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Hierarchical micro-adaptation of biological structures by mechanical stimuli

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ABSTRACT

The objective of this work is to develop a remodeling model for biological matter coupling two different processes in a 3D framework: reorientation of the preferential direction of a given fibered structure and reorientation of the fibrils or filaments that make up such a structure. This work uses the microsphere-based approach to take into account the micro mechanics involved in biological fibered structures regarding both their passive behavior and the reorientation of their micro constituents. Moreover, the macro behavior of the material as a whole is obtained by means of homogenizing the underlying micro response. We associate the orientation space of the integration directions to the physical space of micro-fibrils. To approximate the directional distribution of the fibrils within each fiber bundle, a Bingham probability orientation density function is introduced into the Helmholtz energy function. With all these assumptions, the problem is studied from an energetic point of view, describing the dissipation inherent to remodeling processes, and the evolution equations for both reorientations (change in preferential direction of the network and change in shape of the fibril distribution) re obtained. The model is included in a finite element code which allows computing different geometries and boundary value problems. This results in a complete methodology for characterizing the reorientation evolution of different fibered biological structures, such as cells. Our results show remodeling of fibered structures in two different scales, presenting a qualitatively good agreement with experimental findings in cell mechanics. Hierarchical structures align in the direction of the maximum principal direction of the considered stimulus and narrow in the perpendicular direction. The dissipation rates follows predictable trends although there are no experimental findings to date for comparison. The incorporation of metabolic processes and an insight into cell-oriented mechano-sensing processes can help to overcome the limitations involved.

1. Introduction

Remodeling and other evolving processes such as growth or morphogenesis are key factors in the evolution of biological tissue in response to both external and internal epigenetic stimuli. Based on the description of these processes provided by Taber (1995) and Humphrey et al. (2002) for three important adaptation processes, remodeling, morphogenesis and growth (positive and negative), we shall consider the latter as the increase/decrease of mass via the increase/decrease of the number or size of cells, leading to a change in the volume of the organ. The work of Rodriguez et al. (1994) used the concept of natural configuration previously introduced by Skalak et al. (1982) to formulate volumetric growth. Later, Humphrey et al. (2002) proposed a constrained-mixture theory where changes in the density and mass of different constituents were taken into account. Many other works about biological growth have been presented in recent years, see e.g. Imatani and Maugin (2002), Garikipati et al. (2004), Gleason and Humphrey (2004), Menzel (2004), Amar et al. (2005), Ganghoffer et al. (2005), Ateshian (2007), Goriely et al. (2007), Kuhl et al. (2007), Ganghoffer (2010a), Ganghoffer (2010b) and Goktepe et al. (2010). Morphogenesis is associated to changes in the structure shape (Taber, 1995; Taber, 2009) while remodeling denotes changes in the tissue microstructure via the reorganization of the existing constituents or the synthesis of new ones with negligible volume change. All these processes involve changes in material properties. Although remodeling and growth can, and usually do, occur simultaneously, there are some cases where these processes develop in a decoupled way. For example, Stopak and Harris (1982) reported some experimental results showing remodeling driven by fibroblasts, with no volume growth. We will assume this scenario in this contribution, focusing exclusively on remodeling processes and on the reorientation of fibered biological structures.

It is well known that biological tissue remodels itself when driven by a given stimulus, e.g. mechanical loads such as an increase in

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blood pressure, or changes in the chemical environment that control the signaling processes and the overall evolution of the tissue. Biological remodeling can occur in any kind of biological tissue. In particular, the study of collagen as the most important substance to be remodeled, in all its types (preferentially Type I and III), has attracted considerable attention in recent years (Kuhl et al., 2005; Driessen et al., 2008; Machyshyn et al., 2010a; Machyshyn et al., 2010b). Collagen is considered the main bearing structure in many tissues, such as ligaments, tendons, arteries, etc. Collagen molecules are made up of three chains (α-chains) coiled up in a helical-like structure. These molecules join in the extracellular matrix, creating collagen fibrils that are again assembled into larger collagen fibers (see e.g. the work of Fung (1990) for a general overview). The reorientation of this kind of structure can be assumed to be the consequence of the reorientation of the fibrils or filaments that make them up. This phenomenon leads to changes in the micro-structural orientation and fiber shape due to the reorientation of the fibrils (see e.g. Stopak and Harris (1982) and Sander et al. (2009)). Several remodeling models have been proposed in recent years. Some of them analyze the reorientation of unidimensional fibers driven by different stimuli such as Menzel (2007) or Karsaj et al. (2009). Garikipati et al. (2006) presented an elegant energetic study of the remodeling problem from a thermodynamic point of view. Narayanan et al. (2010) presented a study dealing with the energy rates in growing tumors.

Another important biological structure able to remodel itself is the cell cytoskeleton. The cytoskeleton is composed of microtubules, microfilaments and a network of actin filaments, among many other elements (see e.g the review of Mofrad and Kamm (2006) and references therein for details). Cells move and reorient their inner structure depending on the stiffness and strain of the substrate (Discher et al., 2005; De et al., 2007). The cytoskeleton shape can change by means of the adaptation of the microtubules and filaments in response to a specific external mechano-chemical stimulus (Saez et al., 2005; De et al., 2008). There are several experimental tests reported in the literature showing morphological changes in cells, resulting from mechanical stimulation of the matrix where the cells are located. There are two main procedures which induce morphological changes in cells, static and cyclic loading (De et al., 2007, 2008; Goli-Malekabadi et al., 2011). While static and low-frequency loading lead to reorientation and remodeling of the cellular structure parallel to the stretching direction (Collinsworth et al., 2000; Bischofs et al., 2003), cells in high-frequency cyclic tests align perpendicular to the loading direction. (Hayakawa et al., 2001; Jungbauer et al., 2008; Hsu et al., 2009; Faust et al., 2011; Chen et al., 2012). In the case of a high-frequency stimulus, the mechanosensing elements, the focal adhesions, are not able to follow such a quick changes and neither stress fibers nor miosin motors get activated. However, in static and low-frequency load states, focal adhesions react to such changes by means of an active internal tension of the stress fibers leading to changes in their morphology. These experimental results are characterized by a gradual reorientation of the principal direction of the cell followed by a progressive remodeling of the micro-structure leading to a narrower shape, see e.g. the experimental work of Dai et al. (2004) and the references therein. In Fig. 1 we show some results presented by Hayakawa et al. (2001) illustrating this behavior. In many cases this change of shape, unlike changes in orientation, is measured only by a shape-index (Levesque et al., 1986; Galbraith et al., 1998; Farcas et al., 2009). The underlying biological processes, such as the dynamics of focal adhesions or the tension exerted by molecular motors over actin stress fibers are much more complex (see e.g. Mofrad and Kamm (2006) for an overall understanding of cell behavior). There are not many works describing these features of the inner structure. In terms of the orientation of the preferential direction of the cell, some of the most widely accepted models are those presented in De et al. (2007, 2008). The reorientation is assumed to be controlled by the matrix behavior and the forces that arise from the active regulation of the cell in a dipole-like manner. In terms of modeling changes in cell morphology due to external stimuli, there are few models described in the literature, see e.g. Levesque et al. (1986), Ingber (2003), Ohashi et al. (2005).

Introducing multi-scale techniques is a straightforward approach to take into account underlying evolving processes. The works of Ingber (2008) about tensegrity models of cell structures is a good example in the field of cell mechanics. Miehe et al. (2004) performed a microsphere-based approach to study the microstructural behavior of polymers. Later, Caner et al. (2006) applied this approach, also known as microplane, to vascular tissue. Microplane models were first used by Bazant and Oh (1985), Kuhl et al. (2000) and Carol et al. (2004), among others, for studying the failure and plasticity of brittle materials, and they were later extended to other fields. Alastrué et al. (2009a) used this approximation to model vascular tissue including anisotropy. To gain a deeper insight into the underlying changes in the microstructure, some authors have included information about the dispersion around the main orientation direction by using several statistical distributions. The von Mises distribution was introduced by Gasser et al. (2006) in the vascular framework to account for dispersion. Later Alastrué et al. (2010) used a Bingham distribution function (Bingham, 1974) to include the dispersion of the bundles and presented a comparison of these two statistical functions. In this context, some works (Menzel, 2007; Kroon, 2010; Grytz et al., 2010) have included these statistical functions to account for remodeling. In multiscale homogenization schemes the macroscopic behavior is recovered by averaging the microstructural behavior represented, in the case of biological fibered tissue, by the mechanics of the fibrils or filaments. Previous authors (Alastrué et al., 2010) have used exponential-type models, such as that proposed by Holzapfel et al. (2000). Recently Menzel et al. (2009) presented a microsphere-based approach for remodeling, where the fibrils behavior was modeled by the Worm-like Chain model (WLC). WLC models have been extensively used for analyzing the behavior of the DNA double helix (see e.g. Bustamante et al., 2003) and by Arruda et al. (1993) and Kuhl et al. (2005) to simulate elastomer and soft tissue respectively. Arruda et al. (1993) introduced this model in a non-affine isotropic eight chain model that has also been used by Bischoff et al. (2002). Garikipati et al. (2004) and Kuhl et al. (2005) extended it to anisotropic behavior. Alastrué et al. (2009a) and Alastrué et al. (2010) presented a comparison of both fibril models (exponential and WLC) in a microsphere-based approach. Note that along with the classical point of view of space orientations for microsphere-based models, we also associate the orientations to a physical orientation space of micro-structural elements, e.g., collagen fibrils in collagen bundles or microtubules and actin filaments in cells.

In short, we present a new remodeling model in 3D taking into account the reorientation of the mean direction of a given fibered structure and the reorientation of the individual fibrils or filaments leading to changes in the parameters of the associated probability orientation density function. In Section 2 we begin by discussing the material model used and in particular the WLC model adopted for each fibril. Later in this section, we present the Bingham statistical distribution, its main properties and general shape. We make use of the microsphere-based approach as a homogenization technique to move from the micro to themacro-scale as described in the last part of Section 2. In Section 3, the evolution equations for remodeling are presented. We continue in Section 4 with the thermodynamical formulation of the problem obtaining the expression for the dissipation. The particularization of the model for the biological case is addressed in Section 5. In Section 6 we