov [15], TWs have appealed to the imagination of scientists, providing what is arguably the simplest mathematical model to describe the invasion of a state by another.

An example of a TW is a function of the form $u(x, t) = U(x - \theta t)$ where x is a one-dimensional spatial variable and t is time. These waves propagate along the real line with a fixed profile and with a constant wave speed θ . The function U is usually normalised according to the context of the problem, and is required to satisfy boundary conditions at infinity, say $U(-\infty) = 1$ and $U(\infty) = 0$. Such TWs are called *fronts*. If $\theta > 0$, for example, then the wave front propagates to the right so that the state $u^* = 1$ eventually takes over the state $u^* = 0$.

We point out that fronts are merely a particular case of TWs. Depending on the nature of the underlying biological or physical problem and the relevant space dimension, we can consider pulses [13], target and spiral waves [14], [16], and scroll waves [24], [25], to mention but some of the variety of situations addressed in the literature.

This work is motivated by a model of tumour invasion for which the existence of front-type TWs has been postulated. More precisely, Gatenby and Gawlinski [10], [11] proposed a reaction-diffusion model in which tumour cells, as a consequence of their anaerobic, glycolytic metabolism, produce an excess of H^+ ions. This results in local acidification and subsequent destruction of the surrounding healthy tissue, which in turn facilitates tumour invasion. The situation considered in [10], [11] corresponds to a one-dimensional setting and was later extended to consider higher-dimensional geometries, as well as the occurrence of necrotic cores [19] and the glucose dynamics [6].

After a suitable rescaling, a reaction-diffusion system was obtained in [10] that can be formulated as follows:

$$u_t = u(1 - u) - auw, \tag{1.1}$$

$$v_t = d[(1 - u)v_x]_x + bv(1 - v), \tag{1.2}$$

$$w_t = w_{xx} + c(v - w). \tag{1.3}$$

Here u , v , and w correspond to nondimensional, rescaled versions of the concentrations of healthy tissue, neoplastic tissue, and excess H^+ ions, respectively. As a consequence of the scaling used in [10], these functions satisfy $0 \leq u, v, w \leq 1$ and depend on x and t , which are nondimensional variables obtained from the original space and time coordinates, respectively. The subscripts denote partial derivatives with respect to the corresponding variables. The constants a , b , c , and d are all nonnegative.

Each of the model parameters has a corresponding biological interpretation. For instance, b represents the production rate of neoplastic tissue which according to (1.3) pumps H^+ ions at a rate c . Equation (1.2) describes the variation in space and time of the concentration of malignant tissue as a consequence of its internal population dynamics (as described by the last term) and diffusion. The latter is accounted for by the second term in (1.2), and is of a nonlinear character. Incidentally, when $u \equiv 0$ (i.e., healthy tissue is absent), then (1.2) reduces to the classical Fisher-KPP equation [9], [15]

$$v_t = dv_{xx} + bv(1 - v), \quad (1.4)$$

which is a prototypical example of a reaction-diffusion equation that exhibits front-type TWs. A remarkable fact about it is that a continuum of wave speeds exists that satisfies $\theta \geq 2\sqrt{bd}$. In the case of (1.2) the diffusivity of neoplastic tissue is no longer constant as in (1.4) but is impaired by the presence of healthy tissue.

In the quantitative discussions presented in [10], d was assumed to be a small parameter, i.e.,

$$0 < d \ll 1, \quad (1.5)$$

an assumption which is to be retained throughout this paper. The motivation for (1.5) comes from the fact that d is shown to be of the form $d = D_2/D_3$ where D_2 and D_3 are the respective diffusivities of malignant tissue and H^+ ions. It is therefore natural to assume that D_3 is much larger than D_2 . Finally, the parameter a in (1.1) measures the destructive influence of H^+ ions on the healthy tissue, and therefore its value can be taken as an indicator of tumour aggressivity.

An interesting phenomenon which has been observed experimentally, and also discussed in [10], is the appearance in many cases of tumour propagation of an interstitial gap, i.e., a region practically depleted of cells located right ahead of the invading tumour front. Figure 1 shows a stained micrograph of a specimen corresponding to human squamous cell carcinoma displaying an acellular gap between normal and tumour tissue edges (see arrows). A further discussion of this gap will be provided later.

We now proceed to describe in detail the type of TW solutions to be considered in this work. With a slight abuse of notation, let us write

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

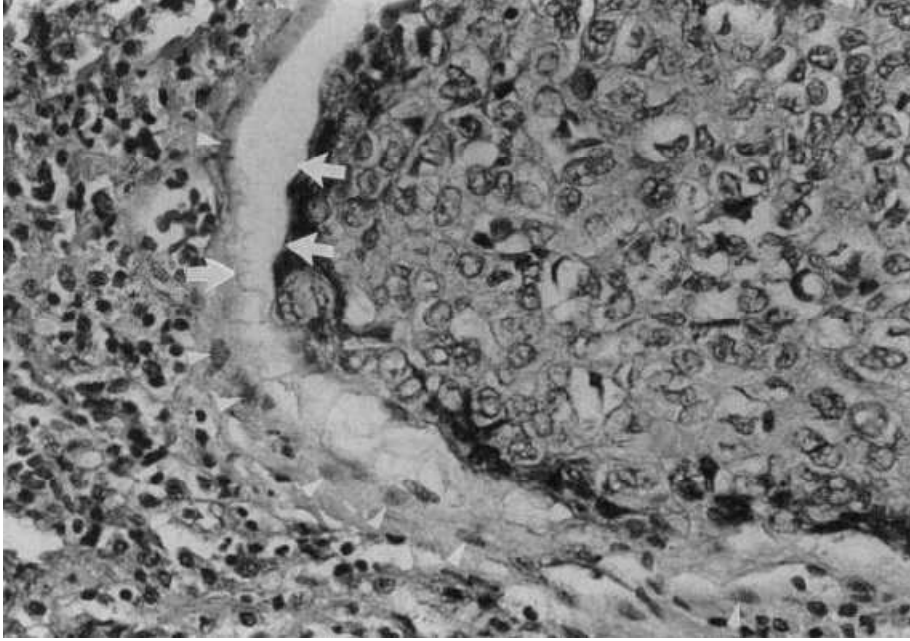


Figure 1: A picture of a human squamous cell carcinoma of head and neck displaying an interstitial gap (reprinted with permission from reference [18])

where $z = x - \theta t$ is a real number and θ is the wave speed. Substituting into (1.1)–(1.3), we obtain

$$0 = \theta u' + u(1 - u) - auw, \quad (1.6)$$

$$0 = d[(1 - u)v'' - u'v'] + \theta v' + bv(1 - v), \quad (1.7)$$

$$0 = w'' + \theta w' + c(v - w), \quad (1.8)$$

where $'$ denotes differentiation with respect to z . Bearing in mind the invasive nature of the process being addressed, (1.6)–(1.8) are to be considered for $\theta > 0$ and supplemented with the boundary conditions

$$(u, v, w)(-\infty) = (0, 1, 1), \quad (u, v, w)(\infty) = (1, 0, 0) \quad (a \geq 1) \quad (1.9a)$$

or

$$(u, v, w)(-\infty) = (1 - a, 1, 1), \quad (u, v, w)(\infty) = (1, 0, 0) \quad (0 < a < 1). \quad (1.9b)$$

We also assume that each component of (u, v, w) is a monotonic function, increasing in the case of u and decreasing in the case of v and w . We shall concentrate hereafter on TWs of (1.1)–(1.3) given by solutions of (1.6)–(1.9) and satisfying the above monotonicity assumptions.

The limiting role of the value $a = 1$ is apparent at once upon identification of the steady states (u^*, v^*, w^*) of (1.6)–(1.8). These are given by $(0, 1, 1), (1, 0, 0)$ for $a \geq 1$ and by $(1 - a, 1, 1), (1, 0, 0)$ for $0 < a < 1$. Thus, for $a \geq 1$ solutions of (1.6)–(1.8), (1.9a) describe a process in which total destruction of healthy tissue occurs after the invasion of neoplastic tissue. On the other hand, for $0 < a < 1$ solutions of (1.6)–(1.8), (1.9b) correspond to a situation where a residual concentration of healthy tissue (with value $1 - a$) remains behind the spreading malignant wave.

Our current study was motivated by a desire to ascertain which wave mechanisms are actually compatible with a system like (1.1)–(1.3). This fact is of some interest, since in the approach of [10] different wave motions should represent different manners of tumour invasion. This goal was only partly addressed in [10], where a number of interesting statements were made. For instance, numerical simulations hinting at the existence of an interstitial gap for large values of the parameter a were reported. Furthermore, arguments pointing toward comparatively faster invasive processes when $a > 1$ were provided.

To put these observations and our forthcoming analysis in a proper perspective, some remarks are in order. These concern the modelling hypotheses leading to (1.1)–(1.3). For example, the assumption of tumour cell diffusion as the dominant mechanism for the motion of malignant cells calls for adequate justification. As a possible alternative, we refer the reader to [17] where TWs are used to describe tumour invasion but instead of diffusion, haptotaxis (i.e., directional mobility up a gradient of cellular adhesion) is considered to be the driving biological phenomenon. Moreover, total mass conservation of cell species is unclear from (1.1)–(1.3), and most flow properties of the underlying processes are ignored therein. Rather than address such issues here, we shall keep to the simplified formalism proposed in [10] and proceed to extract the information on wave motions encoded in (1.1)–(1.3).

As a matter of fact, the analysis of the system (1.6)–(1.9) is the main purpose of our study. In this respect, we should point out that no proof of the existence of TWs for (1.1)–(1.3) is given here. To the best of our knowledge, this remains an open question. As in [10] we shall assume that such waves exist, and set out to identify the key features of the respective

wave motions. To this end, the smallness assumption (1.5) will play a central role. As a consequence of our discussion, necessary conditions for the existence of front-type TWs for (1.1)–(1.3) will be obtained.

We now describe the results of this paper. We begin by recalling the nondimensionalisation process leading to (1.1)–(1.3) in Section 2, where some auxiliary results are also gathered. In Section 3 we consider slow TWs. Here we define a *slow TW* as a solution (u, v, w) of (1.6)–(1.9) whose components are positive and such that $\theta = \theta_0 d^\alpha$ with $\theta_0, \alpha > 0$. In this case a plethora of TWs is admissible when $0 < \alpha \leq 1/2$ (see Proposition 3.1). The bounds for the wave speed are obtained explicitly in terms of the model parameters. An interstitial gap is also identified when $a > 2$ and its width is estimated by z_+ in (2.12). This gap ceases to exist when $0 < a \leq 2$ and slow TWs cannot be found when $\alpha > 1/2$. We then study fast TWs in Section 4. By a *fast TW* we mean a solution (u, v, w) of (1.6)–(1.9) whose components are positive and such that $\theta = O(1)$. We show that such waves are admissible for all positive wave speeds and are linearly stable under small perturbations (see Proposition 4.1). Finally, a discussion of our results and some conclusions thereof constitute Section 5, which also includes some considerations about the choice of the physical parameters.

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2 Preliminary results

2.1 The choice of nondimensional variables

We shall briefly recall below some aspects of the discussion presented in [10] which are useful for our forthcoming analysis. To this end, we slightly modify the notation used in [10] where appropriate, so that the equations obtained will be consistent with those used in our current work. The starting point in

the aforementioned work is the system

$$\begin{aligned}\frac{\partial N_1}{\partial s} &= r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - d_1 L N_1, \\ \frac{\partial N_2}{\partial s} &= r_2 N_2 \left(1 - \frac{N_2}{K_2}\right) + D_2 \frac{\partial}{\partial y} \left[\left(1 - \frac{N_1}{K_1}\right) \frac{\partial N_2}{\partial y} \right], \\ \frac{\partial L}{\partial s} &= r_3 N_2 - d_3 L + D_3 \frac{\partial^2 L}{\partial y^2}.\end{aligned}$$

Here, s denotes a time variable, y stands for a one-dimensional space variable, and N_1 , N_2 , and L respectively denote the concentrations of normal tissue (with carrying capacity K_1), neoplastic tissue (with carrying capacity K_2), and the excess of H^+ ions. Following [10], we now introduce nondimensional variables by setting

$$u = \frac{N_1}{K_1}, \quad v = \frac{N_2}{K_2}, \quad w = \frac{d_3}{r_3 K_2} L, \quad t = r_1 s, \quad x = \sqrt{\frac{r_1}{D_3}} y.$$

It then follows that u , v , and w satisfy our equations (1.1)–(1.3) where

$$a = \frac{d_1 r_3 K_2}{d_3 r_1}, \quad b = \frac{r_2}{r_1}, \quad c = \frac{d_3}{r_1}, \quad d = \frac{D_2}{D_3}. \quad (2.1)$$

A list of possible parameter values was provided in [10], which is recalled here for the convenience of the reader:

Parameter	Estimate
d_1	$0 - 10/\text{M} \cdot \text{s}$
d_3	$1.1 \times 10^{-4}/\text{s}$
r_3	$2.2 \times 10^{-17} \text{M} \cdot \text{cm}^3/\text{s}$
D_3	$5 \times 10^{-6} \text{cm}^2/\text{s}$
D_2	$2 \times 10^{-10} \text{cm}^2/\text{s}$
r_2	$1 \times 10^{-6}/\text{s}$
r_1	$1 \times 10^{-6}/\text{s}$
K_2	$5 \times 10^7/\text{cm}^3$
K_1	$5 \times 10^7/\text{cm}^3$

Note, however, that due to experimental limitations, these values are to be considered as rough approximations, and fluctuations of about one order of magnitude in their values can be considered as admissible (see for instance [22] and [21]). We will return to the question of the choice of parameters in the last section.

2.2 Auxiliary results

Here we gather a number of technical results that will be needed in the sequel. We begin with the following:

Lemma 2.1. *Consider the equation*

$$W'' + \theta W' - \beta W = f \quad (2.2)$$

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

$$W(z) = \frac{1}{r_2 - r_1} [I_1(z) + I_2(z)] \quad (2.3)$$

where

$$r_1 = \frac{-\theta + \sqrt{\theta^2 + 4\beta}}{2} > 0, \quad r_2 = \frac{-\theta - \sqrt{\theta^2 + 4\beta}}{2} < 0 \quad (2.4)$$

and

$$I_1(z) = e^{r_1 z} \int_z^\infty e^{-r_1 s} f(s) ds, \quad I_2(z) = e^{r_2 z} \int_{-\infty}^z e^{-r_2 s} f(s) ds. \quad (2.5)$$

Then (2.3)–(2.5) solves (2.2). Moreover, if f possesses bounded limits at infinity, i.e., $f(\pm\infty) = \lim_{z \rightarrow \pm\infty} f(z)$ both exist, then

$$I_1(\infty) = \frac{f(\infty)}{r_1}, \quad I_1(-\infty) = \begin{cases} 0 & \text{if } \int_{-\infty}^\infty e^{-r_1 s} f(s) ds \text{ is finite,} \\ \frac{f(-\infty)}{r_1} & \text{if } \int_{-\infty}^\infty e^{-r_1 s} f(s) ds \text{ is infinite,} \end{cases} \quad (2.6)$$

$$I_2(-\infty) = -\frac{f(-\infty)}{r_2}, \quad I_2(\infty) = \begin{cases} 0 & \text{if } \int_{-\infty}^\infty e^{-r_2 s} f(s) ds \text{ is finite,} \\ -\frac{f(\infty)}{r_2} & \text{if } \int_{-\infty}^\infty e^{-r_2 s} f(s) ds \text{ is infinite.} \end{cases} \quad (2.7)$$

Proof. Using the standard variation of constants formula, we obtain

$$W(z) = e^{r_1 z} \left[c_1 - \frac{1}{r_2 - r_1} \int_0^z e^{-r_1 s} f(s) ds \right] + e^{r_2 z} \left[c_2 + \frac{1}{r_2 - r_1} \int_0^z e^{-r_2 s} f(s) ds \right]$$

where r_1, r_2 are as given in (2.4) and c_1, c_2 are arbitrary constants. We can choose

$$c_1 = \frac{1}{r_2 - r_1} \int_0^\infty e^{-r_1 s} f(s) ds, \quad c_2 = \frac{1}{r_2 - r_1} \int_{-\infty}^0 e^{-r_2 s} f(s) ds$$

since f is bounded and the above improper integrals converge, thus obtaining (2.3)–(2.5).

A direct calculation gives

$$I_1(\infty) = \lim_{z \rightarrow \infty} \frac{\int_z^\infty e^{-r_1 s} f(s) ds}{e^{-r_1 z}} = \lim_{z \rightarrow \infty} \frac{-e^{-r_1 z} f(z)}{-r_1 e^{-r_1 z}} = \frac{f(\infty)}{r_1}$$

and the first equation of (2.6) holds. If $\int_{-\infty}^\infty e^{-r_1 s} f(s) ds$ is finite, then $I_1(-\infty) = 0$. On the other hand, if $\int_{-\infty}^\infty e^{-r_1 s} f(s) ds$ is infinite, then

$$I_1(-\infty) = \lim_{z \rightarrow -\infty} \frac{\int_z^\infty e^{-r_1 s} f(s) ds}{e^{-r_1 z}} = \lim_{z \rightarrow -\infty} \frac{-e^{-r_1 z} f(z)}{-r_1 e^{-r_1 z}} = \frac{f(-\infty)}{r_1}.$$

Hence, the second equation of (2.6) holds. The other cases in (2.7) follow from a similar argument. \square

The next lemma will be useful when we consider later an equivalent system to (1.6)–(1.9) and to show the stability of the fast TW.

Lemma 2.2. *Let $\Phi(z) = e^{-\int_0^z g(s) ds}$ where g is a continuous function with bounded limits at infinity and suppose that $l > 0$.*

- (i) *If $g(\infty) = l$, then $\Phi(\infty) = 0$.*
- (ii) *If $g(\infty) = -l$, then $\Phi(\infty) = \infty$.*
- (iii) *If $g(-\infty) = l$, then $\Phi(-\infty) = \infty$.*
- (iv) *If $g(-\infty) = -l$, then $\Phi(-\infty) = 0$.*

Proof. We will only prove (i) since the other statements follow from a similar argument. If $g(\infty) = l > 0$, then there exists $M > 0$ such that $|g(s) - l| < l/2$ for all $s > M$, or $-3l/2 < -g(s) < -l/2$. For all $z > M$ we see that

$$0 \leq \Phi(z) = e^{-\int_0^M g(s) ds} e^{-\int_M^z g(s) ds} \leq e^{-\int_0^M g(s) ds} e^{-l(z-M)/2},$$

whence $\Phi(z) \rightarrow 0$ as $z \rightarrow \infty$. \square

Now we show how to obtain an auxiliary system equivalent to (1.6)–(1.9).

Lemma 2.3. *Let $(u, v, w) = (u, v, w)(z; d)$ denote a solution of (1.6)–(1.9), if any. Then the problem (1.6)–(1.9) is equivalent to the following:*

$$0 = d[(1-u)v'' - u'v'] + \theta v' + bv(1-v), \quad v(-\infty; d) = 1, \quad v(\infty; d) = 0 \quad (2.8)$$

where

$$u(z; d) = \frac{\theta \Phi(z; d)}{\int_z^\infty \Phi(s; d) ds}, \quad \Phi(z; d) = e^{-\int_0^z [1-aw(s; d)]/\theta ds} \quad (2.9)$$

and

$$w(z; d) = \frac{c}{r_1 - r_2} \left[e^{r_1 z} \int_z^\infty e^{-r_1 s} v(s; d) ds + e^{r_2 z} \int_{-\infty}^z e^{-r_2 s} v(s; d) ds \right], \quad (2.10a)$$

$$r_1 = \frac{-\theta + \sqrt{\theta^2 + 4c}}{2} > 0, \quad r_2 = \frac{-\theta - \sqrt{\theta^2 + 4c}}{2} < 0. \quad (2.10b)$$

Proof. Equation (2.8) is the same as (1.7) together with the corresponding boundary conditions for v in (1.9).

We can apply Lemma 2.1 to (1.8) where $\beta = c$ and $f = -cv$ to obtain (2.10). Since $f(\infty) = -cv(\infty; d) = 0$ we have $I_1(\infty) = I_2(\infty) = 0$ and therefore $w(\infty; d) = 0$ from (2.6), (2.7). Moreover, since

$$\int_{-\infty}^\infty e^{-r_1 s} f(s) ds = -c \int_{-\infty}^\infty e^{-r_1 s} v(s; d) ds = -\infty$$

we obtain again from (2.6), (2.7) that

$$w(-\infty; d) = \frac{1}{r_2 - r_1} \left[-\frac{cv(-\infty; d)}{r_1} + \frac{cv(-\infty; d)}{r_2} \right] = -\frac{c}{r_1 r_2} = 1.$$

Equation (1.6) is a Bernoulli equation, which can be solved explicitly to yield (2.9). Let $g(s) = [1 - aw(s; d)]/\theta$. Then $g(\infty) = 1/\theta > 0$ and $\Phi(\infty; d) = 0$ from Lemma 2.2 (i). It follows that

$$u(\infty; d) = \theta \lim_{z \rightarrow \infty} \frac{\Phi(z; d)}{\int_z^\infty \Phi(s; d) ds} = \theta \lim_{z \rightarrow \infty} \frac{-\Phi(z; d)g(z)}{-\Phi(z; d)} = \theta g(\infty) = 1$$

for all $a > 0$. Furthermore, $g(-\infty) = (1 - a)/\theta$. If $0 < a < 1$, then we infer that $\Phi(-\infty; d) = \infty$ from Lemma 2.2 (iii), $\int_{-\infty}^\infty \Phi(s; d) ds = \infty$, and

$$u(-\infty; d) = \theta \lim_{z \rightarrow \infty} \frac{\Phi(z; d)}{\int_z^\infty \Phi(s; d) ds} = \theta \lim_{z \rightarrow \infty} \frac{-\Phi(z; d)g(z)}{-\Phi(z; d)} = 1 - a.$$

If $a > 1$, then $\Phi(-\infty; d) = 0$ from Lemma 2.2 (iv), $0 < \int_{-\infty}^{\infty} \Phi(s; d) ds \leq \infty$, and

$$u(-\infty; d) = \frac{\theta\Phi(-\infty; d)}{\int_{-\infty}^{\infty} \Phi(s; d) ds} = 0.$$

Finally, when $a = 1$ we see that g is a nonnegative monotone increasing function satisfying $g(-\infty) = 0$. Lemma 2.2 is not applicable in this case but $0 < \Phi(-\infty; d) \leq \infty$ and therefore $\int_{-\infty}^{\infty} \Phi(s; d) ds = \infty$. Applying L'Hôpital's Rule if necessary, it is straightforward to show that $u(-\infty; d) = 0$. Thus, (1.6)–(1.9) is equivalent to (2.8)–(2.10). \square

The next result will be used in obtaining asymptotic expansions for u .

Lemma 2.4. *Let ϕ be a continuous function and $\alpha, s_L, s_R \in \mathbb{R}$ with $\alpha > 0$. Consider the integral*

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

as $d \rightarrow 0^+$. Then the following statements hold:

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

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

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

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

(iii) *Suppose that ϕ has a unique maximum at some $s_L < s^* < s_R$, which implies that $\phi'(s^*) = 0$ and $\phi''(s^*) < 0$. Then*

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

Proof. The proof follows from a standard application of Laplace's method to approximate integrals containing a large parameter (see pp. 266–267 of [5] for instance). \square

We conclude this section by defining two auxiliary functions that will play a key role later on. For the convenience of the reader, we include here some of their useful properties.

Lemma 2.5. *Let $a, c, \theta_0 > 0$ and define*

$$\begin{aligned}\phi_-(z) &= \frac{1}{\theta_0} \left[(a-1)z + \frac{a}{2\sqrt{c}}(1 - e^{\sqrt{c}z}) \right], \\ \phi_+(z) &= \frac{1}{\theta_0} \left[\frac{a}{2\sqrt{c}}(1 - e^{-\sqrt{c}z}) - z \right].\end{aligned}$$

Then the following properties hold:

- (i) $\phi_-(0) = \phi_+(0) = 0$.
- (ii) *The derivatives of ϕ_- and ϕ_+ satisfy*

$$\begin{aligned}\phi'_-(z) &= \frac{1}{\theta_0} \left(a-1 - \frac{a}{2}e^{\sqrt{c}z} \right), & \phi''_-(z) &= -\frac{a\sqrt{c}}{2\theta_0}e^{\sqrt{c}z}, \\ \phi'_+(z) &= \frac{1}{\theta_0} \left(\frac{a}{2}e^{-\sqrt{c}z} - 1 \right), & \phi''_+(z) &= -\frac{a\sqrt{c}}{2\theta_0}e^{-\sqrt{c}z}.\end{aligned}$$

- (iii) *If*

$$z_- = \frac{1}{\sqrt{c}} \log \frac{2(a-1)}{a} < 0 \quad (1 < a < 2), \quad (2.11)$$

then $\phi_-(z_-) > 0$, $\phi'_-(z_-) = 0$, and $\phi''_-(z_-) < 0$.

- (iv) *If*

$$z_+ = \frac{1}{\sqrt{c}} \log \frac{a}{2} > 0 \quad (a > 2), \quad (2.12)$$

then $\phi_+(z_+) > 0$, $\phi'_+(z_+) = 0$, and $\phi''_+(z_+) < 0$.

Proof. We omit the details since the results follow from elementary computations. \square

3 Slow waves: $\theta = \theta_0 d^\alpha$

In this section we will consider slow TWs and thus assume that

$$\theta = \theta_0 d^\alpha \quad (\theta_0, \alpha > 0) \quad (3.1)$$

where $\theta_0 = O(1)$ as $d \rightarrow 0^+$. Our forthcoming analysis makes use of matched asymptotic expansions (see [5] for instance). In this approach we assume that the wave profiles possess an *outer region* corresponding to $|z| \gg 1$, where the solution and its derivatives undergo comparatively small variations. However, near $z = 0$ a narrow region unfolds where the derivatives experience sharp changes in their values. This is customarily referred to as the *inner region*. Finally, the solutions in the inner and outer regions are assumed to be matched in a sufficiently smooth manner.

From Lemma 2.3 we deduce that the problem (1.6)–(1.9) is equivalent to the following:

$$0 = d[(1-u)v'' - u'v'] + \theta_0 d^\alpha v' + bv(1-v), \quad v(-\infty; d) = 1, \quad v(\infty; d) = 0, \quad (3.2)$$

$$u(z; d) = \frac{\theta_0 d^\alpha \Phi(z; d)}{\int_z^\infty \Phi(s; d) ds}, \quad \Phi(z; d) = e^{-\int_0^z [1-aw(s; d)]/(\theta_0 d^\alpha) ds}, \quad (3.3)$$

$$w(z; d) = \frac{c}{r_1 - r_2} \left[e^{r_1 z} \int_z^\infty e^{-r_1 s} v(s; d) ds + e^{r_2 z} \int_{-\infty}^z e^{-r_2 s} v(s; d) ds \right], \quad (3.4a)$$

$$r_1 = \frac{-\theta_0 d^\alpha + \sqrt{\theta_0^2 d^{2\alpha} + 4c}}{2} > 0, \quad r_2 = \frac{-\theta_0 d^\alpha - \sqrt{\theta_0^2 d^{2\alpha} + 4c}}{2} < 0. \quad (3.4b)$$

Another equivalent system can be obtained by introducing a “stretched” inner variable. Namely, let

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

where $\xi = z/d^\alpha$. Substituting into (3.2)–(3.4) gives

$$0 = d^{1-2\alpha}[(1-U)\ddot{V} - \dot{U}\dot{V}] + \theta_0 \dot{V} + bV(1-V), \quad (3.5)$$

$$U(\xi; d) = \frac{\theta_0 d^\alpha \Phi(d^\alpha \xi; d)}{\int_{d^\alpha \xi}^\infty \Phi(s; d) ds}, \quad (3.6)$$

$$W(\xi; d) = \frac{c}{r_1 - r_2} \left[e^{r_1 d^\alpha \xi} \int_{d^\alpha \xi}^{\infty} e^{-r_1 s} V\left(\frac{s}{d^\alpha}; d\right) ds + e^{r_2 d^\alpha \xi} \int_{-\infty}^{d^\alpha \xi} e^{-r_2 s} V\left(\frac{s}{d^\alpha}; d\right) ds \right], \quad (3.7)$$

where \cdot denotes differentiation with respect to ξ . The appropriate boundary conditions for (3.5)–(3.7) are obtained from the matching requirements

$$U(\pm\infty; d) = u(0\pm; d), \quad V(\pm\infty; d) = v(0\pm; d), \quad W(\pm\infty; d) = w(0\pm; d).$$

3.1 Obtaining a uniform approximation for the excess of H^+ ions w

Define the *outer solution* by

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

and the *inner solution* by

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

The outer (respectively, inner) system is the set of equations obtained by taking $d = 0$ in (3.2)–(3.4) (respectively, (3.5)–(3.7)). Setting $d = 0$ in (3.2) gives

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

Then from (3.4) we deduce that

$$w_{\text{out}}(z) = \frac{\sqrt{c}}{2} \left[e^{\sqrt{c}z} \int_z^{\infty} e^{-\sqrt{c}s} v_{\text{out}}(s) ds + e^{-\sqrt{c}z} \int_{-\infty}^z e^{\sqrt{c}s} v_{\text{out}}(s) ds \right],$$

which simplifies to

$$w_{\text{out}}(z) = \begin{cases} 1 - \frac{1}{2}e^{\sqrt{c}z} & \text{if } z < 0, \\ \frac{1}{2}e^{-\sqrt{c}z} & \text{if } z > 0. \end{cases}$$

On the other hand, setting $d = 0$ in (3.7) yields

$$W_{\text{in}}(\xi) = \frac{\sqrt{c}}{2} \left[\int_0^\infty e^{-\sqrt{c}s} V_{\text{in}}(\infty) ds + \int_{-\infty}^0 e^{\sqrt{c}s} V_{\text{in}}(-\infty) ds \right] = \frac{1}{2}$$

for any $\xi \in \mathbb{R}$ since $V_{\text{in}}(\infty) = v_{\text{out}}(0+) = 0$ and $V_{\text{in}}(-\infty) = v_{\text{out}}(0-) = 1$. Thus, a uniform approximation for w is obtained by adding the corresponding outer and inner solutions and then subtracting the common value in the overlap region [5]. Such common value w_c is given by $w_c = W_{\text{in}}(\pm\infty) = w_{\text{out}}(0\pm) = 1/2$. Therefore,

$$w(z; d) \simeq w_{\text{out}}(z) + W_{\text{in}}\left(\frac{z}{d^\alpha}\right) - w_c = \begin{cases} 1 - \frac{1}{2}e^{\sqrt{c}z} & \text{if } z < 0, \\ \frac{1}{2}e^{-\sqrt{c}z} & \text{if } z > 0. \end{cases} \quad (3.8)$$

3.2 Estimating the normal tissue concentration u as a function of the aggressivity parameter a

Substituting (3.8) into (3.3) gives

$$\Phi(z; d) \simeq \begin{cases} e^{\phi_-(z)/d^\alpha} & \text{if } z < 0, \\ e^{\phi_+(z)/d^\alpha} & \text{if } z > 0, \end{cases}$$

$$u(z; d) \simeq \begin{cases} \frac{\theta_0 d^\alpha e^{\phi_-(z)/d^\alpha}}{\int_z^0 e^{\phi_-(s)/d^\alpha} ds + \int_0^\infty e^{\phi_+(s)/d^\alpha} ds} & \text{if } z < 0, \\ \frac{\theta_0 d^\alpha e^{\phi_+(z)/d^\alpha}}{\int_z^\infty e^{\phi_+(s)/d^\alpha} ds} & \text{if } z > 0, \end{cases} \quad (3.9)$$

where ϕ_-, ϕ_+ are as in Lemma 2.5. We now distinguish among several cases.

3.2.1 $0 < a < 1$

Suppose that $z > 0$. For any $z \leq s < \infty$ we have

$$\phi'_+(s) = \frac{1}{\theta_0} \left(\frac{a}{2} e^{-\sqrt{c}s} - 1 \right) < \frac{1}{\theta_0} \left(\frac{a}{2} - 1 \right) < 0.$$

From Lemma 2.4 (i) we obtain

$$\int_z^\infty e^{\phi_+(s)/d^\alpha} ds \simeq -\frac{d^\alpha e^{\phi_+(z)/d^\alpha}}{\phi'_+(z)}$$

so that (3.9) yields

$$u(z; d) \simeq -\theta_0 \phi'_+(z) = 1 - \frac{a}{2} e^{-\sqrt{c}z} \quad (z > 0).$$

Now suppose that $z < 0$. For any $0 \leq s < \infty$ we have

$$\phi'_+(s) = \frac{1}{\theta_0} \left(\frac{a}{2} e^{-\sqrt{c}s} - 1 \right) \leq \frac{1}{\theta_0} \left(\frac{a}{2} - 1 \right) < 0.$$

From Lemma 2.4 (i) we obtain

$$\int_0^\infty e^{\phi_+(s)/d^\alpha} ds \simeq -\frac{d^\alpha e^{\phi_+(0)/d^\alpha}}{\phi'_+(0)} = \frac{2\theta_0 d^\alpha}{2-a}.$$

For any $z \leq s < 0$ we have

$$\phi'_-(s) = \frac{1}{\theta_0} \left(a - 1 - \frac{a}{2} e^{\sqrt{c}s} \right) < \frac{a-1}{\theta_0} < 0$$

so that Lemma 2.4 (i) gives

$$\int_z^0 e^{\phi_-(s)/d^\alpha} ds \simeq -\frac{d^\alpha e^{\phi_-(z)/d^\alpha}}{\phi'_-(z)}.$$

Hence,

$$\begin{aligned} \int_z^0 e^{\phi_-(s)/d^\alpha} ds + \int_0^\infty e^{\phi_+(s)/d^\alpha} ds &\simeq -\frac{d^\alpha e^{\phi_-(z)/d^\alpha}}{\phi'_-(z)} + \frac{2\theta_0 d^\alpha}{2-a} \\ &\simeq -\frac{d^\alpha e^{\phi_-(z)/d^\alpha}}{\phi'_-(z)} \end{aligned}$$

since $\phi_-(z) > 0$ for $z < 0$ and $0 < a < 1$. Finally, from (3.9) it follows that

$$u(z; d) \simeq -\theta_0 \phi'_-(z) = 1 - a + \frac{a}{2} e^{\sqrt{c}z} \quad (z < 0).$$

Summarising, an approximation for u in the case $0 < a < 1$ is

$$u(z; d) \simeq \begin{cases} 1 - a + \frac{a}{2} e^{\sqrt{c}z} & \text{if } z < 0, \\ 1 - \frac{a}{2} e^{-\sqrt{c}z} & \text{if } z > 0. \end{cases} \quad (3.10)$$

In the inner region we have

$$U(\xi; d) = u(d^\alpha \xi; d) \simeq \begin{cases} 1 - a + \frac{a}{2} e^{\sqrt{c}d^\alpha \xi} & \text{if } \xi < 0, \\ 1 - \frac{a}{2} e^{-\sqrt{c}d^\alpha \xi} & \text{if } \xi > 0. \end{cases}$$

Setting $d = 0$ gives $U_{\text{in}}(\xi) = 1 - a/2$ for any $\xi \in \mathbb{R}$.

3.2.2 $1 < a < 2$

The analysis of this case for $z > 0$ is identical to the case when $0 < a < 1$. Thus,

$$u(z; d) \simeq 1 - \frac{a}{2} e^{-\sqrt{c}z} \quad (z > 0)$$

and

$$\int_0^\infty e^{\phi_+(s)/d^\alpha} ds \simeq \frac{2\theta_0 d^\alpha}{2-a}.$$

For $z < 0$ we need to consider two subcases: $z_- < z < 0$ and $z < z_-$ where z_- is given by (2.11). Suppose that $z_- < z < 0$. Then for any $z \leq s < 0$ we have $s > z_-$ and

$$\phi'_-(s) = \frac{1}{\theta_0} \left(a - 1 - \frac{a}{2} e^{\sqrt{c}s} \right) < \frac{1}{\theta_0} \left(a - 1 - \frac{a}{2} e^{\sqrt{c}z_-} \right) = 0.$$

From Lemma 2.4 (i) we obtain

$$\int_z^0 e^{\phi_-(s)/d^\alpha} ds \simeq -\frac{d^\alpha e^{\phi_-(z)/d^\alpha}}{\phi'_-(z)}$$

so that

$$\begin{aligned} \int_z^0 e^{\phi_-(s)/d^\alpha} ds + \int_0^\infty e^{\phi_+(s)/d^\alpha} ds &\simeq -\frac{d^\alpha e^{\phi_-(z)/d^\alpha}}{\phi'_-(z)} + \frac{2\theta_0 d^\alpha}{2-a} \\ &\simeq -\frac{d^\alpha e^{\phi_-(z)/d^\alpha}}{\phi'_-(z)}. \end{aligned}$$

In the last relation we used the fact that $\phi_-(z) > 0$ for all $z_- < z < 0$. Indeed, we already have that $\phi'_-(z) < 0$ for all such z . Since $\phi_-(0) = 0$ and ϕ_- is continuous, it follows that $\phi_-(z) > 0$ for all $z_- < z < 0$, otherwise the negativity of its derivative will be violated. Therefore, from (3.9) we have

$$u(z; d) \simeq -\theta_0 \phi'_-(z) = 1 - a + \frac{a}{2} e^{\sqrt{c}z} \quad (z_- < z < 0).$$

Now suppose that $z < z_-$. From Lemma 2.4 (iii) and Lemma 2.5 (iii) we have that

$$\int_z^0 e^{\phi_-(s)/d^\alpha} ds \simeq \frac{\sqrt{2\pi} d^{\alpha/2} e^{\phi_-(z_-)/d^\alpha}}{\sqrt{-\phi''_-(z_-)}} = \sqrt{\frac{2\pi\theta_0}{\sqrt{c}(a-1)}} d^{\alpha/2} e^{\phi_-(z_-)/d^\alpha}$$

and

$$\begin{aligned} \int_z^0 e^{\phi_-(s)/d^\alpha} ds + \int_0^\infty e^{\phi_+(s)/d^\alpha} ds &\simeq \sqrt{\frac{2\pi\theta_0}{\sqrt{c}(a-1)}} d^{\alpha/2} e^{\phi_-(z_-)/d^\alpha} + \frac{2\theta_0 d^\alpha}{2-a} \\ &\simeq \sqrt{\frac{2\pi\theta_0}{\sqrt{c}(a-1)}} d^{\alpha/2} e^{\phi_-(z_-)/d^\alpha} \end{aligned}$$

since $\phi_-(z_-) > 0$ from Lemma 2.5 (iii). Thus, (3.9) yields

$$u(z; d) \simeq \sqrt{\frac{\sqrt{c}(a-1)\theta_0}{2\pi}} d^{\alpha/2} e^{[\phi_-(z) - \phi_-(z_-)]/d^\alpha} \quad (z < z_-).$$

Summarising, an approximation for u in the case $1 < a < 2$ is

$$u(z; d) \simeq \begin{cases} \sqrt{\frac{\sqrt{c}(a-1)\theta_0}{2\pi}} d^{\alpha/2} e^{[\phi_-(z) - \phi_-(z_-)]/d^\alpha} & \text{if } z < z_-, \\ 1 - a + \frac{a}{2} e^{\sqrt{c}z} & \text{if } z_- < z < 0, \\ 1 - \frac{a}{2} e^{-\sqrt{c}z} & \text{if } z > 0. \end{cases} \quad (3.11)$$

In the inner region we have

$$U(\xi; d) = u(d^\alpha \xi; d) \simeq \begin{cases} 1 - a + \frac{a}{2} e^{\sqrt{c}d^\alpha \xi} & \text{if } \xi < 0, \\ 1 - \frac{a}{2} e^{-\sqrt{c}d^\alpha \xi} & \text{if } \xi > 0. \end{cases}$$

Setting $d = 0$ gives $U_{\text{in}}(\xi) = 1 - a/2$ for any $\xi \in \mathbb{R}$.

3.2.3 $a > 2$

For $z > 0$ we need to consider two subcases: $z > z_+$ and $0 < z < z_+$ where z_+ is given by (2.12). Suppose that $z > z_+$. For any $z \leq s < \infty$ we have $s > z_+$ and

$$\phi'_+(s) = \frac{1}{\theta_0} \left(\frac{a}{2} e^{-\sqrt{c}s} - 1 \right) < \frac{1}{\theta_0} \left(\frac{a}{2} e^{-\sqrt{c}z_+} - 1 \right) = 0.$$

From Lemma 2.4 (i) we arrive at

$$\int_z^\infty e^{\phi_+(s)/d^\alpha} ds \simeq -\frac{d^\alpha e^{\phi_+(z)/d^\alpha}}{\phi'_+(z)}$$

so that (3.9) gives

$$u(z; d) \simeq -\theta_0 \phi'_+(z) = 1 - \frac{a}{2} e^{-\sqrt{c}z} \quad (z > z_+).$$

Now suppose that $0 < z < z_+$. From Lemma 2.4 (iii) and Lemma 2.5 (iv) we see that

$$\int_z^\infty e^{\phi_+(s)/d^\alpha} ds \simeq \frac{\sqrt{2\pi} d^{\alpha/2} e^{\phi_+(z_+)/d^\alpha}}{\sqrt{-\phi_+''(z_+)}} = \sqrt{\frac{2\pi\theta_0}{\sqrt{c}}} d^{\alpha/2} e^{\phi_+(z_+)/d^\alpha}$$

and from (3.9) we obtain

$$u(z; d) \simeq \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_+(z) - \phi_+(z_+)]/d^\alpha} \quad (0 < z < z_+).$$

Next we take $z < 0$. From Lemma 2.4 (iii) and Lemma 2.5 (iv) we have once more

$$\int_0^\infty e^{\phi_+(s)/d^\alpha} ds \simeq \frac{\sqrt{2\pi} d^{\alpha/2} e^{\phi_+(z_+)/d^\alpha}}{\sqrt{-\phi_+''(z_+)}} = \sqrt{\frac{2\pi\theta_0}{\sqrt{c}}} d^{\alpha/2} e^{\phi_+(z_+)/d^\alpha}.$$

For any $z < s \leq 0$ we have

$$\phi'_-(s) = \frac{1}{\theta_0} \left(a - 1 - \frac{a}{2} e^{\sqrt{c}s} \right) \geq \frac{1}{\theta_0} \left(a - 1 - \frac{a}{2} \right) = \frac{a-2}{2\theta_0} > 0.$$

From Lemma 2.4 (ii) we obtain

$$\int_z^0 e^{\phi_-(s)/d^\alpha} ds \simeq \frac{d^\alpha e^{\phi_-(0)/d^\alpha}}{\phi'_-(0)} = \frac{2\theta_0 d^\alpha}{a-2}$$

and

$$\begin{aligned} \int_z^0 e^{\phi_-(s)/d^\alpha} ds + \int_0^\infty e^{\phi_+(s)/d^\alpha} ds &\simeq \frac{2\theta_0 d^\alpha}{a-2} + \sqrt{\frac{2\pi\theta_0}{\sqrt{c}}} d^{\alpha/2} e^{\phi_+(z_+)/d^\alpha} \\ &\simeq \sqrt{\frac{2\pi\theta_0}{\sqrt{c}}} d^{\alpha/2} e^{\phi_+(z_+)/d^\alpha} \end{aligned}$$

since $\phi_+(z_+) > 0$ from Lemma 2.5 (iv). Thus, (3.9) gives

$$u(z; d) \simeq \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_-(z) - \phi_+(z_+)]/d^\alpha} \quad (z < 0).$$

Summarising, an approximation for u in the case $a > 2$ is

$$u(z; d) \simeq \begin{cases} \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_-(z) - \phi_+(z_+)]/d^\alpha} & \text{if } z < 0, \\ \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_+(z) - \phi_+(z_+)]/d^\alpha} & \text{if } 0 < z < z_+, \\ 1 - \frac{a}{2} e^{-\sqrt{c}z} & \text{if } z > z_+. \end{cases} \quad (3.12)$$

In the inner region we have

$$U(\xi; d) = u(d^\alpha \xi; d) \simeq \begin{cases} \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_-(d^\alpha \xi) - \phi_+(z_+)]/d^\alpha} & \text{if } \xi < 0, \\ \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_+(d^\alpha \xi) - \phi_+(z_+)]/d^\alpha} & \text{if } \xi > 0. \end{cases}$$

We claim that $U_{\text{in}}(\xi) = U(\xi; 0) = 0$ for all $\xi \in \mathbb{R}$. To prove this we compute

$$\begin{aligned} \frac{\phi_-(d^\alpha \xi)}{d^\alpha} &= \frac{1}{\theta_0} \left[(a-1)\xi + \frac{a}{2\sqrt{c}} \cdot \frac{1 - e^{\sqrt{c}d^\alpha \xi}}{d^\alpha} \right] \\ &= \frac{1}{\theta_0} \left[(a-1)\xi + \frac{a}{2\sqrt{c}} \cdot \frac{-\sqrt{c}\xi d^\alpha - (\sqrt{c}\xi)^2 d^{2\alpha}/2! - \dots}{d^\alpha} \right] \\ &= \frac{(a-2)\xi}{2\theta_0} + O(d^\alpha). \end{aligned}$$

Then for $\xi < 0$ we have

$$\lim_{d \rightarrow 0^+} \frac{\phi_-(d^\alpha \xi)}{d^\alpha} = \frac{(a-2)\xi}{2\theta_0}$$

and so $U_{\text{in}}(\xi) = 0$ for $\xi < 0$ since $\phi_+(z_+) > 0$ from Lemma 2.5 (iv). A similar analysis shows that

$$\lim_{d \rightarrow 0^+} \frac{\phi_+(d^\alpha \xi)}{d^\alpha} = \frac{(a-2)\xi}{2\theta_0}$$

and therefore $U_{\text{in}}(\xi) = 0$ for $\xi > 0$. It is clear that $U_{\text{in}}(0) = 0$. Hence, $U_{\text{in}}(\xi) = 0$ for all $\xi \in \mathbb{R}$ as claimed.

3.2.4 Limit cases: $a = 1$ and $a = 2$

The values $a = 1$ and $a = 2$ can be handled by taking lateral limits of the previous cases. For example, taking the limit of (3.10) as $a \rightarrow 1^-$ gives

$$u(z; d) \simeq \begin{cases} \frac{1}{2}e^{\sqrt{c}z} & \text{if } z < 0, \\ 1 - \frac{1}{2}e^{-\sqrt{c}z} & \text{if } z > 0, \end{cases}$$

whilst taking the limit of (3.11) as $a \rightarrow 1^+$ implies that $z_- \rightarrow -\infty$ and we derive the same approximation for u . In the inner region we have

$$U(\xi; d) = u(d^\alpha \xi; d) \simeq \begin{cases} \frac{1}{2}e^{\sqrt{cd^\alpha}\xi} & \text{if } \xi < 0, \\ 1 - \frac{1}{2}e^{-\sqrt{cd^\alpha}\xi} & \text{if } \xi > 0. \end{cases}$$

Setting $d = 0$ gives $U_{\text{in}}(\xi) = 1/2$ for any $\xi \in \mathbb{R}$.

Now let us take the limit as $a \rightarrow 2^-$. Then $z_- \rightarrow 0$ and (3.11) gives

$$u(z; d) \simeq \begin{cases} \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{\phi_-(z)/d^\alpha} & \text{if } z < 0, \\ 1 - e^{-\sqrt{c}z} & \text{if } z > 0. \end{cases}$$

As $a \rightarrow 2^+$ we have $z_+ \rightarrow 0$, and we recover the same u from (3.12). In the inner region we have

$$U(\xi; d) = u(d^\alpha \xi; d) \simeq \begin{cases} \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{\phi_-(d^\alpha \xi)/d^\alpha} & \text{if } \xi < 0, \\ 1 - e^{-\sqrt{cd^\alpha}\xi} & \text{if } \xi > 0. \end{cases}$$

Setting $d = 0$ gives $U_{\text{in}}(\xi) = 0$ for all $\xi \in \mathbb{R}$.

We remark that we only assumed that $\alpha > 0$ when approximating w and u . Moreover, we see that U_{in} is constant for any $a > 0$.

3.3 A uniform approximation for the malignant tissue concentration v

Now we look for a uniform approximation for v . Set $d = 0$ in (3.5). If $\alpha > 1/2$, then $\check{V}_{\text{in}} = 0$ and the matching conditions $V_{\text{in}}(-\infty) = v_{\text{out}}(0^-) = 1$,

$V_{\text{in}}(\infty) = v_{\text{out}}(0+) = 0$ cannot be met simultaneously since V_{in} is a linear function of ξ . If $\alpha < 1/2$, then V_{in} satisfies the Bernoulli equation

$$\theta_0 \dot{V}_{\text{in}} + bV_{\text{in}}(1 - V_{\text{in}}) = 0, \quad V_{\text{in}}(-\infty) = 1, \quad V_{\text{in}}(\infty) = 0$$

for any $\theta_0 > 0$, and whose solution is

$$V_{\text{in}}(\xi) = \frac{1}{1 + e^{b\xi/\theta_0}}.$$

Finally, when $\alpha = 1/2$, V_{in} satisfies the Fisher-KPP equation

$$D\ddot{V}_{\text{in}} + \theta_0 \dot{V}_{\text{in}} + bV_{\text{in}}(1 - V_{\text{in}}) = 0, \quad V_{\text{in}}(-\infty) = 1, \quad V_{\text{in}}(\infty) = 0$$

where $D = a/2$ when $0 < a \leq 2$ and $D = 1$ when $a > 2$. From [9], [15] it is known that there exists a solution $V_{\text{in}}(\xi) = \phi_F(\xi; \theta_0)$ of this equation for all $\theta_0 \geq 2\sqrt{bD}$.

A uniform approximation for v is therefore obtained by adding the corresponding outer and inner solutions and then subtracting the common value in the overlap region. Such common value v_c is $v_c = V_{\text{in}}(\infty) = v_{\text{out}}(0+) = 0$ for $z > 0$, whilst $v_c = V_{\text{in}}(-\infty) = v_{\text{out}}(0-) = 0$ for $z < 0$. Therefore,

$$v(z; d) \simeq v_{\text{out}}(z) + V_{\text{in}}\left(\frac{z}{d^\alpha}\right) - v_c = \begin{cases} \frac{1}{1 + e^{bz/(\theta_0 d^\alpha)}} & \text{if } \alpha < 1/2, \\ \phi_F\left(\frac{z}{\sqrt{d}}; \theta_0\right) & \text{if } \alpha = 1/2. \end{cases}$$

3.4 Statement of results for slow waves

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

Proposition 3.1. *Let $D = a/2$ when $0 < a \leq 2$ and $D = 1$ when $a > 2$. Suppose that $\theta = \theta_0 d^\alpha$ where $\theta_0 > 0$ when $0 < \alpha < 1/2$ whilst $\theta_0 \geq 2\sqrt{bD}$ when $\alpha = 1/2$. Define z_-, z_+ as in (2.11), (2.12), respectively. For $0 < a \leq 1$ let*

$$u(z; d) \simeq \begin{cases} 1 - a + \frac{a}{2} e^{\sqrt{c}z} & \text{if } z < 0, \\ 1 - \frac{a}{2} e^{-\sqrt{c}z} & \text{if } z > 0, \end{cases} \quad (3.13a)$$

for $1 < a \leq 2$ let

$$u(z; d) \simeq \begin{cases} \sqrt{\frac{\sqrt{c}(a-1)\theta_0}{2\pi}} d^{\alpha/2} e^{[\phi_-(z) - \phi_-(z_-)]/d^\alpha} & \text{if } z < z_-, \\ 1 - a + \frac{a}{2} e^{\sqrt{c}z} & \text{if } z_- < z < 0, \\ 1 - \frac{a}{2} e^{-\sqrt{c}z} & \text{if } z > 0, \end{cases} \quad (3.13b)$$

and for $a > 2$ let

$$u(z; d) \simeq \begin{cases} \sqrt{\frac{\theta_0\sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_-(z) - \phi_+(z_+)]/d^\alpha} & \text{if } z < 0, \\ \sqrt{\frac{\theta_0\sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_+(z) - \phi_+(z_+)]/d^\alpha} & \text{if } 0 < z < z_+, \\ 1 - \frac{a}{2} e^{-\sqrt{c}z} & \text{if } z > z_+. \end{cases} \quad (3.13c)$$

These definitions for u are valid for any $0 < \alpha \leq 1/2$. For any $a > 0$ let

$$v(z; d) \simeq \begin{cases} \frac{1}{1 + e^{bz/(\theta_0 d^\alpha)}} & \text{if } \alpha < 1/2, \\ \phi_F\left(\frac{z}{\sqrt{d}}; \theta_0\right) & \text{if } \alpha = 1/2. \end{cases} \quad (3.14)$$

Finally, for any $a > 0$ and $0 < \alpha \leq 1/2$, define

$$w(z; d) \simeq \begin{cases} 1 - \frac{1}{2} e^{\sqrt{c}z} & \text{if } z < 0, \\ \frac{1}{2} e^{-\sqrt{c}z} & \text{if } z > 0. \end{cases} \quad (3.15)$$

Then (3.13)–(3.15) are asymptotic approximations compatible with solutions of (1.6)–(1.9). For $\alpha > 1/2$ no such waves are compatible with (1.6)–(1.9).

We plot the approximating functions found in Proposition 3.1 in the following figures for each of the cases $0 < a < 1$, $1 < a < 2$, and $a > 2$. We took $a = 0.5$ in Figure 2, $a = 1.5$ in Figure 3, and $a = 4$ in Figure 4. For all three cases we fixed $b = 1$, $c = 2$, $d = 4 \times 10^{-10}$, and $\alpha = 1/2$. For θ_0 we took the minimal speed $\theta_0 = 2\sqrt{bD}$. The value of θ shown at the top of each graph was calculated from $\theta = \theta_0 d^\alpha = 2\sqrt{bdD}$.

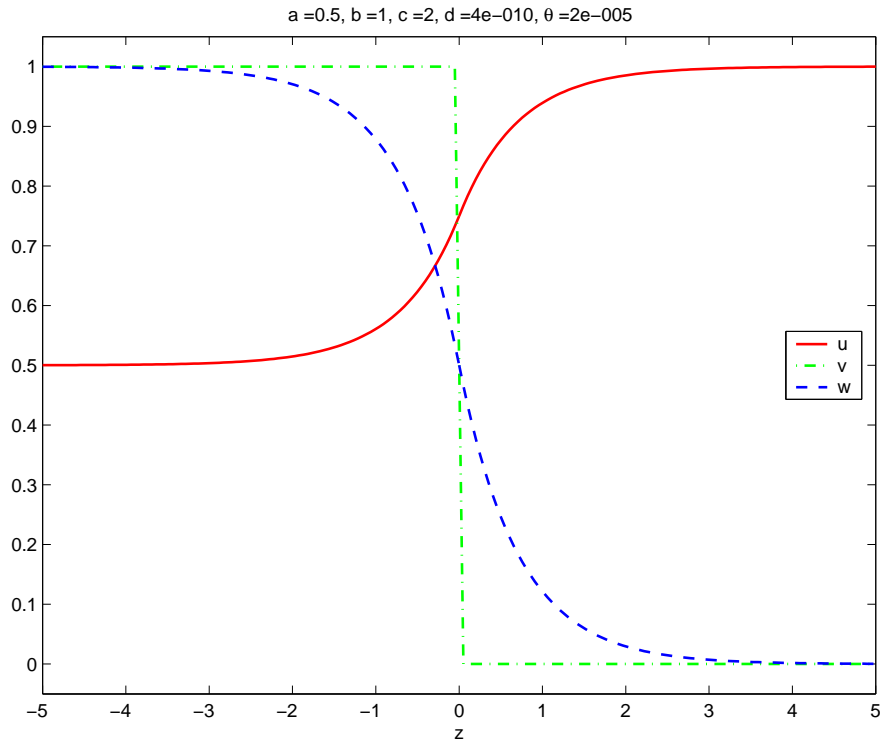


Figure 2: Plot of an approximate slow TW when $0 < a < 1$

At this juncture, it is worth comparing our set of wave velocities compatible with (1.6)–(1.8) with those proposed in [10]. In the latter work, the following implicit equation for θ was suggested:

$$\theta = du'(0; \theta) + 2\sqrt{[1 - u(0; \theta)]bd}, \quad (3.16)$$

where $u(0; \theta)$ denotes the value at $z = 0$ of the wave profile moving with velocity θ , and whose derivative at $z = 0$ is $u'(0; \theta)$. Notice that the wave values given in Proposition 3.1 are explicit, and a continuum of wave speeds is obtained for the case $\theta = \theta_0 d^\alpha$ with $0 < \alpha \leq 1/2$, whereas the situation formally considered in (3.16) deals only with the choice $\alpha = 1/2$.

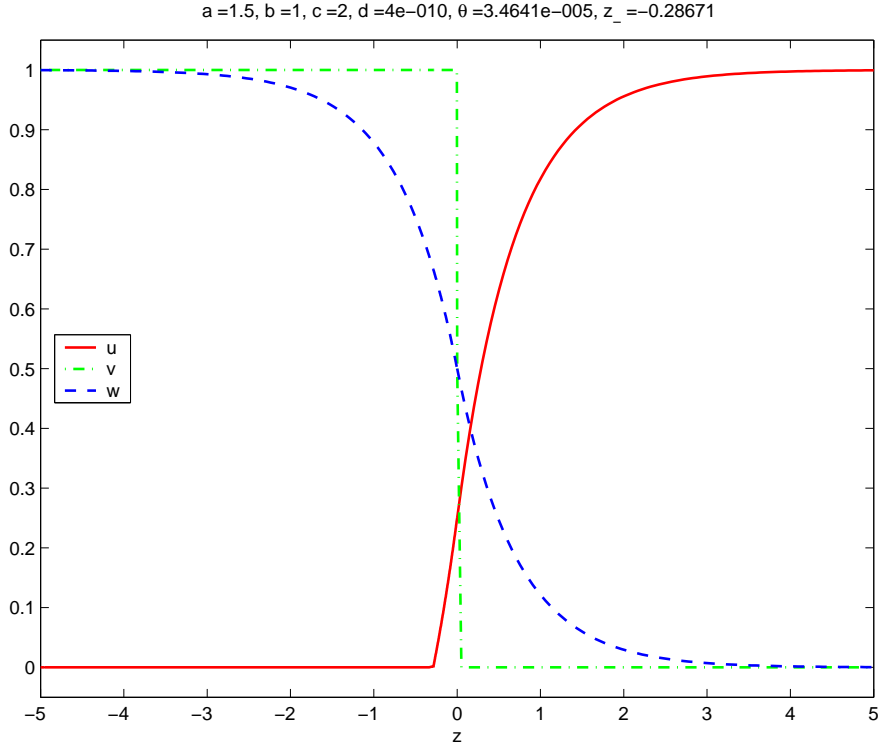


Figure 3: Plot of an approximate slow TW when $1 < a < 2$

3.5 An estimate of the width of the interstitial gap

Now we give a discussion on the existence of an interstitial gap, a fact that deserved considerable attention in [10]. We shall define an interstitial gap to be an interval I , if any, where $u(z; d) + v(z; d) \ll 1$ for all $z \in I$. By looking at the results of Proposition 3.1, we see that $I \simeq (0, z_+)$ so that the width of the gap as given in (2.12) is approximately

$$z_+ = \frac{1}{\sqrt{c}} \log \frac{a}{2} \quad (a > 2). \quad (3.17)$$

Indeed, when $0 < z < z_+$ we have $v(z; d) \simeq v_{\text{out}}(z) = 0$ and

$$u(z; d) \simeq \sqrt{\frac{\theta_0 \sqrt{c}}{2\pi}} d^{\alpha/2} e^{[\phi_+(z) - \phi_+(z_+)]/d^\alpha} = O(d^{\alpha/2} e^{-C/d^\alpha})$$

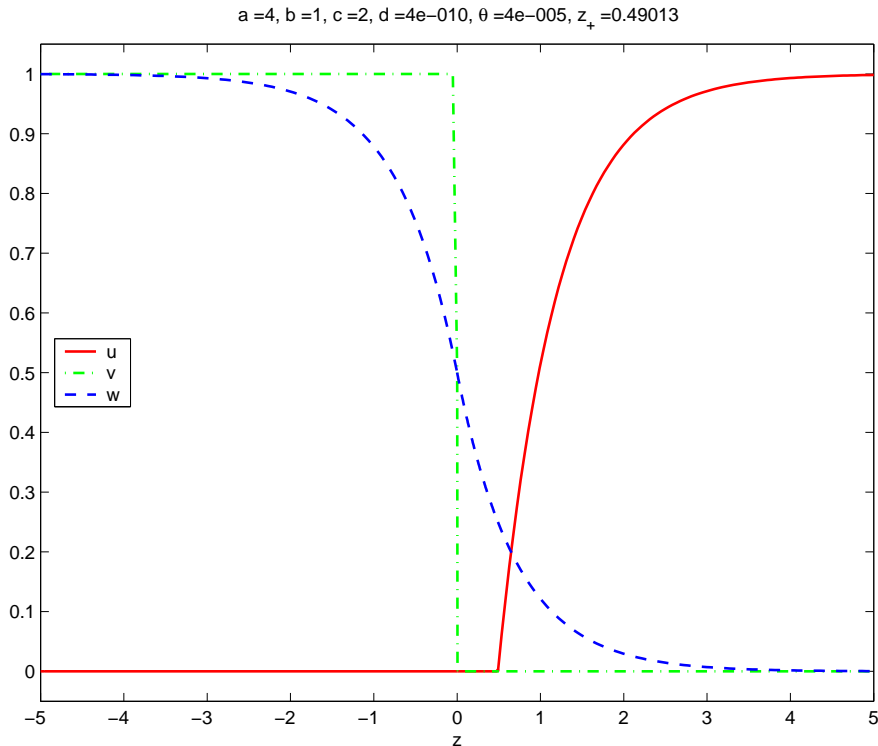


Figure 4: Plot of an approximate slow TW when $a > 2$

for some $C = C(z) > 0$ since $\phi'_+(z) > 0$ for $0 < z < z_+$. For $0 < a \leq 2$ the gap disappears.

Let us compare our estimate for the width of the gap with the value proposed for it in [10, pp. 5748–5749]:

$$z_+ \simeq \frac{1}{\sqrt{c}} \log \frac{a}{2} + \sqrt{\frac{\theta}{\sqrt{c}}} \quad (a \gg 1). \quad (3.18)$$

Whilst no details on the derivation of (3.18) were provided in [10], it is remarkable that our estimate (3.17) is in excellent agreement with (3.18) when $\theta = 2\sqrt{bd}$ not only for $a \gg 1$ but in the full range $a > 2$, provided that $d > 0$ is sufficiently small.

It is also worthwhile to give an interpretation of z_- . Suppose that $1 < a < 2$. Then for $z < 0$ we have $v(z; d) \simeq v_{\text{out}}(z) = 1$. On the other hand, for

$z < z_-$ we see that u is almost zero since

$$u(z; d) \simeq \sqrt{\frac{\sqrt{C}(a-1)\theta_0}{2\pi}} d^{\alpha/2} e^{[\phi_-(z) - \phi_-(z_-)]/d^\alpha} = O(d^{\alpha/2} e^{-C/d^\alpha})$$

for some $C = C(z) > 0$ since $\phi'_-(z) > 0$ for $z < z_-$. For $z_- < z < 0$ we have that $u(z; d) = O(1)$ and leaves $z = 0$ with a positive derivative. Hence, we can think of the interval $(z_-, 0)$ as an overlap region where healthy and neoplastic tissues can be found in the case $1 < a < 2$. The width of this overlap region is therefore approximately given by $-z_-$.

4 Fast waves: $\theta = O(1)$

4.1 Leading order approximation

Here we assume that $\theta = O(1)$ as $d \rightarrow 0^+$. Define

$$u_0(z) = u(z; 0), \quad v_0(z) = v(z; 0), \quad w_0(z) = w(z; 0).$$

From Lemma 2.3 we know that problem (1.6)–(1.9) is equivalent to (2.8)–(2.10). Setting $d = 0$ in (2.8) gives a Bernoulli equation whose solution is

$$v_0(z) = \frac{1}{1 + e^{bz/\theta}}. \quad (4.1)$$

It is clear that $v_0(-\infty) = 1$ and $v_0(\infty) = 0$. Equation (2.10) simplifies to

$$w_0(z) = \frac{c}{r_1 - r_2} \left[e^{r_1 z} \int_z^\infty e^{-r_1 s} v_0(s) ds + e^{r_2 z} \int_{-\infty}^z e^{-r_2 s} v_0(s) ds \right] \quad (4.2)$$

whilst (2.9) yields

$$u_0(z) = \frac{\theta \Phi_0(z)}{\int_z^\infty \Phi_0(s) ds}, \quad \Phi_0(z) = e^{-\int_0^z [1 - a w_0(s)]/\theta ds}. \quad (4.3)$$

Thus, to leading order we can approximate the solution of by (1.6)–(1.9) by

$$u(z; d) \simeq u_0(z), \quad v(z; d) \simeq v_0(z), \quad w(z; d) \simeq w_0(z)$$

where u_0 , v_0 , and w_0 satisfy (4.1)–(4.3) for any $\theta > 0$. We remark that here we have a regular perturbation problem since the solution of the reduced system satisfies all of the boundary conditions [5].

4.2 Stability

Next we show that the above solution is linearly stable. Let

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

where $z = x - \theta t$, $\tau = t$, and $\theta > 0$ is some fixed wave speed. Substituting into (1.1)–(1.3) we obtain

$$\tilde{u}_\tau = \theta \tilde{u}_z + \tilde{u}(1 - \tilde{u}) - a\tilde{u}\tilde{w}, \quad (4.4)$$

$$\tilde{v}_\tau = d[(1 - \tilde{u})\tilde{v}_z]_z + \theta \tilde{v}_z + b\tilde{v}(1 - \tilde{v}), \quad (4.5)$$

$$\tilde{w}_\tau = \tilde{w}_{zz} + \theta \tilde{w}_z + c(\tilde{v} - \tilde{w}). \quad (4.6)$$

We now look for a solution of (4.4)–(4.6) of the form

$$\tilde{u}(z, \tau; d) = u(z; d) + \epsilon e^{-\lambda\tau} \phi_1(z; d) + \cdots,$$

$$\tilde{v}(z, \tau; d) = v(z; d) + \epsilon e^{-\lambda\tau} \phi_2(z; d) + \cdots,$$

$$\tilde{w}(z, \tau; d) = w(z; d) + \epsilon e^{-\lambda\tau} \phi_3(z; d) + \cdots.$$

Here $0 < \epsilon \ll 1$ and (u, v, w) is the TW solution with speed θ found previously. On substituting into (4.4)–(4.6) and retaining the terms of order ϵ (the $O(1)$ system is satisfied automatically since (u, v, w) is a TW solution by hypothesis), we obtain

$$au\phi_3 = \theta\phi_1' + (\lambda + 1 - 2u - aw)\phi_1, \quad (4.7)$$

$$0 = d[(1 - u)\phi_2' - v'\phi_1]' + \theta\phi_2' + (\lambda + b - 2bv)\phi_2, \quad (4.8)$$

$$-c\phi_2 = \phi_3'' + \theta\phi_3' + (\lambda - c)\phi_3. \quad (4.9)$$

For the boundary conditions at infinity, it is natural to assume that

$$\phi_i(\pm\infty; d) = 0 \quad (i = 1, 2, 3). \quad (4.10)$$

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 since a small perturbation of the latter will decay to zero.

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

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

Setting $d = 0$ in (4.7)–(4.8) gives

$$au_0\phi_{3,0} = \theta\phi'_{1,0} + (\lambda + 1 - 2u_0 - aw_0)\phi_{1,0}, \quad (4.11)$$

$$0 = \theta\phi'_{2,0} + (\lambda + b - 2bv_0)\phi_{2,0}, \quad (4.12)$$

$$-c\phi_{2,0} = \phi''_{3,0} + \theta\phi'_{3,0} + (\lambda - c)\phi_{3,0}. \quad (4.13)$$

From (4.1) it follows that

$$1 - 2v_0(z) = \frac{e^{bz/\theta} - 1}{e^{bz/\theta} + 1} = \tanh \frac{bz}{2\theta}, \quad \int_0^z [1 - 2v_0(s)] ds = \frac{2\theta}{b} \log \cosh \frac{bz}{2\theta}.$$

Equation (4.12) can be rewritten as

$$\theta \frac{\phi'_{2,0}}{\phi_{2,0}} + \lambda + b \tanh \frac{bz}{2\theta} = 0,$$

which can be integrated to derive the eigenfunction

$$\phi_{2,0}(z) = \frac{1}{4} e^{-\lambda z/\theta} \operatorname{sech}^2 \frac{bz}{2\theta} = \frac{1}{[e^{(\lambda+b)z/(2\theta)} + e^{(\lambda-b)z/(2\theta)}]^2}.$$

Here we chose the arbitrary constant of integration to be equal to 1/4. We see that $\phi_{2,0}(\infty) = 0$ for any $\lambda > 0$. If we impose that $0 < \lambda < b$, then $\phi_{2,0}(-\infty) = 0$ and $\phi_{2,0}$ satisfies (4.10).

Rewrite (4.13) as

$$\phi''_{3,0} + \theta\phi'_{3,0} - (c - \lambda)\phi_{3,0} = -c\phi_{2,0}$$

and assume also that $0 < \lambda < c$. We can use once again Lemma 2.2 with $\beta = c - \lambda$, $W = \phi_{3,0}$, and $f = -c\phi_{2,0}$ to obtain

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

where

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

It is easy to see that $f(\pm\infty) = -c\phi_{2,0}(\pm\infty) = 0$ and $I_1(\pm\infty) = I_2(\pm\infty) = 0$, so that $\phi_{3,0}(\pm\infty) = 0$, i.e., $\phi_{3,0}$ satisfies (4.10) as well.

Equation (4.11) is a first-order linear equation, whose solution is

$$\phi_{1,0}(z) = -\frac{a \int_z^\infty u_0(s)\phi_{3,0}(s)\Phi(s) ds}{\theta \Phi(z)}, \quad \Phi(z) = e^{-\int_0^z [aw_0(s)+2u_0(s)-\lambda-1] ds}.$$

Let $g(s) = aw_0(s) + 2u_0(s) - \lambda - 1$. Then $g(\infty) = 1 - \lambda$ and there are three possibilities for λ , besides the already assumed restriction $0 < \lambda < \min(b, c)$. If $\lambda < 1$, then $g(\infty) > 0$, $\Phi(\infty) = 0$ from Lemma 2.2 (i), and

$$\begin{aligned} \phi_{1,0}(\infty) &= -\frac{a}{\theta} \lim_{z \rightarrow \infty} \frac{\int_z^\infty u_0(s)\phi_{3,0}(s)\Phi(s) ds}{\Phi(z)} \\ &= -\frac{a}{\theta} \lim_{z \rightarrow \infty} \frac{-u_0(z)\phi_{3,0}(z)\Phi(z)}{-\Phi(z)g(z)} \\ &= 0. \end{aligned}$$

If $\lambda > 1$, then $g(\infty) < 0$, $\Phi(\infty) = \infty$ from Lemma 2.2 (ii), and we obtain $\phi_{1,0}(\infty) = 0$. If $\lambda = 1$, then $g(\infty) = 0$ so Lemma 2.2 does not apply. But $0 < \Phi(\infty) \leq \infty$ and therefore $\phi_{1,0}(\infty) = 0$. In other words, for any $0 < \lambda < \min(b, c)$, we have $\phi_{1,0}(\infty) = 0$.

Next we look at $\phi_{1,0}(-\infty)$. Suppose that $a > 1$ and take $\lambda < a - 1$. Then we have $g(-\infty) = a - \lambda - 1 > 0$, $\Phi(-\infty) = \infty$ from Lemma 2.2 (iii), and $\phi_{1,0}(-\infty) = 0$ if $\int_{-\infty}^\infty u_0(s)\phi_{3,0}(s)\Phi(s) ds$ converges. If the latter diverges to infinity, then

$$\phi_{1,0}(-\infty) = -\frac{a}{\theta} \lim_{z \rightarrow -\infty} \frac{-u_0(z)\phi_{3,0}(z)\Phi(z)}{-\Phi(z)g(z)} = 0.$$

In other words, if $a > 1$ and $0 < \lambda < \min(b, c, a - 1)$, then $\phi_{1,0}(\pm\infty) = 0$. Now suppose that $0 < a < 1$ and take $\lambda < 1 - a$ so that $g(-\infty) = 1 - a - \lambda > 0$ and $\Phi(-\infty) = \infty$ from Lemma 2.2 (iii). The same argument as before leads to $\phi_{1,0}(-\infty) = 0$. Thus, if $0 < a < 1$ and $0 < \lambda < \min(b, c, 1 - a)$, then $\phi_{1,0}(\pm\infty) = 0$.

Since it is possible to find a nontrivial solution of (4.7)–(4.10) to leading order for $0 < \lambda < \min(b, c, 1 - a)$ when $0 < a < 1$ or $0 < \lambda < \min(b, c, a - 1)$ when $a > 1$, then the approximate fast TW we obtained here is linearly stable. Note that the above argument breaks down when $a = 1$.

4.3 Statement of results for fast waves

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

Proposition 4.1. *Let θ be a positive constant such that $\theta = O(1)$ as $d \rightarrow 0^+$. Then for any $a > 0$ the asymptotic wave profiles given by (4.1)–(4.3) are compatible with (1.6)–(1.9). Such profiles are linearly stable when $a \neq 1$; no restriction on the wave speed other than $\theta > 0$ is required.*

5 Concluding remarks

In this article we considered a reaction-diffusion model for tumour invasion proposed by Gatenby and Gawlinski [10]. A paramount feature of this model is that tumour progression is mediated by acidification of the surrounding tissue. In particular, the model postulates that an excess of H^+ ions is produced by tumour cells as a consequence of their anaerobic, glycolytic metabolism. In this way pH is lowered ahead of the advancing tumour front. Moreover, for certain parameter values, healthy tissue could be destroyed prior to the arrival of malignant cells. This would result in the onset of an interstitial gap, where both the normalised concentrations of healthy and tumour cells would be negligible.

We undertook an analytical study of the mathematical model originally proposed in [10]. Here we showed the compatibility of the Gatenby-Gawlinski model with various types of slow (Proposition 3.1) and fast (Proposition 4.1) TWs. The latter type of TWs were not considered in [10], although in our opinion they have some interest on their own. For instance, the functions given in (4.1)–(4.3) provide an explicit example of wave-like tumour invasion when the diffusivity of the neoplastic tissue is completely neglected.

We characterised the conditions for which an interstitial gap exists and gave an analytical approximation for its width. Our results point to the existence of such a gap when $a > 2$, in which case its size can be estimated by the value of z_+ in (2.12). We have already remarked that this value confirms and extends the gap width estimate proposed in [10].

A question that naturally arises is how our estimate of the width of the interstitial gap compares with what is actually observed experimentally, e.g., the result shown in Figure 1. A close inspection of this figure shows that the gap width is of the order of the cellular size, i.e., $10^{-2} \sim 10^{-3}$ cm. If we keep track of the nondimensionalisation performed in [10] and take into account

the parameter values reported therein (both are summarised in Section 2.1 here), it turns out that our estimate (and also the estimate provided in [10], with which we are in good agreement) for the case $c = 70$ and $a = 12.5$ is of the order 10^{-1}cm , which is larger than expected. However, a gap size of about 10^{-2}cm is obtained if we select $a = 3$ instead of $a = 12.5$ and c as before. This change in parameter values is in agreement with our remark at the end of Section 2.1.

In Figure 5 we compare the results of numerical simulations of (1.1)–(1.3) given in [10] with the plots of our approximate solutions of (1.6)–(1.8) using the same parameter values. For $a > 2$ and $z < z_+$ we have from (3.13c)

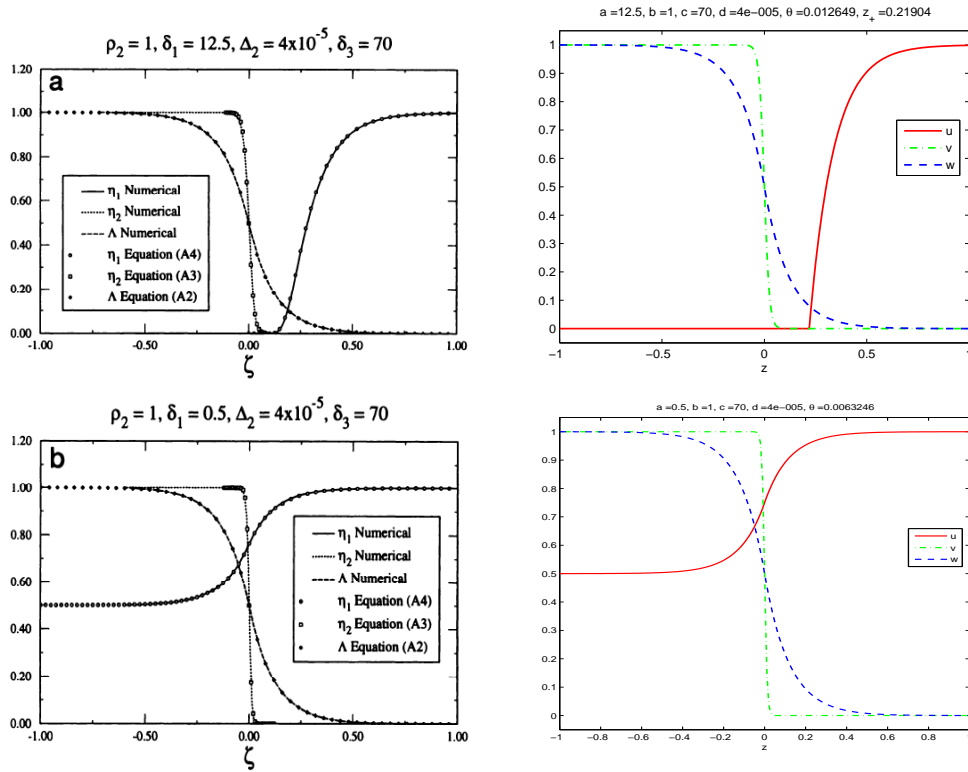


Figure 5: Comparison of the numerical solution in [10] (reprint permission requested), (a) and (b) in the left column, with the approximate analytical functions found here with the same parameter values

that $u(z; d) = O(d^{\alpha/2}e^{-C/d^\alpha})$ for some $C = C(z) > 0$, so we set $u(z; d) = 0$

for $z < z_+$. In the left graph of Figure 6 we provide a representation of the approximations corresponding to u , v , and w (where we again set $u(z; d) = 0$ for $z < z_+$) for the case when $a = 12.5$ is replaced by $a = 3$ and the remaining parameter values are as in Figure 2a of [10]. We have already

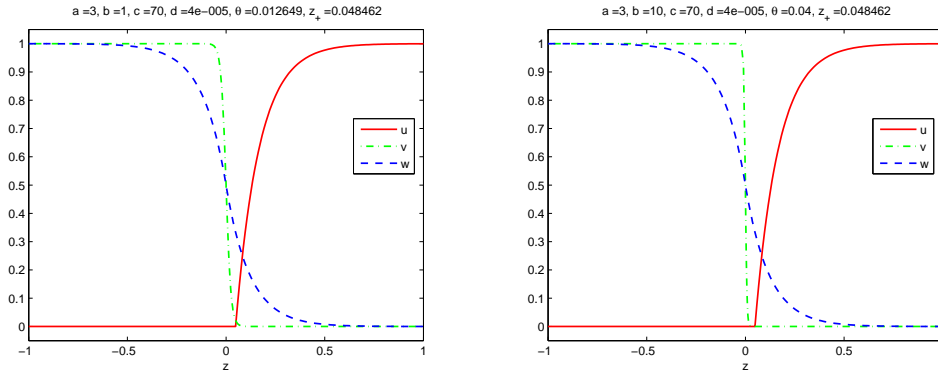


Figure 6: Some plots of the approximate analytical functions for different parameter values

mentioned that the parameter choices in [10] have to be considered only as approximate. For instance, it is arguable whether r_1 should be equal to r_2 in (2.1). A more realistic approximation would be to take, say, $b = r_2/r_1 = 10$ (cf. [20]). When all the remaining parameters are kept fixed, such a change in b would be reflected in a steeper profile of v near the front, as well as in an increase in the minimal wave velocity in the statement of Proposition 3.1. For completeness a plot of the case $a = 3$, $b = 10$, $c = 70$, and $d = 4 \times 10^{-5}$ is provided in the right graph of Figure 6.

We point out that approximating functions for the wave profiles u , v , and w have been proposed in [10, p. 5752], so it is interesting to compare them with our results in Proposition (3.1). The functions described in (A2)–(A4) of [10], which are obtained by setting $d = 0$ in (1.6)–(1.8) here, correspond to the outer solutions we considered in Section 2. However, to obtain uniformly valid expansions, the possible presence of boundary layers near $z = 0$ has to be considered, in which case some of the terms on the right-hand side of (A1) may be of order $O(1)$ even if $0 < d \ll 1$. This is the reason why we undertook the singular perturbation analysis described in Section 3.

The linear stability of fast TWs was shown to hold in the generic case

when $a \neq 1$. A mathematical analysis of the linear stability of the slow TWs discussed here is more involved since the equation associated with the eigenfunction for v is of second order with variable coefficients. Nevertheless, we expect that these slow waves will also be stable, but no proof of this fact has been provided here.

In spite of the modelling limitations associated with a simple system such as (1.6)–(1.8), our analysis points to the existence of an unexpectedly rich dynamics. In particular, a variety of wave propagation behaviours has been uncovered whose detailed study may deserve further consideration. A particularly intriguing fact is the relation between the existence of an interstitial gap, as a consequence of acid-mediated destruction of healthy tissue, and slow wave propagation, which the approach in [10] seems to link to rather slow invasion processes. We hope that our analysis will be helpful in deriving and discussing more refined models that would eventually provide further insight into the actual manner in which tumour invasion takes place.

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