

FACULDADE DE ENGENHARIA DA UNIVERSIDADE DO PORTO

**A holistic biomechanical investigation of the uterine
system at late stages of pregnancy**

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A thesis submitted in conformity with the requirements for the

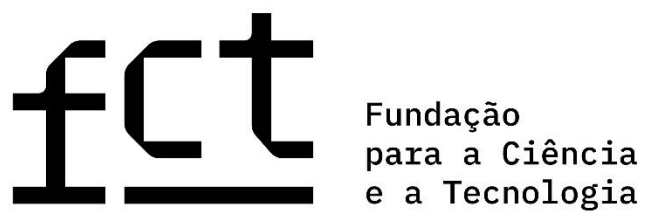
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"Science is not limited to laboratories and equations; it is a way of seeing and understanding the world, and its wonders are accessible to all."

Rachel Carson (1907 – 1964)

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Abstract

The World Health Organization (WHO) defines normal birth as spontaneous onset without identified risks until labor. The infant is born spontaneously between the 37th and 42nd weeks of gestation in the occiput anterior position. Pregnancy's success relies on intricate mechanical interactions among the uterine body, cervix, and fetal membrane, characterized by a synchronized sequence: cervical ripening, decidual activation/rupture of the fetal membrane, and uterine contractions. However, a complete understanding of the biomechanisms behind full-term labor remains elusive, hindering comprehension of late pregnancy complications such as uterine rupture after cesarean and preterm birth.

To enhance childbirth outcomes, investigating several pathologies associated with the late stages of pregnancy is mandatory. Therefore, the following objectives were established: (i) characterize the mechanical response of the uterine body, (ii) characterize the mechanical response of the fetal membrane, and (iii) investigate the mechanical interaction between the cervix, fetal membrane, and uterine body, using a complete biomechanical model of a third-trimester pregnant uterus.

An electro-chemo-mechanical model mimicking uterine contractions was employed to study the mechanical behavior of cesarean scars during vaginal delivery and the impact of irregular uterine contractions. This model was validated using available experimental data. Findings indicate that the fiber

arrangement in cesarean scars significantly influences mechanical behavior, while irregular contractions result in varied stress patterns.

Fetal membranes are multilayered biological structures, comprising the amnion, chorion, and part of the maternal layer decidua. The amnion, the mechanical dominant layer, was characterized through an anisotropic model adapted to a membrane formulation and validated through an experimental dataset retrieved from inflation mechanical tests. Physiological conditions such as fiber orientation, intrauterine pressure, and membrane thickness were found to influence membrane rupture.

After accomplishing the previous steps, all conditions were reunited to develop and characterize a complete biomechanical model of a third-trimester pregnant uterus, comprising the cervix, uterine body, multilayer fetal membrane, and abdomen. Observations included decreased stress values in more dilated and softer cervixes, with reduced cervical stiffness leading to increased cervical dilation. Additionally, cervical contractions impacted stress distribution and potentiated cervical shortening and dilation. Larger intrauterine pressure resulted in increased stress values and cervical opening.

Resumo

A Organização Mundial da Saúde (OMS) define parto normal como aquele que ocorre espontaneamente sem riscos identificados até ao início do trabalho de parto, ocorrendo entre as 37 e 42 semanas de gestação, com o bebé a nascer espontaneamente na posição anterior occipital. O sucesso da gravidez depende significativamente das complexas interações mecânicas entre o corpo uterino, o colo do útero e o saco amniótico, que normalmente seguem a seguinte sequência: amaciamento do colo do útero, ativação decidual/rutura do saco amniótico e contrações uterinas. No entanto, ainda não existe uma completa compreensão dos mecanismos biomecânicos por detrás do parto, o que dificulta o estudo de complicações associadas à gravidez, como a rutura uterina após uma cesariana ou o parto prematuro.

Este trabalho tem como objetivo melhorar os resultados do parto, através da investigação de várias patologias associadas às últimas fases da gravidez. Foram estabelecidos os seguintes objetivos: (i) caracterizar a resposta mecânica do corpo uterino, (ii) caracterizar a resposta mecânica do saco amniótico e (iii) investigar a interação mecânica entre o colo do útero, saco amniótico e corpo uterino, usando um modelo biomecânico completo de um útero no terceiro trimestre de gestação.

Com o objetivo de estudar o comportamento mecânico de cicatrizes de cesariana durante um parto vaginal e o impacto de contrações uterinas irregulares, foi aplicado e validado um modelo electro-químico-mecânico capaz

de reproduzir contrações uterinas. Os resultados indicaram que a disposição das fibras nas cicatrizes de cesariana influencia significativamente o seu comportamento mecânico, enquanto contrações irregulares resultam em padrões de tensão variados.

Os sacos amnióticos são estruturas biológicas com múltiplas camadas, contendo o âmnio, o córion e parte da camada materna decídua. O âmnio, a camada mecânica dominante, foi caracterizado através de um modelo anisotrópico adaptado a uma formulação de membrana e validado através de um conjunto de dados experimentais obtidos a partir de testes mecânicos de inflação. Através desta caracterização, conclui-se que certas condições fisiológicas, como a orientação das fibras, a pressão intrauterina e a espessura das camadas do saco amniótico, influenciam a ruptura da membrana.

Após a conclusão das etapas anteriores, reuniram-se todas as condições para desenvolver e caracterizar um modelo biomecânico completo de um útero durante o terceiro trimestre de gestação, contendo o colo do útero, o corpo uterino, o saco amniótico multicamada e o abdômen. Os resultados revelaram que os valores de tensão diminuem em colos mais dilatados e mais macios, e que uma redução da rigidez cervical leva a uma maior dilatação cervical. Além disso, as contrações cervicais influenciam a distribuição de tensão e potencializam o encurtamento e a dilatação cervical. Uma maior pressão intrauterina resulta em valores de tensão mais elevados e maior abertura cervical.

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PART A: Thesis Report

Introduction

Successful parturition relies on various factors, such as synchronized interaction between three essential biological structures: the uterine body, the cervix, and the fetal membrane (Vink, 2020). In uncomplicated vaginal deliveries, the following ordered sequence occurs: (1) cervical ripening, (2) decidual activation and rupture of fetal membrane, and (3) uterine contractions (Vink & Feltovich, 2016). However, a distinct sequence is verified when, for example, premature rupture of the fetal membrane or preterm labor occurs, and it may include early cervical ripening (cervical insufficiency), preterm premature rupture of the fetal membrane, and preterm uterine contractions (Vink, 2020). Despite extensive research, a complete characterization of the biomechanisms by which women enter labor at full term and preterm birth is still missing (Voltolini et al., 2013). There are currently no accurate methods to determine whether patients will undergo any complications, or any treatments to prevent them effectively (Vink, 2020). Given the inherently mechanical nature of these processes, a better understanding of the mechanical responses of the uterine, cervical, and fetal membranes during birth is crucial.

The fetal membranes comprise two main layers, the amnion and chorion, whose microstructures differ significantly from each other (Helmig et al., 1993). The amnion is the inner layer of the membranes facing the amniotic fluid, while the chorion is the outer layer contacting the uterine wall (Ilancheran et al., 2009; Zhang et al., 2021). The fibrous amnion layer is the mechanically dominant layer

of the fetal membranes (Buerzle & Mazza, 2013; Oyen et al., 2004, 2006). Randomly oriented collagen fibers dominate the material response to tensile loading. The amnion is thinner, stiffer, and stronger than the compliant and more extensible chorion (Buerzle et al., 2012; Buerzle & Mazza, 2013; Oyen et al., 2004). The amnion and chorion are separated by a spongy layer, which comprises proteoglycans and glycoproteins, along with collagen of type III, and the spongy layer interface allows the amnion to slide on the underlying chorion (Joyce et al., 2009; Menon & Richardson, 2017). The decidua, a maternal layer adjacent to the chorion, also plays an essential role in the fetal membranes (Tahan & Tahan, 2014). This layer results from the uterine endometrium's differentiation process under the influence of progesterone (Abbas et al., 2019). It is known that the decidua shares a close anatomical relationship with the chorion (chorio-decidua layer), which might suggest that decidual changes may be associated with chorioamnion membrane alterations (Malak & Bell, 1994). The development of the decidual layer and the chorion is synchronized from the earliest implantation phase, and the smooth chorion becomes fused with the decidua (Ogura et al., 2017). About 3% of all pregnancies worldwide suffer a membrane rupture earlier than the 37th week of gestation, called preterm pre-labor rupture of the fetal membranes (PPROM) (Mercer, 2010). PPRM is responsible for approximately one-third of all preterm births, contributing significantly to perinatal morbidity and mortality (Verbruggen et al., 2017).

Another essential biological structure in pregnancy is the cervix at the base of the uterus, comprising cervical epithelial and stromal layers (Tantengco &

Menon, 2020). The cervix must remain closed to support the mechanical loads developed by the growing fetus throughout most of the gestation (Shi et al., 2019). The cervix softens throughout pregnancy, in preparation for labor (Badir et al., 2013), but if cervical softening occurs too soon, there is a risk of preterm birth (Vink, 2020). Thus, the cervix undergoes an important remodeling process throughout gestation, involving rearrangement and realignment of collagen fibrils, and changes in the extracellular matrix (ECM) (Barnum et al., 2022; K. M. Myers et al., 2009; Nallasamy et al., 2021; Tantengco & Menon, 2020; Yao et al., 2016).

The uterine wall is composed of three distinct layers: (i) endometrium (inner mucosal layer), (ii) myometrium (thick middle layer), and (iii) perimetrium (thin outer layer) (K. M. Myers & Elad, 2017). The endometrium-myometrium interface, known as the junctional zone, is crucial for normal reproduction, but also for the development of pathologies (Dawes et al., 2013). One factor that may contribute to complications during vaginal delivery is an uncoordinated set of uterine contractions. Uncoordinated uterine activity can disturb the uterine contractions pattern and negatively impact fetal and maternal health. Inadequate maternal expulsive efforts, usually associated with larger intra-abdominal pressure, and inadequate uterine contractions are the main reasons for poor labor progress (Ebrahimzadeh et al., 2012; El-Hamamy & Arulkumaran, 2005; Olaby et al., 2006). These irregular contraction patterns occur due to physical and physiological factors, such as lack of energy, dehydration, ketoacidosis, and fatigue (Newton, 1990). There are several abnormal contraction

patterns (Gyselaers et al., 1991), including excessive frequency of contractions (hypercontractility, hyperstimulation, and tachysystole) (Takahashi et al., 2003), excessive contraction duration (tetanic contractions) (Cohen & Friedman, 2015), coupling (two or more contractions without a full return to a normal baseline) (Cronjé & van der Westhuizen, 1988; Dawood, 1995; Ferreira & Odendaal, 1994) and excessively short resting intervals (Hobson et al., 2019).

The complications described in the previous paragraphs are often associated with a preterm birth, defined as a delivery before 37 weeks of gestation. Global rates of preterm birth have increased from 9.8% in 2000 to 10.6% in 2014 (Vink, 2020; Walani, 2020). This trend is alarming, as preterm birth is one of the main complications leading to fetal morbidity and mortality. Surviving babies may suffer certain short-term morbidities such as neonatal respiratory conditions, necrotizing enterocolitis, sepsis, neurological conditions, feeding difficulties, and visual and hearing problems (De Araújo et al., 2012; Mwaniki et al., 2012; Platt, 2014). As long-term complications, they may suffer poorer neurodevelopment, higher rates of hospital admissions, and behavioral, social-emotional, and learning difficulties (Teune et al., 2011; Vogel et al., 2018). An essential problem in preterm birth prevention is an incomplete understanding of normal birthing (Voltolini et al., 2013).

As an alternative to a risky term or preterm vaginal delivery, cesarean section (CS) is commonly performed. Latin America and the Caribbean region have the highest CS rate (40.5%), followed by Northern America (32.3%), Oceania (31.1%), Europe (25%), Asia (19.2%) and Africa (7.3%) (Betrán et al., 2016). CS is

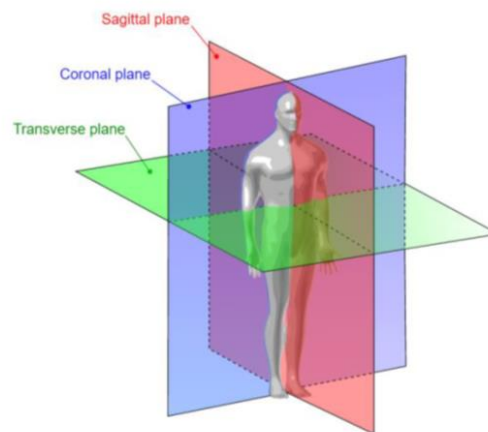
the most common surgical procedure in the United States, where approximately 1 in 3 women who gave birth in 2016 did so by cesarean delivery (Hicklin et al., 2019). It is known that CS may save both the mother and the baby, but the rapid increase in CS rates worldwide has worried the medical community. As a surgery, there are several health risks for the mother and it cannot be performed lightly (Betrán et al., 2016). Besides, obstetricians have realized the importance of uterine wound healing regarding the dehiscence of uterine scars and their rupture (Roeder et al., 2012). It has been hypothesized that an abnormal wound fiber reorientation may contribute to the development of different kinds of uterine pathologies (Roeder et al., 2012). However, there is inconsistent information regarding the fiber orientation in the uterine scars, which represents a great gap in understanding the uterine wound rupture during vaginal birth after cesarean.

The previous paragraphs highlight how many questions remain unanswered, despite all efforts to clarify them. To overcome this obstacle, several investigations have been performed to characterize the complex uterine environment during different stages of pregnancy, resorting to numerical and experimental methods. Vila Pouca et al. simulated uterine contractions to reproduce the initial moments of the second stage of labor (Vila Pouca et al., 2019). Buerzle and Mazza et al. developed a mechanical constitutive model to characterize the fetal membrane response (Buerzle & Mazza, 2013; Fidalgo et al., 2024). Oxlund et al. developed a method to collect uniaxial data concerning the mechanical properties of the fetal membranes (Oxlund et al., 1990). Helmig et al.

studied whether the mechanical properties of the fetal membranes changed during late pregnancy and labor, concluding that pronounced changes were induced in the amnion and chorion mechanical properties (Helmig et al., 1993). Oyen et al. investigated the soft-tissue time-dependent behavior, focusing on the amnion sublayer, and the differences between the amnion and the chorion in terms of failure properties, analyzing the biaxial puncture failure of intact chorio-amnion, and separated amnion and chorion (Oyen et al., 2004). Oyen et al. also performed uniaxial and planar bi-axial mechanical tests to determine the amnion layer's nonlinear and time-dependent mechanical response (Oyen, 2005). Verbruggen et al. developed linear finite element models of fetal membranes to determine the mechanical role of the amnion and the chorion layers, and to simulate the uterine environment in the context of term gestation and PPRM (Verbruggen et al., 2017).

Before advancing to the description of this work, it is necessary to consider the planes and sections of the body and some directional terms (Figure 1). This helps locate different biological structures in relation to one another and identify different regions of the same structure.

Planes and sections of the body



Orientation and directional terms

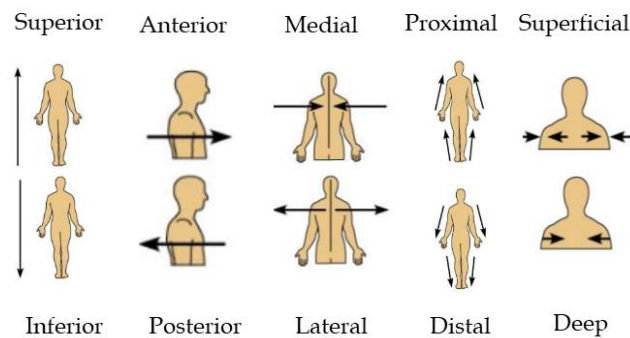


Figure 1. Anatomical planes of reference and directional terms in human anatomy (adapted from (Saladin, 2009)).

Main Goals and Objectives

This work aimed to investigate relevant aspects associated with term and preterm vaginal deliveries, focusing on the mechanical role of the cervix, fetal membrane, the body of the uterus, and the respective mechanical interactions. It intends to contribute to a better understanding of several questions associated with late stages of pregnancy, perform meaningful clinical intervention, and enhance childbirth outcomes. This was achieved through the development and

validation of computational and constitutive models. A detailed explanation of the goals of this work is presented:

- Investigate the mechanical impact of a cesarean scar in a subsequent vaginal delivery, using existing computational and constitutive models.
- Characterize the mechanical response of the uterine body using a mechano-electrochemical constitutive model; represent the passive and active behavior of the body of the uterus, mimicking a set of resting and uterine contractions, respectively; validate the constitutive model with experimental data published in the literature.
- Investigate the mechanical impact of irregular uterine contractions, using the mechanical characterization of the uterine body described in the previous point.
- Characterize the mechanical dominant layer of fetal membranes (amnion), using an anisotropic constitutive model; develop a multilayer fetal membrane model, comprising the amnion, chorion, and part of the maternal layer decidua; validate this model using an experimental dataset obtained from an inflation mechanical test.
- Evaluate what physiological conditions may potentiate a preterm premature rupture of fetal membranes, using the multilayer fetal membrane model described in the previous point.
- Develop a third-trimester complete biomechanical model of pregnancy, comprising the uterine body, multilayer fetal membrane, cervix, and abdomen, and applying the mechanical characterization of the uterine

body and multilayer fetal membrane explained in previous points; evaluate how the mechanical interaction between the cervix, fetal membrane, and uterine body may dictate the outcomes of vaginal delivery and what mechanical factors may potentiate preterm birth and preterm premature rupture of the fetal membrane.

Thesis Structure

This thesis is divided into two main parts: **PART A** and **PART B**. The first part (**PART A**) comprises six subsections:

- **Introduction:** the importance of understanding the mechanical processes leading to term or preterm vaginal delivery is highlighted; the cervix, fetal membrane, and uterine body are described from a mechanical perspective; the need to use computational methods to investigate normal or abnormal vaginal deliveries is explained.
- **Main goals and Objectives:** the main objectives of this work are listed, focusing on the development and characterizations of a complete biomechanical model of pregnancy.
- **Thesis Structure:** the structure of this thesis is presented.
- **Brief description of the developed work:** the work developed throughout this project is briefly described, summarizing the methods applied throughout the investigation.

- **Main findings achieved:** the main contributions and potential clinical applications are listed, based on the results collected throughout this work.
- **Conclusions and future work:** the main conclusions and future perspectives of this work are discussed, aiming to create new investigation paths on pregnancy.

The second part (**PART B**) contains the articles written during this project, exploring different aspects of the biomechanics of vaginal delivery at the late stages of pregnancy. The articles are presented in the following sequence:

- **Article 1**
 - *Title:* Mechanical effects of a Maylard scar during a vaginal birth after a previous cesarean
 - *Authors:* Daniel Fidalgo, Maria Vila Pouca, Dulce Oliveira, Ewelina Malanowska, Kristin Myers, Renato Natal, Marco Parente
 - *Published in:* Annals of Biomedical Engineering, 49(12): 3593-3608, 2021
- **Article 2**
 - *Title:* On the effect of irregular uterine activity during a vaginal delivery using an electro-chemo-mechanical constitutive model
 - *Authors:* Daniel Fidalgo, Margarida Borges, Maria Vila Pouca, Dulce Oliveira, Ewelina Malanowska, Kristin Myers

- *Published in:* Journal of the Mechanical Behavior of Biomedical Materials, 131, 105250, 2022
- **Article 3**
 - *Title:* Development of a multilayer fetal membrane material model calibrated using bulge inflation mechanical tests
 - *Authors:* Daniel Fidalgo, Kayvan Samimi, Michelle Oyen, Melissa Skala, Renato Natal, Marco Parente, Ewelina Malanowska, Dulce Oliveira, Kristin Myers
 - *Published in:* Journal of the Mechanical Behavior of Biomedical Material, 150 106344, 2024
- **Article 4**
 - *Title:* Contributing factors to preterm pre-labor rupture of the fetal membrane: biomechanical analysis of the membrane under different physiological conditions
 - *Authors:* Daniel Fidalgo, Kayvan Samimi, Melissa Skala, Renato Natal, Marco Parente, Ewelina Malanowska, Kristin Myers, Dulce Oliveira
 - *Submitted in:* Mechanics of Materials (under review)
- **Article 5**
 - *Title:* Pregnancy stage before the onset of labor: a holistic mechanical perspective

- *Authors:* Daniel Fidalgo, Renato Natal, Marco Parente, Erin Louwagie, Ewelina Malanowska, Kristin Myers, Dulce Oliveira
- *Published in:* Biomechanics and Modeling in Mechanobiology, (2024): 1-20

Brief description of the developed work

In this thesis, the interaction between the cervix, fetal membrane, and uterine body was planned to be holistically investigated, as well as the characterization of each biological structure from a mechanical perspective. This work aimed to perform meaningful clinical clarifications and contribute to enhancing childbirth outcomes. This was accomplished by resorting to numerical and computational methods, resulting in numerical and constitutive models with clinical and scientific interest.

The developed work can be divided into three main parts. The first part was dedicated to characterizing an electro-chemo-mechanical constitutive model to define the mechanical response of the uterus and replicate a set of uterine contractions. In the second part, a multilayered fetal membrane model was created to capture the physiological response of the fetal membranes within the uterine environment. Finally, in the third part of this work, a complete parameterized biomechanical model of a third-trimester pregnant uterus was developed, based on existing models, to investigate the impact of several

physiological cervical conditions during labor, in interaction with the fetal membrane and uterine body.

Previously, a chemo-mechanical constitutive model was developed to investigate normal uterine contractions during fetal expulsion without an imposed trajectory (Vila Pouca et al., 2019). However, the electrical nature of the uterine contractions was missing in this formulation, interfering with its mechanical outcomes. In this context, an electro-chemo-mechanical constitutive model was implemented and validated to characterize the uterine tissue, mimicking a set of uterine contractions, and obtain more accurate mechanical outcomes. The implementation of the electrical sub-model was validated by comparing the voltage and calcium evolutions with previous works. This first part resulted in the development of two independent works. In the first one, a biomechanical approach was created to analyze different scenarios of fibers arrangements and matrix/fibers stiffness values of a Maylard scar and study its influence in vaginal birth after a cesarean (**Article 1**); the chemo-mechanical model was applied in this study to understand the respective constitutive formulation, facilitating the further implementation of the electrical sub-model; a Maylard cesarean scar was introduced into the uterine model, using clinical information to define the respective dimensions; this was the first work to perform a numerical simulation of vaginal birth after cesarean. A second work was carried out to investigate the mechanical impact of irregular uterine contractions (short resting intervals and tachysystole), where the electro-chemo-mechanical model was used (**Article 2**); this was the first work to investigate the

effect caused by abnormal uterine activity, namely excessively short resting intervals and tachysystole. Both works were developed using a simplified uterine and fetal model, where uterine contractions expel the fetus from the uterine cavity, without an imposed trajectory.

Fetal membranes are multilayered biological structures, comprising the two main layers amnion and chorion, and part of the maternal layer decidua. Understating the complex interaction between the membranes, the cervix, and the uterus at term or preterm requires accurate modeling of the fetal membrane, especially due to the amnion's anisotropic nonlinear behavior, which dominates the membrane's mechanical response, and it is usually neglected (Verbruggen et al., 2017). Therefore, a multilayer fetal membrane biomechanical model capturing the mechanical response of fetal membranes was developed. This model is an improvement over the existing ones by considering the amnion as an anisotropic nonlinear material (**Article 3**). The validation was achieved by comparing the inflation apex displacement of the model with an inflation mechanical dataset (Samimi et al., 2023), and comparing the numerical maximum principal stress values in the amnion and chorion layers with the respective physiological ranges reported in the literature. Taking advantage of this model, the following conditions were analyzed whether they may contribute to preterm pre-labor rupture of the fetal membrane: (i) different contact conditions between the amnion and the chorion, (ii) normal and abnormal intrauterine pressures (from 30th to 40th gestational week), (iii) different amnion and chorion

thicknesses, and (iv) different orientations of the collagen fibers within the amnion layer (**Article 4**).

After completing the mechanical characterization of the uterine body and fetal membrane, all conditions were gathered to initiate the third part of this work. The complex interaction between the cervix, fetal membrane, and uterine contractions was analyzed before the onset of labor, using a complete parameterized biomechanical model of a three-trimester pregnant uterus, comprising the uterine body, fetal membrane, cervix, and abdomen (**Article 5**). This model was created based on the work of Dr. Erin Louwagie, from Columbia University in the United States. Each structure was characterized by appropriate constitutive models: the uterine body and cervix were modeled through the electro-chemo-mechanical, according to the first part of this work; the multilayered fetal membrane was characterized according to the second part of this work; the Neo-Hookean constitutive model characterized the abdomen. The impact of the following physiological conditions on the maximal principal stress distribution, cervical change in terms of shape, and fetal membrane rupture were investigated: (i) initial cervical shape, (ii) cervical stiffness, (iii) cervical contractions, and (iv) intrauterine pressure. The analysis of the first condition was possible due to the parametric nature of the complete pregnant uterus, allowing the generation of different cervical geometries. This was the first numerical study embracing a complete full gravid uterine and cervical model, uterine and cervical contractions, intrauterine pressure, and a diversity of pregnancy-associated features. The objectives of this work were to give more

insight into what conditions could influence a successful vaginal delivery and clarify the complex biomechanical interaction between the cervix, fetal membrane, and body of the uterus, which is not entirely understood.

Main findings achieved

The main results and findings collected from each article are depicted below:

- **Article 1:** the presence of a Maylard scar during the numerical simulation of vaginal delivery after cesarean had an important mechanical impact on the maximum principal stresses and fibers stretch within the scar; the results revealed that a random fiber arrangement in the Maylard scar has a greater impact on its mechanical behavior during vaginal birth after cesarean than the common fibers arrangement in the uninjured uterine tissue; an increase in matrix scar stiffness exhibits a smaller impact, while an increase in the fiber's stiffness has no significant influence; therefore, it is essential to track the fiber reorientation during the wound healing process after cesarean section, since it is related with the risk of rupturing, in subsequent vaginal delivery; this can be achieved through optical coherence tomography, commonly used to access cervical collagen fibers rearrangement.
- **Article 2:** regarding the investigation of irregular uterine contraction patterns during the second stage of labor, the excessively short resting

intervals exhibited larger average maximum principal stresses during the contraction and resting stages, smaller average fiber stretch values in the longitudinal direction, and larger stretches in the circumferential direction; on the other hand, tachysystole exhibited generally smaller stress values during the uterine contraction and larger stress values during the resting stages, larger stretches in the longitudinal direction, and smaller stretches in the circumferential direction.

For excessively short resting intervals, larger stress values will probably result in stronger compressions of the uterine vessels, which may cause oxygenation difficulties reported in the literature.

It has been reported that tachysystole is frequently associated with fetal heart rate decelerations, especially in response to oxytocin administration, and our results are consistent with these findings since the larger stress values at the end of the resting periods will not allow the uterine vessels to achieve the same relaxation states as the control model, which may explain the difficulty in providing oxygen to the fetus and consequently the fetal heart rate decelerations.

This work revealed several practical implications for obstetricians in managing safe and effective labor induction. Prostaglandins are the current recommended induction method, but uterine hyperstimulation syndrome, where contractions become too frequent or long, may lead to adverse effects, such as fetal asphyxia, uterine rupture, or even placental abruption.

- **Article 3:** The layered computational model of the fetal membrane captured the overall behavior of the fetal membranes, with the amnion being the mechanically dominant layer.

According to the experimental dataset, the inclusion of fibers in the amnion material model proved important in obtaining reliable fetal membrane behavior. It was also found that the amnion underwent significant lateral contraction compared to the longitudinal stretch, indicating that the amnion possesses a high Poisson ratio. The fiber-based multi-layer model found that the amnion is subjected to larger stress levels than the chorion, withstanding most loads occurring throughout gestation. Besides, the chorion has a reduction in thickness of 15% while the amnion has a reduction of 47%. These results highlight the potential of this layered model to be integrated into larger biomechanical models of the gravid uterus and cervix to study the mechanical mechanisms of normal and preterm birth.

- **Article 4:** The results collected from this work showed that preterm pre-labor rupture of the fetal membrane could be potentiated under certain physiological circumstances:
 - (i) the existence of friction between the amnion and the chorion, associated with reduced lubrication, led to larger mechanical stresses, promoting its rupture;

- (ii) larger intrauterine pressures and smaller amnion and chorion thicknesses led to the same increase in stress, representing contributing factors to membrane rupture;
 - (iii) different off-plane fiber angles had a strong impact on the fetal membrane behavior, affecting the apex displacement of the membrane, the maximum principal stress, and the thickness variation at the apex region of the amnion and the chorion: the apex displacement was larger for larger off-plane angles, and the maximum principal stresses and thickness variations exhibited a high variability for different angles.
- **Article 5:** Several key observations were collected from this work:
 - (i) maximum principal stress values in the cervix decreased in more dilated, shorter, and softer cervixes;
 - (ii) reduced cervical stiffness produced increased cervical dilation, larger cervical opening, and decreased cervical length;
 - (iii) the initial cervical shape impacted final cervical dimensions;
 - (iv) cervical contractions increased the maximum principal stress values and change the stress distributions;
 - (v) cervical contractions potentiated cervical shortening and dilation;
 - (vi) larger intrauterine pressure (IUP) caused considerably larger stress values and cervical opening, larger dilation, and smaller cervical length;

- (vii) the biaxial strength of the fetal membrane was only surpassed in the cases of the (1) shortest and most dilated initial cervical geometry and (2) larger IUP.

These results reinforce the importance of understanding the interaction between the cervix, fetal membrane, and uterine body to guide the clinical approach to several complications, such as failed induced labor and preterm birth.

Conclusions and Future Works

Any biomechanical phenomenon occurring during pregnancy requires a complete understanding of multiple biological, physical, chemical, and mechanical factors to fully comprehend all events occurring throughout gestation. In this work, the isolated and interactive mechanical responses of the main biological structures in pregnancy (cervix, fetal membrane, and uterine body) were investigated. All the objectives established at the beginning of this work were accomplished, resulting in several biomechanical clarifications about the late stages of pregnancy and labor. An electro-chemo-mechanical model and an anisotropic fetal membrane model were adopted, developed, and validated, using literature and experimental data, and a complete model of pregnancy was created based on previous works and clinical inputs.

This work resulted in the development of a biomechanical basis to study late stages of pregnancy, with significant clinical and scientific applications. Although the initial objectives have been accomplished, it would be interesting to explore the integration of the complete biomechanical model of the third-trimester pregnant uterus in clinical practice due to its parameterized nature. The dimensions and mechanical properties of each biological structure can be adjusted, creating the path to evaluate several patient-specific pathologies associated with pregnancy. However, some efforts still need to be performed. First, it is necessary to explore new ways to access the mechanical properties of the cervix, fetal membrane, and body of the uterus during pregnancy, using tools such as magnetic resonance elastography or ultrasound elastography, which can provide non-invasive assessments of tissue stiffness. Secondly, it is crucial to offer answers and clinical guidance to patients as fast as possible. This can be achieved by implementing artificial intelligence methods, saving time compared to conventional computational methods. For instance, machine learning algorithms can analyze complex datasets from mechanical tests or medical imaging to identify patterns associated with preterm birth risk or abnormal mechanical properties. Deep learning models trained on medical imaging data can automate the segmentation and analysis of cervix or uterine images, facilitating rapid diagnosis and prognosis. Promising directions for future research also include determining whether obstetric complications could be estimated by creating a personalized model for each patient and predicting

PPROM risk based on the model of the shortened cervix in patients after gynecological procedures, such as cold knife conization.

The application of the electro-chemo-mechanical model allowed the simulation of uterine and cervical contractions. However, the viscoelastic behavior of the uterine body and cervix, and the effect of oxytocin on muscular contractions were not considered. In the future, it is important to implement these features into the model.

The cervix is a multilayer structure, comprising epithelial and connective layers. This can be implemented to improve the simplified cervical structure used in this work.

An inflation mechanical test was performed to collect data and validate our fetal membrane model. The initial stress state of the fetal membrane at the beginning of this test is not stress-free. It is difficult to experimentally replicate the existing conditions within the pregnant uterus, and it is also difficult to precisely detect the stress-free configuration of the membrane free of membrane wrinkles. The effect of small pre-stress in the membrane may be investigated in future works through a sensitivity analysis.

The uterine remodeling process and the uterine growth diverge from patient to patient, which will lead to an alteration of the mechanical properties. Different results will be obtained if this phenomenon is introduced into our model, which can be performed as a future task. However, it is challenging to do

so, since uterine remodeling is such a complicated process that is still not completely comprehended by the scientific community.

Finally, the impact of growing twins and abnormal uterine/cervical positions during pregnancy and labor are also important factors with great mechanical impact that must be investigated in future works.

In conclusion, the construction of efficient technologies to track the pathophysiology of pregnant women is still highly dependent on the development of a more complete knowledge foundation. Reinforcing the comprehension of pregnancy is the path to achieving a better understanding of all phenomena occurring during gestation, such as preterm rupture of the membrane, preterm birth, and cervical funneling, among others. It is believed that this work contributed to expand what is known about gestation, clarifying several phenomena occurring at late stages of pregnancy from a mechanical point of view.

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PART B: Article 1

Mechanical effects of a Maylard scar during a vaginal birth after a previous cesarean

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Abstract

The cesarean section is one of the most common surgeries worldwide, even though there is no evidence supporting maternal and perinatal long-term benefits. Furthermore, the mechanical behavior of a cesarean scar during a vaginal birth after cesarean (VBAC) is not well understood since there are several questions regarding the uterine wound healing process. This study aims to investigate the biomechanical Maylard fiber reorientation and stiffness influence during a VBAC through computational methods. A biomechanical model comprising a fetus and a uterus was developed, and a chemical-mechanical constitutive model that triggers uterine contractions was used, where some of the parameters were adjusted to account for the matrix and fiber stiffness increase in the cesarean scar. Several mechanical simulations analyzed different scar fibers arrangements, considering different values for the respective matrix and fibers stiffness. The results revealed that a random fiber arrangement in the Maylard scar has a much larger impact on its mechanical behavior during a VBAC than the common fibers arrangement in the uninjured uterine tissue. An increase in matrix scar stiffness exhibits a smaller impact, while an increase in the fiber's stiffness has no significant influence.

Keywords: Cesarean Section; Maylard Incision; Vaginal Birth After Caesarean; Collagen Fiber Orientation; Numerical Simulation; Finite Element Method.

Abbreviations:

VBAC - Vaginal birth after cesarean

CS - Cesarean section

FE - Finite element

MLCK - Myosin Light Chain Kinase

HGO - Holzapfel-Gasser-Ogden

CM - Control Model

IM - Increased Matrix Stiffness Model

IF - Increases Fiber Stiffness Model

RF - Random Fiber Distribution Model

CF - Circumferential Fibers Model

LF - Longitudinal Fibers Model

SVB - Second Vaginal Birth

MR - Magnetic Resonance

DTI - Diffusion Tensor Imaging

Introduction

Cesarean section (CS) surgery rates have been increasing worldwide (Rusavy et al., 2019). Latin America and the Caribbean region present the highest CS rate (40.5%), followed by Northern America (32.3%), Oceania (31.1%), Europe (25%), Asia (19.2%) and Africa (7.3%) (Betrán et al., 2016). CS is the most common surgical procedure in the United States, where approximately 1 in 3 women who gave birth in 2016 did so by cesarean delivery (Hicklin et al., 2019).

Different cesarean incisions can be performed, and the best approach is chosen according to each pregnancy. One is the Maylard incision, which consists of an extended transverse cut characterized by bilateral ligation of the deep inferior epigastric vessels and transection of the anterior rectus abdominis muscles (Ortiz Molina et al., 2020). It is preferred over the remaining CS when an alternative to midline laparotomy and a good exposure of the pelvis is demanded, due to an abnormal baby's position at term (Giacalone et al., 2002).

It is known that CS may represent a life-saving procedure for both the mother and the baby, but the rapid increase in CS rates worldwide has worried the medical community. As a surgery, there are several health risks for the mother so it cannot be performed lightly (Betrán et al., 2016). The professionals have encouraged women with prior cesarean delivery to give birth vaginally in future pregnancies since 80% of vaginal birth after a cesarean (VBAC) happens successfully (C. S. Buhimschi et al., 2005). However, some authors are concerned with the association between this practice and the risk of uterine rupture, which

can be life-threatening for the mother. The uterine scar rupture happens in about 0.5-1.5% of all women undergoing VBAC (di Pasquo et al., 2020; Landon et al., 2006; Tanos & Toney, 2019).

Over the past years, obstetricians have realized the importance of uterine wound healing regarding the dehiscence of uterine scars and their rupture (Roeder et al., 2012). For instance, it has been hypothesized that an abnormal wound fiber reorientation may contribute to the development of different kinds of uterine pathologies (Roeder et al., 2012). However, there is inconsistent information regarding the fiber orientation in the uterine scars, which represents a great gap in understanding the uterine rupture process during VBAC.

Taking a look at different soft tissues, studies involving rats concluded that the Achilles tendon after recovering from tendinitis exhibits random and disrupted fiber distribution (Davidson et al., 1997). Moreover, scared skin behavior suggests that collagen fibers are aligned with the force applied (Clark et al., 1996). Therefore, different soft tissues may exhibit a different healing process, leading to different collagen fiber reorientations.

To the authors' knowledge, this will be the first work to perform a numerical simulation of a VBAC. The computational methods overcome several ethical and technical questions when it is intended to perform experimental procedures using in vivo uterine tissue. This study aims to develop a biomechanical approach to analyze different scenarios of fibers arrangements and matrix/fibers stiffness values of a Maylard scar and study its influence in a VBAC from a mechanical point of view. This work is a first step towards the

clarification of the mechanisms behind the uterine rupture during a VBAC, assisting in clinical decisions.

Materials and Methods

Constitutive Model

Several constitutive equations have been developed to represent the uterine contractions triggered by electrical or chemical stimuli, as described by several authors (Sharifimajd et al., 2016; Vila Pouca et al., 2019; Yochum et al., 2016). Those models are intended to represent the response of the uterus throughout the second stage of labor, mimicking a set of uterine contractions and rests to expel the fetus (Yochum et al., 2016). It is known that smooth muscle contraction is triggered by an increase in the intracellular calcium concentration, which can be modeled through the macroscale chemical-mechanical constitutive model derived by Sharifimajd et al., which will be used and adjusted for this work (Sharifimajd et al., 2016)

The activation of smooth muscle relies on the concentration of myosin phosphorylation (Bursztyn et al., 2007). The phosphorylation of regulatory myosin light chains by the Ca^{2+} /calmodulin-dependent enzyme myosin light chain kinase (MLCK) is essential to regularize smooth muscle contractions (Goeckeler & Wysolmerski, 1995). Myosin can be in one of the following four

states: unbound unphosphorylated (α_A), unbound phosphorylated (α_B), bound phosphorylated (α_C), and bound unphosphorylated (α_D). $k_1 - k_7$ represent the transitions rates from one state to another: k_1 and k_6 are the rates of phosphorylation of myosin, k_2 and k_5 represent the rates for the dephosphorylation of myosin, k_3 and k_4 are the rates associated with the attachment and detachment of the fast cycling cross-bridges, respectively, and, finally, k_7 is the rate constant for latch-bridge detachment (Stålhand et al., 2008).

The kinetic state model is given by a coupled system of first-order differential equations (Sharifimajd et al., 2016):

$$\begin{bmatrix} \dot{\alpha}_A \\ \dot{\alpha}_B \\ \dot{\alpha}_C \\ \dot{\alpha}_D \end{bmatrix} = \begin{bmatrix} -k_1 & k_2 & 0 & k_7 \\ k_1 & -(k_2 + k_3) & k_4 & 0 \\ 0 & k_3 & -(k_4 + k_5) & k_6 \\ 0 & 0 & k_5 & -(k_6 + k_7) \end{bmatrix} \times \begin{bmatrix} \alpha_A \\ \alpha_B \\ \alpha_C \\ \alpha_D \end{bmatrix} \quad (2.1)$$

It is assumed that $k_6 = k_1$, $k_2 = k_5$, $k_3 = 4k_4$ and (Vila Pouca et al., 2019):

$$k_1 = k_6 = \frac{[Ca^{2+}]_i^{nk_1}}{[Ca^{2+}]_i^{nk_1} + [Ca_{1/2MLCK}^{2+}]_i^{nk_1}} \quad (2.2)$$

where $[Ca_{1/2MLCK}^{2+}]_i^{nk_1}$ is the required calcium ion concentration for half-activation of MLCK by the calcium-calmodulin complex and nk_1 is the Hill coefficient of activation (Vila Pouca et al., 2019).

The actin filaments slip relative to a myosin-coated surface during contraction and the slip velocity depends on the load applied (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014). The macroscopic equivalence to this phenomenon is a friction clutch, which allows it to represent the active force generation (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014). Therefore, the dynamics of the contractile element can be represented by: (a) a friction clutch, which defines the overall effect of cycling cross-bridges; (b) a brake-like mechanism in series with the clutch, associated with the overall effect of all non-cycling, or slow-cycling, cross bridges; (c) a spring attached to the clutch and the brake representing the elasticity of all cross-bridges within the contractile element (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014). The deformation will comprise two steps: an active displacement and an elastic displacement (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014). The first one will cause the clutch and the brake to translate without spring deformation, and the second one stretches the spring without moving the remaining elements of the macroscopic mechanical model (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014). Therefore, the contractile element is completely characterized by this mechanism.

The uniaxial stretch $\bar{\lambda} = \frac{l}{l_0}$ of the contractile element can be defined as (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$\bar{\lambda} = 1 + \bar{\varepsilon}_a + \bar{\varepsilon}_e \quad (2.3)$$

where $\bar{\varepsilon}_a$ and $\bar{\varepsilon}_e$ represent the active and elastic strain, respectively (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014).

It is assumed that the myometrium comprises two fasciculi families, taken to be aligned with the unit vector $\mathbf{M}_i (i = 1, 2)$, defined in the reference configuration. The stretch within each family i in the direction $\mathbf{M}_i$ can be characterized through the isochoric right Cauchy-Green tensor $\bar{\mathbf{C}} = \bar{\mathbf{F}}^T \bar{\mathbf{F}}$ as (Vila Pouca et al., 2019):

$$\bar{\lambda}_i^2 = \bar{I}_j = \bar{\mathbf{C}} : (\mathbf{M}_i \otimes \mathbf{M}_i), \quad i = 1, j = 4 \vee i = 2, j = 6 \quad (2.4)$$

where $\mathbf{F}$ represents the deformation gradient and $\bar{I}_j (j = 4, 6)$ represents the fourth and sixth invariant of the isochoric Cauchy-Green Tensor (Vila Pouca et al., 2019).

The strain energy function can be decoupled in three parts (Vila Pouca et al., 2019):

$$\Psi = \Psi_{vol} + \bar{\Psi}_m + \bar{\Psi}_f \quad (2.5)$$

where Ψ_{vol} represents the volumetric contribution, $\bar{\Psi}_m$ the ground matrix isochoric contribution, and $\bar{\Psi}_f$ the fasciculi isochoric contribution (Vila Pouca et

al., 2019). The uterus is nearly incompressible, and the volumetric contribution is therefore defined by a penalty function (Vila Pouca et al., 2019):

$$\Psi_{vol} = \frac{1}{D_1} \left(\frac{J^2 - 1}{2} - \ln(J) \right) \quad (2.6)$$

where D_1 is a constant (Vila Pouca et al., 2019).

The isochoric matrix contribution, according to the Neo-Hookean model, is given by (Vila Pouca et al., 2019):

$$\bar{\Psi}_m = C_{10}(\bar{I}_1 - 3) \quad (2.7)$$

where $\bar{I}_1 = tr(\bar{\mathbf{C}})$ is the first invariant of $\bar{\mathbf{C}}$ and C_{10} is a constant (Vila Pouca et al., 2019).

The isochoric fiber contribution results from a combination of the Holzapfel-Gasser-Ogden (HGO) passive model and an active contribution from the uterine muscle (Sharifimajd et al., 2017):

$$\bar{\Psi}_f = \zeta_1(\bar{\Psi}_1^p + N_1\bar{\Psi}_1^a) + (1 - \zeta_1)(\bar{\Psi}_2^p + N_2\bar{\Psi}_2^a) \quad (2.8)$$

where $\bar{\Psi}_i^p$ and $\bar{\Psi}_i^a$ represent the passive and active contribution of the i th fasciculi family respectively, while $\zeta_1 \in [0,1]$ is a parameter that describes the fraction of all fasciculi that belong to the first family. N_i is a function that accounts for the overlap between actin and myosin filaments (Sharifimajd et al., 2017).

$\bar{\Psi}_i^p$ is defined by the HGO model (Vila Pouca et al., 2019):

$$\bar{\Psi}_i^p = \begin{cases} \frac{\mu_{i1}}{2\mu_{i2}} \{ \exp[\mu_{i2}(\bar{I}_j - 1)^2] - 1 \}, & \text{if } \bar{I}_j \geq 1 \\ 0, & \text{otherwise} \end{cases} \quad (2.9)$$

where $j \in \{4,6\}$ and μ_{i1} and μ_{i2} are positive constants.

$\bar{\Psi}_i^a$ is defined by (Vila Pouca et al., 2019):

$$\bar{\Psi}_i^a = \frac{1}{2} \alpha_{xb} k_{xb} \bar{\epsilon}_e^2 \quad (2.10)$$

with $\alpha_{xb} = \alpha_c + \alpha_d$, which establishes the connection between the chemical and the mechanical components of the constitutive model and represents the fraction of the bound myosin, and k_{xb} is a constant (Vila Pouca et al., 2019).

Considering the macroscopic mechanic equivalence described before, the dynamics of the clutch from the macroscopic mechanic equivalence is characterized by an evolution law, derived from Sharifimajd and Stålhand et al. (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$\eta \dot{\bar{\varepsilon}}_{ai} = -F_{c,i} - \frac{\partial \bar{\Psi}_f}{\partial \bar{\varepsilon}_{ai}} + \frac{\partial \bar{\Psi}_f}{\partial \bar{\varepsilon}_{ei}} \quad (2.11)$$

where $\dot{\bar{\varepsilon}}_{ai}$ represents the active strain rate, η is a constant and $F_{c,i}$ is the friction force generated by the clutch in the i th fasciculi family (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$F_{c,i} = \begin{cases} N_i k_c \alpha_c (\dot{\bar{\varepsilon}}_{ai} + v_c), & \text{if } \dot{\bar{\varepsilon}}_{ai} \geq 1 \\ 0, & \text{otherwise} \end{cases} \quad (2.12)$$

where v_c is the peripheral clutch velocity, k_c is a constant, and N_i is given by (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$N_i = \exp\left(\frac{-(\bar{\varepsilon}_{opt} - \bar{\varepsilon}_{ai})^2}{2\gamma^2}\right) \quad (2.13)$$

where $\bar{\varepsilon}_{opt}$ represents the active strain at which the muscle generates the maximum force and γ is a constant (Vila Pouca et al., 2019).

A simulation was carried out to demonstrate the model response to a defined input. A finite element model of a unitary cube composed of a single 8-node linear brick finite element (C3D8), with the boundary conditions $v(x, 0, z) =$

0 and $v(x, 1, z) = 0$, was employed. The calcium concentration, which represents the model input, was defined according to Sharifimajd et al. (Sharifimajd et al., 2016) and is illustrated in Figure 1.

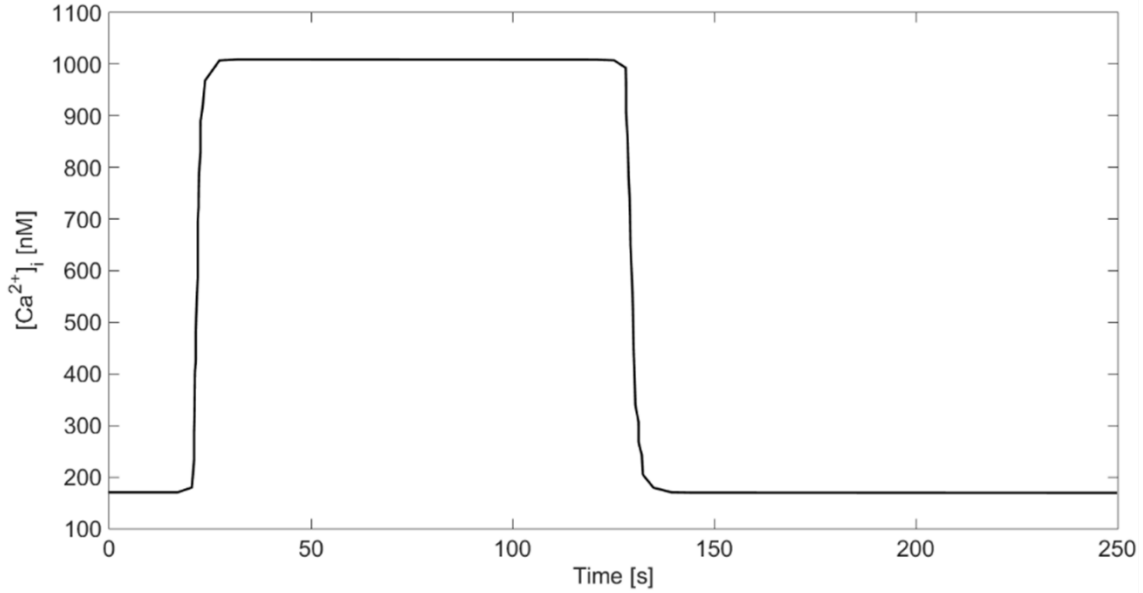


Figure 1. Calcium concentration evolution applied in the exemplary simulation.

Two families of fibers were considered, oriented in the xy plane by 0° and 90° with the x-direction.

The initial value of α_A was set to 1, and the initial values of the remaining myosin states and $\bar{\epsilon}_{ai} (i = 1, 2)$ were set to 0 (Bursztyn et al., 2007; Yochum et al., 2016).

The constitutive parameters are shown in Table 1. The simulation results are presented in Figure 2 and Figure 3: the myosin states evolution and the Cauchy stress σ_{yy} as a function of time, respectively.

Table 1. Material parameters for the exemplary simulation.

	<i>Variable</i>	<i>Description</i>	<i>Value</i>	<i>Units</i>
<i>Chemical Parameters</i> (Bursztyn et al., 2007; Sharifimajd et al., 2016; Vila Pouca et al., 2019)	k_2	Dephosphorylation of myosin rate	0.6193	s^{-1}
	k_3	Attachment and detachment of the fast-cycling cross-bridge rate	0.1419	s^{-1}
	k_7	Latch-bridge detachment rate	0.0378	s^{-1}
	$[Ca_{1/2MLCK}^{2+}]_i$	Calcium ion concentration for half-activation of MLCK	256.98	nM
	n_{k1}	Hill coefficient	8.7613	-
<i>Mechanical Parameters</i> (Bisplinghoff et al., 2012; Cochran & Gao, 2015; Sharifimajd et al., 2016; Vila Pouca et al., 2019)	C_{10}	Stiffness coefficient	0.030	MPa
	D_{10}	Volumetric coefficient	1E-5	MPa^{-1}
	ζ_1	Fraction of fibers of the first family	0.4	-
	μ_{i1} ($i = 1,2$)	Fiber's Stiffness	0.006	MPa
	μ_{i2} ($i = 1,2$)	Fiber's non-linear behavior	1.000	-
	$\bar{\epsilon}_{opt}$	Active strain for maximum force	0.495	-
	γ	Constant	1.000	-
	v_C	Peripheral clutch velocity	0.110	s^{-1}
	η	Constant	0.18	MPa s
	k_{xb}	Constant	8.000	MPa
	k_C	Constant	5.500	MPa s

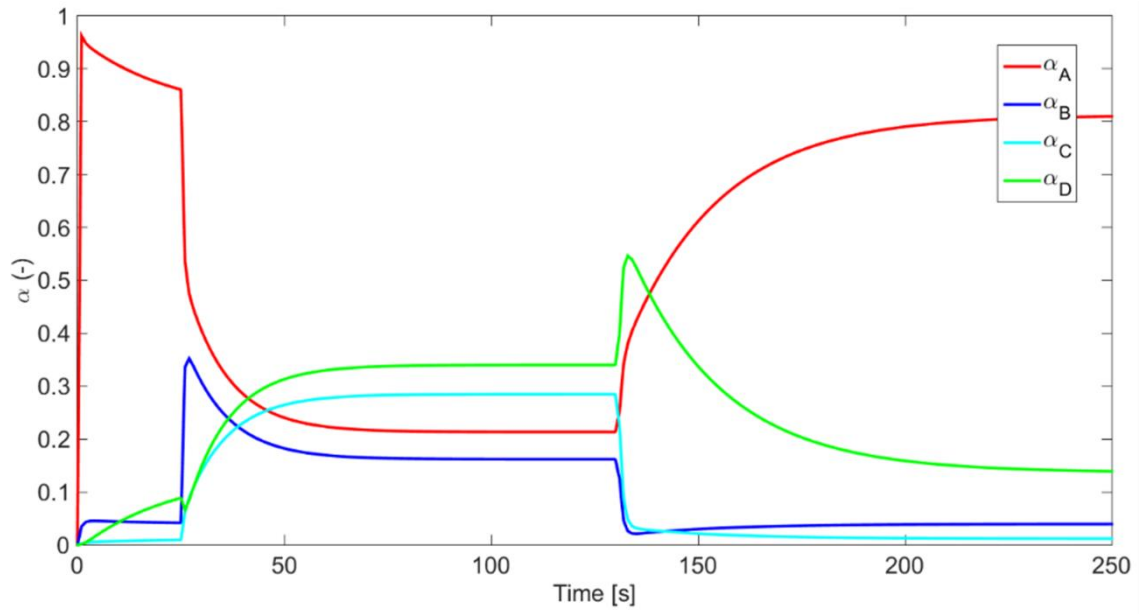


Figure 2. Myosin states dynamics.

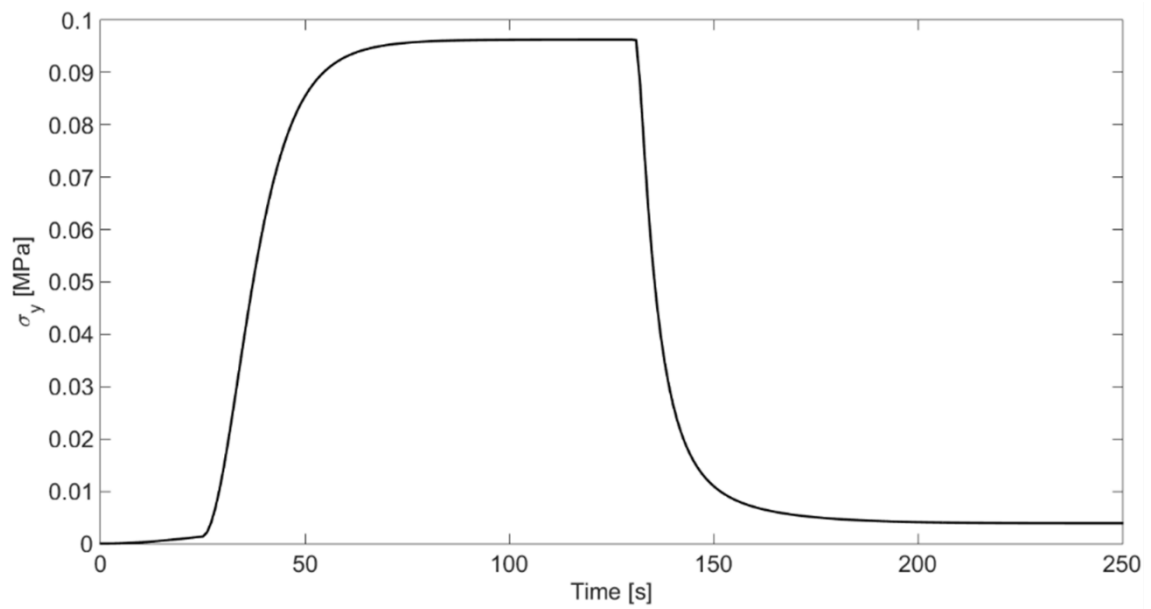


Figure 3. σ_{yy} as a function of time.

Geometrical Model and Boundary Conditions

Aiming to simulate the biomechanical behavior of the uterus during VBAC, a finite element model comprising simplified geometries of a completely developed fetus and pregnant uterus was used.

Fetus

A finite element model was first constructed following the principal obstetrical dimensions of a completely developed fetus, as described in Parente et al (Parente et al., 2010). The finite element mesh was simplified to the final geometry illustrated in Figure 4 to improve the contact algorithm performance.

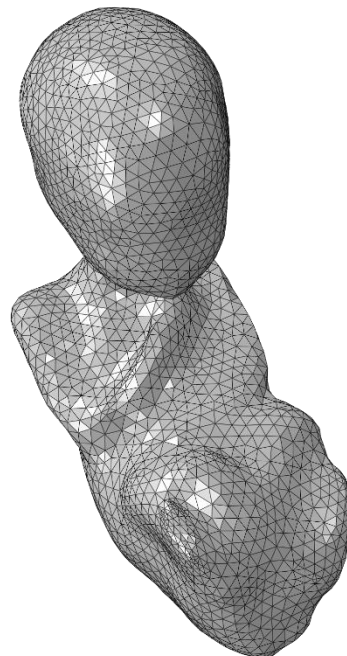


Figure 4. Simplified fetal finite element model applied in the simulations.

According to reported fetal growth data, using the finite element software ABAQUS®, the biparietal diameter and the fetal head circumference were approximately measured, guaranteeing a gestational age between 36 and 40 weeks (Kiserud et al., 2017).

The simplified fetal model was meshed with 10595 nodes and 53732 four-node tetrahedral hybrid (C3D4H) elements.

The fetal rotation in the vertical axis was constrained, allowing a stable descent of the fetus throughout the simulation, per a realistic delivery.

A hyperelastic behavior was considered for the fetal mechanical properties, applying the Neo-Hookean model with the parameter $C_{10} = 0.13$ MPa (Buttin et al., 2013). The volumetric parameter D_1 was set to a low value of 0.05 MPa^{-1} , ensuring fetal incompressibility (Vila Pouca et al., 2019).

Uterus

The uterine geometric model was developed around the simplified fetus, using the commercial SolidWorks® software, and considering a constant thickness of 10 mm (Vila Pouca et al., 2019). Aiming to adjust the uterus walls to the fetus correctly, a thermal finite element simulation was performed, obtaining a tighter model (Vila Pouca et al., 2019). It was considered two families of fascicles, aligned longitudinally and circumferentially, which are the preferred directions of the collagen fibers (Weiss et al., 2006). More information about the

modeling process of this uterine model can be found at Vila Pouca et al (Vila Pouca et al., 2019).

This study aims to analyze different fiber orientations and stiffness values in a Maylard uterine scar during VBAC. The Maylard is an extended transverse incision usually performed at the upper limit of the pubic hair, measuring at least 15 cm (Mathai & Gj, 2009). Additionally, it exhibits a width between 6.1 and 8.9 cm at term (Naji, Daemen, et al., 2013). To introduce the Maylard scar into the uterine model, it was necessary to refine the uterine mesh elements corresponding to the Maylard region. The refinement was performed through the finite element software ABAQUS® and the Maylard dimensions were considered.

The refined uterine mesh has 11891 nodes and 8374 eight-node linear brick hybrid (C3D8H) elements.

Afterward, the refined elements corresponding to the Maylard location were defined, according to Figure 5. Using the finite element software ABAQUS®, both the Maylard scar length and width were measured, to check if the values were within a realistic range. An approximate length of 17 cm and an approximate width of 8.6 cm were measured.

Subsequently, it was necessary to introduce the collagen fibers in the uterine model. The longitudinal and circumferential fibers were maintained outside the Maylard region. Several fiber arrangements were considered in the cesarean scar, as explained further. This step was performed in the finite element

software ABAQUS® and Figure 6 illustrates a general view of the fiber distribution.

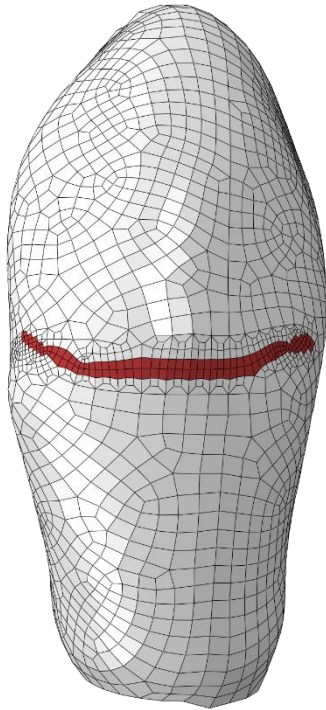


Figure 5. Uterine model with the Maylard scar represented in red.

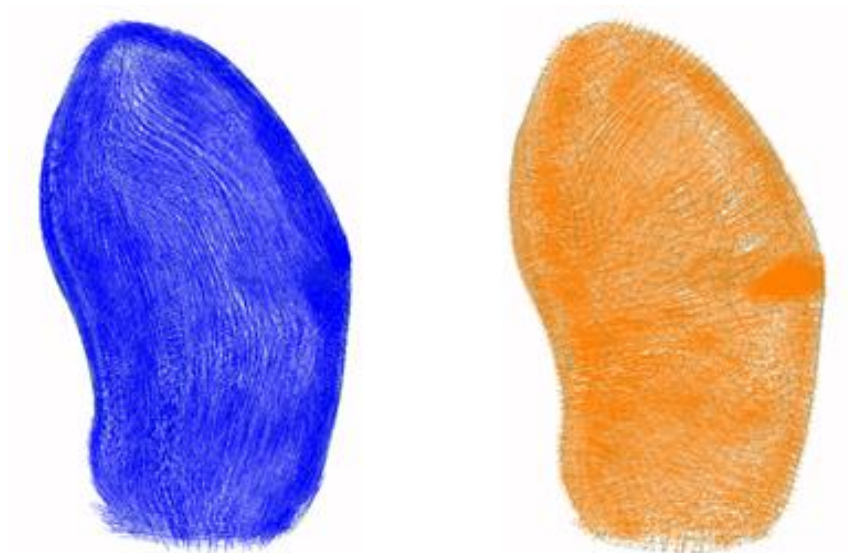


Figure 6. Uterine fibers orientation: longitudinal fibers represented in blue and circumferential fibers represented in orange.

The boundary condition applied to the uterus is illustrated in Figure 7. The node in blue was completely fixed to avoid lateral movements. In contrast, the red nodes were constrained in the vertical direction (Y axis) because the uterus should not sustain vertical movements, since it is attached to the cervical canal.

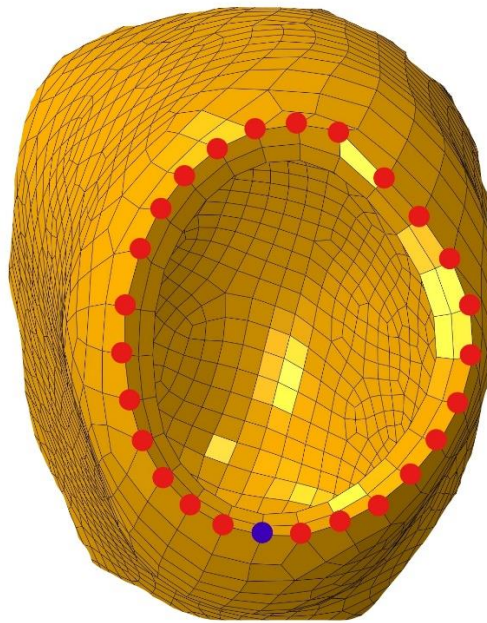


Figure 7. Boundary conditions applied to the uterus border; the blue node was completely fixed; the red nodes were constrained in the vertical direction.

Complete Biomechanical Model

The constitutive model described in the “*Constitutive Model*” section was applied to the uterine finite element (FE) model, aiming to simulate uterine contractions at the second stage of labor during a VBAC.

The parameters α_A , α_B , α_C , α_D (myosin states), and $\bar{\epsilon}_{ai}(i = 1,2)$, both applied to initiate the chemical model, were collected from the work of Bursztyn et al. and Yochum et al. (Bursztyn et al., 2007; Yochum et al., 2016). The initial α_A was set to 1, and the initial values of the remaining parameters were set to 0.

The chemical parameters k_2 , k_3 , k_7 , (transition rates), $[Ca_{1/2MLCK}^{2+}]_i$ (intracellular calcium ion concentration for half activation of MLCK), and nk_1 , (Hill coefficient), were also defined according to Bursztyn et al. and Vila Pouca et al. (Bursztyn et al., 2007; Vila Pouca et al., 2019).

The parameter D_1 (matrix compressibility) was set to a low value, ensuring an incompressible behavior ($J = 1$) (Bisplinghoff et al., 2012). The presence of the fetus and the amniotic fluid will lead to a nearly constant uterine volume during realistic contractions. Therefore, its incompressibility will mechanically represent the effect of both the fetus and the uterine fluid during its expulsion (Yochum et al., 2016). The parameter C_{10} , associated with the matrix stiffness, was collected from Cochran et al. (Cochran & Gao, 2015). Regarding the matrix stiffness of the scar (C_{10} *Maylard*) and the respective fiber stiffness (μ_{i1} *Maylard* and μ_{i2} *Maylard*, where 1 represents the longitudinal direction and 2 the circumferential direction), some studies involving elastography have reported an increase of 80-90% over the uninjured uterine tissue (di Pasquo et al., 2020). Therefore, these parameters were increased by 90% to represent the matrix and fiber stiffness of a Maylard scar, according to the findings of Pasquo et al. (2020) (di Pasquo et al., 2020).

The remaining mechanical parameters were established according to Sharifimajd et al. and Vila Pouca et al. (Sharifimajd et al., 2016; Vila Pouca et al., 2019). The “Maylard” inscription means that those parameters are defined for the Maylard scar tissue. All the parameters are resumed in Table 2.

Table 2. Chemical and mechanical parameters applied in the numerical simulations.

	<i>Variable</i>	<i>Description</i>	<i>Value</i>	<i>Units</i>
Chemical Parameters (Bursztyn et al., 2007; Sharifimajd et al., 2016; Vila Pouca et al., 2019)	k_2	Dephosphorylation of myosin rate	0.6193	s^{-1}
	k_3	Attachment and detachment of the fast-cycling cross-bridge rate	0.1419	s^{-1}
	k_7	Latch-bridge detachment rate	0.0378	s^{-1}
	$[Ca_{1/2MLCK}^{2+}]_i$	Calcium ion concentration for half-activation of MLCK	256.98	nM
	n_{k1}	Hill coefficient	8.7613	-
Mechanical Parameters (Bisplinghoff et al., 2012; Cochran & Gao, 2015; di Pasquo et al., 2020; Sharifimajd et al., 2016; Vila Pouca et al., 2019)	C_{10}	Stiffness coefficient	0.030	MPa
	C_{10} Maylard	Stiffness coefficient	0.00564	MPa
	D_{10}	Volumetric coefficient	1E-5	MPa^{-1}
	ζ_1	Fraction of fibers of the first family	0.4	-
	μ_{i1} ($i = 1,2$)	Fiber's Stiffness	0.006	MPa
	μ_{i1} Maylard ($i = 1,2$)	Fiber's Stiffness	0.01128	MPa
	μ_{i2} ($i = 1,2$)	Fiber's non-linear behavior	1.000	-
	$\bar{\epsilon}_{opt}$	Active strain for maximum force	0.495	-
	γ	Constant	1.000	-
	v_c	Peripheral clutch velocity	0.110	s^{-1}
	η	Constant	0.18	MPa s
	k_{xb}	Constant	8.000	MPa
	k_c	Constant	5.500	MPa s

The reminiscence of amniotic fluid ensures lubrication between the fetus and the uterus (Vila Pouca et al., 2019). This dynamic was considered by creating a surface-to-surface interaction, with a penalty contact algorithm, between the inner uterine wall and the fetus, including friction, which was set to a value of 0.2, according to Lindgren et al (Lindgren & Holmlund, 1969).

A boundary condition was established between that structure and a discrete rigid surface resembling a spine to guide the fetus's head. The surface was discretized by 76 three-dimensional quadrilateral (R3D4) finite elements, containing 100 nodes.

It was assumed that the mother was in the supine position so that the gravity force could be neglected (Jakeman & Jakeman, 2016). No fluids were considered in the existing space between the fetus and the uterus, and no loads were applied since the chemical-mechanical model promoted the fetus's expulsion.

To study the influence on VBAC, from the different Maylard fibers orientations and matrix and fiber stiffness, several numerical simulations were conducted, corresponding to 8 different models, represented by the following initials:

- vaginal delivery without any cesarean scar – Control Model (CM);
- VBAC with an increase of the scar matrix stiffness C_{10} Maylard – Increased Matrix Stiffness Model (IM);
- VBAC with an increase of the scar fibers stiffness μ_{i1} Maylard and μ_{i2} Maylard – Increased Fiber Stiffness Model (IF);

- VBAC with random fiber distribution in the Maylard scar region – Random Fiber Distribution Model (RF);
- VBAC with random fiber distribution in the Maylard scar region and an increase of the scar matrix stiffness – RF + IM;
- VBAC with random fiber distribution in the Maylard scar region and an increase of the scar fibers stiffness – RF + IF;
- VBAC with random and circumferential fibers in the Maylard scar region – RF + Circumferential Fibers Model (CF);
- VBAC with random and longitudinal fibers in the Maylard scar region – RF + Longitudinal Fibers Model (LF).

Each simulation was divided into several steps, following an organized sequence of uterine contractions and relaxations. The muscle contractions are activated by an increase of the intracellular calcium concentration $[Ca^{2+}]_i$, represented by an activation curve.

During the second stage of labor, 3 or 4 contractions occur every 10 minutes, resulting in an average contraction time of 90 seconds and resting time of 60 seconds (Buttin et al., 2013). This information was considered during the definition of each step.

The uterus was divided into 5 layers, L0 to L4, to simulate the electrical stimulus's diffusion process. L0 is the upper uterine region, followed by the L1 zone downwards, and so on. Since the electrical part of the model is not considered, it was assumed that the pacemaker area corresponds to the L0 set. Afterwards, the L1 region is stimulated with a fast increase of calcium concentration, triggering another contraction and so on, until the L4 region is

reached. A set around the Maylard scar was also created to analyze further the mechanical behavior of the cesarean scar throughout each simulation.

Therefore, the L0 and L1 layers were first stimulated with a calcium concentration of 250 nM. In the second contraction, this value was elevated to 600 nM in those sets, and the L2 and L3 layers were submitted to a calcium concentration of 250 nM and 180 nM respectively. The process was repeated throughout the remaining steps, without overcoming a calcium concentration of 1000 nM, according to Sharifimajd et al. (Sharifimajd et al., 2016).

Results

For each simulation we analyzed the maximum principal stress evolution in the Maylard scar region (Figure 8), the average stretch of the Maylard scar fibers in the circumferential and longitudinal directions, (Figure 10), and the vertical displacement of the fetus (Figure 11).

Maximum Principal Stress Evolution in the Maylard Scar Region

Figure 8 represents the maximum principal stress values evolution in the Maylard scar region throughout all simulated scenarios.

In Figure 8a and Figure 8b, it is impossible to see significant differences during the first contraction and resting phases. Only the L0 and L1 uterine layers contract during the first stage, while the L3 layer only starts to contract in the second stage, where the Maylard scar is located. The stress values remain small in all models (11 kPa), during the first contraction and resting phases.

According to Figure 8a, in the second contraction, the maximum principal stress evolution starts to diverge between the models with distinct fibers arrangements in the Maylard scar region. The RF, the RF + IM, and the RF + IF reach a stress value of 75 kPa in the Maylard region, while the remaining models continue with small stress values (11-19 kPa). The maximum principal stress values remain practically equal throughout the second resting stage. In the third contraction, a greater divergence is found in the models with different fibers arrangements. Besides, little difference is noted between the models with no stiffness increase (CM and RF) and those with the matrix stiffness change (IM and RF + IM). In this contraction, the CM and the IF reach a maximum value of 46 kPa, while the IM achieves 68 kPa. Still in the same contraction, the RF, and the RF + IF reach a maximum principal stress of 386 kPa, while the RF + IM achieves 368 kPa. The third resting phase leads to a large decrease in the stress values in all models. In the last simulated contraction, it is possible to observe the largest difference between the models with different fibers arrangements in the cesarean scar. The RF and the RF + IF reach a stress value of 646 kPa, while the RF + IM achieves a smaller value of 617 kPa. The remaining models exhibit significantly smaller stress values, reaching approximately 88 kPa. No significant

differences are found between the CM and the IF, and between the RF and the RF + IF, indicating that increased fiber stiffness does not impact the VBAC from a mechanical point of view. As such, the increased fibers stiffness models will no longer be considered here and throughout the remaining results.

In Figure 8b, where some circumferential or longitudinal fibers were maintained in the Maylard scar, no significant differences are observed until the end of the second resting stage. Currently, the RF presents a stress value of 75 kPa, the RF + CF exhibits 60 kPa, and the RF + LF reaches 48 kPa in terms of maximum principal stress values. In the third contraction, the curves start to evolve differently. The RF achieves 386 kPa, the RF + CF reaches 365 kPa, and the remaining model only achieves 317 kPa. Once more, the third resting stage leads to a notable stress decrease in all models. During the fourth contraction, the curves start to diverge again. Therefore, the RF ends with 646 kPa, the RF + CF with 597 kPa, and the RF + LF with 569 kPa.

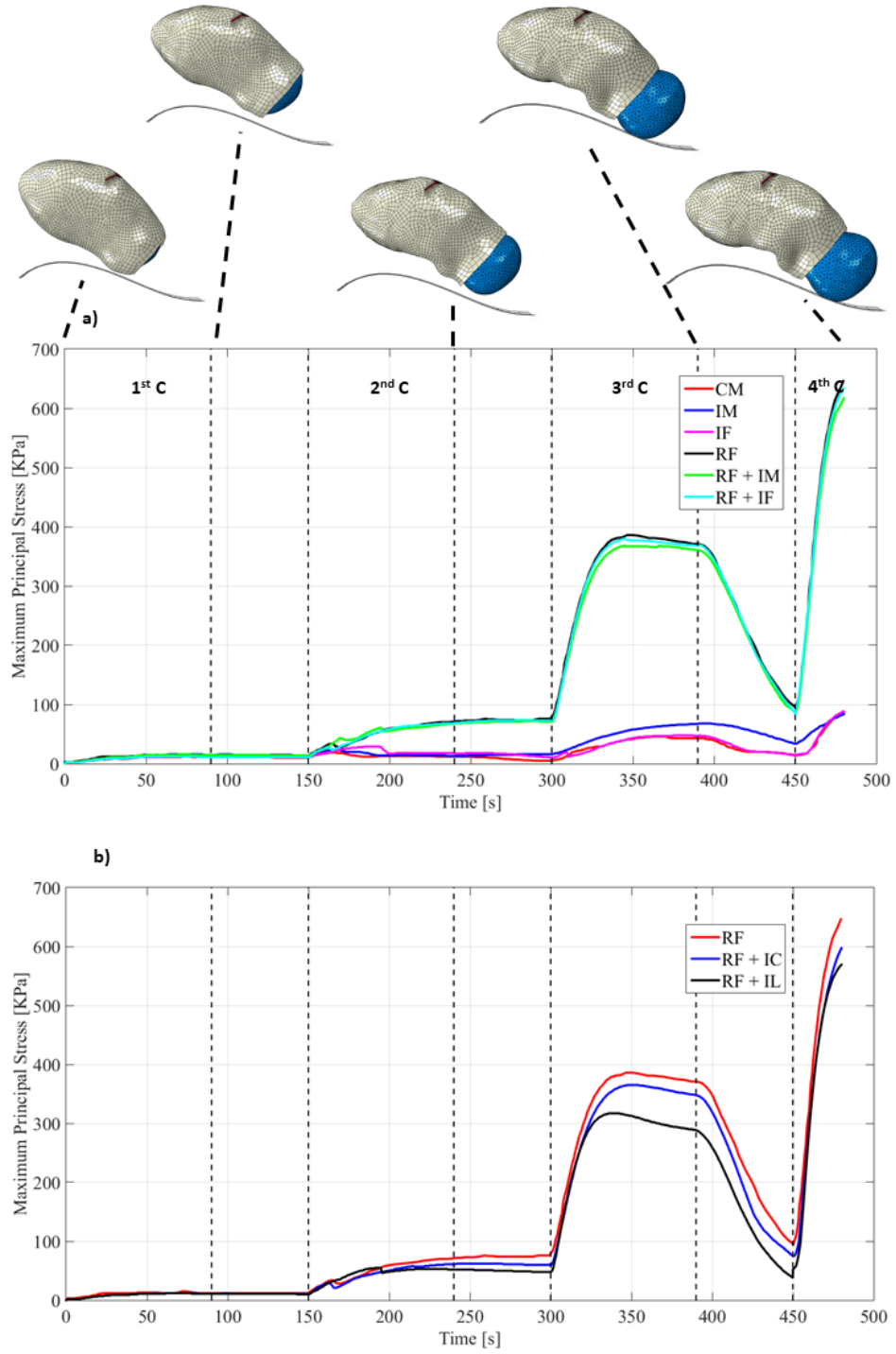


Figure 8. Maximum principal stress evolution for all numerical simulations, highlighting the initial and final moments of each contraction: a) control model (CM), increased matrix stiffness (IM), increased fibers stiffness (IF), random fiber distribution (RF), RF + IM and RF + IF; b) RF, random and circumferential fibers distribution (RF + CF) and random and longitudinal fibers distribution (RF + LF); fetal descent for the CM illustrated at the top; “C” stands for “Contraction”.

Thus, a random fiber arrangement results in larger stress values, submitting the Maylard region to a considerable mechanical effort. Figure 9 illustrates the maximal principal stress distribution in MPa for the RF, where it is possible to visualize a stress concentration in the Maylard zone at the final moment of certain contractions. Only the uterus is exhibited, and the values are computed before averaging (75%). Focusing on Figure 9a and Figure 9b, corresponding to the final moments of the first and second contractions, respectively, the Maylard region does not exhibit large maximum principal stress values compared to the uninjured uterine tissue. Therefore, it is important to note that the scar is not submitted to a significant mechanical effort during the first moments of labor. Conversely, at the final moments of the third and fourth contractions, a stress concentration is seen in the scar zone, highlighting that the Maylard region is subjected to a greater mechanical effort during later moments of labor than the uninjured uterine tissue.

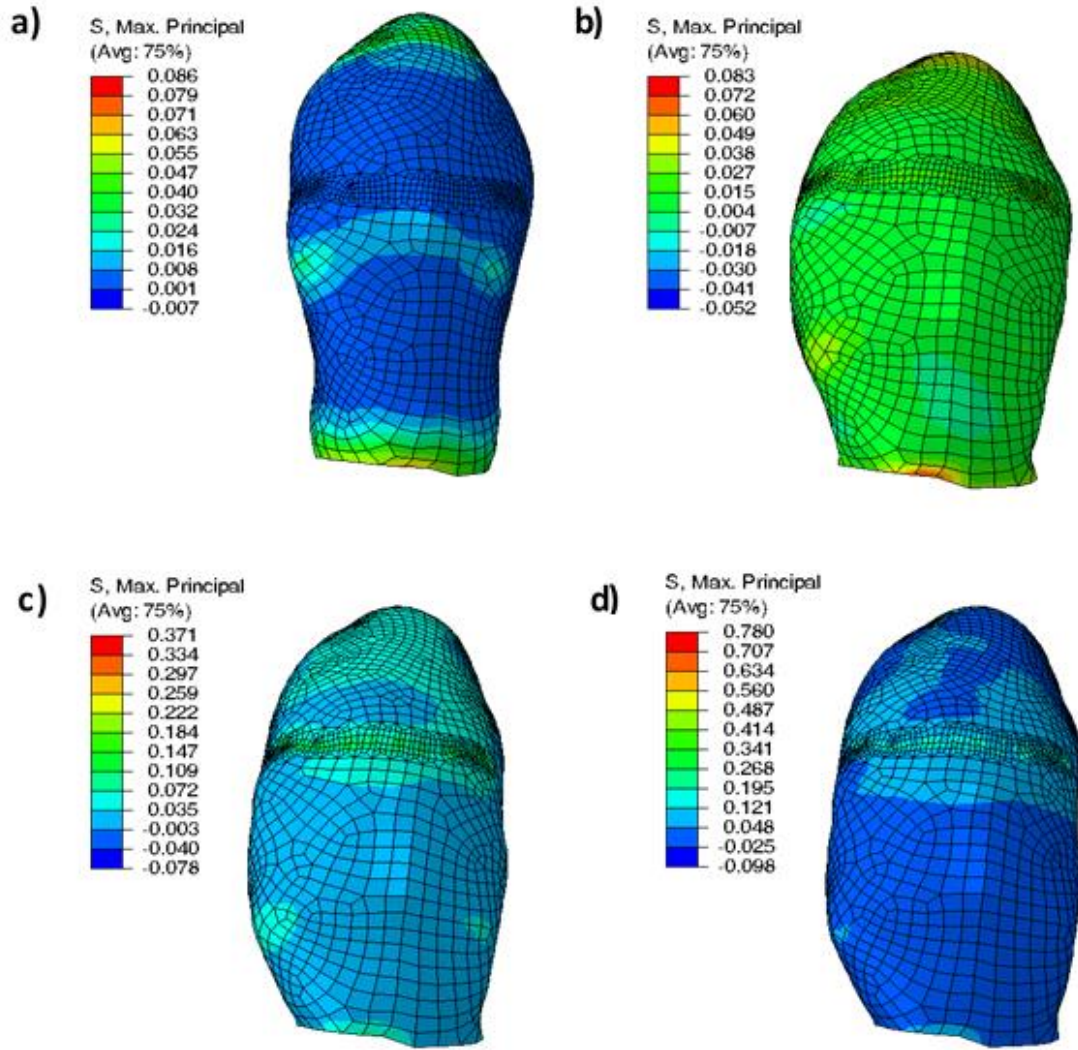


Figure 9. Maximal principal stress distribution for the uterus of the RF, where it is clear a stress concentration in the Maylard region at the final moments of the third and fourth contractions;

a) final moment of the first contraction, b) final moment of the second contraction, c) final moment of the third contraction and d) final moment of the fourth contraction.

Average Stretch of the Maylard Scar Fibers

Aiming to provide a measure of the uterine contractions in the Maylard scar region, the average stretch of the contractile elements on the longitudinal (1) and circumferential (2) directions are presented in Figure 10.

All models reach the lowest stretch values for both directions at the end of the fourth contraction and the differences between all models get more evident with time. A lower stretch value represents a higher contraction, which will be important to discuss the results further. Finally, the stretch values are generally lower than 1, since the Maylard scar is within the active segment of the uterus, which only contracts for such stretch values.

In Figure 10a, it is possible to see that the CM reaches the lowest stretch value in the longitudinal direction (0.81), followed by the IM (0.84), the RF (0.91), and the RF + IM (0.92). The same pattern is verified in Figure 10b on the circumferential direction, being reached, respectively, 0.81, 0.82, 0.86, and 0.87.

In Figure 10c, it is represented the evolution of the average stretch on the longitudinal direction for the RF, RF + CF, and RF + LF. No significant differences were found between the RF and the RF + CF, registering a stretch value of 0.91 and 0.90 at the end of the fourth contraction. The RF + LF reaches the lowest stretch value of 0.84. For the circumferential direction (Figure 10d), no evident differences were observed between all models, registering a stretch value for the RF of 0.86, 0.83 for the RF + CF, and 0.84 for the remaining model.

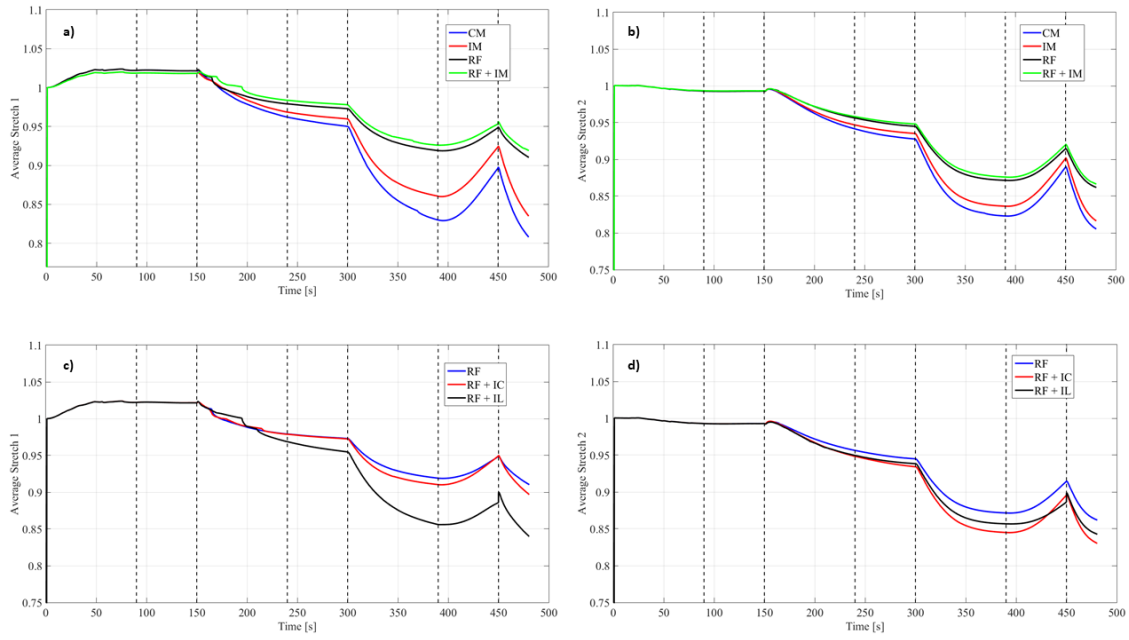


Figure 10. Average stretch evolution of the Maylard fibers on the longitudinal direction (a) and c)) and average stretch evolution of the Maylard fibers on the circumferential direction (b) and d)) for all simulated scenarios, except the IF and the RF + IF.

Vertical Displacement of the Fetus

Figure 11 represents the vertical displacement of the fetal head throughout the simulations, where no significant differences were detected.

Figure 11a illustrates the fetus descent for the CM, IM, RF, and RF + IM. At the second contraction, the curves diverge, especially between the models with different fiber arrangements. That divergence is maintained until the end of the last resting stage. From that moment onwards, the curves start to converge again. Regarding the fetal descent mean velocity, the CM registers 0.17 mm/s, the IM 0.16 mm/s, the RF 0.17 mm/s, and the RF + IM reaches 0.17 mm/s.

Figure 11b also illustrates the fetal head descent evolution for the RF, RF + CF, and RF + LF. No significant differences are identified, except for the second

contraction, although all models start and end with similar fetal head descent values. The RF + CF and the RF + LF present a fetal descent mean velocity of 0.17 mm/s.

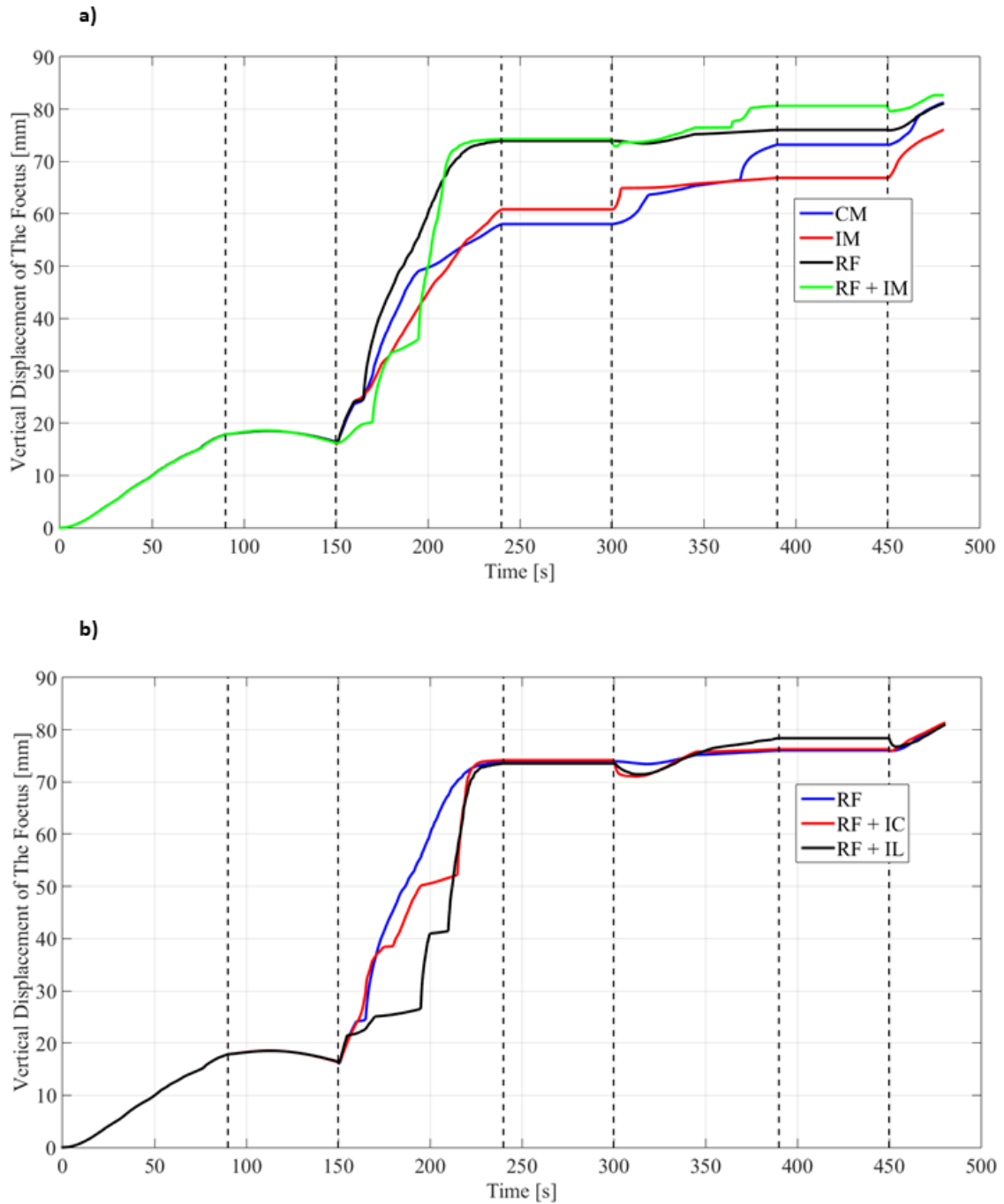


Figure 11. Vertical displacement of the fetal head for (a) CM, IM, RF and RF + IM, and (b) RF, RF + CF and RF + LF.

Parametric Study Concerning the Fetal C_{10}

The C_{10} value for the fetus was collected from Buttin et al. (Buttin et al., 2013). The fetal model considered in that work was divided into three parts: skin tissue ($C_{10} = 0.13$ MPa), skull ($C_{10} = 0.075$ MPa), and body ($C_{10} = 0.070$ MPa) (Buttin et al., 2013). In the current work, the C_{10} parameter was set to 0.13 MPa since the fetus was modeled as a unique structure.

To analyze the C_{10} impact, two more simulations were carried out with the fetal C_{10} set to 0.075 MPa and 0.070 MPa. The steps and activation process were defined similarly to the previous simulations and the control model was considered. The results are presented in Table 3. A larger stress value is obtained for $C_{10} = 0.075$ MPa compared to a stiffer fetus due to its different cinematic.

Table 3. Results collected from the C_{10} sensitivity study.

	<i>Maximum Principal Stress</i> [Kpa]	<i>Maximum Longitudinal Stretch</i>	<i>Maximum Circumferential Stretch</i>	<i>Fetal Descent Mean Velocity</i> [mm/s]
$C_{10} = 0.13$ MPa	88	0.81	0.81	0.17
$C_{10} = 0.075$ MPa	95	0.81	0.80	0.17
$C_{10} = 0.070$ MPa	82	0.78	0.79	0.17

Discussion and Conclusion

Many women who have had cesarean section with their first pregnancy consider a vaginal delivery for their second or later births. It is known that CS in

a first pregnancy confers additional risks in the second pregnancy, such as the risk of uterine rupture, hysterectomy, postpartum hemorrhage, manual removal of the placenta, and others (Taylor et al., 2005). However, different covariates impact the parturition after cesarean delivery (Taylor et al., 2005). It is therefore important to understand the mechanical behavior of the uterus with scarring by cesarean section in a following vaginal delivery.

Some factors during a cesarean section can affect the function of the uterine scar in a subsequent pregnancy, including the extent of the uterine incision (C. Wu et al., 2018). In this work, the length of the scar has remained constant in all models (about 17 mm).

Regarding the maximum principal stress, the values obtained for the control model are within the physiological range of the pregnant human uterus, which validates the numerical models used in this work (Bisplinghoff et al., 2012).

The histopathology of wound healing in the uterus has not been extensively studied, making it difficult to comprehend the myometrial wound healing process, inclusively the uterine fibers reorientation (Roeder et al., 2012). Altered wound healing may lead to different pathologies, resulting in different patterns of fiber arrangement. For instance, keloids represent abnormal uterine healing and lead to disorder patterns of collagen fibril orientation, highlighting the association between the fiber pattern found in uterine scars and each healing mechanism (Roeder et al., 2012). It is known that collagen fibers synthesized from different subtypes of collagen have different thicknesses and arrangements:

collagen fibers formed from type III are relatively thin and exhibit an orderly arrangement, while fibers formed from type I are thicker and have an irregular arrangement (C. Wu et al., 2018). Therefore, several Maylard fiber arrangements were considered in this work to account for this fiber pattern diversity. According to the results (Figure 8a), a random fiber arrangement in the Maylard cesarean scar exposes the injured uterine tissue to a larger mechanical stress compared to IM or IF, potentiating uterine rupture during vaginal delivery. On the other hand, a scar with a predominance of longitudinal fibers seems to prevent uterine rupture during a VBAC (Figure 8b). It is known that collagen alignment dictates the stress distribution in an extracellular matrix soft tissue, which will directly affect the contraction pattern (Yang et al., 2013). Thus, one can expect different mechanical responses with different fiber arrangements. Multilayer sutures are currently a proposed solution. However, the surgical closure technique is not the only element that defines the quality of uterine wound healing (C. S. Buhimschi et al., 2010).

Buttin et al. developed a versatile birth simulator to simulate different scenarios at various difficulty levels and consider some complex deliveries (Buttin et al., 2013). This study found that the final uterus size is approximately 1/3 of its original height at the end of the second stage of labor (Buttin et al., 2013). Considering that the fetal descent corresponds to the mean fetal size at term, a final stretch of 0.33 is expected when the fetus has descended 290 mm (Vila Pouca et al., 2019).

According to the results reported in Figure 11, the fetal descent varies between 76 mm and 83 mm. Thus, it would be expected to reach fasciculi stretch values between 0.81 and 0.82 in a vaginal birth without a cesarean scar. Analyzing Figure 10, the control model exhibits stretch values within the expected range in the region where the cesarean scar will be implemented, according to the literature, which validates the present study. Moreover, it is expected that the uterus contracts and thickens in the active segments and expands in the passive segment due to the passage of the fetus's head (Vila Pouca et al., 2019). So, since the Maylard scar is within the active segment, stretch values smaller than 1 must be verified, which is by the obtained results.

The Maylard fibers arrangement and matrix stiffness will modify the uterine contractions pattern found during a normal vaginal delivery since the models analyzed have stretch values in the longitudinal direction superior to the normal range (Figure 10a and Figure 10c). The same conclusion can be applied to the circumferential direction (Figure 10b and Figure 10d). However, the stretch values observed are not superior to the longitudinal direction relative to the normal range.

The random fibers arrangement models present larger stretch values, which means that the presence of random fibers in the cesarean scar may lead to significantly weaker uterine contractions in the Maylard region. An increased stiffness within the scar may also lead to weaker contractions but with less impact than the fiber reorientation. The presence of longitudinal fibers in the cesarean scar leads to stronger contractions than the circumferential fibers.

According to the illustrated results in Figure 11, no significant differences were found among all the simulated scenarios. However, a distinct fiber arrangement may lead to a slightly different vertical displacement evolution, especially when the Maylard region starts to contract. Additionally, the mean velocity of the fetal descent does not suffer significant alterations (0.16-0.17 mm/s) changing the fibers' orientation or the matrix stiffness in the Maylard region. In fact, according to the statistical results reported by Rusavy et al., there were no differences in the duration of the second stage of labor between women undergoing a second vaginal birth (SVB) and women with a first vaginal delivery after a prior cesarean section (Rusavy et al., 2019). The SVB group registered a mean duration of 23.8 minutes, while the VBAC registered 20.8 minutes (Rusavy et al., 2019). These findings lead to the conclusion that a prior Maylard cesarean section will not affect the mean duration of the second stage of labor, validating the numerical models and the results obtained in this work.

Many studies focused on the role of ultrasound have been developed to describe the evolution of the uterine scar following uterine surgeries (Seinera et al., 1999). Promising preliminary results unfortunately limited its role in predicting uterine rupture (Gonser et al., 2016). Therefore, the lack of data regarding uterine scars, makes it impossible to adopt any preventive measures to avoid complications during a VBAC. Many factors and possible risks should be considered before qualifying the patient for VBAC, such as maternal age, macrosomia, labor induction, and indications for the previous CS, among others (Y. Wu et al., 2019). Many calculators have been created to clarify the chances of

a successful VBAC, such as maternal age, height, weight, body mass index, ethnicity, prior VBAC, prior vaginal delivery, lower uterine scar defect called “niche” or “isthmocele”, among others (Sholapurkar, 2018; Wyckoff et al., 2020).

Naji et al. developed a model based on cesarean scar features examined by transvaginal ultrasonography to predict the possibility of VBAC, suggesting that the scar and its fibers arrangements are major factors in the function of the uterus during a trial of labor (Naji, Wynants, et al., 2013). Magnetic Resonance (MR) Diffusion Tensor Imaging (DTI) is a medical technique applied to access fiber arrangements (Brandão et al., 2013). It estimates overall fiber directionality based on the mathematical description of water diffusivity (Brandão et al., 2013). Establishing the biomechanical pattern for each patient after a cesarean section may allow the development of individually tailored delivery programs, being interesting both to the patient and the obstetrician (by delivery approach planning, the decision to shorten the second stage of labor, etc.).

The biomechanical models presented in this work may result in a discussion area for future research. This tool has not entered the standard-of-care to assess uterine function and remains a research tool to quantify the rate of tissue remodeling. Such pre-delivery assessment could give a hint to a physician before the decision of VBAC is made. However, as the uterus undergoes an intense remodeling process during pregnancy (C. S. Buhimschi et al., 2010), the development of individual models relies on clarifying some aspects concerning pregnancy biomechanics.

In this work, some simplifications were performed in the uterine-fetal biomechanical model, due to the complexity associated with this problem: (i) the constitutive model does not cover the fact that the uterus reaches an almost non-pregnant stage right after the end of the second stage of labor, (ii) the collagen fiber distribution in the uterus was based on the non-pregnant state, (iii) the calcium activation curve was projected to allow a realistic fetal, (iv) it was neglected the viscoelastic passive behavior on the uterine tissue, the pushing force exerted by the mother, the contraction of the abdominal muscles, the baseline intrauterine pressure, the residual strain in the reference configuration, and, finally, the deformability of the fetus head, which was not the focus of this work. It is important to mention that this numerical work represents a theoretical investigation and the methodology presented can be applied to different cesarean sections.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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PART B: Article 2

On the effect of irregular uterine activity during a vaginal delivery using an electro-chemo-mechanical constitutive model

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Abstract

During a normal vaginal delivery, the muscle cells propagate electrical signals throughout the uterine wall, resulting in uterine contractions. However, uncoordinated uterine activity may disturb the uterine contractions pattern and negatively impact fetal and maternal health. Some of the abnormalities identified by the specialists are excessively short resting intervals and tachysystole (a particular case of short resting intervals with reduced contraction time). This work aims to investigate the influence of abnormal uterine activity in terms of maximal principal stress distribution and collagen fibers stretch in the uterine tissue during vaginal delivery with (i) excessively short resting intervals without changing the contraction time, and (ii) tachysystole (contraction and resting time reduced). These patterns are compared with a normal uterine contraction pattern. A biomechanical model was developed to achieve our aims, including finite element models of the uterus and the fetus, and an electro-chemo-mechanical constitutive model. Generally, the excessively short resting intervals exhibited larger average maximum principal stresses during the contraction and resting stages, smaller average fiber stretch values in the longitudinal direction, and larger stretches in the circumferential direction. On the other hand, tachysystole exhibited generally smaller stress values during the uterine contraction and larger stress values during the resting stages, larger stretches in the longitudinal direction, and smaller stretches in the circumferential direction.

Keywords: Irregular Uterine Contractions; Excessively Short Resting Stage; Tachysystole; Vaginal Delivery; Numerical Simulation; Finite Element Method

Abbreviations

MLCK – Myosin light chain kinase

IUP – Intrauterine pressure

IOL – Induction of labor

Introduction

The uterus is a complex organ composed of billions of smooth muscle cells in dense connective tissue (Rudolph & Ivy, 1930). This organ comprises an upper segment, called corpus uteri, a lower segment, named the isthmus, and the cervix (Rudolph & Ivy, 1930).

The uterine wall is composed of three distinct layers: (i) endometrium (inner mucosal layer), (ii) myometrium (thick middle layer), and (iii) perimetrium (thin outer layer) (K. M. Myers & Elad, 2017). The endometrium-myometrium interface, known as the junctional zone, is crucial for normal reproduction and the development of pathologies (Dawes et al., 2013).

The muscle cells can transmit electrical signals along the uterine wall known as action potentials. During a normal vaginal delivery, these electrical impulses are synchronized, creating a propulsive force due to the uterine contraction (Bhogal, 2017; Young, 2016). The electrical activity produced by the uterus has proven to be representative of its contractile activity (C. K. Marque et al., 2007; Schlembach et al., 2009), and it can be recorded directly with electrodes attached to the muscle in animal experiments (C. Buhimschi et al., 1998; Doret et al., 2005), or with surface electrodes placed on the abdominal skin of women for obstetrical proposes (Gondry, 1993; C. Marque et al., 1986).

A coordinated set of uterine contractions is essential during a vaginal delivery (Cohen, 2017). At term, the mild uterine contractions verified during the

gestational period gradually become more frequent and intense, eventually leading to labor (Cohen, 2017). During a normal vaginal delivery, regular uterine contractions will expel the fetus and placenta from the uterine cavity, accompanied by cervical dilation (Bastos et al., 2012). Healthcare providers will regularly evaluate uterine contractions, ensuring they are sufficient for normal progression of labor but not excessive, to avoid insufficient fetal oxygenation (Bastos et al., 2012).

Despite this understanding concerning uterine activity, it is not yet clear how these contractions cause progress in a vaginal delivery (Cohen, 2017). Therefore, clinicians must assess uterine activity during labor to decide on a possible intervention (Cohen, 2017). There are some measurement techniques to clinically assess uterine contractions, such as manual palpation, tocodynamometry, and electro-hysterography (Cohen, 2017).

Most labors occur without any complications (Bastos et al., 2012). However, uncoordinated uterine activity can disturb the uterine contractions pattern and negatively impact fetal and maternal health. Inadequate maternal expulsive efforts, usually associated with higher intra-abdominal pressure, and inadequate uterine contractions are the main causes of poor labor progress (Ebrahimzadeh et al., 2012; El-Hamamy & Arulkumaran, 2005; Olaby et al., 2006).

Inadequate uterine contractions are influenced by physical and physiological factors, such as lack of energy, dehydration, ketoacidosis, and fatigue (Newton, 1990). There are several forms of abnormal uterine contractions

(Gyselaers et al., 1991), including excessive frequency of contractions (hypercontractility, hyperstimulation, and tachysystole) (Takahashi et al., 2003), excessive contraction duration (tetanic contractions) (Cohen & Friedman, 2015), coupling (two or more contractions without a full return to a normal baseline) (Cronjé & van der Westhuizen, 1988; Dawood, 1995; Ferreira & Odendaal, 1994) and excessively short resting intervals (Hobson et al., 2019).

The resting interval is the time between a contraction's end and a new one's beginning. This period is essential since it impacts fetal oxygenation and the removal of carbon dioxide from fetal blood circulation (Bakker et al., 2007; Hayes et al., 2013; Stewart et al., 2012). Inadequate relaxation time is characterized by a resting period shorter than 60s and it can decrease fetal oxygenation to a critically low level, potentiating the risk of fetal metabolic acidosis and hypoxic-ischemic encephalopathy (Bakker et al., 2007; Hayes et al., 2013; Stewart et al., 2012). For instance, the administration of oxytocin may shorten the resting period, increasing the risk of fetal injury (Oppenheimer et al., 2002).

Tachysystole is characterized by uterine contractions of excessively high frequency (more frequent than every 2 to 3 minutes), following a similar concept of uterine hypercontractility and hyperstimulation (Heuser et al., 2013). It is a particular case of short resting intervals with reduced contraction time. It can occur during labor induction or augmentation (Heuser et al., 2013) or be caused by the administration of uterine stimulants such as misoprostol, prostaglandin, or oxytocin (Heuser et al., 2013).

To the best of the authors' knowledge, this is the first work to investigate the effect caused by abnormal uterine activity, namely excessively short resting intervals and tachysystole, from a biomechanical perspective. The computational methods overcome several ethical and technical questions associated with *in vivo* experiments. The main goal of this work is to investigate the biomechanical behavior of the uterine tissue during vaginal delivery with (i) a normal contraction pattern, (ii) excessively short resting intervals, and (iii) tachysystole. An electro-chemo-mechanical model replicating a set of uterine contractions and resting stages was adopted. We believe our approach can help the medical community better understand the implications of uncoordinated uterine activity, which is essential to ensure mothers' and fetuses' safety, especially when relevant clinical decisions must be taken.

Materials and Methods

Constitutive Model

Uterine contractions are triggered by electrical, chemical, and mechanical stimuli, as described by several authors (Sharifimajd et al., 2016; Sharifimajd & Stålhand, 2014; Vila Pouca et al., 2019; Yochum et al., 2016). Several constitutive equations have been developed to represent the response of the uterus throughout the second stage of labor, replicating a set of uterine contractions and rest stages (Yochum et al., 2016).

A change in the electric membrane potential's equilibrium state will allow different ions to flux into or out of the uterine cells, creating an action potential (Sharifimajd & Stålhand, 2014). Eventually, the intracellular calcium concentration will increase, creating a calcium-calmodulin complex, activating the myosin light chain kinase (Sharifimajd & Stålhand, 2014). This will cause a contraction, pushing the fetus out of the uterine cavity (Sharifimajd & Stålhand, 2014).

An application of the electrical, chemical, and mechanical sub-models is presented in the supplementary file, highlighting the connection between them.

Structure of the electro-chemo-mechanical model

The complete model that will be implemented consists of three sub-models:

- electrical model – represents the ionic currents responsible for the smooth muscle cells activity and the output is the $[Ca^{2+}]_i$ dynamics;
- chemical model – determines the fraction of cross-bridges;
- mechanical model – computes passive and active responses of the muscle.

Figure 1 summarizes the simulation process. In this way, at each simulation step, the electrical component is solved first and the relevant variables in the cell models, i.e., $[Ca^{2+}]_i$ is linked to the chemical model. The link through the latter and the mechanical model is given by the fraction of cross-bridges α_c and α_D that will determine the active response of the muscle.

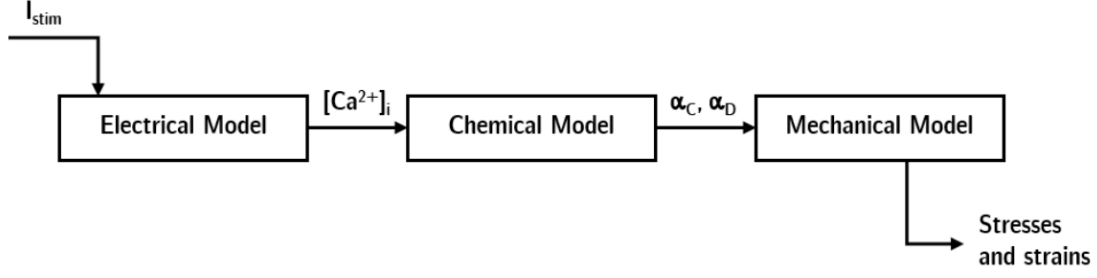


Figure 1. Structure of the electro-chemo-mechanical model.

Electrical Model

The electrical model implemented is based on the Hodgkin-Huxley model (Hodgkin & Huxley, 1952), where each component of an excitable cell is treated as an electrical element: the lipid bilayer is represented as a capacitance (C_m), voltage-gated ion channels are represented by electrical conductance elements (g_n , where n is the specific ion channel), leak channels are represented by linear conductance elements (g_L), the electrochemical gradients driving the flow of ions are represented by voltage sources (E_n), whose voltages are determined by the ratio of the intra- and extra-cellular concentrations of the ionic species of interest, and ion pumps are represented by current sources (I_p) (Hodgkin & Huxley, 1952).

The current following through the lipid bilayer (I_c) can be written as follows, where V_m represents the transmembrane potential (Hodgkin & Huxley, 1952):

$$I_c = C_m \frac{dV_m}{dt} \quad (2.1)$$

The current through a given ion channel is equal to (Hodgkin & Huxley, 1952):

$$I_i = g_i(V_m - V_i) \quad (2.2)$$

where V_i is the reverse potential of the i -th ion channel, thus the transmembrane current can be divided into two components: the capacitive current, due to the bi-lipidic layer of the cell membrane, and the ionic current due to the flux of ions between the intra- and extra-cellular space. Experimentally, the transmembrane current is equal to the stimulation current (I_{stim}) applied to the cell (Hodgkin & Huxley, 1952):

$$I_{stim} = C_m \frac{dV_m}{dt} + \sum I_{ion} \quad (2.3)$$

This work applied an electrical model that describes the ionic currents involved in uterine cell contraction, providing the intracellular calcium concentration as an output parameter (Yochum et al., 2016). This model corresponds to a reduction of Rihana's model, defined only by three variables, where the total ionic current I_{ion} can be expressed as follows (Rihana et al., 2009):

$$I_{ion} = I_{Ca} + I_K + I_{KCa} + I_L \quad (2.4)$$

where I_{Ca} corresponds to the ionic current for the voltage-dependent calcium channel, I_K for the voltage-dependent potassium channel current, I_{KCa} for the calcium-dependent potassium channel current, and I_L for the leakage current (Rihana et al., 2009).

The three variables of the simpler electrical model are described by the following equations (Yochum et al., 2016):

$$\frac{dV_m}{dt} = \frac{1}{C_m} (I_{stim} - I_{Ca} - I_K - I_{KCa} - I_L) \quad (2.5)$$

$$\frac{dn_K}{dt} = \frac{n_{K\infty} - n_K}{\tau_{n_K}} \quad (2.6)$$

$$\frac{d[Ca^{2+}]_i}{dt} = f_c(-AI_{Ca} - K_{Ca}[Ca^{2+}]_i) \quad (2.7)$$

where n_k is the potassium activation variable, K_{Ca} is the calcium extraction factor, $[Ca^{2+}]_i$ the intracellular calcium concentration, A is the current conservation factor, τ_{n_K} expresses a relaxation time, and $h_{K\infty}$ the inactivation steady state, defined respectively by (Yochum et al., 2016):

$$\tau_{n_K} = 23.75 e^{\frac{-V_m}{72.15}} \quad (2.8)$$

$$h_{K\infty} = \left[1 + e^{\frac{4.2 - V_m}{21.1}} \right]^{-1} \quad (2.9)$$

Each ionic current can be expressed as (Yochum et al., 2016):

$$I_{Ca} = J_{back} + G_{Ca}(V_m - E_{Ca}) \frac{1}{1 + e^{\frac{V_{Ca}-V_m}{R_{Ca}}}} \quad (2.10)$$

$$I_K = G_K n_K (V_m - E_K) \quad (2.11)$$

$$I_{KCa} = G_{KCa} \frac{[Ca^{2+}]_i^2}{[Ca^{2+}]_i^2 + K^2} (V_m - E_K) \quad (2.12)$$

$$I_L = G_L (V_m - E_L) \quad (2.13)$$

with (Rihana et al., 2009; Yochum et al., 2016):

$$E_{Ca} = \frac{RT}{2F} \ln \left(\frac{[Ca^{2+}]_e}{[Ca^{2+}]_i} \right) \quad (2.14)$$

The prescribed parameters of this sub-model are: C_m , f_c , K_{Ca} , J_{back} , G_{Ca} , V_{Ca} , R_{Ca} , G_K , E_K , G_{KCa} , G_L , K , E_L , $[Ca^{2+}]_e$, R , T , and F . All of them are obtained from the literature (Rihana et al., 2009; Yochum et al., 2016). I_{stim} is set to 0.17 $\mu A/cm^2$ to initiate a uterine contraction and 0 $\mu A/cm^2$ during a resting stage. The evolution of $[Ca^{2+}]_i$, V_m , n_K , τ_{n_K} , $h_{K\infty}$, I_{Ca} , I_K , I_{KCa} , I_L and E_{Ca} must be

determined for each simulation step. $[Ca^{2+}]_i$ is the output of the electrical sub-model, which will initiate the chemical response of the constitutive model.

The implementation of the electrical sub-model was validated by comparing our results with the ones shown in Yochum's work (Yochum et al., 2016). We set the stimulation current to $0.17 \mu A/cm^2$ and compared the voltage and calcium curves, finding a great agreement in both curves.

Chemical Model

The activation of the smooth muscle depends on the concentration of the myosin phosphorylation (Bursztyn et al., 2007). The phosphorylation of regulatory myosin light chains by the Ca^{2+} /calmodulin-dependent enzyme myosin light chain kinase (MLCK) is important to regularize smooth muscle contractions (Goeckeler & Wysolmerski, 1995). Myosin can be found in different forms, such as unbound unphosphorylated (α_A), unbound phosphorylated (α_B), bound phosphorylated (α_C), and bound unphosphorylated (α_D). $k_1 - k_7$ are the transition rates from one state to another: k_1 and k_6 are the rates of phosphorylation of myosin, while k_2 and k_5 represent the rates for the dephosphorylation of myosin, k_3 and k_4 are the rates associated with the attachment and detachment of the fast cycling cross-bridges, respectively, and k_7 is the rate constant for latch-bridge detachment (Stålhand et al., 2008).

The kinetic state model is given by a coupled system of a first-order differential equation (Sharifimajd et al., 2016):

$$\begin{bmatrix} \dot{\alpha}_A \\ \dot{\alpha}_B \\ \dot{\alpha}_C \\ \dot{\alpha}_D \end{bmatrix} = \begin{bmatrix} -k_1 & k_2 & 0 & k_7 \\ k_1 & -(k_2 + k_3) & k_4 & 0 \\ 0 & k_3 & -(k_4 + k_5) & k_6 \\ 0 & 0 & k_5 & -(k_6 + k_7) \end{bmatrix} \times \begin{bmatrix} \alpha_A \\ \alpha_B \\ \alpha_C \\ \alpha_D \end{bmatrix} \quad (2.15)$$

Assuming that $k_6 = k_1$, $k_2 = k_5$, $k_3 = 4k_4$ (Sharifimajd et al., 2016) and:

$$k_1 = k_6 = \frac{[Ca^{2+}]_i^{nk_1}}{[Ca^{2+}]_i^{nk_1} + [Ca_{1/2MLCK}^{2+}]_i^{nk_1}} \quad (2.16)$$

where $[Ca_{1/2MLCK}^{2+}]_i^{nk_1}$ represents the required calcium ion concentration for half-activation of MLCK by the calcium-calmodulin complex and nk_1 is the Hill coefficient of activation (Sharifimajd et al., 2016; Vila Pouca et al., 2019).

The initial values of α_A , α_B , α_C , and α_D , as well as k_2 , k_3 , k_7 and nk_1 were obtained from the literature (Sharifimajd et al., 2016). $\dot{\alpha}_A$, $\dot{\alpha}_B$, $\dot{\alpha}_C$, and $\dot{\alpha}_D$ are determined for each simulation step. The parameter $\alpha_{xb} = \alpha_C + \alpha_D$, is the output of the chemical sub-model and will dictate the mechanical response of the constitutive model. The evolution of the myosin states was validated by comparing the respective variables' curves with those presented in Sharifimajd's work (Sharifimajd et al., 2016).

Mechanical Model

The actin filaments slip relative to a myosin-coated surface during the contraction and the slip velocity depends on the applied load (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014). Overall, the dynamics of the contractile element can be represented by: (a) a friction clutch, which defines the overall effect of cycling cross-bridges; (b) a brake-like mechanism in series with the clutch, associated with the overall effect of all non-cycling, or slow-cycling, cross bridges; (c) a spring attached to the clutch and the brake representing the elasticity of all cross-bridges within the contractile (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014).

The deformation is divided into two steps: an active displacement and an elastic displacement (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014). The active displacement causes the clutch and the brake to translate without spring deformation, and the elastic displacement stretches the spring without moving the clutch and the brake (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014).

The uniaxial stretch $\bar{\lambda} = \frac{l}{l_0}$ of the contractile element can be defined as (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$\bar{\lambda} = 1 + \bar{\varepsilon}_a + \bar{\varepsilon}_e \quad (2.17)$$

where $\bar{\varepsilon}_a$ and $\bar{\varepsilon}_e$ represent the active and elastic strain, respectively (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014).

The myometrium is assumed to contain two fiber families, aligned with the unit vector $\mathbf{M}_i$ ($i = 1, 2$), defined in the reference configuration. The stretch within each family i in the direction $\mathbf{M}_i$ can be characterized through the isochoric right Cauchy-Green tensor $\bar{\mathbf{C}} = \bar{\mathbf{F}}^T \bar{\mathbf{F}}$ as (Holzapfel, 2000):

$$\bar{\lambda}_i^2 = \bar{I}_j = \bar{\mathbf{C}} : (\mathbf{M}_i \otimes \mathbf{M}_i), \quad i = 1, j = 4 \vee i = 2, j = 6 \quad (2.18)$$

where $\bar{\mathbf{F}}$ represents the isochoric part of the deformation gradient and $\bar{I}_j$ ($j = 4, 6$) represents the fourth and sixth invariant of the isochoric right Cauchy-Green deformation tensor (Holzapfel, 2000).

The strain energy function can be decoupled into three contributions (Holzapfel, 2000; Vila Pouca et al., 2019):

$$\Psi = \Psi_{vol} + \bar{\Psi}_m + \bar{\Psi}_f \quad (2.19)$$

where Ψ_{vol} represents the volumetric contribution, $\bar{\Psi}_m$ the ground matrix isochoric contribution, and $\bar{\Psi}_f$ the fiber isochoric contribution (Vila Pouca et al., 2019).

The uterus is nearly incompressible, and the volumetric contribution is therefore defined by a penalty function (Vila Pouca et al., 2019):

$$\psi_{vol} = \frac{1}{D_1} \left(\frac{J^2 - 1}{2} - \ln(J) \right) \quad (2.20)$$

where D_1 is a constant and $J = \det(\mathbf{F})$ is the volume ratio (Vila Pouca et al., 2019).

The isochoric matrix contribution, according to the Neo-Hookean model, is given by (Holzapfel, 2000; Sharifimajd et al., 2017):

$$\bar{\Psi}_m = C_{10}(\bar{I}_1 - 3) \quad (2.21)$$

where $\bar{I}_1 = \text{tr}(\bar{\mathbf{C}})$ is the first invariant of $\bar{\mathbf{C}}$ and C_{10} is a constant.

The isochoric fiber contribution combines the Holzapfel-Gasser-Ogden (HGO) passive model and an active contribution from the uterine muscle (Sharifimajd et al., 2017):

$$\bar{\Psi}_f = \zeta_1(\bar{\Psi}_1^p + N_1\bar{\Psi}_1^a) + (1 - \zeta_1)(\bar{\Psi}_2^p + N_2\bar{\Psi}_2^a) \quad (2.22)$$

where $\bar{\Psi}_i^p$ and $\bar{\Psi}_i^a$ represent the passive and active contribution of the i th fiber family respectively, while $\zeta_1 \in [0,1]$ is a parameter that describes the fraction of all fiber that belong to the first family. N_i is a function that accounts for the overlap between actin and myosin filaments (Holzapfel, 2000; Sharifimajd et al., 2017).

The passive component $\bar{\Psi}_i^p$ is defined by the HGO model (Holzapfel, 2000):

$$\bar{\Psi}_i^p = \begin{cases} \frac{\mu_{i1}}{2\mu_{i2}} \{ \exp[\mu_{i2}(\bar{I}_j - 1)^2] - 1 \}, & \text{if } \bar{I}_j \geq 1 \\ 0, & \text{otherwise} \end{cases} \quad (2.23)$$

where $j \in \{4,6\}$ and μ_{i1} and μ_{i2} are positive constants.

The active component $\bar{\Psi}_i^a$ is defined by (Sharifimajd et al., 2017):

$$\bar{\Psi}_i^a = \frac{1}{2} \alpha_{xb} k_{xb} \bar{\varepsilon}_e^2 \quad (2.24)$$

with $\alpha_{xb} = \alpha_c + \alpha_D$ linking the chemical and mechanical components of the constitutive model and representing the fraction of the bound myosin, and k_{xb} is a constant (Sharifimajd et al., 2017; Vila Pouca et al., 2019). The active contribution depends on the elastic strain $\bar{\varepsilon}_e$, indicating that the passive stretch of the muscle will directly impact the active stress generated.

Considering the macroscopic mechanic equivalence described before, the dynamics of the clutch are characterized by an evolution law, derived from Sharifimajd and Stålhand et al. (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$\eta \dot{\bar{\epsilon}}_{ai} = -F_{C,i} - \frac{\partial \bar{\Psi}_f}{\partial \bar{\epsilon}_{ai}} + \frac{\partial \bar{\Psi}_f}{\partial \bar{\epsilon}_{ei}} \quad (2.25)$$

where $\dot{\bar{\epsilon}}_{ai}$ represents the active strain rate, η is a constant, and $F_{C,i}$ is the friction force generated by the clutch in the i th fiber family (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$F_{C,i} = \begin{cases} N_i k_c \alpha_c (\dot{\bar{\epsilon}}_{ai} + v_c), & \text{if } \dot{\bar{\epsilon}}_{ai} \geq 1 \\ 0, & \text{otherwise} \end{cases} \quad (2.26)$$

where v_c is the peripheral clutch velocity, $k_c > 0$ is a constant, and N_i is given by (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014):

$$N_i = \exp\left(\frac{-(\bar{\epsilon}_{opt} - \bar{\epsilon}_{ai})^2}{2\gamma^2}\right) \quad (2.27)$$

where $\bar{\epsilon}_{opt}$ represents the active strain at which the muscle generates the maximum force and γ is a constant (Sharifimajd et al., 2017; Sharifimajd & Stålhand, 2014).

$D_1, C_{10}, \mu_{ij}, v_c, \bar{\epsilon}_{opt}, \gamma, \eta, k_{xb}, k_c, \zeta_1$ and the initial value of $\bar{\epsilon}_{ai}$ are prescribed parameters, defined from the literature (Sharifimajd et al., 2016). $\dot{\bar{\epsilon}}_{ai}, F_{C,i}$ and N_i are updated for each simulation step. The output of the mechanical sub-model is the stress distribution. All parameters, except D_1 , were calibrated using an

intrauterine pressure curve measured in a woman at term (38 weeks) in active labor (Sharifimajd et al., 2016).

Geometrical Model

To simulate uterine contractions and the second stage of labor, a finite element model comprising simplified geometries of a fetus and a pregnant uterus was considered.

Fetus

A finite element model was constructed according to the principal obstetrical dimensions of a full-term fetus (Parente et al., 2010). To improve the contact algorithm performance, the finite element mesh was simplified (Figure 2).

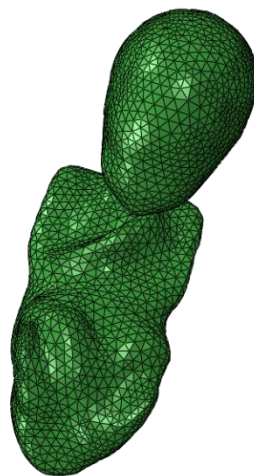


Figure 2. Simplified finite element model of the fetus.

Using the finite element software ABAQUS®, both the biparietal diameter and the fetal head circumference were measured, to guarantee a gestational age between 36 and 40 weeks, according to reported fetal growth data (Kiserud et al., 2017). The simplified mesh contains 10595 nodes and 53732 four-node tetrahedral hybrids (C3D4H) elements.

The fetal rotation in the vertical axis was constrained to allow a stable descent of the fetus throughout the simulation. The fetus was modeled as a hyperelastic material, considering the Neo-Hookean formulation. The parameter C_{10} was set to 0.13 MPa (Buttin et al., 2013), while the volumetric parameter D_1 was set to 0.05 MPa^{-1} , penalizing volume changes (Vila Pouca et al., 2019).

Uterus

The uterine model (Figure 3) was developed around the geometry of the fetus, using the commercial software SolidWorks®. The thickness of the uterine wall was set to 10 mm (Vila Pouca et al., 2019). Aiming to correctly adjust the uterus to the fetus, it was performed a thermal finite element simulation, obtaining a tighter model (Vila Pouca et al., 2019).

The uterine wall is composed of three histologically different layers: the endometrium, the myometrium, and the perimetrium. Since the myometrium is the most prominent layer and is responsible for uterine contractile activity, only this layer is contemplated in the uterine geometrical model (Vila Pouca et al., 2019). The myometrium comprises smooth muscle cells, the myocytes, which in

turn comprise two contractile elements: thin actin and thick myosin (Vila Pouca et al., 2019).

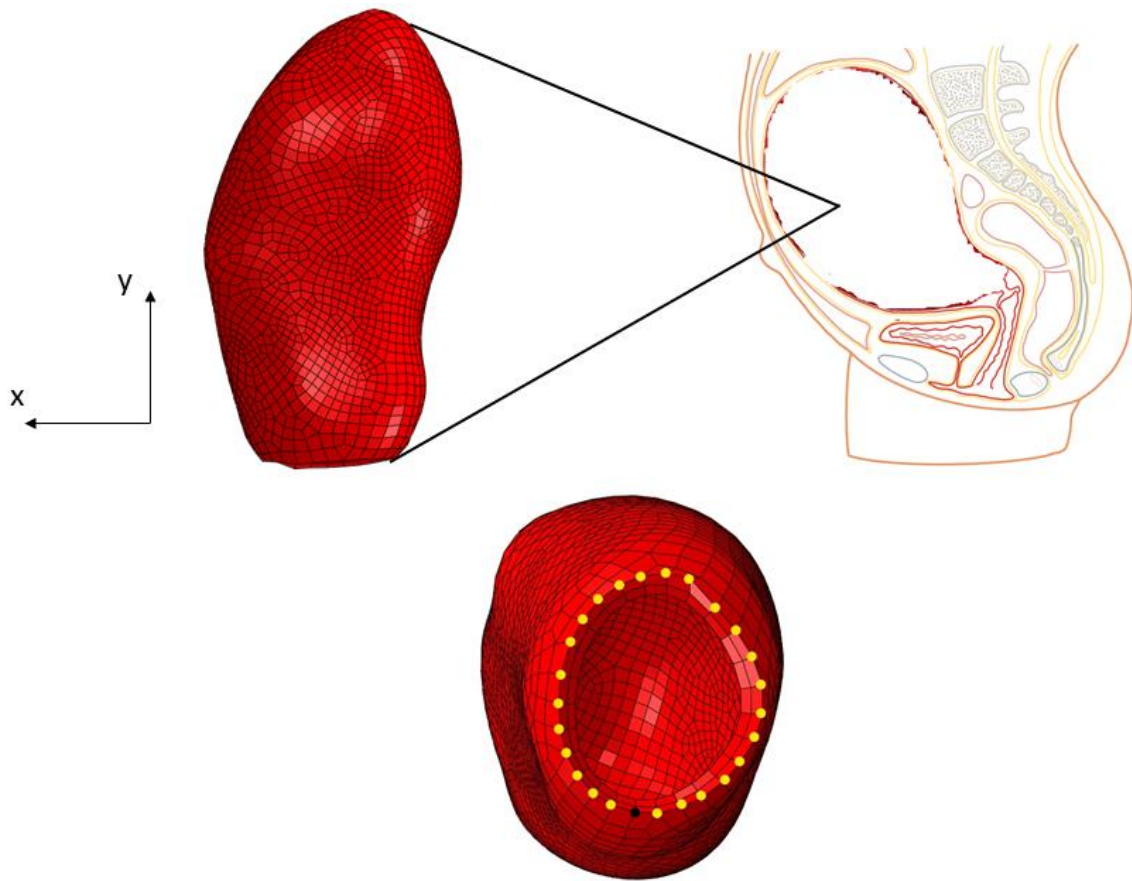


Figure 3. Lateral and bottom view of the finite element model of the uterus; the black node is completely fixed, and the yellow nodes are constrained in the vertical direction.

It is assumed that uterine muscle contraction follows the direction of the collagen fibers since cells tend to spread along those directions (Weiss et al., 2006). Therefore, two families of uterine fibers aligned longitudinally and circumferentially were considered (Weiss et al., 2006).

The direction of each fiber was found resorting to ABAQUS®. Using the uterine finite element model, a heat transfer simulation was carried out. Thermal

boundary conditions and heat sources were defined in the uterus, ensuring that heat propagated longitudinally and circumferentially around it. The boundary conditions and heat sources are defined differently for each flux direction. For instance, a longitudinal flux is obtained by defining a boundary condition at the uppermost region of the uterus and a heat source at the lowermost region. This will create a longitudinal flux from the lower to the upper region of the uterus. For the circumferential flux, the boundary condition and heat source location must be readjusted. The longitudinal and circumferential heat flux directions were then normalized and saved for each finite element, which means that every single finite element of the uterus will comprise two fibers: a longitudinal and a circumferential one. As an input of the electro-chemo-mechanical model, these directions represent the longitudinal and circumferential collagen fibers, respectively.

The uterus comprises 8997 nodes and 5970 linear hexahedral hybrids (C3D8H) elements. Regarding the boundary conditions, the black node was completely fixed to avoid lateral movements. In contrast, the yellow nodes were constrained in the vertical direction (Y-axis, from Figure 3) since the uterus should not sustain vertical movements.

Complete biomechanical model

The electro-chemo-mechanical constitutive equations described in the *Constitutive Model* section were applied to the uterine model, aiming to simulate

three uterine contraction patterns at the second stage of labor: (i) normal contractions (control model), (ii) excessively short resting stages, and (iii) tachysystole.

The electrical parameters were obtained from Yochum et al. and Rihanna et al. (Table 1). The initial transmembrane potential was defined as $V_{m0} = -50$ mV, the initial potassium activation as $n_{k0} = 0.079257$ and the initial intracellular calcium concentration as $[Ca^{2+}]_0 = 1.80 * 10^{-4}$ mM (Rihana et al., 2009; Yochum et al., 2016).

The chemical parameters were defined according to Sharifimajd's work (Sharifimajd et al., 2016) (Table 1), so as the following initial values: $\alpha_A = 1$, $\alpha_B = 0$, $\alpha_C = 0$, and $\alpha_D = 0$.

Finally, the mechanical parameters, except D_1 , were also obtained from Sharifimajd's work (Sharifimajd et al., 2016). D_1 is the volumetric parameter, and it was defined to guarantee an incompressible behavior. Incompressibility is achieved if D_1 is set to a very small value. We verified that $D_1 = 1 * 10^{-5}$ MPa⁻¹ was sufficient to guarantee that $J = 1$ throughout the simulations. The initial value of $\dot{\epsilon}_{ai}(i = 1,2)$ was set to 0. The mechanical parameters are shown in Table 1.

Table 1. Material parameters for the electro-chemo-mechanical model.

	<i>Variable</i>	<i>Description</i>	<i>Equation</i>	<i>Value</i>	<i>Units</i>
<i>Electrical Parameters</i> (Rihana et al., 2009; Yochum et al., 2016)	C_m	Membrane capacitance	(2.1), (2.3), (2.5)	1	μF
	f_c	Calcium influx probability	(2.7)	0.4	-
	A	Current conservation factor	(2.7)	4×10^{-5}	$\text{mol cm}^2/\mu C$
	K_{Ca}	Calcium extraction factor	(2.7)	0.01	mseg^{-1}
	J_{back}	Background calcium current	(2.10)	0.023	$\mu A/\text{cm}^2$
	G_{Ca}	Voltage-operated calcium channels conductance	(2.10)	0.022	mS/cm^2
	V_{Ca}	Half-point of the voltage operated channel activation sigmoid	(2.10)	-20	mV
	R_{Ca}	Maximum slope of the voltage operated channel activation	(2.10)	5.97	mV
	G_k	Potassium channels conductance	(2.11)	0.064	mS/cm^2
	E_k	Potassium nerst potential	(2.11), (2.12)	-83	mV
	K	Half-point potassium concentration	(2.12)	0.01	μmol
	G_{KCa}	Potassium/calcium channels conductance	(2.12)	0.08	mS/cm^2
	G_L	Leak channels conductance	(2.13)	0.0055	mS/cm^2
	E_L	Leak nerst potential	(2.13)	-20	mV
	$[Ca+2]_e$	Extracellular calcium concentration	(2.14)	2	mM
	R	Gas constant	(2.14)	8.134	$\text{JK}^{-1}\text{mol}^{-1}$
	T	Temperature	(2.14)	295	K
	F	Faraday constant	(2.14)	96.487	kCmol^{-1}
<i>Chemical Parameters</i> (Sharifimajd et al., 2016)	k_2	Dephosphorylation of myosin rate	(2.15)	1.2387	seg^{-1}
	k_3	Attachment and detachment of the fast-cycling cross-bridges rate	(2.15)	0.1419	seg^{-1}
	k_7	Latch-bridge detachment rate	(2.15)	0.0378	seg^{-1}
	$[Ca_{1/2MLCK}^{2+}]_i$	Calcium ion concentration for half-activation of MLCK	(2.16)	2.5698×10^{-4}	mM
	n_{k1}	Hill coefficient	(2.16)	8.7613	-
<i>Mechanical Parameters</i>	C_{10}	Stiffness coefficient	(2.21)	0.030	MPa
	ζ_1	Fraction of fibers of the first family	(2.22)	0.4	-
	μ_{i1} ($i = 1,2$)	Fiber's Stiffness	(2.23)	0.006	MPa
	μ_{i2} ($i = 1,2$)	Fiber's non-linear behavior	(2.23)	1	-

(Sharifimajd et al., 2016)	$\bar{\epsilon}_{opt}$	Active strain for maximum force	(2.27)	0.4950	-
	Γ	Constant	(2.27)	1	-
	v_c	Peripheral clutch velocity	(2.26)	0.11	seg ⁻¹
	η	Constant	(2.25)	18	MPa s
	k_{xb}	Constant	(2.24)	6	MPa
	k_c	Constant	(2.26)	3.5	MPa s

A surface-to-surface interaction with a penalty algorithm was considered between the inner uterine wall and the fetus, including a friction coefficient of 0.2 (Lindgren & Holmlund, 1969).

Assuming that the mother is maintained in a supine position, a gravity force can be neglected (Jakeman & Jakeman, 2016). No fluids were considered in the existing space between the fetus and the uterus, and no loads were applied since the electro-chemo-mechanical model promoted the fetus's expulsion.

Validation of the constitutive model to study different contraction patterns

To assess the capability of the electro-chemo-mechanical model to detect mechanical differences for different contraction patterns, a preliminary analysis using $\frac{1}{4}$ cylinder was performed (Figure 4). The constitutive model was applied to the cylinder and a contraction cycle was created:

- step 1 – isometric activation;
- step 2 – loading with constant active stress (displacement control);
- step 3 – isometric inactivation;

- step 4 – passive unloading (displacement control).

The analysis was carried out on a 40 mm long cylinder with a 10 mm radius, discretized in 80 linear hexahedral hybrids elements (C3D8H) and 154 nodes. Regarding the boundary conditions, the displacements are restricted in the left end of the cylinder for all steps, and in the right end are restricted in step 1 and step 3, while axial displacements are allowed in step 2 and step 4. Finally, since we are using $\frac{1}{4}$ cylinder, axisymmetric conditions were implemented in the remaining surfaces. The analysis was carried out for a total simulation time of 400s (100s per step) and 800s (200s per step).

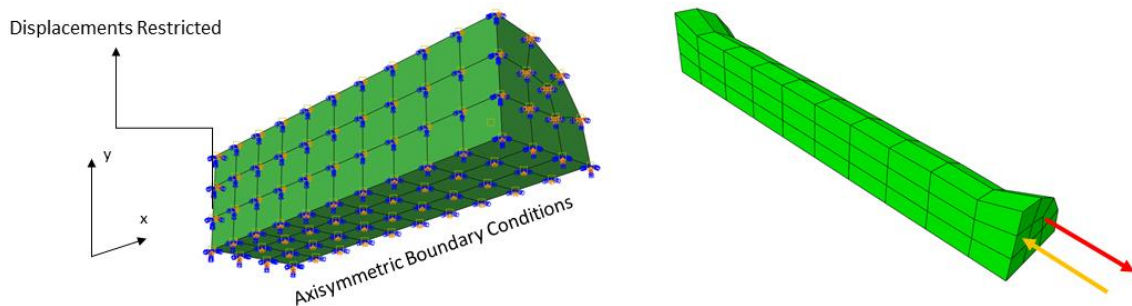


Figure 4. Quarter cylinder used in the preliminary analysis; the red arrow represents the stretching direction, and the orange arrow represents the unloading direction.

The maximum principal stress evolution throughout each analysis is illustrated in Figure 5. A higher average maximum principal stress value is reached during the second step of the 400s long cycle than the corresponding stress for the same step of the 800s one (approximately 13% higher). Therefore, during the vaginal delivery simulations, we expect to detect mechanical differences when the contraction patterns are changed, since the uterine tissue

will be contracting while the fetus stretches the uterine opening during its descent, similarly to what happens during step 2 of this analysis.

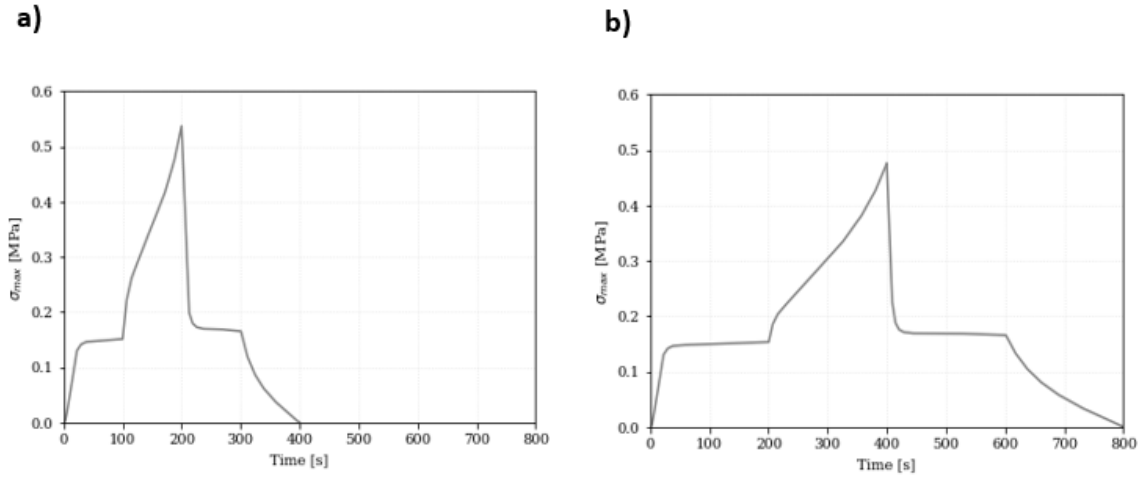


Figure 5. Maximum principal stress evolution for the 1/4-cylinder test; a) 100s step cycle; b) 200s step cycle; the curves represent the average stress across all nodes.

Biomechanical simulation of a vaginal delivery

To study the impact of different uterine contraction patterns in the uterine stress distribution and fiber stretch, three numerical simulations were carried out:

- normal contraction pattern (control model) – one contraction every 2–3 min; contraction time equals to 80s and resting time of 60s (Buttin et al., 2013);
- excessively short resting intervals – the time between one contraction and the beginning of the next one is drastically reduced; contraction time of 80s and resting time of 20s (Stewart et al., 2012); compared to the control

model, the contraction duration is maintained, while the resting duration is reduced in 40s; this contraction pattern tends to exhibit higher stress values during the resting stages compared to tachysystole, according to some clinical observations.

- tachysystole – uterine contractions of excessively high frequency (more frequent than every 2–3 min or more than five contractions every 10 min), causing hyperstimulation of the uterus; contraction time of 55s and resting time of 35s (Heuser et al., 2013); the contraction and resting time is reduced in 25s relatively to the control model; since tachysystole has shorter resting, it can be considered as a specific case of excessively short resting intervals, where the contraction time is also reduced.

It is difficult to distinguish excessively short resting and tachysystole patterns based on intrauterine pressure generated in each scenario, since external tocodynamometry, the most common uterine contraction measure technology, is only able to detect contraction frequency and duration.

Each simulation was divided into several steps, following an organized sequence of uterine contractions and relaxations.

The uterus was divided into 7 segments, L0 to L6, according to Figure 6, aiming to simulate the diffusion process associated with the electrical stimulus. L0 is the upper uterine region, followed by the L1 zone downwards, and so on. The uterine segments were defined so their height was as similar as possible.

Regarding the electro-chemo-mechanical model, a stimulation current of $I_{stim} = 0.17 \mu\text{A}/\text{cm}^2$ was applied. The stimulation current was quickly increased and maintained during each contraction and then decreased during the following resting stage.

Since the pregnant uterus consists of two segments comprising an active upper segment (L0, L1, L2, L3, L4, and L5) and a passive lower segment (L6), the activation curve is only applied to the first segment. In the first contraction, only L0 and L1 are activated by the constitutive model. In the second contraction, L2 and L3 are added, and, in the following contractions, the entire active segment is contracted. During the resting stages, no stimulation is applied to any uterine segment.

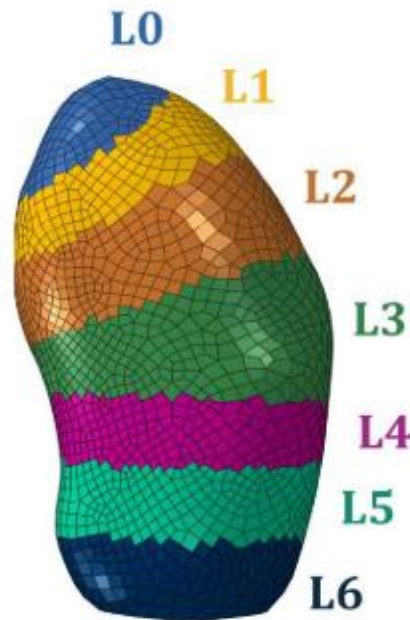


Figure 6. Uterine segments were created to simulate the electrical diffusion process.

Results

For each contraction pattern, we analyzed the maximum principal stress evolution throughout each simulation (Figure 7), and the average fiber stretch in the longitudinal (Figure 8) and circumferential (Figure 9) directions.

Average maximum principal stress evolution

The average maximum principal stress evolution for each uterine segment is illustrated in Figure 7. The maximum principal stress occurs approximately in the fiber directions, which were defined in the uterine model. Smooth muscle tissue tends to contract following the direction of collagen fiber and the muscle contraction will follow those directions (Vila Pouca et al., 2019). Maximum principal stress values increase during each contraction and decrease during the resting stages. All contraction patterns exhibit the largest average maximum principal stress value during the second uterine contraction at the L0 segment (normal and short resting patterns) or the L6 segment (tachysystole). The stress values in the L0 and L6 uterine segments are generally the largest. The curves corresponding to each uterine segment present a similar evolution for the different contraction patterns. However, there are important differences from a quantitative perspective that must be highlighted.

For the normal uterine contraction pattern (control model), the largest average maximum principal stress values found in the first, second, third, and

fourth contractions are, respectively, 18.0 kPa (L0 segment), 26.9 kPa (L0), 21.7 kPa (L6), and 17.2 kPa (L0). On the other hand, the smallest average maximum principal stress values found in the first, second, third, and fourth resting stages are, respectively, 1.1 kPa (L4), 2.4 kPa (L0), 1.9 kPa (L1), and 2.0 kPa (L1) (Figure 7 a)).

The excessively short resting interval pattern exhibits the following largest stress values, at the end of each contraction, respectively: 18.0 kPa (L0), 30 kPa (L0), 19.6 kPa (L0), and 20 kPa (L0). Regarding the smallest values for the resting stages, it is obtained, respectively, 2.1 kPa (L4), 3.3 kPa (L5), 4.0 kPa (L4), and 4.0 kPa (L4) (Figure 7 b)).

Finally, for the tachysystole pattern, the largest stress values are 15.8 kPa (L0), 19.9 kPa (L6), 13.6 kPa (L0), and 15.3 kPa (L0), and for the resting stages, the smallest values are 1.7 kPa (L4), 2.9 kPa (L3), 3.1 kPa (L1), and 3.1 kPa (L4) (Figure 7 c)).

The largest and smallest maximum principal stress values throughout all contractions and resting stages for each uterine segment are summarized in Table 2.

Therefore, the excessively short resting interval simulation exhibits generally larger average maximum principal stresses, both for the contraction and the resting stages, in comparison with the normal contraction pattern. On the other hand, the tachysystole exhibits smaller stress values during the uterine

contraction and larger values during the resting stages in comparison with the control model.

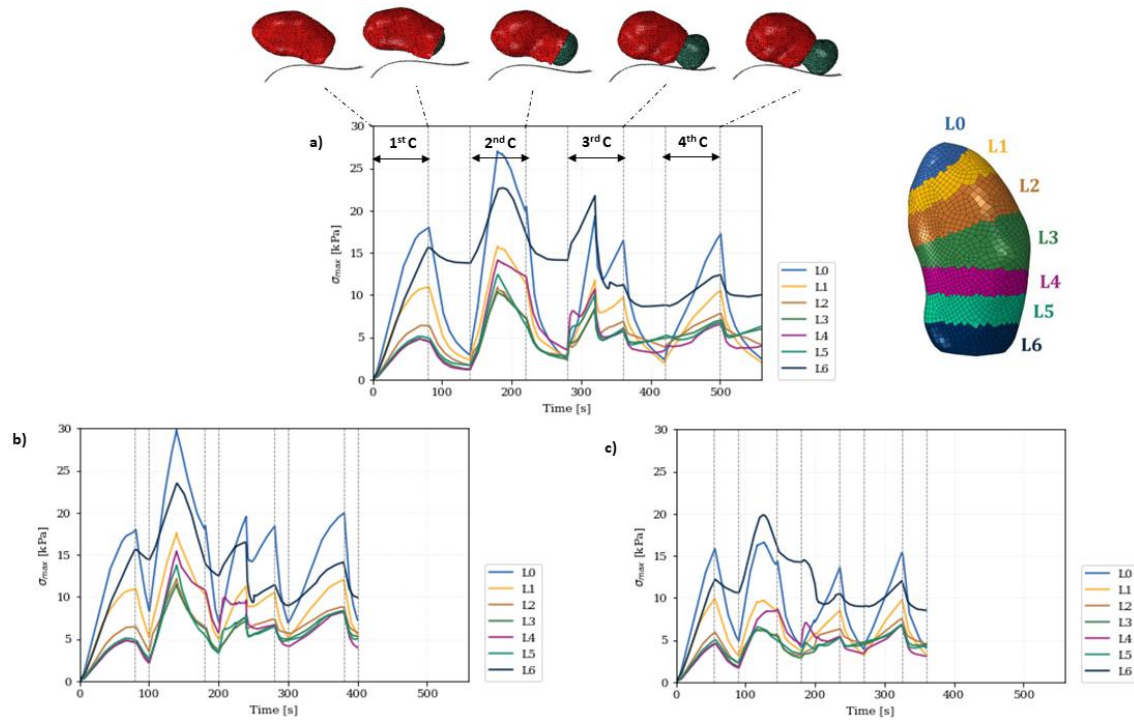


Figure 7. Maximum principal stress evolution for each uterine segment (L0-L6); a) control model; b) excessively short resting intervals; c) tachysystole; the fetal descent is illustrated at the top; "C" stands for "Contraction".

Table 2. The largest and smallest maximum principal stress values verified throughout all contractions and resting stages for each uterine layer; in each cell of the table, the upper value represents the smallest stress value for the respective resting stage, while the lower one represents the largest stress value for the respective uterine contraction; the stress values referred in previous paragraphs are highlighted in bold.

	Uterine Segment	Control							Short Resting							Tachysystole						
		L0	L1	L2	L3	L4	L5	L6	L0	L1	L2	L3	L4	L5	L6	L0	L1	L2	L3	L4	L5	L6
Uterine Resting/Contraction [kPa]	1 st	2.4 18.0	1.9 10.9	1.6 6.4	1.6 4.4	1.1 4.4	1.6 4.7	13.7 15.6	8.3 18.0	5.0 11.0	3.2 6.4	2.1 4.6	2.1 4.6	2.6 4.9	14.4 15.6	4.9 15.8	3.2 9.8	2.2 5.8	1.9 4.6	1.7 4.6	2.2 4.9	10.5 12.0
	2 nd	2.4 26.9	2.7 15.8	2.7 11.2	2.7 10.3	3.5 13.9	2.7 12.3	14.1 22.7	6.6 30.0	4.8 17.6	3.6 12.2	3.4 11.2	5.7 15.4	3.3 13.6	12.5 23.3	3.9 16.5	3.5 9.7	3.4 6.1	2.9 6.1	4.3 8.4	3.4 6.6	14.2 19.9
	3 rd	2.2 19.6	1.9 11.5	3.6 8.8	5.2 8.2	3.9 10.7	5.2 10	8.8 21.7	6.9 19.6	4.9 10.9	5.5 7.2	4.9 7.1	4.0 9.9	4.8 8.0	9.0 16.4	3.7 13.6	3.1 8.4	4.5 6.4	4.5 5.1	3.3 5.3	4.6 5.1	9.0 10.4
	4 th	2.1 17.2	2.0 10.7	4.0 7.8	6.1 7.1	4.0 6.4	6.3 6.5	10.0 12.3	7.2 20.0	5.0 12.0	5.8 8.9	5.0 8.0	4.0 8.0	5.0 8.0	10.0 14.0	4.1 15.3	3.1 9.7	4.4 7.5	4.4 6.8	3.1 6.8	4.3 6.8	8.6 12.0

The average stretch of the collagen fibers

The average stretch of contractile elements provides a measure of the uterine contractions throughout the uterus. For this work, the average stretch is analyzed in the longitudinal direction λ_1 and the circumferential direction λ_2 , for all the simulated scenarios.

The L6 set maintains its stretch values near 1 since it is not subjected to a stimulation current, representing a non-active segment of the uterus (Figure 8 and Figure 9).

Longitudinal average stretch

The average stretch values in the longitudinal direction are generally smaller than 1, which means that the elements are being compressed in this direction (Figure 8). The contraction is more intense for smaller stretch values, and they are minimal at the end of the fourth contraction.

The smallest average stretch values for the control model are 0.75 (L5), 0.73 (L3) for the excessively short resting stages, and 0.78 (L2) for the tachysystole, according to Figure 8 a), b), and c), respectively.

The excessively short resting intervals lead to generally smaller stretch values in the longitudinal direction in comparison with the control model. The opposite is concluded for the tachysystole pattern, where those values are generally larger compared to the normal contraction pattern.

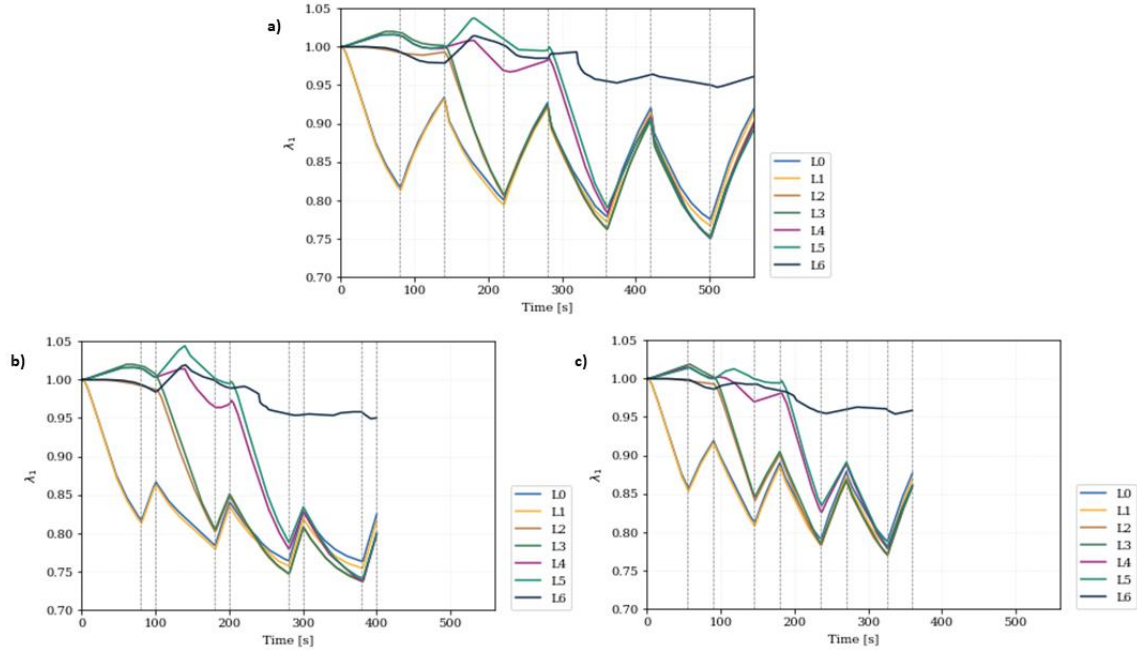


Figure 8. Average stretch evolution on the longitudinal direction for each uterine segment(L0-L6); a) control model; b) excessively short resting stages; c) tachysystole.

Circumferential average stretch

The average stretch values throughout the simulations are larger than 1, which means that the elements expand in the circumferential direction (Figure 9). The largest average stretch values in this direction are also verified at the end of the fourth contraction.

The largest average stretch values are 1.16 (L4) for the control model, 1.18 (L4) for the excessively short resting stages, and 1.13 (L4) for the tachysystole, according to Figure 9 a), b), and c), respectively. The excessively short resting intervals leads generally to larger stretch values in the circumferential direction throughout the simulation compared to the control model. Conversely, the opposite is observed for the tachysystole pattern, where those values are generally smaller compared to the normal contraction pattern scenario.

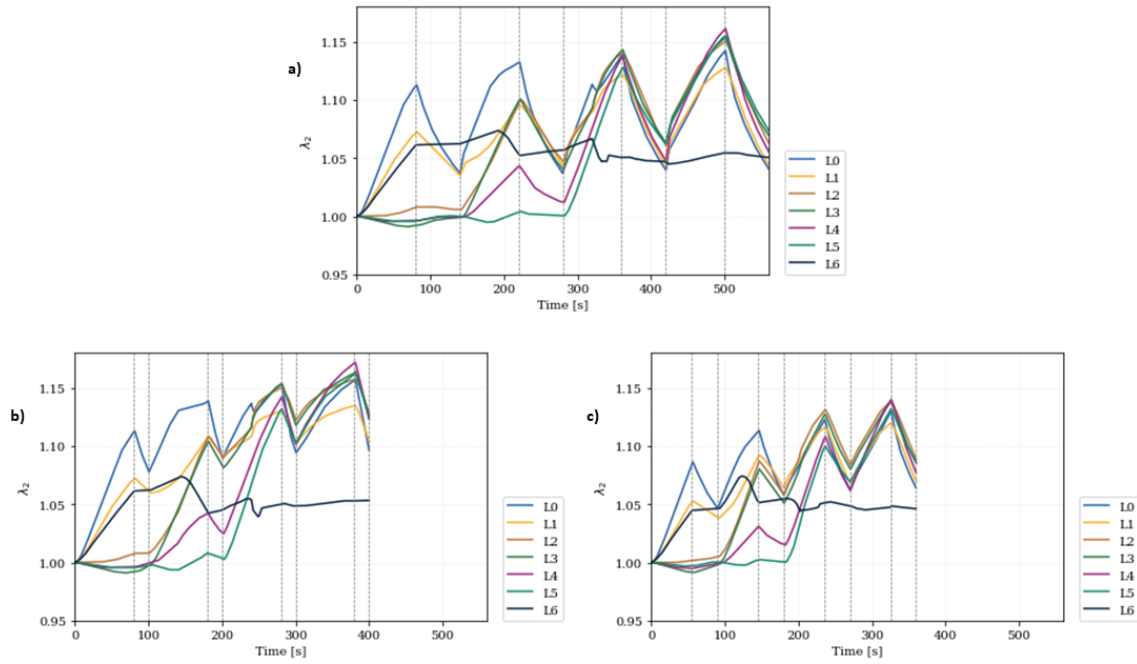


Figure 9. Average stretch evolution on the circumferential direction for each uterine element segment (L0-L6); a) control model; b) excessively short resting stages; c) tachysystole.

Discussion

There is evidence that uterine contractions may have an impact on labor progression (Oppenheimer et al., 2002). For instance, it has been demonstrated that cervical dilation depends on uterine contractile activity (Lindgren, 1973). However, there are still several unanswered questions concerning the connection between uterine contraction and labor progression.

Focusing on the average maximum principal stress, the control model exhibits values within the physiological range of the pregnant human uterus (Bisplinghoff et al., 2012). Concerning the excessively short resting intervals pattern, stress values are generally larger in comparison with the control model, as illustrated in Figure 7 b) and a), respectively. It is also observed that a

reduction of the resting intervals will not only impact the stress during the resting stages but also the uterine contractions. It is known that an inadequate resting time will lead to a critically low level of fetal oxygenation, due to a temporary reduction of maternal-fetal oxygen exchange (Ayres-De-Campos & Arulkumaran, 2015) and now we found that it is also associated with larger stresses. Newborn's health can be immediately compromised or develop complications in the future (Stewart et al., 2012). Furthermore, excessive short resting intervals, influenced by oxytocin, also increase the basal tone of the uterus, leading to reduced filling time and intracerebral oxygenation. This corresponds to oxytocin hyperstimulation labor, where larger intrauterine pressure (IUP) levels are verified. Therefore, the results observed in Figure 7 b) are consistent with the literature, since larger stress values will result very likely in stronger compressions of the uterine vessels, which may cause the oxygenation difficulties reported in the literature. Finally, focusing on Figure 7 c), the tachysystole pattern exhibits generally smaller maximum principal stress values at the end of the contractions and larger maximum principal stress values at the end of the resting stages compared to the control model. It has been reported that tachysystole is frequently associated with fetal heart rate decelerations, especially in response to oxytocin administration (Kunz et al., 2013; Stewart et al., 2012). This can happen due to uteroplacental insufficiency, which means that oxygen is not being provided to the fetus adequately (Hayes et al., 2013). Our results for the tachysystole pattern are consistent with these findings since the larger stress values at the end of the resting periods will not allow the uterine vessels to

achieve the same relaxation states as the control model, which may explain the difficulty in providing oxygen to the fetus and consequently the fetal heart rate decelerations.

Concerning the stretch of the collagen fibers, Zara and Dupuis carried out a childbirth simulation, focusing on uterine behavior during a real-time vaginal delivery (Zara & Dupuis, 2017). The authors studied the evolution of the trajectory of two front-sagittal points and two transversal points of the uterus (Zara & Dupuis, 2017). It was verified that the distance between the front-sagittal points decreased during the vaginal delivery, while the transversal points moved away during the simulation (Zara & Dupuis, 2017). The longitudinal and circumferential stretch of our control model is according to these findings since the average stretch values in the longitudinal direction are smaller than one (front-sagittal distance decrease) and average stretch values in the circumferential direction are larger than one (transversal distance increase), as illustrated in Figure 8 a) and Figure 9 a), respectively. Furthermore, Figure 8 b) shows that short resting stages tend to exhibit smaller average stretch values in the longitudinal direction compared to the control model, which indicates stronger uterine contractions in this direction. This is an important conclusion, especially when most uterine ruptures occur longitudinally (Usta et al., 2007). This observation is also consistent with the literature since stronger contractions will lead to oxygen difficulties, avoiding adequate blood flow through the uterine vessels. On the other hand, Figure 8 c) indicates that average stretch values in the longitudinal direction are larger in comparison with the control model, which

means that weaker uterine contractions are produced. Even though the uterine contractions are not as intense as in the control model, the fetal heart rate decelerations may be justified by the high contraction frequency verified in tachysystole, which will compress the uterine vessels more frequently than the normal contraction pattern.

It is also important to highlight the following points from our results:

- the L0 segment generally exhibits the largest maximum principal stresses and the largest circumferential stretch since we are looking at the most demanded segment of our uterine model: L0 starts contracting from the beginning of the simulations, unlike L2-L6 segments; L1 also starts contracting at the same moment, but the fetus' cinematic will impact this segment differently.
- although the L6 segment exhibits large stress values, these are caused by the fetal head passage; the smaller stretch values in the circumferential direction are associated with little variation in the L6 diameter.

This study reveals several practical implications for obstetricians in managing safe and effective labor inductions. There are many controversies and multiple guides to the induction of labor (IOL), especially in women after cesarean section (Cho, 2018). Obstetricians, being aware of maternal and fetal risk, remain careful with IOL in patients after cesarean section or primary gynecological surgeries on uterine muscle (Cho, 2018). Prostaglandins are the current recommended induction method, but uterine hyperstimulation syndrome, where contractions become too frequent or long, may lead to adverse

effects, such as fetal asphyxia, uterine rupture, or even placental abruption (Leung et al., 1987). The effect of prostaglandins at the electrical/chemical levels can be introduced in our constitutive model, although further experimental evidence is needed.

Scientific data suggest that some women were inadequately or unnecessarily treated with the use of oxytocin or prostaglandins (Selin et al., 2009). Our findings help to reinforce the idea that qualification for IOL should be personalized, considering all potential disadvantages, which can ultimately improve the management of labor and result in successful and safe delivery.

Biomechanical simulations have the potential to be an important tool for future research. A pre-delivery assessment could give a hint to a physician before the decision of vaginal or cesarean delivery, for example (Fidalgo et al., 2021). However, as the uterus undergoes an intense remodeling process during pregnancy, the development of individual models relies on clarifying some aspects concerning pregnancy biomechanics. The uterine remodeling process and the uterine growth diverge from patient to patient, which will lead to an alteration of the mechanical properties. Different results will be obtained if this phenomenon is introduced into our model, which can be performed as a future task. However, it is challenging to do so, since uterine remodeling is such a complicated process that is not completely comprehended by the scientific community.

There is a lack of an experimental/clinical database regarding the intrauterine pressure generated during uterine contractions that can be

compared with our results. The most common method for the measurement of uterine contractions is external tocodynamometry. However, tocodynamometers are used to measure tension across the abdominal wall and detect only contraction frequency and duration. External monitoring may be affected by other factors like maternal habitus, position, gestational age, and monitor location on the abdomen. The intrauterine pressure analysis problem can be overcome through the numerical analyses presented in this work after performing some improvements and adjustments to our model, such as considering the interaction between the uterine wall, fetal membrane, and amniotic fluid. This can be performed as a future task to enrich our simulations and respective results.

In this work, some simplifications were performed in the uterine-fetal biomechanical model, due to the complexity associated with this problem: (i) the constitutive model does not cover the fact that the uterus reaches an almost non-pregnant stage right after the end of the second stage of labor, (ii) the collagen fiber distribution in the uterus was based on the non-pregnant state, (iii) the connection between the layer L6 and the vaginal canal was not considered in the uterine model, which could likewise influence the stress distribution in that uterine layer since more realistic movements would be provided, (iv) it was neglected the viscoelastic passive behavior on the uterine tissue, the pushing force exerted by the mother, the contraction of the abdominal muscles, the baseline intrauterine pressure, and the residual strain in the reference configuration, (v) since the reference state of the model corresponds to the uterus

around the grown fetus, the initial passive-stretch caused by the baby is not considered.

Conclusion

The results obtained with this biomechanical approach highlighted significant differences among all contraction patterns simulated, especially in terms of maximum principal stress and average fiber stretch. Generally, the excessively short resting intervals exhibited larger average maximum principal stresses during the contraction and resting stages, smaller average fiber stretch values in the longitudinal direction, and larger stretches in the circumferential direction. On the other hand, the tachysystole exhibits generally smaller stress values during the uterine contraction and larger stress values during the resting stages, larger stretches in the longitudinal direction, and smaller stretches in the circumferential direction.

The results are consistent with the literature, highlighting the potential of our biomechanical model to study several obstetrical factors and assist in clinical decisions.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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PART B: Article 3

Development of a multilayer fetal membrane material model calibrated using bulge inflation mechanical tests

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Abstract

The fetal membranes are an essential mechanical structure for pregnancy, protecting the developing fetus in an amniotic fluid environment and rupturing before birth. In cooperation with the cervix and the uterus, the fetal membranes support the mechanical loads of pregnancy. Structurally, the fetal membranes comprise two main layers: the amnion and the chorion. The mechanical characterization of each layer is crucial to understanding how each layer contributes to the structural performance of the whole membrane. The in-vivo mechanical loading of the fetal membranes and the amount of tissue stress generated in each layer throughout gestation remains poorly understood, as it is difficult to perform direct measurements on pregnant patients. Finite element analysis of pregnancy offers a computational method to explore how anatomical and tissue remodeling factors influence the load-sharing of the uterus, cervix, and fetal membranes. To aid in the formulation of such computational models of pregnancy, this work develops a fiber-based multilayer fetal membrane model that captures its response to previously published bulge inflation loading data. First, material models for the amnion, chorion, and maternal decidua are formulated, informed, and validated by published data. Then, the behavior of the fetal membrane as a layered structure was analyzed, focusing on the respective stress distribution and thickness variation in each layer. The layered computational model captures the overall behavior of the fetal membranes, with the amnion being the mechanically dominant layer. The inclusion of fibers in the amnion material model is an important factor in obtaining reliable fetal

membrane behavior according to the experimental dataset. These results highlight the potential of this layered model to be integrated into larger biomechanical models of the gravid uterus and cervix to study the mechanical mechanisms of preterm birth.

Keywords: Fetal Membrane; Amnion; Chorion; Inflation Test; Constitutive Model; Numerical Simulation

Abbreviations

ROM – Rupture of the fetal membranes

PPROM – Preterm pre-labor rupture of the fetal membranes

OCT – Optical coherence tomography

Introduction

The fetal membranes are a complex biological structure that surrounds and protects the fetus, serving as a mechanical and immunological barrier throughout pregnancy (Bryant-Greenwood, 1998; Jabareen et al., 2009). It is a multilayered structure undergoing complex microstructural changes by the end of pregnancy (McLaren et al., 1999), contributing to tissue weakening in preparation for birth (Oyen et al., 2006), and undergoing an intense growth and deformation process to adapt to the different stages of pregnancy (Joyce et al., 2016). At term, the following dynamic events occur: cervical deformation, rupture of membranes, and uterine contractions (Vink & Feltovich, 2016). These phenomena involve coordinated responses from the fetal membrane, the cervix, and the uterus, whose interactions are not completely understood (Vink & Feltovich, 2016). The rupture of the fetal membranes (ROM) is an integral part of vaginal delivery but can lead to serious maternal and fetal health problems when it occurs before term (Devlieger et al., 2006). Approximately 3% of all pregnancies worldwide suffer a membrane rupture earlier than 37 weeks gestational age, called preterm pre-labor rupture of the fetal membranes (PPROM) (Mercer, 2010).

Generally, the membranes comprise two main layers, amnion and chorion, whose microstructures differ significantly from each other (Helmig et al., 1993). The amnion is the inner layer of the membranes facing the amniotic fluid, while the chorion is the outer layer contacting the uterine wall (Ilancheran et al., 2009;

Zhang et al., 2021). The amnion layer, a fibrous time-dependent material, is the mechanically dominant layer of the fetal membranes (Buerzle & Mazza, 2013; Oyen et al., 2004, 2006). Randomly oriented collagen fibers dominate the material response to tensile loading. Hence, a constitutive material model capturing fiber stretching and rotation mechanisms helps understand how the fetal membranes help load-share with the uterus and cervix (Buerzle & Mazza, 2013). The amnion is thinner, stiffer, and stronger than the compliant and more extensible chorion (Buerzle et al., 2012; Buerzle & Mazza, 2013; Oyen et al., 2004). The amnion and chorion are separated by a spongy layer, which comprises proteoglycans and glycoproteins, along with collagen of type III, and the spongy layer interface allows the amnion to slide on the underlying chorion (Joyce et al., 2009; Menon & Richardson, 2017).

The decidua, a maternal layer adjacent to the chorion, plays an essential role in the mechanics of the fetal membranes (Tahan & Tahan, 2014). This layer results from the uterine endometrium's differentiation process under the influence of progesterone (Abbas et al., 2019). It is known that the decidua shares a close anatomical relationship with the chorion (chorio-decidua layer), which might suggest that decidual changes may be associated with chorioamnion membrane alterations (Malak & Bell, 1994). The development of the decidual layer and the chorion is synchronized from the earliest implantation phase, and the smooth chorion becomes fused with the decidua (Ogura et al., 2017).

Foundational mechanical tests have been performed on the fetal membranes, often characterizing individual layers from at-term delivered

samples. Oxlund et al. designed a method to retrieve uniaxial data concerning the mechanical properties of the fetal membranes (Oxlund et al., 1990). Helmig et al. analyzed whether the mechanical properties of the fetal membranes changed during late pregnancy and labor, concluding that pronounced changes were induced in the amnion and chorion mechanical properties (Helmig et al., 1993). Oyen et al. investigated the soft-tissue time-dependent behavior, focusing on the amnion sublayer, and the differences between the amnion and the chorion in terms of failure properties, analyzing the biaxial puncture failure of intact chorioamnion, and separated amnion and chorion (Oyen et al., 2004, 2006). Oyen et al. also performed uniaxial and planar biaxial mechanical tests to determine the amnion layer's nonlinear and time-dependent mechanical response (Oyen, 2005). Verbruggen et al. developed isotropic linear elastic finite element models of fetal membranes to determine the mechanical role of the amnion and the chorion layers, and to simulate the uterine environment in the context of term gestation and PPROM (Verbruggen et al., 2017). However, the chorioamnion – and the amnion in particular – is strongly nonlinear in its mechanical response (Oxlund et al., 1990; Oyen, 2005), so the Verbruggen study is limited in its applicability.

This collection of mechanical tests and models highlights the complex material behavior of fetal membranes. It motivates a need to develop a layered model to capture its robust mechanical function. Understating the complex interaction between the membranes, the cervix, and the uterus at term or preterm requires accurate modeling of the fetal membrane, especially due to the amnion's

anisotropic nonlinear behavior, which dominates the membrane's mechanical response. Therefore, this work develops a multilayer fetal membrane biomechanical model capturing the physiological response of fetal membranes within the uterine environment. This model represents an improvement over the existing ones by considering the amnion as an anisotropic nonlinear material. The validation of the model is performed by comparing the inflation apex displacement of the model with an inflation mechanical dataset (Samimi et al., 2023), and comparing the numerical maximum principal stress values in the amnion and chorion layers with the respective physiological ranges reported in the literature.

Materials and Methods

This work is divided into three main parts: (i) mechanical characterization of the amnion, chorion, and decidua, (ii) development of a multilayer fetal membrane model, and (iii) validation of the multilayer model. In part (i), the constitutive model used to characterize the amnion is presented, and the respective material parameters are; the chorion and decidua are characterized using isotropic linear elastic constitutive model with parameters retrieved from the literature. In part (ii), a multilayer fetal membrane model comprising the fetal amnion, chorion, and maternal decidua is developed, applying the constitutive characterization presented in part (i). Finally, in part (iii), the layered model is validated by comparing the outcomes of an inflation numerical simulation (apex

displacement, maximum principal stress, and thickness variation), with experimental data and information reported in the literature.

Amnion, chorion, and decidua models

Amnion constitutive model formulation

In this work, a modified version of the Buerzle-Mazza formulation (Buerzle & Mazza, 2013) developed by Mauri and Ehret (Mauri et al., 2016) was considered to characterize the mechanical response of the amnion (Mauri et al., 2016). The strain energy function, Ψ , represents the strain energy per unit reference volume and accounts for the stretch of the single families of fibers (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$\Psi = \frac{\mu_0}{2q} [e^{qg} - 1] \quad (2.1)$$

where μ_0 is a material constant having the units of stress and q is a dimensionless constant that controls the nonlinearity of the moduli for the different stress responses in the composite structure (Rubin & Bodner, 2002).

The function g is given by the sum of the compressible neo-Hookean material g_2 , and the fiber strain energy g_3 (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$g = g_2(I_1, J) + g_3(\lambda_i) \quad (2.2)$$

$$g_2 = m_2(I_1 - 3) + \frac{m_2}{m_5}(J^{-2m_5} - 1) \quad (2.3)$$

$$g_3 = \frac{m_3}{m_4} \frac{1}{N} \sum_{i=1}^N \langle \lambda_i - 1 \rangle^{2m_4} \quad (2.4)$$

where $\langle \ \rangle$ represent the Macauley brackets, which indicates that the fibers do not bear compression loads (Buerzle & Mazza, 2013) and m_i are model parameters. The parameter N represents the number of representative families and it must be an even number. The first invariant of the right Cauchy-Green deformation tensor is represented by I_1 , while J is the volume ratio, and λ_i is the fiber stretch (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$I_1 = tr(\mathbf{F}^T \mathbf{F}) \quad (2.5)$$

$$J = det \mathbf{F} \quad (2.6)$$

$$\lambda_i = |\mathbf{F} \mathbf{M}_i|, \quad i = 1, 2, \dots, N \quad (2.7)$$

The deformation gradient is represented by $\mathbf{F}$ and $\mathbf{M}$ represent the fiber directions in the reference configuration and it is defined as (Mauri et al., 2016):

$$\mathbf{M}_j = \cos\beta_j \sin\theta_j \mathbf{e}_1 + \sin\beta_j \sin\theta_j \mathbf{e}_2 + \cos\theta_j \mathbf{N} \quad (2.8)$$

$$\mathbf{M}_{j+N/2} = \cos\beta_j \sin\theta_j \mathbf{e}_1 + \sin\beta_j \sin\theta_j \mathbf{e}_2 - \cos\theta_j \mathbf{N} \quad (2.9)$$

$$\beta_j = \frac{2\pi}{N} \left(j - \frac{3}{2} \right) \quad (2.10)$$

$$\theta_j = \frac{\pi}{2} - \varphi \quad (2.11)$$

where φ represents a slight off-plane inclination and $j = 1, 2, \dots, \frac{N}{2}$. The Cauchy stress tensor $\boldsymbol{\sigma}$ is obtained from the derivatives of the strain energy density function with respect to the deformation tensor (Buerzle & Mazza, 2013). The membrane tension $\mathbf{t}$ in the current configuration was calculated through the following equation, where h_0 is the initial thickness of the membrane, and λ_1 and λ_2 are the longitudinal and lateral stretches, respectively (Buerzle & Mazza, 2013):

$$\mathbf{t} = \boldsymbol{\sigma} \frac{h_0}{\lambda_1 \lambda_2} \quad (2.12)$$

In total, eight parameters must be defined: μ_0 , q , m_2 , m_3 , m_4 , m_5 , N and φ .

The fetal membrane may be subjected to large deformations during biaxial mechanical tests. In this scenario, the g_3 function likely reaches considerable values, due to the exponential term e^{qg} . Consequently, the strain energy function will also reach large values, which may result in illogical values for the stress and Jacobian matrices. Therefore, a stability control was considered for the g_3 function, limiting its maximum value to a certain threshold. Every time the limit was surpassed, the iteration was restarted with a smaller value for the time increment. It is important to highlight that this control does not have any effect on the results. The control was implemented in Abaqus/Standard, where the user material subroutine was also developed.

Amnion material parameter characterization

The values of the amnion constitutive parameters were set according to Table 1, provided by Mauri and Ehret (Mauri et al., 2016), except for the μ_0 and φ parameters. The first was determined through trial and error, using a uniaxial finite element setup (*Uniaxial test* subsection). Inflation (*Inflation test* subsection) and puncture (*Puncture test* subsection) setups were also developed to validate μ_0 and evaluate the prediction capabilities of the amnion model. The outcomes from these three numerical tests were compared to experimental data from the literature (Buerzle & Mazza, 2013; Oyen et al., 2004) in the results section. The parameter φ was set to 0 to exclude the impact of the fiber's off-plane inclination.

Table 1. Parameters of the modified Buerzle-Mazza constitutive model, according to Ehret, except for μ_0 , and φ (Mauri et al., 2016); all parameters are dimensionless.

Parameter	q	m_2	m_3	m_4	m_5	N	φ
Value	2.96	0.00228	41.12	1.27	0.463	32	0°

Uniaxial Test

To obtain μ_0 through trial-error analysis, a finite element setup of a uniaxial mechanical test was created according to the experimental setup reported in Buerzle et al. (Buerzle & Mazza, 2013), discretizing a rectangular sample of dimensions 80×15 mm in 320 eight-node brick (C3D8) finite elements and 739 nodes, as illustrated in Figure 1.

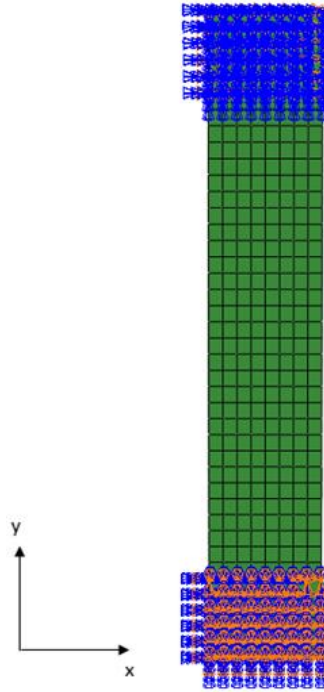


Figure 1. Finite element setup of a uniaxial test and respective boundary conditions.

To simulate the mechanical conditions of the uniaxial test, the tissue corresponding to 10 mm measured from the bottom of the sample was restrained in all directions. The same restriction was applied for 10 mm measured from the top of the sample, except for the y-direction, where a displacement boundary condition was applied. Therefore, the sample starts from an initial free length of 60 mm. A displacement of 15 mm was applied in the upper region of the sample, following the positive direction of the y-axis.

Different uniaxial stretch-tension curves were obtained for different μ_0 values until the numerical curve replicated almost perfectly the experimental curve, especially for smaller stretches (Buerzle & Mazza, 2013).

Inflation test

After obtaining μ_0 , an inflation setup was developed to evaluate the prediction capabilities of the amnion model, comprising the amniotic sample and a clamping ring (Buerzle & Mazza, 2013). To match the literature's mechanical test, the sample was 70 mm in diameter and contained 4667 C3D8 finite elements and 9555 nodes (Figure 2). The clamping ring was characterized as a rigid body with an inner diameter of 50 mm and an outer diameter of 70 mm.

The clamping ring was fixed and the nodes from the border of the amnion were restricted in all directions. The contact between the amnion and the clamping ring was modeled as surface-to-surface, with a large friction coefficient

(0.9). A ramping pressure of 10 kPa distributed across the lower surface of the amnion was applied in the positive direction of the y-axis.

Following a similar procedure as the uniaxial test, the tension-stretch evolution from the model during an inflation test was also compared with averaged biaxial tension-stretch experimental data using amnion samples, maintaining the μ_0 value obtained in the uniaxial test (Haller, 2013).

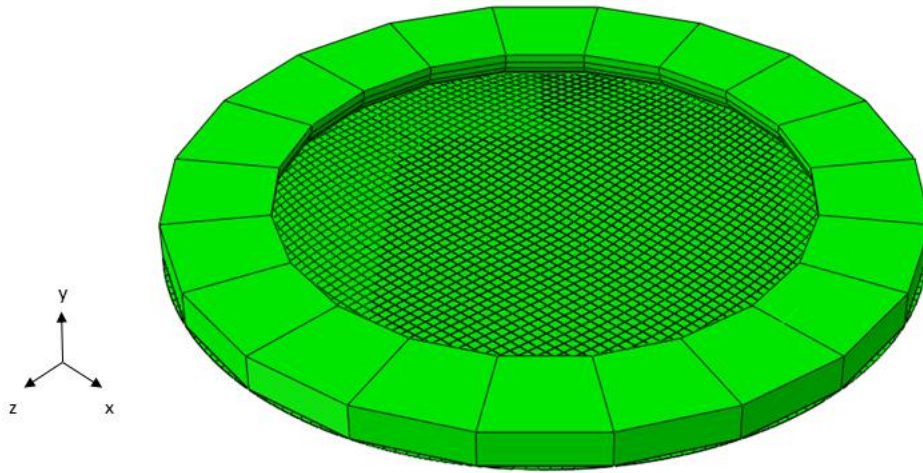


Figure 2. Finite element setup of an inflation mechanical test.

Puncture test

Similarly to the inflation test, a puncture setup was also developed to validate and verify the prediction capabilities of the amnion model, comprising the amniotic sample, an upper clamping ring, a lower clamping ring, and a puncture probe (Oyen et al., 2004). The sample was 60 mm in diameter and contained 1561 C3D8 finite elements and 3427 nodes. The clamping rings and the puncture probe were characterized as rigid bodies. The first had an inner

diameter of 20 mm and an outer diameter of 60 mm, while the latter had 3.2 mm in diameter (Figure 3).

The simulation of the puncture test was divided into three steps: (1) descent of the upper clamping ring, (2) application of a clamping force, and (3) descent of the puncture probe. Steps (1) and (2) represent the necessary preconditioning to perform the puncture test. Step (1) implied that the upper clamping had its movements restricted, except for the y- direction, and the lower clamping ring was fixed. Step (3) allowed the puncture to push the membrane 10–15 mm, a distance that usually causes the amnion to rupture (Oyen et al., 2004); in this step, the puncture probe was restricted in all directions, except for the y-direction; finally, the nodes from the membrane border were fixed. The contact between the amnion and the clamping rings was modeled as surface-to-surface, with a high friction coefficient (0.9), while the contact between the puncture and the membrane was modeled as frictionless contact.

The reaction force caused by the puncture probe was compared with the literature in the Results section, pushing the membrane 10–15 mm. This simulation helped validate the amnion model with μ_0 set to the value obtained in the uniaxial test (Oyen et al., 2004).

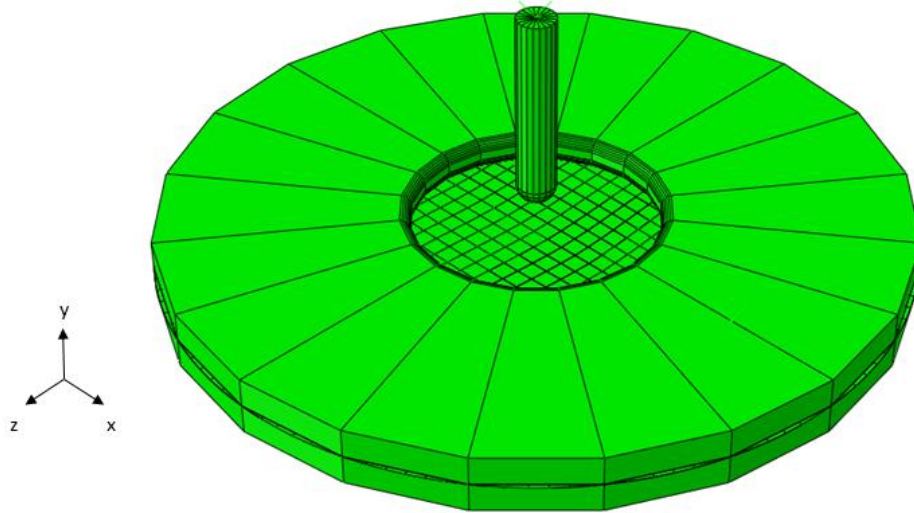


Figure 3. Finite element setup of a puncture mechanical test.

Chorion and decidua characterization

The chorion and decidua are less mechanically dominant than the amnion layer. Therefore, these layers were characterized as isotropic linear elastic materials, with parameters retrieved from the literature (Table 2). In this work, it was hypothesized that the chorion and the decidua shared similar mechanical properties since it is known that the smooth chorion becomes fused with the decidua, which may suggest that they are similar from a stiffness perspective. The respective Poisson's coefficients were set to a value near 0.5 (Roohbakhshan et al., 2016; Verbruggen et al., 2017).

Table 2. Isotropic linear elastic properties of the chorion and the decidua layers (Ophir et al., 2002; Oxlund et al., 1990; Roohbakhshan et al., 2016; Verbruggen et al., 2017).

	Young's Modulus, E [MPa]	Poisson's Ratio, ν
Chorion	1	0.4-0.5
Decidua	1	0.4-0.5

Multilayer fetal membrane model

After modeling the amnion, chorion, and decidua, a multilayer fetal membrane structure was developed to capture the inflation response of the amnion-chorion-decidea layers. A finite element model of the inflation test presented by Samimi et al. was created (Samimi et al., 2023), as illustrated in Figure 4.

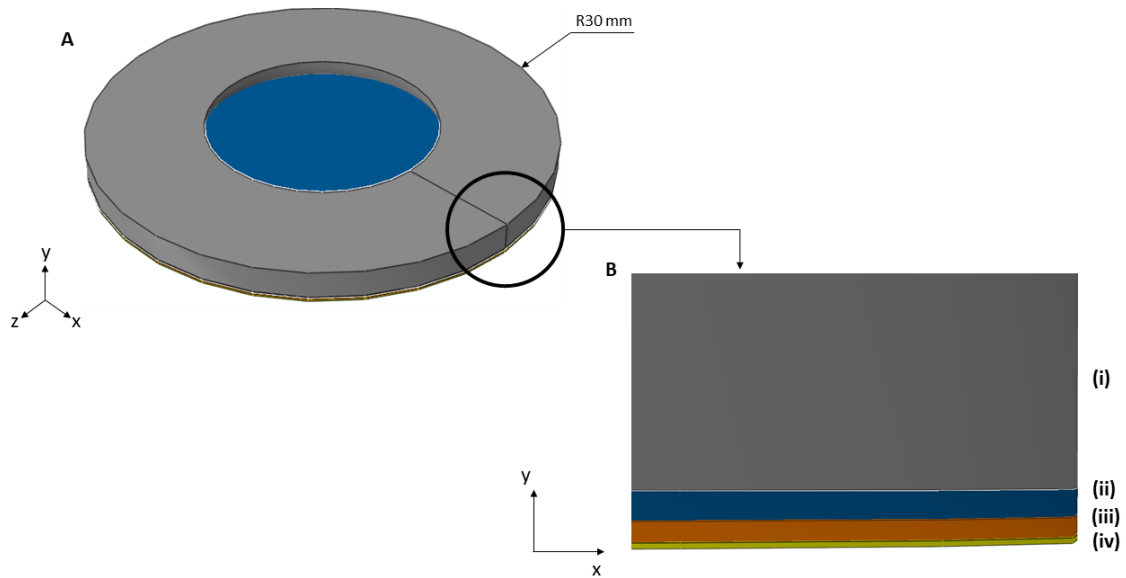


Figure 4. Finite element setup of the inflation mechanical test using the multilayer fetal membrane model; A: three-dimensional view of the model; B: detailed view of the model (grey: clamping ring (i); blue: part of the decidua (ii); orange: chorion (iii); yellow: amnion (iv)).

Details on the mechanical tests are found in (Samimi et al., 2023). Briefly, the fetal membrane samples were tested in a custom inflation mechanical test rig, where membrane pressure and deformation were measured simultaneously. Optical coherence tomography (OCT) and machine learning methods were developed to characterize the ex vivo properties of fetal membranes under

dynamic loading. These were in situ mechanical tests, where the thickness of each layer was updated during inflation using OCT. The test was performed by laying the samples flat on a circular plate, with a 30 mm-diameter opening in the center and an external diameter of 60 mm. A clamping ring with the same dimensions was placed over the samples and secured with equally spaced bolts and nuts. A constant-flow syringe pump connected to an open water column at the base of the setup provided a nearly linear saline pressure ramp at a rate of 10 kPa per minute until rupture. A pre-inflation pressure value of approximately 0.2 kPa was applied before the test to eliminate the initial clamped membrane's slack state. Eighteen 6 cm diameter peri-placental samples from unlabored elective cesarian sections collected between 37 and 41 weeks of gestation were selected for this work.

The multilayer fetal membrane model developed under an inflation setup (Figure 4) comprises the following structure: (i) clamping ring, (ii) part of the decidua, (iii) chorion, and (iv) amnion. The spongy layer was modeled as a contact condition between the amnion and the chorion and not as a physical layer since it only allows the amnion to slide on the underlying chorion. The spongy layer easily disintegrates during the separation process for mechanical testing, making it difficult to characterize it in isolation.

The amnion had a diameter of 60 mm. Its thickness was set to the average value of all selected samples' initial thicknesses reported in the experimental dataset (Table 3). The amnion was mechanically characterized by the modified version of the Buerzle-Mazza constitutive model, setting the respective

constitutive parameters to the values reported in Table 1. Once the solid model was constructed, the amnion was meshed with 3422 C3D8 elements and 7034 nodes.

The chorion and the decidua also had a diameter of 60 mm and the respective thicknesses were set as described for the amnion (Table 3). These layers were characterized as isotropic linear elastic materials (Table 2). The chorion and decidua were both meshed with 3422 C3D8 elements and 7034 nodes.

The clamping ring had an inner diameter of 30 mm and an outer diameter of 60 mm. A fillet edge was considered to avoid cutting the membrane during the mechanical test. This structure was modeled as a rigid body.

The contact condition between the amnion and the chorion was modeled as a surface-to-surface contact with a friction coefficient of 0.5, playing the role of the spongy layer. The chorion and the decidua were tied, representing the fusion process mentioned before. Finally, the contact between the decidua and the clamping ring was modeled as a surface-to-surface contact, with a high value of friction coefficient (0.9). Concerning the boundary conditions, all the border nodes from the three layers were restricted in all directions and the clamping ring was fixed.

Table 3. Amnion, chorion, and decidua thicknesses.

	Amnion	Chorion	Decidua
Thickness [mm]	0.062	0.217	0.311

Simulation steps of the inflation mechanical test

The fetal membrane samples were first submitted to a pre-inflation state, which corresponded to a slightly distended condition of the membrane, and it was completely different from the slack state of the initially clamped membrane. This procedure was performed to obtain a repeatable definition of the reference configuration for the analysis of the experiments (K. M. Myers et al., 2010).

Therefore, the inflation simulation was divided into two main steps: (i) pre-inflation, and (ii) inflation-to-failure. In step (i), a pre-inflation pressure ranging between 0.1 and 0.3 kPa was applied, to reach the pre-inflation state, while in step (ii) a ramping inflation pressure ranging between 10 and 20 kPa was considered. The pre-inflation pressure and the ramping inflation pressures were sequentially applied across the inferior surface of the amnion layer, in the positive direction of the y-axis (Figure 4).

Results

The results are divided into three parts: *Amnion material model calibration and validation* subsection - μ_0 for the amnion material model is obtained by analyzing uniaxial behavior, and the prediction capabilities of the material model are analyzed under inflation and puncture mechanical setups; *Multilayer fetal membrane model* subsection - the apex displacement of the multilayer fetal membranes model (anisotropic amnion) is compared to the experimental apex

displacement and to a case where the multilayer model comprises an elastic linear isotropic amnion material characterization (Verbruggen et al., 2017); *Stress distribution and thickness variation in the amnion and chorion layers* subsection - for the same inflation simulation, the mechanical response of the amnion and the chorion is analyzed.

Amnion material model calibration and validation

The nonlinear behavior of the amnion is featured in the model and experimental response to uniaxial extension, where the longitudinal stretch (λ_1) – tension (T) curves exhibit small stiffness values for smaller stretches, followed by a transition to a larger stiffness (Figure 5). The material parameter μ_0 is set to several values and the best match between the model's stretch-tension curve and the experimental data occurs when μ_0 is set to 2.4 MPa (Figure 5A), especially for smaller deformations. For this value, the mean-squared error for 5% of longitudinal stretch is equal to 0.0000040, for 20% is equal to 0.00023, and for 100% is equal to 0.00030. Lastly, the relation between lateral deformation and longitudinal contraction is analyzed (Figure 5B). In uniaxial extension, the lateral stretch (λ_2) evolution shows that the amnion layer has a remarkable lateral contraction as the membrane stretches longitudinally.

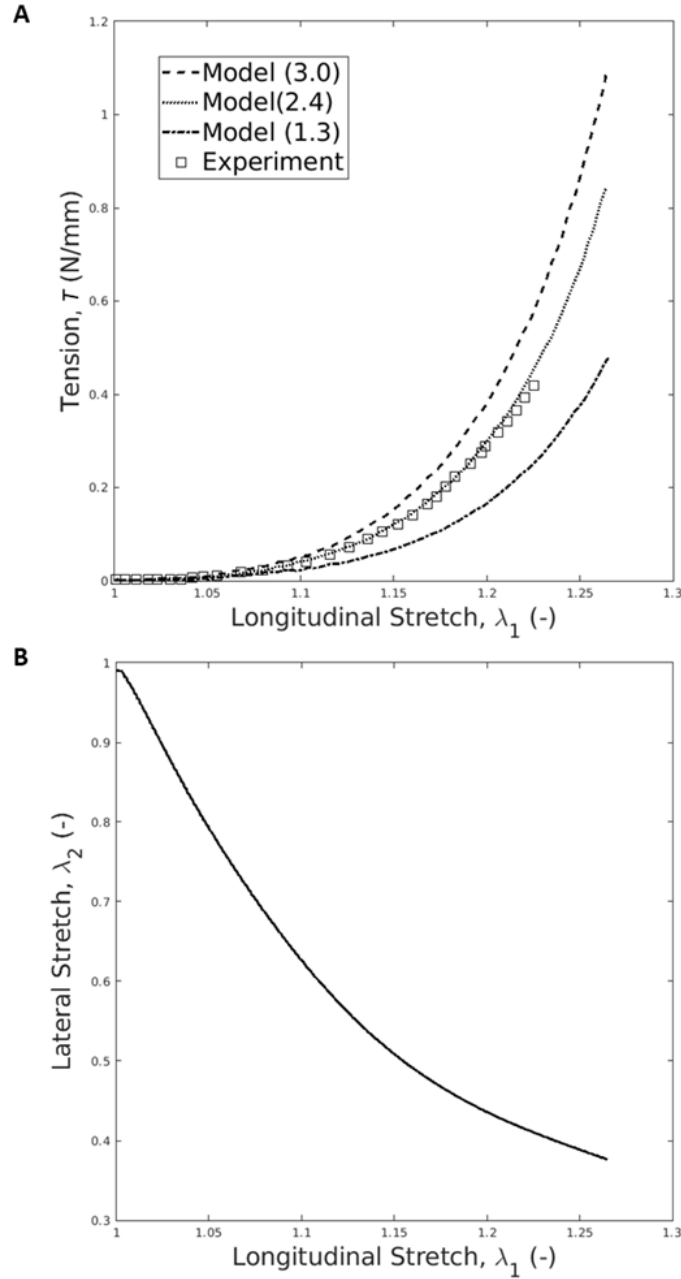


Figure 5. (A) Trial-error analysis to obtain the μ_0 parameter; μ_0 is set to several values (only three are here illustrated) and the respective tension-stretch curves are compared with experimental data; the best match is obtained when μ_0 is set to 2.4 MPa; (B) lateral stretch as a function of longitudinal stretch in our amnion model during the uniaxial test.

The amnion material parameters are validated by comparing computational results with published experimental values. For smaller values of stretches in inflation, the model curve matches the experimental data (Figure 6A). For larger stretch values, the model and experimental curves exhibit a slight

deviation, which is also observed in previous works (Buerzle & Mazza, 2013). Regarding the puncture test, the force caused by the probe (F) increases as it pushes the membrane, registering a maximum value of 3.18N when the probe descends about 11 mm (Figure 6B), like what is verified in the work of Oyen et al. (Oyen et al., 2004).

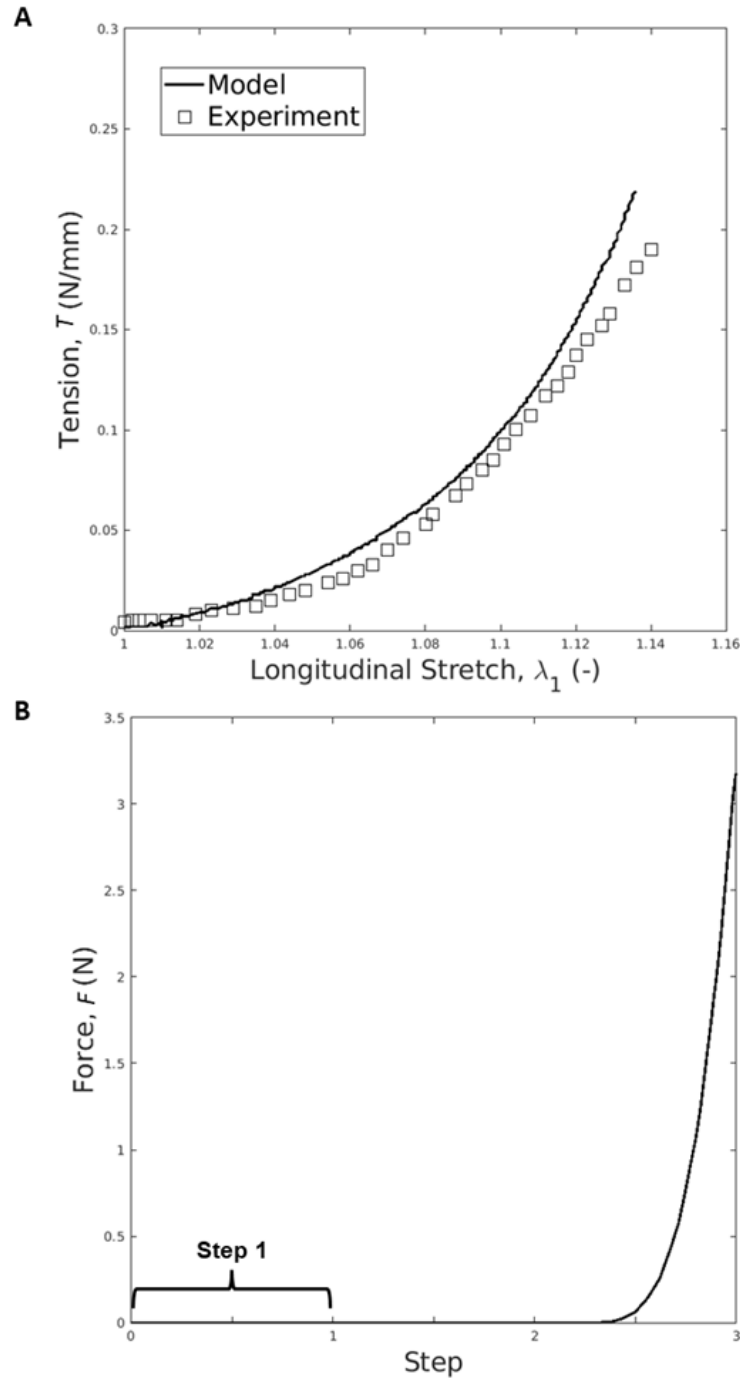


Figure 6. (A) Evolution of tension at the apex region of the amnion as a function of the longitudinal stretch during the inflation test; (B) Evolution of the force caused by the probe during the puncture test.

Multilayer fetal membrane model

The evolution of the membrane's apex displacement (d) for the multilayer finite element model (anisotropic hyperelastic and isotropic linear elastic amnion) and the experimental test is represented in Figure 7. The experimental curve is obtained by averaging the apex displacements of the eighteen C-section fetal membrane samples from the peri-placental region, after performing a data interpolation to obtain a common grid of points along the pressure axis. The

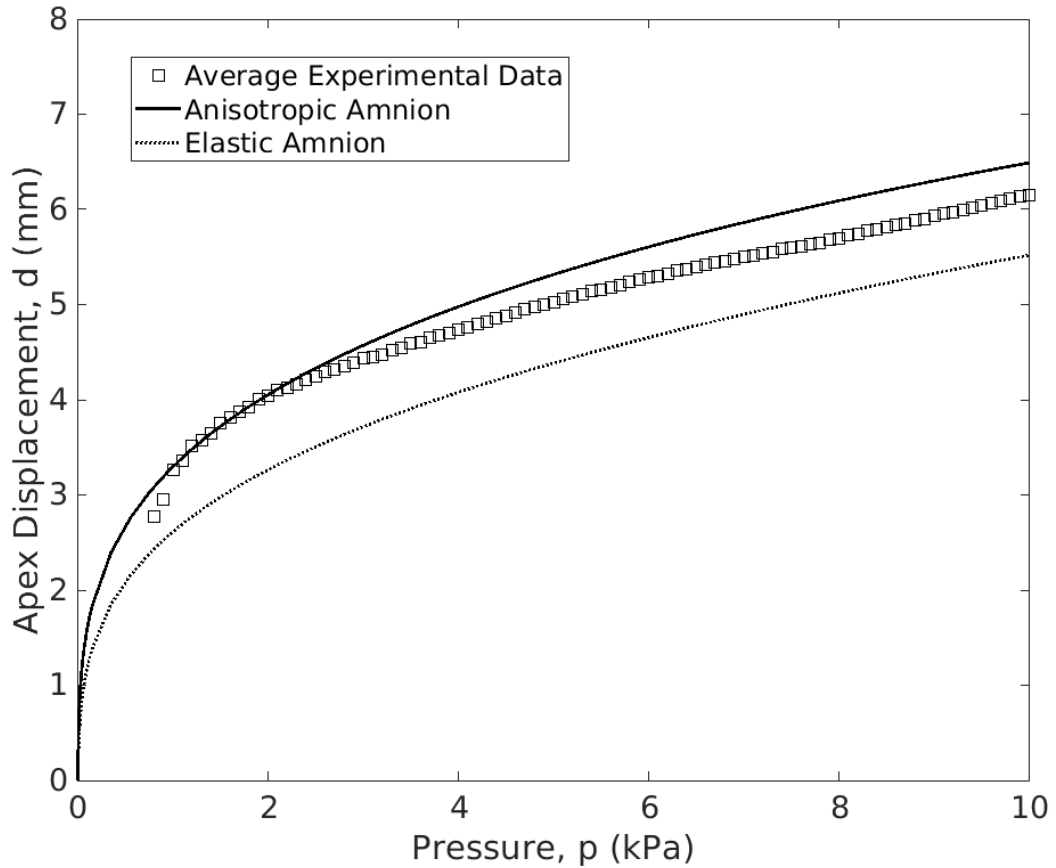


Figure 7. Comparison of the multilayer fetal membrane model (anisotropic hyperelastic and isotropic linear elastic amnion) with experimental data from Samimi et al. (Samimi et al., 2023);

the elastic amnion is characterized according to Verbruggen et al.

(Verbruggen et al., 2017).

common pressure values across all eighteen samples range between 1 kPa and 10 kPa, approximately.

For all cases, the apex displacements tend to increase faster during the initial stage of the inflation simulation, which corresponds to the pre-inflation step, where the membrane is in a slack state. As pressure (p) increases, the curves start to flatten since the membrane is offering more resistance. Therefore, the apex displacement variation tends to decrease throughout the simulation. For smaller pressures (<2 kPa), the apex displacement of the multilayer model containing the anisotropic amnion overlaps the experimental data, while the model containing the elastic amnion leads to considerably smaller apex displacements. For larger pressures, the relative error at 10 kPa, ξ_r , verified between the experimental data and the anisotropic amnion model is 5.0% (equation (3.1)) and 11.0% for the elastic amnion model (equation (3.2)). Moreover, the standard deviation was calculated to measure how dispersed the data was compared to the mean curve. A value of 1.764 was calculated, indicating that the data is spread out around the mean curve.

$$\begin{aligned}\xi_{r\_anisotropic}(\%) &= \frac{\text{Simulation Value} - \text{Experimental Value}}{\text{Experimental Value}} & (3.1) \\ &= \frac{6.49 - 6.18}{6.18} = 5.0\%\end{aligned}$$

$$\xi_{r\_elastic}(\%) = \frac{5.50 - 6.18}{6.18} = 11.0\% \quad (3.2)$$

Stress distribution and thickness variation in the amnion and chorion layers

The maximal principal stress (s_{max}) distribution in the amnion and chorion layers at the end of the inflation simulation is illustrated in Figure 8, and the maximum principal stress evolution throughout the inflation test at the apex region of each fetal membrane layer is represented in Figure 9A. At the end of the inflation test, where an apex displacement of 7.8 mm is verified, the amnion layer exhibits a maximum principal stress value of 4156 kPa at the apex region, while the chorion only exhibits a value of 219 kPa (Figure 8). It is also important to highlight that the amnion is subjected to much larger stresses than the chorion throughout the entire mechanical simulation of the inflation test (Figure 9A). There is a thickness (h) reduction in the amnion and the chorion throughout the simulation at the apex region (Figure 9B): the chorion has a reduction of 15% while the amnion has a reduction of 47%.

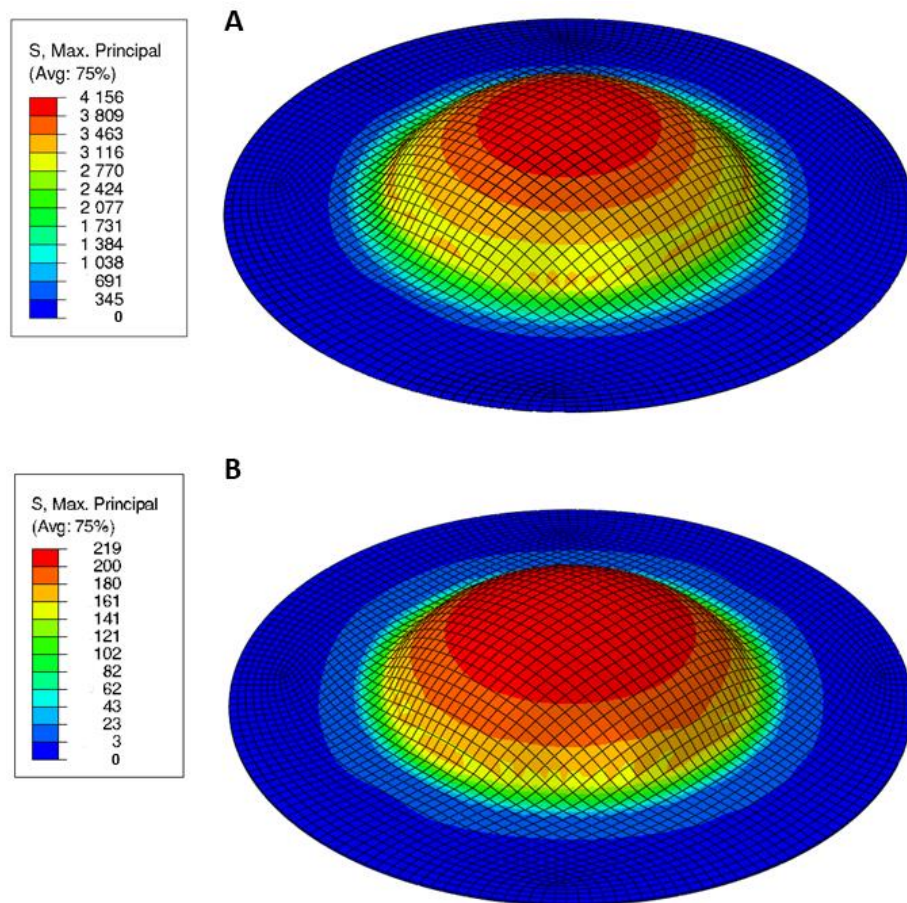


Figure 8. Maximal principal stress distribution in the amnion (A) and chorion (B) layers at the end of the simulation of the inflation mechanical test (units: kPa).

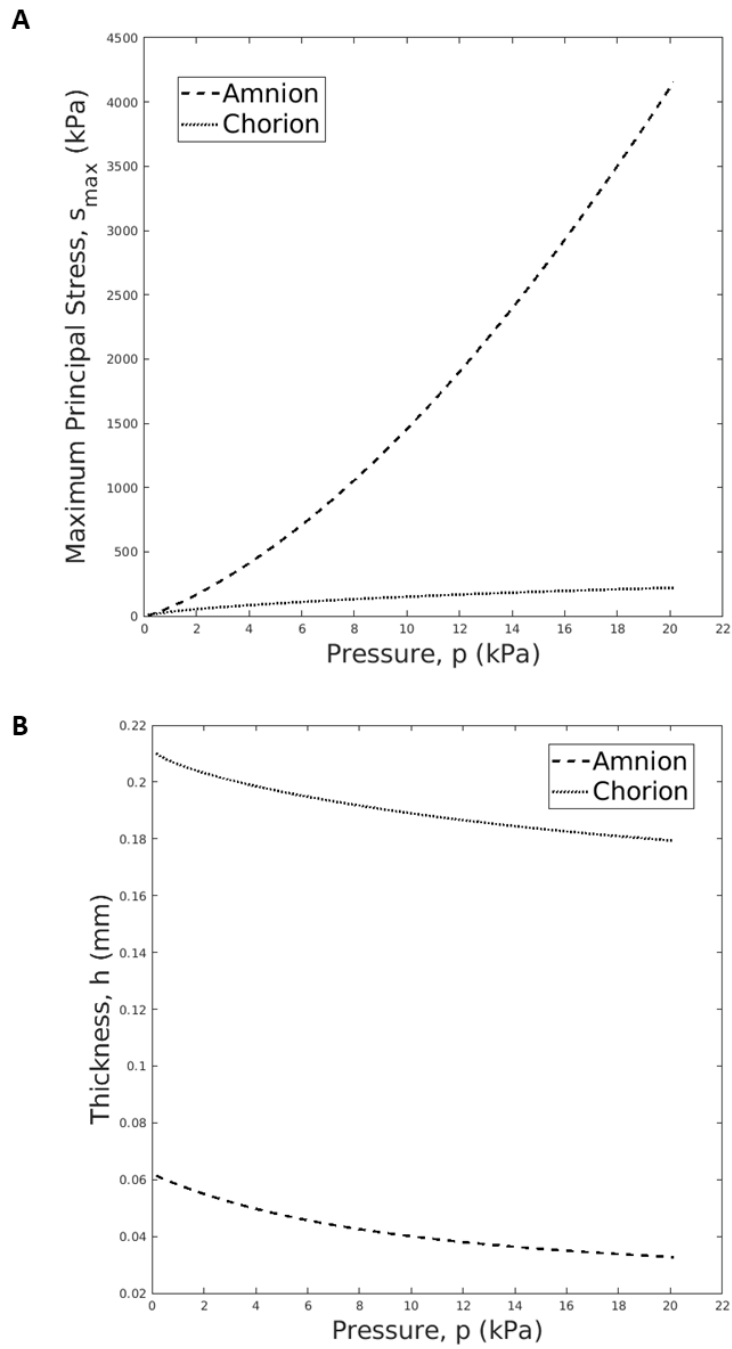


Figure 9. (A) Maximum principal stress evolution in the amnion and chorion layers throughout the simulation of the inflation mechanical test; (B) Thickness evolution of the amnion and chorion throughout the inflation simulation.

Discussion

Term birth involves a set of interrelated biological and biomechanical events, including cervical remodeling and deformation, rupture of the fetal membrane (ROM), and coordinated uterine contractions (Vink & Feltovich, 2016). These events may happen too soon in gestation, such that the mechanical failure of the soft tissues supporting the fetus can lead to spontaneous preterm birth (Vink & Feltovich, 2016). To support pregnancy, there is a complex biomechanical interaction between the cervix, uterus, and fetal membranes. This interaction and how each tissue contributes to load-bearing remains to be understood entirely. In this context, numerical methods are an essential tool to overcome technical and ethical obstacles associated with understanding the biomechanical roles of the soft tissues supporting the fetus.

In this work, a multilayer fetal membrane model, including the amnion, chorion, and maternal decidua, was developed based on robust experimental data from the literature. The mechanically dominant amnion was characterized as an anisotropic nonlinear material to capture its fiber response. This represents an advantage over existing numerical models, where the mechanical role of the amnion fibers can be explored. This multilayer model can be implemented in more complex numerical uterine models of the gravid uterus to investigate the interaction between the fetal membrane, uterus, and cervix, and how the fetal membrane layers interact with the uterus to prevent large deformations for the membrane and the cervix.

Amnion material model

It is hypothesized that collagen fibers play an important role in the mechanical response of the amnion. To understand the extent of this role, a fiber-based hyperelastic constitutive model for the amnion was developed and validated against a set of experimental data (Figure 5 and Figure 6). The amnion model was developed by Buerzle and Mazza, based on a theory developed by Rubin and Bodner, where the nonlinear dissipative response of soft tissue as the amnion was studied (Rubin & Bodner, 2002). Since soft tissue acts as a complex composite structure, where families of fibers are embedded in an isotropic matrix, the constitutive equations presented by Rubin and Bodner comprise a purely elastic component and a dissipative component (Rubin & Bodner, 2002). The model developed by Buerzle and Mazza only accounts for the elastic part of the Rubin-Bodner formulation, since their experimental data does not provide any information on the time and history dependence of the amnion layer (Buerzle & Mazza, 2013).

The fibers embedded in the amnion layer exhibit resistance to elongation, leading to their rotation (Buerzle & Mazza, 2013). These phenomena will reduce their angle with respect to the direction of tension, leading to large lateral contraction, which is in line with the work of Kabla and Mahadevan concerning the nonlinear mechanics of soft fibrous networks (Buerzle & Mazza, 2013; Kabla & Mahadevan, 2007). These mechanical characteristics align with Figure 5B, where the amnion sample underwent significant lateral contraction compared to

the longitudinal stretch, indicating that the amnion possesses a high Poisson's ratio.

The prediction capabilities of the amnion model were also evaluated in Figure 6A, where an inflation test was performed. As the figure suggests, the model predicted the tension evolution, especially for longitudinal stretch values smaller than 1.15. For larger values, the finite element curve diverged from the experimental curve, a tendency also verified by Buerzle and Mazza et al. (Buerzle & Mazza, 2013). Lastly, the amnion model was assessed with a biaxial puncture test, comparing the values of the pushing force to those reported in the literature for specific displacements (Oyen et al., 2004). According to Oyen et al. the puncture force for peri-placental C-section amnion samples varies between 2.81 N and 3.55N (Oyen et al., 2004). The puncture test simulation resulted in a maximum force of 3.18 N (Figure 6B), following the same conditions as Oyen et al. This means that the amnion model can predict the mechanical behavior of the amnion during the loading portion of a puncture test.

Multilayer fetal membranes model

Once the amnion was characterized, as well as the chorion and the decidua, the multilayer fetal membrane model was developed under an inflation setup. The inflation simulation was divided into two steps: (i) pre-inflation and (ii) inflation. The pre-inflation step was performed to identify the “zero stress state” of the membrane, which is difficult to obtain due to its low initial stiffness

(Gao & Desai, 2010). Therefore, it is common to apply a low force, two orders smaller than the maximum force (Buerzle & Mazza, 2013). In this work, a pre-inflation pressure ranging between 0.15 kPa and 0.3 kPa was considered, fulfilling this condition.

The validation of the multilayer fetal membrane model was performed in three phases: (i) comparing the numerical and experimental inflation apex displacements (Figure 7), (ii) comparing the numerical maximum principal stress values observed in the amnion and chorion with the respective physiological stress ranges reported in the literature (Figure 8 and Figure 9A), and (iii) comparing the thickness variation of the chorion throughout the inflation simulation with the experimental data (Figure 9B). The apex displacement of the multilayer fetal membrane model (anisotropic amnion) captured the evolution of the experimental displacement for low-pressure values and exhibited a relative error of 5% at 10 kPa (Figure 7). This forward prediction of the model to newly published inflation experimental data (Samimi et al., 2023) represents an achievement from a computational perspective since the material model parameters were calibrated on different sets of mechanical experiments in the literature.

The fiber-based multi-layer model found that the amnion is subjected to larger stress levels, like the results found in a previous work by Verbruggen et al. In that work, a bilayer fetal membrane model was developed, using isotropic linear elastic mechanical properties to define each layer (Verbruggen et al., 2017). It was found that the amnion was subjected to much larger maximum principal

stresses throughout all gestation ages compared to the chorion (Verbruggen et al., 2017). It was also observed that a maximum stress value of 989 kPa in the amnion and a maximum value of 145 kPa in the chorion at 40 weeks of gestation when a pressure of 6.7 kPa was considered. Some of these observations are in line with Figure 8 and Figure 9A, where the amnion exhibited much larger maximum principal stresses than the chorion during the entire simulation of the inflation test. This means that the amnion is the dominant layer of the fetal membranes, withstanding the loads occurring throughout gestation (Buerzle & Mazza, 2013). Moreover, for a pressure of 6.7 kPa, our model predicted a stress value of 830 kPa in the amnion and 117 kPa in the chorion (Figure 9A). Despite sharing the same order of magnitude, these values differ a little from previous works, probably due to the nonlinear behavior of the amnion considered in our layered model. Lastly, according to Figure 9B, the chorion exhibited a decrease in thickness of 15%, which is in line with experimental data (Samimi et al., 2023). For the amnion layer, nothing can be concluded since its initial thickness is too small to be tracked accurately during mechanical experimenting.

Mechanical assumptions

Some assumptions were considered in this work: (i) a friction coefficient of 0.5 was applied in the interface between the amnion and the chorion, and (ii) the off-plane angle of the collagen fibers in the amnion was set to 0°.

The impact of different interfaces between the amnion and the chorion was investigated and it was verified that no differences were found in terms of maximum principal stress and the membrane's apex displacement for friction and tie contacts. However, when a frictionless contact was applied, the maximum principal stress decreased in the amnion (1150 kPa compared to 1440 kPa at a pressure of 10 kPa), and it increased in the chorion (165 kPa compared to 150 kPa at the same pressure) in comparison with the other two interfaces. In terms of the membrane's apex displacement, a slight increase was verified: 6.9 mm for frictionless contact and 6.5 mm for friction and tie contacts at a pressure of 10 kPa.

Moreover, the impact of different fiber off-plane angles in the amnion was also investigated: for larger pressure values, increasing the off-plane angle from 0° to 10° led to larger maximum principal stresses (1830 kPa compared to 1440 kPa at a pressure of 10 kPa) and larger thickness reduction (0.04 mm compared to 0.02 at a pressure of 10 kPa) in the amnion, despite leading to similar evolutions throughout the simulations. Larger angles led to different evolutions in terms of stress and thickness variations, which highlights the impact of the off-plane angle on fetal membranes' biomechanics.

Limitations

There are limitations to this work associated with the modeling assumptions. First, the following modeling simplifications have been made: (i)

the nonlinear behavior of the chorion and the decidua was not considered in the layered model, since it is particularly difficult to isolate these layers for experimental testing, (ii) the spongy layer was modeled as a mechanical contact between the amnion and the chorion and not as a physical layer, and (iii) the time-dependent material response was not considered. Additionally, the fibers in the amnion were assumed to have an affine deformation with the total solid continuum. Evidence from discrete fiber computational models shows that the nonaffine motion of the fibers protects against membrane rupture (Koh & Oyen, 2015). The material modeling in this work did not explore fracture mechanics, nor the critical mechanical role of the fibers in preventing rupture. Another point that must be highlighted is the fact that the initial stress state of the fetal membrane at the beginning of the inflation mechanical test is not stress-free. It is difficult to experimentally replicate the existing conditions within the pregnant uterus, and it is also difficult to precisely detect the stress-free configuration of the membrane free of membrane wrinkles. The effect of small pre-stress in the membrane may be investigated in future works through a sensitivity analysis.

Conclusions

A multilayer fetal membrane model comprising an anisotropic nonlinear amnion was developed and validated using experimental data and information reported in the literature. The amnion was characterized as an affine continuum fiber-based model, while the chorion and maternal decidua were described as

isotropic linear elastic materials. Results showed that this multilayer model could capture the overall mechanical behavior of the fetal membrane and the respective layers, obtaining good agreement with experimental data and information reported in the literature. This layered model can be integrated into larger models of the fetal membrane, uterus, and cervix to study the complex interaction between these structures in term and premature pregnancies.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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PART B: Article 4

Contributing factors to preterm pre-labor rupture of the fetal membrane: biomechanical analysis of the membrane under different physiological conditions

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Abstract

The fetal membranes are a complex biological structure essential for pregnancy, comprising two main layers: the amnion and the chorion. Characterizing each layer from a mechanical perspective is extremely important to understand the rupture process of the membrane at term or preterm. It is still unclear what factors lead to preterm pre-labor rupture of the membrane (PPROM) due to ethical and technical factors associated with in vivo experimental tests. Numerical simulations may offer some answers, clarifying the biomechanics of the fetal membrane during gestation.

This work used a validated multilayer fetal membrane model to evaluate whether certain physiological conditions occurring during pregnancy contribute to PPRM. The following factors were evaluated: (i) contact conditions between the amnion and the chorion, (ii) normal and abnormal intrauterine pressures, (iii) amnion and chorion thicknesses, and (iv) orientation of the collagen fibers within the amnion layer. Our results showed that PPRM could be potentiated under certain physiological circumstances: (i) the existence of interconnection (friction or tied contact) between the two main layers of the fetal membrane increased the stress in the mechanical dominant amnion, (ii) larger intrauterine pressures and (iii) smaller amnion and chorion thicknesses led to the same increase in stress, and (iv) different off-plane angles of the collagen fibers modified the stress distribution and thickness variation in both layers.

Keywords: Fetal Membrane; Amnion; Chorion; Rupture of The Fetal Membrane;
Numerical Simulation; Finite Element

Abbreviations

ROM – Rupture of the fetal membranes

PPROM – Preterm pre-labor rupture of the fetal membranes

XRD – Non-crystalline X-ray diffraction

Introduction

The fetal membranes are layered biological structures that surround and protect the fetus throughout pregnancy, playing the role of a mechanical and immunological barrier (Bryant-Greenwood, 1998; Jabareen et al., 2009). During pregnancy, the fetal membranes undergo several complex microstructural alterations (McLaren et al., 1999), such as a mechanical weakening near delivery, resulting in its natural rupture (Oyen et al., 2006). The normal rupture of the fetal membranes (ROM) is an integrant part of vaginal delivery. However, serious health problems might occur when the membranes rupture prematurely (Buerzle et al., 2012). About 3% of all pregnancies worldwide suffer a membrane rupture earlier than 37 weeks gestational age, called preterm pre-labor rupture of the fetal membranes (PPROM) (Mercer, 2010). PPRM is responsible for approximately one-third of all preterm births, contributing significantly to perinatal morbidity and mortality (Verbruggen et al., 2017).

Fetal membranes are essential biological tissues integrated in a complex pregnancy structure, comprising also the uterine body and the cervix (Louwagie et al., 2021). The geometry of pregnant uterus is influenced by several factors, such as the position of the fetus within the uterus, shape and size of the uterine body, placental location, and structural anomalies, among others (Louwagie et al., 2021). Accessing pregnancy geometry is crucial for understanding how certain physiological conditions, such as abnormal intrauterine pressure, impact both the mother and the fetus (Louwagie et al., 2021). Magnetic resonance

imaging and ultrasound play complementary roles in evaluating different conditions in pregnancy, allowing to visualize fetal anatomy, fetal growth, amniotic fluid levels, and abnormalities, among others (House et al., 2013).

The fetal membranes comprise two main layers, called the amnion and the chorion, whose microstructures differ significantly from each other (Buerzle & Mazza, 2013). The amnion is the inner layer of the membrane facing the amniotic fluid, while the chorion is the outer layer contacting the uterus (Ilancheran et al., 2009; Zhang et al., 2021). The amnion is a nonlinear viscoelastic material and the mechanical dominant layer of the fetal membranes, where thin randomly oriented collagen fibers dominate the material response to loading. It is thinner, stiffer, and stronger than the more compliant and extensible chorion (Buerzle et al., 2012; Buerzle & Mazza, 2013; Oyen et al., 2004). These layers are separated by a spongy layer, which allows the amnion to slide on the underlying chorion (Joyce et al., 2009; Menon & Richardson, 2017). In a typical anatomical image, these layers envelop the fetus within the uterus (Buerzle and Mazza, 2013). Grasping their arrangement in such images clarifies the spatial relationships and functional roles of each structure in prenatal development (Buerzle and Mazza, 2013). Besides the amnion and chorion, it is also common to consider a maternal layer connected to the chorion, named decidua (Tahan & Tahan, 2014). This layer results from the differentiation process of the uterine endometrium (Abbas et al., 2019) and shares a close anatomical relationship with the chorion (chorio-decdua layer) (Malak & Bell, 1994).

Several factors associated with the mechanical response and the microstructure of the fetal membranes remain unknown. Few studies were performed to accurately characterize its biomechanics (Buerzle & Mazza, 2013). Oxlund et al. developed a method to collect uniaxial data concerning the mechanical properties of the fetal membranes (Oxlund et al., 1990). Helmig et al. studied whether the mechanical properties of the fetal membranes changed during late pregnancy and labor, concluding that pronounced changes were induced in the amnion and chorion mechanical properties (Helmig et al., 1993). Oyen et al. investigated the soft-tissue time-dependent behavior, focusing on the amnion sublayer, and the differences between the amnion and the chorion in terms of failure properties, analyzing the biaxial puncture failure of intact chorio-amnion, and separated amnion and chorion (Oyen et al., 2004). Oyen et al. also performed uniaxial and planar bi-axial mechanical tests to determine the amnion layer's nonlinear and time-dependent mechanical response (Oyen, 2005). Verbruggen et al. developed linear finite element models of fetal membranes to determine the mechanical role of the amnion and the chorion layers, and to simulate the uterine environment in the context of term gestation and PPRM (Verbruggen et al., 2017).

This work aims to study the fetal membrane response under different physiological conditions during pregnancy using a numerical inflation setup of the membrane. The development and validation of this model is explained with more detail in Fidalgo et al. (Fidalgo et al., 2024). It is intended to analyze whether certain conditions may contribute to PPRM, based on numerical simulation

outcomes, namely the maximal principal stress distribution in the amnion and chorion layers. To do so, four finite element models of the fetal membrane were developed to represent those different scenarios: (i) different contact conditions between the amnion and the chorion, (ii) normal and abnormal intrauterine pressures (from 30th to 40th gestational week), (iii) different amnion and chorion thicknesses, and (iv) different orientations of the collagen fibers within the amnion layer. The finite element model of the fetal membrane was modeled as a non-linear multilayer structure (amnion, chorion, and maternal decidua), validated through experimental data retrieved from inflation mechanical testing (Samimi et al., 2023).

It is necessary to properly characterize the fetal membrane response under different physiological conditions to clarify several pregnancy-related phenomena, such as PPRM, cervical funneling, cervical insufficiency, etc. Integrating this layered model into larger numerical models of the gravid uterus represents a step toward the understanding of such events that greatly impact the outcome of pregnancy and maternal-fetal health in the short and long term.

Materials and Methods

This work was divided into three parts: (i) mechanical characterization of the amnion, chorion, and decidua layers, (ii) development of the multilayer fetal membrane model, and (iii) definition of the numerical simulations. Part (i) and part (ii) were developed in previous works (Fidalgo et al., 2024): in part (i), the

non-linear constitutive model used to characterize the amnion is presented, and the respective material parameters are defined; the chorion and decidua are mechanically characterized through isotropic linear elastic models; in part (ii), the multilayer fetal membrane model comprising the amnion, chorion, and decidua is developed, combining the work performed in part (i). Finally, in part (iii), numerical simulations are defined to cover four different physiological conditions using the multilayer fetal membrane model: different contact conditions between the amnion and the chorion, normal and abnormal intrauterine pressures (from 30th to 40th gestational week), different amnion and chorion thicknesses, and different orientations of the collagen fibers within the amnion layer.

Amnion, chorion, and decidua mechanical characterization

Amnion constitutive model formulation

The amnion layer was characterized by a constitutive model able to represent the stretching, rotation, and buckling of the thin randomly oriented collagen fibers (Buerzle & Mazza, 2013; Hollenstein et al., 2011). The fibers play an important role in the mechanical response of the amnion, as suggested by previous works: under uniaxial stress, collagen fibers undergo reorientation at low strains, relying on the elastin matrix for resistance to deformation (Jabareen et al., 2009); however, in biaxial mechanical testing, collagen fibers are important in offering low deformation resistance, without significant overall reorientation

(Buerzle et al., 2012). For this purpose, a modified version of the Buerzle-Mazza formulation (Buerzle & Mazza, 2013) developed by Mauri and Ehret (Mauri et al., 2016) and Fidalgo (Fidalgo et al., 2024) was considered to characterize the mechanical response of the amnion.

The strain energy function, Ψ , is the strain energy per unit reference volume and accounts for the stretch of the single families of fibers (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$\Psi = \frac{\mu_0}{2q} [e^{qg} - 1] \quad (2.1)$$

where μ_0 is a material constant having the units of stress and q is a dimensionless constant that controls the nonlinearity of the moduli for the different stress responses in the composite structure (Rubin & Bodner, 2002).

Function g is given by the sum of the compressible neo-Hookean material g_2 , and the fiber strain energy g_3 (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$g = g_2(I_1, J) + g_3(\lambda_i) \quad (2.2)$$

$$g_2 = m_2(I_1 - 3) + \frac{m_2}{m_5} (J^{-2m_5} - 1) \quad (2.3)$$

$$g_3 = \frac{m_3}{m_4} \frac{1}{N} \sum_{i=1}^N \langle \lambda_i - 1 \rangle^{2m_4} \quad (2.4)$$

where $\langle \rangle$ represent Macauley brackets, indicating that the fibers do not bear compression loads (Buerzle & Mazza, 2013) and m_i are model parameters. The parameter N is the number of representative families and it must be an even number. The parameter I_1 represents the first invariant of the right Cauchy-Green deformation tensor, J the volume ratio, and λ_i is fiber stretch (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$I_1 = \text{tr}(\mathbf{F}^T \mathbf{F}) \quad (2.5)$$

$$J = \det \mathbf{F} \quad (2.6)$$

$$\lambda_i = |\mathbf{F} \mathbf{M}_i|, \quad i = 1, 2, \dots, N \quad (2.7)$$

The parameter $\mathbf{F}$ represents the deformation gradient and $\mathbf{M}$ represents the fiber directions in the reference configuration and it is defined as (Mauri et al., 2016):

$$\mathbf{M}_j = \cos \beta_j \sin \theta_j \mathbf{e}_1 + \sin \beta_j \sin \theta_j \mathbf{e}_2 + \cos \theta_j \mathbf{N} \quad (2.8)$$

$$\mathbf{M}_{j+N/2} = \cos\beta_j \sin\theta_j \mathbf{e}_1 + \sin\beta_j \sin\theta_j \mathbf{e}_2 - \cos\theta_j \mathbf{N} \quad (2.9)$$

$$\beta_j = \frac{2\pi}{N} \left(j - \frac{3}{2} \right) \quad (2.10)$$

$$\theta_j = \frac{\pi}{2} - \varphi \quad (2.11)$$

where φ represents a slight off-plane inclination and $j = 1, 2, \dots, \frac{N}{2}$. The Cauchy stress tensor $\boldsymbol{\sigma}$ is obtained from the derivatives of the strain energy density function with respect to the deformation tensor (Buerzle & Mazza, 2013). The membrane tension $\mathbf{t}$ in the current configuration was calculated through the following equation, where h_0 is the initial thickness of the membrane, and λ_1 and λ_2 are the longitudinal and lateral stretches, respectively (Buerzle & Mazza, 2013):

$$\mathbf{t} = \boldsymbol{\sigma} \frac{h_0}{\lambda_1 \lambda_2} \quad (2.12)$$

Eight parameters were identified throughout the description of the constitutive model: μ_0 , q , m_2 , m_3 , m_4 , m_5 , N and φ . The values were established based on Fidalgo et al 2024, where the constitutive model is presented and validated (Fidalgo et al., 2024). The respective parameters are illustrated in Table 1.

Table 1. Parameters applied to the fetal membrane constitutive model (Fidalgo et al., 2024).

Parameter	μ_0	q	m_2	m_3	m_4	m_5	N	φ
Value	2.4 MPa	2.96	0.00228	41.12	1.27	0.463	32	0°

Fetal membranes undergo large deformations during biaxial mechanical testing, leading to elevated values for the g_3 function (equation 2.3) found in the exponential term e^{qg} (equation 2.1). This can cause the strain energy function to escalate, potentially resulting in illogical values for the stress and Jacobian matrices as per equation 2.1. To overcome this problem, a control able to stabilize g_3 was introduced into the model, limiting its maximum value to a certain threshold. Every time this limit was surpassed, the respective iteration was restarted with a smaller value for the time increment. It is important to highlight that this control does not have any effect on the results. The control was implemented in the material subroutine developed to define the complex constitutive model used to characterize the amnion layer in Abaqus/Standard.

Chorion and decidua characterization

Unlike the amnion, which is crucial for preserving the fetal membrane's integrity and resilience against external forces, the chorion and decidua are comparatively less mechanically relevant since their primary function lies in protecting the fetus, rather than directly contribute to mechanical support or

resistance. Therefore, those layers were characterized as isotropic linear elastic materials, whose properties are written in Table 2. It was hypothesized that the chorion and the decidua share similar mechanical properties since the smooth chorion gets fused with the decidua throughout pregnancy, which may suggest that they are similar from a mechanical perspective. The respective Poisson's ratios were set to a value between 0.4 and 0.5 (Ophir et al., 2002; Roohbakhshan et al., 2016; Verbruggen et al., 2017).

Table 2. Isotropic linear elasti properties of the chorion and the decidua layers (Ophir et al., 2002; Oxlund et al., 1990; Roohbakhshan et al., 2016; Verbruggen et al., 2017).

	Young's Modulus, E [MPa]	Poisson's Ratio, ν
Chorion	1	0.4-0.5
Decidua	1	0.4-0.5

Numerical setup of the inflation mechanical test

The fetal membrane biomechanics under different physiological conditions were studied through a finite element model (Figure 1), able to capture the inflation response of the amnion-chorion-decidua layers. The numerical setup was created based on the inflation mechanical test described by Samimi et al. and validated by matching the numerical and experimental apex displacements reported in the literature (Samimi et al., 2023). More information regarding the development and validation of this model can be found at Fidalgo et al. (Fidalgo et al., 2024).

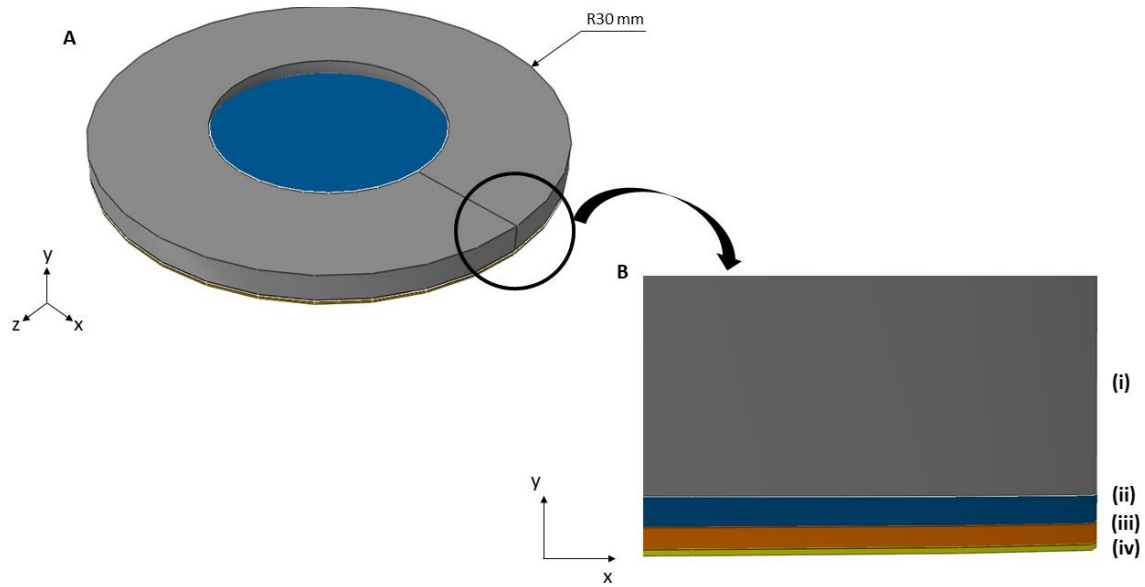


Figure 1. Finite element setup of the inflation mechanical test using a multilayer fetal membrane model; A: three-dimensional view of the model; B: detailed view of the model (grey: clamping ring (i); blue: part of the decidua (ii); orange: chorion (iii); yellow amnion (iv)).

The finite element model of the fetal membrane comprises four structures: (i) clamping ring, (ii) part of the decidua, (iii) chorion, and (iv) amnion. The thicknesses of (ii), (iii), and (iv) were determined based on optical coherence tomography experimental measurements, averaging the initial thicknesses of eighteen peri-placental c-section membrane samples (Samimi et al., 2023).

The amnion had a diameter of 60 mm and a thickness of 0.062 mm. The amnion was mechanically characterized by the modified version of the Buerzle Mazza constitutive model, and the respective constitutive parameters were set to the values reported in Table 1. The amnion was meshed with 3422 eight-node brick elements (C3D8) and 7034 nodes.

The chorion and the decidua had a diameter of 60 mm and a thickness of 0.217 mm and 0.311 mm, respectively. They were characterized through isotropic linear elastic constitutive models, whose parameters were set according to Table 2. The chorion and decidua's finite element model were meshed with 3422 C3D8 elements and 7034 nodes.

The clamping ring was modeled as a rigid body with an inner diameter of 30 mm and an outer diameter of 60 mm.

The contact condition between the amnion and the chorion was initially modeled as a surface-to-surface contact with a friction coefficient of 0.5, playing the role of the interconnecting spongy layer separating those layers. The chorion and the decidua were tied to represent the fusion process occurring during gestation between these layers. Finally, the contact between the decidua and the clamping ring was modeled as a surface-to-surface contact, with a large value of friction coefficient, , to avoid slippage between those structures and replicate the experimental procedure. Concerning the boundary conditions, all the border nodes from the three layers were restricted in all directions and the clamping ring was fixed.

Numerical Simulations

Once the multi-layer model was established, a series of physiologic conditions were explored within the context of bi-axial extension. In experimental practice, it is usual to perform a pre-inflation step to slightly

distend the membrane sample to remove excess slack. This procedure is performed to obtain a repeatable definition of the reference configuration to analyze experiments (K. M. Myers et al., 2010).

Aiming to replicate this process, the simulations of the inflation mechanical test were divided into two main steps: (i) pre-inflation, and (ii) inflation. In step (i) a pre-inflation pressure of 0.15 kPa was applied, to reach a pre-inflation state, and in step (ii) a ramping inflation pressure of 20 kPa was considered, except for the case where different intrauterine pressures values are evaluated, as explained in further subsection *Effect of normal and abnormal intrauterine pressures throughout gestation*. The pre-inflation and inflation pressures were sequentially applied along the inferior surface of the amnion layer, in the positive direction of the y-axis from Figure 1.

Different physiological conditions occurring during gestation were simulated to analyze the mechanical response of the multilayer fetal membrane under a bi-axially inflation setup. The effect of different contact conditions, intrauterine pressures, amnion and chorion thicknesses, and off-plane fiber angles were investigated, as described in the following subsections.

Control Model

The control model was created as a baseline for comparison of different simulated conditions. The friction coefficient between the amnion and the chorion, and the respective initial thicknesses were maintained according to

subsection *Numerical setup of the inflation mechanical test*. The off-plane fiber angle was set to 0, according to Table 1.

Effect of different contact conditions between the amnion and the chorion

The interface between the amnion and the chorion was modeled with different contact conditions:

- frictionless contact;
- contact with a friction coefficient set to 0.5 (control model);
- completely tied contact.

Compared to the control model, only the contact condition between the amnion and the chorion was altered.

Effect of normal and abnormal intrauterine pressures throughout gestation

To investigate the effect of normal and abnormal pressures in fetal membranes, the inflation pressure was set to different ramping pressures (Table 3) according to the intrauterine pressure registered for different gestational weeks (FISK et al., 1992; Lapeer & Prager, 2001; Maul et al., 2004):

Table 3. Intrauterine pressures for different gestational weeks.

Gestational Week	Intrauterine Pressure [kPa]
30th	1.3
35th	1.8
40th	6.7
Abnormal Large Pressure	10

Compared to the control model, all conditions are maintained, except the inflation pressures.

Effect of varying the amnion and chorion thicknesses

Before labor, the amnion and chorion may exhibit different thickness values. The following thicknesses combinations were simulated, setting the initial thicknesses of the amnion and chorion to different values, according to maximum and minimum values reported in the literature (Helmig et al., 1993):

- amnion max: the amnion was set to the maximum thickness value and the chorion thickness was maintained at 0.217 mm;
- amnion min: the amnion was set to the minimum thickness value and the chorion thickness was maintained at 0.217 mm;
- chorion max: the chorion was set to the maximum thickness value and the amnion thickness was maintained at 0.062 mm;
- chorion min: the chorion was set to the minimum thickness value and the amnion thickness was maintained at 0.062 mm;
- both max: both layers were set to the respective maximum values;

- both min: both layers were set to the respective minimum values.

This information is summarized in Table 4:

Table 4. Amnion and chorion initial thicknesses.

	Initial Amnion Thickness [mm]	Initial Chorion Thickness [mm]
Amnion Max	0.070	0.217
Amnion Min	0.025	0.217
Chorion Max	0.062	0.240
Chorion Min	0.062	0.130
Both Max	0.070	0.240
Both Min	0.025	0.130

Compared to the control model, only the initial thicknesses of the fetal membrane layers are changed. Besides, amnion and chorion thicknesses are not constant throughout the inflation test: these simulations only impose the initial thickness values for each layer at the beginning of the inflation and not how they will evolve throughout the test.

Effect of varying the off-plane angle φ of the collagen fibers

To investigate the mechanical impact of the off-plane angle ϕ , this parameter was set to different values, according to Table 5:

Table 5. Different off-plane angles tested in this work.

Off-plane angle ϕ °
0 (control model)
10
20
30

Compared to the control model, all conditions are maintained, except the off-plane angle.

Results

This section presents and describes the results from all the physiological conditions, focusing on the maximal principal stress distribution and thickness variation at the apex region of the amnion and chorion layers, and the overall apex displacement of the fetal membrane.

Control Model

The control model was previously analyzed in Fidalgo et al. 2014 (Fidalgo et al., 2024), where a more detailed description of the respective results can be found. The apex displacement tends to increase faster during the initial stage of the inflation simulation, which corresponds to the pre-inflation step, where the membrane is in a slack state. As pressure increases, the curves start to flatten, since the membrane is now offering more resistance.

At the end of the mechanical test, the amnion layer is submitted to a maximum principal stress value of 4156 kPa at the apex region, while the chorion is only submitted to 219 kPa (Figure 2). It is also important to highlight that the amnion is always submitted to larger maximum principal stresses than the chorion as pressure increases during the inflation simulation.

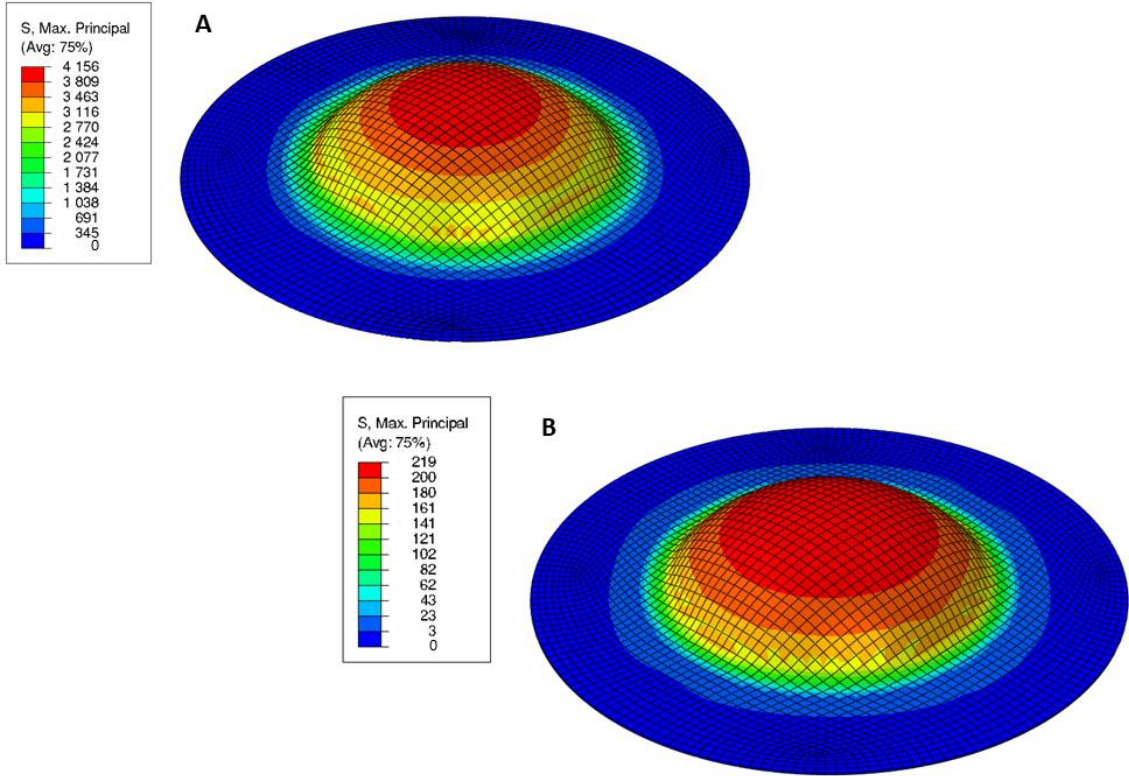


Figure 2. Maximal principal stress distribution in the amnion (A) and the chorion (B) layers by the end of the inflation mechanical test [units: kPa].

Different contact conditions between the amnion and the chorion

Focusing on the amnion layer (Figure 3A), the maximum principal stress values increase for the friction and tied contact, in comparison with the frictionless scenario. The opposite is observed for the chorion, according to Figure 3B. Moreover, no differences in stress values are seen between the friction and tie contact in both layers. Compared with the control model, the order of magnitude of the stress values is maintained in both layers for all scenarios.

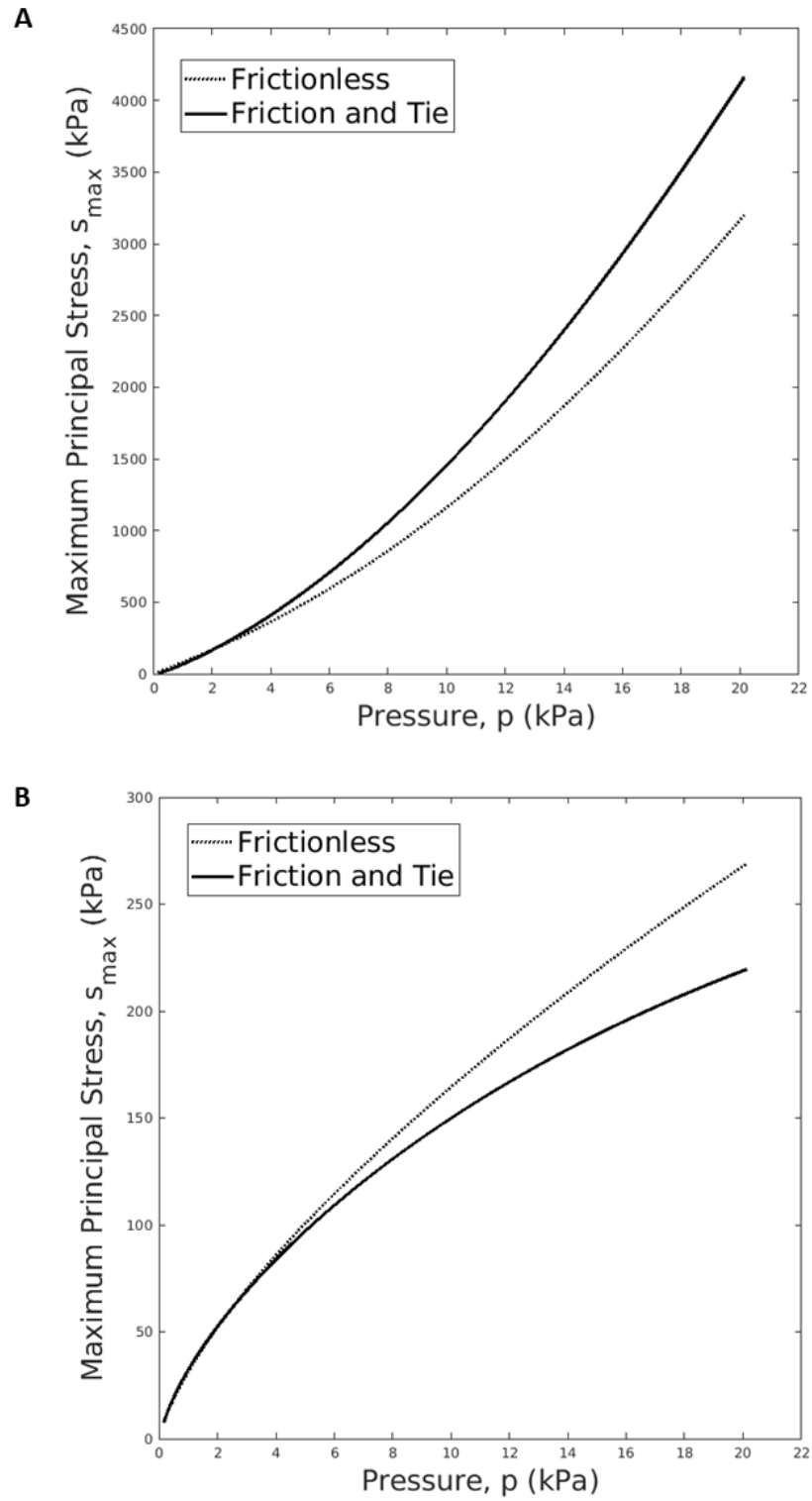


Figure 3. Maximum principal stress evolution at the apex region of the amnion (A) and chorion (B) for different contact conditions.

Normal and abnormal intrauterine pressures

The maximum principal stress values for differential gestational weeks at the apex region of the amnion and the chorion were observed, as illustrated in Figure 4. The results show the amnion layer experiences larger maximum principal stresses for every gestational week, especially near-term (40th gestational week), in comparison with the chorion. Besides that, the stress values associated with the amnion layer increase more significantly throughout the gestational weeks than those for the chorion, whose values are more stable. Finally, it must be highlighted that the application of abnormally high pressure during the inflation simulation tends to increase the maximum principal stresses in both layers and reinforce the discrepancy between them.

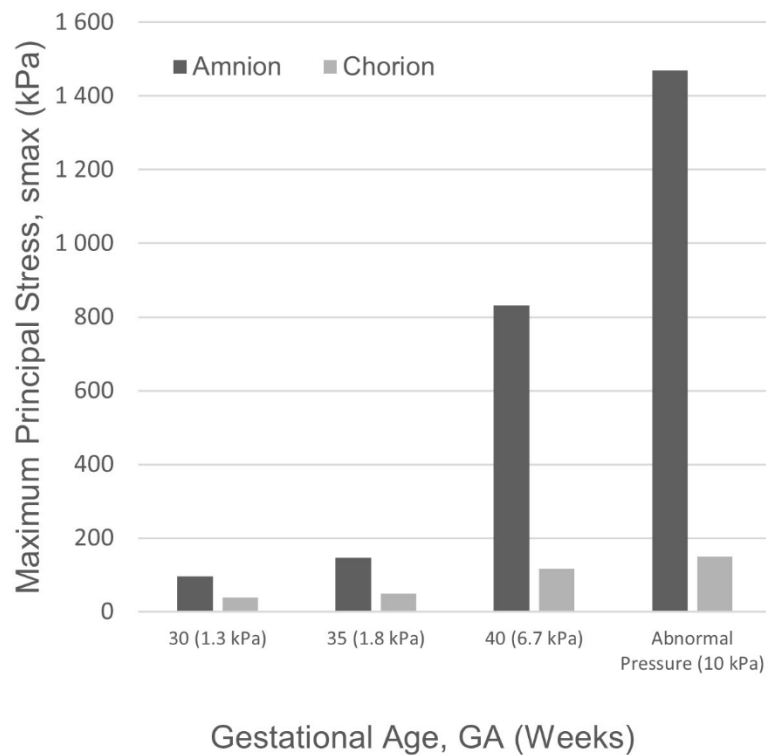


Figure 4. Maximum principal stresses for different gestational weeks and abnormally high pressure measured at the apex region of the amnion and chorion layers.

Variation of the amnion and the chorion thicknesses

Changes in the maximum principal stress values at the apex region of the amnion and chorion layers due to alterations in their thicknesses are illustrated in Figure 5. A large increase in the maximum principal stress values with a reduction in thickness in the amnion layer is observed, while the chorion maintains those values almost constant throughout different thickness combinations. Compared with the control model, for all simulated scenarios, an increase in the amnion and chorion thicknesses results in smaller maximum principal stresses, while the contrary is observed when their thicknesses are reduced. This means smaller maximum principal stress values are verified when the amnion and chorion thicknesses are set to maximum values. Finally, it is also important to highlight that changing the amnion's thickness will affect the chorion's stress values, and vice-versa.

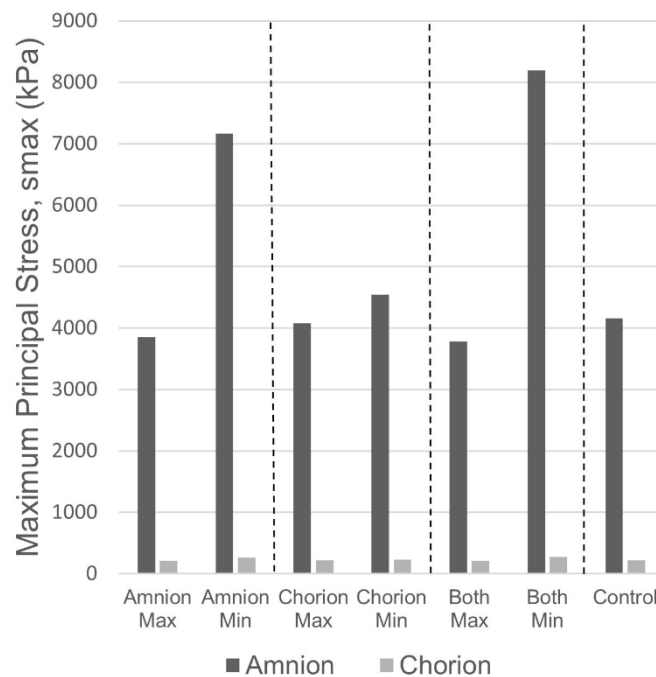


Figure 5. Maximum principal stress values at the apex region of the amnion and the chorion for different layer thicknesses.

Variation of the off-plane angle ϕ

The apex displacement of the fetal membrane is larger when the off-plane angles in the amnion are set to larger values, according to Figure 6. The evolution of the maximum principal stress curves at the apex region of the amnion when ϕ is set to 0° or 10° is different from the cases where the same parameter is set to 20° or 30° . For 0° or 10° , the curves always increase throughout the entire simulation; for the 20° and 30° angles, the stress is 0 for smaller pressures, and a rapid increase in stress is verified for larger pressures (Figure 7A). The maximum principal stress is larger when the angle is changed from 0° to 10° , and from 30° to 20° . In the chorion layer, the maximum principal stress at the apex of the membrane increases with the off-plane angle (Figure 7B).

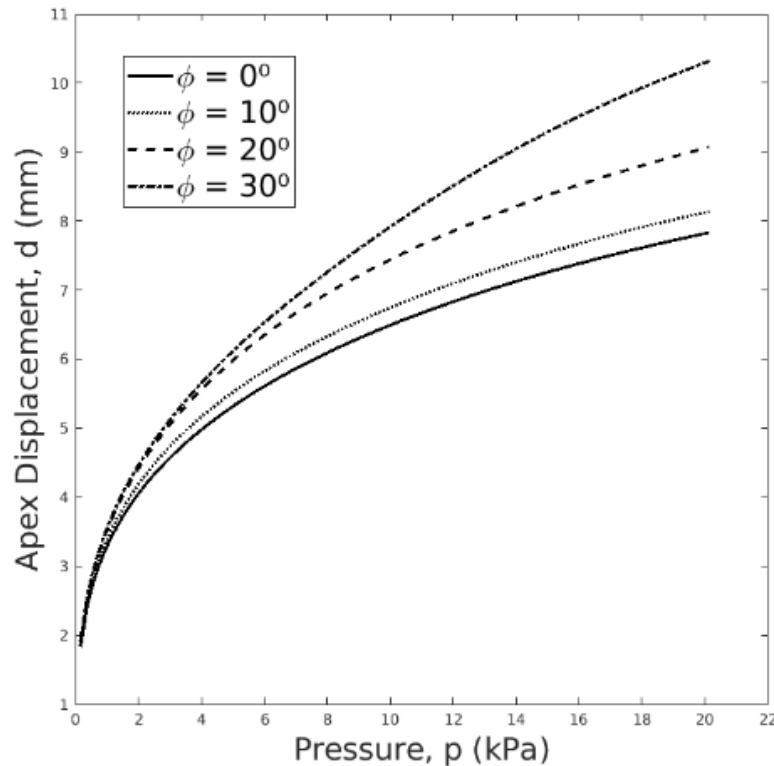


Figure 6. Apex displacement of the fetal membrane during inflation for different off-plane angles.

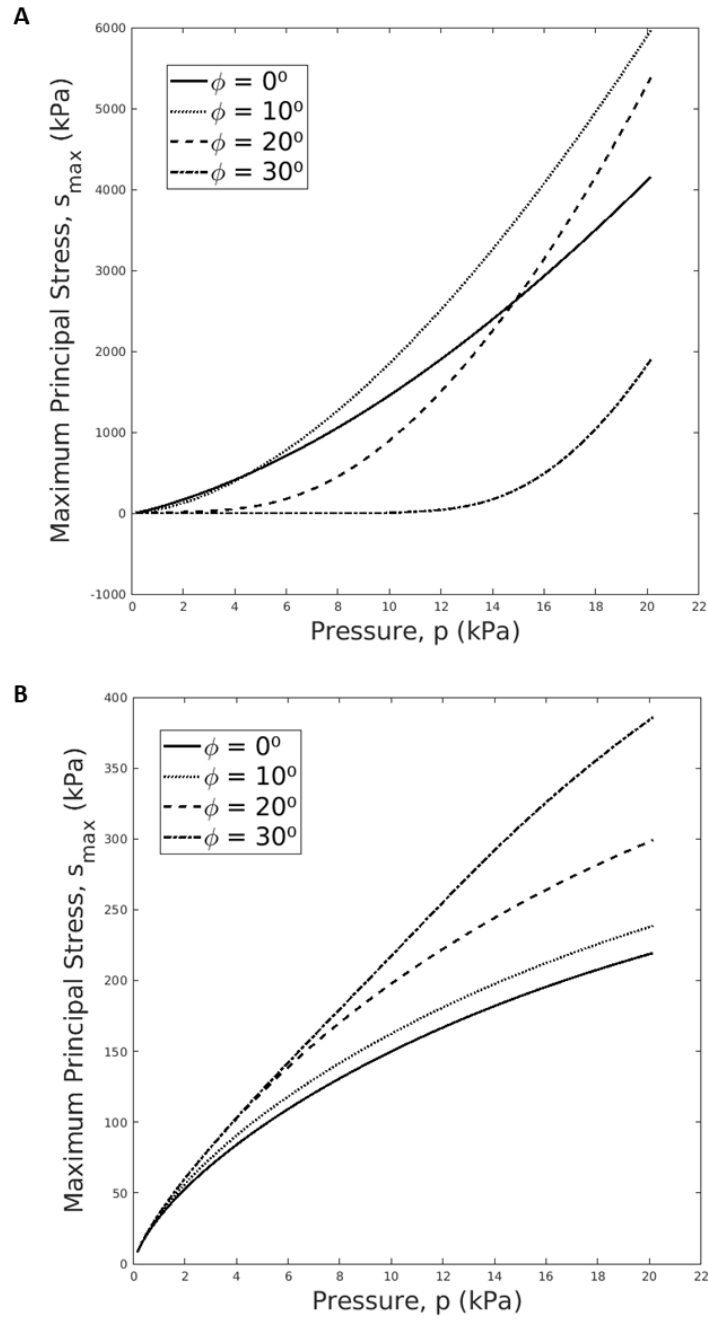


Figure 7. Maximum principal stress evolution at the apex region of the amnion (A) and the chorion (B) for different off-plane angles.

Similarly to the maximum principal stress analysis, the first two curves associated with the thickness variation at the apex region of the amnion (0° and 10°) also exhibit a different evolution than the remaining ones (20° and 30°), according to Figure 8A. At the end of the inflation simulation, the amnion

presents the smaller thickness decrease for 0° and the larger decrease for 30° , followed closely by the 20° off-plane angle. For the chorion layer, the thickness decrease is more pronounced for larger off-plane angles (Figure 8B).

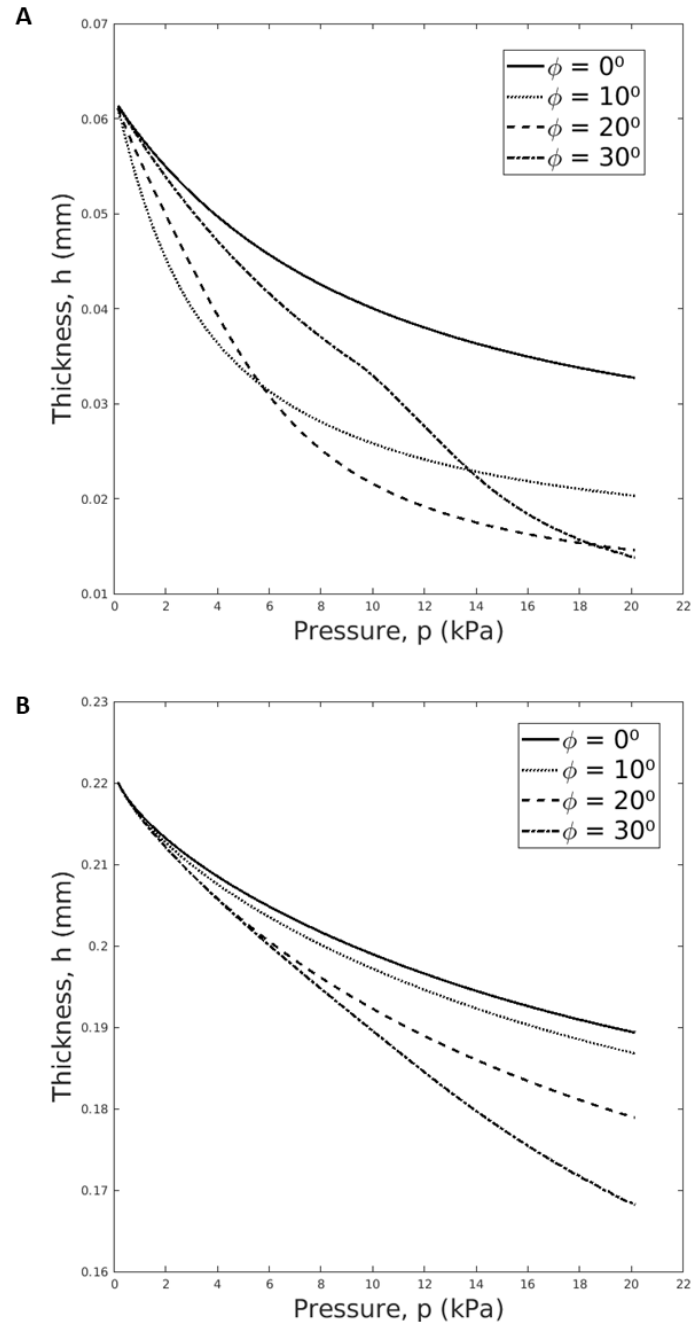


Figure 8. Thickness variation in the amnion (A) and the chorion (B) layers for different off-plane angles.

Discussion

Preterm pre-labor rupture of the fetal membranes (PPROM) is one of the main causes of preterm birth, increasing the rates associated with infant morbidity and mortality. Understanding the causes of PPRM is essential to prevent preterm birth and secure maternal and fetal health. Therefore, studying the biomechanics of fetal membranes is extremely important to understand the deformation leading to its rupture process at term or preterm. However, several complications are associated with in-vivo experimental procedures due to the highly protected environment where fetal membranes are contained during pregnancy. Numerical simulations overcome those difficulties, offering several answers that cannot be accessed in experimental testing.

In this work, a non-linear multilayer fetal membrane model was applied to analyze the impact of the following physiological conditions on the fetal membrane mechanical response: (i) different contact conditions between the amnion and the chorion, (ii) different intrauterine pressures, (iii) different amnion and chorion thicknesses, and (iv) different collagen fiber orientations in the amnion layer (off-plane angle). All these scenarios were analyzed from a mechanical perspective, focusing mainly on the maximal principal stress distribution in the amnion and chorion layers. Ultimately, it was intended to understand if those physiological conditions could represent contributing factors to membrane rupture.

The multilayer fetal membrane model comprises the mechanical dominant amnion characterized as an anisotropic non-linear material to capture its fibril response. This represents an advantage, where the contribution of the amnion fiber architecture can be explored. The validation of the multilayer fetal membrane model was performed in three phases, according to Fidalgo et al. 2014 (Fidalgo et al., 2024): (i) comparing the numerical and experimental inflation apex displacements, (ii) comparing the numerical maximum principal stress values observed in the amnion and chorion with the respective physiological stress ranges reported in the literature, and (iii) analyzing the thickness variation in the amnion and chorion throughout the inflation simulation. A relative error of 5% at larger pressures between the apex displacement of the numerical model and the experimental dataset was calculated (Fidalgo et al., 2024), which represents a great achievement from a computational perspective since the material model parameters were calibrated on different sets of mechanical experiments in the literature. Moreover, the chorion exhibited a decrease in thickness of 15%, which is in line with experimental data (Fidalgo et al., 2024). For the amnion layer, nothing can be concluded since the image resolution of the inflation test is not enough to track its thickness variation (Fidalgo et al., 2024). Besides, according to Verbruggen et al., the amnion is subjected to larger maximum principal stresses than the chorion, representing the mechanical dominant layer of the fetal membrane (Verbruggen et al., 2017). Our control simulation highlighted the mechanical dominance of the amnion layer over the chorion since it was subjected to much larger maximum principal stresses (Figure 2). This conclusion

is aligned with several experimental studies, indicating that the amnion is stiffer and stronger than the chorion (Helmig et al., 1993; Oxlund et al., 1990; Polishuk et al., 1962)

Experimental studies have suggested that a reduction of the lubrication between the chorion and the amnion layers occurs during PPRM (Hills & Cotton, 1984). In fact, it is known that the contact between the amnion and the chorion is normally extremely hydrophobic and effectively frictionless (Verbruggen et al., 2017). In PPRM, it has been hypothesized that the contact is less hydrophobic, resulting in increased friction (Verbruggen et al., 2017). According to Figure 3A, larger maximum principal stresses were found at the apex region of the amnion when the contact between the amnion and the chorion was modeled as friction or tied contact over a frictionless contact. This observation means that the existence of friction between the amnion and the chorion, associated with smaller lubrication, leads to larger mechanical stresses, promoting its rupture and possibly representing a contributing factor to PPRM. On the other side, Figure 3B showed that friction or tie contact led to smaller maximum principal stresses in the chorion layer, suggesting that the amnion withstands the stress concentrations in the membrane when the lubrication between the layers is reduced.

According to our work, the maximum principal stress in the amnion increased significantly over the gestational weeks, while the chorion only experienced a slight increase (Figure 4). This observation is also aligned with the fact that the amnion is the dominant layer in the fetal membranes from a

mechanical perspective, withstanding most of the forces associated with pregnancy and playing a more important role in the fetal membrane integrity as the intrauterine pressure increases (Oxlund et al., 1990).

Some experimental studies have suggested that the thinning of the chorion layer may represent a contributing factor to PPRM, increasing the stress in the fetal membrane (Fortner et al., 2014). In fact, according to Figure 5, a maximum principal stress increase was verified for all scenarios where the amnion and/or the chorion thicknesses were set to minimum values. Therefore, according to our model, smaller amnion and chorion thicknesses may potentiate the rupture of the fetal membranes as stress increases, probably representing another contributing factor to PPRM.

Little is known about the influence of the collagen fibers organization within the amnion in the rupture process of the fetal membranes (Connon et al., 2007). Non-crystalline X-ray diffraction (XRD) has been applied to study the collagen organization in some soft tissues, such as the cornea, breast, bone, cartilage, and, more recently, amnion (Connon et al., 2007). Some studies have suggested that the loss of the regular structure of the collagen fibers in the amnion may represent a contributing factor to PPRM (Connon et al., 2007). In our work, the influence of different collagen fiber orientations in the apex displacement (Figure 6), maximum principal stress (Figure 7), and thickness variation (Figure 8) were analyzed. Different off-plane fiber angles had a strong impact on the fetal membrane behavior, affecting the apex displacement of the membrane, the maximum principal stress, and the thickness variation at the apex

region of the amnion and the chorion: the apex displacement was larger for larger off-plane angles, and the maximum principal stresses and thickness variations exhibited a high variability for different angles. These results highlight the importance of accessing the fiber arrangement in the amnion layer as a method to possibly predict PPROM since the collagen off-plane angle has a strong impact on the biomechanics of the fetal membrane.

This work was developed under some simplifications: (i) the non-linear behavior of the chorion and the decidua was not considered in the layered model, since it is particularly difficult to isolate these layers for experimental testing, (ii) the spongy layer was modeled as a mechanical contact between the amnion and the chorion and not as a physical layer, and (iii) the slippage between the membrane and the clamping ring was neglected in the experimental procedure.

Conclusion

Several factors may contribute to the occurrence of PPROM during pregnancy, such as (i) the presence of friction between the amnion and the chorion, (ii) abnormally large intrauterine pressures, (iii) minimum amnion and chorion thicknesses, and (iv) the orientation of the collagen fibers within the amnion layer. More efforts in clinical practice must be made to better understand the impact of these factors on fetal membrane biomechanics and the outcome of pregnancy.

This layered model can be integrated into larger models of the gravid uterus comprising the fetal membrane, uterus, and cervix to study the complex interaction between these structures. Clinical answers regarding spontaneous preterm birth, cervical funneling, and PPROM, among others, can be offered by applying this model.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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PART B: Article 5

Pregnancy state before the onset of labor: a holistic mechanical perspective

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Abstract

Successful pregnancy highly depends on the complex interaction between the uterine body, cervix, and fetal membrane. This interaction is synchronized, usually following a specific sequence in normal vaginal deliveries: (1) cervical ripening, (2) uterine contractions, and (3) rupture of fetal membrane.

The complex interaction between the cervix, fetal membrane, and uterine contractions before the onset of labor is investigated using a complete third-trimester gravid model of the uterus, cervix, fetal membrane, and abdomen. Through a series of numerical simulations, we investigate the mechanical impact of (i) initial cervical shape, (ii) cervical stiffness, (iii) cervical contractions, and (iv) intrauterine pressure.

The findings of this work reveal several key observations: (i) maximum principal stress values in the cervix decrease in more dilated, shorter, and softer cervixes; (ii) reduced cervical stiffness produces increased cervical dilation, larger cervical opening, and decreased cervical length; (iii) the initial cervical shape impacts final cervical dimensions; (iv) cervical contractions increase the maximum principal stress values and change the stress distributions; (v) cervical contractions potentiate cervical shortening and dilation; (vi) larger intrauterine pressure (IUP) causes considerably larger stress values and cervical opening, larger dilation, and smaller cervical length; (vii) the biaxial strength of the fetal membrane is only surpassed in the cases of the (1) shortest and most dilated initial cervical geometry and (2) larger IUP.

Keywords: Cervical Shortening; Cervical Dilation; Cervical Contraction; Fetal Membrane Rupture; Vaginal Delivery; Numerical Simulation

Abbreviations

ECM – Extracellular matrix

Introduction

Successful parturition relies on synchronized interaction between three biological structures: the body of the uterus, the cervix, and the fetal membrane (Vink, 2020). In normal vaginal deliveries, the following ordered sequence usually occurs: (1) cervical ripening, (2) uterine contractions, and (3) fetal membrane rupture (Vink and Feltovich, 2016). A different sequence is verified when premature rupture of the fetal membrane or preterm labor happens, and it may include early cervical ripening (cervical insufficiency), preterm premature rupture of the fetal membrane, and preterm uterine contractions (Vink, 2020). These may lead to preterm birth, whose global rates have increased from 9.8% in 2000 to 10.6% in 2014 (Vink, 2020; Walani, 2020). Surviving babies may suffer several short-term morbidities (De Araújo et al., 2012; Mwaniki et al., 2012; Platt, 2014) and long-term difficulties (Teune et al., 2011; Vogel et al., 2018). There are currently no accurate methods to determine whether patients will undergo any of these complications, or any treatments to prevent them effectively (Vink, 2020). Cervical cerclage, progesterone, antibiotic prophylaxis, and anti-inflammatory treatments are common procedures applied to prevent preterm birth, but none of them offer total efficiency for every woman (Flood and Malone, 2012). A complete characterization of the biomechanisms by which women go into labor at full term is still missing. Since these phenomena are naturally mechanical, we need a better understanding of the uterine, cervical, and membrane mechanical response during birth (Votolini et al., 2013).

The uterine body is a complex organ that comprises billions of smooth muscle cells able to generate large forces and facilitate birth (Rudolph & Ivy, 1930). These cells transmit electrical signals along the uterine wall (action potentials). During a normal vaginal delivery, these impulses are synchronized, creating a propulsive force due to uterine contractions (Bhogal, 2017; Young, 2016). This process is accompanied by cervical dilation, resulting in the expulsion of the fetus from the uterine cavity (Bastos et al., 2012).

The cervix is at the base of the uterus and comprises cervical epithelial and stromal layers (Tantengco & Menon, 2020). The cervix must remain closed to support the mechanical loads developed by the growing fetus throughout most of the gestation (Shi et al., 2019). The cervix softens throughout pregnancy, in preparation for labor (Badir et al., 2013), but if cervical softening occurs too soon, there is a risk of preterm birth (Vink, 2020). Thus, the cervix undergoes an important remodeling process throughout gestation, involving rearrangement and realignment of collagen fibrils, and changes in the extracellular matrix (ECM) (Barnum et al., 2022; K. Myers et al., 2009; Nallasamy et al., 2021; Tantengco & Menon, 2020; Yao et al., 2016).

It has been hypothesized that the cervix responds passively to uterine contractions during the onset of labor (Tantengco & Menon, 2020). However, some studies have investigated the existence of active cervical contractions during gestation and parturition (Rudel & Pajntar, 1999; Tantengco & Menon, 2020). Smooth muscle fibers represent approximately 10% to 45% of the cervical stroma, besides collagen and ECM (Verdenik et al., 2001; Vink & Feltovich, 2016).

These smooth muscle fibers may create an active response in the cervix and lead to cervical remodeling (Tantengco & Menon, 2020). Other studies have identified longitudinal and circumferential collagen fibers in the cervix: the longitudinal fibers may contract and contribute to cervical dilation, while the circumferentially aligned fibers may keep the cervix closed (Tantengco & Menon, 2020; Vink & Feltovich, 2016; Weiss et al., 2006; Yao et al., 2016).

The fetal membranes are layered biological structures surrounding and protecting the fetus throughout pregnancy, working as a mechanical and immunological barrier (Bryant-Greenwood, 1998; Jabareen et al., 2009). The amnion and the chorion, whose microstructures differ significantly from each other, are the main layers of fetal membranes (Buerzle & Mazza, 2013). The amnion is the thinner, stiffer, and stronger inner layer of the membrane facing the amniotic fluid, while the chorion is the more compliant and extensible outer layer contacting the uterine body (Buerzle et al., 2012; Buerzle & Mazza, 2013; Ilancheran et al., 2009; Mauri et al., 2016; Oyen et al., 2004; Zhang et al., 2021). A maternal layer called decidua shares a close anatomical structure with the chorion and results from the differentiation process of the uterine environment (Malak & Bell, 1994; Tahan & Tahan, 2014).

In the late stages of pregnancy, an area of altered morphology occurs within the region of fetal membranes that overlies the cervix (Verbruggen et al., 2017). This region, known as the “weak zone”, is characterized by reduced strength. It has been hypothesized that fetal membrane rupture initiates in this area (Verbruggen et al., 2017).

Several efforts have been performed to characterize the complex uterine environment during different stages of pregnancy. Vila Pouca et al. simulated uterine contractions to reproduce the initial moments of the second stage of labor (Vila Pouca et al., 2019). Fidalgo et al. studied the impact of irregular uterine contraction on labor progression (Fidalgo et al., 2022). Buerzle and Mazza et al. and Fidalgo et al. developed a mechanical constitutive model to characterize the fetal membrane response (Buerzle & Mazza, 2013; Fidalgo et al., 2024). The novelty of this work resided in bringing all these aspects together in one numerical model to simulate the phenomena occurring moments before the onset of labor.

In this work, the complex interaction between the cervix, fetal membrane, and uterine contractions before the onset of labor was analyzed, more specifically, the impact of the following physiological conditions on the maximal principal stress distribution, cervical remodeling in terms of shape change, and fetal membrane rupture: (i) initial cervical shape, (ii) cervical stiffness, (iii) cervical contractions, and (iv) intrauterine pressure. A complete parametrized numerical model of the full-term gravid uterine environment was developed, comprising the cervix, body of the uterus, fetal membrane, and abdomen. Each structure was characterized by appropriate constitutive models previously developed and validated: the uterine body and cervix were modeled through an electro-chemo-mechanical model able to mimic a set of muscle contractions (Fernandez et al., 2016; Fidalgo et al., 2022); the amnion layer from the fetal membrane was characterized by a set of anisotropic constitutive equations

following a membrane model formulation (Fidalgo et al., 2024); isotropic linear elastic materials characterized the chorion and the decidua (Fidalgo et al., 2024); the Neo-Hookean constitutive model characterized the abdomen (Westervelt et al., 2017).

This is the first numerical study embracing a complete full gravid uterine and cervical model, uterine and cervical contractions, and a diversity of features associated with pregnancy. We hope to gain more insight into what conditions may influence a successful vaginal delivery and clarify the complex biomechanical interaction between the cervix, fetal membrane, and body of the uterus, which is not entirely understood.

Materials and Methods

The active and passive constitutive material models, finite element analysis setup, and numerical simulation parameters for a full-term gravid pregnancy biomechanical model are detailed in this section.

Material Constitutive Models

The constitutive material models used to define the uterus, cervix, and amnion are described in the *Uterine and cervical electro-chemo-mechanical constitutive model* and *Membrane constitutive model* subsections. The remaining components of the parametrized full-term gravid uterine model (chorion,

decidua, and abdomen) were defined by isotropic linear elastic or Neo-Hookean constitutive models.

Uterine and cervical electro-chemo-mechanical constitutive model

Uterine contractions are triggered by electrical, chemical, and mechanical stimuli (Fidalgo et al., 2022; Sharifimajd et al., 2016; Sharifimajd & Stålhand, 2014; Yochum et al., 2016). The complete model that was implemented to define uterine and cervical contractions is divided into three sub-models:

- electric model – represents the ionic currents responsible for the smooth muscle cells' activity and the output is the $[Ca^{2+}]_i$ dynamics;
- chemical model – determines the fraction of cross-bridges;
- mechanical model – computes the passive and active responses of the muscle.

The intracellular calcium concentration $[Ca^{2+}]_i$ links the electrical to the chemical sub-models. The link between the latter and the mechanical model is given by the fraction of cross-bridges α_c and α_d , which determines the active response of the muscle (Figure 1).

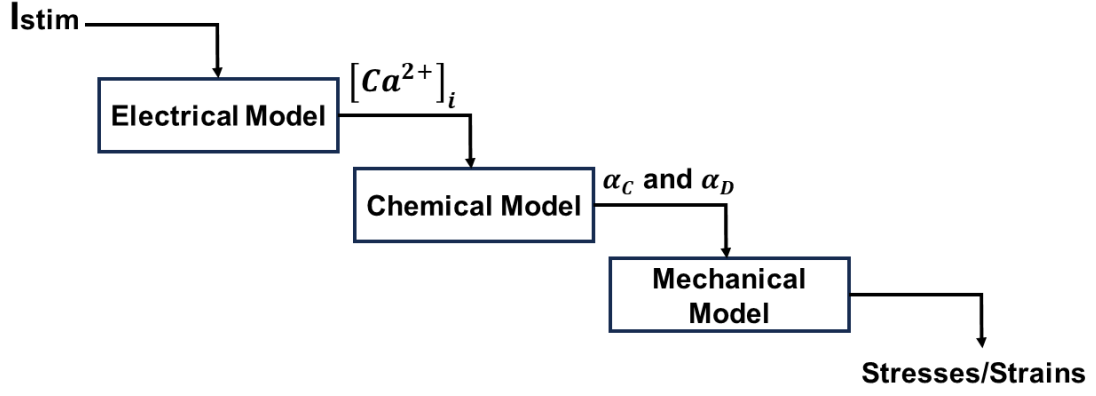


Figure 1. Representative scheme of the electro-chemo-mechanical model. I_{stim} represents the stimulation current which will activate the electrical model and, consequently the entire constitutive model.

Due to the complexity of the electro-chemo-mechanical constitutive model, only the main equations and parameters are described here. A more detailed description of the model can be found at Fidalgo et al. (Fidalgo et al., 2022).

The intracellular calcium concentration $[Ca^{2+}]_i$ is determined through the following equation:

$$\frac{d[Ca^{2+}]_i}{dt} = f_c(-AI_{Ca} - K_{Ca}[Ca^{2+}]_i) \quad (2.1)$$

where f_c represents the calcium influx probability, A is the current conservation factor, I_{Ca} corresponds to the ionic current for the voltage-dependent calcium channel, and K_{Ca} is the calcium extraction factor.

α_C and α_D represent the myosin in a bound phosphorylated and unphosphorylated state, respectively. These parameters are determined through the following coupled system:

$$\begin{bmatrix} \dot{\alpha}_A \\ \dot{\alpha}_B \\ \dot{\alpha}_C \\ \dot{\alpha}_D \end{bmatrix} = \begin{bmatrix} -k_1 & k_2 & 0 & k_7 \\ k_1 & -(k_2 + k_3) & k_4 & 0 \\ 0 & k_3 & -(k_4 + k_5) & k_6 \\ 0 & 0 & k_5 & -(k_6 + k_7) \end{bmatrix} \times \begin{bmatrix} \alpha_A \\ \alpha_B \\ \alpha_C \\ \alpha_D \end{bmatrix} \quad (2.2)$$

where α represents different states of myosin and k are transition rates between different myosin states. $[Ca^{2+}]_i$ will enter the system through k_1 and k_6 :

$$k_1 = k_6 = \frac{[Ca^{2+}]_i^{nk_1}}{[Ca^{2+}]_i^{nk_1} + [Ca_{1/2MLCK}^{2+}]_i^{nk_1}} \quad (2.3)$$

where $[Ca_{1/2MLCK}^{2+}]_i$ is the calcium ion concentration for half-activation of MLCK and nk_1 is the Hill coefficient.

Finally, the strain energy density function in the mechanical model, Ψ_{uterus} , is decoupled into the volumetric contribution Ψ_{vol} , the ground matrix isochoric contribution $\bar{\Psi}_m$, and the fiber isochoric contribution $\bar{\Psi}_f$:

$$\Psi_{uterus} = \Psi_{vol} + \bar{\Psi}_m + \bar{\Psi}_f \quad (2.4)$$

The volumetric contribution is defined by:

$$\Psi_{vol} = \frac{1}{D_1} \left(\frac{J^2 - 1}{2} - \ln(J) \right) \quad (2.5)$$

where D_1 is the incompressibility coefficient, and J is the volume ratio. The isochoric matrix contribution is given by the Neo-Hookean model:

$$\bar{\Psi}_m = C_{10}(\bar{I}_1 - 3) \quad (2.6)$$

where C_{10} is a material parameter, and $\bar{I}_1$ the first invariant of the isochoric right Cauchy-Green deformation tensor. Finally, the fiber isochoric contribution is calculated by:

$$\bar{\Psi}_f = \zeta_1(\bar{\Psi}_1^p + N_1\bar{\Psi}_1^a) + (1 - \zeta_1)(\bar{\Psi}_2^p + N_2\bar{\Psi}_2^a) \quad (2.7)$$

where ζ_1 represents the fraction of all fibers that belong to the first family, N_i is a function that accounts for the overlap between actin and myosin filaments, and $\bar{\Psi}_i^p$ and $\bar{\Psi}_i^a$ represent the passive and active contribution of the i th fiber family, respectively. $\bar{\Psi}_i^a$ is defined by:

$$\bar{\Psi}_i^a = \frac{1}{2} \alpha_{xb} k_{xb} \bar{\varepsilon}_e^2 \quad (2.8)$$

where $\alpha_{xb} = \alpha_c + \alpha_D$ establishes the connection between the chemical and mechanical model, k_{xb} is a constant, and $\bar{\varepsilon}_e$ represents the elastic strain. The passive component $\bar{\Psi}_i^p$ is defined by:

$$\bar{\Psi}_i^p = \begin{cases} \frac{\mu_{i1}}{2\mu_{i2}} \{ \exp[\mu_{i2}(\bar{I}_j - 1)^2] - 1 \}, & \text{if } \bar{I}_j \geq 1 \\ 0, & \text{otherwise} \end{cases} \quad (2.9)$$

Membrane constitutive model

A modified version of the Buerzle-Mazza formulation (Buerzle & Mazza, 2013) developed by Mauri and Ehret (Mauri et al., 2016) was applied to characterize the mechanical response of the amnion (Mauri et al., 2016). The strain energy function, $\Psi_{membrane}$, represents the strain energy per unit reference volume and accounts for the stretch of the single families of fibers (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$\Psi_{membrane} = \frac{\mu_0}{2q} [e^{qg} - 1] \quad (2.10)$$

where μ_0 is a material constant having the units of stress and q is a dimensionless constant that controls the nonlinearity of the moduli for the different stress responses in the composite structure (Rubin & Bodner, 2002).

The function g is given by the sum of the compressible neo-Hookean material g_2 , and the fiber strain energy g_3 (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$g = g_2(I_1, J) + g_3(\lambda_i) \quad (2.11)$$

$$g_2 = m_2(I_1 - 3) + \frac{m_2}{m_5}(J^{-2m_5} - 1) \quad (2.12)$$

$$g_3 = \frac{m_3}{m_4} \frac{1}{N} \sum_{i=1}^N \langle \lambda_i - 1 \rangle^{2m_4} \quad (2.13)$$

where $\langle \rangle$ represents the Macauley brackets, which indicates that the fibers do not bear compression loads (Buerzle & Mazza, 2013) and m_i are model parameters. The parameter N represents the number of representative families and must be even and greater than zero. The first invariant of the right Cauchy-Green deformation tensor is represented by I_1 , while J is the volume ratio, and λ_i is the fiber stretch (Buerzle & Mazza, 2013; Mauri et al., 2016):

$$I_1 = \text{tr}(\mathbf{F}^T \mathbf{F}) \quad (2.14)$$

$$J = \det \mathbf{F} \quad (2.15)$$

$$\lambda_i = |\mathbf{F} \mathbf{M}_i|, \quad i = 1, 2, \dots, N \quad (2.16)$$

The deformation gradient is represented by $\mathbf{F}$ and $\mathbf{M}$ represent the fiber directions in the reference configuration and it is defined as (Mauri et al., 2016):

$$\mathbf{M}_j = \cos \beta_j \sin \theta_j \mathbf{e}_1 + \sin \beta_j \sin \theta_j \mathbf{e}_2 + \cos \theta_j \mathbf{N} \quad (2.17)$$

$$\mathbf{M}_{j+N/2} = \cos \beta_j \sin \theta_j \mathbf{e}_1 + \sin \beta_j \sin \theta_j \mathbf{e}_2 - \cos \theta_j \mathbf{N} \quad (2.18)$$

$$\beta_j = \frac{2\pi}{N} \left(j - \frac{3}{2} \right) \quad (2.19)$$

$$\theta_j = \frac{\pi}{2} - \varphi \quad (2.20)$$

where φ represents a slight off-plane inclination and $j = 1, 2, \dots, \frac{N}{2}$. The Cauchy stress tensor $\boldsymbol{\sigma}$ is obtained from the derivatives of the strain energy density function with respect to the deformation tensor (Buerzle & Mazza, 2013).

Eight parameters must be defined to fully characterize the material response: μ_0 , q , m_2 , m_3 , m_4 , m_5 , N , and φ .

Parametrized numerical model of the gravid uterine body and cervix

A complete parametrized numerical model of the gravid uterine body and cervix (Figure 2) was developed to accomplish the objectives of this work, following the instructions of Louwagie et al. (Louwagie et al., 2021). Since the geometric model is parametrized, it is possible to generate patient-specific geometries by changing the required dimensions. The model was developed for a mid-third-trimester gravid uterine body and cervix, using the average dimensions from different patients retrieved from Louwagie et al. (Louwagie et al., 2021). The model comprises four structures: the body of the uterus, cervix, multilayer fetal membrane (amnion, chorion, and part of the decidua), and abdomen. In the following subsections, a more detailed description of each structure and the respective finite element characterization is presented. The complete model's loads, contact interactions, and boundary conditions are also described.

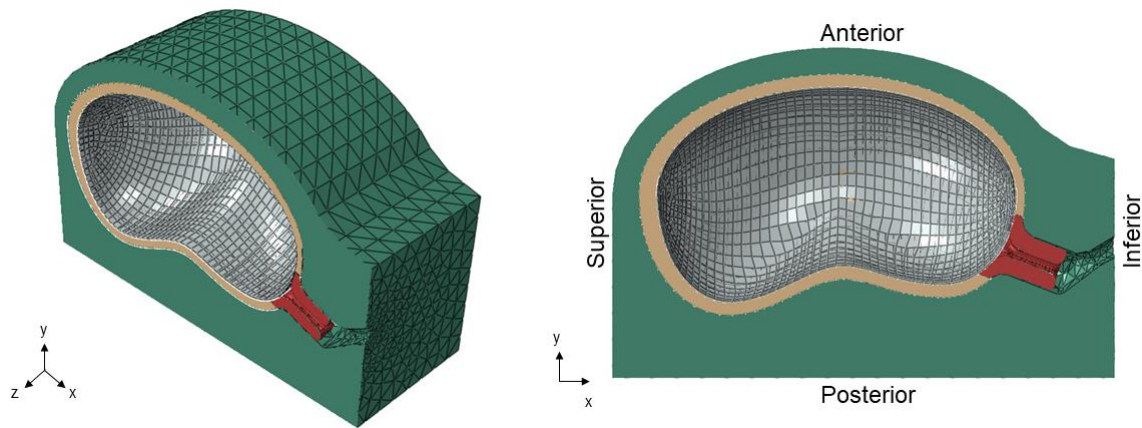


Figure 2. Parametrized finite element model of the gravid uterine body and cervix. The model comprises four structures: body of the uterus (brown), cervix (red), multilayer fetal membrane (gray), and abdomen (green). The anatomical directions (anterior, posterior, superior, and inferior) are also represented.

Body of the uterus

The finite element model of the uterine body (Figure 3) contains 6333 C3D8H hybrid linear brick finite elements and 8536 nodes.

In the longitudinal and circumferential directions, two families of uterine collagen fibers were considered. The direction of each fiber was found through the finite element software ABAQUS®, applying the methodology described in previous works (Fidalgo et al., 2022).

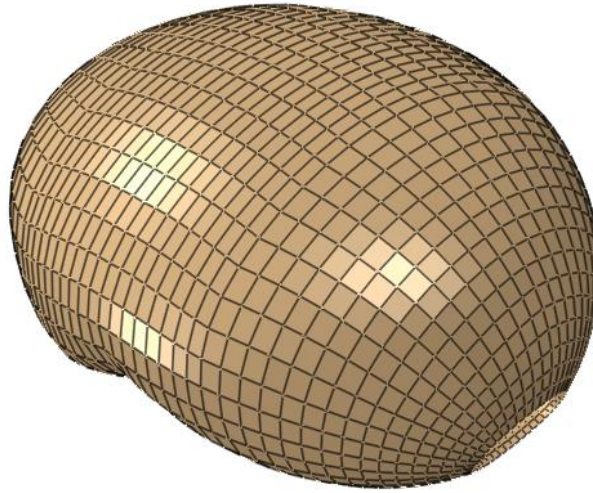


Figure 3. Finite element model of the uterine cavity, meshed with C3D8H finite elements.

The electro-chemo-mechanical constitutive model characterized the uterine body, able to reproduce muscle contractions, as described in Table 1. The electrical component was calibrated using transmembrane potential and calcium concentration curves (Sharifimajd & Stålhand, 2014). The chemical parameters were calibrated using the myosin states and stress evolutions (Sharifimajd et al., 2016). The mechanical parameters were calibrated using an intrauterine pressure curve measured in a woman at term (38 weeks) in active labor (Sharifimajd et al., 2016).

Table 1. Electrical, chemical, and mechanical properties of the uterine body, using the electro-chemo-mechanical constitutive model.

<i>Variable</i>	<i>Description</i>	<i>Value</i>	<i>Units</i>
I_{stm}	Stimulation current	0.17	$\mu A/cm^2$
C_m	Membrane capacitance	1	μF
f_c	Calcium influx probability	0.4	-
A	Current conservation factor	4×10^{-5}	$mol\ cm^2/\mu C$

Electrical Parameters (Rihana et al., 2009; Yochum et al., 2016)	K_{Ca}	Calcium extraction factor	0.01	mseg ⁻¹
	J_{back}	Background calcium current	0.023	$\mu A/cm^2$
	G_{Ca}	Voltage-operated calcium channels conductance	0.022	mS/cm ²
	V_{Ca}	Half-point of the voltage operated channel activation sigmoid	-20	mV
	R_{Ca}	Maximum slope of the voltage operated channel activation	5.97	mV
	G_K	Potassium channels conductance	0.064	mS/cm ²
	E_K	Potassium nerst potential	-83	mV
	K	Half-point potassium concentration	0.01	μmol
	G_{KCa}	Potassium/calcium channels conductance	0.08	mS/cm ²
	G_L	Leak channels conductance	0.0055	mS/cm ²
	E_L	Leak nerst potential	-20	mV
	$[Ca^{2+}]_e$	Extracellular calcium concentration	2	μmol
	R	Gas constant	8.134	JK ⁻¹ mol ⁻¹
	T	Temperature	295	K
	F	Faraday constant	96.487	kCmol ⁻¹
Chemical Parameters (Sharifimajd et al., 2016)	k_2	Dephosphorylation of myosin rate	1.2387	seg ⁻¹
	k_3	Attachment and detachment of the fast-cycling cross-bridges rate	0.1419	seg ⁻¹
	k_7	Latch-bridge detachment rate	0.0378	seg ⁻¹
	$[Ca_{1/2MLCK}^{2+}]_i$	Calcium ion concentration for half-activation of MLCK	2.5698×10^{-4}	mM
	n_{k1}	Hill coefficient	8.7613	-
Mechanical Parameters (Sharifimajd et al., 2016)	C_{10}	Stiffness coefficient	0.030	MPa
	D_{10}	Volumetric coefficient	1E-5	MPa ⁻¹
	ζ_1	Fraction of fibers of the first family	1	-
	μ_{i1} (i = 1,2)	Fiber's Stiffness	0.006	MPa
	μ_{i2} (i = 1,2)	Fiber's non-linear behavior	1	-
	$\bar{\epsilon}_{opt}$	Active strain for maximum force	0.4950	-
	γ	Constant	1	-
	v_C	Peripheral clutch velocity	0.11	seg ⁻¹
	η	Constant	18	MPa s
	k_{xb}	Constant	6	MPa
	k_C	Constant	3.5	MPa s

Cervix

The cervix was modeled with C3D8H hybrid linear-brick finite elements, using 3910 elements and 4794 nodes, as illustrated in Figure 4.

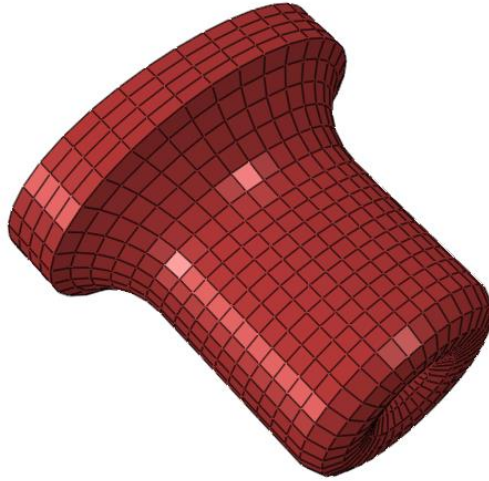


Figure 4. Finite element model of the cervix, meshed with C3D8H finite elements.

Collagen fibers in the longitudinal direction (from the lower to the upper region of the cervix) and circumferential direction (around the cervical canal) were introduced into the cervical model, following the methodology described for the uterus.

The electro-chemo-mechanical model was also applied to describe the material response of the cervix. The parameters were maintained according to Table 1, except for C_{10} and D_{10} , which were adjusted to the tensile properties of non-pregnant human cervical tissue (Fernandez et al., 2016):

$$C_{10} = 0.186 \text{ MPa}$$

$$D_{10} = 2.48 \text{ MPa}^{-1}$$

Active cervical contractions were produced by activating the electrical and chemical components. To simulate a passive cervix, these sub-models were inactivated.

Fetal Membrane

In this work, a multilayer fetal membrane model was developed, comprising the amnion, chorion, and part of the decidua. The fetal membrane is illustrated in Figure 5, and it was modeled with linear brick finite elements: the amnion comprised 2874 C3D8H and 8628 nodes, the chorion contained 2517 C3D8 elements and 7557 nodes, and the decidua was modeled with 2609 C3D8 elements and 7833 nodes.

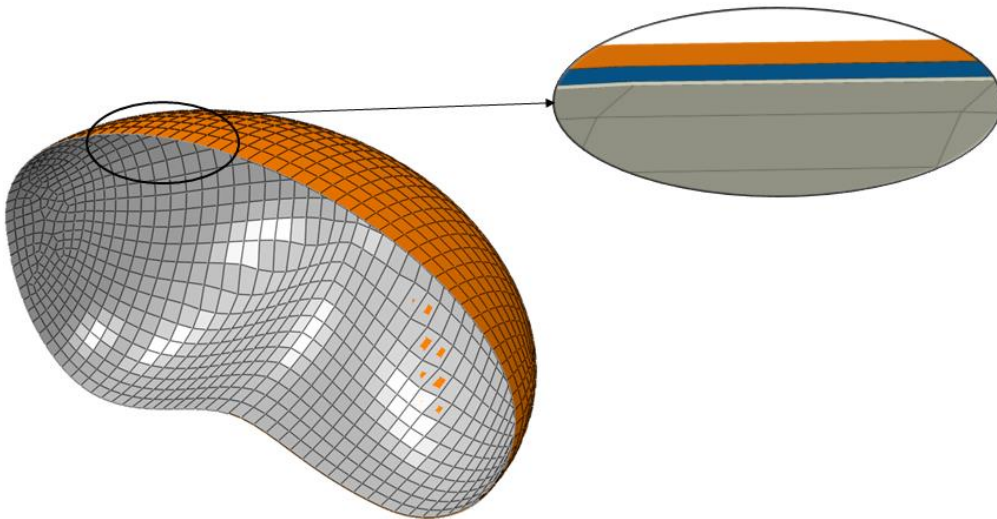


Figure 5. Finite element model of the multilayer fetal membrane, meshed with C3D8(H) finite elements: amnion (gray), chorion (blue), and decidua (orange).

The amnion, the mechanically dominant layer of the fetal membrane, was characterized by the modified version of the Buerzle-Mazza formulation (Buerzle & Mazza, 2013). In Table 2, the mechanical parameters of the amnion layer are presented.

Table 2. Mechanical properties of the amnion, using the modified version of the Buerzle-Mazza constitutive model (Fidalgo et al., 2024; Mauri et al., 2016).

	μ_0 [MPa]	q	m_2	m_3	m_4	m_5	N	ϕ
Amnion	2.4	2.96	0.00228	41.12	1.27	0.463	32	0

Since the chorion and decidua layers are less mechanically dominant than the amnion layer, both layers were characterized as isotropic linear elastic materials (Table 3). It is known that the decidua shares a close anatomical relationship with the chorion, suggesting that decidual changes may be associated with chorioamnion membrane alterations (Malak and Bell, 1994). The development of the decidual layer and the chorion is synchronized from the earliest phase of implantation, and the smooth chorion becomes fused with the decidua (Malak and Bell, 1994).

Table 3. Mechanical properties of the chorion and decidua, using the isotropic linear elastic constitutive model (Ophir et al., 2002; Oxlund et al., 1990; Roohbakhshan et al., 2016; Verbruggen et al., 2017).

	E [MPa]	ν [-]
Chorion	1	0.41
Decidua	1	0.49

Abdomen

The finite element model of the abdomen is illustrated in Figure 6. This structure was meshed with 27836 C3D4H hybrid tetrahedral finite elements and 5887 nodes.

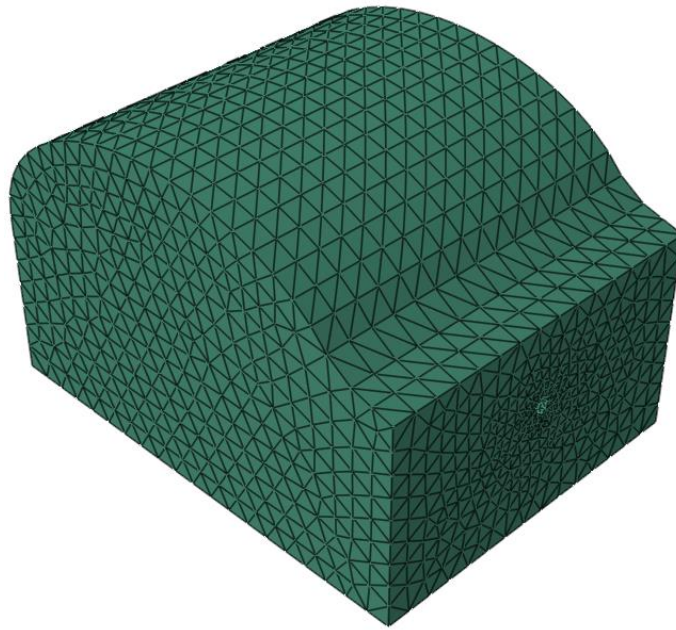


Figure 6. Finite element model of the abdomen, meshed with C3D4H finite elements.

The Neo-Hookean constitutive model was used to characterize the abdomen, and the respective mechanical parameters were set to the values in Table 4.

Table 4. Mechanical properties of the abdomen, using the Neo-Hookean constitutive model (Westervelt et al., 2017).

	C_{10} [MPa]	D_{10} [MPa ⁻¹]
Abdomen	0.005	1E-5

Loads, contact interactions, and boundary conditions

Due to the complexity of the finite element model of the gravid uterine body and cervix (Figure 2), the contact interactions were carefully analyzed and defined according to previous works. Three types of contact interactions were considered (Figure 7):

- **tie contact** (body of the uterus/abdomen; amnion/chorion; chorion/decidua; body of the uterus/cervix);
- **frictionless contact** (cervix/abdomen; body of the uterus/decidua);
- **hard contact** (decidua/cervix).

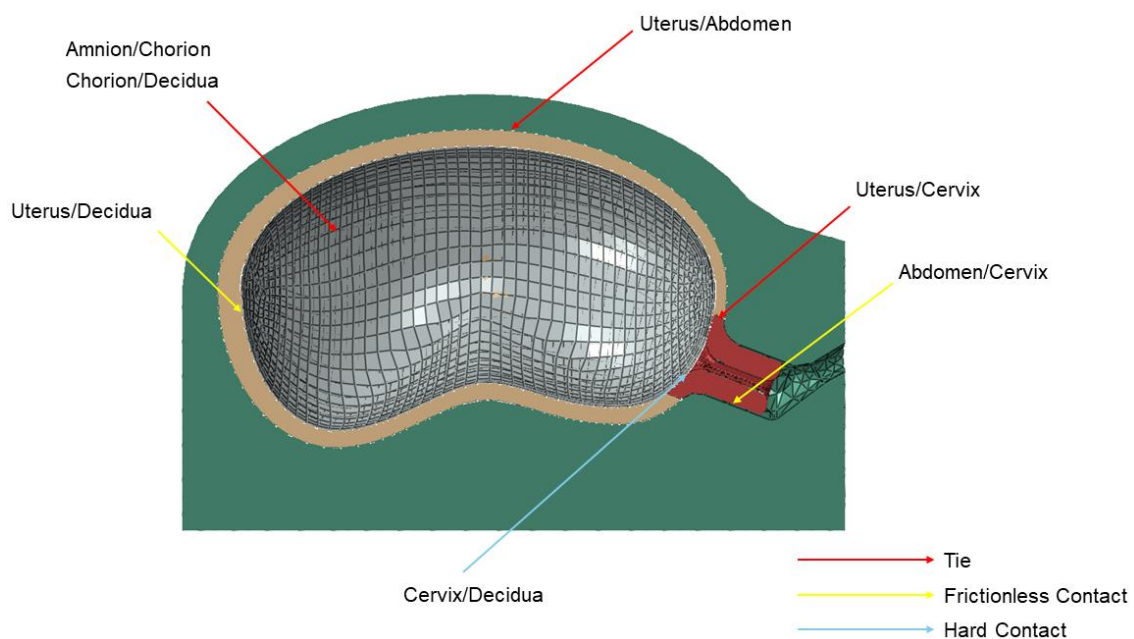


Figure 7. Contact interaction defined in the biomechanical model.

Regarding the load conditions applied in the numerical model, a fluid cavity representing the amniotic fluid was created inside the uterine body, where a ramping intrauterine pressure was defined. The fluid density was set to 1.025 Kg/m³, and the fluid bulk modulus to 2200 MPa, whose values are from blood plasma (Orczyk-Pawilowicz et al., 2016). The intrauterine pressure was set to the labor contraction value of 0.00867 MPa (Grimm, 2021).

Finally, three boundary conditions were established according to Figure 8:

- the nodes located in the posterior wall of the abdomen were restricted in the direction perpendicular to the respective surface;
- the nodes located in the superior wall of the abdomen were restricted in the direction perpendicular to the respective surface;
- the nodes in common between the posterior and superior walls of the abdomen were restricted in all directions.

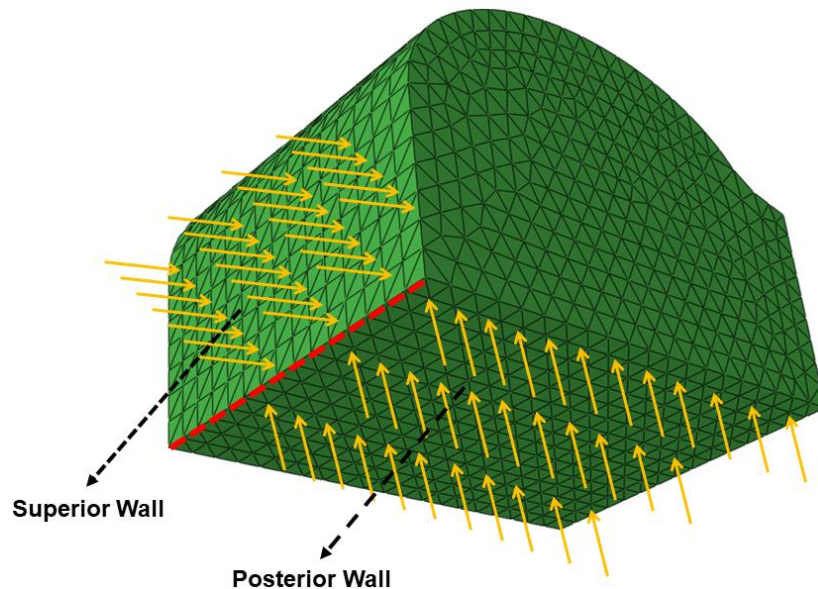


Figure 8. Boundary conditions applied to the posterior and superior surfaces of the abdomen; the yellow arrows represent the restricted directions and the red line represent a restriction in all directions.

Numerical Simulations

The numerical model of the gravid uterine body and cervix was used to study the interaction between the cervix, fetal membrane, and uterine contractions. The following aspects were remained equal across all numerical simulations:

- the body of the uterus was always contracting;
- all simulations had a duration of a normal contraction time (80 seconds) (Buttin et al., 2013).

Four physiological factors associated with the gestation period were investigated to identify their impact on the fast cervical shape change before labor (dilation and shortening) and the fetal membrane rupture: (i) initial cervical shape, (ii) cervical stiffness, (iii) cervical contraction, and (iv) intrauterine pressure. Table 5 summarizes all simulations and an explanation is presented in the following paragraphs.

Table 5. Simulations performed to investigate cervical shape, cervical stiffness, cervical contraction, and IUP.

	Cervical Shape			Cervical Stiffness [MPa]			Cervical Contraction		IUP [MPa]		
Factors	Large	Mid	Small	0.186	0.070	0.020	Yes	No	0.015	0.00867	0.005
Cervical Shape and Cervical Stiffness	X			X				X		X	
	X				X			X		X	
	X					X		X		X	
		X		X				X		X	
		X			X			X		X	
		X				X		X		X	
			X	X				X		X	
			X		X			X		X	
			X			X		X		X	
Cervical Contraction	X					X	X			X	
		X				X	X			X	
			X			X	X			X	
IUP	X					X		X	X		
	X					X		X		X	
	X					X		X			X

Regarding the initial cervical shape (i), three scenarios were considered (Louwagie et al., 2021):

- **“Large” Shape** - large cervical length (**35 mm**) and small cervical dilation (inner diameter of the cervical canal set to **5 mm**) (Figure 9A);
- **“Mid” Shape** - mid cervical length (**28 mm**) and mid dilation (inner diameter of the cervical canal set to **10 mm**) (Figure 9B);
- **“Small” Shape** - small cervical length (**20 mm**) and large cervical dilation (inner diameter of the cervical canal set to **15 mm**) (Figure 9C);

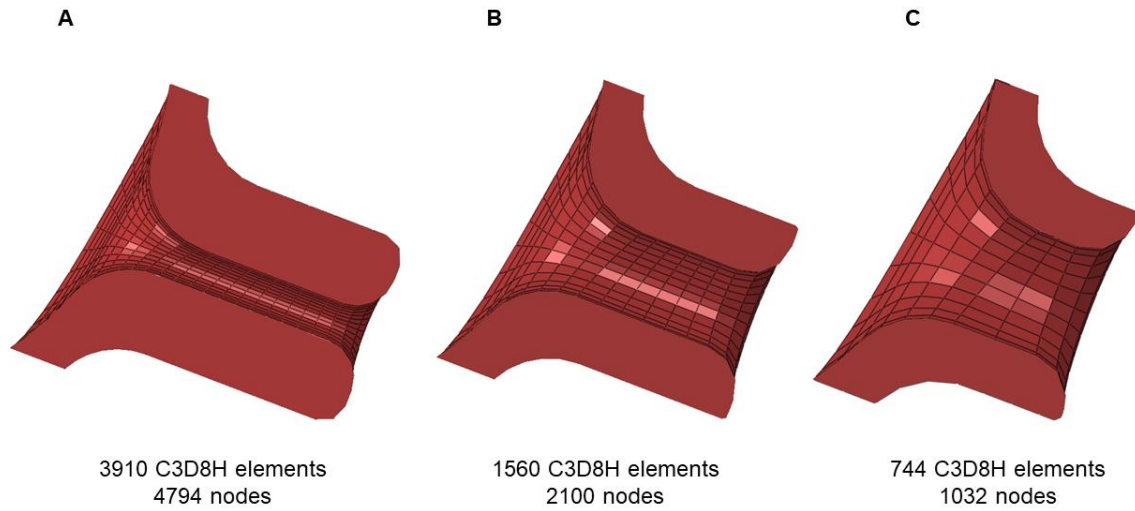


Figure 9. Different initial cervical shapes were analyzed in the numerical simulations: (A) “Large” Shape, (B) “Mid” Shape, and (C) “Small” Shape.

Therefore, the cervical shape got shorter and more dilated from Figure 9 A to C.

For each shape illustrated in Figure 9, the stiffness parameter C_{10} from the cervix (ii) was set to three different values: 0.186 MPa (*Cervix* subsection), 0.070 MPa (reduction of 62%), and 0.020 MPa (reduction of 89%). This accounted for nine numerical simulations: 3 cervical stiffness values per 3 cervical shapes. The cervix did not contract during these nine simulations, and the intrauterine pressure was maintained to be equal to 0.00867 MPa.

Then, the electrical and chemical parts of the electro-chemo-mechanical model were activated for the cervix (iii) to evaluate the impact of cervical contractions on cervical shortening and dilation. Three more numerical simulations were performed for each cervical shape, with C_{10} set to 0.02 MPa. The intrauterine pressure was maintained equal to 0.00867 MPa.

The intrauterine pressure (IUP) effect on cervical shape change and fetal membrane rupture (iv) was also contemplated in this work. Two more simulations were developed, setting the intrauterine pressure to 0.005 MPa and 0.015 MPa. These IUPs were tested in the cervix from **“Large” Shape**, with C_{10} equal to 0.02 MPa.

To analyze the cervical shape change for each simulation, three cervical measurements were defined as illustrated in Figure 10:

- variation of cervical opening (CO);
- variation of cervical length (CL);
- variation of cervical dilation (CD).

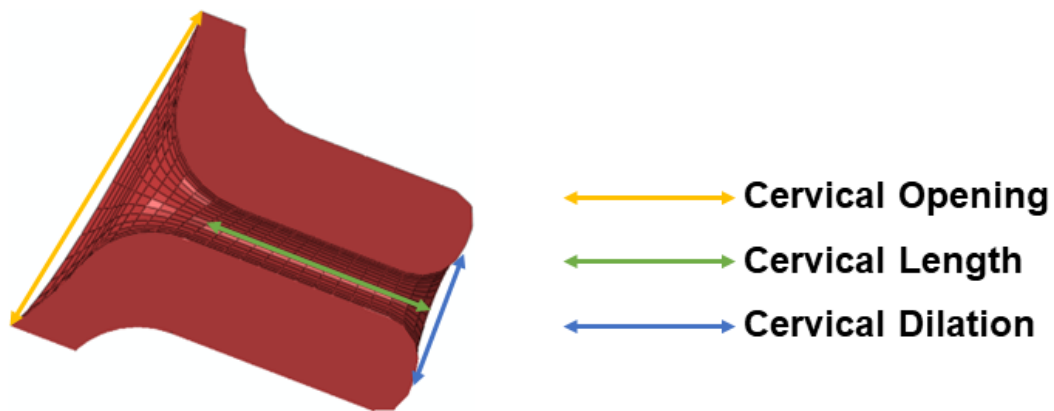


Figure 10. Cervical measurements analyzed in the results section.

These measurements represent the difference between the final and initial cervical configurations (e.g. if the initial cervical length equals 20.00 mm and the final length equals 19.80 mm $CL = 19.80 - 20.00 = - 0.20$ mm).

Finally, the fetal membrane rupture was analyzed by retrieving the maximum principal stress in the amnion layer's protrusion, called the "weak zone" (Figure 11), and compared with the respective biaxial strength in the discussion section. The protrusion occurs in loaded configurations when the amnion is pushed against the cervical opening. The maximum principal stresses were not retrieved for the chorion and decidua since they don't represent the mechanically dominant layers of the fetal membrane.

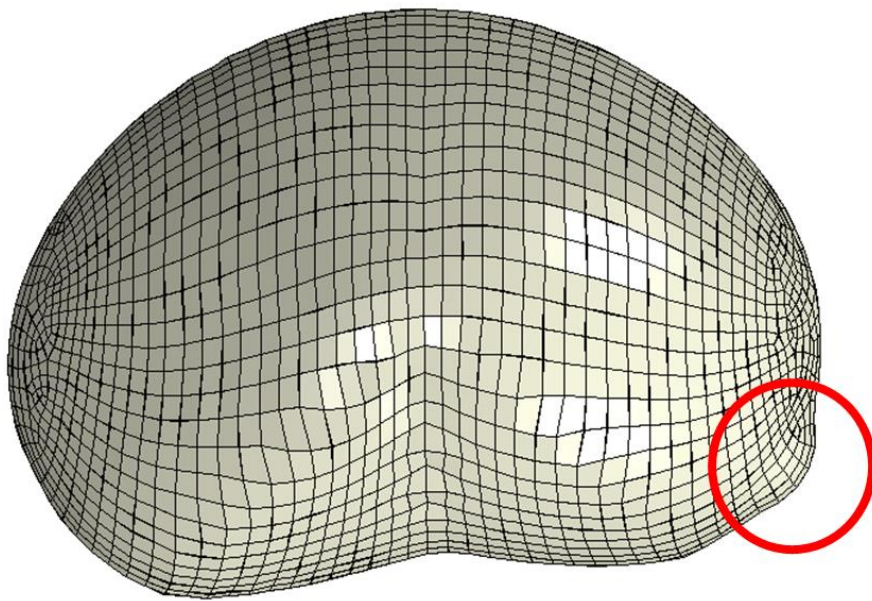


Figure 11. The amnion's protrusion is called the "weak zone" (highlighted in red), where the fetal membrane rupture initiates.

Convergence Study

The cervix assumed different geometries and stiffnesses throughout this investigation. A convergence study was therefore performed, resorting to a simplistic model of the cervix. A pressure of 0.1 MPa was applied to the cervical canal and displacements were restricted in the surface contacting the uterine

body in the gravid model. Three simulations were performed using three different finite element meshes (Figure 12): (A) very refined mesh, (B) refined mesh, and (C) coarse mesh.

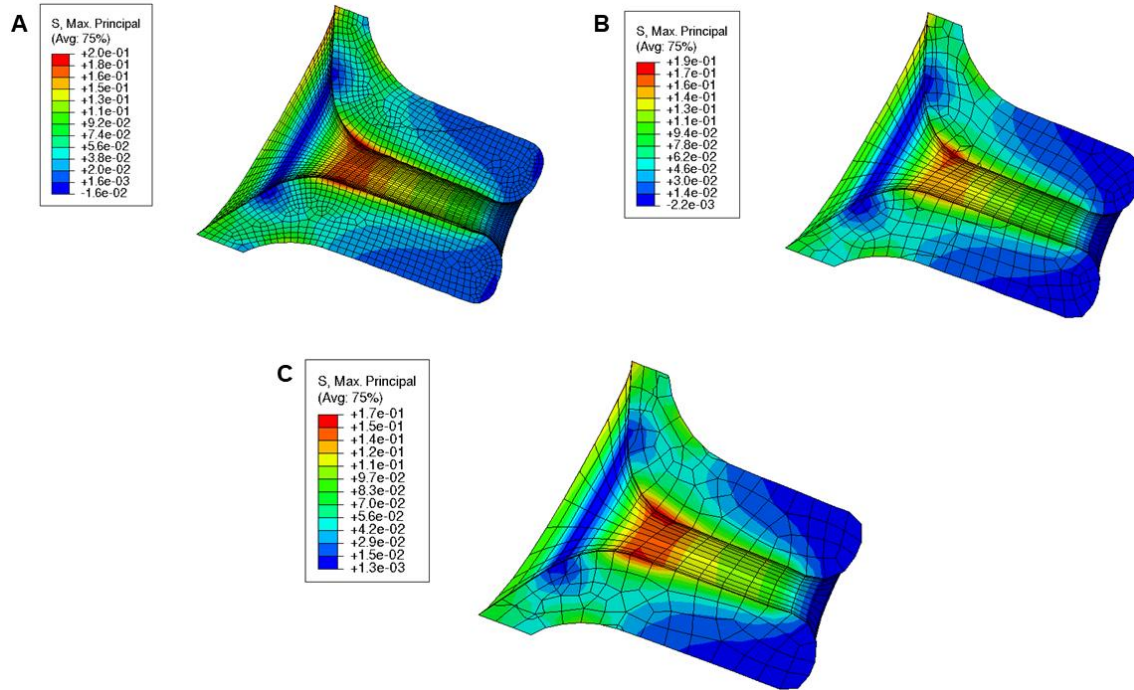


Figure 12. Convergence study on the cervix: (A) very refined mesh, (B) refined mesh, and (C) coarse mesh.

The maximum principal stresses obtained with a refined mesh (Figure 12B) are similar to the stresses obtained with a very refined mesh, while a coarse mesh led to a larger discrepancy. Since the full-gravid uterine model is very complex, the cervix was meshed as illustrated in Figure 12B, to reduce computational costs associated with a very refined mesh without compromising the results. The average finite element size was maintained as close as possible between different cervical geometries.

Results

Numerical simulation results are illustrated and described in this section based on maximal principal stress distribution in the uterus, fetal membrane, and cervix (especially the internal Os region), and cervical shape change.

Uterine body and fetal membrane

The reference and deformed configuration of the entire model is illustrated in Figure 13 for one of the simulations.

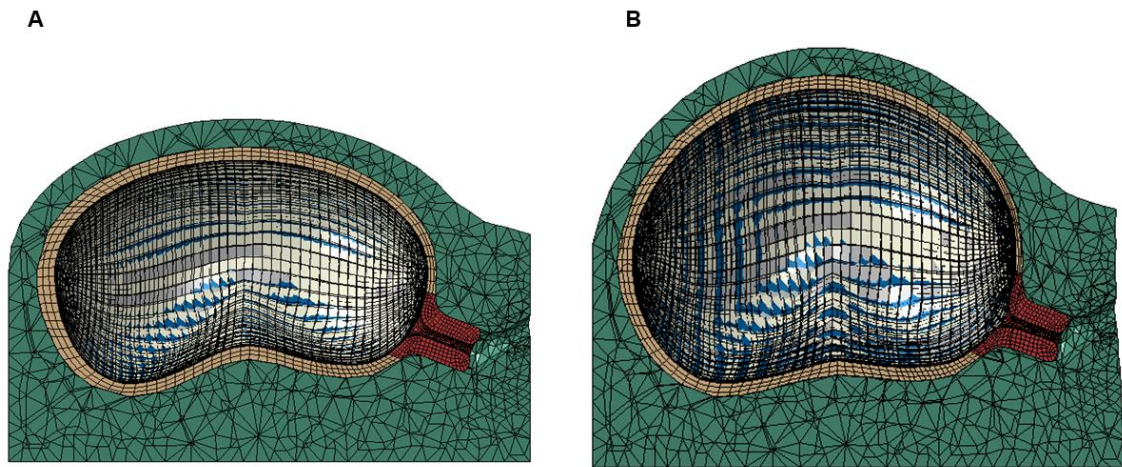


Figure 13. Interaction between the cervix, fetal membrane, and body of the uterus: (A) reference configuration; (B) deformed configuration.

The maximal principal stress values and distributions in the body of the uterus, amnion, and chorion are represented in Figure 14 and Figure 15. Those values and distributions are similar across all simulations, except for those where the IUP is modified.

According to Figure 14, the maximum principal stress in the uterine muscle is verified at the center of the posterior region and corresponds to a value of 0.091 MPa. The uterine contractions cause the uterine body to contract longitudinally and expand circumferentially.

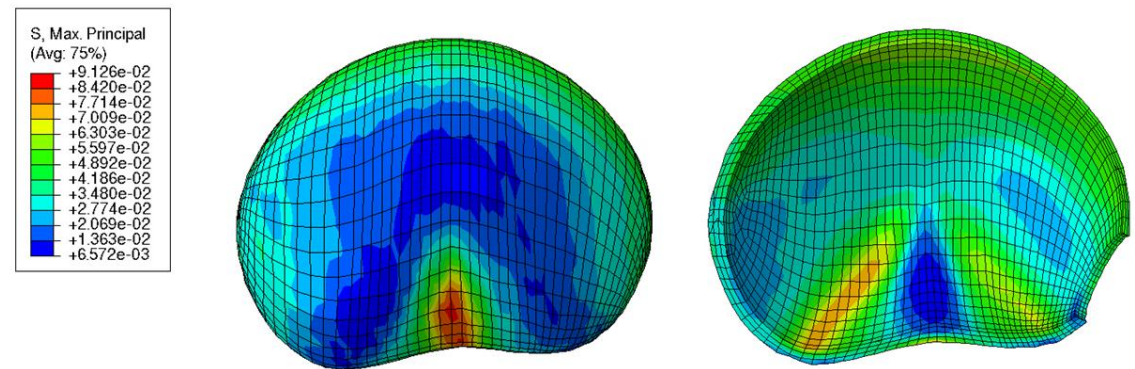


Figure 14. Maximum principal stress in the uterine muscle [units: MPa].

Focusing on the main layers of the fetal membrane (amnion and chorion), illustrated in Figure 15, the amnion is submitted to much larger maximum principal stresses than the chorion. The maximum stress value in the amnion is 2.602 MPa, while in the chorion is 0.319 MPa.

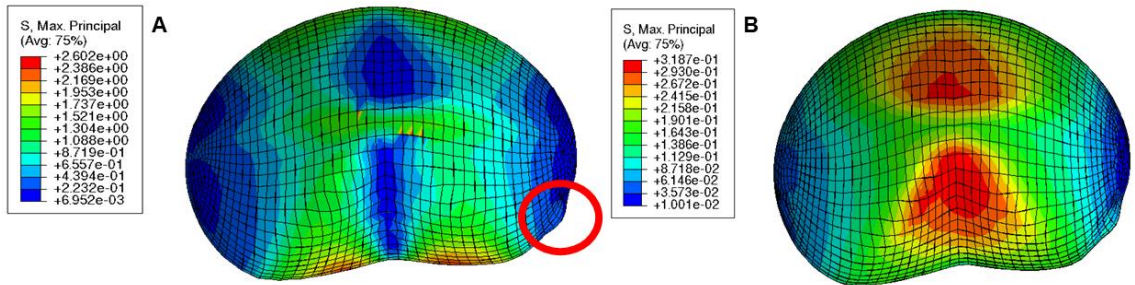


Figure 15. Maximum principal stress in the amnion (A) and chorion (B) layers [units: MPa]. The red circle represents the "weak zone" from the fetal membrane in the amnion layer.

Initial cervical shape and cervical stiffness

The maximum principal stress in the cervix tends to decrease as the reference configuration gets shorter and more dilated, indicating that stress values are influenced by initial cervical shape (Figure 16, Figure 17, and Figure 18; cervixes with equal stiffness values are identified by the same letter A, B, or C).

For the same initial cervical shape, the stress values decrease as the cervix becomes softer (lower C_{10} values). Moreover, stress concentrations are found for all cases at the internal os region, considered the initial site of cervical opening.

The largest maximum principal stress value is equal to 0.182 MPa, verified in Figure 16A, which corresponds to a long, more closed, and stiff cervix. On the other hand, the smallest maximum principal stress value is 0.056 MPa, verified in Figure 18C, where a short, dilated, and soft cervix is illustrated. This corresponds to a decrease of 69.2% in terms of maximum principal stress, highlighting how impactful cervical shape and stiffness are for cervical stresses.

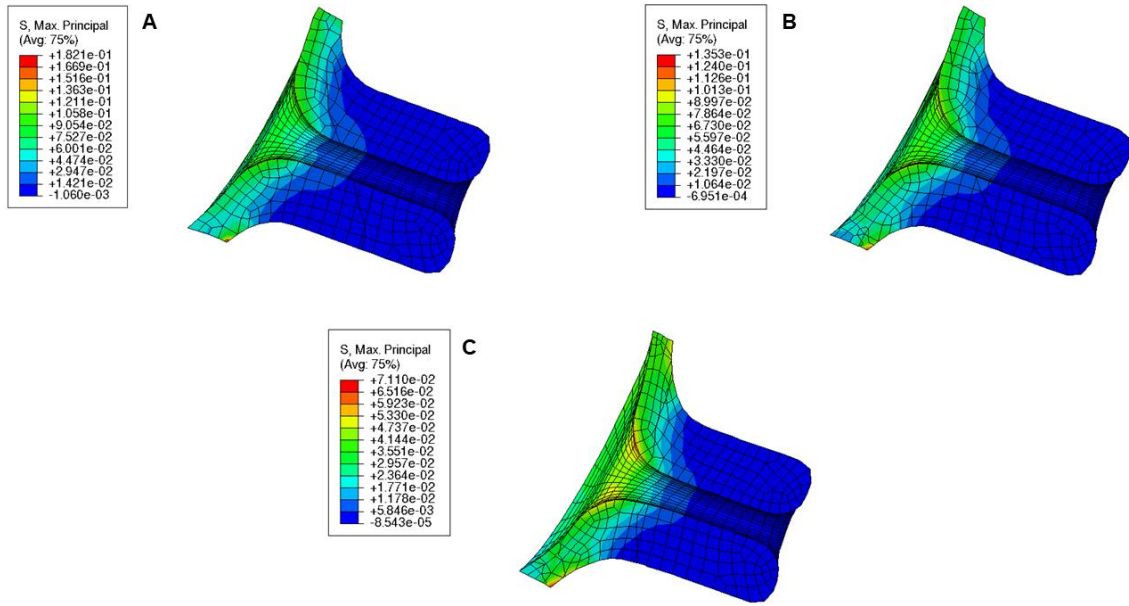


Figure 16. Maximal principal stress distributions for the cervical shape described in “Large” Shape [units: MPa]; A: stiff cervix ($C_{10}=0.186$ MPa); B: mid-cervical stiffness ($C_{10}=0.07$ MPa), C: soft cervix ($C_{10}=0.02$ MPa).

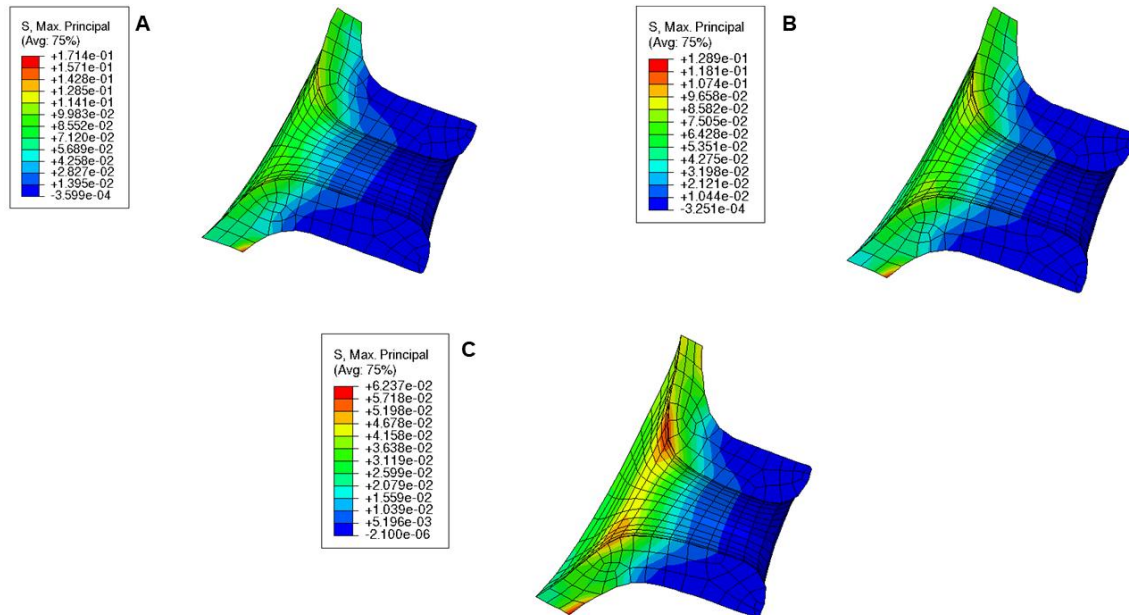


Figure 17. Maximal principal stress distributions for the cervical shape described in “Mid” Shape [units: MPa]; A: stiff cervix ($C_{10}=0.186$ MPa); B: mid-cervical stiffness ($C_{10}=0.07$ MPa), C: soft cervix ($C_{10}=0.02$ MPa).

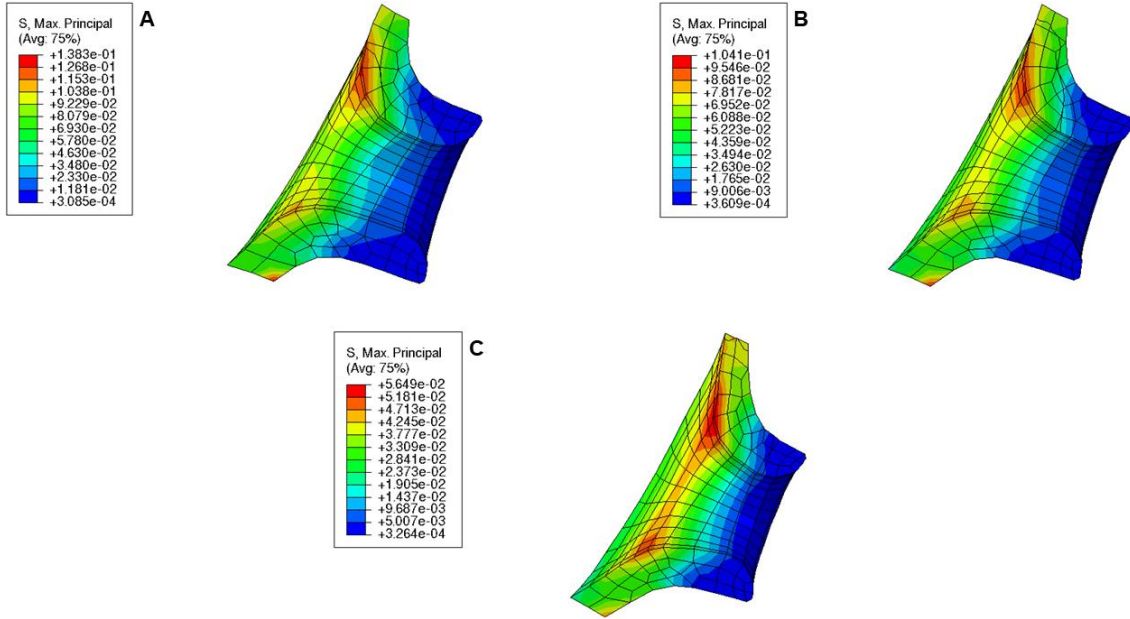


Figure 18. Maximal principal stress distributions for the cervical shape described in "Small" Shape [units: MPa]; A: stiff cervix ($C_{10}=0.186$ MPa); B: mid-cervical stiffness ($C_{10}=0.07$ MPa), C: soft cervix ($C_{10}=0.02$ MPa).

From the analysis of Figure 19, the following observations are valid:

- for each cervical shape, the absolute values of CO, CL, and CD increase as cervical stiffness decreases;
- CO and CD are always positive, which means that the respective measurements increase relative to the initial cervical configuration; the opposite observation is obtained for CL;
- the absolute values of CL and CD are maximum for the "Soft" cervix from "Small" Shape; CO is maximum for the "Soft" cervix from "Mid" Shape;
- CO and CD are minimal for the "Stiff" cervix from "Large" Shape; the absolute value of CL is minimal for the "Stiff" cervix from "Mid" Shape;

- comparing the “Stiff” with the “Soft” cervix, the largest numerical difference for CO is verified in “Mid” Shape, and for CL and CD in “Small” Shape.

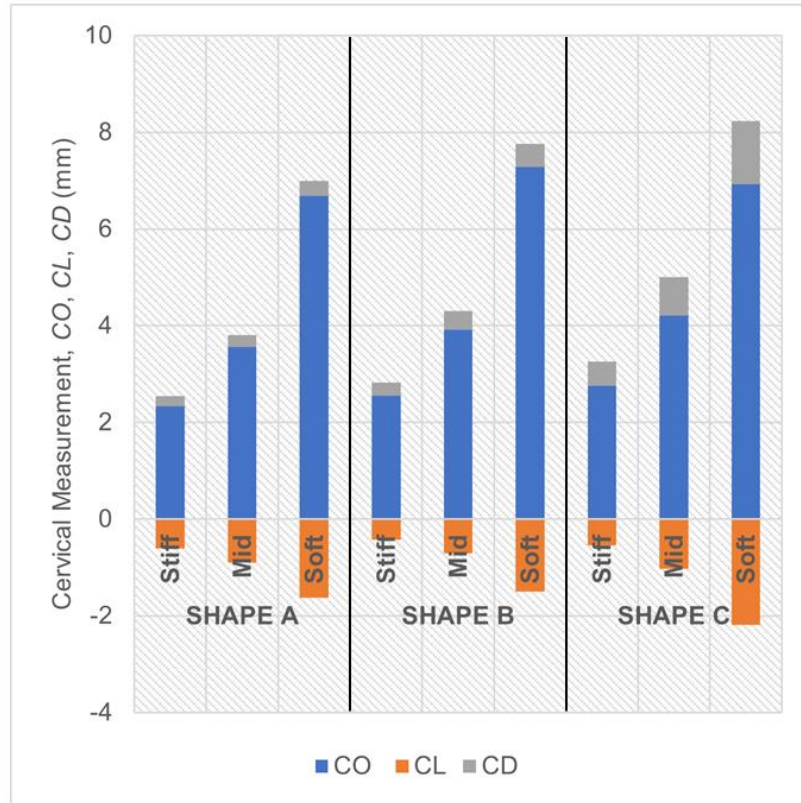


Figure 19. Variations of cervical opening (CO), cervical length (CL), and cervical dilation (CD) for different cervical shapes and stiffnesses. “Large” Shape, “Mid” Shape, and “Small” Shape represent different cervical shapes as described in *Numerical Simulation* section, while “Stiff”, “Mid”, and “Soft” represent different cervical stiffness values.

Finally, in terms of maximum principal stress at the “weak zone” of the amnion layer, the following values are retrieved:

- 0.3 MPa for “Large” Shape, independent of the cervical stiffness;
- 0.5 MPa for “Mid” Shape, independent of the cervical stiffness;

- 0.7 MPa for the “Stiff” and “Mid” cervices from “Small” Shape; 0.8 MPa for the “Soft” cervix from “Small” Shape.

These results reveal that the maximum principal stress in the “weak zone” is highly influenced by the initial cervical shape and almost independent of cervical stiffness.

Cervical Contraction

The maximum principal stress values and distributions caused by cervical contractions are illustrated in Figure 20, Figure 21, and Figure 22. First, the maximum principal stress values increase when cervical contractions are activated, independently of the initial cervical shape. Second, the highest stress values are extended to the cervical canal and not restricted to the internal os region, as observed in previous results. Finally, the cervixes deform differently compared to the respective passive cervix.

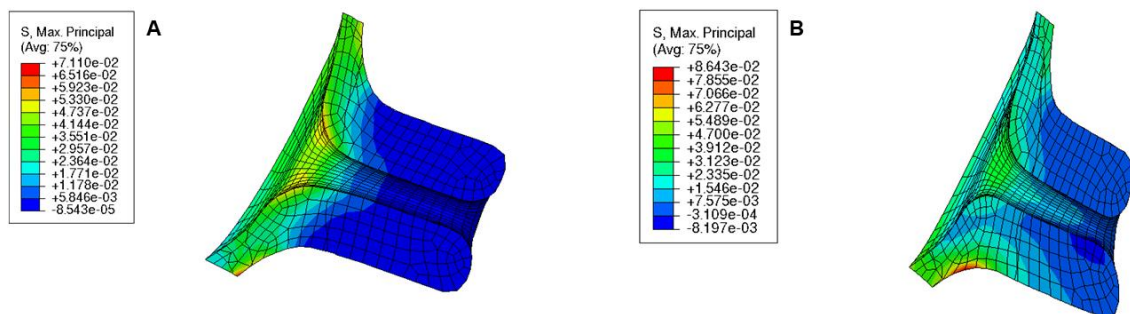


Figure 20. Maximal principal stress distribution for “Large” Shape: (A) passive soft cervix, (B) active soft cervix [units: MPa].

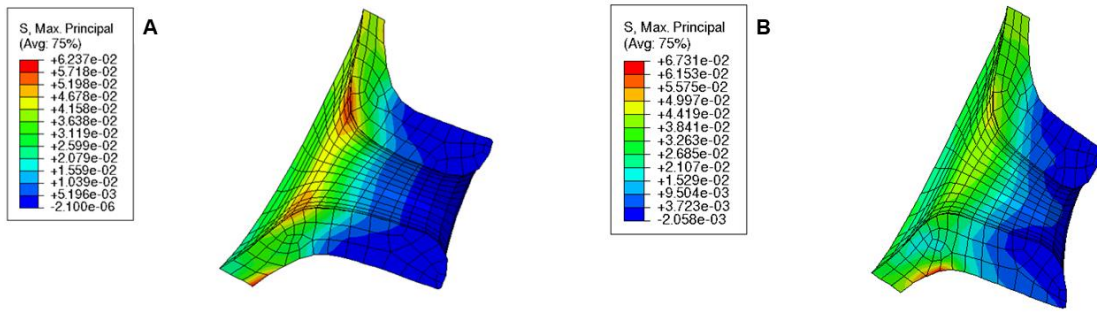


Figure 21. Maximal principal stress distribution for "Mid" Shape: (A) passive soft cervix, (B) active soft cervix [units: MPa].

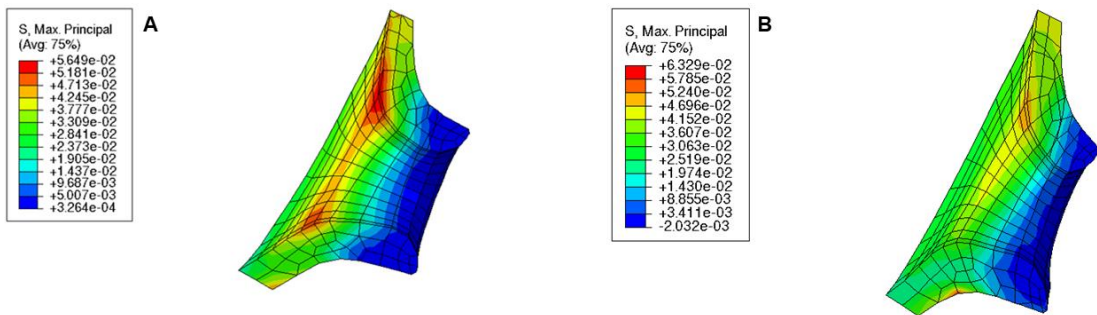


Figure 22. Maximal principal stress distribution for "Small" Shape: (A) passive soft cervix, (B) active soft cervix [units: MPa].

From the analysis of Figure 23, it is possible to affirm for all cervical shapes that active cervical contractions generally increase the absolute values of CO, CL, and CD compared to those from the passive soft cervix. CL is largely affected by cervical contractions, followed by CD and CO. As the cervix gets shorter and more dilated, the impact of cervical contraction on those measurements tends to get less significant.

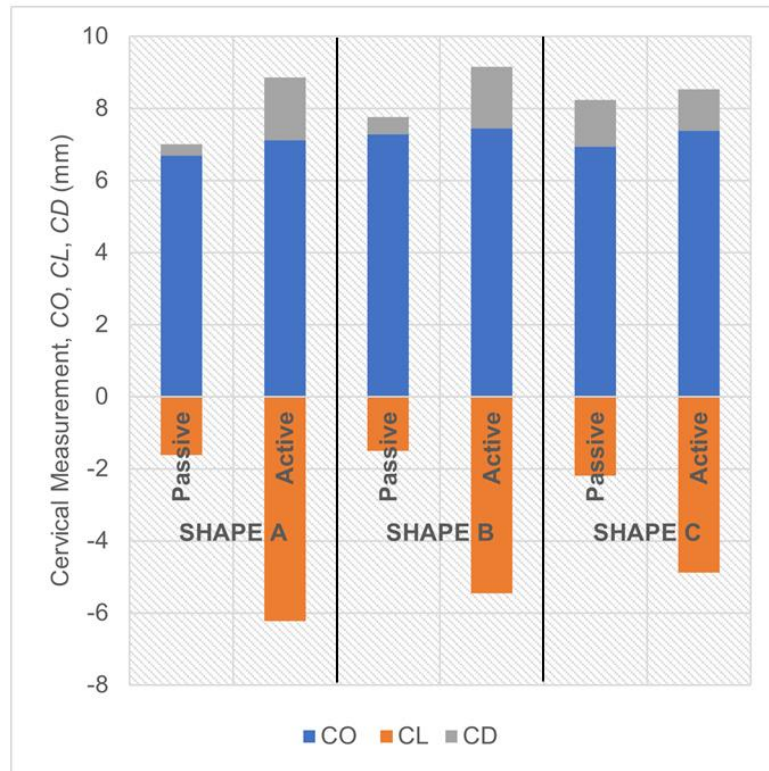


Figure 23. Variations of cervical opening (CO), cervical length (CL), and cervical dilation (CD) for different cervical shapes. “Large” Shape, “Mid” Shape, and “Small” Shape represent different cervical shapes as described in *Numerical Simulation* section, while “Passive” and “Active” represent a soft cervix with no contraction and a soft cervix contracting, respectively.

The cervical contractions do not interfere significantly with the maximum stress values verified at the “weak zone” of the amnion layer, compared to the passive soft cervixes analyzed in the *Initial cervical shape and cervical stiffness* subsection.

Intrauterine Pressure

The maximum principal stress values and distributions caused by different intrauterine pressures (IUP) are illustrated in Figure 24. As expected,

increasing the IUP leads to increased stresses within the cervix, where the internal os region is subjected to larger stresses.

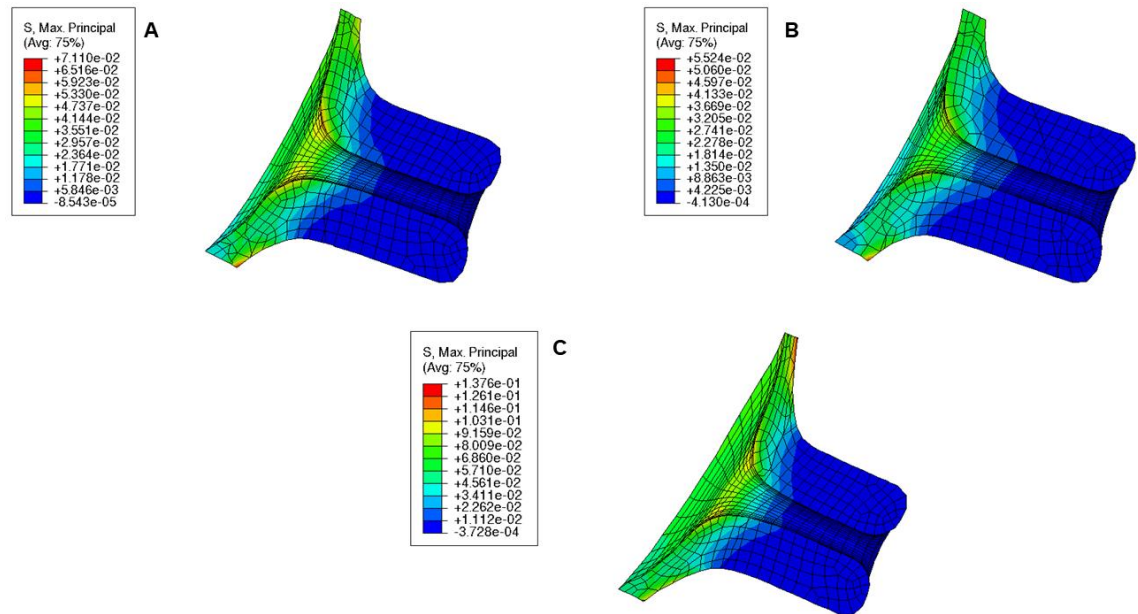


Figure 24. Maximal principal distribution in the cervix for different intrauterine pressures (IUP) values: (A) normal IUP, (B) smaller IUP, (C) larger IUP [units: MPa]. These results were retrieved using the soft cervix from “Large” Shape.

IUP largely influences CO, which experiences a large increase when IUP is elevated and a significant decrease when IUP is also decreased (Table 6). CL also experiences a similar evolution despite being less impactful. A smaller IUP does not largely influence CD, but its value increases when the pressure is elevated.

Finally, in terms of maximum principal stress at the “weak zone” of the amnion layer, the following values are retrieved for the soft cervix from “Large” Shape:

- 0.3 MPa for the normal IUP;
- 0.2 MPa for the smaller IUP;
- 2.0 MPa for the largest IUP.

Table 6. Variations of cervical opening (CO), cervical length (CL), and cervical dilation (CD) for different intrauterine pressures (IUP). “Large” Shape represents the longest and most closed cervix as described in *Numerical Simulation* section.

	“LARGE” SHAPE		
	Smaller IUP	Normal IUP	Larger IUP
CO [mm]	3.736	6.689	14.752
CL [mm]	-1.239	-1.619	-2.520
CD [mm]	0.363	0.312	0.631

Discussion

This work represents the first computational investigation of the mechanical interaction between the cervix, fetal membrane, and uterine body before the onset of labor, employing uterine and cervical contractions and various biological features, such as intrauterine pressure, amniotic fluid, and a multilayer fetal membrane. The impact of (i) initial cervical shape, (ii) cervical stiffness, (iii) cervical contractions, and (iv) intrauterine pressure was investigated on the cervix and fetal membrane in terms of maximum principal stress and cervical shape change.

Uterine contractions influence cervical remodeling in terms of shape before the onset of labor: the cervix can only dilate sufficiently upon the initiation

of uterine contractions (Timmons et al., 2010). Thus, these contractions were added to the uterine model. In our work, the maximum principal stress value in the uterine muscle was 0.091 MPa (Figure 14), and the stress values obtained were within the physiological range of a pregnant human uterine body, as reported by Blisplinghoff et al. (Blisplinghoff et al., 2012).

A multilayer fetal membrane was integrated into the gravid uterine model, comprising the amnion, chorion, and part of the decidua. The amnion was subjected to much larger maximum principal stresses than the chorion (Figure 15). Experimental studies show that the amnion is the fetal membrane's mechanically dominant layer, withstanding most loads occurring during pregnancy (Buerzle & Mazza, 2013). Moreover, the stress values for both layers share the same magnitude as other results from the literature (Verbruggen et al., 2017).

During pregnancy, the cervix goes from a closed structure to one that is soft and compliant (Kitamura et al., 2023; K. M. Myers et al., 2015; Timmons et al., 2010). It must open sufficiently for birth before the onset of labor through a remodeling process that will lead to cervical dilation and shortening (Timmons et al., 2010). Cervical insufficiency occurs when the cervix is weak and unable to remain closed until late delivery, leading to preterm birth (Wierzchowska-Opoka et al., 2021). On the other hand, a closed stiff cervix may create complications during cervical dilation and lead to failed induced labor (Mazza et al., 2014). These phenomena highlight the importance of cervical shape and stiffness to a successful vaginal delivery. According to Figure 16, Figure 17, and Figure 18,

maximum principal stress values decreased as the cervix got more dilated, shorter, and softer. Larger stresses were found in the internal os region of the cervix, where the fetal membrane was allowed to slide freely. This observation agrees with the results obtained by Paskaleva et al., where it was demonstrated that loads were concentrated in the internal os (Anastassia Paskaleva, 2007). Moreover, as cervical stiffness got smaller, cervical dilation and opening increased, and cervical length decreased, independently of the initial cervical shape (Figure 19).

A growing body of work exists on the passive behavior of the cervix, but understanding the role of the cervical smooth muscles during pregnancy has been neglected (Tantengco & Menon, 2020). It has been hypothesized that the contraction and relaxation of the cervical smooth muscle may be involved in cervical remodeling, preparing the cervix for labor (Tantengco & Menon, 2020). In this work, we investigated the impact of cervical contractions in the longitudinal direction on cervical dilation and shortening. First, the cervical contractions increased the maximum principal stress values and changed the stress distributions, interfering with the cervical deformation before labor (Figure 20, Figure 21, and Figure 22). Additionally, the cervical contraction potentiated cervical shortening and dilation, leaving the cervix more prepared for labor than the respective passive cervix (Figure 23). These results highlight the importance of cervical contractions for cervical remodeling and may offer solutions to some complications at the initial stages of vaginal delivery, such as a failed induced labor: to proceed to induction, the cervix must be dilated and short enough to use

oxytocin (Harper et al., 2012); if the cervix is not prepared, some medical alternatives are available, such as cervical ripening; however, none of the methods for cervical ripening try to stimulate cervical contractions to prepare the cervix for labor.

Intrauterine pressure (IUP) is elevated before the onset of labor due to uterine contractions (Smith, 1984). It will push the amniotic sac in the region of the cervical opening against the relaxed cervix, starting the gradual dilation (Smith, 1984). This process was verified in Figure 24 and Table 6, where larger IUP led to considerably larger stresses and cervical openings, larger dilation, and smaller cervical lengths. In clinical practice, if a small IUP is registered, cervical remodeling may be too slow. Inducing uterine contractions may elevate IUP and speed up the cervical remodeling process before labor, as shown in this work.

The rupture of human fetal membranes occurs in the cervical opening region called the “weak zone” (El Khwad et al., 2005). Biaxial strength, defined as the maximum stress at failure, was calculated experimentally through a puncture mechanical test (Oyen et al., 2004). For fetal membrane samples from labored term pregnancies, it was found that the minimum biaxial strength value was approximately 0.6 MPa (Oyen et al., 2004). According to this work, this value was only surpassed for the shortest and more dilated cervix, illustrated in Figure 18, where a value of 0.7/0.8 MPa was verified at the “weak zone”, and for a larger IUP, illustrated in Figure 24C, where a value of 2.0 MPa was observed at the same region. These results highlight the important interaction between fetal membrane rupture, cervical geometry, and IUP, and may explain the preterm premature

rupture of the fetal membrane (PPROM) in spontaneous preterm birth: in this case, cervical softening and opening, as well as uterine contractions, are verified too soon (Mercer, 2010); the premature remodeling and larger IUP caused by uterine contractions may be the cause of PPRM since those factors potentiate fetal membrane rupture according to our results.

Some simplifications were considered in this work: (i) the non-linear behavior of the chorion and the decidua was not considered in the layered fetal membrane model, since it is particularly difficult to isolate these layers for experimental testing, (ii) the poro-viscoelastic behavior of the uterus/cervix was not considered, (iii) the reference configuration is already a deformed state, (iv) collagen fiber dispersion in the uterus/cervix was neglected, and (v) only one contraction was simulated, due to computational cost.

Conclusion

This work investigated the impact of (i) initial cervical shape, (ii) cervical stiffness, (iii) cervical contractions, and (iv) intrauterine pressure on cervical shape change and membrane rupture, highlighting the important interaction between the cervix, fetal membrane, and uterine contractions. Relevant mechanical conclusions were retrieved from this work, reinforcing the importance of understanding this complex interaction to guide the clinical approach to several complications, such as failed induced labor and preterm birth.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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