Numerical Methods for the Calculation of Material Parameter Values for Three-layered Aortic Valve Leaflets

Abstract

Aortic valve leaflets are comprised of three layers, each of which has a different composition and consequently, different mechanical properties. Each layer exhibits non-linear stress-strain behaviour and is modelled using a hyperelastic material model. Our objective is to determine the mechanical properties of each layer from experimental force-indentation depth data, ensuring that the material model parameters in each layer are unique and have converged to their correct values. To achieve this objective, material model parameters are calculated using inverse finite element simulations and non-linear optimization methods. To ensure that these parameters converge to their correct values, mathematical models of the indentation problem are used to obtain approximate values of these parameters to be used as initial conditions in the finite element simulations. This paper describes our progress with the development of these mathematical models and numerical simulations, as well as our ongoing work to achieve our defined objective.

Keywords

- aortic valve — finite element method — hyperelastic material — indentation — inverse problem — material parameter estimates — micromechanical properties

Introduction

Calcific aortic valve disease (CAVD) is the most common disease of heart valves, affecting 25% of the population over the age of 65 years [1]. It is a progressive disease, in which the aortic valve leaflets stiffen and eventually calcify. Currently, there is no medical treatment for this disease and when leaflets become severely calcified, valve replacement is the only treatment. The progression of CAVD in the early stages is not well understood, particularly at the cellular level. It has previously been shown [2, 3] that cells in the valve leaflets, known as valve interstitial cells, differentiate to pathological cell types in response to changes in their mechanical environment and this cell differentiation contributes to the progression of CAVD. Furthermore, the cells sense these changes in their mechanical environment at the microscale. It is therefore essential that more detailed information be obtained concerning the microscale mechanical properties of the extracellular matrix (ECM) surrounding valve interstitial cells in leaflets in both healthy and pathological states.

Aortic valve leaflets are made up of three layers, which are, from the aorta side to the left ventricle side, the fibrosa, the spongiosa, and the ventricularis. Each of these layers has a different ECM composition, with the fibrosa being a collagen-rich layer, the spongiosa being a proteoglycan-rich layer, and the ventricularis containing collagen and elastin. Differences in ECM composition lead to differences in mechanical properties, with the fibrosa being the stiffest layer, followed by the ventricularis, and the spongiosa [4, 5]. Further, the leaflet layers are heterogeneous, with a strong spatial variation in their mechanical properties, and the microscale mechanical properties of the fibrosa and ventricularis layers are nonlinear [5].

The objective of this study is to determine the local microscale mechanical properties of each of the layers of aortic valve leaflets from experimental data obtained from indentation of intact excised leaflets. We use porcine aortic valve leaflets as models for human valves because they are similar in size, have similar structure, and display similar structural and cellular changes during early disease [6]. To achieve our objective, an inverse finite element approach is used in conjunction with non-
linear optimization. With a single set of force-displacement data per measurement location, the inverse finite element problem is ill-posed for a multilayer material. To address this issue, mathematical models are used to approximate the material parameter values, and these approximations are used as initial conditions for the finite element simulations to ensure that the simulations converge to a solution that is both unique and correct. Work on these mathematical models began in July 2012 at the MBI Math Biosciences Problem-Solving Workshop [7] and the work presented in this paper is the result of ongoing collaborations amongst several of the participants from this workshop.

1. Methods

This project is divided into four main parts: indentation experiments, ultrasound imaging, mathematical models, and numerical simulations. Figure 1 is a flow chart illustrating the workflow for the overall project. Because the focus of this paper is on the mathematical and numerical parts of this study, the first two parts, indentation experiments and ultrasound imaging, are only briefly described in the following sections.

1.1 Indentation experiments

Porcine hearts were obtained from a local abattoir (Quality Meat Packers, Ltd., Toronto, ON, Canada). Aortic valve leaflets were isolated and pinned to a silicone substrate, which was embedded in a Petri dish. The leaflets were covered with a small amount of phosphate buffered saline (PBS) and placed on a sample stage for indentation. A purpose-built microindenter was used to indent the leaflets with a cylindrical indenter tip having a diameter in the range of 50-150 µm. Figure 2 is a schematic of the leaflet-indenter system. Indentation forces and the corresponding indentation depths were measured using this system. The measured indentation depths were used as input boundary conditions in the numerical simulations. An example of an indentation force versus indentation depth data for two locations on each of two leaflets is shown in Figure 3.

1.2 Ultrasound

Following a method proposed by Qiu et al. [8], a pre-clinical ultrasound system (Vevo 770; Visualsonics, Inc., Toronto, ON, Canada) was used to obtain B-mode ultrasound images of the aortic valve leaflets. These images, such as the one shown in Figure 4, show a cross-sectional view of the leaflet, including the three layers. Using image processing functions in MATLAB (The MathWorks, Inc., Natick, MA, USA), these images were filtered and segmented. The thicknesses of the layers were then calculated from the segmented images and these thicknesses were used to define the geometry in the numerical simulations.

1.3 Material models

Nonlinear stress-strain (or force-displacement) data can be modelled by a hyperelastic material model, defined by a strain energy density function $W$. In this study, we have chosen an exponential form of $W$, which has previously been used to model soft tissues, including aortic valve leaflets [9]. The incompressible form of this material model is defined as

$$W = \frac{C_1}{2} \left( e^{C_2(l_1-3)} - 1 \right),$$

(1)
where $C_1$ and $C_2$ are material parameter values, $l_i = \sum \lambda_i^2$ is the first invariant of Green’s strain tensor, $\lambda_i = l_i/l_i.0$ are the principle stretches, $l_i$ is the material length, and $l_i.0$ is the undeformed material length.

1.4 Mathematical models
Mathematical models are used to estimate the material properties of the leaflet layers from the experimental data, and these estimated properties are used as initial conditions in the inverse finite element simulations. This section describes the formulations of these models. To simplify the models considerably, contact effects between the indenter and the leaflet have been neglected.

1.4.1 One-dimensional model
Starting from Equation (1), we consider a special case where the only non-zero stress is in the $x = x_1$ direction. In this case, we have $\lambda_2 = \lambda_3 = \sqrt{\lambda_1}$, and assuming incompressibility, we have

$$\lambda_2 = \lambda_3 = \sqrt{\lambda_1}. \quad (2)$$

The strain energy density function is now written as

$$W = \frac{C_1}{2} \left( e^{C_2(\lambda_1^2+2\lambda_1^{-1}-3)} - 1 \right). \quad (3)$$

The stress in the $x$ direction can be obtained as

$$\sigma = p + \lambda_1 \frac{\partial W}{\partial \lambda_1} = p + C_1 C_2 (\lambda_1^2 - \lambda_1^{-1}) e^{C_2(\lambda_1^2+2\lambda_1^{-1}-3)}, \quad (4)$$

where $p$ is the hydrostatic pressure.

1.4.2 One-layer problem
Let us consider a single leaflet layer of thickness $h$, where $x = 0$ is the bottom surface, and $x = h$ is where the force $F$ (per unit area) is applied. From the equilibrium condition $\partial \sigma / \partial x = 0$, we have

$$-p + C_1 C_2 (\lambda^2 - \lambda^{-1}) e^{C_2(\lambda^2+2\lambda^{-1}-3)} = F. \quad (5)$$

To simplify notation, we have dropped the subscript for $\lambda_1$. The value of $p$ depends on the side boundary condition and for simplicity we assume that $p = 0$. Equation (5) predicts a value for $\lambda$ for a given force $F$.

Equivalently, for a given indentation depth $U$ and height $h$, we can compute the stretch $\lambda = (h - U)/h$. From Equation (5), we can compute the force $F$. If we have a pair of indentation depth-force values $U(1)/F(1)$ and $U(2)/F(2)$, we can easily back out the material parameters $C_1$ and $C_2$ by first solving for $C_2$ from the ratio $F(1)/F(2)$, and then solving Equation (5) for $C_1$ with this value of $C_2$. Figure 5 is a plot of a force-indentation depth curve for this one-layer model.

Finally, we note that if the thickness $h$ is unknown, we can take a third pair of measurement $U(3)/F(3)$ and use it to find $h$. However, we cannot do this using the simple approach outlined above. Instead, we need to solve a coupled system of nonlinear equations for $C_1$, $C_2$, and $h$.

1.4.3 Two-layer problem
Let us now consider two layers with different material parameters $C_{i1}$ and $C_{i2}$ ($i = 1, 2$) and thicknesses $h_1$ and $h_2$, as shown in Figure 6. Assuming stress is the same in each layer, we have

$$F = -p_1 + C_{11} C_{12} (\lambda_1^2 - \lambda_1^{-1}) e^{C_{12}(\lambda_1^2+2\lambda_1^{-1}-3)} \quad (6)$$

$$-p_2 + C_{21} C_{22} (\lambda_2^2 - \lambda_2^{-1}) e^{C_{22}(\lambda_2^2+2\lambda_2^{-1}-3)} \quad (7)$$

Equations (6) and (7) give the stretches $\lambda_i$ ($i = 1, 2$) for a prescribed force $F$. Note that the subscript for $\lambda$ is now used to represent the different layers.

At the bottom $x = 0$, we have $u_1(0) = 0$; on the interface between two layers $x = h_1$, we have $u_1(h_1) = u_2(h_1)$; and at the top $x = h_1 + h_2$, we have $u_2(h_1 + h_2) = U$, where $u_1$ and $u_2$ are the displacements in layers 1 and 2, respectively and $U$ is the indentation depth. The stretches are

$$\lambda_1 = 1 - \frac{u_1(h_1)}{h_1}, \quad (8)$$

$$\lambda_2 = 1 - \frac{U - u_1(h_1)}{h_2} = 1 + \frac{h_1}{h_2} - \frac{U}{h_2} - \frac{h_1}{h_2} \lambda_1. \quad (9)$$
To simplify notation, we have used $\lambda_i = \frac{h_i}{h_1}$ for $i = 1, 2$. This simplification is more complicated for multilayer problems. When deformation is small, $\lambda = 1 + \delta$ with $\delta \ll 1$. In this case, $R(\lambda) \sim 3\delta + \delta^3$ and $S(\lambda) \sim 3\delta^2$, from which $R(\lambda) \exp(C_2 S(\lambda)) \sim 3\delta + (1 + 9C_2)\delta^3$. Thus, depending on relative sizes of $\delta$ and $C_2$, we might have a linear or cubic nonlinearity as two special cases. In Section 2.1, we will use these two special cases to illustrate the non-uniqueness for the linear case and a solution procedure for the cubic nonlinear case.

### 1.4.4 Two-dimensional model

The one-dimensional model described in the previous section provides some useful information. However, its ability to accurately predict the material parameters is limited, so we consider a model that will be used to provide reasonable approximations, while being less computationally expensive than the ANSYS finite-element model discussed in detail in Section 1.5. The goal is to use this simpler model to obtain good first estimates of the material parameters, which will ultimately enable faster convergence of the optimization process when using the more physically accurate material model (Equation 1). The results from this model will also provide a means of verifying the results of the ANSYS simulations.

For a general strain energy density function $W = W(F)$, where $F$ is the deformation gradient, the Cauchy stress $\mathbf{T}$ can be related to the deformation by

$$\mathbf{T} = J^{-1}F : \frac{\partial W}{\partial F} - p\mathbf{I},$$

where $p$ is as previously defined and $J$ is the determinant of $F$.

We introduce a Lagrangian measure of the stress, specifically the first Piola-Kirchhoff stress tensor $\mathbf{P}$ given by

$$\mathbf{P} = J\mathbf{T}F^{-T},$$

which relates forces with respect to the current configuration to those with respect to the reference configuration. The reference configuration is defined to be the configuration of the layers when no external force is applied, and the coordinates of the reference configuration are defined as the Cartesian coordinates $(X, Y, Z)$.

In Figure 7, we have plotted force-stretch curves for $\lambda_1$ and $\lambda_2$ to illustrate the nonlinear behaviour.

For simplicity, we assume that the far field side conditions are such that $p_1 = p_2 = 0$. For each force $F$, we have three equations

$$h_1\lambda_1 + h_2\lambda_2 = h_1 + h_2 - U$$

and

$$F = C_{11}C_{12}R(\lambda_1)e^{C_{12}S(\lambda_1)}$$

$$= C_{21}C_{22}R(\lambda_2)e^{C_{22}S(\lambda_2)}.$$

To simplify notation, we have used

$$R(\lambda_i) = \lambda_i^2 - \lambda_i^{-1}, \quad S(\lambda_i) = \lambda_i^2 + 2\lambda_i^{-1} - 3, i = 1, 2$$

In Figure 7, we have plotted force-stretch curves for $\lambda_1$ and $\lambda_2$ with $h_1 = h_2 = 1$, $C_{11} = C_{21} = 1$, $C_{12} = 10$, and $C_{22} = 2C_{12}$.

In general, the procedure for finding the material parameter values is more complicated for multilayer problems. When deformation is small, $\lambda = 1 + \delta$ with $\delta \ll 1$. In this case, $R(\lambda) \sim 3\delta + \delta^3$ and $S(\lambda) \sim 3\delta^2$, from which $R(\lambda) \exp(C_2 S(\lambda)) \sim 3\delta + (1 + 9C_2)\delta^3$. Thus, depending on relative sizes of $\delta$ and $C_2$, we might have a linear or cubic nonlinearity as two special cases. In Section 2.1, we will use these two special cases to illustrate the non-uniqueness for the linear case and a solution procedure for the cubic nonlinear case.
With these assumptions, in the case where there is a single layer, Equation (15) becomes
\[
\frac{\partial P_{XX}}{\partial X} + \frac{\partial P_{XZ}}{\partial Z} = 0, \quad (16a)
\]
\[
\frac{\partial P_{ZX}}{\partial X} + \frac{\partial P_{ZZ}}{\partial Z} = 0, \quad (16b)
\]
\[
u X + w Z + u X w Z - u Z w X = 0, \quad (16c)
\]
where \(u = (u, w)\) is the displacement vector and
\[
P_{XX} = [2C((1 + u X)^2 + u Z^2) - p](1 + w Z) - 2C[(1 + u X)w X + u Z(1 + w Z)]u Z, \quad (17a)
\]
\[
P_{XZ} = -[2C((1 + u X)^2 + u Z^2) - p]w X + 2C[(1 + u X)w X + u Z(1 + w Z)](1 + u X), \quad (17b)
\]
\[
P_{ZX} = 2C[(1 + u X)w X + u Z(1 + w Z)](1 + w Z) - 2C(w X^2 + (1 + w Z)^2 - p)u Z, \quad (17c)
\]
\[
P_{ZZ} = -2C[(1 + u X)w X + u Z(1 + w Z)]w X + 2C(w X^2 + (1 + w Z)^2 - p)(1 + u X). \quad (17d)
\]

The boundary conditions around the outer walls of the rectangular geometry are
\[
u = 0, \quad w = 0, \quad \text{on} \ Z = 0, \quad (18a)
\]
\[
P_{XX} = 0, \quad P_{XZ} = 0, \quad \text{on} \ X = \pm 1, \quad (18b)
\]
\[
P_{ZX} = 0, \quad P_{ZZ} = \tau \delta(x), \quad \text{on} \ Z = h. \quad (18c)
\]

For the case of a two-layered model, Equations (16)–(18) hold in each layer and we use the notation \(u^{(i)}, w^{(i)}, p^{(i)}, i = 1, 2\) to denote \(u, w,\) and \(p\) evaluated in the lower and upper layers, respectively. At the interface of the two layers, \(Z = h_1,\) the associated tractions need to be equal but opposite, which requires the stress to be continuous across \(Z,\) and the vertical displacement must be equal, thus
\[
P_{ZZ}^{(1)} = P_{ZZ}^{(2)}, \quad w^{(1)} = w^{(2)} \quad \text{on} \ Z = h_1, \quad (19)
\]
where \(Z = h_1\) is the interface of the layers in the initial configuration.

### 1.5 Numerical simulations

Finite element simulations were performed using the commercial software ANSYS (ANSYS, Inc., Canonsburg, PA, USA). The leaflet-indenter system was modelled as a two-dimensional axisymmetric geometry. The indenter was modelled as a rectangle with a filleted bottom corner. This filleted corner mimics the actual indenter, which has slightly rounded edges. Layer heights, which were either arbitrarily defined or based on calculations made from segmented ultrasound images, were assumed to be constant over the simulation geometry, and the width of the leaflet geometry was assumed to be sufficiently large to make edge effects negligible, but not too large as to increase the computational time for the simulations unnecessarily. The indenter was meshed using 6-node triangular elements, while the leaflet layers were meshed using 8-node quadrilateral elements, with elements concentrated near the indenter and at the interfaces between layers. An example of the model geometry and mesh is shown in Figure 8.

![Figure 8. Leaflet-indenter system geometry and mesh](image)

Indentation depths, either representative values or values from measurements, were applied as input boundary conditions to the top edge of the indenter. The left edges of the geometry are axisymmetric boundaries, and the right edges are free boundaries. There is no slip between the layers, and no displacement on the bottom. Contact boundary conditions, defined through the use of contact and target elements in ANSYS, were applied to the top edge of the leaflet and the bottom, curved and right edges of the indenter.

Large displacement static simulations of the leaflet indentation were performed. The indenter was assumed to be a linear elastic material with Young’s modulus \(E = 2 \times 10^8\) kPa and Poisson’s ratio \(\nu = 0.49.\) Each leaflet layer was assumed to be slightly compressible (to allow for numerical convergence), isotropic, and homogenous over the simulated geometry. Initial simulations were performed using a neo-Hookean material model, defined as
\[
W = C(I_1 - 3) + \frac{1}{d}(J - 1)^2, \quad (20)
\]

where \(I_1\) is the first deviatoric strain invariant, \(d\) is the incompressibility parameter, and \(J\) is the determinant of the deformation gradient tensor \(F.\)

It has previously been shown [10] that if the incompressibility parameter \(d\) is selected sufficiently small, the compressibility effects in the slightly compressible form of a hyperelastic material model become negligible and the results for the slightly compressible material model converge to those for the equivalent
incompressible material model. Therefore, material parameter values calculated from mathematical models that use the incompressible form of \( W \) are equivalent to values used in simulations performed with the slightly compressible form of the same \( W \).

### 1.6 Nonlinear optimization

To determine the material parameter values for each leaflet layer from the measured data, an inverse finite element approach was used in conjunction with nonlinear optimization in MATLAB. The finite element model has been written in a text-based input format that allows for straightforward modifications to the input parameters. By defining the finite element model in this manner, it allowed the finite element simulations to be modified and run from within MATLAB. The sequence of steps is as follows:

1. Input values for indentation depths, layer heights, and material model parameters are defined either arbitrarily or from measured data and mathematical models.
2. ANSYS input file are automatically modified with these values.
3. Finite element simulations are performed and indentation force versus indentation depth results are output.
4. Indentation force versus indentation depth results are imported into MATLAB and the least squares error is calculated between the measured and calculated force-depth values.
5. If the least squares error is less than a threshold, then the simulations are complete and the material parameter values are determined. If the results have not converged, non-linear optimization, using the fmincon function in MATLAB, is used to calculate new material model parameter values. The simulations are repeated in this manner until convergence has been reached.

### 2. Results and Discussion

#### 2.1 Mathematical models

For the two-layer one-dimensional problem, described in Section 1.4.3, we have performed numerical tests for the linear and cubic nonlinear cases. For these tests, we have assumed the bottom layer (1) to have linear material properties and the top layer (2) to have nonlinear properties. Note that as in Section 1.4.3, we have performed numerical tests for the linear and cubic nonlinear cases. For these tests, we have assumed the bottom layer (1) to have linear material properties and the top layer (2) to have nonlinear properties. Therefore, taking multiple measurements does not help to find the linear case, we have

\[
\begin{align*}
F(1) & = C_1 \delta_1 = C_2 \delta_2 \\
F(2) & = C_1 \delta_1 + h_1 \delta_1 + h_2 \delta_2 = -U,
\end{align*}
\]

These two relationship lead to

\[
\frac{h_1}{C_1} + \frac{h_2}{C_2} = -\frac{F}{U}. \tag{21}
\]

Therefore, taking multiple measurements does not help to find \( C_1 \) and \( C_2 \), and the solution is not unique.

For the nonlinear case, however, things are different. We consider the simplest possible case with a combination of a linear elastic layer with a cubic nonlinear elastic layer, \( F = C_1 \delta_1 = C_2 \delta_2^3 \) and \( h_1 \delta_1 + h_2 \delta_2 = -U \). In this case, we have

\[
\frac{1}{C_1} h_1 F + \frac{1}{C_2^{1/3}} h_2 F^{1/3} = -U. \tag{22}
\]

We can solve for \( C_1 \) and \( C_2 \) using a least squares approach with multiple measurements \( F(k) \) and \( U(k) \) by solving the following over-determined linear system

\[
A x = y \tag{23}
\]

where the \( i \)-th row of \( A \) and \( y \) are given by

\[
A_i = [h_1 F(i); h_2 F^{1/3}(i)], \quad y_i = -U(i), \tag{24}
\]

with two unknowns \( x_1 = 1/C_1 \) and \( x_2 = 1/C_2^{1/3} \).

In Figure 9a, we plot the force-indentation depth relationship from Equation (22) for \( C_1 = 1 \) and \( C_2 = 50 \). In Figure 9b, we added a normally-distributed random noise (with standard deviation \( \sigma = 0.02 \)) and used the least squares procedure to estimate \( C_1 = 1.045 \) and \( C_2 = 45.32 \). This measurement noise shifted it and \( C_2 \) from their exact values by 0.045 and -4.68, respectively.

**Remark.** Note that for the more general nonlinear elasticity \( F = C(\delta + C' \delta^3) \), the procedure is almost the same except that we need to solve for a cubic equation for \( \delta \) before setting up the least squares problem. For the more general exponential elasticity \( R(\lambda) \exp(C(\lambda)) \), however, a numerical method is needed to solve for \( \delta \) in terms of \( F \) and the material parameters.

Work is ongoing to extend the one-dimensional models to three layers and to incorporate nonlinear material properties in all of these layers. A tailor-made solver is being developed to study the two-dimensional nonlinear problem. This solver will initially look at the two layer problem and then will be extended to three layers.

#### 2.2 Numerical simulations

Numerical simulations of the forward problem have been successfully performed with arbitrary indentation depths, layer heights, and material parameter values, using the neo-Hookean material model. Figures 10 and 11 are contour plots of the resulting nodal displacements and von Mises stresses, respectively. These results show the feasibility of performing the finite element simulations of this indentation problem.

The neo-Hookean material model (Equation 20) was chosen for initial simulations, because it only has one unknown and is already implemented in ANSYS. However, the resulting stress-indentation curves (Figure 12) did not have the same trend as the indentation force-depth measurements. More specifically, the numerical results show a weakly nonlinear stress-indentation depth relationship, while the measured indentation force-depth curves had exponential forms. The next step is to perform the simulations with the exponential hyperelastic material model (Equation 1), which is not implemented in ANSYS and requires a user-defined function. Work on this user-defined function is ongoing, and subsequent simulations will be performed using the slightly compressible version of Equation (1), which is defined as

\[
W = \frac{C_1}{2} \left( e^{C_2(\lambda - 3)} - 1 \right) + \frac{1}{4} d(J - 1)^2, \tag{25}
\]
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Figure 9. Force-indentation depth curve for the linear elastic-cubic nonlinear elastic test case with $\tilde{C}_1 = 1$ and $\tilde{C}_2 = 50$: (a) without measurement noise and (b) with normally distributed measurement noise with $\sigma = 0.02$.

Figure 10. Contour plot of nodal displacements (in mm)

Figure 11. Contour plot of von Mises stresses (in kPa)

2.3 Nonlinear optimization

Steps 1-3 of the sequence defined in Section 1.6 have been successfully implemented. That is, the finite element simulations can be run and modified from within MATLAB. These simulations have so far been run using representative data. Upon implementation of the user-defined material model based on Equation (25) in ANSYS, specimen-specific simulations will be performed using the previously described sequence of steps. At this point, the nonlinear optimization function will be added to the workflow so that material parameter values can be calculated from the experimental data.

3. Conclusions

A combined experimental and computational method has been proposed for determining the microscale mechanical properties of aortic valve leaflet layers. A microindenter has been built to measure indentation force and depth, and image processing tools have been developed to calculate leaflet layer heights from ultrasound images. Mathematical models have been developed for one-dimensional problems for one and two layer models. Numerical examples have been presented to illustrate the two cases for a two-layer one-dimensional problem, linear, which does not lead to a unique solution for the material parameters,
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and cubic nonlinear, which does lead to a unique solution for the material parameters assuming sufficient data points are available. A numerical method for two-dimensional problems has been proposed and a custom solver is currently being developed for this problem. Finite element simulations of the leaflet-indenter system have been performed for a simple hyperelastic material model and work is presently underway to implement the proposed exponential hyperelastic material model in ANSYS and repeat the simulations with this model. Upon completion of these simulations, specimen-specific simulations will be performed coupled with non-linear optimization to calculate the material parameter values for each of the leaflet layers.

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