12-21-2021

Mathematical Modeling of Stress Strain Behavior of Newborn Mouse Aorta with Genetic Defects

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Introduction

This project continues to fit the experimental data on the stress-strain behavior of newborn mice's ascending aorta. The stress-strain behavior of newborn mouse aorta is highly nonlinear because of its unique composition of elastin and collagen in the arterial wall. To mathematically describe this behavior, more strain energy functions of different biological materials were used in fitting. Multiple error functions were used to improve accuracy. K-fold cross-validation was applied in regression to avoid overfitting. In addition to the data of aorta with elastin knockout, those of aorta with lysyl oxidase knockout and fibulin 4 knockout are also evaluated in this project using the strain energy functions found. It is noteworthy that in this report, acronyms for these types of aorta are used. Elastin knockout = ELN KO, Fibulin 4 Knockout = FIB 4 KO, Lysyl Oxidase knockout = LOX KO, Wild Type = WT. Regression results from MATLAB shows that while the strain energy functions provide accurate fitting overall, improvements on the regression model can still be made to minimize the errors in cross validation. The strain energy and stiffness in the loading cycle are computed using the results returned by MATLAB: the strain energy for aorta with genetic defects is smaller than that for wild type samples. Comparing this difference may help to understand cardiovascular disease related to genetic defects.

Error Function Selection

The process of fitting minimizes the value of the difference between experimental data and theoretical data. Three error functions were used in fitting, and their fitting performance was tested. The three error functions are respectively:

$$e1 = \sum_{i=1}^{i=N} (\sigma_{zth(i)} - \sigma_{zexp(i)})^2 + (\sigma_{\theta th(i)} - \sigma_{\theta exp(i)})^2 \qquad \text{(Eqn. 1)}$$

$$e2 = \sum_{i=1}^{i=N} (\sigma_{zth(i)} - \sigma_{zexp(i)})^2 / \sigma_{zexp(i)} + (\sigma_{\theta th(i)} - \sigma_{\theta exp(i)})^2 / \sigma_{\theta exp(i)} \qquad \text{(Eqn.2)}$$

$$e3 = \sum_{i=1}^{i=N} (\sigma_{zth(i)} - \sigma_{zexp(i)})^2 / \sigma_{zexp_{avg}} + (\sigma_{\theta th(i)} - \sigma_{\theta exp(i)})^2 / \sigma_{\theta exp_{avg}} \qquad \text{(Eqn. 3)}$$

where *th* denotes theoretical value and *exp* denotes experimental value. The second and third functions are inspired by the error functions listed by Ferruzzi et al [1]. Compared to the first error function, the second and the third ones are normalized. According to Ferruzzi et al, the first error function is useful for fitting 2D planar stress and the second one is useful for fitting 3D stress in low strain regions; the third function is a compromise for fitting stresses at low strain region and at high strain region [1]. Indeed, the numerical performances while using e1 and e3 are both accurate but get erratic when using e2. Therefore, e3 was chosen to further regression fitting in this project.

Strain Energy Function

The aorta is modeled as an incompressible, nonlinear, anisotropic, and homogeneous cylinder with no shearing. The mathe expressions that govern the deformation are the deformation gradient (**F**), Cauchy strain (**C**), and Grain strain tensors (**E**):

$$\mathbf{F} = diag\{\lambda_r, \lambda_\theta, \lambda_z\} \qquad \text{(Eqn. 4)}$$

$$\mathbf{C} = diag\{\lambda_r^2, \lambda_\theta^2, \lambda_z^2\} \qquad \text{(Eqn. 5)}$$

$$\mathbf{E} = diag\{E_r, E_\theta, E_z\}$$

$$= diag\{1/2(\lambda_r^2 - 1), 1/2(\lambda_\theta^2 - 1), 1/2(\lambda_z^2 - 1)\} \qquad \text{(Eqn. 6),}$$

where where λ_r,λ_θ,and $\lambda_z$represent the stretch ratio. Stretch ratio is the ratio between deforme length and undeformed length, in r, θ, and z direction in cylindrical coordinates:

$$\lambda_\theta = r/R \qquad \text{(Eqn. 7)}$$

$$\lambda_r = \partial r/\partial R \qquad \text{(Eqn. 8)}$$

$$\lambda_z = l/L \qquad \text{(Eqn. 9)},$$

where r and l are deformed length and radius; R and L are undeformed length and radius.

Three strain energy functions were used for fitting in this project:

$$W_{valve} = B_0(exp(\frac{b_1 E_\theta^{\,2}}{2}) + exp(\frac{b_2 E_z^{\,2}}{2}) + exp(\frac{b_3 E_\theta E_z}{2}) - 3) \qquad \text{(Eqn. 10)}$$

$$W_{skin} = \frac{1}{2}(\alpha_1 E_\theta^{\,2} + \alpha_2 E_z^{\,2} + \alpha_3 E_{\theta z}^{\,2} + 2\alpha_4 E_\theta E_z) +$$

$$\frac{1}{2}C(exp(a_1 E_\theta^{\,2} + a_2 E_z^{\,2} + a_3 E_{\theta z}^{\,2} + 2\alpha_4 E_\theta E_z +$$

$$\gamma_1 E_\theta^{\,3} + \gamma_2 E_z^{\,3} + \gamma_3 E_\theta^{\,2} E_z + \gamma_4 E_\theta E_z^{\,2})) \qquad \text{(Eqn. 11)}$$

$$W(C, M^i)_{carotid} = \frac{c}{2}(I_c - 3) + \sum_{i=1}^{4}\left\{exp[c_2^i (IV_c^i - 1)^2] - 1\right\},$$

$$I_c = \lambda_\theta^{\,2} + \lambda_z^{\,2} + \frac{1}{\lambda_\theta^{\,2}\lambda_z^{\,2}}; IV_c = \lambda_\theta^{\,2} sin^2\alpha_o^k + \lambda_z^{\,2} sin^2\alpha_o^k \qquad \text{(Eqn. 12)}$$

They are respectively used for expressing the behaviors of heart valve [2], carotid [1], and skin[3]. Eqn. 12 is applied in this project because like the aorta, the carotid is also an artery. Eqn. 10 and 11 are applied because skin and heart valve contain collagen as the structural element under stress. Their strain energy function can be likely applied to the aortae of newborn mice, which also contain collagen. During fitting in this project, it is noteworthy that Eqn. 11 is simplified in two ways–setting all the γ's to 0 or setting $\gamma_1 = \gamma_2 = 0$ and $\gamma_4 = \gamma_5$ [3]. It is also

notable that Eqn. 12 is a four fiber family model that is used for fitting carotid. It contains an isotropic term and an anisotropic term. The isotropic term is often interpreted as the contribution of elastin and the anisotropic term is often interpreted as the contribution of collagen in the stress-strain relationship. The anisotropic term is modeled by a four-fiber family model and enforces symmetricity of the aorta wall.

Types of Genetic Knockout Samples

There are three types of genetic knockout newborn samples in this project: elastin knockout, fibulin 4 knockout, and lysyl oxidase knockout. Newborns with these types of genetic defects die after the day they are born [4]. While elastin knockout samples do not have elastin, fibulin 4 knockout and lysyl oxidase knockout samples have fragmented elastin in the artery as shown in Figure 1. Compared to the behavior of wild type samples, fibulin 4 knockout and lysyl oxidase knockout samples show a longer region of lower stress before they transition to higher stress. Moreover, stiffening (sudden increase of stress) occurs earlier for LOX KO and FIB 4 KO than wild type. This comparison is shown in Figure 2. Theoretically, fragmented elastin does not align with the direction in which mechanical test and pulsation are performed, thus locking the deformation when tensile stress is performed on the specimen.

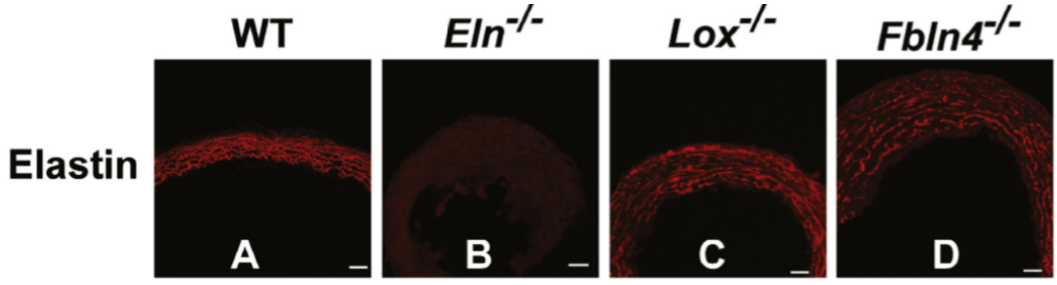

Figure 1[5]: Cross Sectional Images of New-Born Ascending Aorta. The red region indicates elastin.

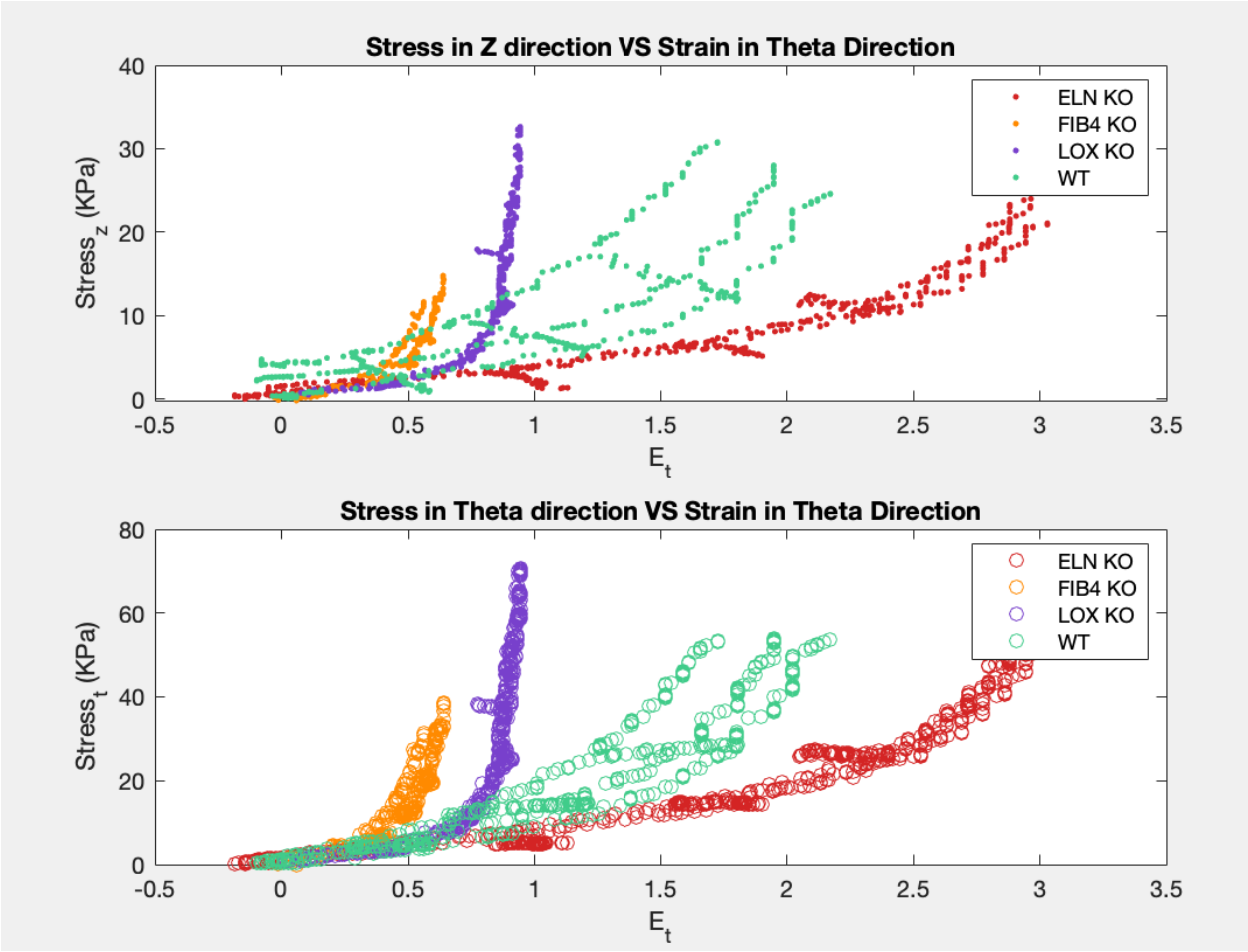

Figure 2: Stress-strain relations of σ_θ and σ_z plotted against E_t. Four types of aorta samples are included: elastin knockout (ELN KO), fibulin 4 knockout (FIB KO), lysyl oxidase knockout (LOX KO), and wild type as indicated on the legend.

Update on Regression Method

Previously, all the experimental data points were trained to find out the optimal parameters of the math models. In this project, k fold cross validation was used to find out the parameters. K-fold cross validation is a strategy that splits all the data points into different subsets. Each subset is taken as a test data set when the remaining *k-1* subsets are combined as the train data set. Once the parameters are found, they are used on the test set, and the performances of the model on the train set and test set are evaluated. Using cross validation in

finding out the parameters prevents over-parametrizing, which indicates that a model takes into account the noises of a dataset. A desired model returns a higher correlation coefficient on the test set than on the train set.

The results of the same sample given by fitting and cross validating are inconsistent in this project. A typical example of this is shown on table 1. In order to see if an error occurred during splitting the data, all the subsets were combined together for fitting, which gave the same result as the original fitting process. Furthermore, the stress-strain plots were plotted for both the cross validation trial and the fitting trial. Figure 3 shows an example of this comparison. Although inconsistent, the parameters returned by the fitting trial and cross validating trial return similar values.

When the performance of the model was re-evaluated on the entire dataset using the parameters associated with the least error in θ direction, the errors using the parameters returned by cross validation on the entire dataset increased dramatically, much larger than the error involved in the trial in which the parameters were returned. Table 2 shows an example.

The performance of the models also dropped when fitting FIB 4 and LOX KO data, as shown from Tables 3-5. For elastin knockout, the performance is consistent except for a few outliers.

Table 1: Parameters and Errors Returned by K(=5) fold Validation VS Parameters and Errors Returned by Fitting for a WT sample. The parameters returned here are the ones for Eqn. 11. Trial 1-5 indicates that five trials of cross-validation were performed on the dataset. The simplification sets $\gamma_1 = \gamma_2 = 0$ and $\gamma_4 = \gamma_5$

Sample 1								
parameters	trial1	trial2	trial3	trial4	trial5		Fitting	
alpha1 (KPa)	4.86	4.94	5.12	5.26	8.68		0.00	
alpha4 (KPa)	5.60	6.27	6.03	6.01	4.20		14.91	
c (KPa)	5.34	5.11	5.27	5.09	3.54		39.21	
gamma4=gamm	1.93	2.08	2.09	2.01	0.00		0.39	
alpha2 (KPa)	0.00	0.00	0.00	0.00	0.00		19.72	
a1	2.33	2.39	2.34	2.38	2.80		0.70	
a4	1.13	1.08	1.06	1.13	2.37		0.00	
a2	0.00	0.00	0.00	0.00	0.23		0.00	
errors	rmse_traint	rmse_testt	rmse_trainz	rmse_testz	r_traint	r_testt	rtrainz	r_testz
trial1	1.63	1.62	2.67	2.76	0.99	0.99	0.98	0.98
trial2	1.66	1.59	2.80	2.75	0.99	1.00	0.98	0.98
trial3	1.63	3.13	2.81	3.01	0.99	0.98	0.98	0.98
trial4	1.62	1.70	2.72	2.77	0.99	0.99	0.98	0.98
trial5	1.62	1.84	2.72	0.96	0.99	0.99	0.98	0.99
Fitting	3.92	--	2.70	--	0.99	--	0.95	--

Table 2: Parameters and Errors Returned by K(=5) fold Validation for a WT sample. The parameters returned here are the ones for Eqn. 11. Trial 1-5 indicates that five trials of cross-validation were performed on the dataset. The row "overall" indicates the model performance of parameters associated with the least error in the testing trial in θ direction. The simplification sets all the γ's to 0.

Sample 1								
parameters	trial1	trial2	trial3	trial4	trial5			
alpha1 (KPa)	12.25	11.98	12.11	11.99	9.89			
alpha4 (KPa)	10.55	10.49	10.41	10.37	10.51			
c (KPa)	2.23	2.42	2.40	2.45	1.25			
a1	0.57	0.56	0.56	0.55	0.73			
a2	0.00	0.00	0.00	0.00	0.00			
a4	0.53	0.52	0.53	0.53	0.64			
alpha2 (KPa)	0.00	0.00	0.00	0.00	0.00			
errors	rmse_traint	rmse_testt	rmse_trainz	rmse_testz	r_traint	r_testt	rtrainz	r_testz
trial1	3.94	4.33	2.39	18.81	0.99	0.99	0.99	1.00
trial2	3.97	3.91	17.97	2.53	0.99	0.99	0.99	0.99
trial3	3.95	6.73	2.40	2.80	0.99	0.98	0.99	0.98
trial4	4.06	3.87	2.46	2.30	0.99	0.99	0.99	0.99
trial5	4.06	6.11	2.46	1.84	0.99	0.98	0.99	0.99
overall	NaN	44.97	NaN	5.69	NaN	0.99	NaN	0.97

Table 3: Parameters and Errors Returned by K(=5) fold Validation for a FIB4 KO sample. The parameters returned here are the ones for Eqn. 11. Trial 1-5 indicates that five trials of cross-validation were performed on the dataset. The row "overall" indicates the model performance of parameters associated with the least error in the testing trial in θ direction. The simplification sets all the γ's to 0.

Sample 1								
parameters	trial1	trial2	trial3	trial4	trial5			
alpha1 (KPa)	20.62	20.69	21.23	18.56	9.57			
alpha4 (KPa)	10.07	9.98	9.97	9.19	9.36			
c (KPa)	0.11	0.10	0.11	0.17	0.08			
a1	6.70	6.86	6.61	6.02	8.70			
a2	0.00	0.00	0.00	0.00	0.00			
a4	2.99	3.14	3.13	2.87	2.70			
alpha2 (KPa)	0.00	0.00	0.00	0.00	0.00			
errors	rmse_traint	rmse_testt	rmse_trainz	rmse_testz	r_traint	r_testt	rtrainz	r_testz
trial1	4.66	4.11	1.78	2.30	0.87	0.90	0.90	0.92
trial2	4.45	4.88	2.19	1.90	0.88	0.87	0.91	0.90
trial3	4.54	4.48	1.73	1.86	0.88	0.87	0.90	0.88
trial4	4.37	5.36	1.69	1.90	0.89	0.83	0.90	0.86
trial5	4.37	6.71	1.69	1.41	0.89	0.89	0.90	0.93
overall	NaN	11.94	NaN	1.99	NaN	0.89	NaN	0.85

Table 4: Parameters and Errors Returned by K(=5) fold Validation for a LOX KO sample. The parameters returned here are the ones for Eqn. 11. Trial 1-5 indicates that five trials of cross-validation were performed on the dataset. The row "overall" indicates the model performance of parameters associated with the least error in the testing trial in θ direction. The simplification sets all the γ's to 0.

Sample 1								
Parameters	trial 1	trial 2	trial 3	trial 4	trial 5			
alpha1 (KPa)	0.00	0.00	0.00	0.00	0.00			
alpha4 (KPa)	7.80	7.88	7.87	7.89	6.41			
c (KPa)	0.04	0.03	0.03	0.03	0.00			
a1	0.70	0.72	0.72	0.73	1.07			
a2	0.55	1.16	0.54	0.82	0.00			
a4	0.45	0.41	0.45	0.44	0.75			
alpha2 (KPa)	0.00	0.00	0.00	0.00	0.00			
errors	rmse_traint	rmse_testt	rmse_trainz	rmse_testz	r_traint	r_testt	rtrainz	r_testz
trial1	11.68	11.63	9.22	32.31	0.94	0.95	0.90	0.95
trial2	11.55	10.79	31.36	9.36	0.95	0.95	0.94	0.88
trial3	11.56	18.16	9.24	10.26	0.95	0.86	0.90	0.87
trial4	11.60	11.60	9.24	9.34	0.95	0.95	0.90	0.90
trial5	11.60	39.64	9.24	7.11	0.95	0.90	0.90	0.90
overall	NaN	15.10	NaN	11.94	NaN	0.93	NaN	0.79

Table 5: Parameters and Errors Returned by K(=5) fold Validation for an ELN KO Sample. The parameters returned here are the ones for Eqn. 11. Trial 1-5 indicates that five trials of cross-validation were performed on the dataset. The row "overall" indicates the model performance of parameters associated with the least error in the testing trial in θ direction. The simplification sets all the γ's to 0.

Sample 1								
parameters	trial1	trial2	trial3	trial4	trial5			
alpha1 (KPa)	5.91	5.73	5.89	5.84	3.66			
alpha4 (KPa)	3.87	3.82	3.83	3.80	3.71			
c (KPa)	0.93	0.99	0.98	1.05	0.52			
a1	0.21	0.20	0.20	0.20	0.28			
a2	0.00	0.00	0.00	0.00	0.00			
a4	0.29	0.28	0.29	0.28	0.31			
alpha2 (KPa)	0.00	0.00	0.00	0.00	0.00			
errors	rmse_traint	rmse_testt	rmse_trainz	rmse_testz	r_traint	r_testt	rtrainz	r_testz
trial1	2.76	2.66	1.40	15.67	0.99	0.99	0.98	0.99
trial2	2.74	2.88	16.68	1.29	0.99	0.99	0.99	0.98
trial3	2.73	2.73	1.38	1.54	0.99	0.99	0.98	0.98
trial4	2.78	2.58	1.39	1.45	0.99	0.99	0.98	0.98
trial5	2.78	6.02	1.39	1.12	0.99	0.97	0.98	0.99
overall	NaN	64.60	NaN	3.31	NaN	0.99	NaN	0.97

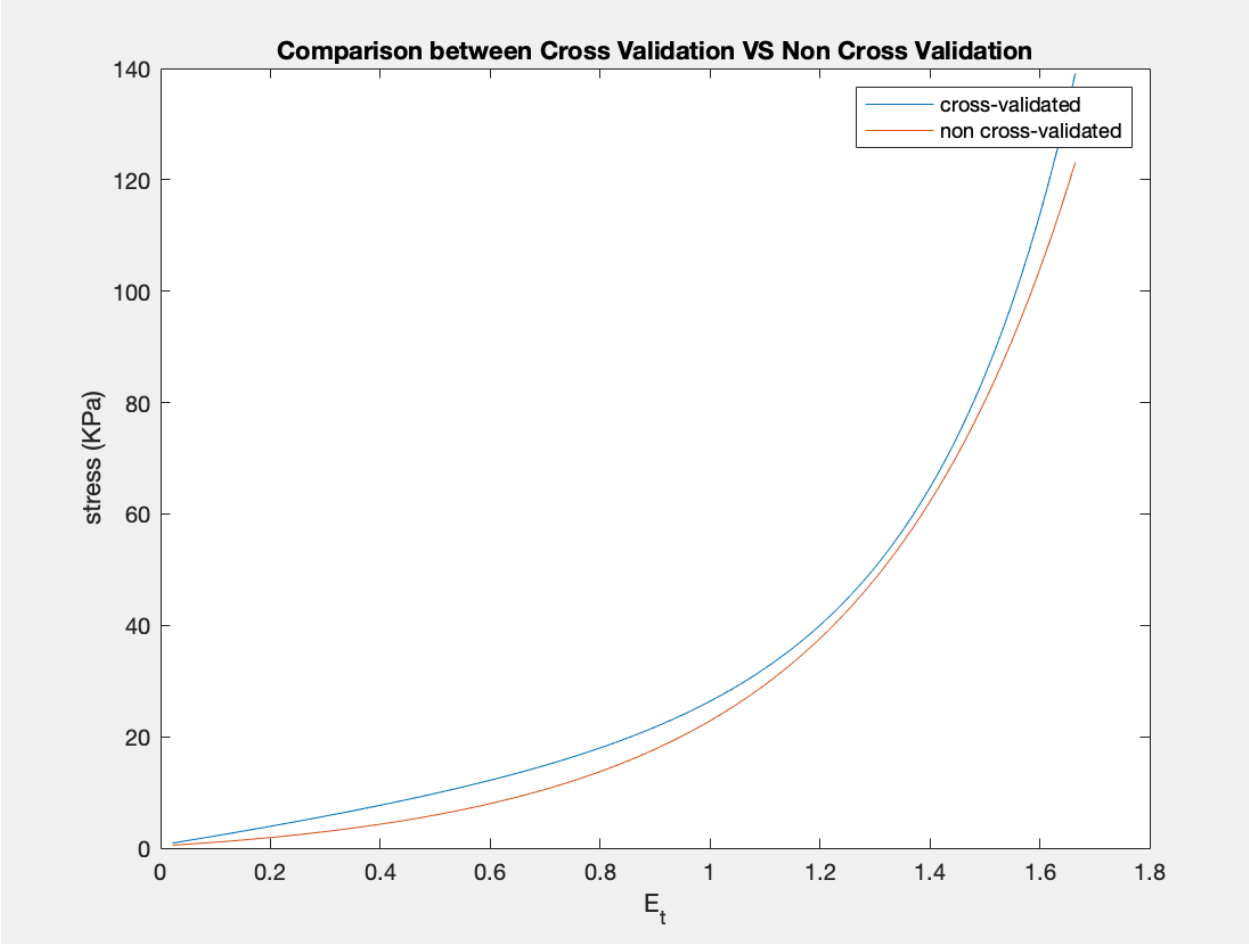

Figure 3: Comparison Between Parameters Returned by Cross-Validation and Fitting Plotted against One Pressure-Diameter Protocol. The protocol used Eqn. 11.

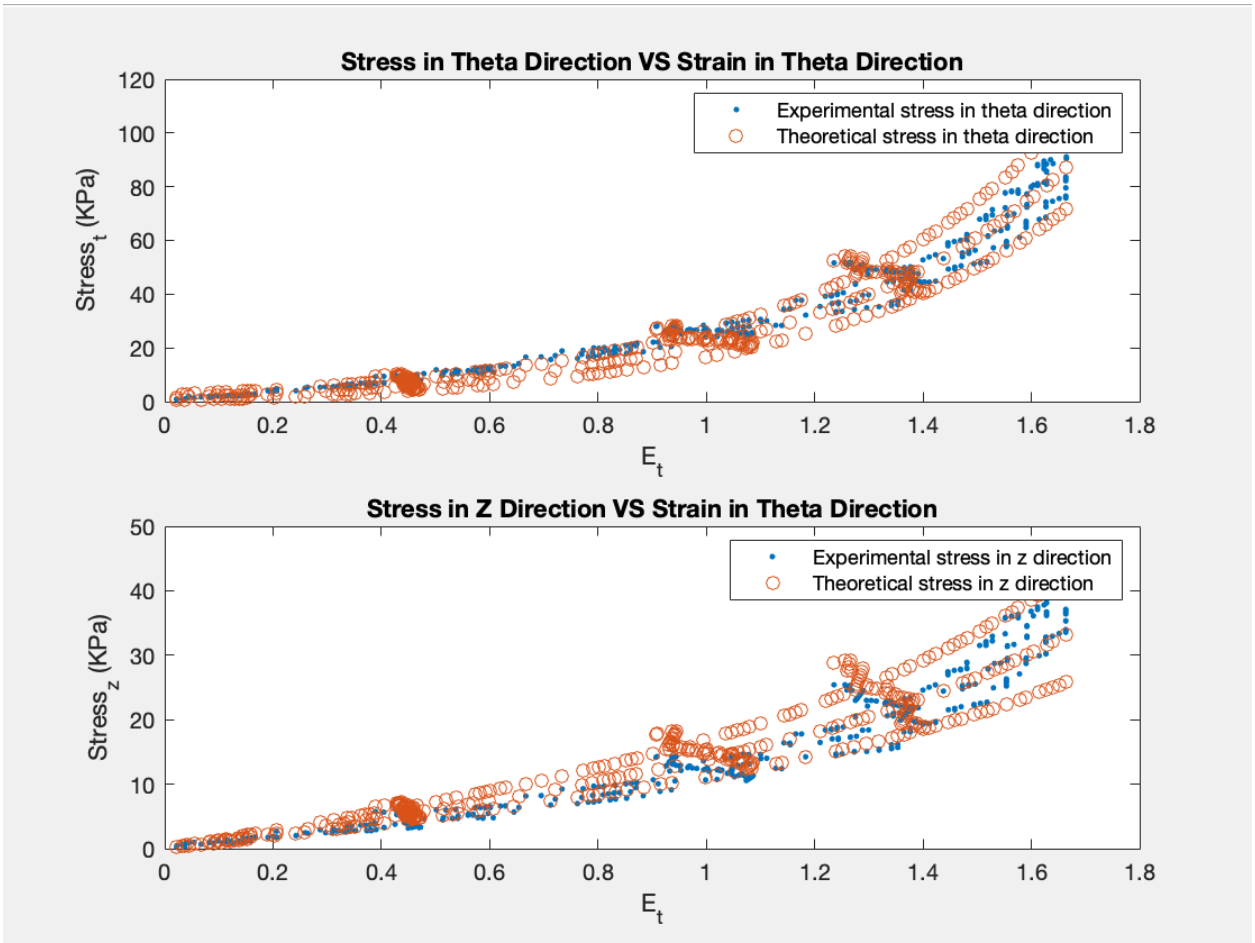

Figure 4: Stress Strain Behavior of a Wild Type Sample in a Fitting Trial. This trial used Eqn. 11.

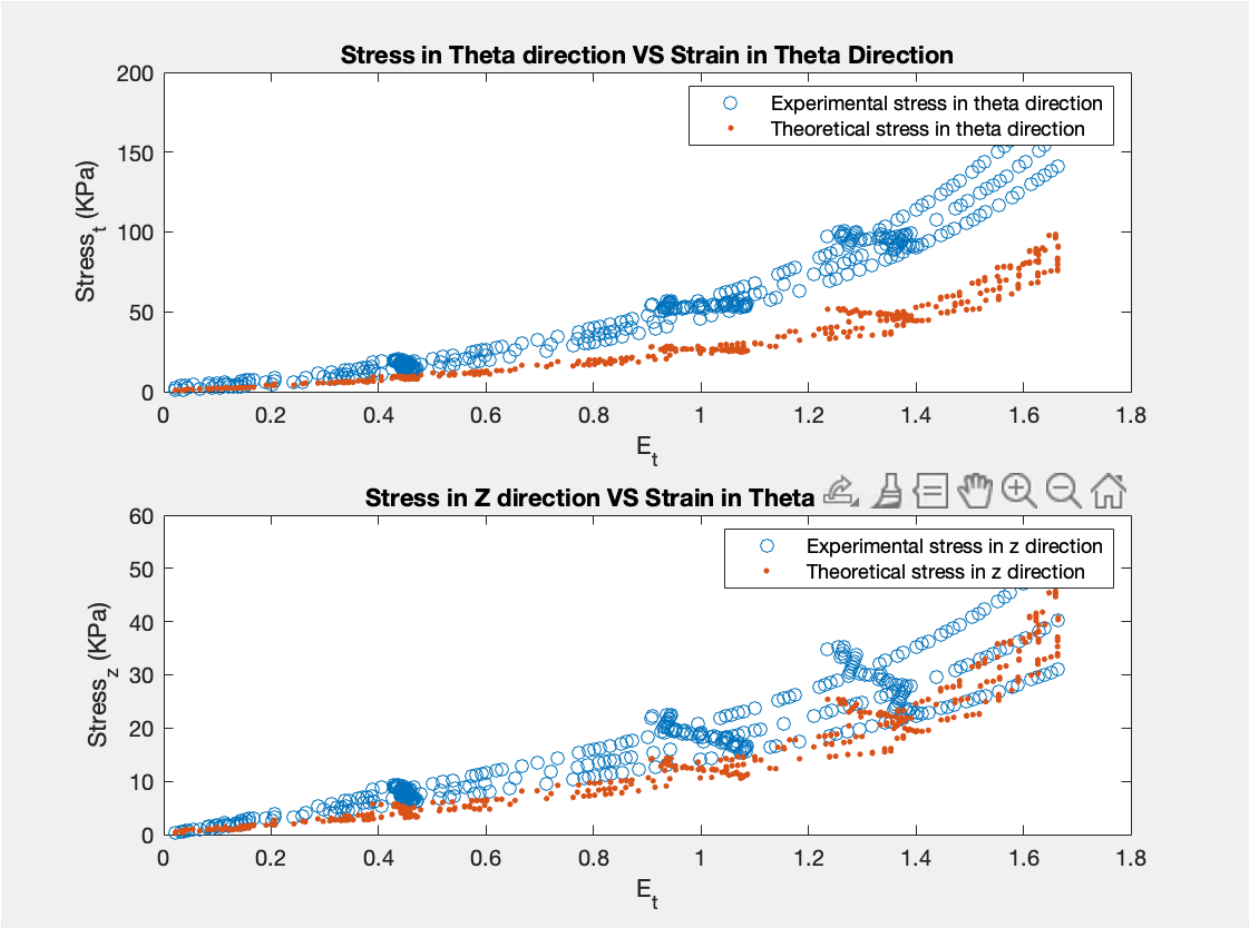

Figure 5: Stress Strain Behavior of a Wild Type Sample When Using the Parameters With Best Performance in Testing Trials in θ Direction.

Stiffness and Strain Energy

The stiffness and strain energy can be calculated after the parameters of the strain energy functions are obtained. Equations 13-14 are used to calculate the stiffness in θ and z directions [5]. The parameters with the highest accuracy in pressure-diameter direction found in cross validation trials are used to find stiffness and strain energy in each sample.

$$\zeta_\theta = \lambda_\theta^4 \frac{\partial^2 W}{\partial E_\theta^2} + \lambda_\theta^2 \frac{\partial W}{\partial E_\theta} \qquad \text{(Eqn. 13)}$$

$$\zeta_z = \lambda_z^4 \frac{\partial^2 W}{\partial E_z^2} + \lambda_z^2 \frac{\partial W}{\partial E_z} \qquad \text{(Eqn. 14)}$$

Strain energy contour plots of different types of samples (wild type, elastin knockout, fibulin 4 knockout, and lysyl oxidase knockout) are attached as Figures 6-9. It is notable that at higher strains, the strain energy for wild type samples is greater than that for KO samples. This behavior corresponds to their respective stress-strain energy curve. Strain energy, W, can be considered as the area under the stress-strain curve. For FIB4 KO and LOX KO samples, the flatness of the curve at low strain region contributes to a smaller area under the curve, thus resulting in smaller values of the contour plot. For ELN KO samples, the contribution of elastin at low strain region is lost; therefore compared to wild type samples, the strain energy contour plot shows smaller values as well.

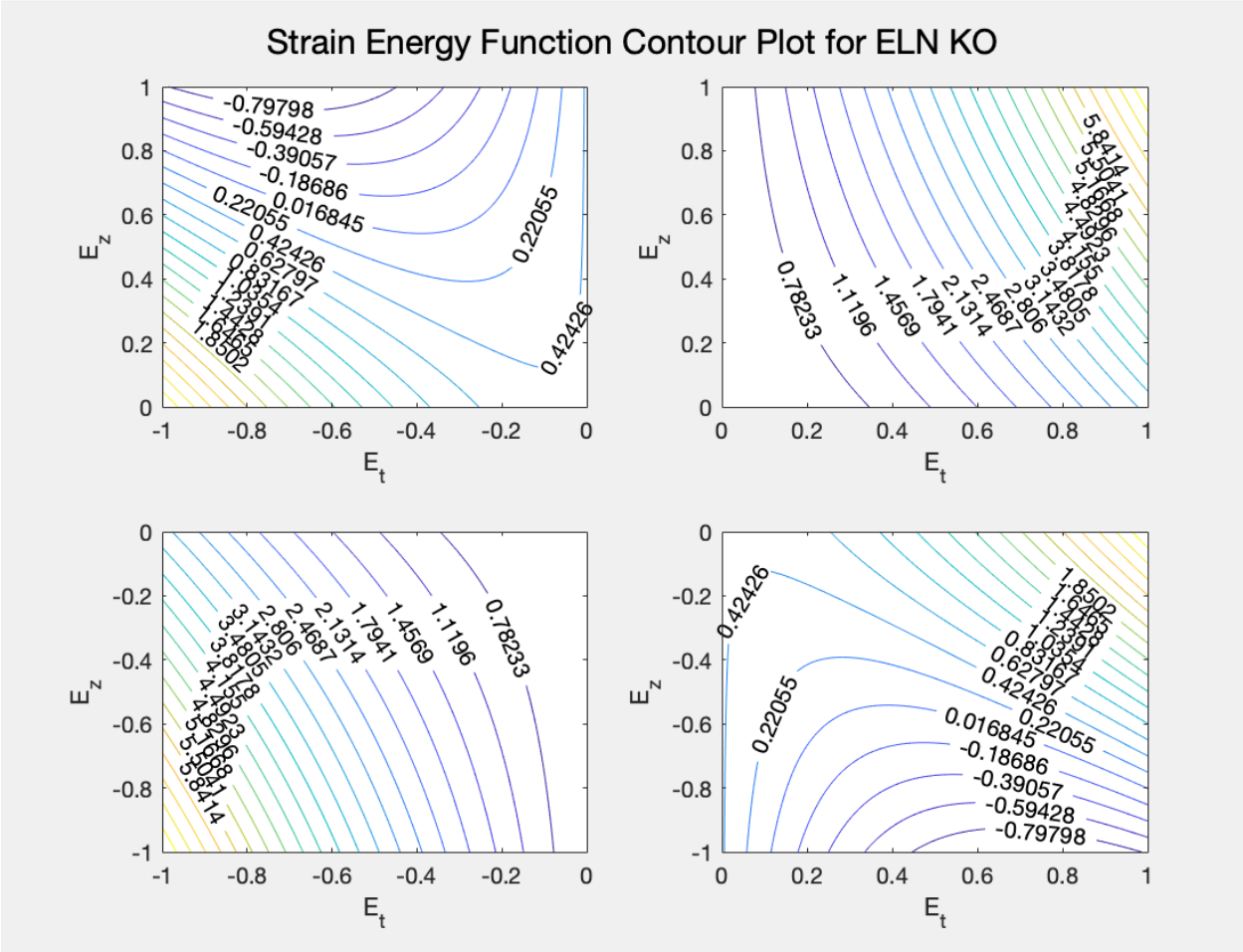

Figure 6: Strain Energy Contour Plot for ELN KO Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

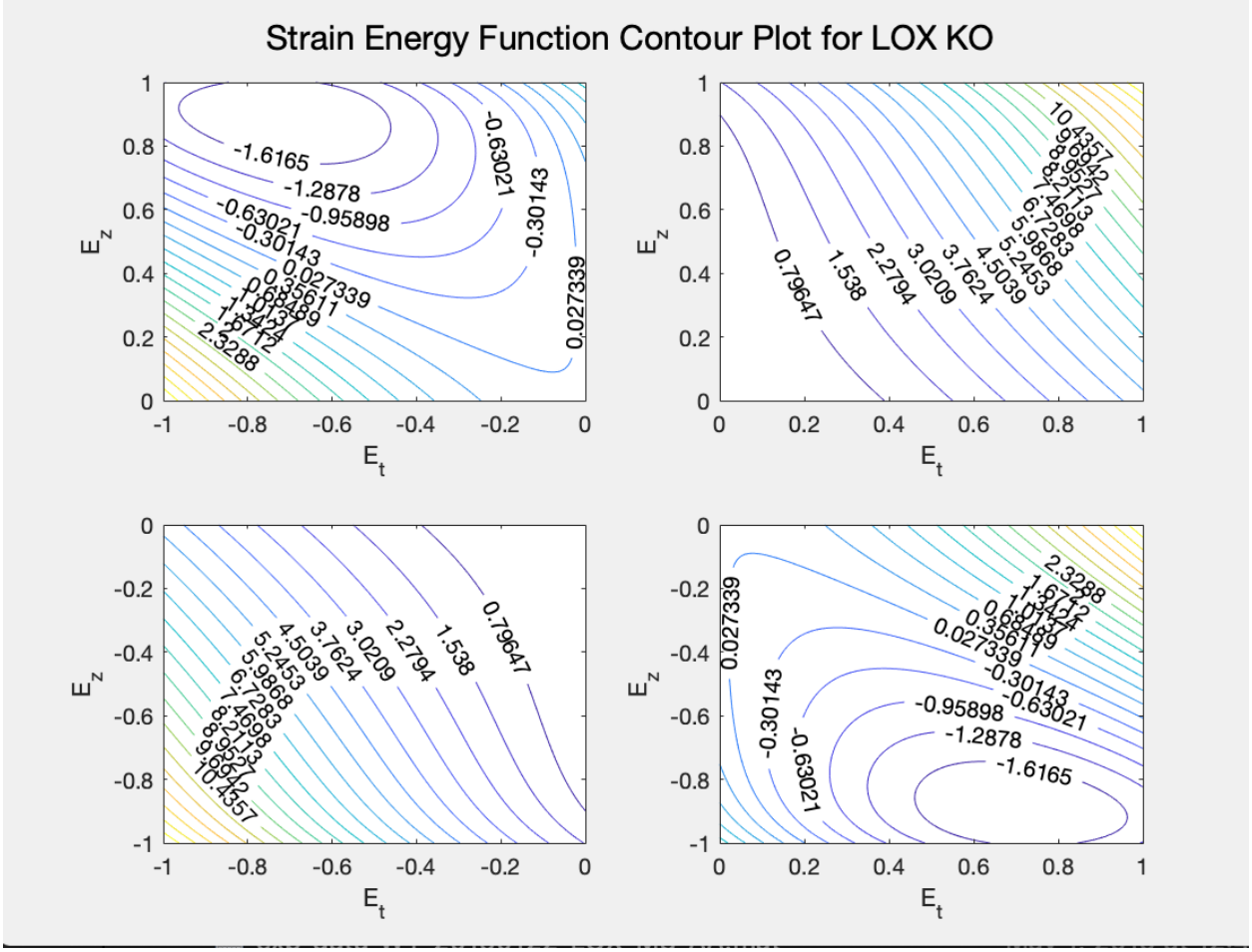

Figure 7: Strain Energy Contour Plot for LOX KO Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

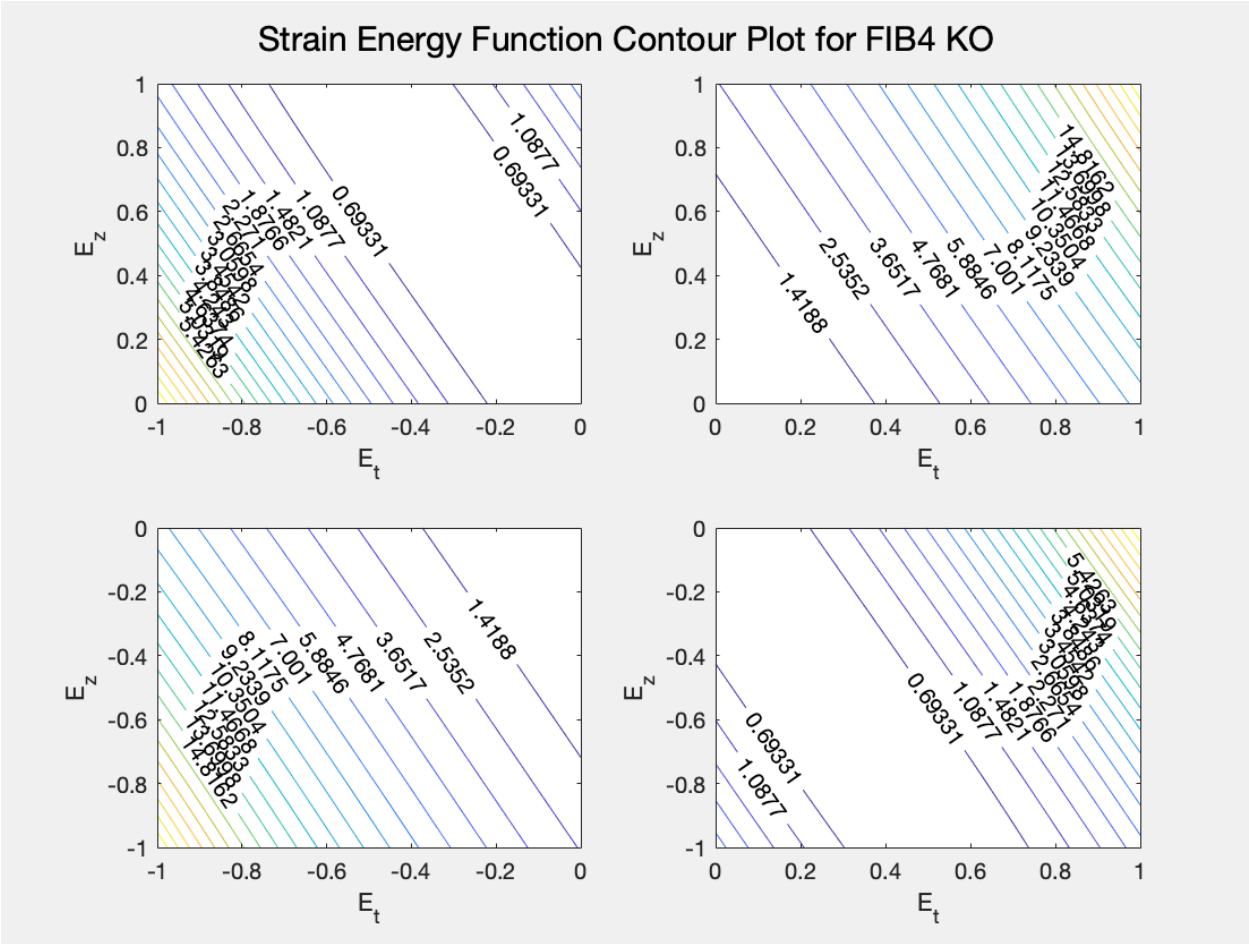

Figure 8: Strain Energy Contour Plot for FIB4 KO Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

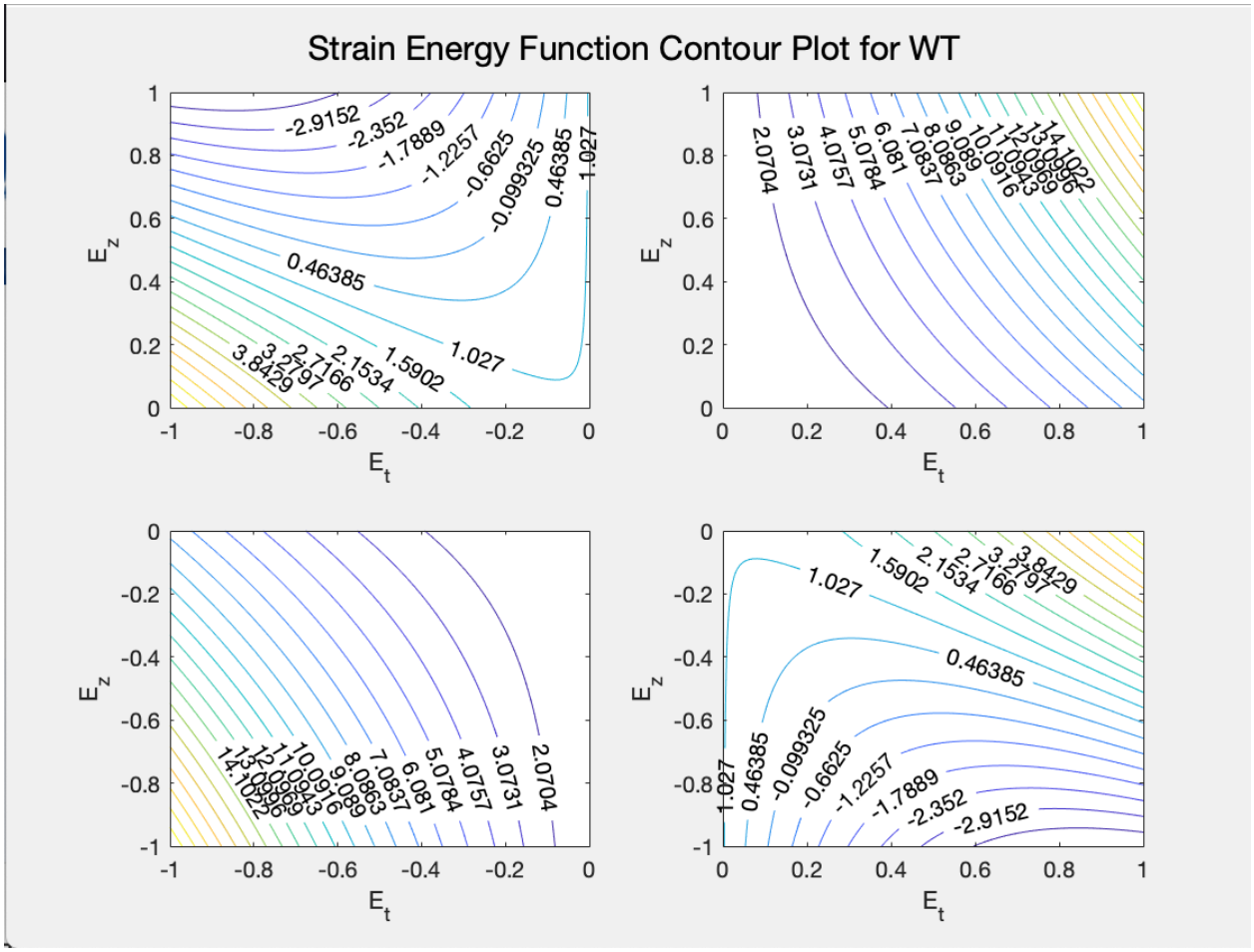

Figure 9: Strain Energy Contour Plot for WT Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

However, as suggested by Holzapfel et al, strain energy contour plots should be locally convex to enforce incompressibility–an assumption in modeling the stress-strain behavior of the aorta. [7] The contour plots shown above are not locally convex, which indicates either that the model is unrealistic or parameters from different starting vectors are needed.

The stiffness for four types of aorta is plotted, as shown from Figure 10-13.

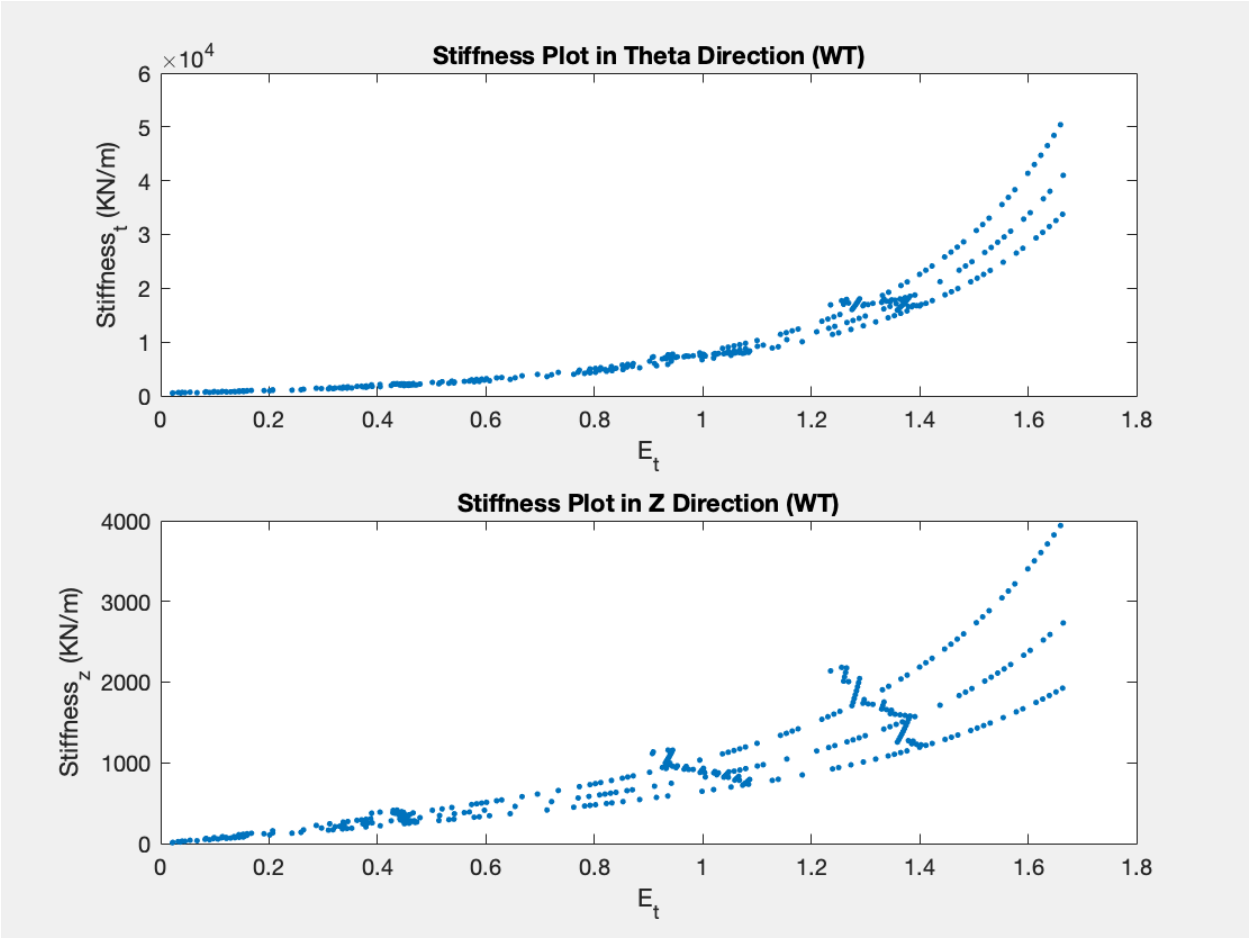

Figure 10: Stiffness VS Strain for a Wild Type Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

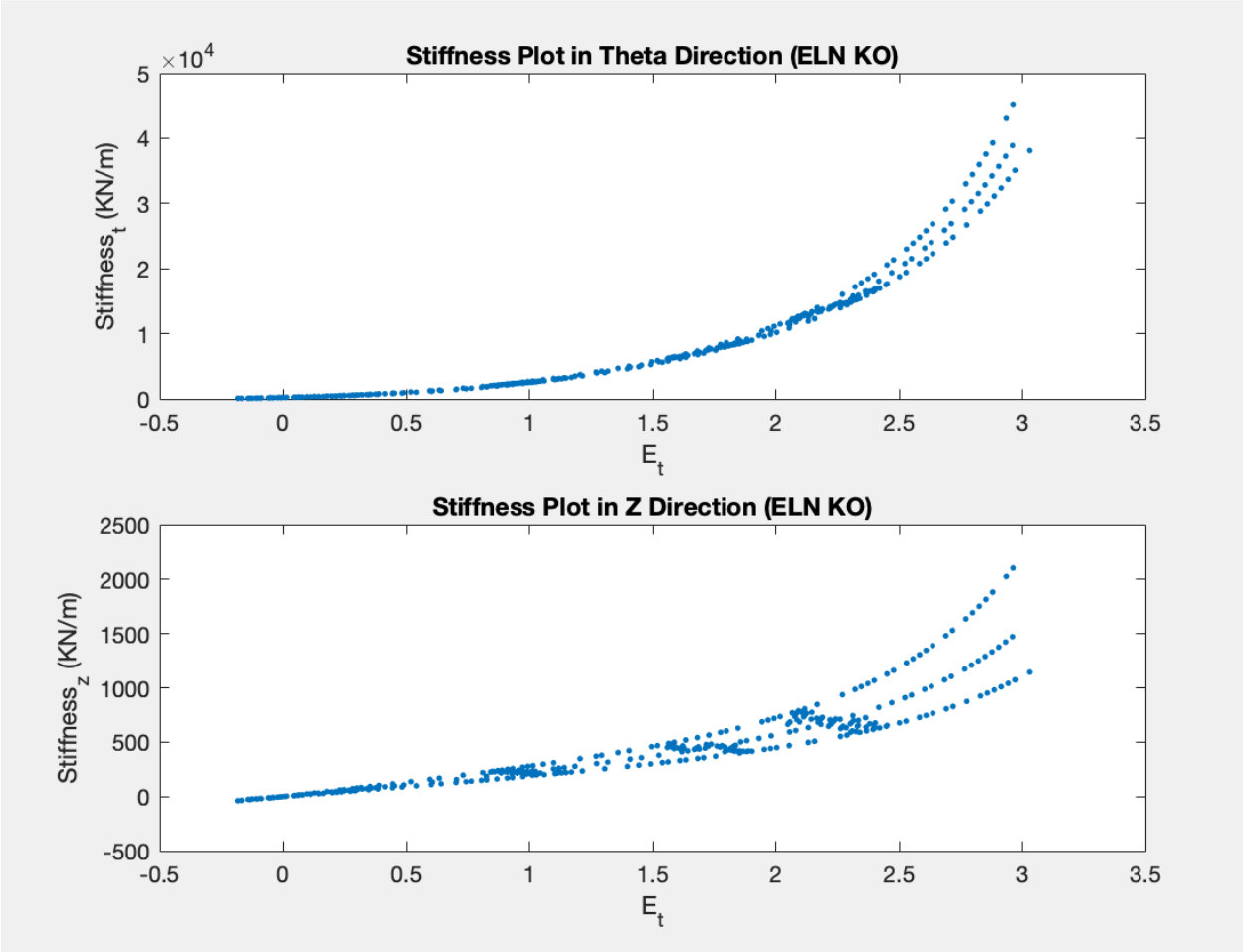

Figure 10: Stiffness VS Strain for an ELN KO Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

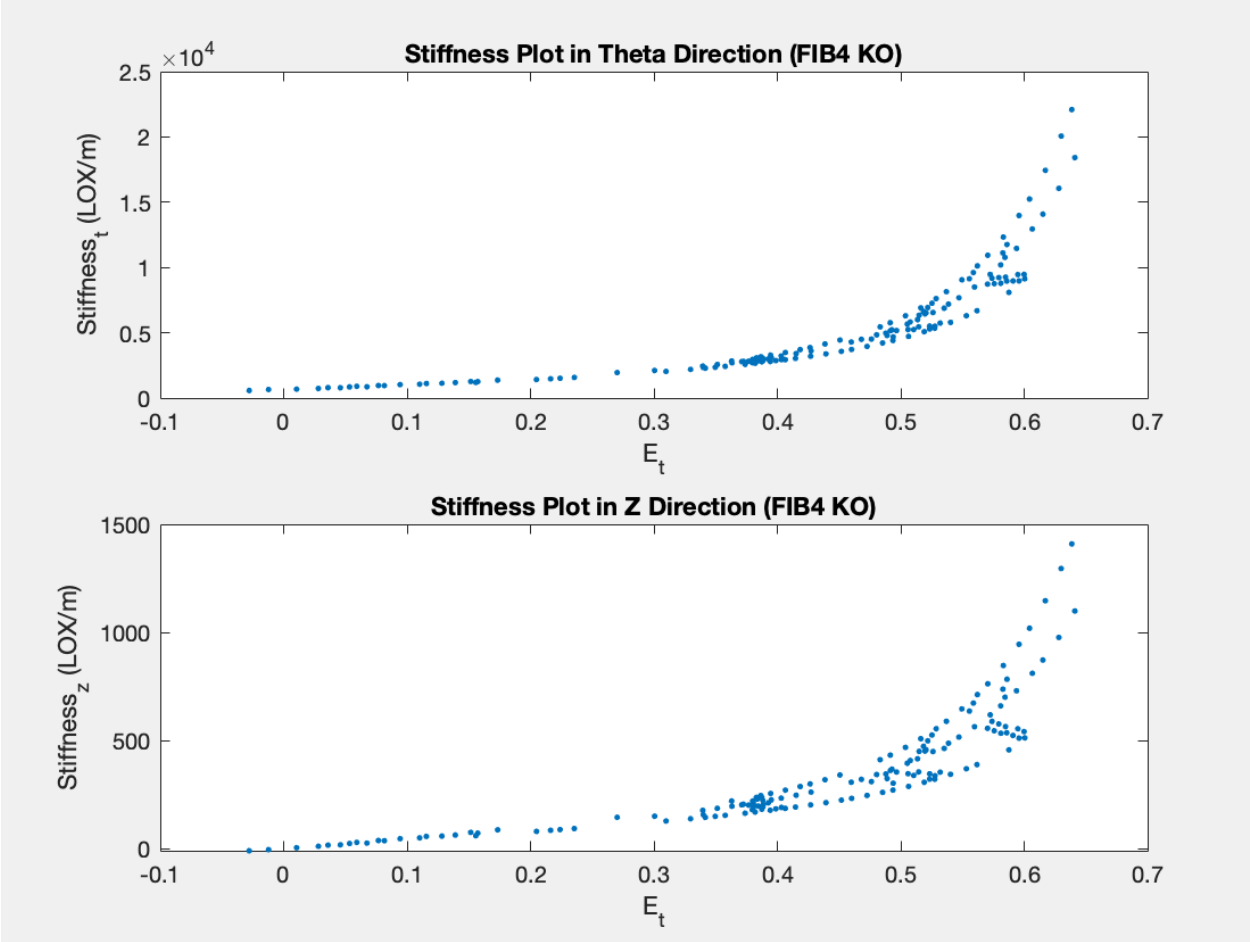

Figure 10: Stiffness VS Strain for a FIB4 KO Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

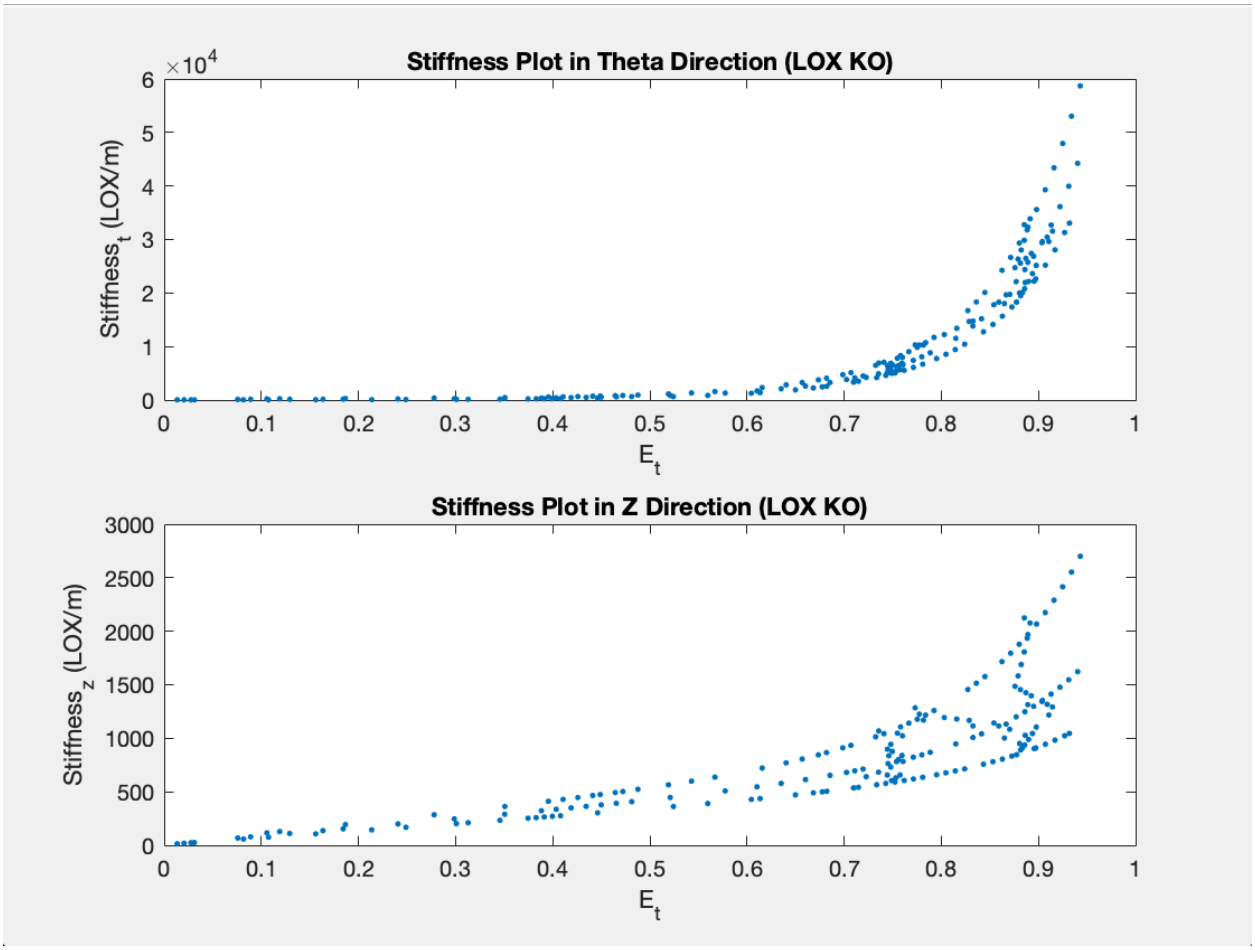

Figure 10: Stiffness VS Strain for a LOX KO Sample. The plot used the parameters returned by Eqn. 11 in cross-validation trials.

Discussion and Conclusion.

In conclusion, the strain energy functions accurately model the stress-strain relationship of wild type samples, but the performance becomes erratic for some of the KO samples. This project can be ameliorated in these following aspects:

1. Regression methods.

The regression method can be further updated by imposing a penalty function as inspired by [6]. Imposing a penalty function can result in lesser amount of zeros in parameters. Specifically, for a microstructural model as Eqn 6, this is useful because with nonzero parameters, this model can

be used to study the contribution of elastin and collagen separately. Additionally, this model uses the zero vector as the starting vector. This might be the reason that many parameters are zeroes. Different starting vectors can be used to find out the global minimum. Furthermore, the best fit parameters were found based on the best performance in θ direction. The parameters can also be found based on the sum of errors in θ and z directions.

2. Stiffness

In addition to plotting the stiffness versus strain curve, the stiffness of a sample can be calculated at physiological stresses. Calculating such values for aortae with different types of genetic defects helps to understand the stiffness in vivo and consequently cardiovascular disease, for example, hypertension.

3. Strain Energy

Finding out different parameters and the global minimum can potentially ameliorate the shape of strain energy plot and return ones that are locally convex. It is still unclear if Eqn. 4 and Eqn. 5 will return plots that are locally convex. Because they are used to model the stress-strain behavior of heart valve and skin, it is possible that the parameters they returned for samples in this project denote a scenario that is not naturally plausible to happen.

4. Energy during Loading and Unloading

It is also worthwhile to compare the energy in the loading and unloading cycle for different types of samples. This project only studies the loading cycle of the aorta. Comparing the difference in loading and unloading cycles can help to understand cardiovascular disease.

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