BIOMECHANICAL MODELING OF TUMOR CLASSIFICATION AND GROWTH

CORINA S. DRAPACA, ANTONY J. PALOCAREN

Abstract. Palpation is an important clinical diagnostic practice which is based on the fact that tumors tend to be stiffer than the surrounding normal tissue. None of the modern, non-invasive, imaging modalities (such as CT scan, Magnetic Resonance Imaging, or Ultrasound) used today by radiologists to find and diagnose tumors provides the critical information about the stiffness of the imaged tissues. The clinical observation of palpation can be explained theoretically by the following hypothesis: the Young's modulus of tissues helps differentiating not only between normal and abnormal tissues but, most importantly, between benign (not cancerous) and malignant (cancerous) tumors. In this paper we study tumor classification and growth with the help of biomechanical modeling. First, we propose a novel mechanical model of differentiating between benign and malignant tumors based on their corresponding Young's moduli obtained using information about tissue microstructure provided by image mass spectroscopy. The second model shows how the mechanical properties of tumors affect their growth. By replacing the first order temporal derivative in this mechano-growth model with a fractional order derivative we are able to predict when a benign tumor turns into cancer.

Key words: biomechanics, tumor classification, mechano-growth model, magnetic resonance elastography.

1. INTRODUCTION

Diagnostic radiology is a rapidly growing multi-disciplinary field that links medicine to science and engineering. It enables noninvasive imaging and investigation of structure and function of the human body, and a unique insight into disease processes *in vivo*. One such imaging technique, called Magnetic Resonance Elastography (MRE), is used to measure the elasticity of biological tissues subject to mechanical stress. The resulting strains are measured using magnetic resonance imaging and the related elastic modulus is computed from models of tissues mechanics. The elastic modulus contains important information about the pathology of the imaged tissues and therefore, MRE can help in tumor detection, determination of characteristics of disease, and in assessment of rehabilitation [1].

* Department of Engineering Science and Mechanics, Pennsylvania State University, USA, E-mail: csd12@psu.edu

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It was noticed experimentally that most biological tissues have incompressible, viscoelastic features: they have a certain amount of rigidity similar to solid bodies, but, at the same time, they flow and dissipate energy as viscous fluids do. The incompressibility assumption for soft tissues is based on the fact that most tissues are made primarily of water. In addition, since the displacements in MRE are usually very small (on the order of microns), a linear constitutive law is usually assumed [2]. However, despite the richness of the data set, the variety of processing techniques and the simplifications made in the biomechanical model, it remains a challenge to extract accurate results at high resolution in complex, heterogeneous tissues from the intrinsically noisy data. Therefore, any improvement in the MRE data processing with the help of biomechanics and computational methods will be of significant importance to modern medicine.

The aim of this paper is to formulate novel mathematical models that will be able to differentiate between benign (not cancerous) and malignant (cancerous) tumors and predict their mechano-growth. As it can be seen in Fig.1, benign tumors are localized, self-contained (encapsulated), and tend to be more isotropic. On the other hand, malignant tumors are neither localized nor self-contained, and are anisotropic. In order for the MRE method to correctly classify the tumors of a given tissue in benign and malignant, biomechanical models of these two classes of tumors need to incorporate the differences between them. In the present paper we propose mathematical models that incorporate information about the mechanical and biochemical and growth processes that take place in tumors. More precisely, our first model assumes that the Young moduli of biological tissues (and tumors) depend on the mass spectra of proteins present in tissues. We will use image mass spectra of low (benign) and high (malignant) grade gliomas to show that our biomechanical model is capable to differentiate between these two types of tumors. Among all the existing mass spectrometry approaches, the image mass spectrometry provides the most useful information for clinicians since it gives a detailed spatial distribution of the concentrations of proteins and ions present in tissues [3] (Fig. 2). Our model shows that the Young's modulus of a high grade glioma is at least 10kPa higher than the Young's modulus of a low grade glioma.

In our second model, we investigate the effect of mechanics on the growth of tumors. We will show that by using a fractional order temporal derivative instead of a first order one in the proposed mechano-growth model, we can predict when a low grade glioma becomes a high grade (cancerous) tumor. While the idea of using fractional order temporal derivatives to describe abnormal processes believed to be involved in the birth of tumors is not new (see, for example, [10]), the study we propose in this paper of the effect of the fractional derivative on the coupling between the growth and biomechanics of tumors is, to the best of our knowledge, novel. The prediction of tumor growth is essential in treatment decision and planning.

Fig. 1 – a) Benign tumor: the fibrous connective tissue capsule (orange) separates the inside benign cells (black boundaries) from the outside normal cells (yellow); b) malignant tumor: the irregularly-shaped cancer cells (red boundaries) are diffusive and non-localized.

The paper is organized as follows. In the next section we will present our first biomechanical model based on information from image mass spectroscopy followed by a section on our mechano-growth model for tumors. In section 4 we present our preliminary results, and we end the paper with a section of conclusions.

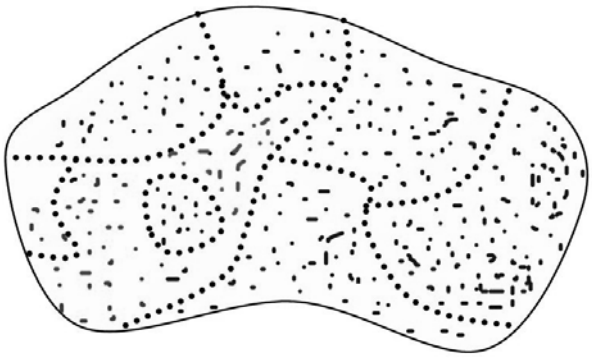

Fig. 2 – A hand-made picture of the usual outcome from the image mass spectroscopy method applied on a tissue showing regions of concentrations of different proteins (marked with different colors).

2. BIOMECHANICAL MODEL BASED ON THE MASS SPECTRA OF TUMORS

In order to find Young's moduli of tissues that can be used to improve the classification of tumors with the MRE method, we propose a novel biomechanical model based on image mass spectroscopy (IMS). Our aim is to relate the Young's modulus of tumors to the concentrations of certain proteins which have been shown

recently to have different concentrations depending on the tumor's grade [3]. In order to use the information provided by the images of mass spectra to calculate the Young's moduli of tumors, we make the following assumptions:

1. the relative intensities of proteins given by IMS are proportional to the corresponding concentrations [4];
2. the (apparent) Young's modulus of a tissue sample is proportional to the concentrations of proteins present in that tissue [5].

Thus, we propose the following expression for the apparent Young's modulus E dependent on the concentrations c_n, $n = 1, 2...N$ of proteins given by IMS:

$$E = \sum_{n=1}^{N} c_n^{\alpha_n (m/z)} . \tag{1}$$

The powers of the concentrations are assumed to depend on the corresponding mass to charge ratios (*m/z*) known from IMS data.

3. MECHANO-GROWTH MODEL

In this section we propose a new model for the one-dimensional growth of tumors under applied uni-axial stretch λ. The tumor's growth is not caused by the applied stretch, it happens independently of the mechanics.

In order to make some progress in this challenging research area, we assume for simplicity that the growth is volumetric and isotropic (the growth depends only on the time variable). As in [8], a volumetric growth describes only geometric changes, the material points are dense during growth, and the intrinsic mechanical properties of the material do not change during growth. In addition, we assume for now that the tissue is an isotropic, homogeneous, linear elastic solid material.

We denote by $\mathbf{F}_d, \mathbf{G}$, and $\mathbf{F} = \mathbf{F}_d \mathbf{G}^{-1}$ the deformation gradient of the applied uni-axial stretch, the growth tensor, and, respectively, the total deformation gradient (see Fig. 3 for more information). Then the Cauchy stress tensor is given by Hooke's law:

$$\sigma = E\left(\frac{\lambda}{g(t)} - 1 \right), \tag{2}$$

where E is the Young's modulus and $g(t)$ is the isotropic growth function.

If we replace the above expression of the stress in the equation of growth proposed in [7], we obtain the following first order, nonlinear differential equation:

$$\frac{\mathrm{d}g(t)}{\mathrm{d}t} = \exp\left(\frac{\gamma E\left(\frac{\lambda}{g(t)} - 1\right)}{k_B T}\right) g(t), \tag{3}$$

where T, k_B, γ are the absolute temperature, Boltzman constant, and, respectively, a parameter depending on the bio-chemical reactions involved in the growth process. Initially, there is no growth: $g(0) = 1$.

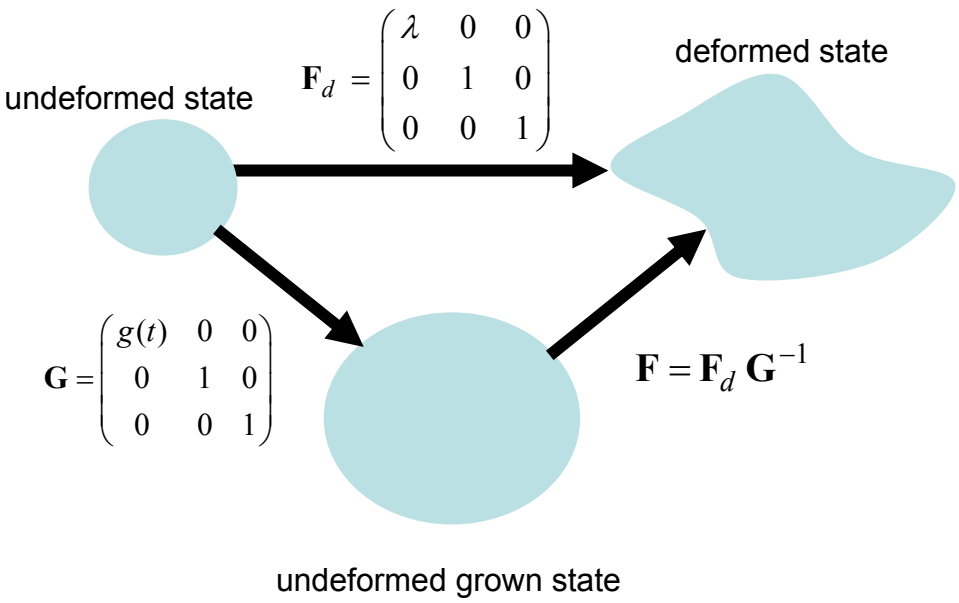

Fig. 3 – Kinematics of the coupled growth-deformation of tumors.

The linearized form of equation (3) is:

$$\frac{\mathrm{d}(\ln(g(t)))}{\mathrm{d}t} = \exp\left(\frac{\gamma E(\lambda - 1)}{k_B T}\right)\left(1 - \frac{\gamma E \lambda}{k_B T}\ln(g(t))\right), \tag{4}$$

with the solution given by:

$$g(t) = \exp\left(\frac{\exp\left(\frac{\gamma}{k_B T}E(\lambda - 1)\right)}{\frac{\gamma}{k_B T}E\lambda}\left(1 - \exp\left(-\exp\left(\frac{\gamma}{k_B T}E(\lambda - 1)\right)\frac{\gamma}{k_B T}E\lambda t\right)\right)\right). \tag{5}$$

We replace now the first order temporal derivative in equation (4) by the left-sided Riemann-Liouville fractional order derivative and we obtain the following growth equation:

$$D^{\alpha}(\ln(g(t)) = \exp\left(\frac{\gamma E(\lambda-1)}{k_B T}\right)\left(1-\frac{\gamma E\lambda}{k_B T}\ln(g(t))\right). \tag{6}$$

By definition, the left-sided Riemann-Liouville fractional order derivative of order $\alpha\in(0, 1]$ of a function $f \in L^1([0, \infty))$ is:

$$D^{\alpha} f(t) = \begin{cases} \dfrac{1}{\Gamma(1-\alpha)}\dfrac{\mathrm{d}}{\mathrm{d}t}\displaystyle\int_0^t \frac{f(s)\mathrm{d}s}{(t-s)^{\alpha}}, & \text{if } \alpha\in(0, 1) \\ \dfrac{\mathrm{d}}{\mathrm{d}t} f(t), & \text{if } \alpha = 1, \end{cases}$$

where $\Gamma(s) = \displaystyle\int_0^{\infty} \mathrm{e}^{-t} t^{s-1}\mathrm{d}t$ is the gamma function. Note that equation (5) is a particular case of equation (6) for $\alpha = 1$. We apply the Laplace transform method to solve equation (6). If we denote by $L(f(t))$ the Laplace transform of f and use the fact that $L\left(D^{\alpha} f(t)\right) = s^{\alpha} L(f(t))$ we obtain (after a few simple algebraic manipulations):

$$\begin{aligned} g(t) &= \exp\left(L^{-1}\left(\frac{\exp\left(\dfrac{\gamma E(\lambda-1)}{k_B T}\right)}{s\left(s^{\alpha} + \exp\left(\dfrac{\gamma E(\lambda-1)}{k_B T}\right)\dfrac{\gamma E\lambda}{k_B T}\right)}\right)\right) = \\ &= \exp\left(\sum_{k=0}^{\infty} \frac{(-1)^k}{\left(\exp\left(\dfrac{\gamma E(\lambda-1)}{k_B T}\right)\right)^k \left(\dfrac{\gamma E\lambda}{k_B T}\right)^{k+1}} \frac{t^{-\alpha k}}{\Gamma(1-\alpha k)}\right), \end{aligned} \tag{7}$$

since $L^{-1}\left(\dfrac{1}{s^{1-\alpha k}}\right) = \dfrac{t^{-\alpha k}}{\Gamma(1-\alpha k)}$.

4. RESULTS

For our first model we use the IMS data from [4] for low and high grade gliomas. The powers α_n are such that the apparent Young's modulus in the healthy brain tissue is approximately equal to the white matter value found by the MRE technique of 14.2 kPa [6]. We investigate the following two cases:

I) $\alpha_n = 1.8 = \text{constant}$;

II) $\alpha_n = 1.6 + 1/(\ln(m/z)_n)$.

From Figs. 4 and 5 we conclude that *high grade gliomas are at least 10kPa stiffer than low grade gliomas.* To the best of our knowledge, this is the first time when such a biomechanical model linking the stiffness of a tissue and the concentrations of proteins present in the tissue and, more importantly, when such a clear differentiation between low and high grade gliomas has been established.

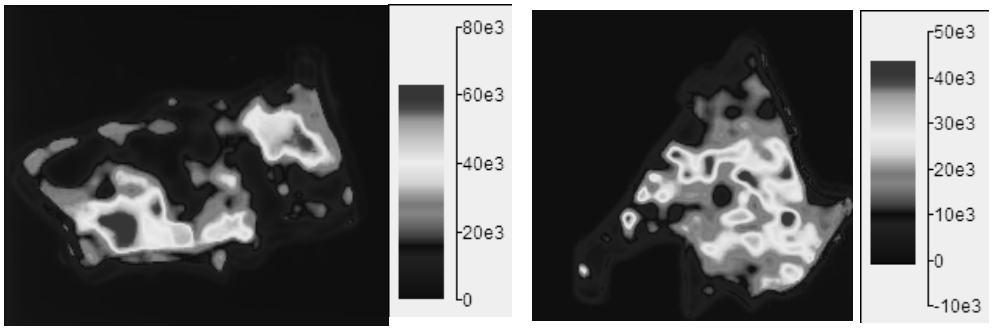

Fig. 4 – Elastograms of high grade (left) and low grade (right) gliomas for case I.

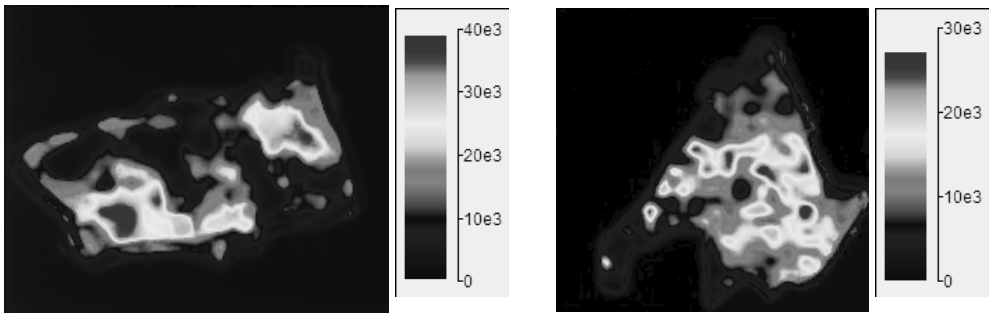

Fig. 5 – Elastograms of high grade (left) and low grade (right) gliomas for case II.

In our mechano-growth model we use the following parameters [7]:

$$\gamma = 1.3\times 10^{-26}\,\mathrm{m}^3, \quad k_B = 1.3\times 10^{-23}\,\mathrm{m}^2\times \mathrm{kg}/(\mathrm{s}^2\times \mathrm{K}), \quad T = 298\mathrm{K}\,.$$

In Figs. 6 and 7 we plot the growth function $g(t)$ as given by formulas (6) and respectively (7) for a low grade glioma of averaged stiffness $E_{low} = 35\mathrm{kPa}$ and for a high grade glioma of averaged Young's modulus $E_{high} = 50\mathrm{kPa}$ at different values of uni-axial stretch λ and different values of the fractional order α. The averaged stiffness values were estimated from Figs. 4 and 5.

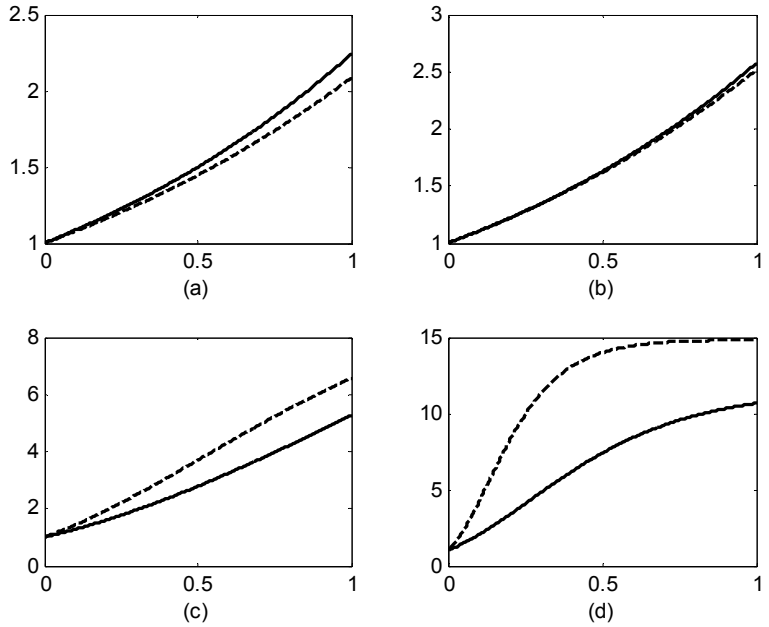

Fig. 6 – Growth functions given by formula (5) of low grade (solid line) and high grade (dashed line) glioma versus a normalized time scale for: a) $\lambda = 0.1$; b) $\lambda = 1$; c) $\lambda = 5$; d) $\lambda = 10$.

From Fig. 6 we notice that as long as the applied uni-axial stretch λ is less than 1, the two types of gliomas present a similar growth behavior. As the stretch increases, the high grade glioma starts to grow faster than the low grade glioma, with both tumors reaching a steady state in their growth for large stretch values (Fig. 6d). However, it is expected that our assumption of a linear elastic tumor will limit the applicability of formula (5) for large but finite stretches, so the behavior seen in Fig. 6d, for example, may be in fact unphysical.

On the other hand, if we use formula (7) to represent the growth process, we noticed that for small values of the applied stretch λ and every value of α between 0 and 1, the growth remains constant for both types of gliomas. However,

as the stretch becomes large but finite, the growth functions of low grade and high grade gliomas not only that increase with time but also show that at a certain moment, *a low grade glioma can grow faster than a high grade glioma, signaling its transformation into cancer* (Fig. 7).

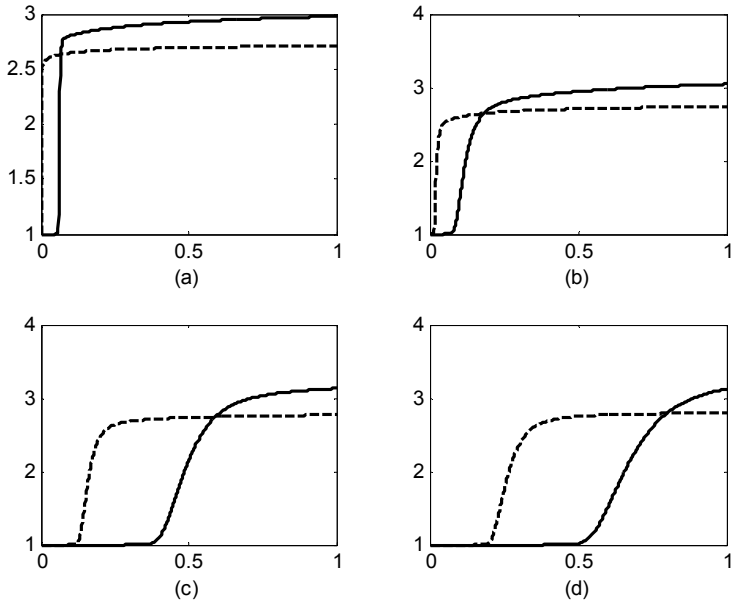

Fig. 7 – Growth functions given by formula (7) of low grade (solid line) and high grade (dashed line) glioma *versus* a normalized time scale for $\lambda = 10$ and: a) $\alpha = 0.25$; b) $\alpha = 0.5$; c) $\alpha = 0.75$; d) $\alpha = 0.9$.

As it can be seen from Fig. 7, as α increases, not only that the very sharp growth of both low and high grade gliomas starts later, but also the time when the low grade becomes a high grade tumor is delayed. Also, since the growth behavior in Fig. 7 is noticed for a relatively large stretch $\lambda = 10$ where the linear elasticity assumption might not be valid anymore, we believe that the fractional order temporal derivative could model some of the microscopic inhomogeneities and nonlinearities which are not captured by the macroscopic Hooke's law. In materials with evolving microstructure the fractional order α might connect not only multiple time scales but also time *and* length scales (see for example [11]).

5. CONCLUSIONS

In this paper we proposed two novel biomechanical models: one that estimates the Young's moduli of low (usually benign) and high (malignant) grade tumors based on the concentrations of proteins as given by image mass

spectroscopy, and another model that predicts the mechano-growth behavior of tumors. Our biomechanical model based on mass spectra of tumors shows that we can differentiate for example between low and high grade gliomas based on their (apparent) stiffness, a high grade being at least 10kPa harder than a low grade glioma. Our mechano-growth model incorporates an inhomogeneous clock that connects the macroscopic global and the microscopic local time (and possibly length) scales through the presence of a fractional order temporal derivative. In this form, the model is able to predict the time when a low grade tumor transforms into cancer at large but finite stretches. We believe that our models can play an important role in the development of better, non-invasive diagnostic and treatment procedures based on image elastography such as MRE.

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REFERENCES

1. MUTHUPILLAI, R., LOMAS, D.J., ROSSMAN, P.J., GREENLEAF, J.F., MANDUCA, A., EHMAN, R.L., *Magnetic resonance elastography by direct visualization of propagating acoustic strain waves*, Science, **269**, pp. 1854-1857, 1995.
2. MANDUCA, A., OLIPHANT, T.E., DRESNER, M.A., MAHOWALD, J.L., KRUSE, S.A., AMROMIN, E., FELMLEE, J.P., GREENLEAF, J.F., EHMAN, R.L., *Magnetic resonance elastography: non-invasive mapping of tissue elasticity*, Med. Imag. Anal., **5**, *4*, pp. 237-254, 2001.
3. CHAURAND, P., SCHWARTZ, S., REYZER, M., CAPRIOLI, R., *Imaging mass spectroscopy: principles and potentials*, Toxicologic Pathology, **33**, *1*, pp. 92-101, 2005.
4. HIRABAYASHI, A., SAKAIRI, M., KOIZUMI, H., *Sonic spray ionization method for atmospheric pressure ionization mass spectroscopy*, Anal. Chem., **66**, *24*, pp. 4557-4559, 1994.
5. NORMAND, V., LOOTENS, D.L., AMICI E., PLUCKNETT, K.P., AYMARD, P., *New insight into agarose gel mechanical properties*, Biomacromolecules, **1**, *4*, pp. 730-738, 2000.
6. KRUSE, S.A., ROSE, G.H., GLASER, K.J., MANDUCA, A., FELMLEE, J.P., CLIFFORD, R.J.Jr., EHMAN, R.L., *Magnetic resonance elastography of the brain*, NeuroImage, **39**, *1*, pp. 231-237, 2008.
7. KIM, J.S., SUN, S.X., *Continuum modeling of forces in growing viscoelastic cytoskeletal networks*, Journal of Theoretical Biology, **256**, *4*, pp. 596-606, 2009.
8. CHEN, Y.C., HOGER, A., *Constitutive functions of elastic materials in finite growth and deformation*, Journal of Elasticity, **59**, pp. 175-193, 2000.
9. DJORDJEVIC, V.D., JARIC, J., FABRY, B., FREDBERG J.J., STAMENOVIC, D., *Fractional derivatives embody essential features of cell rheological behavior*, Annals of Biomedical Engineering, **31**, *6*, pp. 692-699, 2003.
10. JUMARIE, G., *New stochastic fractional models for Malthusian growth, the Poissonian birth process and optimal management of populations*, Mathematical and Computer Modelling, **44**, *3-4*, pp. 231-254, 2006.
11. DRAPACA, C.S., SIVALOGANATHAN, S., *The fractional model of continuum mechanics*, Journal of Elasticity, under review.