Limiting Spheroid Size as a Function of Growth Factor Source Location

J. A. ADAM AND K. Y. WARD
Department of Mathematics and Statistics, Old Dominion University
Norfolk, VA 23529, U.S.A.

Abstract—Solutions $C(r)$ of the time-independent nonhomogeneous diffusion equation for three different piecewise-uniform source terms are used to examine the limiting size of multicell spheroids using a simple model which reproduces concentration-dependent mitotic behavior. A condition is derived under which nontrivial solutions do not exist (in all three cases), and a condition for the existence of a unique nontrivial solution is established for the case of growth-modifying factor (GMF) production throughout the spheroid. Qualitative behavior of the limiting size is established as a function of various physiological parameters. Of fundamental importance is the assumed GMF concentration threshold θ, near which (i.e., as $C \to \theta^-$) mitosis, and hence spheroid growth, is generally strongly inhibited.

Keywords—Growth factor, Spheroids, Mitotic stability, Diffusion-limited growth.

Based on comments by Witten [1], and mathematical models by Shymko and Glass [2], and Adam and Maggelakis [3], we examine the possible self-limiting effects of growth-modifying factor (GMF) on the size of a prevascular multicell spheroid [4]. We posit the presence of a GMF-producing region within the spheroid, which may be the necrotic core (if one exists), the nonnecrotic region, or the whole spheroid. We also posit, following [1] (and references therein), that low concentrations of GMF do not affect the mitotic rate of spheroid cells, somewhat higher concentrations stimulate mitotic activity, increasingly higher concentrations of GMF depress or partially inhibit mitotic activity, and at very high concentrations ($C(r) \to \theta^-$) mitosis is altogether inhibited, resulting in a limiting spheroid size, with outer radius R_∞ ($R \le R_\infty$ being the outer radius of the spheroid; $R_i < R$ is the radius of the necrotic core). The steady state GMF concentration $C(r)$ satisfies the time-independent diffusion equation and associated boundary conditions (see [2,3] for details)

$$D\nabla^2 C - \gamma C = -\lambda S_i(r), \qquad 0 \le r \le R, \tag{1}$$

$$C'(0) = 0, \qquad DC'(R) + PC(R) = 0, \tag{2}$$

where D is the diffusion coefficient within the spheroid, γ is the GMF decay or depletion constant, λ is the GMF production rate, and P is the permeability of the tissue surface. All four are assumed to be constant here. $S_i(r)$ represents the GMF source location within the spheroid, and there are three cases to consider ($i = 1, 2, 3$):

(i)
$$S_1(r) = 1, \qquad 0 \le r \le R,$$

(ii)
$$S_2(r) = \begin{cases} 1, & 0 \le r \le R_i, \\ 0, & R_i \le r \le R, \end{cases}$$

(iii)
$$S_3(r) = \begin{cases} 0, & 0 \le r \le R_i, \\ 1, & R_i \le r \le R. \end{cases}$$

Thus, the source of GMF is uniformly throughout

(i) the whole spheroid, or
(ii) the necrotic core only, or
(iii) the nonnecrotic region.

Since not all spheroids exhibit necrotic cores, Case (i) is a valuable and simpler model which can help validate Cases (ii) and (iii) as $R_i \to R$ or $R_i \to 0$, respectively. In no case do we require $C(r)$ for $r > R$. The solutions corresponding to Case 1 and Cases 2 and 3 can be found in [2] and [3], respectively. In each case $i = 1, 2$, $C_i(r)$ is a monotonically decreasing function of r, and thus $C_i(R) < C_i(r)$ for $0 \le r < R$. It is $C_i(R)$ that is of importance in this note, since growth ceases throughout the spheroid if $C_i(R) \ge \theta$. For Case 3, the behavior of $C(r)$ is more complicated because the source of GMF is in the outer spheroid region; it is possible that $C(R) > C(r)$ for some range of $r \in [0, R_i]$, which would not preclude mitosis occurring, therefore, even if $C(R) \ge \theta$. This will be examined elsewhere; in this note, we assume that $C(r)$, while not monotone in $[0, R]$, is such that $C(R) \le C(r)$ throughout the spheroid.

The above-mentioned qualitative mitotic behavior is perhaps most easily described by a generalization of the logistic model (over a timescale large compared to a typical diffusion time across the spheroid)

$$\frac{dR}{dt} = \alpha C_i(R) \left(1 - \frac{C_i(R)}{\theta} \right), \qquad (R(0) > 0,\ C_i(R) > 0), \quad (i = 1, 2, 3), \tag{3}$$

where α is a constant of proportionality which need not be specified here. The following changes of variable are made: $y = KR$ (where $K = (\gamma/D)^{1/2}$), $\beta = R_i/R = y_i/y$, $m = \lambda/\gamma\theta$, $\tau = \gamma t$, and $\mu = \alpha K \lambda/\gamma^2$. Equation (3) then takes the form, with $C_i(R) = (\lambda/\gamma)\phi_i(y)$,

$$\frac{dy}{d\tau} = \mu \phi_i(y)(1 - m\phi_i(y)). \tag{4}$$

Of interest here are stationary values of y, i.e., those values of y, $y_\infty \ne 0$ say, for which $\phi_i(y) = m^{-1}$ ($\phi_i(y) = 0$ is of no consequence here). In [2], the quantities $\xi = \lambda D/P^2\theta$ and $\eta = (\gamma D)^{1/2}/P$ are defined, from which it follows here that $m = \xi/\eta^2$. The $\phi_i(y)$ are defined as follows:

(i)
$$\phi_1(y) = \frac{\eta(\coth y - y^{-1})}{1 + \eta(\coth y - y^{-1})}. \tag{5}$$

Note that $\phi_1(y) < 1$, which implies that $m > 1$, i.e., $\xi > \eta^2$. The result is sharpened in a theorem below.

(ii)
$$\phi_2(y) = \frac{\eta(\beta y \cosh \beta y - \sinh \beta y)}{y \sinh y[\eta(\coth y - y^{-1}) + 1]}. \tag{6}$$

(iii)
$$\phi_3(y) = 1 - \left\{ \frac{y \sinh y - \eta(\sinh \beta y - \beta y \cosh \beta y)}{y \sinh y[\eta(\coth y - y^{-1}) + 1]} \right\}. \tag{7}$$

We are now in a position to draw some specific conclusions from the model.

THEOREM. *No nontrivial positive solutions of $\phi_i(y) = m^{-1}$ exist for $m \le 1$, i.e., for $\xi \le \eta^2$. Furthermore, a unique nontrivial positive solution exists for $i = 1$ when $\eta(m - 1) > 1$, i.e., $\xi > \eta^2 + \eta$.*

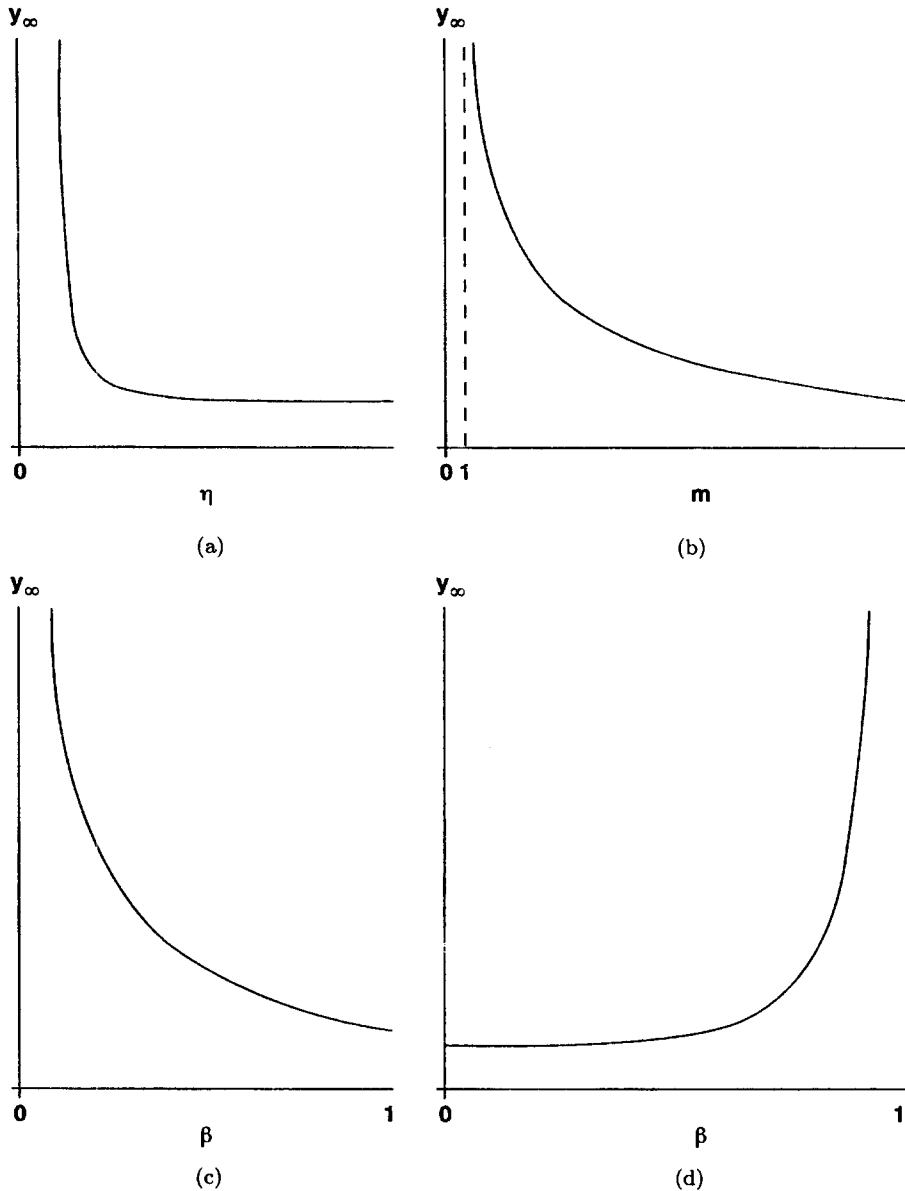In order to prove this we require the following lemma.

Figure 1. Schematic representation of the qualitative dependence of the scaled limiting radius y_∞ for the various models. (a) and (b) are typical of models (i)–(iii); (c) is typical of model (ii); and (d) shows behavior specific to model (iii), where the source of inhibitor is in the outer regions of the spheroid.

LEMMA. $p(\xi) = \xi \cosh \xi - \sinh \xi$ *is a positive increasing function on* $(0, \infty)$.

The proof is trivial. We utilize this result for $i = 1, 2, 3$ in proving the theorem.

PROOF OF THEOREM.

(i) $\phi_1(y) = m^{-1}$ is equivalent to the equation

$$(m - 1)\eta p(y) = y \sinh y, \tag{8}$$

proving the first part. If $a = (m - 1)\eta$, then we may also write this equation as

$$f(y) = \frac{ay}{y + a} = \tanh y. \tag{9}$$

It follows that $f(y)$ has horizontal asymptote $f = a$; if $a \leq 1$, the functions $f(y)$ and $\tanh y$ do not intersect in $(0, \infty)$; a unique intersection occurs for $a > 1$, establishing the result. The proofs are similar for the remaining two cases. Briefly,

(ii) $\phi_2(y) = m^{-1}$ can be written in the alternative form

$$\{p(\beta y)m - p(y)\}\eta = y \sinh y, \tag{10}$$

which by the lemma has no appropriate solutions for $m \leq 1$, and

(iii) $\phi_3(y) = m^{-1}$ can be written in the alternative form

$$\{(m-1)p(y) - mp(\beta y)\}\eta = y \sinh y, \tag{11}$$

which again has no appropriate solutions for $m \leq 1$.

The theorem is thus proven, and is consistent with the asymptotic results stated in [2], namely that (for Case 1 at least) $\xi < \eta^2$ for unstable tissue growth, and $\xi > \eta^2 + \eta$ corresponds to stable, limited growth. On the basis of the model presented here, we have been able to establish our results for any finite value of R.

Note from the definition of η that it is a measure of the competing effects of inhibitor depletion and diffusion with the permeability of the spheroid "tissue" or cellular matrix. Likewise, m is a measure of the competing effects of inhibitor production rate with depletion and threshold concentration; equivalently, since λ/γ has dimensions of concentration, m is also a measure of steady state to threshold concentration; if $m < 1$, growth is never suppressed.

Qualitative features of the solutions of $\phi_i(y) = m^{-1}$, i.e., $y_\infty(\eta, m, \beta)$, are shown in Figures 1a–1d. The behavior of y_∞ is qualitatively the same for each case $i = 1, 2, 3$. In Case 1, $y_\infty(\eta)$ is examined for given $m > 1$ (in the stable region), and $y_\infty(m)$ for given η. In the remaining cases, $y_\infty(\eta)$, $y_\infty(m)$, and $y_\infty(\beta)$ are drawn for fixed values of the remaining parameters. All graphs apart from $y_\infty(\beta)$ in Case (iii) are monotonically decreasing functions of their argument, and concave up. These results may be understood as follows: as m increases away from 1, mitosis is more readily inhibited by increasing λ and/or decreasing the product $\gamma\theta$; as η increases (i.e., by increasing the product γD and/or decreasing P), and for Case (ii), by increasing the size of the source region (increasing β), the spheroid growth is also more readily inhibited. For Case (iii), increasing β *reduces* the size of the source region, thus increasing the limiting spheroid size.

Typical values and parameter ranges were taken from [2]: $K \approx 10\,\text{cm}^{-1}$, $D \approx 5 \times 10^{-7}\,\text{cm}^2\text{s}^{-1}$; $\gamma \approx 5 \times 10^{-5}\,\text{s}^{-1}$; $P \approx 10^{-4}\,\text{cm}\,\text{s}^{-1}$, corresponding to $\eta \approx 0.05$. For this choice of K, a typical spheroid radius of 0.1 cm gives $y \approx 1$. In some cases, y_∞ varied by factors of 3–6 as the dependent variables are changed by similar factors indicating a significant variation of spheroid sizes within physiologically acceptable parameter ranges. This will justify further attention as more spheroid data becomes available.

REFERENCES

1. M. Witten, Mathematical modeling and computer simulation of the aging-cancer interface, Preprint Series, #482, Univ. Minnesota Inst. for Math and its Applics., (February 1989).
2. R.M. Shymko and L. Glass, Cellular and geometric control of tissue growth and mitotic instability, *J. Theor. Biol.* **63**, 355 (1976).
3. J.A. Adam and S.A. Maggelakis, Mathematical models of tumor growth. IV. Effects of a necrotic core, *Math. Biosci.* **97**, 121 (1989).
4. R.M. Sutherland, Cell and environment interactions in tumor microregions: The multicell spheroid model, *Science* **240**, 177 (1988).