ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE ENGINEERING AND TECHNOLOGY

MATHEMATICAL MODELING OF TUMOR GROWTH

M.Sc. THESIS

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Department of Mathematics

Mathematical Engineering Programme

MAY 2014

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İSTANBUL TEKNİK ÜNİVERSİTESİ ★ FEN BİLİMLERİ ENSTİTÜSÜ

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YÜKSEK LİSANS TEZİ

Damla KUTLUOĞLU
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Matematik Mühendisliği Anabilim Dalı

Matematik Mühendisliği Programı

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Damla Kutluoglu, a **M.Sc.** student of ITU **Institute of Science, Engineering and Technology** student ID **509101009**, successfully defended the **thesis** entitled "**MATHEMATICAL MODELING OF TUMOR GROWTH**", which she prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

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Date of Submission : 02 May 2014
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To my devoted mother, my lovely sister and my beloved fiancé,

FOREWORD

This thesis is a study for tumor growth within the framework of Continuum Mechanics. A mechanical model which splits volumetric growth and mechanical response into two separate contributions, is applied to a tumor growing in a vessel where in one case the vessel is rigid and in the second case it is not rigid.

I would like to thank my supervisor Assoc. Prof. Dr. Ali Ercengiz for giving me valuable advice and support always when needed, to my mother Ayla Olgun for her devotion, to my sister Duygu Kutluoglu for always being there for me when I needed and to my fiancé Ersan Akpinar for both his helps as a graphic artist, drawing the figures of this thesis and for being supportive all the time.

May 2014

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(Senior Software Engineer)

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ABBREVIATIONS

TAF **:** Tumor Angiogenic Factors

VEGF **:** Vascular Endothelial Growth Factor

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MATHEMATICAL MODELING OF TUMOR GROWTH

SUMMARY

This thesis is a study for tumor growth within the framework of continuum mechanics. A mechanical model which splits volumetric growth and mechanical response into two separate contributions, is applied to a tumor growing in a vessel where in one case the vessel is rigid and in the second case it is not rigid. As a part of continuum mechanics, Cauchy stress tensor and Piola-Kirchoff stress tensor is used to analyze the motion and the growth of the tumor body.

Firstly, the growth basics for a biological tissue is described. Then kinematics of the growth, related to balance equations and nutrient factors are given with proofs.

Secondly the material type is chosen as Blatz-Ko type and some specific assumptions are given related to the material and the behavior of the balance equation with respect to the growth kinematics.

Later, the equations which construct the tumor growth problems are defined. The problems are analyzed with respect to the cylindrical coordinates. In the first problem, growth of a tumor in a rigid vessel is analyzed. Since the vessel is rigid, only tumor has a deformation and the deformation is only at Z direction. Since there is stress only on R and θ directions, the component of Cauchy stress tensor for Z direction is assumed to be equal to 0. From this equation, a relation between the growth tensor and deformation component at Z direction is obtained. This relation is applied to different Blatz-Ko type materials and as result it is shown that the axial displacement as elongation is increased as the growth tensor is increased. The displacement is an exponentially increasing function of growth.

In the second example, the vessel is taken as a non-rigid elastic material. Since the cylinder can deform the equations are changed to different system. With the vessel is not rigid, there is deformation at both θ and Z directions for the vessel and again there is deformation at both θ and Z directions for the tumor. Since the pressure at the inner side of the cylinder must be equal to R direction component of Piola-Kirchoff stress tensor for a steady balance and the displacement at the inner surface of the vessel is equal to the displacement of the outer surface of the tumor, these fasts lead to a second order non-linear differential equation for function of the displacement of the tumor at R direction. This differential equation is solved via Mathematica with the assumptions of the related material constants of the material and the growth rate and found that the displacement function of tumor at Z direction is a linear function under a restriction relation with the growth tensor, and deformation of the tumor.

TÜMÖR BÜYÜMESİNİN MATEMATİKSEL MODELLENMESİ

ÖZET

Bu çalışmada, tümörün damar içinde büyümesi incelenerek, sürekli ortamlar mekaniği temelleri üzerinden matematiksel bir modelleme yapılmıştır. Biyolojik olarak ele alındığında tümor, uygun ortam oluştuğunda etrafındaki damarlar sayesinde kandan aldığı besinler ile büyüyebilen biyolojik bir kütledir.

Tümörün büyüme evreleri temel olarak ikiye ayrılır. İlk süreçte oluştuğu bölgede hali hazırda bulunan damar sisteminden beslenerek gelişmine devam eder. Bu gelişme esnasında tümör büyüdükçe iç tarafta kalan tümör hücrelerinin kandan direk alamadığı, kendisine komşu olan dış hücrelerden difizyon yöntemi ile aldığı besin ve oksijen git gide azalır. Bu tip durumlarda ikinci evre olan damarlanma sürecinin başlamaması veya geç başlaması durumunda tümör iç hücreleri hipoksi yani oksijensiz kalma durumu ile ölebilir.

Kandaki besin değerinde azalma ile ise büyümenin gerilemesi hatta emilimle küçülme dahi gözlenebilir. İkinci evre olan damarlanma iki farklı büyüme şekli ile gözlenir. Bu büyüme şekillerinden sadece biri oluşabileceği gibi ortamın müsait olması durumda iki tip büyüme aynı anda görülebilir. Damarlanma anjiyogenez ve vaskulogenez olmak üzere ikiye ayrılır. Anjiyogenez kelime anlamı ile yeni damar oluşumu demektir. Yaşadığı ortamda besin değerini yetersiz bulan tümor salgıladığı bir takım anjiyogenisis faktörler (TAF) ile kendisini besleyecek yeni damarların oluşumunu tetikleyebilir. Vaskulagenez ise vücudun tümörün olduğu bölgedeki damarları hasarlı kabul etmesi üzerine bu bölgedeki damarları yeniden oluşturmak ve güçlendirmek için kendi yapı taşları olan vasküler endotel büyüme faktörlerini (VEGF) kullanması ile olur. Her iki yolla da oluşan damar yapısı, insan vücudunun normal damar yapısına göre çok daha kılcallı ve geçirken farklı bir yapıdadır. Bu nedenle tümörden kopan yapı taşları veya hücreler bu damarlardan geçip vücudun farklı yerlerinde uygun ortamlar bulup yeni tümör dokuları oluşturarak metastaza sebebiyet verebilir. Bu tez kampsamında matematiksel olarak modellenen tümör gelişimi, büyümesinin ilk evresinde kabul edilip kan yoluyla aldığı besin damarlanmanın etkisinden bağımsız kabul edilerek kandaki besin oranı değişimine tabi tutulmuştur.

Tümörün damarın içinde büyümesi sürekli oramlar mekaniğinin temelleri esas alınarak iki farklı etkene ayrılmıştır. Bunlardan ilki ortamdaki gerilmelerden bağımsız olarak büyüme etkeni, diğeri ise deformasyon olarak ele alınmıştır. Bu iki etkenin oluturduğu şekil değişimi olarak oluşan kuvvetin etkisi altındaki tümörden bir partikülün kesildiği ve bu partikülün stress ve basınç içeren ortamdan ayrıştırılarak (doğal yapılanma) deformasyondan bağımsız bir büyüme kuvveti tanımlanmıştır. Bu deformasyondan bağımsız büyümüş tümörden, tümörün gerçekte büyümeden sonraki haline getiren deformasyon ise ayrı bir kuvvet olarak ele alınmıştır. Bu doğal yapılanma durumdaki büyüme simetrik olarak kabul edilmiştir. Burada ele alınan büyüme doğrudan kandaki besin oranı ile ilişkilendirilmiş ve

tümörün büyüyebilmesi için kandaki besin değerinin belirli bir eşik değerinin üzerine çıkması gerektiği kabul edilmiştir. Bunun için bir adım fonksiyonu olan Heaviside fonksiyonu büyüme oranı fonksiyonunda eşik değeri ile birlikte kullanılan bir fonksiyon olmuştur.

Uygulanan modelin tutarlı olması adına denge denklemleri modele uygulanmıştır. Öncelikle kütlenin korunumu göz önünde tutulmuş ve büyümeden bağımsız olan deformasyon esnasında kütlenin korunduğu, büyüme de ise büyüme oranıyla arttığı gösterilmiştir. Ayrıca lineer momentumun korunumu yasası gereği oluşan koşullar belirlenip probleme uygulanmıştır. Sonrasında büyüme tensorü ve büyüme oranı arasındaki ilişki incelenmiş ve besin faktörlerininin iç enerjinin korunumu deklemini sağladığı gösterilmiştir. Bu verilerin ışığında oluşan bir takım denklemler ile tümör ve damar için uygun malzeme tipleri seçilmiştir. Tümör için seçilen madde Blatz-Ko tipi olup biyolojik dokular için geliştirilen problemlerde yaygın olarak kullanılan sıkışabilir hiperelastik bir malzemedir. Damar için sıkışabilir olarak kabul edilen örnekte ise elastik malzeme kabulü yapılmıştır.

Tez kapsamında iki ayrı problem tipi incelenmiştir. Her iki problemin çözümü için de silindirik kordinatlar kullanılmıştır. Bu problemlerde büyüme, tümörün büyümesinde zamanın katkısının çok küçük olması nedeniyle zamandan bağımsız, gene aynı sebeple hızdan da bağımsız düşünülmüştür.

İlk problemde tümör sıkışmaz olarak kabul edilen damarın içinde büyümektedir. Damarda deformasyon oluşmayacağı için tümör sadece Z doğrultusunda büyüme yapar ve gene Z doğrultusunda gerilme olmaz. Bu koşullardan elde edilen denklemlerden Z doğrultusunda oluşan deformasyon ile büyüme fonksiyonu arasındaki ilişki belirlenir. Yapılan hesaplamalarda değişik malzeme katsayıları verilerek oluşturulan bu ilişkide Z doğrultusunda oluşan deformasyonun büyümedeki artış ile üstel olarak arttığı gözlemlenir.

İkinci problemde ise damar sıkışabilir kabul edilmiştir. Yani damarda da bir deformasyon gözlenecektir. Bu durumda hem tümör için hem damar için olan şekil değiştirme hem Z hem de R doğrultusunda olur. Burada damarın iç çepherinde oluşan basınç ile tümör için oluşan Piola-Kirchoff gerilme tansörünün R doğrultusundaki bileşenin tümörün çepherindeki değerine eşit olması gerekir. Ayrıca tümörün dış çepherinde oluşan şekil değiştirmenin damarın iç yüzeyinde oluşan şekil değişimi ile aynı kalması beklenir. Bu denklemler ışığında büyüme için, maddenin bünye denklemindeki sabitlere, tümörün R doğrultusundaki şekil değişimine ve gene tümörün Z doğrultusundaki şekil değişimine bağlı ikinci derece lineer olmayan bir diferansiyel denklem elde edilir. Bu denklemi, tümörün R yönündeki şekil değişimi için çözmek adına büyüme fonksiyonuna, bünye denklemindeki sabitlere ve tümörün Z yönününde olan şekil değişikliği bileşenine değerler verilerek Mathematica'da denklem çözülmüştür. Tümörün R yönündeki şekil değişiminin lineer olduğu ve verilen değişik değerler için lineer yapısını koruduğu, değişkenlerin sadece eğimde oluşan değişikliklere etken olduğu görülmüştür. Ayrıca elde edilen denklemlerden büyüme fonksiyonu, tümörün Z yönününde olan şekil değişikliği bileşeninin fonksiyonu ve bu fonksiyonun eğimi için, tümör için seçilen bünye denkleminin sağlanabilmesi için bir takım kısıtlar geldiği görülmüştür.

Sonuç olarak tümörün gelişiminin kandaki besin miktarına bağlı olan büyüme fonksiyonu ile doğru orantılı olduğu gösterilmiştir. Ayrıca damarın malzeme olarak sıkışabilir kabul edildiğinde ise seçilen bünye denklemlerinin tümörün R yönündeki şekil değişimi bileşenine ve Z yönününde olan şekil değişikliği bileşenine doğrudan kısıtlamalar getirdiği gözlenmiştir.

1. INTRODUCTION

1.1 Purpose of Thesis

This thesis is a study for tumor growth within the framework of Continuum Mechanics, analyzing the tumor as a specific case of growing soft tissues. By the notion of multiple natural configurations, a mechanical description that splits volumetric growth and mechanical response into two separate contributions is introduced and growth is described as an increase of the mass of the particles of the body, not as an increase at the particle number.

In their studies, Rajagopal and coworkers [1] have introduced the notion of multiple natural configuration [2] and used it to study many different phenomena, such as metal plasticity [3], twinning [4], shape memory alloys [5], viscoelastic fluids [6] and crystallization in polymers [7]. The theory of materials with multiple natural configurations is an ideal setting to investigate the process of growth.

1.2 The Growth of a Tumor as a Biological Tissue

Biological tissues are generally classified as hard tissues and soft tissues and the generation of biological forms involves three different process: growth which is defined as mass change, remodeling, which involves changes in material properties and morphogenesis, which consists in a change in shape. [8] In this thesis, tumor growth will be analyzed with tumor as a soft tissue.

Growth can occur through cell division (hyperplasia), cell enlargement (hypertrophy), and negative growth (atrophy) can occur through cell death mostly by hypoxia, cell shrinkage or resorption. [9] In this thesis growth is only described as hypertrophy.

There are two distinct phases of growth the relatively benign phase of avascular growth, and more aggressive phase of vascular growth. [10]

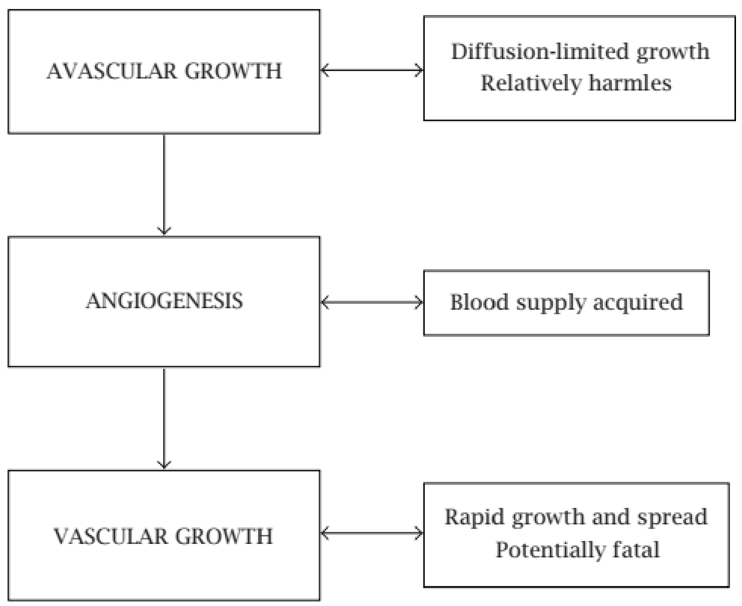

Figure 1.1. A schematic diagram for stages of solid tumor growth

Vascular growth can occur in two different ways. Angiogenesis, is new vessel sprouting, stimulated by TAFs (Tumor Angiogenic Factors), secreted by tumors often as a result of hypoxia. [11] As tumor grows avascular, since the inner cells get nutrient and oxygen only by diffusion, these cells get lower and lower oxygen and nutrient. As a result hypoxia occasionally occurs at the inner part of the tumor and this triggers the TAFs production. The second way of vascular growth is vasculogenesis, which occurs when the living form realizes the tumor as a damaged part of its body. When this happens, the VEGFs (Vascular Endothelial Growth Factors) rate at blood increases. VEGFs are products of bones to construct new vessels for the damaged part of the body. With a higher rate of VEGFs, new vessels are formed around the tumor so that tumor gets more nutrient and oxygen. These new vessels, created either by angiogenesis or vasculogenesis, are different then the vessels in rest of the body. They are thinner and have more capillaries. This causes tumor cells to pass to blood and spread through the body. If these cells find a place eligible for the cell to grow, metastasis can occur and a new tumor can be formed. In this thesis tumor growth is analyzed only as an avascular growth.

The specific problem of avascular tumor growth has been the subject of a number of a number of mathematical papers which focus mainly on modeling diffusion and biochemical interaction of cells and solutes species. [12] In this thesis, the mechanical behavior of a grown tumor is expressed not just in terms of the current configuration but in terms of history of the possible homogeneous mass increment.

Growth is a three dimensional process, that is why to fully describe its rate, tensor measure should be used instead of a single scalar growth rate. [13] While modeling growth, it is assumed that the growth is homogenous in all direction. A function of time for growth is described so that multiplied by the identity tensor will give the growth tensor.

In this study, ductal carcinoma is used as an example. Ductal carcinoma is tumor in an initial growth phase of breast cancer. It is originated from a malignant transformation of epithelial cells. [14] The carcinoma expands inside the lumen of the breast duct.

2. MODELING GROWTH OF A TUMOR

Let a tumor body has an unstressed configuration at time $t = 0$ as K_0, and a configuration K_t with possible application of loads after a growth or a resorption. The motion of the body is [15]

$$\boldsymbol{x} = \boldsymbol{x}(\boldsymbol{X}, t), \tag{2.1}$$

with the corresponding deformation gradient and velocity as

$$\boldsymbol{F} = \frac{\partial \boldsymbol{x}}{\partial \boldsymbol{X}}, \qquad \boldsymbol{v} = \frac{\partial \boldsymbol{x}}{\partial t}. \tag{2.2}$$

The density field at time t and $t = 0$ is

$$\rho = \rho(\boldsymbol{x}, t), \quad \rho_0(\boldsymbol{X}) = \rho(\boldsymbol{x}(\boldsymbol{X}, 0), 0). \tag{2.3}$$

The initial mass of the a particle is

$$dM_0 = \rho_0(\boldsymbol{X}) dV \tag{2.4}$$

Where dV is the volume occupied by a generic particle at time $t = 0$ and the mass of the same particle at time t is

$$dM = \rho(\boldsymbol{x}, t) dv \tag{2.5}$$

where dv is the volume of the same particle at time t and if $dM > dM_0$ growth takes place at $\boldsymbol{x}$ but if $dM < dM_0$ then resorption takes place.

Body has an unstressed configuration at time $t = 0$ as K_0, and a current configuration K_t. The particles in the body either have grown or been resorbed and the stress on the particles may be different from zero. With cutting a generic particle out of the body, the state of stress on the particle will relieve but the mass of the particle will be constant, so a new state K_p different from K_0 and K_t, will be obtained where the particle is only effected by growth. The deformation and the growth can be measured separately with this new configuration as the natural configuration of the body at time t as described at Fig. 3.1.

The deformation can be decomposed to unconstrained growth and deformation as

$$\boldsymbol{F} = \boldsymbol{F_K}\boldsymbol{G}, \quad \textbf{(2.6)}$$

Where $\boldsymbol{G}$ is the growth tensor and $\boldsymbol{F_K}$ is deformation gradient at the state K_p. Here $\boldsymbol{F_K}$ is not directly related to growth because mass does not change along the path to from K_p to K_t. Also it must be noticed that $\boldsymbol{F}$ is a mapping from a tangent space to another while $\boldsymbol{F_K}$ and $\boldsymbol{G}$ shows local changes caused by growth and deformation. Also from (2.6) it can be shown that $\boldsymbol{F_K}$ and $\boldsymbol{G}$ can be invertible since $\boldsymbol{F}$ is invertible.

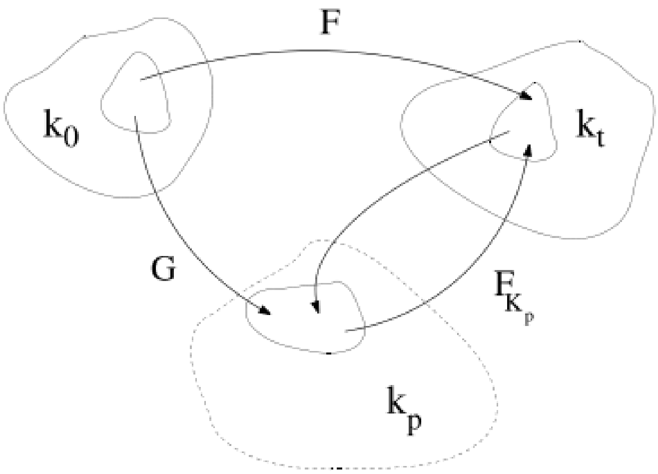

Figure 3.1. Diagram of the motion from the original unstressed configuration to current configuration with relational to natural configuration

Since mass is preserved between K_p and K_t, the volume of the generic particle in the natural configuration, denoted by dV_p, dM can be defined with the following equation below:

$$dM = \rho_0(\boldsymbol{X})dV_p. \quad \textbf{(2.7)}$$

From (2.4) and (2.7), Jacobean for Growth tensor can be obtained as

$$J_G = \det \boldsymbol{G} = \frac{dV_p}{dV} = \frac{dM}{dM_0} \quad \textbf{(2.8)}$$

where $J_G > 1$ represents growth and $J_G < 1$ represents resorption.

3. BALANCE LAWS

In this section, balance of mass, linear momentum and internal energy for the growing model introduced, are analyzed.

3.1 Mass Balance

The motion from state K_0 to K_t obeys the usual equations of balance of mass, where Eulerian form is as [16];

$$\frac{\partial \rho}{\partial t} + div(\rho \boldsymbol{v}) = \dot{\rho} + \rho div\boldsymbol{v} = \Gamma\rho \tag{3.1}$$

where Γ is the growth rate and $(\dot{})$ denotes the material time derivative.

In Lagrange frame (3.1) is rewritten as

$$\dot{(\rho J)} = \Gamma\rho J \tag{3.2}$$

where

$$J = \det \boldsymbol{F} = J_G J_{F_K}. \tag{3.3}$$

The equations which converts (3.1) to (3.2) is given at the section Appendix A.

Since mass conservation satisfied from state K_p to K_t

$$dM = \rho_0 dV_p = \rho dv, \tag{3.4}$$

From (2.8),

$$\rho_0 J_G dV = \rho J dV, \tag{3.5}$$

and

$$\rho_0 = \rho J_{F_K}, \tag{3.6}$$

where

$$J_{F_K} = det\boldsymbol{F_K} . \tag{3.7}$$

Here (3.7) is in the form of the usual Lagrangian version of conservation of mass in the absence mass source, and from K_p to K_t mass is conserved.

3.2 Balance of Linear Momentum

The balance formula for linear momentum is

$$\frac{\partial}{\partial t}(\rho \boldsymbol{v}) + div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) - div\boldsymbol{t} = \rho \boldsymbol{b} + \Gamma \rho \boldsymbol{v}, \tag{3.8}$$

where $\boldsymbol{t}$ is the Cauchy stress tensor, $\boldsymbol{b}$ is the body force and $\Gamma\rho\boldsymbol{v}$ represents the contribution to the momentum due to the mass source. From the mass balance equation (3.1), momentum equation rewrites

$$\rho \dot{\boldsymbol{v}} = div\boldsymbol{t} + \rho \boldsymbol{b}, \tag{3.9}$$

And since the characteristic velocities are so small at biological tissues, the left-hand side of the equation (4.9) can be neglected. Also neglecting the body forces is usual in Solid Mechanics, so the last term at the right-hand side of the equation will disappeared as well, and the momentum equation will take the form

$$div\boldsymbol{t} = 0. \tag{3.10}$$

The equations to retrieve (3.10) is given at section Appendix B.

3.3 Balance of Internal Energy

The balance of internal energy reads

$$\frac{\partial(\rho\varepsilon)}{\partial t} + div(\rho\varepsilon\boldsymbol{v} + \boldsymbol{q}) = \boldsymbol{t} . \boldsymbol{d} + \rho r, \tag{3.11}$$

where $\boldsymbol{q}$ is the non-convective flow of internal energy, r represents the source of energy per unit mass, the symbol $\boldsymbol{t} . \boldsymbol{d}$ indicates the inner product between Cauchy Stress tensor $\boldsymbol{t}$ and the deformation rate tensor $\boldsymbol{d}$. The quantity r in this framework includes the energy externally supplied for the growth process. The internal energy per unit volume ε represents the storage of energy that can be spent for growth only. Despite a formal analogy with thermal internal energy exists (and this is the reason why the same symbols are retained on purpose), ε should not be confused with the thermal energy, which is irrelevant with this context.

For the quasi-steady processes, it is considered, equation (3.11) simplifies to

$$\frac{\partial(\rho\varepsilon)}{\partial t} + div(\boldsymbol{q}) = \rho r, \quad \textbf{(3.12)}$$

or, in a Lagrangian frame of reference,

$$\frac{\partial(J\rho\varepsilon)}{\partial t} + div(J\boldsymbol{q}\boldsymbol{F}^{-\boldsymbol{T}}) = \rho r. \quad \textbf{(3.13)}$$

4. GROWTH TENSOR AND GROWTH RATE

To obtain a relation between growth tensor and its rate, the equation (3.6) is used. Differentiating (3.6) with respect to time,

$$\frac{d\rho_0}{dt} = \frac{d(\rho J_K)}{dt} \tag{4.1}$$

Since

$$\frac{d\rho_0}{dt} = 0, \qquad \frac{d(\rho J_K)}{dt} = \dot{\rho} J_K + \rho \dot{J_K} = 0, \tag{4.2}$$

$$\dot{\rho} = -\rho \frac{\dot{J_K}}{J_K}. \tag{4.3}$$

By using the equation (4.3) into (3.2)

$$(\dot{\rho J}) = \dot{\rho} J + \rho \dot{J} = -\rho \frac{\dot{J_K}}{J_K} J + \rho \dot{J} = \Gamma \rho J, \tag{4.4}$$

and by simplifying the equation (4.4)

$$\frac{\dot{J}}{J} - \frac{\dot{J_K}}{J_K} = \Gamma, \tag{4.5}$$

Using equation (3.3) with (4.5)

$$\frac{\dot{J_G} J_K + J_G \dot{J_K}}{J_G J_K} - \frac{\dot{J_K}}{J_K} = \frac{\dot{J_G}}{J_G} + \frac{\dot{J_K}}{J_K} - \frac{\dot{J_K}}{J_K} = \Gamma, \qquad \frac{\dot{J_G}}{J_G} = \Gamma, \tag{4.6}$$

With standard tensor calculus, as shown in section Appendix C that (4.6) can be transform to the below equation

$$tr\boldsymbol{D}_g = \Gamma, \tag{4.7}$$

where $\boldsymbol{D}_g$ is the symmetric part of $\dot{G}G^{-1}$ and tr represents trace of the tensor and as shown at section Appendix C, for an isotropic growth, i.e. $G = gI$ where g is a scalar, the relation between growth tensor g and growth rate Γ is as

$$\frac{3\dot{g}}{g} = \Gamma. \tag{4.8}$$

5. NUTRIENT FACTORS

The growth of biological tissues depends to the availability of nutrient and growth factors in blood. The tumor is fed by the environment with diffusing in the interstitial liquid. Nutrient factors are dissolved in the interstitial liquid, therefore it is assumed that the concentration of nutrient $n(\boldsymbol{x}, t)$ obeys the following reaction-diffusion equation [17]:

$$\frac{\partial n}{\partial t} + div(n\boldsymbol{v}) - div(D(n)\mathrm{grad}n) = -\gamma n\rho. \tag{5.1}$$

The equation (5.1) is a mass balance law for the nutrient where $\boldsymbol{v}$ is the velocity field of the transport and γ is the absorption rate. The nutrient concentration at a fixed point changes in time because of the diffusion due to Brownian motion. Here, for the sake of simplicity, a linear uptake function is considered. Also it is assumed that the concentration of n is constant at the boundary of tumor, as the boundary condition:

$$n|_{boundary} = n_0. \tag{5.2}$$

The equations which describes the motion of the nutrient, are coupled to the mass and momentum balance equations by the right hand side of the equation (5.1), and by using the Reynolds's transport theorem [18] and by standard calculations, (5.1) can be rewritten in Lagrangian coordinates:

$$\frac{\partial}{\partial t}(n) - div[D(n)J\boldsymbol{F}^{-\mathbf{1}}Div(J\boldsymbol{F}^{-\boldsymbol{T}}n)] = -\gamma n\rho J. \tag{5.3}$$

Since the time needed for a steady state of chemical quantities is usually much smaller than the typical time needed for growth, diffusion and production can be assumed that always balance in equation (5.3) as,

$$div[D\boldsymbol{F}^{-\mathbf{1}}Div(J\boldsymbol{F}^{-\boldsymbol{T}}n)] = \gamma n\rho J. \tag{5.4}$$

and by standard calculation the following equation can easily obtained,

$$div[D\mathrm{grad}n] = \gamma n\rho. \tag{5.5}$$

Another way to obtain an equation for nutrient, which will be further used in this thesis, is that, from a mechanical point of view, the concentrations of nutrient is a measure of the energy that can be spent for growth. Therefore the equation regulating the concentration of nutrient factors can be read as the balance of internal energy (3.13) with the suitable constitutive assumptions. In fact, when assumed as

$$\varepsilon = cn, \qquad q = -cDgrad(n), \qquad r = -\frac{n\rho c}{\tau}, \tag{5.6}$$

Where c is a constant, D is a diffusion coefficient and $1/\tau$ is the absorption rate, the following equation can be obtained,

$$Div[\boldsymbol{F}^{-1}Div(J\boldsymbol{F}^{-1}n)] = \gamma_n n\rho J, \tag{5.7}$$

where $\gamma_n = 1/D\tau,$ which is a reaction diffusion equation for the field $n(\boldsymbol{X}, t)$. Equation (5.7) s the balance law for the nutrient.

The calculations of this section and related theorems are given at section Appendix D.

6. ASSUMPTIONS

Anisotropy is a crucial characteristics of biological tissues. However, for tumor spheroids, isotropy is a reasonable assumption. [19] For this, while modelling the tumor as a material, the experimental evidence found by Helmlinger, Netti, Linchtenbeld, Melder and Jain at 1997 [20] is considered. At their experiments they showed that tumor spheroids are compressible. Under these evidences, using an isotropic compressible non-linearly elastic material will be wise. [21] The specific model referred here is a material of the Blatz-Ko type [16], one of the most used compressible hyperelastic materials which responses the same for each natural configuration.

The strain energy function of a general Blatz-Ko material is

$$W = \frac{vf}{2}\left[\left(I_{C_K} - 3\right) - \frac{2}{q}\left(III_{KC_K}^{q/2} - 1\right)\right] + \frac{v(1-f)}{2}\left[\left(\frac{II_{C_K}}{III_{C_K}} - 3\right) - \frac{2}{q}\left(III_{C_K}^{-(q/2)} - 1\right)\right], \quad \textbf{(6.1)}$$

Where v, q and f are material constants satisfying the following restrictions:

$$v > 0, \qquad 0 < f \leq 1, \qquad q < 0 \quad \textbf{(6.2)}$$

Here f will be taken as $f = 1$ for simplicity and energy function takes the form

$$W = \frac{v}{2}\left[\left(I_{C_K} - 3\right) - \frac{2}{q}\left(III_{C_K}^{q/2} - 1\right)\right]. \quad \textbf{(6.3)}$$

In this case using a viscoelastic constitutive equation would be a better approximation. Nevertheless, the characteristic times of rate dependent response of the material are much less than the characteristic times of growth and of mechanical loading for tumor spheroids, without a significant error the material can be used as a hyperelastic material. [16] Under these assumptions an energy function W_K can be introduced as

$$W = W_K(\boldsymbol{F_K}). \quad \textbf{(6.4)}$$

where $\boldsymbol{F_K}$ is Deformation gradient tensor as

$$\boldsymbol{F_K} = [x_{k,K}], \; x_{k,K} = \frac{dx_k}{dX_K}. \qquad \textbf{(6.5)}$$

Here $\boldsymbol{X}$ and $\boldsymbol{x}$ are location tensors before and after the motion and deformation and X_K and $x_k$are their form at indices notation.

With this energy function the Cauchy stress tensor can be derived with the general formula of Cauchy stress tensor below.

$$\boldsymbol{t} = \rho \boldsymbol{F_K} \left(\frac{\partial W_K}{\partial \boldsymbol{F_K}} \right). \qquad \textbf{(6.6)}$$

The simplest form of growth tensor is

$$\boldsymbol{G}(\boldsymbol{X}, t, n) = g(\boldsymbol{X}, t, n)\boldsymbol{I} \qquad \textbf{(6.7)}$$

where g is the scalar function of growth, $\boldsymbol{X}$ is the three component of the motion, t represents time and n is the nutrient.

Finally from (4.8)

$$\dot{g} = \frac{g}{3} \Gamma(\boldsymbol{X}, t, n, g). \qquad \textbf{(6.8)}$$

7. CAUCHY STRESS TENSOR COMPONENTS FOR TUMOR

In this section Cauchy stress tensor is formed by applying the energy function W_K defined in the section 6. First of all the equation (6.4) is recast to satisfy the principle of material frame indifference as

$$W = W_K(\boldsymbol{C_K}). \tag{7.1}$$

where $\boldsymbol{C_K}$ is Green deformation tensor and

$$\boldsymbol{C_K} = \boldsymbol{F_K^T F_K}. \tag{7.2}$$

Since the assumption is that the material is isotropic, (7.1) can be written in terms of the principle invariants of $\boldsymbol{C_K}$ as

$$W = W_K(I_{C_K}, II_{C_K}, III_{C_K}). \tag{7.3}$$

To apply (7.1) to (6.6), Cauchy stress tensor can be written in the form of indices notation

$$t_{kl} = \rho\left(\frac{\partial W_K}{\partial x_{k,K}}\right)x_{l,K}. \tag{7.4}$$

With using Green deformation tensor (7.4) can be written in the form

$$t_{kl} = \rho\left(\frac{\partial W_K}{\partial C_{K_{MN}}}\right)\left(\frac{\partial C_{K_{MN}}}{\partial x_{k,K}}\right)x_{l,K}, \qquad C_{K_{MN}} = x_{m,M}x_{m,N}\,. \tag{7.5}$$

With more calculation;

$$t_{kl} = \rho\left(\frac{\partial W_K}{\partial C_{K_{MN}}}\right)\left(\delta_{km}\delta_{KM}x_{m,N} + \delta_{km}\delta_{KN}x_{m,M}\right)x_{l,K}, \tag{7.6}$$

$$t_{kl} = \rho\left(\frac{\partial W_K}{\partial C_{K_{MN}}}\right)\left(\delta_{km}x_{k,N} + \delta_{KN}x_{k,M}\right)x_{l,K}, \tag{7.7}$$

$$t_{kl} = \rho\left(\frac{\partial W_K}{\partial C_{K_{MN}}}\right)\left(x_{l,M}x_{k,N} + x_{l,N}x_{k,M}\right), \tag{7.8}$$

$$t_{kl} = \rho \frac{\partial W_K}{\partial C_{K_{MN}}} x_{l,M} x_{k,N} + \rho \frac{\partial W_K}{\partial C_{K_{MN}}} x_{l,N} x_{k,M}, \qquad \textbf{(7.9)}$$

$$t_{kl} = \rho \frac{\partial W_K}{\partial C_{K_{NM}}} x_{l,N} x_{k,M} + \rho \frac{\partial W_K}{\partial C_{K_{MN}}} x_{l,N} x_{k,M}, \quad C_{K_{NM}} = C_{K_{MN}}, \qquad \textbf{(7.10)}$$

$$t_{kl} = 2\rho \frac{\partial W_K}{\partial C_{K_{MN}}} x_{l,N} x_{k,M}, \qquad \textbf{(7.11)}$$

$$t_{kl} = \frac{2\rho_0}{J_K} \frac{\partial W_K}{\partial C_{K_{MN}}} x_{l,N} x_{k,M}, \quad \rho = \frac{\rho_0}{J_K} \qquad \textbf{(7.12)}$$

Here

$$\frac{\partial W_K}{\partial C_{K_{MN}}} = \frac{\partial W_K}{\partial I_{C_K}} \frac{\partial I_{C_K}}{\partial C_{K_{MN}}} + \frac{\partial W_K}{\partial II_{C_K}} \frac{\partial II_{C_K}}{\partial C_{K_{MN}}} + \frac{\partial W_K}{\partial III_{C_K}} \frac{\partial III_{C_K}}{\partial C_{K_{MN}}}, \qquad \textbf{(7.13)}$$

$$I_{C_K} = C_{K_{MM}}, \qquad \frac{\partial I_{C_K}}{\partial C_{K_{MN}}} = \delta_{MK}\delta_{NK} = \delta_{MN}, \qquad \textbf{(7.14)}$$

$$II_{C_K} = \frac{1}{2}\left(I_{C_K}{}^2 - C_{K_{MN}} C_{K_{NM}}\right), \qquad \textbf{(7.15)}$$

$$\frac{\partial II_{C_K}}{\partial C_{K_{MN}}} = \frac{1}{2}\left(2 I_{C_K} \delta_{MN} - \delta_{MK}\delta_{NL} C_{K_{LK}} - \delta_{ML}\delta_{NK} C_{K_{LK}}\right), \qquad \textbf{(7.16)}$$

$$\frac{\partial II_{C_K}}{\partial C_{K_{MN}}} = \frac{1}{2}\left(2 I_{C_K} \delta_{MN} - C_{K_{MN}} - C_{K_{MN}}\right), \qquad \textbf{(7.17)}$$

$$\frac{\partial II_{C_K}}{\partial C_{K_{MN}}} = I_{C_K} \delta_{MN} - 2 C_{K_{MN}}, \qquad \textbf{(7.18)}$$

$$III_{C_K} = \det(\boldsymbol{C_K}), \quad \frac{\partial III_{C_K}}{\partial C_{K_{MN}}} = III_{C_K} \left[C_K{}^{-1}\right]_{MN}, \qquad \textbf{(7.19)}$$

Using (7.13), (7.14), (7.18), (7.19) into (7.12)

$$t_{kl} = \frac{2\rho_0}{J_K} \left[\frac{\partial W_K}{\partial I_{C_K}} \delta_{MN} + \frac{\partial W_K}{\partial II_{C_K}} \left(I_{C_K} \delta_{MN} - 2 C_{K_{MN}}\right) + \frac{\partial W_K}{\partial III_{C_K}} III_{C_K} \left[C_K{}^{-1}\right]_{MN}\right] x_{l,N} x_{k,M}, \qquad \textbf{(7.20)}$$

Tensor notation for of (7.20) is

$$\boldsymbol{t} = \frac{2\rho_0}{J_K}\left[\frac{\partial W_K}{\partial I_{C_K}}\boldsymbol{C_K}^{-1} + \frac{\partial W_K}{\partial II_{C_K}}\left(I_{C_K}\boldsymbol{C_K}^{-1} - \boldsymbol{C_K}^{-2}\right) + \frac{\partial W_K}{\partial III_{C_K}} III_{C_K}\boldsymbol{I}\right], \tag{7.21}$$

When W_K is derived for I_{C_K}, II_{C_K} and III_{C_K}:

$$\frac{\partial W_K}{\partial I_{C_K}} = \frac{v}{2}, \tag{7.22}$$

$$\frac{\partial W_K}{\partial II_{C_K}} = 0, \tag{7.23}$$

$$\frac{\partial W_K}{\partial III_{C_K}} = -\frac{v}{2} III_{C_K}^{\left(\frac{q}{2}-1\right)}. \tag{7.24}$$

(7.21) can be rewritten with (7.22), (7.23), (7.24) as

$$\boldsymbol{t} = \frac{2\rho_0}{J_K}\left[\frac{v}{2}\boldsymbol{C_K}^{-1} + -\frac{v}{2} III_{C_K}^{q/2}\boldsymbol{I}\right],$$
$$III_{C_K} = \det(\boldsymbol{C_K}) = det(\boldsymbol{F_K})^2 = J_K{}^2. \tag{7.25}$$

Defining $\mu = \rho_0 v$ and using (7.2) and (7.12), (7.25) can be simplified as

$$\boldsymbol{t} = \frac{\mu}{J_K}\left[-(J_K)^q\boldsymbol{I} + \boldsymbol{F_K}\boldsymbol{F_K^T}\right]. \tag{7.26}$$

8. IMPLEMENTATIONS

In this section, homogeneous growth problems are solved for spheroid tumors inside rigid cylindrical vessel and spheroid tumors inside non-rigid cylindrical vessel, to apply the general theory illustrated in this study. In the first problem equilibrium equation is directly satisfied since the deformation is homogeneous and vessel is rigid. In the second problem the form of the growth deformation is assumed as inhomogeneous and the vessel is not rigid. In this case there will be a deformation at vessel as well as the tumor.

This implementations are based on the 5 equations below:

No	Equation	Eq. No
1	$\rho_0 = \rho J_{F_K}$	**(3.6)**
2	$div\boldsymbol{t} = 0$	**(3.10)**
3	$div(D\text{grad}n) = \gamma n\rho$	**(5.5)**
4	$\dot{g} = \frac{g}{3}\Gamma(\boldsymbol{X}, t, n, g)$	**(6.8)**
5	$\boldsymbol{t} = \frac{\mu}{J_K}\left[-(J_K)^q\boldsymbol{I} + \boldsymbol{F_K}\boldsymbol{F_K^T}\right]$	**(7.26)**

Table 8.1. Equations building the problems

8.1 Isotropic and homogeneous growth of a tumor inside a rigid vessel

A spheroid tumor with in a rigid cylindrical vessel represents a type of breast cancer named ductal carcinoma. By receiving nutrients through the walls of tumor cells, tumor can grow nearly 10 cm inside a breast duct. [16]

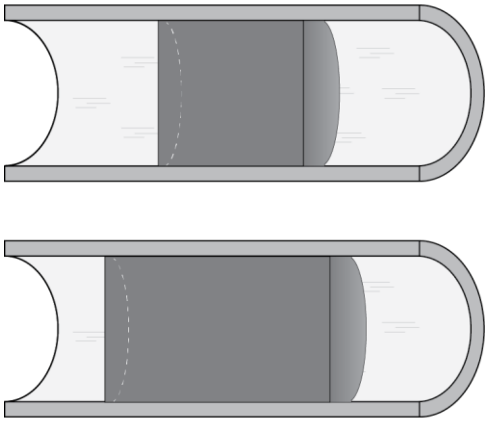

Figure 8.1.1. Tumor growing in a rigid vessel

As the vessel is rigid the deformation is only at Z direction and the motion and its deformation gradient is as:

$$r = R, \qquad \theta = \Theta, \qquad z = \lambda Z, \qquad \boldsymbol{F} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{1}{R} & 0 \\ 0 & 0 & \lambda \end{bmatrix} \tag{8.1}$$

Here λ is the function of deformation on Z direction. Suppose the growth rate is piecewise constant and level of nutrients is above a threshold value;

$$\Gamma = \hat{\Gamma}(n - \hat{n}), \tag{8.2}$$

Where $\hat{n}$ threshold value and H is Heaviside function as;

$$H(\hat{n}) = \begin{cases} 1 & if\ concentration\ of\ nutrient > \hat{n}, \\ 0 & if\ concentration\ of\ nutrient \leq \hat{n} \end{cases}. \tag{8.3}$$

With a nutrient flow given above, the growth can be assumed as homogeneous;

$$g = g(t). \tag{8.4}$$

As shown at equation (6.8)

$$\dot{g} = \frac{g}{3}\Gamma(\boldsymbol{X}, t, n, g). \tag{8.5}$$

When integrated the equation above as

$$\int \frac{1}{g} dg = \int \frac{1}{3} \Gamma\, dt. \tag{8.6}$$

Growth function g can be obtained as:

$$g = e^{\hat{\Gamma}\frac{t}{3}}. \tag{8.7}$$

From (8.1), (8.4) and (2.6), $\boldsymbol{F_K}$ can be obtained as,

$$\boldsymbol{F} = \boldsymbol{F_K}\,\boldsymbol{G}, \qquad \boldsymbol{G} = g\,\boldsymbol{I}, \qquad \boldsymbol{F_K} = \frac{1}{g}\boldsymbol{F}, \tag{8.8}$$

In matrix form $\boldsymbol{F_K}$ can be shown as:

$$\boldsymbol{F_K} = \begin{bmatrix} \frac{1}{g} & 0 & 0 \\ 0 & \frac{1}{gR} & 0 \\ 0 & 0 & \frac{\lambda}{g} \end{bmatrix}, \qquad J_K = \det \boldsymbol{F_K} = \frac{\lambda}{g^3 R}\,. \tag{8.9}$$

Substituting into (7.26)

$$\boldsymbol{t} = \frac{\mu g^3 R}{\lambda}\left[-\left(\frac{\lambda}{g^3 R}\right)^q \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} + \begin{bmatrix} \frac{1}{g} & 0 & 0 \\ 0 & \frac{1}{gR} & 0 \\ 0 & 0 & \frac{\lambda}{g} \end{bmatrix}\begin{bmatrix} \frac{1}{g} & 0 & 0 \\ 0 & \frac{1}{gR} & 0 \\ 0 & 0 & \frac{\lambda}{g} \end{bmatrix}\right], \tag{8.10}$$

$$\boldsymbol{t} = \frac{\mu g^3 R}{\lambda}\left[\begin{bmatrix} \frac{1}{g^2} & 0 & 0 \\ 0 & \frac{1}{g^2 R^2} & 0 \\ 0 & 0 & \frac{\lambda^2}{g^2} \end{bmatrix} - \begin{bmatrix} \left(\frac{\lambda}{g^3 R}\right)^q & 0 & 0 \\ 0 & \left(\frac{\lambda}{g^3 R}\right)^q & 0 \\ 0 & 0 & \left(\frac{\lambda}{g^3 R}\right)^q \end{bmatrix}\right], \tag{8.11}$$

$$\boldsymbol{t} = \frac{\mu g^3 R}{\lambda}\begin{bmatrix} \frac{1}{g^2} - \left(\frac{\lambda}{g^3 R}\right)^q & 0 & 0 \\ 0 & \frac{1}{g^2 R^2} - \left(\frac{\lambda}{g^3 R}\right)^q & 0 \\ 0 & 0 & \frac{\lambda^2}{g^2} - \left(\frac{\lambda}{g^3 R}\right)^q \end{bmatrix}, \tag{8.12}$$

Here, it can be assumed that the bottom and top surface of the cylinder are stress free since the cylinder is rigid and obtained a boundary condition as $\boldsymbol{t}_{zz} = 0$.

λ can be obtained with the following calculations:

$$\boldsymbol{t}_{zz} = \frac{\mu g^3 R}{\lambda}\left[\frac{\lambda^2}{g^2} - \left(\frac{\lambda}{g^3 R}\right)^q\right] = 0, \tag{8.13}$$

$$\frac{\lambda^2}{g^2} - \left(\frac{\lambda}{g^3 R}\right)^q = 0, \tag{8.14}$$

$$\lambda = g^{(2-3q)/(2-q)} R^{-q/(2-q)}. \quad \textbf{(8.15)}$$

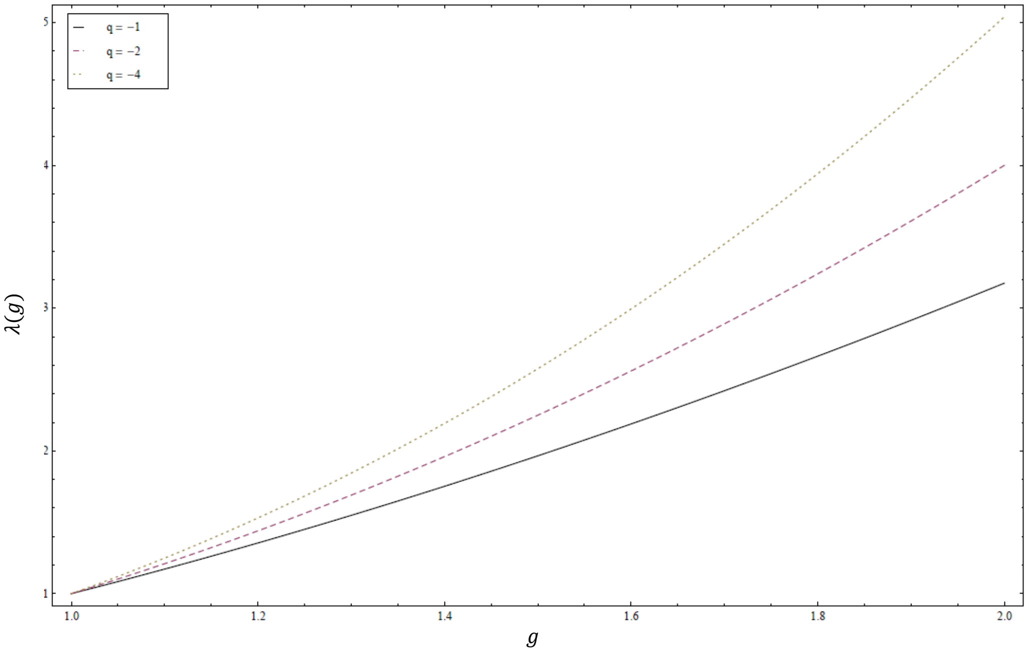

Figure 8.1.2. Growth of a spheroid tumor in a rigid cylindrical vessel: axial displacement of the material as a function of g for different values of q when initial radius R of tumor is 1 cm.

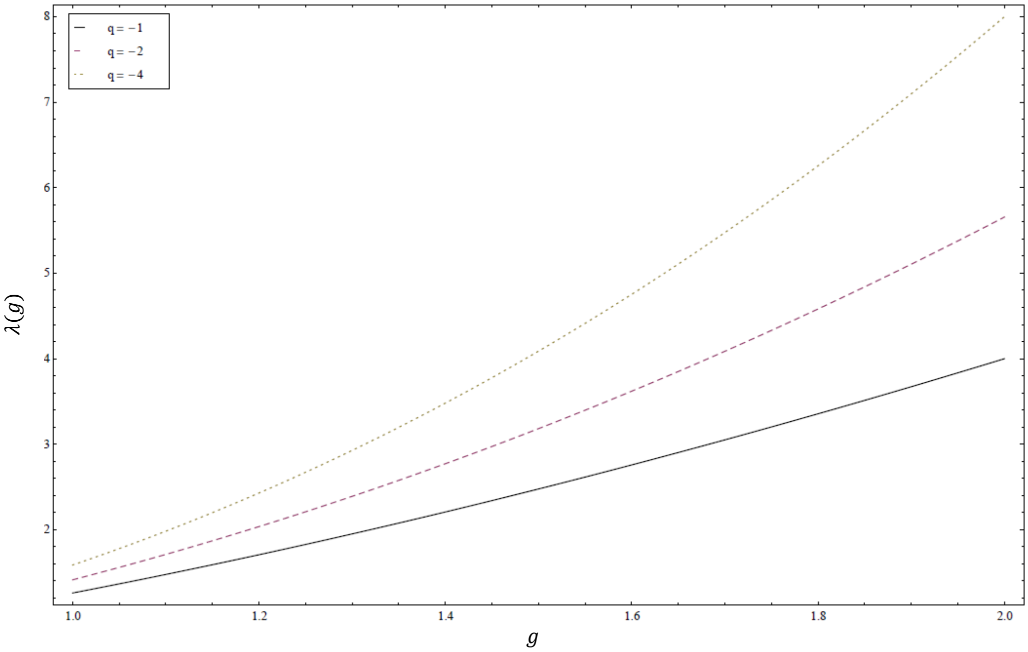

Figure 8.1.3. Growth of a spheroid tumor in a rigid cylindrical vessel: axial displacement of the material as a function of g for different values of q when initial radius R of tumor is 2 cm.

8.2 Isotropic and homogeneous growth of a tumor inside a non-rigid vessel

The problem is solved for a spheroid tumor with in a non-rigid cylindrical vessel is solved here. Since both the vessel and tumor have a deformation, each of their deformation is solved separately and then these equations are used as a boundary conditions for each other where the inner surface of the vessel and surface of the tumor touch each other.

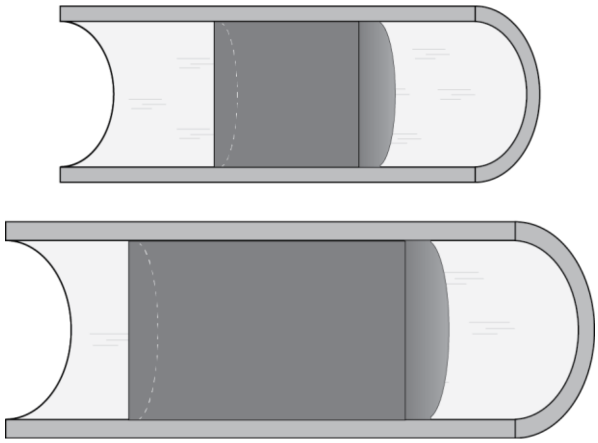

Figure 8.2.1. Tumor growing in a non-rigid vessel

Stress components for vessel:

As the vessel is non-rigid the deformation is at R and Z directions and the motion and its deformation gradient for vessel is as:

$$r = f_1(R), \qquad \theta = \Theta, \qquad z = \lambda Z, \qquad \boldsymbol{F_v} = \begin{bmatrix} f_1{}' & 0 & 0 \\ 0 & \frac{f_1}{R} & 0 \\ 0 & 0 & \lambda \end{bmatrix} \qquad \textbf{(8.16)}$$

Here energy function for vessel is taken as isotropic hyperelastic material,

$$W_v = \alpha(I_v - 3). \qquad \textbf{(8.17)}$$

From (7.20), the Cauchy stress tensor for vessel is

$$t_{kl} = 2\rho\left[\frac{\partial W_v}{\partial I_v}\delta_{MN} + \frac{\partial W_v}{\partial II_v}\left(I_v\delta_{MN} - 2C_{v_{MN}}\right) + \frac{\partial W_v}{\partial III_v} III_v\left[\boldsymbol{C_v}^{-1}\right]_{MN}\right] x_{l,N}x_{k,M}, \qquad \textbf{(8.18)}$$

$$\boldsymbol{t} = 2\rho\left[\frac{\partial W_v}{\partial I_v}\boldsymbol{C_v}^{-1} + \frac{\partial W_v}{\partial II_v}\left(I_v\boldsymbol{C_v}^{-1} - \boldsymbol{C_v}^{-2}\right) + \frac{\partial W_v}{\partial III_v} III_v\boldsymbol{I}\right], \qquad \textbf{(8.19)}$$

Since vessel is assumed to be incompressible and isotropic, Cauchy stress tensor takes the following form

$$\boldsymbol{t} = P\boldsymbol{I} + \left[2\frac{\partial W_v}{\partial I_v}\,\boldsymbol{C_v}^{-\boldsymbol{1}} + 2\,\frac{\partial W_v}{\partial II_v}\left(\,I_v\,\boldsymbol{C_v}^{-\boldsymbol{1}} - \,\boldsymbol{C_v}^{-\boldsymbol{2}}\right)\right], \qquad \textbf{(8.20)}$$

which is shown by Hilmi Demiray [22], here P is hydrostatic pressure function.

Derivatives of W_v are

$$\frac{\partial W_v}{\partial I_v} = \alpha, \qquad \frac{\partial W_v}{\partial II_v} = 0, \qquad \frac{\partial W_v}{\partial III_v} = 0. \qquad \textbf{(8.21)}$$

And $C_v{}^{-1}$is Green deformation tensor where

$$C_v{}^{-1} = \boldsymbol{F}_v\boldsymbol{F}_v^{\boldsymbol{T}}, \qquad \textbf{(8.22)}$$

$$C_v{}^{-1} = \begin{bmatrix} f_1{}' & 0 & 0 \\ 0 & \frac{f_1}{R} & 0 \\ 0 & 0 & \lambda \end{bmatrix}\begin{bmatrix} f_1{}' & 0 & 0 \\ 0 & \frac{f_1}{R} & 0 \\ 0 & 0 & \lambda \end{bmatrix} = \begin{bmatrix} (f_1{}')^2 & 0 & 0 \\ 0 & \frac{(f_1)^2}{R^2} & 0 \\ 0 & 0 & \lambda^2 \end{bmatrix} \qquad \textbf{(8.23)}$$

From (8.18), (8.19) and (8.21) Cauchy stress tensor for vessel takes the following form:

$$\boldsymbol{t} = P + \left[\frac{\partial W_v}{\partial I_v}\,\boldsymbol{C_v}^{-\boldsymbol{1}}\right] = P + 2\alpha\begin{bmatrix} (f_1{}')^2 & 0 & 0 \\ 0 & \frac{(f_1)^2}{R^2} & 0 \\ 0 & 0 & \lambda^2 \end{bmatrix}. \qquad \textbf{(8.24)}$$

Since the vessel is taken as an incompressible material,

$$III_v = \det\left(C_v{}^{-1}\right) = 1, \qquad \textbf{(8.25)}$$

From (8.24)

$$\frac{(f_1{}')^2(f_1)^2}{R^2}\lambda^2 = 1, \qquad \textbf{(8.26)}$$

f_1 can be obtained with the following calculations:

$$f_1{}'f_1 = \frac{R}{\lambda}, \qquad \textbf{(8.27)}$$

$$f_1{}'df_1 = \frac{RdR}{\lambda}, \qquad \textbf{(8.28)}$$

$$\frac{(f_1)^2}{2} = \frac{R^2}{2\lambda} + A, \qquad \textbf{(8.29)}$$

$$f_1 = \sqrt{\frac{R^2}{\lambda} + B}. \quad \textbf{(8.30)}$$

where A and B are integral constants.

Here

$$f_1{}' = \frac{R}{\lambda f_1}, \quad \textbf{(8.31)}$$

will be useful at further calculations. Also to simplify the equations,

$$x = \frac{R}{f_1}, \quad \textbf{(8.32)}$$

is used, with which the Green deformation tensor becomes as below,

$$C_v{}^{-1} = \begin{bmatrix} \frac{x^2}{\lambda^2} & 0 & 0 \\ 0 & \frac{1}{x^2} & 0 \\ 0 & 0 & \lambda^2 \end{bmatrix} \quad \textbf{(8.33)}$$

and Cauchy stress tensor takes the form:

$$\boldsymbol{t} = P + 2\alpha \begin{bmatrix} \frac{x^2}{\lambda^2} & 0 & 0 \\ 0 & \frac{1}{x^2} & 0 \\ 0 & 0 & \lambda^2 \end{bmatrix}. \quad \textbf{(8.34)}$$

These stress components should satisfy the Balance equation:

$$\frac{dt_{rr}}{dr} + \frac{1}{r}\,(t_{rr} - t_{\theta\theta}) = 0. \quad \textbf{(8.35)}$$

From (8.32)

$$x = \frac{R}{f_1} = \frac{R}{r}, \quad \textbf{(8.36)}$$

Then the derivative can be calculated as below:

$$\frac{dt_{rr}}{dr} = \frac{dt_{rr}}{dx}\frac{dx}{dr} = \frac{dt_{rr}}{dx}\frac{\frac{dR}{dr}r - R}{r^2}. \quad \textbf{(8.37)}$$

From (8.30)

$$r^2 = \frac{R^2}{\lambda} + B. \qquad \textbf{(8.38)}$$

Deriving (8.38) and using (8.32)

$$2rdr = \frac{2dR}{\lambda}, \qquad \textbf{(8.39)}$$

$$\frac{dr}{dR} = \frac{x}{\lambda}. \qquad \textbf{(8.40)}$$

When (8.40) applied into (8.37)

$$\frac{dt_{rr}}{dr} = \frac{1}{r}\frac{dt_{rr}}{dx}\left(\frac{\lambda}{x} - x\right). \qquad \textbf{(8.41)}$$

Using (8.34) and (8.41) with balance equation (8.35)

$$\frac{1}{r}\frac{dt_{rr}}{dx}\left(\frac{\lambda}{x} - x\right) + \frac{1}{r}\left(P + 2\,\alpha\frac{x^2}{\lambda^2} - P - 2\,\alpha\frac{1}{x^2}\right) = 0. \qquad \textbf{(8.42)}$$

(8.42) can be simplified as

$$\frac{dt_{rr}}{dx} = \frac{2\alpha}{\lambda^2}\left(x + \frac{\lambda}{x}\right). \qquad \textbf{(8.43)}$$

Integrating the equation (8.43)

$$t_{rr} = \int_{x_i}^{x} \frac{2\alpha}{\lambda^2}\left(\xi + \frac{\lambda}{\xi}\right) d\xi, \qquad \textbf{(8.44)}$$

$$t_{rr} = \frac{2\alpha}{\lambda^2}\left[\left(\frac{\xi^2}{2} + \lambda ln\xi\right)\right]\Bigg|_{x_o}^{x}, \qquad \textbf{(8.45)}$$

$$t_{rr} = \frac{2\alpha}{\lambda^2}\left[\frac{(x^2 - {x_o}^2)}{2} + \lambda ln\frac{x}{x_o}\right], \qquad \textbf{(8.46)}$$

where x_i is the inner boundary of the radius of the vessel and

$$t_{rr}|_{x=x_i} = -P_i, \qquad t_{rr}|_{x=x_o} = 0, \qquad \textbf{(8.47)}$$

as x_o is the outer boundary of the radius of the vessel and P_i is the pressure made by tumor to the inner surface of the vessel.

Stress components for tumor:

As the vessel is non-rigid the deformation is at R and Z directions and the motion and its deformation gradient for tumor is as:

$$r = f_2(R), \qquad \theta = \Theta, \qquad z = \lambda Z, \qquad \boldsymbol{F_t} = \begin{bmatrix} f_2{}' & 0 & 0 \\ 0 & \frac{f_2}{R} & 0 \\ 0 & 0 & \lambda \end{bmatrix} \qquad \textbf{(8.48)}$$

Here λ is the function of deformation on Z direction and $f_2(R)$ is the deformation function on R direction. Suppose the growth rate is piecewise constant and level of nutrients is above a threshold value like the example at section 8.1;

$$\Gamma = \hat{\Gamma}(n - \hat{n}), \qquad \textbf{(8.49)}$$

Where $\hat{n}$ threshold value and H is Heaviside function as;

$$H(\hat{n}) = \begin{cases} 1 & if\ concentration\ of\ nutrient > \hat{n}, \\ 0 & if\ concentration\ of\ nutrient \leq \hat{n} \end{cases}. \qquad \textbf{(8.50)}$$

With a nutrient flow given above, the growth can be assumed as homogeneous;

$$g = g(t). \qquad \textbf{(8.51)}$$

As shown at equation (7.10)

$$\dot{g} = \frac{g}{3}\Gamma(\boldsymbol{X}, t, n, g). \qquad \textbf{(8.52)}$$

When integrated the equation above as

$$\int \frac{1}{g} dg = \int \frac{1}{3}\Gamma\ dt. \qquad \textbf{(8.53)}$$

Growth function g can be obtained as:

$$g = e^{\hat{\Gamma}\frac{t}{3}}, \qquad \textbf{(8.54)}$$

which is exactly the same as example 9.1.

From (8.48), (8.51) and (2.6), $\boldsymbol{F_K}$ can be obtained as,

$$\boldsymbol{F_t} = \boldsymbol{F_K}\,\boldsymbol{G}, \qquad \boldsymbol{G} = g\,\boldsymbol{I}, \qquad \boldsymbol{F_K} = \frac{1}{g}\,\boldsymbol{F_t}, \qquad \textbf{(8.55)}$$

In matrix form $\boldsymbol{F_K}$ can be shown as:

$$\boldsymbol{F_K} = \begin{bmatrix} \frac{f_2{}'}{g} & 0 & 0 \\ 0 & \frac{f_2}{gR} & 0 \\ 0 & 0 & \frac{\lambda}{g} \end{bmatrix}, \qquad J_K = \det \boldsymbol{F_K} = \frac{\lambda f_2{}' f_2}{g^3 R}. \qquad \textbf{(8.56)}$$

Here, to write boundary conditions in the reference configuration, instead of Cauchy stress tensor, Piola-Kirchoff stress tensor, $\boldsymbol{T}$ is used:

$$\boldsymbol{T} = J_G\,\mu\,\boldsymbol{G^{-1}}\left[\boldsymbol{F_K^T} - (J_K)^q \boldsymbol{F_K^{-1}}\right]. \qquad \textbf{(8.57)}$$

Applying (8.55) and (8.56) to (8.57),

$$\boldsymbol{T} = \mu\,\boldsymbol{I}\left[\frac{1}{g}\begin{bmatrix} \frac{f_2{}'}{g} & 0 & 0 \\ 0 & \frac{f_2}{gR} & 0 \\ 0 & 0 & \frac{\lambda}{g} \end{bmatrix} - \left(\frac{\lambda f_2{}' f_2}{g^3 R}\right)^q \begin{bmatrix} \frac{g^2}{f_2{}'} & 0 & 0 \\ 0 & \frac{g^2 R}{f_2} & 0 \\ 0 & 0 & \frac{g^2}{\lambda} \end{bmatrix}\right], \qquad \textbf{(8.58)}$$

By some easy calculations components of $\boldsymbol{T}$ can be defined in the following forms:

$$T_{RR} = \mu\left[\frac{f_2{}'}{g^2} - (J_K)^q \frac{g^2}{f_2{}'}\right], \qquad \textbf{(8.59)}$$

$$T_{\Theta\Theta} = \mu\left[\frac{f_2}{g^2 R} - (J_K)^q \frac{g^2 R}{f_2}\right], \qquad \textbf{(8.60)}$$

$$T_{ZZ} = \mu\left[\frac{\lambda}{g^2} - (J_K)^q \frac{g^2}{\lambda}\right], \qquad \textbf{(8.61)}$$

$$J_K = \frac{\lambda f_2{}' f_2}{g^3 R}. \qquad \textbf{(8.62)}$$

With Piola-Kirchoff stress tensor the equation (3.10) will take the following form:

$$\frac{dT_{RR}}{dR} + \frac{1}{R}\left(T_{RR} - T_{\Theta\Theta}\right) = 0, \tag{8.63}$$

with the boundary conditions given in the reference configuration as,

$$T_{RR}|_{R=R_i} = -P_i, \qquad f_2(0) = 0. \tag{8.64}$$

Since tumor is free of stress at Z direction, $T_{ZZ} = 0$, and this leads to

$$(J_K)^q = \frac{\lambda^2}{g^4}. \tag{8.65}$$

Using (8.65) with (8.59) and (8.60), rewrites the stress components as;

$$T_{RR} = \mu\left[\frac{f_2{}'}{g^2} - \frac{\lambda^2}{g^2 f_2{}'}\right], \tag{8.66}$$

$$T_{\Theta\Theta} = \mu\left[\frac{f_2}{g^2 R} - \frac{\lambda^2 R}{g^2 f_2}\right]. \tag{8.67}$$

These stress components are used at equation (8.62) to obtain the non-linear ordinary differential equation of $f_2(R)$:

$$\frac{d}{dr}\left(f_2' - \frac{\lambda^2}{f_2'}\right) + \frac{1}{R}\left(f_2' - \frac{\lambda^2}{f_2'} - \frac{f_2}{R} + \frac{\lambda^2}{f_2}\right) = 0. \tag{8.68}$$

This equations with the boundary condition given at (8.64) is solved numerically using Mathematica with the codes given at section Appendix F. Here μ as material constant of tumor and α as material constant of vessel are unknown constant. A new constant $\beta$is defined for the relation between these two constant as $\alpha = \beta\mu$. By using this new constant the first boundary condition at (8.64) is rewritten as,

$$f_2'(R_i) = \frac{1}{2}\left(-\beta P_i g^2 + \sqrt{\beta P_i g^2 + 4\lambda^2}\right). \tag{8.68}$$

This equation is numerically solved at $R = R_i$, by giving related values to β and g, and taking values of λ which satisfies the condition $q < 0$ using equation (8.64).

At Figure 8.2.2, for different values of λ and g, changes of f_2 with respect to R is given with $\beta = 2$. Also at 8.2.3, for different values of λ and g, changes of f_2 with respect to R is given with $\beta = 0.5$. When these both graphs are analyzed, with same g value, it is shown that the function $f_2(R)$ is increased when value of λ is increased.

Another important note is that when λ is same, the function $f_2(R)$ is decreases when value of g is increased. As a conclusion, when the rate of expansion function at Z direction λ increase, the contribution of the growth function of tumor g, to the deformation is decreased. This result is not a result mostly expected. But since there is no clue for the value of the material constant rate $\beta = \alpha/\mu$ and there is no study on tumor growth in a non-rigid vessel, there is no way to compare the results with valid solutions.

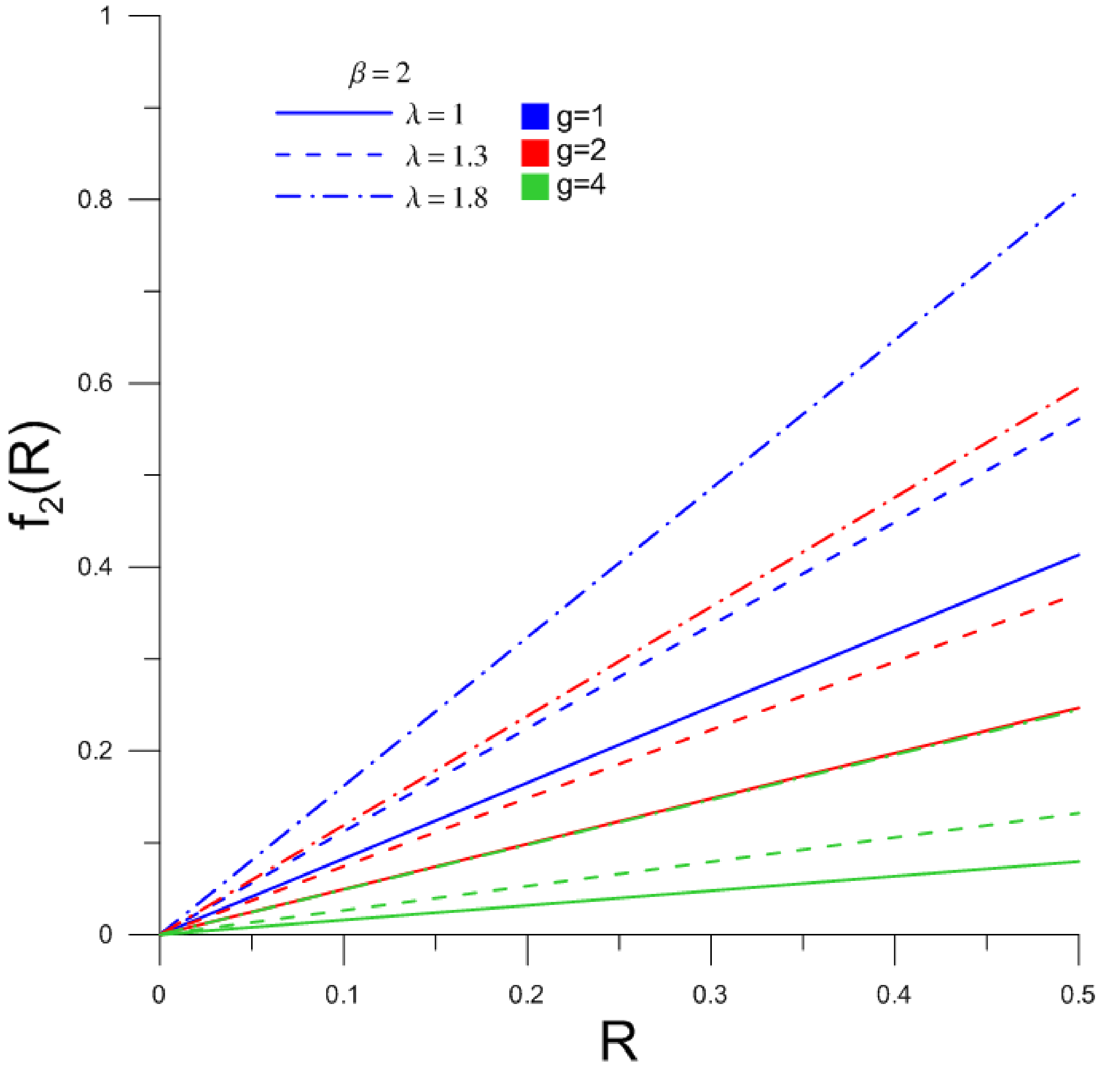

Figure 8.2.2. Changes of f_2 with respect to R is given with $\beta = 2$

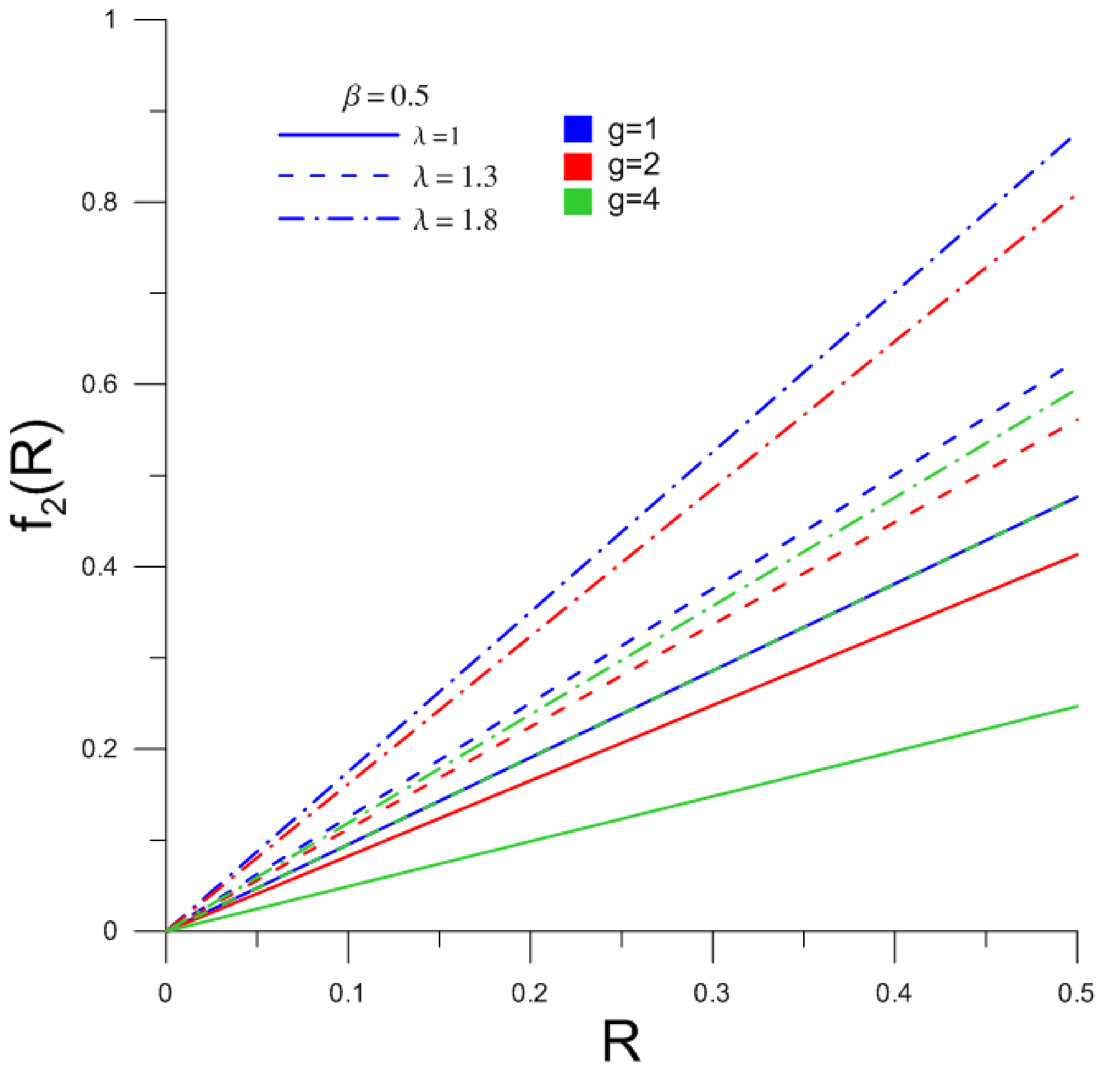

Figure 8.2.3. Changes of f_2 with respect to R is given with $\beta = 0.5$

The other hand, the other material constant q should be negative. As shown at Figure 8.2.4., when $\beta = 3$, and $\lambda = 3$, if g is taken as $g = 2$, then $q = -0.65$ and if g is taken as $g = 2.2$, the $q = -23$. As a result of this, with the model studied in this thesis, it is possible to determine the value of q which determines the structural features of the tumor if the values of g and λ are measured.

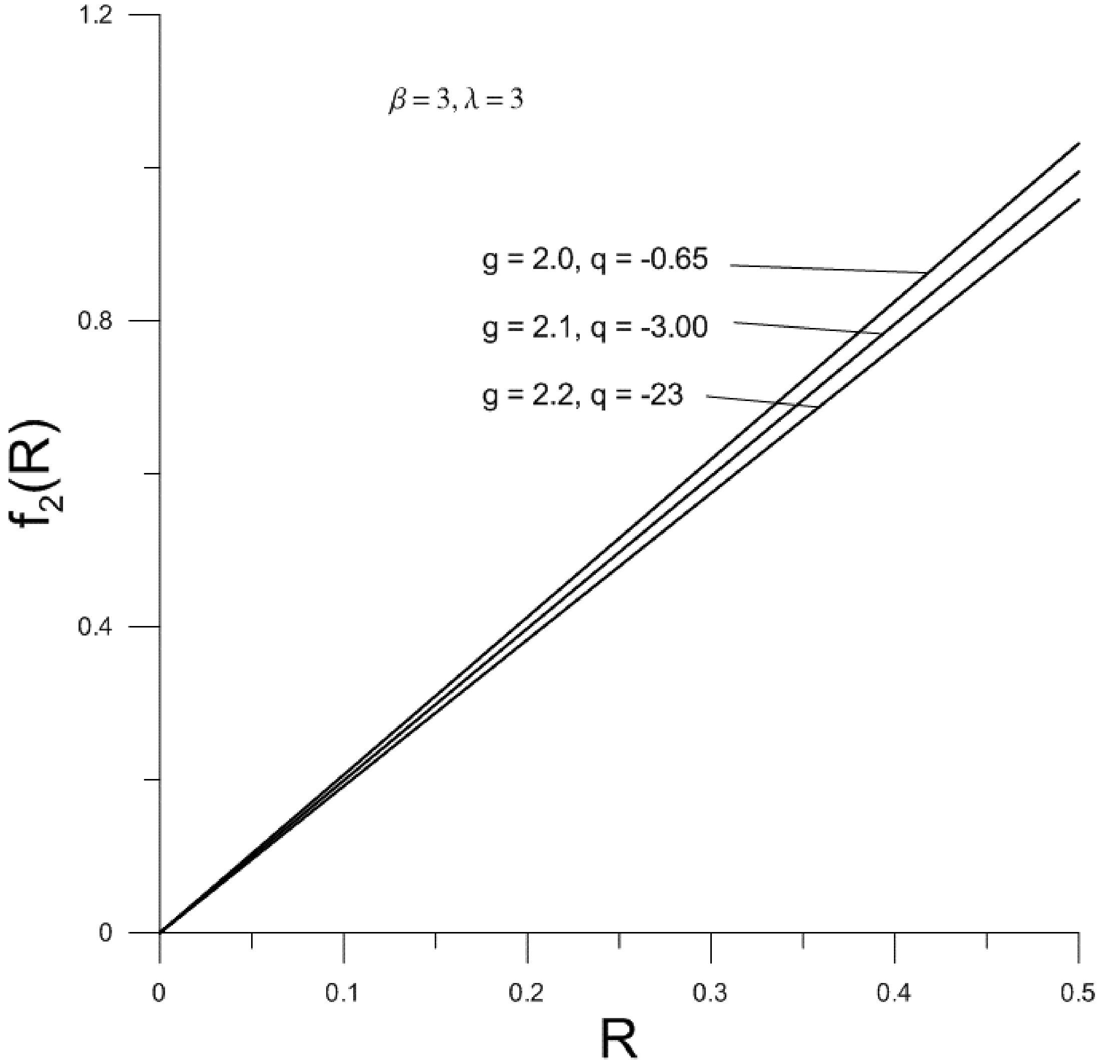

Figure 8.2.4. Changes of f_2 with respect to g

9. CONCLUSIONS AND RECOMMENDATIONS

In this study, a mathematical model for a tumor growing in a cylindrical vessel is proposed. Firstly, a rigid vessel is considered in the model and tumor is considered as a spherical body, and a respectively basic growth tensor $\boldsymbol{G}$ is defined to obtain the relation between the extension and the growth. It is observed that as the growth increases, the elongation is increased as well.

Later the vessel is considered as a non-rigid elastic material and a simple constitutive equation for this material is defined. In the model, tumor is considered as grown enough, in a cylindrical shape and in an interaction with the vessel as a reference state, and let the tumor to deform in radial directions. As a result, opposite to a rigid vessel, with a non-rigid vessel it is observed that as the growth increases the elongation is decreased.

At the evaluation of the model, the unknown material constants and the assumptions to simplify the equations take roles as disadvantages.

For further studies, under the results of this study, it is highly recommended to define tumor as a viscos-elastic material for more realistic solutions. Also the relation between tumor and the vessel should be defined more realistic ways.

REFERENCES

[1]Rajagopal K.R. (1995) Multiple Natural Configurations in Continuum Mechanics, *Rep. Inst. Appl. Mech*. 6

[2]Rajagopal, K.R. and Wineman A.S. (1992) A Constitutive Equation For Nonlinear Solds Which Undergo Deformation Induced Microstructural changes, *Int. J. Plast.*, **8**, 385-395

[3]Rajagopal, K.R. and Srinivasa A.R. (1998) Mechanics of the Inelastic Behavior of Materials, Part II: Inelastic Response, *Int. J. Plast.*, **14**, 969-995

[4]Rajagopal, K.R. and Srinivasa A.R. (1995) On the Inelastic Behavior of Materials, Part I: Twinning, *Int. J. Plast.*, **11**, 653-678

[5]Rajagopal, K.R. and Srinivasa A.R. (1999) On the Thermodynamics of Shape Memory Wires, *ZAP*, **50**, 459-496

[6]Rajagopal, K.R. and Srinivasa A.R. (2000) A Thermodynamics Framework for Rate Type Fluid Models, *J. Non-Newtonian Fluid Mech.*, **88**, 207-227

[7]Rao, I.J. and Rajagopal, K.R. (2000) Phenomenological Modeling of Polymer Crystallization Using the Notion of Multiple Natural Configurations, *Interf. Free Bond*, **2**, 73-94

[8]Ambrosi, D. and Guanna, F. (2007). Mathematics and Mechanics of Solids, *Stress-Modulated Growth*, University of Torino, Italy, 12:319 DOI: 10.1177/1081286505059739.

[9]Taber, Larry A. (1995). Biomechanics of growth, remodeling, and morphogenesis, University Of Rochester, Rochester NY, 14627.

[10]Byrne, Helen (2000). Using Mathematics to Study Solid Tumour Growth, *Meetings of European Women in Mathematics*, University of Nottingham, England.

[11]Stamper, I.J., Byrne H.M., Owen M.R. and Maini P.K. (2007). Modelling the Role of Angiogenesis and Vasculogenesis in Solid Tumour Growth, *Society for Mathematical Biology*, England.

[12]Ambrosi, D. and Mollica, F. (2003). The Role of Stress in the Growth of a Multicell Spheroid. *Mathematical Biology, **48**,* 477-499 DOI:10.1007/s00285-003-0238-2.

[13]Rodriguez, Edvard K., Hoger, Anne and McCulloch, Andrew D. (1994). Stress-Dependent Finite Growth in Soft Elastic Tissues, University of California, SanDiego, USA.

[14]Ciarletta, P., Ambrossi, D. and Maugin, G.A. (2011). Mass Transport in Morphogenetic Processes: A Second Gradient Theory for Volumetric Growth and Material Remodeling. *Journal of Mechanics and Physics of Solid*, 60, 432-450.

[15]Truesdell, C.A. and Noll, W. (1992) The Non-linear Field Theories of Mechanics, Second Edition, *Springer*, Berlin, Germany

[16]Ambrosi, D. and Mollica, F. (2001). On the Mechanics of a Growing Tumor, *International Journal of Engineering Science*, Italy, 40 (2001) 1297-1316.

[17]Murray, J.D. (1993) Mathematical Biology, Third Edition, *Springer*, Berlin, Germany.

[18]Gurtin, M.E. (1981) An Introduction to Continuum Mechanics, *Academic Press*, New York, USA.

[19]Helmlinger, G., Netti, P.A., Linchtenbeld, H.C., Mlder, R.J. and Jain, R.K. (1997). Solid Stress Inhibits the Growth of Multicellular Tumour Spheroids, *Nature Biotech*, 15 (1997) 778-783.

[20]Rajagopal, K.R. and Srinivasa A.R. (1998).Mechanics of the Inelastic Behavior of Materials, *Part I: Theoretical Underpinnings*, Int. J. Plast, **14**, 945-967.

[21]Blatz, P.J. and Ko, W.L. (1962). Application of Finite Elasticity Theory to the Deformation of Rubbery Materials, Trans. Soc. Rheol, 6 (1962) 223-251

[22]Demiray, Hilmi. (1994). A Viscoelastic Model for Arterial Wall Materials. Istanbul Technical University, Istanbul, Turkey, 0020-7225(93)E0003-2.

APPENDICES

APPENDIX A: Balance Law Equations

Equation of the balance law is

$$\frac{\partial \rho}{\partial t} + div(\rho \boldsymbol{v}) = \dot{\rho} + \rho div\boldsymbol{v} = \Gamma \rho. \quad \textbf{(A.1)}$$

As from the law of conservation of mass,

$$\rho(\boldsymbol{x}, t)dV = dm, \quad \textbf{(A.2)}$$

$$M = \int_V \rho(\boldsymbol{x}, t)dv, \quad \textbf{(A.3)}$$

$$\frac{dM}{dt} = \frac{d}{dt}\int_V \rho dv. \quad \textbf{(A.4)}$$

Here if $dM/dt = 0$ the mass is conserved, if $dM/dt > 0$ then there exists growth and if $dM/dt < 0$ there exists resorption.

$$\frac{d}{dt}\int_V \rho dv = \frac{d\rho}{dt} + \rho v_{k,K} = \dot{\rho} + \rho div\boldsymbol{v}. \quad \textbf{(A.5)}$$

Sine in the tumor model there may exist growth, the rate of the growth **Γ** is assumed that is given the form below to the law of conservation of mass,

$$\dot{\rho} + \rho div\boldsymbol{v} = \Gamma \rho. \quad \textbf{(A.6)}$$

To rewrite the this equation as

$$\dot{(\rho J)} = \Gamma \rho J \quad \textbf{(A.7)}$$

The following equations are used:

$$\mathrm{J} = \det(\boldsymbol{F}) = \frac{dv}{dV}, \quad \textbf{(A.8)}$$

$$div\boldsymbol{v} = v_{k,K} = \frac{\partial v_k}{\partial V_K}, \qquad \frac{\partial v_k}{\partial V_K}\frac{dv}{dV} = \dot{\left(\frac{dv}{dV}\right)}, \quad \textbf{(A.9)}$$

Multiplying (A.6) with J

$$\dot{\rho}J + \rho div\boldsymbol{v}J = \Gamma\rho J, \quad \textbf{(A.10)}$$

$$\dot{\rho}\frac{dv}{dV} + \rho\frac{\partial v_k}{\partial V_K}\frac{dv}{dV} = \dot{\rho}\frac{dv}{dV} + \rho\left(\frac{\dot{dv}}{dV}\right) = (\dot{\rho J}), \quad \textbf{(A.11)}$$

And this leads to

$$(\dot{\rho J}) = \Gamma\rho J. \quad \textbf{(A.12)}$$

APPENDIX B: Balance of Linear Momentum Equations

The balance formula for linear momentum is

$$\frac{\partial}{\partial t}(\rho \boldsymbol{v}) + div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) - div\boldsymbol{t} = \rho \boldsymbol{b} + \Gamma \rho \boldsymbol{v}, \qquad \textbf{(B.1)}$$

where t is the Cauchy stress tensor, b is the body force and $\Gamma \rho v$ represents the contribution to the momentum due to the mass source.

From contribution of momentum, the total momentum is

$$\boldsymbol{P} = \int_V \rho \boldsymbol{v} dv. \qquad \textbf{(B.2)}$$

External forces are as

$$\int_V \rho \boldsymbol{b} dv + \int_S \boldsymbol{t}(\boldsymbol{n}) da = \boldsymbol{R} = \frac{d\boldsymbol{P}}{dt}. \qquad \textbf{(B.3)}$$

Where first term at left-hand side of the equation is mass forces and second term of the left-hand side of the equation is surface forces.

This equation is rewritten as

$$\frac{d}{dt}\int_V \rho \boldsymbol{v} dv = \int_V \rho \boldsymbol{b} dv + \int_S \boldsymbol{t}(\boldsymbol{n}) da, \qquad \textbf{(B.4)}$$

$$\frac{d}{dt}\int_V \rho \boldsymbol{v} dv - \int_V \rho \boldsymbol{b} dv - \int_S \boldsymbol{t}(\boldsymbol{n}) da \neq 0, \qquad \textbf{(B.5)}$$

Because mass change is not 0 but it is $\boldsymbol{\Gamma \rho v}$ the equation takes form,

$$\frac{\partial}{\partial t}(\rho \boldsymbol{v}) + div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) - div\boldsymbol{t} = \rho \boldsymbol{b} + \Gamma \rho \boldsymbol{v}, \qquad \textbf{(B.6)}$$

$$\frac{\partial}{\partial t}(\rho \boldsymbol{v}) + div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) - \Gamma \rho \boldsymbol{v} = \rho \boldsymbol{b} + div\boldsymbol{t}, \qquad \textbf{(B.7)}$$

$$\dot{\rho} \boldsymbol{v} + \rho \dot{\boldsymbol{v}} + div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) - \Gamma \rho \boldsymbol{v} = \rho \boldsymbol{b} + div\boldsymbol{t}. \qquad \textbf{(B.8)}$$

From mass balance equation (3.1)

$$\dot{\rho} \boldsymbol{v} + \rho \dot{\boldsymbol{v}} + div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) - (\dot{\rho} + \rho div\boldsymbol{v})\boldsymbol{v} = \rho \boldsymbol{b} + div\boldsymbol{t}, \qquad \textbf{(B.9)}$$

$$\dot{\rho} \boldsymbol{v} + \rho \dot{\boldsymbol{v}} + div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) - \dot{\rho} \boldsymbol{v} - div(\rho \boldsymbol{v} \otimes \boldsymbol{v}) = \rho \boldsymbol{b} + div\boldsymbol{t}, \qquad \textbf{(B.10)}$$

$$\rho \dot{\boldsymbol{v}} = \rho \boldsymbol{b} + div\boldsymbol{t}, \qquad \textbf{(B.11)}$$

With neglecting velocity changes and body forces

$$div\boldsymbol{t} = 0. \qquad \textbf{(B.12)}$$

APPENDIX C: Tensor Calculus for Relation between Growth Tensor and Growth Rate

To show that

$$tr\boldsymbol{D}_g = \Gamma, \quad \textbf{(C.1)}$$

first $\boldsymbol{J_G}$ is shown at the form of indices notation,

$$J_G = e_{ijk}G_{i1}G_{j2}G_{k3}, \quad \textbf{(C.2)}$$

then derived to time

$$\dot{J_G} = e_{ijk}\left[\dot{G_{i1}}G_{j2}G_{k3} + G_{i1}\dot{G_{j2}}G_{k3} + G_{i1}G_{j2}\dot{G_{k3}}\right]. \quad \textbf{(C.3)}$$

Secondly trace of $\boldsymbol{D_g}$, symmetric part of $\dot{\boldsymbol{G}}\boldsymbol{G^{-1}}$, is shown at the form of indices notation,

$$\boldsymbol{D}_g = sym\left(\dot{\boldsymbol{G}}\boldsymbol{G}^{-1}\right), \quad \textbf{(C.4)}$$

$$\boldsymbol{D}_g = \frac{1}{2}\left[\dot{\boldsymbol{G}}\boldsymbol{G}^{-1} + (\dot{\boldsymbol{G}}\boldsymbol{G}^{-1})^T\right] = \frac{1}{2}\left[\dot{\boldsymbol{G}}\boldsymbol{G}^{-1} + (\boldsymbol{G}^{-1})^T\dot{\boldsymbol{G}}^T\right], \quad \textbf{(C.5)}$$

$$\left(\boldsymbol{D}_g\right)_{ij} = \frac{1}{2}\left[\dot{G_{im}}{G_{mj}}^{-1} + ({G}^{-1})_{im}{}^T\dot{G_{mj}}^T\right], \quad \textbf{(C.6)}$$

$$\left(\boldsymbol{D}_g\right)_{ij} = \frac{1}{2}\left[\dot{G_{im}}{G_{mj}}^{-1} + ({G}^{-1})_{mi}\dot{G_{jm}}\right], \quad \textbf{(C.7)}$$

$$\left(tr\boldsymbol{D}_g\right) = \left(\boldsymbol{D}_g\right)_{ii} = \frac{1}{2}\left[\dot{G_{im}}{G_{mi}}^{-1} + ({G}^{-1})_{mi}\dot{G_{im}}\right] = \dot{G_{im}}{G_{mi}}^{-1}, \quad \textbf{(C.8)}$$

Then using (C.2),

$$J_G{G_{i1}}^{-1} = e_{ijk}G_{j2}G_{k3}, \quad \textbf{(C.9)}$$

$$J_G{G_{j2}}^{-1} = e_{ijk}G_{i1}G_{k3}, \quad \textbf{(C.10)}$$

$$J_G{G_{k3}}^{-1} = e_{ijk}G_{i1}G_{j2}, \quad \textbf{(C.11)}$$

and using

$$adj(\boldsymbol{G}) = \det(\boldsymbol{G})\,\boldsymbol{G}^{-1} = J_G\boldsymbol{G}^{-1} \quad \textbf{(C.12)}$$

(C.3) is written in this form;

$$\Gamma = \frac{\dot{J_G}}{J_G} = \dot{G_{i1}} G_{i1}^{-1} + \dot{G_{j2}} G_{j2}^{-1} + G_{k3} \dot{G_{k3}}^{-1} = \dot{G_{im}} G_{mi}^{-1} = tr\boldsymbol{D}_g \ . \quad \textbf{(C.13)}$$

Using $\boldsymbol{G} = \boldsymbol{gI}$,

$$tr\boldsymbol{D}_g = tr\boldsymbol{D}_G = \Gamma = \frac{\dot{J_G}}{J_G}. \quad \textbf{(C.14)}$$

$$J_G = e_{ijk} G_{i1} G_{j2} G_{k3} = e_{123} G_{11} G_{22} G_{33} = e_{123} \ g^3, \quad \textbf{(C.15)}$$

$$\begin{aligned} \dot{J_G} &= e_{ijk} \left[\dot{G_{i1}} G_{j2} G_{k3} + G_{i1} \dot{G_{j2}} G_{k3} + G_{i1} G_{j2} \dot{G_{k3}} \right] \\ &= e_{123} \left[\dot{G_{11}} G_{22} G_{33} + G_{11} \dot{G_{22}} G_{33} + G_{11} G_{22} \dot{G_{33}} \right] \\ &= e_{123} [\dot{g} g g + g \dot{g} g + g g \dot{g}] = 3 e_{123} \dot{g} g^2 \end{aligned} \quad \textbf{(C.16)}$$

with the obtained values the below relation between rate and scalar growth function can be easily shown,

$$\Gamma = \frac{\dot{J_G}}{J_G} = \frac{3 e_{123} \dot{g} g^2}{e_{123} \ g^3} = \frac{3\dot{g}}{g}. \quad \textbf{(C.17)}$$

APPENDIX D: Nutrient Equations

Reaction-Diffusion equation (Diffusion in 3 space dimensions):

$$\frac{\partial}{\partial t}\int_V c(x,t)dv = -\int_S Jds + \int_V fdv, \tag{D.1}$$

Where $\boldsymbol{S}$ is the surface, $\boldsymbol{V}$ is the volume, $\boldsymbol{J}$ is the flux of the material, f is the source of the material i.e. $\boldsymbol{f}(\boldsymbol{c},\boldsymbol{x},\boldsymbol{t},)$, the right hand side of the equation is rate of change of amount of material in $\boldsymbol{V}$, first integration at left hand side of the equation is rate f flow of material across $\boldsymbol{S}$ into $\boldsymbol{V}$ and the second tern at the right hand side of the equation is material created in $\boldsymbol{V}$.

Divergence Theorem:

$$\iiint_V (\nabla.\boldsymbol{F})\, dV = \oiint_S (\boldsymbol{F}.\boldsymbol{n})dS \tag{D.2}$$

Where $\boldsymbol{F}$ is continuously differentiable vector field and $\boldsymbol{n}$ is outward pointing unit normal field.

Reynolds' Transport Theorem:

$$\frac{d}{dt}\int_{P_t} \Phi dV = \int_{P_t} (\Phi + \Phi\nabla.v)dV \tag{D.3}$$

$$\frac{d}{dt}\int_{P_t} \Phi dV = \int_{P_t} \Phi' dV + \int_{\partial P_t} \Phi v.n\, dA \tag{D.4}$$

Equations:

$$Div[\boldsymbol{F}^{-1}Div(J\boldsymbol{F}^{-1}n)] = \left[X_{K,k}\left(JX_{M,k}n\right)_{,M}\right]_{,K} \tag{D.5}$$

$$= \left[X_{K,k}JX_{M,k}n_{,M}\right]_{,K} = \left[X_{K,k}JX_{M,k}n_{,l}x_{l,M}\right]_{,K} \tag{D.6}$$

$$= \left[X_{K,k}J\delta_{kl}n_{,l}\right]_{,K} = \left[X_{K,k}Jn_{,k}\right]_{,K} \tag{D.7}$$

$$= Div[J\boldsymbol{F}^{-1}\boldsymbol{\nabla}n] \tag{D.8}$$

APPENDIX E: Plotting Codes for the Graphs of 8.1

Figure 8.1.2:

```
lamda[g_, q_, R_] := g^((2-3q)/(2-q)) * R ^(-q/(2-q))
Needs["PlotLegends`"]
Plot[{lamda[g, -1, 1], lamda[g, -2, 1], lamda[g, -4, 1]}, {g,
1,       2},       Frame→True,PlotStyle→{Black,Dashed,Dotted},
PlotLegend→{"q = -1","q = -2", "q = -4"}, LegendPosition→{-
0.95,0.45},Joined→{True,True,True},PlotMarkers→Automatic,
ImageSize→Full, LegendSize→{0.2, 0.15}, LegendShadow→{0,-0}]
```

Figure 8.1.3:

```
lamda[g_, q_, R_] := g^((2-3q)/(2-q)) * R ^(-q/(2-q))
Needs["PlotLegends`"]
Plot[{lamda[g, -1, 2], lamda[g, -2, 2], lamda[g, -4, 2]},
{g,  1,  2},  Frame→True,PlotStyle→{Black,Dashed,Dotted},
PlotLegend→{"q    =    -1","q    =    -2",    "q    =    -4"},
LegendPosition→{-
0.95,0.45},Joined→{True,True,True},PlotMarkers→Automatic
,      ImageSize→Full,      LegendSize→{0.2,      0.15},
LegendShadow→{0,-0}]
```

APPENDIX F: Mathematica Codes for Solving the Problem 8.2 and Plotting its Graphs

Solving the Problem 8.2:

```
Ri = 0.4
Ro = 0.6
ri = 0.5
lam = 1.
beta = 0.01
lamd = 1
ro = Sqrt[(Ro^2 - Ri^2)/lamd + ri^2]
xo = Ro/ro
xi = Ri/ri
PPi = ((xo^2 - xi^2)/2 + lamd*Log[xo/xi])/lamd^2
g = 1.
f2t = (-PPi*beta*g^2 + Sqrt[(PPi*beta*g^2)^2 +
4*lam^2])/2
denk = D[(f2'[R] - lam^2/f2'[R]), R] + (f2'[R] -
lam^2/f2'[R] - f2[R]/R + lam^2*R/f2[R])/(R)
Solve[denk == 0, D[f2[R], {R, 2}]]
denk1 = Derivative[2][f2][R] -
(Derivative[1][f2][R]*(lam^2*R*f2[R] -
lam^2*R^2*Derivative[1][f2][R] +
f2[R]^2*Derivative[1][f2][R] -
R*f2[R]*Derivative[1][f2][R]^2))/(R^2*f2[R]*(lam^2 +
Derivative[1][f2][R]^2) + 10^(-6))
Ri = ri
s = NDSolve[{denk1 == 0, f2[0] == 0, f2'[Ri] == f2t}, f2,
{R, 0, Ri}]
Do[WriteString["C:\Users\Damla\Desktop\damla\dat\YazB001L
18g1.txt",R,"\t",f2[R]/.s,"\n"],{R,0,Ri,0.01}]
Plot[Evaluate[f2[R] /. s], {R, 0, Ri}, PlotRange -> All]
trrr = f2'[R]/g^2 - lam^2/(g^2*f2'[R])
Plot[Evaluate[trrr /. s], {R, 0, Ri}, PlotRange -> All]
Plot[Evaluate[f2'[R] rr /. s], {R, 0, Ri}, PlotRange ->
All]
trrr /. R -> Ri
```

With the program above the points of the solution of f_2 is exported to a text file and then using program named Graph, these files are turned in to the graphs given at section 8.2.

CURRICULUM VITAE

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