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A Mathematical Study on Tumour Nutrients Diffusion - Limited Stage and its Instability

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ABSTRACT: In this article, a mathematical study has been carried out about the conditions under which a necrotic core is produced, by modeling the nutrient concentration in the steady state and about the nutrient instability in the limited stage.

KEYWORDS: Nutrients, Diffusion, Necrotic core, Spatial model, Nutrient in-stability.

I. INTRODUCTION

Cancer is a major public health problem. Cancer is one of the main causes of morbidity and mortality in the world. In the prosperous countries of the world about one person in five will die of cancer. Therefore developed countries are investing large sums of money into cancer research in order to find cures and improve existing treatments. There are several different stages in the growth of a tumour before it becomes so large that it causes the patient to die or reduces permanently their quality of life.

Numerous dynamic growth rate functions with applicability to tumor growth have been discussed [9, 11]. The so-called Gompertz growth [6] has been shown to reproduce biological growth that decelerates with population size [12], and is therefore applicable to observed tumor growth slowdown with tumor size.

In order to grow a tumour requires oxygen and other nutrients. Normal tissues have blood vessels passing through them and nutrients in the blood pass into the tissues through the vessel walls. In the early stages of development tumours have no such blood supply and rely on nutrients diffusing from the adjacent normal tissue.

As the tumour grows, diffusion can no longer provide sufficient nutrient, nutrient concentrations near its centre fall and cells die, resulting in a necrotic core. The tumour can grow no further and reaches a diffusion limited steady state. A similar situation can occur after vascularisation (ie.) after the tumour has triggered production of its own blood supply, if the pressure in the tumour gets high enough to collapse the blood vessels in the tumour.

II. NUTRIENTS: THE DIFFUSION - LIMITED STAGE

Let us assume that the problem is spherically symmetric. Let c(r) be the concentration of limiting nutrient at radius r. Let r_1 be the radius of the necrotic core and r_2 be the radius of tumour. Assuming r_2 to be given, we want to investigate how big the necrotic core will be. Let c satisfy the steady state diffusion equation,

$$D\nabla^2 c - k = 0 \qquad (1)$$

which means that as the nutrients diffuse they are consumed by the cells at the rate k and k is negative because the amount of nutrient concentration is reduced. The problem is spherically symmetric and depends on the radius, so

$$\nabla^2 c = \frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) \qquad (2)$$

and the equation (1) becomes

$$D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) - k = 0$$

$$D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right) = k$$

for $r_1 < r < r_2$, where D is a constant diffusion coefficient.

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Since the oxygen is only taken by the living cells,

$$D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dc}{dr}\right)=0, \text{ for } r<r_1. \quad (3)$$

Let c_2 be the concentration of the normal tissue and c1 be the concentration at or below which cells die. Let us first consider small tumours, so that there is no necrotic core (ie.) $r_1 = 0$ the boundary conditions are c(0) = 0 and $c(r_2) = c_2$. Multiplying equation (3) by r^2, we obtain

$$D\frac{d}{dr}\left(r^2\frac{dc}{dr}\right)=kr^2 \quad (4)$$

Integrating equation (4), we get

$$D\left(r^2\frac{dc}{dr}\right)=k\frac{r^3}{3}+A \quad (5)$$

and dividing the above equation by r^2 we obtain

$$D\left(\frac{dc}{dr}\right)=k\frac{r}{3}+\frac{A}{r^2}. \quad (6)$$

Again integrating equation (6), we get

$$c(r)=\frac{1}{6}\frac{k}{D}r^2+\frac{A}{r}+B. \quad (7)$$

Multiplying the equation (7) by r, we arrive at the result

$$rc(r)=\frac{1}{6}\frac{k}{D}r^3+A+Br \quad (8)$$

where A and B are the two constants of integration.

Using the boundary conditions to find the values of the constants of integration, we have

$$c(0)=0\Rightarrow A=0$$

$$c(r_2)=c_2\Rightarrow B=c_2-\frac{1}{6}\frac{k}{D}r_2^2$$

and therefore equation (8) implies that

$$c(r)=-\frac{1}{6}\frac{k}{D}(r_2^2-r^2)+c_2. \quad (9)$$

This is valid as long as $c(0) \geq c_1$, because for a necrotic core to be formed we must have $c(r_1) \leq c_1$. Since we are looking at the situation where there is no necrotic core, $r_1 = 0$, so $c(0) \geq c_1$. From equation (9)

$$c(r_1)=-\frac{1}{6}\frac{k}{D}(r_2^2-{r_1}^2)+c_2 \quad (10)$$

substituting $r_1 = 0$ and using the condition $c(0) \geq c_1$, we have

$$r_2^2 \leq \frac{6D}{k}(c_2-c_1) \quad (11)$$

we define

$$\frac{6D}{k}(c_2-c_1)=r_c^2 \quad (12)$$

to the critical value of r below which tumour will not have necrotic core. Therefore in such case

$$r_2^2 \leq \frac{6D}{k}(c_2-c_1)=r_c^2 \quad (13)$$

Now we assume that $r_2 > r_c$, so that $r_1 > 0$, which means that there is a necrotic core. We want to find how large is r_1 for given size of the tumour. Using the result (7), the necrotic core c must be constant (say $c = \hat{c}$), $\hat{c} \leq c_1$ by definition. Since c_1 is the concentration at or below which cells die, then we have $\hat{c} = c_1$ as the maximum concentration in which a necrotic core will be formed. The boundary conditions for the region of living cells are

$$c(r_1) = c_1;\ c(r_2) = c_2;\ J(r_1) = 0 \quad (14)$$

where $J=-D\frac{dc}{dr}$, J is the (radial) flux of nutrient which is proportional to the gradient of the concentration of nutrient $\left(J\propto\frac{dc}{dr}\right)$ where D > 0 is known as the diffusion coefficient, and the negative sign indicates that the diffusion of nutrients is from a high concentration to low concentration region. The condition at $r = r_2$ is as before the conditions at $r = r_1$ ensure continuity of concentration and flux at the boundary with the necrotic core. Note that there are three boundary conditions, although equation (3) is only a second order differential equation. The extra condition is crucial in allowing us to determine r_1. From (7) and using the boundary conditions, we obtain

$$c_1=\frac{k}{6D}r_1^2+\frac{A}{r_1}+B \quad (15)$$

$$c_2=\frac{k}{6D}r_2^2+\frac{A}{r_2}+B \quad (16)$$

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And $$J(r_1) = 0 \Rightarrow -D\frac{dc}{dr_1} = 0 \Rightarrow \frac{dc}{dr_1} = 0$$

$$D\frac{dc}{dr_1} = \frac{kr_1}{3} + \frac{A}{r_1^2}$$

$$\frac{dc}{dr_1} = \frac{kr_1}{3D} + \frac{A}{r_1^2 D}$$

$$\frac{dc}{dr_1} = \frac{kr_1}{3D} - \frac{A}{r_1^2}, \quad \text{where } \frac{A}{D} = -A$$

$$\Rightarrow \frac{kr_1}{3D} - \frac{A}{r_1^2} = 0 \Rightarrow A = \frac{kr_1^3}{3D}.$$

Using equations (15) and (16), subtracting c_1 from c_2 and substituting the value of A, we have

$$c_2 - c_1 = \frac{k}{6D}(r_2^2 - {r_1}^2) + \frac{kr_1^3}{3D}\left(\frac{1}{r_2} - \frac{1}{r_1}\right)$$

$$= \frac{k}{6D}\left[(r_2^2 - {r_1}^2) - 2r_1^3\left(\frac{1}{r_2} - \frac{1}{r_1}\right)\right]$$

$$= \frac{kr_2^2}{6D}\left[\left(1 - \frac{r_1^2}{r_2^2}\right) - \frac{2r_1^3}{r_2^2}\left(\frac{1}{r_2} - \frac{1}{r_1}\right)\right]$$

$$= \frac{kr_2^2}{6D}\left[\left(1 - \frac{r_1}{r_2}\right)\left(1 - \frac{r_1}{r_2} + 2\frac{r_1}{r_2} - \frac{2r_1^2}{r_2^2}\right)\right]$$

$$= \frac{kr_2^2}{6D}\left(1 - \frac{r_1}{r_2}\right)^2\left(1 + \frac{2r_1}{r_2}\right).$$

Therefore $$c_2 - c_1 = \frac{k}{6D}\left(1 + \frac{2r_1}{r_2}\right)(r_2 - r_1)^2. \qquad (17)$$

If $r_2 \to \infty$, then from (17) the necrotic core also grows with $\frac{r_1}{r_2} \to 1$ and difference between the radius of the tumour and necrotic core become constant, (ie.) $r_2 - r_1 \to h$, a constant, where

$$h^2 = 2\frac{D}{k}(c_2 - c_1). \qquad (18)$$

Hence it gives the thickness of the shell proliferation cells which does not depend on the size of the tumour itself but depends on the excess nutrient concentration above the threshold, that is, how fast the nutrient is consumed and how fast it diffuses. By knowing the size of this shell, the treatment of the tumour can be done so as to kill the tumour cells in this area using therapy or removing them by an operation.

III. SPATIAL MODEL WITH NUTRIENT

It is usual to include nutrients (glucose, oxygen) as a limitation for growth. This is in particular necessary for avascularized tumours to explain appearance of necrotic core: the center of the tumour becomes quiescent by lack of nutrients and then necrotic. In other words cells can die in the core of the tumour. With a single concentration for nutrients, the equation is extended as follows

$$\frac{\partial n}{\partial t} - div\big(n\nabla\pi(n)\big) = nR\big(p(x,t); c(x,t)\big), x \in \Re^d, t \geq 0$$

$$r\frac{\partial c}{\partial t} - \delta c + \lambda cn + rc = rc_b$$

$$\pi(n) = n^\gamma$$

where

1. c(x; t) represents the nutrients which is diffused though the tumour
2. c_b (a constant here) is the fresh nutrient provided by the vasculature with a rate r,
3. R(p; n) is the growth/death rate. We assume that there is a minimal nutrient concentration c_{min} needed for maintenance (if c is below the concentration $c_{min} < c_b$, cells are dying whatever p),

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$$\frac{\partial R(p,c)}{\partial p} < 0, \frac{\partial R(p,c)}{\partial c} < 0, R(p, c_{min}) \leq 0, R(k, c_b) = 0.$$

IV. NECROTIC CORE AND THE NUTRIENT INSTABILITY

Nutrients not only explain the necrotic core in the center of the tumour; they also play a role on stability of the PDE. The growth property $\frac{\partial n}{\partial t} > 0$ is also a type of stability condition. This property becomes wrong when nutrients are included in the model, leading to the `nutrients instability'. The intuition is simple; if some cells are in front of the core of the tumour, they have access to fresh nutrients with higher concentration and thus they can proliferate faster. The numerical simulations are based on a standard variant of system of equations given above, where nutrients are provided from the boundary of the tumour

$$\frac{\partial n}{\partial t} - div\big(n\nabla\pi(\mathrm{n})\big) = \mathrm{nR}\big(\mathrm{c}(\mathrm{x},\mathrm{t})\big), \mathrm{x} \in \Re^{\mathrm{d}}, \mathrm{t} \geq 0$$

$$-\delta c + \lambda cn = 0, c(x) \to c_{b,} \quad \text{for } |\mathrm{x}| \to \infty$$

$$\pi(n) = n^{\gamma}.$$

V. CONCLUSION

An increasing variety of mathematical models has made its way into cancer research over the past couple of decades. Currently the hardest challenges in modeling tumour growth and treatment are estimating parameters in models that are mathematically simple and are broadly applicable. Large numbers of tumour cells can be shed daily into the angiogenic blood vessels that have been recruited to the tumour. Large solid tumours contain cells that release one or more angiogenic factors such as basic fibroblast growth factor and vascular endothelial growth factor. The best strategies for inhibiting angiogenesis repress the ability of the endothelial cell to participate in the angiogenic process rather than prevent tumour cells from producing one particular angiogenic factor, since the plasticity of the tumour cell population generally allows the development of cells that produce other angiogenic factors and thus the tumour may become resistant to treatment. The additional clinical testing of newly identified angiogenic inhibitors using a variety of delivery strategies is eagerly awaited.

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