Acta Biomaterialia xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Fatigue of soft fibrous tissues: Multi-scale mechanics and constitutive modeling

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ARTICLE INFO

Article history:
Received 21 November 2017
Received in revised form 21 February 2018
Accepted 5 March 2018
Available online xxxx

Keywords:
Multi-scale modeling
Soft fibrous tissues
Fatigue

ABSTRACT

In recent experimental studies a possible damage mechanism of collagenous tissues mainly caused by fatigue was disclosed. In this contribution, a multi-scale constitutive model ranging from the tropocollagen (TC) molecule level up to bundles of collagen fibers is proposed and utilized to predict the elastic and inelastic long-term tissue response. Material failure of collagen fibrils is elucidated by a permanent opening of the triple helical collagen molecule conformation, triggered either by overstretching or reaction kinetics of non-covalent bonds. This kinetics is described within a probabilistic framework of adhesive detachments of molecular linkages providing collagen fiber integrity. Both intramolecular and interfibrillar linkages are considered. The final constitutive equations are validated against recent experimental data available in literature for both uniaxial tension to failure and the evolution of fatigue in subsequent loading cycles. All material parameters of the proposed model have a clear physical interpretation.

Statement of significance

Irreversible changes take place at different length scales of soft fibrous tissues under supra-physiological loading and alter their macroscopic mechanical properties. Understanding the evolution of those histologic pathologies under loading and incorporating them into a continuum mechanical framework appears to be crucial in order to predict long-term evolution of various diseases and to support the development of tissue engineering.

1. Introduction

The last two decades came along with significantly increasing attention to the continuum biomechanics of growth and remodeling of soft tissues, necessary e.g. to describe the continuing enlargement of aneurysms [13]. Along with growth and remodeling effects, such modeling techniques require the proper description of cell turnover, in turn, to account for the description of e.g. dilatation due to aging or hypertension. It has been observed that the collagen half-life decreases from 60–70 days down to 16 days due to hypertension [62]. So far, the research has only focused on phenomenological descriptions of collagen turnover (e.g. [25,13]) without any microstructural reasoning. Only few studies have addressed the issue of long-term fatigue modeling of soft fibrous tissues [56,57]. Despite the ability of the proposed models to capture the fatigue enforced stress reduction, the link between damage factors and the histology has not been revealed. Furthermore, tendon injuries are a common issue in modern medicine [53,80] and their purposive treatment is of high importance especially for athletes and the elder generation. It is well known that tendons without pathological findings are less prone to rupture and tendon injuries are mostly accompanied by a changed histology [53,43]. Hence, predictions by a histologically based material model can further strengthen the scientific basis towards better understanding of the long term behavior of soft fibrous tissues as well as the etiology of tendon diseases. Moreover, patient-specific biomechanics has attracted considerable interest, and enormous effort has been dedicated towards understanding of fibrous tissues mechanics. Experimental procedures reported in literature are ranging from macromolecular tests by applying e.g optical/magnetical tweezers or Atomic force microscopy (AFM) to estimate the force-extension behavior [70,29] up to the measurement of collagen fiber dispersion

Abbrevations: CP, Core protein; ECM, Extracellular matrix; (e)WLC, (extensible) worm-like chain; GAG, Glycosaminoglycan; PG, Proteoglycan; IFM, Interfibrillar matrix; SDF, Small diameter fibril; TC, Tropocollagen.

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https://doi.org/10.1016/j.actbio.2018.03.010
1742-7061/

by (polarized) light microscopy in whole tissues/organs (e.g. [26,18]). These procedures deliver valuable input for a multi-scale based constitutive model. Indeed, biological tissues are very patient-specific in their mechanical properties due to their varying micro-structural parameters. For example, their stress response can vary between different individuals by an order of magnitude [38]. Hence, the material model proposed in the present paper aims to incorporate structural and mechanical information at different length-scales accessible by minimal-invasive testing.

Due to the complex hierarchical arrangement of tendon tissue and its main constituent, collagen, the damage progression of the biofilament network represents a versatile interplay between different length scales. Histological changes may be triggered by either biochemical or mechanobiological sources. The latter ones are often related to a dynamic loading of the tissue and mostly involve a high number of loading cycles. Recent experimental investigations under cyclic loading protocols indicate that tendon fatigue is a local damage accumulation on the micro-level, which starts even under physiological loading conditions [23,22,90]. The main underlying damage mechanism is considered to be a permanent opening of the triple helical collagen molecules, which leads to irreversible kinking of collagen fibrils and widening of the interfiber space under long-term loading [21,87]. This mechanism was further experimentally confirmed by utilizing hybridizing peptide, which binds to unfolded TCs, while applying a mechanical overload on rat tail tendon [93]. While the fibrillar damage mainly takes places at high fatigue stages, early fatigue was observed to correlate with an irreversible damage of the interfibrillar matrix (IFM) [83,47]. This was detected by a reduction of interfibrillar sliding, which can be quantified by a debonding between small diameter fibrils (SDFs) and proteoglycans (PGs) surrounding collagen fibrils [83,47,84].

In summary, tendon evolves under cyclic loading as follows. At the low fatigue phase, uncrimping of the collagen fiber network starts due to interfibrillar damage and results in a stiffer loading response, while during the moderate fatigue phase local fiber angulations initiate. Finally, the high fatigue phase is characterized by rupturing of whole collagen fiber layers and ends up with the complete tendon failure [21–23,36,47].

Although, many aspects of tendon fatigue have already been discussed from the experimental point of view [65,67,92,77,76,79], there is still a lack of an integrated material model capturing the alteration from the physiological to the pathological state, while linking them to the tendon histology. To the best of our knowledge, such a fatigue model for soft fibrous tissues has not so far been addressed. Thus, the present work aims to close this gap by introducing a multi-scale constitutive model including damage formulation in accordance with recent experimental findings [87,21,36]. In particular, the model captures irreversible damage of the IFM and the fibrillar structures by a force-time coupled criterion. Finally, this allows to predict long term damage accumulation even under physiological loads. The paper is organized as follows. In Section 2 we discuss mechanics of soft fibrous tissues and present the fatigue model. Predictions of the model are compared against various experimental data and possibilities of the parameter identification are discussed in detail in Section 3.

2. Mechanics of collagen fibers

As mentioned above mechanical properties of soft fibrous tissues result mainly from their complex hierarchical organization. Accordingly, in the following we briefly summarize the hierarchical structure of collagen. With this in mind, the constitutive equations are formulated first for the elastic case in Section 2.3. In Section 2.4 the constitutive equations are further enhanced to inelasticity to take into account the damage evolution due to fatigue mentioned above.

2.1. Hierarchical structure and mechanics of collagen

Tropocollagen is a triple helical arrangement of three coiled collagen-protein chains (see Fig. 1). The chains are bonded together by weak hydrogen bonds. With a D-banding pattern TC molecules are assembled to their higher order-structure referred to as collagen fibrils [42].

The TCs are attached to each other at their tips by covalent cross-linkers which provide intermolecular integrity [7]. In the periodical packing of collagen fibrils there are molecular gaps with the highest molecular disorder [19]. A single collagen fiber is organized by a number of collagen fibrils and embedded into the IFM. The IFM, in turn, consists of small diameter fibrils (SDFs) wrapping bigger diameter fibrils and a large amount of proteoglycans (PGs) [84]. Due to the high negative fixed charge density, the PGs osmot-

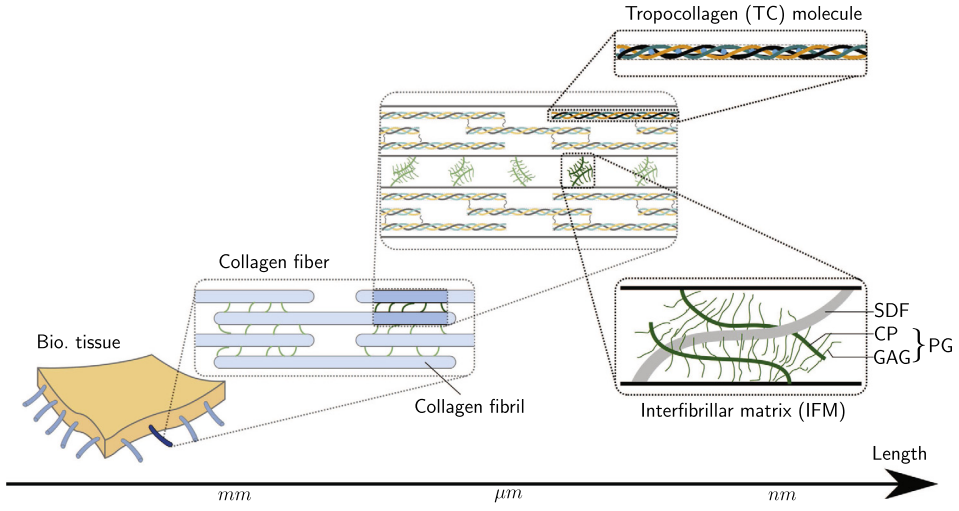

Fig. 1. Multi-scale representation of soft fibrous tissues starting on the meso level with the ground substance reinforced by collagen fibers. A collagen fiber is seen on the micro-level as a composition of collagen fibrils embedded in the interfibrillar materix, in turn, consisting of proteoglycans (PGs) and small diameter fibrils (SDFs). The PGs consist of a core protein (CP) to which one or more GAG side chains are covalently bonded. The fibrils theirself are D-periodically assembled by tropocollagen molecules.

Please cite this article in press as: K. Linka et al., Fatigue of soft fibrous tissues: Multi-scale mechanics and constitutive modeling, Acta Biomater. (2018), https://doi.org/10.1016/j.actbio.2018.03.010