

A Mathematical Model for the Production and Secretion of Tumour Angiogenesis Factor in Tumours

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Solid tumour growth was hypothesized by Folkman (1976) to take place in two phases: the *avascular* phase and the *vascular* phase. In the first (avascular) phase, the tumour obtains its nutrients and disposes of its metabolic wastes by diffusion transport processes alone. Since the mechanism for growth is diffusion-limited, these tumours cannot expand indefinitely, but grow to a dormant state in which they have ceased expanding. The second (vascular) phase involves the eliciting of new blood vessels from the surrounding tissue and there is now firm evidence that tumour cells produce a chemical compound which triggers this process. The compound has been termed *tumour angiogenesis factor* (TAF) and considerable research has been carried out to try and isolate it and identify its biological structure as well as to elucidate its effects on the endothelial cells which form the lining of the blood vessels. In this second phase, the tumour grows rapidly and can spread to other parts of the body via blood-borne metastases.

In this paper, the authors present a theoretical model for the production of the TAF within the tumour while in its diffusion-limited state and prior to its release into the surrounding host tissue. Using experimental results on vascularized tumours in conjunction with the findings of Oosaki *et al.* (1987), it is assumed that the profile of the TAF concentration within the tumour prior to secretion is qualitatively the same as that of the blood vessels found in neovascularized tumours. The TAF concentration $c(x, t)$ is taken to satisfy the diffusion equation and the TAF production is accounted for either by the inclusion of a production term $\phi(c)$ in the diffusion equation itself or via inclusion in the boundary conditions. Taking $\phi(c)$ to be of the form $1/(1-c)$ produces the desired TAF profile and also leads to the possibility of a critical level being reached. It is shown that if the tumour is small enough this critical level can never be attained. However, if the tumour exceeds a certain size, then the critical level is attained and the TAF is subsequently secreted into the external tissue. This is described mathematically by the phenomenon of *quenching*, that is, the solution $c(x, t)$ remains finite while some derivative becomes unbounded in finite time.

Keywords: solid tumour growth; vascularization; tumour angiogenesis factor; quenching.

1. Introduction

FROM his studies and experiments on cell colonies and tumours, *in vitro* and *in vivo*, in the early 1970s, Folkman (1976) put forward the hypothesis that most, if not all, solid tumour growth takes place in and evolves through two phases, the

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avasascular and then the vascular. Unless the tumour derives its blood supply from the adjacent host tissues, it cannot grow beyond a few millimetres in diameter. An intracellular adhesive force keeps the malignant cell colony together as a compact roughly spherical mass, and, in this first stage of its growth, the tumour is *avasascular*, that is, it lacks its own network of blood vessels for supplying nutrients, including oxygen, and for removing its metabolic wastes. The transfer of nutrients and wastes is accomplished by diffusion processes alone through the surrounding healthy tissue. However (Folkman, 1976), since the consumption of nutrients increases at a rate proportional to the tumour volume (i.e. in proportion to the cube of its radius) while the ability to supply nutrients increases at a rate proportional to the surface area of the tumour (i.e. in proportion to the square of its radius), then these diffusion-limited tumours cannot continue to expand indefinitely. The tumour reaches its limiting size when the surface area becomes too small for nutrients to diffuse into the central region and wastes to diffuse out of it. Avascular nodules can be grown easily in the laboratory or observed *in vivo* (Folkman, 1976; Balding & McElwain, 1985), and they develop a central necrotic core and progress to a dormant state in which, although they still retain live proliferating cells, they have ceased to expand. Newly generated cells are balanced by dying cells. They remain in this diffusion-limited state for as long as nutrients are supplied in sufficient quantities and are typically about 1–3 mm in diameter. The theoretical model for tumour growth of Greenspan (1976) takes into account all of the main features of this initial growth period. The gross internal forces are described by a pressure distribution whose non-uniformities effect cell motion. On the surface of the tumour, the pressure balances the surface tension force, thus modelling the cell-to-cell adhesion which keeps the cell colony together (cf. Folkman, 1976). The tumour and surrounding tissue are assumed to be in a state diffusive equilibrium at all times. Nutrients diffuse through the outer surface at a given rate and then are consumed at an equal rate by the cells. In the necrotic interior, the cells die and continually disintegrate into simpler compounds at a constant rate.

An estimate of the ultimate size of the tumour is given in terms of the nutrient supply σ_∞ , the cell volume loss rate S_i , and cell production and loss rates, λ and μ , by

$$R_\infty = \frac{3\lambda}{S_i} \left(\frac{\sigma_\infty}{1 + 3\lambda\mu/S_i} \right)^{\frac{1}{2}}, \quad (1)$$

where R_∞ is the steady-state radius.

Essentially, in this theoretical model, the tumour is regarded as an incompressible fluid within a closed extensible membrane, with the layer of live proliferating cells acting as a fluid source and the necrotic interior acting as a fluid sink.

The critical event which turns the compact colony of cells into a rapidly growing malignancy comes when the tumour becomes *vascularized*. This second, and much more important, phase of the tumour's growth, from a clinical point of view, can only occur *in vivo*. This involves the eliciting of new blood vessels from the surrounding tissue (*angiogenesis*) and there is now firm evidence that the event is triggered when the tumour cells release a diffusible chemical substance which has been termed *tumour angiogenesis factor* (TAF). Much research has

been carried out to try and isolate it and identify its biochemical structure as well as to elucidate its effects on the endothelial cells which form the lining of the blood vessels. From experiments on tumour implants into the cornea of test animals (cf. Ausprunk & Folkman, 1977; Langer *et al.*, 1980; Gross *et al.*, 1981), it has been found that, in response to the initial TAF stimulus, blood vessel growth subsequently occurs in two distinct phases. In the first stage, endothelial cells at the tip of the affected blood vessels become elongated and form a lumen as they attempt to migrate towards the tumour. During this stage, the cells also release proteolytic and collagenolytic enzymes that degrade the intercellular matrix through which they must migrate. In the second stage, the cells immediately behind those at the tip proliferate, pushing the lumen forward (cf. Ausprunk & Folkman, 1977). Thus, these new capillaries, composed of endothelial cells, grow toward the tumour and finally penetrate it, and hence the tumour becomes vascularized. Fresh nutrients now pour in and wastes are speedily removed, with perfusion replacing diffusion as the dominant growth mechanism. This second phase is characterized by rapid growth and provides the tumour with the opportunity to spread via blood-borne metastases.

Using the model of Edelstein (1982) for fungal growth as a basis for their model, Balding & McElwain (1985) subsequently developed a mathematical model of neovascularization which described the formation and growth of the capillary sprouts in response to the secretion of TAF. Indeed, most of the research into TAF and its activity has been carried out on its effects on the blood vessels and endothelial cells *after* it has been secreted into the surrounding tissues. In this paper, we propose a theoretical model which deals primarily with the production of the TAF within the tumour *prior* to release into the host tissue.

2. The mathematical model

The recent results of Lisniak & Sopotsinskaia (1989) have shown that there is a direct correlation between the TAF level and the volume of tumour cell masses, which confirms the present notions about the close correlation of tumour growth and neovascularization. We thus put forward the hypothesis that there is a direct link between the tumour size and the subsequent secretion of the TAF (i.e. depending upon the size of the tumour, TAF may or may not be secreted and consequently vascularization may or may not take place). To this end, in our models, we shall make use of the mathematical phenomenon of *quenching*. This term was introduced by Kawarada (1975), who studied the behaviour of solutions to the following system:

$$\left. \begin{aligned} u_t &= u_{xx} + 1/(1-u) & (0 < t \leq T, -a < x < a), \\ u(a, t) &= u(-a, t) = 0 & (0 < t \leq T), \\ u(x, 0) &= 0 & (-a \leq x \leq a). \end{aligned} \right\} \quad (2)$$

If u exists for all $t > 0$ ($T = \infty$), then we have global existence for our solution. If, on the contrary, $\max \{u(x, t) : x \leq a\}$ reaches one in finite time, $t = T$ say, then u cannot be continued beyond $t = T$ and we say that quenching has occurred or

that our solution $u(x, t)$ has quenched in finite time, that is,

$$\limsup_{t \rightarrow T^-} u_t(x, t) = \infty. \quad (3)$$

Quenching is the phenomenon whereby the solution of the equation remains finite but some derivative of the solution 'blows up'. The problem, thus, consists in determining those values of $a > 0$ such that the solution $u(x, t)$ of (2) exists globally. It can be shown that there exists a positive number a^* such that for $0 < a < a^*$ we have global existence, and for $a > a^*$ quenching occurs, that is,

there exists an $a^* < \infty$ such that

- (i) if $0 < a < a^*$, then $u(x, t)$ exists for all $t \geq 0$;
- (ii) if $a > a^*$, then the solution $u(x, t)$ is defined only on a finite interval $[0, T)$, and $u(0, t) \rightarrow 1^-$ as $t \rightarrow T^-$, with the result that $u_t(0, t) \rightarrow \infty$, and subsequently $u(x, t)$ cannot be continued beyond $t = T$.

Using differential inequality methods, Walter (1976) has found the bounds $0.765 < a^* < \frac{1}{2}\pi$.

With the above definitions, we now turn to modelling the production and secretion of TAF by the tumour. For simplicity, we first consider two models in one spatial dimension, the results of which can be extended to higher dimensions. (For models of one-dimensional cellular growth, see e.g. the model of Greenspan (1974).)

We assume that the tumour has reached its diffusion-limited size, and, as such, occupies the region $0 \leq x \leq L$, where L is the ultimate size of the tumour. We denote the concentration of TAF within the tumour by the function $c(x, t)$, and we assume that initially there is no TAF present, so that we have for an initial condition

$$c(x, 0) = 0. \quad (4)$$

As we have described previously, the Greenspan model (1976) for tumour growth considers the tumour as a thin layer of live proliferating cells surrounding a large necrotic core. By analogy, in the one-dimensional case, on the boundary at $x = L$, there is a small thickness, h say, of these live cells. Now, within the tumour itself, it is these live viable cells *alone* which produce the TAF (cf. Balding & McElwain, 1985; Langer *et al.*, 1980; Thompson *et al.*, 1987). In each of our models, we assume that the basic equation that is satisfied by the TAF concentration within the tumour is the diffusion equation, and we take account of the TAF production through the inclusion of a source term, either in the diffusion equation itself (as in the first model) or else through the boundary condition at $x = L$ (as in the second model). This TAF production will be modelled by the singular function $\phi(c)$. Typically, we take $\phi(c)$ to be of the form

$$\phi(c) = 1/(1 - c), \quad (5)$$

or, more generally,

$$\phi(c) = 1/(1 - c)^\beta,$$

where $\beta > 0$, that is we assume that $\phi : (0, 1) \rightarrow (0, \infty)$ is a continuously differentiable monotone increasing function, with $\lim_{c \rightarrow 1^-} \phi(c) = \infty$. Of course, this can easily be extended to include a singularity at $c = c_0$, say, that is, $\phi : (0, c_0) \rightarrow (0, \infty)$ and $\lim_{c \rightarrow c_0^-} \phi(c) = \infty$.

The results of Langer *et al.* (1980) showed that, within vascularized tumours, capillary blood vessels were found within the densely packed viable tumour cells *around the boundary* and not the central necrotic core. Similarly, from their experiments on mice, Thompson *et al.* (1987) showed that, with increasing tumour size, the proportion of blood vessels within vascularized tumours increased rapidly to reach a plateau of approximately 1.5% of the tumour volume, with the blood vessel density always higher at the *periphery* than at the centre. Sekiya *et al.* (1986) showed that there was a direct correlation between TAF activity and the extent of tumour growth *in vivo*, while Oosaki *et al.* (1987) linked TAF activity directly with the number of blood vessels in vascularized tumours. Hence, from the above results, we feel that we can use the profile of blood vessels found in vascularized tumours to describe the profile of TAF within the tumour prior to its release into the external tissue, that is, we assume a similar qualitative profile for the TAF concentration within the tumour as for that of the blood vessels.

As was shown in the first section, the Greenspan model (1976) in essence views the tumour as a 'fluid' consisting of incompressible cells held together by adhesive forces. The cell proliferation and mitosis in the thin outer layer acts like a source of incompressible fluid, while the central necrotic core plays the role of a fluid sink. Given this and the results of Langer *et al.* (1981) and Thompson *et al.* (1987), we assume that the TAF concentration at $x = 0$ is zero, that is,

$$c(0, t) = 0. \quad (6)$$

We note that a similar hypothesis was forwarded by Ausprunk & Folkman (1977) in order to describe events after the TAF had been secreted into the surrounding tissue. Here they proposed that either the blood vessels or the endothelial cells consumed the TAF and acted as sinks for the TAF. We also note that this parallels the modelling of the internal nutrient supply in the Greenspan model, where σ_1 was effectively taken to be zero in the interior of the solid tumour (i.e. $\sigma_1 = 0$), and the findings of Thomlinson & Gray (1955) regarding oxygen supply in the necrotic centre of solid tumours. Here there was a falling oxygen gradient between the tumour periphery and the centre of the tumour. In solid tumours with necrotic centres, the oxygen concentration must be lower towards the centre than at the periphery and does in fact reach zero at some point in the interior.

As we shall see in the following analysis, the inclusion of the function $\phi(c)$ as the TAF production term, together with the boundary condition $c(x, t) = 0$ at $x = 0$, gives the correct qualitative profile for the TAF within the tumour, in line with the findings of Langer *et al.* and Thompson *et al.*, that is, zero concentration at $x = 0$ (representing the tumour centre), rising to a maximum level at $x = L$, the tumour periphery, with the concentration increasing with tumour size and time.

Thus, our first model is given by the system

$$(*) \quad c_t = c_{xx} + \phi(c) \quad (0 < x < L, t > 0), \quad (7)$$

$$\left. \begin{aligned} c(x, 0) &= 0 & (0 < x < L), \\ c(0, t) &= 0 & (t \geq 0), \\ c_x(L, t) &= 0 & (t \geq 0), \end{aligned} \right\} \quad (8)$$

where the activity of the proliferating cells and the production of TAF have been taken into account via the inclusion of the function $\phi(c)$ in the diffusion equation.

There is a close relationship between solutions of the above system (*) and those solutions of the corresponding 'stationary problem':

$$0 = w_{xx}(x) + \phi(w(x)) \quad (0 < x < L), \quad (9)$$

$$w(0) = w_x(L) = 0. \quad (10)$$

A weak stationary solution of (*) is a once continuously differentiable function g , satisfying (9)–(10) and also

$$g(x) = \int_0^L G(x, y) \phi(g(y)) dy, \quad (11)$$

where $G(x, y)$ is a Green's function associated with the operator $-d^2/dx^2$ on $[0, L]$, with boundary conditions $G(0, y) = G_x(L, y) = 0$. Hence

$$G(x, y) = \begin{cases} x/L & (0 \leq x \leq y \leq L), \\ y/L & (0 \leq y \leq x \leq L). \end{cases} \quad (12)$$

The question of whether or not we have global existence for our system (*) can be reduced to the existence problem for the 'stationary' boundary value problem (11)–(12). We now present the following result, the proof of which we give in the Appendix.

There is an $L_0 > 0$ such that for $L < L_0$ we have global existence for the solution $c(x, t)$, while for $L > L_0$ the solution quenches. This result is in accord with the general principle that small domains are more stable than large domains, an observation which is supported by the Greenspan model (1976).

Biologically, when $c(x, t)$ quenches, we envisage that the TAF concentration has reached a critical level (in this model $c = 1$), and that the activity of the TAF (represented by the term $c_t(x, t)$) has also reached a critical level (i.e. $c_t \rightarrow \infty$). At this finite time $t = T$, the solution $c(x, t)$ cannot be continued, and so the TAF is subsequently secreted into the surrounding tissue, and the process of eliciting new blood vessels can then begin. This, of course, leads to the vascularization of the tumour as has been previously described and the possible spread of the tumour to other parts of the body. Thus the size of the tumour determines whether or not quenching, and hence release of the TAF, occurs.

This hypothesis is supported by the results of Oosaki *et al.* (1987), Ishiwata *et al.* (1988), Thompson *et al.* (1987), Sekiya *et al.* (1986), and most recently by Lisniak & Sopotsinskaia (1989). In these papers, positive correlation has been found linking the activity of the TAF to the tumour size, and linking the level of the TAF with the tumour size.

We now present a second model for the TAF production, in which the activity of the cells on the boundary is modelled through the inclusion of the function $\phi(c)$ (the same function used in our first model) in the boundary conditions. Thus, the solution $c(x, t)$ is driven by the boundary conditions instead of by a source or production term. Our second model is then given by

$$c_t = c_{xx} \quad (t > 0, 0 < x < L), \tag{13}$$

together with initial and boundary conditions

$$\left. \begin{aligned} c(x, 0) &= 0 && (0 < x \leq L), \\ c(0, t) &= 0 && (t \geq 0), \\ c_x(L, t) &= \phi(c(L, t)) && (t > 0). \end{aligned} \right\} \tag{14}$$

By simultaneous scaling in x and t , we can take $L = 1$ with the result that the boundary condition at the right endpoint now becomes

$$c_x(1, t) = L\phi(c(1, t)) \quad (t > 0), \tag{15}$$

and the system now becomes

$$(**) \quad c_t = c_{xx} \quad (t > 0, 0 < x < 1), \tag{16}$$

$$\left. \begin{aligned} c(x, 0) &= 0 && (0 < x \leq 1), \\ c(0, t) &= 0 && (t \geq 0), \\ c_x(1, t) &= L\phi(c(1, t)) && (t > 0), \end{aligned} \right\} \tag{17}$$

where $\phi(c)$ is defined as previously.

Levine (1983) has shown that, for the above system, the maximum value of $c(x, t)$ in any closed domain \bar{D}_T (where \bar{D}_T is the closure of the domain $D_T = (0, 1) \times (0, T)$, with $T < \infty$) must occur at the point $(1, T)$ and that the solution is unique. He then goes on to prove that either

- (a) $c(x, t)$ exists on $D = (0, 1) \times (0, \infty)$ and $\lim_{t \rightarrow \infty} c(x, t) = ax$, where $a = L\phi(a)$ and $a < 1$ (i.e. we have global existence), or
- (b) if L is large enough, then, for some finite $T < \infty$, $\lim_{t \rightarrow T^-} c(x, t) = 1$, and so $c_x(1, t) \rightarrow \infty$ as $t \rightarrow T^-$ (i.e. the solution $c(x, t)$ quenches in finite time T).

Thus, there exists an L_0^* such that if $L \leq L_0^*$ no quenching at all is possible, while if $L > L_0^*$, our solution $c(x, t)$ quenches. Once again, the solution $c(x, t)$ exhibits the desired qualitative profile of increasing from zero at the tumour centre up to a maximum value at the tumour edge or periphery. It should be noted, however, that this occurs in a different manner from the solution obtained via the first model. The stationary solution for (*) was given in terms of transcendental functions (cf. Levine, 1983), while that of (**) was a linear function. However, given the variation that could, and indeed does, exist within the interiors of different tumours, then it is perhaps not surprising that this should be so. Rather, the important thing is that the TAF level increases up to a maximum on the periphery of the tumour in both models, and not the precise manner in which this occurs.

3. Circular and spherical geometries

We now consider the problem for the radially symmetric case in two and three dimensions, that is, we consider the tumour either as a disc or a sphere of radius R . Thus, the system now to be studied is

$$(***) \quad c_t = c_{rr} + \frac{(n-1)}{r} c_r + \phi(c) \quad (0 < r < R, t > 0, n = 2, 3), \tag{18}$$

$$\left. \begin{aligned} c(r, 0) &= 0 & (0 < r < R), \\ c(0, t) &= 0 & (t \geq 0), \\ c_e(R, t) &= 0 & (t \geq 0). \end{aligned} \right\} \tag{19}$$

Now, by the Schauder-type theory for parabolic equations (Friedman, 1964), it follows that $c, c_t, c_r,$ and c_{rr} are continuous in $\mathbb{R}^n \times [0, \infty)$ ($n = 2, 3$). Thus, in view of the smoothness of c , we have $c_r(0, t) = 0$ for all $t \in [0, \infty)$. Then, using the same techniques as the previous section, we can show that $c(r, t)$ takes its maximum value on the boundary $r = R$. Also, if we denote by R_q the supremum of all values of $R > 0$ such that a solution $w_R(r)$ of the stationary problem for (18)–(19) exists, then we have

- (i) global existence for $R < R_q$;
- (ii) quenching for $R > R_q$.

Here, once again, the size of the tumour will determine whether or not the TAF is secreted into the surrounding tissue.

4. Extension to higher dimensions

We now consider the problem (**) in more than one dimension. Let $D \in \mathbb{R}^n$ be a bounded domain having boundary $\partial D = \Sigma \cup \sigma$, with $\Sigma \cap \sigma = \emptyset$ and Σ smooth. Let

$$L_0 = \sup \{ \delta / \phi(\delta) \quad (0 < \delta < 1) \},$$

where ϕ is as defined in the previous sections, and define

$$L_1 = \int_0^1 ds / \phi(s). \tag{20}$$

Then $L_1 > L_0$. Let $w(x)$ ($x \in \bar{D}$) solve $\nabla^2 w = 0$ on $\sigma, \partial w / \partial n = 1$ on Σ , and $w_0 = \max \{ w(x) \mid x \in \bar{D} \}$. Let $c(x, t)$ in $D \times (0, T)$ solve

$$\frac{\partial c}{\partial t} = \nabla^2 c \quad \text{on } D \times (0, T), \tag{21}$$

$$\left. \begin{aligned} c &= 0 & \text{on } \sigma \times (0, T) \text{ and } D \times \{0\}, \\ \frac{\partial c}{\partial n} &= \phi(c) & \text{on } \Sigma \times (0, T) \end{aligned} \right\} \tag{22}$$

It has been shown (Levine & Lieberman, 1983) that, if $w_0 \leq L_0$, then $c \leq a$, where a is the smallest root of $s = L_0 \phi(s)$ in $(0, 1)$. Consequently, c exists for all t

and no quenching is possible. If $w_0 > L_1$, then c reaches 1 in finite time in Σ and so $\nabla_x c$ becomes unbounded in finite time. If $w_0 > L_1$ or $w_0 = L_1$ and c quenches in infinite time, then

$$\lim_{t \rightarrow \infty} c(x, t) = g(x),$$

where $g(x) \geq 0$ solves $\nabla^2 g = 0$ in D , $g = 0$ on σ , and $\partial g / \partial n = \phi(g)$ on Σ . In this last case, $g = 1$ on Σ whenever $w = L_1$. If this boundary value problem has no solution, then c must quench in finite time. Also, if $g_0 = \max \{g(x) \mid x \in D\} < 1$, then $c \leq g_0$ and no quenching can occur.

In the case of finite time quenching, it is not known what, if anything, happens to c_t on $\Sigma \times (0, T)$ in more than one dimension.

5. Conclusions

In both types of model considered for the production and subsequent secretion of the TAF, the inclusion of the function $\phi(c)$ – whether it is included in the boundary equations or as a production term in the diffusion equation itself – plays a critical role in the subsequent analysis. Mathematically, $\phi(c)$ must be singular at some point so that the possibility of quenching arises. From a biological point of view, the inclusion of $\phi(c)$ is an attempt to model the activity of the thin layer of live proliferating cells on the tumour boundary, since it is these cells alone which produce the TAF, and the singularity of $\phi(c)$ allows for the possibility of a critical level of TAF concentration being attained. At present, there is no biological justification for the term $\phi(c) = 1/(1-c)$, other than it represents a source term, simply because there is little or no experimental data concerning the production of TAF *within* tumours, prior to its release into the external tissue. All experimental work carried out on TAF is concerned with its effect on the external blood vessels *after* its secretion into the surrounding tissue. As was stressed in the introduction, we present here a theoretical model, relying, as far as possible, on the available experimental data, and producing the correct qualitative results.

The inclusion of $\phi(c)$ in the model also means that the rate of TAF production increases rapidly as the concentration approaches a critical level. We note that this parallels the findings of Folkman (1976), where tumours grew rapidly upon neovascularization. Also, as a tumour makes the transition from a dormant state to an invasive state, it becomes cannibalistic (cf. Melnikow, 1982), with perfusion replacing diffusion as the method of nutrient supply. The increasing rate of production of TAF mirrors this process. Tumours are essentially autonomous and for malignancies it is in their own interests to supply themselves with new nutrient supply. Hence, as more TAF is produced, there is a greater likelihood of the critical level being reached, and so it is in the interest of the cancer to produce more TAF in order subsequently to attract blood vessels and therefore a fresh nutrient supply. The function $\phi(c)$ may therefore model a type of positive-feedback or symbiosis between the tumour and the production of TAF.

Whether it is better to include $\phi(c)$ in the boundary conditions or in the diffusion equation itself as a production term, is a matter open to question.

Inclusion in the latter case, together with a zero flux condition on the tumour boundary, essentially means that the TAF is confined within the tumour until the critical level is reached. Once this critical level has been reached, this then triggers its release into the surrounding tissue where the external blood vessels can grow towards and into the tumour, eventually leading to its vascularization. Below this critical level, the blood vessels are not attracted to grow. This is consistent with the model of Balding & McElwain (1985), where the blood vessels grew chemotactically towards *high* concentrations of TAF. It is also consistent with the present thinking about the close correlation between tumour growth and neovascularization (cf. Lisniak & Sopotsinskaia, 1989) and with the theoretical hypothesis of Folkman (1976). The diffusion-limited size here seems to indicate that the size of the dormant colony of malignant cells plays a part in determining whether or not vascularization occurs.

Inclusion in the former case (i.e. as part of the flux condition on the boundary) may be more in keeping with the mechanism by which the tumour grows – consuming nutrients and disposing of its wastes via diffusion through its boundary. It is now also thought (cf. Maugh, 1981) that, not only do tumours need a supply of blood vessels to outgrow their diffusion-limited size, but that they must have a supply of blood vessels simply to keep from withering away. It may well be the case, therefore, that, although the TAF does not reach its critical level when still dormant, this subcritical level may be sufficient to obtain from the surrounding tissue a limited supply of blood vessels which is sufficient to prevent it from withering. This proposition could also be used to give an alternative set of initial and interior boundary conditions. It may be that at its diffusion-limited size, there already exists a certain amount of TAF present within the tumour (c^* , say), and so the initial condition could be replaced by $c(x, 0) = c^*$, with the boundary condition at $x = 0$ becoming $c(0, t) = c^*$, thus ensuring a nonzero concentration at the origin. This would not affect the conclusions of the model, but would simply ‘rescale’ the critical value c_0 . We also note that these alternative initial and boundary conditions are automatically included in the model in Section 4, where extensions to higher more realistic dimensions are given. Here the concentration of the TAF at the origin need not remain zero for all time, although initially $c = 0$ at $t = 0$.

Whatever the case, the essential feature of both types of model is the inclusion of the singular function $\phi(c)$.

In both models, we have shown that, depending upon the tumour size, quenching (and hence the release of the TAF, leading to vascularization) may or may not occur. For $R < R_q$ no quenching will occur, while for $R > R_q$ quenching does occur. The tumour size thus plays a role in determining whether or not vascularization takes place, that is, the malignant cell colony becomes nourished with a supply of blood vessels, opening up the possibility of secondary tumours being set up via blood-borne metastases. In the Greenspan model of tumour growth (a diffusion-limited type model), a similar situation also arises. Here there is a critical radius, $R_c(t)$ at which stage external perturbations affecting the tumour’s growth may cause the tumour to break up into two or more separate pieces, and hence spread and invade the surrounding tissue. This critical radius is

given as the solution to the equation

$$f(n, R) = 0, \quad (23)$$

where

$$f(n, R) = \frac{1}{3}S_i - \frac{an(n+2)}{2R^3} + \frac{\frac{1}{2}\lambda\mu}{(n+1) + (\mu R/4\sigma_\infty)[\mu R + (\mu^2 R^2 + 4\sigma_\infty)^{\frac{1}{2}}]}. \quad (24)$$

This may or may not occur depending upon the ultimate size R_∞ of the tumour defined in the first section. If $R_\infty < R_c(t)$, then no break up will occur since the tumour stops growing before the critical radius is reached. However, if $R_c(t) < R_\infty$, then there is the possibility that the internal pressure of the necrotic core will overcome the stabilizing effect of the surface tension force which keeps the tumour together as a compact mass and that the malignancy will now become invasive. Thus we have three special sizes of the tumour: $R_q, R_c(t), R_\infty$. The tendency for the tumour to vascularize or to remain nonvascularized, to invade the surrounding tissue or to stay dormant at some finite size, will depend upon the relationships between these three values. We summarize the possibilities in Table 1, together with the likelihood of invasion.

Our analysis is an attempt to link, in some way, the separate phenomena of angiogenesis, invasiveness, and metastasis. There are two medical observations which suggest a line between tumour angiogenesis and the invasion of the host tissue by cancers (cf. Folkman, 1976). When *in situ* carcinomas in the skin and in the cervix are observed closely, invasion of the tough basement membrane seems to come almost simultaneously with neovascularization. When viewed in cross-section under the microscope, the basement membrane runs like a filament through the skin, through the intestinal, genito-urinary, and respiratory tracts, and through a variety of ducts that open into these tissues, such as ducts from the breast and the liver. Thus the basement membrane, consisting partly of collagen, lies just under the layers of epithelial cells that are next to the outside environment. Normally, the basement membrane separates the epithelial tissues from the vascular system.

TABLE 1
Relationship between vascularization and invasion

$R_\infty < R_c(t) \leq R_q$	Nonvascularization No invasion
$R_\infty < R_q \leq R_c(t)$	Nonvascularization No invasion
$R_c(t) < R_\infty < R_q$	Nonvascularization Invasion
$R_c(t) \leq R_q < R_\infty$	Invasion/vascularization
$R_q \leq R_c(t) < R_\infty$	Vascularization/invasion
$R_q < R_\infty < R_c(t)$	Vascularization Subsequent invasion

Most pathologists believe that the invasion of the basement membrane is followed by neovascularization, but the two events come so close together that it could also be the other way round. It has been suggested that a possible major difference between a *carcinoma* (cancer of the epithelial cells) and a *sarcoma* (cancer of the connective tissue) is that, although both kinds of cancer may require neovascularization for rapid growth, a carcinoma is not invasive until after vascularization whereas a sarcoma is invasive before vascularization (Folkman, 1976). These situations are reflected in the fourth and fifth entries of Table 1.

The last entry in Table 1, however, is perhaps the most instructive and interesting from the point of view of our models. In this situation, the diffusion-limited size R_∞ of the tumour is large enough to allow secretion of the TAF into the surrounding tissue. Once nourished by this extra nutrient supply, the tumour can continue its growth and can reach the critical size $R_c(t)$, whereupon it may invade the surrounding tissue, break up into several pieces, and metastasize according to the analysis of Greenspan (1976).

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Appendix

In the proofs which follow, we shall have recourse to use the following definitions and lemmas.

DEFINITION Let L be an elliptic differential operator, independent of t :

$$Lu = \sum_{i,j=1}^n a_{ij}(x)u_{x_i x_j} + \sum_{i=1}^n b_i(x)u_{x_i} + c(x)u.$$

LEMMA (Nagumo's lemma) If $F(t, x, z)$ is Lipschitz continuous in z and $c(x)$ is bounded, and we have

$$u_t - Lu - F(t, x, u) \leq v_t - Lv - F(t, x, v) \quad \text{in } G$$

and

$$u \leq v \quad \text{on } \Gamma_1 \quad \text{and} \quad \frac{\partial u}{\partial x} \leq \frac{\partial v}{\partial x} \quad \text{on } \Gamma_2,$$

then $u \leq v$ in $G \cup \Gamma_2$, where

$$G = (0, T) \times (0, L),$$

$$\Gamma_1 = (0, T) \times \{0\} \cup \{0\} \times [0, L], \quad \Gamma_2 = (0, T) \times \{L\} \cup \{0\} \times [0, L].$$

STRONG MINIMUM PRINCIPLE Assume a, b, c are bounded functions. If

$$u_t \geq Lu \text{ in } G \quad \text{and} \quad u \geq 0 \text{ on } \Gamma = \Gamma_1 \cup \Gamma_2,$$

then $u \geq 0$ in G . Also, we have that, if $u(x^*, t^*) = 0$, where $(x^*, t^*) \in G$, then $u \equiv 0$ in $[0, t^*] \times [0, L]$.

Both Nagumo's lemma and the strong minimum principle have been stated here in a form suitable for our problem. Proofs and a more general statement of both theorems can be found in Walter (1970).

Using the techniques of Acker & Walter (1976), we now prove the following two theorems.

THEOREM 1. Let $c(x, t)$ be a solution of (7)–(8). Then we have

- (i) $c(x, t)$ is positive in $G = (0, T) \times (0, L)$ and strictly increasing in t for $0 < x \leq L$.
- (ii) $c(x, t)$ is strictly increasing in x for $0 \leq x \leq L$ and for fixed $t > 0$.
- (iii) If $T = \infty$, $0 \leq c(x, t) \leq B < \infty$, and ϕ is Lipschitz continuous in $[0, B]$, then the limit

$$w(x) = \lim_{t \rightarrow \infty} c(x, t)$$

exists uniformly in $[0, L]$. The function w is a solution of the boundary value problem

$$\left. \begin{aligned} w_{xx} + \phi(w) &= 0, & w &\in [0, L], & w(x) &> 0 \text{ in } (0, L), \\ w(0) = w_x(L) &= 0. \end{aligned} \right\} \quad (\text{A.1})$$

Proof

(i) If we assume that c_1 and c_2 are two solutions of (7)–(8), then by applying Nagumo's lemma to the difference $c_1 - c_2$, we see that the solution to (7)–(8) is in fact unique.

Now, since $\phi(c) > 0$, by applying the strong minimum principle, we have $c > 0$ in $G = (0, T) \times (0, L)$.

For any $h > 0$, define $d(x, t) = c(x, t + h)$. Then the function $z(x, t) = d(x, t) - c(x, t)$ satisfies

$$z_t = z_{xx} + \frac{\phi(d) - \phi(c)}{d - c} z,$$

that is,

$$z_t = z_{xx} + f(x, t)z. \quad (\text{A.2})$$

Application of the strong minimum principle to $z(x, t)$ gives $z > 0$ in G . Thus $c(x, t)$ is strictly increasing in t .

(ii) For any h ($0 < h < L$), define the function $z^*(x, t) = c(x + h, t) - c(x, t)$. Then $z^*(x, t)$ satisfies

$$z^* = z^*_{xx} + f^*(x, t)z^*. \quad (\text{A.3})$$

Now, since $z^* \geq 0$ on $(0, T) \times (h, L)$, application of the strong minimum principle gives $z^* > 0$. Hence, for fixed t , $c(x, t)$ is strictly increasing in x .

(iii) Define

$$R(x, t) = \int_t^{t+1} c(x, s) ds. \tag{A.4}$$

Integrating (6), we obtain

$$c(x, t + 1) - c(x, t) = R_{xx} + \int_t^{t+1} \phi(c(x, s)) ds, \tag{A.5}$$

with

$$0 \leq c(x, t) \leq R(x, t) \leq c(x, t + 1) \leq w(x).$$

From Taylor's theorem, we have

$$R(x, t) = R(0, t) + \int_0^x (x - \zeta) R_{xx}(\zeta, t) d\zeta. \tag{A.6}$$

Letting $t \rightarrow \infty$, and using the dominated convergence theorem, gives

$$w(x) = w(0) - \int_0^x (x - \zeta) \phi(w(\zeta)) d\zeta. \tag{A.7}$$

Thus $w \in C^2$ and satisfies

$$w_{xx} + \phi(w) = 0, \quad w \in (0, L). \tag{A.8}$$

To obtain the boundary condition for w at $x = L$, we construct an upper function Ψ for c . Let $\phi(z) \leq 2K$ in $0 \leq z \leq B$, and $\Psi(x) = K(2L - x)x$. Now ϕ may be continued by $\phi(z) = \phi(B)$ for $z \geq B$, and so Ψ is an upper function for c . Hence, we have $0 \leq c(x, t) \leq \Psi(x)$ and $0 \leq w(x) \leq \Psi(x)$. Thus, w solves (A.1).

COROLLARY *The quantity $c(x, t)$ takes its maximum value at $x = L$.*

We now consider the solution for different values of L (i.e. different sizes of the interval $[0, L]$). We denote by $c_L(x, t)$ a solution to the problem (7)–(8) on the interval $[0, L]$.

THEOREM 2

(i) *Let $\lambda > 0$ and $T_L \leq T_{L+\lambda}$. Then we have*

$$c_L(x, t) < c_{L+\lambda}(x, t) \tag{A.9}$$

and

$$c_L(x, t) < \min \{c_{L+\lambda}(x + h, t) : h \leq \lambda\} \quad \text{in } G_L. \tag{A.10}$$

(ii) *Let $w_L(x)$ be a solution of the boundary value problem (9)–(10). Then we have*

$$c_L(x, t) < w_L(x) \quad \text{in } G_L. \tag{A.11}$$

(iii) *Let $T_L = \infty$, $c_L(L, t) \rightarrow 1$ as $t \rightarrow \infty$, and $\phi(c) \rightarrow \infty$ as $c \rightarrow 1^-$. Then $T_{L+\lambda} < \infty$ for $\lambda > 0$, that is, the solution $c_{L+\lambda}$ quenches.*

Proof

(i) Define $y(x, t) = c_{L+\lambda}(x+h, t) - c_L(x, t)$ for $h \leq \lambda$. Then $y(x, t)$ satisfies

$$y_t = y_{xx} + g(x, t)y \quad \text{in } G_L.$$

Also, $Y \geq 0$ on the parabolic boundary of G_L . Hence, applying the strong minimum principle, we find $y > 0$ in G_L , and so we have (i).

(ii) By applying the strong minimum principle to $y^*(x, t) = c_L(x, t+h) - c_L(x, t)$, it follows that $c_L(x, t) < w_L(x)$ in G_L .

(iii) Let $r = c_L(x, t)$ and $R = c_{L+\lambda}(x, t)$. Choose positive numbers ε and t_0 in such a way that

$$\lambda^2 + 2\varepsilon/\lambda^2 \leq \phi(z) \quad \text{for } 1 - \varepsilon \leq t < 1, \quad \text{and } u(0, t_0) \geq 1 - \varepsilon. \quad (\text{A.12})$$

Set $S = (t_0, \infty) \times (L - \lambda, L + \lambda)$. If R exists for all $t > 0$, then $R \geq 1 - \varepsilon$ on the parabolic boundary of S (by Theorem 2(i) and Theorem 1(i)). However, the function

$$v(x, t) = (1 - \varepsilon) + (t - t_0)[-x^2 + 2Lx + (\lambda^2 - L^2)] \quad (\text{A.13})$$

is equal to $1 - \varepsilon$ on the parabolic boundary of S . Also, we have

$$v_t \leq v_{xx} + \phi(v) \quad \text{in } t_0 < t < t_0 + \varepsilon/\lambda^2, \quad L - \lambda < x < L + \lambda.$$

Hence v is a subfunction for r in this rectangle. Now,

$$R(t_0 + \varepsilon/\lambda^2, L) > v(t_0 + \varepsilon/\lambda^2, L) = 1.$$

This contradiction shows that $T_{L+\lambda} \leq t_0 + \varepsilon/\lambda^2$.

Thus, if we denote by L_0 the supremum of all values of $L > 0$ such that a solution $w_L(x)$ of (9)–(10) exists, then we have

- (i) $T_L = \infty$ for $L < L_0$ (i.e. global existence);
- (ii) $T_L < \infty$ for $L > L_0$ (i.e. quenching).