

Effect of an External Medium on Tumor Growth-induced Stress

Matthias Ngwa and Ephraim Agyingi

Abstract—This paper is concerned with modeling the mechanical effect of an external isotropic elastic medium on the stress induced by a growing tumor that is embedded within the medium. Two cases of nutrient availability to the tumor cells are considered: ambient nutrient concentration and diffusion limited nutrient at tumor boundary. The quantitative stress effect of each of these parameters, including the initial radius of the tumor and ratio of cell death rate to proliferation rate, on the tumor growth-induced stress are examined. Numerical simulations that support experimental investigations are provided.

Index Terms—Tumor growth, Induce stress, Nutrient diffusion, External medium.

I. INTRODUCTION

The growth of a solid tumor is strongly influenced by its microenvironment. In addition to well documented microenvironmental parameters, such as hypoxia [1], [2] and angiogenesis [3], [4], mechanical stresses of the medium surrounding the tumor do also play an important role [5], [6], [7], [8], [9], [10]. A solid tumor growing in a confined space defined by surrounding tissue needs to overcome the resulting compressive forces. It has been demonstrated experimentally that the shape of the solid stress field dictates the shape of tumor spheroids. The effect was attributed to suppression of cell proliferation and induction of cell apoptosis in regions of high solid stress [5], [11]. Helmlinger *et al.* [12] also demonstrated experimentally that mechanical effects, such as stress, affect solid tumor growth and hypothesized that the converse may be true.

Some of the factors that influence the evolution of tumors have been incorporated into existing mathematical models [13], [14], [15], [16], [17], [18]. The mechanisms of cell proliferation and cell death, with varying assumptions, are examined in almost all existing models. Most of the existing models have focused on *in vitro* tumors growing in homogeneous environments. These environments are mainly considered to simplify the analysis. The mechanical effect of the medium surrounding the tumor, which may have a significant effect on the tumor growth rate and growth saturation, has been given very little attention in mathematical literature. Guided by the experimental work of Helmlinger *et al.* [12], Chen *et al.* in [19] developed a model to determine the effect of the mechanical properties that a deformable medium had on the growth of an avascular tumor embedded in the medium. The model in [19] predicts that an increase in the stiffness of the gel increases the stress induced and

delays the onset of necrosis, while reducing the growth rate and saturation size of the tumor. Although consistent with the experimental results at macroscopic level, the model in [19] is limited in that it does not allow for stress effects on cell proliferation and death rates.

The present paper is based on a previously reported simpler model by Jones *et al.* [20] which describes the development of a radially-symmetric, solid avascular tumor whose growth is regulated by a single externally supplied nutrient such as glucose or oxygen, that is assumed to diffuse freely throughout the tumor. Following their analysis, we extend the model to incorporate the stress effect of the external medium on the growth of a spherical tumor when nutrients are in abundance or limited supply at the periphery of the tumor.

II. MODEL FORMULATION

Some basic assumptions of previous models, which we also use to formulate the model here, are as follows: (i) the population of normal and abnormal cells form a single population, which is considered as a continuum; (ii) there is adhesion (restraining force) among living tumor cells at the boundary which holds the tumor in the form of a solid and to balance the expansive force caused by internal cell proliferation [21], [22]; (iii) the tumor is a sphere and spherical symmetry is maintained at all times [21], [22]; (iv) the tumor is in a state of diffusive equilibrium [22]; (v) The rate of nutrient consumption and cell proliferation rate are proportional to both the nutrient concentration and tumor cell density, while cell death is proportional to cell density [20]; (vi) the tumor material is incompressible and responds to stress in a purely elastic and isotropic manner; and (vii) the external medium is elastic and incompressible.

In the derivation of the model, the following notation for variables is used:

<i>variable</i>	<i>description</i>
t	time
r	radial coordinate
R	radius of sphere at time t
R_0	radius of sphere at time $t = 0$
$c(r, t)$	nutrient concentration inside tumor
c_0	nutrient concentration at infinity
$v_i, \underline{v}, v(r, t)$	tumor velocity and speed
u, u_i	displacement
σ_{ij}	stress tensor of tumor
σ_{ij}^e	stress tensor of external medium
e_{ij}	strain tensor of tumor
e_{ij}^e	strain tensor of external medium
ρ	tumor cell density

Matthias Ngwa is with the Calgary Board of Education, Calgary, AB T2G 2L9, Canada. (E-mail: matthias.ngwa@gmail.com)

Ephraim Agyingi is with the School of Mathematical Sciences, College of Science, Rochester Institute of Technology, Rochester, NY 14623-5603, USA. (E-mail: eoasma@rit.edu)

Corresponding author: E-mail: eoasma@rit.edu

A. Nutrient Concentration

The tumor grows as a sphere of radius $R(t)$. We consider two situations by which nutrients are made available to the tumor cells:

Case I: Constant nutrient concentration at the tumor boundary, i.e., $c = c_0$ at $r = R$;

Case II: Diffusion limited exterior (constant nutrient concentration at infinity), i.e., $c \rightarrow c_0$ as $r \rightarrow \infty$.

By employing assumptions (iv) and (v) above, the equation of nutrient concentration inside the tumor is

$$\frac{\partial c}{\partial t} + \underline{v} \cdot \nabla c = D_c \nabla^2 c - A_c c \rho, \tag{1}$$

where D_c is the rate of diffusion, which by our assumption is constant; and A_c is the nutrient consumption rate. We assume that the tumor cell density (mass/unit volume) is constant.

We show later that the velocity term v has a magnitude of $\alpha c_0 L$. Hence both of the first two terms on the left hand side of equation (1) have the same order of magnitude. It can then be shown that both of these terms are small in comparison with the diffusion and growth term if $L^2 \alpha c_0 / D_c \ll 1$. Hence in Case I, the equation of nutrient concentration is therefore

$$D_c \nabla^2 c = A_c c \rho, \tag{2}$$

where $c = c_0$ (constant) at the tumor boundary ($r = R$).

In Case II we have the same equation in the interior but there is a diffusion limited exterior. Thus we have

$$D_c \nabla^2 c = \begin{cases} A_c c \rho, & r < R(t), \\ 0, & r > R(t), \end{cases} \tag{3}$$

where $c \rightarrow c_0$ as $r \rightarrow \infty$. At the tumor boundary c and $\partial c / \partial r$ are continuous, where $r > R(t)$ assumes that the diffusion coefficient is the same inside and outside the tumor; physically this condition is that the flux into the boundary equals the flux out of the boundary. Note that tumor cells consume nutrients at a greater rate than normal cells and we have idealized this in equation (3) by assuming that the nutrient consumption outside the tumor is zero.

B. Growth Equation

The competition between cell production (cell proliferation) and cell loss processes is expressed by

$$\text{growth} = \text{cell production} - \text{cell loss}.$$

Also, since cell proliferation is proportional to both nutrient concentration and cell density, and cell death is proportional to cell density, the growth (mass conservation) equation is

$$\underbrace{\frac{\partial \rho}{\partial t} + \nabla \cdot (\underline{v} \rho)}_{\text{Growth}} = \underbrace{\alpha c \rho}_{\text{Cell proliferation}} - \underbrace{k \rho}_{\text{Cell loss (death)}},$$

leading to

$$\frac{\partial \rho}{\partial t} + v \frac{\partial \rho}{\partial x} + \rho \nabla \cdot \underline{v} = (\alpha c - k) \rho, \tag{4}$$

where α and k , being both positive constants, are the proliferation and death rates, respectively.

As a consequence of the assumption of incompressibility of tumor material, $\frac{\partial \rho}{\partial t} + v \frac{\partial \rho}{\partial x} = 0$. The growth equation then takes the form

$$\nabla \cdot \underline{v} = \alpha c - k. \tag{5}$$

C. Kinematic Equation

The equation describing the motion of a surface $F = 0$ is given by [23]

$$\frac{dF}{dt} = 0. \tag{6}$$

Because of radial symmetry, F takes the form $F = r - R(t)$ and the velocity field has the form $\underline{v} = (v, 0, 0)$. Then (6) becomes

$$\frac{dR}{dt} = V(t), \tag{7}$$

where $V(t)$ denotes $v(R, t)$, the speed on the tumor boundary, $r = R$. This equation describes the growth rate of the tumor.

D. Stress Equilibrium

According to Wasserman *et al.* [24], in order to model the reaction of an object to a set of external forces, the stress-strain relationship or constitutive equation for the material under consideration must be known. As a consequence of assumption (i) above, the tumor is considered as a continuum and the forces (or force components) per unit area inside it are represented by the stress tensor σ_{ij} . Considering stress equilibrium with no inertial effects, we have

$$\frac{\partial \sigma_{ij}}{\partial x_j} + F_i = 0, \tag{8}$$

where F_i , ($i = 1, 2, 3$), denotes the components of the body-force per unit volume. We assume that body forces are negligible in comparison to surface forces. The stress equilibrium equation then becomes

$$\frac{\partial \sigma_{ij}}{\partial x_j} = 0. \tag{9}$$

E. Constitutive Equation

The constitutive equation for a given material describes the relationship between the stress, σ_{ij} , on the material element and its strain, e_{ij} . Turning to assumption (vi), and assuming that cell growth is isotropic, so that the strain resulting from it is isotropic, we can approximate the stress-strain relationship by Hooke's law for an isotropic elastic body:

$$e_{ij} = \frac{1 + \nu}{E} \sigma_{ij} - \frac{\nu}{E} \delta_{ij} \sigma_{kk}, \tag{10}$$

where ν is known as *Poisson's ratio* and E is *Young's modulus*, which can be experimentally determined for a given material.

For a small displacement field u_i , the strain tensor, e_{ij} , is defined by

$$e_{ij} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right). \tag{11}$$

The standard stress-strain relationship for an elastic solid in a small displacement field u_i is given by

$$\frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) = \frac{1 + \nu}{E} \sigma_{ij} - \frac{\nu}{E} \delta_{ij} \sigma_{kk}. \tag{12}$$

By an earlier assumption above, we considered the material to be incompressible, so $\nu = \frac{1}{2}$. Thus, it follows that

$$\frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) = \frac{1}{2E} (3\sigma_{ij} - \delta_{ij}\sigma_{kk}). \quad (13)$$

The mechanical behavior of many practical materials such as biological tissues can be treated as elastic only as long as the deformations remain very small. Problems concerning the elastic behavior of these materials therefore lie, in general, within the scope of classical theory of elasticity, which treats the deformations as infinitesimal. It is assumed in the classical theory of elasticity that the stress-deformation relations are linear and independent of time. In the case of biological tissues, strain (deformation) is often dependent both upon the duration of application as well as the rate of application of stresses [24]. That is, the strain experienced by the tumor cells depends on both the rate at which the neoplastic cells undergo growth and the mechanical stress. The effect requires other terms which we do not include in our model here. The growth process influences the stress-strain law. We consider the effect of this by introducing a growth factor. To account for the time dependence of growth, we take a Jaumann derivative of equation (13). (A Jaumann derivative is a material derivative in a frame rotating at a rate equal to the local angular velocity of the medium and it is one way of producing an objective constitutive equation.) The left hand side becomes the rate of strain tensor and the full equation is

$$\frac{1}{2} \frac{\mathcal{D}}{\mathcal{D}t} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) = \left[\begin{array}{c} \text{growth} \\ \text{factor} \end{array} \right] + \frac{1}{2E} \left\{ \frac{\mathcal{D}}{\mathcal{D}t} (3\sigma_{ij} - \sigma_{kk}\delta_{ij}) + 3(\omega_{ik}\sigma_{kj} - \sigma_{ik}\omega_{kj}) \right\}, \quad (14)$$

where ω_{ij} , the vorticity tensor, is given by $\omega_{ij} = -\frac{1}{2} \left(\frac{\partial v_i}{\partial x_j} - \frac{\partial v_j}{\partial x_i} \right)$. Considering the tumor geometry, we see that the vorticity tensor is equal to zero in our problem.

Taking the trace of the rate of strain tensor term, which is the volume strain or the change in volume per unit volume at a given point, gives $\nabla \cdot \underline{v}$. This is the growth term in equation (5). The growth term is given by $\nabla \cdot \underline{v} = 3g$, where g is the linear growth factor. It therefore follows that the stress-strain law inside the tumor is

$$\frac{1}{2} \left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} \right) = \frac{1}{3} (\nabla \cdot \underline{v}) \delta_{ij} + \frac{1}{2E} \left\{ \frac{\mathcal{D}}{\mathcal{D}t} (3\sigma_{ij} - \sigma_{kk}\delta_{ij}) \right\} \quad (15)$$

F. External Medium

We obtain the constitutive law for the medium surrounding the tumor by applying the same assumptions as above. The external medium, assumed to be elastic, satisfies the generalized Hooke's law for a linear elastic solid:

$$\begin{aligned} \sigma_{ij}^e &= \lambda \delta_{ij} e_{kk}^e + 2\mu e_{ij}^e \\ &= \lambda \delta_{ij} \frac{\partial u_k}{\partial x_k} + 2\mu e_{ij}^e, \end{aligned} \quad (16)$$

where λ and μ are known as Lamé constants, and u_i is the displacement of the elastic medium subject to the effect of the stress σ_{ij}^e . By assuming an isotropic elastic material, we

can express λ and μ in terms of E (Young's modulus) and ν (Poisson's ratio) to obtain

$$\sigma_{ij}^e = \frac{E\nu}{(1+\nu)(1-2\nu)} \delta_{ij} \frac{\partial u_k}{\partial x_k} + \frac{E}{(1+\nu)} e_{ij}^e, \quad (17)$$

where we assume that ν (Poisson's ratio) and E (Young's modulus) of the tumor and surrounding tissue are equal.

Since the elastic material under consideration is incompressible, we take the limit $\nu \rightarrow \frac{1}{2}$. By considering the expression for λ in (17) we see that $\lambda \rightarrow \infty$, which by implication makes $\partial u_k / \partial x_k = e_{kk} \rightarrow 0$. The product of the two terms remains finite and we express $\lambda e_{kk} \rightarrow -p$, where p is called the isotropic pressure. In this limit, the stress can then be expressed as

$$\sigma_{ij}^e = -p\delta_{ij} + \frac{2}{3} E e_{ij}^e. \quad (18)$$

We now discuss the boundary conditions on the stress. Without loss of generality, we may take $p_\infty = 0$, so $\sigma_{ij}^e = 0$ as $r \rightarrow \infty$. The radial stress, σ_r , and displacement, u_i , are continuous at the tumor boundary, $r = R$.

III. NONDIMENSIONALISATION

We now express the model's variables in spherically symmetric coordinates and dimensionless form. We shall only do this for Case I; the manipulations for Case II are similar. We introduce constants $L = \sqrt{D_c/A_c\rho}$, $T = 1/\alpha c_0$, and c_0 to denote length scale, tumor growth timescale and fixed externally supplied nutrient concentration respectively. We also define the dimensionless parameter

$$\epsilon = \frac{k}{\alpha c_0},$$

which represents the death rate per unit volume to the maximum growth rate per unit volume. For the tumor to grow significantly this parameter will be small. Using asterisks to denote dimensionless variables, we write

$$\begin{aligned} r^* &= \frac{r}{L}, & \sigma_{ij}^* &= \frac{\sigma_{ij}}{E}, & p^* &= \frac{p}{E}, & v^* &= \frac{v}{\alpha c_0 L}, \\ t^* &= \frac{t}{T}, & c^* &= \frac{c}{c_0}. \end{aligned}$$

These are now substituted into (2), (5), (9), and the equations are further simplified by using the radial symmetry assumption, $\underline{v} = (v, 0, 0)$. Hence, after dropping the asterisks, the model equations are converted to the form

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c}{\partial r} \right) = c \quad (19)$$

subject to the boundary conditions $c = 1$ at $r = R$ and c is finite at $r = 0$;

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 v) = c - \epsilon, \quad (20)$$

subject to $v = 0$ at $r = 0$; and

$$\begin{aligned} &\left\{ \frac{\partial \sigma_r}{\partial r} + \frac{2\sigma_r}{r} - \frac{\sigma_\theta + \sigma_\phi}{r} \right\} \mathbf{e}_r + \left\{ \frac{1}{r} \frac{\partial \sigma_\theta}{\partial \theta} \right. \\ &\left. + \frac{1}{r} \cot \theta (\sigma_\theta - \sigma_\phi) \right\} \mathbf{e}_\theta + \left\{ \frac{1}{\sin \theta} \frac{\partial \sigma_\phi}{\partial \phi} \right\} \mathbf{e}_\phi = 0, \end{aligned} \quad (21)$$

where $(\mathbf{e}_r, \mathbf{e}_\theta, \mathbf{e}_\phi)$ denote the unit vectors of the coordinate system. We have assumed here that, by the geometry of the tumor growth, the off-diagonal elements $(\sigma_{r\theta}, \sigma_{r\phi}, \sigma_{\theta\phi})$ of

the stress tensor are all zero.

Let $f_{11} = 2\sigma_r - \sigma_\theta - \sigma_\phi$, $f_{22} = 2\sigma_\theta - \sigma_r - \sigma_\phi$ and $f_{33} = 2\sigma_\phi - \sigma_r - \sigma_\theta$. With the radially-symmetric geometry under consideration, the constitutive equation, (15), of the model can be expressed as

$$\begin{pmatrix} \frac{\partial v}{\partial r} & 0 & 0 \\ 0 & \frac{v}{r} & 0 \\ 0 & 0 & \frac{v}{r} \end{pmatrix} = \frac{1}{3r^2} \frac{\partial}{\partial r} (r^2 v) \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} + \frac{1}{2} \left(\frac{\partial}{\partial t} + v \frac{\partial}{\partial r} \right) \begin{pmatrix} f_{11} & 0 & 0 \\ 0 & f_{22} & 0 \\ 0 & 0 & f_{33} \end{pmatrix}, \quad (22)$$

from which we obtain three equations from the diagonal elements (termed, respectively, the rr -, $\theta\theta$ -, and $\phi\phi$ -equations).

IV. RESULTS AND DISCUSSION

A. Model simplification for ambient nutrient concentration

We begin by deriving analytical expressions for the nutrient concentration and the cell velocity. The substitution $c = q/r$, where $q = q(r, t)$, reduces equation (19) to an ordinary differential equation for q with solution

$$c(r, t) = \frac{R \sinh r}{r \sinh R}. \quad (23)$$

By substituting this into equation (20), we obtain

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 v) = \frac{R \sinh r}{r \sinh R} - \epsilon, \quad (24)$$

It follows from the boundary condition $v = 0$ at $r = 0$ that

$$v = \frac{R}{r^2 \sinh R} (r \cosh r - \sinh r) - \frac{\epsilon r}{3}. \quad (25)$$

Subtracting the $\phi\phi$ - from the $\theta\theta$ -equation in (22), we obtain

$$\left(\frac{\partial}{\partial t} + v \frac{\partial}{\partial r} \right) (\sigma_\theta - \sigma_\phi) = 0. \quad (26)$$

At the initial moment ($t = 0$), we further assume that there are no stresses acting on the tumor. As such, it follows from equation (26) that

$$\sigma_\theta - \sigma_\phi = 0,$$

implying that $\sigma_\theta = \sigma_\phi$. Using this result in the rr - equation of expression (22), we obtain

$$\left(\frac{\partial}{\partial t} + v \frac{\partial}{\partial r} \right) (\sigma_r - \sigma_\theta) = \frac{2}{3} r \frac{\partial}{\partial r} \left(\frac{v}{r} \right). \quad (27)$$

Since v is a known quantity this equation can be integrated to determine the stress difference $\sigma_r - \sigma_\theta$. In the subsequent discussion, we thus consider $\sigma_r - \sigma_\theta$ to be a known quantity.

We now turn to the stress equilibrium equation (21), from which we obtain

$$\frac{\partial \sigma_{ij}}{\partial x_j} = 0 \Rightarrow \left\{ \begin{array}{l} \frac{\partial \sigma_r}{\partial r} + \frac{2\sigma_r}{r} - \frac{\sigma_\theta + \sigma_\phi}{r} \\ \frac{1}{r} \frac{\partial \sigma_\theta}{\partial \theta} + \frac{1}{r} \cot \theta (\sigma_\theta - \sigma_\phi) \\ \frac{1}{\sin \theta} \frac{\partial \sigma_\phi}{\partial \phi} \end{array} \right\} = 0. \quad (28)$$

Using $\sigma_\theta = \sigma_\phi$ in the first equation of the preceding expression, we have

$$\frac{\partial \sigma_r}{\partial r} + \frac{2}{r} (\sigma_r - \sigma_\theta) = 0. \quad (29)$$

Since $\sigma_r - \sigma_\theta$ is a known quantity this equation can be integrated to determine σ_r (and hence σ_θ also).

We now turn to the region exterior to the tumor. We will solve the constitutive equation there and use it to deduce a boundary condition on σ_r for the tumor region. By the single-coordinate geometry of the model, $u_i = (u_r, 0, 0)$, and by the incompressibility assumption,

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 u_r) = 0, \quad (30)$$

from which we obtain

$$u_r = \frac{A'}{r^2}. \quad (31)$$

Equation (18) can now be used to find the stress at the boundary of the tumor. Using the result from (31) in (18), we have

$$\sigma_r = -p + \frac{2}{3} e_r = -p - \frac{4A'}{3r^3}, \quad (32)$$

and

$$\left. \begin{array}{l} \sigma_\theta = -p + \frac{2}{3} e_\theta = -p + \frac{2A'}{3r^3} \\ \sigma_\phi = -p + \frac{2}{3} e_\phi = -p + \frac{2A'}{3r^3} \end{array} \right\} \Rightarrow \sigma_\theta = \sigma_\phi.$$

From the stress equilibrium equations (28), $p = \text{constant}$. To satisfy the condition at infinity, $p = p_\infty (= 0)$.

If R_0 is the initial radius of the tumor and $r = R$ at its boundary, then it follows that $u_r|_{r=R} = R - R_0$, leading to $A' = R^2(R - R_0)$. Therefore

$$\sigma_r|_{r=R} = -\frac{4(R - R_0)}{3R} \quad (33)$$

and

$$\sigma_\theta|_{r=R} = \sigma_\phi|_{r=R} = \frac{2(R - R_0)}{3R}. \quad (34)$$

By letting $\beta = \sigma_r - \sigma_\theta$, equations (29) and (27) can be written, respectively, as

$$\frac{\partial \sigma_r}{\partial r} + \frac{2\beta}{r} = 0, \quad (35)$$

and

$$\left(\frac{\partial}{\partial t} + v \frac{\partial}{\partial r} \right) \beta = \gamma, \quad (36)$$

where

$$\gamma = \frac{2}{3} r \frac{\partial}{\partial r} \left(\frac{v}{r} \right).$$

Then from (25), we have

$$\gamma = \frac{R}{r \sinh R} \left(\frac{2 \sinh r}{3} - \frac{2 \cosh r}{r} + \frac{2 \sinh r}{r^2} \right). \quad (37)$$

We first solve for β in equation (36). Then σ_r is obtained by substituting for β in equation (35) and integrating. Finally, σ_θ can be obtained directly from $\sigma_\theta = \sigma_r - \beta$.

B. Model simplification for diffusion limited nutrient

By employing the assumption of spherical symmetry, and considering a single coordinate system, the boundary value problem in this case can be expressed in dimensionless variables as

$$\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c}{\partial r} \right) = \begin{cases} c, & r < R(t), \\ 0, & r > R(t), \end{cases} \quad (38)$$

subject to $c \rightarrow 1$ as $r \rightarrow \infty$, and c and $\partial c/\partial r$ being continuous at the tumor boundary.

The boundary value problem (38) has the solution

$$c = \begin{cases} \frac{\sinh r}{r \cosh R}, & r < R(t), \\ \frac{(r - R + \tanh R)}{r}, & r > R(t). \end{cases} \quad (39)$$

However, we only need the value of the nutrient concentration within the region $r < R(t)$ for the numerical values of the stresses within the tumor. Apart from the nutrient concentration equation, the dimensionless versions of the model's equations, which arise from the growth, stress equilibrium, constitutive law, and stress effect of the external medium, are as in Case I, viz:

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 v) = c - \epsilon; \quad (40)$$

$$\frac{\partial \sigma_r}{\partial r} + \frac{2}{r} (\sigma_r - \sigma_\theta) = 0; \quad (41)$$

$$\left(\frac{\partial}{\partial t} + v \frac{\partial}{\partial r} \right) (\sigma_r - \sigma_\theta) = \frac{2}{3} r \frac{\partial}{\partial r} \left(\frac{v}{r} \right); \quad (42)$$

$$\sigma_r|_{r=R} = -\frac{4(R - R_0)}{3R}. \quad (43)$$

Using the nutrient concentration from (39) in (40), with the accompanying boundary conditions, we obtain

$$v = \frac{1}{r^2 \cosh R} (r \cosh r - \sinh r) - \frac{\epsilon r}{3}. \quad (44)$$

As in section IV-A, we call the right side of (42) γ , and let $\beta = \sigma_r - \sigma_\theta$. Expressions for $\partial\gamma/\partial r$ and $\partial\gamma/\partial t$, required for the numerical solution, are:

$$\frac{\partial\gamma}{\partial r} = \frac{1}{r \cosh R} \left(\frac{2 \cosh r}{3} - \frac{8 \sinh r}{3r} + \frac{6 \cosh r}{r^2} - \frac{6 \sinh r}{r^3} \right), \quad (45)$$

$$\frac{\partial\gamma}{\partial t} = -\frac{V \tanh R}{r \cosh R} \left(\frac{2 \sinh r}{3} - \frac{2 \cosh r}{r} + \frac{2 \sinh r}{r^2} \right). \quad (46)$$

C. Numerical simulations

The equations (35) and (36) (for ambient nutrient concentration) and equations (41) and (42) (for diffusion limited nutrient) are solved numerically using the Lax-Wendroff method (see [25] for more details). The Lax-Wendroff method is a finite-difference method used to obtain numerical solutions for first-order partial differential equations. In standard form it is applied on an infinite spatial domain. We extend this method to allow for the finite but varying domain of integration and also the function γ on the right hand sides of (36) and (42). We find the solution on a grid of the rt -plane

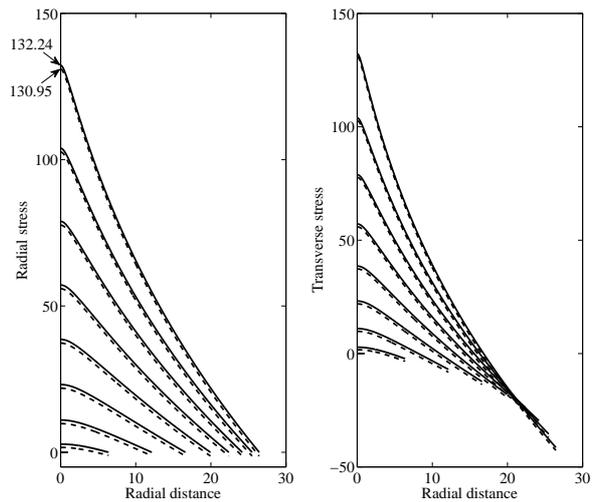


Fig. 1. Tumor growth-induced stress (solid lines) and effect of external medium on the growth-induced stress (dashes lines). Over the integration time considered, the tumor grows to a size of ~ 26.44 from an initial radius $R_0 = 1$ and parameter values $\epsilon = 0.1$, $\delta t = 0.03$

defined by

$$r_i = ih, \quad i = 0, 1, 2, \dots, i_{max};$$

$$t_j = jk, \quad j = 0, 1, 2, \dots, j_{max},$$

so h and k are the respective space and time stepsizes, and i and j denote the corresponding spatial and time counters. The number of spatial grid points is fixed, but the stepsize h is time dependent so that $i_{max}h = R(t)$. Thus the grid lines are evenly distributed over the whole domain in space and are set apart in time by a constant difference δt . However, since the domain is changing with time, the effect of this is that the spatial grid lines are curves, not straight lines.

Graphical outputs of the numerical results are obtained by choosing appropriate values for the physical parameters ϵ , R_0 , and for the integration variables δt , i_{max} and j_{max} . When ϵ (the ratio of death rate to proliferation rate) > 1 , the tumor shrinks to extinction; when $\epsilon \sim 1$, it grows to a small size; and when $\epsilon \ll 1$, it grows to a large size. In our integration we choose the value $\epsilon = 0.1$ and initial radii $R_0 = 1$ and $R_0 = 5$. Thus we are modelling a tumor that is initially small and which grows to a large size. With $\epsilon = 0.1$ the tumor grows to a maximum size $R \simeq 26$.

The integration constants used in the simulations are $\delta t = 0.03$, $i_{max} = 480$, $j_{max} = 80/\delta t$. The plots in figures 1–6 and Figures 7–10 were obtained for ambient nutrient concentration and diffusion limited nutrient respectively.

Figure 1 shows the stresses induced by unrestrained growth and the stresses induced in the presence of an elastic external medium. Examining the transverse stress first we see that it is negative (compressive) in the outer region of the tumor and positive (tensile) in the interior of the tumor. The compressive force is caused by the growth process pushing cells together in the boundary layer near the tumor edge where the nutrient concentration is high. However, as the cells are drawn into the interior the death of some of the cells causes the remaining cells to be stretched apart and so creates the tensile force observed there. The radial stress has only a

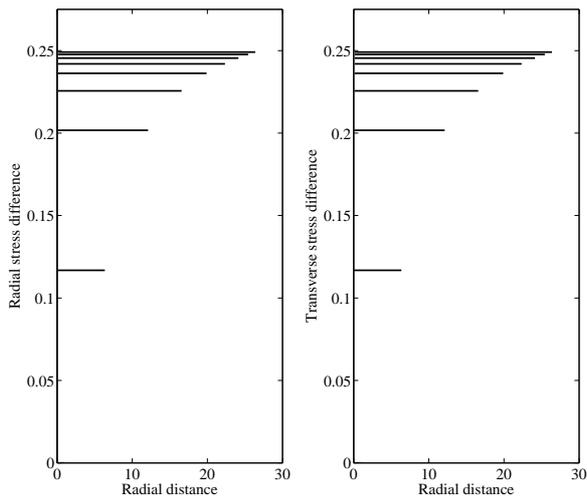


Fig. 2. Linear stress difference against radius at different times. Parameter values: $\epsilon = 0.1$, $R_0 = 1$, $\delta t = 0.03$. The maximum value is ≈ 1.28

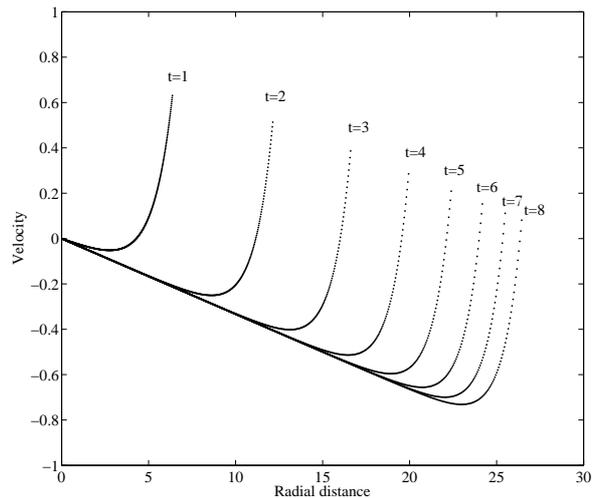


Fig. 4. Plots of velocity against radius for 8 different values of time, t

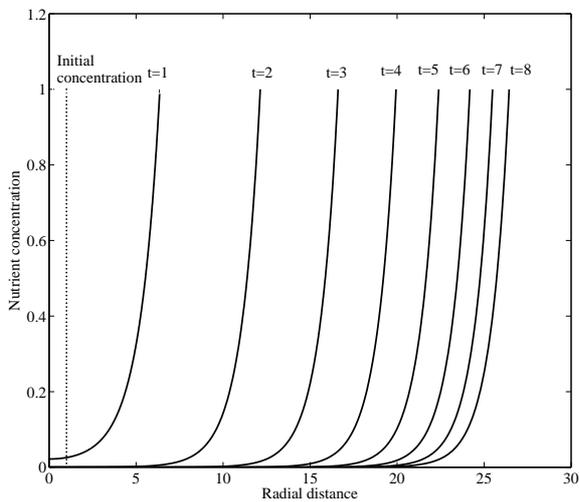


Fig. 3. Plots of nutrient concentration against the radius for 8 different values of t as tumor grows to saturation size, from an initial radius of 1

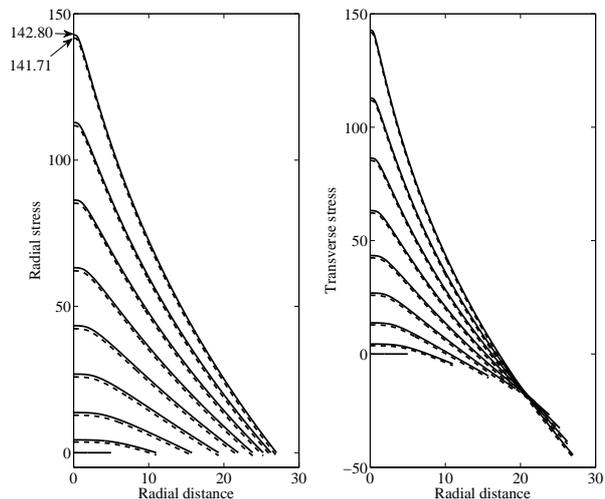


Fig. 5. Tumor growth-induced stress (solid lines) and effect of external medium on the growth-induced stress (dashes lines). Over the integration time considered, the tumor grows to a size of ~ 27.00 from an initial radius $R_0 = 5$

very small region where it is negative (compressive). This is near the tumor boundary and is caused by the elastic effect of the exterior region. Mostly, however, the stress is positive (tensile) so that the force (the divergence of the stress) is such that it pulls the cells towards the center to replace the cells dying there.

The difference in the growth induced stress and the stress effect of the external medium at eight different times ($t = 1, 2, \dots, 8$) is illustrated in Figure 2. The difference approaches a constant at large times since it is due to the compressive effect of the external medium, which eventually becomes constant when the tumor stops expanding. This effect of the external medium is small compared to the stress induced by the growth process.

The induced stress increases with decrease in the initial radius of the tumor (compare Figures 1 and 2 with Figures 5 and 6 respectively).

Figures 3 and 4 illustrate the variation of nutrient concen-

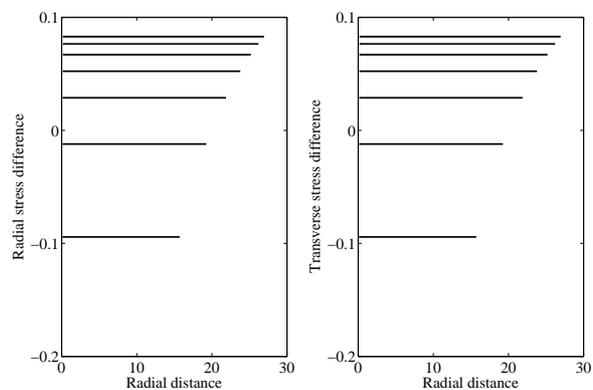


Fig. 6. Linear stress difference against radius at different times. Parameter values: $\epsilon = 0.1$, $R_0 = 5$, $\delta t = 0.03$. The maximum value is ≈ 1.09

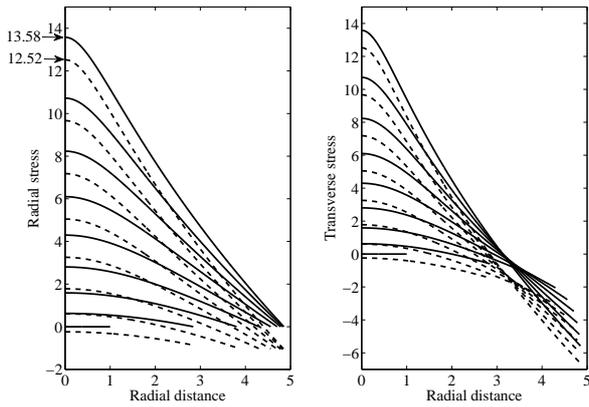


Fig. 7. Initial radius, $R_0 = 1$; Tumor growth-induced stress (solid lines) and effect of external medium on the growth-induced stress (dashes lines). With parameter values $\epsilon = 0.1$, $R_0 = 1$, $\delta t = 0.03$, tumor grows to a size of $R \sim 4.85$

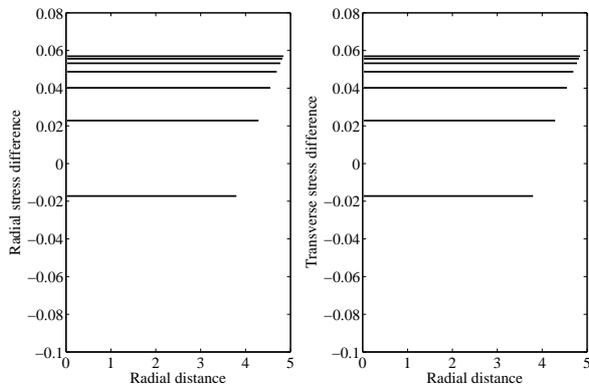


Fig. 8. Linear stress difference of ~ 1.06 at large times. Parameter values: $\epsilon = 0.1$, $R_0 = 1$

tration and tumor growth velocity, respectively, at 8 different times as the tumor increases in size from $R_0 = 1$. When the tumor is small, nutrient availability to the tumor cells is high and proliferating cells are present throughout the tumor. The velocity of the tumor growth is significantly high with a positive profile. As the tumor increases in size, the nutrient concentration decreases from the center of the tumor toward the boundary. There is increased rate of cell death toward the center of the tumor while a proliferating rim begins to develop as a result of sufficient nutrient availability to cells towards the boundary. A high volume loss arises from the disintegrating death cells in the center resulting to an inward movement of cells from the boundary to replace the lost cells. This leads to a steady decrease in the tumor growth velocity.

The general trend in the diffusion limited case is similar to that observed for ambient nutrient concentration. However, with the diffusion limited exterior, the growth rate is much slower than in Case I (compare Figure 10 with Figure 4). This results in a much slower rate of increase in the growth-induced stress (stress related to the elastic behavior of the tumor) although as before, this stress continues to increase without limit (compare Figure 7 with Figure 1). Another consequence of the nutrient limitation is that the tumor equilibrates at a much smaller size ~ 4.88 as compared with ~ 29 in Case I. As a result of this, the confinement stress

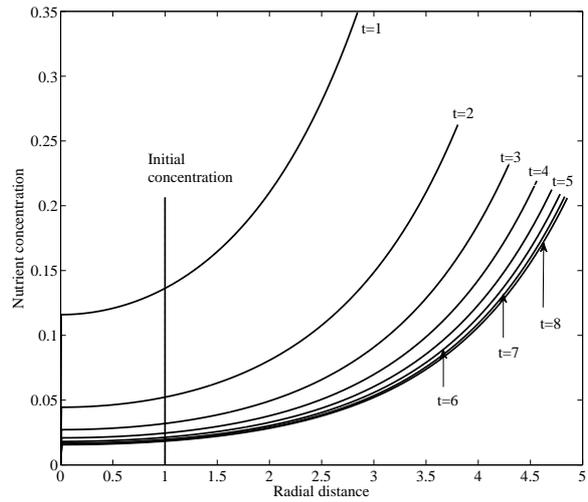


Fig. 9. Plots of nutrient concentration against radius for 8 different values of t

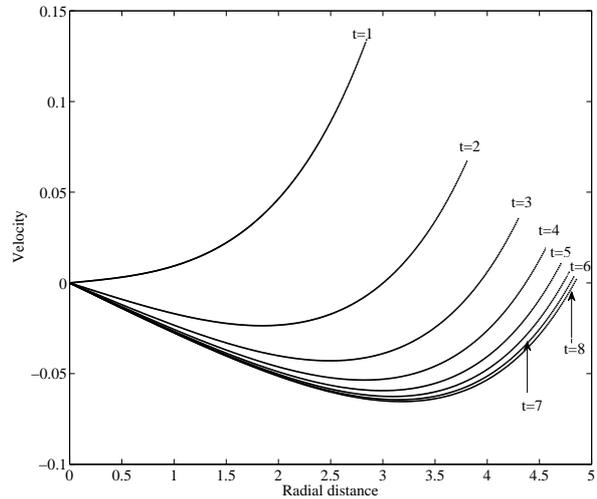


Fig. 10. Plots of velocity against radius for 8 different values of t

(caused by the external medium) is much less than in Case I (compare Figure 8 with Figure 2), although it is relatively larger when compared with the growth-induced stress. The marked differences in the growth velocity and saturation size in Case I and II illustrate the strong dependence of tumor growth rate and saturation size on nutrient supply from the surrounding medium.

V. CONCLUSION

In most existing models, one of the main features is that tumor growth rate and saturation size are regulated by the diffusion limited nutrient supply of the surrounding medium. The mechanical effect of the surrounding medium is usually ignored. In our model, attention has been focussed on the effect of the external isotropic elastic medium. We assume that the tumor is in its early avascular stage and there is no formation of a necrotic core. We have examined the effect of the stress induced by growth in the presence of the

external elastic medium on tumor growth rate and saturation size. The assumption of the dependence of tumor growth rate and saturation size on nutrient supply was also checked by comparing two cases. In one case the nutrient supply was maximized at the tumor surface while in the other the nutrient had to overcome a diffusion gradient from infinity. Simulations of the model show that the direct mechanical effect of the external medium is small when compared to the effect due to growth. The stress effect is dependent on the initial tumor size: stress effect increases with decrease in the initial radius of the tumor. The effect of the external stresses, resulting from the effect of the external medium, is mainly compressive, offering resistance to the growing tumor. The results show that the saturation size of the tumor does depend on the stress effect of the external isotropic medium. There is a significant difference between the saturation size in the two cases considered. This is a clear indication that the limitation of the nutrient supply due to diffusion has significant quantitative effects on the tumor saturation size.

REFERENCES

- [1] A.L. Harris, Hypoxia a key regulatory factor in tumour growth. *Nat Rev Cancer* 2 (2002) pp. 38 – 47.
- [2] K.E. Thompson, J.A. Royds, Hypoxia and reoxygenation: a pressure for mutant p53 cell selection and tumour progression, *Bull Math Biol.* 61 (4) (1999) pp. 759 – 778.
- [3] J. Folkman, Tumor angiogenesis: therapeutic implications. *N Engl J Med* 285 (1971) pp. 1182 - 1186.
- [4] P. Vaupel, The Role of Hypoxia-Induced Factors in Tumor Progression, *Oncologist* 9 (2004) pp. 10 – 17.
- [5] G. Cheng, J. Tse, R.K. Jain, L.L. Mun, Micro-Environmental Mechanical Stress Controls Tumor Spheroid Size and Morphology by Suppressing Proliferation and Inducing Apoptosis in Cancer Cells, *PLoS ONE* 4 (2009) (2): e4632. doi:10.1371/journal.pone.0004632
- [6] S. J. Franks, J. R. King, Interactions between a uniformly proliferating tumour and its surroundings: uniform material properties, *Math Med Biol* 20 (1)(2003) pp. 47 – 89.
- [7] R.P. Araujo, D.L.S. McElwain, The nature of the stresses induced during tissue growth, *Applied Mathematics Letters* 18 (10) (2005) pp. 1081 – 1088.
- [8] M.A. Yousuf, P.C. Rivera, M.P. Diaz, R. Montufar-Chaveznavia, Lung Tumor Tracking and Couch Control - A Feasibility Study, *IAENG International Journal of Applied Mathematics*, 38:4 (2008) pp.249–254, http://www.iaeng.org/IJAM/issues_v38/issue_4/IJAM_38_4_11.pdf
- [9] F. Montel, M. Delarue, J. Elgeti, L. Malaquin, M. Basan, T. Risler, B. Cabane, D. Vignjevic, J. Prost, G. Cappello, J. Joanny, Stress Clamp Experiments on Multicellular Tumor Spheroids, *Physical Review Letters* 107, 188102 (2011) DOI: 10.1103/PhysRevLett.107.188102
- [10] Y. Kim, M.A. Stolarska, H.G. Othmer, The role of the microenvironment in tumor growth and invasion, *Progress in Biophysics and Molecular Biology* 106 (2011) 353–379 DOI: 10.1016/j.pbiomolbio.2011.06.006
- [11] D.S. McNally, M.A. Adams, Internal intervertebral disc mechanics as revealed by stress profilometry, *Spine* 17(1)(1992) pp. 66 – 73.
- [12] G. Helmlinger, P.A. Netti, H.C. Lichtenbeld, R.J. Melder, R.K. Jain, Solid stress inhibits the growth of multicellular tumor spheroids, *Nature Biotechnology* 15 (1997) pp. 778 – 783.
- [13] P. Tracqui, Biophysical models of tumour growth, *Rep. Prog. Phys.* 72 (2009) 056701 doi: 10.1088/0034-4885/72/5/056701
- [14] A.R.A. Anderson, M.A.J. Chaplain, Continuous and Discrete Mathematical Models of Tumor-induced Angiogenesis, *Bulletin of Mathematical Biology* 60 (1998) pp. 857 – 900.
- [15] C.J.W. Breward, H.M. Byrne, C.E. Lewis, The role of cell-cell interactions in a two-phase model for avascular tumour growth, *J. Math. Biol.* 45 (2) (2002) pp. 125 – 152.
- [16] H.M. Byrne, M.A.J. Chaplain, Growth of Nonnecrotic Tumors in the Presence and Absence of Inhibitors, *Mathematical Biosciences* 130 (1995) pp. 151 – 181.
- [17] J.P. Ward, J.R. King, Mathematical modelling of avascular-tumour growth II: Modelling growth saturation, *IMA Journal of Mathematics Applied in Medicine and Biology* 16 (1999) pp. 171 – 211.
- [18] J.P. Ward, J.R. King, Modelling The Effect of Cell shedding on Avascular Tumour Growth, *Journal of Theoretical Medicine* 2 (2000) pp. 155 – 174.
- [19] C.Y. Chen, H.M. Byrne, J.R. King, The influence of growth-induced stress from the surrounding medium on the development of multicell spheroids, *J. Math. Biol.* 43 (2001) pp. 191 – 220.
- [20] A.F. Jones, H.M. Byrne, J.S. Gibson, J.W. Dold, A mathematical model of the stress induced during avascular tumour growth, *J. Math. Biol.* 40 (2000) pp. 473 – 499.
- [21] H.P. Greenspan, Models for the Growth of a Solid Tumor by Diffusion, *Studies in Applied Mathematics* LI (4) (1972) pp. 317 – 340.
- [22] D.L.S. McElwain, L.E. Morris, Apoptosis as a volume loss mechanism in mathematical models of solid tumor growth, *Mathematical Biosciences* 39 (1978) pp. 147 – 157.
- [23] H. Lamb, *Hydrodynamics* 6th ed., Cambridge University Press, 1962.
- [24] R. Wasserman, R. Acharya, A Patient-Specific In Vivo Tumor Model, *Mathematical Biosciences* 136 (1996) pp. 111 – 140.
- [25] M. Ngwa, *Stress-Strain Problems in Biological Systems*, Ph.D thesis, The University of Manchester, UK 2003.