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ANALYSIS OF A MATHEMATICAL MODEL OF ISCHEMIC CUTANEOUS WOUNDS*

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Abstract. Chronic wounds represent a major public health problem affecting 6.5 million people in the United States. Ischemia represents a serious complicating factor in wound healing. In this paper we analyze a recently developed mathematical model of ischemic dermal wounds. The model consists of a coupled system of PDEs in the partially healed region, with the wound boundary as a free boundary. The extracellular matrix (ECM) is assumed to be viscoelastic, and the free boundary moves with the velocity of the ECM at the boundary of the open wound. The model equations involve the concentrations of oxygen, cytokines, and the densities of several types of cells. The ischemic level is represented by a parameter which appears in the boundary conditions, $0 \leq \gamma < 1$; γ near 1 corresponds to extreme ischemia and $\gamma = 0$ corresponds to normal nonischemic conditions. We establish global existence and uniqueness of the free boundary problem and study the dependence of the free boundary on γ.

Key words. ischemia, wound healing, free boundary problem, asymptotic behavior of solution

AMS subject classifications. 35R35, 35M30, 35Q92, 35B40, 92C50

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1. Introduction.

Wound healing represents the outcome of a large number of interrelated biological events that are orchestrated over a temporal sequence in response to injury and its microenvironment. The process involves interactions among different soluble chemical mediators, different types of cells, and the extracellular matrix (ECM). Among the various factors that affect the healing of a wound, the tissue oxygen level is a key determinant [11, 26]. Although hypoxia is generally recognized as a physiological cue to induce angiogenesis [4, 25, 21, 14], severe hypoxia cannot sustain the growth of functional blood vessels [12, 1, 10, 18, 23].

There have been several mathematical models of wound healing which incorporated the effect of angiogenesis [20, 19, 3, 24]. Mathematical models of angiogenic networks, such as through the induction of vascular networks by vascular endothelial growth factors (VEGFs) [5, 6], were developed by McDougall and coworkers [16, 27], based in part on the work of Anderson and Chaplain [2], in connection with chemotherapeutic strategies. The role of oxygen in wound healing was explicitly incorporated in the works of Byrne et al. [3] and Schugart et al. [24]. In particular, it was demonstrated in [24] that enhanced healing can be achieved by moderate hyperoxic treatments. In [22], the impairment of dermal wound healing due to ischemic conditions was addressed in a preclinical experimental model. In a more recent work [28], Xue, Friedman, and Sen developed a mathematical model of ischemic dermal wound healing. The model consists of a system of partial differential equations (PDEs) in the

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partially healed region which is modeled as a viscoelastic medium with a free boundary surrounding the open wound. Simulations of the model were shown to be in agreement with the experimental results in [22].

In this paper we study the model in [28] by mathematical analysis. In particular we prove that the free boundary problem developed in that model has a unique global solution and that the open wound does not close under extreme ischemic conditions. We also show, by simulations, that nonischemic wounds do heal. In section 2 we formulate the mathematical model for a radially symmetric geometry as in [28]. The ischemic level is determined by a parameter γ, $0 \le \gamma \le 1$; γ near 1 corresponds to extreme ischemia and $\gamma = 0$ corresponds to normal nonischemic conditions. In section 3 we show that the free boundary is monotone decreasing, and in section 4 we derive a priori estimates. In section 5 we transform the free boundary problem into a problem in a fixed domain; this is a convenient form for proving, in section 6, local existence and uniqueness of a solution. The extension of the solution to all $t > 0$ is also established in section 6 by using the a priori estimates derived in section 4. In section 7 we consider the case of extreme ischemia (namely, γ near 1) and prove that the wound's boundary stops decreasing after some finite time. In section 8 we establish some properties of the solution for wounds that do not heal. Section 9 simulates the radius of the wound when the parameters of the system are chosen, as in [28], based on biological literature. The simulations suggest the following conjecture: there exists a parameter γ^* such that wounds heal if $0 \le \gamma < \gamma^*$ and do not heal if $\gamma^* < \gamma \le 1$.

2. The mathematical model. It is assumed that the dermal tissue is in a circular domain $\{(r, \theta;\ r \le L)\}$ and the open wound at time t is a disc $\{(r, \theta;\ r < R(t))\}$ with initial radius $R(0) < L$. The partially healed tissue is the annulus $\Omega(t) = \{(r, \theta;\ R(t) \le r \le L)\}$. We introduce the following variables:

- Chemicals:
  - $w(r,t)$: concentration of tissue oxygen.
  - $e(r,t)$: concentration of vascular endothelial growth factor (VEGF).
  - $p(r,t)$: concentration of platelet derived growth factor (PDGF).
- Cells, blood vessels, and matrix:
  - $m(r,t)$: density of macrophages.
  - $f(r,t)$: density of fibroblasts.
  - $n(r,t)$: density of capillary tips.
  - $b(r,t)$: density of capillary sprouts.
  - $\rho(r,t)$: density of the ECM.
  - $v(r,t)$: velocity of the ECM.

In homeostasis, $w = w_0$, $m = m_0$, $f = f_0$, $b = b_0$, and $\rho = \rho_0$. In the remainder of this paper these variables have already been scaled so that $w_0 = m_0 = \rho_0 = b_0 = \rho_0 = 1$.

The continuity equation for the matrix density ρ is

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = G_\rho(f, w, p),$$

where $G_\rho(f, w, \rho)$ is a growth and decay term of the ECM due to collagen secretion by fibroblasts and degradation by matrix metalloproteinases (MMPs). The specific form of G_ρ incorporates the fact that collagen production and maturation require the availability of oxygen [13, 17, 11, 26],

$$G_\rho = \frac{k_\rho w}{w + K_{w\rho}} f \left(1 - \frac{\rho}{\rho_m}\right) - \lambda_\rho \rho,$$

where ρ_m is the maximum matrix volume fraction permitted in the partially healed region, $\rho_m > 1$.

The partially healed tissue is modeled as a quasi-static upper convected Maxwell fluid with velocity $\mathbf{v}$, deviatoric stress tensor given by $\tau = \eta(\nabla\mathbf{v} + \nabla\mathbf{v}^T)$, where η is the shear viscosity, and pressure P. The pressure P is generally a function of the matrix density ρ and is assumed to have the form

$$P(\rho) = \begin{cases} \beta(\rho - 1), & \rho \geq 1, \\ 0, & \rho < 1. \end{cases} \tag{2.1}$$

The total stress $\sigma = \tau - PI$ appears only in the boundary conditions. By further assuming radially symmetric flow, i.e., $\mathbf{v} = v(r,t)\mathbf{e}_r$, the continuity equation becomes

$$\frac{\partial \rho}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(r\rho v) = \frac{k_\rho w}{w + K_{w\rho}} f\left(1 - \frac{\rho}{\rho_m}\right) - \lambda_\rho \rho, \quad R(t) < r < L, \tag{2.2}$$

and the nondimensionalized momentum equation for the ECM becomes (see [28] for supporting information)

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial v}{\partial r}\right) - \frac{v}{r^2} = \frac{\partial P(\rho)}{\partial r}, \quad R(t) < r < L. \tag{2.3}$$

To simplify the analysis and simulations, we wish to have a PDE system in which all variables are radially symmetric. In order to implement ischemic conditions in radially symmetric form we assume that small arcs of length δ are cut off from the healthy tissue at $r = L$ and that the distance between two adjacent δ arcs is ε. If $\delta,\ \varepsilon \to 0$ in such a way that $\varepsilon \sim e^{-c/\delta}$, where c is a positive constant, then, for any diffusion process with boundary conditions

$$\begin{aligned} &\frac{\partial u}{\partial r} = 0 \ \text{ on the } \delta\text{-arcs}, \\ &u = g \quad \text{on the remaining arcs}, \end{aligned}$$

the limiting “homogenized” boundary condition is [8]

$$(1-\gamma)(u - g) + \gamma\frac{\partial u}{\partial r} = 0 \quad \text{on } \ r = L$$

for some constant $\gamma \in [0,1]$ which depends only on c; $\gamma = 0$ corresponds to healthy tissue (i.e., no excision of δ-arcs) and γ near 1 corresponds to extreme ischemia.

The equations for the concentrations of oxygen, PDGF, and VEGF are

$$\begin{aligned} \frac{\partial w}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(rwv) &= \frac{1}{r}\frac{\partial}{\partial r}\left(rD_w\frac{\partial w}{\partial r}\right) \\ &\quad + k_w b\big((1-\gamma)w_b - w\big) - \left[\big(\lambda_{wf} f + \lambda_{wm} m\big)\left(1 + \frac{\lambda_{ww} p}{1+p}\right) + \lambda_{wm}\right] w, \end{aligned} \tag{2.4}$$

$$\frac{\partial p}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(rpv) = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_p\frac{\partial p}{\partial r}\right) + k_p m G_p(w) - \frac{\lambda_{pf} f p}{1+p} - \lambda_p p, \tag{2.5}$$

$$\frac{\partial e}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(rev) = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_e\frac{\partial e}{\partial r}\right) + k_e m G_e(w) - (\lambda_{en} n + \lambda_{eb} b + \lambda_e)e. \tag{2.6}$$

The equations for macrophages, fibroblasts, capillary tips, and capillary sprouts include diffusion, generation, and death of cells, and chemotactic migration of cells:

$$\frac{\partial m}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(rmv) = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_m\frac{\partial m}{\partial r}\right) - \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\chi_m \rho m H(1-m/m_m)\partial p/\partial r}{\sqrt{1+k_{sg}\left|\partial p/\partial r\right|^2}}\right) + \frac{k_m bp}{1+p} - \lambda_m m\left(1+\lambda_d D(w)\right), \tag{2.7}$$

$$\frac{\partial f}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(rfv) = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_f\frac{\partial f}{\partial r}\right) - \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\chi_f \rho f H(1-f/f_m)\partial p/\partial r}{\sqrt{1+k_{sg}\left|\partial p/\partial r\right|^2}}\right) + k_f G_f(w) f\left(1-\frac{f}{f_m}\right) - \lambda_f f(1+\lambda_d D(w)), \tag{2.8}$$

$$\frac{\partial n}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(rnv) = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_n\frac{\partial n}{\partial r}\right) - \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\chi_n \rho n H(1-n/n_m)\partial e/\partial r}{\sqrt{1+k_{sg}\left|\partial e/\partial r\right|^2}}\right) + (k_{nb}b + k_n n)\frac{e}{1+e} - (\lambda_{nb}b + \lambda_{nn}n)n, \tag{2.9}$$

$$\frac{\partial b}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(rbv) = \frac{1}{r}\frac{\partial}{\partial r}\left(rD_b\frac{\partial b}{\partial r}\right) + \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{AD_n b\partial n/\partial r}{\sqrt{1+k_{sg}\left|\partial n/\partial r\right|^2}}\right) - \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{A\chi_n b\rho n H(1-n/n_m)\partial e/\partial r}{\sqrt{1+k_{sg}\left|\partial e/\partial r\right|^2}}\right) + k_b G_b(w) b(1-b) + G_b(w)(\lambda_{nb}b + \lambda_{nn}n)n, \tag{2.10}$$

where the two terms with A (in (2.10)) represent the fact that sprouts follow tips, and the oxygen-dependent functions G and D are given by

$$G_p(w) = \begin{cases} 3w, & 0 \le w < 0.5, \\ 2-w, & 0.5 \le w < 1, \\ \frac{1}{3}w + \frac{2}{3}, & 1 \le w < 4, \\ 2, & w \ge 4, \end{cases} \qquad G_e(w) = \begin{cases} 2w, & 0 \le w < 0.5, \\ 2-2w, & 0.5 \le w < 1, \\ \frac{1}{3}w - \frac{1}{3}, & 1 \le w < 4, \\ 1, & w \ge 4, \end{cases}$$

$$G_f(w) = \frac{(K_{wf}+1)w}{K_{wf}+w}, \quad G_b = \frac{(K_{w\rho}+1)w}{K_{w\rho}+w}, \quad D(w) = 1 - H(5w-1)H(1-w/3).$$

Here H is an approximated Heaviside function

$$H(u) = \begin{cases} \frac{u^6}{10^{-6}+u^6}, & u \ge 0, \\ 0, & u < 0. \end{cases}$$

Note that in (2.4) the supply of oxygen from the vasculature is reduced to $k_w b((1-\gamma)w_b - w)$ due to the ischemic condition. The functions $G_p(w)$ and $G_e(w)$

are constructed to reflect the biological effect of oxygenation: moderate hypoxia and hyperoxia increase the production of PDGF and VEGF compared to normoxia. Equations (2.7)–(2.9) include chemotaxis flux terms that describe the chemotactic movement of macrophages, fibroblasts, and capillary tips. The two terms with A in (2.10) represent the fact that capillary sprouts are dragged along capillary tips. Although the forms of the G functions and the D function are suggested by biological experiments, our mathematical analysis will not depend on the special form of these functions.

The free boundary $r = R(t)$ is moving with velocity v:

$$\dot{R}(t) = v(R(t), t). \tag{2.11}$$

The boundary conditions at $r = L$ are

$$v = 0, \tag{2.12}$$

$$(1-\gamma)(w-1) + \gamma L \frac{\partial w}{\partial r} = 0, \tag{2.13}$$

$$(1-\gamma)p + \gamma L \frac{\partial p}{\partial r} = 0, \quad (1-\gamma)e + \gamma L \frac{\partial e}{\partial r} = 0, \tag{2.14}$$

$$(1-\gamma)m + \gamma L \left(\frac{\partial m}{\partial r} - \frac{\chi_m}{D_m} \frac{\rho m H(1 - m/m_m)\partial p/\partial r}{\sqrt{1 + k_{sg} \left|\partial p/\partial r\right|^2}} \right) = 0, \tag{2.15}$$

$$(1-\gamma)(f-1) + \gamma L \left(\frac{\partial f}{\partial r} - \frac{\chi_f}{D_f} \frac{\rho f H(1 - f/f_m)\partial p/\partial r}{\sqrt{1 + k_{sg} \left|\partial p/\partial r\right|^2}} \right) = 0, \tag{2.16}$$

$$(1-\gamma)n + \gamma L \left(\frac{\partial n}{\partial r} - \frac{\chi_n}{D_n} \frac{\rho n H(1 - n/n_m)\partial e/\partial r}{\sqrt{1 + k_{sg} \left|\partial e/\partial r\right|^2}} \right) = 0, \tag{2.17}$$

$$\begin{aligned} &(1-\gamma)(b-1) \\ &\quad + \gamma L \left(\frac{\partial b}{\partial r} + \frac{A D_n b \partial n/\partial r}{\sqrt{1 + k_{sg} \left|\partial n/\partial r\right|^2}} - \frac{A \chi_n b \rho n H(1 - n/n_m)\partial e/\partial r}{\sqrt{1 + k_{sg} \left|\partial e/\partial r\right|^2}} \right) = 0, \end{aligned} \tag{2.18}$$

and the boundary conditions at $r = R(t)$ are

$$\frac{\partial v}{\partial r} = P, \tag{2.19}$$

$$\frac{\partial w}{\partial r} = \frac{\partial e}{\partial r} = \frac{\partial n}{\partial r} = \frac{\partial b}{\partial r} = 0, \tag{2.20}$$

$$-\frac{\partial p}{\partial r} = \frac{k_{pb} R(t)}{D_p R_0}, \tag{2.21}$$

$$-D_m \frac{\partial m}{\partial r} + \chi_m \frac{\rho m H(1 - m/m_m)\partial p/\partial r}{\sqrt{1 + k_{sg} \left|\partial p/\partial r\right|^2}} = 0, \tag{2.22}$$

$$-D_f \frac{\partial f}{\partial r} + \chi_f \frac{\rho f H(1 - f/f_m)\partial p/\partial r}{\sqrt{1 + k_{sg} \left|\partial p/\partial r\right|^2}} = 0. \tag{2.23}$$

Equation (2.21) represents the fact that secretion of platelets decreases with healing (i.e., as $R(t)$ decreases). The initial conditions for $R_0 \le r \le L$ take the form

$$
\begin{aligned}
&R(0) = R_0, \;\; v = 0, \;\; \rho = f = 1, \;\; w = 1, \;\; b = g\left(\frac{r - R_0}{\epsilon_0}\right), \\
&e = m = n = 0, \;\; p = p_0(r),
\end{aligned} \tag{2.24}
$$

where

$$
g(z) = \begin{cases} 0, & z \le 0, \\ \dfrac{8}{3}z^2, & 0 < z \le \dfrac{1}{4}, \\ \dfrac{4}{3}z - \dfrac{1}{6}, & \dfrac{1}{4} \le z < \dfrac{3}{4}, \\ 1 - \dfrac{8}{3}(1-z)^2, & \dfrac{3}{4} \le z \le 1, \\ 1, & z > 1, \end{cases}
$$

and $p_0(r)$ has three continuous derivatives and satisfies the boundary conditions (2.14) and (2.21), and

$$
\begin{cases} p_0'(r) < 0 & \text{if} \quad R_0 < r < R_0 + \varepsilon_0, \\ p_0(r) = 0 & \text{if} \quad R_0 + \varepsilon_0 < r < L, \end{cases} \tag{2.25}
$$

where $0 < \varepsilon_0 < L - R_0$.

In healthy tissue there is no net growth of ECM, i.e., $G_\rho(f, w, \rho) = 0$ if $f = w = \rho = 1$, which means that

$$
\lambda_\rho = \frac{k_\rho}{1 + K_{w\rho}}\left(1 - \frac{1}{\rho_m}\right). \tag{2.26}
$$

Similarly

$$
k_w = \frac{\lambda_{wf} + \lambda_{wm}}{w_b - 1}, \tag{2.27}
$$

$$
k_f = \frac{\lambda_f}{1 - 1/f_m}. \tag{2.28}
$$

3. $R(t)$ is monotonically decreasing. Set

$$
Q(t) = \int_{R(t)}^{L} yP(y, t)dy, \tag{3.1}
$$

where $P(r, t) = P(\rho(r, t))$.

THEOREM 3.1. *For any solution of* (2.2)–(2.28) *there holds*

$$
\dot{R}(t) \le 0, \;\; \dot{R}(t) < 0 \;\; \textit{if and only if} \;\; Q(t) > 0, \tag{3.2}
$$

$$
R(0)e^{-\frac{2}{L^2}\int_0^t Q(\tau)d\tau} \le R(t) \le R(0)e^{-\frac{1}{L^2}\int_0^t Q(\tau)d\tau}. \tag{3.3}
$$

Proof. Equation (2.3) can be rewritten as

$$
v_{rr} + \frac{v_r}{r} - \frac{v}{r^2} = v_{rr} + \left(\frac{v}{r}\right)_r = P_r.
$$

Integrating over $[R(t), r]$, we obtain

$$v_r(r,t) - v_r(R(t)) + \frac{v(r,t)}{r} - \frac{v(R(t))}{R(t)} = P(r,t) - P(R(t),t).$$

From (2.11) and (2.19) we obtain

$$v_r(r,t) + \frac{v(r,t)}{r} - \frac{\dot{R}(t)}{R(t)} = P(r,t);$$

hence

$$(rv)_r - r\frac{\dot{R}(t)}{R(t)} = rP(r,t). \tag{3.4}$$

Integrating this equation over $[r, L]$ and using (2.12), we obtain

$$-rv(r,t) - \frac{L^2 - r^2}{2}\frac{\dot{R}(t)}{R(t)} = \int_r^L yP(y,t)dy. \tag{3.5}$$

In particular, at $r = R(t)$,

$$-R(t)\dot{R}(t) - \frac{L^2 - R(t)^2}{2}\frac{\dot{R}(t)}{R(t)} = \int_{R(t)}^L yP(y,t)dy$$

or

$$\frac{\dot{R}(t)}{R(t)} = -\frac{2}{L^2 + R(t)^2}Q(t). \tag{3.6}$$

The assertion (3.2) now follows immediately from (3.6). From (3.6) we also obtain

$$-\frac{2}{L^2}Q(t) \leq \frac{\dot{R}(t)}{R(t)} \leq -\frac{1}{L^2}Q(t), \tag{3.7}$$

from which we deduce the estimate (3.3). ☐

If we substitute $\dot{R}/R$ from (3.6) into (3.4), we obtain, after dividing by r,

$$\frac{(rv)_r}{r} = P(r,t) - \frac{2}{L^2 + R(t)^2}Q(t); \tag{3.8}$$

this equation will be needed in the remainder of this paper. If we substitute $\dot{R}/R$ from (3.6) into (3.5) and divide by r, we obtain an expression for v,

$$v(r,t) = \frac{1}{r}\left\{\frac{L^2 - r^2}{L^2 + R(t)^2}Q(t) - \int_r^L yP(y,t)dy\right\}$$

or

$$v(r,t) = \frac{1}{r}\left\{\frac{L^2 - r^2}{L^2 + R(t)^2}\int_{R(t)}^r yP(y,t)dy - \frac{r^2 + R(t)^2}{L^2 + R(t)^2}\int_r^L yP(y,t)dy\right\}. \tag{3.9}$$

COROLLARY 3.2. *Equation* (2.3) *for* v *together with the boundary conditions* (2.12), (2.19) *and the initial condition* $v = 0$ *can be equivalently replaced by the formula* (3.9).

In the remainder of this paper we shall often work with the representation (3.9) for v.

4. A priori estimates. In this section we assume that there exists a classical solution to (2.2)–(2.28) for $0 \le t < T$ and derive a priori estimates which depend on T but remain uniformly bounded for any finite T. We set

$$\Omega_T = \{(r, \theta, t) \mid R(t) < r < L,\ 0 \le \theta \le 2\pi,\ 0 < t \le T\}$$

and introduce the following notation.

$C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)$ is the space of functions $u(r,t)$ with u, $D_r^2 u$, $D_t u$ uniformly Hölder continuous in $\bar{\Omega}_T$, with exponents α in r and $\alpha/2$ in t; the norm in this space is defined by

$$\|u\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} = \|u\|_{L^\infty(\bar{\Omega}_T)} + \|D_r^2 u\|_{C^{\alpha,\alpha/2}_{r,t}(\bar{\Omega}_T)} + \|D_t u\|_{C^{\alpha,\alpha/2}_{r,t}(\bar{\Omega}_T)},$$

where

$$\|v\|_{C^{\alpha,\alpha/2}_{r,t}(\bar{\Omega}_T)} = \|v\|_{L^\infty(\Omega_T)} + \sup_{(r,t),(r',t'))\in\bar{\Omega}_T} \frac{|v(r,t) - v(r',t')|}{|r-r'|^\alpha + |t-t'|^{\alpha/2}}.$$

Similarly we define the spaces $C^{\alpha,\beta}_{r,t}(\bar{\Omega}_T)$, $C^{1+\alpha}[0,T]$, etc.

In the remainder of this paper we shall use the following comparison principle [7, 15].

LEMMA 4.1. *Let v_1, v_2 satisfy*

$$\frac{\partial v_1}{\partial t} - D\Delta v_1 + g(x,t,v_1,\nabla v_1) \ge \frac{\partial v_2}{\partial t} - D\Delta v_2 + g(x,t,v_2,\nabla v_2) \quad \text{in } \Omega_T. \tag{4.1}$$

If

$$\begin{aligned} &\mu_1 \frac{\partial}{\partial \nu}(v_1 - v_2) + \mu_2(v_1 - v_2) \ge 0 \quad \text{on } \partial\Omega_T \cap \{0 < t < T\}, \\ &(v_1 - v_2)|_{t=0} \ge 0 \quad \text{in } \Omega_0, \end{aligned} \tag{4.2}$$

where ν is the outward normal and μ_1, μ_2 are nonnegative functions satisfying, at each point, either $\mu_1 > 0$ or $\mu_1 = 0$, $\mu_2 > 0$, then $v_1 \ge v_2$ in Ω_T. Furthermore, if strict inequalities hold in both (4.1) *and* (4.2)*, then $v_1 > v_2$ in Ω_T.*

LEMMA 4.2. *For any solution of* (2.2)–(2.28)*,*

$$\text{the components } w,\ e,\ p,\ m,\ f,\ n,\ b, \text{ and } \rho \text{ are nonnegative functions.} \tag{4.3}$$

Proof. For any small $\delta > 0$, let us add δ on the right-hand side of each of the equations (2.4)–(2.10) and each of the boundary conditions (2.13)–(2.18), (2.21)–(2.23), replace 0 by $-\delta$ in (2.20), and increase the initial data of b, e, m, n, p by δ. We refer to this new system as the "δ-problem" and to its solution as the "δ-solution." By continuity, each component of the δ-solution is strictly positive in Ω_{t_0} for some $t_0 > 0$. We claim that all the components are strictly positive in Ω_T for all $T > 0$. Indeed, otherwise there is a smallest T such that at least one component of the δ-solution, denoted by z, vanishes at some point $(\bar{r}, T)$. We can then apply the second part of Lemma 4.1 with $v_1 = z$, $v_2 = 0$ to conclude that $z(\bar{r}, T) > 0$, which is a contradiction.

The local existence and uniqueness proof given in sections 4–6 is valid also for the δ-problem. The estimates derived there are uniform in δ so that, as $\delta \to 0$, the δ-solution converges to the original solution. Hence each component of the original solution is nonnegative in a small time interval, say $0 < t < t_*$. We can now repeat the process for $t > t_*$ and conclude step-by-step that each component of the solution is nonnegative in Ω_T for any $T > 0$. ∎

LEMMA 4.3. *If initially $\rho(r,0) < \rho_m$ for $R(0) \le r \le L$, then,*

$$\rho < \rho_m \quad \text{in } \Omega_T. \tag{4.4}$$

Proof. If the assertion (4.4) is not true, then there exists a $t^* > 0$ such that $\rho(r,t) < \rho_m$ in Ω_{t^*}, and $\rho(r^*,t^*) = \rho_m$ for some $R(t^*) \le r^* \le L$. Then, along the characteristic curve with velocity v, through (r^*,t^*),

$$\left.\frac{D\rho}{Dt}\right|_{(r^*,t^*)} \ge 0, \tag{4.5}$$

where $D/Dt = \partial/\partial t + v(\partial/\partial r)$. On the other hand, from (2.2) and (3.8), we get

$$\left.\frac{D\rho}{Dt}\right|_{(r^*,t^*)} = -\lambda_\rho \rho(r^*,t^*) - \left(P(r^*,t^*) - \frac{2}{L^2+R^2}Q(t^*)\right)\rho(r^*,t^*).$$

Since $Q(t^*) \le \frac{L^2-R^2}{2}\max_r P(r,t^*) = \frac{L^2-R^2}{2}P(r^*,t^*)$, we obtain

$$\left.\frac{D\rho}{Dt}\right|_{(r^*,t^*)} = -\lambda_\rho \rho(r^*,t^*) - \frac{2R^2}{L^2+R^2}P(r^*,t^*)\rho(r^*,t^*) < 0,$$

which is a contradiction to (4.5). ∎

Recall that we have assumed $\rho_m > 1$.

LEMMA 4.4. *There holds*

$$\frac{|v(r,t)|}{r} \le \beta(\rho_m - 1), \quad |v_r(r,t)| \le 2\beta(\rho_m - 1) \quad \text{in } \Omega_T. \tag{4.6}$$

Proof. From Lemma 4.3 we obtain

$$\int_{R(t)}^{r} yP(y,t)dy \le \beta(\rho_m - 1)\frac{r^2 - R(t)^2}{2},$$
$$\int_{r}^{L} yP(y,t)dy \le \beta(\rho_m - 1)\frac{L^2 - r^2}{2}.$$

Using these estimates in (3.9), we get

$$\frac{|v(r,t)|}{r} \le \beta(\rho_m - 1)\frac{L^2 - r^2}{L^2 + R(t)^2} \le \beta(\rho_m - 1).$$

Substituting this inequality into (3.8) and estimating P and Q by Lemma 4.3, we also obtain

$$|v_r(r,t)| \le 2\beta(\rho_m - 1). \qquad ∎$$

LEMMA 4.5. *Setting*

$$N = \max\left\{\frac{k_{nb}}{\lambda_{nb}}, \frac{k_n + \beta[\rho_m - 1]}{\lambda_{nn}}, n_m\right\},$$

there holds

$$0 \le n(r,t) \le N \quad \textit{in } \Omega_T. \tag{4.7}$$

Proof. We write (2.9) for n in the form

$$\mathscr{L}[n] = \mathscr{L}_0[n] + \mathscr{F}[n] = 0,$$

where

$$\mathscr{L}_0[\phi] = \frac{\partial \phi}{\partial t} - \frac{1}{r}\frac{\partial}{\partial r}\left(rD_n\frac{\partial \phi}{\partial r}\right) + v\phi_r + \frac{1}{r}\frac{\partial}{\partial r}\left(r\,\frac{\chi_n\rho\phi H(1-\phi/n_m)\partial e/\partial r}{\sqrt{1+k_{sg}\left|\partial e/\partial r\right|^2}}\right)$$

and

$$\mathscr{F}[\phi] = b\left(\lambda_{nb}\phi - k_{nb}\frac{e}{1+e}\right) + \left(\lambda_{nn}\phi + \frac{(rv)_r}{r} - k_n\frac{e}{1+e}\right)\phi.$$

By (3.8) and Lemma 4.3,

$$\frac{1}{r}(rv)_r \ge -\beta[\rho_m - 1],$$

so that, by definition of N,

$$\lambda_{nn}N + \frac{(rv)_r}{r} - k_n\frac{e}{1+e} > \lambda_{nn}N - \beta[\rho_m-1] - k_n > 0$$

and

$$\lambda_{nb}N - k_{nb}\frac{e}{1+e} > \lambda_{nb}N - k_{nb} \ge 0.$$

Since, by (4.3), $b \ge 0$, we conclude that $\mathscr{F}[N] \ge 0$, and hence N is a supersolution, i.e., $\mathscr{L}(N) \ge 0$. Using also the boundary conditions (2.17) and (2.20), we deduce by the comparison lemma that $n(r,t) \le N$. ∎

LEMMA 4.6. *For any $T > 0$, there exists a constant C_T such that*

$$0 \le b(r,t) \le C_T \quad \textit{in } \Omega_T. \tag{4.8}$$

Proof. By the comparison principle,

$$0 \le b(r,t) \le b_1(r,t),$$

where $b_1(r,t)$ is a solution of the same equation as $b(r,t)$ but without the quadratic term $-k_bG_b(w)b^2$ and with the same boundary and initial conditions as for $b(r,t)$. We can write the equation for b_1 in the form

(4.9)
$$r\frac{\partial b_1}{\partial t} - \frac{\partial}{\partial r}\left(rD_b\frac{\partial b_1}{\partial r}\right) + a_1(r,t)b_1(r,t) + a_2(r,t)\frac{\partial b_1}{\partial r}(r,t) + \frac{\partial}{\partial r}\big(a_3(r,t)b_1(r,t)\big) = a_4(r,t),$$

where, by using (4.7), we find that a_1, a_2, a_3, a_4 are all uniformly bounded. From the Nash–Moser estimate [15] we deduce that, for any $0 < t_1 \le T$,

$$\|b_1\|_{C^{\alpha,\alpha/2}(\Omega_{t_1})} \le C_T + C_T\|b_1\|_{L^\infty(\Omega_{t_1})}, \tag{4.10}$$

and by interpolation,

$$\begin{aligned}\|b_1\|_{L^\infty(\Omega_{t_1})} &\le \|b_1(\cdot,0)\|_{L^\infty} + t_1^{\alpha/2}\left(1+\sup_{0\le\tau\le t_1}|\dot{R}(t)|^{\alpha/2}\right)\|b_1\|_{C^{\alpha,\alpha/2}}\\ &\le \|b_1(\cdot,0)\|_{L^\infty} + C^* t_1^{\alpha/2}\big(C_T + C_T\|b_1\|_{L^\infty(\Omega_{t_1})}\big)\\ &\le C^* C_T t_1^{\alpha/2}\|b_1\|_{L^\infty(\Omega_{t_1})} + C.\end{aligned}$$

Choosing t_1 such that

$$C^* C_T t_1^{\alpha/2} = \frac{1}{2},$$

we obtain the estimate

$$\|b_1\|_{L^\infty(\Omega_{t_1})} \le C.$$

Repeating this procedure step-by-step, the assertion (4.8) follows. ▯

The above proof can be applied successively to m, f, p, e, and w to establish the following estimates.

LEMMA 4.7. *For any $T > 0$, there exists a positive constant C_T such that in Ω_T,*

$$\begin{gathered}0 \le m(r,t) \le C_T, \quad 0 \le f(r,t) \le C_T, \quad 0 \le p(r,t) \le C_T,\\ 0 \le e(r,t) \le C_T, \quad 0 \le w(r,t) \le C_T.\end{gathered} \tag{4.11}$$

Since b is bounded (by C_T) in Ω_T, we can write (2.10) for b in the same form as (4.9) for b_1 and thus derive, by the Nash–Moser estimate, a Hölder bound

$$\|b\|_{C^{\alpha,\alpha/2}(\bar{\Omega}_T)} \le C_T.$$

The same bound can be derived for the components n, m, f, p, e, and then also for w. Hence, we obtain the following.

LEMMA 4.8. *For any $T > 0$ there exists a positive constant C_T such that*

$$\|w,p,e,m,f,n,b\|_{C^{\alpha,\alpha/2}(\bar{\Omega}_T)} \le C_T. \tag{4.12}$$

Rewriting (2.2) in the form

$$\rho_t + v\rho_r = \frac{k_\rho w}{w+K_{w\rho}} f\left(1-\frac{\rho}{\rho_m}\right) - \lambda_\rho\rho - \frac{(rv)_r}{r}\rho \equiv \mathcal{F}(r,s), \tag{4.13}$$

we proceed to establish a Hölder estimate for the function ρ.

LEMMA 4.9. *For any $T > 0$ there exists a constant C_T such that*

$$\|\rho\|_{C^{\alpha,\alpha}_{r,t}(\bar{\Omega}_T)} \le C_T. \tag{4.14}$$

Proof. We introduce the characteristic curves X, for (4.13), by

$$\begin{cases}\dfrac{dX_r(r,t,s)}{ds} = v_r(X(r,t,s),s)X_r(r,t,s) \quad \forall s\in[0,t],\\ X_r(r,t,t) = 1.\end{cases}$$

Using Lemma 4.4 we find that

$$|X_r(r,t,s)| \le e^{2\beta(\rho_m-1)(t-s)}.$$

Let $J(r,t,s) = \rho(X(r,t,s),s)$, so that

$$\begin{cases} \dfrac{dJ(r,t,s)}{ds} = \mathcal{F}(X(r,t,s),s), \\ J(r,t,t) = \rho(r,t). \end{cases}$$

Then

$$\begin{aligned} &\frac{|\rho(r_1,t)-\rho(r_2,t)|}{|r_1-r_2|^\alpha} \\ &\qquad \le \frac{1}{|r_1-r_2|^\alpha}\left|\int_0^t \mathcal{F}(X(r_1,t,s),s) - \mathcal{F}(X(r_2,t,s),s)ds\right| \\ &\qquad\quad + \frac{|\rho(X(r_1,t,0),0)-\rho(X(r_2,t,0),0)|}{|r_1-r_2|^\alpha}. \end{aligned}$$

By the initial condition $\rho(r,0)\equiv 1$ the last term vanishes, and

$$\begin{aligned} &\frac{1}{|r_1-r_2|^\alpha}\left|\int_0^t \mathcal{F}(X(r_1,t,s),s) - \mathcal{F}(X(r_2,t,s),s)ds\right| \\ &\le \left|\int_0^t \frac{\mathcal{F}(X(r_1,t,s),s) - \mathcal{F}(X(r_2,t,s),s)}{|X(r_1,t,s)-X(r_2,t,s)|^\alpha}\cdot\left(\frac{|X(r_1,t,s)-X(r_2,t,s)|}{|r_1-r_2|}\right)^\alpha ds\right| \\ &\le (e^{2\beta(\rho_m-1)(t-s)})^\alpha \int_0^t \frac{|\mathcal{F}(X(r_1,t,s),s) - \mathcal{F}(X(r_2,t,s),s)|}{|X(r_1,t,s)-X(r_2,t,s)|^\alpha}ds \\ &\le C_T\int_0^t [\rho(\cdot,s)]_{C_r^\alpha} + [w(\cdot,s)]_{C_r^\alpha} + [f(\cdot,s)]_{C_r^\alpha}ds. \end{aligned}$$

Hence

$$\frac{|\rho(r_1,t)-\rho(r_2,t)|}{|r_1-r_2|^\alpha} \le C_T + C_T\int_0^t [\rho(\cdot,s)]_{C_r^\alpha}ds.$$

Taking the supremum over $r_1,\ r_2 \in [R(t),\, L]$, $r_1 \ne r_2$, we obtain

$$[\rho(\cdot,t)]_{C_r^\alpha} \le C_T + C_T\int_0^t [\rho(\cdot,s)]_{C_r^\alpha}ds,$$

and by Gronwall's inequality,

$$[\rho(\cdot,t)]_{C_r^\alpha} \le C_T. \tag{4.15}$$

Next, taking $t_2 > t_1 > 0$, we can write

$$\rho(r,t_2) - \rho(r,t_1) = \int_{t_1}^{t_2} \mathcal{F}(X(r,t_2,s),s)ds + \rho(X(r,t_2,t_1),t_1) - \rho(r,t_1),$$

so that

$$\rho(r,t_2)-\rho(r,t_1) \le C|t_2-t_1| + [\rho(\cdot,t_1)]_{C_r^\alpha}|X(r,t_2,t_1)-r|^\alpha.$$

Since

$$|X(r,t_2,t_1)-r| = |X(r,t_2,t_1)-X(r,t_2,t_2)| \le \left\| \frac{dX}{ds} \right\|_{L^\infty} |t_2-t_1|,$$

we obtain

$$|\rho(r,t_2)-\rho(r,t_1)| \le C_T|t_2-t_1|^\alpha.$$

Combining this inequality with (4.15), the assertion (4.14) follows. ∎

LEMMA 4.10. *For any $T>0$ there exists a constant C_T such that*

$$\|v\|_{C^{\alpha,\alpha}_{r,t}(\bar{\Omega}_T)} + \|v_r\|_{C^{\alpha,\alpha}_{r,t}(\bar{\Omega}_T)} \le C_T. \tag{4.16}$$

Proof. The proof follows from the representations of $v(r,t)$ and $v_r(r,t)$ in (3.9) and (3.8) by using Lemma 4.9 and the boundedness of $\dot{R}$ (from (3.3)). ∎

LEMMA 4.11. *For any $T>0$ there exists a constant C_T such that*

$$\|R\|_{C^{1+\alpha}([0,T])} \le C_T. \tag{4.17}$$

Proof. This follows from (2.11) and Lemma 4.10. ∎

LEMMA 4.12. *For any $T>0$ there exists a constant C_T such that*

(i)

$$\|p\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T,$$
$$\|e\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T,$$
$$\|w\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T;$$

(ii)

$$\|m\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T,$$
$$\|f\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T,$$
$$\|n\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T,$$
$$\|b\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T;$$

(iii)

$$\|\rho\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T,$$
$$\|v\|_{C^{2+\alpha,1+\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T.$$

Proof. Indeed, (i) follows from Lemmas 4.8–4.11 and the parabolic Schauder estimates [7, 15]. The assertion (ii) follows by the Schauder estimates and (i). To prove (iii) we first formally differentiate (4.13) in r and apply the proof of Lemma 4.9, making use of Lemma 4.10 and (ii). We thus obtain the bound

$$\|\rho_r\|_{C^{\alpha,\alpha/2}_{r,t}(\bar{\Omega}_T)} \le C_T. \tag{4.18}$$

In order to rigorously prove (4.18), we consider the solution $\tilde{\rho}_r$ of the differentiated equation (4.13) and derive the estimate (4.18). By integration of the equation of $\tilde{\rho}_r$

with respect to r, one can verify that $\int^r \tilde\rho_r dr$ coincides with ρ; hence $\partial\rho/\partial r = \tilde\rho_r$ and (4.18) follows.

Differentiating (3.8) in r and using (4.18) we deduce that

$$\|v_{rr}\|_{C^{\alpha,\alpha/2}_{r,t}(\bar\Omega_T)} \le C_T,$$

and this allows us to differentiate the equation for ρ_r once more in r. Proceeding as before, it is then easy to complete the proof of (iii).

5. Transformation to a fixed domain. In order to prove existence and uniqueness of a solution of (2.2)–(2.28) for a small time interval $0 < t < T$, it is convenient to transform the system with the free boundary $r = R(t)$ into a system with a fixed boundary, using the mapping

$$\xi = \frac{r - R(t)}{L - R(t)}, \quad \big(r = (1-\xi)R(t) + \xi L\big). \tag{5.1}$$

In the new system, ξ varies in the interval $0 < \xi < 1$, and for any function $u(r,t) = \tilde u(\xi,t)$,

$$\frac{\partial u}{\partial r} = \frac{1}{L - R(t)}\frac{\partial \tilde u}{\partial \xi}, \tag{5.2}$$

$$\frac{\partial}{\partial r}\left(r\frac{\partial u}{\partial r}\right) = \frac{1}{(L-R(t))^2}\frac{\partial}{\partial\xi}\left(r(\xi)\frac{\partial\tilde u}{\partial\xi}\right), \tag{5.3}$$

and

$$\frac{\partial u}{\partial t} = \frac{\partial \tilde u}{\partial t} + \frac{\partial \tilde u}{\partial \xi}\frac{\partial \xi}{\partial t} = \frac{\partial \tilde u}{\partial t} + \frac{\dot R(t)}{L - R(t)}(\xi - 1)\frac{\partial \tilde u}{\partial \xi},$$

$$\big(\xi - 1\big)\frac{\partial\tilde u}{\partial\xi} = \frac{1}{r}\frac{\partial}{\partial\xi}\left(r\big(\xi-1\big)\tilde u\right) + \left(\frac{(1-\xi)(L-R(t))}{r} - 1\right)\tilde u.$$

Using these formulas we compute

$$\frac{\partial u}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(ruv) = \frac{\partial \tilde u}{\partial t} + B,$$

where

$$\begin{aligned} B = {} & \frac{\dot R(t)}{L-R(t)}(\xi-1)\frac{\partial\tilde u}{\partial\xi} + \frac{1}{(L-R(t))r}\frac{\partial}{\partial\xi}(r\tilde u v), \\ = {} & \frac{\dot R(t)}{L-R(t)}\frac{1}{r}\frac{\partial}{\partial\xi}\left(r\big(\xi-1\big)\tilde u\right) + \frac{1}{(L-R(t))r}\frac{\partial}{\partial\xi}(r\tilde u v) + K\tilde u, \end{aligned}$$

or

$$B = \frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial\xi}\Big(r\tilde u\big(\dot R(t)(\xi-1) + v\big)\Big)\right] + K\tilde u,$$

where

$$K = K(\xi) = \frac{\dot R(t)}{L-R(t)}\left(\frac{(1-\xi)(L-R(t))}{r} - 1\right). \tag{5.4}$$

Hence

$$\frac{\partial u}{\partial t}+\frac{1}{r}\frac{\partial}{\partial r}(ruv)=\frac{\partial \tilde{u}}{\partial t}+\frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(r\tilde{u}\big(\dot{R}(t)(\xi-1)+v\big)\Big)\right]+K\tilde{u}. \tag{5.5}$$

Using (5.2), (5.3), and (5.5), we can transform the PDEs in section 2 into the following system of equations, where we have, for simplicity, dropped the tilda "∼" from all the variables:

$$\frac{\partial \rho}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\Big(r(\xi)\rho M\Big)=\frac{k_\rho w}{w+K_{w\rho}}f\left(1-\frac{\rho}{\rho_m}\right)-\lambda_\rho\rho-K\rho, \tag{5.6}$$

$$\frac{1}{(L-R(t))^2}\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\left(r(\xi)\frac{\partial v}{\partial \xi}\right)-\frac{v}{r^2(\xi)}=\frac{1}{L-R(t)}\frac{\partial P}{\partial \xi}, \tag{5.7}$$

$$\begin{aligned}\frac{\partial w}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\Big(r(\xi)wM\Big)&=\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\left(r(\xi)D_w(t)\frac{\partial w}{\partial \xi}\right)\\&\quad+k_w b\big((1-\gamma)w_b-w\big)-\left[(\lambda_{wf}f+\lambda_{wm}m)\left(1+\frac{\lambda_{ww}p}{1+p}\right)+\lambda_{wm}\right]w-Kw,\end{aligned} \tag{5.8}$$

$$\begin{aligned}\frac{\partial p}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\Big(r(\xi)pM\Big)&=\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\left(r(\xi)D_p(t)\frac{\partial p}{\partial \xi}\right)\\&\quad+k_p m G_p(w)-\frac{\lambda_{pf}fp}{1+p}-\lambda_p p-Kp,\end{aligned} \tag{5.9}$$

$$\begin{aligned}\frac{\partial e}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\Big(r(\xi)eM\Big)&=\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\left(r(\xi)D_e(t)\frac{\partial e}{\partial \xi}\right)\\&\quad+k_e m G_e(w)-(\lambda_{en}n+\lambda_{eb}b+\lambda_e)e-Ke,\end{aligned} \tag{5.10}$$

$$\begin{aligned}&\frac{\partial m}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\Big(r(\xi)mM\Big)\\&\quad=\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\Big(r(\xi)D_m(t)\frac{\partial m}{\partial \xi}\Big)-\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\left(r(\xi)\frac{\chi_m(t)\rho m H(1-m/m_m)\partial p/\partial \xi}{\sqrt{1+k_{sg}(t)\left|\partial p/\partial \xi\right|^2}}\right)\\&\quad\quad+\frac{k_m bp}{1+p}-\lambda_m m\left(1+\lambda_d D(w)\right)-Km,\end{aligned} \tag{5.11}$$

$$\begin{aligned}&\frac{\partial f}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\Big(r(\xi)fM\Big)\\&\quad=\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\left(r(\xi)D_f(t)\frac{\partial f}{\partial \xi}\right)-\frac{1}{r(\xi)}\frac{\partial}{\partial \xi}\left(r(\xi)\frac{\chi_f(t)\rho f H(1-f/f_m)\partial p/\partial \xi}{\sqrt{1+k_{sg}(t)\left|\partial p/\partial \xi\right|^2}}\right)\\&\quad\quad+k_f G_f(w)f\left(1-\frac{f}{f_m}\right)-\lambda_f f(1+\lambda_d D(w))-Kf,\end{aligned} \tag{5.12}$$

(5.13)
$$\frac{\partial n}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\Big(r(\xi)nM\Big)$$
$$=\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\Big(r(\xi)D_n(t)\frac{\partial n}{\partial\xi}\Big)-\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\left(r(\xi)\frac{\chi_f(t)\rho nH(1-n/n_m)\partial e/\partial\xi}{\sqrt{1+k_{sg}(t)\left|\partial e/\partial\xi\right|^2}}\right)$$
$$+(k_{nb}b+k_nn)\frac{e}{1+e}-(\lambda_{nb}b+\lambda_{nn}n)n-Kn,$$

(5.14)
$$\frac{\partial b}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\Big(r(\xi)bM\Big)$$
$$=\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\left(r(\xi)D_b(t)\frac{\partial b}{\partial\xi}\right)+\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\left(r(\xi)\frac{AD_n(t)b\partial n/\partial\xi}{\sqrt{1+k_{sg}(t)\left|\partial n/\partial\xi\right|^2}}\right)$$
$$-\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\left(r(\xi)\frac{A\chi_n(t)b\rho nH(1-n/n_m)\partial e/\partial\xi}{\sqrt{1+k_{sg}(t)\left|\partial e/\partial\xi\right|^2}}\right)$$
$$+k_bG_b(w)b(1-b)+G_b(w)(\lambda_{nb}b+\lambda_{nn}n)n-Kb,$$

where

$$M=\frac{\dot R(t)(\xi-1)+v}{L-R(t)},\qquad k_{sg}(t)=\frac{k_{sg}}{(L-R(t))^2},$$
$$D_u(t)=\frac{D_u}{(L-R(t))^2}\quad\text{for } u=w,p,e,m,f,n,b,$$
$$\chi_u(t)=\frac{\chi_u}{(L-R(t))^2}\quad\text{for } u=m,f,n,b.$$

The free boundary condition remains as before, namely,

$$\dot R(t)=v(R(t),t). \tag{5.15}$$

The boundary conditions at the fixed boundary $\xi=1$ are

$$v=0, \tag{5.16}$$

$$(1-\gamma)(w-1)+\frac{\gamma L}{L-R(t)}\frac{\partial w}{\partial\xi}=0, \tag{5.17}$$

$$(1-\gamma)p+\frac{\gamma L}{L-R(t)}\frac{\partial p}{\partial\xi}=0, \tag{5.18}$$

$$(1-\gamma)e+\frac{\gamma L}{L-R(t)}\frac{\partial e}{\partial\xi}=0, \tag{5.19}$$

$$(1-\gamma)m+\frac{\gamma L}{L-R(t)}\left(\frac{\partial m}{\partial\xi}-\frac{\chi_m}{D_m}\frac{\rho mH(1-m/m_m)\partial p/\partial\xi}{\sqrt{1+k_{sg}(t)\left|\partial p/\partial\xi\right|^2}}\right)=0, \tag{5.20}$$

$$(1-\gamma)(f-1)+\frac{\gamma L}{L-R(t)}\left(\frac{\partial f}{\partial\xi}-\frac{\chi_f}{D_f}\frac{\rho fH(1-f/f_m)\partial p/\partial\xi}{\sqrt{1+k_{sg}(t)\left|\partial p/\partial\xi\right|^2}}\right)=0, \tag{5.21}$$

$$(5.22)\qquad (1-\gamma)n+\frac{\gamma L}{L-R(t)}\left(\frac{\partial n}{\partial \xi}-\frac{\chi_n}{D_n}\frac{\rho n H(1-n/n_m)\partial n/\partial \xi}{\sqrt{1+k_{sg}(t)\left|\partial n/\partial \xi\right|^2}}\right)=0,$$

$$(5.23)\qquad (1-\gamma)(b-1)+\frac{\gamma L}{L-R(t)}\left(\frac{\partial b}{\partial \xi}+\frac{AD_n b\partial n/\partial \xi}{\sqrt{1+k_{sg}(t)\left|\partial n/\partial \xi\right|^2}}-\frac{A\chi_n b\rho n H(1-n/n_m)\partial e/\partial \xi}{\sqrt{1+k_{sg}(t)\left|\partial e/\partial \xi\right|^2}}\right)=0,$$

and at the free boundary $\xi=0$ they are

$$(5.24)\qquad \frac{\partial v}{\partial \xi}=\big(L-R(t)\big)P,$$

$$(5.25)\qquad \frac{\partial w}{\partial \xi}=\frac{\partial e}{\partial \xi}=\frac{\partial n}{\partial \xi}=\frac{\partial b}{\partial \xi}=0,$$

$$(5.26)\qquad \frac{\partial p}{\partial \xi}=-\frac{k_{pb}R}{D_pR_0}\big(L-R(t)\big),$$

$$(5.27)\qquad -D_m\frac{\partial m}{\partial \xi}+\chi_m\frac{\rho m H(1-m/m_m)\partial p/\partial \xi}{\sqrt{1+k_{sg}(t)\left|\partial p/\partial \xi\right|^2}}=0,$$

$$(5.28)\qquad -D_f\frac{\partial f}{\partial \xi}+\chi_f\frac{\rho f H(1-f/f_m)\partial p/\partial \xi}{\sqrt{1+k_{sg}(t)\left|\partial p/\partial \xi\right|^2}}=0.$$

The initial conditions take the form

$$(5.29)\qquad \begin{aligned}&R(0)=R_0,\quad v=0,\quad \rho=f=1,\quad w=1,\quad b=g\left(\frac{\xi(L-R_0)}{\varepsilon_0}\right),\\ &e=m=n=0,\quad p(\xi,0)=p_0\big((1-\xi)R_0+\xi L\big).\end{aligned}$$

6. Existence and uniqueness.

In this section we prove the following theorem.

THEOREM 6.1. *There exists a unique solution of* (2.2)–(2.28) *for* $0\le t<\infty$ *such that, for each* $T>0$, *the estimates of Lemma* 4.12 *hold.*

Proof. We first prove existence and uniqueness for a small time interval $0\le t\le \tau$. For this proof it will be convenient to transform the system (2.2)–(2.24) into the system (5.6)–(5.29) with a fixed boundary. Set

$$G=\{0\le\xi\le 1\},\quad G_T=\{(\xi,t);\xi\in G,0\le t\le T\}\quad\text{for any}\quad T>0,$$

and introduce the Banach space

$$\begin{aligned}Y=\{&(R(t),\rho(\xi,t)); R(0)=R_0,\rho(\xi,0)=1\ \text{ with norm}\\ &\|(R,\rho)\|_Y=\|R\|_{C^{1+\alpha/2}[0,\tau]}+\|(\rho,\rho_\xi)\|_{C^{\alpha,\alpha/2}(\bar G_\tau)}\}\end{aligned}$$

and the ball

$$Y_B=\{(R,\rho)\in Y;\|(R,\rho)\|_Y\le B\}$$

for any $B>1+R_0$.

For any $(R,\rho)\in Y_B$ we wish to solve the system (5.7)–(5.14) with the corresponding boundary and initial conditions from (5.16)–(5.29). Denoting this solution by $u=(w,p,e,m,f,n,b,v)$ we shall then define $(\tilde R,\tilde\rho)$ by

$$(6.1)\qquad \frac{d}{dt}\tilde R(t)=v(R(t),t),\quad \tilde R(0)=R_0,$$

$$\frac{\partial\tilde{\rho}}{\partial t}+\frac{1}{r(\xi)}\frac{\partial}{\partial\xi}\Big(r(\xi)\tilde{\rho}\tilde{M}\Big)=\frac{k_\rho w}{w+K_{w\rho}}f\left(1-\frac{\tilde{\rho}}{\rho_m}\right)-\lambda_\rho\tilde{\rho}-\tilde{K}\tilde{\rho},\quad \tilde{\rho}(\xi,0)=1, \tag{6.2}$$

where

$$\tilde{M}=\frac{(d\tilde{R}/dt)(\xi-1)+v}{L-\tilde{R}(t)},\quad \tilde{K}=\frac{d\tilde{R}/dt}{L-\tilde{R}(t)}\left(\frac{(1-\xi)(L-\tilde{R}(t))}{r}-1\right),$$

and set

$$(\tilde{R},\tilde{\rho})=W(R,\rho).$$

We aim to prove that the mapping W is a contraction mapping, and thus has a unique fixed point.

As in [9] one can prove, by a fixed point argument, that there exists a unique solution u for $0\le t\le\tau$, for τ small, and that

$$\|u\|_{C^{2+\alpha,1+\alpha/2}_{\xi,t}(\bar{G}_\tau)}\le C,\quad u=(w,p,e,m,f,n,b,v). \tag{6.3}$$

The estimate (6.3) can also be established by the argument used in the proof of Lemma 4.12. From (6.1) and (6.3) we get

$$\left\|\frac{d}{dt}\tilde{R}\right\|_{C^{2+\alpha}[0,\tau]}\le C, \tag{6.4}$$

so that

$$\|(\tilde{M},\tilde{K})\|_{C^{2+\alpha,1+\alpha/2}_{\xi,t}(\bar{G}_\tau)}\le C.$$

We next consider (6.2), and use the same arguments as in the proofs of Lemmas 4.9 and 4.12(iii), to derive the estimate

$$\|\tilde{\rho}\|_{C^{2+\alpha,1+\alpha/2}_{\xi,t}(\bar{G}_\tau)}\le C. \tag{6.5}$$

From (6.4), (6.5) we deduce that

$$\begin{cases}\|\tilde{R}\|_{C^{1+\alpha}[0,\tau]}\le R_0+C\tau,\\ \|(\tilde{\rho},\tilde{\rho}_\xi)\|_{C^{\alpha,\alpha/2}_{\xi,t}(\bar{G}_\tau)}\le 1+C\tau^{1/2}.\end{cases} \tag{6.6}$$

Hence if τ is sufficiently small, then W maps Y_B into itself.

We next prove that W is a contraction in Y_B. Let (R_1,ρ_1) and R_2,ρ_2 be any elements in Y_B, and denote the corresponding solution by $u_i=(w_i,p_i,e_i,m_i,f_i,n_i,b_i,v_i)$ for $i=1,2$. Set

$$(\tilde{R}_i,\tilde{\rho}_i)=W(R_i,\rho_i).$$

As in [9] one can show that

$$\|u_1-u_2\|_{C^{2+\alpha,1+\alpha/2}_{\xi,t}(\bar{G}_\tau)}\le C\|(R_1-R_2,\rho_1-\rho_2)\|_Y, \tag{6.7}$$

from which one can easily deduce that

$$\left\|\frac{d}{dt}(\tilde{R}_1-\tilde{R}_2)\right\|_{C^{2+\alpha}[0,\tau]}\le C\|(R_1-R_2,\rho_1-\rho_2)\|_Y \tag{6.8}$$

and

$$\|(\tilde{M}_1 - \tilde{M}_2, \tilde{K}_1 - \tilde{K}_2)\|_{C^{2+\alpha,1+\alpha/2}_{\xi,t}(\bar{G}_\tau)} \leq C\|(R_1 - R_2, \rho_1 - \rho_2)\|_Y.$$

Using arguments as in the proof of Lemmas 4.9 and 4.12(iii) and noting that $\tilde{\rho}_1 - \tilde{\rho}_2 = 0$ at $t = 0$, we derive the estimate

$$\|\tilde{\rho}_1 - \tilde{\rho}_2\|_{C^{2+\alpha,1+\alpha/2}_{\xi,t}(\bar{G}_\tau)} \leq C\|(R_1 - R_2, \rho_1 - \rho_2)\|_Y.$$

Recalling also (6.8) and the fact that $\tilde{R}_1 - \tilde{R}_2 = 0$ at $t = 0$, we deduce, analogously to (6.6), that

$$\|(\tilde{R}_1 - \tilde{R}_2, \tilde{\rho}_1 - \tilde{\rho}_2)\|_Y \leq C\tau^{1/2}\|(R_1 - R_2, \rho_1 - \rho_2)\|_Y.$$

Hence if τ is sufficiently small, then W is a contraction. We have thus established existence and uniqueness for a small time interval $0 \leq t \leq \tau$.

In order to prove existence and uniqueness for all $t > 0$ we suppose that such a global solution does not exist and derive a contradiction. Suppose that a unique solution exists for $0 \leq t < T$ but not for a larger time interval. We then use the a priori estimates of Lemma 4.12 combined with local existence and uniqueness to extend the solution to a larger interval $0 \leq t < T + \tau$, which is a contradiction. ∎

7. Ischemic wounds do not heal. In this section we prove that if the parameter γ in the oxygen equation (2.4) and the boundary conditions (2.13)–(2.18) is near 1, then $R(t) = \text{const.} > 0$ for all t sufficiently large, that is, ischemic wounds do not heal.

For any function $u(r, t)$, we introduce the integral

$$I_u(t) = \int_{R(t)}^{L} ru(r, t)dr. \tag{7.1}$$

Using (2.11), (2.12) we obtain

$$\begin{aligned} \frac{d}{dt}\left(\int_{R(t)}^{L} ru(r, t)dr\right) &= \int_{R(t)}^{L} r\frac{\partial u(r, t)}{\partial t}dr - R(t)u(R(t), t)\dot{R}(t) \\ &= \int_{R(t)}^{L} r\frac{\partial u(r, t)}{\partial t}dr + Lu(L, t)v(L) - R(t)u(R(t), t)v(R(t)) \\ &= \int_{R(t)}^{L} r\frac{\partial u}{\partial t}dr + \int_{R(t)}^{L} \frac{\partial}{\partial r}(ruv)dr \end{aligned}$$

or

$$\frac{d}{dt}I_u(t) \int_{R(t)}^{L} r\left(\frac{\partial u}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(ruv)\right)dr. \tag{7.2}$$

This formula will be used in subsequent lemmas.

For clarity we shall denote the solution u by u_γ, and we consider first the case $\gamma = 1$.

Lemma 7.1. *There holds*

$$I_{w_1}(t) = \int_{R_1(t)}^{L} rw_1(r, t)dr \leq Ce^{-\lambda_{wm}t}, \quad C = I_{w_1}(0). \tag{7.3}$$

Proof. Multiplying (2.4) by r and integrating over $r \in (R_\gamma(t), L)$, we obtain,

$$\frac{d}{dt}\left(\int_{R_\gamma(t)}^{L} r w_\gamma(r,t)dr\right) = LD_w \frac{\partial w_\gamma}{\partial r}(L) - R(t)D_w \frac{\partial w_\gamma}{\partial r}(R(t))$$
$$+ \int_{R(t)}^{L} r\left\{k_w b_\gamma\big((1-\gamma)w_b - w_\gamma\big) - \left[\big(\lambda_{wf} f_\gamma + \lambda_{wm} m_\gamma\big)\left(1 + \frac{\lambda_{ww} p_\gamma}{1+p_\gamma}\right) + \lambda_{wm}\right] w_\gamma\right\} dr$$

so that, for $\gamma = 1$,

$$\frac{d}{dt} I_{w_1}(t) \le -\lambda_{wm} I_{w_1}(t),$$

and (7.3) follows. ∎

Lemma 7.2. *There holds*

$$I_{f_1}(t) = \int_{R_1(t)}^{L} r f_1(r,t)dr \to 0 \quad \textit{as } t \to \infty.$$

Proof. Multiplying (2.8) with $\gamma = 1$ by r and integrating over $r \in (R_1(t), L)$ we obtain, after using the boundary conditions (2.16) and (2.23),

$$\begin{aligned}\frac{d}{dt} I_{f_1}(t) &= \int_{R_1(t)}^{L} r\left\{k_f G_f(w_1) f_1\left(1 - \frac{f_1}{f_m}\right) - \lambda_f f_1(1 + \lambda_d D(w_1))\right\} dr \\ &\le C I_{w_1}(t) - \lambda_f I_{f_1}(t).\end{aligned}$$

Recalling (7.3) we deduce

$$I_{f_1}(t) \le (C_1 t + C_2)e^{-\min\{\lambda_{wm}, \lambda_f\} t} \to 0 \quad \text{as } t \to \infty. \tag{7.4}$$ ∎

Lemma 7.3. *There holds*

$$I_{\rho_1}(t) = \int_{R_1(t)}^{L} r \rho_1(r,t)dr \to 0 \quad \textit{as } t \to \infty.$$

Proof. As in the proof of Lemma 7.2 one can easily derive the inequality

$$I_{\rho_1}(t) \le (C_1 t + C_2)e^{-\min\{\lambda_{wm}, \lambda_\rho\} t} \to 0 \quad \text{as } t \to \infty. \tag{7.5}$$ ∎

From the definition of $Q(r)$ in (3.1) and Lemma 7.3 we obtain the following.

Lemma 7.4. *There holds*

$$Q_1(t) = I_{P_1}(t) = \int_{R_1(t)}^{L} r P_1(r,t)dr \to 0 \quad \textit{as } t \to \infty.$$

We next prove the following.

Lemma 7.5. *There exists a constant C such that*

$$\max_{R_1(t) \le r \le L} w_1(r,t) \le C e^{-\lambda_{wm} t/2} \quad \forall t > 0.$$

Proof. For $\gamma = 1$, the oxygen equation can be written in the form

$$\frac{\partial w_1}{\partial t} - \frac{1}{r}\frac{\partial}{\partial r}\left(r D_w \frac{\partial w_1}{\partial r}\right) + v\frac{\partial w_1}{\partial r} + S_1(r,t)w_1 = 0,$$

where

$$S_1(r,t) = \left[k_w b_1 + \left(\lambda_{wf} f_1 + \lambda_{wm} m_1\right)\left(1 + \frac{\lambda_{ww} p_1}{1+p_1}\right) + \lambda_{wm} + P_1(r,t) - \frac{2Q_1(t)}{L^2 + R_1(t)^2}\right].$$

By Lemma 7.4, there exists a t_1, such that, when $t \geq t_1$, $2Q_1(t)/(L^2 + R_1(t)^2) \leq \lambda_{wm}/2$. Hence

$$S_1(r,t) \geq \lambda_{wm}/2,$$

and by the comparison lemma,

$$w_1(r,t) \leq \max_{R_1(t)\leq r\leq L} w_1(r,t_1)e^{-\lambda_{wm}t/2}. \qquad \square$$

LEMMA 7.6. *There exists a positive constant F_1^*, $F_1^* \geq f_m$, such that*

$$f_1 \leq F_1^* \quad \forall R_1(t) \leq r \leq L, \quad t > 0.$$

Proof. From Lemmas 7.4 and 7.5 it follows that there exists a $t_1 > 0$ such that, for all $t \geq t_1$,

$$\frac{2}{L^2 + R_1(t)^2} Q_1(t) + k_f G_f(w_1)\left(1 - \frac{f_1}{f_m}\right) \leq \lambda_f/2.$$

Using this in (2.8) and setting

$$\bar{f}_1 = \max_{0\leq t\leq t_1, R_1(t)\leq r\leq L} f_1(r,t),$$

we deduce by the comparison lemma that

$$f_1(r,t) \leq \max\{\bar{f}_1, f_m\} \quad \forall t \geq t_1. \qquad \square$$

We next improve Lemma 7.3.

LEMMA 7.7.

$$\max_{R_1(t)\leq r\leq L} \rho_1(r,t) \to 0 \quad \textit{as}\ \ t \to \infty.$$

Proof. By Lemma 7.4,

$$\frac{2}{L^2 + R_1(t)^2} Q_1(t) \leq \lambda_\rho/2 \quad \text{if}\ \ t \geq t_1.$$

Using also Lemmas 7.5 and 7.6 we obtain

$$\frac{D\rho_1}{Dt} \leq -\frac{\lambda_\rho}{2}\rho_1 + \frac{F_1^* k_\rho}{K_{w\rho}} \max_{R_1(t)\leq r\leq L} w_1(r,t)e^{-\lambda_{wm}t/2} \quad \forall t \geq t_1,$$

where D/Dt is the derivative along the characteristic curves, and the assertion of the lemma follows. $\square$

Lemma 7.7 implies that $P_1 \equiv 0$ for all t sufficiently large, say, for $t \geq T_1^*$. Hence also $Q_1(t) \equiv 0$ if $t \geq T_1^*$. Recalling (3.6) we conclude as follows.

LEMMA 7.8. *There exists $R_1^* > 0$ and $T_1^* > 0$ such that*

$$R_1(t) > R_1^* \qquad \forall 0 \leq t < T_1^*,$$
$$R_1(t) \equiv R_1^* \qquad \forall t \geq T_1^*.$$

We next extend this result to all γ near 1.

THEOREM 7.9. *For any $0 \le 1-\gamma \ll 1$, there exists $R_\gamma^* > 0$ and $T_\gamma^* > 0$ such that*

$$\begin{aligned} R_\gamma(t) &> R_\gamma^* \qquad \forall 0 \le t < T_\gamma^*, \\ R_\gamma(t) &\equiv R_\gamma^* \qquad \forall t \ge T_\gamma^*. \end{aligned}$$

Proof. Since the estimates of Lemma 4.12 hold uniformly in γ, any sequence $\gamma_i \to 1$ has a subsequence for which the solution u_γ of (2.2)–(2.28) converges in Ω_τ, for any $\tau > 0$, to a solution u_1 of (2.2)–(2.28) with $\gamma = 1$; the convergence is in the norms of Lemma 4.12 with α replaced by any $0 < \beta < \alpha$. Since (by Theorem 6.1) the solution of (2.2)–(2.28) with $\gamma = 1$ is unique, we conclude that as $\gamma \to 1$ the solution u_γ converges to u_1. It follows that

$$\rho_\gamma(r, \bar t_1) \le \frac{3}{4}, \quad w_\gamma(r, \bar t_1) < \eta_0, \quad f_\gamma(r, \bar t_1) \le F_1^* + 1, \quad R_\gamma(\bar t_1) \ge R_1^*/2$$

if $\bar t_1$ is large enough, provided $\gamma \in (\gamma_0, 1)$ and $1-\gamma_0$ is small enough; here η_0 is chosen small enough so that

$$\frac{2\eta_0 k_\rho (F_1^* + 1)}{K_{w\rho}} \le \frac{3}{4}\lambda_\rho. \tag{7.6}$$

Let $[\bar t_1, t_\gamma)$ be the maximal interval such that

$$\rho_\gamma(r, t) < 1 \quad \forall t \in [\bar t_1, t_\gamma).$$

We want to prove that $t_\gamma = +\infty$. Noting that $Q_\gamma(t) \equiv 0$ for $\bar t_1 \le t < t_\gamma$, we also have $v_\gamma(r, t) \equiv 0$ and $R_\gamma(t) \equiv R_\gamma(\bar t_1)$ for $\bar t_1 < t < t_\gamma$.

Let $W(r, t) = \eta_1 (r - \bar R)^2 + \eta_0$, where $\bar R = R(\bar t_1)$, $\eta_1 = (1-\gamma)/\bar A$, and $\bar A = 2\gamma L(L - \bar R)$. Then $(\partial W/\partial r)(\bar R, t) = 0$ and

$$(1-\gamma)(W - 1) + \gamma L \frac{\partial W}{\partial r} > 0 \quad \text{at } r = L$$

if $1-\gamma$ is small enough. Also

$$W_t - D_w \Delta W \ge k_w b\big((1-\gamma) w_b - W\big) - \lambda_{wm} W \quad \text{if } \eta_1 \ll \eta_0,$$

that is, if γ is restricted to a very small subinterval $(\gamma_1, 1)$ of $(\gamma_0, 1)$. By the comparison lemma we then get

$$w_\gamma(r, t) \le W(r, t) \quad \text{for } t \in [\bar t_1, t_\gamma),$$

and, in particular,

$$w_\gamma(r, t) \le 2\eta_0 \quad \text{for } t \in [\bar t_1, t_\gamma). \tag{7.7}$$

From (2.2), (7.6), and (7.7) we then obtain, for $\gamma \in (\gamma_1, 1)$,

$$\frac{D\rho}{Dt} \le \lambda_\rho \left(\frac{3}{4} - \rho\right) \quad \text{for } t \in [\bar t_1, t_\gamma),$$

so that

$$\rho_\gamma(r, t) \le \frac{3}{4} \quad \text{for } t \in [\bar t_1, t_\gamma).$$

This implies that $t_\gamma = +\infty$, and consequently $Q_\gamma(t) = 0$ for all $t > \bar t_1$, and the theorem follows. ∎

8. Wounds that do not heal. A wound may be considered to be (completely) healed if $R(t) \to 0$ as $t \to \infty$. Indeed, biologically, if $R(t)$ becomes smaller than, say, 10 μm (which is roughly the diameter of a cell), no cell can move in to occupy the remaining open space of the wound. We say that a wound does not heal if

$$\lim_{t\to\infty} R_\gamma(t) = R^*_\gamma > 0. \tag{8.1}$$

In section 7 we proved that if γ is near 1, then the wound does not heal and, moreover, $R_\gamma(t)$ becomes constant for all t large enough. In this section we want to explore some of the implications of (8.1). In particular we show that in wounds that do not heal, the concentration of oxygen and the density of ECM cannot exceed those of a healthy tissue as $t \to \infty$.

THEOREM 8.1. *If* (8.1) *holds, then*

$$\limsup_{t\to\infty} f_\gamma(r,t) \le f_m, \tag{8.2}$$

$$\limsup_{t\to\infty} w_\gamma(r,t) \le \max\{1,(1-\gamma)w_b\}, \tag{8.3}$$

$$\lim_{t\to\infty} \operatorname{ess\,sup} \rho_\gamma(r,t) \le 1. \tag{8.4}$$

Proof. By (3.6) and (3.1), the function $Q(t)$ satisfies

$$Q_\gamma(t) = -\frac{L^2 + R^2_\gamma(t)}{2R_\gamma(t)}\dot{R}_\gamma(t). \tag{8.5}$$

Integrating over $(0,\infty)$ and recalling (8.1), we conclude that

$$\int_0^\infty Q_\gamma(t)dt = \int_{R^*_\gamma}^{R(0)} \frac{L^2+z^2}{2z}\,dz = \frac{L^2}{2}\log\left(\frac{R(0)}{R^*_\gamma}\right) + \frac{R^2(0)-(R^*_\gamma)^2}{4} < \infty.$$

We next prove

$$f(r,t) \le C \quad \text{for } R_\gamma(t) \le r \le L, \quad 0 < t < \infty. \tag{8.6}$$

By (3.8) we can rewrite the left-hand side of (2.8) in the form

$$\frac{\partial f_\gamma}{\partial t} + v_\gamma\frac{\partial f_\gamma}{\partial r} + f_\gamma\left(P_\gamma(r,t) - \frac{2}{L^2+R^2_\gamma(t)}Q_\gamma(t)\right). \tag{8.7}$$

Hence the function $g(t) = f_m e^{\int_0^t \frac{2}{L^2}Q_\gamma(s)ds}$ is a supersolution of (2.8) and, by the comparison lemma,

$$f_\gamma(r,t) \le g(t), \quad R(t) \le r \le L, \quad t > 0.$$

Since, by (8.5), $g(t)$ is uniformly bounded, (8.6) follows.

We next prove that

$$|\dot{Q}_\gamma(t)| \le C \quad \forall t > 0. \tag{8.8}$$

We write (2.2) in the form

$$\frac{\partial(\rho_\gamma - 1)}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}\Big(r(\rho_\gamma - 1)v_\gamma\Big) = -\frac{1}{r}\frac{\partial(rv_\gamma)}{\partial r} + \frac{k_\rho w_\gamma}{w_\gamma + K_{w\rho}} f_\gamma \left(1 - \frac{\rho_\gamma}{\rho_m}\right) - \lambda_\rho \rho_\gamma \triangleq M_\gamma$$

or

$$r\frac{\partial P_\gamma}{\partial t} + \frac{\partial}{\partial r}(rP_\gamma v_\gamma) = r\beta M_\gamma I_{\{(r,t)\colon\, \rho_\gamma(r,t)>1\}}.$$

By (3.8) (or (4.7)), (8.6), and the bound $\rho_\gamma \le \rho_m$, we see that the right-hand side is uniformly bounded in (r,t). Hence, by integration over $R(t) \le r \le L$,

$$\int_{R(t)}^{L} r\frac{\partial P_{\gamma(r,t)}}{\partial t} dr \quad \text{is uniformly bounded.} \tag{8.9}$$

Next, by the definition of $Q_\gamma(t)$ in (3.1),

$$\dot{Q}_\gamma(t) = -\dot{R}(t)R(t)P(R(t),t) + \int_{R(t)}^{L} r\frac{\partial P_{\gamma(r,t)}}{\partial t} dr,$$

and hence, upon using (8.9) and the uniform boundedness of $\dot{R}(t)$, the assertion (8.8) follows.

From (3.6) and (8.8), we obtain the estimate

$$|\ddot{R}_\gamma(t)| \le C. \tag{8.10}$$

Using the interpolation estimate (see [15, p. 48])

$$\|\dot{R}_\gamma\|_{C^\alpha[t^*,t^*+1]} \le C\|R_\gamma - R_\gamma^*\|_{W^{2,\infty}[t^*,t^*+1]}^{\frac{1+\alpha}{2}} \cdot \|R_\gamma - R_\gamma^*\|_{L^\infty[t^*,t^*+1]}^{\frac{1-\alpha}{2}} \to 0$$

and noting that the last factor converges to zero as $t^* \to 0$, we obtain

$$\lim_{t^*\to\infty} \|\dot{R}_\gamma\|_{C^\alpha[t^*,t^*+1]} = 0, \tag{8.11}$$

and then, by (3.6), also

$$\lim_{t^*\to\infty} \|Q_\gamma\|_{C^\alpha[t^*,t^*+1]} = 0 \quad \forall\, 0 < \alpha < 1. \tag{8.12}$$

From (8.12) and (8.5) it easily follows that

$$Q_\gamma(t) \to 0 \quad \text{as } t \to \infty, \tag{8.13}$$

and hence there exists a $T > 0$ such that

$$\frac{2}{L^2} Q_\gamma(t) \le \frac{\lambda_f}{2} \quad \text{if } t > T. \tag{8.14}$$

Writing the left-hand side of (2.8) in the form (8.7) and using (8.13), we can then apply the comparison lemma to f_γ to conclude that

$$f_\gamma(r,t) \le f_m + \max_{R_\gamma(T)\le r\le L} f_\gamma(r,T)e^{-\frac{\lambda_f}{2}(t-T)},$$

and hence (8.2) follows.

Similarly one can prove, by comparison, the estimate (8.3). Finally, (8.4) follows from (8.13). ∎

9. Simulations and a conjecture. We simulated the radius $R_\gamma(t)$ of the wound for different values of γ using the nondimensional parameters of the system (2.2)–(2.28) that were chosen on the basis of experimental results [28]. In Figure 9.1 we present simulation results in the original dimensional variables with $L = 7.5$ mm and initial wound radius $R_0 = 4$ mm. The computation was manually stopped when the wound became 98% closed. From the figure we see that as γ increases, the wound closes more slowly, and when γ is close to 1, the wound radius stops decreasing after a certain time.

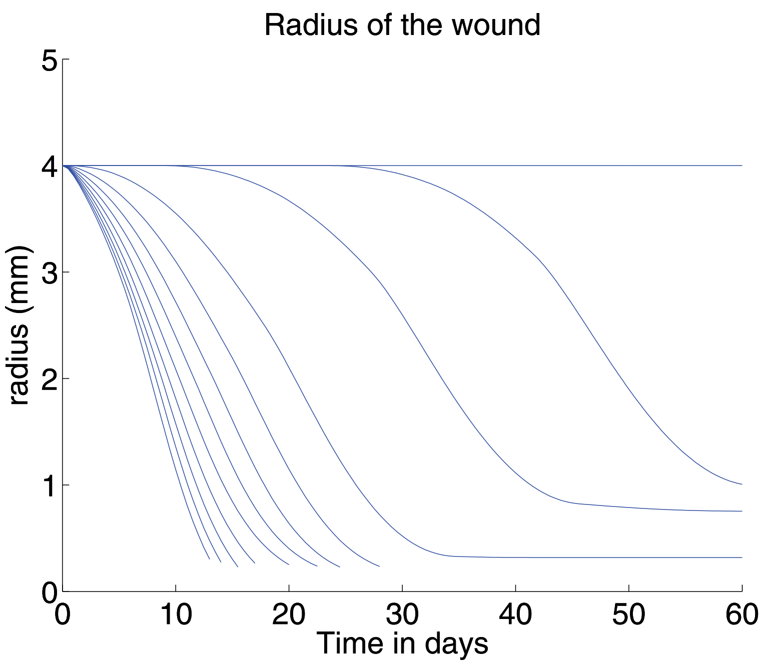

FIG. 9.1. *The radius of the wound as a function of time for different values of γ. From left to right: $\gamma = 0, 0.1, 0.2, \ldots, 0.8, 0.9, 0.92, 0.95, 1$. Other parameters used are the same as in* [28]*; the nondimensionalized values are $L = 5$, $R_0 = 8/3$, $\rho_m = 2$, $K_{w\rho} = K_{wf} = 0.25$, $k_\rho = 5/16$, $\lambda_\rho = 0.1$, $\beta = 10$, $D_w = 0.5$, $D_p = D_e = 1$, $D_m = D_f = 5 \times 10^{-2}$, $D_n = 10^{-3}$, $D_b = 7 \times 10^{-4}$, $\chi_m = \chi_f = 0.1$, $\chi_n = 1$, $m_m = f_m = n_m = 10$, $A = 0.1$, $w_b = 2$, $k_w = 4.39$, $\lambda_{wf} = 0.227$, $\lambda_{wm} = 4.16$, $\lambda_d = 2$, $k_f = 5.78 \times 10^{-3}$, $\lambda_f = 5.2 \times 10^{-3}$, $k_{nb} = k_n = k_b/10 = 2.16 \times 10^{-2}$, $\lambda_{nn} = 100\lambda_{nb} = 2.25$, $k_{sg} = 6.25 \times 10^{-2}$.*

We conjecture that if the parameters of the system (2.2)–(2.28) are chosen on the basis of experimental results, as in [28], then there exists a parameter value γ_* such that (8.1) holds if $\gamma_* < \gamma \leq 1$ and

$$\lim_{t\to\infty} R_\gamma(t) = 0 \quad \text{if } \gamma < \gamma_*.$$

If this conjecture is true then, in particular,

$$\lim_{t\to\infty} R_\gamma(t) = 0 \quad \text{if } \gamma = 0.$$

But even this assertion is still an open question. We can only prove, for the system (2.2)–(2.28), with general parameters, the following result.

THEOREM 9.1. *If $\gamma = 0$, then*

$$\rho(L,t) > 1, \quad 0 < t < \infty, \tag{9.1}$$
$$\dot{R}(t) < 0, \quad 0 < t < \infty, \tag{9.2}$$
$$Q(t) > 0, \quad 0 < t < \infty. \tag{9.3}$$

Proof. Using the boundary conditions $w(L,t) = 1$, $f(L,t) = 1$, $v(L,t) = 0$ and (2.26), we obtain from (2.2) at $r = L$ the relation

$$\begin{aligned}\frac{\partial \rho(L,t)}{\partial t} + \rho(L,t)\frac{\partial v}{\partial r}(L,t) &= \frac{k_\rho}{1+K_{w\rho}}\left(1 - \frac{\rho}{\rho_m}\right) - \frac{k_\rho}{1+K_{w\rho}}\left(1 - \frac{1}{\rho_m}\right)\rho \\ &= -\frac{k_\rho}{1+K_{w\rho}}(\rho - 1),\end{aligned}$$

and from (3.8),

$$\frac{\partial v}{\partial r}(L,t) = P(L,t) - \frac{2}{L^2 + R^2(t)}Q(t).$$

Hence,

$$\frac{\partial \rho(L,t)}{\partial t} = -c_0\Big(\rho(L,t) - 1\Big) - \beta\rho(L,t)\Big(\rho(L,t) - 1\Big)_+ + \frac{2\rho(L,t)}{L^2 + R(t)^2}Q(t). \tag{9.4}$$

where c_0 is a positive constant.

Using the initial conditions

$$\rho(r,0) \equiv 1, \quad w(r,0) \equiv 1, \quad f(r,0) \equiv 1, \quad m(r,0) \equiv 0, \quad v(r,0) \equiv 0 \quad \text{for } R_0 < r < L,$$
$$b(r,0) \equiv 1, \quad p(r,0) \equiv 0 \quad \text{for } R_0 + \varepsilon_0 \leqslant r < L$$

in (2.2) and (2.4) and recalling the relations (2.26) and (2.27), we find that

$$\frac{\partial \rho(r,0)}{\partial t} \equiv 0, \qquad R_0 < r < L, \tag{9.5}$$
$$\frac{\partial w(r,0)}{\partial t} \equiv 0, \qquad R_0 + \varepsilon_0 \leqslant r < L. \tag{9.6}$$

Using (2.25) we also obtain (upon recalling (2.28)) that

$$\frac{\partial f(r,0)}{\partial t} = \frac{\chi_f}{r}H\left(1 - \frac{1}{f_m}\right)p_0'(r)\Big/\sqrt{1 + k_{sg}\left(\frac{k_{pb}}{D_p}\right)^2} > 0, \qquad R_0 < r < R_0 + \varepsilon_0. \tag{9.7}$$

Differentiating (2.2) in t and using (9.5)–(9.7) and the $C_{r,t}^{2+\alpha,1+\alpha/2}$ regularity of w, we deduce that

$$\frac{\partial^2 \rho(r_0,0)}{\partial t^2} > 0 \quad \text{for } 0 < R_0 + \varepsilon_0 - r_0 \ll 1.$$

This implies that, for $0 < R_0 + \varepsilon_0 - r_0 \ll 1$ and $0 < t \ll 1$,

$$\rho(r_0,t) > 1,$$

and hence

$$Q(t) > 0 \quad \text{for } 0 < t \ll 1. \tag{9.8}$$

Since $\rho(0, L) = 1$, from (9.4) and (9.5) it follows that

$$\rho(0, t) > 1 \tag{9.9}$$

for *all* $0 < t < \infty$. This in turn implies that $Q(t) > 1$ for *all* $0 < t < \infty$, and hence $\dot{R}(t) < 0$ and (by (9.4)) $\rho(L, t) > 1$ for *all* $0 < t < \infty$. ◻

10. Conclusion. In this paper we established existence and uniqueness of a solution to a free boundary problem which models ischemic wound healing. The ischemic condition is described in terms of a parameter γ ($0 \leq \gamma \leq 1$) which appears as a coefficient in a Robin boundary condition for the various cells and chemical densities. We also proved that under extreme ischemic conditions (γ near 1) the open wound stops decreasing in finite time. When the parameters of the system are taken on the basis of biological experiments, simulations show that there is a parameter γ_* such that the wound heals if $0 \leq \gamma < \gamma_*$ and does not heal if $\gamma_* < \gamma \leq 1$. This assertion remains a challenging open mathematical problem. Future work should include the introduction of pressure and diabetic conditions in ischemic wounds, as well as inflammatory conditions.

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