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THE EFFECTS OF TUMOR GROWTH FACTORS ON THE GROWTH RATE OF CELL CULTURES

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Abstract—A mathematical model of growth control in a cell culture in which Tumor Growth Factors (TGF) diffuse through intercellular spaces and act locally is constructed.

Growth factors are defined as polypeptides that stimulate cell proliferation [1]. In particular, tumor growth factors (TGF) are multifunctional. They can either stimulate cell proliferation or they can inhibit cell mitosis depending on their concentration in the cell culture [2]. Their molecules diffuse through intercellular spaces and regulate the growth of cells in a culture or *in vivo*. Growth factors can be produced by certain type of cells. There is evidence that there exist cells that produce their own growth factors and therefore respond to them in a growth-stimulatory manner [1].

The object of this model is to study a growth problem which examines the behavior of a cell culture subject to the presence of tumor growth factors. We let $C(r,t)$ denote the concentration of TGF and $r = R$ the size of the cell culture. The diffusion equation that determines this concentration is

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

where D is the diffusion coefficient and λ is the TGF production rate (molecules per unit volume per second). The source term $S(r)$ is defined by

$$S(r) = \begin{cases} 1, & \text{for } 0 \le r \le R_\theta \\ -1, & \text{for } R_\theta \le r \le R \end{cases}$$

and is a measure of uniform production of growth factor within the cell culture. The variables $r(t), R_\theta(t)$, and $R(t)$ are functions of time t under the assumption of diffusive equilibrium. In particular, R_θ is defined by $C(R_\theta) = C_\theta$ with C_θ being a threshold value for the growth factor. When the concentration of TGF is greater than this critical concentration C_θ, cell mitosis is inhibited. On the other hand, if the TGF concentration is less than C_θ, mitotic activity is stimulated [2]. Thus, if $C(r)$ is monotone decreasing, then $C(r) > C_\theta$ in the region $r < R_\theta$ and $C(r) < C_\theta$ in the region $r > R_\theta$. The region $0 \le r \le R_\theta$ then consists of viable cells with proliferation rate below normal due to inhibition of mitosis while the region $R_\theta \le r \le R$, which is formed after the concentration of TGF has fallen below the critical value C_θ, consists of cells with normal proliferation rate. The system to be solved is

$$D\frac{d^2C}{dr^2} = \begin{cases} |\lambda|, & \text{for } 0 \le r \le R_\theta \\ -|\lambda|, & \text{for } R_\theta \le r \le R \end{cases}$$

I thank Professor John A. Adam for the stimulating conversations and interaction which inspired this work.

subject to the conditions that $C(r)$ and $\frac{dC}{dr}$ are continuous at $r = R_\theta$, $\frac{dC}{dr} = 0$ at $r = 0$, and $D\frac{dC}{dr}(R) + PC(R) = 0$ [3]. Growth factors are depleted more rapidly compared to other media components under normal culture conditions [1]. If $\lambda > 0$, we get

$$D\frac{d^2C}{dr^2} = \begin{cases} \lambda, & \text{for } 0 \le r \le R_\theta \\ -\lambda, & \text{for } R_\theta \le r \le R \end{cases}$$

which represents a *sink* of growth factor in the region $0 \le r \le R_\theta$ and a *source* of growth factor in the region $R_\theta \le r \le R$. On the other hand, if $\lambda < 0$ we get

$$D\frac{d^2C}{dr^2} = \begin{cases} -\lambda, & \text{for } 0 \le r \le R_\theta \\ \lambda, & \text{for } R_\theta \le r \le R \end{cases}$$

which represents a *source* of growth factor in the region $0 \le r \le R_\theta$ and a *sink* of growth factor in the region $R_\theta \le r \le R$. The following changes of variables are made

$$y = \frac{C}{C_\theta}$$

and

$$z = \left[\frac{|\lambda|}{DC_\theta}\right]^{1/2} r$$

to yield the system

$$\frac{d^2y}{dz^2} = \begin{cases} \frac{\lambda}{|\lambda|}, & \text{for } 0 \le z \le z_\theta \\ -\frac{\lambda}{|\lambda|}, & \text{for } z_\theta \le z \le z_R \end{cases} \tag{1}$$

with $\frac{dy}{dz}(0) = 0$, $y(z_\theta) = 1$, and $\frac{dy}{dz}(z_R) + \eta y(z_R) = 0$ where $\eta = P[C_\theta/D|\lambda|]^{1/2}$. If we let $\hat{\lambda} = \lambda/|\lambda|$, then the solution to system (1) can be written as

$$y(z) = \frac{\hat{\lambda}}{2}(z^2 - z_\theta^2) + 1, \quad 0 \le z \le z_\theta \tag{2}$$

and

$$y(z) = -\frac{\hat{\lambda}}{2}z^2 + 2\hat{\lambda}z_\theta z + 1 - \frac{3}{2}\hat{\lambda}z_\theta^2, \quad z_\theta \le z \le z_R. \tag{3}$$

Now, if we know the concentration of a tumor growth factor at some point in an intercellular space of the cell culture, we can consider the following expression for the rate of change of the size of the culture at that point [4].

$$\frac{dR}{dt} = \int_{r_0}^{R} C(r)\,\hat{S}(r)\,dr, \tag{4}$$

where $\hat{S}(r)$ is the cell proliferation rate and $r(0) = r_0$. Using the change of variables

$$R = \left[\frac{DC_\theta}{|\lambda|}\right]^{1/2} z_R$$

$$C(r) = C_\theta(y(z))$$

and

$$r_0 = \left[\frac{DC_\theta}{|\lambda|}\right]^{1/2} z_0$$

the growth Equation (4) becomes

$$\frac{dz_R}{dt} = C_\theta \int_{z_0}^{z_R} S(z)\,y(z)\,dz,$$

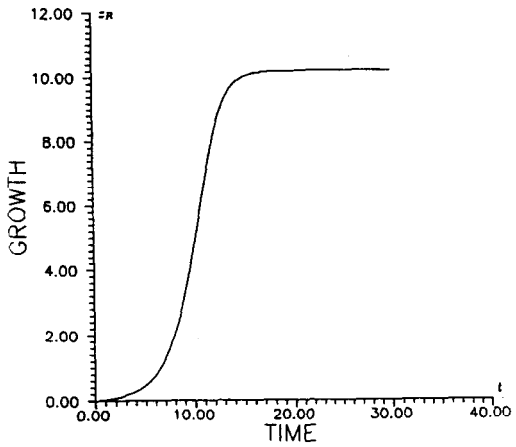

Figure 1. The rate of change for the cell culture size for negative λ.

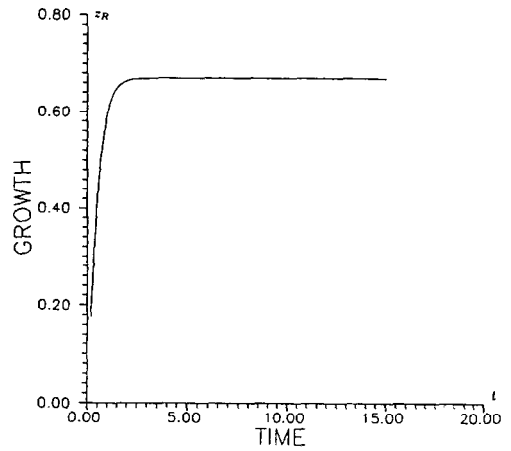

Figure 2. The rate of change for the cell culture size for postive λ.

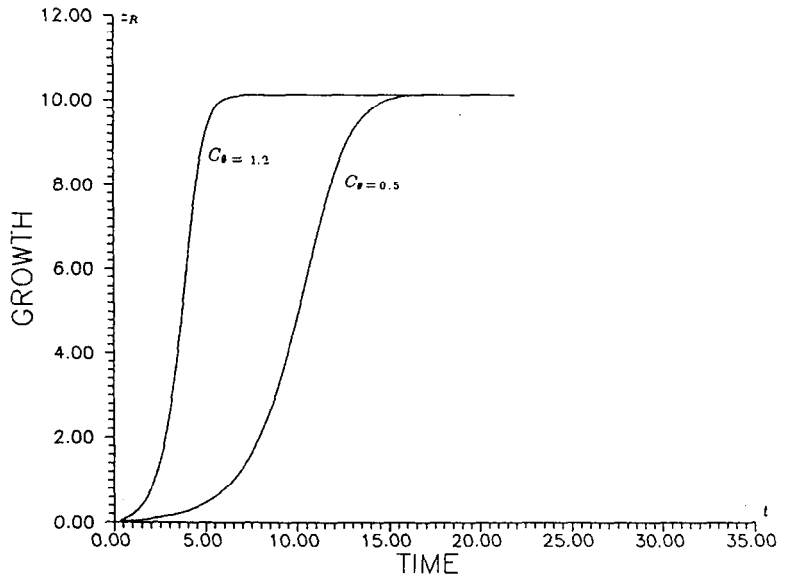

Figure 3. The growth of the cell culture for different values of the critical Tumor Growth Factor (TGF) concentration.

where $S(z) = \hat{S}(r)$ is the cell proliferation rate. Since we are dealing with two regions, (z_0, z_θ) and (z_θ, z_R), we let $S(z) = S_1$ in (z_0, z_θ) and $S(z) = S_2$ in (z_θ, z_R). The growth equation now takes the form

$$\frac{dz_R}{dt} = C_\theta S_1 \int_{z_0}^{z_\theta} y_1(z)\,dz + C_\theta S_2 \int_{z_\theta}^{z_R} y_2(z)\,dz,$$

where $y_1(z)$ and $y_2(z)$ are given by Equations (2) and (3) respectively. This growth equation is solved numerically using a fourth order Runge-Kutta method.

The rate of change of the culture size is illustrated in Figures 1 and 2 for negative and positive λ, respectively. As mentioned above, negative λ represents a *source* of growth factor in the region $0 \leq r \leq R_\theta$ and a *sink* of growth factor in the region $R_\theta \leq r \leq R$. This means that TGF is diffused in the region in which mitosis is inhibited causing higher concentrations of TGF and, therefore, an increase in inhibition of mitosis, and is depleted in the region in which mitosis is stimulated causing an increase in the mitotic activity. Hence, rapid growth is observed followed by growth retardation, and then steady state is reached (i.e., the rate at which the cells are created balances the rate at which cells are inhibited). Positive λ represents a *sink* of TGF in the region $0 \leq r \leq R_\theta$ and a *source* of growth factor in the region $R_\theta \leq r \leq R$. This

means that TGF is diffused in the mitotically active region and is depleted in the region of inhibited growth. As a result, stimulation of mitosis decreases and inhibition of mitosis increases (i.e., exponential growth does not last long, it is almost nonexistent). The growth of the cell culture for different values of the critical TGF concentration is illustrated in Figure 3. As C_θ increases, it takes longer for growth inhibition to take place since the critical value to be reached is greater. Consequently, stimulation of mitosis lasts longer than for smaller values of C_θ. Study of growth factors is important due to their involvment in cancer. There is evidence that growth factors increase transcription of certain proto-oncogenes [1].

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