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Action of body forces in tumor growth

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ABSTRACT

In the present work two mathematical models are proposed to investigate tumor growth within the framework of continuum mechanics. In particular, the tumor is modeled as an ideal saturated mixture, where the mechanical description is based on both the mixtures theory and the notion of multiple natural configurations. The mixture is considered as a porous material composed by a hyperelastic compressible solid and an incompressible viscous fluid. In addition, the growth of a tumor considered as a single hyperelastic solid material is also studied as a particular case. Then, a general mathematical model is formulated using particular constitutive laws for each component involved. The resulting constitutive equation is used to describe the isotropic inhomogeneous growth of an encapsulated spherical solid tumor. During that process, the mixture is assumed to be isothermal. Furthermore, growth is understood as a change in the body mass of the constituents supplemented with diffusion of nutrients. The mechanical modulation of growth by body forces is then illustrated and analyzed by means of computer numerical simulations. To that end, the material parameter values considered were taken from experimental data, and model results describe realistic tumor growth dynamics.

1. Introduction

Despite advances made in recent years, cancer remains a leading cause of death worldwide nowadays. In general, tumors result from an abnormal uncontrolled growth of cells, serving no physiological function, which can be considered harmless (no cancer) or dangerous (with cancerous cells). The attempt to give a unified and standard description of what a tumor is from a mathematical viewpoint, as well as from other points of view, is still hopeless. This fact is mainly due to the existence of many different types of tumors with distinct origins, characteristics and dynamics. Nevertheless, new discoveries relating several scientific areas of cancer research make advanced mathematical modeling a useful and necessary tool to interpret and analyze the increasing volume of experimental findings.

The kinematics (and in general, Mechanics) of large deformations associated with biological growth is still an open problem. However, to model several biological materials, such as soft tissues and cells, continuum mechanics models involving

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two or more interacting constituents have been widely utilized. 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. Concretely, this theory is based on the fundamental assumption that the domain is considered as a continuum, i.e. each point in the continuum consists of particles belonging to each of the constituents. Accordingly, this assumption requires that each component in the material must be dense. Therefore, it follows that each constituent can be homogenized over the region of the mixture.

On the other hand, poroelastic theories are commonly used in the analysis of the coupling between fluid and solid mechanics in porous mediums. As a matter of fact, in the human body several subsystems can be suitably described as deformable porous media permeated by organic liquids, e.g. articular cartilages, arteries, heart, lungs, brain and soft tissues in general. In particular, an ideal porous medium is characterized by fully saturated interconnected pores, having homogeneous isotropic chemically inert solid and fluid phases. Namely, soft tissues are composed by several cell populations coexisting in a porous structure, e.g. the extracellular matrix (ECM). A poroelastic solid tumor is generally assumed to be a porous medium having a network of capillaries with highly permeable walls, which forms the interconnected pore space. In general, poroelastic models can be obtained from the theory of mixtures using suitable approximations in the governing equations and constitutive laws.

More precisely, constitutive models of tumor tissues can be divided into either "single phase continuum models" (solid or fluid constitutive models) or "multiphase continuum models". To mention only some, a nonlinear elastic material model was implemented by Chaplain and Sleeman (1993), where a growing tumor was considered as an inflating balloon characterized by a specific strain energy function. In different works, as those reported by Taber and Eggers (1996) and Taber and Perucchio (2000) among others, the technique of multiplicative decomposition of the total deformation gradient into its elastic and growth parts was considered. Ambrosi and Mollica (2002) proposed a single phase solid elastic model to analyze tumor growth considering multiple natural configurations as described in Rajagopal (1995). On the other hand, in Pozrikidis and Farrow (2003) the fluid flow through a solid tumor was investigated considering the interstitium as an isotropic porous material. In particular, the fluid flow model was analyzed using the Darcy's law. Moreover, Roose, Netti, Munn, Boucher, and Jain (2003) provided a linear poroelastic model to investigate the stress generated due to the growth of a spherical tumor. In addition, McGuire, Zaharoff, and Yuan (2006) considered a spherical tumor as a deformable porous medium with a linear elastic material for the solid phase to study the effect of pressure and induced tissue deformation on the rate at which a drug is infused. Accordingly, all these mathematical models made clear that continuum mechanics together with the mixtures theory can establish a theoretical framework able to produce meaningful results in the analysis of tumor growth dynamics.

In this work, classical methods of continuum mechanics are used to model tumor growth. The tumor is modeled considering different interacting continua in a porous material, which satisfy different biological assumptions. More precisely, the body is considered as an ideal saturated mixture composed by a hyperelastic solid and an incompressible fluid component. The evolution of the tumor is then derived from balance laws as well as conservation principles supplemented with diffusion mechanisms for nutrients such as oxygen or glucose. In particular, this representation allows to compare and analyze this general multiphase model with the particular case in which the tumor is assumed as a single solid hyperelastic compressible phase (see Ramírez-Torres et al. (2013)). To that end, we use the notion of multiple natural configurations to describe the isotropic inhomogeneous growth of a solid encapsulated tumor spheroid. It is worth to be stressed that, the essential difficulty in formalizing the dynamics of growth is the simultaneous modeling of (a) the change in mass and (b) the corresponding stresses associated with that change, possibly caused by growth itself or by the application of external loads. Accordingly, the theory of materials with evolving natural configurations permits to model growth and stress-induced deformation separately. Indeed, this is not merely a "plasticity" approach with multiplicative decomposition of the deformation gradient. The evolution of the natural configuration, developed by Rajagopal and co-workers (see for instance Rajagopal (1995) and Rajagopal & Srinivasa (2000)), is governed by thermodynamics (isothermal processes) and determined by maximization of the dissipation rate. Moreover, during the analysis we assume that the body does not rotate and the corresponding growth is not understood as an increase in the number of cells, but as a change in the body mass of the constituents. On the other hand, the mixture is supposed to be isothermal, i.e. thermal energy is ignored. We also consider two ways in which energy is supplied to the system: (1) work of standard external forces that balance the internal forces and (2) provided specifically for growth. Furthermore, we suppose that the growth rate of the tumor is established by the evolution of nutrients, which are (a) distributed uniformly in the material surrounding the tumor; while in the tumor are (b) being diffused inside the moving fluid and (c) being absorbed by the tumor cells toward the tumor center. It should be noted that, in general, it is very difficult to formulate complete and manageable models to investigate at the same time all the aforementioned complex mechanisms. Therefore, the main goal of this work is to provide a description of tumor growth, as realistic as possible, using relatively simple mathematical models.

The layout of this work is as follows. Firstly, the mixtures theory and the notion of multiple natural configurations are briefly described. In doing so, geometrical assumptions as well as the explicit constitutive laws for a compressible solid constituent and an incompressible viscous liquid are introduced. Moreover, the local interactions between the constituents across the interfaces are also characterized. On the other hand, mass and linear momentum balance equations are derived for the whole mixture. We split the total traction of the boundary domain following Rajagopal and Tao (1995), and write specific traction-boundary conditions for the whole body. In particular, to characterize fluid motion the Darcy's law is used. The energy dissipation analysis provides coupling between stress and growth. Besides, a specific growth law is considered