Supporting Information — A mathematical model of ischemic cutaneous wounds

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A Reduction of Equation [5] to Equation [6]

For an upper convected Maxwell fluid, the stress-strain relationship is given by Equation [5],

$$\lambda\left(\frac{D\tau}{Dt}-(\nabla\cdot\mathbf{v})\tau-\tau(\nabla\cdot\mathbf{v})^T\right)+\tau=\eta(\nabla\mathbf{v}+\nabla\mathbf{v}^T),$$

where η is the shear viscosity, G is the shear modulus and $\lambda=\frac{\eta}{G}$ is the relaxation time of the Maxwell element. For collagen I, $\eta=1.1\times10^8$ dyn $\cdot$ s/cm^2, $G=1.5\times10^4$ dyn/cm^2 (1,2), therefore $\lambda\sim7.3\times10^3$ sec $\sim 2h$. We assume that $\lambda\nabla\cdot\mathbf{v}$ and $\lambda\frac{D\tau}{Dt}$ are small and can be neglected, so that the stress-strain relationship [5] simplifies to Equation [6]

$$\tau=\eta(\nabla\mathbf{v}+\nabla\mathbf{v}^T).$$

To justify the simplification, we nondimensionalize Equation [5] with the characteristic space and time scales in wound healing, $L_0=1$ cm, $T_0=5$ day. The nondimensionalized variables are

$$x'=\frac{x}{L},\ t'=\frac{t}{T},\ \lambda'=\frac{\lambda}{T},\ \mathbf{v}'=\frac{\mathbf{v}}{L/T}\sim\mathcal{O}(1),\ \tau'=\frac{\tau}{\eta/T},$$

in these variables the stress-strain relationship becomes

$$\lambda'\left(\frac{D\tau'}{Dt'}-(\nabla'\cdot\mathbf{v}')\tau'-\tau'(\nabla'\cdot\mathbf{v}')^T\right)+\tau'=(\nabla'\mathbf{v}'+\nabla'\mathbf{v}'^T),\tag{A.1}$$

During wound healing $\nabla'\cdot v'\sim\mathcal{O}(1)$ and $\nabla' v'\sim\mathcal{O}(1)$. Since $\lambda'\approx\frac{1}{60}\ll1$, the terms $\lambda'(\nabla'\cdot\mathbf{v}')\tau'$ and $\lambda'\tau'(\nabla'\cdot\mathbf{v}')^T$ are negligible, and from $\lambda'\frac{D\tau'}{Dt'}+\tau'=\mathcal{O}(1)$ we see that the term $\lambda'\frac{D\tau'}{Dt'}$ may also be neglected, which leads to Equation [6].

B Derivation of Equations [7] – [10] and [12] under radially symmetry

The equations for the ECM are [1], [3] together with the relations [2], [4], [6]. In this section we derive these equations in polar coordinates (r, θ) under the assumption of radial symmetry.

Set

$$\rho = \rho(r), \quad \mathbf{v} = v\mathbf{e}_r, \quad P = P(\rho(r)),$$

then

$$\nabla v = \begin{pmatrix} \dfrac{\partial v}{\partial r} & 0 \\ 0 & \dfrac{v}{r} \end{pmatrix}.$$

Writing the stress tensor τ in polar coordinates

$$\tau = \begin{pmatrix} \tau_{rr} & \tau_{r\theta} \\ \tau_{\theta r} & \tau_{\theta\theta} \end{pmatrix},$$

Equation [6] becomes

$$\begin{pmatrix} \tau_{rr} & \tau_{r\theta} \\ \tau_{\theta r} & \tau_{\theta\theta} \end{pmatrix} = 2\eta \begin{pmatrix} \dfrac{\partial v}{\partial r} & 0 \\ 0 & \dfrac{v}{r} \end{pmatrix},$$

so that

$$\tau_{r\theta} = \tau_{\theta r} = 0,$$

which means that there is no shear stress between neighboring radial sections and annulus. Setting $\tau_1 = \tau_{rr}$ and $\tau_2 = \tau_{\theta\theta}$, we obtain

$$\tau_1 = 2\eta \frac{\partial v}{\partial r}, \quad \tau_2 = 2\eta \frac{v}{r}.$$

By substituting this into the equation $\sigma \equiv -PI + \tau$, we obtain

$$\sigma = \begin{pmatrix} \sigma_1 & 0 \\ 0 & \sigma_2 \end{pmatrix}, \quad \text{where} \quad \sigma_1 = -P + \tau_1, \quad \sigma_2 = -P + \tau_2.$$

Equation [3] in polar coordinates reduces to (see, for instance, the appendix of (3))

$$-\frac{\partial P}{\partial r} + \frac{1}{r}\frac{\partial}{\partial r}(r\tau_1) - \frac{\tau_2}{r} = 0.$$

Substituting the forms of τ_i into the last equation, we obtain

$$-\frac{\partial P}{\partial r} + 2\eta \frac{1}{r}\frac{\partial}{\partial r}(r\frac{\partial v}{\partial r}) - 2\eta \frac{v}{r^2} = 0,$$

or

$$\frac{1}{r}\frac{\partial}{\partial r}(r\frac{\partial v}{\partial r}) - \frac{v}{r^2} = \frac{1}{2\eta}\frac{\partial P}{\partial r}.$$

At the fixed boundary the tissue velocity is assumed to be zero, i.e., $\mathbf{v} = 0$ at $r = L$. Therefore the equation for ρ becomes an ODE and no boundary condition is needed. We assume that there is no external force at the free boundary, that is, $\sigma \cdot \nu = 0$, where ν is the outward normal vector to the free boundary. Under the assumption of radial symmetry, $\nu = -\mathbf{e}_r$, and $\sigma \cdot \nu = -\sigma \cdot \mathbf{e}_r = -\sigma_1$, so that $-P + \tau_1 = \sigma_1 = 0$. Since $\tau_1 = 2\eta \dfrac{\partial v}{\partial r}$, we obtain the boundary condition $\dfrac{\partial v}{\partial r} = \dfrac{P}{2\eta}$ at $r = R(t)$. This way we derived the equations

$$\frac{\partial \rho}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(r\rho v) = \frac{k_\rho w}{w + K_{w\rho}} f(1 - \frac{\rho}{\rho_m}) - \lambda_\rho \rho \quad \text{for } R(t) \le r \le L \tag{B.1}$$

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial v}{\partial r}\right) - \frac{v}{r^2} = \frac{1}{2\eta}\frac{\partial P}{\partial r} \quad \text{for } R(t) \le r \le L \tag{B.2}$$

$$v = 0 \quad \text{at } r = L, \tag{B.3}$$

$$\frac{\partial v}{\partial r} = \frac{P}{2\eta} \quad \text{at } r = R(t). \tag{B.4}$$

The constitutive equations for the cells and chemicals are given by

$$\frac{\partial u}{\partial t} = -\nabla \cdot (\mathbf{J}_u) + G_u,$$

with

$$\mathbf{J}_u = \mathbf{J}_u^c + \mathbf{J}_u^a, \quad \mathbf{J}_u^c = \mathbf{v}u,$$

From the radial symmetry assumption, we have $\mathbf{J}_u \cdot \mathbf{e}_\theta = \mathbf{J}_u^c \cdot \mathbf{e}_\theta = \mathbf{J}_u^a \cdot \mathbf{e}_\theta = 0$, so that $\mathbf{J}_u = J_u \mathbf{e_r} = J_u^c \mathbf{e_r} + J_u^a \mathbf{e_r}$ with $J_u^c = vu$. Therefore the constitutive equation becomes

$$\frac{\partial u}{\partial t} + \frac{1}{r}\frac{\partial}{\partial r}(ruv) = -\frac{1}{r}\frac{\partial}{\partial r} J_u^a + G_u.$$

At the free boundary, $r = R(t)$, there is no lost or gain of cells or chemicals, so no-flux (or Neumann) boundary conditions are imposed. With a moving boundary, the Neumann boundary condition becomes

$$\mathbf{J}_u \cdot \mathbf{e_r} - \dot{R}(t)u = 0.$$

Since $\mathbf{J}_u^c \cdot \mathbf{e_r} = (\mathbf{v} \cdot \mathbf{e_r})u = vu = \dot{R}(t)u$ at the free boundary, this condition simplifies to

$$J_u^a = 0. \tag{B.5}$$

C Nondimensionalization and front-fixing transformation

We nondimensionalize the model equations by taking

$$r' = \frac{r}{L_0}, \quad t' = \frac{t}{T_0}, \quad \rho' = \frac{\rho}{\rho_0}, \quad \mathbf{v}' = \frac{\mathbf{v}}{L_0/T_0}, \quad P' = \frac{P}{\eta/T_0}, \quad R' = \frac{R}{L_0},$$
$$w' = \frac{w}{w_0}, \quad e' = \frac{e}{K_e}, \quad p' = \frac{p}{K_p}, \quad m' = \frac{m}{m_0}, \quad f' = \frac{f}{f_0}, \quad n' = \frac{n}{b_0}, \quad b' = \frac{b}{b_0},$$

where $L_0 = 0.15$ cm, $T_0 = 6.25$ h, and ρ_0, w_0, f_0, b_0 are the healthy tissue steady state values and m_0 is the inactivated macrophage density. Note that the L_0 and T_0 chosen here are different from the characteristic values used in Equation A.1. The reason for introducing the present scales is so that we can immediately use some of the non-dimensionalized parameters from (4). In particular, D_e' (which we take to be the same as D_p') is equal to 1. Note also that $\frac{k_m b_0}{2\lambda_m}$ represents the balanced amount of macrophage when $p = K_p$.

We nondimensionalize the parameters using the above scaling,

$$\{L', R_0', K_R'\} = \frac{1}{L_0}\{L, R_0, K_R\}, \quad \{K_{w\rho}', K_{wf}', w_b'\} = \frac{1}{w_0}\{K_{w\rho}, K_{wf}, w_b\}$$
$$\rho_m' = \frac{\rho_m}{\rho_0}, \quad \beta' = \frac{\beta}{\eta/T_0}, \quad k_\rho' = \frac{k_\rho f_0 T_0}{\rho_0}, \quad \lambda_\rho' = \lambda_\rho T_0,$$
$$\{D_w', D_e', D_p', D_m', D_f', D_n', D_b'\} = \frac{T_0}{L_0^2}\{D_w, D_e, D_p, D_m, D_f, D_n, D_b\},$$
$$\{\chi_m', \chi_f', \chi_n'\} = \frac{T_0}{L_0^2}\{\chi_m K_p, \chi_f K_p, \chi_n K_e\},$$
$$\{k_w', \lambda_{wf}', \lambda_{wm}'\} = T_0\{k_w b_0, \lambda_{wf} f_0, \lambda_{wm} m_0\},$$
$$\{k_p', \lambda_p', k_{pb}', k_e', \lambda_{en}', \lambda_{eb}', \lambda_e'\} = T_0\{k_p \frac{m_0}{K_p}, \lambda_p, k_{pb}\frac{1}{L_0 K_p}, k_e\frac{m_0}{K_e}, \lambda_{en} b_0, \lambda_{eb} b_0, \lambda_e\},$$
$$\{\lambda_m', k_f', \lambda_f', k_{nb}', k_n', \lambda_{nb}', \lambda_{nn}'\} = T_0\{\lambda_m, k_f, \lambda_f, k_{nb}, k_n, \lambda_{nb} b_0, \lambda_{nn} b_0\},$$
$$m_m' = \frac{m_m}{m_0}, \quad f_m' = \frac{f_m}{f_0}, \quad n_m' = \frac{n_m}{b_0}.$$

We drop the primes for simplicity of notation and further introduce the transformation

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

which transforms the free boundary to $\xi = 0$ and the fixed boundary to $\xi = 1$. With this transformation each function $u(r,t)$ becomes $u'(\xi,t)$, but for simplicity we shall drop the primes. From [C.1] one can verify by directed computation that

$$\frac{\partial u}{\partial r} = \frac{1}{L - R(t)}\frac{\partial u}{\partial \xi}, \tag{C.2}$$
$$\frac{\partial}{\partial r}\left(r\frac{\partial u}{\partial r}\right) = \frac{1}{(L-R(t))^2}\frac{\partial}{\partial \xi}\left(r(\xi)\frac{\partial u}{\partial \xi}\right), \tag{C.3}$$
$$\left.\frac{\partial u}{\partial t}\right|_x = \left.\frac{\partial u}{\partial t}\right|_\xi + \left.\frac{\partial u}{\partial \xi}\right|_t \left.\frac{\partial \xi}{\partial t}\right|_x = \left.\frac{\partial u}{\partial t}\right|_\xi + \frac{R'(t)}{L - R(t)}(\xi - 1)\frac{\partial u}{\partial \xi}, \tag{C.4}$$
$$(\xi - 1)\frac{\partial u}{\partial \xi} = \frac{1}{r}\frac{\partial}{\partial \xi}\Big(r(\xi - 1)u\Big) + \left(\frac{(1-\xi)(L - R(t))}{r} - 1\right)u. \tag{C.5}$$

Using these equations and setting

$$K = K(\xi) = \frac{R'(t)}{L - R(t)}\left(\frac{(1-\xi)(L-R(t))}{r} - 1\right), \tag{C.6}$$

we obtain

$$\left.\frac{\partial u}{\partial t}\right|_x + \frac{1}{r}\frac{\partial}{\partial r}(ruv) = \left.\frac{\partial u}{\partial t}\right|_\xi + B,$$

where, by [C.2] and [C.4] ,

$$B = \frac{R'(t)}{L-R(t)}\big(\xi-1\big)\frac{\partial u}{\partial \xi} + \frac{1}{(L-R(t))r}\frac{\partial}{\partial \xi}\big(ruv\big).$$

Then by [C.5] and [C.6] ,

$$\begin{aligned} B = & \frac{R'(t)}{L-R(t)}\frac{1}{r}\frac{\partial}{\partial \xi}\Big(r\big(\xi-1\big)u\Big) + \frac{1}{(L-R(t))r}\frac{\partial}{\partial \xi}\big(ruv\big) + Ku \\ = & \frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(ru\big(R'(t)(\xi-1)+v\big)\Big)\right] + Ku. \end{aligned}$$

Hence

$$\left.\frac{\partial u}{\partial t}\right|_x + \frac{1}{r}\frac{\partial}{\partial r}\big(ruv\big) = \frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(ru\big(R'(t)(\xi-1)+v\big)\Big)\right] + Ku. \tag{C.7}$$

Using [C.7] and [C.3] we obtain the following system with the new variable ξ,

$$\frac{\partial \rho}{\partial t} + \frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(r\rho\big(R'(t)(\xi-1)+v\big)\Big)\right] = \frac{k_\rho w}{w+K_{w\rho}}f(1-\frac{\rho}{\rho_m}) - \lambda_\rho \rho - K\rho, \tag{C.8}$$

$$\frac{1}{(L-R(t))^2}\frac{1}{r}\frac{\partial}{\partial \xi}\left(r\frac{\partial v}{\partial \xi}\right) - \frac{v}{r^2} = \frac{1}{L-R(t)}\frac{\partial P}{\partial \xi}, \tag{C.9}$$

$$\begin{aligned} \frac{\partial w}{\partial t} + \frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(rw\big(R'(t)(\xi-1)+v\big)\Big)\right] &= \frac{D_w}{(L-R(t))^2}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\left(r\frac{\partial w}{\partial \xi}\right)\right] \\ &+ k_w b\big((1-\alpha)w_b - w\big) - \left[\big(\lambda_{wf}f + \lambda_{wm}m\big)\left(1+\frac{\lambda_{ww}p}{1+p}\right) + \lambda_{wm}\right]w - Kw, \end{aligned} \tag{C.10}$$

$$\begin{aligned} \frac{\partial p}{\partial t} + \frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(rp\big(R'(t)(\xi-1)+v\big)\Big)\right] &= \frac{D_p}{(L-R(t))^2}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\left(r\frac{\partial p}{\partial \xi}\right)\right] \\ &+ k_p m G_p(w) - \frac{\lambda_{pf} f p}{1+p} - \lambda_p p - Kp, \end{aligned} \tag{C.11}$$

$$\begin{aligned} \frac{\partial e}{\partial t} + \frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(re\big(R'(t)(\xi-1)+v\big)\Big)\right] &= \frac{D_e}{(L-R(t))^2}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\left(r\frac{\partial e}{\partial \xi}\right)\right] \\ &+ k_e m G_e(w) - (\lambda_{en}n + \lambda_{eb}b + \lambda_e)e - Ke, \end{aligned} \tag{C.12}$$

$$\begin{aligned} \frac{\partial m}{\partial t} + \frac{1}{L-R(t)}&\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(rm\big(R'(t)(\xi-1)+v\big)\Big)\right] \\ &= \frac{1}{(L-R(t))^2}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\left(r\big(D_m\frac{\partial m}{\partial \xi} - \chi_m \rho m H(m_m - m)\frac{\partial p}{\partial \xi}\big)\right)\right] \\ &+ \frac{k_m b p}{1+p} - \lambda_m m\left(1+\lambda_d D(w)\right) - Km, \end{aligned} \tag{C.13}$$

$$\begin{aligned} \frac{\partial f}{\partial t} + \frac{1}{L-R(t)}&\left[\frac{1}{r}\frac{\partial}{\partial \xi}\Big(rf\big(R'(t)(\xi-1)+v\big)\Big)\right] \\ &= \frac{1}{(L-R(t))^2}\left[\frac{1}{r}\frac{\partial}{\partial \xi}\left(r\big(D_f\frac{\partial f}{\partial \xi} - \chi_f \rho f H(f_m - f)\frac{\partial p}{\partial \xi}\big)\right)\right] \\ &+ k_f G_f(w) f\left(1-\frac{f}{f_m}\right) - \lambda_f f(1+\lambda_d D(w)) - Kf, \end{aligned} \tag{C.14}$$

$$\frac{\partial n}{\partial t}+\frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial\xi}\Big(rn\big(R'(t)(\xi-1)+v\big)\Big)\right]$$
$$=\frac{1}{(L-R(t))^2}\left[\frac{1}{r}\frac{\partial}{\partial\xi}\left(r\big(D_n\frac{\partial n}{\partial\xi}-\chi_f\rho nH(n_m-n)\frac{\partial e}{\partial\xi}\big)\right)\right]$$
$$+(k_{nb}b+k_nn)\frac{e}{1+e}-(\lambda_{nb}b+\lambda_{nn}n)n-Kn, \tag{C.15}$$

$$\frac{\partial b}{\partial t}+\frac{1}{L-R(t)}\left[\frac{1}{r}\frac{\partial}{\partial\xi}\Big(rb\big(R'(t)(\xi-1)+v\big)\Big)\right]$$
$$=\frac{1}{(L-R(t))^2}\left[\frac{1}{r}\frac{\partial}{\partial\xi}\left(r\big(D_b\frac{\partial b}{\partial\xi}+AD_nb\frac{\partial n}{\partial\xi}-A\chi_nb\rho nH(n_m-n)\frac{\partial e}{\partial\xi}\big)\right)\right]$$
$$+k_bG_b(w)b(1-b)+(\lambda_{nb}b+\lambda_{nn}n)n-Kb, \tag{C.16}$$

$$\dot{R}(t)=v(R(t),t). \tag{C.17}$$

where

$$K=K(\xi)=\frac{R'(t)}{L-R(t)}\left(\frac{(1-\xi)(L-R(t))}{r}-1\right),$$

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

$$G_f(w)=\frac{2w}{w+K_{wf}},\quad G_b=\frac{2w}{w+K_{w\rho}},\quad D(w)=1-H(w-0.2)H(3-w).$$

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

$$v=0, \tag{C.18}$$
$$(1-\alpha)(w-1)+\frac{\alpha L}{L-R(t)}\frac{\partial w}{\partial\xi}=0, \tag{C.19}$$
$$(1-\alpha)p+\frac{\alpha L}{L-R(t)}\frac{\partial p}{\partial\xi}=0, \tag{C.20}$$
$$(1-\alpha)e+\frac{\alpha L}{L-R(t)}\frac{\partial e}{\partial\xi}=0, \tag{C.21}$$
$$(1-\alpha)m+\frac{\alpha L}{L-R(t)}\left(\frac{\partial m}{\partial\xi}-\frac{\chi_m}{D_m}\rho mH(m_m-m)\frac{\partial p}{\partial\xi}\right)=0, \tag{C.22}$$
$$(1-\alpha)(f-1)+\frac{\alpha L}{L-R(t)}\left(\frac{\partial f}{\partial\xi}-\frac{\chi_f}{D_f}\rho fH(f_m-f)\frac{\partial f}{\partial\xi}\right)=0, \tag{C.23}$$
$$(1-\alpha)n+\frac{\alpha L}{L-R(t)}\left(\frac{\partial n}{\partial\xi}-\frac{\chi_n}{D_n}\rho nH(n_m-n)\frac{\partial n}{\partial\xi}\right)=0, \tag{C.24}$$
$$(1-\alpha)(b-1)+\frac{\alpha L}{L-R(t)}\frac{\partial b}{\partial\xi}-(1-\alpha)\frac{AD_n}{D_b}bn=0, \tag{C.25}$$

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

$$\frac{\partial v}{\partial\xi}=\big(L-R(t)\big)P, \tag{C.26}$$
$$\frac{\partial w}{\partial\xi}=\frac{\partial e}{\partial\xi}=\frac{\partial n}{\partial\xi}=\frac{\partial b}{\partial\xi}=0, \tag{C.27}$$
$$\frac{\partial p}{\partial\xi}=-\frac{k_{pb}R}{D_pR_0}\big(L-R(t)\big), \tag{C.28}$$
$$-D_m\frac{\partial m}{\partial\xi}+\chi_m\rho mH(m_m-m)\frac{\partial p}{\partial\xi}=0, \tag{C.29}$$
$$-D_f\frac{\partial f}{\partial\xi}+\chi_f\rho fH(f_m-f)\frac{\partial p}{\partial\xi}=0. \tag{C.30}$$

The initial conditions take the form

$$
\begin{aligned}
&R(0) = 0,\ v = 0,\ \rho = f = 1,\ w = 1 - \alpha,\ b = g\left(\frac{\xi(L - R_0)}{\epsilon}\right), \\
&e = m = n = 0,\ p = \max\left\{0, \frac{k_{pb}}{D_p}\Big(\epsilon - \xi(L - R_0)\Big)\right\}.
\end{aligned}
\tag{C.31}
$$

D Parameters of the model

Most of the parameters in Table S1 are obtained from the literature cited; the remaining parameters are estimated as described below. Proteins make up about a quarter of body volume, and the dermal tissue protein is mainly ECM protein (5), therefore ρ_0 is approximately 0.25. We assume that the maximally allowed ECM volume fraction is $2\rho_0$, therefore ρ_m is estimated as 0.5. We assume that when $\rho > \rho_0$, the ECM pressure depends on its density linearly with rate $\beta = 10$, which means that if ECM is compressed to twice its normal density ρ_0 and released immediately afterwards, it will relax to ρ_0 in about two hours. This is estimated from the one dimensional ECM equation with no growth term and surface force

$$\begin{aligned} &\frac{\partial \rho}{\partial t} + \frac{\partial(\rho v)}{\partial x} = 0, \quad \rho(0) = 2, \\ &\frac{\partial v}{\partial x} = \beta(\rho - 1)_+ \quad v(0,t) = 0. \end{aligned}$$

whose solution satisfies $v(x,t) = \beta x(\rho - 1)_+$ and $\rho = \rho(t) = 1/(1 - 0.5e^{-\beta t})$, with $\rho(0) = 2$ and $\rho(2 \text{ hours}) \approx 1.02$.

In healthy tissue, there is no net growth of ECM, i.e., $G_\rho(f_0, w_0, \rho_0) = 0$, therefore we can solve for λ_ρ and obtain

$$\lambda_\rho = \frac{k_\rho w_0 f_0}{w_0 + K_{w\rho}} \left(\frac{1}{\rho_0} - \frac{1}{\rho_m} \right). \tag{D.1}$$

Similarly, the transfer rate of oxygen from blood to tissue, k_w, is taken such that, at homeostasis, tissue oxygen net growth is zero, therefore we can solve, from the equation for w,

$$k_w = \frac{(\lambda_{wf} f_0 + \lambda_{wm}) m_0 w_0}{b_0 (w_b - w_0)}. \tag{D.2}$$

Also, the maximum growth rate of fibroblast k_f is taken so that in normal healthy tissue fibroblasts is at steady state f_0, so that, using the equation for f,

$$k_f = \frac{\lambda_f}{1 - f_0/f_m}. \tag{D.3}$$

Note that the process $p \to m \to p$ is autocatalytic. In homeostasis this process should be such that the density of the activated macrophages is $m = 0$ and therefore also $p = 0$. A steady state of (p, m) is the intersection of the two nullclines of the equations for p and m, namely, $k_p m = \frac{\lambda_{pf} p}{K_p + p} + \lambda_p p$ and $\frac{k_m p}{K_p + p} = \lambda_m m$. For simplicity, we assume homeostasis is the only steady state, i.e., the only intersection of the two nullclines. This is satisfied if and only if $\frac{k_m k_p}{\lambda_m} < \lambda_p + \lambda_{pf}$, and the parameter k_p is chosen to abide by this inequality.

We assume that the random motility of fibroblasts in the wound healing environment is the same as that of macrophages, i.e., $D_f = D_m$, which is much smaller than that of soluble chemicals but a little larger than that of blood vessels. As in (4), we estimate the maximum volume fraction of macrophages, fibroblasts and capillary tips in the wound to be 1%, so that we can take $m_m = f_m = n_m = 10^{-2}$ g·cm^{-3}. As in (4), we assume that the oxygen consumption rate by fibroblasts is smaller than that by macrophages, and $\lambda_{wf} = \lambda_{wm}/15$. We also assume that the extra oxygen consumption rate by the skin tissue due to the wound, λ_{ww} (which is a nondimensional parameter), is equal to 2, i.e., when normalized p is equal to 1, the effect of p is to double the intake of oxygen by fibroblasts and by activated macrophages. We assume that the growth rate of fibroblast has the same dependence on oxygen as the synthesis of ECM, i.e., $K_{w\rho} = K_{wf}$. The boundary flux parameter k_{pb} is chosen so that the normal wound heals in 10 – 15 days post wounding as observed experimentally (11). We choose the differentiation rate of monocytes to macrophages, k_m, such that the maximum macrophage in the wound is 6 times that of the healthy tissue, i.e., $k_m = \frac{6\lambda_m m_0}{b_0}$. We assume that under extreme hypoxia or hyperoxia, the death rates of cells are three times that under normoxia, i.e., $\lambda_d = 2$. If we increase L to $2L$, simulation results do not change appreciably.

Table S1: Table of dimensional and nondimensionalized parameters.

Notation	Dimensional	Nondim	Source
L_0	0.15 cm	1	(4)
T_0	6.25 h	1	(4)
ρ_0	0.25	1	(5)
w_0	100 mmHg	1	(6)
K_p	10^{-8} g·cm^{-3}	1	(4, 7)
K_e	10^{-8} g·cm^{-3}	1	(4, 7)
m_0	10^{-3} g·cm^{-3}	1	(4, 7)
f_0	10^{-3} g·cm^{-3}	1	(4, 8)
b_0	10^{-3} g·cm^{-3}	1	(4, 9, 10)
L^*	0.75 cm	5	(11)
R_0	0.4 cm	8/3	(11)
ρ_m	0.5	2	Estimated
$K_{w\rho}$	25 mmHg	0.25	(6, 12–14)
K_{wf}		0.25	Estimated
k_ρ		5/16	(4)
λ_ρ		0.1	Eqn [D.1]
β		10	Estimated
D_w	5×10^{-7} cm^2/s	0.5	(15)
D_p	10^{-6} cm^2/s	1	(16, 17)
D_e	10^{-6} cm^2/s	1	(16, 17)
D_m		5×10^{-2}	(4)
D_f		5×10^{-2}	Estimated
D_n	10^{-9} cm^2/s	10^{-3}	(16, 18)
D_b	7×10^{-10} cm^2/s	7×10^{-4}	(17, 19)
χ_m		0.1	(4)
χ_f	10-500 cm^5 g^{-1}s^{-1}	0.1	(8)
χ_n	1-100 cm^5 g^{-1}s^{-1}	1	(16, 20)
m_m	10^{-2} g·cm^{-3}	10	(4)
f_m	10^{-2} g·cm^{-3}	10	(4)
n_m	10^{-2} g·cm^{-3}	10	(4)
A		0.1	(4)
w_b	200 mmHg	2	(6)
k_w		4.39	Eqn [D.2]
λ_{wf}		0.227	(4, 21)
λ_{wm}	0.185 cm^{3}g^{-1}s^{-1}	4.16	(4, 21)
λ_{ww}		2	Estimated
k_p		1.5	Estimated
λ_{pf}		9	Estimated
λ_p	4 $\times 10^{-5}$ s^{-1}	0.9	(4)
k_{pb}		4	Estimated
k_e		50	(4)
λ_{en}		90	(4)
λ_{eb}	4 cm^{3}g^{-1}s^{-1}	90	(22, 23)
λ_e	4 $\times 10^{-5}$ s^{-1}	0.9	(24, 25)
k_m		2.7 $\times 10^{-1}$	Estimated
λ_m	2 $\times 10^{-6}$ s^{-1}	4.5 $\times 10^{-2}$	(4, 26)
λ_d		2	Estimated
k_f		5.78 $\times 10^{-3}$	Eqn [D.3]
λ_f	2.31 $\times 10^{-7}$ s^{-1}	5.2 $\times 10^{-3}$	(27)
k_{nb}		2.16 $\times 10^{-2}$	(4)
k_n		2.16 $\times 10^{-2}$	(4, 21)
k_b	5.56 $\times 10^{-6}$ - 1.56 $\times 10^{-5}$ s^{-1}	2.25 $\times 10^{-1}$	(19, 20, 28)
λ_{nn}	10^{-1} cm^{3}g^{-1}s^{-1}	2.25	(18)
λ_{nb}	10^{-3} cm^{3}g^{-1}s^{-1}	2.25 $\times 10^{-2}$	(18)

$*$ By increasing L the results don not change appreciably.

E Time evolution figures

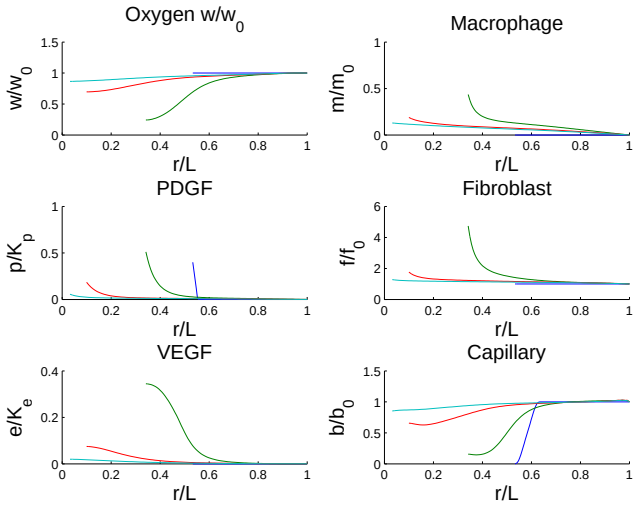

Figure S1: Normal wound healing ($\alpha = 0$): spatial distribution of cells and chemokines at different times. Blue: $t = 0$; green: $t = 5$; red: $t = 10$; cyan: $t = 12.5$.

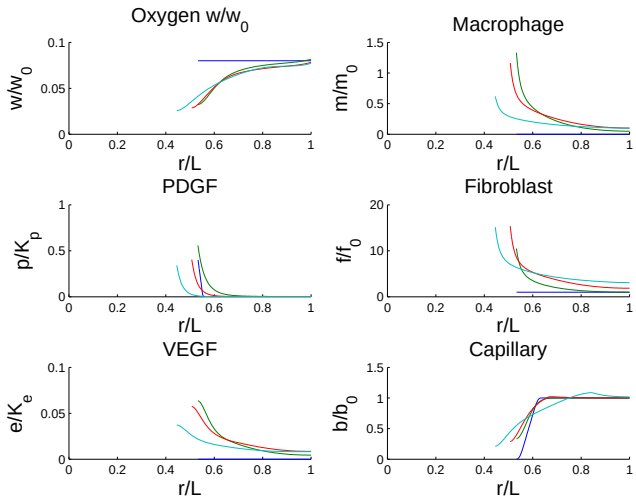

Figure S2: Ischemic wound healing ($\alpha = 0.88$): spatial distribution of cells and chemokines at different times. Blue: $t = 0$; green: $t = 5$; red: $t = 10$; cyan: $t = 15$; yellow: $t = 20$.

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