

## Non-linear micromechanics of soft tissues

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### ABSTRACT

Microstructure-based constitutive models have been adopted in recent studies of non-linear mechanical properties of biological soft tissues. These models provide more accurate predictions of the overall mechanical responses of tissues than phenomenological approaches. Based on standard approximations in non-linear mechanics, we classified the microstructural models into three categories: (1) uniform-field models with solid-like matrix, (2) uniform-field models with fluid-like matrix, and (3) second-order estimate models. The first two categories assume affine deformation field where the deformation of microstructure is the same as that of the tissue, regardless of material heterogeneities; i.e., they represent the upper bounds of the exact effective strain energy and stress of soft tissues. In addition, the first type is not purely structurally motivated and hence cannot accurately predict the microscopic mechanical behaviors of soft tissues. The third category considers realistic geometrical features, material properties of microstructure and interactions among them and allows for flexible deformation in each constituent. The uniform-field model with fluid-like matrix and the second-order estimate model are microstructure-based, and can be applied to different tissues based on micro-structural features.

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### 1. Introduction

The significance of mechanical stress and strain in biology, physiology and pathology is well recognized. The determination of microstructural stress requires a constitutive model based on the ultrastructure and the corresponding material properties. Complex microstructure and strong non-linear mechanical behaviors of soft tissue, however, present significant challenges in constitutive modeling. Despite the complexity, the current trend in biomechanics is to move from phenomenological to micromechanical models in order to predict the overall non-linear and microstructural responses of inhomogeneous soft tissues. New developments in imaging and biochemistry will continue to provide more details of the constitutive properties of soft tissues, and continue to advance the development of structure-based models.

This review introduces non-linear structural models of soft tissues including their utility and limitations. A finite strain micromechanics is introduced, and two homogenization methods (upper bound and SOE approach) are provided. Three types of microstructure-based models of soft tissues are compared in relation to their assumptions and micromechanical basis; i.e., (1) uniform-field models with solid-like matrix, (2) uniform-field

models with fluid-like matrix, and (3) second-order estimate models.

#### 1.1. Ultrastructure of soft tissues

Biological soft tissues are primarily composed of collagen and elastin fibers, ground substance (GS), and cells. The physiological function of each soft tissue necessitates certain degree of structural anisotropy, which is generally realized by variable arrangements of the functional components. Specifically, fibers can have variable densities and topologies such as orientation, length, width, and degree of undulation. For example, tendon has a uniaxial structure with parallel wavy fibers formed by Type I collagen fibrils [1]. Blood vessels, on the other hand, have three layers (i.e., intima, media, and adventitia) from the lumen to the external surface whose mechanical properties are differentiated by the respective arrangement of collagen and elastin fibers, and cells.

As a primary functional component of soft tissues, collagen fibrils are assemblies of subfibrils of about 30 nm diameter, each consisting of microfibrils packed in a tetragonal lattice. The diameter of collagen fibrils ranges from 50 to 500 nm, depending on tissue type and the age of the animal [1], and these fibrils typically run parallel and gather in large collagen bundles [2,3]. Morphological observations show that collagen fibers have undulated structure and mainly arrange in plane with preferred orientations, which results in anisotropic properties of tendon, ligament, and blood vessels (collagen in blood vessel is shown in

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Fig. 1a) [4,5]. Collagen bundles have also been found to run in all directions and form a two-dimensional isotropic network in small intestine [2]. The degree of collagen undulation (waviness) is different in soft tissues; e.g., it is very small in tendon (almost straight), larger in the skin and even larger in the mesentery [6]. At lower macroscopic stretch of the tissue, the undulated collagen fibers contribute little or no effect to the mechanical response. As the macroscopic stretch increases, collagen bundles become straightened gradually and eventually bear most of the load to render a highly non-linear stress–strain relationship [2,7]. It is noted that uncoiled collagen fibrils have a Young's modulus of the order of 0.1–1.0 GPa along the fibril direction, whereas the Young's modulus of elastin is of the order of 100 kPa [8–10].

Elastin fibers are straight rod-like fibrils composed of a central core surrounded by microfibrils with a 10 nm diameter [11]. The arrangement of elastin varies among soft tissues. Elastin fibers distribute relatively randomly and form a net-like structure in coronary arteries [2] (Fig. 1b), but uniformly and preferentially orient with collagen fibers in articular cartilages [12]. Moreover, there are abundant elastin fibers in aortic tissue (more than 40% by dry weight), while tendon contains few elastin fibers (less than 3% by dry weight) [13]. Experimental observations show that elastin fibers gradually extend to take up the load together with cells and GS at very low strain levels [2,7], where the stress–strain behavior of the whole tissue exhibits only weak non-linearity.

The non-fibrous components of soft tissues are GS and cells. GS is an amorphous gel-like structure that mainly contains glycosaminoglycans, proteoglycans and glycoproteins [14,15]. These hydrophilic macromolecules create water-filled compartments that maintain turgor pressures within tissues. In addition, proteoglycans strongly interact with fibers and cells by forming interfibrillar bridges [16,17]. Enzymatic degradation of tissues (specific to GS) shows that the gel-like GS has very low resistance to shear stress and thus has little effect on the mechanical response of tendon, skin and aorta [18,19]. Fibroblasts are the most common cells found in soft tissues, which synthesize and secrete extracellular matrix (ECM, denoting fibers and GS here) and play an important role in healing wounds [20,21]. Smooth muscle cells (SMCs), on the other hand, are only found in vasoactive tissue, such as blood vessel, lymphatic vessel and urinary bladder, where the structure and function of SMC is basically the same. Some studies have shown that cells (fibroblasts and SMCs) have negligible effects on passive mechanical behaviors of tissues [7,22–24]. Other studies, however, suggest that SMCs have a significant role in transmitting stresses through serial connections with collagen fibers [25–28]. The degree of mechanical contribution of SMCs has not been well established, and future studies are needed to resolve this controversy.

The above studies suggest that the mechanical properties of soft tissues largely stem from the microstructural components, and their arrangements determine the functional properties of the resulting structure. Based on these findings, structurally motivated models have become popular [29–34], with the early seminal work of Lanir [5,6].

## 1.2. Non-linear micromechanics of heterogeneous materials

The idea of homogenization of heterogeneous non-biological materials has been proposed for quite some time to predict the macroscopic or effective mechanical properties of composites [35]. Rigorous and reliable methods have been well established and widely applied to linear elastic composites in academia research and industry, including the classical Voigt and Reuss bounds [36], the variational principles of Hashin–Shtrikman [37,38], and the general self-consistent approximations [39,40]. For non-linear composites, however, rigorous methods have become available

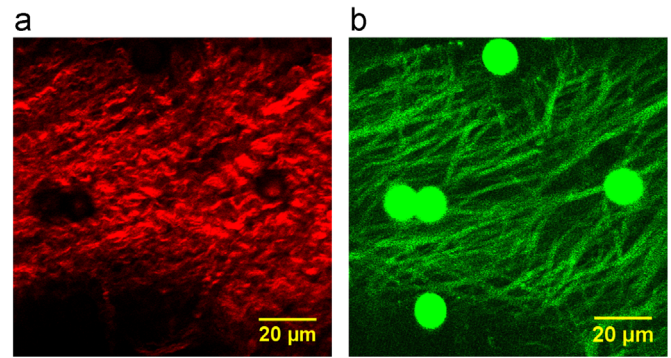


Fig. 1. Morphometry of collagen and elastin fibers of coronary artery adventitia: (a) Paralleled collagen fibers collected in SHG image; (b) Net-like elastin fibers collected in TPEF image. The Figure is reproduced from Ref. [4].

only recently because of difficulties in addressing both strong material non-linearity and heterogeneity. Earlier efforts were made to predict the effective constitutive behaviors of composites by extending linear methods to non-linear materials, such as the extensions of the self-consistent procedures [41], or the Hashin–Shtrikman variational principles for linear composites [42,43].

A general variational procedure for estimating the effective behavior of non-linear composites was proposed by Ponte Castañeda [44]. He introduced a “linear elastic comparison composite” (LCC) with the same microstructure of the non-linear composite, which allows for the use of numerous bounds and estimates for linear composites. Ponte Castañeda further proposed an alternative approach with more sophisticated LCC to generate estimates that are exact to the second-order in the phase contrast [45,46]. This is the so-called second-order estimate (SOE) homogenization, which yields significant improvements over previous micromechanics models. During the past decade, successive developments have been made to the SOE approach by Ponte Castañeda and his colleagues to better predict the non-linear macroscopic properties of heterogeneous materials [29,47–53]. Applications have been extended to various non-linear materials with randomly or periodically distributed microstructure, including viscoplastic polycrystal, porous or reinforced rubbers and fiber-reinforced elastomers. Moreover, the SOE model was recently applied to biological fibrous tissue by Chen et al. [29], to describe the micro- and macroscopic mechanical behaviors of soft tissues.

## 2. Framework of non-linear micromechanics

Finite strain micromechanics can be used to determine the macroscopic constitutive response of biological soft tissues based on structural and mechanical properties of microstructure. Based on the principle of minimum strain energy, the framework can provide multiple approximate solutions for macroscopic strain energy function (SEF) of soft tissues. An “upper bound” and a “second-order” estimate models are discussed below.

### 2.1. Hyperelastic heterogeneous material

A heterogeneous material, such as soft tissue, is made up of  $N+1$  ( $N \geq 1$ ) different phases, which are distributed (randomly or with a certain distribution of orientation or dimension) in a specimen with a volume  $\Omega$  and boundary  $\partial\Omega$  in the reference configuration. The constitutive behavior of each inclusion is characterized by a respective SEF  $W^{(r)}(\mathbf{F})$ , so that the local SEF  $W(\mathbf{X}, \mathbf{F})$  of composites is written as:

$$W(\mathbf{X}, \mathbf{F}) = \sum_{r=0}^N \chi^{(r)}(\mathbf{X}) W^{(r)}(\mathbf{F}), \quad (1)$$

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