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Note On A Diffusion Model of Tissue Growth

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Mathematical Analysis.

The growth of cell population is governed by a conservation law of mass or cell volume. The assumptions and analytical details on how to derive the conservation law have been discussed elsewhere [1], [2] and only a summary of results is given here. Following [2], we consider the growth of a cell culture in a small tube with a small constant cross sectional area, α, and the three interfacial heights $z_0(t), z_g(t), z_i(t)$ to separate the cell culture from the ambient medium, dividing from nondividing cells, and living from dead cells respectively. The rate of cell proliferation S (volume created per unit volume of viable cells) is a function of the nutrient consumption $\sigma(z,t)$ and inhibitor production $\beta(z,t)$ such that

$$S(\sigma,\beta) = \begin{cases} = s\,, \text{ a constant}\,, & \text{for } \sigma > \sigma_\ell\,,\ \beta < \beta_\ell \\ = 0\,, \text{ otherwise} \end{cases}$$

where σ_ℓ is the critical nutrient concentration below which the cells die, and β_ℓ is the critical inhibitor concentration above which mitosis is inhibited. It is assumed that the column of necrotic debris loses cell volume by diffusion of waste material outward at a rate proportional to its volume with λ the proportionality constant. The conservation of mass law is [2]

$$\frac{dz_0}{dt} = s[z_0(t) - \max(z_g(t), z_i(t))] - \lambda z_i(t) \tag{1}$$

subject to initial conditions

$$z_0(0) = h_0,\ z_i(0) = z_g(0) = 0\,.$$

We need to find the relationships between $z_i(t), z_g(t)$, and $z_0(t)$, and to accomplish this we must solve the diffusion equations for the uniform nutrient consumption σ and inhibitor production β. (Since the time-scale for growth is large compared with a typical diffusion time, it is assumed that the culture is in a state of diffusive equilibrium at all times).

This part of our model does not differ from that of [2] and so we merely note his results here. Thus we find from the nutrient diffusion equation for σ

$$\frac{d^2\sigma}{dz^2} = \frac{C}{k}\ ,\quad z_i \le z \le z_0$$

that

$$\left.\begin{aligned} &\sigma = \sigma_\infty\,, && z \ge z_0 \\ &\sigma = \frac{C}{2k}(z^2 - z_0^2) + \frac{C}{k} z_i(z_0 - z) + \sigma_\infty\,, && z_0 \ge z \ge z_i \\ &\sigma = \sigma_i\,, && z_i \ge z \ge 0 \end{aligned}\right\} \tag{2}$$

and

$$z_0 - z_i = \left[\frac{2k}{C}(\sigma_\infty - \sigma_t)\right]^{\frac{1}{2}} = h_c \tag{3}$$

with σ_∞ being the nutrient concentration in the ambient medium, C the constant rate of nutrient consumption, k the diffusivity constant of the nutrient and h_c the critical height of the cell culture. When the culture reaches this critical height h_c, the cells at the bottom of the vial ($z = 0$) start to die.

In distinction to [2], it is assumed that the source of the chemical inhibitor is produced at a non-uniform rate throughout the necrotic region. The diffusion equation for the inhibitor concentration β is

$$\begin{array}{ll} \frac{d^2\beta}{dz^2} = -\frac{P}{\kappa}\left(1 - \frac{bz}{z_i}\right), & z \le z_i \quad , \quad 0 \le b \le 1 \\ = 0, & z \ge z_i \end{array} \tag{4}$$

subject to the conditions that $\frac{d\beta}{dz} = 0$ at $z = 0$ (i.e. no inhibitor flux through the tube), $\beta = 0$ at $z = z_0$ (i.e. the contaminant is removed from the ambient fluid), and β and $\frac{d\beta}{dz}$ are continuous at $z = z_i$. The parameter b used to measure the degree of nonuniformity of the inhibitor production rate, P is the inhibitor production rate, and κ is the inhibitor diffusivity constant. The solution to this system is

$$\left.\begin{array}{ll} \beta = 0, & z \ge z_o \\ \beta = \frac{P}{\kappa} z_i (z_0 - z)(1 - \frac{b}{2}), & z_i \le z \le z_0 \\ \beta = -\frac{P}{\kappa}[\frac{z^2}{2} - z_i(z_0 - \frac{z_i}{2}) - \frac{b}{6z_i}(z^3 + z_i^2(2z_i - 3z_0))], & z \le z_i \end{array}\right\}. \tag{5}$$

When mitotic inhibition is effective the inhibitor concentration β is greater than β_t in the layer $z_i \le z \le z_g$. This concentration is determined by

$$\beta_t = \frac{P}{\kappa} z_i (z_0 - z_g)(1 - \frac{b}{2}). \tag{6}$$

Note that inhibition is first evident when $z_g = z_i$ and

$$\beta_t = \frac{P}{\kappa} z_i (z_0 - z_i)(1 - \frac{b}{2}). \tag{7}$$

The growth of cell population occurs in three distinct stages:

Stage 1: All cells are alive and proliferating so that a period of exponential growth exists until the onset of necrosis, and $z_0(t)$ satisfies the condition

$$\frac{h_0}{h_c} \le \frac{z_0(t)}{h_c} \le 1.$$

The conservation law (1) becomes

$$\frac{dz_0}{dt} = s z_0(t) \tag{8}$$

with the initial condition

$$z_0(0) = h_0.$$

Thus,

$$z_0(t) = h_0 e^{st}, \qquad z_g(t) = z_i(t) = 0 \tag{9}$$

which is valid for times $0 \le t \le t_1$ up until $h_0 = h_c$

$$\text{i.e.} \quad z_0(t_1) = h_c = h_0 e^{st_1} . \tag{10}$$

Hence, the cell culture reaches the critical height h_c at

$$t_1 = \frac{1}{s} \ln \left(\frac{h_c}{h_0} \right) .$$

The growth will, therefore, be exponential for times in

$$0 \leq t \leq \frac{1}{s} \ln \left(\frac{h_c}{h_0} \right) . \tag{11}$$

Stage 2: (Onset of necrosis). The proliferation rate at the bottom of the vial ($z = 0$) begins to slow down and cells begin to die. During this stage, the culture has a two-layer structure. In the outer layer, the cells grow exponentially. Inside this region, a necrotic layer forms so that a period of growth retardation exists, due to cell death, which lasts from the onset of necrosis until $\beta = \beta_\ell$ at the necrotic interface $z = z_i$. The volume of the necrotic debris begins to increase as does the concentration of the inhibitor β. As the growth rate slows down, it can lead to a steady or dormant state in which the volume loss due to necrosis is balanced by the volume gained due to cell division. Hence, under certain conditions, inhibition is not necessary for the existence of a dormant state. If the steady state is not reached, however, a third stage is initiated. The conservation law (1) in this stage becomes

$$\frac{dz_0}{dt} = sz_0(t) - (s + \lambda) z_i(t) \tag{12}$$

with $z_0 - z_i = h_c$ and solution given by

$$\frac{z_0(t)}{h_c} = 1 + \frac{1}{\gamma} - \frac{1}{\gamma} e^{-\lambda(t - t_1)}, \qquad z_g(t) = z_i(t) = z_0(t) - h_c \tag{13}$$

where $\gamma = \dfrac{\lambda}{s}$.

The inhibitor is produced non-uniformly in the necrotic region, and $z_g(t) > z_i(t)$ after $\beta = \beta_\ell$ at $z = z_i$. Thus, inhibition is first evident when $z_g = z_i$ and from (7) and (13) we find that

$$\frac{z_i}{h_c} = \frac{Q^2}{2 - b} = \frac{z_g(t)}{h_c} \tag{14}$$

at the onset of necrosis, where the dimensionless parameter Q is given by

$$Q^2 = \frac{\beta_\ell \kappa C}{(\sigma_\infty - \sigma_\ell) k P} . \tag{15}$$

Q^2 is, therefore, a measure of the competing effects of nutrient consumption/diffusion and inhibitor production/diffusion. As mentioned earlier, under certain conditions a steady state or a third stage is initiated. These cutoff conditions depend critically on the parameters Q, b and γ (see below).

As $z_g(t)$ moves ahead of $z_i(t)$,

$$\frac{z_i}{h_c} \leq \frac{Q^2}{2 - b} .$$

Therefore,

$$\frac{z_o}{h_c} = \frac{z_i}{h_c} + 1 \leq 1 + \frac{Q^2}{2-b}. \tag{16}$$

If necrosis balances growth in this stage then (12) becomes

$$\frac{dz_0}{dt} = 0 = (s+\lambda)h_c - \lambda z_0(t) \tag{17}$$

and

$$\frac{z_0(t)}{h_c} \leq 1 + \frac{1}{\gamma}. \tag{18}$$

Since $z_0(t_1) = h_c$, the range of z_0 for this stage is

$$1 \leq \frac{z_0(t)}{h_c} \leq \min\left\{1 + \frac{1}{\gamma}, 1 + \frac{Q^2}{2-b}\right\}. \tag{19}$$

Thus, if

$$1 + \frac{Q^2}{2-b} \geq 1 + \frac{1}{\gamma},$$

equilibrium has been reached at time t in $t_1 \leq t < \infty$, and the development is completed in this stage. Otherwise

$$1 + \frac{Q^2}{2-b} < 1 + \frac{1}{\gamma},$$

and a further stage of growth ensues.

To find the time t_2, when the inhibitor β reaches the critical value β_c, consider equation (13) for $t = t_2$, i.e.

$$1 + \frac{Q^2}{2-b} = 1 + \frac{1}{\gamma} - \frac{1}{\gamma}e^{-\lambda(t_2 - t_1)},$$

or equivalently

$$t_2 = t_1 - \frac{1}{\lambda}\ln\left(1 - \frac{Q^2\gamma}{2-b}\right). \tag{20}$$

Thus at time t_2 given by (20) inhibition will start, and growth retardation due to cell death will last for times in the interval

$$t_1 \leq t \leq t_2 = t_1 - \frac{1}{\lambda}\ln\left(1 - \frac{Q^2\gamma}{2-b}\right). \tag{21}$$

Stage 3: This is a period of retarded growth due to death of cells and chemical inhibition of mitosis which begins when $\beta = \beta_c$ at the necrotic interface $z_i(t)$ and lasts until the dormant steady state is achieved. During this stage, the cell culture has a three layer structure. In the outer layer, the growth of cells is normal as in Stage 1. Inside this layer, the rate of cell proliferation is below normal, due to inhibition of mitosis, and consists of viable cells only. In the innermost layer, there is accumulation of necrotic debris.

The conservation law now is

$$\frac{dz_0}{dt} = s\{z_0(t) - z_g(t)\} - \lambda z_i(t). \tag{22}$$

From equations (3),(6) and (15) we obtain

$$z_g(t) = z_0(t) - \frac{2\kappa\beta_\ell}{Pz_i(2-b)} = z_i(t) + h_c - \frac{Q^2h_c^2}{z_i(2-b)}. \tag{23}$$

Thus (22) has solution

$$\frac{z_0(t)}{h_c} = 1 + \frac{Q}{\sqrt{\gamma(2-b)}}\left[1 - \left(1 - \frac{Q^2\gamma}{2-b}\right)e^{-2\lambda(t-t_2)}\right]^{\frac{1}{2}}, \quad \text{for } t_2 \le t < \infty. \tag{24}$$

As $t \to t_2$ and $t \to \infty$ in (24) we get the range of $z_0(t)$

$$1 + \frac{Q^2}{2-b} \le \frac{z_0(t)}{h_c} \le 1 + \frac{Q}{\sqrt{\gamma(2-b)}}.$$

It is easily seen that

$$\lim_{t\to\infty} z_i = \left(\frac{2\kappa\beta_\ell}{P\gamma(2-b)}\right)^{1/2} = \lambda$$
$$\lim_{t\to\infty} z_g = \lambda(1-\gamma) + h_c$$
$$\lim_{t\to\infty} z_0 = \lambda + h_c$$

yielding the limiting asymptotic values for this model. The effect of non-uniform inhibitor production is apparent via the term λ.

References

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