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BIOMECHANICAL MODELING OF TUMOR GROWTH: ITS RELEVANCE TO GLIOMA RESEARCH

ANTHONY J. PALOCAREN AND CORINA S. DRAPACA

Abstract. In 2009 the US National Center for Health Statistics showed that cancer is close to becoming the deadliest disease of modern times. Recent years have seen unprecedented advancements in medicine that have contributed to a substantial decrease in the death rates of some serious diseases such as heart disease, stroke, influenza and pneumonia. However, with cancer, equivalent scientific and technological advances have yet to be achieved. Theoretical models capable of explaining the fundamental mechanisms of tumor growth and making reliable predictions are urgently needed. These models can contribute considerably to the design of optimal, personalized therapies that will not only maximize treatment outcomes but also reduce health care costs. Recently [25] we have proposed a non-invasive way of classifying gliomas, primary brain tumors, based on their stiffness. The model uses image mass spectra of proteins present in gliomas and 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 this paper we will use this model to investigate the effect of mechanics on the growth of gliomas. The proposed mechano-growth model is a non-linear evolution differential equation which is solved analytically using the Adomian method. The time evolution is represented in two ways: (1) using a classical first-order derivative, and (2) using a fractional order derivative. Our results show that the fractional order model captures a very interesting temporal multi-scale effect of tumor transition from low grade (benign) to high grade (malignant) glioma when a certain threshold of mechanical strain is reached in the tissue. For comparison, we also reproduce the results we presented in [25] when linearization is used to solve the evolution equations analytically.

Key words. Tumor Mechano-Growth, Adomian Method, Glioma Stiffness.

1. Introduction

In the spring of 2009, the New York Times published data from the National Center for Health Statistics showing that cancer is close to becoming the deadliest disease of modern times [3]. Recent advancements seen in medicine have contributed to a substantial decrease in the death rates of some serious diseases such as heart disease, stroke, influenza and pneumonia. However, in the case of cancer, equivalent scientific and technological advances have yet to be achieved. The annual cancer death rate currently stands at about 200 deaths a year per 100,000 people of all ages and about 1,000 deaths per 100,000 people over the age of 65 [4]. Although a steady increase in diagnoses and survival has been seen over the past sixty years, the treatment of deadly cancers has not improved and thus the cancer death rate has hardly changed. In particular, gliomas are primary brain tumors that, at high grades, are among the deadliest cancers. For instance, a European study published in 2005 showed that around 65% of adults with low grade astrocytoma (a type of glioma) lived for at least 5 years without any tumor growth during that time. However, low grade gliomas in adults may come back or change into high grade gliomas after some time. On the other hand, although more than 30% of brain tumors in children are gliomas, these are usually low grade (benign) and once removed do not recur. More than 87% of children, diagnosed with gliomas, survive

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for more than 5 years post surgery and over 83% will live for more than 10 years [4].

In order to advance our understanding of the fundamental mechanisms underlying tumor growth, we need to develop appropriate mathematical models able to predict evolutionary patterns in diseased tissues as well as recovery after treatment. Such models can contribute considerably to the design of optimal, personalized therapies that will not only maximize treatment outcomes but also reduce health care costs. The last few decades have seen extensive progress in mathematical modeling of solid tumor growth that has provided insight into the understanding of some experimental and clinical data. Most models are either discrete cell-based or continuum models (see some recent reviews in [5, 6, 7, 8, 9]). For example, some models of brain cancer are given in [10, 11, 12]. Modeling has also shown that tumor morphology can be used as a predictor of invasiveness [5, 13, 14, 15, 16]. In [17, 18, 19], the authors proposed cell-cell adhesion and external nutrient concentration as parameters controlling the stability of three-dimensional multi-cellular spheroids. While Greenspan [24] considered necrotic tumors in the avascular stage, where growth is regulated only by nutrient diffusion through the surrounding micro-environment, Byrne and Chaplain [17] modeled non-necrotic tumors where nutrient is supplied through the surrounding vascularized environment. During avascular growth, tumor cells receive oxygen, nutrients and growth factors via diffusion through the host tissue. This phase can be investigated by *in vitro* experiments where cancer cells are cultured in a three dimensional geometry [20, 21, 22, 5]. These experiments show that cancer cells self organize into multi-cellular spheroidal colonies due to cell-cell adhesion in which the outer layer of cells tends to expand and grow while the interior cells die due to lack of nutrients. All the continuum models of tumors are based on reaction-diffusion equations describing the evolution of tumor cell density, extracellular matrix, matrix degrading enzymes, and concentrations of cell substrates such as glucose, oxygen, and growth factors and inhibitors. Different constitutive laws have been employed to describe the deformation and stress fields of tissues. For example, the Darcy model, which models fluid flow through a porous medium, was used in [24, 13, 17, 26], while the Stokes' law of fluids was studied in [27]. Both models were investigated in [28, 29, 30]. Other continuum models have used constitutive laws for (visco-) elastic solids to predict the growth of tumors [23]. More details on such models are given in [7].

The main challenge in using these mathematical models for predicting tumor growth in patients is finding the appropriate model parameters. The clinical evaluation of patients required to determine these parameters must be safe and minimally invasive. An example of a non-invasive technology, that may greatly assist in this endeavor, is imaging elastography. Imaging elastography combines information about mechanical wave propagation through tissues together with advances in medical imaging to diagnose tumors based on their stiffness. This *palpation through imaging* process is based on the well-known fact that tumors tend to be stiffer than the surrounding healthy tissue. In order to improve the outcomes of this novel technology, we recently [25] proposed a non-invasive way of classifying gliomas based on their stiffness. The model uses image mass spectra of proteins present in gliomas and assumes that: 1) the relative intensities of proteins given by the image mass spectroscopy are proportional to the corresponding concentrations, and 2) the Young's modulus of a tissue is proportional to the concentrations of proteins present in that tissue. The results in [25] show that we can differentiate, for example, between low and high grade gliomas based on their stiffness, a high grade

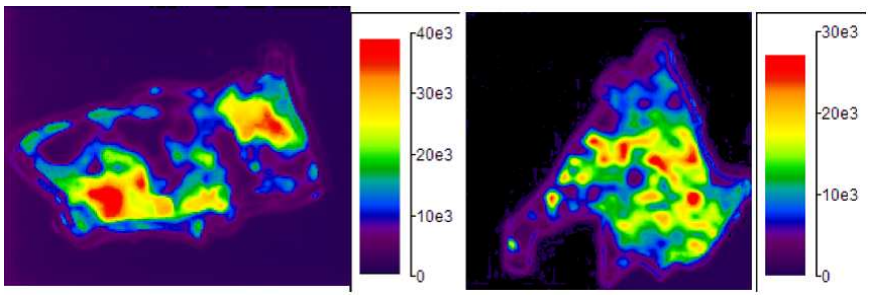


FIGURE 1. Elastograms of high grade (left) and low grade (right) gliomas.

glioma being at least 10kPa stiffer than a low grade glioma. In Fig.1 we present elastograms, maps of stiffness values in a tissue, of low and high grade gliomas obtained using this model.

In this paper we use our model presented in [25] to investigate the effect of mechanics on the growth of gliomas. The mechano-growth model we propose here is a non-linear evolution differential equation inspired by the growth model of cytoskeletal networks given in [34]. We solve this equation analytically using the Adomian decomposition method, a robust and fast convergent method of building approximate series solutions to differential equations (see for instance [1]). The time evolution is represented in two ways: (1) using a classical first-order derivative as in [34], and (2) using a fractional order derivative. While the idea of using fractional order temporal derivatives to describe abnormal processes believed to underlie the development of tumors has been already proposed by Jumarie in [31], the study 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. Our results show that, unlike the classic first order derivative, the fractional order model captures a very interesting temporal multi-scale effect of tumor transition from low grade (benign) to high grade (malignant) glioma when a certain threshold of mechanical strain is reached in the tissue. Such predictability of tumor growth could prove essential for better treatment decision and planning. In addition we will also reproduce here our results obtained in [25] where we used linearization to solve the evolution equations. The linearized solution of the first order evolution equation looks similar to the corresponding Adomian series solution, however the shapes of the linearized and Adomian series solutions for the fractional order evolution equation are different although the transition behavior from low to high grade is captured by both solutions.

The paper is organized as follows. In section 2 we give a brief presentation of the Adomian method and in section 3 we present our mechano-growth model. The results are shown in section 4. The paper ends with a section of conclusions.

2. The Adomian Decomposition Method

Almost thirty years ago, Adomian proposed a new decomposition method to obtain analytical solutions to a wide class of linear and non-linear deterministic

as well as stochastic ordinary and partial differential equations [1]. The Adomian Decomposition Method (ADM) is a robust, accurate and fast convergent method that builds approximate series solutions without linearization, assumptions of weak nonlinearity, or perturbation theory. For example, [32] shows that ADM is as fast and as accurate as the finite element method (FEM) but without the complexity of computer implementation required by FEM.

For the purposes of this paper, we will present the main steps of ADM used in solving an equation of the form $Fu(t) = g(t)$, where F represents a general nonlinear ordinary differential operator involving both linear and nonlinear terms. The linear term is decomposed into $L + R$, where L is an easily invertible operator and R is the remainder of the linear operator. For simplicity, L is usually taken to be the highest order derivative in order to avoid difficult integrations. Then the equation can be written as [1]:

$$Lu + Ru + Nu = g \tag{1}$$

where N stands for the non-linear operator of F. Since the linear operator L is invertible, the intergal operator L^{-1} exists that applied to equation (1) could give for example:

$$u = A + Bt + L^{-1}g - L^{-1}Ru - L^{-1}Nu \tag{2}$$

if L is a second-order linear operator, where A, B are constants of integration. We look for a series solution of the form:

$$u = \sum_{n=0}^{\infty} u_n \tag{3}$$

Formula (3) allows for the non-linear term Nu to be decomposed into an infinite polynomial series

$$Nu = \sum_{n=0}^{\infty} A_n \tag{4}$$

where:

$$\begin{aligned} A_0 &= Nu_0 \\ A_1 &= u_1 \frac{d}{du_0} Nu_0 \\ A_2 &= u_2 \frac{d}{du_0} Nu_0 + \frac{u_1^2}{2!} \frac{d^2}{du_0^2} Nu_0 \\ A_3 &= u_3 \frac{d}{du_0} Nu_0 + u_1 u_2 \frac{d^2}{du_0^2} Nu_0 + \frac{u_1^3}{3!} \frac{d^3}{du_0^3} Nu_0 \\ &\cdots \end{aligned} \tag{5}$$

Each Adomian polynomial A_n depends only on u_0, u_1, ..., u_n, for $n = 0, 1, 2....$ Other definitions of the Adomian polynomials can be found in [2].

Substituting (3) and (4) into equation (2) yields:

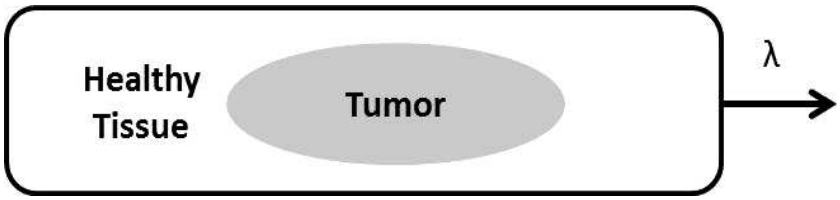


FIGURE 2. Schematic representation of the uni-axial stretch applied on a tissue with a growing tumor.

$$
\begin{aligned}
u_0 &= A + Bt + L^{-1}g \\
u_1 &= -L^{-1}Ru_0 - L^{-1}A_0 \\
u_2 &= -L^{-1}Ru_1 - L^{-1}A_1 \\
&\cdots \\
u_{n+1} &= -L^{-1}Ru_n - L^{-1}A_n
\end{aligned} \tag{6}
$$

The convergence of the series solution (3) with its terms given by (6) to the exact

solution is usually fast, in most cases about 6 terms of the series are sufficient for an accurate result [1]. As shown for example in [33], ADM is applied in the same way for integer order as well as for fractional order differential equations.

3. Mechano-Growth Model of Tumors

3.1. Non-linear Evolution. For simplicity we start by modeling the one-dimensional growth of tumors under an applied uni-axial stretch λ (Fig.2). We assume that the tumor growth is not caused by the applied stretch, and is independent of the mechanical process.

In order to make some progress in this challenging research area, we also assume that the growth is volumetric and isotropic (the growth depends only on the time variable). As in [35], 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

$$
\mathbf{F}_d = \begin{pmatrix} \lambda & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}
$$

the deformation gradient of the applied uni-axial stretch λ,

$$
\mathbf{G} = \begin{pmatrix} g(t) & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}
$$

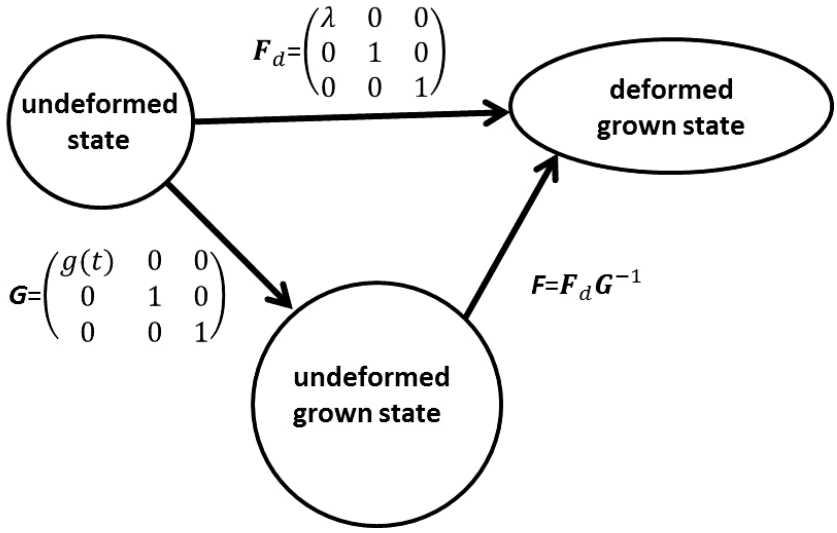


FIGURE 3. Kinematics of the coupled growth-deformation of tumors.

the growth tensor with $g(t)$ the isotropic growth function, and

$$\mathbf{F} = \mathbf{F}_d \mathbf{G}^{-1} \tag{7}$$

the total deformation gradient (see Fig.3 for more information).

Then the Cauchy stress tensor is given by Hooke's law:

$$\sigma = E\left(\frac{\lambda}{g(t)} - 1\right), \tag{8}$$

where E is the Young's modulus.

If we substitute the expression for the stress (8) into the equation of growth proposed in [34], we obtain the following first order, nonlinear differential equation:

$$\frac{dg(t)}{dt} = K\exp\left(\frac{\gamma E\left(\frac{\lambda}{g(t)} - 1\right)}{k_B T}\right) g(t) \tag{9}$$

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. The constant parameter K has units of s^{-1} and is found experimentally [34]. Since we do not have experimental data, we take for now $K = 1\mathrm{s}^{-1}$ and omit this parameter from our further calculations. In the initial undeformed state there is no growth: $g(0) = 1$.

Equation (9) has been proposed in a more general form in [34] to model the growth of viscoelastic cytoskeletal networks. Since the biochemical mechanisms that control tumor growth are to a large extent unknown, we assume that once the process of tumor growth has been initiated, the tumor will grow in a fashion

similar to the growth of cytoskeletal networks. We note that this model is simpler than the models of tumor growth presented thus far in the literature. The atomistic models of tumor growth consider only diffusion and reaction of chemical species, without accounting for the mechanical behavior of the tumor due to cellular mechano-transduction processes while the continuum models of solid tumors are computationally very demanding since they involve solving systems of coupled hyperbolic and parabolic partial differential equations that account for both, mechanics and diffusion-reaction processes. By contrast, equation (9) has been constructed such that it has the following advantages: (1) it incorporates small incremental growth and deformation, which converts an intrinsically nonlinear mechanical problem into a linear one with cumulative elastic quantities; (2) the deformation decomposition is developed for viscoelastic media which is applicable to the cytoskeletal network, and (3) the development allows for coupling of any physically relevant phenomena such as the local stress in the material or local G-actin concentration with the growth tensor [34]. In addition, from a computational point of view, this model requires the solution of only one non-linear differential equation.

We used the Adomian decomposition method for $L = d/dt$ and Mathematica software to solve equation (9). The Adomian series solution (3) converges in only 4 terms:

$$\begin{aligned} g(t) &= 1+\exp\left(\frac{\gamma(\lambda-1)E}{k_BT}\right)t+\frac{\exp\left(\frac{2\gamma(\lambda-1)E}{k_BT}\right)(k_BT-\gamma\lambda E)}{2k_BT}t^2 \\ &+ \frac{\exp\left(\frac{3\gamma(\lambda-1)E}{k_BT}\right)(k_B^2T^2-2\gamma k_B\lambda TE+2\gamma^2\lambda^2E^2)}{6k_B^2T^2}t^3 \\ &+ \frac{\exp\left(\frac{4\gamma(\lambda-1)E}{k_BT}\right)(k_B^3T^3-3\gamma k_B^2\lambda T^2E+4\gamma^2\lambda^2E^2k_BT-6\gamma^3\lambda^3E^3)}{24k_B^3T^3}t^4 \end{aligned} \tag{10}$$

We replace now the first order temporal derivative in equation (9) by the left-sided Riemann-Liouville fractional order derivative and obtain the following generalized growth equation:

$$D^\alpha g(t)=\exp\left(\frac{\gamma E\left(\frac{\lambda}{g(t)}-1\right)}{k_BT}\right)g(t),\ 0<\alpha<1. \tag{11}$$

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

$$D^\alpha f(t)=\begin{cases} \dfrac{1}{\Gamma(1-\alpha)}\dfrac{d}{dt}\displaystyle\int_0^t\frac{f(s)ds}{(t-s)^\alpha} & \text{for} \quad \alpha\in(0,1) \\ \dfrac{d}{dt}f(t) & \text{for} \quad \alpha=1 \\ \dfrac{1}{\Gamma(-\alpha)}\displaystyle\int_0^t\frac{f(s)ds}{(t-s)^{1+\alpha}} & \text{for} \quad \alpha<0 \end{cases} \tag{12}$$

where $\Gamma(s) = \int_0^\infty \mathrm{e}^{-t} t^{s-1} dt$ is the gamma function.

As before, we use the Adomian decomposition method for $L = D^\alpha$ and Mathematica software to find the Adomian series solution of (11). Given the length and complexity of this solution we will not reproduce it here.

3.2. Linearized Evolution. In this subsection we reproduce briefly the results we obtained in [25] by linearization of the non-linear evolution equations (9) and (11).

The linearized form of equation (9) is:

$$\frac{d(\ln(g(t)))}{dt} = \exp\left(\frac{\gamma E(\lambda-1)}{k_B T}\right)\left(1 - \frac{\gamma E\lambda}{k_B T}\ln(g(t))\right) \tag{13}$$

Equation (13) can be easily integrated to yield:

$$g(t) = \exp\left(\frac{\exp\left(\frac{\gamma E(\lambda-1)}{k_B T}\right)}{\frac{\gamma E\lambda}{k_B T}}\left(1 - \exp\left(-\exp\left(\frac{\gamma E(\lambda-1)}{k_B T}\right)\frac{\gamma E\lambda}{k_B T}t\right)\right)\right) \tag{14}$$

The linearized form of equation (11) is:

$$D^\alpha\left(\ln(g(t))\right) = \exp\left(\frac{\gamma E(\lambda-1)}{k_B T}\right)\left(1 - \frac{\gamma E\lambda}{k_B T}\ln(g(t))\right) \tag{15}$$

By applying the Laplace transfom $\mathcal{L}$ to equation (15) and using the fact that $\mathcal{L}\left(D^\alpha f(t)\right) = s^\alpha \mathcal{L}(f(t))$, we get [25]:

$$g(t) = \exp\left(\sum_{k=0}^{\infty} \frac{(-1)^k}{\left(\exp\left(\frac{\gamma E(\lambda-1)}{k_B T}\right)\right)^k \left(\frac{\gamma E\lambda}{k_B T}\right)^{k+1}} \frac{t^{-\alpha k}}{\Gamma(1-\alpha k)}\right) \tag{16}$$

4. Results

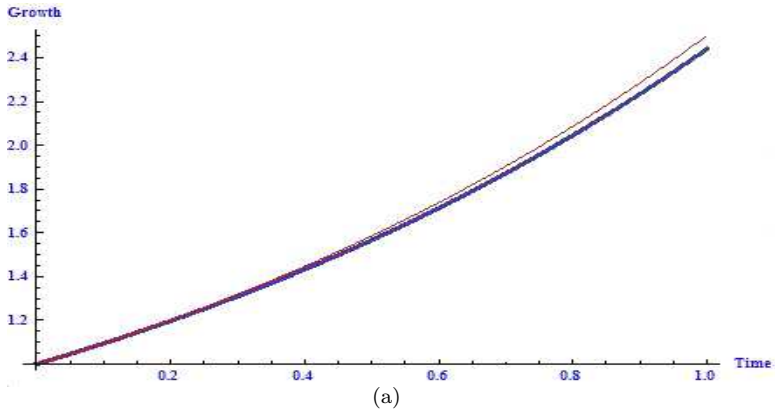
We use the Adomian series solutions to equations (9) and (11) for different values of the stretch λ and of the fractional order α to investigate numerically the growth of low and high grade gliomas. The physical parameters used in our numerical simulations are given in Table 1.

TABLE 1. Physical parameters used in the numerical simulations.

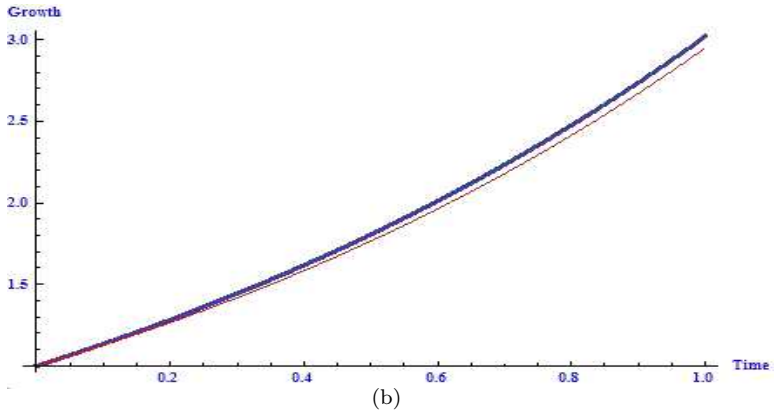
γ	$1.3 \times 10^{-26}\,\mathrm{m}^3$
k_B	$1.30 \times 10^{-23}\,\mathrm{m}^2 \times \mathrm{Kg}/(\mathrm{s}^2 \times \mathrm{K})$
T	$298\,\mathrm{K}$
E_{low}	$30\,\mathrm{kPa}$
E_{high}	$40\,\mathrm{kPa}$

In Table 1, E_{low} and E_{high} stand for averaged Young's moduli for a low and respectively high grade glioma estimated from Fig. 1.

In Fig.4 we show the growth curves $g(t)$ given by (10) for different stretch values. We observe that for small deformations both, the low and high grade gliomas, grow in a similar way.



(a)



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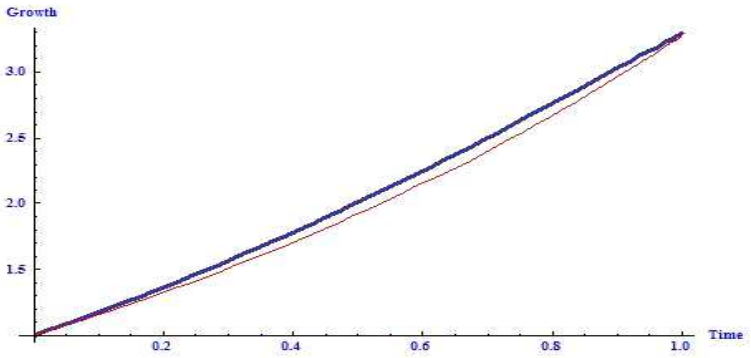


(c)

FIGURE 4. Growth functions given by formula (10)of high grade (red) and low grade (blue) gliomas versus a normalized time scale for (a) $\lambda = 0.25$, (b) $\lambda = 3$, (c) $\lambda = 5$.

In Figs.5 and 6 we show the growth curves $g(t)$, the Adomian series solutions to (11), for $\lambda = 0.25$ and, respectively, $\lambda = 5$ for three different values of the fractional order $\alpha = 0.25, 0.5, 0.9$. From these graphs we see that for larger stretch values the growth of a low grade glioma can become larger than the growth of

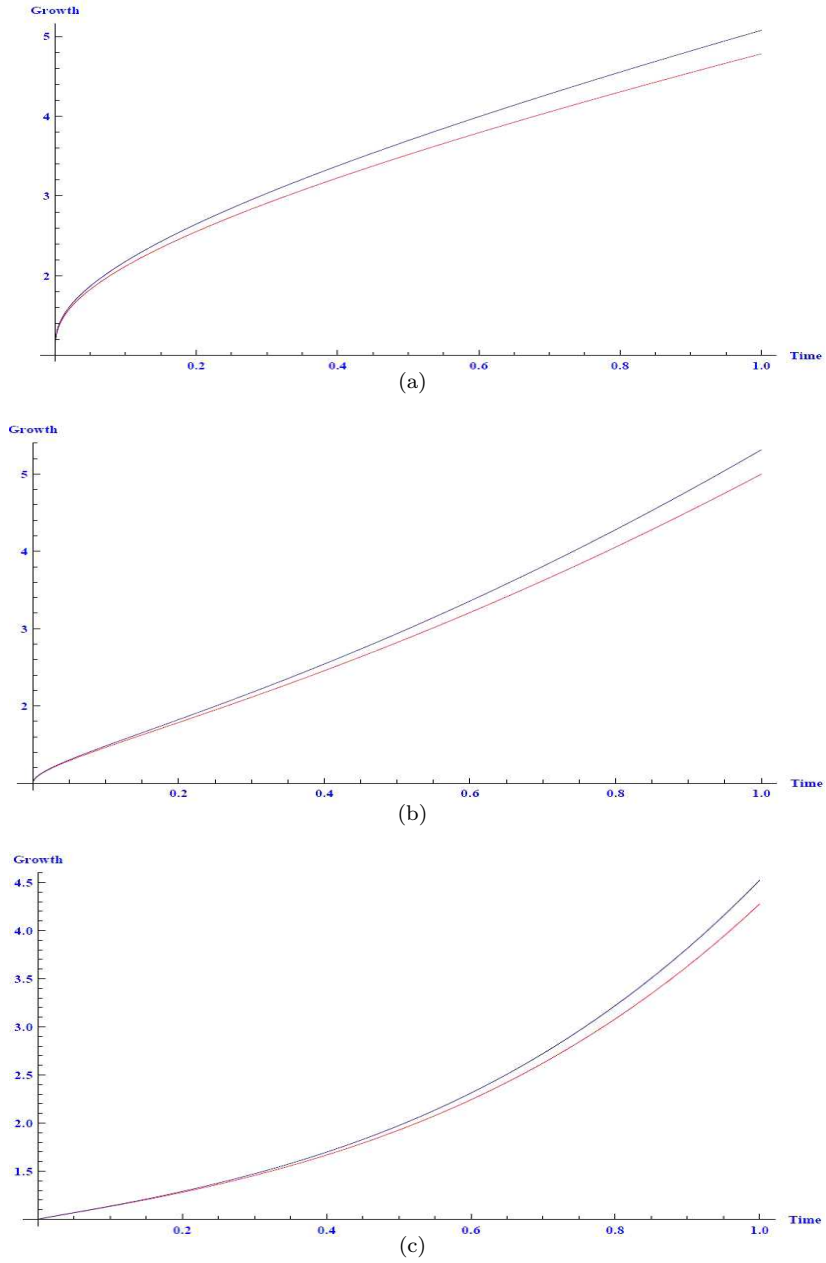
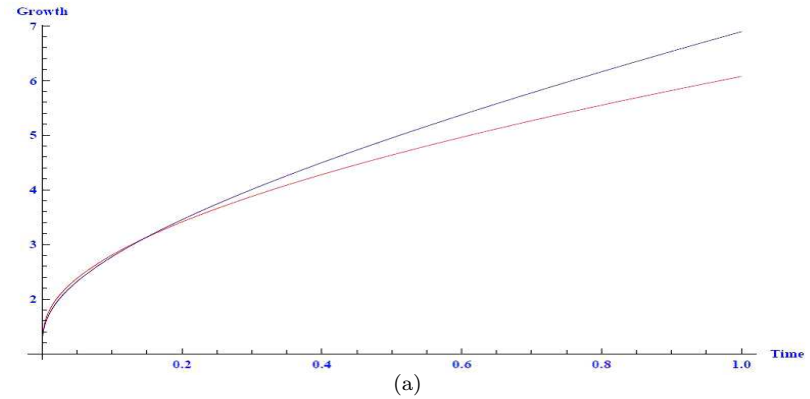
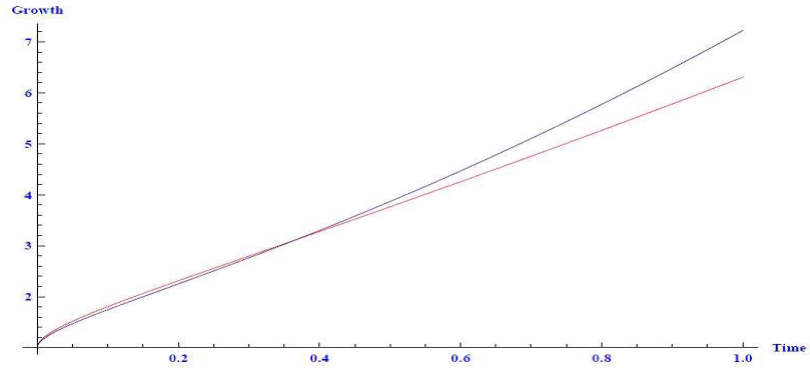


FIGURE 5. Growth functions of high grade (red) and low grade (blue) gliomas versus a normalized time scale for $\lambda = 0.25$ and (a) $\alpha = 0.25$, (b) $\alpha = 0.5$, (c) $\alpha = 0.9$.

a high grade glioma which could mean that a low grade transforms into a high grade glioma if a certain deformation threshold has been reached. We also notice that for a fixed stretch value λ, the convexity of the growth functions changes with increasing α (the curve is concave for $\alpha < 0.5$, and it becomes convex for



(a)



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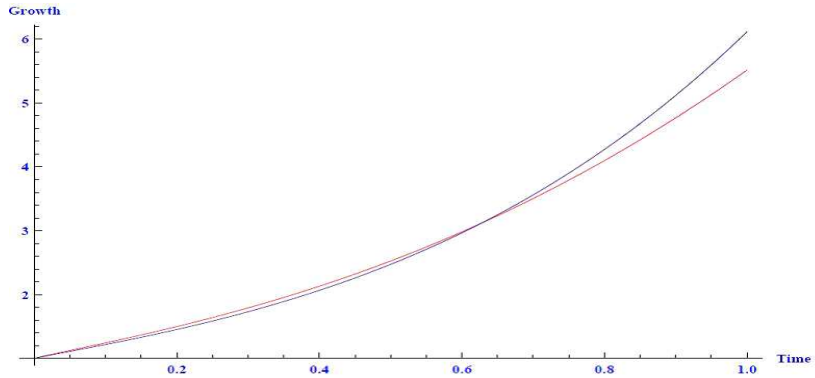

(c)

FIGURE 6. Growth functions of high grade (red) and low grade (blue) gliomas versus a normalized time scale for $\lambda = 5$ and (a) $\alpha = 0.25$, (b) $\alpha = 0.5$, (c) $\alpha = 0.9$.

$\alpha > 0.5$). By comparing Figs.5, 6 for the fractional order model and Fig.4 for the classic model we see that the the classic case does not capture this transition of a glioma from low grade to high grade. This difference may be justified by the fact that the fractional order temporal derivative in (11) could account for some of

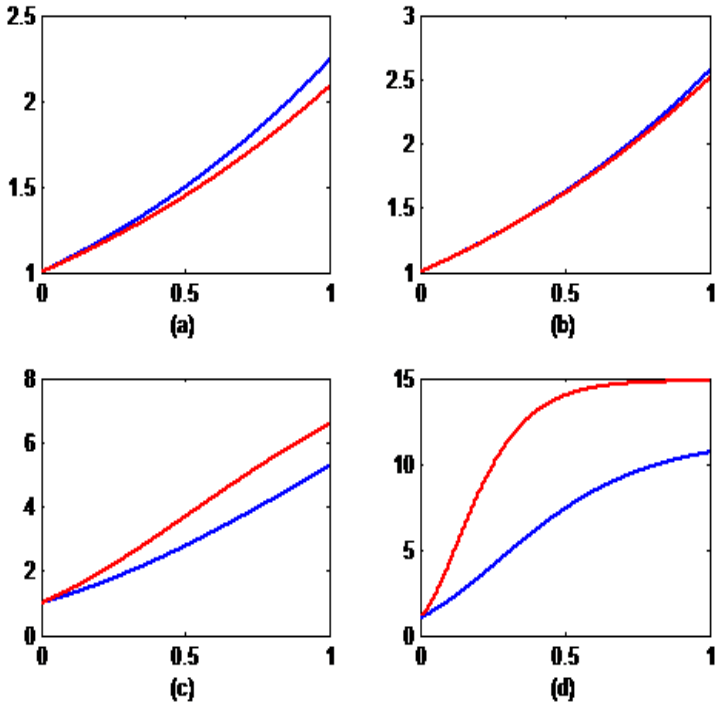

FIGURE 7. Growth functions given by (14) of high grade (red) and low grade (blue) gliomas versus a normalized time scale for (a) $\lambda = 0.1$, (b) $\lambda = 1$, (c) $\lambda = 5$, (c) $\lambda = 10$.

the microscopic heterogeneity and material nonlinearities which are not captured by the macroscopic Hooke's law. The fractional order mechano-growth model (11) incorporates an inhomogeneous clock that connects the macroscopic global and the microscopic local time scales through the presence of a fractional order temporal derivative (we suspect that in materials with evolving microstructure such as living biological tissue the fractional order α might connect not only multiple time scales but also *time and length scales*). In this form, the model is able to predict the time when a low grade tumor transforms into cancer at larger stretches that could occur in the affected tissue due to the growth process itself.

By comparing Figs.4 and 7, we see that the linearized solution and the Adomian series solution of the first order evolution equation (9) are similar. However, from Figs.5, 6 and 8 the linearized solution and the Adomian series solution to the fractional order evolution equation (11) show different trends. The transition from low grade to high grade when a strain threshold has been reached is captured by both solutions, but the linearized solution is bounded and shows a steep growth that is delayed as α increases, while the Adomian series solution changes convexity as α

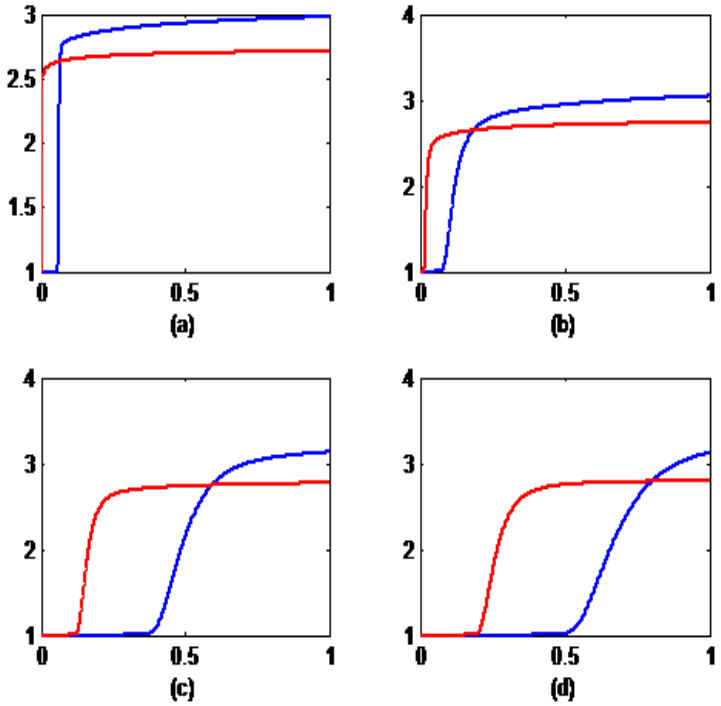

FIGURE 8. Growth functions given by (16) of high grade (red) and low grade (blue) gliomas versus a normalized time scale for $\lambda = 10$ and (a) $\alpha = 0.25$, (b) $\alpha = 0.5$, (c) $\alpha = 0.75$, and (d) $\alpha = 0.9$.

increases and is unbounded. This difference between the two analytical solutions of (11) shows that linearization in this case is not reliable and maybe not even physical, and thus the work done in this paper to find the solution to the non-linear evolution equation using the Adomian decomposition method represents useful first steps to remedy this.

5. Conclusion

In this paper we have proposed a mechano-growth model that predicts the growth behavior of low and high grade gliomas under uniaxial stretch. Our model shows how an applied uni-axial stretch λ can affect the growth of gliomas of different grades. For simplicity we assumed that the tissue is an isotropic homogeneous linear elastic solid for which the stress-strain relationship is given by Hooke's law and that tumor growth is regulated by the growth of the viscoelastic cytoskeletal networks present in the tissue. By considering that tumor growth is similar to the growth of cytoskeletal networks, we obtained the same nonlinear first order evolution equation as in [34]. Inspired by [31] where a fractional order temporal

derivatives is used to describe abnormal processes believed to be involved in the birth of tumors, we generalized this evolution equation by replacing the first order temporal derivative by a fractional order one. We have shown that by using a fractional order temporal derivative instead of a first order one, we can predict when a low grade (benign) glioma transforms into a high grade (malignant) tumor.

Living biological materials are dynamic materials whose microstructure is evolving continuously. The fractional order α can be seen as modeling an inhomogeneous clock that connects the macroscopic global time scale and the microscopic local time scale. We used the Adomian decomposition method to find analytical solutions to both the classical and the generalized fractional order non-linear evolution equations. While the classical model predicts that the high grade tumors grow similar to the low grade ones, the fractional order model captures the transition of a low grade tumor to a high grade one regardless of the amount of mechanical stretch applied. Also, the size of the fractional order α appears to play an important role in this growth process: the shape of the growth curve changes from concave to convex as α increases. This piece of information could prove crucial in treatment decisions and planning. We have also shown the analytic solutions of the corresponding linearized evolution equations presented in [25]. The comparison between the linearized and the Adomian series solutions shows that only for the classical, first order evolution equation is linearization a good approximation. For the fractional order model, the Adomian decomposition method directly solves the non-linear evolution equation and thus should be closer to the physics of tumor growth than the solution obtained through linearization. In our further work we plan to investigate how this fractional order relates to bio-chemical processes (described by diffusion-reaction differential equations) taking place in tissues and tumors. A multiple time and length scales approach might have to be considered in order to incorporate these effects appropriately.

References

[1] Adomian G. A review of the decomposition method in applied mathematics, J.Math.Anal.Appl. 135: 501-544, 1988.

[2] Adomian G. The Decomposition Method, Kluwer Acad. Publ., Boston, 1994.

[3] Kolata G, As other death rates fall, cancer's scarcely moves. The New York Times, April 24, 2009.

[4] Statistics and outlook for brain tumours.
See http://cancerhelp.cancerresearchuk.org/type/brain-tumour/treatment/statistics-and-outlook-for-brain-tumours#glioma

[5] Lowengrub J S, Frieboes H B, Jin F, Chuang Y-L, Li X, Macklin P, Wise S M, Cristini V. Nonlinear modeling of cancer: bridging the gap between cells and tumors. Nonlinearity 23: 1-91, 2010.

[6] Deisboeck T S, Zhang L, Yoon J, Costa J. In silico cancer modeling: is it ready for prime time? Nature Clin. Practice Oncol. 6: 34-42, 2009.

[7] Preziosi L, Tosin A. Multiphase and multiscale trends in cancer modeling. Math.Mod. Nat. Phenom. 4: 1-11, 2009.

[8] Tracqui, P. Biophysical models of tumor growth. Rep. Prog. Phys. 72: 056701, 2009.

[9] Ventura A C, Jackson T L, Merajver S D. On the role of cell signaling models in cancer research. Cancer Res. 69: 400-402, 2009.

[10] Swanson K R, Bridge C, Murray J D, Alvord E C jr. Virtual and real brain tumors: using mathematical modeling to quantify glioma growth and invasion. J. Neuro. Sci. 216: 1-10, 2003.

[11] Jbabdi S, Mandonnet E, Duffau H, Capelle L, Swanson K R, Pelegrini-Issac M,Guillevin R, Benali H. Simulation of anisotropic growth of lowgrade gliomas using diffusion tensor imaging. Magn. Res. Med. 54: 616-624, 2005.

[12] Khain E, Sander L M. Dynamics and pattern formation in invasive tumor growth. Phys. Rev. Lett. 96: 188103, 2006.

[13] Cristini V, Lowengrub JS, Nie Q. Nonlinear simulation of tumor growth. J. Math.Biol. 46: 191-224, 2003.
[14] Cristini V, Frieboes H B, Gatenby R, Caserta S, Ferrari M, Sinek J. Morphologic instability and cancer invasion. Clin. Cancer Res. 11: 6772-6779, 2005.
[15] Frieboes H, Zheng X, Sun C, Tromberg B, Gatenby R, Cristini V. An integrated computational/experimental model of tumor invasion. Cancer Res. 66: 1597-1604, 2006.
[16] Anderson A R A, Quaranta, V. Integrative mathematical oncology. Nat.Rev.Cancer 8: 227-234, 2008.
[17] Byrne H M, Chaplain M A J. Growth of non-necrotic tumors in the presence and absence of inhibitors. Math. Biosciences 130: 151-181, 1995.
[18] Byrne H M, Chaplain M A J. Modelling the role of cell-cell adhesion in the growth and development of carcinomas. Math.Comput.Modelling 24: 1-17, 1996.
[19] Byrne H M, Chaplain M A J. Free boundary value problems associated with the growth and development of multi-cellular spheroids. Eur. J. Appl. Math. 8: 639-658, 1997.
[20] Sutherland R M. Cell and environment interactions in tumor microregions: the multi-cell spheroid model, Science 240: 177-184, 1988.
[21] Sutherland R M, Carlsson J, Durand R E, Yuhas J. Spheroids in cancer research, Cancer Res. 41: 2980-2994, 1981.
[22] Walles T, Weimer M, Linke K, Michaelis J, Mertsching H. The potential of bioartificial tissues in oncology research and treatment, Onkologie 30: 388-394, 2007.
[23] Oliver C, Sermesant M, Bondiau P Y, Delingette H, Warfield S, Malandain G, Ayache N. Realistic simulation of the 3D growth of brain tumors in MR images coupling diffusion with biomechanical deformation. IEEE Trans. Med. Imaging. 24: 1334-1346, 2005.
[24] Greenspan H P. On the growth and stability of cell cultures and solid tumors J. Theor. Biol. 56: 229-242, 1976.
[25] Drapaca C S, Palocaren A J. Biomechanical modeling of tumor classification and growtth, Rev.Roum Sci Techn.Mec.Appl. 55(2): 115-124, 2010.
[26] Friedman A, Reitich F. Analysis of a mathematical model for the growth of tumors. J. Math. Biol. 38: 262-284, 1999.
[27] Friedman A, Bellomo N, Maini P K. Mathematical analysis and challenges arising from models of tumor growth. Math. Models Meth. Appl. Sci. 17: 1751-1772, 2007.
[28] King J R, Franks S J. Mathematical analysis of some multidimensional tissue growth models. Euro.J. Appl. Math. 15: 273-295, 2004.
[29] King J R, Franks S J. Mathematical modelling of nutrient-limited tissue growth. Int. Numer. Math. 154: 273-282, 2007.
[30] Franks S J, King J R. Interactions between a uniformly proliferating tumor and its surrounding: uniform material properties. Math. Med. Biol. 20: 47-89, 2003.
[31] 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): 231-254, 2006.
[32] Geyikli T, Kaya D. Comparison of the solutions obtained by B-spline FEM and ADM of KdV equation, Appl.Math.Comp. 169(1): 146-156, 2005.
[33] El-Wakil S A, Elhanbaly A, Abdou M A. Adomian decomposition method for solving fractional nonlinear differential equations, Appl.Math.Comp. 182:313- 324, 2006.
[34] Kim J S, Sun S X. Continuum modeling of forces in growing viscoelastic cytoskeletal networks, Journal of Theoretical Biology 256 (4):596-606, 2009.
[35] Chen Y C, Hoger A. Constitutive functions of elastic materials in finite growth and deformation, Journal of Elasticity 59:175-193, 2000.

Department of Engineering Science and Mechanics, Pennsylvania State University, University Park, PA 16802, USA
E-mail: csd12@psu.edu