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Bio-chemo-mechanical models of vascular mechanics

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Abstract

Models of vascular mechanics are necessary to predict the response of an artery under a variety of loads, for complex geometries, and in pathological adaptation. Classic constitutive models for arteries are phenomenological and the fitted parameters are not associated with physical components of the wall. Recently, microstructurally-linked models have been developed that associate structural information about the wall components with tissue-level mechanics. Microstructurally-linked models are useful for correlating changes in specific components with pathological outcomes, so that targeted treatments may be developed to prevent or reverse the physical changes. However, most treatments, and many causes, of vascular disease have chemical components. Chemical signaling within cells, between cells, and between cells and matrix constituents affects the biology and mechanics of the arterial wall in the short- and long-term. Hence, bio-chemo-mechanical models that include chemical signaling are critical for robust models of vascular mechanics. This review summarizes bio-mechanical and bio-chemo-mechanical models with a focus on large elastic arteries. We provide applications of these models and challenges for future work.

Key Terms

Artery; biomechanics; extracellular matrix; mechanical modeling

Introduction

Quantification and modeling of the mechanical behavior of arteries are necessary to predict the response under a variety of loading environments, such as normal vascular development and pathological remodeling in disease. A key purpose of these modeling studies is to provide insight for clinical interventions. Interventions may affect the immediate mechanical behavior of the artery, as well as the immediate and long-term biological properties of the cells and extracellular matrix (ECM). Interventions may also induce chemical signaling from the cells, which will further alter the biological and mechanical behavior. Consequently, models that integrate across fields (bio-chemo-mechanical) and across length

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scales (molecular-cellular-tissue) are necessary for a better understanding of vascular behavior in health and disease.

This review discusses vascular constitutive models as they have progressed historically from describing the macroscopic tissue level to subcellular mechanical behavior, with a focus on recent models that integrate mechanical, biological, and chemical information for large elastic arteries. Topics covered include vascular wall structure, typical mechanical characteristics, fundamental assumptions, and constitutive modeling via phenomenological, microstructurally-linked and bio-chemo-mechanical approaches.

Background

Vascular wall structure

For the most part, this review will focus on models of large, elastic arteries. The arterial wall consists of three layers: intima, media, and adventitia. The intima is composed of a single layer of endothelial cells (ECs), which are elongated and aligned in the direction of blood flow. The media consists mainly of repeating layers of elastic lamellae and smooth muscle cells (SMCs) (Fig. 1) and plays a primary role in vascular elasticity. Elastic lamellae are composed mostly of the ECM protein, elastin, but require numerous other ECM proteins for proper assembly⁸². Spindle-shaped SMCs in the media are oriented circumferentially around the wall and can actively contract or relax, as well as synthesize molecules that promote ECM production or degradation. Additional ECM proteins, including collagen and proteoglycans, are also found in the media. The adventitia is the outermost layer and contains collagen, elastin, fibroblasts and nerves. Collagen fiber recruitment in the adventitia is critical for the nonlinear mechanical behavior of arteries at high pressure¹⁷.

Vascular wall cells play an important role in actively regulating arterial geometry and mechanical behavior¹⁴. ECs synthesize vasoactive substances, for example, nitric oxide (NO), endothelin-1 (ET-1), and angiotensin-II (Ang-II), contributing to the overall vascular tone. SMC contractile force depends on the cell length^{15, 16} and on the concentration of free calcium ions (Ca^{2+}) in the intercellular space. An increase in Ca^{2+} concentration causes SMC contraction, while a decrease causes SMC relaxation. Ca^{2+} concentration regulates activity of the actin-myosin filament complex that generates force³⁵. Numerous other factors modulate SMC contraction, including potassium (K^+), O_2 , CO_2 , and prostacyclin (PGI₂).

General mechanical characteristics and assumptions

Arteries have nonlinear, anisotropic material properties that vary with age, location in the vascular tree, species, and pathological condition³⁶. In general, arteries are assumed to be incompressible and pseudoelastic. The artery is a layered, composite material with heterogeneous properties⁴¹, but many models assume the wall to be homogeneous. Circumferential residual strain in the artery wall normalizes the transmural strain and stress distribution²³. For mechanically-motivated remodeling of the wall, it is often assumed that the artery exists in a homeostatic stress state, and that geometric, biological, and chemical changes in the wall result from the artery trying to return to the homeostatic state³⁷. For simplicity, arteries are often modeled as cylindrical tubes with a uniform thickness. There has been a trend toward more realistic and even patient-specific geometry, especially in

complex regions such as the ascending aortic arch or an aortic aneurysm⁹¹. Constitutive models that provide relationships between stress and strain are generally based on continuum mechanics principles and are quantified by strain energy functions. A major challenge lies in linking these continuum-level models to the biological microstructure and chemical environment of the arterial wall.

Constitutive models

Phenomenological models

Classic constitutive models describe the phenomenological stress-strain response of the arterial wall. For example, Chuong and Fung¹¹ proposed an exponential strain energy function, and Takamizawa and Hayashi⁷⁷ introduced a logarithmic strain energy function. These models fit the experimental data well and can be used to predict behavior for a variety of loading conditions. They can also be used to define material behavior for more complicated vascular geometries in finite element modeling. However, the model parameters have no physical meaning with regard to the biological wall structure, so it is difficult to relate parameter changes to physical alterations of the wall. Despite this shortcoming, the Fung-type exponential strain energy function is widely used and is included in several of the models discussed below.

Microstructurally-linked models

Passive mechanical behavior—Histological investigation and mechanical experiments after enzymatic digestion of elastin or collagen provide clues to how the individual ECM components contribute to passive arterial mechanics^{18, 64, 87}. Elastin is often assumed to be isotropic and linear, while collagen is assumed to be anisotropic and nonlinear. One of the earliest microstructurally-linked models was developed by Wuyts et al.⁸⁸ and includes two linearly elastic load-bearing components (collagen fibers and an elastin network with SMCs) to describe the arterial tension-radius relationship. Nonlinearity is introduced through a distribution function for the initial collagen fiber lengths. The authors find that individual collagen fiber stiffness increases with age, but is not affected by atherosclerosis in human artery samples. Microstructurally-linked models can be used to test targeted therapies that specifically affect the passive structural components predicted to be altered in various disease states.

Holzapfel and Weizsacker³⁴ developed a biphasic model to capture the circumferential stress-strain relationship of the arterial wall. The strain energy function is decoupled into an isotropic (neo-Hookean) and anisotropic (Fung-type exponential) contribution. Based on histological data, this idea was expanded as a fiber-reinforced two-layer (media and adventitia) constitutive model in which Holzapfel et al.³³ assume that each layer exhibits similar mechanical characteristics, but that the associated material parameters vary. In the composite model, the fibers represent two families of nonlinear collagen fibers oriented symmetrically in each layer and the bulk material represents linear, isotropic non-collagenous matrix (i.e. elastin and proteoglycans). Changes in the mechanical contribution of each component can be correlated with changes in amounts or mechanical properties due to altered physiological or pathological conditions, such as aging⁵.

The two-layer, fiber-reinforced model³³ has been adapted and extended to a single layer, four-fiber model that includes two families of symmetrically oriented collagen fibers at a certain angle to the principal directions, as well as families of circumferentially and axially oriented collagen fibers embedded in an isotropic elastin matrix. The four-fiber model has been used to describe the mechanical behavior of a variety of types and species of arteries^{6, 20, 79, 84} and was found to better fit passive experimental data for wild-type and mutant mouse carotid arteries than the Fung-type exponential model²⁵. Although the fiber-reinforced models represent an advance toward including biological information about the arterial wall in the constitutive formulation, the discrete families of collagen fibers and the isotropic elastin matrix are an oversimplification. The experimentally measured distribution of collagen fiber angles and the number of distinct fiber families varies by radial and longitudinal location⁷⁰ and there is evidence that arterial elastin is not an isotropic material^{3, 63}.

Other models have been developed to more realistically describe the physical arrangement of collagen fibers. For example, rather than discrete fiber families, a dispersion of collagen fiber orientations can be included in the strain energy function²⁴. Instead of an exponential function for the collagen fiber mechanical behavior, collagen fibers can have linear mechanical behavior, but have a distribution of waviness as introduced by Wuyts et al.⁸⁸. Zulliger et al.⁹³ developed a model decomposed into isotropic and anisotropic parts, with the contribution of each part weighted by the area fractions of elastin (isotropic) and collagen (anisotropic), as determined from histological cross-sections. The elastin is modeled as a neo-Hookean solid, but the collagen is modeled as circumferentially oriented, linear fibers with a distribution of fiber waviness. Additional constitutive models that take into account both the waviness and orientation of collagen fibers have been developed^{2, 19}. There is also a model that includes anisotropic terms for arterial elastin⁶³, which provides better fits than models with isotropic elastin terms for carotid artery data, but limitations include the increased number of parameters and the difficulty in fitting unique strain energy equations when both ECM components are nonlinear.

Enzymatic digestion is often used to separate elastin and collagen mechanical contributions for microstructurally-linked models, but recent experiments show that elastin and collagen are physically linked and that removing one component alters the mechanical behavior and microstructure of the remaining ECM component^{20, 21, 63, 92}. Mouse models with altered amounts of ECM proteins, such as elastin, eliminate the problem of physically removing one component, but experimental data show that the arteries grow and remodel in response to reduced elastin amounts⁴⁵ and there are compensatory changes in the collagen mechanical contributions¹⁰.

To relate the mechanical contribution of collagen to the fiber organization in microstructurally-linked constitutive models, detailed imaging methods such as confocal microscopy⁶² (Fig. 2), multiphoton microscopy⁹, second-harmonic imaging⁸⁴, and small-angle light scattering²⁹ can be used. Imaging can be combined with mechanical testing to investigate how the microstructure changes with load³². The data so far show that the attributes and appropriate mathematical description for the collagen fiber microstructural

organization may vary by artery type, species, longitudinal location, and radial position through the wall.

The collagen fibers visible under light microscopy are collections of smaller collagen fibrils, which are composed of individual collagen molecules. Maceri et al.⁴⁷ developed a multiscale model to link nano, micro, and macrostructural effects of collagen on soft tissue mechanics. Similar nanoscale parameters were combined with variations in micro and macrostructural parameters to predict mechanics of different soft tissues, consistent with the idea that individual collagen molecules have similar mechanical behavior, but are organized differently in various tissues to provide a variety of global mechanical behavior. Stylianopoulos and Barocas⁷⁵ combined a multiscale model for the collagen fibril network with a macroscopic model of the noncollagenous material to describe mechanical behavior of decellularized porcine aortas. Shah et al.⁷¹ extended this model to include individual collagen fibril failure when fibrils were stretched beyond a specified limit to predict failure in thoracic aortic aneurysms. Lai et al.⁴⁴ added passive cells as pressurized inclusions in a collagen fibril network to understand how cells interact with the surrounding ECM and affect global tissue mechanics.

Proteoglycans compose 2–5% by dry weight of the blood vessel wall and affect the viscoelastic behavior⁸⁶. Proteoglycans have been included in a limited number of vascular constitutive models. Finite element and continuum modeling suggest that normal aggregates of proteoglycans support and sense mechanical loads, but that abnormal aggregates may over-pressurize the interlamellar space⁶⁵. Schmidt et al.⁶⁸ introduced a damage model with statistical contributions of an interconnected collagen fibril-proteoglycan network to the overall arterial mechanical behavior. Martufi and Gasser⁴⁹ modeled the vascular wall with a bundle of collagen fibrils interconnected by proteoglycans to predict differences between normal and aneurysmal aortas.

Active mechanical behavior—The most prevalent model of SMC mechanical behavior is the Hill model³¹. The Hill model consists of three elements: 1) a contractile element, 2) in series with an elastic element, 3) in parallel with an additional elastic element. The contractile element is generally associated with the active force generated by sliding actin-myosin filaments, but there is no distinct biological component for the series and parallel elastic elements. Many studies that have adopted versions of the Hill model eliminate the series elastic element and place the modified Hill model in parallel with elastic elements that model the passive tissue mechanics. This allows the total arterial wall stress to be additively decomposed into stress contributions from active and passive SMCs, collagen fibers, and elastin.

The contribution of active SMCs to arterial mechanics has been detailed using drugs to induce SMC contraction (i.e. norepinephrine, K^+ , endothelin-1, Ca^{2+}) or relaxation (i.e. potassium cyanide, sodium nitroprusside, papaverine, Ca^{2+} -free)^{14–16, 25, 40, 83, 94}. These experiments show that SMCs have a parabolic length-tension relationship. SMC tone at a particular length also depends on chemical signals, such as Ca^{2+} concentration³⁵. Rachev and Hayashi⁶⁰ observe that in vivo, SMCs operate along the ascending part of the length-tension relationship and are generally oriented circumferentially. They develop an active

SMC stress equation that is a parabolic function of the circumferential stretch multiplied by a constant that reflects the contractile activity under the current chemical conditions. They find that active SMCs under physiological conditions lead to a reduced transmural stress gradient, which is consistent with the experimental findings of Matsumoto et al.⁵¹. Other studies relate active SMC stress to a parabolic²⁵, Gaussian⁸, or logarithmic⁹⁴ function of circumferential stretch and an activation constant. A few studies have included active SMC stress as functions of both circumferential and axial stretch, as there is experimental evidence that SMCs can also generate active stress in the axial direction^{1, 40, 83}. In general, these models seek to predict arterial mechanical behavior under different conditions of SMC activation.

Bio-chemo-mechanical models

Although the SMC models discussed above include an activation constant that may be linked to concentrations of chemical stimuli, they do not include chemical kinetics equations that modulate the activation state. We define bio-chemo-mechanical models as those that link biological microstructure, chemical kinetics, and mechanics principles in the mathematical formulation to describe arterial mechanical behavior. We will focus on models that include chemical effects on SMC tone and contractility, rather than chemical effects on ECM components.

Hai and Murphy²⁸ present a model that describes the chemical kinetics of myosin phosphorylation and stress development in SMCs. In this model, the myosin heads (crossbridges) exist in one of four states: 1) detached, unphosphorylated crossbridges that cannot interact with actin filaments; 2) detached, phosphorylated crossbridges that can interact with actin filaments; 3) attached, phosphorylated crossbridges that are bound to actin filaments; and 4) attached, dephosphorylated crossbridges that are bound to actin filaments. The crossbridges can cycle between states 2 and 3, which causes filament sliding and generates contractile force. Some crossbridges can also proceed to state 4, known as the “latch state” where there is still a force between filaments (due to the bound crossbridges), but no active filament sliding.

Modified versions of the Hai and Murphy²⁸ model have been combined with mechanical SMC models (generally variations of the Hill³¹) model to produce bio-chemo-mechanical models of SMC activation^{43, 55, 73, 89}. Yang et al.⁸⁹ developed one of the most ambitious models of SMC activation, combining a chemomechanical subsystem with an electrochemical subsystem (Fig. 3). The electrochemical subsystem combines a lumped Hodgkin-Huxley type electrical circuit of the SMC membrane with a fluid compartment model that assumes ion concentrations remain constant in the extracellular media. The complete model is used to simulate contraction of a SMC under sustained isometric tension to lift a weight through a distance and the results closely mimic experimental observations. Yang et al.⁹⁰ embed this bio-chemo-electro-mechanical SMC model in a vessel wall model to sense environmental signals and predict macroscopic changes in the wall from subcellular behavior.

Stalhand et al.⁷³ expand the chemomechanical subsystem in Yang et al.⁸⁹ by explicitly deriving the coupling between chemical kinetics and cell mechanics based on a

thermodynamics approach. Their model is applicable to finite strains and demonstrates the diminished nonlinearity of the active SMC stress-stretch behavior with increased Ca^{2+} concentration. Two similar but slightly different versions of chemomechanically coupled models are proposed by Murtada et al.^{54, 55}. In addition to SMC contraction, passive mechanical behavior of the surrounding matrix is modeled by either isotropic neo-Hookean⁵⁴ or as the sum of isotropic and anisotropic⁵⁵ strain energy functions. While the isotropic neo-Hookean model focuses on the effects of a contractile unit (actin-myosin complex) on active force generation, the isotropic/anisotropic model includes the angular dispersion of smooth muscle myofilaments, providing a better understanding of the structural and functional interactions in SMC contraction. Murtada et al.⁵² add to their previous models by including a function of filament overlap and filament sliding behavior controlled by the cycling crossbridges in the contractile unit.

SMC activation is typically modeled in a one-dimensional (1D) framework, although three-dimensional (3D) continuum models have recently been developed. Stalhand et al.⁷⁴ and Schmitz and Bol⁶⁹ use 3D bio-chemo-mechanical models to predict the time and Ca^{2+} dependent active stress for a uniaxial tensile test. An expanded model for SMC contraction in 3D is proposed by Bol⁷, which incorporates the spatial and temporal progression of Ca^{2+} concentration during SMC activation in the dynamic state. Murtada and Holzapfel⁵³ implement a bio-chemo-mechanical model in a 3D finite element framework. They simulate the influence of time-dependent changes in wall thickness and Ca^{2+} concentration on the active stress of SMCs. Sharifimajd and Stalhand⁷² add SMC membrane excitation back to the bio-chemo-mechanical models to develop a bio-electro-chemo-mechanical model similar to Yang et al.⁸⁹, but applicable to finite deformations in 3D.

One difficulty in bio-chemo-mechanical modeling is linking across scales. Continuum based models at the tissue scale must be connected to models at the cellular and subcellular scale. There have been attempts at linking molecular and tissue scales for passive biomechanical models considering individual collagen fibrils or SMCs^{44, 47, 75}, but connecting molecular-level chemical signaling of active SMCs with tissue-level mechanics is even more challenging. Hayenga et al.³⁰ present an approach to link agent-based chemical models with continuum-based mechanical models that yields consistency across length scales and results similar to in vivo observations. Wang et al.⁸⁵ discuss possible ways in which deformation of the ECM can lead to changes in the cell nucleus and resulting chemical signaling, but there is much work to be done in linking physical and chemical changes across scales. A summary of considerations in bio-chemo-mechanical modeling is shown in Fig. 4.

Applications

Growth and remodeling

One key application of vascular mechanical modeling is to study changes over time during normal or pathological growth and development. In this case, the time course of cellular and ECM response to changes in mechanical, biological, or chemical stimuli must be incorporated into the model. Growth and remodeling of arteries has been modeled using local^{66, 76} or global⁵⁸ stress-dependent growth laws. The global stress model has been extended to include active SMC contributions^{22, 59} and microstructurally-linked passive

strain energy functions⁷⁸. While these models are effective in predicting growth and remodeling of the composite arterial wall due to changes in blood pressure or flow, they do not link the growth and remodeling to changes in specific wall components.

Humphrey and Rajagopal³⁹ propose a constrained mixture model for growth and remodeling of soft tissues. The authors assume that the arterial wall is a growing continuum and the total stress is the sum of the stresses in each constituent. Each constituent is produced in its natural configuration (Fig. 5) and is turned over to maintain mechanical homeostasis. Variations of this model have been employed to study growth and remodeling for hypertension^{26, 30, 79}, altered blood flow^{27, 79}, cerebral vasospasm^{6, 38}, aortic aneurysms^{46, 91}, aortic development^{4, 81}, and aortic aging⁸⁰. Many of the growth and remodeling models are restricted to a membrane or a single-layered wall, but thick-walled or multi-layered models have been studied^{4, 80}.

The stress contribution for each component in the arterial wall (i.e. elastin, collagen, and SMCs) for the constrained mixture models of arterial growth and remodeling are often based on phenomenological constitutive equations. Machyshyn et al⁴⁸ incorporated a microstructurally-linked constitutive equation for collagen that includes fiber angle and waviness¹⁹ into a growth and remodeling model of aneurysm development, which may be useful in determining how physical changes in individual structural components affect overall disease progression. Some of the models of growth and remodeling include general terms in the SMC active stress equation that account for concentrations of chemical stimuli, i.e. ratio of concentration of constrictors over dilators or Ca^{2+} concentration^{6, 38, 59, 79, 80}, but most do not couple detailed chemical signaling to the biomechanical changes. There is a need for new growth and remodeling models that include chemical stimuli.

Abnormal or diseased arteries

Constitutive models have been used to compare mechanical characteristics between normal and abnormal or diseased arteries. Biomechanical models have successfully described the behavior of diseased arteries with aging⁵, atherosclerotic plaques⁸⁸, Marfan syndrome²⁰, and reduced amounts of ECM proteins^{10, 84}. These applications provide insight into how specific wall components change with disease. Growth and remodeling models have also been applied to disease states, as discussed above. However, SMC activation and component turnover equations are usually based on phenomenological relationships, not experimental chemical kinetics. The bio-chemo-mechanical models to date generally predict experimental data for normal, not diseased, SMCs or arteries. Hence, there is room for better incorporation of biological, chemical and mechanical phenomena in models of arterial disease progression.

Aneurysms are often modeled by inducing local elastin degradation and then predicting the resulting remodeling of the artery wall^{48, 91}. However, this is a simplified version of the events occurring in aneurysm progression, which include alterations to SMC organization and phenotype, increases in amounts of matrix metalloproteinases that degrade both elastin and specific types of collagen, and production of dysfunctional type III collagen⁶⁷. These details are not incorporated into current bio-chemo-mechanical models. Le et al.⁴⁶ include altered SMC phenotype, reduced elastin amounts, and stiffening of collagen fibers in a

growth and remodeling model of aortic aneurysm progression in mice that do not express an elastic fiber protein, fibulin-4, in SMCs. Although these changes are able to qualitatively predict differences in mechanical behavior of the affected aortas, they are not linked to specific chemical signaling pathways. For aneurysms or congenital diseases where the gene modifications and some downstream effects are known, for example alterations to ECM proteins, SMC contractile proteins, or expression of specific SMC affecter molecules, it would be informative to start with measured changes to specific bio-chemo-mechanical model parameters, and then determine the effects on arterial mechanics and overall cardiovascular hemodynamics.

Tissue engineering

The main goal of vascular tissue engineering is to recreate the mechanical, biological, and chemical functionality of a native blood vessel. Bio-chemo-mechanical models can be used to design bio-reactors, chemical additives, and matrix materials for efficient production of tissue engineered vessels. Couet and Mantovani¹³ used genetic programming and Markov decision processes to optimize the elastic modulus of a vascular graft in a bioreactor by varying the strain, shear stress, and frequency of pulsatile flow. Presumably, the model could be expanded to include additional output and input variables. Other models have been developed that use mechanically-mediated growth, remodeling, damage, scaffold degradation, and/or ECM production to predict changes in the geometry and mechanical behavior of tissue-engineered vessels over time^{56, 61}. The models may be used to optimize culture conditions for specified outcomes. To our knowledge, there are not any current models that include chemical and mechanical data to optimize culture conditions for tissue-engineered vessels.

Concluding remarks and future directions

This review summarizes vascular constitutive models, as they have progressed from phenomenological, to microstructurally-linked, to bio-chemo-mechanical approaches. Bio-chemo-mechanical models promise to expand our knowledge of vascular behavior in health and disease, but there are several details that require future study. Most bio-chemo-mechanical models focus on SMC contraction through Ca^{2+} concentration and actin-myosin cross-bridge cycling. However, there are other structural changes in a contracting SMC, such as actin polymerization, that may affect the mechanical behavior^{12, 50}. Additionally, chemical interactions outside individual SMCs, for example between SMCs, between SMCs and ECs, and between SMCs and ECM fibers must be considered in future models. Multiscale approaches are needed to bridge length scales between the tissue and cells and the cell and molecules. Multiscale modeling has focused on individual cells or on passive ECM components, such as collagen fibers, and there is a gap in our knowledge as to how various components interact in the composite arterial wall. The short and long-term effects of chemical and mechanical signaling between wall components must be investigated for inclusion in detailed bio-chemo-mechanical models. Current models have focused on the short-term effects of SMC contraction, while effects over the long-term and how SMCs participate in active remodeling of wall components has received less attention. Expansion

of bio-chemo-mechanical models to include disease states and growth and remodeling behavior is needed.

Although we tried to focus on models for large elastic arteries, most of the bio-chemo-mechanical model predictions have been compared to data from a wide variety of tissue sources and from isolated SMCs. The general mechanism of actin-myosin crossbridge cycling may be common to all SMCs, but the appropriate model parameters and linking between chemical and mechanical systems likely vary by artery and tissue-type. Expanding bio-chemo-mechanical models and determining appropriate model parameters will require comprehensive experimental studies of the biological, mechanical, and chemical nature of the wall at instantaneous time points. It is important that these experiments are performed in a loading environment as close to the in vivo state as possible. For example, biaxial loading of arterial segments, rather than uniaxial loading of arterial rings or local loading of isolated SMCs. Experiments provide data needed to refine and improve models, while models provide new hypotheses to test in experiments. Future studies in vascular modelling will be quite challenging, but robust bio-chemo-mechanical models will provide information to predict vascular behavior in response to various mechanical and chemical stimuli. These results may be used for manipulating vascular behavior in disease or recreating it in tissue engineering.

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Figure 1.

Artistic rendering of the medial layer of the rat abdominal aorta based on images from serial block face scanning electron microscopy. Reproduced from O'Connell et al.⁵⁷ with permission from Elsevier. EL = elastic lamellae; EP = elastin pores; ES = elastin struts; Cyt = SMC cytoplasm; N = SMC nucleus. Image is oriented with the arterial lumen at the top and is 80 μm x 60 μm x 45 μm [circumferential (θ) x axial (Z) x radial (r)].

Figure 2.

Confocal image of collagen fibers in the adventitia of a rabbit carotid artery stained with CNA35-OG488, a fluorescently-labeled collagen specific binding protein⁴². Reproduced from Rezakhaniha et al.⁶² under open access agreement. Collagen fiber parameters that can be measured include global angle (a), thickness (t), overall length (L_f), and length of a straight line connecting the ends (L_o).

Figure 3.

Block diagram of the coupled electrochemical-chemomechanical SMC model presented in Yang et al.⁸⁹. A stimulus to the cell membrane causes a Ca^{2+} current to flow into the cell to the internal fluid compartments. This alters Ca^{2+} concentration, which controls actin-myosin contractile kinetics. The phosphorylation state of the myosin crossbridges controls the cell mechanical behavior and consequently the force generation.

Figure 4.

Summary of considerations for bio-chemo-mechanical modeling of vascular mechanics. For this review, we focused on chemical signaling that affects SMC active properties, but SMC passive properties and chemical effects on matrix proteins, such as degradation by proteases, mechanical alteration by crosslinking molecules, and synthesis of new matrix by SMCs are also important considerations in coupled models.

Figure 5.

Illustration of the reference configurations for a constrained mixture model of aortic growth and development. Reproduced from Wagenseil⁸¹ with permission from Springer. Arterial wall components (k = elastin, collagen, and SMCs) are turned over in response to changes in the hemodynamic forces on the arterial wall. They are produced at their natural or homeostatic stretch ratios in each direction ($\lambda_{\theta h}^k, \lambda_{zh}^k$) at some time in development when the mixture (composite arterial wall) is stretched $\lambda_{\theta u}, \lambda_{zu}$ from its unloaded state. At the current time, the mixture is stretched $\lambda_{\theta}, \lambda_z$ from its unloaded state and the components are stretched $\lambda_{\theta}^k, \lambda_z^k$ from their homeostatic states. The stress in the mixture is the sum of the stresses in each component.