BULLETIN OF THE
GREEK MATHEMATICAL SOCIETY
Volume 57, 2010 (189–197)

# On the effect of 3D anisotropic tumour growth on modelling the nutrient distribution in the interior of the tumour

M. Hadjinicolaou and F. Kariotou

**Abstract**

When cancer tumour growth is considered from the continuum mechanics point of view, the determination of the tumour's exterior boundary demands the solution of a differential equation or an integrodifferential equation, which involves the nutrient concentration field. So it is of crucial importance to have an accurate model for determining the nutrient distribution in the interior of the tumour. The common geometrical assumption is that as a tumour grows, it maintains a multilayer structure consisting of concentric spheres. Each layer is occupied by cells that receive different concentration of vital nutrients which affects their living status. The nutrient concentration field in the interior and the exterior of the tumour is proved to exhibit only radial dependence and the tumour's interfaces are characterized by constant nutrient values. In this work we focus on the implications appearing on the nutrient distribution, when we depart from the spherical symmetry and assume ellipsoidal geometry. It is revealed that when a multilayer confocal ellipsoidal model is considered, the regions occupied by cells with different vitality state can no longer be distinguished by interfaces of constant nutrient concentration, and the locus of the critical nutrient values has to be redefined .

## 1. Introduction

When dealing with cancer tumour growth one is faced with many different interrelated proceedures, such as the nutrient diffusion and uptake from the cancer cells, the cell division, death and integration, the elastic interractions between the tumour tissue and the healthy tissue and also the inner pressure effects, the drug diffusion and uptake or the effect of inner produced inhibitors on the tumour's growth. Nowadays, new theories and approaches are developed along with a vast of experimental data. Thus, a mathematical framework is needed more than ever, in order to cope with such an amound of information. The development of mathematical models provide such a framework, through which the different hypotheses cancerning the mechanisms involved, can be evaluated.

Roughly speaking a tumour consists of cells that consume nutrients and proliferate, resulting to a cell colony that grows invading healthy tissue. The colony growth follows

three distinct stages. At the first stage, the tumour is less than 2mm small and all cells enjoy an abundance of nutrient, which is diffused from the surrounding medium and it is enough to keep the cells all alive and proliferating. As the tumour grows, it reaches at the second stage where only the cells which are close to the exterior boundary of the tumour receive enough nutrient to proliferate. These cells form an exterior proliferating layer $V_p$, which includes a region $V_q$ , where the cells live in a quiescent, not proliferating phase. The quiescent layer in turn includes a necrotic core $V_n$ where cells do not receive enough nutrient to sustain life. This is the fully developed stage, which eventually leads to a steady state, when the cell proliferation balances the cell death, due to necrosis or apoptosis and then, the total volume of the tumour remains constant. An avascular tumour, ceases its growth at this stage and can either be surgically removed or remain harmless into the host tissue. Most tumours though, pass to the third stage, that of angiogennesis, where biochemical processes result to the formation of new blood vessels in the vicinity of the tumour, targeting towards the tumour, and they eventually provide constant nutrient supply. Therefore, the vascularized tumour enjoys no nutrient restrictions and its growth becomes explosive.

Three main categories in mathematical modelling of the avascular tumour growth have been developed since 1928, when the first mathematical paper was published on the diffusion mechanism of a nutrient that is consumed by metabolic processes [1]. Most models treat the tumours from the continuum mechanics point of view, while others consider stochastic processes, in order to take into account details of the cell-cell interactions. Recently, hybrid models have been developed, in order to increase the efficiency of the model. These models combine the continuum aspect for some regions and the discrete cell discription for regions highly important in cell activity, such as the proliferative region [2].

In the present work we focus on the continuum modelling of avascular tumour growth, where the majority of the relative litterature deals with the spherically symmetric growth [3-8]. This choise is in a good agreement with experimental results from tumours grown in vitro, having no elastic or nutrition restrictions generated by the surrounding medium. Nevertheless, the effects of physical confinement on tumour growth are profound in vivo and they have been considered in the last decade, both experimentally [9,10] and analytically [11]. In order to study further the analytical effects of an anisotropic avascular growth on the nutrient distribution in the interior of the tumour, we make certain basic assumptions, which we list in the sequel.

The tumour is considered as an incompressible fluid, which receives nutrients by diffusion from its surrounding. All parts of the fully developed tumour are characterized by the same constant of diffusion $k$. The tumour and its surrounding are always in a diffusive equilibrium state. Therefore, the nutrient concentration field has to be harmonic everywhere. Cells occupying the exterior surface of the tumour consume nutrients at a constant rate $\gamma$ and proliferate at a constant rate $\beta$.

The vitality condition of the cells is controlled by the amound of nutrient which is available. The following critical nutrient values are considered: The surrounding of the tumour provides nutrients at a constant concentration $\sigma_0$. The minimum value of $\sigma$ which can support proliferation is denoted by $\sigma_1$and it coincides with the maximum value which provides quiescence. The minimum value of $\sigma$ that can support life, is denoted by $\sigma_2$. In regions where the nutrient concentration is below that value, only dead cells can be met.

The geometrical anisotropy is imposed on the tumour through the elastic properties of the physical means that surrounds the tumour. In particular, we consider the tumour to be consisted of three confocal ellipsoidal regions,that preserve their shape troughout the evolution of the tumour .

When the spherical geometry is used to model the tumour growth, the interfaces between regions of cells with different vitability state, are characterized by constant

nutrient concentration values. This is a consequence of the nutrient radial distribution inside the tumour, and it is in agreement with the definition of the critical values of the nutrient concentration, that determine the position of each cell inside the tumour. On the other hand, in ellipsoidal growth, the interior nutrient distribution is proved to be no longer radial. It turns out that the interfaces inside the tumour are no longer the locus of the cells that enjoy constant nutrient concentration and thus, the critical values alone cannot determine the position of a cell. In the present work we examine closely the effects that the assumption of anisotropic growth has on the nutrient distribution in the interior of the tumour.

In section 2 we formulate the problem in ellipsoidal geometry and we provide the basic notation of the ellipsoidal coordinate system. Section 3 provides the solution of the problem and the basics of the spectral decomposition of the Laplace operator in ellipsoidal coordinates. Also, the corresponding problem in spherical geometry is solved. The analogies between the spherical and the ellipsoidal results, as well as further questions are discussed in section 4.

## 2. Statement of the problem

We consider the confocal ellipsoidal coordinate system $(\rho, \mu, \nu)$ with foci $(\pm h_2, 0, 0)$, $(\pm h_3, 0, 0)$, $(0, \pm h_1, 0)$, defined through the following formulae with respect to the Cartesian coordinates $(x_1, x_2, x_3)$ of the point $\mathbf{r} = (\rho, \mu, \nu)$ [12]

$$x_1 = \frac{\rho\mu\nu}{h_2 h_3} \tag{1}$$

$$x_2 = \frac{\sqrt{\rho^2 - h_3^2}\sqrt{\mu^2 - h_3^2}\sqrt{h_3^2 - \nu^2}}{h_1 h_3} \tag{2}$$

$$x_3 = \frac{\sqrt{\rho^2 - h_2^2}\sqrt{h_2^2 - \mu^2}\sqrt{h_2^2 - \nu^2}}{h_1 h_2} \tag{3}$$

where $0 \leq \nu^2 \leq h_3^2 \leq \mu^2 \leq h_2^2 \leq \rho^2$.

In ellipsoidal terms, the fully developed structure of an avascular tumour is defined as follows. The necrotic region $V_n$ corresponds to the ellipsoidal core $h_2 \leq \rho < \rho_n$ , the quiescent layer $V_q$ corresponds to the next ellipsoidal shell $\rho_n < \rho < \rho_q$ and the proliferating ellipsoidal layer $V_p$ corresponds to $\rho_q < \rho < \rho_p$. An exterior ellipsoidal shell $V_R$ , where $\rho_p < \rho < R$ , surrounds the tumour and models the healthy host surrounding, which provides nutrients at a constant concentration $\sigma_0$ . The boundary interfaces are denoted by $S_i$, and correspond to the values $\rho = \rho_i$, of the ellipsoidal radial coordinate , for $i = n, q, p, R$ respectively.

In all regions $V_i$ , $i = n, q, p, R$ the nutrient concentration $\sigma_i(\rho, \mu, \nu)$ satisfies the Laplace equation:

$$\triangle\, \sigma_i(\mathbf{r}) = 0, \;\; \mathbf{r} \in V_i \tag{4}$$

while $\sigma_1 < \sigma_p(\mathbf{r}) < \sigma_0$ for $\mathbf{r} \in V_p$ and $\sigma_2 < \sigma_q(\mathbf{r}) < \sigma_1$ for $\mathbf{r} \in V_q$ .

By applying the mass conservation law upon a cylindrical control volume on each interface and taking the limit as the control volume vanishes, we obtain the boundary conditions

$$\widehat{\boldsymbol{n}} \cdot \nabla(\sigma_e - \sigma_p)(\mathbf{r}) = -\frac{\beta\gamma}{k} h_\rho(\mathbf{r}) \tag{5}$$

for $\mathbf{r} \in S_p$,

$$\widehat{\boldsymbol{n}} \cdot \nabla(\sigma_p - \sigma_q)(\mathbf{r}) = -\frac{S_q\gamma}{k} h_\rho(\mathbf{r}) \tag{6}$$

for $\mathbf{r} \in S_q$ and for $\mathbf{r} \in S_n$

$$\widehat{\boldsymbol{n}} \cdot \nabla \left(\sigma_q - \sigma_n\right)(\mathbf{r}) = -\frac{S_n \gamma}{k} h_\rho(\mathbf{r}) \tag{7}$$

where $\hat{\boldsymbol{n}}$ is the unit normal vector at the point $\mathbf{r} \in S_i$ which is the ellipsoidal radial unit vector $\hat{\boldsymbol{\rho}}$, $k$ denotes the diffusivity constant, $\gamma$ stands for the nutrient consumption rate at the exterior surface of the tumour, $S_q$ stands for the rate of gain in quiescent cells per unit volume and $S_n$ denotes the cell loss rate per unit volume, due to necrosis or apoptosis. Since $\gamma$ is the rate of nutrient mass exhaustion per unit area and also $S_n$ is the rate of cellular loss per unit volume, these are negative constants. Moreover, the quantity $h_\rho(\mathbf{r})$ represents the ellipsoidal radial metric coefficient at the point $\mathbf{r}$, defined as

$$h_\rho(\mathbf{r}) = \sqrt{\frac{\left(\rho^2 - \mu^2\right)\left(\rho^2 - \nu^2\right)}{\left(\rho^2 - h_2^2\right)\left(\rho^2 - h_3^2\right)}}. \tag{8}$$

For $\mathbf{r} \in S_R$ we assume that

$$\widehat{\boldsymbol{n}} \cdot \nabla \sigma_e(\mathbf{r}) = 0. \tag{9}$$

Furthermore, continuity conditions for the nutrient concentration fields should hold on each interface

$$\sigma_e(\mathbf{r}) = \sigma_p(\mathbf{r}),\ \mathbf{r} \in S_p \tag{10}$$

$$\sigma_q(\mathbf{r}) = \sigma_p(\mathbf{r}),\ \mathbf{r} \in S_q \tag{11}$$

$$\sigma_q(\mathbf{r}) = \sigma_n(\mathbf{r}),\ \mathbf{r} \in S_n \tag{12}$$

Finally,

$$\sigma_e(\mathbf{r}) = \sigma_0,\ \ \mathbf{r} \in S_R. \tag{13}$$

## 3. The nutrient concentration field

### 3.1. The ellipsoidal model

In order to solve the boundary value problem (4)-(13), we hereby give the basic notation and relations of the spectral analysis of the Laplace operator in Ellipsoidal geometry, that we use in the present work. For further analysis one can find detailed theory and relations in [12] and [13] .

The Laplace interior eigenfunctions are the Lami products

$$\mathrm{IE}_n^m(\mathbf{r}) = E_n^m(\rho)\, E_n^m(\mu)\, E_n^m(\nu) \tag{14}$$

and the exterior eigenfunctions are given by

$$\mathrm{IF}_n^m(\mathbf{r}) = (2n+1)\, I_n^m(\rho)\, E_n^m(\rho)\, E_n^m(\mu)\, E_n^m(\nu) \tag{15}$$

where $I_n^m(\rho)$ is the elliptic integral

$$I_n^m(\rho) = \int_\rho^{+\infty} \frac{dt}{\left[E_n^m(t)\right]^2 \sqrt{\left(t^2 - h_2^2\right)\left(t^2 - h_3^2\right)}} \tag{16}$$

and $E_n^m(x)$ ,for $x = \rho, \mu, \nu$, is the, regular at the origin, solution of degree $n$ and order $m$, of the Lami ordinary differential equation [12,13].

The ellipsoidal expansion of the solution of the problem (4)-(13) in each region of the tumour reads as

$$\sigma_e(\mathbf{r}) = \sum_{n=0}^{+\infty} \sum_{m=1}^{2n+1} \left[ g_n^m + (2n+1) I_n^m(\rho) a_n^m \right] \mathrm{IE}_n^m(\mathbf{r}) \tag{17}$$

for $\mathbf{r} = (\rho, \mu, \nu) \in V_R$, i.e. $\rho_p < \rho < R$,

$$\sigma_p(\mathbf{r}) = \sum_{n=0}^{+\infty} \sum_{m=1}^{2n+1} \left[ b_n^m + (2n+1) I_n^m(\rho) c_n^m \right] \mathrm{IE}_n^m(\mathbf{r}) \tag{18}$$

for $\mathbf{r} = (\rho, \mu, \nu) \in V_p$, i.e. $\rho_q < \rho < \rho_p$,

$$\sigma_q(\mathbf{r}) = \sum_{n=0}^{+\infty} \sum_{m=1}^{2n+1} \left[ d_n^m + (2n+1) I_n^m(\rho) e \right] {}_n^m \mathrm{IE}_n^m(\mathbf{r}) \tag{19}$$

for $\mathbf{r} = (\rho, \mu, \nu) \in V_q$, i.e. $\rho_n < \rho < \rho_q$, and

$$\sigma_n(\mathbf{r}) = \sum_{n=0}^{+\infty} \sum_{m=1}^{2n+1} f_n^m \mathrm{IE}_n^m(\mathbf{r}) \tag{20}$$

for $\mathbf{r} = (\rho, \mu, \nu) \in V_n$, i.e. $h_2 \leq \rho < \rho_n$.

In order to apply the boundary conditions (5)-(7) we note that the normal derivative on the ellipsoidal surface is given by

$$\hat{\boldsymbol{\rho}} \cdot \nabla = \frac{1}{h_\rho(\mathbf{r})} \frac{\partial}{\partial \rho}$$

and therefore we make use of the following ellipsoidal expansion of $h_\rho^2(\mathbf{r})$ [11]

$$h_\rho^2(\rho, \mu, \nu) = u(\rho) E_0^1(\mu) E_0^1(\nu) + \upsilon(\rho) E_2^1(\mu) E_2^1(\nu) + w(\rho) E_2^2(\mu) E_2^2(\nu) \tag{21}$$

where

$$u(\rho) = \frac{\left(\rho^2 + \Lambda - a_1^2\right)\left(\rho^2 + \Lambda' - a_1^2\right)}{\left(\rho^2 - h_2^2\right)\left(\rho^2 - h_3^2\right)} \tag{22}$$

$$\upsilon(\rho) = \frac{-\left(\rho^2 + \Lambda' - a_1^2\right)}{\left(\Lambda - \Lambda'\right)\left(\rho^2 - h_2^2\right)\left(\rho^2 - h_3^2\right)} \tag{23}$$

$$w(\rho) = \frac{\left(\rho^2 + \Lambda - a_1^2\right)}{\left(\Lambda - \Lambda'\right)\left(\rho^2 - h_2^2\right)\left(\rho^2 - h_3^2\right)} \tag{24}$$

and the Lami functions $E_0^1(x)$, $E_2^1(x)$, $E_2^2(x)$ for $x = \mu, \nu$ are

$$E_0^1(x) = 1, \;\; E_2^1(x) = x^2 + \Lambda - a_1^2, \;\; E_2^2(x) = x^2 + \Lambda' - a_1^2.$$

In equations (22)-(24) the parameters $\Lambda, \Lambda'$, $a_1$ refer to the reference ellipsoid $\rho = a_1$ of the ellipsoidal coordinate system under consideration, which in Cartesian coordinates is given by

$$\frac{x_1^2}{a_1^2} + \frac{x_2^2}{a_2^2} + \frac{x_3^2}{a_3^2} = 1$$

with $0 < a_3 < a_2 < a_1 < +\infty$ and $\Lambda, \Lambda'$ are roots of the quadratic equation

$$\sum_{i=1}^{3} \frac{1}{(\Lambda - a_i^2)} = 0.$$

Moreover, it can be shown that, due to the confocality of the ellipsoidal boundaries, the following equations hold true

$$\Lambda - a_1^2 = \Lambda_p - \rho_p^2 = \Lambda_q - \rho_q^2 = \Lambda_n - \rho_n^2$$

and similarly

$$\Lambda' - a_1^2 = \Lambda'_p - \rho_p^2 = \Lambda'_q - \rho_q^2 = \Lambda'_n - \rho_n^2,$$

and

$$\Lambda - \Lambda' = \Lambda_p - \Lambda'_p = \Lambda_q - \Lambda'_q = \Lambda_n - \Lambda'_n,$$

where $\Lambda_i$ and $\Lambda'_i$ are the corresponding parameters for the confocal ellipsoids $\rho = \rho_i$, for $i = p, q, n$.

Applying the boundary conditions (5)-(7) and (10)-(13) in the expressions (17)-(20) and using the expansion (21)-(24) appropriately on each boundary, we calculate the unknown coefficients and obtain the following forms of the nutrient concentration

$$\sigma_e(\mathbf{r}) = \sigma_0 + \frac{\gamma}{k}(\beta U_p + S_q U_q + S_n U_n)\left(I_0^1(\rho, R) + \frac{I_2^2(\rho, R)\,\mathrm{IE}_2^2(\mathbf{r}) - I_2^1(\rho, R)\,\mathrm{IE}_2^1(\mathbf{r})}{\Lambda - \Lambda'}\right) \tag{25}$$

for $\mathbf{r} = (\rho, \mu, \nu) \in V_R$, i.e. $\rho_p < \rho < R$,

$$\begin{aligned}\sigma_p(\mathbf{r}) = \sigma_0 &+ \frac{\gamma}{k}\left\{\beta U_p I_0^1(\rho_p, R) + (S_q U_q + S_n U_n) I_0^1(\rho, R)\right\} \\ &- \frac{\gamma}{k}\left\{\beta U_p I_2^1(\rho_p, R) + (S_q U_q + S_n U_n) I_2^1(\rho, R)\right\}\frac{\mathrm{IE}_2^1(\mathbf{r})}{\Lambda - \Lambda'} \\ &+ \frac{\gamma}{k}\left\{\beta U_p I_2^2(\rho_p, R) + (S_q U_q + S_n U_n) I_2^2(\rho, R)\right\}\frac{\mathrm{IE}_2^2(\mathbf{r})}{\Lambda - \Lambda'}\end{aligned} \tag{26}$$

for $\mathbf{r} = (\rho, \mu, \nu) \in V_p$, i.e. $\rho_q < \rho < \rho_p$,

$$\begin{aligned}\sigma_q(\mathbf{r}) = \sigma_0 &+ \frac{\gamma}{k}\left\{\beta U_p I_0^1(\rho_p, R) + S_q U_q I_0^1(\rho_q, R) + S_n U_n I_0^1(\rho, R)\right\} \\ &- \frac{\gamma}{k}\left\{\beta U_p I_2^1(\rho_p, R) + S_q U_q I_2^1(\rho_q, R) + S_n U_n I_2^1(\rho, R)\right\}\frac{\mathrm{IE}_2^1(\mathbf{r})}{\Lambda - \Lambda'}\end{aligned}$$

$$+\frac{\gamma}{k}\left\{\beta U_p I_2^2\left(\rho_p,R\right)+S_q U_q I_2^2\left(\rho_q,R\right)+S_n U_n I_2^2\left(\rho,R\right)\right\}\frac{\mathrm{IE}_2^2\left(\mathbf{r}\right)}{\Lambda-\Lambda'} \tag{27}$$

for $\mathbf{r}=(\rho,\mu,\nu)\in V_q$, i.e. $\rho_n<\rho<\rho_q$, and finally in the necrotic core the nutrient concentration is

$$\sigma_n\left(\mathbf{r}\right)=\sigma_0+\frac{\gamma}{k}\left\{\beta U_p I_0^1\left(\rho_p,R\right)+S_q U_q I_0^1\left(\rho_q,R\right)+S_n U_n I_0^1\left(\rho_n,R\right)\right\}$$

$$-\frac{\gamma}{k}\left\{\beta U_p I_2^1\left(\rho_p,R\right)+S_q U_q I_2^1\left(\rho_q,R\right)+S_n U_n I_2^1\left(\rho_n,R\right)\right\}\frac{\mathrm{IE}_2^1\left(\mathbf{r}\right)}{\Lambda-\Lambda'}$$

$$+\frac{\gamma}{k}\left\{\beta U_p I_2^2\left(\rho_p,R\right)+S_q U_q I_2^2\left(\rho_q,R\right)+S_n U_n I_2^2\left(\rho_n,R\right)\right\}\frac{\mathrm{IE}_2^2\left(\mathbf{r}\right)}{\Lambda-\Lambda'} \tag{28}$$

for $\mathbf{r}=(\rho,\mu,\nu)\in V_n$, i.e. $h_2\leq\rho<\rho_n$.

In equations (25)-(28) $U_i=u\left(\rho_i\right)$, for $i=n,q,p$ where $u\left(\rho\right)$ is given in (8) and $I_n^m\left(x,y\right)=I_n^m\left(x\right)-I_n^m\left(y\right)$ , where $I_n^m\left(x\right)$is the elliptic integral defined in (16).

### 3.2. **The corresponding spherical model**

Following similar arguments for spherical geometry we obtain the corresponding model. All the tumour boundaries are concentric spheres with radii $0\leq r_n<r_q<r_p<R$. The formulation of the problem in spherical geometry is then given in (4)-(13) provided that the unit normal vector on a spherical surface is the radial vector, $\hat{\boldsymbol{n}}=\hat{\mathbf{r}}$ and that the radial metric coefficient in the spherical coordinate system is $h_r\left(\mathbf{r}\right)=1$.

The solution of the problem is obtained in a straightforward manner and reads as follows

$$\sigma_e\left(\mathbf{r}\right)=\sigma_0+\frac{\gamma}{k}\left(\beta r_p^2+S_q r_q^2+S_n r_n^2\right)\left(\frac{1}{r}-\frac{1}{R}\right) \tag{29}$$

for $r_p\leq r\leq R$,

$$\sigma_p\left(\mathbf{r}\right)=\sigma_0+\frac{\gamma}{k}\left\{\beta r_p^2\left(\frac{1}{r_p}-\frac{1}{R}\right)+\left(S_q r_q^2+S_n r_n^2\right)\left(\frac{1}{r}-\frac{1}{R}\right)\right\} \tag{30}$$

for $r_q\leq r\leq r_p$,

$$\sigma_q\left(\mathbf{r}\right)=\sigma_0+\frac{\gamma}{k}\left\{\beta r_p^2\left(\frac{1}{r_p}-\frac{1}{R}\right)+S_q r_q^2\left(\frac{1}{r_q}-\frac{1}{R}\right)+S_n r_n^2\left(\frac{1}{r}-\frac{1}{R}\right)\right\} \tag{31}$$

for $r_n\leq r\leq r_q$, and finally, in the necrotic core the nutrient concentration is constant and equal to $\sigma_n\left(r,\theta,\phi\right)=\sigma_q\left(r_n,\theta,\phi\right)$, where $(r,\theta,\phi)$ are the spherical coordinates of the point $\mathbf{r}$.

## 4. Discussion

As it is shown in equations (29)-(31) the nutrient concentration profile in the spherical model is radially symmetric and enjoys no angular dependence. Thus, the nutrient critical values are defined as the extreme values of the real functions $\sigma_i(r)$, $i = p, q, n$, which are continuous in compact sets and increase monotonically with the distance from the origin. Then,

$$\sigma_2 = \sigma_n(r_n, \theta, \phi) = \underset{r\in(r_q,r_p)}{min}\{\sigma_q(r, \theta, \phi)\} \tag{32}$$

and

$$\sigma_1 = \underset{r\in(r_q,r_p)}{max}\sigma_q(r, \theta, \phi) = \sigma_q(r_q, \theta, \phi) = \underset{r\in(r_p,R)}{min}\{\sigma_p(r, \theta, \phi)\}. \tag{33}$$

The above expressions define the "critical" manifolds for the spherical model, which are the 2-D equidensity spherical interior boundaries of the tumour.

Turning back to the ellipsoidal model, we are interested for a similar consept for the critical nutrient values. From the expressions (25)-(28), it is obvious that the dependance of the nutrient concentration profile in the angular variables $(\mu, \nu)$ enters through the ellipsoidal harmonics $\mathrm{IE}_2^1(\mathbf{r})$ and $\mathrm{IE}_2^2(\mathbf{r})$. As the nutrient field is still a function increasing with the distance from the origin, on passing from these boundaries the nutrient values assume their "radial" critical values, which is $(\mu, \nu)$ dependent. In other words, for every $(\mu, \nu)$ that defines a point on an ellipsoidal interface, the nutrient values $\sigma(\rho, \mu, \nu)$ are such that

$$\underset{\rho\in(h_2,\rho_n)}{max}\{\sigma_n(\rho, \mu, \nu)\} = \sigma_n(\rho_n, \mu, \nu) = \underset{\rho\in(\rho_q,\rho_p)}{min}\{\sigma_q(\rho, \mu, \nu)\} = \sigma_2(\mu, \nu) \tag{34}$$

and

$$\underset{\rho\in(\rho_q,\rho_p)}{max}\{\sigma_q(\rho, \mu, \nu)\} = \sigma_q(\rho_q, \mu, \nu) = \underset{\rho\in(\rho_p,R)}{min}\{\sigma_p(\rho, \mu, \nu)\} = \sigma_1(\mu, \nu). \tag{35}$$

In conclusion, when the geometrical model of the tumour departs from the spherical geometry, the interior boundaries of the tumour cannot be characterized by the constant critical nutrient values, which is the common practice in the mathematical modelling of avascular tumour growth. Therefore, questions are raised concerning the equidensity manifolds of the nutrient concentration profile in ellipsoidal growth and how do these implications of the locus of critical nutrient values affect the evolution of the tumour. These questions are under current investigation.

## References

[1] Hill, A. V., The Diffusion of Oxygen and Lactic Acid through Tissues, *R. Soc. Proc. B*, **104**, 39-96, (1928)

[2] Yangjin, K., Stolarska, m. A., Othmer, H. G., A Hybrid Model for Tumor Spheroid Growth in Vitro I: Theoretical Development and Early Results, *Mathematical Models and Methods in Applied Sciences*, **17**, 1773-1798, (2007)

[3] Roose, T., Chapman, S. J., Maini, P., Mathematical Models of Avascular Tumour Growth, *Siam Review,* **49**, 2, 179-208, (2007)

[4] H. P. Greenspan, "Models for the Growth of a Solid Tumor by Diffusion", *Studies in Applied Mathematics*, Vol. L1, No 4, pp. 317-341, (1972)

[5] R. M. Sutherland, "Cell and Environment Interactions in Tumor Microregions: The Multishell Spheroid Model", Science., 240, pp. 117-184, 1988
[6] H. M. Byrne, "The Role of Mathematics in Solid Tumour Growth", *Math. Today.*, **35**, pp. 59-89, (1999)
[7] M. A. Chaplain, "Avascular Growth, Angiogenesis and Vascular Growth in Solid Tumors: The Mathematical Modeling of the Stages of Tumor Development", Math. Comput. Modeling., 23, pp. 47-87, 1996
[8] B. D. Sleeman and D. S. Jones, "Differential Equations and Mathematical Biology", Chapman & Hall/CRC, 2003
[9] Helminger, G., Netti, P. A., Lichtenbeld, H. C., Melder, R. J., Jain, R. K., Solid Stress inhibits the growth of Multicellular Tumor Spheroids, *Nat. Biotechnol.*, **15**, 778-783, (1997)
[10] Bounaim, A., Holm, S., Wen Chen, Odegard, A., Detectability of Breast Lesions with CARI ultrasonography using a bioacoustic computational approach, *Comp. Math. Applics.*, **54**, 96-106, (2007)
[11] Dassios, G., Kariotou, F, Sleeman,B. D., Tsampas, M., Mathematical Modelling of Avascular Ellipsoidal Tumour Growth, *Quarterly of Applied Mathematics*, in press, (2009)
[12] Hobson, E.W., "The Theory of Spherical and Ellipsoidal Harmonics", Chelsea, N.Y., (1955).
[13] Dassios, G., Kariotou, F., "Magnetoencephalography in Ellipsoidal Geometry", *J. Math. Phys.*, **44**, pp.220-241, (2003)

◇ M. Hadjinicolaou and F. Kariotou
School of Science and Technology,
Hellenic Open University, Greece