A VISCOELASTIC MODEL FOR HUMAN PROLAPSED VAGINAL WALL TISSUE

by

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ABSTRACT

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Pelvic organ prolapse (POP) affects thousands of elderly women each year. Improvements in surgical repair could benefit from the understanding of the biomechanical properties of the vaginal wall (VW) tissues to better tailor the needed repair. VW tissue property has been measured by uniaxial tensile test on excised fresh human anterior VW tissues. Data available, however, are limited to elastic modulus obtained in vitro. Recently, in vivo biomechanical data of VW from POP patients have been obtained by adapting a cutometer-like device, the BTC-2000™ (SRLI). The Voigt and Standard Linear models in conjunction with the framework of quasi-linear viscoelasticity theory have been developed to account for the creep response of the VW tissues. Using these models, we are able to reproduce the time course of the measurements of VW tissue uplift in response to the suction pressure increase from POP patients as recorded using the BTC-2000™. For the majority of the patient sets, the model revealed lower tissue damping and higher elastic response during tissue uplift in the VW tissue as a result of a predominant spring with a miniscule dashpot featured in both viscoelastic models.
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CHAPTER 1
INTRODUCTION

1.1 Background of Pelvic Organ Prolapse

Pelvic organ prolapse (POP), otherwise known as vaginal wall prolapse, has been shown to directly link to urinary incontinence and other pelvic floor disorders. This condition affects about one-third of premenopausal women and half of postmenopausal women. Approximately 135,000 women undergo surgery for urinary incontinence and 225,000 women undergo surgery for POP each year. Women more than 60 years old have a 25% chance of acquiring the causative symptoms. Usually vaginal childbirth would have minimal impact on POP but other factors combined, such as menopause, obesity, age, prior surgery, and genetic disposition, would elevate this risk [1].

Surgical repair can help correct the symptoms of the prolapsed vaginal wall. However, this is hampered by the fact that there is a lack of quantitative human tissue property data resulting in very little research in this area so far. One method to quantify if the patient has prolapsed vaginal wall tissue is to excise during surgery a small tissue sample and run biomechanical uniaxial stretch tests on it. However, the current problem in studying POP resides in the difficulty in procuring said samples of human vaginal wall tissue, as it could otherwise harm the patient. These tissue samples can be obtained during a reconstructive procedure when excess tissue that would be otherwise discarded is preserved for biomechanical testing. This situation results in very few samples available to quantify POP [2].

Thus one of the significant challenges is to test the biomechanical properties of the vaginal wall with no risk to the patient, and preferably pre-operatively to decide if tissue reinforcement might be necessary with a mesh or a biomaterial component. An innovative method has been developed that involves the BTC-2000™ (SRLI), a cutometer-like instrument
that can measure the uplift response of the vaginal wall tissue \textit{in vivo} without excising any tissue \cite{3, 4, 5}. This involves applying suction pressure, ramping to peak pressure on an area of the tissue to measure the uplift and record the creep recovery response after rapidly dropping the pressure to zero during a specific timeframe. After obtaining the experimental results, a more precise model is used to analyze the uplift and creep characteristics of the vaginal wall. This is done by applying viscoelastic properties of Voigt and Standard Linear model in conjunction with quasi-linear viscoelasticity (QLV) to predict the symptoms of vaginal wall prolapse. The closer these models can match the experimental results, the more effective the models can be in providing an accurate diagnosis of vaginal prolapse. Ultimately, such models can be used to design suitable and patient-adjusted biomaterials for tissue replacement or reinforcement.

1.2 Anatomy of the Anterior Vaginal Wall

The anatomy of the vaginal wall is vital into understanding prolapsed tissue. There are three main components of the vaginal wall: mucosa, muscularis, and adventitia, as shown in a histological diagram in Figure 1.1. The mucosa is composed of nonkeratinizing squamous epithelium overlying the lamina propria, a thin, loose connective-tissue layer that lines the inner surface of the anterior vaginal wall. The muscularis layer mainly consists of smooth muscle along with smaller amounts of collagen and elastin. Finally, the adventitial layer is a connective-tissue layer of collagen and elastin between the muscular wall of the vagina and the adjacent paravaginal connective tissue. The thickness of the vaginal wall from these layers is approximately 4 mm \cite{6}. The interaction between the levator muscles, which are part of the pelvic floor muscles, and connective tissue help support the vaginal wall \cite{7}. The anterior vaginal wall is displaced in relation with the base of the bladder with the urethra. Vaginal wall prolapse can induce bladder prolapse which in turn affects bladder function including continence and drainage \cite{8}. There is strong evidence to believe that one of the causes of POP is the loss of collagen architecture (i.e. looser collagen bundles, disorganized bundles and
collagen fibers, loss of connection of the collagen fibers to the elastin backbone) inside the adventitia tissue, causing the vaginal tissue to become gradually laxer and more distensible [8].

![Histological Diagram of the Vaginal Wall Tissue](image)

Figure 1.1: Histological Diagram of the Vaginal Wall Tissue with the thickness being ~4 mm [9]. Note there is no scale or dimensions present in this figure.

### 1.3 Literature Review: Vaginal Wall Studies

Currently, there are few studies that have reported on the mechanical properties of vaginal wall prolapse on human patients. Most of these research groups only analyze the elastic property of the tissue, even though the vaginal wall has a viscoelastic nature. Nevertheless, these studies can provide valuable insight into referencing the state of the prolapsed tissue. Another aspect to consider is the restriction in animal studies because animals (except for a few) are quadrupeds and some do not develop POP. Furthermore, most human studies have been done on cadaveric tissues or frozen/thawed tissues that lead to measurement errors. Only fresh tissues are suitable for analysis and this represents a practical limitation that can only be overcome by a close collaboration between clinicians and their bioengineering research team.

Abramowitch et. al defined the characteristics of the vaginal wall tissue by labeling the properties that are essential for testing. These properties include the tissue has to be characterized as anisotropic nature and that it exhibits viscoelastic instead of elastic properties, which some studies assumed [1].
In Alperin et al. study, they found that the deficiency of lysl oxidase-like1 protein (LOXL1) in mice can increase the chance of prolapse since this protein is an important factor in maintaining the structural integrity of the vagina and its supportive tissue. They analyzed the sample tissues of LOXL1 deficient mice and compared their data with the control Wild-type (WT) mice using uniaxial loading until failure at breakage. As a result of the increase distension of the tissue, they found that there was a 31% decrease in ultimate load at failure for LOXL1 deficient mice versus WT mice [10].

Moalli et al. studied whether using a rat pelvic specimen could be similar enough to humans to serve as a model for biomechanical studies. Under uniaxial testing, the rats had ultimate load at failure between 11.8 N and 15.3 N, linear stiffness from 2.1 N/mm to 4.8 N/mm, ultimate elongation from 5.4 mm to 11.0 mm, and energy absorbed to failure from 25.9 N-mm to 68.9 N-mm. Thus based on these animal studies and comparing to human patients, the structure of the rat vaginal wall and its attachments were similar to that of humans [11]. The same group studied the effects that loss of ovarian hormones estrogen and progesterone would have on the biomechanical properties following oophorectomy (OVX) surgery. They obtained 5 mm of tissue from the distal portion of the vaginal wall of OVX rats ranging from 4-6 months old and healthy control rats of the same age. The results showed a 40% decrease in linear stiffness and 30% decrease in ultimate load at failure comparing OVX and control rats. However, they noticed that an addition of estrogen or estrogen plus progesterone following removal of ovaries eliminated the decrease in linear stiffness and ultimate load in the vaginal wall, which usually occurred in women post-partum and could be related to an increase risk of POP [12].

Rahn et al. studied the effects of Fbln5−/− mice since this specific type of mice have a 91% chance of reaching severe tissue prolapse as a function of age. They compared these results to nonpregnant and pregnant WT mice. Rahn et al. shaped these tissues into a ring-like form with 2 wires attached to each end to perform uniaxial testing as the rings were distended. This procedure would allow the force from the tissue to relax and come to a new steady-state,
which would continue until tissue breakdown or distension reached a plateau. The results showed the Fbln5−/− prolapsed mice behaved similarly to the pregnant WT mice when analyzing the stress-strain curve: large increases in strain resulting in small increases in stress with decreased stiffness, decreased maximal load, increased distensibility, and increased vaginal diameter when compared to normal mice. Therefore, pregnant WT mice can potentially develop POP if left untreated. What was interesting to note was that Fbln5−/− mice were similar to nonpregnant WT mice with no significant differences in load at tissue failure, maximal stress, distance distended, strain, or linear stiffness [13].

One important animal study by Feola et al. researched the effect of collagen composition and alignment in vaginal wall tissue. It has been known that a higher collagen I/(III+V) ratio and increased alignment and compaction of collagen in direction of the applied forces are associated with superior mechanical properties. Also, many studies have confirmed that an increase in collagen III, which is associated with smaller fibrils and larger degree of distensibility, is found in women with POP, however, whether this is a cause or an effect of prolapse is not clear. Obtaining tissues from rhesus macaques from both nulliparous and parous subjects with nonhuman primates as the controls and performing uniaxial testing on them, they noticed that the nulliparous compared to the parous group was more nonlinear beyond 3% strain, have a 52% higher tangent modulus, and 3 times higher tensile strength than parous animals. They also found that the ratio of collagen I/(III+V) was similar between the two groups; however, there was a decrease in collagen alignment in parous animals. But again, the small sample size prevented a definitive correlation between collagen ratio and development of POP [14].

Rubod and Jean-Charles et al. obtained tissue samples from cadavers with stage 2 POP and those with non-pelvic organ prolapse (nPOP). Like other research groups, they did cyclic loading and uniaxial testing on the tissue. Comparing POP and nPOP data, the non-linear response was more pronounced in POP tissues, exhibiting a hyperelasticity nature under large
deformation. Jean-Charles et al. studied whether the location of the vaginal wall, anterior versus posterior, would make any difference in the results of biomechanical testing. Like Rubod’s research, they assumed the tissue to be hyperelastic with large deformation and to be incompressible, elastic, isotropic, and non-linear. Overall, there was a difference in mechanical properties for both anterior and posterior locations when comparing POP vs. nPOP patients with the posterior orientation having the most rigidity [15, 16].

Cosson et al. was one of the few research groups who used vaginal wall tissue from human subjects. They procured 2 cm x 2 cm of excess excised vaginal wall tissues from women undergoing prolapse surgery and did two biomechanical tests that both measure the force and degree of distension of the tissue until it ruptures: tension tests and bending tests. The tension tests were done with a dynamometer in which the tissue was subjected to uniaxial testing. The bending tests involved a piston to penetrate the tissue 1 cm to evaluate the cohesive strength of vaginal tissues and estimate the strength at breakage. For the distribution of tensile strength values, the rupture force was 44.28 N ± 20.29 with elongation of 23.22 mm ± 6.84. As for the distribution of bending strength value, the rupture force was 59.02 N ± 22.02 with elongation of 11.63 mm ± 4.18. The tensile and bending rupture force had extremes of 12-76 N and 14-130 N, respectively. Even though there were no other control tissues to compare the results with due to the unnecessary need of healthy women requiring surgery, these data were nevertheless vital as a reference of symptom of POP [17].

Lei et al. researched the differences in mechanical properties between pre- and post menopausal women by taking excised human vaginal wall samples from women undergoing transvaginal hysterectomy. After the tissues underwent uniaxial testing, they found little difference in ultimate load or relative elongation between the pre- and post-menopausal women. But there was a significant increase in elastic modulus in post menopausal women, possibly from an increase in collagen type III, which has been found to decrease the tangent modulus of tissues [18].
Zimmern et al. studied the biomechanical properties of the human anterior vaginal wall tissue subjected to different types of preservation within the span of two years. There were two groups studied: group 1 was samples immersed with saline and group 2 was wrapped in gauze and moistened with few drops of saline. These samples then underwent uniaxial tension as the results showed that the pre-transition strain, Young’s modulus, and ultimate tensile strength were significantly higher for group 2 than 1. One possible explanation was that hyaluronic acid found in connective tissue is known to retain water and cause swelling, which in effect has been shown to cause disorganized collagen fiber tissues in group 1. Therefore, tissue preservation during transport from the operating room to the biomechanical lab (less than 30 minutes) may influence biomechanical testing. Although the authors stated their preference for method 2, the important conclusion was to disclose the mode of tissue preservation since it can influence the results [19]. In a parallel study looking at the effect of Young’s modulus on long-term surgical outcome, Gilchrist et al. noted that the results were higher in samples transported in saline than wrapped in gauze [20].

Epstein et al. published a few reports on the biomechanical properties of POP studied with cutometer-like devices. One of their studies involved comparing biomechanical parameters of tissue elasticity and tissue extensibility of the skin compared with the left vaginal wall tissue. Using a DermaLab USB skin probe that can measure the elasticity, viscoelasticity, vaginal stiffness index, extensibility time, and retraction time, the left vaginal side wall was subjected to an increasing vacuum force until the tissue can pass through 2 infrared "gates." The results showed no statistically significant differences between the two groups; however, there were weak trends toward higher vaginal parity and lower incontinence severity index in the prolapse group. There was also significant difference in women with POP compared with the control group in all the parameters tested, confirming that women with POP had significantly more extensible vaginal tissue than women with normal pelvic support and no POP [3]. Epstein et al. then studied whether the impact of sacral colpopexy operation to correct POP by analyzing the
vaginal stiffness index before and after surgery. Comparing the results before and after sacral colpopexy within a 6-week follow-up, there was an increase in viscoelasticity (1.55 vs. 4.08 MPa), elasticity (2.26 vs. 3.43 MPa), and vaginal stiffness index (108.65 vs. 164.50 mbar). Patients also noted a decrease in POP symptoms and in urinary incontinence [4]. The final test Epstein et al. researched was to detect the differences in stiffness index and extensibility of vaginal sidewall tissue in women with and without POP. Using the above method, they found that vaginal stiffness index was an independent variable in assessing POP and that stiffer vaginal tissue was associated with less prolapse-related symptom distress. In agreement with other studies, their data confirmed that the loss of collagen/elastin tissue was directly responsible for POP condition. Overall, this study showed that the vaginal stiffness index was inversely correlated with POP distress severity after controlling for POP-Q stage of prolapse [5].

Considering how difficult it is to study POP from vaginal tissue, Gabriel et al. analyzed other tissues that have similar biomechanical properties to the vaginal wall. So their aim was to characterize and compare the biomechanical properties of tissues derived from vagina, abdominal aponeurosis, and skin. After uniaxial testing on the tissues, two parameters of nonlinear elasticity were calculated: C0 is the first half of the stress-strain curve at its beginning phase and C1 is the second half that characterizes the asymptotic nature at the end of the curve. Overall, the mean C0 and C1 values of aponeurosis and skin before rupture were higher than those of the vaginal wall. But aponeurosis, being more rigid and less extensible, had a lower ultimate strain values compared to both vagina and skin. The vaginal tissue was less rigid and more extensible than skin at large skin levels. Therefore, the biomechanical properties of all three tissues differed significantly since C0 and C1 values for skin and aponeurosis were much different than the vaginal wall [21]. Thus, one would have to study the biomechanics of the vagina itself in order to reliably estimate the extent of the disease process. There are no good substitute materials for the vagina wall tissue.
1.4 Objective of the Present Study

The objective of the present study is to analyze data taken from suction pressure of patients with pelvic organ prolapse \textit{in vivo} and apply viscoelastic properties to diagnose this condition. This will ultimately help in determining whether the vaginal tissue has POP damage and eliminate the need for excised tissue that at best provide post-operative data information. Overall, the tissue would be assumed to behave under viscoelastic conditions and would be applied using the Voigt and Standard Linear model. The accuracy of these two models would be dependent on the properties of the tissue itself including the nature of the creep and the maximum uplift of the vaginal wall tissue.
CHAPTER 2
THEORETICAL BACKGROUND

2.1 Problem Statement

The vaginal wall behaves in a non-linear, anisotropic, viscoelastic fashion [1]. Many researchers have analyzed the vaginal wall tissue with the assumption that the tissue is elastic. For example, the cutometer has been used by plastic surgeons to quantify the elastic property of facial skin [22]. In this work, we applied a cutometer-like instrument to study the viscoelastic property of human vaginal wall from patients with POP. Standard approaches to study the viscoelastic properties of a material is either to monitor a) the relaxation response in stress (or force) after the delivery of a step change in strain (or deformation); or b) the creep response in strain after the delivery of a step change in stress. Here, given the equipment availability, we chose the latter using the BTC-2000™ (SRI) as the cutometer to measure the creep response of the prolapsed tissue. However, the limit for the current design of the BTC-2000™ is a negative ramp pressure (150 mmHg) in a finite time duration of 6 seconds. As a result when comparing the tissue uplift in a ramped pressure versus constant pressure response as shown in Figure 2.1, the ramped pressure would have a more non-linear trend. Thus to compensate for this obstacle, a spring-dashpot model of Voigt and Standard Linear type in conjunction with QLV framework is used to analyze the experimental vaginal wall data.

![Figure 2.1: (a.) Increase, ramp pressure instead of (b.) constant pressure used on tissue. Note that the pressure (mmHg) applied by the BTC-2000™ is negative](image-url)
2.2 Literature Review: Viscoelastic Material Models

The human data available from the BTC-2000™ include pressure-time and tissue uplift-time recordings. We shall use pressure in place of stress and use uplift in place of strain in the following equation. A creep response in tissue uplift \( u \) after a step change in suction pressure \( \Delta P \) can be described by

\[
    u(t) = \frac{\Delta P}{E} \left(1 - e^{-\frac{t}{\eta}}\right)
\]

Eq. (2.1)

Where \( E \) and \( \eta \) are the effective spring and dashpot constants for a Voigt model:

![Voigt Model](image)

Figure 2.2: Components of Eq. 2.1 from Voigt model

Section 2.4 describes in more depth the concept of the Voigt model and the derivation of Eq. 2.1. The QLV framework featured in Appendix A can be modified as the pressure at current time \( t \):

\[
    P(t) = \int_{-\infty}^{t} G(t - \tau) \frac{\partial P^c[u(\tau)]}{\partial u} \frac{\partial u(\tau)}{\partial \tau} \, d\tau
\]

Eq. (2.2)

Where \( P(t) \) is the pressure in terms of time, \( G \) is the reduced relaxation response, \( P^c \) is the creep response function, and \( u(\tau) \) is the state of uplift. It can also be rewritten as the following in terms of the creep response:

\[
    u(t) = \int_{0}^{t} c(t - \tau) \frac{\partial P^c[u(\tau)]}{\partial p} \frac{\partial p(\tau)}{\partial \tau} \, d\tau
\]

Eq. (2.3)

Where \( u(t) \) is uplift in terms of time, \( c(t) \) is the normalized creep response, and \( p \) is the pressure load. Also, due to the data starting at initial time \( \sim 0 \), the integral would start from 0 seconds instead of \( -\infty \). By rearranging specific variables, this new uplift equation can be further broken down to be applied in conjunction with viscoelastic models:
\[
    u(t) \approx \sum_{n=0}^{N-1} \Delta p_n \left[ \frac{\partial u}{\partial p} \right]_{t=t_n} \int_0^t c(t-t_n-\tau) \, d\tau
\]
Eq. (2.4)

Here, \( \frac{\partial u^c}{\partial p} \) is the change in uplift over the change in pressure and the reciprocal of this variable can be defined as the Effective Young’s Modulus \( E \), which is described later on. The variable \( \tau \) in our case is assumed to be zero.

Using Eq. 2.4 and applying a ramp pressure load, one can analyze the viscoelasticity properties. Take for example \( n = 4 \), the pressure-time graph is separated into 4 even segments with \( t_0 \) representing one segment, \( t_1 \) the second segment, \( t_2 \) the third segment, and finally \( t_3 \) the fourth segment as shown in Figure 2.3a below. Once the pressure segments are applied, the proposed viscoelastic parameters \( E_n \) and \( \eta_n \) can be inputted to calculate the respective uplift \( u_n \) corresponding to each \( t_n \) as shown in Figure 2.3b. The final uplift is obtained by adding all \( u_n \) as shown in Figure 2.3c.

![Figure 2.3: (a) Applied ramp pressure on the tissue uplift with \( t_n \) representing \( n \) pressure segmentations. (b) Corresponding uplift curve from applied ramp pressure from using Eq. 1 from part a (c) Final uplift response from the superposition of all the uplift segments from part b](image-url)

As to determining which viscoelastic models are used to be applied in Figure 2.2b, the Maxwell, Voigt, and Standard Linear are the three conventional models used when modeling a
sample under viscoelasticity. These models are often depicted in terms of 1-D mechanical analog models with applied force at each end of the circuit containing two distinct components: a spring \((E)\) and a dashpot \((\eta)\). Each of the sections below further describes how Eq. 2.4 can be converted to their respective models.

### 2.3 Maxwell Model

The Maxwell model consists of the spring and dashpot are in series and is shown in the Figure 2.4 below. Eq. 2.5 first shows how the creep equation describe strain is in relation to stress while Eq. 2.6 modifies the equation of uplift in relation to the number of pressure segments.

![Maxwell model](image)

**Figure 2.4: Maxwell model**

\[
\varepsilon(t) = \frac{\sigma_0}{\eta} t + \frac{\sigma_0}{E} \\
\tag{Eq. (2.5)}
\]

\[
u(t) = \frac{P}{\eta} t + \frac{P}{E} \\
\tag{Eq. (2.6)}
\]

Where \(\varepsilon(t)\) is the creep that describes the strain of the model, \(\sigma_0\) is the stress, and \(\eta\) is the dashpot that describes the viscosity of the tissue, \(E\) is the spring that describes the Effective Young’s Modulus of the tissue, \(t\) is the time, \(u(t)\) is the uplift, and \(P\) is the pressure. However, the major problem with the Maxwell model is that when analyzing Eq. 2.6, the material would exhibit a creep that is linear, even though, as stated before, the vaginal wall features a non-linear, viscoelastic nature [23]. Therefore, other models such as the Voigt and Standard Linear model are being considered to analyze the experimental data.

### 2.4 Voigt Model

For the Voigt model, the spring and dashpot are connected in parallel as shown in Figure 2.5. The Voigt model of creep for strain in terms of stress is given in Eq. 2.7 [23]. Using
Eq. 2.4, one can modify this equation of uplift in relation to the number of pressure segments $n$ in Eq. 2.8. But for a more in-depth approach, this Voigt model can be derived from the QLV framework. From Eq. 2.4 above, the creep variable, $c(t - t_n - \tau)$, is dependent on the amount and placement of springs and dashpots in the viscoelastic model. For the Voigt model, the creep variable can be approximated by $1 - e^{-\frac{E_n}{\eta_n(t-t_n-\tau)}}$ where $E$ is the spring constant and $\eta$ is the effective viscosity. Therefore, assuming $\frac{\partial p}{\partial u} = E$, Eq. 2.4 can be rearranged to Eq. 2.8.

$$\varepsilon(t_n) = \frac{\sigma}{E_n} \left(1 - e^{-\frac{E_n\varepsilon_n}{\eta_n(t_n-t)}}\right)$$ \hspace{1cm} \text{Eq. (2.7)}

$$u(t_n) = \frac{(p_n-p_{n-1})}{\varepsilon_n} \left(1 - e^{-\frac{E_n\varepsilon_n}{\eta_n(t_n-t)}}\right)$$ \hspace{1cm} \text{Eq. (2.8)}

Analyzing this equation shows the nonlinearity of the creep when time increases. However, the problem with this equation is that it is bounded to a certain point since there is no initial elongation to account for the observed experimental data and there is a lack of relaxation response [23]. But for the purpose of this study, this initial elongation for our experimental data is particularly small and the relaxation response is beyond the scope of this project. Therefore, the Voigt model would be considered for our analysis purposes. But for a more accurate method, the Standard Linear method can also be considered.

2.5 Standard Linear Model

Finally for the Standard Linear model, an additional spring $E_x$ is added in series with the dashpot of the Voigt model. The depiction of this model is shown in Figure 2.6. The Standard Linear model of the strain in relation to stress is given in Eq. 2.9 while Eq. 2.10 describes the same model of the uplift in relation to the number of pressure segments $n$. Eq. 2.11 condenses Eq. 2.10 for a better analysis. With the additional spring, the QLV framework from Eq. 2.4
can confirm this uplift equation if we assume \( c(t - t_n - \tau) \) to be approximate to

\[
[1 - \left( \frac{1}{1 + \frac{E_n}{E_x}} \right) e^{-\frac{E_n}{\eta_n(E_n + E_x)}(t_n - \tau)}].
\]

Figure 2.6: Standard Linear model

\[
\varepsilon(t) = \sigma \left[ \frac{1}{E_n} + \left( \frac{1}{E_n + E_x} - \frac{1}{E_n} \right) e^{\left(-\frac{E_n E_x}{\eta_n(E_n + E_x)}(t_n - \tau)\right)} \right] \quad \text{Eq. (2.9)}
\]

\[
u(t_n) = (P_n - P_{n-1}) \left[ \frac{1}{E_n} + \left( \frac{1}{E_n + E_x} - \frac{1}{E_n} \right) e^{\left(-\frac{E_n E_x}{\eta_n(E_n + E_x)}(t_n - \tau)\right)} \right] \quad \text{Eq. (2.10)}
\]

\[
u(t_n) = \frac{(P_n - P_{n-1})}{E_n} \left[ 1 - \left( \frac{1}{1 + \frac{E_n}{E_x}} \right) e^{\left(-\frac{E_n}{\eta_n(E_n + E_x)}(t_n - \tau)\right)} \right] \quad \text{Eq. (2.11)}
\]

We determine the new spring \( E_x \), by the ratio with the original spring found in the Voigt model \( E \).

The ratio is defined as:

\[
\text{Ratio} = \frac{E_x}{E} \quad \text{Eq. (2.12)}
\]

Where the ratio can be big or small depending on how closely the shape of the final uplift equation approximates the experimental data. The ratio can range as large as 50 or as small as 0.01 of the spring \( E_x \). Different ratios are obtained and applied to Eq. 2.12 to find \( E_x \) in Figure 2.6. Expanding Eq. 2.10.:  

\[
u(t_n) = (P_n - P_{n-1}) \left[ \frac{1}{E_n} + \left( \frac{1}{E_n + \text{Ratio} E_n} - \frac{1}{E_n} \right) e^{\left(-\frac{E_n + \text{Ratio} E_n}{\eta_n(E_n + \text{Ratio} E_n)}(t_n - \tau)\right)} \right] \quad \text{Eq. (2.13)}
\]

If the ratio is large, the model would become stiffer where the \( E_x \) spring can be ignored and the Standard Linear Model would behave closely to the Voigt Model.

\[
u(t_n) = (P_n - P_{n-1}) \left[ \frac{1}{E_n} + \left(0 - \frac{1}{E_n} \right) e^{\left(-\frac{\text{Large} E_n}{\text{Large} E_n + \eta_n} (t_n - \tau)\right)} \right] \quad \text{Eq. (2.14)}
\]
The effective’s Young’s modulus \( (E) \) would be proportionate to the number of step functions \( (n) \); the larger the \( n \), the larger the slope of \( E \). Therefore, the SL equation behaves more like the Voigt equation. However if the ratio is small, closer to 0, then the spring would be less stiff as the resulting data would behave in a more elastic fashion and have a larger, staircase-like exponential slope trend.

\[
\mathcal{u}(t_n) = (P_n - P_{n-1}) \left[ \frac{1}{E_n} + \left( \frac{1}{E_n + \text{Small } E_n} - \frac{1}{E_n} \right) e^{\left( \frac{\text{Small } E_n}{E_n} \left( \frac{E_n \cdot \text{Small } E_n}{E_n + \text{Small } E_n} \right) (t_n - t) \right)} \right] \quad \text{Eq. (2.16)}
\]

\[
\approx \mathcal{u}(t_n) = (P_n - P_{n-1}) \left[ \frac{1}{E_n} + \left( \frac{1}{E_n} - \frac{1}{E_n} \right) e^{\left( \frac{\text{Small } E_n}{E_n + \text{Small } E_n} \left( \frac{E_n \cdot \text{Small } E_n}{E_n + \text{Small } E_n} \right) (t_n - t) \right)} \right] \quad \text{Eq. (2.17)}
\]

\[
\approx \mathcal{u}(t_n) = (P_n - P_{n-1}) \left[ \frac{1}{E_n} + (\sim 0) e^{\left( \frac{\text{Small } E_n}{E_n + \text{Small } E_n} \left( \frac{E_n \cdot \text{Small } E_n}{E_n + \text{Small } E_n} \right) (t_n - t) \right)} \right] \quad \text{Eq. (2.18)}
\]

\[
\approx \mathcal{u}(t_n) = \frac{(P_n - P_{n-1})}{E_n} \quad \text{Eq. (2.19)}
\]

The Standard Linear model is a combination of the Maxwell and Voigt model: the instantaneous elasticity characteristic of the Maxwell model combined with the nonlinearity of the creep of the Voigt model [23]. The Standard Linear method would only be used if the Voigt model does not provide sufficiently an accurate estimate to the experimental uplift response. Different ratios of \( E_x \) to \( E_n \) from Eq. 2.12 would be used to refine the accuracy of the Standard Linear model. Thus in this study, the tissue data would be modeled using Voigt model first due to its more simplistic nature and compare it with the Standard Linear model to see if there is any difference in analyzing the experimental with the viscoelastic data.

### 2.6 Rate of Deformation

The rate of deformation, known as \( a = E/\eta \), is a segment of the recovery phase, which is the area of the uplift/deformation-time graph from when the tissue reaches peak uplift, after applying maximum suction pressure, to residual uplift after a period of time. Usually different applied max pressure values can influence the rate of deformation. In this research, 50 mmHg would have a higher rate of deformation but with a lower peak uplift value. The converse can be
said with 150 mmHg applied pressure with a lower rate of deformation but with a higher peak uplift value. When analyzing the anterior vaginal wall and suprapubic regions, there would be different trends between the two in terms of biomechanical properties. For the anterior vaginal wall region when applying the viscoelastic models in conjunction with QLV framework, there should be a trend in plotting the patient data of different uplift values since viscoelasticity does apply here.
CHAPTER 3
MATERIALS AND METHODS

3.1 Obtaining Patient Data

Following IRB approval, 23 women with symptomatic stage 2-3 anterior vaginal wall prolapse requiring surgical repair were consented for the study. Patient data was taken and provided by Dr. Zimmern of University of Texas Southwestern Medical Center. Under anesthesia and with an empty bladder, a 10-mm diameter BTC-2000™ probe was applied to the prolapsed anterior vaginal wall at a fixed point at the level with the bladder neck area. A suction pressure ramp from 0 to -150 mmHg in 6 seconds was applied and the corresponding tissue uplift was measured by triangulation, within the probe, of a laser scan pattern, shown in Figure 3.1. The chamber was then returned to atmospheric pressure and the corresponding laser-measured tissue relaxation was recorded for 20 seconds as shown in Figure 3.2.

Figure 3.1: Suction pressure on an area of the vaginal wall tissue
The time, pressure, and deformation variables were obtained from the experimental data. Three types of pressure ramp data were used, 50, 100, and 150 mmHg, with the viscoelastic properties of the anterior vaginal wall (VW) region being analyzed.

### 3.2 Comparing and Modulating Patient Data of Uplift vs. Time

Before analyzing the viscoelastic properties of all the patient data, the overall nature or shape of the line after the peak uplift (recovery phase) has to be analyzed for any inconsistencies. Such inconsistencies include continually increasing creep, continually decreasing creep, or a combination of both of these trends (fluctuating between increasing and decreasing creep instead of reaching a plateau). These could impact the viscoelastic properties of the patient data when applying Voigt and Standard Linear models and are removed from this study. For consistency and the sake of clarity, only the patient data with the 150 mmHg as the max ramped pressure for the anterior vaginal wall region were analyzed. All the comparisons were done by Excel where time was on the x-axis and the pressure and deformation were on the primary and secondary y-axis, respectively. Another graph with uplift being dependent on pressure was also plotted out to observe the cyclic loading-unloading of the patient as well as to calculate the Effective Young’s Modulus.

Afterwards, the data has to be modulated so that the initial deformation and pressure starts at approximately 0 and ends with the pressure being ~150 mmHg. This usually occurs at the 0.5 second range and so, the pressure and deformation would start at 0 here and every time
point afterwards would be modulated by -0.5 seconds while keeping the pressure and deformation points intact. As a result for all the patient data, there was a total of 5.4 seconds with 0.1 second interval in between, consisting of 55 data points overall.

3.3 Obtaining Rate of Deformation $a = \frac{E}{\eta}$

After plotting the patient data of deformation/pressure vs. time using the method above, the peak uplift and residual uplift would be obtained. The peak uplift is the highest deformation value before the pressure quickly drops to 0. The residual uplift is when the creep from the recovery phase becomes constant or plateaus after the sudden drop in pressure. This can be seen in Figure 3.3.

![Figure 3.3: Important variables to calculate the viscoelastic properties of the tissue](image)

After obtaining both the uplift values, the rate of drop in uplift or rate of deformation $a$ has to be determined, which is the area of data points from the peak uplift to residual uplift. This data range would be run under Matlab to obtain a best fit line under Ezyfit program using exponential fit of $y(x) = a \exp(bx) + c$. The $b$ variable would be the rate of deformation $a$ used in solving the viscosity values for each $n$. 

20
3.4 Smoothing Out and Expanding Patient Uplift Data

One factor that has to be taken into consideration is the fact that the pressure-deformation curve has an irregular, rough nature and needs to be smoothed out. This can be done by using Matlab’s CurveFitting toolbox. The obtained experimental values would be smoothed out by Lowess (linear) method for the pressure data. The result would keep the uplift values of the x-axis intact, but the pressure values of the y-axis would be smoothed out to the amount of irregularities, such as any bumps along the experimental data point as a result of moving around of the patient, and obtain a new set of pressure values not far off from the original pressure data set. This new data set would now be able to use for viscoelastic analysis. However, the data set has to be expanded first to ensure the program can calculate the pressure-deformation data easier at higher step pressure functions. Therefore, the initial 55 data points would have to be expanded to ~440 data points. This is done by inputting a value in between each 55 data points and averaging the values before and after the insertion. These 55 data points would be doubled to ~110 points and would continue to expand using the same method until reaching ~440 data points. Now the new pressure-deformation experimental data would then be analyzed under the viscoelastic method using Voigt and Standard Linear model in Eq. 2.8 and 2.10, respectively.

3.5 Analyzing Patient Uplift Data using Viscoelastic Properties

All the calculations would be done under the VBA program in Excel for quick analysis. Along with the rate of deformation \(a\) calculated earlier, the Effective Young’s Modulus \(E_n\) and the viscosity \(\eta_n\) for each pressure segment \(n\) from \(n = 1\) to \(n\) can also be calculated using the VBA program. However, to calculate each \(\eta_n\) for each segment, the maximum viscosity \(\eta_{max}\) and the maximum Effective Young’s Modulus \(E_{max}\) have to be determined first. \(E_{max}\) is the last \(E\) value of \(n\) pressure segment. The calculation for each \(\eta_n\) is given in Eq. 3.2:

\[
\eta_{max} = \frac{E_{max}}{a} \quad \text{Eq. (3.1)}
\]

\[
\eta_n = \frac{E_n}{E_{max}} \eta_{max} \times \text{Percentage} \quad \text{Eq. (3.2)}
\]
As a result, \( a \) is vital in determining each viscosity for each pressure segment of \( n \).

The maximum viscosity should also be modulated since a strong dashpot can affect the overall fitting of the experimental data. In many patients, a large maximum viscosity value can produce an underestimation of the calculated uplift curve when compared with the experimental data. In fact, \( \eta_{\text{max}} \) have to be miniscule in which both the Voigt and Standard Linear equations would have a more elastic than a viscoelastic nature. To determine the new \( \eta_{\text{max}} \) value, different percentages of the original \( \eta_{\text{max}} \) would be used to predict the calculated trend with the experimental curve. Such percentages include using the original 100% of \( \eta_{\text{max}} \), 50%, and finally as low as 0.1%. Any percentage below 0.1% would not have a significant difference compared to the percentage of 0.1% when comparing the least square error and the trend of the calculated uplift curve between the two.

Now with all the viscosities and Effective Young’s Modulus for each \( n \) from 1 to \( n \) calculated, the final uplift result can be determined by applying the Voigt and Standard Linear viscoelastic properties. For this analysis, the \( E_x \) to \( E_n \) ratio of 1 was used in applying Standard Linear viscoelasticity to the data. Ratios of above 10 have an almost exact trend as the Voigt method shown in Eqs. 2.13-2.15. Any ratio below 1 is not significantly different to \( E_x \) to \( E_n \) ratio of 1 when comparing the error and observing the trend of the calculated uplift between the two. Therefore, an \( E_x \) to \( E_n \) ratio of 1 would suffice. Again, obtain the uplift data for each data using the following \( n \) step pressure segmentations: 4, 10, 15, 20, 25, 30, 40, and 50. Then compare each calculated pressure segment uplift data with the experimental data by plotting them on the same graph and observe any differences. Further analysis of comparing the calculated uplift with the experimental data uplift can be done by using the following least square error function:

\[
\text{%Least square percent error} = \frac{\sum_{q=1}^{Q} |u_{\text{mod}}^q - u_{\text{exp}}^q|}{\sum_{q=1}^{Q} |u_{\text{exp}}^q|} \times 100\% \quad \text{Eq. (3.3)}
\]

Where \( u_{\text{mod}}^q \) is the model predicted uplift, \( u_{\text{exp}}^q \) is the experimental uplift measurement, and \( Q \) is the total sampling points. Finally, gather all the least square percent error data from each
segment and plot them as a function of number of segments to observe any decrease in error for increase in step pressure segment. A low least square percentage error would show that the viscoelastic model can predict the experimental data with increasing $n$. 
CHAPTER 4

RESULTS

4.1 Experimental Data

4.1.1 Pressure-Time Patient Data

The patient data with the time, pressure, and deformation information has to be first visually analyzed to uncover any inconsistencies in the creep as well as any distinct comparisons within each patient group. The patient data containing these inconsistencies, as described in Section 3.2, would be removed from the study as they are not typical for a creep response. An ideal tissue uplift response from ramp suction pressure is shown in Figure 3.2b. Out of the entire patient data received, only 22 data set from the anterior vaginal wall region and 20 data set from the suprapubic region were picked in terms of their consistency. Figure 4.1 and Figure 4.2 shows typical creep response from the anterior vaginal wall and suprapubic region patient data, respectively, used in this study.

![Figure 4.1](image)

Figure 4.1: Typical patient response for 150 mmHg data in anterior VW region provided by Dr. Zimmern
Figure 4.2: Typical patient response for 150 mmHg data in SP region provided by Dr. Zimmern

4.1.2 Loading-Unloading Cyclic Data

A typical load-unloading cyclic curve in terms of pressure-uplift was observed as shown in Figure 4.3. In other words, this graph represents the rate of tissue deformation during the upper portion and after the lower portion pressure application. Both the anterior vaginal wall region (blue) and the suprapubic region (red) behaviors are shown in order to visualize the differences.
Figure 4.3: Pressure-Uplift responses for anterior VW region (blue) and SP region (red)

4.2. Viscoelasticity Results-Voigt

In this section, the uplift results, using the Voigt equation model, are analyzed, using step uplift segmentations of $n = 4, 10, 15, 20, 25, 30, 40,$ and $50$. Different $\eta_{\text{max}}$ percentages of 100%, 50%, and 0.1% of the maximum viscosity to determine the uplift are also compared and analyzed. The resulting uplift vs. time plots are compared with the experimental data set of the same scale. Figures 4.4-4.6 shows Patient 66 results using the Voigt model of the anterior vaginal wall patient data with the cited $\eta_{\text{max}}$ percentages.
Figure 4.4: Patient 66 VW Voigt data with $\eta_{\text{max}}$ percentage of 100%

Figure 4.5: Patient 66 VW Voigt data with $\eta_{\text{max}}$ percentage of 50%
4.3. Viscoelasticity Results-Standard Linear

In this section, the uplift results using the Standard Linear model equation are analyzed using step uplift segmentations of \( n = 4, 10, 15, 20, 25, 30, 40, \) and 50. The percentage of 0.1% of the maximum viscosity is only considered since it has the least amount of error. The resulting uplift vs. time plot is compared with the experimental data set of the same scale with an \( E_s \) to \( E \) ratio of 1. Below in Figure 4.7 shows the Standard Linear model results of the same anterior vaginal wall patient data.

Figure 4.6: Patient 66 VW Voigt data with \( \eta_{\text{max}} \) percentage of 0.1%
Figure 4.7: Patient 66 VW SL data with $\eta_{\text{max}}$ percentage of 0.1% and $E_s$ to $E$ ratio of 1

4.4 Error Comparisons

The least square error from Eq. 3.3 can be used to determine the effectiveness of the Voigt and Standard Linear models for each pressure segment step function $n$ with the experimental data. Only the Standard Linear model with max viscosity percentage of 0.1% is compared with the given data set. The different $\eta_{\text{max}}$ percentages were also compared and are shown in Figure 4.8 for the anterior vaginal wall region.
Table 4.1 summarizes the error of the VW region using these four methods from Figure 4.8 for each \( n \) segmentation.

Table 4.1: Average Least Square Error Percentage for VW region

<table>
<thead>
<tr>
<th></th>
<th>4</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>16.49%</td>
<td>11.01%</td>
<td>8.83%</td>
<td>9.22%</td>
<td>10.05%</td>
<td>9.64%</td>
<td>8.61%</td>
<td>9.72%</td>
</tr>
<tr>
<td>B</td>
<td>15.84%</td>
<td>8.03%</td>
<td>4.87%</td>
<td>4.83%</td>
<td>5.53%</td>
<td>5.04%</td>
<td>3.88%</td>
<td>5.03%</td>
</tr>
<tr>
<td>C</td>
<td>17.02%</td>
<td>7.32%</td>
<td>4.19%</td>
<td>3.39%</td>
<td>3.04%</td>
<td>2.49%</td>
<td>1.83%</td>
<td>1.54%</td>
</tr>
<tr>
<td>D</td>
<td>17.06%</td>
<td>7.33%</td>
<td>4.18%</td>
<td>3.38%</td>
<td>3.04%</td>
<td>2.48%</td>
<td>1.81%</td>
<td>1.53%</td>
</tr>
</tbody>
</table>

For the 22 anterior vaginal wall patient data sets, the average least square error was compared for each of the specific \( n \) superpositions. This was to determine the smallest possible \( n \) that can be calculated once the error plateaus and to reduce any need of increasing \( n \) any further for the 22 patient data sets. Figure 4.9 compare and contrasts the average error for a specific \( n \) in the anterior vaginal wall region for both Voigt and Standard Linear models of different max viscosity percentages.
Figure 4.9: Comparison of least square error of the anterior VW area of the average of 22 patients for each segment $n$
CHAPTER 5
DISCUSSION

The objective of this study was to determine, if using selected viscoelastic properties, one can predict the experimental uplift vs. time data. This was done by applying ramp step pressure increases $n$ and applying Voigt or Standard Linear model using a QLV framework [24]. Before analyzing these patient data, the biomechanical properties of the anterior vaginal wall region were compared with the suprapubic region as the control. Such properties include the trend of the creep line, rate of deformation, peak uplift, and residual uplift. The distinctive trends between these two regions can be seen in the pressure-time experimental graph summaries from Figures 4.1 and 4.2. Here, the anterior vaginal wall region has more variation, for all the patients, compared with the suprapubic region. Overall, the rate of deformation is higher for the suprapubic region but has a lower peak and residual uplift compared with the anterior vaginal wall region. The rate of deformation ranges from 0.55-5.40 vs. 2.12-6.17, peak uplift from 1.03-4.59 mm vs. 1.57-4.72 mm, and residual uplift from 0.38-2.34 mm vs. 0.03-0.38 mm for anterior vaginal wall vs. suprapubic region, respectively. In Figure 4.3, there is more loading-unloading applied to the pressure-uplift curve to the anterior vaginal wall region as opposed to the suprapubic region. This shows that there is a higher uplift applied in the anterior vaginal wall vs. the suprapubic region given the same amount of pressure applied on these regions, indicating decreased stiffness for the prolapsed VW tissue. Importantly, the lack of correlation between the two tissues results from different biomechanical properties.

When observing Figure 4.1, each anterior vaginal wall patient graph has a distinct profile, different from one another, as opposed to a more uniform, predictable trend for the suprapubic region (Figure 4.2). This shows each prolapse patient has a different vaginal wall biomechanical property distribution. A reason for this phenomenon could be that the suprapubic
area for each patient has similar structure and biomechanical properties. Supporting this observation, each of them has healthy intact fascia underneath this region [8]. This is opposed to the anterior vaginal wall where the structure and the severity of the prolapsed state would be different. At the molecular level, one may note a direct correlation to the amount of collagen I to III ratio as well as the alignment of the collagen. If the prolapse is severe, then there would be a lower ratio of collagen I to III and more misalignment of the collagen fibers when compared with healthy vaginal wall tissues.

Figure 4.1 shows patient data from both stage II and III prolapse. Thus, the magnitude of the prolapse can affect the rate of deformation, residual uplift, and peak uplift of the patient. Stage III prolapse might have a lower ratio of collagen I to III and more misalignment of collagen fibers compared to stage II prolapse, resulting in different variations in these variables for each patient. However, according to Feola et al., the ratio of collagen I/ (III + V) was similar between the healthy and prolapsed studies and the decrease in collagen alignment in the prolapsed study was the underlying factor [14]. But more patient studies from each stage of prolapse as well as correlating the uplift trends with the tissue histology need to be analyzed to make this prediction more conclusive.

Our modeling approach can predict the vaginal wall tissue uplift with increasing suction pressure to ~150 mmHg in good agreement with the data. For the Voigt model as seen in Figures 4.4-4.6, as the number of step pressure function segments increases, the calculated uplift data is better able to close in on the experimental data. However, at the middle of the timeframe to the peak uplift, there is a slight underestimation between the calculated distribution and experimental data, a trend prevalent for all patient data. This is even with the modified pressure data that can smooth out the irregularities of the experimental pressure-deformation line. Without this smoothing out function, the error would become larger and more erratic.

Plotting the experimental pressure-deformation line can result in an uneven, irregular trend. Operator handling error of the cutometer-like instrument and patient movement during the
BTC-2000™ procedure is one cause of this trend. Analyzing the original data under the viscoelastic models in conjunction with the QLV framework would cause a higher amount of error. Therefore to reduce this error, the Lowess (linear) fit method would be applied to the experimental data. This method is based on the combination of a linear least squares regression with nonlinear regression. The Lowess method can fit the models to localized subsets of data to construct a function, which describes the deterministic part of the variation for each x-y data point [25]. Thus the end result would calculate a new set of pressure y-data points while maintaining the uplift x-data points intact. However, there are some disadvantages to using this smoothing method. One of the biggest disadvantages is that this does not accurately represent the actual data since we are obtaining a new pressure data set. This could potentially produce a different result from the experimental data set. But upon closer inspection, plotting out the original experimental curve alongside the new Lowess data reveals miniscule interval differences between each point. Another disadvantage according to Cleveland et al. is that the Lowess method has less efficient use of data than other least squares methods since it requires large, densely sample data sets to produce a good model. Also, this method relies heavily on computational calculations because of the large amounts of data. But for our purposes, we have a total of ~430 data points for each pressure-deformation data in which the Lowess model can easily calculate these points and Matlab, being a widely used computational program, can handle these calculations. The main advantage of using the Lowess model is that it does not require a specific function to fit a model using all the data, making this method very flexible where no theoretical models exist [25]. This is especially advantageous for our model since initially, there is no theoretical framework to smooth out the experimental data. Therefore with the given facts, the advantages from using the Lowess model far outweigh the disadvantages as we can apply the new pressure data points with minimal consequences.

In theory, when applying increasing pressure segments to generate the uplift response should be able to accurately model the experimental data with minimal underestimation and
with an ideal error percentage of <1%. One reason why there is still a somewhat high error is the fact that this is a simplified viscoelastic model. The Voigt model is comprised of a spring $E$ in parallel with a dashpot $\eta$ while the Standard Linear model is the Voigt model with an additional spring $E_x$ in series with the dashpot. An $x$-element model of more than three can help refine the viscoelastic model where $x$ is the number of springs or dashpots in the circuit. Thus, adding more elements might help in better predicting the experimental data. The Burgers model, otherwise known as a four-element model, adds another dashpot in series with the overall Standard Linear model and has a more non-linear behavior compared to the Voigt and Standard Linear model [26]. Therefore, this new model might be able to predict the experimental data and lower this underestimation. Duenwald et al. shows that QLV framework can have a greater error in their results. Here, they used the QLV function to predict their relaxation response of a tissue. Overall in all their cases, the QLV framework overestimates the relaxation response and was bested by other non-linear theories [27]. Thus, the combination of a simplified viscoelastic model and QLV framework can contribute to the underestimation flaws.

Weakening of the dashpot by applying a percentage as low as 0.1% to the maximum viscosity can also help alleviate the large error, but this does not help eliminate the underestimation persistent for many of the patient data sets, for low values of $n$. This can be seen in Figures 4.4-4.6 in VW region where applying a smaller viscosity percentage can indeed have a greater impact in predicting the experimental uplift vs. time profile. Further evidence of this lower error sensitivity is shown in Figure 4.8, which compares separate effects of $n$ and percentage of max viscosity on least square error for the Voigt model. Therefore, it can be concluded that the original method, e.g., obtaining the maximum viscosity and then applying it to the rest of $n$ step pressure segments is too strong and needs to be weakened by a considerable amount. Although this procedure would make the calculated uplift appear to have a more elastic instead of a viscoelastic behavior, there were many assumptions to be considered to get to this point. These include the method of indirectly determining maximum
viscosity via the ratio between the Effective Young’s Modulus and rate of deformation, and even assuming the overall prolapsed tissue being viscoelastic.

The theory of viscoelasticity is applied to a material exhibiting an elastic and viscous behavior, such as the vaginal wall. When applying the Voigt and Standard Linear models, the spring represents the elastic portion while the dashpot symbolizes the viscous nature [23]. As shown in the previous discussion, in order for the model to predict the experimental data, the dashpot has to be reduced by a significant amount of the original viscosity. This is a result of the dashpot being too strong to estimate the experimental data, resulting in higher tissue damping and reduced elastic response of the calculated uplift data vs. the experimental data. For the majority of the 22 prolapse patient sets, the actual experimental data has lower tissue damping and an increase elastic response than previously predicted. As a result, the spring becomes more predominant in these models with the dashpot becoming nearly nonexistent. If the dashpot has little significance in predicting the uplift, then would there be any need in keeping the dashpot? Removing the dashpot from the model would leave the Voigt and Standard Linear models obsolete since both these models rely on the dashpot. A model that features only springs that represents the elastic nature of the tissue is a worth looking at for future studies. However, even if the dashpot is reduced significantly, it would still play a role in predicting the experimental data, especially at higher pressure segmentations. Nevertheless, there is small viscous nature found in the prolapse tissue that can influence the trend of the calculated uplift, even though the tissue exhibits a predominately elastic nature.

One possible method to further evaluate the effectiveness of the viscoelastic model by decreasing the least square error is to provide a sensitivity analysis, which is a method for systematically changing the variables in a model to determine the effects of these changes. The Effective Young’s Modulus and the viscosity variables for each $n$ segmentation would be subjected to this analysis. After applying Voigt and Standard Linear models with these new values, determine which combination of $E_n$ and $\eta_n$ would provide the least amount of error.
between the calculated uplift versus the experimental data. However, applying this method would infringe on the current method of obtaining the $E_n$ variables, which is a standard as seen in the modified QLV equation in Eq. 2.4. But the sensitivity analysis should be a worth to look at to a) determine whether the original method ($\frac{\partial \mathbf{u}}{\partial u}$) is any different from this new method of obtaining $E_n$ and b) if the new set of the $E_n$ and $\eta_n$ variables can provide a better viscoelastic model.

It is emphasized that the minor influence of the dashpot during the active (tissue uplift) phase may not hold for the tissue relaxation phase (the lower curve depicted in Fig. 4.3). A separate analysis must be conducted to gauge the viscoelastic effect during this phase.

Nevertheless, this analysis shows that employing both the Voigt and Standard Linear model in conjunction with the QLV framework can accurately predict the experimental uplift trend. A least square error percentage between the experimental vs. calculated uplift data can be as low as 3% starting from a step pressure segmentation of $n = 20$, as shown in Figure 4.6 and Table 4.1. This would only be obtainable if the maximum viscosity would be weakened to 0.1%. Increasing the number of step pressure segments beyond 20 would have a diminishing return on the accuracy and error. This is because the viscoelastic model is better able to predict the subsequent experimental uplift response.

When comparing the Voigt and Standard Linear model results, independent of the size of $n$, the Voigt model would suffice in analyzing the experimental data. As proven in Eqs. 2.13-2.15, when having a large $E_x$ as a result of a large ratio, this spring becomes stiffer, thus $E_x$ can be ignored and it behaves like the Voigt model. Ratios of at least 10 and higher applied to the SL model have been shown to behave like the Voigt model. In contrast, in Eqs. 2.16-2.19 when having a small $E_x$ as a result of a small ratio, this spring becomes less stiff and thus, has more impact on early uplift. As a result, the calculated uplift becomes more elastic and features a sharp, stair-case like trend as shown in Figure 4.6 when using a ratio of 1. The effectiveness of the Standard Linear model over the Voigt model is for models with a more non-linear response.
and an initial elongation. An initial elongation is an initial uplift response starting at a higher uplift point instead of zero, resulting in a more non-linear response if going to the same peak uplift point as the original experimental data. For this study, there is no initial elongation in the experimental uplift since all the patient data starts at ~0 mm uplift and the magnitude of the non-linear response is not prevalent enough to justify using the Standard Linear model as opposed to Voigt model. The comparison illustrating this is shown in Figure 5.1. Therefore in this study, the Voigt model is sufficient to predict the experimental data since the initial uplift response starts at zero mmHg.

Figure 5.1: (a) Initial elongation of a typical graph used for SL model. (b) Typical patient experimental data showing no initial elongation [28].

Although using this n-segmentation Voigt model method can predict the experimental prolapse VW data well enough, there is another limitation to this study. There is no effective control to enable comparison in relevant tissues of these results. The best control would be to use healthy VW tissue and apply the Voigt procedure in conjunction with the QLV framework, but unfortunately, no such tissue was available. A less attractive alternative was the pressure-uplift-time data from the suprapubic region due to its a) the testing of this region is non-invasive, b) it is the closest region to the anterior vaginal wall region, giving the logical choice as the control opposed to the non-existent supply of healthy vaginal wall tissue, and c) there is some viscoelastic property in this region. However, several problems arise from analyzing the suprapubic region. One is the fact that the suprapubic region exhibits more of elastic than
viscoelastic nature when compared with the vaginal wall tissue. This is due to the composition of the SP region, consisting of fascia that is mainly responsible for the elastic nature [8]. Analyzing the SP region under Voigt and Standard Linear equations was done; however, the uplift results were not as accurate as in the VW region. When comparing the same set of data from patient 66, there was large underestimation comparing the experimental and calculated data, resulting in a least square error of >10% starting at \( n = 15 \). All of these comparisons are shown in Appendix B. Thus based on these observations, the suprapubic region is not judged to be a viable alternative as a control to the prolapsed vaginal wall tissue.
CHAPTER 6
CONCLUSION AND FUTURE STUDIES

Overall, both the Voigt and Standard Linear models, used in conjunction with quasi-linear viscoelastic theory framework, can predict the experimental data with good agreement. However, there were several assumptions to be considered including a) the method of calculating the viscosity values for each \( n \) pressure segment and b) weakening the viscosity values to 0.1% to limit the underestimation. With the weakening of the dashpot, the model revealed for the majority of the patient data low damping with increased elastic response in the VW tissue. The underestimation can perhaps be attributed to a lack of patient data sets, and the use of a simplified non-linear QLV framework. Nevertheless, using this equation can predict the trend of the experimental data, with relatively low error at increasing \( n \). The anterior vaginal wall region does have viscoelastic properties while in contrast, the suprapubic region has a more elastic nature. These conclusions must be tempered by the large error exhibited by the relatively small number of data sets.

For future studies, a better cutometer-like device that can apply a constant pressure on the tissue should be used. This would more accurately portray and record the viscoelastic response of the tissue. Also, more patient tissue samples are needed to heighten the correlation between the different variables that determine POP. A sensitivity analysis to determine the combination of Effective Young’s Modulus and viscosity variables to better predict the model should be considered. Healthy vaginal wall tissue samples should be included for accurate comparison between prolapsed tissues. More studies need to be conducted when early signs of POP emerge. This would give insights at the tissue-cellular level such, as whether or not the rise of collagen III or collagen disorganization plays a major role in the development of prolapse. The relaxation response of the tissue is also worth looking at in future studies to correlate with 40
the creep response and understand more about the viscoelastic properties of the prolapse vaginal wall tissue. And finally, a better non-linear theory is needed to accurately describe the prolapsed nature of the anterior vaginal wall tissue.
APPENDIX A

QLV FRAMEWORK THEORY
The following set of equations describes a tissue response subjected to tensile load. A step increase in elongation (from $\lambda = 1$ to $\lambda$) is imposed on the tissue as the stress developed would be a function of time as well as the stretch $\lambda$. The relaxation function denoted by $K(\lambda,t)$ is assumed to be the form of

$$K(\lambda,t) = G(t)T^{(e)}(\lambda), G(0) = 1$$

Eq. (A1)

Where $G(t)$ is the reduced relaxation function and $T^{(e)}(\lambda)$ is the elastic response. The stress response to an infinitesimal change in stretch is $\delta\lambda(\tau)$, where it is superposed onto the tissue in a state of stretch $\lambda$ at an instant of time $\tau$ for $t > \tau$:

$$G(t - \tau) \frac{\partial T^{(e)}[\lambda(\tau)]}{\partial \lambda} \delta\lambda(\tau)$$

Eq. (A2)

Finally, applying the superposition principle:

$$T(t) = \int_{-\infty}^{t} G(t - \tau) \frac{\partial T^{(e)}[\lambda(\tau)]}{\partial \lambda} \frac{\partial \lambda(\tau)}{\partial \tau} d\tau$$

Eq. (A3)

Where the tensile stress $T(t)$ at time $t$ is the sum of these components, each governed by the same reduced relaxation function [24].
APPENDIX B

SUPRAPUBIC REGION VISCOELASTIC DATA
Figure B.1: Patient 66 SP Voigt data with $\eta_{\text{max}}$ percentage of 100%

Figure B.2: Patient 66 SP Voigt data with $\eta_{\text{max}}$ percentage of 50%
Figure B.3: Patient 66 SP Voigt data with $\eta_{\text{max}}$ percentage of 0.1%

Figure B.4: Patient 66 SP SL data with $\eta_{\text{max}}$ percentage of 0.1% and $E_x$ to $E$ ratio of 1
Figure B.5: Comparison of least square error of the SP area of Patient 66

Table B.1: Average Least Square Error Percentage for SP region

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<th>20</th>
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<td>10.65%</td>
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<tr>
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<td>10.66%</td>
<td>10.14%</td>
<td>8.07%</td>
<td>8.43%</td>
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</tbody>
</table>
Figure B.6: Comparison of least square error between the anterior VW and SP area of Patient 66

Figure B.7: Comparison of least square error of the SP area of the average of 20 patients for each segment n
REFERENCES


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BIOGRAPHICAL INFORMATION

Milton Ma completed his Bachelor of Science in Biomedical Engineering from University of Houston in May 2009. He joined the Masters program at the graduate school of Bioengineering at University of Texas at Arlington in August 2009. During the course of his education, he worked on various class projects, presentations, and scientific papers. He worked as a Graduate Teaching assistant at the Department of Bioengineering for one semester. The opportunity to work on this project was a unique experience in understanding and analyzing prolapse vaginal wall tissues under a viscoelastic model. The outcome of this study could help in early diagnosis of pelvic floor disorders. In the future, he looks forward to pursue a career in the Biomechanics field and pursue a Doctorate in Philosophy.