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Gerhard Sommer
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Raymond W. Ogden *Editors*

Solid (Bio)mechanics: Challenges of the Next Decade

A Book Dedicated to Professor Gerhard A. Holzapfel

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To Gerhard A. Holzapfel on the occasion of his 60th birthday

Photo by Lunghammer—TU Graz

Preface

Biomechanics is a challenging subject that studies living systems through the development, extension, and application of mechanics to better understand biological and medical phenomena. Nonlinear continuum mechanics, multiscale modeling, advanced 3D imaging techniques along with unprecedented predictive computational power enable us to solve cutting-edge biomechanical problems nowadays with rather complex patient-specific anatomies. Interdisciplinary approaches that address phenomena at the nano, micro-, or macro-levels are often required to solve such problems. Mechanics, natural sciences such as biophysics, biochemistry, and mathematics, as well as biomedical, tissue, healthcare, computer, and biomolecular engineering sciences must be combined with medicine to tackle real-life problems.

Professor Gerhard A. Holzapfel has been an international leader in the field of biomechanics for at least the past two decades through scientific contributions, editorships, conference organization, mentoring, and doctoral training. He is widely known for his outstanding contributions in the field of nonlinear solid (bio)mechanics and the constitutive and computational modeling of fiber-reinforced materials and soft biological tissues. Professor Holzapfel has dealt intensively with the cardiovascular system in health and disease such as aneurysm and aortic dissection, and with therapeutic interventions such as balloon angioplasty and stenting, the development of continuum theories, computational methods, and simulations and experiments in biomechanics and mechanobiology of soft biological materials. This book on *Solid (Bio)mechanics: Challenges of the Next Decade* is dedicated to Professor Gerhard A. Holzapfel on the occasion of his 60th birthday and his eminent career achievements.

Professor Gerhard A. Holzapfel received his master's degree in civil engineering in 1985 and obtained his PhD in mechanical engineering from Graz University of Technology (TU Graz) in 1990. In 1991, he traveled to Shenyang in the northeast of the People's Republic of China to work as a visiting scholar at an institution that is currently part of Shenyang University. He then received a Schrödinger Scholarship from the Austrian Science Fund to work as a post-doctoral fellow at the Division of Applied Mechanics, Department of Mechanical Engineering, Stanford University, CA, USA, with the late Professor Juan C. Simo from 1993 to 1995. He completed his habilitation in mechanics at Vienna University of Technology, Austria, in 1996.

From May 1987 to November 2004, he was an assistant at the Institute of Strength of Materials and Associate Professor at the Institute of Structural Analysis, TU Graz, Austria. He was Professor of Biomechanics at KTH Royal Institute of Technology in Stockholm, Sweden for 9 years (7 years as Adjunct Professor) until 2013. Since 2007, he has been a Full Professor of biomechanics and the head of the institute at TU Graz. He is also the International Chair of Biomechanics (adjunct professorship) at the Norwegian University of Science and Technology (NTNU) in Trondheim and Visiting Professor at the School of Mathematics and Statistics, University of Glasgow, Scotland.

Professor Holzapfel has authored a well-known graduate textbook entitled *Nonlinear Solid Mechanics. A Continuum Approach for Engineering'* (John Wiley & Sons), and he co-edited seven books and five special issues in journals. He contributed chapters to 25 other books, published 230+ peer-reviewed journal articles, 65+ conference proceedings (full papers), and contributed 490+ oral or poster presentations to several conferences all over the world. He is the co-founder and co-editor-in-chief of the international scientific journal *Biomechanics and Modeling in Mechanobiology* (Springer Nature) since the first issue published in June 2002. He supervised 2 habilitation theses, 18 post-doctoral fellows, and 30 doctoral students.

He received many awards and honors, such as the Schrödinger Scholarship for post-doctoral training at Stanford University (1993–1994), the Austrian Start-Prize 1997 from the Austrian Science Fund, the highest Austrian award for young scientists, the Josef-Krainer Würdigungspreis 2003 for exceptional achievements in the field of biomechanics, and the Erwin Schrödinger Prize 2011 from the Austrian Academy of Sciences for lifetime achievements by Austrians in the fields of mathematics and natural sciences. He has been listed as a Highly Cited Researcher in Engineering selected by ISI Web of Science, Thomson Reuters and listed as *The World's Most Influential Scientific Minds: 2014*. He is a Founding Fellow of EAMBES (2012), the European Alliance for Medical and Biological Engineering & Science, and he was elected as a corresponding member of the Austrian Academy of Sciences (2012), a member of the Academia Europaea (2014), a fellow of the European Mechanics Society (2015), a member of the World Council on Biomechanics (2018), and an ordinary member of the European Academy of Sciences and Arts (2019). It is noteworthy that, in 2021, he received the William Prager Medal of the Society of Engineering Science (USA) and the Warner T. Koiter Medal of the American Society of Mechanical Engineers (USA).

This book provides a comprehensive and timely overview of the latest developments in the field of biomechanics and extensive knowledge of tissue structure, function, and modeling. It contains 19 chapters, each of which begins with a personal dedication to Professor Holzapfel. We hope that the book is useful not only for those working as a graduate student, researcher, and (bio)engineer in the challenging field of biomechanics, but also for those in other fields such as biomedical engineering, biophysics, mechanical engineering, materials science, applied mathematics, and medicine.

We have invited some of the most prominent scientists within Professor Holzapfel's research fields to contribute to this book with their latest research results.

This book includes some state-of-the-art advances such as constitutive modeling and computational simulation of biological tissues under physiological and pathological conditions, and mechanical characterization of a range of biological tissues for purposes such as computational simulation and surgical planning. It covers innovative and cutting-edge studies of cardiovascular tissues such as arteries, heart, valvular tissue, but also on other tissues and organs such as thrombus, brain tumor, muscle, liver, kidney, and stomach, to name a few. It also highlights some of the biggest challenges biomechanics will face over the next decade and how we can better prepare for them.

Without the considerable effort and support of all authors, this book would not exist. We would like to express our sincere gratitude to everyone who contributed to this book. Finally, we would like to thank Dr. Leontina Di Cecco, Senior Editor of Applied Sciences and Engineering, and her publishing team at Springer for their support and encouragement in publishing this book.

Graz, Austria — Gerhard Sommer
New York, USA — Kewei Li
Graz, Austria — Daniel Ch. Haspinger
Glasgow, Scotland — Raymond W. Ogden
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Contents

About the Editors

Asst.Prof. Gerhard Sommer finished his Master's Thesis at Graz University of Technology (TUG) in the field of soft tissue biomechanics under the supervision of Christian A.J. Schulze-Bauer and Gerhard A. Holzapfel in 2003. He then began his Ph.D. Thesis in the field of biomechanics supervised by Gerhard A. Holzapfel, where he continued to explore the mechanical properties of human soft tissues, especially of the cardiovascular system. In 2007, together with Gerhard A. Holzapfel, he founded the Institute of Biomechanics at TUG, where he was responsible for setting up the biomechanics laboratory. In October 2008 he completed his Ph.D. From 2013 to 2018 he was Senior Postdoctoral Researcher and became Assistant Professor in 2018. He has published more than 40 articles in international journals and supervised several Master's and Ph.D. students.

Dr. Kewei Li is a Postdoctoral Research Scientist at the Columbia University Irving Medical Center, New York, NY, United States. He earned his Ph.D. in Mechanical Engineering under the supervision of Professor Wei Sun at the University of Connecticut in 2013. After a brief internship at Dassault Systèmes Simulia Corporation, he moved to Austria in 2014 and worked as a (postdoctor) University Assistant at Graz University of Technology with Professors Gerhard A. Holzapfel and Ray W. Ogden. He taught undergraduate and graduate courses in the fields of statics, strength of materials, and computational biomechanics. His research interests include cardiovascular biomechanics, nonlinear elasticity, and finite element analysis. He has published 18 research papers in peer-reviewed journals and has been an Editorial Board member for *Scientific Reports* since 2019.

Dr.techn. Daniel Ch. Haspinger completed his master's and doctoral studies with a strong background in biomechanics at Graz University of Technology, Austria, under the supervision of Prof. Gerhard A. Holzapfel. Working as a teaching and research assistant at the Institute of Biomechanics offered him the rare opportunity to work and learn from some of the world's leading scientists in the field of cardiovascular biomechanics. He has published several peer-reviewed journal articles, presented his research findings at various international scientific conferences, and received the Ing.

F. Schmiedl Award from the City of Graz. His research aims to provide better insights into possible causes and consequences of physiological and pathological adaptation mechanisms in the cardiovascular system from an experimental and computational perspective.

Prof. Raymond W. Ogden A mathematics graduate from Cambridge University. He is George Sinclair Professor of Mathematics at the University of Glasgow. His research interests include nonlinear elasticity theory and its applications to the mechanics of rubberlike materials, soft biological tissues and fibre-reinforced materials. He has published more than 250 papers in international journals, and several books. He is a Fellow of the Royal Society of London and has received numerous awards for his research, including the IUTAM/Elsevier Rodney Hill Prize in Solid Mechanics and the Timoshenko Medal of the American Society of Mechanical Engineers.

Arterial Biomechanics in Health and Disease

Multiscale Experimental Characterization and Computational Modeling of the Human Aorta

Misael Dalbosco, Daniel Ch. Haspinger, Kewei Li, Sae-Il Murtada, Anna Pukaluk, Malte Rolf-Pissarczyk, Selda Sherifova, and Gerhard Sommer

We came to know Professor Gerhard A. Holzapfel at different times from different parts of the world. But we all came to Graz with the same purpose: to learn from the master of biomechanics and to study and work in this thrilling field. Along the way, we have met new colleagues, friends, and also encountered new problems in a completely different cultural environment. Professor Holzapfel himself is aware of such cultural differences and provided us with extraordinary help and guidance beyond the professional level, especially for some of us from afar. We express our profound gratitude to Professor Holzapfel for the wonderful opportunity to be part of his team and his tremendous help both at the personal and professional levels during our times in Graz and beyond. His generous encouragement, helpful guidance, and, most importantly, persistent faith in us, were and are of invaluable help for our scientific careers now and in the future. He will be remembered not only as a master of biomechanics but also as a fine individual, always delightful to be around.

Abstract Advanced imaging techniques, novel experimental approaches and sophisticated computational modeling frameworks to characterize and simulate the mechan-

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ical behavior of soft biological tissues have dramatically improved in the past decades. Particularly, the advancing of multiphoton microscopy and other imaging techniques has enabled a detailed three-dimensional visualization of the underlying microscopic structure of various biological tissues including arterial walls. In addition, mechanical testing combined with sophisticated microscopy techniques allowed us to quantify the tissue microstructural reorganization and the mechanical response under large deformation simultaneously. Multiscale constitutive models incorporating detailed microstructural information such as the 3D dispersion of collagen fibers in the extracellular matrix and experimentally-derived tissue material properties have been developed and employed in the computational simulations of human aortic tissues under various (patho)physiological conditions. Thus, in this chapter, we review some of the most critical advances and developments in experimental approaches and computational modeling strategies to characterize the mechanical behavior of human aortic tissue. In addition, we discuss future challenges to improve our understanding of the aortic tissue and its related pathologies.

1 Introduction

Human aortas, similar to other soft biological tissues, are characterized by their distinct hierarchical structure reaching through multiple scales where nanoscale molecular phenomena are expressed in macroscale mechanical responses (Cranford and Buehler 2010). Thus, multiscale approaches have been employed to deepen our understanding of the relations between the structure, mechanics and (patho)physiological processes of the organ. Advances in microscopy techniques allowed a deeper understanding of the tissue organization (see, e.g., Dingemans et al. 2000; O'Connell et al. 2008), and provided invaluable insights for constitutive modeling.

The healthy aortic wall consists of three distinct layers, i.e., the intima, media, and adventitia. Each layer is characterized by a unique content and organization of its constituents, serves different functions and exhibits specific mechanical responses. In a young healthy adult, the intima consists primarily of a single layer of endothelial cells, supported by a thin basal lamina reinforced by network-like collagen. The media is a complex network of smooth muscle cells (SMCs) and extracellular matrix (ECM) components such as collagen, elastin, and proteoglycans; whereas the adventitia hosts fibroblasts and fibrocytes embedded in an ECM mainly composed of collagen fibers.

Among the ECM components, collagen is a ubiquitous protein found in all aortic layers and is responsible for tissue strength (Holzapfel 2008), although its organization differs in each layer: intimal collagen builds a carpet-like network, circumferentially oriented undulating collagen fibers are found within the media, and the adventitia is primarily composed of thick and wavy bundles of axially oriented collagen fibers (Niestrawska et al. 2016). Elastin forms fenestrated, concentric sheets dividing the media into lamellae, as well as interlamellar elastic fibers connecting

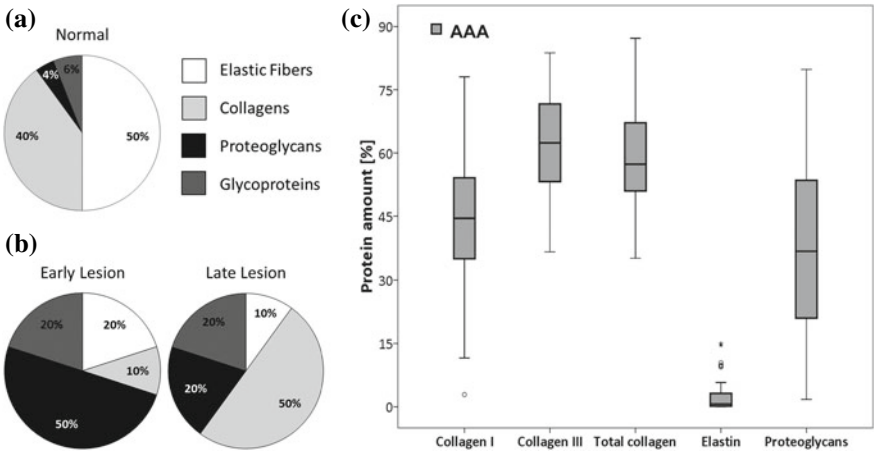

Fig. 1 Composition of the arterial ECM in (a) health and (b), (c) disease. The progression of atherosclerosis (b) is associated with an initial percentage decrease in collagen and elastic fibers contents, as well as an increase in proteoglycans and glycoproteins at early stages, followed by a relative increase in collagen accompanied by elastic fibers loss and reduced proteoglycan content at later stages. Relative elastin loss and increased proteoglycan content is also reported in aneurysms (c). Panels (a) and (b) are reproduced from Wight (2018), (c) from Tanios et al. (2015) with permission

them (Dingemans et al. 2000; O'Connell et al. 2008). Such fibers are also observed in the human aortic adventitia, albeit with a different organization (Koch et al. 2014). Proteoglycans consist of a core protein with one or more glycosaminoglycan chains covalently attached to it (Couchman and Pataki 2012; Schaefer and Schaefer 2010). In human aortas, the major proteoglycan is versican, localized in the media and intima, whereas small leucine-rich proteoglycans such as decorin or biglycan are commonly found within collagen fibers in all aortic layers (Kellerher et al. 2004; Wagenseil and Mecham 2009). Collagen and elastin contents and their arrangements were reported to change due to various factors such as aging (Maurel et al. 1987), aneurysm formation (Carmo et al. 2002; Menashi et al. 1987; Rizzo et al. 1989), or atherosclerosis (Katsuda et al. 1992; Murata et al. 1986). Furthermore, the amount of proteoglycans was increased in the atherosclerotic (Wight 2018) and aneurysmatic (Tanios et al. 2015) aortic wall compared with the healthy wall (Fig. 1).

Vascular SMCs are reported to have a spindle-like shape with an approximate length of 60 μm and a width of 5 μm (Luo et al. 2016), surrounded by elastic lamellae, a dense network of interlamellar elastic fibers and struts, as well as collagen fibers (O'Connell et al. 2008). Current microscopic examinations have shown that SMCs exhibit similar helical orientation patterns in the axial-circumferential plane as the medial collagen fibers with a small additional radial tilt (Holzapfel et al. 2002a; Horný et al. 2010; Luo et al. 2016; O'Connell et al. 2008). The relative SMC content varies along the arterial tree and, in general, increases towards the periphery (Humphrey

2002). Inside SMCs, the mechanical contraction takes place via so-called contractile units, i.e., actomyosin complexes, which consist of thin rope-like actin filaments and thick myosin filaments that slide relative to each other in a ratchet-like manner. SMCs play a significant role in short- and long-term changes of the arterial wall. In the homeostatic state, they are partially contracted providing the blood vessel with a certain tautness. In response to an altered blood pressure or blood flow, they can contract or relax in order to modulate the stiffness of large arteries or the luminal diameter of small arteries to maintain homeostasis (Milnor 1990; Humphrey 2002). However, sustained changes to the loading conditions or pathological alterations, e.g., atherosclerosis or aneurysms, may trigger an increased expression of growth factors leading to phenotypic changes of SMCs, i.e., they exhibit reduced contractility and start synthesizing collagen in an attempt to maintain the mechanical integrity of the arterial wall (Li et al. 1998; Li and Xu 2000; Lehoux et al. 2006; Gomez and Owens 2012). Furthermore, dysfunctional smooth muscle contractility, which usually occurs prior to changes in the ECM properties, is associated with several pathological conditions in the aortic wall. There is, therefore, a pressing need to quantify and assess their contractile functions, where experimental techniques as well as mathematical models play critical roles.

The changes in the ECM components and SMCs in healthy and diseased aortas suggest substantial changes on the organ's mechanical properties. Experimental and computational investigations of the structural changes and the related mechanical behavior are thus indispensable for a better understanding of aortas in health and disease. To gain a deeper insight into the mechanical behavior of the human aortic wall, earlier mechanical experiments aimed at only capturing the response of the tissue under different loading modes (e.g., Mohan and Melvin 1982, 1983). Later, reduced sample preparation time and faster imaging methods enabled correlating the tissue architecture with its mechanical properties (e.g., Niestrawska et al. 2016, 2019; Schriefl et al. 2015; Weisbecker et al. 2012). For example, imaging data from multiphoton microscopy (MPM) were utilized to mathematically describe the organization of collagen fibers in healthy and diseased aortas, and to obtain structural parameters (Niestrawska et al. 2016, 2019; Schriefl et al. 2013) for the constitutive models (Gasser et al. 2006; Holzapfel et al. 2015). Nowadays, the tissue's mechanical response and microstructural changes under loading can also be investigated simultaneously (Chow et al. 2014; Cavinato et al. 2017). Nevertheless, the alterations in the nanostructure in response to the macroscopical load remain largely elusive.

A similar development was seen in constitutive modeling: early models for soft biological tissues were phenomenological in nature, e.g. the classical Fung hyperelastic model (Fung 1993), which has been successfully employed for computational simulations of soft tissues (Li and Sun 2010; Sun et al. 2010). Phenomenological models can fit specific loading modes of measurable tissue behavior such as the stress versus strain relationship. However, the model parameters have no physical meaning. As a result, the set of parameters that could fit to a specific experimental data is often not unique, making it difficult to compare the differences in tissue behavior using these parameters. In contrast, microstructurally-motivated constitutive models can incorporate the mechanical properties of individual constituents and assume

that the overall mechanical behavior of the tissue derives from a combination of their responses. Such constitutive models have gained a tremendous momentum in the past two decades (Holzapfel et al. 2000a; Gasser et al. 2006; Stylianopoulos and Barocas 2007a; Weisbecker et al. 2015; Li et al. 2016, 2018) and have been employed extensively in the computational modeling and simulation of human aortic tissues under various (patho)physiological conditions (Holzapfel et al. 2002b; Joldes et al. 2016; Liang et al. 2018). However, the precise description of the 3D distribution of collagen and elastic fibers in a constitutive model together with the consideration of the smooth muscle contractility pose formidable challenges albeit considerable simplifications and idealizations. Moreover, since some pathological conditions (e.g., aneurysms and aortic dissections) are characterized by damage and failure of microconstituents, incorporation of such dissipative effects at different length-scales also has to be addressed in constitutive models.

In this chapter we provide an overview of multiscale experimental findings and computational modeling approaches for the passive and active behavior of the aorta as well as dissipative phenomena. In Sect. 2, we focus on the passive mechanical behavior of human aortas, and start with a review of experimental findings connecting the macro-, micro- and nanoscale investigations. Then, we present the development of (hyperelastic) multiscale constitutive models from the basic ones with parallel collagen fibers to the more advanced ones with dispersed collagen fibers. In Sect. 3, we discuss the importance of vascular SMCs with respect to the mechanical response of arteries, present the recent advances in experimental quantification of the multiaxial contractile SMC properties, and their incorporation in multi-physical constitutive models. In Sect. 4, we focus on the dissipative phenomena, namely, viscoelasticity, damage and failure. In particular, we present the related experimental findings considering the multiscale microstructural organization of both collagen and elastic fibers, followed by a summary of various computational approaches to the multiscale modeling of such phenomena. Finally, in Sect. 5 we discuss some of the key challenges that have to be addressed in order to improve our knowledge of the mechanical behavior of aortic tissue.

2 Passive Mechanical Behavior

In general, the passive stress-stretch response of the human aorta exhibits nonlinear stiffening, pseudoelasticity and anisotropy with the formation of remarkably small hysteresis upon cyclic loading-unloading (Holzapfel 2006; Schmid et al. 2005; Sherifova et al. 2019; Vande Geest et al. 2004). Out of numerous ECM components, type I and III fibrillar collagen is mainly responsible for the nonlinear stiffening and anisotropy of the tissue, while elastin accounts for its elasticity. Moreover, aortic tissues are capable of withstanding high stresses and strains thanks to these proteins (Holzapfel and Ogden 2018). In short, the mechanics of a tissue is governed by its microstructure—at the very least.

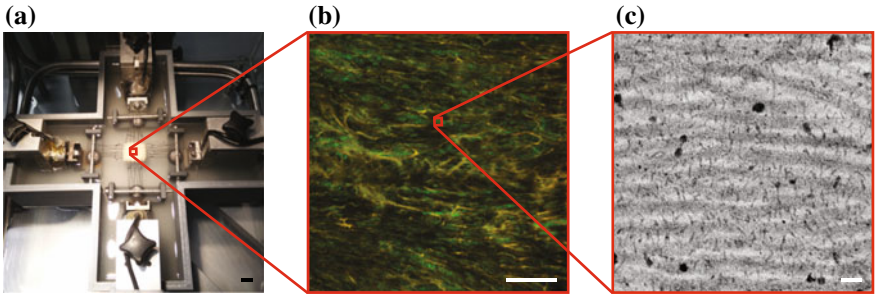

Fig. 2 Example of a multiscale experimental approach: (a) the biaxial extension test of an aortic wall is accompanied by (b) MPM and (c) followed by electron microscopy. Multiphoton microscopy (b) reveals the second-harmonic generation signal of collagen fibers (green) and autofluorescence of elastin fibers (yellow). Transmission electron microscopy (c) shows light gray collagen fibrils connected with spindle-like, dark gray proteoglycans (Wittgenstein 2018 with permission). Scale bars denote (a) 1 cm, (b) 100 μm, (c) 100 nm. Pukaluk et al., unpublished

As introduced in Sect. 1, (patho)physiological processes can lead to changes in the content, structure and orientation of various ECM components at different scales. In turn, these structural changes can have various mechanical manifestations such as stiffening or loss of anisotropy, and multiscale approaches are essential to their understanding. Figure 2 illustrates an example of such an experimental approach, where the macroscale mechanical properties of aortas at different atherosclerotic stages are investigated in connection with the macro-, micro- and nanoscale structural information. Current generations of multiscale constitutive models, which can incorporate these details, are of great importance for realistic simulations of the aortic tissues behavior under distinct (patho)physiological conditions. In this section, therefore, some important developments in experimental methods and computational modeling strategies for characterizing the passive mechanical behavior of human aortic tissues are reviewed.

2.1 Experimental Findings

Since the proteins of the ECM drive the macroscopic behavior of the aorta and define the above-mentioned mechanical properties (Wagenseil and Mecham 2009), one of the experimental approaches is to compare the stress-strain responses of intact and protein deficient tissues (Sherifova and Holzapfel 2020). Alternatively, promising methods for the investigation of the mechanical role of certain proteins include the enzymatic digestion of specific proteins and mechanical testing of the tissues before and after enzymatic treatment. For example, circumferential strips from the human thoracic media subjected to uniaxial extension with gradual collagenase treatment revealed a progressive change of their mechanical behavior from highly nonlinear to nearly linear without a distinct softening, whereby the collagen digested aortic tissue

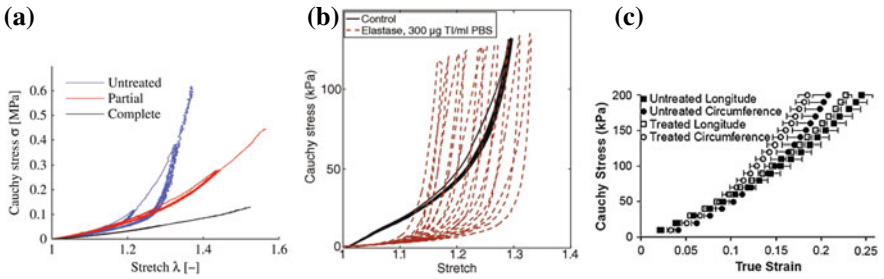

Fig. 3 (a) Effect of collagen, (b) elastin, and (c) glycosaminoglycan digestion on the stress-stretch response of the aortic tissue. Figure **(a)** reprinted from Weisbecker et al. (2013), **(b)** from Schriefl et al. (2015), and **(c)** from Mattson et al. (2017) with permission

lost its characteristic stiffening behavior (Fig. 3a) (Weisbecker et al. 2013). Similar findings were reported for enzymatically treated medial and adventitial strips from human abdominal aortas (Schriefl et al. 2015). In contrast, uniaxial extension experiments on elastin-degraded human thoracic (Weisbecker et al. 2013) and abdominal (Schriefl et al. 2015) aortas suggested that elastin plays a substantial role in maintaining the integrity of the tissue. Specifically, elastase treated samples showed continuous softening with remanent deformations during the subsequent loading and unloading cycles (Fig. 3b), and the stiffness at low deformations/loads was lower in elastin-digested tissues compared to control samples. Although collagen and elastin dominate the tissue content and mechanics, proteoglycans deserve further attention (Sherifova and Holzapfel 2020). The explicit mechanical roles of proteoglycans in arterial mechanics remain elusive, however, Mattson et al. (2017) showed that removal of glycosaminoglycans, the main constituent of proteoglycans, caused earlier stiffening indicated by transition points located at significantly lower strains on the nonlinear stress-strain curves obtained during equibiaxial extension tests (Fig. 3c).

A further promising experimental approach for the investigation of the aortic properties at macro- and microscales involves simultaneous mechanical testing and microscopy imaging. This approach allows the quantification of organizational changes in the tissue components under different loadings. For example, MPM combined with biaxial extension tests on porcine aortas revealed that medial collagen was engaged throughout loading, whereas adventitial collagen only engaged at higher loads (Chow et al. 2014). However, in layer-specific tests, collagen in the porcine adventitia gradually straightened under load with no noted delay (Li et al. 2019). In contrast, prominent elastin engagement was mainly observed at lower strains (Chow et al. 2014). Furthermore, equibiaxial loading caused no significant realignment of collagen or elastic fibers in contrast to non-equibiaxial loading, which caused a realignment of collagen fibers in both layers but not of elastic fibers (Chow et al. 2014). In general, elastic fibers were observed to be less undulated than collagen fibers in the media of rabbit aortas at physiological load (Sugita and Matsumoto 2017). In another study, bulge inflation tests were coupled with MPM to investi-

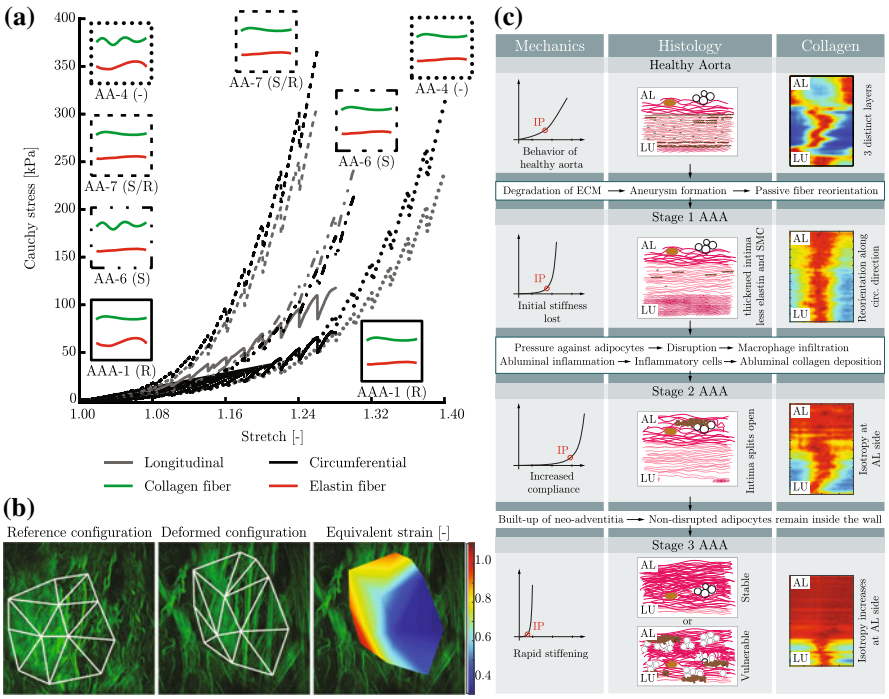

Fig. 4 Global mechanical properties and microstructure of the human aortas: (a) representative mechanical responses of equibiaxial tests (successful (-), interrupted due to the stiffness (S), rupture (R) or stiffness and rupture (S/R)) on the human abdominal media with the schematic representation of collagen and elastic fibers illustrating their waviness at the reference and maximum achieved stretch configurations (Pukaluk et al., unpublished); (b) local equivalent strain field on the human abdominal adventitia subjected to 1.1 global equibiaxial stretch (Pukaluk et al., unpublished); (c) changes in the mechanical behavior of AAA tissue in the course of pathogenesis accompanied by changes in content and collagen fiber orientation (reproduced from Niestrawska et al. 2019 with permission)

gate adventitial collagen in human thoracic aortas (Cavinato et al. 2017). This study showed that dense and undulated collagen bundles in the unloaded state tended to progressively straighten at higher pressure, and initially thick bundles of collagen transitioned into a network of thinner bundles. Ongoing investigations in this regard utilize planar biaxial extension tests coupled with MPM to investigate structural alterations of collagen and elastin in human abdominal aortas (Pukaluk et al., unpublished). Specifically, notable differences in the structural reorganization between the loaded media and adventitia suggest distinct stretching mechanisms reaching beyond different fiber orientations in these layers in the unloaded state, which the waviness of medial collagen and elastic fibers might explain, see Fig. 4a. Moreover, the application of fluorescent beads could help to understand the local strain generated as a response to the global stretch (Fig. 4b).

As previously explained in Sect. 1, content and structure of ECM components are affected by age and diseases. Not surprisingly, the passive mechanical behavior also changes due to aging and pathological conditions (Holzapfel et al. 2004; Vande Geest et al. 2006; Åstrand et al. 2011). For example, Haskett et al. (2010) reported that with advanced age the degree of fiber alignment increased and tissues showed a stiffer response under planar biaxial tests, leading to the assumption that age-related aortic stiffening is also associated with fiber alignment. Deeper insights into the microstructure and the related mechanics of healthy and diseased, i.e. aneurysmatic, human abdominal aortas were reported by Niestrawska et al. (2016, 2019). They found loss of the characteristic three-layered wall structure, significantly higher out-of-plane dispersion of collagen fibers as well as stiffer behavior of the aneurysmatic samples compared with control tissues. The authors also noted a large variability in the mechanical and structural data among the aneurysmatic tissues. Subsequently, Niestrawska et al. (2019) explained this variability with a three-stage disease progression hypothesis, where they related the changes in the in-plane dispersion of collagen fibers with the altered mechanics of the aortic wall (Fig. 4c). More specifically, fiber reorientation towards the circumferential direction in stage I correlated with decreased initial stiffness. Subsequently, in stage II, almost isotropic fiber dispersion at the abluminal side led to increased compliance, and finally, in stage III increased isotropic fiber dispersion throughout the aortic wall thickness correlated with rapid stiffening (Fig. 4c). Niestrawska et al. (2016) also reported a decreased waviness of collagen fibers in aneurysm walls, however, fiber waviness quantification and its correlation to the mechanics of the human aorta has not been reported to date. Further microstructural and mechanical investigations and related quantification in this regard may show rewarding considering that higher stiffness of the aortic tissue is associated with decreased undulation in collagen fibers for porcine aortas (Zeinali-Davarani et al. 2015).

Regarding ultrastructural investigations, several studies focused on the mechanical properties of ECM components at the nanoscale level. Examples include but are not limited to stretching of a collagen monomer by Sun et al. (2002), bending of a collagen fibril by Dutov et al. (2016), bending and indentation of an elastic fiber by Koenders et al. (2009) and stretching of a glycosaminoglycan molecule by Haverkamp et al. (2005). Furthermore, measurements on healthy and atherosclerotic human abdominal aortas provided the local tissue stiffness of elastic lamellae, interlamellar zones as well as different locations of the atherosclerotic plaque such as the fibrous cap, calcification zone, and lipid pool (Rezvani-Sharif et al. 2019). Nevertheless, these studies did not relate the mechanical behavior of single molecules or fibrils to micro- or macromechanics of the tissue. Attempting to narrow this gap between scales, combined planar biaxial tests and electron tomography investigations performed by our group enabled a deeper insight into arrangement of collagen fibrils and proteoglycans inside the aortic layers at different stretches. Preliminary results show that proteoglycans reorient and increase their cross section in response to higher stretch (Pukaluk et al., unpublished). Other scale-bridging experiments on the human aorta were conducted by Lindeman et al. (2010), where the adventitia of healthy and aneurysmatic abdominal aortas was probed by atomic force microscopy

cantilevers at the levels of collagen fibrils (nanoscale) and fibers (microscale). The healthy aorta behaved as a coherent network and mechanical forces were distributed over the tissue, in contrast to the aneurysmatic tissue. These findings emphasize that multiscale mechanical experiments that bridge the nanoscale to higher scales are critical for a better understanding of the (patho)physiological tissue mechanics.

2.2 Constitutive Modeling

Inspired by the pioneering work of Lanir (1983, 2018), soft fibrous tissues have been treated as a fiber-reinforced composite material. The total strain-energy function (SEF) of the material is obtained by a summation of tissue constituents' strain energy under finite deformation. Within this framework, Holzapfel's group proposed the *so-called* HGO model for arterial tissues with collagen fibers predominately distributed around the mean direction within each family (Holzapfel et al. 2000a). In this model, the arterial tissues were treated as a multilayered composite material, and each layer consisted of a ground substance and two families of collagen fibers for the mechanical characterization of their passive behavior. Briefly, following the multiplicative decomposition (Flory 1961; Ogden 1978) of the deformation gradient $\mathbf{F}$ into a volumetric (dilatational) part $J^{1/3}\mathbf{I}$ and an isochoric (distortional) part $\overline{\mathbf{F}} = J^{-1/3}\mathbf{F}$, with $J = \det \mathbf{F} > 0$, the SEF Ψ of the arterial tissue per unit volume in the reference configuration is usually written in a decoupled form for an efficient computational implementation, i.e.

$$\Psi = \Psi_{\text{vol}} + \Psi_{\text{iso}}, \tag{1}$$

where Ψ_{vol} describes the volumetric deformation of the aortic tissue and Ψ_{iso} the isochoric deformation. Since arterial tissues are usually treated as incompressible materials, the volumetric part of the SEF is used as a penalty function, and it is convenient to adopt a form available in the finite element program. For example, the following form could be employed if FEAP (Taylor 2013) is used as the finite element solver,

$$\Psi_{\text{vol}} = \frac{K}{4}(J^2 - 1 - 2\ln J), \tag{2}$$

where K is a penalty parameter.

The isochoric contribution can be further decomposed into two parts,

$$\Psi_{\text{iso}} = \Psi_{\text{g}} + \Psi_{\text{f}}, \tag{3}$$

where Ψ_{g} denotes the isochoric strain energy of the ground substance, which is assumed to be isotropic and to depend only on the modified first invariant $\bar{I}_1 = \text{tr}\overline{\mathbf{C}}$ of the modified right Cauchy–Green tensor $\overline{\mathbf{C}} = \overline{\mathbf{F}}^{\text{T}}\overline{\mathbf{F}}$, and Ψ_{f} represents the total isochoric strain energy of collagen fibers. Since it has been shown that the non-

collagenous ground substance of arterial tissue (Weisbecker et al. 2013) exhibits a nearly linear stress–strain response, the neo-Hookean hyperelastic model is often used for Ψ_g, i.e.,

$$\Psi_g(\bar{I}_1) = \frac{\mu}{2}(\bar{I}_1 - 3), \tag{4}$$

where the constant μ (> 0) is the shear modulus.

To account for the mechanical behavior of the collagen fibers in the arterial wall, the HGO model proposed by Holzapfel et al. (2000a) defines the following exponential SEF for two families of fibers, i.e.

$$\Psi_f = \frac{k_1}{2k_2} \sum_{i=4,6} \left(e^{k_2(\bar{I}_i - 1)^2} - 1 \right), \tag{5}$$

where k_1 and k_2 are the material parameters associated with the collagen fibers, with a dimension of stress and without dimension, respectively. $\bar{I}_4$ and $\bar{I}_6$ are modified counterparts of the squared stretches $I_4 = \mathbf{C} : \mathbf{M}_1 \otimes \mathbf{M}_1$ and $I_6 = \mathbf{C} : \mathbf{M}_2 \otimes \mathbf{M}_2$ along the mean fiber directions, $\mathbf{M}_1$ and $\mathbf{M}_2$, of two symmetrically arranged collagen fiber families. The two families are assumed to be the same type within each layer of arterial tissue. If either fiber stretch in the mean direction is less than unity ($I_4 < 1$ or $I_6 < 1$), then that fiber family is excluded from Ψ_f. Elastin in the arterial wall could be treated as part of the ground substance, or it could also be incorporated in the constitutive model in the form of elastic fibers in a similar manner (Rolf-Pissarczyk et al. 2021).

This 'simple' and yet robust constitutive model (5) captures the mechanical behavior of the essential constituents—ground substance and collagen fibers—of arterial tissue and has been extensively employed in the computational modeling not only of arterial tissues, but also other soft fibrous tissues (Mao et al. 2016). The HGO model initially included two families of collagen fibers, and it was later extended to include four families of fibers by Humphrey and colleagues for a better fit to experimental data of some arterial tissues (Baek et al. 2007).

The HGO model was very efficient in modeling soft biological tissues with collagen fibers predominately distributed around a mean direction within a family or soft tissues with families of parallel collagen fibers such as mitral valve chordae tendineae (Zuo et al. 2016). However, as shown in Sect. 2.1, the distribution of collagen fibers in each layer of the arterial wall is often dispersed within each family in both healthy and aneurysmal conditions (see Fig. 4c). To account for such dispersion in a constitutive equation, two approaches, namely the 'angular integration' (AI) approach and the 'generalized structure tensor' (GST) approach, have been widely used.

The AI approach was originally proposed by Lanir (1983, 2018) in 1983, where the strain energy of a single fiber is only a function of the fiber stretch. Then, an integration of the single fiber SEF over all the fiber directions weighted by a continuous probability density function (PDF) yields the total fiber strain energy Ψ_f (Lanir 1983, 2018). The pioneering work of Lanir has gained growing interest in the past

decades, and there have been numerous constitutive models based on this approach since it was proposed in 1983 (Holzapfel and Ogden 2015).

The fiber contribution to the total SEF can be evaluated by using a numerical integration of the weighted single fiber SEF over the unit sphere, known as the microsphere based model, see Alastrué et al. (2009) and references therein. However, if the fiber dispersion is accounted for as a summation of a finite number of discrete fiber contributions, then it is referred to as the 'discrete fiber dispersion' (DFD) model, see Li et al. (2018). While a numerical integration over the sphere or hemisphere is required in the AI approach, this is not needed in the DFD model since the fibers are treated in a discrete manner.

At first, we describe the AI approach for modeling soft fibrous tissues. Briefly, we introduce unit Cartesian basis vectors $\mathbf{E}_1$, $\mathbf{E}_2$, and $\mathbf{E}_3$, and then any fiber direction $\mathbf{N}$ within a 3D dispersed fiber family in terms of spherical polar angles Θ and Φ relative to $\mathbf{E}_1$, $\mathbf{E}_2$, and $\mathbf{E}_3$ reads,

$$\mathbf{N} = \sin\Theta\cos\Phi\mathbf{E}_1 + \sin\Theta\sin\Phi\mathbf{E}_2 + \cos\Theta\mathbf{E}_3. \tag{6}$$

With that, the fiber contribution Ψ_{f} to the total SEF in the AI model is obtained by integrating the weighted single fiber strain energy $\Psi_n(I_4)$ of each fiber direction $\mathbf{N}$ over the unit sphere $\mathbb{S}^2 = \{(\Theta, \Phi) \mid \Theta \in [0, \pi], \Phi \in [0, 2\pi]\}$, i.e.,

$$\Psi_{\mathrm{f}} = \frac{1}{4\pi}\int_{\mathbb{S}^2} \rho(\Theta, \Phi)\Psi_n(I_4)\sin\Theta \mathrm{d}\Theta\mathrm{d}\Phi, \tag{7}$$

where the PDF $\rho(\Theta, \Phi)$ is the probability density of the fibers in the direction $\mathbf{N}(\Theta, \Phi)$ in the reference configuration. The PDF $\rho(\Theta, \Phi)$ in Eq. (7) must satisfy the normalization condition

$$\frac{1}{4\pi}\int_{\mathbb{S}^2} \rho(\Theta, \Phi)\sin\Theta \mathrm{d}\Theta\mathrm{d}\Phi = 1. \tag{8}$$

The computational implementation of the SEF Eq. (7) requires two-dimensional integration over the unit sphere at each Gauss point during a finite element simulation. Because of the complicated nature of the integrand in Eq. (7), a numerical integration over the sphere is often employed.

Also referred to as the GOH model in the literature, the GST approach was proposed by Holzapfel's group (Gasser et al. 2006) in 2006 where the contribution of the entire fiber family (Ψ_{f}) to the total SEF is 'wrapped' in a generalized structure tensor. The extension of the HGO model (5) to the GOH model is obtained simply by replacing $\bar{I}_i$ in Eq. (5) by $\bar{I}_i^{\star}$ (Holzapfel and Ogden 2015), i.e.,

$$\bar{I}_i^{\star} = \kappa\bar{I}_1 + (1 - 3\kappa)\bar{I}_i, \quad i = 4, 6, \tag{9}$$

where κ is the parameter quantifying the rotationally symmetric dispersion of fibers around the mean direction. A widely used PDF for such a fiber dispersion is the von

Mises distribution over the unit sphere,

$$\rho(\Theta, \Phi) = 4\sqrt{\frac{b}{2\pi}}\frac{\exp[2b(\mathbf{N}\cdot\mathbf{M})^2]}{\mathrm{erfi}(\sqrt{2b})}, \tag{10}$$

where b is the concentration parameter describing how closely the fibers are distributed around the mean fiber direction $\mathbf{M}$ of the fiber family, $\mathrm{erfi}(x) = -\mathrm{i}\,\mathrm{erf}(\mathrm{i}x)$ denotes the imaginary error function, and $\mathrm{erf}(x)$ is the standard error function. Since the microstructural data showed a non-symmetric dispersion of collagen fibers in the arterial wall (Schriefl et al. 2012), the GOH model was then extended to include this information in Holzapfel et al. (2015).

Because of the slenderness and waviness of collagen fibers in the reference configuration, it is usually assumed that they do not have any compressive strength and will buckle if compressed. For strictly incompressible materials with 3D fiber dispersion such as arterial tissues, there will always be some fibers under compression and others under tension under general finite deformation. Thus, the fibers under compression within a subset of the unit sphere should be excluded when computing the total strain energy of the tissue. However, there is some confusion in the literature and in finite element implementation of this tension–compression 'switch' of the fibers as highlighted in Holzapfel and Ogden (2015). In addition, it is not strictly correct to exclude the entire fiber family from the SEF of the tissue when the mean fiber direction is under compression as it is proposed in the GOH model, because some fibers are still under tension even if the mean direction is under compression. Eliminating the contribution of those fibers under tension could underestimate the total strain energy of the tissue unless the contribution of those fibers is negligible under some deformation states.

To circumvent this problem, a more accurate method was proposed by Holzapfel and Ogden (2015) for exclusion of compressed fibers within a dispersion, which was later extended and implemented in FEAP and illustrated with some representative examples in Li et al. (2016). Unfortunately, however, the computational cost for the numerical integration of the weighted single fiber SEF over a subset of the unit hemisphere $\mathbb{S} = \{(\Theta, \Phi) \mid \Theta \in [0, \pi], \Phi \in [0, \pi]\}$ in the model was very high. To overcome this costly numerical difficulty and reduce the computational time, the new DFD model (Li et al. 2018) was proposed by the Holzapfel group recently.

In the DFD model (Li et al. 2018), the dispersion of the collagen fibers in each fiber family was accounted for in a discrete manner. More specifically, the authors discretized the unit sphere into a finite number $2m$ of elementary areas $\Delta\mathbb{S}_n$, $n = 1, \ldots, 2m$, see Fig. 5b for an example of such discretization of the unit sphere with $2m = 180$ spherical triangles where m represents the number of elementary areas over a half of the unit sphere. Note that only the elementary areas over one half of the unit sphere were used in the constitutive model. Without loss of generality, a rotationally symmetric fiber dispersion (10) was used for an illustration of the method. The representative fiber direction (Θ_n, Φ_n) at the centroid of each elementary area and an elementary fiber density ρ_n was defined as

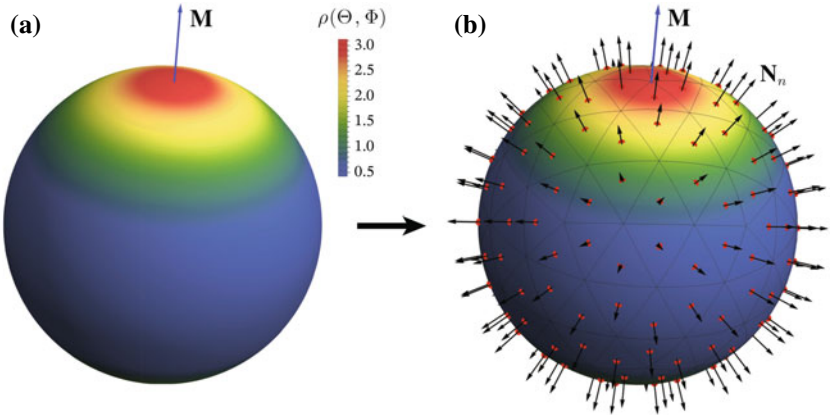

Fig. 5 (a) Contour plot of the PDF $\rho(\Theta, \Phi)$ defined over the unit sphere by the von Mises distribution with mean fiber direction $\mathbf{M}$ and a concentration parameter $b = 1.0$, see Eq. (10); (b) example of a triangular discretization of the unit sphere with $2m = 180$ representative fiber directions $\mathbf{N}_n$ (black arrows) defined at the centroids (red dots) of the spherical triangles. Reprinted from Li et al. (2018) with permission

$$\rho_n = \frac{1}{2\pi} \int_{\Delta \mathbb{S}_n} \rho(\Theta, \Phi) \sin \Theta \mathrm{d}\Theta \mathrm{d}\Phi, \qquad n = 1, \ldots, m. \tag{11}$$

It was required for the PDF $\rho(\Theta, \Phi)$ to be an integrable function over each $\Delta \mathbb{S}_n$. If this is not satisfied, then, the elementary area could be further discretized so that the PDF becomes integrable over each elementary area. The elementary fiber density ρ_n must satisfy the normalization condition, i.e.,

$$\sum_{n=1}^{m} \rho_n = 1, \tag{12}$$

which is the discrete counterpart of Eq. (8) over the unit hemisphere. With a discretized unit hemisphere, the SEF for the total contribution of each fiber family was given as

$$\Psi_{\mathrm{f}} = \sum_{n=1}^{m} \rho_n \Psi_n(I_{4n}), \tag{13}$$

where $I_{4n} = \mathbf{C} : \mathbf{N}_n \otimes \mathbf{N}_n$ and $\mathbf{N}_n$ was defined at the centroid of each spherical triangle via Eq. (6) with $\Theta = \Theta_n$ and $\Phi = \Phi_n$; see the black arrows in Fig. 5b. In order to exclude the fibers under compression within a dispersion, Li et al. (2018) set Ψ_n to zero if $I_{4n} < 1$. This model has been implemented in FEAP and verified with three numerical examples, results of which were consistent with the previously published data in Li et al. (2016). However, Li et al. (2018) achieved these results with a significantly reduced computational time—224 times faster.

Another approach for modeling the collagen fiber dispersion in the arterial wall is the fiber network model (Hadi et al. 2012; Stylianopoulos and Barocas 2007a). Therein, the 3D fiber dispersion is accounted for by generating a network of collagen fibers within a representative volume element (RVE) either randomly (Lake et al. 2012) or based on the imaging data of the tissue. Then, the macroscopic Cauchy stress tensor of the collagen fibers is obtained in terms of the microscopic stress tensor by using the volume-averaging theory (Stylianopoulos and Barocas 2007b). Since the collagen fibers are explicitly represented in those models, fiber damage and fiber–fiber interaction can also be readily incorporated into the model, see, e.g., Hadi et al. (2012). Future measurement of detailed 3D collagen fiber architecture in arterial tissue will certainly improve the accuracy of this approach.

Recently, Holzapfel and Ogden (2020a) proposed a new fiber dispersion model considering the orientation of collagen fiber cross-links relative to the fiber direction and cross-link density on the mechanical response of the tissue. The model was able to predict the stiffening of the artery as the cross-linking density increased. However, since the mechanical properties of cross-links and their interactions with the collagen fibers are largely unknown, the model will need to be refined and extended as new mechanical and structural data become available in the next decade.

3 Active Mechanical Behavior

The mechanical properties of the vascular wall have been associated with various cardiovascular diseases and have mainly been attributed to the ECM. However, more recently the intramural cells, particularly SMCs, have been found to play critical roles in the physiological state of the vascular wall (Li et al. 2020). Two leading risk factors of cardiovascular diseases are hypertension and arterial stiffness, both which are influenced by the SMCs (Lacolley et al. 2017; Spronck et al. 2020). Increased blood pressure can result from an increase in cardiac output or an increase in vascular resistance. The former is the amount of blood pumped by the heart per minute and is the product of the heart rate and the stroke volume, which is the amount of blood pumped out of the heart. The vasculature plays an important role in regulating blood flow through vital properties such as the elastic compliance of arteries as well as the blood capacitance of the veins, both which depend on the SMC active tone. Vascular resistance is mainly regulated by the peripheral blood vessels and is inversely proportional to the fourth power of the inner radius, which makes it highly dependent on the SMC active tone.

In addition, arterial stiffness has been demonstrated to be influenced by the vascular tone and shown to have a significant and complex relationship to the pathophysiological state of the vessel (Lacolley et al. 2017). The arterial stiffness can be clinically measured through the pulse wave velocity PWV and can be calculated through the Moens–Korteweg equation