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Original Publication Citation

Adam, J. A., & Bellomo, C. (1997). Post-surgical passive response of local environment to primary tumor removal. *Mathematical and Computer Modelling*, *25*(6), 7-17. doi:10.1016/s0895-7177(97)00035-6

Pergamon

Mathl. Comput. Modelling Vol. 25, No. 6, pp. 7–17, 1997

0895-7177/97 \$17.00 + 0.00

PII: S0895-7177(97)00035-6

Post-Surgical Passive Response of Local Environment to Primary Tumor Removal

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(Received January 1997; accepted February 1997)

Abstract—Prompted by recent clinical observations on the phenomenon of metastasis inhibition by an angiogenesis inhibitor, a mathematical model is developed to describe the post-surgical response of the local environment to the "surgical" removal of a spherical tumor in an infinite homogeneous domain. The primary tumor is postulated to be a source of growth inhibitor prior to its removal at $t = 0$; the resulting relaxation wave arriving from the disturbed (previously steady) state is studied, closed form analytic solutions are derived, and the asymptotic speed of the pulse is estimated to be about 2×10^{-4} cm/sec for the parameters chosen. In general, the asymptotic speed is found to be $2\sqrt{D\gamma}$, where D is the diffusion coefficient and γ is the inhibitor depletion or decay rate.

Keywords—Tumor, Metastasis, Growth inhibitor, Diffusion, Relaxation wave.

1. INTRODUCTION

In a recent paper by O'Reilly *et al.* [1], the phenomenon of metastasis inhibition by an angiogenesis inhibitor, angiostatin, is discussed. In their animal model, a primary tumor inhibits its remote metastases. The authors discuss various existing hypotheses for the observed inhibitory effects, and propose that a primary tumor, while capable of stimulating angiogenesis in its own vascular bed, may yet inhibit angiogenesis in the vascular bed of a metastasis or other (secondary) tumor. The hypothesis involves the competing effects of angiogenic inhibitor and stimulator (released by the primary) in the vicinity of a remote metastasis. For the proposed mechanism to work, the inhibitor must have a longer half-life in the circulation than the stimulator does; then at the secondary location, inhibition occurs despite the presence of growth stimulatory factors. Upon surgery, the source of inhibition is removed, and the secondary is free to grow, often rapidly, by the usual mechanisms of angiogenesis. The reader is referred to the above paper for further details of the observations and the properties of angiostatin.

Prompted by these clinical observations, we investigate the features associated with an idealized "surgical procedure" representing the removal of a spherical tumor in an infinite domain. We discuss the resulting initial-value problem as the domain, now bounded internally by a sphere of radius R, responds to the evolution of the (previous) steady-state distribution of inhibitor released by the primary prior to its removal. The geometry is shown in Figure 1.

We assume that prior to surgery at $t = 0$, the source of inhibitor (the tumor) has been present for enough time that a steady state concentration $C(r)$ has developed. The "exterior" solution $C(r; 0)$ $(r > R)$ is then the initial condition imposed on the boundary value problem at $t = 0$. This solution is established in the Appendix; it matches the "interior" solution for $r < R$ obtained

The authors are grateful to G. Lasseigne for a very helpful discussion on the analytic representation of the solution given in the text.

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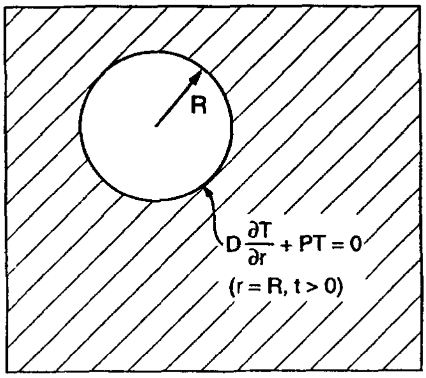

Figure 1. Basic geometry of the problem: a spherical tumor of radius R embedded in an infinite homogeneous domain for $t < 0$, and removed at $t = 0$.

by Shymko and Glass [2]. They were concerned with the internal distribution of growth inhibitor (in various geometries), which enabled them to draw conclusions about the stability or instability of tissue "growth", i.e., whether or not the tissue could reach a stable limiting size, and under what circumstances this could occur.

We do not incorporate the effects of an angiogenic stimulator in this paper. In what follows, $C(r,t)$ is the growth inhibitor concentration in $r > R$, γ is a depletion rate, D is the coefficient of diffusion, and P is a coefficient of permeability (between the tumor and its surroundings). In this paper, γ, D, and P are all constants (in a subsequent paper, in preparation, we consider them to be piecewise constant quantities). Our ultimate concern is the description of $C(r,t)$ at any given location corresponding to a metastatic or secondary site. In particular, for $r = r^* > R$, and $t = t^* > 0$, we wish to describe $f(t) = C(r^*,t)$ and $g(r) = C(r,t^*)$. We posit that if the concentration $C(r,t)$ falls below a critical value θ, say, then metastatic inhibition ceases, though that is not a necessary requirement for our purposes here. We investigate $f(t)$ and $g(r)$ for various values of t and r, and estimate the speed of the "relaxation pulse" after removal of the primary tumor.

2. STATEMENT OF THE PROBLEM

The time-dependent post-surgical problem may be posed as follows:

$$\frac{1}{r}\frac{\partial^2}{\partial r^2}(rC) - \frac{\gamma}{D}C = \frac{1}{D}\frac{\partial C}{\partial t}, \qquad R \le r < \infty, \quad t > 0, \tag{1}$$

$$D\frac{\partial C}{\partial r} + PC = 0, \qquad r = R, \quad t > 0, \tag{2}$$

$$C(r,0) = \frac{G}{r}e^{-\alpha r} \equiv F(r), \qquad t = 0, \quad R \le r < \infty, \tag{3}$$

where $\alpha = (\gamma/D)^{1/2}$.

3. ANALYSIS OF THE PROBLEM

3.1. Reformulation and Solution

Let $C(r,t) \equiv T(r,t)e^{-\gamma t}$. Note that $T(r,0) = C(r,0) = F(r) = (G/r)e^{-\alpha r}$ from equation (3). Setting $T(r,t) = r^{-1}u(x(r),t)$, where $r = x + R$, equations (1)–(3) become

$$\frac{\partial^2 u}{\partial x^2} = \frac{1}{D}\frac{\partial u}{\partial t}, \qquad 0 \le x < \infty, \quad t > 0, \tag{4}$$

$$D\frac{\partial u}{\partial x} + \left(P - \frac{D}{R}\right)u = 0, \qquad x = 0, \quad t > 0, \tag{5}$$

$$u(x,0) = Ge^{-\alpha(x+R)} \equiv M(x), \qquad 0 \le x < \infty, \quad t = 0. \tag{6}$$

We introduce the integral transform pair [3]

$$\overline{u}(\beta,t) = \int_0^\infty K(\beta,\xi)u(\xi,t)\,d\xi, \tag{7}$$

$$u(x,t) = \int_0^\infty K(\beta,x)\overline{u}(\beta,t)\,d\beta, \tag{8}$$

where the kernel,

$$K(\beta,x) = \sqrt{\frac{2}{\pi}}\,\frac{\beta\cos(\beta x) + H\sin(\beta x)}{\sqrt{\beta^2+H^2}}$$

is the normalized solution of

$$\frac{d^2Y}{dx^2} + \beta^2 Y = 0, \qquad 0 \le x < \infty, \tag{9}$$

$$D\frac{dY}{dx} + \left(P - \frac{D}{R}\right)Y = 0, \qquad x = 0, \tag{10}$$

for $\beta \in [0,\infty)$ and $H = 1/R - P/D$.

From equation (4), we find that

$$\int_0^\infty K(\beta,x)\frac{\partial^2 u}{\partial x^2}\,dx = D^{-1}\int_0^\infty K(\beta,x)\frac{\partial u}{\partial t}\,dx = D^{-1}\frac{d}{dt}\,\overline{u}(\beta,t), \tag{11}$$

the left-hand side of which becomes

$$\left[K\frac{\partial u}{\partial x}\right]_0^\infty - \int_0^\infty \frac{dK}{dx}\frac{\partial u}{\partial x}\,dx = \left[K\frac{\partial u}{\partial x} - u\frac{dK}{dx}\right]_0^\infty + \int_0^\infty u\frac{d^2K}{dx^2}\,dx.$$

It is reasonable to assume that $\lim_{x\to\infty} u(x) = 0$ and $\lim_{x\to\infty} u'(x) = 0$. These conditions imply that

$$\left[K\frac{\partial u}{\partial x} - u\frac{dK}{dx}\right]_0^\infty = 0 - K(0)u'(0) + u(0)K'(0).$$

From equation (5), $u'(0) = Hu(0)$. Also, using the definition of $K(\beta,x)$, it follows that

$$\left[K\frac{\partial u}{\partial x} - u\frac{dK}{dx}\right]_0^\infty = u(0)\left[K'(0) - HK(0)\right] = 0.$$

From equations (9) and (7),

$$\int_0^\infty u\frac{d^2K}{dx^2}\,dx = -\beta^2\int_0^\infty uK\,dx = -\beta^2\overline{u}(\beta,t).$$

Using this information, equation (11) becomes

$$\frac{d\overline{u}(\beta,t)}{dt} = -\beta^2 D\overline{u}(\beta,t), \qquad \text{whence } \overline{u}(\beta,t) = \overline{u}(\beta,0)e^{-D\beta^2 t}. \tag{12}$$

Note that from equations (6) and (7),

$$\overline{u}(\beta,0) = \int_0^\infty K(\beta,\xi)u(\xi,0)\,d\xi = \int_0^\infty K(\beta,\xi)M(\xi)\,d\xi \equiv \overline{M}(\beta),$$

where $M(\xi) = (\xi + R)F(\xi + R)$.

Finally, using $\overline{u}(\beta,0) = \overline{M}(\beta)$ in (12) and from equation (8),

$$u(x,t) = \int_0^\infty \overline{M}(\beta) e^{-D\beta^2 t} K(\beta,x)\, d\beta. \tag{13}$$

Using the definition of $K(\beta,\xi)$ and equation (6) in $\overline{M}(\beta) = \int_0^\infty K(\beta,\xi)u(\xi,0)\,d\xi$, we find that

$$\overline{M}(\beta) = Ge^{-\alpha R}\sqrt{\frac{2}{\pi}} \int_0^\infty e^{-\alpha\xi} \frac{\beta\cos(\beta\xi) + H\sin(\beta\xi)}{\sqrt{\beta^2 + H^2}}\, d\xi. \tag{14}$$

Note that

$$\int_0^\infty e^{-(\alpha - i\beta)\xi}\, d\xi = \frac{\alpha + i\beta}{\alpha^2 + \beta^2},$$

so equation (14) reduces to

$$\overline{M}(\beta) = \frac{Ge^{-\alpha R}\sqrt{2/\pi}}{\sqrt{\beta^2 + H^2}} \frac{(\alpha + H)\beta}{\alpha^2 + \beta^2}, \tag{15}$$

where G is the exterior solution (see the Appendix).

$$G = \mathrm{Re}^{\alpha R} \frac{\lambda}{\gamma} \left[1 - \frac{1}{1 + \eta(\coth(\alpha R) - 1/\alpha R)}\right]. \tag{16}$$

Using equation (15) for $\overline{M}$, equation (13) reduces to

$$u(x,t) = \frac{2}{\pi} Ge^{-\alpha R}(\alpha + H)\left[I_1 + HI_2\right],$$

$$\text{where } I_1(\beta,x,t) = \int_0^\infty \frac{\beta^2 e^{-D\beta^2 t}\cos(\beta x)}{(\beta^2 + \alpha^2)(\beta^2 + H^2)}\, d\beta,$$

$$I_2(\beta,x,t) = \int_0^\infty \frac{\beta e^{-D\beta^2 t}\sin(\beta x)}{(\beta^2 + \alpha^2)(\beta^2 + H^2)}\, d\beta.$$

Therefore, we have the solution

$$C(r,t) = \frac{e^{-\gamma t}}{r} \frac{2}{\pi} Ge^{-\alpha R}(\alpha + H)\left[I_1(\beta, r - R, t) + HI_2(\beta, r - R, t)\right].$$

3.2. Nondimensionalization of the Results

Letting $\widetilde{\beta} = \beta R$ and $\widetilde{x} = x/R = r/R - 1$ for $r \geq R$, we have

$$I_1 = R\int_0^\infty \frac{\widetilde{\beta}^2 e^{-g\widetilde{\beta}^2}\cos\left(\widetilde{\beta}\widetilde{x}\right)}{\left(\widetilde{\beta}^2 + \beta_1^2\right)\left(\widetilde{\beta}^2 + \beta_2^2\right)}\, d\widetilde{\beta}, \tag{17}$$

$$I_2 = R^2\int_0^\infty \frac{\widetilde{\beta} e^{-g\widetilde{\beta}^2}\sin\left(\widetilde{\beta}\widetilde{x}\right)}{\left(\widetilde{\beta}^2 + \beta_1^2\right)\left(\widetilde{\beta}^2 + \beta_2^2\right)}\, d\widetilde{\beta}, \tag{18}$$

where the dimensionless quantities g, β_1, and β_2 are defined by

$$g = \frac{Dt}{R^2},$$

$$\beta_1^2 = \alpha^2 R^2 = \frac{\gamma R^2}{D},$$

$$\beta_2^2 = H^2 R^2 = R^2\left(\frac{1}{R} - \frac{P}{D}\right)^2.$$

3.3. Computation of Integrals

The integrals 1 and 2 in equations (17) and (18), respectively, can be found using Fourier transforms.

Computation of Integral 1

We use partial fraction decomposition to obtain

$$I_1 = \frac{R}{\beta_1^2 - \beta_2^2}\left[\int_0^\infty \frac{\beta_1^2 e^{-g\beta^2}\cos(\beta x)}{\beta^2+\beta_1^2}\,d\beta - \int_0^\infty \frac{\beta_2^2 e^{-g\beta^2}\cos(\beta x)}{\beta^2+\beta_2^2}\,d\beta e\right].$$

Note that we need only evaluate

$$I = \int_0^\infty \frac{e^{-g\beta^2}\cos(\beta x)}{\beta^2+Q^2}\,d\beta, \qquad \text{where } Q = \beta_1^2 \text{ or } \beta_2^2.$$

Then we have

$$I = \frac{1}{2}\int_{-\infty}^\infty \frac{e^{-g\beta^2}\cos(\beta x)}{\beta^2+Q^2}\,d\beta = \frac{1}{2}\,\mathrm{Re}\left[\int_{-\infty}^\infty \frac{e^{-g\beta^2}e^{i\beta x}}{\beta^2+Q^2}\,d\beta\right].$$

The Fourier transforms are defined as

$$\Upsilon\left[e^{-a^2x^2}\right] = \left(a\sqrt{2}\right)^{-1} e^{-\xi^2/4a^2}, \text{ for } a>0,$$
$$\text{and } \Upsilon\left[\frac{1}{(a^2+x^2)}\right] = \left(\frac{\pi}{2}\right)^{1/2}\frac{e^{-a|\xi|}}{a}.$$

Therefore, we find

$$\frac{1}{\sqrt{2\pi}}\int_{-\infty}^\infty e^{-g\beta^2}e^{i\beta x}\,d\beta = \frac{1}{\sqrt{2g}}e^{-x^2/4g},$$
$$\text{i.e., } \Upsilon\left(e^{-g\beta^2},x\right) \equiv F(x),$$
$$\frac{1}{\sqrt{2\pi}}\int_{-\infty}^\infty \frac{e^{i\beta x}}{\beta^2+Q^2}\,d\beta = \sqrt{\frac{\pi}{2}}\frac{e^{-Q|x|}}{Q},$$
$$\text{i.e., } \Upsilon\left(\frac{1}{\beta^2+Q^2},x\right) \equiv G(x).$$

Defining $\Upsilon((e^{-g\beta^2})/(\beta^2+Q^2))$ as the convolution $F*G$, we have

$$\begin{aligned}
I &= \frac{1}{2}\,\mathrm{Re}\left[\sqrt{2\pi}\Upsilon\left(\frac{e^{-g\beta^2}}{\beta^2+Q^2}\right)\right] = \frac{1}{2}\,\mathrm{Re}\left[\int_{-\infty}^\infty F(x-\beta)G(\beta)\,d\beta\right] \\
&= \frac{1}{2}\,\mathrm{Re}\left[\int_{-\infty}^\infty \frac{1}{\sqrt{2g}}e^{-(x-\beta)^2/4g}\sqrt{\frac{\pi}{2}}\frac{e^{-Q|\beta|}}{Q}\,d\beta\right] \\
&= \frac{1}{2}\sqrt{\frac{\pi}{2}}\frac{1}{\sqrt{2g}}\frac{1}{Q}\,\mathrm{Re}\left[\int_{-\infty}^\infty e^{-(x-\beta)^2/4g}e^{-Q|\beta|}\,d\beta\right] \\
&= \frac{\sqrt{\pi}}{4\sqrt{g}Q}\,\mathrm{Re}\left[\int_0^\infty e^{-(x-\beta)^2/4g}e^{-Q\beta}\,d\beta + \int_{-\infty}^0 e^{-(x-\beta)^2/4g}e^{Q\beta}\,d\beta\right] \\
&= \frac{\sqrt{\pi}}{4\sqrt{g}Q}\,\mathrm{Re}\int_0^\infty \left[e^{-(x-\beta)^2/4g}+e^{-(x+\beta)^2/4g}\right]e^{-Q\beta}\,d\beta.
\end{aligned} \tag{19}$$

Examining the first term, we note that

$$\begin{aligned}
\int_0^\infty e^{-(x-\beta)^2/4g}e^{-Q\beta}\,d\beta &= \int_0^\infty e^{-1/4g\left[(x-\beta^2)+4gQ\beta\right]}\,d\beta \\
&= e^{-x^2/4g}e^{(x-2gQ)^2/4g}\int_0^\infty e^{-1/4g[\beta-x+2gQ]^2}\,d\beta \\
&= e^{-x^2/4g}e^{(x-2gQ)^2/4g}2\sqrt{g}\int_{\frac{2gQ-x}{2\sqrt{g}}}^\infty e^{-s^2}\,ds.
\end{aligned}$$

From the definition of the complementary error function, i.e.,

$$\mathrm{Erfc}(y) = \frac{2}{\sqrt{\pi}} \int_y^\infty e^{-t^2}\, dt,$$

it follows that

$$\int_0^\infty e^{-(x-\beta)^2/4g} e^{-Q\beta}\, d\beta = e^{-x^2/4g} e^{(x-2gQ)^2/4g} \sqrt{g}\sqrt{\pi}\, \mathrm{Erfc}\left(\frac{2gQ-x}{2\sqrt{g}}\right). \tag{20}$$

Similarly,

$$\int_0^\infty e^{-(x+\beta)^2/4g} e^{-Q\beta}\, d\beta = e^{-x^2/4g} e^{(x+2gQ)^2/4g} \sqrt{g}\sqrt{\pi}\, \mathrm{Erfc}\left(\frac{2gQ+x}{2\sqrt{g}}\right). \tag{21}$$

Substituting the above two equations into equation (19), we obtain

$$\begin{aligned} I &= \frac{\sqrt{\pi}}{4\sqrt{g}Q}\left[e^{-x^2/4g} e^{(x-2gQ)^2/4g} \sqrt{\pi g}\, \mathrm{Erfc}\left(\frac{2gQ-x}{2\sqrt{g}}\right)\right. \\ &\quad \left. + e^{-x^2/4g} e^{(x+2gQ)^2/4g} \sqrt{\pi g}\, \mathrm{Erfc}\left(\frac{2gQ+x}{2\sqrt{g}}\right)\right], \\ &= \frac{\pi}{4Q} e^{gQ^2}\left[e^{-Qx}\, \mathrm{Erfc}\left(\frac{2gQ-x}{2\sqrt{g}}\right) + e^{Qx}\, \mathrm{Erfc}\left(\frac{2gQ+x}{2\sqrt{g}}\right)\right]. \end{aligned}$$

Finally, it follows that

$$I_1 = \frac{\pi R}{4\left(\beta_1^2-\beta_2^2\right)}\left[\begin{array}{l} \beta_1 e^{g\beta_1^2}\left\{e^{-\beta_1 x}\, \mathrm{Erfc}\left(\sqrt{g}\beta_1 - \frac{x}{2\sqrt{g}}\right) + e^{\beta_1 x}\, \mathrm{Erfc}\left(\sqrt{g}\beta_1 + \frac{x}{2\sqrt{g}}\right)\right\} \\ -\beta_2 e^{g\beta_2^2}\left\{e^{-\beta_2 x}\, \mathrm{Erfc}\left(\sqrt{g}\beta_2 - \frac{x}{2\sqrt{g}}\right) + e^{\beta_2 x}\, \mathrm{Erfc}\left(\sqrt{g}\beta_2 + \frac{x}{2\sqrt{g}}\right)\right\} \end{array}\right]. \tag{22}$$

Computation of Integral 2

Using partial fractions as before,

$$I_2 = \frac{R^2}{\beta_2^2-\beta_1^2}\left[\int_0^\infty \frac{\beta e^{-g\beta^2}\sin(\beta x)}{\beta^2+\beta_1^2}\, d\beta - \int_0^\infty \frac{\beta e^{-g\beta^2}\sin(\beta x)}{\beta^2+\beta_2^2}\, d\beta e\right].$$

Note that we need only to evaluate

$$\begin{aligned} I &= \int_0^\infty \frac{\beta e^{-g\beta^2}\sin(\beta x)}{\beta^2+Q^2}\, d\beta, \qquad \text{where } Q = \beta_1^2 \text{ or } \beta_2^2, \\ I &= \frac{1}{2}\int_{-\infty}^\infty \frac{\beta}{\beta^2+Q^2} e^{-g\beta^2}\sin(\beta x)\, d\beta = \frac{1}{2}\,\mathrm{Im}\left[\int_{-\infty}^\infty \frac{\beta}{\beta^2+Q^2} e^{-g\beta^2} e^{i\beta x}\, d\beta\right]. \end{aligned}$$

The Fourier transforms are defined as

$$\begin{aligned} \Upsilon\left[e^{-g\beta^2}\right] &= \left(\sqrt{2g}\right)^{-1} e^{-\xi^2/4g} \\ \text{and } \Upsilon\left[\frac{\beta}{\beta^2+Q^2}\right] &= i\mathrm{Sgn}(\xi)\left(\frac{\pi}{2}\right)^{1/2} e^{-Q|\xi|}. \end{aligned}$$

Using the convolution theorem again (as with the first integral), we have

$$\begin{aligned} I &= \frac{1}{2}\,\mathrm{Im}\left[\int_{-\infty}^\infty \frac{1}{\sqrt{2g}} e^{-(x-\beta)^2/4g} \sqrt{\frac{\pi}{2}} i\mathrm{Sgn}(\beta) e^{-Q|\beta|}\, d\beta\right] \\ &= \frac{\sqrt{\pi}}{4\sqrt{g}}\int_{-\infty}^\infty e^{-(x-\beta)^2/4g}\mathrm{Sgn}(\beta) e^{-Q|\beta|}\, d\beta \\ &= \frac{\sqrt{\pi}}{4\sqrt{g}}\left[\int_0^\infty e^{-(x-\beta)^2/4g} e^{-Q\beta}\, d\beta - \int_{-\infty}^0 e^{-(x-\beta)^2/4g} e^{Q\beta}\, d\beta\right] \\ &= \frac{\sqrt{\pi}}{4\sqrt{g}}\left[\int_0^\infty \left(e^{-(x-\beta)^2/4g} - e^{-(x+\beta)^2/4g}\right) e^{-Q\beta}\, d\beta\right]. \end{aligned}$$

As in the analysis from integral 1, we find

$$I = \frac{\sqrt{\pi}}{4\sqrt{g}} e^{-x^2/4g} \sqrt{\pi g} \left[e^{(x-2gQ)^2/4g} \operatorname{Erfc}\left(\frac{2gQ - x}{2\sqrt{g}}\right) - e^{(x+2gQ)^2/4g} \operatorname{Erfc}\left(\frac{2gQ + x}{2\sqrt{g}}\right) \right]$$

$$= \frac{\pi}{4} e^{gQ^2} \left[e^{-xQ} \operatorname{Erfc}\left(\frac{2gQ - x}{2\sqrt{g}}\right) - e^{xQ} \operatorname{Erfc}\left(\frac{2gQ + x}{2\sqrt{g}}\right) \right].$$

So, integral 2 can be expressed as follows:

$$I_2 = \frac{\pi R^2}{4(\beta_2^2 - \beta_1^2)} \left[\begin{array}{l} e^{g\beta_1^2} \left\{ e^{-\beta_1 x} \operatorname{Erfc}\left(\sqrt{g}\beta_1 - \frac{x}{2\sqrt{g}}\right) - e^{\beta_1 x} \operatorname{Erfc}\left(\sqrt{g}\beta_1 + \frac{x}{2\sqrt{g}}\right) \right\} \\ -e^{g\beta_2^2} \left\{ e^{-\beta_2 x} \operatorname{Erfc}\left(\sqrt{g}\beta_2 - \frac{x}{2\sqrt{g}}\right) - e^{\beta_2 x} \operatorname{Erfc}\left(\sqrt{g}\beta_2 + \frac{x}{2\sqrt{g}}\right) \right\} \end{array} \right]. \tag{23}$$

3.4. When $t = 0$

Note that

$$\lim_{t \to 0} \operatorname{Erfc}\left(\sqrt{g}\beta_1 - \frac{x}{2\sqrt{g}}\right) \approx 2$$

$$\text{and} \lim_{t \to \infty} \operatorname{Erfc}\left(\sqrt{g}\beta_1 - \frac{x}{2\sqrt{g}}\right) = 0.$$

This implies that the integrals reduce to

$$I_1 = \frac{\pi R}{2(\beta_1^2 - \beta_2^2)} \left[\beta_1 e^{-\beta_1 x} - \beta_2 e^{-\beta_2 x}\right], \tag{24}$$

$$I_2 = \frac{\pi R^2}{2(\beta_2^2 - \beta_1^2)} \left[e^{-\beta_1 x} - e^{-\beta_2 x}\right]. \tag{25}$$

3.5. Summary of Results

Ultimately we are interested in the solution given by

$$C(r,t) = \frac{e^{-\gamma t}}{r} \theta \left[I_1 + H I_2\right],$$

where the following constants are given:

R = radius of tumor in cm,
γ = depletion rate in s^{-1} (e.g., $2 \times 10^{-3}, 10^{-2}$),
P = permeability constant in cm/sec (e.g., 10^{-4}),
D = diffusion coefficient in cm^2/sec (e.g., 5×10^{-6}),
$\lambda = 0.1$ in units of concentration/sec,

and the following are determined relationships:

$$\beta_1 = \alpha R,$$

$$\beta_2 = \left(\frac{1}{R} - \frac{P}{D}\right) R,$$

$$\alpha = \sqrt{\frac{\gamma}{D}},$$

$$H = \frac{1}{R} - \frac{P}{D},$$

$$\theta = \frac{2}{\pi} \frac{R\lambda}{\gamma} (\alpha + H) \left[1 - \frac{1}{1 + (D\alpha/P)(\coth(\alpha R) - 1/\alpha R)}\right],$$

$$g(t) = \frac{Dt}{R^2},$$

$$x(r) = \left(\frac{r}{R}\right) - 1,$$

and the values for I_1 and I_2 are given by equations (22) and (23) for $t > 0$ and equations (24) and (25) for $t = 0$.

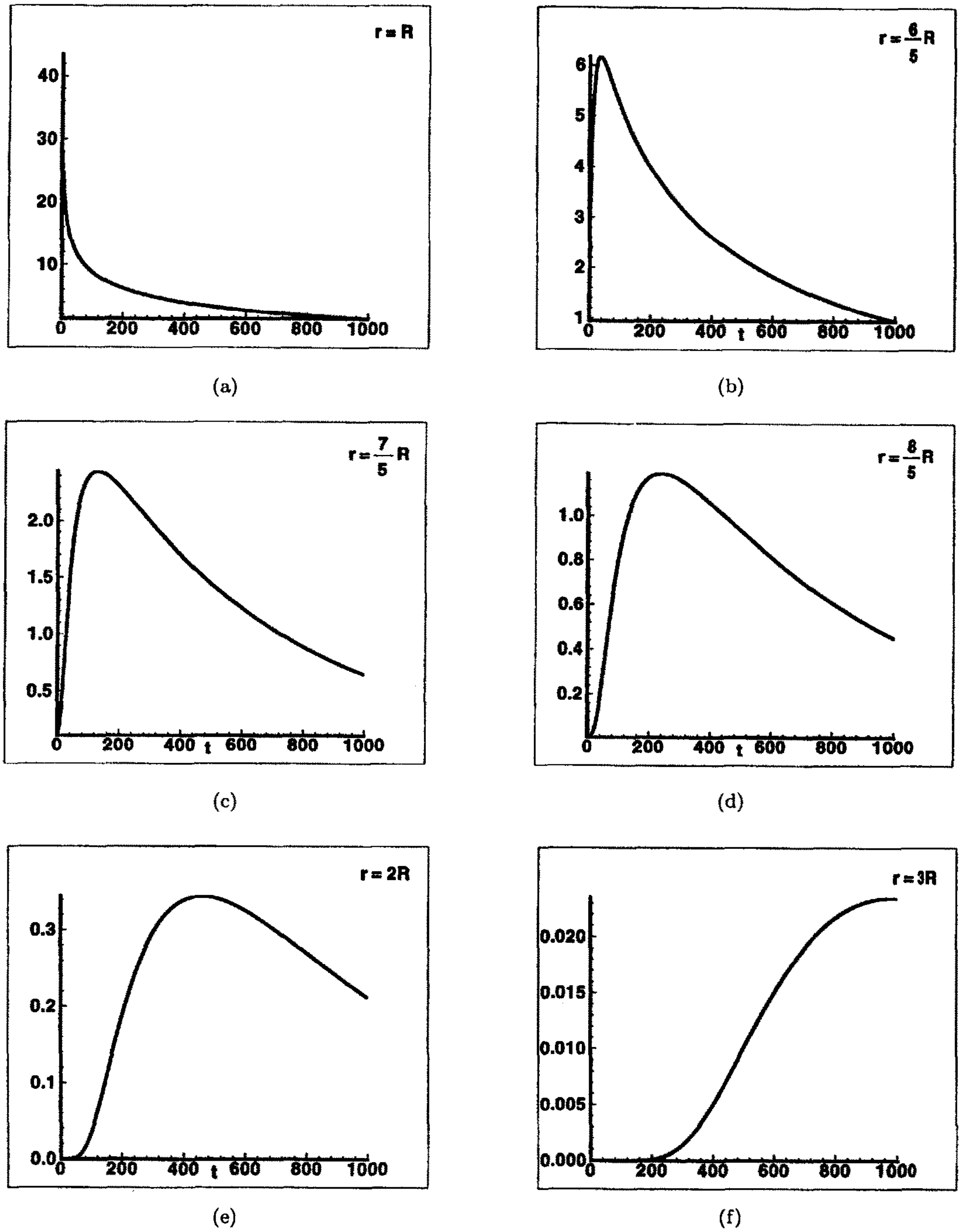

Figure 2. The concentration of inhibitor $C(r, t)$ in arbitrary units for various values of r in the exterior domain (t in seconds).

4. THE RELAXATION PULSE

Note from Figures 2a–2f that the pulse moves outward with decreasing amplitude over the time elapsed since "surgery." To obtain a crude estimate of the speed with which such a pulse propagates, we compare Figure 2e, in which the maximum occurs at $t \approx 460\,\text{sec}$ for $r = 0.2\,\text{cm}$, and Figure 2a, in which the maximum occurs at $t = 0\,\text{sec}$ for $r = 0.1\,\text{cm}$. Therefore, the peak of the pulse moves a distance R ($= 0.1\,\text{cm}$) from the boundary of the tumor region in about 460 seconds, corresponding to an average outward propagation speed of $2.2 \times 10^{-4}\,\text{cm/sec}$.

We can verify this analytically in a nonrigorous fashion as follows: from equation (1), the "dependent" variable $rC(r,t)$ satisfies the equation

$$\frac{\partial^2}{\partial r^2}(rC) - \frac{\gamma}{D}(rC) = \frac{1}{D}\frac{\partial}{\partial t}(rC). \tag{26}$$

Unlike in the case of reaction-diffusion equations, this problem does not yield a lower bound for the propagation speed, but we can still gain some useful information from (26). The fundamental solution or Green's function for (26) corresponding to a unit delta function source at the origin is

$$rC(r,t) = \frac{1}{\sqrt{4\pi Dt}} \exp\left[-\gamma t - \frac{r^2}{4Dt}\right]. \tag{27}$$

For a given r value, the maximum y-value will occur when $\partial(rC)/\partial t = 0$ (there being no minimum), from which it follows that (see [4,5])

$$\frac{r^2}{t^2} = 4D\gamma + \frac{2D}{t}. \tag{28}$$

Clearly, this maximum moves radially outward in time with a speed asymptotically equal to $2\sqrt{D\gamma}$. In Figure 2, $D = 5 \times 10^{-6}\,\mathrm{cm}^2/\mathrm{sec}$ and $\gamma = 2 \times 10^{-3}\,\mathrm{cm/sec}$. This asymptotic lower bound, which is approximately 2×10^{-4}, compares favorably with the estimate from Figure 2a–2e found above. The quantity that is being propagated, $y = rC$, has dimensions of molecules per unit area, so it is obviously a measure of surface concentration at different spatial locations. See Figure 3 for the behavior of $C(r)$ at different times.

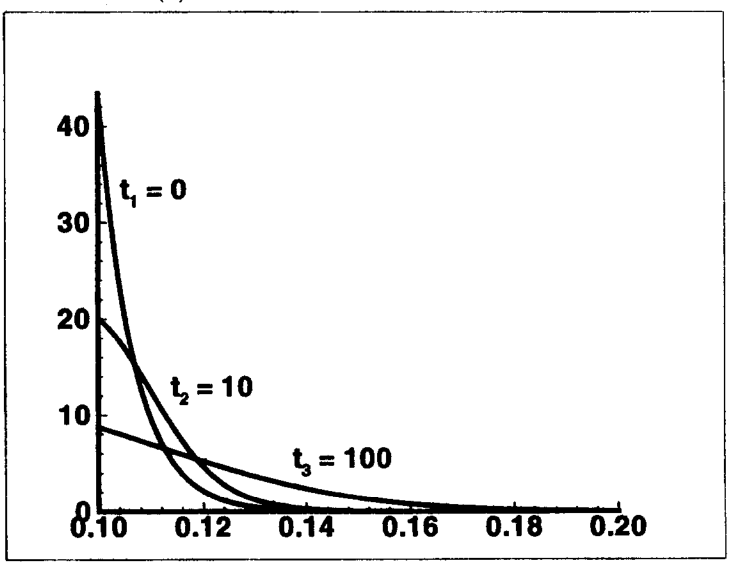

Figure 3. The concentration of inhibitor $C(r,t_i)$ in arbitrary units, $i = 1,2,3$ in the external domain (r in cm).

5. DISCUSSION

We have analyzed the space-time behavior of a "pulse" of growth inhibitor (or other substance produced by a tumor) when the source of inhibitor is removed, and the surrounding medium passively responds to this surgery. It has proven possible to obtain closed form analytic solutions to this boundary/initial value problem, though they are very complicated in form. The equations are also solved numerically for $C(r)$ at different fixed times after surgery and for $C(t)$ at different fixed r-values. In the latter case, it is possible to estimate from the graphs the speed of the relaxation pulse, and this agrees very favorably with the asymptotic speed predicted from a study of the Green's function for the problem. An obvious extension of this problem is to include the effects of tissue inhomogeneity [6].

APPENDIX
THE EXTERIOR SOLUTION

The fundamental equation of interest is

$$\frac{\partial C}{\partial t} = D\nabla^2 C - \gamma C + \lambda S(r),$$

which in the diffusive equilibrium approximation reduces to

$$\begin{aligned} \frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dC}{dr}\right) - \frac{\gamma C}{D} &= -\frac{\lambda}{D}, &\quad \text{for } r \le R,\\ &= 0, &\quad \text{for } r > R. \end{aligned}$$

Therefore, if $\alpha = (\gamma/D)^{1/2}$,

$$\begin{aligned} \frac{d^2C}{dr^2} + \frac{2}{r}\frac{dC}{dr} - \alpha^2 C &= -\frac{\lambda}{D}, &\quad \text{for } r \le R,\\ &= 0, &\quad \text{for } r > R. \end{aligned}$$

For the complementary function, we have

$$C = \frac{A}{r}\sinh(\alpha r) + \frac{B}{r}\cosh(\alpha r).$$

The particular integral must satisfy

$$y'' - \alpha^2 y = \frac{-\lambda r}{D},$$

which implies that

$$C(r) = \frac{A}{r}\sinh(\alpha r) + \frac{\lambda}{\gamma}, \qquad \text{for } r \le R. \tag{29}$$

Note that $C'(0) = 0$.

For $r > R$,

$$C = \frac{F}{r}\sinh(\alpha r) + \frac{G}{r}\cosh(\alpha r),$$

where $\lim_{r\to\infty} C(r) = 0$ implies that

$$C = \frac{G}{r}(\cosh(\alpha r) - \sinh(\alpha r)) = \frac{G}{r}e^{-\alpha r}. \tag{30}$$

Continuity of C at $r = R$ implies from equations (29) and (30), that

$$\frac{A}{R}\sinh(\alpha R) + \frac{\lambda}{\gamma} = \frac{G}{R}[\cosh(\alpha R) - \sinh(\alpha R)]. \tag{31}$$

Also,

$$D\frac{dC}{dr}\bigg|_R + PC(R) = 0,$$

meaning the flux inside the tissue at the bounding surface is equal to the leakage flux. Matching $DC'(R^-)$ with $PC(R^+)$, we have

$$\frac{DA}{R}\left[\alpha\cosh(\alpha R) - \frac{\sinh(\alpha R)}{R}\right] + \frac{PG}{R}[\cosh(\alpha R) - \sinh(\alpha R)] = 0,$$

or from equation (31),

$$\frac{A}{R}\left[D\left[\alpha\cosh\alpha R-\frac{\sinh\alpha R}{R}\right]+P\sinh\alpha R\right]=-\frac{P\lambda}{\gamma}.$$

Therefore,

$$A=\frac{-P\lambda R/\gamma}{D\left(\alpha\cosh\alpha R-(\sinh\alpha R)/R\right)+P\sinh\alpha R}.$$

For $r \le R$,

$$C(r)=\frac{\lambda}{\gamma}\left[1-\frac{PR\sinh\alpha r}{r[D(\alpha\cosh\alpha R-(\sinh\alpha R)/R)+P\sinh\alpha R]}\right].$$

Note that

$$\begin{aligned}\frac{P}{D(\alpha\cosh\alpha R-(\sinh\alpha R)/R)+P\sinh\alpha R}&=\frac{P}{\sinh\alpha R\{D(\alpha\coth\alpha R-1/R)+P\}}\\&=\frac{1/\sinh\alpha R}{D(\alpha/P)\coth\alpha R+1-D/PR}\\&=\frac{1/\sinh\alpha R}{1+\eta(\coth\alpha R-1/\alpha R)}\end{aligned}$$

gives the notation of Shymko and Glass [2], where $\eta = D\alpha/P$ and

$$C(r)=\frac{\lambda}{\gamma}\left[1-\frac{(R\sinh\alpha r)/(r\sinh\alpha R)}{1+\eta(\coth\alpha R-1/\alpha R)}\right],\qquad \text{for } r\le R.$$

From equation (31),

$$\begin{aligned}G&=\mathrm{Re}^{\alpha R}\left(\frac{A}{R}\sinh\alpha R+\frac{\lambda}{\gamma}\right)\\&=\mathrm{Re}^{\alpha R}\frac{\lambda}{\gamma}\left(1-\frac{1}{1+\eta(\coth\alpha R-1/\alpha R)}\right).\end{aligned}\tag{32}$$

Therefore, for $r > R$, $C(r) = (G/r)e^{-\alpha r}$, (see equation (3))

$$\text{i.e., } C(r)=\frac{\lambda}{\gamma}\frac{R}{r}e^{-\alpha(r-R)}\left[1-\frac{1}{1+\eta(\coth\alpha R-1/\alpha R)}\right].$$

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