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Biomechanical modeling the adaptation of soft biological tissue

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External (mechanical) stimuli influence cell function at the level of gene expression and thereby contribute to the overall control of Soft Biological Tissues' (SBT) structure and function. SBT seem to adapt towards stable homeostatic mechanical conditions, and failure of reaching homeostasis may result in pathologies. SBT adaptation has to obey basic physical principles, and even within these constraints, a large number of SBT adaptation models have been proposed. Recent SBT models integrated the tissue's microstructure and directly addressed length scales of individual tissue constituents, which in turn allowed linking biomechanical and biochemical adaptation aspects. Despite adaptation models being based on very different hypotheses, many of them lead to physically reasonable results. Most interestingly, the recently developed homogenized Constrained Mixture Model reported very similar predictions than the original Constrained Mixture Model. This key observation indicates that the simpler kinematics-based approach is indeed able to capture the overall consequences of the continuous production and degradation of SBT constituents. However, mainly due to the scarcity of relevant experiment data, not a single model has been thoroughly validated against clearly specified modeling objectives. Consequently, much more interdisciplinary experimental work is required to guide SBT modeling activities. Nevertheless, predictive biomechanical SBT adaption models would not only be of considerable scientific interest, but would also have a large number of practical applications.

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Introduction

Modeling Soft Biological Tissues (SBT) adaptation may advance our understanding of the physiological and pathological mechanisms of organs, interaction between medical devices and biological material, drug delivery pathways, the interplay between structure and function of tissues and their mechanotransduction mechanisms. Whilst traditional mechanics concepts are directly applicable to solve such biomechanics problems, the inherent property of SBT to adapt to mechanical and biochemical environments, remains a challenging modeling task. Through chemo-mechanotransduction mechanisms, external stimuli influence cell function at the level of gene expression and thereby contribute to the overall control of SBT structure and function. Normal and pathological tissue adaptations can occur through a wide range of mechanisms, including, Smooth Muscle Cell (SMC) activation/relaxation, cell proliferation or apoptosis, pattern formation and synthesis and/or degradation of extracellular matrix (ECM).

While cells in SBT sense and respond to mechanical loads, the ECM is the main load-carrying component that equips the tissue with properties such as elasticity, stiffness, strength, ductility. Most importantly, the ECM is a mechanical structure that controls SBT's micro-mechanical and macro-mechanical environments, and serves as a channel for transmission of mechanical stimuli to the cells. Consequently, the 3D organization of ECM constituents is vital for proper physiological SBT function.

In most SBT, biomechanical characteristics are predominantly determined by the ECM proteins collagen and elastin. Collagen provides the tissue with stiffness, strength and toughness, and is continuously turned over. The maintenance of the collagen structure relies on a delicate (coupled) balance between degradation, mainly through Matrix MetalloProteinases (MMPs), and synthesis by cells like SMCs, fibroblasts and myofibroblasts, [49]. Such cells are anchored to collagen fibers and respond to mechanical strain or stress by adjusting their expression and synthesis of collagen molecules [8,23]. Mechanical stimulus not only promotes collagen synthesis [39], but also protects from collagen degradation [6,48].

Elastin functions in partnership with collagen, and endows SBT with elasticity. Elastin synthesis normally

ceases soon after puberty once the body reaches maturity. Elastin is extremely insoluble and stable with half-life times in the order of tens of years [1]. However, elastin may be degraded by selective MMPs, a process important for many physiological processes like elastogenesis and repair [64].

When exposed to physiological conditions, SBT seem to adjust towards optimal mechanical performance [54], i.e. they adapt towards stable homeostatic mechanical conditions. Following this principle, many SBT models assume homeostasis-driven adaptation, in which cells grow and/or modify tissue properties and/or geometry to achieve a target tissue stress or strain level. Failure of reaching homeostasis, i.e. unbalanced and irreversible tissue adaption can lead to the formation of pathologic tissues such as fibrosis, atrophy, inward and outward vessel remodeling, etc.

Apart from SBT adaptation being relevant for biomechanics studies involving time frames of tissue mass turnover, it also has many other biomechanics-related implications. For example, a direct consequence of SBT adaptation is the existence of residual stresses in load-free configurations of many organs [62]. Neglecting such residual stresses is a severe limitation of many passive soft tissue biomechanics studies leading to unrealistic stress predictions at physiological loading conditions.

Several excellent texts already cover SBT adaptation [3,12,30,31,36,46]. The present mini review aims to provide an update on biomechanics modeling aspects.

Modeling frameworks

SBT are at a state of continuous mass turnover, which causes growth and remodeling at a local tissue level. Specifically, growth changes the material's stress-free configuration, while remodeling alters the material's mechanical properties through modifying its internal structure. SBT growth and remodeling alter the geometry of organs and by that determine their morphogenesis. Mass turn over (or its implications) may either be modeled at the macroscopic length-scale (tissue level), or at the length-scale of tissue constituents like collagen, elastin, SMC, etc.

This review groups the different frameworks into 'Kinematics-based adaptation theory', 'Constrained Mixture Model-based adaptation theory' and 'Other adaption theories'. Details regarding these concepts, together with earlier works in the field, are presented in Appendix A, whereas the latest developments are discussed in the following sections. In addition, Appendix B introduces the general modeling concepts and terminology.

Kinematics-based adaptation theory

Multiplicative kinematics-based formulations postulate that growth-related and non-growth-related SBT deformation can be separated. The kinematics split directly leads to separate constitutive descriptions for growth-related and non-growth-related SBT deformations. Recently one established kinematics-based adaptation model [65] has been further developed [4] by coupling it to signaling path-ways of collagen synthesis and degradation [14]. The model aims at capturing AAAs and considered separate mechanisms in medial and adventitial vessel wall layers. In the media, a prescribed level of immune cells mediates elastase and collagenase, i.e. influences collagen mass and elastin mass in the wall. In the adventitia, fibroblasts mediate the production of procollagen, zymogen, and Tissue Inhibitors of MetalloProteinases (TIMP), each of which influences the collagen mass in the adventitia. On top of that, fibroblasts also produce latent and active Transforming Growth Factor (TFG)-β. The amount of constituents, cells and chemicals is governed by numerous Ordinary Differential Equations (ODE), and the chemo-mechanical coupling is facilitated through the strain-mediated production of latent TFG-β, as well as its activation. At the mechanical side, the model [4] mainly followed its original concept [65], but also introduced a triangular Probability Density Function (PDF) for the collagen attachment stretch distribution, i.e. a concept that has been proposed earlier [45]. Despite many modeling assumptions are based on qualitative information, the model [4] is a successful attempt of integrating chemical and mechanical knowledge, and could be a major step towards better understand SBT adaptation.

Like the original model [65], also the revision [4] described the vascular wall as a membrane, which, together with the rate-based description of the collagen engagement stretch, effectively bypassed the task of specifying the intermediate configuration, i.e the deformation gradient $\mathbf{G}(\tau)$, see Appendix A. However, when generalizing such approaches to volume-based descriptions, one has to specify how added tissue mass (volume) is translated into the increment $\Delta\mathbf{G}$ of growth-related deformation. A recent study [24] demonstrated that such specification has severe influences on model predictions and can even lead to highly non-reasonable results.

Another recent SBT adaptation model [38] is based on the general theory of fibrous connective tissue [37], and considers elastin, collagen and cells embedded in a fluid ground substance. The model is based on a large number of well-documented experimental observations; many of them provide qualitative information though. In addition to modeling suggestions made earlier, the model has several novel features to it. It suggests a strain-based stimulus of turnover for tissue constituents at a fixed