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A Perturbation Problem Arising from a Mechanical Model for Epithelial Morphogenesis

JONATHAN A. SHERRATT

Centre for Mathematical Biology, Mathematical Institute, 24–29 St Giles', Oxford OX1 3LB, UK

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In this paper, the author applies the mechanical model of Murray and Oster (1984) for epithelial morphogenesis to the behaviour of an epithelial sheet after a section of the sheet has been removed. In a radially symmetric geometry, approximate solution of the resulting equation is an interesting problem in perturbation theory. A leading-order approximation using three matched rescalings is obtained, and it is shown that these are the only rescalings that will match to leading order. This approximation is then improved by deriving the leading-order correction, which requires the introduction of logarithmic terms to complete the matching process. The resulting uniformly valid composite expansion is a good approximation to the solution of the model equations for biologically relevant parameter values.

1. Biological background

CONTINUUM mechanochemical models for deformation of epithelial sheets, first proposed by Murray & Oster (1984), are now well established; Murray (1989) gives an in-depth review of mechanical models for morphogenesis. The model of Murray & Oster (1984) treats the epithelial sheet as a viscoelastic continuum, with the cellular contraction forces controlled by the concentration of free calcium. We amend this model to investigate the deformation of an epithelial sheet in the absence of chemical control, which is not relevant here since we are only interested in the equilibrium state. We envisage a section of the sheet being removed, and we want to find the new equilibrium configuration, assuming the response to be purely mechanical. Biologically, it is the variation of intracellular actin density near the free edge that is of interest.

At equilibrium, the stress tensor in the cell sheet is given by

$$\boldsymbol{\sigma} = \underbrace{G(E\boldsymbol{\varepsilon} + \Gamma\nabla\cdot\boldsymbol{u}\mathbf{I})}_{\text{elastic stress}} + \underbrace{\tau G\mathbf{I}}_{\text{active contraction stress}} \tag{1.1}$$

where $\boldsymbol{u}(\boldsymbol{r})$ is the displacement of the material point initially at $\boldsymbol{r}$, the strain tensor $\boldsymbol{\varepsilon} = \frac{1}{2}(\nabla\boldsymbol{u} + \nabla\boldsymbol{u}^{\mathrm{T}})$, $G(\boldsymbol{r})$ is the density of intracellular actin filaments at the material point initially at $\boldsymbol{r}$, E and Γ are positive constants, and $\mathbf{I}$ is the unit tensor. The traction stress per filament, τ, is in general a function of $\nabla\cdot\boldsymbol{u}$. The standard form (1.1) is discussed in detail in Oster (1984), Murray & Oster (1984), and Murray (1989); there is no viscous contribution because we are considering the equilibrium situation.

At equilibrium, these elastic and traction forces balance the elastic restoring forces that arise from attachment to the substratum. Following Murray & Oster (1984) again, we model these forces by $\lambda G\boldsymbol{u}$, where the positive constant λ reflects the strength of the attachments. The term is proportional to G since most of the intracellular actin filaments terminate at, or close to, a region of adhesion to the substratum (Alberts *et al.*, 1989: Chap. 11). Thus the equation to be solved for the new equilibrium configuration is

$$\nabla \cdot \boldsymbol{\sigma} - \lambda G\boldsymbol{u} = \boldsymbol{0}, \tag{1.2}$$

with $\boldsymbol{\sigma}$ as in (1.1). We treat the sheet as infinite, which is valid provided the section removed is small compared with the whole sheet. Thus the boundary conditions are $\boldsymbol{u}(\infty) = \boldsymbol{0}$, and $\boldsymbol{\sigma} \cdot \hat{\boldsymbol{n}} = \boldsymbol{0}$ at the free edge, where $\hat{\boldsymbol{n}}$ is the unit vector normal to this edge. For the relationship between G and $\boldsymbol{u}$, we assume that the total amount of filamentous actin in a given region of cytogel remains constant as that region is deformed, so that $G(1 + \nabla \cdot \boldsymbol{u}) = \kappa$, a constant.

Biological applications of this amended model will be presented in detail elsewhere (Sherratt, Lewis, Martin, & Murray, in preparation). Here we investigate a mathematical problem arising from the model when applied to the removal of a circular section of the epithelial sheet, in the case when τ is taken to be a constant, as, for example, in Murray & Oster (1984). We nondimensionalize (1.2) by setting

$$\bar{r} = \frac{r}{a}, \qquad \bar{T} = \frac{\Gamma}{\tau - \Gamma}, \qquad \bar{E} = \frac{E}{\tau - \Gamma}, \qquad \bar{u} = \frac{u}{a}, \qquad \bar{\lambda} = \frac{\lambda a^2}{\tau - \Gamma},$$

where a is the radius of the section removed, $r = |\boldsymbol{r}|$, and $u = |\boldsymbol{u}|$: the problem is radially symmetric. We assume that $\tau > \Gamma$. Substituting these into (1.2) and omitting the overbars for notational simplicity, we have the dimensionless equation

$$u'' + \frac{u'}{r} - \frac{u}{r^2} = \frac{\lambda r u(1 + u/r + u')}{Eu + (E-1)r}, \tag{1.3}$$

with boundary conditions

$$u'(1) = -\left(\frac{Tu(1) + T + 1}{T + E}\right), \qquad u(\infty) = 0, \tag{1.4}$$

where a prime denotes d/dr. In biological applications, we are interested in the possibility of actin aggregation at the free edge, in which case $G(r)$ has a sharp peak at $r = 1$. Numerical investigation of the solution for a range of values of E, λ, and T shows that for such a peak, $E - 1$ must be small and positive: Fig. 1 shows the solution $u(r)$ and the corresponding $G(r)$ for $E = 1{\cdot}03$, $\lambda = 4$, and $T = 20$. In the remaining sections, we look for a uniformly valid analytic approximation to the solution of (1.3) subject to (1.4) using perturbation theory, with $\epsilon = E - 1$ the small parameter. Such methods are clearly surveyed in the book by Kevorkian & Cole (1985).

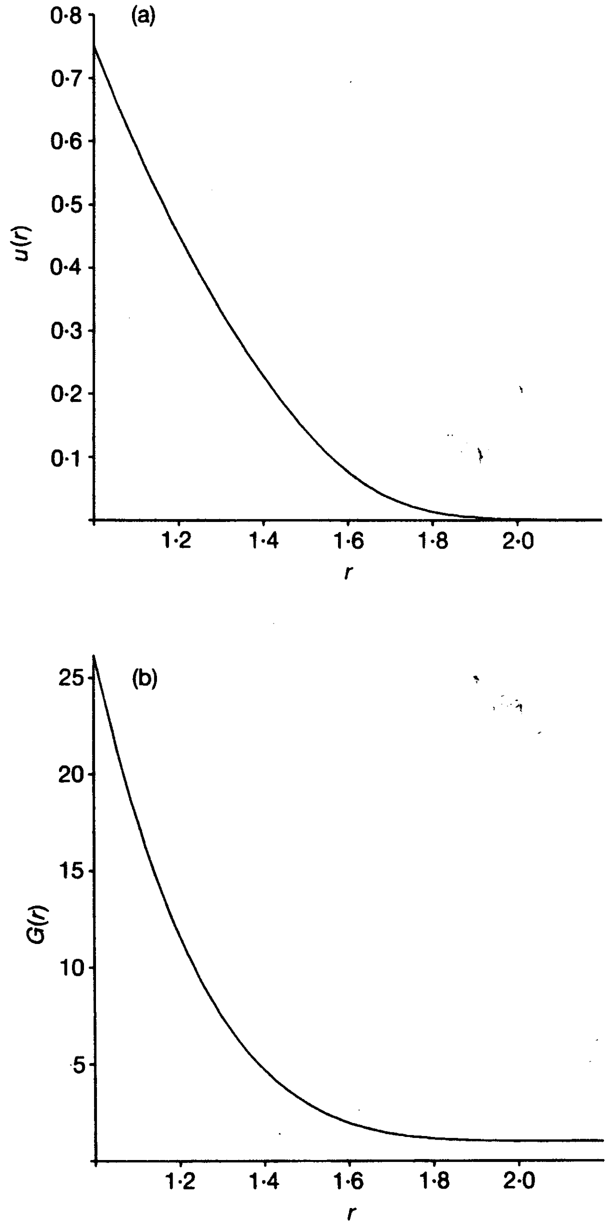

FIG. 1. (a) The numerical solution of (1.3) subject to (1.4), with $E = 1{\cdot}03$, $\lambda = 4$, and $T = 20$. The equation is solved using Newton iteration and deferred correction, with the leading-order composite solution (3.5) as the initial approximation. (b) The corresponding solution for $\kappa^{-1}G(r) = (1 + \nabla \cdot \boldsymbol{u})^{-1}$. This latter solution has a sharp peak at $r = 1$, the free edge.

2. Singular perturbation problem

We begin by attempting to solve equation (1.3) subject to (1.4) when $\epsilon = 0$. This is a linear problem which integrates immediately to give

$$u' - u(\lambda r - 1/r) = \tfrac{1}{2}\lambda r^2 + \text{constant}.$$

The integrating factor here is $r \exp(-\tfrac{1}{2}\lambda r^2)$, which gives the general solution of (1.3) as

$$u = \frac{A}{r} - \tfrac{1}{2}r + \frac{B}{r}\exp[\tfrac{1}{2}\lambda(r^2 - 1)],$$

where A and B are constants of integration. This solution does not satisfy $u(\infty) = 0$ for any values of A and B; thus the perturbation $\epsilon \neq 0$ is singular. Imposing the condition in (1.4) at $r = 1$ gives

$$u = \tfrac{1}{2}\left(\frac{1}{r} - r\right) + \frac{B}{r}\{\lambda T + \lambda - 1 + \exp[\tfrac{1}{2}\lambda(r^2 - 1)]\}. \tag{2.1}$$

This solution is plotted in Fig. 2 for a range of values of B.

We look for a rescaling that will capture the behaviour of the solution of (1.3) subject to (1.4) for large r. Such a rescaling has the general form $\hat{r} = \hat{\mu}(\epsilon)r$, $\hat{u} = u/\hat{v}(\epsilon)$, with $\hat{\mu}(\epsilon) = O(1)$, $\hat{v}(\epsilon) = O(1)$, and $\hat{\mu}\hat{v} = o(1)$ as $\epsilon \to 0$. Here, as usual, the notation $f(\epsilon) = O(1)$ includes the case $f(\epsilon) = o(1)$; the condition $\hat{\mu}\hat{v} = o(1)$ ensures that we do have a genuine rescaling. This gives

$$\hat{\mu}^2\left(\frac{d^2\hat{u}}{d\hat{r}^2} + \frac{1}{\hat{r}}\frac{d\hat{u}}{d\hat{r}} - \frac{\hat{u}}{\hat{r}^2}\right)[\hat{\mu}\hat{v}(1+\epsilon)\hat{u} + \epsilon\hat{r}] = \lambda\hat{r}\hat{u}\left[1 + \hat{\mu}\hat{v}\left(\frac{\hat{u}}{\hat{r}} + \frac{d\hat{u}}{d\hat{r}}\right)\right].$$

Thus $[\hat{u}]_{\epsilon=0} = 0$. Similarly all terms in any asymptotic expansion for $\hat{u}$ are zero.

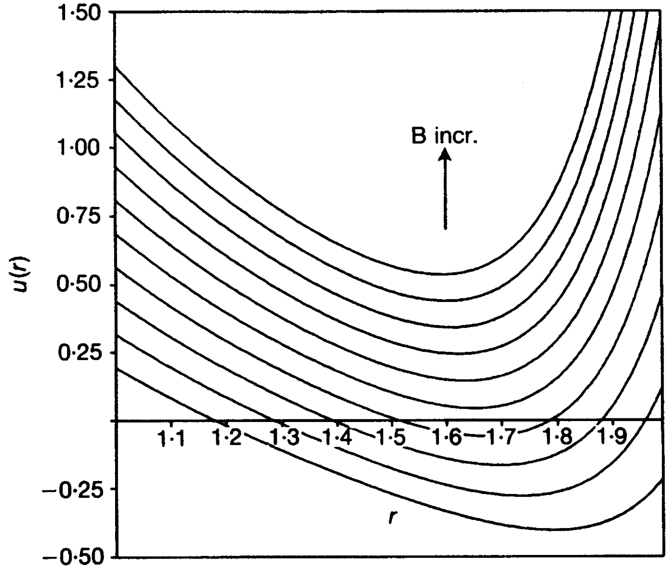

FIG. 2. The solution (2.1) of equation (1.3), for eight evenly spaced values of the constant of integration B, between 0·0023 and 0·0155. The parameter values are $\lambda = 4$ and $T = 20$.

Therefore we have to introduce a layer rescaling to give a solution intermediate between this zero solution at large r and the regular solution (1.3) near $r=1$. The general form of the variables in such a layer is

$$r^* = (r-R)/\mu(\epsilon), \qquad u^* = u/\nu(\epsilon),$$

where $\mu(\epsilon)=o(1)$ and $\nu(\epsilon)=O(1)$ as $\epsilon\to 0$. Here $r=R$ is the centre of the layer. Substituting into (1.3) gives, to leading order,

$$\frac{d^2u^*}{dr^{*2}} = \frac{\mu^2\lambda R u^*}{\nu u^* + \epsilon R}. \tag{2.2}$$

There are then a number of possibilities, according to the orders chosen for μ and ν:

(a) $\mu^2 \sim \nu \sim \epsilon$. This is discussed in detail below.

(b) $\mu^2 \sim \nu \gg \epsilon$. Then $d^2u^*/dr^{*2} = \lambda R$ to leading order; the parabolic layer solution cannot match the zero solution to the right of the layer.

(c) $\mu^2 \sim \epsilon \gg \nu$. Here to leading order $d^2u^*/dr^{*2} = \lambda u^*$, which implies $u^* \propto \exp(-\lambda^{\frac{1}{2}} r^*)$ since $u^*(\infty)=0$. This exponential solution cannot be matched to the left of the layer.

(d) $\mu^2 \gg \nu$ and $\mu^2 \gg \epsilon$. In this case all terms in any asymptotic expansion for u^* are zero.

(e) $\mu^2 \ll \nu$ or $\mu^2 \ll \epsilon$. Here $d^2u^*/dr^{*2}=0$ to leading order; the linear solution cannot match the zero solution to the right of the layer.

Thus the only rescaling that can give an appropriate layer solution is (a), namely $u^* = u/\epsilon$ and $r^* = (r-R)/\epsilon^{\frac{1}{2}}$. Multiplying (2.2) by du^*/dr^*, integrating, and imposing $u^*=0$ at $r^*=\infty$ shows that the leading-order term in the layer solution is then

$$u_0^* = RH^{-1}(C - r^*(2\lambda)^{\frac{1}{2}}) \quad \text{where } H(\xi) = \int_1^{\xi} [\theta - \log(1+\theta)]^{-\frac{1}{2}}\, d\theta.$$

Here C is a constant of integration.

3. Matching to leading order

Matching to the right of the layer is guaranteed by the boundary condition at $r^*=\infty$. For matching to the left of the layer we use an intermediate variable $r_\eta = (r-R)/\eta(\epsilon)$, with $\epsilon^{\frac{1}{2}} \ll \eta(\epsilon) \ll 1$, and consider the behaviour of the left-hand and layer solutions as $\epsilon \to 0$ with r_η fixed. Then $r\to R$ and $r^*\to -\infty$. But $u_0^* \to +\infty$ as $r^* \to -\infty$, and, as shown in Appendix 1,

$$H(\xi) = 2\xi^{\frac{1}{2}} + k + o(1) \quad \text{as } \xi \to +\infty; \tag{3.1}$$

the constant k is defined in Appendix 1. Thus

$$u_0^* = \tfrac{1}{2}\lambda R\left(r^* + \frac{k-C}{(2\lambda)^{\frac{1}{2}}}\right)^2 + o(r^*) \quad \text{as } r^* \to -\infty. \tag{3.2}$$

Matching to leading order therefore requires

$$\frac{1}{\delta(\epsilon)}[\tilde{u}_0(R)+\eta r_\eta \tilde{u}_0'(R)+\tfrac{1}{2}\eta^2 r_\eta^2 \tilde{u}_0''(R)+O(\eta^3)]$$

$$=\frac{\epsilon\lambda R}{2\delta(\epsilon)}\left(\frac{\eta r_\eta}{\epsilon^{\frac{1}{2}}}+\frac{k-C}{(2\lambda)^{\frac{1}{2}}}\right)^2+o\left(\frac{\eta\epsilon^{\frac{1}{2}}+\delta(\epsilon)}{\delta(\epsilon)}\right)$$

as $\epsilon \to 0$, where $\delta(\epsilon)$ is an intermediate scaling for the dependent variable, with $\epsilon \ll \delta \ll 1$, and $\tilde{u}_0$ is the leading-order solution (2.1) near $r=1$, which has been expanded in a Taylor series about $r=R$; as previously, a prime denotes $\mathrm{d}/\mathrm{d}r$. This matching requirement holds provided the following conditions are satisfied:

(i) $\tilde{u}_0(R)=\tilde{u}_0'(R)=0$. This implies that

$$B\{\lambda(T+1)-1+\exp[\tfrac{1}{2}\lambda(R^2-1)]\}=\tfrac{1}{2}(R^2-1) \tag{3.3}$$

$$\lambda B\exp[\tfrac{1}{2}\lambda(R^2-1)]=1. \tag{3.4}$$

These give transcendental equations for B and R with unique real positive solutions, which can easily be found numerically for given values of λ and T.

(ii) $\tilde{u}_0''(R)=\lambda R$. Simplifying the expression for $\tilde{u}_0''(R)$ using (3.3) and (3.4) gives this result.

(iii) $\eta^3 \ll \delta$.

(iv) $\epsilon^{\frac{1}{2}}\eta/\delta=O(1)$. If we further specify $\epsilon^{\frac{1}{2}}\eta \ll \delta$, then C is not determined by the leading-order matching. However, the absence of an $\epsilon^{\frac{1}{2}}$ term in the expansion near $r=1$ (see below) requires that $C=k$.

Thus we have obtained matched asymptotic expansions to leading order for the solution of (1.3) subject to (1.4). We obtain a composite expansion in the usual way:

$$u_{\mathrm{compo}}(r)=\begin{cases}\tilde{u}_0(r)+\epsilon u_0^*(r^*)-\tfrac{1}{2}\lambda R(r-R)^2 & (r<R),\\ \epsilon u_0^*(r^*) & (r>R).\end{cases} \tag{3.5}$$

Figure 3 shows $\tilde{u}_0$, ϵu_0^*, u_{compo}, and the numerical solution of (1.3) subject to (1.4), plotted against r, for $\epsilon=0{\cdot}03$ and $0{\cdot}003$. The difference between u_{compo} and $\tilde{u}_0$ decreases to zero as r decreases below 1.

4. Higher-order corrections

The leading-order composite solution differs significantly from the numerical solution of (1.3) subject to (1.4) for biologically relevant parameter values such as $\epsilon=0{\cdot}03$. We now consider higher-order corrections to the leading-order approximation obtained above. The full equation for u^* contains $\epsilon^{\frac{1}{2}}$ terms, so that the first-order correction to u_0^* is $O(\epsilon^{\frac{1}{2}})$. Substituting $u^*=u_0^*+\epsilon^{\frac{1}{2}}u_1^*$ in the full equation for u^* and equating coefficients of $\epsilon^{\frac{1}{2}}$ gives

$$\frac{\mathrm{d}^2u_1^*}{\mathrm{d}r^{*2}}-\frac{\lambda R^2}{(u_0^*+R)^2}u_1^*=\frac{\lambda u_0^*}{u_0^*+R}\left(\frac{u_0^*r^*}{u_0^*+R}+R\frac{\mathrm{d}u_0^*}{\mathrm{d}r^*}\right)-\frac{1}{R}\frac{\mathrm{d}u_0^*}{\mathrm{d}r^*}.$$

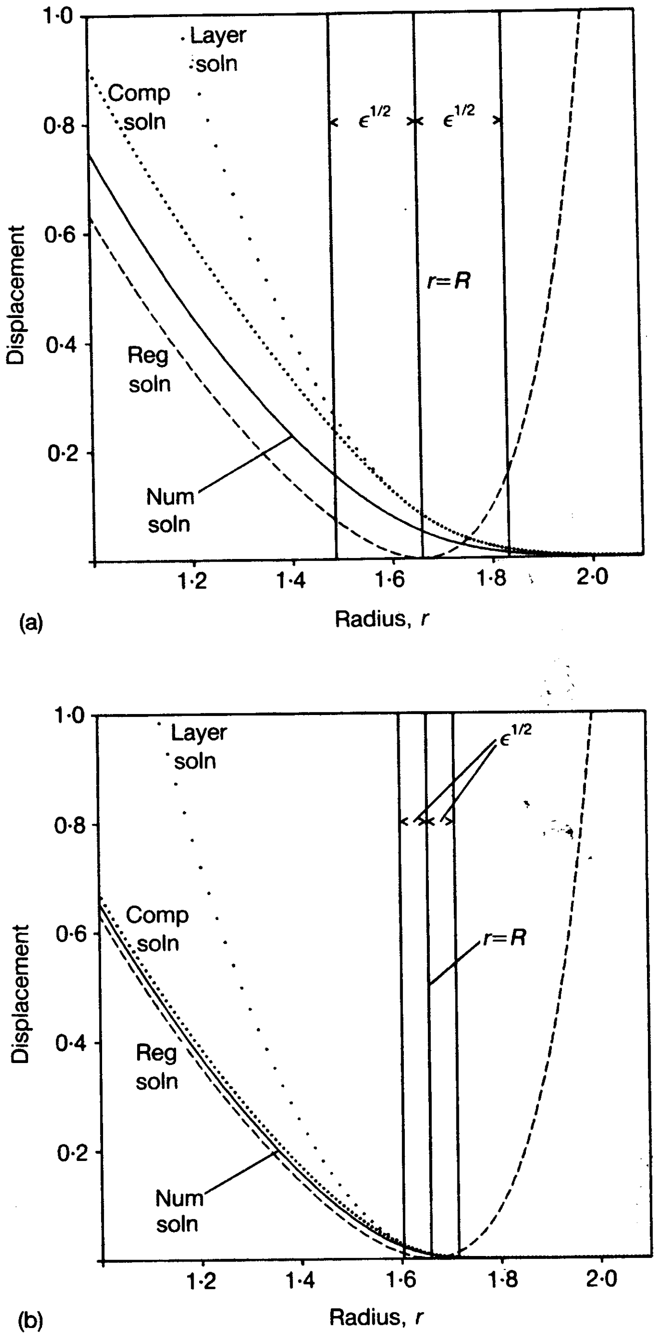

FIG. 3. Plots of the regular solution $\tilde{u}_0(r)$, the leading-order layer solution $\epsilon u_0^*(r^*)$, the leading-order composite solution, $u_{\text{compo}0}(r)$, and the numerical solution of (1.3) subject to (1.4), against r, for (a) $\epsilon = 0{\cdot}03$ and (b) $\epsilon = 0{\cdot}003$, with $\lambda = 4$ and $T = 20$. The numerical solutions were obtained using Newton iteration and deferred correction, with $u_{\text{compo}0}(r)$ as the initial approximation. To indicate the layer regions, the lines $r = R$ and $r = R \pm \epsilon^{\frac{1}{2}}$ are drawn.

Now $u_0^*(r^*)$ is monotonically decreasing, so we can use u_0^* as the independent variable; this is feasible since $\mathrm{d}u_0^*/\mathrm{d}r^*$ and $\mathrm{d}^2u_0^*/\mathrm{d}r^{*2}$ are known functions of u_0^*. We then have

$$2R^2\left[\frac{u_0^*}{R}-\log\left(1+\frac{u_0^*}{R}\right)\right]\frac{\mathrm{d}^2u_1^*}{\mathrm{d}u_0^{*2}}+\frac{Ru_0^*}{u_0^*+R}\frac{\mathrm{d}u_1^*}{\mathrm{d}u_0^*}-\frac{R^2}{(u_0^*+R)^2}u_1^*$$
$$=\frac{u_0^*}{u_0^*+R}\left[\frac{u_0^*r^*}{u_0^*+R}+R\frac{\mathrm{d}u_0^*}{\mathrm{d}r^*}\right]-\frac{1}{\lambda R}\frac{\mathrm{d}u_0^*}{\mathrm{d}r^*}, \quad (4.1)$$

where

$$\frac{\mathrm{d}u_0^*}{\mathrm{d}r^*}=-\left\{2\lambda R^2\left[\frac{u_0^*}{R}-\log\left(1+\frac{u_0^*}{R}\right)\right]\right\}^{\frac{1}{2}} \quad \text{and} \quad r^*=\frac{k-H(u_0^*/R)}{(2\lambda)^{\frac{1}{2}}},$$

subject to $u_1^*=0$ at $u_0^*=0$. Solution of this equation using the method of undetermined coefficients is discussed in Appendix 2. For the purposes of matching, it is the behaviour of u_1^* as $u_0^*\to\infty$ that is of interest, and we show in Appendix 2 that, in this limit,

$$u_1^*=-\tfrac{1}{3}(2\lambda R)^{\frac{1}{2}}u_0^{*\frac{3}{2}}+\left(\frac{6}{(2\lambda)^{\frac{1}{2}}}+\tfrac{1}{6}R^2(2\lambda)^{\frac{1}{2}}\right)\left(\frac{u_0^*}{R}\right)^{\frac{1}{2}}\log u_0^*+U_1^*u_0^{*\frac{1}{2}}+O(\log^2 u_0^*), \quad (4.2)$$

where U_1^* is a constant of integration.

Consider now higher-order corrections to $\bar{u}_0$. Substituting $u=\bar{u}_0+\epsilon^{\frac{1}{2}}\bar{u}_1$ in (1.3) and (1.4), and equating coefficients of $\epsilon^{\frac{1}{2}}$, gives

$$\bar{u}_1''+\frac{\bar{u}_1'}{r}-\frac{\bar{u}_1}{r^2}=\lambda r\left(\frac{\bar{u}_1}{r}+\bar{u}_1'\right) \quad (4.3)$$

subject to $\bar{u}_1'(1)=-T\bar{u}_1(1)/(T+1)$. This can be solved in the same way as (2.1) was obtained, giving

$$\bar{u}_1=\frac{B_1}{r}\{\lambda T+\lambda-1+\exp\left[\tfrac{1}{2}\lambda(r^2-1)\right]\},$$

where B_1 is a constant of integration. Now matching even to $O(\epsilon^{\frac{1}{2}})$ clearly requires $\bar{u}_1(R)=0$, so that $B_1=0$ and thus $\bar{u}_1\equiv 0$.

We therefore look for an $O(\epsilon)$ correction to $\bar{u}_0$. Substituting $u=\bar{u}_0+\epsilon\bar{u}_2$ in (1.3) and (1.4), and equating coefficients of ϵ, gives

$$\bar{u}_2''+\left(\frac{1}{r}-\lambda r\right)\bar{u}_2'-\left(\lambda+\frac{1}{r^2}\right)\bar{u}_2=-\frac{\lambda r}{\bar{u}_0}(\bar{u}_0+r)\left(1+\frac{\bar{u}_0}{r}+\bar{u}_0'\right)$$

subject to $\bar{u}_2'(1)=-[T\bar{u}_2(1)+\bar{u}_0'(1)]/(T+1)$. This equation can again be solved using the method of undetermined coefficients (the homogeneous equation has linearly independent solutions $1/r$ and $\mathrm{e}^{\frac{1}{2}\lambda r^2}/r$). This gives

$$\bar{u}_2(r)=\frac{B_2}{r}\{\lambda T+\lambda-1+\exp\left[\tfrac{1}{2}\lambda(r^2-1)\right)\}-\frac{1+\lambda TB}{r}+$$
$$\frac{\lambda B\mathrm{e}^{-\frac{1}{2}\lambda}}{2r}\int_1^{r^2}\frac{2B\exp\left[\frac{1}{2}\lambda(u-1)\right]+D+u}{2B\exp\left[\frac{1}{2}\lambda(u-1)\right]+D-u}(\mathrm{e}^{\frac{1}{2}\lambda u}-\mathrm{e}^{\frac{1}{2}\lambda r^2})\,\mathrm{d}u,$$

where $D = 1 + 2B(\lambda T + \lambda - 1)$ and B_2 is a constant of integration. Straightforward expansion shows that, as $r \to R^-$, with $\zeta = r - R$,

$$\bar{u}_2 = 2R \log|\zeta| + \bar{U}_2 + (\tfrac{2}{3}\lambda R^2 - 6)\zeta \log|\zeta| + \bar{U}_{2,1}\zeta + O(\zeta^2 \log|\zeta|), \tag{4.4}$$

where $\bar{U}_2$ is an outstanding constant of integration, the value of which determines B_2 and thus the constant $\bar{U}_{2,1}$.

5. Intermediate terms

Comparison of the expansions (4.2), (4.4), and the leading-order expansions in Section 3 indicates that a number of terms remain unmatched at the left of the layer, even to $O(\epsilon^{\frac{1}{2}})$. We found that, in order to complete the process of matching, it was necessary to introduce logarithmic terms between the leading and higher-order terms found previously, in both the left-hand and layer solutions. Specifically, we introduce a term $\epsilon \log \epsilon\, \bar{u}_\ell(r)$ in the left-hand solution and a term $\epsilon^{\frac{1}{2}} \log \epsilon\, u_\ell^*(r^*)$ in the layer solution.

Substituting $u = \bar{u}_0 + \epsilon \log \epsilon\, \bar{u}_\ell$ in (1.3) and (1.4) and equating coefficients of $\epsilon \log \epsilon$ shows that $\bar{u}_\ell$ satisfies the same equation (4.3) and boundary condition as $\bar{u}_1$. Thus

$$\bar{u}_\ell = \frac{B_\ell}{r}\{\lambda T + \lambda - 1 + \exp[\tfrac{1}{2}\lambda(r^2 - 1)]\} \tag{5.1}$$

where B_ℓ is a constant of integration.

The equation satisfied by u_ℓ^* is obtained in the same way; using u_0^* as the independent variable, as in Section 4, gives

$$2R\left[\frac{u_0^*}{R} - \log\left(1 + \frac{u_0^*}{R}\right)\right]\frac{d^2u_\ell^*}{du_0^{*2}} + \frac{u_0^*}{u_0^* + R}\frac{du_\ell^*}{du_0^*} - \frac{Ru_\ell^*}{(u_0^* + R)^2} = 0$$

subject to $u_\ell^* = 0$ at $u_0^* = 0$. This equation can be solved by direct integration; applying the boundary condition at $u_0^* = 0$ gives $u_\ell^* = C_\ell[u_0^*/R - \log(1 + u_0^*/R)]^{\frac{1}{2}}$, where C_ℓ is a constant of integration. Thus, as $u_0^* \to \infty$,

$$u_\ell^* = \frac{C_\ell}{R^{\frac{1}{2}}}u_0^{*\frac{1}{2}} + O(u_0^{*-\frac{1}{2}} \log u_0^*). \tag{5.2}$$

We can now consider matching the amended left-hand and layer solutions: as in Section 3, matching to the right of the layer is trivially satisfied. Using (4.2), (4.4), (5.2), and the leading-order expansions in Section 3, and expanding (5.1) in a Taylor series about $r = R$, we find that the condition for matching to $O(\epsilon^{\frac{1}{2}})$ is

$$\frac{1}{\epsilon^{\frac{1}{2}}\delta(\epsilon)}\Big(\tfrac{1}{6}\bar{u}_0'''(R)\eta^3 r_\eta^3 + O(\eta^4) + \bar{U}_\ell \epsilon \log \epsilon + \frac{\bar{U}_\ell(R^2+1)}{R(R^2-1)}\eta r_\eta \epsilon \log \epsilon + O(\eta^2 \epsilon \log \epsilon)$$

$$+ 2R\epsilon \log|\eta r_\eta| + \bar{U}_2\epsilon + (\tfrac{2}{3}\lambda R^2 - 6)\epsilon \eta r_\eta \log|\eta r_\eta| + \bar{U}_{2,1}\epsilon \eta r_\eta + O(\epsilon \eta^2 \log \eta)\Big)$$

$$= \frac{\epsilon^{\frac{1}{2}}}{\delta(\epsilon)}\left[2R\log\left|\frac{\eta r_\eta}{\epsilon^{\frac{1}{2}}}\right| + R(2+\log\tfrac{1}{2}\lambda) + O\left(\frac{\epsilon^{\frac{1}{2}}}{\eta}\right) - C_\ell(\tfrac{1}{2}\lambda)^{\frac{1}{2}}\left(\frac{\eta r_\eta}{\epsilon^{\frac{1}{2}}}\right)\epsilon^{\frac{1}{2}}\log\epsilon \right.$$

$$+ O\left(\frac{\epsilon\log\epsilon\log\eta}{\eta}\right) + \tfrac{1}{6}\lambda^2R^2\left(\frac{\eta r_\eta}{\epsilon^{\frac{1}{2}}}\right)^3\epsilon^{\frac{1}{2}} + (\tfrac{2}{3}\lambda R^2 - 6)\eta r_\eta\log\left|\frac{\eta r_\eta}{\epsilon^{\frac{1}{2}}}\right|$$

$$\left. + \epsilon^{\frac{1}{2}}U_1^*(\tfrac{1}{2}\lambda R)^{\frac{1}{2}}\left(\frac{\eta r_\eta}{\epsilon^{\frac{1}{2}}}\right) + O(\epsilon^{\frac{1}{2}}\log^2\eta)\right] + o(1) \quad (5.3)$$

as $\epsilon\to 0$, where $\tilde{U}_\ell = B_\ell\{\lambda T + \lambda - 1 + \exp[\frac{1}{2}\lambda(R^2-1)]\}/R$. Here we have obtained higher-order terms in the behaviour of u_0^* as $r^*\to -\infty$, using the expansion of $H^{-1}(\xi)$ for large ξ, which is discussed in Appendix 1. Simplifying the expression for $\tilde{u}_0'''(R)$, using (3.3) and (3.4), shows that $\tilde{u}_0'''(R) = \lambda^2R^2$. Thus the matching condition determines the outstanding constants of integration, as follows:

$$\tilde{U}_\ell = -R, \qquad \tilde{U}_2 = R(2+\log\tfrac{1}{2}\lambda),$$
$$U_1^* = \tilde{U}_{2,1}(2/\lambda R)^{\frac{1}{2}}, \qquad C_\ell = -(2/\lambda)^{\frac{1}{2}}[\tfrac{1}{3}\lambda R^2 - 3 - (R^2+1)/(R^2-1)].$$

We then have matching to $O(\epsilon^{\frac{1}{2}})$ provided that the following conditions are satisfied by $\delta(\epsilon)$ and $\eta(\epsilon)$ as $\epsilon\to 0$:

(a) $\eta^4 = o(\epsilon^{\frac{1}{2}}\delta)$, (b) $\eta^2\epsilon^{\frac{1}{2}}\log\epsilon = o(\delta)$, (c) $\eta^2\epsilon^{\frac{1}{2}}\log\eta = o(\delta)$,
(d) $\epsilon = o(\eta\delta)$, (e) $\epsilon^{\frac{3}{2}}\log\epsilon\log\eta = o(\eta\delta)$, (f) $\epsilon\log^2\eta = o(\delta)$.

Trivially (d)$\Rightarrow$(f). Moreover, $\eta \gg \epsilon^{\frac{1}{2}}$, so that $\log\eta = O(\log\epsilon)$; thus (b)$\Rightarrow$(c) and (d)$\Rightarrow$(e). Also, $\delta \gg \epsilon \gg \epsilon^{\frac{3}{2}}\log^2\epsilon$, and multiplying (a) by this result implies (b).

Thus, for matching to $O(\epsilon^{\frac{1}{2}})$, it is necessary and sufficient that $\eta^4 \ll \epsilon^{\frac{1}{2}}\delta$ and $\epsilon \ll \delta\eta$. These conditions can be portrayed graphically if we consider only orders of magnitude that are powers of ϵ: intermediate orders involving logarithms need not concern us. Thus, we write $\delta = O_s(\epsilon^p)$ and $\eta = O_s(\epsilon^q)$, where, as usual, the notation $f = O_s(g)$ means that $f = O(g)$ and $f \neq o(g)$. The two conditions are then $4q > p + \frac{1}{2}$ and $p + q < 1$. We also require $q < \frac{1}{2}$; the conditions $\eta^3 \ll \delta$ and $\epsilon^{\frac{1}{2}}\eta = O(\delta)$ for leading-order matching are implied by (a) and (d). The (p, q) domain such that these conditions are satisfied is illustrated in Fig. 4(a). For matching to $O(\epsilon)$, the corresponding conditions are $4q > p + 1$ and $p + q < \frac{1}{2}$, and the (p, q) domain in this case is illustrated in Fig. 4(b). The corresponding (p, q) domain exists, so that matching is possible, to any order that is $\gg \epsilon^{\frac{6}{5}}$.

We obtain a higher-order composite expansion as in Section 3, giving

$$u_{\text{compl}}(r) = \begin{cases} \tilde{u}_0(r) + \epsilon\log\epsilon\,\tilde{u}_\ell(r) + \epsilon\tilde{u}_2(r) + \epsilon u_0^*(r^*) + \epsilon^{\frac{3}{2}}\log\epsilon\, u_\ell^*(r^*) \\ \quad + \epsilon^{\frac{3}{2}}u_1^*(r^*) - \frac{1}{2}\lambda R\zeta^2 - \frac{1}{6}\lambda^2R^2\zeta^3 + R\epsilon\log\epsilon \\ \quad + \left(\dfrac{R^2+1}{R^2-1}\right)\zeta\epsilon\log\epsilon - 2R\epsilon\log|\zeta| - R(2+\log\frac{1}{2}\lambda)\epsilon \\ \quad + \epsilon(6 - \frac{2}{3}\lambda R^2)\zeta\log|\zeta| - \epsilon\tilde{U}_{2,1}\zeta \quad (r < R), \\ \epsilon u_0^*(r^*) + \epsilon^{\frac{3}{2}}\log\epsilon\, u_\ell^*(r^*) + \epsilon^{\frac{3}{2}}u_1^*(r^*) \quad (r > R), \end{cases}$$

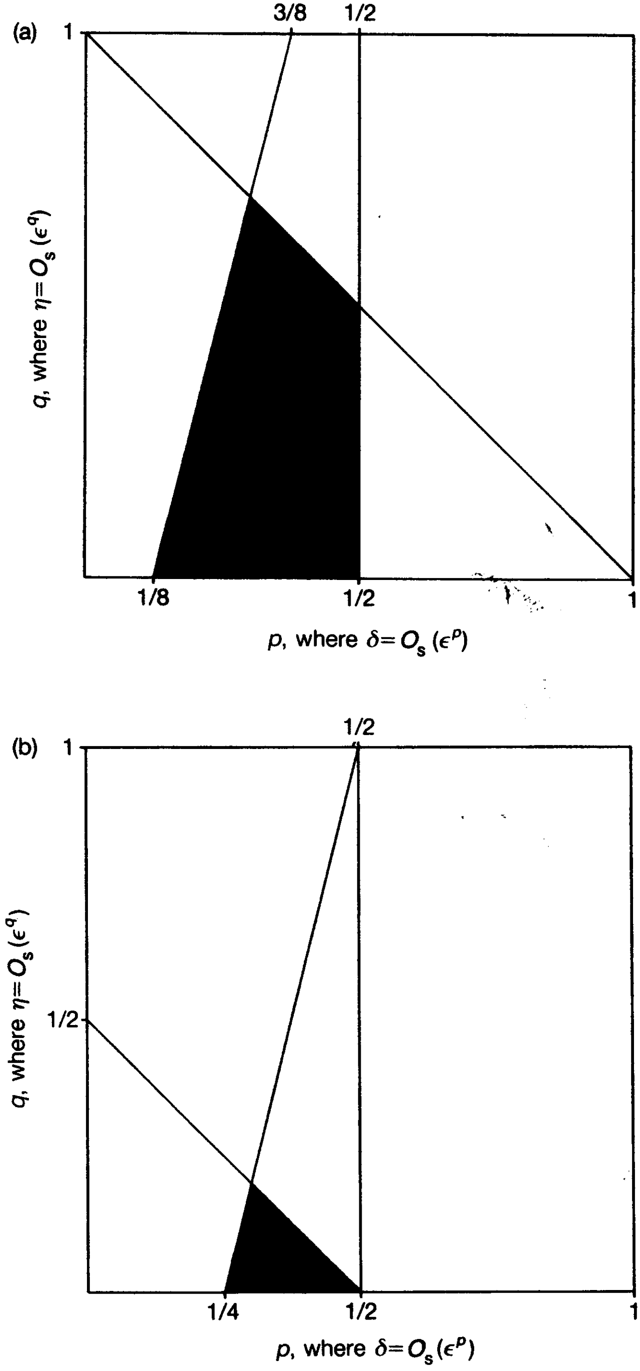

FIG. 4. The domain of orders of magnitude of δ and η for the matching condition (5.3) to be satisfied. We are considering only orders of magnitude that are powers of ϵ, with $\delta = O_s(\epsilon^p)$ and $\eta = O_s(\epsilon^q)$. The shaded region is the (p, q) domain such that the matching condition is satisfied, (a) for matching to $O(\epsilon^{\frac{1}{2}})$, and (b) for matching to $O(\epsilon)$.

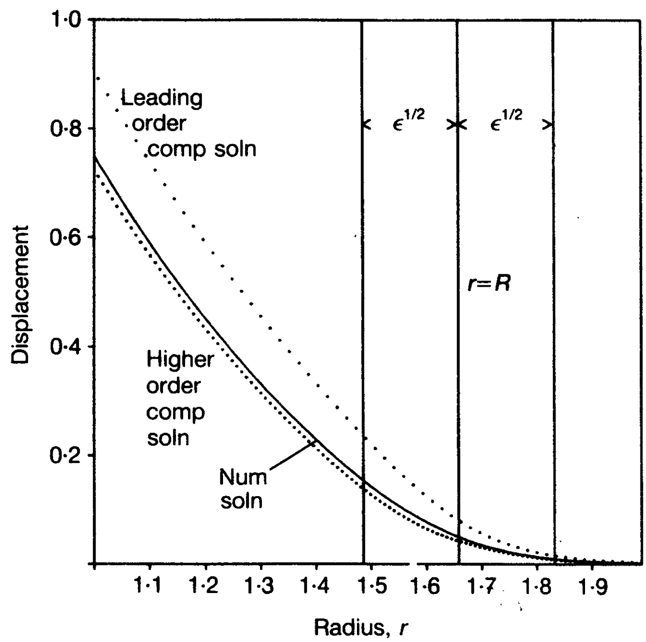

FIG. 5. Plots of the leading-order composite solution $u_{\text{comp0}}(r)$, the higher-order composite solution $u_{\text{comp1}}(r)$, and the numerical solution of (1.3) subject to (1.4), against r, for $\epsilon = 0{\cdot}03$, $\lambda = 4$, and $T = 20$. The numerical solution was obtained using Newton iteration and deferred correction, with $u_{\text{comp0}}(r)$ as the initial approximation. To indicate the layer regions, the lines $r = R$ and $r = R \pm \epsilon^{\frac{1}{2}}$ are drawn.

where $\zeta = r - R$. Figure 5 shows u_{comp1}, u_{comp0}, and the numerical solution of (1.3) subject to (1.4), plotted against r, for $\epsilon = 0{\cdot}03$. The higher-order corrections dramatically improve the quality of the composite solution as an approximation to the exact solution.

6. Conclusions

We have used the mechanical model of Murray & Oster (1984) for epithelial morphogenesis to derive an equation modelling the behaviour of an epithelial sheet after a section of the sheet has been removed, and we have investigated this equation using singular perturbation theory. We have shown that matching to even leading order specifies a unique combination of three rescalings. Further, we have derived a composite expansion that is uniformly valid to $O(\epsilon)$, which provides a good analytic approximation to the solution for parameter values such that the model equation captures the interesting behaviour of actin aggregation at the free edge of the epithelial sheet. The biological implications of the model solutions will be discussed in detail elsewhere (Sherratt, Lewis, Martin, & Murray, in preparation).

This problem is of particular note because the interesting mathematical behaviour occurs in an intermediate layer whose location does not appear, superficially, to have any special significance in either the equation or the

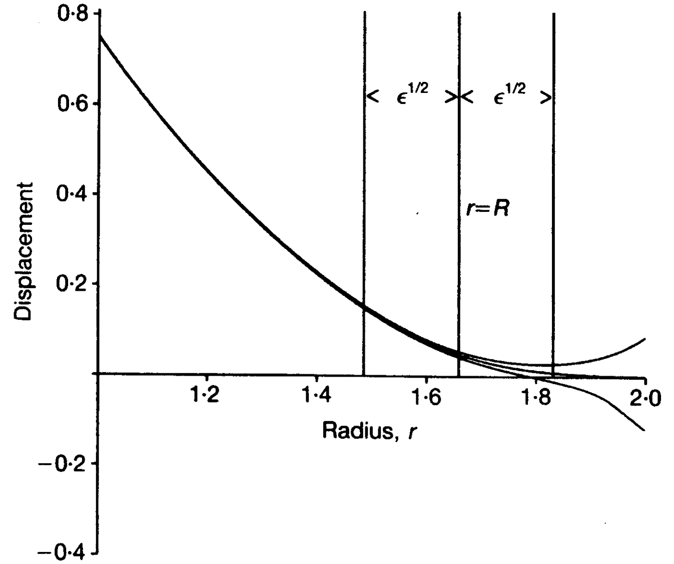

FIG. 6. Numerical solutions of (1.3) as an initial value problem, with $u(1) = u_{bvp}$ and $u(1) = (1 \pm 2 \times 10^{-3})u_{bvp}$, and $u'(1) = -(Tu_{bvp} + T + 1)/(1 + \epsilon + T)$. Here u_{bvp} is the initial value giving $u(\infty) = 0$. The solutions were obtained using a Runge–Kutta–Merson method. The parameter values are $\epsilon = 0{\cdot}03$, $T = 20$, and $\lambda = 4$, and, to indicate the layer regions, the lines $r = R$ and $r = R \pm \epsilon^{\frac{1}{2}}$ are drawn.

numerical solution. However, the importance of this layer region is evidenced by our attempts to solve the equation numerically using shooting methods. This method of numerical solution becomes increasingly difficult as $E \to 1^+$ because solutions with small differences in the values of $u(1)$, though initially close together, begin to diverge considerably in the layer region, as illustrated in Fig. 6. Moreover, divergence also occurs in this region when perturbations are made to the solution at any point $r < R - \epsilon^{\frac{1}{2}}$. Initially we could not understand why these perturbed solutions always diverged very rapidly at approximately the same position, but the layer structure of the equation provides an intuitive explanation for the phenomenon. Thus our application of singular perturbation theory has given considerable insight into the behaviour of the solution of (1.3) subject to (1.4), in addition to providing a good analytic approximation to this solution.

Appendix 1

Here we investigate the behaviour of the functions $H(\xi)$ and $H^{-1}(\xi)$ as $\xi \to \infty$; recall that

$$H(\xi) = \int_1^{\xi} [\theta - \log(1 + \theta)]^{-\frac{1}{2}} \, d\theta.$$

We begin by proving the result (3.1), that $H(\xi) = 2\xi^{\frac{1}{2}} + k + o(1)$ as $\xi \to \infty$, where k is a constant. Expanding the integrand as a power series in $\psi = \xi^{-1} \log(1 + \xi)$

shows that, for sufficiently large ξ,

$$\frac{\mathrm{d}}{\mathrm{d}\xi}[H(\xi)-2\xi^{\frac{1}{2}}]=\tfrac{1}{2}\xi^{-\frac{3}{2}}\log(1+\xi)\left(1+\frac{3}{2}\frac{1}{2!}\psi+\frac{3}{2}\frac{5}{2}\frac{1}{3!}\psi^2+\cdots\right)$$

$$<\xi^{-\frac{3}{2}}\log(1+\xi)\left(1+\frac{3}{2}\psi+\frac{3}{2}\frac{5}{2}\frac{1}{2!}\psi^2+\cdots\right)$$

$$=\xi^{-\frac{3}{2}}\log(1+\xi)(1-\psi)^{-\frac{3}{2}}.$$

Now, for ξ sufficiently large, $\log(1+\xi)<\xi^{\frac{1}{4}}$, so that

$$\frac{\mathrm{d}}{\mathrm{d}\xi}[H(\xi)-2\xi^{\frac{1}{2}}]<\xi^{-\frac{1}{8}}(\xi^{\frac{3}{4}}-1)^{-\frac{3}{2}}.$$

But, for ξ sufficiently large, $\xi^{\frac{3}{4}}-1>\xi^{\frac{3}{4}-\frac{2}{3}\beta}$ for any small β, so that

$$\frac{\mathrm{d}}{\mathrm{d}\xi}[H(\xi)-2\xi^{\frac{1}{2}}]<\xi^{-\frac{5}{4}+\beta}.$$

We now fix $\beta<\frac{1}{4}$ and integrate this inequality between ω and Ω, where ω is sufficiently large and $\Omega>\omega$. This gives

$$H(\Omega)-2\Omega^{\frac{1}{2}}<\frac{\Omega^{\beta-\frac{1}{4}}}{\beta-\frac{1}{4}}+D_\omega<D_\omega,$$

where D_ω is a constant depending on ω. Thus, for Ω sufficiently large, $H(\Omega)-2\Omega^{\frac{1}{2}}$ is bounded above by D_ω; further it increases monotonically for $\Omega>0$. Thus $H(\Omega)-2\Omega^{\frac{1}{2}}$ tends to a finite limit as $\Omega\to\infty$. The value of this limit, k say, is simply

$$k=-2+\int_1^\infty\{[\theta-\log(1+\theta)]^{-\frac{1}{2}}-\theta^{-\frac{1}{2}}\}\,\mathrm{d}\theta,$$

and numerical integration shows that $k\approx 0{\cdot}898996$. Termwise integration of the above series expansion for $(\mathrm{d}/\mathrm{d}\xi)[H(\xi)-2\xi^{\frac{1}{2}}]$ suggests that $H(\xi)-2\xi^{\frac{1}{2}}-k$ has the form $-\xi^{-\frac{1}{2}}\log\xi-2\xi^{-\frac{1}{2}}+O(\xi^{-\frac{3}{2}}\log^2\xi)$ as $\xi\to\infty$, and this is confirmed by numerical integration. It therefore follows that, in this limit,

$$H(\xi)=2\xi^{\frac{1}{2}}+k-\xi^{-\frac{1}{2}}\log\xi-2\xi^{-\frac{1}{2}}+O(\xi^{-\frac{3}{2}}\log^2\xi). \tag{A.1}$$

From (3.1), it is clear that, to leading order, $H^{-1}(x)=\frac{1}{4}(x-k)^2$ as $x\to\infty$. Substituting $H^{-1}(x)=\frac{1}{4}(x-k)^2+y(x)$ into (A.1) and expanding for large x implies that

$$x=x+\frac{2}{x-k}\left[y-2\log x-2(1-\log 2)+\frac{2k}{x}+O\left(\frac{\log^2 x+y^2+y\log x}{x^2}\right)\right],$$

so that, as $x\to\infty$,

$$H^{-1}(x)=\tfrac{1}{4}(x-k)^2+2\log x+2(1-\log 2)-2k/x+o(x^{-1}).$$

Appendix 2

Here we derive the expansion (4.2) of u_1^* for large u_0^*. The function $u_1^*(u_0^*)$ is defined by (4.1), and the corresponding homogeneous equation can be integrated directly, giving linearly independent solutions

$$y_1(u_0^*) = \left[\frac{u_0^*}{R} - \log\left(1+\frac{u_0^*}{R}\right)\right]^{\frac{1}{2}},$$

$$y_2(u_0^*) = \left[\frac{u_0^*}{R} - \log\left(1+\frac{u_0^*}{R}\right)\right]^{\frac{1}{2}} I(u_0^*/R),$$

where $I(\xi) = \int_1^\xi [\theta - \log(1+\theta)]^{-\frac{3}{2}}\,d\theta$. The inhomogeneous equation can thus be solved using the method of undetermined coefficients, giving the general solution of (4.1) as

$$u_1^* = \tfrac{1}{2}\left[\frac{u_0^*}{R} - \log\left(1+\frac{u_0^*}{R}\right)\right]^{\frac{1}{2}}$$
$$\times\left(I(u_0^*/R)\int_0^{u_0^*/R} F(\xi)\,d\xi - \int_1^{u_0^*/R} I(\xi)F(\xi)\,d\xi + P + QI(u_0^*/R)\right), \quad \text{(B.1)}$$

where $F(u_0^*/R)$ is the right-hand side of (4.1), and P and Q are constants of integration. The function F is integrable near zero, since straightforward series expansion shows that, as $\xi \to 0$, $F(\xi) = \xi/\lambda^{\frac{1}{2}} + O(\xi^2 \log \xi)$. Now, as $u_0^* \to 0$, $u_1^* = -\frac{1}{6}Q(3Ru_0^{*-1} + 5) + o(1)$, and thus the boundary condition at $u_0^* = 0$ requires that $Q = 0$.

For the purposes of matching, it is the behaviour of u_1^* as $u_0^* \to \infty$ that is of interest. Expanding for large ξ gives

$$F(\xi) = R^2(\tfrac{1}{2}\lambda)^{\frac{1}{2}}[-2\xi^{\frac{1}{2}} + \xi^{-\frac{1}{2}}\log\xi + (6/(\lambda R^2)+2)\xi^{-\frac{1}{2}}] + O(\xi^{-\frac{3}{2}}\log^2\xi),$$

$$I(\xi)F(\xi) =$$
$$R^2(\tfrac{1}{2}\lambda)^{\frac{1}{2}}[-2I_\infty\xi^{\frac{1}{2}} + 4 + I_\infty\xi^{-\frac{1}{2}}\log\xi + I_\infty(6/(\lambda R^2)+2)\xi^{-\frac{1}{2}} - 4(3/(\lambda R^2)+\tfrac{2}{3})\xi^{-1}]$$
$$+ O(\xi^{-\frac{3}{2}}\log^2\xi),$$

where $I_\infty = \lim_{\xi\to\infty} I(\xi)$. Here we have used the expansion of $H(\xi)$ for large ξ, which is discussed in Appendix 1. Integrating termwise and substituting into (B.1) suggests that, as $u_0^* \to \infty$,

$$u_1^* = -\tfrac{1}{3}(2\lambda R)^{\frac{1}{2}}u_0^{*\frac{3}{2}} + \left(\frac{6}{(2\lambda)^{\frac{1}{2}}} + \tfrac{1}{6}R^2(2\lambda)^{\frac{1}{2}}\right)\left(\frac{u_0^*}{R}\right)^{\frac{1}{2}}\log u_0^* + U_1^* u_0^{*\frac{1}{2}} + O(\log^2 u_0^*),$$

where the constant U_1^* is dependent on the outstanding constant of integration P. This is the result (4.2), and the expansion is confirmed by numerical integration.

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References

ALBERTS, B., BRAY, D., LEWIS, J., RAFF, M., ROBERTS, K., & WATSON, J. D. 1989 *The Molecular Biology of the Cell.* New York: Garland.

KEVORKIAN, J., & COLE, J. D. 1985 *Perturbation Methods in Applied Mathematics.* Berlin: Springer.

MURRAY, J. D. 1989 *Mathematical Biology.* Berlin: Springer.

MURRAY, J. D., & OSTER, G. F. 1984 Generation of biological pattern and form. *IMA J. Math. Appl. Med. Biol.* **1**, 51–75.

OSTER, G. F. 1984 On the crawling of cells. *J. Embryol. Exp. Morphol.* **83** Suppl., 329–64.