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A MATHEMATICAL MODEL OF TUMOR GROWTH BY DIFFUSION

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Abstract. A diffusion model of the prevascular stage of tumor growth is presented. The basic feature of such a model is the diffusion of growth inhibitor, which is produced at a spatially non-uniform rate within the tissue. Régimes of limited and unlimited tissue growth are determined, and the consistency of this and simpler models is discussed in the light of observational results.

INTRODUCTION

The effects of diffusion of growth inhibitor on the stability of tissue growth has been of interest in recent years in connection with mathematical models of tumor growth (Glass, 1973; Shymko and Glass, 1976; Adam, 1986, 1988a, 1988b). In the latter three papers, tissue growth was examined for the cases in which the production rate of growth inhibitor is spatially non-uniform throughout the tissue, for a variety of geometrical configurations. In this paper we summarize a model (for a spherical configuration of cells) that is used to discuss some experimental results obtained by Folkman and Hochberg (1973) (see also Shymko and Glass, 1976) for multicellular spheroids of V-79 Chinese hamster lung tissue. Built into the mathematical model is a parameter b which is a measure of the degree of non-uniformity of the inhibitor production rate. The "inverse problem" is solved by finding the value of b necessary to account for results with which the uniform model is incompatible. The resulting value of b enables a good estimate to be made for the observed width of peripheral mitotic zones in the V-79 spheroids, and the resulting stability parameters lie in appropriate ranges for the model to be a significant improvement over uniform models.

THE MATHEMATICAL MODEL

Since a typical diffusion time for these multicellular spheroids (of the order of minutes) is small compared with their growth time (of the order of days) we may consider the tissue size to be stationary. The steady-state distribution $C(r)$ for the concentration of growth inhibitor produced by the cells is determined by the following system of equations (' refers to derivative with respect to r)

$$-Dr^{-2}(r^2C')' + \gamma C = S(r) \quad (1)$$

$$\text{and} \quad (DC' + PC)_{r=R} = 0 \quad (2)$$

$$\text{where} \quad S(r) = \begin{cases} \lambda(1-br/R), & 0 \leq r \leq R \\ 0, & r > R \end{cases}; \quad (3)$$

$C(0)$ is bounded, and $0 \leq b \leq 1$.

In these equations D is a diffusion coefficient, γ is a decay constant, $r=R$ defines the spherical surface of the tissue, and P is the permeability of the tissue surface. $S(r)$ is the source term for the inhibitor, λ being a production rate (in molecules per unit volume per second) and b is a measure of the non-uniformity of that production rate ($b=0$ corresponds to a uniform rate throughout the tissue).

Following Glass (1973), it is assumed that mitosis is controlled by a discontinuous switch-like mechanism such that, if anywhere in the tissue, $C < \theta$ say, mitosis occurs, while if $C \geq \theta$, mitosis is inhibited. The unique solution for the system (1)-(3) is given by

$$C(r) = \lambda\gamma^{-1}\{1-br/R + \tilde{\eta} \sinh kr / kr \sinh kR [1 + \eta(\coth kR - 1/kR)]\} \quad (4)$$

$$\text{where} \quad \eta = (\gamma D)^{1/2} / P, \quad k = (\gamma D)^{1/2},$$

$$\text{and} \quad \tilde{\eta} = \eta b + (b-1)kR$$

It can be shown that $C(r)$ decreases monotonically in $[0, R]$.

Régimes of Stability and Instability

Some useful information about tissue "instability" (ie. mitosis occurs) and "stability" follows from considering the limits $C(R)$ and $C(0)$ as R increases without bound. (Of course this is totally unrealistic physically but it does provide some extreme constraints within which more realistic analysis (see e.g. equation (13)) will lie).

$$\text{Thus} \quad \lim_{R \rightarrow \infty} C(R) = \lambda(1-b)D/P^2(\eta^2 + \eta) \quad (5)$$

$$\text{and} \quad \lim_{R \rightarrow \infty} C(0) = \lambda D/P^2 \eta^2 \quad (6)$$

We introduce the dimensionless parameter $n = \lambda D/P^2 \theta$. If $\lim_{R \rightarrow \infty} C(R) < \theta$, then the concentration of inhibitor is never sufficient to inhibit mitosis, i.e.

$$n(1-b) < \eta^2 + \eta \quad (7)$$

In fact it can be shown that if

$$(1-b)\eta^2 < n(1-b) < \eta^2 + \eta \quad (8)$$

then tissue growth is "unstable", with mitosis confined to a peripheral region of the tissue (the limiting width of this region is referred to below as W). If however,

$$n < \eta^2 \quad (9)$$

then mitosis occurs throughout the tissue. If

$$n(1-b) > \eta^2 + \eta \quad (10)$$

then "stable" limited tissue growth occurs. Thus, the patterns of tissue growth depend fairly sensitively on the parameter n , which itself depends on cellular parameters. The quantity however, depends not only on cellular parameters but also on the tissue geometry (see Shymko and Glass, 1976; Adam, 1988a).

An explicit expression can be obtained for the limiting peripheral width W as $R \rightarrow \infty$ by examining

$$\lim_{R \rightarrow \infty} C(R-W) = 0 \quad (11)$$

On solving this for W it is found that

$$W = -k^{-1} \ln\{(1-\eta^2/n(1-b))(1+\eta)\} \quad (12)$$

$$\text{provided } \eta^2 < n(1-b).$$

More generally, for $R < \infty$, the condition $C(R) \geq 0$ for limited "stable" growth yields the following inequality in $L (=kR)$ and n :

$$n\{b/L + (1-b)(\coth L - 1/L)\} \geq \eta + \eta^2(\coth L - 1/L) \quad (13)$$

The implications of this result for régimes of stable and unstable growth are discussed in detail in Adam (1988b)

Discussion

It is possible to formulate an "inverse problem" associated with this mathematical model by using observational results to determine the value of b necessary to be consistent with that data. After the appropriate algebraic manipulations on data quoted by Shymko and Glass (1976), the value found for the inhomogeneity parameter is $b=0.05$. For the data used inequality (8) is satisfied: the regime corresponds to unstable peripheral tissue growth. This is consistent with the assumption made here of no central necrosis occurring, which would tend to balance the effects of peripheral mitosis. For the same data, and this value of b , the limiting peripheral width W for the tumor sphere is found from equation (12) to be 1.15×10^{-3} cm. The efficacy and sensitivity of the model to values of b is clear when one notes that, for corresponding data, the value of W when $b=0$ is negative! Furthermore, the parameters lie in the regime (10) of complete stability (despite the absence of necrosis).

In one and two dimensional structures, the expression (13) involves hyperbolic functions and modified Bessel functions respectively. While one-dimensional models are of interest primarily for their relative analytic simplicity (while still retaining the basic physics of the problem), the two- and three-dimensional models do have relevance for experimental cultures in vitro.

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