Biomechanics of Cervical Function in Pregnancy - Case of Cervical Insufficiency

by

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Abstract

The uterine cervix is a passive organ in the female body. Its normal function in pregnancy is to stay firm and closed for the duration of the gestation. At term, under the action of coordinated contractions from the myometrium the cervix dilates sufficiently to allow for the delivery of the fetus. Cervical insufficiency refers to a condition in which the cervix dilates asymptomatically and painlessly in the absence of contractions from the uterine smooth muscle and results in a spontaneous pregnancy loss between the second and third trimester of pregnancy. An elusive and often misdiagnosed condition, cervical insufficiency accounts for a significant percentage of extremely premature deliveries with high incidence of infant mortality and morbidity. Accurate diagnostic criteria and treatment guidelines for this condition are not established and remain a clinical and research challenge. In an attempt to better understand the biomechanics of cervical insufficiency, a fully three-dimensional constitutive model for the large strain, time dependent mechanical behavior of the cervical stroma is proposed.

The constitutive model is implemented numerically and integrated with a three dimensional solid model of the lower pelvic region of a pregnant patient into a finite element framework. The resulting finite element model provides a tool to study the effects of different clinical features on the biomechanics of the pregnant cervix and uterus, and allows to investigate the conditions that lead to a premature dilation in the case of cervical insufficiency.

New findings on the mechanical behavior of the stroma emphasize the complexity of the stress-strain and volume change behavior of the stroma as well as the intricate correlation between the two. The challenges involved in prescribing a constitutive behavior for the cervical tissue include characteristics such as nonlinearity, viscoelasticity, anisotropy, inhomogeneity and preconditioning. Additionally, the tissue behavior exhibits marked differences in tension and compression with associated stress levels differing more than an order of magnitude between the different modes of deformation.

A new constitutive framework capable of capturing the complexity of tissue behavior is proposed and material properties in compression are obtained by fitting finite element model simulations to experimental data. The model is further extended to incorporate effects of anisotropy of the cervical stroma. Suitable choice of the levels of tissue anisotropy is shown to accommodate the differences between the mechanical behavior in tension and compression.
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Chapter 1

Cervical Insufficiency

1.1 Introduction

The uterine cervix is a collagenous organ in the female body situated at the neck of the uterus. The cervix acts as a physical barrier between the unborn fetus and the outside world (see figure 1-1). The normal function of the cervix in pregnancy is to stay firm and closed for the duration of the gestation in order to contain the fetus in the uterine cavity (see figure 1-2).

At term, under the action of coordinated contractions from the uterine smooth muscle (the myometrium) the cervix undergoes a dramatic metamorphosis opening sufficiently to allow for the delivery of the fetus [25]. In its physiologic nonpregnant condition the cervix does not bear loads and has a well defined compositional balance of the main constituents which comprise its stroma. During gestation the cervix undergoes a very complex compositional change associated with an altered balance of the main constituents which takes a physical manifestation in a significant softening of the stroma. This process of continual evolution of the cervical composition is referred to as cervical maturation and is a prerequisite for vaginal delivery.

Cervical dilation precedes every spontaneous vaginal delivery. In some patients, a malfunction of the cervical structure can lead to a premature delivery and a potential adverse outcome in the newborn. Other pathological conditions associated with preterm delivery can include an early onset of uterine contractions (preterm labor), and premature rupture of the amniotic membranes. In some particular cases the aforementioned cervical dilation proceeds
Figure 1-1: Anatomical environment around the cervix and the uterus in pregnancy. Modified from "Sobotta Atlas of Human Anatomy" [76].

Figure 1-2: Healthy cervix during gestation. (A) Closed cervix. (B) Effaced cervix at term. Published with permissions, Copyright Krames/Stay Well.
in the absence of such complicating factors. Cervical insufficiency is an example of such case and is defined as a condition characterized by a gradual, progressive and asymptomatic cervical funneling [69]. Initiating at the inner os of the insufficient cervix, the dilation has a typical onset at the end of the second trimester or early third trimester. The dilation of the insufficient cervix happens in the absence of uterine contractions and is usually accompanied by a prolapse of the amniotic membrane into the endocervical canal [74], [72], [18].

The progression of the deformation of the cervical canal in the case of cervical insufficiency follows a T, Y, V, U pattern and starts at the internal os of the cervix and progresses towards the external os assuming a U shape in its final stage with amniotic membranes protruding at the site of the external os (see figure 1-3) [23]. A schematic representation of the dilation of the cervix is presented in Fig 1-4.

1.2 Definition and Diagnosis

The condition of cervical insufficiency accounts for a number of recurrent late second- or early third-trimester pregnancy losses. It differs from other causes of preterm delivery such as preterm labour and preterm ruptured membranes, bleeding and intra-amniotic infection [24], [47]. There exists a great variation in the incidence of this condition, with reports ranging between 0.05% and 2% of all deliveries [22]. The substantial variation in the reported numbers is partly due to the rarity of the condition, and partly due to the difficulty of making a correct diagnosis. In his 1980 publication McDonald [62] proposed a clinical definition for cervical insufficiency: a "history of one or more mid-trimester abortions, with early rupture of the membranes, usually before the onset of labor. There is absence of significant hemorrhage. The labors are short and relatively pain-free; the fetus is born alive. Repeated middle term trimester miscarriages at the same gestation are significant." Evidence shows that this definition is insufficient for diagnosis and requires the loss of at least one pregnancy in order to be contemplated [58].

The diagnosis of cervical insufficiency has long been a subject of controversy in the field of obstetrics. This elusive condition is most confidently established by an obstetric history of passive and painless dilation of the cervix in the late second- or early third-trimester of pregnancy. This asymptomatic effacement of the cervix, which happens in the absence of
Figure 1-3: Fetal membranes prolapsing into the endocervical canal of the insufficient cervix.

Figure 1-4: T, Y, V, U progression of the cervical dilation in the case of insufficiency. From www.thefetus.net with permission.
contractions from the uterine smooth muscle or labor, is often but not always accompanied by a protrusion of the amniotic membranes into the endocervical canal [74], [18], [72], [32]. The aforementioned criteria are used in current clinical practice but are essentially inconclusive for objective diagnosis of cervical insufficiency [32]. Other than the case of most classic presentation of gross cervical malformation, the condition of cervical insufficiency is very hard to detect, especially in the absence of previous obstetric history of the patient. The diagnosis is usually made in retrospect after a poor obstetric outcome of a previous gestation and careful monitoring during a subsequent pregnancy [69].

The origin of the diagnostic controversy around cervical insufficiency lies ultimately in the existence of 2 different theories for the cervical function during pregnancy. Traditionally, the function of the cervix has been considered categorical in the sense that the cervix was regarded as either completely functional (competent) or nonfunctional (incompetent) based on the obstetric history of the patient or digital examination of the organ [74]. More recent studies based on ultrasonographic measurements of the length of the cervix and its obstetric performance challenge the idea of the cervix as a categorical variable and propose a treatment of the cervical function along a continuum of "competence" [47].

Even though a standard method for evaluation of the cervix in pregnancy, digital examination proves an unsatisfactory method for cervical assessment due to the large variations among examiners [46]. Transvaginal sonography, in contrast, is a better reproducible method of examination and has been used for years to study the dilation and length of the cervix of women with preterm birth [32].

In their 1995 study Iams et al. used digital and transvaginal ultrasound sonography to assess the cervices of pregnant women at different gestational age with a history of one or more preterm births between 16 and 35 weeks of gestation [47]. The different group constituted women who delivered before 26 weeks, between 27 and 32 weeks, and between 33 and 35 weeks. The study also included a group of women with insufficient cervices and a control group of normal subjects. The analysis of the cervical length during the current pregnancy among the different groups clearly indicated a strong correlation between the obstetric history of the patient and the length of the cervix. Higher incidence of previous premature birth was associated with short cervical length, which supported the working hypothesis of the authors of cervical competence
as a continuum. Therefore the findings of this study are not consistent with the traditional theory of the cervical function as fully competent of fully insufficient. The authors support the idea of a multifactorial model of spontaneous birth in which the competence of the cervix is a continuous variable, thus providing an explanation for the relatively low predictive capabilities of individual risk factors associated with preterm delivery.

Another study assessing the correlation between the length of the cervix and the risk of spontaneous preterm delivery indicates the usefulness of this anatomical factor in predicting the successful outcome of pregnancy [46]. In their study Iams et al. performed transvaginal ultrasonographic assessment of the cervix of 2915 pregnant patients between 22 and 24 and 6/7 weeks gestational age. 2531 of those patients were examined again at 28 weeks. The reported values for cervical length at 24 weeks were 34.0 (±7.8 SD) mm for women with no previous deliveries and 36.1 (±8.4 SD) mm for parous women. The comparable results at 28 weeks reported cervical length of 32.6 (±8.1 SD) mm for nulliparous patients and 34.5 (±8.7 SD) mm for women with previous gestation. The reported differences in the values between parous and nulliparous patients were clinically unimportant and the number of previous deliveries in parous women was found to have no effect on the length of the cervix. Therefore the data were combined for analysis. Further investigation of the preterm birth predictive capabilities of funneling showed comparable clinical value of this test. The findings of Iams et al confirmed the existence of a direct relation between the duration of pregnancy and the length of the cervix: the shorter the cervix, the greater the likelihood of giving birth prematurely. Figure 1-5 shows the relative risk of a premature delivery before 35 weeks and patient distribution versus percentile cervical length as measured by Transvaginal Ultrasonography of women at 24 weeks of gestation. For example, this study shows that if the cervix is shorter than 1.5 cm, the risk of preterm birth is 10 times greater than the background risk. Supporting the hypothesis that there exists a continuum of cervical performance, the authors ascribe to the idea of spontaneous delivery as a multifactorial phenomenon in which the length of the cervix is an indirect indicator of cervical competence.

The presented studies confirm the crucial importance of the competency of the cervix in maintaining a healthy gestation and confirm the role of the cervix as a structure with variable performance along a continuum (rather than a dichotomous variable). These publications also
emphasize the multifactorial nature of premature delivery in which anatomical features such as cervical length individually provide an insufficient evidence for objective clinical diagnosis.

1.3 Risk Factors

1.3.1 Loading Conditions on the Structure of the Cervix and the Uterus in Pregnancy

It is well recognized in the medical community that the loading conditions on the cervical structure play an important role in controlling the outcome of the gestation. Clinicians agree that factors such as gravity, intra-amniotic pressure and uterine contractility are crucial in establishing the risk of preterm delivery for each patient. Notwithstanding the awareness of the relevance of these individual factors, the complexity of their interplay and their combined effect on the outcome of the pregnancy is not well understood and still a subject of clinical investigations [74].
Effects of Fundal/Intra-Amniotic Pressure

MacDonald et al investigated the use of transvaginal sonography in monitoring the cervical anatomy and deformation of women at high risk of a preterm delivery in order to diagnose cervical insufficiency [58]. A cohort of 106 patients at high risk of preterm labor was surveyed via means of transvaginal sonography for the duration of the pregnancy starting at the second trimester between the 14th and the 21st week of gestation. This observational study performed between 1995 and 1997 aimed at studying the cervical changes after an initial appearance of open cervix at the site of the internal os. The anatomical variables monitored included the length and the width of the cervix, as well as any deformation of the internal cervical os. Opening of the internal os of more than 5mm, protrusion of amniotic membranes into the cervical canal as well as shortening of the cervical length of > 5mm served as a definition of cervical change.

Figure 1-6: Transvaginal sonography at 24 weeks’ gestation. (A) Closed cervical canal in the absence of transfundal pressure. (B) Breaking of the cervix at the site of the internal os of the same patient as a result of application of transfundal pressure. Reproduced from MacDonald et al [58].

The study demonstrated a significant changes in cervical length with the application of fundal or suprapubic pressure (see figure 1-7). The results showed a decrease in the median cervical length in the surveyed group from 21 mm to 16 mm and in all cases the change was progressive. Figure 1-7 A shows the progression of the decrease in the length of the cervix from 21 mm to 8 mm at rest and figure 1-7.B demonstrates the same progression after fundal
pressure with a reduction of the cervical length from 16 mm to 6 mm at the time of surgical intervention. The investigators concluded that a progressive cervical change initiated before 24 weeks suggests that a cervix which appears to be open at the internal os, at rest or under the application of a fundal pressure, is most likely the sonographic visualization of cervical insufficiency. The authors emphasized that cervical length alone is not suggestive of a risk of preterm delivery, but in combination with a deformed cervical geometry and bulging fetal membranes may be an indicator of an incompetent cervix. The importance of the application of fundal pressure in order to identify an insufficient cervix was apparent.

![Graph](image)

Figure 1-7: (A) Length of cervix at the time of onset of cervical change and prior to clinical intervention without the application of fundal pressure. (B) Length of cervix at the time of onset of cervical change and prior to clinical intervention with the application of fundal pressure. Reproduced from MacDonald et al [58].

Effects of Multiple Gestation

Women carrying multiple gestations (twins or triplets) are at a higher risk of delivering preterm. A comparison of singleton and multiple pregnancies performed by Goldenberg et al in 1996 [36] revealed that short cervical length (≤ 25mm) was more common among twin pregnancies, both at 24 and 28 weeks, and that there are no other significant differences in the risk factors for preterm birth between singleton and multiple gestations. Cervical length of ≤ 25mm measured at 24 weeks was concluded to be the best predictor for SPTB at < 32 weeks, < 35 weeks and <37 weeks in twin gestations, while after the 28th week fetal fibronectin measurements proved to be the better indicator for potential preterm birth before 32nd week.
Bergelin et al [12] observed the cervical changes in twin pregnancies via means of transvaginal ultrasonography in the later part of pregnancy in order to determine the normal course of cervical deformation in the case of multiple gestation. A comparison between the changes in the geometry of the cervix of women with twins who gave birth preterm and at term was made as well. The results showed an accelerated cervical opening, open inner cervical os and dynamic changes earlier in the gestation, lesser extent of broadening of the cervix, and more frequently observed dynamic changes in preterm twin pregnancies (at 32-35 weeks gestation) as compared to twin pregnancies carried to full term (≥ 37 weeks gestation).

The results collected for twin pregnancies were also compared with previous studies performed by the researchers, which established some differences between the cervical geometries and changes in twin and singleton pregnancies carried to full term (≥ 37 weeks gestation). Initial length of the cervix at first examination at 24 weeks was comparable for both twins and singleton pregnancies. The differences became more acute with the advance of the gestation in both cases with much faster cervical length reduction in the case of twin pregnancies. The length reduction rates were 1.0 mm/week for singleton pregnancies and 1.8 mm/week for twin pregnancies, and in both cases the reported results were for pregnancies that reached full term (≥ 37 weeks gestation). The authors speculated that the increased shortening rate of the cervix could be attributed to overdistension of the uterus and increased pressure on the cervix rather than cervical ripening.

**Effects of Uterine Contractions**

Uterine contractions are the most important risk factor for preterm delivery and are present throughout the course of pregnancy. There is a significant difference between the early pregnancy contractions which do not affect the course of the pregnancy and contractions causing preterm birth. Saito et al [82] investigated the length of the cervix before, during and after a contraction by means of transvaginal sonography in the initial stage of labor in an attempt to determine whether the changes in the cervix during contraction can be used to distinguish between active and latent labor and between normal and abnormal labor. 73 patients with uncomplicated labor with gestational age varying between 37 and 42 weeks (full term) were monitored for this study. The degree of shortening of the cervix was expressed as a percentage
and was defined as the ratio of the contracted length of the cervix during a contraction and the length of the cervix prior to the contraction. The transvaginal ultrasound observations revealed that on average the cervix shortened about 50% during an active contraction in the normal course of labor. The shortening of the cervix in the case of insufficient contractile activity was significantly smaller, such as in the cases of false labor and uterine dysfunction. It was concluded that measurements of the length of the cervix during an inactive state and during contraction can facilitate the identification of inefficient vs normal labor and can be helpful for providing a guideline for appropriate labor management.

**Figure 1-8:** Transvaginal ultrasound images of the uterine cervix. (A) Pre-contraction. (B) At the peak of contraction. Reproduced from Saito [82].

### 1.3.2 Anatomical Risk Factors

The role of anatomical risk factors has been also recognized. In his seminal study discussed in the previous section, Iams et al [47] correlated a shorter cervical length with an increased risk for preterm delivery. A study by Goldenberg et al investigates the role of a large number of risk factors for preterm birth in order to better understand the strength of one risk factor versus another, as well as their complex interdependence [35]. The authors identified a number of risk factors for preterm birth (PTB), which were categorized in several groups. Some of the monitored variables included cervical length or funneling as measured by ultrasonography, as
well as effacement, dilatation and consistency as determined by digital examination. Uterine contractile activity, presence of cervical or vaginal fetal fibronectin (FFN) and obstetric history were surveyed as well. The study included more than 3000 women at approximately 24 weeks of gestation and was conducted at 10 medical centers in the US between the years 1993 and 1996. The monitored patients were evaluated at 24, 26, 28 and 30 weeks' gestation. The findings of this study indicate that previous obstetric history of preterm birth, in particular an early one, vaginal or cervical FFN presence especially between 24 and 26 weeks and anatomically short cervix are strong predictors of preterm birth. The most important factors associated with spontaneous preterm birth (SPTB) at less than 32 weeks of gestations were announced as a positive cervical-vaginal fetal fibronectin test of $\geq 50$ ng/mL, cervix shorter than 25 mm and a history of a previous SPTB.

A very recent study conducted by Schmitz et al [83] assesses the predictive potential of selective fetal fibronectin detection after cervical cerclage measurement. A cohort of 359 women hospitalized for preterm labour between 18 and 34 weeks' gestation participated in the study. Cervical length $\leq 25$ mm and FFN $\geq 50$ ng/mL were chosen as the best indicators for predicting PTB before 35 weeks of gestation. The results indicated that cervical length $\leq 25$ mm was less specific than FFN $\geq 50$ ng/mL for positive preterm birth. In order to assess the selective use of FFN after cervical length measurement, risk patient were identified as having cervical length $\leq 15$ mm or between 16 and 30 mm with FFN concentration $\geq 50$ ng/mL. Selective FFN measurements posterior to cervical length measurement indicated excellent negative predictive values (94%) for delivery before 35 weeks thus suggesting that selective use of FFN in daily obstetric practice could provide a better assessment of the potential preterm risk and subsequent treatment of the patient.

Guzman et al [37] surveyed a cohort of 469 women at high risk of PTB between 15 and 24 weeks' gestation using transvaginal sonography and transfundal pressure. The anatomical factors investigated in this study were funnel width and length, cervical length, percent funnelling and cervical index. The investigators concluded that there is no additional advantage of measurement of funnel width and length, percent funnelling and cervical index over the cervical length. Moreover, cervical length appeared to be a better predictor especially in the case of earlier PTB (at $< 28$ and $< 30$ weeks) in comparison with the other anatomical parameters.
Simpler to obtain, sonographic measurements of the cervical length were shown to be the most beneficial for the prediction of prematurity in conjunction with the patient history of prior mid-trimester loss and/or a prior preterm birth. Based on their findings the investigators propose possible treatment guidelines and intervention strategies. For a cervical length of 2.1-2.5 cm the patients were advised to reduce physical activities, while the recommendation in the case of cervical length between 1.6 and 2.0 cm was bed rest. Cervical length of less than 1.5 cm was chosen as a cut-off value for surgical intervention (i.e. cerclage).

Other studies suggest that cervical length may be more efficient in predicting the outcome of a high-risk singleton gestation than assessing the risk of a premature delivery in the case of multiple gestations.

1.3.3 Consistency of the Cervical Stroma (Mechanical Properties)

Finally, the consistency of cervical stroma, as assessed by the attending clinician in a physical exam of the patient, can also be an indicator of risk. While a normal cervix progressively softens during pregnancy and dramatically weakens (ripens) sub-partum, an insufficient cervix can be found to be already in a weakened soft state in earlier stages of gestation or even in non-pregnant patients. During a physical examination, an increased softness of the cervix is an indication of altered biochemical composition of the stroma [42], [64], [29], [27].

Several studies assessing the resistance of non-pregnant cervices via methods of in-vivo balloon and dilators showed that mechanical testing of the cervix in the non-pregnant state can predict cervical insufficiency in subsequent pregnancies [91]. Zlatnik et al studied a cohort of 184 patients with a history of spontaneous second-trimester abortions and early preterm deliveries performing hysterography, catheter traction and dilator passage tests to calculate a compliance score. Women with potentially insufficient cervices had higher compliance scores (corresponding to less cervical resistance) and delivered earlier in gestation than women with low scores.

Anthony et al [2] measured the "cervical resistance index" (CRI) defined as the force required to achieve short-range dilation of the cervix in 20 patients with an obstetric history of previous spontaneous mid-trimester abortion. The CRI of patients with a history of potential cervical insufficiency was much lower (2.44±0.78) in comparison with the index of parous patients with
normal menstrual cycles (4.91±0.41), which indicated a lower cervical resistance associated with insufficiency.

Kiwi et al performed a study assessing the elastance of the cervix, defined as the change in volume of a compliant balloon placed within the endocervical canal, in patients with a history of one or more previous spontaneous mid-term pregnancy losses. The study concluded that the elastance of the cervices of non-pregnant patients with an obstetric history of preterm birth associated a diagnosis of cervical insufficiency is lower than the normal control group. The authors also speculated that this decreased resistance is suggestive of actual physical changes in the cervix, which facilitates dilatation of the cervix during labor.

1.3.4 Conclusions
Mechanicians can easily recognize these three classes of risk factors as the underlying conditions governing any problem of structural integrity: loading, geometry, and material properties. Ideally, the structural integrity of a cervix, in its load bearing function, can be assessed and predicted for individual patients using conventional tools of structural mechanics, such as the finite element method. Numerical simulations, integrating anatomical factors, loading conditions, and tissue properties can be a powerful tool to gain a deeper insight into the biomechanics of pregnancy and to investigate the complex interplay of risk factors for preterm delivery. A better understanding of the mechanical behavior of the cervical tissue is an imperative prerequisite to pursue these objectives.

1.4 Preventive Methods and Treatment
A major issue in obstetric management is the prevention of preterm delivery. A correct prediction of the potential risk of a preterm birth for the individual patient is prerequisite for an effective intervention and treatment. In current clinical practice, a short cervix is one of the main factors leading to clinical interventions (cerclage, bed rest) to prevent premature delivery.
1.4.1 Surgical Procedures

Cerclage

Among the possible treatments of cervical insufficiency is the use of a cerclage: a surgical intervention where a suture is placed around the cervix in order to keep it closed. The efficacy of cerclage interventions has not been fully confirmed in randomized clinical trials and depends largely on the accuracy of the diagnosis [69]. Despite the abundance of clinical data on the use of cerclage in order to prevent preterm birth there is still a pronounced lack of conclusive evidence supporting the efficacy of a cerclage utility. Regardless of its value, the use of a cerclage as an intervention strategy is still the most popular preventive management of cervical insufficiency [69]. Because there is substantial clinical confusion surrounding cerclage placement, the NIH is conducting a randomized trial in order to better understand its efficacy [70].

Types of Cerclage

There are various forms of cerclage treatment used in the medical practice which can be broadly categorized as transvaginal or transabdominal procedures. The transvaginal cerclage is the more commonly used procedure, which utilizes temporary stitches around the lower site of the cervix (closer to the external os) in order to mechanically augment the cervical function and keep the cervix closed (see figure 1-9). The two main forms of transvaginal cerclage are the Shirodkar procedure designed in 1955 and the McDonald procedure designed in 1957. In both procedures sutures are weaved through the cervix. In the case of Shirodkar cerclage the sutures are placed higher compared to the MacDonald procedure (closer to the internal cervical os) and in both cases the sutures are knotted. The success rates of both procedures are comparable. Nevertheless the ease of suture removal in the case of MacDonald cerclage makes the latter the preferred choice in clinical practice.

In the case of transabdominal cerclage the suture is permanent and further surgical intervention is necessary in order to deliver the fetus. Such a procedure necessities that all subsequent pregnancies are delivered through a cesarean section. Transabdominal cerclage is the treatment method of choice for patients in which vaginal treatments have failed or for patients with very short or amputated cervices [32]. The reported success rates in the case of transabdominal
cerclage are higher (82-100%) in comparison with the transvaginal interventions.

In both cases of transvaginal or transabdominal procedures the patients are advised to reduce physical activities. Bed rest is a usual recommendation following a cerclage intervention. Sexual activities are usually prohibited [32].

Risks of Cerclage

In the United States cerclage is not commonly performed after the 26th week of gestation due to the increased risk of premature rupture of membranes (PROM), premature labor (PTL), and the potential success of prolonging the pregnancy with non-surgical procedures, such as bed-rest. The risk of PROM and PTL, as well as inflammation (chorioamnionitis) varies with the presence and degree of cervical funneling and the duration of the pregnancy. In the case of MacDonald procedure the most commonly reported morbidity owes to the formation of scar tissue at the site of the stitch resulting in cervical injury at the time of delivery.

There is a small risk of infection for elective cerclage at the beginning of the second trimester, as well as a risk of a suture displacement. The success rates of a second cerclage are much lower [32].

Audu et al [6] investigated the complications associated with the utility of cervical cerclage
for patients with cervical insufficiency. The review presented the complications of cervical cerclage in 141 pregnant women with cervical incompetence between January 1993 and December 1997 in the University of Maiduguri Teaching Hospital in Nigeria. The authors report the onset of premature contractions as the most common complication associated with cerclage ranging between 36 and 39% of the cases. The remaining patients had either a spontaneous abortion (21.1%) or premature delivery (40.4%). Premature rupture of fetal membranes (PROM) was the next most common complication with an incidence of 21.3% of the cases. The study also reports complications such as hemorrhage (14.9%), early failure (11.3%) and labor with suture in-situ (10.6%) among others.

**Efficacy of Cerclage for Cervical Insufficiency**

The efficacy of cerclage for cervical insufficiency has not been fully confirmed in randomized clinical trials.

Owen et al [69] published a review of cerclage trials for patients with potential diagnosis of cervical insufficiency as well as women exhibiting risk factors for spontaneous preterm birth or questionable sonographic findings in the mid trimester. The researchers conclude that in the case of cerclage for "risk factors" for cervical insufficiency such as multiple gestation, prior induced or spontaneous abortion, uterine anomalies or obvious cervical defects among others, the utility of a cerclage has a limited clinical benefit and is associated with more medical complications and interventions. In the case for a cerclage for sonographic indications of an insufficient cervix, which identify women with anomalous cervical features, such as reduction of the length of the cervix or funneling at the internal os, cerclage is potentially a more beneficial intervention procedure [69]. Owen et al also argues that the utility of a cerclage therapy may be successful in the case in which a cervix has diminished competence and shortens and dilates. Whether the cerclage procedure will be able to arrest the progression of deformation of already dilating cervix was deemed speculative.

In a randomized controlled trial of the Medical Research Council/Royal College of Obstetricians and Gynecologists [73] a cohort of 1292 pregnant patients with suspected cervical insufficiency were surveyed in order to assess the benefit of cervical cerclage to prolong pregnancy. The study concluded that prophylactic cerclage was beneficial in only 1 out of 25 cases
of insufficiency.

Althuisius et al [1] performed a cervical insufficiency prevention study in which the benefit of a therapeutic MacDonald cerclage treatment followed by bed rest was compared with the efficacy of bed-rest alone. In this randomized cerclage trial preterm delivery rates (< 34 weeks gestation) and neonatal morbidity and mortality were compared for patients with risk factors or symptoms of cervical insufficiency. Cervical cerclage was administered to patients based on the criterion of cervical length < 25 mm before 27 weeks of gestation. The results reported that the preterm delivery rates in the cerclage group (0 out of 19 cases) were much lower than the bed-rest only group (7 out of 16). Similarly, the neonatal morbidity or neonatal death rates were much lower in the cerclage group (1 out of 19) versus the bed-rest only group (8 out of 16). In conclusion it was stated that therapeutic cerclage with bed-rest reduces preterm delivery before 34 weeks gestation and compound neonatal morbidity in women with symptoms and/or risk factors of cervical insufficiency and cervical length of < 25 mm at 27 weeks of gestation.

In a similar investigation, Rust et al [8] studied patients between 16 and 24 weeks of gestation, which via means of sonography exhibited dilation of the cervix at the internal os, and either protrusion of fetal membranes into the endocervical canal at least 25% of the length of the cervix or reduced cervical length of < 25 mm. The patients were randomly assigned to cerclage or no cerclage treatment. The study concluded that there is no benefit of cerclage utility. The difference of the conclusions of Rust et al and Althuisius et al may be attributed to the difference in the studied populations [38] and the size of the studied groups.

Heath et al [39] studied the benefit of a Shirodkar cerclage in 22 women with cervix shorter than 15 mm at 23 weeks of gestation vs a control group of 21 women who were administered expectant treatment. The results of the study associated the application of a Shirodkar suture in women with very short cervices with a 10-fold reduction of the risk of very preterm delivery.

Progressively receding cervical length as a result of the application of fundal pressure to a length of < 10 mm before 24 weeks gestation was shown to be an indication for potential cerclage management as discussed by MacDonald et al [58].
1.4.2 Non-Surgical Procedures

Pessary and Bed rest

Use of a pessary, a device placed at the external os of the cervix in order to provide mechanical support for the insufficient cervix and bed-rest are alternative treatments of cervical insufficiency with limited clinical benefit [74].

Medical Treatment

Administering of tocolytic agents in order to inhibit uterine contractions and therefore reduce the load on the cervix has been a common practice since 1961. Due to controversy associated with this form of treatment the use of tocolytic agents has lost popularity [38].

1.5 Conclusions

An elusive and often misdiagnosed condition, cervical insufficiency is particularly hard to detect in the case of no previous obstetric history. There are many factors, which need to be taken into account if the risk of premature delivery is to be assessed. There exist numerous techniques for the assessment of the cervical function currently used in the clinical practice. Transvaginal ultrasonography is one of the more reliable techniques to diagnose cervical insufficiency. However none of the existent techniques alone is sufficient for a positive diagnosis of an insufficient cervix.

The most popular surgical treatment of cervical insufficiency is the placement of a cerclage. Among the nonsurgical procedures is the placement of a pessary and bed rest. The efficacy of these treatment methods is still subject to controversy as the success of these procedures is largely dependent on the accuracy of the diagnosis.

A substantial quantitative assessment of all contributing factors is necessary in order to improve the accuracy and the reliability of the diagnosis of cervical insufficiency.
Chapter 2

Biochemical Composition of the Cervical Tissue

2.1 Introduction: The Extracellular Matrix (ECM)

In order to study the biomechanical function of the cervix, the main biochemical constituents governing its mechanical behavior need to be identified.

On the microstructural level the stroma of the cervix is composed of sparse distribution of cells embedded in extracellular matrix (ECM). Sparse smooth muscle cells and fibroblasts constitute the cellular component of the cervix. The cellular content of the stroma is ~5-10% per weight [84]. The ECM of the stroma is believed to be the load-bearing component of the tissue [71]. The ECM of the cervix is composed of highly kinked collagen fibrils organized in a three-dimensional network, which is intertwined with sparsely scattered elastin fibers amounting to approximately 1% dry tissue weight [27]. The predominant components of the ECM of the cervix are type I and III collagen, and some small percentage of collagen type IV is detected in the basement membranes [53]. Ground substance composed of interstitial fluid, proteoglycans (PGs) and glycosaminoglycans (GAGs) completes the composition of the cervical stroma [53]. The glycosaminoglycans are present either in the form of proteoglycans such as dermatan sulfate in decorin, or they are embedded in the matrix without a core protein as in the case of hyaluronic acid. The ECM supports cervical cells, mainly fibroblasts and small amount of muscle cells. Collagen accounts for ~70% of dry tissue weight, while the GAGs and the PGs represent
between 0.2% and 1.5% of the dry weight of the tissue. Table 2.1 summarizes the percentage of each constituent.

Because of their negative fixed charge density, the glycosaminoglycans attract free positive ions from the interstitial fluid to create charge disbalance. As a result, a high osmotic pressure is created in the tissue, which governs fluid flow and swells the cervical stroma.

The uterine tissue, in contrast to the uterine cervix, is composed almost entirely of smooth muscle.

![Figure 2-1: Idealized representation of the composition of the human cervical stroma.](image)

**2.2 Collagen**

The collagen glycoprotein is one of the main constituents of the extracellular matrix of soft tissues. Polypeptide chains called collagen α chains make up the collagen protein. The polypeptide chains in the collagen can assemble into stable triple helical structures (see figure 2-2.A (center) and (right)) because of the abundance of three amino acids: glycine, proline and hydroxiproline [55]. These amino acids make up the main feature of the collagen polypeptide chain - a repeated Gly-X-Y sequence (see figure 2-2.A (left)), where X and Y can be any acid, but are
frequently proline and hydroxyproline amino acids [50]. Glycine amino acid is essential for the triple helical structure formation, because of its small side chain, a hydrogen atom, which can fits into the center of the triple helix. Hydrogen forms bonds, thus keeping the three strands together (see figure 2-2.B).

The ability of the collagens to form highly organized supramolecular assemblies in the extracellular space is a very distinctive functional feature of these protein molecules [10]. The collagen macromolecules are covalently linked to each other to form collagen fibrils of varying diameter, depending on the primary function of the tissue they comprise. There exist more than 20 different collagen types, which have been identified, even though they have not been well characterized.

![Figure 2-2: The collagen triple helix.](image)

Type I and III collagens are fibrillar collagens and the main components in the ECM of the human cervical stroma, as was shown using gel electrophoresis of the acetic acid-soluble fraction of the collagen comprising the human cervix [54]. Type I collagen accounts for about 70% of the collagen composition and type III accounts for the remaining 30% of collagen in the stroma [29]. Type IV collagen has also been detected [50]. The same collagen types I, III and IV have
also been found in the fetal membranes [50]. In the case of type I and III collagens, the collagen monomers spontaneously form fibrils by means of alignment of charged and hydrophobic clusters of amino-acids which form intermolecular cross-links. Once the collagen fibrils assemble, they aggregate into bundles to form, in turn, higher order aggregates. The 64-nm staggering of the trimers give the collagen its striated appearance on electron micrographs (see figure 2-3). The cross-linking process is the last step in the biosynthesis of collagens and is particularly important for fibrillar collagens as it increases the tensile strength of the fibers and promotes tissue integrity. Collagen fibers are the structural component of the stroma contributing the most to the mechanical strength and resilience of the ECM.

Figure 2-3: Fibril assembly and crosslinking. After secretion from the Golgi apparatus the trimers are assembled into fibrils and are covalently cross-linked. The 64-nm staggering of the trimers give the collagen its striated appearance on electron micrographs.
2.3 Proteoglycans and Glycosaminoglycans

Another type of molecules abundant in the extracellular matrix of all connective tissues are the proteoglycans, which are a group of glycoproteins that cushion cells and bind a great variety of ECM molecular components. Proteoglycans are a subset of glycoproteins, whose brush-like structure consists of glycosaminoglycan molecules covalently attached to a long protein spine. The glycosaminoglycans (GAG) are long linear polymers of sulfated polysaccharides composed of repeating disaccharide units [50]. Hyaluronic acid is not sulfated and it never attaches to a core protein, therefore it is not considered a member of the proteoglycan family. A characteristic of the GAGs of the ground substance is their high negative fixed charge density. Due to the negative charge of the ground substance large quantities of interstitial fluid are drawn into the extracellular matrix via means of a Donnan effect. Hydration of the ECM allows PGs and GAGs to slide past one another and change their configuration, thus acting as lubricants or force damping mechanisms in some types of connective tissues such as tendon and skin [20].

The different proteoglycans vary significantly in size and can be categorized according to their glycosaminoglycan units, the structure of their protein core and their length in terms of number of disaccharides found in each GAG chain. The major proteoglycan in the human cervix is decorin. Decorin (on average 90 - 140 kilodaltons (kDa) in size) belongs to a "small proteoglycan" family and consists of a core protein with one glycosaminoglycan chain consisting of either dermatan sulfate or chondroitin sulfate (see figure 2-4). Medium sized glycosaminoglycans found in the stroma of the cervix are chondroitin sulfate, dermatan sulfate and keratan sulfate. Decorin has also been isolated from human fetal membranes [50].

Dermatan sulfate accounts for 76% of GAG content. Heparan sulfate accounts for 13% of the GAG content and the remaining 11% are hyaluronic acid [78]. Smooth muscle cells have only sparse amounts in the human cervix (6-8%) [50].

During pregnancy the total amount of glycosaminoglycans increases in association with the process of cervical remodeling, which will be discussed in more detail in the following subsection. Moreover, in conjunction with the ripening or remodeling of the cervix, literature reports have shown a significant decrease in dermatan sulfate, which is concurrent to the decrease of the collagen content during gestation. Increase of hyaluronic acid concentration is linked to the increase of the water content of the stroma. Increase in the heparan sulfate has also been
During funneling at parturition a significant decrease in the concentration of dermatan sulfate takes place. Dilatation of 6-8 cm is associated with 12% fall of the dermatan sulfate concentration [78].

![Decorin proteoglycan with core protein and dermatan sulfate GAGs with molecular weight 90-140 kDa.](image)

**Figure 2-4:** Decorin proteoglycan with core protein and dermatan sulfate GAGs with molecular weight 90-140 kDa.

### 2.4 Elastin

Elastic fibers are another major component of the extracellular matrix, which complex structure contains elastin, microfibrillar proteins, and lysyl oxidase. The major protein of mature elastic fibers is elastin, characterized by a high degree of reversible extensibility and capability of sustaining large deformation with the application of small forces [11]. Elastin provides the elastic fibers with the characteristic properties of elastic recoil.

The cervical stroma has a small composition of mature and cross-linked elastin ranging between 0.9% and 2.4% of dry tissue weight, which does not change during pregnancy [54]. In the uterus, at parturition, the elastin increases to 800% over its normal level and decreases rapidly after the delivery [54]. The uterine elastin contributes significantly to the restoration of the extended organ by means of elastic recoil [54]. In contrast to the stiff collagen fibrils of the cervix, the elastic tissues in the uterus are soft and extensible [54].

The thin elastic fibers in the nonpregnant cervix form a loose network structure composed
of membranes and fibrils interconnected to give a fishnet-like appearance, which runs parallel
to and between the layers of the collagen fibers. Late in pregnancy, the elastin fibers have a
slightly increased diameters and demonstrate very little organization. Immediately postpartum
certain dissociation and branching of the fibers has been observed. The elastic membranes in
the uterus have a sponge-like appearance and are freely stretchable in any direction. Such a
structure provides support for the growing fetus without exerting any excess pressure.

The precise biomechanical properties of the elastin have not been fully characterized. It is
believed that elastin has rubberlike characteristics and therefore can be modeled as a network
or cross-linked and randomly oriented chains to which the theory for rubberlike materials can
be applied. According to the rubber theory such a network is in a state of maximum disorder
or entropy, and extension of the material aligns the elastic fibers in the direction of the applied
deformation, thus reducing the number of possible configurations for the fibers and decreasing
the entropy of the system. The two configurations are depicted in figure 2-5, where 2-5.A shows
the unstretched elastic fiber network and 2-5.B shows the aligned network under uniaxial exten-
sion. Upon release, the elastic fibrils spontaneously return to their initial random configuration
in order to restore the original entropy level. Because of their mechanical behavior it is believed
that the elastic fibers play a major role after parturition, when by means of elastic recoil they
facilitate the recovery of the distended organ of the uterus [54], [53]. Leppert argues that
decreased levels of elastin in the cervical stroma of women with cervical insufficiency provide
evidence for the role of this protein in pregnancy [53]. In their work Bank et al [7] report an
estimated Young's modulus of 0.3x10^6 Pa for elastin, while the corresponding value for collagen
is 0.1x10^9 Pa for collagen fibrils [89]. Danforth reports that elastic fibers appear to constitute
but a fraction of 1% of the total fibrous tissue in the human cervix [27].

2.5 Fetal Fibronectin

The decidua is the tissue layer connecting the fetal membrane to the uterus. Fetal fibronectin
is a protein synthesized by choriodecidual cells and is distinct from the fibronectin found in the
extracellular matrix of the cervix. Fetal fibronectin is thought to promote adhesion between the
membranes and the decidua. Increased fetal fibronectin detected in the cervicovaginal secretions
is associated with an increased risk of subsequent preterm birth, possibly reflecting decreased adhesion between the fetal membranes and decidua [53].

2.6 Cervical maturation

During gestation, the balance of the main biochemical constituents of the cervical stroma is continually evolving [27]. On the tissue level these compositional changes of the stroma physically manifest themselves in a significant softening of the cervix, as evidenced by the ability to indent the surface of the organ with the slight application of pressure as in the case of a palpation test [27]. This process of tissue remodeling and associated softening is called cervical maturation and is a prerequisite for the normal labor and delivery [29].

Many scientists have investigated the compositional changes associated with maturation or ripening of the pregnant human cervix.

Higher hydration levels in the stroma are typical towards the end of the gestation [26]. A 5% increase in the hydration levels of the cervix at the end of pregnancy was reported by Aspden [4]. Danforth speculates that the increase of the water content can contribute to softening of the organ. Another cause for the softened consistency of the stroma according to Danforth may be the loss of collagen, although there has been insufficient evidence for this hypothesis in specimens examined throughout the 4th month of pregnancy [27].
A decrease in the collagen concentration to 30% of that in the nonpregnant cervix as well as a decrease of 50% in the concentration of sulfated GAGs and hyaluronic acid were reported by Ekman et al [29]. According to the authors, the decrease in the connective tissue constituents is indicative of the process of thorough remodeling of the cervix in late pregnancy [29]. Ekman also established a correlation between cervical dilatation time and total collagen concentration in the ripened cervix [29]. In the same discussion high cervical collagen concentration is associated with prolonged cervical dilation time. Rechberger et al [79] reports higher extractability values for collagen at term concluding that the old and non-extractable collagen in the stroma is replaced by newly synthesized extractable collagen with unstable cross-links leading to a 7% decrease in the tensile strength of the stroma after delivery.

A key factor affecting the physiological maturation if the cervical tissue in late pregnancy is the overall GAG distribution, according to Rath et al [78]. It is argued that an increase in certain GAG percent in the stroma during pregnancy as well as altered compositional balance of the separate GAGs cause increased tissue hydration and control cervical ripening [74], [53]. For a detailed overview of the composition of the cervical ECM the reader is referred to table 2.1.

Rath et al observed a significant decrease in dermatan sulfate concentration concurrent to progressive cervical dilatation with a 12% reduction of the concentration of dermatan sulfate at 6-8cm dilatation [78], which was not observed over the course of pregnancy but occurred at the onset of labor. The investigators suggested that loss of dermatan sulfate may promote flexibility and distensibility of the ripened cervix associated with disruption of the collagen fiber organization.

Shimizu also reports that hyaluronic acid, chondroitin sulfate, and heparan sulfate in postpartum tissue greatly increased in comparison with the non-pregnant tissue, and confirmed the decrease of dermatan sulfate in the former. Decrease in dermatan sulfate content concurrent to an increase of other GAGs content may be important to ripening, since dermatan sulfate is considered to maintain the elastic hard nature of cervical tissue [85]. Danforth found a "new" keratan sulfate-like substance [26] but Shimizu et al did not confirm this finding [85].

Hyaluronic acid shows only weak affinity to bond to collagen and fibronectin [78], therefore its physiological function has been speculated to be that of a space filler between the collagen
fibers. A correlation between increased hyaluronic acid concentration and weakened fibronectin affinity to collagen has also been demonstrated, which could in turn contribute to the loosening of the network of the collagen at time of parturition [78].

The factors that regulate the remodeling of the tissue in pregnancy have not yet been well understood. Cytokines are known to be influencing the metabolism of connective tissues, therefore it was speculated that they play a substantial role in the remodeling process [29]. Macrophages, neutrophils, mast cells are examples of inflammatory cells present in the pregnant cervix suspected to take part in the ripening process [29], [84]. Hormonal activity is another possible cause of the remodelling of connective tissue which have not been well investigated [29].

The process of cervical maturation is a necessary (but not sufficient) condition for the

<table>
<thead>
<tr>
<th>Dry tissue</th>
<th>Non-pregnant</th>
<th>Pregnant (at term)</th>
<th>Post partum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collagen</strong></td>
<td>~85% (per dry weight)</td>
<td><strong>concentration</strong> ↓ by 30%, 70% [72]</td>
<td><strong>trend</strong></td>
</tr>
<tr>
<td>Type I</td>
<td>70% (of total collagen)</td>
<td><strong>same</strong> - [89]</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>30% (of total collagen)</td>
<td><strong>same</strong> - [89]</td>
<td></td>
</tr>
<tr>
<td><strong>GAG</strong></td>
<td>~0.75%, ~1.17% (per dry weight)</td>
<td><strong>concentration</strong> ↓ by 50% [29]</td>
<td></td>
</tr>
<tr>
<td>Dermatan sulfate</td>
<td>66%, 76% (of total GAG)</td>
<td><strong>concentration</strong> ↓ by 12% [78]</td>
<td>33.7% ↓ [85]</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>9.3% (of total GAG)</td>
<td>4-fold increase ↑ [78]</td>
<td>15.2% ↑ [85]</td>
</tr>
<tr>
<td>Heparan sulfate</td>
<td>4.8%, 13% (of total GAG)</td>
<td>-</td>
<td>14.2% ↑ [85]</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>11.6% (of total GAG)</td>
<td>12-fold increase ↑ [78]</td>
<td>17.7% ↑ [85]</td>
</tr>
<tr>
<td>Elastin</td>
<td>0.9-2.4% (per dry weight)</td>
<td><strong>same</strong> - [54]</td>
<td>same - [54]</td>
</tr>
<tr>
<td>Smooth muscle cells</td>
<td>6-8%, 10-15% (per dry weight)</td>
<td>↑ by 10-15% [89]</td>
<td></td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td>80%</td>
<td>increase by 5% ↑ [4]</td>
<td>↓ ↓ [89]</td>
</tr>
</tbody>
</table>

Table 2.1: Composition of the ECM
successful outcome of pregnancy, as opposed to insufficient cervical ripening, which could potentially lead to protracted labor and clinical interventions [29]. As discussed previously, the change in the GAG and collagen concentrations as well as altered balance of the GAG distribution during the maturation process are associated with changes of the mechanical properties of the stroma, even though a direct correlations between the two have not been established. Close to term, increased hyaluronic acid concentrations lead to swelling of the tissue thus resulting in more tissue hydration. Additionally, a reduction in the concentration of dermatan sulfate results in a reduction in the number of dermatan sulfate bridges between the individual collagen fibrils. These changes have been shown to result in cervical distension and dilatation [20]. The changes occurring in the cervix over the time of the time of the gestation encompass the transformation of the collagen network from an alignable fibrous matrix to an amorphous, hydrated matrix capable of undergoing large distention [20].

Despite the extensive research in the area of biochemical composition of the uterine cervix, a very few studies have been able to correlate the biochemical composition of the cervix with its mechanical properties. Even less have investigated the correlation between biochemical parameters and mechanical properties of the stroma in the case of cervical insufficiency [79], [72]. A few studies have been able to establish a correlation between the biochemical composition of the stroma and clinical variables, such as the obstetric history of the patient. Petersen et al [72] associates increased hydration levels with women with previous vaginal deliveries. The same research group reports a decrease in collagen concentration of 70% with an increase of the extractability of collagen from 67% to 90%. The authors hypothesize that this increased extractability might reflect decreased stability of the cross-linking between the collagen molecules. A possible conclusion from this report is that pregnancy induced changes of concentration of collagen in the cervix are not fully reversible. This study also reports increased collagen extractability, decreased number of elastic fibers, decreased elastin content, and higher concentrations of smooth muscle cells in women with an insufficient cervical stroma as compared with normal patients. These observations are indicative of decreased cervical resistance in women with cervical insufficiency even in the non-pregnant state. The findings of Myers et al [64] confirm the increase collagen extractability from 28.6% and 33.1% (for nonpregnant patients with no previous deliveries and previous vaginal deliveries correspondingly) to 78.5%
extractability of pregnant patients. Increased hydration levels are also reported by Myers et al in agreement with previously reported biochemical results for human cervical tissue. Finally, Rechberger performed biochemistry and mechanical tests on second-trimester specimens taken from women with cervical insufficiency and reported high collagen extractability exceeding post-partum values, as well as very low strength and high distensibility of the insufficient stroma. Rechberger conclusion confirmed the assumption made previously by Petersen et al: namely that the findings of the study are an evidence for high turnover of collagen in the insufficient cervical stroma, which results in the replacement of old stabilized and crosslinked collagen with newly synthesized biomechanically weak collagen.

The morphology of the cervical stroma undergoes substantial changes immediately after the delivery of the placenta by exhibiting a markedly different structure from the one observed in the non-pregnant cervix or at 4th month of gestation [27]. As evidenced by digital examination, the collagen fibers in the stroma immediately after parturition are diminished in number and are separated into their fibrillar components, in contrast to the dense and tightly packed organization of the collagen network in the case of non-pregnant or 4th month pregnant stroma [27].

2.7 Collagen Fibril Orientation

Aspden et al [5] investigated the organization of the collagen in the cervix in relation to the mechanical function it carries out. The researchers differentiated between three different zones of collagen orientation in the human pregnant and non-pregnant cervix with gradual transition between them. Zone 1 and 3 encompassed regions close to the exterior of the cervix and close to the endocervical canal where the collagen fibrils are organized longitudinally, parallel to the length of the canal. The intermediate zone 2 was characterized with collagen orientation that is circumferential (see figure 2-6). Close to the external os the three zones were not well observed and zone 3 adjacent to the endocervical canal with longitudinal fibrils almost did not exist. In the central part of the cervix the three zones were well defined with thickness of 3-5 mm in the outer region (zone 1) and the region adjacent to the endocervical canal (zone 3) and 5-12 mm thickness in the middle region (zone 2). The collagen fibrils play an effective
mechanical role when subjected to loads oriented parallel to the length of the fibers, which tend to stretch and align the collagen fibrils. The orientation of the collagen fibrils in the human stroma observed by Aspden suggests that the such a distribution of fibers oriented both circumferentially and longitudinally parallel to the length of the endocervical canal will provide strength of the stroma both around and along the tissue. Circumferential fibers would provide resistance against dilatation of the organ, while the longitudinal fibers would restrict the pull of the myometrium (e.g. contraction) and will ensure that the cervix would not be torn off the uterus as a result of the growth of the fetus and stretching of the myometrium, for example. In conclusion Aspden states that the cervical stroma can be considered as a composite material in which collagen concentration and fiber orientation determine the direction in which the cervix can most effectively withstand distention. Together with other factors such as the concentrations and the types of GAG present in the stroma and tissue hydration level, the collagen orientation and concentration governs the mechanical behavior of this tissue.

Weiss et al [88] also studied the fiber architecture in the human uterus and cervix using MRI diffusion tensor imaging (DTI). DTI is a noninvasive imaging method based on the assumption that water diffuses inside and along directed structures rather than perpendicular to them. This method is used by Weiss to visualize the anisotropy of the human cervix and uterus. In contrast to the findings of Aspden [5], the measurement of the diffusion vectors of the uterine cervix by Weiss showed circumferentially oriented fibers in the outer part of the cervix. The
collagen fibers in the inner part of the cervix were found to have a longitudinal orientation (see figure 2-7). The findings of Weiss were not consistent with the results published by Aspden. Nevertheless these studies confirm the existence of directional structures in the collagen fiber architecture and increase our appreciation for the complexity of the fiber arrangement.

2.8 Simplified and Idealized Model for Human Cervical Stroma

For the purposes of mechanical constitutive modelization of the cervical stroma we propose an idealized tissue model composed of four major components.

The wavy kinked collagen fibrils will constitute the fibrous network of the cervical stroma. The highly negatively charged glycosaminoglycans and proteoglycans would constitute the second component of the idealized stroma, in which no further differentiation between the separate GAG will be made and in particular, and hyaluronic acid will be considered to be a part of the ground substance. The third constituent of the stroma is the network of the elastic fibers, which although present in very scarce amounts in the stroma, play a shape restorative role via the action of elastic recoil. The last component of the idealized tissue model is the interstitial fluid, which flows through the porous extracellular matrix of the cervix.
We will use this idealized representation of the stroma to associate mechanical behavior with each individual component and to prescribe network constitutive behavior which comes as a combination of the responses of the individual constituents.
Chapter 3

Mechanical Properties of the Cervical Tissue

3.1 Overview of the Mechanical Properties of the Human Cervix

Modeling the mechanical properties of load bearing soft tissues has intrigued researchers for years. There is a great variety in the types, each exhibiting a unique microstructure and functionality, but their underlying composition is essentially the same and is comprised of cells and ECM. Notwithstanding the differences in their mechanical behavior, usually commensurate with their specific functionality, soft tissues share some typical characteristic behavior which can be described by nonlinearity, inelasticity, heterogeneity and anisotropy [44].

The underlying composition of these materials consists of a sparse distribution of cells embedded in an extracellular matrix, which is believed to be largely responsible for their mechanical properties. The characteristic features of soft tissue behavior can be largely attributed to different components of its ECM, (such as the collagen and elastin network, the ground substance of negatively charged PGs and GAGs) and the interstitial fluid, which flows through the porous matrix of the stroma.

In particular, the mechanical properties of the human cervical tissue have not been thoroughly investigated. A number of animal models such as rat and rabbit cervical stroma have been developed aiming at understanding the mechanical properties of these kinds of soft tissue. Due to the differences in the biochemical composition of the cervical stoma of humans and
animals, only a review of the data obtained for human cervical stroma will be presented in this section.

Conrad et al [21] tested in-vitro nonpregnant human cervical strips in uniaxial extension. The specimens were excised from various sites of the organ and stroma properties were measured as a function of location both longitudinally (along the length of the cervix) and axially (at different radial distances from the endocervical canal). Additionally, a comparison between the stiffnesses of non-pregnant and pregnant cervical stroma was made. Figure 3-1.A shows the differences between the stiffness of the stroma during pregnancy and in non-pregnant state. As it can be observed from the graph, there is approximately 5-fold reduction in the stress peak values from the non-pregnant to the pregnant state, which corresponds to 2-3 fold reduction of the stiffness modulus of the pregnant tissue. The non-pregnant cervical stroma exhibited a very non-linear stiffening as the applied elongation was increased. At the same time, in the case of a pregnant cervical stoma, for the same amount of applied deformation the stress quickly reached the tissue maximum yield point, which was significantly lower than the recorded value in the non-pregnant stroma. A comparison among the stress-strain behavior of cervical specimen collected from the same patient at the level of the internal os at different axial locations is presented in figure 3-1.B. The testing speed was 0.1cm/min. The presented results clearly showed a substantial difference in the stiffness of the cervix in the region of the inner os as a function of axial distance from the endocervical canal. The recorded stiffness in the region close to the periphery of the cervix was roughly 3 times less than the stiffness of the stroma close to the canal. The mean values for the measured stiffness modulus were recorded as 64.32 KPa close to the internal os, 41.31 KPa in the middle region and 24.21 KPa at the site of the periphery of the cervix.

The results by Conrad showed that the stiffness of the cervix decreases above and below the site of the inner os and it was concluded that the internal cervical os is the site with maximum resistance to dilatation, an observation which was in accord with the common clinical impression.

Another study by Petersen et al [71] aiming at assessment of the passive biomechanical properties as well as muscular contractile ability of the human cervical stroma concluded that the passive tensile strength substantially exceeds the active contractility of the cervical stroma.
The investigators tested cervical tissue samples from 28 nonpregnant women by excising circular tissue strips and testing them in isometric tension. The reported results 0.16±0.005 KPa for the distal part and 0.84±0.47 KPa for the proximal part of the cervix, and compared to values of 4.85±1.0 KPa in tissues from the isthmus and 6.50±1.4 KPa in the fundus of the organ. The passive tensile strength recorded was 1.5-1.7 MPa, a 10^4-fold factor increase in the value from the contractile ability. The mean tensile stiffness were reported to be 3.9 MPa for longitudinal stripes and 4.0 MPa for circular stripes from the proximal part of the cervix. The corresponding values for the distal part were 3.2 MPa for the longitudinal stripes and 3.6 MPa for the circular stripes. The testing speed in this case was 1cm/min as compared to the study of Conrad, which used 0.1 cm/min as a testing speed. The results by the two groups report passive tensile strength results that differ by an order of magnitude. Such a difference could be partially attributed to the difference in the testing speeds used in the different studies but the testing speed alone could not account for such substantial result discrepancies. Nevertheless, the recorded difference between the passive and the active strength of the cervical tissue could be attributed to the biochemical composition of the cervical stroma, which is characterized by a high collagen content and very low smooth muscle content. Such a conclusion confirms the hypothesis that the load bearing capacity of the cervical tissue could be entirely attributed to the cervical ECM.

A very recent study by Mazza et al [61] published in 2006 assesses the mechanical behavior of human cervical specimens in an in-vivo study via means of an aspiration device. This study is the first of its kind to attempt to characterize the cervical stroma in the in-vivo state. In the work of Mazza in-vivo and ex-vivo mechanical properties were compared and the reproducibility of the experiments was analyzed. Testing of the stroma was performed by creating a time variable vacuum inside a tube brought in contact with the external part of the tissue at the accessible site of the external os. Tissue was sucked through the aspiration device area with diameter of 10 mm creating a vacuum of 400 mbar (eq. to 40 KPa) absolute pressure for a load cycle of approximately 20 sec., which was chosen in order to avoid tissue damage, and was followed by an unloading cycle. For some of the tests the procedure was repeated 4 to 5 times. The cervices of 8 menopausal women was tested in-vivo and 4 of the organs were tested ex-vivo as well. The obstetric history of the patients was recorded.
Figure 3-1: Stress-strain relationships for human cervical tissue. (A) Comparison between non-pregnant and pregnant specimens. (B) Nonpregnant specimens from the same patient tested at the site of the internal os at various radial distances from the endocervical canal. Reproduced from Conrad et al [21].

The researchers calculated a stiffness $\eta$ for each cervix (see figure 3-2). The reported results show a variability of approximately 5-fold increase in the stiffness of the cervixes from the weakest to the strongest. The average results vary between 9.5 KPa/mm to 24.0 KPa/mm, which results in a factor of 2.5 difference. Mazza also reports an average of the normalized values of 1.0 with SD of 19% and a normalized ex-vivo values of 1.045 with SD of 27% which can be used as an indication that the ex-vivo mechanical response of the cervix does not differ considerably from the in-vivo one. A second argument made by the authors claims a stronger history dependence of ex-vivo data with respect to in-vivo data. By studying a softening parameter $\gamma$ the researchers confirmed a dependence of the mechanical response on preconditioning to a larger extent for the ex-vivo experiments. The authors argue that the differences in the time dependence of the response can be masked by the variability of the measured data.
Figure 3-2: Siffness parameter $\eta$ calculated by Mazza et al [61] for tests performed in- and ex-vivo. Reproduced by Mazza et al [61].

3.2 Experimental Behavior of the Cervical Tissue: A Comprehensive Study of Biochemical Composition and Mechanical Properties

The most recent study of the mechanical properties of the cervical stroma by Myers et al [64] attempts at establishing a connection between the biochemical composition and the macroscopic mechanical properties of the human cervical stroma. The specimens collected from patients who underwent hysterectomy were collected at the Tufts New England Medical Center. Most of the organs were from non-pregnant women, but some were taken out from pregnant patients at the time of cesarean section. Custom made stainless steel slicing device was used to excise 4mm thick parallel disks perpendicular to the endocervical canal from the site of the internal cervical os (see figure 3-3.A). After excision from the organ the cervical slices were stored at -80 °C. It has been shown by Febvay [30] that upon freezing the mechanical properties of the human cervical tissue do not alter, which is consistent with the findings of Kiefer et al for the cryopreservation of the biomechanical properties bovine articular cartilage [48]. Mechanical
and biochemical specimens were cut from the organ and caution was exercised in order to avoid the mucous tissue around the stroma.

Figure 3-3: Compression specimen preparation. (A) Custom made slicing device for ex-vivio excision of circular specimen slices. (B) Core punch for excising cylindrical specimens from the slices. (C) Zwick universal testing machine. (D) Specimen dimensions.

For the mechanical testing cylindrical samples were cored out from the circular disks with a 8mm core punch after the disks were let to thaw for approximately 3 minutes (see figure 3-3.B and D). The detailed schematic of the specimen preparation is depicted in figure 3-4. The placement of the cervix and the uterus as collected after a hysterectomy is shown in figure 3-4.A. Figure 3-4.B shows the numbering of the slices and the orientation of the cervical disks with respect to the anatomical sites of the cervix. Figure 3-4.C presents the convention for the anatomical orientation. As presented in 3-4.C, tissue regions close to the inner canal (mucosa) and the outer tissue layer (fascia) of the cervix were avoided in the specimen preparation, as their soft cellular structure substantially differs in its mechanical characteristics from the load bearing stroma of the organ. For the biochemical tests ~20mg of tissue adjacent to the mechanical testing samples was excised.

In order to experimentally characterize the mechanical behavior of the cervical tissue, the hysterectomy specimens were tested in a lab environment in different modes of deformation. The
obstetric history of the patients was collected and the tested stroma was categorized according to parity [64]. Prior to testing, all mechanical specimens were submersed in PBS solution and equilibrated overnight. The mechanical tests were carried out with the tissue samples immersed in PBS bath. The mechanical setup for the laboratory tests was comprised of a universal testing machine (Zwick z2.5/TSIS, Ulm, Germany) and custom designed acrylic fixtures (see figure 3-3 C and 3-5 B).

The specimens were subjected to load unload cycles and stress relaxation tests in confined and unconfined compression. Each compression test consisted of three load-unload cycles to 15% nominal axial strain and the testing rate was 0.1% s⁻¹. For the stress relaxation tests the specimens were subjected to 10%, 20% and 30% nominal axial strain for the unconfined compression tests and the deformation was held for 30 minutes at each strain level to let the specimens equilibrate and obtain the stress relaxation response of the stroma. Correspondingly, for the confined compression tests the specimens were subjected to 5%, 10% and 15% nominal axial strain and the testing strain rate of 0.017% s⁻¹.

A protocol for testing the tissue of the cervix in tension was also developed. Circular disks
obtained by excision of the stroma via means of 2 concentric circular punches rendered a ring-
shaped specimens, which were placed in tension jaws via means of woven Kevlar strips (see figure
3-5.C and D). The specimens were airbrushed with a speckle pattern and the specimen were
extended along the diagonal of the ring. The whole ring together with the Kevlar strips were
submersed in a PBS bath for the duration of the test. The imposed testing history comprises
multiple tension load unload cycles with 30 minute of equilibration time in the unloaded state
in between loading ramps. Strain fields were calculated in the central regions of homogeneous
deformation of the cervical disks as indicated in figure 3-5.C.

Figure 3-5: Specimen geometry for the experimental tests. (A) Specimen compression geometry.
(B) Testing setup for compression. (C) Specimen tension geometry. (D) Testing setup for
tension.

For a more detailed description of the experimental setup and the testing procedure the
reader is referred to Myers et al [64]. The testing protocol developed by Myers et al. 2005 made
it possible to collect consistent experimental data from tests performed on equivalent samples,
defined as samples located at the same anatomical site of the cervical specimen.

Video images of deformation history of the specimen were recorded with Qimaging Retiga
1300 CCD camera. The collected images were postprocessed through means of Digital Image
Correlation techniques and strain data was extracted for the purposes of mechanical character-
ization of the cervical stroma behavior.

Analysis of the experimental results shows that for constant strain rate load-unload tests the stroma of the cervix exhibits a very nonlinear response with marked hysteresis [3-6]. As it can be observed in figure 3-6, the first loading cycle exhibits a stiffer response as compared with subsequent loading cycles. Additional loading of the tissue in a cyclic manner yields a more compliant response with a reduction of the hysteresis loop. This phenomenon of tissue softening from the initial to the subsequent loading cycles is observed in other classes of soft tissues and is often referred to as “conditioning” (e.g., see Humphrey, 2002 [44] and Mazza, 2005 [61]). The unloading behavior does not differ significantly between cycles. In the presented data a distinction is made between the obstetric history of the patients and the different obstetric cases are labeled NPND, referring to non-pregnant with no previous vaginal deliveries, NPPD which refers to non-pregnant with previous vaginal deliveries and PCS denoting a pregnant specimen excised at time of cesarean section.

![Figure 3-6](image)

Figure 3-6: Response of the cervical stroma to load-unload cycles in unconfined compression. (A) Differences between non-pregnant specimens-with (NPPD) or without (NPND) previous vaginal deliveries and pregnant specimens (PCS). (B) Differences between different equilibration times for specimens collected from the same cervical slice.

The response of the non-pregnant tissue is shown to be significantly stiffer than the response of the pregnant stroma, which is consistent with the clinical observation (e.g. see Conrad et al [21]). A summary of the unconfined compression results is presented in table 3.1. The pregnant
Table 3.1: Comparison between peak and equilibrium stresses for uniaxial unconfined compression for three different obstetric cases. NPND - non-pregnant no previous deliveries; NPPD - non-pregnant with previous vaginal deliveries; PCS - pregnant taken out at the time of cesarian section.

<table>
<thead>
<tr>
<th>Obstetric case</th>
<th>10% Peak (kPa)</th>
<th>20% Peak (kPa)</th>
<th>30% Peak (kPa)</th>
<th>10% Equilibrium (kPa)</th>
<th>20% Equilibrium (kPa)</th>
<th>30% Equilibrium (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPND</td>
<td>0.66±0.46</td>
<td>3.2±3.2</td>
<td>12.0±14.0</td>
<td>0.31±0.24</td>
<td>0.72±0.53</td>
<td>1.2±0.18</td>
</tr>
<tr>
<td>NPPD</td>
<td>0.39±0.38</td>
<td>1.6±2.3</td>
<td>6.0±9.6</td>
<td>0.21±0.17</td>
<td>0.50±0.39</td>
<td>0.82±0.76</td>
</tr>
<tr>
<td>PCS</td>
<td>0.15±0.12</td>
<td>0.3±0.24</td>
<td>0.56±0.64</td>
<td>0.10±0.006</td>
<td>0.17±0.15</td>
<td>0.28±0.23</td>
</tr>
</tbody>
</table>

cervical specimen clearly exhibit a much more compliant response than the two non-pregnant cases as can be observed from the peak and equilibrium stress values reported in the table. The differences in the response between the two non-pregnant cases also shows that the cervical stroma of women with previous vaginal deliveries is more compliant that the stroma of women with no previous vaginal deliveries, confirming a clinical observation that the previous obstetric history of the patient affects the mechanical properties of her cervix.

Figure 3-7 presents averaged results from ramp-relaxation test for unconfined (see figure 3-7.A) and confined (see figure 3-7.B) compression tests.

Averaged results from ramp-relaxation tests are presented in figure 3-7 and table 3.2 summarizes the findings in this case. The results show a markedly stiffer response in confined compression as compared to the unconfined compression test. The results indicate that for both the confined and unconfined cases the equilibrium response depends linearly with the applied nominal axial strain, while the peak values of the stress changes nonlinearly with the strain. The relaxation times are comparable within the same test for different levels of the applied strain but vary from the unconfined to the confined state.

All the presented data is averaged between a number of specimen obtained from different patients and/or different cervical slices and locations within the same cervical slice.

Figure 3-8 show preliminary experimental results from uniaxial extension load-unload test. Figure 3-8.A presents the response from specimens obtained from patients with different obstetric history and figure 3-8.B shows differences between two specimen obtained from different anatomical sites form the same cervix. As it can be clearly seen in figure 3-8.A, the nonpregnant cervical stroma exhibits a response which is orders of magnitude stiffer than the pregnant.
Figure 3-7: Response of the cervical stroma to ramp-relaxation compression tests. (A) Unconfined compression test. (B) Confined compression test.

<table>
<thead>
<tr>
<th>Obstetric case</th>
<th>5% Peak (kPa)</th>
<th>10% Peak (kPa)</th>
<th>15% Peak (kPa)</th>
<th>5% Equilibrium (kPa)</th>
<th>10% Equilibrium (kPa)</th>
<th>15% Equilibrium (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPND</td>
<td>1.8±3.7</td>
<td>5.6±9.4</td>
<td>14.0±17.0</td>
<td>0.38±0.57</td>
<td>0.99±1.1</td>
<td>1.5±1.4</td>
</tr>
<tr>
<td>NPPD</td>
<td>0.82±2.0</td>
<td>2.9±5.7</td>
<td>7.8±13.0</td>
<td>0.23±0.40</td>
<td>0.55±0.78</td>
<td>1.1±1.2</td>
</tr>
<tr>
<td>PCS</td>
<td>0.12±0.07</td>
<td>0.17±0.10</td>
<td>0.28±0.18</td>
<td>0.07±0.07</td>
<td>0.10±0.08</td>
<td>0.12±0.08</td>
</tr>
</tbody>
</table>

Table 3.2: Comparison between peak and equilibrium stresses for uniaxial confined compression for three different obstetric cases. NPND - non-pregnant no previous deliveries; NPPD - non-pregnant with previous vaginal deliveries; PCS - pregnant taken out at the time of cesarian section.

tissue. This finding is consistent with the trend observed for the compression behavior. The results presented in 3-8.B also show that the mechanical behavior of the stroma is dependent on the anatomical site from where the specimen was excised. The response of the specimen collected from a site close to the internal cervical os was more compliant than the one collected from a site closer to the external os. Furthermore, as in the case of compression the tissue exhibits a very nonlinear mechanical behavior with big hysteresis loops. The hysteresis loops become bigger with higher levels of applied nominal axial strain. The tension response for the non-pregnant specimens exhibits a certain amount of preconditioning. For the case of pregnant cervical stroma the tissue continued to elongate with each subsequent loading cycle.
Figure 3-8: Experimental results from uniaxial extension load-unload test. Between cycles, the unloaded specimens were equilibrated for 30 min in PBS. (A) Results collected for 3 specimens from 3 patients with different obstetrics background. (B) Experimental response of cervical stroma for 2 specimens from a single pregnant patient. Specimen 1 was excised close to the external OS and specimen 2 was excised close to the internal OS.

As discussed in this work the nature of the cervical stroma renders handling of the tissue and repeatability of the experiments exceptionally challenging. A comparison plot between the results collected from tests in unconfined compression and tension are presented in figure 3-9. Certain discrepancies between the tangent stiffness moduli can be observed in the data from the different tests. A magnification of the small stress regime, presented in the upper left corner of figure 3-9.A, exemplifies this inconsistency in the experimental data. The same inconsistencies are observed in the stress-relaxation data as well, as presented in figure 3-9.B. An obvious discontinuity in the stiffness tangents in the small stress regime can be attributed to the fact that the tension experiments were performed along the circumferential direction of the cervix (see figure 3-4), while the compression experiments were performed along a direction parallel to the length of the endocervical canal of the organ. Preliminary histological studies performed on the cervical stroma did not identify any significant degree of anisotropy in the collagen bundle arrangement and subsequently the testing orientation was not considered to be central to the task of designing a experimental testing protocol for the stroma. Differences in the values of the different transverse stretches were not expected to be significant and the large
variability in the lateral stretch was not taken into consideration for preliminary constitutive modeling for the cervical stroma.

![Graph](image)

Figure 3-9: Comparison between the tension and the compression results. (A) Load-unload unconfined compression test. (B) Stress-relaxation test in unconfined compression.

Apparently, inconsistencies in the collected transverse stretches data are indicative of tissue anisotropy and call for a revised experimental protocol reflecting these new findings. Immediate action was taken and the geometry for the test specimens was modified to a block shape for the compression experiments (see figure 3-10.A). The new experimental protocol tests the compression specimen in all directions, as shown in figure 3-10.B. New cervical stripes with a rectangular geometry are proposed for the tension testing protocol as well (see figure 3-10.B). A thorough experimental investigation (Myers, 07, in preparation [65]) provides novel data on the volume changes experienced by the cervical stroma under different modes of loading. While the tension testing protocol for the cervical stroma is still in the course of refinement, the compression protocol proposed renders consistent, repeatable results.

Each cube specimen in the new experimental procedure was subjected to multiple load-unload cycles and ramp-relaxation tests in compression along the circumferential and the longitudinal directions. For the load-unload cycles the specimen were ramped to either 30 or 45% axial true strain at a rate of 0.1% s$^{-1}$ and unloaded at the same rate. Between the loading cycles the specimens were held at zero strain for 620 or 720 seconds. The revised experimental
Figure 3-10: (A) Specimen preparation of compression cubes and tension strips. (B) Anatomical directions of the cervix. Multiple samples are cut along the radial direction to capture different fiber orientations. (C) Collagen fiber orientation. Circles indicate fibers in the circumferential direction (out of plane).

protocols for testing the specimens in a conformable manner in tension and compression (e.g. the new data presented was consistently tested in the circumferential direction) render continuous stress-stretch curves and volume change plots as depicted in figure 3-20 and 3-21, as well as consistent and continuous stress tangent moduli in the small stress regime.

3.3 Variability in the Tissue Response

There exists a substantial variability of the tissue response from patient to patient. Load-unload behavior of cervical stroma in compression collected from different patients is presented in figures 3-11, 3-12 and 3-13. The corresponding stress relaxation data is presented in figures 3-14, 3-15 and 3-16. Tension load-unload results are presented in figures 3-17 and 3-19. A big degree of variability of the tissue response was found between patients, while the variability between samples from the same cervical specimen was on average smaller. The data collected exhibited a substantial variation in the amplitude of the stress response for different tissue samples; nonetheless the qualitative characteristics of the response were markedly consistent.
3.4 Preconditioning

The initial loading cycle in compression in the presented cases (see figure 3-11.A, 3-12.A and 3-13.A) is characterized by a stiffer stress response with greater hysteresis loop as compared with the subsequent loading ramps. Additional loading of the tissue in a cyclic manner yields a more compliant response with a reduction of the hysteresis loop. This result is consistent with the previous compression results and the observed preconditioning of the tissue as discussed earlier. The experiments also show that there is repeatability in the subsequent loading ramps which indicates that there is no permanent damage of the material as a result of the cyclic loading. Furthermore, the tension data for cyclic loading also exhibits preconditioning.

3.5 Tension vs Compression

The characteristics of the mechanical behavior of the cervical stroma as analyzed from the presented experimental results can be used to get a better insight into the complex response of the stroma and to propose an appropriate constitutive model for such kind of behavior. The stress-stretch response of the cervix is markedly nonlinear in both tension and compression. Moreover,
Figure 3-12: Compression data for three load-unload cycles to -30% true axial strain applied in the circumferential direction for nonpregnant patient Mar 1. (A) Nominal stress vs axial stretch [Mpa]. (B) Volume changes vs axial stretch.

The response in tension is much stiffer than compression. Figures 3-7 and 3-8 exemplify the differences in the peak values for the same level of strain in both tension and compression, from which we see 2-orders of magnitude difference in the peak values for 10% true axial strain. Figures 3-18 and 3-20 presenting more recent results for tension and compression experiments on the same cervical stroma further confirm this observation.

The nonlinearity of the stress strain characteristics can also be observed from the relationship between the peak values from the stress-relaxation results for both unconfined and confined compression (see figure 3-7) and load-unload results in tension (see figures 3-8 and 3-19.A). In contrast, the equilibrium stress values for compression for three different values of strain seem to follow a linear relationship, as can be observed in the equilibrium values for the stress-relaxation test in both unconfined and confined compression presented in figure 3-7.

3.6 Pregnant vs Nonpregnant

Non-pregnant stroma tends to be stronger in comparison with the pregnant one. Additionally, the strength of the stroma can be correlated with the obstetric history of the patient. The stroma of patients who have previously delivered vaginally is less stiff than the stroma of nonparous
Figure 3-13: Compression data for three load-unload cycles to -45% true axial strain applied in the circumferential direction for non-pregnant patient Mar 15. (A) Nominal stress vs axial stretch [Mpa]. (B) Volume changes vs axial stretch.

patients (see figure 3-6). The peak stress levels for both tension and compression for the stroma of healthy, non pregnant patients were orders of magnitude higher than the equilibrium stress levels. For pregnant stroma, however, the peaks were within the same magnitude as the equilibrium levels (see figure 3-7). As the stress peaks are associated with the transient response of the tissue arising from fluid diffusion it can be hypothesized that this difference from the non-pregnant to the pregnant state reflects the structural changes experienced by the stroma during gestation and perhaps associate the less crosslinked collagen organization at term with higher permeability of the stroma.

In consideration of the observed variation in the stress amplitude and volume change data in compression a representative cervical tissue response will be analyzed in order to describe the observed trends. For the purposes of constitutive characterization of the tissue response figure 3-11 was chosen as representative of the tissue behavior in compression and will be discussed in further detail.

Figure 3-11 shows a characteristic load-unload behavior of the cervical tissue. Figure 3-11.A depicts the associated developed stresses and figure 3-11.B captures the corresponding volume changes experienced by the stroma. In order to further appreciate the complexity
Figure 3-14: Compression data for a stress-relaxation test to -45% true axial strain applied in the circumferential direction for non-pregnant patient Feb 16. (A) Nominal stress vs time [Mpa]. (B) Volume changes vs time.

of the of the stress and volumetric changes experienced by the stroma and their intricate correlation we propose a schematic identifying the different stress and volume loss regimes and the associated responses in bulk and in shear in order to establish a connection between the changes experienced by the stroma in shear and bulk (see figure 3-22).

Figure 3-22 presents the stress and the volume changes developed in the stroma and a schematic identifying different regions associated with loading and unloading for three compression cycles to -45% true axial strain applied in the circumferential direction for non-pregnant patient Feb 16. The left part of the schematic represents the different deformation stages and the right part shows the tissue response with the corresponding associated regions of the response.

The change in the volume of the stroma in all three loading ramps appears as almost linear with three markedly different volume loss regimes. At small levels of the applied compressive axial strain corresponding to levels of 1 to 0.9 axial stretch in the toe region volume is lost in a linear fashion with a minimal penalty in the recorded stresses. This situation is described schematically to the right of figure 3-22 in the transition from stage 1) to stage 2). Subsequent higher levels of the applied axial strain (corresponding to axial stretches of 0.9 to 0.7) in the
transition region lead to a negligible volume reduction, which happens at a slower rate and is associated with a significant steepening of the stress response. Schematic representation is portrayed in figure 3-22 (going from stage 2) to stage 3)). At higher deformation levels corresponding to axial stretches of 0.7 to 0.64 in the stiffening region a third volume loss regime is observed. The stiffening region is also characterized with a significantly stiffer stress response approaching a tangent. This situation is schematically depicted in figure 3-22 in the transition between stages 3) and 4).

The differences between the different volume loss regimes due to compressive loading are more pronounced in the second and third loading ramps. Less volume is lost in the initial loading ramp as compared with the subsequent ramps; nonetheless the volume loss profiles have the same underlying characteristics in all three loading ramps.

Upon unloading, on average, in all three ramps the tissue initially preserves its current volume. Some stroma specimens continue to lose volume (see figure 3-13.B) while in other specimens some instant recovery of the volume is observed (see figure 3-13.B). Concurrently a dramatic reduction in the stress takes place. This substantial reduction of the stress at a constant volume defines the very stiff unloading region and is presented schematically in figure
Figure 3-16: Compression data for a stress-relaxation test to -45% true axial strain applied in the circumferential direction for non-pregnant patient Mar 15. (A) Nominal stress vs time [Mpa]. (B) Volume changes vs time.

3-22 stage 4) and stage 5). After this significant stress decrease the tissue continues to exhibit reduction in the stress response which happens at constant volume in the shallow unloading region depicted schematically in figure 3-22 in the transition from stage 5) to stage 6). At levels of 0.85 axial stretch the stress in the specimens is substantially reduced to zero. In the low (zero) stress region the stroma starts to gain volume in a linear fashion at approximately the same rate as the corresponding initial volume loss regime in the toe and stiffening region. This volume recovery happens at poisson's ratio \( v = 0 \).

The new findings about the response of the cervical tissue and the associated volumetric changes clearly establish a very complex link between the tissue response in bulk and in shear. The presented mechanical data will be used as a basis for the development of a three dimensional constitutive model for the large strain, time dependent material behavior of the cervical stroma. Furthermore, a significant part of the nonlinear behavior of the stroma with high associated stress levels is attributed to the mechanical behavior of the collagen fibers in the extracellular matrix. The exhibited behavior of the tissue with large volume deformations which happen at negligible or no stress change suggest the existence of regions of the stroma which are not controlled by the collagen. We will use this hypothesis to propose a constitutive framework for
Figure 3-17: Tension data for three load-unload cycles to 15% applied axial strain (measured 17% true axial strain) for patient Feb 16. (A) Nominal stress vs axial stretch [Mpa]. (B) Volume changes vs axial stretch.

the material behavior of the stroma which differentiates between different regions of the ECM.
Figure 3-18: Combined tension and compression data for three load-unload cycles in tension to 15% applied axial strain and three load-unload cycles in compression to -45% applied axial strain for patient Feb 16. (A) Nominal stress vs axial stretch [Mpa]. (B) Volume changes vs axial stretch.

Figure 3-19: Tension data for three load-unload cycles to 3 levels of applied strain (15%, 20% and 25%) for patient Mar 1. (A) Nominal stress vs axial stretch [Mpa]. (B) Volume changes vs axial stretch.
Figure 3-20: Combined tension and compression data for three load-unload cycles in tension to 15%, 20% and 25% applied axial strain and three load-unload cycles in compression to -35% applied axial strain for patient Mar 1. (A) Nominal stress vs axial stretch [Mpa]. (B) Volume changes vs axial stretch.

Figure 3-21: Magnification of the small stress regime for the combined tension and compression data for three load-unload cycles in tension to 15%, 20% and 25% applied axial strain and three load-unload cycles to -35% applied axial strain in the circumferential direction in compression for patient Mar 1.
Figure 3-22: Compression data for three load-unload cycles to -45% true axial strain applied in the circumferential direction for non-pregnant patient Feb 16. Left: schematic representation of the different deformation stages; Right: Nominal stress [MPa] vs axial stretch and volume changes vs axial stretch with the identified regions of the mechanical response.
Chapter 4

The Biomechanics of the Cervical Function: Healthy vs Insufficient Stroma

4.1 Introduction

In order to study the biomechanics of the cervical function and the complex physiological changes that occur to the cervix during pregnancy a better understanding of the anatomy of the cervix and the uterus, as well as the mechanical environment surrounding these structures, is necessary. An important factor affecting the cervical function is the anatomy of the organ during gestation [42]. Factors such as the geometrical dimensions of the organ and the inclination of the cervix with respect to a vertical os affect the biomechanics of the cervix and will be discussed in further detail in this chapter.

Two imaging techniques have been widely used in the clinical practice to visualize and to examine the changes in the physical characteristics of the cervix during pregnancy: ultrasound (see figure 4-1) and magnetic resonance imaging (MRI). For many years transvaginal sonography (TVS) imaging has been a common method to observe the cervix [58]. Nowadays transvaginal ultrasound has gained popularity in the surveillance of high risk pregnancies such as the case of cervical insufficiency [58] or twin pregnancies [12]. The ease of use as well as the added advantage
Figure 4-1: Ultrasound imaging of pregnancy. (A) Sagittal, midline view of the cervix at 21 weeks of gestation. (B) The same view with structures identified with a color code: yellow - cervical stroma; red - cervical mucosa.

of not requiring an empty bladder makes TVS the method of choice over the conventional transabdominal imaging technique commonly used to monitor the progress of pregnancy [81]. Ultrasound is a noninvasive method used to find flaws in materials by sending cyclic sound pressure waves with a frequency greater than 20 kilohertz.

Magnetic resonance imaging (MRI) is also a noninvasive method to visualize objects via utilization of non-ionizing radio frequency (RF) signals to acquire images and is best suited for non-calcified tissue. MRI can generate multiple two-dimensional cross-sectional images of tissue which can be used as a basis for a three-dimensional reconstruction. One major advantage of MRI imaging over ultrasonography is the better contrast and resolution of the images obtained via this technique [42].

Magnetic resonance (MR) diffusion tensor imaging (DTI) is another imaging method based on the Brownian motion of water molecules in objects and is based on the assumption that water more strongly diffuses inside and along directed structures in tissues rather than orthogonal to them. This imaging method has been successfully used to visualize anisotropy in the human uterus, as well as to visualize neuronal fibers in the living human brain, and to study fiber orientation in the myocardium [88].

Other examples of imaging techniques used in practice are, among others, computerized tomography (CT), stroboscopes and X-ray diffraction.
In general, MRI visualization of the cervix displays 3 distinct regions or zones in the organ [42]. The endocervical canal, a region which is composed predominantly of mucosa, is a region of a high signal intensity as visualized on a MR image. The stroma of the cervix comprises 2 distinct zones. The inner zone of the cervix is characterized by low signal intensity, while the outer region of the stroma is a zone of medium intensity. The zonal anatomy has been correlated to histological examinations of the stroma.

Figure 4-2: Sagittal ultrasound image showing the cervix, part of the uterus, the border between the mucosa and the stroma of the cervix and the following angles: 1) Cervical canal - cranio-caudal axis, 2) cervical canal - posterior uterus; 3) Cervical canal - anterior uterus. Copyright Dr. House.

4.2 Gross Characterization of the Cervix and the Uterus in Pregnancy

Dimensions of the normal nonpregnant human cervix available in the literature report an average length of 2.5 to 3 cm with an anteroposterior diameter of 2 to 2.5 cm and lateral diameter of 2.5 to 3 cm [27]. A cross-sectional representation of the cervix in the sagittal image would
visualize the shape of the endocervical canal as straight while in the frontal plane it would be "spindle shaped". Cervical wall thickness is reported as 1 cm throughout the length of the cervix. There are two sections of the cervix that can be differentiated. Portio supravaginalis and portio vaginalis are correspondingly the names of the sections above and below the vaginal reflection, which is identified as the site at about the junction of the inferior and middle thirds of the uterus. The uterus is supported via means of fascia and ligaments which can be collectively referred to as uterine supports. At the site of the cervix the uterine supports attach immediately superior to the vaginal reflection. The role of the of the uterine supports in the non-pregnant state is to stabilize the cervix in the center of the pelvis. Danforth compares the uterine supports to "guy ropes" with which the uterus pulls on the cervix during pregnancy in order to expel the fetus during the second stage of delivery [27].

The connection between the cervix and the uterus is referred to as the fibromuscular junction and is quite variable between different specimens. The exact point of transition between the myometrium, which is predominantly muscular tissue, and the cervix, which is predominantly collagenous tissue, is not well defined and can be determined at microscopic examination. The fibromuscular junction usually spans a few millimeters (2 or 3 mm), but in some organs can be more abrupt and still, in others, can be wider. The transition can also be determined by histological examination. A stained slide held in front of a light or a viewbox exhibits a discernible difference between the uterus, which shows in red, and the collagenous cervix, which shows in blue in the Masson's trichrome.

4.3 Construction of an Idealized 3-D Solid Geometry of the Abdominal and Lower Pelvic Region of a Pregnant Patient

House et al [42] used MR imaging to study the effect of gestational age and prior vaginal birth on the anatomy of the cervix during pregnancy. The second objective of this study was the reconstruction of the lower pelvic region geometry and real anatomy for the potential purposes of biomechanical modeling. The limitations of the ultrasound probe examinations, such as dependency on transducer position and distortion of the image, make such data unavailable with ultrasound measurements. MRI, with its superior image quality and resolution was the
House et al. studied a group of 57 patients with gestational ages between 17 and 36 weeks. MR images were available for 53 of these patients. For the purposes of the study by House et al., both the low and medium signal intensity zones of the cervix have been investigated. A stack of images obtained from the plane transverse to the endocervical canal was analyzed and measurements were taken for: 1) The area of the endocervical canal in cm². 2) The area of the cervical stroma. 3) The contents of the bladder. Additionally, three more geometrical parameters were analyzed: 1) The angle between the cervical canal and an axis running through the skull and the tail of the patient called the cranio-caudal axis. 2) The angle between the cervical canal and the posterior lower uterine segment. 3) The angle between the cervical canal and the anterior lower uterine segment (see figure 4-2).

Figure 4-3: MRI scan of the lower pelvis of a pregnant patient. (A) MR image. (B) Object map superposed on the MR image. Object map: green - bones; light pink - amniotic sac; dark pink - cervix; yellow - bladder; red - right obturator internus; orange - levator ani.

The oblique sections module of the Analyze software was used to analyze a stack of images from a plane transverse to the endocervical canal. Figure 4-3 shows an example of an MR image taken in a plane orthogonal to the canal (figure 4-3.A) and the object map of the identified structures superposed on the same MR image (figure 4-3.B). Manual segmentation was performed on each image based on signal intensity. Representative transverse slices were chosen and the areas of interest and average signal intensity were determined. This method...
was utilized to construct the solid geometry presented in figure 4-4.

Figure 4-4: 3-D reconstruction of the lower pelvis. Color code: gray - bones; light pink - amniotic sac; dark pink - cervix; yellow - bladder; red - right obturator internus; orange - levator ani.

Figure 4-5 shows an alternative method of solid model reconstruction, in which medical images are used to guide solid model creation with the solid modeling software from SolidWorks. Figure 4-5.A shows a stack of confocal ultrasound images with a superposed solid reconstruction of the lower uterine segment. Figure 4-5.B presents a single MR image with a superposed solid reconstruction.

Figure 4-6 shows a 3-D solid geometry constructed with SolidWorks. Figure 4-6.A shows a sagittal view of the structures of the cervix, the uterus and the amniotic sac. The posterior view of the same model is presented in figure 4-6.B. A cross-sectional view of the 3-D model reveals the detail of the cervix and the cervical canal and the apparent discernible characteristics of the zones of the mucosa, which fills the region of the cervical canal, and the collagenous region comprising the cervix (see figure 4-6.C).

The study by House et al [42] reported novel data about cervical anatomy, which is central to our work and was used as a basis for the development of a three-dimensional idealized solid geometry of the lower pelvic region of a pregnant patient. The findings reported an averaged angle between the cervical canal and the posterior uterine segment which is more acute than the angle between the cervical canal and the anterior uterine segment. For example the cervical canal - posterior uterus angle was reported as 95 degrees and the cervical canal - anterior uterus angle...
was reported as 127 degrees, which stayed the same throughout the duration of the study and were unaffected by previous vaginal deliveries.

Increased hydration of the cervical stroma was shown to correlate positively with increasing gestational age. The same dependency was established between gestational age and cervical size. Measurements of the endocervical canal reported mean cross-sectional area of 89 mm$^2$ at 20 weeks of gestation and 117 mm$^2$ at 32 weeks of gestation, which represented a 31% increase in the dimensions of the canal. An increase of the mean cross-sectional area of the cervix was also observed which corresponded to 31% increase from 672 mm$^2$ at 20 weeks to 880 mm$^2$ at 32 weeks. The mean cervical length was found to be 35.8±8.6 mm. In addition, it was found that the dimensions of the cervix were not affected by prior vaginal birth.

4.3.1 Anatomical Features

In cooperation with Tufts-NEMC an idealized 3-D computer model using solid modeling software from SolidWorks was constructed, which was based on anatomical data found by House et al [42]. A collection of images from MRI scans of pregnant patients was used as a guideline
to identify the basic features of the mechanical environment surrounding the cervix. Based on this study, the essential anatomical features comprising the idealized pelvis and abdomen were identified and include:

- cervical length
- cervical thickness
- diameter of the endocervical canal
- transverse and anteroposterior diameter of the pelvic outlet
- position and altitude of the cervix with respect to the pelvic floor and the pelvic inlet
- thickness and altitude of the pubovesical ligaments at the site of the cervix and the site of the pelvic bones
- dimensions of the amniotic sac as a function of gestational age (see figure 4-8).

Figure 4-6: 3-D solid model of the cervix, uterus and the amniotic sac. (A) Sagittal view. (B) Posterior view. (C) A sagittal cross-sectional view. Copyright Dr. House.

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Each of these features has been parameterized and can be varied independently in accordance with specific data collected from the individual patient.

The anatomical structures defining an idealized geometry of the abdominal region were created as separate assemblies in a single SolidWorks file (see figure 4-9). The separate geometrical regions were exported to ACIS files containing both the position and the topology of the model. Defeaturing and removal of excessive detail was performed prior to export in order to facilitate subsequent meshing. The data files were imported into the ABAQUS Part module where the model geometry was further repaired to attain the necessary precision. The finalized geometry was meshed into the ABAQUS Mesh module where virtual topology was used to ignore small features and produce smooth and continuous meshes. The resulting geometry is presented in figure 4-10.

### 4.3.2 Mechanical Support

The cervix attaches circumferentially to the uterus via means of the endopelvic fascia, which attaches at the site of the lower uterine segment. The fascia is composed by flat layer of
Figure 4-8: A sagittal view of a pregnant patient at 20 weeks of gestation showing the structure of the cervix (outlined in white) and dimensions of the amniotic sac.

fibrous tissue and ligaments. The major mechanical support of the cervix is provided by the pubovesical ligaments, which define the position of the organ and support it against longitudinal movement in a plane of symmetry. The pubovesical ligaments attach to the pubic symphysis and surround the bladder and the cervix. Transverse support of the cervical structure is provided by the cardinal ligaments, which ensheathe the cervix and attach at the site of the greater sciatic foramen at the back of the pelvis. In order to complete the definition of the pelvic geometry the thickness and the altitude of the cardinal and the pubovesical ligaments at the site of the cervix and at the site of the pelvic bones were identified as essential features affecting the mechanical environment of the uterine cervix.

4.3.3 Loading Conditions

The loading acting on the structure of the uterus and cervix in pregnancy can be categorized as active and inactive. Active loading is defined as the action of the myometrium which is referred to as uterine contraction. The passive loading of the structure comprises loads that tend to deform the organ in the absence of uterine contractions. As the fetus grows in the amniotic cavity the cavity expands and the amniotic sac comes in contact with the cervix around the time of the second trimester. The growth of the uterus and the amniotic membrane imposes tensile
Figure 4-9: Idealized 3-D geometry of a pregnant patient at the 20th week of gestation. (A) Solidworks model of the abdomen and pelvis. (B) Pelvic bones. (C) Superposition of the idealized abdominal and pelvic geometry and the structure of the bones.

loading by pulling on the structure of the cervix. Amniotic fluid pressures recorded at the 18th week of gestation by Barbera et al [8] range between 1 and 12 mmHg (133.3-1733.2 Pa). Under normal physiologic conditions at the 24th week of gestation the uterine cervix is subjected to mean intra-amniotic pressure of 8.4 ±3.3 cmH₂O (823.8±323.6 Pa) for uncomplicated gestations [34]. Another example of a passive load acting on the cervix in pregnancy is the hydrostatic loading due to the weight of the fetus and the contents of the amniotic membrane. The cervix is also loaded by a tissue layer connecting the fetal membranes and the inside of the uterus. The decidua establishes the contact between the membranes and the cervix. Evidence of loss of fetal fibronectin in patients with cervical insufficiency is thought to be an indication of a loss of the adhesion between the amniotic membranes and the uterus [43]. Estimating the loads on the cervix in pregnancy imposes a significant challenge as it is unique to the geometry and the pelvic forces of the individual patient.

4.4 Preliminary Constitutive Model for the Mechanical Behavior of the Cervix

A preliminary three-dimensional constitutive model for the large strain, time dependent mechanical behavior of the healthy cervical stroma was proposed by Socrate et al [31]. The
proposed model captures certain characteristics of the response of the tissue and reflects the microstructure of tissue. In this model, the major constituents of the extracellular matrix are identified as the collagenous network, the ground substance of negatively charged PGs and GAGs and interstitial fluid flow. The global response of the cervix comes from the contributions of each individual constituent, which undergo the same degree of macroscopic deformation. The rheological model for the proposed model is presented in figure 4-11. In this section only a brief summary of the model will be presented. For a more detailed discussion of the constitutive modelization of the cervical tissue the reader is referred to chapter 5 of this work.

4.4.1 Collagen Network

The collagen network is represented by an 8-chain unit cell with Langevin statistics for the force stretch behavior of the individual fibril. The following expression for the Cauchy stress is proposed

\[ T_c = \frac{N k_B \theta \lambda_L}{3} \left[ \frac{1}{\lambda_{fibril}} \beta_{fibril} \left( \frac{\lambda_{fibril}}{\lambda_L} \right) \mathbf{B} - \beta_0 \mathbf{I} \right] + K_c (J - 1) \mathbf{I}, \tag{4.1} \]

where \( N \) is the number of chains in a molecular network, \( k_B \) is the Boltzmann's constant, \( \theta \) is the absolute temperature and \( \lambda_L = \sqrt{n} \) is the collagen fibril locking stretch corresponding to the length of the fibril when fully distended. The last term on the right hand side of eq. 4.1

Figure 4-10: Idealized 3-D geometry of the abdomen and lower pelvic region of a pregnant patient at 20 weeks of gestation with identified structures.
Figure 4-11: Rheological model for the preliminary model for the stroma of the cervix [30].

is a linear bulk corrective term accounting for energy contributions, while the first term arises from entropic considerations. The stretch of the individual collagen fibril is given by

$$\lambda_{fibril} = \sqrt{\frac{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}{3}},$$  \hspace{1cm} (4.2)

where $\lambda_1$, $\lambda_2$, $\lambda_3$ are the principal stretches.

We identified 3 material parameters in the model for the collagen, which need to be fitted to experimental data:

- $\frac{N_k n^\theta}{3}$ initial modulus for the collagen
- $\lambda_L$ limiting stretch for the collagen fibril and $\lambda_L = \sqrt{n}$
- $K_c$ linear bulk modulus.
4.4.2 Glycosaminoglycan Network

The response of the GAGs in this model comes from the osmotic pressure, which arises due to the negative fixed charge density of the ground substance. The rheology of the GAG model includes an elastic part accounting for the osmotic pressure effects and a shear modulus, and a viscous element, accounting for the effect of relative sliding of neighboring GAG chains which give rise to the time-dependent non-equilibrium effects in the tissue response. Utilizing a multiplicative decomposition of the deformation gradient $F_G$ into an elastic $F_G^e$ and viscous parts $F_G^f$ we have

$$F_G = F_G^e F_G^f. \quad (4.3)$$

The elastic response is modeled by a linear elastic shear modulus and an osmotic pressure term:

$$T_G = \frac{1}{J} \left[ 2\mu_G E_G^e + \lambda_G (tr E_G^e) I \right] - \Pi_{os} I, \quad (4.4)$$

where $\mu_G$ is the shear elastic modulus, and $\lambda_G = K_G - \frac{2\mu_G}{3}$ is the second Lame coefficient, which for a case of bulk modulus $K_G = 0$ reduces to $\lambda_G = -\frac{2\mu_G}{3}$. Imposing the restriction of a volume preserving viscous flow, in the sense of $\det F_G^f = 1$, eq. 4.4 can be rewritten as

$$T_G = \frac{1}{J} \left[ 2\mu_G E_G^e - \frac{2\mu_G}{3} (tr E_G^e) I \right] - \Pi_{os} I. \quad (4.5)$$

$E_G^e$ in equations 4.4 and 4.5 is the Hencky strain given by

$$E_G^e = \ln V_G^e = \frac{1}{2} \ln B_G^e = \frac{1}{2} \ln F_G^e F_G^{eT}. \quad (4.6)$$

The osmotic pressure term $\Pi_{os}$ accommodates entirely the volumetric response of the GAG network.

Next, the velocity gradient $L$ for the viscous flow need to be constitutively prescribed in order to evolve the deformation gradient $F$.

$$L = \dot{F} F^{-1} = (F_G^e F_G^f) (F_G^e F_G^f)^{-1} \quad (4.7)$$

$$L = \dot{F}_G^e F_G^e^{-1} + F_G^e \dot{F}_G^f F_G^f^{-1} F_G^e^{-1} = L_G + \dot{L}_G \quad (4.8)$$
Separating the flow contribution to the velocity gradient into a symmetric (stretching) and skew (spin) parts as \( \mathbf{\tilde{L}}_G = \mathbf{\tilde{D}}_G + \mathbf{\tilde{W}}_G \) and prescribing an irrotational flow in order to satisfy the principles of material frame indifference we have

\[
\mathbf{\tilde{L}}_G = \mathbf{\tilde{D}}_G
\]

(4.9)

\[
\mathbf{\tilde{W}}_G = 0.
\]

(4.10)

The stretching tensor \( \mathbf{\tilde{D}}_G \) is constitutively specified as:

\[
\mathbf{\tilde{D}}_G = \gamma_f \mathbf{N}_G,
\]

(4.11)

where \( \mathbf{N}_G \) is the tensorial direction of the deviatoric part of the Cauchy stress \( \mathbf{T}_G = \mathbf{T}_G - \frac{1}{3}(\text{tr}\mathbf{T}_G)\mathbf{I} \) and

\[
\mathbf{N}_G = \frac{1}{\sqrt{2\tau_G}} \mathbf{T}_G', \quad \tau_G = \sqrt{\frac{1}{2} \mathbf{T}_G' \mathbf{T}_G'}. \]

The magnitude of the rate of viscous flow \( \dot{\gamma}_f \) is taken to depend linearly on \( \tau_G \) through an initial strain rate coefficient \( \dot{\gamma}_0 \) as given by eq. 4.12

\[
\dot{\gamma}_f = \dot{\gamma}_0 \tau_G.
\]

(4.12)

We identified three more material parameters in the model for the GAGs, which need to be fitted to experimental data:

- \( \mu_G \) elastic shear modulus for the GAGs
- \( K_G \) bulk modulus for the GAGs
- \( \dot{\gamma}_0 \) initial strain rate coefficient.

4.4.3 Interstitial Fluid Flow

Interstitial fluid flows through the porous extracellular matrix of the cervical stroma and attributes to the time-dependent non-equilibrium characteristics of the tissue behavior. The frictional effects arising as a result of a drag between the fluid flow and the porous ECM create a pressure drop in the fluid. In order to account for these effects fluid flow is created in the
tissue which can be described by a linear Darcy's law given by

\[ q = -k_D \nabla P_{\text{fluid}}. \]  

In equation 4.13, \( k_D \) is the Darcy hydraulic permeability coefficient, \( P_{\text{fluid}} \) is the dynamic fluid pressure, and \( q \) is the macroscopic volume flow rate.

The volume flow rate is linear and represents a flow in an isotropic material, and therefore does not account for variations with the pressure gradient. Nevertheless, this description of flow suffices for the purposes of a 3-D treatment of transient flow through the porous extracellular matrix.

### 4.5 Growth of the Cervix and the Uterus

The motivation to incorporate growth in the constitutive framework for the cervical tissue stems from the direct observation that the uterus grows throughout the gestational period with a small decrease in the thickness of the uterine wall. Moreover, House et al [42] reported slight increase in the dimensions of the cervix with the progression of pregnancy.

Growth is a fundamental process occurring in the development of biological tissues. A clear motivation for studying material growth of biological materials arises from the fact that the mechanical properties of biological materials directly depend on underlying cellular growth and death. Consequently, a biological material has the ability to adapt to its surroundings; therefore cells grow to accommodate specific mechanical loadings. This coupling effect of stress and growth is known as stress-modulated growth. A historic example of such growth is covered in the biomechanical literature of bone growth.

Growth (or resorption) is the process of continuously adding (or removing) material points. Several investigators have researched the growth in soft tissues [28], [33], [57], [45], [77].

There are several underlying assumptions and techniques adopted in the constitutive treatment of growth of soft tissues:

- the deformation gradient is multiplicatively decomposed into growth and mechanical part
- mass growth only occurs at a material point that already exists
- material points are added with same properties as surrounding material points
growth causes residual stress and reversely, residual stress causes growth
mass grows in a way not to alter prescribed material directions
different approaches are adopted to constitutively prescribe a growth deformation tensor.

4.5.1 Kinematics

Central to our treatment of growth is multiplicative decomposition of the total deformation gradient into its growth, plastic and elastic components. The decomposition of the total deformation gradient into an elastic and plastic part has been introduced in the constitutive theory by Kroner (1960) and Lee (1969).

We further hypothesize that growth occurs as an eigen-stretch at each material point. We define the initial configuration of the material as $B_0$ and assume the configuration is stress free. The deformed configuration $B_t$ is defined as the configuration that the material will occupy at some later time $t$ after it has undergone a deformation due to growth and due to some externally applied stress. If we elastically unload the material from the current deformed configuration to zero stress we can define a new stress free configuration $B_R$. The total deformation gradient $F$ is a map that relates an infinitesimal element in the reference configuration $dX$ and an infinitesimal element $dx$ in the current configuration according to

$$dx = FdX.$$  \hspace{1cm} (4.14)

Adopting the Kroner-Lee idea for multiplicative decomposition of the deformation gradient $F = F^eF^p$ and further expanding it we introduce a new multiplicative split of the deformation gradient into its growth, plastic and elastic parts given by

$$F = F^eF^pF^g,$$  \hspace{1cm} (4.15)

where $F^e$ is the corresponding map between the current and the intermediate (relaxed) configuration, $F^p$ is the map between the two relaxed configurations, and $F^g$ is the map between the reference and the grown (relaxed) configurations.

The two intermediate configurations introduced are not real configuration in the sense, that they do not represent a real physical state of the material. They are defined as configurations in
which the material is in a stress free state. This can be viewed in a way that if the material in the current configuration was dissected into small pieces and each one of these pieces was stressed elastically, the whole collection of material points will end in a configuration in which is stress free and incompatible. However, this does not pose a difficulty for establishing constitutive relationships, because it suffices for analysis to establish a constitutive theory for any of the small material pieces (see figure 4-12). Additionally, the two stress-free configurations are non-unique, since an arbitrary rotations of intermediate configuration will result in an infinite number of stress free configurations.

Figure 4-12: Decomposition of the total deformation gradient into growth, plastic and elastic parts. $B_0$ is the initial configuration, $B_g$ and $B_R$ is the intermediate unstressed configurations.

4.5.2 Rate Quantities

We define the total deformation gradient $L$ as the gradient of the velocity field in the current configuration (see figure 4-12). Presented further is an additive split of $L$ into $L^e$ that controls how much the material deforms elastically, $L^f$ that controls how much the material flows, and $L^g$, that controls how much the material grows. $L^e$, $\tilde{L}^f$, and $\tilde{L}^g$ are the velocity gradients in
the current configuration. The split of \( L \) into \( L^e \), \( \bar{L}^f \), and \( \tilde{L}^g \) is as follows:

\[
\begin{align*}
L &= \dot{F}F^{-1} \quad (4.16) \\
&= (F^eF^fF^g)(F^eF^fF^g)^{-1} \quad (4.17) \\
&= \dot{F}eF^{e-1} + F^e\dot{F}^fF^{f-1}F^{e-1} + F^eF^f\dot{F}^gF^{g-1}F^{f-1}F^{e-1} \quad (4.18) \\
&= L^e + F^eL^fF^{e-1} + F^eF^fL^gF^{g-1}F^{f-1}F^{e-1} \quad (4.19) \\
&= L^e + \bar{L}^f + \tilde{L}^g. \quad (4.20)
\end{align*}
\]

Next we separate the growth contribution to the velocity gradient into a symmetric (stretching) and skew (spin) parts as

\[
\tilde{L}^g = \tilde{D}^g + \tilde{W}^g, \quad (4.21)
\]

where \( \tilde{D}^g \) and \( \tilde{W}^g \) are respectively the symmetric and the skew parts of \( \tilde{L}^g \):

\[
\tilde{D}^g = \text{sym} \tilde{L}^g, \quad (4.22)
\]
\[
\tilde{W}^g = \text{skw} \tilde{L}^g. \quad (4.23)
\]

In order to address the issue of the non-uniqueness of the decomposition of \( F = F^eF^pF^g \) we prescribe an irrotational spin part of the growth velocity gradient \( \tilde{W}^g \) as proposed by Boyce et al [17] which in general results in elastic, plastic and growth components that contain rotations:

\[
\tilde{W}^g = 0. \quad (4.24)
\]

We further prescribe the stretching tensor as composed of two parts: a isotropic part, which accounts for isotropic growth, and a biased growth term in the direction of the deviator of the stress state given by

\[
\tilde{D}^g = \tilde{D}_{\text{iso}}^g + \tilde{D}_{\text{bias}}^g. \quad (4.25)
\]

The isotropic term is simply prescribed by a growth in equal amounts in all directions \( \tilde{D}_{\text{iso}}^g \| I \) as in eq. 4.26:

\[
\tilde{D}_{\text{iso}}^g = \alpha I, \quad (4.26)
\]
where $\alpha$ is the isotropic growth stretching rate, which needs to be prescribed. The biased growth stretching term is prescribed parallel to the tensorial direction $N_{T'}$ of the deviator of the total stress in the current configuration $T'$, $\mathbf{D}_{\text{bias}}^g \parallel T'$,

$$
\mathbf{D}_{\text{bias}}^g = \beta N_{T'},
$$

where $\beta$ is a biased growth stretching rate, and $T'$ is the deviator of the total stress in the current configuration:

$$
T' = T - \frac{1}{3} tr T, \quad N_{T'} = \frac{1}{\sqrt{2}\tau} T', \quad \tau = \frac{||T'||}{\sqrt{2}}.
$$

Finally, the evolution of the growth deformation gradient is given by

$$\dot{F}^g = \mathbf{D}^g F^g. \quad (4.28)$$

### 4.5.3 Results: Growth of the Healthy Cervical Stroma and Uterus

Our preliminary study of the biomechanics of cervical dilation investigates two particular cases of cervical function in pregnancy. The first case studies the growth of the healthy cervix and the material properties for the individual structures were selected to reflect the normal cervical tissue and presented in Table 4.1.

Transient effects associated with the flow of the interstitial fluid through the porous extracellular matrix and relative sliding of neighboring GAG molecules are associated with shorter times spanning periods on the time scale of minutes, which are consistent with the experimental times. The dilation of the insufficient cervix occurs over the course of days and weeks. Over such long time periods the transient effects associated with the aforementioned mechanisms die off and the material response reaches an equilibrium. Subsequently, a reduced model taking into account only the shear part of the network response and equilibrium hydrostatic response was implemented in the finite element simulation of growth of the healthy cervical stroma (see Figure 4-13).
Figure 4-13: Reduced rheological model for the material behavior of the healthy cervical stroma.

**Finite Element Implementation**

The commercially available finite element solver ABAQUS Explicit version 6.3 and 6.4 were used for the simulations of the dilating cervix. The proposed constitutive model for a healthy cervical tissue was implemented as a three-dimensional FORTRAN user subroutine. The elements used for the structure of the uterus and the cervix were C3D4, continuum 4-node linear tetrahedron elements and the elements chosen for the membrane were S3R, a 3-node triangular general-purpose shell with finite membrane strains.

**Material Properties of the Cervix and the Uterus**

Angle dependent material properties were assigned for the structures of the stroma and the uterus in order to establish the difference in the mechanical behavior of these structures. The transition was selected as a narrow zone above the internal cervical os. Table 4.1 summarizes the material parameters chosen for the simulation of the healthy cervical stroma.

The viscous flow of the ground substance was not incorporated in the simulation of the healthy cervical stroma.

The material properties chosen for the surrounding structures necessitates the prescription of mechanical properties for these entities. Since our main focus is the mechanical behavior
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_G$</td>
<td>Pa</td>
<td>Shear modulus GAGs</td>
<td>1,650</td>
</tr>
<tr>
<td>$K_G$</td>
<td>Pa</td>
<td>Bulk modulus GAGs</td>
<td>60,000</td>
</tr>
<tr>
<td>$\Pi_{os}$</td>
<td>Pa</td>
<td>Osmotic pressure GAGs</td>
<td>50,186</td>
</tr>
<tr>
<td>$\lambda_{initial}$</td>
<td></td>
<td>Collagen prestretch</td>
<td>1.16</td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td></td>
<td>Collagen locking stretch</td>
<td>1.2</td>
</tr>
<tr>
<td>$N_{E_{coll}}$</td>
<td>Pa</td>
<td>Initial collagen modulus</td>
<td>1,000</td>
</tr>
<tr>
<td>$K_c$</td>
<td>Pa</td>
<td>Bulk modulus collagen</td>
<td>50,000</td>
</tr>
</tbody>
</table>

Table 4.1: Constitutive parameters for the healthy cervical stroma

of the cervical stroma only, the mechanical properties for the surrounding structures were prescribed such as to provide a realistic, but not necessarily exact representation of the mechanical environment around the cervix and the uterus in pregnancy. Simple linear elastic or hyperelastic were used with corresponding coefficients in the bull park of the data reported in the literature.

**Abdominal Organs**

Material properties for the abdominal organs were reported by Miller [63]. The abdominal organs were constitutively prescribed as non-linear viscoelastic and the organs of the kidney and the liver were studied in particular. Equilibrium material coefficients are reported as 6,206 Pa for liver and 898 Pa for kidney. For our finite element mode implementation the mechanical behavior of the structure of the abdominal organs was simplified and prescribed as linear elastic. The corresponding parameter choice for our simulation was Young’s modulus $E_{organs} = 10,000$ Pa and Poisson’s ratio $\nu = 0.2$.

**Endopelvic and Abdominal Fascia**

The tensile strength of fascia has been researched by Zeng et al [90]. Tensile strength of 2-3 MPa were estimated from the data. Linear elastic constitutive behavior for the fascia was chosen for our finite element simulations with Young’s modulus $E_{organs} = 100,000$ Pa and Poisson’s ratio $\nu = 0.4$.  

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Amniotic Membrane

Despite the extensive research on the topic, the mechanical properties of the human chorioamnion are not well characterized. The properties of the amniotic membrane have been thoroughly investigated by Prevost [75] in our research group. Prevost proposes a microstructurally based constitutive model for the mechanical behavior of the membrane, which allows for a non-linear hyperelastic response at large deformation. Based on this work, a simplified hyperelastic material response for the amniotic membrane was implemented in our 3-D simulations.

The form of the reduced polynomial strain energy potential is given by

\[ U = C_{10}(\tilde{I}_1 - 3) + C_{20}(\tilde{I}_1 - 3)^2 + C_{30}(\tilde{I}_1 - 3)^3 + \frac{1}{D_1}(J^{el} - 1)^2 + \frac{1}{D_2}(J^{el} - 1)^4 + \frac{1}{D_3}(J^{el} - 1)^6, \] (4.29)

where \( \tilde{I}_1 = \lambda_1^2 + \lambda_2^2 + \lambda_3^2 \) is the first isochoric invariant and \( \lambda_i = J^{-1/3}\lambda_i \) are the isochoric stretches.

The initial shear and bulk modulus for a material with such hyperelastic behavior are given by

\[ \mu_0 = 2C_{10} \quad \text{and} \quad K_0 = \frac{2}{D_1}. \]

The material parameters for the model were chosen as \( C_{10} = 15,000 \) Pa, \( C_{20} = 0 \) Pa, and \( C_{30} = 300 \) Pa.

Finite Element Simulations

The dilation of the insufficient cervix occurs at the end of the second trimester or early in the third trimester of pregnancy, approximately at the 20th week of the gestation. The dilation of the cervix happens over prolonged times spanning on average a period of 3 to 4 weeks. Therefore, for the finite element simulations a initial configuration at the 20th week of gestation was chosen (see figure 4-14). The uterine dimensions were chosen to represent average dimensions of the myometrium at this stage of the gestation (20 cm between the inner os of the cervix and the highest point of the uterus and 7 cm between the anterior and posterior wall of the uterus in the bulkiest part).
Figure 4-14: Solid model of the abdominal and pelvic region of a pregnant patient at the 20th week of gestation.

**Loading History**

The loading conditions were selected to simulate the physiologic loading conditions of the cervix and the uterus from the twentieth to the twenty-fourth week of pregnancy. The loading history of the simulation followed 4 steps.

Step 1 incorporated stabilizing the membrane and application of intrauterine pressure of 250 Pa until the structure of the membrane established contact with the structure of the uterus. In Step 2 the constraint on the amniotic membrane was released. A hydrostatic pressure of 1500 Pa, which was linearly increased during the simulation step to 2000 Pa, and intrauterine pressure of 1000 Pa, were applied. This load simulated the effect of gravity on the stress distribution in the uterus and the cervix. In Step 3 and Step 4 the uterus was allowed to grow, and the further gravity and linearly varying pressure of 2000 Pa at the beginning of the 3rd and 3000 Pa at the beginning of the 4th step were applied.

The uterus was allowed to grow both isotropically and preferentially in the direction of the deviator of the applied stress with a very small decrease in the thickness of the uterine wall over the duration of the simulation. The amniotic membrane was aligned with the internal wall of the
uterus. The amniotic sac was simulated as a shell element with hyperelastic material properties. The contact conditions between the two structures were imposed as a frictional exponential contact between the two structures which was implemented due to clinical observation of good adhesion between the uterus and the amniotic membrane in the case of a normal pregnancy.

The resulting growth of the uterus is portrayed in figure 4-15 where the changes in the initial state at the 20th week of gestation, shown in figure 4-15.A, and the 24th week of gestation, shown in figure 4-15.B, are apparent.

It is clinically observed that the uterus grows throughout pregnancy with a very small reduction in the thickness of the uterine wall. Average uterine dimensions at the 20th week of gestation are reported as 20 cm length of the longer diagonal between the site of the internal cervical os and the highest point of the uterus. At 24 weeks of gestation this dimension increases to 25 cm. Growth was implemented in order to reproduce the realistic boundary conditions around the cervix at the 24th week of the gestation. The constitutive parameters for the isotropic stretching rate $\dot{\alpha}$ and the biased stretching rate $\dot{\beta}$ were chosen to account for the correct anatomical dimensions of the uterus at the 24th week of pregnancy.

Figure 4-16 shows the distribution of the Mises stress in the cervix and the uterus. A higher
stress distribution is observed in the area of the middle section of the uterus, where as a result of the expansion of the membrane, the applied intrauterine pressure, and the inclination of the structure, the wall of the uterus experiences tensile stresses.

Figure 4-16: Growth from 20th week to 24th week of gestation - Mises stress distribution. (A) Reference state at 20th week of gestation. (B) Grown uterus at the 24th week of gestation.

4.6 Biomechanics of Funneling

Funneling of the uterine cervix at term is a prerequisite for the normal course of delivery. In the case of a healthy cervical stroma, the dilation of the cervix is facilitated by contractions from the uterine smooth muscle. The funneling of the insufficient cervix occurs gradually and asymptotically over the course of weeks and is not accompanied by uterine contractions. Funneling can be visualized by ultrasound as a dilation of the internal os and sometimes a herniation of the fetal membranes into the endocervical canal. Such a configuration of dilated internal os is associated with 33% risk of premature delivery. Together with a cervical length shorter than 3cm, funneling can be diagnostic of potential risk of preterm birth [13].

It is well known to the medical community that the outcome of pregnancy is affected by a number of factors. The geometry of the cervix, the physiologic loads comprising the mechani-
ical environment around the cervix and the uterus in pregnancy, as well as the adhesion of the fetal membranes to the uterine walls are key parameters influencing the funneling of the uterine cervix. Notwithstanding the importance of these factors individually, there is a lack of understanding of the complex interplay among them as well as the physical mechanisms leading to a preterm birth.

Our objective is to investigate the individual as well as the combined effect of the aforementioned biomarkers on the progress of cervical dilation.

4.6.1 Constitutive Prescription of Funneling

Healthy (competent) cervical tissue undergoes substantial restructuring during pregnancy, which is called cervical maturation, as previously discussed in detail in chapter 2. The insufficient cervical tissue is also associated with altered tissue biochemistry, which can be a tissue restructuring at a premature stage of pregnancy or, in some cases, a congenital condition predating pregnancy.

We hypothesize that the cervical tissue dilates due to a relaxation of the collagen network and is based on the evidence that the extractability of collagen increases and the cross-linked density of the fibrous network decreases in the insufficient stroma. Additionally, fetal fibronectin discharge in patients with cervical insufficiency is suggestive of a weakened membrane adhesion resulting in a protrusion of the membranes into the endocervical canal of the patient. Indeed, based on clinical observations, in the case of healthy cervical stroma cervical dilation occurs in a normal fashion proceeding from the internal os towards the external os and the amniotic membranes remain firm and tout, as we could also observe in our finite element simulation of the growing healthy cervix.

Relaxation of the Collagen Network

A similar framework for the relaxation of the collagen network was adopted as the previously proposed for the viscous flow of the ground substance. The decomposition of the velocity gradient into an elastic and relaxation components is as follows

\[ L = \dot{\mathbf{F}} \mathbf{F}^{-1} = (\mathbf{F}_c^e \mathbf{F}_c^r)^{-1} (\mathbf{F}_c^e \mathbf{F}_c^r)^{-1} \]  

(4.30)
\[ L = \hat{F}_c^e F_c^{e-1} + F_c^e \hat{F}_c^e F_c^{e-1} = L_c + \tilde{L}_c. \] (4.31)

Again the relaxation contribution to the velocity gradient is presented as as sum of a symmetric (stretching) and skew (spin) parts as \( \tilde{L}_c = \tilde{D}_c^r + \tilde{W}_c^r \). We prescribe an irrotational flow in order to ensure uniqueness of the intermediate configuration such as

\[ \tilde{L}_c^r = \tilde{D}_c^r \]

(4.32)
\[ \tilde{W}_c^r = 0. \] (4.33)

The next step calls for constitutive prescription of the stretching tensor \( \tilde{D}_c^f \) which is specified as

\[ \tilde{D}_c^r = \dot{\gamma}^r N_c, \] (4.34)

where \( N_c \) is the tensorial direction of the deviatoric part of the Cauchy stress in the collagen network \( T_c' = T_c - \frac{1}{3} (trT_c) I \) and

\[ N_c = \frac{1}{\sqrt{2} \tau_c} T_c', \quad \tau_c = \frac{||T_c'||}{\sqrt{2}}. \]

The magnitude of the rate of relaxation \( \dot{\gamma}^r \) is chosen as presented in 4.35

\[ \dot{\gamma}^r = \dot{\gamma}_0^r \left( \frac{\tau_c}{\tau_0 c} \right)^{m_c}, \] (4.35)

where \( \tau_0 c, \dot{\gamma}_0^r \) and \( m_c \) are material parameters and \( \dot{\gamma}_0^r \) has the units of \( 1/\text{s} \). Such a form for the relaxation rate has been successfully used, for example, in the constitutive modeling of ultra-high molecular weight polyethylene [14].

**Decreased Cross-link Density**

In order to capture the effects of the decrease in the cross-linking of the tissue, the material parameters chosen for our simulations have been modified to reflect these changes. Our hypothesis of weakening of the stroma due to reduced cross-linking can be captured by a lower initial collagen modulus and an increased collagen locking stretch. These changes in turn affect the osmotic pressure of the GAGs. A slightly reduced bulk modulus for the collagen was chosen,
<table>
<thead>
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<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td><em>Intrauterine pressure</em></td>
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<tr>
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<td>Pa</td>
<td><em>Hydrostatic pressure</em></td>
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<td>Pa</td>
<td><em>Intrauterine pressure</em></td>
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<tr>
<td></td>
<td>Pa</td>
<td><em>Hydrostatic pressure</em></td>
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</tr>
<tr>
<td>3</td>
<td>Pa</td>
<td><em>Intrauterine pressure</em></td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>Pa</td>
<td><em>Hydrostatic pressure</em></td>
<td>1000</td>
</tr>
<tr>
<td>4</td>
<td>Pa</td>
<td><em>Intrauterine pressure</em></td>
<td>3000</td>
</tr>
<tr>
<td></td>
<td>Pa</td>
<td><em>Hydrostatic pressure</em></td>
<td>1000</td>
</tr>
</tbody>
</table>

Table 4.2: Loading history for the funneling simulation

in order to reflect the fact of increased hydration of the stroma and smaller bulk resistance to expel the water out of the tissue. The parameter choice for the simulation is presented in table 4.3.

### 4.6.2 Results: Funneling of the Insufficient Cervix

**Loading History**

The same loading history was applied as for the case of growth of the healthy cervix. A summary of the applied loads is presented in table 4.2. Additionally, the structure of the fetal membrane was allowed to grow simultaneously at the same rate of the growth of the uterus. There was no adhesion between the structure of the uterus and the structure of the membrane in the lower uterine region close to the internal os. Frictional contact interaction properties were assigned in a narrow region between the external top surface of the membrane and the internal top surface of the myometrium in order to stabilize the structure of the membrane.

**Material Properties of the Cervix and the Uterus**

The material parameter choice for insufficient cervical stroma is presented in table 4.3. Three more parameters were included in the description of the insufficient cervix, which account for the different mechanical behavior of the insufficient stroma as compared with the healthy case.

Representative simulation results for the distribution of stress in the cervix and the uterus are plotted in figure 4-17. The corresponding deformation can be better observed in figure 4-18. The results show that the stress distribution around the cervix is not constant. Stress
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_G$</td>
<td>Pa</td>
<td>Shear modulus GAGs</td>
<td>1,650</td>
</tr>
<tr>
<td>$K_G$</td>
<td>Pa</td>
<td>Bulk modulus GAGs</td>
<td>60,000</td>
</tr>
<tr>
<td>$\Pi_{os}$</td>
<td>Pa</td>
<td>Osmotic pressure GAGs</td>
<td>3,627</td>
</tr>
<tr>
<td>$\lambda_{initial}$</td>
<td></td>
<td>Collagen prestretch</td>
<td>1.16</td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td></td>
<td>Collagen locking stretch</td>
<td>1.36</td>
</tr>
<tr>
<td>$N_{c,0}$</td>
<td>Pa</td>
<td>Initial collagen modulus</td>
<td>500</td>
</tr>
<tr>
<td>$K_c$</td>
<td>Pa</td>
<td>Bulk modulus collagen</td>
<td>5,000</td>
</tr>
<tr>
<td>$\dot{\gamma}_0$</td>
<td>1/s</td>
<td>Rate of relaxation</td>
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</tr>
<tr>
<td>$\tau_{0c}$</td>
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<td>Flow strength for collagen</td>
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</tr>
<tr>
<td>$m_c$</td>
<td></td>
<td>Flow sensitivity coefficient</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.3: Constitutive parameters for the insufficient cervical stroma

Concentration is observed at the site of the lower uterus where funneling begins at the internal os of the cervix. In the case of an impaired cervical function due to insufficiency, the deformation of the dilating cervix is shown to progress from the internal os to the external os of the endocervical canal following a T (see figure 4-17.A and figure 4-18.A), Y (see figure 4-17.B and figure 4-18.B), V (see figure 4-17.C and figure 4-18.C), and U (see figure 4-17.D and figure 4-18.D) progression of deformation. When completely dilated the cervix assumes a “U” shape (see figure 4-17.D and 4-18.D) with fetal membranes bulging out at the site of the external os (figure 4-18.D), consistent with clinical observations (figure 1-3). In comparison, when the simulations were performed with material parameters chosen to represent the healthy state of the stroma (see the discussion about the growth of the healthy cervical stroma and uterus), opening of the cervix and protrusion of the amniotic sac into the canal was not observed.

The results show that once the stresses around the internal cervical os reach a certain level, the affected stroma experiences creep and a funnel starts to form. Further increase in the level of the applied load broadens the high stress concentration zone around the internal os and more material starts to flow, therefore allowing for the formation of a funnel.

Additionally, what can be clearly observed in the simulation results presented in figure 4-18, is the deformation of the structure of the fetal membrane. The mechanical behavior of the fetal chorioamnion is a peculiar one as well. As observed by Prevost [75], when subjected to biaxial extension, the structure of the fetal membrane is capable of withstanding a substantial amount of load. Interestingly, when subjected to uniaxial extension, the fetal membrane exhibits...
creep and stress relaxation. As funnelling initiates, the fetal membrane makes its way into the endocervical canal, which in the case of insufficient stroma readily opens at the internal os (figure 4-18.B) by making a small bulge with hemispherical shape. Based on the results of our simulation we hypothesize that such a configuration for the membrane is possibly the one that is necessary in order for the membranes to start experiencing uniaxial tension in a direction parallel to the cervical canal and therefore start to undergo creep. Once the membranes start protruding into the canal they additionally apply load on the internal cervical walls and facilitate the dilation of the cervical structure. The results clearly show that the progression of

![Figure 4-17: Stress distribution and the progression of funnelling. (A) Initial configuration. (B) Funnelling initiates at the internal cervical os. (C) Characteristic "V" shape of the progression. (D) Fully dilated cervix in the "U" shape.](image)

the funnelling of the cervix can be captured with modeling tools such as finite element solvers. Unfortunately, at the stage when the simulations were carried out there were insufficient data
available to correlate the simulation parameters and experimental values. Therefore, in this initial implementation of the constitutive model and three dimensional geometry we were only able to assess the progression of the deformation, rather than draw conclusions about the exact material parameters for the stroma. The material model constitutive parameters were selected to give a good agreement of the finite element model simulation and the actual mechanical behavior of the dilating cervix in the case of cervical insufficiency.

Figure 4-18: The progression of deformation of the dilating insufficient cervix. (A) Initial configuration. (B) Funneling initiates at the internal cervical os and the cervix assumes characteristic "Y" shape. (C) Characteristic "V" shape of the progression. (D) Fully dilated cervix in the final "U" shape with fetal membranes protruding at the site of the external os.

In conclusion, our preliminary results obtained from the 3-D simulation give a good qualitative representation of the stress distribution and typical deformation history for the insufficient cervix. Essential features captured with the simulations are the high stress concentration in a narrow area close to the internal cervical os and protrusion of the amniotic membrane into the
endocervical canal.

4.7 Contractionsof the Uterus and the Progress of Cervical Dilation

It is well known that the myometrium is not a latent structure in pregnancy [67]. Uterine contractility is typical for the entire duration of the gestation. In an early stage of pregnancy the uterus undergoes regular increases of intrauterine pressure of very low amplitude by means of contractions, which were described by Braxton-Hicks in 1890 and therefore are nowadays referred to as Braxton-Hicks contractions. This uterine activity though differs from the uterine activity during labor in a substantial way. Uterine contractions are a prerequisite for delivery and are well documented. A way to assess the contractile activity of the myometrium is to analyze individual events characterizing the contractions such as the duration and the amplitude of the contraction, as well as intrauterine pressure increase. We used our three dimensional solid model together with the material parameters of a healthy cervical stroma in order to demonstrate the effect of uterine contractions on the cervical effacement and dilation.

The effect of uterine contraction was implemented as negative growth of the uterus. The constitutive parameters for the isotropic stretching rate $\alpha$ and the biased stretching rate $\beta$ were accordingly chosen to produce the effect of shrinkage of the uterus in order to simulate the contractile activity at term.

4.7.1 Results: Contraction of the Uterus and the Progress of Cervical Dilation

Loading History

The loading history for the contraction simulations is summarized in table 4.4. The structure of the fetal membrane has no adhesion to the uterine structure in its lower segment. Frictional contact interaction properties were assigned between the external top surface of the membrane and the internal top surface of the myometrium in order to stabilize the structure of the membrane.
### Table 4.4: Loading history for the simulation of uterine contractions

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intrauterine pressure</td>
</tr>
<tr>
<td>2</td>
<td>Gravity at 20 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Intrauterine pressure</td>
</tr>
<tr>
<td>4</td>
<td>Growth to 24 weeks</td>
</tr>
<tr>
<td>5</td>
<td>Gravity at 24 weeks</td>
</tr>
<tr>
<td>6</td>
<td>Uterine contraction</td>
</tr>
<tr>
<td>7</td>
<td>Rest</td>
</tr>
<tr>
<td>8</td>
<td>Uterine contraction</td>
</tr>
</tbody>
</table>

### Table 4.5: Constitutive parameters for the healthy cervical stroma chosen for the simulation of uterine contractions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>$\mu_G$</td>
<td>Pa</td>
<td>Shear modulus GAGs</td>
<td>1,650</td>
</tr>
<tr>
<td>$K_G$</td>
<td>Pa</td>
<td>Bulk modulus GAGs</td>
<td>60,000</td>
</tr>
<tr>
<td>$\Pi_{os}$</td>
<td>Pa</td>
<td>Osmotic pressure GAGs</td>
<td>3,627</td>
</tr>
<tr>
<td>$\lambda_{initial}$</td>
<td>Pa</td>
<td>Collagen prestretch</td>
<td>1.16</td>
</tr>
<tr>
<td>$\lambda_f$</td>
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<td>Collagen locking stretch</td>
<td>1.36</td>
</tr>
<tr>
<td>$N_{k,b}$</td>
<td>Pa</td>
<td>Initial collagen modulus</td>
<td>2000</td>
</tr>
<tr>
<td>$K_c$</td>
<td>Pa</td>
<td>Bulk modulus collagen</td>
<td>5,000</td>
</tr>
</tbody>
</table>

### Material Properties of the Cervix and the Uterus

Again, the difference in the mechanical behavior of the cervix and the uterus is accounted for by angle varying properties chosen to account for the case of a healthy stroma. For a summary of the material parameter choice the reader is referred to table 4.5.

### Abdominal Organs

Linear elastic material properties were assigned to the structure of the internal organs with Young’s modulus $E_{organs} = 10,000$ Pa and Poisson’s ratio $\nu = 0.2$.

### Endopelvic and Abdominal Fascia

The abdominal fascia was simulated as a linear elastic material with Young’s modulus $E_{abdominal fascia} = 100,000$ Pa and Poisson’s ratio $\nu = 0.4$. The structure of the endopelvic fascia was implemented
as an transversely isotropic elastic material with coefficients $C_{11} = 100,000 \text{ Pa}$, $C_{12} = C_{13} = 1,000 \text{ Pa}$, and $C_{44} = 350 \text{ Pa}$.

**Amniotic Membrane**

The material parameters for the amniotic membrane were chosen to be hyperelastic with coefficients $C_{10} = 1,740 \text{ KPa}$ and $C_{30} = 300 \text{ Pa}$.

Representative simulation results are shown in figure 4-19 and figure 4-20. Figure 4-19 left represents the deformation profiles generated due to contractile activity of the uterus. The corresponding maximum principal strains are presented in the middle of figure 4-19 together with their strain levels (right).

The initial configuration at the 20th week of gestation is presented in figure 4-19.A. After growth to the 24th week the enlarged structure of the uterus is presented in figure 4-19.B. Figure 4-19.C shows the initiation of the first contraction in our simulation. A narrow area around the internal cervical os is the site of the highest maximum principal strain concentration. Already at this state of the simulation the reduction of cervical length can be observed. Figure 4-19.D depicts the deformation of the cervix and the peak of the first contraction. The shortened cervical length is apparent. Figure 4-20.B and C shows the associated stress distribution at the beginning and the peak of the contraction. The simulation shows that the entire structure of the uterus undergoes tension. The structure of the cervix exhibits a complex stress state. Close to the internal os the cervix is in a state of tension due to the pull of the strong myometrium. The bottom part of the cervix does not feel the myometrial activity and is in a stress free state. Subsequent to the first contraction a period of rest was simulated, in order to reproduce a realistic myometrial activity. During this period, in the absence of load from the uterus, the stresses in both the structure of the cervix and the uterus decrease substantially and become more evenly distributed over the two entities. This situation is presented in figures 4-19.E and 4-20.D. The effect of a second contraction can be observed in 4-19.F and 4-20.E. Higher levels of stress are recorded as a result of the second contraction. The area of maximum principal strain distribution is enlarged substantially and affects a significant portion of the cervix around the internal cervical os. The cervix is also substantially shortened and the opening of the endocervical canal at the internal os is greatly increased. The amniotic membrane is slightly
Figure 4-19: Uterine contractile activity. Left: deformation profile, middle: strain distribution, right: strain levels. (A) Initial configuration: the cervix and the uterus at the 20th week of gestation. (B) The grown uterus and cervix at the 24th week of gestation. (C) Initiation of contraction. (D) Peak of the first contraction. (E) Resting state following the contraction. (F) Peak of the second contraction.
protruding into the endocervical canal.

In the case of funneling the cervix was dilating under the action of much lesser loads. Unlike the case of insufficient stroma, which starts to dilate progressively once the funnel initiates, following a TYVU deformation pattern accompanied by membrane protrusion into the endocervical canal, as a result of a contraction in the healthy case the cervix opens at the internal os assuming a "Y" shape which does not proceed to the subsequent "V" state of deformation typical for dilation. Rather, the cervix shortens while the geometry of the deformation remains the same. The pull of the myometrium causes the opening of the canal to become bigger, but the stroma posterior to the affected one is providing sufficient structural support to keep the cervix in a closed state. The membrane, even though making its way into the canal, does not herniate in the canal as in the case of dilation.

Figures 4-21, 4-22, and 4-23 show the development of pressure, Mises and maximum principal stresses at the internal os, correspondingly. We can see how the intrauterine pressure increased to reach a peak value during the contraction, then decreased during the resting stages of the simulation. Subsequent contraction causes increased intrauterine pressure levels, consistent with clinical observations. The intrauterine pressure increased from \(\sim 1000\text{Pa} \ (10\text{mmHg})\) to \(4000\text{Pa} \ (30\text{mmHg})\) at the peak of the first contraction. Subsequently during the second contraction the intrauterine pressure increased from \(\sim 2800 \text{ Pa} \ (20\text{mmHg})\) to \(7000 \text{ Pa} \ (50\text{mmHg})\) at the peak of the contraction, which is consistent with the clinically reported data. The increase in the Mises and the maximum principal stresses at the site of the internal os underwent a similar increase. The cervical length shortened progressively, nevertheless a funnel failed to form.

### 4.8 Axisymmetric vs 3-D Geometry

Next we assessed the possibility of implementing a simplified axisymmetric geometry in order to carry out parametric studies and investigate the role of different anatomical factors on the strength of the stroma. As a first step we created an idealized axisymmetric geometry of the abdominal and the pelvic region of a pregnant patient at the 20th week of gestation, capturing essential geometrical detail comprising the mechanical environment of the cervix and
Figure 4-20: Stress distribution in the uterus and the cervix during uterine contractile activity. Left: Mises stress distribution, right: corresponding stress levels. (A) Initial grown configuration: the cervix and the uterus at the 24th week of gestation. (B) Initiation of contraction. (C) Peak of the first contraction. (D) Resting state following the contraction. (E) Peak of the second contraction.
Figure 4-21: Internal uterine pressure as a function of time arising as a result of a contractile activity of the myometrium.

Figure 4-22: Mises stresses at the internal os as a function of time arising as a result of a contractile activity of the myometrium.
the uterus (see figure 4-24). The identified structures for the axisymmetric geometry include abdominal fascia, abdominal region, uterus, endopelvic fascia, amniotic membrane and cervix. Furthermore we included scaled gravitational effects in the axisymmetric model to account for the differences with the 3-D geometry.

Two simulations were carried out. In the first one intrauterine pressure of 10 mmHg was applied through the structure of the membrane. The results for the contact pressure distribution are displayed in figure 4-25. In the second one the effect of intrauterine pressure of 10 mmHg and gravity were simulated. The contact pressures resulting from the applied load are presented in figure 4-26.

As it can be seen from the model predictions, the resulting stress distribution displayed in the figures in both cases is quantitatively and qualitatively similar. As a result from this comparison between the 3D and axisymmetric model predictions we concluded that implementation of the model with an axisymmetric geometry to perform parametric studies is justified.
Figure 4-24: Comparison between a 3-D and axisymmetric geometry. (A) Axisymmetric geometry. (B) 3-D geometry. Top: All the identified structures included; bottom: The essential structures without the structure of the abdominal organs.
Figure 4-25: Contact pressures as a result of application of intrauterine pressure of 10 mmHg. (A) Axisymmetric geometry. (B) 3-D solid geometry.

Figure 4-26: Contact pressures as a result of application of intrauterine pressure of 10 mmHg and gravity. (A) Axisymmetric geometry. (B) 3-D solid geometry.
4.9 Funneling Revisited

The previously discussed funneling of the insufficient cervix was simulated once again with an axisymmetric geometry and the results for the maximum principal stress distribution are displayed in figure 4-27. Funneling of the insufficient cervix is shown to initiate at the internal os and to proceed towards the external os following the TYVU deformation pattern (see figure 4-27.A-D). In its final state of deformation the cervical structure assumes a "U" shape with fetal membranes protruding at the external cervical os.

Also, the stress at the site of the inner os is shown to decrease radially outward along the thickness of the cervix.

4.10 Cerclage

Placement of a cerclage transabdominally or transvaginally is the most common preventive method for the case of high risk pregnancy, such as cervical insufficiency. Next we investigated the effectiveness of a cerclage utility as a method to arrest the progression of a funnel formation in the case of dilating insufficient cervix. The material properties selected for the simulation are summarized in table 4.3. The material properties of the surrounding structures were as previously reported for the case of funneling of the insufficient cervix (see the discussion on funneling). The objective in this case was to examine whether or not a cerclage provides structural support.

The cerclage was implemented as a hard elastic band placed at three different positions along the length of the cervix. The choice of material parameters for the band was Young’s modulus $E_{\text{cerclage}} = 1.0$ MPa and Poisson’s ratio $\nu = 0.3$.

Figure 4-28 shows the different scenarios for cerclage. The case of a high cerclage was a computer implementation of the transabdominal cerclage used in the clinical practice and is displayed in figure 4-28.A. Figures 4-28.B and C present two possible cases for the case of transvaginal cerclage. Lastly, figure 4-28.D shows the situation when no preventive measures were taking and the cervix was let to dilate without obstruction.

The far left of figure 4-28 shows the initial axisymmetric configuration for the different cases. The cerclage is visualized as a yellow band, the cervix and the uterus are displayed in red, and
the membrane is displayed in cyan.

In the left (middle) of figure 4-28 the corresponding deformation profiles at the end of the simulation are displayed. After the application of intrauterine and hydrostatic pressure the cervical dilation initiated in all the cases. Depending on the height of the cerclage placement, the funneling of the cervix was arrested at three different stages of the TYVU progression of deformation.

In the case of a high cerclage (figure 4-28.A) the funneling initiated at the site of the internal os, but only managed to proceed to a final "Y" shape. The membranes expanded and filled in the newly opened space close to the internal cervical os, but funnel of the canal failed to form.

In the case of a cerclage, which was placed midway down the length of the cervix (see figure 4-28.B), the final deformation profile reached a "V" shape and in this case a partial funnel can be observed. Additionally the fetal membranes are displayed to have protruded into the endocervical canal.

When the cerclage is placed very close to the external os, as in the case shown in figure 4-28.C, as a result of the internal stresses acting on the cervix and the uterus, a complete funnel formed and the membrane herniated into the cervical canal. Moreover, negligible differences can be observed between the case of a low cerclage and no cerclage at all. The case of no cerclage is displayed in figure 4-28.D and a comparison between the deformation profile and the stress distribution in the 2 cases shows that the two situations are almost identical.

A comparison of the maximum principal stress distribution for the three cases is displayed in the right (middle) of figure 4-28. Figure 4-29 shows the forces in the stitch. It can be seen from the graphs that due to the action of passive loads in pregnancy high stress concentration formed at the internal os where funneling initiated in all three cases. A cerclage placed at the external os provided almost no support as very minimal load was transferred to the cerclage stitch (see figure 4-29). Such a cerclage was the equivalent of a transvaginal cerclage scenario. A cerclage placed closer to the internal os is more capable of structurally supporting the load and therefore we speculate that it will be a more effective prevention method. The results show, that this scenario, which is the equivalent to the transabdominal cerclage, is more efficient in arresting the progression of funnel formation. Indeed, the simulations show, that the funnel progression was stopped at the "Y" shape of deformation progression. We speculate that this
configuration does not allow the fetal membrane to assume the shape needed for the stress state to transition from biaxial extension to uniaxial extension. As discussed previously, once the fetal membrane is subjected to uniaxial extension it starts to undergo creep and stress relaxation, thus facilitating its entry into the endocervical canal and furthermore loading the cervical stroma. Additionally, we conclude that whether a funnel formed or not depends on the height of the cerclage and the relative distance from the mechanical load, as well as the stress state in the amniotic membrane. Higher cerclage is shown to be much more efficient than the middle and low cerclage scenarios.

This conclusion is consistent with clinical results which prove the transabdominal cerclage a more successful preventive method in comparison with the transvaginal one.

4.11 Anatomical Variables

Next, the relevance of geometrical dimensions of the cervix on the stress distribution in the cervix was investigated. Three different cases were investigated: the effect of cervical length, the effect of the internal diameter of the endocervical canal and the effect of membrane adhesion. The material properties for the cervix were as previously selected for the case of healthy cervical stroma (see table 4.1).

4.11.1 Effect of the Diameter of the Endocervical Canal

The effect of the diameter of the endocervical canal on the distribution of the out of plane (circumferential) stress in the cervix is displayed in figure 4-30. Figure 4-30.A shows an endocervical canal of diameter 12 mm, figure 4-30.B shows the results for a canal of diameter 8 mm, and figure 4-30.C shows a canal of diameter 4 mm. In a real anatomical case the endocervical canal is filled with a soft tissue layer with no load bearing properties called the mucosa as previously discussed in the beginning of this chapter.

The simulation results show a region of high stress concentration close to the internal cervical os in all the tree cases. Interestingly, the stress state in the cervix is predominantly tensile in the circumferential direction, as displayed in the plots. The stress levels in all the three cases are comparable. The major difference among the three scenarios consists in the dimensions of
the affected area of high stress concentration. In the case of a very small cervical canal the high stress concentration is observed in a very narrow ring at the internal os, while in the case of a much bigger endocervical diameter the high stress area covers a substantially bigger part of the internal cervical os. We hypothesize that the case of a big cervical diameter displayed in figure 4-30.A is the one in which more of the area around the cervical canal will start to undergo stress relaxation and creep and subsequently facilitate the dilation of the cervix.

4.11.2 Effect of Cervical Length

In order to simulate the effect of cervical length on the stress distribution of the cervix three different scenarios were investigated as well. Figure 4-31 shows the distribution of the circumferential stress for cervical length of 1.5 cm (4-31.A), 2.5 cm (4-31.B), and 3.5 cm (4-31.C) as a result of the application of the same load in the three cases. Again, high stress concentration is observed in the region of the internal os. The simulated stress values do not seem to differ significantly. The dimensions of the high stress concentration area seem to be of comparable size as well. Nevertheless, we see that the three scenarios differ in the percent of the stroma that is experiencing high stresses. While in the case of a long cervix the affected area represents only a small percent of the organ, in the very short cervix scenario the affected area spans almost the entire cervix. We believe that a situation as the one presented in figure 4-31 A is the one which will favor formation of a funnel, since once the funnel initiates, there is not stroma left to structurally support the cervix and prevent the canal from opening. The case of a longer cervix will most likely be the only case of the presented three, in which cerclage placement as a preventive measure may be beneficial.

4.11.3 Effect of Membrane Adhesion

The last biomechanical parameter investigated is the effect of membrane adhesion. Often in the case of cervical insufficiency a prolapse of the amniotic sac into the endocervical canal occurs with the incidence of cervical funneling (see figure 1-3). The amniotic sac encloses the fetus in a fluid environment and is attached to the uterine lining by a tissue layer called the decidua. Adhesion between the amniotic membrane and the decidua is believed to be promoted by the multiadhesive matrix protein fibronectin. Freely sliding amniotic membranes at the lower uterus
and cervix in patients with cervical insufficiency may suggest a disruption of the decidua layer. Also, increased levels of fetal fibronectin in patients diagnosed with cervical insufficiency is suggestive of possible disruption in the tissue layer providing adhesion between the membrane and the uterus and is associated with an increased risk of subsequent preterm birth. Therefore we investigated the effect of membrane adhesion in two cases. Simulation results presenting the effect of membrane adhesion on the distribution of the out of plane (circumferential) stress in the cervix are displayed in figure 4-32 for the case of no adhesion (4-32.A) and adhesion (4-32.B).

Interestingly, the differences in the two cases are quite substantial. In the no adhesion case we observe a high stress concentration in a narrow area at the site of the internal os. The stress values at this very narrow region are much higher than the corresponding stresses in the case of adhesion between the uterus and the membrane. In the latter case we have smooth stress distribution over the entire area of the uterus. The stress distribution observed in the case of no adhesion could be the one experienced by the cervix in the case of insufficiency, where due to the disruption of the adhesive contact between the structures the stress at the internal os of the cervix is substantially higher than a situation in which the membrane is attached to the uterus.

4.12 Conclusions

Our study focused on investigating the multifactorial etiology of the dilating cervix. A critical element of this study is the construction of an idealized solid geometry of the pelvic and the abdominal region of a pregnant patient, reflecting the essential features of the mechanical environment around the cervix and the uterus in pregnancy. The effect of different anatomical dimensions and stroma consistency was assessed by axisymmetric and full 3-D simulations. By varying the combination of critical loads and material properties of the cervix and the uterus we are able to identify the essential factors governing the dilation of the cervix, which include softness of the cervix and the uterus, gravitational and uterine loads, stiffness of the amniotic membrane and membrane adhesion, as well as the geometry of the cervix. By varying each parameter independently we investigate the corresponding effect on the progression of dilation
and are able to study different sets of conditions leading to funneling of the cervix.

The observed results show that simulations of the effect of various biomarkers can provide insight into the complex biomechanics of cervical funneling.
Figure 4-27: Funneling of the insufficient cervix (axisymmetric geometry) and the maximum principal stress distribution. (A) Initial configuration. (B) Initiation of funneling and a characteristic "Y" shape of the deformation. (C) Characteristic "V" shape of the deformation. (D) Final "U" shape of the deformation with fetal membranes protruding into the endocervical canal.
Figure 4-28: Cerclage effectiveness. Far left: initial axisymmetric configuration; left middle: deformation profiles at the end of the simulation; right middle: corresponding maximum principal stress distribution; far right: corresponding stress values. (A) High cerclage. (B) Middle cerclage. (C) Low cerclage. (D) No cerclage.
Figure 4-29: Force in the cerclage stitch as a function of normalized time. Color code: red - high cerclage; green - middle cerclage; blue - low cerclage.
Figure 4-30: Effect of the diameter of the endocervical canal on the distribution of the out of plane (circumferential) stress in the cervix. (A) Canal diameter 12 mm. (B) Canal diameter 8 mm. (C) Canal diameter 4 mm.
Figure 4-31: Effect of cervical length on the distribution of the out of plane (circumferential) stress in the cervix. (A) Cervical length of 1.5 cm. (B) Cervical length of 2.5 cm. (C) Cervical length of 3.5 cm.
Figure 4.32: Effect of membrane adhesion on the distribution of the out of plane (circumferential) stress in the cervix. (A) Case of no adhesion. (B) Case of adhesion.
Chapter 5

Constitutive Modeling of the Cervical Tissue During Pregnancy

5.1 Introduction

The challenging task of constitutively prescribing the mechanical behavior of soft tissue has been accomplished to various degrees with some soft tissue classes, such as cartilage and skin. The initial endeavor in investigating the mechanics of soft tissue matter entails harvesting tissue specimens from the tissue stroma and subjecting the specimens to a comprehensive experimental investigation in-vivo or in-vitro. Subsequently, based on the analysis of the experimental data, a constitutive framework is proposed and its merits are verified. Unlike other well studied types of soft tissue, the particular nature of the cervical stroma and specific applications under consideration introduce additional complexity in its mechanical characterization. In particular, our investigation will address the following three challenges.

1) Our goal encompasses simulating the material response of the stroma under substantially different time scales.

Most of the physiological changes relevant in pregnancy are associated with large time scales. Examples of such changes are the growth of the uterus or the dilation of the cervix in the case of insufficiency, which occur over the course of several days to weeks. There are, nevertheless, exceptions, such as the uterine contractile activity, which is associated with much shorter time scales consistent with the laboratory testing time.
2) There exist a substantial variability in the material properties of the cervical stroma from the non-pregnant to the pregnant state [64], [66]. Additionally, the tissue response can exhibit some qualitatively different behavior based on the obstetric history of the patient.

3) The mechanical properties of the stroma evolve during pregnancy, which necessitates a unique constitutive framework capturing the long-term tissue behavior in both the pregnant and the non-pregnant state, taking into account long-term effects of tissue growth and remodeling. In order to achieve our task and describe the mechanical behavior of the cervical stroma in its complexity and variability we need a model that accounts for its individual components and combines their effect with the specific deformation mechanisms. The superposition of the underlying tissue constituents with assigned weights will enable us to represent the cervical tissue mechanics in the large range of the observed material properties.

In this work we present a constitutive framework to capture the 3D large strain time-dependent response of the cervical tissue. The new fully 3D experimental compression data collected from non-pregnant cervical stroma tested in the circumferential direction was used as the basis for the current undertaking. In our preliminary attempt to prescribe the constitutive behavior of the cervical stroma we idealize the material as an isotropic and use averaged data for the transverse stretches in order to propose a framework for the cervical tissue behavior. A single framework is proposed capable of capturing extremes of tissue behavior (pregnant and non-pregnant) under compressive loading. This preliminary tissue model attempts to account for the underlying material (micro)-structure and composition but does not include anisotropy of the material, or the effects of growth and remodeling.

5.2 Review of Existing Models for Human Cervical Tissue

The paucity of data on the mechanical behavior of the human cervical tissue renders its constitutive characterization an extremely challenging task. To date, there are only two known such models which attempt at constitutive modeling of the stroma and relating the changes in the mechanical properties of the uterine cervix with the altered biochemical composition of the stroma during pregnancy. In a considerably simplified model assuming linear behavior of the underlying load bearing components, small strains and neglecting volume changes, Aspden [4]
treats the stroma of the cervix as a fiber-reinforced composite material. Despite the simplicity of the proposed model, it suffices to enlighten the inherent features of the theory in order to provide an insight into the mechanical behavior of the cervix. A more sophisticated model proposed by Febvay et al [31], [30] manages to better capture specific aspects of the biomechanical response of the cervix accounting for the contributions of the individual constituents as well as their complex interaction. This model was thoroughly presented in chapter 4 of this thesis. Here we will briefly introduce the model proposed by Aspden.

Aspden [4] considers the stroma of the human cervix as a composite material in which the collagen fibers are embedded into a gel-like structure of GAGs. In his theory the linear superposition of the strengths of the individual components of the stroma gives the tensile strength of the entire composite. Aspden calculated the breaking stress of the cervical tissue \( \sigma_{\text{breaking}} \) as a weighted sum of the breaking stress of the collagen fibers \( \sigma_{\text{fibers}} \) and the breaking stress of the ground substance \( \sigma_{\text{GAG}} \) given by

\[
\sigma_{\text{breaking,\,total}} = \beta \sigma_{\text{fibers}} + (1 - \beta) \sigma_{\text{GAG}}, \tag{5.1}
\]

where \( \beta \) is the volume fraction of the collagen in the intact fully hydrated tissue. The cellular volume is neglected in the above relation. As the breaking stress of the GAGs is much smaller in comparison with the breaking stress of the collagen fibers the second term in 5.1 is negligible.

\( \beta \) is referred to as the degree of reinforcement and has been shown to fall at parturition to approximately half the value in the non-pregnant stroma of rats therefore reducing the tensile strength as calculated in 5.1. Accounting for the fiber orientation of the collagen in the cervical stroma Aspden introduces a new parameter \( \eta \) which is called the efficiency of reinforcement. The efficiency of reinforcement \( \eta \) is a function of the angle between the fibers and the applied stress \( \varphi \) and was defined as

\[
\eta = \cos^4 \varphi. \tag{5.2}
\]

Therefore \( \eta \) varies between 1 for perfectly aligned fibers with maximum efficiency and 0 for fibers aligned perpendicularly to the direction of the applied load. For randomly organized fibers \( \eta = 0.2 \) which signifies low efficiency, which is nevertheless uniform in every direction.
Accounting for the efficiency, 5.1 modifies to

\[ \sigma_{\text{breaking, total}} = \beta \eta \sigma_{\text{fibers}} + (1 - \beta) \sigma_{GAG}. \]  

(5.3)

Assuming the same relationship between the Young's moduli of the individual constituents, the Young's modulus of the substrate \( E_{\text{total}} \) is given by a weighted sum of the Young's moduli of the collagen fibers \( E_{\text{fibers}} \) and the ground substance \( E_{GAG} \), and is given by

\[ E_{\text{total}} = \beta \eta E_{\text{fibers}} + (1 - \beta) E_{GAG}. \]  

(5.4)

Poisson effects are neglected in the above simplified expression. The strains involved are assumed to be small and the behavior of the fibers and the ground substance are assumed to be linear.

A previous study by the same investigator uses X-ray diffraction to measure the collagen fibril orientation in the non-pregnant cervixes of humans and mice, based on which an orientation distribution function describing the probability of finding a fibril at a given angle to a chosen reference axis is derived. The result of the same study showed that in the non-pregnant state the collagen fibril organization is associated with an efficiency of 0.6 both along and around the cervix, which dropped down to 0.2 at delivery. This result signifies the fact that at parturition the collagen organization is more random and therefore the effective strength and stiffness of the stroma decreases by a factor of 3 from the non-pregnant to the pregnant state at term.

The collagen organization accounts partially for the variation of the stiffness and the strength of the stroma during pregnancy. Additionally, Aspden investigated the effectiveness of the stress transfer between the strong fibers and the weak ground substance. A critical length \( l_c \) of the collagen fiber is defined as

\[ l_c = \frac{r \sigma_{\text{fibers}}}{\tau}, \]  

(5.5)

where \( \sigma_{\text{fibers}} \) is the breaking stress of the collagen fibers, \( \tau \) is the shear stress exerted on a fiber by the ground substance, and \( r \) is the radius of the fibre. Equation 5.5 signifies that an individual fiber can only be stressed maximally if its length exceeds the critical length \( l_c \), since a length shorter than the critical length renders the fiber ineffective in reinforcing the
surrounding ground substance of glycosaminoglycans. The shear stress exerted from the ground substance to the collagen fibers depends on the specific glycosaminoglycans in the stroma. Changes in the ground substance composition at term may alter the shear strength of the stroma and therefore affect the critical length. A comparison between the different shear strengths exerted by specific GAG present in the cervical stroma renders the relation $\tau_{\text{dermatan sulfate}} > \tau_{\text{hyaluronic acid}} > \tau_{\text{keratan sulfate}}$. Aspden reports a marked change in the relative amounts of these GAGs, which leads to decrease in the shear stress exerted on the collagen fibers therefore yielding an increase in the critical length. Assuming that the collagen fibril length remains the same throughout pregnancy the increase in $l_c$ renders most of the collagen fibers shorter than $l_c$, therefore reducing the effectiveness of the reinforcing they provide.

Another aspect of the mechanical behavior of the cervical stroma considered by Aspden is the water content of the stroma. At term, the water content of the human cervical stroma is increased by 5%. The amount of water in the tissue affects the concentration of the separate species in the stroma and therefore affecting the possibility for molecular rearrangement. This molecular reconfiguration governs the creep properties of viscoelastic materials and the cervical stroma as such, affecting the Young's modulus in 5.4 which becomes effectively a function of time, $E_{\text{total}}(t)$. Increased water content at parturition would increase the freedom for molecular rearrangement in the stroma, therefore increasing the creep properties and reducing the stiffness of the cervix.

Aspden also suggests that elastin, a highly extensible rubberlike protein with almost constant weight throughout the gestation, may be component of the stroma providing a restoring stress post-partum and facilitating recovery of the strength and stiffness of the stroma.

5.3 Constitutive Modeling of the Cervical Stroma

As previously described in Chapter 2 of this work, the major components of the cervical stroma governing its mechanical behavior are the collagen fibril network, the hydrated proteoglycans (PGs) and glycosaminoglycans (GAGs) and the elastin network. The hydration of the tissue is due to negatively charged PGs, which attract positive ions from the surrounding fluid and swell the structures of the PGs. We propose a constitutive model for the cervical tissue which
characterizes the stroma as a composite comprised of kinked collagen fibrils, hydrated ground substance of glycosaminoglycans and proteoglycans and a volume restoring elastin network. Flow of interstitial fluid through the porous matrix of the ECM completes the characterization of the cervical stroma.

The data for the behavior of the cervical tissue in compression presented by Myers et al [64] indicates that there exists a complex correlation between the behavior of the cervical stroma in bulk and in shear. We propose a rheological model for the cervix, in which the bulk deformation of the stroma is connected with the shear tissue response through a complex interplay between the major constituents of the stroma.

In the subsequent discussion a distinction is made between different compartments comprising the stroma of the cervix. The idea of individual compartments of the ECM of a cartilaginous tissue was originally introduced by Maroudas et al [60] for the articular cartilage of the intervertebral disk. The significance of separate water compartments on the mechanical properties of articular cartilage has been investigated by other research groups as well [56]. In the work of Maroudas [60] two compartments occupied by different constituents of the ECM are presented: an intrafibrillar water compartment occupied by collagen fibrils which excludes the PGs and an extrafibrillar water compartment of fluid and PGs with highly negatively charged groups. The water amount in the intrafibrillar and the extrafibrillar compartment varies with the type of tissue and is governed by the concentration of charged PGs in the particular type of stroma. The space occupied by the extrafibrillar water comprised by a PG-water gel is compared to a porous mesh of very thin solid PGs filled with liquid. The authors argue that the swelling tendency of the tissue due to the osmotic pressure of PGs depends on the PGs’ content in the extrafibrillar space and the collagen fiber organization. This reasoning is used to justify the higher hydration levels (swelling tendency) of excised specimens immersed in physiological saline in which the collagen fiber organization is disrupted due to the excision of the tissue from the surrounding organ.

It is well known that the ECM of articular cartilage and cervical stroma share a number of similarities in the structure of their ECM and mechanical behavior. Both tissues are comprised of a network of highly negatively charged ground substance intertwined with the kinked structure of the collagen. The GAGs present in the cartilage are bigger than the ones present
in the cervical stroma. The small GAGs of the cervical tissue, such as the decorin, organize the collagen bundles and are essentially a part of the collagen structure.

Due to similarities of the two types of stroma and their mechanical behavior, in the current publication we adopt the idea of Maroudas for the existence of separate compartments in the cervical ECM. We further extend this idea and differentiate between PGs hydrated to different levels depending on the specific region of the stroma they occupy. We separate the PGs of the cervical stroma into two disparate categories, namely Bound Water PGs (BG) and Free Water PGs (FG).

5.4 Different PGs Compartments

Excess of ions from the negatively charged groups of the PGs creates an imbalance in the ionic concentration in the cervical stroma and therefore creates osmotic pressure in the cervical tissue. The imbalance in the ionic concentration attracts positive ions from the surrounding fluid and causes water to get absorbed by the PGs. The swelling tendency of the PGs to imbibe water...
and change conformation is balanced by the tensile stresses in the collagen fiber network and the loads applied externally to the tissue. In the following discussion such compartments in the cervical stroma where the high osmotic pressure due to negatively charged glycosaminoglycan groups of the PGs is balanced off by the tensile stiffness of the dense collagen fiber network are referred to as Bound Water PG regions.

The protocol for ex-vivo testing of the cervical specimens entails excision of the cervical specimen from the surrounding stroma which results in disruption of the collagen fibril arrangement and breakage of collagen links. These regions of disrupted collagen organization provide less tensile resistance to the swelling tendency of the neighboring PGs thus introducing local regions of higher water content in the excised specimens. Additionally, local inhomogeneities in the stroma can also form such compartments in the tissue where due to disrupted collagen structure and the high osmotic pressures the PGs can change conformation and swell considerably. In the subsequent discussion such compartments of “swollen” PGs are referred to as Free Water PG regions.

Thus for the purposes of modelization of cervical tissue material behavior we introduce two separate compartments in the stroma. The first compartment (compartment 1) is shared by the collagen bundles and the bound water proteoglycans and glycosaminoglycans. The second compartment (compartment 2) is not controlled by the collagen structure and is comprised entirely by the structure of the free water PGs and GAGs.

For a schematic view of the ECM of the cervical tissue the reader is referred to figure 5-1. Figure 5-1.A presents an idealization of the cervical stroma, which is shown to be comprised of collagen, free and bound GAGs, water and elastin. The flow through the porous extracellular matrix is presented with light blue arrows. Dark blue arrows present the exchange of water between the different compartments. Figure 5-1.B presents the different compartments. The collagen compartment is populated by collagen, bound GAG and water associated with the bound GAGs. The compartment of the free GAGs is not controlled by the collagen and is inhabited only by free GAGs and water. Elastin is found in both the compartments.

The deformation of compartment 1 can be described by a deformation gradient $F_1$ and the deformation of the second compartment 2 by a deformation gradient $F_2$. 

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Given an overall macroscopic deformation gradient $\mathbf{F}$, both compartments share the same isochoric deformation gradient $\mathbf{F}_n$ ($n = 1, 2$):

$$\mathbf{F}_1 = \mathbf{F}_2 = \mathbf{F}_{\text{compartment}},$$

(5.6)

where by $\mathbf{F}_{\text{compartment}}$ we refer to the isochoric gradient of the individual compartments. The two compartments accommodate the total volumetric stretch $J$ in different proportions:

$$J_1 \neq J_2 \neq J.$$  

(5.7)

The volumetric compatibility constraint is simply enforced as

$$V = V_1 + V_2 = JV^0.$$  

(5.8)

The relationships between the current and initial volumes of the two compartments are given by:

$$V_1 = J_1 V_1^0,$$

(5.9)

$$V_2 = J_2 V_2^0.$$  

(5.10)

The volume fractions of the two compartments in their undeformed configuration are correspondingly $f_1^0$ and $f_2^0$ and are defined as

$$f_1^0 = \frac{V_1^0}{V^0},$$  

(5.11)

where 5.11 is the ratio of the initial volume of compartment 1 to the entire initial volume of the tissue and

$$f_2^0 = \frac{V_2^0}{V^0}.$$  

(5.12)

where 5.12 is correspondingly the ratio of the initial volume of compartment 2 to the entire initial volume. Therefore from 5.8 it follows that:
\[ J_1 f_1^0 + J_2 f_2^0 = \tilde{J}, \]  

where the relationship between the two volume fractions can also be expressed as

\[ f_1^0 = 1 - f_2^0. \]

Representation of the overall deformation gradient \( \tilde{F} \) as unweighted volume average over the RVE in the initial undeformed configuration is given by:

\[
\tilde{F} = \frac{1}{V_0} \int_{V_0} \mathbf{F}(X,t) \, dV_0.
\]

Utilizing the multiplicative decomposition of the deformation gradient into its dilatational (\( J \)) and volume preserving (\( \tilde{F} \)) components often used in elastoplasticity (see, for example the work of Lee from 1969 [52]), the deformation gradients in the different compartments and the macroscopic deformation gradient \( \tilde{F} \) can be expressed as:

\[
\tilde{F} = J^{1/3} \tilde{F}
\]

\[
\mathbf{F}_1 = J_1^{1/3} \tilde{F}_1 = J_1^{1/3} \mathbf{F}_{\text{compartment}}
\]

\[
\mathbf{F}_2 = J_2^{1/3} \tilde{F}_2 = J_2^{1/3} \mathbf{F}_{\text{compartment}},
\]

where \( J_1 \) and \( J_2 \) are correspondingly the volumetric stretches of compartments 1 and 2 and \( \tilde{J} \) is the macroscopic volumetric stretch. \( \tilde{F} \) is the macroscopic isochoric deformation gradient of the cervical stroma and \( \mathbf{F}_{\text{compartment}} \) is the isochoric gradient of the individual compartments.

From 5.15 it follows that the macroscopic deformation gradient \( \tilde{F} \) can be presented as the volume average of the deformation gradients of the individual compartments weighted by their corresponding volume fractions:

\[
\tilde{F} = f_1^0 \mathbf{F}_1 + f_2^0 \mathbf{F}_2.
\]
Using 5.6, 5.13, 5.17 and 5.18 we obtain

\[ \mathbf{F}_{\text{compartment}} = \frac{(J_1 f_1^0 + J_2 f_2^0)^{1/3}}{(f_1^0 J_1^{1/3} + f_2^0 J_2^{1/3})} \mathbf{F}. \] (5.20)

In terms of the macroscopic deformation gradient the corresponding deformation gradients of compartments 1 and 2 are given by:

\[ \mathbf{F}_1 = \frac{J_1^{1/3}}{(f_1^0 J_1^{1/3} + f_2^0 J_2^{1/3})} \mathbf{F}. \] (5.21)

\[ \mathbf{F}_2 = \frac{J_2^{1/3}}{(f_1^0 J_1^{1/3} + f_2^0 J_2^{1/3})} \mathbf{F}. \] (5.22)

The difference in the hydrostatic stress in the two compartments at each material point drives a pointwise diffusion of interstitial fluid between the compartments. In addition to the stress contribution of the solid matrix the proposed model considers the hydrostatic contribution from the porous flow of the interstitial fluid across the tissue within the framework of Darcy's Law.

Each compartment exhibits a stress response according to its prescribed constitutive behavior. The macroscopic stress in the stroma is obtained as a volume average of the stresses of the individual components following [68]

\[ \ddot{\sigma}(t) = \frac{1}{V} \int_{\partial V} \sigma(x,t) dV. \] (5.23)

This results in a macroscopic stress in the cervical stroma calculated as:

\[ \ddot{\sigma} = \frac{1}{J} (J_1 f_1^0 J_1 \sigma_1 + J_2 f_2^0 J_2 \sigma_2) + \sigma_{\text{elastin}} + \Delta P_{\text{Darcy}}. \] (5.24)

### 5.5 GAG Response

In the proposed model both the transient and the equilibrium shear response of the GAG network to isochoric deformations is neglected. The main contribution of the GAG network considered by the model is the resistance to volumetric deformation. Although more complex
forms can be chosen to relate the bulk deformation and the volumetric response of the GAGs, we
utilize a simple logarithmic characterization relating the volumetric stretch and the hydrostatic
stress of the GAG network through a single material parameter $K_{GAG}$.

From the theory of compressible hyperelasticity a suitable form for compressible isotropic
hyperelastic materials is based on the assumption that the strain energy function can have a
decoupled form expressed as

$$W(B) = W_{vol}(J) + W_{iso}(J). \quad (5.25)$$

The derivative of the volume ratio $J = \sqrt{\text{det}(B)}$ is given by [40]

$$\frac{\partial J}{\partial B} = \frac{J}{2} B^{-1}. \quad (5.26)$$

Subsequently, the spatial description for the stress is

$$\sigma = 2J^{-1}B \frac{\partial W(B)}{\partial B} = 2J^{-1} \frac{\partial W(J)}{\partial B} B = 2J^{-1} \frac{\partial W(J)}{\partial B} B + 2J^{-1} \frac{\partial W(B)}{\partial B} B = \sigma_{vol} + \sigma_{iso}. \quad (5.27)$$

We propose an expression for the strain energy density function for the GAG network, which
only depends on the jacobian of the deformation and is given by

$$W_{GAG} = K_{GAG} J_{GAG} (\ln J_{GAG} - 1). \quad (5.28)$$

We assume that the GAG response to deformation has only a volumetric component in
which case equation 5.25 reduces to

$$W_{GAG}(B) = W_{GAG,vol}(J_{GAG}), \quad (5.29)$$

therefore

$$\sigma_{GAG} = 2J_{GAG}^{-1} \frac{\partial W_{GAG}(J_{GAG})}{\partial B} B \quad (5.30)$$

and using equation 5.26 we obtain

$$\sigma_{GAG} = 2J_{GAG}^{-1} \frac{\partial W_{GAG}(J_{GAG})}{\partial J_{GAG}} \frac{\partial J_{GAG}}{\partial B} B = \frac{\partial W_{GAG}(J_{GAG})}{\partial J_{GAG}} I. \quad (5.31)$$
Differentiating the strain energy function for the GAG (eq. 5.28) we have

\[ \sigma_{GAG} = K_{GAG}\ln(J_{GAG})I. \] (5.32)

More generally we can express the hydrostatic stress for either of the compartments as

\[ \sigma_{GAG}^n = K_{GAG}\ln(J_n), \quad n = FG, BG. \] (5.33)

The resistance to volumetric deformation of compartment 2 is described through the volumetric stretch of this compartment \( J_2 \) such as

\[ \sigma_{BG}^n = K_{GAG}\ln(J_{FG}) = K_{GAG}\ln(J_2) \] (5.34)

The initial value of the Jacobian for this compartment is \( J_2^0 = 1 \).

The hydrostatic stresses in the compartment of the bound GAGs arising from the application of volumetric deformations result in a hydrostatic stress in this compartment given by

\[ \sigma_{BG}^h = K_{GAG}\ln(J_{BG}), \] (5.35)

where \( J_{BG} \) is obtained from 5.41 as discussed in the following section.

**Collagen Prestretch**

In the proposed constitutive model for the mechanical behavior of the cervical tissue the collagen in the ECM is modeled to respond to the entire deformation of the compartment it occupies (compartment 1). In its physiological unloaded configuration the collagen fibrils from compartment 1 in the cervical stroma are in a state of tension which balances the high osmotic pressure from the negatively charged ground substance of glycosaminoglycans and proteoglycans occupying this compartment [59]. The role of the collagen prestretch was first investigated by Basser et al. for articular cartilage [9]. Contrary to the belief that in compression the response of the cartilage can largely be attributed to the osmotic pressure of the PGs, Basser et al show the importance of the collagen prestretch, which brings the collagen fibers to higher stress levels. Once the collagen stretch levels reach the transition region, the stiffer response of the collagen
network becomes important for the overall macroscopic state of stress.

In the absence of externally applied loads the initial collagen deformation gradient is given by

$$ F_c^0 = \xi I, \quad (5.36) $$

where $\xi$ is the level of the prestretch of the collagen fibers and $I$ is the identity tensor. The instantaneous response of the collagen network to a deformation gradient imposed on the collagen compartment (compartment 1) reflects the entire deformation gradient of the collagen $F_c$ and can be expressed as

$$ F_c = F_1 F_c^0 = \xi F_1. \quad (5.37) $$

Correspondingly, in the absence of externally applied loads, the bound GAGs of compartment 1 are in a state of precompression, which is described by an initial deformation gradient $F_{BG}^0$ given by

$$ F_{BG}^0 = J_{BG}^{0 \times 3} I. \quad (5.38) $$

A deformation gradient imposed on the compartment 1 results in a deformation gradient for the bound GAGs given by

$$ F_{BG} = F_1 F_{BG}^0 = J_{BG}^{0 \times 3} F_1. \quad (5.39) $$

The initial equilibrium of compartment 1 is simply enforced as a zero stress state in this compartment:

$$ \sigma_c^0 + \sigma_{BG}^0 = 0. \quad (5.40) $$

This condition renders an initial volume of the GAGs in this compartment $J_{BG}^0 \neq 1$, and can be determined from the initial equilibrium between the tensile stress in the collagen fibers and the osmotic stress in the PGs. Therefore, the volume of the bound GAGs in compartment 1 can be expressed as

$$ J_{BG} = J_{BG}^0 J_1. \quad (5.41) $$

### 5.6 Collagen Response

The collagen network response comprises both a deviatoric and a hydrostatic component.
5.6.1 Collagen Network Response

Overview

The collagen network of the cervical stroma is composed of bundles of kinked collagen fibers connected by chemical cross-links. The structure of the collagen provides resistance of the network in tension. The network-like structure of the collagen fibers, connected at specific binding sites through chemical cross-links, is presented in figure 5-2.

When subjected to a certain level of deformation the collagen fibrils stretch and align with the direction of the applied load [80], [20], mimicking the behavior of a polymer network subjected to external loads. The basic characteristic of the stress-strain behavior of the collagen network can be well captured by statistical mechanics treatment of rubber-elasticity. The force-stretch behavior of a molecular chain differs from the kinked fibril in the physical origin of their behavior. The force-stretch behavior of a molecular chain is entropic in origin and is a result from the change in the configurational entropy of the chain. On the other hand, the physical origin of the force-stretch behavior of a fibril arises from the change of the internal energy of the fibril due to unbending. Despite these differences, the force-stretch behaviors of these two structures are quite similar.

The stress-strain behavior of the collagen fibril network of soft tissues [41] can be characterized by three separate regions. An initially compliant behavior at small levels of stretch characterizes the first region and is associated with uncrimpling of the wavy collagen fibrils in the stroma. Small levels of the applied axial strain render large deformations of the material and are associated with no corresponding stretch of the individual collagen fibers. Higher levels of the applied strain lead to breakage of weak chemical cross-links between the individual collagen fibers and reorientation of the fibers with the direction of the load. In the second region the stiffness of the response undergoes a steep upturn associated with further alignment of the network and stretch of the individual fibers. At higher levels of stretch in the third region the stress response of the fibril reaches a limiting tangent level corresponding to stretching of the aligned collagen fibers. The stresses approach a limiting stiffness level as the limiting extensibility of the fibers is reached, which corresponds to the length of the collagen fibril \( L \) when fully distended (see figure 5-2).
Figure 5-2: Micrograph of a collagen matrix. (A) Undeformed state. (B) Reorientation and stretching of the collagen fibrils under the action of uniaxial extension. (Modified from Roeder et al [80]).

For a complete review of the constitutive models used in rubber elasticity the reader is referred to the work of Treloar [87] and Arruda and Boyce [16].

**Force-Stretch Behavior of the Individual Fibril**

The individual collagen fibril can be presented as a randomly oriented long molecular chain. In its undeformed state the chain the chain is characterized by a end-to-end length $r$. The probability of a length $r$ can be described by a Gaussian distribution given by

$$P(r) = 4\pi \left(\frac{3}{2\pi n l^2}\right)^{3/2} r^2 \exp\left(\frac{3r^2}{2nl}\right). \quad (5.42)$$

In equation 5.42 $n$ is the number of links in each chain and $l$ is the length of each link. The initial chain length $L_0$ is given by a root mean-square value of the end-to-end length $r$

$$L_0 = (\bar{r}^2)^{1/2} = (nl^2)^{1/2} = \sqrt{nl}. \quad (5.43)$$
When distended, a chain structure stretches, the possible number of configurations for the chain decreases, therefore decreasing the configurational entropy of the chain. The elastic strain energy function of the chain can be derived from the change of the configurational entropy expressed as

\[ W_G = \frac{1}{2} N k_B \theta (\lambda_1^2 + \lambda_2^2 + \lambda_3^2), \quad (5.44) \]

where \( N \) is the number of chains, \( \lambda_1, \lambda_2, \lambda_3 \) are the principal stretches, \( k_B \) is the Boltzmann’s constant and \( \theta \) is the absolute temperature and the stretch is such, that the length \( r \) does not reach the fully extended length \( n_1 \). By differentiating the strain energy function with respect to the stretch the stress-stretch relationship can be derived. Such stress-stretch relationship deviates significantly from the observed behavior of the molecular network at large stretches in the limit of \( r \to n_1 \).

In order to capture the behavior of the collagen network we propose a force-stretch relationship of the individual fibril based on Langevin chain statistics adopted by Kuhn and Gruen [51]. Kuhn and Gruen derived a non-Gaussian force-extension relationship for the individual chain \( f_c \) given by

\[ f_{\text{chain}} = \frac{k_B \theta}{l} \mathcal{L}^{-1} \left( \frac{r}{n_1} \right) = \frac{k_B \theta}{l} \mathcal{L}^{-1} \left( \frac{\lambda}{\sqrt{n}} \right), \quad (5.45) \]

where \( \mathcal{L}^{-1} \left( \frac{r}{n_1} \right) \) is the inverse Langevin function defined as:

\[ \frac{r}{n_1} = \coth \beta - \frac{1}{\beta} = \mathcal{L}(\beta) \quad (5.46) \]

\[ \beta = \mathcal{L}^{-1} \left( \frac{r}{n_1} \right). \quad (5.47) \]

In eq. 5.46 and 5.47 \( n_1 \) is the length of the chain when fully extended. The average initial length \( L_0 \) of a chain is calculated as \( \sqrt{n} l \), where \( \sqrt{n} \) is the limiting stretch of the chain called the locking stretch \( \lambda_L \). The stretch of the chain is defined as \( \lambda = \frac{r}{L_0} = \frac{r}{\sqrt{n} l} \). In order to incorporate the individual chain statistics into a constitutive framework, a network representative behavior needs to be proposed to connect the stretch of the individual fibril to the macroscopically applied deformation.
Figure 5-3: The 8-chain unit cell. The cell deforms along the principal directions $b_1, b_2, b_3$ of the left Cauchy-Green tensor $B$ with stretches $\lambda_1, \lambda_2, \lambda_3$ equal to the principal stretches.

Representative Unit Element

Arruda and Boyce [3] proposed the 8-chain model in which the individual chains are located along the main diagonals of a unit cell and have a junction point in the center of the cube (see figure 5-3). The individual chains deform with the cell and due to symmetry the junction point always remains in the center of the unit cell, throughout the deformation. The individual chain deformation is given by a root mean-square of the principal values of the macroscopic stretch $\lambda_1, \lambda_2, \lambda_3$ given by

$$\lambda_{\text{chain}} = \sqrt{\frac{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}{3}}. \quad (5.48)$$

The strain energy density of the collagen network $W_c$ can be determined as the product of the number of fibrils per unit volume (or fibril density), $m$, and the strain energy of an individual fibril in the 8-chain network, $w_{\text{chain}}$.

$$W_{\text{network}} = mw_{\text{chain}} \quad (5.49)$$

$$w_{\text{chain}} = \int f_{\text{chain}}dl_j, \quad (5.50)$$

where $l_j$ is the current junction to junction distance of the chain, $l_{j0}$ is the initial junction to junction distance of the chain and $l_j = \lambda_{\text{chain}}l_{j0}$. Therefore,

$$w_{\text{chain}} = \int f_{\text{chain}}l_{j0}d\lambda_{\text{chain}} \quad (5.51)$$
where $\lambda_{\text{chain}}$ is given by equation 5.48 and $f_{\text{chain}}$ is given by equation 5.45 (2) with $n$ being the number of links in each chain and $l$ being the length of each link. Integrating we obtain

$$W_{\text{network}} = mk_B \theta \lambda_L (\beta_{\text{chain}} \lambda_{\text{chain}} + \lambda_L \ln\left(\frac{\beta_{\text{chain}}}{\sinh \beta_{\text{chain}}} \right) + \frac{\beta_0}{3} \ln \frac{1}{I}) \quad (5.52)$$

$$\beta_{\text{chain}} = \mathcal{L}^{-1}(\lambda_{\text{chain}} \lambda_L), \quad \mathcal{L}(\beta_{\text{chain}}) = \coth \beta_{\text{chain}} - \frac{1}{\beta_{\text{chain}}}, \quad \beta_0 = \mathcal{L}^{-1}(\frac{1}{\lambda_L}) \quad (5.53)$$

Differentiating equation 5.52 with respect to the invariants of $B$ we derive an expression for the associated Cauchy stress $\sigma_{\text{network}}$

$$\sigma_{\text{network}} = \frac{2}{J} \frac{\partial W_{\text{network}}}{\partial I_1} B + \frac{\partial W_{\text{network}}}{\partial J} I, \quad (5.54)$$

where $B = \mathbf{F}^T \mathbf{F}$ is the left Cauchy Green tensor, $I_1 = \text{tr}(B) = \lambda_1^2 + \lambda_2^2 + \lambda_3^2$ and $J = I_3 = \sqrt{\det(B)} = \lambda_1 \lambda_2 \lambda_3$ are the first and the third invariants of $B$, and the network stress is taken not to depend on the second invariant of $B$. The resulting network stress is given by

$$\sigma_{\text{network}} = \frac{mk_B \theta \lambda_L}{3} \left(\frac{\beta_{\text{chain}}}{\lambda_{\text{chain}}} B - \beta_0 I\right). \quad (5.55)$$

Constitutive Modeling for the Collagen Network

We adopt the constitutive framework for the material behavior of a molecular chain network, based on Langevin statistics, in order to derive a constitutive relationship for the collagen fibrillar network.

The 8-chain model together with the representative force-stretch behavior of the individual fibril can be combined to derive the full 3-D stress-strain relationship of the collagen network. The stresses arising in the collagen can be calculated by appropriately differentiating the strain energy density of the structure to give the constitutive relationship between the stress and the stretch of the collagen network. In the proposed constitutive model for the mechanical behavior of the cervical tissue the collagen in the ECM is modeled to respond to the entire deformation of the compartment it occupies (compartment 1).

Based on the 8-chain Arruda-Boyce model we calculate the level of stretch $\lambda_c$ experienced
by the collagen fibrils occupying compartment 1 of the cervical tissue as

$$\lambda_c = \sqrt{\frac{\text{tr}(B_c)}{3}},$$  \hspace{1cm} (5.56)

where $B_c$ is the left Cauchy-Green tensor, $F_c$ and $J_1$ and are the deformation gradient and the volumetric stretch of the collagen compartment (compartment 1). In terms of the macroscopic deformation gradient $\tilde{F}$ the collagen deformation gradient $F_c$ can be expressed as:

$$F_c = F_1 F_c^0 = \left(\frac{j_1^{1/3}}{(f_1^0 j_1^{1/3} + f_2^0 j_2^{1/3})}\right)\tilde{F},$$  \hspace{1cm} (5.57)

from where we can derive an expression for the left Cauchy-Green tensor $B_c$ in terms of the total deformation gradient $\tilde{F}$:

$$B_c = F_c F_c^T = \xi^2 \frac{j_1^{2/3}}{(f_1^0 j_1^{1/3} + f_2^0 j_2^{1/3})^2} \tilde{B},$$  \hspace{1cm} (5.58)

where $\tilde{B}$ is the macroscopic left Cauchy-Green tensor

$$\tilde{B} = \tilde{F}\tilde{F}^T.$$  \hspace{1cm} (5.59)

In terms of the macroscopic deformation gradient the fibril stretch and the Cauchy stress in the collagen network can be expressed as follows:

$$\lambda_c = \xi \frac{j_1^{1/3}}{(f_1^0 j_1^{1/3} + f_2^0 j_2^{1/3})} \sqrt{\frac{\text{tr}(B)}{3}},$$  \hspace{1cm} (5.60)

$$\sigma_c = \frac{1}{J_1} \left[\mu_0 \frac{\lambda_L}{\lambda_c} \beta (\frac{\lambda_c}{\lambda_L}) B - \mu_0 \lambda_L \beta_0 I\right],$$  \hspace{1cm} (5.61)

$$\sigma_c = \frac{1}{J_1} \left[\mu_0 \frac{\lambda_L}{\xi^3} \sqrt{\frac{\text{tr}(B)}{3}} \beta (\frac{j_1^{1/3}}{(f_1^0 j_1^{1/3} + f_2^0 j_2^{1/3})}) \frac{\text{tr}(B)}{3}\frac{j_1^{1/3}}{(f_1^0 j_1^{1/3} + f_2^0 j_2^{1/3})} \tilde{B} - \mu_0 \frac{\xi^3}{\lambda_L \beta_0} I\right],$$  \hspace{1cm} (5.62)
where
\[ J_c = \det(F_c) = \det(F_1 F_0^T) = \det(F_1) \det(I) = \xi^3 \det(F_1) = \xi^3 J_1. \quad (5.63) \]

Separating the contribution of the stress into its deviatoric and volumetric components and assigning the deviatoric part of the response to the contribution of the collagen network completes the constitutive modeling of the isochoric part of the healthy non-pregnant cervical stroma. The resulting expression for the stress in the deviatoric collagen network is
\[ \sigma'_c = \frac{1}{J_c} \mu_0 \frac{\lambda_L}{\lambda_c} \beta \frac{\lambda_c}{\lambda_L} B'_c, \quad (5.64) \]

where
\[ B'_c = B_c - \frac{tr(B_c)}{3} I. \quad (5.65) \]

The corresponding rheological model for the deviatoric collagen network is presented in figure 5-4.

This representation of the stress state in the collagen network relies on 3 material parameters in the model for the collagen, which need to be fitted to experimental data:
- \( \mu_0 \) is the initial collagen modulus and by analogy with a molecular network \( \mu_0 = \frac{mk_B^0}{3} \)
- \( \lambda_L \) is the limiting stretch for the collagen fibril and \( \lambda_L = \sqrt{n} \)
- \( \xi \) is the collagen prestretch.

Since in this constitutive model for the mechanical behavior of the cervical tissue the GAGs do not provide a deviatoric component to the shear response the collagen contribution accounts
for the entire deviatoric stress in the tissue, given by
\[
\bar{\sigma}' = f_1^0 \frac{J_1}{J} \sigma_c.
\]  

(5.66)

### 5.6.2 Transient Tissue Response

The main structural component that controls the mechanical behavior of the cervical tissue is the collagen network. We propose a constitutive formulation in which the entire transient response for the nonpregnant tissue can be interpreted in terms of a time-varying volume of the collagen compartment. In this formulation the collagen responds to the entire deformation gradient of compartment 1 at all times of the deformation history. In the case of modelization of pregnant cervical stroma this condition is relaxed and the collagen is allowed to flow as discussed in a subsequent section.

In order to present the formulation of the transient model response we refer to a schematic rheological model of the volumetric response 5-5.

Due to their negative charge density the PGs create high osmotic pressures and attract positive ions from the surrounding interstitial fluid thus swelling the tissue by a significant amount [59]. The high osmotic pressures in the ground substance are responsible for the
compressive stiffness of the cervical stroma. The physical origin of the resistance of soft tissues to compressive loads arises from the changes in the electrostatic intermolecular repulsion forces between adjacent charges on the GAG chains of the PGs. Basser et al. [9] presents the osmotic pressure of the PGs as a function of hydration of the tissue for the case of human articular cartilage indicating a significant drop in the stiffness of the response with increased hydration levels.

The one dimensional representation of the model 5-6 incorporates a spring element used to characterize the response of the highly hydrated ground substance of the glycosaminoglycans and proteoglycans.

In compartment 2, occupied by the free GAGs, the proteoglycans are free to imbibe water assuming a swollen conformation. As previously discussed, the GAGs in compartment 1 are in a state of uniform compressive stress due to the tensile stresses in the collagen fibers occupying the same domain (see Fig. 5-7), which restrict them from swelling to the extent of the PGs in compartment 2.

The initial equilibrium condition for the hydrostatic stress in compartment 1 renders a zero overall stress state in this compartment. This equilibrium is given by a balance of the hydrostatic stresses of the collagen and bound GAG components of compartment 1 such as:

\[ \sigma_c^h + \sigma_{BG}^h = 0. \]  

(5.67)
The initial volume of the bound GAGs is calculated as

\[ J_{BG}^0 = \exp\left(-\frac{\mu L \lambda L (\xi \beta (\xi L_{\xi} - \beta_0))}{K_{GAG}}\right). \]  

(5.68)

As previously stated, the current volume of the bound GAGs is given by

\[ J_{BG} = J_{BG}^0 J_1. \]  

(5.69)

The equilibrium hydrostatic stress in compartment 2 occupied by the free GAGs is given by

\[ \sigma_{FG}^h = K_{GAG} \ln(J_{FG}) = K_{GAG} \ln(J_2). \]  

(5.70)

Flow of fluid between the two compartments is driven by the imbalance of the hydrostatic stresses of the two compartments. This imbalance is the intercompartmental (IC) pressure given by

\[ \sigma_{IC}^h = \sigma_{FG}^h - (\sigma_{BG}^h + \sigma_c^h) \]  

(5.71)

and is the driving force for fluid flow between the bound GAGs and the free GAGs compartments.
The evolution of the volumetric Jacobian of the collagen compartment is given by

\[ \dot{J}_1 = \varepsilon_v J_1, \quad (5.72) \]

where \( \varepsilon_v \) is the volumetric flow rate. In order to fully characterize the intercompartmental flow, the rate of change of the volumetric strain \( \varepsilon_v \) needs to be constitutively prescribed.

The flow equation for the intercompartmental flow is given by:

\[ \dot{\varepsilon}_v = \varepsilon_v^0 \left( \frac{\sigma_{IC}^h}{\sigma_0^v} \right)^m \quad (5.73) \]

In the above equation, \( \varepsilon_v^0 \) is the initial rate of change of the volumetric strain, \( \sigma_0^v \) can be considered as flow strength and \( m \) is a flow rate sensitivity parameter.

The limit of \( m \rightarrow 1 \) recovers linear flow behavior and in this case the flow equation reduces to linear flow between the compartments:

\[ \dot{\varepsilon}_v = \left( \frac{\varepsilon_v^0}{\sigma_0^v} \right) \sigma_{IC}^h, \quad (5.74) \]

where \( \varepsilon_v^0 \) is a lumped material parameter to be fitted to experimental data.

### 5.7 Pregnant Cervical Tissue

As it is our intention to extend the constitutive model of the cervix to capture the behavior of pregnant tissue and account for the state of an impaired cervical function such as the case of cervical insufficiency, for completeness of the presentation we include a brief discussion of a preliminary implementation of viscous flow of the collagen network.

The competent cervical tissue undergoes substantial restructuring during pregnancy, which is referred to as cervical maturation. This transformation of the cervical stroma happens throughout the gestation and is associated with a substantial softening of the stroma, as well as an altered tissue biochemistry. For a more detailed discussion on cervical maturation of the healthy stroma, the reader is referred to chapter 2 of this thesis. This softening of the stroma was confirmed by the experimental characterization of the cervical tissue by Myers et al [64].
Figure 5-8: Rheological model for the deviatoric collagen network and backstress.

The experimental results show that when subjected to cyclic loading intensity, the pregnant cervical stroma exhibits stress relaxation (see figure 3-8). Furthermore the results indicate that there is a substantial drop in the peak values of the stress from the non-pregnant to the pregnant state.

As the tensile response of the stroma is governed predominantly by the extension of the collagen fibers, we propose to account for the aforementioned characteristics of the response by incorporating a viscous component to the collagen network. The viscous element captures the time-dependent characteristics of the material response and the tendency of the collagen network to reconfigure itself by viscous shearing and sliding of neighboring collagen fibers.

As a result of network reconfiguration and decreased cross-linking of the pregnant stroma the effective stretch in the collagen increases, which in turn leads to a reduction of the peak stress levels. Furthermore, the increased softness of the stroma can be accounted for by a reduced initial modulus of the collagen.

The extent of collagen reconfiguration and relaxation is restricted by chemical cross-links and physical entanglements between the adjacent fibers, which limiting action is implemented in the model as an elastic “backstress” (see figure 5-8).

The macroscopic Cauchy stress in the collagen network is equal to the sum of the backstress
and the viscous stress and is given by

\[ \sigma_v' = \sigma_c^{BACK'} + \sigma_v'. \]  

(5.75)

### 5.7.1 Viscous Stress in the Collagen Network

The deviatoric viscous stress \( \sigma_v' \) drives the flow in the collagen part of the network and is calculated as the difference between the collagen macroscopic stress and the backstress of compartment 1 expressed as

\[ \sigma_v' = \sigma_v - \sigma_c^{BACK'}. \]  

(5.76)

The constitutive modelization of the collagen compartment is based on the central hypothesis for the multiplicative decomposition of the deformation gradient into an elastic \( F_1^{el} \) and viscous \( F_1^v \) components, given by

\[ F_1 = F_1^{el} F_1^v. \]  

(5.77)

The velocity gradient in the collagen compartment is expressed as

\[ L_1 = \dot{L}_1 F_1^{-1}. \]  

(5.78)

\[ L_1 = (F_1^{el}) (F_1^v)^{-1} \]  

(5.79)

\[ L_1 = \dot{F}_1^{el} F_1 ^v F_1^{-1} + F_1^{el} \dot{F}_1^v F_1^{-1} F_1^{el} \]  

(5.80)

\[ L_1 = \dot{F}_1^{el} F_1 ^v F_1^{-1} + F_1^{el} \dot{F}_1^v F_1^{-1} F_1^{el} \]  

(5.81)

\[ L_1 = L_1^{el} + \dot{L}_1^v F_1^{el} F_1^{-1}. \]  

(5.82)

The additive split of the velocity gradient into its elastic and viscous components can be finalized as

\[ L_1 = L_1^{el} + L_1^v. \]  

(5.83)

Next we decompose the flow velocity gradient into its symmetric (stretching) and skew (spin) parts

\[ L_1^v = D_1^v + W_1^v \]  

(5.84)
The flow spin tensor $W'_1$ in the current configuration is prescribed to be irrotational, which renders uniqueness of the decomposition of the deformation gradient of compartment 1[17]:

$$W'_1 = 0. \quad (5.85)$$

In order to evolve the viscous part of the deformation gradient in compartment 1 we need to constitutively prescribe the stretching part of the velocity gradient. Due to the prescription of irrotational flow the velocity gradient is reduced to

$$L'_1 = D'_1. \quad (5.86)$$

The stretching part of the velocity gradient is assigned to be proportional to the direction of the deviatoric viscous stress $\sigma'_c$, which drives the flow in the collagen compartment, expressed by

$$D'_1 = \dot{\gamma}'_1 N, \quad (5.87)$$

where $N = \frac{\sigma'_c}{|\sigma'_c|}$ is the tensorial direction of the deviator of the viscous stress in the current configuration. The viscous strain rate coefficient $\dot{\gamma}'_1$ needs to be constitutively prescribed in order to fully characterize the flow part of the network. The proposed relation is given by equation 5.88

$$\dot{\gamma}'_1 = \dot{\gamma}^0_1 \left( \frac{|\sigma'_c|}{S'_c} \right)^{m'_c}. \quad (5.88)$$

Such a form for the plastic flow has successfully been implemented in the constitutive modeling of ultra-high molecular weight polyethylene by Bergstroem et al [14]. In equation 5.88 $\dot{\gamma}^0_1$ is the initial collagen viscous stretching rate, $S'_c$ is the strength of the viscous flow, and $m'_c$ is the viscous flow sensitivity.

Therefore, the stretching tensor can be expressed as

$$D'_1 = \dot{\gamma}^0_1 \left( \frac{|\sigma'_c|}{S'_c} \right)^{m'_c} \frac{\sigma'_c}{|\sigma'_c|}. \quad (5.89)$$

The deformation gradient for the collagen compartment is evolved in the intermediate con-
figuration and using equation 5.78 and 5.82 can be derived as:

$$
\dot{E}_I^v = \dot{L}_I^v F_I^v
$$  \hspace{1cm} (5.90)

$$
\dot{L}_I^v = F_I^v L_I^v F_I^v
$$  \hspace{1cm} (5.91)

$$
\dot{F}_I^v = F_I^{e-1} D_I^v F_I^{e} F_I^v
$$  \hspace{1cm} (5.92)

$$
\dot{F}_I^v = F_I^{e-1} D_I^v F_I^v
$$  \hspace{1cm} (5.93)

5.7.2 Backstress in the Collagen Network

The backstress $\mathcal{B}_{c}^{BACk'}$ is defined in the intermediate (unloaded) configuration, therefore the backstress must be pushed forward to the current configuration. This operation is expressed as

$$
\sigma_{c}^{BACk'} = \frac{1}{J_1} F_I^{e} \sigma_{c}^{BACk'} F_I^{e T}
$$  \hspace{1cm} (5.94)

The deviatoric backstress $\dot{\sigma}_{c}^{BACk'}$ in the intermediate configuration is taken to be linear and is defined as:

$$
\dot{\sigma}_{c}^{BACk'} = \frac{1}{J_1} \left( 2 G e_1^{e} - \frac{2}{3} G \text{tr}(e_1^{e}) I \right),
$$  \hspace{1cm} (5.95)

where $G$ is the backstress modulus and $e_1^{e}$ is the viscous part of the Hencky strain tensor of compartment 1, given by

$$
e_1^{e} = \ln(B_1^{e})^{1/2} = \ln(F_1^{e} F_1^{e T})^{1/2},
$$  \hspace{1cm} (5.96)

where $B_1^{e}$ is the left Cauchy-Green tensor.

This completes the modelization of flow in the collagen network.

5.8 Elastin

The elastin in the elastic fibers is characterized by a high degree of reversible extensibility. The elastin has the capability of sustaining large deformation with the application of small forces as discussed in chapter 2 of this thesis [11] and can be viewed as the “elastic memory of the tissue”. Under the action of a macroscopic deformation gradient $F$ the elastin provides a contribution
to the stress, which was implemented as a simple linear relationship between the hydrostatic stress and the macroscopic volumetric deformation. Such a description of the stress state of the elastin depends on a single constitutive parameter, namely the bulk modulus $K_{elastin}$ of the elastin in the stroma and is given by

$$
\sigma_{elastin}^h = K_{elastin}(\bar{J} - 1)I.
$$

The shear response of the elastin is negligible as compared with the collagen. Its contribution is regarded as a part of the collagen deviatoric response.

### 5.9 Interstitial Fluid Flow

The last component in the constitutive model for the isotropic cervical stroma is the interstitial flow, which flows through the porous ECM. The fluid flow accounts for a proportion of the time-dependent effects of the mechanical response of the cervical stroma. The nature of the interaction between the ECM composed of collagen fibers, PGs and elastin, and the stroma and the flow is frictional. We have adopted a framework for the fluid flow, which is governed by a linear Darcy’s Law. The frictional drag between the fluid and the constituents of the stroma creates a pressure drop in the fluid and is represented by the proportionality between the macroscopic flow rate and the pressure gradient given by Darcy’s law:

$$
q = -k \nabla P_{fluid},
$$

where $k$ is a linear permeability coefficient.

Finally, the microscopic hydrostatic stress in the cervical stroma is the volume average of the stresses experienced by the individual constituents and is derived as:

$$
\bar{\sigma}_{MACRO}^h = \sigma_{FG}^h + \sigma_{elastin}^h + \Delta P_{Darcy}.
$$

The macroscopic mechanical response of the cervical tissue is a combination of the individual responses of the main constituents and is presented in figure 5-9. This representation of the cervical stroma relies on 9 material parameters, which are summarized in table 5.1.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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<tbody>
<tr>
<td>$f_2^0$</td>
<td>Initial volume fraction of compartment 2</td>
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<tr>
<td>$\mu_0$</td>
<td>Collagen initial modulus</td>
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<tr>
<td>$\xi$</td>
<td>Collagen prestretch</td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td>Collagen limiting stretch</td>
</tr>
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<td>$K_{GAG}$</td>
<td>Bulk modulus of the proteoglycans</td>
</tr>
<tr>
<td>$K_{elastin}$</td>
<td>Bulk modulus of the elastin</td>
</tr>
<tr>
<td>$K_{Darcy}$</td>
<td>Darcy permeability coefficient</td>
</tr>
<tr>
<td>$\frac{\varepsilon^0}{\sigma^0 m}$</td>
<td>Lumped flow parameter</td>
</tr>
<tr>
<td>$m$</td>
<td>Flow sensitivity</td>
</tr>
</tbody>
</table>

Table 5.1: Material parameters for the cervical stroma.

Figure 5-9: Rheological model for the macroscopic response of the stroma of the cervix.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
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<td>Initial Free GAG volume fraction</td>
<td>0.07</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>Pa</td>
<td>Initial collagen modulus</td>
<td>210</td>
</tr>
<tr>
<td>$\xi$</td>
<td></td>
<td>Collagen prestretch</td>
<td>1.03</td>
</tr>
<tr>
<td>$\lambda_L$</td>
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<td>Collagen locking stretch</td>
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<tr>
<td>$K_{GAG}$</td>
<td>Pa</td>
<td>Bulk modulus GAG</td>
<td>10</td>
</tr>
<tr>
<td>$K_{elastin}$</td>
<td>Pa</td>
<td>Bulk modulus elastin</td>
<td>1000</td>
</tr>
<tr>
<td>$\frac{\phi^0}{\sigma^0}$</td>
<td></td>
<td>Lumped flow parameter</td>
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</tr>
<tr>
<td>$m$</td>
<td></td>
<td>Flow sensitivity</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5.2: Isotropic material parameters for the healthy cervical stroma.

5.10 Numerical Implementation of the Isotropic Constitutive Model for the Cervical Stroma

5.10.1 Fit of the Simulation to Experimental Data in Compression

Finite element simulations attempting to reproduce the experimentally observed behavior in compression were carried out. Three load-unload compression ramps to -45% true axial strain were simulated. Between each loading ramp a step of zero applied deformation was simulated. The choice for the material parameters is summarized in table 5.2. Darcy flow of fluid through the porous extracellular matrix was not considered.

This implementation of the model simulates the mechanical behavior of the healthy cervical stroma. Thus, the viscous deformation of the collagen network was not implemented. Due to this simplification the number of material parameters that needed to be fitted to experimental data was reduced to 8. Additionally, the flow rule for the interstitial flow between the different compartment was implemented as a linear. The limit of $m \rightarrow 1$ recovers linear flow behavior and in this case the initial rate of change of the volumetric strain $\dot{\varepsilon}_v^0$ and the interstitial flow strength $\sigma^0$ can be combined into a single lumped model parameter $\frac{\phi^0}{\sigma^0}$ which needs to be fitted to experimental data. Thus, the material parameter choice is reduced to 7 parameters, which were fitted to the experiments. The final material parameter choice implemented in the simulation is summarized in table 5.3.

The fit between the compression experimental data and the numerical simulation is displayed in figure 5-10. The tree experimental loading ramps are displayed in color as follows: the
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f^0 )</td>
<td>-</td>
<td>Initial Free GAG volume fraction</td>
<td>0.07</td>
</tr>
<tr>
<td>( \mu_0 )</td>
<td>Pa</td>
<td>Initial collagen modulus</td>
<td>210</td>
</tr>
<tr>
<td>( \xi )</td>
<td>-</td>
<td>Collagen prestretch</td>
<td>1.03</td>
</tr>
<tr>
<td>( \lambda_L )</td>
<td>-</td>
<td>Collagen locking stretch</td>
<td>1.1</td>
</tr>
<tr>
<td>( K_{GAG} )</td>
<td>Pa</td>
<td>Bulk modulus GAG</td>
<td>10</td>
</tr>
<tr>
<td>( K_{elastin} )</td>
<td>Pa</td>
<td>Bulk modulus elastin</td>
<td>1000</td>
</tr>
<tr>
<td>( \frac{\dot{\varepsilon}^0}{\varepsilon} )</td>
<td>1/(Pa*s)</td>
<td>Initial rate of change of volumetric strain</td>
<td>1e - 7</td>
</tr>
</tbody>
</table>

Table 5.3: Isotropic material parameters for the healthy cervical stroma (reduced).

initial loading ramp is shown in red, and the second and the third loading ramps are displayed respectively in blue and green. The model fit for three compression ramps is displayed in black. Figure 5-10.A represents the nominal stress vs axial stretch data and figure 5-10.B displays the volumetric change vs axial stretch data. The simulation fit is superposed onto the experimental data. This implementation of the model assesses the ability of the model to qualitatively and quantitatively capture the mean experimentally observed behavior of the stroma.

As it can be seen from figure 5-10, the essential characteristics of the experimentally observed behavior, such as nonlinearity, hysteresis, stress and volume peak levels, as well as preconditioning were successfully captured by the model.

The initial loading ramp in the simulation results is associated with emptying the volume from the compartment of the free GAGs. Small values of the applied axial strain (up to compressive stretch values of 0.9) result in depletion of this compartment (see figure 5-11). The macroscopic volume of the stroma is reduced in an almost linear fashion during this initial loading ramp and the associated stress levels are negligible, which is consistent with the experimentally observed stress levels. Subsequent to the emptying the compartment of the free GAGs, a build up of non-equilibrium stress levels in the compartment of the bound GAGs is created (see figure 5-12). These non-equilibrium stress levels between the two compartments initiate the flow of fluid from the bound GAGs compartment and result in stretching of the collagen fibers. As a result, the stress levels in the stroma are increased and the volume of the bound GAG compartment is reduced. Upon reversal of the load the stretched collagen fibrils instantaneously tend to rotate back to their undeformed configuration thus reducing the effective stretch of the collagen. This results in instantaneous drop of the level of the stress.
Further decrease of the stress levels occurs at constant volume which allows for the reorientation of the collagen fibrils. When the stress levels in the two compartment reach equal levels the intercompartmental pressure is equal to zero. At zero driving stress for the intercompartmental flow under the action of the elastic component of the elastin network the compartment of the free GAGs starts to recover its initial volume. Driven by the elastic component of the elastin network the stress of compartment 2 continues to decrease and meanwhile the initial equilibrium of compartment 1 is recovered.

Subsequent loading of the stroma leads to a slightly more compliant behavior, and can be explained with the accumulation of the volumetric strain in the bound GAGs compartment during the initial loading ramp, which is not fully recovered during the initial unloading of the specimen. The simulation captures the effect of preconditioning of the stroma, as well as all the essential features of the experimental response, including the reproducibility of the response in the subsequent loading cycles.

The material parameter accounting for the initial volume fraction of the compartment of the free GAGs $f_2^0$ was directly fitted to the experimental data plots as the value at which the
volume loss regime transitions from a compliant volumetric deformation regime, which happens at $\Delta \sigma \sim 0$ to a new regime, which is associated with $\Delta \sigma \gg 0$ and corresponds to a level of axial stretch $\lambda_{axial} \sim 0.87$ for which $\dot{J} \sim 0.93$.

The experimentally observed high levels of the macroscopic stress of the stroma were only possible to reproduce when the level of the collagen prestretch was chosen to be $\xi > 1$. An initially unbiased ($\xi = 1$) isotropic collagen network is not capable of reproducing the effective levels of stretch in the collagen, which governs the stress of the collagen and results in the high stress levels experimentally observed in compression. The nonlinearity of the stress in the collagen compartment is a combination of the initial collagen modulus $\mu_0$ and the collagen limiting stretch $\lambda_L$. Collagen extensibility is reported as 8-10% in the literature [19] which results in $\lambda_L = 1.08 - 1.1$. A level of $\lambda_L = 1.1$ was chosen for the model implementation. The initial modulus of the collagen was chosen to give the correct initial slope of the stress curve and was chosen as $\mu_0 = 210$ Pa.

Figure 5-13 presents the fit of the experimental data (in red) and the simulation results (in black). Figure 5-13.A presents the nominal stresses [MPa] vs time and figure 5-13.B displays the

Figure 5-11: Model simulation results vs axial stretch. Upper left: Macroscopic stress in MPa; upper right: Total volumetric stress; lower left: volume of the bound GAG/collagen compartment; lower right: volume of the free GAG compartment.
Figure 5-12: Model simulation results. Upper left: Hydrostatic stress in the elastin; upper right: hydrostatic stress in the free GAGs; middle left: hydrostatic stress in the bound GAGs; middle right: hydrostatic stress in the collagen; lower left: intercompartmental stress; lower right: deviatoric stress in the collagen.
volumetric change vs time. The set of data to model the experimental results is as previously reported in table 5.3. The characteristics such as the nonlinearity of the stress response as well as the transition between different volume loss regimes is successfully captured by the simulation results. There exist a certain mismatch between the experimental stress peaks and the model results. As previously discussed in chapter 4 of this thesis, the variability of the data between different patients is far greater than the difference of the fit and the averaged experimental response presented in the figure. Nevertheless, the simulation successfully manages to account for the qualitative material behavior. Additionally, the model is shown to successfully capture the intricate correlation between the stress-strain and volume change behavior exhibited by the experimental data.

5.10.2 Sensitivity of the Parameters

In order to assess the sensitivity of the material model parameters, a series of finite element simulations were conducted, aiming at qualitatively reproducing the limiting cases of the experimental behavior of the cervical stroma, as previously presented in chapter 4 on the mechanical response of the cervix. In the parameter sensitivity assessment an alternative set of material
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_2^0$</td>
<td>Initial volume fraction of compartment 2</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>Collagen initial modulus</td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td>Collagen limiting stretch</td>
</tr>
<tr>
<td>$K_{FG}$</td>
<td>Bulk modulus of the free GAGs</td>
</tr>
<tr>
<td>$K_{BG}$</td>
<td>Bulk modulus of the bound GAGs</td>
</tr>
<tr>
<td>$K_{elastin}$</td>
<td>Bulk modulus of the elastin</td>
</tr>
<tr>
<td>$\frac{v}{\sigma_{fr}}$</td>
<td>Lumped flow parameter</td>
</tr>
<tr>
<td>$m$</td>
<td>Flow sensitivity</td>
</tr>
</tbody>
</table>

Table 5.4: Alternative set of material parameters for the cervical stroma.

parameters was utilized and is summarized in table 5.4.

In our proposed constitutive description the material behavior of the free and the bound GAGs was characterized by a single bulk modulus of the glycosaminoglycans $K_{GAG}$. The state of prestretch of the collagen fibers is balanced by the state of precompression of the bound GAGs as previously discussed. In order to account for this initial equilibrium of compartment one we imposed the requirement for zero initial stress state of this compartment, from where the initial volume of the bound GAGs was calculated and given by equation 5.68. This situation is depicted in figure 5-14 with the set of solid black axes representing the zero stress state of the collagen (5-14.top) and the bound GAGs (5-14.bottom). The state of pretension of the collagen and the precompression of the bound GAGs are marked with a $\star$ in the figure. If alternatively one chooses the broken blue axes as the reference axes to describe this initial equilibrium state, the collagen can be characterized as having no initial prestretch ($\xi = 1$) and an augmented bulk compressibility coefficient $K_{BG}$ can be introduced, $K_{BG} > K_{FG}$, which accounts for the bigger initial bulk compressibility of the bound GAGs. The difference between the bulk moduli of the GAGs is captured by the different slopes of the tangents to the GAGs response in figure 5-14.bottom. In this equivalent representation the initial volume of the bound GAGs compartment is $J_{BG}^0 = 1$.

Table 5.5 summarizes the choice of material parameters used to fit the tissue response presented in figure 5-15. Respectively, table 5.6 and table 5.7 present the choice of material parameters selected for the fit of experimental data presented in figures 5-16 and 5-17. Figures 5-15.left, 5-16.left and 5-17.left present the experimental data for three extreme cases of tissue behavior and figures 5-15.right, 5-16.right and 5-17.right depict the corresponding simulation
Figure 5-14: Description of the initial equilibrium of compartment one: solid black axes represent the initial situation in which the prestretched collagen fibers are equilibrated by the precompressed bound GAGs (depicted by *). Broken blue axes represent an alternative description of the equilibrium stress state which treats the collagen as having no initial prestretch and associates a bigger bulk compressibility coefficient of the bound GAGs. Top: collagen response; bottom: GAG response.
Table 5.5: Isotropic material parameters for the healthy cervical stroma (choice II).

<table>
<thead>
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<th>Parameter</th>
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<th>Value</th>
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<tr>
<td>$f_2^0$</td>
<td></td>
<td><em>Initial Free GAG volume fraction</em></td>
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</tr>
<tr>
<td>$\mu_0$</td>
<td>Pa</td>
<td><em>Initial collagen modulus</em></td>
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</tr>
<tr>
<td>$\xi$</td>
<td></td>
<td><em>Collagen prestretch</em></td>
<td>1</td>
</tr>
<tr>
<td>$\lambda_L$</td>
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<td><em>Collagen locking stretch</em></td>
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<tr>
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<tr>
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<td>Pa</td>
<td><em>Bulk modulus bound GAG</em></td>
<td>300</td>
</tr>
<tr>
<td>$K_{elastin}$</td>
<td>Pa</td>
<td><em>Bulk modulus elastin</em></td>
<td>1000</td>
</tr>
<tr>
<td>$\frac{\delta}{\alpha_{3F}}$</td>
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<td><em>Lumped flow parameter</em></td>
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</tr>
<tr>
<td>$m$</td>
<td></td>
<td><em>Flow sensitivity</em></td>
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</tbody>
</table>

Table 5.6: Isotropic material parameters for the healthy cervical stroma (choice III).

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<tr>
<th>Parameter</th>
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<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_2^0$</td>
<td></td>
<td><em>Initial Free GAG volume fraction</em></td>
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</tr>
<tr>
<td>$\mu_0$</td>
<td>Pa</td>
<td><em>Initial collagen modulus</em></td>
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<tr>
<td>$\xi$</td>
<td></td>
<td><em>Collagen prestretch</em></td>
<td>1</td>
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<tr>
<td>$\lambda_L$</td>
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<td><em>Collagen locking stretch</em></td>
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</tr>
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<td>$K_{FG}$</td>
<td>Pa</td>
<td><em>Bulk modulus free GAG</em></td>
<td>100</td>
</tr>
<tr>
<td>$K_{BG}$</td>
<td>Pa</td>
<td><em>Bulk modulus bound GAG</em></td>
<td>1000</td>
</tr>
<tr>
<td>$K_{elastin}$</td>
<td>Pa</td>
<td><em>Bulk modulus elastin</em></td>
<td>500</td>
</tr>
<tr>
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<td><em>Lumped flow parameter</em></td>
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</tr>
<tr>
<td>$m$</td>
<td></td>
<td><em>Flow sensitivity</em></td>
<td>1</td>
</tr>
</tbody>
</table>

fits to both the stress-stretch (A) and volume change (B) behavior of the stroma. The three fits are qualitative and describe the fitness of the model to capture various characteristics of extreme tissue behavior by a small change in the selection of the set of material parameters. As shown in the figures, the qualitative fits are satisfactory for all the three limiting cases of tissue mechanical behavior.

5.10.3 Tension and Compression

In this investigation, the ability of the isotropic model to capture the behavior of the stroma in both tension and compression was assessed. With the choice of material parameters, that were shown to successfully capture the behavior of the material in compression (table 5.3), we carried out a finite element simulation of uniaxial tension to 17% true tissue strain. The combined results for tension and compression are presented in figure 5-18. It can be clearly seen from the
Figure 5.15: Sensitivity of the parameters: choice of material parameters II. Left: experimental response; right: simulation fit. (A) Nominal stress [MPa] vs axial stretch. (B) Volume change vs axial stretch.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_2^0$</td>
<td></td>
<td>Initial Free GAG volume fraction</td>
<td>0.1</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>Pa</td>
<td>Initial collagen modulus</td>
<td>10</td>
</tr>
<tr>
<td>$\xi$</td>
<td></td>
<td>Collagen prestretch</td>
<td>1</td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td>Pa</td>
<td>Collagen locking stretch</td>
<td>1.14</td>
</tr>
<tr>
<td>$K_{FG}$</td>
<td>Pa</td>
<td>Bulk modulus free GAG</td>
<td>10</td>
</tr>
<tr>
<td>$K_{BG}$</td>
<td>Pa</td>
<td>Bulk modulus bound GAG</td>
<td>1000</td>
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<tr>
<td>$K_{elastin}$</td>
<td>Pa</td>
<td>Bulk modulus elastin</td>
<td>1000</td>
</tr>
<tr>
<td>$\frac{\varepsilon^2}{\alpha_{10}}$</td>
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<tr>
<td>$m$</td>
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<td>Flow sensitivity</td>
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Table 5.7: Isotropic material parameters for the healthy cervical stroma (choice IV).
Figure 5-16: Sensitivity of the parameters: choice of material parameters III. Left: experimental response; right: simulation fit. (A) Nominal stress [MPa] vs axial stretch. (B) Volume change vs axial stretch.
Figure 5-17: Sensitivity of the parameters: choice of material parameters IV. Left: experimental response; right: simulation fit. (A) Nominal stress [MPa] vs axial stretch. (B) Volume change vs axial stretch.
Figure 5-18: Fit of the model simulation and the experimental data in both tension and compression. Color code: red - first loading ramp; blue - second loading ramp; green - third loading ramp; black - simulation fit (three load-unload ramps). (A) Nominal stress [MPa] vs axial stretch. (B) Volumetric change vs stretch. (A) Nominal stress [MPa] vs axial stretch. (B) Volumetric change vs stretch.

plots that the fit is rather unsatisfactory. First, the peak stress levels in tension predicted by the simulation differ by two orders of magnitude from the experimentally exhibited stress level peaks (see figure 5-18.A). Second, the predicted peak values differ significantly even from the corresponding compressive stress peaks. The volume change behavior of the stroma (see figure 5-18.B), characterized by initial gain of volume at small levels of tensile axial stretch followed by a significant volume loss at higher stretch levels in the loading ramp is only partially predicted by the simulation results. Moreover, there is no volume and stress hysteresis in the simulation predictions. A magnification of the tension model fits superposed on the experimental data is presented in figure 5-19. In the time domain the predictions of the volume are equally unsatisfactory and are presented in figure 5-20.

The nonlinearity of the mechanical response of soft tissue and high peak levels of the stress are associated to a very large extent with the behavior of the collagen fibrils in the extracellular matrix of soft tissue stroma. A brief discussion of the effective collagen stretch based on different deformation measures is presented in the subsequent paragraph.

Figure 5-21 presents an assessment of the effective collagen fibril stretch, which controls the
Figure 5-19: Fit of the model simulation and the experimental data in tension. Color code: red - first loading ramp; blue - second loading ramp; green - third loading ramp; black - simulation fit (three load-unload ramps). (A) Nominal stress [MPa] vs axial stretch. (B) Volumetric change vs stretch.

Figure 5-20: Fit of the model simulation and the experimental data in tension. (A) Nominal stress [MPa] vs time. Color code: red - experimental material response; black - simulation fit. (B) Volumetric change vs time. Color code: red - first loading ramp; blue - second loading ramp; green - third loading ramp; black - simulation fit (three load-unload ramps).
collagen stress response, based on three different stress measures. An effective collagen fibril stretch calculated with the macroscopic left Cauchy-Green tensor $\mathbf{B}$ and given by $\lambda = \sqrt{\frac{\text{tr}\mathbf{B}}{3}}$ is shown in figure 5-21.A. Such a deformation measure renders a level of the effective stretch, which are higher than the corresponding stretch levels in tension. Moreover, for higher levels of the applied axial tensile stretch the effective stretch undergoes a downward kink associated with the reduction of the volume of the specimen. Clearly such an effective collagen fibril stretch cannot accommodate the differences of the stress-strain behavior exhibited by the stroma in tension and compression and is unsuitable for our analysis.

Figure 5-21.B presents an effective collagen stretch based on the isochoric left Cauchy-Green tensor $\mathbf{\tilde{B}}$, which is calculated as $\overline{\lambda} = \sqrt{\frac{\text{tr}\mathbf{\tilde{B}}}{3}}$. By making the effective collagen fibril stretch isochoric the problem at higher levels of axial stretch is resolved. Despite the slight improvement, this modification still fails to render the desired bias of the effective stretch towards higher levels in tension.

Our constitutive model for the collagen fibril proposes an effective stretch of the collagen fibril, which is based on the modified left Cauchy-Green tensor $\mathbf{B}_e = \lambda^2 \frac{j^{2/3}}{(f_1^2 j_1^{1/3} + f_2^2 j_2^{1/3})^2} \mathbf{\tilde{B}}$. The model predictions calculate an effective stretch which is presented in figure 5-21.C. This correction of the deformation measure is still insufficient to accommodate the differences between the tension and compression deformation case.

The observed experimental behavior with much higher peak stress levels in tension differing an order of magnitude from the corresponding peak levels of stress in compression for significantly lesser values of the applied axial load suggests that a simplified isotropic constitutive model might not be capable of capturing the observed experimental response of the cervical stroma. Indeed, MRI Diffusion tensor imaging of the uterine cervix performed by Weiss et al [88] confirms the existence of directional structures in the collagen fiber architecture. Concurrently, in an ongoing investigation, Myers et al [65] assesses the anisotropy of the cervical tissue response by mechanically testing the stroma in different directions and reports certain level of anisotropy of the human cervical tissue.
Figure 5-21: Assessment of the effective collagen fibril stretch. (A) Fibril stretch based on the macroscopic left Cauchy-Green tensor, $\lambda = \sqrt{\frac{\text{tr} \mathbf{B}}{3}}$. (B) Fibril stretch based on the isochoric left Cauchy-Green tensor, $\bar{\lambda} = \sqrt{\frac{\text{tr} \mathbf{B}}{3}}$. (C) Fibril stretch based on the modified left Cauchy-Green tensor, $\lambda_c = \sqrt{\frac{\text{tr} \mathbf{B}}{3}}$. 
5.11 Anisotropy of the Tissue

Many engineering materials exhibit anisotropic behavior due to the presence of fibers in the homogeneous matrix material, which determine a preferred orientation in the material as a whole. These materials are referred to as composite or fiber-reinforced materials and wood and soft tissues are good examples of materials exhibiting such heterogeneity. The collagen fibrils are the main source of anisotropy [86] in soft tissues due to their preferred orientation in the extracellular matrix, which is generally considered isotropic. The collagen organization in the cervix has been studied by X-ray diffraction [5] and MRI diffusion tensor imaging [88]. Even though these studies fail to establish a global model for the collagen fiber arrangement in the cervical tissue, they confirm the existence of directional structures in the cervix and therefore, the anisotropy of the tissue. For a more detailed description of these studies and their findings the reader is referred to the discussion on collagen fibril orientation (see chapter 2). Recent work by Myers et al [65] (in preparation) confirms tissue anisotropy by developing mechanical testing protocols and analyzing the influence of collagen fiber orientation on the mechanical properties of the stroma.

Attempts to model the anisotropic, time-dependent and highly nonlinear behavior of soft tissue have been partially successful. In 2002 Bischhoff et al [15] proposed a microstructurally based orthotropic hyperelastic constitutive law for a general case class of polymer and polymer-like materials, which exhibit hyperelastic orthotropic mechanical behavior. Due to the similarities of the force-stretch behavior of the polymer and the collagen network, the basic characteristics of the stress-strain behavior of the collagen network can be well captured with classical rubber-elasticity constitutive models. Therefore we address the issue of cervical tissue anisotropy by incorporating the Bischoff-Arruda constitutive model into our 3-D model for the large strain time-dependent material behavior for the cervix.

The constitutive modelization of the anisotropic mechanical behavior of the cervix can be viewed as a three step process, which includes:

1) modelization of the constitutive response for a single collagen fibril;
2) modelization of the constitutive response for a representative unit cell;
3) homogenization of the unit cell into a 3-D continuum constitutive model.

The stages of model development will be discussed in further detail.
5.11.1 Force-Stretch Behavior for a Single Collagen Fiber

The detailed discussion on modeling the constitutive response for a single collagen fibril was presented earlier in this section (see the discussion on Collagen network response in 5.6.1).

5.11.2 Representative Unit Cell

Bischoff and Arruda [15] propose a representative unit cell that allows for initial orthotropy of a network with preferred fiber orientation. Such a unit cell is an extension of the unit cell initially proposed by Arruda and Boyce [3]. The two unit cells are presented in figure 5-22.

The fixed orientation of the orthotropic unit cell is specified by the orthogonal principal material axes \( a, b, \) and \( c \) (presented in green in figure 5-22). This orientation is rotated relative to a reference coordinate system \( X_1, X_2, X_3 \). The dimensions of the unit cell are \( a, b, \) and
The axes $a, b, c$, respectively, along the axes $a, b, c$, are normalized by $l$ and therefore dimensionless. The fixed orientation of the unit cell together with the unit cell dimensions give rise to the orthotropy of the mechanical response of a network with preferred fiber orientation.

Additionally, the 8 chains in the undeformed configuration can be described by the vectors

\[
P^{(1)} = -P^{(5)} = \frac{a}{2}a + \frac{b}{2}b + \frac{c}{2}c; \tag{5.100}
\]

\[
P^{(2)} = -P^{(6)} = \frac{a}{2}a + \frac{b}{2}b - \frac{c}{2}c; \tag{5.101}
\]

\[
P^{(3)} = -P^{(7)} = \frac{a}{2}a - \frac{b}{2}b + \frac{c}{2}c; \tag{5.102}
\]

\[
P^{(4)} = -P^{(8)} = \frac{a}{2}a - \frac{b}{2}b - \frac{c}{2}c. \tag{5.103}
\]

The generalized vector description can be given by

\[
P^{(i)} = \pm \frac{a}{2}a \pm \frac{b}{2}b \pm \frac{c}{2}c, \quad i = 1..8. \tag{5.104}
\]

The length of each chain in the undeformed configuration is given by

\[
P = \frac{1}{2} \sqrt{a^2 + b^2 + c^2}. \tag{5.105}
\]

The deformed lengths of the individual chains are calculated as

\[
r^{(i)} = \sqrt{P^{(i)T} \cdot CP^{(i)}}, \tag{5.106}
\]

where $C$ is the right Cauchy-Green tensor and $C = F^T F$.

5.11.3 Homogenization of the Unit Cell into a 3-D Continuum Constitutive Model

In order to derive the fully three dimensional strain energy density function for the orthotropic hyperelastic model the unit cell presented in the previous section can be homogenized. The
strain energy function that results has the following form:

\[ W(x) = W_0 + \frac{nk\theta}{4} \left( N \sum_{i=1}^{4} \left[ \frac{\rho^{(i)}}{N} \beta^{(i)}_\rho + \ln \frac{\beta^{(i)}_\rho}{\sinh \beta^{(i)}_\rho} \right] - \frac{\beta_\rho}{\sqrt{N}} \ln \left[ \lambda_a^2 \lambda_b^2 \lambda_c^2 \right] \right), \]  

(5.107)

where \( \sqrt{N} = P \) is the undeformed length of the chain, \( n \) is the chain density, \( k = 1.38 \times 10^{-23} \) J/K is the Boltzmann’s constant, \( \theta \) is the absolute temperature, \( \beta^{(i)}_\rho \) is the inverse Langevin function, and \( \lambda_a = \sqrt{a^T \cdot Ca}, \lambda_b = \sqrt{b^T \cdot Cb}, \lambda_c = \sqrt{c^T \cdot Cc} \) are the stretches along the principal material axes. \( W_0 \) is a constant.

This strain energy function can be used in order to calculate the second Piola-Kirchhoff stress tensor \( \tilde{T} = \partial W/\partial E \) by differentiating the strain energy function with respect to the Lagrangian strain \( E = \frac{1}{2} (F^TF - I) \). This results in an expression for the second Piola-Kirchhoff stress tensor given in indicial notation such as

\[ \tilde{T}_{jk} = \frac{nk\theta}{4} \sum_{i=1}^{4} \frac{P^{(i)}_j P^{(i)}_k}{\rho^{(i)}_\rho} - \frac{\beta_\rho}{\sqrt{N}} \left( \frac{a_j^2 a_k}{\lambda_a^2} + \frac{b_j^2 b_k}{\lambda_b^2} + \frac{c_j^2 c_k}{\lambda_c^2} \right). \]  

(5.108)

Finally, the relationship between the second Piola-Kirchhoff stress tensor and the Cauchy stress tensor is expressed as

\[ \sigma = \frac{1}{J} F^T \tilde{T} F. \]  

(5.109)

5.11.4 Numerical Implementation of the Anisotropic Constitutive Model for Cervical Tissue Behavior

In our implementation of the proposed anisotropic hyperelastic constitutive law the principal material axes are aligned with the reference coordinate system axes \( X_1, X_2, \) and \( X_3 \). The choice of material parameters for the finite element fit is summarized in table 5.8.

The fit between the experimental data and the numerical simulation is displayed in figure 5-23. The experimental loading ramps are displayed in color and the following color code applies: the initial loading ramp is shown in red, and the second and the third loading ramps are displayed respectively in blue and green. The model fit for three compression ramps is displayed in black. Figure 5-23.A represents the nominal stress vs axial stretch data and figure 5-23.B displays the volumetric change vs axial stretch data. The simulation fit is superposed
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_0^I$</td>
<td></td>
<td>Initial Free GAG volume fraction</td>
<td>0.1</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>Pa</td>
<td>Initial collagen modulus</td>
<td>100</td>
</tr>
<tr>
<td>$\lambda_L$</td>
<td></td>
<td>Collagen locking stretch</td>
<td>1.02</td>
</tr>
<tr>
<td>$K_{FG}$</td>
<td>Pa</td>
<td>Bulk modulus free GAG</td>
<td>50</td>
</tr>
<tr>
<td>$K_{BG}$</td>
<td>Pa</td>
<td>Bulk modulus bound GAG</td>
<td>3e5</td>
</tr>
<tr>
<td>$K_{elastin}$</td>
<td>Pa</td>
<td>Bulk modulus elastin</td>
<td>1000</td>
</tr>
<tr>
<td>$\alpha^{\text{off}}$</td>
<td></td>
<td>Lumped flow parameter</td>
<td>$4.67e-8$</td>
</tr>
<tr>
<td>$m$</td>
<td></td>
<td>Flow sensitivity</td>
<td>1</td>
</tr>
<tr>
<td>$a^2$</td>
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<td>Structural parameter</td>
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</tr>
<tr>
<td>$b^2$</td>
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<td>Structural parameter</td>
<td>1.3</td>
</tr>
<tr>
<td>$c^2$</td>
<td></td>
<td>Structural parameter</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Table 5.8: Anisotropic material parameters for the healthy cervical stroma.

onto the experimental data. Separate plots for the tension and compression fit vs axial stretch are presented respectively in figures 5-24 and 5-26. The corresponding simulation fits in the time domain are presented in figures 5-25 and 5-27.

The corresponding levels of the effective fibril stretch in the stroma were calculated and are presented in figure 5-28.

The results show, that by suitably choosing the degree of tissue anisotropy, a single set of material constants is capable of fitting the experimental material response in tension and compression. The presented constitutive model based on an orthotropic unit cell alleviates the difficulties of the isotropic model to capture the mechanical tissue response by accommodating the difference in the levels of peak stresses between tension and compression to a satisfactory level. The relative heights of the different stress peaks are well captured by the model and the large difference between the levels of the stress experienced in the two modes of deformation is reflected in the simulation. Further adjustment of the material parameters was necessary in order to capture certain characteristics of the mechanical behavior such as the initial stiffness of the stress response and the width of the hysteresis loop.

In the finite element implementation of the anisotropic model the structural coefficients $a$, $b$, and $c$, were treated as material parameters which needed to be fitted to the experimental data. Future morphological studies on the anisotropy level of the cervical tissue are necessary in order to relate mechanical model parameters to actual compositional and microstructural...
Figure 5-23: Fit of the anisotropic model simulation and the experimental data in both tension and compression. Color code: red - first loading ramp; blue - second loading ramp; green - third loading ramp; black - simulation fit (three load-unload ramps). (A) Nominal stress [MPa] vs axial stretch. (B) Volumetric change vs stretch.

Figure 5-24: Fit of the anisotropic model simulation and the experimental data in tension. Color code: red - first loading ramp; blue - second loading ramp; green - third loading ramp; black - simulation fit (three load-unload ramps). (A) Nominal stress [MPa] vs axial stretch. (B) Volumetric change vs stretch.
Figure 5-25: Fit of the anisotropic model simulation and the experimental data in tension. (A) Nominal stress [MPa] vs time. Color code: red - experimental data; black - simulation fit. (B) Volumetric change vs time. Color code: red - first loading ramp; blue - second loading ramp; green - third loading ramp; black - simulation fit (three load-unload ramps).

Figure 5-26: Fit of the anisotropic model simulation and the experimental data in compression. Color code: red - first loading ramp; blue - second loading ramp; green - third loading ramp; black - simulation fit (three load-unload ramps). (A) Nominal stress [MPa] vs axial stretch. (B) Volumetric change vs stretch.
characteristics of the tissue.

Figure 5-27: Fit of the anisotropic model simulation and the experimental data in compression. (A) Nominal stress [MPa] vs time. Color code: red - experimental data; black - simulation fit. (B) Volumetric change vs time.

Figure 5-29 presents preliminary predictions of the model from finite element simulations in uniaxial compression in the longitudinal direction. Figure 5-29.A portrays finite element model predictions (green - loading in the circumferential direction; black - loading in the longitudinal direction). Figure 5-29.B presents experimental data from loading in two different tissue directions (red - loading in the longitudinal direction; blue - loading in the circumferential direction). The model predictions are in good qualitative agreement with the experimentally observed mechanical behavior of the stroma. Further adjustment of the material parameters is necessary in order to capture more accurately the specific peak levels of the stress and the effect of preconditioning.
Figure 5-28: Effective stretches in both tension and compression for the anisotropic material model.

Figure 5-29: Preliminary predictions of the model from uniaxial compression tests in the longitudinal direction. (A) Model predictions. (B) Experimental data. Color code: red - loading in the longitudinal direction; blue - loading in the circumferential direction.
Chapter 6

Conclusions and Recommendations
for Future Work

6.1 Concluding Remarks

During gestation, the cervix and the uterus are subjected to complex time-varying physiological loading conditions. New findings on the mechanical behavior of the stroma emphasize the complexity of the stress-strain and volume change behavior of the cervical stroma, as well as the intricate correlation between the two. The challenges involved in prescribing a constitutive behavior of the stroma include characteristics such as nonlinearity, viscoelasticity, anisotropy, inhomogeneity and preconditioning. Additionally, the mechanical response of the stroma exhibits marked differences in tension and compression with associated stress levels differing more than an order of magnitude between the different modes of deformation.

A fully three-dimensional constitutive model, capable of capturing the complex mechanical behavior of human cervical tissue both in bulk and in shear, was developed. The contribution of the individual constituents of the stroma was accounted for and integrated in the model. The proposed model was shown to successfully capture the mechanical behavior of the cervix including effects of tissue restructuring associated with cervical insufficiency, softening, remodeling and growth. Finite element model simulations were fitted to experimental mechanical response in compression in order to obtain the "mechanical properties" of the tissue in vitro. The model was further extended to incorporate effects of anisotropy of the material. It was
shown that by suitably choosing the level of tissue anisotropy, the differences in the levels of stress experienced in tension and compression can be accommodated.

The proposed constitutive model was integrated with a three dimensional solid model of the lower pelvic region of a pregnant patient. The resulting finite element model was used as a tool to study the effects of different clinical features on the biomechanics of the pregnant cervix and uterus and to investigate the conditions that lead to a premature dilation in the case of cervical insufficiency. The effects of uterine contractions on the stress distribution in the tissue was investigated. Additionally, the constitutive model was implemented with an axisymmetric geometry in order to perform parametric studies and investigate the biomechanics of the cervical function. The performed parametric studies showed that:

- membrane adhesion affects the funneling of the insufficient cervix;
- the effectiveness of the cerclage as a treatment for insufficiency depends on the location of the stitch;
- cervical length affects the strength of the cervix.

### 6.2 Recommendations for Future Work

Future work should include further assessment of the capability of the model to capture the effects of anisotropy of the tissue. Additionally, future morphological studies on the anisotropy level of the cervical tissue are necessary in order to relate mechanical model parameters to actual compositional and microstructural characteristics of the tissue.

A number of characteristics of the mechanical response need to be investigated as well. These include:

- the effect of different levels of strain;
- the effects of different strain rates.

The effect of these features needs to be incorporated into the constitutive characterization of the cervical stroma.

An implementation of a new remodeling rule for the collagen capturing the mechanically induced continuous reorientation of the collagen fibrils, decreased cross-linking of the collagen in the insufficient cervix, as well as the effect of cyclic mechanical loading on the degradation.
of the collagen, is necessary.

The model can immensely benefit from further validation in order to characterize the underlying reasons for weaker material properties of the insufficient cervix.
Appendix A

Derivations

A.1 Jacobian Relationship

\[ \frac{V_1}{V_0} + \frac{V_2}{V_0} = \bar{J} \]  

(A.1)

The relationships between the current and initial volumes of the two compartments are given by:

\[ V_1 = J_1 V_1^0 \]  

(A.2)

\[ V_2 = J_2 V_2^0 \]  

(A.3)

from ?? it follows that

\[ \frac{J_1 V_1^0}{V_0} + \frac{J_2 V_2^0}{V_0} = \bar{J} \]  

(A.4)

The volume fractions of the two compartments in their undeformed configuration are correspondingly \( f_1^0 \) and \( f_2^0 \) and are defined as

\[ f_1^0 = \frac{V_1^0}{V_0} \]  

(A.5)

where 5.11 is the ratio of the initial volume of compartment 1 to the entire initial volume of the tissue and

\[ f_2^0 = \frac{V_2^0}{V_0} \]  

(A.6)

is 5.12 correspondingly the ratio of the initial volume of compartment 2 to the entire initial
volume. Therefore ?? reduces to:

\[ J_1 f_1^0 + J_2 f_2^0 = \bar{J} \]  \hspace{1cm} (A.7)

### A.2 Deformation Gradient Relationship

Representation of the overall deformation gradient \( \bar{F} \) as unweighted volume averages over the RVE is given by:

\[ \bar{F} = \frac{1}{V} \int_V F(X, t) \, dV \]  \hspace{1cm} (A.8)

\[ \bar{F} = \frac{1}{V_0} (V_1^0 F_1 + V_2^0 F_2) \]  \hspace{1cm} (A.9)

\[ \bar{F} = \frac{V_1^0}{V_0} F_1 + \frac{V_2^0}{V_0} F_2 \]  \hspace{1cm} (A.10)

The overall deformation gradient \( \bar{F} \) can be presented as the volume average of the deformation gradients of the individual compartments weighted by their corresponding volume fractions:

\[ \bar{F} = f_1^0 F_1 + f_2^0 F_2 \]  \hspace{1cm} (A.11)

Utilizing the multiplicative decomposition of the deformation gradient into its dilatational \((J)\) and volume preserving \((\bar{F})\) components often used in elastoplasticity (see, for example the work of Lee from 1969 \([52]\)), the deformation gradients in the different compartments can be expressed as:

\[ F_1 = J_1^{1/3} \bar{F}_1 \]  \hspace{1cm} (A.12)

\[ F_2 = J_2^{1/3} \bar{F}_2 \]  \hspace{1cm} (A.13)

Using 5.6, 5.13, 5.17 and 5.18 we obtain

\[ \bar{J}^{1/3} \bar{F} = f_1^0 J_1^{1/3} \bar{F}_1 + f_2^0 J_2^{1/3} \bar{F}_2 \]  \hspace{1cm} (A.14)

\[ (J_1 f_1^0 + J_2 f_2^0)^{1/3} \bar{F} = (J_1^{1/3} + J_2^{1/3}) \bar{F}_{\text{compartment}} \]  \hspace{1cm} (A.15)
Where \( \mathbf{F} \) in ?? is the overall isochoric deformation gradient of the cervical stroma and \( \mathbf{F}_{\text{compartment}} \) is the isochoric gradient of the individual compartments.

\[
\mathbf{F}_{\text{compartment}} = \frac{(J_1 f_1^0 + J_2 f_2^0)^{1/3}}{(f_1^0 J_1^{1/3} + f_2^0 J_2^{1/3})} \mathbf{F}
\]  
(A.16)

\[
\sigma_c = \frac{1}{J_c} \left[ \mu_0 \frac{\lambda_L}{\lambda_c} \beta (\frac{\lambda_c}{\lambda_L}) \mathbf{B}_c - \mu_0 \lambda_L \beta_0 I \right]
\]  
(A.17)

\[
\sigma_c = \frac{1}{\xi^3 J_1} \left[ \mu_0 \frac{\lambda_L}{\lambda_c} \beta \left( \frac{J_1^{1/3}}{(f_1^{1/3} J_1^{1/3} + f_2^{1/3} J_2^{1/3})^{3/2}} \mathbf{B} \right)^{1/3} \right. \\
- \left. \mu_0 \lambda_L \beta_0 I \right]
\]  
(A.18)

\[
\sigma_c = \frac{1}{\xi^3 J_1} \left[ \mu_0 \frac{\lambda_L}{\lambda_c} \beta \left( \frac{J_1^{1/3}}{(f_1^{1/3} J_1^{1/3} + f_2^{1/3} J_2^{1/3})^{3/2}} \mathbf{B} \right)^{1/3} \right. \\
- \left. \mu_0 \lambda_L \beta_0 I \right]
\]  
(A.19)

### A.3 Macroscopic Hydrostatic Stress

\[
\overline{\sigma}^h = \frac{1}{V} \int_{V} \sigma^h dV
\]  
(A.20)

\[
\overline{\sigma}_{\text{MACRO}}^h = \frac{(\sigma_c^h + \sigma_{BG}^h + \sigma_{IC}^h) V_{BG} + \sigma_J^h V_{FG}}{V} + \sigma_{\text{elastin}}^h + \Delta P_{\text{Darcy}}
\]  
(A.21)

\[
\overline{\sigma}_{\text{MACRO}}^h = (\sigma_c^h + \sigma_{BG}^h + \sigma_{IC}^h) \frac{V_1}{V_{0}} + \sigma_{FG}^h \frac{V_2}{V_{0}} + \sigma_{\text{elastin}}^h + \Delta P_{\text{Darcy}}
\]  
(A.22)

\[
\overline{\sigma}_{\text{MACRO}}^h = (\sigma_c^h + \sigma_{BG}^h + \sigma_{IC}^h) \frac{V_1 V_{0}}{J_1 V_{0}} + \sigma_{FG}^h \frac{V_2 V_{0}}{J_2 V_{0}} + \sigma_{\text{elastin}}^h + \Delta P_{\text{Darcy}}
\]  
(A.23)

\[
\overline{\sigma}_{\text{MACRO}}^h = (\sigma_c^h + \sigma_{BG}^h + \sigma_{IC}^h) J_1 \frac{J_1}{J} + \sigma_{FG}^h J_2 \frac{J_2}{J} + \sigma_{\text{elastin}}^h + \Delta P_{\text{Darcy}}
\]  
(A.24)

\[
\overline{\sigma}_{\text{MACRO}}^h = (\sigma_c^h + \sigma_{BG}^h + \sigma_{IC}^h) J_1 \frac{J_1}{J} + \sigma_{FG}^h J_2 \frac{J_2}{J} + \sigma_{\text{elastin}}^h + \Delta P_{\text{Darcy}}
\]  
(A.25)

But \( (\sigma_c^h + \sigma_{BG}^h + \sigma_{IC}^h) = \sigma_{FG}^h \)

\[
\overline{\sigma}_{\text{MACRO}}^h = \sigma_{FG}^h \left( \frac{J_1}{J} + \frac{J_2}{J} \right) + \sigma_{\text{elastin}}^h + \Delta P_{\text{Darcy}}
\]  
(A.26)
and $f_1^0 J_1 + f_2^0 J_2 = \tilde{J}$

\[
\tilde{\sigma}^{h}_{\text{MACRO}} = \sigma^{h}_{FG} + \sigma^{h}_{\text{elastin}} + \Delta P_{\text{Darcy}}
\]  
(A.27)
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