Interpreting Uterine Contractions Using Physiological Models and Statistical Signal Processing

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Interpreting Uterine Contractions Using Physiological Models
and Statistical Signal Processing

by

Uri Goldsztejn

A dissertation presented to
the Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

May 2022
St. Louis, Missouri
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Figure 2.2  

(a) The APs obtained at various cells along the fiber. Downstream cells activate later in time. The AP amplitude decays slightly as it travels along the first cells and then stabilizes.  
(b) The intracellular calcium traces for the same cells as in (a). These traces present rapid upstrokes and slow decay rates.  
(c) The cellular length over time for the same cells as in (a). Cells with higher concentrations of myosin in force-producing states contract, while their relaxed neighbours dilate to satisfy the isometric condition.  
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b The average number of active electrodes during the Braxton-Hicks contractions measured in each EHG recording is shown as a solid circle.  The positive trend is statistically significant as evaluated through a two-tailed Pearson’s correlation test.  The dashed line shows the linear fit of the data points.  Each line connecting at least two data points corresponds to a different mother.  
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c, Similar to a, but using the predictions based on EHG measurements alone. 
d, Similar to b, but using the predictions based on EHG measurements alone. 
e, Similar to a, but using the predictions based on clinical information combined with EHG measurements. 
f, Similar to b, but using the predictions based on clinical information combined with EHG measurements. All values are presented as mean with 95% CI.

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List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>Action potential</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the receiver-operating characteristic curve</td>
</tr>
<tr>
<td>BPF</td>
<td>Bandpass filter</td>
</tr>
<tr>
<td>BiLSTM</td>
<td>bidirectional long short-term memory</td>
</tr>
<tr>
<td>BRTF</td>
<td>Bayesian Robust Tensor Factorization</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CP-ALS</td>
<td>Canonical polyadic decomposition - alternating least squares algorithm</td>
</tr>
<tr>
<td>CPD</td>
<td>Canonical polyadic decomposition</td>
</tr>
<tr>
<td>CV</td>
<td>Conduction velocity</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiograms</td>
</tr>
<tr>
<td>ECGI</td>
<td>Electrocardiographic imaging</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EHG</td>
<td>Electrohysterogram</td>
</tr>
<tr>
<td>EM</td>
<td>Expectation-maximization algorithm</td>
</tr>
<tr>
<td>EMMI</td>
<td>Electromyometrial imaging</td>
</tr>
<tr>
<td>FHN</td>
<td>FitzHugh–Nagumo model</td>
</tr>
<tr>
<td>FWH</td>
<td>Fast Wave High</td>
</tr>
<tr>
<td>FC</td>
<td>Fully connected</td>
</tr>
<tr>
<td>FWL</td>
<td>Fast Wave Low</td>
</tr>
<tr>
<td>GJ</td>
<td>Gap junction</td>
</tr>
<tr>
<td>HOSVD</td>
<td>Higher order singular value decomposition</td>
</tr>
<tr>
<td>HUAM</td>
<td>Home uterine activity monitoring devices</td>
</tr>
<tr>
<td>IR</td>
<td>Intercellular resistivity</td>
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<tr>
<td>IUPC</td>
<td>Intrauterine pressure catheters</td>
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<tr>
<td>IQR</td>
<td>Interquantile range</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>MLCK</td>
<td>Myosin light chain kinase</td>
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<tr>
<td>MMG</td>
<td>Magentomyography</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MSE</td>
<td>Mean squared error</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>pdf</td>
<td>Probability distribution function</td>
</tr>
<tr>
<td>PSD</td>
<td>Power Spectral Density</td>
</tr>
<tr>
<td>RMSE</td>
<td>Root mean square error</td>
</tr>
<tr>
<td>RPCA</td>
<td>Robust principal component analysis</td>
</tr>
<tr>
<td>RNN</td>
<td>recurrent neural network</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-noise ratio</td>
</tr>
<tr>
<td>SQUID</td>
<td>Superconducting quantum interference devices</td>
</tr>
<tr>
<td>STFT</td>
<td>short-time Fourier transform</td>
</tr>
<tr>
<td>TPEHGD</td>
<td>Term-Preterm EHG Database</td>
</tr>
<tr>
<td>TPEHGT DS</td>
<td>Term-preterm EHG dataset with tocogram</td>
</tr>
<tr>
<td>USMC</td>
<td>Uterine smooth muscle cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

Table 1: Abbreviations used in this dissertation.
## Glossary of Nomenclature

<table>
<thead>
<tr>
<th>Notation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I$</td>
<td>Transmembrane ion current</td>
</tr>
<tr>
<td>$g$</td>
<td>Maximal conductance for an ion current</td>
</tr>
<tr>
<td>$y_i$</td>
<td>Gating variables</td>
</tr>
<tr>
<td>$v$</td>
<td>Membrane potential</td>
</tr>
<tr>
<td>$E_{rev}$</td>
<td>Nernst potential</td>
</tr>
<tr>
<td>$R$</td>
<td>Gas constant</td>
</tr>
<tr>
<td>$T$</td>
<td>Absolute temperature</td>
</tr>
<tr>
<td>$F$</td>
<td>Faraday constant</td>
</tr>
<tr>
<td>$[X]_{out}$</td>
<td>Extracellular ion concentrations</td>
</tr>
<tr>
<td>$[X]_{in}$</td>
<td>Intracellular ion concentrations</td>
</tr>
<tr>
<td>$y_{\infty i}$</td>
<td>Steady state constant for ion channel $i$</td>
</tr>
<tr>
<td>$\tau y_i$</td>
<td>Time constant for ion channel $i$</td>
</tr>
<tr>
<td>$M$</td>
<td>Unphosphorylated myosin</td>
</tr>
<tr>
<td>$M_p$</td>
<td>Phosphorylated myosin</td>
</tr>
<tr>
<td>$AM_p$</td>
<td>Phosphorylated myosin forming crossbridges with actin</td>
</tr>
<tr>
<td>$AM$</td>
<td>Myosin in latched state</td>
</tr>
<tr>
<td>$K_{1,\ldots,6}$</td>
<td>Myosin cycling parameters</td>
</tr>
<tr>
<td>$nm$</td>
<td>Hill coefficient</td>
</tr>
<tr>
<td>$CaMLCK$</td>
<td>Half-saturation concentration of MLCK</td>
</tr>
<tr>
<td>$V(x,t)$</td>
<td>Transmembrane voltage</td>
</tr>
<tr>
<td>$I_{ion}(x,t)$</td>
<td>Ionic current</td>
</tr>
<tr>
<td>$I_{stimulus}(x,t)$</td>
<td>Injected depolarization current</td>
</tr>
<tr>
<td>$C_m$</td>
<td>Specific membrane capacitance</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Intercellular conductivity</td>
</tr>
<tr>
<td>$\chi$</td>
<td>Cell’s surface to volume ratio</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$A_{ics}$</td>
<td>Intercellular cross sectional area</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Intercellular resistivity</td>
</tr>
<tr>
<td>$K_p$</td>
<td>Parallel element stiffness constant</td>
</tr>
<tr>
<td>$\alpha_p$</td>
<td>Length modulation for passive element</td>
</tr>
<tr>
<td>$l_c$</td>
<td>Cell’s length</td>
</tr>
<tr>
<td>$l_0$</td>
<td>Length of cell at zero passive force</td>
</tr>
<tr>
<td>$l_a$</td>
<td>Length of active component of cell</td>
</tr>
<tr>
<td>$l_s$</td>
<td>Length of spring component of cell</td>
</tr>
<tr>
<td>$l_x$</td>
<td>Length of cross bridge component of cell</td>
</tr>
<tr>
<td>$l_{opt}$</td>
<td>Optimal length of active contractile component</td>
</tr>
<tr>
<td>$l_{s0}$</td>
<td>Length of series viscoelastic component at zero force</td>
</tr>
<tr>
<td>$K_{x1}$</td>
<td>Phosphorylated cross-bridge stiffness constant</td>
</tr>
<tr>
<td>$K_{x2}$</td>
<td>Latch bridge stiffness constant</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Length modulation constant for active and cross-bridge elements</td>
</tr>
<tr>
<td>$f_{AMP}$</td>
<td>Friction constant for phosphorylated cross-bridge</td>
</tr>
<tr>
<td>$f_{AM}$</td>
<td>Friction constant for latch bridges</td>
</tr>
<tr>
<td>$\nu_x$</td>
<td>Cross-bridge cycling velocity</td>
</tr>
<tr>
<td>$\mu_s$</td>
<td>Viscosity coefficient of series element</td>
</tr>
<tr>
<td>$k_s$</td>
<td>Series element stiffness constant</td>
</tr>
<tr>
<td>$\alpha_s$</td>
<td>Length modulation for series viscoelastic element</td>
</tr>
<tr>
<td>$l_{c0}$</td>
<td>Initial cell’s length</td>
</tr>
<tr>
<td>$x \in \mathbb{R}^I$</td>
<td>Column vector of length $I$</td>
</tr>
<tr>
<td>$X \in \mathbb{R}^{I_1 \times I_2}$</td>
<td>$I_1 \times I_2$ matrix</td>
</tr>
<tr>
<td>$\mathcal{X} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$</td>
<td>$I_1 \times I_2 \times \cdots \times I_N$ tensor</td>
</tr>
<tr>
<td>$\mathcal{X}_{i_1, \ldots, i_n}$</td>
<td>$(i_1, \ldots, i_n)$-th element of $\mathcal{X}$</td>
</tr>
<tr>
<td>$\text{vec}(\mathcal{X})$</td>
<td>Vectorized tensor</td>
</tr>
<tr>
<td>$\mathbb{E}_{q(\theta)}$</td>
<td>Expected value with respect to $q(\theta)$</td>
</tr>
<tr>
<td>$\mathbb{E}_{q(\theta \setminus \theta_j)}$</td>
<td>Expected value with respect to $q(\theta)$ except to $q(\theta_j)$</td>
</tr>
<tr>
<td>$\otimes$</td>
<td>Kronecker product</td>
</tr>
<tr>
<td>$\otimes_n$</td>
<td>Sequential Kronecker product</td>
</tr>
<tr>
<td>$\times_n$</td>
<td>$n$-th mode product</td>
</tr>
<tr>
<td><strong>X</strong>&lt;sub&gt;(n)&lt;/sub&gt;</td>
<td>Matrix unfolding along the n-th dimension</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>x</strong>&lt;sub&gt;i&lt;sub&gt;n&lt;/sub&gt;</td>
<td>i&lt;sub&gt;n&lt;/sub&gt;-th row vector of X</td>
</tr>
<tr>
<td><strong>x</strong>&lt;sub&gt;r&lt;sub&gt;n&lt;/sub&gt;&lt;/sub&gt;</td>
<td>r&lt;sub&gt;n&lt;/sub&gt;-th column vector of X</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>tr(A)</td>
<td>Trace operator</td>
</tr>
<tr>
<td><strong>N</strong>&lt;sub&gt;2&lt;/sub&gt;</td>
<td>The set of natural numbers larger than or equal to two</td>
</tr>
<tr>
<td>N</td>
<td>Number of samples</td>
</tr>
<tr>
<td><strong>w</strong>&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Penalization weight of class i</td>
</tr>
<tr>
<td><strong>T</strong>&lt;sub&gt;n&lt;/sub&gt;</td>
<td>Label of sample n</td>
</tr>
<tr>
<td><strong>y</strong>&lt;sub&gt;n&lt;/sub&gt;</td>
<td>Score of sample n</td>
</tr>
<tr>
<td><strong>S</strong>&lt;sub&gt;i&lt;/sub&gt;</td>
<td>Number of samples from class i</td>
</tr>
<tr>
<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Coefficient of determination</td>
</tr>
</tbody>
</table>

Table 2: Nomenclature used in this dissertation.
Acknowledgments

Throughout my doctoral work, I have received invaluable support and assistance, for which I am very grateful.

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Uri Goldsztejn

Washington University in St. Louis
May 2022
Dedicated to my parents.
Pregnancy and labor are important stages in every mother and child’s life. Unfortunately, complications during pregnancy and labor are common. Every day, globally, about 800 mothers and 7000 newborns in their first month of life die from medical complications. Additionally, these complications result in about 5000 stillbirths daily around the world. Preterm births, labor dystocia, and postpartum hemorrhage are leading causes of maternal and child morbidity and mortality and are associated with inappropriate uterine contractile activity. Preterm births, i.e., those that occur before completing 37 weeks of gestation, are a leading cause of child morbidity and mortality. Preterm birth are a major health burden since about 10% of all births are preterm. Labor dystocia refers to labors that progress slowly. Labors may progress slowly because the uterine contractions are too weak to deliver the child. Slowly progressing labors are associated with various medical complications including infections, neonatal distress and asphyxia, and uterine rupture. Postpartum hemorrhage
Various technologies and treatments have been developed to predict uterine contraction disorders and to improve their outcomes. These technologies include devices for monitoring uterine contractions and biochemical tests that infer uterine conditions. The drugs used to treat these conditions usually regulate uterine activity by modulating the ion currents responsible for uterine contractions. However, these technologies and treatments have limited efficacy. Moreover, these treatments can have serious side effects and cause additional medical complications. Two important limitations on developing safer and more efficient technologies and therapies for these conditions are our incomplete understanding of uterine electrophysiology and the difficulty of measuring uterine activity accurately.

Here, we developed a uterine muscle fiber model and a statistical tensor decomposition method to address these limitations. Our fiber model incorporates various models of uterine cellular functions and a novel set of differential equations that simulates how the electrical and mechanical activities propagate along a uterine fiber. Using this model, we investigated how cellular excitability and intercellular coupling regulate electrical conduction and contractile force generation in uterine fibers. Among other observations, we found that cellular coupling plays a major role in regulating contractile force generation. We observed that if the cells are well coupled, then the fiber can generate a stable tension. However, the fiber may not generate significant force when cellular coupling is low.

We developed a statistical tensor decomposition method to estimate uterine activity more reliably. Electrohysterogram (EHG) recordings measure uterine electrical activity noninvasively using abdominal electrodes. EHG measurements are compelling because they capture
informative physiological activity and can be used to develop portable applications for monitoring uterine activity. However, localized electrical activity in the uterus generates distributed electric potentials at the abdomen. Furthermore, EHG measurements also record electric potentials that originate from other sources besides the uterine section directly below the electrodes. Our method estimates the localized uterine electrical activity reliably based on a statistical generative model. We assessed the performance of our method using simulated and real EHG measurements. Then, using our method and two public EHG databases, we found that the fraction of the myometrium that is recruited during contractions is a potential biomarker to monitor uterine contractions. We found that the fraction of the myometrium recruited during contractions is higher in pregnant mothers who eventually delivered preterm than in those who delivered at term. Moreover, we show that this metric increases towards labor and that it may be used to monitor labor contractions.

Our results at the fiber level and at the whole organ level suggest that uterine coupling is an important characteristic of uterine contractions that can be used for monitoring and treating abnormal contractions. Our work advances our understanding of uterine electrophysiology and contributes to the development of better technologies and more efficient drugs to monitor and regulate uterine contractions.

Lastly, we develop a machine learning model to predict preterm births based on clinical information and EHG measurements. Although imminent preterm birth can be predicted about one week in advance in mothers with symptoms of preterm labor, predicting preterm birth more than one week in advance in asymptomatic mothers remains elusive. EHG measurements have been proposed to identify pregnant mothers at high risk of preterm labor. However, the predictive accuracy obtained using EHG measurements is limited. Here, we
developed a machine learning model that predicted preterm birth directly from EHG measurements more accurately than existing models. Our model and results advance the research efforts for developing a screening tool to identify pregnant mothers at high risk of preterm birth, facilitating targeted treatments to reduce the incidence of preterm birth and improve the outcomes.
Chapter 1

Introduction

1.1 Motivation

Complications during pregnancy and labor are frequent [53, 61]. Every day, about 800 mothers die from preventable complications related to pregnancy and childbirth worldwide [155]. Preterm births, i.e., those that take place before completing 37 weeks of gestation and are a main cause of mortality and long-term morbidity, are increasing and treatment options are limited [24, 154]. In addition, about 40% of all labors progress slowly and are assisted with oxytocin [242]. Moreover, about 5% of all labors lead to postpartum hemorrhage, which is a leading cause of maternal mortality in low-income countries [47].

Whereas many treatments have been developed to manage these medical conditions, the safety and efficacy of these treatments is limited. For example, some of these treatments have been discontinued because they showed no benefit in large clinical trials [40, 41, 89, 165]. Additionally, oxytocin, a hormone used to induce labor and stop postpartum hemorrhage, consistently ranks among the top medications involved in malpractice and medical litigation [50, 114].

Poor pregnancy and labor care has negative implications for newborns, their families, and societies. Preterm births and intrapartum complications, mainly birth asphyxia, are leading causes for neonatal death [153]. Moreover, many preterm babies who survive suffer from permanent disability, including learning disabilities and neurological problems [154, 220].
Since about 10% of all births worldwide are preterm and up to 15% of births in very low-income settings result in fetal asphyxia, improving pregnancy and labor care is a major global health priority [2, 154].

Pregnancy and intrapartum complications can also have dire consequences for families. About 300,000 mothers die during pregnancy and birth per year, mostly in low-income areas [155]. In high-income areas, these complications add financial burdens to expecting families [53]. Moreover, pregnancy and labor complications cause emotional distress in expectant families [66, 141].

Pregnancy and labor complications impose a burden on societies. This burden results from maternal and fetal morbidity and mortality which limit the potential contributions throughout life of mothers and their babies to societies [138]. The United Nations recognized this need and many of their targets for sustainable development are directly related to improving pregnancy and labor [32].

1.2 Technologies for Uterine Contraction Monitoring

The uterus continuously adapts to accommodate a growing fetus and to deliver it eventually. In the last trimester of pregnancy, the uterus becomes electrically active in preparation for labor, and pregnancy contractions, known as Braxton-Hicks contractions, begin [73]. In particular, the myometrium, which is the uterine muscle responsible for contractions, remains quiescent during the first two trimesters of pregnancy and becomes active around the beginning of the last trimester of gestation [73]. This transformation is mediated by multiple interconnected factors. Notably, the uterine smooth muscle cells (USMC), which form the myometrium, become electrically excitable and couple together to form continuous regions of excitable muscle. These changes are brought about by gene expression changes that regulate ion channels and gap junctions [100, 184]. These processes are altered in uterine contraction disorders, including preterm births, slow progression of labor, and postpartum hemorrhage [21, 27, 79, 157, 181]. Therefore, these processes are targeted with drugs to improve pregnancy outcomes. Moreover, the uterine electromechanical activity that results from these processes can be monitored to diagnose uterine contraction disorders.
Many technologies have been developed to diagnose uterine contraction disorders; however, they have limitations. These technologies measure different physical phenomena that are associated with uterine activity including uterine pressure, as in the case of tocodynamometers and intrauterine pressure catheters (IUPC); biochemical changes, as in the case of fibronectin alpha; magnetic activity, as in the case of magnetomyograms (MMG); or electrical activity, as in the case of electrohysterograms (EHG) and electromyometrial imaging (EMMI). We describe these technologies and their limitations in the rest of this subsection.

Tocodynamometers are amongst the simplest technologies to monitor uterine contractions. Tocodynamometers are force sensors that are attached around a pregnant mother’s abdomen with a belt. These devices are used to record tocograms, which show the uterine pressure generated during uterine contractions. Tocograms are currently used during labor, in conjunction with fetal electrocardiography, to assess fetal well-being and identify possible fetal hypoxia [178]. At their inception, tocodynamometers were used to develop home uterine activity monitoring devices (HUAM) with the aim of identifying mothers at high risk of preterm births. However, these devices proved unable to predict preterm births, and the American College of Obstetricians and Gynecologists does not recommend their use for preterm birth prediction [165].

Another technology to monitor uterine pressure is IUPCs. IUPCs are placed inside the uterus transvaginally and provide accurate measurements of contraction strength, frequency, and duration. However, these devices are invasive and can cause maternal complications [97, 168]. Therefore, they are only used during slowly progressing labors in which an objective measurement of uterine activity is needed during labor augmentation.

Various biochemical changes occur before labor that can be used to predict birth. Notably, fetal fibronectin is the standard biomarker for preterm birth. Fetal fibronectin is a glycoprotein produced by fetal membranes and its presence in the vagina between the 20th and 34th week of gestation is a predictor of preterm birth [166]. Fibronectin presence in the vagina is measured using vaginal swabs. This test is indicated for women with threatened preterm labor [80]. However, fibronectin tests can only predict preterm births within one week from when the test is performed and achieve an area under the receiver-operating characteristic curve (AUC) of 0.78 (95% CI 0.73–0.84) [1]. Hence, this test is only useful to detect imminent preterm births and its accuracy is not optimal.
Uterine activity results from electrical currents that generate magnetic potentials that can be used to monitor uterine contractions. MMG measurements record this magnetic activity and have been useful to understand how uterine contractions evolve during pregnancy [59]. The electrical currents that propagate along uterine myofibers and induce myometrial contractions generate magnetic fields, which can be modeled by the Ampère-Maxwell law. These magnetic fields can be recorded noninvasively using superconducting quantum interference devices (SQUID) and are useful for uterine contraction monitoring. MMG measurements have been used for a range of applications, including predicting imminent term and preterm births, localizing and tracking the magnetic activity associated with uterine contractions, and for investigating the evolution of uterine contraction patterns towards labor [58, 83, 243].

A major advantage of magnetic over electrical measurements is that magnetic recordings achieve a higher spatial resolution because magnetic fields have a sharper spatial decay than electric fields. However, MMG measurements require an electromagnetically shielded room and SQUID sensors, making this system impractical for widespread use.

EHG recordings also measure electric potentials associated with uterine contractions. EHGs are measured noninvasively using electrodes placed over pregnant mothers' abdomens. EHG measurements are compelling because they capture valuable physiological information and can be implemented with portable devices. Over the past decades, EHG measurements have been used to study the electrophysiological changes that precede labor and to probe labor contractions [112]. More recently, EHG recordings have been used to develop practical applications such as predicting premature births and estimating intrauterine pressure during contractions [110, 185]. Additionally, many signal processing and machine learning methods for EHG analysis have been developed over the past decade. This increase in EHG research has been stimulated by two main factors: the surge in research and development of wearable technologies based on biosignal data analysis, and the availability of public datasets of EHG recordings [6, 62, 110].

Although EHG recordings are a promising technology to improve pregnancy outcomes, analyzing these measurements has been challenging. Some of the challenges of analyzing EHG measurements are inherent to the recording technology, whereas others stem from the complexity of uterine anatomy and physiology. The uterine ionic currents responsible for uterine contractions are usually diffused throughout the myometrium and have low amplitudes [112]. Therefore, EHG measurements, which are recorded noninvasively at a distance from
the sources, tend to have low signal-to-noise ratios (SNR) and low spatial resolutions [5]. Moreover, uterine anatomy and electrophysiology are very variable, both among different pregnant mothers and for the same pregnant mother over time. For example, consecutive uterine contractions in the same mother may neither originate from the same area in the myometrium nor propagate with the same pattern [60, 133].

More recently, electromyometrial imaging (EMMI) was developed to address some of the limitations of EHG measurements. This technology integrates magnetic resonance imaging (MRI), which can reconstruct the abdominal anatomy of a pregnant woman, with close to 200 electrodes placed on her torso that measure the electrical activity generated over the entire myometrium [222, 228]. This technology can estimate the propagation of uterine electrical activity reliably and is currently used to study uterine electrophysiology. However, this imaging modality is complex and cannot be easily implemented as part of routine pregnancy examinations. Additionally, it is still unclear whether the improved imaging capabilities obtained with EMMI can translate into better diagnostic capabilities.

1.3 Biological Mechanisms of Uterine Electrophysiology

In this section, we will first detail the current understanding of the physiological mechanisms responsible for uterine contractions. Then, we will present some fundamental questions about these mechanisms that are still unanswered and the work being done to address them.

1.3.1 Physiology of Uterine Contractions

Spontaneous labor results from the coordinated activity of three important mechanisms: rupture of fetal membranes, which is mediated by degrading enzymes; cervical ripening, which opens a channel to deliver the fetus and creates a singularity point for electromechanical uterine activity; and strong uterine contractile activity, which is the focus of this dissertation [148].
Multiple components contribute to the generation of uterine contractions. Hormones are a main regulator of uterine activity. Progesterone promotes a quiescent uterine state by regulating many cellular components responsible for excitability and electrical conduction [187]. In particular, progesterone has been shown to prevent gap junction formation and to regulate ion-channel expression to prevent action potential (AP) formation [10, 234]. On the other hand, oxytocin promotes labor contractions through multiple mechanisms, including increasing intracellular calcium concentrations [10, 105, 137, 218]. As pregnancies approach normal labor, the influence of progesterone on the uterus decreases, while oxytocin production increases [148].

In clinical settings, progesterone is used to prevent preterm births in mothers at risk of preterm birth or with a clinical history of recurrent preterm births [131, 132]. Conversely, oxytocin is used to induce labors, enhance labor contractions during slowly progressing labors, and to stop postpartum hemorrhage [31, 101, 224].

Uterine contractility is further regulated by anatomical changes, prostaglandins, inflammation activity, and stretch-activated ion channels. These mechanisms have been reported and reviewed elsewhere and are beyond the scope of this dissertation [113, 136, 152, 182, 201, 221].

Uterine contractions result from changes in the electric potentials of USMCs’ membranes, known as action potentials. When a USMC is depolarized beyond a threshold by an external stimulus, such as ions flowing from an upstream cell, calcium channels open and calcium ions flow into the cell. This calcium current further depolarizes the cell and generates a membrane voltage upstroke. After this initial upstroke, potassium channels activate and create an efflux of potassium ions, which restores the resting membrane potential. Finally, cell membrane transporters restore the resting intracellular ion concentration [176, 236].

During action potentials, the transient increase of intracellular calcium concentration activates a series of cascaded signaling pathways that results in the activation of myosin light chain kinase (MLCK). MLCK, in turn, promotes the formation of cross bridges between myosin and actin. These cross bridges generate contractile force that contracts the cell [225]. Intracellular calcium concentrations are further regulated by the sarcoplasmic reticulum, which is described in detail in [227].
Action potentials travel across the myometrium. During each action potential, the excess positive ions in each cell diffuse to neighboring cells through gap junctions [134]. Gap junctions are molecular channels that connect adjacent cells. This flow of ions serves as a depolarizing stimulus that can generate action potentials. This mechanism coupled with refractory periods, which prevent successive action potentials with short temporal separation in the same cell, enables action potentials to travel across the myometrium.

In normal labor contractions, the entire myometrium contracts in a coordinated fashion. Trains of spiked, or plateaued-type, action potentials travel across the myometrium and progressively increase intracellular calcium concentrations to generate strong contractions, which last around one minute [202]. As cells contract, they increase the intrauterine pressure to deliver the fetus. The relationship between the wall tension generated by cellular contraction and the intrauterine pressure can be modeled using Laplace’s law [16].

1.3.2 Unresolved Questions of Uterine Electrophysiology

Our ability to monitor uterine contractions and develop clinical applications is limited by insufficient understanding of how uterine contractions start and propagate [240]. Identifying the triggers of uterine contractions and the mechanisms that regulate how uterine activity propagates through the myometrium could be useful to design better therapies to regulate contractions and more accurate technologies to monitor them.

Uterine contractions are thought to be coordinated though a mechanotransduction mechanism [240]. Previously, researchers have hypothesized that contractions either start from a single spike impulse generator, similar to the sinoatrial node in the heart, or from multiple slow-wave generators, akin to the pacemakers in the gastrointestinal tract, and then propagate across the myometrium [43, 240]. However, pacemaker regions have not been identified in the uterus so far. More recent experimentation by Young and Goloman and others showed that the uterus can coordinate contractile activity exclusively through mechanical feedback [238]. This line of thought was pioneered by Takeda in 1965, when he showed that a rat uterus cut in half could contract in a coordinated fashion when the two halves were mechanically connected, but the two halves contracted independently when the mechanical connection was removed [196].
Currently, uterine contractions are thought to be orchestrated by an electromechanical positive feedback loop. Experimental evidence shows that action potentials only travel a few centimeters in the myometrium [237, 240]. This propagation is thought to create a small increase in intrauterine pressure and, following Laplace’s law, in wall tension. This additional wall tension is believed to trigger cells in the myometrium to generate more action potentials through stretch-sensitive ion channels. These new action potentials would further increase the uterine pressure and create a positive feedback loop. However, further evidence is required to validate this theory.

Additionally, whereas many elements responsible for smooth muscle cell excitation, contraction, and propagation have been identified, and their properties in isolation have been quantified, the interplay between their dynamics is not fully understood. Understanding the dynamics of this system is also important to develop safer and more efficient therapeutics. We will describe these elements in detail and explore their interactions in Chapter 2.

Finally, much effort is invested into understanding the pathophysiology of uterine electrophysiology [226]. In particular, to develop safer and more efficient therapeutics for uterine contraction disorders, it is crucial to investigate the causes and risk factors responsible for premature labors, labors that progress slowly, and pregnancies that fail to initiate labor spontaneously.

1.4 Challenges for Developing Applications to Monitor Uterine Contractions

In this section we will describe the general challenges for developing applications to monitor uterine contractions and the current directions of research. Then, in the next section, we will outline the specific challenges that we addressed.

Developing clinical applications based on uterine contraction monitoring is also challenging because of the limitations of existing methods for analyzing uterine activity. These applications generally begin by measuring physical phenomena generated by uterine contractions such as the electrical activity associated with uterine contractions, as in the case of EHG
and EMMI; the pressure generated by myometrial contractions, as in the case of IUPCs and
tocograms; or the magnetic activity associated with uterine contractions, as in the case of
MMG. Next, the segments of the entire measurements that contain uterine activity are iden-
tified. In the case of multi-sensor measurements, it is also necessary to identify the subset of
sensors that capture uterine activity. Then, a set of signal features and physiological param-
eters are calculated and used to infer uterine properties that have clinical or investigational
value [193, 230].

Whereas much research effort has been devoted to address the challenges associated with
each of these steps, open challenges remain. The first question is how to measure uterine
activity optimally in terms of obtaining the most informative recordings, ideally using a
simple device that be widely implemented. Among the aforementioned technologies, EHG
measurements are at the center of current research and innovation because of they can be
recorded using simple electrodes and capture valuable physiological information.

Designing EHG measurement systems that maximize the information recorded using a sim-
ple device that can be deployed in clinical settings is a priority. For example, how many
electrodes to use, where to position them, and which type of electrodes to use for optimal
acquisition results is unclear. The largest public EHG database, developed by Fele-Zorž et
al., was acquired using just four unipolar electrodes positioned on the corners of a 7-cm wide
square, centered at the navel of pregnant mothers [62]. Whereas this configuration is very
simple, it has enabled numerous researchers to identify biomarkers and to develop prediction
algorithms for preterm birth. Alexandersson et al. used an expanded grid of four-by-four
unipolar electrodes, positioned below the pregnant mothers’ navels, centered on the median
axis of the uterus, and with an interelectrode separation of 1.75 cm [6]. This larger config-
uration has enabled researchers to explore uterine connectivity and electrical propagation,
which are useful to characterize uterine contractions. Wu et al. further expanded the con-
cept of multielectrode recordings to develop EMMI using close to 200 unipolar electrodes
[228]. This technology further enables researchers to record electrical activity from the entire
uterus with high spatial resolution.

On the other hand, various researchers proposed bipolar and other electrode configurations
to obtain more informative recordings. For example, Gao et al. and Athira and Asmi showed
that bipolar EHG recordings have better spatial resolution and discriminative power than
unipolar recordings [12, 71]. Moreover, Gao et al. and Alberola-Rubio et al. showed that Laplacian electrode configurations can further enhance the spatial resolution and classification ability of EHG recordings [5, 71]. Further computational and experimental studies are needed to determine the optimal EHG recording configuration that maximizes information content and implementation ease. Optimal experimental design approaches can be useful to address this challenge.

The next problem for developing applications for uterine contraction monitoring is localizing uterine activity in time and in space. Some researchers use manual annotations of uterine contractions [110]. Although manual annotations provide accurate segmentations of contraction bursts in EHG recordings, this approach is too time consuming for practical applications. Other researchers developed various algorithms for automatic uterine contraction activity segmentation. For example, La Rosa et al. developed a segmentation algorithm for MMG recordings based on a change point estimator and a clustering algorithm [119]. This algorithm is able to identify uterine contractions accurately in MMG recordings. However, MMG measurements have higher SNRs than EHG measurements, which facilitate activity segmentation. More recently, additional methods have been developed for uterine segmentation in EHG recordings. For example, Tyclz et al. leveraged the correlations between multiple EHG electrodes to identify uterine contractions [207]. Additionally, Hao et al. used a transfer learning approach to classify segments containing uterine contractions and baseline activity [96].

Despite the efforts to develop automatic contraction segmentation algorithms, this problem has not yet been fully addressed. Some of the challenges for this task result from the difficulty in obtaining reliable ground truth segmentations. Ground truth indications of uterine activity can be obtained using simultaneously recorded tocograms [110]. However, tocograms measure the mechanical rather than the electrical activity, and therefore the start and end points of activity across modalities do not necessarily coincide. Moreover, uterine electrical activity, especially during early pregnancy, may not generate sufficient force to be recorded by tocograms. Alternatively, ground truth segmentations can be obtained by annotating when the mothers perceive abdominal pressure [6]. This approach, however, is not useful to identify the beginning and end times of the contraction activity and, more importantly, sometimes the mother may confuse uterine contractions with fetal movements.
Differentiating uterine contractions from fetal movements in EHG recordings is complicated and has not been addressed thoroughly in the literature.

Besides temporal segmentation of uterine activity, it is necessary to localize uterine activity in space. Uterine electrical activity propagates through the myometrium and, particularly during pregnancy, may not be generated by the entire myometrium. For example, Escalona-Vargas et al. observed that not all sensors positioned over a pregnant mother’s abdomen measure electrical activity during contractions, so they calculated electrical activity propagation speed by considering only those contractions that recruit more than 20% of the sensors [56]. Additionally, Nader et al. and Zhang et al. used source localization methods to estimate the spatial distribution of uterine activity [143, 243]. Spatio-temporal localization of uterine electrical activity will be discussed in further detail in Chapter 3.

The next step to develop applications for monitoring uterine contractions is identifying informative signal features. Numerous researchers have identified signal features in the spectral domain which are useful to differentiate non-labor from labor contractions and to predict preterm labors. These features usually include peak, median, and centroid frequencies of different frequency bands [193, 230]. Alternative features include synchronization indexes, non-linear correlations, sample entropy metrics, conduction velocities, and instantaneous frequencies [110, 129, 160, 198]. Many of these features have shown good classification performance for multiple birth-related tasks. Although some studies have been criticized for using small datasets or for methodological flaws, growing evidence suggests the utility of EHG-derived features to diagnose and predict birth related medical conditions [109, 214]. The growing literature in this field suggests that machine learning approaches, coupled with large EHG databases, will soon be used to diagnose pregnancy and labor conditions in the clinic. We will discuss this avenue of research in further detail in Chapter 4.

1.5 Summary of Doctoral Work

In the next subsections, we summarize the contributions of my doctoral work. These contributions are organized according to the publications that resulted from this work and will be discussed in further detail in the next Chapters.
1.5.1 Excitation and Contraction of Uterine Smooth Muscle Cells

The myometrium transforms throughout the last months of pregnancy in preparation for labor, when strong and rhythmic contractions expel the fetus [73]. However, this process may proceed abnormally and lead to uterine contraction disorders, including preterm births, slow progression of labor, and postpartum hemorrhage, which are associated with increased morbidity and mortality for the mother and for the newborn.

Various pharmaceutical treatments are available to treat these disorders [10]. However, these drugs have limited efficacy and frequent serious side effects. For instance, tocolytic drugs have been developed to arrest uterine contractions and delay labor. Tocolytic drugs are currently prescribed to mothers with confirmed preterm labor with the aim of delaying their labors for up to a few days. These drugs are used in conjunction with therapies and drugs that prepare the fetus for birth, including corticosteroids that prepare the newborns’ lungs to breathe and neuroprotective drugs that mitigate neurological damage from premature birth. Additionally, the birth delay obtained with tocolytic drugs facilitates logistical arrangements, such as scheduling a birth in a hospital with a neonatal intensive care unit (NICU). Together with these treatments, tocolytic drugs reduce the morbidity and mortality of preterm births. However, these drugs are not able to prevent preterm births altogether and are associated with various maternal and fetal side effects, including tachycardia, myocardial ischemia, nausea, hallucinations, lethargy, and even death [42, 90].

Another class of drugs used to treat uterine contraction disorders are uterotonic agents, which invigorate uterine contractions, and are used to induce labor, to accelerate slowly progressing labors, and to stop postpartum hemorrhage [31, 101, 224]. One of the most common uterotonic agents is the hormone oxytocin. Although these drugs routinely facilitate labors and reduce mortality associated with labor complications, they are responsible for numerous side effects. Side effects include nausea, tachycardia, and severe headache [171]. Moreover, oxytocin misuse can lead to serious complications including uterine rupture and fetal asphyxia. Oxytocin is a widely used drug and, unfortunately, oxytocin misuse is frequent [50]. Every year, oxytocin ranks amongst the top medications associated with medical malpractice and litigation [50].
To develop safer and more effective drugs to treat uterine contraction disorders, we need to understand the cellular mechanisms targeted by these drugs. These drugs mostly target membrane proteins of USMCs which are responsible for electrical excitability, impulse propagation, and contractile force production. The cellular targets of these drugs include ion channels, gap junctions, and cellular components associated with the actin-myosin machinery [10].

While various experimental and computational studies have investigated cellular-level and whole-organ level properties of excitation, propagation, and contraction, the fiber and tissue-level dynamics have not been explored in depth. For instance, Tong et al. and Testrow et al. developed very detailed ion channel models for USMCs based on a plethora of experimental observations that recapitulate many properties of USMC excitability [200, 202]. On the other hand, La Rosa et al. and Yochum et al. developed whole organ uterine models, which are useful to investigate global properties of uterine conduction and to solve forward and inverse problems of uterine electrophysiology [118, 235]. However, detailed fiber- and tissue-level models to investigate the interplay between cellular components and electromechanical dynamics are needed.

In Chapter 2, we describe our myofiber model, which recreates electromechanical propagation along a string of USMCs. We also describe the insights on uterine excitation-contraction dynamics we derived using our model. Briefly, we developed a set of differential equations to model how action potentials propagate and generate contractile force in a myofiber composed of cells concatenated longitudinally. Our model expands the single-cell ion-channel model introduced by Tong et al. and the single-cell contractile force models developed by Hai et al. and Yang et al. to include the interactions between adjacent cells [94, 202, 232]. Our work is detailed in Goldsztejn and Nehorai [81]. In addition, our model is publicly available online to facilitate further experimentation and research.

Using our model, we studied the effects of cellular coupling and excitability on conduction velocity and force production. We found that as long as electrical conduction is not blocked, the force generated by myofibers is robust to intercellular coupling. Moreover, we suggested a cellular mechanism to explain this phenomenon. Additionally, we observed that intercellular coupling is the main regulator of conduction velocity and that the transient calcium current ($I_{CaL}$) is an important regulator of force production.
Our observations suggest that the force generated by a myofiber has a binary behavior. If the entire myofiber is recruited, then a high contractile force is generated. In contrast, if the electrical activity does not propagate along the entire fiber, then almost no force is generated. In Chapter 3, we will show that this effect translates to whole-organ in-vivo behavior.

1.5.2 Measuring electrical propagation in the uterus via statistical tensor decomposition of abdominal electric potentials

EHG measurements record the electrical activity associated with uterine contractions non-invasively and are useful to develop monitoring applications for uterine contraction disorders. Numerous researchers have shown how EHG measurements can be useful to diagnose preterm births, predict imminent labor, and monitor labor contractions [46, 110, 198]. More recent studies suggest that EHG recordings can also be used to identify fertility disorders, endometriosis, and painful menstruation cycles, known as dysmenorrhea [175].

However, a fundamental problem for analyzing EHG measurements is that localized electric sources in the myometrium generate diffuse electric potentials on the abdomen. Therefore, recovering the uterine sources that generate abdominal electric potentials is an ill-posed problem, especially when the number of electrodes on the abdomen is small [240].

The problem of localizing uterine electrical sources has been tackled using two approaches: developing more complex measurement systems, such as MMG and EMMI, and developing specialized computational methods. Complex measurement systems capture more information to reduce the ill-posedness of this problem, but cannot be easily implemented for widespread use. Computational methods based on connectivity measures, such as correlations, phase synchronization, and mutual coherence, have been proposed to analyze EHG measurements and infer patterns of propagation of uterine electrical activity [52, 198]. However, these methods provide only quantitative metrics rather than estimating the underlying electrical activity. Moreover, these methods were originally devised for pairs of electrodes and then expanded to multielectrode grids, and therefore do not fully exploit the spatial information encoded in multielectrode EHG recordings.
To estimate the localized electrical activity in EHG measurements, we developed a Bayesian tensor decomposition method. Our method estimates the localized and distributed components of multielectrode EHG measurements. We first developed a hierarchical tensor model of EHG measurements. Then, we used variational inference to estimate the latent variables of our model that maximize the posterior probability of the model parameters given the EHG measurements.

Our method is based on two main assumptions. We assume that the localized electrical activity is sparse in time and space because uterine contractions are confined in time and because the entire myometrium does not necessarily activate simultaneously. We also assume that the distributed electrical activity, which results from the noninvasive nature of the measuring modality, has low-rank dynamics because localized electrical sources generate diffuse electric potentials at a distance, which have low spatial variation.

Using our method and two public EHG datasets, we show that the number of active electrodes during uterine contractions, which is a surrogate for the fraction of the myometrium recruited during those contractions, is useful for contraction monitoring. Specifically, we found that the number of active electrodes during contractions is higher during pregnancies that resulted in preterm births, increases towards term labor, and may be used to monitor the efficiency of labor contractions to regulate oxytocin administration.

1.5.3 Predicting preterm births from electrohysterogram measurements via deep learning

Uterine electrical activity has been proposed to be predictive of preterm births and we explore this potential application in Chapter 4 [110, 230].

About one in ten babies is born preterm, which can result in permanent neurologic deficit and is a leading cause of child mortality [220, 154]. Moreover, preterm babies usually require NICU stays, imposing further emotional and financial burdens on families [154]. Therefore, preterm birth is an important public health problem.

Although various technologies have been proposed for predicting preterm births and imminent preterm labor can be detected, predicting preterm births more than one week in
advance remains elusive [151]. Currently, imminent preterm labor is detected using cervical length measurements and biochemical tests [151, 102, 189]. However, these technologies are not sufficiently accurate to screen the general population of pregnant mothers for risk of preterm birth.

Various researchers have proposed different biomarkers derived from electrical measurements of uterine activity to predict preterm birth [104, 110, 230]. Although the literature reports that uterine electrical activity evolves towards labor and can be used to anticipate labor, the evidence supporting that EHG measurements can predict preterm births is inconclusive [213, 214].

In Chapter 4, using deep learning algorithms trained on EHG recordings and clinical information from two public datasets, we show that, even without symptoms of preterm labor, preterm births can be predicted for pregnant mothers around their 31st week of gestation.

Our results shown in Chapter 4, support using EHG measurements to supplement existing technologies to predict preterm births, prompting beneficial treatments to reduce the incidence of preterm births and improve their outcomes [154].

1.6 Summary of Contributions

We contributed to better understanding the cellular mechanisms behind uterine contractions. Our myofiber model is useful for exploring uterine excitation-contraction dynamics and we made it publicly available to foster further related research. Using our model, we elucidated various properties of electrical propagation and force production in uterine fibers. Moreover, we explored the interplay between multiple cellular elements responsible for uterine contractions. Importantly, we identified intercellular coupling as a fundamental regulator of excitation and contraction.

Intercellular coupling, mediated by gap junctions, is an important factor of uterine contractions and a potential target for drug development. In Goldsztejn and Nehorai, we show that intercellular coupling determines how far action potentials can travel across the myometrium.
Only when action potentials can traverse an entire muscle fiber do they generate contractile force. This mechanism is modulated by progesterone, which reduces intercellular coupling [10]. Progesterone is a hormone that promotes a quiescent uterine state and is used to delay births in women at high risk of preterm births. On the other hand, many tocolytic and uterotonic drugs work by altering calcium handling dynamics in uterine muscle cells [9, 74, 218]. Therefore, our observations suggest that combination drugs which target both calcium-handling dynamics and intercellular coupling may be more efficient in regulating uterine contractions.

Our fiber model and results can be useful to develop safer and more efficient drugs to regulate uterine activity. Our model, which is publicly available, can be used to test hypotheses and to investigate mechanisms of uterine excitation and contraction \textit{in-silico}, thus contributing to the research efforts to develop safer and more effective drugs to act on the myometrium. Additionally, our observations elucidate various behaviors of uterine fibers. These observations are useful to understand experimental observations and to identify targets for drug development.

Ultimately, our model may contribute to develop new drugs to delay preterm births, facilitate labor progression, and stop postpartum hemorrhage, with fewer and less severe complications than existing drugs.

We also contributed to developing more reliable applications for monitoring uterine contractions. Our distinction between localized and distributed electrical activity in EHG measurements is helpful to interpret EHG recordings more accurately. Additionally, our statistical tensor decomposition approach enables us to leverage the spatial and temporal characteristics of EHG measurements and estimate the localized electrical activity more accurately than other existing methods.

Our observations using our method on two EHG datasets are aligned with our observations using the myofiber model. Our findings suggest that the distance traveled by action potentials across the myometrium is not only a potential drug target, but also useful to evaluate the vigor of uterine contractions. Specifically, we found the fraction of the myometrium recruited during contractions is a potential biomarker for preterm births and may be used to monitor labor contractions.
Our statistical tensor decomposition method can be used to develop applications for monitoring uterine contractions using multielectrode EHG measurements. For example, it could be used for analyzing Braxton-Hicks contractions to monitor the well-being of the fetus and the mother [31]. Additionally, our method may be used to monitor labor contractions and assess labor progression, which can be useful to regulate oxytocin administration when needed. Furthermore, it may be used as a preprocessing step to predict uterine contraction disorders, such as preterm births or postpartum hemorrhage.

Lastly, our machine learning models can be used to identify pregnant mothers at risk for preterm birth, which may help target treatments to reduce preterm birth incidence and reduce complications associated with preterm birth.

In summary, throughout my doctoral work, we investigated uterine excitation-contraction characteristics and contributed to the understanding of uterine electrophysiology. Additionally, we developed a better method to estimate localized electrical activity from EHG measurements. Moreover, we identified electrical activation surface as an important gauge of uterine contraction strength and as a possible drug target. Finally, we developed a machine learning application to predict preterm births from clinical information and EHG measurements.
Chapter 2

Computational Modeling of Uterine Excitation-Contraction Dynamics

2.1 Introduction

Each year, globally, about 15 million births are preterm, 25 million labors are induced, and 4 million laboring mothers suffer from postpartum hemorrhage [19, 154, 156, 170, 190]. These medical conditions are associated with increased morbidity and mortality for the mother and fetus, and these statistics are raising [23, 30, 216]. Since these medical conditions usually result from uterine contraction disorders, these medical conditions are routinely treated with drugs that regulate the uterine contractile activity.

As we described in the previous Chapter, both tocolytic and uterotonic drugs are used to treat uterine contraction disorders [10, 31, 101, 131, 224]. However, both types of agents are associated with serious side effects and complications [42, 50, 90, 171]. Moreover, their efficacy is often limited. To develop safer and more efficient drugs for uterine contraction disorders, we need to understand the cellular mechanisms responsible for uterine contractions.

Labor contractions result from excitation and contraction of USMCs. Although the mechanisms that trigger uterine contractions and coordinate the synchronous contractions of the myometrium are not fully understood, the propagation of APs through fibers of USMCs has been identified as a key component of uterine contractions [55, 128].
Experimental studies have elucidated many of the components responsible for AP generation, propagation, and force production in the uterus. Similar to other smooth muscles, USMC depolarization is mainly driven by L-type calcium currents [202, 239]. These currents have very different dynamics from the well-studied sodium currents that drive the depolarization in skeletal and cardiac muscle, as well as in neurons. Mainly, L-type calcium currents create slower depolarization rates and USMC usually sustain prolonged contractions [93]. USMC depolarization is further supported by T-type calcium currents and additional sodium currents [200, 202]. Following depolarization, USMCs are repolarized through various potassium currents, which are regulated through the transmembrane voltage and cellular calcium concentrations. Finally, ionic concentrations are restored through ion pumps and exchangers, including a sodium-potassium pump and a sodium-calcium exchanger [202, 206].

Ion pumps use energy stored in ATP molecules to transport ions across cellular membranes, while exchangers leverage concentration gradients across the membrane to transport ions. Additional ion currents identified in USMCs are reported by Tong et al. [202]. Intracellular calcium concentrations are further regulated by the sarcoplasmic reticulum [227].

**Intracellular calcium concentrations** activate a series of cellular mechanisms that ultimately generate crossbridges between actin and myosin that contract USMCs. Briefly, when intracellular concentrations increase, calcium ions bind to calmodulin. In turn, calmodulin activates MLCK, which phosphorylates myosin’s light chain. Once myosin is phosphorylated, it can bind to actin to form crossbridges, which contract the cell [117]. Force production in USMCs may also be regulated by hormones and neurotransmitters through alternative pathways, however this is beyond the scope of this dissertation [10, 117].

Computational models complement experimental uterine electrophysiology research. Computational models generally use differential equations to integrate experimental observations and infer electrophysiological properties. For example, Bursztyn et al., Rihana et al., Tong et al., and Testrow et al. developed increasingly complex models of USMC electrophysiology [29, 167, 200, 202]. These models simulate a single USMC and are very detailed. These models incorporate various decades of experimental observations and model the various ion currents identified in USMCs. Additionally, most of these models include an additional set of differential equations to recapitulate force generation dynamics. Besides recreating experimental observations, these models have been useful to examine the effects of drugs.
and hormones that regulate uterine contraction and to elucidate the physiological roles of different ion currents.

On the other hand, whole-organ models simulate uterine contractions over the entire myometrium and rely on simplifications of cellular-level dynamics. A standard model used to simplify cellular-level dynamics is the FitzHugh–Nagumo model (FHN) [64, 145]. This model can recreate trains of APs using just two coupled differential equations. Following the FHN model, additional simplified models were developed to simulate cellular dynamics in a computationally efficient manner. Whole-organ models have been useful to explain the patterns observed in EHG signals, to study electrical conduction in the uterus, and to investigate the effects of multiple drugs on the myometrium. A comprehensive review of uterine models developed in the last decade can be found in [231].

Fiber- and tissue-level models combine advantages of single-cell models and whole-organ models. Specifically, fiber models that simulate longitudinal concatenations of cells can model detailed cellular dynamics and intercellular propagation simultaneously. In the field of cardiac electrophysiology, these models were useful to understand electrophysiological properties of cardiac conduction such as the contribution of cellular excitability and cellular coupling to electrical conduction [179, 180]. Many of the dynamics that are observable at the fiber-level cannot be perceived neither in cellular-level models because they lack intercellular interactions, nor in whole-organ-level models because they overlook many of the AP dynamics by simplifying the cellular-level electrical activity.

To further understand uterine excitation and contraction, we developed a fiber-level model of the myometrium. Our model combines a uterine cellular model with a set of differential equations that regulate how APs and mechanical deformations travel along a uterine myofiber. To the best of our knowledge, this is the first uterine fiber-level model reported in the literature. Using our model, we explored the dependency of both electrical conduction and force development on cellular excitability and intercellular coupling. We identified various properties of conduction and force generation. Furthermore, we proposed mechanistic insights that explain these properties based on the dynamics of USMC APs.

Our work is a step forward to developing safer and more efficient therapeutics for uterine contraction disorders. We investigated the mechanisms targeted by these drugs and offer
new insights into these mechanisms. Moreover, our model, which is publicly available online, can serve as a platform for further experimentation.

In the rest of this Chapter, we will detail our model and then describe our observations. Our work is detailed in [81]. Here, we will also expand on the implications of our findings.

2.2 Methods

2.2.1 Model Overview

We model a uterine myofiber as a concatenation of 70 cells. Our model simulates two physiological scales: cellular-level ion currents and fiber-level propagation. At the cellular level, we include a detailed ionic current model, calcium handling dynamics, actin-myosin interactions, and a force-producing mechanism. At the fiber-level, we use a set of differential equations to simulate how APs and the consequent mechanical deformation travel across the fiber. We choose to model the fiber using 70 cells because this length is sufficient to capture entire depolarization and contraction waveforms, yet not so long that the simulations become computationally expensive. To exclude end effects, the first and last 10 cells of the myofiber are not considered for analysis.

To create APs, we inject a depolarizing current to the first cell in the fiber. For consistency, we used a 30 ms-long stimulus of -5 pA/pF in all of our experiments. While APs in the myometrium usually appear as trains of APs, we used a single AP to study propagation dynamics. We used a single AP to simplify the analysis. For example, by considering a single AP, we exclude the effects of the number of APs in a train as well as the effects of the firing rate on propagation and contractions dynamics. Additionally, while standard parameters used to study excitability and propagation, such as conduction velocity (CV) and AP duration (APD) are clearly defined for a single AP, they are less standard when we consider an AP train. For instance, the APD may depend on the number of previous AP and the time intervals between them [204, 223].
2.2.2 USMC AP Model

Each cell in our model can generate APs. We integrated the detailed ion current model developed by Tong et al. into each cell [202]. The complete formulation of this model can be found in the original publication. In short, this model uses over 100 differential equations to simulate 15 ion currents identified in USMCs. These currents are modeled using variations of the Hodgkin-Huxley formalism, i.e.,

\[
I = \bar{g} \prod_{i=1}^{n} y_i (v - E_{rev}),
\]

\[
E_{rev} = \frac{RT}{F} \ln \frac{[X]_o}{[X]_i},
\]

\[
\frac{dy_i}{dt} = \frac{y_{\infty_i} - y_i}{\tau_{y_i}},
\]
where \( I \) is the transmembrane ion current, \( \bar{g} \) is the maximal conductance for the given current, \( y_i \) are the gating variables, \( v \) is the membrane potential, \( E_{rev} \) is the Nernst potential for the ion X, \( R \) is the gas constant, \( T \) is the absolute temperature, \( F \) is the Faraday constant, \([X]_o\) and \([X]_i\) are the extracellular and intracellular ion concentrations, and \( y_\infty_i \) and \( \tau_{y_i} \) are the steady state and time constants for channel \( i \) and depend on the transmembrane voltage and intracellular calcium concentration, respectively.

### 2.2.3 USMC Contraction Model

We simulated actin-myosin cycling dynamics using Hai and Murphy’s model. Triggered by intracellular calcium concentrations, myosin transitions through an unphosphorylated state (M), a phosphorylated state (Mp), a phosphorylated state forming crossbridges with actin (AMp), and a latch state (AM), where AMp and AM are the force-generating states. Here, \( M \), \( M_p \), \( AM_p \), and \( AM \) represent the fraction of myosin in each state, respectively. The transition between the states is governed by the following transition system:

\[
\begin{pmatrix}
\frac{dM}{dt} \\
\frac{dM_p}{dt} \\
\frac{dAM_p}{dt} \\
\frac{dAM}{dt}
\end{pmatrix} =
\begin{pmatrix}
-K_1 & K_2 & 0 & K_7 \\
K_1 & -K_2 - K_3 & K_4 & 0 \\
0 & K_3 & -K_4 - K_5 & K_6 \\
0 & 0 & K_5 & -K_6 - K_7
\end{pmatrix}
\begin{pmatrix}
M \\
M_p \\
AM_p \\
AM
\end{pmatrix}, \tag{2.4}
\]

where \( K_1 \) and \( K_6 \) are regulated by \([Ca^{2+}]_i\) via:

\[
K_1 = K_6 = \frac{[Ca^{2+}]_{nm}^{i} \cdot MLCK^{nm}}{[Ca^{2+}]_{i}^{nm} + C_M MLCK^{nm}}. \tag{2.5}
\]

Here, \( nm \) is the Hill coefficient; \( CaMLCK \) is the half-saturation concentration of MLCK; and \( K_2, K_3, K_4, K_5, \) and \( K_7 \) are myosin state transition constants.

Furthermore, we modeled the contractile force and mechanical deformation of a single USMC based on the cycling dynamics of actin-myosin crossbridges. To model mechanical contractions, we leveraged the model developed by Yang et al. [232]. This model includes a passive
element, which simulates the passive elasticity of the cell, and three force generation elements, which simulate different force generation mechanisms in the cell. The definition of the mechanical parameters used in the equations below appear in Table 2.

The passive force \( p \) is given by

\[
F_p = K_p \left( e^{\alpha_p \frac{l_c - l_0}{l_0}} - 1 \right).
\] (2.6)

The force generated by the cross bridge elasticity \( x \) is given by

\[
F_x = (k_{x1} AMP + k_{x2} AM) l_e e^{-\beta \left( \frac{l_a - l_{opt}}{l_{opt}} \right)^2}.
\] (2.7)

The active force \( a \) generated is given by

\[
F_a = f_{AMP} AMP \left( \nu_x + \frac{dl_a}{dt} \right) + f_{AM} AM \frac{dl_a}{dt} e^{-\beta \left( \frac{l_a - l_{opt}}{l_{opt}} \right)^2}.
\] (2.8)

The series viscoelastic force \( s \) is given by

\[
F_s = \mu_s \frac{dl_s}{dt} + k_s \left( e^{\alpha_s \frac{l_s - l_{s0}}{l_{s0}}} - 1 \right).
\] (2.9)

Since the length of the cell \( l_c \) is spanned by the serially connected elements, we can write

\[
l_c = l_a + l_x + l_s.
\] (2.10)

Using Newton’s third law we get

\[
F_s = F_a = F_x.
\] (2.11)

Lastly, the tensile force generated by the cell is given by

\[
F_t = F_p + F_a.
\] (2.12)
We used the parameter values reported for USMC by Testrow et al. [200].

2.2.4 Electrical Propagation Model

We used the cable equation to model AP propagation. Electrical activity travels across USMCs through gap junctions. At the fiber-scale level, this propagation can be modeled as an electrical impulse that travels across a uniform cable. Assuming a homogenous extracellular medium, the cable equation is given by [68]

\[
\partial_x (\sigma \partial_x v(x, t)) = \chi (C_m \partial_t v(x, t) + I_{ion}(x, t) + I_{stimulus}(x, t)),
\]

where \( V(x, t) \) is the transmembrane voltage along the cable; \( I_{ion}(x, t) \) is the ionic current based on the model of Tong et al.; \( I_{stimulus}(x, t) \) is the injected depolarization current; \( C_m \) is the specific membrane capacitance; \( \sigma \) is the intercellular conductivity; and \( \chi \) represents the cell’s surface to volume ratio.

In our model, we assume that the cells’ volume and surface are deformable but incompressible. In other words, while the cells’ shape can change, the total volume and surface area remain constant. Therefore, in our model the surface to volume ratio (\( \chi \)) remains constant.

The intercellular coupling is the product of the intercellular cross-sectional area, \( A_{ics} \), that is the cross-sectional area at the intercellular junction, and the intercellular conductivity, \( \sigma \). The intercellular coupling is inversely proportional to intercellular resistivity (IR), denoted by \( \rho \), and given by:

\[
\text{Intercellular coupling} := A_{ics} \sigma = \frac{A_{ics}}{\rho}.
\]

Here, we assume that the intercellular cross-sectional area, \( A_{ics} \), remains constant throughout our simulations. This is supported by the fact that the intercellular junctions are rich in anchoring protein complexes that hold the membrane’s surface area at the intercellular junction [139]. We do not assume, however, that the cellular cross-sectional area remains
constant throughout the cell. On the contrary, the cellular cross-sectional area can change,
under the constraints that the total volume, total surface area, and cross-sectional area at
the intercellular junction remain constant.

2.2.5 Fiber Contraction Model

Based on the model developed by Yang et al. and Newton’s laws, we introduced a set of
differential equations to model the contractile force generated by the fiber, as well as the
mechanical deformation of all the cells in the fiber simultaneously.

Combining equations (2.7), (2.8), and (2.11) we get

\[
(k_{x1}A^MP^{(i)} + k_{x2}A^M^{(i)})l_x^{(i)}(t) = f_{AM}^{(i)} + f_{AM}^{(i)} \frac{dl_{a}^{(i)}}{dt} \forall i = 1...n .
\]  

(2.15)

Combining equations (2.7), (2.9), and (2.11), we then get

\[
(k_{x1}A^MP^{(i)} + k_{x2}A^M^{(i)})l_x^{(i)} e^{-\beta \left(\frac{l_x^{(i)} - l_{opt}}{l_{opt}}\right)^2} = \mu_s \frac{dl_s^{(i)}}{dt} + k_s \left(e^{\alpha_s \frac{l_x^{(i)} - l_0}{l_0}} - 1\right) \forall i = 1...n .
\]  

(2.16)

From Newton’s third law we can write that

\[
F_t^{(i)} = F_t^{(i+1)} \forall i = 1...n - 1 .
\]  

(2.17)

Combining equations (2.12) and (2.17), we get

\[
(k_{x1}A^MP^{(i)} + k_{x2}A^M^{(i)})l_x^{(i)} e^{-\beta \left(\frac{l_x^{(i+1)} - l_{opt}}{l_{opt}}\right)^2} + K_p \left(e^{\alpha_p \frac{l_x^{(i+1)} - l_0}{l_0}} - 1\right) = \\
(k_{x1}A^MP^{(i+1)} + k_{x2}A^M^{(i+1)})l_x^{(i+1)} e^{-\beta \left(\frac{l_x^{(i+1)} - l_{opt}}{l_{opt}}\right)^2} + K_p \left(e^{\alpha_p \frac{l_x^{(i+1)} - l_0}{l_0}} - 1\right) \forall i = 1...n - 1 .
\]  

(2.18)
The last equation needed to solve the system comes from the isometric condition. The myofiber’s total length, but not an individual cell’s length, is held constant. This condition is justified because, rather than being driven by uterine volume changes, intrauterine pressure buildup is driven by increases in wall tension, as described by Laplace’s law [212]:

\[ \sum_{i=1}^{n} l_a^{(i)} + l_x^{(i)} + l_s^{(i)} = n \cdot l_c^0. \] (2.19)

Since the length of every cell is given by

\[ l_c^{(i)} = l_a^{(i)} + l_x^{(i)} + l_s^{(i)}, \] (2.20)

equation (2.19) can be rewritten as

\[ \sum_{i=1}^{n} l_c^{(i)} = n \cdot l_c^0. \] (2.21)

### 2.2.6 Multiphysics Interactions

Since all the model’s variables are coupled, the entire system described by the equations above needs to be solved concurrently to calculate the model outputs. For example, to calculate the length of every cell \( l_c^{(i)} \) from equation (2.20), the internal cells’ lengths \( l_a^{(i)}, l_x^{(i)}, \) and \( l_s^{(i)} \) need to be calculated using equations (2.15-2.19), which in turn require calculating the myosin phosphorylation states (equations 2.4 and 2.5), and the cable equation (2.13), which requires solving the cells’ ionic currents (equations 2.1-2.3). Due to the complexity of this system, we solved using the GNU scientific library implemented in C++ [69].

The excitation and contraction waves are coupled. While the electrical activity produces mechanical deformations and tensile force, the mechanical deformations feed back into the electrical activity through the geometrical parameters of the cable equation. This feedback is obtained through the left hand side of the cable equation (2.13).
To solve the cable equation (2.13) at every time step, we discretize the myofiber and consider each cell as an infinitesimal element. Using discrete operators, the left hand side of equation (2.13) becomes:

\[
\sigma \frac{v^{(i+1)}(t) - 2v^{(i)}(t) + v^{(i-1)}(t)}{\left(\ell^{(i)}(t)\right)^2}
\]

where the superscript \((i)\) denotes the \(i^{th}\) cell in the myofiber. This expression closes the feedback loop since the length of the \(i^{th}\) cell in the myofiber is used to calculate the electrical propagation across that cell and depends on the mechanical state of that cell.

### 2.3 Results

We simulated AP propagation along our modeled fiber and verified that the waveforms and values obtained were in agreement with those observed experimentally [28, 202]. In Fig. 2.2 we show the AP, intracellular calcium concentrations, and cellular length waveforms obtained for various cells along the fiber as an AP travels along the fiber. Additionally, we show the force waveform generated by the entire fiber.
Figure 2.2: (a) The APs obtained at various cells along the fiber. Downstream cells activate later in time. The AP amplitude decays slightly as it travels along the first cells and then stabilizes. (b) The intracellular calcium traces for the same cells as in (a). These traces present rapid upstrokes and slow decay rates. (c) The cellular length over time for the same cells as in (a). Cells with higher concentrations of myosin in force-producing states contract, while their relaxed neighbours dilate to satisfy the isometric condition. (d) The force developed by the myofiber in response to the depolarizing stimulus. The cellular response to a depolarization stimulus is long lasting and decays monotonically until it returns to its base value after 12 s. Figure replicated from Goldsztejn and Nehorai [81].

2.3.1 Trains of APs

Our model can generate trains of APs when an intermittent stimulus current is injected to the first cell, as shown in Fig. 2.3. Here, we set the firing rate of the stimulus current such that the interval between successive APs is longer than the absolute refractory period of these USMCs. The absolute refractory period is the time interval after an AP during which the cell cannot sustain another AP. In this simulation, we show how a train of APs can create an intracellular calcium buildup that results in a stronger contractile force.
Figure 2.3: Burst stimulation. Bursts of APs appear in the contracting myometrium. To simulate the bursting type AP, we stimulated a 20-cell-long myofiber from one end with 6 consecutive depolarizing stimuli. The stimuli were 30 ms long, injected a current of -5 pA/pF, and were activated at a rate of 1 Hz. We used a shorter myofiber than in the previous simulations because consecutive APs are fired before the cells fully repolarize and therefore travel a shorter distance. The intercellular resistivity of the myofiber is 100 Ωcm. The traces shown correspond to the internal parameters of the 10th cell. Our model returns to its initial state about 14 s after stimulation. (a) The transmembrane voltage shows consecutive spiked APs. (b) The intracellular calcium concentration rises sharply after the onset of each AP and has a slow recovery. Therefore, intracellular calcium accumulates with consecutive APs. (c) The fraction of myosin bound to actin determines the contractile force developed and is regulated by the intracellular calcium dynamics. (d) The contractile force developed increases sharply with each AP and declines slowly. (e) With each AP, the cell expands as its upstream neighbors contract. Then, it contracts as its myosin binds to actin. Lastly, after the AP travels across the myofiber, the cells return to their initial lengths but continue producing a higher contractile force.
2.3.2 CV regulation by Cellular Excitability

We used our model to investigate the effects of modulating the main ion currents responsible for cellular depolarization. USMC depolarization is mainly driven by $I_{\text{CaL}}$ and supported by $I_{\text{CaT}}$ and $I_{\text{Na}}$. Importantly, oxytocin enhances uterine contractions partially by upregulating calcium currents.

To understand the role of these three ion currents, we progressively varied the maximal conductance of each channel. We varied the conductance from 30% to 200% of the conductance reported by Tong et al. [202]. We repeated these experiments for various values of IR to obtain a more complete description of the interactions between cellular excitability and cellular coupling.

We observed that when cellular coupling is sufficiently low to prevent APs from propagating across the myometrium, upregulating any of these ion currents can restore conduction. In other words, $I_{\text{CaL}}$ (Fig. 2.4a), $I_{\text{CaT}}$ (Fig. 2.4b), and $I_{\text{Na}}$ (Fig. 2.4c) upregulation can restore conduction that was blocked by low cellular coupling.

Although upregulating cellular excitability, as oxytocin does, can restore conduction, enhanced excitability cannot restore conduction velocity. Specifically, we observed that the conduction velocity of poorly coupled fibers with increased cellular excitability is considerably smaller than that of well coupled fibers with normal cellular excitability.

2.3.3 Contractile Force regulation by Cellular Excitability

We repeated the experiment described in the previous subsection to measure the effects of cellular excitability on the force generated by the entire fiber. To compare amongst different contractions using a single metric, we measured the total force generated by the fiber over the duration of the contraction, which is the impulse generated by the fiber.

Using our model, we observed that the impulse generated by the fiber has a binary dependence on $I_{\text{CaL}}$ (Fig. 2.4d) and $I_{\text{Na}}$ (Fig. 2.4f). If the conductance for these currents is not sufficient to overcome a conduction block, then the fiber does not generate contractile
force. On the other hand, if the conductance of these channels is sufficient to enable AP propagation, then a stable contractile force is generated.

The contractile force generated by the fiber has a different behavior with respect to $I_{CaT}$ (Fig. 2.4e). We observed a continuous increase of force generated with increasing $I_{CaT}$ conductance. This suggests that this current may play an important role in regulating the vigor of uterine contractions.
Figure 2.4: Electrical conduction and force development dependency on cellular excitability. (a)-(c) Conduction velocity (CV) as a function of $I_{CaL}$, $I_{CaT}$, and $I_{Na}$ conductivity modulation, respectively. A zero CV indicates conduction block. Ionic channel current modulation is implemented as a multiplicative factor of the ionic channel conductivity: a modulation of 1.0 represents normal conductivity. The simulations were run under varying coupling levels, $IR = 10, 100, 300,$ and $1000 \ \Omega cm$. (d)-(f) Normalized cumulative force developed by the myofiber under varying intercellular coupling levels and conductivity modulation of $I_{CaL}$, $I_{CaT}$, and $I_{Na}$, respectively. Data points are shown at modulation = 0.3, 0.5, 0.8, 0.9, 1, 1.1, 1.2, 1.5, and 2. Figure replicated from Goldsztejn and Nehorai [81].

2.3.4 CV regulation by IR

Intercellular coupling is regulated by GJs. GJ expression increases towards labor to enable APs to travel across USMCs. Importantly, progesterone prevents GJ formation and helps maintain the uterus in a quiescent state during pregnancy.

We used our model to investigate how CV changes as a function of IR. We progressively varied the value of the conductivity between the cells and measured the resulting CV. Additionally, we measured how the AP morphology changes as a function of IR to understand how cellular dynamics are related to CV.

Conduction velocity in the myometrium usually ranges between 1-3 cm/s *in-vivo* [22]. We observed that conduction velocity behaves differently for high and low values of intercellular coupling. Therefore, we differentiate these domains using a threshold value of 25 $\Omega cm$. In
the high intercellular coupling domain, i.e., below 25 Ωcm, CV is very sensitive to IR value changes, whereas CV has a low sensitivity for IR in the low intercellular coupling domain, i.e., above 25 Ωcm, as shown in Fig. 2.5a.

Conduction block first occurs at 200 Ωcm. For IR values above that threshold, a stimulus propagates to only a few cells. From the reported data on CV and our simulations, we infer that the IR in excitable myometrium ranges between 10 and 100 Ωcm.

As intercellular coupling increases, membrane depolarization becomes faster. The maximal upstroke slope increases with increasing intercellular coupling (Fig. 2.5b), while the upstroke duration decreases with increasing intercellular coupling (Fig. 2.5c). As with conduction velocity, the sensitivity of the upstroke slope, and its duration, to intercellular coupling is high in the high intercellular coupling domain and low in the low intercellular coupling domain.

![Figure 2.5: Electrical conduction characteristics with respect to intercellular resistivity (IR).](image)

(a) Conduction velocity (CV) with respect to IR. CV decreases with increasing IR until block occurs at 200 Ωcm. (b) The maximal slope of the depolarization upstroke ($\max_t \frac{dv_m}{dt}$) with respect to IR. Its behavior is similar to that of CV. (c) The upstroke duration with respect to IR. Upstroke duration increases with increasing IR. (a)-(c) The black lines identify the high intercellular coupling domain, and the blue lines identify the low intercellular coupling domain. Data points are shown at IR = 1, 5, 10, 25, 50, 100, and 150 Ωcm. Figure replicated from Goldsztejn and Nehorai [81].

### 2.3.5 Regulation of Contractile Force Generation by IR

Using our model, we observed that as long as APs can propagate along the entire fiber, the contractile force developed by the fiber is insensitive to IR. As in subsection 2.3.3, we calculated the impulse generated by the fiber under varying values of intercellular resistivity.
As shown in Fig. 2.6, both the total force and the amplitude of the force waveform display a binary behavior with respect to IR. For low IR values, these parameters are stable at a high value, but when the IR increases and forms a conduction block, the force generated rapidly decreases. At high IR values, the force generated is mostly a product of the passive force, i.e., the force generated by the elastic components of the fiber in response to the isometric condition. Conduction block first takes place for IR values around 200 Ωcm.

Figure 2.6: Force development with respect to intercellular resistivity (IR). (a) The normalized cumulative force developed by the myofiber is stable at low IR values, but it drops sharply as the IR approaches 200 Ωcm, where conduction block occurs. Then it remains at unity, reflecting that no force is generated besides passive tension. The normalized cumulative force value is defined as the integral of the force over 14 s after the initial stimulus, normalized by the passive force (i.e., without stimulation) developed by the myofiber over the same period. (b) The amplitude of the force generated follows a similar pattern as the normalized force. (a)-(b) The blue lines mark the buffered domain, and the red lines mark the conduction block domain. Data points are shown are at IR = 1, 5, 10, 25, 50, 100, 150, 200, 250, 300, and 400 Ωcm. Figure replicated from Goldsztejn and Nehorai [81].

**Cellular Basis for Contractile Force Robustness**

We used our model to understand why the contractile force generated by the fiber is invariant to IR changes, as long as APs can propagate along the entire fiber. We studied how the multiple components responsible for USMC contraction vary as we modify the IR. In Fig. 2.7, we show how these components are affected in a cell positioned at the middle of the fiber.

The AP morphology changes in response to increasing IR, as shown in Fig. 2.7a. In Fig. 2.7b, we show that for increasing IR, the AP amplitude decreases while the AP duration at
90% repolarization (APD$_{90}$) increases. The APD$_{90}$ is defined as the duration between the beginning of the depolarization until the cell restores 90% of the resting membrane potential.

The opposing trends of the AP amplitude and APD$_{90}$ in response to varying IR values balance the total influx of calcium ions. In Fig. 2.7c and Fig. 2.7d, we show that the inward calcium flux and the resulting intracellular calcium concentration remain unchanged for varying IR values, as long as there is no conduction block.

Next, in Fig. 2.7e and Fig. 2.7f, we show that this mechanism ultimately preserves the fraction of myosin that binds to actin to generate contractile force and maintains the total force generated by the fiber.

Figure 2.7: Mechanism for force robustness against intercellular resistivity (IR). (a) Simulated AP traces for various IR values (see figure’s legend) at the 30$^{th}$ cell in a 70 cell long myofiber. (b) The AP duration at 90% repolarization (APD$_{90}$) and the AP amplitude of the traces in (a). (c) The intracellular calcium levels for the same conditions as in (a). (d) The calcium load over 14 s of simulation, calculated as the area under the curve of the traces in (c). (e) The fraction of myosin bound to actin over time. (f) The tensile force developed by the myofiber over time. Figure replicated from Goldsztejn and Nehorai [81].
2.4 Discussion

We developed a uterine fiber model and used it to study multiple aspects of electrical conduction and contractile force generation. Our model incorporates multiple cellular-level models and includes a novel set of equations to simulate the simultaneous propagation of electrical activity and mechanical deformation. We implemented our model using C++ for computational efficiency and made our code publicly available for further experimentation.

Using our model, we investigated how cellular excitability and intercellular coupling modulate both AP propagation and the force developed by the entire fiber. We observed that intercellular coupling is the main regulator of CV. Additionally, we observed that increasing cellular excitability can recover conduction lost due to low intercellular coupling. However, modulating cellular excitability does not recover CV in low intercellular coupling settings.

Additionally, we observed that the contractile force developed by the fiber has a binary behavior. This force has a stable high value if APs can propagate across the entire fiber and a negligible value if APs cannot propagate. These observations suggest that AP propagation is a main regulator of uterine contraction strength. Accordingly, in normal pregnancy progression the electrical connectivity of the myometrium increases in preparation for labor. Conversely, progesterone increases IR and maintains a quiescent uterine state during pregnancy.

In this Chapter, we showed that unobstructed AP propagation along a uterine fiber is instrumental in generating contractile force. In agreement with these observations, we will show in the next Chapter that the surface of the myometrium recruited during uterine contractions is associated with the vigor of those contractions. In other words, we will show that the force dynamics we observed at the fiber level share some properties with the dynamics at the whole-organ level.

2.4.1 Limitations

All models, including the model described in this Chapter, have limitations. Since we aimed to understand the fundamental properties of AP dynamics and propagation in a fiber, we
considered only a single spike AP. However, alternative AP morphologies have been observed in the myometrium. Moreover, APs in the myometrium usually appear in trains of successive APs [200].

We used the USMCs AP model developed by Tong et al. because it was extensively validated with experimental measurements [202]. Nonetheless, alternative USMCs are available in the literature and more accurate models will likely be developed in the future [167, 200, 231]. To address this limitation, we used an object-oriented methodology to develop our model that enables to modify the AP model, or other components of our model, without altering the rest of the model.

A major limitation of our model is that we incorporated existing smooth muscle models, rather than developing every component of our model from dedicated experimental observations. Specifically, we integrated models that were developed by various groups using different experimental conditions and animal species. Moreover, the models used to describe myosin cycling [94] and the subsequent cellular contraction [232], were developed for vascular smooth muscles. Our model and results are encouraging to develop more accurate models entirely from USMCs with consistent experimental conditions and animal species.

### 2.4.2 Future Directions

In the future, our model can be extended to incorporate additional mechanisms that regulate electrical propagation and force generation. For example, stretch activated ion channels are have been identified in the myometrium and including these channels in our model could be useful to investigate their role in uterine activity.

Moreover, our model could be used to study the effects of baseline stretch on AP propagation and force generation. Uterine fibers present variable properties depending on their baseline stretch. For example, loose fibers cannot contract and stretched fibers can generate APs spontaneously, i.e., without external stimulation [44, 122]. Our model may be expanded to simulate these conditions, e.g., by varying the resting stretch of the fiber, to investigate these phenomena.
2.5 Conclusion

We developed a uterine fiber model to simulate AP propagation and force generation. Then, we used our model to study various properties of uterine excitation and contraction. Importantly, we observed that IR is an important regulator of AP propagation and force generation. Our work advances our understanding of uterine electrophysiology and could be useful to identify safer and more effective therapies to treat uterine contraction disorders.
Chapter 3

Characterizing Uterine Contractions Using EHG Measurements and Statistical Tensor Decomposition

3.1 Introduction

The electrical activity associated with uterine contractions was first measured more than 60 years ago and, since then, various researchers around the world have been analyzing these measurements [120, 230]. However, predicting medical conditions from EHG measurements is challenging. To develop EHG-based applications that can be translated to clinical settings, we need to further understand the physiology behind these measurements and develop more reliable tools to analyze them.

In this Chapter, we will first describe EHG measurements and their limitations. Then, we will introduce a Bayesian tensor decomposition method to localize uterine activity using EHG measurements and develop more reliable applications. Finally, using our method and two public databases, we will demonstrate that the surface of the myometrium recruited during contractions is a useful biomarker for preterm births, term births, and to monitor labor contractions.
3.1.1 Components of EHG Measurements

Abdominal electrical recordings measure various physiological phenomena. Each of these phenomena generates a different spectral component in the frequency domain. The uterine activity creates two components that have different frequency ranges: the slow wave and the fast wave. The slow wave component appears at low frequencies, usually between 0.01 and 0.03 Hz, and is thought to be associated with the mechanical component of uterine contractions. The fast wave is further subdivided into the fast wave low (FWL) and the fast wave high (FWH). The FWL has been reported to appear in EHG recordings as a spectral component ranging between 0.13 to 0.26 Hz, while the FWH is identified as a component ranging between 0.36 and 0.88 Hz [18, 199, 230]. Additional reports suggest that the FWH may have frequency components as high as 3 Hz [48, 186]. Although these spectral components have been associated with uterine contractions, the physiological basis for each component has not yet been fully determined. A possible explanation is that the FWL is associated with AP propagation and activates myometrial regions, while the FWH is created by the repetitive depolarization of the myometrium [72].

Besides uterine activity, EHG recordings measure additional physiological phenomena. The maternal respiration creates a strong component with frequencies ranging between 0.2 to 0.34 Hz [18]. The maternal cardiac activity generates a frequency component that can range between 0.7 and 1.5 Hz [18]. Additionally, if the measuring system is sufficiently sensitive, the fetal cardiac activity may be recorded, which may appear as a frequency component between 1.8 and 2.6 Hz [217]. Additional spectral components are present at higher frequencies, including spectral harmonics of the components mentioned before, electromyography noise, and mains hum noise [110, 230]. However, since the spectra of these components does not overlap with the uterine activity, they are usually filtered out in signal preprocessing steps [230]. The characteristic frequency components of EHG measurements are shown in Fig. 3.1.

Moreover, EHG measurements may record signal artifacts. These artifacts can be caused by maternal, fetal, and electrode movements [123, 142]. Maternal movements can have high amplitudes and wide spectra. These artifacts can be removed either by annotating when the mother moves or by integrating an accelerometer in the recording device [233]. Fetal movements, on the other hand, are more challenging to remove because they can have similar spectra as uterine contractions and they can also have temporal associations with uterine
Figure 3.1: Power spectral density (PSD) of an EHG recording. This PSD was obtained from the first minute of measurements from a single electrode of a recording from the “Icelandic 16-electrode Electrohysterogram Database.” The DC level and linear trend of the signal were removed by subtracting the linear approximation of the measurements. The spectral components of the signal are labeled in the figure and include, in ascending frequency: slow wave, FWL, maternal respiration component, FWH, and the maternal heart rate.

contractions [233, 249]. Lastly, electrode movements create very high amplitude artifacts and can be removed based on their amplitude.

EHG measurements also present temporal characteristics. When labor approaches, uterine contractions become stronger, more rhythmic, and the timing between consecutive contractions decreases [107, 172]. We show an example of an EHG recording in Fig. 3.2. Although contraction timing is useful to identify the onset of labor and to track labor progression, it is not predictive of preterm labor [107, 147].

Using the “Icelandic 16-electrode Electrohysterogram Database,” we identified various temporal components during uterine contractions. First, a background signal consisting mainly of cardiac and respiratory activity spans the entire recording. Second, in most contractions, a twitch of one to three spikes precedes the contraction and lasts for a few seconds. These twitches may be related to a pacemaker mechanism. Third, soon after these twitches, the
uterine contraction takes place. EHG signals of uterine contractions present three distinct segments: i) a rising phase, in which the EHG amplitude increases as a result from the advance of a myometrial depolarization wave towards the recording electrode, ii) a plateau phase, in which the depolarization wavefront is near the electrode, and ii) a declining phase, in which the EHG amplitude decreases and the signal becomes erratic [244]. The declining phase results from a combination of the depolarization wavefront traveling far away from the electrode and mechanical movement corresponding to the uterine contraction. These signal segments are shown in Fig. 3.3.

Uterine electrical activity also displays spatial patterns [228]. Although the spatial patterns of propagation are variable among pregnancies, these patterns can be useful for contraction monitoring [109]. The spatial patterns of activation of the myometrium can be measured using multiple electrodes. EHG measurement devices usually have to balance between the range covered and the spatial resolution of the measurements. For example, de Lau et al. acquired EHG measurements using an eight-by-eight electrode grid embedded in a 28-by-28 mm adhesive patch [45]. This device provides excellent spatial resolution but limited spatial scope. Using this device, de Lau et al. measured the CV of electrical patterns associated with

Figure 3.2: A representative EHG recording from the “Icelandic 16-electrode Electrohystero-
gram Database.” Instants at which the expectant mother perceived a uterine contraction, a
pressure sensation possibly associated with a contraction, or a fetal movement, are indicated
with “C”, “(c)”, and “fm”, respectively.
uterine contractions and found that this CV is a biomarker of imminent labor. As described before, EMMI and MMG devices use complex setups to obtain broad measurement scopes and good spatial resolutions. However, these devices cannot be easily implemented for widespread use.

3.1.2 Uterine Electrical Activity Localization

 Regardless of the setup used to measure uterine electrical activity, a major challenge is to differentiate between electrical activity that is present directly under the electrodes from the nonspecific electrical activity recorded by the same electrodes. Throughout this Chapter, we will refer to the electrical activity directly under the electrodes as the localized electrical activity and to the nonspecific electrical activity as the distributed electrical activity.
The distributed electrical activity results from multiple phenomena. Two main effects that can create distributed electrical activity are the common input effect and the volume conductor effect. The common input effect results from electrical activity, usually generated farther away from the electrodes than the sources of interest, which is captured simultaneously by multiple electrodes on the grid [17, 98]. For example, uterine electrical activity that takes place on the back side of the uterus can create a common input signal on a grid of abdominal electrodes.

The volume conductor effect results from measuring electrophysiological activity noninvasively. Since uterine depolarization wavefronts are measured distantly at the abdomen, every electrode captures a diffused projection of the depolarization wavefront [17, 244].

Estimating the localized and distributed uterine electrical activities is useful to analyze EHG measurements reliably. For instance, convoluted propagation patterns, such as simultaneously propagating electrical waves or waves travelling with unusual angles, may be mistakenly measured as a single wave travelling in a different direction. This may result in unreliable data interpretations, such as unrealistically high CV values [162, 240].

Estimating the localized and distributed electrical activities is challenging for two main reasons. First, the distributed electrical activity may generate different projections on different electrodes. If we approximate the wavefront of a uterine electrical depolarization wave using electric dipole moments, we obtain that the projection of the resulting electric field is dependent on the relative position of the electrodes with respect to the depolarization wave. Thus, the variations in waveform across different electrodes limit the efficacy of using reference electrodes to estimate the localized electrical activity. In second place, the localized and distributed electrical activities usually have overlapping spectra. Therefore, the localized and distributed activities cannot be easily separated using spectral filtering techniques.

Multiple algorithms have been devised for solving inverse problems in electrophysiology. Bioelectrical source localization using noninvasive electric potential measurements has been extensively studied for electroencephalography (EEG) applications [86]. Bioelectric source localization has also been investigated in electrocardiography and resulted in electrocardiographic imaging (ECGI) [169]. More recently, a similar approach was used to localize uterine
electrical activity [228]. Although these approaches can estimate the entire propagation pattern of the electrical activity, these methods require imaging modalities to reconstruct the underlying anatomy and delicate arrays of many electrodes.

Various approaches have been proposed to analyze measurements of uterine electrical activity using a limited number of abdominal electrodes in the presence of distributed electrical activity. The simplest method is to consider bipolar, instead of unipolar, measurements. Bipolar measurements are usually obtained by subtracting the measurements of a single reference electrodes from the measurements of the rest of the electrodes in the grid, or by considering the differences between the measurements of adjacent electrodes. While this approach is useful to attenuate common input signals, such as those generated by the maternal respiration, this approach is suboptimal to remove measurement components that have different projections over different electrodes. For example, a fetal kick may generate an artifact in all the electrodes simultaneously, but that artifact needs not generate the same waveform in all the electrodes. The maternal cardiac activity is another example that illustrates the limitations of bipolar measurements. Subtracting the cardiac activity measured by multiple electrodes will generate vector projections of the cardiac activity, akin to those recorded in electrocardiograms (ECG), rather than remove the cardiac activity from the measurements.

Alternative approaches for analyzing multielectrode EHG recordings in the presence of distributed electrical activity infer properties of uterine connectivity that are useful for practical applications. For example, Hassan et al. and Nader et al. used phase synchronization and mutual coherence metrics, respectively, to differentiate pregnancy from labor measurements [99, 144]. Additionally, Alamedine et al. showed that non-linear correlations are also useful to predict imminent labor [4].

These approaches quantify the relationships between the signals measured across the electrode grid. However, these methods do not estimate the localized and the distributed electrical activities [158]. Moreover, these approaches were devised for interactions between pairs of electrodes and later expanded to electrode grids, and therefore they do not fully consider concurrent measurements from the entire electrode grid [158].

To estimate the localized and distributed electrical activities in EHG measurements, we draw an analogy between this problem and the problem of separating a moving foreground
from a static background in video signal processing. In video signal processing, statistical
tensor decompositions achieve state-of-the-art results in identifying moving objects [248, 247].
These methods stack the video frames to form tensors, where the first two coordinates encode
spatial locations, a third coordinate represents time, and additional coordinates can encode
the image colors. Then, based on assumptions about the structures of the foreground and
the background, these methods separate the original tensor measurements into a tensor
containing the foreground activity and a tensor capturing the background activity. For
example, Zhao et al. and Zhou et al. developed a robust Bayesian tensor decomposition that
separates the foreground from the background activity in videos with very good accuracy and
computational speed [246, 247, 248]. These methods are compelling for the analysis of tensor
EHG measurements. However, they are optimized for videos with mostly static backgrounds,
while the distributed electrical activity in EHG measurements is highly non-stationary [49].

In this Chapter, we introduce a statistical tensor method to estimate the localized and
distributed uterine activities. We represent EHG measurements as tensors, where the first
two dimensions represent the spatial locations of the electrodes on the abdomen and a third
dimension encodes the acquisition time. Based on this representation, we reformulate the
Bayesian tensor decomposition method introduced by Zhao et al. for video signal processing
(BRTF) to estimate localized and distributed electrical activity in EHG measurements [247].
Importantly, we address the non-stationarity of the distributed electrical activity using a
more general tensor model.

We first demonstrate the ability of our method to estimate localized and distributed electrical
activity using synthetic and real EHG measurements. Our experiments illustrate the unique
advantages of our method for this task and show that tensor methods outperform standard
methods for estimating the localized electrical activity.

Then, we leverage our method to analyze uterine contractions during pregnancy and labor.
Using our method and two publicly available EHG databases, we found that the number of
electrodes that are active during uterine contractions is a biomarker of contraction strength.
Specifically, we observed that the number of active electrodes during Braxton-Hicks contrac-
tions around the 30th week of gestation is a potential biomarker for preterm births. We
also show that the number of active electrodes during contractions increases during the last
month of pregnancy. Finally, we observed that the fraction of the myometrium recruited during labor contractions is correlated with whether labor contractions are sufficiently strong to deliver the fetus, or they require augmentation with oxytocin.

Our work is useful for researchers and engineers developing applications based on EHG measurements. Our method overcomes some of the intrinsic limitations of noninvasive electrophysiological measurements and can be used to develop more reliable applications.

Our results suggest that the fraction of the myometrium that is recruited during contractions regulates their strength. This observation agrees with our conclusions from the previous Chapter. Namely, that whether APs can propagate through the myometrium is a main regulator of the contractile force generated by muscle fibers.

Our findings may be used for multiple applications based on uterine contraction monitoring. For example, they can be useful to identify pregnant mothers at high risk of preterm birth, predict imminent labor, and monitor oxytocin administration when inducing labors.

3.2 Methods

3.2.1 Tensor Model Description

Model Assumptions and Justifications

Our model relies on two main assumptions. Firstly, we assume that the localized electrical activity is sparse in space and time. We make this assumption because uterine electrical activity travels over the myometrium during contractions. Therefore, the myometrium below each electrode will be active only during a limited period of time. Moreover, only the electrodes that are positioned directly over the active surface of the myometrium should measure localized electrical activity.

In second place, we assume that the distributed electrical activity has low-rank dynamics. We make this assumption for two reasons. First, because the common input signal is shared at any given time by multiple electrodes in the grid [241]. Second, because the distribution of the
volume conduction effect across the electrodes in the grid is continuous and slowly varying [244]. Hence, we presume that the distributed electrical activity will generate correlated waveforms across the multiple EHG electrodes. Moreover, we infer that the distributed electrical activity will tend to have less fluctuations over time than the localized electrical activity.

**Statistical Measurement Model**

In our model, if we record electric potentials from a pregnant woman’s abdomen using an $m \times n$ grid of electrodes during $T$ time-steps, we will obtain the measurement tensor $\mathbf{Y} \in \mathbb{R}^{m \times n \times T}$.

These measurements may include localized electrical activity resulting from a uterine depolarization wavefront travelling underneath the electrodes. We aim to capture this activity in the sparse tensor $\mathbf{S} \in \mathbb{R}^{m \times n \times T}$. Additionally, these measurements may include distributed electrical activity generated, for example, by the volume conductor effect and the maternal respiration. We aim to capture this distributed electrical activity in the low-rank tensor $\mathbf{X} \in \mathbb{R}^{m \times n \times T}$.

Therefore, as summarized in Fig. 3.4, we aim to decompose this measurement tensor ($\mathbf{Y} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$) into the sum of a sparse tensor of localized electrical activity ($\mathbf{S} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$), a low-rank tensor of distributed electrical activity ($\mathbf{X} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$), and a tensor of white Gaussian noise ($\mathbf{E} \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$), i.e.,

$$\mathbf{Y} = \mathbf{S} + \mathbf{X} + \mathbf{E}. \quad (3.1)$$
Figure 3.4: Tensor decomposition of multielectrode EHG measurements. (a) Schematic physical measurement setup. (b) A dense, full-rank tensor stores the measurements. (c) Localized and distributed electrical activity tensors.

**Low-Rank Tensor Model**

Low-rank models can extract the underlying dynamics of physical processes recorded with measurement systems. While physical processes tend to have low-rank structures, measurement matrices and tensors are usually full-rank due to random noise and unmodeled dynamics [208]. Therefore, in many cases, approximating the measurements with low-rank structures recovers the underlying physical process by removing the measurement noise and the unmodeled dynamics [183].

There exist various low-rank tensor models, including the canonical polyadic decomposition (CPD), the Tucker model, and the low-tubal-rank model [183, 248]. The CPD is an extension of PCA to tensor measurements and is among the simplest low-rank tensor models. CPD is mostly used when there exist linear relationships among the tensor dimensions [36, 183]. The Tucker model decomposes the original tensor into a dictionary matrix for every dimension and a sparse core tensor describing the interactions between the dictionaries [36, 183]. The Tucker model can be seen as a generalization of CPD. The low-tubal-rank model was proposed more recently, and it is an extension of eigenvalue truncation valid for 3D tensors only [248].
Choosing an optimal low-rank model depends on the intended application. Simpler models can represent less complicated dynamics well but may not capture more convoluted physical processes entirely. On the other hand, more elaborated models can describe more complex physical processes more accurately but can overfit simpler physical processes.

We chose to model the distributed electrical activity using the Tucker model. We use the Tucker model because it is sufficiently complex to capture non-stationary, distributed electrophysiological phenomena of any tensor dimension and can be prevented from representing the localized electrical activity by using appropriate constraints [183].

The Tucker model is given by:

$$\mathcal{X} = \mathcal{G} \times_1 U^{(1)} \times_2 U^{(2)} \times_3 \cdots \times_N U^{(N)}, \quad (3.2)$$

where $U^{(n)} \in \mathbb{R}^{I_n \times R_n}$ are a set of factor matrices of ranks $R_n$, which contain the atoms of each dimension, $\mathcal{G} \in \mathbb{R}^{R_1 \times \cdots \times R_N}$ is the core tensor, which contains the interactions between the atoms of all the dimensions, $\times_j$ is the $j$-th mode product, and $R_n \in \mathbb{N}_2$ is the multilinear rank of the tensor.

Additionally, the Tucker model can also be written in alternate forms that facilitate calculations, including the [246]:

matrix form

$$X^{(n)} = U^{(n)} G^{(n)} \left( \otimes_{k \neq n} U^{(k)T} \right), \quad (3.3)$$

vector form

$$\text{vec}(\mathcal{X}) = \left( \otimes_n U^{(n)} \right) \text{vec}(\mathcal{G}), \quad (3.4)$$

and the element-wise form
\[ \mathcal{X}_{i_1, \ldots, i_N} = \left( \otimes_n u^{(n)T}_{i_n} \right) \text{vec}(\mathcal{G}). \]  

where \( u^{(n)}_{i_n} \) are the rows of \( U^{(n)} \). The superscript \( (n) \) indicates the dimension and the double subscript \( i_n \) indicates the row of each matrix. The subscripts are indexed because we have a different index \( i \) for each dimension.

**Bayesian Model**

We aim to estimate the tensors \( S \) and \( \mathcal{X} \) such that (i) their sum recovers \( Y \) up to white Gaussian noise, (ii) \( S \) is as sparse as possible, and (iii) \( \mathcal{X} \) has a low multilinear rank, i.e., the entries of \( R_{n=1}^{N} \) are as small as possible.

There are multiple approaches to estimate these tensors. For example, we could write this problem as an optimization problem and solve it using gradient methods, or alternating optimization algorithms [183, 75]. Alternatively, we could formulate a probabilistic model and search for optimal parameters under a specified criterion. Specifically, we could search for the parameters that maximize the likelihood of the observations under a maximal likelihood estimation (MLE) framework. We could also search for the most likely parameters given the observations using a maximum a posteriori probability (MAP) estimation approach.

A major difficulty in this estimation problem is determining the multilinear rank of \( \mathcal{X} \). Unlike matrix ranks, there exist multiple definitions of tensor rank and determining a tensor’s rank, or even bounding it, is difficult [183, 247]. Moreover, the quality of the solutions can be very dependent on the multilinear rank. Additionally, modifying the multilinear rank alters the rest of the parameters in the model [183]. Therefore, estimating the tensor rank appropriately is important to obtain optimal solutions.

Various methods have been developed to estimate tensor ranks. For example, minimizing the nuclear norm is a compelling approach in matrix problems because it leads to convex optimization problems and has been extended to tensor problems [125, 164]. However, this approach usually requires tuning several hyperparameters, which can lead to underestimation or overestimation of the tensor rank [247]. Another alternative is using Monte Carlo sampling.
methods to estimate the model parameters and tensor rank jointly [163]. However, Monte Carlo simulations are computationally expensive and can become prohibitively slow for large tensors.

Recently, Zhao et al. proposed variational-Bayes inference methods for tensor decomposition problems in video signal processing and achieved state-of-the-art results in terms of decomposition accuracy and computational speed [246, 247]. This approach is compelling because it addresses the limitations of the methods aforementioned. Namely, this approach enables to estimate the model parameters and tensor rank jointly with computational efficiency. Additionally, this method can infer the model hyperparameters automatically. Because of these advantages, we will follow a similar approach to derive an iterative optimization algorithm to search for the optimal $S$ and $X$. A limitation of variational Bayes inference is that we need to manually compute the variational probability distributions of the model parameters, which we will do in the next subsections. Since these computations can become very complicated and even intractable, it is customary to use combinations of Gaussian distributions and conjugated priors [37]. Moreover, we will vectorize the tensors to define their probability distributions because the probability distribution functions (pdf) of random vectors have been studied thoroughly and are easier to manipulate than the pdfs of random tensors. Although tensor pdfs have been explored, these pdfs are beyond the scope of this dissertation [70, 229]. These choices of pdfs usually works well in practice while enabling to compute the variational probability distributions explicitly.

We model the tensor of EHG measurements using a hierarchical Bayesian model. We model the likelihood function for the tensor measurements $\mathcal{Y}$ using a similar approach as Zhao et al. [247]:

$$\text{vec}(\mathcal{Y})|S, \mathbf{U}^{(n)}, \mathcal{G}, \tau \sim \mathcal{N}\left(\text{vec}(S) + \left(\otimes_n \mathbf{U}^{(n)}\right) \text{vec}(\mathcal{G}), \tau^{-1}I\right),$$

where $\text{vec}(\mathcal{X}) = \left(\otimes_n \mathbf{U}^{(n)}\right) \text{vec}(\mathcal{G})$ is a low-rank Tucker tensor capturing the distributed electrical activity, $\mathbf{U}^{(n)}$ are dictionary matrices of each dimension in the Tucker model, and $\mathcal{G}$ is the core tensor of the Tucker model. This core tensor is a compact and sparse tensor containing the interactions between the factor matrices. Additionally, $\otimes_n$ denotes the
sequential Kronecker product, which expands the factor matrices and the core tensor into a tensor with the same dimensions as the measurement tensor. Lastly, $\tau$ is the white Gaussian noise precision.

To obtain the sparse tensor $S$, we impose a sparsity-inducing conjugate prior over each element of $S$, as shown by Zhao et al. [247]:

$$S_{i_1,\ldots,i_N}|D \sim \mathcal{N}(0, (D_{i_1,\ldots,i_N})^{-1}) \quad (3.7)$$

where

$$D_{i_1,\ldots,i_N} \sim \text{Ga}(a_D^{0}, b_D^{0}). \quad (3.8)$$

Furthermore, we impose prior distributions on the core tensor $G$ and the factor matrices $U^{(n)}$ given by:

$$\text{vec}(G)|\lambda^{(n)} \sim \mathcal{N}(0, (\beta \otimes \Lambda^{(n)})^{-1}) \quad (3.9)$$

and

$$u_{i_n}^{(n)}|\lambda^{(n)} \sim \mathcal{N}(0, \Lambda^{(n)-1}), \forall n, \forall i_n, \quad (3.10)$$

which in turn are modulated by hyper-prior parameters that follow gamma distributions:

$$\beta \sim \text{Ga}(a_\beta^{0}, b_\beta^{0}), \quad (3.11)$$

$$\lambda^{(n)} \sim \text{Ga}(a_\lambda^{0}, b_\lambda^{0}), \quad (3.12)$$

$$\tau \sim \text{Ga}(a_\tau^{0}, b_\tau^{0}), \quad (3.13)$$
\[ \Lambda^{(n)} = \text{diag}(\lambda^{(n)}) \] and \[ \lambda^{(n)} = \lambda^{(n) R_n}_{r_n, r_n=1}. \]

By pairing conjugate gamma prior distributions with Gaussian likelihoods, which leads to Student-t distributed posterior distributions centered around zero, we concentrate the columns of the factor matrices and the elements of the core tensor around zero. This strategy induces a low-rank structure in \( X \), as shown by Zhao et al. [246, 247]. Importantly, the variance of the core tensor elements and the columns of the factor matrices are regulated by the same hyper-prior parameters. Thus, when the multilinear rank of \( X \) is reduced, both the dimensions of the core tensor and the dimensions of the factor matrices are reduced simultaneously. The multilinear rank of \( X \) is reduced when an element of \( \lambda^{(n) R_n}_{r_n, r_n=1} \) becomes zero.

Based on this formulation, the joint pdf of the tensor measurements and the model parameters is given by:

\[
p(Y, \theta) = p(Y|S, \{U^{(n)}\}_{n=1}^{N}, G, \tau) \prod_{i_1, \cdots, i_N} p(S_{i_1, \cdots, i_N}|D_{i_1, \cdots, i_N}) \cdot \prod_{i_1, \cdots, i_N} p(D_{i_1, \cdots, i_N}) \left[ \prod_{n} p(U^{(n)}|\lambda^{(n)}) \right] \cdot (G|\lambda^{(n)})^{N}_{n=1} p(\lambda^{(n)}) p(\beta) p(\tau),
\]

where \( \theta \) is the set of all the unknown parameters, namely: \( S, \{U^{(n)}\}_{n=1}^{N}, G, \tau, \beta, \lambda^{(n)} \), and the multilinear rank of \( X \).

### 3.2.2 Variational-Bayes Inference

We search for the optimal model parameters using the variational-Bayes inference framework [219]. We use this framework for two reasons: Firstly, because it enables us to estimate the model parameters and the multilinear rank of the Tucker model simultaneously. Secondly, because it is computationally efficient [246, 247].
Variational-Bayes inference is a useful technique to approximate posterior probability distributions. The aim of variational-Bayes inference is to find a variational posterior distribution that minimizes the Kullback-Leibler (KL) divergence with the true posterior distribution. We will denote the variational posterior distribution of the model parameters by $q(\theta)$.

We can rewrite the KL divergence variational posterior distribution and the true posterior distribution as follows [37, 67]:

$$\text{KL} \left[ q(\theta) \mid\mid p(\theta|\mathcal{Y}) \right] = \int_{\theta} q(\theta) \ln \frac{q(\theta)}{p(\theta|\mathcal{Y})} = \mathbb{E}_{q(\theta)} \ln \frac{q(\theta)}{p(\theta|\mathcal{Y})}$$

$$= \mathbb{E}_{q(\theta)} \ln q(\theta) - \mathbb{E}_{q(\theta)} \ln p(\theta, \mathcal{Y}) + \ln p(\mathcal{Y})$$

$$= - \left[ \mathbb{E}_{q(\theta)} \ln p(\theta, \mathcal{Y}) - \mathbb{E}_{q(\theta)} \ln q(\theta) \right] + \ln p(\mathcal{Y})$$

$$= - \mathcal{L}(q(\theta)) + \ln p(\mathcal{Y}),$$

where

$$\mathcal{L}(q(\theta)) = \mathbb{E}_{q(\theta)} \ln p(\theta, \mathcal{Y}) - \mathbb{E}_{q(\theta)} \ln q(\theta) = \int q(\theta) \ln \left[ \frac{p(\mathcal{Y}, \theta)}{q(\theta)} \right] d\theta$$

(3.16)

is called the model evidence and $\ln p(\mathcal{Y})$ is a constant that does not depend on the model parameters.

The first term in the model evidence, $\mathbb{E}_{q(\theta)} \ln p(\theta, \mathcal{Y})$, can be seen as a data fidelity term. We may interpret this term as the inner product between the variational posterior distribution and the logarithm of the joint pdf of the measurements and the model parameters.

The second term in the model evidence, $\mathbb{E}_{q(\theta)} \ln q(\theta)$, is the entropy of the variational posterior distribution. We may interpret this term as a regularization component.

Additionally, using Gibb’s inequality [126], we get that
\[ \text{KL} \left[ q(\theta) \mid\mid p(\theta|\mathcal{Y}) \right] \geq 0 \]
\[ \Rightarrow -\mathcal{L}(q(\theta)) + \ln p(\mathcal{Y}) \geq 0 \]
\[ \Rightarrow \ln p(\mathcal{Y}) \geq \mathcal{L}(q(\theta)). \]

In the variational-Bayes framework, we search for the parameters \( \theta \) that maximize the model evidence and, hence, minimize the KL divergence between the variational posterior distribution and the true posterior distribution, i.e., we search for

\[ q^*(\theta) = \arg\min_{q(\theta)} \text{KL} \left[ q(\theta) \mid\mid p(\theta|\mathcal{Y}) \right] = \arg\min_{q(\theta)} \left\{ \ln[p(\mathcal{Y})] - \mathcal{L}[q(\theta)] \right\} \]
\[ = \arg\max_{q(\theta)} \{ \mathcal{L}[q(\theta)] \}. \] (3.18)

If \( q(\theta) = p(\theta|\mathcal{Y}) \) almost everywhere, then we get that \( \text{KL} \left[ q(\theta) \mid\mid p(\theta|\mathcal{Y}) \right] = 0 \) and \( \ln p(\mathcal{Y}) = \mathcal{L}(q(\theta)) \).

We use the mean field approximation to decouple the latent variables in the variational distribution. The mean field approximation is usually used in variational inference to simplify the calculations [37]. Using this approximation, we get that

\[ q(\theta) = \prod_{i_1, \ldots, i_N} q(S_{i_1, \ldots, i_N}) q(D_{i_1, \ldots, i_N}) \prod_{n=1}^{N} q(\mathcal{U}^{(n)}) q(\mathcal{G}) q(\beta) q(\tau). \] (3.19)

By substituting the variational distribution in the model evidence (3.16) with the expression (3.19) we can decouple the model parameters and we get that

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\[ L(q(\theta)) = \int \cdots \int \prod_j q(\theta_j) \ln p(Y, \theta) \, d\theta_1 \cdots d\theta_N \]
\[ - \int \cdots \int \prod_j q(\theta_j) \sum_j \ln q(\theta_j) \, d\theta_1 \cdots d\theta_N. \] (3.20)

Since, under the mean field approximation, the model parameters are decoupled, we can maximize the model evidence with respect to each parameter while keeping the other parameters constant [37, 67].

If we remove the components of (3.20) that do not depend on \( q(\theta_j) \) for a given \( j \), we obtain

\[ L_j(q(\theta)) = \mathbb{E}_{q(\theta_j)}[\mathbb{E}_{q(\theta \setminus \theta_j)} \ln p(Y, \theta) - \mathbb{E}_{q(\theta_j)} \ln q(\theta_j)] \] (3.21)

To find a general expression for the variational distribution of each parameter, we differentiate (3.21) with respect to the variational distribution of each parameter and set the derivative equal to zero

\[ \frac{dL_j(q(\theta))}{dq(\theta_j)} = \mathbb{E}_{q(\theta \setminus \theta_j)} \ln p(Y, \theta) - \ln q(\theta_j) - 1 = 0 \] (3.22)

After algebraic manipulation, we finally get that

\[ q^*(\theta_j) \propto \exp \mathbb{E}_{q(\theta \setminus \theta_j)}[\ln p(Y, \theta)]. \] (3.23)

In the next subsection, we will use expression 3.23 to find the variational posterior distributions of all the model parameters.
3.2.3 Variational Posterior Distributions

In this subsection we derive the variational posterior distributions for each of the model parameters. We derived these distributions following a similar approach as Zhao et al. [247]. Since the variational posterior distributions exhibit a hierarchical dependence, we can combine these expressions into an iterative algorithm to search for the optimal tensors $S$ and $X$. We will develop this algorithm in the next subsections.

Joint Probability Distribution Function of the Model Parameters and Measurements

To derive the variational posterior distributions, we first need the logarithm of the joint pdf, which is given by:

$$
\ln p(Y, \theta) = \sum_{i_1, \ldots, i_N} \frac{1}{2} \ln(\tau) - \frac{1}{2} \tau \left\{ Y_{i_1, \ldots, i_N} - \left[ \otimes_n u^{(n)}_{i_n}^T \text{vec}(G) + S_{i_1, \ldots, i_N} \right] \right\}^2 
+ \sum_{i_1, \ldots, i_N} \frac{1}{2} \left[ \ln(D_{i_1, \ldots, i_N}) - D_{i_1, \ldots, i_N} \mathcal{S}_{i_1, \ldots, i_N}^2 \right] 
+ \sum_{i_1, \ldots, i_N} \left[ (a^D_0 - 1) \ln(D_{i_1, \ldots, i_N}) - b^D_0 D_{i_1, \ldots, i_N} \right] 
- \sum_{n} \sum_{i_n} \frac{1}{2} \ln|\Lambda^{(n)}| - \frac{1}{2} \left( u^{(n)}_{i_n} \Lambda^{(n)} u^{(n)}_{i_n} \right) - \frac{1}{2} \ln \left| (\beta \otimes \Lambda^{(n)})^{-1} \right| 
- \frac{1}{2} \text{vec}(G)^T (\beta \otimes \Lambda^{(n)}) \text{vec}(G)) + \sum_{n} \sum_{r_n} \left[ (a^\lambda_0 - 1) \ln(\lambda^{(n)}_{r_n}) - b^\lambda_0 \lambda^{(n)}_{r_n} \right] 
+ (a^\beta_0 - 1) \ln \beta - b^\beta_0 \beta + (a^\tau_0 - 1) \ln \tau - b^\tau_0 \tau + C.
$$

where $C$ is a constant.

Here, we used the element-wise form of the Tucker model to simplify the notation of the first term.
Throughout this subsection, we will not calculate the constant terms in the logarithmic expressions of the probability functions, which are the normalization factors of the probability distributions. Instead, to obtain the variational probability distributions, we will rearrange the parameters in a standard form, and we will infer the probability distributions from these forms. Furthermore, we will determine the parameters of the variational distribution probabilities by matching the parameters in these expressions with known expressions of probability distributions.

**Variational Posterior Distribution of the Sparse Tensor $S$**

We will calculate the variational posterior distribution of $S$ using equation (3.23). Specifically, we will take the expected value of expression (3.24) with respect to all the parameters except from $S$. Since we are not interested in the normalizing factor, we will aggregate the expected value of all the terms that do not depend on $S$ in the constant value. In other words, we will only calculate the excepted value of the terms that involve $S$.

Using this procedure, we get

$$
\ln q(S) = \mathbb{E}_{q(\theta, S)} \ln (p(Y, \theta))
\quad
\begin{align*}
&= \mathbb{E}_{q(\theta, S)} \left[ \sum_{i_1, \ldots, i_N} \left\{ -\frac{\tau}{2} \left[ Y_{i_1, \ldots, i_N} - \otimes_n u^{(n)T}_{i_n} \text{vec}(G) - S_{i_1, \ldots, i_N} \right]^2 - \frac{1}{2} D_{i_1, \ldots, i_N} S^2_{i_1, \ldots, i_N} \right\} + C \right] \\
&= \mathbb{E}_{q(\theta)} \left[ \sum_{i_1, \ldots, i_N} \left\{ -\frac{\tau}{2} \left[ -2Y_{i_1, \ldots, i_N} S_{i_1, \ldots, i_N} + 2S_{i_1, \ldots, i_N} \otimes_n u^{(n)T}_{i_n} \text{vec}(G) + S^2_{i_1, \ldots, i_N} \right] \right\} \\
&\quad - \frac{1}{2} D_{i_1, \ldots, i_N} S^2_{i_1, \ldots, i_N} \right\} + C \right] \\
&= \sum_{i_1, \ldots, i_N} S_{i_1, \ldots, i_N} \mathbb{E}_{q(\theta)}[\tau] \left( Y_{i_1, \ldots, i_N} - \otimes_n u^{(n)T}_{i_n} \text{vec}(G) \right) - \frac{1}{2} S^2_{i_1, \ldots, i_N} \left( \mathbb{E}_{q(\theta)}[\tau + D_{i_1, \ldots, i_N}] \right) + C.
\end{align*}
$$

(3.25)
In the last equality, we can recognize the logarithm of the probability function of \( N \) independent Gaussian variables. If \( \mathbf{x} = [x_1, \ldots, x_N]^T \) are independent Gaussian random variables, then

\[
\ln p(\mathbf{x}) \propto \sum_{i=1}^{N} -\frac{1}{2} \left( \frac{x_i - \mu_i}{\sigma_i} \right)^2 \\
\propto \sum_{i=1}^{N} \frac{x_i \mu_i}{\sigma_i^2} - \frac{x_i^2}{2\sigma_i^2}.
\]

(3.26)

Therefore, the variational posterior distribution for the sparse tensor \( \mathbf{S} \) is given by:

\[
q(\mathbf{S}) \sim \prod_{i_1, \ldots, i_N} \mathcal{N}(\tilde{S}_{i_1, \ldots, i_N}, \sigma_{i_1, \ldots, i_N}^2)
\]

(3.27)

where

\[
\tilde{S}_{i_1, \ldots, i_N} = \sigma_{i_1, \ldots, i_N}^2 \mathbb{E}_{q(\theta)}[\tau] \left( Y_{i_1, \ldots, i_N} \otimes u_{i_n}^{(n)T} \text{vec}(G) \right)
\]

(3.28)

and

\[
\sigma_{i_1, \ldots, i_N}^2 = \left[ \mathbb{E}_{q(\theta)}(\tau + \mathcal{D}_{i_1, \ldots, i_N}) \right]^{-1}.
\]

(3.29)

**Variational Posterior Distribution of the Sparse Tensor \( \mathcal{D} \)**

Here, we follow the same procedure as before and obtain
\[\ln q(\mathcal{D}) = E_{q(\theta \mid \mathcal{D})} \ln(p(\mathcal{Y}, \theta))\]

\[= E_{q(\theta \mid \mathcal{D})} \left[ \sum_{i_1, \ldots, i_N} \frac{1}{2} \left[ \ln(\mathcal{D}_{i_1, \ldots, i_N}) - \mathcal{D}_{i_1, \ldots, i_N} S_{i_1, \ldots, i_N}^2 \right] + (a_0^D - 1) \ln(\mathcal{D}_{i_1, \ldots, i_N}) - b_0^D \mathcal{D}_{i_1, \ldots, i_N} \right] + C\]

\[= \sum_{i_1, \ldots, i_N} (a_D^0 + \frac{1}{2}) - 1 \ln \mathcal{D}_{i_1, \ldots, i_N} - \left[ b_0^D + \frac{1}{2} E_{q(\theta)} \left(S_{i_1, \ldots, i_N}^2\right) \right] \mathcal{D}_{i_1, \ldots, i_N} + C\]

\[= \sum_{i_1, \ldots, i_N} (a_D^0 + \frac{1}{2}) - 1 \ln \mathcal{D}_{i_1, \ldots, i_N} - \left[ b_0^D + \frac{1}{2} \left( \sigma_{i_1, \ldots, i_N}^2 + S_{i_1, \ldots, i_N}^2 \right) \right] \mathcal{D}_{i_1, \ldots, i_N} + C.\]

(3.30)

We notice that the expression in the last line resembles the logarithm of the probability distribution of \(N\) independent Gamma random variables.

The logarithm of the probability distribution of \(N\) independent Gamma random variables, with parameters \(\alpha = [\alpha_1, \ldots, \alpha_N]^T\) and \(\beta = [\beta_1, \ldots, \beta_N]^T\), is given by

\[\ln p(x) \propto \sum_{i=1}^{N} (\alpha_i - 1) \ln x_i - \frac{x_i}{\beta_i}.\]  

(3.31)

Therefore, the variational posterior distribution for \(\mathcal{D}\) is given by:

\[q(\mathcal{D}_{i_1, \ldots, i_N}) \sim \prod_{i_1, \ldots, i_N} \text{Ga}(a_D^0, b_D^{i_1, \ldots, i_N})\]  

(3.32)

where

\[a_D^0 = a_0^D + \frac{1}{2}\]  

(3.33)
\[ b^{D_{i_1, \ldots, i_N}} = b_0^D + \frac{1}{2} \left( \sigma^2_{i_1, \ldots, i_N} + \tilde{S}^2_{i_1, \ldots, i_N} \right). \] (3.34)

**Variational Posterior Distribution of the Factor Matrices \( U^{(n)} \)**

We derive these distributions using the matrix notation of the Tucker model. By using this notation, we can calculate the expected value of the first term below using its trace. In this model, each row of \( U^{(n)} \), has a multivariate normal distribution given in expression (3.10). Therefore, we seek the variational distribution of each row of \( U^{(n)} \), denoted by \( u_{i_n}^{(n)} \).

By taking the expectation described in expression (3.23) of the logarithm of the joint distribution, we get
\[ \ln q(U^{(n)}) = \mathbb{E}_{q(\theta \mid U^{(n)})} \ln(p(Y, \theta)) = \mathbb{E}_{q(\theta \mid U^{(n)})} \left[ -\frac{1}{2} \| Y - X - S \|_F^2 - \frac{1}{2} \sum_{i=1}^{I_n} u^{(n)}_{i,n} T \Lambda^{(n)} u^{(n)}_{i,n} \right] + C \]

\[ = \mathbb{E}_{q(\theta \mid U^{(n)})} \left[ \tau \text{tr} \left( U^{(n)} G^{(n)} \otimes U^{(k)T} Y^{(n)T} \right) - \frac{1}{2} \text{tr} \left( U^{(n)} G^{(n)} \otimes U^{(k)T} \otimes U^{(k)G^{(n)T}} U^{(n)T} \right) \right] - \frac{1}{2} \sum_{i=1}^{I_n} u^{(n)}_{i,n} T \Lambda^{(n)} u^{(n)}_{i,n} + C \]

\[ = \sum_{i=1}^{I_n} \mathbb{E}_{q(\theta \mid U^{(n)})} u^{(n)T}_{i,n} \mathbb{E}_{q(\theta)} \left[ \left( G^{(n)} \otimes U^{(k)T} \right) \left( Y^{(n)T} - S^{(n)T} \right) \right]_{i,n} - \frac{1}{2} \sum_{i=1}^{I_n} u^{(n)T}_{i,n} \Lambda^{(n)} u^{(n)}_{i,n} + C \]

\[ = \sum_{i=1}^{I_n} \mathbb{E}_{q(\theta \mid U^{(n)})} u^{(n)T}_{i,n} \mathbb{E}_{q(\theta)} \left[ \left( G^{(n)} \otimes U^{(k)T} U^{(k)} \right) G^{(n)T} \right]_{i,n} + \Lambda^{(n)} \int_{i,n} \}

Therefore, the variational posterior distributions of the factor matrices are given by:

\[ q(U^{(n)}) \sim \prod_{i=1}^{N} \mathcal{N} \left( \hat{u}^{(n)}_{i,n}, \Sigma^{(n)}_U \right) , \quad n = 1, \ldots, N \quad (3.36) \]

where

\[ \hat{u}^{(n)}_{i,n} = \sum_{l} \mathbb{E}_{q(\theta)} [\tau] \mathbb{E}_{q(\theta)} \left[ G^{(n)} \otimes U^{(k)T} \left( Y^{(n)T} - S^{(n)T} \right) \right]_{i,n} \quad (3.37) \]

and

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\[
\sum_{u_{(n)}} = \left\{ \mathbb{E}_{q(\theta)}[\tau] \mathbb{E}_{q(\theta)} \left[ G_{(n)} \left( \bigotimes_{k \neq n} U^{(k)T} U^{(k)} \right) G_{(n)}^T + \Lambda_{(n)} \right] \right\}^{-1}. \tag{3.38}
\]

**Variational Posterior Distribution of the Core Tensor \( G \)**

In this model, the vectorized form of \( G \) has a multivariate Gaussian distribution. The structure of this distribution associates the elements of \( G \) with the corresponding elements of \( U^{(n)} \) by using the same prior distribution. Since we use a vectorized form of \( G \) to derive this variational posterior distribution, we will use the vector form of the Tucker model.

\[
\ln (G) = \mathbb{E}_{q(\theta|G)} \ln (p(Y, \theta)) \\
= \mathbb{E}_{q(\theta|G)} \left[ -\frac{\tau}{2} \left\| \text{vec}(Y) - \text{vec}(X) - \text{vec}(S) \right\|_F^2 - \frac{1}{2} \text{vec}(G)^T (\beta \otimes \Lambda_{(n)}) \text{vec}(G) \right] + C \\
= \mathbb{E}_{q(\theta)}[\tau] \mathbb{E}_{q(\theta|G)} \left[ \text{vec}(X)^T \text{vec}(Y) - \frac{1}{2} \text{vec}(X)^T \text{vec}(X) - \text{vec}(X)^T \text{vec}(S) \\
- \frac{1}{2} \text{vec}(G)^T (\beta \otimes \Lambda_{(n)}) \text{vec}(G) \right] + C \\
= \mathbb{E}_{q(\theta)}[\tau] \mathbb{E}_{q(\theta|G)} \left[ \text{vec}(G)^T \left( \bigotimes_{n} U^{(n)T} \right) \text{vec}(Y) - \frac{1}{2} \text{vec}(G)^T \left( \bigotimes_{n} U^{(n)T} \right) \left( \bigotimes_{n} U^{(n)} \right) \text{vec}(G) \\
- \text{vec}(G)^T \left( \bigotimes_{n} U^{(n)} \right) \text{vec}(S) - \frac{1}{2} \text{vec}(G)^T (\beta \otimes \Lambda_{(n)}) \text{vec}(G) \right] + C \\
= \mathbb{E}_{q(\theta)}[\tau] \mathbb{E}_{q(\theta)} \left[ \left( \bigotimes_{n} U^{(n)T} \right) \text{vec}(Y) - \left( \bigotimes_{n} U^{(n)T} \right) \text{vec}(S) \\
- \frac{1}{2} \text{vec}(G)^T \left( \bigotimes_{n} U^{(n)} \right) \text{vec}(Y) + \beta \otimes \Lambda_{(n)} \right] \text{vec}(G) + C \\
= \text{vec}(G)^T \mathbb{E}_{q(\theta)}[\tau] \left[ \left( \bigotimes_{n} \mathbb{E}_{q(\theta)}[U^{(n)T}] \right) \text{vec}(Y) - \left( \bigotimes_{n} \mathbb{E}_{q(\theta)}[U^{(n)T}] \right) \mathbb{E}_{q(\theta)}[\text{vec}(S)] \\
- \frac{1}{2} \text{vec}(G)^T \left\{ \mathbb{E}_{q(\theta)}[\tau] \left( \bigotimes_{n} \mathbb{E}_{q(\theta)}[U^{(n)T}] \right) + \mathbb{E}_{q(\theta)}[\beta] \otimes \mathbb{E}_{q(\theta)}[\Lambda_{(n)}] \right\} \text{vec}(G) \right] + C. \tag{3.39}
\]

Thus, the variational posterior distribution of the core tensor is given by:
\[ q(\mathcal{G}) \sim \mathcal{N}(\text{vec}(\tilde{\mathcal{G}}), \Sigma_{\mathcal{G}}), \tag{3.40} \]

where

\[
\text{vec}(\tilde{\mathcal{G}}) = \Sigma_{\mathcal{G}} \mathbb{E}_{q(\theta)}[\tau] \left[ \left( \otimes_{n} \mathbb{E}_{q(\theta)}[U^{(n)}] \right) \left( \text{vec}(\mathcal{Y}) - \mathbb{E}_{q(\theta)}[\text{vec}(\mathcal{S})] \right) \right] \tag{3.41}
\]

and

\[
\Sigma_{\mathcal{G}} = \left\{ \mathbb{E}_{q(\theta)}[\tau] \left( \otimes_{n} \mathbb{E}_{q(\theta)}[U^{(n)}U^{(n)T}] \right) + \mathbb{E}_{q(\theta)}[\beta] \otimes_{n} \mathbb{E}_{q(\theta)}[\Lambda^{(n)}] \right\}^{-1}. \tag{3.42}
\]

Since the matrix inversion in expression (3.42) can be very slow and require a large amount of memory, we will use theorem 4.2 in [246] to compute this matrix inversion efficiently.

**Variational Posterior Distribution of \( \Lambda \)**

The hyper-prior parameters \( \lambda_{n}^{(n)} \) regulate the multilinear rank of \( \mathcal{X} \). If the value of these parameters becomes large, then the distributions of the respective elements of \( U^{(n)} \) and \( \mathcal{G} \) become concentrated around zero. Once a row of \( U^{(n)} \) and the corresponding elements in \( \mathcal{G} \) become close to zero, we can remove these elements without modifying the model and thus, reduce the rank of the model.

By taking the expectation of (3.24) according to expression (3.23) we get
\[ \ln q(\Lambda) = \mathbb{E}_{q(\theta|\Lambda)} \ln(p(Y, \theta)) \]

\[ = \mathbb{E}_{q(\theta|\Lambda)} \left[ \sum_{n} \sum_{r_n} \left[ -\frac{1}{2} \ln |\Lambda^{(n)}|^{-1} - \frac{1}{2} (\mathbf{u}_{i_n}^{(n)})^T \Lambda^{(n)} \mathbf{u}_{i_n}^{(n)} \right] - \frac{1}{2} \ln |(\beta \otimes \Lambda^{(n)})|^{-1} \right] 
- \frac{1}{2} \text{vec}(\mathcal{G})^T (\beta \otimes \Lambda^{(n)}) \text{vec}(\mathcal{G}) + \sum_{n} \sum_{r_n} [(a_0^\lambda - 1) \ln (\lambda^{(n)}_{r_n}) - b_0^\lambda \lambda^{(n)}_{r_n}] + C \]

\[ = \mathbb{E}_{q(\theta|\Lambda)} \left\{ \sum_{n} \frac{I_n}{2} \sum_{r_n} \ln \lambda^{(n)}_{r_n} - \frac{1}{2} \sum_{n} \sum_{r_n} \lambda^{(n)}_{r_n} \mathbf{u}_{i_n}^{(n)}^T \mathbf{u}_{i_n}^{(n)} + \frac{1}{2} \sum_{n} \prod_{k \neq n} R_k \sum_{r_n} \ln \lambda^{(n)}_{r_n} \right. 
- \frac{1}{2} \sum_{n} \sum_{r_n} \beta \text{vec}(\mathcal{G}_{r_n \ldots \ldots \ldots \ldots})^T (\otimes \lambda^{(k)}) + \sum_{n} \sum_{r_n} [(a_0^\lambda - 1) \ln (\lambda^{(n)}_{r_n}) - b_0^\lambda \lambda^{(n)}_{r_n}] \left. \right\} + C, \] (3.43)

where in the first transition we used

\[ -\ln |(\beta \otimes \Lambda^{(n)})|^{-1} = \ln |(\beta \otimes \Lambda^{(n)})| = \ln \left( \beta \prod_{n=1}^{N} R_n |\Lambda^{N} \otimes \ldots \otimes \Lambda^{1}| \right) \]

\[ = \ln \left( \beta \prod_{n=1}^{N} R_n |\Lambda^{N} | \prod_{n=1}^{N-1} |\Lambda^{N-1} \otimes \ldots \otimes \Lambda^{1}| R_N \right) \]

\[ = \ln \left( \beta \prod_{n=1}^{N} R_n \prod_{n=1}^{N} |\Lambda^{n} | \prod_{k \neq n} R_k \right) \]

\[ = \sum_{n=1}^{N} R_n \ln(\beta) + \sum_{n} \prod_{k \neq n} R_k \sum_{r_n} \ln \lambda^{(n)}_{r_n}. \] (3.44)

Therefore, the variational posterior distributions for \( \lambda^{(n)} \), \( n = 1, \ldots, N \) are given by:

\[ q(\lambda^{(n)}) \sim \prod_{r_n=1}^{R_n} \text{Ga} \left( a^{\lambda^{(n)}_{r_n}}, b^{\lambda^{(n)}_{r_n}} \right) \] (3.45)

where
\[ a^{\lambda \{n\}} = a_0^\lambda + \frac{I_n}{2} + \frac{1}{2} \prod_{k\neq n} R_k \]  \hspace{1cm} (3.46)

and

\[ b^{\lambda \{n\}} = b_0^\lambda + \frac{1}{2} \mathbb{E}_{q(\theta)}[u_{\lambda,n}^T u_{\lambda,n}^{(n)}] + \frac{1}{2} \mathbb{E}_{q(\theta)}[\beta] \mathbb{E}_{q(\theta)} \left[ \text{vec}(G_{\ldots n} \Lambda_{\ldots n})^T (\otimes \Lambda^{(k)}) \right]. \hspace{1cm} (3.47) \]

**Variational Posterior Distribution of \( \beta \)**

Below, we show the derivation for this distribution. Here we used (3.44) again.

\[
\ln q(\beta) = \mathbb{E}_{q(\theta \setminus \beta)} \ln(p(Y, \Theta)) = -\frac{1}{2} \ln \left( \beta \otimes \Lambda^{(n)} \right)^{-1} - \frac{1}{2} \text{vec}(G)^T (\beta \otimes \Lambda^{(n)}) \text{vec}(G) + (a_0^\beta - 1) \ln \beta - b_0^\beta \beta + C \\
= \frac{1}{2} \prod_{n} R_n \ln \beta - \frac{1}{2} \text{vec}(G)^T (\beta \otimes \Lambda^{(n)}) \text{vec}(G) + (a_0^\beta - 1) \ln \beta - b_0^\beta \beta + C.
\]

(3.48)

Therefore, the variational posterior distribution for \( \beta \) is given by:

\[ q(\beta) \sim \text{Ga}(a^\beta, b^\beta) \hspace{1cm} (3.49) \]

where

\[ a^\beta = a_0^\beta + \frac{1}{2} \prod_{n} R_n \hspace{1cm} (3.50) \]

and
\[ b^\beta = b_0^\beta + \frac{1}{2} \mathbb{E}_{q(\theta)} \left[ \text{vec}(\mathcal{G})^T (\otimes \Lambda^{(n)}) \text{vec}(\mathcal{G}) \right]. \] (3.51)

**Variational Posterior Distribution of \( \tau \)**

Lastly, we derive the distribution of the measurement noise precision \( \tau \).

\[
\ln q(\tau) = \mathbb{E}_{q(\theta, \tau)} \ln(p(Y, \Theta)) \\
= \mathbb{E}_{q(\theta, \tau)} \left[ \prod_{n=1}^{N} \frac{I_n}{2} \ln \tau - \frac{1}{2} ||Y - X - S||^2_F \tau + (a_0^{\tau} - 1) \ln \tau - b_0^{\tau} \right] + C \quad (3.52)
\]

Thus, the variational posterior distribution for \( \tau \) is given by:

\[ q(\tau) \sim \text{Ga}(a^{\tau}, b^{\tau}) \] (3.53)

where

\[ a^{\tau} = a_0^{\tau} + \prod_{n=1}^{N} \frac{I_n}{2} \] (3.54)

and

\[ b^{\tau} = b_0^{\tau} + \frac{1}{2} \mathbb{E}_{q(\theta)} ||Y - X - S||^2_F. \] (3.55)

Furthermore, we can calculate \( \mathbb{E}_{q(\theta)} ||Y - X - S||^2_F \) using the vectorial notation:
\[
\mathbb{E}_q(||\mathcal{Y} - \mathcal{X} - S||_F^2) = \mathbb{E}_q(\theta) \left\{ [\text{vec}(\mathcal{Y})^T - \text{vec}(\mathcal{X})^T - \text{vec}(\mathcal{S})^T] [\text{vec}(\mathcal{Y}) - \text{vec}(\mathcal{X}) - \text{vec}(\mathcal{S})] \right\}
\]

\[
= \mathbb{E}_q(\theta) \left[ \text{vec}(\mathcal{Y})^T \text{vec}(\mathcal{Y}) - 2\text{vec}(\mathcal{Y})^T \text{vec}(\mathcal{X}) - 2\text{vec}(\mathcal{Y})^T \text{vec}(\mathcal{S}) + \text{vec}(\mathcal{X})^T \text{vec}(\mathcal{X}) + 2\text{vec}(\mathcal{X})^T \text{vec}(\mathcal{S}) + \text{vec}(\mathcal{S})^T \text{vec}(\mathcal{S}) \right]
\]

\[
= ||\mathcal{Y}||_F^2 - 2\text{vec}(\mathcal{Y})^T \mathbb{E}_q(\theta) \text{vec}(\mathcal{X}) - 2\text{vec}(\mathcal{Y})^T \mathbb{E}_q(\theta) \text{vec}(\mathcal{S}) + 2\text{vec}(\mathcal{Y})^T \mathbb{E}_q(\theta) [\text{vec}(\mathcal{S})]
\]

\[
+ 2\mathbb{E}_q(\theta) \text{vec}(\mathcal{S})^T \mathbb{E}_q(\theta) \text{vec}(\mathcal{X}) + 2 \mathbb{E}_q(\theta) \text{vec}(\mathcal{X})^T \text{vec}(\mathcal{X}) + 2 \mathbb{E}_q(\theta) \text{vec}(\mathcal{X})^T \text{vec}(\mathcal{S}) + \mathbb{E}_q(\theta) [\text{vec}(\mathcal{S})^T \text{vec}(\mathcal{S})].
\]

(3.56)

In the last equality, we used the mean field approximation to decouple expected values.

**Model Evidence**

In the previous subsection, we sought a variational pdf \( q(\theta) \) to approximate the true posterior distribution of the model parameters \( p(\theta|\mathcal{Y}) \) by maximizing the model evidence. In this subsection, we derive an expression for the model evidence. We will use this expression to both monitor the convergence of our algorithm and update the model hyperparameters, using a similar approach as Zhao et al. \([246, 247]\).

The model evidence is given by:
\[ \mathcal{L}(q(\theta)) = \int q(\theta) \ln \left[ \frac{p(y, \theta)}{q(\theta)} \right] d\theta = \mathbb{E}_{q(\theta)} \ln(p(y, \theta)) - \mathbb{E}_{q(\theta)} \ln(q(\theta)) \]

\[ = \mathbb{E}_{q(\{u^{(n)}\}_{n=1}^{N}, g, s, \tau)} \ln[p(y|\{u^{(n)}\}_{n=1}^{N}, g, s, \tau)] + \mathbb{E}_{q(\{u^{(n)}\}_{n=1}^{N}, \lambda^{(n)})} \ln \left( \prod_{n=1}^{N} p(\{u^{(n)}\}_{n=1}^{N}|\lambda^{(n)}) \right) \]

\[ + \mathbb{E}_{q(\{\lambda^{(n)}\}_{n=1}^{N}, \beta)} \ln[p(\mathcal{H}|\{\lambda^{(n)}\}_{n=1}^{N}, \beta)] + \mathbb{E}_{q(s, \mathcal{D})} \ln[p(\mathcal{S}|\mathcal{D})] + \mathbb{E}_{q(\lambda^{(n)})} \ln \left( \prod_{n=1}^{N} p(\lambda^{(n)}) \right) \]

\[ + \mathbb{E}_{q(\beta)} \ln[p(\beta)] + \mathbb{E}_{q(\mathcal{D})} \ln[p(\mathcal{D})] + \mathbb{E}_{q(\tau)} \ln[p(\tau)] \]

\[ - \mathbb{E}_{q(\{u^{(n)}\}_{n=1}^{N})} \ln \left( \prod_{n=1}^{N} q(u^{(n)}) \right) - \mathbb{E}_{q(\mathcal{G})} \ln[q(\mathcal{G})] - \mathbb{E}_{q(\{\lambda^{(n)}\}_{n=1}^{N})} \ln \left( \prod_{n=1}^{N} q(\lambda^{(n)}) \right) \]

\[ - \mathbb{E}_{q(s)} \ln[q(s)] - \mathbb{E}_{q(\beta)} \ln[q(\beta)] - \mathbb{E}_{q(\mathcal{D})} \ln[q(\mathcal{D})] - \mathbb{E}_{q(\tau)} \ln[q(\tau)], \]

(3.57)

where each of the terms above can be calculated as shown below. For simplicity, we use \( \mathbb{E}_q \) on the right hand side of the expressions below to denote the expectation with respect to \( q(\Theta) \), where \( \Theta \) is the set of relevant parameters. In the expressions below, \( \psi(\cdot) \) denotes the digamma function and \( \Gamma \) denotes the gamma function.

The data fidelity terms in expression (3.57) are given by:

\[ \mathbb{E}_{q(\{u^{(n)}\}_{n=1}^{N}, g, s, \tau)} \ln[p(y|\{u^{(n)}\}_{n=1}^{N}, g, s, \tau)] \]

\[ = \frac{1}{2} \prod_{n=1}^{N} I_n \mathbb{E}_q \ln(\tau) - \frac{1}{2} \mathbb{E}_q[\tau] \mathbb{E}_q \|y - \mathcal{X} - \mathcal{S}\|_F^2 - \frac{1}{2} \prod_{n=1}^{N} I_n \ln(2\pi) \]

\[ = \frac{1}{2} \prod_{n=1}^{N} I_n (\psi(a^\tau) - \ln(b^\tau)) - \frac{1}{2} \frac{\alpha^\tau}{b^\tau} \mathbb{E}_q \|y - \mathcal{X} - \mathcal{S}\|_F^2 - \frac{1}{2} \prod_{n=1}^{N} I_n \ln(2\pi), \]

(3.58)
\[
\mathbb{E}_q(\{U^{(n)}\}_{n=1}^N, \lambda^{(n)}) \ln \prod_{n=1}^N [p(\{U^{(n)}\}_{n=1}^N | \lambda^{(n)})]
\]

\[
= \mathbb{E}_q \frac{1}{2} \sum_n \sum_{i_n} \left[ \ln |\Lambda^{(n)}| - \mathbf{u}_{i_n}^{(n)}^T \Lambda^{(n)} \mathbf{u}_{i_n}^{(n)} - R_n \ln(2\pi) \right]
\]

\[
= \frac{1}{2} \sum_n \sum_{i_n} \left\{ \mathbb{E}_q \left[ \ln \left( \prod_{r_n} \lambda_{r_n}^{(n)} \right) \right] - \text{tr} \left[ \mathbb{E}_q \Lambda^{(n)} \text{cov}(\mathbf{u}_{i_n}^{(n)}) + \mathbb{E}_q \mathbf{u}_{i_n}^{(n)} \mathbb{E}_q \Lambda^{(n)} \mathbb{E}_q \mathbf{u}_{i_n}^{(n)} \right] - R_n \ln(2\pi) \right\}
\]

\[
= \frac{1}{2} \sum_n I_n \sum_{r_n} \mathbb{E}_q \ln(\lambda_{r_n}^{(n)}) - \frac{1}{2} \sum_n \sum_{i_n} \left\{ \mathbb{E}_q \text{tr} \left[ \mathbb{E}_q \Lambda^{(n)} \text{cov}(\mathbf{u}_{i_n}^{(n)}) + \mathbb{E}_q \mathbf{u}_{i_n}^{(n)} \mathbb{E}_q \Lambda^{(n)} \mathbb{E}_q \mathbf{u}_{i_n}^{(n)} \right] \right\}
\]

\[
- \frac{1}{2} \sum_n I_n R_n \ln(2\pi)
\]

\[
= \sum_n \frac{I_n}{2} \sum_{r_n} (\psi(a^{(n)}_{r_n}) - \ln(b^{(n)}_{r_n}))
\]

\[
- \frac{1}{2} \sum_n \sum_{i_n} \left\{ \mathbb{E}_q \text{tr} \left[ \mathbb{E}_q \Lambda^{(n)} \text{cov}(\mathbf{u}_{i_n}^{(n)}) + \mathbb{E}_q \mathbf{u}_{i_n}^{(n)} \mathbb{E}_q \Lambda^{(n)} \mathbb{E}_q \mathbf{u}_{i_n}^{(n)} \right] \right\}
\]

\[
- \frac{1}{2} \sum_n I_n R_n \ln(2\pi),
\]

(3.59)
\[
\mathbb{E}_{q(\mathcal{G}, \{\lambda^{(n)}\}_{n=1}^N, \beta)} \ln[p(\mathcal{G} | \{\lambda^{(n)}\}_{n=1}^N, \beta)]
\]

\[
= \frac{1}{2} \mathbb{E}_q \left[ \ln \left( \beta \otimes \lambda^{(n)} \right) - \text{vec}(\mathcal{G})^T (\beta \otimes \lambda^{(n)}) \text{vec}(\mathcal{G}) - \frac{1}{2} \prod_{n=1}^N R_n \ln(2\pi) \right]
\]

\[
= \frac{1}{2} \prod_{n=1}^N R_n \ln(\beta) + \frac{1}{2} \sum_n \prod_{n \neq k} R_k \sum_{r_n=1}^{R_n} \mathbb{E}_q \ln(\lambda^{(n)}_{r_n})
\]

\[
- \frac{1}{2} \mathbb{E}_q \beta \sum_{(r_1, \ldots, r_N)} \mathbb{E}_q \mathcal{G}^2_{(r_1, \ldots, r_N)} [\lambda^{(n)}_{r_n} \times \cdots \lambda^{(1)}_{r_1}] - \frac{1}{2} \prod_{n=1}^N R_n \ln(2\pi)
\]

\[
= \frac{1}{2} \prod_{n=1}^N R_n \ln(\beta) + \frac{1}{2} \sum_n \prod_{n \neq k} R_k \sum_{r_n=1}^{R_n} \left[ \psi(a^{\lambda^{(n)}_{r_n}}) - \ln(b^{\lambda^{(n)}_{r_n}}) \right]
\]

\[
- \frac{1}{2} \frac{\alpha_{a}}{b_{\beta}} \sum_{(r_1, \ldots, r_N)} \mathbb{E}_q \mathcal{G}^2_{(r_1, \ldots, r_N)} \left[ \mathbb{E}_q (\lambda^{(n)}_{r_n}) \times \cdots \mathbb{E}_q (\lambda^{(1)}_{r_1}) \right] - \frac{1}{2} \prod_{n=1}^N R_n \ln(2\pi),
\]

(3.60)

\[
\mathbb{E}_{q(\mathcal{S}, \mathcal{D})} \ln[p(\mathcal{S} | \mathcal{D})] = \frac{1}{2} \sum_{i_1, \ldots, i_N} \left[ \mathbb{E}_q \ln(D_{i_1, \ldots, i_N}) - \mathbb{E}_q D_{i_1, \ldots, i_N} \mathbb{E}_q S^2_{i_1, \ldots, i_N} - \ln(2\pi) \right]
\]

\[
= \frac{1}{2} \sum_{i_1, \ldots, i_N} \left[ \psi(a^\mathcal{D}) - \ln(b^\mathcal{D}_{i_1, \ldots, i_N}) - \frac{a^\mathcal{D}}{b^\mathcal{D}_{i_1, \ldots, i_N}} (\sigma^2_{i_1, \ldots, i_N} + S_{i_1, \ldots, i_N}) - \ln(2\pi) \right],
\]

(3.61)

\[
\mathbb{E}_{q(\lambda^{(n)})_{n=1}^N} \ln \left[ \prod_{n=1}^N p(\lambda^{(n)}) \right] = \sum_n \sum_{r_n} \left[ (a^\lambda_0 - 1) \mathbb{E}_q \ln(\lambda^{(n)}_{r_n}) - b^\lambda_0 \mathbb{E}_q \lambda^{(n)}_{r_n} + a^\lambda_0 \ln(b^\lambda_0) - \ln[\Gamma(a^\lambda_0)] \right]
\]

\[
= \sum_n \sum_{r_n} \left\{ (a^\lambda_0 - 1) \left[ \psi(\lambda^{(n)}_{r_n}) - \ln(b^{\lambda^{(n)}_{r_n}}) \right] - b^\lambda_0 \frac{a^{\lambda^{(n)}_{r_n}}}{b^{\lambda^{(n)}_{r_n}}} + a^\lambda_0 \ln(b^\lambda_0) - \ln[\Gamma(a^\lambda_0)] \right\},
\]

(3.62)
\[ \mathbb{E}_q(\beta) \ln[p(\beta)] = [(a_0^\beta - 1)\mathbb{E}_q \ln(\beta) - b_0^\beta \mathbb{E}_q \beta] \]
\[ = (a_0^\beta - 1)[\psi(a^\beta) - \ln(b^\beta)] - b_0^\beta a^\beta + a_0^\beta \ln(b_0^\beta) - \ln[\Gamma(a_0^\beta)], \quad (3.63) \]

\[ \mathbb{E}_q(D) \ln[p(D)] = \sum_{i_1, \ldots, i_N} \left\{ (a_0^D - 1)\mathbb{E}_q \ln(D_{i_1, \ldots, i_N}) - b_0^D \mathbb{E}_q D_{i_1, \ldots, i_N} + a_0^D \ln(b_0^D) - \ln[\Gamma(a_0^D)] \right\} \]
\[ = \sum_{i_1, \ldots, i_N} \left\{ (a_0^D - 1)[\psi(a^D) - \ln(b^D_{i_1, \ldots, i_N})] - b_0^D \frac{a^D}{b^D_{i_1, \ldots, i_N}} + a_0^D \ln(b_0^D) - \ln[\Gamma(a_0^D)] \right\}, \quad (3.64) \]

\[ \mathbb{E}_q(\tau) \ln[p(\tau)] = [(a_0^\tau - 1)\mathbb{E}_q \ln(\tau) - b_0^\tau \mathbb{E}_q \tau] \]
\[ = (a_0^\tau - 1)[\psi(a^\tau) - \ln(b^\tau)] - b_0^\tau a^\tau + a_0^\tau \ln(b_0^\tau) - \ln[\Gamma(a_0^\tau)]. \quad (3.65) \]

The terms below correspond to the entropy terms in the model evidence. To calculate these terms, we use known expressions for the entropy of standard distributions.

The entropy terms are given by:

\[ -\mathbb{E}_q(U^{(n)}) \ln \left[ \prod_{n=1}^N q(U^{(n)}) \right] = -\sum_n \mathbb{E}_q(U^{(n)})[\ln q(U^{(n)})] \]
\[ = \sum_n \sum_{i_n} \frac{1}{2} \ln |\Sigma_{u_{i_n}}| + \frac{1}{2} \sum_n I_n R_n [1 + \ln(2\pi)], \quad (3.66) \]
\[- \mathbb{E}_q[\ln q(G)] = \frac{1}{2} \ln |\Sigma_G| + \frac{1}{2} \prod_n R_n [1 + \ln(2\pi)], \quad (3.67)\]

\[- \mathbb{E}_q[\ln q(S)] = \frac{1}{2} \sum_{i_1, \ldots, i_N} \ln[(\sigma^2_{i_1, \ldots, i_N})^{2\pi e}], \quad (3.68)\]

\[- \mathbb{E}_q(\Lambda^{(n)}) \prod_{n=1}^{N} q(\Lambda^{(n)}) = - \sum_n \mathbb{E}_q(A^{(n)}) \ln q(A^{(n)})] = \sum_n \sum_r \ln \Gamma(a^{(n)}_{r_n}) - (a^{(n)}_{r_n} - 1) \psi(a^{(n)}_{r_n}) - \ln(b^{(n)}_{r_n}) + a^{(n)}_{r_n}, \quad (3.69)\]

\[- \mathbb{E}_q(\beta) \ln q(\beta) = \ln(\Gamma(a^\beta)) - (a^\beta - 1) \psi(a^\beta) - \ln(b^\beta) + a^\beta, \quad (3.70)\]

\[- \mathbb{E}_q(D) \ln q(D) = \sum_{i_1, \ldots, i_N} \ln(\Gamma(a^P_{i_1, \ldots, i_N})) - (a^P_{i_1, \ldots, i_N} - 1) \psi(a^P_{i_1, \ldots, i_N}) - \ln(b^P_{i_1, \ldots, i_N}) + a^P_{i_1, \ldots, i_N}, \quad (3.71)\]

and

\[- \mathbb{E}_q(\tau) \ln q(\tau) = \ln(\Gamma(a^\tau)) - (a^\tau - 1) \psi(a^\tau) - \ln(b^\tau) + a^\tau. \quad (3.72)\]
3.2.4 Algorithm Implementation

We use an iterative algorithm to find the optimal tensors $S$ and $X$. In the previous subsection, we obtained expressions for the variational posterior distributions of the model parameters. However, the parameters of these distributions are coupled in a hierarchical structure. Thus, to find these parameters we can update them iteratively, using an approach similar to the expectation-maximization (EM) algorithm. To maintain the flow of information from the measurements towards the hyper-parameters, we first update the variational posterior distributions of the lowest-level parameters (i.e., $S$, $U^{(n)}$, $G$, and $\tau$), next we update their prior parameters (i.e., $D$, $\lambda_{r_n}^{(n)}$, and $\beta$), and then we update the hyperparameters. We repeat this procedure until convergence, as shown by Zhao et al. [247].

We initialize our algorithm by first setting all the top-level hyperparameters ($a_D^0$, $b_D^0$, $a_\lambda^0$, $b_\lambda^0$, $a_\beta^0$, $b_\beta^0$, $a_\tau^0$, and $b_\tau^0$) to $10^{-6}$ so that we begin the iterations using noninformative priors, as shown by [247]. Afterwards, for initialization, we draw the prior parameters ($D$, $\lambda_{r_n}^{(n)}$, and $\beta$) from their respective probability distributions. Then, we draw the sparse tensor ($S$), the factor matrices ($U^{(n)}$), and the core tensor ($G$) from Gaussian distributions with zero mean and standard deviation according to their respective prior parameters. We initialize the multilinear rank of $X$, which determines the ranks of the factor matrices and the core tensor as $R_{n=1}^N = \min(I_n, \prod_{k=1; k \neq n}^N I_k)$.

In each iteration, we update the variational posterior distributions of the model parameters using the expressions shown in the previous subsection. Additionally, we update the model hyperparameters by maximizing the model evidence with respect to these hyperparameters. Specifically, the model evidence depends on $a_D^0$ and $b_D^0$ only through equation (3.64), on $a_\lambda^0$ and $b_\lambda^0$ only through equation (3.62), on $a_\beta^0$ and $b_\beta^0$ only through equation (3.63), and on $a_\tau^0$ and $b_\tau^0$ only through equation (3.65). We update these parameters to the values that maximize these equations in each iteration. We iterate our algorithm until the model evidence converges.

The pseudocode for our statistical tensor decomposition method is presented below.
Algorithm

**Input:** Measurement tensor ($Y \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$)

**Output:** Localized activity tensor ($S \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$) and distributed activity tensor ($X \in \mathbb{R}^{I_1 \times I_2 \times \cdots \times I_N}$)

1. **Initialize:** $a_0^D$ and $b_0^D$, $D$, $S$, $a_0^\beta$, $b_0^\beta$, $\beta$, $a_0^\lambda$, $b_0^\lambda$, $\lambda_{(n)}$, $G$, $U^{(n)}$, $a_0^\tau$, $b_0^\tau$, and $\tau$

2. repeat

3. Update $q\left(U^{(n)}\right)$ using (3.36)

4. Update $q\left(G\right)$ using (3.40)

5. Update $q(\lambda^{(n)})$ using (3.45)

6. Update $a_0^\lambda$ and $b_0^\lambda$ using (3.62)

7. Update $q(\beta)$ using (3.49)

8. Update $a_0^\beta$ and $b_0^\beta$ using (3.63)

9. Update $q(S)$ using (3.27)

10. Update $q(D_{i_1, \ldots, i_N})$ using (3.32)

11. Update $a_0^D$ and $b_0^D$ using (3.64)

12. Update $q(\tau)$ using (3.53)

13. Update $a_0^\tau$ and $b_0^\tau$, using (3.65)

14. if The rank of a factor matrix decreases then

15. Reduce the multilinear rank of $X$

16. end if

17. until Model evidence converges

### 3.3 Results

#### 3.3.1 Algorithm Validation Using Simulated EHG Measurements

An important challenge to analyze the performance of estimation algorithms is the lack of ground truth measurements. A possible approach to validate our algorithm would be to record uterine electrical activity directly from the myometrium and from the abdomen simultaneously. Such experimental setups have been used to validate algorithms that reconstruct brain, cardiac, and uterine electrical activity [13, 76, 85, 228]. However, this approach has some limitations. First and foremost, these experiments are complicated and costly. These experiments are particularly complicated since ewes are the most appropriate animal model.
for uterine physiology [15]. Moreover, the invasive aspect of this approach may alter the uterine electrical activity. Additionally, since spontaneous contractions may not occur during the experiment, oxytocin administration is usually used to elicit contractions [195, 228]. As we described before, oxytocin alters uterine electrophysiology and therefore these contractions do not necessarily mimic spontaneous contractions.

An alternative approach to evaluate the performance of these algorithms is to use simulated data. Using appropriate physical models, we can synthesize both the electrical activity we aim to estimate and the measurements that were recorded. This approach is a compelling alternative to experimental measurements mainly because simulating data is simpler than performing invasive experimental recordings. However, the reliability of the simulated data depends on the validity of the physical models.

We first validated our algorithm and compared its performance with existing methods using simulated EHG measurements. In the next subsections, we will also assess our algorithm’s performance using noninvasive EHG measurements.

### Description of Simulated EHG Measurements

We simulated an EHG recording made with a four-by-four electrode grid on the mother’s abdomen. We show the simulated measurements in Fig. 3.5. We also show an enlarged view of the data associated with the electrodes in the upper left quadrant in Fig. 3.6.

Each subpanel in Figs. 3.5 and 3.6 corresponds to a different electrode on the grid and is identified by a set of coordinates marked on its upper left corner, where the (1,1) electrode is the closest to the mother’s right arm and the (4,4) electrode is the closest to her left leg.

The measurements recorded by each electrode contain the sum of five components, each simulating a separate phenomenon. The upper measurement curve in each subpanel shows a simulated travelling depolarization wavefront, which generates localized electrical activity [118]. We simulated this wavefront using a sinusoidal wave with a frequency of 0.25 Hz, whose amplitude is modulated by a Gaussian envelope. This frequency is characteristic for the FWL and the Gaussian envelope simulates the temporal localization of the uterine activity [199]. This wavefront travels at one fortieth of the distance between adjacent electrodes per second,
moving along the second column from the uppermost position (2,4) towards the lowermost position (4,4). We chose this velocity so that the localized activity is always present on just one electrode.

The next three measurement components simulate different aspects of the distributed electrical activity. The second measurement component recreates the volume conduction effect [244]. As the depolarization wavefront travels, it creates a potential difference that is measured in all the electrodes rather than just on the electrodes directly over the travelling wavefront. This component’s amplitude in each electrode is inversely related to the distance between the position of the wavefront and the electrode.

The third component simulates the effect of the mechanical component of a uterine contraction on the EHG measurements [161]. The travelling depolarization wavefront generates this mechanical component. We simulate this component using a sine wave with a frequency of 0.02 Hz that is shared across all the electrodes during the time in which the depolarization wavefront travels near the electrode grid. This component recreates the slow wave measured in EHG recordings [230].

The fourth component shown in each electrode simulates a common input signal reflected on all the electrodes, such as that generated by the maternal respiration activity [98]. This component is simulated as the sum of two sine waves, one with a frequency of 0.2 Hz and the other with a frequency of 0.35 Hz [18]. This measurement component has a decreasing amplitude along the main diagonal; in other words, it has a maximal amplitude in the (1,1) electrode and a minimal amplitude in the (4,4) electrode.

The fifth component recreates measurement noise and is simulated as white Gaussian noise. This noise has zero mean and variance such that the SNR of the measured signal is 15 dB, which is standard in electrophysiological recordings [197].

Lastly, the lowermost measurements in each subpanel simulate the electrode measurements and consist of the sum of the components numbered one through five. In these electrode measurements, the signal created by the travelling wavefront is concealed among the other measurement components. These measurements are stored as a tensor, where the first two dimensions encode the electrode position and the third dimension corresponds to the acquisition time.
Figure 3.5: Simulated EHG tensor measurements. Each subpanel corresponds to an individual electrode within a four-by-four electrode grid placed over a pregnant mother’s abdomen. The first five measurements in each subpanel recreate different phenomena as measured from abdominal electrodes, namely: (1) a travelling depolarization wavefront, (2) the volume conduction effect, (3) the mechanical component of a uterine contraction, (4) a common source signal present in all the electrodes, and (5) measurement noise. The lowermost measurements in each subpanel (6) consist of the sum of the measurement components labeled one through five and simulate abdominal EHG measurements.
Localized and Distributed Electrical Activity Estimation

We used our method to estimate the localized and distributed electrical activities in the simulated EHG measurements. We show our results in Figs. 3.7 and 3.8. Again, each subpanel in Figs. 3.7 and 3.8 corresponds to the same electrodes as in Figs. 3.5 and 3.6, respectively. The first curve in each subpanel shows the simulated EHG measurements and duplicates the bottommost curves in Figs. 3.5 and 3.6.
The second component in each subpanel shows the localized activity estimated with our method. This component recovers the true position of the traveling wavefront along the second column, as highlighted with black boxes.

The third component in each subpanel shows the distributed electrical activity obtained with our tensor decomposition method. This component contains the distributed electrical activity, which is simulated by the second, third, and fourth components shown in Figs. 3.5 and 3.6. The low-rank tensor of distributed activity recovers the amplitude decay effect along the main diagonal of the electrode grid.

The lowermost curve in each subpanel is the difference between the original measurements and the sum of the localized and distributed activities obtained using our algorithm. The lowermost curve contains predominantly white Gaussian noise, as expected from our model formulation.

Figure 3.7: Tensor decomposition of the simulated EHG measurements. The measurements in each subpanel correspond to: (1) the simulated measurements, (2) the localized activity obtained using our algorithm, (3) the distributed activity obtained using our algorithm, and (4) the difference between the simulated measurements and the sum of the localized and distributed activities.
Figure 3.8: Enlarged view of the estimated localized and distributed electrical activities. Here we show the four electrodes in the upper-left quadrant of the previous figure.

### 3.3.2 Comparison with Existing Methods

We used the simulated measurements to compare the performance of various methods to estimate localized and distributed electrical activities. As detailed in Fig. 3.9 and Table 3.1, our method outperformed existing methods in this task.

We estimated the localized and distributed electrical activities using methods from three categories. In first place, we used two standard approaches to obtain bipolar measurements. We used the upper-left (1,1) electrode as a reference electrode and considered that electrode as the distributed activity and its difference with the other electrodes as the localized activity. We also considered bipolar measurements where the original measurements represent
the distributed activity and the difference between adjacent rows of electrodes represent the localized activity. In second place, we used two methods that approximate measurement tensors using low-rank approximations (CP-ALS and HOSVD) [183]. In this case, we interpreted the low-rank approximations as the distributed activity and the difference between the original measurements and the low-rank approximations as the localized activities. Lastly, we used two methods (RPCA and BRTF) that decompose measurement tensors into a low-rank tensor and a sparse tensor [8, 247]. Based on our assumptions, we interpret the low-rank tensor to be the distributed activity and the sparse tensor to be the localized activity. We used these methods for comparison because they are representative of the existing approaches. Additionally, we chose these methods because their implementation is publicly available.

We used the cosine similarity to evaluate the similarity between the estimated localized and distributed electrical activities with their respective ground truth measurements. For fair comparison, we fine-tuned the hyper-parameters of all the methods to obtain the best possible performance on the simulated measurements.

In Fig. 3.9, we show the estimates obtained using our method, the second best performing method (BRTF), and using the upper-left electrode as a reference electrode. In Table 3.1, we compare the results obtained with all the methods.

Figure 3.9: Localized and distributed activity estimation by the best performing methods. The leftmost panel shows the original measurements. The panels in the second column show the ground truth localized and distributed activities. The panels in the third to fifth columns show the localized and distributed activities recovered by various methods. All the panels correspond to the (2,2) electrode of the simulated EHG measurements.

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<table>
<thead>
<tr>
<th>Method</th>
<th>Cosine similarity</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Localized activity</td>
<td>Distributed activity</td>
<td></td>
</tr>
<tr>
<td>Reference electrode</td>
<td>0.093</td>
<td>0.972</td>
<td></td>
</tr>
<tr>
<td>Bipolar measurements</td>
<td>0.176</td>
<td>0.989</td>
<td></td>
</tr>
<tr>
<td>CP-ALS [183, 26]</td>
<td>0.163 (0.157, 0.169)</td>
<td>0.995 (0.995, 0.995)</td>
<td></td>
</tr>
<tr>
<td>HOSVD [183, 26]</td>
<td>0.003 (0.003, 0.003)</td>
<td>0.988 (0.988, 0.988)</td>
<td></td>
</tr>
<tr>
<td>RPCA [8]</td>
<td>0.213 (0.190, 0.235)</td>
<td>0.987 (0.987, 0.987)</td>
<td></td>
</tr>
<tr>
<td>BRTF [247]</td>
<td>0.557 (0.540, 0.574)</td>
<td><strong>0.998 (0.998, 0.998)</strong></td>
<td></td>
</tr>
<tr>
<td>Our method</td>
<td><strong>0.730 (0.715, 0.786)</strong></td>
<td><strong>0.997 (0.997, 0.997)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1: Comparison of localized and distributed electrical activity estimation by various methods. Each category of methods is indicated with a different background color. The best results are indicated with bold fonts and the second-best results are underlined. These results express the average results of 100 runs with 95% confidence intervals.

### 3.3.3 Analysis of Pregnancy and Labor Contractions

In the next subsections, we use our Bayesian tensor decomposition method to examine EHG measurements of uterine contractions during pregnancy and labor from two public datasets.

We investigated data from “The Term-Preterm EHG dataset with tocogram (TPEHGT DS),” which includes EHG measurements from 26 pregnant mothers recorded around the 30th week of gestation [110]. Half of these mothers eventually delivered preterm, while the other 13 mothers delivered at term. These recordings were made using a two-by-two electrode grid. We supplemented the bipolar measurements in these recordings with a fourth signal defined as $s_4 = -s_1 + s_2 - s_3$, following the notation in the original publication [110]. While this additional signal does not add information, it is useful to store the measurements as tensors. We stored these recordings as two-by-two-by-$T$ tensors, where $T$ is the temporal length of the measurements.

Additionally, we analyzed data from “The Icelandic 16-electrode electrohysterogram database,” which includes EHG recordings from 45 pregnant mothers during their third trimester of pregnancy and during labor [6]. These recordings were made using a four-by-four electrode grid.

The recordings in both datasets are supplemented with annotation files, which include clinical information and annotations of when the mothers felt uterine contractions. While the
TPEHGT DS contains annotations clearly delimiting the beginnings and endings of uterine contractions perceived by the mothers, the annotations in “The Icelandic 16-electrode electrohysterogram database” do not delimit the beginnings and endings of contractions. We used these two datasets because they include information to identify the uterine contractions in the recordings.

**Signal Preprocessing**

We preprocess all the measurements in the next subsections using the same filtering steps. We filtered the original measurements using a bandpass Butterworth filter with cutoff frequencies of 0.05 Hz and 0.7 Hz to extract the electrical activity associated with uterine contractions [199]. After this step, the measurements contained mostly electrical activity associated with the fast wave of uterine activity and maternal respiration. Afterwards, we downsampled the recordings to 1.5 Hz to improve the computational speed without losing information. We filtered and downsampled the measurements along the temporal dimension, i.e., we filtered the measurements from each electrode independently.

**Tensor Decomposition of EHG Measurements**

In Figs. 3.10 and 3.11, we show how our method estimates the localized and distributed electrical activities from an EHG recording of “The Icelandic 16-electrode electrohysterogram database.”
Figure 3.10: Localized and distributed electrical activity estimation from a labor EHG recording. Each subpanel corresponds to an individual electrode within a four-by-four electrode grid placed over a pregnant mother’s abdomen. The first measurements in each subpanel, marked with the number one, show the original EHG measurements. The second measurements in each subpanel, marked with the number two, show the localized activity estimated with our method. The third measurements in each subpanel, marked with the number three, show the distributed activity estimated with our method. The fourth and last measurements in each subpanel show the measurement noise estimated with our method, calculated as the difference between the original measurements and the sum of the localized and distributed activities.
Figure 3.11: Enlarged view of the localized and distributed electrical activity estimated from a labor EHG recording. Here we show the four electrodes in the upper-left quadrant of the previous figure.

During this recording, the mother’s uterus contracted four times, as indicated by simultaneous tocography. The mother’s uterus contracted around 50, 150, 300, and 400 s into the recording. In these two Figs. we observe that while the original measurements in most of the electrodes present electrical activity, only a fraction of the electrodes exhibit localized activity. Moreover, while the original measurements show activity throughout the entire recording, the estimated localized activity is mostly confined to the contraction intervals. Moreover, we observe that the distributed electrical activity is mostly stationary along time and across the multiple electrodes in the grid.

Next, we compare how our method and other existing methods estimate the localized electrical activity in a recording from the TPEHGT DS. We first preprocessed the measurements
as described above and then estimated the localized electrical activity using the methods mentioned in Table 3.1. We show the results in Fig. 3.12.

![Figure 3.12](image)

Figure 3.12: Localized electrical activity estimation of an EHG recording. Each curve shows the measurements from the same electrode of one recording from the TPEHGT DS. The first curve, marked with the number one, shows the original measurements. The second through seventh curves show measurements obtained using alternative methods: using a reference electrode, bipolar measurements, CP-ALS, HOSVD, RPCA, and BRTF, respectively. The eighth curve was obtained using our method. In each panel, the dotted and dashed black lines indicate when the pregnant mother started and ended feeling uterine contractions, respectively.

Here, we observe that the localized electrical activity estimated with our method is more concentrated during the contractions than the localized electrical activity estimated with the other methods.
3.3.4 Practical Applications

Using our method, we can measure how many electrodes are active during uterine contractions. This number is a surrogate of the fraction of the myometrium that is recruited during a contraction. As described before, electrical propagation is a key regulator of contractile force generation. Therefore, we propose that vigorous contractions result from the recruitment of a large surface of the myometrium. In the next subsections, we will show how using our method to measure the number of active electrodes can be useful for practical applications.

Preterm Birth Prediction

About 10% of the labors worldwide are preterm [154]. As explained before, preterm births are associated with increased child mortality and morbidity, including permanent neurological damage [154]. Although there exist treatments to improve the outcomes of preterm births, predicting these births is challenging.

We found that the number of active electrodes during Braxton-Hicks contractions is associated with the risk of preterm births. For this task, we analyzed EHG measurements from the TPEHGT DS [110]. We first preprocessed these measurements as described before. Then, we estimated the localized activity using our method. Finally, we counted the number of electrodes that exhibit a higher energy, in the localized activity, than a threshold of activity, as described by Giannakopoulos [77]. We show our results in Fig. 3.13a.

Electrophysiological Evolution of Braxton-Hicks Contractions

In this subsection, we examine how the number of active electrodes in Braxton-Hicks contractions evolves through the last month of pregnancy. As we explained before, understanding how the uterus adapts for labor is useful to develop both monitoring applications and medical treatments.

For this task, we used data from “The Icelandic 16-electrode electrohysterogram database.” To quantify temporal changes, we included the measurements of mothers for whom the dataset includes at least two recordings with uterine contractions during the last month of
pregnancy. We first preprocessed the measurements as described before. Then, we identified the uterine contractions in the measurements using the accompanying annotations. From each contraction, we identified a 100-sample long interval that spans the electrical activity associated with that contraction. Since we downsample the measurements to a sampling rate of 1.5 Hz, this interval corresponds to about 67 s, which is sufficiently long to span the duration of the electrical activity associated with uterine contractions based on our observations. Finally, we estimated the localized electrical activity using our method and counted the number of active electrodes, as described in the previous subsection.

We show our results in Fig. 3.13b. We observe that the number of active electrodes during contractions increases. Although this increase is statistically significant, we observe a large variability across mothers. This variability is expected since uterine physiology, and pregnancy outcomes, are also very variable across mothers.

**Monitoring Labor Contractions**

Finally, we use our method to quantify the number of active electrodes during labor contractions. As we explained in the Introduction, many labors are augmented with oxytocin, which is associated with serious side effects and medical complications. Medical complications usually result from inappropriate oxytocin administration.

When needed, oxytocin is progressively administered during labor. Intravenous oxytocin has a half-life of under five minutes and therefore needs to be delivered continuously. Moreover, while low doses of oxytocin may not be sufficient to generate vigorous labor contractions, very high doses can cause overly strong contractions that may lead to uterine rupture and fetal asphyxia. Therefore, administering oxytocin can be difficult and may result in complications.

We examined the eight EHG measurements recorded during spontaneous term labor in “The Icelandic 16-electrode electrohysterogram database [6].” These eight EHG measurements consist of recordings from two laboring mothers who did not require labor augmentation, three recordings of laboring mothers before their labors were augmented, and three recordings of laboring mothers during labor augmentation. We measured the number of active electrodes during contractions of laboring mothers as described before.
Our observations, presented in Fig. 3.13c, suggest that the fraction of the myometrium recruited is associated with the vigor of labor contractions. From the three groups, we found that the measurements of mothers who needed oxytocin, recorded before they received oxytocin, exhibit the lowest number of active electrodes during contractions. We also found that the number of active electrodes is higher in mothers who were receiving oxytocin during the recordings than in those who have not yet received oxytocin. However, the number of active electrodes is very variable in the former group. Finally, we observed that the mothers who did not require oxytocin presented the highest number of active electrodes during uterine contractions. Although these observations are aligned with our expectations from the previous sections, the sample size in this cohort is limited. Therefore, our observations from labor EHG measurements are preliminary findings.

Figure 3.13: Number of active electrodes during different types of uterine contractions. 

a Each circle or square shows the average number of active electrodes during the Braxton-Hicks contractions of each mother who delivered preterm or at term, respectively; error bars, mean ± standard deviation (s.d.); n = 26; p-value corresponds to two-tailed Student’s t-test. 

b The average number of active electrodes during the Braxton-Hicks contractions measured in each EHG recording is shown as a solid circle. The positive trend is statistically significant as evaluated through a two-tailed Pearson’s correlation test. The dashed line shows the linear fit of the data points. Each line connecting at least two data points corresponds to a different mother. 

c The number of active electrodes during labor contractions across contractions of mothers who required oxytocin administration after the EHG was recorded, mothers who were receiving oxytocin while the EHG was being recorded, and mothers who did not require oxytocin administration for labor. Data points from each color represent contractions from the same mother; error bars, mean ± s.d.; all differences between means with p < 0.05 are indicated; n(pre-oxytocin use) = 15, n(during oxytocin administration) = 13, n(no oxytocin needed) = 9; p-values correspond to two-tailed Student’s t-tests and an ANOVA test.

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Comparison with Existing Methods in Practical Applications

In this subsection, we show the advantage of our method over existing alternatives for practical applications. We repeated the experiments detailed in the previous subsections, while varying the method used to estimate the localized electrical activity. Again we compared our method with the alternative methods mentioned in Table 3.1. We reran the three tasks described above 100 times using each of the various methods. For each task, we counted how many times each method provided the lowest $p$-value. We used the $p$-values as a proxy of the ability of each method to differentiate between different categories. We repeated the experiments 100 times to account for the variability that results from the stochastic components of these methods. We show the results of this experiment in Table 3.2.

Our results show that estimating the localized electrical activity with tensor methods produces better results than using the original measurements or standard differences across electrodes. In particular, we observe that our method produces the best results in two out of the three tasks.
<table>
<thead>
<tr>
<th>Method</th>
<th>Predicting preterm births (two-tailed t-test; ( n = 26^* ))</th>
<th>Evolution of pregnancy contractions (two-tailed Pearson correlation test; ( n = 38^* ))</th>
<th>Monitoring of labor contractions (ANOVA; ( n = 37^# ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original measurements</td>
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<td>0</td>
</tr>
<tr>
<td>Reference electrode</td>
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</tr>
<tr>
<td>Bipolar measurements</td>
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<td>4</td>
<td>0</td>
</tr>
<tr>
<td>CP-ALS [183, 26]</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>HOSVD [183, 26]</td>
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<td>26</td>
<td>29</td>
</tr>
<tr>
<td>RPCA [8]</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>BRTF [247]</td>
<td>3</td>
<td>27</td>
<td>45</td>
</tr>
<tr>
<td>Our method</td>
<td><strong>48</strong></td>
<td><strong>42</strong></td>
<td><strong>22</strong></td>
</tr>
</tbody>
</table>

* number of participants.

# total number of contractions.

Table 3.2: Comparison of the discriminative power of the myometrium fraction recruited during uterine contractions estimated with various methods. These results express the number of times each method yielded the smallest \( p \)-value out of 100 runs. From the 300 smallest \( p \)-values obtained across all the tasks and methods, 274 were smaller than 0.1 and 192 were smaller than 0.05. Each category of methods is indicated with a different background color. The best results are indicated by bold fonts, and the second-best results are underlined.

### 3.4 Discussion

We addressed an important limitation of noninvasive electrophysiological measurements. We developed a Bayesian tensor decomposition algorithm that estimates the localized and distributed electrical activities in EHG measurements. Our method estimates the electrical activity associated with uterine contractions directly under the abdominal electrodes. By using our method, we obtain more reliable measurements of uterine electrical activity than when using the original measurements or bipolar measurements. Moreover, using our method, we identified the fraction of the myometrium recruited during uterine contractions as an informative biomarker of the vigor of labor contractions.

Our experiments on simulated and real EHG measurements show the advantage of our method over existing methods to estimate the localized electrical activity. Using a simplified
model of localized and distributed electrical activity, we showed that tensor decomposition method can outperform standard bipolar measurements in estimating the localized electrical activity. Moreover, we showed that our method recovers the localized electrical activity more accurately than other existing methods. Additionally, we observed that the estimation obtained with our method is more correlated with the contractions in the recordings than the activity identified with other methods. Furthermore, we showed that the localized activity obtained with our method is more informative for uterine contraction monitoring applications than other existing methods.

Using our method and two public databases, we found that the number of active electrodes during contractions is a potential biomarker for uterine contraction monitoring. The number of active electrodes during Braxton-Hicks contractions around the 30th week of gestation is indicative of preterm births. Moreover, the number of active electrodes during Braxton-Hicks contractions increases towards birth.

We also analyzed labor contractions. Our preliminary results suggest that the number of active electrodes during contractions can be used to assess the vigor of labor contractions. We found that the number of active electrodes during contractions is lowest in mothers who later required oxytocin administration. We also found that this number increases with oxytocin administration. Moreover, the mothers who did not require oxytocin exhibited the highest number of active electrodes during labor contractions. Therefore, our method may be useful to determine whether oxytocin administration is necessary and if so, to monitor oxytocin administration. However, our observations are based on a limited dataset and need to be validated with more labor EHG measurements.

3.4.1 Limitations

Our method has limitations that result from our assumptions. We assumed that the localized electrical activity is sparse in time and space while the distributed activity has low-rank dynamics. The first assumption, however, may not always hold. For example, if the conduction velocity is high or the spacing between the electrodes is small, the localized activity may not be spatially sparse. In these cases, the localized activity may appear as distributed electrical activity due to the limitations of the measurement system. The second assumption implies
that the distributed activity is mostly deterministic and therefore can be approximated accurately with a low-rank tensor. However, if the measurements have a low SNR, then the distributed activity may not be adequately modeled with a low-rank tensor model. Finally, an empirical validation of the localized and distributed activity estimation requires a dataset of both invasive electrical measurements recorded directly from the myometrium and simultaneous noninvasive measurements from abdominal electrodes. As described before, this experimental setup is outside the scope of our work.

### 3.4.2 Future Directions

In the future, the localized and distributed electrical activities could be estimated using a more general tensor decomposition method that does not rely on a generative model defined by a combination of probability distributions. Instead, the localized and distributed activities may be more accurately estimated based only on the measurements. Additionally, a larger database could be acquired to validate our observations and translate them into uterine monitoring applications.

Additionally, our method can be expanded for various multidimensional data analysis applications. For example, our method could be adapted to estimate localized and distributed electrical activities in EEG recording or to analyze multidimensional RNA sequencing data [39, 103]. Moreover, our method could be used for alternative applications such as hyperspectral imaging and video signal processing [245, 247].

### 3.5 Conclusion

We developed a Bayesian tensor decomposition method to estimate the localized and distributed electrical activities in EHG measurements. Our method addresses the inherent limitations of noninvasive electrophysiological measurements and outperforms existing methods in this task. Using our method, we found that the number of active electrodes during uterine contractions is a potential biomarker for preterm and term births, as well as to monitor labor contractions.
Chapter 4

Predicting preterm births using electrohysterogram measurements and machine learning

4.1 Introduction

Preterm birth is an important health problem, as described in Chapter 1. Around 10% of all livebirths, which amounts to about 15 million babies per year, are born preterm, that is, before completing 37 weeks of gestation [154, 220]. Preterm births are a leading cause of newborn mortality [121]. Moreover, many preterm babies suffer from long-term morbidity, including permanent neurological damage [154, 174]. As treatments to delay preterm births and to improve their outcomes are available, identifying pregnant mothers at high risk of preterm birth is paramount, as recognized by the World Health Organization (WHO) [87, 154].

Several methods have been developed to predict preterm births; however, they have limitations. Risk factors, such as previous preterm births or multiple gestations, can identify some mothers at higher risk of preterm birth [25, 79]. But, these risk factors are not sufficiently accurate to predict which mothers will delivery preterm [79].

Preterm birth is currently predicted by measuring cervical length, the Bishop score, or the concentration of cervico-vaginal fibronectin alpha [151]. These tests are minimally invasive and can predict births within one week in mothers with symptoms of preterm labor [102, 189].
However, these tests are not effective to predict preterm births more than one week in advance or in asymptomatic mothers [57, 102]. Therefore, these tests are not appropriate to predict preterm births in the general population.

Home uterine activity monitors (HUAMs) were developed to measure uterine contractions and to predict preterm births. The first devices were based on tocodynamometer recordings, which measure the pressure changes associated with uterine contractions [192]. Unfortunately, these devices could not predict preterm births and current clinical guidelines discourage the use of tocodynamometer measurements to predict preterm births [165, 192].

More recently, electrohysterogram (EHG) recordings have been proposed to predict preterm births [104, 230]. EHG recordings measure the electrical activity associated with uterine contractions using noninvasive abdominal electrodes. EHG measurements are compelling because they can be recorded with portable devices equipped with algorithms to monitor uterine contractions [95, 104]. A series of algorithms have been developed to predict preterm births based on various features derived from EHG measurements [4, 104, 230]. These features are generally calculated from intervals that capture uterine contractions, which are either manually selected or identified using dedicated algorithms [110, 230]. These intervals can also be identified with the aid of simultaneous tocodynamometer recordings [95, 110].

To the best of our knowledge, EHG measurements have not yet been shown to predict preterm births in asymptomatic mothers with a performance comparable to the clinical standards, i.e., measurements of cervical length or fibronectin alpha in mothers with symptoms of preterm labor. Although many researchers have reported nearly perfect predictions of preterm births based on EHG measurements, meticulous analysis revealed that these results were overoptimistic and resulted from data leakage. Namely, these works inadvertently introduced strong correlations between the data used to train the prediction models and the data used to test the performance of these models, as shown by Vandewiele et al. [213, 214, 230]. This problem was caused by flawed attempts to improve the models’ performance by balancing the number of term and preterm samples used to develop these models. After Vandewiele et al. corrected this problem, these models were no longer able to predict preterm births accurately [213, 214]. Additional works with sound methodology suggest that some features derived from EHG measurements can be used to distinguish between recordings of mothers who eventually delivered at term from those who delivered preterm [62, 111, 149, 173]. However,
neither of these works could predict preterm births with a performance useful for clinical practice.

Here, we developed an end-to-end, deep learning model to predict preterm births. Our model does not rely on handcrafted features, rather, it predicts preterm births directly from EHG measurements. Therefore, our model is not sensitive to varying implementations of specific features or to how uterine contractions are segmented. We developed our work using EHG measurements and supplementary clinical information from two public databases. Importantly, we developed our model with prudence to avoid data leakage. Using our model, we could predict preterm births in mothers without symptoms of preterm labor, around their 31st week of gestation, with similar performance as cervical length and fibronectin alpha measurements predict preterm labors in mothers with symptoms of preterm labor and within one week of delivery. Moreover, by investigating the measurement components that contribute to the predictions of our model, we showed that it is possible to predict preterm births using short recording times, thus facilitating clinical adoption, and at-home implementation, of EHG measurements. Our work and results encourage using EHG measurements and deep learning for predicting preterm births in real-world scenarios to reduce newborn mortality and morbidity, especially in populations with limited access to healthcare, who suffer more from preterm birth [154].

4.2 Methods

4.2.1 Study Participants

We developed our work using data from two datasets obtained from the Physionet repository. We aggregated data from the “Term-Preterm EHG Database” (TPEHG DB) and from the “Term-Preterm ElectroHysteroGram DataSet with Tocogram” (TPEHGT DS) [62, 110]. These datasets contain 30-minute-long bipolar EHG measurements and clinical information of pregnant mothers recorded during regular pregnancy checkups. Both datasets were acquired at the University Medical Centre Ljubljana using the same recording protocol and device. The TPEHG DB consists of 300 records, where each record was obtained from a different mother either around the 22nd or the 32nd week of gestation. Additionally, the
TPEHGT DS contains 26 records from 18 different mothers obtained around the 30th week of gestation. Half of the samples in the TPEHGT DS correspond to mothers who eventually delivered preterm while the other 13 records correspond to term deliveries. We combined these two datasets to increase the amount of data available for training and testing our models.

We included in our work the records from both datasets obtained after the 28th week of gestation. This selection criterion concentrates the data samples around a mean gestational age. Since pregnancy is an evolving process, we hypothesise that reducing the spread of gestational ages at the time of recording, we can reduce the variability of the data. We excluded records from the TPEHGT DS that correspond to the same mother. When multiple records were available for a single mother in the TPEHGT DS, we included only the latest record during the pregnancy. We identified different records that corresponded to a single mother by comparing the clinical information. By using a single record per mother, we prevent our models from learning features that characterize mothers rather than features that are predictive of pregnancy outcomes because the datasets we used contain a single recording for the vast majority of the mothers. Overall, we used 151 records from different mothers. Among these mothers, 18.5% delivered preterm. We detail the clinical information of these mothers in Table 4.1.

Additionally, we illustrate the distribution of gestational ages of the mothers included at the times of recording and at birth in Figs. 4.1 and 4.2. Whereas the gestational ages at measurement follow a Gaussian distribution centered around 31 weeks, the distribution of the gestational ages at birth is left skewed, as shown in Fig. 4.2.
Table 4.1: Clinical information from the records included in our work.  

We characterized the data distributions using the median values and interquartile ranges (IQR). We assessed the predictive power of the continuous predictors using the area under the receiver-operating characteristic curve (AUC) and calculated the 95% confidence interval (CI) using the logit method.  

For the binary predictors, we show the number of positive samples in the dataset and the percent of positive samples in the dataset (%). We assessed the predictive power, with 95% CI, of these predictors through the risk ratio test.

| Table 4.1: Clinical information from the records included in our work.  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td><strong>Predictive power</strong></td>
<td><strong>No. of missing entries</strong></td>
<td></td>
</tr>
<tr>
<td>Number of participants</td>
<td>151</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of preterm births (%)</td>
<td>28 (18.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Continuous predictors</strong></td>
<td>Median (IQR)</td>
<td>AUC (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>28 (26, 32)</td>
<td>0.51 (0.28, 0.63)</td>
<td>23</td>
</tr>
<tr>
<td>Gestational age at recording [weeks/days]</td>
<td>31/1 (30/6, 31/6)</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>Weight [Kg]</td>
<td>72 (66, 76.8)</td>
<td>0.54 (0.40, 0.67)</td>
<td>28</td>
</tr>
<tr>
<td><strong>Binary predictors</strong></td>
<td>No. of positives (%)</td>
<td>Risk ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Parous</td>
<td>47 (31.1)</td>
<td>1.86 (1.16, 2.99)</td>
<td>0</td>
</tr>
<tr>
<td>Previous abortions</td>
<td>21 (13.9)</td>
<td>1.03 (0.38, 2.83)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>0 (0.0)</td>
<td>N/A</td>
<td>16</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>1 (0.7)</td>
<td>N/A</td>
<td>16</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>63 (51.6)</td>
<td>1.50 (1.07, 2.11)</td>
<td>29</td>
</tr>
<tr>
<td>Bleeding in 1st trimester</td>
<td>12 (8.9)</td>
<td>0.26 (0.02, 4.27)</td>
<td>16</td>
</tr>
<tr>
<td>Bleeding in 2nd trimester</td>
<td>3 (2.2)</td>
<td>14.50 (1.24, 169.16)</td>
<td>16</td>
</tr>
<tr>
<td>Funneling</td>
<td>5 (3.7)</td>
<td>1.63 (0.19, 13.73)</td>
<td>16</td>
</tr>
<tr>
<td>Smoker</td>
<td>9 (6.0)</td>
<td>2.20 (0.58, 8.25)</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 4.1: Distribution of gestational ages at the times of recording and at the times of birth. 

**a**, Gestational ages at birth plotted against gestational ages at the times of recording. **b**, Elapsed times between recordings and births, plotted against gestational ages at recording. 

**a-b**, The dashed black lines separate preterm (red circles) and term births (blue diamonds).
Figure 4.2: Distribution of gestational ages at the times of recording and delivery. Note dissimilar scale ranges between graph pairs. 

- **a**, Histogram of the gestational ages when the EHGgs were recorded. 
- **b**, Same as **a**, but using only the samples used from the TPEHG DB. 
- **c**, Histogram of the gestational ages at the times of delivery. This distribution is left skewed (skewness = -1.7) and does not appear to follow a Gaussian distribution ($p = 7.7 \times 10^{-10}$). 
- **d**, Same as **c**, but using only the samples used from the TPEHG DB. This distribution is also left skewed (skewness = -1.9) and does not appear to follow a Gaussian distribution ($p = 6.4 \times 10^{-10}$). 
- **e**, Histogram of the gestational ages at the times of delivery for the preterm births. Preterm births are more common at older gestational ages. 
- **f**, Same as **e**, but using only the samples used from the TPEHG DB. 
- **g**, Histogram of the gestational ages at delivery for the term births. This distribution appears to follow a Gaussian distribution ($p = 0.06$). 
- **h**, Same as **g**, but using only the samples used from the TPEHG DB. This distribution also appears to follow a Gaussian distribution ($p = 0.07$). 

**c, d, g, h**, Normality was assessed using the Shapiro-Wilk test.
4.2.2 Prediction Models

To predict whether each pregnancy resulted in a term or a preterm birth, we developed classification and regression models. We trained the classification models to predict categorical outcomes, i.e., whether the delivery would be at term or preterm. In contrast, we trained the regression models to predict the gestational age at delivery. When using regression models, we labeled the predictions that were higher than 37 weeks, or 259 days, as term and those below 37 weeks as preterm. We developed classification and regression models using metadata alone, EHG measurements alone, and metadata combined with EHG measurements. These prediction models, developed using MATLAB 2020a, are detailed in the next subsections and summarized in a block diagram in Fig. 4.3.

Metadata models

First, using only the clinical information of the records, we predicted whether each mother delivered preterm or at term. We used most of the predictors shown in Table 4.1, namely maternal age, gestational age at the time of the recording, weight, whether the mothers had given birth previously (parous), had aborted pregnancies previously, had a placenta partially or completely covering the cervix (placenta previa), had reported vaginal bleeding in the first trimester, had reported vaginal bleeding in the second trimester, had a cervical funneling, or were smokers. We excluded diagnoses of hypertension and diabetes because these diagnoses are mostly absent in this dataset. We completed the missing entries for each variable in the training and testing datasets using the mode of that variable in the training set. To prevent data leakage, rather than using the modes of the entire dataset, we used the modes of the samples in the training set to complete missing entries in both the training and testing sets.

Then, we trained a logistic regression and a linear regression model to predict whether deliveries were preterm and the gestational age at birth, respectively. In the logistic regression model, we discarded the redundant predictors using lasso regularization. We regularized only the classification model, and not the regression model, because we observed that the lasso regularization improved the performance of the logistic regression model slightly while worsening the performance of the linear regression model marginally. Since we regularized the logistic regression model, we also normalized the predictors in this model to prevent the
regularization term from penalizing the model parameters based on the scale of the predictors. Again, to prevent data leakage, we normalized both the training and testing sets using the means and standard deviations of the samples in the training set.

**EHG Measurements Models**

Then, using only the EHG measurements, we predicted whether the mothers delivered preterm or at term. We used only the first signal (s1) in the databases. This signal measures the electric potential difference between two electrodes aligned horizontally on the abdomen, 3.5 cm above the navel, and separated by seven cm.

We preprocessed all the EHG measurements to improve the data quality. We removed the first minute of the recordings to remove transient effects. Next, we filtered the measurements to remove baseline wander and high frequency noise. Specifically, we filtered the recordings using a fourth-order, Butterworth bandpass filter with zero-phase and cutoff frequencies of 0.05 Hz and 4 Hz. Although most uterine activity is concentrated between 0.05 Hz and 0.7 Hz, we included a higher frequency range because higher frequency components have been proposed to be predictive of preterm birth [18, 110]. Finally, we downsampled the measurements to 10 Hz to improve computational speed without losing information.

Next, we transformed the preprocessed EHG measurements to the time-frequency domain using the short-time Fourier transform (STFT). The STFT is useful to represent how the spectral components of the measurements change over time. This transformation is helpful to analyze non-stationary processes such as the contractile activity during the recordings.

We used a deep recurrent neural network (RNN) to predict the pregnancies’ outcomes from EHG measurements, developing a dedicated network architecture for this task. The first layer in our network is an input layer that rearranges the STFTs so that the spectral components at each time become a set of features for each time step in the RNN. This input layer feeds into a series of bidirectional long short-term memory (BiLSTM) cells. The BiLSTM cells are able to learn patterns from sequential data and, in our case, these cells are intended to learn patterns from the spectral changes of the EHG measurements over time. Next, we connected the last BiLSTM cell to a fully connected layer consisting of two neurons, and finally we connected the fully connected layer to an output layer.
We used two different output layers depending on whether we intended to predict the categorical outcome of the pregnancy or to predict the gestational age at birth. For the classification problem, we used a softmax output layer and trained the network using a weighted cross-entropy loss function. We used a weighted loss function that penalizes more the errors on the preterm birth predictions. We determined the weights of the loss function based on the relative frequency of each class in the training set. This strategy addresses the class-imbalance problem of predicting preterm births. Namely, because term labors are more frequent in the general population and in the database, classification models trained on these data are naturally biased towards predicting term labors and may learn to predict term labors for every input. This loss function is given by:

$$\text{loss} = -\frac{1}{N} \sum_{n=1}^{N} [w_1 T_n \ln(y_n) + w_0 (1 - T_n) \ln(1 - y_n)],$$

where $N$ is the number of samples in each training batch, $w_i$ is the penalization weight of each class, $T_n = \{0, 1\}$ is the label of sample $n$, and $y_n$ is the output score of the sample $n$. We set the penalization weight for class $i$ to be:

$$w_i = \frac{2S_{(1-i)}}{S_0 + S_1},$$

where $S_i$ is the number of samples from class $i$ in the training set, as suggested in [116].

For the regression problem, we used a regression layer as the output of the network. This layer implements a mean squared error (MSE) loss function to train the network. Since the regression models are trained on a continuous output, i.e., the gestational age at birth, these models are less sensitive to the class imbalance problem.

We fine-tuned the learning parameters based on a single run of a five-fold cross-validation. Namely, we selected an appropriate mini-batch size, number of training iterations, learning rate, and regularization hyperparameter.
Combined Models

We developed both a classification and a regression model that combine clinical information with EHG measurements to predict pregnancies’ outcomes. We first trained the network described in the previous subsection. Then, we extracted the activation values of the fully connected layer and concatenated these values with the clinical information. Next, we used the combined data to train the logistic regression model to predict the outcome of the pregnancy, and the linear regression model to predict the gestational age at delivery. We implemented these logistic and linear regression models as described before. The difference between these models and those used for predictions based only on clinical information is that, in this case, the data vectors included the activations of the fully connected layers in addition to the clinical information.

4.2.3 Cross-Validation

We evaluated the performance of our models using a stratified five-fold cross-validation. We partitioned the data into a training set, containing 80% of the data, and a test set, containing the remaining 20% of the data, so that both the training and testing sets included the same proportion of preterm samples. We used the training set to train our models and the testing set to evaluate the models’ performance. We repeated this process five times, each time using a different set of samples for the training and testing set, so that all the samples were used for testing throughout the five runs.

4.2.4 Statistical Analysis

To evaluate the performance of the prediction models with confidence intervals, we repeated the cross-validation routine 20 times, as recommended in [115]. Each time, we used a different random partition of the data. By repeating the cross-validation routine with various random partitions, we prevented our models from possibly producing over-optimistic results due to fitting of the training hyperparameters to a specific cross-validation partition. We then
Figure 4.3: Block diagram of the three classification and regression models developed. The clinical information model is illustrated in the upper part of the diagram using shapes with blue outlines. This model uses clinical information, in tabular format, to predict preterm births using logistic or linear regression models, which are represented as a block with schematic illustrations. The EHG model is illustrated in the lower part of the diagram using shapes with black outlines. The combined model uses clinical information and EHG measurements to predict preterm births and is illustrated in the middle part of the diagram using shapes with red outlines.

calculated the mean and 95% CI of the performance statistics, assuming that the performance statistics had Gaussian distributions with unknown means and variances.

4.3 Results

First, we attempted to predict preterm births using the metadata alone. The metadata supplements the EHG measurements and consists of the clinical information described in Table 4.1. We developed a logistic regression model to determine whether a pregnancy would result in a preterm birth and a linear regression model to predict the gestational age at delivery, as detailed in Methods. When using the regression model, we predicted that a birth would be preterm if the estimated gestational age at delivery was less than 37 completed weeks, or 259 days. The classification model predicted preterm births with an
area under the receiver-operating characteristic curve (AUC) of 0.56 (95% confidence interval (CI): 0.53-0.58), whereas the regression model predicted preterm births with an AUC of 0.57 (95% CI: 0.54-0.59). As expected, clinical information alone was not able to predict preterm births accurately.

Next, we examined whether EHG measurements could be used to predict preterm births using end-to-end deep-learning, directly from EHG measurements and without requiring handcrafted features. Specifically, we trained a recurrent neural network to predict whether the pregnant mothers would deliver preterm and to predict their gestational ages at delivery, as described in Methods. This network’s predictions surpassed those of the clinical information models. The classification model trained on EHG measurements was able to predict preterm births with an AUC of 0.75 (95% CI: 0.74-0.77), whereas the regression model predicted preterm births with an AUC of 0.71 (95% CI: 0.68-0.73).

We also developed models to predict preterm births based on metadata combined with EHG measurements, as described in Methods. We hypothesized that integrating metadata and EHG measurements could result in more accurate prediction models because the models trained independently on metadata alone and EHG measurements alone could predict preterm births better than random guessing. Moreover, the metadata and the EHG measurements provide complementary information about the pregnancy. Consistently with our hypothesis, the prediction models trained on both metadata and EHG measurements outperformed the models trained on metadata alone and on EHG measurements alone. Our classification model predicted preterm births with an AUC of 0.79 (95% CI: 0.77-0.80) and the regression model predicted preterm births with an AUC of 0.75 (95% CI: 0.73-0.77).

To better evaluate the performance of our prediction models, we estimated a performance bound on this classification problem. In our work, as well as in the obstetrics literature and clinical practice, births are considered preterm if the mother delivers the fetus before completing 37 weeks of gestation. However, the gestational age of the mother has an uncertainty that depends on the method used to estimate it. Generally, gestational age is estimated based on a first trimester ultrasound examination or on the timing of the last menstrual period (LMP) [91]. When the gestational age is estimated based on early ultrasound examination, the estimate has a standard deviation of about five days, whereas estimates based on the LMP have standard deviations of about seven days [106]. Notably, the incidence
of preterm births depends on the method used to estimate the gestational age [51]. This estimation error translates into uncertainty in the ground truth labels and limits the possible performance of classification algorithms. We estimated the upper bound of the AUC due to this limitation by measuring the AUC obtained when predicting the gestational age at delivery using a noisy version of the true gestational ages at delivery. We corrupted the gestational ages at delivery by adding independent and identically distributed (i.i.d.) Gaussian noise with zero mean and a standard deviation of six days. After repeating this procedure 20 times to estimate the mean and 95% CI of this AUC using this approach, we found that the AUC limit for this classification problem is 0.97 (95% CI: 0.97-0.97).

In Fig. 4.4, we present the receiver-operating characteristic curves (ROC) for the classification and regression models trained on clinical information alone, EHG measurements alone, and clinical information combined with EHG measurements. We observe that the classification models consistently outperform the regression models trained on the same data. Moreover, we notice that regardless of whether we use the classification or regression approach, the EHG-based models outperform the clinical information-based models and that the models that leverage both the clinical information and the EHG measurements achieve the best performance.

To further assess the performance of our models, we measured the sensitivity, positive predictive value (PPV), and negative predictive value (NPV) at various specificity levels, as shown in Table 4.2. Since the classification models systematically outperformed the regression models, we present the results only for the classification models. Whereas the sensitivity and specificity are useful to evaluate the models’ ability to identify mothers who will and who will not deliver preterm, respectively, these metrics do not convey the likelihood that if the test is positive or negative the mothers will deliver preterm or at term, respectively [203]. Moreover, the sensitivity and specificity values are insensitive to the incidence of the disease. To address these limitations, the PPV and NPV are reported in the literature. Since the PPV and NPV depend on the incidence of preterm births in the dataset and our dataset over-represents preterm births, we randomly removed preterm samples from each prediction fold when estimating the PPV and NPV so that the preterm birth incidence in our dataset was similar to the incidence in the TPEHG DB.
Figure 4.4: Performance of the models for predicting preterm births. **a**, ROC curves for predicting preterm births using the classification models trained with clinical information alone, EHG measurements alone, and clinical information combined with EHG measurements. **b**, ROC curves for the same tasks as in a, but using the regression models instead of the classification models. **a-b**, The performance bound is shown in both panels by a black curve. The greyed area delimited by this bound indicates unattainable performance due to the uncertainty in the ground truth labels. The AUCs of the models are presented with 95% CIs.

In Table 4.2, we observe that the combined model outperforms the models trained on clinical information alone or EHG measurements alone in sensitivity, PPV, and NPV at various specificity levels. Moreover, we observe that our models have a much higher NPV than PPV, which results from the low incidence of preterm births. In other words, our predictions of term births are more reliable than our predictions of preterm births.

We verified that our model was not discriminating between the two datasets used in our work. The TPEHG DB and the TPEHGT DS datasets were acquired with the same device and following the same protocol, so we did not expect that our model would discriminate between the samples of either dataset. We confirmed that our model does not assign one label to the samples from one dataset and another label to the samples of the other dataset. Moreover, when we trained the classification models using only the TPEHG DB, we obtained similar AUCs to those obtained when we trained the models using data from both datasets.
Table 4.2: Performance of classification models in predicting preterm birth. All values are presented with 95% CIs. Bold fonts indicate the best performing model for each metric and for the different specificity levels. PPV, positive predictive value; NPV, negative predictive value.

Although our regression models could predict preterm births more accurately than random guessing, these models were not able to predict the gestational ages at delivery with a much lower MSE than the MSE obtained using the mean gestational age at delivery in the training set, i.e., the minimum MSE estimator. Although the correlation between the predicted and true gestational ages at delivery is positive, the accuracy of the predictions is low, as shown in Fig. 4.5.
Figure 4.5: Predictions of gestational ages at delivery using the regression models. **a**, Predicted gestational ages at birth, using the clinical information alone plotted against the true gestational ages at birth. Each blue circle shows the gestational age at delivery, predicted based on the clinical information and the true gestational age at delivery for a single mother. The solid black line represents the linear fit between the predictions and the true values. The dashed black line represents a perfect correspondence between predictions and true values. The legend shows the root mean square error (RMSE) of the predictions, the coefficient of determination ($R^2$) of the predictions, and the slope of the linear fit. **b**, Bland–Altman plot for the predicted gestational ages at birth, using the clinical information alone and the true gestational ages at birth. Each blue circle represents the difference between predicted and true gestational ages at birth, and the mean of these values. The solid and dashed black lines show the mean of the difference between the predicted and the true values, and the 95% limits of agreement, calculated as mean $\pm 1.96$ standard deviations, respectively. **c**, Similar to **a**, but using the predictions based on EHG measurements alone. **d**, Similar to **b**, but using the predictions based on EHG measurements alone. **e**, Similar to **a**, but using the predictions based on clinical information combined with EHG measurements. **f**, Similar to **b**, but using the predictions based on clinical information combined with EHG measurements. All values are presented as mean with 95% CI.

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Further, we investigated how various components of the EHG measurements contribute to the preterm birth predictions by altering the STFT representations of the data. We first explored the predictive power of various frequency bands, as shown in Fig. 4.6a and b. We extracted four frequency bands (B0 through B3) by using only the relevant rows of the STFT for training and testing. We considered the same frequency bands as Jager et al., where B0, B1, B2, and B3, cover the frequency ranges between 0.05 Hz and 1.0 Hz, 1.0 Hz and 2.2 Hz, 2.2 Hz and 3.5 Hz, and 3.5 Hz and 5.0 Hz, respectively [110]. Notably, we observed that the models trained on higher frequency bands achieved higher AUCs, as shown in Fig. 4.6b.

Next, we examined how the temporal patterns of the measurements contribute to the models’ predictions. We disrupted the temporal patterns by randomly rearranging a random subset of columns of the STFTs, as illustrated in Fig. 4.6c. We observed that although the AUC of the model decreased as larger fractions of columns of the STFTs were rearranged, this decline was moderate, as shown in Fig. 4.6d. Notably, when all the columns of the STFTs were randomly rearranged, i.e., when all the temporal patterns were disrupted, our classification model trained on disrupted EHG measurements alone was able to predict preterm births with an AUC of 0.70 (95% CI: 0.68-0.73).

Based on our observations from disrupting the spectral and temporal patterns, we hypothesized that the predictions of our model are guided more by the spectral composition of the measurements than by their temporal patterns. Hence, we sought to predict preterm births using shorter EHG recordings. The duration of EHG recordings, usually between 30 and 60 minutes, is an important hindrance to their implementation in clinical settings, where personnel resources are often limited [6, 62]. To test this hypothesis, we trained and tested our model using cropped STFTs, as shown in Fig. 4.6e. We removed columns at the beginning and at the end of the STFTs to simulate shorter EHG measurements. Since the initial point selected for these shortened STFTs slightly affects the resulting AUC, we selected a random initial point for each shortened sample. Remarkably, the performance of our model decreased only marginally with decreasing measurement duration, as shown in Fig. 4.6f. When we trained our model using one-minute long recordings, we could predict preterm births with an AUC of 0.73 (95% CI: 0.71-0.75), which is only slightly lower than the 0.75 (95% CI: 0.73-0.77) AUC we obtained using the entire 30-minute long recordings.
4.4 Discussion

We developed a deep learning method to predict preterm births from EHG measurements and clinical information obtained from two public databases. We predicted preterm births with good accuracy directly from the data and without using handcrafted features, manual annotations, or simultaneous tocography measurements. Thus, our method potentially enables automatic prediction of preterm births from EHG recordings.
To assess the performance of our method from the perspective of clinical practice, we compare the performance of our method with other available technologies and methods to predict preterm births, as shown in Table 4.3. For this comparison, we included results only from studies published in peer-reviewed journals, with sound methodology, that report the AUC of the predictions, and which include at least 50 pregnant mothers. From this comparison, we observe that the performance of our method is superior to the performance of existing methods to predict preterm births that take place before completing 37 weeks of gestation. Importantly, our method outperforms the gold standard biomarkers of preterm birth, i.e., cervical length and fibronectin alpha, in this task. Moreover, the performance of our method to predict preterm births in asymptomatic mothers around their 31st week of gestation is closer to the performance of the gold standard tests to predict preterm birth within one week in mothers with symptoms of preterm labor.

<table>
<thead>
<tr>
<th>Technology</th>
<th>Population</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction of birth before 37 weeks of gestation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical information [54]</td>
<td>Singleton pregnancies, asymptomatic mothers</td>
<td>0.64 (0.61, 0.67)</td>
</tr>
<tr>
<td>Fibronectin alpha [102]</td>
<td>Asymptomatic mothers</td>
<td>0.65 (0.63, 0.66)</td>
</tr>
<tr>
<td>Fibronectin alpha [102]</td>
<td>Symptomatic mothers</td>
<td>0.71 (0.69, 0.73)</td>
</tr>
<tr>
<td>Cervical length [57]</td>
<td>Nulliparous, singleton pregnancies, asymptomatic mothers</td>
<td>0.67 (0.64, 0.7)</td>
</tr>
<tr>
<td>Clinical information and placental measurements [54]</td>
<td>Singleton pregnancies, asymptomatic mothers</td>
<td>0.72 (0.66, 0.77)</td>
</tr>
<tr>
<td>EHG [173]</td>
<td>Asymptomatic mothers</td>
<td>0.60</td>
</tr>
<tr>
<td>EHG and tocography [110, 214]a</td>
<td>Asymptomatic mothers</td>
<td>0.65</td>
</tr>
<tr>
<td>EHG [63, 214]a</td>
<td>Asymptomatic mothers</td>
<td>0.61</td>
</tr>
<tr>
<td>Our method (combined classification model)</td>
<td>Asymptomatic mothers</td>
<td>0.79 (0.77, 0.80)</td>
</tr>
<tr>
<td>Prediction of preterm birth within one week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibronectin alpha [102]</td>
<td>Symptomatic mothers</td>
<td>0.84 (0.8, 0.87)</td>
</tr>
<tr>
<td>Cervical length [189]</td>
<td>Symptomatic mothers</td>
<td>0.84b</td>
</tr>
</tbody>
</table>

Table 4.3: Accuracy of several technologies and methods to predict preterm births. a We considered the performance of these methods after their methodology was corrected by Vandewiele et al. [214]. b The AUC was obtained by extrapolating the ROC curve. AUCs are presented with 95% CI in parenthesis when available.
Additionally, we investigated how the temporal and spectral components of the EHG measurements contribute to our model’s predictions. Following the spectral partitioning suggested by Jager et al., we observed that the higher frequency components of the EHG measurements are more predictive of preterm births [110]. A possible explanation of this phenomenon is that the higher frequency bands contain spectral harmonics of the electrical activity in EHG measurements, which may contain more detailed spectral information about this electrical activity. Therefore, more spectral information may be coded in higher frequency bands. However, further research is needed to decipher the sources of the various spectral components of EHG measurements.

Importantly, we observed that the temporal patterns measured in EHG measurements are not crucial to predicting preterm births. This observation agrees with the results published by Iams et al., who showed that the frequency of uterine contractions is not predictive of preterm births [107]. Moreover, this observation also might also explain the inability of tocography, which measures the temporal patterns of uterine contractions, to predict preterm births [192]. Inspired by this observation, and specifically by our results presented in Fig. 4.6d, we explored whether we could use shorter EHG measurements to predict preterm births.

Whereas the classification and regression models could predict preterm births with good accuracy, surprisingly, the regression models could not predict the gestational ages at delivery accurately, as shown in Fig. 4.5. This effect can be explained by the pathology of preterm births and by analyzing the distribution of the gestational ages at delivery. Preterm birth is an abnormal physiological condition, not just a pregnancy that happened to end early. Therefore, we may expect that physiological measurements, such as EHG recordings, may show a stronger dichotomy between pregnancies that end with either preterm or term deliveries than is shown in continuous characteristics correlated with gestational age at delivery.

We can observe the dichotomous aspect of preterm and term births through the distribution of the gestational ages at delivery, shown in Fig. 4.1 and in Fig. 4.2. The distribution of the gestational ages at birth of the mothers included in this work only from the TPEHG DB is left-skewed and does not appear to follow a Gaussian distribution, as shown in Fig. 4.2d. This skewness may can be caused by either an excess of preterm births compared to what would be expected if the gestational ages at birth followed a Gaussian distribution and
by the induction of postterm births, which skews the distribution towards earlier deliveries. However, when we exclude the preterm births the distribution of gestational ages at birth appears to follow a Gaussian distribution, as shown in Fig. 4.2h. This observation suggests that the skewness results from an over-representation of preterm births rather than from the induction of postterm births. Since the gestational ages at delivery do not follow a Gaussian distribution where the left tail accounts for preterm births, we suggest that the dynamics that dictate the gestational age at delivery do not follow a continuum between preterm and term births. Therefore, we propose that predicting the gestational age at delivery is more complicated than predicting preterm births using categorical outputs.

Predicting preterm births in mothers without symptoms of preterm labor and several weeks before delivery can be helpful to delay preterm births and improve their outcomes. For example, clinical providers can prescribe progesterone to these mothers to prolong their pregnancies [14, 65]. Additionally, medical providers could screen more frequently the mothers at high risk of preterm birth to identify and treat hypertensive disease and cervical insufficiency [84, 92]. Moreover, anticipating preterm births can be useful to plan for the birth to take place at a hospital with a neonatal intensive care unit (NICU), rather than at home, in birthing centers, or in hospitals without a NICU. Hence, avoiding ambulance rides and delays before admitting the newborn to a NICU and improving the outcomes [33, 35, 177]. Furthermore, identifying asymptomatic mothers at high risk of preterm birth may be useful for researchers to assess the efficacy of potential approaches and therapies to delay preterm births and improve their outcomes.

4.4.1 Limitations

Our work is limited by the etiology of preterm birth and the dataset that we used to develop our models. Because preterm birth is a syndrome with many causes, it is most likely that no single physiological measurement will predict preterm births with perfect or nearly perfect accuracy [87, 215]. A combination of measurements of various physiological processes is likely to produce better results [78, 87].

The limited size of the dataset limits our work. In first place, we evaluated the performance of our prediction models using crossvalidation rather than separating a subset of the data
exclusively for testing after developing our models because such a testing set would not be
sufficiently large to evaluate the performance of our models accurately. For example, if we
set apart 20% of the data for the final testing, this dataset would contain five preterm and
25 term samples. If we evaluated the performance of our models with this test set only,
our performance estimates would not be accurate [115]. Secondly, all the samples in the
dataset were acquired in a single hospital and therefore, our model may not generalize well
to measurements from mothers of different populations. A larger database could not only
be useful to address these limitations, but would also enable us to train larger and more
complex prediction models which may produce better results [194].

4.4.2 Future Directions

Our work can be expanded to improve its performance and clinical value. Firstly, fol-
lowing the same approach we used to combine EHG measurements with clinical data to
predict preterm births, our method could incorporate other data such as cervical length
and fibronectin alpha measurements, which is likely to improve its performance. Addition-
ally, multiple EHG measurements could be recorded throughout pregnancy for each mother
to track the evolution of EHG activity towards birth and develop a dynamic prediction
model. Moreover, EHG measurements could be recorded from mothers presenting symp-
toms of preterm labor to develop a deep learning model for predicting imminent preterm
birth within one week.

Furthermore, our model could be expanded to assess the efficacy of therapies to delay or
prevent preterm birth. For example, our method could be used to determine whether the
risk of preterm birth changes following an intervention.

Lastly, our neural network could be implemented as a Bayesian neural network (BNN), which
besides predicting preterm births, would also provide an uncertainty estimate of the predic-
tions. This implementation could help healthcare providers better interpret the predictions
[140].
4.5 Conclusion

In summary, we developed a deep learning model to predict preterm births using clinical information and EHG measurements. Our method predicted preterm births in pregnant mothers without symptoms of preterm labor more accurately than existing technologies. We also showed that preterm births can be predicted using short EHG recordings. Our work and results are useful for developing applications to predict preterm births early during pregnancy and for ultimately improving their outcomes.
Chapter 5

Conclusion

In this Chapter, we will summarize the main contributions of this doctoral work. We will review our methodological advances and our physiological findings. Additionally, we will discuss the implications and significance of our contributions. Finally, we will discuss the limitations of this work and propose opportunities for future research.

5.1 Contributions From Uterine Fiber Model

We developed a uterine fiber-level model to address an important challenge for developing better monitoring technologies and therapeutics for uterine contractions. Uterine contraction disorders are associated with preterm births, slowly progressing labors, and postpartum hemorrhage [79, 157, 181]. While various technologies and drugs have been developed to predict these complications and to treat them, their effectiveness is limited. Our ability to develop better technologies and treatments for uterine contraction disorders is partly restricted by our incomplete understanding of the physiological mechanisms responsible for uterine contractions.

To better understand these mechanisms, we developed a fiber-level uterine model. This model, which is described in Chapter 2, recreates a uterine muscle fiber composed of USMCs concatenated longitudinally. This model integrates multiple USMC models and introduces a novel set of equations to model the propagation of electrical and mechanical activity along the fiber.
Using this model, we investigated the excitation and contraction dynamics of uterine contractions. Specifically, we studied how cellular excitability and intercellular coupling regulate the propagation of electrical activity and the development of contractile force. We observed that good intercellular coupling is fundamental for generating contractile force. Moreover, we observed that, as long as APs can propagate along the entire fiber, the USMC fiber can regulate itself to produce a stable contraction force.

Our contributions from the work described in Chapter 2 advance our understanding of uterine electrophysiology. While various researchers had developed electrophysiological models of both isolated USMCs and the entire uterus, the literature lacks electrophysiological models of uterine muscle fibers. Our model enabled us, and other researchers in the future, to simulate the electrical and mechanical dynamics of a uterine muscle fiber.

Our observations from this model elucidate some of the mechanisms that regulate uterine contractions. In turn, this understanding can be used to identify potential therapeutic targets for uterine contraction disorders. For example, our observations suggest a potential approach to develop better uterotonic drugs. When labor contractions are insufficiently strong, labor may not proceed normally and the mother may bleed excessively postpartum [157]. In these cases, uterine contractions are usually invigorated with uterotonic drugs, including oxytocin, that enhance uterine excitability and regulate the contractile mechanisms of USMCs [31]. However, our experiments show that upregulating cellular excitability is inefficient when AP propagation is limited by poor intercellular coupling. In other words, uterotonic drugs, oxytocin in particular, may be of less assistance when the underlying cause for the impaired contraction vigor is related to intercellular coupling.

This observation opens a possibility for personalized medicine. For mothers with limited intercellular coupling, who may be less responsive to oxytocin, a uterotonic drug that enhances AP conductivity may be more appropriate. Additionally, a combination drug that enhances conductivity and excitability may be more effective to augment labor contractions.
5.2 Contributions From Statistical Tensor Decomposition Method

Another important limitation for improving the outcomes of uterine contraction disorders is our suboptimal ability to predict these complications [86]. Various technologies have been developed for monitoring uterine contractions [59, 166, 178, 228]. Particularly, applications based on EHG measurements are a compelling option because these measurements capture informative physiological information and these devices can be implemented for widespread use [230]. However, EHG measurements have limitations that restrict our ability to develop reliable applications.

To address an important limitation of noninvasive electrophysiological recordings, we developed a statistical tensor decomposition method, which is described in Chapter 3. Our method estimates both the localized electrical activity that results from the uterine activity taking place directly under the electrodes and the distributed electrical activity, which is shared among the electrodes. Using our method, we can obtain more reliable measurements of the uterine activity and mitigate the effects through which localized electric potentials are measured as distributed electric potentials when measured noninvasively. These effects are an important limitation of noninvasive electrophysiological recordings in general, and EHG measurements in particular, because they conceal the electrophysiological activity that is intended to be measured [17].

Our methodology and results described in Chapter 3 contribute to the development of more reliable and accurate applications for monitoring uterine contractions based on EHG measurements. By drawing an analogy with video signal processing, we developed a statistical tensor decomposition method tailored to EHG measurements. Our distinction between localized and distributed electrical activity and our approach to estimate them create opportunities to develop new uterine contraction monitoring applications based on the underlying uterine electrical activity inferred from EHG measurements.

Using our method, we found that the fraction of the myometrium recruited during uterine contractions is a useful biomarker for uterine contraction monitoring. We assessed the fraction of the myometrium recruited during uterine contractions by counting the number of
electrodes that exhibit localized electrical activity during those contractions. Specifically, we found that this number is higher in Braxton-Hicks contractions of mothers who eventually gave birth prematurely than in those who delivered on term. Moreover, we observed that this metric increases towards birth. Lastly, we found that this biomarker can potentially be used to assess the efficiency of labor contractions.

Our observations suggest that measuring the surface of the myometrium that becomes active during contractions can be useful to evaluate uterine contractions in different scenarios. As discussed in the Introduction, multiple features from various signal domains have been proposed to infer medical conditions from EHG measurements. Our findings described in Chapter 3 contribute to the research efforts to identify EHG features that can be used to infer medical conditions from EHG measurements [230].

Our observations from Chapter 2 are aligned with our observations from Chapter 3. In Chapter 2 we observed that intercellular coupling is an important regulator of contractile force generation in uterine muscle fibers; when USMCs are well coupled, APs can propagate and the entire fiber generates contractile force. In Chapter 3 we observed that more efficient uterine contractions are associated with a higher surface of active myometrium. A larger area of active myometrium is to be expected from better coupled muscle fibers in the myometrium [240]. Therefore, our observations from Chapter 3 suggest that organ-level coupling contributes to better force generation. To summarize, our observations imply that coupling at the fiber level and at the organ level regulates the efficiency of uterine contractions.

5.3 Contributions From Machine Learning Model

Our machine learning model to predict preterm births from clinical information and EHG measurements, detailed in Chapter 4, is more accurate than existing methods that use similar data. Moreover, we showed that preterm births can be predicted for pregnant mothers, without signs of preterm labor, around their 31st week of gestation with comparable accuracy as imminent preterm labor is currently identified in clinical settings.

Our machine learning work to predict preterm births contributes to developing technologies for this task in two additional important aspects. In first place, our model predicts
preterm birth directly from EHG measurements, without requiring handcrafted features. Learned predictive features may supplement handcrafted features to predict preterm birth more accurately [124].

Additionally, by inspecting the EHG measurement components, we found that the predictions rely more on the spectral than on the temporal components of the measurements. Based on this observation, we showed that the predictions can be made with short EHG recordings, facilitating clinical implementation.

5.4 Limitations

Our work has limitations, which are described in the Discussions of Chapters 2 and 3. An important limitation of this work is the lack of experimental validation. Our model and observations described in Chapter 2 can be validated using ex-vivo uterine strips. Moreover, such experiments may be used to further develop our model [135]. Additionally, our method and observations in Chapter 3 can be validated using animal models and by acquiring EHG measurements from pregnant humans using a protocol designed to validate our observations.

Moreover, due to the limited size of the datasets used to develop our machine learning model, which is described in Chapter 4, we our model only through cross-validation and not with a previously unseen dataset. A larger dataset would enable us not only to evaluate our dataset using unseen data, but also could improve the accuracy of our predictions [194].

Another general limitation of our work is that we assumed that uterine contractions are a major determinant of pregnancy and labor progression. However, as we mentioned in the Introduction, several other factors regulate pregnancy and labor processes, including cervical dilation, membrane rupture, and hormonal factors [148, 150]. It is plausible that uterine contractions, and in particular Braxton-Hicks contractions, are only moderately related to the time remaining for birth and to labor progression.
5.5 Future Directions

Our work and results create new possibilities for future research and to develop practical applications. As described in Chapter 2, our fiber model can be expanded to simulate additional cellular mechanisms that regulate excitation and contraction. Importantly, our model can be expanded to also simulate stretch-regulated ion channels. As described in 2, these channels are important for maintaining a quiescent uterine state during pregnancy and for enabling contractile activity towards labor. To facilitate the expansion of our model to include stretch-regulated currents and other ion currents, we implemented our model following an object oriented approach. Additionally, our fiber model can be used to simulate additional experimental conditions and to elucidate more cellular and fiber-level mechanisms responsible for uterine excitation and contraction. Furthermore, our model can be used for investigating the mechanisms of action of existing drugs that regulate uterine activity and for identifying potential targets to develop safer and more efficient therapeutics that regulate uterine contractions.

Our tensor decomposition method can be used to develop more reliable applications to monitor uterine contractions. Our method and results may be used to assess the vigor of Braxton-Hicks contractions and track their evolution throughout pregnancy, which in turn could be useful to anticipate births. Specifically, it could be used to predict preterm births and to help mothers and healthcare providers to delay these births or prepare better to improve their outcomes [154]. Furthermore, our method may be used for monitoring slowly progressing labors and to guide oxytocin administration. This application could help reduce the number of complications caused by overdose of oxytocin in labor [50].

Our tensor decomposition method can be expanded to overcome its limitations that arise from our assumptions. Further research could expand our work to localize uterine activity directly from the EHG measurements rather than using a generative model. This approach could be applicable in a wider range of scenarios that do not satisfy our assumptions, as detailed in Chapter 3.

Our machine learning model can expanded to use more data to predict preterm births more accurately. Firstly, a larger database could enable training a more complex prediction model that better characterizes uterine activity, without overfitting [194]. Additionally, our model
can be combined with other tests to predict preterm birth, such as cervical length measurements, to improve accuracy by incorporating information from different biological processes associated with preterm birth. Lastly, our model can be expanded to incorporate EHG measurements acquired at different times during pregnancy to make predictions based on the evolution of uterine activity throughout pregnancy.

5.6 Conclusion

In summary, we developed a uterine fiber model and a statistical tensor decomposition method to investigate various aspects of uterine electrophysiology. Using these advances, we found that uterine coupling at various levels is an important regulator of uterine contractions. Our contributions expand our understanding of uterine electrophysiology and are a step forward towards developing better technologies to monitor uterine contractions and more effective therapeutics to treat uterine contraction disorders. Additionally, based on EHG measurements and clinical information, we developed a machine learning model to predict preterm births, advancing the research efforts to reduce the incidence of preterm birth and improve the outcomes.
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