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CELLULAR GROWTH CONTROL AND TRAVELLING WAVES OF CANCER*

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Abstract. One of the major differences between cancer cells and normal cells is an increase in cell proliferation, caused by the escape of cancer cells from the normal biochemical regulation of mitosis. This increased proliferation results from genetic mutations causing the expression of oncogenes, or the loss of anti-oncogenes. A reaction diffusion model is developed for the initial growth of a tumour following an oncogenic mutation of a single cell. This model incorporates the possibility of an immune response to the cancer cells. Numerical solutions of the model rapidly evolve into an advancing wave of tumour cells and a receding wave of normal cells. The author analyses the ordinary differential equation system governing these travelling wave solutions and obtains a lower bound on the wave speed. Under biologically relevant approximations, a necessary and sufficient condition is derived for the existence of a travelling wave solution, and it is shown how the qualitative form of the wave fronts of normal and mutant cells depends on the parameter values. Finally, an analytic approximation for the wave fronts in the case of small mutations is derived. Biologically, these results suggest that, for certain types of mutations, which are quantified, growing tumours can initially contain a significant proportion of normal cells. Moreover, this model predicts that there is a critical level of immune response, which again is quantified, above which the immune system prevents the initial growth of the tumour.

Key words. cancer, travelling waves, oncogenes, reaction diffusion

1. Introduction. Cancer cells and normal cells differ genetically, due to mutations that are often caused by carcinogenic agents. This genetic difference is reflected in a number of phenotype differences, and perhaps the most notable of these is a marked increase in the rate of cell division. Over the last decade, experimental research has led to the characterization of a number of *oncogenes*, whose expression in tumour cells promotes cell proliferation [16], [26], [27]. More recently, *anti-oncogenes* have been discovered, whose role in normal cells is to suppress excessive cell proliferation and whose loss can give rise to a tumour cell [15], [21].

Both oncogenes and anti-oncogenes affect cell division via growth regulatory chemicals [1], [14, Chap. 9], [28]. The growth of cells in a normal tissue is controlled by a number of such chemicals, which either activate or inhibit cell proliferation. This complex regulatory system stabilizes a normal tissue while allowing increased cell division when appropriate, for example, in wound healing [22], [23]. However, oncogenic and anti-oncogenic mutations remove a cell from these growth controls, so that the mutant cell may divide uncontrollably, giving rise to a tumour. In this paper, we use a mathematical model to investigate the breakdown of growth control in a tumour cell and the extent to which the expansion of the tumour can be checked by an immune response to the mutant cells.

During the 1970s, a number of theoretical studies of growth control in cancer were published. These divide broadly into two categories: those considering the expansion of a tumour in the presence of biochemical regulators of mitosis and those investigating possible instabilities in normal proliferative control. In the first category, Greenspan [12], [13] presented a detailed model for tumour growth based on the availability of nutrients and growth regulators, while Glass [11] and Shymko and Glass [24] showed that the growth of a tumour could be limited or unlimited, depending on parameters affecting the concentration of a biochemical inhibitor of cell division. Adam [2]–[5]

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subsequently extended the work of Glass [11] to consider the effects of tumour geometry and spatial nonuniformity. Recently, Michelson and Leith [17] investigated the role of autocrine and paracrine regulators in tumour growth, by varying the parameters in a simple logistic model for cell proliferation. A similar approach was used by Albert, Freedman, and Perelson [6], who considered the effects of time-varying coefficients in a predator-prey model for the immune response to cancer cells; these variations were attributed to changes in the concentrations of mitotic regulators.

However, our work in this paper is more closely related to the second category of study. In particular, Wheldon [29] showed that mutations affecting the control of cell growth by a single biochemical inhibitor are of two distinct types, depending on whether the production of, or response to, the chemical is affected by the mutation. In a similar study, Bell [8] used a stochastic model to derive the probability of a mutant cell giving rise to a macroscopic tumour. Both of these studies consider cell growth regulated by a single biochemical inhibitor in a spatially homogeneous tissue. Subsequent experimental work has shown the importance of both biochemical activators and inhibitors of cell division and has enabled the various types of mutations to be characterized in terms of the corresponding oncogenes and anti-oncogenes. We will build on these experimental results to develop a reaction diffusion model in which cellular growth control results from the interaction of a number of biochemical regulators. Moreover, we will investigate the stabilizing effect of an immune response to the tumour cells.

2. The governing equations. We consider mixed populations of normal and mutant cells, with densities $n(\mathbf{x}, t)$ and $m(\mathbf{x}, t)$ per unit volume; here $\mathbf{x}$ and t denote space and time coordinates. Our model is intended to be a generic representation of the competition between normal and mutant cells. For simplicity, we consider only a single cell type and we neglect the details of interactions between the cells and the extracellular matrix. We suppose that both cell types are motile and, following a number of previous authors (see [19] for review), we represent their movement by linear diffusion with diffusion coefficient D in both cases. In reality, the mutant cells may have increased motility due to mutations affecting cell-cell adhesion, but we neglect such effects to focus specifically on mitotic regulation. We suppose that cell growth is regulated by j chemicals, which are produced by the cells on which they act. We take the rate of production of each chemical per normal cell to have the constant value hc_i^e, while the division rate per normal cell is $R_0 r(n + m)s_1(c_1)\cdots s_j(c_j)$. Here $c_1(\mathbf{x}, t), \ldots, c_j(\mathbf{x}, t)$ are the concentrations of the chemical growth regulators, and the function s_i is strictly increasing if chemical i is an activator of cell division and strictly decreasing if chemical i is an inhibitor. The constant R_0 is the growth rate in normal tissue, for which $n = n^e$, $m = 0$, $c_i = c_i^e$ $(1 \le i \le j)$, and therefore $r(n^e)s_1(c_1^e)\cdots s_j(c_j^e) = 1$; we assume that the chemicals control cell division independently, so that $r(n^e) = s_i(c_i^e) = 1$ for all i. This growth rate will normally be balanced by a corresponding rate of cell death. The function r reflects the physical constraints on the growth of the total cell population, and we take $r(n) = (N - n)/(N - n^e)$; here N is the maximum possible density of cells.

There are three possible mutations that a cell can undergo with respect to growth control.

1. The mutant cell detects extracellular chemical concentration incorrectly. We suppose that chemical 1 is detected to have concentration $\xi c_1(\mathbf{x}, t)$ by the mutant cells, where the positive constant ξ is greater than 1 if chemical 1 is a mitotic activator, and less than 1 if chemical 1 is an inhibitor.

2. The mutant cell produces chemical at an inappropriate rate. We suppose that chemical 1 is produced at rate Phc_1^e per mutant cell, where the positive constant P is

greater than 1 if chemical 1 is an activator, and less than 1 if chemical 1 is an inhibitor. (Recall that hc_i^e is the rate of chemical production per normal cell.)

3. The mutant cells partially escape from their dependence on biochemical regulators. We suppose that the rate of mutant cell division is increased by the additive factor $s_0 r(n+m)$ per cell, where s_0 is a positive constant.

Oncogenes and anti-oncogenes corresponding to each of these three types of mutation have been characterized in recent experiments [27], [28].

Our model equations are conservation equations for normal cells, mutant cells, and each associated chemical, in a spatially heterogeneous mixture of normal and mutant cells, and have the following form:

(2.1)

$$\begin{aligned}
\frac{\partial n}{\partial t} &= \overbrace{D\nabla^2 n}^{\text{Cell migration}} + \overbrace{R_0 n r(n+m) s_1(c_1)\cdots s_j(c_j)}^{\text{Biochemically regulated cell division}} - \overbrace{dn}^{\text{Cell death}}, \\
\frac{\partial m}{\partial t} &= D\nabla^2 m + mr(n+m)[R_0 s_1(\xi c_1) s_2(c_2)\cdots s_j(c_j) + s_0] - dm - \overbrace{\delta m}^{\text{Immune response}}, \\
\frac{\partial c_1}{\partial t} &= D_c\nabla^2 c_1 + hc_i^e(n+Pm) - d_c c_1, \\
\frac{\partial c_i}{\partial t} &= \underbrace{D_c\nabla^2 c_i}_{\text{Chemical diffusion}} + \underbrace{hc_i^e(n+m)}_{\text{Chemical production by cells}} - \underbrace{d_c c_i}_{\text{Chemical decay}}
\end{aligned}$$

$(2 \le i \le j)$. Here D_c is the chemical diffusion coefficient, which we assume to be the same for each chemical. We take cell death and chemical decay to be simple first-order processes, with rate constants d and d_c, respectively. Since $n = n^e$, $m = 0$, $c_i = c_i^e$ $(1 \le i \le j)$ is an equilibrium state, and $r(n^e) = s_i(n^e) = 1$ for all i, we have $d = R_0$ and $d_c = hne$.

We represent the immune response to mutant cells by including an additional first-order death term, with linear death rate δ. In animals, the ability of the immune system to selectively kill tumour cells has long been realised [7], [10]. Moreover, one of the most rapidly developing treatments for human cancer is *immunotherapy*, in which the natural immune response to cancer is enhanced [18], [20], [25].

We consider these equations in one space dimension, with $-\infty < x < \infty$, and we take the initial conditions to be

$$n(x,0) = \begin{cases} 0, & -L < x < L, \\ n^e, & |x| > L, \end{cases} \qquad m(x,0) = \begin{cases} n_e, & -L < x < L, \\ 0, & |x| > L, \end{cases} \qquad c_i(x,0) \equiv c_i^e$$

$(1 \le i \le j)$. Here L is half a typical cell diameter, so that these conditions correspond to the mutation of a single cell, centred at $x = 0$. The appropriate boundary conditions are $n = n^e$, $m = 0$, and $c_i = c_i^e$ at $x = \pm\infty$. The one-dimensional geometry facilitates mathematical analysis, and numerical solutions in two and three dimensions with radial symmetry are qualitatively very similar to these one-dimensional solutions. However, we have not investigated the effects of asymmetries in these more realistic geometries.

We nondimensionalize system (2.1) using the following rescalings, with * denoting a dimensionless quantity:

$$n^* = n/n^e, \quad m^* = m/n^e, \quad c_i^* = c_i/c_i^e, \quad x^* = x/L, \quad t^* = R_0 t,$$

$$D^* = D/(R_0 L^2), \quad D_c^* = D_c/(R_0 L^2), \quad s_0^* = s_0/R_0, \quad h^* = h/(R_0 n^e),$$

$$\delta^* = \delta/R_0, \quad N^* = N/n^e, \quad s_i^*(c_i^*) = s_i(c_i), \quad r^*(n^*) = r(n).$$

Henceforth, we drop the asterisks for notational simplicity. The dimensionless governing equations are then

$$\frac{\partial n}{\partial t} = D\nabla^2 n + nr(n+m)s_1(c_1)\cdots s_j(c_j) - n, \tag{2.2a}$$

(2.2b)

$$\frac{\partial m}{\partial t} = D\nabla^2 m + mr(n+m)s_1(\xi c_1)s_2(c_2)\cdots s_j(c_j) + s_0 mr(n+m) - (1+\delta)m,$$

$$\frac{\partial c_1}{\partial t} = D_c\nabla^2 c_1 + h(n + Pm - c_1), \tag{2.2c}$$

$$\frac{\partial c_i}{\partial t} = D_c\nabla^2 c_i + h(n + m - c_i), \tag{2.2d}$$

$(2 \le i \le j)$ subject to

$$n(x,0) = \begin{cases} 0, & -1 < x < 1, \\ 1, & |x| > 1, \end{cases} \qquad m(x,0) = \begin{cases} 1, & -1 < x < 1, \\ 0, & |x| > 1, \end{cases} \qquad c_i(x,0) \equiv 1, \tag{2.3a}$$

$$n = 1, \quad m = 0, \quad c_i = 1 \quad \text{at } x = \pm\infty. \tag{2.3b}$$

Since (2.2d) holds for each c_i with $2 \le i \le j$, with the same end conditions, the value of $c_i(x,t)$ is the same for each $i \ge 2$. (This assumes uniqueness of solution to (2.2) subject

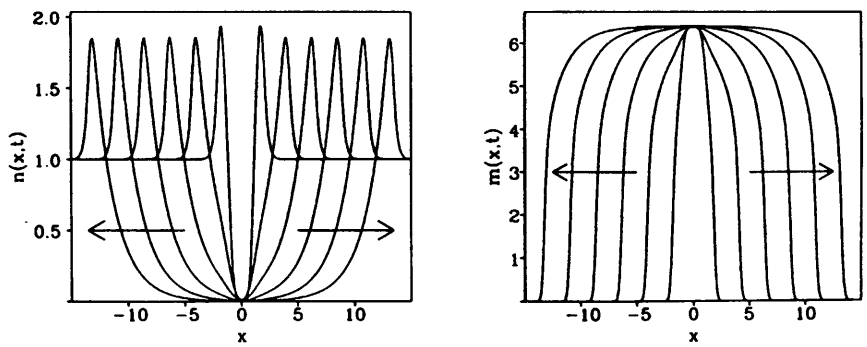

FIG. 1. *The numerical solution of* (2.2) *subject to* (2.3) *for parameter values* $\xi = 2$, $P = 2$, $s_0 = 2$, $\delta = 1.5$, $D = 0.01$, $D_c = 1$, $h = 20$, $k = 15$, $N = 10$, $j_A = 1$, $j_I = 1$, *with chemical* 1 *an activator of mitosis. We plot* n *and* m *as functions of* x *at equally spaced times (dimensionless time interval* $= 7.5$*). For brevity, we omit the solutions for* c_1 *and* c_2*; these also have travelling wave form, with* $c_1 \approx 12$ *and* $c_2 \approx 6$ *near the origin, and* $c_1 = c_2 = 1$ *for large* $|x|$*. The arrows indicate the direction in which the solution moves as* t *increases. This solution corresponds to an advancing wave of mutant cells and a receding wave of normal cells. The growing tumour is composed entirely of mutant cells, at a density of about six times that of cells in normal tissue. The solution is qualitatively very similar if more chemicals are introduced.*

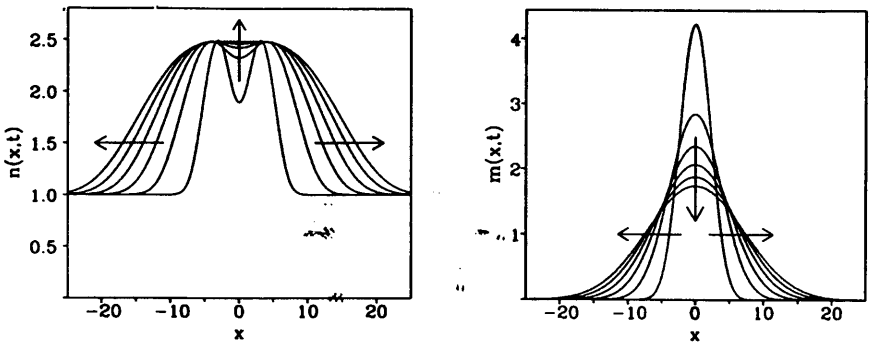

FIG. 2. *The numerical solution of* (2.2) *subject to* (2.3) *for parameter values* $\xi = 1$, $P = 0.2$, $s_0 = 0$, $\delta = 0$, $D = 0.01$, $D_c = 1$, $h = 20$, $k = 15$, $N = 10$, $j_A = 1$, $j_I = 1$, *with chemical* 1 *an inhibitor of mitosis. We plot n and m as functions of x at equally spaced times (dimensionless time interval* = 333). *For brevity, we omit the solutions for* c_1 *and* c_2; *these are very closely approximated by* $n + Pm$ *and* $n + m$, *respectively. The arrows indicate the direction in which the solution moves as t increases. This solution corresponds to a rapid increase in both normal and mutant cell densities near the origin, followed by a very slow outward spread of these cells. The timescale over which the solution evolves is very long compared to that in Figs.* 1 *and* 3. *The solution is qualitatively very similar if more chemicals are introduced.*

to (2.3); see Britton [9, Chap. 5] and papers cited there for the proof of uniqueness.) Henceforth, we write $c_i(x, t) \equiv c(x, t)$ $(i \geq 2)$.

It remains to consider the functional forms of $s_i(c)$, which are subject to the constraint $s_i(1) = 1$. We suppose that j_A of the chemicals are activators of mitosis and that the remaining $j_I = j - j_A$ are inhibitors. For the activators, s_i must be an increasing function, and we take $s_i(c) = c$. For the inhibitors, s_i must be decreasing, and we take $s_i(c) = k/[1 + (k - 1)c]$; for simplicity, we suppose that the positive constant $k(>1)$ is the same for each inhibitor.

We solved (2.2) subject to (2.3) numerically for a range of parameter values. The general form of the solutions is as illustrated in Fig. 1: a wave of mutant cells moving out from the origin, with a corresponding receding wave of normal cell density. In the

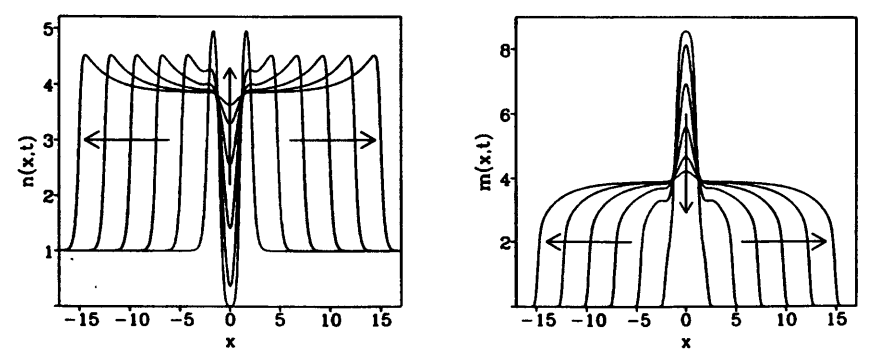

FIG. 3. *The numerical solution of* (2.2) *subject to* (2.3). *The parameter values are as in Fig.* 1 *except that* $P = 6.5$. *We plot n and m as functions of x at equally spaced times (dimensionless time interval* = 7.5). *For brevity, we omit the solutions for* c_1 *and* c_2; *these also have travelling wave form, with* $c_1 \approx 30$ *and* $c_2 \approx 8$ *near the origin, and* $c_1 = c_2 = 1$ *for large* $|x|$. *The arrows indicate the direction in which the solution moves as t increases. This solution corresponds to an advancing wave of mutant cells and a receding wave of normal cells. The growing tumour has a cell density of eight times that in normal tissue and is composed of a roughly equal mixture of normal and mutant cells. The solution is qualitatively very similar if more chemicals are introduced.*

figure, the dimensionless wave speed is about 0.25. This speed increased with $|\xi - 1|$ and s_0, and decreased with δ, but seemed essentially independent of P. Indeed, when $\xi = 1$ and $s_0 = \delta = 0$, so that the mutation was only with respect to the production of chemical 1, the solution did not have travelling wave form, but rather there was a very slow diffusion of mutant cells out from the origin, as illustrated in Fig. 2. This marked qualitative difference between mutations affecting the response to, and production of, mitotic regulators was noted previously by Wheldon [29] in a simpler, spatially homogeneous model for tumour growth. In most cases, we found that behind the wave front $n = 0$ and $m > 1$, as in Fig. 1, with the value of m increasing with $|\xi - 1|$, $|P - 1|$, and s_0, and decreasing with δ. However, for certain parameter values, both n and m were nonzero behind the front, as illustrated in Fig. 3; this case only arose for fairly large values of $|P - 1|$. The analysis we present below predicts all of these phenomena.

3. Steady states. We begin our analysis of (2.2) by considering the spatially homogeneous steady states. These satisfy $c_1 = n + Pm$ and $c = n + m$, with

$$n = nr(n + m)s_1(n + Pm)s_2(n + m)\cdots s_j(n + m),$$

$$(1 + \delta)m = s_0 mr(n + m) + mr(n + m)s_1(\xi n + \xi Pm)s_2(n + m)\cdots s_j(n + m).$$

We divide the steady states into four categories.

(i) $n = m = 0$.

(ii) $m = 0$, $n \neq 0$. Then n must satisfy

$$\left(\frac{N - n}{N - 1}\right) n^{j_A}\left[\frac{k}{1 + (k - 1)n}\right]^{j_I} = 1$$

$$\Leftrightarrow n = \left(\frac{N - 1}{N - n}\right)^{1/j_A}\left[\frac{1 + (k - 1)n}{k}\right]^{j_I/j_A} \equiv R_n(n). \tag{3.1}$$

One solution of this is clearly $n = 1$, which is the dimensionless cell density in normal tissue. When $m \equiv 0$, a biological requirement of the model is that this solution $n \equiv 1$ is stable to small, local perturbations in n or c_i, and straightforward linear analysis shows that this holds if and only if $r'(1) + s_1'(1) + \cdots + s_j'(1) < 0$, that is,

$$j_I + \frac{1}{N - 1} > j_A + \frac{j_I}{k}. \tag{3.2}$$

This is independent of the diffusion coefficients since the spatially homogeneous mode is the most unstable. In particular, since we anticipate that $N \gg 1$, this implies that $j_I \geq j_A$. In this case, straightforward calculation shows that R_n is a strictly increasing function with strictly increasing derivative on $(0, N)$. Moreover, $R_n(0) > 0$ and $R_n(n) \to +\infty$ as $n \to N^-$. Therefore (3.1) has exactly two roots on $(0, N)$; the stability condition (3.2) implies that $R_n'(1) > 1$, so that $n = 1$ is the larger of these two roots.

(iii) $n = 0$, $m \neq 0$. We first consider the case of chemical 1 being a mitotic activator. The corresponding equation for m is then

$$m = \left(\frac{1 + \delta}{P\xi}\right)^{1/j_A}\left[\frac{N - 1}{N - m} - \frac{s_0}{1 + \delta}\right]^{1/j_A}\left[\frac{1 + (k - 1)m}{k}\right]^{j_I/j_A} \equiv R_m(m). \tag{3.3}$$

Again, R_m is a strictly increasing function with strictly increasing derivative on any regions of $(0, N)$ in which $R_m(m) > 0$, and $R_m(m) \to +\infty$ as $m \to N^-$. Moreover, $R_m(m) = 0$ on $(0, N) \Leftrightarrow s_0/(1 + \delta) > 1 - 1/N \Leftrightarrow \delta < s_0 N/(N - 1) - 1$. In this case, (3.3) will have exactly one root on $(0, N)$, while, if $\delta > s_0 N/(N - 1) - 1$, there will be either two roots or no roots (Fig. 4). Since, for each $m \in (0, N)$, $R_m(m)$ increases with δ, the condition

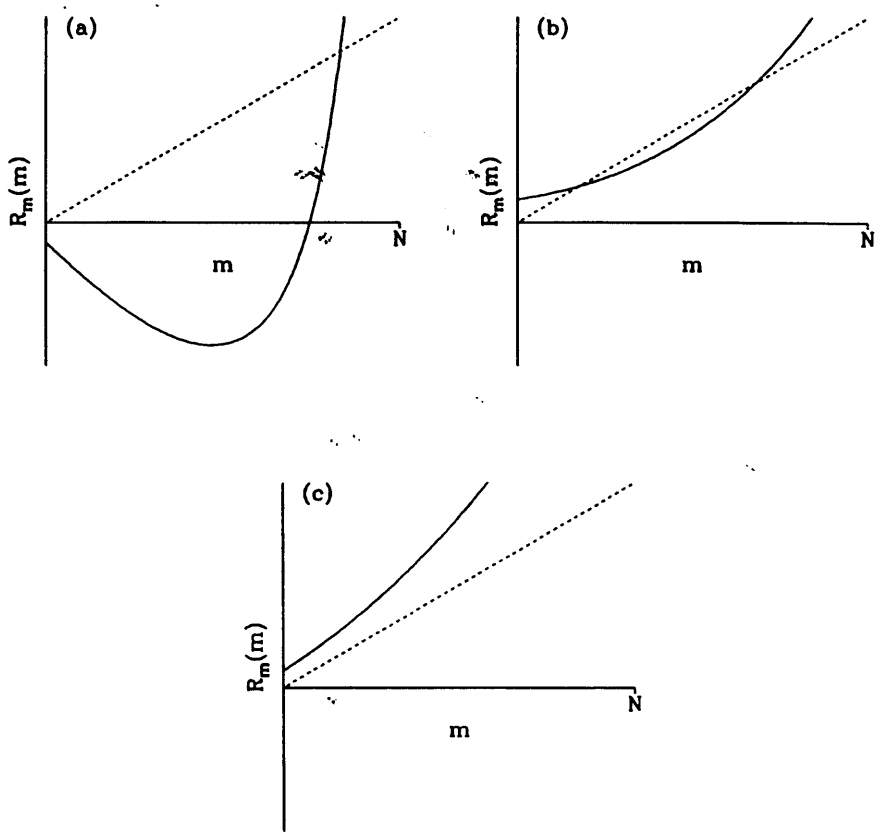

FIG. 4. *The qualitative forms of the function* $R_m(m)$, *defined in* (3.3), *for different values of* δ. (a) $\delta < s_0N/(N-1) - 1$; (b) $s_0N/(N-1) < \delta < \delta_c(P, \xi, s_0)$; (c) $\delta > \delta_c(P, \xi, s_0)$. *The number of roots of* (3.3) *on* $(0, N)$ *is* 1, 2, *and* 0, *respectively. The solid line represents* $y = R_m(m)$, *and the dotted line represents* $y = m$.

for there to be no roots has the form $\delta > \delta_c(P, \xi, s_0)$. It is straightforward to show that the analogous results hold when chemical 1 is an inhibitor.

(iv) $n, m \neq 0$. In this case, the values of n and m must satisfy

$$s_1(v)f(u) = 1,$$

$$s_0r(u) + s_1(\xi v)f(u) = 1 + \delta,$$

where $u = n + m$, $v = n + Pm$ and $f(u) = r(u)s_2(u)\cdots s_j(u)$. Suppose first that chemical 1 is an activator. Then $s_1(\xi v) = \xi s_1(v)$, so that

$$s_0r(u) = 1 + \delta - \xi \Rightarrow u = N - (N-1)\left(\frac{1 + \delta - \xi}{s_0}\right) = u_s, \quad \text{say}$$

$$\Rightarrow v = \frac{1}{f(u_s)} = v_s, \quad \text{say}.$$

Therefore, provided that $P \neq 1$, there is a unique solution for n and m, given by $n = n_s = (Pu_s - v_s)/(P-1)$, $m = m_s = (v_s - u_s)/(P-1)$. (If $P = 1$, we have two independent equations for $u = v$, and thus there are no steady states off the coordinate axes.) We require both n_s and m_s to be positive, and thus this solution is relevant if and only if

$$v_s > u_s \quad \text{and} \quad Pu_s > v_s \Leftrightarrow u_s > 0 \quad \text{and} \quad P > v_s/u_s > 1.$$

When chemical 1 is an inhibitor, we have $v_s = s_1^{-1}[1/f(u_s)]$, where u_s satisfies

$$1 + \delta = s_0 r(u_s) + f(u_s)s_1(\xi s_1^{-1}[1/f(u_s)])$$
$$= s_0\left(\frac{N - u_s}{N - 1}\right) + \frac{kf(u_s)}{\xi k f(u_s) + 1 - \xi} \equiv \Phi(u_s). \tag{3.4}$$

The number of roots of this equation depends on the form of Φ. When $j_A = 0$, f is strictly decreasing, and thus Φ is also strictly decreasing, with $\Phi(N) = 0$, so that (3.4) has either zero or one root, depending on $\Phi(0)$. When $j_A > 0$, the form of Φ is more difficult to determine. In this case,

$$f(u) = \left(\frac{N - u}{N - 1}\right)u^{j_A}\left[\frac{k}{1 + (k - 1)u}\right]^{j_I - 1},$$

which can easily be shown to have a unique maximum on $(0, N)$, say at $u = u_m$, with $f(0) = 0$ and $f(N) = 0$. Therefore $kf(u_s)/[\xi k f(u_s) + 1 - \xi] \equiv F(u_s)$ also has a unique maximum at $u_s = u_m$, with $F(0) = F(N) = 0$. Moreover, $F'(0)$ is strictly positive if

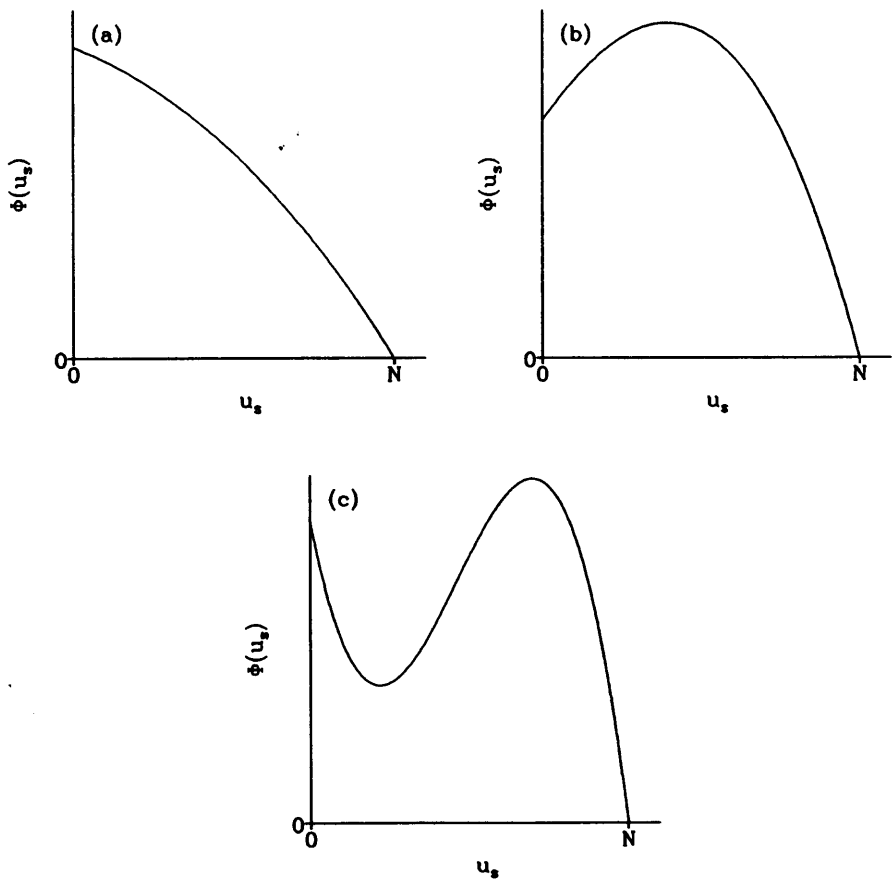

FIG. 5. *The qualitative form of the function* $\Phi(u_s)$, *defined in* (3.4), *on the interval* $(0, N)$, *when the parameter* s_0 *is sufficiently small.* (a) $j_A = 0$; (b) $j_A = 1$; (c) $j_A \geq 2$. *In* (c), *we have shown a case for which the value of* Φ *at its unique local maximum is greater than* $\Phi(0)$; *however, the value can also be less than* $\Phi(0)$, *depending on the parameter values. Although we have only proved these to be the qualitative forms of* Φ *when* s_0 *is sufficiently small, numerical investigation suggests that they hold for a wide range of values of* s_0.

$j_A = 1$ and zero if $j_A \geq 2$. The function Φ is given by adding the linear term $s_0(N - u_s)/(N - 1)$ to $F(u_s)$, so that $\Phi' = F' - s_0/(N - 1)$. To calculate the general form of Φ, it is therefore necessary to find the zeros of F'', which is algebraically unfeasible, and, moreover, we will not require the full detail of Φ in what follows. However, from the form of F, it is clear that for sufficiently small s_0, the qualitative features of Φ are as illustrated in Fig. 5. Numerical investigation suggests that these qualitative forms hold for a wide range of values of s_0. Therefore, when chemical 1 is an inhibitor, there can be up to three steady states with $n, m \neq 0$, depending on the parameter values.

In summary, the model has two nontrivial steady states on the n axis, at $n = 1$ and $n \in (0, 1)$. There will also be at least one steady state on the m-axis, provided that δ is sufficiently small, and, in addition, there may be off-axis equilibria, depending on the parameter values.

4. Travelling wave solutions. The partial differential equation solutions discussed above appear to evolve rapidly to waves moving with constant shape and speed. We therefore look for solutions of the form $n(x, t) = \tilde{n}(z)$, $m(x, t) = \tilde{m}(z)$, $c(x, t) = \tilde{c}(z)$, where $z = x + at$ is the travelling wave variable, with a the dimensionless wave speed. Henceforth, we will only be considering these travelling wave solutions, and we drop the tildes for notational simplicity. Substituting these solution forms into (2.2) gives the following system of ordinary differential equations:

$$an' = Dn'' + nr(n + m)s_1(c_1)s_2(c)\cdots s_j(c) - n, \tag{4.1a}$$

$$am' = Dm'' + mr(n + m)s_1(\xi c_1)s_2(c)\cdots s_j(c) + s_0 mr(n + m) - (1 + \delta)m, \tag{4.1b}$$

$$ac_1' = D_c c_1'' + h(n + Pm - c_1), \tag{4.1c}$$

$$ac' = D_c c'' + h(n + m - c) \tag{4.1d}$$

$(2 \leq i \leq j)$, where prime denotes d/dz.

A solution of (4.1) corresponding to a travelling wave solution of (2.2) must originate from the steady state $n = c_1 = c = 1$, $m = m' = n' = c_1' = c' = 0$, and, to investigate the trajectories leaving this equilibrium point, we consider linear stability. Calculation of the stability matrix at this steady state shows that an eigenvector $(\hat{n}, \hat{n}', \hat{m}, \hat{m}', \hat{c}_1, \hat{c}_1', \hat{c}, \hat{c}')$ corresponding to an eigenvalue λ must satisfy $\hat{n}' = \lambda\hat{n}$, $\hat{m}' = \lambda\hat{m}$, $\hat{c}_1' = \lambda\hat{c}_1$, and $\hat{c}' = \lambda\hat{c}$, with

$$[D\lambda^2 - a\lambda + r'(1)]\hat{n} + r'(1)\hat{m} + s_1'(1)\hat{c}_1 + s'(1)\hat{c} = 0, \tag{4.2a}$$

$$[D\lambda^2 + a\lambda + A]\hat{m} = 0, \tag{4.2b}$$

$$h\hat{n} + Ph\hat{m} + [D_c\lambda^2 - a\lambda - h]\hat{c}_1 = 0, \tag{4.2c}$$

$$h\hat{n} + h\hat{m} + [D_c\lambda^2 - a\lambda - h]\hat{c} = 0. \tag{4.2d}$$

Here $A = s_0 + s_1(\xi) - 1 - \delta$ and $s(c) = s_2(c)\cdots s_j(c)$. This implies that λ must satisfy either

$$D\lambda^2 - a\lambda + A = 0 \tag{4.3}$$

or

$$Q(\lambda) \equiv (D_c\lambda^2 - a\lambda - h)(D\lambda^2 - a\lambda - 1/(N - 1)) - h[s'(1) + s_1'(1)] = 0. \tag{4.4}$$

Therefore, for all parameter values, there is an eigenvalue with positive real part; the trajectory corresponding to the travelling wave solution will leave this equilibrium point along the eigenvector corresponding to the eigenvalue with smallest positive real part.

TABLE 1

The comparison between numerical solutions of (2.2) *and the model prediction* (6.2) *of the lower limit on D_c for the wave of normal cell density to have a bump. For four sets of parameter values, we list the critical value of D_c given by* (6.2) *and the value of* $\max_{-\infty<x<\infty} n(x, t = 100)$ *when this value of D_c is used in a numerical solution of* (2.2). *The fact that, at this critical value, n is slightly greater than* 1 *even at a large time such as t = 100 is expected intuitively: The peak in n gradually reduces in height as t increases, and in the critical case its height decreases to* 1 *only in the limit as $t \to \infty$. For each of the four parameter sets, condition* (6.2) *is valid, since* (4.6) *is satisfied at the critical value of D_c. In the table, we also list the predicted wave speed $a_{theor} = 2\sqrt{D(s_0 + s_1(\xi) - 1 - \delta)}$ and the wave speed a_{obs} in the numerical solution of* (2.2) *at t = 100: in each case, the comparison is very good. The third column indicates whether chemical* 1 *is an activator or inhibitor of mitosis (denoted by* A *and* I, *respectively).*

j_A	j_I	Chem. 1	P	ξ	s_0	δ	a_{theor}	a_{obs}	Crit. D_c	n_{max}
1	1	A	1.0	2.0	1.0	1.5	0.2	0.1999	0.44	$1 + 6.4 \times 10^{-10}$
1	3	A	2.7	2.0	2.0	2.0	0.283	0.287	0.99	$1 + 9.1 \times 10^{-5}$
1	2	I	0.1	0.65	1.0	1.0	0.197	0.1967	1.32	$1 + 9.6 \times 10^{-8}$
1	1	I	1.0	0.8	0.2	0.1	0.162	0.159	0.65	$1 + 1.2 \times 10^{-7}$

Now the root of (4.3) with the smallest (positive) real part is

$$\Lambda = \frac{a - \sqrt{a^2 - 4AD}}{2D}. \tag{4.5}$$

Suppose first that this has a smaller real part than any of those roots of (4.4) that have positive real part. Then, since $m \geq 0$ and the eigenvector corresponding to Λ has a nonzero m component, we require that $\Lambda \in \mathbb{R}$, that is, $a \geq 2\sqrt{AD}$. (We will show in §5 that $A > 0$ is a necessary condition for our model to predict tumour growth.) Numerical simulations suggest that, in solutions of the partial differential equations, waves in fact move with the minimum possible speed, $2\sqrt{AD}$, whenever the parameter values are such that Λ is the eigenvalue with the smallest positive real part (see Table 1); this phenomenon is familiar from scalar reaction-diffusion equations such as the Fisher equation (see [19] for review). Therefore, we assume that $a = 2\sqrt{AD} \Rightarrow \Lambda = \sqrt{A/D}$. Now both of the bracketed quadratics in (4.4) have one positive and one negative real root, and $Q(0) = j_I - j_A + 1/(N-1) - j_I/k \geq 0$, from (3.2). Therefore (4.4) has exactly two roots with positive real part, and these real parts are greater than Λ if and only if $Q'(\sqrt{A/D}) < 0$ and $Q(\sqrt{A/D}) > 0$ when $a = 2\sqrt{AD}$. Straightforward calculation shows that these inequalities hold if and only if

$$\frac{D_c}{D} < 2 + \frac{h}{A}\left[1 - \frac{s_1'(1) + s'(1)}{A + 1/(N-1)}\right] \tag{4.6}$$

and $D_c > D$ (note that $s_1'(1) + s'(1) = j_A - j_I + j_I/k$, which can be either positive or negative). The second of these will obviously hold for biologically relevant parameter values, so that (4.6) is a necessary and sufficient condition for Λ to be the eigenvalue with smallest positive real part. When this condition is not satisfied, the travelling wave speed in numerical solutions of (2.2) appears to always be greater than $2\sqrt{AD}$, typically by about 10% or 20%; however, we have been unable to investigate the wave speed analytically in this case.

5. A simplified travelling wave system. Cells in vivo move at speeds of only a few cell diameters per hour, while the cell division cycle lasts several days, and thus we anticipate that the dimensionless cell diffusion coefficient $D \ll 1$. Also, we expect the kinetics of the regulatory chemicals to be very fast compared to cell division, so that

$h \gg 1$. Thus, to a first approximation, we can assume $D = 0$ and $h = \infty$. System (4.1) then reduces the following two coupled ordinary differential equations for $n(z)$ and $m(z)$:

$$dn/d\hat{z} = nf(n + m)s_1(n + Pm) - n, \tag{5.1a}$$

$$dm/d\hat{z} = mf(n + m)s_1(\xi n + \xi Pm) + s_0 mr(n + m) - (1 + \delta)m, \tag{5.1b}$$

where $\hat{z} = z/a$, and, as previously, $f = r \cdot s_2 \cdot \cdots \cdot s_j$. We look for a solution of this system subject to the initial condition $n = 1$, $m = 0$ at $\hat{z} = -\infty$.

The steady state values of n and m for (5.1) are the same as for the full system (2.2). In particular, (1, 0) is a steady state. (Here we use coordinates (n_0, m_0) to denote the point $n = n_0$, $m = m_0$ in phase space.) The stability matrix of (5.1) at this steady state is given by

$$\begin{bmatrix} f'(1) + s_1'(1) & f'(1) + Ps_1'(1) \\ 0 & s_0 + s_1(\xi) - 1 - \delta \end{bmatrix}.$$

Now (3.2) implies that $f'(1) + s_1'(1) < 0$, and thus a necessary and sufficient condition for the existence of a solution satisfying $n = 1$, $m = 0$ at $\hat{z} = -\infty$ is

$$s_0 + s_1(\xi) > 1 + \delta. \tag{5.2}$$

Provided that this condition is satisfied, there is a unique trajectory originating from (1, 0), which corresponds to a travelling wave solution of (2.2). We now consider where this trajectory terminates. We have $f(N) = 0$, so that n' and m' are both nonpositive on $n + m = N$, and similarly $n' \geq 0$, $m' > 0$ on $n + m = 1$, provided that (5.2) holds, since $s_1(\xi + \xi(P - 1)m) > s_1(\xi)$ for $m > 0$ when chemical 1 is either an activator or an inhibitor. Also, $n' = 0$ on the m-axis and $m' = 0$ on the n-axis, so that the trapezoid enclosed by $n + m = 1$, $n + m = N$, and the coordinate axes is a confined set, $\mathscr{S}$ say. Moreover, for the trajectory leaving (1, 0),

$$\left.\frac{dm}{dn}\right|_{(1,0)} = \frac{s_0 + s_1(\xi) - 1 - \delta - f'(1) - s_1'(1)}{f'(1) + Ps_1'(1)} \in [-\infty, -1) \cup (0, \infty],$$

since when chemical 1 is either an activator or an inhibitor, $(P - 1)s_1'(1) \geq 0$. Therefore this trajectory enters $\mathscr{S}$, and thus terminates at some equilibrium point in $\bar{\mathscr{S}}$.

Condition (5.2) has important implications for the remaining equilibrium points. We have shown that when chemical 1 is an activator, there is a steady state with $n = 0$, provided that $\delta < \delta_c(P, \xi, s_0)$, and that this steady state then satisfies $m = R_m(m)$, defined in (3.3). Now $R_m(1) = [(1 + \delta - s_0)/(P\xi)]^{1/j_A}$, and thus (5.2) and the fact that $P \geq 1$ together imply that $R_m(1) < 1$. Therefore $\delta_c > s_0 + s_1(\xi) - 1$, and there is exactly one steady state on the m-axis with $m > 1$, say $m = M$, whenever (5.2) holds; if $\delta > s_0 N/(N - 1) - 1$, there will be another solution on the m-axis with $m < 1$ (see Fig. 4). A similar argument shows that this result is also true when chemical 1 is an inhibitor.

The stability matrix at $(0, M)$ is

$$\begin{bmatrix} f(M)s_1(PM) - 1 & 0 \\ M[f'(M)s_1(\xi PM) + \xi f(M)s_1'(\xi PM) + s_0 r'(M)] & M[f'(M)s_1(\xi PM) + \xi Pf(M)s_1'(\xi PM) + s_0 r'(M)] \end{bmatrix}.$$

Now, when chemical 1 is an activator, $[f'(M)s_1(\xi PM) + \xi Pf(M)s_1'(\xi PM) + s_0 r'(M)] < 0$, since $R_m'(M) > 1$, and a similar argument holds in the inhibitor case: Intuitively, these inequalities both hold because $m = M$ is stable to small perturbations in m when

n is constrained to be zero. Therefore, if $f(M)s_1(PM) < 1$, $(0, M)$ is a stable node, while, if $s_1(PM)f(M) > 1$, $(0, M)$ is a saddle point, with stable manifold along the m-axis.

Consider now steady states off the coordinate axes. When chemical 1 is an activator, we have shown that there is exactly one such steady state, and that it lies in the positive quadrant, provided that $u_s > 0$ and $P > v_s/u_s > 1$. Here $v_s = 1/f(u_s)$ and $r(u_s) = (1 + \delta - \xi)/s_0$. Condition (5.2) therefore implies that $r(u_s) < 1$, so that $u_s > 1$; also, $u_s < N \Leftrightarrow r(u_s) > 0 \Leftrightarrow 1 + \delta > \xi$. Now $v_s/u_s = 1/[u_s f(u_s)] = [R_n(u_s)/u_s]^{j_A}$, where R_n is defined in (3.1), and we have shown that $R_n(u_s) > u_s$ when $1 < u_s < N$. Thus, when chemical 1 is an activator, this steady state is located within $\mathscr{S}$ if and only if $1 + \delta > \xi$ and $P > v_s/u_s$.

Continuing the case of chemical 1 being a mitotic activator, $(0, M)$ is an equilibrium point, so that $\xi PMf(M) + s_0 r(M) = 1 + \delta$. Therefore

$$\begin{aligned}(0, M) \text{ is a saddle point} &\Leftrightarrow 1 > s_1(PM)f(M) = PMf(M)\\ &\Leftrightarrow r(M) > (1 + \delta - \xi)/s_0 = r(u_s)\\ &\Leftrightarrow M < u_s,\end{aligned}$$

since r is a decreasing function. Now, when $P = v_s/u_s$, $Pu_s f(u_s) = 1$. Therefore $P\xi u_s f(u_s) + s_0 r(u_s) = \xi + s_0 r(u_s) = 1 + \delta$, so that $(0, \mu_s)$ is an equilibrium point of (5.1). However, $u_s > 1$, and $(0, M)$ is the unique equilibrium point on the portion $1 \le m \le N$ of the m-axis. Therefore, when $P = v_s/u_s$ and $1 + \delta > \xi$ (so that $u_s < N$), $M = u_s$. However, u_s is independent of the parameter P while M increases monotonically with P. Thus $(0, M)$ is a saddle point if and only if $P > v_s/u_s$ and $1 + \delta > \xi$; that is, if and only if $(n_s, m_s) \in \mathscr{S}$. If $(n_s, m_s) \notin \mathscr{S}$, the trajectory leaving $(1, 0)$ must terminate at $(0, M)$. Straightforward calculation shows that (n_s, m_s) is a stable steady state whenever it lies in $\mathscr{S}$. This suggests that, in this case, the trajectory leaving $(1, 0)$ terminates at (n_s, m_s), since it cannot terminate at $(0, M)$. Formally, there remains the outstanding possibility of a semistable limit cycle in $\mathscr{S}$, but extensive numerical solution suggests that such a limit cycle never exists.

When chemical 1 is an inhibitor, we have shown that for steady states off the coordinates axes, $u = n + m$ and $v = n + Pm$ satisfy $\Phi(u) = 1 + \delta$, $v = s_1^{-1}[1/f(u)]$; the function Φ is defined in (3.4). Now $\Phi(1) = s_0 + s_1(\xi)$, and thus (5.2) implies that $\Phi(1) > 1 + \delta$. Moreover, $f'(1) = 1 + j_A - j_I + (j_I - 1)/k - 1/(N - 1)$. We anticipate that k will be large, while j_I will be relatively small, so that $1 > 1/(N - 1) > j_I/k$. Thus, if $j_I > j_A$, $f'(1) < 0$, while if $j_I = j_A$, $f'(1) > 0$. In the former case, we thus have $u_m < 1$ (u_m is the unique maximum of f and F on $[0, N]$), so that $\Phi = F + s_0 r$ is monotonically decreasing on $[1, N]$, with $\Phi(1) > 1 + \delta$ and $\Phi(N) = 0$. Therefore there is a unique root, $u = u_s$ say, on $(1, N)$.

When $j_I = j_A$, a straightforward calculation shows that $f'' < 0$ on $[1, N]$, provided that $1/(N - 1) > j_I/k$ is satisfied. Then $F'' = f''/[1 + f]^2 - f'^2/[1 + f]^3$ is strictly negative on $[1, N]$. Thus F' decreases monotonically on $[1, N]$, as does $\Phi' = F' - s_0/(N - 1)$. Thus Φ either decreases monotonically on $[1, N]$ or has a unique maximum on $[1, N]$. In either case, since $\Phi(1) > 1 + \delta$ and $\Phi(N) = 0$, there is exactly one root for u, u_s, say, on $[1, N]$.

The values of n and m corresponding to the root u_s are given by $n = n_s = (v_s - Pu_s)/(1 - P)$, $m_s = (u_s - v_s)/(1 - P)$, where $v_s = s_1^{-1}[1/f(u_s)]$. Since $n_s + m_s = u_s \in (1, N)$, this point lies in $\mathscr{S}$ if and only if $P < v_s/u_s < 1$. Now $u = 1$ is the largest root of $f(u)s_1(u) = 1$, and $f(N) = 0$. Therefore

$$u_s > 1 \Rightarrow f(u_s)s_1(u_s) < 1 \Rightarrow s_1(u_s) < 1/f(u_s) \Rightarrow u_s > s_1^{-1}[1/f(u_s)] = v_s,$$

since s_1 is a decreasing function. Therefore the steady state (n_s, m_s) lies in $\mathscr{S}$ if and only if $P < v_s/u_s$. Now

$$\begin{aligned}(0, M) \text{ is a saddle point} &\Leftrightarrow 1 > s_1(PM)f(M)\\ &\Leftrightarrow s_1^{-1}[1/f(M)] < PM\\ &= (1/\xi)s_1^{-1}[\{1 + \delta - s_0 r(M)\}/f(M)]\\ &\Leftrightarrow s_1(\xi s_1^{-1}[1/f(M)]) > \{1 + \delta - s_0 r(M)\}/f(M)\\ &\Leftrightarrow \Phi(M) > 1 + \delta = \Phi(u_s)\\ &\Leftrightarrow M < u_s,\end{aligned}$$

since both u_s and M are >1, and $\Phi(1) > 1 + \delta$, $\Phi(N) = 0$, with $\Phi(u) = \Phi(u_s)$ on $(1, N) \Leftrightarrow u = u_s$. From the definition of $(0, M)$ as a steady state, it follows that when $P = v_s/u_s$, $\Phi(M) = \Phi(u_s)$, and thus $M = u_s$. However, u_s is independent of P, while M increases as P decreases below 1. Thus $(0, M)$ is a saddle point if and only if $P < v_s/u_s$, that is, if and only if $(n_s, m_s) \in \mathscr{S}$. These conditions may not hold for any positive value of P, since it may happen that $f(u_s) > k$, in which case $v_s = s_1^{-1}[1/f(u_s)] < 0$. As in the activator case, (n_s, m_s) is a stable steady state whenever it lies in $\mathscr{S}$.

We have shown the following:

(i) System (5.1) has a solution of the form required for a travelling wave if and only if $s_0 + s_1(\xi) > 1 + \delta$;

(ii) When chemical 1 is a mitotic activator, the trajectory corresponding to this solution is a heteroclinic connection between the equilibrium points $(1, 0)$ and $(0, M)$ if $1 + \delta < \xi$. Otherwise, the trajectory connects these points if and only if $P < v_s/u_s$, and, for larger values of P, the trajectory links $(1, 0)$ with (n_s, m_s);

(iii) When chemical 1 is a mitotic inhibitor, the trajectory corresponding to the solution connects $(1, 0)$ and $(0, M)$ if and only if $P > v_s/u_s$, and for smaller values of P, the trajectory links $(1, 0)$ with (n_s, m_s).

Typical phase portraits in the various parameter regimes are illustrated in Fig. 6. For given values of the other parameters, as P increases above v_s/u_s in the activator case or decreases below v_s/u_s in the inhibitor case, n_s increases from zero, while m_s decreases from u_s, with $n_s + m_s$ having the constant value u_s. In the activator case, both the trace T and the determinant Δ of the stability matrix at (n_s, m_s) increase linearly with $1/(P - 1)$. Moreover, the trace is always strictly negative, while the determinant is zero at $P = v_s/u_s$. Therefore $(T^2 - 4\Delta)$ decreases monotonically from a strictly positive value as P increases above v_s/u_s. Now (n_s, m_s) is a node or a focus according to the sign of $(T^2 - 4\Delta)$. Thus, for given values of the other parameters, (n_s, m_s) will either be a stable node for all P or will change from a node to a focus as P increases, according to whether $\lim_{P\to\infty}(T^2 - 4\Delta)$ is positive or negative. Explicit calculation of the stability matrix shows that the condition for (n_s, m_s) to be a focus for sufficiently large P is

$$[u_s v_s f'(u_s) + \xi - (\xi - 1)u_s f(u_s)]^2 < \frac{4s_0 u_s}{N - 1}[1 - u_s f(u_s)].$$

In the inhibitor case, (n_s, m_s) can also be either a node or a focus, but the way in which this depends on the parameter values is not so simple.

These results only apply to the travelling wave differential equations under the approximations $h = \infty$ and $D = 0$. However, they are all confirmed in numerical solutions of the full partial differential equation system (2.2), provided that h is fairly large and

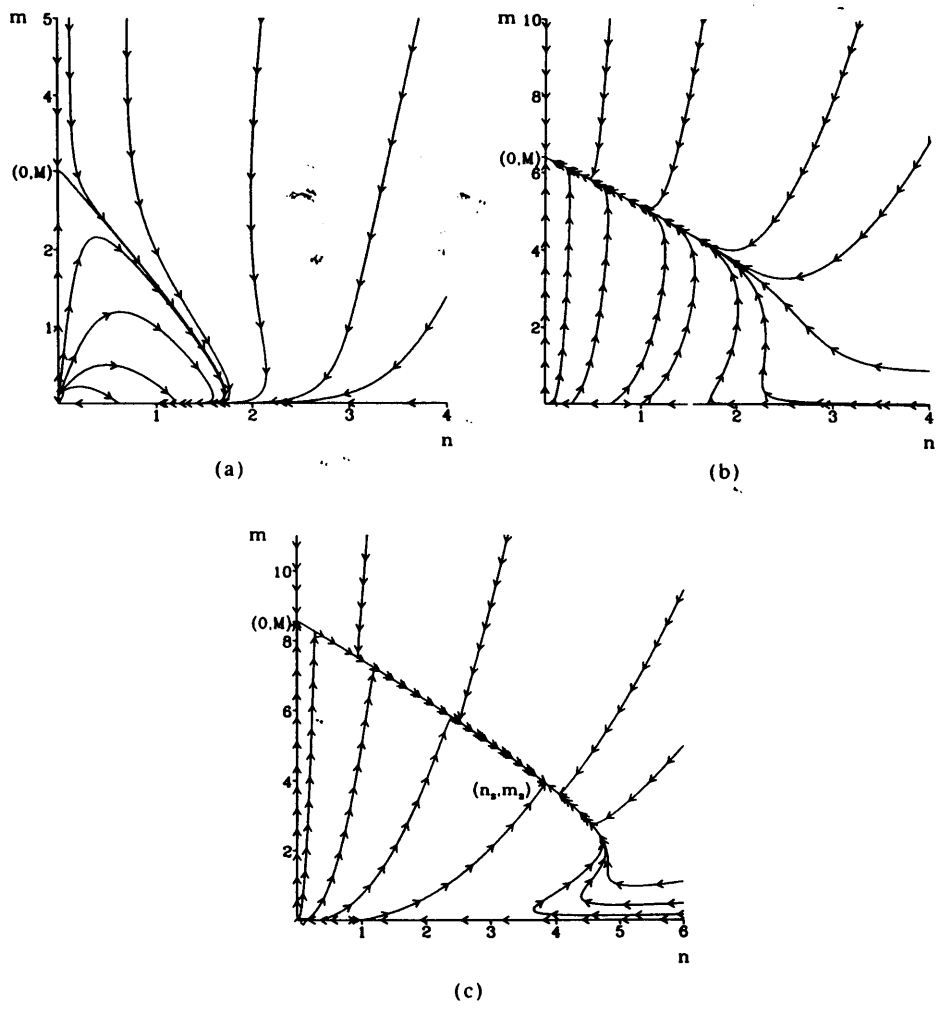

FIG. 6. *Typical phase portraits of* (5.1) *in the various parameter regimes, when chemical* 1 *is a mitotic activator*; (a) $s_0 + \xi < 1 + \delta$. *Here* (1, 0) *is a stable node, and there is not a trajectory corresponding to a travelling wave solution of* (2.2); (b) $s_0 + \xi > 1 + \delta > \xi$, $P < v_s/\mu_s$. *Here* (1, 0) *is a saddle point, and the unique trajectory leaving* (1, 0) *terminates at* (0, M), *which is a stable node. The steady state* (n_s, m_s) *is not in the first quadrant*; (c) $s_0 + \xi > 1 + \delta > \xi$, $P > v_s/u_s$. *Here* (1, 0) *is a saddle point, and the unique trajectory leaving* (1, 0) *terminates at* (n_s, m_s), *which is a stable node; the steady state* (0, M) *is also a saddle point. The actual parameter values used in* (b) *and* (c) *are the same as in Figs.* 1 *and* 3, *respectively; in* (a), *the parameter values are* $\xi = 2$, $P = 2$, $s_0 = 1$, $\delta = 3$, $k = 15$, $N = 10$, $j_A = j_I = 1$.

D is fairly small (see §2 and Figs. 1–3). Moreover, the results do not depend on the value of the wave speed a, which was discussed in §4. Conclusion (i) has particularly important biological implications, since it suggests that a critical level of immune response is required to prevent a tumour developing after an initial mutation. Moreover, when the mutation is only with respect to chemical production, *any* level of immune response is sufficient, since the critical level is zero.

6. The wave shape. One of the most striking features of the partial differential equation solutions illustrated in Figs. 1 and 2 is that the wave of normal cells increases above 1 before decreasing again to its steady state value of 1. Under the approximation

$h = \infty$ and $D = 0$, such a "bump" will occur if and only if $dn/dm|_{(1,0)} > 0$ for the solution trajectory. The analysis of the previous section shows that this condition is simply $Ps_1'(1) + f'(1) > 0$, so that the difference between the chemical production rate in normal and tumour cells must be sufficiently great for a bump to occur. Intuitively, such a bump occurs because the density of biochemical regulators within the growing tumour is such as to promote cell growth, and thus the growth of normal cells near the edge of the tumour is also promoted. Thus, we anticipate that the existence of a bump will depend crucially on the chemical diffusion coefficient D_c as well as the parameter P, and numerical solutions confirm that, for any given values of the other parameters, there will be a bump for sufficiently large D_c. To investigate this further, we return to the behaviour of the full travelling wave equations (4.1) near $z = -\infty$.

We suppose that (4.6) is satisfied and $a = 2\sqrt{AD}$, so that the solution emerges from the initial steady state along the eigenvector corresponding to eigenvalue Λ, defined in (4.5). The validity of the approximation $a = 2\sqrt{AD}$ was discussed in §4. Equations (4.2) then imply that the ratio of the components $\hat{n}$ and $\hat{m}$ of the eigenvector satisfy

$$[A - r'(1) + \{s_1'(1) + s'(1)\}\psi]\hat{n} + [-r'(1) + \{Ps_1'(1) + s'(1)\}\psi]\hat{m} = 0,$$

where $\psi = h/(AD_c/D - 2A - h)$. Now we require that $m \geq 0$, so that $\hat{m} > 0$, while the wave of normal cell density has a bump if and only if $\hat{n} > 0$. Therefore the solution has such a bump if and only if

$$(6.1) \qquad [A - r'(1) + \{s_1'(1) + s'(1)\}\psi] \cdot [-r'(1) + \{Ps_1'(1) + s'(1)\}\psi] < 0.$$

Now, if $\psi > 0$, (4.6) implies that $[A - r'(1) + \{s_1'(1) + s'(1)\}\psi] < 0$, while, if $\psi < 0$, (4.6) implies that $[A - r'(1) + \{s_1'(1) + s'(1)\}\psi] > 0$. In either case, (6.1) holds if and only if $r'(1)/\psi < Ps_1'(1) + s'(1)$. Therefore, when (4.6) holds, the wave of n has a bump if and only if

$$(6.2) \qquad D_c > 2D + (hD/A)[1 - (N-1)\{Ps_1'(1) + s'(1)\}]$$

since $r'(1) = -1/(N-1)$. We must stress that this result does rely on taking the wave speed $a = 2\sqrt{AD}$, which is an approximation based on the observed wave speed in numerical solutions; analytically, we have only shown that $a \geq 2\sqrt{AD}$. However, the result (6.2) agrees very well with numerical solutions of the full partial differential equation system (2.2), as illustrated in Table 1.

7. The wave form. When the mutations giving rise to tumour cells result in only small differences in the growth control parameters, we can derive an analytical approximation to the functional form of the wave fronts. Specifically, we suppose that $\xi = 1 + \varepsilon\xi_\varepsilon$, $s_0 = \varepsilon s_\varepsilon$, and $P = 1 + \varepsilon P_\varepsilon$, where $\varepsilon \ll 1$. When chemical 1 is an activator, ξ_ε and P_ε are positive, and, when it is an inhibitor, they are negative; in both cases, s_ε is positive. Condition (5.2) then implies that $\delta = O(\varepsilon)$ as $\varepsilon \to 0$, say $\delta = \varepsilon\delta_\varepsilon$. In terms of these parameters, (5.1) has the form

$$(7.1a) \qquad \frac{dn}{d\hat{z}} = n[f(n+m)s_1(n + m + \varepsilon P_\varepsilon m) - 1],$$

$$(7.1b) \qquad \frac{dm}{d\hat{z}} = m[f(n+m)s_1(n + m + \varepsilon\xi_\varepsilon n + \varepsilon P_\varepsilon m + \varepsilon\xi_\varepsilon m + \varepsilon^2 P_\varepsilon \xi_\varepsilon m) + \varepsilon s_\varepsilon r(n+m) - 1 - \varepsilon\delta_\varepsilon].$$

We reformulate these equations in terms of the dependent variables $u = n + m$ and $w = n/m$, and we use the rescaled independent variable $\zeta = \varepsilon\hat{z}$. Substituting (7.1a),

(7.1b) into these expressions and simplifying gives

$$\varepsilon \frac{du}{d\zeta} = u[f(u)s_1(u) - 1] + \frac{\varepsilon u}{1+w} \cdot[(P_e + \xi_e)f(u)s_1'(u)u + s_e r(u) - \delta_e] + O(\varepsilon^2), \tag{7.2a}$$

$$\frac{dw}{d\zeta} = -w[\xi_e f(u)s_1'(u)u + s_e r(u) - \delta_e] - \varepsilon u w\left[\frac{P_e \xi_e f(u)}{1+w}\{s_1'(u) + us_1''(u)\} + \frac{1}{2}\xi_e^2 u f(u)s_1''(u)\right] + O(\varepsilon^2). \tag{7.2b}$$

The rescaling of the independent variable that we have used is the only one giving w nonconstant to leading order. We consider these equations on $-\infty < \zeta < \infty$, with initial conditions $u(-\infty) = 1$, $w(-\infty) = 0$ and, to avoid arbitrary translations in ζ, we specify $w(0) = 1$. We look for a solution of (7.2) as a power series in ε, that is,

$$u(\zeta;\varepsilon) = u_0(\zeta) + \varepsilon u_1(\zeta) + \varepsilon^2 u_2(\zeta) + \cdots,$$

$$w(\zeta;\varepsilon) = w_0(\zeta) + \varepsilon w_1(\zeta) + \varepsilon^2 w_2(\zeta) + \cdots.$$

Substituting these into (7.2) and equating coefficients of ε^0 gives

$$0 = u_0[f(u_0)s_1(u_0) - 1],$$

$$\frac{dw_0}{d\zeta} = -w_0[\xi_e f(u_0)s_1'(u_0)u_0 + s_e r(u_0) - \delta_e].$$

These zeroth-order equations are subject to $u_0(-\infty) = 1$, $w_0(-\infty) = 0$, and $w_0(0) = 1$, and thus writing $\nu = s_e + \xi_e s_1'(1) - \delta_e$, we have

$$u_0(\zeta) = 1, \tag{7.3a}$$

$$w_0(\zeta) = e^{-\nu\zeta}. \tag{7.3b}$$

Using these solutions and equating coefficients of ε in (7.2) gives

$$0 = u_1[f'(1) + s_1'(1)] + [(P_e + \xi_e)s_1'(1) + s_e - \delta_e]\frac{1}{1+e^{-\nu\zeta}},$$

$$\frac{dw_1}{d\zeta} = -\nu w_1 - \{\xi_e[f'(1)s_1'(1) + s_1'(1) + s_1''(1)] + s_e r'(1)\}e^{-\nu\zeta}u_1 - \left[\frac{P_e\xi_e\{s_1'(1) + s_1''(1)\}}{1+e^{+\nu\zeta}} + \frac{1}{2}\xi_e^2 s_1''(1)e^{-\nu\zeta}\right].$$

These equations are subject to $u_1(-\infty) = w_1(-\infty) = w_1(0) = 0$, which gives

$$u_1(\zeta) = -\frac{(P_e + \xi_e)s_1'(1) + s_e - \delta_e}{f'(1) + s_1'(1)}\frac{1}{1+e^{-\nu\zeta}}, \tag{7.4a}$$

$$w_1(\zeta) = \frac{1}{\nu}\left[\frac{\{(P_e+\xi_e)s_1'(1) + s_e - \delta_e\}\{\xi_e[f'(1)s_1'(1) + s_1'(1) + s_1''(1)] + s_e r'(1)\}}{f'(1) + s_1'(1)} - P_e\xi_e\{s_1'(1) + s_1''(1)\}\right]e^{-\nu\zeta}\log\left(\frac{1+e^{+\nu\zeta}}{2}\right) + \frac{\xi_e^2 s_1''(1)}{2\nu}[e^{-2\nu\zeta} - 1]. \tag{7.4b}$$

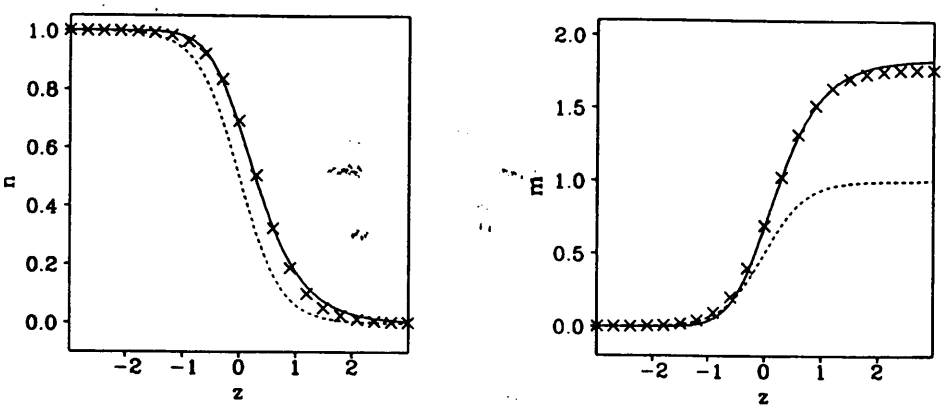

FIG. 7. *The zeroth-order and first-order approximations to the travelling wave solutions for n and m. The approximations are calculated as* $n = uw/(1+w)$, $m = u/(1+w)$, *with the zeroth- and first-order approximations to u and w as* $\varepsilon \to 0$ *given by* (7.3) *and* (7.4), *and with the wave speed taken to be* $2\sqrt{AD}$. *These are compared to the solution of the partial differential equation system* (2.2) *at a large time t, with the origin of space translated so that* $n = m$ *at the origin. The first-order approximation agrees very well with this partial differential equation wave front. The parameter values are* $\varepsilon = 0.3$, $\xi_\varepsilon = 0.5$, $s_\varepsilon = 1$, $P_\varepsilon = 1.5$, $\delta_\varepsilon = 0.5$, $k = 15$, $N = 10$, $D = 0.01$, $D_c = 1$, $h = 20$, $j_A = 1$, $j_I = 2$, *with chemical 1 an activator of mitosis. The dotted line represents the zeroth-order approximation;* × *represents the first-order approximation; the solid line represents the partial differential equation wave front.*

Higher-order terms can be derived in the same way. However, (7.3) and (7.4) together already give a very good approximation to the full partial differential equation wave front, as illustrated in Fig. 7. To plot the analytical approximation in this figure, we require an expression for the wave speed a, since $\zeta = \varepsilon\hat{z} = \varepsilon z/a$. However, $A = O(\varepsilon)$, and thus for sufficiently small ε, (4.6) will be satisfied, so that we expect that to a good approximation, $a = 2\sqrt{AD}$. One simple consequence of the analytical approximations (7.3) and (7.4) is the following expression for the total cell density in the tumour that forms behind the front:

$$u(+\infty) = 1 - \varepsilon \frac{(P_\varepsilon + \xi_\varepsilon)s_1'(1) + s_\varepsilon - \delta_\varepsilon}{f'(1) + s_1'(1)} + O(\varepsilon^2);$$

this is not dependent on our approximation for the wave speed a.

8. Conclusions. We developed a reaction diffusion model for the initial growth of a tumour following a mutation that affects the biochemical control mechanisms of cell division. Numerical solutions of the model rapidly evolve into an advancing wave of tumour cells and a receding wave of normal cells. We analysed these travelling wave forms under biologically relevant approximations and derived a necessary and sufficient condition for the existence of a travelling wave solution. We proceeded to predict the qualitative form of the wave fronts in the various parameter domains and we estimated the wave speed. Finally, we derived an analytic approximation for the wave fronts in the case of small mutations. Biologically, our results suggest that, for certain types of mutations, which we quantified, growing tumours can initially contain a significant proportion of normal cells. Moreover, our model predicts that there is a critical level of immune response, which we quantified, above which the immune system will prevent the initial growth of the tumour.

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REFERENCES

[1] S. A. AARONSON, *Growth factors and cancer*, Science, 254 (1991), pp. 1146–1153.
[2] J. A. ADAM, *A simplified mathematical model of tumor growth*, Math. Biosci., 81 (1986), pp. 229–244.
[3] ———, *A mathematical model of tumor growth. II. Effects of geometry and spatial nonuniformity on stability*, Math. Biosci., 86 (1987), pp. 183–211.
[4] ———, *A mathematical model of tumor growth, III. Comparison with experiment*, Math. Biosci., 86 (1987), pp. 213–227.
[5] ———, *Activator-inhibitor control of tissue growth*, SIAM Rev., 33 (1991), pp. 462–466.
[6] A. ALBERT, M. FREEDMAN, AND A. S. PERELSON, *Tumors and the immune system: The effects of a tumor growth modulator*, Math. Biosci., 50 (1980), pp. 25–58.
[7] R. W. BALDWIN, *Immunity to methylcholanthrene induced tumours in inbred rats following atrophy and regression of implanted tumours*, British J. Cancer, 9 (1955), pp. 652–657.
[8] G. I. BELL, *Models of carcinogenesis as an escape from mitotic inhibitors*, Science, 192 (1976), pp. 569–572.
[9] N. F. BRITTON, *Reaction-Diffusion Equations and Their Applications to Biology*, Academic Press, London, 1986.
[10] E. J. FOLEY, *Antigenic properties of methylcholanthrene induced tumours in mice of the strain of origin*, Cancer Res., 13 (1953), pp. 835–837.
[11] L. GLASS, *Instability and mitotic patterns in tissue growth*, J. Dynamics Systems Meas. Control, 95 (1973), pp. 324–327.
[12] H. P. GREENSPAN, *Models for the growth of a solid tumor by diffusion*, Stud. Appl. Math., 51 (1972), pp. 317–340.
[13] ———, *On the self-inhibited growth of cell cultures*, Growth, 38 (1974), pp. 81–95.
[14] D. G. HARDIE, *Biochemical Messengers*, Cambridge University Press, Cambridge, UK, 1991.
[15] G. KLEIN, *The approaching era of tumour suppressor genes*, Science, 238 (1987), pp. 1539–1545.
[16] C. J. MARSHALL, *Oncogenes and cell proliferation: An overview*, in Oncogenes, D. M. Glover and B. D. Hames, eds., IRL Press, Oxford, 1989, pp. 1–22.
[17] S. MICHELSON AND J. LEITH, *Autocrine and paracrine growth factors in tumor growth: A mathematical model*, Bull. Math. Biol., 53 (1991), pp. 639–656.
[18] D. L. MORTON AND J. ECONOMOU, *Cancer immunology and immunotherapy*, in Cancer Treatment, C. M. Haskell, ed., W. B. Saunders, Philadelphia, PA, 1990, pp. 102–119.
[19] J. D. MURRAY, *Mathematical Biology*, Springer-Verlag, New York, 1989.
[20] S. A. ROSENBERG, *The development of new immunotherapies for the treatment of cancer using interleukin-2*, Ann. Surg., 208 (1988), pp. 121–135.
[21] R. SAGER, *Tumor suppressor genes: The puzzle and the promise*, Science, 246 (1989), pp. 1406–1412.
[22] J. A. SHERRATT AND J. D. MURRAY, *Models of epidermal wound healing*, Proc. Roy. Soc. London Ser. B, 241 (1990), pp. 29–36.
[23] ———, *Mathematical analysis of a basic model for epidermal wound healing*, J. Math. Biol., 29 (1991), pp. 389–404.
[24] R. M. SHYMKO AND L. GLASS, *Cellular and geometric control of tissue growth and mitotic instability*, J. Theoret. Biol., 63 (1976), pp. 355–374.
[25] S. L. TOPALIAN AND S. A. ROSENBERG, *Tumor-infiltrating lymphocytes: Evidence for specific immune reactions against growing cancers in mice and humans*, in Important Advances in Oncology, V. T. DeVita, S. Hellman, and S. A. Rosenberg, eds., J. B. Lippincott, Philadelphia, PA 1990, pp. 19–41.
[26] R. A. WEINBERG, *Oncogenes, anti-oncogenes, and the molecular bases of multistep carcinogenesis*, Cancer Res., 49 (1989), pp. 3713–3721.
[27] ———, *Growth factors and oncogenes*, in Oncogenes and the Molecular Origins of Cancer, R. A. Weinberg, ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, pp. 45–66.
[28] ———, *Tumour suppressor genes*, Science, 254 (1991), pp. 1138–1146.
[29] T. E. WHELDON, *Mitotic autoregulation of normal and abnormal cells: Alternative mechanisms for the derangement of growth control*, J. Theoret. Biol., 53 (1975), pp. 421–433.