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The influence of anisotropic growth and geometry on the stress of solid tumors

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ABSTRACT

Solid stresses can affect tumor patho-physiology in at least two ways: directly, by compressing cancer and stromal cells, and indirectly, by deforming blood and lymphatic vessels. In this work, we model the tumor mass as a growing hyperelastic material. We enforce a multiplicative decomposition of the deformation gradient to study the role of anisotropic tumor growth on the evolution and spatial distribution of stresses. Specifically, we exploit radial symmetry and analyze the response of circumferential and radial stresses to (a) degree of anisotropy, (b) geometry of the tumor mass (cylindrical versus spherical shape), and (c) different tumor types (in terms of mechanical properties). According to our results, both radial and circumferential stresses are compressive in the tumor inner regions, whereas circumferential stresses are tensile at the periphery. Furthermore, we show that the growth rate is inversely correlated with the stresses' magnitudes. These qualitative trends are consistent with experimental results. Our findings therefore elucidate the role of anisotropic growth on the tumor stress state. The potential of stress-alleviation strategies working together with anticancer therapies can result in better treatments.

1. Introduction

Tumor growth involves the generation of mechanical forces both within the tumor and between the tumor and the host tissue. The development of a tumor could be closely associated with the generation and accumulation of mechanical stresses (Stylianopoulos, 2017; Stylianopoulos & Jain, 2013). These mechanical forces, coupled with neovascularization, can induce abnormal solid and fluid stresses that facilitate tumor progression and hinder the response to various anti-cancer

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treatments (Jain, Martin, & Stylianopoulos, 2014). As shown in several experimental studies (see e.g. Cheng, Tse, Jain, & Munn, 2009; Demou, 2010; Helmlinger, Netti, Lichtenbeld, Melder, & Jain, 1997; Tse, Cheng, Tyrrell, Wilcox-Adelman, & Boucher, 2012), mechanical stresses can determine in part the progression of solid tumors. Solid stresses (Jain, Martin, and Stylianopoulos, 2014) can affect tumor patho-physiology directly, by compressing cancer and stromal cells, and indirectly, by deforming blood and lymphatic vessels (Stylianopoulos, 2017). On one hand, cell compression can alters gene expression, cancer cell proliferation, apoptosis and invasiveness, stromal cell function, and extracellular matrix synthesis and organization (Cheng, Tse, Jain, & Munn, 2009; Tse, Cheng, Tyrrell, Wilcox-Adelman, & Boucher, 2012). On the other hand, compression of blood and lymphatic vessels can reduce the delivery of oxygen, nutrients and drugs. Compromising the effectiveness of anti-cancer therapies (Padera et al., 2004; Stylianopoulos & Jain, 2013). Anti-cancer therapies by stress-relief have been proposed to improve and complement drug treatments delivery efficacy (Jain, 2013; Stylianopoulos & Jain, 2013). These strategies are based on the reduction of the stress levels, which causes reopening of compressed tumor blood vessels, thus leading to enhanced fluid and, in turn, drug transport within the tumor mass. In Stylianopoulos, Martin, Chauhan, Jain, and Diop-Frimpong (2012) it is shown that pharmacological depletion of tumor stroma with saridegib (an inhibitor of the sonic hedgehog pathway Jain, Martin, & Stylianopoulos, 2014), alleviates stress levels and increases blood vessels diameter and tumor perfusion without affecting vascular density. In Olive, Jacobetz, Davidson, Gopinathan, and McIntyr (2009), the authors show that the use of saridegib improves the effectiveness of chemotherapy in murine pancreatic cancers and increases the mice survival rate. Furthermore, clinical studies in humans show that antiangiogenic agents can normalize tumor vasculature, so patients whose tumor blood perfusion increases survive longer (Jain, 2013). Morover, in Penta and Ambrosi (2015) and Mascheroni and Penta (2017), the authors solve the homogenized fluid and drug transport models developed in Shipley and Chapman (2010) and Penta, Ambrosi, and Quarteroni (2015) for vascularized tumors, respectively. Their analysis, which was extended to mechanic deformations in Penta and Merodio (2017), supports the argument that geometric regularization of the microvasculature improves transport of blood and advected drugs transported into the tumor mass. Cancer evolution is extremely complex and cannot be reduced only to its mechanical stress response; however some features in the tumor progression can be associated with the generation and accumulation of mechanical stresses.

An increased awareness of the mechanical response of a growing tumor mass can also contribute to a more informed design of anti-cancer therapies that rely on cancer tissue destruction, such as those based on ultrasounds. For example, the High-Intensity Focused Ultrasound (HIFU) is a well-known technique which exploits ultrasounds to remove the malignat tissue. In fact, it has been successfully applied in the treatment of solid tumors (pancreas, liver, colon, etc.) (Ahrar et al., 2005). Although tissue destruction takes normally place via thermal ablation, the interest in mechanical HIFU (where ultrasounds are used to generate mechanical ablation) is increasing (see, e.g. Hoogenboom et al., 2015), and its working mechanisms are strongly related to the mechanical response of different tissue types. Moreover, mechanical forces can be used for medical simulations involving the discover of tumors (Jeon, Choi, & Harders, 2012). Our study is therefore motivated by the importance of stresses in determining tumors' progression and treatment. Given the lack of *in vivo* data, the development of theoretical investigations that can provide reliable predictions can support the design of effective anti-cancer treatments.

In the present work we model the tumor mass as a growing hyperelastic material and investigate the role of anisotropic tumor growth on tumor stresses. Growth take place when conversion of mass is present from one constituent to another, and once a mixture is considered then there are subtle issues concerning boundary conditions that have to be clearly discussed (see e.g. Humphrey & Rajagopal, 2002; Humphrey, Rao, & Rajagopal, 2002; Rao, Humphrey, & Rajagopal, 2003). In particular, we assume that the solid tumor is surrounded by a compressible, isotropic and hyperelastic medium. We extend the analysis reported in Ramírez-Torres et al. (2015a) by performing for the first time a parametric analysis in terms of (a) degree of anisotropy, (b) tumor shape (cylindrical versus spherical), and (c) tumor types that are characterized by different mechanical properties. In fact, cylindrical and spherical tumor shapes have been experimentally observed as shown in Franks, Byrne, Mudhar, Underwood, and Lewis (2003b) and Weiswald, Bellet, and Dangles-Marie (2015), respectively.

The reminder of this work is organized as follows. In Section 2 we describe the multiplicative decomposition of the deformation gradient tensor to account for both the elastic response and growth of the tumor contributions. The theory of materials with evolving natural configurations developed by Rajagopal and co-workers (see for instance Rajagopal, 1995) is used since it permits to model growth and stress-induced deformation separately. In Section 3 we introduce the Ciarlet's strain energy function which is exploited to model the hyperelastic response of the tumor. In Section 4 we introduce the balance equations for mass and linear momentum. In Section 5 we describe the adopted evolution law for growth. In Section 6 we summarize the mathematical model and then specialize it for spherical and cylindrical geometries, assuming radial symmetry in both cases. In Section 7 we present and discuss our results obtained via numerical simulations of the mathematical model. In Section 8 we present our conclusions.

2. Multiplicative decomposition of the deformation gradient tensor

Tumor growth is modeled using the multiplicative decomposition of the deformation gradient tensor **F**. In fact, the essential difficulty in formalizing the dynamics of biological growth is the simultaneous modeling of the change in mass and how the latter affects the stresses. The theory of materials with evolving natural configurations (Humphrey & Rajagopal, 2002) overcomes this complexity by separating such stress contributions (Ambrosi & Mollica, 2002). Then,

$$\boldsymbol{F} = \boldsymbol{F}_{el}\boldsymbol{G}, \tag{1}$$