Biomechanical Investigation of the Female Pelvic Region

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Manfred Matthias Maurer

Dipl.-Ing., RWTH Aachen
born November 28, 1986
citizen of Germany

accepted on the recommendation of

Prof. Dr. Edoardo Mazza, examiner
Prof. Dr. Steven Abramowitch, co-examiner

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Abstract

The female pelvic region is a complex mechanical system consisting of a variety of structural elements, such as muscles, ligaments and connective tissues. These are supporting the organs within the pelvic cavity inferiorly against gravitational loads and intra abdominal pressure. Weakness or failure of one or several of the supportive structures can lead to mechanical instability, which in turn may cause pelvic dysfunction, in particular pelvic organ prolapse (POP). While the majority of cases remains without symptoms, 11% of women showing symptomatic POP undergo surgery, amounting to around 300000 patients per year in the US alone. In recent years, treatment included the implantation of synthetic meshes, woven structures based on polymer filaments. These are supposed to restore anatomical form and support the organs, directly inducing a restoration of function. However, 29% of patients require recurrent surgical intervention due to severe clinical complications such as mesh erosion, shrinkage or fibrosis. Recently it has been suggested that these adverse phenomena can be linked to mechanical causes, in particular a mismatch of mechanical properties and behavior of the mesh on several length scales, reaching from a global macro level of the structure down to a local meso or micro scale at a filament or tissue level. This led to the coining of the term “mechanical biocompatibility”, or the ability of an implant to display a mechanical behavior compatible with its function and favoring its integration in the surrounding tissue. The assessment of the mechanical biocompatibility of any implant however, requires the knowledge of the mechanical environment, i.e. forces and deformations, in which it is supposed to perform. Not only is the awareness of loads in the pelvic region necessary as a physiological reference for implant design, but it could also serve as a means to detect and track pathologies, such as pelvic muscle weakening or pre-term softening of the uterine cervix during gestation. However, it is intuitively clear that a direct measurement of forces acting on muscles within the pelvic cavity in vivo is challenging if not impossible. In this work, the powerful tool of finite element analysis has applied to investigate the highly complex mechanical system of the female pelvic cavity.

While analytical models based on Laplace’s Law of thin walled pressure containers are
used in the context of the female pelvic floor, they can only estimate the global mechanical environment within the pelvic region. The detailed finite element model developed in this work allows for a more in-depth mechanical analysis. The present study allowed for a quantification of tensions and deformations within the pelvic muscles, which were found to be an order of magnitude lower than those within the abdominal wall. Initial analytical calculations based on Laplace’s Law could be confirmed. The FE model also gave indications of the effects of local geometry variability on loads within the muscles. It is a valuable tool for in-vivo estimation of forces and deformations of healthy and pelvic prolapse patients. After successful clinical outcomes in the abdominal wall, meshes initially designed for hernia repair were first used for POP repair. However, these implants were designed to fit abdominal loading, exhibiting excessive stiffness compared to the organs and tissues in the pelvic region. The present model can provide an important reference for design and mechanical dimensioning of prostheses for pelvic prolapse repair, since their mechanical biocompatibility, i.e. a match of mechanical properties of implant and tissue, is of major importance when investigating clinical complications.

In a second application, the finite element model was adapted and used to evaluate the physiological mechanical regime in which mesh implants have to perform in the framework of a specific repair strategy. For the first time, a repair method for pelvic prolapse, the sacrocolpopexy after a hysterectomy procedure, has been modeled with the aid of the finite element method, allowing for the analysis of global in vivo forces and displacements in the mesh and vagina. The influence of surgical technique, mesh material and local non-affine deformation patterns on a meso-scale unit cell level have been evaluated and their possible contribution to observed clinical complications discussed. The analysis clearly showed the importance of mesh material and surgical technique when implanting a sacrocolpopexy mesh. A softer implant can reduce forces in vagina and sacrum, however a small amount of prestretch might shift its mechanical response to a zone of higher apparent stiffness, diminishing the force reduction effects. On the other hand, prestretch might be purposefully applied by the surgeon in order to manipulate the mesh compliance to a desired value. The present study gives valuable indications and warrants further, systematic in silico and in vivo studies in order to investigate the complex mechanisms and verify the results, ultimately allowing for a clear set of guidelines for medical doctors.

While the assessment of the mechanical environment in-vivo is important to evaluate the mechanical biocompatibility of mesh prostheses, knowledge of the mechanical behavior of the implants themselves is clearly needed to complete the picture. That requires a meaningful definition and general acceptance of mechanical tests and parameters in order to consistently characterize these prostheses. In an effort to provide such data, an extensive, multiscale experimental protocol has been developed and nine different mesh types...
have been evaluated in terms of their mechanical properties. A set of nine parameters have been proposed, including uniaxial and biaxial stiffness, anisotropy and the influence of tissue ingrowth or multiple cycles on the mechanical behavior. In order to facilitate simple comparison of meshes, these parameters have been visualized in a circle graph, allowing for immediate evaluation of mesh performance, even for the untrained eye.

Another important organ with a mechanical function in the female pelvic region is the uterine cervix. It closes the uterus inferiorly and is crucial to mechanically maintain pregnancy. At term it softens in a controlled manner and allows for the passage of the fetus through the birth canal. If this change in mechanical properties happens before term, it might lead to preterm birth and thus a high risk of mortality and morbidity for the fetus. In the field of obstetrics, transvaginal quasistatic elastography has been recently suggested to be suitable for the detection of mechanical changes in the cervix during gestation, determining its stiffness. However, with the help of experiments and finite element investigations, it has been shown that the proposed method is not suited to detect cervical softening over time. In fact, quasistatic elastography was developed to evaluate relative differences in tissue compliance based on kinematic data and is successfully used in e.g. liver cancer detection. The working principle of this method has then been translated into a computational elastography approach. A new methodology for detection of pelvic muscle weakness, and thus possibly prolapse, has been proposed, based on finite element analysis and purely kinematic data of the pelvic muscle sheet. As a proof of concept, artificial pelvic organ prolapse cases have investigated using the finite element model developed in this work, showing promising results.
Zusammenfassung

dass die direkte in vivo Messung von Kräften, die auf die Muskeln und inneren Organe wirken, schwierig oder sogar völlig unmöglich ist. In dieser Arbeit wurde daher das wirkungsvolle Werkzeug der Finite Elemente Analyse angewendet, um das hochkomplexe mechanische System der weiblichen Beckenhöhle zu untersuchen.


auf einer finite Elemente Analyse und rein kinematischen Daten der Beckenbodenmuskulatur. Als ein Machbarkeitsnachweis wurden mit Hilfe des in dieser Arbeit entwickelten finite Elemente Modells künstliche Fälle von Beckenbodenschwäche in silico untersucht und vielversprechende Ergebnisse gezeigt.
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Chapter 1

Introduction

The female pelvic region is a complex mechanical system consisting of a variety of structural elements, such as muscles, ligaments and connective tissues. These are supporting the organs within the pelvic cavity inferiorly against gravitational loads and intra abdominal pressure [113, 211]. Weakness or failure of one or several of the supportive structures can lead to mechanical instability, which in turn may cause pelvic dysfunction, in particular pelvic organ prolapse (POP) [37]. While the majority of cases remains without symptoms, 11% of women showing symptomatic POP undergo surgery, amounting to around 300000 patients per year in the US alone [127, 196]. In recent years, treatment included the implantation of synthetic meshes, woven structures based on polymer filaments. These are supposed to restore anatomical form and support the organs, directly inducing a restoration of function. However, 29% of patients require recurrent surgical intervention due to severe clinical complications such as mesh erosion, shrinkage or fibrosis [80, 75, 136, 196]. Recently it has been suggested that these adverse phenomena can be linked to mechanical causes [52, 69, 86, 87, 160], in particular a mismatch of mechanical properties and behavior of the mesh on several length scales, reaching from a global macro level of the structure down to a local meso or micro scale at a filament or tissue level. This led to the coining of the term “mechanical biocompatibility”, or the ability of an implant to display a mechanical behavior compatible with its function and favoring its integration in the surrounding tissue [173, 175, 224, 227].

The assessment of the mechanical biocompatibility of any implant however, requires the knowledge of the mechanical environment, i.e. forces and deformations, in which it is supposed to perform. Not only is the awareness of loads in the pelvic region necessary as a physiological reference for implant design, but it could also serve as a means to detect and track pathologies, such as pelvic muscle weakening or pre-term softening of the uterine cervix during gestation. However, it is intuitively clear that a direct measurement of
forces acting on muscles within the pelvic cavity in vivo is challenging if not impossible. In this work, the powerful tool of finite element analysis is applied to investigate the highly complex mechanical system of the female pelvic cavity. In particular, the following questions have been addressed:

- Develop a three dimensional finite element model of the female pelvic region.
- Using the model, evaluate the mechanical environment in the pelvic floor for healthy and pelvic prolapse patients. Can the finite element analysis provide quantitative insights?
- Develop and execute an extensive multiscale experimental protocol to evaluate the mechanical biocompatibility of synthetic meshes for hernia and pelvic prolapse repair. Can a mismatch of mechanical properties be a possible cause for clinical complications?
- Implement a repair strategy using mesh implants into the finite element model. Can the FE analysis indicate possible adverse mechanical effects leading to clinical complications?
- Assess the effectiveness of quasistatic elastography for estimation of mechanical properties of tissues and organs within the pelvic cavity. Can this methodology be used to (i) track stiffness changes of the uterine cervix during gestation and (ii) detect muscle weakening in the pelvic muscle sheet?

The thesis is structured as follows:

Chapter 2 gives an introduction to the female pelvic floor anatomy and its major structural elements. The pathology of pelvic organ prolapse is presented including prevalence and treatment. A literature overview of pelvic finite element models is given, setting the backdrop for the generation and use of the finite element model developed in the framework of this project. In a first application, it is used to evaluate tensions within the pelvic muscle sheet of a healthy and POP patient with impaired musculature. It shows the capabilities of the in silico mechanical analysis of the pelvic cavity, the structures of which are mostly inaccessible for direct measurement of forces and deformations.

Chapter 3 addresses the question of the mechanical biocompatibility of mesh prostheses used for hernia and pelvic prolapse repair. An introduction to the existing knowledge on pelvic prolapse repair using synthetic meshes is given, including prevalent clinical complications. Subsequently, an extensive yet simple mechanical testing protocol for
characterization of implants is proposed. Nine different mesh types were tested. Each mesh is represented by several mechanical and physical parameters, which are presented in a newly developed circle graph. This allows for a quick visual inspection of mesh properties and mechanical biocompatibility. In addition, the groups of POP and hernia meshes are compared and their suitability for their respective area of application discussed. Furthermore, the finite element model of the pelvic region developed in Chapter 2 is used to evaluate the physiological mechanical regime in which the implants have to perform. For the first time, a repair method for pelvic prolapse, the sacrocolpopexy after a hysterectomy procedure, has been modeled with the aid of the finite element method, allowing for the analysis of global in vivo forces and displacements in the mesh and vagina. The influence of surgical technique, mesh material and local non-affine deformation patterns on a mesoscale unit cell level are evaluated and their possible contribution to observed clinical complications is discussed.

Chapter 4 is concerned with another important organ in the female pelvic region, the uterine cervix. It closes the uterus inferiorly and is crucial to mechanically maintain pregnancy. At term it softens in a controlled manner and allows for the passage of the fetus through the birth canal. If this change in mechanical properties happens before term, it might lead to preterm birth and thus a high risk of mortality and morbidity for the fetus. In the field of obstetrics, transvaginal quasistatic elastography has been recently suggested to be suitable for the detection of mechanical changes in the cervix during gestation, determining its stiffness. However, with the help of experiments and finite element investigations, it is shown that the proposed method is not suited to detect cervical softening over time. In fact, quasistatic elastography was developed to evaluate relative differences in tissue compliance based on kinematic data and is successfully used in e.g. liver cancer detection. The working principle of this method is then translated into a computational elastography approach. A new methodology for detection of pelvic muscle weakness, and thus possibly prolapse, is proposed, based on finite element analysis and purely kinematic data of the pelvic muscle sheet. As a proof of concept, artificial POP cases are investigated using the finite element model developed in Chapter 2.

Main findings are summarized in Chapter 5 along with indications of future research.
3-dimensional Finite Element Model of the Female Pelvic Floor

2.1 Introduction

2.1.1 Pelvic Anatomy

**Bony Frame.** The rigid framework of the pelvic cavity supporting all soft tissues within is comprised of the two lateral innominate bones, each composed of the ilium, ischium and pubis [113], see Figure 2.1. They are fused posteriorly to the sacrum and anteriorly to each other at the pubic symphysis. The female pelvic cavity is usually wider and more circular in shape in order to allow for passage of the fetal head during child birth [133]. However, this widened dimensions predispose the female pelvis to pelvic floor weaknesses following parturition [113]. The rigid bony frame provides attachment points for muscles, ligaments and connective tissue within the pelvic floor [211].

**Pelvic Organs.** The organs suspended within the female pelvic cavity are the bladder anteriorly, vagina and uterus centrally as well as rectum posteriorly (see Figure 2.2). The pelvic muscular structure provides inferior openings for urethra and vaginal canal anteriorly and rectum posteriorly, separated by the perineal body [211, 246]. The pelvic organs are supported inferiorly by the hammock-like structure of the pelvic muscle sheet as well as ligamentous structures [113, 211].

**Muscular Structure.** The major muscle structure supporting the pelvic cavity inferiorly against gravitational forces and increased intra abdominal pressure is the pelvic diaphragm (Figure 2.3). It is divided into two major groups, the levator ani and the
coccygeus muscle from medial to lateral [113]. The levator ani is further subdivided into levator plate posteriorly, iliococcygeus laterally as well as pubococcygeus and puborectalis medially and anteriorly, named according to their origin of insertion [125]. The pubococcygeus connects pubis and coccyx anterio-posteriorly and passes laterally around urethra, vaginal canal and rectum, forming the urogenital hiatus. The medial parts of the muscle adhere to all three organs and are specifically referred to as pubourethralis, pubovaginalis and puboanalis, respectively [113]. The puborectalis forms a sling-like support of the rectum, originating on both lateral sides at the pubis, serving an important role in rectal continence [125]. The medio-lateral portion of the levator ani is formed on both lateral sides by the iliococcygeus muscle. It is a wide, thin sheet originating from the obturarius
2.1. Introduction

Internus fascia laterally and inserting posteriorly along the lateral margin of the coccyx and lower sacrum [113, 125]. The individual sides come together medially to form, together with the lateral part of the pubococcygeus muscle, the levator plate between anus and coccyx. It forms the shield on which the rectum and upper two thirds of the vagina rest [113]. Weakness of the levator ani may cause the levator plate to sag, widening the urogenital hiatus and predisposing it to prolapse [25]. In fact, women with pelvic prolapse have been shown to have a wider urogenital hiatus [66]. The most posterior muscle of the pelvic floor is the coccygeus, originating directly at the bony ischial spine on both lateral sides and inserting at the coccyx and lower sacrum [148]. Connective tissue referred to as superior and inferior fascia covers both surfaces of the pelvic floor muscle sheet [11].

**Connective Tissues and Ligaments.** The major connective tissue structure connecting the pelvic organs (urethra and bladder, vagina, uterus) to the pelvic walls is collectively referred to as endopelvic fascia, forming a fine mesh-like structure of collagen fibers [113]. It is divided into different parts according to location, has varying thickness, and condenses into ligamentous structures in several strategic places. Anteriorly, the median umbilical ligament connects the bladder to the umbilicus. The paravaginal fascia, subdivided into paracolpium and parametrium, is a division of the endopelvic fascia, located in the medial pubocervical segment on both lateral sides of the vagina, connecting it to the pelvic wall [113, 222]. The cardinal ligaments connect the uterus to the pelvic wall, thus supporting it [113]. The uterosacral ligaments are posterior condensations of the endopelvic fascia [169], suspending the upper vagina and cervix over the levator ani [113].

Figure 2.3: Pelvic muscle structure, including levator ani, coccygeus, iliococcygeus and external anal sphincter. Reprinted with permission from Primal Pictures 2009.
2.1.2 Pelvic Organ Prolapse

Pelvic organ prolapse (POP) is an abnormal change of the female pelvic anatomy [37, 250], related to histological changes in pelvic floor tissues [134]. These could be both, cause for prolapse [34, 55] or consequence thereof due to remodeling processes initiated by prolapse [183]. From a mechanical point of view, changes in pelvic tissue structures or material behavior can be linked to POP. In fact, several studies have investigated the mechanical behavior of pelvic floor structures and tissues [56, 181, 186, 233] in order to elucidate the complex chain of anatomical and histological events associated with POP.

![Figure 2.4: The most common forms of pelvic organ prolapse. (a) Normal pelvic anatomy. (b) Cystocele, prolapse of the bladder into the anterior vaginal wall. (c) Rectocele, prolapse of the rectum into the posterior vaginal wall. (d) Procidentia, prolapse of the uterus into the vaginal canal at the apex. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.](image)

Pelvic organ prolapse can in general be described as a descent of pelvic organs and herniation into the vagina [37]. The most common types of prolapse are the (i) cystocele, a descent of the bladder into the anterior vaginal wall (Figure 2.4 b)), (ii) rectocele, a descent of the rectum into the vaginal canal through the posterior vaginal wall (Figure 2.4 c)), and (iii) procidentia, a uterine prolapse into the vaginal canal through the vaginal vault (Figure 2.4 d)) [109]. The severity of POP is described by the standardized POP-Quantification system (POP-Q) [37] (see Figure 2.5). This method is based on four stages, which allow the classification of the progress of the disease. Nine points and distances are defined based on anatomical landmarks within the pelvic cavity, the position and extent of which with respect to the hymen at full protrusion determine the stage of prolapse. Stage 0 represents the intact pelvic floor, with Aa, Ba, Ap, Bp at $-3cm$. Stage I indicates that the most distal point is still proximal to the hymen, i.e. at $< -1cm$. Stage II marks a prolapse crossing the hymenal ring, with the most distal point at $-1cm < 0 < +1cm$. At Stage III the most distal point is at $< +2cm$ and at stage IV it is at $+2cm$ or more.
Figure 2.5: POP quantification system (POP-Q). Six landmarks used for pelvic organ prolapse quantification: \( Aa \) and \( Ba \) at the anterior vaginal wall, \( C \) cervix, \( D \) posterior fornix, \( Bp \) and \( Ap \) at the posterior vaginal wall. Three measures of length: \( gh \) genital hiatus, \( pb \) perineal body and \( tvl \) total vaginal length. The position of all points are measured with respect to the hymen, negative values indicate positions proximal to the hymen, positive values indicate positions distal to the hymen. Figure reprinted from [37], with permission of the American Journal of Obstetrics and Gynecology.

distal, representing a complete eversion of the vagina [37].

Pelvic floor disorders occur in 37\% of the adult female population, with 30.8\% of that subgroup showing pelvic organ prolapse of stage I to III [147]. In the age group older than 60 years, that portion increases to 60\% [196]. However, in 98\% of cases the disease is not symptomatic and no diagnosis and treatment occurs [80]. 11\% of women showing symptomatic POP undergo surgery [126], with 29.2\% of patients requiring reoperation for recurrent prolapse and incontinence [196]. In the USA, the total incidence of surgical intervention is around 300000 patients per year [18, 32, 127].

Risk factors for pelvic prolapse have been identified as increased age, body weight, parity, number of births, hysterectomy, persistent straining of pelvic muscles and abnormalities of the tissue [165, 196, 232]. These might lead to excessive muscle strains, thus weakening and abnormally loading pelvic structures, resulting in persistent impairment.

Pathological weakening of the levator ani can lead to a load imbalance on the pelvic system, predisposing it to prolapse [126, 125]. In fact, within the pelvic cavity, the direction of load and the direction of maximal muscle strength do not coincide. Intra abdominal pressure acts perpendicular to the main muscle fiber direction, in contrast to the locomotor system [126]. While the loads are indeed transferred to the muscle plane by membrane
Chapter 2. 3-dimensional Finite Element Model
of the Female Pelvic Floor

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deformations [200], this peculiar characteristic might play a role in the susceptibility for
damage. Large tissue strains, as experienced during child birth or heavy lifting, have an
essential damaging effect on load carrying ligaments and connective tissues, such as the
endopelvic fascia [127], leading to persistent stretching, weakening or rupturing of most
commonly the levator ani muscle or attachment points of the vagina [211].

Treatment and repair of pelvic organ prolapse aim at restoring form, directly inducing
a restoration of function [211]. These treatments can be divided into a conservative ap-
proach with passive treatment or active, invasive surgery, depending on the type and
severity of the pathology. A change in lifestyle to reduce weight or physical exercise to
strengthen the weakened muscle tissue can be conservative approaches [28]. The most
common and well known exercise is the so called Kegel exercise, where the pelvic floor
muscles are activated similarly to when urination is stopped [36]. Another, non-invasive
approach uses pessaries, devices of different form and material, depending on application,
that are inserted transvaginally and provide mechanical support for the pelvic organs [35].
However, these do not provide long-term relief and are often used to postpone the point
of surgical intervention. Surgical correction of POP can be divided into two main cate-
gories. These are (i) reconstructive procedures using the vaginal or abdominal route to
correct anterior and posterior wall defects and resuspend the vaginal apex or (ii) obliter-
ative procedures to close off the vagina [33]. Before the widespread use of synthetic mesh
implants in pelvic prolapse repair [223] (see also Chapter 3), repair with autologous or
other biological tissue was common. That included the use of vaginal tissue [230], porcine
dermis [103, 248], human fascia lata [99], submucosa xenografts [42], among others, or the
reattachment of the uterosacral ligament [18]. While synthetic mesh-augmented repair
was indeed associated with lower rates of anatomic failure than standard repair (espe-
cially in the case of anterior defects [223] and urinary incontinence [196]), complications
associated with meshes are in fact prevalent [141, 196, 252, 257]. For an in-depth overview
of prosthetic mesh implants and associated complications, refer to Chapter 3.

2.1.3 Pelvic Finite Element Modeling

Pelvic organ prolapse is a complex, highly patient specific pathology, varying with age,
race, ethnicity, physique, medical history and lifestyle [71, 104]. While there is an increas-
ing interest in an in vivo mechanical characterization of pelvic floor structures and tissues
[12, 23, 29, 76, 175, 226], computational finite element analysis provides an invaluable
tool to investigate the complexity of the pelvic system and mechanical causes for related
pathologies, as well to bridge the gap between engineering and medical disciplines. This
section will give an overview of existing numerical models of the female pelvic system and
pelvic organ prolapse.
A wealth of studies has been conducted to elucidate mechanics related questions within
the female pelvic region based on finite element modeling. The most common form of
vaginal prolapse, the cystocele, has been investigated by the group of DeLancey and
Ashton-Miller [46, 44, 45, 47] in order to determine underlying mechanisms and decisive
factors for its formation. A 3D finite element (FE) model of the anterior vaginal wall
and its supports has been developed based on patient specific magnetic resonance (MR)
images [49, 157], with material properties from literature [22, 265]. Levator ani as well as
ligaments were consecutively weakened and intra abdominal pressure applied perpendicu-
larly to the ventral surface of the vaginal wall. Abdominal pressure, connective tissue and
muscle impairments were found to significantly affect cystocele formation, with a combi-
nation of levator ani and apical connective tissue weakness having the greatest effect.
Noakes et al. (2008) [194, 193] reconstructed pelvic geometries based on high fidelity ca-
daveric images of the Visible Human Project [243, 244] and compared it to T2 MR images.
While the cadaveric images provided very high resolution and simplified segmentation of
organs and muscles, they lacked muscle tone and showed artifacts related to postmortem
changes. MR images of the live subject provided a more accurate representation of the
in-vivo geometrical structures and context, despite lower resolution [193]. This served as
a basis to simulate the bear-down maneuver and compare levator ani muscle displacement
with deformation data in the sagittal plane obtained from dynamic MR images [194].
Another complex 3D FE model has been implemented by Mayeur et al. (2014) [174].
Pelvic organs including the bladder, vagina, uterus and rectum, as well as pelvic floor
muscle structures, connective tissues and ligamentous support structures have been in-
cluded based on 3T MR scans. Elastic material properties were derived from the nonlinear
characterization of Chantereau et al. (2014) [43]. Bladder displacement was taken as the
decisive parameter for cystocele quantification and results were compared between differ-
ent stiffness values of the paravaginal ligaments, vagina and bladder. While alterations
of the fascia between bladder and vagina or the paravaginal ligament were shown to have
the highest influence on cystocele formation, it was stated that geometrical aspects have
a stronger influence than material properties [174].
Venugopala et al. (2010) [260] have used a similar method of patient specific, MRI based
FE modeling of the pelvic cavity, including muscles, organs and ligaments, in order to in-
vestigate prolapse. Nonlinear material properties were based on own experimental results.
They found maximal strains within the anterior part of the vagina when applying intra
abdominal pressure as a distributed load on the exposed anterior surface of pelvic organs,
coinciding with the location of predominant incidences of cystocele formation [260].
Finite element models have also been used for inverse approaches. Cosson and Brieu
[60, 258] use a 3D model of the pelvic cavity to optimize the topology of ligamentous structures. These are not readily visible on MR images [258] and were initially introduced into the model based on anatomical descriptions. Comparing the model behavior under intra abdominal pressure with patient specific, dynamic MR images in a sagittal plane, the position and material properties of supportive structures as well as their influence on the normal pelvic mobility could be investigated [60]. In a similar approach, Lecomte-Grosbras et al. (2013) [150] built and verified an initial model of a healthy pelvic region based on patient specific MR scans. This model has been modified in terms of material properties and ligament geometries based on ex-vivo experimental results of POP tissue, in order to achieve a match of pathological mobility in case of a cystocele as observed on dynamic MR images. This inverse approach allows for non-invasive investigation of the impact of mechanical properties of the involved supportive structures within the pelvic cavity on the formation of pathologies.

Another important application of finite element modeling in the field of reproductive biomechanics is the simulation of child birth and its effects on the mechanical integrity of the pelvic floor. Li et al. (2011) [153, 154] have generated a patient specific model of the pelvic cavity including pelvic bones, bladder, vagina and rectum as well as the pelvic muscle sheet, based on MR images. The study investigated the influence of muscle anisotropy on the mechanical response of the levator ani muscle during the second stage of labor. It was found that increasing anisotropy leads to a substantial decrease in force required to push the fetal head through the birth canal, underlining the importance of this mechanical property in this application [154].

D’Aulignac et al. (2005) [63] developed a shell finite element model of the pelvic floor muscles, reconstructed manually from cadaver measurements, with anisotropic material behavior incorporating passive and active muscle fibers. Directionality of fibers was determined based on maximum principal stress directions under uniform pressure of isotropic muscles. This model served as a basis for further investigations on the effects of vaginal delivery on the pelvic muscles [168, 204, 205]. The model was extended to include the pelvic bones and a fetus model of unprecedented realism [168]. This allowed for simulation of clinically observed fetus motions during the birth cycle, namely descent, rotation, flexion and head molding [204]. Stretches induced in the pelvic muscles reached a maximum of about 1.6, which is higher than the non-injurious stretch for muscles as found in literature [31].

Lepage et al. (2014) [152] built a complete model of the pregnant pelvic region based on MR images of a nulliparous patient at 34 weeks pregnancy, based on the experience of the group gathered from previous studies [60, 260]. It included bladder, vagina, pregnant uterus, rectum, pelvic floor musculature as well as ligamentous structures. The effect
of child birth on the uterosacral ligaments was investigated, with a strain of 30% being reported during the passage of the fetal head. The uterosacral ligaments are the major pelvic sustaining structures, thus their damage might predispose the patient to pelvic prolapse [152].

Lien et al. (2004) [157, 158] followed the path of geometrical simplification to investigate levator ani muscle stretch during child birth. Their 3D FE model is based on MR scans of several patients. The pelvic muscles were modeled as 24 individual model muscle bands that follow the parallel-fibered architecture of the levator ani muscle and its subunits. Each band passes from origin to insertion point through points extracted from MR images. Passing of an idealized fetal head through the birth canal resulted in stretches from 2.28 (puborectalis muscles) to 3.26 (medial pubococcygeus muscle). The location of maximum stretch being in the medial pubococcygeus muscle in fact coincides with the majority of muscle injuries post partum [67].

2.1.4 Applications and Open Questions

One clear limitation when studying the human physiology remains, i.e. it is nearly impossible to directly and non-invasively measure physiological ranges of forces and tissue properties within the human body. This is still an unanswered and highly current topic and a solution of this problem would lay the basis for recognition of pathologies based on biomechanical properties and contexts. While nowadays it may be possible to extract deformation data from advanced medical imaging techniques such as dynamic MRI or ultrasound, these are usually restricted in fidelity, resolution and information content, only providing global, macro-scale clues (see Section 4.3.1 for more details). This opens the door for finite element analysis as an invaluable tool for modern research, both as a direct forward as well as inverse approach. Biological tissues can be mechanically characterized ex-vivo, forming a basis for constitutive material descriptions implemented in patient specific FE models, thus allowing to virtually measure strains and forces acting on organ structures and tissues [44, 45, 46, 47, 152, 157, 158, 168, 174, 193, 194, 204, 205, 260]. However, this is still an approximation, since the physiological configuration in vivo might differ from that in the experiments ex vivo. Load application, geometry, state of stress as well as residual strains and stresses in the tissue are restricted by the testing apparatus and may only be idealizations of the in vivo state of the tissue, where it works as part of a larger structural system. In an inverse analysis, known deformation data within the pelvic region, usually in a sagittal plane or other landmarks, can be used to optimize topology and material behavior of simulated tissue to match the kinematics observed in vivo, thus allowing to conclude on tissue stiffness or pathological mechanical behavior.
Chapter 2. 3-dimensional Finite Element Model
of the Female Pelvic Floor

[60, 150, 153, 154, 258].
The present investigation presents applications of pelvic finite element modeling based on both approaches, allowing to answer several open questions. The model developed herein is used to investigate tensions within the pelvic floor region for healthy subjects and patients with pelvic organ prolapse (Section 2.3), which can provide valuable information for the evaluation and future design of prostheses used for pelvic prolapse repair [172]. Furthermore, the sacrocolpopexy procedure is simulated (Section 3.4), a surgical intervention using mesh implants to support the vaginal apex after hysterectomy, the complete removal of the uterus. This is the first time that a pelvic prolapse repair strategy has been modeled in silico, elucidating the complex topic of mechanical biocompatibility and the role of mechanics in the occurrence of clinical complications. This investigation allows for the analysis of the physiological range of deformations and forces acting on the mesh and underlying tissue on a macro and micro scale as well as the influence of surgical technique hereon. Finally, the model provides a proof of concept of an idea for a new diagnostic tool for pelvic muscle deficiencies (Section 4.3), based on the working principle of quasistatic elastography. It allows to detect relative differences in tissue compliance within a homogeneous organ structure based purely on kinematic data, not requiring exact knowledge of tissue properties or forces acting on the tissue.
2.2 Generation of the Finite Element Model

The model developed within this project is based on segmented geometry data provided by the group of Prof. Brieu, Lille Nord University, see Figure 2.6. The geometry has been extracted from T2 MR images of a pregnant patient (34 weeks) [152]. Raw surface data for the pelvic bones, pelvic floor muscle structure, vagina, pregnant uterus, bladder and rectum formed the starting point for the implementation into the commercial finite element software Abaqus 6.10ef1 (Abaqus, 2010, Simulia, Providence RI, USA).

2.2.1 Geometry Preparation

The raw surface data including normals at each point of the 3D organ objects had to be further processed in order to prepare for import into Abaqus and further develop the FE model. This process included several steps and was performed in Geomagic Studio 9.0 (3D Systems, Inc., Rock Hill SC, USA).
Surface Clean Up and Smoothing. As usual for this type of data, the initial raw geometry data showed defects and artifacts such as surface holes, intersecting surfaces or very sharp, discontinuous edges (Figure 2.7). Geomagic provides powerful tools for geometry manipulation on a polygon level for smoothing and clean-up. That allowed for erosion of spiked surface points to decrease local curvature, closing of surface holes taking into account the curvature of areas around the hole perimeter as well as reducing high frequency noise on a local level. The overall smoothing of the geometry allows to avoid later unnecessary FE mesh size reduction to account for local non-smoothness.

![Figure 2.7: Exemplary defects in raw geometry of the pelvic bones, necessitating cleanup. Intersecting surfaces (left) and sharp edges as well as general high frequency noise (right).](image)

Surface Contour Definition for Automatic Meshing. Geomagic includes an automatic meshing algorithm that generates an orphan mesh, subdividing the surface into quadrilateral faces with user definable size. However, due to the irregularity of most of the organ surfaces, such as large local variation in surface curvature, spiky edges or holes, the automatic face generation did not provide satisfactory results with regular face geometry, which is needed for later clean FE meshing within Abaqus. Therefore, critical contours, which were compulsory for the meshing algorithm to follow, were manually defined, following edges, ridges or hole perimeters, thus guiding the face generation to regular results (see Figure 2.8). Individual, irregular faces could be corrected manually after automatic meshing.
2.2. Generation of the Finite Element Model

NURBS Surface and CAD Geometry Generation. In the next step, a fine grid was generated on the faces, serving as control points for NURBS (non-uniform, rational B-spline) surfaces. These were automatically interpolated, forming the basis for the CAD geometry, which could be exported in the standardized .step-file format, including points, surfaces, normals and edges of the model geometry (Figure 2.9). This procedure was repeated for all organs, which were then imported as "parts" into Abaqus. All geometry definitions were automatically expressed with respect to a global coordinate system encoded within the original raw data, ensuring proper positioning of the parts with respect to each other.

2.2.2 Finite Element Model

The final model includes the pelvic floor muscle structure, bladder, vaginal canal, uterus-sacral and ombelica-media ligaments as well as paravaginal fascia. Pelvic bones serve as display bodies only and do not influence FE calculations. The rectum and uterus are not included in the analysis (Figures 2.10, 2.12). Note that the original geometry is of a pregnant woman in the 34th week, such that the shape of vaginal canal (superior widening) and

Figure 2.8: Surface contours. (a) Manually defined critical contours (orange) mandatory for the automatic meshing algorithm to follow. (b) Automatically generated surface contours (black) after manual critical contour placement.
Figure 2.9: (a) Automatically generated grid, serving as control points for NURBS surface interpolation. (b) Automatically generated NURBS surfaces.

bladder (anterior flattening) are not necessarily representative for a non-pregnant subject, however the pelvic floor muscle structure resembles that of a non-pregnant woman and is comparable to other FE models [150, 174, 193, 260]. The pelvic muscle geometry has been available as one continuous sheet with no geometrical separation of individual muscle subgroups. These have been realized by manually matching their shape to anatomical images and assigning individual faces to their respective muscle section (see Section 4.3 for details).

Soft organs, i.e. bladder, vagina and pelvic musculature, were modeled using planar elements since their thickness is significantly smaller than the in-plane dimensions. They were discretized using general purpose, plane stress, finite membrane-strain, linear, fully integrated, four-node quadrilateral shell elements S4. As finite strain elements, they allow large deformations with three translational and three rotational degrees of freedom. In contrast to membrane elements, shell elements do have a bending stiffness and provide five integration points through the thickness, based on Simpson’s rule assuming a linear stress distribution transmurally. This fact is crucial for numerical stability. Elements that only have in-plane stiffness and do not resist bending will lead to convergence and a stable equilibrium when applying loads perpendicular to their surface plane, only if their geom-
2.2. Generation of the Finite Element Model

Figure 2.10: 3D finite element model implemented in Abaqus. Shown are pelvic bones and vertebrae (display bodies), ligaments as well as FE meshes of vagina, bladder and pelvic floor musculature.

Geometry is compatible with membrane deformations. This is not fulfilled here, necessitating some bending stiffness for the system to overcome initial numerical instabilities. The intra-abdominal pressure as applied in the present model (see below) is in fact a load perpendicular to the element surface. On the other hand, a muscle sheet such as the pelvic floor will not resist bending similar to a homogeneous and continuous material of equal thickness. Rather the sliding motion of individual muscle strands and fibers within the muscle plane will lead to a lower, but still non-zero bending stiffness [113]. In order to account for this phenomenon, the bending stiffness was reduced without altering the in-plane response of the element by reducing the thickness by a factor of 4 and simultaneously increasing the in-plane stiffness by a factor of 4, according to the following calculations. Consider a thin shell with thickness $t$ and width $b$ under tension. The in-plane stress $\sigma$ in case of linear
material behavior with Young’s Modulus $E$ and applied uniaxial force $F$ is

$$\sigma = E \varepsilon = \frac{F}{bt}. \quad (2.1)$$

Its bending stiffness $\beta$ is

$$\beta = EI_z = \frac{E b t^3}{12}. \quad (2.2)$$

Decreasing the thickness $t$ by a factor of $\alpha$ to $t^* = t/\alpha$ and increasing Young’s modulus, i.e. in-plane stiffness, by the same factor to $E^* = \alpha E$ leads to the following:

$$\sigma^* = \alpha E \varepsilon = \alpha \frac{F}{bt/\alpha} = \frac{F}{bt} = \sigma, \quad (2.3)$$

the in-plane stresses remain identical. However,

$$\beta^* = \alpha EI_z = \alpha E \frac{b(t/\alpha)^3}{12} = \alpha E \frac{b t^3}{12} \frac{1}{\alpha^3} = \beta \frac{1}{\alpha^2}, \quad (2.4)$$

the bending stiffness is reduced by a factor of $\alpha^2$. After a convergence analysis, $\alpha = 4$ was chosen as an optimum between numerical stability and bending stiffness reduction.

The material behavior of the soft tissues was as a first approximation modeled as isotropic linear elastic, with near incompressibility due to the high water content of biological tissues [60, 150, 230]. Material properties and thickness values (note the thickness of the pelvic floor muscles is modified as described above) were taken from the literature, based on anatomical data (see Table 2.1). Note that while soft biological tissues in general show a hyperelastic behavior, the choice of a linear elastic approximation is in fact valid, as Young’s modulus can be seen as a tangent modulus for the hyperelastic response in the range of strains the tissue operates in.

Ligaments are implemented as one-dimensional beam elements in three-dimensional space with circular cross section (Figure 2.11). The beam assumption holds true, since their cross section is small compared to their length. They are discretized as general purpose, linear, 2-node beam elements B31. The paravaginal fascia on both lateral sides of the vaginal canal are idealized as a triple of short beams each, connecting the vagina to the perimeter of the pelvic floor musculature. The geometrical position and length of each ligament are based on the data provided within the initial geometrical model, which in turn is an idealization of the anatomical structures based on topological optimization [60, 258] since these ligamentous structures are not visible on MR images [152]. Their material behavior was again modeled as linear elastic, with cross-sectional area and stiffness parameters taken from the literature (see Table 2.1).
### 2.2. Generation of the Finite Element Model

<table>
<thead>
<tr>
<th>Organ</th>
<th>Stiffness</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic floor</td>
<td>12 MPa</td>
<td>Lecomte-Grosbras et al. (2013) [150]</td>
</tr>
<tr>
<td></td>
<td>2.5 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td># elements</td>
<td>2318</td>
</tr>
<tr>
<td>Vagina</td>
<td>15 MPa</td>
<td>Cosson et al. (2013) [60]</td>
</tr>
<tr>
<td></td>
<td>3.3 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td># elements</td>
<td>2153</td>
</tr>
<tr>
<td>Bladder</td>
<td>2.4 MPa</td>
<td>Cosson et al. (2013) [60]</td>
</tr>
<tr>
<td></td>
<td>0.5 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td># elements</td>
<td>2938</td>
</tr>
<tr>
<td>Ombelical lig.</td>
<td>9.1 MPa</td>
<td>Martins et al. (2013) [169]</td>
</tr>
<tr>
<td></td>
<td>2 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td># elements</td>
<td>4</td>
</tr>
<tr>
<td>Uterosacral lig.</td>
<td>14.1 MPa</td>
<td>Martins et al. (2013) [169]</td>
</tr>
<tr>
<td></td>
<td>4 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td># elements</td>
<td>10</td>
</tr>
<tr>
<td>Paravaginal lig.</td>
<td>9.1 MPa</td>
<td>Martins et al. (2013) [169]</td>
</tr>
<tr>
<td></td>
<td>1 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td># elements</td>
<td>5</td>
</tr>
<tr>
<td>Interface</td>
<td>0.1 MPa</td>
<td></td>
</tr>
<tr>
<td></td>
<td># elements</td>
<td>1759</td>
</tr>
</tbody>
</table>

Table 2.1: List of material and geometrical parameters for implemented anatomical structures.

In order to represent connective tissue between the posterior wall of the bladder and anterior wall of the vaginal canal, an interface part was added to the assembly. It allows the bladder and the umbilical ligament connected to it to contribute to the mechanical integrity and support system of the pelvic floor. In a submodel assembly, bladder and vaginal canal were moved apart, a block-like structure meshed with 3D quadratic hexahedral elements of type C3D20R inserted inbetween and both organs in an implicit simulation step moved to their initial positions again. Since bladder and vagina were assumed to be rigid bodies, whereas the interface was modeled as very soft, the compression produced
in the interface part molded perfectly to the posterior bladder wall and anterior vaginal wall, respectively. The deformed interface was reimported into the full pelvic floor model and provided the connection between bladder and vagina. It is modeled as linear elastic, representing mostly fatty connective tissue (Figure 2.11). Boundary conditions applied to the model were based on the anatomical context. At adhesion points of the muscular sheet to the pelvic bones, all three translational as well as all three rotational degrees of freedom were restricted, assuming fixed connections at origin and insertion site of muscles. These were in particular the fixation of levator ani...
anteriorly to the pubic symphysis and posteriorly to the sacrum, as well as of the iliococcygeus and coccygeus laterally to the ischial spine (Figure 2.13). The origins of ligaments at bones, specifically the ombilical and uterosacral ligaments, are restricted in all translational degrees of freedom, whereas rotation is allowed at these points. They are assumed to be one-dimensional structures, thus can freely rotate at their origin and insertion into organs.

Figure 2.13: Blue lines indicate areas of muscle fixation to bone. All three translational degrees of freedom are fixed.

Insertion points of ligaments into soft organs, i.e. ombilical ligament to bladder as well as uterosacral ligaments to vaginal canal, were realized as equation conditions, tying the three translational degrees of freedom of the medial end of the ligament to the attachment site within the organ. In order to avoid numerical discontinuities and convergence problems due to stress peaks, the insertion site at the organ consisted of a set of three to five nodes, depending on exact site, thus distributing introduced forces over a small area. The stiffness of the connection is solely due to the compliance of the ligament and organ themselves. This approach of connecting ligaments to organs has also been taken for the paravaginal fascia, which is idealized here as a pair of three short ligaments each. Lateral and medial ends of each segment is tied to a set of nodes on pelvic floor and vaginal canal, respectively.

Similarly, the anatomical adherence of the pubococcygeus muscle medially to the vaginal canal is modeled as a direct bond based on constraining translational degrees of freedom of the circumference of the inferior vaginal canal to the perimeter of the inferior opening within the pelvic floor muscles, through which the vaginal canal passes.

The geometrical assembly and expected downward movement of organs under application
of intra abdominal pressure only necessitate the contact definition inbetween interface and bladder as well as vagina. It is realized as tied contact, allowing no separation or sliding, thus ensuring transmission of load between the two organs.

The load case which forms the basis for several applications evaluated within this project, is the Valsalva maneuver, which significantly increases intra abdominal pressure due to the activation of the abdominal muscles and is used to quantify maximum pelvic organ descent in a POP patient [37]. Several finite element studies apply this pressure selectively on the anterior vaginal wall or at an incline projected onto the anterior surfaces of the pelvic organs [45, 150, 174, 260]. However, it is arguable whether this is a reasonable assumption. Increased intra abdominal pressure acts as a hydrostatic pressure within the pelvic cavity. The major effect is a descent of the pelvic floor muscle sheet due to a pressure difference between the inside of the pelvic cavity and the outside of the body. The pelvic organs residing within will indeed be pulled downwards, however not due to a pressure acting from above (note that a hydrostatic pressure acts from all sides equally), but rather due to connective tissue and other support structures interconnecting organs and pelvic muscles. Based on this argumentation, intra abdominal pressure within the FE model is applied here solely on the superior surface of the pelvic muscle sheet. Note also that the initial, undeformed geometry is in fact already loaded by an intra abdominal pressure at rest. The Valsalva load of 3.5 kPa will in fact be the pressure difference between Valsalva and rest as measured during urodynamics and is taken from the literature [200].
2.3 Calculation of Membrane Tension in Various Regions of the Pelvic Floor

2.3.1 Introduction

Pelvic organ prolapse nowadays often requires surgery, which is aimed at restoring anatomy and function of the pelvic region [126, 196, 211, 223]. While repair using prosthetic meshes seems to improve anatomical outcome, graft related complications (GRCs) start to play an increasing role [1, 8, 162]. It is believed that a mismatch of mechanical properties of the implant and the underlying tissue is an important contributor to adverse clinical outcomes [52, 69, 86, 87, 160]. That led to an increased interest in the mechanical biocompatibility of mesh implants, or their ability to display a mechanical behavior compatible with its function, thus favoring its integration in the surrounding tissue [173, 175, 224, 227]. While meshes provide a tensile strength larger than necessary [130, 136, 144, 182], their deformation behavior in a suitable in-vivo working range is of major importance [173, 172]. However, one crucial question still to answer in order to provide meaningful analysis and design targets for future synthetic prostheses remains: the physiological range of loads and deformations within the embedding tissue that the implant is supposed to match. It is intuitive that this mechanical environment is not directly measurable in-vivo.

The results presented in this section are based on the findings reported in [177].

2.3.2 Methods

Evaluation of Membrane Tensions Based on an Idealized Geometry

In a recent study by Ozog et al. (2014) [200], an attempt has been made to evaluate patient specific membrane tensions and global deformations based on a mathematical description of the pelvic cavity. It can be geometrically simplified as a funnel like structure, with the top and bottom planes forming ellipses at the midpelvic plane and urogenital hiatus, respectively [200]. The geometrical dimensions of the ellipses are defined based on anatomical landmarks. At the midpelvis, the ellipse spans from the upper symphysis anteriorly to the inferior border of the sacral vertebra 5 posteriorly, as well as laterally between the ischial spines. At the urogenital hiatus level, the major axes of the ellipse is defined inbetween the inferior symphysis anteriorly and the posterior border of the external anal sphincter, as well as laterally between the medial borders of the pubococcygeus muscle at the level of the perineum [200]. Half of the anterior-posterior major axis of the ellipse is denoted as semimajor $a$, half of the lateral major axis of the ellipse as semimajor $b$.

This geometrical construct was interpreted as a thin-walled container under internal pres-
sure, allowing for calculation of wall stresses based on Laplace’s Law. In short, forces within the wall of a thin walled container are in static equilibrium with the forces due to internal pressure (Figure 2.14). Assuming the walls of the container being perpendicular to the plane of the ellipse,

\[
F_W = F_p \tag{2.5}
\]

\[
\sigma_W \cdot t \cdot \pi \left(3(a+b) - \sqrt{3(a+b)(a+3b)}\right) = p \cdot ab \pi \tag{2.6}
\]

\[
\sigma_W = \frac{p \cdot A}{t \cdot c} \tag{2.7}
\]

with \(\sigma_W\) the stresses in the wall, \(t\) the thickness of the thin walled container, \(c = \pi \left(3(a+b) - \sqrt{3(a+b)(a+3b)}\right)\) the approximate circumference of an ellipse with semimajors \(a\) and \(b\) \([218]\) and \(A = ab \pi\) the area of an ellipse with semimajors \(a\) and \(b\). This is further adjusted to wall membrane tensions \(M_t\) as

\[
M_t = \sigma_W \cdot t = \frac{p \cdot ab \pi}{c} \tag{2.8}
\]

as a measure of force per unit length, independent of wall thickness \(t\).

Note that the assumption of perpendicular container walls does not hold true within the pelvic cavity, especially at the urogenital hiatus (Figure 2.14 (d)). Here the calculated membrane tensions \(M_t\) are a projection of the actual tensions within the tissue onto the vertical anatomical plane. Ozog et al. (2014) [200] corrected for that at the urogenital hiatus level by defining an angle \(\alpha\) in the sagittal cut between the horizontal anatomical plane and the muscle tissue tangential plane, back-projecting the calculated \(M_t\) onto \(M_t^\alpha\), both anteriorly and posteriorly. The corrected membrane tensions are

\[
M_t^\alpha = \frac{M_t}{\sin \alpha} \tag{2.9}
\]

The landmarks described above were discernible on ultrasound and MR images and could be clinically measured [200], allowing for a patient specific calculation of geometrical dimensions and membrane tensions, both for healthy as well as pelvic organ prolapse patients at rest and during the Valsalva maneuver.

**Evaluation of Membrane Tensions with a Finite Element Model** In order to compare and validate results of the analytical approach presented by Ozog et al. (2014) [200] with the herein developed finite element model of the pelvic floor, the landmarks described before were defined within the pelvic muscle sheet of the model. Note that the focus is on the urogenital hiatus, it being the most affected region in terms of geometrical
2.3. Calculation of Membrane Tension in Various Regions of the Pelvic Floor

Figure 2.14: (a) Idealized geometry within the pelvic cavity based on landmarks within anatomical structures. Illustration of the static equilibrium between forces due to internal pressure $F_p$ and wall forces $F_W$ at (b) the midpelvic plane and (c) the urogenital hiatus. Note that the influence of the angle between the direction of wall forces and internal pressure is small enough to be neglected in equations 2.5 to 2.7, as in Ozog et al. (2014) [200]. (d) Sagittal cut through anterior and posterior landmarks, illustrating correction factor for membrane tension calculation.

and material changes in case of pelvic organ prolapse. The landmarks are illustrated in Figure 2.15.

Membrane tensions in the directions indicated in Figure 2.15 were extracted in four elements adjacent to the landmark position and averaged. These directions are tangential to the tissue plane and point superiorly, thus can be seen as an approximation of the corrected membrane tensions presented by Ozog et al. They coincide with the element-local 1-direction and 2-direction at the lateral and posterior landmarks, respectively. Note that
Figure 2.15: Illustration of landmarks, major axis and directions of evaluated membrane tensions at the urogenital hiatus. (a) Top view, (b) frontal view. Landmarks are (1) inferior symphysis, (2) posterior border of the external anal sphincter, (3) right medial border of the pubococcygeus muscle, (4) left medial border of the pubococcygeus muscle. Due to the proximity of landmark 1 to the attachment to the symphysis, boundary conditions have a large influence on tensions in that region. Therefore this landmark position will be excluded from analysis. Tensions are extracted at the midpoint throughout the thickness, thus excluding the influence of bending and only representing stresses due to membrane deformations.

For a comparison of average membrane tensions within the pelvic floor, the maximum in-plane principal tensions are averaged over the whole muscle sheet as follows. Each element value $M_t^i$ is scaled by the respective element volume $V^i$. This yields the average membrane tension at Valsalva pressure as

$$\overline{M_t^{\text{Valsalva}}} = \frac{1}{n} \sum_{i=1}^{n} M_t^i \cdot V^i$$

Results are compared at increased intra abdominal pressure due to Valsalva for healthy as well as POP patients. Note that the undeformed FE model is in fact in an equilibrium state with the intra abdominal pressure at rest. Therefore, the applied Valsalva pressure of 3.5 kPa is in fact the difference between measured pressures during Valsalva and at rest [200]. Similarly, the membrane tension reported for the FE model in the results has to be interpreted as the difference between $M_t^{\text{Valsalva}}$ and $M_t^{\text{rest}}$. The corresponding values of
Ozog et al. (2014) [200] have been interpreted accordingly by subtracting the membrane tension at rest. Pelvic dysfunction is modeled as an impairment in pelvic muscle strength [45], reducing their Young’s modulus by a factor of 6.

### 2.3.3 Results

First, the order of magnitude of average membrane tensions obtained numerically with the FE model are compared with those reported by Ozog et al. Note that the tensions obtained by the FE analysis are in fact the difference between the total tensions at Valsalva and tensions at rest, since the undeformed geometry is already in an equilibrium with the intra abdominal pressure at rest (see Section 2.3.2). In order to estimate the total average membrane tension within the pelvic muscle sheet, the average tension at rest reported by Ozog et al. ($M_{\text{rest, Ozog}} = 0.036 \text{ N/mm}$) is added to the average tension obtained by the FE simulation:

$$\bar{M}_{\text{Valsalva, tot}} = M_{\text{rest, Ozog}} + \bar{M}_{\text{Valsalva}}.$$

(2.11)

For the POP finite element model, this yields $\bar{M}_{\text{Valsalva, tot}} = 0.23 \text{ N/mm}$, which is in line with the values reported in Ozog et al. of 0.13-0.17 N/mm, confirming the order of magnitude of the analytical calculations. This relation can also be seen in Figure 2.16 (Note that for the sake of simplicity, values of membrane tension are now and for the rest of the chapter shown only as the delta between Valsalva and rest; tensions reported by Ozog et al. are calculated accordingly). Average maximum in-plane tensions as well as those evaluated at the lateral and posterior landmarks are in the same order as those reported by Ozog et al. In addition, using the landmark positions in the FE model in order to analytically calculate membrane tensions with Laplace’s Law, the results are almost identical to Ozog et al, see also Table 2.2. Furthermore, tensions in the pelvic muscle sheet are clearly one order of magnitude lower than those in the abdominal wall as reported by Klinge et al. (1996) [136] (Figure 2.16 right). This also becomes apparent in Figure 2.17 a), which shows maximum in-plane tensions scaled to the values in the abdominal wall [136], confirming the findings in Ozog et al. (2014) [200].

However, there are also discrepancies between the FE model and the analytical approach. Membrane tensions within the pelvic cavity as calculated analytically with Laplace’s Law by Ozog et al. [200] increase at Valsalva pressure when comparing POP (0.065 N/mm) with healthy patients (0.124 N/mm), nearly doubling (see Figure 2.16). In fact, they are directly related to geometrical dimensions of the idealized ellipse at the urogenital hiatus (see equation 2.8), which are larger for pelvic prolapse than for healthy patients, as stated before. And in fact, tensions calculated with Laplace’s Law based on semimajor dimensions in the FE model follow this trend.
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Figure 2.16: Membrane tension within the urogenital hiatus at lateral and posterior landmarks as well as the global average for healthy and POP patients. Comparison between results reported in Ozog et al. (2014) [200] and finite element calculations. For reference, the tension in the abdominal wall reported by Klinge et al. (1996) [136] is shown. Note that membrane tensions are reported as the difference between Valsalva and rest.

Figure 2.17: Maximum in-plane tensions within the pelvic floor muscle sheet for the case of POP with impaired muscles. (a) Scaled to tensions within abdominal wall according to Klinge et al. (1996) [136], (b) scaled for best visualization. Note that the effect of bending has been eliminated by visualizing the mid plane of the shell structure, thus only showing tensions due to in-plane membrane deformations. Membrane tensions are reported as the difference between Valsalva and rest.

Membrane tensions evaluated at the landmarks of the FE model as well as the global average tension however show a different trend when decreasing muscle stiffness. The average maximum in-plane tension in the pelvic sheet is almost identical for healthy and POP patients, with the latter increasing by about 5% compared to the former. While there are large differences by a factor of 2 between the left lateral (0.125 N/mm) and right lateral (0.213 N/mm) as well as posterior landmark (0.248 N/mm) in the healthy case (Figure
2.3. Calculation of Membrane Tension in Various Regions of the Pelvic Floor

2.16, left), they are all in a similar range around \(0.12 \text{ N/mm}\) as those reported by Ozog et al. (2014) [200] in case of impaired muscles (Figure 2.16, center).

However, the measurements taken in the finite element model are very localized around the respective landmark and do not paint a complete picture. In fact, the stress distribution within the pelvic muscle sheet, exemplary shown for the POP case of impaired muscle strength in Figure 2.17, allows for a more detailed analysis. On the one hand, and most importantly, it confirms that tensions in the pelvic cavity are much lower than those in the abdominal wall, as reported by Klinge et al. (1996) [136]. On the other hand, suitable scaling reveals a wide range and local variability (2.17 b). The largest maximum in-plane tensions can be observed within the posterior part of the pelvic floor, in the region of the coccygeus and iliococcygeus muscle as well as the levator plate. Moreover, in some regions, such as the anterior iliococcygeus and pubococcygeus muscle, tensions are negative, indicating in-plane compression.

<table>
<thead>
<tr>
<th></th>
<th>Healthy (Ozog et al.)</th>
<th>Healthy (present model)</th>
<th>POP (Ozog et al.)</th>
<th>POP (present model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sem. (a), rest [mm]</td>
<td>29.5</td>
<td>36.57</td>
<td>32.7</td>
<td>36.57</td>
</tr>
<tr>
<td>sem. (b), rest [mm]</td>
<td>22.0</td>
<td>14.65</td>
<td>24.5</td>
<td>14.65</td>
</tr>
<tr>
<td>sem. (a), Valsalva [mm]</td>
<td>32.5</td>
<td>36.12</td>
<td>38.0</td>
<td>35.91</td>
</tr>
<tr>
<td>sem. (b), Valsalva [mm]</td>
<td>24.0</td>
<td>16.62</td>
<td>30.0</td>
<td>18.59</td>
</tr>
<tr>
<td>(M_t), Valsalva [N/mm]</td>
<td>0.085</td>
<td>0.089</td>
<td>0.128</td>
<td>0.125</td>
</tr>
</tbody>
</table>

(Laplace Law)

Table 2.2: Semimajor dimensions at the urogenital hiatus at rest and at Valsalva pressure for healthy and pelvic prolapse patients. Membrane tension based on analytical calculations with Laplace’s Law for both FE model and Ozog et al. Values from Ozog et al. (2014) [200] are mean values based on ultrasound measurements.

Table 2.2 lists semimajor dimensions at the urogenital hiatus at rest and Valsalva, comparing results obtained from FE simulations of healthy as well as impaired pelvic muscle tissue with those measured during ultrasound reported in Ozog et al. (2014) [200]. Semimajor \(a\) (anterior-posterior) is larger in the FE model compared to patient data, whereas for semimajor \(b\) the opposite is the case. However, already at rest both dimensions increase for POP patients, while for the FE model the undeformed geometry corresponds to the state ”at rest” and serves as a starting point for simulation of Valsalva in both healthy and POP conditions.

Note that for increased abdominal pressure at Valsalva, Ozog et al. (2014) [200] report
an increase of dimensions in the range of 10% for healthy patients and 15-22% for pelvic prolapse patients (see Figure 2.18 (a)). Not only is the urogenital hiatus wider at rest for the POP population, it also increases more substantially when increasing the pressure. While the model does indeed provide an increase in semimajor $b$ in a similar order of magnitude for both healthy (13%) and pelvic prolapse simulations (27%), semimajor $a$ reduces its length slightly when applying Valsalva pressure ($-1-2\%$). This is an artifact due to the definition of the posterior landmark, which rotates downwards at the application of pressure, thus decreasing its distance to the fixed, anterior landmark at the symphysis. The general conclusions reported by Ozog et al. (2014) [200], that the pelvic sheet of POP patients shows an increased deformation at increased intra abdominal pressure compared to healthy patients is confirmed. In fact, comparing the top row of Figure 2.19 (healthy tissue) with the bottom row (impaired muscle strength), a much more severe deformation is visible for the POP case. In the anterior and middle compartment of the pelvic cavity, the muscle diaphragm laterally widens considerably more with weaker muscles. Similarly, the posterior compartment (coccygeus and iliococcygeus muscles) exhibit a larger inferior bulging, changing their curvature from convex to concave. The conconvex shape of the posterior pelvic muscle sheet at rest has been described by Janda (2006) [125] and hints at the fact that this “flipping” behavior can occur in vivo. In fact, Noakes et al. (2008) [194] describe this phenomenon based on dynamic MR images during the Valsalva maneuver for the levator ani muscle. However, even though semimajor dimensions are different from Ozog et al. (2014), using these to calculate membrane tensions analytically with Laplace’s Law yields almost identical results (see Table 2.2). This confirms the representativeness of the present model.
2.3. Calculation of Membrane Tension in Various Regions of the Pelvic Floor

2.3.4 Discussion and Conclusion

The structures within the pelvic cavity are mostly inaccessible for direct measurement of mechanical data (deformations and forces), which may provide valuable information for physicians to more accurately determine the condition of pelvic tissues, or for manufacturers of pelvic prolapse implants to provide a benchmark of a physiological range of the mechanical environment. Finite element analysis allows to peek inside the human body and may give indications of the mechanical behavior of tissues in-vivo. The analytical approach by Ozog et al. (2014) [200] simplifies the pelvic cavity geometry to a elliptical, thin-walled cylinder under internal pressure with dimensions based on patient-specific medical images, allowing the application of Laplace’s Law, thus estimating global tensions within the pelvic muscles. Membrane tension at rest was found to be $0.033 - 0.036 \, N/mm$, with that value increasing to $0.13 \, N/mm$ during the Valsalva maneuver. These values of tension are in fact one order of magnitude lower than those in the abdominal wall, reported by Klinge et al. (1996) [136], based on similar analytical computations of the equilibrium between the wall tension and intra abdominal pressure. These findings might seem counter intuitive, however simply due to larger geometrical dimensions of the abdominal cavity, the tensions therein must be greater to satisfy equilibrium with internal pressures.
Chapter 2. 3-dimensional Finite Element Model of the Female Pelvic Floor

Figure 2.20: Illustration of tensions within the muscle sheet (represented as the one-dimensional centerline of the thin structure) when applying pressure $p$ perpendicular to its plane. Starting from a convex configuration (left), the tissue is under compression (blue arrows) when deformed to a planar configuration (center) and starts to be loaded in tension (blue arrows) once the curvature is concave and $l_2 > l_0$. Assuming the lateral pivot points remain fixed, $l_2 > l_0 > l_1$.

The order of magnitude of membrane tensions in the pelvic floor found by Ozog et al. (2014) [200] could be confirmed by finite element calculations, simulating the Valsalva maneuver for healthy and pelvic prolapse patients and extracting the membrane tension at anatomical landmarks. However, the FE method allows for a more detailed analysis of local tensions and deformations, emerging from the shadows of a global analytical simplification. While the pelvic muscle sheet does indeed describe a global downward movement when subjected to an increased pressure, the distribution of displacements varies locally. The anterior compartment, in the region of the pubococcygeus muscle, exhibits a pronounced lateral widening, whereas the posterior compartment, consisting of coccygeus and iliococcygeus muscles, shows a strong inferior bulging. These effects are intensified when reducing muscle strength, leading to pelvic support deficiencies [45]. The complex geometrical shape of the pelvic muscle sheet necessitates these locally varying deformation patterns to be in equilibrium, which is similarly reflected by the distribution of tensions within the muscles. While regions with a concave shape tend to have large in-plane stresses, other regions are under compression. These areas are initially convex and are compressed in-plane by the application of pressure normal to their outer surface. Only after they "flip" through a planar state and become concave, are they loaded in tension (see illustration in Figure 2.20). These phenomena are a clear indication of the mechanical complexity of the pelvic region, purely due to its geometrical shape, and have already been described in Noakes et al. (2008) [194].

In addition, the shell structure of the pelvic muscle sheet in the model might still exhibit bending stiffness that is too large with respect to in vivo muscles, thus having a larger
effect on the local in-plane response of the model than expected. Further reduction of the contribution of bending effects might improve the results reported here.

It has to be noted that the geometry available for the analysis within this study is in fact based on MR images of a pregnant woman at a later stage of pregnancy [152]. The enlarged uterus naturally leads to a rearrangement of organs within the pelvic cavity, widening the vaginal canal superiorly, squeezing the bladder anteriorly and in general widening the pelvic cavity, even at rest. This is also indicated by the differences in semi-major dimensions of Ozog et al. and the finite element model (Table 2.2). However, while Ozog et al. had access to a large number of medical images and thus better data on anatomical references, the applied mechanical model for the analytical calculation of membrane tensions was strongly simplified. On the other hand, the FE model relies on one specific anatomy, but presents a more sophisticated mechanical model to capture the complex effects within the pelvic cavity. The discrepancy in $a$, $b$, $\Delta a$ and $\Delta b$ indicates that the present anatomy and selected boundary conditions might not be fully representative of non-pregnant healthy and POP subjects. However, the range of membrane tensions at the landmarks as well as the average tension in the pelvic muscle sheet are clearly similar to values reported by Ozog et al. [200]. In addition, the FE analysis allows for assessment of local effects, as described above.

Furthermore, organs and connective tissue were considered to be isotropic, linear elastic as a first approximation, whereas in fact they exhibit a degree of anisotropy and non-linearity at higher strains [74, 87, 119, 155, 170, 209]. However, maximum in-plane strains in the pelvic muscle sheet at maximum Valsalva pressure in the FE model are in the range of $4.15 \pm 3\%$ (mean $\pm$ standard deviation) with very localized maxima of around 30$\%$ in the region of fixation points to bone. These rather low values support the use of a linear material model with a tangent modulus representing the material response in the low strain region, making it a valid assumption. Nevertheless, future improvements of the model could include non-linear material models and in particular anisotropic effects in order to improve the analysis and predictions of pelvic floor behavior at a more local level.

To conclude, the female pelvic cavity is a complex region in terms of its geometry, interaction and support structure. The present study allowed for a quantification of tensions and deformations within the pelvic muscles, which were found to be an order of magnitude lower than those within the abdominal wall [136]. Initial analytical calculations performed by Ozog et al. (2014) [200] could be confirmed. The FE model also gave indications of the effects of local geometry variability on loads within the muscles. It is a valuable tool for in-vivo estimation of forces and deformations of healthy and pelvic prolapse patients. In addition, after successful clinical outcomes in the abdominal wall, meshes initially designed for hernia repair were first used for POP repair [80, 61, 83, 195], see also Chapter 3.
However, these implants were designed to fit abdominal loading [136], exhibiting excessive stiffness compared to the organs and tissues in the pelvic region. The present model can provide an important reference for design and mechanical dimensioning of prostheses for pelvic prolapse repair, since their mechanical biocompatibility, i.e. a match of mechanical properties of implant and tissue, is of major importance when investigating clinical complications [173, 175, 228, 227].
Prosthetic Meshes for Hernia and Pelvic Prolapse Repair

3.1 Introduction

Prosthetic Meshes. Prosthetic meshes are implants in a flat, network-like, regular structure of interwoven monofilaments of synthetic materials (see Figure 3.1), usually polypropylene (PP) [106, 238]. Polyvinylidene fluoride (PVDF), polytetrafluorethylene (PTFE) or absorbable filaments (polyglactin or polyglecaprone) can also be found as the base material for the filaments [175]. Mesh implants today are used mainly for hernia repair and reconstruction of pelvic organ prolapse (POP).

Figure 3.1: Close-up image of a prosthetic mesh (Ethicon UltraproTM). Clearly visible are the intricately interwoven polypropylene filaments, arranged in a regular, network-like pattern.
In 1958, Usher et al. (1958) [221, 256, 255] first introduced the polypropylene mesh Marlex for hernia repair as an alternative to the current method of suturing, which led to about 50% of recurrence [39, 208]. Significantly reduced incidence of recurring surgeries for mesh implants drove the major use and development of these prostheses [30, 38, 161, 234]. These successes and positive clinical outcomes motivated the use of meshes also for pelvic organ prolapse reconstruction, repairing damaged and weakened tissue by implanting supportive prostheses. In the late 1970s, meshes initially designed for hernia repair were first used for abdominal sacrocolpopexy, repairing vaginal vault prolapse [80, 61, 83, 195]. In the 1990s, urethral slings were introduced to treat stress urinary incontinence [27, 149, 185, 196], with the first specifically designed mesh cleared by the FDA in 1996 [80]. Soon thereafter, transvaginal procedures for POP repair using surgical meshes became more and more prevalent [26, 41, 64, 72, 79, 101]. Rogo-Gupta et al. (2012) [223] investigated the management of POP between 2000 and 2010 and found a continuous increase in the use of mesh implants after the FDA approved usage of the first mesh specifically designed for POP in 2002 [80]. Implants were available as large sheets to be cut by the surgeon to the specific application [116, 180, 192] or as precut mesh kits including tools for standardized implantation techniques [8, 70, 79, 101]. Narrow mesh strips are typically used in line-type suspensions such as urethral slings or abdominal sacrocolpopexy, whereas wider sheets are applied for pelvic fascia support [173, 175]. Fixation to the tissue is usually performed by “single button sutures” or by stapling techniques in case of fixation to connective tissue [97]. However, this initial enthusiasm, which led to a more widespread use of new mesh products, also increased the prevalence of clinical complications compared to the more traditional treatments of POP, such as pelvic muscle training or autologous graft repair [3, 48].

Clinical Complications. At the time of approval, only few clinical trials could be found dealing with the success of mesh implants for pelvic organ prolapse and urinary incontinence repair [106]. While surgical repair of POP using synthetic implants may aid in reconstructing pelvic anatomy and support weak native tissue [81, 128] with the aim of being safe, effective and durable [14], the recurrence and reoperation rate is still high, with reports of up to 45% [141, 196, 252, 257]. One of the most severe and common type of graft related complications (GRCs) is mesh erosion or exposure [65, 70, 121]. It is characterized by a degeneration of tissue adjacent to the mesh and a protrusion of the implant through the vagina, bladder, urethra or bowel, thus allowing for visualization of the mesh in the vaginal lumen [14, 19]. Symptoms include vaginal bleeding, dyspareunia, pain or infections [14]. Erosion rates are reported
to be up to 25% for anterior vaginal wall prolapse [131], 13% for posterior vaginal wall prolapse [159] and 16% for apical vaginal repair [257].

Another important and common clinical complication following implantation of synthetic meshes is shrinkage or contraction [75, 139, 142, 202]. It is characterized by a reduction of apparent surface area of up to 50% [82, 101] and has been associated with vaginal pain and dyspareunia [82].

As a response to the prevalence of GRCs and increasing number of entries into the MAUDE (Manufacturer and User Facility Device Experience) database related to adverse clinical outcomes after transvaginal placement of meshes, the FDA issued a public health notification [80]. It stated that "the risks of serious complications associated with transvaginal POP repair with mesh are NOT rare, contrary to what was stated in the 2008 PHN" [80], clearly indicating the severity of the situation. In fact, it has been shown that there is yet no proven benefit with respect to quality of life when using synthetic meshes compared to native tissue repair [162, 192].

While mechanical properties of mesh implants have not been explicitly linked with clinical outcome, several studies address this problem [52, 69, 86, 87, 160]. Theoretical and clinical indications point at advantages related to meshes designed to mimic biomechanical properties of the area of application [201, 202, 227], improving mechanical biocompatibility and affecting the clinical outcome of the treatment [2, 95, 199].

Chapter Structure. The many open questions concerning the suitability of mesh implants for POP repair and the increased interest in mechanical properties of synthetic mesh implants as well as a clear need for standardized experimental procedures and mechanical parameters [238] motivated the following investigations:

- Section 3.2 is based on the publication [173] and proposes an extensive yet simple mechanical testing protocol for characterization of prosthetic meshes. Nine different implant types are tested. Each mesh is represented by several mechanical and physical parameters, which are presented in a newly developed circle graph. This allows for a quick visual representation of mesh properties and mechanical biocompatibility.

- Section 3.3 is based on the publication [172]. The data analysis presented in Section 3.2 is extended and meshes used for hernia and pelvic organ prolapse repair are grouped and compared. The question is posed as to what constitutes a physiological, in-vivo reference state of stress and strain to which the implanted mesh and underlying tissue are subjected. These values are indeed of great importance in order to analyze current meshes with respect to their mechanical biocompatibility as well as to define a reasonable design target for future implant design.
Section 3.4 is an application of the finite element model presented in Chapter 2. A specific case of pelvic organ prolapse repair using meshes, the so called sacrocolpopexy, is simulated. This allows for qualitative evaluation of mesh performance and provides further insight into physiological conditions to which implants and underlying vaginal tissue might be subjected in-vivo. Further, the influence of specific aspects of the surgical technique is analyzed.
3.2 Mechanical Biocompatibility of Prosthetic Meshes: Experimental Protocol for Mechanical Characterization

The following section 3.2 is based on the publication [173]:


3.2.1 Introduction

Motivation  Mechanical properties of prosthetic meshes for hernia repair and pelvic floor reconstruction are known to be a crucial factor determining their performance. When they were first proposed for clinical application, implants were expected to provide sufficient resistance to physiological loads, with a primary focus on load to rupture and implant strength [48, 59, 212, 230]. Since these early implants the deformation behavior has received increasing attention, as an excessive stiffness of the implants has been associated with the occurrence of clinical complications. Fenner (2000) [86] related high material stiffness with the likelihood of tissue erosion and exposure. In hernia repair postoperative pain has been correlated to the stiffness of explants [52]. Liang et al. (2013) [156] and Feola et al. (2013a) [87] observed biomechanical and biological degeneration of vaginal tissue after implantation with high stiffness meshes, which was also associated with postoperative pain and vaginal dysfunction in previous studies [108, 160]. Dietz et al. (2003) [69] argued that a mismatch between implant and tissue properties hinders an appropriate transmission of loads at the implant-tissue interface leading to poor clinical results. Klinge et al. (2002) [138] and Klosterhalfen et al. (2005) [140] analyzed the influence of weight and pore size of meshes for hernia repair on clinical outcome. Heavyweight meshes with small pores maximize mechanical stability, whereas lightweight meshes with large pores better mimic the properties of host tissue. It was concluded that mechanical properties of meshes should be optimized in order to provide the mechanical support required for abdominal wall function. Recent work from our groups [201, 202, 227] points at advantages related to meshes designed to mimic biomechanical properties of the area of application. The FDA safety communication issued in 2011 [80] further motivates investigations aiming at identifying implants which might reduce the risk of complications.
The ability of implants to display a mechanical behavior compatible with its function and favoring its integration in the surrounding native tissue is referred to as the mechanical biocompatibility of the implant \cite{224, 227}. Ideally, an implant should provide mechanical properties matching those of the tissue to be substituted \cite{230}, at the macroscopic as well as the microscopic length scales. Although generally accepted, this criterion cannot be quantitatively formulated for comparison and selection of implants for specific clinical applications. This is due to a lack of quantitative measures and commonly accepted parameters to describe the complex mechanical behavior of both, the mesh implants and the corresponding native tissues to be supported.

**Previous Work** A wealth of studies were performed to characterize the mechanical properties of implants as well as biological and biochemical factors related to their application for hernia or pelvic repair, including comparisons of synthetic materials to biological graft materials \cite{10, 68, 115, 144, 212}.

Cosson et al. (2003) \cite{59} reviewed mechanical mesh implant behavior and clinical complications and concluded that polypropylene meshes are best characterized among available products and thus represent reliable graft materials for pelvic repair in terms of durability and compliance. Based on uniaxial testing pre- and post-implantation, Mangera et al. (2012) \cite{163} tried to find direct correspondence between biomechanical parameters of prostheses and clinical outcomes, but concluded that current evidence does not allow determining simple correlations.

Research on meshes for hernia repair include the pioneering in vivo studies by the group of Klinge, with Klinge et al. (1998) \cite{139} determining shrinkage, local infections and shortening of polypropylene meshes in dogs. Further, Klinge et al. (2002) \cite{138} has examined the influence of weight and porosity on integration, inflammation and fibrosis in rat models. The same group compared the deformation characteristics of meshes used for hernia repair with the compliance of the abdominal wall, highlighting significant mismatch by, in average, a factor of 2 (mesh too stiff) \cite{132}. More recently they proposed to classify meshes according to pore size \cite{137}. Mühl et al. (2008) \cite{187} introduced a new definition of mesh porosity: instead of a standard measurement of the ratio of pore area to total area, they proposed the use of effective porosity, taking into account only pores ”greater than 1000\(\mu m\) in all directions”, being beneficial for avoiding fibrotic bridging and permitting ingrowth of host tissue. This is in line with the findings reported in \cite{239}, who compared the in vivo response of suburethral sling materials and observed more extensive fibrous tissue integration for the large porous mesh. Ozog et al. (2011a) and Ozog et al. (2011b) \cite{201, 202} investigated biomechanical and biological parameters of meshes for hernia repair in a rabbit model, reporting corresponding values of low and high stiffness,
anisotropy before and after implantation, maximum stress and strain, shrinkage, as well as evidence of inflammation and fibrosis. Similar to Jones et al. (2009) [130], low and high stiffness parameters were proposed to characterize the nonlinear mechanical behavior of meshes and corresponding values reported. Mesh anisotropy was shown to persist after implantation in low strain regions. Anisotropy indices were also examined by Saberski et al. (2011) [231] for a range of hernia meshes. Similarly, Konerding et al. (2012) [142] reports on biomechanical and histological characteristics of hernia explants, including shrinkage, low and high stiffness as well as foreign body reaction to mesh prostheses after implantation.

Most studies on meshes for pelvic repair were based on uniaxial tension testing of implant or explant samples. Suburethral or vaginal slings and tapes are well suited for uniaxial testing methods, as used in Choe et al. (2001) [48], Spiess et al. (2004) [242] and Moalli et al. (2008) [182]. Boukerrou et al. (2007) [29] analyzed biomechanical properties of explanted meshes uniaxially, reporting on retraction, maximal resistance to traction and maximal elongation. Afonso et al. (2008) [4] tested a variety of meshes uniaxially and reported low and high stiffness values. Dietz et al. (2003) [69], Krause et al. (2008) [145], Jones et al. (2009) [130] and Shepherd et al. (2012) [235] applied uniaxial loads until failure to various mesh types and extracted stiffness parameters in the low and high force range as well as load to failure. Krause et al. (2008) [145], Jones et al. (2009) [130] and Shepherd et al. (2012) [235] additionally tested uniaxial cyclic behavior, reporting residual deformation after load cycles.

Several in-vivo investigations of meshes for pelvic repair have been carried out, including Konstantinovic et al. (2010) [143], who compared alternative graft materials to polypropylene meshes in a rat model and reported uniaxial tensiometry results at several time points after implantation. Ozog et al. (2012) [203] investigated the effects of polyglecaprone fibers on biomechanical properties and clinical complications in a rabbit model, showing that uniaxial strength and compliance were not significantly affected. Although polyglecaprone fibers lead to a milder inflammatory response [140], vaginal extrusion and contraction was not prevented. Manodoro et al. (2013) [164] studied graft-related complications and biaxial mechanical properties of vaginal meshes in a sheep model, reporting a possible dependence of complications on mesh size. Feola et al. (2013b) [88] and Röhrnbauer and Mazza (2013) [226] report stiffness results for biaxial testing procedures, where Feola et al. (2013b) [88] used a ball burst to failure test, whereas Röhrnbauer and Mazza (2013) [226] applied an inflation experiment to explants as well as implants embedded in an elastomer matrix. Röhrnbauer (2013) [224] also investigated local deformation mechanisms of a pelvic mesh, identifying potential mismatch of deformation between implant and host tissue at the meso- and micro-scale. Recent work by Ulrich et al. (2012) [254]
and Edwards et al. (2013) [73] compared biological and biomechanical properties of their new meshes with clinically available implants, showing that multi-axial analysis in addition to uniaxial testing is needed to better differentiate meshes based on their mechanical properties.

**Present Work** Based on the data reported in the literature, the mechanical characterization of mesh implants cannot be limited to one or two scalar parameters (such as low and high stiffness moduli) extracted from uniaxial tension experiments. Instead, a range of parameters addressing stiffness under uniaxial and biaxial loading conditions, anisotropy, influence of prior deformation history and changes in mechanical properties when embedded in a homogeneous matrix should be considered, since all these properties are likely to affect the mechanical biocompatibility of implants. Here, we propose a simple and robust experimental protocol and a set of parameters which can form the basis for comparison of different mesh types and for evaluation of their mechanical biocompatibility. Experimental procedures and mechanical parameters were selected as a compromise between simplicity and robustness of their determination and completeness towards potential influence of mechanical behavior on clinical applications. Measurements were performed on nine mesh types used for hernia and/or pelvic repair, including heavier as well as lighter implants and covering a wide range of mechanical responses.

### 3.2.2 Materials and Methods

**Mesh Types and Loading Conditions** Nine knitted mesh implants were selected for the present investigation. Table 3.1 summarizes the main characteristics of each mesh type, the materials used for the knitting filaments, and their application for pelvic organ repair or hernia repair.

Mechanical experiments were performed under uniaxial as well as biaxial loading conditions. In vivo, uniaxial tension is the state of loading predominant in long narrow strips of meshes as used for line-type suspensions, whereas wider sheets of meshes (such as the ones used for fascia replacement) are subjected to multiaxial tension in their plane. In order to characterize the anisotropy of textile meshes, measurements were performed in two perpendicular directions. The mechanisms of deformation of textile meshes involved a progressive collapse of the pores with increasing mechanical load and this mechanism is known to be influenced by the presence of a tissue ingrown within the pores [227]. In order to represent the influence of this interaction, mechanical measurements were repeated with the mesh samples embedded in a soft elastomer matrix (see below). These considerations led to the following test matrix including eight experimental conditions for
3.2. Mechanical Biocompatibility of Prosthetic Meshes: Experimental Protocol for Mechanical Characterization

<table>
<thead>
<tr>
<th>Mesh</th>
<th>Picture</th>
<th>Application</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bard\textsuperscript{T\textregistered} Mesh Marlex (BM), standard</td>
<td><img src="image1" alt="Picture" /></td>
<td>Hernia</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>DynaMesh\textsuperscript{®} ENDOLAP (DM), standard</td>
<td><img src="image2" alt="Picture" /></td>
<td>Hernia</td>
<td>PVDF (Polyvinylidene Fluoride)</td>
</tr>
<tr>
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<td>POP</td>
<td>PVDF</td>
</tr>
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<td>POP</td>
<td>Polypropylene</td>
</tr>
<tr>
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<td><img src="image5" alt="Picture" /></td>
<td>Hernia</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Coloplast Restorelle\textsuperscript{T\textregistered} (Rest), ultralight</td>
<td><img src="image6" alt="Picture" /></td>
<td>POP</td>
<td>Polypropylene</td>
</tr>
<tr>
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<td>POP</td>
<td>Polypropylene</td>
</tr>
<tr>
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<td><img src="image8" alt="Picture" /></td>
<td>Hernia</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Parietex Ugytex\textsuperscript{®} (UT), light</td>
<td><img src="image9" alt="Picture" /></td>
<td>POP</td>
<td>Polypropylene</td>
</tr>
</tbody>
</table>

Table 3.1: List of mesh types used for the present investigation, with their weight classified as ultralight, light, standard according to Coda et al. (2012) [54]. Principal directions of testing are marked in red. Scale bar (lower right): 5\text{mm}. Their clinical application is listed as used for pelvic organ prolapse (POP) or hernia repair.
each mesh type:

\[2 \text{(uniaxial tension OR biaxial tension)} \times 2 \text{(dry OR embedded)} \times 2 \text{(0° OR 90° direction)}\]

A specimen is referred to as "dry" if the naked mesh is tested as delivered, whereas "embedded" refers to a specimen being manually embedded into an elastomer matrix of 0.5\(mm\) thickness (Ecoflex® Supersoft Silicone, Smooth-On, Inc., Easton, PA, USA). The 0° and 90° testing directions were determined visually as preferred directions of the knitting pattern, as illustrated in Table 3.1.

Two types of experiments were performed, uniaxial tension and uniaxial strain. In the case of uniaxial tension, the sample is free to contract in the direction transverse to the main loading direction, thus leading to a vanishing transverse tension (uniaxial state of tension). As shown in Figure 3.2, the free sample area is 30\(mm \times 15mm\). The validity of the uniaxial tension data is provided by the fact that elongation was measured optically in the center of the sample (see next section and Figure 3.2).

In case of uniaxial strain, transverse contraction is constrained and deformation occurs only in one direction. This leads to a biaxial state of loading where the tension perpendicular to the stretch direction is lower but of the same order of magnitude as the tension in the main direction. This configuration is realized by a large aspect ratio of width to length and a free sample area of 50\(mm \times 15mm\) (3.2), which is in the range of the aspect ratio used in Hollenstein et al. (2011) [117].

The uniaxial strain configuration was selected since it provides a means to realize a biaxial tension experiment with well controlled boundary conditions and homogeneous state of deformation using a tensile test arrangement, as available in most laboratories. Comparison with other biaxial loading configurations (equibiaxial testing, ball burst or inflation [226]) confirmed the uniaxial strain test to be representative of the mechanical response of mesh implants to a biaxial state of tension. In fact, uniaxial strain experiments generate a biaxial loading state (with the load in transverse direction lower than in loading direction). Our previous work [226] quantified the ratio of stiffness in equibiaxial to uniaxial loading. While the stiffness ratio is higher in case of equibiaxial loading (> 3 for the meshes considered), the biaxial configuration used in the present work leads to a stiffness which is considerably higher (factors typically > 2) than for the uniaxial case.

**Experimental Setup**  All experiments were performed at room temperature on a custom-made testing device, as described in detail in Hollenstein et al. (2011) [117] and Röhrnbauer (2013) [224]. It consists of a tensile test machine with two hydraulic actuators (242 Actuator, MTS Systems Corp., Eden Prairie, MN, USA), each with 2.7\(kN\) capacity,
Figure 3.2: Sample dimensions and loading conditions for a) uniaxial tension and c) uniaxial strain, with the clamped specimen on the left and the free specimen on the right, respectively. b) and d) show the deformed configurations with the region for optical strain measurement marked with a red circle.
mounted horizontally on a solid steel plate. For force measurements 100N load cells (SMT S-Type, Interface Inc., Scottsdale, AZ, USA) were used, to which clamps – custom made for uniaxial tension and uniaxial strain tests, respectively – were mounted. The mounting surfaces of the clamps were covered with sand paper for better gripping of the specimen. All samples were clamped previous to mounting into the tensile machine using a custom made supporting device that allowed for exact observance of free length between clamps as well as reduced slacking of the specimen. A mounted biaxial tension sample is shown in Figure 3.3.

![Mesh sample mounted in tensile test machine.](image)

To measure local in-plane deformation in the specimen in a contact-free manner, the central portion was filmed during testing by a video extensiometer system with triggered image acquisition (uniDAC FAST, Chemnitzer Werkstoffmechanik GmbH, Chemnitz, Germany). The local in-plane deformation field was then evaluated using the software VEDDAC cam 3.2 (Chemnitzer Werkstoffmechanik GmbH). The software allows the user to set an arbitrary number of markers in the initial image of an image sequence which it then tracks throughout the sequence using a greyscale digital image correlation algorithm. After analysis, the user is provided with a history of \( x \)- and \( y \)-coordinates for each marker. In the current application, 15 markers were set on nodes of each mesh in order to capture up to 8 unit cells, depending on the specific knitting pattern (see Figure 3.4). The extracted \( x \)- and \( y \)-positions tracked over all 10 deformation cycles were then further analyzed in Matlab (The MathWorks Inc., Natick, Massachusetts, US), see below. Nominal membrane tension \([N/mm]\) was calculated as current force \([N]\) divided by the
initial width \textit{[mm]} of the sample.

![Diagram showing marker positions for deformation tracking in VEDDAC](image)

Figure 3.4: Marker position for deformation tracking in the program VEDDAC for (a) mesh with rectangular unit cells (e.g. DynaMesh PRS, Restorelle) and (b) mesh with diamond shaped unit cells (e.g. DynaMesh Endolap, Ultrapro)

**Loading Protocol**  Each specimen for the uniaxial tension or uniaxial strain tests was loaded and unloaded for 10 cycles. This procedure was selected in order to characterize the modification in mechanical response associated with the initial loading of the implants. The experiment was set to start at a pre-force level of 0.01 N, as specified by the user in the control software of the tension machine. Samples were then stretched at $10^{-3}/s$ to a stretch of 1.3 (calculated as current divided by initial clamp-to-clamp distance, corresponding to 30% nominal strain) and subsequently unloaded until the measured force reached the level of the pre-force, thus avoiding slacking of the specimen. Loading back to the same nominal strain of 30% and unloading back to the level of pre-force followed for 9 subsequent cycles (totaling 10 cycles) with no delay between two subsequent cycles.

**Deformation Analysis**  The deformation associated with each measured force level was determined in longitudinal and transverse direction in the central region of each sample, using the results of the image analysis algorithm, developed by Barbara Röhrnbauer and described in detail in Röhrnbauer and Mazza (2014) [227] and Röhrnbauer (2013) [224]. In short, the in-plane displacement field of the nodal points of the mesh is evaluated with a greyscale correlation algorithm. Based on line elements between two nodes along the edges of each unit cell the local deformation gradient is determined for each time point and unit cell and the Green-Lagrange strain tensor calculated. As a measure of intra-specimen variability the local strain analysis was carried out for up to 8 unit cells in each
specimen, depending on mesh type (Figures 3.4 and 3.5), yielding a mean local strain and standard deviation. In a structure with repetitive identical unit cells (oriented in the same direction), the material is expected to display the same state of deformation at the level of the unit cell as at the global level. The variability seen in these mesh structures is due to variations in material and geometry from cell to cell. The local strain analysis is more accurate compared to the global nominal strain, since it is not affected by boundary effects related to clamping. This local strain analysis is more accurate compared to the global nominal strain. Due to boundary effects at the clamps which prevents lateral contraction, the central region of the specimen experiences larger strain levels than the outer regions near the clamps. This effect becomes more pronounced for more compliant meshes, where boundary effects have a larger reach into the specimen. Additionally, local deformations and displacements at the clamps, which particularly affect embedded meshes, may lead to lower local strains in the specimen. These effects result in dissimilar strain levels on a local level compared to the applied global strain, as is reflected in the range of maximum local strains for the different mesh types (see Table 7.4 and 7.5 in the Appendix 7).

Figure 3.5: Mesh sample in the undeformed (left) and deformed (right) configuration, with exemplary unit cells used for local strain evaluation marked with red circles.

Mechanical Parameters From the experimental observations a selection of scalar parameters was extracted which were deemed representative of the mechanical behavior of the implants. Each parameter is introduced in the following sections along with its potential relevance in terms of mechanical biocompatibility. Most of the parameters are extracted from the tension-strain curves represented at the example of uniaxial and biaxial strain experiments in Figure 3.6.

Uniaxial Stiffness $K_{\text{uni}} [\text{N/mm}]$: The response in the uniaxial tension experiment is evaluated for the initial cycle, representing the response of the mesh in "as delivered" conditions. Previous approaches extracted low and high tangent stiffness parameters, ex-
3.2. Mechanical Biocompatibility of Prosthetic Meshes: Experimental Protocol for Mechanical Characterization

Figure 3.6: Exemplary tension-strain curves for DynaMesh (DM) for illustration of parameter extraction. a) uniaxial tension in 0° direction, dry mesh, loading and unloading. b) uniaxial tension in 90° direction, dry mesh. c) uniaxial tension in 0° direction, embedded mesh. d) biaxial tension in 0° direction, dry mesh, loading and unloading.

Pressing the two domains of stiffness of a mesh in the low and high strain regions. Here, for simplicity one single parameter is selected, namely the secant stiffness at 10% local strain. This level of deformation was selected as it might be representative of a physiological range of strain for the implant [140, 202]. \( K_{uni} \) is calculated as the ratio of membrane tension and strain at 10% strain (Figure 3.6 a)).

The stiffness under uniaxial tension loading conditions is a common parameter for evaluation of mechanical behavior of mesh implants. It might be relevant to describe the deformation behavior of long mesh strips used for line-type suspension in pelvic floor reconstructive interventions. Excessive uniaxial stiffness might reduce organ mobility and create regions of localized stress and deformations at the points of implant attachment to pelvic tissue.
**Biaxial Stiffness** $K_{bi} [N/mm]:$ Similar to uniaxial stiffness, this value corresponds to the secant stiffness at 10% local strain in the first cycle of the uniaxial strain experiment (Figure 3.6 d)).

Bull burst tests and inflation experiments were previously carried out to assess the biaxial resistance to deformation of mesh implants. Due to the deformation mechanisms of textile fabrics, the biaxial stiffness is typically much higher than the uniaxial stiffness. For this reason compliance of implants might be severely overestimated when judgment is based on uniaxial stiffness only. Mesh implant sheets are used for hernia repair as well as for pelvic floor repair. Both applications lead to simultaneous tensioning of the implant in $0^\circ$ and $90^\circ$ directions. Excessive stiffness might lead to stress and strain concentration, and might contribute to implant shrinkage, as observed for hernia and prolapse repair [59]. An additional experiment was performed to qualitatively illustrate the mechanisms of shrinkage (contraction) induced by a mechanical biaxial load in case of excessive biaxial stiffness of the implant. An implant (UP) is laid between two layers of a soft elastomer matrix (Ecoflex® Supersoft Silicone, Smooth-On, Inc., Easton, PA, USA), placed as a cover on a cylinder and subjected to deformation induced by internal pressure, see Figure 3.7 b). Upon unloading mesh shrinkage is clearly visible in Figure 3.7 c), qualitatively demonstrating that additionally to scar tissue contraction [140] mechanical effects are also at play. Biaxial stiffness of the implant is much larger than the one of the elastomer, so that during loading the mesh deforms less and thus tends to slide with respect to the elastomer. When unloaded the mesh is contracted to the reference position of the elastomer region it was in contact with at the end of the loading process.

![Image](image-url)

Figure 3.7: Shrinkage Experiment: a) Circular sample of UltraPro mesh placed in between two layers of soft elastomer. b) Circumference of elastomer is clamped down and internal pressure applied, leading to inflation of the elastomer-mesh-elastomer complex. c) After releasing the pressure, mesh shrinkage is clearly visible.

**EvsD: Embedded vs. Dry [—]:** Each mesh was also tested after it was embedded into a polymer matrix, mimicking the ingrown state in vivo. This parameter quantifies
the change in stiffness which might occur shortly after implantation in the body. The parameter is calculated as the ratio of stiffness in the dry and embedded state (EvsD: Figure 3.6 a), e)).

The desired compliance might not be offered by an implant with a very strong stiffening related to tissue ingrowth (large values of EvsD). On the other hand, if higher stiffness originating from tissue ingrowth is required for the functionality of the repair, mechanical loading should be minimized in the initial period after implantation in case of large EvsD values.

It is expected that stiffness increases with embedding; however, due to local effects on the polymer filaments (elastomer embedding leads to opening of the nodes), situations were observed where stiffness decreases with embedding. Such measurements may not be representative of the mechanical response following tissue ingrowth.

\( \varepsilon_{res} \): **Preconditioning** [−]: Changes in mechanical response are also related to internal rearrangement of implant microstructure when subjected to a history of mechanical load. This phenomenon is well known for biological tissues and is called ”preconditioning” [94]. It refers to the change in mechanical response when cyclically loading a material. In the present experiments it is demonstrated by the difference in the tension-strain curve between the first cycle and later cycles. With reference to Figure 3.6 a), the parameter \( \varepsilon_{res} \) is calculated as the ratio of the residual strain \( \varepsilon_{res}^{10} \) at the end of the experiment (after all 10 cycles) and the maximum local strain \( \varepsilon_{max} \) reached in the first cycle. This is selected as a representative scalar quantity to describe the shift of the initial point. Significant preconditioning might strongly affect the mechanical response of a mesh after implantation. Softening and permanent deformation due to preconditioning might be significantly influenced by implant manipulation during the intervention or by the loading applied during implant fixation in the body.

\( dGV \): **Local Delamination** [−]: Figure 3.8 shows a mesh embedded into an elastomer matrix before the first load cycle (left) and before the 10\( ^{th} \) load cycle (right). Marked with arrows are local regions of delamination leading to darker color because of light scattering at the location of separation between mesh filaments and the elastomer. Local delamination is due to a mismatch in deformation mechanisms between the filament structure and the homogeneous matrix, as explained in Röhrnbauer and Mazza (2014) [227]. Due to the textile structure of the knitted mesh, local non-affine deformations occur compared to the far field global deformation. This results in a relative movement and progressive delamination. This effect is quantified with the parameter dGV, calculated as the ratio between mean grey values in the image before the beginning of first and the 10\( ^{th} \) cycle. In
order to ensure repeatable measurements, parameter extraction consists of the following steps for each of the two images: two areas of each mesh image are taken – one central portion of $7mm \times 16mm$, only including the embedded mesh (see Figure 3.8, left); and one in the upper left corner, only including background grey (not depicted). After inverting the images (which is necessary to achieve a larger numerical value for darker images, i.e. for more delamination) and determining the mean grey value for both sub-images, the background mean grey is subtracted from the mesh mean grey value, thus giving one numerical value for each of the two images per mesh – i.e. before the 1st and 10th cycle – the ratio of which determines the final parameter dGV. The intermediate inverting of the sub-images is done for convenience, yielding a larger value for dGV if the image is darker, i.e. contains more areas of delamination. Subtracting the background increases robustness of this approach with respect to global illumination changes.

The microstructure of host tissue is of a much smaller length scale ($\mu m$) as compared to the one of mesh implants ($mm$). Non-affine deformation of the mesh implant with respect to the host tissue might thus arise based on the same mechanisms observed when embedding the mesh into a homogeneous elastomer matrix. Inconsistency of local deformation mechanisms are likely to occur also in case of mesh implants with global compliance matching the one of the host tissue. The parameter dGV might contribute identifying textile structures more prone to such local delaminations.

Figure 3.8: Mesh embedded into elastomer matrix, before first load cycle (left), before 10th load cycle (right). The area used for extraction of the parameter dGV is marked with a rectangle. Local delaminations are marked with arrows.

**p: Porosity [-]**: Mesh porosity influences the mechanical behavior of implants and also has a significant effect on the host tissue ingrowth [138, 140]. Porosity is determined as the ratio of open area to the total area including filaments of one unit cell, as for example in Chu and Welch (1985) [50] or Pourdeyhimi (1989) [217]. This approach goes back to
an intuitive measure of porosity for a simple, easy to replicate protocol, in contrast to the more sophisticated measure of effective porosity introduced by Mühl et al. (2008) [187]. The parameter was calculated as the ratio of mesh to background from images at the initial configuration without loading during mechanical experiments with dry meshes.

**d: Density [-]**: Meshes are classified according to their density (calculated here as weight per unit area, \([\text{g/m}^2]\)) as ultralight (UL), light (L) and standard (S) in accordance with the system proposed by Coda et al. (2012) [54]. Dry mesh samples of known dimensions were weighted before mechanical testing using a high resolution balance and their density calculated accordingly.

**Anisotropy:** \(A_{\text{uni}}\) (uniaxial), \(A_{\text{biax}}\) (biaxial) [-]: As described above, each mesh was tested in two perpendicular directions, defined as reported in Table 3.1. The \(A_{\text{uni}}\) parameter is the ratio of uniaxial stiffness in the stiffer direction to the one in the less stiff direction (Figure 3.6 a, b). Similar to the uniaxial anisotropy index, \(A_{\text{biax}}\) describes the stiffness ratio of stiffer vs. less stiff direction for the biaxial loading condition. Strong mesh anisotropy might lead to unanticipated strongly oriented forces between implant and host tissue, leading to mesh dislocation. Cosson et al. (2003) [59] considered a pronounced anisotropy as ”clinically unjustifiable, as the resistance for prolapse repair is not always oriented in space.”

**Presentation of Results** All relevant values to calculate the above parameters were determined for each mesh and each curve of the test matrix. All values are reported in corresponding tables in the appendix. A subset of parameters was selected for representation within a circle, facilitating comparison among mesh types. In particular, dGV and EvsD are taken from uniaxial tension tests. \(\varepsilon_{\text{res}}\) is also extracted from uniaxial tension of meshes in dry conditions and scaled according to \(\varepsilon_{\text{scale}}^{\text{res}} = 1 + 2\varepsilon_{\text{res}}\) in order to maximize the space and visual representation in the scale from zero to three of the circle graph. \(p\) is reported as the inverse of porosity (again for better visual representation in the chosen scale) for the mesh in a reference state, before mechanical testing. Density is normalized to 35g/m\(^2\) [54] leading to a classification of meshes according to ultralight \((d < 35\text{g/m}^2)\), light \((35\text{g/m}^2 \leq d < 70\text{g/m}^2)\) and standard \((d \leq 70\text{g/m}^2)\). The anisotropy indices \((A_{\text{uni}}, A_{\text{biax}})\) are given for the initial cycle of dry mesh tests. Numerical values for each parameter are reported in Table 3.3 to complement the visualization in the circle (Figures 3.9 and 3.10). Each segment of the circle corresponds to one parameter, with the segment size (angle of the segment) representing the proposed relative importance of the respective parameter. The blue arc in each segment enclosing the shaded blue area represents
the value of the respective parameter. If not otherwise noted they are represented in a
scale from 1 to 3, whereas values of parameters larger than 3 and thus outside the circle
are not visible. 1 is marked as a red circle. This value is chosen as a reference which
might be seen as a favorable value from a mechanical point of view. The definition of the
parameters $E_{\text{vsD}}$, $\varepsilon_{\text{scale res}}$, $dG$, $A_{\text{uni}}$ and $A_{\text{biax}}$ reflect this choice of reference. Additional
markings in green in the uniaxial stiffness area correspond to stiffness values of reference
biological tissues as taken from literature [95, 129, 209].

3.2.3 Results

A total of 93 experiments were performed. Correspondingly, 279 parameters were ex-
tracted, which are reported in the appendix.

<table>
<thead>
<tr>
<th>mesh</th>
<th>dry</th>
<th>embedded</th>
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<tr>
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<td></td>
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<tr>
<td>UT</td>
<td>3.2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Table 3.2: Intra-specimen variability [%].

Variability For 8 out of 9 mesh types (with the exception of BM due to lack of material)
dry, uniaxial and biaxial experiments in at least one direction were repeated in order to
compare the repeatability of the present measurements with corresponding scatter values
from the literature. The relative difference between extracted stiffness values were in
the range of up to 12%. This is in line with the level of variability reported in the
literature for experiments on these mesh implants [73, 88, 235]. Note that the variability
is much larger when explants (samples extracted after implant permanence in the body in
animal experiments) are considered [87]. The intra-specimen variability (Table 3.2) was
calculated as the standard deviation of local strain values obtained from the analysis of 5 to 7 unit cells of each sample. The variability was evaluated at 10% mean local strain and provided lower values, but in the same order of magnitude as the scatter between different specimens, see appendix.

### Selected Parameters for Mesh Comparison

The parameters used for comparison of the meshes investigated are reported in Table 3.3. Results are presented in this section for lighter and heavier implants.

<table>
<thead>
<tr>
<th>mesh</th>
<th>$K_{\text{biax}}$</th>
<th>$K_{\text{uni}}$</th>
<th>EvsD</th>
<th>$\varepsilon_{\text{res}}^\text{scale}$</th>
<th>dGV</th>
<th>$1/p$</th>
<th>d</th>
<th>$A_{\text{uni}}$</th>
<th>$A_{\text{biax}}$</th>
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<tr>
<td></td>
<td>[N/mm]</td>
<td>[N/mm]</td>
<td></td>
<td>[-]</td>
<td>[-]</td>
<td>[-]</td>
<td>[-]</td>
<td>[mm]</td>
<td>[mm]</td>
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<td>1.8</td>
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<td>1.3</td>
<td>1.2</td>
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<td>7.5</td>
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</tr>
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<td>1.0</td>
<td>2.3</td>
<td>2.1</td>
<td>1.5</td>
<td>1.0</td>
<td>2.8</td>
<td>1.1</td>
</tr>
<tr>
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<td>2.2</td>
<td>2.6</td>
<td>1.4</td>
<td>1.2</td>
<td>0.9</td>
<td>1.2</td>
<td>3.4</td>
</tr>
<tr>
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<td>2.2</td>
<td>1.6</td>
<td>1.3</td>
<td>0.2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
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<td>2.5</td>
<td>1.3</td>
<td>1.7</td>
<td>1.6</td>
<td>2.4</td>
<td>2.9</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td>UP</td>
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<td>2.0</td>
<td>2.2</td>
<td>1.4</td>
<td>1.5</td>
<td>1.3</td>
<td>4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>UT</td>
<td>12.0</td>
<td>5.1</td>
<td>1.2</td>
<td>2.4</td>
<td>2.0</td>
<td>2.4</td>
<td>1.7</td>
<td>2.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Table 3.3: Parameters reported in the circle graphs in the following section.

### Lighter Meshes

Results are grouped according to mesh classification in terms of lightness, following the criterion proposed by Coda et al. (2012) [54]. Figure 3.9 reports parameter values for meshes classified as ultralight and light. Large differences in stiffness were obtained, ranging from 1.14 N/mm (UP) to 12.01 N/mm (UT) biaxially and 0.12 N/mm (PM) to 5.06 N/mm (UT) uniaxially, compared to a uniaxial membrane stiffness of 1.17 N/mm for vaginal tissue [209], 1.47 N/mm of iliococcygeal muscle [129] and 2.25 N/mm for abdominal skin [95]. Biaxial stiffness is consistently larger than uniaxial stiffness, with ratios of 1.3 (Rest) to 56.5 (PM). Considering the factor EvsD (embedded vs dry stiffness) it seems that embedding tends in several cases to reduce the difference in stiffness observed for dry meshes. For the PM, UP and DM meshes, their very low dry uniaxial stiffness increases by a factor of 2.17, 1.97 and 1.74, respectively, with embedding into the polymer matrix. For the Restorelle mesh on the other hand, uniaxial stiffness decreases by a factor of 1.4 ($E_{\text{vsD}} = 0.71$) when embedding, lowering dry stiffness to a
Figure 3.9: Results for lighter meshes.
value closer to vaginal tissue. PE and UT mesh show smaller changes.
The preconditioning parameter varies within a range from 2.1 (DM) to 2.6 (PM), which corresponds to residual strains of 21.1% and 33.1% respectively. Considering that the initial deformation range is up to 30% strain globally, these results indicate a significant change in mechanical response in the initial loading history of lighter meshes.
The parameter dGV varies from 1.27 (DM) to about 2.08 (PE), indicating differences in knitting patterns and local deformation mismatches for different mesh types. UP for example has a rather regular pattern with few fibers interweaved, whereas the extreme case of PE exhibits a quite open knitting structure with fibers spanning open unit cells, thus possibly enhancing local non-affine deformations.
Ultralight and light meshes are expected to have large porosity, corresponding to a small value of the parameter displayed in the figures, and this is confirmed for the meshes in this category. The only exception here is UT, which classifies as light, but has small pores. This is in line with the high uniaxial and biaxial stiffness for this mesh, as well as moderate changes when embedded.
When considering anisotropy, a wide variety of behaviors can be observed. While PE shows similar stiffness in both directions under biaxial loading, its uniaxial response is highly dependent on direction. A similar tendency is visible for UT, although not to such a large extent. The contrary is true for PM, with a very high anisotropy index in case of biaxial testing compared to uniaxial loads. In terms of anisotropy, Rest shows identical results in both directions for uniaxial as well as biaxial states of stress. This result was expected since its layout is symmetrical with respect to a 90° rotation. UP is highly anisotropic in both loading configurations with values of 4.54 and 3.95 for uniaxial and biaxial loads, respectively. DM on the other hand is well behaved with very small anisotropy in both uniaxial as well as biaxial conditions.

**Heavier Meshes:** Heavier meshes, classified as "standard" in terms of density, are shown in Figure 3.10. A large range of stiffness can be observed, but on average values are significantly larger compared to lighter meshes. DMPRS and SPMM display large stiffness uniaxially as well as biaxially, with DMPRS being the stiffest mesh of all tested (15.75 N/mm biaxial stiffness and 14.72 N/mm uniaxial stiffness). When looking at BM, an inversion of the relation of uniaxial vs. biaxial stiffness can be seen, with $K_{uni}$ being larger than $K_{biax}$ by a factor of 4. SPMM behaves stiffer when embedded into a polymer matrix, but the other meshes have similar (but somewhat lower) stiffness when integrated into the elastomer. In terms of preconditioning, values are significantly lower when compared to the lighter meshes, with values of 1.6 (corresponding to 6.6% residual strain) for DMPRS to 1.8 (corresponding to 12.4% residual strain) for BM. Heavier meshes seem to
have more stable mechanical properties. The parameter dGV varies from 1.21 (DMPRS) to 1.82 (BM), being dependent on knitting patterns, similar to lighter meshes. DMPRS exhibits a rather simple rectangular knitting pattern with few individual fibers, reflected in a low value for dGV, whereas both BM and SPMM are knitted in a more complicated fashion. Porosity values for BM and SPMM are in line with expectation for heavier meshes, with small pores leading to parameter values between 2.26 and 2.38. DMPRS on the other hand displays larger pores, comparable to all lighter meshes. No large influence of directionality is observed for SPMM in both uniaxial and biaxial loading conditions, whereas large anisotropy in both loading cases is obtained for BM (anisotropy index of 3) and DMPRS (anisotropy index of 7.5).
3.2.4 Discussion and Conclusions

We have shown a simple yet thorough testing protocol which allows extracting a wide range of relevant mechanical parameters and displaying mode in order to analyze the mechanical biocompatibility of mesh prostheses. As shown in Figure 3.9 and 3.10, the proposed set of parameters differentiates between the meshes and the values span a large part of the measurable ranges. No proportionality or direct relation between single parameters could be found, thus making each parameter relevant and non-redundant. Porosity for example does not necessarily predict stiffness, as can be seen when comparing Rest with UP: Even though they exhibit similar porosity, their stiffness differs by a factor of 9 (uniaxial) to 3 (biaxial). Similarly, permanent deformation cannot be predicted by stiffness values. UT, PE and PM exhibit similar levels of residual strain, however their uniaxial stiffness ranges from 0.12 to 5.06 N/mm.

Some of the meshes characterized in this study were already investigated in previous studies [130, 231, 235]. Jones et al. (2009) [130] and Shepherd et al. (2012) [235] found that even though Gynemesh (PE) and Ultrapro (UP) have similar porosities, PE proves to be among the stiffer meshes when tested uniaxially, which is in line with our findings. Similarly, UP was found to be very compliant. Findings with respect to preconditioning, expressed in terms of residual deformation, differ compared to Shepherd et al. (2012) [235]. We found a residual strain after uniaxial loading significantly larger than values reported in Shepherd et al. (2012) [235] for UP, but much smaller for PE. This may be due to a difference in preconditioning protocols: while we perform 10 strain controlled cycles, Shepherd et al. (2012) [235] applies force controlled preconditioning. UP has also been reported to have a large anisotropy index [231], which is in line with our present values.

Qualitatively comparing the difference of uniaxial stiffness of UltraPro (UP) in Shepherd et al. (2012) [235] to biaxial stiffness in Feola et al. (2013b) [88], similar trends as in the present study in stiffness increase from uniaxial to biaxial states of tension are visible. An increase of up to two orders of magnitude can be observed. However, quantitative comparison to ball burst data [88] is not possible. The ball burst test does not account for directionality of the mesh, since a circular mesh sample is clamped at the circumference and punctured by a spherical indenter, thus incorporating the global response of the mesh and not allowing for reporting of distinctive mechanical characteristics in different directions. In addition, the uniaxial strain configuration as presented here allows for a more precise and controllable determination of the threshold force and thus a consistent reference configuration for all experiments.

Note that a key factor influencing mechanical experiments is the pre-force level, which
determines the reference configuration of each sample. Application of a consistent pre-force level is necessary to ensure comparability of stiffness values based on strain, as well as residual strain values for the given sample geometries. In a very recent study, Endo et al. (2014) [75] performed postoperative in vivo measurements of apparent surface area of different implants with the aid of magnetic resonance images (MRI). Ultrapro, reported in the study as the mesh with the lowest biaxial stiffness, showed lower shrinkage compared to its initial area prior to implantation, whereas DynaMesh PR4 with a biaxial stiffness larger than Ultrapro by a factor of 1.4, showed a larger decrease in area after 30 days of implantation. These results support the hypothesis that excessive biaxial stiffness might lead to more pronounced shrinkage of meshes (see Figure 3.7).

Plausible trends emerge in a comparison of lighter vs. heavier meshes. Heavier meshes appear to be more stable in terms of preconditioning, which can be attributed to their denser structure, leading to fewer mechanism-like deformation patterns on a local level, thus making them less susceptible to preconditioning effects. Similarly, they do not change much when embedded into a matrix, their stiffness is generally larger. But the local mismatch of deformation (dGV) is similar to lighter meshes.

Anisotropy parameters are calculated comparing the principal directions as defined in Table 3.1. It should be noted that these directions might not correspond to extremes of stiffness or compliance. For instance, the Rest mesh provides the weakest response in the 45° direction, which was not tested here. Röhrnbauer and Mazza (2014) [227] report on the mechanical response to uniaxial and biaxial stress of Gynemesh M in off-axis directions aligned with the filament directions. Dependent on the state of stress, off-axis stiffness can be lower or higher than in principal directions. Additionally note that the stiffness of the source material (for PVDF or polypropylene in the range of GPa) is several orders of magnitude larger than the meshes themselves. Obviously one cannot simply infer properties of the knitted mesh from the source material, rather the implants need to be analyzed as a structure, comprised of the material, extruded filaments and specific knitting pattern, behaving softer than the raw bulk material. This mismatch of material properties at the micro- and macro-scale may lead to uncontrolled local behavior, despite global properties matching the underlying tissue. Local deformation was determined in the present work at the level of the unit cell ("meso"-scale) and differences between deformation mechanisms of the mesh structure as compared to a homogeneous elastomer were addressed with the parameter dGV. Quantitative analysis of the strain distribution at a lower length scale (filaments, their intersection and loops at knots) might provide relevant insight into the mechanical environment of the cells of the host tissue.

From a mechanical viewpoint, desirable properties correspond to a parameter value close to 1 in the diagram representation of Figure 3.9 and 3.10. In fact, stiffness should be
carefully matched to the underlying tissue. A too stiff prosthesis might lead to stress shielding and extensive shrinkage or cause discomfort [52, 86, 87, 156], whereas meshes with a too low stiffness might lose their supportive function and give it inappropriate handling properties [202]. The effects of embedding a mesh into a polymer matrix (as expressed by the parameter $E_{\text{vsD}}$), along with preconditioning effects (parameter $\varepsilon_{\text{scale}}^{\text{res}}$) might affect the possibility to control mechanical function of the implant. Local delamination and non-affinity of deformation at a local level may inhibit ingrowth of tissue and lead to irritation at a local tissue level. As stated in Klinge et al. (2002) [138] and Mühl et al. (2008) [187], lightweight and large-pore-sized meshes show better tissue integration. Finally, anisotropy increases the complexity of mesh application: when cutting patient specific implants from large sheets, the principal directions of the mesh implants should be considered and its anisotropy matched with the underlying tissue to avoid a mismatch of deformation behavior.

The presentation of parameters in a circle graph per mesh allows for easy evaluation and comparison of prostheses at a glance. While the trained mechanical engineer might indeed be able to interpret the raw tension-strain curves (see Figures 7.1 to 7.9 in the Appendix 7) and come to similar conclusions as described above, the visual impact of the circle graphs can assist doctors and clinicians in evaluating the mechanical biocompatibility of different surgical implants.

Although no systematic evidence is available, meshes showing overall parameter values close to 1 (such as UP) have been named to have more favorable biological and biochemical outcomes [87, 156]. Systematic collection of observations from clinical experience will allow for the definition of criteria for prediction of clinical performance of a mesh based on its mechanical characteristics. This analysis would also provide evidence for determining the relative importance of each parameter.

A limitation of the present study is the lack of systematic repetition of tests for all loading conditions and all meshes, which was due to limited availability of material. However, where repeated measurements were possible (see Tables 7.1-7.5 in the Appendix 7), inter-specimen variability was in the range of variability reported in literature for this type of experiments.

At the 2nd IUGA Grafts Roundtable [238] consensus was reached with respect to a recommendation of a standardized, pragmatic, minimum clearance track for new implants before introduction to the market, including standardized product descriptions, biological property description and compulsory registration of the first 1000 patients. We propose to broaden the recommendation and include a standardized mechanical biocompatibility analysis, and the methodology applied in this study might provide a basis for defining corresponding protocols. We see the mechanics of implants as a critical factor determining
clinical performance which should be accounted for in mesh selection and for development of future implants.
3.3 Comparison of Biomechanical Properties of Hernia and Pelvic Prolapse Meshes

The following section 3.3 is based on the publication [172]:


3.3.1 Introduction

Mechanical biocompatibility of prosthetic meshes for hernia and pelvic organ prolapse (POP) is related to the ability of implants to display a mechanical behavior compatible with its function and favoring its integration in the surrounding native tissue [142, 156, 163, 175, 224, 227]. This approach for implant assessment has received increased attention in recent years. While initial investigations focused on the ability of a mesh to provide sufficient strength and resistance to maximum loads [48, 51, 59, 132, 136, 230], it recently became clear that the deformation behavior in a physiological range, also called "comfort zone", is of major importance [130, 202]. A mismatch of mechanical properties of the implants compared to native tissue has been associated with clinical complications [52, 69, 86, 87, 160], although none of these works explicitly link mechanical properties with clinical outcome. It has recently been suggested that meshes designed to mimic biomechanical properties of the area of application are advantageous [201, 202, 227]. These investigations are further motivated by an FDA safety communication [80] pointing at risks associated with existing prosthetic meshes and corresponding surgery procedures for repair of POP.

A wealth of studies has been conducted analyzing either hernia or POP meshes (see [173, 175] for an extensive literature overview). However, little work was performed to compare the mechanical response of these two groups, which may shed light on the prevalent clinical complications. The mechanical environment and loading conditions these implants are exposed to, differs significantly between the abdominal wall and pelvic floor. Physiological loads in terms of membrane tension were calculated based on Laplace’s Law to be around 0.035 N/mm in the pelvic region and 0.136 N/mm at the abdominal wall at rest, but can be orders of magnitude higher at increased intra-abdominal pressures [136, 163, 200]. This gives an indication of the range of load at which mesh implants should work best in supporting and mimicking native tissue, thus ensuring mechanical
biocompatibility.
Based on the experimental study presented in Maurer et al. (2014) [173], the data analysis in the present investigation is extended to compare the mechanical properties of hernia and POP mesh implants with respect to physiological loading conditions.

3.3.2 Experimental Section
Nine mesh implants were investigated. They were grouped into hernia \((n = 5)\) and POP \((n = 4)\) implants based on the manufacturer’s information available on their respective websites and analyzed accordingly. All products are described in Table 3.4.
The mechanical testing procedure has been previously described in detail [173]. In short, each mesh type was tested in eight different configurations:

\[2 \text{ (uniaxial tension OR biaxial tension)} \times 2 \text{ (dry OR embedded)} \times 2 \text{ (0\degree OR 90\degree direction)}\]

These test configurations represent the in-vivo loading and environmental conditions of the mesh implants. Long, narrow strips of meshes used in ”line-type” suspensions are mainly loaded in uniaxial tension, whereas wider sheets such as for hernia repair are typically subjected to multiaxial tension states. Our earlier study examined the anisotropic behavior of these meshes along two perpendicular directions following the main knitting patterns. However, here the focus is on the stiffer of the two directions on a per mesh basis. A dry mesh is tested as delivered, whereas embedded infers a specimen being embedded into a soft elastomer matrix (Young’s modulus 0.0276 \(N/mm^2\) [77]), mimicking in-vivo, ingrown conditions.
Experiments with uniaxial tension and biaxial tension (realized as uniaxial strain test, also called ”strip biaxial” [117]) were performed on the same tensile test machine. In the uniaxial strain test, lateral contraction of the specimen is constrained, leading to stresses in the direction perpendicular to the loading axis, thus subjecting the sample to a biaxial state of tension. Test piece dimensions were selected to generate a free area of 30\(mm\) \(\times\) 15\(mm\) (uniaxial) and 50\(mm\) \(\times\) 15\(mm\) (biaxial). Each specimen was loaded to a maximum of 30\% nominal strain (loading rate 10\(^{-3}\)\(s^{-1}\)) and unloaded back to a pre-force threshold of 0.01\(N\) for 10 cycles.
Deformation analysis was performed in an optical, non-contact procedure in the center of the specimen, allowing for extraction of local strains (\(\varepsilon_{loc}\)) as the result of an image analysis algorithm, thus avoiding edge and clamp effects at the specimen boundaries. Force measurements at the clamps were converted to nominal membrane tension \((M_t [N/mm])\) by dividing by the undeformed width of the sample. For an in-detail description of the
3.3. Comparison of Biomechanical Properties of Hernia and Pelvic Prolapse Meshes

<table>
<thead>
<tr>
<th>Mesh</th>
<th>Picture</th>
<th>Application</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bard&lt;sup&gt;TM&lt;/sup&gt; Mesh Marlex (BM), standard</td>
<td><img src="image" alt="Bard Mesh" /></td>
<td>Hernia</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>DynaMesh&lt;sup&gt;®&lt;/sup&gt; ENDOLAP (DM), standard</td>
<td><img src="image" alt="DynaMesh ENDOLAP" /></td>
<td>Hernia</td>
<td>PVDF (Polyvinylidene Fluoride)</td>
</tr>
<tr>
<td>DynaMesh&lt;sup&gt;®&lt;/sup&gt; PRS (DMPRS), standard</td>
<td><img src="image" alt="DynaMesh PRS" /></td>
<td>POP</td>
<td>PVDF</td>
</tr>
<tr>
<td>Gynecare PROLIFT&lt;sup&gt;TM&lt;/sup&gt; (PE), ultralight</td>
<td><img src="image" alt="Gynecare PROLIFT" /></td>
<td>POP</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Ethicon Physiomesh&lt;sup&gt;®&lt;/sup&gt; (PM), ultralight</td>
<td><img src="image" alt="Ethicon Physiomesh" /></td>
<td>Hernia</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Coloplast Restorelle&lt;sup&gt;TM&lt;/sup&gt; (Rest), ultralight</td>
<td><img src="image" alt="Coloplast Restorelle" /></td>
<td>POP</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Surgipro&lt;sup&gt;TM&lt;/sup&gt; Polypropylene Monofilament Mesh (SPMM), standard</td>
<td><img src="image" alt="Surgipro Mesh" /></td>
<td>POP</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Ethicon Ultrapro&lt;sup&gt;TM&lt;/sup&gt; (UP), light</td>
<td><img src="image" alt="Ethicon Ultrapro" /></td>
<td>Hernia</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Parietex Ugytex&lt;sup&gt;®&lt;/sup&gt; (UT), light</td>
<td><img src="image" alt="Parietex Ugytex" /></td>
<td>POP</td>
<td>Polypropylene</td>
</tr>
</tbody>
</table>

Table 3.4: List of mesh types used for the present investigation, with their weight classified as ultralight, light, standard according to Coda et al. (2012) [54]. Principal directions of testing are marked in red. Scale bar (lower right): 5mm. Their clinical application is listed as used for pelvic organ prolapse (POP) or hernia repair.
loading protocol and data extraction refer to Maurer et al. (2014) [173].

The resulting $M_t - \varepsilon_{loc}$ curves of each of the 8 specimens of each type, as well as area density and porosity measurements form the basis for the analysis and comparison of mesh groups. Dry mesh samples of known dimensions were weighted before mechanical testing using a high resolution balance and their area density calculated as weight per area [$g/m^2$]. Porosity is determined as the ratio of open area to the total area including filaments of one undeformed unit cell of the knitting pattern [50, 217].

From the $M_t - \varepsilon_{loc}$ curves the secant stiffness $K$ [N/mm] in the stiffer direction at the reference membrane tension $M_t^{ref} = 0.035$ N/mm (for hernia as well as POP meshes) was extracted, for both the $1^{st}$ and $10^{th}$ cycle (see Figure 3.11). It is defined as

$$K = \frac{M_t^{ref}}{\Delta\varepsilon},$$

where $\Delta\varepsilon$ is the difference of local strain at the reference membrane tension $M_t^{ref}$ and at the beginning of the current cycle.

The specific value of $M_t$ was chosen as a load representative of the membrane tension in the pelvic region under physiological intra-abdominal pressure (IAP) at rest [200]. Each mesh is thus characterized by 10 parameters, i.e. a secant stiffness value for each of the tested configurations (uniaxial and biaxial tension, dry and embedded) in $1^{st}$ and $10^{th}$ cycle, as well as area density and porosity.
3.3. Comparison of Biomechanical Properties of Hernia and Pelvic Prolapse Meshes

The implants are grouped into POP and hernia meshes as indicated on their official product insert. Each parameter is shown in a bar graph as well as standard box plots in order to visualize differences between the two groups. To determine statistical significance, the Wilcoxon-rank sum-test (equivalent to the Mann-Whitney U-test) is applied for each parameter.

3.3.3 Results and Discussion

**Results**  Figure 3.12 shows the uniaxial secant stiffness \( K_{uni} \) [N/mm] of each specimen grouped – according to the manufacturer indication – into POP (red) and hernia (blue) meshes, with the mean of each group shown in darker red and blue, respectively. The specific testing conditions (dry/embedded and 1\(^{st}\)/10\(^{th}\) cycle) are indicated in each sub-graph. Figure 3.13 represents the corresponding biaxial secant stiffness \( K_{bi} \) [N/mm]. The respective stiffness values for each configuration are reported in Tables 3.5 (POP meshes) and 3.6 (hernia meshes).

<table>
<thead>
<tr>
<th>( K ) [N/mm] POP meshes</th>
<th>DMPRS</th>
<th>PE</th>
<th>Restorelle</th>
<th>UT</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>uniaxial, dry, 1st cycle</td>
<td>19.2</td>
<td>1.8</td>
<td>5.2</td>
<td>4.0</td>
<td>7.5</td>
</tr>
<tr>
<td>uniaxial, dry, 10th cycle</td>
<td>19.9</td>
<td>1.3</td>
<td>2.1</td>
<td>4.5</td>
<td>6.9</td>
</tr>
<tr>
<td>uniaxial, embedded, 1st cycle</td>
<td>14.6</td>
<td>1.7</td>
<td>4.8</td>
<td>2.4</td>
<td>5.9</td>
</tr>
<tr>
<td>uniaxial, embedded, 10th cycle</td>
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<td>1.2</td>
<td>1.8</td>
<td>4.7</td>
<td>6.9</td>
</tr>
<tr>
<td>biaxial, dry, 1st cycle</td>
<td>6.2</td>
<td>2.0</td>
<td>4.0</td>
<td>2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>biaxial, dry, 10th cycle</td>
<td>13.1</td>
<td>4.1</td>
<td>3.2</td>
<td>11.8</td>
<td>8.1</td>
</tr>
<tr>
<td>biaxial, embedded, 1st cycle</td>
<td>1.6</td>
<td>2.2</td>
<td>0.5</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td>biaxial, embedded, 10th cycle</td>
<td>11.3</td>
<td>3.2</td>
<td>2.5</td>
<td>1.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Table 3.5: Numerical values of stiffness for all POP meshes and all tested configurations.

Figures 3.14 and 3.15 depict the summarizing box plots for the two groups, for uniaxial and biaxial stiffness in each configuration.

The variability for the POP group is very large for all parameters, thus affecting the statistical significance of the differences observed. The Wilcoxon-rank-sum-test indicates a statistically significant difference between the POP and hernia groups for the biaxial stiffness in dry condition, both at the 1\(^{st}\) and 10\(^{th}\) cycle (\( p = 0.016 \) for both), see Figures 3.14 a), b) and 3.15 a), b). The POP meshes were 4 or 5 fold stiffer than the hernia meshes in the 1\(^{st}\) cycle and 10\(^{th}\) cycle, respectively.
Table 3.6: Numerical values of stiffness for all hernia meshes and all tested configurations.

<table>
<thead>
<tr>
<th></th>
<th>BM</th>
<th>DM</th>
<th>PM</th>
<th>SPMM</th>
<th>UP</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2.5</td>
<td>0.3</td>
<td>0.2</td>
<td>2.0</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>uniaxial, dry, 10th cycle</td>
<td>3.5</td>
<td>0.4</td>
<td>1.1</td>
<td>1.1</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>uniaxial, embedded, 1st cycle</td>
<td>1.4</td>
<td>0.5</td>
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<td>0.5</td>
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</tr>
<tr>
<td>uniaxial, embedded, 10th cycle</td>
<td>2.1</td>
<td>0.5</td>
<td>0.2</td>
<td>2.5</td>
<td>0.5</td>
<td>1.2</td>
</tr>
<tr>
<td>biaxial, dry, 1st cycle</td>
<td>0.4</td>
<td>1.4</td>
<td>1.3</td>
<td>0.7</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>biaxial, dry, 10th cycle</td>
<td>0.9</td>
<td>2.0</td>
<td>1.4</td>
<td>2.1</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>biaxial, embedded, 1st cycle</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>biaxial, embedded, 10th cycle</td>
<td>1.6</td>
<td>0.7</td>
<td>0.5</td>
<td>1.2</td>
<td>1.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

When comparing the mean and median stiffness for all configurations, POP implants are overall less compliant than hernia implants. Since the abdominal wall is known to be stiffer than vaginal tissue [132, 209], and if mechanical biocompatibility would be mainly dependent on similar properties to the implant area, one would expect a more compliant design for implants for POP compared to hernia. Embedding a mesh into a polymer matrix, thus reflecting interaction with native tissue, affects the mechanical response of the implants. The differences between the groups are still evident also for this case (see Figures 3.12 to 3.15, c, d)).

High density and small pores are often linked to high stiffness in prosthetic meshes [138, 140]. When comparing the POP and hernia groups, no statistically significant difference can be found in these parameters (see Figures 3.16 and 3.17). However, tendencies can be seen with the hernia meshes being heavier (and similarly porous), while still being in general more compliant.

**Discussion**  Better clinical outcome might be expected from meshes designed to mimic the physiologically relevant deformation behavior of the underlying native tissue, thus ensuring mechanical biocompatibility. This entails a meaningful stiffness reference target for mesh design. However, the physiological loading configuration as well as the range of load levels in terms of membrane tension in the abdominal and vaginal wall still remain largely uncertain. While membrane tensions in the abdominal wall are generally higher [136] than in the pelvic region (simply due to geometric reasons, as shown in Ozog et al. (2014) [200]), increasing the level of membrane tension at which the secant stiffness is evaluated for the hernia meshes to a level of 0.136 N/mm (reported in Ozog et al. (2014)
Figure 3.12: Uniaxial secant stiffness $K_{uni}[N/mm]$ for all meshes in 4 configurations: a) dry mesh, 1st cycle; b) dry mesh, 10th cycle; c) embedded mesh, 1st cycle; d) embedded mesh, 10th cycle. POP meshes are shown in red, hernia meshes in blue. The mean of each group is plotted darker.

[200] as a tension at rest in the abdominal wall), only marginally increases their stiffness and does not change the trends reported in Figures 3.12-3.17.

The range of stiffness values for native tissue reported in the literature shows large variation and is mostly based on uniaxial tensile tests, while the predominant loading state in vivo is biaxial. Song et al. (2006) [240] report a Young’s Modulus of 0.042 $N/mm^2$ and 0.0225 $N/mm^2$ in transverse and sagittal plane, respectively, for human abdominal wall during in-vivo insufflation, which would translate to membrane stiffness values of 1.26 $N/mm$ and 0.675 $N/mm$, respectively, multiplying by the reported thickness of around 30mm [240]. Analyzing the uniaxial stress-strain graphs shown in Gabriel et al. (2011) [95], abdominal skin has a secant stiffness of 1.7 $N/mm$ at a membrane tension reference of 0.136 $N/mm$, whereas vaginal wall stiffness is 1.45 $N/mm$ at a reference of
0.035 $N/mm$ membrane tension. Rabbits are one model system for mesh performance evaluation. Analysis of the stress-strain curves in Hernandez et al. (2011) [110] yields uniaxial stiffness values for the abdominal wall complex of rabbits of $0.87 - 0.98 N/mm$, whereas Röhrnbauer et al. (2013) [228] report $0.28 N/mm$ at the same reference membrane tension of $0.136 N/mm$. Biaxial stiffness under inflation however increases by an order of magnitude to $2.41 N/mm$. Similarly, vaginal wall tissue stiffness values at a reference membrane tension of $0.035 N/mm$ reach from $0.155 N/mm$ (prolapsed tissue [209]), $0.675 N/mm$ (healthy tissue [95]), $1.4 N/mm$ (prolapsed tissue [230]), up to $6.47 N/mm$ (healthy tissue [230]).

This variability is due to differences in experimental methodology, in-vivo vs. ex-vivo testing, cadaver testing, animal tissue vs. human tissue, pathological vs. healthy tissue,
3.3. Comparison of Biomechanical Properties of Hernia and Pelvic Prolapse Meshes

Figure 3.14: Box plots for uniaxial secant stiffness $K_{uni}$ [N/mm] for all meshes in 4 configurations: a) dry mesh, 1st cycle; b) dry mesh, 10th cycle; c) embedded mesh, 1st cycle; d) embedded mesh, 10th cycle. The red line marks the median of the group, the box represents the 25th and 75th percentile, the extended whiskers the most extreme data points. The + sign indicates an outlier.

as well as the inherent variability of biological soft tissues. This scatter poses a significant problem in determining meaningful mechanical design targets for prosthetic mesh implants and warrants further investigation. Focus should be on the definition of consistent testing procedures based on physiological, in-vivo loading and stress magnitude conditions.

It has to be noted that the approach of mimicking the ingrown state of the mesh using an elastomer matrix is only partially representative of the in-vivo condition. This is mainly due to the differences between the embedding procedure and the process of tissue ingrowth. A mesh sample is simply laid into liquid elastomer and the elastomer left to cure. This results in an elastomer-mesh complex that is formed in an unloaded initial configuration, while in-vivo ingrowth might be expected to happen in a loaded state. Due
Figure 3.15: Box plots for biaxial secant stiffness $K_{bi}$ [N/mm] for all meshes in 4 configurations: a) dry mesh, 1\textsuperscript{st} cycle; b) dry mesh, 10\textsuperscript{th} cycle; c) embedded mesh, 1\textsuperscript{st} cycle; d) embedded mesh, 10\textsuperscript{th} cycle. The red line marks the median of the group, the box represents the 25\textsuperscript{th} and 75\textsuperscript{th} percentile, the extended whiskers the most extreme data points. The + sign indicates an outlier.

to this discrepancy the definition of a secant stiffness between tension values chosen here (pre-force threshold as defined in the experimental protocol and reference membrane tension) might not be representative of the actual in-vivo load range. This further highlights the need to investigate the expected in-vivo loading conditions of mesh implants so to define testing protocols that reproduce physiological states.

When comparing individual meshes in terms of their physical and mechanical parameters, an instructive example can be seen in two meshes manufactured by FEG Textiltechnik: Dynamesh Endolap (DM), used in hernia repair, and Dynamesh PRS (DMPRS), used for pelvic prolapse repair. While their porosity is similar and DM is indeed the heavier of the two, as expected for a hernia mesh, DMPRS is much stiffer in all tested configurations, and up to two orders of magnitude in case of uniaxial tension.
3.3. Comparison of Biomechanical Properties of Hernia and Pelvic Prolapse Meshes

Figure 3.16: a) Porosity and b) area density of all meshes. POP meshes are shown in red, hernia meshes in blue, with their respective mean values plotted darker. Porosity is shown as the inverse of pore size, i.e. higher values represent smaller pores.

Figure 3.17: Box plots for a) porosity and b) area density of all meshes. The red line marks the median of the group, the box represents the 25th and 75th percentile, the extended whiskers the most extreme data points. Porosity is shown as the inverse of pore size, i.e. higher values represent smaller pores.

Similarly, Restorelle (a POP mesh) is the lightest implant with the largest pores, however its stiffness is clearly above average for most tested configurations. Restorelle is less compliant in the configurations tested here than SPMM, the heaviest, small-pore implant. Note that in previous studies [88, 130, 235] Restorelle was shown to be more compliant than some of the meshes tested here. This can be attributed to the differences in experimental protocols. In particular, the present experiments evaluate the response of meshes at a physiological tension level. Thus the low deformation regime determines the measured stiffness in the present work, whereas the ball burst test in Feola et al. (2013)
Lightweight and large porous meshes might be expected to be more compliant than heavy, small porous implants [88]. However, the present analysis shows that while POP meshes are on average indeed lighter and often have larger pores, they are generally stiffer in the physiological loading regime. In these loading configurations porosity and density alone cannot be predictors for mesh stiffness. Their specific knitting pattern and microstructure can lead to mechanism-like behavior in a physiological loading range, effects that determine their compliance. This calls for a careful evaluation of the mechanical properties of each mesh on several length scales, in conditions representative of those expected in-vivo. The present experimental results do not take into account loads in directions other than the main knitting patterns. In fact, the meshes are usually implanted such that their knitting pattern aligns with principal loading directions, such as in line type suspensions (e.g. urethral slings) or sacrocolpopexy procedures. Some meshes, as DM, UP and PE even have colored filaments interwoven, guiding the physician during implantation. Deviation from this rule might lead to a mechanical response which strongly differs from the data reported here. Similarly, while each mesh was tested in two perpendicular directions, only the stiffer of the two is considered for the present analysis, being indicative of an upper bound of stiffness. Knitted meshes do indeed tend to behave in an anisotropic way, as investigated in [173], with anisotropy indices ranging from 1.0 for SPMM (similar stiffness in both evaluated directions) to 8.0 for DMPRS. In addition, only one sample per configuration has been tested due to limited availability of raw mesh material, which also limited sample size. However, the level of variability for mesh implants reported in literature [73, 87, 173, 235] is low, justifying the conducted analysis.

3.3.4 Conclusions

The mechanical biocompatibility of prosthetic mesh implants for hernia and POP repair very likely is an important factor in ensuring their functionality and integration into the host tissue. We see matching mechanical properties in a physiological loading range as desirable and an important step towards reducing clinical complications. This study has shown that some meshes designated as suited for POP repair tend to be stiffer than those used for hernia repair, even though the abdominal wall has been shown to be less compliant than the vaginal wall. Additionally, the expectation of lightweight, large porous meshes being more compliant than their counterparts was contradicted by the present data and specific testing configurations, indicating that a biomechanical analysis of each product is necessary to determine its mechanical suitability. Knowledge of
the physiological, in-vivo mechanical environment in terms of loading configuration and magnitude is required in order to define a suitable design target for optimization of implants. Data reported in literature show large variations in testing configurations and corresponding stiffness values for pelvic organs and abdominal wall tissue. Consensus for a standardized, physiological mechanical testing procedure is needed for native tissues and implants, opening the path for a conscious mechanical design of prosthetic meshes.
3.4 Repair of Pelvic Pathologies: Finite Element Simulation of Sacrocolpopexy

3.4.1 Introduction

Total hysterectomy is an invasive procedure entailing the removal of the cervix and whole uterus due to fibrosis, cervical or uterine cancer, abnormal uterine bleeding or prolapse of the uterus [124, 178, 261]. Over 600,000 hysterectomies are performed each year in the US, with 23.3% of women aged 18 or older being affected [178]. The most common approach is abdominal hysterectomy (approximately 60%), with vaginal and laparoscopically assisted vaginal hysterectomy accounting for the rest [78, 178]. The procedure can lead to a relief of POP symptoms in case of a uterine descent [211], however a major consequence of this removal of support to the vagina is the vaginal vault prolapse, accounting for more than 30,000 surgical procedures [215]. Abdominal sacrocolpopexy is considered the most durable procedure to repair vaginal vault prolapse, with a long-term success rate of 74% [114]. It consists of attaching the two lower arms of a Y-shaped synthetic mesh implant to the anterior and posterior wall of the vaginal stump. The remaining upper mesh arm is affixed posteriorly to the sacrum, thus suspending the vagina superiorly and restoring stability to the system [83, 91, 123], see Figure 3.18. The goal is to attach the mesh in a tension-free state [247]. While these procedures are in general successful [24], mesh erosion is reported in up to 10% of the cases and requires additional interventions [141, 262]. A mismatch of mechanical properties of the implants compared to native tissue has been proposed as a possible cause of clinical complications [52, 69, 86, 87, 160], and it has recently been suggested that meshes designed to mimic biomechanical properties of the area of application, thus providing mechanical biocompatibility, are advantageous [173, 175, 201, 202, 227].

The finite element model presented in Chapter 2 forms the basis for the investigation of the sacrocolpopexy procedure as well as the influence of mechanical properties of the mesh, surgical technique and local effects on the outcome and interaction of mesh and vagina. To the author’s knowledge this represents the very first attempt at modeling a repair procedure of pelvic prolapse.

The results presented in this section are based on the findings reported in [177].

3.4.2 Methods

The original geometry of the vaginal canal had to be adapted to form the vaginal stump after removal of the uterus. This was realized by eroding the raw geometry of the vagina
3.4. Repair of Pelvic Pathologies: Finite Element Simulation of Sacrocolpopexy

Figure 3.18: Illustration of the sacrocolpopexy procedure after hysterectomy. The vaginal stump is suspended by a Y-shaped mesh implant superiorly at the sacrum. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography ©2015. All Rights Reserved.

Figure 3.19: Geometrical adjustment from (a) original vaginal canal to (b) vaginal stump. The lower mesh arms were adapted to mold around the vaginal surface (c). Note that the shells are displayed without thickness information, accounting for the apparent gap between the two parts. Shown are FE meshes in Abaqus.

superiorly within Geomagic until a stump shape fitting to anatomical descriptions was generated (see Figure 3.19). The steps described in Section 2.2.1 were repeated to prepare the part for import into Abaqus, remeshing it and replacing the original vaginal canal in the main assembly of the FE model.

A total hysterectomy includes removal of uterus and cervix, thus disrupting all superior supportive structures to the vaginal canal [211]. Therefore all ligaments (uterosacral liga-
ments, paravaginal ligaments) as well as the bladder – and with it the omiblical ligament – and the interface between bladder and vagina were removed from the FE model accordingly. The pelvic floor muscle sheet and vaginal stump are the sole biological structural elements considered for the present analysis (Figures 3.20 and 3.22).

![Image of FE model](image.png)

Figure 3.20: Reduced FE model for simulation of sacrocolpopexy after hysterectomy. Shown are the pelvic muscle sheet, vaginal stump and sacrocolpopexy mesh. The bony frame serves as a display body and has no influence on the analysis.

The new vaginal stump was remeshed with 3923 S4 elements, with thickness identical to the vaginal canal as implemented in the full model.

DynaMesh PRS (see Section 3.2) was implemented as the mesh for the sacrocolpopexy procedure. It is specifically advertised by the manufacturer for repair of vaginal vault prolapse after hysterectomy. Geometry and shape of the implant are adopted from the description of the manufacturer. It is a 15 mm wide, Y-shaped construct consisting of two lower arms of 40 mm length, enclosing the vaginal stump, and one upper arm of 90 mm length, affixed to the sacrum superiorly (Figure 3.21).
3.4. Repair of Pelvic Pathologies: Finite Element Simulation of Sacrocolpopexy

The two sections of the mesh were implemented separately as individual parts in Abaqus as continuum shells and meshed with a total of 2520 linear quadrilateral shell elements of type S4R with reduced integration, necessitated by the modeling as a non-linear hyperelastic material (see below). Note that this continuum approach allows for the analysis of the global mechanical response of the model, however cannot predict local, non-affine effects on a pore-level [173].

In order to adapt the geometrical shape of the initially flat and straight lower mesh arms to the surface of the vaginal canal, a submodel was built and simulated. The vaginal stump was modeled as a rigid body, fixed in space. The V-shaped lower mesh arms were positioned superior-inferiorly to the vagina and all six degrees of freedom fixed at the apex of the V-shape, thus allowing only the mesh arms to move and deform. By applying pressure to the outer surfaces of the soft mesh, it could be molded around the superior and inferior surfaces of the vaginal stump, matching its surface topology (Figure 3.19 c). Penetration of mesh into vagina was prevented by defining hard surface-to-surface contact between the respective surfaces. The deformed, adapted geometry of the lower mesh arms was reimported into the sacrocolpopexy FE model (Figure 3.22).

The mesh was modeled as a hyperelastic material with a reduced polynomial material description \( (n = 2) \) with strain energy potential \( U = C_{10} (I_1 - 3) + C_{20} (I_1 - 3)^2 \). In order to compare the influence of mesh material on the response of the model, two sets of material parameters were generated representing DynaMesh PRS in \( 0^\circ \) direction as a stiffer mesh intended for sacrocolpopexy, and DynaMesh Endolap in \( 0^\circ \) direction, representative of a softer mesh. Note that while mechanical parameters representative of DynaMesh Endolap were applied, the geometry selected corresponds as before to the DynaMesh PRS implant. Parameters \( C_{10} \) and \( C_{20} \) were obtained by fitting of the tension-strain response to uniaxial and strip biaxial experimental data gathered in the framework of the study described in Section 3.2. The material parameters of the lower mesh arms in contact with the vaginal stump were based on experimental data of the respective mesh embedded.
into an elastomer matrix, representative of tissue ingrowth [173], with the thickness of the mesh-elastomer complex of 1 mm assigned to the FE shells of the lower arms. The upper mesh arm on the other hand was assumed to be in a dry, as delivered state, since it is not attached to any tissue. Therefore, experimental data of the dry meshes served as a basis for material parameter fitting as well as thickness assignment (0.2 mm) within the FE model. Note that a hyperelastic model implies that the loading and unloading response of the material are identical, whereas for the meshes this is not necessarily the case due to unrecoverable structural changes in the first cycle, leading to energy dissipation and residual strains (refer to the tension-strain curves of the experimental campaign in Section 3.2 and Appendix 7). An extension to the model to capture these effects might improve the accuracy, however also increases numerical complexity. Refer to Table 3.7 for an overview of geometrical and material parameters, with the respective experimental data and material fit shown in Figure 3.23.

Upper and lower mesh arms were coupled in all six degrees of freedom at their connection line. The fixation of the upper mesh arm to the sacrum was modeled by restricting all three translational degrees of freedom at the most superior line. Attachment of the lower mesh arms to the superior and inferior vaginal wall is realized by sutures in vivo,
3.4. Repair of Pelvic Pathologies: Finite Element Simulation of Sacrocolpopexy

<table>
<thead>
<tr>
<th>thickness [mm]</th>
<th>upper mesh arm dry</th>
<th>lower mesh arms embedded</th>
</tr>
</thead>
<tbody>
<tr>
<td>material parameters</td>
<td>DynaMesh PRS</td>
<td>DynaMesh Endolap</td>
</tr>
<tr>
<td>$C_{10}$ [MPa]</td>
<td>12.00</td>
<td>0.18</td>
</tr>
<tr>
<td>$C_{20}$ [MPa]</td>
<td>0.77</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Table 3.7: Thickness and material parameters for the upper and lower mesh arms as well as different mesh materials.

the exact positioning of which depend on the surgeon as well as accessibility [247]. In a first approximation, 8 suture positions were implemented in the FE model, with each 4 symmetrical sutures on the superior and anterior surfaces (Figure 3.24). For each suture, a set of 4 neighboring nodes on the mesh were connected to an adjacent set of 4 neighboring nodes on the underlying vaginal stump. Connections were modeled as linear elastic, axial connectors with large axial stiffness of $20 N/[-]$ (equivalent of about $1 GPa$ for a filament of diameter $0.15 mm$) in tension and no stiffness in compression, representative of polypropylene sutures.

Material properties and boundary conditions for the pelvic muscle sheet as well as the interaction of vaginal canal and pelvic muscles in the inferior opening of the pelvic diaphragm remained identical to the full pelvic cavity model of the POP case described in Chapter 2.

The void inbetween vaginal canal and pelvic muscles is not empty in vivo, but rather filled with the rectum and connective tissue. The main contribution to the interaction between vagina and pelvic floor before hysterectomy is their connection through the paravaginal fascia, the support of which is lost after removal of uterus and cervix. In order to model their connection after hysterectomy, equations between the degrees of freedom of the nodes of the two organs are introduced, coupling the displacement between posterior vaginal wall and posterior region of the levator ani, allowing for mechanical interaction and transmission of loads.

Two sets of load cases were defined in order to examine the influence of surgical technique, in particular pretensioning of the mesh during implantation: (i) Valsalva pressure of $3.5 kPa$ on the superior surface of the pelvic muscle sheet, see Chapter 2; (ii) prestretch of $8 mm$ applied to the upper arm of the mesh, followed by Valsalva pressure of $3.5 kPa$ on the superior surface of the pelvic muscle sheet. The prestretch was applied as a dis-
Figure 3.23: Experimental data of the first loading cycle and material model fit for DynaMesh PRS (a) dry and (b) embedded as well as DynaMesh Endolap (c) dry and (d) embedded. For DynaMesh PRS, uniaxial and strip biaxial tension-strain data were fit simultaneously with one parameter set, whereas for DynaMesh Endolap only uniaxial tension-strain data were fit.

placement to the superior boundary of the upper mesh arm, along the direction of its longitudinal axis, pointing towards the sacrum.

**Discrete Mesh Model**  While the representation of a mesh implant as a continuum might give valuable insight into the global deformation behavior, it cannot represent interaction with native tissue and local meso- and micro-scale non-affine deformations [173, 224, 227]. This mismatch of deformation mechanisms at a micro scale may lead to uncontrolled local behavior, despite global properties matching the underlying tissue. This has already been demonstrated in controlled experiments with biaxial loading in Section 3.2. However, FE modeling allows for analysis of these effects in a state of deformation closer to physiological in vivo conditions.
3.4. Repair of Pelvic Pathologies: Finite Element Simulation of Sacrocolpopexy

In order to investigate local interactions between mesh and vaginal tissue, the lower portion of the inferior lower mesh arm in the FE model, which is in contact with the inferior wall of the vaginal stump, has been replaced by a discrete beam model (see Figure 3.25). The geometrical dimensions and shape are based on the DynaMesh PRS implant, where each beam represents multiple interwoven strands of polypropylene and corresponds to one edge of a unit cell of the mesh. The submodel consists of $12 \times 14$ rectangular unit cells, with $1.25 \, mm$ width and $1.5 \, mm$ height each. That results in a total amount of 362 beams, implemented in Abaqus as linear line elements of type B31 with circular cross-section of diameter $0.2 \, mm$, based on average thickness measurements of the dry
DynaMesh PRS implant. Beams were modeled as linear elastic with stiffness of 75 $MPa$, matching the uniaxial stiffness of the PRS mesh in experiments (Section 3.2, Figure 3.26). The beam model is oriented along one of the main orientations of the mesh, matching the sacrocolpopexy kit as supplied by the manufacturer. The molding process described above for the continuum mesh model has been similarly applied to the discrete beam model, allowing it to reshape and fit the surface topology of the inferior vaginal wall. Beam model and remaining continuum model were connected by coupling all six degrees of freedom of the most superior nodes of the discrete model and most inferior nodes of the continuum model. Sutures were again realized by axial connectors between one node in the beam model and one adjacent node of the vaginal stump, at two symmetrical positions (Figure 3.25, red circles). Contact was implemented as normal hard contact, allowing for separation of master and slave surface, as well as frictionless tangential contact.

![Graph](image)

Figure 3.26: Comparison of uniaxial experimental data for dry DynaMesh PRS in $0^\circ$ direction (black curve) and the linear elastic uniaxial response for the beam material with equivalent elastic modulus of 75 $MPa$ (grey curve).

Note that the discrete beam model represents the dry mesh, i.e. the condition immediately after implantation. Therefore the geometrical and material parameters of the remaining continuum model of the lower mesh arms had to be adjusted from an embedded state to the dry state, see Table 3.7. The model therefore represents mesh-tissue interaction in an initial phase after implantation.

In order to directly compare the full continuum with the discrete approach in terms of...
global and local mechanical response, the continuum model was adjusted as well, replicating the dry mesh mechanical behavior with only two inferior sutures at the same locations compared to the discrete beam model.

Quantitative Comparison of the Local State of Deformation. As a quantitative measure of local non-affinity of the deformation in the mesh with respect to the vaginal canal, the local state of deformation was characterized as follows.

Let \( G_1, G_2 \) be the two normalized base vectors in the undeformed reference configuration, spanning a unit cell of the discrete beam model of the mesh adjacent to the suture position (Figure 3.27). The third base vector \( G_3 \) is orthogonal to both \( G_1 \) and \( G_2 \) and is defined as the cross product

\[
G_3 = G_1 \times G_2.
\]  

The triple \( g_1, g_2, g_3 \) are their deformed equivalents in the current configuration. \( (G_1, G_2, G_3) \) and \( (g_1, g_2, g_3) \) form curvilinear bases in the reference and current configuration, respec-

Figure 3.27: Normalized base vectors in undeformed (a, c) and deformed (b, d) configuration for the continuum mesh model (a, b) and discrete beam mesh model (c, d).
The components of the metric \([G_{ij}]\) are defined as
\[
G_{ij} = G_i \cdot G_j, \quad i, j = 1..3, \tag{3.3}
\]
with \([G^{ij}] = [G_{ij}]^{-1}\) being its inverse. This allows for the definition of the contravariant base vectors in the reference configuration as
\[
\vec{G}^i = G^{ij} \vec{g}_j, \quad i = 1..3, \tag{3.4}
\]
with the Einstein summation convention to be used for the index \(j = 1..3\). The deformation gradient \(F\), the right Cauchy-Green tensor \(C\) and the Green-Lagrange strain tensor \(E\) are then defined as
\[
F = g_i \otimes G^i, \tag{3.5}
\]
\[
C = F^T F, \tag{3.6}
\]
\[
E = \frac{1}{2} (C - I), \tag{3.7}
\]
with \(I\) being the identity tensor in \(\mathbb{R}^3\) and again the Einstein summation convention to be used for index \(i = 1..3\).

This derivation is repeated for two equivalent base vectors along the edges of a continuum element adjacent to the suture point within the continuum mesh model as well as the vaginal canal, leading to the triple of strain tensors \(E^\text{beam}\) (discrete beam model of the implant), \(E^\text{conti}\) (continuum model of the implant) and \(E^\text{vag}\) (vaginal canal). Based on these, the following two affinity measures are introduced, with \(\text{case}\) being either \(\text{conti}\) or \(\text{beam}\):

(i) The norm of the second order tensor \(\Delta E^\text{case}\) \([122]\) as a doublecontraction of itself onto itself
\[
\| \Delta E^\text{case} \| = \sqrt{\Delta E^\text{case} : \Delta E^\text{case}}, \tag{3.8}
\]
where \(\Delta E^\text{case} = E^\text{case} - E^\text{vag}\). It is a measure of global difference in deformation of the mesh and the vaginal canal.

(ii) The difference of shear strain between mesh and vaginal canal in the plane of the mesh
\[
n^\text{case}_\gamma = \Delta [E]^\text{case}_{12}. \tag{3.9}
\]
3.4.3 Results

In this first part, global results of the initial sacrocolpopexy model are presented, with 4 symmetrical sutures on each the superior and inferior mesh arm as well as the embedded material model for the lower mesh arms.

Comparing the downward motion of the vaginal stump at Valsalva pressure in the state after the hysterectomy procedure with no implanted mesh to the case with implanted mesh, a clear reduction of 50% is apparent (Figure 3.30 a). In addition, applying a pre-stretch before the Valsalva maneuver does reduce the downward motion further by about 30% (Figure 3.30 a). The reduction of vaginal movement is also clearly visible in sagittal cuts of the deformed geometry, see Figure 3.28. The upward pull applied to the mesh prior to increasing intra abdominal pressure pretensions it, increasing vaginal superior support and preventing greater downward displacement.

![Figure 3.28: Sagittal cut of the deformed sacrocolpopexy model at Valsalva pressure. (a) Without prestretch, (b) with prestretch.](image)

The pronounced effects of mesh pretensioning are also observable in the forces acting at the mesh fixation sites at the sacrum and inferior and superior vaginal wall (Figure 3.29). While they are in the range of $0.3\, N$ at the sacrum and $0.1\, N$ at the suture positions when applying Valsalva pressure without prior prestretching of the implant, they do rise significantly by an order of magnitude when applying prestretch. In fact, pretensioning of the mesh accounts for 86%, 62% and 91% of the total reaction force at the sacrum, inferior and superior vagina, respectively. The Valsalva maneuver only leads to a small additional increase.
Forces at Sacrum
Force [N]
vallsalva prestretch + vallsalva
after prestretch
at Valsalva

Forces at Inferior Vagina
1.4
valsalva prestretch + vallsalva

Forces at Superior Vagina
1.4
valsalva prestretch + vallsalva

Figure 3.29: Forces in (a) the mesh at the sacrum fixation, (b) the inferior vaginal suture positions, (c) the superior vaginal suture positions. Sacrocolpopexy model without (left bar) and with prestretch (right bars).

The use of a softer mesh, represented here by DynaMesh Endolap and 2 orders of magnitude more compliant than DynaMesh PRS, has a strong impact on both, vaginal displacement and especially forces acting within the mesh. While the downward motion increases by only about 12% for the soft mesh when applying only Valsalva pressure, the difference is much larger for the case with prestretch (Figure 3.30 a). In fact, pretensioning the softer implant does not significantly reduce vaginal motion during Valsalva.

Vaginal Displacement
Displacement [mm]
no mesh PRS Endolap
valsalva
valsalva prestretch + vallsalva

Forces at Sacrum
Force [N]
PRS Endolap PRS Endolap
valsalva prestretch + vallsalva

Figure 3.30: (a) Vaginal displacement, (b) forces in the mesh at the sacrum fixation. Comparison of sacrocolpopexy model without and with prestretch as well as stiff mesh (DynaMesh PRS) and soft mesh (DynaMesh Endolap).

Most interestingly however, are the changes in reaction forces acting in the mesh at its fixation points when implementing a softer mesh. Without prestretch, forces in the Endolap implant are only about 9% of the ones in the stiff PRS mesh. An additional pretensioning naturally does increase loads in the implants, however the large difference of one order of
magnitude between the two remains. However, forces during the Valsalva maneuver are notably similar comparing the stiff PRS mesh without prestretch to the softer Endolap implant with prestretch (Figure 3.30 b).

**Local Interaction Between Mesh and Vaginal Tissue.** The absolute values of maximum in-plane stresses as well as the stress patterns in the inferior vaginal canal are almost identical for the continuum and discrete beam model (Figure 3.31). Maxima are naturally found at the suture positions in the order of $0.12 - 0.14 \, N/mm^2$, a factor of 15 to 50 smaller than the rupture strength of $2.12-6.06 \, MPa$ reported for vaginal tissue of POP patients [230]. However, while the continuum mesh model allows for a global analysis of the mechanical behavior, it intrinsically behaves affinely to the far field deformation. The discrete beam model on the other hand behaves mechanism-like on a meso-scale, exhibiting non-affine deformation patterns on a local unit-cell length-scale. This difference is clearly highlighted comparing the deformed configuration of both models (Figure 3.32) with identical loads applied to the whole system (prestretch and consecutive Valsalva pressure). The continuum elements deform similarly within the whole mesh arm (Figure 3.32 a), dictated by the global deformation, whereas the beam model exhibits a strong variation in deformation pattern from region to region. While the most superior unit cells connected to the remaining continuum mesh model deform uniformly, the cells close to the suture position locally show a strongly non-affine behavior with filament

![Figure 3.31: Maximum in-plane stresses in the vaginal stump after application of pre-stretch and Valsalva pressure. (a) Continuum model, (b) beam model. Maxima are indicated separately.](image-url)
Figure 3.32: Deformed configuration of the mesh models after application of prestretch and Valsalva pressure. (a) Continuum model, (b) beam model.

Figure 3.33: Non-affinity measures comparing the continuum and discrete beam model with two symmetrical suture. (a) Tensor norm of the difference of Green-Lagrange Strain tensors of the mesh and vagina ($\| \Delta E^{\text{case}} \|$) as a global non-affinity measure. (b) Shear parameter $n_{\gamma}^{\text{case}}$ as a measure of difference in shear deformation in the mesh and vagina.

This qualitative assessment can be quantitatively supported by the affinity parameters introduced in Section 3.4.2. The tensor norm is a strong indication of the deformation differences between vaginal canal and mesh model in the vicinity of the sutures. While it is rather small for the continuum model ($\| \Delta E^{\text{conti}} \| = 0.06$), it is indeed one order of magnitude larger for the discrete model ($\| \Delta E^{\text{beam}} \| = 0.83$) (see also Figure 3.33 a). Going further into detail and quantifying the differences in shear mode deformation, the non-affine patterns in the beam model become even more pronounced. A value of 0 for
In order to compare these measures of local deformation mismatch at the sutures with the far field deformation of mesh and vaginal canal, the relative sliding displacement in the superior region of the mesh-vagina contact patch has been evaluated (Figure 3.25). It amounts to about 2.6 $mm$ for the continuum model and about 3.5 $mm$ for the discrete mesh model with two sutures, about 17% – 23% of the total contact patch length of approximately 15 $mm$. However, the normal contact forces in that superior region are only 0.03 $N$ for the continuum model and 0.025 $N$ for the beam model. In addition, the outer most edges in the inferior mesh portion close to the sutures separate from the underlying vaginal canal, curling outwards, which is shown in detail in Figure 3.34.

3.4.4 Discussion

For the first time, a pelvic organ prolapse repair strategy, in particular the sacrocolpopexy after a hysterectomy procedure, has been simulated with the aid of the finite element method. Relevant questions regarding the in vivo mechanical behavior of prosthetic meshes were raised and qualitatively, but also quantitatively answered.
How does surgical technique influence mechanical outcome? The goal of the sacrocolpopexy procedure is to suspend the vagina superiorly and restore stability to the pelvic system [83, 123]. It is desirable to attach the mesh in a tension-free state [6, 91, 247]. In fact, several studies suggest that excessive tension in the mesh might lead to undesirable clinical complications. Gadonneix et al. (2004) [96] mention obstructed defecation or de novo urinary incontinence as a consequence of overtensioned mesh, whereas Fatton et al. (2007) [79] state that it increases the risk of post-operative pain and shrinkage, which has also been noted by Milani et al. (2009) [179]. Tension in the mesh is believed to result in mesh disjunction at the sacrum or alterations of anterior vaginal wall anatomy with resultant stress incontinence [166].

However, no clear explanation as to the possible reasons of these complications is given. With the results presented here, conclusions with respect to the mechanical causes might be drawn. As expected, the implantation of a mesh improves mechanical support of the vaginal stump, reducing its downward movement by 50%. In addition, applying a prestretch of 10 mm, which amounts to only about 10% of the upper mesh arm length, further improves superior support, as it reduces downward motion during the Valsalva maneuver by another 30% (Figures 3.30 a) and 3.28). Note that the POP-Q System [37] defines a relative motion of the anterior and posterior vaginal wall with respect to the hymen, resulting from an outward protrusion of the vagina, as a parameter for classification of POP. The downward motion of the vagina as observed here might not be a clinically relevant parameter for the assessment of pelvic prolapse, however it is a measure of the mechanical effectiveness of the suspension by the mesh.

The forces acting at the sacrum fixation, and most crucially at the suture positions to the vagina, increase by an order of magnitude (Figure 3.29). These high loads at concentrated points of force introduction might lead to adverse tissue reactions and increased tissue deformation, which has been related to nerve damage, the major cause of pain [62, 216, 219]. In fact, Fisher et al. (2011) [90] mention mechanical distortion of nerves as possible causes for pain after retropubic sling implantation for urinary incontinence.

Surgical technique includes fixation of the mesh to the vaginal canal and sacrum by suturing, the influence of which will be discussed below.

How does mesh material influence mechanical outcome? Another profound effect on the outcome of the procedure can be observed when changing the mesh material to a softer implant, with a uniaxial stiffness lower by two orders of magnitude. While the vaginal displacement does, as expected, increase for both, the Valsalva maneuver without prestretch as well as with prestretch, it is within a range of 20-50% when compared to the stiff mesh. In fact, the specific geometrical relations in the present model may be the
reason for the relatively small differences in downward movement for the soft and stiff mesh. Figure 3.35 is a simplified representation of the pelvic floor, vaginal stump and mesh. Application of Valsalva pressure onto the pelvic sheet results in downward rotation of the vaginal stump. Without a mesh, this movement is governed by the compliance of the pelvic floor. The mesh, being in effect much stiffer than the pelvic sheet, will add support to the vagina. However, the main axis of loading in the mesh and the displacement vector of the vaginal canal do not coincide, especially in the beginning of the Valsalva maneuver, leading to the pelvic floor compliance (lower spring) dominating the support of the vagina. As the pressure and thus the vaginal downward rotation increase, the long axis of the mesh and displacement vector of the vagina start to converge, increasing the influence of the mesh (upper spring) in the support of the vaginal stump. This peculiar geometrical relation can give indications as to the relatively small difference in vaginal movement comparing a very stiff with a very soft mesh, since the support of the vagina in a part of the displacement range is dominated by the compliance of the pelvic floor, rather than the mesh itself.

Figure 3.35: Simplified representation of the sacrocolpopexy model with the vaginal stump (represented as a rigid beam), the mesh (represented by the upper spring) and the pelvic muscles and their interaction with the vaginal stump via coupling of degrees of freedom (represented by the lower spring and sheet). Application of Valsalva pressure onto the pelvic sheet results in downward rotation of the vaginal stump.

However, the resulting forces at the sacrum fixation are significantly lower for the soft mesh, by one to two orders of magnitude. The increase in loads within the mesh and thus also within the tissue when applying prestretch prior to Valsalva pressure is in a similar range for the DynaMesh PRS and DynaMesh Endolap meshes. Most notably, the appli-
cation of prestretch to the softer implant prior to increased abdominal pressure results in forces similar to those in the stiff mesh without prestretch (Figure 3.30 b)), indicating that the soft and possibly favourable response of the Endolap mesh is counteracted by a pretensioning. This again hints at the importance of proper surgical technique, being crucial for a mechanical response of the system as can be expected by the mesh properties. It might not only be necessary to implant softer meshes, but also to ensure desired handling of the material during implantation in order to provide mechanical biocompatibility.

It has to be noted, that the mesh type chosen here for the soft implant (DynaMesh Endolap) is in fact not used for the sacrocolpopexy procedure. It served here as a demonstration of an extreme case with a very low stiffness compared to the DynaMesh PRS mesh, allowing to accentuate the differences and resulting outcomes. In addition, experimental data for material parameter fitting were readily available from the extensive experimental campaign presented in Section 3.2.

**Further insights with a discrete mesh model.** The continuum mesh model allows for global assessment of the mechanical behavior and interaction between implant and underlying tissue. Global strains in the mesh arms, kinematic behavior of the pelvic system or forces and stresses acting in the sutures can be analyzed, as demonstrated above. However, synthetic prostheses do not behave like a continuum on a local scale, but rather like a mechanism, exhibiting non-affine deformation patterns on a local, filament level, not matching the global far field [173, 224, 225, 175]. In order to evaluate such phenomena, a simplified discrete beam model of the DynaMesh PRS mesh has been implemented in the sacrocolpopexy model. The stresses acting in the vaginal canal at the suture positions are very similar when comparing continuum to discrete model (Figure 3.31), the stiffness of which has been chosen to mimic the uniaxial response of the continuum model. However, already purely visual inspection of the local deformation behavior at the level of unit cells reveals stark differences (Figure 3.32). In the region close to suture points, individual unit cells of the discrete model distort strongly, exhibiting large shearing motions. The outer edges, particularly in the inferior portion of the model, detach from the vaginal canal and bend outwards, as is intuitively common for such woven textiles in similar situations of load introduction at isolated points. The continuum model on the other hand behaves homogeneously, as expected from such an approach. These folding effects due to specific boundary conditions induced by suturing has recently been examined systematically by Barone et al. (2015) [19]. Both tested meshes (GyneMesh and Restorelle) show pronounced longitudinal wrinkling and folding of the edges when introducing forces through single suture points (Figure 3.36 c, f). It has to be noted that while the forces applied in the controlled uniaxial experiments are at least one order of magnitude higher (i.e. 10 N)
than those in the FE model, similar tendencies of edge folding and wrinkling emerge in the simulations (Figure 3.34). These large distortions, both in-plane (i.e. shear deformation and pore collapse) as well as out of plane (i.e. folding and wrinkling) lead to a local mesh material concentration and could lead to a stronger foreign body response of the tissue, leading to complications such as mesh exposure [19].

![Figure 3.36: Contour map of Gynemesh (a)-(c) and Restorelle (d)-(f) at 10 N uniaxial extension, with different suture configurations. Figure reprinted from [19] with permission of the Journal of Biomechanics.](image)

In order to quantify the effects described above, a global and local non-affinity parameter have been introduced. They are a measure of (i) the difference in unit cell deformation of the mesh compared to the vaginal canal ($\|\Delta E^{\text{case}}\|$) and (ii) the local rotation and shear of a mesh unit cell compared to the global, homogeneous deformation of the vaginal canal ($n^{\gamma}_{\text{case}}$). And in fact, the observations described above hold true in a quantifiable manner. The difference in global deformation between vaginal canal and mesh in the vicinity of the suture points, including both axial stretches as well as shear components in all directions ($\|\Delta E^{\text{case}}\|$), is an order of magnitude larger for the discrete beam model. Isolating just the shear component in the plane of the mesh ($n^{\gamma}_{\text{case}}$), yields even bigger differences of two orders of magnitude comparing discrete to continuum mesh model (Figure 3.33), supporting the impressions gathered by visual inspection. These non-affine local effects could, similar to the localized force introduction, be an important mechanical factor contributing to clinical complications, causing adverse tissue reactions, micro injuries, inflammation...
and erosion. This might matter specifically in close proximity to the sutures, where the tissue is strongly fixed to the implant and already stressed. In the far field close to the apex of the vaginal stump, relative motion between organ and mesh is still prevalent, as shown by the relative sliding length of about $2 - 3 \, \text{mm}$. However, the very low normal contact forces of around $0.03 \, \text{N}$ indicate that the sliding motion of the mesh over the upper portion of the vaginal stump might not be as detrimental to the tissue as the interaction at the sutures. Tissue and implant move independently and more homogeneously, and while they may be in contact, they are not immovably fixed to each other. Note that the simulations might only be representative of a state right after implantation, before tissue ingrowth occurs, which might in fact change the tissue-implant interaction and result in a different global and local behavior.

The discrete mesh model increases the numerical complexity of the calculation. In general, when using implicit finite element methods, possible convergence problems might arise due to nonlinearities in the material, the geometry, the contact formulation, or a combination of all, which need to be managed carefully. Nevertheless, the discrete model is a valuable extension of the continuum approach. It clearly provides crucial, quantifiable measures of local non-affinity of the deformation field comparing mesh and vaginal canal, in addition to global measures of stresses and forces within the mesh.

To summarize, the present analysis clearly shows the importance of mesh material and surgical technique when implanting a sacrocolpopexy mesh. A softer implant can reduce forces in vagina and sacrum, however a small amount of prestretch might shift its mechanical response to a zone of higher apparent stiffness, diminishing the force reduction effects. On the other hand, prestretch might be purposefully applied by the surgeon in order to manipulate the mesh compliance to a desired value. While we are not in the position to give clear guidelines to the physician, the present study gives valuable indications and warrants further, systematic in silico and in vivo studies in order to investigate the complex mechanisms and verify the results, ultimately allowing for a clear set of guidelines for medical doctors.
4.1 Introduction

Ultrasound imaging is widely used in medical practice for non-invasive tissue visualization. While the working principle of acoustic reflections permits to image the morphology of organs, tissue stiffness cannot be determined directly [17]. In an effort to quantify compliance in-vivo, quasi-static elastography was developed.

Elastography measurements are performed as follows: A force is applied to the tissue by the ultrasound probe and the corresponding displacement or velocity field is obtained using image analysis algorithms that track the position of specific particles during their motion in the ultrasound B-mode image. Local strains are calculated from the displacement gradient and displayed in a colored image overlayed on top of the B-mode image, called ”elastogram” (Figure 4.1 and 4.2), indicating regions of large and small deformations, which can be a measure of local relative stiffness within the organ. In fact, assuming a homogeneous, sufficiently large organ that allows for local lateral extension and applying a controlled load with a linear ultrasound probe, the system can be approximated by springs of length $L_0$ and different stiffness in series, exemplifying the working principle (Figure 4.3). When applying an axial load onto the system, all three springs experience an identical compressive force. The smaller stiffness $k_S$ of the two outside springs (representing the surrounding tissue) leads to a larger compression ($\Delta x = F/k$, $L_S < L_H$), and thus strain, than for the central spring with stiffness $k_H > k_S$, representative of a stiff inclusion. While it is not possible to determine the value of $k_H$ or $k_S$ without measuring the applied force, knowledge of $L_S$ and $L_H$ allows determining the ratio $k_H/k_S$ as follows.
Chapter 4. Quasi-static Elastography as a Diagnostic Tool in the Female Pelvic Region

Figure 4.1: Elastogram of a homogeneous ultrasound phantom (see Section 4.2.2 for details) with a stiff inclusion. While not easily distinguishable in the traditional B-mode image (right), the inclusion is clearly visible and marked blue (hard) in the elastogram (left).

Since the force $F_H$ in the hard spring and $F_S$ in the soft spring are the same,

$$F_H = F_S$$

$$k_H \Delta x_H = k_S \Delta x_S$$

$$k_H (L_H - L_0) = k_S (L_S - L_0)$$

$$\frac{k_H}{k_S} = \frac{L_S - L_0}{L_H - L_0}.$$ 

However, as the system in question gets more complex in terms of geometry, boundary conditions and load application, this simple representation no longer holds true, as explained in more detail in Section 4.2.4.

Depending on the system, the force is applied by a hand-held probe, or the breathing movement of the patient and arterial pulsation is used to generate tissue motion [17]. Note that while the exact magnitude of applied force is unknown, thus not allowing for direct quantification of absolute tissue stiffness, the stress-strain relationship of stiff vs. soft materials allows for detection of local relative differences in tissue compliance.

Quasi-static elastography was initially introduced to differentiate malignant tumors and normal tissue by quantifying local tissue deformability [198]. In fact, malignant tissue
4.1. Introduction

Figure 4.2: Illustration of quasi-static elastography. The physician uses the ultrasound probe to apply compression to the tissue, which deforms uniformly. However, the stiff inclusion (circled) deforms significantly less, displaying lower strains and thus appearing red in the elastogram (bottom).

is usually stiffer than its surroundings. In a homogeneous organ, a stiff inclusion shows lower deformability when applying a load with the ultrasound probe, allowing to detect the relative difference in compliance with the help of the elastogram [17], see Figure 4.1. The procedure has since proven to be an excellent tool to detect pathologies related to relative stiffness changes within an organ, such as liver fibrosis [40, 58, 92, 263] or breast lesions [20, 58, 100, 151].
Figure 4.3: Representation of quasi-static elastography as a series of springs being compressed. The two outside, soft springs represent the surrounding tissue, while the stiffer spring in the center can be seen as a stiff inclusion.

Applications soon extended to the pelvic region. Prostate cancer in men has usually been detected by digital rectal examination and invasive, transrectal ultrasound (TRUS) guided biopsies [5]. Detection rates however were low (40-60%) [146]. A significant improvement in detection could be achieved with quasi-static elastography techniques [7, 53, 57, 241]. In the female pelvic region, elastography techniques have been applied to the detection of tumors in the ovaries [197, 264] as well as uterine disorders [9, 245]. All described methods are again based on relative differences in tissue stiffness within the observed organ.

First elastography measurements on pregnant cervices were published by Thomas et al. (2007) [251]. These results however demonstrated no correlation of the calculated tissue quotient with the duration of pregnancy. Similar findings were reported by Hernandez-Andrade et al. (2013) [111] and Molina et al. (2012) [184], showing no correlation between their measurement outcomes and current state of gestation. These results are contradictory to studies of Parra-Saavedra et al. (2011) [206] and Fruscalzo et al. (2012) [93], that use maximum compressibility as a measure of cervical compliance, as well as Badir et al. (2013) [13], which showed a decrease in cervical stiffness during gestation using the aspiration technique.

The following chapter is based on the publication Maurer et al. (2015) [171] and aims at rationalizing results obtained with the different quasi-static procedures based on a simple mechanical analysis of each configuration and corresponding simulations.
4.2 In-vivo Assessment of Biomechanical Properties of the Uterine Cervix Based on Quasi-static Ultrasound Procedures

The following section 4.2 is based on the publication [171]:


4.2.1 Introduction

In normal pregnancy, a firm and closed uterine cervix is important to withstand increasing uterine pressure and allow fetal development within the uterine cavity. Spontaneous preterm parturition is a pathological condition that is defined as childbirth before completion of 37 weeks of gestation. In clinical practice, measurement of cervical length by trans-vaginal ultrasound is performed to identify women at risk, since a short cervix is related to a greater risk of preterm delivery (PTD) [229]. However, most women at risk are not identified due to the low sensitivity of this parameter [120]. Additional measurement of the stiffness of the cervix might be useful in the prediction of preterm delivery. Existing data on the mechanical behavior of cervical tissue is mainly based on ex-vivo experiments with non-pregnant or at-term tissue [89, 188, 190, 191, 266]. Characterization of the development of cervical stiffness during pregnancy remains an open challenge. Several methods have recently been proposed for quasi-static mechanical characterization of the pregnant cervix, providing measurements at different gestational ages: quasi-static elastography [111, 112, 184], maximum deformability [93, 206], and aspiration [13]. The results of these studies are contradictory in that elastography indicates very modest changes in the course of pregnancy, whereas aspiration and maximum deformability show a strong decrease in stiffness, which starts early in pregnancy and continues until delivery. Thomas et al. (2007) [251] published the first elastography measurements on pregnant cervices and calculated an elasticity tissue quotient (TQ). These results demonstrated no correlation of the TQ with the duration of pregnancy. Similar findings were reported by Hernandez-Andrade et al. (2013) [111] and by Molina et al. (2012) [184]. In both studies, pregnant subjects were included in the study. Slow loading cycles were applied to obtain the strain maps. Since the applied force cannot be measured in current ultra-
sound systems, different standardization procedures were proposed aiming at a repeatable loading of the cervix in different measurements. Molina et al. (2012) [184] controlled the procedure by limiting the probe displacement up to one centimeter. Hernandez-Andrade et al. (2013) [111] used the provided "pressure bar" on the ultrasound monitor of their equipment to control compression. The question of how to standardize elastography measurements on the cervix has been discussed in recent review publications [84, 85]. Hee et al. (2013) [107] manufactured a soft elastomer to be applied on the vaginal probe and used it to provide a reference.

Ultrasound measurement of the maximum deformability of the cervix was first introduced by Parra-Saavedra et al. (2011) [206] and later Fruscalzo et al. (2012) [93]. This trans-vaginal ultrasound based procedure does not use the elastography strain maps to determine cervical consistency. For the measurement the sagittal plane of the cervix is visualized, as during cervical length measurements. The cervix is then manually compressed with the probe until no further cervical deformation is observed in the ultrasound monitor image (maximum deformation). The ratio of the anterior-posterior distance (thickness) before (reference configuration) and after compression application (compressed configuration) is calculated and quantifies maximum deformability of the cervix. In Parra-Saavedra et al. (2011) [206] this measure is called cervical consistency index (CCI). The differences in the procedure of Parra-Saavedra et al. (2011) [206] and Fruscalzo et al. (2012) [93] is that the latter limits maximum compression of the anterior lip instead of the whole cervix. The results of both methods are consistent [176] and have shown an increase in compliance with gestational age. These findings are in line with those obtained with aspiration measurements [13] on the pregnant ecto-cervix indicating a progressive decrease of stiffness during gestation. This indicates that biomechanical characterization might contribute to the detection of increased risk of preterm delivery, while clinical studies using quasi-static elastography could so far not show a potential for diagnosis.

The objective of the present study is to rationalize the findings obtained with the different quasi-static procedures based on a simple mechanical analysis of each configuration and corresponding simulations. These simulations are not aimed at an accurate representation of the complex anatomy of the cervix and its surroundings, but rather focus on demonstrating fundamental mechanical principles and qualitatively representing the effect.

### 4.2.2 Methods

Two approaches were used for the present analysis: (i) Quasi-static elastography was conducted on phantoms with known mechanical properties, to evaluate the effectiveness of
4.2. In-vivo Assessment of Biomechanical Properties of the Uterine Cervix Based on Quasi-static Ultrasound Procedures

the compression standardization procedure proposed in Hernandez-Andrade et al. (2013) [111] and Molina et al. (2012) [184]. (ii) Finite element simulations of a representative system were performed to rationalize the maximum deformability measurements from Parra-Saavedra et al. (2011) [206] and Fruscalzo et al. (2012) [93] as well as the findings of Hee et al. (2013) [107] using a reference elastomer on the ultrasound probe.

Elastography on Reference Phantoms  Two tissue-mimicking ultrasound phantoms [105] were manufactured using agar powder hydrated in boiling water. The stiffness of the phantoms was controlled by the amount of powder (0.002 g/ml, 0.001 g/ml) mixed into the solution. While the gel solution was liquid, Metamucil fibers were added to increase the absorption and scattering characteristics for ultrasound imaging. The mixture was stirred to obtain a homogenous material. The solution was then poured into a cylindrical container with 80 mm inner diameter and 60 mm depth. In this container gelation occurred at room temperature overnight. A thin plastic film covered the containers to assure hydrated surfaces.

The phantoms were mechanically characterized prior to elastography measurements using our indentation setup. The indenter tip with diameter of 25 mm (similar dimensions as ultrasound probe) was positioned centrally on the phantoms with ultrasound coupling gel between the transducer and the phantom to reduce friction. The tip was indented up to 15 mm into the samples with a strain rate of 0.1 %/s. Compressive strains under the indenter would thus be in the range of 25%. The corresponding load-displacement curve was measured with a load cell (Stentor II, Andilog Industries, France, 50N).

The experimental setup for elastography measurements is shown in Figure 4.4. It consisted of an ultrasound machine equipped with elastography software, a transvaginal probe (Hitachi 7MHz, Hitachi VISION Preirus, Hitachi Medical Corporation, Tokyo, Japan) and a balance (Grundig Küchenwaage KW 5040). The measurements were performed according to the protocol of Hernandez-Andrade et al. (2013) [111] on the two reference phantoms. The phantoms were positioned on the balance to measure the applied force during the measurement, thus providing the information which is missing in all elastography equipments. Slow cyclic motion (constant amplitude and frequency) by the hand-held transducer was applied to the phantoms and the level of compression standardized as done in Hernandez-Andrade et al. (2013) [111]. Elastography images were recorded and synchronized with the recordings of measured force magnitude. Synchronization was possible since all instruments used during the experiments, specifically the displays of the ultrasound device and the balance, were simultaneously visible in the images of a recorded video.
Finite Element Simulations  An FE model was built in the commercial FE software Abaqus 6.10ef1 (Abaqus, 2010, Simulia, Providence RI, USA) with geometrical dimensions and curvature of the cervix according to the images shown in Parra-Saavedra et al. (2011) [206] (internal os to external os distance of 67 mm, cervical diameter of 46 mm, diameter of ultrasound probe 48 mm). It consisted of a curved cylinder representing the cervix, a curved support structure (vaginal wall and rectum) and the half-spherical ultrasound probe, as seen in Figure 4.5. The proximal surfaces of the cervix and support (at the internal os) were fixed in proximal direction; the posterior surface of the support was fixed in posterior direction. Probe and cervix as well as cervix and support were allowed to slide freely with respect to each other. The model was set up to be symmetrical with symmetry conditions on the according medial surfaces.

The ultrasound probe was considered as a rigid body; the support structure was modeled to be very stiff (Young’s Modulus of 5 MPa) with respect to the cervix, which in turn was modeled as a hyperelastic material with a reduced polynomial material description ($n = 2$). Material models for the cervix in the first, second and third trimester of pregnancy (T1, T2, T3, respectively) were generated as follows: Data of Myers et al. (2010) [191] for uniaxial tension and compression curves for non-pregnant cervical samples were chosen as a reference. A material model was generated to fit the intermediate stress-strain response of those two loading modes, due to the complex loading conditions generated during lateral compression of the cervix. This reference material was then scaled for T1, T2 and T3 with compliance ratios corresponding to the evolution from non-pregnant to T1,
4.2. In-vivo Assessment of Biomechanical Properties of the Uterine Cervix Based on Quasi-static Ultrasound Procedures

Figure 4.5: Finite element (FE) model used for CCI and elastography simulations, with ultrasound probe (gray), cervix (light red), support (dark red).

<table>
<thead>
<tr>
<th>Trimester</th>
<th>$C_{10}$ $[Pa]$</th>
<th>$C_{30}$ $[Pa]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1100</td>
<td>150000</td>
</tr>
<tr>
<td>T2</td>
<td>70</td>
<td>7000</td>
</tr>
<tr>
<td>T3</td>
<td>8</td>
<td>1150</td>
</tr>
</tbody>
</table>

Table 4.1: Material parameters for the reduced polynomial strain energy potential $(U = C_{10} \left(I_1 - 3\right) + C_{30} \left(I_1 - 3\right)^3)$ used for the cervix.

T2, and T3 reported in Badir et al. (2012) [12]. The resulting material parameters are reported in Table 4.1.

The final model consisted of 1739 elements, 176 of which were quadratic hexahedral hybrid elements of type C3D20H (cervix), 500 were quadratic hexahedral elements of type C3D20 (support) and 1063 were quadratic tetrahedral elements of type C3D10 (probe).

In order to additionally simulate a reference material between probe and cervix [107], an elastomer cap was modeled as a hollow half sphere and placed between probe and cervix (see Figure 4.6). This extended the model by 1364 quadratic hexahedral hybrid elements of type C3D20H for the cap. Two different material models were used for the elastomer. The first cap model was an incompressible hyperelastic material using reduced polynomial material formulation $n = 2$. Parameters for this material (nonlinear cap, see Table 4.2) were set according to the stiffness ratio of cap to cervix of full-term pregnant women (cap/cervix = 7.3) as reported in Hee et al. (2013) [107]. The second cap model was an incompressible hyperelastic material using reduced polynomial material formulation $n = 1$, Neo-Hookean with stiffness of $C_{10} = 36666 Pa \ (C_{10} = E/6)$, equivalent to a Young’s modulus $(E)$ of 0.22 MPa as reported in Hee et al. (2013) [107], see Table 4.2.
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in the Female Pelvic Region

Figure 4.6: Finite element (FE) model used elastography with reference cap simulations, with ultrasound probe (gray), reference cap (light grey), cervix (light red), support (dark red).

<table>
<thead>
<tr>
<th>Material</th>
<th>Material parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set 1: Nonlinear cap (reduced polynomial, ( n = 2 ))</td>
<td>( C_{10} = 58.67 \text{ Pa}, C_{30} = 8433.33 \text{ Pa} )</td>
</tr>
<tr>
<td>Set 2: Linear cap (Neo-Hookean)</td>
<td>( C_{10} = 36666 \text{ Pa} )</td>
</tr>
</tbody>
</table>

Table 4.2: Material parameters for the elastomer cap. Formulation of strain energy potential for set 1: \( U = C_{10} (I_1 - 3) + C_{30} (I_3 - 3)^3 \); Formulation for set 2: \( U = C_{10} (I_1 - 3) \).

Note that while this material is referred to as ‘soft’ in Hee et al. (2013) [107], it is indeed far stiffer than the non-pregnant cervix.

Three sets of simulations were performed with the model:

1. CCI: A ramp force up to a (arbitrarily selected) maximum of 14N was applied to the probe in posterior direction. Global compressive strain as well as strain fields within the cervix served as an output. This was repeated for T1, T2 and T3.

2. Elastography: the probe was displaced in a sinusoidal fashion in posterior-anterior direction with a maximum amplitude of 12 mm and the reaction force at the probe as well as strain fields within the cervix served as an output. This was repeated for T1, T2, and T3.

3. Elastography with reference cap: The probe was displaced up to a large global compressive strain in the cervix. This was repeated for the following two material model combinations: (i) Cervix material T3 (see Table 4.1) and nonlinear cap material (reduced polynomial) with scaled material parameters (set 1, Table 4.2);
(ii) cervix material T3 and linear cap (set 2, Table 4.2). Compressive strain of the anterior cervical lip and the cap were reported.

Note that in the CCI simulations the ultrasound probe is not displaced until the cervix "deforms no further", as stated in the original study by Parra-Saavedra et al. (2011) [206]. However, the approach chosen here to apply a force boundary condition is equivalent to that deformation state. In fact, the physician not seeing any further compression of the cervix indicates that significant increases in force do not lead to large increases in compressive strain. This is a consequence of the nonlinear nature of the tissue response, indicating that the cervix entered the high stiffness regime of the force-deformation curve, where the strain is rather insensitive to force increases. The force magnitude of the FE simulations was chosen based on this criterion, ensuring a kinematic response in the high stiffness regime.

4.2.3 Results

Elastography on Reference Phantoms Using the proposed standardization protocol reported in Hernandez-Andrade et al. (2013) [111], the same magnitude of deformation was induced in the soft and the stiff phantom, as reflected by the elastograms in Figure 4.7 (red indicates high strain and blue indicates low strain). Note that due to the difference in stiffness (ratio of Young’s modulus stiff/soft $\approx 1.4$) the level of applied force measured by the balance was different: $136 \pm 6 \, g$ for the stiff and $81 \pm 5 \, g$ for the soft phantom (see Table 4.3), i.e. a ratio of $1.6 \pm 0.3$. The (modest) difference between stiffness ratio and the ratio of applied forces is an effect of the nonlinearity of the mechanical properties of the phantoms, which were deformed to a strain level of about 25%. Note that the strain images shown in Figure 4.7 indicate significantly larger deformability close to the phantom surface compared to deeper regions, reflecting the magnitude reduction of the force while transmitted through the tissue [198, 213, 214].

<table>
<thead>
<tr>
<th>phantom</th>
<th>force peaks under compression [g]</th>
<th>mean [g]</th>
<th>STD [g]</th>
</tr>
</thead>
<tbody>
<tr>
<td>soft</td>
<td>89 77 85 75 83 78 81</td>
<td>81.1</td>
<td>4.9</td>
</tr>
<tr>
<td>hard</td>
<td>131 139 132 129 135 144 143</td>
<td>136.1</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Table 4.3: Forces measured during elastography measurements on ultrasound phantoms of different stiffness.

These results clearly illustrate that the loading standardization procedure lead to repeatable strain values, however for different loading forces. Two materials with different stiffness were interrogated with elastography, but since the applied force cannot be stan-
Figure 4.7: The elastogram image for (a) soft phantom and (b) stiff phantom.

dardized, this approach could not discriminate between stiff and soft. The same is true for cervical tissue, thus this approach cannot detect cervical softening in pregnancy. Note that even combining force and displacement data for the cervix does not allow for quantitative estimation of tissue properties. In fact, non-linearity and inhomogeneity in the material behavior as well as non-linear geometric effects and far field boundary conditions influence the determination of mechanical parameters.

Simulation of Ultrasound Based Compression of the Cervix

Cervical Consistency Index (CCI): Simulating the maximum deformability procedure, a significant distinction between the trimesters in terms of global cervical strain is possible [206]. While the maximum force level chosen in the present simulation is identical for all three trimesters, the high nonlinearity of the chosen material law lead to consistent differences in deformability. Maximum deformation is reached in the nonlinear part of the force-displacement curves (Figure 4.8), so that only small deviations in probe displacement (and therefore cervical strain) occur for changes in compressive force. These results demonstrate the relative insensitivity of the kinematic response of the material to the force level applied in the measurement.

Comparing our results to the CCI measures published in Parra-Saavedra et al. (2011) [206] (Figure 4.8), we see a close match of compressive strain, clearly distinguishing between cervical consistency in the trimesters. The strain for T3 is more than twice that of T1 independent of the force level, see Figure 4.8.
4.2. In-vivo Assessment of Biomechanical Properties of the Uterine Cervix Based on Quasi-static Ultrasound Procedures

Figure 4.8: Results of CCI simulations. Top left: current/initial cervical diameter for T1, T2, T3. Top right: force-displacement curves for T1, T2, T3. Bottom: strain fields for T1, T2, T3.

**Elastography:** Simulations of the measurement procedure according to Hernandez-Andrade et al. (2013) [111] leads to global compressive strain in the cervix similar for all three trimesters. The sinusoidal shape of the curves (Figure 4.9, top left) mimicks that of the applied probe displacement. However, the resulting reaction force in the probe head is vastly different, ranging from $14 \, N$ in the first trimester, $0.7 \, N$ in the second trimester down to $0.1 \, N$ in the third trimester (Figure 4.9, top left, bottom).

The strain fields in the cervix obtained by the FE simulations are qualitatively similar to the elastograms generated during phantom ultrasound measurements. Strains are highest in the region close to the probe and decrease in a nonlinear fashion towards the posterior end of the cervix [198, 213, 214]. As expected, the strain fields are very similar for all three trimesters (scaling is identical for all three images in Figure 4.9, bottom). This shows that standardizing ultrasound probe displacement [184] or controlling the level of "pressure" leads to equivalent results, i.e. repeatable levels of deformation in the tissue, but for different forces.
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Figure 4.9: Results of elastography simulations. Top left: global nominal compressive strains in the cervix over time for T1, T2, T3. Top right: Applied force on the cervix over time for T1, T2, T3. Bottom: Strain fields and applied forces maximum for T1, T2, T3.

Elastography With Reference Elastomer (Cap): Set 1 (Table 4.2) corresponds to the interpretation proposed in Hee et al. (2013) [107], in that cap stiffness is expected to scale with respect to cervical tissue according to the observed ratio of strain (factor 7.3). Comparing compressive strains of the anterior cervical lip and elastomer cap for the cervix material T3 and the nonlinear cap material (set 1, Table 4.2), (Figure 4.10, black solid and dashed line, respectively), the strain ratio starts at 2.7 for low probe displacements and soon stabilizes at 1.3. According to Hee et al. (2013) [107] the strain ratio of anterior lip vs. cap should have reached the value of 7.3. This simulation indicates that the assumed material model for the cap (set 1) is too soft with respect to the cervical tissue, and thus it is not possible to reproduce the strain distribution as reported in Hee et al. (2013) [107].

Changing the material law for the reference elastomer to a linear, Neo-Hookean model (set 2, Table 4.2) with the modulus of the elastomer as reported in Hee et al. (2013) [107] (soft cap), the cap becomes much stiffer in relation to the cervix. This leads to a strong decrease in compressive strain in the cap (see Figure 4.10, grey dashed line). The cap deforms significantly only at large probe displacements and at large cervical strains.
4.2. In-vivo Assessment of Biomechanical Properties of the Uterine Cervix Based on Quasi-static Ultrasound Procedures

(see Figure 4.10, grey solid line). The strain ratio anterior lip vs. cap is large (due to low strains in the cap) and reaches the reported value of 7.3 [107] for global compressive strains in the cervix in the range of 50%. It is important to note that for both simulations, the strain ratio of anterior cervical lip vs. elastomer cap strongly depends on absolute probe displacement. The non-linearity of the system in terms of geometrical effects as well as material behavior makes it difficult to determine the stiffness of the cervix based on the deformation of the reference elastomer.

Figure 4.10: Results of elastography with cap simulations. Left: Strain ratio anterior lip/cap for cap material set 1. Inset: corresponding strain fields at 15 mm probe displacement. Right: Compressive strains in anterior lip (solid lines) and cap (dashed lines) for cap material set 1 (black) and set 2 (grey).

4.2.4 Discussion

Evidence from histological and clinical studies [188, 190, 191, 220] indicates that the cervix softens during pregnancy. The magnitude and timeline describing this softening behavior as reported for CCI measurements [206] agree with the findings of aspiration measurements [13]. In fact, when scaling the "non-pregnant" stress-strain curves from Myers according to the stiffness ratios of T3, T2 and T1 obtained by aspiration [13], the cervix deformability obtained by CCI can be reproduced (see Figure 4.8. Note that microstructural changes over the course of pregnancy might lead to changes in mechanical response for which a modification of the material model formulation is needed, rather than a simple scaling of an assumed non-pregnant material law. The agreement of aspiration and CCI measurement holds true despite limitations of each method: Aspiration is conducted at the ecto-cervix and depends on tissue properties on a very local scale. The
CCI procedure on the other hand relates to a global measure of bulk properties of the cervix, but standardization of assessment of maximum deformability is difficult. The findings from Badir et al. (2013) [13] and Parra-Saavedra et al. (2011) [206] seem contradicted by the data from quasi-static elastography [111, 184]. Two tissue mimicking phantoms with different stiffness provided a basis to rationalize this discrepancy, demonstrating that despite an identical "pressure" value, the loading cycles applied different forces. Since quasi-static elastography is based on a purely kinematic measure, i.e. signals are proportional to strain or strain rate, no direct, quantitative measures of biomechanical properties can be obtained. The displayed information (a bar with values from 1 to 7) on the ultrasound monitor is incorrectly referred to as a "pressure bar" by Hernandez-Andrade et al. (2013) [111], suggesting a standardized force being applied. But this is clearly misleading. In our phantom measurements, consistent values of this bar correspond to identical elastograms but different forces for the two phantoms. This effect is also seen in the accompanying simulations of quasistatic elastography (Figure 4.9), which show that for identical applied probe displacements and thus strains in the tissue, forces needed for similar compression of the cervix differ vastly for T1, T2 and T3. In order to assess the stiffness of a material, a measure of deformation has to be combined with a measure of force. In this sense, the term "elastogram" is also misleading, in that it does not provide an absolute elasticity or stiffness measure, but is rather a representation of the relative compliance as seen from kinematic data. In fact, elastography was developed for imaging local variations in stiffness in homogeneous tissues, such as detecting malignant tumors in the breast or prostate [198]. Applying this method in case of highly non-homogeneous loading states or in order to assess absolute tissue stiffness contradicts the original assumptions underlying this technique as well as its related terminology. Our results show that the method as described in Hernandez-Andrade et al. (2013) [111] and Molina et al. (2012) [184] does not allow for a quantitative assessment of absolute values of cervical stiffness and its softening in pregnancy.

The method of maximum compressibility as applied for CCI measurements combined with the knowledge of the nonlinear nature of the mechanical response of biological tissues provides a feasible approach for semi-quantitative determination of cervical consistency during gestation. When the cervix is deformed to a degree that no more compression can be achieved, hence "maximum compressibility", the material response is in the stiff region of the nonlinear response (see Figure 4.8). Here a variation in force does not result in a significant variation in strain, thus implicitly making the measurement insensitive of the applied force and ensuring reproducibility. This underlying principle is confirmed by our CCI simulations, which allowed to rationalize the findings of Parra-Saavedra et al. (2011) [206].
4.2. In-vivo Assessment of Biomechanical Properties of the Uterine Cervix Based on Quasi-static Ultrasound Procedures

In an attempt to introduce a method for extracting quantitative stiffness values from quasi-static elastography, Hee et al. (2013) [107] applied an elastomer cap of known stiffness between the ultrasound probe and the cervix during measurement. While the general idea was shown in Hee et al. (2013) [107] to be useful in extracting relative difference in cervical consistency for different subjects and detecting the softening behavior of the cervix during gestation, the present results indicate that care has to be taken when trying to draw quantitative conclusions regarding tissue stiffness. Hee et al. (2013) [107] proposed to scale Young’s modulus of the cap with the strain ratio cap/cervix in order to estimate cervical stiffness. This requires a homogeneous stress state. For small strains and uniaxial stress state

\[ \sigma = E \varepsilon. \] 

Assuming the same stress for both cervix and cap:

\[ E_{\text{cervix}} \varepsilon_{\text{cervix}} = E_{\text{cap}} \varepsilon_{\text{cap}} \] 

and thus

\[ E_{\text{cervix}} = E_{\text{cap}} \frac{\varepsilon_{\text{cap}}}{\varepsilon_{\text{cervix}}}. \] 

This assumption however is only true for a simple, one-dimensional configuration for which cap and cervix would deform as springs in series. In the case of elastography, this assumption is far from true due to two reasons: (i) the system leads to a complex three-dimensional stress distribution in the materials. Geometric nonlinearities in the shape of the probe head and contact patch with the cervical tissue lead to a nonlinear, compressive force distribution through the tissue, where the force decreases with depth. This results in the distinctive strain patterns (high strains close to the probe and low strains farther away from the probe) seen in elastograms of the cervix or phantoms as well as in all simulations. Differences in the magnitude of strain in cap and cervix as well as in the response of the anterior and posterior cervical lip are strongly dependent on the level of probe displacement. (ii) Due to the curved shape and the support by the underlying ultrasound probe, the cap experiences lateral constraints, thus reducing thickness deformation due to the high bulk modulus of the elastomer. As a consequence the apparent stiffness of the cap increases. In fact, the mode of deformation during elastography measurements is close to confined compression for the elastomer, leading to a bulk-modulus dominated, very stiff response. These two factors influence the material response of the cap, so that the relative stiffness of cap and cervix cannot be estimated from simple formulas. Due to the non-linearity of the system, a repeatable quantitative determination of relative stiffness requires repeatable
values of applied probe displacement. Our simulations also show that when evaluating relative differences in consistency within the cervix using quasi-static elastography [249], probe displacement should be carefully controlled, since a large range of strain ratio values can be generated dependent on probe impression depth.

4.2.5 Conclusions

The mechanical characterization of the cervix and its development during gestation still represents an open challenge. A combination of information from different methods is required in order to improve our understanding of the mechanical behavior of cervical tissue, and thus help towards diagnosis of pre-term delivery.

We have demonstrated that the quasi-static elastography protocol as proposed by Hernandez-Andrade et al. (2013) [111], Hernandez-Andrade et al. (2014) [112] and Molina et al. (2012) [184] does not allow to distinguish between a stiff and soft cervix. This conclusion is based on experiments on reference phantoms as well as FE simulations.

Extending this method by introducing a reference elastomer into the elastogram [107] is a promising new idea. However special care should be taken when interpreting results, since the geometric and material nonlinearities encountered during measurement are expected to strongly influence the interaction and mechanical response of the cap and the cervix, making the outcome highly dependent on ultrasound probe displacement. This necessitates careful standardization of the measurement procedure (i.e. constant strain in the elastomer) in order to obtain meaningful results allowing for inter-subject comparison.

In any case, determination of absolute stiffness values from such measurements requires solving the corresponding inverse problem.

The simulations of the maximum compressibility approach, as introduced by Parra-Saavedra et al. (2011) [206], indicate that this procedure can deliver a repeatable assessment of cervical consistency and is able to differentiate between subjects and time point in gestation. This result is due to the nonlinear nature of the mechanical behavior of cervical tissue. Phantoms of representative geometry could be used in future experimental investigations to more closely evaluate the effectiveness of CCI measurements. The findings of Parra-Saavedra et al. (2011) [206] were shown to be in line with the evolution of stiffness in gestation as determined by aspiration measurements [13].

Quantitative mechanical measurements and formulation of corresponding constitutive model equations for cervical tissue [189] are necessary for an improved understanding of the physiology of cervix deformation as well as for development of new diagnostic methods.
4.3 Pelvic Floor Elastography: An Idea for a New Diagnostic Tool

Traditionally, elastography was developed for non-invasive, imaging based detection of tumors and similar pathologies in homogeneous tissues, such as the liver or female breast [17, 58]. With the ultrasound probe, pressure is applied to the tissue in question and from the displacement field in the B-mode images the strain field is extracted. The applied pressure or force is not known, however the stress strain relationship of stiff vs. soft materials allows for detection of relative differences in tissue compliance and thus for clear indication of the location of stiff inclusions or lesions in homogeneous surrounding tissue (see Section 4.1). In fact, the magnitude of the applied force is unknown, but also not required for the principle of quasi-static elastography to work.

This purely kinematic approach of exploiting the deformation behavior of soft tissues in order to detect relative stiffness within an organ can also be applied to the pelvic floor region. The following outlines this novel, patient specific computational approach for detecting mechanical causes of pelvic disorders and describes a first proof of concept based on the 3D finite element model described in Chapter 2.

Currently, pelvic organ prolapse severity is measured in a stage system proposed and standardized by Bump et al. (1996) [37] and is based on a visual inspection of the vaginal canal and the protrusion of anterior or posterior landmarks therein (see Section 2.1.2). Pelvic muscle integrity may be assessed by inspection of movement of externally visible landmarks such as the perineum during contraction or by palpation through vagina or rectum. However, Bump et al. (1996) clearly state that there "are pitfalls in the measurement of pelvic floor muscle function because the muscles are invisible to the investigator" [37]. While modern medical imaging techniques might support the physician in assessing muscle integrity, the herein proposed method allows for easy, non-invasive and targeted evaluation of muscle compliance.

4.3.1 Methods

**Working Principle.** The proposed method to detect relative differences in pelvic floor muscle mechanical properties requires in an ideal case the high resolution 3D segmented geometry of a patient’s muscle sheet in an undeformed state as well as similar images in a deformed, loaded state. These could be for example magnetic resonance (MR) images of the patient at rest and during the Valsalva maneuver, which significantly increases intra abdominal pressure due to the activation of the pelvic and abdominal muscles and is
Figure 4.11: Working principle of the proposed methodology for pelvic elastography. High resolution MR images of the unloaded pelvic floor (a) are used to generate a patient specific FE model of the pelvic muscle sheet (b). Dynamic MR images of the loaded (by e.g. Valsalva) pelvic floor (c) are used to extract the displacement field of the pelvic muscle sheet (d), which is applied to the FE model to generate the computational elastogram (e).

used to quantify maximum pelvic organ descent in a POP patient [37]. As in quasi-static elastography, the exact magnitude of load is not and does not need to be known, since the interest is not in absolute but relative tissue compliance.

Mapping of the undeformed onto the deformed pelvic floor muscle geometry allows for the extraction of the displacement field at each point within the sheet. This can be applied as a kinematic boundary condition onto a finite element model based on the undeformed geometry with – assumed – homogeneous material properties. Note that these material properties do not need to be accurate in magnitude if only the pelvic sheet is assumed to be homogeneous. The resulting stress and strain maps can then be interpreted as a computational elastogram, showing local relative differences in tissue compliance, thus identifying weakened pelvic floor muscle structures, potentially providing the physician with possibilities for targeted therapy. The working principle is illustrated in Figure 4.11.

**Proof of Concept.** In order to test the viability of the proposed method before clinical, patient specific application, the computational pelvic elastography procedure was applied
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Figure 4.12: Segmented pelvic floor muscle sheet. (a) coccygeous muscle (CM), (b) iliococcygeous muscle (IM), (c) levator ani muscle (LA), (d) external anal sphincter (EAS).

using the 3D finite element model presented in Chapter 2 as a proof of concept. The full implementation including all organs (vaginal canal, bladder, pelvic muscles) and ligaments served as a reference model, representing a patient with weakened pelvic muscle structures (Figure 4.13 (a)). In order to manually weaken individual muscle groups within the pelvic sheet, thus simulating different pathological cases of the pelvic floor to test the sensitivity of the method, the muscle sheet was segmented into parts representative of major muscle groups in vivo (see Figure 4.12). They include the iliococcygeous muscle (IM), coccygeous muscle (CM), levator ani muscle (LA, consisting of pubococcygeous, puborectalis and levator plate) as well as the external anal sphincter (EAS).

The stiffness of one such region is reduced by a factor of 10 and the Valsalva maneuver simulated. The resulting, artificially generated displacement field (Figure 4.13 (b)) can be viewed as representative of the displacement field extracted from dynamic MR images of the Valsalva maneuver of a POP patient. It is then applied as kinematic boundary conditions to a model of the separate pelvic muscle sheet with homogeneously distributed material properties (Figure 4.13 (c)), which serves as a model of the pelvic floor geometry generated from high resolution MR images of the patient at rest. Since regions with higher compliance in the full, patient specific model will likely deform more compared to surrounding, healthy muscle tissue under uniform, increased intra abdominal pressure during Valsalva, they will exhibit larger strains and will be indicated as “soft” in the computational elastogram (Figure 4.13 (d)), thus allowing for relative compliance assessment and detection of pathological regions. While strain fields can be a good indicator of weakened pelvic muscle regions, the FE analysis allows to similarly evaluate corresponding stress fields. In fact, since the material is assumed to be homogeneous in the last step of the analysis, large strains will result in larger stresses, again indicating relative differences within the pelvic sheet. Note that while larger strains will really occur in a weaker pelvic region, larger stress is an artifact associated with the (wrong) assumption
of homogeneous mechanical properties. Weaker regions would display in reality similar stresses as the surroundings. The artifact however might help detecting the origin of POP.

**Regions of Interest.** The methodology described above represents the ideal case of full knowledge of the deformed pelvic sheet geometry and thus full 3D displacement field. However, this would not necessarily be the case in clinical practice due to resolution lim-
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In order to evaluate the influence of low resolution and thus lack of exact spatial information of the displacement field on the proposed computational elastography method, the following procedure has been adopted. Instead of applying the full displacement field at every node to the muscle sheet model (Figure 4.13 (b),(c)), a reduced set of displacement information is used as kinematic boundary conditions. This sparse displacement information could be extracted at clearly visible landmarks or regions of interest (ROI) in the pelvic region, such as the perineal body, border between the vaginal canal and muscle sheet, or attachments to fascias, ligaments or connective tissue, depending on the visibility on dynamic MR images. In the proof of concept model it consists of displacement vectors at the outermost perimeter of the pelvic sheet and the opening for the vaginal canal near the perineal body (see Figure 4.14). After applying this reduced set of kinematic boundary conditions, the resulting stress- and strain fields are again analyzed and interpreted as elastograms with respect to relative compliance differences.

4.3.2 Results

Full Displacement Field. Figures 4.15 to 4.18 show the computational elastograms of the four initial test cases of intentionally weakened muscle regions, as indicated in the top left of each figure. The Tresca-like strain ($\varepsilon_{\text{max}} - \varepsilon_{\text{min}}$) and Tresca stress ($\sigma_{\text{max}} - \sigma_{\text{min}}$) fields are depicted on the left and right, respectively. The full displacement field at every point of the pelvic muscle sheet has been applied as described in Section 4.3.1.2. In case of the weakened coccygeous muscle (Figure 4.15), strain and stress fields clearly...
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Figure 4.15: Weakened coccygeous muscle (CM). (a) Tresca-like strains ($\varepsilon_{\text{max}} - \varepsilon_{\text{min}}$), (b) Tresca stresses ($\sigma_{\text{max}} - \sigma_{\text{min}}$).

Figure 4.16: Weakened illiococcygeous muscle (IM). (a) Tresca-like strains ($\varepsilon_{\text{max}} - \varepsilon_{\text{min}}$), (b) Tresca stresses ($\sigma_{\text{max}} - \sigma_{\text{min}}$).

indicate which region was artificially softened in the reference model. Strains as well as stresses are an order of magnitude larger in the coccygeous muscle than in the rest of the pelvic sheet. Both fields follow the border of the muscle region as indicated in the top left of Figure 4.15. Note that the absolute magnitude of strains and stresses is of no importance for assessment of relative differences. For this reason, no quantitative scale bar is included in the figures.

Comparing the results of the pelvic elastogram simulations of the illiococcygeous muscle (Figure 4.16) to those of the coccygeous, the strain fields are no longer as clearly indicative, as also the coccygeous shows increased strains. However, the finite element analysis allows for the evaluation of stresses, which in this case helps the cause. The illiococcygeous muscle is clearly outlined in the Tresca stress image, indicating that while the strains in the weak region are not decisively large enough compared to the surrounding tissue to highlight the respective region, they are indeed sufficiently large to induce high stresses. The same is true for the weak levator ani muscle (Figure 4.17). While strains are in
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Figure 4.17: Weakened levator ani muscle (LA). (a) Tresca-like strains ($\varepsilon_{\text{max}} - \varepsilon_{\text{min}}$), (b) Tresca stresses ($\sigma_{\text{max}} - \sigma_{\text{min}}$).

Figure 4.18: Weakened external anal sphincter (EAS). (a) Tresca-like strains ($\varepsilon_{\text{max}} - \varepsilon_{\text{min}}$), (b) Tresca stresses ($\sigma_{\text{max}} - \sigma_{\text{min}}$).

fact increased in the anterior part of the levator ani, the perineal body and between rectum and sacrum, the strains in the rest of the muscle sheet are increased as well. The combined analysis of strain and stress fields allows for a more precise assessment of relative differences in compliance. Even reduced stiffness in small muscles, such as the external anal sphincter (Figure 4.18), could be detected with the proposed pelvic elastography method applied as a proof of concept to the reference model. Both strain and stress field are indicating the weakened region reliably.

Reduced Displacement Field. In this section, results are presented for the application of the reduced displacement field at specific regions of interaction as described in Section 4.3.1. Figures 4.19 to 4.22 show the computational elastograms of the four test cases of intentionally weakened muscle regions, as indicated in the top left of each figure. The Tresca-like strains ($\varepsilon_{\text{max}} - \varepsilon_{\text{min}}$) and Tresca stresses ($\sigma_{\text{max}} - \sigma_{\text{min}}$) are again depicted.
Figure 4.19: Weakened coccygeous muscle (CM). (a) Tresca-like strains \((\varepsilon_{\text{max}} - \varepsilon_{\text{min}})\), (b) Tresca stresses \((\sigma_{\text{max}} - \sigma_{\text{min}})\). Results for the reduced displacement field.

Figure 4.20: Weakened illiococcygeous muscle (IM). (a) Tresca-like strains \((\varepsilon_{\text{max}} - \varepsilon_{\text{min}})\), (b) Tresca stresses \((\sigma_{\text{max}} - \sigma_{\text{min}})\). Results for the reduced displacement field.

on the left and right, respectively.

Figure 4.19 shows the strain and stress fields within the pelvic muscle sheet with a weak coccygeous muscle. Even though the displacement extracted from the prototype POP model has only been applied at the very perimeter of the pelvic muscle sheet, the coccygeous is clearly delineated and presented as soft in the computational elastogram.

The strain and stress images in case of a weakened illiococcygeous with kinematic boundary conditions only applied at the outside border (Figure 4.20) do not show the artificially weakened region as clearly as when applying the full displacement field. In fact, both Tresca-like strain as well as Tresca stress are high in close proximity to the boundary, where the displacement has been applied.

A similar picture can be seen for a weakened levator ani (Figure 4.21) and external anal sphincter (Figure 4.22). Both illustrate the limitations of this modified approach. Both muscle regions do not include boundaries at which the displacement field is applied (the levator ani does have anterior and posterior perimeters, however they attach to the bone
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Figure 4.21: Weakened levator ani muscle (LA). (a) Tresca-like strains \( (\varepsilon_{\text{max}} - \varepsilon_{\text{min}}) \), (b) Tresca stresses \( (\sigma_{\text{max}} - \sigma_{\text{min}}) \). Results for the reduced displacement field.

Figure 4.22: Weakened external anal sphincter (EAS). (a) Tresca-like strains \( (\varepsilon_{\text{max}} - \varepsilon_{\text{min}}) \), (b) Tresca stresses \( (\sigma_{\text{max}} - \sigma_{\text{min}}) \). Results for the reduced displacement field.

and have zero displacement), resulting in them not being stretched, thus not being visible in the computational elastogram.

4.3.3 Discussion and Conclusion

A computational method to detect pelvic muscle deficiencies based on the working principle of static elastography has been developed. It allows to detect relative differences of compliance within the pelvic floor, specifically weakened regions with lower stiffness than their surroundings. The presented approach does not require exact knowledge of material behavior of the organ in question, but rather relies on the assumption of homogeneity of an organ structure, where a region that falls out of the norm in terms of compliance can be detected based purely on kinematic measures.

The method has been applied successfully to a range of synthetic examples of weakened pelvic muscles as a validation and proof of concept. The results are promising, since the
majority of regions with artificially reduced stiffness could be detected. However, these initial tests revealed some limitations. One critical aspect can be the amount of displacement data that can be extracted from medical images of the POP patient’s pelvic floor under load. The Valsalva maneuver is used in the urogenital field for diagnosis and demonstration of maximal organ descent in POP patients [37]. Khurana et al. (2011) [135] found a low level of difficulty for healthy patients at 10s maximum duration. However, anecdotal evidence suggests that POP patients can not hold intra-abdominal pressure that long or steady due to weakened muscle structures and greater age. This necessitates a short acquisition time during dynamic MR imaging in order to capture the deformed pelvic muscles. Dynamic MR however is conventionally based on a sequential and thus slow image acquisition, the speedup of which leads to a loss in image quality or necessitates the choice of a lower spatial resolution [98]. Stronger magnetic fields with increased energy could improve the signal to noise ratio and thus resolution. While there are first studies with up to 9.4T magnetic field strength used in human trials, the standard today is 1.5-3T [259].

Markl et al. (2006) [167] used a 3T MRI to acquire 2D multislice static images of $\mu m$ resolution, at the expense of an acquisition time of almost 6min. Switching to parallel acquisition, 3D static images were captured within 21s at $mm$ resolution. However, these are still static MR images. Recently, Uecker et al. (2010) [253] have shown a method for 2D real time dynamic MR image capture with 20ms temporal and 1.5-2$mm$ spatial resolution, based on parallel acquisition and complex image analysis algorithms. While the temporal resolution is excellent, images still lack the third dimension. Including this spatial information again complicates matters and lowers resolution. Huang et al. (2005) [118] have shown dynamic 3D images of a beating heart, however at the cost of increased complexity and combination of multiple imaging modalities, dynamic 3D ultrasound and MR imaging. To summarize, conventional static MRI can be of very high spatial resolution in all three dimensions, but images acquire long acquisition time. Dynamic MRI however might provide sufficient spatial resolution only in 2D when imaging the Valsalva maneuver. To illustrate, compare the image fidelity in Figure 4.11 (a) (static MRI) and 4.11 (c) (dynamic MRI).

While the proposed methodology does indeed show some good results in case of a reduced set of kinematic boundary conditions, care has to be taken when interpreting the results, as the reliability of the detection of weak regions depends on the available information of the deformed pelvic floor. Displacement data at landmarks which are not within or near a weak region will not contribute to the detection, as is exemplified by the weakened LA and EAS in Section 4.3.2. The kinematic boundary conditions are applied to the perimeter of
the pelvic sheet, which is not sufficiently close to both affected muscle groups, which are
shielded from significant deformation and thus do not show large strains in the computa-
tional elastogram. However, if displacement data is indeed available at landmarks within
a weak region, even sparse information is sufficient for detection, alleviating the need for
exact segmentation of the whole deformed pelvic muscle sheet.
One way to overcome the restricted resolution of dynamic MRI in combination with the
short acquisition time during the Valsalva maneuver is the application of an external,
artificial load to the pelvic cavity that does not require an active effort by the patient.
The geometry of the pelvic muscle sheet at rest, serving as the reference FE model, could
be extracted with the patient in supine position, as is common for MR scans. The second
scan could then be taken in prone position with the patient lying with their abdomen
on a pillow or foam block, thus indenting the abdominal wall and increasing the intra
abdominal pressure without active muscle contraction. This would allow for static MR
imaging, since the patient’s muscles would not fatigue and could hold that position with-
out effort for longer periods of time. The resulting high resolution images would allow for
similarly high fidelity segmentation of the deformed pelvic floor as for the undeformed,
giving access to very dense displacement data. Another method to apply controlled loads
to the pelvic muscle system could be the Bakri balloon [15, 16]. It has been developed to
treat post-partum hemorrhages within the uterus. It consists of a catheter with a balloon
like structure at the tip, that is inserted through the vaginal canal into the uterus and
inflated. This could be used in the presented application as a tool to exert force unto
the pelvic system by gently pulling it outwards, thus loading the pelvic floor.
While these methods would provide medical images of the undeformed and deformed
muscles, segmentation of the relevant structures and subsequent preparation of geomet-
rical data for FE simulation (as described in Section 2.2) are necessary further steps and
present a major challenge in the process. While semi-automatic procedures for segmen-
tation of pelvic organs such as the prostate or bladder [207, 210] exist, the pelvic muscle
structure proves difficult even in high resolution MR images, mainly due to their small
thickness and lack of contrast between it and surrounding tissue [126]. Human operator
intervention is almost always necessary, especially in the later stage of geometry smooth-
ing and preparation for finite element analysis. The described methodology would clearly
benefit from advances in the field of automatic medical image segmentation. In addition,
point to point registration between unloaded and loaded geometry necessary for the ex-
traction and application of kinematic boundary conditions can be problematic. While
certain clearly visible landmarks might be identified in both configurations, this would
not be the case for the majority of the pelvic muscle sheet. Normal projection of the
unloaded geometry onto the loaded pelvic floor would provide an initial estimate, but
could introduce local undesirable errors. A possibility to tackle this challenge could be a point-wise, energy-minimizing "relaxation" of the model, as described by Gessat et al. (2014) [102] for the estimation of reaction forces in aortic valve stents.

While the proposed method will need to be tested in clinical trials before it can find its way into clinical practice, it shows great promise as a valuable tool to help doctors and patients detect pelvic disorders more reliably and accurately. In addition, it offers the possibility to be applied to other homogenous organs where a controlled load can be applied.
Conclusion and Outlook

The complex mechanical system of the female pelvic floor has been investigated in this work. A detailed three dimensional finite element model of the pelvic cavity has been developed, including pelvic organs, muscle sheet and ligamentous support structures. Several applications of the model have been shown, based around one fundamental question: What is the physiological, in vivo mechanical environment in the pelvic floor? In fact, it is intuitively clear that a direct measurement of forces within the pelvic cavity in vivo is challenging if not impossible. This is where the powerful tool of finite element analysis can provide valuable information.

It was shown that tensions within the pelvic cavity are much lower than in the abdominal wall, questioning the application of high stiffness mesh implants in this region. This new insights could provide a benchmark of the physiological range of forces and the mechanical environment in vivo for the assessment of the mechanical biocompatibility of current meshes as well as for the development of future implants. However, that requires a meaningful definition and general acceptance of mechanical tests and parameters in order to consistently characterize these prostheses. In an effort to provide such data, an extensive, multiscale experimental protocol has been developed and nine different mesh types have been evaluated in terms of their mechanical properties. A set of nine parameters have been proposed, including uniaxial and biaxial stiffness, anisotropy and the influence of tissue ingrowth or multiple cycles on the mechanical behavior. In order to facilitate simple comparison of meshes, these parameters have been visualized in a circle graph, allowing for immediate evaluation of mesh performance, even for the untrained eye. It is in fact a very important task for today’s biomechanical engineers to improve communication with clinicians and physicians and provide a common language in order to tackle health challenges on a familiar basis.

The foundation of knowledge of the ex vivo mechanical behavior of mesh implants in a
controlled environment, both on a macro and micro scale, has been extended in a simulation study. For the first time, a pelvic disorder repair strategy, i.e. the sacrocolpopexy after a hysterectomy procedure, has been implemented in silico. Again, the question of the mechanical environment in physiological conditions drove this effort. On a global level, the great importance of surgical technique on the forces acting on mesh and vaginal canal has been demonstrated. In fact, pretensioning of a mesh may have a strong influence on its mechanical biocompatibility, as relevant as the mechanical properties of the mesh itself. On a local scale, the effects seen in the controlled experimental campaign could also be observed in the FE simulations of a more realistic geometrical and mechanical environment in terms of loads and deformations. Pore collapse and non-affine deformation patterns on a unit cell level compared to the underlying tissue may lead to detrimental tissue injuries and complications such as mesh erosion.

Another application of the finite element model of the pelvic cavity as a diagnostic tool was suggested. Based on the principle of quasistatic elastography, which allows for the evaluation of relative differences in tissue compliance within a homogeneous organ structure, a methodology was developed to detect weakened muscle regions of the pelvic floor. Purely kinematic data, i.e. the displacement field of the pelvic musculature under controlled loading, is required to assess muscle stiffness in a patient with the aid of a computational elastogram. A first proof of concept based on artificial pelvic prolapse cases simulated in silico showed promising results.

The knowledge of the in vivo, physiological mechanical environment and behavior is not only important for the assessment and repair of pelvic organ prolapse. In fact, the uterine cervix also plays an invaluable, mechanical role in the female pelvic region, in that it maintains the structural integrity necessary for a successful pregnancy. And again, the question of mechanical behavior is central to its function. Recently, several studies suggested the use of transvaginal, quasistatic elastography to evaluate cervical softening during gestation. However, this technique does not measure forces applied to the cervix directly and relies purely on kinematic data to assess relative differences in stiffness within an organ. With the help of a finite element model of the cervix, the efficacy of quasistatic elastography was evaluated in comparison with other methods reported in literature. It was shown that techniques such as aspiration or CCI measurements do indeed provide meaningful data, whereas quasistatic elastography lacks a force standardization and can not be used to track cervical changes during gestation. The main culprit which lead to the application of the quasistatic elastography technique in the assessment of cervical stiffness is a misleading terminology used by the manufacturers of ultrasound and elastography machines and software: The term "pressure bar" or a scale from "soft" to "hard" assigned to a colorful elastogram mapping strain differences may indeed misguide the mechanical
layman to interpret it as values related to absolute stiffness. An in-depth mechanical analysis shows that this cannot be the case, due to the lack of force measurement. This again stresses the need for better communication and a common language for both, biomechanical engineers and medical doctors.

Figure 5.1: Visible mesh pores with ultrasound imaging in water. Images provided by Dr. Sanabria.

Several challenges and open questions as well as possible improvements for the finite element model remain. The model presented in this work is based on geometrical data of a pregnant woman, and while the overall shape and geometrical relations of the pelvic cavity are similar to a non-pregnant subject, a model of such could improve the results seen here, being a more accurate geometrical representation of the system. On the other hand, creation of a complex FE model is a time consuming task, which can be improved by automatic segmentation of medical images and improved automatic meshing algorithms [21, 193]. This would also be helpful for the verification and application of the proposed diagnostic tool of the computational elastogram, which requires segmentation and analysis of undeformed and deformed pelvic musculature. In a future step, the approach should
be taken from the proof of concept state into clinical tests, assessing its feasibility for
detection of muscle weakness in clinical patients.
The proposed experimental protocol and parameters for the characterization of the me-
chanical biocompatibility of synthetic meshes needs to be linked to clinical data. The cor-
relation of mechanical properties and adverse clinical indications is an important future
challenge, which requires a step in the direction of a centralized database of complications
related to mesh implants. This would open the door for an in depth analysis of possible
mechanical causes of erosion, shrinkage, fibrosis and other pathological effects. In addi-
tion, an improvement of in vivo measurement of deformation of implants is necessary to
enhance ex vivo experimental protocols for mesh performance evaluation. In fact, first
steps in that direction are underway. Meshes visible on magnetic resonance imaging have
been developed and their global kinematic behavior in vivo under physiological conditions
very recently evaluated [75, 236, 237]. While this may provide an estimation of global
strains within the mesh and thus of the possible global mismatch of mechanical behavior,
a local analysis is of equal importance. As demonstrated in this work, the woven mesh
structures do not behave like a continuum on a meso- and micro scale, but exhibit local
non-affine, mechanism-like deformation patterns on a filament level. These effects may
increase the risk of complications on a micro scale and necessitate higher resolution imag-
ing techniques in order to visualize pore collapse or filament movement in a physiological
environment in vivo. In a first attempt in collaboration with Dr. Sanabria (Computer
Vision Lab, Prof. Goksel, ETH Zurich), it was possible to visualize the mesh pattern of
Ultrapro down to a unit cell level with advanced ultrasound techniques (see Figure 5.1).
While a proof of concept in vivo is still in the future, it shows the promising potential of
this technique to non-invasively evaluate mesh deformations on a small scale in physi-
ological conditions.
Acknowledgements

Dear reader, this is usually the part where the author gives a list of names and thanks everyone for their specific contributions. However, I do not intend to do it the conventional way, as I believe that the time spent during one’s doctorate is a very personal experience and thus warrants a personal piece within the body of the thesis.

These last years that I spent at the Institute of Mechanical Systems at ETH Zurich were very special indeed. I had an extraordinarily enriching, educational and not least enjoyable time, in no small part due to the amazingly talented and friendly people who I was and still am lucky enough to call friends. This created a stimulating environment in which to do research, grow – both professionally and personally – as well as challenge and get challenged. It has been a thrilling experience that I do not want to miss as part of my life.

And while I think that I do not need to call out names I wish to thank, as I am convinced that every person involved in this journey – be it friends, colleagues, collaborators or students – are very much aware of their part and know how grateful I am, I do feel that a few people warrant further mention.

First that would be my supervisor, Prof. Edoardo Mazza, who offered to take me into his group as I hung in the air half a year after starting my doctorate at ETH. He gave me guidance when I needed it and freedom when I desired it. It was an inspiring experience, giving me the opportunity to grow, learn and expand my horizon.

I also wish to thank Michela Perrini for being such a great research colleague, friend and awesome and supportive partner for life, who taught me the Italian way of life and made the time in the group even more gratifying and whole.

Another important piece in the puzzle is Alexander Ehret, without whom I very probably would not have ended up at ETH. He steered me clear of my plans to do automotive engineering and introduced me to the field of biomechanics in the early years of my studies.
at RWTH Aachen, for which I will always be grateful.
And of course I have to mention my parents, who gave me the freedom I needed and
supported me whichever decision I took and whichever direction I went (mostly south).
Last but not least I am grateful to all my colleagues, collaborators and advisors here at
ETH Zurich, University Zurich, University Hospital Zurich, in Switzerland, at University
of Lille in France, at KU Leuven in Belgium, and at University of Pittsburgh in the USA.
Their welcome contributions were crucial to the success of this project.

Manfred M. Maurer
Zurich, November 2015
## Appendix

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*Table 7.1: Stiffness [N/mm] for all dry meshes and all performed experiments.*
### Table 7.2: Residual strain [%] for all dry meshes and all performed experiments.

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### Table 7.3: Intra-specimen variability [%] for all dry meshes and all performed experiments.

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Table 7.4: Maximum strain [%] reached in the first cycle for all dry meshes and all performed experiments.
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Table 7.5: a) stiffness [N/mm], b) residual strain [%], c) intra-specimen variability [%], d) maximum strain [%] reached in 1st cycle for all embedded meshes and all performed experiments.
Figure 7.1: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for Bard Mesh Marlex.
Figure 7.2: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for DynaMesh Endolap.
Figure 7.3: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for DynaMesh PRS.
Figure 7.4: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for Gynecare Prolift.
Figure 7.5: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for Ethicon Physiomesh.
Figure 7.6: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for Coloplast Restorelle.
Figure 7.7: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for Surgipro PMM.
Figure 7.8: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for Ethicon Ultrapro.
Figure 7.9: Membrane tension – local strain curves in all tested configurations for the first and 10th cycle for Parietex Ugytex.
Bibliography


