Mathematical analysis of some multi-dimensional tissue-growth models

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Mathematical models for the growth of nutrient-rich tissue are presented and a number of properties of the resulting models outlined. The focus is on obtaining broadly applicable results for the simplest appropriate formulations by using matched-asymptotic, moving-boundary and thin-film approaches; the relevance of the results to a variety of specific biological applications will be addressed elsewhere, as will the inclusion of additional physical phenomena.

1 Introduction

The class of models with which we are concerned here is one of the simplest able to predict certain key stages in the growth of tumours (which provided the original motivation for the modelling) and of other types of tissue, namely the growth phases in which all cells have an adequate supply of nutrient due either to the tissue being small in volume or to it being well perfused by the blood supply; for further background and related considerations we refer to the recent studies [3, 12, 13] and references therein. Our purpose is three-fold. Firstly, we aim to establish a mathematical framework for studying a variety of aspects of tissue growth, moving-boundary and thin-film formulations playing a central role; applications of these general results in analysing a range of specific biological issues will be presented elsewhere. Secondly, we seek to summarise some of the novel features of the resulting models in the context of related classes of moving-boundary problem; these novelties result largely from the presence of cellular division, which leads to source terms that are absent in typical applications from the physical sciences. Finally, we investigate in some detail the role played by cellular diffusion in these growth models.

The conservation laws for the two species with which we are concerned take the form

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\mathbf{v}) = \nabla \cdot (D_n \nabla n) + kn,$$
$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho\mathbf{v}) = \nabla \cdot (D_\rho \nabla \rho) + \kappa\rho, \qquad (1.1)$$
$$n + \rho = 1,$$

where n is the volume fraction of one cell type (malignant, in the tumour context) and ρ that of the second (normal cells, with the mitotic rates typically satisfying $0 \leqslant \kappa < k$, or another surrounding material, such as a fluid or gel (so that $\kappa = 0$) in the case of *in*

vitro growth; we shall assume throughout that $0 \leqslant \kappa \leqslant k$, with $k \gg \kappa$ being appropriate for malignant tumour growth); in the case of growth within a porous scaffold, n and ρ represent volume fractions of the available void space. Both phases are thus assumed to be incompressible and to form a single continuum, whose macroscopic velocity field $\mathbf{v}$ can be deduced from (1.1) to satisfy

$$\nabla \cdot \mathbf{v} = \nabla \cdot (D_n \nabla n + D_\rho \nabla \rho) + kn + \kappa \rho. \tag{1.2}$$

The (cellular) diffusivities D_n and D_ρ can be taken to be composition (i.e. n) dependent; they can be expected often to be negligible in practice, but are in any case useful numerically since they ensure smooth solutions. To complete a multi-dimensional model, a constitutive assumption is needed, but we first describe the one-dimensional case in which (1.1) provides a closed model. For transparency we work with dimensional versions of the problem for most of the paper; in §5, however, a non-dimensionalisation is needed in order to extract the relevant distinguished limits.

2 The one-dimensional problem

2.1 Formulation

To illustrate the properties of the growth model and to investigate the effects of cellular diffusion we first consider the one-dimensional problem, taking the growth to be in the x-direction.

Eliminating ρ and denoting the velocity by u in (1.1)–(1.2), we have

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(nu) = \frac{\partial}{\partial x}\left(D_n \frac{\partial n}{\partial x}\right) + kn,$$

$$\frac{\partial u}{\partial x} = \frac{\partial}{\partial x}\left((D_n - D_\rho)\frac{\partial n}{\partial x}\right) + (k - \kappa)n + \kappa. \tag{2.1}$$

For definiteness we impose

$$\frac{\partial n}{\partial x} = 0, \quad u = 0 \qquad \text{at} \ \ x = 0,$$
$$n \to 0 \qquad \qquad \text{as} \ \ x \to +\infty, \tag{2.2}$$

so that the tissue is symmetrical about the $x = 0$ axis. Noteworthy features of (2.1) include its invariance under arbitrary translations

$$x = s(t) + \hat{x}, \quad t = \hat{t}, \quad n = \hat{n}, \quad u = \dot{s}(t) + \hat{u} \tag{2.3}$$

and the availability of an exact first integral. It is convenient first to subtract off the velocity due to differences in the rates of interdiffusion (cf. the Kirkendall effect – Crank [4, Chap. 10] contains discussion of a number of points relevant to the modelling here) by writing

$$u = (D_n - D_\rho)\frac{\partial n}{\partial x} + U \tag{2.4}$$

and we then obtain for $\kappa \neq k$

$$n = \frac{1}{(k - \kappa)} \frac{\partial}{\partial x} (U - \kappa x),$$

$$\frac{\partial U}{\partial t} + U \frac{\partial U}{\partial x} = \frac{1}{(k - \kappa)} \left(k D_n - \kappa D_\rho - (D_n - D_\rho) \frac{\partial U}{\partial x} \right) \frac{\partial^2 U}{\partial x^2} + (k + \kappa) U - k \kappa x \tag{2.5}$$

(because $0 \leqslant n \leqslant 1$, the diffusivity in the second of (2.5) is necessarily positive), while for $\kappa = k$ we have

$$U = kx,$$

$$\frac{\partial n}{\partial t} + k x \frac{\partial n}{\partial x} = \frac{\partial}{\partial x} \left((D_n(1 - n) + D_\rho n) \frac{\partial n}{\partial x} \right). \tag{2.6}$$

While we shall not pursue radially-symmetric problems further here, it is worth noting that these first integrals generalise to this case; in N dimensions, with $r = |\mathbf{x}|$ and $U = \partial n / \partial r = 0$ on $r = 0$, we have (with x replaced by r in (2.4)) for $\kappa \neq k$ that

$$n = \frac{1}{(k - \kappa)} \left(\frac{1}{r^{N-1}} \frac{\partial}{\partial r} (r^{N-1} U) - \kappa \right),$$

$$\frac{\partial U}{\partial t} + \frac{U}{r^{N-1}} \frac{\partial}{\partial r} (r^{N-1} U) = (D_n(1 - n) + D_\rho n) \frac{\partial n}{\partial r} + (k + \kappa) U - \frac{k \kappa}{N} r$$

and for $\kappa = k$ that

$$U = \frac{k}{N} r,$$

$$\frac{\partial n}{\partial t} + \frac{k}{N} r \frac{\partial n}{\partial r} = \frac{1}{r^{N-1}} \frac{\partial}{\partial r} \left(r^{N-1} (D_n(1 - n) + D_\rho n) \frac{\partial n}{\partial r} \right).$$

2.2 The role of cellular diffusion

We now consider the initial boundary value problem in which (2.1) is subject to (2.2) and

$$n = 1 \quad \text{for} \ \ 0 < x < a, \qquad n = 0 \quad \text{for} \ \ x > a \qquad \text{at} \ \ t = 0, \tag{2.7}$$

where $x = a$ represents the initial (sharp) tumour boundary. From (2.1) we then have

$$\int_0^\infty n(x, t) dx = a e^{kt}, \tag{2.8}$$

so that

$$U = \kappa x + a(k - \kappa) e^{kt} + o(1) \qquad x \to +\infty. \tag{2.9}$$

For $D_n = D_\rho = 0$ (so that $U = u$), it follows from (2.5) or (2.6) that the solution is simply

$$\begin{aligned} u &= kx, & n &= 1 & \text{for} \ \ x < a e^{kt} \\ u &= \kappa x + a(k - \kappa) e^{kt}, & n &= 0 & \text{for} \ \ x > a e^{kt} \end{aligned} \tag{2.10}$$

where the interface $s(t) = ae^{kt}$ satisfies

$$\frac{ds}{dt} = u$$

and is of course a characteristic projection of the relevant first order partial differential equation. Obviously, such exponential growth is to be expected for a population of cells with no constraints on its growth.

For non-zero diffusivities, the large-time behaviour is most readily unravelled for $\kappa = k$, when the mitotic rates of n and ρ are equal (this case being mathematically instructive but of limited biological interest). Writing

$$X = x/e^{kt}, \qquad T = \frac{1}{2k}(1 - e^{-2kt})$$

yields from (2.6) that

$$\frac{\partial n}{\partial T} = \frac{\partial}{\partial X}\left((D_n(1-n) + D_\rho n)\frac{\partial n}{\partial X}\right). \tag{2.11}$$

Since T remains bounded as $t \to \infty$ it follows that

$$n \sim n_\infty(X) \qquad \text{as } t \to \infty$$

where n_∞ depends on the initial data (thus the diffusion terms are negligible for large t, but they act to smooth the solution for $t = O(1)$). For discontinuous initial data, the nonlinear diffusion equation (2.11) leads for small T to the usual Boltzmann similarity solution (the $T^{1/2}$ behaviour being characteristic of diffusive spreading).

$$n \sim n_a\left((X-a)/T^{\frac{1}{2}}\right) \qquad \text{as } T \to 0 \qquad \text{with } X - a = O\left(T^{\frac{1}{2}}\right),$$

with $n_a(\eta) \to 1$ as $\eta \to -\infty$, $n_a(\eta) \to 0$ as $\eta \to +\infty$, and in the limit $D_n, D_\rho \to 0$ this similarity solution furnishes the asymptotic behaviour for all t, with

$$n_\infty(X) \sim n_a(\sqrt{2k}(X-a));$$

this profile varies on the scale $X = a + O(\sqrt{D/k})$, where the constant D is a representative diffusivity and for $D_n = D_\rho = D$ it is of error function form.

The large-time behaviour for $0 < \kappa < k$ is surprisingly subtle. For $x/e^{kt} < a$ we have

$$u \to kx, \qquad n \to 1 \qquad \text{as } t \to \infty, \tag{2.12}$$

as in (2.10), and we translate to the frame of the 'interface' via

$$x = ae^{kt} + z, \qquad U = ake^{kt} + W \tag{2.13}$$

to give

$$\frac{\partial W}{\partial t} + W\frac{\partial W}{\partial z} = \frac{1}{(k-\kappa)}\left(kD_n - \kappa D_\rho - (D_n - D_\rho)\frac{\partial W}{\partial z}\right)\frac{\partial^2 W}{\partial z^2} + (k+\kappa)W - k\kappa z. \tag{2.14}$$

We first need to determine the large z behaviour of W from (2.14); in view of (2.9) we write

$$W = \kappa z + \Phi(z, t)$$

with $\Phi \ll 1$, and linearise to give

$$\frac{\partial \Phi}{\partial t} + \kappa z \frac{\partial \Phi}{\partial z} \sim D_n \frac{\partial^2 \Phi}{\partial z^2} + k\Phi$$

where for brevity we take D_n to be constant. Writing

$$\Phi = e^{kt} \Psi(\zeta, \tau), \qquad \zeta = z/e^{\kappa t}, \qquad \tau = \frac{D_n}{2\kappa}(1 - e^{-2\kappa t}) \qquad (2.15)$$

gives the heat equation

$$\frac{\partial \Psi}{\partial \tau} \sim \frac{\partial^2 \Psi}{\partial \zeta^2},$$

so that

$$\Psi \sim -\frac{1}{\tau^{\frac{1}{2}}} F\left(\frac{\zeta}{\tau}\right) e^{-\frac{\zeta^2}{4\tau}} \qquad \text{as } \zeta \to +\infty \qquad (2.16)$$

(which implies that n is exponentially small) follows in the usual way on application of the WKBJ technique; in (2.16), F is an arbitrary positive function which can be determined only be solving the full problem (2.14). We note from (2.15) that the lengthscale $z = O(e^{\kappa t})$ over which this smoothing occurs is dictated by the growth of the surrounding material, while the location of the interface (see (2.13)) is of course determined by the growth of the tumour itself. It follows from (2.16) that as $z \to +\infty$, $t \to \infty$ we have

$$W \sim \kappa z - e^{kt} \sqrt{\frac{2\kappa}{D_n}} F\left(\frac{2\kappa z}{D_n e^{\kappa t}}\right) e^{-\kappa z^2/2D_n e^{2\kappa t}}. \qquad (2.17)$$

The expression (2.17) is valid for sufficiently large z; it turns out that it ceases to apply for $\zeta = O(1)$, where

$$z = e^{\kappa t}\left(\sqrt{\frac{2D_n(k-\kappa)t}{\kappa}} + \sqrt{\frac{D_n}{2\kappa(k-\kappa)t}} \ln\left(\sqrt{\frac{2\kappa t}{D_n}} F\left(2\sqrt{\frac{2\kappa(k-\kappa)t}{D_n}}\right)\right) + \frac{\xi}{\sqrt{t}}\right) \quad (2.18)$$

(the relevant argument is akin to that sometimes used in determining the wavefront location for Fisher's equation), whereby (2.17) implies the matching condition

$$\Phi(\zeta, t) \sim -\frac{1}{\sqrt{t}} e^{\kappa t} e^{-\sqrt{2\kappa(k-\kappa)/D_n}\zeta} \qquad \text{as } \zeta \to +\infty. \qquad (2.19)$$

Writing

$$\Phi = e^{\kappa t} \phi(\zeta, t),$$

we have

$$\frac{\partial \phi}{\partial t} + \phi \frac{\partial \phi}{\partial \zeta} = e^{-2\kappa t}\left(D_n - \frac{D_n - D_\rho}{k - \kappa} \frac{\partial \phi}{\partial \zeta}\right)\frac{\partial^2 \phi}{\partial \zeta^2} + (k - \kappa)\phi,$$

so the diffusion terms are again exponentially small for large t. In view of (2.19) we then set

$$\phi \sim \frac{1}{\sqrt{t}} \psi(\xi) \qquad \text{for } \xi = O(1), \ t \to \infty,$$

so that

$$-\sqrt{\frac{D_n(k-\kappa)}{2\kappa}}\frac{d\psi}{d\xi} + \psi\frac{d\psi}{d\xi} = (k-\kappa)\psi,$$

this balance being that which identifies the appropriate scaling for ξ in (2.18). Hence

$$\psi - \sqrt{\frac{D_n(k-\kappa)}{2\kappa}}\ln(-\psi) = (k-\kappa)\xi,$$

which matches with (2.19) as $\xi \to +\infty$ and satisfies

$$\psi \sim (k-\kappa)\xi \qquad \text{as } \xi \to -\infty,$$

thus matching with (2.12) also.

Finally, in the important special case $\kappa = 0$ the expression (2.12) again provides the outer solution; the leading order inner solution is obtained by setting

$$W \sim W_0(Z), \quad Z = z - S(t), \quad S(t) \sim qt \qquad \text{as } t \to +\infty$$

in (2.14) (with $\kappa = 0$) whereby

$$-q\frac{dW_0}{dZ} + W_0\frac{dW_0}{dZ} = \left(D_n - \frac{(D_n - D_\rho)}{k}\frac{dW_0}{dZ}\right)\frac{d^2W_0}{dZ^2} + kW_0 \tag{2.20}$$

subject to

$$\begin{aligned} W_0 &\sim kZ && \text{as } Z \to -\infty \\ W_0 &\to 0 && \text{as } Z \to +\infty, \end{aligned} \tag{2.21}$$

the latter following from (2.9). The growth of the tumour alone would lead to the interface being located exactly at ae^{kt} (see (2.13)); the additional distance qt here is thus due to normal cells being trapped in steadily-increasing numbers behind the advancing front. The constant q is determined (as with Fisher's equation) as the minimum wavespeed for which (2.20)–(2.21) has a non-positive solution; if the relevant criterion is the local behaviour as $z \to +\infty$ (i.e. if one has 'linear selection'/a 'pulled front') then

$$q = 2\sqrt{kD_n} \tag{2.22}$$

if D_n is a constant. This travelling wave forms a 'capsule' comprising a mixture of malignant and normal cells which surrounds the growing tumour.

The role of cellular diffusion can thus be summarised as follows. For $\kappa > 0$ its direct effect is negligible as $t \to \infty$ but, because it smooths the interface (the tumour boundary) for $t = O(1)$, it has the indirect effect of leading to a slow transition in n from 1 to 0 over the range $x - s(t) = O(\sqrt{D}e^{kt}/\sqrt{k})$ for $k = \kappa$ (where D again denotes a representative diffusivity) and $x - s(t) = O(\sqrt{D}e^{\kappa t}/\sqrt{kt})$ for $0 < \kappa < k$, with $s \sim ae^{kt} + O(\sqrt{D}te^{\kappa t})$ (where $s(t)$ can be defined by $n(s,t) = 0.5$, for example; the smoothing is in effect convected by the growth of the tissue ρ). Finally, for $\kappa = 0$ the smoothing occurs over the range $x - s(t) = O(\sqrt{D/k})$ with $s(t) \sim ae^{kt} + qt$, where $q = O(\sqrt{kD})$. These results are in sharp contrast to those for the pure interdiffusion problem $k = \kappa = 0$ in which it follows from (2.6) that the smoothing is purely diffusion controlled and thus proceeds over the range

$x - a = O(\sqrt{Dt})$. For $k > 0$, the growth of the tissue ρ when $\kappa > 0$ greatly enhances the range of smoothing, but for $\kappa = 0$ it is limited to $x - s(t) = O(\sqrt{D/k})$, so the interface remains relatively sharp, the travelling wave outrunning its attempts to smear out by diffusion. In view of (2.8), $s(t) - ae^{kt}$ is representative of the number of ρ cells trapped behind the advancing interface; for $\kappa = 0$ these are not able to reproduce and their numbers grow linearly with t, while for $\kappa > 0$ increasing numbers are swept up by the expanding front.

For the purpose of the subsequent discussion, it is worth recording the far-field behaviour when $\kappa = 0$. We have

$$W \sim -\frac{1}{t^{\frac{1}{2}}} F\left(\frac{z}{t}\right) e^{kt - z^2/4D_n t}, \qquad n \sim \frac{1}{2kD_n t^{\frac{1}{2}}} \frac{z}{t} F\left(\frac{z}{t}\right) e^{kt - z^2/4D_n t} \qquad \text{as } z \to +\infty \qquad (2.23)$$

while far behind the 'interface' (for all t for $D \ll 1$ and for large t for $D = O(1)$)

$$W \sim kz - \frac{1}{(1 - e^{-2kt})^{\frac{1}{2}}} G\left(\frac{k(-z)}{\sinh(kt)}\right) e^{-kz^2/2D_\rho(e^{2kt} - 1)},$$

$$\rho \sim \frac{e^{-kt}}{2D_\rho(1 - e^{-2kt})^{\frac{1}{2}}} \frac{(-z)}{\sinh(kt)} G\left(\frac{k(-z)}{\sinh(kt)}\right) e^{-kz^2/2D_\rho(e^{2kt} - 1)}, \qquad (2.24)$$

where G depends on the evolution over all time; matching with the large-time travelling wave requires that $G(\tau) \sim -q \ln \tau$ as $\tau \to 0^+$ (and the second of (2.24) does not hold in this limit because the G' term in ρ cannot be neglected). For large time, the decay of ρ behind the front with z is thus very slow (having z scaling with e^{kt}), but on this lengthscale ρ decreases with t as e^{-kt} due to dilution, by the growing n population, of the ρ material that has been left behind the front.

The special case $D_\rho = 0$, in which (2.24) evidently does not apply, is worth expanding upon. Writing

$$W = kz - \Lambda(z, t)$$

then gives

$$\frac{\partial \Lambda}{\partial t} + kz \frac{\partial \Lambda}{\partial z} = \frac{D_n}{k} \frac{\partial \Lambda}{\partial z} \frac{\partial^2 \Lambda}{\partial z^2} + \Lambda \frac{\partial \Lambda}{\partial z}$$

and, because of the degeneracy of the diffusion term, $\Lambda = \rho \equiv 0$ holds in place of (2.24) for $z \leqslant -\sigma(t)$, say, with $\sigma \sim \sigma_\infty e^{kt}$ as $t \to \infty$ for some constant $\sigma_\infty \in (0, a)$; for small D we have $\sigma_\infty = O(\sqrt{D/k})$.

3 Multi-dimensional models: Darcy flow

3.1 Formulation

On the (slow) timescale of tissue growth, elastic effects can typically be neglected (the viscoelastic relaxation time being much less than the timescale of growth, cf. Fung [14]) and the tissue treated as a (Newtonian) fluid. A Darcy constitutive relation has often been adopted in modelling tumour growth [1], [2], [15], though apparently often more for mathematical simplicity than on physical grounds (see Please *et al.* [21] and Landman & Please [20], however, for an example of a physically based derivation; we stress that

in contrast to such approaches we are for simplicity concerned here with tissue through which both nutrient and extracellular fluid are readily transported, so cell division is not restricted by a shortage of either). We address this case first, *I* part because of its historical prevalence and in part for its relevance to the growth of engineered tissue in porous scaffolds.

We thus supplement (1.1) by the constitutive law

$$\mathbf{v} = -\frac{K}{\mu(n)}\nabla p \tag{3.1}$$

where K is the permeability of the scaffold, $\mu(n)$ is the viscosity of the growing continuum and p is the pressure field. We note from (1.1) that the velocities of the n and ρ phases are given respectively by

$$\mathbf{v}_n = \mathbf{v} - D_n\nabla(\ln n), \qquad \mathbf{v}_\rho = \mathbf{v} - D_\rho\nabla(\ln \rho)$$

and how the constitutive law (whether Darcy or Stokes) should be formulated in terms of the various possible velocity fields is not without controversy (e.g. see Joseph [17] and Camacho & Brenner [4] for a discussion of related matters; we stress that such issues are not relevant to the one-dimensional case). Here we are primarily concerned with the case of small D_n and D_ρ and shall not dwell further on such matters; in (3.1) and (4.1) we adopt a simple-minded approach whereby diffusion (operating at the cellular level) is in effect regarded as a process separate from the macroscopic tissue deformation described by $\mathbf{v}$. Indeed, in this section we shall focus exclusively on the sharp interface limit with $D_n = D_\rho = 0$ in which

$$\begin{aligned} n = 1, &\qquad \mu = \mu_n &\qquad \text{in}\ \ \Omega_n(t), \\ n = 0, &\qquad \mu = \mu_\rho &\qquad \text{in}\ \ \Omega_\rho(t), \end{aligned}$$

and we denote the interface which separates Ω_n and Ω_ρ by $\Gamma(t)$. Thus

$$\begin{aligned} \nabla \cdot \left(\frac{K}{\mu_n}\nabla p\right) = -k &\qquad \text{in}\ \ \Omega_n(t), \\ \nabla \cdot \left(\frac{K}{\mu_\rho}\nabla p\right) = -\kappa &\qquad \text{in}\ \ \Omega_\rho(t), \end{aligned} \tag{3.2}$$

and

$$[p]_-^+ = 0, \qquad q_v = -\frac{K}{\mu_n}\frac{\partial p}{\partial v}\Big|_- = -\frac{K}{\mu_\rho}\frac{\partial p}{\partial v}\Big|_+ \qquad \text{on}\ \Gamma(t),$$

where '$-$' denotes the limit as Γ is approached from within Ω_n and '$+$' from within Ω_ρ; $\partial/\partial v$ is the normal derivative pointing into Ω_ρ and q_v is the normal velocity of the interface in the same direction. In the two-dimensional case, the moving-boundary problem (3.2) is of the Hele–Shaw squeeze film type (cf. Entov *et al.* [10], Lacey [19] and Shelley *et al.* [23] for example; see also Howison [16] for a discussion of two-phase Hele–Shaw problems) but the rates of 'squeezing' (k and κ) in the two phases can differ in this biological context, this being a novel feature of the current formulation; in the case of engineered growth in a scaffold, the second (ρ) phase will typically be largely

water, so that $\kappa = 0$. Moreover, whereas such formulations of Hele-Shaw squeeze films are intrinsically two-dimensional, problems in three dimensions are also of interest here. A linear stability analysis [11] shows a planar interface to be stable for $\mu_n > \mu_\rho$ and unstable for $\mu_n < \mu_\rho$, as with conventional Hele–Shaw problems.

3.2 Baiocchi transform

In one-phase cases (cf. Elliott & Janovsky [9], Lacey [18] and below), the Baiocchi transform provides a useful reformulation of (3.2). Here we pursue briefly the two-phase case in large part to clarify its limitations. We write $\Gamma(t)$ as $t = \omega(\mathbf{x})$, so that

$$\text{on } t = \omega(\mathbf{x}) \qquad [p]_-^+ = 0, \qquad -1 = \frac{K}{\mu_n}\nabla\omega \cdot \nabla p|_- = -\frac{K}{\mu_\rho}\nabla\omega \cdot \nabla p|_+, \qquad (3.3)$$

and introduce

$$w = K\int_0^t e^{-\lambda t'}p(x,y,t')dt', \qquad (3.4)$$

where $\lambda = (k\mu_n - \kappa\mu_\rho)/(\mu_n - \mu_\rho)$, provided $\mu_n \ne \mu_\rho$. We assume $q_v > 0$; then it follows from (3.2)–(3.3) that

$$\nabla^2 w = -\frac{k\mu_n}{\lambda}(1 - e^{-\lambda t}) \qquad \text{in } \Omega_n(0),$$

$$\nabla^2 w = -\left(\frac{\kappa\mu_\rho}{\lambda} - \frac{k\mu_n}{\lambda}e^{-\lambda t}\right) \qquad \text{in } \Omega_n(t)\backslash\Omega_n(0), \qquad (3.5)$$

$$\nabla^2 w = -\frac{\kappa\mu_\rho}{\lambda}\left(1 - e^{-\lambda t}\right) \qquad \text{in } \Omega_\rho(t);$$

the choice of the value of λ given above is required in order that the right-hand side of the second of these not be dependent on ω. We also have w and ∇w continuous at $\partial\Omega_n(0)$ and

$$\text{at } t = \omega(\mathbf{x}) \quad [w]_-^+ = \left[\frac{\partial w}{\partial v}\right]_-^+ = 0, \quad \nabla\omega \cdot \nabla\left.\frac{\partial w}{\partial t}\right|_- = -\mu_n e^{-\lambda t}\left(\nabla\omega \cdot \nabla\left.\frac{\partial w}{\partial t}\right|_+ = -\mu_\rho e^{-\lambda t}\right). \qquad (3.6)$$

Thus enhanced smoothness of the solution is attained, with w and ∇w continuous everywhere (this is already the case for (3.2) when $\mu_n = \mu_\rho$, no integral then being required; it is worth emphasising that the moving-boundary problem (3.2) is far from trivial even when $\mu_n = \mu_\rho$, provided that $\kappa \ne k$), but in view of the third boundary condition in (3.6), and unlike the corresponding one-phase problems, t does not appear only parametrically.

3.3 One-phase limits

3.3.1 $\mu_n \gg \mu_\rho$

This limit (which also arises in §4.2.1), whereby the tissue is much more viscous than the surrounding medium, i.e. $\mu_\rho/\mu_n = \epsilon$, $0 < \epsilon \ll 1$, is often relevant *in vitro* (for example, when ρ is an aqueous medium) and sometimes *in vivo* (such as the growth of a cancer into the digestive fluid or along a duct in the breast). We set $p = \epsilon P$ in Ω_ρ and (3.2) reduces

at leading order to the usual Hele–Shaw squeeze film problem

$$\nabla \cdot \left(\frac{K}{\mu_n} \nabla p \right) = -k \qquad \text{in } \Omega_n(t),$$

$$p|_- = 0, \qquad q_v = -\frac{K}{\mu_n} \frac{\partial p}{\partial v}\bigg|_- \qquad \text{on } \Gamma(t), \tag{3.7}$$

with the leading-order pressure in the ρ phase being determined by

$$\nabla \cdot \left(\frac{K}{\mu_n} \nabla P \right) = -\kappa \qquad \text{in } \Omega_\rho(t),$$

$$q_v = -\frac{K}{\mu_n} \frac{\partial P}{\partial v}\bigg|_+ \qquad \text{on } \Gamma(t),$$

where q_v and Γ are given by (3.7). We have $\lambda \sim k$ and (3.5)–(3.6) reduce at leading order to

$$\nabla^2 w = -\mu_n(1 - e^{-kt}) \qquad \text{in } \Omega_n(0),$$

$$\nabla^2 w = \mu_n e^{-kt} \qquad \text{in } \Omega_n(t) \backslash \Omega_n(0), \tag{3.8}$$

$$\text{at } \quad t = \omega(\mathbf{x}) \qquad w = \frac{\partial w}{\partial v} = 0,$$

(the third boundary condition in (3.6) being satisfied automatically in this limit) so that t now does appear only parametrically, with the associated ('moment') conservation laws (cf. Richardson [22] and Entov *et al.* [10], for example) taking the form

$$\int_{\Omega_n(t)} F(\mathbf{x}) \, d\mathbf{x} = e^{kt} \int_{\Omega_n(0)} F(\mathbf{x}) \, d\mathbf{x}, \tag{3.9}$$

when $\nabla^2 F = 0$ in $\Omega_n(t)$; these follow at once from

$$\int_{\Omega_n(t)} (F\nabla^2 w - w\nabla^2 F) \, d\mathbf{x} = 0.$$

3.3.2 $\mu_n \ll \mu_\rho$

The converse limit to that in the previous section, addressed here and in §4.2.2, may be relevant to a very poorly differentiated tumour growing into healthy surrounding tissue. We set $\mu_n/\mu_\rho = \epsilon$ and $p = P/\epsilon$ in Ω_ρ to give for $|\mathbf{x}| = O(1)$ the leading-order problem

$$\nabla \cdot \left(\frac{K}{\mu_n} \nabla p \right) = -k \qquad \text{in } \Omega_n(t),$$

$$\nabla \cdot \left(\frac{K}{\mu_n} \nabla P \right) = -\kappa \qquad \text{in } \Omega_\rho(t), \tag{3.10}$$

$$P|_+ = 0, \qquad q_v = -\frac{K}{\mu_n} \frac{\partial p}{\partial v}\bigg|_- = -\frac{K}{\mu_n} \frac{\partial P}{\partial v}\bigg|_+ \qquad \text{on } \Gamma(t).$$

It is thus the volume production in the n phase which drives the ρ phase, but it is only the total rate of production which is significant, i.e. we can re-express (3.10) as the one-phase

problem

$$\nabla \cdot \left(\frac{K}{\mu_n} \nabla P \right) = -\kappa \qquad \text{in } \Omega_\rho(t),$$

$$P|_+ = 0, \qquad q_v = -\frac{K}{\mu_n} \frac{\partial P}{\partial v}\bigg|_+ \qquad \text{on } \Gamma(t), \tag{3.11}$$

$$-\int_{\Gamma(t)} \frac{K}{\mu_n} \frac{\partial P}{\partial v} dS = kV_n(0)e^{kt}.$$

The last condition, which is obvious on physical grounds with $V_n(t)$ being the volume of $\Omega_n(t)$, follows because

$$\frac{dV_n}{dt} = \int_\Gamma q_v dS = -\int_\Gamma \frac{K}{\mu_n} \frac{\partial p}{\partial v} dS = -\int_{\Omega_n} \nabla \cdot \left(\frac{K}{\mu_n} \frac{\partial p}{\partial v} \right) d\mathbf{x} = kV_n$$

$$= -\int_\Gamma \frac{K}{\mu_n} \frac{\partial P}{\partial v} dS = -\int_{\Omega_\rho \backslash \{r > R\}} \kappa d\mathbf{x} - \int_{r=R} \frac{K}{\mu_n} \frac{\partial P}{\partial r} dS,$$

where Ω_n is contained within $r < R$ and R can be arbitrarily large. Setting

$$P = kV_n(0)e^{kt}P', \quad t' = V_n(0)\left(e^{kt} - 1\right), \quad q_v = kV_n(0)e^{kt}q_v'$$

maps (3.11) with $\kappa = 0$ to the usual ill-posed Hele–Shaw/Saffman–Taylor problem with a constant prescribed flux to infinity (some of the details above assume $\Omega_n \cup \Omega_\rho = \mathbb{R}^N$, but generalisation to other geometries, such as (semi-)infinite channels, involves only very minor modifications). Ill-posedness may be an issue for (3.2) whenever $\mu_n < \mu_\rho$, with the less viscous tissue pushing out the surrounding material; a number of regularisations may be of biological relevance, including cellular diffusion.

The Baiocchi transform for such ill-posed cases is usually expressed in a slightly different way from that given above. We set $w = W/\epsilon$ and then introduce

$$\hat{W}(\mathbf{x}, t) = W(\mathbf{x}, t) - W_\omega(\mathbf{x}),$$

where $W_\omega = W(\mathbf{x}, \omega(\mathbf{x}))$; it is readily seen that to leading order we have $W_\omega = 0$ for $\mathbf{x} \in \Omega_n(0)$, while (using $\lambda \sim k$) the Cauchy problem

$$\nabla^2 W_\omega = -\mu_n \qquad \text{in } \Omega_\rho(0),$$

$$W_\omega = \frac{\partial W_\omega}{\partial v} = 0 \qquad \text{on } \Gamma(0), \tag{3.12}$$

determines W_ω elsewhere. Moreover, it is also apparent from (3.4) that, again to leading order in ϵ, $\hat{W} = 0$ for $\mathbf{x} \in \Omega_n(t)$ and hence (3.5)–(3.6) imply

$$\nabla^2 \hat{W} = \mu_n e^{-\kappa t} \qquad \text{in } \Omega_\rho(t),$$

$$\text{at } t = \omega \qquad \hat{W} = \frac{\partial \hat{W}}{\partial v} = 0, \tag{3.13}$$

the third condition on (3.6) again being satisfied identically. The dependence on k enters only through the behaviour as $r \to \infty$, which follows from that for P indicated above.

The one-phase problem (3.12) again depends only parametrically on t. Since

$$\frac{\partial \hat{W}}{\partial t} = K e^{-\kappa t} P,$$

if P, and hence W, have no driving singularities then the singularities of $\hat{W}$ are those of $-W_\omega$. Moreover, from (3.12)–(3.13) the associated conservation laws take the form

$$\int_{\Omega_\rho(0)\backslash\Omega_\rho(t)} F(\mathbf{x})d\mathbf{x} = -\frac{1}{\mu_n} \int_{r\to\infty} \left(F\left(e^{\kappa t} \frac{\partial \hat{W}}{\partial r} + \frac{\partial W_\omega}{\partial r} \right) - \frac{\partial F}{\partial r}(e^{\kappa t}\hat{W} + W_\omega) \right) dS \quad (3.14)$$

for $\nabla^2 F = 0$ in $\Omega_\rho(0)$, since the left-hand side of (3.14) is equal to

$$\int_{\Omega_\rho(0)} F(e^{\kappa t}\nabla^2\hat{W} + \nabla^2 W_\omega)\, d\mathbf{x}.$$

The analysis above glosses over the fact that in this ill-posed case the solution will typically cease to exist in finite time; there is substantial discussion of such matters in the literature on the Hele–Shaw problem (see, for example, Cummings *et al.* [7] and references therein) and we shall not comment further here. The tissue interface can thus be expected to develop a complicated fingering morphology (familiar in the Hele-Shaw context), which would correlate with rapid penetration into the surrounding tissue; tumour cells around the tip of a finger might then be prone to break off from the main tumour mass, possibly resulting in metastatic spread, attaching to (and growing at) other parts of the body.

We conclude this section by returning to the two-phase version of the Baiocchi transform. Both one-phase problems have conserved integrals, but these are mutually exclusive and thus not applicable to the two-phase case (if F is bounded and $\nabla^2 F = 0$ in both phases, then F is necessarily constant, the resulting integral corresponding to mass conservation). The formulation (3.4)–(3.6) (in particular the value of λ) does, however, identify very economically two special cases, namely $\mu_n = \mu_\rho$, at which the stability properties of the problem change dramatically, and $k\mu_n = \kappa\mu_\rho$, for which $\lambda = 0$ and

$$\begin{aligned}
\nabla^2 w &= -k\mu_n t & &\text{in } \Omega_n(0) \text{ and } \Omega_\rho(t),\\
\nabla^2 w &= \mu_n - \mu_\rho - k\mu_n t & &\text{in } \Omega_n(t)\backslash\Omega_n(0),
\end{aligned}$$

with $\nabla \cdot (K\nabla p) = -k\mu_n$ for all $\mathbf{x}$; the significance, if any, of this second special case is unclear, however.

4 Multi-dimensional models: Stokes flow

4.1 Formulation

We now turn to Stokes flow, which is probably the simplest appropriate formulation when the tissue is growing freely, rather than within a porous material.

In this case we have momentum equations

$$\frac{\partial \sigma_{ij}}{\partial x_j} = 0$$

and constitutive law

$$\sigma_{ij} = -\left(p + \frac{2}{3}\mu(n)\frac{\partial v_k}{\partial x_k}\right)\delta_{ij} + \mu(n)\left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i}\right), \tag{4.1}$$

where the pressure p is defined by

$$p = -\frac{1}{3}\sigma_{kk}$$

and the summation convention is being adopted; we stress that even though the material is taken to be incompressible, we do not have $\nabla \cdot \mathbf{v} = 0$ because of cell division. We also note that, for these viscous dominated flows, the momentum carried by newly born cells is not an issue; such considerations would, however, be relevant were there circumstances in which non-negligible inertial effects could arise. In the sharp interface limit we therefore obtain

$$0 = -\nabla p + \mu_n\nabla^2\mathbf{v}, \qquad \nabla \cdot \mathbf{v} = k \qquad \text{in } \Omega_n(t), \tag{4.2}$$

$$0 = -\nabla p + \mu_\rho\nabla^2\mathbf{v}, \qquad \nabla \cdot \mathbf{v} = \kappa \qquad \text{in } \Omega_\rho(t), \tag{4.3}$$

$$[\mathbf{v}]_-^+ = \mathbf{0}, \qquad [\sigma_{ij}v_j]_-^+ = \mathbf{0}, \qquad q_v = \mathbf{v} \cdot \mathbf{v} \qquad \text{on } \Gamma(t), \tag{4.4}$$

where $\mathbf{v} = (v_j)$ is the unit normal into Ω_ρ. For appropriate boundary conditions, planar interfaces are unstable for this problem, whatever the value of μ_n/μ_ρ (see [11]); however, we note that, depending upon the parameter values, perturbations typically decay relative to the tumour size (which is itself exponentially increasing in the stages of tumour growth described by the current model).

4.2 One-phase limits

4.2.1 $\mu_n \gg \mu_\rho$

Writing $\mu_\rho/\mu_n = \epsilon$ (as in §3.3.1) and requiring $p \to 0$ as $r \to \infty$ we have $p = O(\epsilon)$ in $\Omega_\rho(t)$, while (4.2) holds subject to (at leading order)

$$\sigma_{ij}v_j|_- = 0, \qquad q_v = \mathbf{v} \cdot \mathbf{v}|_- \qquad \text{on } \Gamma(t), \tag{4.5}$$

which are the usual stress-free and kinematic free-surface conditions. The system (4.2), (4.5) can be regarded as a Stokes-flow analogue of the Hele–Shaw squeeze film problem and it warrants further investigation by complex variable methods and so forth (cf. Franks [7], for example), as does the converse one-phase problem which is described below; in two dimensions, writing $\mathbf{v} = (u, v)$ and

$$u = \frac{1}{2}kx + \frac{\partial\psi}{\partial y}, \qquad v = \frac{1}{2}ky - \frac{\partial\psi}{\partial x}, \qquad \omega = \frac{\partial v}{\partial x} - \frac{\partial u}{\partial y},$$

$$\sigma_{11} = \frac{\partial^2 A}{\partial y^2}, \qquad \sigma_{12} = -\frac{\partial^2 A}{\partial x \partial y}, \qquad \sigma_{22} = \frac{\partial^2 A}{\partial x^2},$$

(here only, ω denotes the vorticity not the moving-boundary location) we have

$$\frac{\partial^2 A}{\partial y^2} - \frac{\partial^2 A}{\partial x^2} = 4\mu_n\frac{\partial^2\psi}{\partial x \partial y}, \qquad \mu_n\left(\frac{\partial^2\psi}{\partial y^2} - \frac{\partial^2\psi}{\partial x^2}\right) = -\frac{\partial^2 A}{\partial x \partial y},$$

so A and $2\mu_n\psi$ are, in the usual way, biharmonic conjugates and

$$\nabla^2 A = -2p + \frac{2}{3}k\mu_n, \qquad \nabla^2 p = 0,$$
$$\nabla^2 \psi = -\omega, \qquad \nabla^2 \omega = 0.$$

Related formulations arise in fibre drawing [8, 6], but in such applications the focus is usually on cases with $k < 0$; here $k \geqslant 0$, which would correspond to axial fibre compression in the fibre analogy, necessarily holds. Moreover, in the fibre-drawing context the relevant formulations are necessarily two-dimensional, whereas three-dimensional problems are again also of interest here.

For unconstrained growth, $\Gamma = \partial\Omega_n$, we have (up to rigid body motions) in three dimensions

$$\mathbf{v} = \frac{1}{3}k(x, y, z), \qquad p = 0 \tag{4.6}$$

(so $\sigma_{ij} = 0$ for all i, j) and in two dimensions (cylindrical tissue)

$$\mathbf{v} = \frac{1}{2}k(x, y, 0), \qquad p = \frac{1}{3}k\mu_n \tag{4.7}$$

($\sigma_{ij} = 0$ for all i, j except that $\sigma_{33} = -k\mu_n$); in both cases the tissue simply grows in size without changing shape.

4.2.2 $\mu_n \ll \mu_\rho$

Setting $\mu_n/\mu_\rho = \epsilon$ (as in §3.3.2) and $p = P/\epsilon$, then to leading order P is uniform, $P = P_n(t)$ say, in Ω_n and

$$0 = -\nabla P + \mu_n\nabla^2\mathbf{v}, \qquad \nabla \cdot \mathbf{v} = \kappa \qquad \text{in } \Omega_\rho(t),$$
$$\sigma_{ij}v_j|_+ = -P_n(t)v_i, \qquad q_v = \mathbf{v} \cdot \mathbf{v}|_+ \qquad \text{on } \Gamma(t).$$

The additional constraint which in effect determines P_n again follows from the total rate of volume production in $\Omega_n(t)$, whereby

$$V_n(t) = V_n(0)e^{kt} \tag{4.8}$$

and

$$\int_\Gamma \mathbf{v} \cdot \mathbf{v}\,dS = kV_n(0)e^{kt},$$

which can be used together with the divergence theorem to deduce the behaviour of $\mathbf{v}$ as $r \to \infty$. The transformation

$$P = kV_n(0)e^{kt}P', \quad \mathbf{v} = kV_n(0)e^{kt}\mathbf{v}', \quad t' = V_n(0)(e^{kt} - 1), \quad q_v = kV_n(0)e^{kt}q_v'$$

maps the problem with $\kappa = 0$ to a standard one-phase Stokes free-boundary problem with a constant flux of material to infinity.

5 Thin-film models

5.1 Preliminaries

Thin-film approaches are particularly pertinent to the types of model formulated above because of the propensity of the latter to exhibit fingering instabilities; these fingers rapidly grow to become much longer than they are wide, the asymptotic descriptions derived below thus playing an important role in their nonlinear analysis. We restrict ourselves here to deriving the relevant thin-film formulations, these having a variety of different applications.

We consider two-dimensional growth in a 'channel' $0 < x < \infty$, $0 < y < H$ with periodicity/symmetry conditions at $y = 0, H$ and symmetry conditions at $x = 0$. We take D_n and D_ρ to be constant and adopt the non-dimensionalisation

$$x = L\hat{x}, \quad y = H\hat{y}, \quad t = \hat{t}/k, \quad u = Lk\hat{u}, \quad v = Hk\hat{v}, \tag{5.1}$$

where L is a representative finger length and $\epsilon = H/L \ll 1$ (note that the quantity ϵ has different meanings in different sections). Thus (1.1) becomes, on dropping ˆ's,

$$\frac{\partial n}{\partial t} + \frac{\partial}{\partial x}(nu) + \frac{\partial}{\partial y}(nv) = d_n \left(\frac{\partial^2 n}{\partial y^2} + \epsilon^2 \frac{\partial^2 n}{\partial x^2} \right) + n,$$

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(\rho u) + \frac{\partial}{\partial y}(\rho v) = d_\rho \left(\frac{\partial^2 \rho}{\partial y^2} + \epsilon^2 \frac{\partial^2 \rho}{\partial y^2} \right) + \alpha\rho, \tag{5.2}$$

$$n + \rho = 1,$$

where $d_n = D_n/kH^2$, $d_\rho = D_\rho/kH^2$, $\alpha = \kappa/k$. For either constitutive law, we have boundary conditions

$$\text{at} \quad y = 0, 1 \qquad v = 0, \qquad d_n \frac{\partial n}{\partial y} = d_\rho \frac{\partial \rho}{\partial y} = 0,$$

$$\text{at} \quad x = 0 \qquad u = 0, \qquad d_n \frac{\partial n}{\partial x} = d_\rho \frac{\partial \rho}{\partial y} = 0, \tag{5.3}$$

$$\text{as} \quad x \to \infty \qquad v \to 0, \qquad n \to 0.$$

The most concise way to proceed with the thin-film limit involves introducing

$$\bar{n}(x, t) = \int_0^1 n(x, y, t)\, dy, \qquad \bar{\rho}(x, t) = \int_0^1 \rho(x, y, t)\, dy \tag{5.4}$$

to give

$$\frac{\partial \bar{n}}{\partial t} + \frac{\partial}{\partial x} \left(\int_0^1 nu\, dy \right) = \epsilon^2 d_n \frac{\partial^2 \bar{n}}{\partial x^2} + \bar{n},$$

$$\frac{\partial \bar{\rho}}{\partial t} + \frac{\partial}{\partial x} \left(\int_0^1 \rho u\, dy \right) = \epsilon^2 d_\rho \frac{\partial^2 \bar{\rho}}{\partial x^2} + \alpha\bar{\rho}, \tag{5.5}$$

$$\bar{n} + \bar{\rho} = 1.$$

One distinguished limit (that of large cellular diffusion) has $d_n, d_\rho = O(1/\epsilon^2)$, in which

case (5.2) implies $n \sim n_0(x,t)$, $\rho \sim \rho_0(x,t)$ and (5.5) then becomes, on introducing

$$\bar{u}(x,t) = \int_0^1 u(x,y,t)\, dy,$$

equivalent to the one-dimensional model discussed in §2; in this case, diffusion is more than sufficient to counteract any attempt of the 'interface' to finger. A second distinguished limit (corresponding to intermediate cellular diffusivities) has $d_n, d_\rho = O(1)$, but no systematic reduction in dimensionality is in general then possible for Darcy flow. Here, however, we are most concerned with the case $d_n, d_\rho \ll 1$ which appears most biologically relevant and leads to a sharp interface limit with

$$n = 1, \quad \rho = 0 \ \text{ in } \ 0 < y < h(x,t), \qquad n = 0, \quad \rho = 1 \ \text{ in } \ h(x,t) < y < 1,$$

say (i.e. we have in mind a finger of the n phase in the lower part of the channel, with the ρ phase above). Thus

$$\bar{n} = h, \qquad \bar{\rho} = 1 - h$$

and (5.5) with $d_n = d_\rho = 0$ becomes

$$\frac{\partial h}{\partial t} + \frac{\partial}{\partial x}\left(\int_0^h u\, dy\right) = h,$$

$$\frac{\partial}{\partial t}(1 - h) + \frac{\partial}{\partial x}\left(\int_h^1 u\, dy\right) = \alpha(1 - h),$$

(5.6)

so that

$$\frac{\partial \bar{u}}{\partial x} = h + \alpha(1 - h). \tag{5.7}$$

5.2 Darcy flow

Scaling the pressure according to

$$p = \frac{\mu_n k L^2}{K}\hat{p}$$

and again dropping ˆ's, we have

$$u = -\frac{\partial p}{\partial x}, \qquad \epsilon^2 v = -\frac{\partial p}{\partial y}, \qquad 0 < y < h,$$

$$u = -\beta\frac{\partial p}{\partial x}, \qquad \epsilon^2 v = -\beta\frac{\partial p}{\partial y}, \qquad h < y < 1,$$

(5.8)

where $\beta = \mu_n/\mu_\rho$. Hence

$$p \sim p_0(x,t) \tag{5.9}$$

and (5.6) yields the leading order system (note that p and $\mathbf{v} \cdot \mathbf{v}$, but not u, are continuous at the interface $y = h$ for Darcy flow)

$$
\begin{aligned}
\frac{\partial h_0}{\partial t} &= \frac{\partial}{\partial x}\left(h_0\frac{\partial p_0}{\partial x}\right) + h_0, \\
\frac{\partial}{\partial t}(1 - h_0) &= \beta\frac{\partial}{\partial x}\left((1 - h_0)\frac{\partial p_0}{\partial x}\right) + \alpha(1 - h_0).
\end{aligned}
\tag{5.10}
$$

In the special case $\mu(n) \equiv \mu_n$, further progress can also be made in the distinguished limit $d_n, d_\rho = O(1)$, since (5.9) remains valid, with $u_0 = -\partial p_0/\partial x$, and (5.5) then implies

$$
\begin{aligned}
\frac{\partial \bar{n}_0}{\partial t} + \frac{\partial}{\partial x}(\bar{n}_0 u_0) &= \bar{n}_0, \\
\frac{\partial \bar{\rho}_0}{\partial t} + \frac{\partial}{\partial x}(\bar{\rho}_0 u_0) &= \alpha\bar{\rho}_0, \\
\bar{n}_0 + \bar{\rho}_0 &= 1,
\end{aligned}
\tag{5.11}
$$

which is equivalent to (5.10) with $\beta = 1$; it follows from (5.2) that $n_0(x, y, t)$, $\rho_0(x, y, t)$ and $v_0(x, y, t)$ are in turn determined by

$$
\begin{aligned}
\frac{\partial n_0}{\partial t} + \frac{\partial}{\partial x}(n_0 u_0) + \frac{\partial}{\partial y}(n_0 v_0) &= d_n\frac{\partial^2 n_0}{\partial y^2} + n_0, \\
\frac{\partial \rho_0}{\partial t} + \frac{\partial}{\partial x}(\rho_0 u_0) + \frac{\partial}{\partial y}(\rho_0 v_0) &= d_\rho\frac{\partial^2 \rho_0}{\partial y^2} + \alpha\rho_0, \\
n_0 + \rho_0 &= 1,
\end{aligned}
\tag{5.12}
$$

with u_0 given by (5.11).

The system (5.10) is amenable to further simplification. We define

$$
\Lambda = -(h_0 + \beta(1 - h_0))\frac{\partial p_0}{\partial x}
$$

so that

$$
(1 - \alpha)h_0 = \frac{\partial \Lambda}{\partial x} - \alpha
\tag{5.13}
$$

and for $\alpha \neq 1$ we may integrate (5.10) to give

$$
\frac{\partial \Lambda}{\partial t} = -\alpha x + \frac{\alpha h_0 + \beta(1 - h_0)}{h_0 + \beta(1 - h_0)}\Lambda,
\tag{5.14}
$$

so that Λ satisfies the first order, fully nonlinear partial differential equation

$$
\frac{\partial \Lambda}{\partial t} = -\alpha x + \frac{\alpha\left(\frac{\partial \Lambda}{\partial x} - \alpha\right) + \beta\left(1 - \frac{\partial \Lambda}{\partial x}\right)}{\frac{\partial \Lambda}{\partial x} - \alpha + \beta\left(1 - \frac{\partial \Lambda}{\partial x}\right)}\Lambda
\tag{5.15}
$$

(we note from (5.13) that $\alpha \leqslant \frac{\partial \Lambda}{\partial x} \leqslant 1$), which can be solved in the usual way by characteristic methods. Equation (5.15) simplifies significantly in the special case $\alpha = \beta$

(i.e. $k\mu_n = \kappa\mu_\rho$) noted above in the Baiocchi-transform context. For $\alpha = 1$ we have $\Lambda = x$ and

$$\frac{\partial h_0}{\partial t} + \frac{\beta x}{(h_0 + \beta(1 - h_0))^2} \frac{\partial h_0}{\partial x} = -\frac{(1 - \beta)h_0(1 - h_0)}{h_0 + \beta(1 - h_0)}. \tag{5.16}$$

Much more information can be gleaned from these evolution equations for specific initial value problems but we shall not proceed further in that direction here.

5.3 Stokes flow

Here the conditions (5.3) are supplemented by

$$\begin{aligned} \text{at} \quad y = 0, 1 \qquad &\sigma_{12} = 0, \\ \text{at} \quad x = 0 \qquad &\sigma_{12} = 0, \end{aligned} \tag{5.17}$$

so that

$$\frac{\partial}{\partial x} \int_0^1 \sigma_{11}(x, y, t)\, dy = 0;$$

defining the pressure origin such that $\sigma_{11} \to 0$ as $x \to +\infty$, we thus have

$$\int_0^1 \sigma_{11}(x, y, t)\, dy = 0. \tag{5.18}$$

Appropriate stress scalings are

$$p = \mu_n k \hat{p}, \quad \sigma_{11} = \mu_n k \hat{\sigma}_{11}, \quad \sigma_{22} = \mu_n k \hat{\sigma}_{22},$$

so in the sharp interface limit we have, dropping ^'s,

$$\begin{aligned} 0 = \frac{\partial^2 u_0}{\partial y^2}, \qquad 0 = -\frac{\partial p_0}{\partial y} + \frac{\partial^2 v_0}{\partial y^2}, \qquad \frac{\partial u_0}{\partial x} + \frac{\partial v_0}{\partial y} = 1, \qquad &0 < y < h_0, \\ 0 = \frac{1}{\beta}\frac{\partial^2 u_0}{\partial y^2}, \qquad 0 = -\frac{\partial p_0}{\partial y} + \frac{1}{\beta}\frac{\partial^2 v_0}{\partial y^2}, \qquad \frac{\partial u_0}{\partial x} + \frac{\partial v_0}{\partial y} = \alpha, \qquad &h_0 < y < 1. \end{aligned} \tag{5.19}$$

It follows at once, using (5.17) that

$$u_0 = u_0(x, t) \tag{5.20}$$

so (5.6)–(5.7) yield the system

$$\begin{aligned} \frac{\partial h_0}{\partial t} + \frac{\partial}{\partial x}(h_0 u_0) &= h_0, \\ \frac{\partial u_0}{\partial x} &= h_0 + \alpha(1 - h_0), \end{aligned} \tag{5.21}$$

for h_0 and u_0, this being independent of β. This system is identical to (5.10) with $\beta = 1$ (and $u_0 = -\partial p_0/\partial x$) and is equivalent to (2.1) with $D_n = D_\rho = 0$ (with h_0 playing the role of n). Thus the simplifications already noted for (5.10) and (2.1) are also effective in this case.

To complete the analysis, we note that

$$v_0 = (1 - \alpha)(1 - h_0)y, \quad 0 < y < h_0, \qquad v_0 = (1 - \alpha)h_0(1 - y), \quad h_0 < y < 1,$$

and that

$$p_0 = P_0(x, t) - \frac{2}{3} + 2(1 - \alpha)(1 - h_0) \qquad 0 < y < h_0,$$

$$p_0 = P_0(x, t) - \frac{2\alpha}{3\beta} - \frac{2}{\beta}(1 - \alpha)h_0 \qquad h_0 < y < 1; \tag{5.22}$$

due to the volumetric sources, p is discontinuous at the interface $y = h$, $\sigma_{22} \sim -P_0(x, t)$ being continuous to leading order. The solvability condition (5.18) is needed to determine P_0; we have to leading order that

$$\sigma_{11} = -P_0 + 2 - 4(1 - \alpha)(1 - h_0), \qquad 0 < y < h_0,$$

$$\sigma_{11} = -P_0 + \frac{2\alpha}{\beta} + \frac{4}{\beta}(1 - \alpha)h_0, \qquad h_0 < y < 1,$$

so from (5.18) we have

$$P_0 = \frac{2}{\beta}(\beta h_0 + \alpha(1 - h_0)) + \frac{4}{\beta}(1 - \alpha)(1 - \beta)h_0(1 - h_0).$$

Because (5.20) holds in the thin-film limit whatever the values of d_n and d_ρ, (5.5) reduces for any β to (5.11) and (5.12) again governs the variations with y. Thus in particular the Stokes flow problem for any $\mu(n)$ can in the thin-film limit be approximated by the constant viscosity ($\mu(n) \equiv \mu_n$) Darcy formulation.

There is a distinct, more involved, limit problem when $\beta = O(1/\epsilon^2)$ (and similarly when $\beta = O(\epsilon^2)$, when the appropriate pressure scaling is $p = \mu_n k \hat{p}/\epsilon^2$); writing $\beta = \gamma/\epsilon^2$ and considering the sharp interface limit, (5.19) is modified in $h_0 < y < 1$ to

$$0 = -\frac{\partial p_0}{\partial x} + \frac{1}{\gamma}\frac{\partial^2 u_0}{\partial y^2}, \quad 0 = -\frac{\partial p_0}{\partial y}, \quad \frac{\partial u_0}{\partial x} + \frac{\partial v_0}{\partial y} = \alpha, \qquad h_0 < y < 1.$$

Thus in $0 < y < h_0$ we have

$$u_0 = U_0(x, t), \quad v_0 = \left(1 - \frac{\partial U_0}{\partial x}\right)y, \quad p_0 = P_0(x, t) + \frac{4}{3} - 2\frac{\partial U_0}{\partial x} \tag{5.23}$$

and in $h_0 < y < 1$

$$p_0 = P_0(x, t), \quad u_0 = U_0 + \frac{1}{2}\gamma\left((1 - y)^2 - (1 - h_0)^2\right)\frac{\partial P_0}{\partial x}. \tag{5.24}$$

Since to leading order

$$\sigma_{11} = -P_0 + 4\frac{\partial U_0}{\partial x} - 2, \quad 0 < y < h_0, \qquad \sigma_{11} = -P_0, \quad h_0 < y < 1,$$

(5.18) implies that

$$P_0 = 4h_0\frac{\partial U_0}{\partial x} - 2h_0 \tag{5.25}$$

and (5.23)–(5.24) give

$$\bar{u}_0 = U_0 - \frac{1}{3}\gamma(1 - h_0)^3 \frac{\partial P_0}{\partial x}.$$ (5.26)

Finally, (5.6)–(5.7) yield the coupled system

$$\frac{\partial h_0}{\partial t} + \frac{\partial}{\partial x}(h_0 U_0) = h_0,$$

$$\frac{\partial}{\partial x}\left(U_0 - \frac{1}{3}\gamma(1 - h_0)^3 \frac{\partial}{\partial x}\left(4h_0 \frac{\partial U_0}{\partial x} - 2h_0\right)\right) = h_0 + \alpha(1 - h_0),$$ (5.27)

from which an exact first integral can again be obtained. In the limit $\gamma \to \infty$, i.e. in the corresponding one-phase case (as in §4.2.1), we have (until $1 - h_0$ becomes small)

$$P_0 = 0, \qquad \frac{\partial U_0}{\partial x} = \frac{1}{2},$$

(cf. (4.7)) and the first of (5.27). This result corresponds to near radial growth of the tip of the finger, which thus tends to block the whole of the channel.

We again restrict ourselves here to deriving the governing formulations; specific applications will be described elsewhere.

5.4 Effects of cellular diffusion

We conclude the discussion of thin-film limits by considering the distinguished limit $d_n, d_\rho = O(1)$, focusing on the cases when (5.11)–(5.12) hold with $u \sim u_0(x, t)$. Significant progress is possible in simplifying the two-dimensional governing equations (5.12). We write

$$v_0 = V_0 + (d_n - d_\rho)\frac{\partial n_0}{\partial y}$$

to obtain for $\alpha \neq 1$

$$\frac{\partial n_0}{\partial t} + \frac{\partial}{\partial x}(n_0 u_0) + \frac{\partial}{\partial y}(n_0 V_0) = \frac{\partial}{\partial y}\left((d_n(1 - n_0) + d_\rho n_0)\frac{\partial n_0}{\partial y}\right) + n_0,$$

$$n_0 = \bar{n}_0 + \frac{1}{1 - \alpha}\frac{\partial V_0}{\partial y}.$$

For $\alpha \neq 1$ we may then integrate to give (using (5.11))

$$\frac{\partial V_0}{\partial t} + u_0 \frac{\partial V_0}{\partial x} + V_0 \frac{\partial V_0}{\partial y} = \left(d_n - (d_n - d_\rho)\left(\bar{n}_0 + \frac{1}{1 - \alpha}\frac{\partial V_0}{\partial y}\right)\right)\frac{\partial^2 V_0}{\partial y^2} + (1 - \alpha)(1 - 2\bar{n}_0)V_0,$$ (5.28)

with (from (5.11))

$$\frac{\partial u_0}{\partial x} = (1 - \alpha)\bar{n}_0 + \alpha.$$

Introducing the Lagrangian coordinate x', where

$$\frac{dx}{dt} = u_0(x, t), \qquad x = x' \quad \text{at } t = 0,$$

we obtain from (5.11) (after integrating as in §2.1) that

$$\bar{n}_0 = \frac{\bar{N}_0(x')}{\bar{N}_0(x') + (1 - \bar{N}_0(x'))e^{-(1-\alpha)t}},$$

where $\bar{n}_0 = \bar{N}_0(x)$ at $t = 0$. From (5.28), $V_0(y, t; x')$ then satisfies

$$\frac{\partial V_0}{\partial t} + V_0 \frac{\partial V_0}{\partial y} = \left(d_n - (d_n - d_\rho) \left(\bar{n}_0 + \frac{1}{1 - \alpha} \frac{\partial V_0}{\partial y} \right) \right) \frac{\partial^2 V_0}{\partial y^2} + (1 - \alpha)(1 - 2\bar{n}_0)V_0, \quad (5.29)$$

having only parametric dependence upon x'; the behaviour in the two directions, x and y, can thus be decoupled. We remark that the quadratically-nonlinear reaction-convection-diffusion equation (5.29) has a family of solutions of the form

$$V_0 = A(t; x') + B(t; x') \cos \left(\sqrt{\frac{1 - \alpha}{d_n - d_\rho}} y \right) + C(t; x') \sin \left(\sqrt{\frac{1 - \alpha}{d_n - d_\rho}} y \right). \quad (5.30)$$

The linear stability analysis of (5.30) is straightforward and instructive. In particular, $V_0 \sim C(t; x') \sin (\pi y)$ with $C \ll 1$ is exponentially growing in t for small $\bar{n}_0$ if $\alpha + d_n \pi^2 < 1$ but, provided $\alpha < 1 + d_\rho \pi^2$, it subsequently becomes linearly stable as $\bar{n}_0$ grows towards unity; in the special case $d_n - d_\rho = (1 - \alpha)/\pi^2$ this analysis extends into the nonlinear regime in view of (5.30) with $A, B \equiv 0$.

For $\alpha = 1$, we have $u_0 = x$, $V_0 = 0$ and, setting $x' = x/e^t$, it follows that $n_0(y, t; x')$ satisfies

$$\frac{\partial n_0}{\partial t} = \frac{\partial}{\partial y} \left((d_n(1 - n_0) + d_\rho n_0) \frac{\partial n_0}{\partial y} \right).$$

6 Discussion

An aspect of modelling which is of particular significance in the tumour growth context is whether the models shed light on the mechanisms underpinning tumour invasiveness. The cells of aggressive tumours may perhaps detach readily from their neighbours and diffuse into the surrounding tissue ($D_n \gg D_\rho$) and, for related reasons (because the tumour cells are poorly differentiated), we can anticipate that $\mu_n \ll \mu_\rho$ may apply when the tumour is surrounded by normal tissue. While we cannot of course expect to capture reliably the behaviour of individual cells within a continuum, deterministic framework, our results indicate that cellular diffusion is much less effective in promoting invasion than the (intrinsically multi-dimensional) instabilities which can result from the continuum mechanics of tumour growth. Thus, the concentration of n (i.e. of cells which could be responsible for metastatic spread) drops off rapidly in front of the advancing interface (see (2.23)); as discussed at the end of §2.2, taking the limit $D_\rho/D_n \to 0$ restricts the extent to which the surrounding cells penetrate the growing tumour but has very little bearing on the behaviour of tumour cells outside the interface. By contrast, fingering instabilities, with preferential advance of the tumour along the fingers, leads (particularly in view of the global constraint (4.8), which holds for any constitutive assumption) to significantly enhanced penetration of the tumour into the surrounding tissue. Thus in the

framework of the current model, which it should be stressed includes only growth-driven and random (diffusive) cellular motion and not directional effects such as chemotaxis, gross fingering of the tumour, rather than the diffusive motion of its component cells into the surrounding tissue, is the dominant mechanism for invasion by the tumour as a whole (the importance for metastatic spread of the diffusion of individual cells a significant distance away from the tumour mass should nevertheless not be underestimated; this is difficult to capture in a modelling framework such as this, though the far-field analysis of § 2.2 provides some crude measures of the likelihood of this type of infiltration). We note in passing that fingering will typically increase the concentration gradient of n normal to the finger and will thus enhance diffusion in that direction.

It will be clear that numerous important effects, including nutrient and waste-material transport limitations and various mechanisms for the destruction of normal cells by a growing tumour, have not been incorporated in the current modelling; some of these will be addressed in subsequent publications (cf. Franks [11]). The preliminary analysis outlined above leaves numerous open questions and, we hope, motivates the further investigation of some interesting types of moving-boundary problem. We conclude by noting that several aspects of the modelling are also relevant to the growth of other colonies of cells, such as to the early stages in the growth of bacterial biofilms.

References

[1] BREWARD, C. J. W., BYRNE, H. M. & LEWIS, C. E. (2001) Modelling the interactions between tumour cells and a blood vessel in a microenvironment within a vascular tumour. *Euro. J. Appl. Math.* **12**, 529–556.

[2] BYRNE, H. M. & CHAPLAIN, M. A. J. (1997) Free boundary value problems associated with the growth and development of multicellular spheroids. *Euro. J. Appl. Math.* **8**, 639–658.

[3] BYRNE, H. & PREZIOSI, L. (2003) Modelling solid tumour growth using the theory of mixtures. *Math. Med. Biol.* **20**, 341–366.

[4] CAMACHO, J. & BRENNER, H. (1995) On convection induced by molecular diffusion. *Ind. Eng. Chem. Res.* **34**, 3326–3335.

[5] CRANK, J. (1975) *The Mathematics of Diffusion (2nd Edition)*. Oxford University Press.

[6] CUMMINGS, L. J. & HOWELL, P. D. (1999) On the evolution of non-axisymmetric viscous fibres with surface tension, inertia and gravity. *J. Fluid Mech.* **389**, 363–389.

[7] CUMMINGS, L., HOWISON, S. D. & KING, J. R. (1999) Two-dimensional Stokes and Hele-Shaw flow with free surfaces. *Euro. J. Appl. Math.* **10**, 681–706.

[8] DEWYNNE, J. N., OCKENDON, J. R. & WILMOTT, P. (1992) A systematic derivation of the leading-order equations for extensional flows in slender geometries. *J. Fluid Mech.* **244**, 323–338.

[9] ELLIOTT, C. M. & JANOVSKY, V. (1981) A variational inequality approach to Hele-Shaw flow with a moving boundary. *Proc. Roy. Soc. Edin. A-Math.* **88**, 93–107.

[10] ENTOV, V. M., ETINGOF, P. I. & KLEINBOCK, D. YA. (1995) On nonlinear interface dynamics in Hele-Shaw flows. *Euro. J. Appl. Math.* **6**, 399–420.

[11] FRANKS, S. J. (2001) *Mathematical modelling of tumour growth and stability*. PhD Thesis, University of Nottingham.

[12] FRANKS, S. J., BYRNE, H. M., MUDHAR, H. S., UNDERWOOD, J. C. E. & LEWIS, C. E. (2003) Mathematical modelling of comedo ductal carcinoma in situ of the breast. *Math. Med. Biol.* **20**, 277–308.

[13] FRANKS, S. J. & KING, J. R. (2003) Interactions between a uniformly proliferating tumour and its surroundings: uniform material properties. *Math. Med. Biol.* **20**, 47–89.

[14] FUNG, Y. C. (1993) *Biomechanics: Mechanical properties of living tissues*. Springer.

[15] GREENSPAN, H. P. (1976) On the growth and stability of cell cultures and solid tumors. *J. Theo. Biol.* **56**, 229–242.

[16] HOWISON, S. D. (2000) A note on the two-phase Hele-Shaw problem. *J. Fluid Mech.* **409**, 243–249.

[17] JOSEPH, D. D. (1990) Fluid dynamics of two miscible liquids with diffusion and gradient stresses. *Euro. J. Mech. B-Fluids*, **9**, 565–596.

[18] LACEY, A. A. (1982) Moving boundary problems in the flow of liquid through porous media. *J. Austral. Math. Soc. B*, **24**, 171–193.

[19] LACEY, A. A. (1995) Bounds on solutions of one-phase Stefan problems. *Euro. J. Appl. Math.* **6**, 509–516.

[20] LANDMAN, K. A. & PLEASE, C. P. (2001) Tumour dynamics and necrosis: surface tension and stability. *IMA J. Math. Appl. Med. Biol.* **18**, 131–158.

[21] PLEASE, C. P., PETTET, G. J. & MCELWAIN, D. L. S. (1999) Avascular tumour dynamics and necrosis. *Math. Models Meth. Appl. Sci.* **9**, 569–579.

[22] RICHARDSON, S. (1972) Hele-Shaw flows with a free boundary produced by the injection of fluid into a narrow channel. *J. Fluid Mech.* **56**, 609–618.

[23] SHELLEY, M. J., TIAN, F.-R. & WLODARSKI, K. (1997) Hele-Shaw flow and pattern formation in a time-dependent gap. *Nonlinearity*, **10**, 1471–1495.