IDENTIFICATION OF MATERIAL AND GEOMETRIC PARAMETERS OF ARTERIAL WALL FOR PATIENT-SPECIFIC VASCULAR GROWTH AND REMODELING MODELS

By

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ABSTRACT

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The uncertainty associated with an individual abdominal aortic aneurysm (AAA) rupture carries a considerable amount of health risks as well as social and economic burden. There is a need for advanced technologies to mitigate this burden by early detection, patient-specific risk assessment and clinical management. Computational vascular mechanics has been of great interest along with the recent advances in medical imaging, experimental technique and computational simulations. In particular, computational modeling of vascular growth and remodeling (G&R) has provided further understanding of the G&R process that occurs in vascular diseases. Despite rapid expansion of our knowledge of vascular G&R, developing patient-specific models of AAA evolution is still an open problem and subject to numerous challenges.

In this study, a framework is presented where, first the identification of the intrinsic material and geometric parameters for patient-specific modeling is addressed and then a finite element model of AAA G&R that accounts for medical image-based geometrical models is introduced. With regard to the material parameters, estimation of parameters of a multifiber family model for passive arteries in the presence of the measurement noise is considered. First, the uncertainty propagation due to the errors in variables is carefully characterized using the constitutive model. Then, the parameter estimation of the artery model is formulated into nonlinear least squares optimization with an appropriately chosen weight from the uncertainty model. The proposed technique is evaluated using multiple sets of synthesized data with fictitious measurement noises. The results of the estimation are compared with those of the conventional nonlinear least squares optimization without a proper weight factor. The proposed method significantly improves the quality of parameter estimation as the amplitude of the errors in variables becomes larger. We also investigate model selection criteria to decide the optimal number of fiber families in the multi-fiber family model with respect to the experimental data. The effect of multiple models for mechanical behavior of arteries is also investigated.

Distribution of the geometric parameters, being wall thickness and fiber orientations, are estimated using a 2-D parameterization of the vessel wall surface and a global approximation scheme integrated within an inverse optimization routine. Two conditions determine the objective of the optimization. First, the fundamental assumption in adaptation models, namely the existence of vascular homeostasis in normal vessels, should be maintained in a vessel model built from medical images. Second, the deviation of vessel wall from the original/image geometry subject to the normal pressure should be minimized. The same inverse technique is used to investigate the consequence of different homeostasis assumptions on the optimized distribution of parameters. The numerical optimization method results in a considerable improvement in both satisfying homeostatic condition and minimizing the deviation of geometry from the original shape based on in-vivo images.

Then, a finite element model of stress-mediated G&R of arteries based on medical imagebased geometries is presented for simulation of AAAs. Degradation of elastin initiates a local dilatation of the aorta while stress-mediated turnover of collagen and smooth muscle compensates the loss of elastin. Stress distributions and expansion rates during the aneurysm growth are studied for multiple spatial distributions of elastin degradation and kinetic parameters of the growth. Temporal variations of the elastin degradation and kinetic parameters are also investigated with either direct time-dependent degradation or stretch-induced degradation as possible biochemical and biomechanical mechanisms for elastin degradation. The results show that this computational model has the capability to capture the complexities of aneurysm progression due to variations of geometry, extent of damage, and stress-mediated turnover as an important step towards patient-specific modeling. To my parents whose endless patience, unwavering love and selflessness have been inspirational to me.

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Chapter 1

INTRODUCTION

1.1 Anatomy, structure and function of the aorta

The aorta is the largest artery that supplies oxygenated blood from the heart to other organs and tissues. It first extends from the heart in upward direction (called ascending aorta) towards the aortic bend (called aortic arch) and then turns downward into the body towards the diaphragm (called descending thoracic aorta). The portion of aorta below the diaphragm (descending abdominal aorta), located in front of spine, extends downward until it bifurcates into common iliac arteries supplying blood to legs. The aortic wall is comprises three distinct layers of tunica intima, tunica media, and tunica adventitia. The intima is the innermost layer of an aorta and consists of a layer of endothelial cells and a subendothelial layer of connective tissue. The internal elastic lamina separates the intima and the media. The media is the middle layer consisting if concentrically arranged smooth muscle cells, collagen fibers and elastin. The external elastic lamina separates the media and the adventitia. Finally, the outermost layer of an aorta, the adventitia, is primarily composed of fibroblasts, elastin and longitudinally arranged collagen fibers. The primary structural proteins that determine the mechanical properties of a ortic wall are collagen fibers and elastin, contents of which vary with age and physiological and pathological conditions and the anatomical location throughout the body.



Figure 1.1: Cross-section of the aorta, stained for smooth muscle cells using H&E (a) stained for elastin fibers using VVG(b), stained for collagen fibers using picosirius red in light microscopy (c) or observed under polarized microscope (d). (For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation).

A histological image of the cross-section of an aorta with different stains revealing different constituents is shown in Fig. 1.1. The cell nuclei are blue in (a), elastin is shown in black (b) while the collagen is red (c). In order to examine the orientation of collagen fibers, polarized light microscopy can be used (d).

1.2 Mechanical behavior of the aortic tissue

Like many other biological soft tissues, an aorta undergoes relatively large deformations and its behavior is nonlinear, inelastic, and anisotropic over finite strains. Figure 1.2 shows a typical stress-strain response of arterial tissue during the uniaxial test. During the first few loading cycles, the arterial tissue displays stress softening (Fig. 1.2). It then exhibits a nearly repeatable behavior (Fung et al., 1979), due to which the mechanical behavior of arterial tissues is commonly described by pseudo-elasticity. Also, as mentioned earlier, an artery is considered a layered mixture-composite of elastin, collagen fibers and smooth muscle cells as well as significant amount of water (Humphrey, 2002). Incompressibility has been found to be reasonable assumption in arterial mechanics (Chuong and Fung, 1984).



Figure 1.2: Typical stress-strain curves of a circumferential strip of an artery during the uniaxial test (Holzapfel et al., 2000).

1.3 Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA) is the focal dilation of the abdominal aorta that enlarges over the years and eventually rupture which is considered as one the leading causes of mortality. AAAs affect 2 million people in the US alone and are associated with some environmental risk factors such as smoking, hypertension and genetic predisposition (Powell, 2002). Despite the abundant clinical studies, the etiology and the natural history of AAAs remains poorly understood. Aortic aneurysm may reach to 3.5-13 cm in diameter with an expansion rate of 0.1-1.5 cm/year (Humphrey, 2002). Aneurysmal wall is commonly devoid of elastin and smooth muscle with a higher ratio of mass for collagen (He and Roach, 1994), thus giving rise to a fibrotic wall with a stiffer structure. Disruption of elastin, either as a cause or as a consequence of the disease process, is associated with aneurysm dilation, while collagen failure was found necessary for rupture (Dobrin et al., 1984).

Current treatments of AAA include either open repair which involves invasive surgery with extensive tissue dissections or minimally invasive endovascular repair (Vorp and Vande Geest, 2005). Both treatments are costly and associated with significant amount of risks. The current clinical decision making for surgical treatments is based on "maximum diameter criterion". That is, the likelihood of AAA rupture is assumed to be higher than the risk of surgical treatments when the aneurysm reaches 5-5.5 cm in diameter (Vorp, 2007). Yet it is not clear when an individual AAA may rupture since a considerable amount of AAAs may rupture at smaller sizes. As the population of elderly people grows, the social and economic burden, imposed by the uncertainty of AAA rupture, will increase. In order to reduce this public health burden, there are crucial needs for advanced technologies that can provide AAA patients with early detection, patient-specific risk assessment, and safe clinical interventions.

1.4 Computational analysis of AAA

Mechanically rupture of the tissue occurs when the local stress exceeds the tissue strength. In that sense, computational stress analysis based on 3D Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) using nonlinear constitutive models of the vessel enabled researchers to estimate wall stress more accurately (Dorfmann et al., 2010; Fillinger et al., 2002; Raghavan et al., 2000; Rissland et al., 2009; Speelman et al., 2007) and, hence, led to a better prediction of AAA rupture risk than the maximum diameter criterion.

However estimation of the stress alone may not provide a reliable estimation of rupture potential since the rupture potential depends also on the strength (Vorp and Vande Geest, 2005). Strength of AAA wall tissue depends on its integral microstructure which is constantly evolving in an abnormal fashion. Furthermore, finite element (FE) analysis based on a patient-specific geometry yields the stress distribution only for a fixed geometry and does not account for the time evolution of AAA shape and the wall mechanics.

1.5 Computational modeling of vascular growth

During normal or disease conditions (e.g. aortic aneurysms), arterial wall undergoes continuous changes in terms of morphology, histology and biomechanics in an adaptive manner. Vascular tissue exhibits a remarkable ability to adapt in various physiological and pathological conditions, often thought to be governed by mechanical factors (Driss et al., 1997; Jackson et al., 2005; Mulvany, 1992). Understanding adaptive processes involving aortic tissue growth (i.e. change in mass) and remodeling (i.e. change in structure) is instrumental in developing models capable of simulating AAA evolution.

For the past decade, computational modeling of vascular growth and remodeling (G&R) have been developed and used to test multiple hypotheses based on experimental and clinical studies (Watton et al., 2004; Menzel, 2005; Baek et al., 2006; Hariton et al., 2007b; Kroon and Holzapfel, 2007; Kuhl et al., 2007; Figueroa et al., 2009; Kroon and Holzapfel, 2009a;

Watton and Hill, 2009). Mechanical stress/strain is the parameter driving adaptation process in all models. Mechanical homeostasis is the fundamental assumption of most G&R models, meaning there is a tendency toward a preferred level of mechanical stress/strain throughout the arterial tissue. Despite being focused on symmetric or idealized geometries, those models revealed a great potential in understanding basic features of vascular G&R. However, in-vivo aortic aneurysms normally evolve into irregular 3-D shapes and idealized models of G&R are not sophisticated enough to capture patient-specific features of an in-vivo AAA.

1.6 Motivations

Ultimately, for clinical applications, the current stage of modeling needs to be improved to utilize patient-specific geometries of AAAs. Along with the recent advances in medical imaging, this can revolutionize the state-of-the-art analyses and clinical interventions. Patient-specific modeling raises new challenges with regard to characterization of patientspecific parameters of the vessel wall or aneurysmal tissue under certain conditions.

With regard to material parameters intrinsic to the material, mechanical experiments have been widely conducted to develop appropriate constitutive forms for the mechanical behavior of arteries and to estimate the associated constitutive parameters. Meanwhile, less attention has been paid to the fact that measurements are not error-free and precise and unbiased parameter estimation in vascular mechanics requires one to consider the uncertainty in all measured variables when estimating parameters. Furthermore, identification of geometric parameters, e.g. wall thickness and material anisotropy, becomes challenging for patient-specific models when certain conditions are to be satisfied. First condition to be met is the mechanical homeostatic state as the main assumption for G&R models. Second condition stems from the fact that the stress-free configuration is not available when a medical image-based geometry is used. That is, during the computation, the geometry no longer coincides with the original or image geometry under the physiological loads.

1.7 Objectives

The ultimate goal of this study is to develop patient-specific models of AAA G&R. Toward that goal, multiple specific aims are set in this study based on the existing challenges as:

- Develop an enhanced least squares method to account for the measurement noise in estimation of material constitutive parameters.
- Develop an optimization scheme needed to estimate arterial wall thickness and anisotropy such that the patient-specific conditions are satisfied.
- Develop a 3-D finite element framework capable of modeling AAAs growth using patient-specific geometries.

In chapter 2 a weighted nonlinear least squares method that incorporates a noise model is proposed and its advantage over the conventional nonlinear least squares is demonstrated. In chapter 3, different constitutive relations are tested for parameter estimation of mechanical behavior of mouse carotid and rabbit basilar arteries. In chapter 4 an inverse optimization technique is developed to estimate the distributions of wall thickness and material anisotropy such that the vascular homeostatic as well as the geometric conditions are satisfied simultaneously. Using the proposed technique in chapter 4, different hypotheses for mechanical homeostasis are examined in chapter 5. In chapter 6 an image-based finite element model for vascular adaptation is presented and its application to AAA is demonstrated in sample simulation cases. Chapter 7 presents a framework for simulation of AAA, demonstrates the potential utility of the framework with additional simulation cases, and discusses its shortcomings and future developments.

Chapter 2

ESTIMATION OF MATERIAL PARAMETERS OF ARTERIAL WALL TISSUE USING A WEIGHTED NONLINEAR LEAST SQUARES METHOD

2.1 INTRODUCTION

Mechanical properties of the arterial wall vary with anatomical variations and for different species. It has also been suggested that the structure and material properties of the arterial wall alter under various physiological or pathological conditions (Langille, 1993; Humphrey, 2008). In such studies, precise parameter estimation is essential to quantify the difference in mechanical behavior. In vascular mechanics, mechanical behavior of the arterial wall is typically described by a nonlinear equation,

$$\mathbf{y} = \mathbf{f}(\mathbf{x}, \boldsymbol{\Theta}), \tag{2.1}$$

where \mathbf{x} and \mathbf{y} are vectors of independent and dependent variables and Θ is a set of unknown parameters. Experimental studies in vascular mechanics normally utilize a nonlinear least squares (NLS) technique in which the sum of the squares of the difference between the experimental measurements and the calculated responses of dependent variables \mathbf{y} (e.g., pressure and axial force) is minimized, while independent variables \mathbf{x} (e.g., outer diameter and axial stretch) are considered free of error (Pandit et al., 2005; Schulze-Bauer and Holzapfel, 2003; Wang et al., 2006). All variables, however, are measured with errors and it is known that an NLS method results in biased parameter estimation when uncertainty exists in all variables in a constitutive model (Emery et al., 2000; Fadale et al., 1995). In such a case, parameter estimation should be correctly formulated as the nonlinear least squares optimization with an appropriately chosen objective function (Fadale et al., 1995; Schwetlick and Tiller, 1985).

It appears that the arterial wall owes its main mechanical characteristics, such as the progressive stiffening and anisotropy, to collagen fibers and their orientations (Holzapfel et al., 2000). Many constitutive models have been proposed to account for the distribution of collagen fibers (e.g. Lanir et al., 1996; Gasser et al., 2006). These models use exponential functions for collagen fibers in their constitutive models and in general fitted well the progressive stiffening with the increasing stretch. When there exist measurement noises in experimental data, however, one often experiences difficulty in obtaining a good fit in the high stretch region, which also causes inaccurate estimation of vascular stiffness. In this paper, a weighted nonlinear least squares (WNLS) optimization is presented to estimate the parameters of a multi-fiber model of arteries (Baek et al., 2007a; Hu et al., 2007; Masson et al., 2008) considering the uncertainty due to the measurement errors in all variables. An uncertainty model is first derived from the constitutive equation assuming that experimental measurements are corrupted by the independent and identically distributed Gaussian noise. Then, the WNLS optimization is formulated using the inverse of the covariance matrix of the uncertainty as a correct weight factor. The proposed technique is evaluated using multiple sets of fictitious data containing the measurement errors (with multiple noise levels) in all variables and the estimation results are compared with those of the conventional NLS optimization (without a proper weight factor).

In parameter estimation, the larger number of parameters for a model provides more flexibility and generally gives better fitting, i.e., decreases the residual error. However, too many parameters increase the bias error as well as the complexity of the model. When the degrees of freedom in parameter estimation exceed the information in the data, the resulting estimated model cannot be generalized beyond the fitting data. In statistics, this phenomenon is usually referred to as *overfitting* (Naik et al., 2007). Therefore, there is a tradeoff between descriptive accuracy and parsimony, which can be addressed by a model selection criterion (Wagenmakers and Farrell, 2004). Multiple model selection criteria are utilized to investigate an optimal number of parameters (or fiber families) for two different arteries.

2.2 METHODS

2.2.1 Constitutive relations for the mechanical behavior of the passive artery

Cyclic inflation of an arterial segment at multiple fixed lengths is a typical biaxial test in vascular mechanics. The measurements include the axial force and internal pressure (recorded by the load cell and pressure transducer) versus changes in the diameter and axial stretch (recorded by the optical system). Experimental data from the test is used to determine appropriate constitutive relations based on the assumption of an ideal cylindrical geometry of the artery (Humphrey, 2002). In the current study, a microstructurally motivated, multi-fiber family model is used. That is, a constitutive strain energy including an isotropic neo-hookean strain energy function (associated with elastin) and strain energy functions due to multiple collagen fiber families is assumed (Holzapfel et al., 2000; Baek et al., 2007a):

$$\hat{W} = \frac{c}{2}(I_1 - 3) + \sum_k \frac{c_1^{(k)}}{4c_2^{(k)}} \left\{ \exp\left(c_2^{(k)}(\lambda^{(k)^2} - 1)^2\right) - 1 \right\},$$
(2.2)

where, $c, c_1^{(k)}$ and $c_2^{(k)}$ are material parameters, such that $c, c_1^{(k)}$ and $c_2^{(k)} \ge 0$, (Holzapfel, 2006; Holzapfel et al., 2004). $I_1 = \text{tr } \mathbf{C}$, where \mathbf{C} is the right Cauchy-Green deformation

tensor. $\lambda^{(k)}$ is the stretch of the k^{th} fiber family, given by

$$\lambda^{(k)} = \sqrt{\left(\lambda_{\theta} \sin \alpha^{(k)}\right)^2 + \left(\lambda_z \cos \alpha^{(k)}\right)^2},\tag{2.3}$$

where $\alpha^{(k)}$ is the orientation of the fiber family, and λ_z and λ_{θ} are the axial and circumferential stretches. The intramural stress can be obtained as

$$\mathbf{T} = -p\mathbf{I} + \hat{\mathbf{T}}, \qquad \hat{\mathbf{T}} = \frac{2}{J}\mathbf{F}\frac{\partial W}{\partial \mathbf{C}}\mathbf{F}^{T}, \qquad (2.4)$$

where p is a Lagrange multiplier, **F** is the deformation gradient, and J is its determinant. For an ideal straight tube, the Eq. (2.4) expands to the following three equations

$$T_{\theta\theta} = -p + c\left(\frac{r}{R}\right)^2 + \left(\frac{r}{R}\right)^2 \sum_k \left\{ c_1^{(k)} (\lambda^{(k)^2} - 1) \exp\left(c_2^{(k)} (\lambda^{(k)^2} - 1)^2\right) \sin^2 \alpha^{(k)} \right\}, \quad (2.5)$$

$$T_{zz} = -p + c\lambda_z^2 + \lambda_z^2 \sum_k \left\{ c_1^{(k)} (\lambda^{(k)^2} - 1) \exp\left(c_2^{(k)} (\lambda^{(k)^2} - 1)^2\right) \cos^2 \alpha^{(k)} \right\},$$
(2.6)

$$T_{rr} = -p + c \left(\frac{R}{r\lambda_z}\right)^2.$$
(2.7)

For a thin membrane, the transmural pressure P_i and the axial force F_z can be approximated by (See Appendix A)

$$P_i = \frac{h\left(\hat{T}_{\theta\theta} - \hat{T}_{rr}\right)}{r_m} \tag{2.8}$$

$$F_{z} = 2\pi r_{m} h \left(\hat{T}_{zz} - \hat{T}_{rr} \right) - \pi \left(r_{m}^{2} - r_{c}^{2} \right) P_{i}, \qquad (2.9)$$

where, $r_m = (r_i + r_o)/2$, $h = r_o - r_i$, and r_c is the radius of cannula. \hat{T}_{rr} , $\hat{T}_{\theta\theta}$ and \hat{T}_{zz} are the normal components of stress in the radial, circumferential, and axial directions respectively. Thus, by substituting (3.1)-(2.4) into (2.8) and (2.9), the theoretical relation between a force vector $\mathbf{y} = [F_z, P_i]^T$ and a displacement vector $\mathbf{x} = [\lambda_z, d_o]^T$ can be derived as in Eq. (2.1).

2.2.2 WNLS optimization for a biaxial test of the artery

In experiments, all variables are measured with errors and we denote the measured variables as $\hat{\mathbf{x}}_n = [\lambda_z(t_n), d_o(t_n)]^T$ and $\hat{\mathbf{y}}_n = [F_z(t_n), P_i(t_n)]^T$ at time t_n for $n = 1, \ldots, m$. The true values of the variables are denoted by $\tilde{\mathbf{x}}_n$ and $\tilde{\mathbf{y}}_n$, which are corrupted by the measurement errors, $\boldsymbol{\epsilon}_n$ and \mathbf{e}_n during the experiment, i.e. the measured variables can be written as

$$\hat{\mathbf{x}}_n = \tilde{\mathbf{x}}_n + \boldsymbol{\epsilon}_n \tag{2.10}$$

$$\hat{\mathbf{y}}_n = \tilde{\mathbf{y}}_n + \mathbf{e}_n, \tag{2.11}$$

where $\epsilon_n \sim WN(0, \Sigma_{\epsilon})$ and $\mathbf{e}_n \sim WN(0, \Sigma_{\mathbf{e}})$ are assumed to be independent and identically distributed Gaussian noises with zero means and corresponding covariance matrices.

In order to consider the measurement errors in all variables, the total least squares estimation problem can be formulated by the following objective function (Beck and Arnold, 1977; Schwetlick and Tiller, 1985):

$$S = \sum_{n=1}^{m} \begin{pmatrix} \hat{\mathbf{y}}_n - \mathbf{f}(\mathbf{x}_n, \mathbf{\Theta}) \\ \hat{\mathbf{x}}_n - \mathbf{x}_n \end{pmatrix}^T \Sigma_n^{-1} \begin{pmatrix} \hat{\mathbf{y}}_n - \mathbf{f}(\mathbf{x}_n, \mathbf{\Theta}) \\ \hat{\mathbf{x}}_n - \mathbf{x}_n \end{pmatrix},$$
(2.12)

where Σ_n is a collective covariance matrix of the measurement errors. Then, we need to solve for $2m + N(\Theta)$ unknowns to minimize Eq. (2.12), where *m* is the number of data points and $N(\Theta)$ is the number of parameters in Θ . Considering a nonlinear function, such as Eq. (2.1), an iterative scheme (e.g., Gauss-Newton method) has to be employed. Solving the nonlinear regression problem with such a large number of unknown variables is very difficult. Schwetlick and Tiller (1985) stated that for the NLS optimization, solving the total least squares estimation problem using a standard software "cannot be recommended unless the problem is small." Consequently, in this study, we use the classical parameter estimation method with only $N(\Theta)$ unknowns in the objective function:

$$S = \sum_{n=1}^{m} \left(\hat{\mathbf{y}}_{n} - \mathbf{f} \left(\hat{\mathbf{x}}_{n}, \boldsymbol{\Theta} \right) \right)^{T} \mathbf{W}_{n} \left(\hat{\mathbf{y}}_{n} - \mathbf{f} \left(\hat{\mathbf{x}}_{n}, \boldsymbol{\Theta} \right) \right)$$
(2.13)

where \mathbf{W}_n are appropriately chosen weight matrices. The problem is, then, to solve for Θ by minimizing Eq. (2.13) with correct weights obtained by the uncertainty model which will be referred to as the WNLS optimization. Let the uncertainty model \mathbf{v}_n represent the uncertainty in $\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \Theta)$. The uncertainty in $\mathbf{f}(\hat{\mathbf{x}}_n, \Theta)$ is propagated from the measurement noise of $\boldsymbol{\epsilon}_n$, and it can be approximated by using the Taylor series of \mathbf{f} with respect to $\boldsymbol{\epsilon}_n$ and ignoring the higher order terms of $\boldsymbol{\epsilon}_n$ in the series. Then, the uncertainty model \mathbf{v}_n for $\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \Theta)$ can be obtained as:

$$\mathbf{v}_n = -\frac{\partial \mathbf{f}}{\partial \mathbf{x}}(\tilde{\mathbf{x}}_n, \mathbf{\Theta}) \ \boldsymbol{\epsilon}_n + \mathbf{e}_n. \tag{2.14}$$

Note that the uncertainty model for the force measurement now includes the effect of measurement noise in the displacement. Eq. (2.14) shows that the uncertainty increases with an increase in $\partial \mathbf{f}/\partial \mathbf{x}$, which is a stiffness term in vascular mechanics. To incorporate the uncertainty model into Eq. (2.13), the inverse of the covariance matrix of the uncertainty has to be used as the weight factor (Beck and Arnold, 1977; Emery et al., 2000). The covariance matrix for \mathbf{v}_n is derived as:

$$\boldsymbol{\Sigma}_{v_n} = \mathbb{E}(\mathbf{v}_n \mathbf{v}_n^T) = \left(\frac{\partial \mathbf{f}}{\partial \mathbf{x}}\right) \boldsymbol{\Sigma}_{\boldsymbol{\epsilon}} \left(\frac{\partial \mathbf{f}}{\partial \mathbf{x}}\right)^T + \boldsymbol{\Sigma}_{\mathbf{e}},\tag{2.15}$$

where $\mathbb{E}(A)$ is the expectation of A. Finally, using the uncertainty model Eq. (2.14), the objective function Eq. (2.13) can be written as:

$$S = \sum_{n=1}^{m} \left(\hat{\mathbf{y}}_{n} - \mathbf{f} \left(\hat{\mathbf{x}}_{n}, \boldsymbol{\Theta} \right) \right)^{T} \boldsymbol{\Sigma}_{v_{n}}^{-1} \left(\hat{\mathbf{y}}_{n} - \mathbf{f} \left(\hat{\mathbf{x}}_{n}, \boldsymbol{\Theta} \right) \right).$$
(2.16)

The correct modeling of the measurement error and the formulation of the WNLS optimization will provide the minimum estimation error variance. For the computation, however, the initial estimates Θ^o are obtained by the NLS optimization without the uncertainty model. Then, the covariance matrix Σ_{v_n} in Eq. (2.16) is approximated using the estimates Θ^o and $\hat{\mathbf{x}}_n$. With Σ_{v_n} , the new estimates of Θ^1 are obtained by minimizing Eq. (2.16). The covariance matrix Σ_{v_n} is then updated iteratively using the previous estimates for the next optimization. The estimates in each iteration are obtained by using constrained optimization in Matlab (The Mathworks Inc.) with multiple choices of initial points, and one to three iterations are used to obtain the final estimates in this paper.

Vascular stiffness changes according to alterations in physiological and pathophysiological conditions, such as aging (O'Rourke and Hashimoto, 2007), hypertension (Hu et al., 2007), during pregnancy (Hu et al., 1998), and diabetes mellitus (Oxlund et al., 1989). Accurate assessment of the arterial wall stiffness in physiological range can play an important role in understanding the pathophysiology and progression of vascular diseases. The linearized circumferential stiffness from both the WNLS and NLS methods is calculated and compared for its accuracy (see Baek et al., 2007a for linearization). The results demonstrate that our proposed scheme provides a more accurate assessment of the arterial stiffness.

2.2.3 Model selection criteria for optimal number of parameters

In order to find the optimal number of parameters (or number of fiber families) for the multifiber family model (Eq. (3.1)), three different criteria for model selection are utilized; Akaike information criterion (AIC; Glatting et al., 2007), a modified form of AIC (AICc; Glatting et al., 2007), and the root mean square error measure (RMS; Holzapfel et al., 2005), given by

AIC =
$$m \ln\left(\frac{S}{m}\right) + 2(N+1)$$
 (2.17)

AICc = AIC +
$$\frac{2(N+1)(N+2)}{m-N-2}$$
 (2.18)

$$RMS = \sqrt{\frac{S}{m-N}}$$
(2.19)

where S, N, and m are, respectively, the residual, the number of parameters, and the sample size. AIC was first introduced by Akaike (1974, 1981) based on the concept of entropy to describe the tradeoff between bias and variance in model construction. AIC has been used as a model selection criterion that selects an optimal model by considering both the precision of fitting and the complexity of the model (Anderson et al., 1994). While the first term in the right hand side of Eq. (2.17) decreases with a decrease in the residual, the second term penalizes it for increasing the size (number of parameters) of the model and prevents *overfitting*. RMS in Eq. (2.19) has also been used as a heuristic criterion in selecting among models although no statistical justification exists (Myung, 2000). The number of parameters that minimizes a given criterion is considered as being optimal for the model.

In the multi-fiber family model, the number of parameters increases with an increase in the number of fiber families. The fibers are assumed to be symmetric with respect to the axial axis on the vessel wall. In order to evaluate the model selection criteria, the residual Eq. (2.16) is obtained by increasing the number of fiber families from 2 to 10 for each data set. Briefly, the 2-fiber-family model has 4 independent parameters ($c, c_1^1 = c_1^2$, $c_2^1 = c_2^2$ and $\alpha^1 = -\alpha^2$). For the 3-fiber-family model, one more fiber family is added in either circumferential direction or axial direction to minimize the residual, which results in 6 (independent) unknown parameters. The 4-fiber-family model has two symmetric fibers in helical directions, one in the axial direction, and one in the circumferential direction resulting in 8 independent parameters. From 6 fiber families, two additional symmetric fibers are added at each step, yielding three additional parameters (an angle and two parameters for the exponential function). Hence, 11, 14, and 17 independent parameters are assumed for 6-, 8-, and 10-fiber-family models respectively.

The model selection criteria are specific to the experimental data. Hence, experimental data from two rabbit basilar arteries and three mouse carotid arteries are tested in order to investigate optimal number of fiber families.

2.3 RESULTS

2.3.1 Comparison between the proposed WNLS optimization and the conventional NLS optimization

In order to demonstrate the effectiveness of the proposed WNLS method, noise-corrupted, fictitious experimental data were generated and the parameter estimation was performed using the WNLS method as well as the standard approach (NLS) without an uncertainty model. Assuming a set of "true" parameters, the synthesized true data was generated for the inflation test at fixed axial stretches ($\lambda_z = 1.2, 1.3, 1.4$), i.e., the pressure and axial force data were obtained from Eq. (2.1) for a given radius and axial stretch using the true parameters. Gaussian noises with given noise levels were numerically generated and added to the synthesized data of { d_o, λ_z, F_z, P_i } to produce fictitious experimental data. The noise level was defined as the ratio of the standard deviation of the noise to the maximum value of the data. Figure 2.1 shows the pressure vs. radius plots for $\lambda_z = 1.2, 1.3, 1.4$ for the true as well as the fictitious data at noise levels of 0.005 and 0.01.

Then, the NLS and proposed WNLS methods were used to estimate parameters for each fictitious data set. Figure 2.2 shows pressure-radius and axial force-radius plots using the true material parameters and the data calculated with estimated parameters of the 4-fiber-family model for both the NLS and WNLS methods. Evidently, the graphs show better fitting curves for pressure and axial force when the uncertainty model is incorporated (Figures



Figure 2.1: Pressure versus radius plots for the 4-fiber-family model for a set of true data (solid lines) and fictitious noisy data (dotted lines) at noise levels of 0.005 (a) and 0.01 (b) and different axial stretches $\lambda_z = 1.2, 1.3, 1.4$.

2.2(b) and (d)).

Figure 2.3 shows another set of fictitious data with higher slopes in the high stretch region and the corresponding fitting curves using both the NLS and WNLS methods. The WNLS significantly improved the slope of the fit especially in the high stretch region (Figures 2.2 and 2.3).

The advantage of the WNLS method over the standard NLS method is more obvious for the data with higher slopes (Figure 2.3). Table 2.1 summarizes all true and estimated values of parameters corresponding to Figures 2.2 and 2.3.

For a quantitative measure of estimation errors, the following normalized error was defined as (Baek et al., 2007a):

$$e = \frac{1}{2} \left(\sqrt{\frac{\sum (P_{est} - P_{true})^2}{\sum (P_{true})^2}} + \sqrt{\frac{\sum (F_{est} - F_{true})^2}{\sum (F_{true})^2}} \right), \tag{2.20}$$

where P_{est} and P_{true} are the estimated and true values of pressure. F_{est} and F_{true} are the estimated and true values of axial force. Normalized errors, e, were obtained and averaged over a set of five different random noise sequences at each noise level. Table 2.2 shows the averaged, normalized errors obtained from both the NLS and WNLS methods at noise



Figure 2.2: Comparison between the NLS (a and c) and WNLS (b and d) optimizations for the 4-fiber-family model. Pressure and axial force versus radius are plotted using true parameters (dotted lines) and estimated parameters (solid lines) for the data with moderate slopes at different axial stretches $\lambda_z = 1.2, 1.3, 1.4$



Figure 2.3: Comparison between the NLS (a and c) and WNLS (b and d) optimizations for the 4-fiber-family model. Pressure and axial force versus radius are plotted using true parameters (dotted lines) and estimated parameters (solid lines) for the data with stiff slopes in the high stretch region at different axial stretches $\lambda_z = 1.2, 1.3, 1.4$.

		c(kPa)	$c_1^1(kPa)$	$c_1^2(kPa)$	c_1^3 (kPa)	c_{2}^{1}	c_{2}^{2}	c_{2}^{3}	α^1 (°)
Fig. 2.2	True NLS WNLS	0 0 0	$0.36 \\ 0.71 \\ 0.39$	7.9 14.2 8.7	1.2 1.1 1.1	$ 4.3 \\ 3.72 \\ 4.23 $	$1.64 \\ 1.12 \\ 1.56$	$3.07 \\ 3.1 \\ 3.15$	$40.3 \\ 42 \\ 41.4$
Fig. 2.3	True NLS WNLS	0 0 0	$0.28 \\ 1.3 \\ 0.28$	$1.73 \\ 9.34 \\ 3.4$	$0.2 \\ 0.22 \\ 0.27$	$4.73 \\ 3.05 \\ 4.73$	$2.96 \\ 1.52 \\ 2.36$	$4.92 \\ 4.63 \\ 4.53$	$45.6 \\ 40.5 \\ 44.5$
Fig. 2.4(a)	WNLS	42	7.29	14	0.0003	0.152	0	3.11	55.9
Fig. 2.4(b)	WNLS	0	18	14	6.2	1.37	1.48	5.64	47.9

Table 2.1: True and estimated parameters for the fictitious data with moderate and high slopes (corresponding to Figures 2.2 and 2.3) and the experimental data from mouse carotid and rabbit basilar arteries (corresponding to Figures 2.4(a) and 2.4(b)).

levels of 0.005, 0.008, 0.01, 0.02, and 0.03. The WNLS method resulted in normalized errors smaller than those from the NLS method at all noise levels.

True and estimated values of the circumferential stiffness at $P_i = 75$ mmHg and $\lambda_z = 1.3$ corresponding to Figures 2.2 and 2.3 are shown in Table 2.3. The WNLS method resulted in much better estimation than the NLS method for both cases. For example, corresponding to the data of Figure 2.2, the error of estimated stiffness using the NLS method was about 15 percent whereas it was less than 3 percent when using the WNLS method.

2.3.2 Optimal number of fiber families

Experimental data from two rabbit basilar arteries (Baek et al., 2007a) and three mouse carotid arteries (Dye et al., 2007) were used to investigate the optimal number of fiber families for the proposed model. Figures 2.4(a) and 2.4(b) depict experimental data for these arteries as well as the best-fit curves using the WNLS optimization with the 4-fiber-family model. For all sets of data tested, residuals for the WNLS optimization reduced significantly up to

Noise level	0.005	0.008	0.01	0.02	0.03
$e_{NLS} e_{WNLS}$	$0.0093 \\ 0.009$	$\begin{array}{c} 0.018\\ 0.01 \end{array}$	$0.03 \\ 0.0123$	$0.07 \\ 0.025$	$0.12 \\ 0.078$
$\frac{\mathrm{e}_{NLS}}{\mathrm{e}_{WNLS}}$	1.033	1.8	2.44	2.8	1.54

Table 2.2: Averaged normalized error e at different noise levels using the NLS and WNLS methods.

Table 2.3: True and estimated linearized stiffness at $P_i = 75$ mmHg and $\lambda_z = 1.3$ corresponding to Figures 2.2 and 2.3 using the NLS and WNLS methods.

	True stiffness(kPa)	NLS stiffness(kPa)	WNLS stiffness(kPa)	
Fig. 2.2	1114	944	1085	
Fig. 2.3	1580	1105	1381	

3-fiber-family model (6 parameters), and then slightly decreased for further increase in the number of fiber families (see e.g. Figures 2.4(c) and 2.4(d)). Interestingly, three different criteria led to an identical optimal number of parameters for each mouse and rabbit data, which were found to be 11 parameters (6 fiber families). Estimated parameters corresponding to Figures 2.4(a) and 2.4(b) are listed in Table 2.1.

2.4 DISCUSSION

Parameter estimation using the NLS optimization has been widely used in characterizing mechanical behavior of soft tissues from the experiments. In this study, we proposed an improved parameter estimation technique considering the measurement errors in variables. If the measurement errors in independent variables are negligible (i.e., $\Sigma_{\epsilon} \sim 0$), then the proposed method becomes identical to the conventional NLS method. However, in many



Figure 2.4: Pressure-radius-axial stretch curves are plotted from fitting of the experimental data for the mouse carotid artery (a) and rabbit basilar artery (b) using the WNLS optimization. Circles show data points and solid lines show the estimated values. AICc and the residual are plotted against the number of parameters; 4, 6, 8, 11, 14, 17 (or the number of fiber families; 2, 3, 4, 6, 8, 10) for the mouse carotid (c) and rabbit basilar (d) arteries using the WNLS optimization.
studies (i.e., arterial inflation and extension tests) such measurement errors are not negligible. For example, Saravanan et al. (2006) reported that when the deformation was approximated by a linear polynomial using three markers, the error in the first invariant of the right Cauchy-Green deformation tensor was ± 0.06 , which is comparable with noise levels we considered in this study. Although these problems can be treated as *total least squares* problems or errors-in-variables models (Beck and Arnold, 1977; Huffel and Vandewalle, 1991), solving a nonlinear problem with a large number of unknown variables is still very challenging. Instead, we developed a WNLS technique based on accurate modeling of uncertainty given by Eq. (2.14). It was shown that the WNLS optimization with a proper uncertainty model improves the quality of parameter estimation significantly compared to the conventional NLS optimization at all noise levels. Especially, for a collagenous tissue, $\partial \mathbf{f} / \partial \mathbf{x}$ is larger in the high stretch region, so it produces a higher level of uncertainty propagation and, hence, the estimation results are biased when the displacement measurement error is not considered within a proper uncertainty model (Figure 2.3). The advantage of using the WNLS was more pronounced at higher noise levels. The WNLS method provided a better fit in the high stretch region and proved to be advantageous when estimating the linearized stiffness within the physiological range.

In the current work, synthesized data was used along with Gaussian noises to evaluate the WNLS optimization. In experiments, however, the measurement noise should be carefully characterized. Furthermore, although the proposed WNLS optimization helps eliminate the biased error due to the measurement errors, it is noteworthy that parameter estimation can be limited by the model error induced by the chosen constitutive relation.

The presented constitutive model is similar to the one developed by Holzapfel et al. (2000) and Holzapfel et al. (2004), but has been used in thin wall models (Baek et al., 2007a; Hu et al., 2007; Masson et al., 2008). It has also been utilized in modeling of vascular adaptation during progression of vascular diseases (Baek et al., 2006, 2007b). However, the vessel wall presents more dispersed fiber orientation in the adventitia and intimal layers and the use of an orientation density function has been proposed (Lanir et al., 1996; Gasser et al., 2006). The choice of the functional form of the constitutive relation may involve multiple factors such as the anatomic location of the artery, available microstructural information, and the specific application and, hence, it is beyond the scope of the present work. Instead, our focus has been on the situation that one has a functional form of a constitutive relation and needs to find optimal number of parameters and best parameters from experimental data. The presented parameter estimation method is, however, general enough and can be utilized with various models for vascular mechanics.

Three criteria were used to evaluate optimal number of parameters (fiber families) for the chosen constitutive model of arteries. The best model between several competing models is one that provides an adequate account of the data while using a minimum number of parameters. Based on the available data and using three different criteria, we found that the model with 11 parameters (6 fiber families) minimized our criteria.

In closing, the need for the optimal design of experiments and optimal sampling protocols in vascular mechanics is emphasized (for example, see Lanir et al., 1996). In optimally designed experiments, the effect of parameter changes is maximized with respect to the noise and, hence, the estimation error variance can be reduced.

Chapter 3

COMPARISON OF DIFFERENT CONSTITUTIVE MODELS OF VASCULAR TISSUE MECHANICAL BEHAVIOR FROM PARAMETER ESTIMATION PERSPECTIVE

3.1 Constitutive modeling of arterial wall

Due to large deformation of vascular tissue, constitutive modeling based on finite elasticity has been extensively used to understand the mechanical behavior of healthy or diseased arteries. Constitutive modeling of arteries requires estimation of constitutive parameters from ex-vivo biaxial or inflation-extension experiments. In chapter 2, an aspect of the parameter estimation in vascular mechanics was discussed with regard to the measurement error. The form of the constitutive relation/model, assumed to describe the mechanical behavior of the tissue, was considered to be known and fixed. Nonetheless mechanical behavior of arteries may vary between species and even may be different within a subject depending on the anatomical location (See Fig. 2.4a and b, for example). Thus the question remained is which constitutive form is adequately describes the mechanical behavior arteries or even whether one constitutive form is adequate to model all arteries. Variety of constitutive models, either phenomenological or microstructurally-motivated, has been suggested for arteries in literature, some of which have been reviewed by Holzapfel et al. (2000). In this chapter, given two sets of data mouse carotid and rabbit basilar arteries, we test different constitutive relations by comparing their parameter estimation results.

Briefly, fibers and ground substance (mainly elastin) are main constituents that determine the mechanical behavior of the vascular tissues (Holzapfel and Ogden, 2010; Humphrey, 2002). Under low loading condition, crimped collagen fibers contribute little to the mechanical response while elastin is mainly responsible for the mechanical behavior. Arterial elastin (and ground substance in general) has been generally assumed to be isotropic and modeled as the neo-Hookian material (Gundiah et al., 2007). At higher loads the undulated fibers begin to stretch out and contribute to the progressive stiffening of the tissue in the fiber direction. That has motivated exponential forms of the strain energy function for collagen with anisotropy effect (Fung, 1967; Holzapfel et al., 2000). An additive split for the strain energy function is suggested as $W = W_e + W_c$, where W_e represents the strain energy due to isotropic elastin (independent of fiber alignment) and W_c represents the anisotropic strain energy due to collagen fibers (Holzapfel et al., 2000; Holzapfel and Ogden, 2010). Here we consider different functional forms of the strain energies for isotropic and anisotropic parts in contrast with the popular Holzapfel-type model. First we assume the anisotropy part as an exponential form and use different models for isotropic part. Then we consider the isotropic part as neo-Hookian and test different models for anisotropic part.

3.2 Holzapfel-type model

A multi-fiber family model, as introduced in chapter 2, has been suggested by Hu et al. (2007) and Baek et al. (2007a) which is mainly inspired by Lanir (1983) and Holzapfel et al. (2000). The strain energy function is rewritten as

$$\hat{W} = \frac{c}{2}(I_1 - 3) + \sum_k \frac{c_1^{(k)}}{4c_2^{(k)}} \left\{ \exp\left(c_2^{(k)}(\lambda^{(k)^2} - 1)^2\right) - 1 \right\},\tag{3.1}$$



Figure 3.1: Pressure-radius data and the estimated values (left) with the corresponding normalized residuals (right) for mouse carotid (top) and rabbit basilar (bottom) arteries using Holzapfel-type model. Dots show the data points and solid lines show the estimated values.

Accordingly, Fig. 3.1 shows the pressure-radius data and the estimated lines along with the normalized residuals between data and estimated values (i.e., $(P_{est} - P_{data})/P_{nominal}$) for mouse carotid and rabbit basilar arteries. Existing trends of variation in residuals around the zero, underscores the signature behavior associated with the model used to fit both sets of data. However, the model shows a better fit to basilar artery data in general.



Figure 3.2: Pressure-radius data of mouse carotid artery and the estimated values (left) with the corresponding normalized residuals (right) using Zulliger model. Dots show the data points and solid lines show the estimated values.

3.3 Models for elastin contribution

3.3.1 Zulliger model

Zulliger et al. (2004a) proposed a modification to the strain energy function of elastin which we combine with exponential part of the Holzapfel-type model as

$$\hat{W} = \frac{c}{2}(I_1 - 3)^{3/2} + \sum_k \frac{c_1^{(k)}}{4c_2^{(k)}} \left\{ \exp\left(c_2^{(k)}(\lambda^{(k)^2} - 1)^2\right) - 1 \right\}.$$
(3.2)

Figure 3.2 show the data and fitted lines as well as the normalized residuals for carotid artery. There is no improvement in terms of fitting and the trend in residuals with respect to neo-Hookian form of strain energy for elastin.

3.3.2 Demiray model

Ogden and Saccomandi (2007) suggested the exponential model of isotropic part, proposed by Demiray (1972) and Fung (1967), to be combined with anisotropic part of Holzapfel-type model as

$$\hat{W} = \frac{c}{2b} \left\{ \exp\left(b(I_1 - 3)\right) - 1 \right\} + \sum_k \frac{c_1^{(k)}}{4c_2^{(k)}} \left\{ \exp\left(c_2^{(k)}(\lambda^{(k)^2} - 1)^2\right) - 1 \right\}$$
(3.3)



Figure 3.3: Pressure-radius data and the estimated values (left) with the corresponding normalized residuals (right) for mouse carotid (top) and rabbit basilar (bottom) arteries using Demiray model. Dots show the data points and solid lines show the estimated values.

3.4 Models for collagen contribution

3.4.1 Zulliger model

As described before, collagen fibers are originally undulated and under loading condition more collagen fibers become straightened and engaged in carrying the increasing load (since each collagen fiber is assumed to become straightened at a different stretch ratio). Based on that Zulliger et al. (2004a) assumed a log-logistic probability distribution function for engagement strain. Inspired by them, we consider

$$\hat{W} = \frac{c}{2}(I_1 - 3) + \sum_k \nu_k \Psi_k(\epsilon_k)$$
(3.4)

where $\epsilon_k = \lambda_k - 1$ and $\Psi_k(\epsilon_k) = \psi_f * \rho_f = \int_{-\infty}^{\infty} \psi_f(\epsilon_k - x) \rho_f(x) dx$. The distribution function ρ_f and the strain energy of a single fiber ψ_f are given as

$$\rho_f(\epsilon_k) = \begin{cases}
0 & \text{for } \epsilon \le 0 \\
\frac{a_k}{b_k} \frac{\left(\frac{\epsilon_k}{b_k}\right)^{a_k - 1}}{\left[1 + \left(\frac{\epsilon_k}{b_k}\right)^{a_k}\right]^2} & \text{for } \epsilon > 0
\end{cases}$$
(3.5)

$$\psi_f(\epsilon_k) = \begin{cases} 0 & \text{for } \epsilon \le 0\\ c_f(\epsilon_k - \log(\epsilon_k + 1)) & \text{for } \epsilon > 0 \end{cases}$$
(3.6)

where a_k and b_k are the parameters associated with kth fiber family (k = 1, ..., 4) and c_f is an intrinsic parameter for a single fiber. b_k is a scaling parameter while a_k defines the shape of the distribution (Rezakhaniha et al., 2011). Figure 3.4 shows the fitting results and the normalized residuals for both mouse carotid and rabbit basilar arteries. Apparently the parameter estimation has not been improved using this model.



Figure 3.4: Pressure-radius data and the estimated values (left) with the corresponding normalized residuals (right) for mouse carotid (top) and rabbit basilar (bottom) arteries using Zulliger model. Dots show the data points and solid lines show the estimated values.

3.4.2 Lanir model

Again based on the idea of gradual engagement of collagen fibers, Lanir (1979) considered a normal distribution for the fiber engagement and its load bearing capacity. He also considered the engaged individual fibers to be linearly elastic. Similarly, we consider

$$\hat{W} = \frac{c}{2}(I_1 - 3) + \sum_k \nu_k \Psi_k(\epsilon_k), \qquad \Psi_k(\epsilon_k) = \int_{1.0}^{\lambda_k} \psi_f(x)\rho_f(x)dx$$
(3.7)

where $\psi_f(x) = 1/2c_f((\lambda_k - x)/x)^2$ is the strain energy of the a single fiber and ρ_f is the normal distribution defined as

$$\rho_f(x) = b_k \exp\left(-\frac{(x-c_k)^2}{2a_k^2}\right), \quad \text{where} \quad b_k = \frac{1}{a_k\sqrt{2\pi}}.$$
(3.8)

Figure 3.5 depicts the fitting results and the normalized residuals for both mouse carotid and rabbit basilar arteries.

3.5 Discussion

Concerning the difference between species, Holzapfel-type model showed relatively a better fit to the basilar artery data (as well as lower residuals). This can be due to the simple exponential trend observed for rabbit basilar artery whereas mouse carotid artery showed a sigmoid-like trend emphasizing more contribution for elastin under low loads. Comparison between different models did not show a clear advantage for other constitutive models over the Holzapfel-type model in terms of parameter estimation. Holzapfel-type together with Demiray-type showed the best results for the parameter estimation and fitting residuals. For an ideal model, residuals should be oscillating around zero without any obvious signature trend. Whereas the signature behavior can be obviously seen in residuals of all models used in the study.

However, as mentioned earlier, Holzapfel-type model represents multiple fiber families of



Figure 3.5: Pressure-radius data and the estimated values (left) with the corresponding normalized residuals (right) for mouse carotid (top) and rabbit basilar (bottom) arteries using Lanir model. Dots show the data points and solid lines show the estimated values.

collagen fibers along with elastin. This is favorable to be used in G&R models where arteries are considered as a mixture of constituents which are produced and removed at their own turnover rates.

Chapter 4

ESTIMATION OF THE ARTERIAL WALL THICKNESS AND ANISOTROPY FOR IMAGE-BASED MODELS OF ARTERIES

4.1 INTRODUCTION

Many of the computational models of vascular adaptation (Baek et al., 2006, 2007b; Figueroa et al., 2009; Kroon and Holzapfel, 2009b; Watton and Hill, 2009) have been built upon the theoretical framework of modeling tissue G&R presented by Humphrey and Rajagopal (2002). They introduced a constrained mixture approach focusing on stress-mediated mass production and removal in evolving stressed configurations. They also offered key remarks that are central to guiding the later development of theories of soft tissue G&R. One of their key remarks is "Normal growth and remodeling tends to be a stable dynamical process, one that seeks to optimize structure and function with respect to yet unidentified parameters. In comparison to processes during development, there appear to be genetic and perhaps epigenetic constraints on this optimization process during maturity". Furthermore, they emphasized a need to identify both a set of optimization parameters and the associated constraints. Most of the previous computational simulations of vascular adaptation, however, have been developed using idealized geometries for which the identification of homogeneous parameters does not pose a problem.

This chapter addresses two technical challenges associated with patient-specific modeling

of AAA evolution and proposes possible solutions. First, as stated earlier, theory of G&R is based on a key assumption, the existence of mechanical homeostasis (Humphrey, 2008; Kassab, 2008), whereas it is difficult to prescribe the *in vivo* parameters such that the assumption of a homeostatic state is satisfied at every point in the vessel wall model. For an idealized model, where the blood vessel is assumed to be an ideal thin hollow cylinder, the *in vivo* material properties are typically assumed to be uniform over the domain. When a medical image-based geometric model is used, however, it is not a trivial task to prescribe the distribution of material and structural parameters such as thickness and fiber orientations.

Second, another difficulty associated with using an image-based model stems from the fact that the *in vivo* image is obtained under the pressure and the stress-free configuration is not available. Hence, it is difficult to maintain the original patient-specific model in a computational simulation under the *in vivo* pressure. Inverse elastostatic methods have been pursued to estimate the stress-free state from a pre-deformed *in vivo* geometry obtained medical images (Lu et al., 2008; Zhou et al., 2010). Others have used a Lagrangian-Eulerian formulation to obtain the meaningful prestressed state (Gee et al., 2010, 2009).

In this chapter, first, the constitutive parameters intrinsic to the material are estimated by fitting the *ex vivo* biaxial mechanical test data of a healthy human aorta using the same parameter estimation approach presented in chapter 2. Second, an optimization problem is solved to estimate the distributions of the wall thickness and anisotropy such that homeostasis is maintained while the geometry deviates minimally from the *in vivo* configuration.

4.2 METHOD

4.2.1 Estimation of material constitutive parameters

As the first step, the constitutive parameters are estimated by fitting biaxial mechanical test data of a healthy human aorta (Vande Geest et al., 2004, 2006). Here, the kinematics of the biaxial test and the constitutive relations are briefly explained.



Figure 4.1: Kinematics of the deformation associated with biaxial mechanical test and the corresponding deformation gradients. λ_1 and λ_2 are stretches in circumferential and axial directions during the biaxial test

Figure 4.1 shows a schematic drawing for the kinematics of deformation related to a biaxial test of a healthy aorta. The *in vivo* configuration of a healthy aorta is assumed to be the prestressed reference configuration κ_R , whereas κ_I represents the intermediate configuration of the square-cut sample under the traction-free condition. The deformation gradient \mathbf{F}^R corresponds to the mapping from κ_R to κ_I . It is assumed that there is no active tone presented during the biaxial test. The deformation gradient \mathbf{F}^I corresponds to the deformed configuration during the biaxial test, resulting in $\mathbf{F} = \mathbf{F}^I \mathbf{F}^R$. Assuming incompressibility in an ideal geometry,

$$\mathbf{F}^{R} = \operatorname{diag}\left\{F_{1}^{R}, F_{2}^{R}, \frac{1}{F_{1}^{R}F_{2}^{R}}\right\}$$
$$\mathbf{F}^{I} = \operatorname{diag}\left\{\lambda_{1}, \lambda_{2}, \frac{1}{\lambda_{1}\lambda_{2}}\right\}, \qquad (4.1)$$

where F_1^R , $F_2^R < 1.0$ and λ_1 , $\lambda_2 > 1.0$.

The arterial wall is assumed to be a mixture of constituents 'i' such as elastin (i = e), multiple collagen families (i = 1, ..., k, ..., 4), and smooth muscle (i = m). The strain energy of the mixture per unit reference area is $w = \sum_{i} w^{i} = w^{e} + \sum_{k} w^{k} + w^{m} + w^{m}_{act}$ and the membrane stress is given as (Baek et al., 2006; Humphrey, 2002)

$$\mathbf{T} = \frac{2}{J} \mathbf{F} \frac{\partial w}{\partial \mathbf{C}} \mathbf{F}^T, \tag{4.2}$$

where J is a determinant of the 2-D deformation gradient \mathbf{F} and $\mathbf{C} = \mathbf{F}^T \mathbf{F}$. The stretches of the smooth muscle (SM) and collagen fiber 'k' from their natural (stress-free) configuration to the current configuration are given as

$$\lambda_n^k = G_h^c \lambda^k \tag{4.3}$$

$$\lambda_n^m = G_h^m \lambda_1, \tag{4.4}$$

where G_h^m and G_h^c are homeostatic stretches of SM and collagen. We define a new tensor

$$\tilde{\mathbf{G}}^{e} = \text{diag}\left\{G_{1}^{e}, \ G_{2}^{e}, \ \frac{1}{G_{1}^{e}G_{2}^{e}}\right\},$$
(4.5)

which represents a mapping from the natural configuration of elastin to the reference configuration such that,

$$\mathbf{F}_{n}^{e} = \mathbf{F}\tilde{\mathbf{G}}^{e}, \qquad \mathbf{C}_{n}^{e} = \mathbf{F}_{n}^{e\,T}\mathbf{F}_{n}^{e} = [\tilde{\mathbf{G}}^{e}]^{T}\mathbf{C}\tilde{\mathbf{G}}^{e}.$$
(4.6)

Strain energies of the constituents i per unit reference area, w^i , are given as

$$w^{e}(\mathbf{C}_{n}^{e}(t)) = M^{e} \frac{c_{1}}{2} \left(C_{n[11]}^{e} + C_{n[22]}^{e} + \frac{1}{C_{n[11]}^{e} C_{n[22]}^{e} - C_{n[12]}^{e}}^{2} - 3 \right)$$
(4.7)

$$w^{k}(\lambda_{n}^{k}) = M^{k} \frac{c_{2}}{4c_{3}} \left\{ \exp\left[c_{3}\left((\lambda_{n}^{k})^{2} - 1\right)^{2}\right] - 1 \right\}$$
(4.8)

$$w^{m}(\lambda_{n}^{m}) = M^{m} \frac{c_{4}}{4c_{5}} \left\{ \exp\left[c_{5}\left((\lambda_{n}^{m})^{2}-1\right)^{2}\right] - 1 \right\}$$
(4.9)

$$w_{act}^m = M^m \frac{S}{\rho} \Big\{ \lambda_1 + \frac{1}{3} \frac{(\lambda_M - \lambda_1)^3}{(\lambda_M - \lambda_o)^2} \Big\},$$
(4.10)

where M^i is the mass per unit reference area for the constituent *i*. $C_{n[11]}^e$, $C_{n[22]}^e$ and $C_{n[12]}^e$ are components of \mathbf{C}_n^e . λ_M and λ_o are stretches at which the SM contraction is maximum and at which active force generation ceases, *S* is the stress at the maximum contraction of SM.

Components of \mathbf{F}^R are obtained by considering stress as a function of deformation gradient, i.e. $\mathbf{T} = \hat{\mathbf{T}}(\mathbf{F})$, and assuming that membrane stresses vanish at $\mathbf{F} = \mathbf{F}^R$ such that

$$\hat{\mathbf{T}}(\mathbf{F}^R) = \mathbf{0}.\tag{4.11}$$

Material parameters (summarized in Table 4.1) are determined in three different ways. The first set of parameters, such as density (ρ), mass fraction of constituents (ν^i) and (λ_0 , λ_M , S), are prescribed from the literature (He and Roach, 1994; Holzapfel et al., 2002; Menashi

Elastin:	$c_1 = 50.6 \ Nm/kg, \ G_1^e = 1.22, \ G_2^e = 1.23,$
	$\nu^e = 0.2.$
Collagen:	$c_2 = 3195 \ Nm/kg, \ c_2^{(comp)} = 0.1c_2, \ c_3 = 25.0,$
	$G_h^c = 1.034, \ \sigma_h^c = 143 \ kPa,$
	$\nu^k = [0.06, 0.06, 0.24, 0.24],$
	$\alpha^k = [0^\circ, 90^\circ, 45^\circ, 135^\circ].$
Smooth muscle:	$c_4 = 16.45 \ Nm/kg, \ c_5 = 14.14, \ G_h^m = 1.165,$
	$\nu^m = 0.2, \ \sigma^m_h = 81 \ kPa, \ \lambda_M = 1.4,$
	$\lambda_0 = 0.8, \ S = 54 \ kPa.$
Homeostatic cyclic stretch:	$\lambda_h^{cyc} = 1.02.$
Density:	$ \rho = 1050 \ kg/m^3. $

Table 4.1: Summary of material parameters used in the optimization.

et al., 1987). The second set of parameters $(c_1, c_2, c_3, c_4, c_5, G_1^e, G_2^e, G_h^c, G_h^m)$ are estimated via the weighted nonlinear least squares optimization, proposed in chapter 2 using the biaxial mechanical test data of healthy human aorta (Vande Geest et al., 2004, 2006). Figure 4.2 shows the biaxial data as well as the fitted values using the estimated parameters.

Although the existence of mechanical homeostasis in vasculature is generally accepted, the theoretical formulation that describes vascular adaptations in response to diverse stimuli is not completely established yet. Nevertheless, we utilize scalar measures of stress as the intramural stress of constituents (Baek et al., 2006; Figueroa et al., 2009)

$$\sigma^{k} = ||(\sum_{k} \nu^{k} \boldsymbol{\sigma}^{k}) \mathbf{n}^{k}||, \qquad \sigma^{m} = ||\boldsymbol{\sigma}^{m} \mathbf{n}^{m}||, \qquad (4.12)$$

where $\boldsymbol{\sigma}^k$ and $\boldsymbol{\sigma}^m$ are the stresses of the k^{th} collagen fiber and SM, respectively, and \mathbf{n}^k and \mathbf{n}^m are unit vectors in the directions of the k^{th} collagen fiber and SM. Then, using the estimated parameters and assuming an idealized geometry, the target homeostatic values (σ_h^m, σ_h^c) are calculated.



Figure 4.2: Stress versus stretch plots in both directions. Biaxial test data (empty markers) and fitted values (filled markers) using the estimated parameters. Different markers correspond to a different ratios of tension applied simultaneously in both directions.

4.2.2 Inverse optimization problem statement

As the next step, the distributions of wall thickness and material anisotropy are estimated using an inverse optimization method where both the deviation of geometry from the *in vivo* configuration and the deviation of stress from the homeostatic value are minimized. Then, the objective function to minimize is,

$$W = \frac{\int_{\Omega} ||\mathbf{x}(h,\alpha^k) - \mathbf{X}_{image}||^2 dA}{\int_{\Omega} ||\mathbf{X}_{image} - \bar{\mathbf{X}}||^2 dA} + \xi \sum_{i} \frac{\nu^i \int_{\Omega} (\sigma^i(h,\alpha^k) - \sigma^i_h)^2 dA}{\int_{\Omega} (\sigma^i_h)^2 dA}$$
(4.13)

where i = m, 1, ..., k and **x** is the FE solution for the nodal position vector (see chapter 6 for details of the image-based FE model of the pressurized artery). \mathbf{X}_{image} constitutes the target geometry and is the nodal position vector of the FE mesh that is generated based on the 3-D models of arteries. The geometric model of the artery is reconstructed from MRI images of a normal aorta and the computational mesh is generated using triangular elements (see Sheidaei et al. (2011)). X is the geometric center of the artery and is used as a fixed reference point for normalizing the first term. σ^i is a scalar measure of stress in the direction of the constituent i obtained from the FE analysis. σ_h^i and ν^i are the homeostatic stress and mass fraction assumed for the constituent i. (h, α^k) are the unknown wall thickness and anisotropy, i.e. orientation of the collagen fiber k. The deviation of stress for each constituent is scaled by its mass fraction and integrated over the computational domain. Therefore, constituents such as fiber families in helical directions will be given more weight in minimizing the objective function (see Table 4.1). The objective function is composed of two additive terms and a weight parameter ξ ; first term is related to the deviation of geometry (named " \mathcal{GD} " hereafter) and the second term is related to the deviation of stress (named " \mathcal{SD} " hereafter). Since we are interested in minimizing both terms, each term is normalized and a weight parameter ξ (or a Lagrange multiplier) is used to adjust the minimization weight for each normalized term.

However, solving this optimization problem for the thickness and anisotropy at all nodal points of the FE model is not practical, even if possible. Thickness and anisotropy distributions can be approximated with a smaller (I) number of variables with associated base functions, independent from the FE mesh as

$$h(x, y, z) = \sum_{j=1}^{I} \{\beta_j^h \phi_j(x, y, z)\} \qquad (x, y, z) \in \Omega$$
$$\alpha^k(x, y, z) = \sum_{j=1}^{I} \{\beta_j^k \psi_j(x, y, z)\} \qquad (x, y, z) \in \Omega,$$
(4.14)

where (β_j^h, β_j^k) are variables for thickness and anisotropy associated with the approximation point *j*. $\phi_j(x, y, z)$ and $\psi_j(x, y, z)$ are basis/approximation functions defined on the computational domain Ω . The objective function then can be rewritten with respect to the new design variables as

$$W = \frac{\int_{\Omega} ||\mathbf{x}(\beta_j^h, \beta_j^k) - \mathbf{X}_{image}||^2 dA}{\int_{\Omega} ||\mathbf{X}_{image} - \bar{\mathbf{X}}||^2 dA} + \xi \sum_{i} \frac{\nu^i \int_{\Omega} (\sigma^i(\beta_j^h, \beta_j^k) - \sigma_h^i)^2 dA}{\int_{\Omega} (\sigma_h^i)^2 dA}.$$
 (4.15)

To facilitate the approximation in (4.14), the computational domain (the mid-surface of the vessel wall) can be parameterized by two spatial variables (s, θ) where s and θ represent, respectively, the longitudinal distance and azimuthal position on the arterial wall (explained in next section). Then, equation (4.14) can be rewritten as

$$h(s,\theta) = \sum_{j=1}^{I} \{\beta_j^h \phi_j(s,\theta)\}$$

$$\alpha^k(s,\theta) = \sum_{j=1}^{I} \{\beta_j^k \psi_j(s,\theta)\}.$$
 (4.16)

Towards solving the optimization problem (equation 4.15), we use initial values of (β_j^h, β_j^k) that approximate a homogenous field of thickness and anisotropy (h_0, α_0^k) . That is, the

initial values are obtained by solving the following sets of least-squares optimizations

$$S^{h} = \sum_{e=1}^{N_{e}} \left(\sum_{j=1}^{I} \beta_{j}^{h} \phi_{j}(s_{e}, \theta_{e}) - h_{0} \right)^{2}$$
(4.17)

$$S^{k} = \sum_{e=1}^{N_{e}} \left(\sum_{j=1}^{I} \beta_{j}^{k} \psi_{j}(s_{e}, \theta_{e}) - \alpha_{0}^{k} \right)^{2}, \qquad (4.18)$$

where N_e and I are the number of elements and approximation points, respectively.

4.2.3 Parameterizing the aortic wall surface with two variables

A point on the vessel wall can be parameterized by two variables, one that characterizes its longitudinal position (s) and the other which characterizes its orientation (θ) with respect to a reference direction. To do so, we need to approximate the centerline of the vessel considering some of the points on the centerline as nodal points (Figure 4.3) and

$$\mathbf{X}(s) = \sum_{i} \Phi^{i}(s) \mathbf{X}^{i}, \tag{4.19}$$

where \mathbf{X}^{i} and Φ^{i} are the position vector and interpolation function corresponding to the nodal point *i* on the centerline. **X** is the position vector of any point on the centerline as a function of *s*. A fourth order interpolation function is assumed with the general form of

$$\Phi(s) = c(s-a)^2(s-b)^2.$$
(4.20)

The interpolation functions associated with nodal points j = 1, ..., J can be defined as

$$\Phi^{1}(s) = \frac{(s - L_{3})^{2}(s + L_{3})^{2}}{(L_{1} - L_{3})^{2}(L_{1} + L_{3})^{2}} \qquad L_{1} \le s < L_{3}$$

$$(4.21)$$

$$\Phi^2(s) = \frac{(s-L_1)^2(s-L_4)^2}{(L_2-L_1)^2(L_2-L_4)^2} \qquad L_1 \le s < L_4$$
(4.22)

$$\Phi^{k}(s) = \frac{(s - L_{k-2})^{2}(s - L_{k+2})^{2}}{(L_{k} - L_{k-2})^{2}(L_{k} - L_{k+2})^{2}} \quad L_{k-2} \le s < L_{k+2}$$
(4.23)

$$\Phi^{J-1}(s) = \frac{(s - L_{J-3})^2 (s - L_J)^2}{(L_{J-1} - L_{J-3})^2 (L_{J-1} - L_J)^2} L_{J-3} \le s < L_J$$
(4.24)

$$\Phi^{J}(s) = \frac{(s - L_{J-2})^{2}(s + L_{J-2})^{2}}{(L_{J} - L_{J-2})^{2}(L_{J} + L_{J-2})^{2}} \quad L_{J-2} \le s < L_{J}$$
(4.25)

where k = 3, ..., J - 2 and L_j is the value of s at the nodal point j (Figure 4.3). These interpolation functions, however, do not satisfy the condition $\sum_{j=1}^{J} \Phi^j(s) = 1$. In order to provide this condition, we need to normalize interpolation functions as

$$\hat{\Phi}^{i}(s) = \frac{\Phi^{i}(s)}{\sum_{j=1}^{J} \Phi^{j}(s)}.$$
(4.26)

Now, using the interpolation in (4.19) we can find the parameter s associated with any point on the artery, e.g. center point of a triangular element on the surface (\mathbf{X}_c). That is, for a given point on the aortic wall, the variable s is calculated by minimizing the distance from the point on the wall to the centerline ($||\mathbf{X}(s) - \mathbf{X}_c||$). The function to be minimized is given as

$$d(s) = \left(\sum_{i} \hat{\Phi}^{i}(s)x^{i} - x_{c}\right)^{2} + \left(\sum_{i} \hat{\Phi}^{i}(s)y^{i} - y_{c}\right)^{2} + \left(\sum_{i} \hat{\Phi}^{i}(s)z^{i} - z_{c}\right)^{2}.$$
(4.27)

Minimizing d(s) with respect to s results in

$$\frac{\partial d(s)}{\partial s} = 2\left(\sum_{i} \hat{\Phi}^{i}(s)x^{i} - x_{c}\right)\sum_{i} \hat{\Phi}^{i}_{,s}x^{i}
+ 2\left(\sum_{i} \hat{\Phi}^{i}(s)y^{i} - y_{c}\right)\sum_{i} \hat{\Phi}^{i}_{,s}y^{i}
+ 2\left(\sum_{i} \hat{\Phi}^{i}(s)z^{i} - z_{c}\right)\sum_{i} \hat{\Phi}^{i}_{,s}z^{i} = 0.$$
(4.28)

Numerical solution of the nonlinear equation (4.28) is obtained using Newton-Raphson method which also requires the second derivative of the function. The iterative scheme for the Newton-Raphson is formulated as

$$s^{n+1} = s^n - \frac{\frac{\partial d(s)}{\partial s}|_{s=s^n}}{\frac{\partial^2 d(s)}{\partial s^2}|_{s=s^n}}.$$
(4.29)

This is repeated for any other point of interest on the wall in order to find the corresponding value of s. If s_0 is the solution associated with a center point of an element (Figure 4.3), the vector **v** connecting the point on the centerline at $s = s_0$ (**X** $(s = s_0)$) and the center point of the element is given as

$$\mathbf{v} = \mathbf{X}_c - \sum_i \hat{\Phi}^i(s_0) \mathbf{X}^i.$$
(4.30)

The normalized vector **n** tangent to the centerline at $s = s_0$ is then given by

$$\mathbf{n} = \frac{\frac{\partial \mathbf{X}(s)}{\partial s}|_{s=s_0}}{||\frac{\partial \mathbf{X}(s)}{\partial s}|_{s=s_0}||} \quad \text{where} \quad \frac{\partial \mathbf{X}(s)}{\partial s} = \sum_i \hat{\Phi}^i_{,s} \mathbf{X}^i.$$
(4.31)

The vector **n** is also a normal vector to the plan of cross section at $s = s_0$. Projection of an arbitrary vector **a** on the plan of cross section (Figure 4.3) can be assumed as the reference direction

$$\mathbf{a}_p = \mathbf{a} - (\mathbf{a} \cdot \mathbf{n})\mathbf{n}. \tag{4.32}$$

The angle θ between \mathbf{a}_p and \mathbf{v} characterizes the orientation associated with the current point on the wall (i.e., \mathbf{X}_c). Figure 4.4 illustrates the 3-D geometry of the model of aorta mapped in 2-D plane of longitudinal (s) and azimuthal (θ) variables.

4.2.4 Global approximation approach

For approximations in equations (4.14), products of Legendre polynomials and periodic functions, respectively, for longitudinal and azimuthal directions are used

$$h(s,\theta) = \sum_{m,n=0}^{m=M-1,n=N-1} \beta_{mn}^{h} P_m(s) F_n(\theta)$$
(4.33)

$$\alpha^{k}(s,\theta) = \sum_{m,n=0}^{m=M-1,n=N-1} \beta_{mn}^{k} P_{m}(s) F_{n}(\theta), \qquad (4.34)$$

where M and N are, respectively, the total number of Legendre polynomials and periodic functions (i.e. $I = M \times N$). $P_m(s)$ is a univariate Legendre polynomials of order m such that $P_0(s) = 1$, $P_1(s) = s$ and

$$P_{m+1}(s) = s\left(\frac{2m+1}{m+1}\right)P_m(s) - \left(\frac{m}{m+1}\right)P_{m-1}(s).$$
(4.35)

Also, we consider $F_0(\theta) = 1$ and

$$F_{2n-1} = \sin(n\theta)$$

$$F_{2n} = \cos(n\theta).$$
(4.36)

4.2.5 Optimization algorithm

The Nelder-Mead Simplex method is employed for the optimization (Lagarias et al., 1998; Nelder and Mead, 1965). As a direct search method, it does not require gradients of the function, which is desirable in applications where the calculation of gradients of the function



Figure 4.3: Geometry of an arbitrary model of the arterial wall with its centerline; Approximation/nodal points with their associated length $s = L_j$ (j = 1, ..., J). **a** is an arbitrary vector used in order to find the orientation θ associated with a point (X_c) on the wall



Figure 4.4: Geometry of the vessel wall parameterized with longitudinal and azimuthal (s and θ) variables. Dots represent center points of all elements on the wall

is computationally expensive. Another feature of the Nelder-Mead Simplex method is the fast reduction in the objective function after the first few iterations (Wright, 1996). See Appendix B for details of the algorithm used. A stopping criterion is chosen based on both the relative size of the simplex and function values at vertices of the simplex as (Torczon, 1989):

$$\frac{1}{\Delta} \max_{1 \le j \le I} ||v_j^k - v_0^k|| < \delta \tag{4.37}$$

$$W(v_I^k) - W(v_0^k) < \epsilon$$
, (4.38)

where v_j^k is the j^{th} vertex of the simplex and a vector comprised of all optimization variables at k^{th} iteration. v_0^k and v_I^k are the "best" and "worst" vertices of the simplex at k^{th} iteration and $\Delta = \max(1, ||v_0^k||)$.

4.3 RESULTS

As a parametric study, the effect of variation of the weight parameter ξ is first investigated. Figure 4.5 shows the \mathcal{GD} and \mathcal{SD} corresponding to minimum values of the objective function obtained with different values of ξ and using two different combinations of Legendre polynomials and periodic functions (M = 3, N = 3) and (M = 6, N = 5).

In both cases small values of ξ puts more weight on \mathcal{GD} to minimize the objective function and increasing ξ shifts the weight towards \mathcal{SD} . The tradeoff choice according to both cases appears to be $\xi = 0.01$ such that both parts can be minimized at the same time (Figure 4.5).

4.3.1 Finding the optimal distributions of thickness and anisotropy

In general higher number of approximating polynomials increases the flexibility for better approximation but at the cost higher computational cost. Then we choose to use six Legendre polynomials (M = 6) and 3 periodic functions (N = 3) for the approximation assuming



Figure 4.5: The effect of variation of the parameter ξ on both \mathcal{GD} and \mathcal{SD} using (M = 3, N = 3; top) and (M = 6, N = 5; bottom)



Figure 4.6: Changes in the objective function and its associated compartments versus optimization iterations using 36 variables (18 variables for approximating thickness and 18 variables for approximating fiber orientation) considering $\xi = 0.01$



Figure 4.7: Deviation of the geometry from the *in vivo* geometry without (a) and with (b) optimized distributions of thickness and anisotropy $(||\mathbf{x} - \mathbf{X}_{image}||)$

 $\xi = 0.01$. This constitutes 18 variables (I = 18) for thickness and anisotropy, including a total of 36 variables into the optimization process. Note that fibers oriented in circumferential and axial directions are considered fixed and only helical fibers orientations are assumed to be changing $(\alpha^3 = \alpha^4)$. Least-squares estimation of variables associated with a homogenous field of thickness and anisotropy (e.g., 0.8 mm for thickness and 50.0° for anisotropy) yielded estimates such as $\beta_{00}^h = 0.8$, $\beta_{00}^k = 50.0$ and 0 for all other parameters. Figure 4.6 illustrates the convergence history of the objective function as well as its compartments, \mathcal{GD} and \mathcal{SD} , until the stopping criterion is met. A fast decrease in the objective function during the first 100 iterations is noticeable, which is accompanied by sharp decreases in \mathcal{GD} and \mathcal{SD} . The appearance of the plateau regions is associated with the iterations during which searching the space has not led to a new minimum.

For the sake of comparison, the distributions of thickness are prescribed using the same method employed by Zeinali-Davarani et al. (2011) and the results were compared with the current method. Figure 6.4 contrasts the deviation from the *in vivo*/image geometry $(||\mathbf{x} - \mathbf{X}_{image}||)$ using both methods. A significant decrease in the maximum deviation (about 70%) is achieved using the optimization approach.

The normalized deviation of stress from the homeostatic value $((\sigma^k - \sigma_h^k)/\sigma_h^k)$ in the



Figure 4.8: Deviation of the stress $((\sigma^k - \sigma_h^k)/\sigma_h^k)$ from the target homeostatic stress in a helical fiber (k = 3) without (a) and with (b) optimized distributions of thickness and anisotropy

direction of helical fiber families (k = 3, 4) using both methods are shown in Figures 4.8 and 4.9. For fiber families of both helical directions, the maximum deviations of stress from the homeostatic value are significantly decreased by 70% using the optimization method.

Figure 4.10 depicts the distributions of wall thickness and anisotropy obtained by the optimization with $\xi = 0.01$, M = 6, and N = 3. The resulting spatial variation of anisotropy is not large although thickness considerably varied especially on the convex and concave regions with higher values on the concave side and lower values on the convex side.

4.4 **DISCUSSION**

The existence of the vascular mechanical homeostasis and the subsequent adaptation in response to mechanical stimuli have been fundamental assumptions in mathematical models of vascular G&R (Baek et al., 2006, 2007b; Figueroa et al., 2009; Kroon and Holzapfel, 2009b; Watton and Hill, 2009). There has been a growing interest in using such models on a patient-specific basis (Humphrey and Taylor, 2008; Taylor and Humphrey, 2009). Towards that goal, image-based arterial geometries have been incorporated into stress-mediated vascular



Figure 4.9: Deviation of the stress $((\sigma^k - \sigma_h^k)/\sigma_h^k)$ from the target homeostatic stress in a helical fiber (k = 4) without (a) and with (b) optimized distributions of thickness and anisotropy



Figure 4.10: Distributions of thickness (a) and anisotropy (b) obtained from the optimization results using $\xi = 0.01$, M = 6, and N = 3

adaptation models (Sheidaei et al., 2011; Zeinali-Davarani et al., 2011). Zeinali-Davarani et al. (2011) utilized the G&R model itself as an optimization tool to drive the mechanical state towards the target homeostatic value before the main G&R simulations begun. This approach, however, alters the *in vivo* configuration even though it provides a desirable stress distribution. Rather, the present study provides an optimization technique to minimize both deviations from the homeostatic stress and the *in vivo* configuration simultaneously.

Numerous methods have been presented in order to compensate for the lack of information about stress-free or load-free configurations in patient-specific modeling. Raghavan et al. (2006) used an optimization technique as an approximate method to find the zero-pressure geometry assuming consistency of displacement field patterns. Using an inverse elastostatic method, Lu et al. (2007) were able to determine load-free configuration of an AAA as well as accurate wall tension in a cerebral aneurysm (Lu et al., 2008). Recently, Zhou and Lu (2009) used the same inverse technique to estimate the open configuration of vessels. In a different approach, Gee et al. (2009, 2010) showed the utility of the "modified updated Lagrangian" method in finding meaningful stress analysis results for complex shapes of aneurysms.

However, all of those studies assumed homogenous distributions of the wall thickness and anisotropy whereas variation of these parameters can have a great impact on the stress/strain distribution. Instead of finding the load-free configuration, the presented approach focused on the *in vivo* configuration and its associated material and geometric parameters of arteries using an inverse optimization method such that the homeostatic condition was restored while the deviation of geometry from the original *in vivo* configuration was minimized. In a somewhat similar approach, Kroon and Holzapfel (2008a) estimated the distribution of elastic properties of an inhomogeneous and anisotropic membrane using an inverse optimization method and applied the technique to find material properties of the cerebral aneurysm (Kroon and Holzapfel, 2008b). They used an element partition method for the robust estimation of properties over the domain. That is, they divided the domain into large sub-domains and performed the optimization for each sub-domain with homogeneous properties. In the next levels of partitioning, they refined each sub-domain while repeating the estimation process with updated initial values. Alternatively, in the current method, a global approximation scheme is used in order to reduce the number of unknown variables of optimization and to facilitate estimation of the inhomogeneous properties in a global fashion. Increasing the number of approximation variable theoretically improves the objective function even more, but at the cost of more computation time. Deviation of stress from the homeostatic value in both helical directions was dropped by more than 70%, whereas there was no significant reduction in stress of axial and circumferential fibers (not shown), mainly because of much lower mass fractions assumed in those directions (See equation 4.15). Results of the AAA simulations using the optimal material parameters, wall thickness and anisotropy were generally comparable with Zeinali-Davarani et al. (2011), but more advantageous as the current method reduced the deviation of geometry from the *in vivo* configuration before the G&R process initiated.

Direct validation of the optimal distributions of the wall thickness and fiber orientations requires more experimental data using animal or human arteries. Nevertheless, the proposed optimization technique provides a useful initialization step, indispensable to patient-specific G&R simulations.

In closing, in this chapter a scalar measure of stress was used as a mechanical state governing the mechanosensitive vascular adaptation (Baek et al., 2006). However, it is still controversial what quantity is responsible for the mechanical homeostatic state (stress, strain, material stiffness, or their combination?). Next chapter considers the proposed inverse method to discriminate among different hypotheses of homeostasis.

Chapter 5

TESTING DIFFERENT HYPOTHESES OF VASCULAR HOMEOSTASIS USING IMAGE-BASED GEOMETRIC MODELS AND AN INVERSE OPTIMIZATION METHOD

5.1 Introduction

In their seminal paper, Humphrey and Rajagopal (2002) introduced a new theoretical framework, called a constrained mixture model for modeling growth and remodeling (G&R) of soft tissues. They presented a modeling framework that utilizes ideas from classical mixture and homogenization theories while avoiding the technical difficulties associated with mixture theory. This allows the model to capture the complexity that occurs during soft tissue G&R such as deposition of multiple structural components (e.g., fibrous collagen, elastin, and smooth muscle cells) with different natural configurations and turnover rates, whereas the governing equation can be solved as if the soft tissue were made of a single constituent. Often not mentioned, but another important contribution of their paper is the philosophy and guidance in developing a model of G&R of biological tissues, summarized in six remarks in the paper. Based on their pioneering work, during the past decade, many constrained mixture models have been developed in the studies of vascular mechanics (Hansen et al., 2009; Gleason and Humphrey, 2004a; Valentín et al., 2009a; Wan et al., 2010), progression of cardiovascular diseases (Baek et al., 2006, 2007b; Figueroa et al., 2009; Gleason and Humphrey, 2004b; Sheidaei et al., 2011) and mechanosensitive cellular behavior (Humphrey et al., 2008; Hsu et al., 2009).

While most studies after Humphrey and Rajagopal (2002) have focused on modeling the evolution of biological or engineered tissues after the alteration of physiological and pathological conditions, in this paper we study one of the most fundamental, but often overshadowed, assumption that soft tissue has an optimal structure during the maintenance or normal G&R period. Humphrey and Rajagopal (2002) stated in Remark 2.3 that "Normal growth and remodeling tends to be a stable dynamical process, one that seeks to optimize structure and function with respect to yet unidentified parameters." They further stated that "Although one ultimately seeks parameters that govern the underlying mechanisms of mechanotransduction, it will be sufficient for certain modeling purposes to identify parameters that simply correlate well with the overall process."

The question that has long been asked and is yet to be answered in biomechanics research is what are the parameters that correlate well with the G&R process? Are they stress, strain, or strain rate that cells respond to? Humphrey (2001) claimed that the question may be ill-posed. Stress and strain are merely convenient mathematical concepts and are not unique observable or physical quantities. He suggested, however, that "the concepts of stress and strain will continue to be convenient metrics in both empirical correlations and phenomenological constitutive relations that seek to relate certain cellular responses to particular stimuli." A practical question still remains as to what are the constitutive relations for such mechanical quantities, that best describe the maintenance of vascular tissues. During the maintenance, the turnover of cells and extracellular matrix is balanced and unchanged; hence, there is no net change in mass, structure, or the properties. Therefore, it is plausible that we may find the right constitutive relation or at least discriminate between different constitutive relations by numerically investigating the consequence of the constitutive relation in tissue structures and comparing the results with experimental studies. Stress and strain are interrelated (Humphrey, 2001; Kassab, 2008), and using an idealized symmetric
model, such as a straight tube, it may be difficult to distinguish the difference in optimal structures obtained from different hypotheses.

In this chapter, it is proposed that in medical image-based models different hypotheses for a mechanical homeostatic state may lead to distinct consequences with regard to the distributions of wall thickness and anisotropy, giving us the opportunity to better understand the governing rules of tissue adaptation. Toward this end, an inverse optimization method, developed in the previous chapter is employed to estimate material and structural parameters of image-based models of arteries corresponding to a given constitutive relation, the results were compared with regard to multiple hypotheses of a homeostatic condition.

5.2 Hypotheses on vascular mechanical homeostasis

Vascular tissue tends to adapt in response to changes in its mechanical environment and a variety of evidence offers diverse hypotheses on this homeostatic tendency. In response to a sustained pressure increase, the thickness of the blood vessel increases, implying a tendency toward uniformity of circumferential stress (Matsumoto and Hayashi, 1994; Wolinsky, 1971; Xu et al., 2000). Blood vessel diameter increases in response to an increase in blood flow, thereby normalizing the wall shear stress (Kamiya and Togawa, 1980; Langille et al., 1989). Some studies underscore the importance of strain mechanosensitivity along the coronary arterial tree (Guo and Kassab, 2004; Lu et al., 2001), whereas others indicate strain rate as an important component of vascular homeostasis (McKnight and Frangos, 2003). Meanwhile, the vascular system is under pulsatile forces and several observations emphasize the role of pulsatility in vascular homeostasis (Cummins et al., 2007; Leung et al., 1976). In an *in vivo* study, Eberth et al. (2009) observed a strong correlation between morphology and pulsatility of pressure and flow rather than mean values, which is consistent with a study by Boutouyrie et al. (1999).

Stress and strain are both tensorial quantities and previous studies have sought simpler

scalar measures of mechanical stimuli for modeling vascular adaptation. For example, Baek et al. (2006) utilized the magnitude of traction on the plane normal to the fiber direction as a scalar measure of the fiber stress. In another stress-driven model, Hariton et al. (2007a) and Driessen et al. (2008) used the normal component of traction on the plane normal to the fiber direction as the remodeling stimulus. These models assumed that the mechanical stimuli that vascular cells sense correlate with tension or shear on the fibrous tissue that they reside on. The stretch of collagen fibers was also used by Watton and Hill (2009) as the mechanical quantity governing the G&R. Nevertheless, these studies assumed that fibers have the same mechanical properties and, hence, the uniform stretch of fibers means the uniform tension.

In a more phenomenological study, Guo and Kassab (2004) examined the distributions of circumferential stress and strain along the porcine aorta and the coronary arterial tree. They found that the circumferential stretch ratio (from the zero-stress state to the loaded state) is relatively uniform compared to the stress and suggested that the vascular system closely regulates the degree of deformation. It is difficult, however, to explain how the cells in vascular tissues can regulate the deformation given that cells do not experience the zero-stress state of the blood vessel *in vivo*. Lillie and Gosline (2007) suggested that the strain of elastin during the cardiac cycle is nearly constant along the porcine thoracic aorta. Our recent study with the porcine thoracic aorta also showed that the cyclic strain during the cardiac cycle is relatively uniform in the circumferential direction compared to the circumferential component of stress (Kim and Baek, 2011).

In this chapter, the following three scalar measures are chosen to be associated with the homeostatic state:

- Case 1: $\sigma^k = ||\boldsymbol{\sigma}^k \mathbf{n}||$
- Case 2: $\sigma^k = \mathbf{n} \cdot \boldsymbol{\sigma}^k \mathbf{n}$
- Case 3: $\lambda^{cyc} = \lambda_1^{sys} / \lambda_1^{dias}$,

where $\boldsymbol{\sigma}^{k}$ and **n** are the partial stress and the unit vector representing the alignment of the k^{th} constituent. λ_{1}^{sys} and λ_{1}^{dias} are circumferential stretches at systolic and diastolic pressures. The distributions of thickness and fiber alignment are obtained by an inverse optimization using the above three cases.

5.3 Constitutive relations and an inverse optimization method

First, constitutive relations and material parameters of a healthy human artery are chosen based on chapter 4. Then, the distributions of wall thickness and fiber alignment are estimated using the inverse optimization integrated with the finite element model of two different inflated blood vessels.

For Cases 1 and 2, the objective function is similar to chapter 4 as

$$W = \frac{\int_{\Omega} ||\mathbf{x}(h, \alpha^k) - \mathbf{X}_{image}||^2 dA}{\int_{\Omega} ||\mathbf{X}_{image} - \bar{\mathbf{X}}||^2 dA} + \xi \sum_{i} \frac{\nu^i \int_{\Omega} (\sigma^i(h, \alpha^k) - \sigma^i_h)^2 dA}{\int_{\Omega} (\sigma^i_h)^2 dA},$$
(5.1)

and the corresponding objective function to minimize in Case 3 is defined as

$$W = \frac{\int_{\Omega} ||\mathbf{x}(h, \alpha^k) - \mathbf{X}_{image}||^2 dA}{\int_{\Omega} ||\mathbf{X}_{image} - \bar{\mathbf{X}}||^2 dA} + \xi \frac{\int_{\Omega} (\lambda^{cyc}(h, \alpha^k) - \lambda^{cyc}_h)^2 dA}{\int_{\Omega} (\lambda^{cyc}_h)^2 dA},$$
(5.2)

where λ^{cyc} is the cyclic stretch in the circumferential direction. Thickness and anisotropy distributions are then approximated, using the same technique in chapter 4

$$h(s,\theta) = \sum_{j=1}^{I} \{\beta_j^h \phi_j(s,\theta)\}, \qquad \alpha^k(s,\theta) = \sum_{j=1}^{I} \{\beta_j^k \psi_j(s,\theta)\},$$
(5.3)



Figure 5.1: Change in the objective function and its associated compartments versus optimization iterations in Cases 1 and 2 using 60 variables $(M = 6; N = 5; \xi = 0.01)$.

5.4 Results

Two 3-D geometric models, one from a healthy aorta and the other from a healthy internal iliac artery, are used as computational domains. For simplicity, fibers oriented in circumferential and axial directions are considered fixed and only helical fiber orientations (α^3 , α^4) are considered as variables of anisotropy such that $\alpha^3 = -\alpha^4$.

Figure 5.1 illustrates the convergence history of the objective function and its compartments, \mathcal{GD} and \mathcal{SD} , corresponding to Cases 1 and 2 for the aorta model. A sharp decrease in \mathcal{GD} and a similar reduction in \mathcal{SD} are noticed for both stress hypotheses when the convergence is achieved. Note that the small plateau regions are associated with the search periods when a new minimum has not been reached yet. Figure 5.2 contrasts the corresponding optimized distributions of wall thickness and anisotropy for the aorta model in Cases 1 and 2. In both cases, the concave side is found to be relatively thicker than the convex side. Helical fibers on the convex side tend to orient themselves more in the circumferential direction as opposed to the concave side, even though the overall anisotropy variation is not as large as the thickness variation. The similar convergence level for both hypotheses (Figure 5.1) follows from the similar inhomogeneous distributions of thickness and anisotropy variation is not as not cases. In spite of a similar trend of distribution, a larger circumferential anisotropy variation is noticeable in Case 2 (Figure 5.2d).

An analogous comparison between Cases 1 and 2 has been made for the internal iliac artery model (Figure 5.3). In both cases, relatively similar distributions of wall thickness are observed. However, fiber orientations are distributed with more variability between the two cases than for the aorta model. For the iliac artery model in Case 1, Figure 5.4 illustrates the geometric deviation from the *in vivo* configuration ($||\mathbf{x} - \mathbf{X}_{image}||$) as well as the normalized deviation of stress in a helical fiber from the homeostatic value ($(\sigma^k - \sigma_h^k)/\sigma_h^k$) when (M = 5; N = 3) (a, c) and (M = 6; N = 5) (b, d). As expected, the geometric deviation is minimized (< 0.3 mm) in both conditions (Figure 5.4a,b).

The maximum deviation of fiber stress from the homeostatic value still seems to be large (< 80%) although on average the deviation has been minimized (Figure 5.4c,d). Some adaptive provisions in the optimization may be useful to reduce the localized high values of deviations in future improvements of the proposed technique. Apparently, increasing the number of approximation points (from I = 15 to I = 30) in the optimization results in only a minor improvement in reducing the average deviations, while the maximum deviations remains the same. That is, a further increase in approximation points may not be computationally justifiable.

With regard to Case 3, Figure 5.5 shows the geometric deviation from the original *in vivo* configuration (a), the normalized deviation of the circumferential cyclic stretch (b) as well as the optimized distributions of wall thickness (c) and anisotropy (d) for the aorta



Figure 5.2: Optimized distributions of thickness (a, b) and anisotropy (c, d) for the aorta model obtained in Cases 1 and 2 (M = 6; N = 5; $\xi = 0.01$). Black arrows identify the direction of one set of corresponding collagen fibers.



Figure 5.3: Optimized distributions of thickness (a, b) and anisotropy (c, d) for the internal iliac artery model obtained in Cases 1 and 2 ($M = 5; N = 3; \xi = 0.1$).



Figure 5.4: Deviation of the geometry from the *in vivo* configuration $(||\mathbf{x} - \mathbf{X}_{image}||)$ and deviation of stress in a helical fiber direction from the homeostatic value $((\sigma^k - \sigma_h^k)/\sigma_h^k)$ when (M = 5; N = 3) (a, c) and when (M = 6, N = 5) (b, d) for the iliac artery model.

model. As required by the objective function, the geometric deviation from the image is minimized (to a maximum value of 0.05 mm). Cyclic stretch is also homogenized toward the target homeostatic value (i.e., 1.02) on most parts with the largest deviation on areas close to the fixed boundaries (maximum normalized deviation of 1.5%). When compared to Cases 1 and 2 (Figure 5.2), lower levels of thickness are predicted by the cyclic stretch hypothesis (Figure 5.5c). More circumferential and less longitudinal variations of anisotropy are noticeable in Case 3 (Figure 5.5), whereas anisotropy is more locally distributed in Cases 1 and 2. Convergence of the optimization is an issue when the cyclic stretch hypothesis is applied to a more complex geometry such as the iliac artery model (not shown).

5.5 Discussion

In this chapter, a numerical optimization method was utilized to find the optimal distributions of structural parameters of healthy arteries based on different homeostatic assumptions (i.e., uniform stress and cyclic stretch). It was found that for medical image-based models different homeostatic assumptions lead to different inhomogeneous distributions of wall thickness and anisotropy. The potential application of the proposed optimization method to arteries with higher levels of geometric complexity was also illustrated by using the internal iliac artery model.

Different assumptions for stress homeostasis (Cases 1 and 2) led to homologous overall distributions of thickness, but differing distributions of anisotropy for both arteries (Figures 5.2 and 5.3). Interestingly, the arterial wall on the concave regions was found to be thicker than on the convex regions and the variation of anisotropy was small. Possible correlations between the wall thickness and anisotropy variation and other geometric parameters such as the surface curvature and tortuosity of the vessel wall can be examined in an independent study by systemic application of the technique using multiple image-based arterial geometries. Case 3 (stretch-based homeostasis) produced noticeably contrasting results with Cases



Figure 5.5: Deviation of the geometry (a), cyclic stretch in circumferential direction $(\lambda^c)(b)$ and corresponding distributions of thickness (c) and anisotropy (d) for the aorta model obtained in Case 3 ($M = 6; N = 3; \xi = 0.01$). Black arrows identify the direction of one set of corresponding collagen fibers.

1 and 2. Indeed, in Cases 3, the wall thickness was predicted to be in general smaller than in Cases 1 and 2 (stress-based homeostasis), while a less longitudinal anisotropy variation was observed (Figure 5.5). The assumption of a uniform cyclic stretch resulted in a remarkable improvement for both terms of the objective function (Figure 5.5a,b), thereby revealing a stronger potential for the cyclic stretch homeostatic assumption, which remains to be further validated with experimental data.

Meanwhile, here, a constant proportion of the constituents as well as a uniform distribution of the material parameters were assumed and the more attention was given to the variation of structural parameters such as the wall thickness and fiber orientation. Some studies, however, indicated non-uniform deformations of the arterial wall during the cardiac cycle (Draney et al., 2004) and observed a circumferential variation of material properties of the aortic wall. In a recent *ex vivo* inflation test of aorta Kim and Baek (2011) found that the posterior region of the arterial wall is thinner, but stiffer than the anterior region. This may be due to the influence of surrounding tissue as well as the local variation in the content of each constituent. Our study excluded the effect of anatomical variation of boundary condition due to the surrounding tissue which may have influenced our results. This effect can be more pronounced when a complex *in vivo* geometry such as the internal iliac artery (Figure 5.3) is involved. Also, the fixed boundary conditions considered at both ends are inconsistent with the cyclic stretch homeostatic assumption, thereby resulting in large deviations at both ends (Figure 5.5b).

Based on the preliminary results, the error or deviation of geometry relative to the image geometry is less sensitive to the fiber orientations than the wall thickness. Removing the condition $\alpha_3 = -\alpha_4$ (i.e., adding one more set of optimization variables) did not result in more variability in optimal fiber orientations, whereas it doubled the computational cost. Considering variable orientations for fibers in the axial and circumferential directions greatly adds up to the numerical complexity of the optimization.

It is worth mentioning that the mechanical homeostasis of the normal tissue maintenance

may also change under various additional conditions, such as aging and vascular diseases. The application of the current technique to diseased arteries will require more understanding of tissue growth and remodeling under pathological conditions. Nevertheless, the current method showed a distinguishing capability in terms of the optimal structure based on various forms of constitutive relations and homeostatic assumptions. There is a clear need for more experimental data in order to validate and exploit the current technique in understanding the multifactorial process of vascular homeostasis and possible implementation in patient-specific models of vascular diseases.

Chapter 6

A FINITE ELEMENT MODEL OF STRESS-MEDIATED VASCULAR ADAPTATION: APPLICATION TO ABDOMINAL AORTIC ANEURYSMS

6.1 Introduction

FEM-based vascular G&R simulations typically utilize microstructural information of structural components (collagen, elastin, and smooth muscle) to define the mechanical state at a given time (either stress or strain), which is iteratively fed back for calculating the evolution of microstructural properties of the components due to mechano-sensitive cellular activities. Humphrey and coworkers presented FEM models of stress-mediated G&R using a constrained mixture approach and modeled intracranial aneurysms (Baek et al., 2005, 2006; Figueroa et al., 2009). Hariton et al. (2007b) studied the stress-driven collagen fibers remodeling in a human carotid bifurcation. On the other hand, strain-mediated models of vascular adaptation have also been developed and implemented to model cerebral and aortic aneurysms (Watton et al., 2004; Kroon and Holzapfel, 2007, 2009a; Watton and Hill, 2009). Driessen et al. (2004, 2008) investigated stretch-mediated remodeling of collagen fibers in arterial tissues.

Elastin degradation and collagen turnover are main biomechanical processes in enlargement of aneurysms. Abdominal aortic aneurysms (AAAs) have been associated with a decrease in elastin content (Rizzo et al., 1989; He and Roach, 1994; Ghorpade and Baxter, 1996; Powell, 2002) resulting from proteolytic activity. It has also been suggested that stress(strain)-mediated collagen turnover plays an important role in aneurysm enlargement and it may differ among individuals depending on physiological and pathological conditions (Choke et al., 2005). Hence, both elastin degeneration and collagen turnover should be considered in the computational models of AAAs development. Watton et al. (2004) and Watton and Hill (2009) were the first to develop a mathematical model of the evolution of an AAA by accounting for elastin degradation and collagen turnover. In their study, spatial and temporal alterations of elastin concentration were prescribed and collagen remodeling acted to maintain the strain in fibers to an equilibrium value.

Previous modeling of evolving vascular diseases have mainly focused on hypothesis-testing with simple geometries, however, and there is a need to account for patient-specific anatomical and physiological information in FEM simulations of vascular diseases (Taylor and Humphrey, 2009). In this work, we extend the previous FEM model of stress-mediated G&R developed by Baek et al. (2005, 2006) to incorporate a non-axisymmetric geometry obtained from medical images. The computational method is, then, applied to model an enlarging AAA assuming that an AAA grows by elastin degradation/damage and stressmediated collagen turnover governed by the local state of intramural stress. We contrast stress distributions and expansion rates of the computationally grown AAAs for multiple kinetic parameters and different spatial distribution of elastin damage.

Toward this end, we employ a theoretical model of arterial G&R based on a constrained mixture approach and use a nonlinear FEM with linear triangular elements.

6.2 Theoretical modeling of arterial G&R

6.2.1 Kinematics and important configurations

There are two very different timescales in arterial mechanics: a short-term timescale associated with pulsatile motion during the cardiac cycle (seconds) and a long-term timescale for G&R (days to weeks or months). Following Figueroa et al. (2009), t denotes time associated with the cardiac cycle, during which we assume no G&R, and s denotes time during G&R. The configuration κ_t is the current configuration and $\mathbf{x}(t)$ denotes the position of a particle in κ_t . Here we make a tacit assumption that there exist a stress-free configuration κ_{sf} of the vessel wall which is fixed at a given s. The vector $\mathbf{X}_{sf}(s)$ denotes the position vector of the particle in the stress-free configuration and $\mathbf{F}_{sf}(t)$ denotes the deformation gradient corresponding to the mapping from $\mathbf{X}_{sf}(s)$ to $\mathbf{x}(t)$. In arterial mechanics, the effect of the inertial forces in arterial wall motion are negligible (Humphrey and Na, 2002) and we define the current (*in vivo*) configuration κ_s in the G&R timescale as the configuration κ_t under the mean pressure during the cardiac cycle.

For modeling arterial G&R, it appears to be advantageous to introduce additional configurations shown in Figure 6.1 (Baek et al., 2006; Figueroa et al., 2009). The configurations κ_{τ} trace the *in vivo* configurations of body through time $\tau \in [0, s]$. Particularly, the configuration κ_0 represents a loaded *in vivo* configuration of a healthy artery. We assume that each constituent is pre-stretched when deposited into the tissue at time τ and the tensor $\mathbf{G}^i(\tau)$ represents the deposition stretch of constituent *i*. For computational purposes, we introduce a configuration κ_R , called the (computational) reference configuration, that is a fixed configuration. Although the configuration κ_R is fixed in space, we assume that particles can be created or removed so that there is one-to-one mapping between κ_R and κ_s at time *s*. This assumption also implies that the total mass in κ_R changes with time and becomes always the same as the total mass in κ_s . The position of a given particle in κ_R is denoted by **X** and the deformation gradient $\mathbf{F}(s)$ is given corresponding to the mapping from κ_R to κ_s . The stress-free configuration κ_{sf} evolves in the G&R time scale and **P** is the tensor representing its evolution. Because the total mass is preserved in the mapping from κ_R to κ_s at time s, the density with respect to the reference configuration, $\rho_R(s)$, can be calculated by

$$\rho_R(s) = J(s)\rho(s),\tag{6.1}$$

where $J(s) = \det [\mathbf{F}(s)]$ and $\rho(s)$ is the mass density in the current configuration at time s. Let $\varphi^i(s)$ denote the mass fraction of constituent i, i.e., $\sum_i \varphi^i(s) = 1$. The mass density of constituent i with respect to the reference configuration, $\rho^i_R(s)$, is defined as

$$\rho_R^i(s) = \varphi^i(s)\rho_R(s). \tag{6.2}$$

The deformation gradient for each constituent *i* at time *t*, relative to its natural configuration, $\mathbf{F}_{n(\tau)}^{i}(t)$, is given as (Baek et al., 2006)

$$\mathbf{F}_{n(\tau)}^{i}(t) = \mathbf{F}(t)\mathbf{F}^{-1}(\tau)\mathbf{G}^{i}(\tau), \qquad (6.3)$$

where $\mathbf{F}^{-1}(\tau)\mathbf{G}^{i}(\tau)$ is the tensor representing the pre-stretch of the constituent *i* that has been produced at τ with respect to the reference configuration (see Figure 6.1). The deformation gradient $\mathbf{F}_{n(\tau)}^{i}(t)$ can also be written as

$$\mathbf{F}_{n(\tau)}^{i}(t) = \mathbf{F}_{sf}(t)\mathbf{P}(s)\mathbf{F}^{-1}(\tau)\mathbf{G}^{i}(\tau), \qquad (6.4)$$

where, now, $\mathbf{P}(s)\mathbf{F}^{-1}(\tau)\mathbf{G}^{i}(\tau)$ represents the pre-stretch of the constituent *i* that has been produced at τ with respect to κ_{sf} .



Figure 6.1: Schematic view of configurations involved in the G&R simulation. A fixed reference configuration is considered for the computation of deformation associated with G&R time $\tau = [0, s]$. It is chosen to coincide with the configuration of a healthy *in vivo* artery at time $\tau = 0$ (i.e., κ_0). We imagine the existence of a stress-free configuration, κ_{sf} , associated with the current configuration κ_s .

6.2.2 Stress response and constitutive assumptions

Consider an arterial wall tissue consisting of multiple structural components, e.g., elastin, multiple collagen families, and smooth muscle (SM). Following previous convention, we use the subscript 'i' to refer each constituent (e.g., elastin, collagen families, muscle) and the superscript 'k' to the k^{th} family of collagen fibers. Thus, i = e, 1, ..., k, ..., m where e denotes elastin and m denotes SM. Although we adopt the G&R formulation based on the constrained mixture approach (Humphrey and Rajagopal, 2002), following its later modification (Baek et al., 2006; Figueroa et al., 2009) we take the point of view of a biological tissue comprising multiple constituents as a single continuum, where the mass fraction of each constituent and its pre-stretch are considered as attributes for a particle of the biological tissue. We assume further that for a given time s the mechanical behavior of the artery can be characterized by a hyperelastic model and we solve inflation problems with the principle of virtual work. Hence, let the Cauchy stress be given by (Truesdell and Noll, 1965),

$$\mathbf{t}(t) = 2\rho(t)\mathbf{F}_{sf}(t)\frac{\partial\Psi(\mathbf{C}_{sf}(t))}{\partial\mathbf{C}_{sf}(t)}\mathbf{F}_{sf}^{T}(t),$$
(6.5)

where $\mathbf{C}_{sf}(t) = \mathbf{F}_{sf}^{T}(t)\mathbf{F}_{sf}(t)$ and $\Psi(\mathbf{C}_{sf}(t))$ is the stored-energy function (per unit mass).

Since the stress-free configurations κ_{sf} change with G&R, we utilize a fixed computational reference configuration κ_R . Thus, (6.5) can be rewritten with respect to κ_R , by using $\mathbf{F}(t) = \mathbf{F}_{sf}(t)\mathbf{P}(s)$, (6.1), and the chain rule, as

$$\mathbf{t}(t) = \frac{2}{J(t)} \mathbf{F}(t) \frac{\partial \{\rho_R(s) \hat{\Psi}(\mathbf{C}(t))\}}{\partial \mathbf{C}(t)} \mathbf{F}^T(t), \tag{6.6}$$

where $\hat{\Psi}(\mathbf{C}(t)) = \hat{\Psi}(\mathbf{P}^T(s)\mathbf{C}_{sf}(t)\mathbf{P}(s)) = \Psi(\mathbf{C}_{sf}(t))$. For a membrane model, using $J = J_{2D}h/h_R$ for the thickness h, the membrane stress \mathbf{T} can be given as

$$\mathbf{T}(t) = \frac{2}{J_{2D}(t)} \mathbf{F}_{2D}(t) \frac{\partial M_R(s) \tilde{\Psi} (\mathbf{C}_{2D}(t))}{\partial \mathbf{C}_{2D}(t)} \mathbf{F}_{2D}^T(t),$$
(6.7)

where the areal density $M_R(s) = h_R \rho_R(s)$ and $\tilde{\Psi}(\mathbf{C}_{2D}(t)) = \hat{\Psi}(\mathbf{C}(t))$ (e.g., see Holzapfel et al. (2000) for two-dimensional formulation). For simplicity, we omit the subscript '2D' and define $w_R(s) = M_R(s)\tilde{\Psi}(\mathbf{C}(t))$. Then (6.6) becomes

$$\mathbf{T}(t) = \frac{2}{J(t)} \mathbf{F}(t) \frac{\partial w_R(\mathbf{C}(t))}{\partial \mathbf{C}(t)} \mathbf{F}^T(t).$$
(6.8)

To simulate arterial G&R, we employ the stored energy equation $w_R(t; s)$, the stored energy (per unit area) due to the deformation of $\mathbf{x}(t)$ at a given G&R time s, as (Figueroa et al., 2009)

$$w_R(t;s) = \sum_i \left\{ M_R^i(0)Q^i(s)\Psi^i(\mathbf{C}_{n(0)}^i(t)) + \int_0^s m_R^i(\tau)q^i(s,\tau)\Psi^i(\mathbf{C}_{n(\tau)}^i(t)) \, d\tau \right\}, \quad (6.9)$$

where $\Psi^i (\mathbf{C}_{n(\tau)}^i(t))$ is the stored energy of constituent *i* that has been produced $\mathbf{C}_{n(\tau)}^i(t) = [\mathbf{F}_{n(\tau)}^i(t)]^T \mathbf{F}_{n(\tau)}^i(t), Q^i(s)$ is the fraction of the constituent *i* that was present at time 0 and still remains at time *s* (i.e., has not yet been removed), $m_R^i(\tau)$ is the mass production rate of the constituent *i* at time τ per unit reference area, and $q^i(s,\tau)$ is its survival function, that is, the fraction produced at time τ that remains at time *s*.

We employ constitutive relations for deposition tensors and stored energy functions for constituents used by Baek et al. (2006, 2007b) and Figueroa et al. (2009). The mechanical property and the "deposition stretch", named G_h^c , of the newly synthesized collagen fibers are assumed to be always the same. Let $\mathbf{m}^k(\tau)$ be the unit vector in the direction of the k^{th} collagen fiber produced at time τ . The angle between $\mathbf{m}^k(\tau)$ and the first principal direction at time τ is denoted by $\alpha^k(\tau)$. We can find a unit vector $\mathbf{M}^k(\tau)$ in the reference configuration that corresponds to $\mathbf{m}^k(\tau)$, i.e.

$$\mathbf{M}^{k}(\tau) = \frac{\mathbf{F}^{-1}(\tau)\mathbf{m}^{k}(\tau)}{|\mathbf{F}^{-1}(\tau)\mathbf{m}^{k}(\tau)|}.$$
(6.10)

If the angle between $\mathbf{M}^{k}(\tau)$ and the first axis of the coordinate system is denoted by $\alpha_{R}^{k}(\tau)$,

the stretch (of the fiber produced at time τ) in the fiber direction from the reference to the current configuration is given by

$$\lambda^{k}(t) = \sqrt{\mathbf{F}(t)\mathbf{M}^{k}(\tau) \cdot \mathbf{F}(t)\mathbf{M}^{k}(\tau)} .$$
(6.11)

The stretch of the k^{th} fiber family from its natural to the current configuration can be, then, calculated as (Baek et al., 2006)

$$\lambda_{n(\tau)}^{k}(t) = G_{h}^{c} \frac{\lambda^{k}(t)}{\lambda^{k}(\tau)}, \qquad (6.12)$$

where $\lambda^k(\tau)$ is stretch of the unit vector in the k^{th} fiber direction from the reference configuration to the configuration at time τ . A similar approach can be adopted for SM, which are oriented primarily in the circumferential direction. Thus, the stretch of SM is given by $\lambda_{n(\tau)}^m(t) = G_h^m \lambda_2(t)/\lambda_2(\tau)$, where G_h^m is the homeostatic stretch for the SM. The main structure of cross-linked elastin is formed at early stages of development, thus it is difficult to trace its production time and to specify $\mathbf{F}^{-1}(\tau)$ in (6.3). So we define a new tensor $\tilde{\mathbf{G}}^e = \mathbf{F}^{-1}(\tau)\mathbf{G}_h^e$, which represents a mapping from the natural configuration of elastin to the computational reference configuration. Then, $\mathbf{F}_n^e = \mathbf{F}(t)\tilde{\mathbf{G}}^e$ and $\tilde{\mathbf{G}}^e$ is postulated as $\tilde{\mathbf{G}}^e = \text{diag}\left\{G_1^e, G_2^e, \frac{1}{G_1^e G_2^e}\right\}$.

The stored energy functions for the elastin-dominated amorphous, collagen fiber families $(\Psi^k = \Psi^c)$ and passive SM are given as

$$\Psi^{e}(\mathbf{C}_{n}^{e}(t)) = \frac{c_{1}}{2} \left(C_{n[11]}^{e} + C_{n[22]}^{e} + \frac{1}{C_{n[11]}^{e} C_{n[22]}^{e} - C_{n[12]}^{e}} - 3 \right), \quad (6.13)$$

$$\Psi^{c}(\lambda_{n(\tau)}^{k}(t)) = \frac{c_{2}}{4c_{3}} \Big\{ \exp\Big[c_{3}\big(\lambda_{n(\tau)}^{k}(t)^{2} - 1\big)^{2}\Big] - 1 \Big\},$$
(6.14)

$$\Psi^{m}(\lambda_{n(\tau)}^{m}(t)) = \frac{c_{4}}{4c_{5}} \Big\{ \exp\Big[c_{5} \big(\lambda_{n(\tau)}^{m}(t)^{2} - 1 \big)^{2} \Big] - 1 \Big\},$$
(6.15)

where $C_{n[11]}^e$, $C_{n[22]}^e$ and $C_{n[12]}^e$ are components of $\mathbf{C}_n^e = \begin{bmatrix} \mathbf{F}_n^e \end{bmatrix}^T \mathbf{F}_n^e$. Although the constitutive

form is the same for collagen fiber families and SM, SM is much more compliant than collagen fiber families and has less contribution to the passive mechanical behavior of the wall (Burton, 1954). We use a potential function for the active tone of vascular SM as (Baek et al., 2007b; Zulliger et al., 2004b)

$$\Psi_{act}^{m}(t) = \frac{S}{\rho} \Big\{ \lambda_{2}(t) + \frac{1}{3} \frac{(\lambda_{M} - \lambda_{2}(t))^{3}}{(\lambda_{M} - \lambda_{o})^{2}} \Big\},$$
(6.16)

where λ_M and λ_o are stretches at which the active force generation is maximum and zero, λ_2 is the stretch in circumferential direction at time t, and S is the stress at the maximum contraction. Then, the total membrane strain energy becomes $w_R = w_{R(passive)} + M_R^m(t)\Psi_{act}^m$.

6.2.3 Stress-mediated G&R

In arteries, constituents can be continuously produced and removed and normal tissue maintains its mass and configuration by balanced turnover of constituents. The rates of production and removal change from their balanced normal (basal) values in response to changes in mechanical environment. Here, we assume that $m_R^e(s) = 0$ and the rates of mass production for collagen fibers and SM are functions of a scalar measure of intermural stress, given by (Baek et al., 2006)

$$m_{R}^{k}(s) = \frac{M_{R}^{c}(s)}{M_{R}^{c}(0)} \left(K_{g}^{k}(\sigma^{k}(s) - \sigma_{h}^{c}) + m_{basal}^{k} \right)$$
(6.17)

$$m_{R}^{m}(s) = \frac{M_{R}^{m}(s)}{M_{R}^{m}(0)} \Big(K_{g}^{m}(\sigma^{m}(s) - \sigma_{h}^{m}) + m_{basal}^{m} \Big)$$
(6.18)

where $M_R^c(0)$ and $M_R^m(0)$ are the mass of collagen and SM per reference area of a healthy artery at time 0, respectively. K_g^i (i = 1, 2, ..., k, ..., m) is a scalar parameter that controls the stress-mediated growth, m_{basal}^i is a basal rate of mass production for the constituent *i*, and

$$\sigma^{k}(s) = \frac{||\mathbf{T}^{c}(s)\mathbf{m}^{k}(s)||}{h^{c}(s)} \quad \sigma^{m}(s) = \frac{||\mathbf{T}^{m}(s)\mathbf{m}^{m}(s)||}{h^{m}(s)}.$$
(6.19)

where $\mathbf{T}^{c}(s)$ and $\mathbf{T}^{m}(s)$ are the Cauchy membrane stress contributed by collagen and SM at time s (i.e. $\mathbf{T}^{c}(s) = \sum_{k} \mathbf{T}^{k}(s)$). $h^{c}(s)$ and $h^{m}(s)$ are contributions of collagen and SM to the total thickness at time s. Also, let

$$q^{i}(s,\tau) = \begin{cases} \exp\left(-\int_{\tau}^{s} k_{q}^{i}(\tilde{\tau})d\tilde{\tau}\right) & s-\tau \leq a_{max}^{i} \\ 0 & s-\tau > a_{max}^{i} \end{cases}$$
(6.20)

where $k_q^i(\tilde{\tau})$ can be a function of circumferential stress, wall shear stress, or other state variables. a_{max}^i is the maximum life span of the constituent *i*.

The new collagen is deposited with a preferred alignment. Following Baek et al. (2006), we assume that the alignment of the newly produced collagen is influenced by the orientation of the existing collagen and it consequently aligns along the direction of the existing collagen family.

6.3 Computational considerations

6.3.1 Local Cartesian coordinate system

We assume that the wall is a thin membrane, with $\mathbf{X} = \{X_1, X_2, X_3\}$ and $\mathbf{x} = \{x_1, x_2, x_3\}$ being the reference and current positions in the global Cartesian coordinate system with base vectors $\{\mathbf{E}_1, \mathbf{E}_2, \mathbf{E}_3\}$ (Figure 6.2). We use linear triangular elements for developing a nonlinear FEM model of a non-axisymmetric cylindrical membrane and define a local Cartesian coordinate system for each element in order to facilitate calculation of the local deformation gradient and prescribe material anisotropy. The centroid of an element $\mathbf{X}^c =$ $\{X_1^c, X_2^c, X_3^c\}$ becomes the origin of the local Cartesian coordinate system and 'elementwise' orthogonal surface coordinates ξ_1 and ξ_2 are allocated to any point on the element with respect to the origin (Figure 6.2).



Figure 6.2: Orthonormal base vectors for a global Cartesian coordinate system are $\{\mathbf{E}_1, \mathbf{E}_2, \mathbf{E}_3\}$. Those for a local Cartesian coordinate system are $\mathbf{E}_1^e, \mathbf{E}_2^e$ (associated with ξ_1 , ξ_2), and $\mathbf{E}_3^e = \mathbf{N}^e$ at a point set to be the center point of a linear triangular element tangent to the membrane at \mathbf{X}^c . \mathbf{E}_1^e and \mathbf{E}_2^e are orthonormal bases on the tangent plane and \mathbf{N}^e is the outward unit normal vector.

A linear triangular element has three nodal points $\{\mathbf{X}^{(1)}, \mathbf{X}^{(2)}, \mathbf{X}^{(3)}\}$ in the reference and $\{\mathbf{x}^{(1)}, \mathbf{x}^{(2)}, \mathbf{x}^{(3)}\}$ in the current configurations and $X_i^c = \frac{1}{3} \sum_k X_i^{(k)}$ (i, k = 1, 2, 3). Now, we introduce local bases \mathbf{E}_1^e and \mathbf{E}_2^e in the plane of a linear triangular element (i.e. tangent plane) and $\mathbf{E}_3^e \equiv \mathbf{N}^e$ the outward normal to that plane (Figure 6.2). The base vector \mathbf{E}_1^e is set to a unit vector aligned toward the axial direction of a model of the artery (a unit tangent vector to ξ_1 at the element center point). The outward normal vector \mathbf{N}^e is readily obtained by cross product of vectors connecting nodal points. The base vector \mathbf{E}_2^e is then calculated as $\mathbf{E}_2^e = \mathbf{N}^e \times \mathbf{E}_1^e$. If $\mathbf{X}^e = \{X_1^e, X_2^e, X_3^e\}$ and $\mathbf{x}^e = \{x_1^e, x_2^e, x_3^e\}$ are the reference and current position vectors in the local Cartesian coordinate system, the two-dimensional right Cauchy-Green deformation tensor is calculated by (Kyriacou et al., 1996; Park and Youn, 1998)

$$\mathbf{C} = \left(\frac{\partial \mathbf{x}^e}{\partial \xi_\alpha} \cdot \frac{\partial \mathbf{x}^e}{\partial \xi_\beta}\right) \mathbf{E}^e_\alpha \otimes \mathbf{E}^e_\beta \tag{6.21}$$

where $\alpha, \beta = 1, 2$.

6.3.2 Finite element formulation

The weak form for the membrane can be obtained from the principle of virtual work (Kyriacou et al., 1996),

$$\delta I = \int_{S} \delta w dA - \int_{S} P \mathbf{n} \cdot \delta \mathbf{x} da = 0.$$
(6.22)

In a FEM model, we seek an approximate solution to (6.22). Let a finite approximation of the current position be

$$\mathbf{x} = \mathbf{\Phi} \mathbf{x}^p, \qquad x_i = \Phi_{iA} x_A^p, \tag{6.23}$$

where \mathbf{x}^p and $\boldsymbol{\Phi}$ are the nodal vector for the current position and shape function matrix, respectively. Then, the governing equation for an element can be obtained from (6.22) as

$$\left\{\mathcal{F}\right\}_{P}^{e} = \int_{S^{e}} \left(\frac{\partial w}{\partial C_{\alpha\beta}} \frac{\partial C_{\alpha\beta}}{\partial x_{P}^{p}} - \tilde{P}_{i} \Phi_{iP}\right) dA = 0, \tag{6.24}$$

where for a linear triangular element,

$$\tilde{P}_{i} = P \frac{\epsilon_{ijk} (x_{j}^{(2)} - x_{j}^{(1)}) (x_{k}^{(3)} - x_{k}^{(1)})}{||\epsilon_{lmn} (X_{m}^{(2)} - X_{m}^{(1)}) (X_{n}^{(3)} - X_{n}^{(1)})||}.$$
(6.25)

We use the Newton-Raphson method to solve (6.24) and the tangent matrix can be given by

$$\begin{bmatrix} \mathbf{K} \end{bmatrix}_{PQ} = \begin{bmatrix} \frac{\partial \mathcal{F}}{\partial x^p} \end{bmatrix}_{PQ}^e = \int_{S^e} \left(\frac{\partial^2 w}{\partial C_{\alpha\beta} \partial C_{\gamma\omega}} \frac{\partial C_{\alpha\beta}}{\partial x_P^p} \frac{\partial C_{\gamma\omega}}{\partial x_Q^p} + \frac{\partial w}{\partial C_{\alpha\beta}} \frac{\partial^2 C_{\alpha\beta}}{\partial x_P^p \partial x_Q^p} - \Phi_{iP} \tilde{P}_{i,Q} \right) dA$$
(6.26)

Note that (i, j, k, l, m, n = 1, 2, 3), $(\alpha, \beta, \gamma, \omega = 1, 2)$, and $(A, B, M, P, Q = 1, 2, 3, ..., n_p)$, where n_p is the number of nodes in an element multiplied by 3, i.e., $n_p = 9$.

Any point $\mathbf{X} = \{X_1, X_2, X_3\}$ in the global Cartesian coordinate system can be transformed to $\mathbf{X}^e = \{X_1^e, X_2^e, X_3^e\}$ in the local coordinate system using

$$X_i^e = \mathbf{E}_i^e \cdot (\mathbf{X} - \mathbf{X}^c) = Q_{ij}(X_j - X_j^c)$$
(6.27)

where $Q_{ij} = \mathbf{E}_i^e \cdot \mathbf{E}_j$. We use linear triangular element which is flat and has 9 translational degrees of freedom to discretize the domain (Flores and Onate, 2001). Now, we define linear interpolation function for the triangular element with respect to i^{th} nodal point as

$$\phi^{i}(\xi_{1},\xi_{2}) = a^{i}\xi_{1} + b^{i}\xi_{2} + c^{i}, \qquad (i = 1,2,3)$$
(6.28)

where a^i , b^i , and c^i are constants and $\sum_{i}^{(all \ node)} \phi^i(\xi_1, \xi_2) = 1$. The interpolation functions have the following properties:

$$\phi^{i}(X_{1}^{e(j)}, X_{2}^{e(j)}) = \delta_{ij}, \text{ where } X_{k}^{e(j)} = \mathbf{E}_{k}^{e} \cdot (\mathbf{X}^{(j)} - \mathbf{X}^{c}).$$
 (6.29)

Thus, a^i , b^i , and c^i can be obtained by solving (6.29), for example,

$$\left\{ \begin{array}{c} a^{1} \\ b^{1} \\ c^{1} \end{array} \right\} = \left[\begin{array}{c} X_{1}^{e(1)} & X_{2}^{e(1)} & 1 \\ X_{1}^{e(2)} & X_{2}^{e(2)} & 1 \\ X_{1}^{e(3)} & X_{2}^{e(3)} & 1 \end{array} \right]^{-1} \left\{ \begin{array}{c} 1 \\ 0 \\ 0 \end{array} \right\}.$$
(6.30)

It is convenient to define 9×1 vectors for the nodal points as

$$\mathbf{X}^{ep} = \{X_1^{e(1)}, X_2^{e(1)}, X_3^{e(1)}, X_1^{e(2)}, X_2^{e(2)}, X_3^{e(2)}, X_1^{e(3)}, X_2^{e(3)}, X_3^{e(3)}\}^T$$
(6.31)

$$\mathbf{x}^{ep} = \{x_1^{e(1)}, x_2^{e(1)}, x_3^{e(1)}, x_1^{e(2)}, x_2^{e(2)}, x_3^{e(2)}, x_1^{e(3)}, x_2^{e(3)}, x_3^{e(3)}\}^T$$
(6.32)

$$\mathbf{X}^{p} = \{X_{1}^{(1)}, X_{2}^{(1)}, X_{3}^{(1)}, X_{1}^{(2)}, X_{2}^{(2)}, X_{3}^{(2)}, X_{1}^{(3)}, X_{2}^{(3)}, X_{3}^{(3)}\}^{T}$$
(6.33)

$$\mathbf{x}^{p} = \{x_{1}^{(1)}, x_{2}^{(1)}, x_{3}^{(1)}, x_{1}^{(2)}, x_{2}^{(2)}, x_{3}^{(2)}, x_{1}^{(3)}, x_{2}^{(3)}, x_{3}^{(3)}\}^{T}$$
(6.34)

$$\mathbf{X}^{c} = \{X_{1}^{c}, X_{2}^{c}, X_{3}^{c}, X_{1}^{c}, X_{2}^{c}, X_{3}^{c}, X_{1}^{c}, X_{2}^{c}, X_{3}^{c}\}^{T}$$

$$(6.35)$$

The coordinate transformation between global and local coordinates can be expressed by:

$$\mathbf{X}^{ep} = \tilde{\mathbf{Q}}(\mathbf{X}^p - \mathbf{X}^c), \qquad \mathbf{x}^{ep} = \tilde{\mathbf{Q}}(\mathbf{x}^p - \mathbf{X}^c)$$
(6.36)

where a 9×9 matrix \tilde{Q} is given by:

$$\tilde{\mathbf{Q}} = \begin{bmatrix} \mathbf{Q} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{Q} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{Q} \end{bmatrix}.$$
(6.37)

Note that the local position vectors of element nodes in the current configuration, \mathbf{x}^{ep} , are expressed with respect to the local coordinate system associated with that element in the reference configuration. The position vector in the local coordinate system is

$$\mathbf{x}^e(\xi_1,\xi_2) = \mathbf{\Phi}\mathbf{x}^{ep} \tag{6.38}$$

where

$$\boldsymbol{\Phi} = \begin{bmatrix} \phi^1 & 0 & 0 & \phi^2 & 0 & 0 & \phi^3 & 0 & 0 \\ 0 & \phi^1 & 0 & 0 & \phi^2 & 0 & 0 & \phi^3 & 0 \\ 0 & 0 & \phi^1 & 0 & 0 & \phi^2 & 0 & 0 & \phi^3 \end{bmatrix}.$$

and ϕ^1 , ϕ^2 , and ϕ^3 are linear shape functions of ξ_1 and ξ_2 for the element. Using (6.36), (6.38) can be rewritten as

$$\mathbf{x}^{e} = \mathbf{\Phi}\tilde{\mathbf{Q}}(\mathbf{x}^{p} - \mathbf{X}^{c}), \qquad \left[x_{i}^{e} = \Phi_{iA}\tilde{Q}_{AB}(x_{B}^{p} - X_{B}^{c})\right]$$
(6.39)

For convenience, let us define $\mathbf{\Phi}^e$ as

$$\Phi^e_{iB} = \Phi_{iA} \tilde{Q}_{AB}. \tag{6.40}$$

The components of the derivative of the local position vector with respect to the local coordinate are

$$x_{i,\alpha}^e = \Phi_{iA,\alpha} \tilde{Q}_{AB} x_B^p, \quad \text{or} \quad x_{i,\alpha}^e = \Phi_{iA,\alpha}^e x_A^p \tag{6.41}$$

Thus, components of the right Cauchy-Green tensor (6.21) can be obtained as

$$C_{\alpha\beta} = x_{i,\alpha}^e x_{i,\beta}^e = \Phi_{iA,\alpha}^e x_A^p \Phi_{iM,\beta}^e x_M^p, \tag{6.42}$$

where the basis is $\mathbf{E}^{e}_{\alpha} \otimes \mathbf{E}^{e}_{\beta}$. Also each component in (6.26) can be obtained by

$$\frac{\partial C_{\alpha\beta}}{\partial x_P^p} = x_{i,\alpha}^e \Phi_{iP,\beta}^e + x_{i,\beta}^e \Phi_{iP,\alpha}^e$$
(6.43)

$$\frac{\partial^2 C_{\alpha\beta}}{\partial x_P^p \partial x_Q^p} = \Phi^e_{iP,\alpha} \Phi^e_{iQ,\beta} + \Phi^e_{iP,\beta} \Phi^e_{iQ,\alpha}$$
(6.44)

$$\frac{\partial^2 w}{\partial C_{\alpha\beta} \partial C_{\gamma\omega}} \frac{\partial C_{\alpha\beta}}{\partial x_P^p} \frac{\partial C_{\gamma\omega}}{\partial x_Q^p} = \frac{\partial^2 w}{\partial C_{\alpha\beta} \partial C_{\gamma\omega}} x_{i,\beta}^e x_{j,\omega}^e \Phi_{iP,\alpha}^e \Phi_{jQ,\gamma}^e
+ \frac{\partial^2 w}{\partial C_{\alpha\beta} \partial C_{\gamma\omega}} x_{i,\beta}^e x_{j,\gamma}^e \Phi_{iP,\alpha}^e \Phi_{jQ,\omega}^e
+ \frac{\partial^2 w}{\partial C_{\alpha\beta} \partial C_{\gamma\omega}} x_{i,\alpha}^e x_{j,\omega}^e \Phi_{iP,\beta}^e \Phi_{jQ,\gamma}^e
+ \frac{\partial^2 w}{\partial C_{\alpha\beta} \partial C_{\gamma\omega}} x_{i,\alpha}^e x_{j,\gamma}^e \Phi_{iP,\beta}^e \Phi_{jQ,\omega}^e$$
(6.45)

$$\frac{\partial w}{\partial C_{\alpha\beta}} \frac{\partial^2 C_{\alpha\beta}}{\partial x_P^p \partial x_Q^p} = \frac{\partial w}{\partial C_{\alpha\beta}} \left(\Phi_{iP,\alpha}^e \Phi_{iQ,\beta}^e + \Phi_{iP,\beta}^e \Phi_{iQ,\alpha}^e \right).$$
(6.46)

For the linear triangle element, the following relation can be obtained:

$$\tilde{\mathbf{P}} = \frac{P}{|(\mathbf{X}^{(2)} - \mathbf{X}^{(1)}) \times (\mathbf{X}^{(3)} - \mathbf{X}^{(1)})|} (\mathbf{x}^{(2)} - \mathbf{x}^{(1)}) \times (\mathbf{x}^{(3)} - \mathbf{x}^{(1)}).$$
(6.47)

$$\frac{\partial \tilde{\mathbf{P}}}{\partial \mathbf{x}^{p}} = \frac{P}{|(\mathbf{x}^{(2)} - \mathbf{x}^{(1)}) \times (\mathbf{x}^{(3)} - \mathbf{x}^{(1)})|} \frac{\partial \{(\mathbf{x}^{(2)} - \mathbf{x}^{(1)}) \times (\mathbf{x}^{(3)} - \mathbf{x}^{(1)})\}}{\partial \mathbf{x}^{p}} \quad (6.48)$$

$$= \frac{P}{|(\cdot)|} \begin{bmatrix} 0 & x_{3}^{(2)} - x_{3}^{(3)} & x_{2}^{(3)} - x_{2}^{(2)} \\ x_{3}^{(3)} - x_{3}^{(2)} & 0 & x_{1}^{(2)} - x_{1}^{(3)} \\ x_{2}^{(2)} - x_{2}^{(3)} & x_{1}^{(3)} - x_{1}^{(2)} & 0 \\ 0 & x_{3}^{(3)} - x_{3}^{(1)} & x_{2}^{(1)} - x_{2}^{(3)} & 0 & x_{3}^{(1)} - x_{3}^{(2)} & x_{2}^{(2)} - x_{2}^{(1)} \\ x_{3}^{(1)} - x_{3}^{(3)} & 0 & x_{1}^{(3)} - x_{1}^{(1)} & x_{3}^{(2)} - x_{3}^{(1)} & 0 & x_{1}^{(1)} - x_{1}^{(2)} \\ x_{2}^{(3)} - x_{2}^{(1)} & x_{1}^{(1)} - x_{1}^{(3)} & 0 & x_{2}^{(1)} - x_{2}^{(2)} & x_{1}^{(2)} - x_{1}^{(1)} & 0 \end{bmatrix} .$$

6.3.3 Numerical solutions

The spatial integration in (6.24) is approximated by using Gauss integration. At every Gauss point, the temporal integrations in (6.22) are calculated by using the trapezoidal rule (Press et al., 1992) over past times. Although the survival function (6.20) is given by an exponential function, we define a maximum lifetime a_{max}^i and truncate the value if $s - \tau \leq a_{max}^i$. Thus, the numerical integration can be done over the time interval $[s - a_{max}^i, s]$ using fixed number of discretization points. Equations (6.17), (6.18), and (6.24) are solved iteratively for the nodal positions and rates of mass production at a given time s. Briefly, an initial guess of $m_R^i(s)$ is made at each Gauss point based on the previous time step, and (6.24) is solved for the current positions using the nonlinear FEM technique prescribed in the previous section. Then, $m_R^i(s)$ is updated using the FEM solution along with (6.17) and (6.18). In this way, rates of mass production and displacements at the current time s are updated iteratively until solutions converge to the prescribed tolerance.

For testing the utility of the present work, we apply the computational model for simulation of an AAA. One Gauss point is used for the integration. It has been found that the nonlinear FEM analysis does not always converge well with (6.26). To remedy this, we modify the tangent matrix by

$$\begin{bmatrix} \mathbf{K} \end{bmatrix}_{PQ} = \zeta \int_{S^e} \left(\frac{\partial^2 w}{\partial C_{\alpha\beta} \partial C_{\gamma\omega}} \frac{\partial C_{\alpha\beta}}{\partial x_P^p} \frac{\partial C_{\gamma\omega}}{\partial x_Q^p} + \frac{\partial w}{\partial C_{\alpha\beta}} \frac{\partial^2 C_{\alpha\beta}}{\partial x_P^p \partial x_Q^p} \right) dA - \int_{S^e} \Phi_{iP} \tilde{P}_{i,Q} dA,$$
(6.50)

where $\zeta = 2.0$ shows a good convergence for all simulations in this work.

6.4 Simulation of an AAA growth

6.4.1 A geometric model and mesh generation

A 3D computational geometry of a healthy aorta is reconstructed from magnetic resonance (MR) images of a healthy subject using Simvascular (Cardiovascular lab, Stanford University). The computational domain is extended to the upper part of abdominal aorta (proximal side) and iliac branches (distal side) for future use in hemodynamic simulations (Sheidaei et al., 2011). For simulation of the aneurysm, we use only the central region of the geometric model which is separately meshed with triangular elements (1584 elements) using Gambit (Lebanon, NH, USA).

6.4.2 Initialization for G&R simulation

In normal physiological conditions, production and removal of each constituent are balanced such that the vessel maintains its shape under a preferred homeostatic state. For an idealized model of the blood vessel, the *in vivo* material properties are typically assumed to be constant over the domain with parameter values estimated from experimental data while the homeostatic assumption is imposed as a constraint (Baek et al., 2007b; Figueroa et al., 2009; Valentín et al., 2009b). When medical image-based geometric models are used, however, it is not a trivial task to prescribe the distribution of material and geometric parameters while maintaining the homeostatic mechanical state under physiological pressure. For an approximation, we first prescribe material constitutive parameters shown in Table 6.1. Other parameters, c_1 , c_2 , and c_4 , are calculated inversely assuming that all constituents have the same homeostatic stress value (i.e., $\sigma^i = \sigma_h$) in a healthy state. For that, four discrete fiber families are assumed to be initially aligned in 0, 90, 45, and -45 (axial, circumferential, and helical directions, respectively) and constant volume fractions for all constituents are

Table 6.1: Constitutive and kinetic parameters for each constituents used in initialization and G&R simulations.

$$\begin{array}{ll} \text{Elastin:} & c_1 = 112 \ Nm/kg, \ G_1^e = 1.25, \ G_2^e = 1.25 \\ \text{Collagen:} & c_2 = 917 \ Nm/kg, \ c_3 = 25, \ G_h^c = 1.07, \ k_q^c = 0.02 \\ \text{SM:} & c_4 = 27 \ Nm/kg, \ c_5 = 8.5, \ G_h^m = 1.2, \ k_q^m = 0.02, \\ & S = 50 \ kPa, \ \lambda_M = 1.2, \ \lambda_0 = 0.7 \\ \text{Others:} & \rho = 1050 \ kg/m^3, \ \sigma_h^c = \sigma_h^m = 135 \ kPa \end{array}$$

prescribed. Then, using strain energy functions (6.13)-(6.16), c_1 , c_2 , and c_4 are obtained by

$$c_1 = \sigma_h \left\{ \rho \left(G_1^{e^2} - (G_1^e G_2^e)^{-2} \right) \right\}^{-1}, \tag{6.51}$$

$$c_2 = \sigma_h \left\{ \rho G_h^{c\,2} (G_h^{c\,2} - 1) \exp\left\{ c_3 (G_h^{c\,2} - 1)^2 \right\} \sum_{k=1}^4 \frac{M_R^k}{M_R^c} \sin^2 \alpha^k \right\}^{-1}, \qquad (6.52)$$

$$c_4 = \frac{\sigma_h - S\{1 - (\frac{\lambda_M - 1}{\lambda_M - \lambda_0})^2\}}{\rho G_h^{m2} (G_h^{m2} - 1) \exp\left\{c_5 (G_h^{m2} - 1)^2\right\}}.$$
(6.53)

Regional wall thickness is initially approximated by estimating the cross sectional mean radius and using the Laplace equation, $\sigma = Pr/h$. Then, using the G&R simulation, we let the vessel wall adapt to an equilibrium state with a high value of stress-mediated parameters $(K_g^k = K_g^m = 1)$. Deviation of stress in three families of collagen fibers (i.e., axial and helical directions) from the desired homeostatic stress $((\sigma^k - \sigma_h^c)/\sigma_h^c)$ is plotted before and after 300 "days" of this initial simulation in Figure 6.3. Stress deviation of the fiber family along the circumferential direction was less than the other fibers (not shown). Figures 6.4(a) and (b), respectively, depict the displacement and the change in the geometry from the reference configuration after 300 days of this initial simulation. The stress deviation of each fiber family is reduced substantially after the initialization process while causing little change in the geometry from its original/reference configuration (maximum displacement is about 1.5 mm).



Figure 6.3: Deviation of the intramural stress from the homeostatic value $((\sigma^k - \sigma_h^c)/\sigma_h^c)$ in axial and two helical fiber directions before (a, b, and c) and after (d, e, and f) 300 days of the initial simulation.



Figure 6.4: Magnitude of the displacement (mm) calculated from the reference configuration after 300 days of the initial simulation (a) and the corresponding geometry before and after 300 days (b).

6.4.3 Simulation Cases

After initialization, an AAA is initiated by introducing damage to the aorta, where elastin is degraded/removed from the blood vessel. The spatial and temporal function for elastin damage is given as

$$D(\mathbf{X},s) = \left(1 - 0.01^{s/T}\right) f(\mathbf{X}), \tag{6.54}$$

where T is a time constant and $f(\mathbf{X})$ defines the spatial distribution of damage. $D(\mathbf{X}, s) \in [0, 1]$ is the ratio of the degenerated elastin to the initial amount, where $D(\mathbf{X}, s) = 1$ for complete degradation. First, we assume a limiting case when $T \to 0^+$ such that $D(\mathbf{X}, s)$ becomes only a spatial function, $f(\mathbf{X})$. That is, the damage (elastin removal) is applied immediately after the initial simulation for a homeostatic condition and the amount of damage is kept constant during G&R. Four spatial functions are used for representing different cases of elastin damage. The areal density of elastin after applying different damages is plotted in Figure 6.5. Cases (1) and (2) correspond to damage shapes distributed to a relatively large area on the concave and convex sides, respectively. Cases (3) and (4) correspond to more localized damage shapes applied at multiple locations. Second, the 'time dependent' elastin degradation is investigated using (6.54) with a spatial function of Case (3) considering $T = 10 \times 365$ (days). For final simulation, we assume 'stretch-induced' degradation, where additional removal of elastin occurs during aneurysm growth due to stretch-induced damage. Specifically, the function for elastin damage can be written as,

$$D(\mathbf{X},s) = f(\mathbf{X}) + g(I_1^e(\mathbf{X},s)) \Big[1 - f(\mathbf{X}) \Big],$$
(6.55)

where $I_1^e(\mathbf{X}, s)$ is the first invariant of the \mathbf{C}_n^e and

$$g(I_1^e) = \begin{cases} 1 & (I_1^e - 3) \ge 4.48\\ 1 - \sin\left(\frac{\pi\left(7.48 - I_1^e\right)}{2 \times 1.48}\right) & 3 \le (I_1^e - 3) < 4.48\\ 0 & (I_1^e - 3) < 3 \end{cases}$$
(6.56)

It is believed that elastin plays an important role in controlling SM cells migration/proliferation (Karnik et al., 2003; Li et al., 1998) as well as their phenotype modulation (Ailawadi et al., 2009) by stabilizing extracellular matrix. The amount of SM in our model is changed proportionally with the initial elastin degradation which reduces both passive and active contributions of SM to the wall mechanical properties.

6.4.4 Results

Distribution of the maximum principal stress and the areal mass density of collagen at 50, 1200, and 2700 days of G&R for Case (3) are shown in Figure 6.6. The damage to elastin introduced at s = 0 causes a sharp increase in stress at the location of the damage. Stress-mediated collagen production increases the areal density of collagen as the lesion enlarged, compensating the loss of elastin, and the value of the peak stress initially starts to decrease. As the aneurysm enlarges further, however, the stress level is shown to increase again (see Figure 6.6(c)). The shape of aneurysm and stress distributions resulted from Cases (1), (2), and (4) are plotted at 50 and 2700 days of the G&R simulation in Figure 6.7. The simulation



Figure 6.5: Areal mass density of elastin (kg/m^2) for different simulation Cases (1)-(4). Cases (1) and (2) correspond to different damages shapes distributed to relatively large area which are applied at different locations (concave and convex sides) and Cases (3) and (4) correspond to more localized damage shapes, but at multiple locations.

suggests that the aneurysmal wall tends to enlarge more in the convex side of the vessel than the concave side.

For example, Figure 6.7(d) shows a large amount of dilatation in the convex side even with the initial damage introduced in the concave side. Different spacial functions for elastin damage result in variety of shapes with different expansion rates although in all cases the same kinetic parameter ($K_g = 0.05$) was used. Figure 6.8 plots expansion rates (maximum diameter increase per unit time) for simulations with four different cases. Cases (1) and (2) result in higher expansion rates compared to Cases (3) and (4), which might be due to the wider area of the damage prescribed for Cases (1) and (2). The effect of kinetic parameter (K_g =0.02, 0.05, and 0.1) on the expansion rate of the aneurysm is shown for Case (2) in Figure 6.9. Apparently, simulation with K_g =0.02 results in an increase in the aneurysm expansion rate, simulation with K_g = 0.05 causes a linear enlargement over time (constant expansion rate), and a higher value of the kinetic parameter (K_g =0.1) even stabilizes the aneurysm growth.

Figure 6.10 shows the areal density of elastin and the maximum principal stress for the 'time dependent' case at 50 and 2700 days of the G&R simulation. At 50 days, changes in stress are small because of the small amount of elastin degradation (Figure 6.10(a)). The stress increases gradually as the amount of elastin degradation increases and at 2700 days the maximum principal stress reaches a similar value as in the Case (3) at 2700 days (see Figures 6.6(c) and 6.10(d)). For the last simulation, the damage shape is initially the same as in Case (3) (Figure 6.11(a)) but elastin is degraded further with the 'stretch-induced' elastin damage. The simulation shows that the affected area gradually increases with stretch-induced damage (Figure 6.11(b)) and, hence, the principal stress increases to a level higher than Case (3) at 2700 days without the stretch-induced damage (see Figures 6.6(c) and 6.11(d)).


Figure 6.6: Maximum principal stress distribution (kPa) for the simulation Case (3) at 50, 1200, and 2700 days after the initial damage (a, b, and c) and the corresponding areal mass density of collagen (d, e, and f) (kg/m^2) .



Figure 6.7: Maximum principal stress (kPa) for simulation Cases (1), (2), and (4) after 50 (a, b, and c) and 2700 (d, e, and f) days.



Figure 6.8: Expansion rates of the lesion in simulation Cases (1)-(4) as the maximum diameter of the lesion versus time and their best linear fit ($K_g = 0.05$).

6.5 Discussion

In this work, a FEM model of vascular adaptation is presented and applied to model the enlargement of an AAA without considering thrombus formation. We use a membrane model of arterial wall. Although a membrane model has some limitations, it is still preferable in many G&R simulations (Gleason et al., 2004; Baek et al., 2006; Watton and Hill, 2009). Watton and Hill (2009) suggested that the ratio of thickness of the wall to the diameter of the aneurysm decreases as an AAA enlarges and also the remodeling process tends to naturally maintain a uniform strain (or stress) field through the thickness. Hence, a membrane model suits to model the deformation of the abdominal aorta and the development of an aneurysm at physiological pressure. Moreover, a full 3D model of vascular adaptation needs more information about the variation of constituent properties through the thickness and their evolution during the vascular adaptation.

Following Watton et al. (2004) and Watton and Hill (2009), elastin degradation was assumed to initiate our G&R simulations and a similar form was used for spatial and temporal



Figure 6.9: Expansion rates of the lesion in simulation Case (2) with different values of the kinetic parameter ($K_g = 0.02$, 0.05 and 0.1).



Figure 6.10: Areal mass density of elastin (kg/m^2) for the case of 'time-dependent' degradation after 50 and 2700 days (a, b) and the corresponding maximum principal stress distribution (c, d) (kPa).



Figure 6.11: Areal mass density of elastin (kg/m^2) for the case of 'stretch-induced' degradation after 50 and 2700 days (a, b) and the corresponding maximum principal stress distribution (c, d) (kPa).

distribution of degradation. We considered, however, multiple spatial functions for elastin degradation which resulted in variety of aneurysm shapes with different stress distributions and growth rates indicating the potential clinical application of computational simulation of G&R with realistic geometries. Consistent with Watton and Hill (2009), it appears that collagen production tends to compensate for the loss of elastin. The computations suggest, however, that as a lesion evolves into a more complex shape, stress may be elevated at a location which was not necessarily a damage site (see Figure 6.6). In Cases 1 and 2, stress initially increased at locations where damage was introduced. Later, in the course of enlargement, the convex side of both aneurysms became the region of maximum stress leading to more dilation on this side. The results suggest that the location and the geometry of the lesion can influence AAA enlargement and rupture. For an AAA in vivo, however, the effect of geometry may be through its influence on both hemodynamics (e.g., wall shear stress; Hoi et al. (2004)) and wall stress distribution (Doyle et al., 2009; Vorp et al., 1998). Asymmetric flow patterns have been associated with formation of aneurysm in lower limb amputees via asymmetric distribution of wall shear stress (Vollmar et al., 1989; Paes et al., 1990; Naschitz and Lenger, 2008). As expected, in our simulations, damage shapes which were more dispersed resulted in more dilation than localized damage shapes (see Figure 6.7). The 'time dependent' simulation for Case (3) did not result in a substantial difference in the aneurysm shape, but different time constants showed significant effects on the expansion rate (Figure 6.12). Although we used simple spatial and temporal functions for elastin degradation, elastin degradation during AAA growth involves multiple biological and mechanical parameters. It has been suggested that in AAAs, elastin degradation is due to the proteolytic activity which may have several causes including abnormal distribution of wall shear stress (Miller, 2002; Hoshina et al., 2003; Sho et al., 2004), circumferential stress (Humphrey, 2002), influx of inflammatory cells (Choke et al., 2005; Pearce and Shively, 2006; Shimizu et al., 2006; Middleton et al., 2007), and the formation of the intraluminal thrombus layer (Vorp et al., 2001; Fontaine et al., 2002; Vorp and Vande Geest, 2005). In our following



Figure 6.12: Expansion rates of the lesion in the 'time dependent' simulation case associated with different time constants (T=3, 6, 10, and 15 years).

study (Sheidaei et al., 2011) the current model is coupled with hemodynamic simulation in an iterative manner and the effects of wall shear stress on the elastin degradation and, hence, on the aneurysm growth are investigated.

In our final simulation, we assumed that further degradation of elastin is induced by the stretch of elastin. Although it is not clear how much mechanical factors influence elastin degradation during the aneurysmal growth, previous *ex vivo* studies show that arterial elastin fails under uniaxial stretch (Gosline et al., 2002; Lillie and Gosline, 2007). Then, it might not be unreasonable to hypothesize that the over-stretch of elastin accelerates elastin degradation. Previously, Wulandana and Robertson (2005) presented a model of a cerebral arterial tissue that accounts for a stretch-dependent failure mechanism of elastin. Recently, Li and Robertson (2009) have utilized a strain-induced damage model in a more structurally complicated model for balloon angioplasty.

We assumed that the amount of SM reduced proportionally with the initial elastin dam-

age in our model. The results do not indicate significant role of SM on AAA progression possibly because we did not incorporate direct effects of SM loss on the extracellular matrix turnover. However, there are increasing evidence on the critical role of vascular SM cells in the aneurysm pathobiology through their activity and quantity (Curci, 2009). Vascular SM cells are capable of producing high levels of matrix degrading enzymes in AAAs (Patel et al., 1996; Crowther et al., 2000) as well as their inhibitors preventing the degeneration (Allaire et al., 1998). Stretch/stress induced synthesis of extracellular matrix by SM cells has also been documented (O'Callaghan and William, 2000; Sumpio et al., 1988). Apparently, the imbalance between proteolytic and synthetic activities of SM cells contributes to the structural deterioration of arterial wall. In addition, advanced stages of AAA have been associated with marked apoptosis of SM cells (López-Candales et al., 1997; Zhang et al., 2003; Thompson et al., 1997) which can exacerbate the weakening process. We need, however, more data to build a better model and predict the progressive weakening of the wall structure and its failure.

The half-life of collagen in the arterial wall is reported to be 60-70 days in normal conditions (Humphrey, 2002) which can be reduced to 17 days in pathological conditions (Nissen et al., 1978). Watton and Hill (2009) showed that reducing the half-life time nonlinearly increased the expansion rate. Our preliminary results also showed that expansion rate is inversely related to half-life time. We chose the half-life time to be about 35 days in our simulations. Our results demonstrated that the kinetic parameter, K_g , has a key effect on the expansion rate (Figure 6.9) consistent with other studies (Baek et al., 2005, 2006). Nonetheless, the collagen half-life as well as the kinetic parameters were assumed to be fixed during the evolution of aneurysm in our model, whereas in an actual AAA, these parameters may change during aneurysm growth due to pathological changes. Dynamic changes of turnover parameters are multifaceted and complex and, hence, more studies are required to quantify these pathological changes in aneurysm growth. Also, individuals may have different degrees of mechano-sensitivity and stress-mediated turnover of collagen depending of their physiological and pathological conditions. In fact, findings on the collagen content variation during AAA growth are highly variable, e.g., decreased (Sumner et al., 1970), increased (Ghorpade and Baxter, 1996), and no change (Rizzo et al., 1989). The simulation showed that $K_g = 0.05$ provides almost linear growth for all damage shapes (Figure 6.8) and, especially, for Cases (1) and (3), growth rates were within the range observed for small aneurysms (Nevitt et al., 1989; Baxter et al., 2008). With $K_g \leq 0.05$ the lesion enlarged continuously implying that the stress-mediated collagen turnover was not enough to return the stress back to the homeostatic level although it reduced the local damage-induced stress (Figure 6.9).

Results from the current model represent the early stage of aneurysms. As AAAs grow, other factors such as intraluminal thrombus and perivascular boundary conditions should also be taken into account for the model. Intraluminal thrombus not only has a direct mechanical effect (Wang et al., 2002) but also changes the chemomechanical environment and influences the strength of the lesion and its progression (Vorp et al., 2001; Taylor and Humphrey, 2009).

Remodeling of the constituents and the mechanism involved in their deposition can have a great impact on the mechanical properties of the evolved tissue. Computational models of collagen remodeling assumed that either the principal strains (Driessen et al., 2004, 2008; Boerboom et al., 2003) or stresses (Hariton et al., 2007b; Baek et al., 2006) govern the orientation of collagen fibers. With regard to AAA, marked increase of anisotropy was found in the diseased tissue (Vande Geest et al., 2006) suggesting structural changes in aneurysm formation. Watton et al. (2004) assumed fixed fiber directions for collagen fibers in their AAA growth and remodeling simulations. In our model, collagen aligned towards existing fiber directions. With newly deposited collagen during enlargement, anisotropy increased in the circumferential direction, which is consistent with Vande Geest et al. (2006). In addition, we chose the mechanical property of newly synthesized collagen fibers to be the same (Gleason et al., 2004; Baek et al., 2006, 2007b; Humphrey, 1999). Elastin degradation alone does not conduce to rupture in normal vessels (Dobrin et al., 1984). Impaired collagen networking and its microstructural defects have been associated with advanced AAAs despite an increase in the collagen concentration (Lindeman et al., 2010). Therefore, in addition to alteration of fiber distribution, it might also be desirable to account for changes of collagen type, cross-linking and fiber thickness in the model (Driessen et al., 2008). A future extension of the current model can be towards accounting for alteration of collagen structure during the AAA progression and different mechanical properties of the newly synthesized collagen fibers.

Prescribing the *in vivo* material and geometric parameters that satisfy the balance of momentum and homeostatic conditions is a major challenge for patient-specific G&R simulations. In the current work we approximated the thickness by the Laplace relation, $\sigma_h = Pr/h$ where r is the first principal radius of curvature. For a more complex geometry, however, there is a need for developing numerical techniques to identify the spatial distribution of parameters and integrating them with the developed vascular adaptation model.

Previous computational studies of vascular adaptation have considered mostly axisymmetric and simple geometries, while clinical application of the G&R simulation demands patient-specific anatomical information. Watton et al. (2004) simulated an asymmetric aneurysm by assuming an axisymmetric degradation and considering an effective pressure (instead of constant pressure) which resembles the contact with spine. Although varying the effective pressure resulted in an asymmetric aneurysm growth, their initial configuration was still axisymmetric. Recently, Kuhl et al. (2007) simulated stress-induced growth of a medical image-based model of human aorta based on the concept of incompatible growth combined with open system thermodynamics. They simulated the effect of balloon or stent exposure in atherosclerotic patients by a high internal pressure locally applied to the wall. Their work, however, was based on a single constituent approach and did not consider growth and remodeling of multiple constituents. On the other hand, many studies have used patientspecific geometries for estimating accurate stress levels and the rupture risk of aneurysms without a G&R mechanism (Raghavan and Vorp, 2000; Fillinger et al., 2002, 2003; Speelman et al., 2007). However, Vorp and Vande Geest (2005) suggested that "despite recent reports, it should be noted that evaluation of rupture potential based on only one of these parameters –stress or strength – is not sufficient because a region of the AAA wall that is under elevated wall stress may also have a higher wall strength". We submit that, by coupling a G&R model with a patient-specific geometric model, a computational simulation can provide information about both stress and structural strength during aneurysm growth and, hence, better prediction of the rupture can be acquired. Therefore, the computational model presented here will provide a useful foundation towards a patient-specific modeling of AAAs.

Chapter 7

MEDICAL IMAGE-BASED SIMULATION OF ABDOMINAL AORTIC ANEURYSM GROWTH

7.1 A framework for modeling of AAA growth based on medical images

Here we summarize our efforts in previous chapters and present a framework for simulation of AAA enlargement with more simulation examples. Figure 7.1 illustrates a schematic diagram of the steps taken. First, a 3-D computational geometry of a healthy aorta is constructed by segmentation of medical images of a healthy aorta. For the aneurysm simulation, we use a central region of the geometric model. Considering the vessel wall as a thin membrane, it is convenient to parameterize the 3-D wall surface geometry with only two spatial parameters. That is, any point on the wall surface can be characterized by its longitudinal position (l) along the centerline of the artery as well as its azimuthal orientation (θ) with respect to a reference direction (See the 2-D plot in Fig. 7.1 and chapter 4 for technical details).

Here, we employ the proposed inverse optimization (chapter 4) to estimate spatial distribution of geometric properties, e.g. wall thickness and anisotropy, such that a target mechanical homeostasis is satisfied and the *in-vivo* geometry is maintained under *in-vivo*



Figure 7.1: Schematic diagram of the steps taken for simulating AAAs using a medical image-based geometry and material parameters of a healthy aorta as the initial state.

condition. The general form of the optimization objective function is given as

$$\mathcal{J} = \int_{\Omega} ||\mathbf{u}(h, \alpha^k) - \mathbf{u}_{image}||^2 dA + \xi \int_{\Omega} \sum_k \left(\frac{\sigma^k(h, \alpha^k)}{\sigma_h} - 1\right)^2 dA$$
(7.1)

where **u** is the FE solution for displacement field and \mathbf{u}_{image} is the displacement field from the biomedical image. That is $\mathbf{u}_{image} = 0$ when the *in vivo* configuration obtained from the medical image is assumed to be the reference configuration. σ^k is a scalar measure of stress of the constituent k obtained from the FE analysis and σ_h is its homeostatic value. ξ adjusts the minimization weight on each additive term in the objective function. (h, α^k) are the unknown wall thickness and the orientation of the major diagonal fiber family controlling the tissue anisotropy, approximated by

$$h(l,\theta) = \sum_{j=1}^{I} \{\beta_j^h \phi_j(l,\theta)\}$$
(7.2)

$$\alpha^k(l,\theta) = \sum_{j=1}^{I} \{\beta_j^k \phi_j(l,\theta)\},\tag{7.3}$$

where (β_j^h, β_j^k) are unknown variables associated with their base functions, $\phi_j(l, \theta)$, which are defined on the 2-D computational domain. A direct search method (Nelder-Mead Simplex) is used to estimate spatial distributions of thickness and collagen fiber orientation that minimize the objective function (See chapter 4 for details).

Elastin has been widely observed to be deficient in ruptured and unruptured AAAs. Even though the factors that trigger AAA G&R have not been completely identified yet, elastin degeneration is considered the pathologic factor contributing to the growth of AAAs in this study. Then, as in chapter 6, G&R simulations are triggered by inducing damage/degradation to elastin with different spatial and temporal distributions as

$$\mathcal{R}(\mathbf{X},t) = \mathcal{R}(l,\theta,t) = \mathcal{R}_s(l,\theta)\mathcal{R}_t(t), \tag{7.4}$$

where the damage ratio, $\mathcal{R} \in [0, 1]$, is the ratio of the degenerated elastin mass to the initial mass. Note that the spatial distribution, \mathcal{R}_s , is defined on the mapped domain of (l, θ) .

7.2 Simulation cases

In the first set of simulations, AAAs are initiated by inducing instantaneous damage to elastin with different spatial shapes considering homogeneous distribution of kinetic parameters (Cases 1-6). Case 7 considers an instantaneous damage but with either homogeneous or inhomogeneous distribution of K_g (= K_g^i). In Case 8, after a portion of elastin is instantaneously removed, further time dependent degradation (\mathcal{R}_t) occurs while K_g is assumed to depend on the local damage at the given time, i.e. $\mathcal{R}(l, \theta, t)$ (See Fig. 7.2).



Figure 7.2: Variation of damage ratio with respect to time (\mathcal{R}_t vs. time) and variation of the sensitivity parameter with respect to the local damage (K_g vs. $\mathcal{R}(l, \theta, t)$). Solid line represents the time dependent damage ratio and dashed line represents the damage dependent variation of K_g .



7.3 Results

Figure 7.3 shows a set of distinct shapes of spatial damage (distributions of elastin areal mass density) and the resulting AAAs with the corresponding von Mises stress distributions.

The time histories of the variations of the peak von Mises stress during enlargement of 5 aneurysms are plotted in Fig. 7.4a. Evidently, inducing damage is followed by a sharp increase in the peak stress (on regions that match the degenerated regions) which, after a time delay, begins to gradually diminish via stress-mediated collagen production. The



Figure 7.3: left: Areal mass distributions (kg/m^2) for elastin after introducing damage. right: the resultant distributions of von Mises stress (kPa) due to G&R. The arrows indicate the regions of elevated stress during AAA expansion.

decline of peak stress is initially sharper but becomes slower during the AAA expansion. In some cases the stress slightly increases again after some time (e.g. around 4 years) on the regions where the degradation is not necessarily maximal (See regions specified by black arrows in Fig. 7.3). The maximum diameter of aneurysms in all cases changes linearly over time but at different rates depending on the damage shape (Fig. 7.4b).

Figures 7.5 and 7.6 compare spatial correlations between von Mises stress and both the rate of mass production and the rate of nodal displacement for Cases 1 and 5. The maximum rates of mass production and displacement gradually increase with aneurysm expansion while the peak stress reduces. In general, the rate of mass production increases with the stress, but regions of high stress correspond to a wider range of mass production and displacement rates especially in advanced stages. Compared to the rate of mass production, the rate of displacement (i.e., radial expansion) has a weaker correlation with wall stress.

In a different simulation case (Case 7), an aneurysm is generated with a homogeneous (Fig. 7.7a) as well as inhomogeneous (Fig. 7.7b) distribution of the kinetic/sensitivity parameter. Assuming lower value for the kinetic parameter (i.e. $K_g = 0.02$) on the region where aneurysm sac forms leads to lower rates of the local mass production and further enlargement. Insufficient local mass production leads to an increasing trend in the local wall stress during enlargement (Fig. 7.7b).

Figure 7.8 shows the distributions of elastin and collagen areal mass density and the von Mises stress for Case 8 where the elastin damage is time-dependent and K_g is assumed to be damage-dependent (relations shown in Fig 7.2). Increasing degradation along with gradually decreasing K_g accelerate the AAA enlargement and heightens wall stress (up to 450 kPa).

7.4 Discussion

Consistent with previous studies (Watton and Hill, 2009), collagen turnover showed to compensate for the loss of elastin and tended to normalize wall stress via the stress-mediated



Figure 7.4: Variations of peak von Mises stress (a) and maximum diameter (b) with G&R time for different cases. Equations for best fit lines are shown (lines are not included in the graph).



Figure 7.5: Spatial relations between von Mises stress and both the rate of collagen mass production as well as the rate of wall displacement for Cases 1 at different stages of growth. Wall thickness distribution and collagen concentration are illustrated for each case corresponding to 2700 days of G&R.



Figure 7.6: Spatial relations between von Mises stress and both the rate of collagen mass production as well as the rate of wall displacement for Cases 5 at different stages of growth. Wall thickness distribution and collagen concentration are illustrated for each case corresponding to 2700 days of G&R.



Figure 7.7: Spatial relation between the rate of collagen mass production and von Mises stress for Case 7 using a homogeneous distribution of kinetic parameters (a; $K_g = 0.05$) as well as spatially variable kinetic parameter (b; $K_g = 0.02$ at the AAA sac and $K_g = 0.05$ otherwise) at different times.



Figure 7.8: Elastin (a) and collagen mass (b) areal density along with von Mises stress (c) distributions for Case 8 after 7 years (2700 days) of G&R. Time history of maximum diameter and peak von Mises stress is also shown (d).

kinetics of G&R process. Nevertheless, assuming $K_g = 0.05$, the peak wall stress never returned to the homeostatic value leading to continuous enlargement with a linear trend which is typical of small AAAs (Fig. 7.4). The high stress regions in Cases 1 and 5 (Fig. 7.3) were found to be consistent with other FE studies (Vorp et al., 1998; Scotti et al., 2005; Doyle et al., 2010; Hua and Mower, 2001; Giannoglou et al., 2006), suggesting regions of inflections as the high stress regions. We noticed a strong spatial correlation between the rate of collagen production and wall stress in earlier stage of growth. Later, even though the peak wall stress was reduced, collagen was produced at an increasing rate leading to high rates of wall displacement (Figs. 7.5 and 7.6). This seems to be mainly because the rate of mass production was assumed to be linearly related to the number of cells (depending on the collagen mass) at a given time. Although there was a strong spatial correlation between damage and the rate of mass production at all times (not shown), a weaker correlation was found between the local damage and wall displacement in advanced AAAs (Fig. 7.9). In Case 1, wall displacement was more global and not restricted to the damaged regions while in Case 3 the damaged regions were subject to high wall displacement (i.e., large radial expansion) (Fig. 7.9). Interestingly, in Case 1, although the damage was uniformly distributed around the circumference (Fig. 7.3), points on the convex side were subject to more displacement than points on the concave side (See Figs. 7.3 and 7.9).

The time-dependent case was inspired by a possibility of increasing elastin degradation due to exacerbated hemodynamic conditions in AAAs as the geometry evolves (Mohan et al., 1999; Walpola et al., 1993). Sheidaei et al. (2011) demonstrated that low wall shear stress may induce further degradation during aneurysm progression and accelerate the lesion expansion. In addition, the damage-induced weakening of the G&R sensitivity was introduced because some studies have suggested an increase in apoptosis (Lopez-Candales et al., 1997; Thompson et al., 1997) or phenotype modulation (Ailawadi et al., 2009) of SM cells during the AAA enlargement. The imbalance between extracellular matrix synthesis (Sumpio et al., 1988) and degradation (Crowther et al., 2000), mediated by altered SM cells can be



Figure 7.9: Spatial relation between the nodal displacement and the damage ratio for Cases 1 and 3 at different times. A number of points on the convex and concave regions (with reference to the healthy geometry) are distinguished with different markers at 2700 days.

the reason for progressive weakening and rupture of the wall. Recently, Maier et al. (2011) have quantitatively found a spatial correlation between wall stress and the level of *in vivo* tissue reactions which can indicate either synthetic or proteolytic activities in the arterial wall tissue.

In this study, we were able to capture relatively complex 3-D shapes of AAAs by prescribing distinct shapes for spatial damages. Even with a fixed spatial distribution of elastin damage, we noticed that regions of elevated wall stress can change in the course of expansion (Fig. 7.3). Interestingly, during the evolution of some AAA shapes, the peak wall stress locally increased again (Fig. 7.4). In Cases 1 and 5, the lesions were larger in diameter while in Cases 3 and 6 the lesions developed higher wall stress after 2700 days (7 years), implying the influence of aneurysm shape on the peak wall stress, beyond what the maximum diameter criterion may solely suggest.

Together, these results emphasize the impact of geometrical complexities on complex stress distributions during AAA expansion as suggested by Sacks et al. (1999). Other studies have sought correlations between wall stress and quantified AAA shapes, asymmetry, tortuosity, as alternative indicators of rupture (Shum et al., 2011; Vorp et al., 1998; Georgakarakos et al., 2010; Doyle et al., 2009; Giannoglou et al., 2006). Moreover, we found that the regions of low wall thickness initially coincide with the damaged regions but they too change as the lesions evolve. In some cases they may correspond to high stress regions (e.g. Cases 1 and 5; Figs. 7.3 and 7.5 and 7.6) while in other cases there may be no correspondence (other cases not shown). Coincidence of the low wall thickness and elevated wall stress could be indicative of an impending rupture in advanced stages. As an advantage, current study is capable of capturing morphological complexities during enlargement while at the same time the evolution of wall properties during G&R is being reflected.

Aneurysms are often accompanied by bending of the proximal neck area which influences the hemodynamics and possibly intraluminal thrombus formation (Biasetti et al., 2010). Figure 7.10 depicts the axial stretch distributions for different simulation cases. Aneurysms



Figure 7.10: Distributions of axial stretch for different aneurysms.

enlarge in both circumferential and axial directions and because of the fixed boundary condition, axial stretch on the neck region reduces to values less than 1. Even if not the main reason, this can be used as an indicator of where bending may occur in later stages (Jackson et al., 2005). It is noteworthy that we have modeled the vessel wall as a membrane while models that account for bending of the wall are necessary to study buckling of the vessel walls.

Chapter 8

CONCLUSION

From the practical point of view, we are ultimately interested to model AAA expansion from an existing AAA, which is an intermediate stage of the disease. While the current model uses the assumption of homeostatic condition for the healthy aorta to prescribe initial conditions (e.g. thickness, fiber alignment, kinetic parameters) of the simulation, less information is available for the spatial and temporal distribution of the parameters for a diseased artery. Despite this challenge, we believe that the current model can be used for estimating the material and kinetic parameters of an existing AAA and, hence, predicting patient-specific AAA expansion if used in a broader framework. For example, using the same model but in an inverse scheme, it seems feasible to regenerate a patient-specific AAA shape by estimating spatio-temporal distributions of elastin degradation as well as the G&R sensitivity/kinetic parameter. Cyclic strain quantified from medical images can also be incorporated into the inverse scheme such that not only the AAA shape but also the local strain is predicted more accurately. That requires further development of the model regarding the boundary condition, e.g. the spine support, which as a growth barrier significantly changes the resulting AAA shape and stress/strain distributions in the G&R model.

Lack of verification for the estimated distributions of the wall thickness and fiber orientation in healthy condition (prior to G&R) and during the AAA development is a limitation of the current study. Recent advances in medical imaging and segmentation techniques make



Figure 8.1: A comprehensive simulation framework aimed at patient-specific modeling of AAA G&R.

it possible to quantify *in-vivo* wall thickness (Shum et al., 2010; Martufi et al., 2009) and verify the patient-specific simulations of AAAs. Another limitation of the current model is that the role of intraluminal thrombus layer (ILT) is overlooked. Thrombus has been found to either protect the wall by reducing the wall stress (Inzoli et al., 1993; Thubrikar et al., 2003; Wang et al., 2002) or compromise its integrity via biochemical environment (Vorp et al., 2001; Fontaine et al., 2002). Figure 8.1 shows all the required elements of a comprehensive patient-specific model of AAA G&R. This study basically covers the topics in black and red boxes, but the focus has been mainly on identification of in-vivo properties. The model of ILT and perivascular tissue are the steps needed to enhance the G&R simulation which, on the other hand, has a strong coupling with hemodynamic simulation (blue or green boxes). Hemodynamic simulations in evolving aneurysms have been performed in collaborative studies either with rigid wall assumption (Sheidaei et al., 2011) or as fluid-solid interaction framework (Figueroa et al., 2009).

In conclusion the current study is an important step toward patient-specific modeling of AAAs. Apparently accurate estimation of rupture potential requires further developments of the model as well as more detailed information about pathophysiology and biochemical reaction involved. Appendices

Appendix A

Equilibrium equations considered for inflation-extension test of tubular vessels

We use a cylindrical coordinate system to model axial extension and inflation of a thin artery. The positions of a particle can be expressed by cylindrical coordinates $\{R, \Theta, Z\}$ and $\{r, \theta, z\}$ in the reference (unloaded) and current (loaded) configuration, respectively (Humphrey, 2002). The motion due to the inflation and axial stretch is assumed as

$$r = r(R), \qquad \theta = \Theta, \qquad z = \lambda_z Z.$$
 (A.1)

The deformation gradient for the large deformation is

$$\mathbf{F} = \begin{bmatrix} \frac{\partial r}{\partial R} & 0 & 0\\ 0 & \frac{r}{R} & 0\\ 0 & 0 & \lambda_z \end{bmatrix}$$
(A.2)

We assume that the arterial wall material is incompressible, so that

$$\frac{\partial r}{\partial R} = \frac{R}{r\lambda_z}.\tag{A.3}$$

Using the incompressibility, the inner diameter can be obtain as

$$r_i = \sqrt{r_o^2 - \frac{(R_o^2 - R_i^2)}{\lambda_z}} \tag{A.4}$$

where R_i, R_o and r_o are the inner and outer diameter in the reference configuration and outer diameter in the current configuration. For axisymmetric condition, the equations of motion in the absence of body force and the force due to acceleration are reduced to

$$\frac{1}{r}\frac{\partial(rT_{rr})}{\partial r} + \frac{\partial T_{zr}}{\partial z} - \frac{T_{\theta\theta}}{r} = 0$$
(A.5)

$$\frac{\partial T_{z\theta}}{\partial z} + \frac{1}{r} \frac{\partial (rT_{r\theta})}{\partial r} + \frac{T_{\theta r}}{r} = 0$$
(A.6)

$$\frac{\partial T_{zz}}{\partial z} + \frac{1}{r} \frac{\partial (rT_{rz})}{\partial r} = 0.$$
 (A.7)

Furthermore, $T_{r\theta} = T_{rz} = 0$ for the thin tube, and $T_{z\theta} = 0$ for the absence of torsion. Then, the remaining equation is

$$\frac{\partial T_{rr}}{\partial r} + \frac{T_{rr} - T_{\theta\theta}}{r} = 0 \tag{A.8}$$

$$\frac{\partial T_{zz}}{\partial z} = 0, \tag{A.9}$$

where assuming incompressible material

$$T_{rr} = -p + \hat{T}_{rr} \tag{A.10}$$

$$T_{\theta\theta} = -p + \hat{T}_{\theta\theta} \tag{A.11}$$

$$T_{zz} = -p + \hat{T}_{zz}. \tag{A.12}$$

The internal pressure P_i is given for the inflated tube, and $T_{rr}(r = r_i) = -P_i$ and $T_{rr}(r = r_o) = 0$ where r_i and r_o are in and out radius for the tube. The integration of (A.8) gives

$$T_{rr}(r) = \int_{r}^{r_{o}} \frac{\hat{T}_{rr} - \hat{T}_{\theta\theta}}{\xi} d\xi.$$
(A.13)

Internal pressure P_i and the axial force F_z are given by integral forms as

$$P_i = -\int_{r_i}^{r_o} \frac{\hat{T}_{rr} - \hat{T}_{\theta\theta}}{r} dr \tag{A.14}$$

$$F_z = \int_{r_i}^{r_o} (-p + \hat{T}_{zz})(2\pi r)dr - \pi (r_i^2 - r_c^2)P_i.$$
(A.15)

where r_c is inner diameter of cannula. The Lagrange multiplier p can be solved using (A.10) and (A.13), then (A.15) becomes

$$F_{z} = 2\pi \int_{r_{i}}^{r_{o}} \left(\int_{r}^{r_{o}} \frac{\hat{T}_{rr} - \hat{T}_{\theta\theta}}{\xi} d\xi - \hat{T}_{rr} + \hat{T}_{zz} \right) r dr - \pi (r_{i}^{2} - r_{c}^{2}) P_{i}.$$
(A.16)

Since,

$$\int_{r_i}^{r_o} r \int_{r}^{r_o} \frac{\hat{T}_{rr} - \hat{T}_{\theta\theta}}{\xi} d\xi dr = \frac{r_i^2 P_i}{2} + \int_{r_i}^{r_o} \frac{r}{2} (\hat{T}_{rr} - \hat{T}_{\theta\theta}) dr$$
(A.17)

The equation (A.16) results in

$$F_{z} = 2\pi \int_{r_{i}}^{r_{o}} \left(\hat{T}_{zz} - \frac{\hat{T}_{\theta\theta} + \hat{T}_{rr}}{2}\right) r dr + \pi r_{c}^{2} P_{i}.$$
 (A.18)

For a thin membrane, the integration $\int_{r_i}^{r_o} f(r) dr$ can be approximated by $f(r_m)h$ where $r_m = (r_i + r_o)/2$ and $h = r_o - r_i$. Hence

$$P_i = \frac{h(\hat{T}_{\theta\theta} - \hat{T}_{rr})}{r_m} \tag{A.19}$$

$$F_z = 2\pi r_m h(\hat{T}_{zz} - \hat{T}_{rr}) - \pi (r_m^2 - r_c^2) P_i.$$
 (A.20)

Considering $\hat{T}_{\theta\theta} = \hat{T}_{rr} + \pi r_m^2 P_i$ we also have

$$F_{z} = \pi r_{m} h (2\hat{T}_{zz} - \hat{T}_{rr} - \hat{T}_{\theta\theta}) + \pi r_{c}^{2} P_{i}.$$
 (A.21)

The inner radius (A.4) can be rewritten as

$$r_i = \sqrt{r_o^2 - \frac{2R_m H}{\lambda_z}} \tag{A.22}$$

where $R_m = (R_o + R_i)/2$ and $H = R_o - R_i$.

Appendix B

Nelder-Mead Simplex Algorithm

B.1 Introduction

Since its publication in 1965, the Nelder-Mead simplex algorithm (Nelder and Mead, 1965) has been widely used for nonlinear unconstrained optimization. The Nelder-Mead, as direct search method, attempts to minimize a scalar-valued nonlinear function of n variables $(f(x); x \in \mathbb{R}^n)$ using only function calculation, without any derivative information. Each iteration of the algorithm starts with a simplex, specified by its n+1 vertices and the associated function values. Four scalar parameters must be specified for the algorithm: coefficients of reflection (ρ) , expansion (μ) , contraction (γ) , and shrinkage (σ) . The universal choices for those parameters are (Lagarias et al., 1998):

$$\rho = 1, \ \mu = 2, \ \gamma = 0.5 \text{ and } \sigma = 0.5$$
 (B.1)

B.2 Algorithm statement

At the beginning of the k^{th} a simplex is given consisting of n + 1 vertices (points in \mathcal{R}^n). Then the following steps are taken (Lagarias et al., 1998):
1. **ORDER**. Order the n + 1 vertices, $\mathbf{x}_1^k, ..., \mathbf{x}_{n+1}^k$, such that

$$f_1^k \le f_2^k \le \dots \le f_{n+1}^k \quad \text{where} \quad f_i^k = f(\mathbf{x}_i^k). \tag{B.2}$$

2. **REFLECT**. Compute the reflection point as

$$\mathbf{x}_{r}^{k} = \hat{\mathbf{x}}^{k} + \rho(\hat{\mathbf{x}}^{k} - \mathbf{x}_{n+1}^{k}) \quad \text{where} \quad \hat{\mathbf{x}}^{k} = \sum_{i=1}^{n} \mathbf{x}_{i}^{k} / n.$$
(B.3)

Evaluate $f_r^k = f(\mathbf{x}_r^k)$. If $f_1^k \leq f_r^k \leq f_n^k$, accept the reflected point and terminate iteration. 3. **EXPAND**. If $f_r^k < f_1^k$, calculate the expansion point as

$$\mathbf{x}_e^k = \hat{\mathbf{x}}^k + \mu(\mathbf{x}_r^k - \hat{\mathbf{x}}^k). \tag{B.4}$$

Evaluate $f_e^k = f(\mathbf{x}_e^k)$. If $f_e^k < f_r^k$, accept \mathbf{x}_e^k and terminate the iteration. Otherwise, accept \mathbf{x}_r^k and terminate the iteration.

- 4. CONTRACT. If $f_r^k \ge f_n^k$, perform a contraction as
 - a. **OUTSIDE**. If $f_n^k \leq f_r^k \leq f_{n+1}^k$, perform outside contraction as

$$\mathbf{x}_c^k = \hat{\mathbf{x}}^k + \gamma (\mathbf{x}_r^k - \hat{\mathbf{x}}^k). \tag{B.5}$$

Evaluate $f_c^k = f(\mathbf{x}_c^k)$. If $f_c^k \leq f_r^k$, accept \mathbf{x}_c^k and terminate the iteration. Otherwise, go to step 5.

b. **INSIDE**. If $f_r^k \ge f_{n+1}^k$, perform inside contraction as

$$\mathbf{x}_{cc}^{k} = \hat{\mathbf{x}}^{k} - \gamma(\hat{\mathbf{x}}^{k} - \mathbf{x}_{n+1}^{k}).$$
(B.6)

Evaluate $f_{cc}^k = f(\mathbf{x}_{cc}^k)$. If $f_{cc}^k \leq f_{n+1}^k$, accept \mathbf{x}_{cc} and terminate the iteration. Otherwise, go to step 5.

3. SHRINK. Evaluate f at n points, $\mathbf{v}_i^k = \mathbf{x}_1^k + \sigma(\mathbf{x}_i^k - \mathbf{x}_1^k), i = 2, ..., n+1$. The unordered

vertices for the simplex at the next iteration consist of \mathbf{x}_1^k , \mathbf{v}_2^k , ..., \mathbf{v}_{n+1}^k .

B.3 Stopping criteria

A stopping criterion is chosen based on both the relative size of the simplex and function values at vertices of the simplex as (Torczon, 1989):

$$\frac{1}{\Delta} \max_{2 \le j \le n+1} ||\mathbf{x}_j^k - \mathbf{x}_1^k|| < \delta$$
(B.7)

$$f(\mathbf{x}_{n+1}^k) - f(\mathbf{x}_1^k) < \epsilon , \qquad (B.8)$$

where \mathbf{x}_{j}^{k} is the j^{th} vertex of the simplex and a vector comprised of all optimization variables at k^{th} iteration. \mathbf{x}_{1}^{k} and \mathbf{x}_{n+1}^{k} are the "best" and "worst" vertices of the simplex at k^{th} iteration and $\Delta = \max(1, ||\mathbf{x}_{1}^{k}||)$.

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