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Mathematical Approach for Effect of Growth on the Mechanical Stresses during Soft Tissues and Avascular Tumor

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Abstract: In this Paper, the mathematical model for the study of the distribution of mechanical stresses by the cells within the soft tissues and tumor tissue is discussed. To describe the impact of isotropic growth on the mechanical stresses based on the linear elasticity theory and to study the process of continuous growth. Constitutive law to describe a linearly elastic tumor with continuous volume growth is combined in the model. Two examples is discussed, First case, in one dimensional model of tumor growth in rectangular tube, The model is solved in terms of radial displacement and stresses. In the second case, the effect of isotropic growth during a compressible material is solved in terms of radial displacement and stresses. The implications of two examples and possible model developments are investigated. Comparisons are made with the results in the two cases and numerical results are given and illustrated graphically for each case considered.

Keywords: Avascular tumor, Mathematical model, Soft tissues, Isotropic growth.

1 Introduction

A number of mathematical models of residual stress development in tumors have been proposed over recent years, using both single phase and multiphase frameworks. Progress in the field of experimental techniques (such as gene sequencing, fluorescent staining techniques) are enabling experimentalists to identify many physical mechanisms whose normal function is impaired in solid tumor growth. For example, with a population of tumor cells that contain mutated versions of the p53 gene can survive in low pressure abnormally oxygen (such as hypoxia) [1, 2]. The above description highlights the importance of genetic mutations in the growth of solid tumors. This is an area of active research in the field of oncology. Other factors that have been known for a long time affects the growth of the tumor is to provide vital nutrients, such as oxygen and glucose and chemotherapy drugs [7, 9, 20, 21], they studied model of a hybrid agent-based model of the developing mammary terminal end bud , and model of theory and Experimental Validation of a Spatio-temporal Model of Chemotherapy Transport to Enhance Tumor Cell Kill. . According to more recent experimental results show that the mechanical effects, such as stress, plays an important role in the growth of solid tumors [5]. Similarly, you can get the stress field of cell growth or remodeling during cytokinesis [6]. In fact, the main purpose of the new aspect of this work is to develop a mathematical model, which describes the way in which growth is generating pressure regularly in solid tumors. Such phenomena have not been studied extensively in sports literature. Instead, most of the existing models either spherical multicellular response to changing food and chemotherapy focused [7–11] can be set externally or the blood vessels of cancer [12–14] the process that tumors acquire flow the blood to the tissues of the host [15–17]. The notable exception is the material Chaplain and Sleeman [18], which is used to describe the elasticity of tumor invasion theory.

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Other models include mechanical influences include work by Drozdov et al. [19]. For example, it discussed in [19] a simple example is the cut growth from the main square and going on the corresponding field of growth-induced stress. Landman, Byrne developed an alternative model for the structure, which is dealing with a multi-tumor relatively stages as with cell growth, proliferation and death of the interview phase transitions between the cell and the water phase of which [9, 20, 21].

Since the development of a mathematical model, which couples with stress and growth, will be very difficult. Our approach is based directly on the current models of the growth of solid tumors [3, 6] and that the growth and death of cells to determine the levels of vital nutrients and does not rely on mechanical effects, such as stress. This model is limited growth spread to simulate the growth of multi-spherical homogeneous distinct cells, the cells near the perimeter of proliferating cells nutrient-rich quickly, while the tumor center, deprived of food, and thus less rapidly multiply [22, 25]. They study the mechanics of a continuous medium of tumor-induced capillary growth, Necrosis and apoptosis: distinct cell loss mechanisms in a mathematical model of avascular tumor growth and also they discussed Analysis of a mathematical model for the growth of tumors.

2 Formulation of the problem

Case I: Effect of isotropic growth in soft tissues.

Mathematical approach discussed here represents the effect of a given fixed growth–strain distribution is considered rather than an evolution of stresses over a period of growth. Moreover, spherical symmetry is assumed, which has particular relevance to solid tumor growth. Hence, the constitutive equation of linear elasticity [3, 6] is given as:

$$\varepsilon_r - \gamma_r g = \frac{1}{E}\left(\sigma_r - 2\nu\sigma_\theta\right) \tag{1}$$

$$\varepsilon_\theta - \gamma_\theta g = \frac{1}{E}\left(\sigma_\theta - \nu\left(\sigma_r - \sigma_\theta\right)\right) \tag{2}$$

Where r and θ denote the actual radial and circumferential strains respectively, and $g = g(r)$denotes the relative volume change due to growth. The anisotropic multipliers, γ_r andγ_θ, represent the proportion of the volumetric growth directed into the radial and circumferential directions respectively. Thus,

$$\gamma_r + 2\gamma_\theta = 1, \tag{3}$$

The constants E and ν denote Young's modulus and Poisson's ratio respectively. Eqs. (1) and (2) may be arranged to give

$$\begin{aligned}\sigma_r &= \tfrac{E}{(1+\nu)(1-2\nu)}\left(\left(1-\nu\right)\varepsilon_r + 2\nu\varepsilon_\theta - \left(\left(1-\nu\right)\gamma_r + 2\nu\gamma_\theta\right)g\right)\\ &= \tfrac{E}{(1+\nu)(1-2\nu)}\left(\left(1-\nu\right)\tfrac{\partial u}{\partial r} + 2\nu\tfrac{u}{r} - \left(\left(1-\nu\right)\gamma_r + 2\nu\gamma_\theta\right)g\right)\end{aligned} \tag{4}$$

$$\begin{aligned}\sigma_\theta &= \tfrac{E}{(1+\nu)(1-2\nu)}\left(\varepsilon_\theta + \nu\varepsilon_r - \left(\nu\gamma_r + \gamma_\theta\right)g\right)\\ &= \tfrac{E}{(1+\nu)(1-2\nu)}\left(\tfrac{u}{r} + \nu\tfrac{\partial u}{\partial r} - \left(\left(\nu - \tfrac{1}{2}\right)\gamma_r + \tfrac{1}{2}\right)g\right),\end{aligned} \tag{5}$$

where radial and circumferential stresses, u is the radial displacement respectively. Now, neglecting inertial effects and external body forces, the conservation of momentum requires.

$$\frac{\partial\sigma_r}{\partial r} + \frac{2\beta}{r} = 0. \tag{6}$$

$$\beta = \sigma_r - \sigma_\theta \tag{7}$$

Substituting Eqs. (4) and (5) into Eq. (6) yields.

$$\begin{aligned}&\tfrac{\partial}{\partial r}\left(\tfrac{1}{r^2}\tfrac{\partial}{\partial r}\left(r^2 u\right)\right) = \tfrac{1}{1-\nu}\left[\left(\nu - \left(2\nu-1\right)\gamma_r\right)\tfrac{\partial g}{\partial r}\right.\\ &\left. - \left(3\left(2\nu-1\right)\tfrac{\gamma_r}{r} + \left(2\nu-1\right)\tfrac{\partial\gamma_r}{\partial r} - \tfrac{(2\nu-1)}{r}\right)g\right],\end{aligned} \tag{8}$$

This is the general equation for the displacement in a growing linear elastic material, considering both anisotropy and compressibility.

Case II: Effect of growth on stresses during avascular tumor.

In this section, One present a mathematical model that describes the evolution of an avascular tumor whose growth regulates nutrient provided from abroad, such as oxygen or glucose, one follow [3–6]. Then the scalar equations for the concentration of nutrients $c(r,t)$. are:

$$Dc\left(\frac{2}{r}\frac{\partial}{\partial r}c(r,t) + \frac{\partial^2}{\partial r^2}c(r,t)\right) - mc(r,t) = 0, \tag{9}$$

$$\frac{2v(r,t)}{r} + \frac{\partial v(r,t)}{\partial r} = \alpha c(r,t) - k. \tag{10}$$

Where $c(r,t)$, the concentration of nutrients and $n(r,t)$ is mass density of tumor cells, $v(r,t)$ is the velocity of tumor cells, Here is no body forces except gravity, hich is supposed to be slim, so the balance of our crops,

$$\frac{\partial\tau_r}{\partial r} + \frac{2}{r}\tau_r = 0, \tag{11}$$

Finally, One formulate the constitutive law, which connects the strain inside the tumor to the stress upon it, One assume that the material is compressed. A combination of the above assumptions results in the following equation:

$$\frac{1}{2}\left(\nabla u + \nabla u^T\right) = \frac{1}{3}g\delta + \frac{1}{2E}\left(3\tau - Tr(\tau)\delta\right) \tag{12}$$

where u is the change in strain, g the volume per unit volume produced at a given point by growth, δ is the Kronecker-delta , Tr represents the trace of the tensor and the Young modulus E, the value of which is different for different tumors. The equation (11) may reduces to

another form subject to continues growth volume, is as follows:

$$\frac{1}{2}\left(\nabla v+\nabla v^{T}\right)=\frac{1}{3}\left(\nabla\cdot v\right)\delta+\frac{1}{2E}\left\{\frac{D}{Dt}\left(3\tau-Tr(\tau)\delta\right)+3\left(\omega\cdot\tau-\tau\cdot\omega\right)\right\}, \tag{13}$$

where ω is the second order vorticity tensor and $\omega=-\frac{1}{2}(\nabla v-\nabla v^{T})$. The remainder of this work, One look only to the status quo for $\omega=0$. Set quantities dimensionless, One write

$$L=\sqrt{D_c/m},\ T=1/\alpha C_0\ ,\ \tilde{r}=r/L,\quad \tilde{t}=t/T, \tag{14a}$$

$$\tilde{c}=c/C_0,\quad \tilde{v}=vT/L,\quad \tilde{\tau}=\tau/E,\quad \tilde{\omega}=\omega T. \tag{14b}$$

where the concentration of nutrients with external feed value C_0 (which is assumed constant). Under this transformation the model equations become (dropping the tildes for clarity)

$$\left(\frac{2}{r}\frac{\partial}{\partial r}c(r,t)+\frac{\partial^2}{\partial r^2}c(r,t)\right)-c(r,t)=0, \tag{15}$$

$$\frac{2v(r,t)}{r}+\frac{\partial v(r,t)}{\partial r}=c(r,t)-\varepsilon, \tag{16}$$

$$\frac{\partial\Gamma(r,t)}{\partial t}+\left(\frac{2v(r,t)}{r}+\frac{\partial v(r,t)}{\partial r}\right)\Gamma(r,t)=0\ \ on\ \ \Gamma(r,t)=0, \tag{17}$$

$$\begin{pmatrix}\frac{\partial\tau_r}{\partial r}+\frac{1}{r}(2\tau_r-\tau_\theta-\tau\varphi)\\ \frac{\partial\tau_\theta}{\partial\theta}+\frac{\cot(\theta)}{r}(\tau_\theta-\tau\varphi)\\ \frac{1}{\sin(\theta)}\frac{\partial\tau_\varphi}{\partial\varphi}\end{pmatrix}=0, \tag{18}$$

$$\frac{1}{2}\left(\nabla v+\nabla v^{T}\right)=\frac{1}{3}\left(\nabla\cdot v\right)\delta+\frac{1}{2}\left\{\frac{D}{Dt}\left(3\tau-Tr(\tau)\delta\right)+3\left(\omega\cdot\tau-\tau\cdot\omega\right)\right\}. \tag{19}$$

where $\omega=-\frac{1}{2}(\nabla v-\nabla v^{T})$, and ε satisfies $\varepsilon=T\,k=\frac{k\alpha}{C_0}$.

3 Solution of the problem

Application for case 1: The effect of isotropic growth during a compressible material.

One consider the proportion of the volumetric growth directed into the radial $\gamma_r=\frac{1}{3}$ and circumferential directions $\gamma_\theta=\frac{1}{3}$

so that Equ (8). $\frac{\partial c}{\partial x}\to 0\ as\ x\to-\infty$,

$$\frac{\partial}{\partial r}\left(\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2u\right)\right)=\frac{1}{3}\left(\frac{1+v}{1-v}\right)\frac{\partial g}{\partial r}, \tag{20}$$

Whose solution is

$$u=\frac{1}{3}\left(\frac{1+v}{1-v}\right)\frac{1}{r^2}\int_0^r g\hat{r}^2d\hat{r}+C_1r+\frac{C_2}{r^2}, \tag{21}$$

Where C_1 and C_2 are constants of integration.

Boundary conditions :

The term in $C_2=0$ must be zero, however, for the displacement to be bounded in the center of the tumor, since $u=0$ at $r=0$by symmetry. Considering a sphere of radius a with a constant hydrostatic pressure of -p at the surface,

$$u=0,\qquad at\qquad r=0, \tag{22a}$$

$$\tau_r=-p\qquad at\qquad r=a, \tag{22b}$$

The constant C_1 is obtained from the substitution of Eq. (21) into (4).

Therefore, the constitutive equations are given by

$$\sigma_r=-p+\frac{2E}{3(1-v)}\left(\frac{1}{a^3}\int_0^a g\hat{r}^2d\hat{r}-\frac{1}{r^3}\int_0^r g\hat{r}^2d\hat{r}\right) \tag{23}$$

$$\sigma_\theta=-p+\frac{2E}{3(1-v)}\left(\frac{1}{r^3}\int_0^r g\hat{r}^2d\hat{r}+\frac{2}{a^3}\int_0^a g\hat{r}^2d\hat{r}-g\right) \tag{24}$$

The quantity β , being the difference between the radial and circumferential stress components, will now be used to study the genesis of tissue stresses since it is independent of both the external hydrostatic pressure and the outer radius of the tissue, and determines the distribution of stresses as reflected in Eq. (6).

Subtracting Eq. (24) from (23) now gives

$$\beta=\frac{E}{3\,(1-v)}\left[g-\frac{3}{r^3}\int_0^r g\hat{r}^2d\hat{r}\right] \tag{25}$$

Note, however, that the volume average of g in a sphere of tissue of radius r is

$$g_{av}=\frac{3}{r^3}\int_0^r g\hat{r}^2d\hat{r} \tag{26}$$

$$\beta=\frac{E}{3\,(1-v)}\,(g-g_{av}) \tag{27}$$

Further, appealing to Eqs. (6) and (7) gives

$$\frac{\partial\sigma_r}{\partial r}=\frac{2E}{3r\,(1-v)}\,(g_{av}-g) \tag{28}$$

$$\frac{\partial\sigma_r}{\partial r}=\frac{2E}{3r\,(1-v)}\left(\frac{1}{r}\,(g_{av}-g)-\frac{\partial g}{\partial r}\right) \tag{29}$$

The nature of the induced stresses is now considered for two growth distributions, first $g=\frac{a\sinh r}{r\sinh a}$ as above discussed, and similarly in case $g=1-\frac{r^2}{a^2}$.

Application for case 2: One dimensional tumor growth in rectangular tube.

In this case , one consider the rectangular tube is semi-infinite, therefore the equation given in (16) takes the form.

$$\frac{\partial^2c(x,t)}{\partial x^2}=c(x,t), \tag{30}$$

One solve equation (22) subject to the boundary

$c(a(t),t)=1$ and $\frac{\partial c}{\partial x}\to 0$ as $x\to-\infty$,

the latter condition ensuring that the solutions are bounded. In this method One find.

$$c(x,t)=e^{x-a(t)}, \tag{31}$$

With $\varepsilon=0$ equation (22) reduces to

$$\frac{\partial v(x,t)}{\partial x}=c(x,t), \tag{32}$$

Again, to ensure bounded solutions, One solve equation (32) subject to the condition

$$v(x,t)\to 0 \text{ as } x\to\infty,$$

and deduce that

$$(x,t)=e^{x-a}, \tag{33}$$

Using equation (18) One note that on the tumor surface

$$\frac{da}{dt}=v(a(t),t)=1, \text{ with } a(0)=0, \tag{34}$$

Thus $a=t$, that is, the tumor grows linearly with time. One consider that the non-diagonal elements of the stresses tensor $\tau_{xy}=\tau_{yz}=\tau_{zx}=0$. the component of equation (18) in the x-direction leads to the equation.

$$\frac{\partial\sigma_x}{\partial x}=0, \tag{35}$$

Assuming that there is no normal stress at the tumor boundary and scaling pressure so that the pressure outside the tumor is zero, One integrate equation (35) subject to the boundary condition in which case.

$$\tau_{xx}=0 \quad \forall x,t. \tag{36}$$

Resolution of equation (18) in the y- and z-directions leads to ordinary differential equations for τ_{yy} and τ_{zz} which are similar in form to equation (35) and can be integrated to show the more limited results.

$$\tau_{yy}=\tau_{yy}(x,z;t), \qquad \tau_{zz}=\tau_{zz}(x,y;t). \tag{37}$$

From Eq. (20) One can write

$$\frac{1}{2}\left(\nabla v+\nabla v^T\right)-\frac{1}{3}(\nabla\cdot v)\,\delta=\frac{1}{3}\frac{\partial v(x,t)}{\partial x}\begin{pmatrix}2&0&0\\0&-1&0\\0&0&-1\end{pmatrix}$$

Finally, One turn to the constitutive law; equation (**??**) is now expressed with more general form in Cartesian coordinates as:

$$\frac{1}{3}\frac{\partial v(x,t)}{\partial x}\begin{pmatrix}2&0&0\\0&-1&0\\0&0&-1\end{pmatrix}=\frac{1}{2}\left(\frac{\partial}{\partial t}+v(x,t)\frac{\partial}{\partial x}\right)$$

$$\begin{pmatrix}-\tau_{yy}-\tau_{zz}&0&0\\0&2\tau_{yy}-\tau_{zz}&0\\0&0&2\tau_{zz}-\tau_{yy}\end{pmatrix} \tag{38}$$

Thus, there are only three non-trivial equation, only two of which are linearly independent, since the trail system is required to be reduced to zero. Linearly independent equations can be combined to get a more convenient form. For example, subtraction of the *zz*- from the *yy* all lead to the equation.

$$\left(\frac{\partial}{\partial t}+v(x,t)\frac{\partial}{\partial x}\right)(\tau_{yy}-\tau_{zz})=0, \tag{39}$$

Using the boundary conditions that

$$\tau_{yy}\to 0\,,\ \tau_{zz}\to 0 \qquad \text{when} \qquad x\to\infty$$

$$\tau_{yy}=\tau_{zz}=0 \qquad \text{at} \qquad t=0,$$

One deduce that, since $v\geq 0, \tau=\tau_{zz}$ throughout the tumor.

$$\tau_{yy}=\tau_{zz}=\tau(x,t), \tag{40}$$

Substituting equation (40) into any of equations (38) leads to the following expression for

$$\left(\frac{\partial}{\partial t}+v(x,t)\frac{\partial}{\partial x}\right)\tau=-\frac{2}{3}\frac{\partial v(x,t)}{\partial x} \tag{41}$$

Since v is already known, equation (41) may be solved, subject to the initial condition that $\tau=0$, *at* $t=0$, giving

$$\tau(x,t)=-\frac{2}{3}\left[x+\ln\left(1+e^{-x}-e^{-t}\right)\right]. \tag{42}$$

Using equation (42), allowing $t\to\infty$ the equation (42) become as:

$$\tau\simeq-\frac{2}{3}\left[x+\ln\left(1+e^{-x}\right)\right], \quad t\to\infty \tag{43}$$

$$\text{as } x\to-\infty \text{ and } \tau\simeq-\frac{2}{3}x \text{ for } 1\ll x<a. \tag{44}$$

4 Numerical results

Results mentioned above apply to this situation stable condition, where the tumor was originally inspired, and on the size $a=a^*$ of their equilibrium. It is clear from the numerical results of the tumors grow, One fix $\varepsilon=0.1$ and assumed that the tumor tension in origin, size and$a=10$. Plots of β, $\tau_r$and τ_θ with equal amounts of time in the figure. 6, and during this period the tumor reaches effectively the size of its equilibrium$a^*=28.96$.

In Fig. (1-3) the employs the constitutive of linear elasticity to discuss the nature of growth-due to stresses in soft tissues. The solution of the simpler case of isotropic growth obtained insight into the influence of the spatial non-uniformity of the growth process on case of the nature and in case of distribution, tissue stresses. The nature of the induced stresses is considered for two growth distributions with $g=\frac{a\sinh r}{r\sinh a}$.

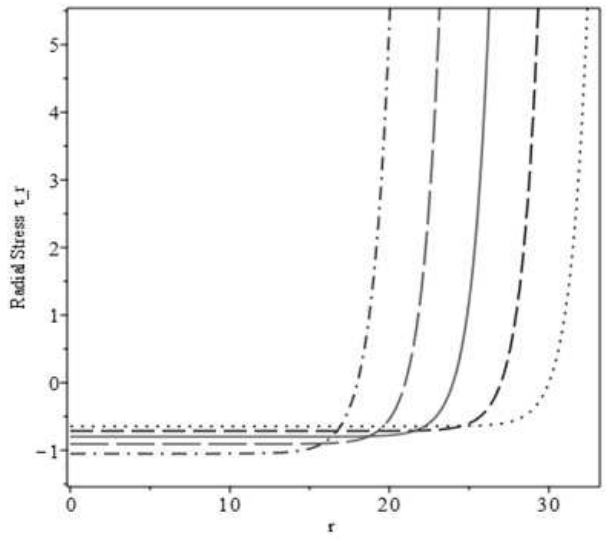

Fig. 1: Dispersion curves for the effect of the spatial non-uniformity of the growth process on both the nature and distribution tissue stresses , versus r with different as growth is $\tau_r a = 18, 21,\ 24,\ 27, 30 \frac{a \sinh r}{r \sinh a}$

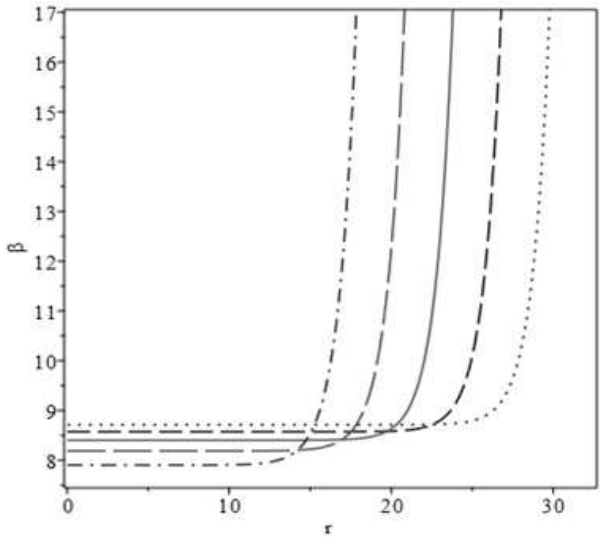

Fig. 3: Dispersion curves for the effect of the spatial non-uniformity of the growth process on both the nature and distribution tissue difference stresses τ_θ , versus r with different $a = 18, 21,\ 24,\ 27, 30$ as growth is $\frac{a \sinh r}{r \sinh a}$.

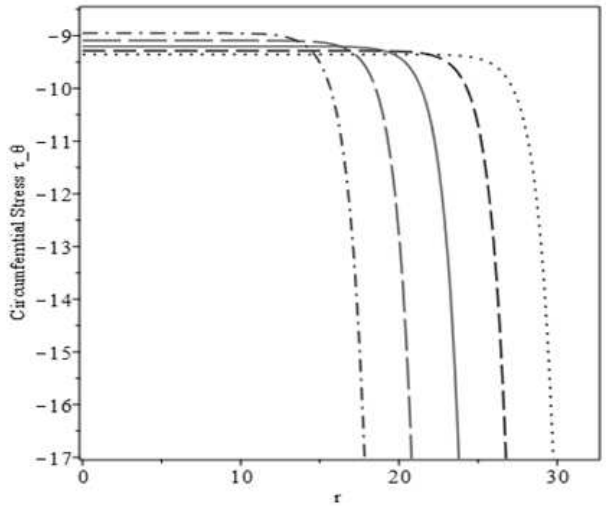

Fig. 2: Dispersion curves for the effect of the spatial non-uniformity of the growth process on both the nature and distribution tissue stresses τ_r , versus r with different $a = 18, 21,\ 24,\ 27, 30$ as growth is $\frac{a \sinh r}{r \sinh a}$.

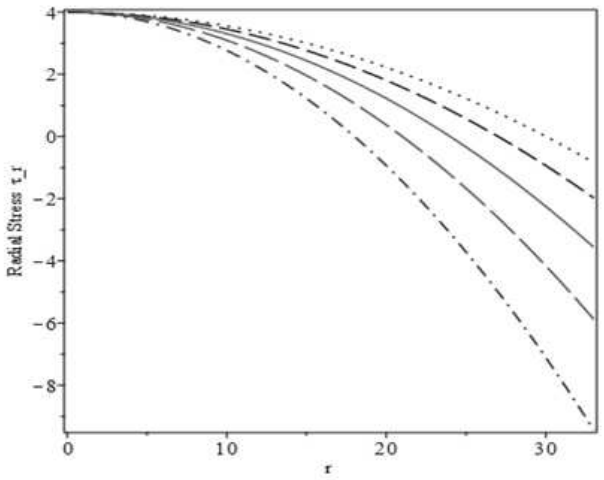

Fig. 4: Dispersion curves for the effect of the spatial non-uniformity of the growth process on both the nature and distribution tissue stresses τ_θ , versus r with different $a = 18, 21,\ 24,\ 27, 30$ as growth is $1 - \frac{r^2}{a^2}$

Figs (4-6) shows the case at the nature of the induced stresses is considered for two growth distributions with $g = 1 - \frac{r^2}{a^2}$.

Anisotropic growth is also examined; demonstrate its important role in relieving growth-due to stresses. Fig. 7 Here One show how the transverse component of the stress tensor develops into a tumor growing in a rectangular tube smooth semi-infinite. As depicted pressures personal cross that corresponds to the stable where the tumor and features dynamic evolving situation. Initially, the tumor without stress. However, since the border tube prevents lateral movement of cells near the surface of the spread of the tumor creates pressure and occasional pressure. In the absence of cell death, and the

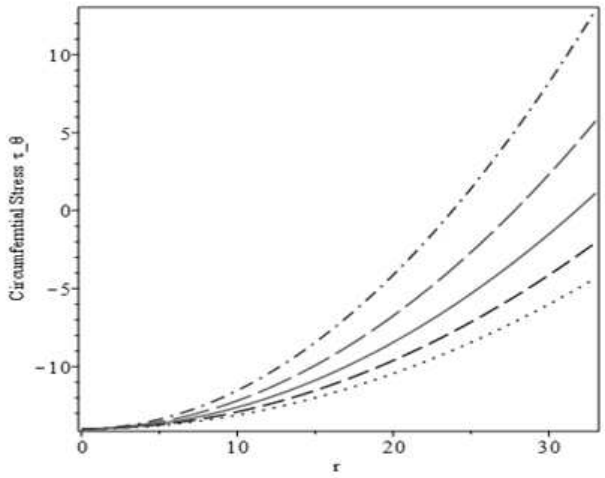

Fig. 5: Dispersion curves for the effect of the spatial non-uniformity of the growth process on both the nature and distribution tissue stresses τ_θ , versus r with different $a = 18, 21, 24, 27, 30$ as growth is $1 - \frac{r^2}{a^2}$

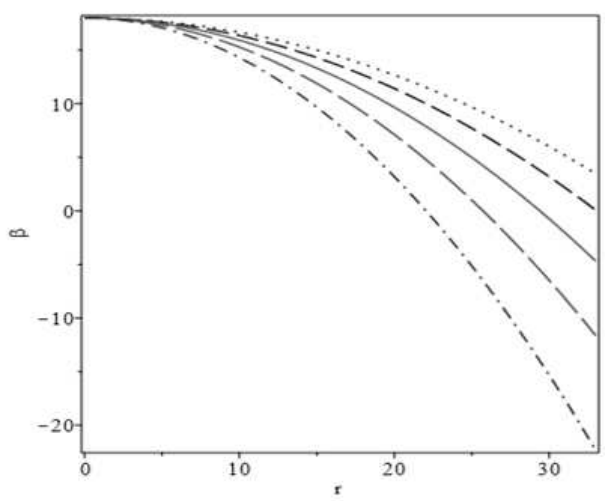

Fig. 6: Dispersion curves for the effect of the spatial non-uniformity of the growth process on both the nature and distribution tissue difference stresses β, versus r with different $a = 18, 21, 24, 27, 30$,as growth is $1 - \frac{r^2}{a^2}$

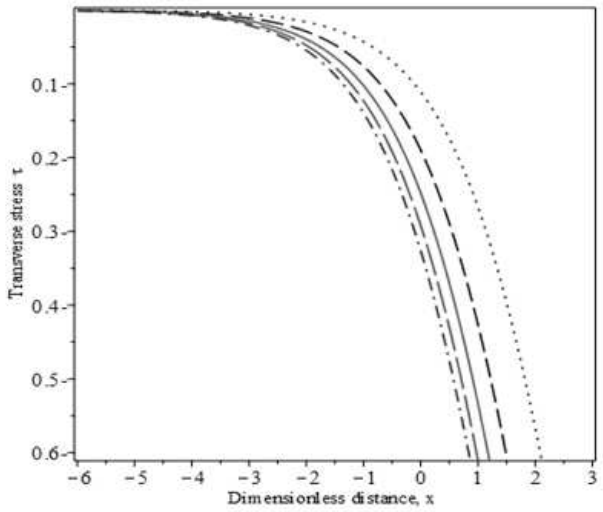

Fig. 7: Dispersion curves for Transverse stress τ_x versus x with different t $(\ldots t = 0.2, --t = 0.4, U2015t = 0.6, \_\_t = 0.8, t = 1), a = 28$.

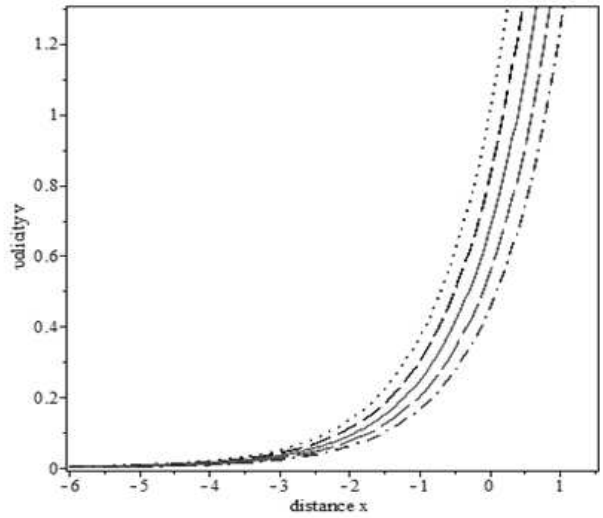

Fig. 8: Dispersion curves for velocity v versus x with different t $(\ldots t = 0, --t = 0.2, U2015t = 0.4, \_\_t = 0.6, t = 0.8)$, $a = 28$.

stress of the surface of the tumor remains constant in values. That was when the surface passes through these points. One are draw $\tau_y = \tau_z = \tau(x,t)$ at times $t = 0.2, 0.4, 0.6, 0.8, 1$analytical results for the cultivation of the tumor (solid line). Analytical results stationary state of the tumor (the dotted line). Value of the parameter $\varepsilon = 0$.

As it is shown in the Fig. 7, tumor cells near the border came under pressure stress ($\tau < 0$) those increases linearly with time scale. However, tumor cells near the center, where there is the death of the spread undergo transverse tensile strength of the cells ($\tau > 0$), which also increases linearly with time. One plot σ at times $t = 0.2, 0.4, 0.6, 0.8, 1$. Parameter values: $\varepsilon = 0.1$, $a^* \sim 1/\varepsilon = 10$. Fig. 8, Here One show how velocity v develops within an equilibrium size spherical tumor with

radial symmetry. The fact that the velocity is increasing with radius at times $t = 0,\ 0.2, 0.4,\ 0.6,\ 0.8$.

5 Conclusions

The mathematical model for the study of the distribution of mechanical stresses by the cells within the soft tissues and tumor tissue is discussed. Constitutive law to describe a linearly elastic tumor with continuous volume growth is combined in the model. Two examples is discussed, Anisotropic growth is also examined, demonstrate its important role in relieving growth-due to stresses. The implications of two examples and possible model developments are investigated. Comparisons are made with the results in the two cases and numerical results are given and illustrated graphically for each case.

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