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Mathematical modeling of anisotropic avascular tumor growth

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ABSTRACT

Cancer represents one the most challenging problems in medicine and biology nowadays, and is being actively addressed by many researchers from different areas of knowledge. The increasing development of sophisticated mathematical models and computer-based procedures has had a positive impact on our understanding of cancer-related mechanisms and the design of anticancer treatment strategies. However, further investigation and experimentation are still required to completely elucidate the tumor-associated mechanical responses, as well as the effect of mechanical forces on the net tumor growth. In this work we develop a theoretical framework in the context of continuum mechanics to investigate the anisotropic growth of avascular tumor spheroids. To that end, a specific anisotropic growth deformation tensor is considered, which also describes an isotropic growth law as a particular case. Mixtures theory and the notion of multiple natural configurations are then used to formulate a mathematical model of avascular tumor growth. More precisely, mass, momentum balance and nutrients diffusion equations are derived, where solid tumors are assumed as hyperelastic and compressible materials. Moreover, mechanical interactions with a rigid extracellular matrix (ECM) are considered, and the mechanical modulation of growing tumors in a rigid surrounding tissue is investigated by means of numerical simulations. Finally, the model results are compared with experimental data previously reported in the literature.

1. Introduction

Despite tremendous progress in medicine during last decades, as well as the constant development of novel treatment techniques, cancer is one of the most frequent causes of death worldwide. In general, this disease results from an uncontrolled growth of abnormal cells serving no physiological functions. Solid tumor growth is a complicated phenomenon involving many inter-related complex processes. Such processes are dominated by a large number of interacting mechanisms described by highly nonlinear dynamics. Indeed, tumor-associated responses are difficult to approach by experimental procedures alone and can typically be better understood by using appropriate mathematical models and sophisticated computer simulations. Mathematical modeling has the potential to provide new insights into these interactions, and specifically to describe the main aspects of solid tumor growth dynamics through models based on physical and mechanical processes that consider cancer as an evolving system. Accordingly, simulation of tumor growth and treatment responses have been approached using a diverse variety of mathematical models over the past decades. However, regardless of the valuable findings reached in this field, the underlying tumor growth mechanisms are far from being completely understood.

Bearing these facts in mind, the goal of this work is to investigate through a mathematical model the early avascular phase of tumor growth taking into account the effects of an anisotropic growth law, where, in addition, the mechanical interactions with a rigid extracellular matrix (ECM) and the surrounding host tissue are considered. It is worth pointing out that several mathematical models have been proposed to simulate and analyze tumor growth with remarkable contributions. For instance, Ambrosi and

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Mollica [3] studied tumor growth using the notion of multiple natural configurations. The theory of materials with evolving natural configurations, developed by Rajagopal and co-workers (see Rajagopal et al. [21] and Wineman et al. [31] for further details), was used to model growth and stress-induced deformation separately, considering the tumor as a hyperelastic and compressible material. The kinematics, and in general mechanics, of large deformations associated with biological growth is still an open problem. However, to model different biological materials, such as soft tissues and cells, continuum mathematical models involving two or more interacting constituents have been widely considered. Indeed, a possible theoretical framework that can be successfully employed to describe the complex interactions that take place between the constituents of a mixture is the theory of mixtures. A two-phase model is presented by Breward et al. [8] to describe avascular tumor growth, where a mixture model is used to simulate the tumor cells and extracellular water, which leads to strong coupling between the phases. Byrne et al. [9] proposed a two-phase material model based on the theory of mixtures to investigate the avascular growth of tumors represented by a solid cellular phase (living tumor cells) and a liquid phase (the extracellular fluid in the tumor microenvironment). Although the continuum mechanical treatment of biological growth has reached considerable improvements there are still many open questions and challenges that should be addressed. In particular, reliable and advanced experimental procedures involving vascular tumor growth phases are difficult to be performed. Significant efforts have been dedicated to investigate the growth of avascular solid tumors through *in vitro* cultures, where the role played by nutrients and oxygen diffusion and consumption in sustaining the growth are reinforced. In these experiments the mechanical effects have been shown to play a crucial role in the resulting tumor growth dynamics. For instance, considering several *in vitro* avascular tumor growth in gels of different stiffness, Helmlinger et al. [13] demonstrated that the resistance or stress exerted on tumor cells by the surrounding microenvironment affects the growth dynamic and, furthermore, that stiffer gels are associated with smaller tumors. The influence of mechanical forces on tumor growth has been recently addressed by Ambrosi et al. [5] and Preziosi and Vitale [20]. In particular, an excellent review article on the trends and challenges on cancer modelling is due to Preziosi and Tosin [19].

In this work, we consider classical methods of continuum mechanics together with mixtures theory and the notion of multiple natural configurations to model growth of an avascular tumor represented by a hyperelastic and compressible solid spherical phase interacting with a rigid ECM and the surrounding host tissue. It should be noted that this theoretical framework provides a starting point to incorporate additional phases, as it is required to describe more complex mechanisms of (solid) tumor growth. In particular, tumor growth is derived from balance laws as well as conservation principles supplemented with diffusion of nutrients, e.g. oxygen, glucose, etc. The growth process is assumed isothermal, i.e. thermal energy is not considered. We further assume that the body does not rotate and growth is understood as an increase of body mass. Indeed, as most soft biological tissues possess a highly anisotropic microstructure, we provide an anisotropic growth law, where the corresponding isotropic law is obtained as a particular case. It should be noted that the formulation of general mathematical models that can take into account all or most of the mechanisms involved in tumor growth is a very difficult task, if not impossible. Therefore, one of the main goals of this work is to propose a mathematical model as simple as possible to increase our understanding of the influence of anisotropic growth on avascular tumor growth. The effect of tumor-surrounding tissue is also considered.

2. Preliminaries

2.1. Multiple natural configurations in the modeling of growth

The essential difficulty in formalizing the dynamics of biological growth is the simultaneous modeling of the change in mass and the stresses associated with this change, possibly caused by growth itself or by the application of external loads. The theory of materials with evolving natural configurations overcomes this problem by separating such stress contributions. Therefore, this theory is an adequate framework to investigate tumor growth. We adopt the concept of evolving natural (stress-free) configurations (see Humphrey and Rajagopal [14] for more details). Recently, a different approach was proposed by Ateshian and Ricken [6], where the concept of evolving natural configurations was not considered. The authors assumed that a given material can be composed by multiple solid constituents, each one of them (each generation) being produced during a particular growth spurt and having its own invariant stress-free reference configuration. An advantage of this approach is that each generation can be treated using the conventional kinematics of continua, where the reference configuration is stress-free and time-invariant.

Let us consider the motion of a generic particle of the i-th component from its reference configuration κ_i^0, which is assumed to be stress free. We denote by $\kappa_i^{\mathrm{el}(t)}$ the *natural configuration* of the body associated with the current configuration κ_i^t. $\kappa_i^{\mathrm{el}(t)}$ depends on time t, but in what follows is referred as κ_i^{el} for the sake of simplicity in the notation. The natural configuration is the reference configuration chosen to represent the elastic responses of the material and it is considered the primary configuration of interest. It is important to recall that the relaxation to the natural configuration is a local process, not a global process. Now, the (local) deformation from κ_i^{el} to κ_i^t is measured through the tensor $\boldsymbol{F}_i^{\mathrm{el}}$. In particular, the change from κ_i^0 to the natural configuration κ_i^{el} can be interpreted as an unconstrained growth described by the tensor $\boldsymbol{G}_\alpha$. Hence, it is possible to write $\boldsymbol{F}_i = \boldsymbol{F}_i^{\mathrm{el}}\boldsymbol{G}_i$. It should be also noted that since the body mass is preserved from κ_i^{el} to κ_i^t the tensor $\boldsymbol{F}_i^{\mathrm{el}}$ is associated with the stress responses of the material and it is not directly related to growth. The tensor $\boldsymbol{G}_i$ is directly connected to growth, and therefore it is referred to as the growth tensor. Then, it follows that the contributions due to pure growth and stress-induced deformations have been split. Moreover, the deformation gradient $\boldsymbol{F}_i$ contains information about the (local) deformation from κ_i^0 to κ_i^t. Since $\boldsymbol{F}_i$ has an inverse, it follows that $\boldsymbol{F}_i^{\mathrm{el}}$ and $\boldsymbol{G}_i$ are also invertible. Finally, we remark that since the natural configuration of the body is unique at each instant of time t, then the density field in κ_i^{el} is identical to that in the original reference configuration.

From the assumption of preservation of mass between κ_i^{el} to κ_i^t, it is well known that (see for instance Ambrosi and Mollica [3])

$$J_{\boldsymbol{G}_i} = \det\boldsymbol{G}_i = \frac{\mathrm{d}m_i}{\mathrm{d}m_{i0}}, \tag{1}$$

where $\mathrm{d}m_i$ and $\mathrm{d}m_{i0}$ represent the mass of a particle in the current and reference configurations, respectively. The tensor $\boldsymbol{G}_i$ contains the information regarding mass production or resorption. In what follows, J is used to denote the determinant of a tensor. Furthermore, since $J_i = J_i^{\mathrm{el}} J_{\boldsymbol{G}_i}$, where $J_i^{\mathrm{el}} = \det(\boldsymbol{F}_i^{\mathrm{el}})$, we have that

$$\rho_{i0} = \rho_i J_i^{\mathrm{el}}, \tag{2}$$

which resembles the usual Lagrangian version of the conservation of mass in the absence of mass sources. In (2) ρ_{i0} and ρ_i are the density fields of the i-th component at time $t = 0$ and in the actual configuration, respectively.