

# Optimization of Passive Tissue Model Parameters of Intrinsic Laryngeal Tissues

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*This memo serves as a supplement to Hunter and Titze (2007)\*, which reports the passive tissue properties of the larynx with implications toward tissue function. This memo reviews a modified-Kelvin model of axial tissue properties that includes both exponential stress-strain and stress hysteresis during a stress-strain cycle. Given are details of the automated curve fitting strategy that was used to obtain the parameters of the model based on laboratory data, along with computer scripts and examples of the implementation. Updates to this memo can be downloaded at [http://www.ncvs.org/research\\_techbriefs.html](http://www.ncvs.org/research_techbriefs.html).*

**Keywords:** Canine muscles, muscles, PCA, LCA, IA, posturing, laryngeal muscles, muscle, optimization, muscle model, passive characteristics, Young's modulus, stress-strain, material properties, mechanical properties.

<b>List of Symbols:</b>	Symbol	Description
	$\sigma_0$	<i>parameter, the stress at <math>\varepsilon = 0</math></i>
	$\sigma_2$	<i>parameter, the scaling factor of the exponential portion</i>
	$\varepsilon_1$	<i>parameter assumed constant, the strain when the stress is zero</i>
	$\varepsilon_2$	<i>parameter, the strain at which the exponential function begins</i>
	$B$	<i>parameter, the exponential strain constant</i>
	$t_p$	<i>parameter, a parallel time constant with units of seconds</i>
	$t_s$	<i>parameter, a series time constant with units of seconds</i>
	$\sigma_p$	<i>function, the static passive tissue stress for a given strain</i>
	$E$	<i>function, tangent Young's modulus</i>
	$\varepsilon$	<i>independent variable, strain (fractional elongation)</i>
	$\sigma$	<i>dependent variable, stress (force per unit area)</i>

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\* Hunter and Titze (2007) was in press at the time this technical note was written. The full citation was added after publication.

## Introduction

The passive properties of canine laryngeal muscles are instrumental in global shaping and displacement of the larynx (Hunter, Titze, & Alipour, 2004), as well as to pitch control (Doellinger, Berry, & Berke, 2005; Hunter & Titze, 2005b; Titze, 1994). Due to the difficulty in obtaining fresh human laryngeal muscles, most of the previous investigations of stress-strain (passive property) have been conducted on canine tissue (Alipour & Titze, 1999; Alipour, Titze, Hunter, & Tayama, 2005; Alipour-Haghighi, Perlman, & Titze, 1991; Broniatowski et al., 2002; Hunter & Titze, 2005a; Perlman, Titze, & Cooper, 1984). Because the similar size and gross structure of the canine larynx have made it a popular research substitute for the human larynx (Cox, Alipour, & Titze, 1999; Kim, Hunter, & Titze, 2004; Mineck, Tayama, Chan, & Titze, 2000), it is expected that the study described below applies equally well to human tissue.

This report describes the automated curve-fitting strategy used to predict (calculate) the passive properties of canine laryngeal muscles. The five intrinsic muscles of the larynx are the thyroarytenoid (TA) muscle, the cricothyroid (CT) muscle, the interarytenoid (IA) muscle, the lateral cricoarytenoid (LCA) muscle, and the posterior cricoarytenoid (PCA) muscle. To date, only the mechanical tissue characteristics have been studied (Alipour & Titze, 1999; Alipour et al., 2005; Alipour-Haghighi & Titze, 1991; Min, Titze, & Alipour-Haghighi, 1995; Perlman et al., 1984). While useful, these studies have been limited by their use of simple equations to report a Young's modulus value at a particular strain or lossless stress-strain curves. Further, none of these studies have quantified the dynamic losses which occur during vocal posturing and phonation. In this report, quantified in terms of detailed nonlinear differential equations from force-elongation data by parameter optimization of a modified Kelvin model are: 1) the passive properties of the human vocal ligament; 2) the canine LCA and IA; and 3) the two compartments of the PCA<sup>13</sup>, the oblique (PCA<sub>O</sub>) and the vertical (PCA<sub>V</sub>).

## Materials and Methods

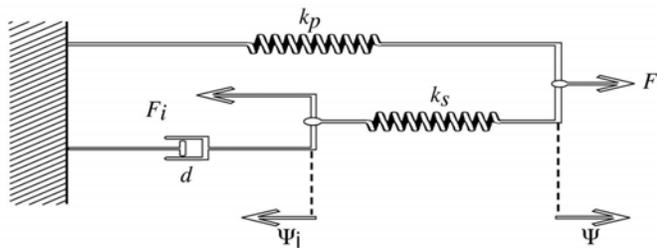
This section is divided into several parts: 1) a review of the modified Kelvin model; 2) an example of laboratory data; 3) an implementation of the model in MATLAB; 4) an optimization of the model parameters; 5) sensitivity analysis; and 6) data sets.

### 1. REVIEW OF THE TISSUE MODEL

Using the Hill muscle model as a guide, Titze (1996) applied the classical one-dimensional Kelvin model (Fig. 1) to

the laryngeal muscles, where  $k_p$  represents parallel stiffness,  $k_s$  represents series stiffness, and  $d$  represents internal viscous damping. With one node representing the internal contraction of the sarcomere and another representing the endpoint of the whole muscle, the differential equation for the modeled stress,  $\sigma_m$ , from dynamic strain  $\epsilon$  can be written as Equation 1.

$$t_s \dot{\sigma}_m + \sigma_m = \sigma_i + \sigma_p + Et_p \dot{\epsilon} \quad (1)$$



**Figure 1.** A typical optimized model fit of the muscle data (specimen 5, LCA). The dark lines are the original muscle data.

From Equation 1,  $t_s$  is a series time constant,  $t_p$  is a parallel time constant,  $\sigma_i$  is the modeled contractile stress (assumed to be zero in this case for passive muscles),  $\sigma_p$  is the passive stress at zero strain rate,  $E$  is the tangent Young's modulus, dynamic strain  $\varepsilon$  is  $(L-L_0)/L_0$ , and  $\dot{\varepsilon}$  is the strain rate. The two time constants are functions of  $d$ ,  $k_p$  and  $k_s$ . A ratio of the time constants is a constant itself,  $t_p/t_s$  being equal to  $(k_p + k_s) / k_p$ . It should be noted that other similarly based models have been used to describe a wide range of experimentally observable mechanical behaviors in polymers and soft tissue (*e.g.*, vocal fold mucosa [Zhang, Mongeau, Frankel, Thomson, & Park, 2004]).

Titze's primary contribution is his representation of the one-dimensional static stress-strain relationship as a piecewise function, continuous in both function and its first derivative, including a linear and an exponential portion.

$$\sigma_p = -\frac{\sigma_0}{\varepsilon_1}(\varepsilon - \varepsilon_1) - B\sigma_2(\varepsilon - \varepsilon_2) + \sigma_2[e^{B(\varepsilon - \varepsilon_2)} - 1], \quad \varepsilon > \varepsilon_2 \quad (2)$$

$$\sigma_p = -\frac{\sigma_0}{\varepsilon_1}(\varepsilon - \varepsilon_1), \quad \varepsilon \leq \varepsilon_2 \quad (3)$$

In the above equation,  $\varepsilon_1$  is the strain at zero stress,  $\varepsilon_2$  is the strain at which the nonlinear exponential function begins,  $\sigma_0$  is the stress at  $\varepsilon = 0$ ,  $\sigma_2$  is a scale factor for the exponential function, and  $B$  is an exponential strain constant. The derivative of both Equations 2 and 3 is the tangent Young's modulus.

$$E = \frac{\partial \sigma_p}{\partial \varepsilon} \quad (4)$$

Titze makes the assumption that the parameter  $\varepsilon_1$ , the strain at which zero stress occurs, is between 0 and -1.5 for laryngeal muscles.

The constitutive relation (Eq. 2) is based on a linearized strain  $\varepsilon$  not Green strain. It is assumed that experimental error in tissue measurement (Hunter, Alipour, & Titze, 2007) would be on the same order as the error introduced by linearized strain. Also assumed is the usefulness of a one-dimensional relation in representing the three-dimensional properties of the muscles when using a gel-fiber model. In a gel-fiber model, the muscle is a homogeneous hyperelastic ground substance, with extensible one-dimensional fibers embedded to represent the nonlinear stress-strain curve. This is similar to an approach used in a previous three-dimensional model of the anterior cruciate ligament (Hirokawa & Tsuruno, 2000). Finally, while Green strain may be the most correct representation of strain, the linearized case, when optimized to the data, produces repeatable results. In large deformation calculations, strain is usually defined as principal stretches  $\lambda$ . For uniaxial loading of a tissue assumed to be anisotropic, the axial principal stress can be assumed to be  $\lambda=1+\varepsilon$ .

2. LABORATORY DATA EXAMPLE

A canine PCA muscle fiber bundle was prepared for use in an experimental setup as described in Alipour *et al.* (2005) (Figure 2). In summary, standard dissection equipment was used to dissect and prepare a PCA muscle bundle sample. The fiber bundle mass was measured with a Mettler electronic balance (model AE 100,  $\pm 0.1$  mg) immediately after dissection. The sample was attached to a force-displacement transducer (dual servo Aurora Scientific ergometer:  $\pm 0.05$  g,  $\pm 0.02$  mm), while hydration was maintained in a temperature-controlled hydration bath (Radnoti Glass Technologies). Digital and analog calipers were used to measure muscle length and approximate diameter. With the fiber bundle placed in the apparatus,  $\Delta L$  and the resulting  $F$  data were obtained from a slow cyclic stretch (Figure 3) at 1 Hz.

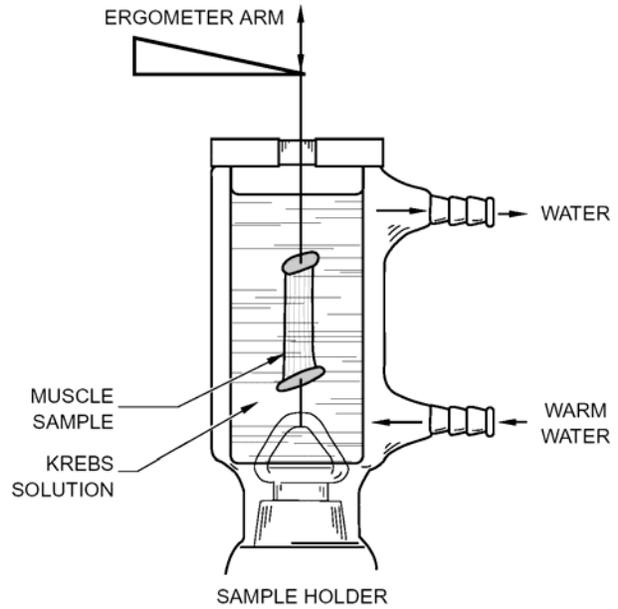


Figure 2. *In Vitro* laboratory apparatus for measuring muscle elasticity

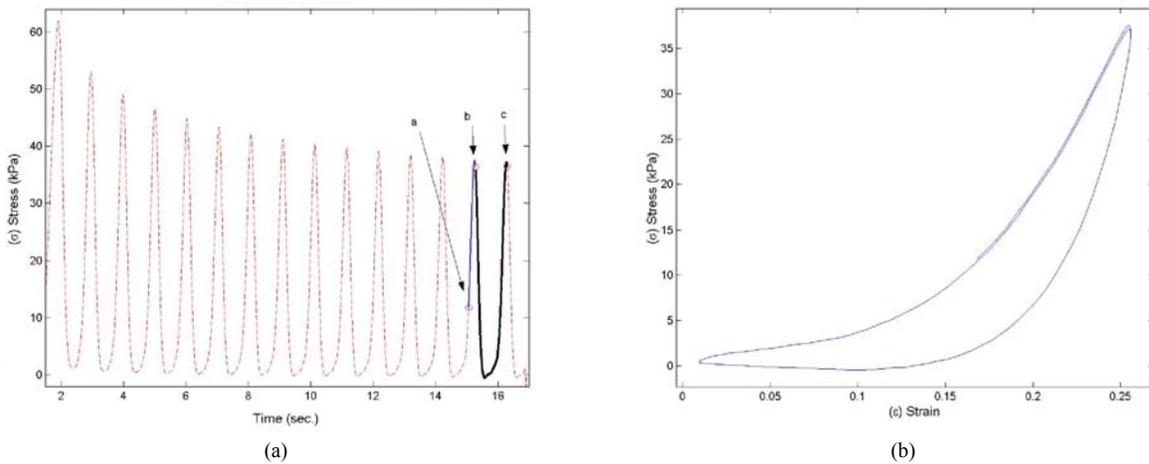


Figure 3. Stress from a sinusoidal (1 Hz) elongation of a PCAv muscle. (a) Stress in time with the solid line between Points b and c being the portion of the data modeled (see next section), the thin line between Points a and b being the stress history of 0.15 seconds needed by the model for preconditioning. (b) Stress-strain curve of selected section in graph (a).

### 3. IMPLEMENTING THE MODEL IN MATLAB

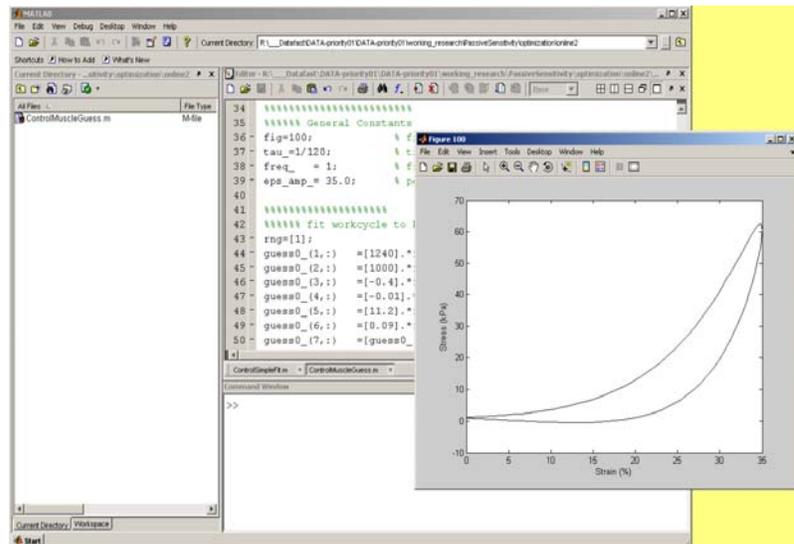
In this section, the muscle equations from the paper are shown in terms of scripts written in MATLAB. It should be noted that these scripts are also available in APDL (the script language for the finite element package ANSYS) (Hunter et al., 2004). While a knowledge of the basic uses of MATLAB is assumed in this memo, the scripts included in this memo are likely to be understood by those with limited programming experience and can be translated into another analysis language. It is requested that any use of these scripts in any form or translation make reference to this memo.

Some of the scripts include built-in MATLAB functions which were modified or inserted for conciseness. To protect the copyright of MATLAB, such modified scripts were parsed so they cannot be read/edited; nevertheless, they can be executed. The modifications made to these scripts were minor and do not contribute to the theory of this manuscript. No scripts used require extended MATLAB toolboxes. Original renderings of the modified MATLAB scripts are available in the basic MATLAB package by anyone with a MATLAB license.

#### EXAMPLE 1

##### ControlMuscleGuess.m

At the MATLAB command window, execute the script `ControlMuscleGuess.m` (Fig. 4). The result is a figure window with a simulated stress-strain curve for a tissue. Tissue model properties can be adjusted in lines 21-27 of the script. General properties of the script are found in lines 13-15. It should be noted that to increase the elongation frequency (line 15), the time step (line 14) should be decreased in size to allow the modeled differential equations to stay valid. The script is self-contained with all dependent functions included. This script is likely the simplest to dissect when understanding the implementation of the muscle model. The script contains two dependent functions, `model_bananafun` (where the equations above are implemented) and `Rkfor` a fourth-order Runge-Kutte routine.



**Figure 4.** `ControlMuscleGuess.m` in the MATLAB command window with constants to edit, along with the graphical output of the current parameters.

### 4. OPTIMIZING MODEL PARAMETERS TO DATA

Optimization was completed using the Nelder and Mead Simplex method (NMSM), a direct-search method. This particular method was chosen for its (1) handling of functions with multiple parameters; (2) performance on both deterministic objective functions (Nelson, 1985) and stochastic functions (Dennis & Woods, 1987); and (3) lack of sensitivity to starting values, relying neither on derivatives nor on the continuity of the objective function.

Using MATLAB, a computer script was written to solve Equations 1-4. This script calculated modeled stress,  $\sigma_m$ , from the differential equation (Equation 1) given a time-varying strain by using the fourth-order Runge-Kutta method. The four steps of the fourth-order Runge-Kutta implementation required that the equations be updated before each step in a manner similar to the *FORTRAN* routine described in Press *et al.* (1989). With a data sampling rate of 120 Hz, the routine needed a previous strain rate computation history of about 0.125 seconds to establish an accurate output; therefore, to ensure accuracy, the equation solver was always run for 0.15 seconds, or 18 data points, before any comparisons to the data were made.

A NMSM routine written in MATLAB was based on the methods found in an algorithm described in Barton and Ivey, Jr (1996). The original implementation used a built-in MATLAB script called “fminsearch”. While effective, it became necessary to add some bounds to the range of a variable. Thus, a modified version of a boundary implementation NMSM script, “fminsearchbnd” (donated by John D’Errico as found on MATLAB.com’s Matlab Central), was used.

The NMSM routine controlled the differential equation solution by regulating the parameters  $\sigma_0$ ,  $\sigma_2$ ,  $\epsilon_1$ ,  $\epsilon_2$ ,  $B$ ,  $t_p$ , and  $t_s$  given a strain,  $\epsilon$ . Seed values, or first-guess values, were based on hand-picked matches of the stress-strain curves for each muscle.

A summed square error of the point-by-point difference between the measured stress and the modeled stress was defined as Equation 5

$$Error\ Function = \sum_m [\sigma_d(n) - \sigma_m(n)]^2 \tag{5}$$

with  $\sigma_d$  representing the muscle stress data, and  $\sigma_m$  representing the modeled stress from Equation 1. For each strain value,  $\epsilon$  (corresponding to measured muscle stress value,  $\sigma_d$ ), the optimizer estimated a set of parameter values before calculating a modeled stress value,  $\sigma_m$ , and, thus, an error function value. The error function was minimized by repeatedly updating the different values and combinations of parameters, as controlled by the NMSM routine. Optimization was concluded when the NMSM routine’s two types of tolerance values were met: 1) the difference in each parameter from attempt to attempt; and 2) the value of the error function. Because the change in optimized parameters when tolerance was set from 1.0% to 0.1% was on the order of 0.0005%, a tolerance of 1.0% was maintained.

The cyclic stress-strain curves showed a preconditioned phase for the first several cycles of elongation, where the maximum stress peaks gradually became more level (stress leakage, a property of viscous material). Therefore, a cycle of data to be used in optimization was selected after about 14 cycles from the start of the elongation (Figure 3a). No attempt was made to parameterize the preconditioning portion. Figure 4 depicts a good fit.

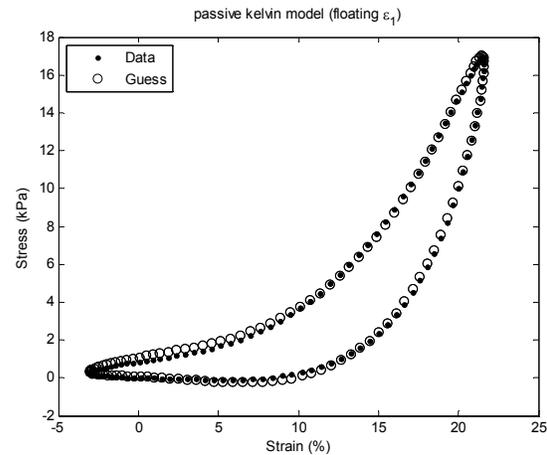
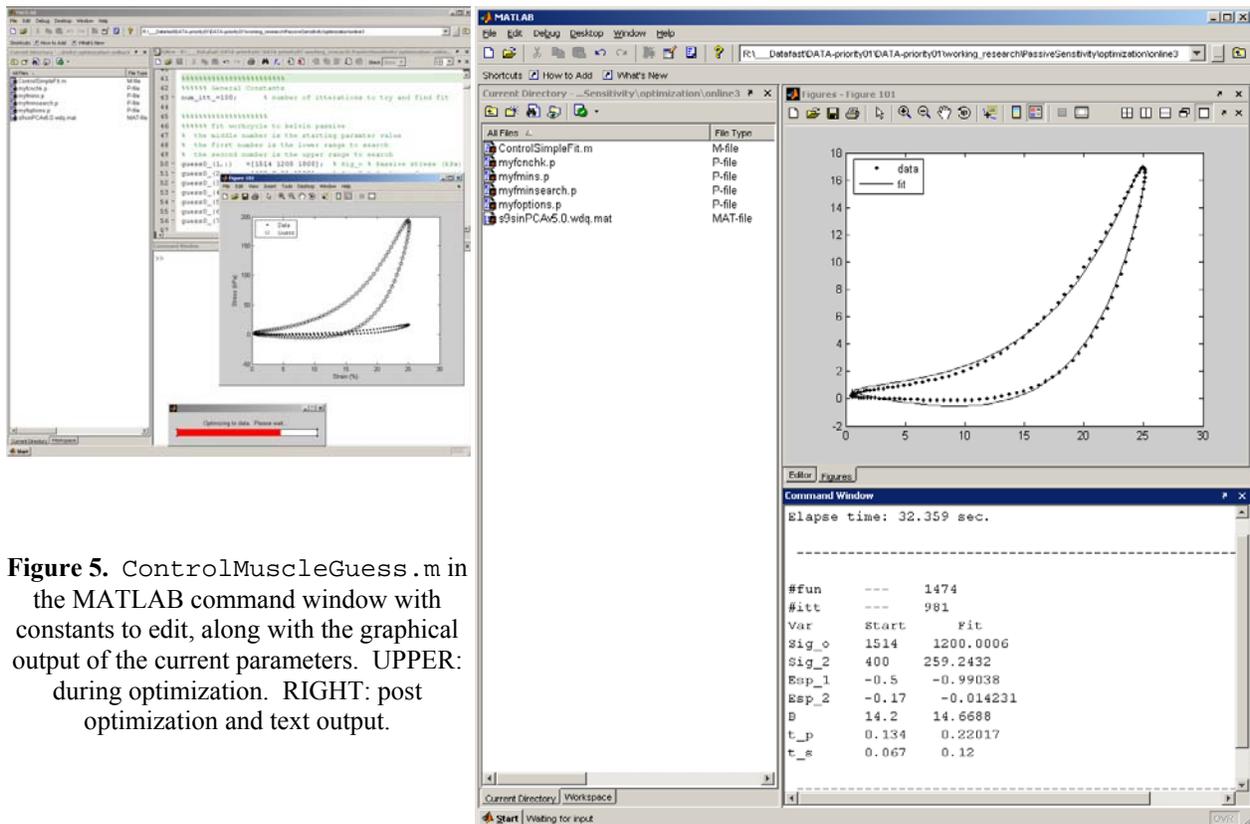


Figure 4. Typical fit of model to data.

## EXAMPLE 2

ControlSimpleFit.m - MATLAB script to optimize data  
 myfminsearch.p - built in MATLAB scripts (modified slightly)  
 myfcnchk.p processed so not to infringe MATHWORKS  
 myfoptions.p copyright  
 myfmins.p  
 S9sinPCAv5.0.wdq.mat -tissue data file to optimize

At the MATLAB command window, execute ControlSimpleFit.m (Figure 5). The data in S9sinPCAv5.0.wdq.mat are fit to the muscle model. As it is, the data will be fit using 100 iterations. This is not nearly enough iterations to produce a good fit. The maximum number of iterations can be changed on line 17 (I have found that 10,000 is a good maximum). The seed values and the upper/lower bounds can be edited on lines 24-30. The execution will pause at line 67 after the fit has been made with emphasis sent back to the command line so that internal variables can be seen.



**Figure 5.** ControlMuscleGuess.m in the MATLAB command window with constants to edit, along with the graphical output of the current parameters. UPPER: during optimization. RIGHT: post optimization and text output.

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EXAMPLE 3

- BatchAnalyze2.m -MATLAB script to optimize data
- myfminsearch.p  
myfcnchk.p  
myfoptions.p  
myfmins.p } -built in MATLAB scripts (modified slightly) processed so not to infringe MATHWORKS copyright
- model\_exponfun.m -dependent MATLAB script
- fitfun\_expon.m -dependent MATLAB script
- S9sinPCAv5.0.wdq -tissue data file to optimize
- output.xls -result file of batch process

At the MATLAB command window, execute BatchAnalyze2.m (Figure 6). While there is not any difference in the optimization methodology over Example 2, this script is much more sophisticated. First, it batch processes any tissue stress-strain files in the current directory. Second, it fits the data to both the modified Kelvin model and the exponential model. Finally, it stores the results in a preformed EXCEL file, output.xls. Results in this file show the straight optimization and the “mass-adjusted” optimization, as discussed in . Results also include images (saved in the directory with the script files) of the optimized fits for later comparisons.

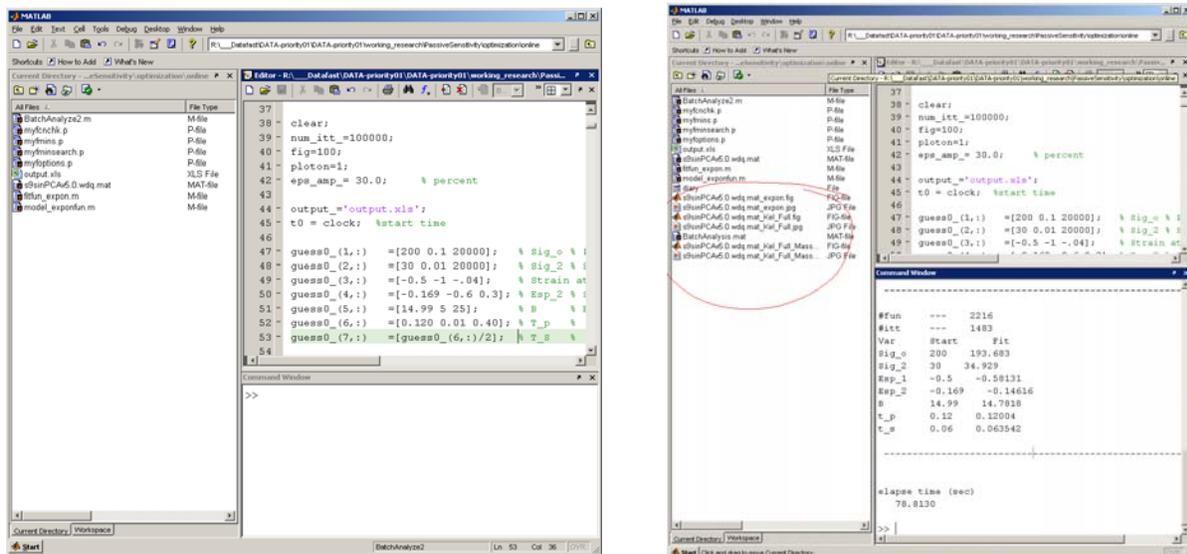


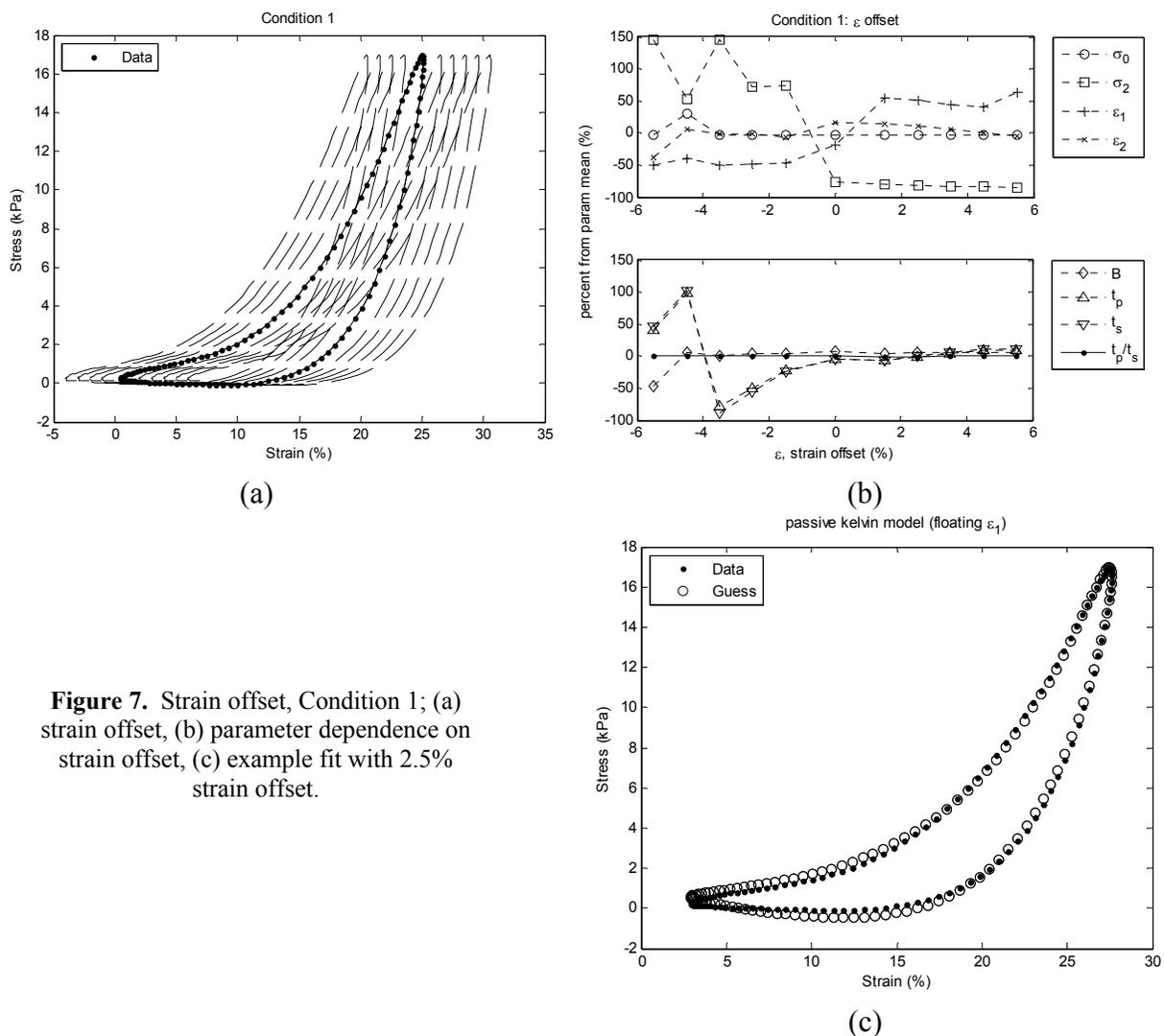
Figure 6. LEFT: pre-optimization seed values and maximal number of iterations. RIGHT: the result of the batch optimization. The graphical results of each optimization is saved to graphic files, circled in the left pair of right figure.figure results are shown

5. SENSITIVITY ANALYSIS

Because of the small size of laryngeal tissues, their passive tissue properties are particularly susceptible to small errors and uncertainties in laboratory measurements (Hunter & Titze, 2007). In his study, Hunter demonstrates that the most significant of these are uncertainties/errors in length and cross-sectional area measurements. The length uncertainties/errors were shown to be about  $\pm 1/3$  mm, potentially resulting in an 8% error in Young's Modulus calculation. The calculated cross-sectional area (Perlman et al., 1984) uncertainties/errors were shown to be primarily the result of tissue absorption of hydration fluid.

This increase of mass during the course of an excised tissue experiment should be, but usually is not, adjusted for (an increase of about  $13\pm 3\%$ ).

In light of these uncertainties/errors, it is important to determine their potential effect on the model. Therefore, to test the effect of these uncertainties on the modelled parameters, two potential conditions were simulated before the stress-strain data from one PCA muscle sample was optimized. Condition 1 was a straight strain offset to correspond to uncertainties/errors in length. As discussed in (Hunter et al., 2007), this uncertainty might be anywhere between  $\pm 1.5\%$  and  $\pm 5.5\%$  depending on the length of the laryngeal muscle. Condition 2 was a multiplier on the stress to account for the uncertainty/error in mass (and, thus, calculated cross-sectional area) due to hydration absorption. This multiplier applies directly to stress from measured data (110% to 116%).



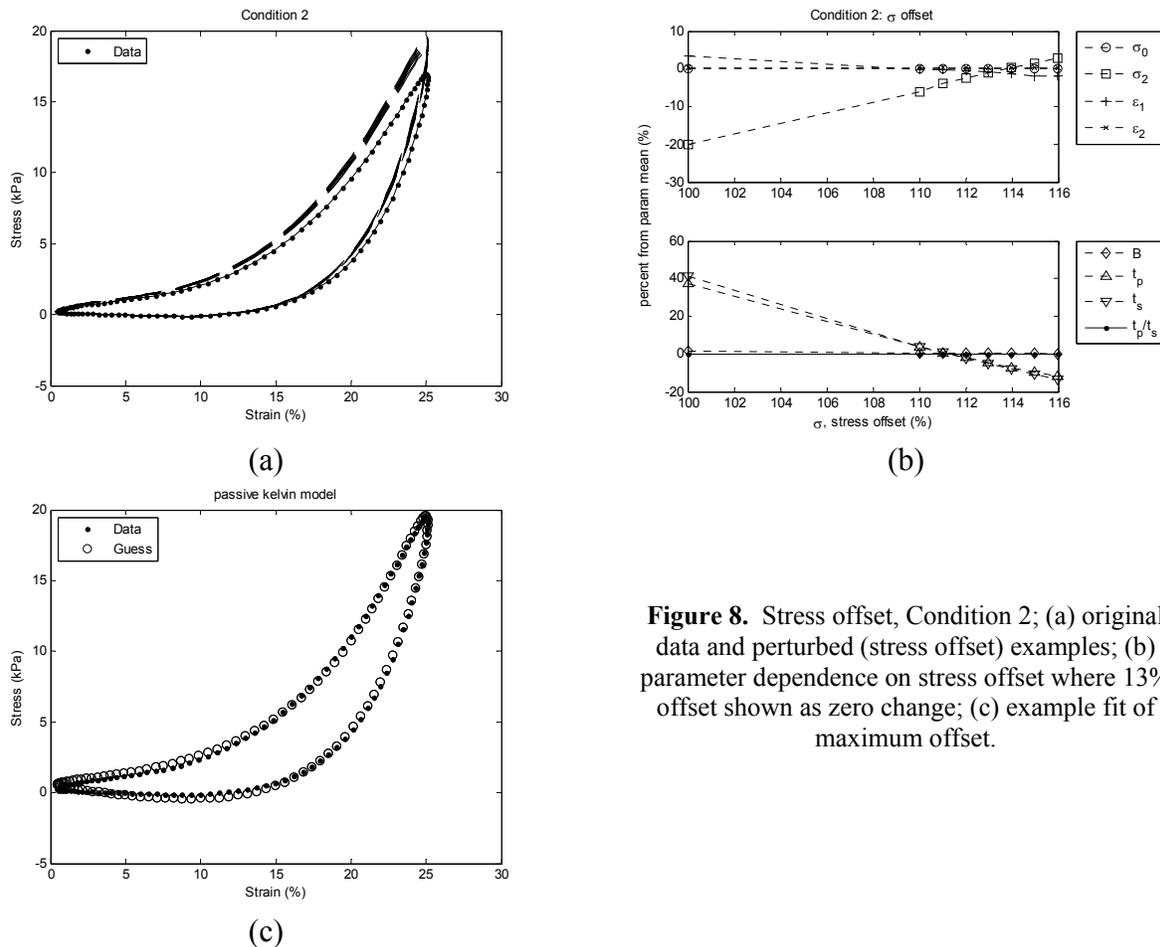
**Figure 7.** Strain offset, Condition 1; (a) strain offset, (b) parameter dependence on strain offset, (c) example fit with 2.5% strain offset.

The model optimized stress-strain data from a tissue after the uncertainties/errors from Conditions 1 and 2 were simulated. Figure 7.a illustrates the original stress-strain data and the perturbed cases, which simulate the potential uncertainties/errors from Condition 1. Optimized parameters allow the model to match the perturbed cases (Figure 7.c; note the strain axis shifted

on the figure), with some of the parameters being insensitive to the perturbations ( $\sigma_0$ ,  $\varepsilon_2$ ,  $B$ , ratio  $t_p/t_s$ ) and others being sensitive ( $\sigma_2$ ,  $\varepsilon_1$ ,  $t_p$ ,  $t_s$ ); Figure 7.b shows the change in the parameters for all conditions of strain perturbations (Condition 1).

The metric shown in Figure 7.b is the percent of a parameter's mean across Condition 1. Generally,  $\sigma_2$ , the stress at  $\varepsilon_1$ , was about 100-200% greater when the perturbation was below zero percent; on the other hand, the stress at  $\varepsilon_1$  was not significantly affected when the perturbation was greater than zero (compared to the 0 perturbation case). As might be expected, since  $\sigma_2$  and  $\varepsilon_1$  are defined together,  $\varepsilon_1$  has an inverse sensitivity to  $\sigma_2$ 's sensitivity to strain perturbation, being negatively affected by -50% at perturbations below zero and +50% at perturbations above zero. The time constants  $t_p$  and  $t_s$  were sensitive to negative strain perturbations. The ratio of the time constants was not sensitive to any strain perturbations, which was expected given that the ratio of the time constants was defined in terms of the two spring constants in the Kelvin model.

Figure 8.a illustrates the original stress data, as well as the perturbations of that data ( $+13\pm 3\%$ ) for Condition 2. The model could satisfactorily fit all perturbed data. Three parameters ( $\sigma_2$ ,  $t_p$ ,  $t_s$ ) were strongly affected by the increase in stress, while  $\varepsilon_1$  was slightly affected at the upper range of the perturbation. With the perturbation of increased stress,  $\sigma_2$  increased linearly (more than 20% over the original stress data value). The time constants were also affected linearly by the increase in stress (nearly -50% over the original data at the upper perturbation range). Again, the ratio of the time constants was stable and did not change, implying that the ratio is a constant for a given muscle.



**Figure 8.** Stress offset, Condition 2; (a) original data and perturbed (stress offset) examples; (b) parameter dependence on stress offset where 13% offset shown as zero change; (c) example fit of maximum offset.

## 6. DATA SETS

Samples of each of four different laryngeal muscles (IA, LCA, PCA<sub>o</sub>, and PCA<sub>v</sub>) were extracted from five viable canine larynges using procedures as described in the literature (Alipour & Titze, 1999; Alipour et al., 2005; Alipour-Haghighi & Titze, 1991). These muscles were elongated sinusoidally at 1 Hz under displacement control, and the resulting force was measured. Zero strain corresponds to the *in situ* measure of the cadaveric muscle length,  $L_0$ . Measured force and elongation were digitized at 120 samples per second. The measured force and elongation were converted to stress and strain; the stress-strain curves were fit to the equations defining a modified Kelvin model fibrous tissue. The data are stored in MATLAB ‘.mat’ files and were stored in one file Data.7z (a compressed file from free software, [www.7-zip.com](http://www.7-zip.com)).

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## Acknowledgements

This work was supported by NIDCD grant No DC04347 from National Institutes of Health. Thanks to the Denver Center for the Performing Arts and their continued support as the NCVS Denver site host. The authors would like to thank the research team at the National Center for Voice and Speech with many supporting roles in this work. Muscle data was collected with support from DC004347 (NIH/NIDCD) and with special help from Fari Alipour, Doug Montequin, Roger Chan and Niro Tayama. The analysis and modeling presented here were conducted as part of a research program entitled, “A Computational Tool for Simulation of Phonosurgical Procedures”, also supported by the NIDCD (R03 DC006801). Thank you to Laura M. Hunter for the technical review.

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## Revisions

- 1.0 Eric Hunter, main content (Nov-2001)
- 1.1 Eric Hunter, updated references and formatted for NCVS Technical Memo (Feb-2005)
- 2.0 Eric Hunter, updated text, added section on sensitivity, analysis redone, added ligament data, added examples, added data links (July 2006).
- 2.1 Laura Hunter, technical writing edits. Original was published with 'in press' (May 2015).