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## On parameter estimation for biaxial mechanical behavior of arteries

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## ABSTRACT

This article considers the parameter estimation of multi-fiber family models for biaxial mechanical behavior of passive arteries in the presence of the measurement errors. First, the uncertainty propagation due to the errors in variables has been carefully characterized using the constitutive model. Then, the parameter estimation of the artery model has been 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 balancing between variance and bias errors.

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## 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,

$$\mathbf{y} = \mathbf{f}(\mathbf{x}, \Theta), \quad (1)$$

where  $\mathbf{x}$  and  $\mathbf{y}$  are vectors of independent and dependent variables and  $\Theta$  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 NLS 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, we present the weighted nonlinear least squares (WNLS) optimization 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. We first derive an uncertainty model from the constitutive equation by assuming that experimental measurements are corrupted by the independent and identically distributed white noise. We then formulate the WNLS optimization using the inverse of the covariance matrix of the uncertainty as a correct weight factor. We evaluate the proposed technique with multiple sets of fictitious data containing the measurement errors in all variables at different noise levels by comparing the estimation results with those from the 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

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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). We utilize multiple model selection criteria to investigate an optimal number of parameters (or fiber families) for two different arteries.

## 2. Methods

### 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. It measures axial force and internal pressure versus changes in diameter and axial stretch. Experimental data from the test are used to determine appropriate constitutive relations based on the assumption of an ideal cylindrical geometry of the artery (Humphrey, 2002). In the current study, we use a microstructurally motivated, multi-fiber family model, i.e., we assume a constitutive strain energy with an isotropic neo-hookean strain energy function and strain energy functions due to multiple fiber families (cf. Holzapfel et al., 2000; Baek et al., 2007a):

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

where  $c$ ,  $c_1^{(k)}$  and  $c_2^{(k)}$  are material parameters, such that  $c$ ,  $c_1^{(k)}$  and  $c_2^{(k)} \geq 0$  (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

$$\lambda^{(k)} = \sqrt{(\lambda_\theta \sin \alpha^{(k)})^2 + (\lambda_z \cos \alpha^{(k)})^2}, \quad (3)$$

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

$$\mathbf{T} = -p\mathbf{I} + \hat{\mathbf{T}}, \quad \hat{\mathbf{T}} = \frac{2}{J} \mathbf{F} \frac{\partial W}{\partial \mathbf{C}} \mathbf{F}^T, \quad (4)$$

where  $p$  is a Lagrange multiplier,  $\mathbf{F}$  is the deformation gradient, and  $J$  is its determinant. For a thin membrane, the transmural pressure  $P_i$  and the axial force  $F_z$  can be approximated by

$$P_i = \frac{h(\hat{T}_{\theta\theta} - \hat{T}_{rr})}{r_m}, \quad (5)$$

$$F_z = 2\pi r_m h(\hat{T}_{zz} - \hat{T}_{rr}) - \pi(r_m^2 - r_c^2)P_i, \quad (6)$$

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 (2)–(4) into (5) and (6), 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 written as in Eq. (1).

### 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  $n = 1, \dots, m$ . The true values of the variables are denoted by  $\mathbf{x}_n$  and  $\mathbf{y}_n$ , which are corrupted by the measurement errors,  $\boldsymbol{\varepsilon}_n$  and  $\mathbf{e}_n$  during the experiment, i.e.,

the measured variables can be written as

$$\hat{\mathbf{x}}_n = \mathbf{x}_n + \boldsymbol{\varepsilon}_n, \quad (7)$$

$$\hat{\mathbf{y}}_n = \mathbf{y}_n + \mathbf{e}_n, \quad (8)$$

where  $\boldsymbol{\varepsilon}_n \sim WN(0, \boldsymbol{\Sigma}_\varepsilon)$  and  $\mathbf{e}_n \sim WN(0, \boldsymbol{\Sigma}_e)$  are assumed to be independent and identically distributed white 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):

$$\sum_{n=1}^m \left( \begin{array}{c} \hat{\mathbf{y}}_n - \mathbf{f}(\mathbf{x}_n, \boldsymbol{\Theta}) \\ \hat{\mathbf{x}}_n - \mathbf{x}_n \end{array} \right)^T \boldsymbol{\Sigma}_n^{-1} \left( \begin{array}{c} \hat{\mathbf{y}}_n - \mathbf{f}(\mathbf{x}_n, \boldsymbol{\Theta}) \\ \hat{\mathbf{x}}_n - \mathbf{x}_n \end{array} \right), \quad (9)$$

where  $\boldsymbol{\Sigma}_n$  is a collective covariance matrix of the measurement errors. Then, we have to solve for  $2m + N(\boldsymbol{\Theta})$  unknowns to minimize Eq. (9), where  $m$  is the number of data points and  $N(\boldsymbol{\Theta})$  is the number of parameters in  $\boldsymbol{\Theta}$ . For a nonlinear function of Eq. (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.” In this study, we use the classical parameter estimation method with only  $N(\boldsymbol{\Theta})$  unknowns in the objective function:

$$\sum_{n=1}^m (\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta}))^T \mathbf{W}_n (\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta})), \quad (10)$$

where  $\mathbf{W}_n$  are appropriately chosen weight matrices. The problem is, then, to solve for  $\boldsymbol{\Theta}$  by minimizing Eq. (10) 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  $\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta})$ . The uncertainty in  $\mathbf{f}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta})$  is propagated from the measurement noise of  $\boldsymbol{\varepsilon}_n$ , and it can be approximated by using the Taylor series of  $\mathbf{f}$  with respect to  $\boldsymbol{\varepsilon}_n$  and ignoring the higher order terms of  $\boldsymbol{\varepsilon}_n$  in the series. Then, we can obtain the uncertainty model  $\mathbf{v}_n$  for  $\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta})$  as

$$\mathbf{v}_n = -\frac{\partial \mathbf{f}}{\partial \mathbf{x}}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta}) \boldsymbol{\varepsilon}_n + \mathbf{e}_n. \quad (11)$$

Note that the uncertainty model for the force measurement now includes the effect of measurement noise in the displacement. Eq. (11) 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. (10), 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

$$\boldsymbol{\Sigma}_{v_n} = \mathbb{E}(\mathbf{v}_n \mathbf{v}_n^T) = \left( \frac{\partial \mathbf{f}}{\partial \mathbf{x}} \right) \boldsymbol{\Sigma}_\varepsilon \left( \frac{\partial \mathbf{f}}{\partial \mathbf{x}} \right)^T + \boldsymbol{\Sigma}_e, \quad (12)$$

where  $\mathbb{E}(A)$  is the expectation of  $A$ . Finally, using the uncertainty model Eq. (11), the objective function equation (10) can be written as

$$S = \sum_{n=1}^m (\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta}))^T \boldsymbol{\Sigma}_{v_n}^{-1} (\hat{\mathbf{y}}_n - \mathbf{f}(\hat{\mathbf{x}}_n, \boldsymbol{\Theta})). \quad (13)$$

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  $\boldsymbol{\Theta}^\circ$  are obtained by the NLS optimization without the uncertainty model. Then, the covariance matrix  $\boldsymbol{\Sigma}_{v_n}$  in Eq. (13) is approximated using the estimates  $\boldsymbol{\Theta}^\circ$  and  $\hat{\mathbf{x}}_n$ . With  $\boldsymbol{\Sigma}_{v_n}$ , the new

estimates of  $\Theta^1$  are obtained by minimizing Eq. (13). The covariance matrix  $\Sigma_{v_n}$  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. We calculate the linearized circumferential stiffness from both the WNLS and NLS methods and compare its accuracy (see Baek et al., 2007a, for linearization). The results will demonstrate that our proposed scheme provides a more accurate assessment of the arterial stiffness.

### 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 multi-fiber family model Eq. (2), we utilize three different criteria for model selection: 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

$$\text{AIC} = m \ln \left( \frac{S}{m} \right) + 2(N + 1), \quad (14)$$

$$\text{AICc} = \text{AIC} + \frac{2(N + 1)(N + 2)}{m - N - 2}, \quad (15)$$

$$\text{RMS} = \sqrt{\frac{S}{m - N}}, \quad (16)$$

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 considering both precision of fitting and complexity of the model (Anderson et al., 1994). While the first term in the right-hand side of Eq. (14) 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. (16) has 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 equation (13) is obtained by increasing the number of fiber families from 2 to 10 for each data set. Briefly, the 2-fiber-family model has four 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 six (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 eight independent parameters. From six fiber families, two additional symmetric fibers are added at each step, yielding three additional

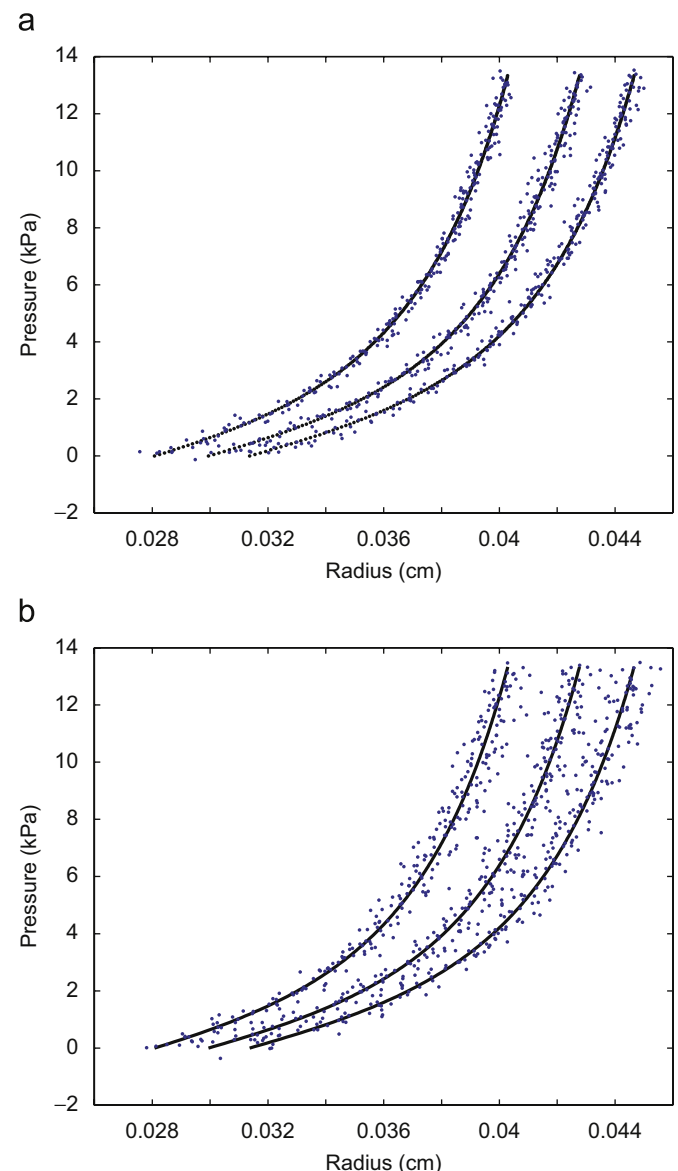
parameters (an angle and two parameters for exponential function). Hence, 11, 14, and 17 independent parameters are assumed for 6-, 8-, and 10-fiber-family models, respectively.

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.

## 3. Results

### 3.1. Comparison between the proposed WNLS optimization and the conventional NLS optimization

In order to demonstrate the effectiveness of the proposed WNLS method, we generated noise-corrupted, fictitious experimental data and performed the parameter estimation using the WNLS method as well as the standard approach (NLS) without an uncertainty model. We assumed a set of "true" parameters and



**Fig. 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  $\lambda_z = 1.2, 1.3, 1.4$ .

generated synthesized true data 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. (1) for a given radius and axial stretch using the true parameters. White Gaussian noises with given noise levels were numerically generated and added to the synthesized data of  $\{d_o, \lambda_z, F_z, P_i\}$  to produce fictitious experimental data. The noise level is defined as the ratio of the standard deviation of the noise to the maximum value of the data. Fig. 1 shows the pressure vs. radius plots for  $\lambda_z = 1.2, 1.3, 1.4$  for the true data, 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. Fig. 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 (Figs. 2(b) and (d)). Fig. 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 (Figs. 2 and 3). The advantage of the WNLS method over the standard NLS method is more obvious for the data with higher slopes (Fig. 3). Table 1 summarizes all true and estimated values of parameters corresponding to Figs. 2 and 3. For a quantitative measure of estimation errors, the following normalized error was defined as (Baek et al., 2007a)

$$e = \frac{1}{2} \left( \sqrt{\frac{\sum (P_{est} - P_{true})^2}{\sum (P_{true})^2}} + \sqrt{\frac{\sum (F_{est} - F_{true})^2}{\sum (F_{true})^2}} \right), \quad (17)$$

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 for a set of five different random noise sequences at each noise level. Table 2 shows the averaged, normalized errors obtained from both the NLS and WNLS methods at noise 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 Figs. 2 and 3 are shown in Table 3. The WNLS method resulted in much better estimation than the NLS method for both cases. For example, corresponding to the data of Fig. 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.

### 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. Figs. 4(a) and (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 3-fiber-family model (six parameters), and then slightly decreased for further increase in the number of fiber families (see e.g., Figs. 4(c) and (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 (six fiber

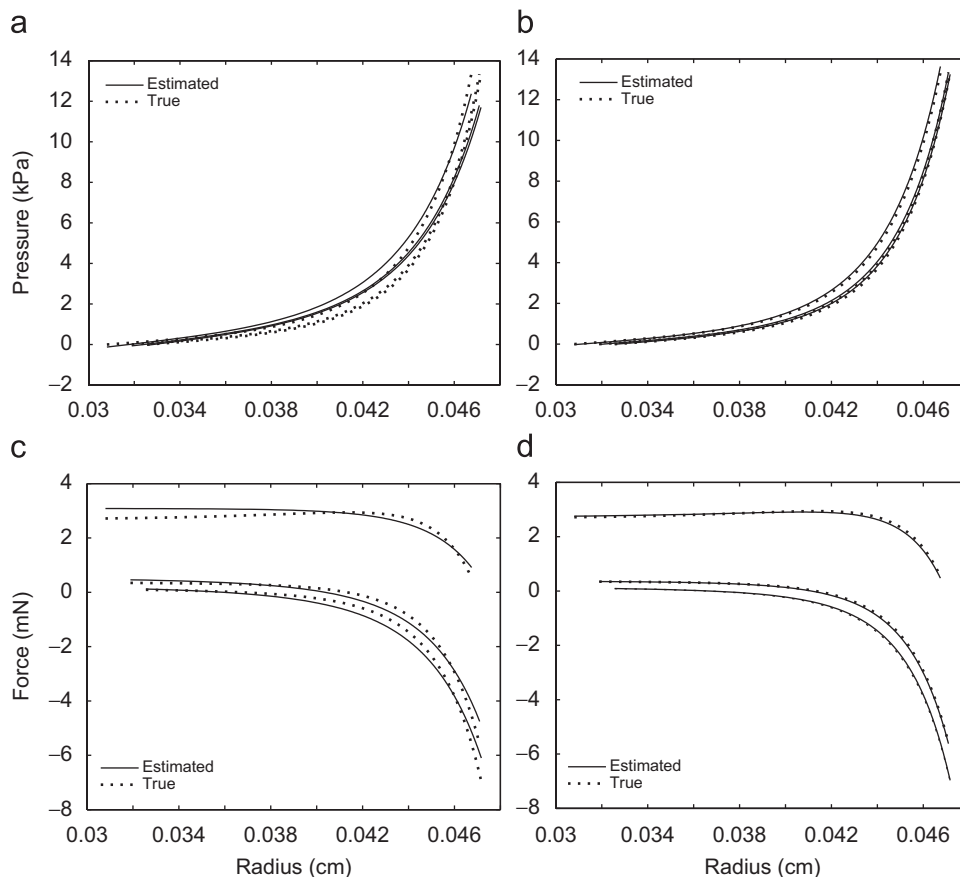
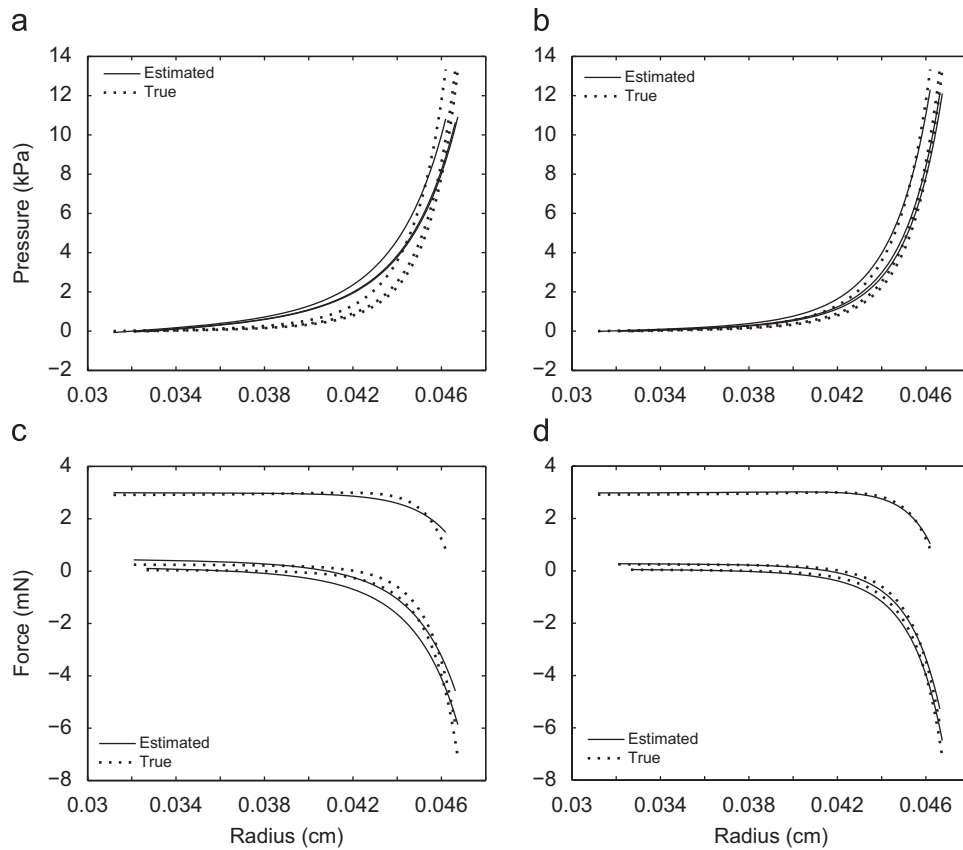


Fig. 2. Comparison between the NLS (a and c) and WNLS (b and d) optimizations for the 4-fiber-family model. Pressure and axial force versus radius are plotted using true parameters (dotted lines) and estimated parameters (solid lines) for the data with moderate slopes at different axial stretches  $\lambda_z = 1.2, 1.3, 1.4$ .



**Fig. 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  $\lambda_2 = 1.2, 1.3, 1.4$ .

**Table 1**

True and estimated parameters for the fictitious data with moderate and high slopes (corresponding to Figs. 2 and 3) and the experimental data from mouse carotid and rabbit basilar arteries (corresponding to Figs. 4(a) and (b)).

		$c$ (kPa)	$c_1^1$ (kPa)	$c_1^2$ (kPa)	$c_1^3$ (kPa)	$c_2^1$	$c_2^2$	$c_2^3$	$\alpha^1$ ( $^\circ$ )
Fig. 2	True	0	0.36	7.9	1.2	4.3	1.64	3.07	40.3
	NLS	0	0.71	14.2	1.1	3.72	1.12	3.1	42
Fig. 3	True	0	0.28	1.73	0.2	4.73	2.96	4.92	45.6
	WNLS	0	1.3	9.34	0.22	3.05	1.52	4.63	40.5
Fig. 4(a)	WNLS	0	0.28	3.4	0.27	4.73	2.36	4.53	44.5
Fig. 4(a)	WNLS	42	7.29	14	0.0003	0.152	0	3.11	55.9
Fig. 4(b)	WNLS	0	18	14	6.2	1.37	1.48	5.64	47.9

**Table 2**

Averaged normalized error  $e$  at different noise levels using the NLS and WNLS methods.

Noise level	0.005	0.008	0.01	0.02	0.03
$e_{NLS}$	0.0093	0.018	0.03	0.07	0.12
$e_{WNLS}$	0.009	0.01	0.0123	0.025	0.078
$e_{NLS}/e_{WNLS}$	1.033	1.8	2.44	2.8	1.54

families). Estimated parameters corresponding to Figs. 4(a) and (b) are listed in Table 1.

#### 4. Discussion

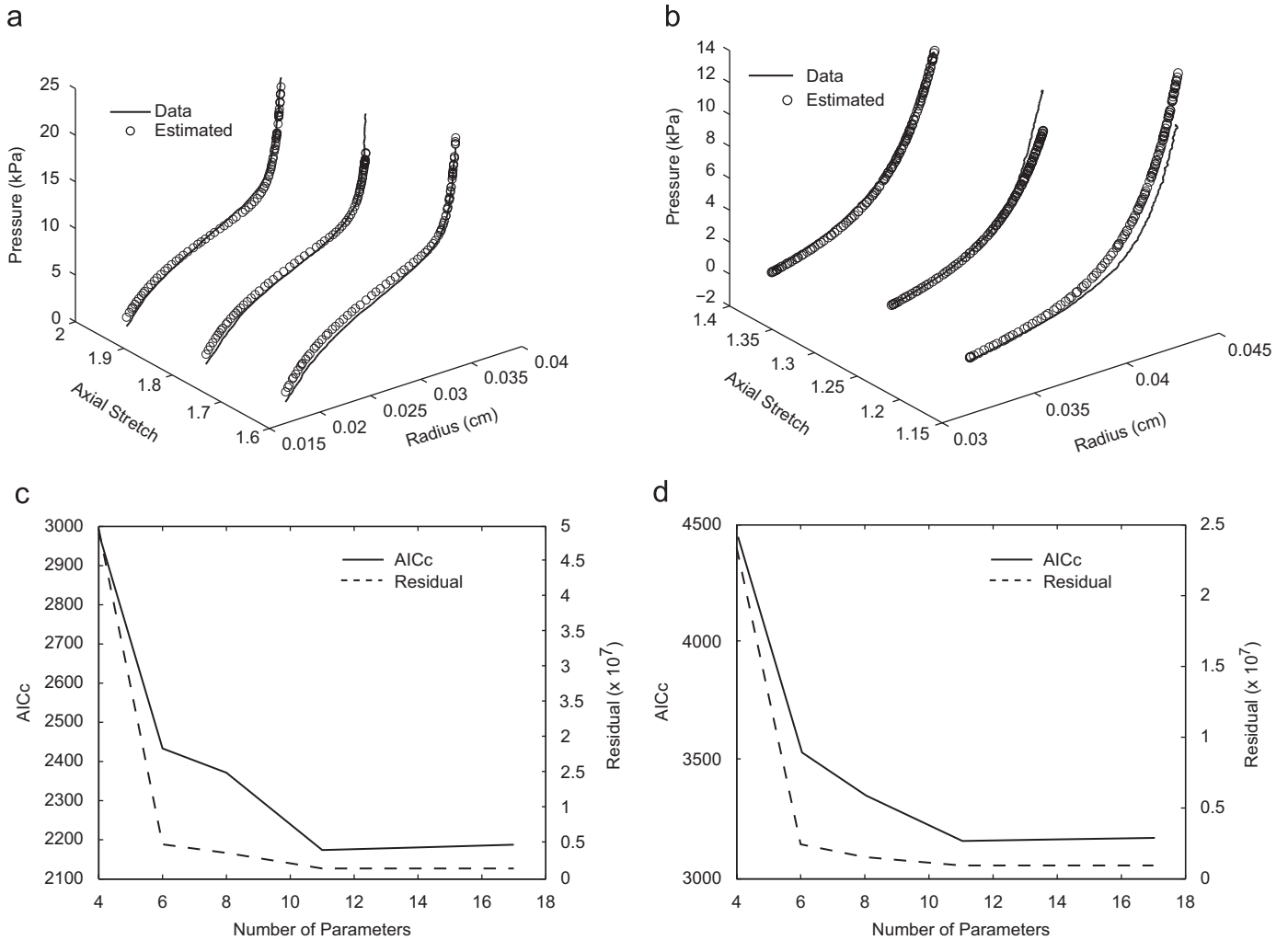
Parameter estimation using the NLS optimization has been widely used in characterizing mechanical behavior of soft tissues from the experiments. In this study, we proposed an improved

**Table 3**

True and estimated linearized stiffness at  $P_i = 75$  mmHg and  $\lambda_2 = 1.3$  corresponding to Figs. 2 and 3 using the NLS and WNLS methods.

	True stiffness (kPa)	NLS stiffness (kPa)	WNLS stiffness (kPa)
Fig. 2	1114	944	1085
Fig. 3	1580	1105	1381

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 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



**Fig. 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. 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.

$\pm 0.06$ , 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. (11). We showed 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,  $\partial f / \partial \mathbf{x}$  is larger in the high stretch region, so it produces a higher level of uncertainty propagation and, hence, estimation results are biased when the displacement measurement error is not considered within a proper uncertainty model (Fig. 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 this work, we used synthesized data 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, we have to note

that parameter estimation can be limited by the model error of the chosen constitutive relation.

The presented constitutive model is similar to the one developed by Holzapfel et al. (2000, 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). The vessel wall presents more dispersed fiber orientation in the adventitia and intimal layers and the use of an orientation density function was proposed (Lanir et al., 1996; Gasser et al., 2006). The choice of the functional form 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, we focused more on the situation where one has a functional form for a constitutive relation and needs to find optimal number of parameters and best parameter estimates from experimental data. However, the presented parameter estimation method is general enough and can be utilized with various models for vascular mechanics.

We used three criteria 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 (six fiber families) minimized our criteria.

In closing, we emphasize the need for the optimal design of experiments and optimal sampling protocols in vascular mechanics (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.

### Conflict of interest statement

We do not have conflict of interest with anyone or any organization.

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